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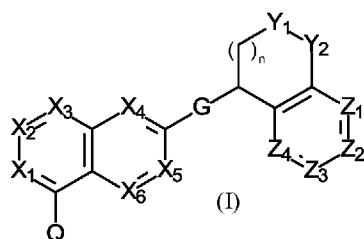
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(54) Title: BICYCLIC DERIVATIVES



(57) Abstract: The present invention provides compounds of formula (I): (I) which are useful in the control of endoparasites, for example heartworms, in warm-blooded animals.



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## BICYCLIC DERIVATIVES

### FIELD

The present invention relates to medicinal chemistry, pharmacology, and veterinary and  
5 human medicine. More particularly, the present invention relates to compounds of  
formula (I) and their use in the control of endoparasites, for example heartworms, in  
warm-blooded animals.

### BACKGROUND

10 Heartworm (*Dirofilaria immitis*) is a parasitic roundworm that is spread from host to host  
through the bites of mosquitoes. The lifecycle starts when a female mosquito takes a  
blood meal from an infected host. The mosquito ingests immature heartworms which then  
molt to the infective larvae stage and travel to the mosquitoes' mouth parts. The mosquito  
then feeds on a susceptible host, such as a dog or cat, depositing the infective larvae. The  
15 larvae then molt to the next larval stage in the new host and then migrate through the  
body, eventually ending up in the blood vessels. As the larvae migrate through the tissues  
they molt into juvenile adults. The juvenile adults eventually move into the blood vessels  
of the lungs where they mature into sexually active adults. The adult heartworms then  
breed and release immature heartworms completing the cycle. Heartworm infection may  
20 result in serious disease for the host.

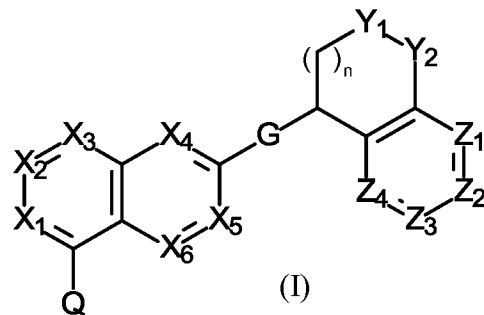
Adult heartworm infections may be treated with arsenic-based compounds; the treatment  
is time consuming, cumbersome, and often only partly successful. Accordingly, treatment  
is focused on the control of heartworm infection. Heartworm control is currently  
25 performed exclusively by year round periodical administration of drugs. Typical  
treatments include macrocyclic lactones such as ivermectin, moxidectin, and milbemycin  
oxime. Unfortunately, developing resistance of *Dirofilaria immitis* to macrocyclic  
lactones has been observed. Accordingly, there is a need for new compounds which  
effectively control heartworm infections either by way of prophylaxis or by directly  
30 killing heartworms. Certain treatments of endoparasites are described in WO

2017/178416, WO 2018/087036, WO 2018/197401, WO 2019/025341, and WO 2019/002132.

### SUMMARY

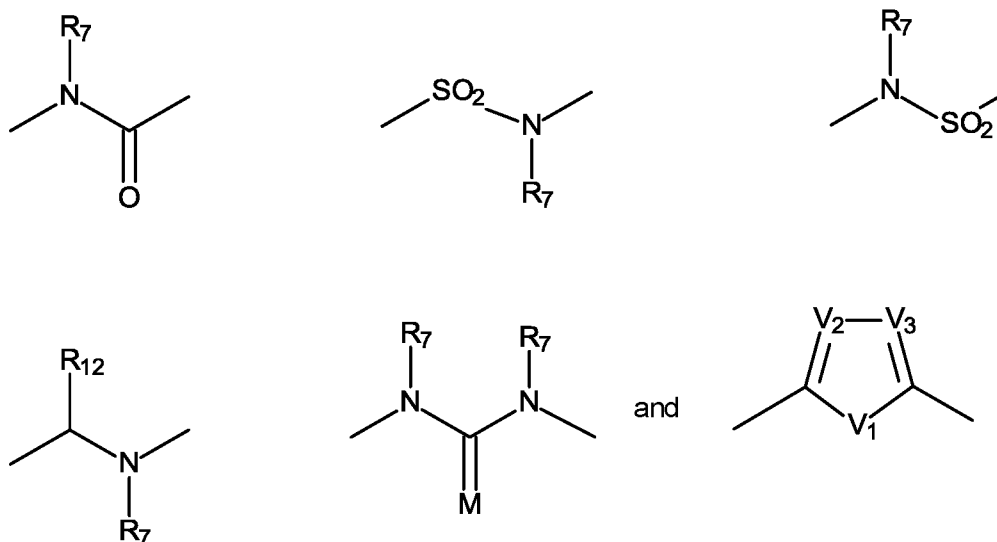
- 5 The present invention provides compounds of formula (I) which effectively treat and/or control endoparasites (e.g., heartworm) in warm-blooded animals.

In one embodiment, the present invention provides a compound of formula (I):



- 10 wherein  
 n is 0 or 1;  
 X<sub>1</sub> is selected from the group consisting of N and CR<sub>1</sub>;  
 X<sub>2</sub> is selected from the group consisting of N and CR<sub>2</sub>;  
 X<sub>3</sub> is selected from the group consisting of N and CR<sub>3</sub>;  
 15 X<sub>4</sub> is selected from the group consisting of N and CR<sub>4</sub>;  
 X<sub>5</sub> is selected from the group consisting of N and CR<sub>5</sub>;  
 X<sub>6</sub> is selected from the group consisting of N and CR<sub>6</sub>;  
 G is the group

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;

$Y_1$  is selected from the group consisting of  $CR_8R_9$ , O, S, and  $NR_{10}$ ;

$Y_2$  is selected from the group consisting of  $CR_8R_9$ , O, S, and  $NR_{10}$ ;

wherein at least one of the groups  $Y_1$  or  $Y_2$  is  $CR_8R_9$ ;

5  $Z_1$  is selected from the group consisting of N, O, S, and  $CR_{11}$ ;

$Z_2$  is selected from the group consisting of nil, N, and  $CR_{11}$ ;

$Z_3$  is selected from the group consisting of nil, N and  $CR_{11}$ ;

$Z_4$  is selected from the group consisting of N, O, S, and  $CR_{11}$ ;

wherein no more than 2 of  $Z_1$ ,  $Z_2$ ,  $Z_3$ , and  $Z_4$  are N and wherein only one of  $Z_1$  and

10  $Z_4$  is O or S,  $Z_2$  is nil only when  $Z_1$  is O or S, and  $Z_3$  is nil only when  $Z_4$  is O or S;

$R_1$  is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, - $SC_{1-C_4}$  alkyl, - $S(O)(C_{1-C_4}$  alkyl, - $S(O)_2(C_{1-C_4}$  alkyl, cyano,  $C_{1-C_4}$  alkyl,  $C_{1-C_4}$  halogenoalkyl,  $C_{1-C_4}$ -alkoxy, - $B(OR_{16})(OR_{17})$  wherein  $R_{16}$  is, each time taken, selected from the group

15 consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl,  $R_{17}$  is, each time taken, selected from the group consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl, or  $R_{16}$  and  $R_{17}$  together with the oxygen atoms to which they are attached form a 5- to 7-membered ring which is optionally substituted with 1 to 4  $C_{1-C_4}$  alkyl; - $NH_2$ , - $NH(C_{1-C_4}$  alkyl), and - $N(C_{1-C_4}$  alkyl) $_2$ ;

20  $R_2$  is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, - $SC_{1-C_4}$  alkyl, - $S(O)(C_{1-C_4}$  alkyl, - $S(O)_2(C_{1-C_4}$  alkyl, cyano,  $C_{1-C_4}$  alkyl,  $C_{1-C_4}$  halogenoalkyl,  $C_{1-C_4}$ -alkoxy, - $B(OR_{16})(OR_{17})$  wherein  $R_{16}$  is, each time taken, selected from the group

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consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7-membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

R<sub>3</sub> is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)(C<sub>1</sub>-C<sub>4</sub> alkyl), -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -B(OR<sub>16</sub>)(OR<sub>17</sub>) wherein R<sub>16</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7-membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

R<sub>4</sub> is selected from the group consisting of halogen, cyano, -CHO, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy substituted-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl optionally substituted with 1 to 5 halogen atoms, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NH(4- to 7-membered heterocycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(4- to 7-membered heterocycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkoxy), -C(O)NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -B(OR<sub>16</sub>)(OR<sub>17</sub>) wherein R<sub>16</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7- membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; 6- or 10 membered aryl; and a monocyclic heterocycle selected from the group of 4- to 7-membered heterocycloalkyl, 5-membered heteroaryl having at least one nitrogen atom via which the 5-membered heteroaryl ring is connected to the rest of the molecule; 6-membered heteroaryl having at least one nitrogen atom; each of the aryl,

heterocycloalkyl, and heteroaryl ring in R<sub>4</sub> is optionally substituted with 1, 2 or 3

- substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; and wherein each C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl and C<sub>1</sub>-C<sub>4</sub> alkoxy in R<sub>4</sub> may be optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, cyano, carboxyl, carbamoyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -C(O)NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, and C<sub>1</sub>-C<sub>4</sub> alkoxy;
- 5 R<sub>5</sub> is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)(C<sub>1</sub>-C<sub>4</sub> alkyl), -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -B(OR<sub>16</sub>)(OR<sub>17</sub>) wherein R<sub>16</sub> is, each time taken, selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken, selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7-
- 10 membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- R<sub>6</sub> is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)(C<sub>1</sub>-C<sub>4</sub> alkyl), -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -B(OR<sub>16</sub>)(OR<sub>17</sub>) wherein R<sub>16</sub> is, each time taken, selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken, selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7-
- 15 membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;
- 20 R<sub>7</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted with 1 to 5 halogen atoms, -C(H)O, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, and C<sub>1</sub>-C<sub>4</sub>-alkoxy;
- R<sub>8</sub> is, each time selected, independently selected from the group consisting of hydrogen, fluoro, and C<sub>1</sub>-C<sub>4</sub> alkyl;
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R<sub>9</sub> is, each time selected, independently selected from the group consisting of hydrogen, fluoro, and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>10</sub> is selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>11</sub> is, each time selected, independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>; and

Q is selected from the group consisting of 6- or 10 membered aryl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, wherein the 6- or 10 membered aryl is optionally fused with a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the heterocycloalkyl are optionally substituted with 1, 2 or 3 substituents independently selected from the group halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heterocycloalkyl is, valency permitting, substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 substituents independently

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selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heterocycloalkyl is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; 6- or 10 membered aryloxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; 6- or 10 membered arylthio-oxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; and 5- to 10-membered heteroaryloxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl;

M is selected from the group consisting of N-R<sub>13</sub>, O, and S;

R<sub>13</sub> is selected from the group consisting of hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, and -NH<sub>2</sub>;

V<sub>1</sub> is selected from the group consisting of NR<sub>14</sub>, O, and S;

25 R<sub>14</sub> is hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

V<sub>2</sub> and V<sub>3</sub> are, independently, selected from the group consisting of CR<sub>15</sub> and N;

R<sub>15</sub> is selected from the group consisting of hydrogen, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

or a salt thereof.

30



In one embodiment, the present invention also provides compositions, comprising: a compound of formula (I) or a salt thereof and an acceptable excipient, the composition optionally further comprising at least one additional active compound.

- 5 In one embodiment, the present invention also provides a method for treating parasites, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.
- 10 In one embodiment, the present invention also provides a method for controlling parasites, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.
- 15 In one embodiment, the present invention also provides a method for treating or controlling parasites, comprising: contacting a subject's environment with an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.
- 20 Thus, the invention provides for the use of the compounds of the invention as a medicament, including for the manufacture of a medicament. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of formula (I) or a salt thereof for treating parasites. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of formula (I) or a salt thereof for  
25 controlling parasites.

The present invention also provides processes from making compounds of the invention and intermediates thereof.

**DETAILED DESCRIPTION**

The term “C<sub>1</sub>-C<sub>4</sub> alkyl” refers to a straight or branched alkyl chain having from one to four carbon atoms and includes methyl, ethyl, propyl, isopropyl, butyl, and the like.

5

The term “C<sub>1</sub>-C<sub>4</sub> halogenoalkyl” refers to a straight or branched alkyl chain having from one to four carbon atoms and 1 to 5 halogen and includes fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, 1,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, and the like.

10

The term “C<sub>2</sub>-C<sub>4</sub> alkenyl” refers to a straight or branched alkenyl chain having from two to four carbon atoms and one carbon-carbon double bond, and includes ethylene, propylene, iso-propylene, butylene, iso-butylene, sec-butylene, and the like.

15

The term “C<sub>2</sub>-C<sub>4</sub> alkynyl” refers to a straight or branched alkynyl chain having from two to four carbon atoms and one carbon-carbon triple bond, and includes acetylene, propargyl, and the like.

20

The term “C<sub>1</sub>-C<sub>4</sub> alkoxy” refers to a C<sub>1</sub>-C<sub>4</sub> alkyl attached through an oxygen atom and includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, and the like.

The term “C<sub>3</sub>-C<sub>6</sub> cycloalkyl” refers to an alkyl ring of three to six carbon atoms, and includes cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

25

The terms “halogen” and “halogeno” refers to a chloro, fluoro, bromo or iodo atom.

The term “C<sub>6</sub>- or C<sub>10</sub>- membered aryl” refers to phenyl or naphthyl.

30

The term “C<sub>6</sub>- or C<sub>10</sub>- membered aryloxy” refers to phenyl or naphthyl attached through an oxygen atom and includes phenoxy and naphthyloxy.

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The term “C<sub>6</sub>- or C<sub>10</sub>- membered arylthio-oxy” refers to phenyl or naphthyl attached through an sulfur atom and includes phenthio-oxy and naphtylthio-oxy. Further it is understood that the term “C<sub>6</sub>- or C<sub>10</sub>- membered arylthio-oxy” also encompasses in which the sulfur is the -SO<sub>2</sub>- and -S(O)-.

5

The term “4- to 7-membered heterocycloalkyl” refers to a 4 to 7 membered monocyclic saturated or partially (but not fully) unsaturated ring having one or two heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur and the ring optionally includes a carbonyl to form a lactam or lactone. It is understood that where sulfur is included that the sulfur may be either -S-, -SO-, or -SO<sub>2</sub>-. For example, but not limiting, the term includes azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, thiomorpholiny, oxetany, dioxolany, tetrahydropyrany, tetrahydrothiopyrany, tetrahydrofuryl, hexahydropyrimidiny, tetrahydropyrimidiny, dihydroimidazolyl, and the like.

15

The term “5-membered heteroaryl” refers to a five membered, monocyclic, fully unsaturated, ring with one to four carbon atoms and one to four heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. For example, but not limiting, the term includes furyl, thienyl, pyrrolyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, and the like. It is understood that a 5-membered heteroaryl can be attached as a substituent through a ring carbon or a ring nitrogen atom where such an attachment mode is available, for example for a pyrrolyl, imidazolyl, pyrazolyl, triazolyl, and the like.

25 The term “6-membered heteroaryl” refers to a six membered, monocyclic, fully unsaturated ring with one to five carbon atoms and one or more, typically one to four, heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. For example, but not limiting, the term includes pyraziny, pyrazolyl, pyridaziny, pyridyl, pyrimidyl, and the like. It is understood that a 6-membered heteroaryl can be attached as a substituent through a ring carbon or a ring nitrogen atom where such an attachment mode is available.

30

The term “5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N” refers to a five to ten membered, monocyclic or polycyclic fully unsaturated, ring or ring system with one to nine carbon atoms and one or two

5 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur. For example, but not limiting, the term includes furyl, thienyl, pyrrolyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxazolyl, thiazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidyl, azepinyl, diazepinyl, benzofuryl, benzothienyl, indolyl, isoindolyl, benzimidazolyl, benzisothiazolyl, benzisoxazolyl, benzoxazolyl,

10 benzopyrazinyl, benzopyrazolyl, quinazolyl, thienopyridyl, quinolyl, isoquinolyl benzothiazolyl, and the like. It is understood that a 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N can be attached as a substituent through a ring carbon or a ring nitrogen atom where such an attachment mode is available.

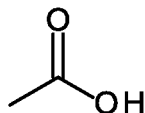
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The term “5- to 10-membered heteroaryloxy” refers to a 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N attached through an oxygen atom and includes imidazolyl, pyrazolyl, pyridyl, pyrimidyl, quinolyl, and the like

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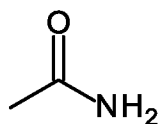
The term “oxo” refers to an oxygen atom doubly bonded to the carbon to which it is attached to form the carbonyl of a ketone or aldehyde. For example, a pyridone radical is contemplated as an oxo substituted 6-membered heteroaryl.

25 The term “carboxyl” refers to the group below:

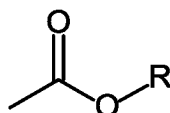


The term “carbamoyl” refers the group below:

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The term “C<sub>1</sub>-C<sub>4</sub> alkoxy carbonyl” refers the group below:



5 wherein R is a C<sub>1</sub>-C<sub>4</sub> alkyl.

The term “nil” as used herein with reference to a group, substituent, moiety, or the like, indicates that that group, substituent, or moiety is not present. Wherein a group, substituent, or moiety is ordinarily bonded to two or more other groups, substituents, or moieties, the others are bonded together in lieu of the group, substituent, or moiety which is nil. For example, with a compound having the structure A-B-C; wherein B is nil, then A is directly bonded to C and the compound is A-C. As another example, with a compound having the structure A-B-C; wherein C is nil, then the compound is A-B.

15 The term “salt” refers to salts of veterinary or pharmaceutically acceptable organic acids and bases or inorganic acids and bases. Such salts are well known in the art and include those described in *Journal of Pharmaceutical Science*, 66, 2-19 (1977). An example is the hydrochloride salt.

20 The term “substituted,” including when used in “optionally substituted” refers to one or more hydrogen radicals of a group being replaced with non-hydrogen radicals (substituent(s)). It is understood that the substituents may be either the same or different at every substituted position. Combinations of groups and substituents envisioned by this invention are those that are stable or chemically feasible.

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The term “stable” refers to compounds that are not substantially altered when subjected to conditions to allow for their production. In a non-limiting example, a stable compound or

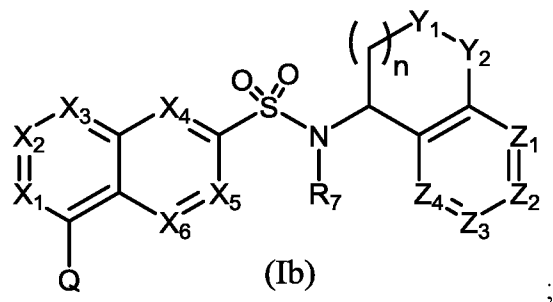
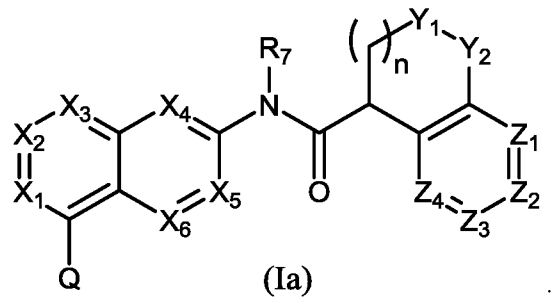
chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for about a week.

- 5 It is understood that, where the terms defined herein mention a number of carbon atoms, that the mentioned number refers to the mentioned group and does not include any carbons that may be present in any optional substituent(s) thereon or any carbons that may be present as part of a fused ring, including a benzo-fused ring.
- 10 The skilled artisan will appreciate that certain of the compounds of the present invention exist as isomers. All stereoisomers of the compounds of the invention, including geometric isomers, enantiomers, and diastereomers, in any ratio, are contemplated to be within the scope of the present invention.
- 15 The skilled artisan will also appreciate that certain of the compounds of the present invention exist as tautomers. All tautomeric forms the compounds of the invention are contemplated to be within the scope of the present invention.

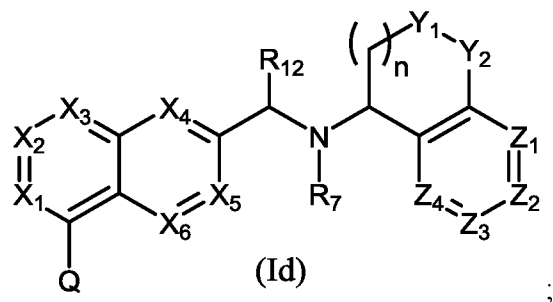
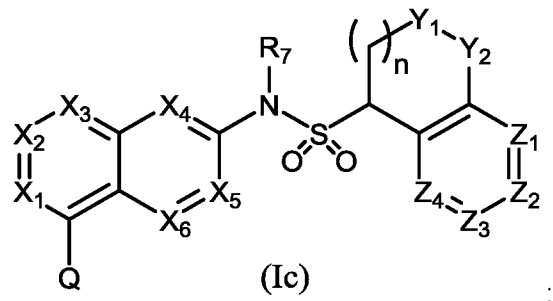
Compounds of the invention also include all isotopic variations, in which at least one  
20 atom of the predominant atom mass is replaced by an atom having the same atomic number, but an atomic mass different from the predominant atomic mass. Use of isotopic variations (*e.g.*, deuterium,  $^2\text{H}$ ) may afford greater metabolic stability. Additionally, certain isotopic variations of the compounds of the invention may incorporate a radioactive isotope (*e.g.*, tritium,  $^3\text{H}$ , or  $^{14}\text{C}$ ), which may be useful in drug and/or  
25 substrate tissue distribution studies. Substitution with positron emitting isotopes, such as  $^{11}\text{C}$ ,  $^{18}\text{F}$ ,  $^{15}\text{O}$  and  $^{13}\text{N}$ , may be useful in Positron Emission Topography (PET) studies.

The terms “compounds of the invention” and “a compound of the invention” and  
“compounds of the present invention” and a like include the embodiment of formula (I)  
30 and the other more particular embodiments encompassed by formula (I) described herein and the exemplified compounds described herein and a salt of each of these embodiments.

The compound of formula (I) with G as defined has the formulae:

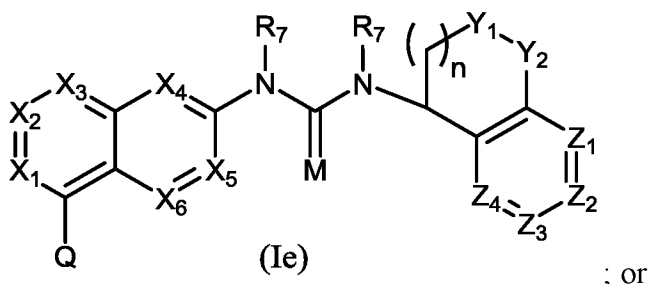


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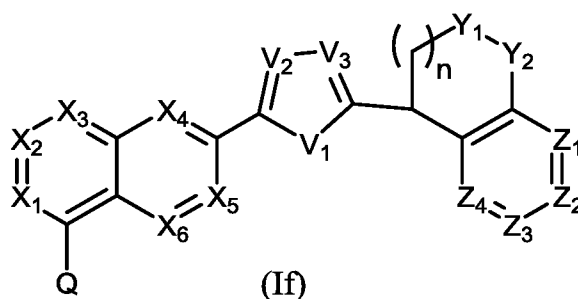


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; or



- 5 Further embodiments of compounds of the invention are provided below:
- (a) One embodiment relates to a compound of formula (I).
- (b) One embodiment relates to a compound of formula (I) wherein G is as in a compound of formula (Ia); or a salt thereof.
- (c) One embodiment relates to a compound of formula (I) wherein G is as in a compound of formula (Ib); or a salt thereof.
- 10 (d) One embodiment relates to a compound of formula (I) wherein G is as in a compound of formula (Ic); or a salt thereof.
- (e) One embodiment relates to a compound of formula (I) wherein G is as in a compound of formula (Id); or a salt thereof.
- 15 (f) One embodiment relates to a compound of formula (I) wherein G is as in a compound of formula (Ie); or a salt thereof.
- (g) One embodiment relates to a compound of formula (I) wherein G is as in a compound of formula (If); or a salt thereof.
- (1) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), and (g) wherein at
- 20 least one of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, and X<sub>5</sub> is N.



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- (h) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), and (1) wherein  $X_1$  is  $CR_1$ ;  $X_2$  is  $CR_2$ ;  $X_3$  is  $CR_3$ ;  $X_4$  is  $CR_4$ ;  $X_5$  is  $CR_5$ ; and  $X_6$  is  $CR_6$ ; or a salt thereof.
- (i) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), and (g) wherein  $X_1$  is N;  $X_2$  is  $CR_2$ ;  $X_3$  is  $CR_3$ ;  $X_4$  is  $CR_4$ ;  $X_5$  is  $CR_5$ ; and  $X_6$  is N; or a salt thereof.
- 5 (j) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), and (1) wherein  $X_1$  is  $CR_1$ ;  $X_2$  is  $CR_2$ ;  $X_3$  is  $CR_3$ ;  $X_4$  is  $CR_4$ ;  $X_5$  is N; and  $X_6$  is N; or a salt thereof.
- (k) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), and (1) wherein  $X_1$  is  $CR_1$ ;  $X_2$  is  $CR_2$ ;  $X_3$  is  $CR_3$ ;  $X_4$  is  $CR_4$ ;  $X_5$  is N; and  $X_6$  is  $CR_6$ ; or a salt thereof.
- (l) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), and (1) wherein
- 10  $X_1$  is  $CR_1$ ;  $X_2$  is  $CR_2$ ;  $X_3$  is  $CR_3$ ;  $X_4$  is N;  $X_5$  is N; and  $X_6$  is N; or a salt thereof.
- (m) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (1), (h), (i), (j), (k), and (l) wherein Q is a 6- or 10 membered aryl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>,
- 15 -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; or a salt thereof.
- (n) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (1), (h), (i), (j), (k), and (l) wherein Q is 6-membered aryl optionally substituted with 1, 2 or 3
- 20 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, wherein the 6-membered aryl is
- 25 fused with a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the heterocycloalkyl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxy, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the
- 30 heterocycloalkyl is substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; or a salt thereof.

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(o) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (1), (h), (i), (j), (k), and (l) wherein Q is a 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, -OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heteroaryl is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; or a salt thereof.

(p) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (1), (h), (i), (j), (k), and (l) wherein Q is a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the heterocycloalkyl or optionally benzo-fused heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxy, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heterocycloalkyl is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; or a salt thereof.

(q) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (1), (h), (i), (j), (k), and (l) wherein Q is a 6- or 10 membered aryloxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; or a salt thereof.

(r) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (1), (h), (i), (j), (k), and (l) wherein Q is a 5- to 10-membered heteroaryloxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub>

alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; or a salt thereof.

(s) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (l), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), and (r) wherein n is 1; or a salt thereof.

5 (t) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (l), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), and (s) wherein Y<sub>1</sub> is CR<sub>8</sub>R<sub>9</sub> and Y<sub>2</sub> is O; or a salt thereof.

(u) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (l), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), and (t) wherein Z<sub>1</sub> is CR<sub>11</sub>, Z<sub>2</sub> is CR<sub>11</sub>, Z<sub>3</sub> is CR<sub>11</sub>,  
10 and Z<sub>4</sub> is CR<sub>11</sub>; or a salt thereof.

(v) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (l), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), and (t) wherein Z<sub>1</sub> is CR<sub>11</sub>, Z<sub>2</sub> is CR<sub>11</sub>, Z<sub>3</sub> is nil, and Z<sub>4</sub> is S; or a salt thereof.

(w) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (l), (h), (i), (j),  
15 (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u) and (v) wherein R<sub>4</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, and 4- to 7-membered heterocycloalkyl; or a salt thereof.

(v) One embodiment relates to embodiments (a), (b), (c), (d), (e), (f), (g), (l), (h), (i), (j), (k), (l), (m), (n), (o), (p), (q), (r), (s), (t), (u) and (v) wherein R<sub>4</sub> is -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>; or a  
20 salt thereof.

(w) Another embodiment relates to a salt of each of the exemplified compounds.

The compounds of the invention can be prepared by a variety of procedures, some of which are described below. All substituents, unless otherwise indicated, are as previously  
25 defined.

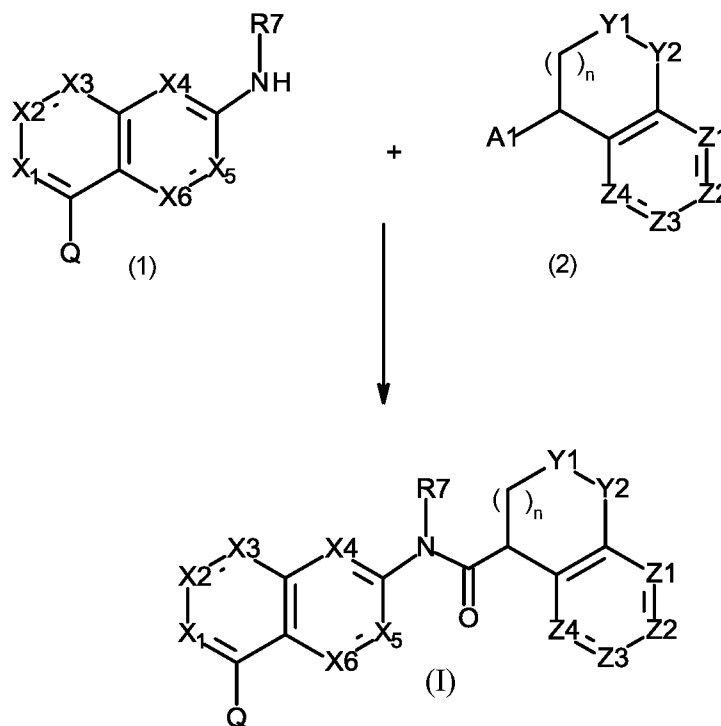
The products of each step can be recovered by conventional methods including extraction, evaporation, precipitation, chromatography, filtration, trituration, crystallization, and the like. The procedures may require protection of certain groups, for  
30 example hydroxy, thiol, amino, or carboxy groups to minimize unwanted reactions. The selection, use, and removal of protecting groups are well known and appreciated as

standard practice, for example T.W. Greene and P. G. M. Wuts in Protective Groups in Organic Chemistry (John Wiley and Sons, 1991).

As used herein: AcOH refers to acetic acid; aq. refers to aqueous, br refers to broad,  
5 CH<sub>3</sub>CN refers to acetonitrile, CH<sub>2</sub>Cl<sub>2</sub> refers to methylene chloride, d refers to doublet, dd refers to doublet of doublet, DIPEA refers to N-diisopropylethylamine, DMA refers to N,N-dimethylacetamide, DMF refers to N,N-dimethylformamide, DMSO refers to dimethylsulfoxide, ee: refers to enantiomeric excess, eq. refers to equivalent, ES refers to electrospray ionization, EtOAc refers to ethyl acetate, EtOH refers to ethanol, HATU  
10 refers to 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate, HPLC refers to high performance liquid chromatography, iPrOH refers to isopropanol, J refers to coupling constant, KOAc refers to potassium acetate, K<sub>2</sub>CO<sub>3</sub> refers to potassium carbonate, LCMS refers to liquid chromatography – mass spectrometry, m/z: refers to mass-to-charge ratio, M refers to molarity, m refers to  
15 multiplet, MeOH refers to methanol, min. refers to minutes, NaHCO<sub>3</sub> refers to sodium bicarbonate, Na<sub>2</sub>CO<sub>3</sub> refers to sodium carbonate, NEt<sub>3</sub> refers to triethylamine, NMR refers to nuclear magnetic resonance, NMP refers to N-methylpyrrolidone, q refers to quartet, rt refers to room temperature, R<sub>t</sub> refers to retention time, s refers to singlet, sat. refers to saturated, T refers to temperature, t refers to triplet, td refers to triplet of  
20 doublets, THF refers to tetrahydrofuran, wt refers to weight, and δ refers to chemical shift.

Scheme A

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Scheme A depicts the reaction of a compound of formula (1) and a compound of formula (2) to give a compound of formula (I). The depicted compound of formula (1) Q, R<sub>7</sub>, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> are as desired in the final compound of formula (I) or a group that gives rise to Q, R<sub>7</sub>, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> as desired in the final compound of formula (I). For example, a compound of formula (1) can be one in which the depicted group “Q” is a halogen which is further elaborated, in a subsequent step, not shown, to give a compound in which Q is as defined in formula (I). The preparation of such compounds of formula (1) is readily appreciated in the art. A compound of formula (2) is one in which is one in which the group A<sub>1</sub> is a carboxy group, or an activating groups as is discussed below, or a sulfonyl halide and n, Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub>, Z<sub>2</sub>, Z<sub>3</sub>, and Z<sub>4</sub> are as desired in the final product of formula (I) or a group that gives rise to Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub>, Z<sub>2</sub>, Z<sub>3</sub>, and Z<sub>4</sub> as desired in the final product of formula (I). The preparation of such compounds of formula (2) is readily appreciated in the art.

15

As mentioned above, Scheme A depicts the amidation of a compound of formula (1) in which using a compound of formula (2) to give a compound of formula (I). Typical groups A<sub>1</sub> are sulfonyl chloride, carboxy or an acid chloride or acid bromide, or

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imidazide, an activating moiety, a mixed anhydride of another carboxylic acid, such as formic acid, acetic acid, or represents the other part of a symmetrical anhydride formed from two compounds of formula (2) in which A<sub>1</sub> is carboxy. For example, standard carboxy amide forming conditions can be used, such as those using coupling agents, including those used in peptide couplings, such as 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium (HATU), dicyclohexylcarbodiimide (DCC), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide·HCl. If necessary or desired, an additive such as 4-(dimethylamino)pyridine, 1-hydroxybenzotriazole, and the like may be used to facilitate the reaction. Such reactions are generally carried out using a base, such as N-methylmorpholine or triethylamine, in a wide variety of suitable solvents such as CH<sub>2</sub>Cl<sub>2</sub>, DMF, N-methylpyrrolidone (NMP), DMA, THF, and the like. Such carboxy amide forming reactions are well understood and appreciated in the art. The formation of sulfonyl amides likewise are generally carried out using a base, such as N-methylmorpholine or triethylamine, in a wide variety of suitable solvents such as CH<sub>2</sub>Cl<sub>2</sub>, toluene, THF, and the like. Such sulfonyl amide forming reactions are well understood and appreciated in the art.

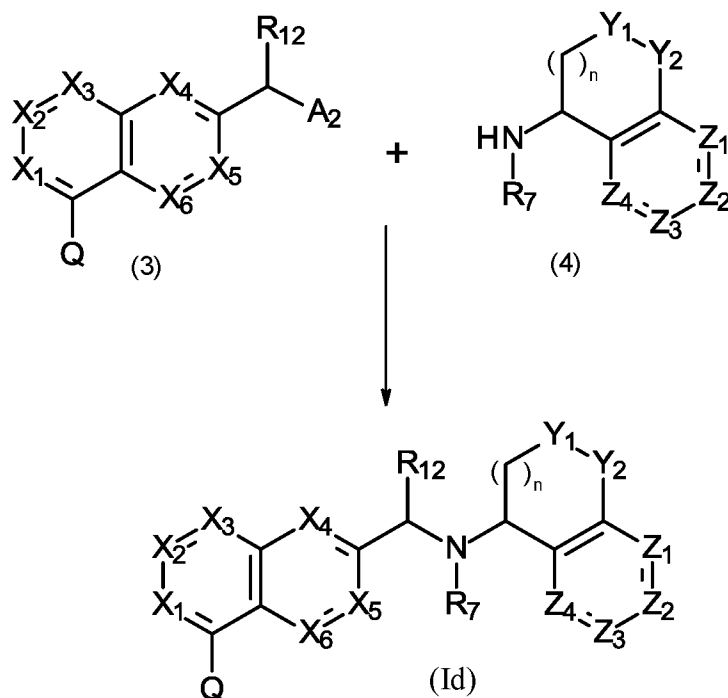
It will be recognized by one of ordinary skill in the art that a compound of formula (I) can be elaborated in a variety of ways to give other compounds of formula (I). Such reactions include hydrolysis, oxidation, reduction, alkylation, arylation (including heteroaryl groups) amidations, sulfonations, and the like.

Also, in an optional step, not shown, the compounds of formula (I) can be converted to salts by methods well known and appreciated in the art.

The skilled person will readily appreciate that compounds of formula Ib are readily prepared by the methodology of Scheme A using compounds for formula (1) in which -NHR<sub>7</sub> is replaced by a sulfonyl halide and compounds of formula (2) in which "A<sub>1</sub>" is -NHR<sub>7</sub>.

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Scheme B

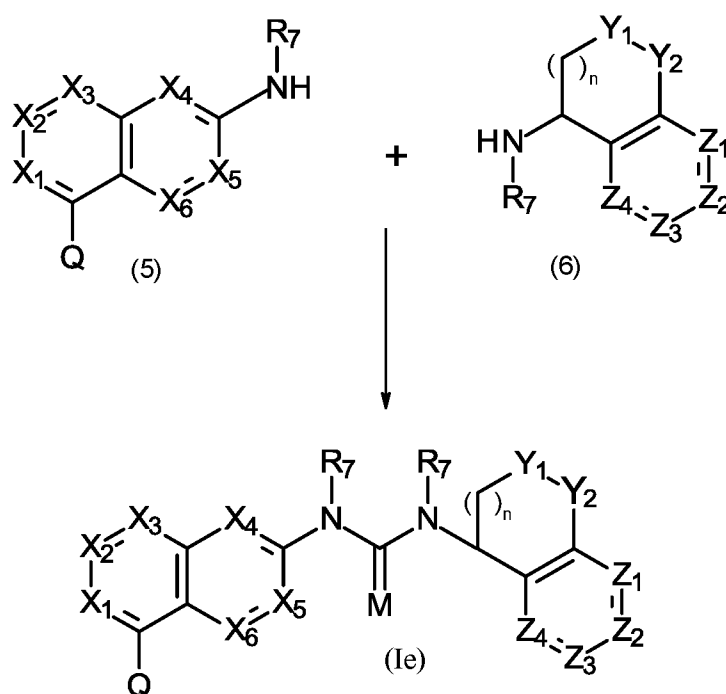


Scheme B depicts the Mitsunobu-type reaction of a compound of formula (3) and a compound of formula (4) to give a compound of formula (I). The depicted compound of formula (3) is one in which the group A<sub>2</sub> is an –OH group and Q, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> are as desired in the final compound of formula (I) or a group that gives rise to Q, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> as desired in the final compound of formula (I). For example, a compound of formula (3) can be one in which the depicted group “Q” is a halogen which is further elaborated, in a subsequent step, not shown, to give a compound in which Q is as defined in formula (I). The preparation of such compounds of formula (1) is readily appreciated in the art. A compound of formula (4) is one in which n, R<sub>7</sub>, Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub>, Z<sub>2</sub>, Z<sub>3</sub>, and Z<sub>4</sub> are as desired in the final product of formula (I) or a group that gives rise to R<sub>7</sub>, Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub>, Z<sub>2</sub>, Z<sub>3</sub>, and Z<sub>4</sub> as desired in the final product of formula (I). The preparation of such compounds of formula (4) is readily appreciated in the art. Such Mitsunobu-type reactions of alcohols and acidic components are well-known and appreciated in the art.

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Alternatively, Scheme B depicts a reductive amination of a compound of formula (3), as described above except that A<sub>2</sub> is an oxygen atom and a double bond between A<sub>2</sub> and the carbon to which it is attached and a compound of formula (4), as described above to give a compound of formula (I). Such reductive amination of aldehydes or ketones with amines are well-known and appreciated in the art.

Scheme C



Scheme C depicts the reaction of a compound of formula (5) and a compound of formula (6) to give a compound of formula (I) in which M is O. The depicted compound of formula (5) is one in which the depicted R<sub>7</sub> and Q, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> are as desired in the final compound of formula (I) or a group that gives rise to the depicted R<sub>7</sub>, and Q, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub>, X<sub>4</sub>, X<sub>5</sub>, and X<sub>6</sub> as desired in the final compound of formula (I). As above, a compound of formula (5) can be one in which the depicted group “Q” is a halogen which is further elaborated, in a subsequent step, not shown, to give a compound in which Q is as defined in formula (I). The preparation of such compounds of formula (5) is readily appreciated in the art. A compound of formula (6) is one in which is one in which the depicted R<sub>7</sub> and n, Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub>, Z<sub>2</sub>, Z<sub>3</sub>, and Z<sub>4</sub> are as desired in the final product



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of formula (I) or a group that gives rise to the depicted R<sub>7</sub>, and Y<sub>1</sub>, Y<sub>2</sub>, Z<sub>1</sub>, Z<sub>2</sub>, Z<sub>3</sub>, and Z<sub>4</sub> as desired in the final product of formula (I). The preparation of such compounds of formula (6) is readily appreciated in the art. The formation of unsymmetrical ureas is well known using phosgene, carbonyldiimidazole, and isopropenyl carbamates.

5

The following examples are intended to be illustrative and non-limiting, and represent specific embodiments of the present invention.

Analyses methods A and B were performed using an Agilent 1200 Infinity Series Liquid  
10 Chromatography (LC) system, consisting of a 1260 HiP degasser (G4225A), 1260 Binary Pump (G1312B), 1290 auto-sampler (G4226A), 1290 thermo-stated column compartment (G1316C) and a 1260 Diode Array Detector (G4212B) coupled to an Agilent 6150 single quadrupole mass spectrometry (MS) detector. The injection volume was set to 1  $\mu$ L by default. The UV (DAD) acquisition was performed at 40 Hz, with a scan range of 190-  
15 400 nm (by 5nm step). A 1:1 flow split was used before the MS detector. The MS was operated with an electro-spray ionization source (ESI) in both positive & negative ion mode. The nebulizer pressure was set to 50 psi, the drying gas temperature and flow to 350  $^{\circ}$ C and 12 L/min respectively. The capillary voltages used were 4000V in positive mode and 3500V in negative mode. The MS acquisition range was set to 100-800 m/z  
20 with a step size of 0.2 m/z in both polarity modes. Fragmentor voltage was set to 70 (ESI+) or 120 (ESI-), Gain to 0.40 (ESI+) or 1.00 (ESI-) and the ion count threshold to 4000 (ESI+) or 1000 (ESI-). The overall MS scan cycle time was 0.15s/cycle. Data acquisition was performed with Agilent Chemstation software.

25 Method A: Analyses were carried out on a Phenomenex Gemini-NX C18 column of 50 mm length, 2.1 mm internal diameter and 3  $\mu$ m particle size. The mobile phase used was: A1=Water with 0.1% formic acid / B1= CH<sub>3</sub>CN with 0.1% formic acid. The run was performed at a temperature of 50  $^{\circ}$ C and a flow rate of 1.2 mL/min, with a gradient elution from 5% to 95% (B1) over 1.5 min followed by a 0.5 min hold at 95% (B1).

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Method B: Analyses were carried out on a Waters XBridge C18 column of 50 mm length, 2.1 mm internal diameter and 3.5  $\mu$ m particle size. The mobile phase used was: A2=Water with 10mM ammonium bicarbonate, adjusted at pH 9 with ammonium hydroxide / B2= CH<sub>3</sub>CN. The run was performed at a temperature of 50°C and a flow rate of 1.2 mL/min, with a gradient elution from 5% to 95% (B2) over 1.5 min followed by a 0.5 min hold at 95% (B2).

Analyses methods C and D were performed using a Waters Acquity UPLC Liquid Chromatography (LC) system, coupled to an Waters SQ Detector 2 single quadrupole mass spectrometry (MS) detector. The UV (DAD) acquisition was performed with a scan range of 200-400 nm (by 1.2nm resolution). The MS was operated with an electro-spray ionization source (ESI) in both positive & negative ion mode. Capillary Voltage 3.50(kV), Cone Voltage 35(V), and Desolvation Temperature of 550 °C. Desolvation gas flow 1000(L/Hr), Cone gas flow 50(L/Hr). The MS acquisition range was set to 100-1500 m/z . MS scan cycle time was 0.5s. Data acquisition was performed with Waters Masslynx software.

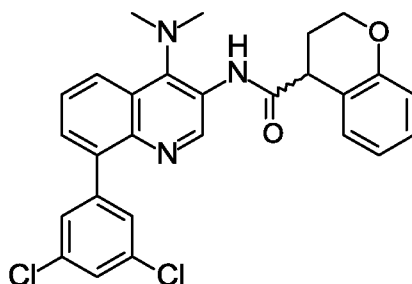
Method C: Analyses were carried out on an Acquity UPLC BEH C18 column of 50 mm length, 2.1 mm internal diameter and 1.7  $\mu$ m particle size. The mobile phase used was: A1= Water with 0.1% formic acid / B1= CH<sub>3</sub>CN with 0.1% formic acid. The injection volume was 1 $\mu$ L. The run was performed at a temperature of 40 °C and a flow rate of 0.6 mL/min, with a gradient elution. Method info (Time (min) and B %): 0-5; 0.3-5; 2.5-95; 3.7-95; 4-5; 4.6-5.

Method D: Analyses were carried out on an Acquity UPLC BEH C18 column of 50 mm length, 2.1 mm internal diameter and 1.7  $\mu$ m particle size. The mobile phase used was: A1= Water with 10 mM Ammonium acetate / B1= CH<sub>3</sub>CN with 0.1% formic acid. The injection volume was 0.1 $\mu$ L. The run was performed at a temperature of 45 °C and a flow rate of 0.5 mL/min, with a gradient elution. Method info (Time (min) and A %): 0-98; 0.3-98; 3.2-2; 4.4-2; 4.7-98.

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## Examples 1.1 and 1.2

(4R) and (4S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide



5 To a stirred solution of 8-bromoquinolin-4-ol (2 g, 8.82 mmol) in propionic acid (20 mL, 265 mmol) at 100°C was added nitric acid (1 mL, 16 mmol) slowly over 5 min. The reaction was heated to 125°C and left to stir for 45 min. The reaction was then allowed to cool to rt to give the precipitate. The solid was collected by filtration and was washed with water (3x10 mL), iPrOH (10 mL), isohexane (10 mL), and then dried in the vacuum oven for 1 hour to give 8-bromo-3-nitro-quinolin-4-ol. LCMS (method B):  $R_t = 0.54$  min,  $m/z = 269$  [M+H]<sup>+</sup>.

To a solution of 8-bromo-3-nitro-quinolin-4-ol (1.52 g, 5.37 mmol) was added POCl<sub>3</sub> (10 mL, 107 mmol). The suspension was heated to reflux and left to stir for 2 hours. The reaction mixture was allowed to cool to rt, and left to stand overnight. The reaction mixture was concentrated *in vacuo* (azeotroping with toluene) to give 8-bromo-4-chloro-3-nitro-quinoline which was used directly in the next step.

To a solution of 8-bromo-4-chloro-3-nitro-quinoline (2.32 g, 5.38 mmol,) in THF (30 mL) was slowly added dimethylamine (2 M in THF, 7 mL, 14 mmol, 2 M). The reaction was left to stir at rt for 1.5 hour. The reaction mixture was partitioned between EtOAc and sat. aq. NaHCO<sub>3</sub> (50 mL of each). Brine (50 mL) was added. The layers were separated, and the aq. layer was extracted with EtOAc (2x50 mL). The combined organic layers were concentrated *in vacuo* to give 8-bromo-N,N-dimethyl-3-nitro-quinolin-4-amine. LCMS (method B):  $R_t = 1.13$  min,  $m/z = 296$  [M+H]<sup>+</sup>.

To a solution of 8-bromo-N,N-dimethyl-3-nitro-quinolin-4-amine (505 mg, 1.62 mmol), was added (3,5-dichlorophenyl)boronic acid (314 mg, 1.61 mmol), tetrakis(triphenylphosphine)palladium(0) (92 mg, 0.079 mmol), and Na<sub>2</sub>CO<sub>3</sub> (351 mg, 3.28 mmol). The vial was sealed, then evacuated and back-filled with N<sub>2</sub> three times. 1,4-

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Dioxane (9 mL) was added, followed by water (3 mL) and the reaction was heated to 100°C in the microwave for 1 hour. The reaction mixture was partitioned between EtOAc and sat. aq. NaHCO<sub>3</sub> (50 mL of each). The layers were separated, and the aq. layer was extracted with EtOAc (2x25 mL). The combined organic layers were concentrated *in vacuo*, then purified by column chromatography to give 8-(3,5-dichlorophenyl)-N,N-dimethyl-3-nitro-quinolin-4-amine. LCMS (method B): R<sub>t</sub>= 1.57 min, m/z= 362 [M+H]<sup>+</sup>.

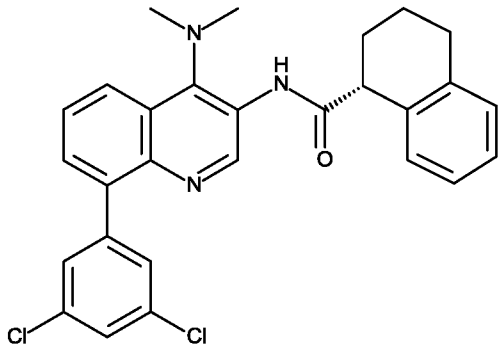
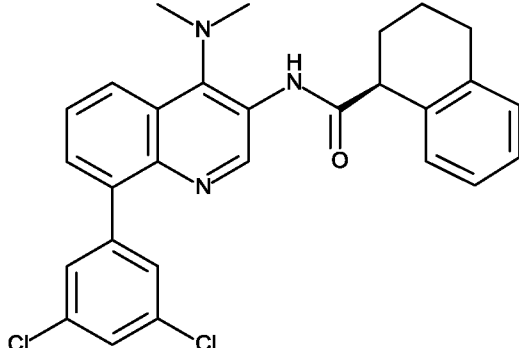
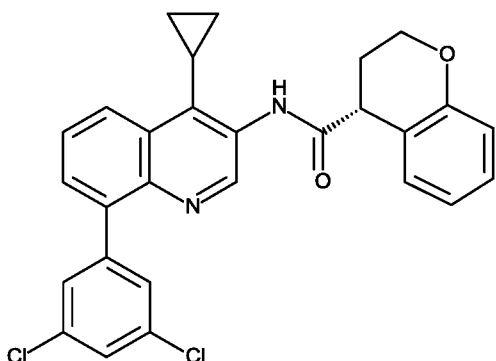
To a stirred suspension of 8-(3,5-dichlorophenyl)-N,N-dimethyl-3-nitro-quinolin-4-amine (401 mg, 1.052 mmol) in THF (5 mL), EtOH (5 mL) and water (2.5 mL) was added iron (184 mg, 3.23 mmol) and NH<sub>4</sub>Cl (168 mg, 3.13 mmol). The reaction was heated to 75°C and left to stir for 45 min. The reaction was allowed to cool to rt, then partitioned between sat. aq. NaHCO<sub>3</sub> and EtOAc (25 mL of each). The mixture was filtered through Celite<sup>®</sup> (washing with EtOAc), and the layers of the filtrate were separated. The aq. layer was extracted with EtOAc (2x25 mL), and the combined organic layers were concentrated *in vacuo* before being purified by column chromatography to give 8-(3,5-dichlorophenyl)-N<sub>4</sub>,N<sub>4</sub>-dimethyl-quinoline-3,4-diamine. LCMS (method B): R<sub>t</sub>= 1.48 min, m/z= 3632 [M+H]<sup>+</sup>.

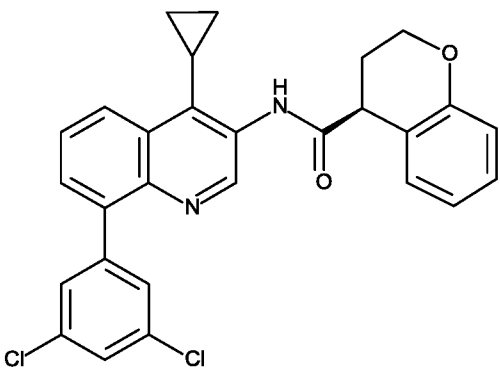
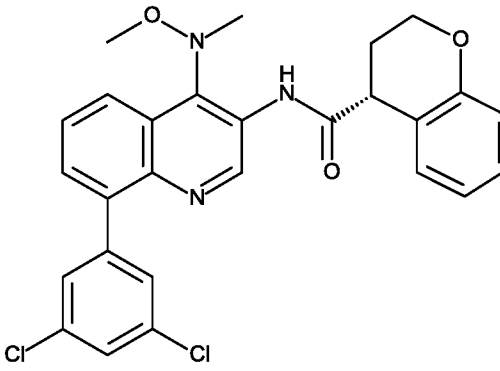
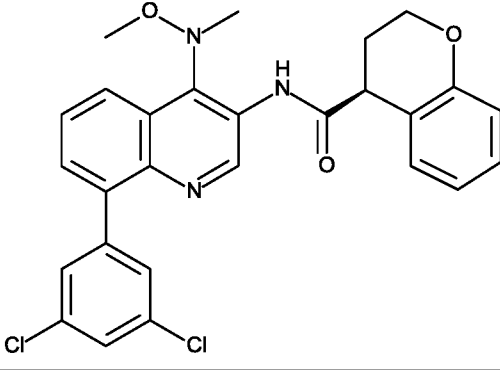
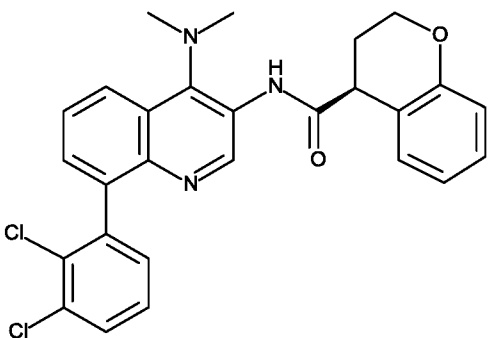
To a stirred solution of (rac)-chromane-4-carboxylic acid (182 mg, 0.97 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) under N<sub>2</sub>-atmosphere was added oxalyl chloride (172 μL, 1.94 mmol), followed by DMF (4 μL, 0.0516 mmol). The reaction was left to stir at rt for 45 min. The reaction mixture was concentrated *in vacuo* to give (rac)-chromane-4-carboxylic acid chloride which used directly in the next step.

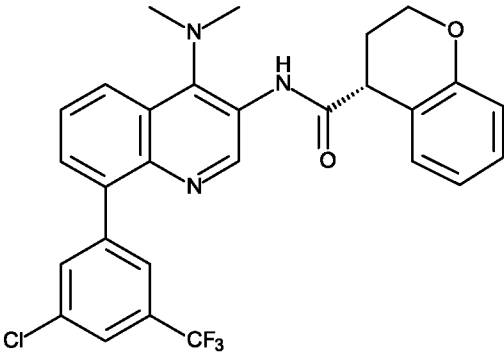
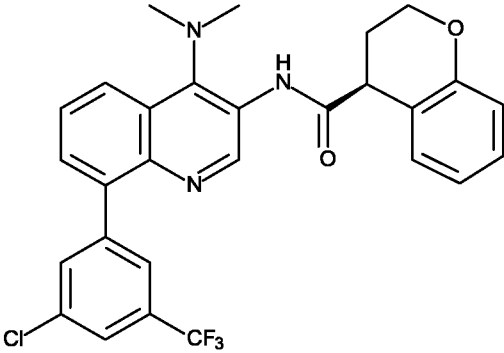
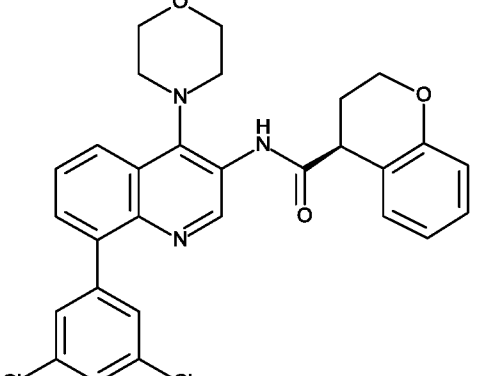
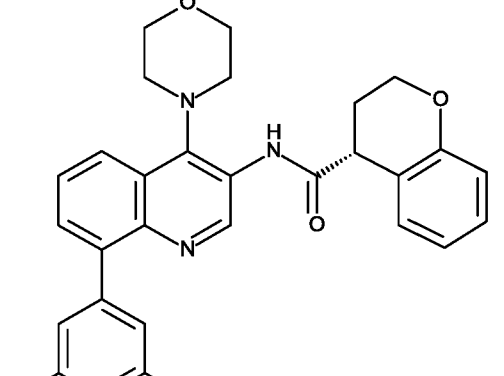
To a stirred suspension of 8-(3,5-dichlorophenyl)-N<sub>4</sub>,N<sub>4</sub>-dimethyl-quinoline-3,4-diamine (0.237 g, 0.62 mmol) and NEt<sub>3</sub> (262 μL, 1.86 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) under N<sub>2</sub> was added (rac)-chromane-4-carbonyl chloride (242 mg, 0.97 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) dropwise. The reaction was left to stir at rt for 15 min. The reaction mixture was partitioned between sat. aq. NaHCO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub> (25 mL of each). The combined layers were filtered and the aq. layer was separated and washed with CH<sub>2</sub>Cl<sub>2</sub> (2x25 mL). The combined organic layers were concentrated *in vacuo* and the resulting residue was purified by column chromatography to give the title compounds. LCMS (method B): R<sub>t</sub>= 1.58 min, m/z= 492 [M+H]<sup>+</sup>. Chiral SFC separation was performed on Chiralpak<sup>®</sup> IG with column dimensions of 250 mm × 30 mm (5 μm), a flow rate of 118 g/min, and a

- CO<sub>2</sub>-based mobile phase with 40% iPrOH containing 0.2% isopropylamine as additive to give (4R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide and (4S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ [ppm]: 9.98 (s, 1H), 8.87 (s, 1 h), 7.86 (dd, J= 1.6, 8 Hz, 1 H), 7.51 (m, 4 H), 7.38 (t, J= 2 Hz, 1 H), 7.33 (t, J= 8.4Hz, 1 H), 7.04 (t, J=7.6 Hz, 1 H), 6.98 (d, J= 8 Hz, 1 H), 4.37 (d, J= 11.6 Hz, 1 H), 4.09 (td, J= 2, 12 Hz, 1 H), 3.88 (d, J= 2.8 Hz, 1 H), 2.7 (s, 6 H), 2.65 (m, 1 H), 2.25 (m, 1 H).

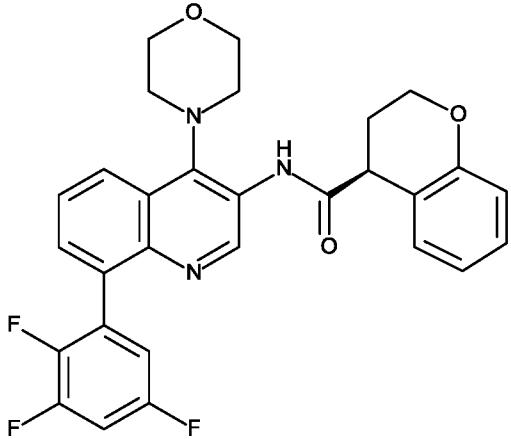
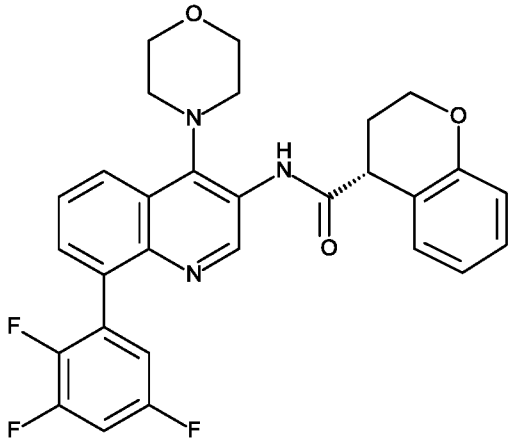
The following compounds were prepared analogously by the methodology of Example 1:

Ex.	Name	Structure
1.3	(1R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]tetralin-1-carboxamide	
1.4	(1S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]tetralin-1-carboxamide	
1.5	(4R)-N-[4-cyclopropyl-8-(3,5-dichlorophenyl)-3-quinolyl]chromane-4-carboxamide	

1.6	(4S)-N-[4-cyclopropyl-8-(3,5-dichlorophenyl)-3-quinolyl]chromane-4-carboxamide	
1.7	(4R)-N-[8-(3,5-dichlorophenyl)-4-[methoxy(methyl)amino]-3-quinolyl]chromane-4-carboxamide	
1.8	(4S)-N-[8-(3,5-dichlorophenyl)-4-[methoxy(methyl)amino]-3-quinolyl]chromane-4-carboxamide	
1.9	(4S)-N-[8-(2,3-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide	

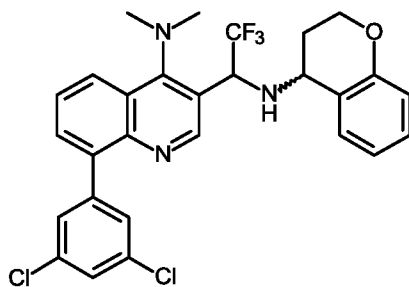
1.10	(4R)-N-[8-[3-chloro-5-(trifluoromethyl)phenyl]-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide	
1.11	(4S)-N-[8-[3-chloro-5-(trifluoromethyl)phenyl]-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide	
1.12	(4S)-N-[8-(3,5-dichlorophenyl)-4-morpholino-3-quinolyl]chromane-4-carboxamide	
1.13	(4R)-N-[8-(3,5-dichlorophenyl)-4-morpholino-3-quinolyl]chromane-4-carboxamide	

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1.14	(4S)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-3-quinolyl]chromane-4-carboxamide	
1.15	(4R)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-3-quinolyl]chromane-4-carboxamide	

## Example 2.1

3-[1-[[4R and S)-chroman-4-yl]amino]-2,2,2-trifluoro-ethyl]-8-(3,5-dichlorophenyl)-N,N-dimethyl-quinolin-4-amine



5

8-Bromoquinolin-4-ol (1 g, 4.46 mmol) was charged into a microwave vial and was suspended in POCl<sub>3</sub> (3 mL, 32.3 mmol). The mixture was submitted to microwave irradiation for 1 hour at 100°C. The reaction mixture was poured onto an ice/water mixture and was stirred for ca. 5 min. pH was adjusted to pH= 9 with solid K<sub>2</sub>CO<sub>3</sub>. The



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mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The layers were separated and the aq. layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x25 mL). Combined organic layers were concentrated *in vacuo* to give 8-bromo-4-chloro-quinoline. LCMS (method B): R<sub>t</sub>=1.13 min, m/z= 241.8 [M+H]<sup>+</sup>.

5 8-Bromo-4-chloro-quinoline (0.99 g, 4 mmol) was charged into a microwave vial and was dissolved in 1,4-dioxane (13 mL). To this solution dimethylamine·HCl (650 mg, 7.97 mmol) was added followed by addition of DIPEA (2.8 mL, 16 mmol). The mixture was submitted to microwave irradiation at 150°C for 2.5 hours. The reaction mixture was concentrated under reduced pressure and purified by column chromatography to give 8-  
10 bromo-N,N-dimethyl-quinolin-4-amine. LCMS (method B): R<sub>t</sub>= 1.04 min, m/z= 251.0 [M+H]<sup>+</sup>.

4-Dimethylaminopyridine (1.2 g, 9.8 mmol) was dissolved in o-xylene (16 mL). To this solution, trifluoroacetic anhydride (1.4 mL, 10 mmol) was added and the mixture was stirred for 30 min at rt. Then, a solution of 8-bromo-N,N-dimethyl-quinolin-4-amine  
15 (0.85 g, 3.3 mmol) in o-xylene (6 mL) was added to the flask and the mixture was stirred at reflux for 3 hours. The reaction mixture was cooled down to rt and was quenched by addition of sat. aq. NaHCO<sub>3</sub> solution. The layers were separated and the aq. layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x25 mL). Combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and reduced *in vacuo* to give crude material which was purified by  
20 column chromatography and afforded 1-[8-bromo-4-(dimethylamino)-3-quinolyl]-2,2,2-trifluoro-ethanone. LCMS (method A): R<sub>t</sub>= 0.90 min, m/z= 346.8 [M+H]<sup>+</sup>.

1-[8-Bromo-4-(dimethylamino)-3-quinolyl]-2,2,2-trifluoro-ethanone (1.13 g, 2.93 mmol) was loaded into a microwave vial together with (3,5-dichlorophenyl)boronic acid (560 mg, 2.93 mmol), 1,1'-bis(diphenylphosphino) ferrocene-Pd(II)·CH<sub>2</sub>Cl<sub>2</sub> complex  
25 (125 mg, 0.150 mmol) and Na<sub>2</sub>CO<sub>3</sub> (620 mg, 5.85 mmol). Then, 1,4-dioxane (10 mL) and water (5 mL) was added to the vial and the mixture was submitted to microwave irradiation for 1 hour at 100°C. The crude reaction mixture was reduced to dryness, and then purified by column chromatography to give 1-[8-(3,5-dichlorophenyl)-4-(  
30 (dimethylamino)-3-quinolyl]-2,2,2-trifluoro-ethanone. LCMS (method A): R<sub>t</sub>= 1.34 min, m/z= 413.0 [M+H]<sup>+</sup>.

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1-[8-(3,5-Dichlorophenyl)-4-(dimethylamino)-3-quinolyl]-2,2,2-trifluoro-ethanone (513 mg, 0.95 mmol) was dissolved in MeOH (3 mL). The solution was cooled down to 0°C and then NaBH<sub>4</sub> (72 mg, 1.90 mmol) was added to the flask. The mixture was stirred at 0°C for 15 min and then it was allowed to warm to rt. The reaction mixture was

5 quenched by addition of water (50 mL). The layers were separated and the aq. layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x25 mL). The combined organic layers were reduced to dryness *in vacuo* to give (1R)-1-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]-2,2,2-trifluoro-ethanol. LCMS (method A): R<sub>t</sub>= 1.34 min, m/z= 415.0 [M+H]<sup>+</sup>.

(1R)-1-[8-(3,5-Dichlorophenyl)-4-(dimethylamino)-3-quinolyl]-2,2,2-trifluoro-ethanol

10 (360 mg, 0.67 mmol) and (4S)-chroman-4-amine·HCl (250 mg, 1.35 mmol) were dissolved in 1,4-dioxane (2.5 mL) and NEt<sub>3</sub> (0.1 mL, 0.72 mmol). Then, PPh<sub>3</sub> (880 mg, 3.32 mmol) and DIAD (0.660 mL, 3.33 mmol) were added to the flask at rt. The mixture was heated to 90°C overnight. The reaction mixture was cooled down to rt, reduced to dryness under vacuum and purified by chromatography (0-20% EtOAc in cyclohexane) to

15 give the title compound. LCMS (method B): R<sub>t</sub>=1.81 min, m/z= 546.0 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ [ppm]: 9.14 (s, 1 H), 8.19 (dd, J= 0.8, 8.4 Hz, 1 H), 7.85 (t, J= 7.2 Hz, 1 H), 7.46-7.76 (m, 4 H), 7.41 (dd, J= 0.8, 7.6 Hz, 1 H), 7.1 (m, 1 H), 6.97 (dd, J= 0.8, 7.6 Hz, 1 H), 6.85 (t, J= 7.6 Hz, 1 H), 6.8 (t, J= 7.6 Hz, 1 H), 6.72 (t, J= 9.6 Hz, 1 H), 5.34 (m, 1 H), 4.29 (t, J= 10 Hz, 1 H), 3.97-4.19 (m, 2 H), 3.54-3.59 (m, 1 H), 3.06

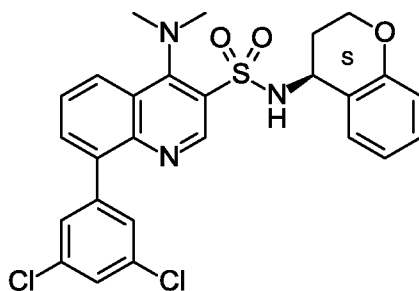
20 (s, 3 H), 3.02 (s, 3 H), 1.64-2.04 (m, 2 H).

## Example 3.1

N-[(4S)-chroman-4-yl]-8-(3,5-dichlorophenyl)-4-(dimethylamino)quinoline-3-

25 sulfonamide

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A solution of 8-bromoquinolin-4-ol (496.4 mg, 2.21 mmol) in chlorosulfonic acid (5 mL, 75.22 mmol) under N<sub>2</sub>-atmosphere was heated to 100°C. The reaction was then cooled to  
5 rt and poured onto ice, causing solid to precipitate. This solid was filtered off, washed with water (50 mL) and air dried to afford a colorless solid. 8-Bromo-4-hydroxy-quinoline-3-sulfonyl chloride was taken on to the next step without any further purification.

A suspension of 8-bromo-4-hydroxy-quinoline-3-sulfonyl chloride (571.9 mg, 1.59  
10 mmol) in POCl<sub>3</sub> (5 mL, 53.8 mmol,) was heated to 130°C under N<sub>2</sub>-atmosphere. The reaction was cooled to rt, then concentrated *in vacuo*. The residue was then azotroped with toluene (2x15 mL) to give 8-bromo-4-chloro-quinoline-3-sulfonyl chloride as a brown oil. LCMS (method B): R<sub>t</sub>=1.27 min, m/z=340 [M+H]<sup>+</sup>.

To a chilled solution of 8-bromo-4-chloro-quinoline-3-sulfonyl chloride (985 mg,  
15 2.54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0°C under N<sub>2</sub>-atmosphere was added (4S)-chroman-4-amine·HCl (365 mg, 1.96 mmol) followed by NEt<sub>3</sub> (0.54 mL, 3.9 mmol). The reaction was stirred at 0°C, and slowly allowed to warm to rt overnight. The reaction mixture was concentrated *in vacuo* and the solid was then purified by column chromatography to give 8-bromo-4-chloro-N-[(4S)-chroman-4-yl]quinoline-3-sulfonamide. LCMS (method B):  
20 R<sub>t</sub>=1.25 min, m/z=453 [M+H]<sup>+</sup>.

A mixture of 8-bromo-4-chloro-N-[(4S)-chroman-4-yl]quinoline-3-sulfonamide (420 mg, 0.88 mmol), dimethylamine·HCl (144 mg, 1.77 mmol) and DIPEA (0.62 mL, 3.6 mmol) in 1,4-dioxane (4 mL) in a 5 mL microwave vial was irradiate to 100°C for 1 hour. The reaction was concentrated, and the resulting residue was purified by column  
25 chromatography to give 8-bromo-N-[(4S)-chroman-4-yl]-4-(dimethylamino)quinoline-3-sulfonamide. LCMS (method B): R<sub>t</sub>= 1.26 min, m/z=462 [M+H]<sup>+</sup>.

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To a mixture of (3,5-dichlorophenyl) boronic acid (158.3 mg, 0.83 mmol), Na<sub>2</sub>CO<sub>3</sub> (192 mg, 1.81 mmol) and 1,1'-bis(diphenylphosphino) ferrocene-Pd(II)·CH<sub>2</sub>Cl<sub>2</sub> complex (38.8 mg, 0.047 mmol) in a 5mL microwave vial was added 8-bromo-N-[(4S)-chroman-4-yl]-4-(dimethylamino)quinoline-3-sulfonamide (383 mg, 0.78 mmol) in 1,4-dioxane (3 mL) followed by water (1.5 mL). The microwave vial was then sealed and irradiated to 100°C for 1 hour. The reaction was diluted with EtOAc (20 mL) and passed through a pad of Celite<sup>®</sup>. The Celite<sup>®</sup> was washed through with EtOAc (100 mL). The combined filtrates were then concentrated *in vacuo* and the residue was purified by column chromatography to afford the title compound. LCMS (method B): R<sub>t</sub>=1.58 min, m/z=528.1 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ [ppm]: 9.15 (s, 1H), 8.50 (d, J=8.4 Hz, 1h), 8.29 (dd, J= 1.2, 8.4 Hz, 1 H), 7.93 (dd, J= 1.2, 7.2 Hz, 1 H), 7.75 (t, J= 7.2 Hz, 1 H), 7.67 (s, 3 H), 7.12 (m, 2 H), 6.75 (m, 2 H), 4.58 (q, J= 7.8 Hz, 1 H), 4.18 (m, 2 H), 3.18 (s, 6 H), 1.87 (q, J= 5.8 Hz, 2 H).

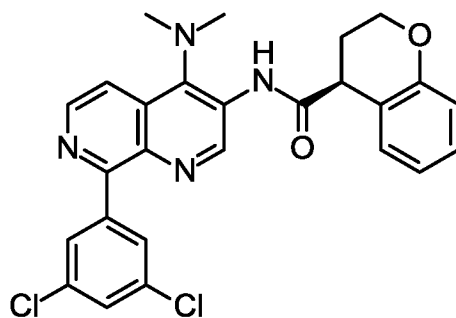
The following compounds were prepared analogously by the methodology of Example 3.1:

Ex.	Name	Structure
3.2	N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinoly]-4-(4R and S)-chromane-4-sulfonamide	

## Example 4.1

(4S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridin-3-yl]chromane-4-carboxamide

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A solution of 2-chloro-3-fluoro-pyridine-4-carboxylic acid (15.1 g, 84.2 mmol) and thionyl chloride (60 mL, 821 mmol,) was heated to 80°C for 2 hours. The reaction was allowed to cool to rt, and concentrated *in vacuo* to give 2-chloro-3-fluoro-pyridine-4-carbonyl chloride as a residue which was used directly in the next step.

To a stirring solution of 2-chloro-3-fluoro-pyridine-4-carbonyl chloride (17.5 g, 83.9 mmol) in toluene (210 mL) was added NEt<sub>3</sub> (14 mL, 99.4 mmol) followed by ethyl 3-(dimethylamino)prop-2-enoate (14.7 g, 101 mmol). The reaction was heated to 80°C and left to stir for 45 min. The reaction was allowed to cool to rt, and filtered through Celite<sup>®</sup> (washing with EtOAc). The filtrate was concentrated *in vacuo*, and the residue was partitioned between EtOAc and aq. 2M HCl (200 mL of each). The layers were separated, and the aq. layer was extracted with EtOAc (200 mL). The combined organics were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give ethyl 2-(2-chloro-3-fluoro-pyridine-4-carbonyl)-3-[(4-methoxyphenyl)methylamino]prop-2-enoate.

LCMS (method B) R<sub>t</sub>=0.86min, m/z= 301.0 [M+H]<sup>+</sup>.

To a stirring solution of ethyl 2-(2-chloro-3-fluoro-pyridine-4-carbonyl)-3-[(4-methoxyphenyl)methylamino]prop-2-enoate (19.37 g, 46.8 mmol) in DMF (90 mL) was added K<sub>2</sub>CO<sub>3</sub> (19.3 g, 140 mmol). The reaction was heated to 50°C and left to stir for 2 hours. The reaction was allowed to cool to rt and was concentrated under vacuum. The mixture was then partitioned between EtOAc and water. The aq. layer was extracted with EtOAc (2x), and the combined organics were washed with, brine, dried over anhydrous MgSO<sub>4</sub>, and filtered. The combined organic layers were concentrated *in vacuo* and the residue was triturated with Et<sub>2</sub>O. The solvent was removed under reduced pressure to give ethyl 8-chloro-1-[(4-methoxyphenyl)methyl]-4-oxo-1,7-naphthyridine-3-carboxylate.

LCMS (method B) R<sub>t</sub>= 1.02, m/z= 373.0 [M+H]<sup>+</sup>.

To a stirring solution of ethyl 8-chloro-1-[(4-methoxyphenyl)methyl]-4-oxo-1,7-

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naphthyridine-3-carboxylate (9.00 g, 22.93 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (115 mL) was added anisole (12.5 mL, 114 mmol), followed by TFA (35 mL, 458.3 mmol). The reaction was left to stir at rt for 1 hour. The reaction was concentrated *in vacuo* and the crude product was partitioned between sat. aq. NaHCO<sub>3</sub> and EtOAc (300 mL of each). The suspension was stirred vigorously for 15 min. The precipitate was isolated by filtration (washing with water, then EtOAc) to give ethyl 8-chloro-4-hydroxy-1,7-naphthyridine-3-carboxylate. LCMS (method B) R<sub>t</sub>= 0.47min, m/z= 253.0 [M+H]<sup>+</sup>.

To a stirring suspension of ethyl 8-chloro-4-hydroxy-1,7-naphthyridine-3-carboxylate (4.76 g, 18.85 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (190 mL) was added oxalyl chloride (2.5 mL, 28 mmol), followed by DMF (73 μL, 0.94 mmol) at 0°C. The reaction was left to stir at rt for 4 hours. The reaction was quenched by the addition into NaHCO<sub>3</sub> (200mL), and the reaction mixture was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organics were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give ethyl 4,8-dichloro-1,7-naphthyridine-3-carboxylate. LCMS (method B) R<sub>t</sub>= 1.07 min, m/z= 271.0 [M+H]<sup>+</sup>.

To ethyl 4,8-dichloro-1,7-naphthyridine-3-carboxylate (5.23 g, 18.33 mmol) in THF (18 mL), dimethylamine in THF (18 mL, 36 mmol, 2 M) was added, immediately forming a yellow solution with precipitate. The reaction was left to stir at rt for 20 min. EtOAc (250 mL) was added followed by aq. NaHCO<sub>3</sub> (200 mL). The layers were separated, and the aq. layer was extracted with EtOAc (250mL). The combined organics were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give ethyl 8-chloro-4-(dimethylamino)-1,7-naphthyridine-3-carboxylate. LCMS (method B) R<sub>t</sub>= 0.96 min, m/z= 280.0 [M+H]<sup>+</sup>.

To a mixture of ethyl 8-chloro-4-(dimethylamino)-1,7-naphthyridine-3-carboxylate (3.00 g, 10.2 mmol), (3,5-dichlorophenyl)boronic acid (1.89 g, 9.68 mmol), Na<sub>2</sub>CO<sub>3</sub> (2.12 g, 20.4 mmol) was added 1,4-dioxane (50 mL), followed by water (17 mL). N<sub>2</sub>-gas was bubbled through the mixture for 5 min. 1,1'-Bis(diphenylphosphino) ferrocene-Pd(II)·CH<sub>2</sub>Cl<sub>2</sub> complex (380 mg, 0.51 mmol) was then added and the reaction was heated at 80°C for 90 min. The reaction was cooled to rt and diluted with CH<sub>2</sub>Cl<sub>2</sub> /water. The layers were separated. The CH<sub>2</sub>Cl<sub>2</sub> layer was collected and the solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography (0-40% EtOAc:cyclohexane) to give ethyl 8-(3,5-

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dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridine-3-carboxylate. LCMS (method B)  $R_t = 1.52$  min,  $m/z = 390.0$   $[M+H]^+$ .

To a solution of ethyl 8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridine-3-carboxylate (4.46 g, 9.71 mmol) in THF (95 mL) and MeOH (32 mL) was added lithium hydroxide (712 mg, 29.1 mmol) in water (32 mL). The reaction was heated to 50°C and left to stir for 4 hours. The mixture was concentrated under reduced pressure, water was added and the aq. layer was washed with EtOAc. The aq. layer was adjusted to pH 4 by the addition of 2 M HCl, forming a yellow precipitate which was isolated by filtration to give 8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridine-3-carboxylic acid.

LCMS analysis (method B)  $R_t = 0.78$  min,  $m/z = 362.0$   $[M+H]^+$ .

A suspension of 8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridine-3-carboxylic acid (0.42 g, 0.93 mmol) in DMF (10 mL) was placed under  $N_2$ -atmosphere and treated with  $NEt_3$  (2.9 mmol, 0.4 mL). The resulting solution was treated with diphenylphosphoryl azide (0.41 g, 1.5 mmol, 0.325 mL) before being allowed to stir for 45 min at rt. The reaction mixture was then treated with MeOH (4 mL) and was left to stir overnight. The reaction mixture was quenched by the addition of sat. aq.  $NaHCO_3$  (25 mL) and extracted with  $CH_2Cl_2$  (3x20 mL). The combined organic layers were filtered and concentrated *in vacuo*. The residue containing methyl N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridin-3-yl]carbamate was carried into the next step without further purification.

A solution of methyl N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridin-3-yl]carbamate (1.23 g, 0.932 mmol) in 1,4-dioxane (10 mL) was treated with sodium hydroxide (2 mol/L) in water (10 mL) and was heated at 100°C for 2 hours. The reaction mixture was allowed to cool to rt, diluted with water (20 mL) and extracted with  $CH_2Cl_2$  (3x 20mL). The combined organic layers were filtered and concentrated *in vacuo*. The residues were purified by column chromatography (0-25% EtOAc in cyclohexane) to give 8-(3,5-dichlorophenyl)-N,N-dimethyl-1,7-naphthyridine-3,4-diamine. LCMS analysis (method B)  $R_t = 1.29$  min,  $m/z = 333.0$   $[M+H]^+$ .

A mixture of 8-(3,5-dichlorophenyl)-N,N-dimethyl-1,7-naphthyridine-3,4-diamine (105 mg, 0.3 mmol) and S-chromane-4-carboxylic acid (0.065 g, 0.35 mmol) was placed under  $N_2$ -atmosphere, treated with EtOAc (1.5 mL) and cooled over ice. The reaction

mixture was then treated with pyridine (0.075 mL, 0.918 mmol) and T<sub>3</sub>P (50 wt% in EtOAc; 0.608 mmol, 0.365 mL) before being allowed to stir overnight. The reaction mixture was diluted with water (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 mL). The combined organic layers were filtered and concentrated *in vacuo*. The residues were

5 dissolved in MeOH, filtered and purified by prep-HPLC ((Phenomenex Gemini 5 Micron 30x100mm C-18) (Acetonitrile and water adjusted to approx. pH 9 with conc. ammonium hydroxide solution [0.5 mL of conc. ammonium hydroxide per 2.5 L of water], 30% to 100% CH<sub>3</sub>CN over 9 min at 60 mL/min) to give the title compound. LCMS analysis (method B) R<sub>t</sub>= 1.47 min, m/z= 493.0 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ [ppm]:

10 10.15 (s, 1 H), 8.8 (s, 1 H), 8.63 (d, J= 5.6 Hz, 1 H), 8.09 (d, J= 2 Hz, 2 H), 8.00 (d, J= 2.8 Hz, 1 H), 7.72 (t, J= 2 Hz, 1 H), 7.27 (d, J= 7.6 Hz, 1 H), 7.16 (m, 1 H), 6.91 (m, 1 H), 6.82 (d, J= 8 Hz, 1 H), 4.38 (m, 1 H), 4.2 (m, 1 H), 4.08 (t, J= 6 Hz, 1 H), 3.04 (s, 6 H), 2.25 (m, 2 H).

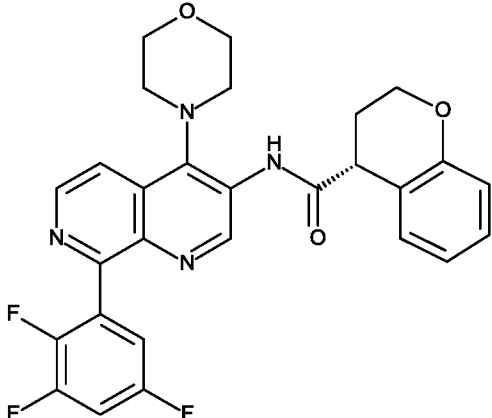
The following compounds were prepared analogously by the methodology of Example

15 4.1:

Ex.	Name	Structure
4.2	(4R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridin-3-yl]chromane-4-carboxamide	
4.3	(4S)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-1,7-naphthyridin-3-yl]chromane-4-carboxamide	

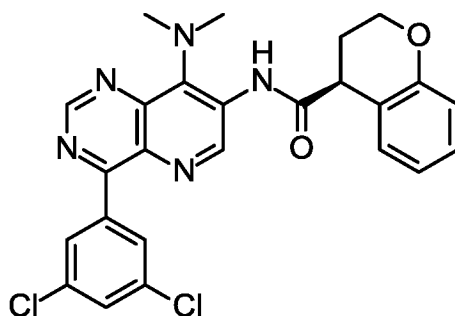


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4.4	(4R)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-1,7-naphthyridin-3-yl]chromane-4-carboxamide	
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## Example 5.1

(4S)-N-[4-(3,5-dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidin-7-yl]chromane-4-carboxamide



5

To a suspension of ethyl 6-hydroxypyrimidine-4-carboxylate (5.04 g, 28.7 mmol) in DMF (25 mL, 323 mmol) under N<sub>2</sub>-atmosphere was added 1,3-dichloro-5,5-dimethylhydantoin (3.48 g, 17.3 mmol). The mixture was stirred overnight at rt. The reaction was partitioned between water (200 mL) and EtOAc (100 mL). The aq. layer was separated and extracted with EtOAc (2x75 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. LCMS (method B) R<sub>t</sub>= 0.54 min, m/z=203.0 [M+H]<sup>+</sup>.

To a suspension of ethyl 5-chloro-6-hydroxy-pyrimidine-4-carboxylate (8.74 g, 28.1 mmol) in CH<sub>3</sub>CN (100 mL) at rt under N<sub>2</sub>-atmosphere was added DIPEA (6.4 mL, 36 mmol) and then phosphorous oxybromide (9.44 g, 31.28 mmol). The resulting mixture was stirred at rt. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and slowly poured into water (100 mL). The mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x100 mL).

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The combined organic layers were dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. The oil was purified by column chromatography (0-10% EtOAc in cyclohexane) to give ethyl 6-bromo-5-chloro-pyrimidine-4-carboxylate. LCMS (method B)  $R_t = 0.98$  min,  $m/z = 265.0$   $[\text{M}+\text{H}]^+$ .

5 To a stirred solution of ethyl 6-bromo-5-chloro-pyrimidine-4-carboxylate (4.31 g, 14.9 mmol) and (3,5-dichlorophenyl) boronic acid (2.71 g, 14.20 mmol) in 1,4-dioxane (55 mL) under  $\text{N}_2$ -atmosphere was added  $\text{K}_2\text{CO}_3$  (8.69 g, 62.87 mmol) followed by tetrakis (triphenylphosphine) palladium (0) (732 mg, 0.63 mmol). The reaction was degassed and put under  $\text{N}_2$ -atmosphere, then heated at  $90^\circ\text{C}$  for 16 hours. The mixture  
10 was diluted with EtOAc (50 mL) and passed through Celite<sup>®</sup>. The combined organic filtrates were concentrated *in vacuo*. The residue was purified by column chromatography (0-20% EtOAc in cyclohexane) to give ethyl 5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carboxylate. LCMS (method A)  $R_t = 1.43$  min,  $m/z = 331.0$   $[\text{M}+\text{H}]^+$ .

To a mixture of ethyl 5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carboxylate (2.90 g, 8.75 mmol) in THF (85 mL) and water (30 mL) at rt under  $\text{N}_2$ -atmosphere was added  
15 lithium hydroxide (624.4 mg, 25.55 mmol). The resulting mixture was heated to  $50^\circ\text{C}$  for 1 hour. The reaction was cooled to rt, then concentrated *in vacuo* to remove THF. The resulting solution was diluted with water (50 mL) then acidified with 2M HCl until the pH=1, causing a solid to precipitate. The precipitate was filtered off and washed with  
20 water (25 mL). The precipitate was then dried *in vacuo* at  $50^\circ\text{C}$  to give 5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carboxylic acid. LCMS (method A)  $R_t = 0.72$  min,  $m/z = 303.0$   $[\text{M}+\text{H}]^+$ .

A suspension of 5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carboxylic acid (2.49 g, 7.82 mmol) in thionyl chloride (30 mL, 411 mmol) was heated to  $80^\circ\text{C}$  under  $\text{N}_2$ -  
25 atmosphere. DMF (0.5 mL, 6 mmol) was added and the reaction fully dissolved. The reaction was then concentrated *in vacuo*. The residue was taken up in toluene (20 mL) and azotroped (3 x) to give 5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carbonyl chloride which was used in the next step without further purification.

To a solution of 5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carbonyl chloride (2.65 g, 7.82 mmol) in toluene (20 mL) at rt under  $\text{N}_2$ -atmosphere was added  $\text{NEt}_3$  (2 mL,  
30 14 mmol) followed by ethyl 3-(dimethylamino)prop-2-enoate (1.4 mL, 9.7 mmol). The

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reaction was stirred at rt under N<sub>2</sub>-atmosphere. The reaction was diluted with EtOAc (125 mL), filtered through Celite<sup>®</sup>. The Celite<sup>®</sup> was washed through with EtOAc (125 mL). The combined organic filtrates were concentrated *in vacuo*. The residues were taken up in EtOAc (250 mL) and 2M HCl (aq, 100 mL). The aq. layer was separated and  
5 extracted with EtOAc (125 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give ethyl 2-[5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carbonyl]-3-(dimethylamino)prop-2-enoate. LCMS (method A) R<sub>t</sub>= 1.24 min, m/z= 428.0 [M+H]<sup>+</sup>.

4-Methoxybenzylamine (1.20 mL, 9.09 mmol) was added to a solution of ethyl 2-[5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carbonyl]-3-(dimethylamino)prop-2-enoate  
10 (3.59 g, 6.29 mmol) in diethyl ether (25 mL) and EtOH (6 mL) at rt under N<sub>2</sub>-atmosphere for 1 hour. The reaction was diluted with water (150 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (4x75 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give ethyl 2-[5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carbonyl]-3-[(4-methoxyphenyl) methylamino] prop-2-enoate which was taken on without further purification. LCMS (method A) R<sub>t</sub>= 1.49 min, m/z= 520.0 [M+H]<sup>+</sup>.

To a solution of ethyl 2-[5-chloro-6-(3,5-dichlorophenyl)pyrimidine-4-carbonyl]-3-[(4-methoxyphenyl) methylamino] prop-2-enoate (4.4 g, 5.66 mmol) in DMF (15 mL,  
20 194 mmol) at rt under N<sub>2</sub>-atmosphere was added K<sub>2</sub>CO<sub>3</sub> (2.37 g, 17.1 mmol). The resulting mixture was heated to 90°C for 24 hours. The reaction was cooled to rt, then poured into water (300 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0-5% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to give ethyl 4-(3,5-dichlorophenyl)-5-[(4-methoxyphenyl)methyl]-8-oxo-pyrido[3,2-d] pyrimidine-7-carboxylate. LCMS (method A) R<sub>t</sub>= 1.17 min, m/z= 484.0 [M+H]<sup>+</sup>.

To a solution of ethyl 4-(3,5-dichlorophenyl)-5-[(4-methoxyphenyl)methyl]-8-oxo-pyrido[3,2-d] pyrimidine-7-carboxylate (1.89 g, 3.70 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (75 mL) and DMF  
30 (0.5 mL, 6 mmol) at rt under N<sub>2</sub>-atmosphere was added slowly oxalyl chloride (2 mL, 23.1 mmol). The reaction was heated to reflux at 60°C for 1 hour. The reaction was

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cooled down to rt, then quenched by the addition of sat. aq. NaHCO<sub>3</sub> (200 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x100 mL). The combined organic layers were combined and concentrated *in vacuo* to give ethyl 8-chloro-4-(3,5-dichlorophenyl)pyrido[3,2-d]pyrimidine-7-carboxylate. LCMS (method A) R<sub>t</sub>= 1.52 min, m/z= 382.0 [M+H]<sup>+</sup>.

5 To a suspension of ethyl 8-chloro-4-(3,5-dichlorophenyl)pyrido[3,2-d]pyrimidine-7-carboxylate (1.04 g, 1.93 mmol) in THF (10 mL) at rt under N<sub>2</sub>-atmosphere was added dimethylamine in THF (2 mL, 4 mmol, 2 M). The reaction was stirred at rt for 1 hour. The mixture was poured into sat. aq. NaHCO<sub>3</sub> (50 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x25 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and  
10 concentrated *in vacuo*. The residue was purified by column chromatography (0-15% EtOAc in cyclohexane) to give ethyl 4-(3,5-dichlorophenyl)-8-(dimethylamino) pyrido [3,2-d]pyrimidine-7-carboxylate. LCMS (method B) R<sub>t</sub>=1.58 min, m/z= 391.0 [M+H]<sup>+</sup>.

To a mixture of ethyl 4-(3,5-dichlorophenyl)-8-(dimethylamino) pyrido [3,2-d]pyrimidine-7-carboxylate (571 mg, 1.34 mmol) in 1,4-dioxane (14 mL) and water  
15 (4.5 mL) at rt under N<sub>2</sub>-atmosphere was added lithium hydroxide (107 mg, 4.375 mmol). The resulting mixture was heated to 80°C for 4 hours. The reaction was concentrated *in vacuo* to remove dioxane. The residue was taken up in water (20 mL) and acidified with 2M HCl (aq, 2.2 mL). The resulting yellow precipitate was filtered off and washed with water (20 mL). The yellow solid was then dried *in vacuo* at 60°C to give 4-(3,5-  
20 dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidine-7-carboxylic acid. LCMS (method B) R<sub>t</sub>=0.78 min, m/z= 363 [M+H]<sup>+</sup>.

To a solution of 4-(3,5-dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidine-7-carboxylic acid (209 mg, 0.52 mmol) in DMF (5.2 mL) at rt under N<sub>2</sub>-atmosphere was added NEt<sub>3</sub> (0.22 mL, 1.6 mmol) followed by diphenylphosphoryl azide (0.17 mL,  
25 0.79 mmol). After 2 hours at rt, anhydrous MeOH (2.1 mL, 52 mmol) was added and the reaction was left to stir at rt overnight under N<sub>2</sub>-atmosphere.

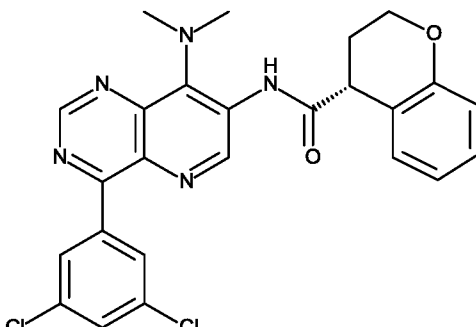
The reaction was quenched by the addition of sat. aq. NaHCO<sub>3</sub> (25 mL) and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give methyl N-[4-(3,5-  
30 dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidin-7-yl]carbamate. LCMS (method B) R<sub>t</sub>=1.47 min, m/z=392 [M+H]<sup>+</sup>.

A solution of methyl N-[4-(3,5-dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidin-7-yl]carbamate (0.517 mmol, 0.517 mmol) in 1,4-dioxane (5.2 mL) at rt under N<sub>2</sub>-atmosphere was treated with sodium hydroxide (aq., 2 M). The mixture was then heated to 100°C. The reaction was cooled to rt, diluted with water (25 mL) and  
 5 extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (0-25% EtOAc in cyclohexane) to give 4-(3,5-dichlorophenyl)-N,N-dimethyl-pyrido[3,2-d]pyrimidine-7,8-diamine. LCMS (method B) R<sub>t</sub>=1.41 min, m/z=334.0 [M+H]<sup>+</sup>.

10 A suspension of 4-(3,5-dichlorophenyl)-N,N-dimethyl-pyrido[3,2-d]pyrimidine-7,8-diamine (114 mg, 0.32 mmol) and (4S)-chromane-4-carboxylic acid (69.4 mg, 0.39 mmol) in EtOAc (5 mL) was under N<sub>2</sub>-atmosphere cooled to 0°C with an ice bath. Then pyridine (0.08 mL, 1 mmol) was added to the reaction at 0°C followed by T<sub>3</sub>P (50 wt% in EtOAc; 0.39 mL, 0.65 mmol). The reaction was allowed to slowly warm to rt  
 15 and was stirred overnight. The reaction mixture was diluted with water (25 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x25 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The oil was purified by column chromatography (0-15% EtOAc in cyclohexane) to give the title compound. LCMS (method B) R<sub>t</sub>=1.61 min, m/z= 494.0 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO) δ [ppm]  
 20 10.15 (s, 1 H), 9.32 (s, 1 H), 8.93 (s, 1 H), 8.29 (d, J= 1.6Hz, 2 H), 7.84 (t, J= 2 Hz, 1 H), 7.27 (d, J= 7.2 Hz, 1 H), 7.17 (t, J= 7.2 Hz, 1 H), 6.91 (t, J= 7.2 Hz, 1 H), 9.82 (d, J= 8 Hz, 1 H), 4.33-4.41 (m, 1 H), 4.16-4.24 (m, 1 H), 4.11 (t, J= 7.2 Hz, 1 H), 3.17 (s, 6 H), 2.17-2.27 (m, 2 H).

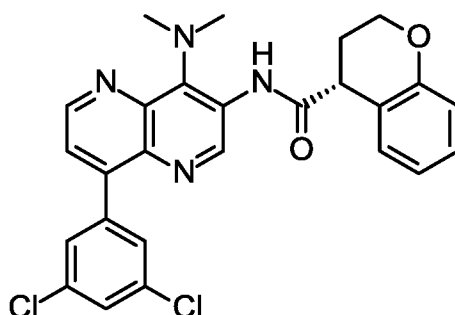
The following compounds were prepared analogously by the methodology of Example  
 25 5.1:

Ex.	Name	Structure
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5.2	(4R)-N-[4-(3,5-dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidin-7-yl]chromane-4-carboxamide	
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## Example 6.1

(4R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridin-3-yl]chromane-4-carboxamide



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Thionyl chloride (15 mL, 205 mmol) was added to 3,4-dichloropyridine-2-carboxylic acid (3.96 g, 20.6 mmol) and the reaction was heated at 80°C for 1 hour. The reaction was allowed to cool to rt, and concentrated *in vacuo* to give 3,4-dichloropyridine-2-carbonyl chloride which was used without further purification in the next step.

10

To a solution of 3,4-dichloropyridine-2-carbonyl chloride (20.6 mmol, 4.76 g) in toluene (50 mL) was added NEt<sub>3</sub> (3.5 mL, 2.5 g) followed by ethyl 3-(dimethylamino)prop-2-enoate (3.6 mL, 25 mmol). The reaction was stirred at rt overnight. The reaction was filtered through Celite<sup>®</sup> (washing with EtOAc). The filtrate was concentrated *in vacuo*, and the residue was partitioned between EtOAc and aq. 1 M HCl (100 mL of each). The layers were separated, and the aq. layer was extracted with EtOAc (50 mL). The combined organic layers were concentrated *in vacuo* to give ethyl 2-(3,4-dichloropyridine-2-carbonyl)-3-(dimethylamino)prop-2-enoate. LCMS (method B) R<sub>t</sub> = 0.88 min, m/z = 317.0 [M+H]<sup>+</sup>.

15

To a stirring solution of ethyl 2-(3,4-dichloropyridine-2-carbonyl)-3-(dimethylamino)

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prop-2-enoate (5.58 g, 12.7 mmol) in diethyl ether (50 mL) and EtOH (12 mL) was added 4-methoxybenzylamine (1.9 mL, 14 mmol). The reaction was left to stir at rt for 2 hours. The reaction mixture was diluted with water (100 mL). Layers were separated and the aq. layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL). The combined organic layers were dried  
5 over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give ethyl 2-(3,4-

dichloropyridine-2-carbonyl)-3-[(4-methoxyphenyl) methylamino] prop-2-enoate. Ethyl 2-(3,4-dichloropyridine-2-carbonyl)-3-[(4-methoxyphenyl) methylamino] prop-2-enoate (5.92 g, 9.40 mmol) was dissolved in DMF (24 mL). K<sub>2</sub>CO<sub>3</sub> (4.00 g, 28.9 mmol) was added and the mixture was stirred at 90°C for 6 hours. The reaction was cooled down  
10 to rt. The reaction mixture was quenched by addition of water (250 mL) and was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The layers were separated and the aq. layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x50 mL). The combined organic layers were filtered through Celite<sup>®</sup> and then washed with brine (100 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude material was purified by chromatography (0-6% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) to  
15 give ethyl 8-hydroxy-1-[(4-methoxyphenyl) methyl]-4-oxo-1,5-naphthyridine-3-carboxylate.

Ethyl 8-hydroxy-1-[(4-methoxyphenyl) methyl]-4-oxo-1,5-naphthyridine-3-carboxylate (840 mg, 1.09 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (11 mL) and DMF (0.05 mL). To this mixture, oxalyl chloride (0.48 mL, 5.5 mmol) was added and the mixture was heated to  
20 reflux for 3 hours. The reaction mixture was then cooled down and was quenched by addition of sat. aq. NaHCO<sub>3</sub> solution (50 mL). The layers were separated and the aq. layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x25 mL). The combined organic layers were reduced *in vacuo* to give ethyl 4,8-dichloro-1,5-naphthyridine-3-carboxylate.

Ethyl 4,8-dichloro-1,5-naphthyridine-3-carboxylate (950 mg, 2.21 mmol) was dissolved  
25 in THF (5 mL). To this solution, dimethylamine in THF (1.1 mL, 2.2 mmol, 2 M) was added dropwise and the mixture was stirred at rt for 30 min. The reaction mixture was concentrated under reduced pressure and the resulting residue was purified by chromatography (20-50% EtOAc in cyclohexane) to give ethyl 8-chloro-4-(dimethylamino)-1,5-naphthyridine-3-carboxylate. LCMS (method B) R<sub>t</sub>= 1.07 min, m/z=  
30 280.0 [M+H]<sup>+</sup>.

Ethyl 8-chloro-4-(dimethylamino)-1,5-naphthyridine-3-carboxylate (315 mg, 0.93 mmol)

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was dissolved in 1,4-dioxane (3 mL) and water (1 mL). To this mixture, 1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II) (40 mg, 0.048 mmol) was added, followed by addition of (3,5-dichlorophenyl)boronic acid (215 mg, 1.13 mmol) and Na<sub>2</sub>CO<sub>3</sub> (300 mg, 2.83 mmol). The mixture was submitted to microwave irradiation for 1 hour at 100°C. The crude reaction mixture was reduced to dryness and the residue was purified by column chromatography (5-40% EtOAc in cyclohexane) to give ethyl 8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridine-3-carboxylate. LCMS (method B) R<sub>t</sub>= 1.56 min, m/z= 390.0 [M+H]<sup>+</sup>.

To a stirring solution of ethyl 8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridine-3-carboxylate (272 mg, 0.65 mmol) in 1,4-dioxane (2 mL) was added lithium hydroxide (32 mg, 1.34 mmol) in water (2 mL). The reaction was heated to 100°C overnight. The reaction mixture was cooled down. The reaction mixture was quenched by addition of water (50 mL) and EtOAc (50 mL). pH was adjusted to pH= 4 with 2M HCl. The layers were separated and the aq. layer was extracted with EtOAc (2x50 mL). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and reduced *in vacuo* to give 8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridine-3-carboxylic acid. LCMS (method B) R<sub>t</sub>= 0.82 min, m/z= 362.0 [M+H]<sup>+</sup>. To a solution of 8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridine-3-carboxylic acid (282 mg, 0.71 mmol) in DMF (7 mL) at rt under N<sub>2</sub>-atmosphere was added NEt<sub>3</sub> (3 equiv., 2.12 mmol) followed by diphenylphosphoryl azide (230 μL, 1.06 mmol). The mixture was stirred for 1 hour at rt. Anhydrous MeOH (2.90 mL) added and the reaction was left to stir at rt overnight under N<sub>2</sub>-atmosphere. The reaction was quenched by the addition of sat. aq. NaHCO<sub>3</sub> (25 mL). The organic layer was separated and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo* to give methyl N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridin-3-yl] carbamate. LCMS (method B) R<sub>t</sub>= 1.43 min, m/z=391 [M+H]<sup>+</sup>.

A solution of methyl N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridin-3-yl] carbamate (0.71 mmol) in 1,4-dioxane (12 mL) at rt under N<sub>2</sub>-atmosphere was treated with sodium hydroxide in water (10.6 mL, 21.2 mmol, 2 M). The mixture was heated to 100°C for 90 min. The reaction was diluted with water (25 mL) and extracted with

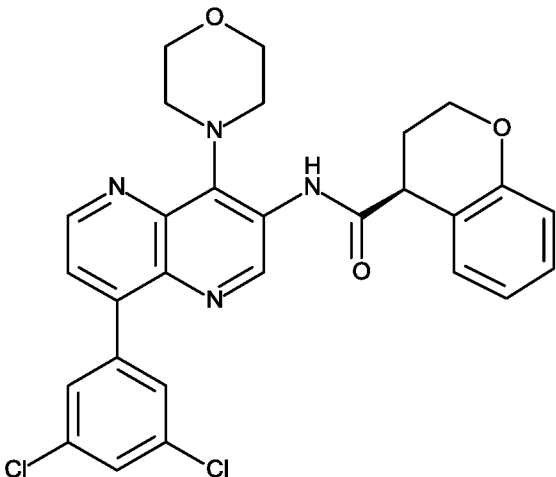


CH<sub>2</sub>Cl<sub>2</sub> (3x50 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (5-10% EtOAc in cyclohexane) to give 8-(3,5-dichlorophenyl)-N<sub>4</sub>,N<sub>4</sub>-dimethyl-1,5-naphthyridine-3,4-diamine. LCMS (method B) R<sub>t</sub>=1.41 min, m/z=333 [M+H]<sup>+</sup>.

- 5 A solution of 8-(3,5-dichlorophenyl)-N<sub>4</sub>,N<sub>4</sub>-dimethyl-1,5-naphthyridine-3,4-diamine (93.7 mg, 0.28 mmol) and (S)-chromane-4-carboxylic acid (65.7 mg, 0.35 mmol) in EtOAc (4 mL) under N<sub>2</sub>-atmosphere was cooled to 0°C with an ice bath. Pyridine (0.07 mL, 0.9 mmol) was added to the reaction at 0°C followed by T<sub>3</sub>P (50 wt% in EtOAc; 0.34 mL, 0.57 mmol). The reaction was allowed to slowly warm to rt and was
- 10 stirred overnight. The reaction mixture was diluted with water (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x15 mL). The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (5-15% EtOAc in cyclohexane) to give the title compound. LCMS (method B) R<sub>t</sub>=1.61 min, m/z= 493 [M+H]<sup>+</sup>. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>) δ [ppm]: 9.97 (s, 1 H), 8.92 (d, J= 4 Hz, 1 H), 8.88 (s, 1 H), 7.74 (m, 4 H), 7.28 (d, J= 7.6 Hz, 1 H), 7.17 (td, J= 1.6, 8.4 Hz), 1 H), 6.91 (td, J= 1.2, 7.2 Hz, 1 H), 6.82 (dd, J= 1.2, 8 Hz, 1 H), 4.35 (m, 1 H), 4.20 (m, 1 H), 4.10 (t, J= 5.6 Hz, 1 H), 3.12 (s, 6 H), 2.26 (m, 2 H).

The following compounds were prepared analogously by the methodology of Example 6.1:

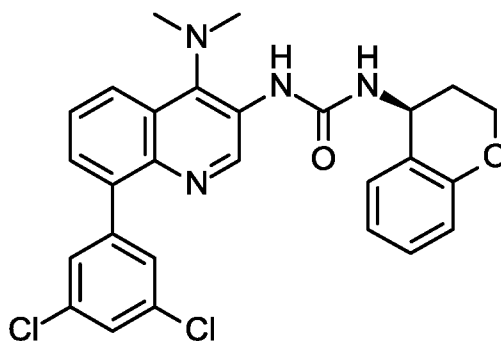
Ex.	Name	Structure
6.2	(4S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridin-3-yl]chromane-4-carboxamide	

6.3	(4S)-N-[8-(3,5-dichlorophenyl)-4-morpholino-1,5-naphthyridin-3-yl]chromane-4-carboxamide	
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## Example 7.1

1-[(4S)-Chroman-4-yl]-3-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]urea

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To a stirred solution of 8-bromoquinolin-4-ol (2.0 g, 8.82 mmol) in propionic acid (20 mL, 265 mmol) at 100°C was added nitric acid (1 mL, 16 mmol) slowly over 5 min. The reaction was heated to 125°C and left to stir for 45 min. The reaction was then allowed to cool to rt, causing the product to precipitate. The solid was collected by filtration and washed with water (3x10 mL), iPrOH (10 mL), isohexane (10 mL), and then dried in the vacuum oven for 1 hour to give 8-bromo-3-nitro-quinolin-4-ol. LCMS (method B):  $R_t = 0.54$  min,  $m/z = 269$   $[M+H]^+$ .

To a solution of 8-bromo-3-nitro-quinolin-4-ol (1.52 g, 5.37 mmol) was added  $POCl_3$  (10 mL, 107 mmol). The suspension was heated to reflux for 2 hours. The reaction mixture was allowed to cool to rt, and left to stand overnight. The reaction mixture was

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concentrated *in vacuo* (azeotroping with toluene) to give 8-bromo-4-chloro-3-nitro-quinoline which was used directly in the next step without further purification.

To a solution of 8-bromo-4-chloro-3-nitro-quinoline (2.32 g, 5.38 mmol,) in THF (30 mL) was slowly added dimethylamine (2 M in THF, 7 mL, 14 mmol). The reaction was left to stir at rt for 1.5 hour. The reaction mixture was partitioned between EtOAc and sat. aq. NaHCO<sub>3</sub> (50 mL of each). Brine (50 mL) was added. The layers were separated, and the aq. layer was extracted with EtOAc (2x50 mL). The combined organic layers were concentrated *in vacuo* to give 8-bromo-N,N-dimethyl-3-nitro-quinolin-4-amine. LCMS (method B): R<sub>t</sub>= 1.13 min, m/z= 296 [M+H]<sup>+</sup>.

To a solution of 8-bromo-N,N-dimethyl-3-nitro-quinolin-4-amine (505 mg, 1.62 mmol), was added (3,5-dichlorophenyl) boronic acid (314 mg, 1.61 mmol), tetrakis (triphenyl phosphine) palladium(0) (92 mg, 0.08 mmol,), and Na<sub>2</sub>CO<sub>3</sub> (351 mg, 3.28 mmol). The vial was sealed, then evacuated and back-filled with N<sub>2</sub>-atmosphere three times. 1,4-Dioxane (9 mL) was added, followed by water (3 mL) and the reaction was heated to 100°C in the microwave for 1 hour. The reaction mixture was partitioned between EtOAc and sat. aq. NaHCO<sub>3</sub> (50 mL of each). The layers were separated, and the aq. layer was extracted with EtOAc (2x25 mL). The combined organic layers were concentrated *in vacuo*, then purified by column chromatography to give 8-(3,5-dichlorophenyl)-N,N-dimethyl-3-nitro-quinolin-4-amine. LCMS (method B): R<sub>t</sub>= 1.57 min, m/z= 362 [M+H]<sup>+</sup>.

To a stirred suspension of 8-(3,5-dichlorophenyl)-N,N-dimethyl-3-nitro-quinolin-4-amine (401 mg, 1.05 mmol) in THF (5 mL), EtOH (5 mL) and water (2.5 mL) was added iron (184 mg, 3.23 mmol) and NH<sub>4</sub>Cl (168 mg, 3.13 mmol). The reaction was heated to 75°C and left to stir for 45 min. The reaction was allowed to cool to rt, then partitioned between sat. aq. NaHCO<sub>3</sub> and EtOAc (25 mL of each). The mixture was filtered through Celite<sup>®</sup> (washing with EtOAc), and the layers of the filtrate were separated. The aq. layer was extracted with EtOAc (2x25 mL), and the combined organic layers were concentrated *in vacuo* before being purified by column chromatography to give 8-(3,5-dichlorophenyl)-N,N-dimethyl-quinoline-3,4-diamine. LCMS (method B): R<sub>t</sub>= 1.48 min, m/z= 363.2 [M+H]<sup>+</sup>.

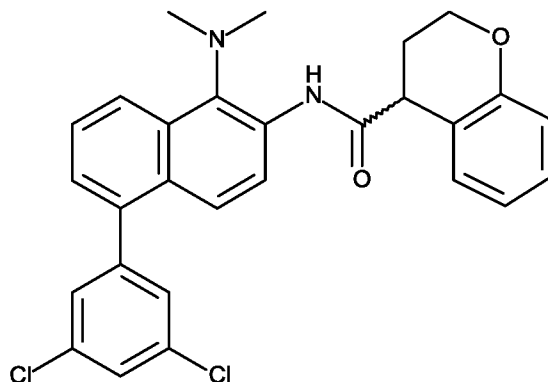
To a solution of 4-nitrophenyl chloroformate (94 mg, 0.45 mmol) in THF (2 mL) at 0°C under N<sub>2</sub>-atmosphere was added 8-(3,5-dichlorophenyl)-N,N-dimethyl-quinoline-3,4-

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diamine (151 mg, 0.43 mmol) in THF (2.5 mL) dropwise over 2 min. The reaction was left to stir at 0°C for 1 hour. To the reaction mixture was added (4S)-chroman-4-amine·HCl (90 mg, 0.47 mmol) and NEt<sub>3</sub> (179 μL, 1.27 mmol). The reaction was allowed to warm to rt, and stirred for 30 min. The reaction mixture was partitioned between sat. aq. NaHCO<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub> (20 mL of each). The layers were separated, and the aq. layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x20 mL). The combined organic layers were filtered and concentrated *in vacuo*. The residue was purified by column chromatography. LCMS (method B) R<sub>t</sub> = 1.49 min, m/z = 507 [M + H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ [ppm]: 9.51 (s, 1 H), 7.98 (m, 1 H), 7.56 (m, 4 H), 7.38 (t, J = 2 Hz, 1 H), 7.31 (m, 2 H), 7.18 (t, J = 8.4 Hz, 1 H), 6.91 (t, J = 7.6 Hz, 1 H), 6.83 (d, J = 8 Hz, 1 H), 5.12 (q, J = 6.8 Hz, 1 H), 4.94 (d, J = 7.2 Hz, 1 H), 4.2 (m, 2 H), 3.06 (s, 6 H), 2.23 (m, 2 H).

## Examples 8.1 and 8.2

(4S and 4R)-N-[5-(3,5-Dichlorophenyl)-1-(dimethylamino)-2-naphthyl]chromane-4-carboxamide



To a stirred solution of 1-bromo-5-nitronaphthalene (6.0 g, 23.90 mmol) and 3,5-dichlorophenyl boronic acid (4 g, 21.05 mmol) in 1,4-dioxane (80 mL)-water (26 mL) was added Na<sub>2</sub>CO<sub>3</sub> (5.06 g, 47.73 mmol) and the reaction mixture was degassed using N<sub>2</sub> for 10 min. After adding Pd(dppf)Cl<sub>2</sub> (0.87 g, 1.19 mmol), the resulting reaction mixture was stirred for 45 min at 80°C. The reaction mixture was quenched by adding water (50 mL) and extracted with EtOAc (2x50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude

compound was purified by column chromatography eluting with 50% EtOAc in ether to obtain 1-(3,5-dichlorophenyl)-5-nitronaphthalene.

To a stirred solution of 1-(3,5-dichlorophenyl)-5-nitronaphthalene (5 g, 15.77 mmol) and NH<sub>4</sub>Cl (2.6 g, 48.88 mmol) in THF (70 mL), EtOH (70 mL) and water (35 mL) was added iron powder (2.6 g, 47.31 mmol) and the resulting reaction mixture was stirred for 16 hours at 75°C. The reaction mixture was filtered through Celite<sup>®</sup> and washed with EtOH (30 mL). The filtrate was concentrated, then quenched with sat. aq. NaHCO<sub>3</sub> solution (30 mL) and extracted with EtOAc (3x40 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated *in vacuo*. The crude compound was triturated with Et<sub>2</sub>O and pentane (1:1) to obtain 5-(3,5-dichlorophenyl)naphthalen-1-amine.

To a stirred solution of 5-(3,5-dichlorophenyl)naphthalen-1-amine (3.3 g, 11.49 mmol) in DMF (10 mL) was added NBS (2.04 g, 11.49 mmol) at -5°C and the reaction mixture was stirred for 30 min. The reaction mixture was quenched by adding sat. aq. NaHCO<sub>3</sub> solution (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2x30 mL). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude compound was purified by flash column eluting with 30% EtOAc in ether to obtain 2-bromo-5-(3,5-dichlorophenyl)naphthalen-1-amine. LCMS (method D) R<sub>t</sub>= 2.69 min, m/z= 368.05 [M+H]<sup>+</sup>.

A stirred solution of 2-bromo-5-(3,5-dichlorophenyl)naphthalen-1-amine (1.6 g, 4.38 mmol) in formaldehyde solution (37 % in water, 15 mL) and formic acid (15 mL) was stirred for 1 hour at 100°C. The reaction was quenched by adding sat. aq. NaHCO<sub>3</sub> solution (2x20 mL) at 0°C and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude compound was purified by column chromatography eluting with 30% EtOAc in Et<sub>2</sub>O to obtain 2-bromo-5-(3,5-dichlorophenyl)-N,N-dimethylnaphthalen-1-amine. LCMS (method D) R<sub>t</sub>= 3.76 min, m/z= 394.09 [M+H]<sup>+</sup>. To a stirred solution of 2-bromo-5-(3,5-dichlorophenyl)-N,N-dimethylnaphthalen-1-amine (1.2 g, 3.06 mmol) in toluene (25 mL) was added tert-butylcarbamate (537 mg, 4.59 mmol), cesium carbonate (5.23 g, 9.18 mmol) and degassed using N<sub>2</sub> for 10 min. Pd<sub>2</sub>(dba)<sub>3</sub> (0.248 g, 0.15 mmol) and Xantphos (0.162 g, 0.15 mmol) were added

sequentially and the resulting reaction mixture was stirred for 16 hours at 110°C. The reaction mixture was quenched by adding water (10 mL) and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude compound was purified by column chromatography eluting with 50% EtOAc in ether to obtain tert-butyl (5-(3,5-dichlorophenyl)-1-(dimethylamino)naphthalen-2-yl)carbamate. LCMS (method D) R<sub>t</sub>= 3.06 min, m/z= 431 [M+H]<sup>+</sup>.

To a stirred solution of tert-butyl (5-(3,5-dichlorophenyl)-1-(dimethylamino)naphthalen-2-yl)-carbamate (0.56 g, 1.30 mmol) in EtOH (5 mL), 5M HCl in EtOH (5 mL), was added at rt and stirred for 16 hours at 50°C. The reaction mixture was cooled to rt and then concentrated under reduced pressure. The crude compound was purified by triturating with diethyl ether and pentane (1:1). LCMS (method D) R<sub>t</sub>= 2.7 min; m/z= 331.21 [M+H]<sup>+</sup>.

To a stirred solution of 5-(3,5-dichlorophenyl)-N1,N1-dimethylnaphthalene-1,2-diamine·HCl (0.44 g, 1.34 mmol), (S)-chromane-4-carboxylic acid (0.2 g, 1.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was added and DIPEA (0.6 mL, 3.37 mmol) and T<sub>3</sub>P (50 wt% in EtOAc, 0.5 mL, 1.68 mmol) at 0°C. The resulting reaction mixture was stirred for 24 hours at 50°C. The reaction mixture was quenched by adding water (5 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL). The combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude compound was purified by SFC: Chiralpak IC (30x250mm), 5μ % CO<sub>2</sub>: 65% Co solvent: 35% (MeOH) Total Flow:100 g/min Back Pressure : 100 bar Temperature : 35°C UV : 260nm) to give the title compounds. LCMS (method D) R<sub>t</sub>= 3.83; m/z= 491.0 [M+H]<sup>+</sup>. <sup>1</sup>H NMR (400 MHz, DMSO) δ [ppm]: 9.63 (s, 1 H), 8.26 (d, J= 9.2 Hz, 1 H), 8.02 (d, J= 8.4 Hz, 1 H), 7.72 (t, J= 2 Hz, 1 H), 7.49-7.59 (m, 4 H), 7.33-7.38 (m, 2 H), 7.26 (td, J= 1.2, 8 Hz, 1 H), 6.99 (t, J= 7.6 Hz, 1 H), 6.88 (d, J= 8.4 Hz, 1 H), 4.05-4.25 (m, 3 H), 2.79 (s, 6 H), 2.33-2.37 (m, 1 H), 2.07-2.18 (m, 1 H).

Experimental details for compounds in the tables:

Ex.	HPLC	NMR

1.3	R <sub>t</sub> = 1.69; m/z (ES+)= 490.0 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.98 (s, 1 H), 8.44 (s, 1 H), 7.83 (dd, J= 1.6, 7.6 Hz, 1 H), 7.51 (m, 5H), 7.37 (t, J= 1.6 Hz, 1 H), 7.27 (m, 2 H), 3.93 (m, 1 H), 2.89 (m, 2 H), 2.65 (s, 6H), 2.56 (m, 1 H), 1.91 (m, 3 H)
1.4	R <sub>t</sub> = 1.69; m/z (ES+)= 490.0 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.98 (s, 1 H), 8.44 (s, 1 H), 7.83 (dd, J= 1.6, 7.6Hz, 1 H), 7.51 (m, 5H), 7.37 (t, J= 1.6 Hz, 1 H), 7.27 (m, 2 H), 3.93 (m, 1 H), 2.89 (m, 2 H), 2.65 (s, 6H), 2.56 (m, 1 H), 1.91 (m, 3 H)
1.5	R <sub>t</sub> = 1.59; m/z (ES+)= 489.0 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.78 (s, 1H), 8.36 (dd, J= 2.8, 7.6Hz, 1 H), 8.22 (s, 1 H), 7.56 (m, 2 H), 7.53 (d, J= 2 Hz, 2 H), 7.37 (d, J= Hz, 1 H), 7.31 (m, 2 H), 7.01 (m, 2 H), 4.37 (m, 1 H), 4.12 (m, 1 H), 3.93 (m, 1 H), 2.67 (m, 1 H), 2.27 (m, 1 H), 1.63 (m, 1 H), 0.91 (m, 1 H), 0.72 (m, 1 H), 0.46 (m, 1 H), 0.39 (m, 1 H)
1.6	R <sub>t</sub> = 1.59; m/z (ES+)= 489.0 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.78 (s, 1H), 8.36 (dd, J= 2.8, 7.6Hz, 1 H), 8.22 (s, 1 H), 7.56 (m, 2 H), 7.53 (d, J= 2 Hz, 2 H), 7.37 (d, J= Hz, 1 H), 7.31 (m, 2 H), 7.01 (m, 2 H), 4.37 (m, 1 H), 4.12 (m, 1 H), 3.93 (m, 1 H), 2.67 (m, 1 H), 2.27 (m, 1 H), 1.63 (m, 1 H), 0.91 (m, 1 H), 0.72 (m, 1 H), 0.46 (m, 1 H), 0.39 (m, 1 H)
1.7	R <sub>t</sub> = 1.67; m/z (ES+)= 508.2 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.88 (s, 1H), 9.25 (s, 1 H), 8.25 (dd, J= 1.6, 8.4 Hz, 1 H), 7.51-7.59 (m, 4 H), 7.38 (t, J= 2 Hz, 1 H), 7.23-7.31 (m, 32 H), 6.96-7.02 (m, 2 H), 4.35-4.39 (m, 1 H), 4.11 (td, J= 2, 12 Hz, 1 H), 3.88 (s, 1 H), 3.28 (s, 3 H), 2.93 (s, 3 H), 2.6-2.65 (m, 1 H), 2.22-2.31 (m, 1 H)
1.8	R <sub>t</sub> = 1.67; m/z (ES+)= 508.2 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.88 (s, 1H), 9.25 (s, 1 H), 8.25 (dd, J= 1.6, Hz, 1 H), 7.51-7.59 (m, 4 H), 7.38 (t, J= 2 Hz, 1 H), 7.23-7.31 (m, 2 H), 6.96-7.02 (m, 2 H), 4.35-4.39 (m, 1 H), 4.11 (td, J= 2, 12 Hz, 1 H), 3.88 (s, 1 H), 3.28 (s, 3 H), 2.93 (s, 3 H), 2.6-2.65 (m, 1 H), 2.22-2.31 (m, 1 H)
1.9	R <sub>t</sub> = 1.45; m/z (ES+)= 492.2 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.95 (s, 1H), 8.86 (s, 1 H), 7.89 (dd, J= 1.2, 8 Hz, 1 H), 7.46-7.54 (m, 5 H), 7.01-7.05 (t, J= 8 Hz, 1 H), 6.97 (d, J= 8 Hz, 1 H), 4.35 (d, J= 11 Hz, 1 H), 4.08 (q, J= 12 Hz, 1 H), 3.86 (d, J= 2.8 Hz, 1 H), 3.49 (d, J= 5.2 Hz, 1 H), 2.71 (s, 3 H), 2.70 (s, 3 H), 2.65 (d, J= 14 Hz, 2 H), 2.24 (m, 1 H)
1.10	R <sub>t</sub> = 1.45; m/z (ES+)= 526.2 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.98 (s, 1H), 8.89 (s, 1 H), 7.88 (dd, J= 1.6, 8 Hz, 1 H), 7.84 (s, 1 H), 7.78 (s, 2 H), 7.63 (s, 1 H), 7.51-7.59 (m, 2 H), 7.34 (td, J= 8.4, 1.6 Hz, 1 H), 7.26 (m, 1 H), 7.04 (td, J= 7.2, 1.2 Hz, 1 H), 6.98 (d, J= 8.4 Hz, 1 H), 4.38 (m, 1 H), 4.09 (td, J= 12.4, 2 Hz, 1 H), 3.89 (d, J= 3.2 Hz, 1 H), 2.7 (s, 6 H), 2.62 (m, 1 H)

1.11	R <sub>t</sub> = 1.45; m/z (ES+)= 526.2 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.98 (s, 1H), 8.89 (s, 1 H), 7.88 (dd, J= 1.6, 8 Hz, 1 H), 7.84 (s, 1 H), 7.78 (s, 2 H), 7.63 (s, 1 H), 7.51-7.59 (m, 2 H), 7.34 (td, J= 8.4, 1.6 Hz, 1 H), 7.26 (m, 1 H), 7.04 (td, J= 7.2, 1.2 Hz, 1 H), 6.98 (d, J= 8.4 Hz, 1 H), 4.38 (m, 1 H), 4.09 (td, J= 12.4, 2 Hz, 1 H), 3.89 (d, J= 3.2 Hz, 1 H), 2.7 (s, 6 H), 2.62 (m, 1 H)
1.12	R <sub>t</sub> = 2.49; m/z= 534-35[M+H] <sup>+</sup> / Method C	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 10.7 (s, 1 H), 8.64 (s, 1 H), 8.23 (dd, J= 1.6, 8.8 Hz, 1 H), 7.78 (dd, J= 1.2, 7.2 Hz, 1 H), 7.68 (dd, J= 1.2, 7.2 Hz, 1 H), 7.63-7.66 (m, 3 H), 7.30 (d, J= 7.2 Hz, 1 H), 7.17 (td, J= 1.6, 8.4 Hz, 1 H), 6.92 (td, J= 1.2, 7.6 Hz, 1 H), 6.82 (dd, J= 1.2, 8.4 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.19-4.23 (m, 1 H), 4.06 (t, J= 5.6 Hz, 1 H), 3.82 (m, 4 H), 3.27-3.29 (m, 4 H), 2.21-2.28 (m, 2 H)
1.13	R <sub>t</sub> = 2.49; m/z= 534-35[M+H] <sup>+</sup> / Method C	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 10.7 (s, 1 H), 8.64 (s, 1 H), 8.23 (dd, J= 1.6, 8.8 Hz, 1 H), 7.78 (dd, J= 1.2, 7.2 Hz, 1 H), 7.68 (dd, J= 1.2, 7.2 Hz, 1 H), 7.63-7.66 (m, 3 H), 7.30 (d, J= 7.2 Hz, 1 H), 7.17 (td, J= 1.6, 8.4 Hz, 1 H), 6.92 (td, J= 1.2, 7.6 Hz, 1 H), 6.82 (dd, J= 1.2, 8.4 Hz, 1 H), 4.36-4.42 (m, 1 H), 4.19-4.23 (m, 1 H), 4.06 (t, J= 5.6 Hz, 1 H), 3.82 (m, 4 H), 3.27-3.29 (m, 4 H), 2.21-2.28 (m, 2 H)
1.14	R <sub>t</sub> = 3.13 ; m/z= 520.1 [M+H] <sup>+</sup> / Method D	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 8.58 (s, 1 H), 8.27 (dd, J= 1.6, 8.4 Hz, 1 H), 7.68-7.76 (m, 2 H), 7.56-7.61 (m, 1 H), 7.29 (d, J= 7.2 Hz, 1 H), 7.18-7.24 (m, 2 H), 6.91 (td, J= 1.2, 7.6 Hz, 1 H), 6.82 (dd, J= 1.2, 8.4 Hz, 1 H), 4.35-4.45 (m, 1 H), 4.19-4.22 (m, 1 H), 4.05 (t, J= 5.6 Hz, 1 H), 3.82 (t, J= 4.4 Hz, 4 H), 3.20-3.32 (m, 4H), 2.24 (m, 2 H)
1.15	R <sub>t</sub> = 3.13 ; m/z= 520.1 [M+H] <sup>+</sup> / Method D	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 8.58 (s, 1 H), 8.27 (dd, J= 1.6, 8.4 Hz, 1 H), 7.68-7.76 (m, 2 H), 7.56-7.61 (m, 1 H), 7.29 (d, J= 7.2 Hz, 1 H), 7.18-7.24 (m, 2 H), 6.91 (td, J= 1.2, 7.6 Hz, 1 H), 6.82 (dd, J= 1.2, 8.4 Hz, 1 H), 4.35-4.45 (m, 1 H), 4.19-4.22 (m, 1 H), 4.05 (t, J= 5.6 Hz, 1 H), 3.82 (t, J= 4.4 Hz, 4 H), 3.20-3.32 (m, 4H), 2.24 (m, 2 H)
3.2	R <sub>t</sub> =1.39 min, m/z= 526.0 [M-H] <sup>-</sup> / Method B	<sup>1</sup> H NMR (400 MHz, CDCl <sub>3</sub> ) δ [ppm]: 9.14 (s, 1 H), 7.98-8.01 (m, 2 H), 7.57-7.62 (m, 2 H), 7.52 (d, J= 1.6 Hz, 2 H), 7.40 (t, J= 1.6 Hz, 1 H), 7.25-7.27 (m, 2 H), 6.68-6.88 (m, 2 H), 4.62 (td, J= 2.4, 12 Hz, 1 H), 4.53 (d, J= 4.4 Hz, 1 H), 4.27-4.34 (m, 1 H), 3.05 (s, 6 H), 2.67-2.75 (m, 1 H), 2.35-2.45 (m 1 H),
4.2	R <sub>t</sub> = 1.46; m/z (ES+)= 491.0 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 10.15 (s, 1 H), 8.8 (s, 1 H), 8.63 (d, J= 5.6 Hz, 1 H), 8.09 (d, J= 2 Hz, 2 H), 8.00 (d, J= 2.8 Hz, 1 H), 7.72 (t, J= 2 Hz, 1 H), 7.27 (d, J= 7.6 Hz, 1 H), 7.16 (m, 1 H), 6.91 (m, 1 H), 6.82 (d, J= 8 Hz, 1 H), 4.38 (m, 1 H), 4.2 (m, 1 H), 4.08 (t, J= 6 Hz, 1 H), 3.04 (s, 6 H), 2.25 (m, 2 H)
4.3	R <sub>t</sub> = 2.15 ; m/z (ES+)= 521.33	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 10.19 (s, 1 H), 8.72 (s, 1 H), 8.68 (d, J= 5.6 Hz, 1 H), 8.07 (d, J= 6 Hz, 1 H), 7.65-7.72 (m, 1 H), 7.28-7.33 (m, 2 H), 7.17 (t, J= 7.2 Hz, 1 H), 6.91



	[M+H] <sup>+</sup> / Method C	(t, J= 7.6 Hz, 1 H), 6.82 (d, J= 8 Hz, 1 H), 4.35 (m, 1 H), 4.18-4.22 (m, 1 H), 4.06 (t, J= 5.6 Hz, 1 H), 3.82 (s, 4 H), 3.31 (s, 4 H), 2.25 (m, 2 H)
4.4	R <sub>t</sub> = 2.15 ; m/z (ES <sup>+</sup> )= 521.33 [M+H] <sup>+</sup> / Method C	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 10.19 (s, 1 H), 8.72 (s, 1 H), 8.68 (d, J= 5.6 Hz, 1 H), 8.07 (d, J= 6 Hz, 1 H), 7.65-7.72 (m, 1 H), 7.28-7.33 (m, 2 H), 7.17 (t, J= 7.2 Hz, 1 H), 6.91 (t, J= 7.6 Hz, 1 H), 6.82 (d, J= 8 Hz, 1 H), 4.35 (m, 1 H), 4.18-4.22 (m, 1 H), 4.06 (t, J= 5.6 Hz, 1 H), 3.82 (s, 4 H), 3.31 (s, 4 H), 2.25 (m, 2 H)
5.2	R <sub>t</sub> = 1.61; m/z (ES <sup>+</sup> )= 494.0 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 10.15 (s, 1 H), 9.32 (s, 1 H), 8.93 (s, 1 H), 8.29 (d, J= 1.6Hz, 2 H), 7.84 (t, J= 2 Hz, 1 H), 7.27 (d, J= 7.2 Hz, 1 H), 7.17 (t, J= 7.2 Hz, 1 H), 6.91 (t, J= 7.2 Hz, 1 H), 9.82 (d, J= 8 Hz, 1 H), 4.33-4.41 (m, 1 H), 4.16-4.24 (m, 1 H), 4.11 (t, J= 7.2 Hz, 1 H), 3.17 (s, 6 H), 2.17-2.27 (m, 2 H)
6.2	R <sub>t</sub> = 1.61; m/z (ES <sup>+</sup> )= 493.0 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 9.97 (s, 1 H), 8.92 (d, J= 4 Hz, 1 H), 8.88 (s, 1 H), 7.74 (m, 4 H), 7.28 (d, J= 7.6 Hz, 1 H), 7.17 (td, J= 1.6, 8.4 Hz), 6.91 (td, J= 1.2, 7.2 Hz, 1 H), 6.82 (dd, J= 1.2, 8 Hz, 1 H), 4.35 (m, 1 H), 4.20 (m, 1 H), 4.10 (t, J= 5.6 Hz, 1 H), 3.12 (s, 6 H), 2.26 (m, 2 H)
6.3	R <sub>t</sub> = 1.57; m/z (ES <sup>+</sup> )= 535.2 [M+H] <sup>+</sup> / Method B	<sup>1</sup> H NMR (400 MHz, DMSO-d <sub>6</sub> ) δ [ppm]: 9.81 (s, 1 H), 9.20 (s, 1 H), 9.87 (d, J= 4.4 Hz, 1 H), 7.73-7.77 (m, 4 H), 7.32 (d, J= 7.6 Hz, 1 H), 7.22 (td, J= 1.6, 8.4 Hz, 1 H), 6.95 (td, J= 0.8, 7.2 Hz, 1 H), 6.87 (dd, J= 0.8, 8 Hz, 1 H), 4.22-4.31 (m, 2 H), 4.09 (t, J= 5.2 Hz, 1 H), 3.63-3.72 (m, 4 H), 3.38-3.48 (m, 4 H), 2.15-2.33 (m, 2 H)

The compounds of formula (I) of the present invention are useful for the treatment and/or control, in particular helminths, in which the endoparasitic nematodes and trematodes may be the cause of serious diseases of mammals and poultry. Typical nematodes of this indication are: *Filariidae*, *Setariidae*, *Haemonchus*, *Trichostrongylus*, *Ostertagia*, *Nematodirus*, *Cooperia*, *Ascaris*, *Bunostomum*, *Oesophagostomum*, *Charbertia*, *Trichuris*, *Strongylus*, *Trichonema*, *Dictyocaulus*, *Capillaria*, *Heterakis*, *Toxocara*, *Ascaridia*, *Oxyuris*, *Ancylostoma*, *Uncinaria*, *Toxascaris* and *Parascaris*. The trematodes include, in particular, the family of *Fasciolidae*, especially *Fasciola hepatica*.

Certain parasites of the species *Nematodirus*, *Cooperia* and *Oesophagostomum* infest the intestinal tract of the host animal, while others of the species *Haemonchus* and

*Ostertagia* are parasitic in the stomach and those of the species *Dictyocaulus* are parasitic in the lung tissue. Parasites of the families and may be found in the internal cell tissue and in the organs, e.g. the heart, the blood vessels, the lymph vessels and the subcutaneous tissue. A particularly notable parasite is the heartworm of the dog, *Dirofilaria immitis*.

5

The parasites which may be treated and/or controlled by the compounds of formula (I) also include those from the class of *Cestoda* (tapeworms), e.g. the families

*Mesocestoidae*, especially of the genus *Mesocestoides*, in particular *M. lineatus*;

*Dipylidiidae*, especially *Dipylidium caninum*, *Joyeuxiella* spp., in particular *Joyeuxiella*

10 *pasquali*, and *Diplopylidium* spp., and *Taeniidae*, especially *Taenia pisiformis*, *Taenia cervi*, *Taenia ovis*, *Taenia hydatigena*, *Taenia multiceps*, *Taenia taeniaeformis*, *Taenia serialis*, and *Echinococcus* spp., most particularly *Taenia hydatigena*, *Taenia ovis*, *Taenia multiceps*, *Taenia serialis*; *Echinococcus granulosus* and *Echinococcus multilocularis*.

15 Furthermore, the compounds of formula (I) are suitable for the treatment and/or control of human pathogenic parasites. Of these, typical representatives that appear in the digestive tract are those of the genus *Ancylostoma*, *Necator*, *Ascaris*, *Strongyloides*, *Trichinella*, *Capillaria*, *Trichuris* and *Enterobius*. The compounds of the present invention are also against parasites of the genus *Wuchereria*, *Brugia*, *Onchocerca* and *Loa* from the family  
20 of *Dracunculus* and parasites of the genus *Strongyloides* and *Trichinella*, which infect the gastrointestinal tract in particular.

A particular parasite to be treated and/or and controlled by the compounds of the invention is the heartworm (*Dirofilaria immitis*). Particular subjects for such treatment are  
25 dogs and cats.

The compounds of the invention can be administered alone or in the form of a composition. In practice, the compounds of the invention are usually administered in the form of compositions, that is, in admixture with at least one acceptable excipient. The  
30 proportion and nature of any acceptable excipient(s) are determined by the properties of

the selected compound of the invention, the chosen route of administration, and standard practice as in the veterinary and pharmaceutical fields.

In one embodiment, the present invention provides compositions comprising: a  
5 compound of invention and at least one acceptable excipient.

In effecting such treatment and/or control, a compound of the invention can be administered in any form and route which makes the compound bioavailable. The compounds of the invention can be administered by a variety of routes, including orally,  
10 in particular by tablets and capsules. The compounds of the invention can be administered parenteral routes, more particularly by inhalation, subcutaneously, intramuscularly, intravenously, intraarterially, transdermally, intranasally, rectally, vaginally, ocularly, topically, sublingually, and buccally, intraperitoneally, intraadiposally, intrathecally and via local delivery for example by catheter or stent.  
15 One skilled in the art can readily select the proper form and route of administration depending upon the particular characteristics of the compound selected, the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances. The pharmaceutical compositions of the invention may be administered to the subject, for example, in the form of tablets, capsules, cachets, papers, lozenges,  
20 wafers, elixirs, ointments, transdermal patches, aerosols, inhalants, suppositories, drenches, solutions, and suspensions.

The term “acceptable excipient” refers to refers to those typically used in preparing veterinary and pharmaceutical compositions and should be pure and non-toxic in the  
25 amounts used. They generally are a solid, semi-solid, or liquid material which in the aggregate can serve as a vehicle or medium for the active ingredient. Some examples of acceptable excipients are found in Remington’s Pharmaceutical Sciences and the Handbook of Pharmaceutical Excipients and include diluents, vehicles, carriers, ointment bases, binders, disintegrates, lubricants, glidants, sweetening agents, flavoring agents, gel  
30 bases, sustained release matrices, stabilizing agents, preservatives, solvents, suspending agents, buffers, emulsifiers, dyes, propellants, coating agents, and others.

In one embodiment, the composition is adapted for oral administration, such as a tablet or a capsule or a liquid formulation, for example, a solution or suspension, adapted for oral administration. In one embodiment, the composition is adapted for oral administration,  
5 such as chewable formulation, adapted for oral administration. In still another embodiment, the composition is a liquid or semi-solid formulation, for example, a solution or suspension or a paste, adapted for parenteral administration.

Particular compositions for usage on subjects in the treatment and/or control of  
10 nematodes/ helminths comprise solutions; emulsions including classical emulsions, microemulsions and self-emulsifying compositions, that are waterless organic, preferably oily, compositions which form emulsions, together with body fluids, upon addition to the subject's body; suspensions (drenches); pour-on formulations; food additives; powders; tablets including effervescent tablets; boli; capsules including micro-capsules; and  
15 chewable treats. Particularly composition forms are tablets, capsules, food additives or chewable treats.

The compositions of the present invention are prepared in a manner well known in the veterinary and pharmaceutical art and include at least one of the compounds of the  
20 invention as the active ingredient. The amount of a compound of the present invention may be varied depending upon its particular form and may conveniently be between 1% to about 50% of the weight of the unit dose form. The present pharmaceutical compositions are preferably formulated in a unit dose form, each dose typically containing from about 0.5 mg to about 100 mg of a compounds of the invention. One or  
25 more unit dose form(s) may be taken to affect the treatment dosage.

In one embodiment, the present invention also provides a method for treating parasites, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective  
30 amount of at least one additional active compound.

In one embodiment, the present invention also provides a method for controlling parasites, comprising: administering to a subject in need thereof an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

5

In one embodiment, the present invention also provides a method for treating or controlling parasites, comprising: contacting a subject's environment with an effective amount of a compound of formula (I) or a salt thereof, the method optionally further comprising an effective amount of at least one additional active compound.

10

Thus, the invention provides for the use of the compounds of the invention as a medicament, including for the manufacture of a medicament. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of formula (I) or a salt thereof for treating parasites. In one embodiment, the invention provides the manufacture of a medicament comprising a compound of the invention or a salt thereof for controlling parasites.

15

The terms "treating", "to treat", "treated", or "treatment", include without limitation restraining, slowing, stopping, reducing, ameliorating, reversing the progression or severity of an existing symptom, or preventing a disorder, condition, or disease. For example, an adult heartworm infection would be treated by administering a compound of the invention. A treatment may be applied or administered therapeutically.

20

The terms "control", "controlling" or "controlled" refers to include without limitation decreasing, reducing, or ameliorating the risk of a symptom, disorder, condition, or disease, and protecting an animal from a symptom, disorder, condition, or disease.

25

Controlling may refer to therapeutic, prophylactic, or preventative administration. It is well understood that a larvae or immature heartworm infection may be asymptomatic and infection by mature parasites is symptomatic and/or debilitating. Therefore, for example, a heartworm infection would be controlled by acting on the larvae or immature parasite preventing the infection from progressing to an infection by mature parasites.

30

Thus, the use of the compounds of the invention in the treatment and/or control of parasites, in particular helminths, in which the endoparasitic nematodes and trematodes refers to the use of the compounds of the invention to act on the various forms of the parasites throughout its life cycle, independent of whether a subject is manifesting a symptom, including morbidity or mortality, and independently of the phase(s) of the parasitic challenge.

As used herein, “administering to a subject” includes but is not limited to cutaneous, subcutaneous, intramuscular, mucosal, submucosal, transdermal, oral or intranasal administration. Administration could include injection or topical administration.

10

The terms “subject” and “patient” refers includes humans and non-human mammalian animals, such as dogs, cats, mice, rats, guinea pigs, rabbits, ferrets, cows, horses, sheep, goats, and pigs. It is understood that a more particular subject is a human. Also, a more particular subject are mammalian pets or companion animals, such as dogs and cats and also mice, guinea pigs, ferrets, and rabbits.

15

The term “effective amount” refers to an amount which gives the desired benefit to the subject and includes administration for both treatment and control. The amount will vary from one individual subject to another and will depend upon a number of factors, including the overall physical condition of the subject and the severity of the underlying cause of the condition to be treated, concomitant treatments, and the amount of compound of the invention used to maintain desired response at a beneficial level.

20

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount, the dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of patient; its size, age, and general health; the specific condition, disorder, infection, or disease involved; the degree of or involvement or the severity of the condition, disorder, or disease, the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of

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the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances. An effective amount of the present invention, the treatment dosage, is expected to range from 0.5 mg to 100 mg. Specific amounts can be determined by the skilled person. Although these dosages are based on a  
5 subject having a mass of about 1 kg to about 20 kg, the diagnostician will be able to determine the appropriate dose for a subject whose mass falls outside of this weight range. An effective amount of the present invention, the treatment dosage, is expected to range from 0.1 mg to 10 mg/kg of the subject. The dosing regimen is expected to be daily, weekly, or monthly administration.

10

The compounds of the invention may be combined with one or more other active compounds or therapies for the treatment of one or more disorders, diseases or conditions, including the treatment of parasites, for which it is indicated. The compounds of the invention may be administered simultaneously, sequentially or separately in combination  
15 with one or more compounds or therapies for treating parasites and other disorders.

For example, when used to treat parasites, including heartworm, a compound of the invention may be combined with a macrocyclic lactone such as ivermectin, moxidectin, or milbemycin oxime, or with imidacloprid. Particular combinations for treating parasites  
20 include a compound of the invention and ivermectin. Another particular combination for treating parasites include a compound of the invention and milbemycin oxime.

Thus, it is understood that the compositions and methods of the present invention optionally include comprising an effective amount of at least one additional active  
25 compound.

The activity of compounds as parasiticides may be determined by a variety of methods, including in vitro and in vivo methods.

30

## Example A

Dog heart worm microfilariae

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*D. immitis* microfilariae are isolated by filtration from beagle blood of an infected donor and allowed to incubate in appropriate media. Test compounds are diluted in DMSO and added to a 96-well plate containing parasites. Plates are incubated for the desired time and motility is assessed using an LCD camera imaging system. Effect of serum is tested by  
5 addition of up to 20% fetal bovine serum in the assay. Percent motility inhibition values are generated relative to the average of the DMSO-only wells.

In this test for example, the following compounds from the preparation examples showed  $EC_{50} < 0.1 \mu\text{g/mL}$ : 1.1, 1.3, 1.4, 1.6, 1.7, 1.9, 1.11, 1.12, 6.2, and 6.3.

10

## Example B

Ruminant gastrointestinal (*H. contortus* (*H.c.*)):

*H.c.* eggs isolated from lamb fecal matter are allowed to hatch overnight. Test compounds are diluted in DMSO and added to a 96-well plate containing appropriate media. *H.c.* larvae are added to each well and plates are incubated for the desired time(s). Motility is  
15 assessed using an LCD camera imaging system. Percent motility inhibition values are generated relative to the average of the DMSO-only wells.

In this test for example, the following compounds from the preparation examples showed  $EC_{50} < 1 \mu\text{g/mL}$ : 1.1, 1.4, 1.6, 1.9, 1.11, 1.12, 4.2, 6.1, 6.2, 6.3, and 7.1.

20

## Example C

Gastro intestinal nematodes

Jirds (*Meriones unguiculatus*), are artificially infected by gavage with third instar larvae each of *T. colubriformis* and *H. contortus*. Then treated orally with the test compound formulated in eg DMSO/PEG 2/1, on Day 6 after infection at a dose in a range between  
25  $1 \times 3 \text{ mg/kg}$  up to  $1 \times 32 \text{ mg/kg}$ . Three days after treatment, gerbils are euthanized and dissected to recover *H. contortus* from stomach and *T. colubriformis* from the small intestine. Efficacy is expressed as a % reduction in worm numbers in comparison with a placebo treated group, using the Abbot's formula.

The compound of example 1.1 was  $> 80\%$  effective against Hc and Tc. The compound of  
30 examples 1.4 and 1.11 were  $> 80\%$  effective against Hc.



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## Example D

Filarial nematodes

Av model: Gerbils, injected subcutaneously with infective *A. viteae* larvae, were subsequently treated with the test article formulated in eg DMSO/PEG 2/1, by oral gavage at a dose in a range between 1x3 mg/kg up to 5x32mg/kg (one dose per day for 5 consecutive days). At necropsy 12 weeks after infection, efficacy is expressed as a % reduction in worm numbers in comparison with the placebo treated group, using the Abbot's formula.

The compound of examples 1.1, 1.4, and 1.11 were >80% effective against Av.

10

## Example E

*L.s.* model

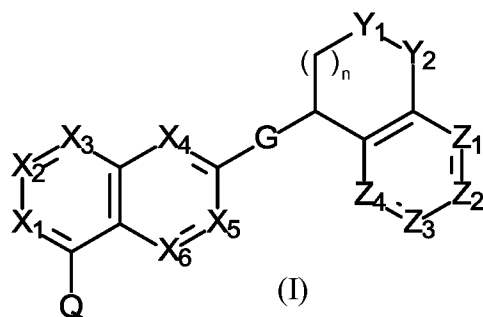
Mice, injected subcutaneously with infective *L. sigmodontis* larvae, were subsequently treated with the test article formulated in eg DMSO/PEG 2/1, by oral gavage at a dose in a range between 1x3 mg/kg up to 5x32mg/kg (one dose per day for 5 consecutive days). At necropsy 5 weeks after infection, efficacy is calculated by counting developed larvae vs. untreated animals using Abbot's formula.

The compound of example 1.4 was >80% effective against Ls.

20

WE CLAIM:

1. A compound of compounds of formula (I):



5

wherein

n is 0 or 1;

X<sub>1</sub> is selected from the group consisting of N and CR<sub>1</sub>;

X<sub>2</sub> is selected from the group consisting of N and CR<sub>2</sub>;

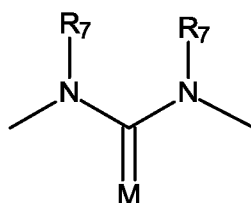
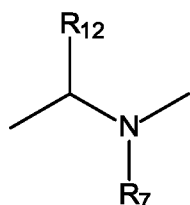
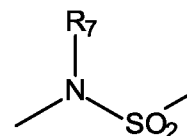
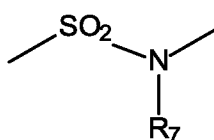
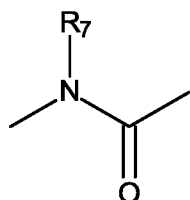
10 X<sub>3</sub> is selected from the group consisting of N and CR<sub>3</sub>;

X<sub>4</sub> is selected from the group consisting of N and CR<sub>4</sub>;

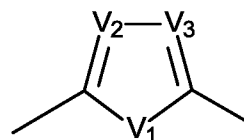
X<sub>5</sub> is selected from the group consisting of N and CR<sub>5</sub>;

X<sub>6</sub> is selected from the group consisting of N and CR<sub>6</sub>;

G is the group



and



15

;

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$Y_1$  is selected from the group consisting of  $CR_8R_9$ , O, S, and  $NR_{10}$ ;

$Y_2$  is selected from the group consisting of  $CR_8R_9$ , O, S, and  $NR_{10}$ ;

wherein at least one of the groups  $Y_1$  or  $Y_2$  is  $CR_8R_9$ ;

$Z_1$  is selected from the group consisting of N, O, S, and  $CR_{11}$ ;

5  $Z_2$  is selected from the group consisting of nil, N, and  $CR_{11}$ ;

$Z_3$  is selected from the group consisting of nil, N and  $CR_{11}$ ;

$Z_4$  is selected from the group consisting of N, O, S, and  $CR_{11}$ ;

wherein no more than 2 of  $Z_1$ ,  $Z_2$ ,  $Z_3$ , and  $Z_4$  are N and wherein only one of  $Z_1$  and

$Z_4$  is O or S,  $Z_2$  is nil only when  $Z_1$  is O or S, and  $Z_3$  is nil only when  $Z_4$  is O or S;

10  $R_1$  is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, - $SC_{1-C_4}$  alkyl, - $S(O)(C_{1-C_4}$  alkyl, - $S(O)_2(C_{1-C_4}$  alkyl, cyano,  $C_{1-C_4}$  alkyl,  $C_{1-C_4}$  halogenoalkyl,  $C_{1-C_4}$ -alkoxy, - $B(OR_{16})(OR_{17})$  wherein  $R_{16}$  is, each time taken, selected from the group consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl,  $R_{17}$  is, each time taken, selected from the group consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl, or  $R_{16}$   
 15 and  $R_{17}$  together with the oxygen atoms to which they are attached form a 5- to 7-membered ring which is optionally substituted with 1 to 4  $C_{1-C_4}$  alkyl; - $NH_2$ , - $NH(C_{1-C_4}$  alkyl), and - $N(C_{1-C_4}$  alkyl)<sub>2</sub>;

$R_2$  is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, - $SC_{1-C_4}$  alkyl, - $S(O)(C_{1-C_4}$  alkyl, - $S(O)_2(C_{1-C_4}$  alkyl, cyano,  $C_{1-C_4}$  alkyl,  $C_{1-C_4}$  halogenoalkyl,  $C_{1-C_4}$ -alkoxy, - $B(OR_{16})(OR_{17})$  wherein  $R_{16}$  is, each time taken, selected from the group consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl,  $R_{17}$  is, each time taken, selected from the group consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl, or  $R_{16}$   
 20 and  $R_{17}$  together with the oxygen atoms to which they are attached form a 5- to 7-membered ring which is optionally substituted with 1 to 4  $C_{1-C_4}$  alkyl; - $NH_2$ , - $NH(C_{1-C_4}$  alkyl), and - $N(C_{1-C_4}$  alkyl)<sub>2</sub>;

$R_3$  is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, - $SC_{1-C_4}$  alkyl, - $S(O)(C_{1-C_4}$  alkyl, - $S(O)_2(C_{1-C_4}$  alkyl, cyano,  $C_{1-C_4}$  alkyl,  $C_{1-C_4}$  halogenoalkyl,  $C_{1-C_4}$ -alkoxy, - $B(OR_{16})(OR_{17})$  wherein  $R_{16}$  is, each time taken, selected from the group consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl,  $R_{17}$  is, each time taken,  
 25 selected from the group consisting or hydrogen,  $C_{1-C_4}$  alkyl, and  $C_3-C_6$  cycloalkyl, or  $R_{16}$   
 30 and  $R_{17}$  together with the oxygen atoms to which they are attached form a 5- to 7-

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membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

R<sub>4</sub> is selected from the group consisting of halogen, cyano, -CHO, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy substituted-C<sub>1</sub>-C<sub>4</sub> alkyl, benzyl optionally substituted with 1 to 5 halogen atoms, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NH(4- to 7-membered heterocycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(4- to 7-membered heterocycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> alkoxy), -C(O)NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -B(OR<sub>16</sub>)(OR<sub>17</sub>) wherein R<sub>16</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7- membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; 6- or 10 membered aryl; and a monocyclic heterocycle selected from the group of 4- to 7-membered heterocycloalkyl, 5-membered heteroaryl having at least one nitrogen atom via which the 5-membered heteroaryl ring is connected to the rest of the molecule; 6-membered heteroaryl having at least one nitrogen atom; each of the aryl, heterocycloalkyl, and heteroaryl ring in R<sub>4</sub> is optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; and wherein each C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl and C<sub>1</sub>-C<sub>4</sub> alkoxy in R<sub>4</sub> may be optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, hydroxyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, cyano, carboxyl, carbamoyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -C(O)NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -C(O)N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

R<sub>5</sub> is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)(C<sub>1</sub>-C<sub>4</sub> alkyl), -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -B(OR<sub>16</sub>)(OR<sub>17</sub>) wherein R<sub>16</sub> is, each time taken, selected from the group

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consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7-membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

R<sub>6</sub> is selected from the group consisting of hydrogen, halogen, hydroxyl, -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)(C<sub>1</sub>-C<sub>4</sub> alkyl), -S(O)<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -B(OR<sub>16</sub>)(OR<sub>17</sub>) wherein R<sub>16</sub> is, each time taken, selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, R<sub>17</sub> is, each time taken,

10 selected from the group consisting or hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl, or R<sub>16</sub> and R<sub>17</sub> together with the oxygen atoms to which they are attached form a 5- to 7-membered ring which is optionally substituted with 1 to 4 C<sub>1</sub>-C<sub>4</sub> alkyl; -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>;

R<sub>7</sub> is selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl optionally substituted with 1 to 5 halogen atoms, -C(H)O, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, and C<sub>1</sub>-C<sub>4</sub>-alkoxy;

R<sub>8</sub> is, each time selected, independently selected from the group consisting of hydrogen, fluoro, and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>9</sub> is, each time selected, independently selected from the group consisting of hydrogen, fluoro, and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>10</sub> is selected from the group consisting of hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>11</sub> is, each time selected, independently selected from the group consisting of hydrogen, halogen, hydroxyl, cyano, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>; and

25 Q is selected from the group consisting of 6- or 10 membered aryl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, 30 -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, wherein the 6- or 10 membered aryl is optionally fused with a 4- to 7-membered heterocycloalkyl having 1 or 2

heteroatoms selected from the group O, S, and N and wherein the carbons of the heterocycloalkyl are optionally substituted with 1, 2 or 3 substituents independently selected from the group halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heterocycloalkyl is, valency permitting, substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the 5- to 10-membered heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heteroaryl, valency permitting, is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the 4- to 7-membered heterocycloalkyl or optionally benzo-fused 4- to 7-membered heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heterocycloalkyl is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; 6- or 10 membered aryloxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; 6- or 10 membered arylthio-oxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-

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C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl; and 5- to 10-membered heteroaryloxy optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxyl, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl;

M is selected from the group consisting of N-R<sub>13</sub>, O, and S;

R<sub>13</sub> is selected from the group consisting of hydroxy, C<sub>1</sub>-C<sub>4</sub> alkoxy, and -NH<sub>2</sub>;

10 V<sub>1</sub> is selected from the group consisting of NR<sub>14</sub>, O, and S;

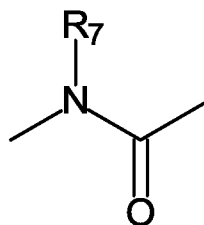
R<sub>14</sub> is hydrogen and C<sub>1</sub>-C<sub>4</sub> alkyl;

V<sub>2</sub> and V<sub>3</sub> are, independently, selected from the group consisting of CR<sub>15</sub> and N;

R<sub>15</sub> is selected from the group consisting of hydrogen, halogen, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

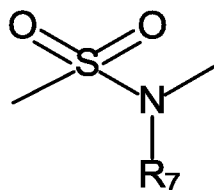
15 or a salt thereof.

2. A compound according to claim 1 wherein G is



or a salt thereof.

3. A compound according to claim 1 wherein G is

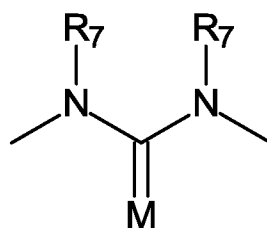


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or a salt thereof.

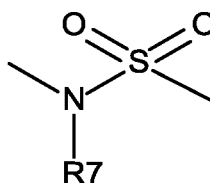
4. A compound according to claim 1 wherein G is

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or a salt thereof.

5. A compound according to claim 1 wherein G is



5 or a salt thereof.

6. A compound according to any one of claims 1 to 5 wherein X<sub>1</sub> is CR<sub>1</sub>; X<sub>2</sub> is CR<sub>2</sub>; X<sub>3</sub> is CR<sub>3</sub>; X<sub>4</sub> is CR<sub>4</sub>; X<sub>5</sub> is CR<sub>5</sub>; and X<sub>6</sub> is CR<sub>6</sub>; or a salt thereof.

7. A compound according to any one of claims 1 to 5 wherein X<sub>1</sub> is CR<sub>1</sub>; X<sub>2</sub> is CR<sub>2</sub>; X<sub>3</sub> is CR<sub>3</sub>; X<sub>4</sub> is CR<sub>4</sub>; X<sub>5</sub> is CR<sub>5</sub>; and X<sub>6</sub> is N; or a salt thereof.

10 8. A compound according to any one of claims 1 to 5 wherein X<sub>1</sub> is N; X<sub>2</sub> is CR<sub>2</sub>; X<sub>3</sub> is CR<sub>3</sub>; X<sub>4</sub> is CR<sub>4</sub>; X<sub>5</sub> is CR<sub>5</sub>; and X<sub>6</sub> is N; or a salt thereof.

9. A compound according to any one of claims 1 to 5 wherein X<sub>1</sub> is CR<sub>1</sub>; X<sub>2</sub> is CR<sub>2</sub>; X<sub>3</sub> is CR<sub>3</sub>; X<sub>4</sub> is CR<sub>4</sub>; X<sub>5</sub> is CR<sub>5</sub>; and X<sub>6</sub> is N; or a salt thereof.

10. A compound according to any one of claims 1 to 9 wherein

15 Q is a 6- or 10 membered aryl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl,  
 20 -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl;  
 or a salt thereof.

11. A compound according to any one of claims 1 to 9 wherein



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Q is 6-membered aryl optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub>, -NH(C<sub>3</sub>-C<sub>6</sub> cycloalkyl), -N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>3</sub>-C<sub>6</sub>-cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl),  
5 -SC<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -S(O)C<sub>1</sub>-C<sub>4</sub>-halogenoalkyl and -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, wherein the 6-membered aryl is fused with a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the heterocycloalkyl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro,  
10 hydroxy, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heterocycloalkyl is substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl;  
or a salt thereof.

12. A compound according to any one of claims 1 to 9 wherein  
Q is a 5- to 10-membered heteroaryl having 1 or 2 heteroatoms selected from the group O, S, and N and wherein the carbons of the heteroaryl are optionally substituted with 1, 2 or 3 substituents independently selected from the group consisting of halogen, cyano, nitro, -OH, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub> halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>,  
20 -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in the heteroaryl is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl;  
or a salt thereof.

13. A compound according to any one of claims 1 to 9 wherein  
25 Q is a 4- to 7-membered heterocycloalkyl having 1 or 2 heteroatoms selected from the group O, S, N, wherein the heterocycloalkyl is optionally benzo-fused, wherein the carbons of the heterocycloalkyl or optionally benzo-fused heterocycloalkyl are optionally substituted with 1, 2, 3, or 4 substituents independently selected from the group consisting of halogen, cyano, nitro, hydroxy, oxo, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, C<sub>1</sub>-C<sub>4</sub>  
30 halogenoalkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, -NH<sub>2</sub>, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), and -N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> and any N in

the heterocyclalkyl is optionally substituted with a substituent selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>3</sub>-C<sub>6</sub> cycloalkyl; or a salt thereof.

14. The compound according to any one of claims 1 to 13 wherein  
5 n is 1; or a salt thereof.

15. The compound according to any one of claims 1 to 14 wherein  
Y<sub>1</sub> is CR<sub>8</sub>R<sub>9</sub> and Y<sub>2</sub> is O; or a salt thereof;

16. The compound according to any one of claims 1 to 15 wherein  
R<sub>4</sub> is selected from the group consisting of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -N(C<sub>1</sub>-C<sub>4</sub>  
10 alkyl)<sub>2</sub>, and 4- to 7-membered heterocycloalkyl; or a salt thereof.

17. A compound of claim 1 wherein the compound is selected from the group  
consisting of

- (4R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide;  
(4S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide;  
15 (1R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]tetralin-1-carboxamide  
(1S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]tetralin-1-carboxamide;  
(4R)-N-[4-cyclopropyl-8-(3,5-dichlorophenyl)-3-quinolyl]chromane-4-carboxamide;  
(4S)-N-[4-cyclopropyl-8-(3,5-dichlorophenyl)-3-quinolyl]chromane-4-carboxamide;  
(4R)-N-[8-(3,5-dichlorophenyl)-4-[methoxy(methyl)amino]-3-quinolyl]chromane-4-  
20 carboxamide;  
(4S)-N-[8-(3,5-dichlorophenyl)-4-[methoxy(methyl)amino]-3-quinolyl]chromane-4-  
carboxamide;  
(4S)-N-[8-(2,3-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]chromane-4-carboxamide;  
(4R)-N-[8-[3-chloro-5-(trifluoromethyl)phenyl]-4-(dimethylamino)-3-quinolyl]chromane-  
25 4-carboxamide;  
(4S)-N-[8-[3-chloro-5-(trifluoromethyl)phenyl]-4-(dimethylamino)-3-quinolyl]chromane-  
4-carboxamide;  
(4S)-N-[8-(3,5-dichlorophenyl)-4-morpholino-3-quinolyl]chromane-4-carboxamide;  
(4R)-N-[8-(3,5-dichlorophenyl)-4-morpholino-3-quinolyl]chromane-4-carboxamide;  
30 (4S)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-3-quinolyl]chromane-4-carboxamide;  
(4R)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-3-quinolyl]chromane-4-carboxamide;]

- 3-[1-[[[(4R)-chroman-4-yl]amino]-2,2,2-trifluoro-ethyl]-8-(3,5-dichlorophenyl)-N,N-dimethyl-quinolin-4-amine;
- 3-[1-[[[(4S)-chroman-4-yl]amino]-2,2,2-trifluoro-ethyl]-8-(3,5-dichlorophenyl)-N,N-dimethyl-quinolin-4-amine;
- 5 N-[(4S)-chroman-4-yl]-8-(3,5-dichlorophenyl)-4-(dimethylamino)quinoline-3-sulfonamide;
- N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]-(4R and S)-chromane-4-sulfonamide;
- (4S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridin-3-yl]chromane-4-
- 10 carboxamide;
- (4R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,7-naphthyridin-3-yl]chromane-4-carboxamide;
- (4S)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-1,7-naphthyridin-3-yl]chromane-4-carboxamide;
- 15 (4R)-N-[4-morpholino-8-(2,3,5-trifluorophenyl)-1,7-naphthyridin-3-yl]chromane-4-carboxamide;
- (4S)-N-[4-(3,5-dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidin-7-yl]chromane-4-carboxamide;
- (4R)-N-[4-(3,5-dichlorophenyl)-8-(dimethylamino)pyrido[3,2-d]pyrimidin-7-
- 20 yl]chromane-4-carboxamide;
- (4R)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridin-3-yl]chromane-4-carboxamide;
- (4S)-N-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-1,5-naphthyridin-3-yl]chromane-4-carboxamide;
- 25 (4S)-N-[8-(3,5-dichlorophenyl)-4-morpholino-1,5-naphthyridin-3-yl]chromane-4-carboxamide;
- 1-[(4S)-Chroman-4-yl]-3-[8-(3,5-dichlorophenyl)-4-(dimethylamino)-3-quinolyl]urea;
- (4R)-N-[5-(3,5-dichlorophenyl)-1-(dimethylamino)-2-naphthyl]chromane-4-
- carboxamide; and
- 30 (4S)-N-[5-(3,5-dichlorophenyl)-1-(dimethylamino)-2-naphthyl]chromane-4-carboxamide;
- or a salt of each of the above-mentioned compounds.

18. A composition comprising a compound of any one of claims 1 to 17, or a salt thereof, and at least one acceptable carrier.

19. The use of a compound of any one of claims 1 to 17, or a salt thereof, as a medicament.

5       20. The use of a compound of any one of claims 1 to 17, or a salt thereof, in the manufacture of a medicament for treating parasites.

21. The use of a compound of any one of claims 1 to 17, or a salt thereof, in the manufacture of a medicament for controlling heartworm.

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2019/066302

**A. CLASSIFICATION OF SUBJECT MATTER**  
 INV. A61P33/00 C07D215/42 C07D311/58 C07D405/12 C07D471/04  
 A61K31/4709 A61K31/4706 A61K31/5377 A61K31/4375 A61K31/519  
 A61K31/353  
 According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**  
 Minimum documentation searched (classification system followed by classification symbols)  
 A61P C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 EPO-Internal, CHEM ABS Data, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2018/087036 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 17 May 2018 (2018-05-17) cited in the application claims 1, 10-12, 14 -----	1-15, 17-21
A	WO 2017/178416 A1 (BAYER ANIMAL HEALTH GMBH [DE]) 19 October 2017 (2017-10-19) cited in the application claims 1, 10-12, 14 -----	1-21

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search  4 February 2020	Date of mailing of the international search report  12/02/2020
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer  Brandstetter, T
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# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2019/066302

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

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

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

see additional sheet

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

### Remark on Protest

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

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-21

compounds of formula I and subject-matter referring to them

1.1. claims: 2(completely); 1, 6-21(partially)

compounds of formula I, wherein G is N(R7)C(O) and subject-matter referring to them

1.2. claims: 3, 5(completely); 1, 6-21(partially)

compounds of formula I, wherein G is SO<sub>2</sub>N(R7) or N(R7)SO<sub>2</sub> and subject-matter referring to them

1.3. claims: 1, 6-21(all partially)

compounds of formula I, wherein G is CH(R<sub>12</sub>)N(R7) and subject-matter referring to them

1.4. claims: 4(completely); 1, 6-21(partially)

compounds of formula I, wherein G is N(R7)C(M)N(R7) and subject-matter referring to them

1.5. claims: 1, 6-16, 18-21(all partially)

compounds of formula I, wherein G is the 5-membered ring carrying V1 to V3 and subject-matter referring to them

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/066302

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
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			CA 3020793 A1	19-10-2017
			CL 2018002920 A1	01-02-2019
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			DO P2018000226 A	15-11-2018
			EP 3442974 A1	20-02-2019
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