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(54) Title: COMPOUNDS AND METHODS FOR TREATMENT OF *CHLAMYDIA* INFECTIONS

(57) Abstract: The present invention provides new compounds, pharmaceutical compositions and methods for the treatment and diagnosis of *Chlamydia* infections. The compounds are substituted ring-fused 2-pyridones and are shown to reduce the infectivity of *Chlamydia*. The invention further identifies the membrane-localized hexose-phosphate permease (UhpC) of *Chlamydia* as drug target and provides methods for the identification and development of new anti-*Chlamydia* compounds



## Compounds and methods for treatment of *Chlamydia* infections

### FIELD OF THE INVENTION

The present invention relates to new compounds and methods for the treatment of *Chlamydia* infections.

### BACKGROUND

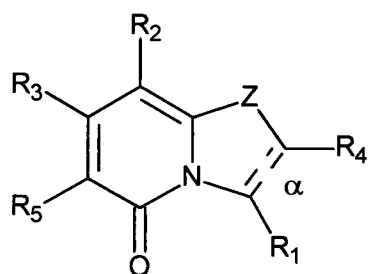
Chlamydiae are obligate intracellular pathogens that cause infections in human and animals (Horn 2008). *Chlamydia trachomatis* is the causative agent of many sexually transmitted diseases (Haggerty et al. 2010), as well as trachoma, a chronic eye infection (Burto & Mabey 2009). Without antibiotic treatment, infections of the genital tract can lead to infertility, thus *C. trachomatis* is considered a major public health problem (Paavonen & Eggert-Kruse 1999). The majority of chlamydial infections are treatable with currently available antibiotics, however, treatment failures have been described (Somani et al. 2000) and antibiotic resistant *C. suis* strains have been identified (Borel et al. 2012), which foreshadows the need for new therapeutics. Alternative anti-chlamydial treatment strategies include anti-bacterial compounds that target virulence factors so as to avoid unintended consequences to the normal bacterial flora (Cegelski et al. 2008), and compounds that allow limited bacterial proliferation but not allow transition to infectious stages (Nguyen et al. 2012; Valdavia 2012). *Chlamydiae* have been traditionally difficult to study because of their obligate intracellular lifestyle and their lack of a system for molecular genetic manipulation. *Chlamydia* spp. display a stereotypical developmental cycle that alternates between two forms. The elementary body (EB) is the infectious form that attaches to and invades target epithelial cells. After entry, the EB form transitions to a reticulate body (RB), which proliferates within the expanding parasitophorous vacuole, termed the inclusion (Field & Hackstadt 2002). Upon triggering by an undefined signal, RBs transition to infectious progeny, which are later released to the surrounding milieu either by lysis or an extrusion mechanism, to infect new host cells (Hybiske & Stephens 2007).

### DESCRIPTION OF THE INVENTION

The present inventors have employed compounds from the chemical class ring-fused 2-pyrridones to study *C. trachomatis* pathogenesis. By using a phenotypic screen a class of

compounds which blocks the generation of infectious *C. trachomatis* progeny has been discovered. The compound KSK120 has been shown to specifically target glucose metabolism of *C. trachomatis*. Additionally, a role for the membrane-localized hexose-phosphate permease (UhpC) in coordinating the generation of infectious *C. trachomatis* progeny has been discovered

Accordingly, in one aspect the invention provides compounds according to Formula (I)



Formula (I)

wherein

Z is selected from O, S and SO<sub>2</sub>,

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO<sub>2</sub>Y, wherein Y is selected from hydrogen and alkyl, -CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety -(CH<sub>2</sub>)<sub>b</sub>- wherein b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- wherein c+d is an integer from 2 to 5, and Q is O or N, including spiro compounds thereof,

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A, wherein

n is an integer from 0 to 5, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R<sub>3</sub> is -(CH<sub>2</sub>)<sub>m</sub>-D or -CHW-(CH<sub>2</sub>)<sub>m</sub>-D, wherein

m is an integer from 0 to 5,

W is halogen unsubstituted or substituted alkyl, and

D is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted

alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy,

R<sub>4</sub> is -(CH<sub>2</sub>)<sub>p</sub>-E, -CO-E, or -CO-NH-E, wherein

p is an integer from 0 to 5,

E is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy;

R<sub>5</sub> is -(CH<sub>2</sub>)<sub>q</sub>-G, wherein

q is an integer from 0 to 1, and

G is selected from hydrogen, -N<sub>3</sub>, -NO<sub>2</sub>, -OH, -alkoxy, -alkyl, -NY<sub>1</sub>Y<sub>2</sub> wherein Y<sub>1</sub> and Y<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,

and pharmaceutically acceptable salts, prodrugs and stereoisomers thereof, for use in prophylaxis, prevention and/or treatment of *Chlamydia* infections.

For Formula (I) it should be noted that the bond  $\alpha$  between the carbon atom 2 bonded to R<sub>1</sub> and carbon atom 3 bonded to R<sub>4</sub> may either be a single bond or a double bond.

In another embodiment, the stereochemical configuration around the carbon which is covalently bound to R<sub>4</sub> is (*R*).

In another embodiment, the stereochemical configuration around the carbon which is covalently bound to R<sub>4</sub> is (*S*).

In another preferred embodiment the compound for use in prophylaxis, prevention and treatment of *Chlamydia* infections according to Formula (I) is a compound wherein R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO<sub>2</sub>Y wherein Y is selected from hydrogen and alkyl,

-CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, X<sub>2</sub> is selected from hydrogen, alkyl or substituted alkyl, or wherein both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl and together form a moiety -(CH<sub>2</sub>)<sub>b</sub>- where b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- where c+d is an integer from 2 to 5 and Q is O or N, including spiro compounds thereof.

In one preferred embodiment the compound for use in prophylaxis, prevention and treatment of *Chlamydia* infections according to Formula (I) is a compound wherein R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A wherein n is an integer from 0 to 1, and A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.

In another preferred embodiment the compound for use in prophylaxis, prevention and treatment of *Chlamydia* infections according to Formula (I) is a compound wherein R<sub>3</sub> is -(CH<sub>2</sub>)<sub>m</sub>-D or -CHW-(CH<sub>2</sub>)<sub>m</sub>-D wherein m is an integer from 0 to 1, W is halogen, or-C<sub>1</sub>-C<sub>3</sub>alkyl, and D is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy.

In another preferred embodiment the compound for use in prophylaxis, prevention and treatment of *Chlamydia* infections according to Formula (I) is a compound wherein R<sub>4</sub> is -(CH<sub>2</sub>)<sub>p</sub>-E, -CO-E, or -CO-NH-E, p is an integer from 0 to 1, and E is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.

In another preferred embodiment the compound for use in prophylaxis, prevention and treatment of *Chlamydia* infections according to Formula (I) is a compound wherein R<sub>5</sub> is selected from hydrogen, -N<sub>3</sub>, -NO<sub>2</sub>, -OH, -C<sub>1</sub>-C<sub>3</sub>alkoxy, -C<sub>1</sub>-C<sub>3</sub>alkyl, -NH<sub>2</sub>. Most preferably R<sub>5</sub> is selected from hydrogen, -N<sub>3</sub>, -NO<sub>2</sub>, -NH<sub>2</sub>.

In one preferred embodiment Z is S.

Most preferably the compound for use in prophylaxis, prevention and treatment of *Chlamydia* infections according to Formula (I) is selected from

8-Cyclopropyl-7-[(4-methyl-1-naphthyl)methyl]-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (KSK67)

8-Cyclopropyl-7-(1,2-dihydroacenaphthyl-5-ylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (KSK58)

7-[(4-Bromo-1-naphthyl)methyl]-8-cyclopropyl-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (KSK69)

2-benzyl-8-cyclopropyl-7-(1-naphthylmethyl)thiazolo[3,2-a]pyridin-5-one (KSK129)

2-benzoyl-8-cyclopropyl-7-(1-naphthylmethyl)-5-oxo-thiazolo[3,2-a]pyridine-3-carboxylic acid (EC 177)

8-Isopropyl-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (EC 215)

7-(1-Naphthyloxymethyl)-5-oxo-8-(2-thienyl)-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (EC 218)

8-Cyclopropyl-7-[(6-methoxy-2-naphthyl)methyl]-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (CB 158)

8-(3,5-Dimethylphenyl)-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (SS 23)

8-Cyclopropyl-7-(1-naphthylmethyl)-3-(4H-triazol-5-yl)-2,3-dihydrothiazolo[3,2-a]pyridin-5-one (VA 147)

8-Cyclopropyl-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrooxazolo[3,2-a]pyridine-3-carboxylic acid (NP 239)

8-cyclopropyl-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid (C10)

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2-(phenylcarbamoyl)-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (EC 178)

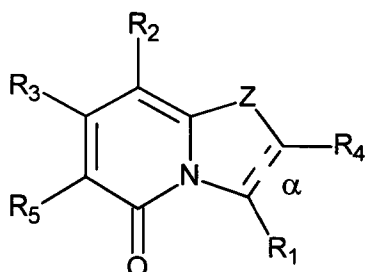
(3R)-6-amino-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (MS 68)

(3R)-8-Cyclopropyl-7-(4-fluoro-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 63)

(3R)-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (FN 075)

The compounds according to Formula (I) and pharmaceutically acceptable salts, and enantiomers thereof, can be used for prophylaxis, prevention and treatment of infections caused other intra cellular pathogens, preferably *Rickettsia*, *Coxiella burnetii*, *Anaplasma* *pagocytophilum*, *Neoehrlichia mikurensis*, *Mycoplasma pneumonia*.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of the general Formula (I), and pharmaceutically acceptable salts, prodrugs and enantiomers thereof:



Formula (I)

wherein

Z is selected from O, S and SO<sub>2</sub>,

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO<sub>2</sub>Y, wherein Y is selected from hydrogen and alkyl, -CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety - (CH<sub>2</sub>)<sub>b</sub>- wherein b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- wherein c+d is an integer from 2 to 5, and Q is O or N, including spiro compounds thereof,

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A, wherein

n is an integer from 0 to 5, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R<sub>3</sub> is -(CH<sub>2</sub>)<sub>m</sub>-D or -CHW-(CH<sub>2</sub>)<sub>m</sub>-D, wherein

m is an integer from 0 to 5,

W is halogen unsubstituted or substituted alkyl, and

D is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy,

$R_4$  is  $-(CH_2)_p-E$ ,  $-CO-E$ , or  $-CO-NH-E$ , wherein

p is an integer from 0 to 5,

E is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy;

$R_5$  is  $-(CH_2)_q-G$ , wherein

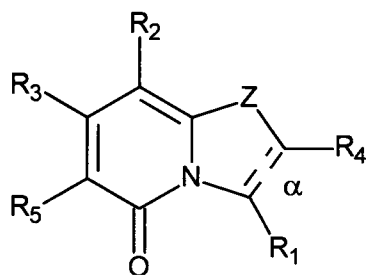
q is an integer from 0 to 1, and

G is selected from hydrogen,  $-N_3$ ,  $-NO_2$ ,  $-OH$ , -alkoxy, -alkyl,  $-NY_1Y_2$  wherein  $Y_1$  and  $Y_2$  are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,

and pharmaceutically acceptable salts, prodrugs and stereoisomers thereof.

Preferably the pharmaceutical composition is for use in prophylaxis, prevention and treatment of *Chlamydia* infections.

In yet another aspect, the present invention provides a method for the prophylaxis, prevention and/or treatment of *Chlamydia* infections, said method comprising the administering a therapeutically effective amount of a compound according to Formula (I)



Formula (I)

wherein

Z is selected from O, S and  $SO_2$ ,

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO<sub>2</sub>Y, wherein Y is selected from hydrogen and alkyl, -CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety -(CH<sub>2</sub>)<sub>b</sub>- wherein b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- wherein c+d is an integer from 2 to 5, and Q is O or N, including spiro compounds thereof,

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A, wherein

n is an integer from 0 to 5, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R<sub>3</sub> is -(CH<sub>2</sub>)<sub>m</sub>-D or -CHW-(CH<sub>2</sub>)<sub>m</sub>-D, wherein

m is an integer from 0 to 5,

W is halogen unsubstituted or substituted alkyl, and

D is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy,

R<sub>4</sub> is -(CH<sub>2</sub>)<sub>p</sub>-E, -CO-E, or -CO-NH-E, wherein

p is an integer from 0 to 5,

E is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy;

R<sub>5</sub> is -(CH<sub>2</sub>)<sub>q</sub>-G, wherein

q is an integer from 0 to 1, and

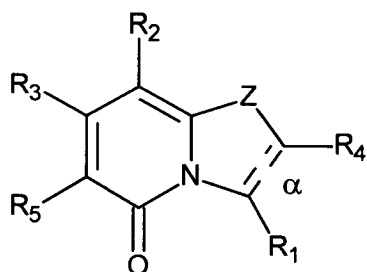
G is selected from hydrogen, -N<sub>3</sub>, -NO<sub>2</sub>, -OH, -alkoxy, -alkyl, -NY<sub>1</sub>Y<sub>2</sub> wherein Y<sub>1</sub> and Y<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted

or substituted aryl, unsubstituted or substituted heteroaryl,

and pharmaceutically acceptable salts, prodrugs and stereoisomers thereof to a subject.

The subject to be treated according to the present invention can be human, or an animal such as monkeys, primates, dogs, cats, horses, cows.

In yet another aspect the present invention provides compounds according to Formula (I)



Formula (I)

wherein

Z is selected from O, S and SO<sub>2</sub>,

R<sub>1</sub> is selected from -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,

or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety - (CH<sub>2</sub>)<sub>b</sub>- wherein b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- wherein c+d is an integer from 2 to 5 and Q is O or N, including spiro compounds thereof;

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A, wherein

n is an integer from 0 to 5, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R<sub>3</sub> is -(CH<sub>2</sub>)<sub>m</sub>-D or -CHW-(CH<sub>2</sub>)<sub>m</sub>-D, wherein

m is an integer from 0 to 5,

W is halogen or alkyl, and

D is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy;

R<sub>4</sub> is -(CH<sub>2</sub>)<sub>p</sub>-E, -CO-E, or -CO-NH-E, wherein

p is an integer from 0 to 5,

E is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy; and

R<sub>5</sub> is -(CH<sub>2</sub>)<sub>q</sub>-G, wherein

q is an integer 0 to 1, and

G is selected from hydrogen, -N<sub>3</sub>, -NO<sub>2</sub>, -OH, -alkoxy, -alkyl, -NY<sub>1</sub>Y<sub>2</sub> wherein Y<sub>1</sub> and Y<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

a pharmaceutically acceptable salt, prodrug or stereoisomer thereof.

For Formula (I) it should be noted that the bond  $\alpha$  between the carbon atom 2 bonded to R<sub>1</sub> and carbon atom 3 bonded to R<sub>4</sub> may either be a single bond or a double bond.

In another embodiment, the stereochemical configuration around the carbon which is covalently bound to R<sub>4</sub> is (*R*).

In another embodiment, the stereochemical configuration around the carbon which is covalently bound to R<sub>4</sub> is (*S*).

In one preferred embodiment the compound according to Formula (I) is a compound wherein

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or

substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,  $X_2$  is selected from hydrogen, unsubstituted or substituted alkyl or wherein both  $X_1$  and  $X_2$  are alkyl or substituted alkyl  $X_1$  and  $X_2$  together form a moiety  $-(CH_2)_b-$  where  $b$  is an integer from 3 to 6, or a moiety  $-(CH_2)_c-Q-(CH_2)_d-$  where  $c+d$  is an integer from 2 to 5 and  $Q$  is O or N, including spiro compounds thereof.

In one preferred embodiment the compound according to Formula (I) is a compound wherein  $R_2$  is  $-(CH_2)_n-A$ , wherein  $n$  is an integer from 0 to 1, and  $A$  is selected from unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.

In another preferred embodiment the compound according to Formula (I) is a compound wherein  $R_3$  is  $-(CH_2)_m-D$  or  $-CHW-(CH_2)_m-D$ , wherein  $m$  is an integer from 0 to 1,  $W$  is halogen or  $-C_1-C_3$ alkyl, and  $D$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy.

In another preferred embodiment the compound according to Formula (I) is a compound wherein  $R_4$  is  $-(CH_2)_p-E$ ,  $-CO-E$ , or  $-CO-NH-E$ ,  $p$  is an integer from 0 to 1,  $E$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.

In another preferred embodiment the compound according to Formula (I) is a compound wherein  $R_5$  is selected from hydrogen,  $-N_3$ ,  $-NO_2$ ,  $-OH$ ,  $-C_1-C_3$ alkoxy,  $-C_1-C_3$ alkyl,  $-NH_2$ . Most preferably  $R_5$  is selected from hydrogen,  $-N_3$ ,  $-NH_2$ .

In one preferred embodiment  $Z$  is S.

Preferred compounds according to the invention are:

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 120)

- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 165)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 6)
- (3*S*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 16)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-methylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 20)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(2-fluorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 21)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-methoxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 22)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-fluorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 23)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one (JG 24)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(pyridin-3-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 27)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(pyridin-4-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 28)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(1,3-thiazol-2-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 29)
- (3*R*)-*N*-Benzyl-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 30)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-*N*-(4-carbamoylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 33)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-*N*-methoxy-*N*-methyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 34)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-sulfamoylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 37)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3,4-difluorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 40)
- (3*R*)-7-(2,3-Dimethylbenzyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 42)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-methoxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 43)

- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-fluorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 44)
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(pyridin-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 45)
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-chlorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 46)
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 47)
- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-methylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 49)
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-ethylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 51)
- (3R)-7-(Benzyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 60)
- (3R)-7-(3,4-Dimethylbenzyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 66)
- (3R)-7-(4-Azidonaphthalen-1-yl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 67)
- (3R)-7-(Naphthalen-1-ylmethyl)-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 68)
- (3R)-7-(Naphthalen-1-ylmethyl)-8-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 69)
- (3R)-7-(Naphthalen-1-ylmethyl)-N-(2-fluoro-5-methylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 70)
- (3R)-7-(Naphthalen-1-ylmethyl)-N-(5-chloropyridin-2-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 71)
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(pyrimidin-4-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 79).
- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-(3-methylphenyl)-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 91)
- (3R)-8-cyclopropyl-7-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 93)
- (3R)-7-((4-Azidonaphthalen-1-yl)methyl)-N-(3-ethynylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 95)
- (3R)-7-(Naphthalen-1-ylmethyl)-N-(2-fluoropyridin-4-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 98)

- (3*R*)-7-(Naphthalen-1-ylmethyl)-*N*-(2-methoxypyridin-4-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 100)
- (3*R*)-7-(Fluoro(phenyl)methyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (JG 102)
- (3*R*)-*N*-(4-Azidophenyl)-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 195)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-((4-methylpiperazin-1-yl)carbonyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one (KSK 196)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-*N*-cyclohexyl-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 220)
- (3*R*)-*N*-(1,3-Benzodioxol-5-yl)-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 223)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-chlorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 224)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-(trifluoromethyl)phenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 226)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(morpholin-4-ylcarbonyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one (KSK 227)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-fluoropyridine-2-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (MK 12)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-ethynylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (MK 14)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(6-methylpyridine-2-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (MK 15)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-ethynylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (MK 17)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(6-methoxypyridine-2-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (MK 18)
- 2-((((3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-3-yl)carbonyl)amino)ethanaminium chloride (PS 49)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one (JG 48)
- (3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one (JG 52)
- (3*S*)-3-Amino-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one (KSK 214)

*N*-((3*S*)-7-(Naphthalen-1-ylmethyl)-8-methyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-3-yl)benzamide (KSK 215)

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one (JG 107)

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide 1,1-dioxide (KSK 193)

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-2-carboxamide (KSK 166)

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-*N*-phenyl-2-benzyl-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 218)

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-*N*-phenyl-2-phenyl-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 219)

(3*R*)-6-Azido-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 207)

(3*R*)-6-Amino-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (KSK 213)

a pharmaceutically acceptable salt, prodrug or stereoisomer thereof.

In yet another aspect the present invention provides a compound selected from

8-Cyclopropyl-7-[(4-methyl-1-naphthyl)methyl]-5-oxo-2,3-dihydrothiazolo[3,2-*a*]pyridine-3-carboxylic acid (KSK67)

8-Cyclopropyl-7-(1,2-dihydroacenaphthylen-5-ylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-*a*]pyridine-3-carboxylic acid (KSK58)

7-[(4-Bromo-1-naphthyl)methyl]-8-cyclopropyl-5-oxo-2,3-dihydrothiazolo[3,2-*a*]pyridine-3-carboxylic acid (KSK69)

Methyl (3*R*)-8-cyclopropyl-7-methyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 87)

Methyl (3*R*)-8-cyclopropyl-7-(fluoro(phenyl)methyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 90)

Methyl (3*R*)-8-cyclopropyl-5-oxo-7-(1-phenylethyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 103)

Methyl (3*R*)-8-cyclopropyl-7-benzyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 57)

Methyl (3*R*)-8-cyclopropyl-7-(4-methoxybenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 94)

Methyl (3*R*)-8-cyclopropyl-7-(4-chlorobenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 108)

Methyl (3*R*)-8-cyclopropyl-7-(2-fluoro-5-methylbenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 101)

Methyl (3R)-8-cyclopropyl-7-(2,3-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 19)

Methyl (3R)-8-cyclopropyl-7-(3,4-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 59)

Methyl (3R)-8-cyclopropyl-7-((4-fluoronaphthalen-1-yl)methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (KSK 62)

Methyl (3R)-8-cyclopropyl-7-(4-bromo-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylate (KSK 68)

Methyl (3R)-8-cyclopropyl-7-((4-methylnaphthalen-1-yl)methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (KSK 56)

Methyl (3R)-7-(1,2-dihydroacenaphthylen-5-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (KSK 50)

(3R)-8-Cyclopropyl-7-methyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 89)

(3R)-8-cyclopropyl-7-(fluoro(phenyl)methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 92)

(3R)-8-cyclopropyl-5-oxo-7-(1-phenylethyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 109)

(3R)-8-cyclopropyl-7-benzyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 49)

(3R)-7-(naphthalen-1-yl-methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 65)

(3R)-8-Cyclopropyl-7-(4-chlorobenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 110)

(3R)-8-Cyclopropyl-7-(4-methoxybenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 97)

(3R)-8-Cyclopropyl-7-(2-fluoro-5-methylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 104)

(3R)-8-Cyclopropyl-7-(2,3-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 26)

(3R)-8-Cyclopropyl-7-(3,4-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 63)

(3R)-8-Cyclopropyl-7-(4-fluoro-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 63)

a pharmaceutically acceptable salt, prodrug or stereoisomer thereof.

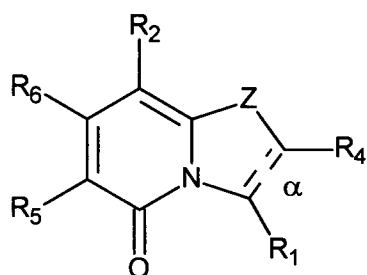
In one embodiment the present invention provides a compound according to the invention any of its prodrugs, enantiomers or pharmaceutically acceptable salts thereof, for use as a medicament.

In one embodiment the present invention provides a compound according to the invention any of its prodrugs, enantiomers or pharmaceutically acceptable salts thereof, for use in the prevention, prophylaxis and/or treatment of *Chlamydia* infections.

In one embodiment the present invention provides pharmaceutical compositions comprising a compound according to the invention, any of its pharmaceutically acceptable salts, prodrugs or stereoisomers, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In another embodiment the present invention provides pharmaceutical compositions comprising a compound according to the invention for the use in the prophylaxis, prevention and/or treatment of *Chlamydia* infections.

In one aspect the invention provides fluorescent compounds according to Formula (II)



Formula (II)

wherein

Z is selected from O, S and SO<sub>2</sub>,

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl,

-CO<sub>2</sub>Y wherein Y is selected from hydrogen and alkyl,

-CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted and substituted heteroaryl,

or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety - (CH<sub>2</sub>)<sub>b</sub>- where b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- where c+d is an integer from 2 to 5 and Q is O or N, including spiro compounds thereof;

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A, wherein

n is an integer from 0 to 5, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

$R_4$  is  $-(CH_2)_p-E$ ,  $-CO-E$ , or  $-CO-NH-E$ , wherein

p is an integer from 0 to 5,

E is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy;

$R_5$  is  $-(CH_2)_q-G$ , wherein

q is an integer from 0 to 1, and

G is selected from hydrogen,  $-N_3$ ,  $-NO_2$ ,  $-OH$ ,  $-alkoxy$ ,  $-alkyl$ ,  $-NY_1Y_2$  wherein  $Y_1$  and  $Y_2$  are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

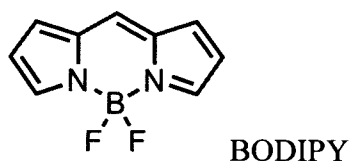
$R_6$  is  $-(CH_2)_m-L$  or  $-CHW-(CH_2)_m-L$ , wherein

m is an integer from 0 to 5,

W is alkyl or halogen, and

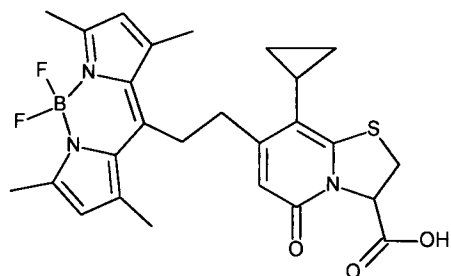
L is fluorescent group.

Preferably L is a fluorescent group comprising the BODIPY core 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene,



The BODIPY core can be unsubstituted or substituted.

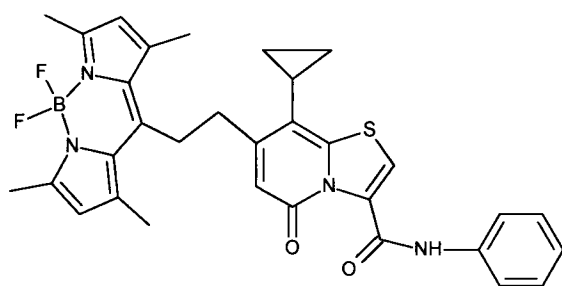
Preferably the fluorescent compound is the compound EC 364 according to Formula (IIa)



Formula (IIa)

(3R)-8-Cyclopropyl-7-(2-(1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene-8-yl)ethyl)-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylic acid,

or the compound KSK 170 according to formula (IIb)



Formula (IIb)

(3R)-8-cyclopropyl-7-(2-(1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene-8-yl)ethyl)-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide.

The fluorescent compounds according to the invention can be used in methods for diagnosis of *Chlamydia* infections, more specifically for the detection, quantification, and localization of *Chlamydia* cells and inclusions. The methods can be spectroscopical or histological. The methods comprise exposing a biological sample expected to be infected with *Chlamydia* to the fluorescent compounds according to the invention and subsequently measuring the fluorescence emission from the fluorescent compounds when bound to the *Chlamydia*.

The present inventors have demonstrated that the compounds of the invention bind to and/or interfere with the membrane-localized hexose-phosphate permease (UhpC) of *Chlamydia*. Binding of compounds to UhpC reduces the infectivity of *Chlamydia*. Accordingly, UhpC is a target for the identification and development of compounds potentially useful for the prophylaxis, prevention and/or treatment of *Chlamydia* infections.

One aspect of the invention provides methods for the identification and characterization of compounds potentially useful for the prophylaxis, prevention and/or treatment of *Chlamydia* infections. The methods can comprise one or more of the steps,

- (i) providing a cell or a cellular preparation, comprising the *Chlamydia* UhpC,
- (ii) providing one or more test compound,
- (iii) determining the binding of the test compound to said cell, cellular preparation, or *Chlamydia* UhpC,
- (iv) determining the effect of the test compound on the activity of said *Chlamydia* UhpC.

The binding of the test compounds to UhpC can be determined in a competition assay using one of the fluorescent compounds according to the invention.

Determining the effect of the test compound on the activity of UhpC can be determined by measuring hexose, preferably glucose, uptake, or by measuring glycogen accumulation.

In another embodiment the methods can comprise one or more of the steps,

- (i) determining the 3D-structure of the *Chlamydia* UhpC or a part thereof using NMR, X-ray crystallography, or molecular modeling based on homologous structures,
- (ii) analyzing and/or quantifying the binding of a test compound by computational methods using said 3D structure information,
- (iii) designing new test compounds by computational methods using said 3D structure information.

## LEGENDS TO FIGURES

### Figure 1. Dose response of compound KSK120 and determination of EC<sub>50</sub>.

HeLa cells infected with *C. trachomatis* LGV-2 were treated with KSK120 or DMSO, and at 44 h p.i. infectious progeny were collected for re-infection of new cells. DMSO treatment was set to 100.

Figure 2. Compound KSK120 blocks the generation of infectious *C. trachomatis* progeny.

(A) Transmission electron micrographs of cells infected with *C. trachomatis* LGV-2 treated with 10  $\mu$ M KSK120 or the corresponding amount DMSO (44 h p.i.).

(B) Inclusion sizes of 100 inclusions at 44 h p.i., treated with 10  $\mu$ M KSK120 or DMSO, which was arbitrarily set to 1 for each *C. trachomatis* serovar. Left DMSO, right KSK120 for each serovar. Inclusion sizes were statistically analyzed using the Mann-Whitney test, \*  $P < 0.05$ , \*\*\*  $P < 0.001$ , two-tailed.

Figure 3. Compound KSK120 blocks the generation of infectious *C. trachomatis* progeny.

(A) Relative amounts of *C. trachomatis* DNA (44 h p.i.), normalized to host cell genomic DNA, infected cells were treated with 10  $\mu$ M KSK120 or DMSO, which was set to 100 for each *C. trachomatis* serovar. Filled bar serovar LGV-2, open bar serovar D, shaded bar serovar A.

(B) Generation of infectious EB progeny in the presence of 10  $\mu$ M KSK120 (44 h p.i) and infectivity (recoverable infectious EBs) was normalized to DMSO-treated infections, which were set to 100. Filled bar serovar LGV-2, open bar serovar D, shaded bar serovar A. By using unpaired two-tailed student's T-test, the reduced infectivity due to KSK120 treatment was statistically significant ( $P < 0.001$ ) for all serovars.

Figure 4. KSK120 targets the replicating form of *C. trachomatis* LGV-2.

(A) Illustration of KSK120 treatment intervals.

(B) At 44 h p.i., infectious EBs were collected and subsequently used to infect new HeLa cells. Infectious EB progeny is normalized to infections treated with DMSO for the entire infection. Data presented was acquired from an experiment performed in triplicate, representative of results acquired from three independent experiments.

Figure 5. KSK120 targets glucose metabolism of *C. trachomatis*.

(A) *C. trachomatis* (MOI: 0.5) were grown in different amounts of glucose in the presence of 10  $\mu$ M KSK120 or the corresponding amount DMSO. At 44 h p.i. cells were fixed and stained. Inclusion areas were determined from acquired transmission micrographs where the inclusion membrane is clearly visualized. A) 0.1mg/ml glucose, B) 0.1mg/ml glucose + 10  $\mu$ M KSK 120, C) 1 mg/ml glucose, D) 10 mg/ml glucose + 10  $\mu$ M KSK 120, E) 10 mg/ml glucose, F) 10 mg/ml glucose + 10  $\mu$ M KSK 120. Inclusion sizes were statistically analyzed by the Mann-Whitney test, \*  $P < 0.05$ , \*\*\*  $P < 0.001$ , two-tailed.

(B) At 44 h p.i., infectious EBs were collected following treatment and subsequently incubated in 37°C. At the indicated time points, post-incubation infectivity was measured by infection of fresh HeLa cells. -■- DMSO, -▲- 2.5  $\mu$ M KSK120, -◆- 10  $\mu$ M KSK120, -●- 25  $\mu$ M KSK120. Statistical analysis were performed using unpaired student's t-test, \*  $P < 0.05$ , two-tailed.

Figure 6. The response to G-6-P limitation varies between isolated mutant strains.

(A) *C. trachomatis* LGV-2 strains (MOI: 0.1) were grown in the presence of 2.5 mM 2-DG (2-deoxy-D-glucose), a glucose analogue that inhibits host cell hexokinase leading to, e.g., G-6-P starvation, or low amounts of glucose (0.1 mg mL<sup>-1</sup>). At 48 h p.i. infectious EBs were collected and used for re-infection of fresh HeLa cells. In parallel to the primary infection the titer (input inclusion forming units (IFUs)) of each strain was determined. Treated wild-type was arbitrarily set to 1, for each treatment. Filled bars 2-DG, open bars low amount glucose. Statistical analysis was performed using unpaired student's t-test, \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , two-tailed.

(B) UhpC activity and glucose metabolism play a major role in the generation of infectious *C. trachomatis* progeny. Isolated *C. trachomatis* LGV-2 strains were grown (MOI: 0.01) in the presence of 10  $\mu$ M KSK120 or the corresponding amount of DMSO and at indicated time-points post-infection infectious EBs were collected for re-infection of new cells. In parallel to the primary infection the titer (input inclusion forming units (IFUs)) of each strain was determined. --●-- wt-1 DMSO, --- ● --- wt-1 + KSK120, ---▲--- UhpC<sup>L429I</sup>, --▼--- UhpC<sup>L429I, M315I</sup> + DMSO, ---▼--- UhpC<sup>L429I, M315I</sup> + KSK120, --○--- UhpC<sup>A394T</sup> + DMSO, ---○--- UhpC<sup>A394T</sup> + KSK120. Statistical analysis was performed using unpaired student's t-test, \*\* $P < 0.01$ , two-tailed. In the presence of DMSO, the strain with the UhpC<sup>L429I</sup> substitution generated similar amounts of infectious EBS to that of the wild-type strain and was therefore omitted for clarification.

### Definitions

As used herein, alkyl means an alkyl group being straight or branched having from 1 to 10 carbon atoms. Examples include methyl, ethyl, propyl, isopropyl, butyl, hexyl, heptyl, octyl, nonyl, decyl and the like. The alkyl groups may be unsubstituted or substituted. Substituents include alkoxy, preferably methoxy and ethoxy, halogen, hydroxyl, alkyl,

preferably C<sub>1</sub>-C<sub>3</sub> alkyl, aryl, alkenyl, preferably C<sub>1</sub>-C<sub>3</sub> alkenyl, alkynyl, preferably C<sub>1</sub>-C<sub>3</sub> alkynyl, acyl, preferably acetyl, nitro, amino, amido, trifluoromethyl, sulfonamide.

As used herein, C<sub>1</sub>-C<sub>3</sub> alkyl means an alkyl group being straight or branched having from 1 to 3 carbon atoms. Examples include methyl, ethyl, propyl, isopropyl.

As used herein, alkoxy means an alkoxy group being straight or branched having from 1 to 10 carbon atoms. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, hexoxy, heptoxy, octoxy, nonoxy, decoxy and the like. The alkoxy groups may be unsubstituted or substituted. Substituents include alkoxy, preferably methoxy and ethoxy, halogen, hydroxyl, alkyl, preferably C<sub>1</sub>-C<sub>3</sub> alkyl, aryl, alkenyl, preferably C<sub>1</sub>-C<sub>3</sub> alkenyl, alkynyl, preferably C<sub>1</sub>-C<sub>3</sub> alkynyl, acyl, preferably acetyl, nitro, amino, amido, trifluoromethyl, sulfonamide.

As used herein, C<sub>1</sub>-C<sub>3</sub> alkoxy means an alkoxy group being straight or branched having from 1 to 3 carbon atoms. Examples include methoxy, ethoxy, propoxy, isopropoxy.

As used herein, alkenyl means an alkenyl group being straight or branched having from 2 to 10 carbon atoms. Examples include ethenyl, propenyl, isopropenyl, butenyl, hexenyl, heptyl, heptenyl, octenyl, nonenyl, docenyl and the like. The alkenyl groups may be unsubstituted or substituted. Substituents include alkoxy, preferably methoxy and ethoxy, halogen, hydroxyl, alkyl, preferably C<sub>1</sub>-C<sub>3</sub> alkyl, aryl, alkenyl, preferably C<sub>1</sub>-C<sub>3</sub> alkenyl, alkynyl, preferably C<sub>1</sub>-C<sub>3</sub> alkynyl, acyl, preferably acetyl, nitro, amino, amido, trifluoromethyl, sulfonamide.

As used herein, C<sub>1</sub>-C<sub>3</sub> alkenyl means an alkenyl group being straight or branched having from 2 to 3 carbon atoms.

As used herein, alkynyl means an alkynyl group being straight or branched having from 2 to 10 carbon atoms. Examples include ethynyl, propynyl, butynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl and the like. The alkynyl groups may be unsubstituted or substituted. Substituents include alkoxy, preferably methoxy and ethoxy, halogen, hydroxyl, alkyl, preferably C<sub>1</sub>-C<sub>3</sub> alkyl, aryl, alkenyl, preferably C<sub>1</sub>-C<sub>3</sub> alkenyl, alkynyl,

preferably C<sub>1</sub>-C<sub>3</sub> alkynyl, acyl, preferably acetyl, nitro, amino, amido, trifluoromethyl, sulfonamide.

As used herein, C<sub>1</sub>-C<sub>3</sub> alkynyl means an alkynyl group being straight or branched having from 2 to 3 carbon atoms.

As used herein, cycloalkyl means a cycloalkyl group being straight or branched having from 3 to 10 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like. The cycloalkyl groups may be unsubstituted or substituted. Substituents include alkoxy, preferably methoxy and ethoxy, halogen, hydroxyl, alkyl, preferably C<sub>1</sub>-C<sub>3</sub> alkyl, aryl, alkenyl, preferably C<sub>1</sub>-C<sub>3</sub> alkenyl, alkynyl, preferably C<sub>1</sub>-C<sub>3</sub> alkynyl, acyl, preferably acetyl, nitro, amino, amido, trifluoromethyl, sulfonamide.

As used herein, acyl means an acyl group being straight or branched having from 1 to 10 carbon atoms. Examples include formyl, acetyl, propionyl, isopropionyl, butyryl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl and the like. The acyl groups may be unsubstituted or substituted.

The aryl moieties described here, either alone or with various substituents, contain from 6 to 15 carbon atoms and include phenyl, 1-naphthalenyl and 2-naphthalenyl, indanyl, and indenyl. Substituents include alkoxy, preferably methoxy and ethoxy, halogen, hydroxyl, alkyl, preferably C<sub>1</sub>-C<sub>3</sub> alkyl, aryl, alkenyl, preferably C<sub>1</sub>-C<sub>3</sub> alkenyl, alkynyl, preferably C<sub>1</sub>-C<sub>3</sub> alkynyl, acyl, preferably acetyl, nitro, amino, amido, trifluoromethyl, sulfonamide.

The aryloxy moieties described here, either alone or with various substituents, contain from 6 to 15 carbon atoms and include phenoxy, 1-naphthalenoxy and 2-naphthalenoxy. Substituents include alkoxy, preferably methoxy and ethoxy, halogen, hydroxyl, alkyl, preferably C<sub>1</sub>-C<sub>3</sub> alkyl, aryl, alkenyl, preferably C<sub>1</sub>-C<sub>3</sub> alkenyl, alkynyl, preferably C<sub>1</sub>-C<sub>3</sub> alkynyl, acyl, preferably acetyl, nitro, amino, amido, trifluoromethyl, sulfonamide.

The term "heteroaryl," as used herein, means an aromatic monocyclic ring or an aromatic bicyclic ring. The aromatic monocyclic rings are five or six membered rings wherein 1, 2, 3, or 4 atoms are independently selected from the group consisting of N, O, and S. The five

membered aromatic monocyclic rings have two double bonds and the six membered aromatic monocyclic rings have three double bonds. The aromatic bicyclic rings are composed of an aromatic monocyclic ring fused to a phenyl group, alternatively, an aromatic monocyclic ring is fused to another aromatic monocyclic ring. The aromatic monocyclic rings and the aromatic bicyclic rings are connected to the parent molecular moiety through a carbon or nitrogen atom. Representative examples of heteroaryl include, but are not limited to, benzimidazole, benzothienyl, benzoxadiazolyl, cinnolinyl, dibenzofuranyl, furopyridinyl, furyl, imidazolyl, indazolyl, indolyl, isoxazolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, quinolinyl, tetrazolyl, thiadiazolyl, thiazolyl, thienopyridinyl, thienyl, triazolyl, and triazinyl.

The term tetrazol-5-yl includes 1H-tetrazol-5-yl, 2H-tetrazol-5-yl, and 5H-tetrazol-5-yl.

As used herein, the term “halogen” denotes a fluoro, chloro, bromo, or iodo group.

As used herein, when two or more groups are used in connection with each other, it means that each group is substituted by the immediately preceding group. For instance, trifluoromethylphenyl means a phenyl group substituted by a trifluoromethyl group.

As used herein, the terms “prevent” or “prevention” and prophylaxis are given their ordinary meaning and thus means the avoidance or alleviation of the serious consequences of a disease or a side-effect by early detection.

As used herein, the term “mammal” means a human or an animal such as monkeys, primates, dogs, cats, horses, cows, etc.

As used herein, the single enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention, where such isomers exist. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two or more diastereomers), tautomers, and atropisomers are within the scope of the invention.

As used herein, the term "pharmaceutically acceptable salts" includes acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of the invention with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. in vacuo or by freeze-drying). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion using a suitable ion exchange resin.

As used herein the term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs, as described in Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

Suitable acids are non-toxic and include e.g., but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, nitric acid, acetic acid, citric acid, ascorbic acid, lactic acid, malic acid, and tartaric acid. Suitable bases are non-toxic and include e.g., but are not limited to, sodium hydroxide, potassium hydroxide, lithium hydroxide, ammonia, methylamine, dimethylamine, trimethylamine, and triethylamine.

In the context of the present specification, the term “treat” also includes “prophylaxis” unless there are specific indications to the contrary. The term “treat” within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring condition and continued therapy for chronic disorders.

The compounds of the present invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracically, intravenously, epidurally, intrathecally, intracerebroventricularly and by injection into the joints.

In one embodiment of the present invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of the present invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in mixture with the finely divided compound of the present invention, or the active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogenous mixture is then poured into conveniently sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents, stabilizers, and thickening agents as desired. Aqueous solutions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will according to one embodiment of the present invention include 0.05% to 99% weight (percent by weight), according to an alternative embodiment from 0.10 to 50% weight, of the compound of the present invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

The above-mentioned subject-matter for a pharmaceutical composition comprising a compound according to the present invention is applied analogously for a pharmaceutical composition comprising a combination according to the present invention.

Another object of the present invention is a compound as disclosed above for use in medicine.

Another object of the present invention is a pharmaceutical formulation comprising a compound as disclosed above in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

It is contemplated that any embodiment discussed in this specification can be implemented with respect to any method or composition of the invention, and vice versa.

## EXAMPLES

### Cell culture, bacterial infections and plaque assay.

The HeLa cell line (DSMZ) was grown at 37°C (5 % CO<sub>2</sub>) in RPMI 1640 (Sigma) supplemented with 10% FBS (Sigma) and 20 mM HEPES. Vero cells (ATCC) were grown in DMEM (Gibco) supplemented with 10% FBS (Sigma) at 37°C (5% CO<sub>2</sub>). *Chlamydia trachomatis* serovar LGV-L2 454/Bu (ATCC VR902B), *C. trachomatis* serovar D (gift from S. Muschiol) and *C. trachomatis* serovar A (ATCC VR571B) were propagated in HeLa cells in the absence of cycloheximide and elementary bodies was purified as previously described by Caldwell et al. (1981) and stored in SPG buffer (0.25 M Sucrose, 10 mM sodium phosphate, 5 mM L-glutamic acid). Generally, HeLa cells were infected by *C. trachomatis* diluted in Hanks balance salt solution (HBSS)(GIBCO®, Invitrogen) with a multiplicity of infection (MOI) of 0.5-1 for one hour at 37°C (5% CO<sub>2</sub>). Subsequently HBSS was removed and complete RPMI media supplemented with the indicated

compounds was added to the infected cells. Cycloheximide was excluded in all experiments. Clonal populations were collected by plaque assay as described elsewhere (Nguyen & Valdivia 2012). Briefly, Vero cells were infected with 100-10 IFUs for 2 hours and infected cells were overlaid with an agarose/DMEM overlay. Plaques were collected 10-20 days after infection and propagated in HeLa cells. Vero cells, HeLa cells and *C. trachomatis* strains were negative for mycoplasma infection as determined by a detection kit according to the manufacturer's instructions (Stratagene).

#### Phenotypic screen and immunofluorescence.

Hela cells grown on cover slips were infected as described above. Compounds presented in Table 1 were at first tested at a concentration of 100  $\mu$ M and treated infections were observed by light microscopy for 44 hours. Subsequently, treated infections were fixed with methanol for 5 minutes and blocked with 5% bovine serum albumin (BSA) for at least 1 hour, and thereafter incubated with primary anti-MOMP antibody (gift from Ken Fields) and primary anti-Hsp60 antibody (Santa Cruz biotechnology). Next, an LRSC-conjugated anti-rabbit antibody was used to detect the MOMP antibody and a FITC-conjugated anti-mouse antibody (both from Jackson ImmunoResearch laboratories) to detect the Hsp60 antibody. DNA was stained with 200 nM 4',6-diamidino-2-phenylindole (DAPI). Coverslips were mounted on glass slides with fluorescence mounting media (Dako). Images was obtained by confocal laser scanning microscopy (Nikon Eclipse C1 plus) and processed by Adobe Photoshop software (Adobe Systems Inc.). The effect of the compounds was scored according to the distribution of *C. trachomatis* inside the inclusion, before and after fixation. Heterogeneous distribution was equivalent to a strong phenotypic effect.

#### Localization of a fluorescent analogue compound.

At 18 hours post infection (h p.i.) RPMI media was changed to media supplemented with 100  $\mu$ M of the fluorescent analogue EC 364. DMSO was used as control. At 44 h p.i. infected cells were washed twice with PBS and then fixed with methanol or 4% paraformaldehyde (PFA), and stained with the anti-MOMP antibody and DAPI as described above. Penicillin-G was added at 18 h p.i., at a concentration of 100 U/ml and EC 364 was either added concomitantly (18 h p.i.) or at 29 h p.i. Treated infections were fixed and stained. Images were obtained and processed as described above.

#### Determination of *C. trachomatis* inclusion sizes and infectivity.

At the indicated time point media was completely removed and the infected cells were disrupted with ice-cold sterile water to release infectious EB progeny. Released bacteria were diluted in HBSS and fresh HeLa cells were infected, and 30-40 hours after re-infection the *C. trachomatis* inclusions were counted. Data are represented as the relative numbers of EBs in treated infections compared to the numbers of EBs in DMSO-treated infections. When multiple strains were analyzed, a titration was performed in parallel to the primary treated infections to calculate the exact number of infectious EB progeny per treated inclusion forming unit IFU. Inclusion size of *C. trachomatis* fixed at 44 h p.i. was measured in confocal images processed by the EZ-C1 software (Nikon). Because KSK120 treatment results in heterogeneous distribution of the bacteria, inclusion sizes were determined from acquired transmission pictures. Representative data are from at least one hundred measured *C. trachomatis* inclusions.

#### Glucose experiments.

*C. trachomatis* infected cells were washed twice with RPMI lacking glucose and thereafter grown in complete RPMI with a glucose concentration ranging between 0.1-10 mg/ml in the presence of 10  $\mu$ M KSK120 or a corresponding amount of DMSO. The RPMI media was also supplemented with 5 mM sodium pyruvate, which is known to be metabolized by the host cell but not by chlamydiae (Lin et al. 2009). At 44 h p.i. infected cells were fixed and stained. Images were taken by confocal microscopy and inclusion sizes were measured from the obtained images as described above.

#### Glycogen staining.

Potassium iodine and iodine (both from Sigma) was dissolved in 100% methanol. Subsequently an equal amount of glycerol was added to the solution. At indicated time-points post-infection culture media were removed and infected cells were washed once with PBS before incubation in iodine solution for 30 minutes. Thereafter, the iodine solution was removed and samples were air-dried for 90 minutes prior to microscopic analysis.

#### Mutant selections.

HeLa cells grown in large flasks were infected with an MOI of 5 (~108 IFUs) and treated with a sub-inhibitory concentration of compound of KSK120 for serial passage. From each

mutant passage infectious EB progeny were collected at 44-48 h p.i. and used for re-infection. During the first 4-6 passages the treated bacteria were grown at an MOI of 2 or higher, thereafter the selection proceeded with a MOI of 2 or lower (preferentially lower than a MOI of 1). From each mutant passage an aliquot of bacteria was saved for later analysis.

#### Whole genome sequencing and genotyping.

*C. trachomatis* genomic DNA prepared for whole genome sequencing (WGS) was purified from density gradient purified bacteria with the DNeasy Blood & Tissue Kit (Qiagen, purification of total DNA from Gram-negative bacteria) according to the manufacturer's instructions. DNA was concentrated by sodium acetate-ethanol precipitation, and the pellets were dissolved in AE-buffer (Elution buffer for genomic DNA, Qiagen) to avoid aggregation. For WGS, 1 µg of enriched chlamydial DNA was fragmented with an Adaptive Focused Acoustics S220 instrument (Covaris, Inc. Woburn, MA), and DNA sequencing libraries were prepared with a library construction kit (TruSeq DNA Sample Preparation Kit v2, Illumina, Inc. San Diego, CA) according to the manufacturer's instructions. Libraries were sequenced on a MiSeq DNA Sequencing Platform (Illumina, Inc. San Diego, CA) at Duke Universities IGSP DNA Core sequencing facility. Genome assembly and single nucleotide variant (SNV) identification was performed with Geneious version 6 from Biomatters (available at <http://www.geneious.com/>). The *C. trachomatis* L2 434/Bu genome (GenBank no, NC\_010287) was used as reference sequence. A mutation is herein defined as a nucleotide variant present at a frequency above 15% and strand-bias below 80%, detectable both by WGS and capillary sequencing in a bacterial population. To identify mutations by capillary sequencing templates were regions PCR amplified. PCR products were sequenced by capillary sequencing (Big Dye; Applied Biosystems). The intensity of the fluorescence peaks detected by capillary DNA sequencing was used as estimates of the relative abundance of any single nucleotide variant in the bacterial population. Estimated frequencies were consistent with the obtained values from WGS (data not shown).

#### Transmission electron microscopy (TEM).

At 44 h p.i, infected cells were processed for TEM as previously described (28). Briefly, cells were fixed with 2.5% glutaraldehyde/0.05% malachite green (EMS) in 0.1 M sodium cacodylate buffer (pH 6.8) and then post-fixed with 0.5% osmium tetroxide/0.8%

potassium ferricyanide in 0.1 M sodium cacodylate, 1% tannic acid and 1% uranyl acetate. Samples were dehydrated with graded amounts of ethanol and embedded in Spur resin, subsequently imaged on a Tecnai G2 Twin microscope (FEI).

## Results

### Compound library and initial structure-activity relationships

A collection of compounds with variations in the substitution pattern around the 2-pyridone central fragment was tested in a phenotypic screen using a HeLa cell-based *C. trachomatis* LGV-2 infection model. Compounds were added to cells immediately after infection, and the effect on the infection phenotype was observed over a period of two days using an inverted light microscope. The effect of the compounds on the infection phenotype was scored according to the bacterial distribution inside the chlamydial inclusion. Compounds were at first screened at a concentration of 100  $\mu$ M, seven compounds had a strong effect on the infection phenotype, with bacteria observed in foci inside the inclusion instead of homogeneously distributed as observed in control treatments. A moderate effect was observed with nine compounds, nineteen compounds were cell toxic, and the remaining 43 compounds affected neither the *C. trachomatis* distribution nor the host cell (Table 1).

**Table 1. Compound used in the phenotypic screen<sup>a</sup>**

| Strong effect | Moderate effect | No effect |       |         | Cell toxic <sup>b</sup> |             |
|---------------|-----------------|-----------|-------|---------|-------------------------|-------------|
| EC177         | KSK163          | CL014     | CL015 | CL016   | EC306                   | EC309       |
| EC215         | C-10            | EC123     | EC217 | EC221   | EC312                   | EC238       |
| EC364         | FN075           | EC223     | EC224 | EC227   | EC240                   | SS28        |
| KSK58         | EC218           | EC228     | EC229 | EC230   | VA140                   | VA142       |
| KSK67         | S-C-10          | EC231     | EC232 | EC244   | VAB086                  | C-10-methyl |
| KSK69         | NP239           | EC253     | EC308 | EC350   | VAC088                  | CB160       |
| SS23          | VA145           | EC351     | EC352 | EC353   | CB162                   | CB180       |
|               | VA147           | EC354     | EC355 | BIBC6   | CB186                   | CB191       |
|               | CB158           | PHPYRR    | NP240 | VA121   | CB193                   | KSK88       |
|               |                 | CB157     | CB159 | TSLB225 |                         |             |
|               |                 | TSLB227   | MS67  | MS69    |                         |             |
|               |                 | MS71      | MS73  | MS74    |                         |             |
|               |                 | MS76      | MS89  | KSK29   |                         |             |
|               |                 | KSK30     | KSK32 | KSK49   |                         |             |
|               |                 | KSK55     |       |         |                         |             |

<sup>a</sup>Compounds (100  $\mu$ M) were judged by phenotypic alteration, an effective compound induce intra-inclusion redistribution of *C. trachomatis* with bacteria heterogeneous distributed.

<sup>b</sup>HeLa cells with altered morphology 44 hour after addition of compound was determined to be cell toxic

The assay used in the screening is a whole-cell assay containing both a eukaryotic host cell and the intracellular parasite and it is performed over a time course of 44 hours. Hence, compared to a simple *in vitro* assay with a direct interaction and a known target, phenotypic screen represents a more rigorous test of activity. The observed structure

activity relationships (SAR) are therefore not just affected by target affinity but also on cellular and/or parasite uptake and other physical chemical properties. Despite the fact of a complex system clear trends were observed in the SAR, in which the most pronounced effect was with a large (e.g. phenyl) substituent in position R<sup>1</sup> which resulted in decreased activity. On the other hand, compounds with a cyclopropyl substituent in position R<sup>1</sup> showed high activity. The most active compounds had a 1-naphthyl substituent connected to the central fragment via a methylene group, and if the 1-naphthyl group had additional substituents it was critical how these were positioned. To potentially improve activity, a small collection of 2-pyridones were synthesized in which the carboxylic acid was exchanged with other functional groups. Interestingly, all analogues showed lower activity compared to the corresponding carboxylic acid except the aryl amide KSK120. Next, KSK120 was tested in an assay where generation of infectious EB progeny was determined. KSK120 was added to the cells immediately after infection with *C. trachomatis*, and at 44 hour post infection (h p.i.) infectious EBs were collected for infection of new HeLa cells. Formed inclusions in the re-infection correspond to one infectious EB progeny generated in the primary infection. Surprisingly, KSK120 almost completely blocked the generation of infectious EBs at concentration of 10  $\mu$ M and higher, and the EC<sub>50</sub>-value was determined to be ~1.25  $\mu$ M (Figure 1). Thus, as a primary lead compound, KSK120 showed desirable biological activity. In addition, KSK120 did not show any pilicide or curlicide effect, and it did not affect growth of *E. coli* (data not shown), indicating a different mode of action.

The novel inhibitory compound KSK120 blocks the generation of infectious *C. trachomatis* progeny.

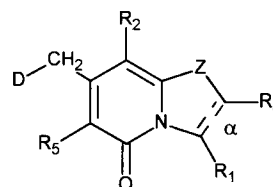
To further study the effect of KSK120 on *C. trachomatis* the effect of KSK120 on *C. trachomatis* serovar LGV-2, serovar D and serovar A infections were investigated. The genome content of these *C. trachomatis* serovars are highly similar but some functional differences have been suggested including metabolic capacities (Thomson et al. 2008). Morphologic analysis of *C. trachomatis* LGV-2 within infected host cells indicated that 10  $\mu$ M of KSK120 inhibited RB proliferation and the generation of EBs. Notably, the few bacteria observed were morphologically unaffected by KSK120 treatment (Figure 2A). Inclusion expansion is associated with bacterial growth and therefore inclusion sizes were measured at 44 h p.i.; a modest reduction was observed in the case of serovar D (15%) while the reduction was more pronounced for LGV-2 (28%) and serovar A (37%) (Figure

2B). To further characterize the effect of KSK120, the relative amounts of DNA in the different serovars after treatment were quantified. It was clear that KSK120 strongly inhibited replication of LGV-2 (10-fold reduction, Figure 3A), however the effects on serovar D and serovar A were not as pronounced (~3-fold reduction, Figure 3A). The final step in the chlamydial developmental cycle is the generation of infectious EB progeny (Fields & Hackstadt 2002) and because KSK120 allows replication, it was of interest to quantify the generation of infectious EBs. Infected cells treated with KSK120 were lysed at 44 h p.i. and released bacteria were used to infect new HeLa cells; formed inclusions in the re-infection correspond to one infectious EB progeny generated in the primary infection. Strikingly, KSK120 treatment almost completely blocked the generation of infectious EB for all the three serovars, with more than 10,000-fold fewer infectious EB progeny compared to DMSO-treated infections (Figure 3B). These data show that the response to KSK120 treatment varies between *C. trachomatis* serovars, however the blocked infectivity is consistent with very few infectious EB progeny generated.

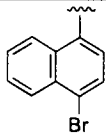
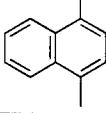
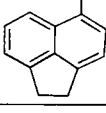
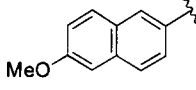
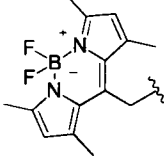
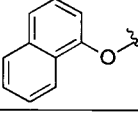
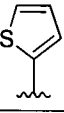
#### Inhibitory activity of carboxylic acids and analogues

A selection of carboxylic acids and carboxylic acid derivatives and analogues were tested for their ability to influence the infectivity of *C. trachomatis* at a concentration of 100  $\mu$ M. Results presented in Table 3.

**Table 3 – Activity of selected amides acids of the general formula**



| Cmpd    | Z | $\alpha$ bond | R4     | R1                     | R5              | D          | R2   | Activity |
|---------|---|---------------|--------|------------------------|-----------------|------------|------|----------|
| NP 239  | O | Single        | H      | (R)-CO <sub>2</sub> H  | H               | 1-Naphthyl | c-Pr | ++/+     |
| VA 147  | S | Single        | H      | (R)-(1H-tetrazol-5-yl) | H               | 1-Naphthyl | c-Pr | ++/+     |
| C10     | S | Single        | H      | (R)-CO <sub>2</sub> H  | H               | 1-Naphthyl | c-Pr | ++/+     |
| (S)-C10 | S | Single        | H      | (S)-CO <sub>2</sub> Li | H               | 1-Naphthyl | c-Pr | ++/+     |
| EC 177  | S | Double        | COPh   | CO <sub>2</sub> H      | H               | 1-Naphthyl | c-Pr | +++      |
| EC 178  | S | Double        | CONHPh | CO <sub>2</sub> H      | H               | 1-Naphthyl | c-Pr | +++      |
| MS 68   | S | Single        | H      | (R)-CO <sub>2</sub> Li | NH <sub>2</sub> | 1-Naphthyl | c-Pr | +++      |
| KSK 63  | S | Single        | H      | (R)-CO <sub>2</sub> H  | H               |            | c-Pr | ++/+     |

| Cmpd   | Z | $\alpha$ bond | R4 | R1                     | R5 | D                                                                                     | R2                                                                                    | Activity |
|--------|---|---------------|----|------------------------|----|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------|
| KSK 69 | S | Single        | H  | (R)-CO <sub>2</sub> H  | H  |    | <i>c</i> -Pr                                                                          | +++      |
| KSK 67 | S | Single        | H  | (R)-CO <sub>2</sub> H  | H  |    | <i>c</i> -Pr                                                                          | +++      |
| KSK 58 | S | Single        | H  | (R)-CO <sub>2</sub> H  | H  |    | <i>c</i> -Pr                                                                          | +++      |
| CB 158 | S | Single        | H  | (R)-CO <sub>2</sub> H  | H  |     | <i>c</i> -Pr                                                                          | ++/+     |
| EC 364 | S | Single        | H  | (R)-CO <sub>2</sub> H  | H  |     | <i>c</i> -Pr                                                                          | +++      |
| EC 215 | S | Single        | H  | (R)-CO <sub>2</sub> Li | H  | 1-Naphthyl                                                                            | <i>i</i> -Pr                                                                          | +++      |
| FN 075 | S | Single        | H  | (R)-CO <sub>2</sub> Li | H  | 1-Naphthyl                                                                            | 3-CF <sub>3</sub> -Ph                                                                 | ++/+     |
| SS 23  | S | Single        | H  | (R)-CO <sub>2</sub> Li | H  | 1-Naphthyl                                                                            | 3,5-Me-Ph                                                                             | +++      |
| EC 218 | S | Single        | H  | (R)-CO <sub>2</sub> H  | H  |  |  | ++/+     |

#### Inhibitory activity of selected amides and analogues

A selection of amides and analogues were tested for their ability to influence the infectivity of *C. trachomatis* at a range of concentrations. Results presented in Table 4.

**Table 4. Activity of selected amides & related analogues**

| Cmpd  | First Cycle<br>(20 $\mu$ M) | First Cycle<br>(10 $\mu$ M) | First Cycle<br>(2.5 $\mu$ M) | Progeny<br>(10 $\mu$ M) | Progeny<br>(2.5 $\mu$ M) | Progeny<br>(1.0 $\mu$ M) | Progeny<br>(0.5 $\mu$ M) |
|-------|-----------------------------|-----------------------------|------------------------------|-------------------------|--------------------------|--------------------------|--------------------------|
| JG 06 | 87                          | 72                          | 23                           | 99.3                    | 78.2                     | 11.2                     | -5.3                     |
| JG 16 | 90                          | 68                          | 37                           | 100                     | 78.8                     | -7.4                     | -1.2                     |
| JG 20 | 85                          | 96                          | 68                           | 99.4                    | 99.9                     | 98.3                     | 33.5                     |
| JG 21 | 84                          | 51                          | 21                           | 100                     | 58.1                     | -9.2                     | 32                       |
| JG 22 | 66                          | 46                          | 6                            | 100                     | 66.7                     | -5.3                     | 32.6                     |
| JG 23 | 84                          | 60                          | 59                           | 100                     | 96                       | 28.2                     | 25.4                     |
| JG 24 | 30                          | -4                          | -18                          | 36.9                    | 17.9                     | -12.7                    | 25.6                     |
| JG 27 | 93                          | 25                          | -15                          | 97.4                    | 17.1                     | -10.9                    | 22.6                     |
| JG 28 | 89                          | 53                          | 8                            | 99.3                    | 54.3                     | 7.2                      | 32.2                     |
| JG 29 | 92                          | 20                          | -12                          | 100                     | 24.2                     | -2.3                     | 35.1                     |
| JG 30 | 95                          | 43                          | -11                          | 99.3                    | 22.7                     | -6.3                     | 39.8                     |
| JG 33 | 91                          | 36                          | -3                           | 100                     | 100                      | -1.2                     | 13.5                     |
| JG 34 | 37                          | 14                          | -23                          | 67.9                    | 95.5                     | -2.2                     | -1                       |

| Cmpd    | First Cycle<br>(20 $\mu$ M) | First Cycle<br>(10 $\mu$ M) | First Cycle<br>(2.5 $\mu$ M) | Progeny<br>(10 $\mu$ M) | Progeny<br>(2.5 $\mu$ M) | Progeny<br>(1.0 $\mu$ M) | Progeny<br>(0.5 $\mu$ M) |
|---------|-----------------------------|-----------------------------|------------------------------|-------------------------|--------------------------|--------------------------|--------------------------|
| JG 37   | 94                          | 30                          | 14                           | 100                     | 100                      | 1.8                      | 22.1                     |
| JG 40   | 24                          | 10                          | 12                           | 100                     | 96.5                     | 8.2                      | 30                       |
| JG 42   | 94                          | 94                          | 42                           | 100                     | 100                      | 18.8                     | 35                       |
| JG 43   | 69                          | 73                          | 58                           | 100                     | 100                      | 25.2                     | 35.3                     |
| JG 44   | 86                          | 62                          | 36                           | 100                     | 100                      | 35.9                     | 5.6                      |
| JG 45   | 92                          | 47                          | 20                           | 99.3                    | 100                      | 22.9                     | -0.7                     |
| JG 46   | 63                          | 70                          | 50                           | 98.6                    | 100                      | 51.8                     | 34.3                     |
| JG 47   | 95                          | 57                          | 12                           | 99.4                    | 100                      | 24.2                     | 22                       |
| JG 48   | 94                          | 30                          | -13                          | 100                     | 100                      | 11.9                     | 29.4                     |
| JG 49   | 87                          | 84                          | 63                           | 100                     | 100                      | 73                       | 27.9                     |
| JG 51   | 83                          | 78                          | 56                           | 98.4                    | 100                      | 65.3                     | 13.2                     |
| JG 52   | 44                          | -2                          | -6                           | 97.6                    | 99.8                     | -6.9                     | 20.5                     |
| JG 60   | 88                          | 27                          | 7                            | 100                     | 100                      | 16.5                     | 42.1                     |
| JG 66   | 95                          | 31                          | 42                           | 100                     | 99.6                     | 27.8                     | 54                       |
| JG 67   | 30                          | 88                          | 4                            | 100                     | 100                      | -6                       | 49                       |
| JG 68   | -                           | 26                          | 4                            | 100                     | 99.7                     | 36                       | 31                       |
| JG 69   | -                           | 0.5                         | -2                           | 100                     | 99.8                     | 12.9                     | 48.6                     |
| JG 70   | 61                          | 28                          | 27                           | 100                     | 99.7                     | 38.2                     | 47.2                     |
| JG 71   | 56                          | -                           | 49                           | -                       | 99.1                     | 31.2                     | 50.8                     |
| JG 79   | -                           | -                           | 20                           | -                       | -                        | 31                       | -23                      |
| JG 91   | -                           | -                           | 12                           | -                       | -                        | 30                       | 6.3                      |
| JG 93   | -                           | -                           | 2                            | -                       | -                        | 19.2                     | 1.5                      |
| JG 95   | -                           | -                           | 5                            | -                       | -                        | 33.5                     | 8.1                      |
| JG 98   | -                           | -                           | 19                           | -                       | -                        | 37.8                     | -13.2                    |
| JG 100  | -                           | -                           | 12                           | -                       | -                        | 34.9                     | 0.8                      |
| JG 102  | -                           | -                           | -2                           | -                       | -                        | 32.3                     | -10.2                    |
| KSK 120 | 20                          | 37                          | 32                           | 100                     | 89                       | 14.6                     | 67.9                     |
| KSK 165 | 87                          | 82                          | 18                           | 100                     | 42.9                     | 3.3                      | -0.5                     |
| KSK 166 | -                           | -                           | 0                            | -                       | -                        | 67                       | 56.4                     |
| KSK 170 | -                           | -                           | -6                           | 99.7                    | -                        | 4                        | 25.2                     |
| KSK 193 | 41                          | 20                          | -10                          | 100                     | -7.7                     | 2.2                      | 7.5                      |
| KSK 195 | 52                          | 30                          | 13                           | 100                     | 33.1                     | -11.2                    | 6.7                      |
| KSK 196 | -                           | -                           | -4                           | -                       | -                        | 33.5                     | 17.7                     |
| KSK 199 | -                           | -                           | -11                          | -                       | -                        | -33.3                    | -14.7                    |
| KSK 207 | -6                          | 3                           | -24                          | 100                     | -3.6                     | -21.5                    | 0.5                      |
| KSK 213 | 0                           | 9                           | 19                           | 99.3                    | 96.6                     | 85.6                     | 93.9                     |
| KSK 214 | 57                          | 27                          | -6                           | 100                     | -7.7                     | 10.6                     | 20.4                     |
| KSK 215 | 92                          | 94                          | 18                           | 100                     | 80.5                     | 35.5                     | 12.4                     |
| KSK 218 | -14                         | 6                           | -2                           | 98.9                    | 75.1                     | 25.2                     | 19.7                     |
| KSK 219 | 28                          | 19                          | 16                           | 98.2                    | 94.6                     | 54.5                     | 39.5                     |
| KSK 220 | 92                          | 88                          | -3                           | 100                     | -5                       | 16.2                     | 25.6                     |
| KSK 223 | 40                          | 56                          | 32                           | 100                     | 96.6                     | 43.4                     | 33.6                     |
| KSK 224 | 61                          | 67                          | 61                           | 100                     | 99.5                     | 72                       | 29.5                     |
| KSK 226 | 14                          | 33                          | 25                           | 100                     | 90.3                     | 57.4                     | -6.2                     |
| KSK 227 | 45                          | 24                          | -11                          | 70.1                    | 12.6                     | -22.8                    | 3.5                      |
| MK 12   | -                           | -                           | 12                           | -                       | -                        | -26.2                    | -                        |
| MK 14   | -                           | -                           | 31                           | -                       | -                        | -37.7                    | -                        |
| MK 15   | -                           | -                           | 18                           | -                       | -                        | -49.1                    | -                        |
| MK 17   | 47                          | -                           | 17                           | -                       | 100                      | 53                       | 65.4                     |
| MK 18   | 69                          | -                           | 5                            | -                       | 100                      | 74.3                     | 53.2                     |
| PS 49   | 12                          | 2                           | -8                           | 97.3                    | 99.4                     | -5.9                     | 10.5                     |

Notes: (-) not determined; number refers to percentage reduction in the level of infection relative to DMSO controls; each data point represents the average of triplicate

measurements. First cycle refers to the effect on primary infection. Progeny refers to infectiousness of first cycle progeny following treatment.

KSK120 targets a membrane component in the replicating form of *C. trachomatis* LGV-2.

To investigate at which stage of the infection compound KSK120 is effective, treatment of cells infected with *C. trachomatis* LGV-2 was initiated and terminated at different time points (Figure 4A). Infectivity was determined at 44 h p.i. and quantified relative to DMSO treatment. When KSK120 treatment was initiated immediately after infection (0 h p.i.) or at 16 h p.i., the reduced yield of infectious EBs was similar (~10,000-fold fewer infectious EB progeny). In contrast, when treatment was initiated at 30 h p.i., we observed a modest inhibition of infectivity (Figure 4B). Thus, compound KSK120 targets a component that is expressed between 16 and 30 h p.i. During this time span of the infection, there are mainly replicating RBs while infectious EB progenies are few, suggesting that the compound targets a component expressed in RBs.

Analogue compounds with fluorescent properties might be useful to identify the molecular target and thereafter function as molecular probes (Chorell et al. 2012b). Therefore, we designed two analogues, which potentially could have the desired biological effect in combination with fluorescent properties. One of the analogues contained a coumarin substituent instead of the 1-naphtyl substituent and in the other analogue we introduced a BODIPY fluorophore (EC364). The fluorescent compound EC364 was tested in the HeLa cell-based *C. trachomatis* LGV-2 infection model and we observed that this compound affected the infection phenotype in a manner indistinguishable from the effect of KSK120. We also synthesized the aryl amide analogue of EC364 in an effort to improve the biological activity and to mimic KSK120. This analogue turned out to be difficult to evaluate properly due to solubility problems and since EC364 was fairly potent with the desirable phenotype we decided to use this analogue in our further studies. To elucidate the localization of fluorescent EC364 during a *C. trachomatis* infection, treatment was initiated 18 h p.i., fixed at 44 h p.i. and subsequently stained with an antibody generated against the major outer membrane protein (MOMP). Clearly, EC364 was enriched where *C. trachomatis* was localized, while less fluorescence with a grainier appearance was observed in host cell compartments. Furthermore, the fluorescent compound was observed punctuated in the bacterial membrane, however this localization was uncertain due to the limited resolution of standard confocal microscopy.

### Identification of spontaneous mutations that mediate resistance to KSK120.

It has previously been shown that antibiotic-resistant *Chlamydia* strains can acquire mutations in the antibiotic target proteins (Binet & Maurelli 2009; Binet & Maurelli 2005; Binet & Maurelli 2007). Thus, a mutant selection was performed to identify potential KSK120-target molecules. Wild-type *C. trachomatis* was grown for serial passages in the presence of the compound and from the resistant mutant population (passage 15) clonal populations were collected by limiting dilution. Two clonal mutant KSK120-resistant strains were sequenced by whole genome sequencing (WGS) and the same four mutations were identified in both strains. Two mutations were identified in a gene encoding the hexose-phosphate permease (*uhpC*), an inner membrane protein that has been shown to facilitate the uptake of glucose-6-phosphate (G-6-P) and erythrose-4-phosphate (E-4-P) in *C. pneumoniae* (Scwopet et al. 2002). The mutations in *uhpC* led to M315I and L429I substitutions. WGS also identified a mutation in elongation factor P (*efp*) that leads to an R131C substitution. The last mutation was identified in the RNA polymerase beta prime subunit (*rpoC*) and the mutation results in a C1224F substitution (Table 5).

**Table 5.** Identified substitutions in each mutant population

| Parental                                                         | Selected mutant populations with indicated substitutions                                       |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Mixed population:<br>1/10 UhpC <sup>L429I</sup> , 9/10 Wild-type | UhpC <sup>L429I</sup> , UhpC <sup>M315I</sup> , EF-P <sup>R131C</sup> , RpoC <sup>C1224F</sup> |
| wild-type                                                        | Pgi <sup>H378P</sup> , RecC <sup>M415I</sup> , UhpC <sup>A394T</sup>                           |
| UhpC <sup>L429I</sup>                                            | RpsA <sup>A11V</sup> , UhpC <sup>L429I</sup>                                                   |

Knowing the mutational order, insight into the role of individual mutations might be revealed. Therefore, DNA was isolated from collected mutant passages and subsequently genotyped by capillary sequencing. From the chromatograms generated, the frequency of each mutation was estimated in the bacterial population. It was found that the UhpC<sup>L429I</sup> substitution is selected from the mixed wt-population and is initially enriched until passage 6 but is thereafter reduced until passage 10. Identified in the passage 8 population were the UhpC<sup>M315I</sup> and EF-P<sup>R131C</sup> substitutions while the RpoC<sup>C1224F</sup> substitution was not identified until passage 11. Thereafter the four mutations were enriched simultaneously, independent of selective pressure. Detected in the passage 9 population were the UhpC<sup>L429I, M315I</sup> and EF-P<sup>R131C</sup> substitutions; however the mutational linkage was not certain. Therefore, plaque-purified strains were collected from this mutant population; twenty-seven strains were isolated and thereafter genotyped. It was found that two strains have the UhpC<sup>L429I</sup> substitution while three strains have both the UhpC<sup>L429I, M315I</sup> substitutions. In addition, four

strains have the EF-P<sup>R131C</sup> substitution but lack the mutations in *uhpC*. The remaining eighteen strains were wild-type. Thus, the UhpC<sup>M315I</sup> substitution arises in a bacterium where the UhpC<sup>L429I</sup> substitution already exists. In contrast, the EF-P<sup>R131C</sup> substitution arises in a bacterium that lacks mutations in *uhpC*. These data suggest that the UhpC<sup>L429I</sup>, M315I and EF-P<sup>R131C</sup> substitutions have a direct role in mediating KSK120 resistance because these mutations are present within individual KSK120-resistant strains in this population. In contrast, the mutation in *rpoC* most likely has a compensatory function because this mutation appears to arise in a bacterium that already has the mutation in *uhpC* (Table 6).

**Table 6.** Collected clonal *C. trachomatis* strains and their KSK120 susceptibility

| Strains <sup>a</sup> with indicated substitution(s)                           | Origin             | Fold increase infectious EBs <sup>c</sup> |
|-------------------------------------------------------------------------------|--------------------|-------------------------------------------|
| Wild-type                                                                     | Wt-population      | 1 (+/- 0.38)                              |
| UhpC <sup>L429I</sup>                                                         | Wt-population      | 18.7 (+/- 1.33)                           |
| UhpC <sup>L429I</sup> , M315I                                                 | Mutant selection 1 | 141 (+/- 19.2)                            |
| UhpC <sup>A394T</sup>                                                         | Mutant selection 2 | 205 (+/- 42.65)                           |
| Pgi <sup>H378P</sup>                                                          | Mutant selection 2 | 74.44 (+/- 17)                            |
| RecC <sup>M415I</sup>                                                         | Mutant selection 2 | 118 (+/- 20.1)                            |
| EF-P <sup>R131C</sup>                                                         | Mutant selection 1 | 186.83 (+/- 19.61)                        |
| UhpC <sup>L429I</sup> , M315I, RpoC <sup>C1224F</sup>                         | Mutant selection 1 | 242.52 (+/- 30.38)                        |
| UhpC <sup>L429I</sup> , M315I, RpoC <sup>C1224F</sup> , EF-P <sup>R131C</sup> | Mutant selection 1 | 169.86 (+/- 23.76)                        |
| UhpC <sup>L429I</sup> , RpsA <sup>A11V</sup>                                  | Mutant selection 3 | 78.2 (+/- 8.68)                           |

<sup>a</sup>Isolated by limiting dilution or plaque-purification, lacking the other identified mutations.

<sup>b</sup>Mixed mutant population containing both the RpsA<sup>A11V</sup> (73 % vf) and UhpC<sup>L429I</sup> (100% vf) substitutions.

<sup>c</sup>Infectious EBs progeny generated (at 44 h p.i.) in the presence of 10 µM KSK120, normalized to input IFU, values for wt were set to 1, representative data is from an experiment performed in triplicate. IFU is an abbreviation for inclusion forming unit. vf, variant frequency.

Selection and isolation of independent mutants, starting from strains with different genetic backgrounds might reveal further information about the molecular target and downstream pathways. Therefore, additional mutant selections starting from clonal strains isolated from the mixed wild-type population were performed. First, a strain that lacks the UhpC<sup>L429I</sup> substitution was grown by serial passage in the presence of KSK120. The selected mutant population (passage 10) was subjected to WGS and two mutations were identified with variant frequencies above 15%. The most enriched mutation was identified in a gene encoding the G-6-P -isomerase (*pgi*) (45% variant frequency, Table 1), which is an enzyme

that catalyzes the interconversion of G-6-P to fructose-6-phosphate, the second step of glycolysis (Table 7).

**Table 7.** Function of proteins mutated

| Gene        | Predicted function of encoded protein                                                                                                                             |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>uhpC</i> | Sugar phosphate permease that specifically facilitates the uptake of G-6-P and E-4-P in <i>C. pneumoniae</i> (Schwoppe et al. 2002).                              |
| <i>pgi</i>  | G-6-P isomerase, catalyzes the interconversion of G-6-P to fructose-6-P in the second step of glycolysis (Munoz-Elias & McKinney 2006).                           |
| <i>recC</i> | RecBCD complex is an enzyme that has both helicase and nuclease activity involved in degradation of foreign DNA and recombination DNA repair (Handa et al. 2012). |
| <i>efp</i>  | Elongation factor P (EF-P), eases ribosome stalling at polyproline stretches (Doerfel et al. 2013; Ude et al. 2013).                                              |
| <i>rpoC</i> | RNA polymerase beta prime subunit required for transcription.                                                                                                     |
| <i>rpsA</i> | 30S ribosomal protein S1 required for translation.                                                                                                                |

The mutation in *pgi* leads to a H378P substitution, the His at residue 378 is conserved among bacteria and higher organisms and has been shown to be essential for its catalytic activity (Lin et al. 2009; Meng et al. 1999), suggesting that the Pgi<sup>H378P</sup> substitution is a loss-of-function mutation. The second mutation was identified in *recC* (19% variant frequency, Table 2), which encodes the exodeoxyribonuclease V gamma chain (Table 4); the mutation in *recC* leads to a M415I substitution. Next, this second derived mutant population was grown for additional passages in the presence or absence of KSK120. Surprisingly, both the mutation in *pgi* and *recC* were negatively selected independent of selective pressure. Instead, in this mutant population (passage 16), a mutation in *uhpC* that leads to an A394T substitution was identified (Table 2). Apparently, the UhpC<sup>A394T</sup> substitution has a lower fitness cost than the Pgi<sup>H378P</sup> and the RecC<sup>M415I</sup> substitutions because this mutation was enriched in the absence of KSK120. Furthermore, plaque-purified strains were isolated from the second mutant population (passage 12) and subsequently genotyped. Three isogenic strains with the Pgi<sup>H378P</sup> substitution (data not shown), one isogenic strain with the RecC<sup>M415I</sup> substitution and one isogenic strain with the UhpC<sup>A393T</sup> substitution were isolated (Table 2). Next, an additional mutant selection was performed starting from the strain that has the UhpC<sup>L429I</sup> substitution. In this mutant population (passage 15) a mutation in *rpsA* (73% variant frequency) was identified, encoding the 30S ribosomal protein S1; the mutation in *rpsA* leads to a G11A substitution. Notably, the UhpC<sup>L429I</sup> substitution remained at a variant frequency of 100% in this mutant population. To verify that the isolated mutant strains are KSK120-resistant, the yield of infectious progeny after KSK120 treatment was quantified. Compound was added immediately after infection and EBs were harvested at 44 h p.i. and used to infect a

monolayer of HeLa cells. In aggregate, this experiment showed that strains with mutations in *uhpC*, *efp*, *pgi* and *recC* are directly associated with KSK120 resistance while mutations in *rpsA* and *rpoC* have secondary effect(s) (Table 2). Altogether, the high incidence of resistance mutations in genes that are directly coupled to glucose uptake and metabolism indicate that KSK120 targets a component of this metabolic circuit.

KSK120 targets glucose metabolism of *C. trachomatis*.

The mutant selections identified mutations that are directly coupled to glucose uptake and metabolism, indicating that KSK120 targets this metabolic pathway. To further explore a potential inhibitory effect on glucose metabolism, treated and untreated infected cells were stained with iodine for detection of glycogen. Glycogen biosynthesis is a secondary metabolic pathway that is activated when excess sources of carbon such as glucose are available (Preiss 1984). First, it was established that intra-inclusion glycogen accumulation was most prominent at 36 h p.i., and therefore this time point was used in these experiments. Additionally, 30  $\mu\text{M}$  iron-saturated (IS) INP0341 inhibits the generation of infectious *C. trachomatis* progeny identical to inhibition by 5  $\mu\text{M}$  KSK120. IS-INP0341 was therefore used as a negative control. As expected, IS-INP0341 did not affect glycogen accumulation while KSK120 clearly reduced glycogen accumulation. Moreover, KSK120 also reduced glycogen accumulation for *C. trachomatis* serovar D, further supporting our hypothesis that KSK120 specifically targets glucose metabolism of *C. trachomatis* serovars. It has been shown that *C. trachomatis* infected cells consume all the supplemented glucose ( $\text{mg mL}^{-1}$ ), however, when excess glucose ( $10 \text{ mg mL}^{-1}$ ) was supplemented the majority of glucose remained in the media (Iliffe-Lee & McClarty 2000). Consequently, to further investigate if KSK120 targets the glucose metabolism of *C. trachomatis* the bacteria were grown in different amounts of glucose and the treated infections were fixed at 44 h p.i. Excess glucose ( $10 \text{ mg mL}^{-1}$ ) suppressed the inhibitory effect of KSK120 on inclusion sizes such that inclusions were similar in size to those of untreated infections. In contrast, when the media was supplemented with  $1 \text{ mg mL}^{-1}$  glucose, KSK120 treatment reduced inclusion sizes by 27%. The effect of KSK120 was elevated with decreased amounts of glucose, and in the case of  $0.1 \text{ mg mL}^{-1}$  glucose, KSK120 treatment reduced the inclusion sizes by 43% (Figure 5A). These data show that excess glucose suppresses the inhibitory effect on inclusion expansion by KSK120, validating the hypothesis that this compound targets glucose metabolism of *C. trachomatis*. Recently, Omsland et al (2012) elegantly showed that EBs are metabolically active and

consume G-6-P while RBs use ATP as a primary energy source. Thus, the infectious EB progeny generated in the presence of KSK120 have reduced storage of metabolites, which potentially could result in these EBs remaining infectious a shorter time extra-cellularly. Therefore, EBs from infections that had been grown in the presence or absence of KSK120 for 44 hours were collected and it was compared how long these EBs remained infectious extra-cellularly. Clearly, infectious EBs formed in the presence of 10  $\mu$ M or 25  $\mu$ M of the compound remained infectious a significantly shorter time than EBs collected from infections treated with DMSO (Figure 5B). These data indicate that EBs formed in the presence of KSK120 have reduced storage of energy-containing molecules such as G-6-P. Altogether, these data shows that KSK120 targets glucose metabolism of *C. trachomatis*.

UhpC activity and glucose metabolism is essential for generation of infectious *C. trachomatis* progeny.

The above data shows that the compound KSK120 targets glucose metabolism of *C. trachomatis* likely by inhibiting the uptake of G-6-P via UhpC. Therefore, it was of interest to characterize the *uhpC* mutant strains while the other mutant strains were excluded because of possible pleiotropic effects (Table 2). The mutant *uhpC* strains were tested in assays where G-6-P was limited by different means to potentially identify phenotypes that are linked to the effect of KSK120. First, the mutant strains were grown in the presence of 2-deoxy-D-glucose (2-DG), a glucose analogue that is known to inhibit the hexokinase of the host cell which leads to metabolic stress including G-6-P starvation of chlamydiae (O'Connell 2011). Treatments were initiated directly after infection and infectious progeny were collected at 48 h p.i. In comparison with the wild-type strain, the strains with the UhpC<sup>M315I</sup> and/or the UhpC<sup>L429I</sup> substitutions showed significantly increased infectivity with 2- to 3-fold more infectious EB progeny generated in the presence of 2-DG. In contrast, the strain with the UhpC<sup>A394T</sup> substitution showed decreased infectivity with almost no recoverable infectious EB progeny after 2-DG treatment (Figure 6A). Next, these strains were grown in cell culture media containing a low amount of glucose and infectivity was quantified as described above, the strain with the UhpC<sup>L429I, M315I</sup> substitutions showed significantly increased infectivity with 3-fold more infectious progeny generated while the strain with the UhpC<sup>A394T</sup> substitution showed decreased infectivity with 5-fold fewer infectious progeny compared to our wild-type strain (Figure 6A). Finally, glycogen accumulation was determined in the different mutant strains when grown under normal in vitro conditions. Strikingly, the strain with the UhpC<sup>A394T</sup>

substitution showed impaired glycogen accumulation while the other strains accumulate glycogen in a manner similar to the wild-type strain. Together, these data strongly suggest that the UhpC<sup>M315I, L429I</sup> substitution are gain-of-function mutations with increased uptake of G-6-P. On the other hand, the UhpC<sup>A394T</sup> substitution appears to be a partial loss-of-function mutation with reduced uptake of G-6-P. To explore if the mutant strains have altered development in the absence of KSK120, infectious bacteria were collected and quantified at different time points post-infection. It is known that *C. trachomatis* inclusions fuse when two or more bacteria infect the same host cell (Matsumoto et al. 1991; Ridderhof & Barnes 1989), which results in faster development with more infectious EBs early in the infection. Therefore, to avoid interpretation of results where different strains develop at high MOI, less than every 100 HeLa cells were infected with a bacterium. Interestingly, from 24 to 30 h p.i., it was observed that the strain with the UhpC<sup>M315I, L429I</sup> substitutions generated more infectious EBs than the wild-type, while the strain with the UhpC<sup>A394T</sup> substitution had fewer recoverable infectious EBs. Later in the infection (48 h p.i.) this order changed, with slightly more infectious EBs for the strain with the UhpC<sup>M315I, L429I</sup> substitutions compared to the strain with the UhpC<sup>A394T</sup> substitution (Figure 6B). These data suggest that generation of infectious EBs in early *C. trachomatis* development is directly coupled to G-6-P uptake.

In parallel to the above experiment these strains were grown in the presence of KSK120. In the case of the wild-type strain no or few infectious EBs were recoverable at the time-point tested, while the strains with mutations in *uhpC* showed increased infectivity with 10- to 100-fold more infectious EBs at both 36 and 48 h p.i. When comparing the different mutant strains, it was observed that the strain with the UhpC<sup>M315I, L429I</sup> substitutions had significantly more infectious progeny at 36 h p.i., compared to the two other mutant strains. In contrast, at 48 h p.i., the strain with the UhpC<sup>A394T</sup> substitution has slightly more infectious progeny than the strain with the UhpC<sup>M315I, L429I</sup> substitutions (Figure 4). Altogether, these data show that UhpC activity and glucose metabolism coordinate the generation of infectious *C. trachomatis* progeny.

In summary, the present inventors have established that compound KSK120 targets glucose metabolism of *C. trachomatis* likely by targeting the inner membrane localized hexose-phosphate permease, UhpC. Furthermore, it is demonstrated that treatment with KSK120 blocks *C. trachomatis* infectivity, which reveals that glucose metabolism is

essential for the generation of infectious EBs. In addition, it is demonstrated that UhpC activity is directly linked to the generation of infectious EBs, further emphasizing a role for G-6-P uptake and metabolism in the intracellular transition to infectious EBs.

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### Chemistry

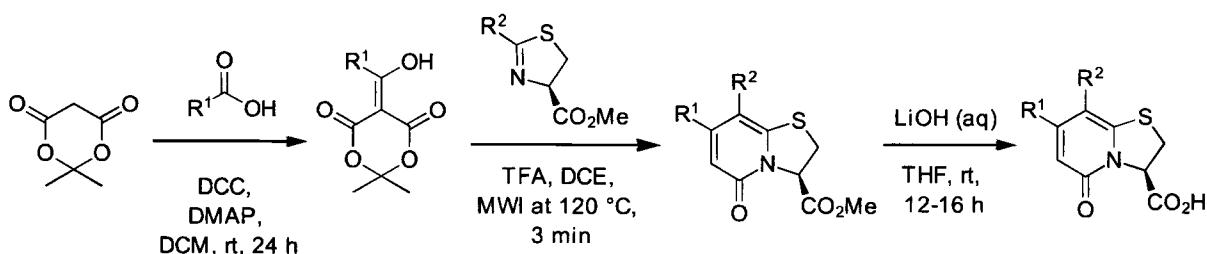
All reagents and solvents were used as received from commercial suppliers, unless indicated otherwise. Triethylamine, *N,N*-diisopropylethylamine and pyridine were passed through activated alumina oxide and dried over 3 Å molecular sieves prior to use. CH<sub>2</sub>Cl<sub>2</sub>, THF and DMF were dried in a solvent drying system (CH<sub>2</sub>Cl<sub>2</sub> and THF drying agent: neutral alumina; DMF drying agent: activated molecular sieves equipped with an isocyanate scrubber) and collected fresh prior to every reaction. NaH was prewashed with pentane and dried under vacuum prior to use. Microwave reactions were performed using a Biotage Initiator microwave synthesizer in sealed vessels with temperature monitoring by an internal IR probe. TLC was performed on aluminum backed silica gel plates (median pore size 60 Å) and detected with UV light at 254 nm. Column chromatography was performed using silica gel with average particle diameter 50 µm (range 40-65 µm, pore diameter 53 Å) and eluents are given in brackets. Preparatory HPLC purifications were performed on a system equipped with a 250 × 21.5 mm Nucleodur® C18 HTEC (particle size 5 µm) column using a flow rate of 20 mL/min and detection at 220 nm. Optical rotation was measured with a polarimeter at 25 °C at 589 nm. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a 400 or 600 MHz spectrometer at 298 K and calibrated by using the residual peak of the solvent as the internal standard (CDCl<sub>3</sub>: δ<sub>H</sub> = 7.26 ppm; δ<sub>C</sub> = 77.16 ppm; DMSO-*d*<sub>6</sub>: δ<sub>H</sub> = 2.50 ppm; δ<sub>C</sub> = 39.50 ppm). HRMS was performed by using a mass spectrometer with ESI-TOF (ESI+); sodium formate was used as the calibration chemical. Compounds are named according to IUPAC nomenclature by ACD ChemSketch 12.01 (Windows, Advanced Chemistry Development, Toronto, Canada).

Preparation of intermediates:

- The carboxylic acid **EC 030** was synthesized as described previously.<sup>1-3</sup>
- The carboxylic acid, 8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (**EC 104**), was prepared from the corresponding methyl ester (prepared as previously described)<sup>4</sup> by hydrolysis using a literature procedure using LiBr and Et<sub>3</sub>N in (98/2) CH<sub>3</sub>CN/H<sub>2</sub>O and purification by column chromatography.<sup>5</sup>
- The 2-substituted amide, methyl 8-Cyclopropyl-7-(Naphthalen-1-ylmethyl)-5-oxo-2-(phenylcarbamoyl)-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (**EC 178 methyl ester**) was prepared as previously reported.<sup>4</sup>
- The bromo-thiazole, 7-(naphthalen-1-ylmethyl)-2-bromo-8-cyclopropyl-5-oxo-*N*-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (**KSK 217**) was prepared by tandem oxidation and bromination of **KSK 165** by our previously reported method.<sup>1</sup>
- The azide, (3*R*)-6-azido-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylic acid (**KSK 205**), was prepared by diazotransfer with imidazole-1-sulfonyl azide hydrogen sulfate<sup>6, 7</sup> and methyl (3*R*)-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate and subsequent hydrolysis following literature procedures.<sup>1</sup>
- The aldehyde, (3*R*)-7-(naphthalen-1-ylmethyl)-6-formyl-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide (**KSK 209**) was prepared by formylation of **KSK 165** by our previously reported method.<sup>8</sup>
- The chloromethyl analogue, methyl (3*R*)-7-(chloromethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate, (**JG 4**) was prepared as described previously.<sup>9</sup>
- The methyl ester, methyl (3*R*)-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate, (**HE 3B**) was prepared as described previously.<sup>10</sup>
- The 2-alkyl- $\Delta^2$ -thiazoline, methyl (4*R*)-2-(cyclopropylmethyl)-4,5-dihydro-1,3-thiazole-4-carboxylate, was prepared by published procedures.<sup>10</sup>

Preparation of novel ring-fused thiazolino 2-pyridone carboxylic acids

New compounds, derivatised at the C7 and C8 position, were synthesized from substituted acyl Meldrum's acids by our previously developed route (Scheme 1).<sup>10</sup> Cyclocondensation of the acylated Meldrum's acid derivatives with thiazolines afforded ring-fused 2-pyridones, which were subsequently hydrolysed to the carboxylic acid. These carboxylic acids could be converted to the amide derivatives of interest by the methods described below.



**Scheme 1 – General route for the synthesis of C7 and C8 substituted 2-pyridone amides.**

**General procedure for the synthesis of ring-fused thiazolino 2-pyridones**

Ring-fused thiazolino 2-pyridones were prepared from dihydrothiazolines and acyl Meldrum's acid by adaptation of the procedure reported by Chorell *et al.*<sup>11</sup> TFA (1.0 eq.) was added to a solution of the 2-alkyl- $\Delta^2$ -thiazoline (1.0 eq.) and acyl Meldrum's acid (2.75 eq.) in 1,2-dichloroethane (5 mL) and heated by MWI at 120 °C for 3 min. After cooling to rt, the reaction mixture was quenched with saturated aqueous NaHCO<sub>3</sub> solution (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic extracts were washed successively with H<sub>2</sub>O and brine (50 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, EtOAc in heptane) afforded the product.

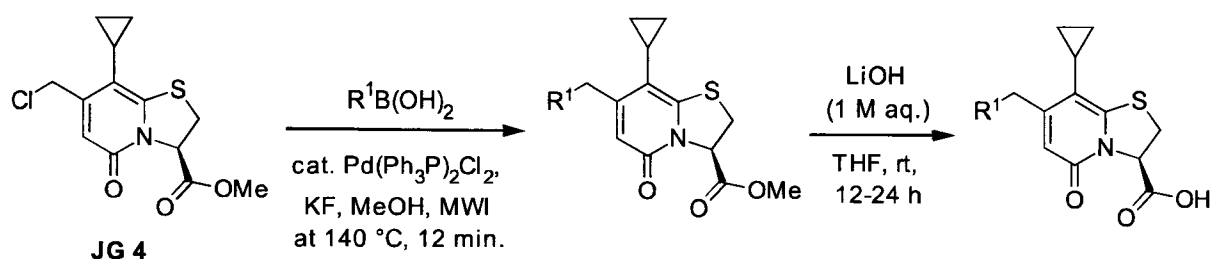
**General methyl ester hydrolysis procedure**

LiOH (1 M aqueous, 2.0 eq.) was added drop wise to a stirred solution of the methyl ester in THF (30 mL/mmol) at 0 °C. The solution was allowed to attain room temperature and was stirred for 12 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and acidified with aqueous HCl (1 M) to *circa* pH 1. The separated organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The residue purified by trituration with diethyl ether (3×) or flash

chromatography (SiO<sub>2</sub>, MeOH/CH<sub>2</sub>Cl<sub>2</sub>) and lyophilized (H<sub>2</sub>O:MeCN; ~ 8:2) to afford the carboxylic acid.

Preparation of ring-fused thiazolino 2-pyridone carboxylic acids derivatised in the C7 position.

Other new compounds derivatised in the C7 position were synthesized as shown by Suzuki-Miyaura cross coupling with the chloromethyl intermediate compound **JG 4**, which was prepared as described previously (Scheme 2).<sup>12</sup> Hydrolysis of the obtained methyl esters in aqueous lithium hydroxide by the general procedure afforded the carboxylic acids, and the corresponding amides were prepared as described below.

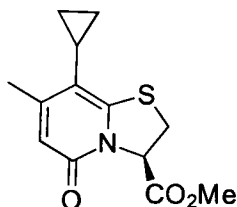


**Scheme 2 - General route for the synthesis of R7 substituted intermediate carboxylic acids.**

**General procedure for Suzuki-Miyaura cross-couplings**

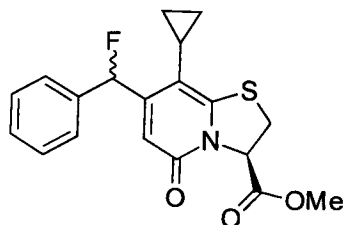
The chloromethyl derivative **JG 4** (1.0 eq.), boronic acid (2 eq.), Pd(Ph<sub>3</sub>P)<sub>2</sub>Cl<sub>2</sub> (0.05 eq.) and KF (2.0 eq.) were dissolved in anhydrous MeOH (4.5 mL) and heated by microwave irradiation (MWI) at 140 °C for 12 min. The reaction mixture was diluted with EtOAc (15 mL) and washed successively with saturated aqueous NaHCO<sub>3</sub>, water and brine (15 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>; EtOAc/heptane) afforded the cross-coupled product.

Examples of novel ring-fused thiazolino 2-pyridone carboxylic acids prepared by this route:



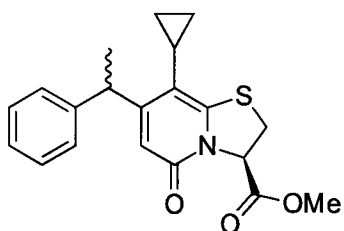
**Methyl (3R)-8-cyclopropyl-7-methyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 87)**

Following the general procedure with methyl (4*R*)-2-(cyclopropylmethyl)-4,5-dihydro-1,3-thiazole-4-carboxylate (299 mg, 1.50 mmol) and 5-(1-hydroxyethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (768 mg, 4.13 mmol) with purification by flash chromatography (SiO<sub>2</sub>, 15-100% EtOAc in heptane) afforded the product as a colorless oil (380 mg, 95%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.54-0.64 (m, 2H), 0.83-0.96 (m, 2H), 1.50-1.59 (m, 1H), 2.26 (d, *J* = 0.9 Hz, 3H), 3.47 (dd, *J* = 2.4, 11.8 Hz, 1H), 3.63 (dd, *J* = 8.6, 11.7 Hz, 1H), 3.78 (s, 3H), 5.57 (dd, 2.4, 8.6 Hz, 1H), 6.12 (d, *J* = 0.9 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.4, 7.5, 11.3, 20.4, 31.8, 53.3, 62.8, 114.3, 115.1, 146.7, 154.9, 161.4, 168.9.



**Methyl (3*R*)-8-cyclopropyl-7-(fluoro(phenyl)methyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 90)**

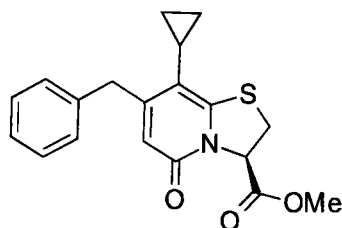
Following the general procedure with methyl (4*R*)-2-(cyclopropylmethyl)-4,5-dihydro-1,3-thiazole-4-carboxylate (249 mg, 1.25 mmol) and 5-(2-fluoro-1-hydroxy-2-phenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (963 mg, 3.44 mmol) with purification by flash chromatography (SiO<sub>2</sub>, 15-100% EtOAc in heptane) afforded the product as a pale yellow solid (394 mg, 88%). Mixture of diastereomers (~1:1 as determined by <sup>19</sup>F NMR). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.60-0.68 (m, 2H), 0.71-0.93 (m, 2H), 0.99-1.21 (m, 1H), 3.46-3.53 (m, 1H), 3.61-3.69 (m, 1H), 3.79-3.83 (m, 3H), 5.56-5.67 (m, 1H), 6.54 (m, 1H), 7.35-7.42 (m, 5H). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ = -165.2, -164.6. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.4, 7.9, 8.5, 8.8, 10.7, 11.0, 31.6, 31.9, 53.5, 62.9, 63.1, 89.7, 89.9, 91.4, 91.6, 110.76, 110.80, 110.9, 111.0, 111.7, 111.8, 112.6, 112.7, 128.25, 128.30, 128.43, 128.43, 128.9, 129.63, 129.65, 129.7, 136.6, 136.7, 136.8, 136.9, 148.3, 148.4, 154.3, 154.47, 154.51, 154.7, 161.28, 161.31, 161.32, 168.6, 168.7.



**Methyl (3*R*)-8-cyclopropyl-5-oxo-7-(1-phenylethyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate (JG 103)**

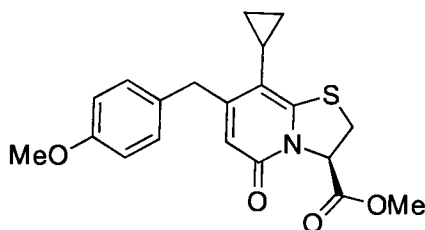
Following the general procedure with methyl (4*R*)-2-(cyclopropylmethyl)-4,5-dihydro-1,3-thiazole-4-carboxylate (249 mg, 1.25 mmol) and 5-(1-hydroxy-2-phenylpropylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (950 mg, 3.44 mmol) with purification by flash chromatography (SiO<sub>2</sub>, 15-100% EtOAc in heptane) and subsequent freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as an off-white solid (159 mg, 36%). Mixture of diastereomers. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.57-0.66 (m, 2H), 0.72-0.99 (m, 2H),

1.13-1.34 (m, 1H), 1.48-1.54 (m, 3H), 3.44-3.50 (m, 1H), 3.58-3.66 (m, 1H), 3.78-3.81 (m, 3H), 4.51-4.62 (m, 1H), 5.54-5.64 (m, 1H), 6.25-6.38 (m, 1H), 7.15-7.31 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.4, 8.1, 8.65, 8.72, 11.2, 11.5, 22.1, 22.2, 31.6, 31.8, 40.9, 41.0, 53.4, 62.8, 63.0, 113.2, 113.7, 113.9, 114.1, 126.5, 126.6, 127.7, 127.8, 128.7, 144.2, 144.6, 147.3, 147.4, 161.2, 161.67, 161.69, 161.74, 168.78, 168.82.



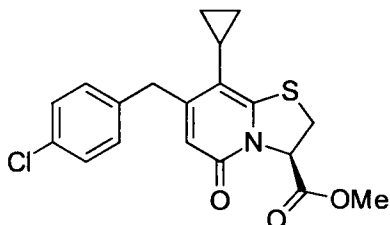
**Methyl (3R)-8-cyclopropyl-7-benzyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 57)**

Following the general procedure with **JG 4** (150 mg, 0.50 mmol) and 2,3-phenylboronic acid (122 mg, 1.00 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 10-100% EtOAc in heptane) gave the product as a pale brown solid (119 mg, 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.66-0.69 (m, 2H), 0.82-0.96 (m, 2H), 1.36-1.46 (m, 1H), 3.48 (dd, *J* = 2.3, 11.7 Hz, 1H), 3.64 (dd, *J* = 8.6, 11.8 Hz, 1H), 3.80 (s, 3H), 3.94 (d, *J* = 15.8 Hz, 1H), 4.01 (d, *J* = 15.8 Hz, 1H), 5.59 (dd, *J* = 2.3, 8.5 Hz, 1H), 6.04 (s, 1H), 7.16-7.32 (m, 5H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.7, 8.1, 11.4, 31.8, 39.4, 53.4, 62.9, 114.0, 115.8, 126.7, 128.7, 129.3, 138.2, 147.4, 157.1, 161.5, 168.8.



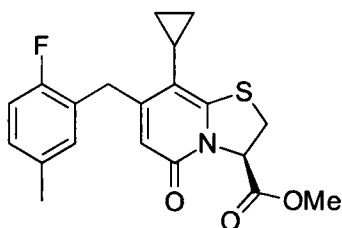
**Methyl (3R)-8-cyclopropyl-7-(4-methoxybenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 94)**

Following the general procedure with **JG 4** (150 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (150 mg, 1.00 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 5-100% EtOAc in heptane) gave the product as a pale yellow solid (140 mg, 75%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.58-0.69 (m, 2H), 0.81-0.96 (m, 2H), 1.36-1.45 (m, 1H), 3.48 (dd, *J* = 2.3, 11.7 Hz, 1H), 3.63 (dd, *J* = 8.6, 11.8 Hz, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 3.87 (d, *J* = 15.8 Hz, 1H), 3.96 (d, *J* = 15.8 Hz, 1H), 5.58 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.02 (s, 1H), 6.81-6.86 (m, 2H), 7.06-7.11 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.7, 8.0, 11.3, 31.8, 38.6, 53.4, 55.4, 62.8, 114.0, 114.2, 115.6, 130.1, 130.2, 147.3, 157.6, 158.5, 161.5, 168.8.



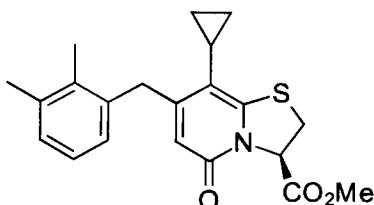
**Methyl (3R)-8-cyclopropyl-7-(4-chlorobenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 108)**

Following the general procedure with **JG 4** (150 mg, 0.50 mmol) and 4-chlorophenylboronic acid (150 mg, 1.00 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 15-100% EtOAc in heptane) gave the product as an off-white solid (120 mg, 64%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.58-0.68 (m, 2H), 0.81-0.95 (m, 2H), 1.32-1.40 (m, 1H), 3.49 (dd,  $J$  = 2.3, 11.8 Hz, 1H), 3.64 (dd,  $J$  = 8.6, 11.7 Hz, 1H), 3.80 (s, 3H), 3.90 (d,  $J$  = 15.9 Hz, 1H), 3.99 (d,  $J$  = 15.9 Hz, 1H), 5.59 (dd,  $J$  = 2.3, 8.6 Hz, 1H), 6.01 (s, 1H), 7.09-7.13 (m, 2H), 7.24-7.29 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.8, 8.1, 11.3, 31.8, 38.8, 53.4, 62.9, 113.8, 115.7, 128.9, 130.6, 132.6, 136.7, 147.8, 156.6, 161.3, 168.7.



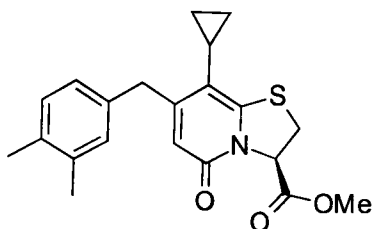
**Methyl (3R)-8-cyclopropyl-7-(2-fluoro-5-methylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 101)**

Following the general hydrolysis procedure with **JG 101** (80 mg, 0.214 mmol), purification by HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.75% formic acid each, 20-100% for 30 min;  $t_R$  = 19.87 min) and subsequent freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) gave the product as a white solid (47 mg, 66%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 0.49-0.58 (m, 1H), 0.60-0.69 (m, 1H), 0.83-0.98 (m, 2H), 1.49-1.64 (m, 1H), 2.27 (s, 3H), 3.50 (dd,  $J$  = 1.8, 11.9 Hz, 1H), 3.79 (dd,  $J$  = 9.1, 11.9 Hz, 1H), 3.92 (d,  $J$  = 16.4 Hz, 1H), 4.00 (d,  $J$  = 16.4 Hz, 1H), 5.38 (dd,  $J$  = 1.7, 9.1 Hz, 1H), 5.54 (s, 1H), 7.05-7.15 (m, 3H), 13.40 (br s, 1H). <sup>19</sup>F NMR (376 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = -122.67. <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 7.3, 7.5, 10.6, 20.2, 31.2, 31.2 (d,  $J_{CF}$  = 3.0 Hz), 62.4, 111.7, 113.2, 115.0 (d,  $J_{CF}$  = 21.7 Hz), 124.8 (d,  $J_{CF}$  = 16.0 Hz), 129.1 (d,  $J_{CF}$  = 7.9 Hz), 131.8 (d,  $J_{CF}$  = 4.3 Hz), 133.6 (d,  $J_{CF}$  = 3.4 Hz), 148.3, 155.3, 157.5, 159.9, 169.6.



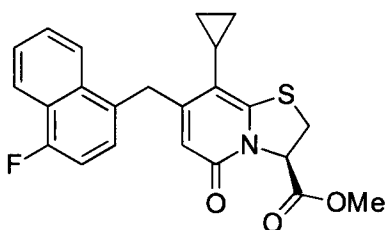
**Methyl (3R)-8-cyclopropyl-7-(2,3-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 19)**

Following the general procedure with **JG 4** (150 mg, 0.50 mmol) and 2,3-dimethylphenylboronic acid (150 mg, 1.00 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 15-100% EtOAc in heptane) gave the product as a pale brown solid (145 mg, 79%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) = 0.65-0.73 (m, 2H), 0.87-1.02 (m, 2H), 1.56-1.65 (m, 1H), 2.08 (s, 3H), 2.29 (s, 3H), 3.50 (dd, *J* = 2.3, 11.7 Hz, 1H), 3.66 (dd, *J* = 8.5, 11.7 Hz, 1H), 3.79 (s, 3H), 3.94 (d, *J* = 17.5 Hz, 1H), 4.01 (d, *J* = 17.5 Hz, 1H), 5.57 (dd, *J* = 2.3, 8.5 Hz, 1H), 5.70 (br s, 1H), 6.90-6.93 (m, 1H), 7.01-7.09 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.6, 7.8, 11.2, 15.6, 20.8, 31.9, 37.6, 53.4, 62.8, 113.8, 114.8, 125.9, 128.3, 128.9, 135.3, 136.1, 137.4, 146.7, 157.3, 161.6, 168.9.



**Methyl (3R)-8-cyclopropyl-7-(3,4-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (JG 59)**

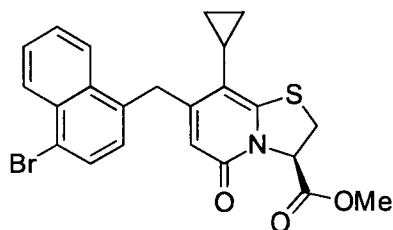
Following the general procedure with **JG 4** (150 mg, 0.50 mmol) and 3,4-dimethylphenylboronic acid (150 mg, 1.00 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 15-100% EtOAc in heptane) gave the product as an off-white solid (127 mg, 69%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.60-0.69 (m, 2H), 0.82-0.97 (m, 2H), 1.39-1.48 (m, 1H), 2.22 (s, 6H), 3.48 (dd, *J* = 2.3, 11.8 Hz, 1H), 3.63 (dd, *J* = 8.6, 11.7 Hz, 1H), 3.79 (s, 3H), 3.85 (d, *J* = 15.6 Hz, 1H), 4.01 (d, *J* = 15.6 Hz, 1H), 5.58 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.03 (s, 1H), 6.88-6.95 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.7, 8.1, 11.4, 19.5, 19.9, 31.8, 38.9, 53.3, 62.8, 114.0, 115.7, 126.7, 129.9, 130.5, 134.9, 135.4, 136.9, 147.1, 157.6, 161.5, 168.9.



**Methyl (3R)-8-cyclopropyl-7-((4-fluoronaphthalen-1-yl)methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (KSK 62)**

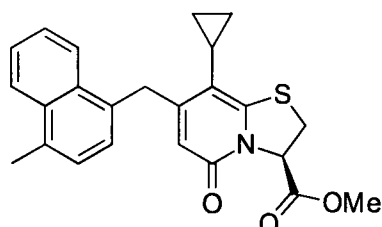
Following the general procedure with **JG 4** (270 mg, 0.9 mmol) and 4-fluoro-1-naphthaleneboronic acid (491 mg, 1.80 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 5% acetone in CH<sub>2</sub>Cl<sub>2</sub>) gave the product as a pale yellow solid (269 mg, 73%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.64-0.74 (m, 2H), 0.87-0.92 (m, 2H), 1.41-1.49 (m, 1H), 3.53 (dd, 1H, *J* = 2.6, 11.6 Hz), 3.74 (dd, 1H, *J* = 9.2, 11.6 Hz), 3.95 (s, 3H), 4.34 (d, 1H, *J* = 17.6 Hz), 4.44 (d, 1H, *J* = 17.6 Hz), 5.56 (dd, 1H, *J* = 2.6, 9.2 Hz), 5.99 (s, 1H), 7.34-7.39 (m, 2H), 7.64-7.68 (m, 2H), 7.91-7.94 (m, 1H), 8.09-8.12 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.3, 7.8, 10.7, 31.9, 39.0, 55.9, 63.3, 109.2 (d, *J*<sub>CF</sub> = 20 Hz), 111.9,

113.6, 120.5 (d,  $J_{CF} = 5$  Hz), 123.0 (d,  $J_{CF} = 16.3$  Hz), 124.6, 126.5, 127.4, 127.8, 130.9 (d,  $J_{CF} = 4$  Hz), 132.8 (d,  $J_{CF} = 5.2$  Hz), 148.3, 155.9, 157.3 (d,  $J_{CF} = 248$  Hz), 159.8, 169.9.



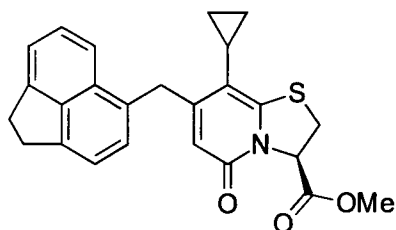
**Methyl (3R)-8-cyclopropyl-7-(4-bromo-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylate (KSK 68)**

Following the general procedure with **JG 4** (275 mg, 0.92 mmol), 4-bromo-1-naphthaleneboronic acid (345 mg, 1.38 mmol) and MWI at 110 °C, gave after purification by flash chromatography (SiO<sub>2</sub>, 10% acetone in CH<sub>2</sub>Cl<sub>2</sub>) the product as a yellow foam (220 mg, 51%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.56-0.62 (m, 1H), 0.64-0.73 (m, 1H), 0.82-0.90 (m, 2H), 1.61-1.71 (m, 1H), 3.44 (d,  $J = 11.2$  Hz, 1H), 3.58 (dd,  $J = 8.2, 11.0$  Hz, 1H), 3.97 (s, 3H), 4.43 (d,  $J = 17.2$  Hz, 1H), 4.53 (d,  $J = 17.2$  Hz, 1H), 5.20 (d,  $J = 8.4$  Hz, 1H), 5.29 (s, 1H), 7.27 (d,  $J = 7.6$  Hz, 1H), 7.60 (t,  $J = 7.8$  Hz, 1H), 7.69 (t,  $J = 8.0$  Hz, 1H), 7.89 (d,  $J = 7.4$  Hz, 1H), 8.01 (d,  $J = 8.4$  Hz, 1H), 8.28 (d,  $J = 8.4$  Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.9, 7.2, 10.6, 32.0, 35.6, 56.1, 64.0, 111.8, 114.1, 120.9, 124.4, 127.3, 127.5, 127.9, 128.4, 129.7, 131.4, 132.6, 135.3, 148.3, 154.9, 160.4, 170.3.



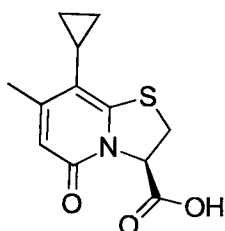
**Methyl (3R)-8-cyclopropyl-7-((4-methylnaphthalen-1-yl)methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (KSK 56)**

Following the general procedure with **JG 4** (138 mg, 0.46 mmol), 4-methyl-1-naphthaleneboronic acid (128 mg, 0.69 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 15-100% EtOAc in heptane) gave the product as a white solid (153 mg, 82%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.61-0.70 (m, 2H), 0.87-0.97 (m, 2H), 1.35-1.45 (m, 1H), 2.71 (s, 3H), 3.50 (dd, 1H,  $J = 2.2, 11.6$  Hz), 3.62 (dd,  $J = 8.6, 11.6$  Hz, 2H), 3.94 (s, 3H), 4.32 (d, 1H,  $J = 17.2$  Hz), 4.42 (d, 1H,  $J = 17.2$  Hz), 5.54 (dd, 2H,  $J = 2.2, 8.6$  Hz), 6.00 (s, 1H), 7.25 (d, 1H,  $J = 7.1$  Hz), 7.33 (d, 1H,  $J = 7.2$  Hz), 7.52-7.59 (m, 2H), 7.77 (d, 1H,  $J = 7.9$  Hz), 8.01 (d, 1H,  $J = 7.6$  Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.7, 8.0, 11.3, 20.3, 31.5, 39.2, 55.3, 62.8, 112.6, 113.5, 125.1, 125.4, 126.2, 126.3, 126.4, 127.6, 132.2, 133.0, 133.1, 133.7, 148.0, 156.9, 160.1, 170.6.



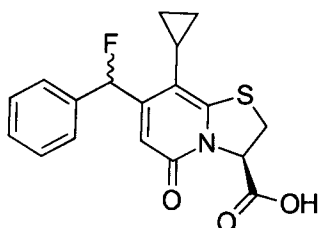
**Methyl (3R)-7-(1,2-dihydroacenaphthylen-5-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (KSK 50)**

Following the general procedure with **JG 4** (345 mg, 1.15 mmol), acenaphthene-5-boronic acid (342 mg, 1.73 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 10% acetone in CH<sub>2</sub>Cl<sub>2</sub>) gave the product as a pale yellow foam (400 mg, 83%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.65-0.78 (m, 2H), 0.83-0.94 (m, 2H), 1.64 -1.70 (m, 1H), 3.38-3.49 (m, 4H), 3.46 (d, *J* = 11.4 Hz, 1H), 3.66 (dd, *J* = 9.2, 11.4, Hz, 1H), 3.99 (s, 3H), 4.32 (d, *J* = 17.2 Hz, 1H), 4.42 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 8.2 Hz, 1H), 5.36 (s, 1H), 7.04 (s, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.6, 7.7, 10.8, 29.5, 30.4, 31.3, 34.0, 55.9, 63.2, 111.3, 113.9, 118.3, 119.2, 119.4, 128.1, 128.8, 130.1, 131.0, 139.5, 144.9, 146.7, 148.2, 155.9, 160.6, 170.4.



**(3R)-8-Cyclopropyl-7-methyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 89)**

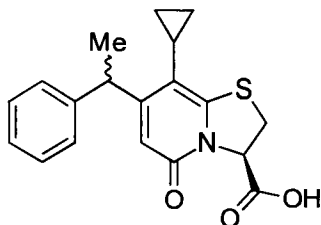
Following the general hydrolysis procedure with **JG 87** (251 mg, 0.945 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 0-22.5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> with 0.75% formic acid) gave the product as an off-white solid (200 mg, 84%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.44-0.60 (m, 2H), 0.80-0.91 (m, 2H), 1.52-1.61 (m, 1H), 2.21 (m, 3H), 3.48 (dd, *J* = 1.8, 11.9 Hz, 1H), 3.77 (dd, *J* = 9.1, 11.9 Hz, 1H), 5.38 (dd, 1.7, 9.1 Hz, 1H), 5.97 (m, 1H), 13.36 (br s, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.08, 7.13, 10.7, 19.7, 31.1, 62.4, 112.3, 113.8, 147.5, 153.9, 160.0, 169.7.



**(3R)-8-cyclopropyl-7-(fluoro(phenyl)methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 92)**

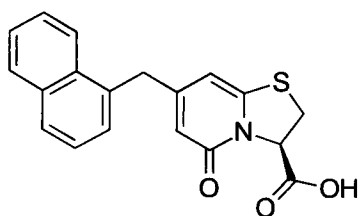
Following the general hydrolysis procedure with **JG 90** (100 mg, 0.278 mmol) with purification by HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.75% formic acid each, 25-100% for 35 min; *t*<sub>R</sub> = 16.48 min) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) gave the product as a

white solid (80 mg, 84%). Mixture of diastereomers (~1:2 as ascertained by  $^{19}\text{F}$  NMR).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 0.38-1.10 (m, 5H), 3.49-3.51 (m, 1H), 3.76-3.81 (m, 1H), 5.41-5.48 (m, 1H), 6.10-6.29 (m, 1H), 6.73-6.91 (m, 1H), 7.41-7.48 (m, 5H), 13.48 (br s, 1H).  $^{19}\text{F}$  NMR (376 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = -164.11, -164.01.  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.1, 7.6, 8.1, 8.6, 10.3, 10.5, 31.2, 31.3, 62.6, 62.7, 89.25, 89.33, 91.0, 91.1, 108.77, 108.81, 108.9, 109.0, 109.6, 109.7, 110.3, 110.5, 127.85, 127.90, 128.16, 128.21, 128.8, 129.47, 129.51, 129.54, 136.6, 136.7, 136.8, 136.9, 149.7, 149.8, 153.6, 153.7, 153.8, 153.9, 159.77, 159.79, 159.83, 169.5.



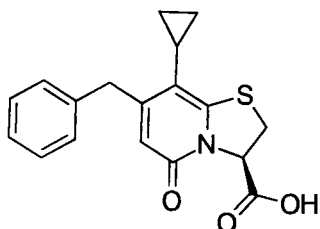
**(3R)-8-cyclopropyl-5-oxo-7-(1-phenylethyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 109)**

Following the general hydrolysis procedure with **JG 103** (85 mg, 0.239 mmol), purification by HPLC (mobile phase:  $\text{MeCN}/\text{H}_2\text{O}$  with 0.75% formic acid each, 30-100% for 30 min;  $t_R$  = 15.89 min) and subsequent freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) gave the product as a white solid (64 mg, 78%). Mixture of diastereomers.  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 0.45-0.64 (m, 2H), 0.74-1.02 (m, 2H), 1.17-1.43 (m, 1H), 1.44-1.50 (m, 3H), 3.44-3.49 (m, 1H), 3.73-3.81 (m, 1H), 4.53-4.63 (m, 1H), 5.34-5.41 (m, 1H), 5.93-6.13 (m, 1H), 7.17-7.34 (m, 5H), 13.40 (br s, 1H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.17, 7.78, 8.25, 10.73, 11.00, 21.47, 21.52, 31.04, 31.12, 40.06, 62.46, 62.52, 111.59, 111.74, 111.82, 112.11, 126.28, 126.39, 127.45, 127.58, 128.48, 144.27, 144.57, 148.30, 148.36, 160.19, 160.21, 160.36, 161.04, 169.61, 169.66.



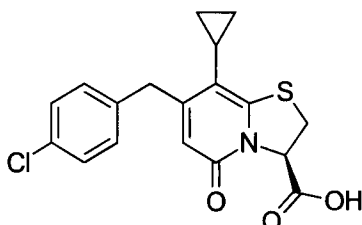
**(3R)-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 65)**

Following the general hydrolysis procedure with **HE 3B** (75 mg, 0.213 mmol) and purification by flash chromatography ( $\text{SiO}_2$ , 0-22.5%  $\text{MeOH}$  in  $\text{CH}_2\text{Cl}_2$ ) gave the product as a white solid (51 mg, 71%).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 3.54-3.64 (m, 2H), 4.19 (s, 2H), 5.06-5.12 (m, 1H), 5.79 (s, 1H), 6.05 (s, 1H), 7.44-7.56 (m, 4H), 7.81-7.97 (m, 1H), 7.90-7.95 (m, 1H), 8.00-8.05 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 32.9, 37.5, 65.0, 100.3, 112.6, 124.2, 125.7, 125.8, 126.3, 127.3, 127.7, 128.6, 131.5, 133.5, 134.7, 148.3, 153.7, 161.2, 170.3.



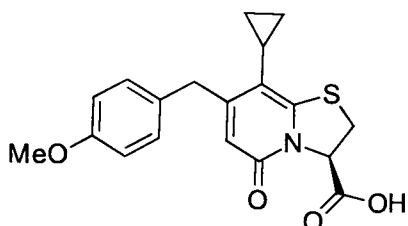
**(3R)-8-cyclopropyl-7-benzyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 49)**

Following the general hydrolysis procedure with **JG 57** (23 mg, 0.067 mmol) with purification by trituration with diethyl ether (3×) gave the product as a white solid (19 mg, 87%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 7.32-7.28 (m, 2H), 7.23-7.19 (m, 3H), 5.68 (s, 1H), 5.18 (d, 1H, *J* = 8.0 Hz), 3.99 (d, 1H, *J* = 15.6 Hz), 3.92 (d, 1H, *J* = 15.6 Hz), 3.63-3.58 (m, 1H), 3.52 (d, 1H, *J* = 10.4 Hz), 1.41-1.35 (m, 1H), 0.92-0.79 (m, 2H), 0.62-0.50 (m, 2H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.3, 7.7, 10.8, 32.3, 38.1, 64.5, 111.4, 114.1, 126.3, 128.4 (2C), 129.0 (2C), 138.8, 148.7, 155.3, 160.3, 170.2.



**(3R)-8-Cyclopropyl-7-(4-chlorobenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 110)**

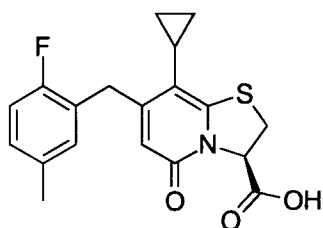
Following the general hydrolysis procedure with **JG 108** (74 mg, 0.196 mmol), purification by HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.75% formic acid each, 30-100% for 30 min; *t*<sub>R</sub> = 17.34 min) and subsequent freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) gave the product as a white solid (47 mg, 66%). <sup>1</sup>H NMR (600 MHz, DMSO-*d*<sub>6</sub>) δ = 0.48-0.55 (m, 1H), 0.58-0.64 (m, 1H), 0.80-0.92 (m, 2H), 1.33-1.40 (m, 1H), 3.49 (dd, *J* = 1.3, 11.9 Hz, 1H), 3.78 (dd, *J* = 9.2, 11.8 Hz, 1H), 3.94 (d, *J* = 15.6 Hz, 1H), 4.00 (d, *J* = 15.6 Hz, 1H), 5.38 (dd, *J* = 1.4, 9.1 Hz, 1H), 5.77 (s, 1H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 2H), 13.36 (s, 1H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ = 7.4, 7.6, 10.8, 31.2, 37.5, 62.4, 111.8, 114.1, 128.4, 130.9, 131.1, 137.7, 148.5, 156.0, 160.0, 169.6.



**(3R)-8-Cyclopropyl-7-(4-methoxybenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 97)**

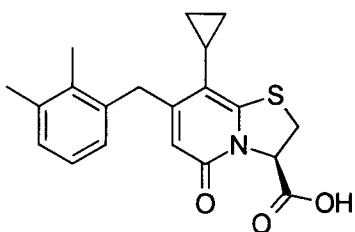
Following the general hydrolysis procedure with **JG 94** (82 mg, 0.220 mmol) with purification by HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.5% formic acid each, 25-100% for 35 min; *t*<sub>R</sub> = 17.16 min) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) gave the product as a

white solid (19 mg, 24%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.47-0.66 (m, 2H), 0.80-0.97 (m, 2H), 1.35-1.46 (m, 1H), 3.48 (dd,  $J$  = 1.6, 11.9 Hz, 1H), 3.71-3.80 (m, 4H), 3.84-3.95 (m, 2H), 5.36 (dd,  $J$  = 1.6, 9.0 Hz, 1H), 5.73 (s, 1H), 6.86-6.91 (m, 2H), 7.12-7.17 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.4, 7.6, 10.8, 31.2, 37.3, 38.9, 40.1, 55.0, 62.4, 111.9, 113.9, 128.7, 128.8, 130.3, 131.4, 131.5, 148.1, 157.0, 157.8, 160.0, 169.7.



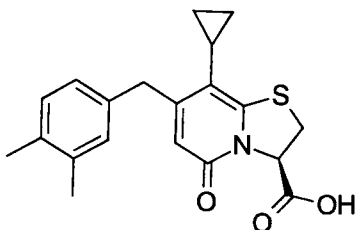
**(3R)-8-Cyclopropyl-7-(2-fluoro-5-methylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 104)**

Following the general hydrolysis procedure with **JG 101** (80 mg, 0.214 mmol), purification by HPLC (mobile phase: MeCN/ $\text{H}_2\text{O}$  with 0.75% formic acid each, 20-100% for 30 min;  $t_R$  = 19.87 min) and subsequent freeze-drying ( $\text{H}_2\text{O}$ :MeCN; ~ 3:1) gave the product as a white solid (47 mg, 66%).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 0.49-0.58 (m, 1H), 0.60-0.69 (m, 1H), 0.83-0.98 (m, 2H), 1.49-1.64 (m, 1H), 2.27 (s, 3H), 3.50 (dd,  $J$  = 1.8, 11.9 Hz, 1H), 3.79 (dd,  $J$  = 9.1, 11.9 Hz, 1H), 3.92 (d,  $J$  = 16.4 Hz, 1H), 4.00 (d,  $J$  = 16.4 Hz, 1H), 5.38 (dd,  $J$  = 1.7, 9.1 Hz, 1H), 5.54 (s, 1H), 7.05-7.15 (m, 3H), 13.40 (br s, 1H).  $^{19}\text{F}$  NMR (376 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = -122.67.  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.3, 7.5, 10.6, 20.2, 31.2, 31.2 (d,  $J_{CF}$  = 3.0 Hz), 62.4, 111.7, 113.2, 115.0 (d,  $J_{CF}$  = 21.7 Hz), 124.8 (d,  $J_{CF}$  = 16.0 Hz), 129.1 (d,  $J_{CF}$  = 7.9 Hz), 131.8 (d,  $J_{CF}$  = 4.3 Hz), 133.6 (d,  $J_{CF}$  = 3.4 Hz), 148.3, 155.3, 157.5, 159.9, 169.6.



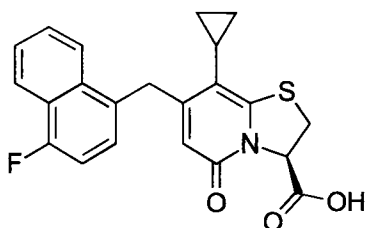
**(3R)-8-Cyclopropyl-7-(2,3-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 26)**

Following the general hydrolysis procedure with **JG 19** (137 mg, 0.372 mmol) and purification by flash chromatography ( $\text{SiO}_2$ , 0-22.5% MeOH in  $\text{CH}_2\text{Cl}_2$ ) gave the product as a white solid (107 mg, 81%).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 0.50-0.65 (m, 2H), 0.80-0.96 (m, 2H), 1.54-1.63 (m, 1H), 2.06 (s, 3H), 2.26 (s, 3H), 3.52-3.62 (m, 2H), 3.88-4.02 (m, 2H), 5.10-5.15 (m, 1H), 5.25 (s, 1H), 6.91-6.96 (m, 1H), 7.03-7.10 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.1, 7.5, 10.7, 15.1, 20.3, 32.7, 36.4, 65.2, 111.4, 112.9, 125.5, 127.9, 128.4, 134.9, 136.6, 136.8, 148.5, 155.1, 160.5, 170.7.



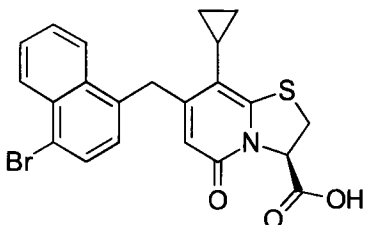
**(3R)-8-Cyclopropyl-7-(3,4-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 63)**

Following the general hydrolysis procedure with **JG 59** (122 mg, 0.330 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 0-22% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) gave the product as a white solid (113 mg, 97%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.47-0.60 (m, 2H), 0.78-0.96 (m, 2H), 1.35-1.45 (m, 1H), 2.17-2.20 (m, 6H), 3.53-3.57 (m, 2H), 3.83 (d, *J* = 15.5 Hz, 1H), 3.89 (d, *J* = 15.5 Hz, 1H), 5.09-5.15 (m, 1H), 5.64 (s, 1H), 6.90-6.94 (m, 1H), 6.98-7.00 (m, 2H), 7.07 (d, *J* = 7.7 Hz, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.3, 7.7, 10.8, 19.0, 19.4, 32.6, 37.7, 65.1, 111.5, 114.0, 126.5, 129.5, 130.2, 134.0, 136.0, 136.1, 148.7, 155.6, 160.5, 170.7.



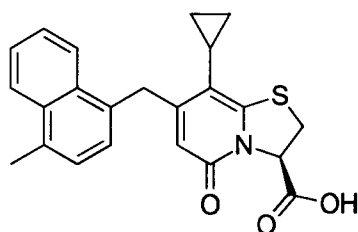
**(3R)-8-Cyclopropyl-7-(4-fluoro-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 63)**

Following the general hydrolysis procedure with **KSK 62** (250 mg, 0.61 mmol) and purification by trituration with diethyl ether (3×) gave the product as a pale yellow solid product (202 mg, 84%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.60-0.66 (m, 1H), 0.71-0.77 (m, 1H), 0.86-0.93 (m, 2H), 1.67-1.74 (m, 1H), 3.51 (d, *J* = 11.6 Hz, 1H), 3.72 (dd, *J* = 9.2, 11.6 Hz, 1H), 4.37 (d, 1H, *J* = 17.6 Hz), 4.46 (d, *J* = 17.6 Hz, 1H), 5.23 (s, 1H), 5.25 (d, *J* = 8.8 Hz, 1H), 7.31-7.37 (m, 2H), 8.10-8.13 (m, 1H), 7.92-7.95 (m, 1H), 7.64-7.67 (m, 2H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.1, 7.4, 10.7, 31.7, 34.8, 63.3, 109.2 (d, *J*<sub>CF</sub> = 20 Hz), 111.5, 113.3, 120.4 (d, *J*<sub>CF</sub> = 5 Hz), 123.1 (d, *J*<sub>CF</sub> = 16 Hz), 124.5, 126.5, 127.3, 127.5, 130.9 (d, *J*<sub>CF</sub> = 4 Hz), 132.7 (d, *J*<sub>CF</sub> = 5 Hz), 148.3, 155.6, 157.1 (d, *J*<sub>CF</sub> = 248 Hz), 159.9, 169.7.



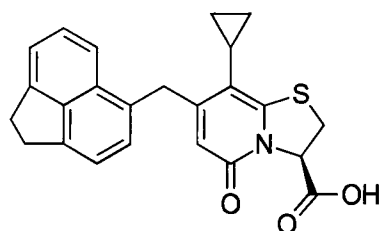
**(3R)-8-Cyclopropyl-7-(4-bromo-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 69)**

Following the general hydrolysis procedure with **KSK 68** (42 mg, 0.089 mmol) and purification by trituration with diethyl ether (3×) gave the product as a white solid (32 mg, 79%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.59-0.65 (m, 1H), 0.68-0.74 (m, 1H), 0.84-0.91 (m, 2H), 1.64-1.71 (m, 1H), 3.54 (d, *J* = 11.2 Hz, 1H), 3.62 (dd, *J* = 8.2, 11.0 Hz, 1H), 4.38 (d, 1H, *J* = 17.2 Hz), 4.48 (d, *J* = 17.2 Hz, 1H), 5.15 (d, 1H, *J* = 8.4 Hz), 5.23 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.4 Hz, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.0, 7.4, 10.7, 32.4, 35.0, 64.6, 111.3, 113.5, 120.8, 124.9, 127.1, 127.4, 127.7, 128.2, 129.8, 131.3, 132.9, 135.5, 148.7, 154.7, 160.1, 169.8.



**(3R)-8-Cyclopropyl-7-(4-methyl-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 67).**

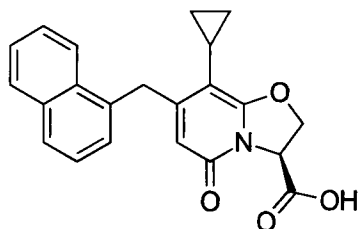
Following the general hydrolysis procedure with **KSK 56** (45 mg, 0.11 mmol) and purification by trituration with diethyl ether (3×) gave the product as a pale yellow solid (33 mg, 76%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.60-0.65 (m, 1H), 0.70-0.74 (m, 1H), 0.85-0.93 (m, 2H), 1.67-1.72 (m, 1H), 2.66 (s, 3H), 3.50 (d, *J* = 11.2 Hz, 1H), 3.62-3.68 (m, 1H), 4.33 (d, *J* = 17.2 Hz, 1H), 4.43 (d, *J* = 17.2 Hz, 1H), 5.19-5.21 (m, 2H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.58-7.50 (m, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.7, 7.9, 11.2, 19.6, 31.7, 35.8, 62.8, 112.4, 113.9, 125.1, 125.3, 126.2, 126.5, 126.8, 127.8, 132.1, 133.0, 133.1, 133.7, 148.4, 157.1, 160.4, 170.1.



**(3R)-7-(1,2-dihydroacenaphthylen-5-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (KSK 58)**

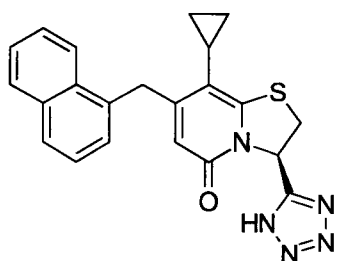
Following the general hydrolysis procedure with **KSK 50** (40 mg, 0.095 mmol) and purification by trituration with diethyl ether (3×) gave the product as a white solid (32 mg, 83%). <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>, 400 MHz) δ = 0.60-0.75 (m, 2H), 0.83-0.93 (m, 2H), 1.62-1.71 (m, 1H), 3.32-3.41 (m, 4H), 3.50 (d, *J* = 11.6 Hz, 1H), 3.72 (dd, *J* = 11.6, 9.2 Hz, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 4.39 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 8.4 Hz, 1H), 5.31 (s, 1H), 7.29 (s, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.6, 7.8, 10.9, 29.1, 30.1, 31.7, 34.4, 63.2, 111.8,

113.4, 119.1, 119.3, 119.4, 128.0, 128.9, 130.1, 130.2, 139.1, 144.7, 146.3, 148.1, 156.1, 160.0, 170.0.

Preparation of other ring-fused thiazolino 2-pyridones

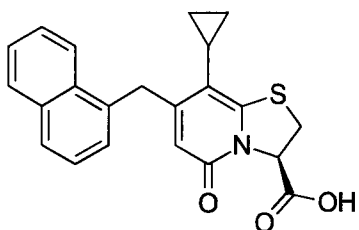
**(3S)-8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-[1,3]oxazolo[3,2-a]pyridine-3-carboxylic acid (NP 239)**

Prepared by published procedures.<sup>13</sup>



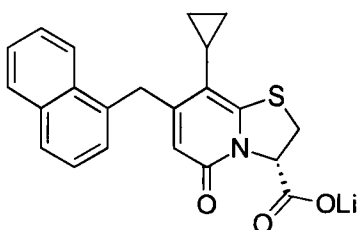
**(3R)-8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-3-(1H-tetrazol-5-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (VA 147)**

Prepared by published procedures.<sup>2, 14</sup>



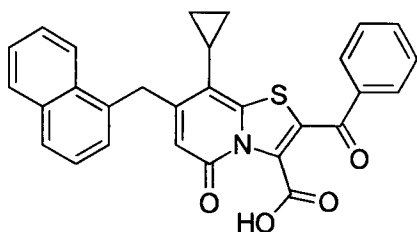
**(3R)-8-Cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (C10)**

Prepared by published procedures.<sup>1</sup>



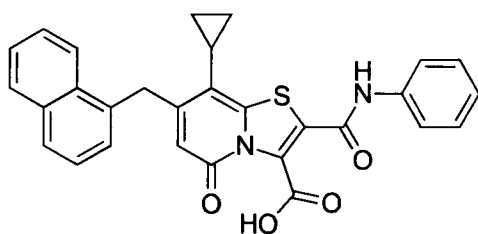
**Lithium (3S)-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate ((S)-C10))**

Prepared by published procedures.<sup>2</sup>



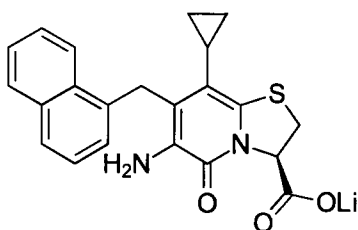
**2-Benzoyl-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (EC 177)**

Prepared by published procedures.<sup>1, 4</sup>



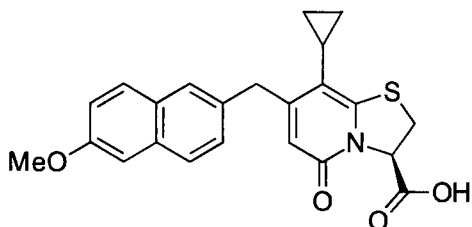
**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2-(phenylcarbamoyl)-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (EC 178)**

Prepared by published procedures.<sup>1</sup>



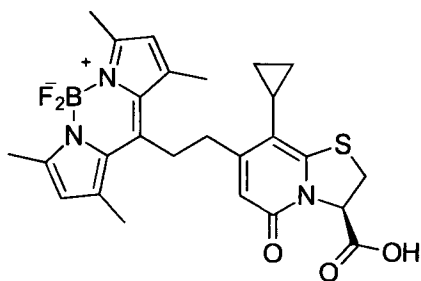
**Lithium (3R)-6-amino-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (MS 68)**

Prepared by published procedures.<sup>15</sup>



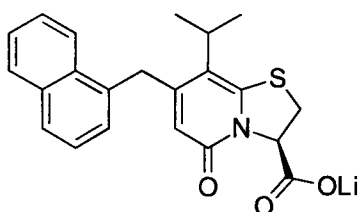
**(3R)-8-cyclopropyl-7-((6-methoxynaphthalen-2-yl)methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (CB 158)**

Prepared by published procedures.<sup>16</sup>



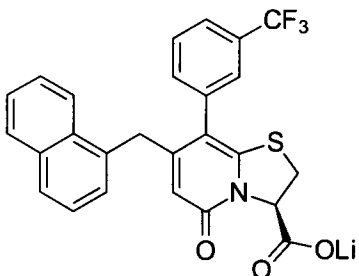
**(3R)-8-Cyclopropyl-7-(2-(1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene-8-yl)ethyl)-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylic acid (EC 364)**

Prepared by published procedures.<sup>17</sup>



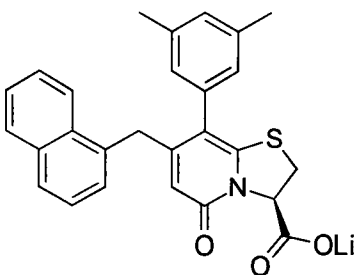
**Lithium (3R)-7-(naphthalen-1-ylmethyl)-5-oxo-8-(propan-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (EC 215)**

Prepared by published procedures.<sup>18</sup>



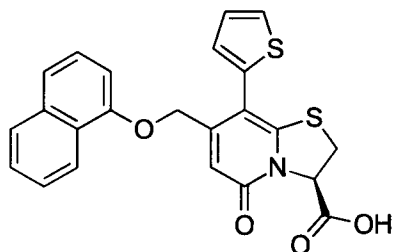
**Lithium (3R)-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (FN 075)**

Prepared by published procedures.<sup>3</sup>



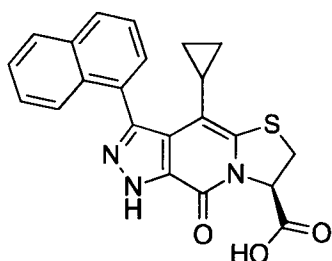
**Lithium (3R)-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3,5-dimethylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylate (SS 23)**

Prepared by published procedures.<sup>19</sup>



**(3R)-7-((Naphthalen-1-yloxy)methyl)-5-oxo-8-(thiophen-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (EC 218)**

Prepared by published procedures.<sup>18</sup>

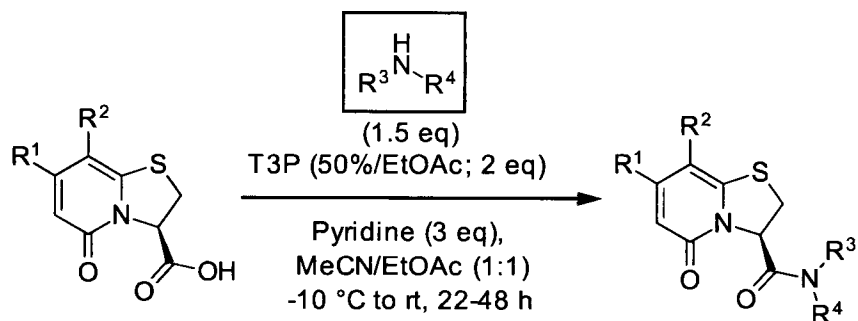


**(7R)-4-Cyclopropyl-3-(naphthalen-1-yl)-9-oxo-1,6,7,9-tetrahydropyrazolo[4,3-d][1,3]thiazolo[3,2-a]pyridine-7-carboxylic acid (MS 68)**

Prepared by published procedures.<sup>20</sup>

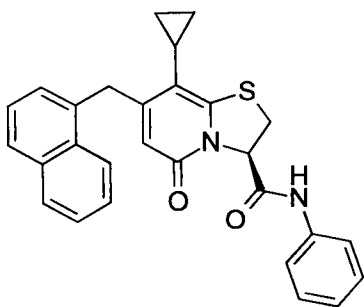
#### Preparation of novel ring-fused thiazolino 2-pyridone amides

The compounds of interest were provided by amide coupling of the appropriate carboxylic acid by a propylphosphonic anhydride (T3P<sup>®</sup>) mediated amide coupling (Scheme 3) based on the procedure reported by Dunetz *et al.*<sup>21</sup> A representative procedure is provided for the synthesis of **JG 6**. In other cases, TBTU or HATU amide coupling reagents were used to provide the compounds of interest. In the cases where these methods were not successful, the amides were prepared by activation to the acid chloride with oxalyl chloride and subsequent amide coupling.<sup>17</sup>



**Scheme 3 – General route for the synthesis of amides by T3P<sup>®</sup> mediated coupling.**

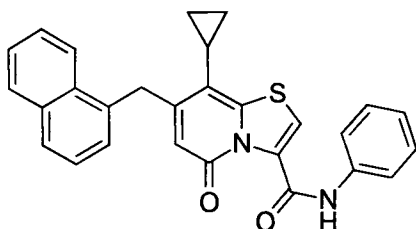
*General procedure for the amide coupling of carboxylic acids with T3P<sup>®</sup>*



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 6)**

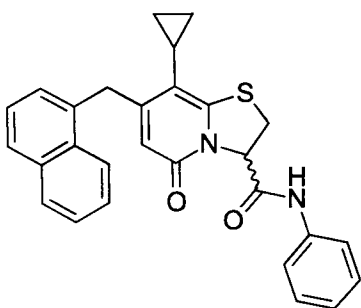
The title compound was prepared by adaptation of the procedure reported by Dunetz *et al.*<sup>21</sup> The carboxylic acid **C10** (386 mg, 1.02 mmol) was dissolved in anhydrous MeCN/EtOAc (1:1, 11 mL) under an inert atmosphere, and after cooling the suspension to ~ -10 °C (NaCl/ice), pyridine (247  $\mu$ L, 3.06 mmol) was added. The reaction mixture was stirred for 5 min, and aniline (140  $\mu$ L, 1.53 mmol) added, followed by dropwise addition of T3P<sup>®</sup> (50% in EtOAc; 1.202 mL, 2.04 mmol). The reaction was stirred for 1 h, then allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C, quenched with HCl (1 M aq) and extracted with EtOAc (3 $\times$ ). The organic extracts were washed successively with water (3 $\times$ ) and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, 0-30% EtOAc in heptane) afforded the amide as a white solid (450 mg, 97%).  $[\alpha]_D^{20} = -12.0$  ( $c = 1.0$ , CHCl<sub>3</sub>). The <sup>1</sup>H and <sup>13</sup>C NMR data were in agreement with that recorded for **KSK 165**.

*Examples of novel ring-fused thiazolino 2-pyridone amides prepared by this route:*



**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 120)**

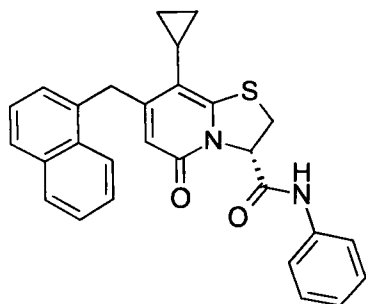
The carboxylic acid **EC 104** (100 mg, 0.27 mmol) was dissolved in dry dichloromethane (5 mL) and cooled to 0 °C. Oxalyl chloride (34  $\mu$ L, 0.40 mmol) was added dropwise and the solution was allowed to reach rt and stirred for 1 h. After the evaporation of the solvent, the residue was redissolved in  $\text{CH}_2\text{Cl}_2$ , followed by the addition of  $\text{NEt}_3$  (110  $\mu$ L, 0.79 mmol) and aniline (49  $\mu$ L, 0.54 mmol). The solution was stirred for 4 h, concentrated and purified by column chromatography on silica gel, to afford the amide as a white solid (90 mg, 75%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.78-0.84 (m, 2H), 1.11-1.19 (m, 2H), 1.84-1.91 (m, 1H), 4.58 (s, 2H), 6.03 (s, 1H), 7.03 (t,  $J$  = 7.4 Hz, 1H), 7.21-7.26 (m, 2H), 7.29 (d,  $J$  = 6.8 Hz, 1H), 7.42-7.51 (m, 3H), 7.63 (d,  $J$  = 7.6 Hz, 2H), 7.83-7.78 (m, 2H), 7.91-7.88 (m, 1H), 8.04 (s, 1H), 13.15 (s, 1H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.4 (2C), 11.1, 36.0, 112.7, 114.6, 120.4 (2C), 123.7, 124.1, 124.3, 125.6, 125.9, 126.4, 127.8, 128.0, 128.8 (2C), 129.1, 131.9, 133.8, 134.1, 138.3, 138.8, 150.7, 153.8, 155.3, 161.3.



**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 165)**

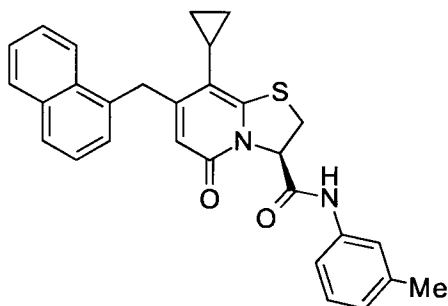
**C10** (160 mg, 0.42 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (6 mL) under an inert atmosphere, and cooled to 0 °C. Oxalyl chloride (80 mg, 0.63 mmol) was added drop wise and the reaction allowed to warm to room temperature and stirred for 1 h. The reaction mixture was then concentrated and the crude residue dissolved in  $\text{CH}_2\text{Cl}_2$  (6 mL), cooled to 0 °C and aniline (60  $\mu$ L, 0.63 mmol) and  $\text{NEt}_3$  (0.17 mL, 1.3 mmol) added and the reaction stirred at room temperature overnight. The reaction was quenched with HCl (0.5 M aq.) and extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organics were washed with  $\text{H}_2\text{O}$  and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Purification by flash chromatography ( $\text{SiO}_2$ , 0-50% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}$ :MeCN; ~ 3:1) afforded the product as a white solid (165 mg, 86%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.69-0.76 (m, 1H), 0.88-0.99 (m, 2H), 1.03-1.11 (m, 1H), 1.69-1.77 (m, 1H), 3.54 (dd,  $J$  = 8.0, 11.1 Hz, 1H), 4.12-4.18 (m, 1H), 4.34 (d,  $J$

= 17.6 Hz, 1H), 4.45 (d,  $J$  = 17.6 Hz, 1H), 5.76-5.81 (m, 2H), 7.09-7.14 (m, 1H), 7.28-7.36 (m, 3H), 7.40-7.55 (m, 5H), 7.68-7.71 (m, 1H), 7.89-7.99 (m, 2H), 9.96 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.1, 8.3, 11.5, 21.5, 29.7, 36.4, 64.7, 114.9, 115.7, 117.1, 120.6, 123.9, 125.2, 125.7, 125.9, 126.5, 127.9, 128.0, 128.9, 129.0, 132.1, 133.7, 134.1, 137.9, 139.0, 148.6, 157.8, 162.7, 164.7.



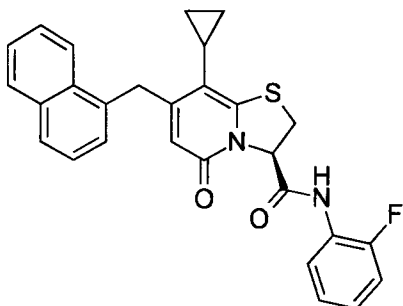
**(3S)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 16)**

The title compound was prepared by a modified version of the general procedure with (*S*)-**C10** (130 mg, 0.34 mmol; prepared as described previously<sup>2</sup>), pyridine (125  $\mu\text{L}$ , 1.61 mmol), aniline (47  $\mu\text{L}$ , 0.51 mmol) and T3P<sup>®</sup> (50% in DMF; 201  $\mu\text{L}$ , 0.34 mmol). Purification by flash chromatography ( $\text{SiO}_2$ , 0-100% EtOAc in heptane) afforded the amide as a white solid (74 mg, 48%). The  $^1\text{H}$  and  $^{13}\text{C}$  NMR data were in agreement with that recorded for **KSK 165**.  $[\alpha]_{\text{D}}^{20}$  = + 22.0 ( $c$  = 1.0,  $\text{CHCl}_3$ ).



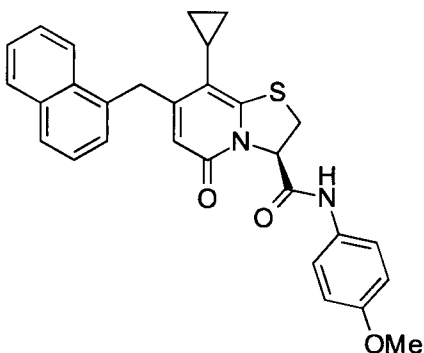
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-methylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 20)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 3-methylaniline (22  $\mu\text{L}$ , 0.199 mmol) afforded after purification by flash chromatography ( $\text{SiO}_2$ , 0-60% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) the product as a white solid (59 mg, 96%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.65-0.73 (m, 1H), 0.76-0.84 (m, 1H), 0.86-0.96 (m, 1H), 0.99-1.08 (m, 1H), 1.65-1.74 (m, 1H), 2.28 (s, 3H), 3.56 (dd,  $J$  = 8.0, 11.1 Hz, 1H), 4.14-4.19 (m, 1H), 4.36 (d,  $J$  = 17.5 Hz, 1H), 4.46 (d,  $J$  = 17.4 Hz, 1H), 5.76-5.80 (m, 2H), 6.87 (d,  $J$  = 7.3 Hz, 1H), 7.12-7.17 (m, 1H), 7.25-7.30 (m, 1H), 7.32-7.35 (m, 2H), 7.41-7.51 (m, 3H), 7.72-7.77 (m, 1H), 7.78-7.83 (m, 1H), 7.86-7.91 (m, 1H), 10.22 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.1, 8.3, 11.5, 21.5, 29.7, 36.4, 64.7, 114.9, 115.7, 117.1, 120.6, 123.9, 125.2, 125.7, 125.9, 126.5, 127.9, 128.0, 128.9, 129.0, 132.1, 133.7, 134.1, 137.9, 139.0, 148.6, 157.8, 162.7, 164.7.



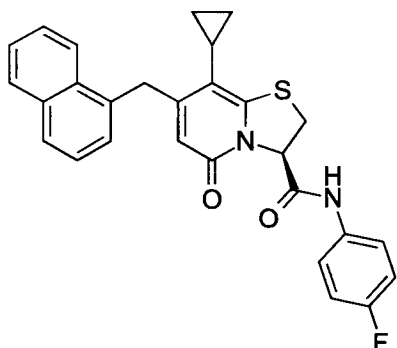
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(2-fluorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 21)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 2-fluoroaniline (19  $\mu$ L, 0.199 mmol) afforded after purification by flash chromatography ( $\text{SiO}_2$ , 0-60% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) the product as a white solid (50 mg, 81%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.66-0.73 (m, 1H), 0.75-0.83 (m, 1H), 0.86-0.96 (m, 1H), 0.99-1.08 (m, 1H), 1.65-1.74 (m, 1H), 3.59 (dd,  $J$  = 8.0, 11.3 Hz, 1H), 4.15 (d,  $J$  = 11.3 Hz, 1H), 4.35 (d,  $J$  = 17.5 Hz, 1H), 4.50 (d,  $J$  = 17.5 Hz, 1H), 5.81 (d,  $J$  = 7.9 Hz, 1H), 5.84 (s, 1H), 7.00-7.10 (m, 3H), 7.25-7.29 (m, 1H), 7.40-7.50 (m, 3H), 7.72-7.83 (m, 2H), 7.86-7.90 (m, 1H), 8.23-8.29 (m, 1H), 10.37 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.1, 8.2, 11.5, 29.7, 36.4, 64.5, 115.06, 115.13, 115.2, 115.6, 121.9, 123.9, 124.4 (d,  $J_{\text{CF}}$  = 3.7 Hz), 124.8 (d,  $J_{\text{CF}}$  = 7.4 Hz), 125.7, 125.9, 126.4, 126.5, 127.9, 128.0, 129.0, 132.0, 133.7, 134.2, 148.2, 152.8 (d,  $J_{\text{CF}}$  = 247.0 Hz), 157.7, 162.5, 165.2.



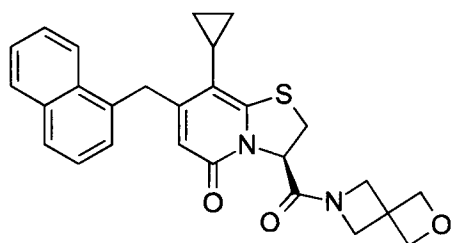
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-methoxyphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 22)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 4-methoxyaniline (19  $\mu$ L, 0.199 mmol) afforded after purification by flash chromatography ( $\text{SiO}_2$ , 0-60% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) the product as a white solid (57 mg, 90%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.66-0.74 (m, 1H), 0.76-0.84 (m, 1H), 0.88-0.96 (m, 1H), 0.99-1.08 (m, 1H), 1.66-1.74 (m, 1H), 3.53-3.59 (m, 1H), 3.76 (s, 3H), 4.13-4.18 (m, 1H), 4.36 (d,  $J$  = 17.5 Hz, 1H), 4.49 (d,  $J$  = 17.5 Hz, 1H), 5.74-5.79 (m, 2H), 6.76-6.82 (m, 2H), 7.26-7.30 (m, 1H), 7.40-7.51 (m, 5H), 7.73-7.83 (m, 2H), 7.86-7.91 (m, 1H), 10.13 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.1, 8.3, 11.5, 29.7, 36.4, 55.6, 64.6, 114.1, 114.9, 115.7, 121.4, 123.9, 125.7, 125.9, 126.5, 127.9, 128.0, 129.0, 131.3, 132.1, 133.8, 134.1, 148.7, 156.4, 157.8, 162.6, 164.5.



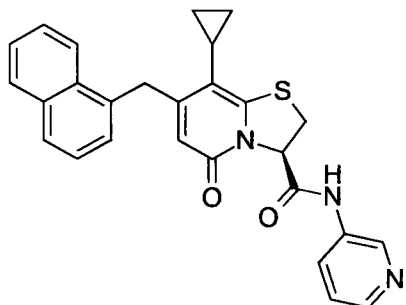
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-fluorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 23)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 4-fluoroaniline (19  $\mu$ L, 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 0-80% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) the product as a white solid (38 mg, 62%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.67-0.73 (m, 1H), 0.77-0.83 (m, 1H), 0.90-0.96 (m, 1H), 1.01-1.07 (m, 1H), 1.68-1.74 (m, 1H), 3.58 (dd,  $J$  = 8.1, 11.3 Hz, 1H), 4.13-4.16 (m, 1H), 4.36 (d,  $J$  = 17.5 Hz, 1H), 4.49 (d,  $J$  = 17.5 Hz, 1H), 5.75-5.78 (m, 2H), 6.92-6.96 (m, 2H), 7.26-7.29 (m, 1H), 7.40-7.50 (m, 5H), 7.74 (d,  $J$  = 8.2 Hz, 1H), 7.81 (d,  $J$  = 8.1 Hz, 1H), 7.87-7.90 (m, 1H), 10.35 (br s, 1H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.2, 8.3, 11.5, 29.6, 36.4, 64.6, 114.9, 115.6, 115.7, 115.8, 121.6, 121.7, 123.9, 125.7, 126.0, 126.5, 128.0, 128.1, 129.1, 132.1, 133.7, 134.1 (d,  $J_{CF}$  = 2.4 Hz), 134.2, 148.7, 158.0, 159.4 (d,  $J_{CF}$  = 245.0 Hz), 162.7, 164.8.



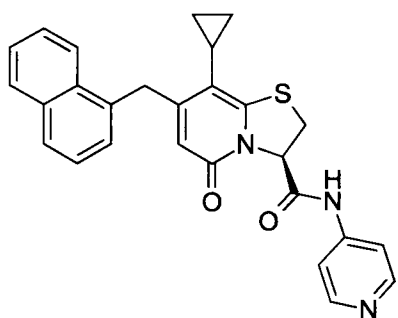
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (JG 24)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and the oxalate salt of 2-oxa-6-azaspiro[3.3]heptane (2:1 oxetane:oxalate; 28.6 mg, 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 0-20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) the spirooxetane product as a white solid (30 mg, 50%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.71-0.84 (m, 2H), 0.93-1.00 (m, 2H), 1.62-1.70 (m, 1H), 3.42-3.55 (m, 2H), 4.04-4.10 (m, 1H), 4.20-4.30 (m, 2H), 4.35-4.47 (m, 2H), 4.59-4.64 (m, 1H), 4.70-4.81 (m, 4H), 5.15-5.20 (m, 1H), 5.65 (s, 1H), 7.24-7.28 (m, 1H), 7.38-7.50 (m, 3H), 7.73-7.79 (m, 2H), 7.84-7.89 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.8, 8.2, 11.3, 31.6, 36.4, 38.2, 58.2, 60.7, 60.9, 80.8, 81.0, 113.7, 115.1, 123.9, 125.7, 125.9, 126.4, 127.8, 127.8, 129.0, 132.0, 134.09, 134.11, 148.4, 157.3, 161.4, 168.5.



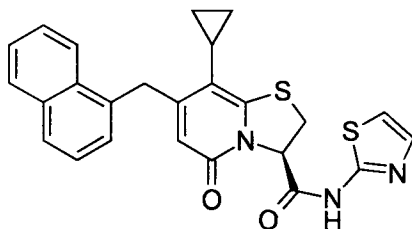
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(pyridin-3-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 27)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 3-aminopyridine (19 mg, 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 0-20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) the product as a white solid (28 mg, 47%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.68-0.84 (m, 2H), 0.90-0.99 (m, 1H), 1.00-1.10 (m, 1H), 1.67-1.77 (m, 1H), 3.60 (dd, *J* = 8.2, 11.4 Hz, 1H), 4.08 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 17.4 Hz, 1H), 4.51 (d, *J* = 17.4 Hz, 1H), 5.76-5.82 (m, 2H), 7.22-7.31 (m, 2H), 7.41-7.51 (m, 3H), 7.71-7.77 (m, 1H), 7.86-7.90 (m, 1H), 8.05-8.10 (m, 1H), 8.28-8.31 (m, 1H), 8.73 (br s, 1H), 10.78 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.1, 8.1, 11.4, 29.6, 36.3, 64.5, 114.7, 115.8, 123.7, 123.9, 125.6, 125.9, 126.4, 127.9, 128.0, 128.1, 128.9, 131.9, 133.5, 134.0, 135.3, 140.3, 144.0, 148.6, 158.1, 162.5, 165.6.



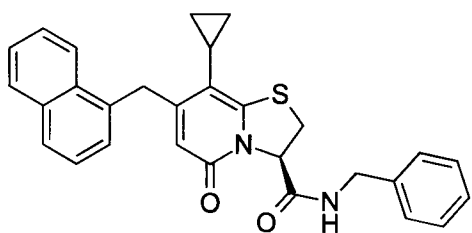
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(pyridin-4-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 28)**

The title compound was prepared by adaptation of the general procedure with **C10** (50 mg, 0.132 mmol), NEt<sub>3</sub> (92 μL, 0.662 mmol), 4-aminopyridine (32 mg, 0.331 mmol) and T3P® (50% in DMF; 193 μL, 0.331 mmol). Purification by flash chromatography (SiO<sub>2</sub>, 0-25% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) afforded the product as a white solid (27 mg, 45%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.62-0.70 (m, 1H), 0.74-0.82 (m, 1H), 0.87-0.99 (m, 2H), 1.70-1.79 (m, 1H), 3.58 (dd, *J* = 2.2, 12.1 Hz, 1H), 3.89 (dd, *J* = 9.2, 12.0 Hz, 1H), 4.42 (d, *J* = 17.4 Hz, 1H), 4.51 (d, *J* = 17.4 Hz, 1H), 5.27 (s, 1H), 5.49 (dd, *J* = 2.2, 9.2 Hz, 1H), 7.39 (d, 7.0 Hz, 1H), 7.48-7.58 (m, 5H), 7.86-7.92 (m, 2H), 7.94-7.99 (m, 1H), 8.38-8.52 (m, 2H), 10.78 (br s, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.3, 7.5, 10.8, 31.3, 35.3, 63.9, 111.8, 113.2, 113.3, 124.0, 125.7, 125.8, 126.3, 127.3, 127.6, 128.6, 131.6, 133.5, 134.6, 145.6, 149.0, 150.0, 156.6, 159.9, 167.3.



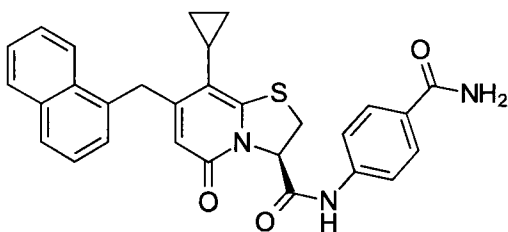
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(1,3-thiazol-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 29)**

The title compound was prepared by adaptation of the general procedure with **C10** (50 mg, 0.132 mmol) and 2-aminothiazole (20 mg, 0.199 mmol). After stirring for 24 h, a further 2 equivalents of T3P® (50% in EtOAc; 158  $\mu$ L, 0.264 mmol) were added and the reaction stirred a further 48 h. Purification by flash chromatography (SiO<sub>2</sub>, 0-100% EtOAc in heptane) afforded the product as a pale yellow solid (20 mg, 33%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>/MeOD; 9:1)  $\delta$  = 0.57-0.68 (m, 2H), 0.75-0.92 (m, 2H), 1.51-1.62 (m, 1H), 3.50-3.67 (m, 2H), 4.23-4.43 (m, 2H), 5.52-5.64 (m, 2H), 6.83-6.91 (m, 1H), 7.09-7.17 (m, 1H), 7.23-7.37 (m, 4H), 7.59-7.77 (m, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>/MeOD; 9:1)  $\delta$  = 7.1, 7.7, 11.1, 30.5, 36.1, 63.6, 114.0, 114.2, 115.2, 123.5, 125.3, 125.6, 126.1, 127.4, 127.6, 128.6, 131.7, 133.5, 133.8, 136.7, 148.6, 158.1, 158.2, 162.0, 165.6.



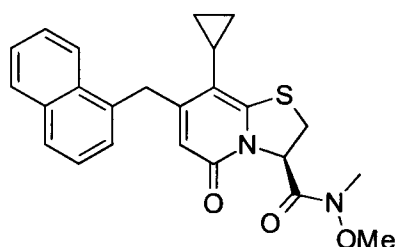
**(3R)-N-Benzyl-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 30)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and benzylamine (15  $\mu$ L, 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 20-90% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) the product as a white solid (38 mg, 62%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.67-0.84 (m, 2H), 0.88-1.06 (m, 2H), 1.63-1.73 (m, 1H), 3.51 (dd,  $J$  = 8.0, 11.2 Hz, 1H), 4.04 (d,  $J$  = 11.2 Hz, 1H), 4.26-4.50 (m, 4H), 5.65 (d,  $J$  = 7.9 Hz, 1H), 5.76 (s, 1H), 7.14-7.28 (m, 6H), 7.39-7.51 (m, 3H), 7.73-7.82 (m, 2H), 7.85-7.91 (m, 1H), 8.30 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.4, 8.2, 11.5, 30.3, 36.4, 43.8, 64.1, 114.8, 115.4, 123.8, 125.7, 125.9, 126.4, 127.3, 127.6, 127.8, 128.0, 128.7, 129.0, 132.0, 133.8, 134.1, 138.0, 148.9, 157.7, 162.2, 167.2.



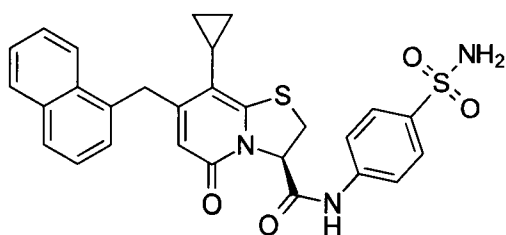
**(3R)-7-(Naphthalen-1-ylmethyl)-N-(4-carbamoylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 33)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 4-aminobenzamide (27 mg, 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 0-25% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) and freeze-drying (H<sub>2</sub>O:MeCN; ~3:1) the product as a white solid (35 mg, 53%). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.68-0.84 (m, 2H), 0.90-1.07 (m, 2H), 1.67-1.74 (m, 1H), 3.52-3.63 (m, 1H), 3.84-3.93 (m, 1H), 4.30-4.40 (m, 1H), 4.49 (d,  $J$  = 17.3 Hz, 1H), 5.69-6.00 (m, 3H), 6.21-6.55 (br s, 1H), 7.23-7.28 (m, 1H), 7.38-7.52 (m, 5H), 7.56-7.63 (m, 2H), 7.73 (d,  $J$  = 7.8 Hz, 1H), 7.78 (d,  $J$  = 8.2 Hz, 1H), 7.86 (d,  $J$  = 7.8 Hz, 1H), 10.84 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.3, 8.2, 11.5, 30.2, 36.4, 64.9, 114.4, 116.0, 119.4, 123.9, 125.7, 126.0, 126.5, 127.98, 128.04, 128.5, 129.1, 132.0, 133.7, 134.1, 141.5, 149.3, 158.5, 162.3, 165.6, 169.2.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-methoxy-N-methyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 34)**

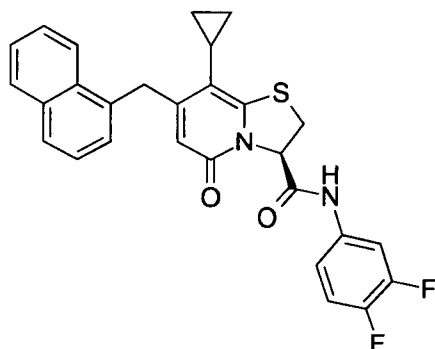
The title compound was prepared by adaptation of the general procedure with **C10** (50 mg, 0.132 mmol), pyridine (42  $\mu$ L, 0.530 mmol), *N,O*-dimethylhydroxylamine hydrochloride (19 mg, 0.199 mmol) and T3P<sup>®</sup> (50% in EtOAc; 158  $\mu$ L, 0.264 mmol). Purification by flash chromatography (SiO<sub>2</sub>, 0-20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) and freeze-drying (H<sub>2</sub>O:MeCN; ~3:1) afforded the product as a white solid (43 mg, 77%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.67-0.81 (m, 2H), 0.84-0.95 (m, 2H), 1.58-1.67 (m, 1H), 3.24 (s, 3H), 3.34 (dd,  $J$  = 2.7, 11.8 Hz, 1H), 3.69 (dd,  $J$  = 9.3, 11.8 Hz, 1H), 3.86 (s, 3H), 4.34 (d,  $J$  = 17.2 Hz, 1H), 4.52 (d,  $J$  = 17.2 Hz, 1H), 5.78 (s, 1H), 5.84 (dd,  $J$  = 2.6, 9.2 Hz, 1H), 7.23-7.27 (m, 1H), 7.38-7.52 (m, 3H), 7.34-7.88 (m, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.5, 8.0, 11.3, 31.1, 32.3, 36.4, 61.3, 61.6, 113.8, 115.1, 124.0, 125.7, 125.8, 126.3, 127.5, 127.7, 128.9, 132.1, 134.0, 134.3, 148.9, 157.1, 161.4, 167.6.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-sulfamoylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 37)**

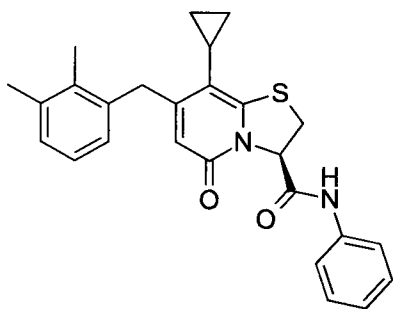
Following the general procedure with **C10** (50 mg, 0.132 mmol) and sulfanilamide (19  $\mu$ L, 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 20-100% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~3:1) the product as a white solid (46 mg, 65%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 0.63-0.73 (m, 1H), 0.73-0.81 (m, 1H), 0.87-0.99 (m, 2H), 1.69-1.78 (m, 1H), 3.57 (dd,  $J$  = 2.1, 12.0 Hz, 1H), 3.89 (dd,  $J$  = 9.2, 11.9

Hz, 1H), 4.42 (d,  $J = 17.4$  Hz, 1H), 4.51 (d,  $J = 17.4$  Hz, 1H), 5.27 (s, 1H), 5.49 (dd,  $J = 2.1, 9.2$  Hz, 1H), 7.27 (br s, 2H), 7.39 (d,  $J = 6.7$  Hz, 1H), 7.49-7.59 (m, 3H), 7.67-7.79 (m, 4H), 7.86-7.92 (m, 2H), 7.95-7.99 (m, 2H), 10.76 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta = 7.3, 7.5, 10.8, 31.5, 35.3, 63.8, 111.8, 113.2, 118.7, 124.1, 125.7, 125.8, 126.4, 126.8, 127.3, 127.6, 128.6, 131.6, 133.5, 134.6, 138.7, 141.5, 149.0, 156.6, 160.0, 166.6$ .



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3,4-difluorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 40)**

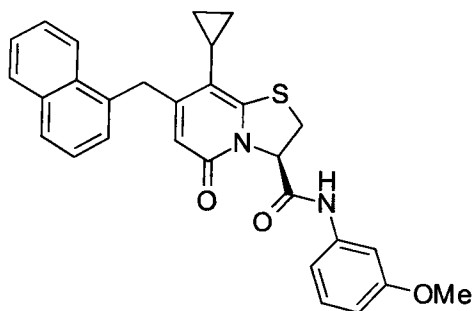
Following the general procedure with **C10** (50 mg, 0.132 mmol) and 3,4-difluoroaniline (19  $\mu\text{L}$ , 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 0-20% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) the product as a white solid (27 mg, 42%).  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta = 0.62$ -0.70 (m, 1H), 0.73-0.81 (m, 1H), 0.86-1.00 (m, 2H), 1.69-1.79 (m, 1H), 3.54 (dd,  $J = 2.3, 12.0$  Hz, 1H), 3.88 (dd,  $J = 9.3, 12.0$ , 1H), 4.41 (d,  $J = 17.3$  Hz, 1H), 4.51 (d,  $J = 17.3$  Hz, 1H), 5.26 (s, 1H), 5.44 (dd,  $J = 2.3, 9.3$  Hz, 1H), 7.22-7.28 (m, 1H), 7.35-7.43 (m, 2H), 7.48-7.58 (m, 3H), 7.69-7.76 (m, 1H), 7.85-7.91 (m, 2H), 7.94-8.00 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta = 7.3, 7.5, 10.8, 31.4, 35.3, 63.7, 107.9, 108.1, 111.8, 113.2, 115.3$ -115.4 (m), 117.5, 117.7, 124.1, 125.7, 125.8, 126.3, 127.3, 127.6, 128.6, 131.6, 133.5, 134.6, 149.0, 156.5, 159.9, 166.3.



**(3R)-7-(2,3-Dimethylbenzyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 42)**

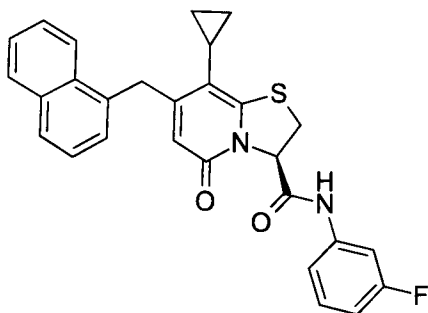
Following the general procedure with **JG 26** (47 mg, 0.132 mmol) and aniline (18  $\mu\text{L}$ , 0.199 mmol) and purification by flash chromatography (SiO<sub>2</sub>, 0-60% EtOAc in heptane) afforded the product as a white solid (30 mg, 53%).  $^1\text{H}$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta = 0.58$ -0.67 (m, 1H), 0.70-0.82 (m, 1H), 0.85-0.96 (m, 1H), 0.97-1.07 (m, 1H), 1.57-1.70 (m, 1H), 2.08 (s, 3H), 2.30 (s, 3H), 3.57 (dd,  $J = 8.1, 11.1$  Hz, 1H), 3.92-4.05 (m, 2H), 4.17 (d,  $J = 11.2$  Hz, 1H), 5.76-5.83 (m, 2H), 6.89-6.94 (m, 1H), 7.03-7.16 (m, 3H), 7.24-7.34 (m, 3H),

7.50-7.69 (m, 2H), 10.34 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.1, 8.1, 11.4, 15.6, 20.8, 29.7, 37.5, 64.7, 114.2, 115.9, 120.0, 124.4, 126.0, 128.3, 129.0, 129.1, 135.3, 135.7, 137.5, 138.1, 148.4, 158.2, 162.8, 164.8.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-methoxyphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 43)**

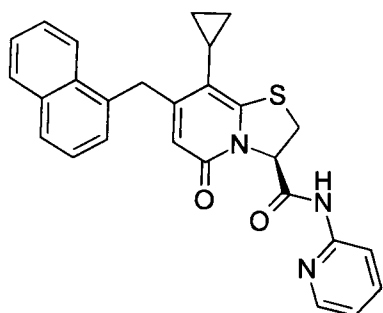
The title compound was prepared by adaptation of the general procedure with **C10** (50 mg, 0.132 mmol), pyridine (43  $\mu\text{L}$ , 0.534 mmol), 3-methoxyaniline (36  $\mu\text{L}$ , 0.320 mmol) and T3P<sup>®</sup> (50% in EtOAc; 237  $\mu\text{L}$ , 0.398 mmol). Purification by flash chromatography ( $\text{SiO}_2$ , 0-80% EtOAc in heptane) afforded the product as a white solid (41 mg, 65%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.65-0.74 (m, 1H), 0.75-0.85 (m, 1H), 0.87-0.97 (m, 1H), 0.99-1.09 (m, 1H), 1.66-1.76 (m, 1H), 3.57 (dd,  $J$  = 8.0, 11.2 Hz, 1H), 3.76 (s, 3H), 4.15 (d,  $J$  = 11.3 Hz, 1H), 4.36 (d,  $J$  = 17.4 Hz, 1H), 4.49 (d,  $J$  = 17.4 Hz, 1H), 5.74-5.81 (m, 2H), 6.62 (dd,  $J$  = 2.3, 8.2 Hz, 1H), 6.95-6.99 (m, 1H), 7.14 (t,  $J$  = 8.2 Hz, 1H), 7.25-7.30 (m, 2H), 7.40-7.51 (m, 3H), 7.72-7.78 (m, 1H), 7.80 (d,  $J$  = 8.2 Hz, 1H), 7.86-7.92 (m, 1H), 10.29 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.0, 8.1, 11.4, 29.5, 36.3, 55.3, 64.6, 105.1, 110.7, 112.2, 114.8, 115.6, 123.8, 125.6, 125.8, 126.4, 127.8, 127.9, 128.9, 129.6, 131.9, 133.6, 134.0, 139.1, 148.4, 157.7, 160.1, 162.6, 164.7.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-fluorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 44)**

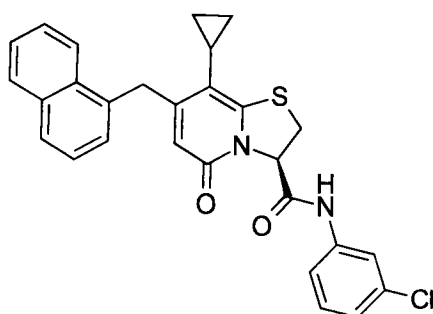
Following the general procedure with **C10** (60 mg, 0.159 mmol) and 3-fluoroaniline (23  $\mu\text{L}$ , 0.199 mmol) with purification by flash chromatography ( $\text{SiO}_2$ , 10-80% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) afforded the product as a white solid (42 mg, 67%).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 0.63-0.71 (m, 1H), 0.73-0.84 (m, 1H), 0.86-1.00 (m, 2H), 1.68-1.78 (m, 1H), 3.55 (dd,  $J$  = 2.2, 11.9 Hz, 1H), 3.88 (dd,  $J$  = 9.3, 11.9, 1H), 4.42 (d,  $J$  = 17.3 Hz, 1H), 4.51 (d,  $J$  = 17.3 Hz, 1H), 5.27 (s, 1H), 5.46 (dd,  $J$  = 2.1, 9.2 Hz, 1H), 7.23-7.27 (m, 1H), 7.31-7.41 (m, 2H), 7.48-7.58 (m, 4H), 7.86-7.92 (m, 2H),

7.94-7.99 (m, 1H), 7.94-7.99 (m, 1H), 10.63 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  = 7.3, 7.5, 10.8, 31.5, 35.3, 63.8, 105.9 (d,  $J_{\text{CF}}$  = 26.5 Hz), 110.1 (d,  $J_{\text{CF}}$  = 21.0 Hz), 111.8, 113.2, 114.9 (d,  $J_{\text{CF}}$  = 2.5 Hz), 124.1, 125.7, 125.8, 126.4, 127.3, 127.6, 128.7, 130.5 (d,  $J_{\text{CF}}$  = 9.0 Hz), 131.6, 133.5, 134.6, 140.4 (d,  $J_{\text{CF}}$  = 11.5 Hz), 149.1, 156.5, 160.0, 162.1 (d,  $J_{\text{CF}}$  = 241.6 Hz), 166.5.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(pyridin-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 45)**

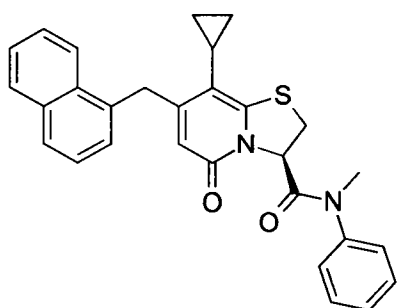
The carboxylic acid **C10** (60 mg, 0.159 mmol), TBTU (56 mg, 0.175 mmol) and *N,N*-diisopropylethylamine (60  $\mu\text{L}$ , 0.342 mmol) were stirred in  $\text{CH}_2\text{Cl}_2$  (1.5 mL) for 10 min at rt, then 2-aminopyridine (20 mg, 0.207 mmol) was added and the reaction mixture stirred at rt for 18 h. The volatiles were removed under reduced pressure, and the residue was dissolved in EtOAc (15 mL) and washed successively with aqueous  $\text{Na}_2\text{CO}_3$  solution (5% w/v, 3 $\times$ ),  $\text{H}_2\text{O}$ , HCl (0.125 M aq.),  $\text{H}_2\text{O}$  and brine (15 mL each), dried  $\text{Na}_2\text{SO}_4$  and the solvent removed under reduced pressure. Purification by flash chromatography ( $\text{SiO}_2$ , 10-100% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ;  $\sim 3:1$ ) afforded the product as a white solid (39.1 mg, 65%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) = 0.67-0.81 (m, 2H), 0.88-1.05 (m, 2H), 1.64-1.74 (m, 1H), 3.59 (dd,  $J$  = 8.2, 11.5 Hz, 1H), 4.04 (d,  $J$  = 11.5 Hz, 1H), 4.34 (d,  $J$  = 17.4 Hz, 1H), 4.50 (d,  $J$  = 17.4 Hz, 1H), 5.79-5.84 (m, 2H), 7.24-7.30 (m, 1H), 7.39-7.50 (m, 3H), 7.61-7.68 (m, 1H), 7.73-7.81 (m, 2H), 7.85-7.90 (m, 1H), 8.04-8.08 (m, 1H), 8.24-8.27 (m, 1H), 10.85 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.2, 8.2, 11.5, 30.0, 36.4, 64.7, 114.6, 115.33, 115.35, 120.0, 123.9, 125.7, 125.9, 126.4, 127.9, 128.0, 129.0, 132.0, 133.8, 134.1, 138.7, 147.6, 148.2, 151.0, 157.6, 162.4, 165.8.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-chlorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 46)**

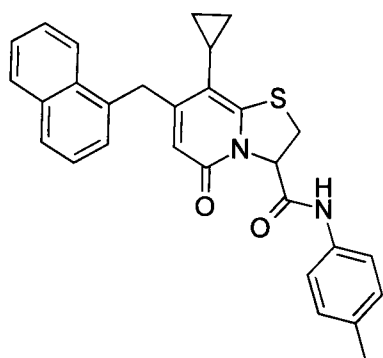
Following the general procedure with **C10** (60 mg, 0.159 mmol) and 3-chloroaniline (25  $\mu\text{L}$ , 0.238 mmol), purification by flash chromatography ( $\text{SiO}_2$ , 10-75% EtOAc in heptane)

and freeze-drying afforded the product as a white solid (28 mg, 43%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.66-0.74 (m, 1H), 0.76-0.84 (m, 1H), 0.88-0.97 (m, 1H), 1.00-1.09 (m, 1H), 1.64-1.76 (m, 1H), 3.58 (dd,  $J$  = 8.0, 11.3 Hz, 1H), 4.13 (dd,  $J$  = 2.0, 11.3 Hz, 1H), 4.36 (d,  $J$  = 17.4 Hz, 1H), 4.50 (d,  $J$  = 17.4 Hz, 1H), 5.75-5.81 (m, 2H), 7.00-7.05 (m, 1H), 7.16 (t,  $J$  = 8.2 Hz, 1H), 7.25-7.35 (m, 2H), 7.40-7.52 (m, 3H), 7.67-7.70 (m, 1H), 7.72-7.76 (m, 1H), 7.78-7.83 (m, 1H), 7.86-7.91 (m, 1H), 10.46 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.2, 8.3, 11.5, 29.6, 36.4, 64.7, 114.8, 116.0, 118.1, 120.2, 123.9, 124.5, 125.7, 126.0, 126.5, 128.0, 128.1, 129.1, 130.0, 132.0, 133.7, 134.2, 134.7, 139.1, 148.7, 158.1, 162.7.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 47)**

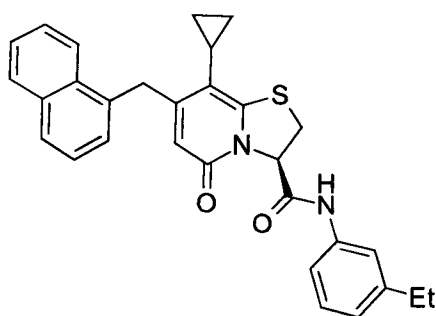
Following the general procedure with **C10** (50 mg, 0.132 mmol) and *N*-methylaniline (22  $\mu\text{L}$ , 0.199 mmol) afforded after purification by flash chromatography ( $\text{SiO}_2$ , 0-80% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) the product as a white solid (42 mg, 68%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.66-0.81 (m, 2H), 0.81-0.95 (m, 2H), 1.54-1.63 (m, 1H), 3.21-3.38 (m, 5H), 4.31 (d,  $J$  = 17.1 Hz, 1H), 4.47 (d,  $J$  = 17.1 Hz, 1H), 5.39 (dd,  $J$  = 5.0, 8.9 Hz, 1H), 5.67 (s, 1H), 7.23 (d,  $J$  = 6.9 Hz, 1H), 7.33-7.49 (m, 8H), 7.73-7.81 (m, 2H), 7.82-7.87 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.5, 8.1, 11.3, 31.0, 36.3, 38.0, 61.9, 113.0, 115.3, 124.0, 125.7, 125.8, 126.3, 127.5, 127.6, 127.9, 128.6, 128.9, 130.3, 132.1, 134.0, 134.3, 142.9, 148.7, 156.7, 161.3, 168.1.



**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-methylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 49)**

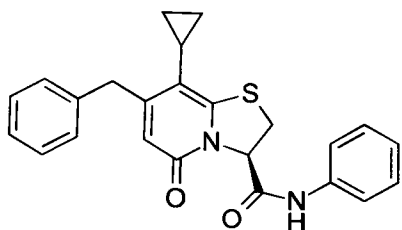
Following the general procedure with **C10** (50 mg, 0.132 mmol) and 4-methylaniline (21 mg, 0.199 mmol), purification by flash chromatography ( $\text{SiO}_2$ , 0-65% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) afforded the racemic product as a white solid (49 mg, 80%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.65-0.73 (m, 1H), 0.76-0.84 (m, 1H), 0.86-

0.96 (m, 1H), 0.99-1.08 (m, 1H), 1.65-1.74 (m, 1H), 2.28 (s, 3H), 3.57 (dd,  $J = 8.0, 11.2$  Hz, 1H), 4.15 (d,  $J = 11.2$  Hz, 1H), 4.36 (d,  $J = 17.3$  Hz, 1H), 4.49 (d,  $J = 17.3$  Hz, 1H), 5.77-5.81 (m, 2H), 7.06 (d,  $J = 8.2$  Hz, 1H), 7.25-7.28 (m, 1H), 7.38-7.51 (m, 5H), 7.73-7.77 (m, 2H), 7.80 (d,  $J = 8.2$  Hz, 1H), 7.86-7.91 (m, 1H), 10.20 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 7.1, 8.2, 11.5, 21.0, 29.8, 36.4, 64.7, 114.8, 115.8, 120.0, 123.9, 125.7, 125.9, 126.5, 127.9, 128.0, 129.0, 129.5, 132.0, 133.7, 134.0, 134.1, 135.5, 148.8, 157.8, 162.6, 164.6$ .



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-ethylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 51)**

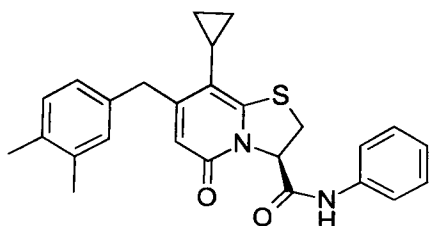
Following the general procedure with **C10** (50 mg, 0.132 mmol) and 3-ethylaniline (25  $\mu\text{L}$ , 0.199 mmol), purification by flash chromatography ( $\text{SiO}_2$ , 0-60% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ;  $\sim 3:1$ ) afforded the product as a white solid (43 mg, 68%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 0.65$ -0.73 (m, 1H), 0.75-0.83 (m, 1H), 0.87-0.96 (m, 1H), 0.99-1.08 (m, 1H), 1.18 (t,  $J = 7.6$  Hz, 3H), 1.65-1.74 (m, 1H), 2.58 (q,  $J = 7.6$  Hz, 2H), 3.58 (dd,  $J = 8.0, 11.3$  Hz, 1H), 4.14 (d,  $J = 11.3$  Hz, 1H), 4.36 (d,  $J = 17.4$  Hz, 1H), 4.49 (d,  $J = 17.4$  Hz, 1H), 5.77-5.84 (m, 2H), 6.90 (d,  $J = 7.6$  Hz, 1H), 7.17 (t,  $J = 7.8$  Hz, 1H), 7.25-7.29 (m, 1H), 7.32-7.51 (m, 5H), 7.72-7.77 (m, 1H), 7.78-7.83 (m, 1H), 7.86-7.91 (m, 1H), 10.27 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 7.1, 8.2, 11.5, 15.7, 29.0, 29.8, 36.4, 64.8, 114.7, 116.0, 117.3, 119.5, 123.9, 124.0, 125.7, 125.9, 126.5, 127.9, 128.0, 128.9, 129.0, 132.0, 133.7, 134.1, 138.0, 145.4, 148.9, 157.9, 162.6, 164.7$ .



**(3R)-7-(Benzyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 60)**

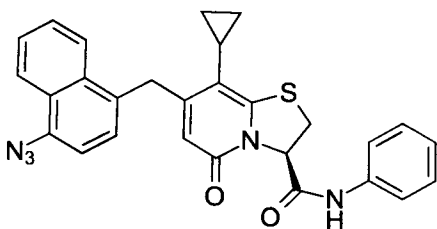
The title compound was prepared by adaptation of the general procedure with **KSK 49** (41 mg, 0.125 mmol), pyridine (30  $\mu\text{L}$ , 0.377 mmol), aniline (18  $\mu\text{L}$ , 0.199 mmol) and T3P<sup>®</sup> (50% in EtOAc; 222  $\mu\text{L}$ , 0.377 mmol). Purification by flash chromatography ( $\text{SiO}_2$ , 0-75% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ;  $\sim 3:1$ ) afforded the product as a white solid (18 mg, 34%).  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta = 0.55$ -0.76 (m, 2H), 0.81-1.04 (m, 2H), 1.40-1.50 (m, 1H), 3.53-3.61 (m, 1H), 3.95 (d,  $J = 16.0$  Hz, 1H), 4.05 (d,  $J = 16.0$

Hz, 1H), 4.16 (d,  $J = 11.0$  Hz, 1H), 5.82-5.87 (m, 1H), 6.11 (s, 1H), 7.05-7.12 (m, 1H), 7.15-7.22 (m, 2H), 7.23-7.35 (m, 5H), 7.53-7.60 (m, 2H), 10.38 (br s, 1H).  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta = 7.3, 8.4, 11.6, 29.7, 39.3, 64.7, 115.2, 116.0, 120.1, 124.4, 126.9, 128.9, 129.0, 129.3, 137.8, 138.1, 149.0, 158.0, 162.7, 164.8$ .



**(3R)-7-(3,4-Dimethylbenzyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 66)**

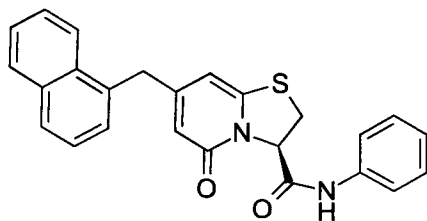
The title compound was prepared by adaptation of the general procedure with **JG 63** (51 mg, 0.144 mmol), pyridine (35  $\mu\text{L}$ , 0.430 mmol), aniline (23  $\mu\text{L}$ , 0.251 mmol) and T3P<sup>®</sup> (50% in EtOAc; 171  $\mu\text{L}$ , 0.287 mmol) in anhydrous MeCN (1.5 mL). Purification by flash chromatography ( $\text{SiO}_2$ , 0-75% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) afforded the product as a white solid (44 mg, 71%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 0.54-0.62$  (m, 1H), 0.66-0.75 (m, 1H), 0.81-0.91 (m, 1H), 0.94-1.03 (m, 1H), 1.43-1.53 (m, 1H), 2.23 (s, 3H), 2.24 (s, 3H), 3.55 (dd,  $J = 8.0, 11.2$  Hz, 1H), 3.86 (d,  $J = 16.0$  Hz, 1H), 3.97 (d,  $J = 16.0$  Hz, 1H), 4.13 (d,  $J = 11.2$  Hz, 1H), 5.83 (d,  $J = 7.9$  Hz, 1H), 6.09 (s, 1H), 6.85-6.91 (m, 1H), 6.93 (s, 1H), 7.04-7.10 (m, 2H), 7.25-7.30 (m, 2H), 7.53-7.57 (m, 2H), 10.39 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 7.3, 8.4, 11.6, 19.5, 19.9, 29.7, 38.8, 64.8, 115.0, 116.2, 120.0, 124.4, 126.7, 129.0, 130.0, 130.6, 135.06, 135.11, 137.0, 138.1, 149.0, 158.6, 162.7, 164.8$ .



**(3R)-7-(4-Azidonaphthalen-1-yl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 67)**

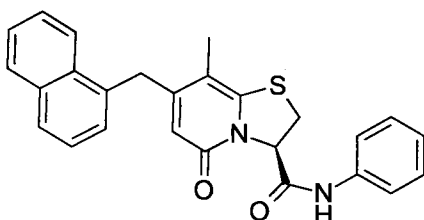
The title compound was prepared by adaptation of the general procedure with (3R)-7-(4-azidonaphthalen-1-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (43 mg, 0.103 mmol), pyridine (25  $\mu\text{L}$ , 0.308 mmol), aniline (14  $\mu\text{L}$ , 0.153 mmol) and T3P<sup>®</sup> (50% in EtOAc; 122  $\mu\text{L}$ , 0.205 mmol) in THF. Purification by flash chromatography ( $\text{SiO}_2$ , 0-70% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) afforded the product as a pale orange solid (20 mg, 40%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 0.64-0.72$  (m, 1H), 0.75-0.84 (m, 1H), 0.86-0.96 (m, 1H), 0.98-1.08 (m, 1H), 1.63-1.74 (m, 1H), 3.57 (dd,  $J = 8.0, 11.2$  Hz, 1H), 4.17 (d,  $J = 11.2$  Hz, 1H), 4.32 (d,  $J = 17.6$  Hz, 1H), 4.44 (d,  $J = 17.6$  Hz, 1H), 5.75 (s, 1H), 5.78 (d,  $J = 7.9$  Hz, 1H), 7.03-7.09 (m, 1H), 7.20-7.29 (m, 4H), 7.48-7.53 (m, 4H), 7.68-7.72 (m, 1H), 8.14-8.19 (m, 1H),

10.26 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.2, 8.2, 11.5, 29.8, 36.1, 64.8, 113.7, 114.6, 115.9, 120.0, 123.6, 123.9, 124.4, 126.2, 127.0, 127.5, 127.7, 129.0, 130.5, 132.8, 136.3, 138.0, 149.1, 157.8, 162.5, 164.7.



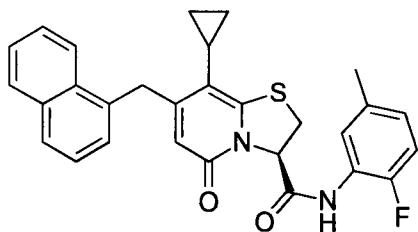
**(3R)-7-(Naphthalen-1-ylmethyl)-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 68)**

The title compound was prepared by adaptation of the general procedure with **JG 65** (38 mg, 0.113 mmol), pyridine (36  $\mu\text{L}$ , 0.449 mmol), aniline (31  $\mu\text{L}$ , 0.337 mmol) and T3P<sup>®</sup> (50% in EtOAc; 206  $\mu\text{L}$ , 0.346 mmol) in anhydrous MeCN (1.1 mL). Purification by flash chromatography ( $\text{SiO}_2$ , 0-60% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) afforded the product as a white solid (16 mg, 34%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.60 (dd,  $J$  = 8.0, 11.0 Hz, 1H), 4.12-4.24 (m, 3H), 5.74 (d,  $J$  = 7.9 Hz, 1H), 6.11 (s, 1H), 6.16 (s, 1H), 7.05-7.11 (m, 1H), 7.24-7.37 (m, 3H), 7.40-7.57 (m, 5H), 7.77-7.91 (m, 3H), 10.25 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 30.0, 38.9, 64.6, 103.9, 113.8, 120.1, 123.9, 124.5, 125.7, 126.1, 126.7, 128.1, 128.3, 129.0, 129.0, 132.0, 133.2, 134.1, 138.0, 148.6, 156.4, 163.5, 164.5.



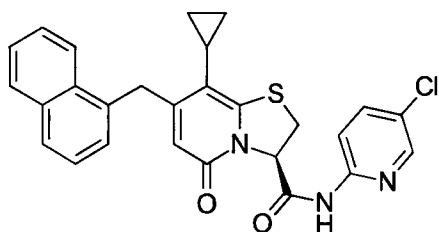
**(3R)-7-(Naphthalen-1-ylmethyl)-8-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 69)**

The title compound was prepared by adaptation of the general procedure with lithium carboxylate **EC 030** (47 mg, 0.132 mmol), pyridine (32  $\mu\text{L}$ , 0.397 mmol), aniline (21  $\mu\text{L}$ , 0.230 mmol) and T3P<sup>®</sup> (50% in EtOAc; 158  $\mu\text{L}$ , 0.264 mmol) in anhydrous MeCN (1.32 mL). Purification by flash chromatography ( $\text{SiO}_2$ , 0-60% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) gave the product as a white solid (22 mg, 39%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 2.09 (s, 3H), 3.63 (dd,  $J$  = 7.9, 11.2 Hz, 1H), 4.13-4.26 (m, 3H), 5.83 (d,  $J$  = 7.8 Hz, 1H), 5.88 (s, 1H), 7.03-7.09 (m, 1H), 7.18-7.30 (m, 3H), 7.39-7.57 (m, 5H), 7.71-7.83 (m, 2H), 7.86-7.92 (m, 1H), 10.35 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 16.0, 29.9, 36.4, 65.4, 111.3, 115.3, 120.1, 123.6, 124.4, 125.7, 126.0, 126.5, 127.4, 128.1, 128.98, 129.04, 131.9, 133.0, 134.1, 138.0, 146.2, 155.6, 162.6, 164.8.



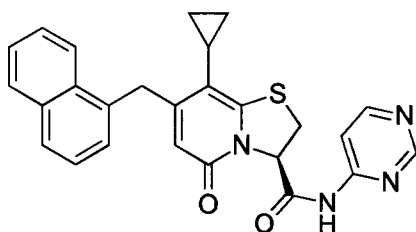
**(3R)-7-(Naphthalen-1-ylmethyl)-N-(2-fluoro-5-methylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 70)**

The title compound was prepared by following the general procedure with **C10** (50 mg, 0.132 mmol) and 2-fluoro-5-methylaniline (25 mg, 0.199 mmol). Purification by flash chromatography (SiO<sub>2</sub>, 0-55% EtOAc in heptane) and HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.005% formic acid each, 30-100% for 25 min; *t<sub>R</sub>* = 24.06 min) with subsequent freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as a white solid (32 mg, 50%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.65-0.73 (m, 1H), 0.76-0.84 (m, 1H), 0.87-0.96 (m, 1H), 0.99-1.07 (m, 1H), 1.65-1.74 (m, 1H), 2.28 (s, 3H), 3.59 (dd, *J* = 7.9, 11.2 Hz, 1H), 4.14 (d, *J* = 11.2 Hz, 1H), 4.34 (d, *J* = 17.3 Hz, 1H), 4.50 (d, *J* = 17.3 Hz, 1H), 5.80 (d, *J* = 7.8 Hz, 1H), 5.83 (s, 1H), 6.77-6.83 (m, 1H), 6.87-6.99 (m, 1H), 7.25-7.28 (m, 1H), 7.40-7.50 (m, 3H), 7.73-7.81 (m, 2H), 7.85-7.90 (m, 1H), 8.09 (dd, *J* = 1.4, 7.4 Hz, 1H), 10.27 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.1, 8.2, 11.5, 21.2, 29.7, 36.4, 64.4, 114.7 (d, *J<sub>CF</sub>* = 19.0 Hz), 115.2, 115.6, 122.3, 123.9, 125.1 (d, *J<sub>CF</sub>* = 7.4 Hz), 125.7, 125.9 (d, *J<sub>CF</sub>* = 11.0 Hz), 125.9, 126.4, 127.9, 128.0, 129.0, 132.0, 133.8, 134.0 (d, *J<sub>CF</sub>* = 3.7 Hz), 134.2, 148.2, 151.1 (d, *J<sub>CF</sub>* = 243.4 Hz), 157.7, 162.5, 165.2.



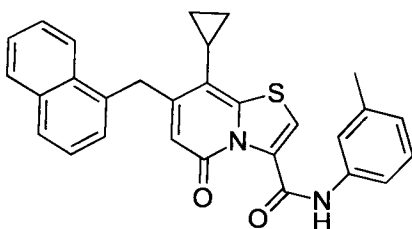
**(3R)-7-(Naphthalen-1-ylmethyl)-N-(5-chloropyridin-2-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 71)**

The title compound was prepared by following the general procedure with **C10** (50 mg, 0.132 mmol) and 2-amino-5-chloropyridine (30 mg, 0.232 mmol). Purification by flash chromatography (SiO<sub>2</sub>, 15-65% EtOAc in heptane) and HPLC (mobile phase: MeCN/H<sub>2</sub>O, each with 0.005% formic acid, 30-100% for 25 min; *t<sub>R</sub>* = 24.00 min) with subsequent freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as a white solid (47 mg, 73%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.66-0.82 (m, 2H), 0.87-0.97 (m, 1H), 0.98-1.07 (m, 1H), 1.64-1.74 (m, 1H), 3.59 (dd, *J* = 8.0, 11.2 Hz, 1H), 4.08 (d, *J* = 11.4 Hz, 1H), 4.34 (d, *J* = 17.4 Hz, 1H), 4.50 (d, *J* = 17.4 Hz, 1H), 5.80 (d, *J* = 7.8 Hz, 1H), 5.84 (s, 1H), 7.23-7.28 (m, 1H), 7.39-7.51 (m, 3H), 7.60 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.72-7.76 (m, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.86-7.91 (m, 1H), 8.08 (d, *J* = 8.9 Hz, 1H), 8.18-8.20 (m, 1H), 10.74 (br s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.2, 8.2, 11.5, 29.7, 36.4, 64.6, 115.1, 115.4, 115.6, 123.8, 125.7, 125.9, 126.5, 127.1, 127.9, 128.0, 129.1, 132.0, 133.7, 134.1, 137.9, 146.9, 148.2, 149.6, 157.8, 162.5, 165.5.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(pyrimidin-4-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 79).**

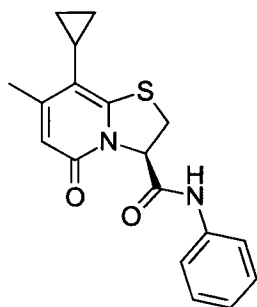
The carboxylic acid **C10** (75 mg, 0.199 mmol) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (1 mL) under an inert atmosphere and cooled to 0 °C. Oxalyl chloride (25  $\mu\text{L}$ , 0.298 mmol) was added and the reaction mixture stirred for 1 h. A solution of 4-aminopyrimidine (38 mg, 0.397 mmol) and pyridine (64  $\mu\text{L}$ , 0.795 mmol) in anhydrous THF (2 mL) was then added dropwise and the reaction mixture allowed to attain rt and stirred for 25 h. The reaction mixture was quenched with  $\text{H}_2\text{O}$  (10 mL), extracted with EtOAc ( $3 \times 15$  mL), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under reduced pressure. Purification by HPLC (mobile phase: MeCN/ $\text{H}_2\text{O}$ , with 0.005% formic acid each, 25-100% for 45 min;  $t_R$  = 30.50 min) with subsequent freeze-drying ( $\text{H}_2\text{O}$ :MeCN; ~ 3:1) afforded the product as a white solid (19 mg, 21%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.66-0.82 (m, 2H), 0.88-1.10 (m, 2H), 1.66-1.75 (m, 1H), 3.60 (dd,  $J$  = 8.0, 11.5 Hz, 1H), 4.06 (d,  $J$  = 11.5 Hz, 1H), 4.34 (d,  $J$  = 17.5 Hz, 1H), 4.50 (d,  $J$  = 17.5 Hz, 1H), 5.81 (dd,  $J$  = 7.8, 11.0, Hz, 1H), 5.85 (s, 1H), 7.24-7.28 (m, 1H), 7.39-7.51 (m, 3H), 7.80 (d,  $J$  = 8.2 Hz, 1H), 7.71-7.75 (m, 1H), 7.80 (d,  $J$  = 8.2 Hz, 1H), 7.86-7.90 (m, 1H), 8.06 (dd,  $J$  = 1.0, 5.8 Hz, 1H), 8.59 (d,  $J$  = 5.8 Hz, 1H), 11.03 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.2, 8.2, 11.5, 29.4, 36.4, 64.6, 110.8, 115.4, 115.9, 123.8, 125.7, 126.0, 126.5, 127.9, 128.1, 129.1, 132.0, 133.6, 134.2, 148.0, 157.3, 158.1, 158.1, 158.6, 162.6, 166.5.



**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-(3-methylphenyl)-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 91)**

The carboxylic acid **EC 104** (25 mg, 0.057 mmol) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (1 mL) under an inert atmosphere and cooled to 0 °C. Oxalyl chloride (15  $\mu\text{L}$ , 0.172 mmol) was added and the reaction mixture stirred at rt for 2 h. The volatiles were removed under reduced pressure, the residue dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (2 mL), and 3-methylaniline (9  $\mu\text{L}$ , 0.086 mmol) and  $\text{NEt}_3$  (24  $\mu\text{L}$ , 0.172 mmol) added. The reaction was stirred at rt for 18 h, diluted with  $\text{CH}_2\text{Cl}_2$  (15 mL), washed successively with HCl (1 M aq.),  $\text{H}_2\text{O}$  and brine (10 mL each) and dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under reduced pressure. Purification by flash chromatography ( $\text{SiO}_2$ ; 0-70% EtOAc in heptane) and freeze-drying afforded the product as a yellow solid (16 mg, 59%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.81-0.88 (m, 2H), 1.14-1.21 (m, 2H), 1.86-1.93 (m, 1H), 2.20 (s, 3H), 4.59 (s, 2H), 6.05

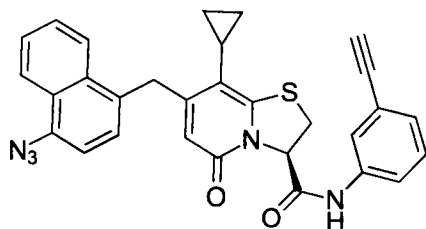
(s, 1H), 6.89 (d,  $J = 7.5$  Hz, 1H), 7.17 (t,  $J = 7.8$  Hz, 1H), 7.29 (d,  $J = 6.9$  Hz, 1H), 7.41-7.54 (m, 5H), 7.76-7.84 (m, 2H), 7.87-7.90 (m, 1H), 8.19-8.22 (m, 1H), 13.42 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 8.5, 11.2, 21.5, 36.1, 112.8, 115.2, 117.7, 121.2, 123.7, 125.3, 125.4, 125.7, 126.0, 126.5, 127.9, 128.1, 128.8, 129.1, 132.0, 133.8, 134.2, 138.3, 138.8, 139.2, 151.1, 154.0, 155.4, 161.5$ .



SUBSTITUTE SHEET (Rule 26)

**(3R)-8-cyclopropyl-7-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 93)**

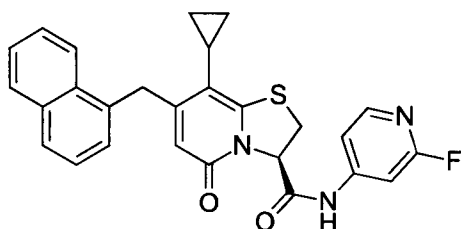
The title compound was prepared by adaptation of the general procedure with **JG 89** (38 mg, 0.150 mmol) and aniline (24  $\mu\text{L}$ , 0.263 mmol) in anhydrous MeCN (1.5 mL). Purification by flash chromatography ( $\text{SiO}_2$ , 10-100% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ;  $\sim 3:1$ ) afforded the product as a white solid (38 mg, 77%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 0.48\text{-}0.55$  (m, 1H), 0.60-0.69 (m, 1H), 0.80-0.91 (m, 1H), 0.92-1.01 (m, 1H), 1.51-1.62 (m, 1H), 2.28 (s, 3H), 3.57 (dd,  $J = 8.0, 11.3$  Hz, 1H), 4.12 (d,  $J = 11.3$  Hz, 1H), 5.87 (dd,  $J = 2.5, 7.9$  Hz, 1H), 6.24 (s, 1H), 7.04-7.09 (m, 1H), 7.24-7.30 (m, 2H), 7.54-7.58 (m, 2H), 10.45 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 7.0, 7.8, 11.5, 20.3, 29.7, 29.8, 64.77, 64.79, 114.60, 114.62, 116.5, 116.6, 119.9, 120.0, 124.4, 129.0, 138.1, 148.6, 148.7, 155.81, 155.84, 162.5, 164.9$ .



**(3R)-7-((4-Azidonaphthalen-1-yl)methyl)-N-(3-ethynylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 95)**

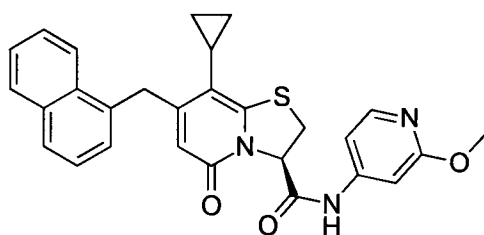
The title compound was prepared by adaptation of the general procedure with (3R)-7-(4-azidonaphthalen-1-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (41 mg, 0.098 mmol) and 3-ethynylaniline (18  $\mu\text{L}$ , 0.172 mmol) in anhydrous MeCN (1 mL). Purification by flash chromatography ( $\text{SiO}_2$ , 5-100% EtOAc in heptane) and HPLC (mobile phase: MeCN/ $\text{H}_2\text{O}$  with 0.005% formic acid each, 30-100% for 35 min;  $t_R = 32.67$  min) with subsequent freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ;  $\sim 3:1$ ) afforded the product as a pale yellow solid (44 mg, 87%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 0.65\text{-}0.73$  (m, 1H), 0.75-0.84 (m, 1H), 0.88-0.98 (m, 1H), 0.99-1.09 (m, 1H), 1.65-1.74 (m, 1H), 3.02 (s, 1H), 3.57 (dd,  $J = 8.0, 11.3$  Hz, 1H), 4.15 (d,  $J = 11.3$  Hz, 1H), 4.33 (d,  $J = 17.5$  Hz, 1H), 4.45 (d,  $J = 17.5$  Hz, 1H), 5.74-5.79 (m, 1H), 7.16-7.30 (m, 4H), 7.46-7.54 (m,

3H), 7.67-7.73 (m, 2H), 8.14-8.20 (m, 1H), 10.35 (br s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.1, 8.2, 11.5, 29.5, 36.1, 64.6, 77.5, 83.2, 113.7, 114.8, 115.7, 120.5, 122.9, 123.5, 123.6, 123.9, 126.2, 127.0, 127.5, 127.7, 128.1, 129.0, 130.5, 132.8, 136.3, 138.0, 148.7, 157.7, 162.6, 164.9.



**(3R)-7-(Naphthalen-1-ylmethyl)-N-(2-fluoropyridin-4-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 98)**

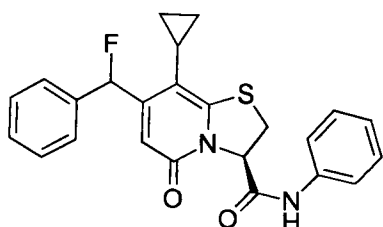
A solution of carboxylic acid **C10** (50 mg, 0.132 mmol), 4-amino-2-fluoropyridine (22 mg, 0.199 mmol) and *N,N*-diisopropylethylamine (46  $\mu\text{L}$ , 0.265 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1.32 mL) were cooled to 0 °C under an inert atmosphere. HATU (76 mg, 0.199 mmol) was added, and the reaction was allowed to warm to rt and stirred for 23 h. The reaction was quenched with HCl (0.25 M aq., 5 mL), extracted EtOAc (4  $\times$  10 mL), washed successively with  $\text{H}_2\text{O}$  and brine (25 mL each), dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under reduced pressure. Purification by HPLC (mobile phase: MeCN/ $\text{H}_2\text{O}$ , each with 0.005% formic acid, 25-100% for 35 min;  $t_R$  = 26.22 min) and subsequent freeze-drying ( $\text{H}_2\text{O}$ :MeCN;  $\sim$  3:1) afforded the product as a white solid (14 mg, 23%).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 0.63-0.71 (m, 1H), 0.74-0.82 (m, 1H), 0.87-1.00 (m, 2H), 1.70-1.80 (m, 1H), 3.60 (dd,  $J$  = 2.2, 12.0 Hz, 1H), 3.91 (dd,  $J$  = 9.4, 12.0 Hz, 1H), 4.42 (d,  $J$  = 17.3 Hz, 1H), 4.52 (d,  $J$  = 17.3 Hz, 1H), 5.28 (s, 1H), 5.48 (dd,  $J$  = 2.2, 9.3 Hz, 1H), 7.31-7.37 (m, 1H), 7.40 (d,  $J$  = 6.9 Hz, 1H), 7.49-7.58 (m, 3H), 7.86-7.92 (m, 2H), 7.95-8.00 (m, 1H), 8.12 (d,  $J$  = 5.6 Hz, 1H), 11.17 (br s, 1H).  $^{19}\text{F}$  NMR (376 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = -67.5.  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 7.3, 7.5, 10.8, 31.1, 35.3, 63.9, 97.8 (d,  $J_{CF}$  = 43.1 Hz), 111.9, 113.2, 124.0, 125.7, 125.8, 126.3, 127.3, 127.6, 128.6, 131.5, 133.5, 134.5, 148.1 (d,  $J_{CF}$  = 18.2 Hz), 148.9, 149.8 (d,  $J_{CF}$  = 11.8 Hz), 156.7, 159.9, 163.9 (d,  $J_{CF}$  = 231.6 Hz), 167.6.



**(3R)-7-(Naphthalen-1-ylmethyl)-N-(2-methoxypyridin-4-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 100)**

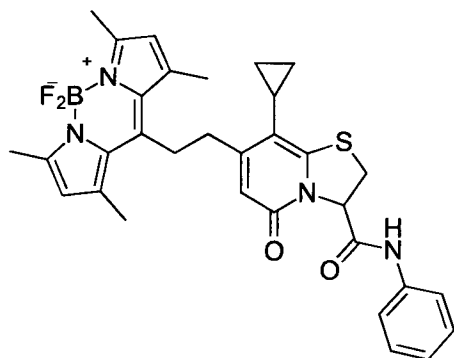
A solution of carboxylic acid **C10** (50 mg, 0.132 mmol), 4-amino-2-methoxypyridine (25 mg, 0.199 mmol) and *N,N*-diisopropylethylamine (46  $\mu\text{L}$ , 0.265 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (1.32 mL) were cooled to 0 °C under an inert atmosphere. HATU (76 mg, 0.199 mmol) was added, and the reaction was allowed to warm to rt and stirred for 23 h. The reaction was quenched with HCl (0.25 M aq., 5 mL), extracted EtOAc (3  $\times$  10 mL),

washed successively with H<sub>2</sub>O and brine (25 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. Purification by HPLC (mobile phase: MeCN/H<sub>2</sub>O, each with 0.005% formic acid, 20-100% for 35 min;  $t_R$  = 27.34 min) and subsequent freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as a white solid (31 mg, 49%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 0.62-0.70 (m, 1H), 0.74-0.82 (m, 1H), 0.86-0.99 (m, 2H), 1.69-1.78 (m, 1H), 3.55 (dd,  $J$  = 2.1, 12.0 Hz, 1H), 3.80 (s, 3H), 3.88 (dd,  $J$  = 9.3, 12.0 Hz, 1H), 4.41 (d,  $J$  = 17.4 Hz, 1H), 4.51 (d,  $J$  = 17.3 Hz, 1H), 5.26 (s, 1H), 5.47 (dd,  $J$  = 2.0, 9.2 Hz, 1H), 7.03-7.06 (m, 1H), 7.39 (d,  $J$  = 6.9 Hz, 1H), 7.48-7.57 (m, 3H), 7.86-7.92 (m, 2H), 7.94-7.99 (m, 1H), 8.01-8.05 (m, 1H), 10.87 (br s, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  = 7.3, 7.5, 10.8, 31.3, 35.3, 53.2, 63.8, 98.4, 108.0, 111.8, 113.2, 124.0, 125.7, 125.8, 126.3, 127.3, 127.6, 128.6, 131.5, 133.5, 134.5, 147.5, 147.6, 149.0, 156.6, 159.9, 164.6, 167.2.



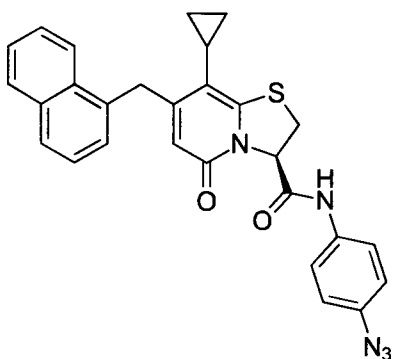
**(3R)-7-(Fluoro(phenyl)methyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (JG 102)**

The title compound was prepared by adaptation of the general procedure with **JG 92** (41 mg, 0.119 mmol) and aniline (19  $\mu$ L, 0.207 mmol) in anhydrous MeCN (1.5 mL). Purification by flash chromatography (SiO<sub>2</sub>, 10-100% EtOAc in heptane) and HPLC (mobile phase: MeCN/H<sub>2</sub>O, each with 0.005% formic acid, 30-100% for 30 min;  $t_R$  = 20.27 min) with subsequent freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as a white solid (25 mg, 50%) and a mixture of diastereomers (~3:4 as ascertained by <sup>19</sup>F NMR). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.48-0.97 (m, 4H), 0.97-1.31 (m, 1H), 3.53-3.63 (m, 1H), 4.13-4.20 (m, 1H), 5.83-5.92 (m, 1H), 6.58-6.80 (m, 2H), 7.05-7.13 (m, 1H), 7.27-7.33 (m, 2H), 7.34-7.42 (m, 5H), 7.54-7.61 (m, 2H), 10.29 (br s, 1H). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) = -165.13, -164.52. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.25, 8.26, 8.45, 8.71, 10.95, 11.15, 29.62, 29.76, 64.85, 64.89, 89.53, 89.78, 91.29, 91.52, 110.99, 111.13, 112.45, 112.57, 112.76, 112.80, 113.10, 113.15, 120.11, 120.14, 124.57, 128.11, 128.16, 128.38, 128.42, 128.95, 128.96, 129.00, 129.02, 129.09, 129.69, 129.72, 129.82, 129.85, 136.36, 136.55, 137.95, 137.99, 149.95, 150.01, 154.96, 155.16, 155.31, 155.53, 162.67, 162.76, 164.51, 164.56.



**(3R)-8-cyclopropyl-7-(2-(1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene-8-yl)ethyl)-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 170)**

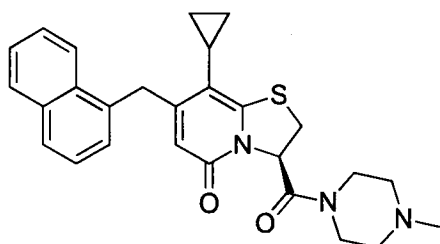
Compound EC 364 (7 mg, 0.014 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (0.41 mL) and cooled to 0 °C. Oxalyl chloride (8 µL, 0.042 mmol) was added stirred for 1 h at rt. After evaporation of the solvent, the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, followed by the addition of NEt<sub>3</sub> (2 µL, 0.028 mmol) and aniline (6 µL, 0.064 mmol). The solution was stirred for 4 h, and then the solvent was removed under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>, 0-100% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as a reddish brown solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.40-0.48 (m, 1H), 0.60-0.68 (m, 1H), 0.81-1.00 (m, 1H), 1.44-1.52 (m, 1H), 2.34 (s, 6H), 2.54 (s, 6H), 2.85-3.09 (m, 2H), 3.23-3.34 (m, 2H), 3.57 (dd, *J* = 8.0, 11.2 Hz, 1H), 4.19 (d, *J* = 11.2 Hz, 1H), 5.85 (d, *J* = 7.9 Hz, 1H), 6.07 (s, 2H), 6.35 (s, 1H), 7.07-7.12 (m, 1H), 7.29-7.34 (m, 2H), 7.56-7.60 (m, 2H), 10.29 (br s, 1H).



**(3R)-N-(4-Azidophenyl)-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 195)**

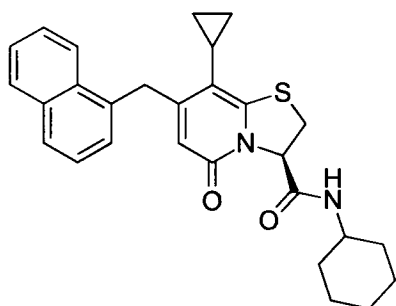
The title compound was prepared by adaptation of the general procedure with C10 (50 mg, 0.132 mmol), pyridine (53 µL, 0.657 mmol) and 4-azidoaniline hydrochloride (34 mg, 0.198 mmol) and T3P® (50% in EtOAc; 155 µL, 0.263 mmol). Purification by flash chromatography (SiO<sub>2</sub>, 0-30% EtOAc in heptane), trituration with MeCN and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as colorless solid (49 mg, 75%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.67-0.73 (m, 1H), 0.77-0.83 (m, 1H), 0.89-0.96 (m, 1H), 1.00-1.08 (m, 1H), 1.67-1.75 (m, 1H), 3.57 (dd, *J* = 8.0, 11.2 Hz, 1H), 4.10 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 17.6 Hz, 1H), 4.49 (d, *J* = 17.6 Hz, 1H), 5.77-5.79 (m, 2H), 6.88-6.91 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.41-7.51 (m, 5H), 7.73-7.89 (m, 3H), 10.41 (s, 1H). <sup>13</sup>C

NMR (100 MHz, CDCl<sub>3</sub>) $\delta$  = 7.1, 8.2, 11.4, 29.7, 36.3, 64.6, 114.6, 115.9, 119.3, 121.2, 123.8, 125.6, 125.8, 126.4, 127.8, 127.9, 128.9, 131.9, 133.5, 134.0, 135.0, 135.6, 148.8, 158.0, 162.5, 164.7.



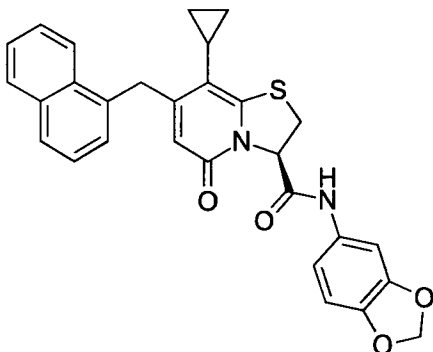
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-((4-methylpiperazin-1-yl)carbonyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (KSK 196)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 1-methylpiperazine (22  $\mu$ L, 0.198 mmol), purification by flash chromatography (SiO<sub>2</sub>, 0-60% MeOH in CH<sub>2</sub>Cl<sub>2</sub> with 1% NH<sub>4</sub>OH) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as a white solid (43 mg, 71%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.73-0.84 (m, 2H), 0.89-0.99 (m, 2H), 1.63-1.69 (m, 1H), 2.37 (s, 3H), 2.47-2.59 (m, 3H), 2.64-2.71 (m, 2H), 3.29 (dd, *J* = 3.6, 11.6 Hz, 1H), 3.50-3.60 (m, 2H), 3.65 (dd, *J* = 9.2, 11.2 Hz, 1H), 3.76-3.82 (m, 1H), 3.88-3.96 (m, 1H), 4.36 (d, *J* = 17.2 Hz, 1H), 4.50 (d, *J* = 17.2, 1H), 5.70 (s, 1H), 5.78 (dd, *J* = 3.2, 8.8 Hz, 1H), 7.27 (d, *J* = 6.8 Hz, 1H), 7.41-7.51 (m, 3H), 7.78-7.89 (m, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) $\delta$  = 7.4, 7.9, 11.2, 31.2, 36.2, 42.3, 45.7, 54.3, 54.5, 60.4, 113.2, 115.0, 123.9, 125.6, 125.7, 126.2, 127.6, 128.8, 132.0, 133.9, 134.1, 148.3, 156.8, 161.3, 166.4.



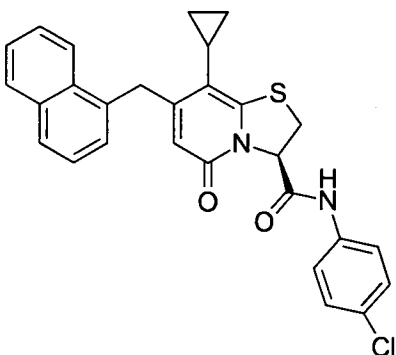
**(3R)-7-(Naphthalen-1-ylmethyl)-N-cyclohexyl-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 220)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and cyclohexylamine (23  $\mu$ L, 0.199 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 0-40% EtOAc in heptane) the product as a white solid (53 mg, 87%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.68-0.75 (m, 1H), 0.78-0.84 (m, 1H), 0.88-0.95 (m, 1H), 0.98-1.04 (m, 1H), 1.09-1.36 (m, 6H), 1.49-1.89 (m, 6H), 3.50 (dd, *J* = 8.4, 11.2 Hz, 1H), 3.68-3.72 (m, 1H), 4.05 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 17.6 Hz, 1H), 4.49 (d, *J* = 17.6 Hz, 1H), 5.58 (d, *J* = 7.6 Hz, 1H), 5.77 (s, 1H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.42-7.52 (m, 3H), 7.75-7.77 (m, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.88-7.91 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.2, 8.0, 11.4, 24.3, 25.5, 29.9, 32.4, 32.5, 36.3, 48.5, 63.9, 114.8, 123.8, 125.6, 125.8, 126.2, 127.7, 127.8, 128.9, 131.9, 133.9, 134.0, 148.6, 157.2, 162.2, 165.9.



**(3R)-N-(1,3-Benzodioxol-5-yl)-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 223)**

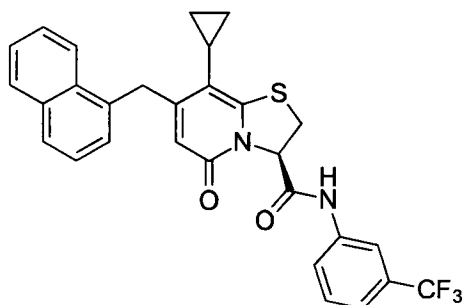
The title compound was prepared by adaptation of the general procedure with **C10** (30 mg, 0.079 mmol), pyridine (19  $\mu$ L, 0.237 mmol), 1,3-benzodioxol-5-amine (17 mg, 0.119 mmol) and T3P<sup>®</sup> (50% in EtOAc; 150  $\mu$ L, 0.254 mmol). After stirring for 7 h, a further 1 equivalent of T3P<sup>®</sup> (50% in EtOAc; 75  $\mu$ L, 0.127 mmol) was added and the reaction stirred a further 16 h. Purification by flash chromatography (SiO<sub>2</sub>, 0-30% EtOAc in heptane) afforded the product as an off-white solid (8 mg, 41%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.69-0.74 (m, 1H), 0.78-0.85 (m, 1H), 0.91-0.99 (m, 1H), 1.02-1.10 (m, 1H), 1.68-1.77 (m, 1H), 3.57-3.65 (m, 1H), 4.09-4.17 (m, 1H), 4.39 (d,  $J$  = 17.6 Hz, 1H), 4.51 (d,  $J$  = 17.6 Hz, 1H), 5.82 (s, 2H), 5.93 (s, 2H), 6.69 (d,  $J$  = 8.0 Hz, 1H), 6.85-6.88 (m, 1H), 7.27-7.29 (m, 2H), 7.43-7.51 (m, 3H), 7.76-7.91 (m, 3H), 10.33 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.1, 8.1, 11.4, 29.9, 36.3, 64.8, 101.2, 102.3, 108.0, 112.9, 114.5, 116.1, 123.8, 125.6, 125.9, 126.4, 127.8, 127.9, 128.9, 131.9, 132.3, 133.6, 134.0, 144.1, 147.6, 149.2, 158.1, 162.4, 164.4.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-chlorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 224)**

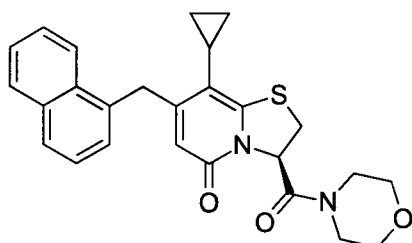
Following the general procedure with **C10** (31 mg, 0.079 mmol) and 4-chloroaniline (16 mg, 0.119 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 0-30% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) the product as a white solid (27 mg, 70%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.71-0.76 (m, 1H), 0.79-0.86 (m, 1H), 0.92-0.99 (m, 1H), 1.03-1.10 (m, 1H), 1.69-1.75 (m, 1H), 3.58 (dd,  $J$  = 8.0, 10.8 Hz, 1H), 4.08 (d,  $J$  = 11.2 Hz, 1H), 4.39 (d,  $J$  = 17.2 Hz, 1H), 4.51 (d,  $J$  = 17.2 Hz, 1H), 5.76-5.79 (m, 2H), 7.20 (d,  $J$  = 8.4 Hz, 1H), 7.29 (d,  $J$  = 8.0 Hz, 1H), 7.43-7.53 (m, 5H), 7.75 (d,  $J$  = 7.2 Hz, 1H), 7.82 (d,  $J$  = 8.4 Hz, 1H), 7.89-7.92 (m, 1H), 10.47 (s, 1H). <sup>13</sup>C NMR (100 MHz,

$\text{CDCl}_3$ )  $\delta$  = 7.2, 8.1, 11.4, 29.8, 36.3, 64.7, 114.5, 116.0, 121.1, 123.8, 125.6, 125.9, 126.4, 127.8, 127.9, 128.8, 128.9, 129.2, 131.9, 133.5, 134.0, 136.5, 148.9, 158.2, 162.4, 164.9.



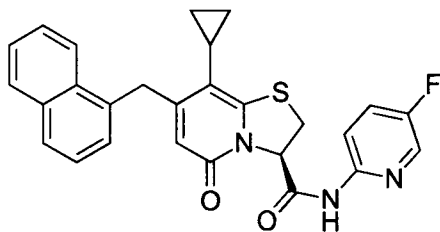
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-(trifluoromethyl)phenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 226)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 3-(trifluoromethyl)aniline (32 mg, 0.199 mmol) afforded after purification by flash chromatography ( $\text{SiO}_2$ , 0-30% EtOAc in heptane) and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) the product as a white solid (48 mg, 70%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.71-0.77 (m, 1H), 0.80-0.87 (m, 1H), 0.94-0.99 (m, 1H), 1.04-1.10 (m, 1H), 1.71-1.79 (m, 1H), 3.60 (dd,  $J$  = 7.6, 10.8 Hz, 1H), 4.05 (d,  $J$  = 10.8 Hz, 1H), 4.39 (d,  $J$  = 17.6 Hz, 1H), 4.53 (d,  $J$  = 17.6 Hz, 1H), 5.78-5.81 (m, 2H), 7.27-7.35 (m, 3H), 7.44-7.54 (m, 4H), 7.75-7.78 (m, 1H), 7.82 (d,  $J$  = 8.0 Hz, 1H), 7.89-7.92 (m, 1H), 7.96 (s, 1H), 10.62 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.1, 8.1, 11.4, 29.8, 36.3, 64.6, 114.6, 115.9, 116.6, 116.7, 120.7, 120.8, 122.9, 123.8, 125.2 (q,  $J$  = 271.2 Hz), 125.6, 125.9, 126.4, 127.8, 127.9, 128.9, 129.3, 131.5 (q,  $J$  = 32.2 Hz), 131.9, 133.6, 134.0, 138.4, 148.8, 158.2, 162.5, 165.2.



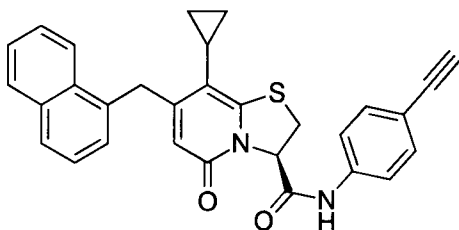
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(morpholin-4-ylcarbonyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (KSK 227)**

The title compound was prepared by adaptation of the general procedure with **C10** (50 mg, 0.132 mmol), pyridine (32  $\mu\text{L}$ , 0.396 mmol), morpholine (17  $\mu\text{L}$ , 0.199 mmol) and T3P® (50% in EtOAc; 220  $\mu\text{L}$ , 0.373 mmol). Purification by flash chromatography ( $\text{SiO}_2$ , MeOH in  $\text{CH}_2\text{Cl}_2$ , 3:97) afforded the product as a white solid (40 mg, 68%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.71-0.81 (m, 2H), 0.81-0.99 (m, 2H), 1.60-1.68 (m, 1H), 3.25 (dd,  $J$  = 2.8, 11.2 Hz, 1H), 3.48-3.55 (m, 1H), 3.59-3.81 (m, 8H), 4.34 (d,  $J$  = 17.2 Hz, 1H), 4.48 (d,  $J$  = 17.2 Hz, 1H), 5.70 (s, 1H), 5.75 (dd,  $J$  = 2.8, 9.2 Hz), 7.24 (d,  $J$  = 7.2 Hz, 1H), 7.40 (t,  $J$  = 8.0 Hz, 5H), 7.44-7.48 (m, 2H), 7.75-7.87 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.4, 7.9, 11.3, 31.2, 36.3, 42.9, 46.5, 60.4, 66.4, 66.7, 113.6, 114.9, 123.9, 125.5, 125.7, 126.3, 127.5, 127.6, 128.8, 132.0, 133.9, 134.1, 148.5, 157.1, 161.2, 166.6.



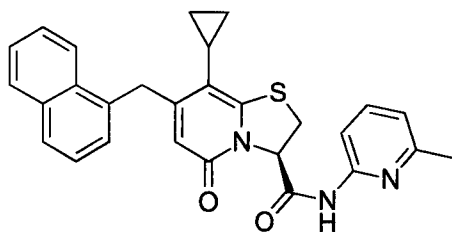
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-fluoropyridine-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (MK 12)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 2-amino-5-fluoropyridine (23 mg, 0.204 mmol), the crude was purified by flash chromatography (SiO<sub>2</sub>, 20-100% EtOAc in heptane), HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.005% formic acid each, 30-100% for 25 min; *t<sub>R</sub>* = 21.94 min) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) to afford the product as a white solid (36 mg, 57%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.66-0.73 (m, 1H), 0.74-0.81 (m, 1H), 0.86-0.97 (m, 1H), 0.98-1.06 (m, 1H), 1.65-1.74 (m, 1H), 3.60 (dd, *J* = 8.1, 11.4 Hz, 1H), 4.13 (d, *J* = 11.4 Hz, 1H), 4.34 (d, *J* = 17.4 Hz, 1H), 4.50 (d, *J* = 17.4 Hz, 1H), 5.81 (d, *J* = 8.1 Hz, 1H), 5.84 (s, 1H), 7.24-7.28 (m, 1H), 7.32-7.51 (m, 4H), 7.72-7.82 (m, 2H), 7.88 (m, 1H), 8.04-8.14 (m, 2H), 10.70 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.2, 8.1, 11.5, 29.8, 36.3, 64.5, 115.0 (d, *J<sub>CF</sub>* = 4.2), 115.3, 115.4, 123.8, 124.9 (d, *J<sub>CF</sub>* = 19.9), 125.6, 125.9, 126.4, 127.86, 127.94, 129.0, 132.0, 133.7, 134.1, 135.9 (d, *J<sub>CF</sub>* = 25.1), 147.5 (d, *J<sub>CF</sub>* = 2.4), 148.2, 156.45 (d, *J<sub>CF</sub>* = 251.9), 157.6, 162.5, 165.3.



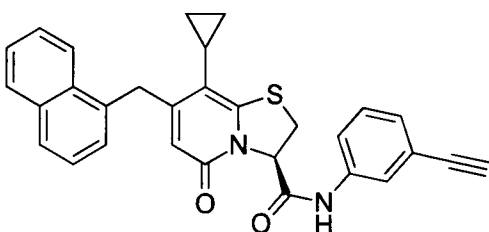
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-ethynylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (MK 14)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 4-ethynylaniline (30 mg, 0.256 mmol), the crude was purified by flash chromatography (SiO<sub>2</sub>, 20-100% EtOAc in heptane), HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.005% formic acid each, 30-100% for 25 min; *t<sub>R</sub>* = 23.23 min) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1), to afford the product as a white solid (26 mg, 41%). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.67-0.75 (m, 1H), 0.77-0.85 (m, 1H), 0.89-0.97 (m, 1H), 0.99-1.07 (m, 1H), 1.67-1.75 (m, 1H), 3.55 (dd, *J* = 2.2, 12.0, 1H), 3.88 (dd, *J* = 9.2, 12.0 Hz, 1H), 4.41 (d, *J* = 17.3 Hz, 1H), 4.09 (s, 1H), 4.50 (d, *J* = 17.3 Hz, 1H), 5.27 (s, 1H), 5.47 (dd, *J* = 2.2, 9.2 Hz, 1H), 7.27-7.35 (m, 3H), 7.39-7.52 (m, 5H), 7.73-7.83 (m, 2H), 7.85-7.91 (m, 1H), 10.58 (s, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.3, 7.5, 10.8, 31.5, 35.3, 63.8, 80.0, 83.4, 111.8, 113.2, 116.5, 118.9, 124.0, 125.7, 125.8, 126.3, 127.3, 127.6, 128.6, 131.6, 132.4, 133.5, 134.6, 139.2, 149.1, 156.5, 159.9, 166.3.



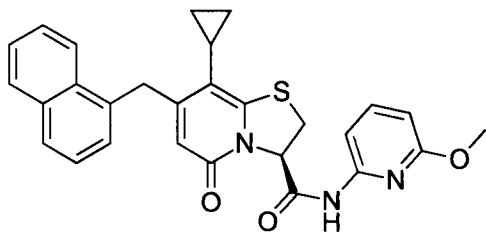
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(6-methylpyridine-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (MK 15)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 2-amino-6-methylpyridine (26 mg, 0.240 mmol), purification by flash chromatography (SiO<sub>2</sub>, 20-100% EtOAc in heptane), HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.005% formic acid each, 30-100% for 25 min; *t<sub>R</sub>* = 22.12 min) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) gave the product as a white solid (28 mg, 46%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.64-0.73 (m, 1H), 0.74-0.82 (m, 1H), 0.86-0.96 (m, 1H), 0.97-1.06 (m, 1H), 1.64-1.72 (m, 1H), 2.38 (s, 3H), 3.58 (dd, *J* = 8.1, 11.4 Hz, 1H), 4.07 (d, *J* = 11.4 Hz, 1H), 4.33 (d, *J* = 17.4 Hz, 1H), 4.50 (d, *J* = 17.4 Hz, 1H), 5.79 (d, *J* = 8.1 Hz, 1H), 5.84 (s, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 7.23-7.29 (m, 1H), 7.39-7.56 (m, 4H), 7.73-7.82 (m, 2H), 7.84-7.92 (m, 2H), 10.25 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.1, 8.1, 11.5, 24.2, 30.0, 36.3, 64.5, 111.2, 115.3, 115.4, 119.6, 123.9, 125.7, 125.9, 126.4, 127.88, 127.95, 129.0, 132.0, 133.8, 134.1, 138.3, 184.1, 150.5, 157.4, 157.5, 162.4, 165.3.



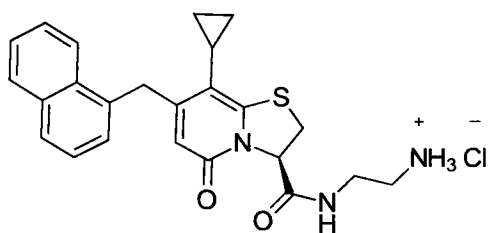
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-ethynylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (MK 17)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 3-ethynylaniline (30 mg, 0.256 mmol) afforded after purification by flash chromatography (SiO<sub>2</sub>, 20-100% EtOAc in heptane) the product as a white solid (47 mg, 75%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.67-0.76 (m, 1H), 0.76-0.84 (m, 1H), 0.88-0.96 (m, 1H), 0.99-1.08 (m, 1H), 1.66-1.75 (m, 1H), 3.01 (s, 1H), 3.53 (dd, *J* = 8.1, 11.3 Hz, 1H), 4.06 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 17.5 Hz, 1H), 4.50 (d, *J* = 17.5 Hz, 1H), 5.74 (d, *J* = 8.1 Hz, 1H), 5.77 (s, 1H), 7.14-7.20 (m, 2H), 7.27-7.31 (m, 1H), 7.41-7.51 (m, 4H), 7.69-7.72 (s, 1H), 7.73-7.78 (m, 1H), 7.78-7.83 (m, 1H), 7.86-7.91 (m, 1H), 10.39 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.2, 8.3, 11.6, 29.7, 36.4, 64.7, 77.5, 83.3, 114.9, 115.7, 120.5, 122.9, 123.5, 124.0, 125.8, 126.0, 126.5, 128.0, 128.07, 128.08, 129.0, 129.1, 132.1, 133.8, 134.2, 138.1, 148.7, 158.0, 162.7, 165.1.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(6-methoxypyridine-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (MK 18)**

Following the general procedure with **C10** (50 mg, 0.132 mmol) and 2-amino-6-methoxypyridine (24  $\mu$ L, 0.220 mmol) and purification by flash chromatography ( $\text{SiO}_2$ , 20-100% EtOAc in heptane) afforded the product as a pale yellow solid (60 mg, 94%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 0.65-0.73 (m, 1H), 0.75-0.82 (m, 1H), 0.87-0.96 (m, 1H), 0.98-1.06 (m, 1H), 1.65-1.74 (m, 1H), 3.57 (dd,  $J$  = 8.1, 11.3 Hz, 1H), 4.04 (d,  $J$  = 11.3 Hz, 1H), 3.76 (s, 3H), 4.35 (d,  $J$  = 17.4 Hz, 1H), 4.49 (d,  $J$  = 17.4 Hz, 1H), 5.80 (s, 1H), 5.81 (s, 1H), 6.42 (d,  $J$  = 8.1 Hz, 1H), 7.25-7.30 (m, 1H), 7.39-7.53 (m, 4H), 7.59-7.65 (m, 1H), 7.73-7.82 (m, 2H), 7.85-7.90 (m, 1H), 10.25 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.2, 8.2, 11.5, 29.9, 36.4, 53.5, 64.4, 106.0, 106.5, 115.0, 115.2, 123.89, 125.7, 125.9, 126.4, 127.9, 127.9, 129.0, 132.0, 133.8, 134.1, 140.5, 148.25, 148.9, 157.5, 162.9, 165.2.

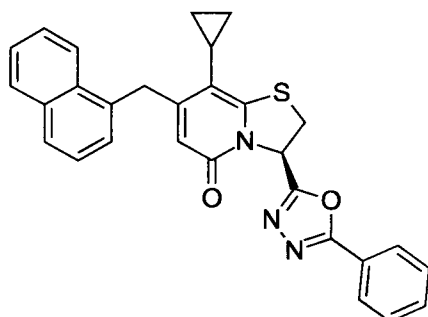


**2-((((3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-3-yl)carbonyl)amino)ethanaminium chloride (PS 49)**

HATU (145 mg, 0.38 mmol) was added to a stirred solution of compound **C10** (100 mg, 0.25 mmol) in DMF at rt and the reaction mixture was stirred for 5 min. *N*-Boc-ethylenediamine (44 mg, 0.28 mmol) was then added, followed by *N,N*-diisopropylethylamine (120  $\mu$ L, 0.71 mmol). After 15 minutes, cold water was added resulting in the formation of white precipitates. The precipitates were filtered and washed twice with cold water, and dried under vacuum and were used directly in next step without further purification. The precipitates were suspended in dioxane and 1M HCl in dioxane (2.5ml/mmol) added. The reaction mixture was stirred at room temperature for 1 hour. After completion of the reaction (monitoring by TLC), a white precipitate had formed, which was filtered, washed with diethyl ether and dried under high vacuum to afford the product as a white solid which was used without further purification (96 mg, 77%).  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO}-d_6$ )  $\delta$  = 0.65-0.68 (m, 1H), 0.72-0.75 (m, 1H), 0.87-0.95 (m, 2H), 1.69-1.74 (m, 1H), 2.81-2.89 (m, 2H), 3.24-3.30 (m, 2H), 3.55 (dd,  $J$  = 2.9, 9.8 Hz, 1H), 3.75 (dd,  $J$  = 9.8, 9.0 Hz, 1H), 4.46 (q,  $J$  = 17.3 Hz, 2H), 5.25 (s, 1H), 5.29 (dd,  $J$  = 2.8, 9.0 Hz, 1H), 6.80 (broad s, 1H), 7.37 (d,  $J$  = 6.7 Hz, 1H), 7.49-7.55 (m, 3H), 7.88 (d,  $J$  = 8.5 Hz, 2H), 7.96 (t,  $J$  = 4.2 Hz, 1H), 8.12 (broad s, 3H), 8.72 (t,  $J$  = 5.4 Hz, 1H),  $^{13}\text{C}$  NMR

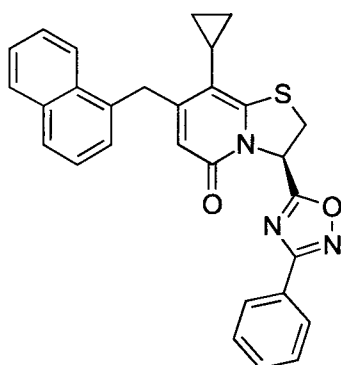
(150 MHz, DMSO- $d_6$ )  $\delta$  = 7.7, 7.9, 11.2, 31.9, 35.7, 37.0, 38.7, 64.0, 112.4, 113.6, 124.5, 126.1, 126.8, 127.7, 128.0, 129.1, 132.0, 133.9, 135.0, 149.5, 156.9, 159.0, 160.4, 168.6.

Preparation of ring-fused thiazolino 2-pyridone amide isosteres



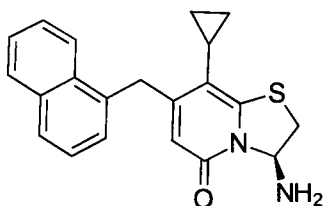
**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (JG 48)**

The title compound was prepared by adaption of the protocol reported by Li *et al.*<sup>23</sup> The carboxylic acid **C10** (50 mg, 0.132 mmol), benzhydrazide (18 mg, 0.132 mmol) and *N,N*-diisopropylethylamine (46  $\mu$ L, 0.265 mmol) were dissolved in anhydrous THF (1.32 mL) under an inert atmosphere. HATU (50 mg, 0.132 mmol) was added and the reaction mixture stirred for 1 h at rt. Burgess reagent (79 mg, 0.331 mmol) was then added and the reaction mixture stirred for 15 h at rt, whereupon further Burgess reagent (25 mg, 0.104 mmol) was added and the reaction stirred for a further 6 h. The reaction mixture was adsorbed onto silica and purified by flash chromatography (SiO<sub>2</sub>, 0-100% EtOAc in heptane). After freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1), the product was obtained as a white solid (16 mg, 25%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.72-0.82 (m, 2H), 0.88-1.04 (m, 2H), 1.66-1.74 (m, 1H), 3.79 (dd, *J* = 1.5, 11.8 Hz, 1H), 3.87 (dd, *J* = 7.5, 11.8 Hz, 1H), 4.38 (d, *J* = 17.3 Hz, 1H), 4.50 (d, *J* = 17.3 Hz, 1H), 5.78 (s, 1H), 6.42 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.40-7.56 (m, 6H), 7.76-7.81 (m, 2H), 7.86-7.90 (m, 1H), 7.95-7.99 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.4, 7.9, 11.3, 32.9, 36.4, 56.7, 114.2, 115.7, 123.4, 123.8, 125.6, 125.8, 126.3, 127.1, 127.7, 127.8, 128.9, 129.0, 131.9, 132.0, 133.9, 134.0, 146.5, 157.2, 161.0, 162.6, 165.7.



**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (JG 52)**

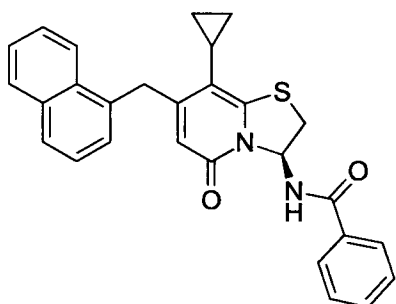
The title compound was prepared by adaption of the procedure reported by Evans *et al.*<sup>24</sup> The carboxylic acid **C10** (65 mg, 0.172 mmol), benzamide oxime (27 mg, 0.198 mmol), *N,N*-diisopropylethylamine (76  $\mu$ L, 0.405 mmol) and TBTU (64 mg, 0.198 mmol) were dissolved in anhydrous DMF (700  $\mu$ L) and heated by MWI at 190 °C for 5 min. The reaction mixture was diluted with HCl (0.5 M aq., 10 mL) and extracted with EtOAc (3  $\times$  10 mL). The combined organic extracts were washed successively with aqueous KHSO<sub>4</sub> solution (3% w/v, 2 $\times$ ), H<sub>2</sub>O and brine (25 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, 0-65% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN;  $\sim$  3:1) afforded the product as an off-white solid (32 mg, 39%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.71-0.84 (m, 2H), 0.86-1.05 (m, 2H), 1.65-1.74 (m, 1H), 3.67 (dd, *J* = 1.2, 11.8 Hz, 1H), 3.89 (dd, *J* = 8.0, 11.8 Hz, 1H), 4.40 (d, *J* = 17.3 Hz, 1H), 4.53 (d, *J* = 17.3 Hz, 1H), 5.81 (s, 1H), 6.41 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.30 (d, *J* = 6.8 Hz, 1H), 7.41-7.54 (m, 6H), 7.77-7.84 (m, 2H), 7.85-7.91 (m, 1H), 8.00-8.05 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.6, 8.0, 11.4, 36.5, 58.0, 114.5, 115.9, 123.9, 125.7, 125.9, 126.4, 127.8, 127.9, 128.9, 129.0, 131.5, 132.1, 134.0, 134.1, 146.6, 157.4, 161.2, 168.9, 175.4.



**(3S)-3-Amino-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (KSK 214)**

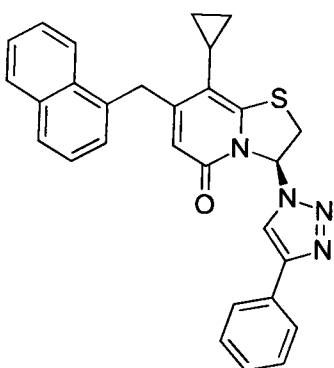
The carboxylic acid **C10** (150 mg, 0.397 mmol) was dissolved in anhydrous tBuOH (1.96 mL) under an inert atmosphere and NEt<sub>3</sub> (67  $\mu$ L, 0.437 mmol) and diphenylphosphoryl azide (DPPA, 94  $\mu$ L, 0.437 mmol) added. The reaction mixture was heated with stirring at 85 °C for 2 h, after which additional NEt<sub>3</sub> (12  $\mu$ L, 0.087 mmol) and DPPA (17  $\mu$ L, 0.079 mmol) were added and the reaction mixture heated for a further 3 h. After cooling to room temperature, the solvent was removed under reduced pressure. The crude residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL), washed successively with aqueous NaOH (10% w/v, 10 mL), H<sub>2</sub>O and brine (10 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>; 10-100% EtOAc in heptane) afforded the BOC protected amine as a white solid (133.7 mg). This was suspended in 30% TFA/CH<sub>2</sub>Cl<sub>2</sub> (v/v, 2 mL) and stirred at rt for 5 h. The solvent was removed under reduced pressure and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL), washed with saturated aqueous NaHCO<sub>3</sub> solution (2 $\times$  10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. Purification by flash chromatography (SiO<sub>2</sub>; 0-20% MeOH in EtOAc with 2% NEt<sub>3</sub>) and consequent freeze-drying (H<sub>2</sub>O:MeCN;  $\sim$  4:1) afforded the amine as a white solid (91 mg, 66% over 2 steps). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.60-0.68 (m, 2H), 0.82-0.92 (m, 2H), 1.51-1.58 (m, 1H), 3.01 (dd, 1H, *J* = 1.4, 12.0 Hz, 1H), 3.50 (dd, 1H, *J* = 7.6, 12.0 Hz, 1H), 4.28 (d, *J* = 17.2, 1H), 4.34 (d, 1H, *J* = 17.2 Hz), 5.60 (s, 1H), 5.81 (dd, 1H, *J* = 1.4, 7.4 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.30-7.40 (m, 3H), 7.67-7.79 (m, 3H). <sup>13</sup>C NMR (100 MHz,

CDCl<sub>3</sub>)  $\delta$  = 7.6, 7.9, 10.9, 35.1, 36.2, 72.1, 113.2, 115.4, 123.8, 125.6, 125.7, 126.2, 127.6, 127.7, 128.9, 131.9, 134.0, 134.1, 145.8, 156.6, 161.6.



**N-((3S)-7-(Naphthalen-1-ylmethyl)-8-methyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-3-yl)benzamide (KSK 215)**

To a solution of **KSK 214** (40 mg, 0.11 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added DCC (37 mg, 0.18 mmol), benzoic acid (40 mg, 0.33 mmol) and DMAP (27 mg, 0.22 mmol) and the solution stirred overnight. After complete conversion of the starting material by LCMS, the mixture was washed with saturated aqueous NaHCO<sub>3</sub> and filtered 3 times to remove the urea byproduct. Purification by flash chromatography (SiO<sub>2</sub>; 0-70% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 4:1) afforded the amide as a white solid (32 mg, 65%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 0.78-0.87 (m, 2H), 0.98-1.08 (m, 2H), 1.69-1.74 (m, 1H), 3.55 (dd, 1H, *J* = 1.6, 12.0 Hz, 1H), 3.63 (dd, 1H, *J* = 6.8, 12.0 Hz, 1H), 4.40-4.48 (m, 2H), 5.74 (s, 1H), 6.59-6.63 (m, 1H), 7.28-7.32 (m, 2H), 7.41-7.50 (m, 5H), 7.69-7.72 (m, 2H), 7.80 (t, *J* = 8.6 Hz, 2H), 7.88-7.91 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.8, 7.9, 11.1, 34.6, 36.3, 69.0, 113.9, 115.1, 123.8, 125.6, 125.8, 126.2, 127.3, 127.7, 127.8, 128.4, 128.9, 131.9, 133.1, 133.9, 148.4, 157.5, 160.9, 167.4.

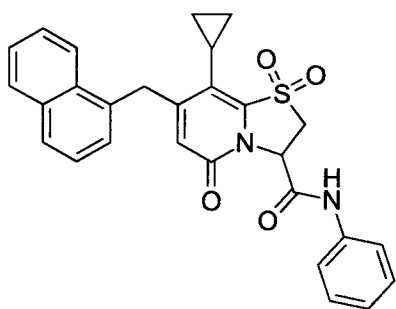


**(3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one (JG 107)**

The title compound was prepared by adaptation of diazotransfer methodology developed by Goddard-Borger *et al.*<sup>6</sup> followed directly by adaption of the CuAAC procedure reported by Bengtsson *et al.*<sup>25</sup> Imidazole-1-sulfonyl azide hydrogen sulfate (59.8 mg, 0.220 mmol) was added to a solution of amine **KSK 214** (48.0 mg, 0.138 mmol), K<sub>2</sub>CO<sub>3</sub> (36.2 mg, 0.262 mmol) and CuSO<sub>4</sub> (3.3 mg, 0.021 mmol) in MeOH (0.69 mL). The reaction mixture was stirred at rt for 23 h, after which additional K<sub>2</sub>CO<sub>3</sub> (4.8 mg, 0.035 mmol) and imidazole-1-sulfonyl azide hydrogen sulfate (4.7 mg, 0.017 mmol) were added. After 48 h

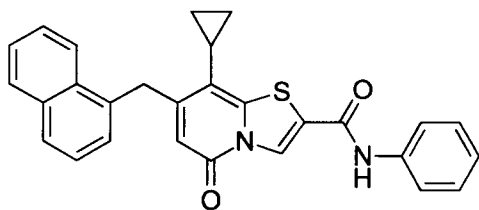
stirring at rt, the reaction mixture was diluted with brine (~ 2 mL) and extracted with EtOAc (3 × 5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced. The resultant residue was dissolved in DMF/H<sub>2</sub>O (1:1, 1.38 mL), and phenylacetylene (30.3 µL, 0.276 mmol), CuSO<sub>4</sub> (2.2 mg, 0.014 mmol) and sodium ascorbate (5.5 mg, 0.028 mmol) added, and heated at 35 °C for 22 h. After cooling to rt, the reaction mixture was diluted with EtOAc (15 mL) and washed successively with saturated aqueous NaHCO<sub>3</sub> solution, H<sub>2</sub>O and brine (10 mL each), dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>, 0-85% EtOAc in heptane), followed by HPLC (mobile phase: MeCN/H<sub>2</sub>O with 0.005% formic acid each, 30-100% for 40 min; *t*<sub>R</sub> = 30.46 min) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the triazole as a white solid (17 mg, 26%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.71-0.86 (m, 2H), 0.92-1.08 (m, 2H), 1.66-1.75 (m, 1H), 3.95 (dd, *J* = 7.2, 12.5 Hz, 1H), 4.28 (d, *J* = 12.5 Hz, 1H), 4.35 (d, *J* = 17.5 Hz, 1H), 4.47 (d, *J* = 12.5 Hz, 1H), 5.68 (s, 1H), 7.24-7.34 (m, 3H), 7.36-7.50 (m, 5H), 7.71-7.82 (m, 4H), 7.84-7.90 (m, 1H), 8.18 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 7.4, 8.1, 11.4, 33.2, 36.5, 72.6, 114.4, 115.4, 121.0, 123.9, 125.7, 126.0, 126.5, 127.9, 128.0, 128.4, 128.9, 129.0, 130.2, 132.0, 133.6, 134.1, 147.3, 147.9, 158.4, 161.0.

Examples of other ring-fused thiazolino 2-pyridone amides



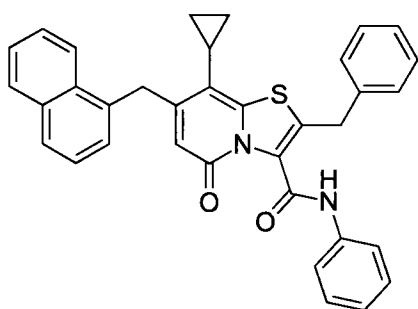
**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide 1,1-dioxide (KSK 193)**

**KSK 165** (50 mg, 0.11 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and cooled to 0 °C. A solution of *m*-CPBA (57 mg, 0.33 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added over 10 min. The resulting mixture was stirred for 1 h at 0 °C and then at rt overnight. The reaction was quenched by the addition of aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> solution (10% w/v) and saturated aqueous NaHCO<sub>3</sub>. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic phases dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (0-50% EtOAc in heptane) to give the product as a white solid (42 mg, 79%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.64-0.70 (m, 1H), 1.14-1.26 (m, 2H), 1.53-1.63 (m, 1H), 1.85-1.94 (m, 1H), 3.58 (dd, *J* = 9.2, 13.2 Hz, 1H), 4.57 (s, 2H), 4.64 (d, *J* = 13.2 Hz, 1H), 5.73 (d, *J* = 8.8 Hz, 1H), 6.19 (s, 1H), 7.08-7.12 (m, 1H), 7.26-7.34 (m, 4H), 7.44-7.54 (m, 5H), 7.67-7.69 (m, 1H), 7.87-7.95 (m, 2H), 9.96 (s, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 6.6, 7.6, 8.4, 36.5, 49.6, 55.9, 120.0, 121.4, 122.6, 123.5, 124.8, 125.7, 126.1, 126.8, 128.2, 128.5, 128.9, 129.1, 129.9, 130.2, 131.7, 132.4, 133.7, 134.2, 137.3, 139.7, 159.2, 160.7, 162.2.



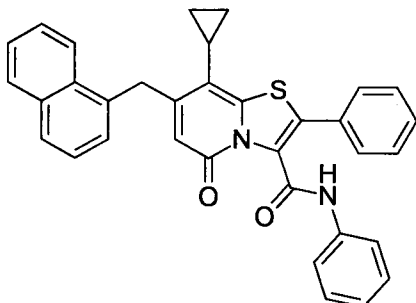
**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-5H-[1,3]thiazolo[3,2-a]pyridine-2-carboxamide (KSK 166)**

LiI (10 eq.) was added to a solution of **EC 178 methyl ester** in pyridine. The solution was heated by MWI at 120 °C for 10 min. The reaction mixture was acidified with aq. KHSO<sub>4</sub> (6% w/v) and extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and the solvent removed under reduced pressure. The crude product was purified by silica gel chromatography (0-50% EtOAc in heptane) to give the product as a pale yellow solid. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ = 0.78-0.83 (m, 1H), 1.02-1.09 (m, 1H), 1.88-1.97 (m, 1H), 4.60 (s, 2H), 5.56 (s, 1H), 7.12-7.17 (m, 1H), 7.35-7.41 (m, 3H), 7.48-7.58 (m, 3H), 7.70-7.76 (m, 2H), 7.87-8.02 (m, 3H), 9.16 (s, 1H), 10.65 (s, 1H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>) δ = 7.4, 10.6, 35.6, 109.1, 111.4, 120.0, 124.0, 124.3, 125.7, 125.9, 126.4, 127.4, 127.6, 128.7, 128.9, 131.5, 133.5, 134.6, 138.2, 147.4, 154.9, 157.8, 158.0.



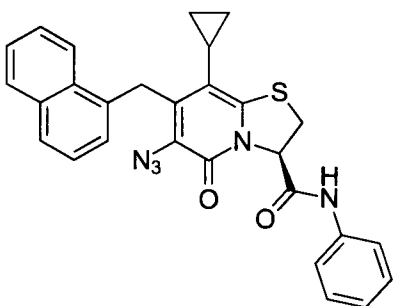
**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-phenyl-2-benzyl-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 218)**

**KSK 217** (20 mg, 0.038 mmol), benzylboronic acid (25 µl, 0.11 mmol), Pd(dppf)<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (3.2 mg, 0.004 mmol), K<sub>2</sub>CO<sub>3</sub> (21 mg, 0.15 mmol) was dissolved in MeOH (0.5 mL) and the reaction was heated in a sealed tube by MWI at 110 °C for 10 min. The resulting mixture was diluted with saturated aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>; 0-70% EtOAc in heptane) afforded after freeze-drying (H<sub>2</sub>O:MeCN; ~ 4:1) the product as a white solid (4 mg, 17%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.61-0.66 (m, 2H), 0.92-0.97 (m, 2H), 1.63-1.69 (m, 1H), 3.93 (s, 2H), 4.42 (s, 2H), 5.82 (s, 1H), 6.89-6.94 (m, 1H), 7.07-7.17 (m, 2H), 7.21-7.25 (m, 7H), 7.31-7.35 (m, 1H), 7.40-7.47 (m, 3H), 7.70-7.74 (m, 2H), 7.79-7.82 (m, 1H), 8.82 (br s, 1H).



**7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-phenyl-2-phenyl-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 219)**

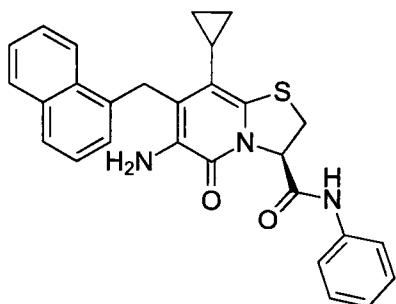
**KSK 217** (20 mg, 0.038 mmol), phenylboronic acid (14 mg, 0.11 mmol), Pd(OAc)<sub>2</sub> (0.9 mg, 0.004 mmol), KF (6.6 mg, 0.11 mmol) was dissolved in MeOH (0.5 mL) and the reaction was heated in a sealed tube by MWI at 100 °C for 10 min. The resulting mixture was diluted with saturated aqueous NaHCO<sub>3</sub> and extracted with EtOAc. The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent removed under reduced pressure. Purification by flash chromatography (SiO<sub>2</sub>; 0-70% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) afforded the product as a white solid (10 mg, 52%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.76-0.84 (m, 2H), 1.05-1.12 (m, 2H), 1.79-1.86 (m, 1H), 4.48 (s, 2H), 5.73 (s, 1H), 6.74-6.79 (m, 1H), 6.87-6.92 (m, 2H), 7.11 (d, *J* = 6.8 Hz, 1H), 7.16-7.19 (m, 2H), 7.21-7.29 (m, 4H), 7.36-7.42 (m, 4H), 7.67-7.72 (m, 2H), 7.79-7.82 (m, 1 H), 9.00 (brs, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ = 8.2, 11.1, 36.3, 111.8, 120.2, 123.8, 124.3, 125.5, 125.9, 126.4, 127.7, 127.8, 128.5, 128.6, 128.9, 129.1, 129.9, 131.9, 133.8, 133.9, 137.5, 146.9, 153.4, 158.1, 159.2.



**(3R)-6-Azido-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 207)**

Compound **KSK 205** (30 mg, 0.07 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and cooled to 0 °C. Oxalyl chloride (12 μL, 0.14 mmol) was added dropwise and the solution was allowed to reach rt and stirred for 1 h. After the evaporation of solvent to remove HCl, the residue was redissolved in CH<sub>2</sub>Cl<sub>2</sub>, followed by the addition of NEt<sub>3</sub> (30 μL, 0.21 mmol) and aniline (14 μL, 0.14 mmol). The solution was then continuously stirred for 4 h and then concentrated and purified by flash column chromatography (SiO<sub>2</sub>, 0-50% EtOAc in heptane) and freeze-drying (H<sub>2</sub>O:MeCN; ~ 3:1) to afford the product as a pale yellow solid (25 mg, 76%). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 0.44-0.50 (m, 1H), 0.59-0.75 (m, 3H), 1.34-1.40 (m, 1H), 3.69 (dd, 1H, *J* = 8.0, 11.6 Hz, 1H), 4.13 (d, 1H, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 15.6 Hz, 1H), 4.63 (d, *J* = 15.6, 1H), 5.98 (d, 1H, *J* = 7.6 Hz), 6.85 (d, *J* = 7.2 Hz, 1H), 7.09-7.13 (m, 1H), 7.29-7.39 (m, 3H), 7.55-7.65 (m, 4H), 7.76 (d, *J* = 8.4 Hz, 1H),

7.92 (d,  $J = 8.0$  Hz, 1H), 8.18 (d,  $J = 8.4$  Hz, 1H), 10.12 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 6.7, 7.7, 11.9, 30.0, 31.1, 65.2, 116.4, 119.9, 123.1, 123.7, 124.4, 124.5, 125.5, 125.8, 126.6, 127.1, 128.8, 128.9, 131.9, 133.5, 133.8, 137.8, 143.3, 143.7, 158.2, 164.4$ .



**(3R)-6-Amino-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide (KSK 213)**

TFA (0.11 ml) dropwise was added to a solution of **C10** (50 mg, 0.11 mmol) and  $\text{NaNO}_2$  (8.5 mg, 0.12 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at rt. The reaction mixture was stirred overnight and quenched by the addition of saturated aqueous  $\text{NaHCO}_3$ . The organic phase was washed with saturated aqueous  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under reduced pressure. The crude product was dissolved in acetic acid (0.7 mL). Zn dust (36 mg, 0.55 mmol) was added in portions and the mixture was allowed to stir for 2 h at rt. After filtration through a pad of Celite®, the mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and washed with saturated aqueous  $\text{NaHCO}_3$ , dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent removed under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ , 20-50% EtOAc in heptane), and freeze-drying ( $\text{H}_2\text{O}:\text{MeCN}$ ; ~ 3:1) afforded the product as a white solid (36 mg, 69%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 0.47\text{--}0.58$  (m, 2H), 0.64-0.77 (m, 2H), 1.34-1.41 (m, 1H), 3.75 (d, 1H,  $J = 11.8$  Hz, 1H), 3.96-4.07 (m, 1H), 5.05 (d,  $J = 16.0$ , 1H), 5.09 (d, 1H,  $J = 16.0$  Hz), 5.77 (d,  $J = 8.8$  Hz, 1H), 6.98 (d,  $J = 6.8$  Hz, 1H), 7.11 (t,  $J = 7.4$  Hz, 1H), 7.31-7.37 (m, 3H), 7.57-7.67 (m, 4H), 7.78 (d,  $J = 8.0$  Hz, 1H), 7.93 (d,  $J = 8.0$  Hz, 1H), 8.21 (d,  $J = 8.4$  Hz, 1H), 10.40 (s, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 6.6, 12.1, 29.7, 30.9, 65.0, 116.8, 120.0, 123.1, 123.4, 124.3, 125.7, 126.4, 127.5, 128.9, 129.0, 130.3, 131.9, 132.1, 133.9, 134.1, 138.1, 157.4, 164.9$ .

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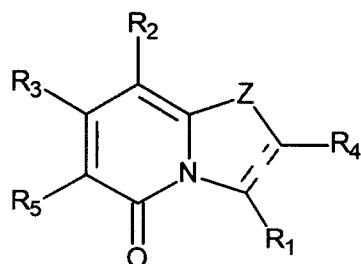
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## CLAIMS

1. A compound according to formula I



Formula I

wherein

Z is selected from O, S and SO<sub>2</sub>,

R<sub>1</sub> is selected from -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,

or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety -(CH<sub>2</sub>)<sub>b</sub>- wherein b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- wherein c+d is an integer from 2 to 5 and Q is O or N, including spiro compounds thereof;

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A, wherein

n is an integer from 0 to 5, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R<sub>3</sub> is -(CH<sub>2</sub>)<sub>m</sub>-D or -CHW-(CH<sub>2</sub>)<sub>m</sub>-D, wherein

m is an integer from 0 to 5,

W is halogen or alkyl, and

D is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted

heteroaryl, unsubstituted or substituted aryloxy;

$R_4$  is  $-(CH_2)_p-E$ ,  $-CO-E$ , or  $-CO-NH-E$ , wherein

$p$  is an integer from 0 to 5,

$E$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy; and

$R_5$  is  $-(CH_2)_q-G$ , wherein

$q$  is an integer 0 to 1, and

$G$  is selected from hydrogen,  $-N_3$ ,  $-NO_2$ ,  $-OH$ ,  $-alkoxy$ ,  $-alkyl$ ,  $-NY_1Y_2$  wherein  $Y_1$  and  $Y_2$  are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

a pharmaceutically acceptable salt, prodrug or stereoisomer thereof.

2. The compound according to claim 1, wherein

$R_1$  is selected from,  $-NH_2$ , tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl,  $-CO-NX_1X_2$ ,  $-NH-COX_1$ , and  $-NH-SO_2-X_1$ , wherein  $X_1$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,  $X_2$  is selected from hydrogen, unsubstituted or substituted alkyl

or wherein both  $X_1$  and  $X_2$  are alkyl or substituted alkyl  $X_1$  and  $X_2$  together form a moiety  $-(CH_2)_b-$  where  $b$  is an integer from 3 to 6, or a moiety  $-(CH_2)_c-Q-(CH_2)_d-$  where  $c+d$  is an integer from 2 to 5 and  $Q$  is O or N, including spiro compounds thereof.

3. The compound according to claim 1, wherein

$R_2$  is  $-(CH_2)_n-A$ , wherein

$n$  is an integer from 0 to 1, and

$A$  is selected from unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.

4. The compound according to claim 1, wherein  
 $R_3$  is  $-(CH_2)_m-D$  or  $-CHW-(CH_2)_m-D$ , wherein  
 $m$  is an integer from 0 to 1,  
 $W$  is halogen or  $-C_1-C_3$ alkyl, and  
 $D$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy.
  
5. The compound according to claim 1, wherein  
 $R_4$  is  $-(CH_2)_p-E$ ,  $-CO-E$ , or  $-CO-NH-E$ ,  
 $p$  is an integer from 0 to 1,  
 $E$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.
  
6. The compound according to claim 1, wherein  
 $R_5$  is selected from hydrogen,  $-N_3$ ,  $-NO_2$ ,  $-OH$ ,  $-C_1-C_3$ alkoxy,  $-C_1-C_3$ alkyl,  $-NH_2$ .
  
7. The compound according to claim 1 selected from  
7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide  
7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide  
(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide  
(3*S*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide  
(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-methylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide  
(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(2-fluorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide  
(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-methoxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide  
(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-fluorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(2-oxa-6-azaspiro[3.3]hept-6-ylcarbonyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridin-5-one

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(pyridin-3-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(pyridin-4-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(1,3-thiazol-2-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-*N*-Benzyl-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-*N*-(4-carbamoylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-*N*-methoxy-*N*-methyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(4-sulfamoylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3,4-difluorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(2,3-Dimethylbenzyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-methoxyphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-fluorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(pyridin-2-yl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-chlorophenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-*N*-methyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-methylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-(3-ethylphenyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

(3*R*)-7-(Benzyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

- (3R)-7-(3,4-Dimethylbenzyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(4-Azidonaphthalen-1-yl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-N-(2-fluoro-5-methylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-N-(5-chloropyridin-2-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(pyrimidin-4-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-(3-methylphenyl)-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-8-cyclopropyl-7-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-((4-Azidonaphthalen-1-yl)methyl)-N-(3-ethynylphenyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-N-(2-fluoropyridin-4-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-N-(2-methoxypyridin-4-yl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Fluoro(phenyl)methyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-N-(4-Azidophenyl)-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-((4-methylpiperazin-1-yl)carbonyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one
- (3R)-7-(Naphthalen-1-ylmethyl)-N-cyclohexyl-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-N-(1,3-Benzodioxol-5-yl)-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-chlorophenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide

- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-(trifluoromethyl)phenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(morpholin-4-ylcarbonyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-fluoropyridine-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(4-ethynylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(6-methylpyridine-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(3-ethynylphenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-(6-methoxypyridine-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- 2-((((3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-3-yl)carbonyl)amino)ethanaminium chloride
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(3-phenyl-1,2,4-oxadiazol-5-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one
- (3S)-3-Amino-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one
- N-((3S)-7-(Naphthalen-1-ylmethyl)-8-methyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-3-yl)benzamide
- (3R)-7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-3-(4-phenyl-1H-1,2,3-triazol-1-yl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridin-5-one
- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide 1,1-dioxide
- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-5H-[1,3]thiazolo[3,2-a]pyridine-2-carboxamide
- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-phenyl-2-benzyl-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- 7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-N-phenyl-2-phenyl-5-oxo-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide
- (3R)-6-Azido-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide

(3R)-6-Amino-7-(naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-*N*-phenyl-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxamide

a pharmaceutically acceptable salt, prodrug or stereoisomer thereof.

8. A compound selected from

8-Cyclopropyl-7-[(4-methyl-1-naphthyl)methyl]-5-oxo-2,3-dihydrothiazolo[3,2-*a*]pyridine-3-carboxylic acid

8-Cyclopropyl-7-(1,2-dihydroacenaphthylen-5-ylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-*a*]pyridine-3-carboxylic acid

7-[(4-Bromo-1-naphthyl)methyl]-8-cyclopropyl-5-oxo-2,3-dihydrothiazolo[3,2-*a*]pyridine-3-carboxylic acid

Methyl (3R)-8-cyclopropyl-7-methyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-(fluoro(phenyl)methyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-5-oxo-7-(1-phenylethyl)-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-benzyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-(4-methoxybenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-(4-chlorobenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-(2-fluoro-5-methylbenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-(2,3-dimethylbenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-(3,4-dimethylbenzyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-((4-fluoronaphthalen-1-yl)methyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-(4-bromo-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-8-cyclopropyl-7-((4-methylnaphthalen-1-yl)methyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

Methyl (3R)-7-(1,2-dihydroacenaphthylen-5-ylmethyl)-8-cyclopropyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylate

(3R)-8-Cyclopropyl-7-methyl-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylic acid

(3R)-8-cyclopropyl-7-(fluoro(phenyl)methyl)-5-oxo-2,3-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyridine-3-carboxylic acid

(3R)-8-cyclopropyl-5-oxo-7-(1-phenylethyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-8-cyclopropyl-7-benzyl-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-7-(naphthalen-1-yl-methyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-8-Cyclopropyl-7-(4-chlorobenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-8-Cyclopropyl-7-(4-methoxybenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-8-Cyclopropyl-7-(2-fluoro-5-methylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid (JG 104)

(3R)-8-Cyclopropyl-7-(2,3-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

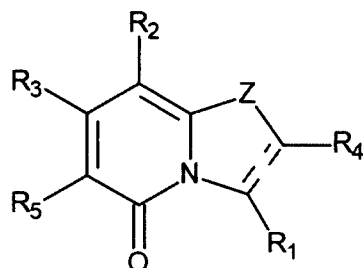
(3R)-8-Cyclopropyl-7-(3,4-dimethylbenzyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-8-Cyclopropyl-7-(4-fluoro-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid

a pharmaceutically acceptable salt, prodrug or stereoisomer thereof.

9. A compound according to any one of claims 1 to 8, any of its prodrugs, enantiomers or pharmaceutically acceptable salts thereof, for use as a medicament.
10. A compound according to any one of claims 1 to 8, any of its prodrugs, enantiomers or pharmaceutically acceptable salts thereof, for use in the prevention and/or treatment of *Chlamydia* infections.
11. A pharmaceutical composition comprising a compound according to any of claims 1 to 8, any of its pharmaceutically acceptable salts, prodrugs or stereoisomers, together with at least one pharmaceutically acceptable carrier, excipient or diluent.
12. The pharmaceutical composition according to claim 11 for use in the prophylaxis, prevention and/or treatment of *Chlamydia* infections.

13. A compound according to Formula I



Formula I

wherein

Z is selected from O, S and SO<sub>2</sub>,

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl, -CO<sub>2</sub>Y, wherein Y is selected from hydrogen and alkyl, -CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,

or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety -(CH<sub>2</sub>)<sub>b</sub>- wherein b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- wherein c+d is an integer from 2 to 5, and Q is O or N, including spiro compounds thereof,

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A, wherein

n is an integer from 0 to 5, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

R<sub>3</sub> is -(CH<sub>2</sub>)<sub>m</sub>-D or -CHW-(CH<sub>2</sub>)<sub>m</sub>-D, wherein

m is an integer from 0 to 5,

W is halogen unsubstituted or substituted alkyl, and

D is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy,

R<sub>4</sub> is -(CH<sub>2</sub>)<sub>p</sub>-E, -CO-E, or -CO-NH-E, wherein

p is an integer from 0 to 5,

E is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy;

R<sub>5</sub> is -(CH<sub>2</sub>)<sub>q</sub>-G, wherein

q is an integer from 0 to 1, and

G is selected from hydrogen, -N<sub>3</sub>, -NO<sub>2</sub>, -OH, -alkoxy, -alkyl, -NY<sub>1</sub>Y<sub>2</sub> wherein Y<sub>1</sub> and Y<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl,

and pharmaceutically acceptable salts, prodrugs and stereoisomers thereof, for use in prophylaxis, prevention and treatment of *Chlamydia* infections.

14. The compound for use according to claim 13, wherein

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl,

-CO<sub>2</sub>Y wherein Y is selected from hydrogen and alkyl,

-CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, X<sub>2</sub> is selected from hydrogen, alkyl or substituted alkyl,

or wherein both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl and together form a moiety -(CH<sub>2</sub>)<sub>b</sub>- where b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- where c+d is an integer from 2 to 5 and Q is O or N, including spiro compounds thereof.

15. The compound for use according to claim 13, wherein

R<sub>2</sub> is -(CH<sub>2</sub>)<sub>n</sub>-A wherein n is an integer from 0 to 1, and

A is selected from unsubstituted or substituted alkyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.

16. The compound for use according to claim 13, wherein  
 $R_3$  is  $-(CH_2)_m-D$  or  $-CHW-(CH_2)_m-D$  wherein  
 $m$  is an integer from 0 to 1,  
 $W$  is halogen, or  $-C_1-C_3$ alkyl, and  
 $D$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy.
17. The compound for use according to claim 13, wherein  
 $R_4$  is  $-(CH_2)_p-E$ ,  $-CO-E$ , or  $-CO-NH-E$ ,  
 $p$  is an integer from 0 to 1, and  
 $E$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl.
18. The compound for use according to claim 13 wherein  
 $R_5$  is selected from hydrogen,  $-N_3$ ,  $-NO_2$ ,  $-OH$ ,  $-C_1-C_3$ alkoxy,  $-C_1-C_3$ alkyl,  $-NH_2$ .
19. The compound for use according to claim 13 selected from  
 8-Cyclopropyl-7-[(4-methyl-1-naphthyl)methyl]-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid  
 8-Cyclopropyl-7-(1,2-dihydroacenaphthylen-5-ylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid  
 7-[(4-Bromo-1-naphthyl)methyl]-8-cyclopropyl-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid  
 2-benzyl-8-cyclopropyl-7-(1-naphthylmethyl)thiazolo[3,2-a]pyridin-5-one  
 2-benzoyl-8-cyclopropyl-7-(1-naphthylmethyl)-5-oxo-thiazolo[3,2-a]pyridine-3-carboxylic acid  
 8-Isopropyl-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid  
 7-(1-Naphthyloxymethyl)-5-oxo-8-(2-thienyl)-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid  
 8-Cyclopropyl-7-[(6-methoxy-2-naphthyl)methyl]-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid  
 8-(3,5-Dimethylphenyl)-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid  
 8-Cyclopropyl-7-(1-naphthylmethyl)-3-(4H-triazol-5-yl)-2,3-dihydrothiazolo[3,2-a]pyridin-5-one

8-Cyclopropyl-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrooxazolo[3,2-a]pyridine-3-carboxylic acid

8-cyclopropyl-7-(1-naphthylmethyl)-5-oxo-2,3-dihydrothiazolo[3,2-a]pyridine-3-carboxylic acid

7-(Naphthalen-1-ylmethyl)-8-cyclopropyl-5-oxo-2-(phenylcarbamoyl)-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

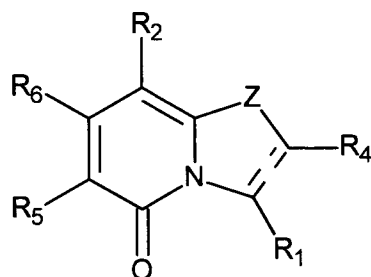
(3R)-6-amino-8-cyclopropyl-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-8-Cyclopropyl-7-(4-fluoro-naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-thiazolo[3,2-a]pyridine-3-carboxylic acid

(3R)-7-(naphthalen-1-ylmethyl)-5-oxo-8-(3-(trifluoromethyl)phenyl)-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxylic acid

a pharmaceutically acceptable salt, prodrug or stereoisomer thereof.

20. A compound according to Formula II



Formula II

wherein

Z is selected from O, S and SO<sub>2</sub>,

R<sub>1</sub> is selected from, -NH<sub>2</sub>, tetrazol-5-yl, unsubstituted or substituted oxodiazol-2-yl, unsubstituted or substituted triazol-1-yl,

-CO<sub>2</sub>Y wherein Y is selected from hydrogen and alkyl,

-CO-NX<sub>1</sub>X<sub>2</sub>, -NH-COX<sub>1</sub>, and -NH-SO<sub>2</sub>-X<sub>1</sub>, wherein X<sub>1</sub> and X<sub>2</sub> are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkoxy, unsubstituted or substituted aryl, unsubstituted and substituted heteroaryl,

or when both X<sub>1</sub> and X<sub>2</sub> are alkyl or substituted alkyl X<sub>1</sub> and X<sub>2</sub> together form a moiety -(CH<sub>2</sub>)<sub>b</sub>- where b is an integer from 3 to 6, or a moiety -(CH<sub>2</sub>)<sub>c</sub>-Q-(CH<sub>2</sub>)<sub>d</sub>- where c+d is an integer from 2 to 5 and Q is O or N, including spiro compounds thereof;

$R_2$  is  $-(CH_2)_n-A$ , wherein

$n$  is an integer from 0 to 5, and

$A$  is selected from unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

$R_4$  is  $-(CH_2)_p-E$ ,  $-CO-E$ , or  $-CO-NH-E$ , wherein

$p$  is an integer from 0 to 5,

$E$  is selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkynyl, unsubstituted or substituted cycloalkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted aryloxy;

$R_5$  is  $-(CH_2)_q-G$ , wherein

$q$  is an integer from 0 to 1, and

$G$  is selected from hydrogen,  $-N_3$ ,  $-NO_2$ ,  $-OH$ , -alkoxy, -alkyl,  $-NY_1Y_2$  wherein  $Y_1$  and  $Y_2$  are independently selected from hydrogen, unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

$R_6$  is  $-(CH_2)_m-L$  or  $-CHW-(CH_2)_m-L$ , wherein

$m$  is an integer from 0 to 5,

$W$  is alkyl or halogen, and

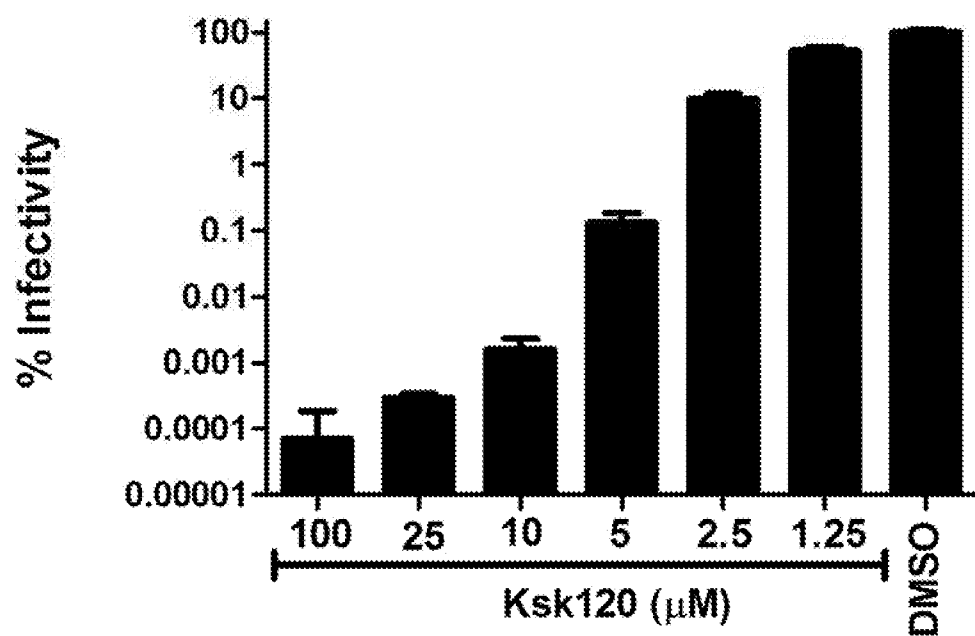
$L$  is fluorescent group.

21. The compound according to claim 20 wherein  $L$  is a fluorescent group comprising the BODIPY core 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene.
22. The compound according to claim 20 selected from  
 (3R)-8-Cyclopropyl-7-(2-(1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene-8-yl)ethyl)-5-oxo-3,5-dihydro-2H-thiazolo[3,2-a]pyridine-3-carboxylic acid  
 (3R)-8-cyclopropyl-7-(2-(1,3,5,7-tetramethyl-4,4-difluoro-4-bora-3a,4a-diaza-s-indacene-8-yl)ethyl)-methyl-5-oxo-N-phenyl-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]pyridine-3-carboxamide.

23. A method for the diagnosis of *Chlamydia* infections, or for the detection, quantification, and/or localization of *Chlamydia* cells and inclusions, said method comprising the use of a compound according to any of claims 20 to 22.

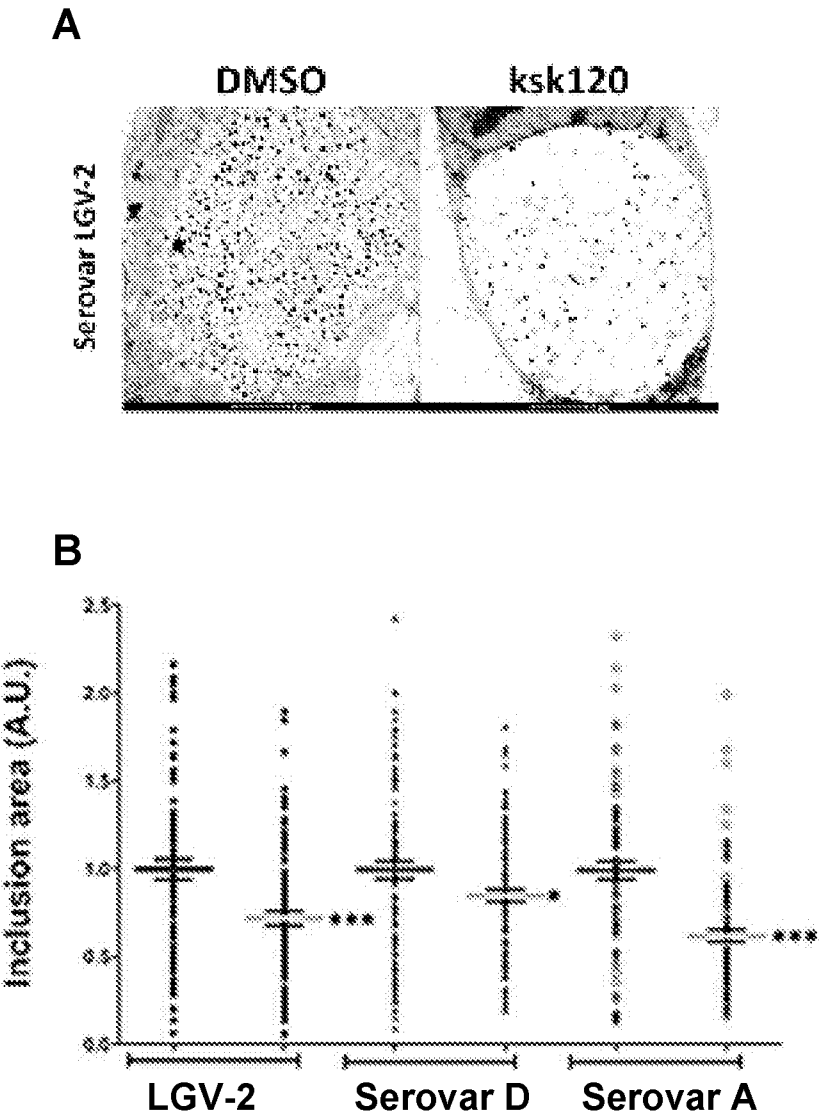
1(6)

Figure 1



2(6)

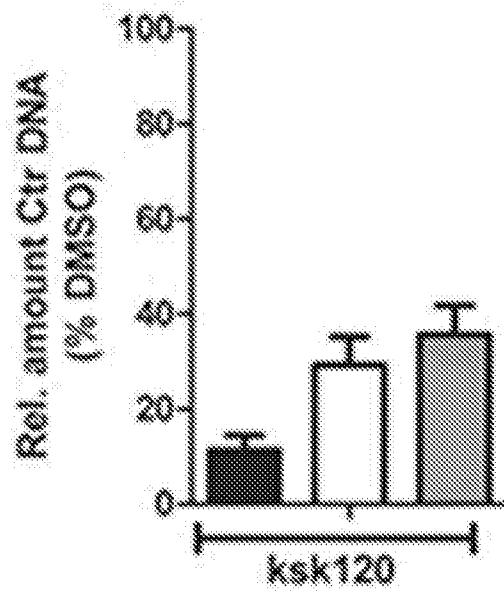
Figure 2



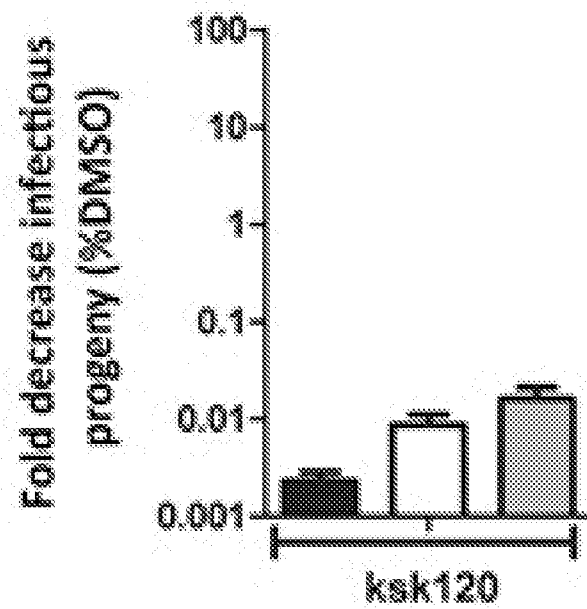
3(6)

Figure 3

A

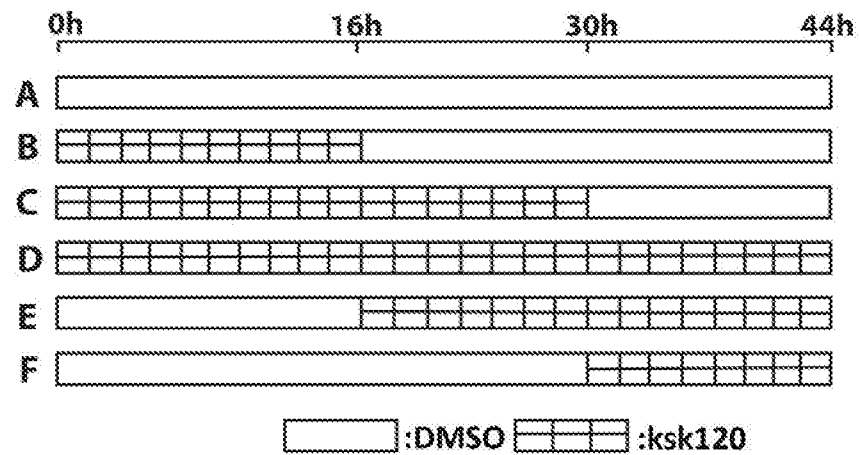
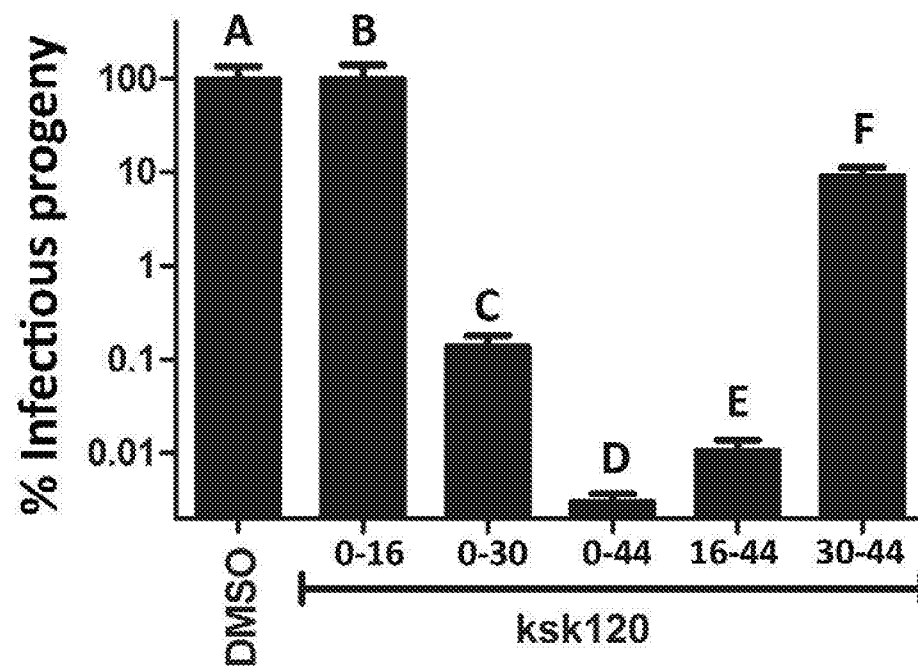


B



4(6)

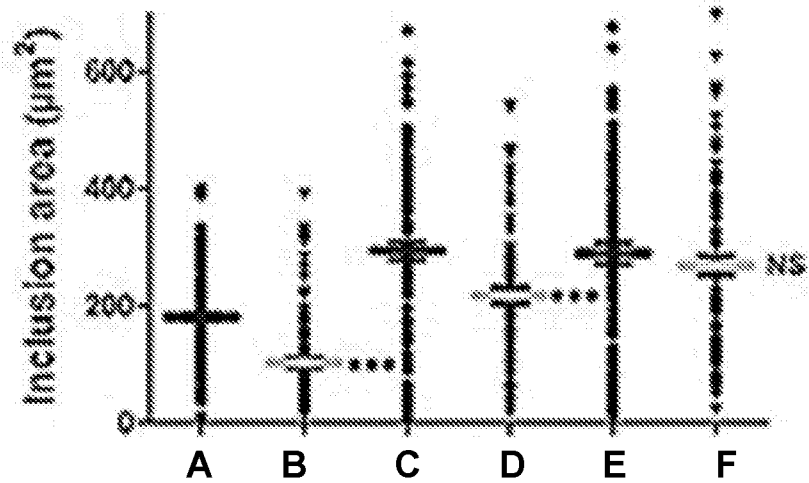
Figure 4

**A****B**

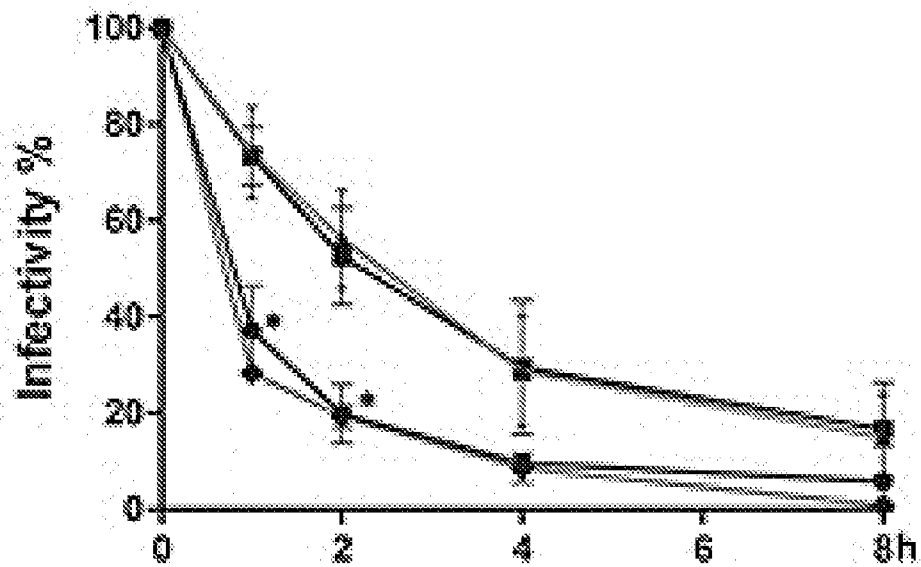
5(6)

Figure 5

A



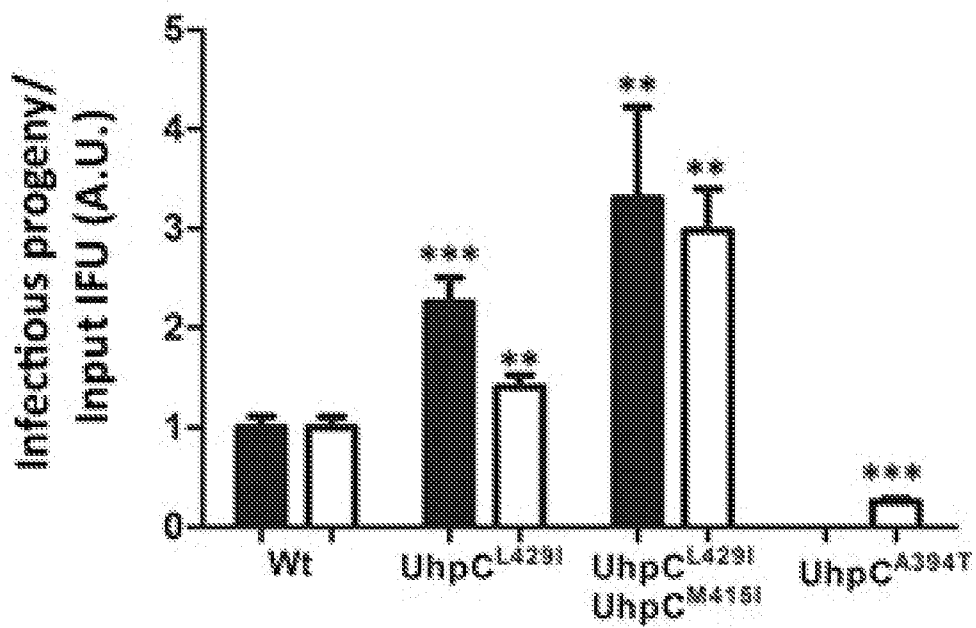
B



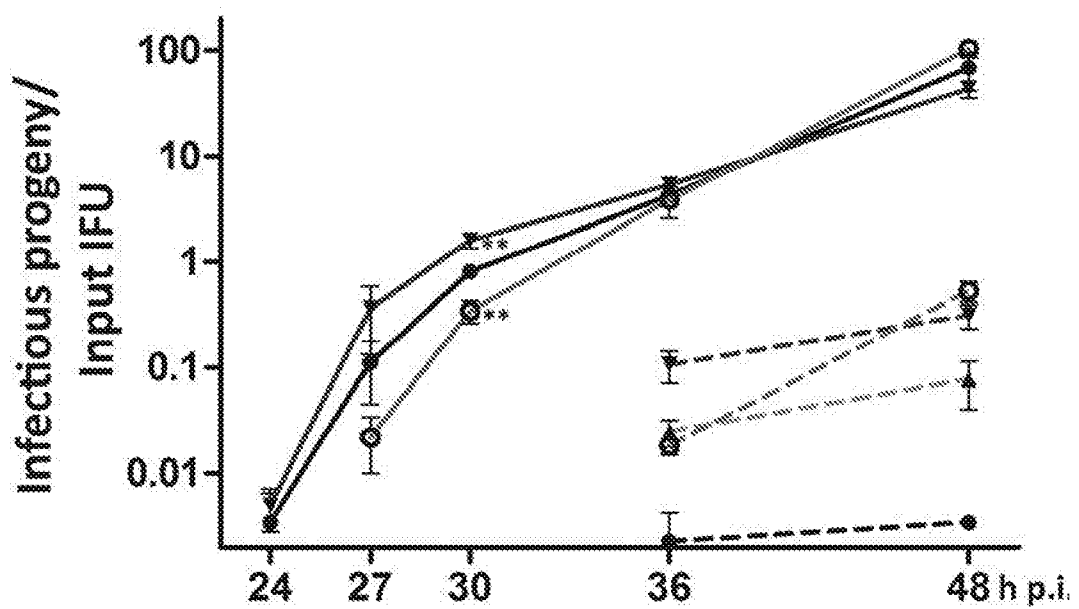
6(6)

Figure 6

A



B



## INTERNATIONAL SEARCH REPORT

 International application No.  
 PCT/SE2014/050584

## A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, A61P, C07D, C07F, C12Q, G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data, MEDLINE, Registry

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                      | Relevant to claim No. |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| P, X      | KRISHNAN K S et al., "Synthesis of fluorescent ring-fused 2-pyridone peptidomimetics", Journal of Organic Chemistry, 2013, (vol 78), pp. 12207-12213; page 12207; examples 5,6<br>--                                                    | 20-22                 |
| X         | ABERG V et al., "Carboxylic acid isosteres improve the activity of ring-fused 2-pyridones that inhibit pilus biogenesis in E. coli", Bioorganic & medicinal chemistry letters, 2008, 18, pp. 3536-3540; page 3538; examples 13-16<br>-- | 1-6, 9, 11            |
| X         | WO 2011076687 A1 (BAYER SCHERING PHARMA AG), 30 June 2011 (2011-06-30); pages 233-234; example 4.1, 4.2<br>--                                                                                                                           | 1-5, 9-11             |

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

01-09-2014

Date of mailing of the international search report

02-09-2014

Name and mailing address of the ISA/SE

Patent- och registreringsverket

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## INTERNATIONAL SEARCH REPORT

 International application No.  
 PCT/SE2014/050584

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                 | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | US 20080139607 A1 (ALMQVIST FREDRIK ET AL), 12 June 2008 (2008-06-12); [0126], examples 15-17,18a,18b. [0154], examples 16,18b,52-53<br>--                                                                                                                                                         | 1-6, 9, 11            |
| X         | CHORELL E et al., "Design and synthesis of C-2 substituted thiazolo and dihydrothiazolo ring-fused 2-pyridones: pilicides with increased antivirulence activity", J Med Chem, 2010, (53), pp. 5690-5695; page 5629, example 5a<br>--                                                               | 8                     |
| X         | CHORELL E. et al., "Design and synthesis of fluorescent pilicides and curlicides: bioactive tools to study bacterial virulence mechanisms", Chemistry (Weinheim an der Bergstrasse, Germany), 10 April 2012, vol 18, nr 15, pp. 4522-4532; page 4526, examples 10,34,37, page 4528, examples 33,34 | 20-21                 |
| A         | --                                                                                                                                                                                                                                                                                                 | 22-23                 |
| A         | BENGTSSON C et al., "Design, synthesis and evaluation of triazole functionalized ring-fused 2-pyridones as antibacterial agents", European Journal of Medicinal Chemistry (2012), 54, pp. 637-646; whole document<br>--                                                                            | 1-19                  |
| A         | CHORELL E et al., "Mapping pilicide anti-virulence effect in Escherichia coli, a comprehensive structure-activity study", Bioorg Med Chem, 2012, May 1, 20(9):3128-3142; whole document<br>--                                                                                                      | 1-19                  |
| A         | WO 2009073534 A2 (MAXTHERA INC), 11 June 2009 (2009-06-11); whole document<br>--                                                                                                                                                                                                                   | 1-19                  |
| A         | WO 2005102330 A2 (WASHINGTON UNIVERSITY), 3 November 2005 (2005-11-03)<br>--<br>-----                                                                                                                                                                                                              | 1-19                  |

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE2014/050584

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 1,7-11,13,19  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
The scope of the claims 1,7-11,13 and 19, in as far as the expression "prodrug" is  
  
.../...
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The following separate inventions were identified:

- 1: Claims 1-19, directed to ring-fused-2-pyridone compounds, useful in the prevention and/or treatment of Chlamydia infections.
- 2: Claims 20-23, directed to fluorescent ring-fused-2-pyridone compounds, useful for the detection, quantification and/or localization of Chlamydia cells and inclusions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

**Continuation of:** Box No. II

concerned, is so unclear (Article 6 PCT) that a meaningful search is impossible with regard to this expression. Thence it follows that a reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability only can be established for those parts which have been searched.

**Continuation of:** second sheet**International Patent Classification (IPC)*****C07D 513/04*** (2006.01)***A61K 31/4355*** (2006.01)***A61K 31/4365*** (2006.01)***A61K 31/69*** (2006.01)***A61P 31/04*** (2006.01)***C07D 498/04*** (2006.01)***C07F 5/02*** (2006.01)***C12Q 1/04*** (2006.01)***G01N 33/571*** (2006.01)

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SE2014/050584

|    |                |            |    |                |            |
|----|----------------|------------|----|----------------|------------|
| WO | 2011076687 A1  | 30/06/2011 | AR | 079688 A1      | 15/02/2012 |
|    |                |            | TW | 201130854 A    | 16/09/2011 |
| US | 20080139607 A1 | 12/06/2008 | AR | 063417 A1      | 28/01/2009 |
|    |                |            | CL | 2007003160 A1  | 22/08/2008 |
|    |                |            | PE | 14732008 A1    | 07/12/2008 |
|    |                |            | TW | 200823225 A    | 01/06/2008 |
|    |                |            | UY | 30673 A1       | 31/05/2008 |
|    |                |            | WO | 2008054290 A1  | 08/05/2008 |
| WO | 2009073534 A2  | 11/06/2009 | EP | 2225250 A2     | 08/09/2010 |
|    |                |            | JP | 2011505373 A   | 24/02/2011 |
|    |                |            | US | 20090203730 A1 | 13/08/2009 |
|    |                |            | US | 8124616 B2     | 28/02/2012 |
| WO | 2005102330 A2  | 03/11/2005 | US | 20080311644 A1 | 18/12/2008 |
|    |                |            | US | 20070082887 A1 | 12/04/2007 |
|    |                |            | US | 7915417 B2     | 29/03/2011 |
|    |                |            | US | 7411066 B2     | 12/08/2008 |