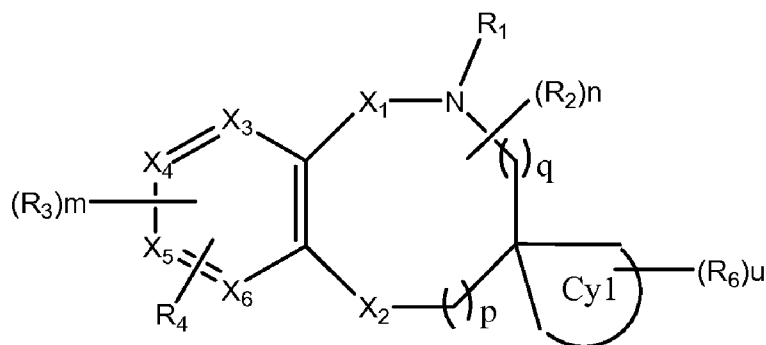




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(54) **Title:** SMALL MOLECULE INHIBITORS FOR TREATING PARASITIC INFECTIONS



Formula I.

(57) **Abstract:** The invention relates to a compound of Formula I or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof.

## SMALL MOLECULE INHIBITORS FOR TREATING PARASITIC INFECTIONS

## RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No.  
5 61/692,661 filed August 23, 2012 and 61/721,804 filed November 2, 2012. The entire  
contents of the above applications are incorporated by reference herein.

## GOVERNMENT SUPPORT

The invention was made with government support under U54-HG005032, awarded by  
the National Institutes of Health and under 1RO3-MH085673-01, awarded by the National  
10 Institutes of Health. The Government has certain rights in the invention.

## FIELD OF THE INVENTION

This invention relates to small molecule pharmaceutical compounds and to their uses  
for treatment of parasitic infections, in particular as antitrypanosomal therapeutic compounds  
to treat infections with protozoa, most particularly *Trypanosoma cruzi*.

## 15 BACKGROUND OF THE INVENTION

Trypanosomatids are a group of kinetoplastid protozoa distinguished by having only a  
single flagellum. Trypanosomatids are responsible for human diseases such as South  
American trypanosomiasis (Chagas Disease) caused by *Trypanosoma cruzi* and African  
trypanosomiasis (Sleeping Sickness) caused by *Trypanosoma brucei*. These diseases are  
20 predominately diseases of the third world.

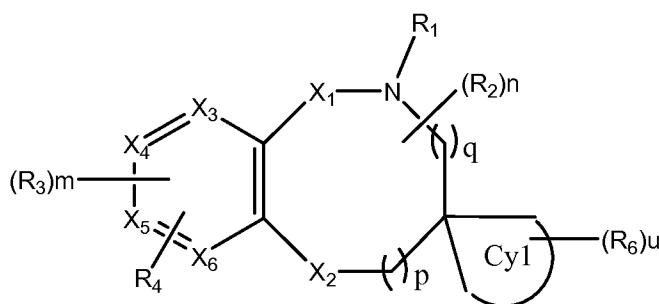
Chagas disease is endemic to 18 Latin American countries, with 13 million people  
chronically infected. Approximately 30% of chronically infected patients will suffer from  
irreversible damage to the heart and digestive tract leading to death.

Sleeping Sickness is endemic in some regions of sub-Saharan Africa, covering  
25 approximately 36 countries. It is estimated that 50,000-70,000 people are currently infected  
however it is also believed that many cases go unreported. The disease has 2 stages and  
without treatment is fatal. The first stage is characterized by fever, headaches, joint pain and  
itching. In the second phase of the disease the parasite invades the central nervous system by  
passing through the blood brain barrier and causes progressive mental deterioration leading to  
30 coma and death. Resistance is a problem with current treatments. In addition, current  
treatments are dosed via IV, which is difficult in many areas and adverse reaction to  
treatment can be severe and even life threatening.

In addition, Malaria is present in over 100 countries with more than 300 million new cases reported a year. 50% of malaria cases are caused by Plasmodium Falciparum. Plasmodium falciparum resistance has developed to many currently available malaria treatments.

## 5 SUMMARY OF THE INVENTION

The invention relates to a compound of Formula I or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula I

10 wherein

n is 0, 1, 2, 3, 4 or 5;

m is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

15 u is 0, 1, 2, 3, 4, 5, 6, 7, 8 or 9;

X<sub>1</sub> is C(O), C(S), S(O)<sub>2</sub>, CH<sub>2</sub>;

X<sub>2</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), CH<sub>2</sub>;

Each X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently selected from CR<sub>14</sub> and N;

wherein R<sub>14</sub> is selected from -CN, -S(O)<sub>2</sub>R<sub>10</sub>, hydrogen, alkyl, substituted

20 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

Cyl represents an optionally substituted cycloalkyl, cycloalkenyl, heterocyclyl or aryl  
25 containing one, two or three rings;

R<sub>1</sub> is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio,

aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl,  $-(CH_2)_z$ -heterocyclyl,  $-(CH_2)_z$ -heteroaryl or  $-(CH_2)_z$ -aryl wherein z is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

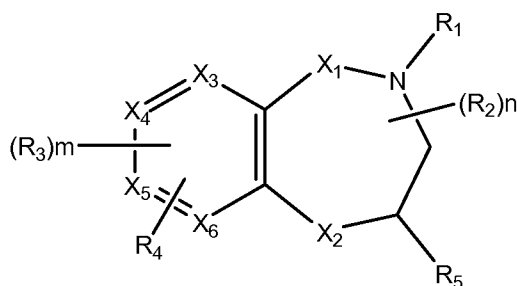
each  $R_2$  and  $R_3$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

wherein each  $R_{10}$  and  $R_{11}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{10}$  and  $R_{11}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring; and,

$R_4$  is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ ; and,

each  $R_6$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively two  $R_6$  groups together with the atoms to which they are attached to form an optionally substituted ring.

The invention relates to a compound of Formula II or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula II

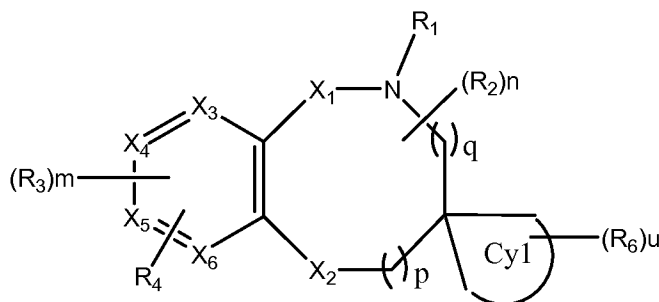
wherein  $R_5$  is hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,

- 5 heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio.

- The invention further relates to the treatment of a parasitic infection comprising the step of administering a compound of Formula I to a subject in need thereof. In a preferred embodiment, the invention relates to the treatment of a disease or disorder caused by Trypanosomatids comprising the step of administering a compound of Formula I to a subject in need thereof. In a more preferred embodiment, the disease or disorder is caused by *Trypanosoma cruzi* or *Trypanosoma brucei*. In a preferred embodiment, the disease or disorder is selected from Chagas disease, sometimes referred to as South American trypanosomiasis or African trypanosomiasis. In a more preferred embodiment, the disease is Chagas disease.

#### DETAILED DESCRIPTION OF THE INVENTION

- The invention relates to a compound of Formula I or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula I

wherein

n is 0, 1, 2, 3, 4 or 5;

m is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

5 u is 0, 1, 2, 3, 4, 5, 6, 7, 8 or 9;

X<sub>1</sub> is C(O), C(S), S(O)<sub>2</sub>, CH<sub>2</sub>;

X<sub>2</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), CH<sub>2</sub>;

Each X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently selected from CR<sub>14</sub> and N;

wherein R<sub>14</sub> is selected from -CN, -S(O)<sub>2</sub>R<sub>10</sub>, hydrogen, alkyl, substituted

10 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

Cyl represents an optionally substituted cycloalkyl, cycloalkenyl, heterocyclyl or aryl  
15 containing one, two or three rings;

R<sub>1</sub> is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted  
20 heteroaryl-(CH<sub>2</sub>)<sub>z</sub>-heterocyclyl, -(CH<sub>2</sub>)<sub>z</sub>-heteroaryl or -(CH<sub>2</sub>)<sub>z</sub>-aryl wherein z is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

each R<sub>2</sub> and R<sub>3</sub> is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or  
25 substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

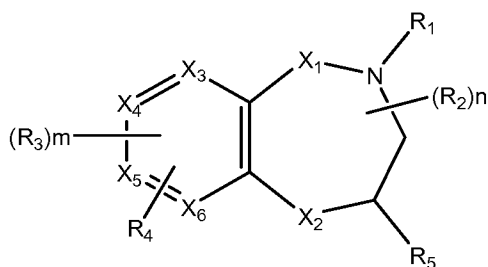
wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl,

30 substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring; and,

R<sub>4</sub> is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>; and,

each R<sub>6</sub> is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively two R<sub>6</sub> groups together with the atoms to which they are attached to form an optionally substituted ring.

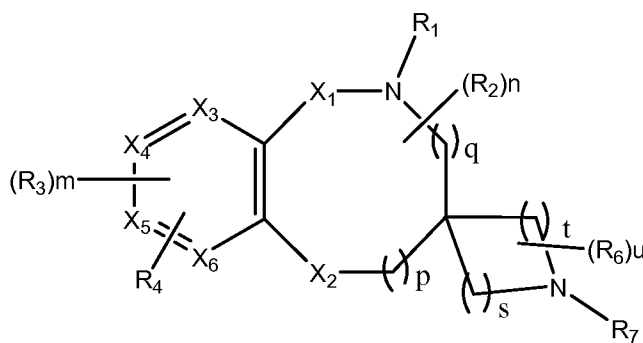
The invention relates to a compound of Formula II or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula II

wherein R<sub>5</sub> is hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio.

The invention relates to a compound of Formula III or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;

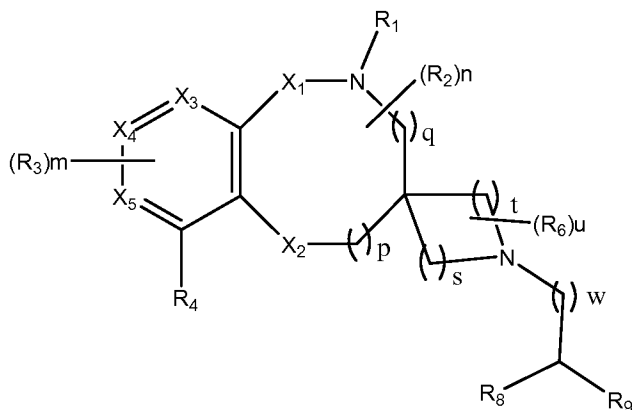


### Formula III

wherein each s and t is independently 0, 1, 2, 3, 4, 5, or 6;

5 R<sub>7</sub> is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio.

10           The invention relates to a compound of Formula IIIA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



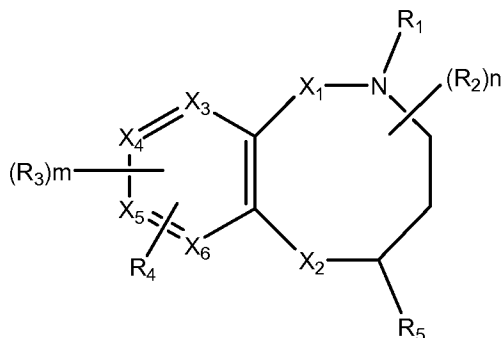
### Formula IIIA

wherein w is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

15 R<sub>8</sub> and R<sub>9</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio

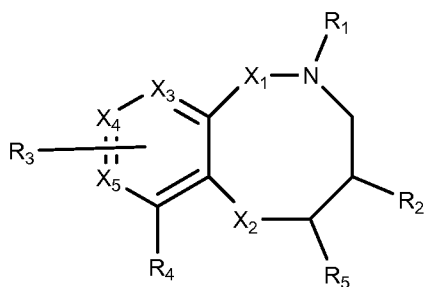
or substituted alkylthio; alternatively  $R_8$  and  $R_9$  together with the atom they are attached may form an optionally substituted two, three or four membered ring.

The invention relates to a compound of Formula IV or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula IV.

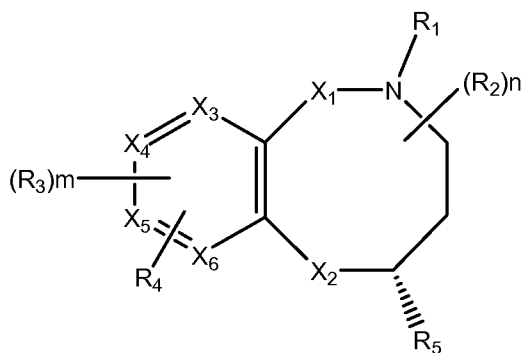
In a preferred embodiment, the invention relate to a compound of Formula IVA:



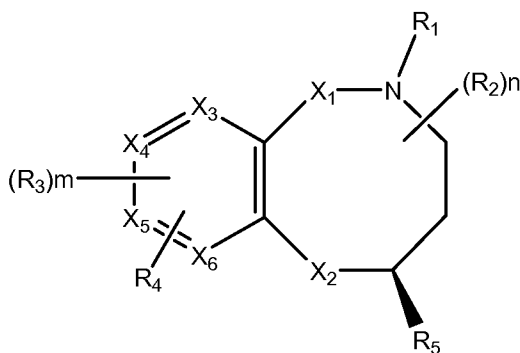
Formula IVA.

In a preferred embodiment, the invention relates to a compound of Formula IVA wherein  $R_4$  is heterocyclyl, substituted heterocyclyl, heteroaryl or substituted heteroaryl.

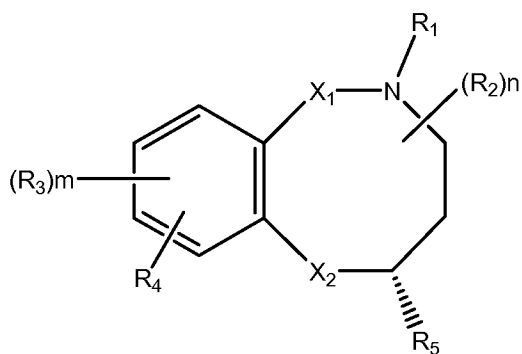
In a preferred embodiment, the invention relates to a compound of Formula IVB, IVC, IVD, IVE or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



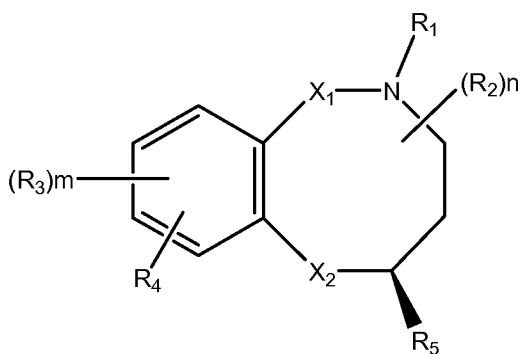
Formula IVB



Formula IVC

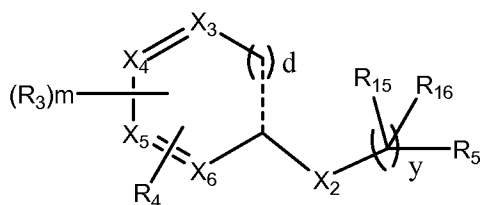


Formula IVD



Formula IVE.

The invention relates to a compound of Formula V or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula V

wherein

m is 0, 1, 2, 3 or 4;

d is 0, 1, 2 or 3;

y is 0, 1, 2 or 3;

X<sub>2</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), CH<sub>2</sub>;

Each X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently selected from CR<sub>14</sub> and N;

wherein R<sub>14</sub> is selected from -CN, -S(O)<sub>2</sub>R<sub>10</sub>, hydrogen, alkyl, substituted

alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy,

substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino,

substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl,

heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

Each R<sub>3</sub>, R<sub>15</sub> and R<sub>16</sub> is independently selected from hydrogen, halogen, alkyl,

substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic,

substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl,

heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -

C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted

alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino,

alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring;

wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring;

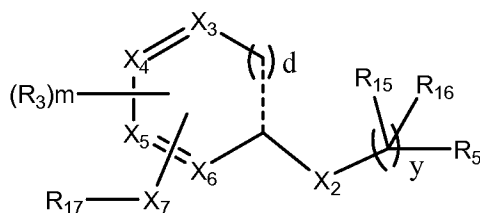
R<sub>4</sub> is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>; and,

$R_5$  is  $-G_1-X_{10}$ ;

wherein G<sub>1</sub> is absent, C<sub>1</sub>-C<sub>12</sub>-alkyl, substituted C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenyl, C<sub>2</sub>-C<sub>12</sub>-alkynyl or substituted C<sub>2</sub>-C<sub>12</sub>-alkynyl; and, X<sub>10</sub> is -NR<sub>12</sub>R<sub>13</sub>, -OR<sub>12</sub>, -SR<sub>12</sub>, -C(O)R<sub>12</sub>, -C(O)OR<sub>12</sub>, -C(O)NR<sub>12</sub>R<sub>13</sub>, -N(R<sub>12</sub>)C(O)R<sub>13</sub>, -S(O)R<sub>12</sub> or S(O)<sub>2</sub>R<sub>12</sub>.

wherein each R<sub>12</sub> and R<sub>13</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>12</sub> and R<sub>13</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

The invention relates to a compound of Formula VA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VA

wherein

m is 0, 1, 2, 3 or 4;

$d$  is 0, 1, 2 or 3;

y is 0, 1, 2 or 3;

X<sub>2</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), CH<sub>2</sub>;

X<sub>7</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

Each X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently selected from CR<sub>14</sub> and N;

5            wherein R<sub>14</sub> is selected from -CN, -S(O)<sub>2</sub>R<sub>10</sub>, hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

10          Each R<sub>3</sub>, R<sub>15</sub> and R<sub>16</sub> is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring;

             wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring;

R<sub>17</sub> is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and,

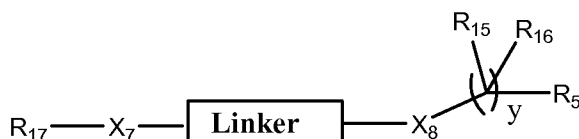
25          R<sub>5</sub> is -G<sub>1</sub>-X<sub>10</sub>;

             wherein G<sub>1</sub> is absent, C<sub>1</sub>-C<sub>12</sub>-alkyl, substituted C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenyl, C<sub>2</sub>-C<sub>12</sub>-alkynyl or substituted C<sub>2</sub>-C<sub>12</sub>-alkynyl; and, X<sub>10</sub> is -NR<sub>12</sub>R<sub>13</sub>, -OR<sub>12</sub>, -SR<sub>12</sub>, -C(O)R<sub>12</sub>, -C(O)OR<sub>12</sub>, -C(O)NR<sub>12</sub>R<sub>13</sub>, -N(R<sub>12</sub>)C(O)R<sub>13</sub>, -S(O)R<sub>12</sub> or S(O)<sub>2</sub>R<sub>12</sub>;

30            wherein each R<sub>12</sub> and R<sub>13</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>12</sub> and R<sub>13</sub> together with the atoms to which

they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

The invention relates to a compound of Formula VI or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VI

wherein

y is 0, 1, 2 or 3;

X<sub>8</sub> is absent, O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

X<sub>7</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

Linker is a bivalent aliphatic, substituted aliphatic, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl group;

Each R<sub>15</sub> and R<sub>16</sub> is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring;

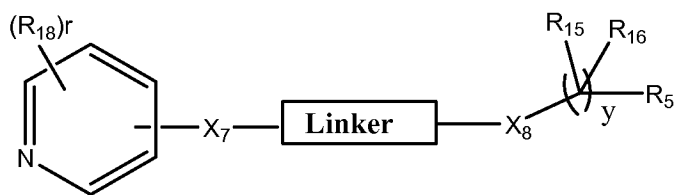
wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring;

R<sub>17</sub> is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and, R<sub>5</sub> is -G<sub>1</sub>-X<sub>10</sub>;

wherein  $G_1$  is absent,  $C_1$ - $C_{12}$ -alkyl, substituted  $C_1$ - $C_{12}$ -alkyl,  $C_2$ - $C_{12}$ -alkenyl, substituted  $C_2$ - $C_{12}$ -alkenyl,  $C_2$ - $C_{12}$ -alkynyl or substituted  $C_2$ - $C_{12}$ -alkynyl; and,  $X_{10}$  is  $-NR_{12}R_{13}$ ,  $-OR_{12}$ ,  $-SR_{12}$ ,  $-C(O)R_{12}$ ,  $-C(O)OR_{12}$ ,  $-C(O)NR_{12}R_{13}$ ,  $-N(R_{12})C(O)R_{13}$ ,  $-S(O)R_{12}$  or  $S(O)_2R_{12}$ ;

5                    wherein each  $R_{12}$  and  $R_{13}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{12}$  and  $R_{13}$  together with the atoms to which they are attached and any intervening atoms may form an additional  
10                    optionally substituted, 3, 4, 5, 6 or 7 membered ring.

The invention relates to a compound of Formula VIA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



15                    Formula VIA

wherein

$y$  is 0, 1, 2 or 3;

$r$  is 0, 1, 2 or 3;

$X_8$  is absent, O, S,  $S(O)_2$ ,  $NR_{10}$ ,  $C(O)$ ,  $C(O)NR_{10}$ ,  $C(S)$ ,  $C(S)NR_{10}$ ,  $C(R_{10})(R_{11})$ ;

20                     $X_7$  is O, S,  $S(O)_2$ ,  $NR_{10}$ ,  $C(O)$ ,  $C(O)NR_{10}$ ,  $C(S)$ ,  $C(S)NR_{10}$ ,  $C(R_{10})(R_{11})$ ;

Linker is a bivalent aliphatic, substituted aliphatic, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl group;

25                    Each  $R_{15}$ ,  $R_{16}$  and  $R_{18}$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted  
30                    alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino,

alkylthio or substituted alkylthio; alternatively  $R_{15}$  and  $R_{16}$  together may form an optionally substituted three, four, five, six or seven membered ring;

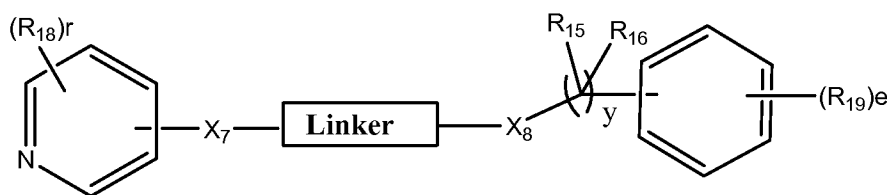
wherein each  $R_{10}$  and  $R_{11}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{10}$  and  $R_{11}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring; and,

$R_5$  is  $-G_1-X_{10}$ ;

wherein  $G_1$  is absent,  $C_1-C_{12}$ -alkyl, substituted  $C_1-C_{12}$ -alkyl,  $C_2-C_{12}$ -alkenyl, substituted  $C_2-C_{12}$ -alkenyl,  $C_2-C_{12}$ -alkynyl or substituted  $C_2-C_{12}$ -alkynyl; and,  $X_{10}$  is  $-NR_{12}R_{13}$ ,  $-OR_{12}$ ,  $-SR_{12}$ ,  $-C(O)R_{12}$ ,  $-C(O)OR_{12}$ ,  $-C(O)NR_{12}R_{13}$ ,  $-N(R_{12})C(O)R_{13}$ ,  $-S(O)R_{12}$  or  $S(O)_2R_{12}$ ;

wherein each  $R_{12}$  and  $R_{13}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{12}$  and  $R_{13}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

The invention relates to a compound of Formula VIB or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VIB

wherein

$y$  is 0, 1, 2 or 3;

$r$  is 0, 1, 2 or 3;

$e$  is 0, 1, 2 or 3;

$X_8$  is absent, O, S,  $S(O)_2$ ,  $NR_{10}$ ,  $C(O)$ ,  $C(O)NR_{10}$ ,  $C(S)$ ,  $C(S)NR_{10}$ ,  $C(R_{10})(R_{11})$ ;

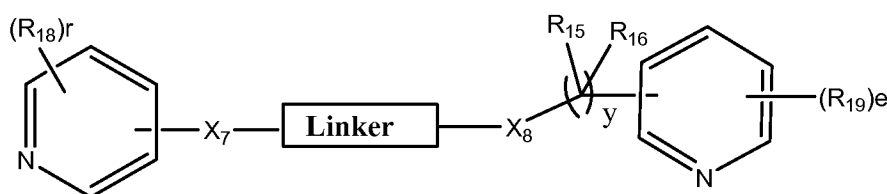
$X_7$  is O, S,  $S(O)_2$ ,  $NR_{10}$ ,  $C(O)$ ,  $C(O)NR_{10}$ ,  $C(S)$ ,  $C(S)NR_{10}$ ,  $C(R_{10})(R_{11})$ ;

Linker is a bivalent aliphatic, substituted aliphatic, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl group;

Each  $R_{15}$ ,  $R_{16}$ ,  $R_{18}$  and  $R_{19}$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively  $R_{15}$  and  $R_{16}$  together may form an optionally substituted three, four, five, six or seven membered ring; and,

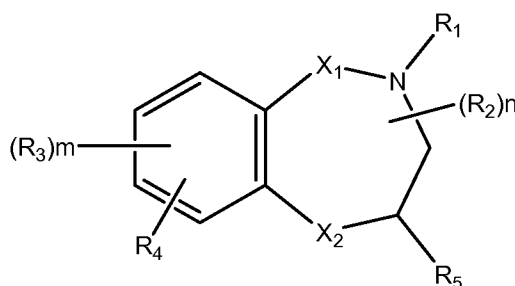
wherein each  $R_{10}$  and  $R_{11}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{10}$  and  $R_{11}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

The invention relates to a compound of Formula VIC or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VIC.

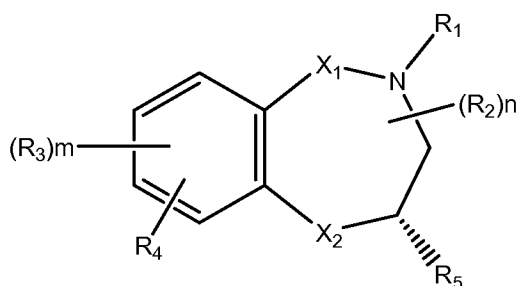
The invention relates to a compound of Formula IIA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



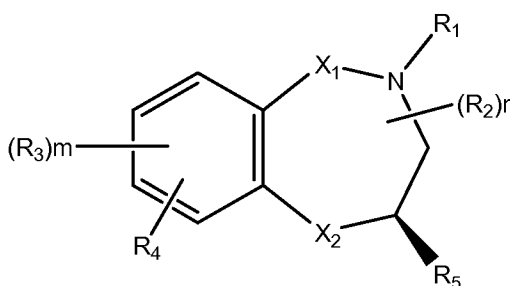
Formula IIA

wherein  $R_5$  is hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively two  $R_2$  groups, or an  $R_2$  group and an  $R_5$  group, together forms an optionally substituted ring.

In a preferred embodiment, the invention relates to a compound of Formula IIB or IIC, or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof:



Formula IIB



Formula IIC.

The invention further relates to the treatment of a parasitic infection comprising the step of administering a compound of Formula I-IV to a subject in need thereof. In a preferred embodiment, the invention relates to the treatment of a disease or disorder caused by Trypanosomatids comprising the step of administering a compound of Formula I to a subject in need thereof. In a more preferred embodiment, the disease or disorder is caused by *Trypanosoma cruzi* or *Trypanosoma brucei*. In a preferred embodiment, the disease or disorder is Chagas disease.

In a preferred embodiment,  $X_1$  is C(O). In a preferred embodiment,  $X_2$  is O.

In a preferred embodiment,  $R_1$  is selected from C<sub>1</sub>-C<sub>12</sub>-alkyl, substituted C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenyl, C<sub>2</sub>-C<sub>12</sub>-alkynyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkynyl, C<sub>1</sub>-C<sub>12</sub>-alkylhydroxy, substituted C<sub>1</sub>-C<sub>12</sub>-alkylhydroxy, C<sub>2</sub>-C<sub>12</sub>-alkenylhydroxy, substituted C<sub>2</sub>-C<sub>12</sub>-alkenylhydroxy, C<sub>2</sub>-C<sub>12</sub>-alkynylhydroxy, substituted C<sub>2</sub>-C<sub>12</sub>-alkynylhydroxy, C<sub>1</sub>-C<sub>12</sub>-alkylthio, substituted C<sub>1</sub>-C<sub>12</sub>-alkylthio, C<sub>2</sub>-C<sub>12</sub>-alkenylthio, substituted C<sub>2</sub>-C<sub>12</sub>-alkenylthio, C<sub>2</sub>-C<sub>12</sub>-alkynylthio, substituted C<sub>2</sub>-C<sub>12</sub>-alkynylthio, C<sub>3</sub>-C<sub>12</sub> cycloalkyl and substituted C<sub>3</sub>-C<sub>12</sub>-cycloalkyl.

In a preferred embodiment, the invention relates to a compound of Formula I-IV wherein  $R_2$  is selected from hydrogen, halogen, C<sub>1</sub>-C<sub>12</sub>-alkyl, substituted C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-

C<sub>12</sub>-alkenyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenyl, C<sub>2</sub>-C<sub>12</sub>-alkynyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkynyl, C<sub>5</sub>-C<sub>12</sub> aryl, substituted C<sub>5</sub>-C<sub>12</sub> aryl C<sub>3</sub>-C<sub>12</sub> cycloalkyl and substituted C<sub>3</sub>-C<sub>12</sub>-cycloalkyl.

In a preferred embodiment the invention relates to a compound of Formula II wherein R<sub>5</sub> is selected from -G<sub>1</sub>-X<sub>10</sub>;

5 wherein G<sub>1</sub> is absent, C<sub>1</sub>-C<sub>12</sub>-alkyl, substituted C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenyl, C<sub>2</sub>-C<sub>12</sub>-alkynyl or substituted C<sub>2</sub>-C<sub>12</sub>-alkynyl; and, X<sub>10</sub> is -NR<sub>12</sub>R<sub>13</sub>, -OR<sub>12</sub>, -SR<sub>12</sub>, -C(O)R<sub>12</sub>, -C(O)OR<sub>12</sub>, -C(O)NR<sub>12</sub>R<sub>13</sub>, -N(R<sub>12</sub>)C(O)R<sub>13</sub>, -S(O)R<sub>12</sub> or S(O)<sub>2</sub>R<sub>12</sub>;

10 wherein each R<sub>12</sub> and R<sub>13</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>12</sub> and R<sub>13</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

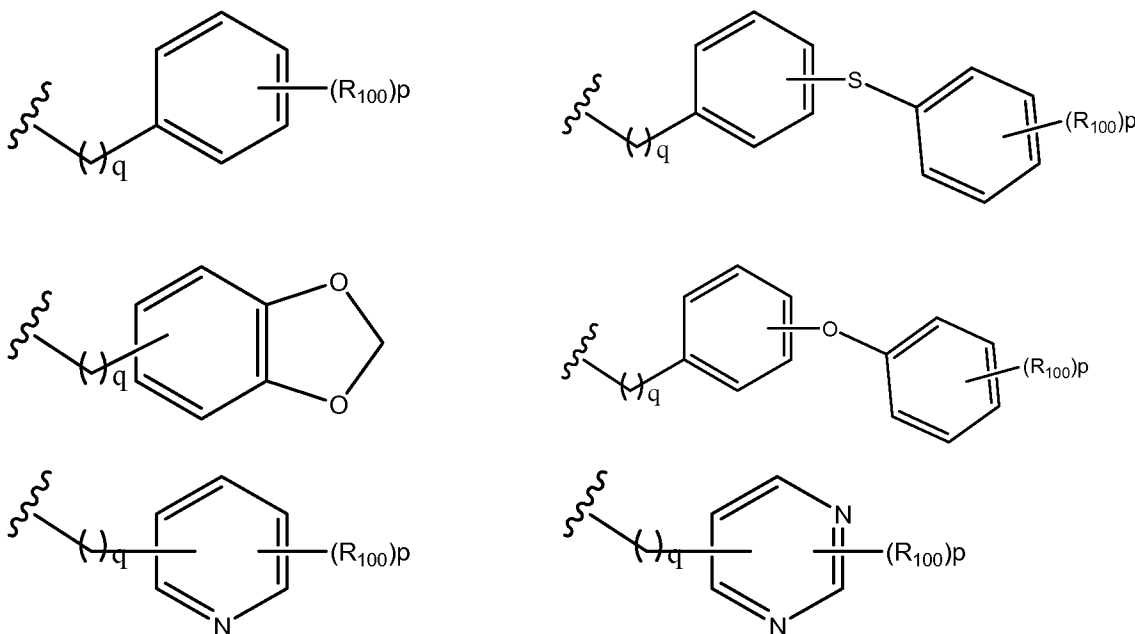
15 In a preferred embodiment, R<sub>12</sub> is C<sub>1</sub>-C<sub>12</sub>-alkylaryl, substituted C<sub>1</sub>-C<sub>12</sub>-alkylaryl, C<sub>2</sub>-C<sub>12</sub>-alkenylaryl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenylaryl, C<sub>2</sub>-C<sub>12</sub>-alkynylaryl or substituted C<sub>2</sub>-C<sub>12</sub>-alkynylaryl.

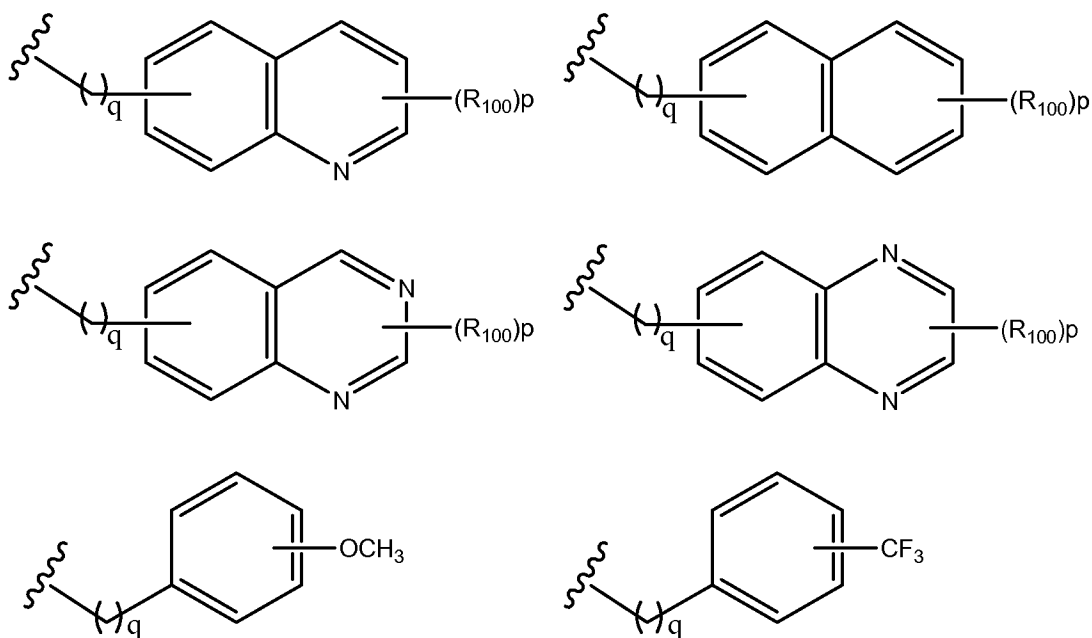
In a preferred embodiment, R<sub>13</sub> is hydrogen, methyl, ethyl, propyl or isopropyl.

In a preferred embodiment, R<sub>12</sub> is selected from Table A:

20

TABLE A





wherein  $q$  is 0, 1, 2, 3, 4, 5, or 6;

$p$  is 0, 1, 2, 3, 4 or 5;

$R_{100}$  is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,  $-OR_{101}$ ,  $-SR_{101}$ ,  $-NR_{101}R_{102}$ ,  $-C(O)R_{101}$ ,  $-C(O)OR_{101}$ ,  $-C(O)NR_{101}R_{102}$ ,  $-N(R_{101})C(O)R_{102}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

wherein each  $R_{101}$  and  $R_{102}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{101}$  and  $R_{102}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

In a preferred embodiment,  $R_4$  is  $-X_{11}-G_2$ ;

wherein  $X_{11}$  is absent,  $C_1-C_{12}$ -alkyl, substituted  $C_1-C_{12}$ -alkyl,  $C_2-C_{12}$ -alkenyl, substituted  $C_2-C_{12}$ -alkenyl,  $C_2-C_{12}$ -alkynyl, substituted  $C_2-C_{12}$ -alkynyl,  $-NR_{14}$ ,  $-O-$ ,  $-S-$ ,  $-C(O)-$ ,  $-C(O)O-$ ,  $-C(O)NR_{14}$ ,  $-N(R_{14})C(O)-$ ,  $-S(O)-$  or  $S(O)_2-$ ;

wherein  $R_{14}$  is selected from hydrogen,  $-CN$ ,  $-S(O)_2R_{10}$ , alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted

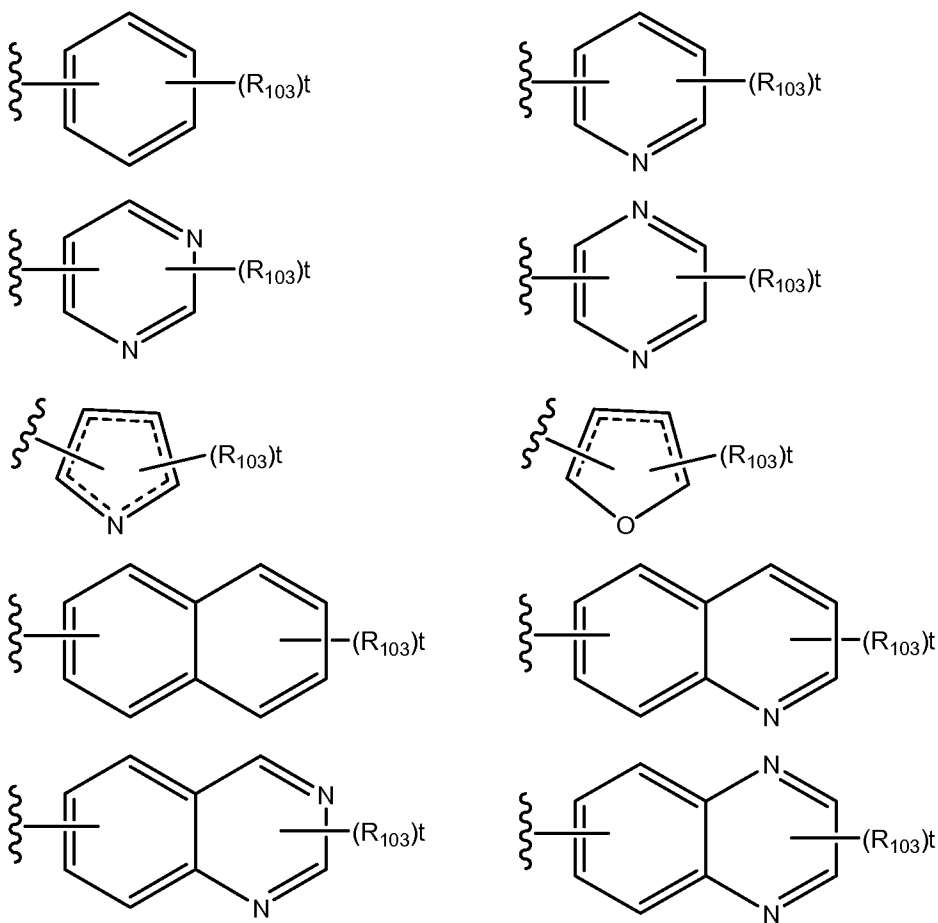
alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,  
heteroaryl, substituted heteroaryl, heterocyclic or substituted  
heterocyclic; and,

$G_2$  is aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or  
substituted heterocyclic.

In a more preferred embodiment,  $R_4$  is  $-X_{11}-G_2$  wherein  $-X_{11}-$  is  $-NHC(O)-$ ,  $-C(O)N(CH_3)-$ ,  $-C(O)-$ ,  $-C(O)O-$  or  $-NH-$ .

In a preferred embodiment,  $G_2$  is selected from Table B:

TABLE B



$t$  is 0, 1, 2, 3, 4 or 5;

$R_{103}$  is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,  $-OR_{101}$ ,  $-SR_{104}$ ,  $-NR_{104}R_{105}$ ,  $-C(O)R_{104}$ ,  $-C(O)OR_{104}$ ,  $-C(O)NR_{104}R_{105}$ , -

$N(R_{104})C(O)R_{105}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino,

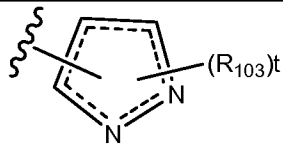
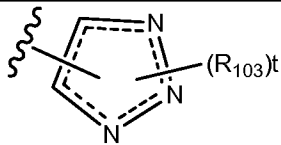
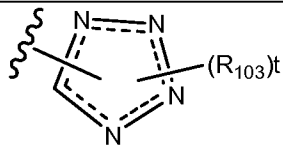
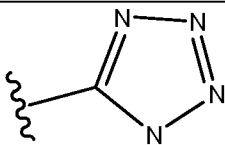
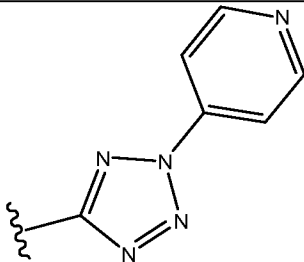
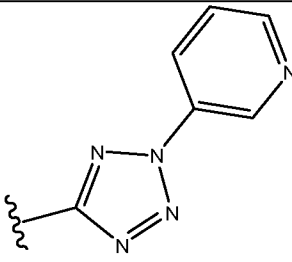
substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

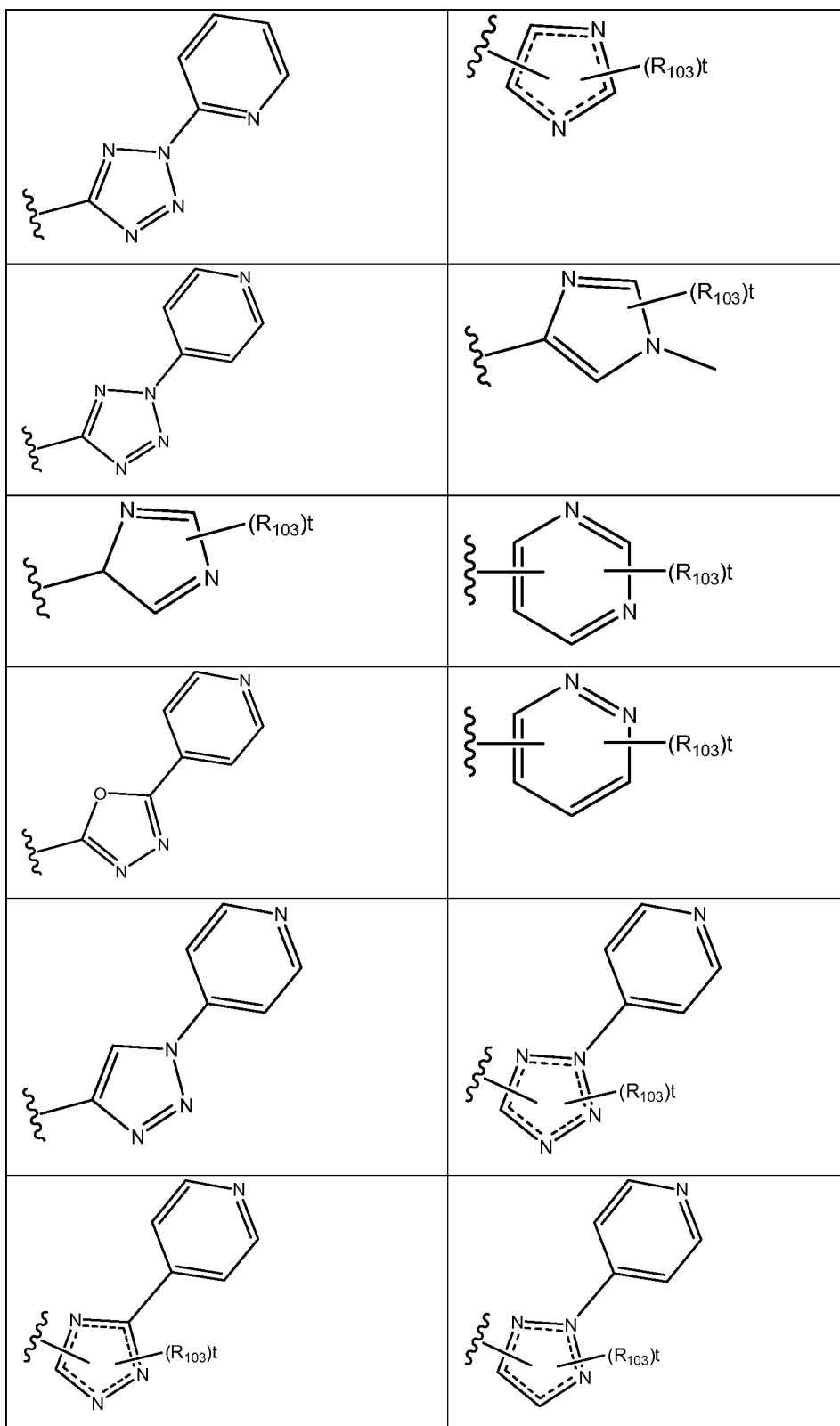
wherein each  $R_{104}$  and  $R_{105}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic; alternatively two  $R_{104}$  and  $R_{105}$  groups together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

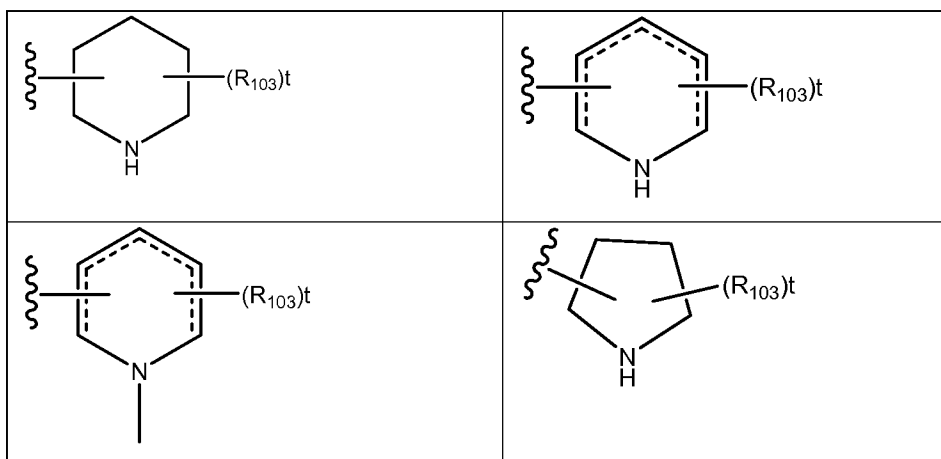
- 10 In a more preferred embodiment,  $R_1$  is  $C_1$ - $C_8$ -alkyl,  $C_1$ - $C_8$ -alkenyl or  $C_1$ - $C_8$ -alkynyl.
- In a more preferred embodiment,  $R_1$  is a  $C_1$ - $C_4$ -alkyl  $C_1$ - $C_4$ -alkenyl or  $C_1$ - $C_4$ -alkynyl. In a more preferred embodiment,  $R_1$  is a  $C_1$ - $C_4$ -alkylhydroxy, substituted  $C_1$ - $C_4$ -alkylhydroxy,  $C_2$ - $C_4$ -alkenylhydroxy, substituted  $C_2$ - $C_4$ -alkenylhydroxy,  $C_2$ - $C_4$ -alkynylhydroxy, substituted  $C_2$ - $C_4$ -alkynylhydroxy,  $C_1$ - $C_4$ -alkylthio, substituted  $C_1$ - $C_4$ -alkylthio,  $C_2$ - $C_4$ -alkenylthio, substituted  $C_2$ - $C_4$ -alkenylthio,  $C_2$ - $C_4$ -alkynylthio, substituted  $C_2$ - $C_4$ -alkynylthio.

In another preferred embodiment,  $G_2$  is selected from Table B2:

TABLE B2

|                                                                                     |                                                                                      |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|  |  |
|  |  |
|  |  |





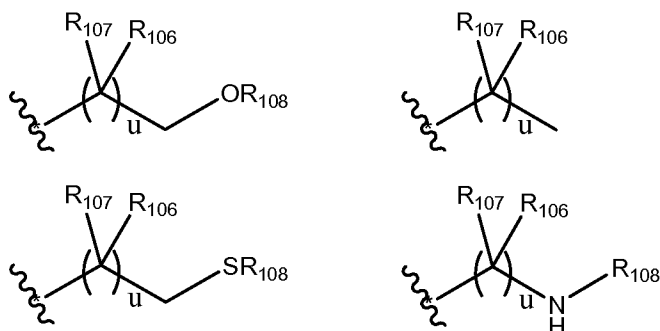
t is 0, 1, 2, 3, 4 or 5;

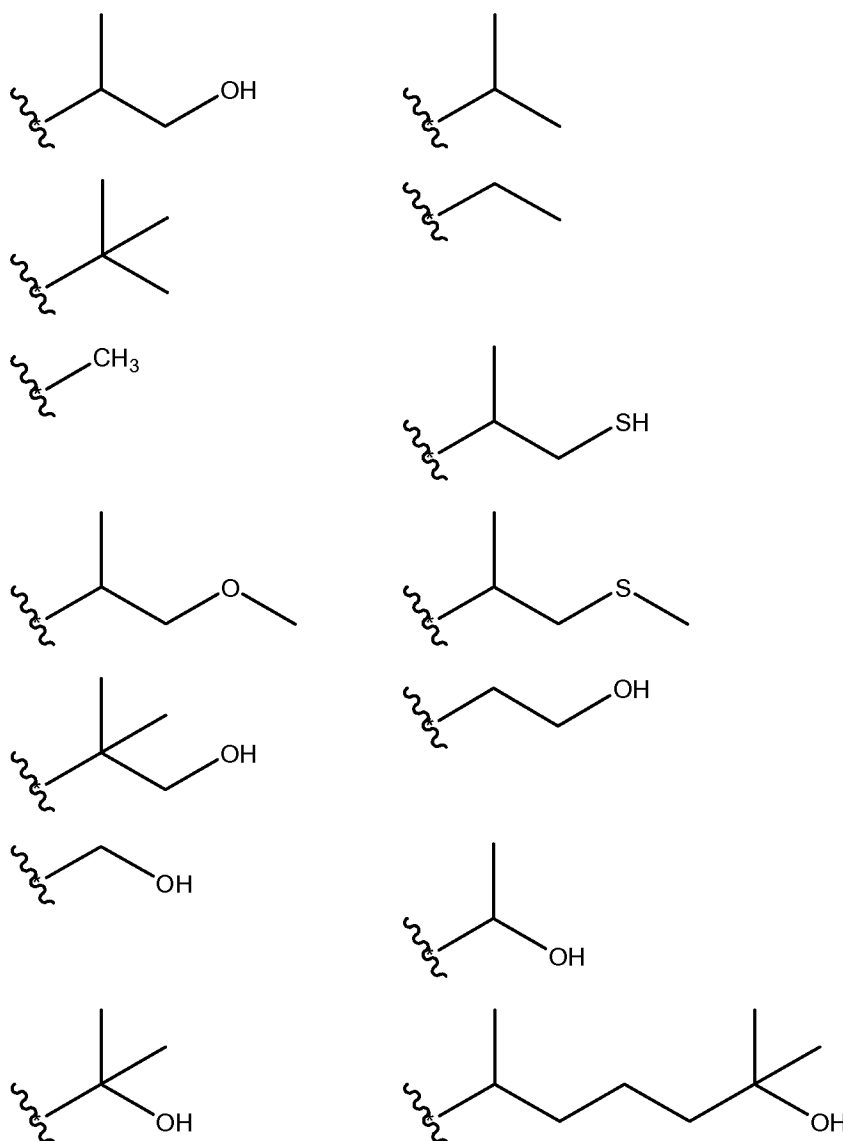
R<sub>103</sub> is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, -OR<sub>101</sub>, -SR<sub>104</sub>, -NR<sub>104</sub>R<sub>105</sub>, -C(O)R<sub>104</sub>, -C(O)OR<sub>104</sub>, -C(O)NR<sub>104</sub>R<sub>105</sub>, -  
 5 N(R<sub>104</sub>)C(O)R<sub>105</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

wherein each R<sub>104</sub> and R<sub>105</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic; alternatively two R<sub>104</sub> and R<sub>105</sub> groups together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7  
 10 membered ring.

In a more preferred embodiment, R<sub>1</sub> is selected from Table C:

TABLE C





u is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;

each  $R_{106}$ ,  $R_{107}$  and  $R_{108}$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,  $-OR_{109}$ ,  $-SR_{109}$ ,  $-NR_{109}R_{110}$ ,  $-C(O)R_{109}$ ,  $-C(O)OR_{109}$ ,  $-C(O)NR_{109}R_{110}$ ,  $-N(R_{109})C(O)R_{110}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

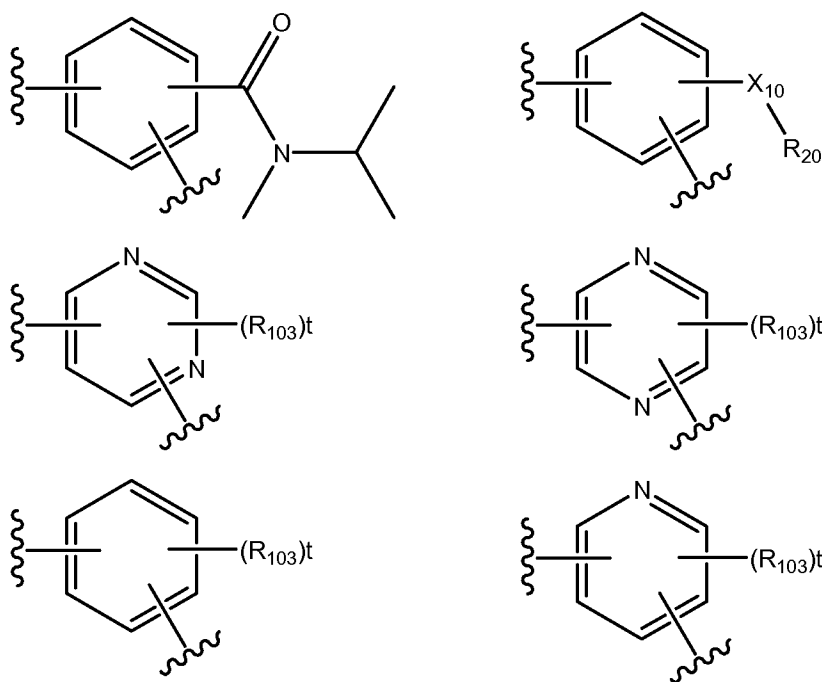
wherein each  $R_{109}$  and  $R_{110}$  is independently selected from hydrogen, alkyl,

substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two  $R_{109}$  and  $R_{110}$  groups together

with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7.

In a preferred embodiment, the Linker is selected from Table D:

TABLE D



5 t is 0, 1, 2, 3, 4 or 5;

R<sub>103</sub> is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, -OR<sub>101</sub>, -SR<sub>104</sub>, -NR<sub>104</sub>R<sub>105</sub>, -C(O)R<sub>104</sub>, -C(O)OR<sub>104</sub>, -C(O)NR<sub>104</sub>R<sub>105</sub>, -N(R<sub>104</sub>)C(O)R<sub>105</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

15 wherein each R<sub>104</sub> and R<sub>105</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic or substituted heterocyclic; alternatively two R<sub>104</sub> and R<sub>105</sub> groups together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring;

X<sub>10</sub> is absent, O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

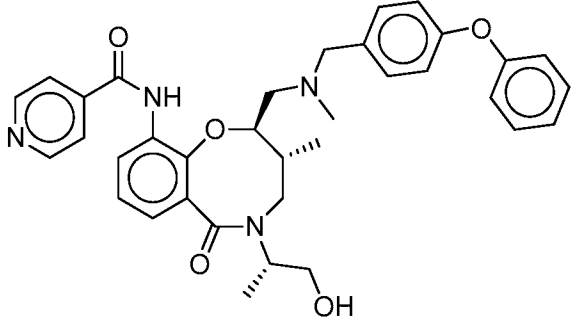
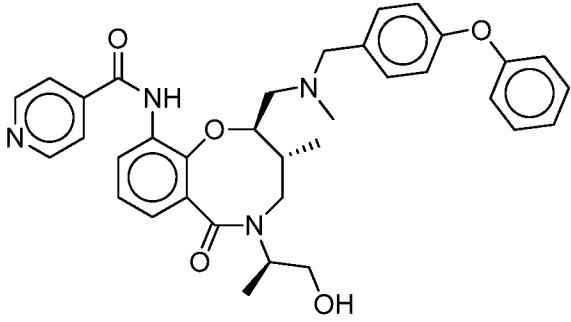
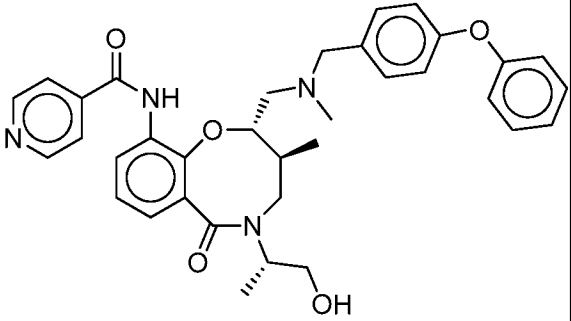
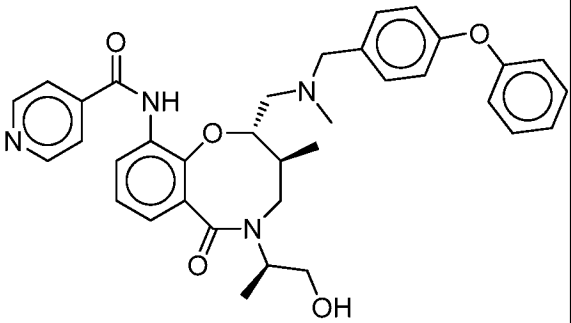
R<sub>20</sub> is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring; and,

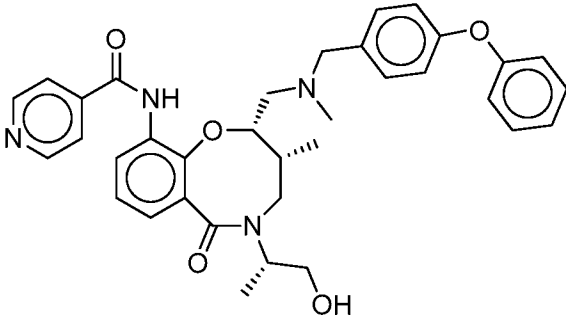
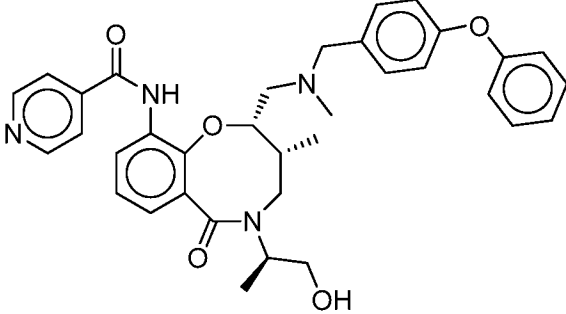
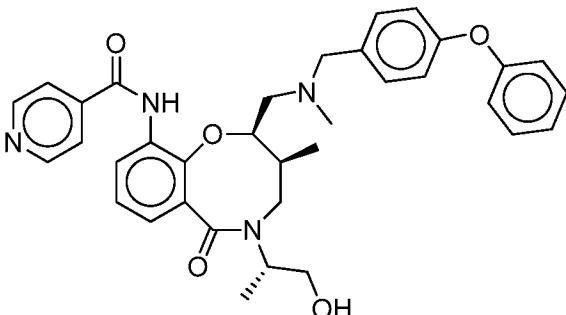
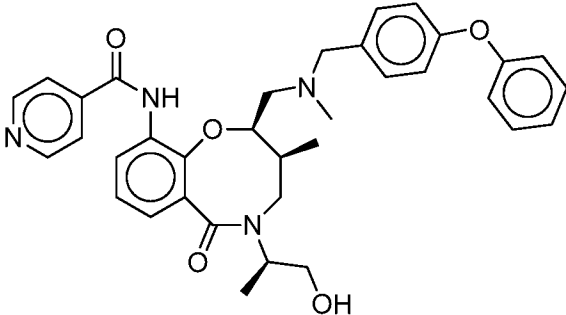
wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

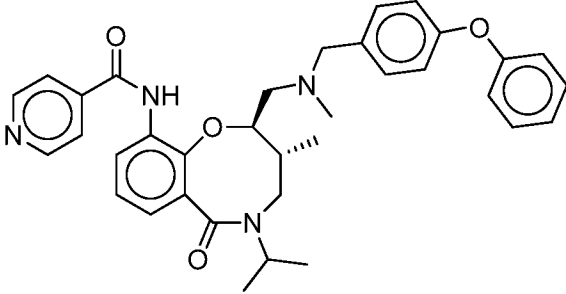
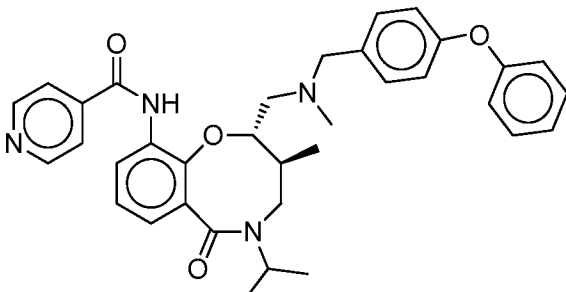
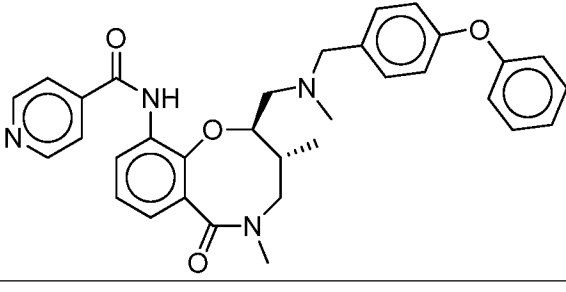
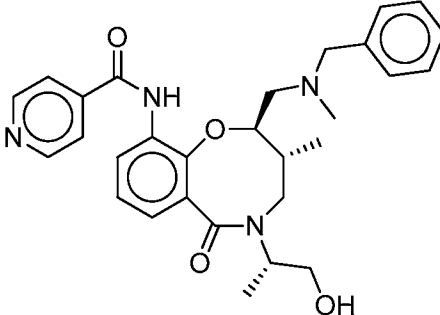
The invention further relates to the treatment of a parasitic infection comprising the step of administering a compound of Formula I-VI to a subject in need thereof. In a preferred embodiment, the invention relates to the treatment of a disease or disorder caused by Trypanosomatids comprising the step of administering a compound of Formula I-VI to a subject in need thereof. In a more preferred embodiment, the disease or disorder is caused by *Trypanosoma cruzi* or *Trypanosoma brucei*. In a preferred embodiment, the disease or disorder is Chagas disease.

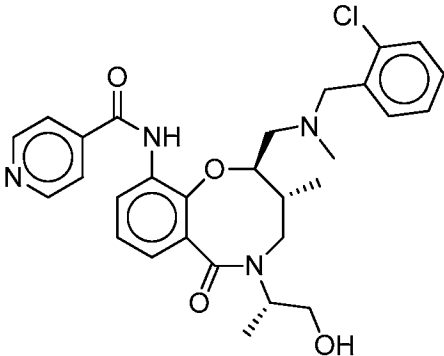
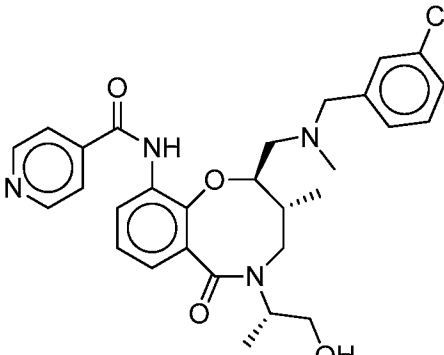
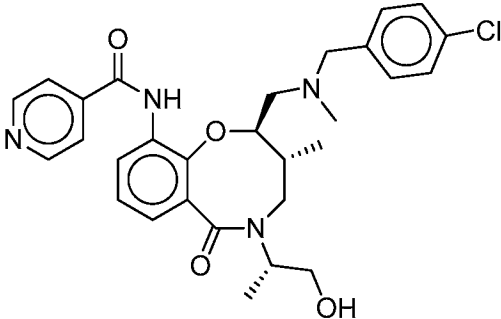
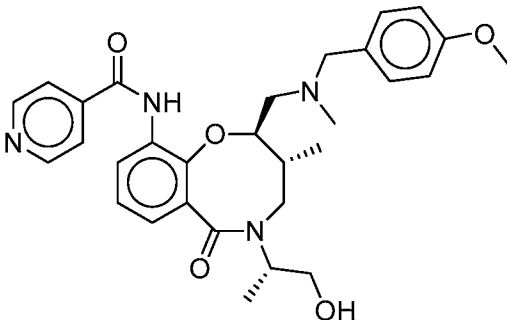
In a preferred embodiment, the invention relates to a compound selected from Table 1:

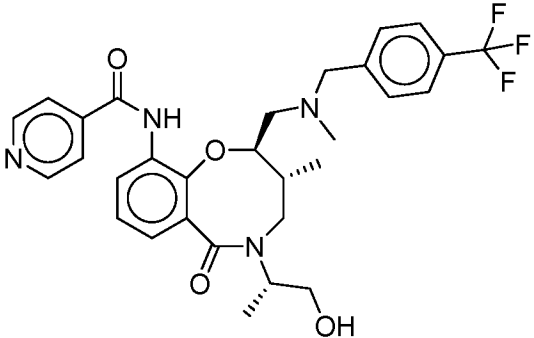
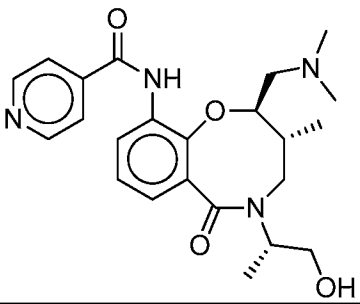
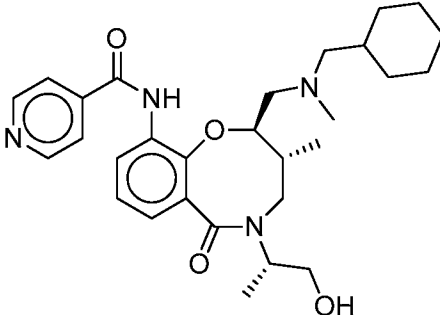
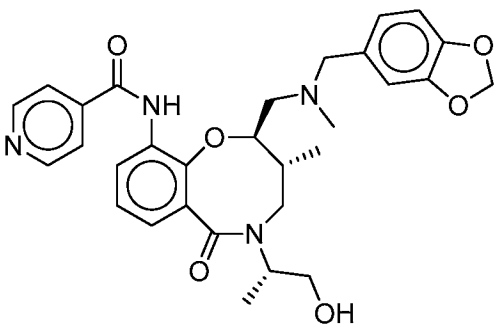
Table 1

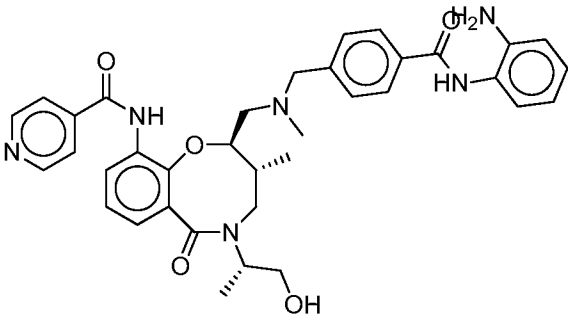
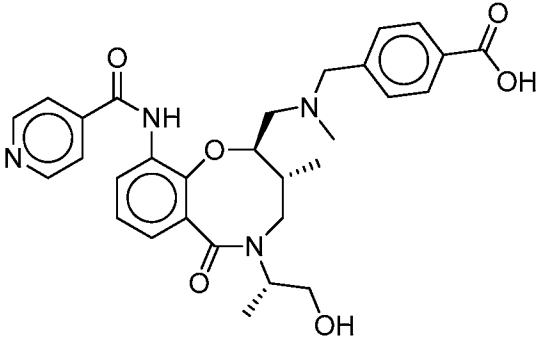
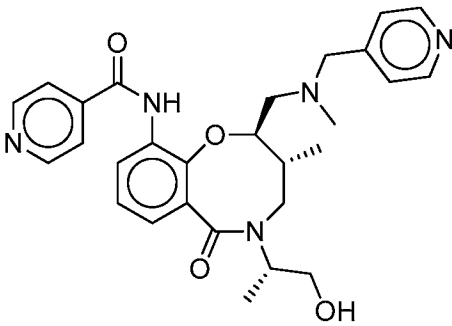
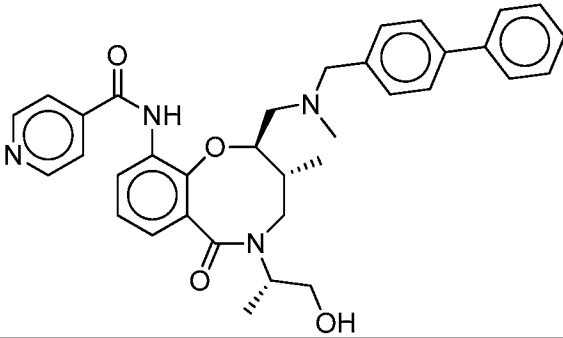
| Compound                                                                            | Broad<br>T. cruzi (IC <sub>50</sub> , nM) | Broad<br>Cytotox (IC <sub>50</sub> , nM) |
|-------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------|
|    | 1                                         | 3970                                     |
|   | 5                                         | 8200                                     |
|  | 1                                         | 8250                                     |
|  | 2                                         | 15900                                    |

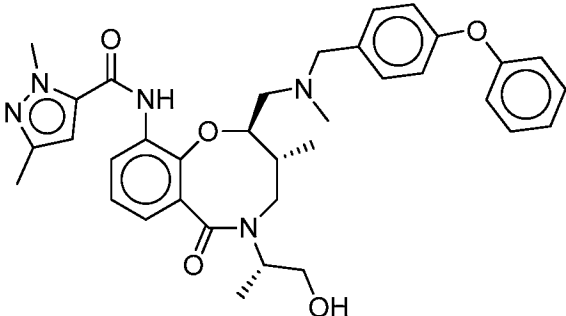
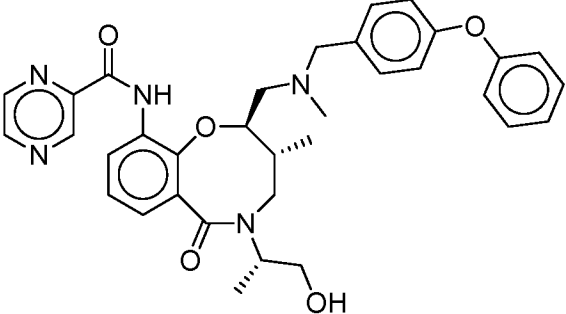
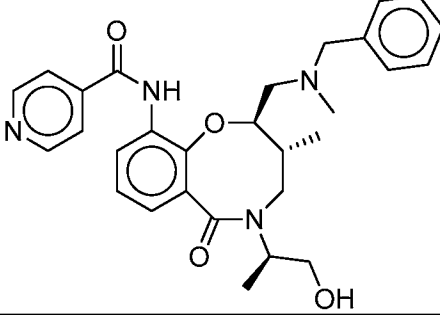
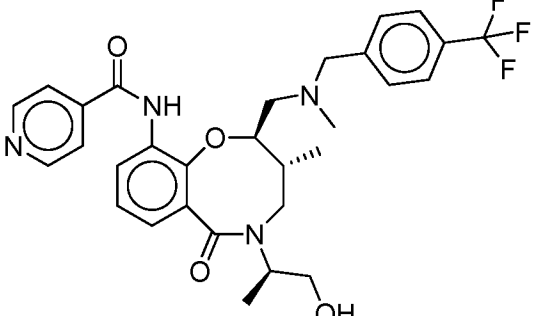
|                                                                                     |     |        |
|-------------------------------------------------------------------------------------|-----|--------|
|    | 450 | >32000 |
|    | 260 | >32000 |
|  | 23  | 19200  |
|  | 16  | 20000  |

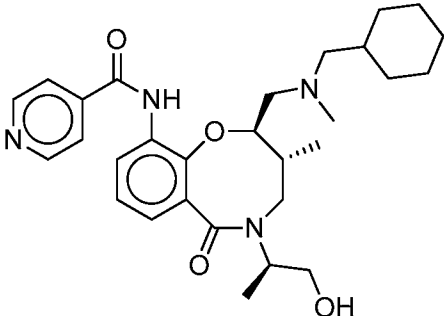
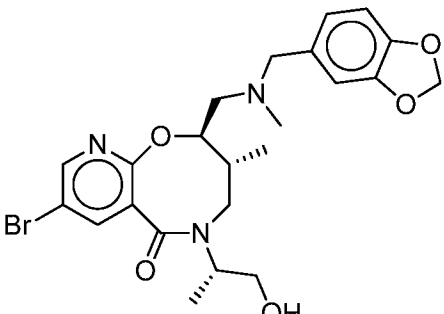
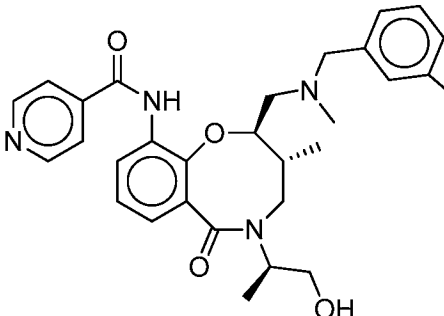
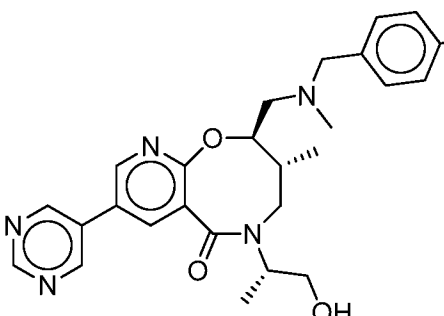
|                                                                                     |    |        |
|-------------------------------------------------------------------------------------|----|--------|
|    | 7  | 10600  |
|   | 1  | 25000  |
|  | 38 | 26000  |
|  | 17 | >32000 |

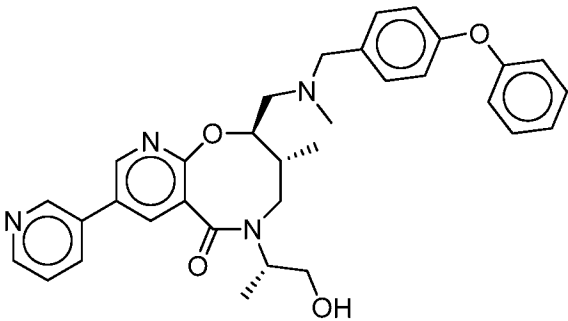
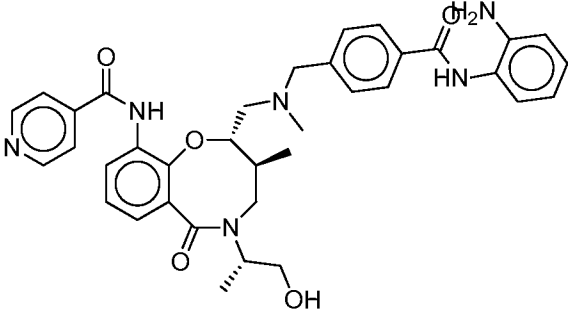
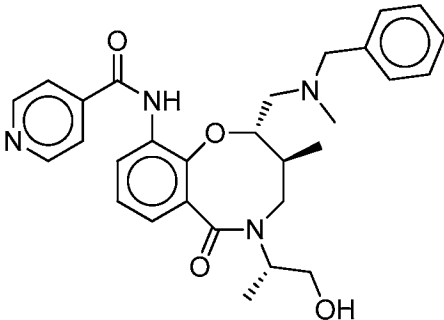
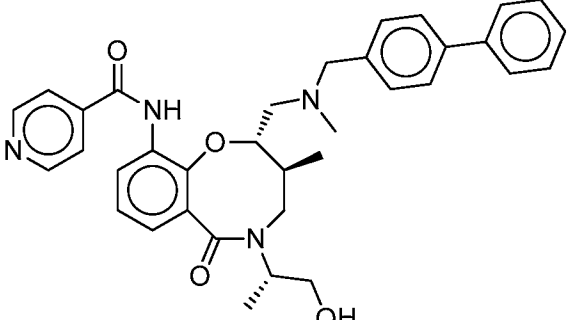
|                                                                                     |     |        |
|-------------------------------------------------------------------------------------|-----|--------|
|    | 120 | >32000 |
|   | 63  | 32000  |
|  | 32  | 30000  |
|  | 57  | >32000 |

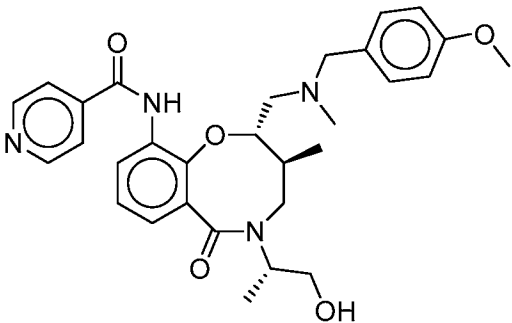
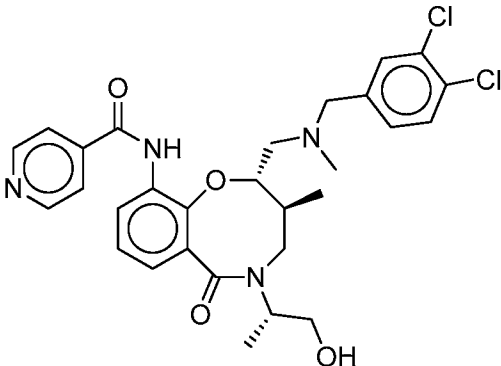
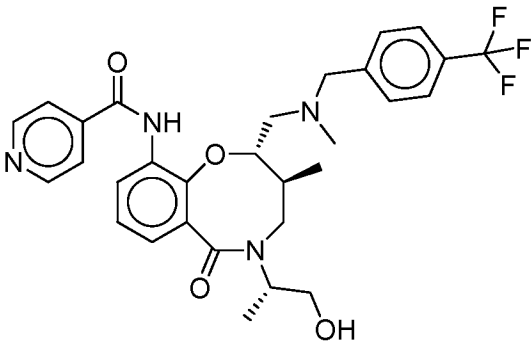
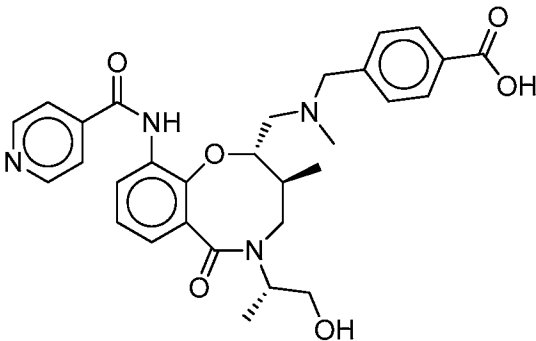
|                                                                                     |       |        |
|-------------------------------------------------------------------------------------|-------|--------|
|    | 11    | 11000  |
|   | 23000 | >32000 |
|  | 140   | 32000  |
|  | 50    | 26700  |

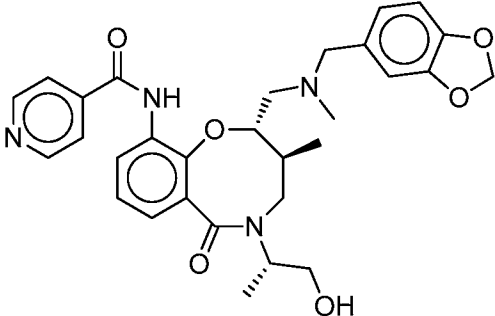
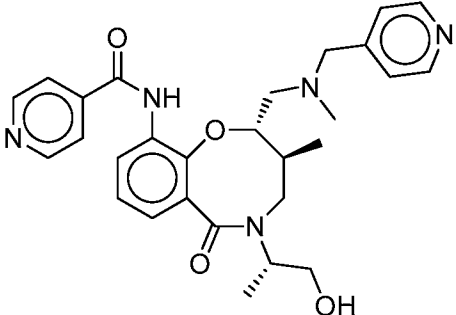
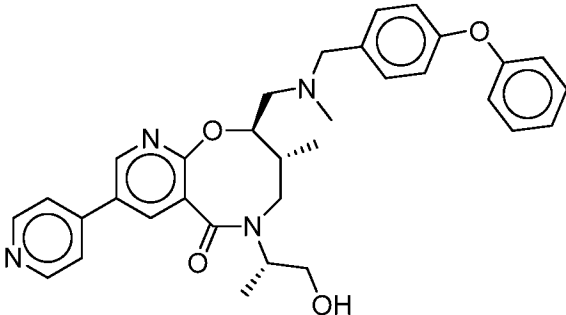
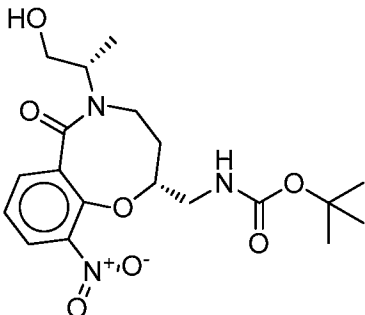
|                                                                                     |        |        |
|-------------------------------------------------------------------------------------|--------|--------|
|    | >32000 | >32000 |
|   | 3800   | >3200  |
|  | >32000 | >32000 |
|  | 1      | 8000   |

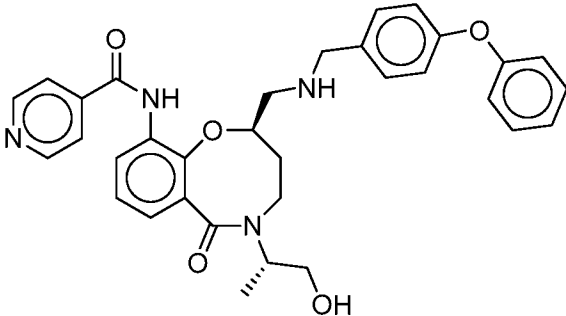
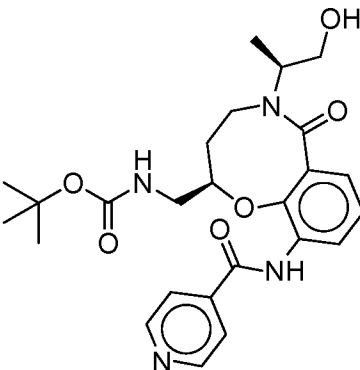
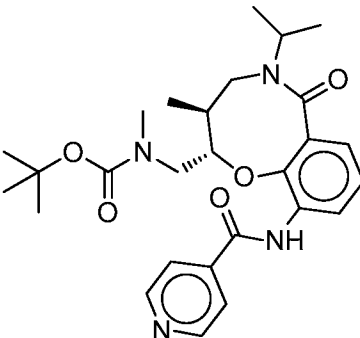
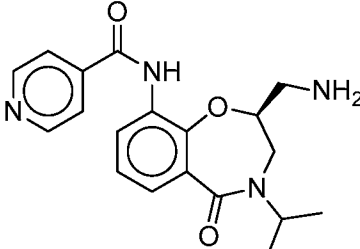
|                                                                                     |      |       |
|-------------------------------------------------------------------------------------|------|-------|
|    | 4140 | 25300 |
|    | 2600 | 20000 |
|  | 57   | 27000 |
|  | 60   | 13000 |

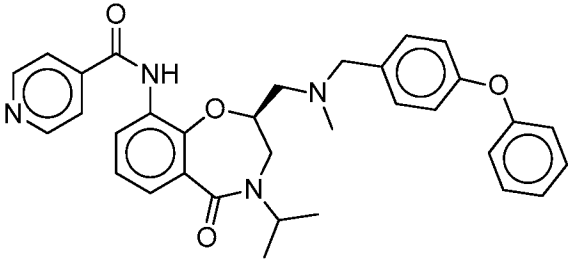
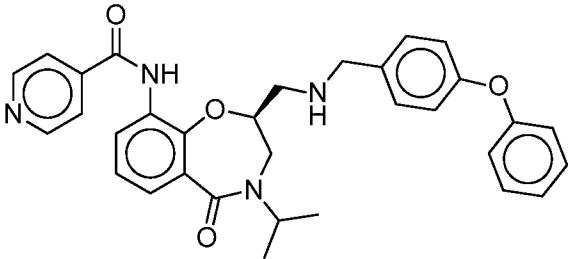
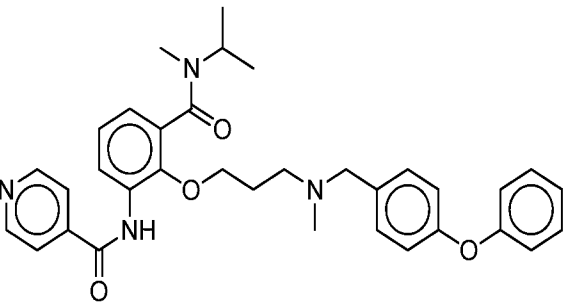
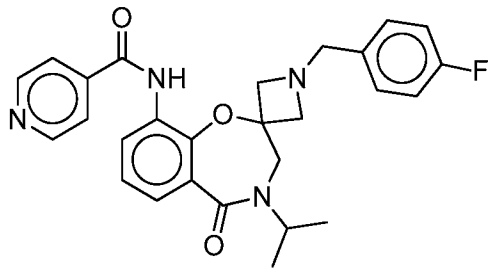
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|-------------------------------------------------------------------------------------|-------|-------|
|    | 390   | 28000 |
|    | 13000 | 32000 |
|  | 270   | 32000 |
|  | 2800  | 30000 |

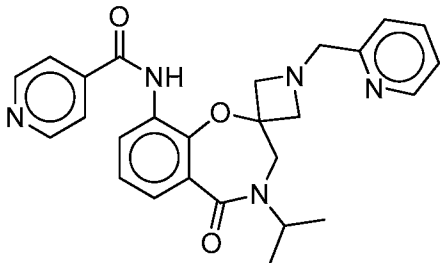
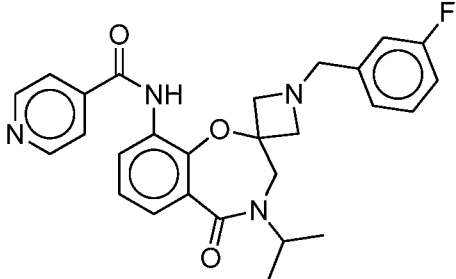
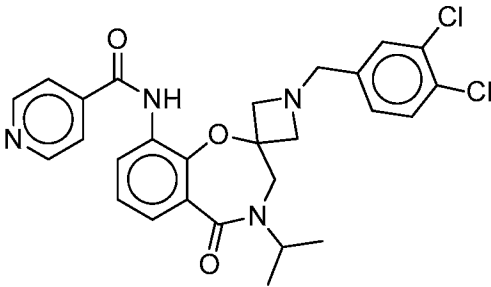
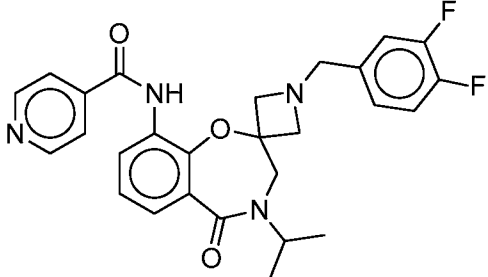
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|-------------------------------------------------------------------------------------|--------|--------|
|    | 1600   | 13000  |
|    | >32000 | >32000 |
|  | 22     | >32000 |
|  | 6      | 15000  |

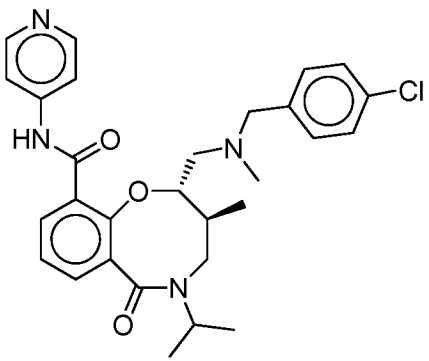
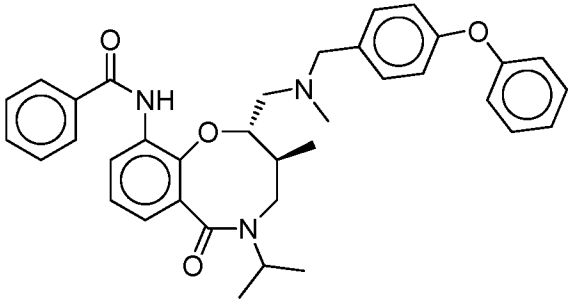
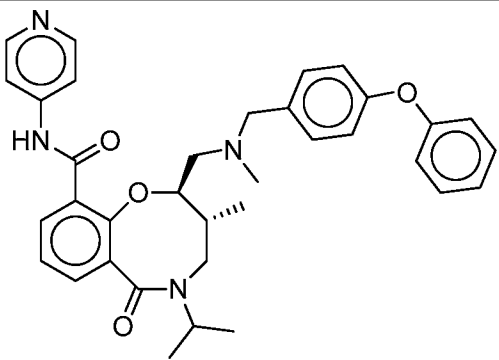
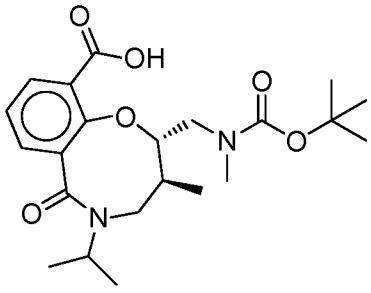
|                                                                                                                                                                                                                  |        |        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|--------|
| <br><chem>CN(C)[C@H]1CC[C@@H](C[C@H](C1)C[C@H](C)CO)O[C@@H]2C(=O)N(c3ccc(NC(=O)c4ccncc4)cc3)C(=O)N2Cc5ccc(OC)cc5</chem>         | 160    | >32000 |
| <br><chem>CN(C)[C@H]1CC[C@@H](C[C@H](C1)C[C@H](C)CO)O[C@@H]2C(=O)N(c3ccc(NC(=O)c4ccncc4)cc3)C(=O)N2Cc5ccc(Cl)c(Cl)c5</chem>    | 0.1    | 20000  |
| <br><chem>CN(C)[C@H]1CC[C@@H](C[C@H](C1)C[C@H](C)CO)O[C@@H]2C(=O)N(c3ccc(NC(=O)c4ccncc4)cc3)C(=O)N2Cc5ccc(C(F)(F)F)cc5</chem> | 12     | >32000 |
| <br><chem>CN(C)[C@H]1CC[C@@H](C[C@H](C1)C[C@H](C)CO)O[C@@H]2C(=O)N(c3ccc(NC(=O)c4ccncc4)cc3)C(=O)N2Cc5ccc(C(=O)O)cc5</chem>   | >32000 | >32000 |

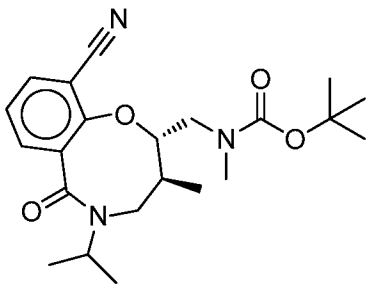
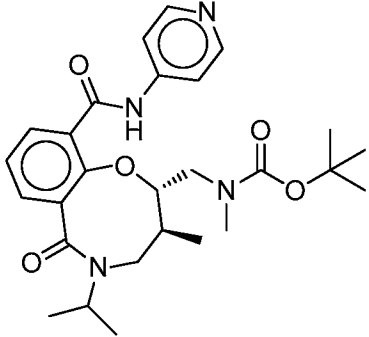
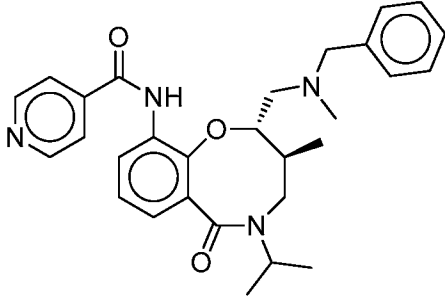
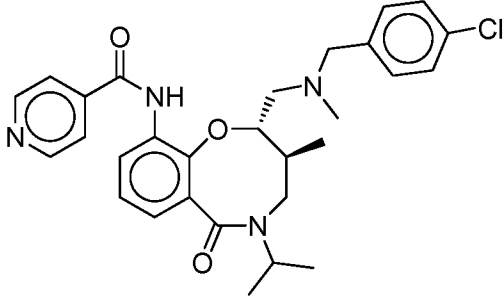
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|-------------------------------------------------------------------------------------|--------|--------|
|    | 190    | >32000 |
|    | >32000 | >32000 |
|  | 2500   | 13000  |
|  | >32000 | >32000 |

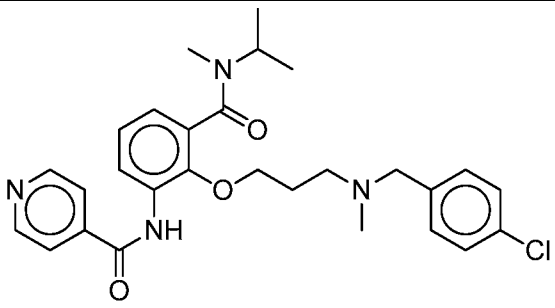
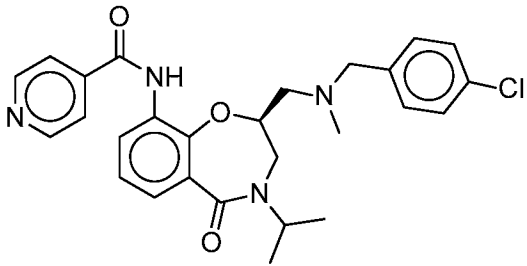
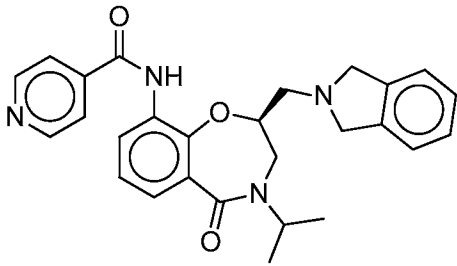
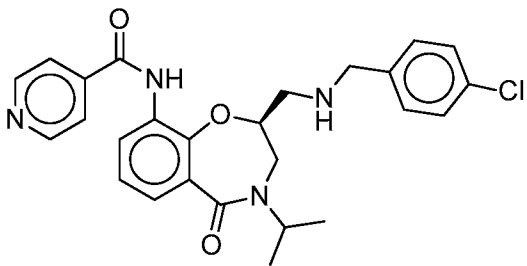
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|-------------------------------------------------------------------------------------|--------|--------|
|    | 16     | 14000  |
|   | 8300   | >32000 |
|  | 17000  | 32000  |
|  | >32000 | >32000 |

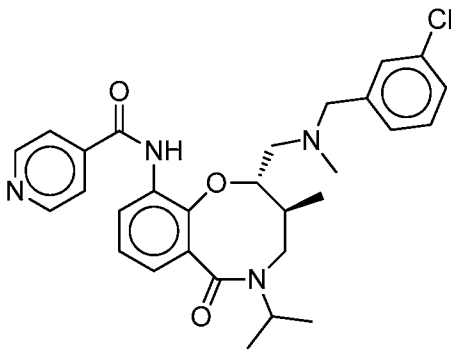
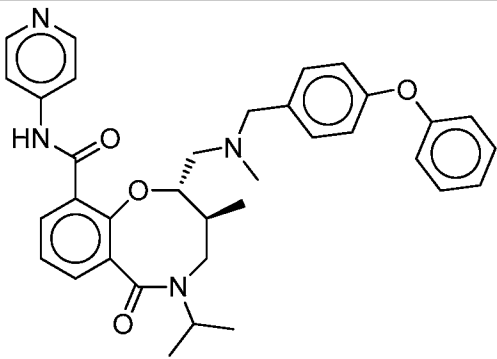
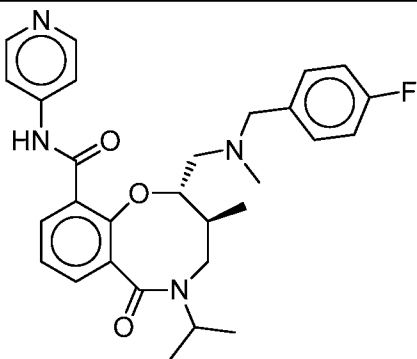
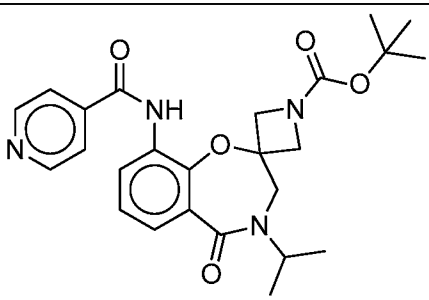
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|-------------------------------------------------------------------------------------|-----|--------|
|    | 2   | 18000  |
|    | 18  | >32000 |
|  | 390 | 14000  |
|  | 800 | >32000 |

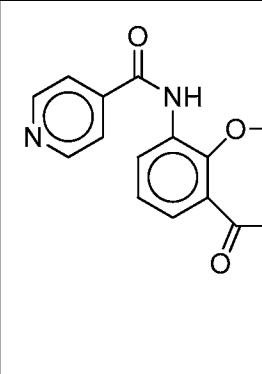
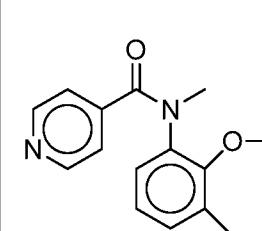
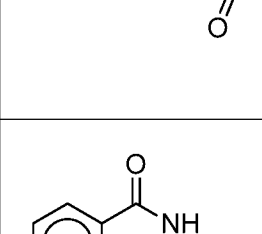
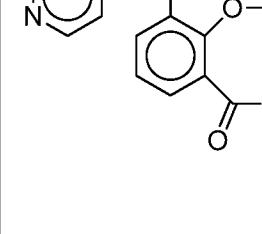
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|-------------------------------------------------------------------------------------|------|--------|
|    | 1800 | >32000 |
|    | 330  | 32000  |
|  | 200  | >32000 |
|  | 1100 | >32000 |

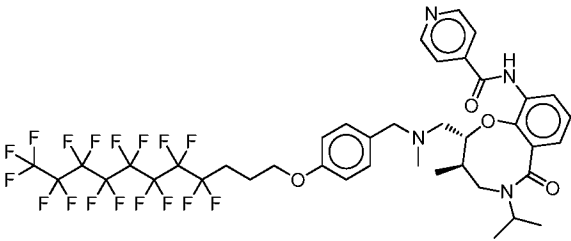
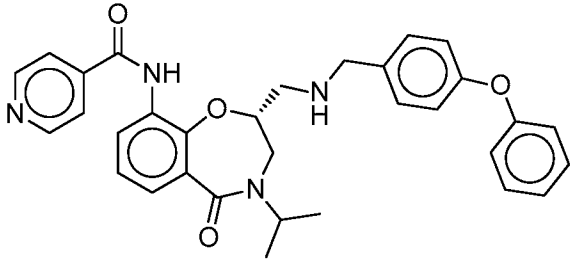
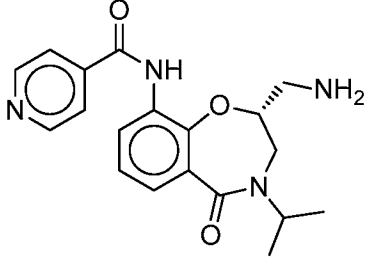
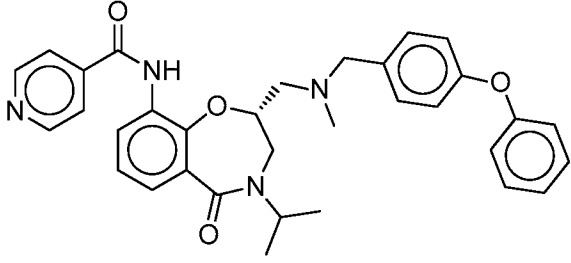
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|-------------------------------------------------------------------------------------|--------|--------|
|    | 120    | >32000 |
|   | 370    | >32000 |
|  | 21     | 6800   |
|  | >32000 | >32000 |

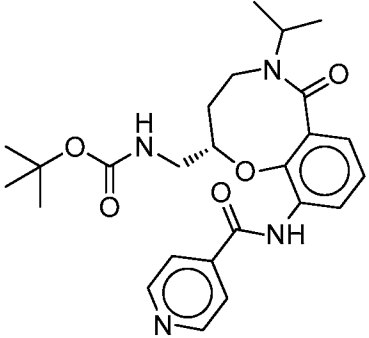
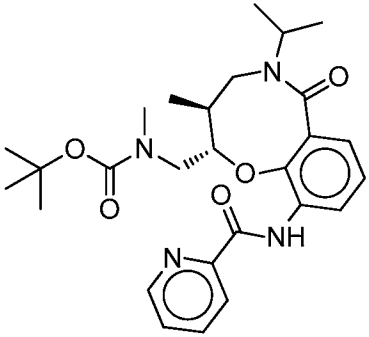
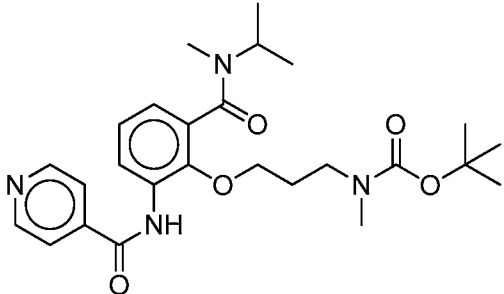
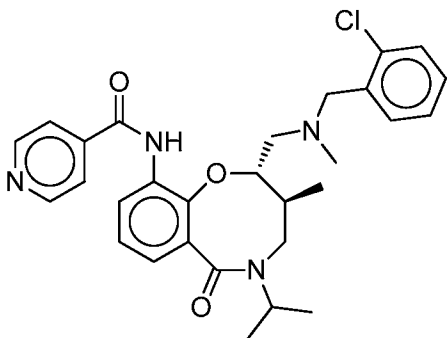
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|-------------------------------------------------------------------------------------|--------|--------|
|    | >32000 | >32000 |
|   | >32000 | >32000 |
|  | 0.34   | >32000 |
|  |        |        |

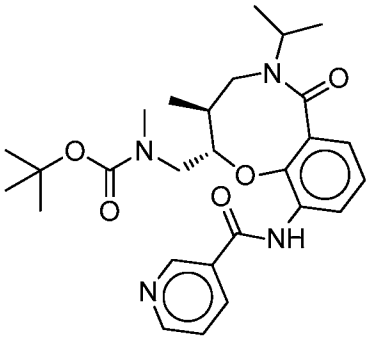
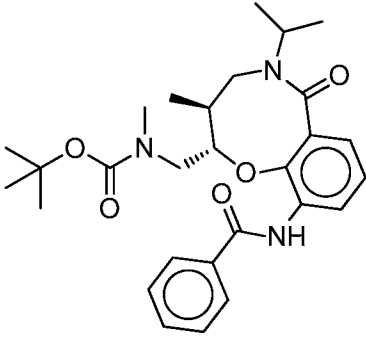
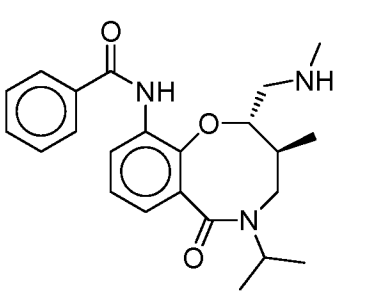
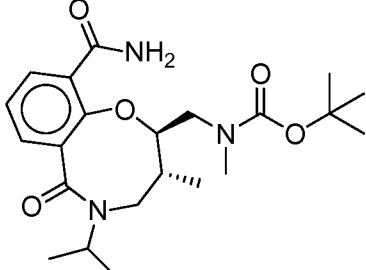
|                                                                                     |      |        |
|-------------------------------------------------------------------------------------|------|--------|
|    | 200  | 32000  |
|    | 7    | >32000 |
|  | 5000 | >32000 |
|  | 820  | 32000  |

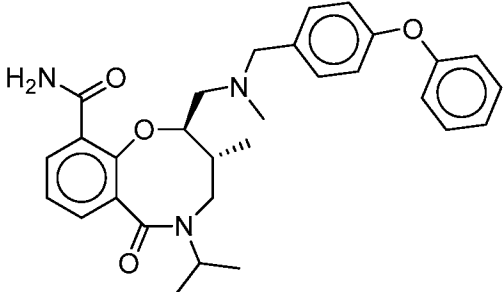
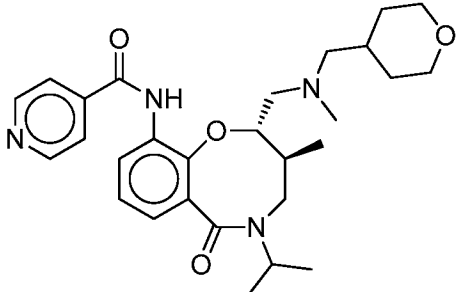
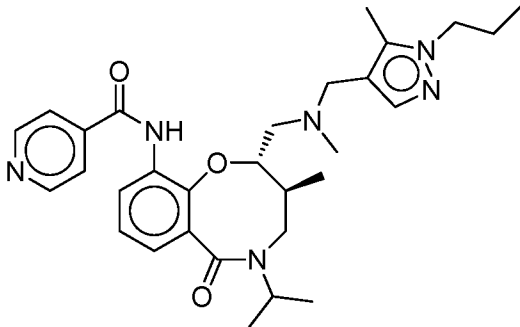
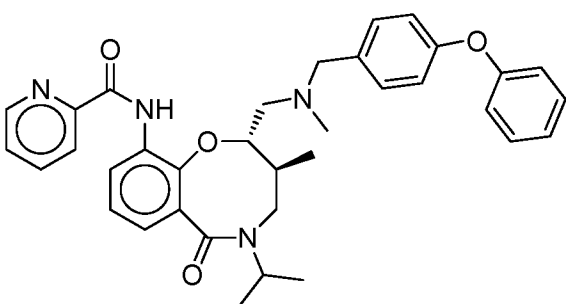
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|-------------------------------------------------------------------------------------|--------|--------|
|    | 4      | 32000  |
|   | 250    | 7900   |
|  | 280    | 24000  |
|  | >32000 | >32000 |

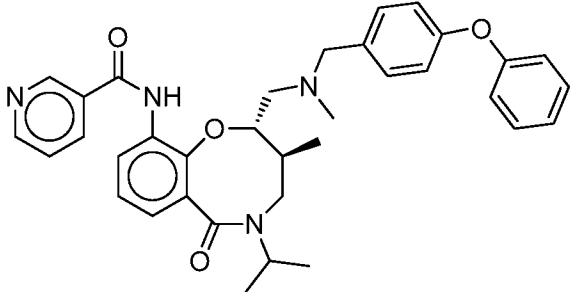
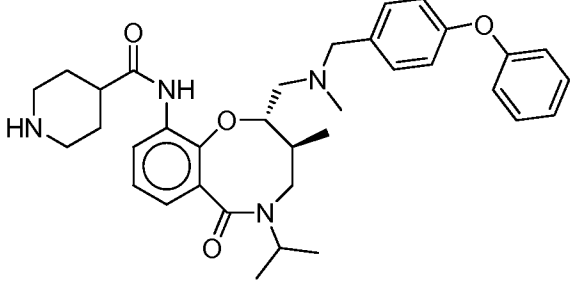
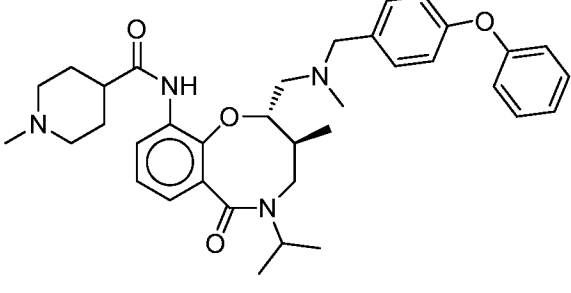
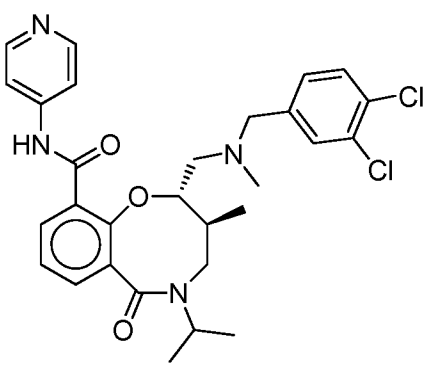
|                                                                                     |        |        |
|-------------------------------------------------------------------------------------|--------|--------|
|    | >32000 | >32000 |
|    | 380    | >32000 |
|   | 83     | 26000  |
|  | 20     | 23000  |

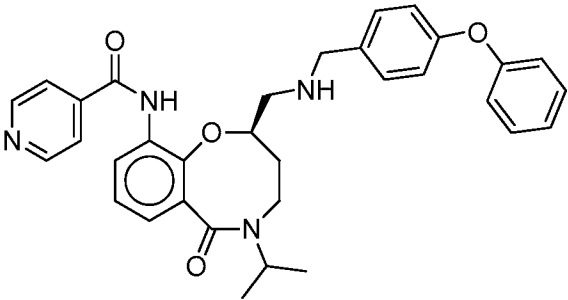
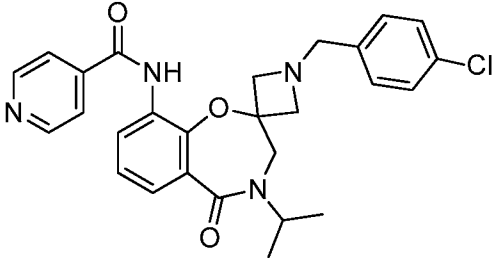
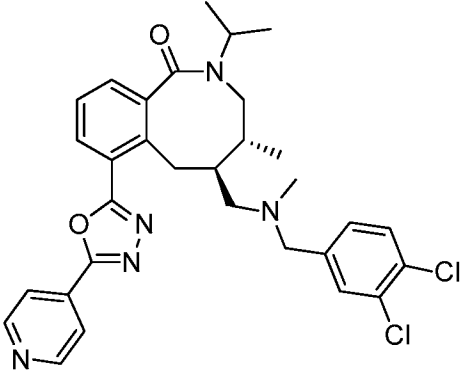
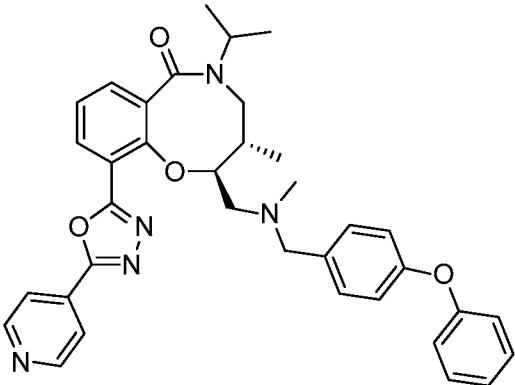
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|-------------------------------------------------------------------------------------|--------|--------|
|    | >32000 | >32000 |
|    | 7      | 32000  |
|  | >32000 | >32000 |
|  | 2      | 2300   |

|                                                                                     |        |        |
|-------------------------------------------------------------------------------------|--------|--------|
|    | 3200   | >32000 |
|   | >32000 | >32000 |
|  | 5000   | >32000 |
|  | 20     | >32000 |

|                                                                                     |        |        |
|-------------------------------------------------------------------------------------|--------|--------|
|    | 17000  | >32000 |
|   | 10000  | >32000 |
|  | >32000 | >32000 |
|  | >32000 | >32000 |

|                                                                                     |      |        |
|-------------------------------------------------------------------------------------|------|--------|
|    | 6600 | 10000  |
|    | 1800 | >32000 |
|  | 490  | >32000 |
|  | 490  | >32000 |

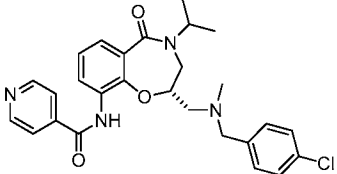
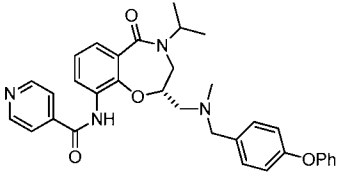
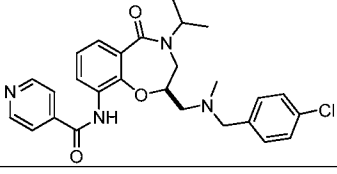
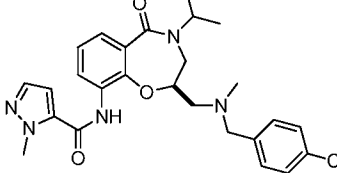
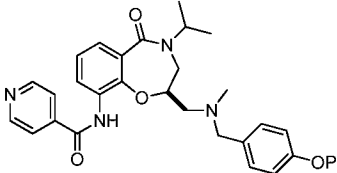
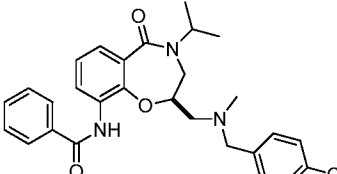
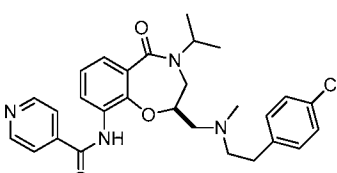
|                                                                                     |      |        |
|-------------------------------------------------------------------------------------|------|--------|
|    | 100  | >32000 |
|    | 97   | 7200   |
|  | 2400 | 6400   |
|  | 29   | 14000  |

|                                                                                     |     |        |
|-------------------------------------------------------------------------------------|-----|--------|
|    | 15  | 15000  |
|    | 110 | >32000 |
|  | 20  | 18000  |
|  | 130 | 7000   |

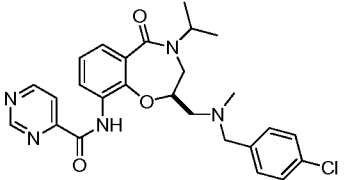
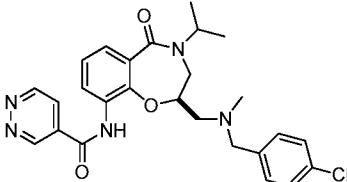
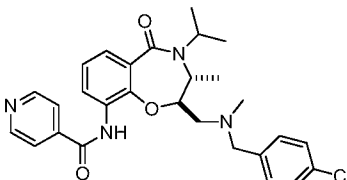
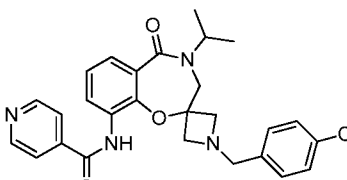
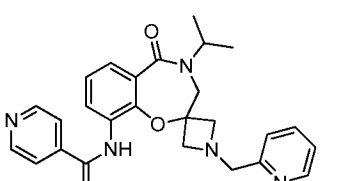
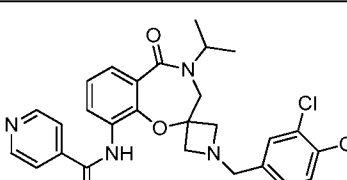
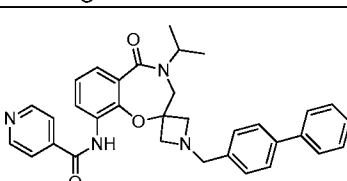
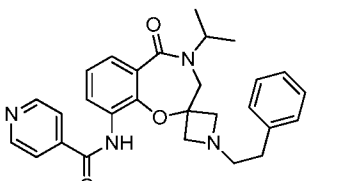
In a preferred embodiment, the invention relates to a compound selected from Table

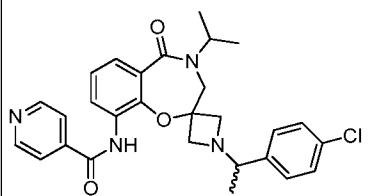
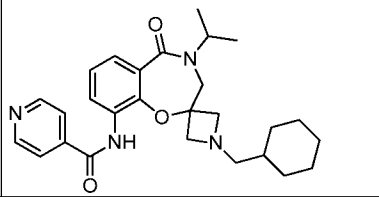
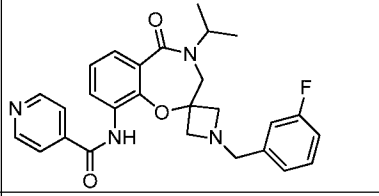
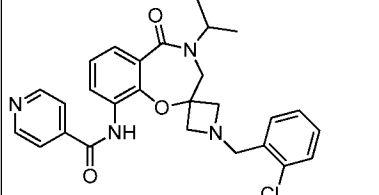
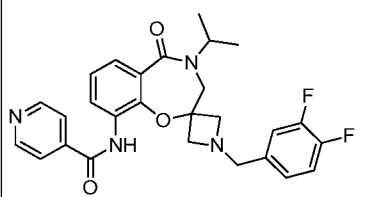
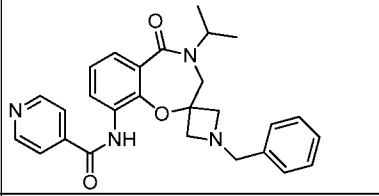
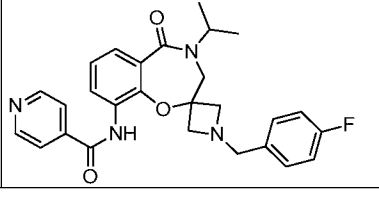
2:

Table 2

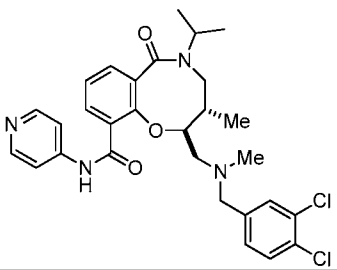
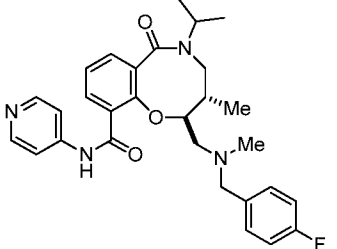
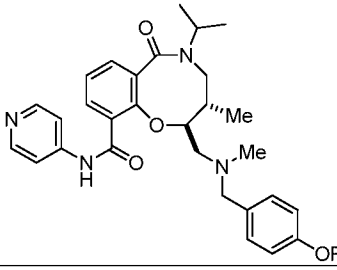
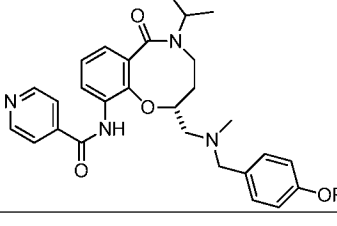
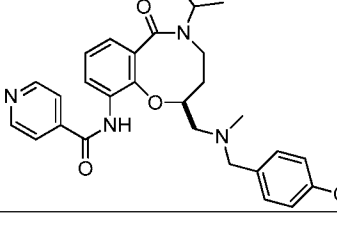
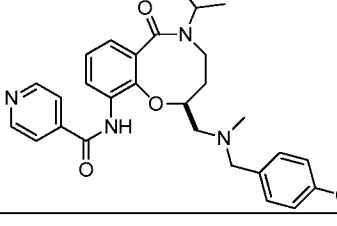
| Cmpd # | Molecular Weight | LCMS   | LCMS purity | <i>T. cruzi</i> (STPH) IC <sub>50</sub> (μM) | Cytotox (STPH) CC <sub>50</sub> (μM) | <i>T. cruzi</i> (Broad) IC <sub>50</sub> (μM) | Cytotox (Broad) CC <sub>50</sub> (μM) | Structure                                                                             |
|--------|------------------|--------|-------------|----------------------------------------------|--------------------------------------|-----------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------|
| 1.01   | 492.193          | 493.25 | 100         | 0.002                                        | 42                                   | 0.004                                         | 32                                    |    |
| 1.02   | 550.258          | 551.33 | 85          | 0.008                                        | 16                                   |                                               |                                       |    |
| 2.01   | 492.193          | 493.38 | 91          | 0.027                                        | 40                                   | 0.004                                         | 32                                    |  |
| 2.02   | 495.204          | 496.37 | 87          | 2.5                                          | 24                                   | 0.334                                         | >32                                   |  |
| 2.03   | 550.258          | 551.25 | 99          |                                              |                                      | 0.002                                         | 2                                     |  |
| 2.04   | 491.198          | 492.84 | 98          | 8                                            | 66                                   | 1                                             | >32                                   |  |
| 2.05   | 506.208          | 507.34 | 99          | 0.092                                        | 32                                   | <0.001                                        | 32                                    |  |

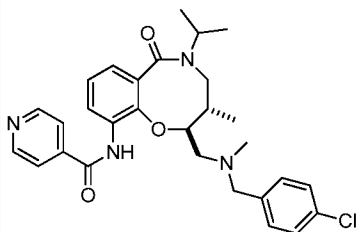
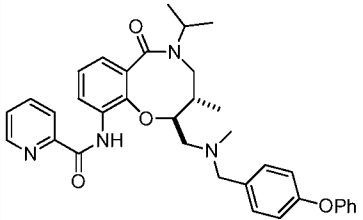
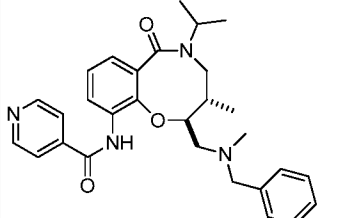
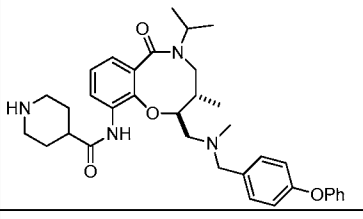
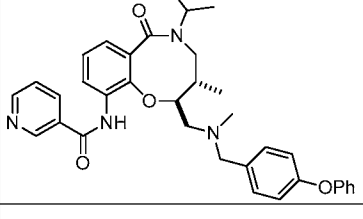
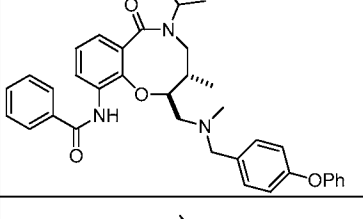
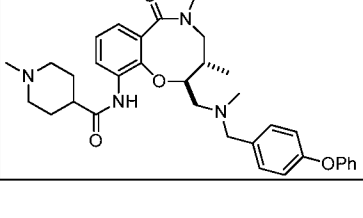
|      |         |        |    |       |    |        |     |  |
|------|---------|--------|----|-------|----|--------|-----|--|
| 2.06 | 482.183 | 483.34 | 92 | 27    | 45 | 6      | >32 |  |
| 2.07 | 506.208 | 507.36 | 97 | 0.095 | 35 | 0.054  | 18  |  |
| 2.08 | 540.169 | 541.32 | 98 | 0.023 | 17 | <0.001 | 24  |  |
| 2.09 | 526.154 | 527.34 | 85 | 0.006 | 23 | <0.001 | 20  |  |
| 3.01 | 510.183 | 511.34 | 97 | 0.689 | 33 | 0.003  | 27  |  |
| 4.01 | 492.193 | 493.39 | 98 | 0.012 | 46 | <0.001 | 32  |  |
| 4.02 | 493.188 | 494.24 | 97 | 0.17  | 81 | 0.299  | >32 |  |
| 5.01 | 495.204 | 496.33 | 93 | 0.466 | 44 | 0.020  | 27  |  |

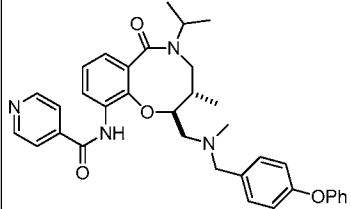
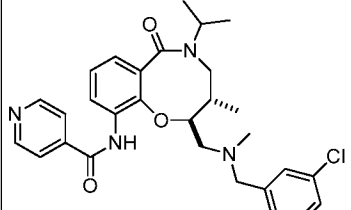
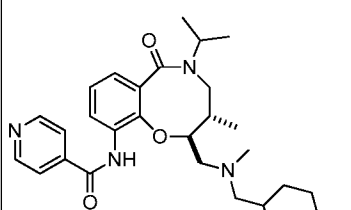
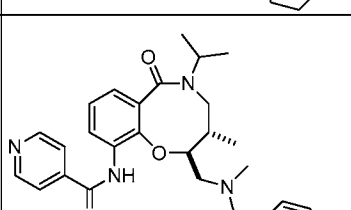
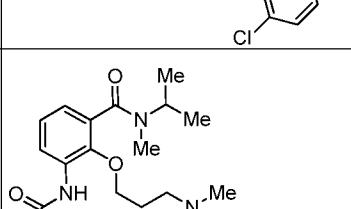
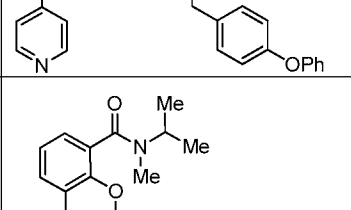
|      |         |        |    |       |      |        |     |                                                                                       |
|------|---------|--------|----|-------|------|--------|-----|---------------------------------------------------------------------------------------|
| 5.02 | 493.188 | 494.36 | 98 | 0.024 | 33   | 0.005  | 32  |    |
| 5.03 | 493.188 | 494.35 | 96 | 0.921 | 43   | 0.197  | >32 |    |
| 6.01 | 506.208 | 507.38 | 97 | 0.026 | 58   | <0.001 | >32 |    |
| 7.01 | 490.177 | 491.73 | 87 | 22    | >100 | 0.136  | >32 |   |
| 7.02 | 457.211 | 458.7  | 96 | 12    | >100 | 1      | >32 |  |
| 7.03 | 524.138 | 525.61 | 89 | 0.419 | 86   | 2      | 23  |  |
| 7.04 | 532.247 | 533.73 | 97 | 0.949 | 75   | 0.001  | 14  |  |
| 7.05 | 470.232 | 471.41 | 93 | 1     | 61   | 0.251  | 17  |  |

|      |         |        |    |       |      |       |     |                                                                                       |
|------|---------|--------|----|-------|------|-------|-----|---------------------------------------------------------------------------------------|
| 7.06 | 504.193 | 505.36 | 98 | 0.592 | 56   | 0.556 | >32 |    |
| 7.07 | 462.263 | 463.44 | 98 | 9     | 67   | 1     | >32 |    |
| 7.08 | 474.207 | 475.67 | 86 | 7     | >100 | 0.41  | 28  |    |
| 7.09 | 490.177 | 491.63 | 94 | 8     | 57   | 0.462 | >32 |   |
| 7.10 | 492.197 | 493.67 | 88 | 31    | 85   | 1     | >32 |  |
| 7.11 | 456.216 | 457.39 | 98 | 6     | 63   | 0.427 | >32 |  |
| 7.12 | 474.207 | 475.69 | 96 | 3     | 70   | 0.877 | >32 |  |

|       |         |        |    |       |    |       |     |  |
|-------|---------|--------|----|-------|----|-------|-----|--|
| 8.01  | 545.231 | 546.7  | 94 |       |    | 0.119 | >32 |  |
| 9.01  | 603.285 | 604.45 | 98 |       |    | 0.116 | 6   |  |
| 9.02  | 579.18  | 580.33 | 96 |       |    | 0.062 | 18  |  |
| 9.03  | 517.188 | 518.23 | 93 | 0.003 | 50 |       |     |  |
| 10.01 | 602.301 | 603.84 | 95 |       |    | 0.020 | 11  |  |
| 11.01 | 520.224 | 521.66 | 95 | 2     | 44 | 0.119 | >32 |  |

|       |         |        |     |       |    |        |    |                                                                                       |
|-------|---------|--------|-----|-------|----|--------|----|---------------------------------------------------------------------------------------|
| 11.02 | 554.185 | 555.16 | 97  | 0.869 | 17 | 0.045  | 20 |    |
| 11.03 | 504.254 | 506.61 | 96  | 3     | 17 | 0.313  | 26 |    |
| 11.04 | 578.289 | 579.46 | 95  | 0.153 | 16 | 0.167  | 9  |   |
| 12.01 | 564.274 | 565.27 | 100 |       |    | <0.001 | 32 |  |
| 12.02 | 506.21  | 507.26 | 78  |       |    | 0.028  | 47 |  |
| 12.03 | 564.274 | 565.29 | 98  | 0.053 | 32 | 0.019  | 26 |  |

|       |         |        |    |       |    |        |     |                                                                                       |
|-------|---------|--------|----|-------|----|--------|-----|---------------------------------------------------------------------------------------|
| 13.01 | 520.224 | 521.28 | 92 | 0.061 | 21 | 0.001  | 32  |    |
| 13.02 | 578.289 | 579.49 | 92 | 13    | 58 | 0.344  | >32 |    |
| 13.03 | 486.263 | 487.53 | 89 | 0.164 | 51 | <0.001 | >32 |    |
| 13.04 | 584.336 | 585.51 | 85 | 0.907 | 6  | 0.982  | 9   |   |
| 13.05 | 578.289 | 579.5  | 93 | 2     | 15 | 0.081  | >32 |  |
| 13.06 | 577.294 | 578.58 | 91 | 7     | 55 | 0.506  | >32 |  |
| 13.07 | 598.352 | 599.45 | 89 | 1     | 6  | 1      | 9   |  |

|       |         |        |    |       |    |       |     |                                                                                       |
|-------|---------|--------|----|-------|----|-------|-----|---------------------------------------------------------------------------------------|
| 13.08 | 578.289 | 579.36 | 99 | 0.288 | 18 | 0.001 | 26  |    |
| 13.09 | 520.224 | 521.29 | 97 | 0.061 | 23 | 0.002 | 32  |    |
| 13.10 | 494.289 | 495.52 | 97 | 2     | 75 | 3     | 32  |    |
| 13.11 | 520.224 | 521.2  | 94 | 0.318 | 48 | 0.045 | >32 |   |
| 14.01 | 566.289 | 567.26 | 97 | 0.617 | 25 | 0.386 | 14  |  |
| 14.02 | 508.224 | 509.16 | 96 | 3     | 56 | 0.110 | 32  |  |

The synthetic protocols as well as biological assays for Tables 1 and 2 are given below. Table 2 includes data from repeated assays for some of the compounds listed in Table 1.

In one embodiment, the invention further provides for the use of one or more compounds of the invention in the manufacture of a medicament for halting or decreasing diseases involving parasitic infections, in particular diseases or disorders related to Trypanosomatids. In one embodiment, the invention relates to a method of treating parasitic infection in a subject in need of treatment comprising administering to said subject a therapeutically effective amount of a compound of the invention.

### Definitions

Listed below are definitions of various terms used to describe this invention. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "aliphatic group" or "aliphatic" refers to a non-aromatic moiety that may be saturated (e.g., single bond) or contain one or more units of unsaturation, e.g., double and/or triple bonds. An aliphatic group may be straight chained, branched or cyclic, contain carbon, hydrogen or, optionally, one or more heteroatoms and may be substituted or unsubstituted. In addition to aliphatic hydrocarbon groups, aliphatic groups include, for example, polyalkoxyalkyls, such as polyalkylene glycols, polyamines, and polyimines, for example. Such aliphatic groups may be further substituted. It is understood that aliphatic groups may include alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, and substituted or unsubstituted cycloalkyl groups as described herein.

The term "acyl" refers to a carbonyl substituted with hydrogen, alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, or heteroaryl. For example, acyl includes groups such as (C<sub>1</sub>-C<sub>6</sub>) alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, t-butylacetyl, etc.), (C<sub>3</sub>-C<sub>6</sub>)cycloalkylcarbonyl (e.g., cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcabonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrrolyl-2-carbonyl, 1H-pyrrolyl-3-carbonyl, benzo[b]thiophenyl-2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions. When indicated as being "optionally substituted", the acyl group may be unsubstituted or optionally substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the

definition for "substituted" or the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be substituted as described above in the preferred and more preferred list of substituents, respectively.

The term "alkyl" is intended to include both branched and straight chain, substituted  
5 or unsubstituted saturated aliphatic hydrocarbon radicals/groups having the specified number of carbons. Preferred alkyl groups comprise about 1 to about 24 carbon atoms ("C<sub>1</sub>-C<sub>24</sub>"). Other preferred alkyl groups comprise at about 1 to about 8 carbon atoms ("C<sub>1</sub>-C<sub>8</sub>") such as about 1 to about 6 carbon atoms ("C<sub>1</sub>-C<sub>6</sub>"), or such as about 1 to about 3 carbon atoms ("C<sub>1</sub>-C<sub>3</sub>"). Examples of C<sub>1</sub>-C<sub>6</sub> alkyl radicals include, but are not limited to, methyl, ethyl, propyl,  
10 isopropyl, *n*-butyl, *tert*-butyl, *n*-pentyl, neopentyl and *n*-hexyl radicals.

The term "alkenyl" refers to linear or branched radicals having at least one carbon-carbon double bond. Such radicals preferably contain from about two to about twenty-four carbon atoms ("C<sub>2</sub>-C<sub>24</sub>"). Other preferred alkenyl radicals are "lower alkenyl" radicals having two to about ten carbon atoms ("C<sub>2</sub>-C<sub>10</sub>") such as ethenyl, allyl, propenyl, butenyl and  
15 4-methylbutenyl. Preferred lower alkenyl radicals include 2 to about 6 carbon atoms ("C<sub>2</sub>-C<sub>6</sub>"). The terms "alkenyl", and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations.

The term "alkynyl" refers to linear or branched radicals having at least one carbon-carbon triple bond. Such radicals preferably contain from about two to about twenty-four carbon atoms ("C<sub>2</sub>-C<sub>24</sub>"). Other preferred alkynyl radicals are "lower alkynyl" radicals having two to about ten carbon atoms such as propargyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne and 1-pentyne. Preferred lower alkynyl radicals include 2 to about 6 carbon atoms ("C<sub>2</sub>-C<sub>6</sub>").  
20

The term "cycloalkyl" refers to saturated carbocyclic radicals having three to about twelve carbon atoms ("C<sub>3</sub>-C<sub>12</sub>"). The term "cycloalkyl" embraces saturated carbocyclic radicals having three to about twelve carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.  
25

The term "cycloalkenyl" refers to partially unsaturated carbocyclic radicals having three to twelve carbon atoms. Cycloalkenyl radicals that are partially unsaturated carbocyclic radicals that contain two double bonds (that may or may not be conjugated) can be called  
30 "cycloalkyldienyl". More preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having four to about eight carbon atoms. Examples of such radicals include cyclobutenyl, cyclopentenyl and cyclohexenyl.

The term "alkylene," as used herein, refers to a divalent group derived from a straight chain or branched saturated hydrocarbon chain having the specified number of carbon atoms. Examples of alkylene groups include, but are not limited to, ethylene, propylene, butylene, 3-methyl-pentylene, and 5-ethyl-hexylene.

5       The term "alkenylene," as used herein, denotes a divalent group derived from a straight chain or branched hydrocarbon moiety containing the specified number of carbon atoms having at least one carbon-carbon double bond. Alkenylene groups include, but are not limited to, for example, ethenylene, 2-propenylene, 2-butenylene, 1-methyl-2-buten-1-yne, and the like.

10       The term "alkynylene," as used herein, denotes a divalent group derived from a straight chain or branched hydrocarbon moiety containing the specified number of carbon atoms having at least one carbon-carbon triple bond. Representative alkynylene groups include, but are not limited to, for example, propynylene, 1-butyne, 2-methyl-3-hexynylene, and the like.

15       The term "alkoxy" refers to linear or branched oxy-containing radicals each having alkyl portions of one to about twenty-four carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having one to about ten carbon atoms and more preferably having one to about eight carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy.

20       The term "alkoxyalkyl" refers to alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals.

      The term "aryl", alone or in combination, means an aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, 25 tetrahydronaphthyl, indane furanyl, quinazolinyl, pyridyl and biphenyl.

      The terms "heterocyclyl", "heterocycle" "heterocyclic" or "heterocyclo" refer to saturated, partially unsaturated and unsaturated heteroatom-containing ring-shaped radicals, which can also be called "heterocyclyl", "heterocycloalkenyl" and "heteroaryl" correspondingly, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. 30 Examples of saturated heterocyclyl radicals include saturated 3 to 6-membered heteromonocyclic group containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl, etc.); saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms

(e.g., thiazolidinyl, etc.). Examples of partially unsaturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Heterocyclyl radicals may include a pentavalent nitrogen, such as in tetrazolium and pyridinium radicals. The term "heterocycle" also embraces radicals where heterocyclyl radicals are fused with aryl or  
5 cycloalkyl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

The term "heteroaryl" refers to unsaturated aromatic heterocyclyl radicals. Examples of heteroaryl radicals include unsaturated 3 to 6 membered heteromonocyclic group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl,  
10 pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.) tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclyl group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated  
15 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic group containing a sulfur atom, for example, thienyl, etc.; unsaturated 3- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated  
20 condensed heterocyclyl group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclyl group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g.,  
25 benzothiazolyl, benzothiadiazolyl, etc.) and the like.

The term "heterocycloalkyl" refers to heterocyclo-substituted alkyl radicals. More preferred heterocycloalkyl radicals are "lower heterocycloalkyl" radicals having one to six carbon atoms in the heterocyclo radical.

The term "alkylthio" refers to radicals containing a linear or branched alkyl radical, of  
30 one to about ten carbon atoms attached to a divalent sulfur atom. Preferred alkylthio radicals have alkyl radicals of one to about twenty-four carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkylthio radicals have alkyl radicals which are "lower alkylthio" radicals having one to about ten carbon atoms. Most preferred are alkylthio

radicals having lower alkyl radicals of one to about eight carbon atoms. Examples of such lower alkylthio radicals include methylthio, ethylthio, propylthio, butylthio and hexylthio.

The terms "aralkyl" or "arylalkyl" refer to aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl.

5       The term "aryloxy" refers to aryl radicals attached through an oxygen atom to other radicals.

The terms "aralkoxy" or "arylalkoxy" refer to aralkyl radicals attached through an oxygen atom to other radicals.

The term "aminoalkyl" refers to alkyl radicals substituted with amino radicals.

10       Preferred aminoalkyl radicals have alkyl radicals having about one to about twenty-four carbon atoms or, preferably, one to about twelve carbon atoms. More preferred aminoalkyl radicals are "lower aminoalkyl" that have alkyl radicals having one to about ten carbon atoms. Most preferred are aminoalkyl radicals having lower alkyl radicals having one to eight carbon atoms. Examples of such radicals include aminomethyl, aminoethyl, and the  
15       like.

The term "alkylamino" denotes amino groups which are substituted with one or two alkyl radicals. Preferred alkylamino radicals have alkyl radicals having about one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkylamino radicals are "lower alkylamino" that have alkyl radicals having one to about ten  
20       carbon atoms. Most preferred are alkylamino radicals having lower alkyl radicals having one to about eight carbon atoms. Suitable lower alkylamino may be monosubstituted N-alkylamino or disubstituted N,N-alkylamino, such as N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-diethylamino or the like.

The term "substituted" refers to the replacement of one or more hydrogen radicals in a  
25       given structure with the radical of a specified substituent including, but not limited to: halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl,  
30       arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, aryl, heteroaryl, heterocyclic, and aliphatic. It is understood that the substituent may be further substituted.

For simplicity, chemical moieties that are defined and referred to throughout can be univalent chemical moieties (e.g., alkyl, aryl, etc.) or multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, an "alkyl" moiety can be referred to a monovalent radical (e.g.,  $\text{CH}_3\text{-CH}_2\text{-}$ ), or in other instances, a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (e.g.,  $\text{-CH}_2\text{-CH}_2\text{-}$ ), which is equivalent to the term "alkylene." Similarly, in circumstances in which divalent moieties are required and are stated as being "alkoxy", "alkylamino", "aryloxy", "alkylthio", "aryl", "heteroaryl", "heterocyclic", "alkyl", "alkenyl", "alkynyl", "aliphatic", or "cycloalkyl", those skilled in the art will understand that the terms alkoxy, "alkylamino", "aryloxy", "alkylthio", "aryl", "heteroaryl", "heterocyclic", "alkyl", "alkenyl", "alkynyl", "aliphatic", or "cycloalkyl" refer to the corresponding divalent moiety.

The terms "halogen" or "halo" as used herein, refers to an atom selected from fluorine, chlorine, bromine and iodine.

The terms "compound", "drug", and "prodrug" as used herein all include pharmaceutically acceptable salts, co-crystals, solvates, hydrates, polymorphs, enantiomers, diastereoisomers, racemates and the like of the compounds, drugs and prodrugs having the formulas as set forth herein.

Substituents indicated as attached through variable points of attachments can be attached to any available position on the ring structure.

As used herein, the term "effective amount of the subject compounds," with respect to the subject method of treatment, refers to an amount of the subject compound which, when delivered as part of desired dose regimen, brings about management of the disease or disorder to clinically acceptable standards.

"Treatment" or "treating" refers to an approach for obtaining beneficial or desired clinical results in a patient. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: alleviation of symptoms, diminishment of extent of a disease, stabilization (i.e., not worsening) of a state of disease, preventing spread (i.e., infection of others) of disease, and amelioration of the disease state (whether partial or total).

"Combination therapy" includes the administration of the subject compounds in further combination with other biologically active ingredients (such as, but not limited to, a second and different antineoplastic agent) and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the invention can be used in

combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compounds of the invention. The compounds of the invention can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy. In general, a combination therapy  
5 envisions administration of two or more drugs during a single cycle or course of therapy.

#### Pharmaceutical Compositions

The pharmaceutical compositions of the present invention comprise a therapeutically effective amount of a compound of the present invention formulated together with one or more pharmaceutically acceptable carriers or excipients.

10 As used herein, the term "pharmaceutically acceptable carrier or excipient" means a non-toxic, inert solid, semi-solid, gel or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers are sugars such as lactose, glucose and sucrose; cyclodextrins such as alpha- ( $\alpha$ ), beta- ( $\beta$ ) and gamma- ( $\gamma$ ) cyclodextrins; starches such as  
15 corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols such as propylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium  
20 hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to  
25 the judgment of the formulator.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. In a preferred embodiment, administration is parenteral administration by injection.

30 The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular,

intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable suspension or emulsion, such as INTRALIPID®, LIPOSYN® or OMEGAVEN®, or solution, in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. INTRALIPID® is an intravenous fat emulsion containing 10-30% soybean oil, 1-10% egg yolk phospholipids, 1-10% glycerin and water. LIPOSYN® is also an intravenous fat emulsion containing 2-15% safflower oil, 2-15% soybean oil, 0.5-5% egg phosphatides 1-10% glycerin and water. OMEGAVEN® is an emulsion for infusion containing about 5-25% fish oil, 0.5-10% egg phosphatides, 1-10% glycerin and water. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, USP and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating

excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or: a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this invention.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes,

paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and  
5 polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux  
10 of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

For pulmonary delivery, a therapeutic composition of the invention is formulated and administered to the patient in solid or liquid particulate form by direct administration e.g., inhalation into the respiratory system. Solid or liquid particulate forms of the active  
15 compound prepared for practicing the present invention include particles of respirable size: that is, particles of a size sufficiently small to pass through the mouth and larynx upon inhalation and into the bronchi and alveoli of the lungs. Delivery of aerosolized therapeutics is known in the art (see, for example U.S. Pat. No. 5,767,068 to VanDevanter *et al.*, U.S. Pat. No. 5,508,269 to Smith *et al.*, and WO 98/43650 by Montgomery).

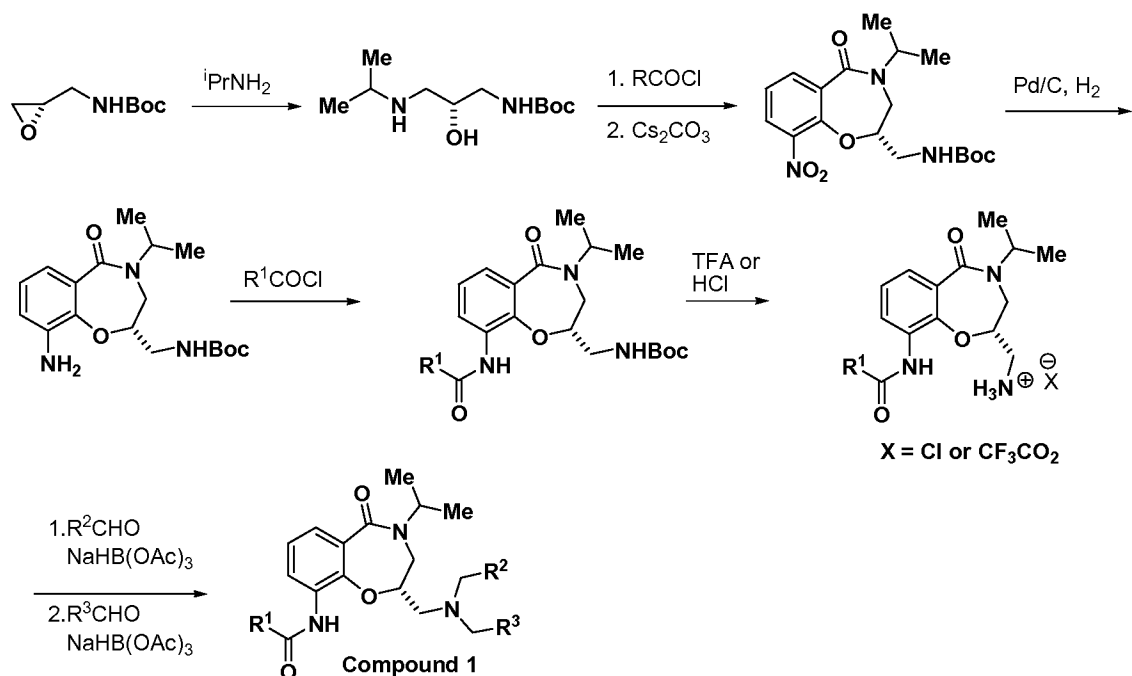
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#### Examples

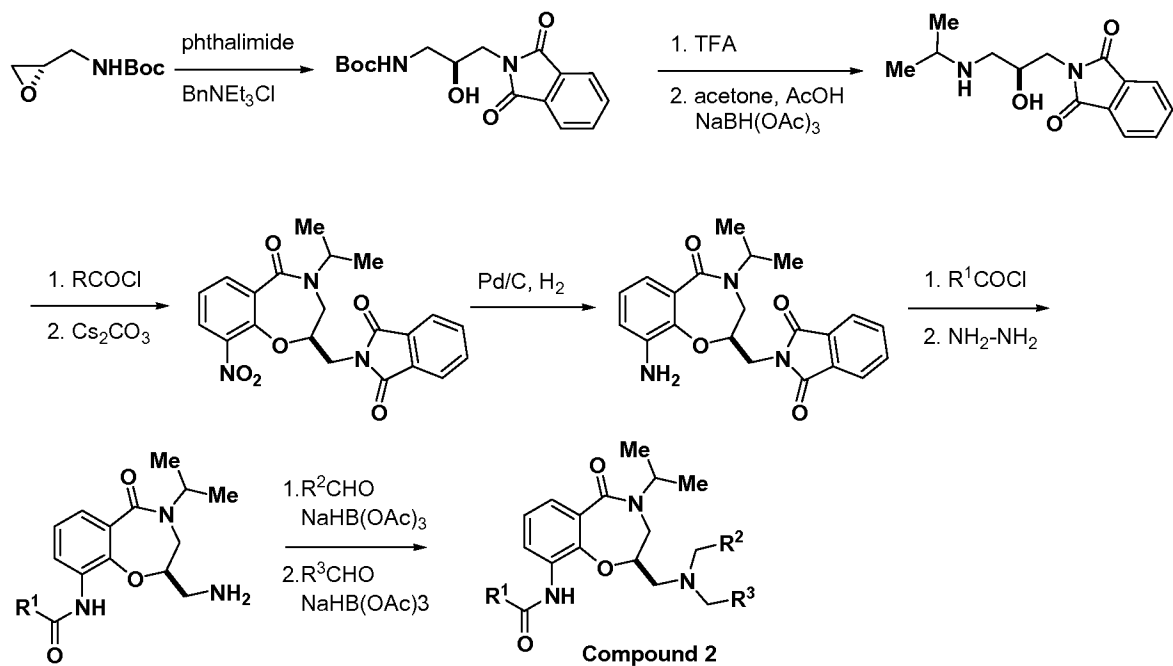
#### SYNTHESIS

General methods of synthesizing compounds of the instant application are described in the general procedures set forth in PCT/US2012/025071. A synthetic protocol for the  
25 synthesis of macrocyclic compounds is described in Marcaurelle, L.A. et al., *J. Am. Chem. Soc.* 132, 16962–16976, 2010. Compounds listed in Tables 1-4 were synthesized using a similar general procedure. The following are general synthetic schemes used for the synthesis of the compounds of Formula I. The substituent marked as R1, R2 or R3 are distinct from the substituents described in the context of variables above and in the claims,  
30 and are generic in nature and can be any substituent that will not interfere with the reactions.

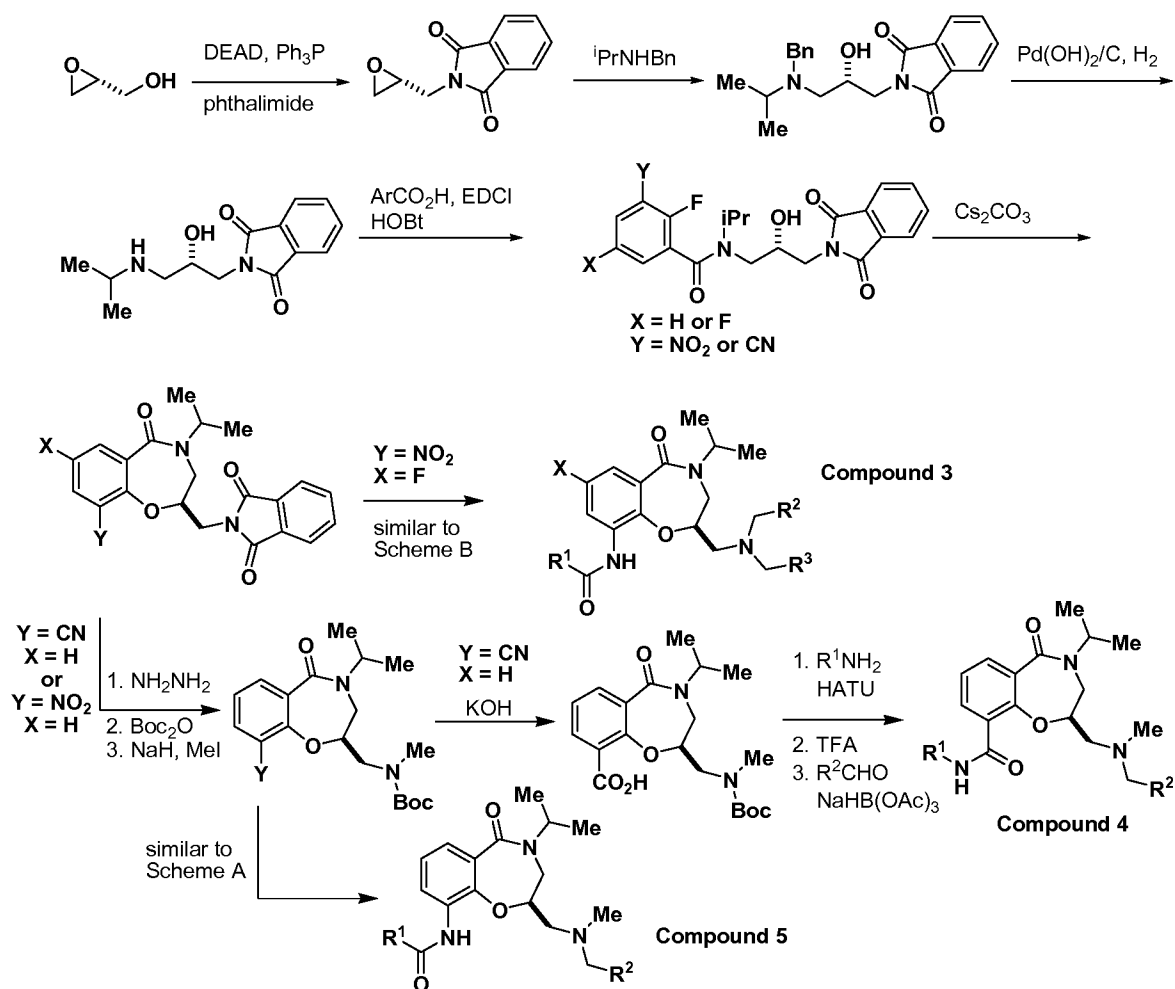
Scheme A: 7-membered ring through epoxide opening with primary amine



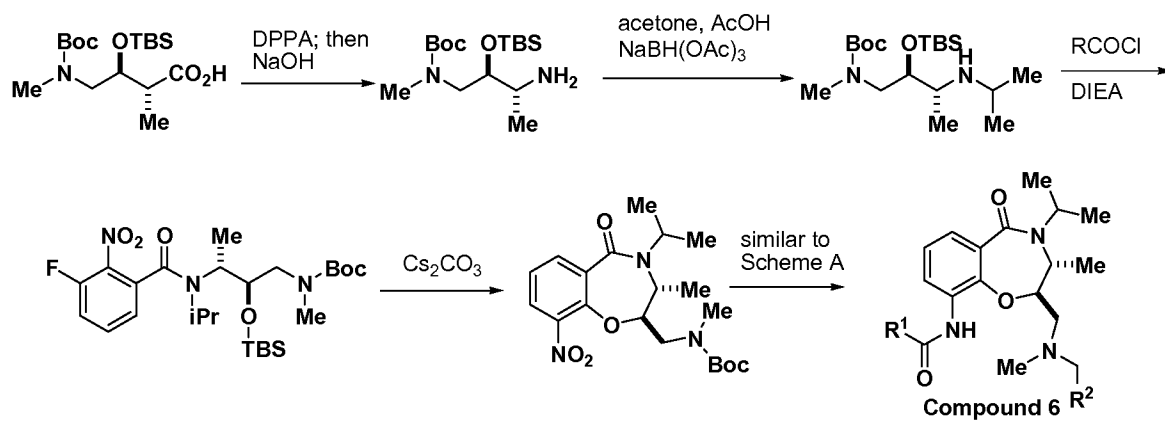
Scheme B: 7-membered ring through epoxide opening with phthalimide



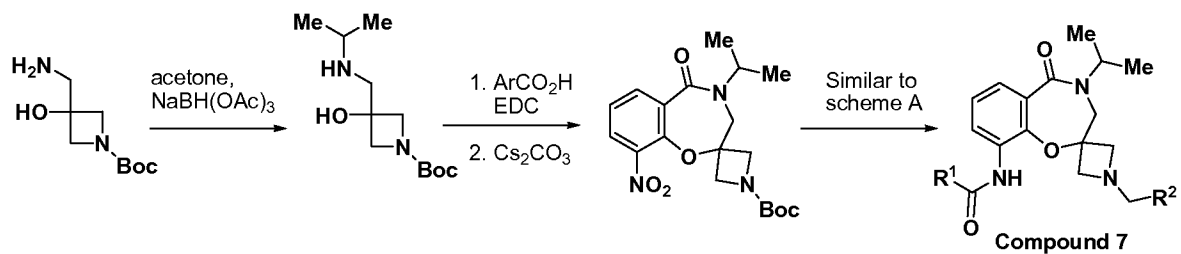
Scheme C: 7-membered ring from glycidol and reverse amides



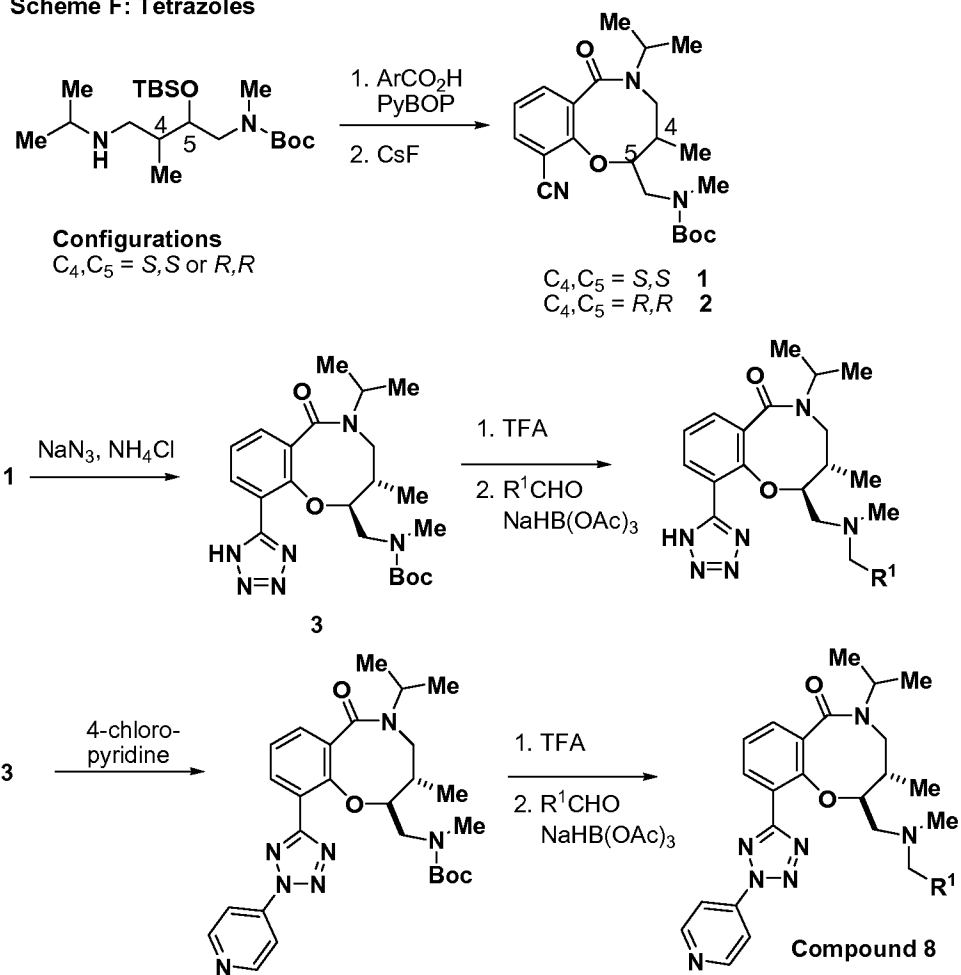
Scheme D: Curtius rearrangement to 7-membered ring



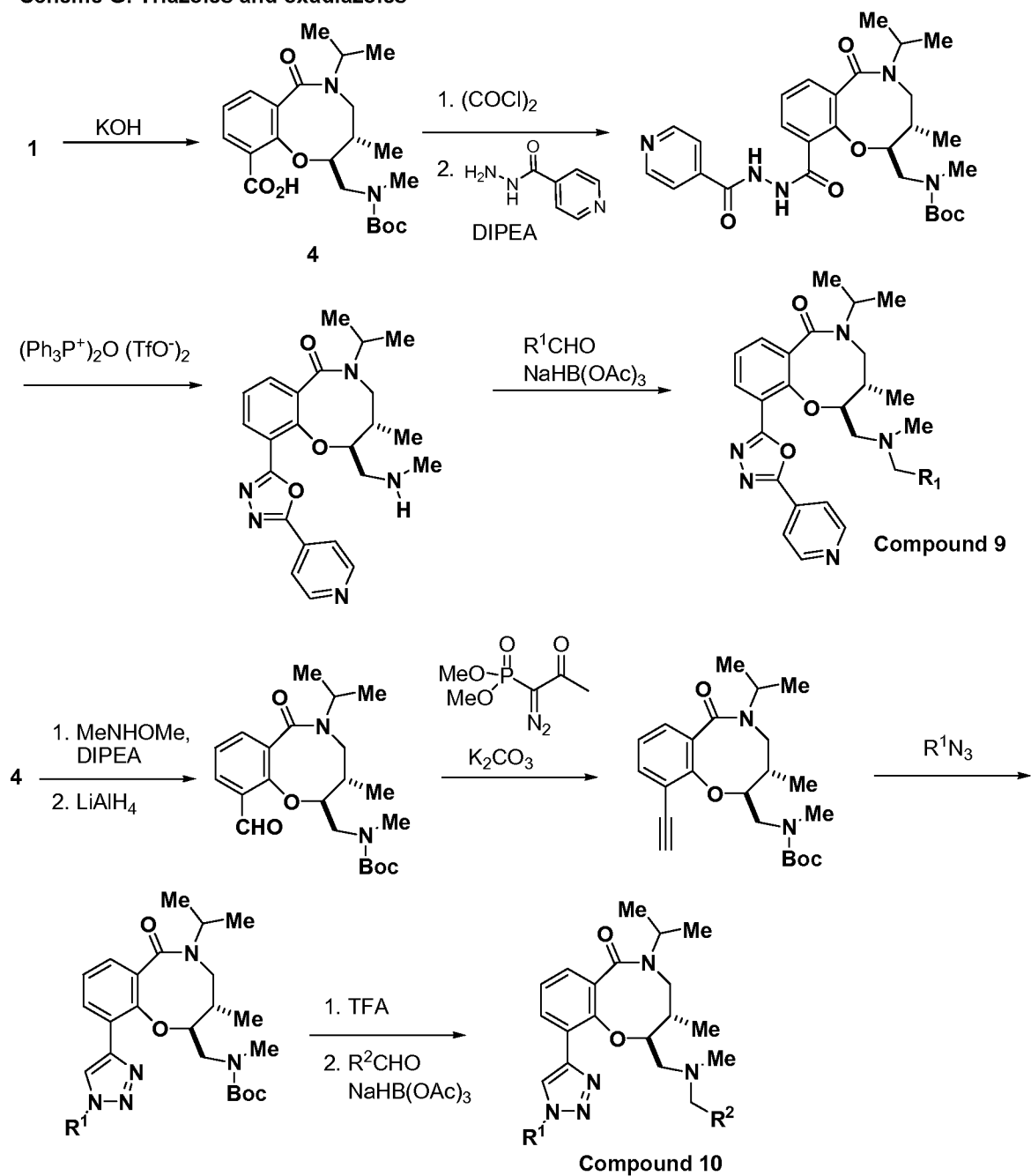
## Scheme E: Spiroazetidines



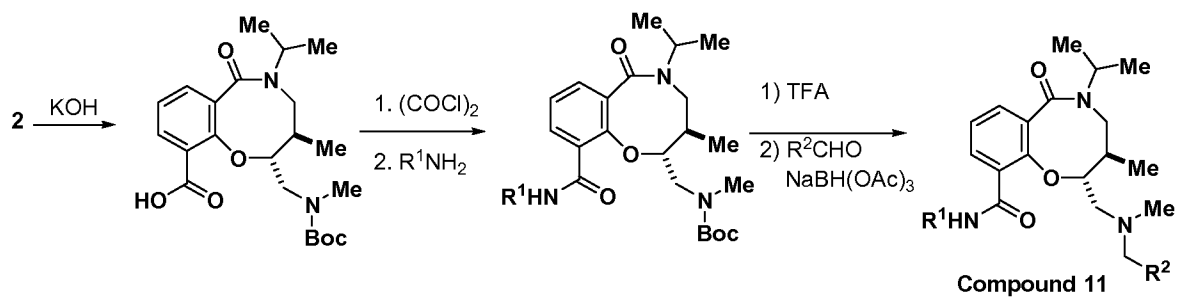
## Scheme F: Tetrazoles



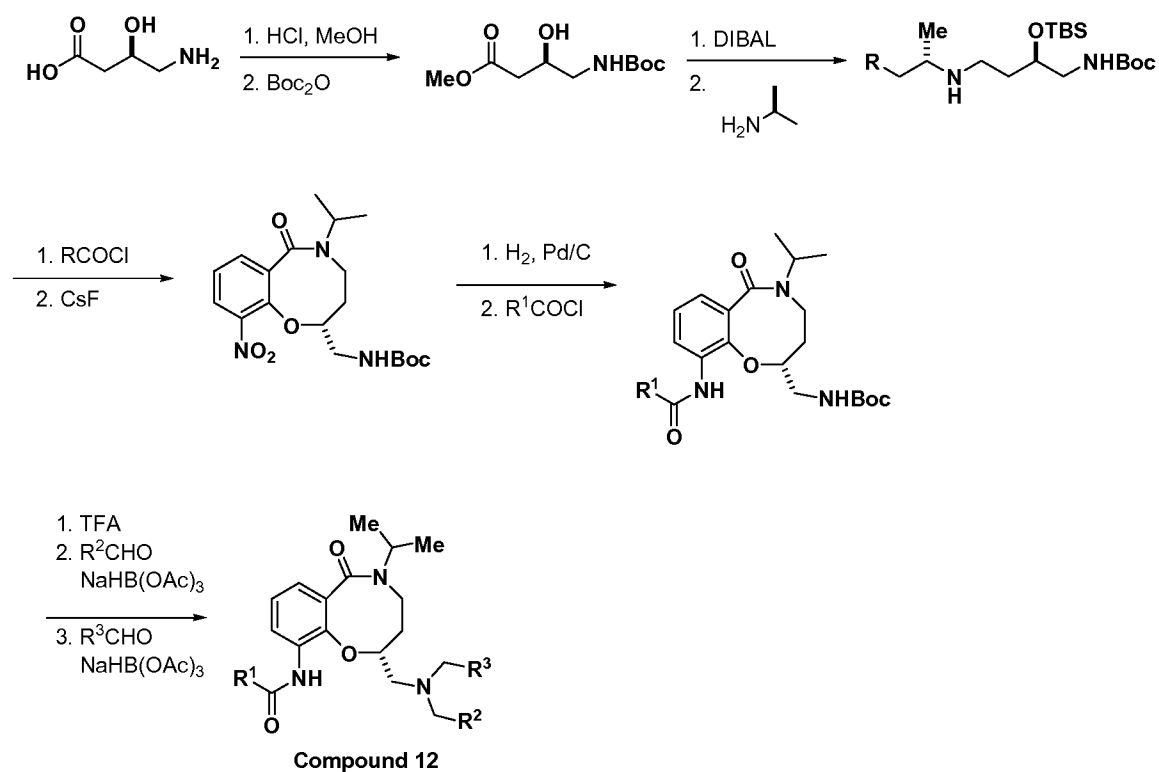
## Scheme G: Triazoles and oxadiazoles



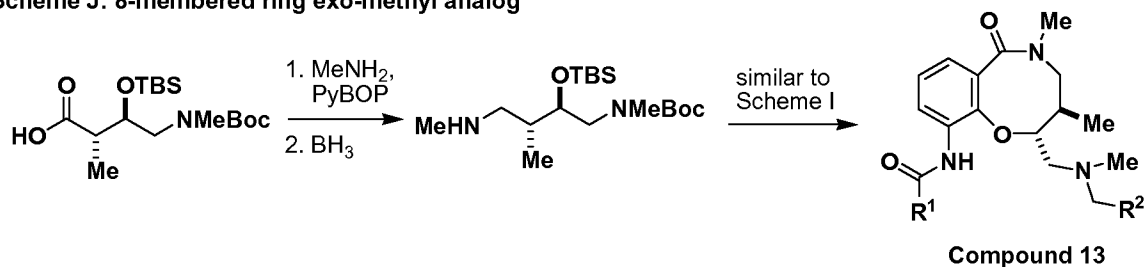
Scheme H: 8-membered ring reverse amide



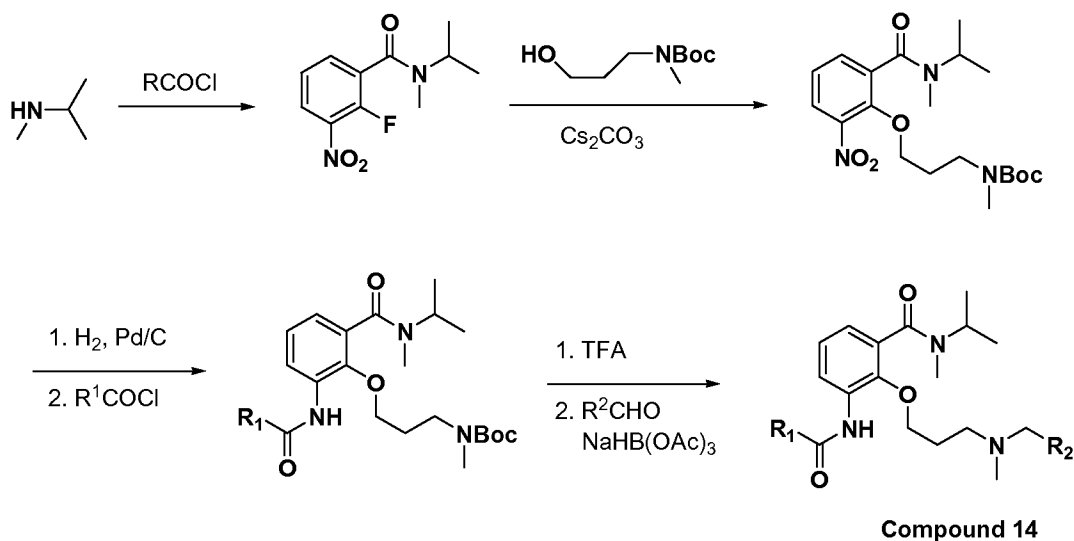
Scheme I: Des-methyl 8-membered ring analog



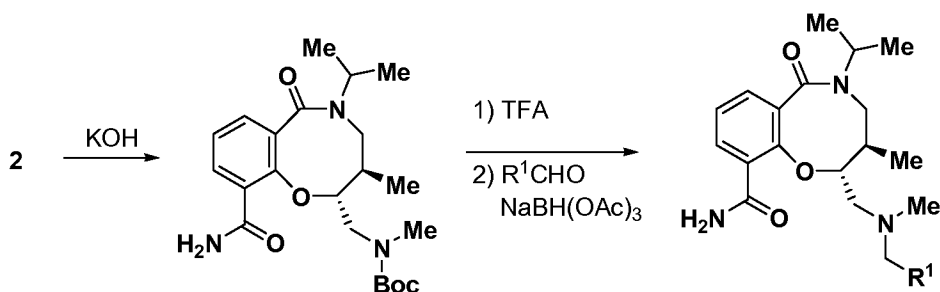
Scheme J: 8-membered ring exo-methyl analog



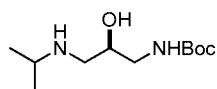
Scheme K: Acyclic amide analog



Scheme L: Free primary amide.



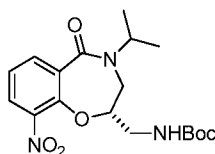
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**Preparation of Compound 1.01 (Scheme A)**

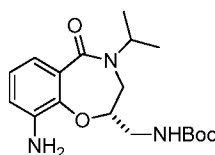
**(R)-tert-butyl (2-hydroxy-3-(isopropylamino)propyl)carbamate:** Propan-2-amine (40 ml, 489 mmol) was added in one portion to a 250 mL round-bottomed flask containing (*S*)-tert-butyl oxiran-2-ylmethylcarbamate (1.98 g, 11.43 mmol) dissolved in acetone (110 mL). The

10

reaction mixture was stirred at room temperature for 2.5 h, concentrated (30 °C) and dried under high vacuum. The reaction mixture was then concentrated from Et<sub>2</sub>O followed by toluene (35 °C) and dried under high vacuum. Transferred to a fresh flask with CH<sub>2</sub>Cl<sub>2</sub>, concentrated and placed under high vacuum to yield the product (2.65 g, 11.41 mmol) in  
 5 quantitative yield. MS (ESI) calcd for C<sub>11</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 232.18 Found: 233.30.



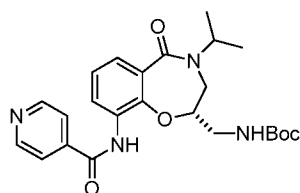
**(S)-tert-butyl ((4-isopropyl-9-nitro-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)carbamate:** In a flame-dried 5 mL round-bottomed flask 2-fluoro-3-nitrobenzoyl  
 10 chloride (0.96 g, 4.72 mmol) was dissolved in dry DMF (52 mL) under argon. *N,N*-diisopropylamine (1.639 mL, 9.38 mmol) was added, the reaction mixture was cooled to 0 °C and (*R*)-tert-butyl 2-hydroxy-3-(isopropylamino)propylcarbamate (1.09 g, 4.69 mmol) was added, as a solution in dry DMF (42 mL). The reaction was stirred for 10 min, the ice-bath was removed and the reaction mixture was stirred for an additional 5.5 h. Cesium carbonate  
 15 (1.528 g, 4.69 mmol) was added and the reaction mixture was stirred at room temperature for 10.5 h following which the reaction was heated to 60 °C for 6 h. The reaction mixture was concentrated and residue was partitioned between EtOAc (75 mL) and water (120 mL). The aqueous layer was extracted with EtOAc (30 mL x 5) and the combined organic layers were washed with sat. brine (40 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product  
 20 was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver the product (1.00 g, 2.64 mmol) in 56% yield. MS (ESI) calcd for C<sub>18</sub>H<sub>25</sub>N<sub>3</sub>O<sub>6</sub> [M+H-O<sup>t</sup>Bu]<sup>+</sup>: 324.11 Found: 324.22.



**(S)-tert-butyl ((9-amino-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)carbamate:** Absolute EtOH (50 mL) was added to a 250 mL round bottom flask which was evacuated and back-filled with nitrogen (x 3). Palladium on carbon (10%; 280 mg) was added to the reaction mixture followed by evacuation and back filling with nitrogen (x3). (*S*)-tert-butyl (4-isopropyl-9-nitro-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-  
 25

yl)methylcarbamate (1.00 g, 2.64 mmol) in absolute EtOH (36 mL) was added after which the flask was evacuated and back filled with nitrogen. A balloon of hydrogen was fitted to the flask and it was heated to 35 °C with stirring for 5.5 h. The hydrogen balloon was removed, a vent needle was added and a balloon of argon was run through the vessel. The reaction was  
 5 evacuated and back filled with nitrogen (x3). Celite was added and stirred for ~ 5 minutes. The resulting slurry was filtered through Celite, rinsed with MeOH (x3), and concentrated. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub>, concentrated, and dried under high vacuum to deliver the product (0.89 g, 2.55 mmol) in 97% yield. MS (ESI) calcd for C<sub>18</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 350.20 Found: 350.19.

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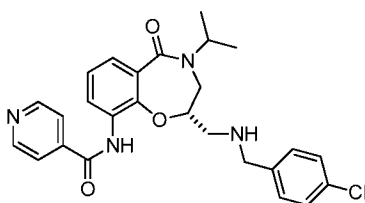


**(R)-tert-butyl ((9-(isonicotinamido)-4-isopropyl-5-oxo-2,3,4,5-**

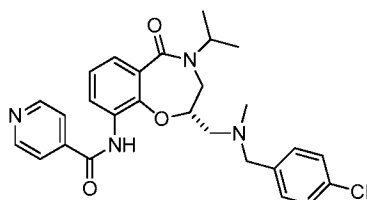
**tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)carbamate:** In a nitrogen flushed 50 mL

round-bottomed flask (S)-tert-butyl (9-amino-4-isopropyl-5-oxo-2,3,4,5-

15 tetrahydrobenzo[f][1,4]oxazepin-2-yl)methylcarbamate (0.89 g, 2.55 mmol) and 4-(chlorocarbonyl)pyridinium chloride (0.907 g, 5.09 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) under argon in an ice-bath. 2,6-Lutidine (1.780 ml, 15.28 mmol) was added, the reaction mixture was stirred for 10 minutes, the ice bath was removed and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL)  
 20 and 1 M HCl (25 ml). The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (25 mL x 3), the combined organic layers were washed with sat. Na<sub>2</sub>CO<sub>3</sub> (40 mL), water (20 mL) and sat. brine (40 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol to deliver the product (979 mg, 2.15 mmol) in 85% yield. MS (ESI) calcd for C<sub>24</sub>H<sub>30</sub>N<sub>4</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 455.22  
 25 Found: 455.31.



**(R)-N-(2-(((4-chlorobenzyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide:** (*S*)-*tert*-butyl (9-(isonicotinamido)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methylcarbamate (121 mg, 0.266 mmol) was suspended in Et<sub>2</sub>O (1 mL) and dry THF (0.3 mL) and cooled to 0 °C under argon. 2 M HCl in Et<sub>2</sub>O (2.4 mL) was added gradually to the reaction and it was stirred for 5 minutes. The ice bath was removed and the reaction mixture was stirred for 2 h. The reaction mixture was concentrated and dried on the high vacuum. The crude product and 4-chlorobenzaldehyde (43.5 mg, 0.309 mmol) were dissolved in CH<sub>3</sub>CN (2 mL), CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and MeOH (0.5 mL) under argon and stirred for 15 minutes. Sodium cyanoborohydride (33.4 mg, 0.532 mmol) was added and the reaction was stirred for 10.5 h. Added sodium cyanoborohydride (40 mg) and stirred for 3.5 days. Sat. Na<sub>2</sub>CO<sub>3</sub> (3 mL) and water (2 mL) were added, the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL x 3), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude material, sodium cyanoborohydride (33.4 mg, 0.532 mmol), and 4-chlorobenzaldehyde (43.5 mg, 0.309 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and MeOH (2 mL) and stirred under argon for 5 h. Sat. Na<sub>2</sub>CO<sub>3</sub> (3 mL) and water (2 mL) were added, the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL x 5), dried (MgSO<sub>4</sub>), filtered and concentrated. Piperazine (300 mg) was added to the crude product dissolved in EtOAc (4 mL), and stirred for ~24 h. Water (6 mL) was added, the mixture was stirred for 2 h, the organic layer was separated, dried (MgSO<sub>4</sub>) and concentrated. The crude product was purified by column chromatography on silica gel eluting with 7 M NH<sub>3</sub> in methanol/dichloromethane to deliver the product (31 mg, 0.07 mmol) in 24% yield. MS (ESI) calcd for C<sub>26</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 479.18 Found: 479.33.

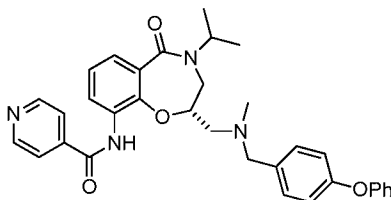


**(S)-N-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (1.01):** (*S*)-N-(2-((4-chlorobenzylamino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (25.8 mg, 0.054 mmol) and acetic acid (77 μL, 1.347 mmol) were dissolved in MeOH (0.6 mL). Formalin (110 μL) was added and the reaction was stirred for 10 minutes. Sodium triacetoxyborohydride (114 mg, 0.539 mmol) was added and the reaction

was stirred for 14 h (LCMS shows some remaining starting material). Formalin (50  $\mu$ L) was added, the temperature was increased to 40 °C and the reaction mixture was stirred for 6 h. Additional acetic acid (77  $\mu$ L, 1.347 mmol), formalin (43.7  $\mu$ L, 0.539 mmol) and sodium triacetoxymethylborohydride (114 mg, 0.539 mmol) were added and the reaction mixture was stirred at 50 °C for 14.5 h. Added 1 M NaOH (2 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL x 3), dried (MgSO<sub>4</sub>), filtered and concentrated. . The crude product was purified by column chromatography on silica gel eluting with 7 M NH<sub>3</sub> in methanol/dichloromethane to deliver the product (17 mg, 0.04 mmol) in 64% yield. MS (ESI) calcd for C<sub>27</sub>H<sub>29</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 493.19 Found: 493.25. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  10.47 (s, 1H), 8.76 (d, *J* = 8.1 Hz, 1H), 8.66 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.72 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.53 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.33 – 7.24 (m, 3H), 7.03 (d, *J* = 8.3 Hz, 2H), 5.14 – 4.99 (m, 1H), 4.83 – 4.69 (m, 1H), 3.54 (d, *J* = 13.5 Hz, 1H), 3.25 (dd, *J* = 15.6, 4.0 Hz, 1H), 3.15 – 3.02 (m, 2H), 2.42 (dd, *J* = 13.0, 11.2 Hz, 1H), 2.16 – 2.04 (m, 5H), 1.30 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H).

### Compound 1 series

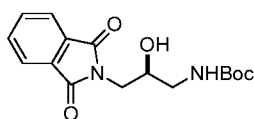
The following compounds were synthesized as outlined in Scheme A and exemplified by the synthesis of compound 1.01.



**(S)-N-(4-isopropyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-5-oxo-2,3,4,5-**

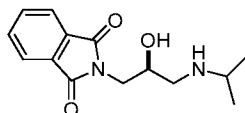
**tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (1.02):** Synthesized by the procedure described for compound 1.01. Yield 33%. MS (ESI) calcd for C<sub>33</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 551.26 Found: 551.33.

### Preparation of Compound 2.01 (Scheme B)

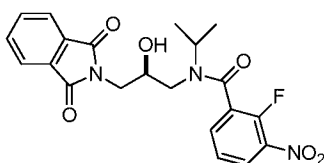


**(S)-tert-butyl (3-(1,3-dioxoisindolin-2-yl)-2-hydroxypropyl)carbamate:** (S)-tert-butyl oxiran-2-ylmethylcarbamate (946 mg, 5.46 mmol), isindoline-1,3-dione (884 mg, 6.01 mmol), and *N,N,N*-triethyl-2-phenylethanaminium chloride (132 mg, 0.546 mmol) were suspended in acetonitrile (11 ml). The reaction was heated to 70 °C with stirring for 6 days.

The reaction was concentrated and partitioned between EtOAc (40 mL) and 25% sat. brine (40 mL). The aqueous layer was extracted with EtOAc (20 mL x 2) and the combined organic layers were dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver the product (684 mg, 2.14 mmol) in 39% yield. MS (ESI) calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>5</sub> [M+H-O<sup>t</sup>Bu]<sup>+</sup>: 265.07 Found: 265.17.

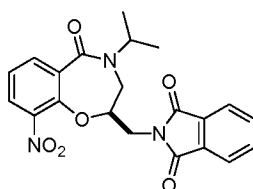


**(S)-2-(2-hydroxy-3-(isopropylamino)propyl)isoindoline-1,3-dione:** In a nitrogen flushed 25 mL round-bottomed flask (S)-tert-butyl 3-(1,3-dioxoisindolin-2-yl)-2-hydroxypropylcarbamate (684 mg, 2.135 mmol) was dissolved in dichloromethane (21 mL) under argon and cooled to 0 °C. Trifluoroacetic acid (1.481 mL, 19.22 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred for 25 minutes; the ice-bath was removed and the reaction mixture was stirred for 5 h. The reaction mixture was concentrated and dried under high vacuum. The crude (S)-3-(1,3-dioxoisindolin-2-yl)-2-hydroxypropan-1-aminium 2,2,2-trifluoroacetate (714 mg, 2.135 mmol) was suspended in dichloromethane (21 mL) under argon and cooled to 0 °C. Sodium triacetoxyborohydride (3.17 g, 14.95 mmol) and acetone (0.78 mL, 10.68 mmol) were added to the reaction mixture and it was stirred at 0 °C for 25 min. The ice bath removed and reaction mixture was stirred for 12 h. The reaction was quenched with sat. Na<sub>2</sub>CO<sub>3</sub> (40 mL) and stirred for 10 minutes. Sat. brine (15 mL) was added and the organic layer was separated. The aqueous layer was diluted with water (40 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL x 4) and the combined organic layers were washed with sat. brine (20 mL), dried (MgSO<sub>4</sub>), filtered, concentrated and dried under high vacuum to deliver the product (489 mg, 1.86 mmol) in 87% yield. MS (ESI) calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 263.13 Found: 263.24.

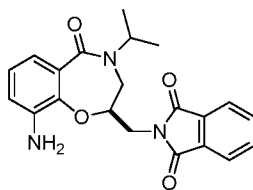


**(S)-N-(3-(1,3-dioxoisindolin-2-yl)-2-hydroxypropyl)-2-fluoro-N-isopropyl-3-nitrobenzamide:** (S)-2-(2-hydroxy-3-(isopropylamino)propyl)isoindoline-1,3-dione (489 mg, 1.86 mmol) was dissolved in dry dichloromethane (24 mL) under argon and cooled to 0

°C. *N,N*-diisopropylamine (0.977 mL, 5.59 mmol) was added to the reaction mixture followed by 2-fluoro-3-nitrobenzoyl chloride (379 mg, 1.864 mmol) dropwise as a solution in dry dichloromethane (5 mL). The reaction mixture was stirred at 0 °C gradually warming to room temperature over 5 h. The reaction mixture was concentrated, partitioned between CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and water (70 mL), and extracted with CH<sub>2</sub>Cl<sub>2</sub> (25 mL x 2). The combined organic layers were washed with sat. brine (30 mL), dried (MgSO<sub>4</sub>), filtered and concentrated to deliver the product (563 mg, 1.31 mmol) in 70% yield. MS (ESI) calcd for C<sub>21</sub>H<sub>20</sub>FN<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup> : 430.13 Found: 430.18.

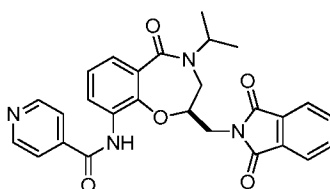


**(S)-2-((4-isopropyl-9-nitro-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)isoindoline-1,3-dione:** To (*S*)-*N*-(3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropyl)-2-fluoro-*N*-isopropyl-3-nitrobenzamide (51.9 mg, 0.121 mmol) in dry DMF (2.5 mL) under argon at 0 °C was added cesium carbonate (51.2 mg, 0.157 mmol). The reaction was stirred for 10 min, the ice-bath was removed and the reaction was stirred for 25.5 h. The reaction mixture was concentrated and partitioned between EtOAc (3 mL) and 20% sat NH<sub>4</sub>Cl (3 mL). The aqueous layer was extracted with EtOAc (2 mL x 3) and the combined organic layers were washed with water (1.5 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol to deliver the product (36.8 mg, 1.31 mmol) in 74% yield. MS (ESI) calcd for C<sub>21</sub>H<sub>19</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup> : 410.13 Found: 410.18.

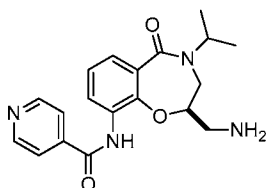


**(S)-2-((9-amino-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)isoindoline-1,3-dione:** Ethyl acetate (15 mL) was added to a 100 mL round bottom flask which was evacuated and back-filled with nitrogen. Palladium on carbon (10%; 280 mg) was added to the reaction mixture followed by evacuation and back filling with nitrogen. (*S*)-2-((4-isopropyl-9-nitro-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-

yl)methyl)isoindoline-1,3-dione (359 mg, 0.877 mmol) in a mixture of ethyl acetate (15 mL) and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added. The flask was evacuated, back filled with nitrogen and a balloon of hydrogen was fitted to the flask. The reaction mixture was heated to 35 °C with stirring for 3 h. The hydrogen balloon was removed, a vent needle was added and a balloon of argon was run through the vessel. The reaction was evacuated and back filled with nitrogen. The reaction mixture was filtered through Celite, rinsed with MeOH and concentrated. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub>, concentrated, and dried under high vacuum to deliver the product (251 mg, 0.662 mmol) in 75% yield. MS (ESI) calcd for C<sub>21</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> [M+H]<sup>+</sup> : 380.15 Found: 380.00.

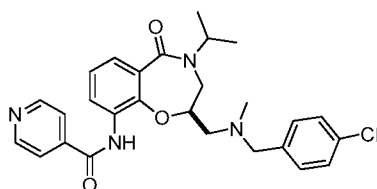


**(S)-N-(2-((1,3-dioxoisoindolin-2-yl)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide:** In a nitrogen flushed 15 mL round-bottomed flask (S)-2-((9-amino-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)isoindoline-1,3-dione (51 mg, 0.662 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) under argon and cooled on ice. 2,6-lutidine (0.462 ml, 3.97 mmol) was added followed by 4-(chlorocarbonyl)pyridinium chloride (236 mg, 1.323 mmol). The reaction was stirred for 20 minutes, the ice bath was removed and the reaction was stirred at room temperature for 3.5 h. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL) and 1 M HCl (3 mL). The reaction was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 mL x 3), the combined organic layers were washed sequentially with sat. Na<sub>2</sub>CO<sub>3</sub> (4 mL), water (2 mL) and sat. brine (2 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol to deliver the product (199 mg, 0.41 mmol) in 62% yield. MS (ESI) calcd for C<sub>27</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub> [M+H]<sup>+</sup> : 485.18 Found: 485.16.



**(R)-N-(2-(aminomethyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide:** (S)-N-(2-((1,3-dioxoisoindolin-2-yl)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (183 mg, 0.378 mmol) was

dissolved/suspended in abs. EtOH (10 mL). Anhydrous hydrazine (600  $\mu$ L) was added and the reaction was stirred at room temperature for 15.5 h. The reaction mixture was filtered, the solid rinsed with  $\text{CHCl}_3$  (20 mL) and the combined eluent filtrate was concentrated. The concentrate was partitioned between  $\text{CH}_2\text{Cl}_2$  (4 mL) and water (4 mL). Sodium hydroxide (8 drops, 1 N) was added and the reaction mixture was extracted with  $\text{CH}_2\text{Cl}_2$  (3 mL x 3). The combined organic layers were washed with water (4 mL) and sat. brine (4 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol to deliver the product (100 mg, 0.28 mmol) in 75% yield. MS (ESI) calcd for  $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_3$   $[\text{M}+\text{H}]^+$ : 355.17 Found: 355.25.



**(R)-N-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-**

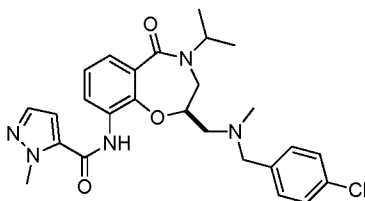
**tetrahydrobenzo[f][1,4] oxazepin-9-yl)isonicotinamide (2.01):** A solution of (R)-N-(2-(aminomethyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-

yl)isonicotinamide (25 mg, 0.071 mmol) and 4-chlorobenzaldehyde (12 mg, 0.085 mmol) in THF (1.4 mL) was stirred at a temperature between 60-70  $^{\circ}\text{C}$  for 6 h. The reaction mixture was cooled to room temperature, sodium triacetoxyborohydride (22 mg, 0.106 mmol) and DMF (0.20 mL) were added and the reaction mixture was stirred for 18 h. Additional sodium triacetoxyborohydride (22 mg, 0.106 mmol) was added and the reaction mixture was stirred for 10 h. Formalin (0.11 mL, 1.411 mmol) and sodium triacetoxyborohydride (22.43 mg, 0.106 mmol) were added and the reaction was stirred for 36 h. The reaction mixture was diluted with DMF (0.5 mL), THF (0.5 mL) and  $\text{H}_2\text{O}$  (0.1 mL). Formalin (0.11 mL, 1.411 mmol) and sodium triacetoxyborohydride (45 mg, 0.212 mmol) were added, and the reaction mixture was stirred overnight. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and sat.  $\text{NaHCO}_3$  (10 mL), extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol/ ammonia to deliver the product (23 mg, 0.071 mmol) in 63% yield. MS (ESI) calcd for  $\text{C}_{27}\text{H}_{29}\text{ClN}_4\text{O}_3$   $[\text{M}+\text{H}]^+$ : 493.19 Found: 493.38.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.40 (s, 1H), 8.67 (d,  $J$  = 8.2 Hz, 1H), 8.58 (d,  $J$  = 5.9 Hz, 2H), 7.64 (dd,  $J$  = 4.5, 1.4 Hz, 2H), 7.43 (dd,  $J$  = 7.7, 1.5 Hz, 1H), 7.20 (t,  $J$  = 7.5 Hz, 3H), 6.94 (d,  $J$  = 8.3 Hz, 2H), 4.96 (dq,  $J$  = 13.1, 6.6 Hz, 1H), 4.67 (ddd,  $J$  = 11.1, 7.0, 2.8 Hz, 1H), 4.12 – 3.99 (m,

1H), 3.45 (d,  $J = 13.4$  Hz, 1H), 3.16 (dt,  $J = 9.6, 4.8$  Hz, 1H), 3.08 – 2.92 (m, 2H), 2.33 (dd,  $J = 12.9, 11.3$  Hz, 1H), 2.03 (s, 3H), 1.21 (d,  $J = 6.9$  Hz, 3H), 1.10 (d,  $J = 6.7$  Hz, 3H).

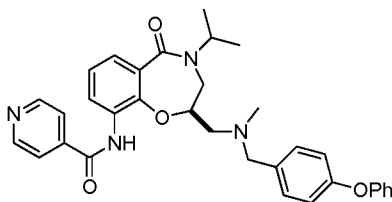
### Compound 2 series

- 5 The following compounds were synthesized as outlined in Scheme B and exemplified by the synthesis of compound 2.01.



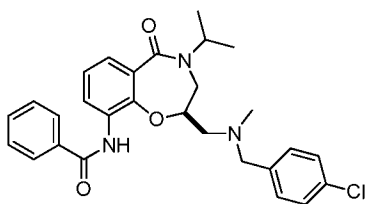
**(R)-N-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)-1-methyl-1H-pyrazole-5-carboxamide (2.02):**

- 10 Synthesized by the procedure described for Compound 2.01. Yield 61%. MS (ESI) calcd for  $C_{26}H_{30}ClN_5O_3$   $[M+H]^+$ : 496.20 Found: 496.37.

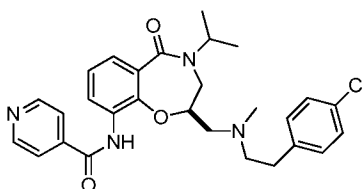


**(R)-N-(4-isopropyl-2-(((methyl(4-phenoxybenzyl)amino)methyl)-5-oxo-2,3,4,5-**

- 15 **tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (2.03):** Synthesized by the procedure described for Compound 2.01. Yield 19%. MS (ESI) calcd for  $C_{33}H_{34}N_4O_4$   $[M+H]^+$ : 551.26 Found: 551.25.

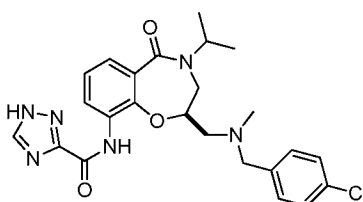


- 20 **(R)-N-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)benzamide(2.04):** Synthesized by the procedure described for Compound 2.01. Yield 25%. MS (ESI) calcd for  $C_{28}H_{32}ClN_3O_3$   $[M+H]^+$ : 492.20 Found: 492.84.



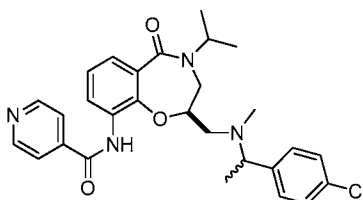
**(R)-N-(2-(((4-chlorophenethyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (2.05):** Synthesized by the procedure described for Compound 2.01. Yield 96%. MS (ESI) calcd for  $C_{28}H_{31}ClN_4O_3$

5  $[M+H]^+$  : 507.21 Found: 507.34.



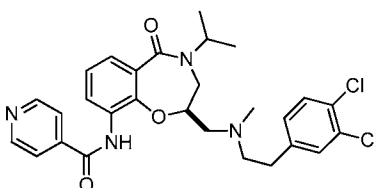
**(R)-N-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)-1H-1,2,4-triazole-3-carboxamide (2.06):**

10 Synthesized by the procedure described for Compound 2.01. Yield 27%. MS (ESI) calcd for  $C_{24}H_{27}ClN_6O_3$   $[M+H]^+$  : 483.18 Found: 483.34.



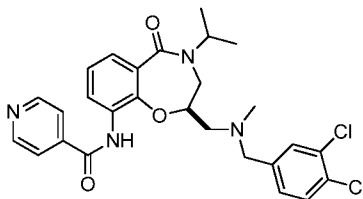
**N-((2R)-2-(((1-(4-chlorophenyl)ethyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (2.07):** Synthesized by the

15 procedure described for Compound 2.01. Yield 15%. MS (ESI) calcd for  $C_{28}H_{31}ClN_4O_3$   $[M+H]^+$  : 507.21 Found: 507.36.



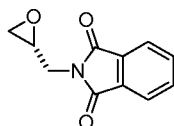
20 **(R)-N-(2-(((3,4-dichlorophenethyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (2.08):** Synthesized by the

procedure described for Compound 2.01. Yield 98%. MS (ESI) calcd for  $C_{28}H_{30}Cl_2N_4O_3$   $[M+H]^+$ : 541.17 Found: 541.32.

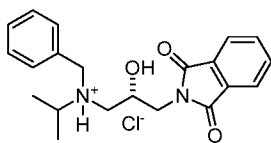


- 5 **(R)-N-(2-(((3,4-dichlorophenethyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (2.09):** Synthesized by the procedure described for Compound 2.01. Yield 93%. MS (ESI) calcd for  $C_{27}H_{28}Cl_2N_4O_3$   $[M+H]^+$ : 527.15 Found: 527.34.

10 **Preparation of Compound 3.01 (Scheme C)**

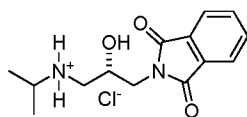


- (R)-2-(oxiran-2-ylmethyl)isoindoline-1,3-dione:** In a flame-dried 100 mL pear-shaped flask isoindoline-1,3-dione (8.53 g, 58.0 mmol) and triphenylphosphine (15.21 g, 58.0 mmol) were dissolved in dry THF (290 mL) under argon. (R)-oxiran-2-ylmethanol (4.6 ml, 69.3 mmol) was added to the reaction mixture in one portion. The reaction was cooled to 0 °C and diethylazodicarboxylate (23 ml, 58.0 mmol) was added to the reaction mixture dropwise over 25 minutes. The reaction mixture was gradually warmed to room temperature and stirred for 26.5 h. The reaction was concentrated and Et<sub>2</sub>O (~200 mL) was added, the reaction was stirred for 38 h and the resulting suspension was filtered. The filtrate was partially concentrated, filtered again and dry loaded onto silica gel. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver the product (9.38 g, 46.1 mmol) in 80% yield. MS (ESI) calcd for  $C_{11}H_9NO_3$   $[M+H]^+$ : 204.06 Found: 204.24.

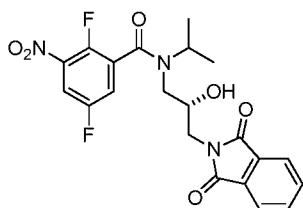


- 25 **(2R)-N-benzyl-3-(1,3-dioxoisoindolin-2-yl)-2-hydroxy-N-isopropylpropan-1-aminium chloride:** In an oven-dried 50 mL round-bottomed flask N-benzylpropan-2-amine (1.033 g,

6.92 mmol) was dissolved in *t*-BuOH (23 mL). (*R*)-2-(oxiran-2-ylmethyl)isoindoline-1,3-dione (1.407 g, 6.92 mmol) was added to the reaction mixture in one portion. The reaction mixture was heated at 65 °C for 8 h. The heat was turned off and the reaction mixture was stirred for 15 h and then heated at 65 °C for 10 h. The reaction mixture was concentrated and dried under high vacuum. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) and sat. NaHCO<sub>3</sub> (150 mL). The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (25 mL x 3), the combined organic layers were washed with sat. brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol to deliver the free base which was dissolved in ether, treated with 2 M HCl solution in ether, filtered and dried to deliver the product (1.88 g, 5.32 mmol) in 77% yield. Free base MS (ESI) calcd for C<sub>21</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 353.18 Found: 353.35.

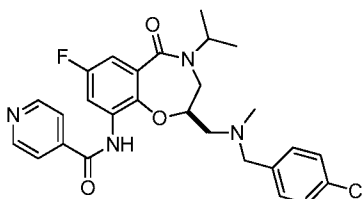


**(*S*)-3-(1,3-dioxisoindolin-2-yl)-2-hydroxy-*N*-isopropylpropan-1-aminium chloride:** In a 25 mL round-bottomed flask absolute EtOH (5 mL) was added. The flask was evacuated and back-filled with nitrogen, dihydroxypalladium (18.06 mg, 0.026 mmol) was added and the flask was evacuated and back-filled with nitrogen. (*2R*)-*N*-benzyl-3-(1,3-dioxisoindolin-2-yl)-2-hydroxy-*N*-isopropylpropan-1-aminium chloride (100 mg, 0.257 mmol) was added and the flask was evacuated and back-filled with nitrogen. The flask was evacuated and back-filled with hydrogen. The reaction was stirred under a balloon of hydrogen at 40 °C for 3 h. The reaction mixture was evacuated and back-filled with nitrogen. Celite was added and the reaction mixture was stirred for 10 minutes before being filtered through a pad of Celite, rinsed with methanol and concentrated to yield the product (65.3 mg, 0.258 mmol) in 96% yield. Free base MS (ESI) calcd for C<sub>14</sub>H<sub>19</sub>N<sub>2</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 263.31 Found: 263.23.



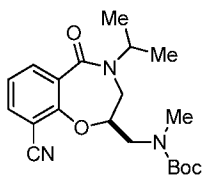
**(*S*)-*N*-(3-(1,3-dioxisoindolin-2-yl)-2-hydroxypropyl)-2,5-difluoro-*N*-isopropyl-3-nitrobenzamide** In an oven-dried 50 mL round-bottomed flask 2,5-difluoro-3-nitrobenzoic acid (348 mg, 1.713 mmol), HOBt (46.3 mg, 0.343 mmol), and (*S*)-3-(1,3-dioxisoindolin-2-

yl)-2-hydroxy-*N*-isopropylpropan-1-aminium chloride (512 mg, 1.714 mmol) were dissolved in DCM (17 mL) under argon. Triethylamine (0.956 mL, 6.86 mmol) was added to the reaction mixture. The reaction mixture was cooled to 0 °C, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (394 mg, 2.057 mmol) was added and the reaction mixture was stirred for 20.5 h gradually warming to room temperature. Additional EDCI (205 mg) was added to the reaction mixture and it was stirred for 7 h. Additional EDCI (200 mg), HOBt (50 mg) and TEA (1 mL) were added and the reaction mixture was stirred for 16 h. The reaction mixture was heated to 32 °C and stirred for 16 h. 1 N HCl (25 mL) was added to the reaction mixture and the resultant layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL x 2). The combined organic layers were washed with 1 N HCl (25 mL), sat. NaHCO<sub>3</sub> (25 mL), water (25 mL) and sat. brine (25 mL) and then dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol to deliver the product which employed directly in the cyclization step (as in the synthesis of compound 2.01). MS (ESI) calcd for C<sub>21</sub>H<sub>20</sub>F<sub>2</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 448.39 Found: 448.30.



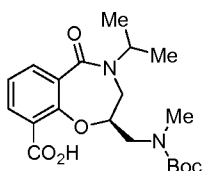
**(*R*)-*N*-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-7-fluoro-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)isonicotinamide (3.01):** Synthesized by the procedure described for Compound 2.01. Yield 26%. MS (ESI) calcd for C<sub>27</sub>H<sub>28</sub>ClFN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 511.18 Found: 511.34.

#### **Preparation of Compound 4.01 (Scheme C)**

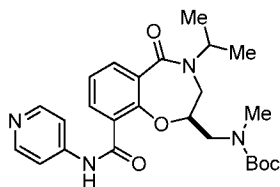


**(*S*)-*tert*-Butyl ((9-cyano-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)(methyl)carbamate:** In a 22 mL vial, fitted with a magnetic stirring bar, (*R*)-*tert*-butyl ((9-cyano-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)carbamate (51 mg, 0.142 mmol) was dissolved in DMF (2.8 mL). Iodomethane (17

μL, 0.284 mmol)) was added and the resulting mixture was cooled to 0 °C. Sodium hydride (60% w/w, 8.51 mg, 0.213 mmol) was then added in one portion. Upon complete conversion of starting material the reaction was quenched with sat. NH<sub>4</sub>Cl (aq) (5 mL) and transferred to a separation funnel with sat. aqueous NH<sub>4</sub>Cl (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The organic layer was separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the volatiles were removed to provide an oil which was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH /NH<sub>3</sub> gradient) to give the title compound (39.2, 0.100 mmol) as a yellow solid (74% yield). MS (ESI) calcd for C<sub>40</sub>H<sub>55</sub>N<sub>6</sub>O<sub>8</sub> [2M+H]<sup>+</sup>: 747.41. Found: 747.61.

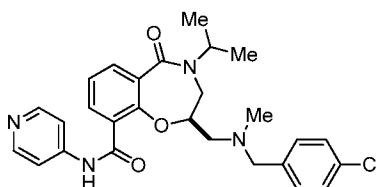


**(S)-2-(((tert-butoxycarbonyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-9-carboxylic acid:** Synthesized following procedure described for (2*S*,3*S*)-2-(((tert-butoxycarbonyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[b][1,5]oxazocine-10-carboxylic acid. Yield: >95%. MS (ESI) calcd for C<sub>40</sub>H<sub>56</sub>N<sub>4</sub>NaO<sub>12</sub> [2M+Na]<sup>+</sup>: 807.38. Found: 807.56.



**(S)-tert-Butyl ((4-isopropyl-5-oxo-9-(pyridin-4-ylcarbamoyl)-2,3,4,5-**

**tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)(methyl)carbamate:** In a 3 mL vial, fitted with a magnetic stirring bar, (S)-2-(((tert-butoxycarbonyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-9-carboxylic acid (13.75 mg, 0.035 mmol) was dissolved in DMF (701 μL). Pyridin-4-amine (6.59 mg, 0.070 mmol), DIPEA (30.6 μL, 0.175 mmol) and HATU (33.3 mg, 0.088 mmol) were added. Upon full conversion of starting material, the volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH /NH<sub>3</sub> gradient) to give the title compound (14.2 mg, 0.030 mmol) as a foam (86% yield). MS (ESI) calcd for C<sub>25</sub>H<sub>33</sub>N<sub>4</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 469.25. Found: 469.44.



**(R)-2-(((4-Chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-N-(pyridin-4-yl)-**

**2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-9-carboxamide (4.01):**

In a 3 mL vial, fitted with a magnetic stirring bar, (*S*)-*tert*-butyl ((4-isopropyl-5-oxo-9-(pyridin-4-ylcarbamoyl)-2,3,4,5-

5 tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)(methyl)carbamate (14.2 mg, 0.030 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (606 μL). Trifluoroacetic acid (46.7 μL, 0.606 mmol) was added and the resulting mixture was stirred at room temperature. Upon complete conversion of the starting material, the volatiles were removed *in vacuo*. The remaining oil was azeotroped with toluene several times, to yield the intermediate ammonium salt as a yellow solid. MS (ESI) calcd for

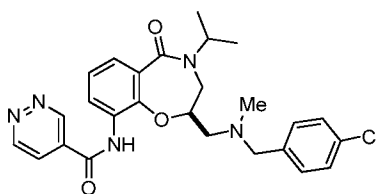
C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 369.19. Found: 369.32. In a 3 mL vial, fitted with magnetic stirring bar, the intermediate ammonium salt was dissolved in THF: DMF (2:1, 606 μL). 4-Chlorobenzaldehyde (8.52 mg, 0.061 mmol) and NaBH(OAc)<sub>3</sub> (32.1 mg, 0.152 mmol) were then added and the resulting mixture was stirred at room temperature for 3 hours. Saturated aqueous Rochelle salt solution (1.5 mL) was added and vigorously stirred at 45 °C overnight.

The mixture was transferred to a separation funnel with sat. aqueous NaHCO<sub>3</sub> (10 mL) and CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The organic layer was separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Et<sub>3</sub>N gradient) to give the title compound (7.9 mg, 0.015

mmol) (50% yield over 2 steps). MS (ESI) calcd for C<sub>27</sub>H<sub>30</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 493.20. Found: 493.39. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.07 (s, 1H), 8.50 (d, 2H), 8.29 (dd, 1H), 7.91 (dd, 1H), 7.69-7.60 (m, 2H), 7.36 (t, 1H), 7.31-7.24 (m, 2H), 7.14 (d, 2H), 5.04 – 4.84 (m, 1H), 4.77 – 4.60 (m, 1H), 3.60 – 3.38 (m, 3H), 3.15 (dd, 1H), 2.80 (dd, 1H), 2.37 (dd, 1H), 2.16 (s, 3H), 1.26 (d, 3H), 1.21 (d, 3H).

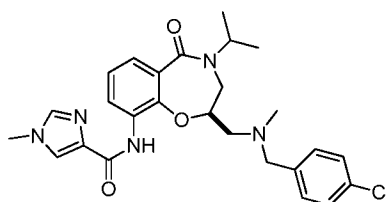
**Compound 4 series**

The following compounds were synthesized as outlined in Scheme B and exemplified by the synthesis of compound 4.01.



(*R*)-*N*-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)pyridazine-4-carboxamide (**4.02**): Synthesized by the procedure described for Compound 4.01. Yield 68%. MS (ESI) calcd for C<sub>26</sub>H<sub>28</sub>ClN<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 494.19 Found: 494.24.

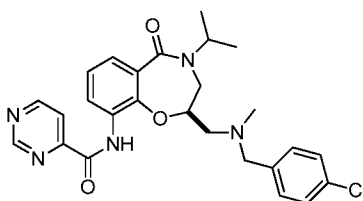
#### Preparation of Compound 5.01 (Scheme C)



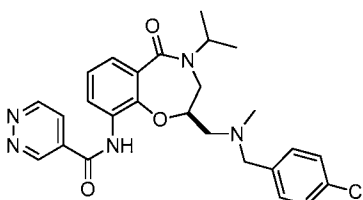
(*R*)-*N*-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)-1-methyl-1H-imidazole-4-carboxamide (**5.01**): To a solution of (*S*)-*tert*-butyl ((9-amino-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)(methyl)carbamate (15 mg, 0.032 mmol) in DCM (0.64 ml) was added TFA (0.05 ml, 0.636 mmol) and solution was stirred at room temperature for 3.5 hours. The crude material was concentrated and washed with DCM/Toluene (x 3). TFA salt obtained as a fine yellow powder (11.82 mg, 0.032 mmol) which was dissolved in THF (0.42 ml) and DMF (0.21 ml), 4-chlorobenzaldehyde (8.95 mg, 0.064 mmol) was added and after 1 hour, sodium triacetoxyborohydride (33.7 mg, 0.159 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated directly onto silica gel purified by silica gel column chromatography eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH the product (12 mg, 0.024 mmol) in 76% yield. MS (ESI) calcd for C<sub>26</sub>H<sub>31</sub>ClN<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 496.20. Found: 496.33.

#### Compound 5 series

The following compounds were synthesized as outlined in Scheme E and exemplified by the synthesis of compound 5.01.

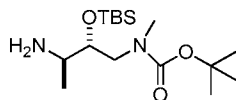


(*R*)-*N*-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)pyrimidine-4-carboxamide (**5.02**): Synthesized by the procedure described for Compound 5.01. Yield 64%. MS (ESI) calcd for C<sub>26</sub>H<sub>28</sub>ClN<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 494.19 Found: 494.36.

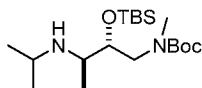


(*R*)-*N*-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-9-yl)pyridazine-4-carboxamide (**5.03**): Synthesized by the procedure described for Compound 5.01. Yield 49%. MS (ESI) calcd for C<sub>26</sub>H<sub>28</sub>ClN<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 494.19 Found: 494.35.

#### Preparation of Compound 6.01 (Scheme D)



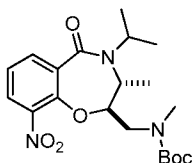
**tert-butyl ((2R,3R)-3-amino-2-((tert-butyldimethylsilyl)oxy)butyl)(methyl)carbamate:** In a 1 dram vial (2*R*,3*S*)-4-(tert-butoxycarbonyl(methyl)amino)-3-(tert-butyldimethylsilyloxy)-2-methylbutanoic acid (1.014 g, 2.80 mmol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.977 mL, 5.61 mmol) were dissolved in acetonitrile (28 mL) under argon. Diphenyl phosphorazidate (0.907 mL, 4.21 mmol) was added to the reaction mixture in one portion, reaction was heated to 60 °C and stirred for 4 h. The reaction mixture was added dropwise to 1M NaOH (56 mL) and stirred for 2.5 h. The reaction mixture was extracted with EtOAc (50 mL x 3), washed with sat. NaHCO<sub>3</sub> (40 mL), sat. brine (40 mL), 1 M HCl (40 mL), water (40 mL), sat NaHCO<sub>3</sub> (60 mL), sat. brine (50 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol to deliver the product (367 mg, 1.10 mmol) in 39% yield. MS (ESI) calcd for C<sub>16</sub>H<sub>36</sub>ClN<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 333.25 Found: 333.39.



**tert-butyl ((2R,3R)-2-((tert-butyldimethylsilyloxy)-3-**

**(isopropylamino)butyl(methyl)carbamate:** In an oven-dried 2 mL vial tert-butyl (2R,3R)-

- 5 3-amino-2-(tert-butyldimethylsilyloxy)butyl(methyl)carbamate (357 mg, 1.074 mmol) was dissolved in dichloromethane (10.7 mL) under argon and cooled to 0 °C. Sodium triacetoxyborohydride (1.59 g, 7.51 mmol) and propan-2-one (0.39 mL, 5.37 mmol) were added to the reaction mixture. The reaction mixture was gradually warmed to room temperature and stirred for 23 h. Added 1 M NaOH (10 mL) and stirred for 10 minutes. Sat.
- 10 brine (~2 mL) was added and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL x 4). The combined organic layers were washed with sat. brine (20 mL), dried (MgSO<sub>4</sub>), filtered, concentrated and dried under high vacuum to deliver the crude product (354 mg, 0.45 mmol) in 88% yield. MS (ESI) calcd for C<sub>19</sub>H<sub>42</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 375.23 Found: 375.45.

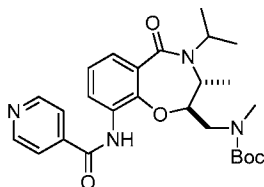


**tert-butyl (((2R,3R)-4-isopropyl-3-methyl-9-nitro-5-oxo-2,3,4,5-**

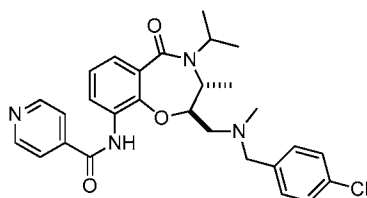
**tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl(methyl)carbamate:** A solution of crude tert-butyl (2R,3R)-2-(tert-butyldimethylsilyloxy)-3-(isopropylamino)butyl(methyl)carbamate

- (354 mg, 0.945 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added to a solution of 2-fluoro-3-nitrobenzoyl chloride (202 mg, 0.993 mmol) and triethylamine (395 μL, 2.84 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (9 mL) under argon at 0 °C. The reaction was stirred for 20 min, the ice-bath was removed and the reaction mixture was stirred for an additional 5 h. Additional 2-fluoro-3-nitrobenzoyl chloride (15 mg) was added and the reaction mixture stirred for 18.5 h. Sat. Na<sub>2</sub>CO<sub>3</sub> (10 mL) was added and the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL x 2).
- 25 The combined organic layers were washed with water (7 mL) and sat. brine (7 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was partially purified by column chromatography on silica gel eluting with ethyl acetate/hexanes. The resulting crude product was dissolved in dry DMF (24 mL) under argon. Cesium carbonate (606 mg, 1.86 mmol) and cesium fluoride (150 mg, 0.99 mmol) were added and the reaction mixture was heated to 75
- 30 °C for 3 h. The heat was turned off and the reaction was allowed to cool over 2 h. The

reaction mixture was concentrated and the residue was partitioned between EtOAc (30 mL) and sat.  $\text{NH}_4\text{Cl}$  (50 mL). The aqueous layer was extracted with EtOAc (15 mL x 3) and the combined organic layers were washed with water (25 mL x 2 mL), sat. brine (40 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver the product (161 mg, 0.394 mmol) in 42% yield. MS (ESI) calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_6$   $[\text{M}+\text{H}-\text{O}^t\text{Bu}]^+$  : 352.35 Found: 352.32.



- 10 **tert-butyl (((2R,3R)-9-(isonicotinamido)-4-isopropyl-3-methyl-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl)(methyl)carbamate:** In a 15 mL round-bottomed flask *tert*-butyl ((2*R*,3*R*)-4-isopropyl-3-methyl-9-nitro-5-oxo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-2-yl)methyl(methyl)carbamate (160.6 mg, 0.394 mmol) was dissolved in EtOAc (4 mL) under nitrogen. The flask was evacuated and back-filled with nitrogen (x 3), palladium on carbon (10%; 84 mg, 0.039 mmol) was added and the flask was evacuated and back-filled with nitrogen (x 2). The flask was evacuated and back-filled with hydrogen (x 3). The reaction was stirred under a balloon of hydrogen at 40 °C for 13 h. The reaction mixture was evacuated and back-filled with nitrogen (x 4). Celite was added and the reaction mixture was stirred for 10 minutes before being filtered through a pad of Celite, rinsed with methanol and concentrated. This process was repeated thrice and the resultant crude product was dissolved in  $\text{CH}_2\text{Cl}_2$  (4 mL) under argon and cooled on ice. 2,6-lutidine (0.275 mL, 2.364 mmol) was added followed by 4-(chlorocarbonyl)pyridinium chloride (140 mg, 0.788 mmol). The reaction mixture was stirred for 5 minutes, the ice bath was removed and the reaction mixture was stirred at room temperature for 2.5 h. The reaction was diluted with  $\text{CH}_2\text{Cl}_2$  (7 mL) and 1 M HCl (10 mL) and extracted with  $\text{CH}_2\text{Cl}_2$  (5 mL x 3). The combined organic layers were washed with sat.  $\text{Na}_2\text{CO}_3$  (7 mL), water (7 mL) and sat. brine (10 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with 7 M  $\text{NH}_3$  in methanol/dichloromethane to deliver the product (141 mg, 0.29 mmol) in 74% yield. MS (ESI) calcd for  $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_6$   $[\text{M}+\text{H}]^+$ : 483.25 Found: 483.40.

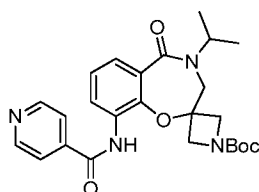


***N*-((2*R*,3*R*)-2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-3-methyl-5-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepin-9-yl)isonicotinamide (6.01):**

A solution of *tert*-butyl ((2*R*,3*R*)-9-(isonicotinamido)-4-isopropyl-3-methyl-5-oxo-2,3,4,5-

- 5 tetrahydrobenzo[*f*][1,4]oxazepin-2-yl)methyl(methyl)carbamate (140.8 mg, 0.292 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was cooled to 0 °C under argon. Trifluoroacetic acid (250 µL) was added dropwise to the reaction mixture, stirred for 10 min, the ice bath was removed and the reaction mixture was stirred for 3 h. The reaction mixture was concentrated and dried on the high vac. A solution of 4-chlorobenzaldehyde (80 mg, 0.569 mmol) in dry DMF (1 mL) was
- 10 added to a portion the resultant crude salt (54 mg, 0.109 mmol) under argon and the solution was stirred for 8 minutes. Sodium triacetoxborohydride (189 mg, 0.892 mmol) was added and the reaction was stirred for 2 h. The reaction was quenched with 1 M NaOH (~10 drops), stirred for 5 minutes and concentrated. A mixture of 1 M NaOH (1 mL) and sat. brine (3 mL) was added and the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL x 3). The combined
- 15 organic layers were washed with sat. brine (1 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with 7 M NH<sub>3</sub> in methanol/dichloromethane to deliver the product (51 mg, 0.101 mmol) in 93% yield. MS (ESI) calcd for C<sub>28</sub>H<sub>31</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 507.21 Found: 507.38. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.72 (s, 0.5H), 8.80 – 8.57 (m, 3H), 7.72 (t, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 7.7 Hz,
- 20 1H), 7.32 – 7.15 (m, 3H), 7.08 (d, *J* = 8.1 Hz, 2H), 4.52 (s, 0.5H), 4.32 (s, 1H), 3.65 (dd, *J* = 13.2, 6.6 Hz, 1H), 3.53 (d, *J* = 13.3 Hz, 1H), 3.34 (d, *J* = 12.4 Hz, 1H), 2.67 (s, 1H), 2.30 (d, *J* = 12.1 Hz, 1H), 2.20 (s, 3H), 1.36 (d, *J* = 6.8 Hz, 6H), 1.14 (d, *J* = 7.1 Hz, 3H).

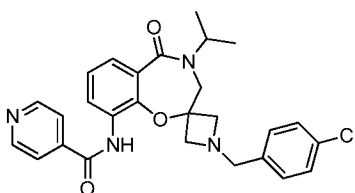
**Preparation of Compound 7.01 (Scheme E)**



***tert*-butyl 9'-(isonicotinamido)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-**

**3,2'-benzo[*f*][1,4]oxazepine]-1-carboxylate:** Acetic acid (0.28 mL, 4.94 mmol) and sodium

triacetoxyborohydride (2.01 g, 9.89 mmol) were added to a solution of *tert*-butyl 3-(aminomethyl)-3-hydroxyazetidine-1-carboxylate (1.00 g, 4.94 mmol) in acetone (3.63 mL, 49.40 mmol) and the reaction mixture was stirred until the starting material was consumed. The reaction was quenched through the addition of sodium bicarbonate, diluted with ethyl acetate, washed with sodium bicarbonate, brine, dried, filtered and concentrated. The crude product, 1H-benzo[d][1,2,3]triazol-1-ol (0.133 g, 0.982 mmol), triethylamine (2.054 mL, 14.73 mmol) and 2-fluoro-3-nitrobenzoic acid (0.91 g, 4.91 mmol) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) under nitrogen and the reaction mixture was cooled to 0 °C. EDCI (1.13 g, 5.89 mmol) was added, the ice-bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 1 M HCl. The organic layer was washed with 1 N HCl, 50% sat. NaHCO<sub>3</sub> (x2), and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The mixture was re-dissolved in dry DMF (100 mL) and cesium carbonate was added (3.20 g, 9.82 mmol) and the reaction was stirred at room temperature overnight. The reaction mixture was concentrated, taken up in ethyl acetate, washed with 1N HCl, sat. NaHCO<sub>3</sub>, and brine, dried, filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver the product (610 mg, 1.558 mmol) in 32% yield. Palladium on carbon (10%; 166 mg, 0.156 mmol) was added to a solution of *tert*-butyl 4'-isopropyl-9'-nitro-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepine]-1-carboxylate (610 mg, 1.558 mmol) in ethanol (20 mL). The reaction mixture was charged with hydrogen, stirred at 40 °C for 1.5 h, cooled, filtered through Celite and concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) to which 2,6 lutidine (1.01 mL, 9.35 mmol) and isonicotinoyl chloride hydrochloride (555 mg, 3.12 mmol). The reaction mixture was stirred overnight, concentrated and purified by column chromatography on silica gel to deliver the product (557 mg, 1.195 mmol) in 77% yield. MS (ESI) calcd for C<sub>19</sub>H<sub>25</sub>ClN<sub>3</sub>O<sub>6</sub> [M+H-O<sup>t</sup>Bu]<sup>+</sup>: 411.16 Found: 411.61.



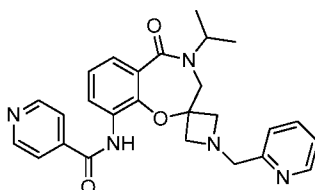
***N*-(1-(4-chlorobenzyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-**

**benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.01):** Sodium triacetoxyborohydride (114 mg, 0.536 mmol) was added to a solution of *tert*-butyl 9'-(isonicotinamido)-4'-isopropyl-5'-

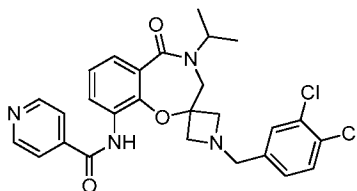
oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepine]-1-carboxylate (50 mg, 0.107 mmol) and 4-chlorobenzaldehyde (45.2 mg, 0.322 mmol) in 2% AcOH in DMF (1 mL). The reaction mixture was stirred at room temperature overnight, quenched with K<sub>2</sub>CO<sub>3</sub>, partially concentrated and partitioned between EtOAc and water. The reaction mixture was extracted with EtOAc, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated. The reaction mixture was stirred overnight, concentrated and purified by column chromatography on silica gel to deliver the product (30 mg, 1.195 mmol) in 56% yield. MS (ESI) calcd for C<sub>27</sub>H<sub>27</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 491.18 Found: 491.73. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.22 (s, 1H), 8.80 (d, *J* = 5.9 Hz, 2H), 8.76 – 8.67 (m, 1H), 7.96 (d, *J* = 6.0 Hz, 2H), 7.55 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 – 7.25 (m, 3H), 7.20 (d, *J* = 8.4 Hz, 2H), 4.97 (dt, *J* = 13.5, 6.7 Hz, 1H), 3.69 (s, 2H), 3.58 (d, *J* = 9.7 Hz, 2H), 3.43 (s, 2H), 3.12 (d, *J* = 9.5 Hz, 2H), 1.23 (d, *J* = 6.8 Hz, 6H).

### **Compound 7 series**

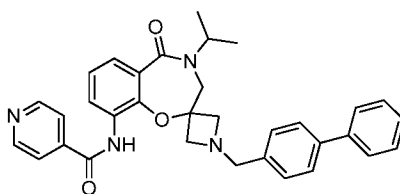
The following compounds were synthesized as outlined in Scheme E and exemplified by the synthesis of compound 7.01.



***N*-(4'-isopropyl-5'-oxo-1-(pyridin-2-ylmethyl)-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.02):** Synthesized by the procedure described for compound 7.01. Yield 64%. MS (ESI) calcd for C<sub>26</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 458.21 Found: 458.70.

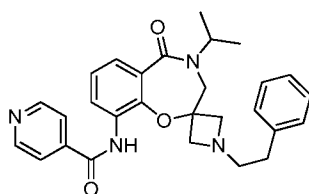


***N*-(1-(3,4-dichlorobenzyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.03):** Synthesized by the procedure described for compound 7.01. Yield 66%. MS (ESI) calcd for C<sub>27</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 525.14 Found: 525.61.



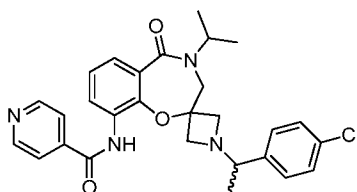
***N*-(1-([1,1'-biphenyl]-4-ylmethyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.04):** Synthesized by the procedure described for compound 7.01. Yield 80%. MS (ESI) calcd for  $C_{33}H_{32}N_4O_3$   $[M+H]^+$ : 533.25

5 Found: 533.73.



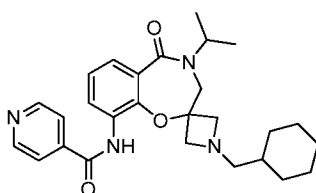
***N*-(4'-isopropyl-5'-oxo-1-phenethyl-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.05):** Synthesized by the procedure

10 described for compound 7.01. Yield 74%. MS (ESI) calcd for  $C_{28}H_{30}N_4O_3$   $[M+H]^+$ : 471.23  
Found: 471.41.



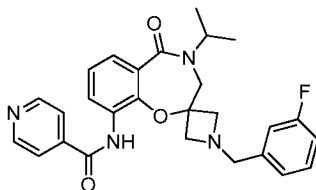
***N*-(1-(1-(4-chlorophenyl)ethyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-**

15 **3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.06):** Synthesized by the procedure described for compound 7.01. Yield 87%. MS (ESI) calcd for  $C_{28}H_{29}ClN_4O_3$   $[M+H]^+$ : 505.19 Found: 505.36.

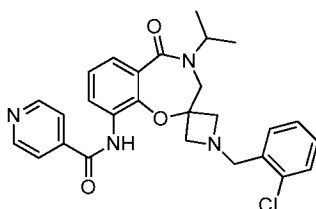


20 ***N*-(1-(cyclohexylmethyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.07):** Synthesized by the procedure

described for compound 7.01. Yield 91%. MS (ESI) calcd for  $C_{27}H_{34}N_4O_3$   $[M+H]^+$ : 463.26  
Found: 463.44.



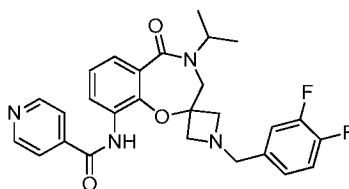
- 5 ***N*-(1-(3-fluorobenzyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.08)**: Synthesized by the procedure described for compound 7.01. Yield 12%. MS (ESI) calcd for  $C_{27}H_{27}FN_4O_3$   $[M+H]^+$ : 475.21  
Found: 475.67.



10

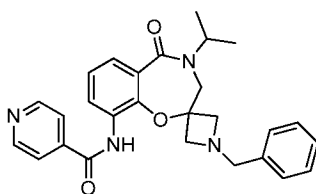
- N*-(1-(2-chlorobenzyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.09)**: Synthesized by the procedure described for compound 7.01. Yield 94%. MS (ESI) calcd for  $C_{27}H_{27}ClN_4O_3$   $[M+H]^+$ : 491.18 Found: 491.63.

15

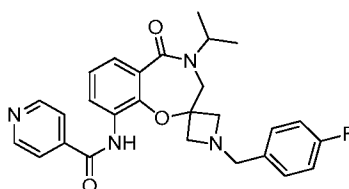


- N*-(1-(3,4-difluorobenzyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.10)**: Synthesized by the procedure described for compound 7.01. Yield 70%. MS (ESI) calcd for  $C_{27}H_{26}F_2N_4O_3$   $[M+H]^+$ : 493.20 Found: 493.67.

20

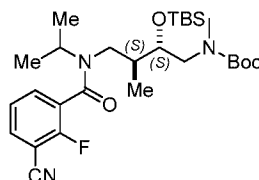


***N*-(1-benzyl-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.11):** Synthesized by the procedure described for compound 7.01. Yield 90%. MS (ESI) calcd for  $C_{27}H_{28}FN_4O_3$   $[M+H]^+$ : 457.21  
 5 Found: 457.39.

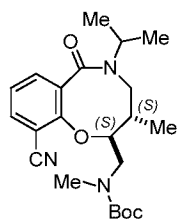


***N*-(1-(4-fluorobenzyl)-4'-isopropyl-5'-oxo-4',5'-dihydro-3'H-spiro[azetidine-3,2'-benzo[f][1,4]oxazepin]-9'-yl)isonicotinamide (7.12):** Synthesized by the procedure described for compound 7.01. Yield 61%. MS (ESI) calcd for  $C_{27}H_{27}FN_4O_3$   $[M+H]^+$ : 475.21  
 10 Found: 475.69.

#### **Preparation of Compound 8.01 (Scheme F)**

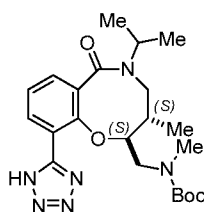


***tert*-butyl ((2*S*,3*S*)-2-((*tert*-butyldimethylsilyloxy)-4-(3-cyano-2-fluoro-*N*-isopropylbenzamido)-3-methylbutyl)(methyl)carbamate:** In a 22 mL vial, fitted with a magnetic stirring bar, *tert*-butyl (2*S*,3*S*)-2-((*tert*-butyldimethylsilyloxy)-4-(isopropylamino)-3-methylbutyl(methyl)carbamate (1g, 2.57 mmol) was dissolved in  $CH_2Cl_2$  (3.2 mL). 3-Cyano-2-fluorobenzoic acid (0.467 g, 2.83 mmol), DIPEA (1.348 mL, 7.72 mmol) and PyBOP (1.473 g, 2.83 mmol) were added. Upon full conversion of starting material, the volatiles were removed and the crude remaining oil was purified by silica gel column chromatography (hexanes/EtOAc gradient) to give the title compound (1.157 g, 2.052 mmol) (80% yield).  
 15  
 20 MS (ESI) calcd for  $C_{56}H_{92}F_2N_6NaO_8Si_2$   $[2M+Na]^+$ : 1093.64. Found: 1093.58.



**tert-butyl (((2S,3S)-10-cyano-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-**

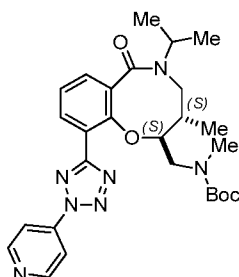
**benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** A flamed-dried 100 mL RBF, fitted with a magnetic stirring bar, was charged with cesium fluoride (3.17 g, 20.90 mmol). A solution of tert-butyl (2S,3S)-2-(tert-butyldimethylsilyloxy)-4-(3-cyano-2-fluoro-N-isopropylbenzamido)-3-methylbutyl(methyl)carbamate (1.1196 g, 2.090 mmol) in dry DMF (41.8 ml) was then added. The resulting mixture was stirred at 85 °C for 2 days, by which time all volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (hexanes/EtOAc gradient) to give the title compound (687 mg, 1.627 mmol) (78% yield). MS (ESI) calcd for C<sub>22</sub>H<sub>31</sub>N<sub>3</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 424.22. Found: 424.31.



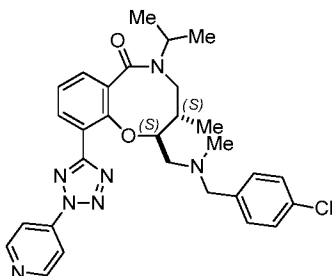
**tert-Butyl (((2S,3S)-5-isopropyl-3-methyl-6-oxo-10-(1H-tetrazol-5-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** Behind a blast shield, a 22 mL

vial, fitted with magnetic stirring bar, was charged with tert-butyl (((2S,3S)-10-cyano-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate (182 mg, 0.453 mmol), sodium azide (442 mg, 6.80 mmol) and ammonium chloride (364 mg, 6.80 mmol). DMF (4.1 mL) was added and the vial was capped. The reaction mixture was heated to 110 °C and stirred for 3 days, whereupon it was transferred to a separation funnel with water (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (80 mL). The organic layer was separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (8 x 40 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the volatiles were removed to give the title compound (200 mg, 0.427 mmol) as a white solid (94% yield), which was used in the next step without further purification. MS (ESI) calcd for C<sub>22</sub>H<sub>33</sub>N<sub>6</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 445.26.

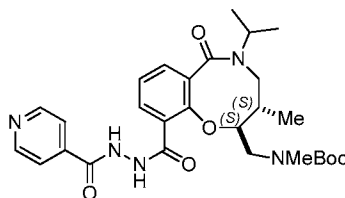
Found: 445.21.



**tert-Butyl (((2S,3S)-5-isopropyl-3-methyl-6-oxo-10-(2-(pyridin-4-yl)-2H-tetrazol-5-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** In a 3 mL vial, fitted with magnetic stirring bar, *tert*-butyl (((2S,3S)-5-isopropyl-3-methyl-6-oxo-10-(1H-tetrazol-5-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate (32.8 mg, 0.074 mmol) and 4-chloropyridine hydrochloride (55.3 mg, 0.369 mmol) were dissolved in DMF (369  $\mu$ L). Triethylamine (61.7  $\mu$ L, 0.443 mmol) was added and the reaction vessel was capped. The reaction mixture was heated to 110  $^{\circ}$ C and stirred overnight. The volatiles were then removed, and the remaining oil was purified by silica gel column chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  gradient) to give the title compound (10 mg, 0.020 mmol) (26% yield), which was used in the next step without further characterization. MS (ESI) calcd for  $\text{C}_{54}\text{H}_{71}\text{N}_{14}\text{O}_8$   $[\text{2M}+\text{H}]^+$ : 1043.56. Found: 1043.67.

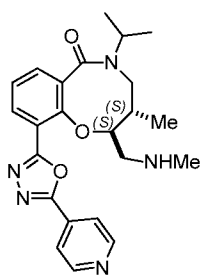


**(2S,3S)-2-(((4-Chlorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-10-(2-(pyridin-4-yl)-2H-tetrazol-5-yl)-4,5-dihydro-2H-benzo[b][1,5]oxazocin-6(3H)-one (8.01):** Synthesized following the procedure described for (2S,3S)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-10-(1-(pyridin-4-yl)-1H-1,2,3-triazol-4-yl)-4,5-dihydro-2H-benzo[b][1,5]oxazocin-6(3H)-one. Yield: 55% (2 steps). MS (ESI) calcd for  $\text{C}_{29}\text{H}_{33}\text{ClN}_7\text{O}_2$   $[\text{M}+\text{H}]^+$ : 546.24. Found: 546.70.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.89 (d, 2H), 8.13 (d, 2H), 7.92 (d, 1H), 7.67 (d, 1H), 7.34 (t, 1H), 7.23 (d, 2H), 7.16 (d, 2H), 4.80 – 4.60 (m, 1H), 3.63-3.46 (m, 2H), 3.34 (dd, 1H), 3.21 (d, 1H), 3.02 (d, 1H), 2.65-2.43 (m, 3H), 2.16 (s, 3H), 1.42-1.20 (m, 6H), 0.66 (d, 3H).

**Preparation of Compound 9.01 (Scheme G)**

***tert*-butyl (((2*S*,3*S*)-10-(2-isonicotinoylhydrazinecarbonyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** A 10 mL

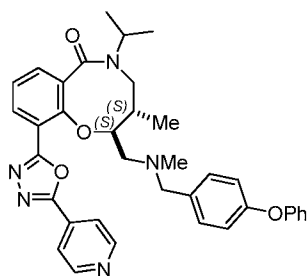
round-bottomed flask was equipped with a stir bar and was charged with a solution of (2*S*,3*S*)-2-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocine-10-carboxylic acid (55 mg, 0.13 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.70 mL). At 0 °C, three drops of DMF were added, followed by oxalyl chloride (22.9 μL, 0.26 mmol). The mixture was stirred at 0 °C for two hours and concentrated, yielding a crude acyl chloride that was azeotroped three times with toluene and placed under high vacuum at room temperature for one hour. The intermediate thus obtained was diluted in dry CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) and transferred dropwise *via* syringe to a solution of isoniazid (26.9 mg, 0.20 mmol) and 2,6-lutidine (45.7 μL, 0.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.6 mL), at 0 °C. The mixture was allowed to reach room temperature progressively and was stirred overnight. The solution was diluted in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), transferred to a separatory funnel and washed with sat. NH<sub>4</sub>Cl solution (5 mL). The phases were separated and the aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The crude was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Methanol/Ammonia gradient) and afforded the title compound (61 mg, 0.11 mmol) with 86% yield over two steps. MS (ESI) calcd for C<sub>28</sub>H<sub>38</sub>N<sub>5</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 540.28. Found: 540.25.



**(2*S*,3*S*)-5-isopropyl-3-methyl-2-((methylamino)methyl)-10-(5-(pyridin-4-yl)-1,3,4-**

**oxadiazol-2-yl)-4,5-dihydro-2*H*-benzo[*b*][1,5]oxazocin-6(3*H*)-one:** A solution of triphenylphosphine oxide (93 mg, 0.33 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was cooled to 0 °C and

triflic anhydride (28  $\mu$ L, 0.17 mmol) was slowly added *via* syringe to the mixture. After 5 minutes at 0 °C, the temperature was adjusted to room temperature, upon which a white precipitate was formed. A solution of *tert*-butyl (((2*S*,3*S*)-10-(2-  
 5 benzo[*b*][1,5]oxazocin-2-yl)methyl)(methyl)carbamate (60 mg, 0.11 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was transferred to the reaction vessel and the mixture was stirred at room temperature overnight. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> and quenched with sat. NaHCO<sub>3</sub> aqueous solution. The aqueous layer was separated and extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined  
 organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated to afford a crude material  
 10 which was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Methanol/Ammonia gradient). The title compound was obtained as a colorless gum (37 mg, 0.09 mmol) with 79% yield. MS (ESI) calcd for C<sub>23</sub>H<sub>28</sub>N<sub>5</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 422.22. Found: 422.36.

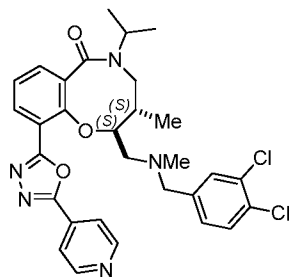


15 **(2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-10-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-4,5-dihydro-2*H*-benzo[*b*][1,5]oxazocin-6(3*H*)-one (9.01)**: To a solution of (2*S*,3*S*)-5-isopropyl-3-methyl-2-((methylamino)methyl)-10-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-4,5-dihydro-2*H*-benzo[*b*][1,5]oxazocin-6(3*H*)-one (18  
 mg, 0.04 mmol) in THF (1 mL) was added 4-phenoxybenzaldehyde (11  $\mu$ L, 0.06 mmol). The  
 20 mixture was heated to 60 °C for two hours then cooled down to room temperature. Sodium triacetoxyborohydride (27.2 mg, 0.13 mmol) was added in one portion as a solid and the mixture was stirred overnight. The reaction was quenched with sat. aqueous NH<sub>4</sub>Cl solution and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic phases were dried over  
 Na<sub>2</sub>SO<sub>4</sub>, filtered, concentrated and purified by silica gel chromatography  
 25 (CH<sub>2</sub>Cl<sub>2</sub>/Methanol/Ammonia gradient). The title compound (12 mg, 0.02 mmol) was isolated with 46% yield. MS (ESI) calcd for C<sub>36</sub>H<sub>38</sub>N<sub>5</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 604.29. Found: 604.45. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  8.86 (d, *J* = 4.7 Hz, 2H), 7.99 (d, *J* = 4.6 Hz, 2H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 2H), 7.08 (ap t, *J* = 7.3 Hz, 1H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 4.79 – 4.57 (m, 1H), 3.64 (br

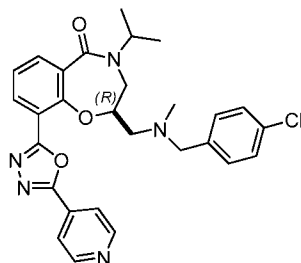
d,  $J = 7.9$  Hz, 1H), 3.56 (d,  $J = 13.0$  Hz, 1H), 3.29 (dd,  $J = 15.8, 10.3$  Hz, 1H), 3.19 (d,  $J = 13.3$  Hz, 1H), 3.03 (br d,  $J = 16.1$  Hz, 1H), 2.72 (dd,  $J = 13.5, 3.1$  Hz, 1H), 2.64 – 2.50 (m, 2H), 2.22 (s, 3H), 1.36 (d,  $J = 6.7$  Hz, 3H), 1.30 (d,  $J = 6.7$  Hz, 3H), 0.64 (d,  $J = 6.9$  Hz, 3H).

## 5 Compound 9 series

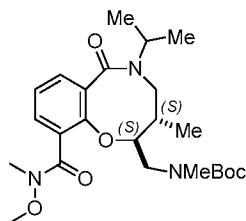
The following compounds were synthesized as outlined in Scheme G and exemplified by the synthesis of compound 9.01.



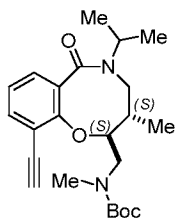
- 10 **(2*S*,3*S*)-2-(((3,4-dichlorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-10-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-4,5-dihydro-2*H*-benzo[*b*][1,5]oxazocin-6(3*H*)-one (9.02)**: Synthesized by the procedure described for compound 9.01. Yield 68%. MS (ESI) calcd for  $C_{30}H_{32}Cl_2N_5O_3$   $[M+H]^+$ : 580.19. Found: 580.33.



- 15 **(*R*)-2-(((4-chlorobenzyl)(methyl)amino)methyl)-4-isopropyl-9-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-one (9.03)**: Synthesized by the procedure described for compound 9.01 starting from (*S*)-2-(((*tert*-Butoxycarbonyl)(methyl)amino)methyl)-4-isopropyl-5-oxo-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-9-carboxylic acid. Yield 40%. MS (ESI) calcd for  
20  $C_{28}H_{29}ClN_5O_3$   $[M+H]^+$ : 518.20. Found: 518.23.

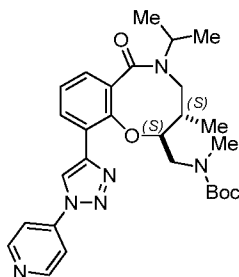
**Preparation of Compound 10.01 (Scheme G)**

**tert-butyl (((2S,3S)-5-isopropyl-10-(methoxy(methyl)carbamoyl)-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** In a 22 mL vial, fitted with magnetic stirring bar, (2S,3S)-2-(((tert-butoxycarbonyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocine-10-carboxylic acid (300 mg, 0.713 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3.6 mL). The solution was cooled to 0 °C, whereupon oxalyl dichloride (125 μL, 1.427 mmol) and 2 drops of DMF were added. The reaction mixture was stirred for 2 hours at 0 °C. Then, all volatiles were removed and the remaining oil was azeotroped with toluene several times. The crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3.6 mL). DIPEA (623 μL, 3.57 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (209 mg, 2.140 mmol) were then added. The reaction mixture was stirred at room temperature overnight and was transferred to a separation funnel with EtOAc (30 mL), and water (20 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient) to give the title compound (300 mg, 0.648 mmol) (91% yield). MS (ESI) calcd for C<sub>24</sub>H<sub>38</sub>N<sub>3</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 464.28. Found: 464.23.



**tert-butyl (((2S,3S)-10-ethynyl-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** In a 22 mL vial, fitted with a magnetic stirring bar, *tert*-butyl (((2S,3S)-5-isopropyl-10-(methoxy(methyl)carbamoyl)-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate (150mg, 0.324 mmol) was dissolved in THF (1.6 mL). The solution was cooled to 0 °C. A solution of LiAlH<sub>4</sub> (1M in THF, 404 μL, 0.404 mmol) was then added dropwise. After 30

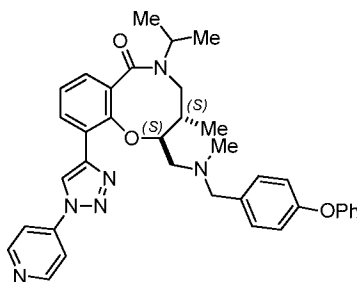
min at 0 °C, the reaction was quenched by addition of sat. aqueous citric acid (1 mL). The reaction mixture was transferred to a separation funnel with EtOAc (25 mL) and water (10 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was quickly purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient) to give the intermediate aldehyde. MS (ESI) calcd for C<sub>22</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 405.24. Found: 405.36. In a 22 mL vial, fitted with a magnetic stirring bar, the intermediate aldehyde was dissolved in methanol (4.6 ml). Potassium carbonate (112 mg, 0.810 mmol) and dimethyl 1-diazo-2-oxopropylphosphonate (72.9 μL, 0.486 mmol) were added, and the reaction mixture was stirred at room temperature. Upon full conversion of the starting material, the reaction mixture was diluted with diethylether (50 mL) and transferred to a separation funnel. The organic layer was washed with sat. aqueous NaHCO<sub>3</sub> (10mL), dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed *in vacuo*. The crude remaining oil was purified by silica gel column chromatography (hexanes/EtOAc gradient) to give the title compound (86 mg, 0.215 mmol) (66% yield over two steps). MS (ESI) calcd for C<sub>23</sub>H<sub>32</sub>N<sub>2</sub>NaO<sub>4</sub> [M+Na]<sup>+</sup>: 423.23. Found: 423.40.



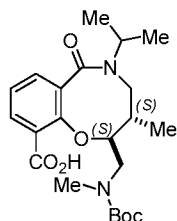
***tert*-Butyl (((2*S*,3*S*)-5-isopropyl-3-methyl-6-oxo-10-(1-(pyridin-4-yl)-1*H*-1,2,3-triazol-4-**

**yl)-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** In a 22 mL vial, fitted with a magnetic stirring bar, *tert*-butyl (((2*S*,3*S*)-10-ethynyl-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocin-2-yl)methyl)(methyl)carbamate (49.6 mg, 0.124 mmol) was dissolved in acetonitrile (1.2 mL). Copper(I) iodide (4.72 mg, 0.025 mmol), 4-azidopyridine (29.7 mg, 0.248 mmol), and DIPEA (43.3 μL, 0.248 mmol) were added. The reaction was stirred at room temperature, and upon complete conversion of starting material the mixture was transferred to a separation funnel with EtOAc (80 mL). The organic layer was washed with sat. aqueous NH<sub>4</sub>Cl (25 mL), dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was purified by silica gel column

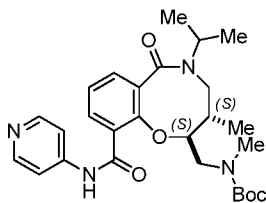
chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient) to give the title compound (48 mg, 0.091 mmol) (74% yield). MS (ESI) calcd for C<sub>28</sub>H<sub>37</sub>N<sub>6</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 521.63. Found: 521.27.



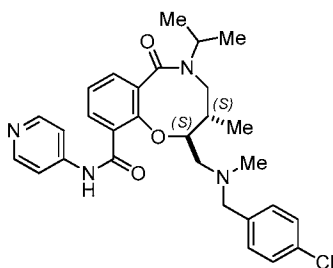
- 5 **(2S,3S)-5-Isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-10-(1-(pyridin-4-yl)-1H-1,2,3-triazol-4-yl)-4,5-dihydro-2H-benzo[b][1,5]oxazocin-6(3H)-one (10.01):** In a 3 mL vial, fitted with a magnetic stirring bar, *tert*-butyl ((2S,3S)-5-isopropyl-3-methyl-6-oxo-10-(1-(pyridin-4-yl)-1H-1,2,3-triazol-4-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl(methyl)carbamate (23.8 mg, 0.0455 mmol) was dissolved
- 10 in CH<sub>2</sub>Cl<sub>2</sub> (457  $\mu$ L). Trifluoroacetic acid (106  $\mu$ L, 1.371 mmol) was added and the resulting mixture was stirred at room temperature. Upon complete conversion of the starting material, the volatiles were removed. The remaining oil was azeotroped with toluene several times, to yield the intermediate ammonium salt. MS (ESI) calcd for C<sub>23</sub>H<sub>29</sub>N<sub>6</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 421.24. Found: 421.14. In a 3 mL vial, fitted with a magnetic stirring bar, the intermediate
- 15 ammonium salt was dissolved in THF (962  $\mu$ L). 4-Phenoxybenzaldehyde (18.18  $\mu$ L, 0.106 mmol) was added and the resulting mixture was stirred at 60 °C for 2 hours. The reaction mixture was then allowed to cool to room temperature and added NaBH(OAc)<sub>3</sub> (30.6 mg, 0.144 mmol) in one portion. The reaction mixture was stirred at room temperature overnight, and volatiles were removed. The remaining oil was taken up in EtOAc (15 mL), transferred
- 20 to a separation funnel and washed with sat. aqueous NaHCO<sub>3</sub> (3 mL). The organic layer was separated, and the aqueous phase was further extracted with EtOAc (2 x 15 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> gradient) to give the title compound (11 mg, 0.017 mmol) (35% yield over 2 steps). MS (ESI)
- 25 calcd for C<sub>36</sub>H<sub>39</sub>N<sub>6</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 603.31. Found: 603.84. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, rotamers)  $\delta$  8.89-8.72 (m, 2H), 8.69-8.56 (m, 1H), 7.97-6.84 (m, 14H), 4.84-4.56 (m, 1H), 3.61-2.88 (m, 5H), 2.69-2.54 (m, 1H), 2.39 – 1.75 (m, 5H), 1.43-1.12 (m, 6H), 0.72-0.51 (m, 3H).

**Preparation of Compound 11.01 (Scheme H)****(2S,3S)-2-(((tert-butoxycarbonyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocine-10-carboxylic acid:**

A 22 mL vial, fitted with a magnetic stirring bar, was charged with finely ground potassium hydroxide (2.26 g, 40.2 mmol) and water (2 mL). A solution of *tert*-butyl ((2*S*,3*S*)-10-cyano-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl(methyl)carbamate (323 mg, 0.804 mmol) in ethanol (6 mL) was then added. The reaction vessel was capped and stirred at 75 °C. After 4 days, the reaction mixture was transferred to a 500 mL round-bottomed flask, diluted with water (100 mL), cooled to 0 °C, and then slowly acidified with 1M HCl to pH 3-4. The mixture was transferred to a separation funnel with EtOAc (100 mL), and the organic layer was separated. The aqueous phase was further extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the volatiles were removed. The crude remaining oil was then purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH gradient) to give the title compound (320 mg, 0.723 mmol) (90% yield). MS (ESI) calcd for C<sub>44</sub>H<sub>65</sub>N<sub>4</sub>O<sub>12</sub> [2M+H]<sup>+</sup>: 841.46. Found: 841.58.

***tert*-Butyl (((2*S*,3*S*)-5-isopropyl-3-methyl-6-oxo-10-(pyridin-4-ylcarbamoyl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:**

Synthesized following the procedure described for *tert*-butyl (((2*S*,3*S*)-5-isopropyl-10-(methoxy(methyl)carbamoyl)-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate. Yield: 57%. MS (ESI) calcd for C<sub>27</sub>H<sub>37</sub>N<sub>4</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 497.28. Found: 497.66.



**(2S,3S)-2-(((4-Chlorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-N-(pyridin-4-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocine-10-carboxamide (11.01) :**

In a 3 mL vial fitted with a magnetic stirring bar, *tert*-butyl ((2S,3S)-5-isopropyl-3-methyl-6-oxo-10-(pyridin-4-ylcarbamoyl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl(methyl)carbamate (36.7 mg, 0.074 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (739  $\mu$ L).

Trifluoroacetic acid (114  $\mu$ L, 1.478 mmol) was added and the resulting mixture was stirred at room temperature. Upon complete conversion of the starting material, the volatiles were removed. The remaining oil was transferred to a separation funnel with EtOAc (40 mL), sat.

aqueous NaHCO<sub>3</sub> (17 mL) and water (17 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 40 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed to yield the intermediate amine which was used in the next step without further characterization. MS (ESI) calcd for

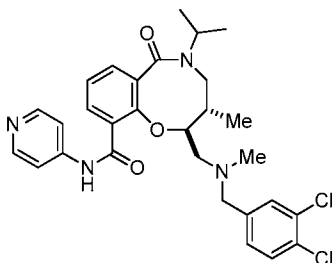
C<sub>22</sub>H<sub>29</sub>N<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 379.22. Found: 397.11. In a 3 mL vial, fitted with magnetic stirring

bar, the intermediate amine was dissolved in 2% AcOH in DMF (724  $\mu$ L). 4-

Chlorobenzaldehyde (12.47 mg, 0.089 mmol) was added and the resulting mixture was stirred for 10 min at room temperature. NaBH(OAc)<sub>3</sub> (62.6 mg, 0.296 mmol) was added in one portion and stirred at room temperature overnight. CH<sub>2</sub>Cl<sub>2</sub> (2 mL), and sat. aqueous Rochelle salt solution (2 mL) were added and vigorously stirred for 4 hours. The crude reaction mixture

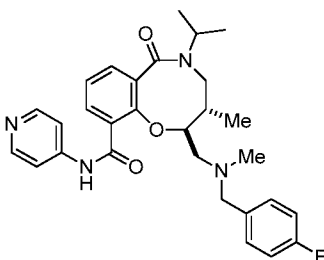
was transferred to a separation funnel with sat. aqueous NaHCO<sub>3</sub> (5 mL), water (5 mL) and EtOAc (15 mL). The organic layer was separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 40 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Et<sub>3</sub>N gradient) to give the title compound (22 mg, 0.042

mmol) as a colourless oil (57% yield over 2 steps). MS (ESI) calcd for C<sub>29</sub>H<sub>34</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 521.23. Found: 521.66. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.13 (s, 1H), 8.57 (d, 2H), 7.83 (d, 2H), 7.59 (d, 1H), 7.32-7.09 (m, 5H), 7.02 (t, 1H), 4.64-4.42 (m, 1H), 3.61 (d, 1H), 3.59-3.45 (m, 1H), 3.18-3.02 (m, 2H), 2.92 (d, 1H), 2.73-2.31 (m, 3H), 2.15 (s, 3H), 1.24 (d, 6H), 0.61 (d, 3H).

**Compound 11 series**

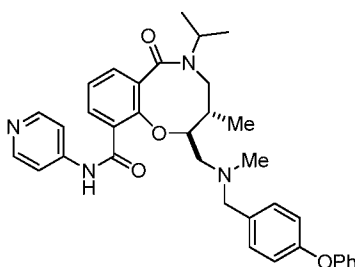
**(2S,3S)-2-(((3,4-dichlorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-N-(pyridin-4-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocine-10-carboxamide (11.02):**

- 5 Synthesized by the procedure described for compound 11.01. Yield 60%. MS (ESI) calcd for  $C_{29}H_{33}Cl_2N_4O_3$   $[M+H]^+$ : 555.19 Found: 555.16.



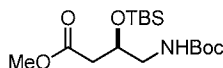
**(2S,3S)-2-(((4-fluorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-N-(pyridin-4-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocine-10-carboxamide (11.03):**

- 10 Synthesized by the procedure described for compound 11.01. Yield 95%. MS (ESI) calcd for  $C_{29}H_{33}FN_4O_3$   $[M+H]^+$ : 505.25 Found: 505.61.

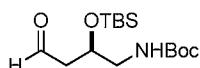


**(2S,3S)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-N-(pyridin-4-yl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocine-10-carboxamide (11.04):**

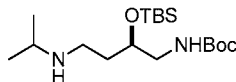
- 15 Synthesized by the procedure described for compound 11.01. Yield 49%. MS (ESI) calcd for  $C_{35}H_{38}N_4O_4$   $[M+H]^+$ : 579.29 Found: 579.46.

**Preparation of Compound 12.01 (Scheme I)**

**(*R*)-methyl 4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate:** To a 20 mL vial, equipped with a magnetic stir bar, was added a solution of (*R*)-methyl 4-((*tert*-butoxycarbonyl)amino)-3-hydroxybutanoate (1.79 g, 7.67 mmol) in DMF (12.80 mL). At 0 °C, imidazole (1.57 g, 23.02 mmol) was added, followed by TBSCl (2.89 g, 19.18 mmol). The mixture was allowed to reach room temperature and was stirred overnight. The crude was then partitioned between brine and ether and the aqueous layer was extracted twice with ether. The combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated and then purified by silica gel chromatography (hexanes/EtOAc gradient) to give the title compound (2.17 g, 6.24 mmol) (81% yield). MS (ESI) calcd for C<sub>16</sub>H<sub>33</sub>NNaO<sub>5</sub>Si [M+Na]<sup>+</sup>: 370.20. Found: 370.05.

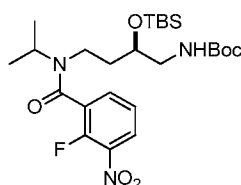


**(*R*)-*tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)-4-oxobutyl)carbamate:** To an oven-dried 100 mL round-bottomed flask equipped with a magnetic stir bar, under Argon, was added a solution of (*R*)-methyl 4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate (860 mg, 2.47 mmol) in DCM (20 mL). At -78 °C, neat DIBAL (0.97 mL, 5.44 mmol) was added dropwise *via* syringe at such rate that the internal temperature remained unchanged. The reaction was kept at -78 °C for 45 minutes and was carefully quenched with MeOH (5 mL), followed by Rochelle's solution (20 mL). The mixture was vigorously stirred overnight at room temperature before being partitioned between water and ether. The aqueous layer was extracted twice with ether and the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to afford the title compound (745 mg, 2.35 mmol) (95% yield) which was used in the next step without further purification. MS (ESI) calcd for C<sub>15</sub>H<sub>31</sub>NNaO<sub>4</sub>Si [M+Na]<sup>+</sup>: 340.19. Found: 340.15.

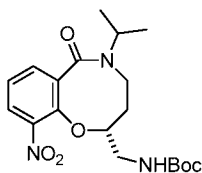


**(*R*)-*tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)-4-(isopropylamino)butyl)carbamate:** To a solution of (*R*)-*tert*-butyl (2-((*tert*-butyldimethylsilyl)oxy)-4-oxobutyl)carbamate (380 mg, 1.20 mmol) and isopropylamine (0.31 mL, 3.59 mmol) in MeOH:DCE=1:1 (2 % AcOH, 12

mL) was added, at room temperature, sodium triacetoxyborohydride (1.02 g, 4.79 mmol). Upon complete conversion of the aldehyde (16 h at room temperature), the reaction was quenched with careful addition of saturated aqueous NaHCO<sub>3</sub> (10 mL). The crude was partitioned between EtOAc and water and the aqueous phase was extracted twice with  
 5 EtOAc. The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated to provide a crude material that was purified *via* silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> gradient). The title compound was isolated (161 mg, 0.45 mmol) with 37% yield. MS (ESI) calcd for C<sub>18</sub>H<sub>41</sub>N<sub>2</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 361.29. Found: 361.48.



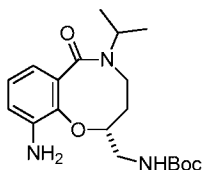
**(*R*)-tert-butyl (2-((tert-butyldimethylsilyl)oxy)-4-(2-fluoro-*N*-isopropyl-3-nitrobenzamido)butyl)carbamate:** To a 100 mL, round-bottomed flask, equipped with a stir bar and under nitrogen, was added a solution of (*R*)-tert-butyl (2-((tert-butyldimethylsilyl)oxy)-4-(isopropylamino)butyl)carbamate (161 mg, 0.45 mmol) and 2,6-lutidine (130  $\mu$ L, 1.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4.5 mL). The flask was cooled to 0  $^{\circ}$ C (iced water bath) and 2-fluoro-3-nitrobenzoyl chloride (109 mg, 0.54 mmol) was added as a solid, in one portion. The ice bath was immediately removed and the mixture was allowed to reach room temperature and stirred until complete conversion of the starting material (4 hours). The crude was concentrated to dryness and was purified by silica gel chromatography  
 15 (Hexanes/EtOAc gradient) to afford the title compound (210 mg, 0.40 mmol) (89% yield). MS (ESI) calcd for C<sub>25</sub>H<sub>42</sub>FN<sub>3</sub>NaO<sub>6</sub>Si [M+Na]<sup>+</sup>: 550.27. Found: 550.23.



**(*R*)-tert-butyl ((5-isopropyl-10-nitro-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocin-2-yl)methyl)carbamate:** At 0  $^{\circ}$ C, cesium fluoride (236 mg, 1.55 mmol) was quickly added in one portion to a solution of (*R*)-tert-butyl (2-((tert-butyldimethylsilyl)oxy)-4-(2-fluoro-*N*-isopropyl-3-nitrobenzamido)butyl)carbamate (205 mg, 0.39 mmol) in dry DMF (7.8 mL), under Argon. Once the addition was complete, the iced bath was removed and the  
 25

temperature was increased to 55-60 °C and the mixture was stirred overnight. The mixture was concentrated to dryness and the crude material was purified by silica gel chromatography (Hexanes/EtOAc gradient). The title compound was isolated (146 mg, 0.37 mmol, 96% yield). MS (ESI) calcd for  $C_{19}H_{27}N_3NaO_6$   $[M+Na]^+$ : 416.18. Found: 416.27.

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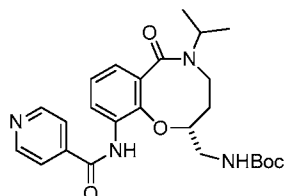


**(R)-tert-butyl ((10-amino-5-isopropyl-6-oxo-3,4,5,6-tetrahydro-2H-**

**benzo[b][1,5]oxazocin-2-yl)methyl)carbamate:** At room temperature, palladium (10 % on carbon, 78 mg, 0.07 mmol) was added to a solution of (R)-tert-butyl ((5-isopropyl-10-nitro-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)carbamate (145 mg, 0.37 mmol) in EtOAc (7.4 mL). The flask was purged with a hydrogen sparge for 30 minutes and the mixture was stirred under a hydrogen atmosphere overnight. The solution was filtered through a pad of Celite which was rinsed three times with EtOAc. The filtrate was concentrated to dryness to afford a crude material (116 mg, 0.32 mmol, 87% yield) which was used in the next step without further purification. MS (ESI) calcd for  $C_{19}H_{30}N_3O_4$   $[M+H]^+$ : 364.22. Found: 364.29.

10

15

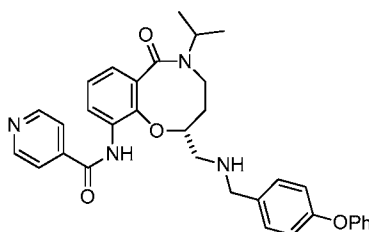


**(R)-tert-butyl ((10-(isonicotinamido)-5-isopropyl-6-oxo-3,4,5,6-tetrahydro-2H-**

**benzo[b][1,5]oxazocin-2-yl)methyl)carbamate:** To a solution of crude (R)-tert-butyl ((10-amino-5-isopropyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)carbamate (116 mg, 0.32 mmol) and 2,6-lutidine (149  $\mu$ L, 1.28 mmol) in  $CH_2Cl_2$  (3.2 mL) was added, at 0 °C, isonicotinoyl chloride hydrochloride (85 mg, 0.48 mmol) in one portion. The mixture was allowed to warm up to room temperature and was stirred overnight. The solvent was removed and the resulting oil was purified by chromatography on silica gel ( $CH_2Cl_2$ /MeOH/ $NH_3$  gradient). The title compound was isolated (139 mg, 0.30 mmol, 93% yield). MS (ESI) calcd for  $C_{25}H_{33}N_4O_5$   $[M+H]^+$ : 469.25. Found: 469.36.

20

25



**(R)-N-(5-isopropyl-6-oxo-2-(((4-phenoxybenzyl)amino)methyl)-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)isonicotinamide:** To a 15 mL round-bottomed flask, equipped

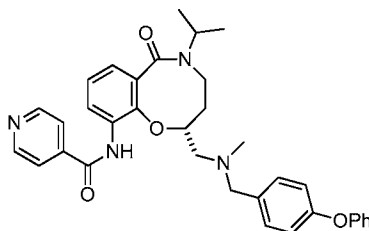
with a stir bar and under nitrogen, was added a solution of (*R*)-*tert*-butyl ((10-

(isonicotinamido)-5-isopropyl-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[b][1,5]oxazocin-2-yl)methyl)carbamate (139 mg, 0.30 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5.9 mL). At 0 °C, neat trifluoroacetic acid (343 µL, 4.45 mmol) was added dropwise to the mixture *via* syringe and the iced bath was removed. The mixture was stirred at room temperature for four hours and was quenched

with sat. NaHCO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated to afford a dark yellow oil (98 mg, 0.27 mmol, 90 % yield) which was azeotroped with toluene three times and placed under high vacuum for one hour.

MS (ESI) calcd for C<sub>20</sub>H<sub>25</sub>N<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 369.19. Found: 369.28. The crude material was suspended in THF (2.7 mL) and a few drops of methanol were added to the mixture. 4-Phenoxybenzaldehyde (50.3 µL, 0.29 mmol) was added and the temperature was increased to 60 °C for two hours, then cooled to room temperature. Sodium triacetoxyborohydride (169 mg, 0.80 mmol) was quickly added to the mixture and the reaction was stirred overnight at room temperature. Sat. NaHCO<sub>3</sub> solution (5 mL) was added to quench the reaction and the mixture was separated between water and CH<sub>2</sub>Cl<sub>2</sub>. The aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub> and the combined organic phases were dried over silica. The solvents

were evaporated and the crude was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Methanol/Ammonia gradient) to afford the title compound (110 mg, 0.20 mmol) with 75% yield over two steps. MS (ESI) calcd for C<sub>33</sub>H<sub>35</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 551.27. Found: 551.37.

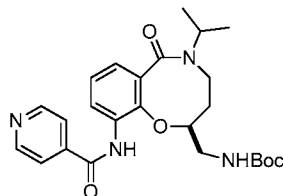


**(R)-N-(5-isopropyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[b][1,5]oxazocin-10-yl)isonicotinamide (12.01):** To a 10 mL round-

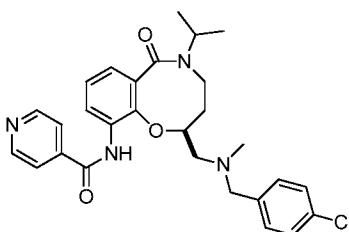
bottomed flask, at room temperature was added a solution of (*R*)-*N*-(5-isopropyl-6-oxo-2-(((4-phenoxybenzyl)amino)methyl)-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocin-10-yl)isonicotinamide (98 mg, 0.18 mmol) and formaldehyde (37 % by wt. in water, 40  $\mu$ L, 0.53 mmol) in THF (3.6 mL). Sodium triacetoxyborohydride (113 mg, 0.53 mmol) was added in one portion as a solid and the mixture was stirred at room temperature for 60 hours. CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was added and the reaction was quenched with sat. NaHCO<sub>3</sub> solution (7 mL). The phases were separated and the aqueous layer was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over silica gel and the solvents were removed. The crude was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/Methanol/Ammonia gradient) and afforded the title compound (46 mg, 0.08 mmol) with 46% yield. MS (ESI) calcd for C<sub>34</sub>H<sub>37</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 565.28. Found: 565.39. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  10.42 (br s, 1H), 8.29 (br s, 3H), 7.33 – 7.15 (m, 1H), 6.97 (t, *J* = 7.7 Hz, 2H), 6.91 – 6.82 (m, 3H), 6.80 – 6.70 (m, 3H), 6.64 (d, *J* = 7.9 Hz, 2H), 6.59 (d, *J* = 8.2 Hz, 2H), 4.57 – 4.39 (m, 1H), 3.44 (br s, 1H), 3.13 – 2.92 (m, 2H), 2.92 – 2.70 (m, 2H), 2.62 – 2.37 (m, 1H), 1.66 (br s, 1H), 1.51 – 1.19 (m, 5H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H).

### **Compound 12 series**

The following compounds were synthesized as outlined in Scheme I and exemplified by the synthesis of compound 12.01.

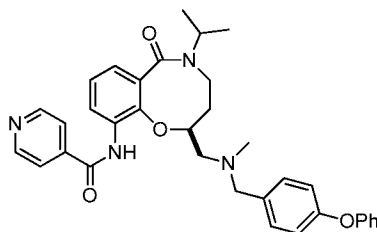


**(*S*)-tert-butyl ((10-(isonicotinamido)-5-isopropyl-6-oxo-3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,5]oxazocin-2-yl)methyl)carbamate:** The title compound (542 mg, 1.16 mmol) was prepared following the entire sequence described above, starting from (*S*)-methyl 4-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)butanoate (4.00 g, 8.48 mmol) and was isolated with 14% yield over seven steps.



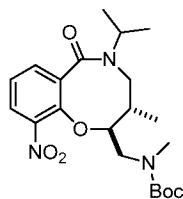
**(S)-N-(2-(((4-chlorobenzyl)(methyl)amino)methyl)-5-isopropyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)isonicotinamide (12.02):** At 0 °C, to a solution of (*S*)-*tert*-butyl ((10-(isonicotinamido)-5-isopropyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b]-

- 5 [1,5]oxazocin-2-yl)methyl)carbamate (10.7 mg, 0.023 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (450 μL) was slowly added neat trifluoroacetic acid (26.4 μL, 0.34 mmol). After 30 min, the reaction was brought to room temperature and stirred overnight. Toluene was added (500 μL) to the mixture and the solvents were removed to afford a crude material which was azeotroped twice more with toluene. The same sequence of reductive alkylation reactions described above has been
- 10 applied to the crude, using 4-chlorobenzaldehyde (3.9 mg, 0.028 mmol) instead of 4-phenoxybenzaldehyde. The title compound was obtained (4.2 mg, 8.3 μmol) with 36% yield over three steps. MS (ESI) calcd for C<sub>28</sub>H<sub>32</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 507.22. Found: 507.26.



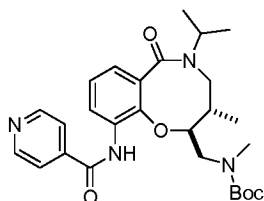
- 15 **(S)-N-(5-isopropyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)isonicotinamide (12.03):** Synthesized by the procedure described for compound 12.01. Yield 70%. MS (ESI) calcd for C<sub>34</sub>H<sub>36</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 565.27 Found: 565.29.

20 **Preparation of Compound 13.01 (Scheme J)**



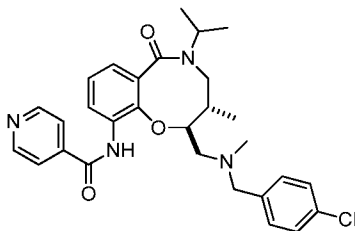
***tert*-butyl (((2*S*,3*S*)-5-isopropyl-3-methyl-10-nitro-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** To a solution of *tert*-butyl

((2*S*,3*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(isopropylamino)-3-methyl-4-oxobutyl)(methyl)carbamate (1.9 g, 4.89 mmol) and triethylamine (3.41 ml, 24.44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (49 ml) was added 2-fluoro-3-nitrobenzoic acid (0.936 g, 4.6 mmol) at 0 °C. The reaction mixture was warmed to room temperature and was allowed to stir at room temperature overnight. Water was added and the mixture extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic extracts were dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver the product (1.93 g, 3.47 mmol) in 71% yield. To a solution of *tert*-butyl ((2*S*,3*R*)-2-((*tert*-butyldimethylsilyl)oxy)-4-(2-fluoro-*N*-isopropyl-3-nitrobenzamido)-3-methyl-4-oxobutyl)(methyl)carbamate (1.9 g, 3.42 mmol) in DMF (68.4 mL) was added cesium fluoride (2.077 g, 13.68 mmol). The resulting suspension was heated at 85 °C for 21.5 h. Additional cesium fluoride (1.04 g, 6.84 mmol) was added to the reaction mixture at the reaction mixture was stirred for 1 h at 85 °C. The reaction mixture was concentrated, taken up in EtOAc, washed with water and the organic layer was dried (MgSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver the product (1.18 g, 3.47 mmol) in 82% yield. MS (ESI) calcd for C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>O<sub>6</sub> [M+H-O<sup>t</sup>Bu]<sup>+</sup>: 365.16 Found: 365.99.



***tert*-butyl (((2*S*,3*S*)-10-(isonicotinamido)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate:** A solution of *tert*-butyl (((2*S*,3*S*)-5-isopropyl-3-methyl-10-nitro-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-2-yl)methyl)(methyl)carbamate (1.40 g, 3.32 mmol) and 10% palladium on carbon in EtOAc (27.7 mL) and MeOH 5.54 mL) was stirred under a hydrogen atmosphere at room temperature for 48 h. The reaction mixture was filtered through Celite and concentrated. The crude material was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and 2,6-lutidine (0.446 ml, 3.83 mmol) and isonicotinoyl chloride hydrochloride (0.227 g, 1.277 mmol) were added. The reaction mixture was stirred at room temperature overnight. Water was added, the reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried (NaSO<sub>4</sub>), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with ethyl acetate/hexanes to deliver

the product (0.238 g, 0.479 mmol) in 75% yield. MS (ESI) calcd for  $C_{27}H_{36}N_4O_6$   $[M+H]^+$ : 497.27 Found: 497.31.

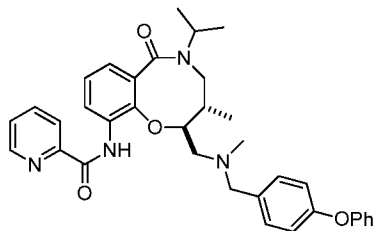


5 ***N*-((2*S*,3*S*)-2-(((4-chlorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]oxazocin-10-yl)isonicotinamide (13.01):**

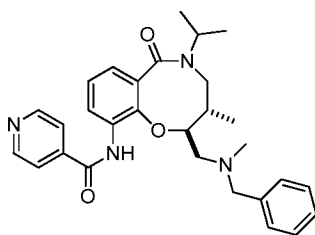
Trifluoroacetic acid (0.372 ml, 4.83 mmol) was added to a solution of *tert*-butyl (((2*S*,3*S*)-10-(isonicotinamido)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]oxazocin-2-yl)methyl)(methyl)carbamate (0.24 g, 0.483 mmol) in  $CH_2Cl_2$  (4 mL) was added and  
 10 stirred at room temperature. The reaction was quenched with sodium bicarbonate, extracted with ethyl acetate, dried ( $MgSO_4$ ), filtered and concentrated. The crude product was dissolved in dichloroethane (1.3 mL), 4-chlorobenzaldehyde (0.018 g, 0.126 mmol) was added and the reaction mixture was stirred for 45 min. Sodium triacetoxyborohydride (0.040 g, 0.189 mmol) was added as a solid, in one portion and the reaction mixture was stirred at  
 15 room temperature overnight. Additional 4-chlorobenzaldehyde (0.013 ml, 0.126 mmol) and sodium triacetoxyborohydride (0.040 g, 0.189 mmol) stirred at rt. still SM remained. The reaction mixture was concentrated and the crude material was dissolved in  $CH_2Cl_2$  (4 mL) and methanol (3 drops). Sodium triacetoxyborohydride (0.040 g, 0.189 mmol) was added as a solid, in one portion and the reaction mixture was stirred at room temperature overnight. The  
 20 reaction mixture was quenched with sat. Rochelle's salt (1 mL) and stirred at 50 °C for 2 h. The reaction mixture was extracted with  $CH_2Cl_2$ , dried ( $MgSO_4$ ), filtered and concentrated. The crude product was purified by column chromatography on silica gel eluting with dichloromethane/methanol/triethylamine followed preparative TLC (dichloromethane/methanol/triethylamine) to deliver the product (14.4 mg, 0.028 mmol) in  
 25 44% yield. MS (ESI) calcd for  $C_{29}H_{33}ClN_4O_3$   $[M+H]^+$ : 521.22 Found: 521.28.  $^1H$  NMR (300 MHz,  $CDCl_3$ )  $\delta$  12.53 – 12.46 (m, 1H), 10.76 (s, 1H), 8.63 (t,  $J$  = 6.1 Hz, 3H), 7.56 (d,  $J$  = 5.0 Hz, 2H), 7.37 – 7.09 (m, 6H), 4.73 (dt,  $J$  = 13.3, 6.6 Hz, 1H), 3.46 – 3.23 (m, 3H), 3.18 (d,  $J$  = 14.5 Hz, 1H), 3.08 – 2.91 (m, 1H), 2.82 (dd,  $J$  = 13.6, 9.9 Hz, 1H), 2.17 (d,  $J$  = 14.0 Hz, 1.5H), 2.00 (d,  $J$  = 5.8 Hz, 0.5H), 1.84 – 1.58 (m, 4H), 1.24 (dd,  $J$  = 16.1, 6.7 Hz, 6H),  
 30 0.73 (d,  $J$  = 6.7 Hz, 3H).

**Compound 13 series**

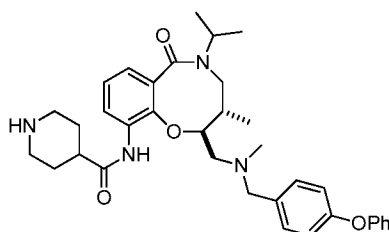
The following compounds were synthesized as outlined in Scheme J and exemplified by the synthesis of compound 13.01.



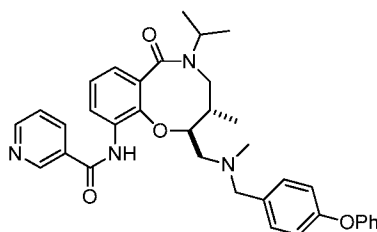
- 5 ***N*-((2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)picolinamide (13.02):** Synthesized by the procedure described for compound 13.01. Yield 34%. MS (ESI) calcd for C<sub>35</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 579.29 Found: 579.32.



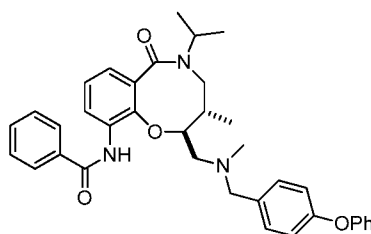
- 10 ***N*-((2*S*,3*S*)-2-((benzyl(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)isonicotinamide (13.03):** Synthesized by the procedure described for compound 13.01. Yield 28%. MS (ESI) calcd for C<sub>29</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 487.26 Found: 487.18.



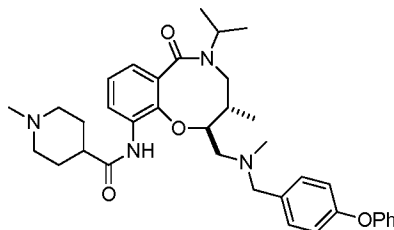
- 15 ***N*-((2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)piperidine-4-carboxamide (13.04):** Synthesized by the procedure described for compound 13.01. Yield 83%. MS (ESI) calcd for C<sub>35</sub>H<sub>44</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 585.34 Found: 585.47.
- 20



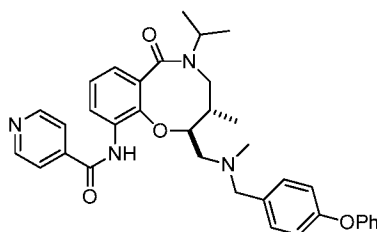
***N*-((2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)nicotinamide (13.05):** Synthesized by the procedure described for compound 13.01. Yield 9%. MS (ESI) calcd for C<sub>35</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 579.29 Found: 579.32.



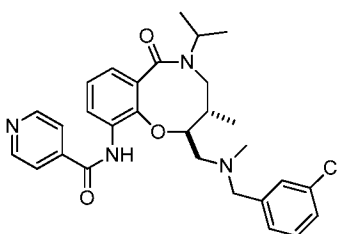
***N*-((2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)benzamide (13.06):** Synthesized by the procedure described for compound 13.01. Yield 85%. MS (ESI) calcd for C<sub>36</sub>H<sub>39</sub>N<sub>3</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 578.29 Found: 578.58.



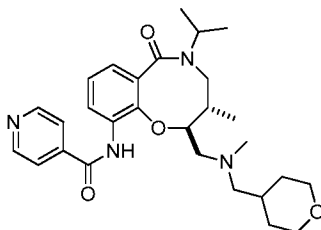
***N*-((2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[b][1,5]oxazocin-10-yl)-1-methylpiperidine-4-carboxamide (13.07):** Synthesized by the procedure described for compound 13.01. Yield 88%. MS (ESI) calcd for C<sub>36</sub>H<sub>46</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 599.35 Found: 599.48.



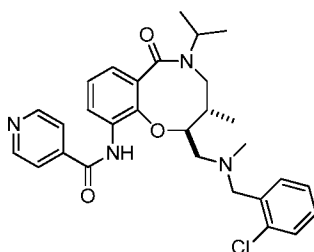
***N*-((2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl(4-phenoxybenzyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]oxazocin-10-yl)isonicotinamide (13.08):** Synthesized by the procedure described for compound 13.01. Yield 73%. MS (ESI) calcd for C<sub>35</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 579.29 Found: 579.25.



***N*-((2*S*,3*S*)-2-(((3-chlorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]oxazocin-10-yl)isonicotinamide (13.09):** Synthesized by the procedure described for compound 13.01. Yield 60%. MS (ESI) calcd for C<sub>29</sub>H<sub>33</sub>ClN<sub>4</sub>O<sub>3</sub> [M+H]<sup>+</sup>: 521.22 Found: 521.20.



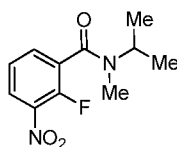
***N*-((2*S*,3*S*)-5-isopropyl-3-methyl-2-((methyl((tetrahydro-2H-pyran-4-yl)methyl)amino)methyl)-6-oxo-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]oxazocin-10-yl)isonicotinamide (13.10):** Synthesized by the procedure described for compound 13.01. Yield 10%. MS (ESI) calcd for C<sub>28</sub>H<sub>38</sub>N<sub>4</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 495.29 Found: 495.52.



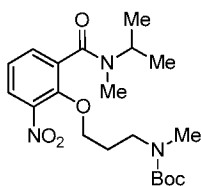
***N*-((2*S*,3*S*)-2-(((2-chlorobenzyl)(methyl)amino)methyl)-5-isopropyl-3-methyl-6-oxo-3,4,5,6-tetrahydro-2H-benzo[*b*][1,5]oxazocin-10-yl)isonicotinamide (13.11):** Synthesized by the procedure described for compound 13.01. Yield 65%. MS (ESI) calcd for

5  $C_{29}H_{33}ClN_4O_3$   $[M+H]^+$ : 521.22 Found: 521.20.

#### **Preparation of Compound 14.01 (Scheme K)**

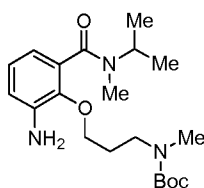


**2-Fluoro-*N*-isopropyl-*N*-methyl-3-nitrobenzamide:** In a 250 mL round-bottomed flask fitted with a magnetic stirring bar, *N*-methylpropan-2-amine (0.712 mL, 6.84 mmol) and Et<sub>3</sub>N (4.76 mL, 34.2 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (90 mL). The resulting mixture was cooled to 0 °C. 2-Fluoro-3-nitrobenzoyl chloride (2.78 g, 13.67 mmol) was then added. The reaction mixture was warmed to room temperature and stirred overnight. Water (50 mL) was then added and the mixture was transferred to a separation funnel. The organic layer was separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the volatiles were removed *in vacuo*. The crude remaining oil was purified by silica gel column chromatography (hexanes/EtOAc gradient) to give the title compound (1.3 g, 5.41 mmol) in 79% yield. MS (ESI) calcd for C<sub>13</sub>H<sub>17</sub>FN<sub>3</sub>O<sub>3</sub>  $[M + H + MeCN]^+$ : 282.13. Found: 282.05.



***tert*-butyl (3-(2-(isopropyl(methyl)carbamoyl)-6-nitrophenoxy)propyl)(methyl)carbamate:**

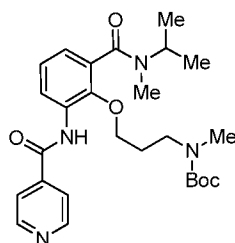
In a flame-dried 250 mL round-bottomed flask, fitted with a magnetic stirring bar *tert*-butyl (3-hydroxypropyl)(methyl)carbamate (1.733 g, 9.16 mmol) was dissolved in THF (46 mL). The solution was cooled to -60 °C. LiHMDS (1M in THF, 11.45 mL, 11.45 mmol) was then slowly added, and the resulting mixture was stirred at -60 °C for 30 min, whereupon a solution of 2-fluoro-*N*-isopropyl-*N*-methyl-3-nitrobenzamide (1.1 g, 4.58 mmol) in THF (45.8 ml) was added dropwise. The reaction mixture was then slowly allowed to warm to room temperature and stirred overnight. The reaction was then quenched with sat. aqueous NH<sub>4</sub>Cl (20 mL) and all volatiles were removed *in vacuo*. The remaining aqueous phase was added EtOAc (50 mL) and transferred to a separation funnel. The organic layer was separated and the aqueous phase was further extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (hexanes/EtOAc gradient) to give the title compound (1.5 g, 3.66 mmol) in 79% yield. MS (ESI) calcd for C<sub>20</sub>H<sub>32</sub>N<sub>3</sub>O<sub>6</sub> [M + H]<sup>+</sup>: 410.23. Found: 410.06.



***tert*-Butyl (3-(2-amino-6-**

**(isopropyl(methyl)carbamoyl)phenoxy)propyl)(methyl)carbamate:**

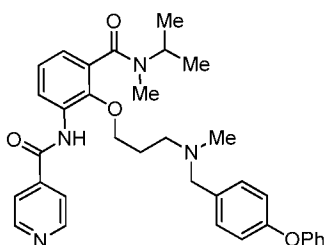
In a flame-dried 100 mL round-bottomed flask, fitted with a magnetic stirring bar, *tert*-butyl (3-(2-(isopropyl(methyl)carbamoyl)-6-nitrophenoxy)propyl)(methyl)carbamate (600 mg, 1.465 mmol) was dissolved in EtOAc (9.5 mL). Pd/C (10% w/w, 156 mg, 1.465 mmol) was added and the flask was evacuated and back-filled with H<sub>2</sub> several times. The reaction was left stirring under H<sub>2</sub> atmosphere at room temperature overnight. Upon full conversion of starting material, the reaction mixture was filtered through a plug of Celite, and the volatiles were removed to give a crude product which was used in the next step without further purification. MS (ESI) calcd for C<sub>20</sub>H<sub>34</sub>N<sub>3</sub>O<sub>4</sub> [M + H]<sup>+</sup>: 380.25. Found: 380.05.



**tert-Butyl (3-(2-(isonicotinamido)-6-**

**(isopropyl(methyl)carbamoyl)phenoxy)propyl)(methyl)carbamate:** In a 100 mL round-bottomed flask, fitted with a magnetic stirring bar, *tert*-butyl (3-(2-amino-6-

- 5 (isopropyl(methyl)carbamoyl)phenoxy)propyl)(methyl)carbamate was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The resulting mixture was added 2,6-lutidine (0.921 mL, 7.91 mmol), isonicotinoyl chloride hydrochloride (0.469 g, 2.64 mmol) and stirred at room temperature overnight. Water (10 mL) was then added, and the mixture was transferred to a separation funnel. The organic layer was separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the volatiles were removed. The crude remaining oil was purified by silica gel column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Et<sub>3</sub>N gradient) to give the title compound (560 mg, 1.156 mmol) in 88% yield. MS (ESI) calcd for C<sub>26</sub>H<sub>37</sub>N<sub>4</sub>O<sub>5</sub> [M + H]<sup>+</sup>: 485.28. Found: 485.15.



**N-(3-(isopropyl(methyl)carbamoyl)-2-(3-(methyl(4-**

**phenoxybenzyl)amino)propoxy)phenyl)isonicotinamide (14.01):** In a 100 mL round-

- bottomed flask, fitted with a magnetic stirring bar, (*tert*-butyl (3-(2-(isonicotinamido)-6-(isopropyl(methyl)carbamoyl)phenoxy)propyl)(methyl)carbamate (0.4 g, 0.825 mmol)) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (8.2 mL). Trifluoroacetic acid (0.636 mL, 8.25 mmol) was added and the resulting mixture was stirred at rt. Upon complete conversion of the starting material, the volatiles were removed. The remaining oil was transferred to a separation funnel with EtOAc (40 mL), sat. aqueous NaHCO<sub>3</sub> (20 mL) and water (20 mL). The organic layer was separated and the aqueous phase was further extracted with EtOAc (5 x 40 mL). The combined organic layers were dried over MgSO<sub>4</sub> and the volatiles were removed *in vacuo* to yield the intermediate amine (300 mg, 0.780 mmol) which was used in the next step without further

characterization (95% yield). MS (ESI) calcd for  $C_{21}H_{29}N_4O_3$   $[M+H]^+$ : 385.22. Found:

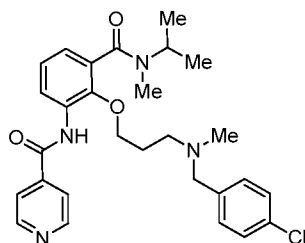
385.09. In a 100 mL round-bottomed flask fitted with magnetic stirring bar, the intermediate amine was dissolved in 1,2-dichloroethane (10.4 mL). 4-Phenoxybenzaldehyde (0.179 mL, 1.040 mmol) was added and the mixture was stirred at room temperature for 45 min.

- 5 NaBH(OAc)<sub>3</sub> (0.331 g, 1.561 mmol) was added in one portion and the reaction was stirred at room temperature overnight. The reaction mixture was then added a sat. aqueous Rochelle salt solution (1.5 mL), water (1.5 mL) and vigorously stirred at 50 °C overnight. The mixture was then transferred to a separation funnel with CH<sub>2</sub>Cl<sub>2</sub> (10 mL). The organic layer was separated and the aqueous phase was further extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The  
10 combined organic layers were dried over MgSO<sub>4</sub> and the volatiles were removed *in vacuo*. The crude remaining oil was purified by silica gel column chromatography

(CH<sub>2</sub>Cl<sub>2</sub>/MeOH/Et<sub>3</sub>N gradient) to give the title compound (118 mg, 0.208 mmol) as a white foamy solid (40% yield). MS (ESI) calcd for  $C_{34}H_{39}N_4O_4$   $[M+H]^+$ : 567.30. Found: 567.26. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, rotamers)  $\delta$  8.77 (d, 2H), 8.73 – 8.66 (m, 1H), 8.51 (d, 1H), 7.73 – 7.63 (m, 2H), 7.41 – 6.84 (m, 11H), 5.13 – 4.92 (m, 0.4H), 4.24 – 4.00 (m, 2H), 3.86 – 3.66 (m, 0.6H), 3.41 – 3.32 (m, 2H), 2.98 (s, 2H), 2.71 (s, 1H), 2.60 – 2.41 (m, 2H), 2.13 – 2.06 (m, 3H), 2.04 – 1.90 (m, 2H), 1.25 – 1.00 (m, 6H).

### Compound 14 series

- 20 The following compounds were synthesized as outlined in Scheme K and exemplified by the synthesis of compound 14.01.



***N*-(2-(3-((4-Chlorobenzyl)(methyl)amino)propoxy)-3-**

**(isopropyl(methyl)carbamoyl)phenyl)isonicotinamide (14.02):** Synthesized following

- 25 procedure described for compound 15.01. Yield: 40%. MS (ESI) calcd for  $C_{28}H_{34}ClN_4O_3$   $[M+H]^+$ : 509.23. Found: 509.16.

### BIOLOGICAL ASSAYS

#### I. Broad Assays

- 30 A high-throughput screen of small molecules was performed in duplicate in the

recombinant Tulahuen strain of *T. cruzi* stably expressing a beta-galactosidase reporter gene. Trypomastogote-stage parasites were co-cultured with mouse fibroblast NIH/3T3 host cells, (Buckner FS, Verlinde CL, La Flamme AC, Van Voorhis WC. Efficient technique for screening drugs for activity against *Trypanosoma cruzi* using parasites expressing beta-galactosidase. Antimicrob Agents Chemother. 1996; 40(11): 2592-2597). Signal was  
5 normalized to neutral (DMSO) controls, and a 75% inhibition cutoff was used to define a hit. Compounds initially designated as hits were retested in dose in the primary assay to confirm their inhibitory activity. In parallel, compounds were tested in toxicity assays against NIH/3T3 host cells to determine if these compounds were cytotoxic to mammalian cells and  
10 thus, false positives. Compounds that reduced the viability of NIH/3T3 cells were excluded as viable hits. A subset of hits were then tested in a similar infection assay with the Tulahuen strain of *T. cruzi* infecting murine L-6 cells and the intracellular *T. cruzi* immunofluorescence assay described below.

## 15 A. METHODS

### 1. Materials and Methods

The methods in this section were either performed as described in Bettiol *et al.*, Identification of three classes of heteroaramtic compounds with activity against intracellular *Trypanosoma cruzi* by chemical library screening. LPoS Negl Trop Dis 2009; 3(2); e384.  
20 Epub 2009 Feb 24 (i.e., immunofluorescence) or modified for high throughput screening (co-culture and host cell toxicity).

- **Assay Materials:** Dulbecco's modified Eagle's medium (DMEM) with Phenol Red, high glucose, with L-glutamine and sodium pyruvate was obtained from Cellgro (Mediatech Inc, Manassas, VA; Catalog no. 10-013-CM). PSG or Penicillin-streptomycin-L-glutamine (Catalog no. 10378-016), FBS-heat inactivated fetal bovine  
25 serum (FBS, Catalog no.16140-089), and 0.25% Trypsin-EDTA 1X (Catalog no. 25200-072) were purchased from Gibco-Invitrogen. Sterile horse serum, from donor herd (if appearance of epimastigotes) was obtained from Sigma (Catalog no. H1270). Sterile, Ca<sup>++</sup>/ Mg<sup>++</sup>- free Phosphate Buffer Saline (PBS) 1X was prepared in house.  
30 GAL-SCREEN<sup>®</sup> Buffer B was obtained from Applied Biosystems (Carlsbad, CA; Catalog no.T1031). Alexa Fluor 488 goat anti-rabbit IgG secondary antibody was from MOLECULAR PROBES<sup>®</sup>, Invitrogen (Carlsbad, CA). Polyclonal rabbit anti-*T. cruzi* was a gift from Dr. B. Burleigh, Harvard School of Public Health, Boston, MA).

- **Cell Lines:** The following cell lines were used in this study: LLC-MK2 cells (rhesus monkey kidney epithelial cell line) and NIH/3T3 cells (mouse embryonic fibroblastic cell line) were obtained from ATCC. *T. cruzi* expressing  $\beta$ -galactosidase (*T. cruzi* - $\beta$ -gal: Tulahuen strain, clone C4; refer to Buckner *et al.*, 1996).

## 5 B. ASSAYS

### 1. *T. cruzi* Inhibition Assay

**For cell propagation:** 90% DMEM, Phenol Red, 10% FBS, and 1% PSG were mixed and filtered through a 0.2 microns membrane. The cells were kept at 4°C, then warmed up to 37°C in a water bath before use.

- 10 **For *T. cruzi* culture and assays:** 98% DMEM, Phenol Red, 2% FBS, and 1% PSG were mixed and filtered through a 0.2 microns membrane. The cells were kept at 4°C, then warmed up to 37°C in a water bath before use.

**Solutions:** Gal-Screen. Using a Gal-Screen base kit, Buffer B (Catalog no. T2361) was mixed with 1:25 substrate (Catalog no. T2359).

- 15 **NIH/3T3 Cell Culture:** NIH/3T3 cells were cultivated in DMEM supplemented with 10% FBS and 1% PSG in T175 in 50 mL total of medium.

**LLC-MK2 Cell Culture:** LLC-MK2 cells were cultivated in DMEM supplemented with 10% FBS and 1% PSG in T175 flasks in 50 mL total of medium. Cells were usually passaged twice a week at 1:4 to 1:8 ratios.

- 20 **Parasite Culture: *T. cruzi*  $\beta$ -gal (Tc):** *T. cruzi* - $\beta$ -gal were cultivated in DMEM supplemented with 2% FBS and 1% PSG in T175 flasks with vented caps in 50 mL total of medium.

### 2. Growth Inhibition Assay for HTS (384-well plates)

- The medium was warmed up with 2% FBS/DMEM. The parasites were harvested in 50-  
 25 mL tubes, and spun for 10 minutes at 2200 rpm. Approximately 15 mL of media was aspirated, and the samples were incubated for 3-5 h. The NIH/3T3 cells were trypsinized (refer to cell culture protocol). When the NIH/3T3 cells were detached, the cells were harvested in DMEM, 2% FBS, and 1% PSG, then counted using the Nexcelom cellometer. The cells were diluted to 166,667 cells/mL, then added to a flask and plated 5,000 cells/  
 30  $\mu$ L per well using a standard cassette multiwall drop Combi. The cells were incubated for 3 h, then *T. cruzi* cells were counted, diluted to 0.166 million cells/mL, and transferred to a 2-liter flask. Then, 100 nL compounds/DMSO were pinned to each well with NIH/3T3 cells. Next, 30  $\mu$ L/well of parasites (5000 *T. cruzi*) were added with a standard cassette multiwall drop Combi on slow speed, and incubated for 4 days (or a minimum of 90 h). Gal-Screen

was prepared, 30  $\mu$ L per well were dispensed in a 384-well plate, incubated for 60 minutes, and the luminescence was read using Envision (Perkin-Elmer) at 0.1 sec/well.

### 3. Cell Toxicity Assay: NIH/3T3 Cells

For the cell toxicity assay with NIH/3T3 cells, the same materials as for *T. cruzi* co-culture assay were used. NIH/3T3 cells were cultivated in DMEM supplemented with 10% FBS and 1% PSG in T175 in 50 mL total of medium.

### 4. Intracellular *T. cruzi* Immunofluorescence Assay

Fifty thousand NIH/3T3 cells were seeded on sterile glass coverslips in 12-well plates and allowed to adhere overnight. Five million *T. cruzi* parasites were added (multiplicity of infection 100:1) and allowed to infect for 2 h in DMEM+2% FBS and PSG. Parasites were rinsed out 3X with PBS, and compounds were added at 10X their IC<sub>50</sub> (as determined in AID 2044 and AID 2294). Infected cells were further incubated for 4 days and fixed for 15 min with 4% paraformaldehyde.

Fixed cells on coverslips were rinsed with PBS and permeabilized for 15 min in PBS with 0.1% Triton X-100. After blocking for 20 min in PBS with 10% goat serum, 1% bovine serum albumin (BSA), 100 mM glycine, and 0.05% sodium azide, cells were incubated for 1 h at room temperature with a polyclonal rabbit anti-*T. cruzi* at 1:2000 dilution. After rinsing, an Alexa Fluor 488 goat anti-rabbit IgG secondary antibody was added for 1 h at a 1:800 dilution. DNA was stained with DAPI, and coverslips were mounted with anti-fade mounting media. Images were taken using an inverted Olympus IX70 microscope with a 60X oil objective.

### 5. Counter Screens

*In vitro* counter screens were performed to confirm our findings. The results of these screens are tabulated in Table 1 and Table 2 designated as Broad Assays.

## II. STPH Assays

### ***T. cruzi* Tulahuen strain C2C4 Assay amastigote study (Swiss Tropical Public Health Institute, STPH)**

Rat skeletal myoblasts (L-6 cells) were seeded in 96-well microtitre plates at 2000 cells/well in 100  $\mu$ L RPMI 1640 medium with 10% FBS and 2 mM l-glutamine. After 24 h the medium was removed and replaced by 100  $\mu$ L per well containing 5000 trypomastigote forms of *T. cruzi* Tulahuen strain C2C4 containing the  $\beta$ -galactosidase (Lac Z) gene [Buckner FS, Verlinde CL, La Flamme AC, Van Voorhis WC (1996) Efficient technique for screening drugs for activity against *Trypanosoma cruzi* using parasites expressing betagalactosidase.

Antimicrob Agents Chemother 40: 2592-2597]. After 48 h the medium was removed from the wells and replaced by 100  $\mu$ l fresh medium with or without a serial drug dilution of eleven 3-fold dilution steps covering a range from 100 to 0.002  $\mu$ g/ml. After 96 h of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterility. Then the substrate CPRG/Nonidet (50  $\mu$ l) was added to all wells. A color reaction developed within 2-6 h and could be read photometrically at 540 nm. Data were analyzed with the graphic programme Softmax Pro (Molecular Devices), which calculated IC<sub>50</sub> values by linear regression from the sigmoidal dose inhibition curves. Benznidazole is used as control.

#### **L-6 rat myocyte toxicity (Swiss Tropical Public Health Institute, STPH)**

Assays were performed in 96-well microtiter plates, each well containing 100  $\mu$ l of RPMI 1640 medium supplemented with 1% L-glutamine (200mM) and 10% fetal bovine serum, and 4000 L-6 cells (a primary cell line derived from rat skeletal myoblasts). Serial drug dilutions of eleven 3-fold dilution steps covering a range from 100 to 0.002  $\mu$ g/ml were prepared. After 70 hours of incubation the plates were inspected under an inverted microscope to assure growth of the controls and sterile conditions. 10  $\mu$ l of Alamar Blue was then added to each well and the plates incubated for another 2 hours. Then the plates were read with a Spectramax Gemini XS microplate fluorometer (Molecular Devices Cooperation, Sunnyvale, CA, USA) using an excitation wave length of 536 nm and an emission wave length of 588 nm. The IC<sub>50</sub> values were calculated by linear regression [14] from the sigmoidal dose inhibition curves using SoftmaxPro software (Molecular Devices Cooperation, Sunnyvale, CA, USA). Podophyllotoxine is used as control.

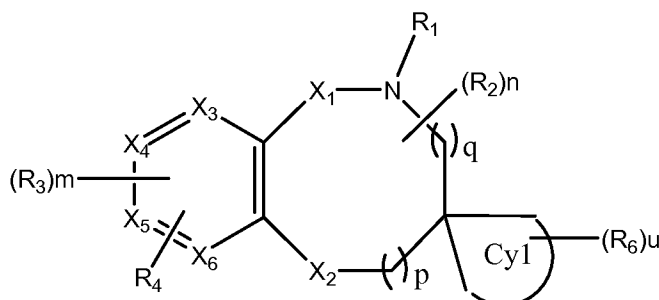
The patent and scientific literature referred to herein establishes the knowledge that is available to those with skill in the art. All United States patents and published or unpublished United States patent applications cited herein are incorporated by reference. All published foreign patents and patent applications cited herein are hereby incorporated by reference. All other published references, documents, manuscripts and scientific literature cited herein are hereby incorporated by reference.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

## CLAIMS

What is claimed is:

1. A compound of Formula I or a pharmaceutically acceptable ester, salt, prodrug or  
5 metabolite thereof:



Formula I

wherein

n is 0, 1, 2, 3, 4 or 5;

10 m is 0, 1, 2, 3 or 4;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

u is 0, 1, 2, 3, 4, 5, 6, 7, 8 or 9;

X<sub>1</sub> is C(O), C(S), S(O)<sub>2</sub>, CH<sub>2</sub>;

15 X<sub>2</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), CH<sub>2</sub>;

each X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently selected from CR<sub>14</sub> and N;

wherein R<sub>14</sub> is selected from -CN, -S(O)<sub>2</sub>R<sub>10</sub>, hydrogen, alkyl, substituted

alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy,

substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino,

20 substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl,

heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

Cyl represents an optionally substituted cycloalkyl, cycloalkenyl, heterocyclyl or aryl  
containing one, two or three rings;

R<sub>1</sub> is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl,

25 substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted

alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio,

aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted

heteroaryl  $-(CH_2)_z$ -heterocyclyl,  $-(CH_2)_z$ -heteroaryl or  $-(CH_2)_z$ -aryl wherein z is 0, 1, 2, 3, 4, 5, 6, 7, 8, or 9;

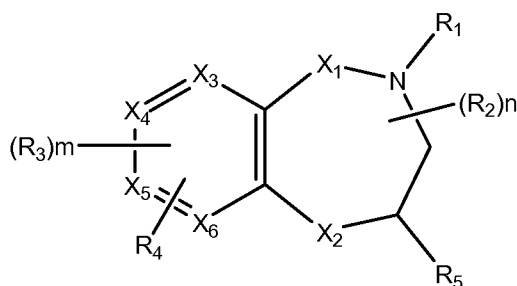
each  $R_2$  and  $R_3$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio;

wherein each  $R_{10}$  and  $R_{11}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{10}$  and  $R_{11}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring; and,

$R_4$  is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ ; and,

each  $R_6$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively two  $R_6$  groups together with the atoms to which they are attached to form an optionally substituted ring.

2. A compound of Formula II or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof:

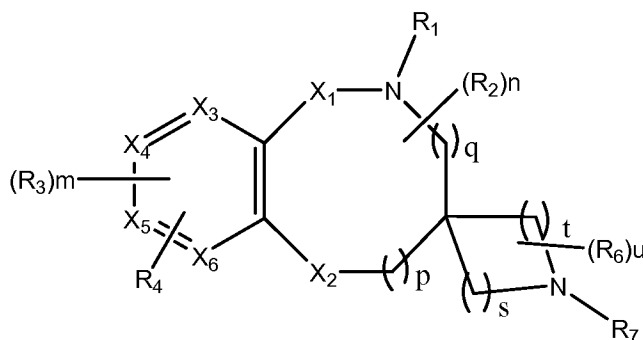


Formula II

wherein  $R_5$  is hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,

- 5 heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio.

- 10 3. A compound of Formula III or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof:



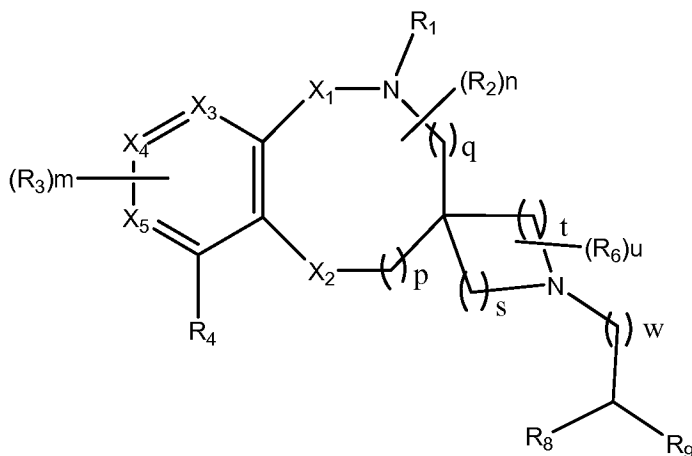
Formula III

wherein each  $s$  and  $t$  is independently 0, 1, 2, 3, 4, 5, or 6;

- 15  $R_7$  is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio.

20

4. A compound of Formula IIIA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof:

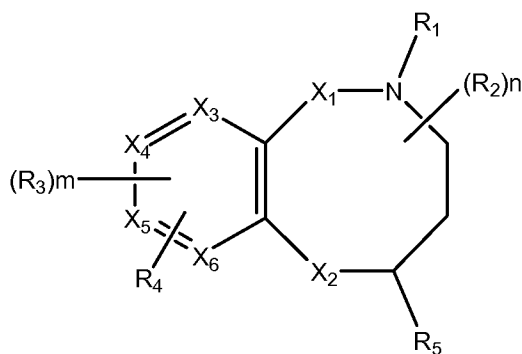


Formula IIIA

5 wherein w is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

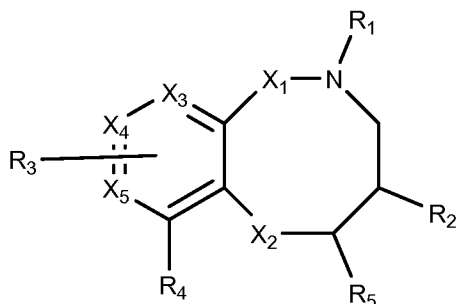
R<sub>8</sub> and R<sub>9</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>8</sub> and R<sub>9</sub> together with the atom they are attached may form an optionally substituted two, three or four membered ring.

5. A compound of Formula IV or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof:



Formula IV.

6. A compound of Formula IVA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof:

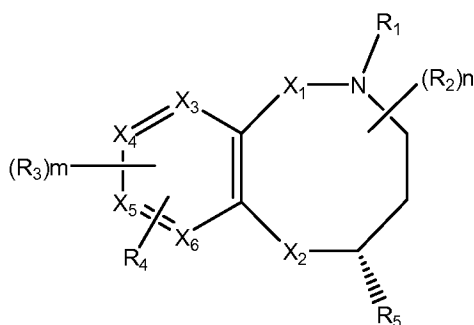


Formula IVA.

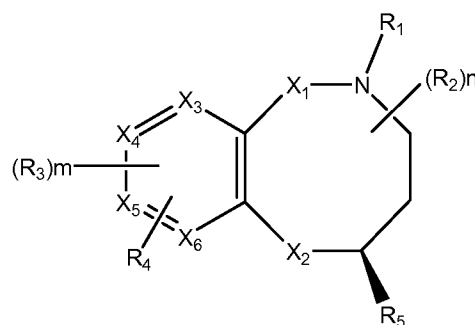
5

7. A compound of claim 5, wherein R<sub>4</sub> is selected from heterocyclyl, substituted heterocyclyl, heteroaryl or substituted heteroaryl.

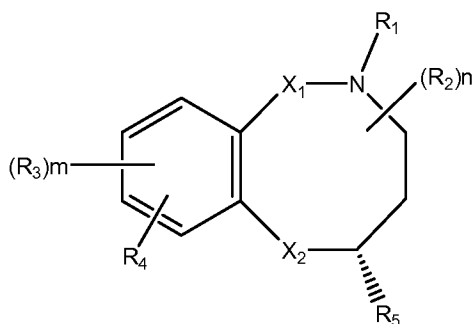
8. A compound of Formula IVB, IVC, IVD, IVE or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



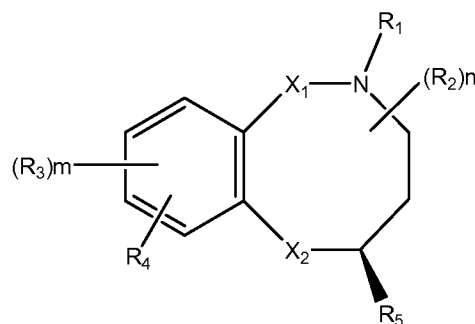
Formula IVB



Formula IVC



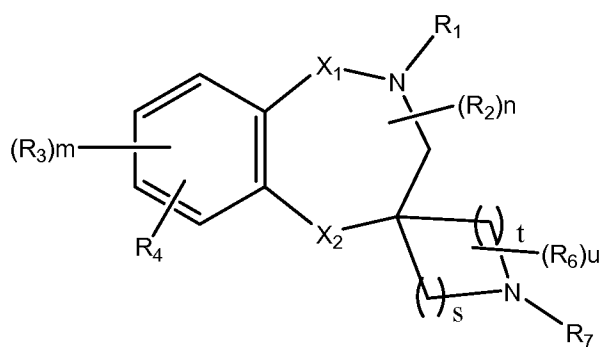
Formula IVD



Formula IVE.

15

9. A compound of Formula IIIC or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof:



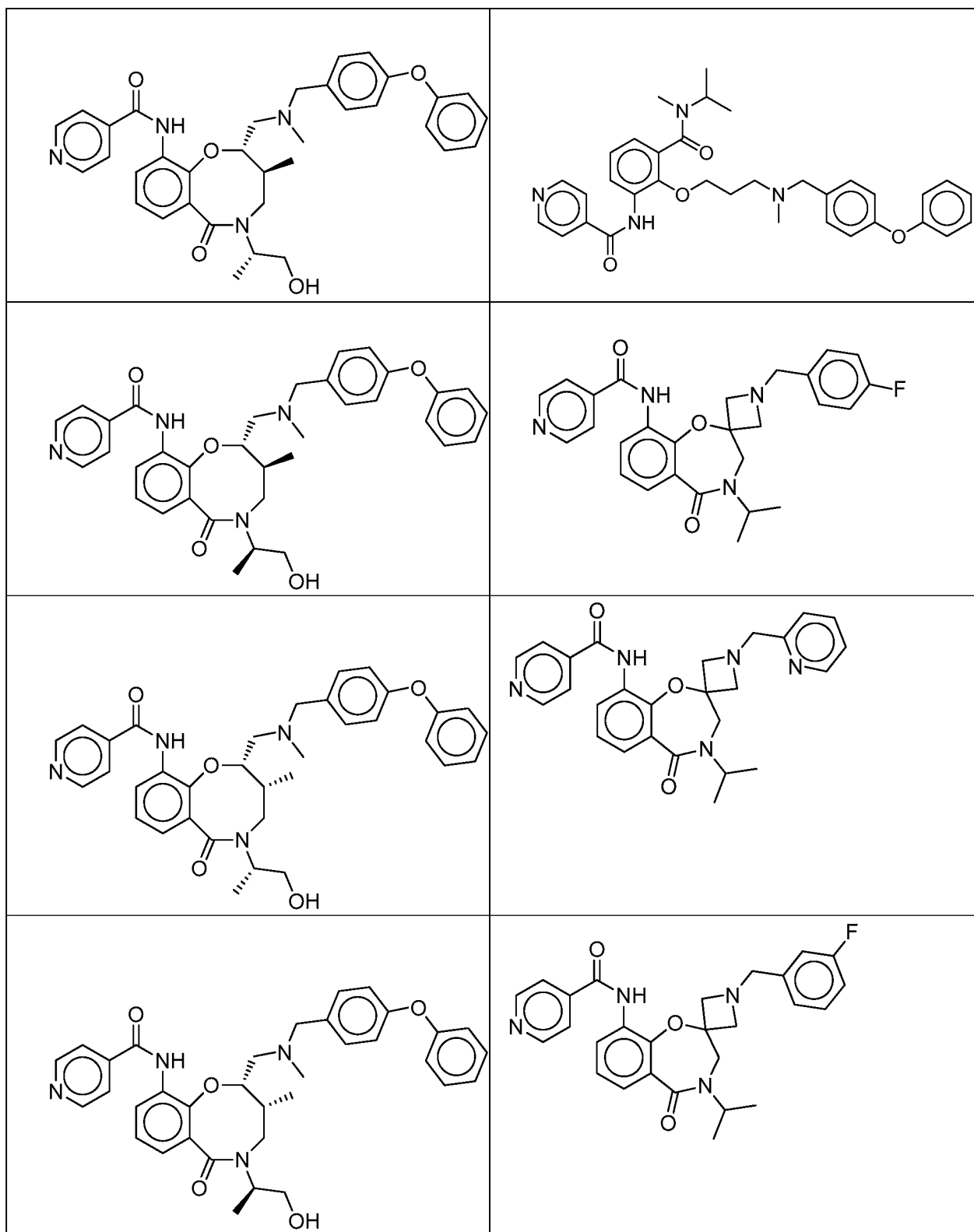
Formula IIIC.

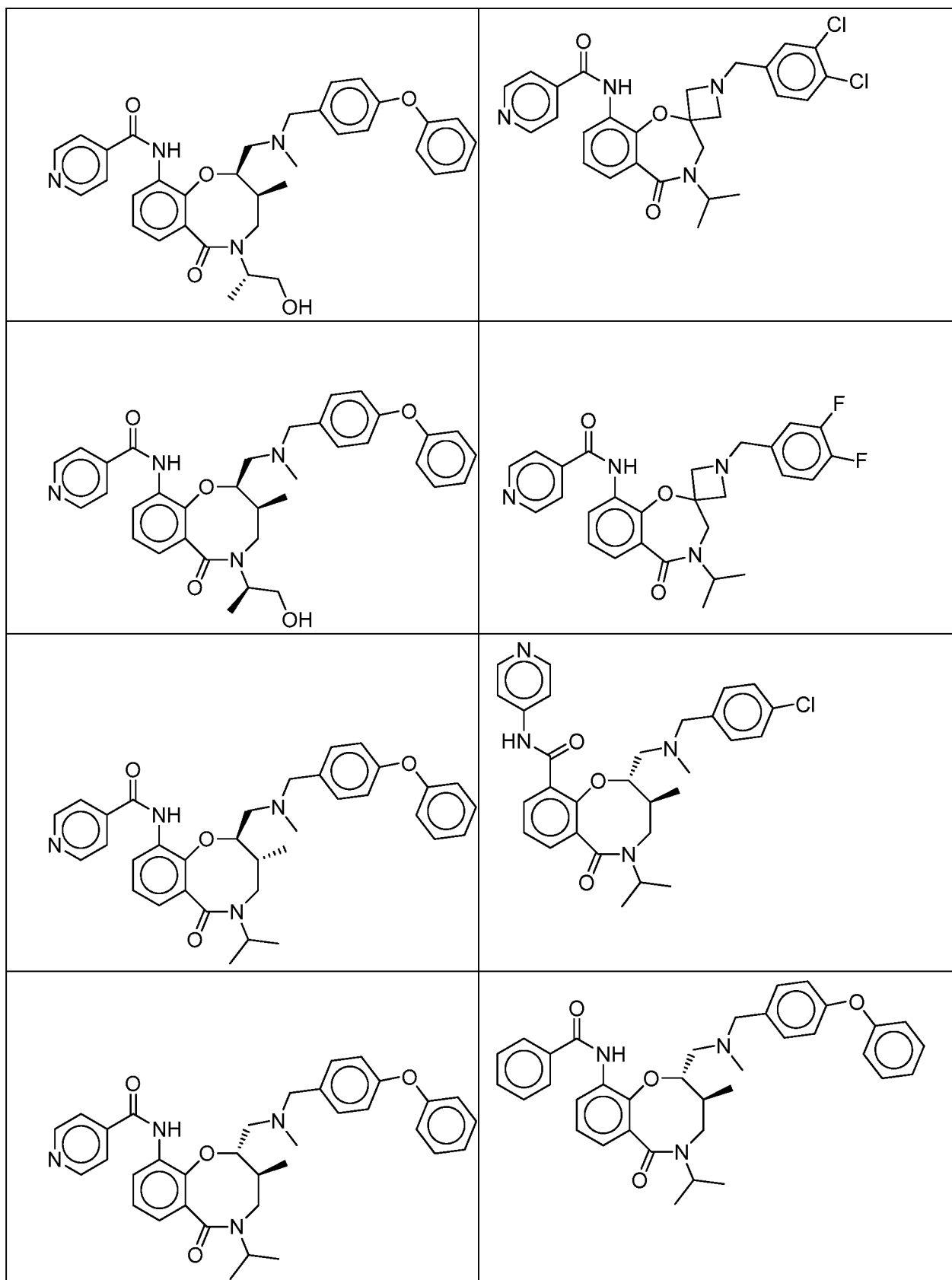
10. A compound of Table 1:

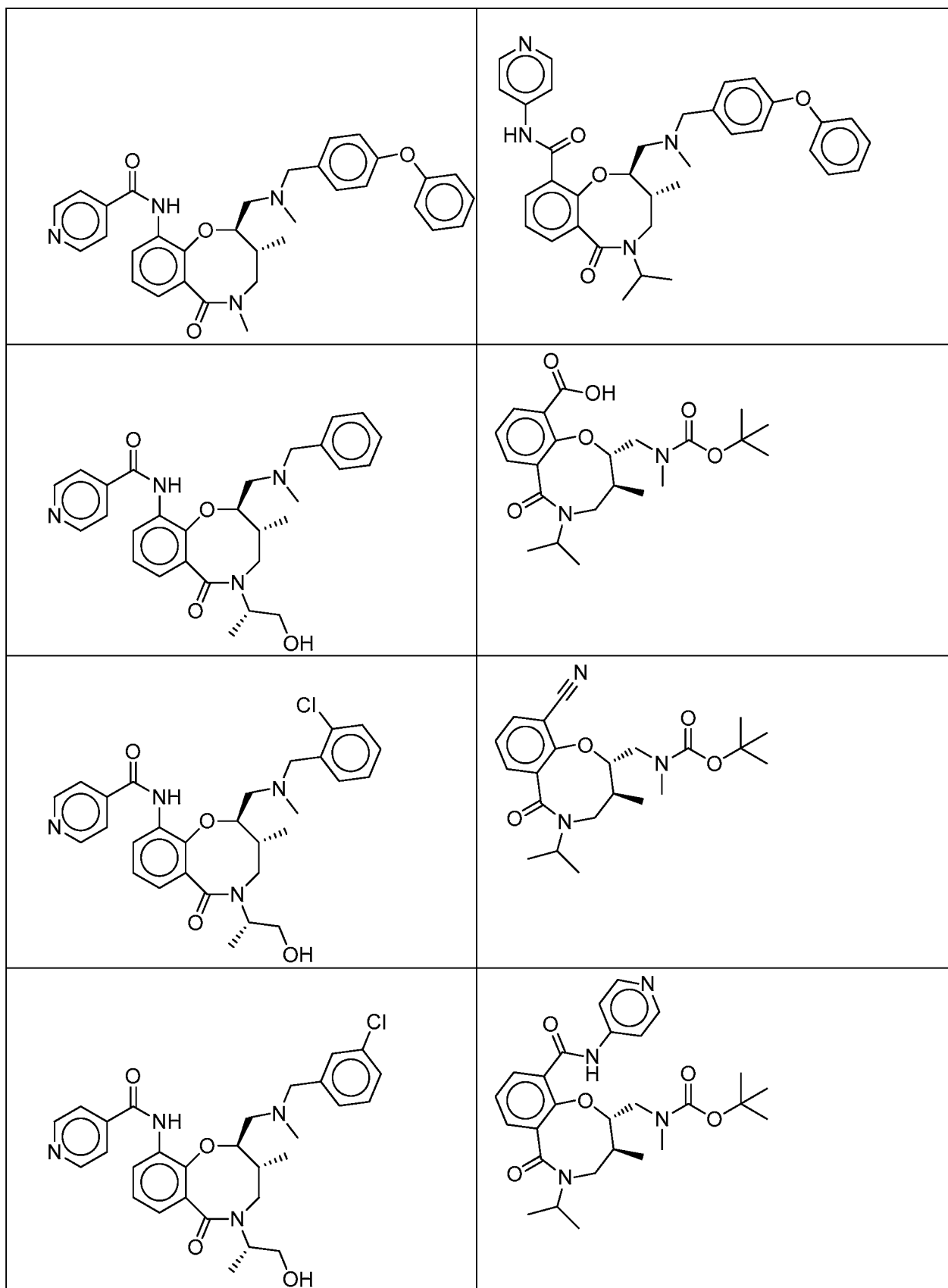
5

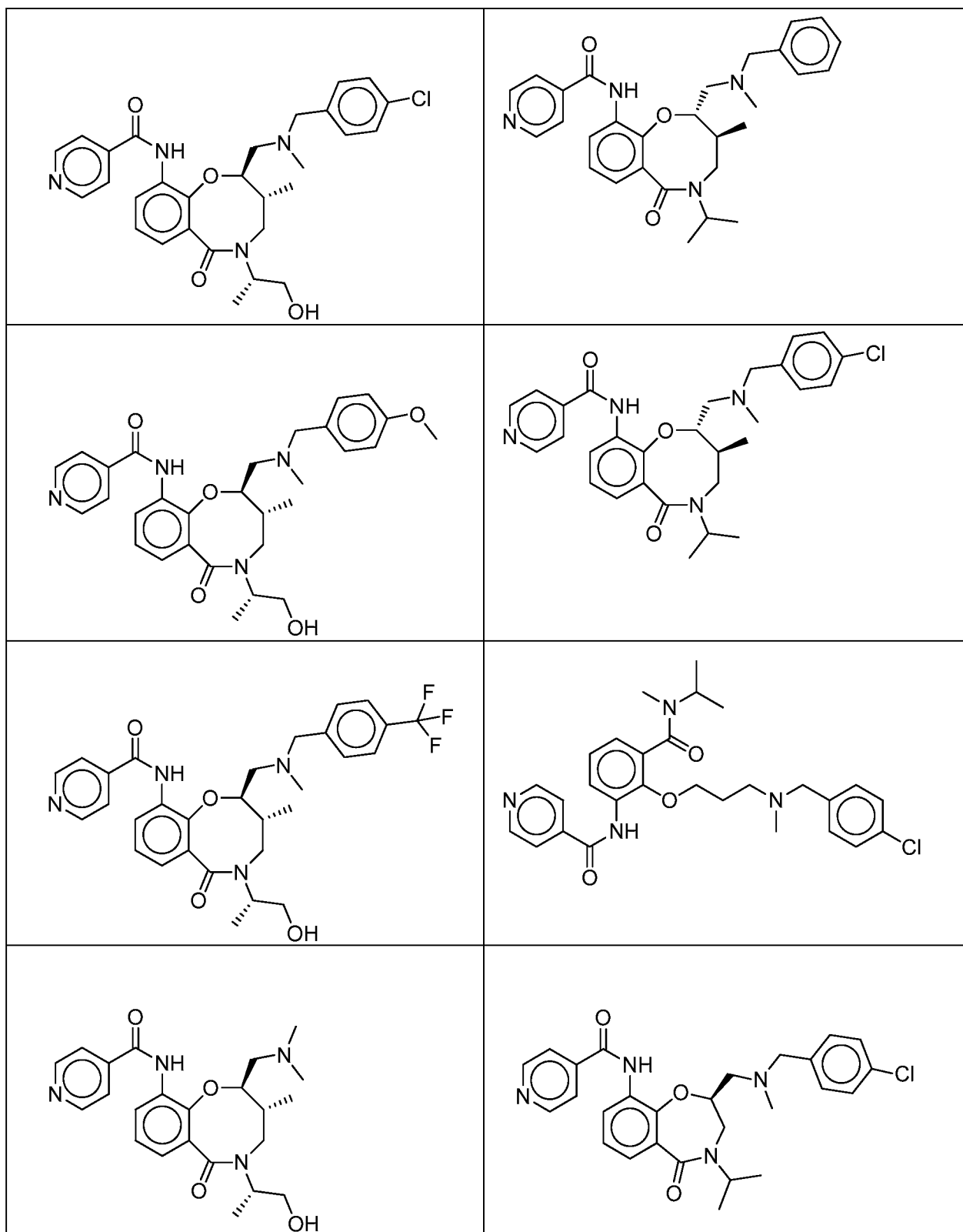
TABLE 1

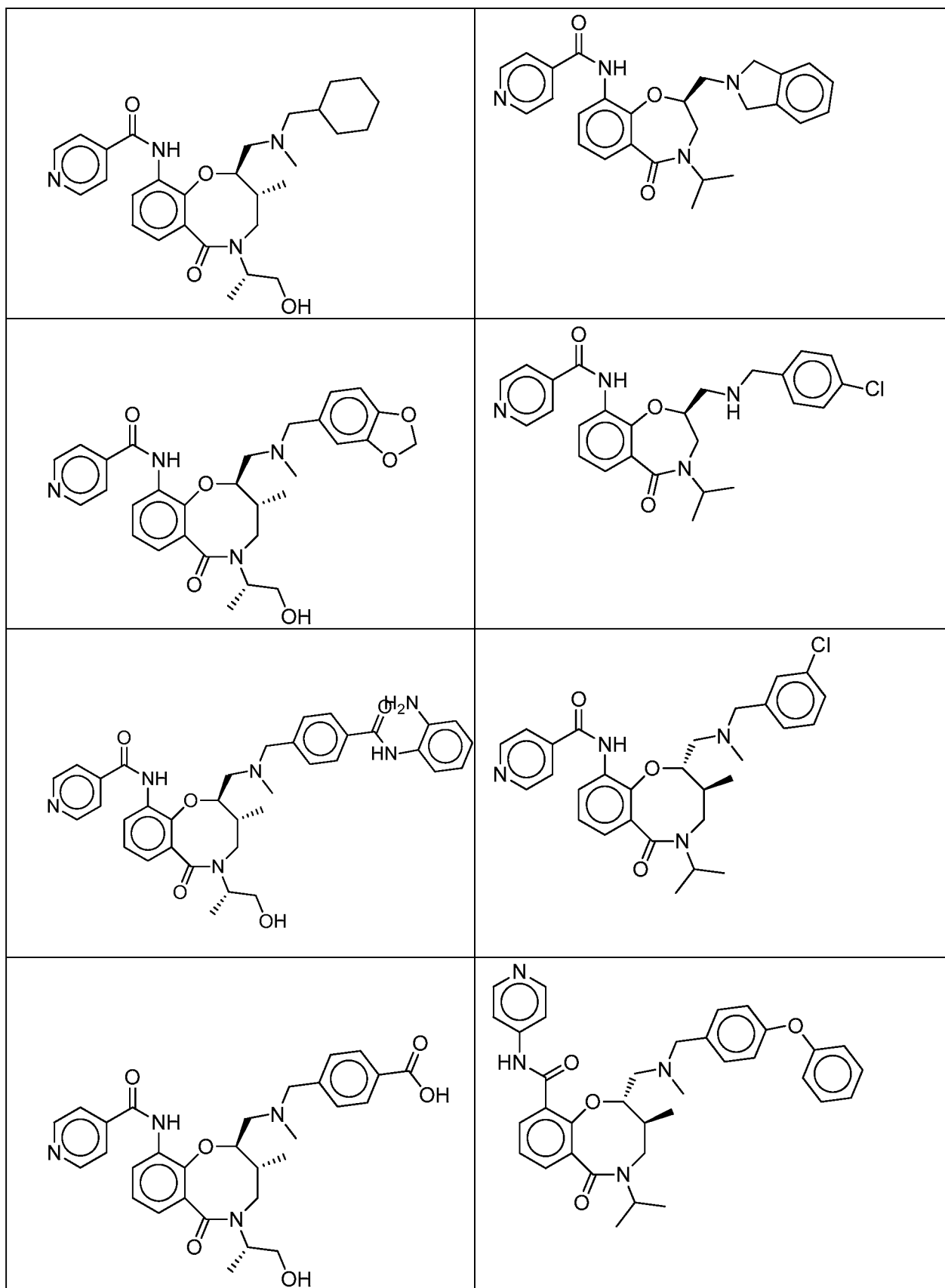
| Compound |  |
|----------|--|
|          |  |
|          |  |

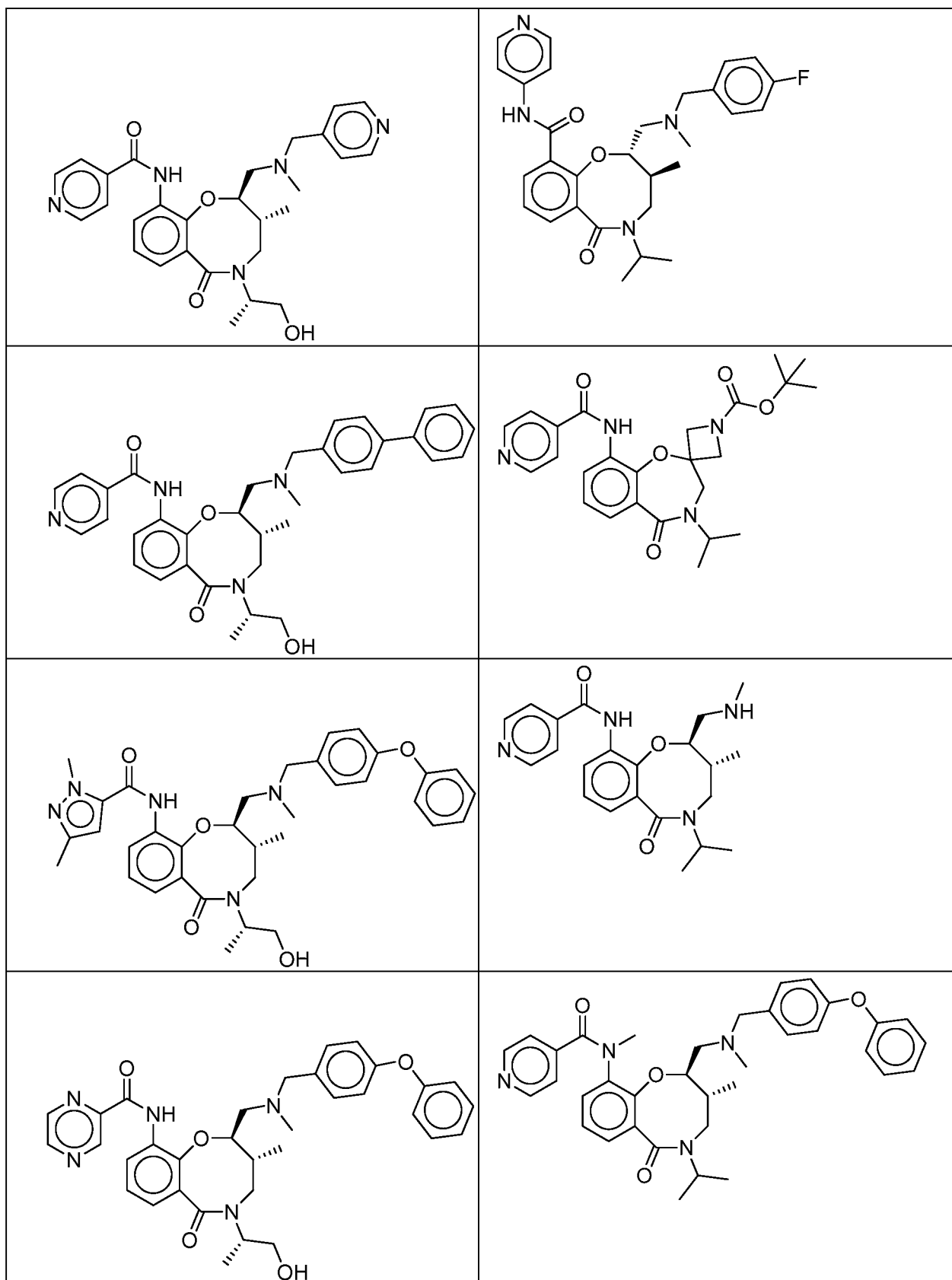


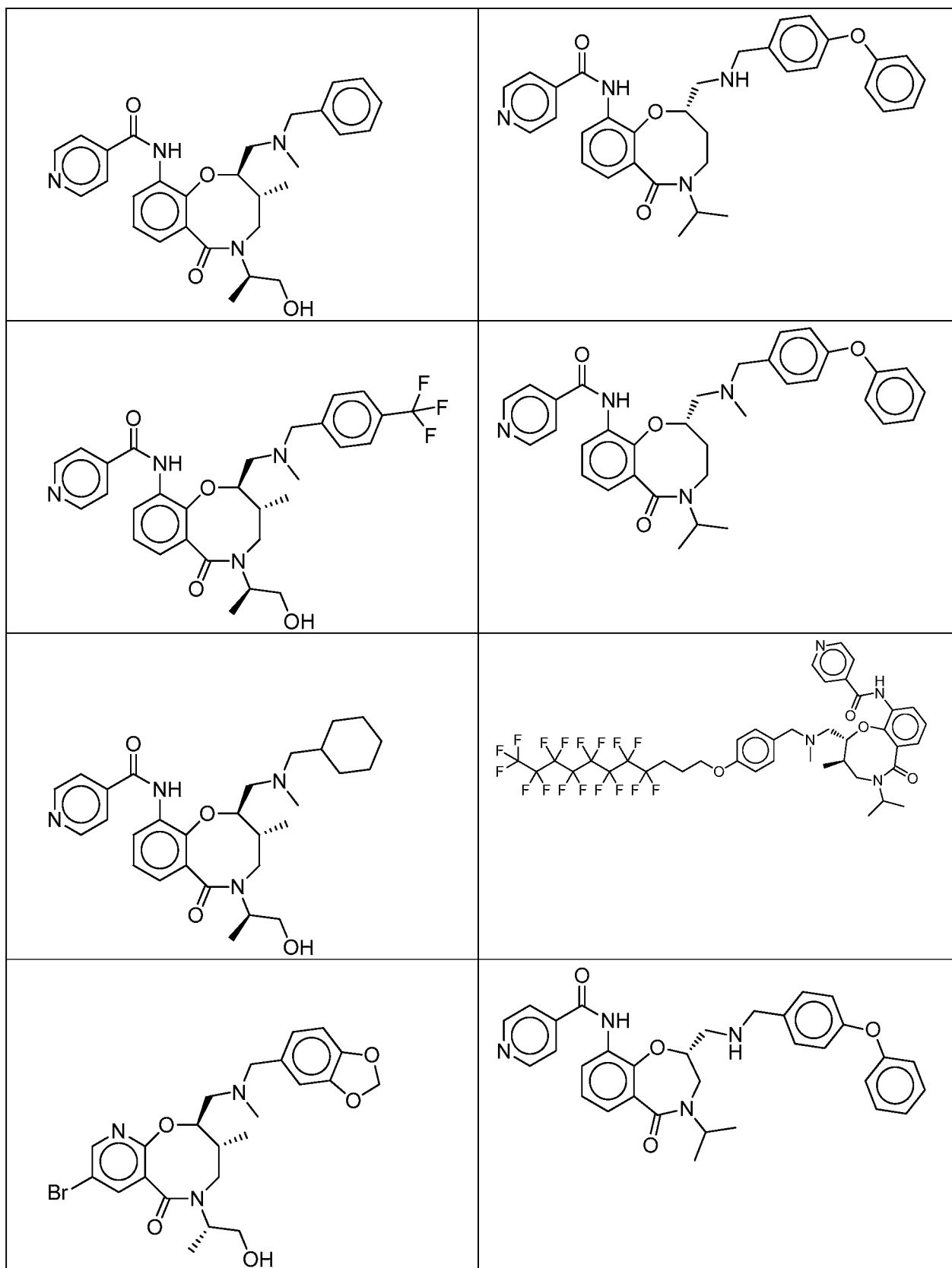


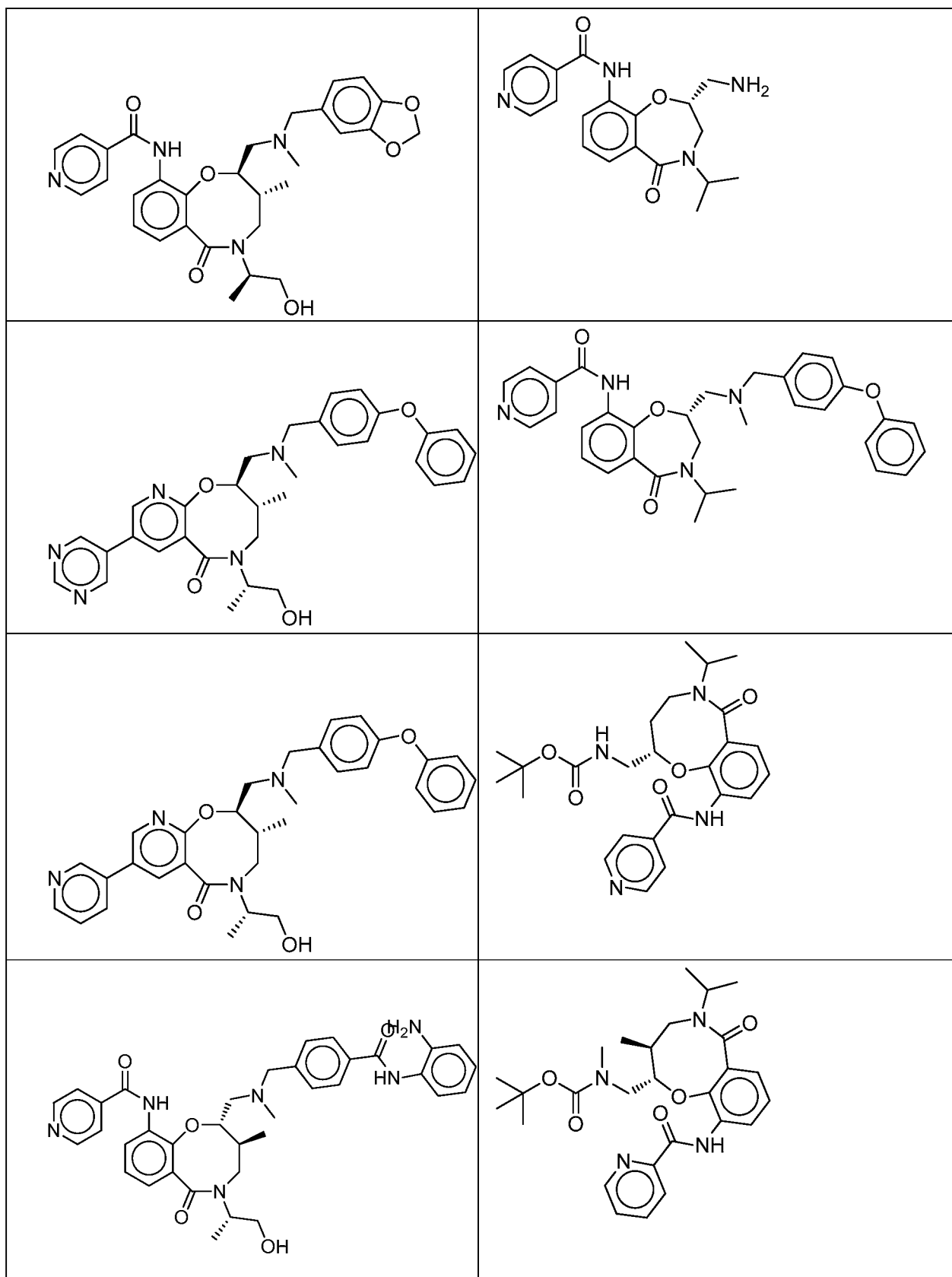


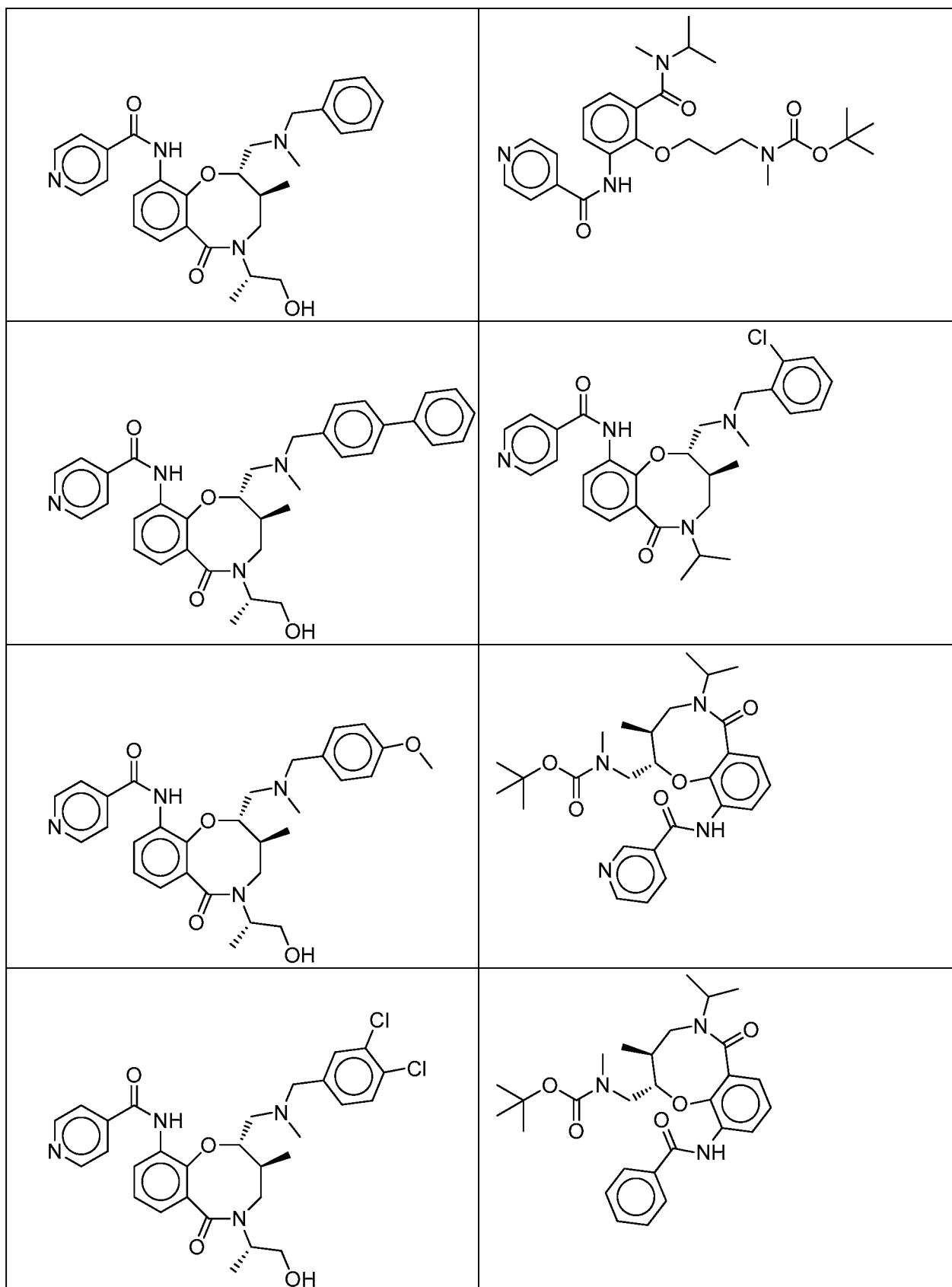


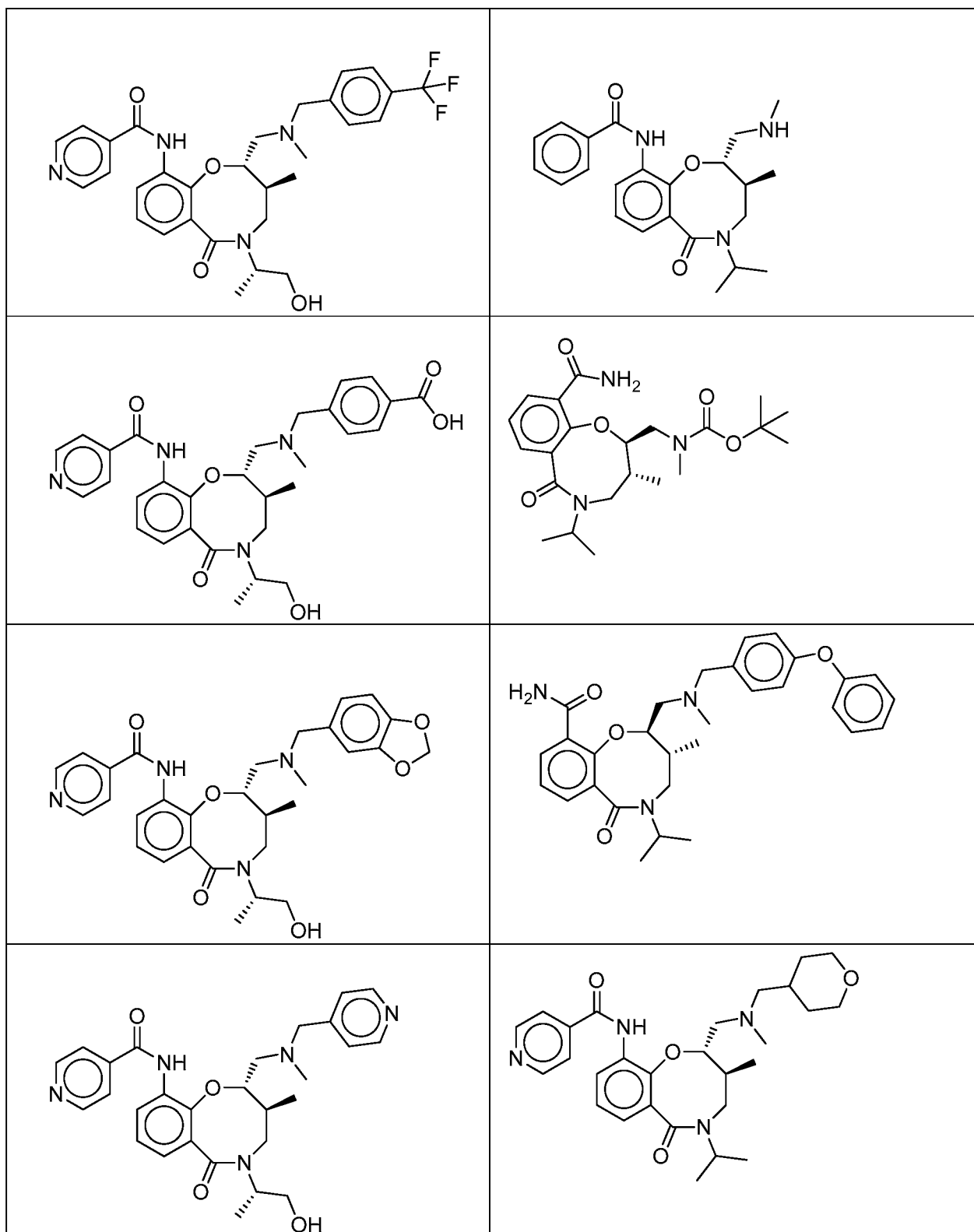


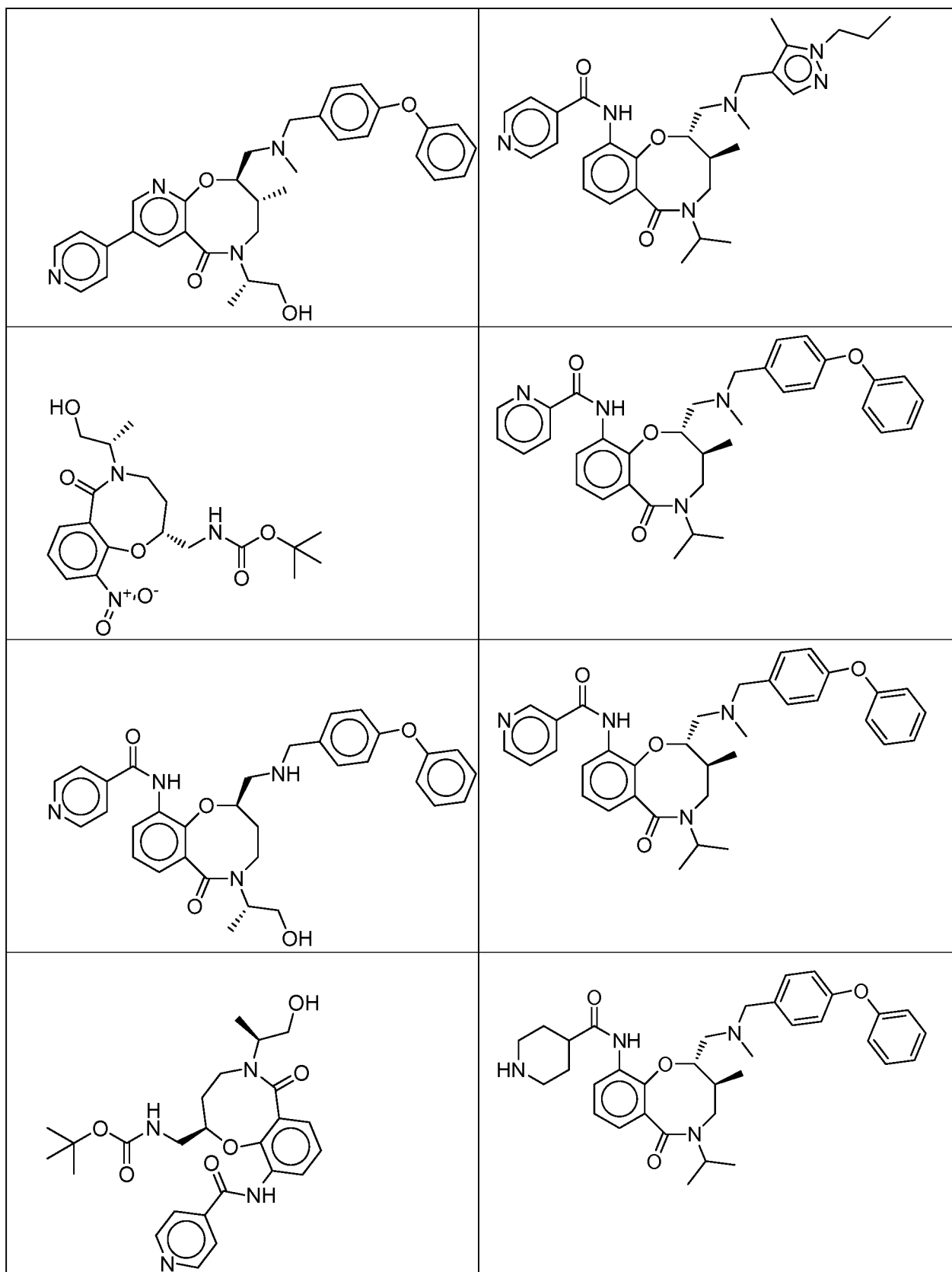


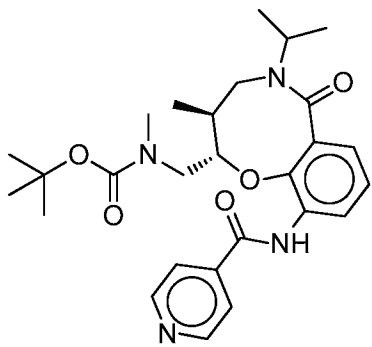
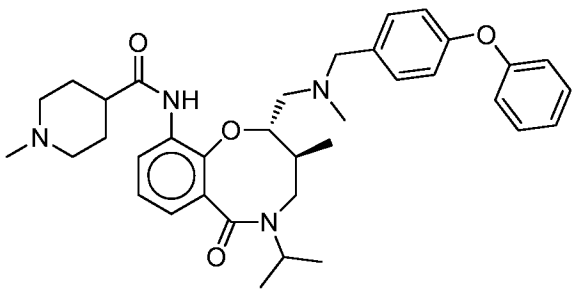
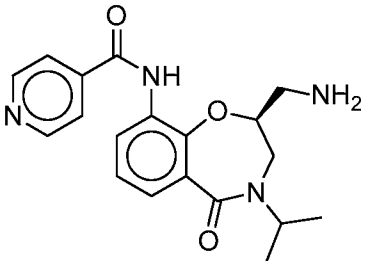
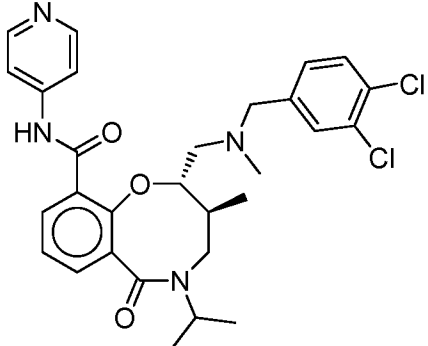
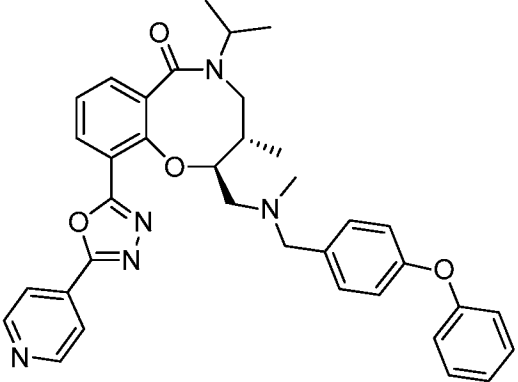
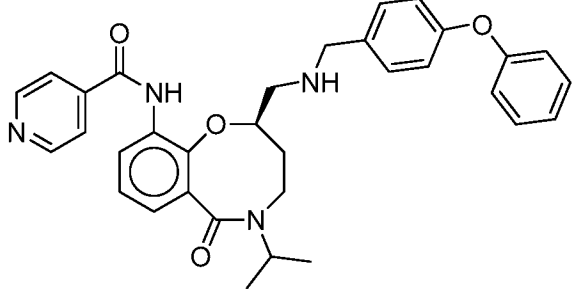
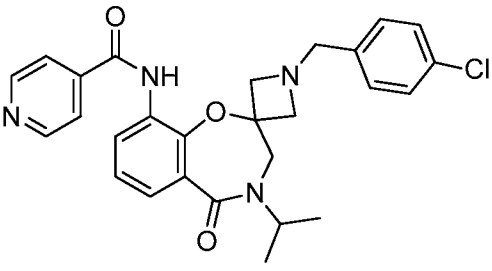
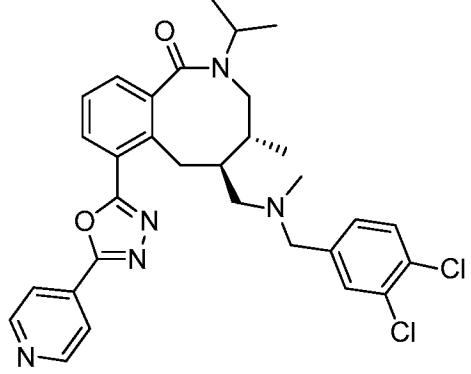










|                                                                                     |                                                                                      |
|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
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|  |  |
|  |  |

or a pharmaceutically acceptable salt thereof.

11. A composition comprising a compound according to any of claims 1-10 and a pharmaceutically acceptable carrier.

5 12. A method of treating a parasitic infection or a disease or disorder caused by a parasitic infection comprising the step of administering a compound according to any of claims 1-10 to a subject in need thereof.

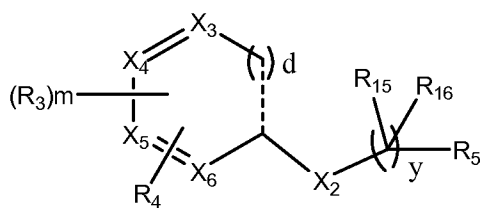
13. The method according to claim 12, wherein said parasitic infection, disease or disorder  
10 is caused by Trypanosomatids infection or Plasmodium falciparum infection.

14. The method according to claim 12, wherein said disease is South American trypanosomiasis (Chagas disease) or Malaria.

15 15. A method of treating a disease or disorder caused by *Trypanosoma cruzi* comprising the step of administering a compound according to any of claims 1-10 to a patient in need thereof.

16. A method of manufacturing a medicament comprising the step of adding a compound  
20 according to any of claims 1-10 to a pharmaceutical composition for the treatment of a parasitic infection.

17. A compound of Formula V or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula V

wherein

m is 0, 1, 2, 3 or 4;

d is 0, 1, 2 or 3;

30 y is 0, 1, 2 or 3;

$X_2$  is O, S,  $S(O)_2$ ,  $NR_{10}$ ,  $C(O)$ ,  $CH_2$ ;

each  $X_3$ ,  $X_4$ ,  $X_5$  and  $X_6$  is independently selected from  $CR_{14}$  and N;

Wherein  $R_{14}$  is selected from -CN,  $-S(O)_2R_{10}$ , hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

each  $R_3$ ,  $R_{15}$  and  $R_{16}$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl - $OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ , acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively  $R_{15}$  and  $R_{16}$  together may form an optionally substituted three, four, five, six or seven membered ring;

wherein each  $R_{10}$  and  $R_{11}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{10}$  and  $R_{11}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring;

$R_4$  is selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl,  $-OR_{10}$ ,  $-SR_{10}$ ,  $-NR_{10}R_{11}$ ,  $-C(O)R_{10}$ ,  $-C(O)OR_{10}$ ,  $-C(O)NR_{10}R_{11}$ ,  $-N(R_{10})C(O)R_{11}$ ,  $-CF_3$ ,  $-CN$ ,  $-NO_2$ ,  $-N_3$ ; and,

$R_5$  is  $-G_1-X_{10}$ ;

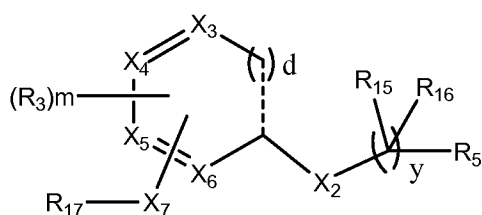
wherein  $G_1$  is absent,  $C_1-C_{12}$ -alkyl, substituted  $C_1-C_{12}$ -alkyl,  $C_2-C_{12}$ -alkenyl, substituted  $C_2-C_{12}$ -alkenyl,  $C_2-C_{12}$ -alkynyl or substituted  $C_2-C_{12}$ -alkynyl; and,  $X_{10}$  is  $-NR_{12}R_{13}$ ,  $-OR_{12}$ ,  $-SR_{12}$ ,  $-C(O)R_{12}$ ,  $-C(O)OR_{12}$ ,  $-C(O)NR_{12}R_{13}$ , -

$N(R_{12})C(O)R_{13}$ ,  $-S(O)R_{12}$  or  $S(O)_2R_{12}$ ;

wherein each  $R_{12}$  and  $R_{13}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{12}$  and  $R_{13}$  together with the atoms to which

they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

18. A compound of Formula VA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VA

wherein

m is 0, 1, 2, 3 or 4;

d is 0, 1, 2 or 3;

y is 0, 1, 2 or 3;

X<sub>2</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), CH<sub>2</sub>;

X<sub>7</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

each X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub> and X<sub>6</sub> is independently selected from CR<sub>14</sub> and N;

wherein R<sub>14</sub> is selected from -CN, -S(O)<sub>2</sub>R<sub>10</sub>, hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, alkylhydroxy, substituted alkylhydroxy, alkylamino, substituted alkylamino, alkylthio, substituted alkylthio, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl;

each R<sub>3</sub>, R<sub>15</sub> and R<sub>16</sub> is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring;

wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl,

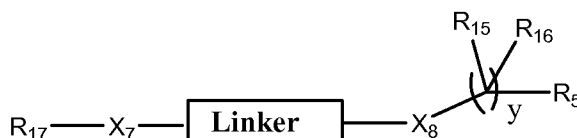
aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{10}$  and  $R_{11}$  together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring;

5  $R_{17}$  is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and,  $R_5$  is  $-G_1-X_{10}$ ;

wherein  $G_1$  is absent,  $C_1$ - $C_{12}$ -alkyl, substituted  $C_1$ - $C_{12}$ -alkyl,  $C_2$ - $C_{12}$ -alkenyl, substituted  $C_2$ - $C_{12}$ -alkenyl,  $C_2$ - $C_{12}$ -alkynyl or substituted  $C_2$ - $C_{12}$ -alkynyl; and,  $X_{10}$  is  $-NR_{12}R_{13}$ ,  $-OR_{12}$ ,  $-SR_{12}$ ,  $-C(O)R_{12}$ ,  $-C(O)OR_{12}$ ,  $-C(O)NR_{12}R_{13}$ , -  
10  $N(R_{12})C(O)R_{13}$ ,  $-S(O)R_{12}$  or  $S(O)_2R_{12}$ ;

wherein each  $R_{12}$  and  $R_{13}$  is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of  $R_{12}$  and  $R_{13}$  together with the atoms to which they are attached and any intervening atoms may form an additional  
15 optionally substituted, 3, 4, 5, 6 or 7 membered ring.

19. A compound of Formula VI or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VI

wherein

$y$  is 0, 1, 2 or 3;

$X_8$  is absent, O, S,  $S(O)_2$ ,  $NR_{10}$ ,  $C(O)$ ,  $C(O)NR_{10}$ ,  $C(S)$ ,  $C(S)NR_{10}$ ,  $C(R_{10})(R_{11})$ ;

25  $X_7$  is O, S,  $S(O)_2$ ,  $NR_{10}$ ,  $C(O)$ ,  $C(O)NR_{10}$ ,  $C(S)$ ,  $C(S)NR_{10}$ ,  $C(R_{10})(R_{11})$ ;

Linker is a bivalent aliphatic, substituted aliphatic, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl group;

30 each  $R_{15}$  and  $R_{16}$  is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted

aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring;

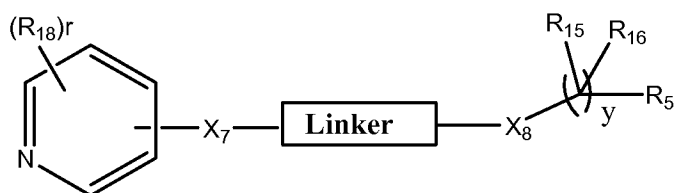
wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring;

R<sub>17</sub> is selected from aryl, substituted aryl, heteroaryl and substituted heteroaryl; and, R<sub>5</sub> is -G<sub>1</sub>-X<sub>10</sub>;

wherein G<sub>1</sub> is absent, C<sub>1</sub>-C<sub>12</sub>-alkyl, substituted C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenyl, C<sub>2</sub>-C<sub>12</sub>-alkynyl or substituted C<sub>2</sub>-C<sub>12</sub>-alkynyl; and, X<sub>10</sub> is -NR<sub>12</sub>R<sub>13</sub>, -OR<sub>12</sub>, -SR<sub>12</sub>, -C(O)R<sub>12</sub>, -C(O)OR<sub>12</sub>, -C(O)NR<sub>12</sub>R<sub>13</sub>, -N(R<sub>12</sub>)C(O)R<sub>13</sub>, -S(O)R<sub>12</sub> or S(O)<sub>2</sub>R<sub>12</sub>;

wherein each R<sub>12</sub> and R<sub>13</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>12</sub> and R<sub>13</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

20. A compound of Formula VIA or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VIA

wherein

y is 0, 1, 2 or 3;

r is 0, 1, 2 or 3;

X<sub>8</sub> is absent, O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

X<sub>7</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

5 Linker is a bivalent aliphatic, substituted aliphatic, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl group;

each R<sub>15</sub>, R<sub>16</sub> and R<sub>18</sub> is independently selected from hydrogen, halogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring;

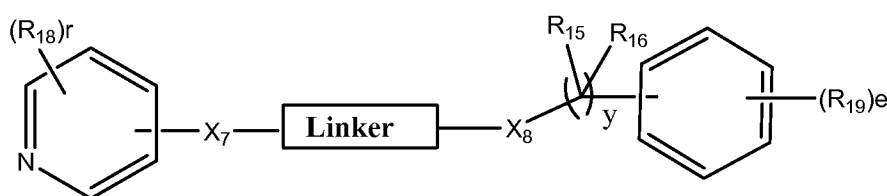
wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring; and,

R<sub>5</sub> is -G<sub>1</sub>-X<sub>10</sub>;

wherein G<sub>1</sub> is absent, C<sub>1</sub>-C<sub>12</sub>-alkyl, substituted C<sub>1</sub>-C<sub>12</sub>-alkyl, C<sub>2</sub>-C<sub>12</sub>-alkenyl, substituted C<sub>2</sub>-C<sub>12</sub>-alkenyl, C<sub>2</sub>-C<sub>12</sub>-alkynyl or substituted C<sub>2</sub>-C<sub>12</sub>-alkynyl; and, X<sub>10</sub> is -NR<sub>12</sub>R<sub>13</sub>, -OR<sub>12</sub>, -SR<sub>12</sub>, -C(O)R<sub>12</sub>, -C(O)OR<sub>12</sub>, -C(O)NR<sub>12</sub>R<sub>13</sub>, -N(R<sub>12</sub>)C(O)R<sub>13</sub>, -S(O)R<sub>12</sub> or S(O)<sub>2</sub>R<sub>12</sub>;

wherein each R<sub>12</sub> and R<sub>13</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>12</sub> and R<sub>13</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

21. A compound of Formula VIB or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



Formula VIB

5 wherein

y is 0, 1, 2 or 3;

r is 0, 1, 2 or 3;

e is 0, 1, 2 or 3;

X<sub>8</sub> is absent, O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

10 X<sub>7</sub> is O, S, S(O)<sub>2</sub>, NR<sub>10</sub>, C(O), C(O)NR<sub>10</sub>, C(S), C(S)NR<sub>10</sub>, C(R<sub>10</sub>)(R<sub>11</sub>);

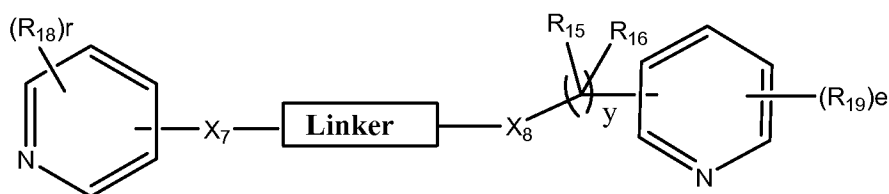
Linker is a bivalent aliphatic, substituted aliphatic, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl group;

15 each R<sub>15</sub>, R<sub>16</sub>, R<sub>18</sub> and R<sub>19</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aliphatic, substituted aliphatic, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl -OR<sub>10</sub>, -SR<sub>10</sub>, -NR<sub>10</sub>R<sub>11</sub>, -C(O)R<sub>10</sub>, -C(O)OR<sub>10</sub>, -C(O)NR<sub>10</sub>R<sub>11</sub>, -N(R<sub>10</sub>)C(O)R<sub>11</sub>, -CF<sub>3</sub>, -CN, -NO<sub>2</sub>, -N<sub>3</sub>, acyl, alkoxy, substituted alkoxy, alkylamino, substituted alkylamino, dialkylamino, substituted dialkylamino, alkylthio or substituted alkylthio; alternatively R<sub>15</sub> and R<sub>16</sub> together may form an optionally substituted three, four, five, six or seven membered ring; and,

wherein each R<sub>10</sub> and R<sub>11</sub> is independently selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl,

25 aliphatic, substituted aliphatic, aryl and substituted aryl; alternatively two of R<sub>10</sub> and R<sub>11</sub> together with the atoms to which they are attached and any intervening atoms may form an additional optionally substituted, 3, 4, 5, 6 or 7 membered ring.

22. A compound of Formula VIC or a pharmaceutically acceptable ester, salt, prodrug or metabolite thereof;



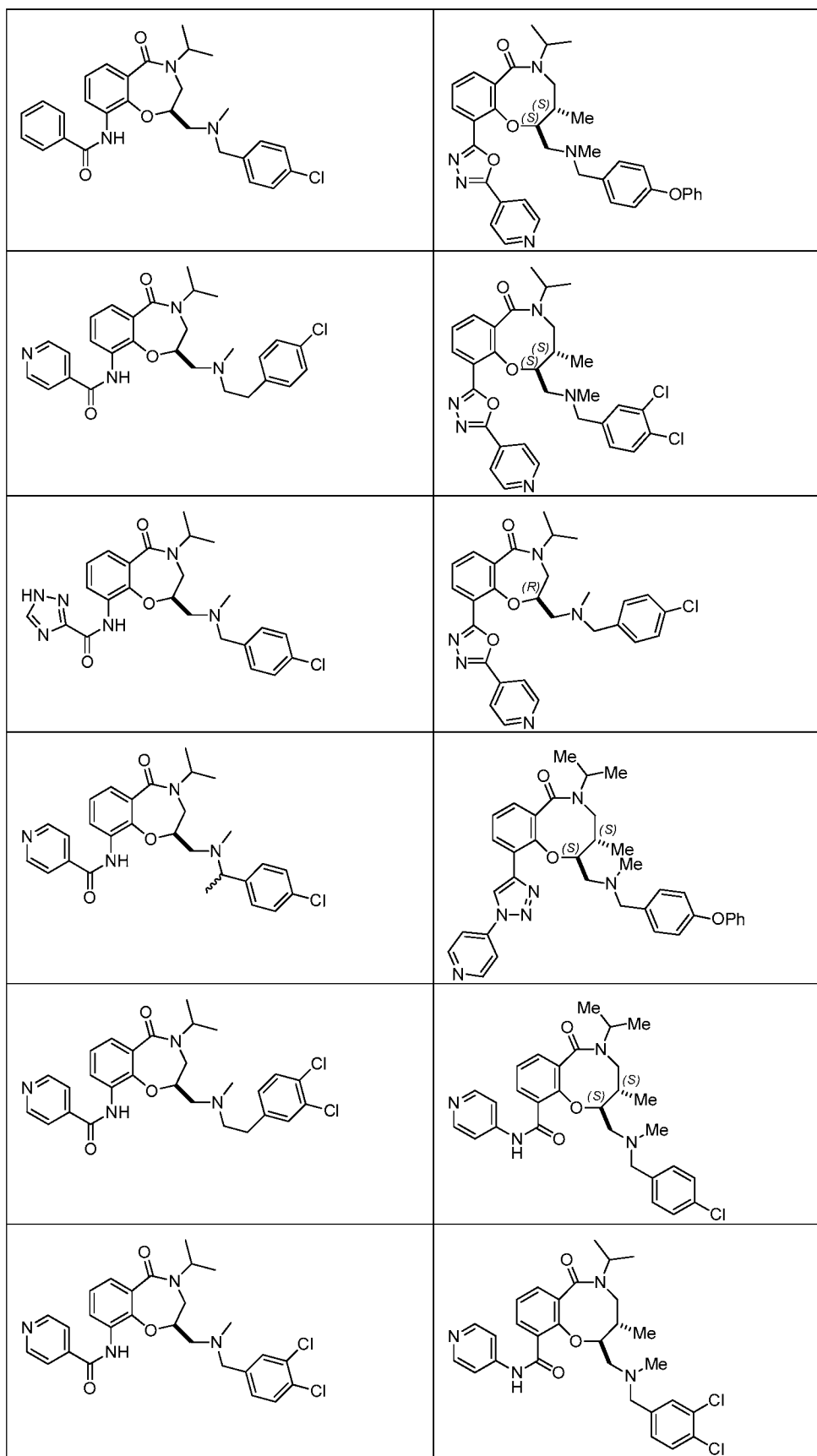
Formula VIC

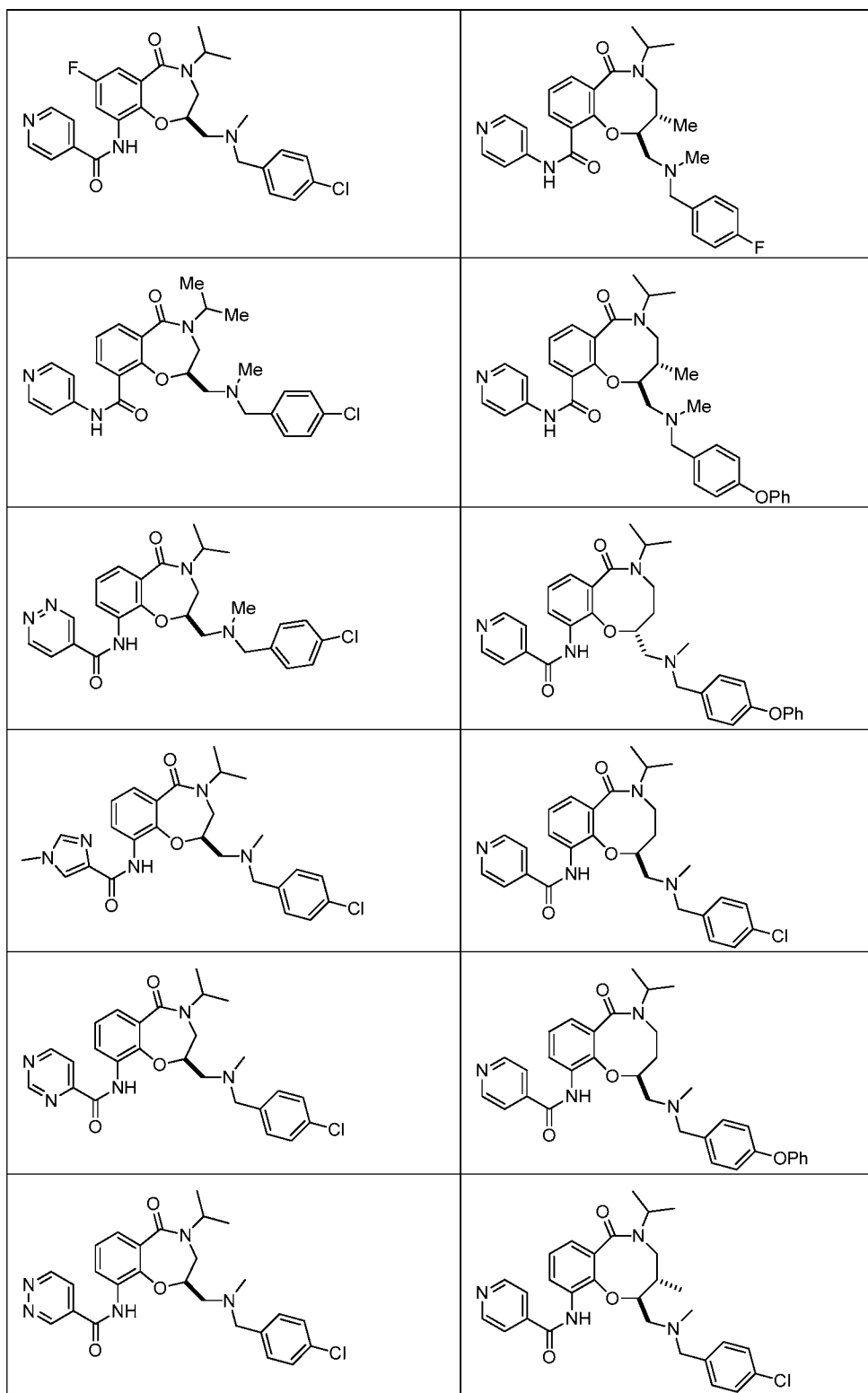
5 wherein,  $r$ ,  $y$ ,  $e$ ,  $X_7$ ,  $X_8$ ,  $R_{15}$ ,  $R_{16}$ ,  $R_{18}$ ,  $R_{19}$  and Linker are as defined in claim 21.

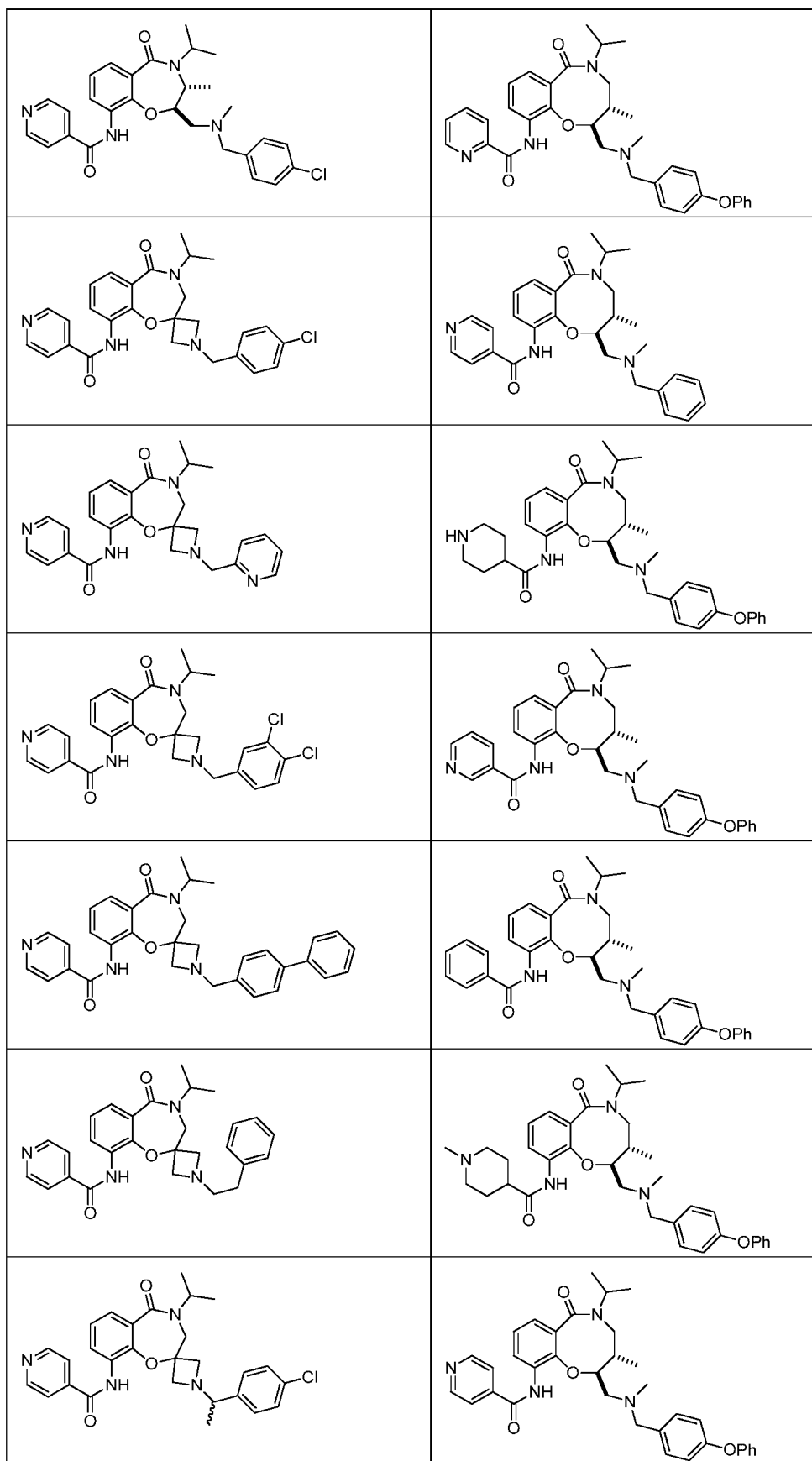
23. A compound of Table 3 or a pharmaceutically acceptable salt thereof:

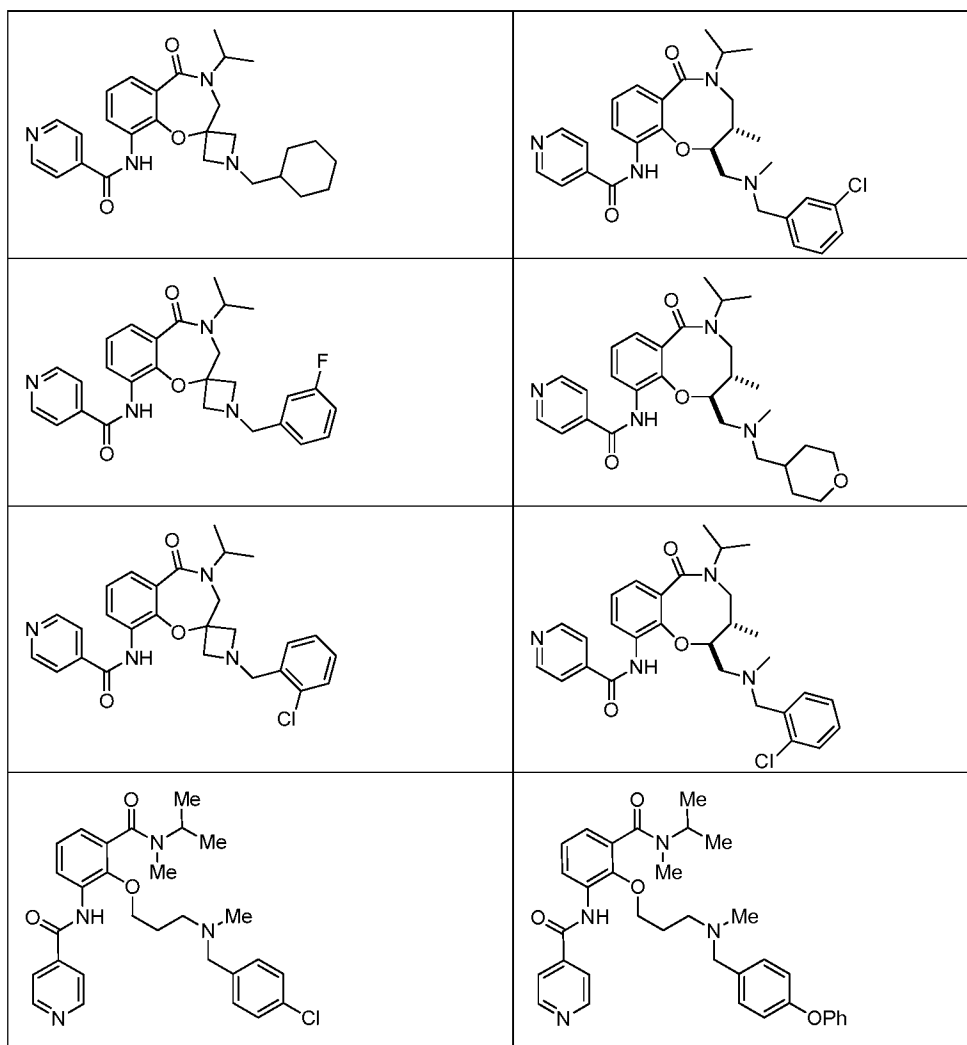
TABLE 3

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24. A composition comprising a compound according to any of claims 17-23 and a pharmaceutically acceptable carrier.

5

25. A method of treating a parasitic infection or a disease or disorder caused by a parasitic infection comprising the step of administering a compound according to any of claims 17-23 to a subject in need thereof.

10

26. The method according to claim 25, wherein said parasitic infection, disease or disorder is caused by Trypanosomatids infection or Plasmodium falciparum infection.

27. The method according to claim 25, wherein said disease is South American trypanosomiasis (Chagas disease) or Malaria.

28. A method of treating a disease or disorder caused by *Trypanosoma cruzi* comprising the step of administering a compound according to any of claims 17-23 to a patient in need thereof.

5

29. A method of manufacturing a medicament comprising the step of adding a compound according to any of claims 17-23 to a pharmaceutical composition for the treatment of a parasitic infection.

10 30. A compound according to any of claims 1-10 or 17-23, wherein  $R_{12}$  is selected from Table A.

31. A compound according to any of claims 1-10 or 17-23, wherein  $G_2$  is selected from Table B.

15

32. A compound according to any of claims 1-10 or 17-23, wherein  $G_2$  is selected from Table B2.

20 33. A compound according to any of claims 1-10 or 17-23, wherein  $R_1$  is selected from Table C.

34. A compound according to any of claims 19-22, wherein the Linker is selected from Table D.