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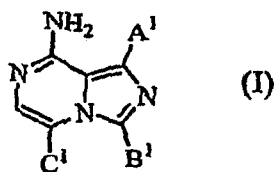
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(54) Title: CONDENSED HETEROCYCLIC COMPOUNDS AS INHIBITORS OF PROTEIN KINASES

(57) Abstract: Compounds having Formula (I) that inhibit Aurora-kinases,  
compositions containing the compounds and methods of treating diseases using  
the compounds are disclosed.



## CONDENSED HETEROCYCLIC COMPOUNDS AS INHIBITORS OF PROTEIN

### FIELD OF THE INVENTION

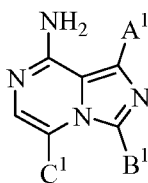
This invention pertains to compounds that inhibit protein kinases such as Aurora-kinases, compositions containing the compounds and methods of treating diseases using the compounds.

### 5 BACKGROUND OF THE INVENTION

Mitosis is a process by which a complete copy of a duplicated genome is segregated by the microtubule spindle apparatus into two daughter cells. Aurora-kinases, key mitotic regulators required for genome stability, have been found to be overexpressed in human tumors. There is therefore an existing need in the therapeutic  
 10 arts for compounds which inhibit Aurora-kinases, compositions comprising the inhibitors and methods of treating diseases during which Aurora-kinases are unregulated or overexpressed.

### SUMMARY OF THE INVENTION

15 One embodiment of this invention, therefore, pertains to compounds that inhibit Aurora-kinases, the compounds having Formula I



(I),

20 and therapeutically acceptable salts thereof, wherein

$A^1$  is  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $OC(O)OR^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$  or  $R^5$ ;

25

$B^1$  and  $C^1$  are independently H,  $C(O)NHR^1$ ,  $C(O)N(R^1)_2$ ,  $NHC(O)R^1$ ,  $NR^1C(O)R^1$ ,  $NHC(O)NHR^1$ ,  $NHC(O)N(R^1)_2$ ,  $NR^1C(O)NHR^1$ ,  $NR^1C(O)N(R^1)_2$ ,  $SO_2NHR^1$ ,  $SO_2N(R^1)_2$ ,  $NHSO_2R^1$ ,  $NR^1SO_2R^1$ ,  $OC(O)OR^1$ ,  $NHC(O)OR^1$ ,  $NR^1C(O)OR^1$  or  $R^5$ ; wherein

30

$R^1$  is  $R^2$ ,  $R^3$  or  $R^4$ ;

$R^2$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{2A}$ ;  $R^{2A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

35

$R^3$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{3A}$ ;  
 $R^{3A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of  
 5 which is unfused or fused with benzene, heteroarene or  $R^{4A}$ ;  $R^{4A}$  is cycloalkane,  
 cycloalkene, heterocycloalkane or heterocycloalkene;

$R^5$  is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted  
 with one, two, three, four or five of independently selected  $R^6$ ,  $OR^6$ ,  $SR^6$ ,  $S(O)R^6$ ,  
 10  $SO_2R^6$ ,  $NH_2$ ,  $NHR^6$ ,  $N(R^6)_2$ ,  $C(O)R^6$ ,  $C(O)NH_2$ ,  $C(O)NHR^6$ ,  $C(O)N(R^6)_2$ ,  
 $NHC(O)R^6$ ,  $NR^6C(O)R^6$ ,  $NHSO_2R^6$ ,  $NR^6SO_2R^6$ ,  $NHC(O)OR^6$ ,  $NR^6C(O)OR^6$ ,  
 $SO_2NH_2$ ,  $SO_2NHR^6$ ,  $SO_2N(R^6)_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)R^6$ ,  $NHC(O)N(R^6)_2$ ,  
 $NR^6C(O)N(R^6)_2$ , OH, (O), C(O)OH, CN,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

15  $R^6$  is  $R^7$ ,  $R^8$ ,  $R^9$ , or  $R^{9A}$ ;

$R^7$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{7A}$ ;  $R^{7A}$   
 is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20  $R^8$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{8A}$ ;  
 $R^{8A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^9$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of  
 which is unfused or fused with benzene, heteroarene or  $R^{9A}$ ;  $R^{9A}$  is cycloalkane,  
 25 cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{9A}$  is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted  
 with one, two, three, four or five of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $SO_2NH_2$ ,  
 $NHC(O)NH_2$ , OH, (O), C(O)OH, CN,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

30

wherein each foregoing cyclic moiety is independently unsubstituted or  
 substituted with one or two or three or four or five of independently selected  $R^{30}$ ,  
 $OR^{30}$ ,  $OCH_2R^{30}$ ,  $SR^{30}$ ,  $S(O)R^{30}$ ,  $SO_2R^{30}$ ,  $C(O)R^{30}$ ,  $CO(O)R^{30}$ ,  $OC(O)R^{30}$ ,  
 $OC(O)OR^{30}$ ,  $NO_2$ ,  $NH_2$ ,  $NHR^{30}$ ,  $N(R^{30})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{30}$ ,  $C(O)N(R^{30})_2$ ,  
 35  $NHC(O)R^{30}$ ,  $NHC(O)NHR^{30}$ ,  $NHC(O)N(R^{30})_2$ ,  $NR^{30}C(O)NHR^{30}$ ,  $NR^{30}C(O)N(R^{30})_2$ ,  
 $C(O)NHOH$ ,  $C(O)NHOR^{30}$ ,  $C(O)NHSO_2R^{30}$ ,  $C(O)NR^{30}SO_2R^{30}$ ,  $SO_2NH_2$ ,  
 $SO_2NHR^{30}$ ,  $SO_2N(R^{30})_2$ ,  $CF_3$ ,  $CF_2CF_3$ , C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>30</sup>,  
 $C(N)N(R^{30})_2$ , CNOH, CNOCH<sub>3</sub>, OH, (O), N<sub>3</sub>,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ , F, Cl,  
 Br or I;

40

$R^{30}$  is  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$  or  $R^{34}$ ;

R<sup>31</sup> is phenyl which is unfused or fused with benzene, heteroarene or R<sup>31A</sup>;  
 R<sup>31A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

5 R<sup>32</sup> is heteroaryl which is unfused or fused with benzene, heteroarene or R<sup>32A</sup>;  
 R<sup>32A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>33</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each  
 of which is unfused or fused with benzene, heteroarene or R<sup>33A</sup>; R<sup>33A</sup> is cycloalkane,  
 cycloalkene, heterocycloalkane or heterocycloalkene;

10

R<sup>34</sup> is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted  
 with one, two, three, four or five of independently selected R<sup>35</sup>, OR<sup>35</sup>, SR<sup>35</sup>, S(O)R<sup>35</sup>,  
 SO<sub>2</sub>R<sup>35</sup>, NH<sub>2</sub>, NHR<sup>35</sup>, N(R<sup>35</sup>)<sub>2</sub>, C(O)R<sup>35</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>35</sup>, C(O)N(R<sup>35</sup>)<sub>2</sub>,  
 NHC(O)R<sup>35</sup>, NR<sup>35</sup>C(O)R<sup>35</sup>, NHSO<sub>2</sub>R<sup>35</sup>, NR<sup>35</sup>SO<sub>2</sub>R<sup>35</sup>, NHC(O)OR<sup>35</sup>,  
 15 NR<sup>35</sup>C(O)OR<sup>35</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>35</sup>, SO<sub>2</sub>N(R<sup>35</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)NHR<sup>35</sup>,  
 NHC(O)R<sup>35</sup>, NHC(O)N(R<sup>35</sup>)<sub>2</sub>, NR<sup>35</sup>C(O)N(R<sup>35</sup>)<sub>2</sub>, OH, (O), C(O)OH, CN, CF<sub>3</sub>,  
 OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

20

R<sup>35</sup> is R<sup>36</sup>, R<sup>37</sup>, R<sup>38</sup> or R<sup>39</sup>;

R<sup>36</sup> is phenyl which is unfused or fused with benzene, heteroarene or R<sup>36A</sup>;  
 R<sup>36A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

25

R<sup>37</sup> is heteroaryl which is unfused or fused with benzene, heteroarene or R<sup>37A</sup>;  
 R<sup>37A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>38</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each  
 of which is unfused or fused with benzene, heteroarene or R<sup>38A</sup>; R<sup>38A</sup> is cycloalkane,  
 cycloalkene, heterocycloalkane or heterocycloalkene;

30

R<sup>39</sup> is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted  
 with  
 R<sup>40</sup>;

35

R<sup>40</sup> is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl;

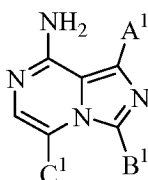
wherein the moieties represented by R<sup>31</sup>, R<sup>32</sup>, R<sup>33</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> are  
 independently unsubstituted or substituted with one or two or three of independently  
 selected F, Cl, Br, I, OH, (O)OH, NO<sub>2</sub>, NH<sub>2</sub>, CF<sub>3</sub>, OH, R<sup>45</sup>, OR<sup>45</sup>, SR<sup>45</sup>, S(O)R<sup>45</sup>,  
 40 SO<sub>2</sub>R<sup>45</sup>, C(O)NHR<sup>45</sup>, C(O)N(R<sup>45</sup>)<sub>2</sub>, NHC(O)R<sup>45</sup>, NR<sup>45</sup>C(O)R<sup>45</sup>, NHC(O)NHR<sup>45</sup>,  
 NHC(O)N(R<sup>45</sup>)<sub>2</sub>, NR<sup>45</sup>C(O)NHR<sup>45</sup>, NR<sup>45</sup>C(O)N(R<sup>45</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>45</sup>, SO<sub>2</sub>N(R<sup>45</sup>)<sub>2</sub>,  
 NHSO<sub>2</sub>R<sup>45</sup>, NR<sup>45</sup>SO<sub>2</sub>R<sup>45</sup>, OC(O)OR<sup>45</sup>, NHC(O)OR<sup>45</sup> or NR<sup>45</sup>C(O)OR<sup>45</sup>;

$R^{45}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{50}$ , F, Cl, Br, I, OH, C(O)OH,  $NO_2$  or  $NH_2$ ; and

5  $R^{50}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl.

Still another embodiment pertains to compositions comprising an excipient and a therapeutically effective amount of a compound having Formula I.

10 Still another embodiment pertains to methods of treating diseases involving overexpression or unregulation of Aurora-kinases in a mammal, the methods comprising administering thereto a therapeutically effective amount of a compound having Formula I,



15

(I),

and therapeutically acceptable salts thereof, wherein

20  $A^1$  is C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup> or R<sup>5</sup>;

25  $B^1$  and  $C^1$  are independently H, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup> or R<sup>5</sup>; wherein

$R^1$  is  $R^2$ ,  $R^3$  or  $R^4$ ;

30  $R^2$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{2A}$ ;  $R^{2A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^3$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{3A}$ ;  $R^{3A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

35

$R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{4A}$ ;  $R^{4A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

5  $R^5$  is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $R^6$ ,  $OR^6$ ,  $SR^6$ ,  $S(O)R^6$ ,  $SO_2R^6$ ,  $NH_2$ ,  $NHR^6$ ,  $N(R^6)_2$ ,  $C(O)R^6$ ,  $C(O)NH_2$ ,  $C(O)NHR^6$ ,  $C(O)N(R^6)_2$ ,  $NHC(O)R^6$ ,  $NR^6C(O)R^6$ ,  $NHSO_2R^6$ ,  $NR^6SO_2R^6$ ,  $NHC(O)OR^6$ ,  $NR^6C(O)OR^6$ ,  $SO_2NH_2$ ,  $SO_2NHR^6$ ,  $SO_2N(R^6)_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)R^6$ ,  $NHC(O)N(R^6)_2$ ,  $NR^6C(O)N(R^6)_2$ , OH, (O), C(O)OH, CN,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

$R^6$  is  $R^7$ ,  $R^8$ ,  $R^9$ , or  $R^{9A}$ ;

10  $R^7$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{7A}$ ;  $R^{7A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^8$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{8A}$ ;  $R^{8A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

15  $R^9$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{9A}$ ;  $R^{9A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20  $R^{9A}$  is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $SO_2NH_2$ ,  $NHC(O)NH_2$ , OH, (O), C(O)OH, CN,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

25 wherein each foregoing cyclic moiety is independently unsubstituted or substituted with one or two or three or four or five of independently selected  $R^{30}$ ,  $OR^{30}$ ,  $OCH_2R^{30}$ ,  $SR^{30}$ ,  $S(O)R^{30}$ ,  $SO_2R^{30}$ ,  $C(O)R^{30}$ ,  $CO(O)R^{30}$ ,  $OC(O)R^{30}$ ,  $OC(O)OR^{30}$ ,  $NO_2$ ,  $NH_2$ ,  $NHR^{30}$ ,  $N(R^{30})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{30}$ ,  $C(O)N(R^{30})_2$ ,  $NHC(O)R^{30}$ ,  $NHC(O)NHR^{30}$ ,  $NHC(O)N(R^{30})_2$ ,  $NR^{30}C(O)NHR^{30}$ ,  $NR^{30}C(O)N(R^{30})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{30}$ ,  $C(O)NHSO_2R^{30}$ ,  $C(O)NR^{30}SO_2R^{30}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{30}$ ,  $SO_2N(R^{30})_2$ ,  $CF_3$ ,  $CF_2CF_3$ , C(O)H, C(O)OH, C(N)NH<sub>2</sub>, C(N)NHR<sup>30</sup>, C(N)N(R<sup>30</sup>)<sub>2</sub>, CNOH, CNOCH<sub>3</sub>, OH, (O), N<sub>3</sub>,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ , F, Cl, Br or I;

35  $R^{30}$  is  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$  or  $R^{34}$ ;

$R^{31}$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{31A}$ ;  $R^{31A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

40  $R^{32}$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{32A}$ ;  $R^{32A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{33}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{33A}$ ;  $R^{33A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

5  $R^{34}$  is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $R^{35}$ ,  $OR^{35}$ ,  $SR^{35}$ ,  $S(O)R^{35}$ ,  $SO_2R^{35}$ ,  $NH_2$ ,  $NHR^{35}$ ,  $N(R^{35})_2$ ,  $C(O)R^{35}$ ,  $C(O)NH_2$ ,  $C(O)NHR^{35}$ ,  $C(O)N(R^{35})_2$ ,  $NHC(O)R^{35}$ ,  $NR^{35}C(O)R^{35}$ ,  $NHSO_2R^{35}$ ,  $NR^{35}SO_2R^{35}$ ,  $NHC(O)OR^{35}$ ,  $NR^{35}C(O)OR^{35}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{35}$ ,  $SO_2N(R^{35})_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{35}$ ,  
10  $NHC(O)R^{35}$ ,  $NHC(O)N(R^{35})_2$ ,  $NR^{35}C(O)N(R^{35})_2$ , OH, (O), C(O)OH, CN,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

$R^{35}$  is  $R^{36}$ ,  $R^{37}$ ,  $R^{38}$  or  $R^{39}$ ;

15  $R^{36}$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{36A}$ ;  $R^{36A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{37}$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{37A}$ ;  $R^{37A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20  $R^{38}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{38A}$ ;  $R^{38A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

25  $R^{39}$  is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with  $R^{40}$ ;

$R^{40}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl;

30 wherein the moieties represented by  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$ ,  $R^{36}$ ,  $R^{37}$  and  $R^{38}$  are independently unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I, OH, (O)OH,  $NO_2$ ,  $NH_2$ ,  $CF_3$ , OH,  $R^{45}$ ,  $OR^{45}$ ,  $SR^{45}$ ,  $S(O)R^{45}$ ,  $SO_2R^{45}$ ,  $C(O)NHR^{45}$ ,  $C(O)N(R^{45})_2$ ,  $NHC(O)R^{45}$ ,  $NR^{45}C(O)R^{45}$ ,  $NHC(O)NHR^{45}$ ,  
35  $NHC(O)N(R^{45})_2$ ,  $NR^{45}C(O)NHR^{45}$ ,  $NR^{45}C(O)N(R^{45})_2$ ,  $SO_2NHR^{45}$ ,  $SO_2N(R^{45})_2$ ,  $NHSO_2R^{45}$ ,  $NR^{45}SO_2R^{45}$ ,  $OC(O)OR^{45}$ ,  $NHC(O)OR^{45}$  or  $NR^{45}C(O)OR^{45}$ ;

$R^{45}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected  $R^{50}$ , F, Cl, Br, I, OH, C(O)OH,  $NO_2$  or  $NH_2$ ; and

$R^{50}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl.

with or without also administering radiotherapy thereto.

5 Still another embodiment pertains to methods of treating bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer and thyroid cancer in a mammal, the methods comprising administering thereto a therapeutically effective amount of a compound having Formula I, with or without also administering radiotherapy thereto..

10 Still another embodiment pertains to compositions comprising an excipient and a therapeutically effective amount of a compound having Formula I and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

15 Still another embodiment pertains to methods of treating diseases involving overexpression or unregulation of Aurora-kinases in a mammal, the methods comprising administering thereto a therapeutically effective amount of a compound having Formula I and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent with or without also  
20 administering radiotherapy thereto..

Still another embodiment pertains to methods of treating bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin  
25 cancer, stomach cancer and thyroid cancer in a mammal, the methods comprising administering thereto a therapeutically effective amount of a compound having Formula I and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent, with or without also administering radiotherapy thereto.

30 Still another embodiment pertains to compounds

8-amino-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

35 8-amino-N-(4-((anilino)carbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

40 8-amino-N-(4-(benzoylamino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,



8-amino-3-methyl-N-(4-(((3-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide,

5 8-amino-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

8-amino-N-(3-(((anilino)carbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

10

8-amino-N-(3-(((2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

15 8-amino-N-(3-(((4-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

8-amino-3-methyl-N-(3-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide,

20

8-amino-N-(4-(((3-(2-hydroxyethyl)phenyl)amino)carbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

25 8-amino-N-(4-(((4-(2-hydroxyethyl)phenyl)amino)carbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide

8-amino-3-cyclopropyl-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

30 8-amino-N-(4-(((anilino)carbonyl)amino)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(4-(((3-methylphenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

35 8-amino-3-cyclopropyl-N-(4-(((2-fluoro-5-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

40 8-amino-3-cyclopropyl-N-(4-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(3-(((pyridin-3-ylamino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

5 8-amino-3-cyclopropyl-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)-3-methylphenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(4-(((2-fluorophenyl)amino)carbonyl)amino)-3-methylphenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

10 8-amino-3-cyclopropyl-N-(3-methyl-4-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

15 8-amino-3-cyclopropyl-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

20

8-amino-N-(3-(((4-chloro-2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropyl)imidazo[1,5-a]pyrazine-1-carboxamide;

25 8-amino-N-(3-(((anilinocarbonyl)amino)methyl)phenyl)-3-cyclopropyl)imidazo[1,5-a]pyrazine-1-carboxamide;

30 8-amino-3-cyclopropyl-N-(3-(((3,4-difluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

35 8-amino-3-cyclopropyl-N-(3-(((2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

35

8-amino-3-cyclopropyl-N-(3-(((4-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

40 8-amino-N-(3-(((3-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-N-(3-((((4-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide;

5 8-amino-3-cyclopropyl-N-(4-(((pyridin-3-ylamino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(3-(((phenylsulfonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

10 8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(3-((((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

15 8-amino-N-(3-((((4-chloro-2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)imidazo[1,5-a]pyrazine-1-carboxamide;

20 8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(3-((((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(4-((((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

25 8-amino-3-cyclopropyl-N-(3-((((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

30 and therapeutically acceptable salts, prodrugs, esters, amides, salts of prodrugs, salts of esters, and salts of amides thereof.

#### DETAILED DESCRIPTION OF THE INVENTION

35 Variable moieties of compounds herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

It is meant to be understood that proper valences are maintained for all moieties and combinations thereof, that monovalent moieties having more than one atom are attached through their left ends.

40

It is also meant to be understood that a specific embodiment of a variable moiety may be the same or different as another specific embodiment having the same identifier.

The term "cyclic moiety," as used herein, means benzene, cycloalkane, cycloalkyl, cycloalkene, cycloalkenyl, heteroarene, heteroaryl, heterocycloalkane, heterocycloalkyl, heterocycloalkene, heterocycloalkenyl and phenyl.

5

The term "cycloalkane," as used herein, means C<sub>3</sub>-cycloalkane, C<sub>4</sub>-cycloalkane, C<sub>5</sub>-cycloalkane and C<sub>6</sub>-cycloalkane.

10 The term "cycloalkyl," as used herein, means C<sub>3</sub>-cycloalkyl, C<sub>4</sub>-cycloalkyl, C<sub>5</sub>-cycloalkyl and C<sub>6</sub>-cycloalkyl.

The term "cycloalkene," as used herein, means C<sub>4</sub>-cycloalkene, C<sub>5</sub>-cycloalkene and C<sub>6</sub>-cycloalkene.

15 The term "cycloalkenyl," as used herein, means C<sub>4</sub>-cycloalkenyl, C<sub>5</sub>-cycloalkenyl and C<sub>6</sub>-cycloalkenyl.

20 The term "heteroarene," as used herein, means furan, imidazole, isothiazole, isoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, triazine and 1,2,3-triazole.

25 The term "heteroaryl," as used herein, means furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl and 1,2,3-triazolyl.

30 The term "heterocycloalkane," as used herein, means cycloalkane having one or two or three CH<sub>2</sub> moieties replaced with independently selected O, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkane having one or two or three CH<sub>2</sub> moieties unreplaced or replaced with independently selected O, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties replaced with N.

35 The term "heterocycloalkyl," as used herein, means cycloalkyl having one or two or three CH<sub>2</sub> moieties replaced with independently selected O, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkyl having one or two or three CH<sub>2</sub> moieties unreplaced or replaced with independently selected O, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties replaced with N.

40

The term "heterocycloalkene," as used herein, means cycloalkene having one or two or three CH<sub>2</sub> moieties replaced with independently selected O, S, S(O), SO<sub>2</sub> or

NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkene having one or two or three CH<sub>2</sub> moieties unreplaced or replaced with independently selected O, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties replaced with N.

5

The term "heterocycloalkenyl," as used herein, means cycloalkenyl having one or two or three CH<sub>2</sub> moieties replaced with independently selected O, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkenyl having one or two or three CH<sub>2</sub> moieties unreplaced or replaced with independently selected O, S, S(O), SO<sub>2</sub> or NH and one or two CH moieties replaced with N.

10

The term "alkenyl," as used herein, means C<sub>2</sub>-alkenyl, C<sub>3</sub>-alkenyl, C<sub>4</sub>-alkenyl, C<sub>5</sub>-alkenyl and C<sub>6</sub>-alkenyl.

15

The term "alkyl," as used herein, means C<sub>1</sub>-alkyl, C<sub>2</sub>-alkyl, C<sub>3</sub>-alkyl, C<sub>4</sub>-alkyl, C<sub>5</sub>-alkyl and C<sub>6</sub>-alkyl.

20

The term "alkynyl," as used herein, means C<sub>2</sub>-alkynyl, C<sub>3</sub>-alkynyl, C<sub>4</sub>-alkynyl, C<sub>5</sub>-alkynyl and C<sub>6</sub>-alkynyl.

25

Compounds of this invention may contain asymmetrically substituted carbon atoms in the R or S configuration, wherein the terms "R" and "S" are as defined in Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those atoms. Atoms having excess of one configuration over the other are assigned the configuration in excess, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention is meant to embrace racemic mixtures and relative and absolute diastereoisomers of the compounds thereof.

30

Compounds of this invention may also contain carbon-carbon double bonds or carbon-nitrogen double bonds in the Z or E configuration, in which the term "Z" represents the larger two substituents on the same side of a carbon-carbon or carbon-nitrogen double bond and the term "E" represents the larger two substituents on opposite sides of a carbon-carbon or carbon-nitrogen double bond. The compounds of this invention may also exist as a mixture of "Z" and "E" isomers.

35

Compounds of this invention may also exist as tautomers or equilibrium mixtures thereof wherein a proton of a compound shifts from one atom to another. Examples of tautomers include, but are not limited to, keto-enol, phenol-keto, oxime-nitroso, nitro-aci, imine-enamine and the like.

40

Compounds of this invention containing NH, C(O)OH, OH or SH moieties may have attached thereto prodrug-forming moieties. The prodrug-forming moieties are removed by metabolic processes and release the compounds having the freed NH, C(O)OH, OH or SH in vivo. Prodrugs are useful for adjusting such pharmacokinetic properties of the compounds as solubility and/or hydrophobicity, absorption in the gastrointestinal tract, bioavailability, tissue penetration, and rate of clearance.

Metabolites of compounds having Formula I produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with overexpression or unregulation of protein kinases.

Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds having Formula I may also have utility for treating diseases associated with overexpression or unregulation of protein kinases.

Compounds having Formula I may exist as acid addition salts, basic addition salts or zwitterions. Salts of compounds having Formula I are prepared during their isolation or following their purification. Acid addition salts are those derived from the reaction of a compound having Formula I with acid. Accordingly, salts including the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate and undecanoate salts of the compounds having Formula I are meant to be embraced by this invention. Basic addition salts of compounds are those derived from the reaction of the compounds having Formula I with the bicarbonate, carbonate, hydroxide or phosphate of cations such as lithium, sodium, potassium, calcium and magnesium.

Compounds having Formula I may be administered, for example, buccally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperitoneally, intrasternally, intravenously, subcutaneously), rectally, topically, transdermally, vaginally and intraarterially as well as by intraarticular injection, infusion, and placement in the body, such as, for example, the vasculature.

Therapeutically effective amounts of a compound having Formula I depend on recipient of treatment, disease treated and severity thereof, composition comprising it, time of administration, route of administration, duration of treatment, potency, rate of clearance and whether or not another drug is co-administered. The amount of a compound having Formula I used to make a composition to be administered daily to a patient in a single dose or in divided doses is from about 0.03 to about 200 mg/kg

body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

5 Compounds having Formula I may be administered with or without an excipient. Excipients include, but are not limited to, encapsulators and additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents, mixtures thereof and the like.

15 Excipients for preparation of compositions comprising a compound having Formula I to be administered orally include, but are not limited to, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl cellulose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, mixtures thereof and the like. Excipients for preparation of

20 compositions comprising a compound having Formula I to be administered ophthalmically or orally include, but are not limited to, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water, mixtures thereof and the like. Excipients for preparation of compositions

30 comprising a compound having Formula I to be administered osmotically include, but are not limited to, chlorofluorohydrocarbons, ethanol, water, mixtures thereof and the like. Excipients for preparation of compositions comprising a compound having Formula I to be administered parenterally include, but are not limited to, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil,

35 liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water, mixtures thereof and the like. Excipients for preparation of compositions comprising a compound having Formula I to be administered rectally or vaginally include, but are not limited to, cocoa butter, polyethylene glycol, wax, mixtures thereof and the like.

40

Compounds having Formula I are also expected to be useful as chemotherapeutic agents in combination with actinomycins, alkylating agents, anthracyclines, antifolates, antiestrogen agents, anti-metabolites, anti-androgens,

antimicrotubule agents, aromatase inhibitors, bleomycins, Ca<sup>2+</sup> adenosine triphosphate (ATP)ase inhibitors, cytosine analogs, deltsoids/retinoids, dihydrofolate reductase inhibitors, deoxyribonucleic acid (DNA) topoisomerase inhibitors, dopaminergic neurotoxins, glucocorticoids, histone deacetylase inhibitors, hormonal therapies, immunotherapeutic agents, inosine monophosphate (IMP) dehydrogenase inhibitors, isoprenylation inhibitors, luteinizing hormone-releasing hormone agonists, mammalian target of rapamycin (mTOR) inhibitors, multi-drug resistance (MDR) inhibitors, mitomycins, photodynamic therapies, proteasome inhibitors, platinum containing compounds, radiation, receptor tyrosine kinase inhibitors, ribonucleotide reductase inhibitors, thrombospondin mimetics, uracil analogs, vinca alkaloids, and vitamin D3 analogs such as, but not limited to,  $\gamma$ -radiation or an additional chemotherapeutic agent or additional chemotherapeutic agents such as N-Ac-Sar-Gly-Val-D-alloIle-Thr-Nva-Ile-Arg-Pro-NHCH<sub>2</sub>CH<sub>3</sub> or a salt thereof, actinomycin D, AG13736, 17-allylamino-17-demethoxygeldanamycin, 9-aminocamptothecin, N-(4-(3-amino-1H-indazol-4-yl)phenyl)-N'-(2-fluoro-5-methylphenyl)urea or a salt thereof, N-(4-(4-aminothieno(2,3-d)pyrimidin-5-yl)phenyl)-N'-(2-fluoro-5-(trifluoromethyl)phenyl)urea or a salt thereof, anastozole, AP-23573, asparaginase, azacitidine, bevacizumab, bicalutamide, bleomycin a2, bleomycin b2, bortezomib, busulfan, campathecins, carboplatin, carmustine (BCNU), CB1093, cetuximab, CHOP (C: Cytosan® (cyclophosphamide); H: Adriamycin® (hydroxydoxorubicin); O: Vincristine (Oncovin®); P: prednisone), chlorambucil, CHIR258, cisplatin, CNF-101, CNF-1001, CNF-2024, CP547632, crisnatol, cytarabine, cyclophosphamide, cytosine arabinoside, daunorubicin, dacarbazine, dactinomycin, dasatinib, daunorubicin, deferoxamine, demethoxyhypocrellin A, depsipeptide, dexamethasone, 17-dimethylaminoethylamino-17-demethoxygeldanamycin, docetaxel, doxifluridine, doxorubicin, EB1089, epothilone D, epirubicin, 5-ethynyl-1- $\beta$ -D-ribofuranosylimidazole-4-carboxamide (EICAR), erlotinib, etoposide, everolimus, 5-fluorouracil (5-FU), floxuridine, fludarabine, flutamide, gefitinib, geldanamycin, gemcitabine, goserelin, N-(2-(4-hydroxyanilino)-3-pyridinyl)-4-methoxybenzenesulfonamide or a salt thereof, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon- $\alpha$ , interferon- $\gamma$ , IPI-504, irinotecan, KH 1060, lapatanib, LAQ824, leuprolide acetate, letrozole, lomustine (CCNU), lovastatin, megestrol, melphalan, mercaptopurine, methotrexate, 1-methyl-4-phenylpyridinium, MG132, mitomycin, mitoxantrone, MLN-518, MS-275, mycophenolic acid, mitomycin C, nitrosoureas, oxaliplatin, paclitaxel, PD98059, peplomycin, photosensitizer Pc4, phtalocyanine, pirarubicin, plicamycin, prednisone, procarbazine, PTK787, PU24FC1, PU3, radicicol, raloxifene, rapamycin, ratitrexed, retinoids such as pheuretinide, ribavirin, rituximab (Rituxin®), sorafenib, staurosporine, steroids such as dexamethasone and prednisone, suberoylanilide hydroxamic acid, sunitinib, tamoxifen, taxol, temozolamide, temsirolimus, teniposide, thapsigargin, thioguanine, thrombospondin-1, tiazofurin, topotecan, trapoxin, trastuzumab, treosulfan, trichostatin A, trimetrexate, trofosfamide, tumor necrosis factor, valproic acid,



VER49009, verapamil, vertoporphin, vinblastine, vincristine, vindesine, vinorelbine  
vitamin D3, VX-680, zactima, ZK-EPO, zorubicin or combinations thereof.

To determine activity of representative compounds of the invention, Active  
5 Aurora B enzyme (recombinant residues 1-344) and INCENP (recombinant GST  
fusion protein from Upstate) were incubated in wells of a 384 well plate with  
biotinylted histone H3 peptide residues 1-21 (Upstate), 1 mM ATP, and various  
concentrations of inhibitors in a Hepes buffer, pH 7.4 containing MgCl<sub>2</sub>, sodium  
othrovanadate, and Triton X-100. After 1 hour, the reaction was stopped with EDTA  
10 and anti-phospho-histone H3 Europium Cryptate (Cis-Bio) and SA-APC (Phycolink,  
Prozyme) were added to detect the phosphopeptide. The amount of phosphorylation  
was determined by the time-resolved fluorescence ratio of signals at 665 nm and 615  
nm. The IC<sub>50</sub>'s were calculated by an exponential fit of the inhibition values with the  
inhibitor concentrations using Assay Explorer software and are shown in TABLE 1.

15

TABLE 1

0.003	0.005	0.008	0.008
0.008	0.009	0.010	0.010
0.011	0.014	0.015	0.017
0.020	0.025	0.027	0.029
0.029	0.035	0.035	0.036
0.038	0.045	0.071	0.087
0.087	0.103	0.146	0.168
0.192	0.440	0.670	0.715
1.016	1.596	1.765	1.817

These data demonstrate the utility of compounds having Formula I as  
inhibitors of Aurora-kinase B.

20

It is expected that, because compounds having Formula I inhibit the activity of  
Aurora-kinase B, they could also have utility as inhibitors of protein kinases having  
close structural homology thereto, such as, for example, Aurora-kinase A and  
Aurora-kinase C.

25

The structural homology between Protein Kinases A, B and C is reported in  
Nature Reviews/Cancer, Vol. 4 december, 2004.

Accordingly, compounds having Formula I are expected to have utility in  
30 treatment of diseases during which protein kinases such as any or all Aurora-kinase  
family members are expressed.

Diseases involving overexpression or unregulation of Aurora-kinase family  
members include, but are not limited to, acoustic neuroma, acute leukemia, acute

lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute t-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, 5 chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial 10 carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer, lymphagioendotheliosarcoma, 15 lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, 20 myeloma, myxosarcoma, neuroblastoma, non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, 25 small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenström's macroglobulinemia, testicular tumors, uterine cancer and Wilms' tumor.

30 It is also expected that compounds having Formula I would inhibit the growth of cells derived from a cancer or neoplasm such as breast cancer (including estrogen-receptor positive breast cancer), colorectal cancer, endometrial cancer, lung cancer (including small cell lung cancer), lymphoma (including follicular or Diffuse Large B-cell), lymphoma (including non-Hodgkin's lymphoma), neuroblastoma, ovarian 35 cancer, prostate cancer (including hormone-insensitive prostate cancer) and testicular cancer (including germ cell testicular cancer).

It is also expected that compounds having Formula I would inhibit the growth of cells derived from a pediatric cancer or neoplasm such as embryonal 40 rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoid/rhabdoid tumor of the central nervous

system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal tumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric osteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer.

Compounds having Formula I are expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, aurora kinase inhibitors, Bcl-2 family protein (for example, Bcl-xL, Bcl-2, Bcl-w, Bfl-1) inhibitors, Bcr-Abl kinase inhibitors, biologic response modifiers, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein HSP-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, intercalating antibiotics, kinase inhibitors, mammalian target of rapamycin inhibitors, mitogen-activated extracellular signal-regulated kinase inhibitors, non-steroidal anti-inflammatory drugs (NSAID's), platinum chemotherapeutics, polo-like kinase inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, topoisomerase inhibitors and the like.

Alkylating agents include altretamine, AMD-473, AP-5280, apaziquone, bendamustine, brostallicin, busulfan, carboquone, carmustine (BCNU), chlorambucil, Cloretazine™ (VNP 40101M), cyclophosphamide, decarbazine, estramustine, fotemustine, glufosfamide, ifosfamide, KW-2170, lomustine (CCNU), mafosfamide, melphalan, mitobronitol, mitolactol, nimustine, nitrogen mustard N-oxide, ranimustine, temozolomide, thiotepa, treosulfan, trofosfamide and the like.

Angiogenesis inhibitors include endothelial-specific receptor tyrosine kinase (Tie-2) inhibitors, epidermal growth factor receptor (EGFR) inhibitors, insulin growth factor-2 receptor (IGFR-2) inhibitors, matrix metalloproteinase-2 (MMP-2) inhibitors, matrix metalloproteinase-9 (MMP-9) inhibitors, platelet-derived growth factor receptor (PDGFR) inhibitors, thrombospondin analogs vascular endothelial growth factor receptor tyrosine kinase (VEGFR) inhibitors and the like.

Aurora kinase inhibitors include AZD-1152, MLN-8054, VX-680 and the like.

Bcl protein family member inhibitors include AT-101 ((-)-gossypol), GENASENSE® (G3139 or oblimersen (Bcl-2-targeting antisense oligonucleotide)), IPI-194, IPI-565, N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide) (ABT-737), N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-

cyclohex-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-((trifluoromethyl)sulfonyl)benzenesulfonamide (ABT-263), GX-070 (obatoclax) and the like.

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Bcr-Abl kinase inhibitors include DASATINIB<sup>®</sup> (BMS-354825), GLEEVEC<sup>®</sup> (imatinib) and the like.

CDK inhibitors include AZD-5438, BMI-1040, BMS-032, BMS-387, CVT-2584, flavopyridol, GPC-286199, MCS-5A, PD0332991, PHA-690509, seliciclib (CYC-202, R-roscovitine), ZK-304709 and the like.

COX-2 inhibitors include ABT-963, ARCOXIA<sup>®</sup> (etoricoxib), BEXTRA<sup>®</sup> (valdecoxib), BMS347070, CELEBREX<sup>™</sup> (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX<sup>®</sup> (deracoxib), JTE-522, 4-methyl-2-(3,4-dimethylphenyl)-1-(4-sulfamoylphenyl)-1H-pyrrole), MK-663 (etoricoxib), NS-398, parecoxib, RS-57067, SC-58125, SD-8381, SVT-2016, S-2474, T-614, VIOXX<sup>®</sup> (rofecoxib) and the like.

EGFR inhibitors include ABX-EGF, anti-EGFr immunoliposomes, EGF-vaccine, EMD-7200, ERBITUX<sup>®</sup> (cetuximab), HR3, IgA antibodies, IRESSA<sup>®</sup> (gefitinib), TARCEVA<sup>®</sup> (erlotinib or OSI-774), TP-38, EGFR fusion protein, TYKERB<sup>®</sup> (lapatinib) and the like.

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), Herceptin<sup>®</sup> (trastuzumab), TYKERB<sup>®</sup> (lapatinib), OMNITARG<sup>®</sup> (2C4, petuzumab), TAK-165, GW-572016 (ionafarnib), GW-282974, EKB-569, PI-166, dHER2 (HER2 vaccine), APC-8024 (HER-2 vaccine), anti-HER/2neu bispecific antibody, B7.her2IgG3, AS HER2 trifunctional bispecific antibodies, mAB AR-209, mAB 2B-1 and the like.

Histone deacetylase inhibitors include depsipeptide, LAQ-824, MS-275, trapoxin, suberoylanilide hydroxamic acid (SAHA), TSA, valproic acid and the like.

HSP-90 inhibitors include 17-AAG-nab, 17-AAG, CNF-101, CNF-1010, CNF-2024, 17-DMAG, geldanamycin, IPI-504, KOS-953, MYCOGRAB<sup>®</sup>, NCS-683664, PU24FC1, PU-3, radicicol, SNX-2112, STA-9090 VER49009 and the like.

MEK inhibitors include ARRY-142886, ARRY-438162 PD-325901, PD-98059 and the like.

mTOR inhibitors include AP-23573, CCI-779, everolimus, RAD-001, rapamycin, temsirolimus and the like.

5 Non-steroidal anti-inflammatory drugs include AMIGESIC<sup>®</sup> (salsalate), DOLOBID<sup>®</sup> (diflunisal), MOTRIN<sup>®</sup> (ibuprofen), ORUDIS<sup>®</sup> (ketoprofen), RELAFEN<sup>®</sup> (nabumetone), FELDENE<sup>®</sup> (piroxicam) ibuprofen cream, ALEVE<sup>®</sup> and NAPROSYN<sup>®</sup> (naproxen), VOLTAREN<sup>®</sup> (diclofenac), INDOCIN<sup>®</sup> (indomethacin), CLINORIL<sup>®</sup> (sulindac), TOLECTIN<sup>®</sup> (tolmetin), LODINE<sup>®</sup> (etodolac), TORADOL<sup>®</sup> (ketorolac), DAYPRO<sup>®</sup> (oxaprozin) and the like.

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PDGFR inhibitors include C-451, CP-673, CP-868596 and the like.

15 Platinum chemotherapeutics include cisplatin, ELOXATIN<sup>®</sup> (oxaliplatin) eptaplatin, lobaplatin, nedaplatin, PARAPLATIN<sup>®</sup> (carboplatin), satraplatin and the like.

Polo-like kinase inhibitors include BI-2536 and the like.

20 Thrombospondin analogs include ABT-510, ABT-567, ABT-898, TSP-1 and the like.

25 VEGFR inhibitors include AVASTIN<sup>®</sup> (bevacizumab), ABT-869, AEE-788, ANGIOZYME<sup>™</sup>, axitinib (AG-13736), AZD-2171, CP-547,632, IM-862, Macugen (pegaptamib), NEXAVAR<sup>®</sup> (sorafenib, BAY43-9006), pazopanib (GW-786034), (PTK-787, ZK-222584), SUTENT<sup>®</sup> (sunitinib, SU-11248), VEGF trap, vatalanib, ZACTIMA<sup>™</sup> (vandetanib, ZD-6474) and the like.

30 Antimetabolites include ALIMTA<sup>®</sup> (premetrexed disodium, LY231514, MTA), 5-azacitidine, XELODA<sup>®</sup> (capecitabine), carmofur, LEUSTAT<sup>®</sup> (cladribine), clofarabine, cytarabine, cytarabine ocfosphate, cytosine arabinoside, decitabine, deferoxamine, doxifluridine, eflornithine, EICAR, enocitabine, ethnylcytidine, fludarabine, hydroxyurea, 5-fluorouracil (5-FU) alone or in combination with leucovorin, GEMZAR<sup>®</sup> (gemcitabine), hydroxyurea, ALKERAN<sup>®</sup> (melphalan), mercaptopurine, 6-mercaptopurine riboside, methotrexate, mycophenolic acid, 35 nelarabine, nolatrexed, ocfosphate, pelitrexol, pentostatin, raltitrexed, Ribavirin, triapine, trimetrexate, S-1, tiazofurin, tegafur, TS-1, vidarabine, UFT and the like.

40 Antibiotics include intercalating antibiotics aclarubicin, actinomycin D, amrubicin, annamycin, adriamycin, BLENOXANE<sup>®</sup> (bleomycin), daunorubicin, CAELYX<sup>®</sup> or MYOCET<sup>®</sup> (doxorubicin), elsamitrucin, epirubicin, glarbuicin, ZAVEDOS<sup>®</sup> (idarubicin), mitomycin C, nemorubicin, neocarzinostatin, peplomycin, pirarubicin, rebeccamycin, stimalamer, streptozocin, VALSTAR<sup>®</sup> (valrubicin), zinostatin and the like.

Topoisomerase inhibitors include aclarubicin, 9-aminocamptothecin, amonafide, amsacrine, becatecarin, belotecan, BN-80915, CAMPTOSAR<sup>®</sup> (irinotecan hydrochloride), camptothecin, CARDIOXANE<sup>®</sup> (dexrazoxine),  
5 diflomotecan, edotecarin, ELLENCE<sup>®</sup> or PHARMORUBICIN<sup>®</sup> (epirubicin), etoposide, exatecan, 10-hydroxycamptothecin, gimatecan, lurtotecan, mitoxantrone, orathecin, pirarubicin, pixantrone, rubitecan, sobuzoxane, SN-38, tafluposide, topotecan and the like.

10 Antibodies include AVASTIN<sup>®</sup> (bevacizumab), CD40-specific antibodies, chTNT-1/B, denosumab, ERBITUX<sup>®</sup> (cetuximab), HUMAX-CD4<sup>®</sup> (zanolimumab), IGF1R-specific antibodies, lintuzumab, PANOREX<sup>®</sup> (edrecolomab), RENCAREX<sup>®</sup> (WX G250), RITUXAN<sup>®</sup> (rituximab), ticilimumab, trastuzimab and the like.

15 Hormonal therapies include ARIMIDEX<sup>®</sup> (anastrozole), AROMASIN<sup>®</sup> (exemestane), arzoxifene, CASODEX<sup>®</sup> (bicalutamide), CETROTIDE<sup>®</sup> (cetorelix), degarelix, deslorelin, DESOPAN<sup>®</sup> (trilostane), dexamethasone, DROGENIL<sup>®</sup>, (flutamide), EVISTA<sup>®</sup> (raloxifene), fadrozole, FARESTON<sup>®</sup> (toremifene), FASLODEX<sup>®</sup> (fulvestrant), FEMARA<sup>®</sup>, (letrozole), formestane, glucocorticoids,  
20 HECTOROL<sup>®</sup> or RENAGEL<sup>®</sup> (doxercalciferol), lasofoxifene, leuprolide acetate, MEGACE<sup>®</sup> (megesterol), MIFEPREX<sup>®</sup> (mifepristone), NILANDRON<sup>™</sup> (nilutamide), NOLVADEX<sup>®</sup> (tamoxifen citrate), PLENAXIS<sup>™</sup> (abarelix), predisone, PROPECIA<sup>®</sup> (finasteride), rilostane, SUPREFACT<sup>®</sup> (buserelin), TRELSTAR<sup>®</sup> (luteinizing hormone releasing hormone (LHRH)), vantas, VETORYL<sup>®</sup>, (trilostane or  
25 modrastane), ZOLADEX<sup>®</sup> (fosreltin, goserelin) and the like.

Deltoids and retinoids include seocalcitol (EB1089, CB1093), lexacalcitrol (KH1060), fenretinide, PANRETIN<sup>®</sup> (aliretinoin), ATRAGEN<sup>®</sup> (liposomal tretinoin), TARGRETIN<sup>®</sup> (bexarotene), LGD-1550 and the like.

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Plant alkaloids include, but are not limited to, vincristine, vinblastine, vindesine, vinorelbine and the like.

35 Proteasome inhibitors include VELCADE<sup>®</sup> (bortezomib), MG132, NPI-0052, PR-171 and the like.

Examples of immunologicals include interferons and other immune-enhancing agents. Interferons include interferon alpha, interferon alpha-2a, interferon alpha-2b, interferon beta, interferon gamma-1a, ACTIMMUNE<sup>®</sup> (interferon gamma-1b), or  
40 interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE<sup>®</sup>, BAM-002, BEROMUN<sup>®</sup> (tasonermin), BEXXAR<sup>®</sup> (tositumomab), CamPath<sup>®</sup> (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE<sup>®</sup> (lenograstim), lentinan, leukocyte alpha

interferon, imiquimod, MDX-010, melanoma vaccine, mitumomab, molgramostim, MYLOTARG™ (gemtuzumab ozogamicin), NEUPOGEN® (filgrastim), OncoVAC-CL, OvaRex® (oregovomab), pemtumomab (Y-muHMFG1), PROVENGE®, sargaramostim, sizofilan, teceleukin, TheraCys®, ubenimex, VIRULIZIN®, Z-100, 5 WF-10, PROLEUKIN® (aldesleukin), ZADAXIN® (thymalfasin), ZENAPAX® (daclizumab), ZEVALIN® (90Y-Ibritumomab tiuxetan) and the like.

Biological response modifiers are agents that modify defense mechanisms of living organisms or biological responses, such as survival, growth, or differentiation of tissue cells to direct them to have anti-tumor activity and include include krestin, 10 lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

Pyrimidine analogs include cytarabine (ara C or Arabinoside C), cytosine arabinoside, doxifluridine, FLUDARA® (fludarabine), 5-FU (5-fluorouracil), 15 floxuridine, GEMZAR® (gemcitabine), TOMUDEX® (ratitrexed), TROXATYL™ (triacetyluridine troxacitabine) and the like.

Purine analogs include LANVIS® (thioguanine) and PURI-NETHOL® (mercaptapurine). 20

Antimitotic agents include batabulin, epothilone D (KOS-862), N-(2-((4-hydroxyphenyl)amino)pyridin-3-yl)-4-methoxybenzenesulfonamide, ixabepilone (BMS 247550), paclitaxel, TAXOTERE® (docetaxel), PNU100940 (109881), patupilone, XRP-9881, vinflunine, ZK-EPO and the like.

Compounds of the present invention are also intended to be used as a radiosensitizer that enhances the efficacy of radiotherapy. Examples of radiotherapy include, but are not limited to, external beam radiotherapy, teletherapy, brachtherapy 25 and sealed and unsealed source radiotherapy.

Additionally, compounds having Formula I may be combined with other chemtherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN®, ALTOCOR® or MEVACOR® (lovastatin), 30 AMPLIGEN® (poly I:poly C12U, a synthetic RNA), APTOSYN™ (exisulind), AREDIA® (pamidronic acid), arglabin, L-asparaginase, atamestane (1-methyl-3,17-dione-androsta-1,4-diene), AVAGE® (tazarotne), AVE-8062, BEC2 (mitumomab), cachectin or cachexin (tumor necrosis factor), canvaxin (vaccine), CeaVac™ (cancer vaccine), CELEUK® (celmoleukin), CEPLENE® (histamine dihydrochloride), 35 CERVARIX™ (human papillomavirus vaccine), CHOP® (C: CYTOXAN® (cyclophosphamide); H: ADRIAMYCIN® (hydroxydoxorubicin); O: Vincristine (ONCOVIN®); P: prednisone), CyPat™, combrestatin A4P, DAB(389)EGF or TransMID-107R™ (diphtheria toxins), dacarbazine, dactinomycin, 5,6-dimethylxanthenone-4-acetic acid (DMXAA), eniluracil, EVIZON™ (squalamine

lactate), DIMERICINE<sup>®</sup> (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906, GARDASIL<sup>®</sup> (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), gastrimmune, genasense, GMK (ganglioside conjugate vaccine), GVAX<sup>®</sup> (prostate cancer vaccine),

5 halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon- $\alpha$ , interferon- $\gamma$ , JUNOVAN<sup>™</sup> or MEPACT<sup>™</sup> (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine),

10 NEOVASTAT<sup>®</sup> (AE-941), NEUTREXIN<sup>®</sup> (trimetrexate glucuronate), NIPENT<sup>®</sup> (pentostatin), ONCONASE<sup>®</sup> (a ribonuclease enzyme), ONCOPHAGE<sup>®</sup> (melanoma vaccine treatment), OncoVAX (IL-2 Vaccine), ORATHECIN<sup>™</sup> (rubitecan), OSIDEM<sup>®</sup> (antibody-based cell drug), OvaRex<sup>®</sup> MAb (murine monoclonal antibody), paditaxel, PANDIMEX<sup>™</sup> (aglycone saponins from ginseng comprising

15 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC<sup>®</sup>-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB<sup>®</sup> (catumaxomab), REVLIMID<sup>®</sup> (lenalidomide), RSR13 (efaproxiral), SOMATULINE<sup>®</sup> LA (lanreotide),

SORIATANE<sup>®</sup> (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN<sup>®</sup> (bexarotene), Taxoprexin<sup>®</sup> (DHA-paclitaxel), TELCYTA<sup>™</sup>

20 (TLK286), temilifene, TEMODAR<sup>®</sup> (temozolomide), tesmilifene, thalidomide, THERATOPE<sup>®</sup> (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFerade<sup>™</sup> (adenovector: DNA carrier containing the gene for tumor necrosis factor- $\alpha$ ), TRACLEER<sup>®</sup> or ZAVESCA<sup>®</sup> (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX<sup>®</sup> (arsenic trioxide),

25 VIRULIZIN<sup>®</sup>, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti- $\alpha$ 5 $\beta$ 3 antibody), XCYTRIN<sup>®</sup> (motexafin gadolinium), XINLAY<sup>™</sup> (atrasentan), XYOTAX<sup>™</sup> (paclitaxel poliglumex), YONDELIS<sup>™</sup> (trabectedin), ZD-6126, ZINECARD<sup>®</sup> (dexrazoxane), zometa (zoledronic acid), zorubicin and the like.

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It is also expected that compounds having Formula I would inhibit growth of cells derived from a pediatric cancer or neoplasm including embryonal rhabdomyosarcoma, pediatric acute lymphoblastic leukemia, pediatric acute myelogenous leukemia, pediatric alveolar rhabdomyosarcoma, pediatric anaplastic ependymoma, pediatric anaplastic large cell lymphoma, pediatric anaplastic medulloblastoma, pediatric atypical teratoid/rhabdoid tumor of the central nervous system, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal tumors, pediatric diffuse anaplastic Wilm's tumor, pediatric favorable histology Wilm's

35 tumor, pediatric glioblastoma, pediatric medulloblastoma, pediatric neuroblastoma, pediatric neuroblastoma-derived myelocytomatosis, pediatric pre-B-cell cancers (such as leukemia), pediatric osteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer

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and the like (commonly-owned United States Application Serial No. 10/988,338), Cancer Res., 2000, 60, 6101-10); and autoimmune disorders include, acquired immunodeficiency disease syndrome, autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, thrombocytopenia and the like (Current Allergy and Asthma Reports 2003, 3:378-384; Br. J. Haematol. 2000 Sep; 110(3): 584-90; Blood 2000 Feb 15;95(4):1283-92; and New England Journal of Medicine 2004 Sep; 351(14): 1409-1418).

For example, involvement of Aurora-kinases in bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer and thyroid cancer is reported in Nature Reviews/Cancer, Vol. 4 december, 2004.

Compounds having Formula I may be made by synthetic chemical processes, examples of which are shown hereinbelow. It is meant to be understood that the order of the steps in the processes may be varied, that reagents, solvents and reaction conditions may be substituted for those specifically mentioned, and that vulnerable moieties may be protected and deprotected, as necessary.

Protecting groups for C(O)OH moieties include, but are not limited to, acetoxymethyl, allyl, benzoylmethyl, benzyl, benzyloxymethyl, tert-butyl, tert-butyldiphenylsilyl, diphenylmethyl, cyclobutyl, cyclohexyl, cyclopentyl, cyclopropyl, diphenylmethylsilyl, ethyl, para-methoxybenzyl, methoxymethyl, methoxyethoxymethyl, methyl, methylthiomethyl, naphthyl, para-nitrobenzyl, phenyl, n-propyl, 2,2,2-trichloroethyl, triethylsilyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, triphenylmethyl and the like.

Protecting groups for C(O) and C(O)H moieties include, but are not limited to, 1,3-dioxylketal, diethylketal, dimethylketal, 1,3-dithianylketal, O-methyloxime, O-phenyloxime and the like.

Protecting groups for NH moieties include, but are not limited to, acetyl, alanyl, benzoyl, benzyl (phenylmethyl), benzylidene, benzyloxycarbonyl (Cbz), tert-butoxycarbonyl (Boc), 3,4-dimethoxybenzyloxycarbonyl, diphenylmethyl, diphenylphosphoryl, formyl, methanesulfonyl, para-methoxybenzyloxycarbonyl, phenylacetyl, phthaloyl, succinyl, trichloroethoxycarbonyl, triethylsilyl, trifluoroacetyl, trimethylsilyl, triphenylmethyl, triphenylsilyl, para-toluenesulfonyl and the like.

Protecting groups for OH and SH moieties include, but are not limited to, acetyl, allyl, allyloxycarbonyl, benzyloxycarbonyl (Cbz), benzoyl, benzyl, tert-butyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, 3,4-dimethoxybenzyl,

3,4-dimethoxybenzyloxycarbonyl, 1,1-dimethyl-2-propenyl, diphenylmethyl, formyl, methanesulfonyl, methoxyacetyl, 4-methoxybenzyloxycarbonyl, para-methoxybenzyl, methoxycarbonyl, methyl, para-toluenesulfonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-trichloroethyl, triethylsilyl, trifluoroacetyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-trimethylsilylethyl, triphenylmethyl, 2-(triphenylphosphonio)ethoxycarbonyl and the like.

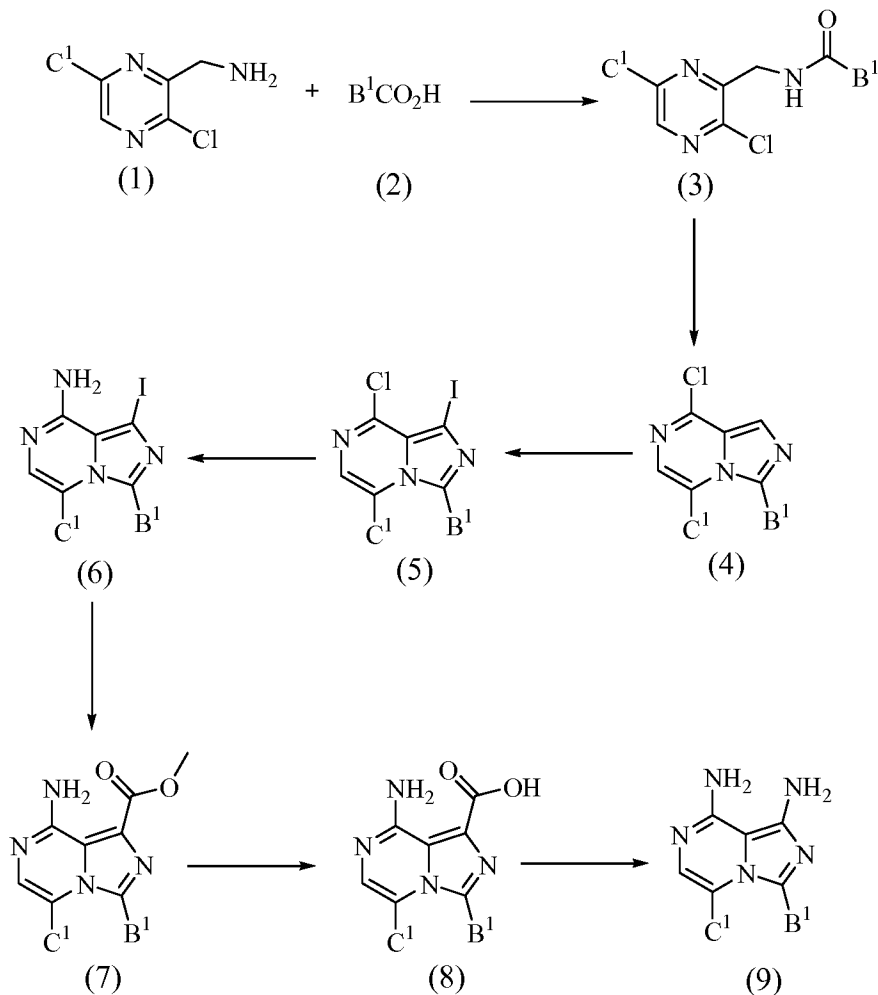
The following abbreviations have the meanings indicated.

ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix- $\beta$  means a mixture of (DHQD)<sub>2</sub>PHAL, K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>SO<sub>4</sub>; AIBN means 2,2'-azobis(2-methylpropionitrile); 9-BBN means 9-borabicyclo(3.3.1)nonane; Cp means cyclopentadiene; (DHQD)<sub>2</sub>PHAL means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo(5.4.0)undec-7-ene; DCC means 1,3-dicyclohexylcarbodiimide, DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DME means 1,2-dimethoxyethane; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; dppa means diphenylphosphoryl azide; dppb means 1,4-bis(diphenylphosphino)butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC or EDCI or EDC means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; HOAT means 1-hydroxy-7-azabenzotriazole; HOBt means 1-hydroxybenzotriazole hydrate, IPA means isopropyl alcohol; LDA means lithium diisopropylamide; LHMDS means lithium bis(hexamethyldisilylamide); MP-BH<sub>3</sub> means macroporus triethylammonium methylpolystyrene cyanoborohydride; LAH means lithium aluminum hydride; NCS means N-chlorosuccinimide; PyBOP means benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; TBTU means O-benzotriazol-1-yl-N,N',N'-tetramethyluronium tetrafluoroborate; TDA-1 means tris(2-(2-methoxyethoxy)ethyl)amine; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine; PPh<sub>3</sub> means triphenylphosphine.

The following scheme and examples are presented to provide what is believed to be the most useful and readily understood description of procedures and conceptual aspects of this invention.

Compounds having Formula (1) can be prepared a number of ways, such as ones described in WO2005/097800.

SCHEME 1



5

As shown in SCHEME 1, compounds having Formula (1) can be converted to compounds having Formula (3) by reacting the former, compounds having Formula (2), a coupling agent, and a first base, with or without a coupling auxiliary. Examples of coupling agents include DCC, EDCI, HATU, TBTU and the like. Examples of bases include DIEA, TEA, NMM and the like. Examples of coupling auxiliaries include DMAP, HOAT, HOBT and the like. The reaction is typically conducted between about 25°C to 45°C, over about 1 to about 24 hours, in solvents such as THF, DMF, dichloromethane, ethyl acetate, mixtures thereof and the like.

15 Compounds having Formula (3) can be converted to compounds having Formula (4) by reacting the former, POCl<sub>3</sub> and DMF. The reaction is typically conducted, over about 0.5 to about two hours, in refluxing acetonitrile.

20 Compounds having Formula (4) can be converted to compounds having Formula (5) by reacting the former and NIS. The reaction is typically conducted, over

about one to about five hours, between about 40°C and 80°C in solvents such as DMF and the like.

5 Compounds having Formula (5) can be converted to compounds having Formula (6) by reacting the former and ammonia. The reaction is typically conducted in a sealed container between about 40°C and 150°C in the ammonia or in solvents such as methanol, ethanol, isopropanol, mixtures thereof and the like.

10 Compounds having Formula (6) can be converted to compounds having Formula (7) by reacting the former, carbon monoxide, methanol, a palladium catalyst, and a second base. Examples of palladium catalysts include palladium acetate, (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II), and the like. Examples of second bases include TEA, pyridine and the like. The reaction is typically conducted (in a sealed container), over about one to about three hours, between about 80°C and  
15 120°C, in methanol.

Compounds having Formula (7) can be converted to compounds having Formula (8) by reacting the former and a third base. Examples of third bases include lithium hydroxide, sodium hydroxide, potassium hydroxide and the like. The reaction  
20 is typically conducted over about 1 hour to about 48 hours, between about 0°C and 35°C, in solvents such as water, methanol, ethanol, isopropanol, mixtures thereof and the like.

25 Introduction of moieties represented by A<sup>1</sup> can be accomplished by reacting compounds having formula (8), a primary or a secondary amine, a coupling agent, a first base, with or without a coupling auxiliary, using the reaction conditions described hereinabove for conversion of compounds having Formula (1) to compounds having Formula (3).

30 Compounds having Formula (8) can be converted to compounds having Formula (9) by reacting the former and DPPA followed by hydrolysis of the isocyanate intermediate with water. The reactions are typically conducted over about 1 hour to about 24 hours, between about 50°C and 110°C, in solvents such as benzene, toluene, THF, water, mixtures thereof and the like.

35 Introduction of moieties represented by A<sup>1</sup> can be accomplished by reacting the compounds having formula (9) and the appropriate isocyanate, carbonyl chloride, sulfonyl chloride, carbamoyl chloride. The reactions are typically conducted over  
40 THF, ethyl acetate, dichloromethane, DMF, DMSO, chloroform, mixtures thereof and the like.

#### EXAMPLE 1A

A mixture of (3-chloropyrazin-2-yl)methanamine (4.9 g), acetic acid (2.25 g), EDC (7.2 g), HOBT (5.75 g) and NMM (6.9 g) in dichloromethane (40 mL) was stirred at room temperature for 48 hours, treated with water and extracted with ethyl acetate. The extract was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated.

5 The concentrate was purified by flash chromatography on silica gel with 0-5% methanol/ dichloromethane.

#### EXAMPLE 1B

A mixture of EXAMPLE 1A (3.98 g) and acetonitrile (100 mL) was treated with DMF (100 μL) and POCl<sub>3</sub> (9.8 mL). The mixture was heated at 55°C for 30 minutes cooled to room temperature and concentrated. The concentrate was dissolved in dichloromethane, neutralized with pre-cooled ammonia in isopropanol and concentrated. The concentrate was partitioned between dichloromethane and water, and the extract was washed with brine and dried (MgSO<sub>4</sub>), filtered and concentrated.

10  
15 The concentrate was dissolved in dichloromethane and purified by flash chromatography on silica gel with 0-5% methanol/dichloromethane.

#### EXAMPLE 1C

A mixture of EXAMPLE 1B (2.83 g) and NIS (4.94 g) in DMF (20 mL) was heated at 60°C for 3 hours, cooled to room temperature, diluted with water and extracted with ethyl acetate. The extract was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated; and the concentrate was triturated with hexanes and filtered.

#### EXAMPLE 1D

In a stainless steel reactor, EXAMPLE 1C (3.3 g) in 2M NH<sub>3</sub> in isopropanol (45 mL) and THF (4mL) was cooled with a dry ice-acetone bath and treated with anhydrous NH<sub>3</sub> (15mL). The mixture was heated at 110°C for 48 hours, cooled to room temperature and vented. The mixture was concentrated, and the concentrate was triturated with water and filtered. The filtrate was extracted with ethyl acetate and the extract was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was purified by flash chromatography on silica gel with 0-5% methanol/dichloromethane.

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#### EXAMPLE 1E

A mixture of EXAMPLE 1D (1.3 g), PdCl<sub>2</sub>(dppf) (150 mg) and triethylamine (0.480 g) in methanol (10 mL) was purged with CO, sealed and heated at 100°C for 2 hours under 60 psi. The reaction mixture was concentrated and the concentrate was purified by flash chromatography on silica gel with 0-5% methanol/dichloromethane.

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#### EXAMPLE 1F

A mixture of EXAMPLE 1E (0.87 g) and 2N LiOH (10 mL) in methanol (10 mL) was stirred at room temperature for 3 hours, neutralized with 2N HCl to pH 6-7, and filtered.

## EXAMPLE 1G

1-fluoro-3-isocyanatobenzene (0.56 mL) was added to a solution of (4-aminophenyl)carbamic acid tert-butyl ester (1.04 g) in dichloromethane (20 mL) at 0°C. The mixture was stirred at ambient temperature for 4 hours and filtered. The filtrant was collected was suspended in dichloromethane (20 mL), cooled in an ice bath, treated with TFA (5 mL), stirred for 15 minutes at ambient temperature for 3 hours and concentrated. The concentrate was concentrated twice from methanol and toluene and dried to provide the title compound as the trifluoroacetate salt.

## EXAMPLE 1H

A mixture of TEA (61 mg), EXAMPLE 1F (0.038 g), EXAMPLE 1G trifluoroacetate (0.072 g) and HATU (0.084 g) in DMF (2 mL) was stirred at ambient temperature for 20 hours and extracted with ethyl acetate. The extract was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was purified by flash chromatography on silica gel with 0 to 5% methanol/dichloromethane. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 2.62 (s, 3H), 6.55-6.90 (m, 1H), 6.98-7.64 (m, 8H), 7.75 (d, J=8.85 Hz, 2H), 8.71 (s, 1H), 8.88 (s, 1H), 9.26 (s, 1H), 10.22 (s, 1H).

## EXAMPLE 2

This example was prepared by substituting 1-(4-aminophenyl)-3-phenylurea for EXAMPLE 1G in EXAMPLE 1H. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 2.62 (s, 3H), 6.96 (t, J=7.36 Hz, 1H), 7.18 (d, J=4.91 Hz, 1H), 7.28 (t, J=7.83 Hz, 2H), 7.38-7.58 (m, 5H), 7.74 (d, J=8.90 Hz, 2H), 8.62 (s, 2H), 10.18 (s, 1H).

## EXAMPLE 3

This example was prepared by substituting N-(4-aminophenyl)benzamide for EXAMPLE 1G in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.63 (s, 3H), 7.19 (d, J=4.76 Hz, 1H), 7.46-7.64 (m, 4H), 7.71-7.86 (m, 4H), 7.91-8.01 (m, 2H), 10.24 (s, 1H), 10.28 (s, 1H).

## EXAMPLE 4

This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-3-(trifluoromethyl)benzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.62 (s, 3H), 7.18 (d, J=4.76 Hz, 1H), 7.30 (d, J=7.14 Hz, 1H), 7.39-7.64 (m, 5H), 7.76 (d, J=8.73 Hz, 2H), 8.02 (s, 1H), 8.76 (s, 1H), 9.02 (s, 1H), 10.22 (s, 1H).

## EXAMPLE 5

This example was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate for (4-aminophenyl)carbamic acid tert-butyl ester in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.62 (s, 3H), 4.31 (d,

J=5.95 Hz, 2H), 6.58-6.81 (m, 2H), 7.05 (d, J=7.93 Hz, 2H), 7.15-7.35 (m, 3H), 7.39-7.57 (m, 2H), 7.68 (d, J=9.12 Hz, 1H), 7.83 (s, 1H), 8.82 (s, 1H), 10.27 (s, 1H).

#### EXAMPLE 6

5 This example was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.61 (s, 3H), 4.30 (d, J=5.76 Hz, 2H), 6.61 (t, J=5.76 Hz, 1H), 6.89 (t, J=7.29 Hz, 1H), 7.06 (d, J=8.14 Hz, 1H), 7.15-7.46 (m, 6H), 7.67 (d, J=8.14 Hz, 1H), 7.67 (d, J=8.14 Hz, 1H), 7.84 (s, 1H), 8.55 (s, 1H), 10.26 (s, 1H).

#### EXAMPLE 7

15 This example was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 1-fluoro-2-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.62 (s, 3H) 4.33 (d, J=5.76 Hz, 2H) 6.87-6.98 (m, 1H) 7.03-7.24 (m, 5H) 7.32 (t, J=7.80 Hz, 1H) 7.55 (d, J=4.75 Hz, 1H) 7.62-7.74 (m, 1H) 7.84 (s, 1H) 8.00-8.22 (m, 1H) 8.39 (d, J=2.37 Hz, 1H) 10.31 (s, 1H).

#### EXAMPLE 8

25 This example was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 1-fluoro-4-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively, in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.61 (s, 3H) 4.30 (d, J=5.76 Hz, 2H) 6.61 (t, J=5.76 Hz, 1H) 6.97-7.13 (m, 3H) 7.19 (d, J=4.75 Hz, 1H) 7.30 (t, J=7.80 Hz, 1H) 7.36-7.46 (m, 3H) 7.52 (d, J=4.75 Hz, 1H) 7.67 (d, J=8.14 Hz, 1H) 7.83 (s, 1H) 8.59 (s, 1H).

#### EXAMPLE 9

30 This example was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 1-isocyanato-4-trifluoromethylbenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively, in EXAMPLE 1G. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.61 (s, 3H) 4.33 (d, J=5.95 Hz, 2H) 6.80 (t, J=5.75 Hz, 1H) 7.07 (d, J=7.54 Hz, 1H) 7.19 (d, J=4.76 Hz, 1H) 7.31 (t, J=7.73 Hz, 1H) 7.45-7.74 (m, 6H) 7.85 (s, 1H) 9.02 (s, 1H) 10.26 (s, 1H).

#### EXAMPLE 10A

40 A solution of 2-(3-aminophenyl)ethanol (0.6 g) and 1-isocyanato-4-nitrobenzene (0.82 g) in dichloromethane (20 mL) was stirred at ambient temperature for 1 hour. The resulting suspension was filtered and the solid collected was dried.

## EXAMPLE 10B

A mixture of EXAMPLE 10A (1 g) and 5% Pd/carbon (100 mg) was stirred under hydrogen for 10 hours and filtered. The filtrate was diluted with ethyl acetate and washed with water. A white precipitate that formed in the aqueous layer which was filtered and dried. Additional product was obtained after drying (MgSO<sub>4</sub>), filtering and concentrating.

## EXAMPLE 10C

This example was prepared by substituting EXAMPLE 10B for EXAMPLE 1G in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.62 (s, 3H), 2.69 (t, J=7.12 Hz, 2H), 3.49-3.68 (m, 2H), 4.63 (t, J=5.26 Hz, 1H), 6.82 (d, J=7.46 Hz, 1H), 7.07-7.22 (m, 2H), 7.24-7.33 (m, 2H), 7.42 (d, J=9.15 Hz, 2H), 7.52 (d, J=5.09 Hz, 1H), 7.73 (d, J=8.81 Hz, 2H), 8.59 (s, 1H), 8.62 (s, 1H), 10.20 (s, 1H).

## EXAMPLE 11

This example was prepared as described in EXAMPLE 10 by substituting 2-(4-aminophenyl)ethanol for 2-(3-aminophenyl)ethanol. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 2.62 (s, 3H), 2.66 (t, J=6.90 Hz, 2H), 3.49-3.78 (m, 2H), 4.58 (t, J=4.91 Hz, 1H), 6.89-7.62 (m, 9H), 7.73 (d, J=8.59 Hz, 2H), 8.52 (s, 1H), 8.57 (s, 1H), 9.29 (s, 1H), 10.17 (s, 1H).

## EXAMPLE 12A

A mixture of 3-iodo-1H-pyrrole-2-carbaldehyde (2.6 g) and NH<sub>2</sub>OH.HCl (0.9 g) in pyridine (915 mL) was stirred overnight at ambient temperature, treated with acetic anhydride (1.24 mL) and heated to 90°C for 6 hours. The reaction mixture was concentrated, the concentrate was partitioned between ethyl acetate and water and the organic extract was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was purified by flash chromatography on silica gel with 0-20% ethyl acetate/hexanes.

## EXAMPLE 12B

A solution of EXAMPLE 12A (0.97 g) in DMF (60 mL) was treated with NaH (214 mg, 60% oil dispersion), stirred at ambient temperature for 5 min, treated with O-(diphenylphosphoryl)hydroxylamine (2.13 g) and stirred an additional 2 hours. The reaction was quenched with pH 7.2 phosphate buffer and extracted with ethyl acetate. The organic extract was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was purified by flash chromatography on silica gel with ethyl acetate/hexanes.

## EXAMPLE 12C

A mixture of EXAMPLE 12B (0.7 g), triethylorthoformate (10 mL) and (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub> (40 mg) was refluxed for 3 hours, cooled to ambient temperature treated



with 7N ammonia in methanol (30 mL) and stirred at ambient temperature overnight. The reaction mixture was concentrated, and the concentrate was triturated with water and filtered.

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## EXAMPLE 12D

This example was prepared as described in EXAMPLES 1E-F by substituting EXAMPLE 12C for EXAMPLE 1D.

## EXAMPLE 12E

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This example was prepared by substituting EXAMPLE 12D for EXAMPLE 1F in EXAMPLE 1H.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  6.68-6.84 (m, 1H), 7.06-7.16 (m, 1H), 7.22-7.37 (m, 1H), 7.40-7.66 (m, 6H), 7.75 (d,  $J = 3.05$  Hz, 1H), 7.93 (s, 1H), 8.16 (s, 1H), 8.72 (s, 1H), 8.87 (s, 1H), 9.97 (s, 1H), 10.08 (s, 1H).

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## EXAMPLE 13

This example was prepared as described in EXAMPLES 1G-1H by substituting 1-fluoro-4-isocyanatobenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  7.12 (t,  $J=8.99$  Hz, 2H) 7.39-7.52 (m, 4H) 7.53-7.66 (m, 3H) 7.75 (d,  $J=3.05$  Hz, 1H) 7.93 (s, 1H) 8.17 (s, 1H) 8.65 (s, 1H) 8.67 (s, 1H) 9.97 (s, 1H) 10.08 (s, 1H)

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## EXAMPLE 14

This example was prepared as described in EXAMPLES 1G-1H by substituting 1-fluoro-2-isocyanatobenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  6.93-7.06 (m, 1H) 7.08-7.30 (m, 2H) 7.45 (d,  $J=9.16$  Hz, 2H) 7.53-7.68 (m, 3H) 7.75 (d,  $J=3.05$  Hz, 1H) 7.94 (s, 1H) 8.09-8.26 (m, 2H) 8.52 (d,  $J=2.37$  Hz, 1H) 9.07 (s, 1H) 9.98 (s, 1H) 10.09 (s, 1H).

25

## EXAMPLE 15

This example was prepared as described in EXAMPLES 1G-1H by substituting isocyanatobenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  6.97 (t,  $J=7.29$  Hz, 1H), 7.28 (t,  $J=7.97$  Hz, 2H), 7.39-7.50 (m, 4H), 7.53-7.64 (m, 3H), 7.75 (d,  $J=3.05$  Hz, 1H), 7.93 (s, 1H), 8.17 (s, 1H), 8.65 (d,  $J = 6.10$  Hz, 2H), 9.99 (s, 1H), 10.08 (s, 1H).

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## EXAMPLE 16

This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-3,5-dimethylbenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H.  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  2.23 (s, 6H) 6.61 (s, 1H) 7.07 (s, 2H) 7.44 (d,  $J=8.81$  Hz, 2H) 7.52-7.66

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(m, 3H) 7.75 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.17 (s, 1H) 8.48 (s, 1H) 8.62 (s, 1H) 9.99 (s, 1H) 10.07 (s, 1H).

#### EXAMPLE 17

5 This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-3-methylbenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.28 (s, 3H) 6.79 (d, J=7.12 Hz, 1H) 7.08-7.27 (m, 2H) 7.30 (s, 1H) 7.45 (d, J=8.82 Hz, 2H) 7.52-7.68 (m, 3H) 7.75 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.17 (s, 1H) 8.56 (s, 1H) 8.64 (s, 1H) 9.84-10.05 (m, 1H) 10.08 (s, 1H).

#### EXAMPLE 18

15 This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-4-methylbenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.24 (s, 3H) 7.08 (d, J=8.14 Hz, 2H) 7.34 (d, J=8.48 Hz, 2H) 7.44 (d, J=9.16 Hz, 2H) 7.52-7.64 (m, 3H) 7.74 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.16 (s, 1H) 8.52 (s, 1H) 8.60 (s, 1H) 9.99 (s, 1H) 10.07 (s, 1H)

#### EXAMPLE 19

20 This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-2-methylbenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.25 (s, 3H) 6.86-6.98 (m, 1H) 7.07-7.22 (m, 2H) 7.42-7.52 (m, 2H) 7.54-7.65 (m, 3H) 7.79 (d, J=3.39 Hz, 1H) 7.85 (d, J=7.12 Hz, 1H) 7.93 (s, 1H) 7.97 (s, 1H) 8.33 (s, 1H) 9.07 (s, 1H) 10.12 (s, 1H) 10.17 (s, 1H)

#### EXAMPLE 20

30 This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-3-methoxybenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 3.74 (s, 3H) 6.55 (dd, J=7.97, 2.20 Hz, 1H) 6.83-7.01 (m, 1H) 7.09-7.27 (m, 2H) 7.35-7.50 (m, 2H) 7.52-7.67 (m, 3H) 7.75 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.17 (s, 1H) 8.65 (d, J=2.03 Hz, 2H) 9.99 (s, 1H) 10.08 (s, 1H)

#### EXAMPLE 21

40 This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-4-methoxybenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 3.72 (s, 3H) 6.76-6.95 (m, 2H) 7.28-7.49 (m, 4H) 7.52-7.66 (m, 3H) 7.75 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.17 (s, 1H) 8.44 (s, 1H) 8.57 (s, 1H) 9.99 (s, 1H) 10.07 (s, 1H)

## EXAMPLE 22

This example was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-3-trifluoromethylbenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (500  
5 MHz, DMSO-d<sub>6</sub>) δ 7.31 (d, J=7.63 Hz, 1H) 7.43-7.68 (m, 7H) 7.75 (d, J=2.75 Hz, 1H) 7.94 (s, 1H) 8.04 (s, 1H) 8.19 (s, 1H) 8.82 (s, 1H) 9.06 (s, 1H) 10.00 (s, 1H) 10.11 (s, 1H).

## EXAMPLE 23

10 This example was prepared as described in EXAMPLES 1G-1H by substituting isocyanatocyclopropane for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 0.33-0.45 (m, 2H) 0.56-0.68 (m, 2H) 2.52-2.61 (m, 1H) 6.35 (d, J=2.71 Hz, 1H) 7.39 (d, J=8.82 Hz, 2H) 7.49-7.60 (m, 3H) 7.74 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.17 (d, J=3.39 Hz, 1H) 8.27 (s, 1H) 10.03 (s, 2H).  
15

## EXAMPLE 24

This example was prepared as described in EXAMPLES 1G-1H by substituting isocyanatocyclopentane for 1-fluoro-3-isocyanatobenzene in EXAMPLE  
20 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.21-1.45 (m, 2H) 1.45-1.70 (m, 4H) 1.73-1.97 (m, 2H) 3.71-4.11 (m, 1H) 6.11 (d, J=7.12 Hz, 1H) 7.36 (d, J=8.82 Hz, 2H) 7.44-7.62 (m, 3H) 7.73 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.15 (s, 1H) 8.23 (s, 1H) 10.02 (s, 2H).

25 EXAMPLE 25

This example was prepared as described in EXAMPLES 1G-1H by substituting 3-isocyanatothiophene for 1-fluoro-3-isocyanatobenzene in EXAMPLE  
1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ  
7.05 (dd, J=5.09, 1.36 Hz, 1H) 7.21-7.33 (m, 1H) 7.37-7.48 (m, 3H) 7.51-7.66 (m,  
30 3H) 7.75 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.17 (s, 1H) 8.62 (s, 1H) 8.90 (s, 1H) 10.00 (s, 1H) 10.07 (s, 1H).

## EXAMPLE 26

This example was prepared as described in EXAMPLES 1G-1H by  
35 substituting 2-isocyanatopyridine for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 7.31 (dd, J=8.14, 4.75 Hz, 1H) 7.41-7.52 (m, 2H) 7.54-7.67 (m, 3H) 7.75 (d, J=3.05 Hz, 1H) 7.87-8.00 (m, 2H) 8.19 (dd, J=4.75, 1.36 Hz, 2H) 8.61 (d, J=2.71 Hz, 1H) 8.81 (d, J=5.76 Hz, 2H) 9.98 (s, 1H) 10.09 (s, 1H).

40

## EXAMPLE 27

This example was prepared as described in EXAMPLE 1H by substituting N-(4-aminophenyl)benzamide and 12D, for 1G and 1F respectively. <sup>1</sup>H NMR (300

MHz, DMSO-d<sub>6</sub>) δ 7.46-7.64 (m, 4H) 7.64-7.84 (m, 5H) 7.89-8.01 (m, 3H) 8.13-8.19 (m, 1H) 9.97 (s, 1H) 10.14 (s, 1H) 10.26 (s, 1H).

#### EXAMPLE 28

5 This example was prepared as described in EXAMPLES 1G-1H by substituting 1-fluoro-2-isocyanato-4-methylbenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 12D for 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.28 (s, 3H) 6.64-6.85 (m, 1H) 7.10 (dd, J=11.53, 8.48 Hz, 1H) 7.46 (d, J=9.16 Hz, 2H) 7.54-7.70 (m, 3H) 7.76 (d, J=2.71 Hz, 1H) 7.90-8.07 (m, 2H) 10 8.24 (s, 1H) 8.47 (d, J=2.03 Hz, 1H) 9.10 (s, 1H) 10.06 (s, 1H) 10.11 (s, 1H).

#### EXAMPLE 29

This example was prepared as described in EXAMPLE 1H by substituting 1-(4-aminophenyl)-3-(4-(2-hydroxyethyl)phenyl)urea and 12D, for 1G and 1F 15 respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.66 (t, J=7.12 Hz, 2H), 3.57 (t, J=7.12 Hz, 2H), 7.12 (d, J=8.48 Hz, 2H), 7.35 (d, J=8.14 Hz, 2H), 7.45 (d, J=9.16 Hz, 2H), 7.55-7.64 (m, 3H), 7.80 (d, J=3.05 Hz, 1H), 7.99 (s, 1H), 8.39 (s, 1H), 8.61 (s, 1H), 8.69 (s, 1H), 10.14 (s, 1H), 10.24 (s, 1H).

20

#### EXAMPLE 30

This example was prepared as described in EXAMPLE 1H by substituting EXAMPLE 10B and 12D, for 1G and 1F respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.69 (s, 2H) 3.59 (s, 2H) 4.63 (s, 1H) 6.83 (s, 1H) 7.06-8.01 (m, 10H) 8.17 (s, 1H) 8.57 (s, 1H) 8.63 (s, 1H) 9.97 (s, 1H) 10.08 (s, 1H)

25

#### EXAMPLE 31

This example was prepared as described in EXAMPLE 1H by substituting 1-(4-aminophenyl)-3-(3-(hydroxymethyl)phenyl)urea and 12D for EXAMPLES 1G and 1F, respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 4.47 (s, 2H), 6.91 (d, J=7.46 Hz, 1H), 7.13-7.27 (m, 1H), 7.28-7.36 (m, 1H), 7.39-7.51 (m, 3H), 7.55-7.66 (m, 3H), 30 7.78 (d, J=3.05 Hz, 1H), 7.97 (s, 1H), 8.32 (s, 1H), 8.68 (d, J=2.03 Hz, 2H), 10.12 (s, 1H) 10.16 (s, 1H).

#### EXAMPLE 32A

35 A solution of 1-(3-hydroxyphenyl)-3-(4-nitrophenyl)urea (1.37 g), Cs<sub>2</sub>CO<sub>3</sub> (3.25 g), 3-bromopropan-1-ol (1.4 mL) in ethanol (30 mL) was refluxed for 30 hours, cooled to ambient temperature and partitioned between ethyl acetate and water. The organic extract was washed with 1N NaOH, brine, dried (MgSO<sub>4</sub>), filtered and concentrated. A mixture of the concentrate and iron (2 g), NH<sub>4</sub>Cl (0.29 g) in ethanol 40 (10 mL)/water (10 mL) was refluxed for 24 hours, treated with 5 drops of 3N HCl and stirred at reflux for 3 hours. The mixture was cooled and filtered through diatomaceous earth (Celite®). The filtrate was extracted with ethyl acetate, and the

extract was concentrated. The concentrate was triturated with boiling diethyl ether and filtered.

#### EXAMPLE 32B

5 This example was prepared as described in EXAMPLE 1H by substituting 32A and 12D, for 1G and 1F respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.77-1.94 (m, 2H) 3.50-3.62 (m, 2H) 4.01 (t, J=6.44 Hz, 2H) 4.53 (t, J=5.09 Hz, 1H) 6.54 (dd, J=8.14, 1.70 Hz, 1H) 6.89 (d, J=9.16 Hz, 1H) 7.16 (t, J=8.14 Hz, 1H) 7.22 (t, J=2.03 Hz, 1H) 7.44 (d, J=8.82 Hz, 2H) 7.56 (d, J=3.39 Hz, 1H) 7.61 (d, J=8.82 Hz, 10 2H) 7.74 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.16 (s, 1H) 8.63 (d, J=4.41 Hz, 2H) 9.99 (s, 1H) 10.07 (s, 1H).

#### EXAMPLE 33

15 This example was prepared as described in EXAMPLE 1H by substituting 1-(3-aminophenyl)-3-phenylurea and 12D, for 1G and 1F respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 6.97 (t, J=7.29 Hz, 1H) 7.19-7.36 (m, J=14.24, 6.78 Hz, 5H) 7.46 (d, J=7.80 Hz, 2H) 7.62 (d, J=3.05 Hz, 1H) 7.76 (d, J=3.05 Hz, 1H) 7.95 (s, 2H) 8.23 (s, 1H) 8.62 (s, 1H) 8.77 (s, 1H) 9.95 (s, 1H) 10.16 (s, 1H).

#### EXAMPLE 34

20 This example was prepared as described in EXAMPLE 1H by substituting 1-(3-aminophenyl)-3-m-tolylurea and 12D, for 1G and 1F respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.28 (s, 3H) 6.79 (d, J=7.46 Hz, 1H) 7.07-7.37 (m, 6H) 7.61 (d, J=3.05 Hz, 1H) 7.76 (d, J=3.05 Hz, 1H) 7.87-8.01 (m, 2H) 8.20 (s, 1H) 8.53 (s, 1H) 25 8.74 (s, 1H) 9.94 (s, 1H) 10.13 (s, 1H).

#### EXAMPLE 35

30 This example was prepared as described in EXAMPLE 1H by substituting 2-(2-aminothiazol-5-yl)-N-(3-fluorophenyl)acetamide and 12D, for 1G and 1F respectively. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 3.90 (s, 2H) 6.80-6.98 (m, 1H) 7.23-7.47 (m, 3H) 7.61 (d, J=11.60 Hz, 1H) 7.78 (s, 2H) 7.99 (s, 1H) 8.33 (s, 1H) 9.66 (s, 1H) 10.46 (s, 1H) 12.43 (s, 1H).

#### EXAMPLE 36A

35 A solution of 3-(morpholinomethyl)aniline (0.46 g), TEA (0.37 mL) and 4-nitrophenyl carbonochloridate (530 mg) in THF (18 mL) was stirred at ambient temperature for 2 hours, treated with tert-butyl 4-aminophenylcarbamate (500mg) and an additional 0.37mL of TEA. the resulting mixture was stirred at ambient temperature for 48 hours, poured into water and exatrceted 3x with ethyl acetate. The 40 extract was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The concentrate was purified by flash chromatography on silica gel with 2% methanol/dichloromethane to provide 1-(3-(morpholinomethyl)phenyl)-3-(4-nitrophenyl)urea which was dissolved in dichloromethane (30 mL), cooled in an ice

bath, and treated with TFA (1.8 mL). The reaction mixture was stirred for 30 minutes at 0°C and for 12 hours at ambient temperature, and concentrated three times from methanol/toluene.

5

## EXAMPLE 36B

This example was prepared as described in EXAMPLE 1H by substituting 36A and 12D, for 1G and 1F respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.31-2.40 (m, 4H) 3.43 (s, 2H) 3.52-3.62 (m, 4H) 6.90 (d, J=7.46 Hz, 1H) 7.22 (t, J=7.63 Hz, 1H) 7.34 (d, J=9.15 Hz, 1H) 7.41-7.50 (m, 3H) 7.53-7.64 (m, 3H) 7.75 (d, J=3.05 Hz, 1H) 7.93 (s, 1H) 8.17 (s, 1H) 8.62 (s, 1H) 8.66 (s, 1H) 10.00 (s, 1H) 10.08 (s, 1H).

10

## EXAMPLE 37A

The title compound was prepared by first substituting tert-butyl 4-aminobenzylcarbamate and 12D for EXAMPLES 1G and 1F respectively, in EXAMPLE 1H, removing the N<sub>boc</sub> protecting group as described in EXAMPLE 1G.

15

## EXAMPLE 37B

A mixture of EXAMPLE 37A (0.1 mmol) and TEA (0.2 mmol) in dichloromethane at -20°C (3 mL) was treated with 1-isocyanato-3-methylbenzene (0.1 mmol), stirred at ambient temperature for 1 hour, and filtered. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 2.24 (s, 3H) 4.23-4.39 (m, 2H) 6.56 (t, J=5.59 Hz, 1H) 6.71 (d, J=6.78 Hz, 1H) 7.01-7.35 (m, 5H) 7.53-7.82 (m, 4H) 7.94 (s, 1H) 8.19 (s, 1H) 8.45 (s, 1H) 9.93 (s, 1H) 10.13 (s, 1H).

20

25

## EXAMPLE 38

This example was prepared as described in EXAMPLE 37B by substituting 1-fluoro-3-isocyanatobenzene for 1-isocyanato-3-methylbenzene. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 4.29 (d, J=5.43 Hz, 2H) 6.43-6.83 (m, 2H) 7.05 (d, J=7.80 Hz, 1H) 7.15-7.36 (m, 3H) 7.41-7.81 (m, 5H) 7.94 (s, 1H) 8.19 (s, 1H) 8.80 (s, 1H) 9.93 (s, 1H) 10.13 (s, 1H).

30

## EXAMPLE 39

This example was prepared as described in EXAMPLE 37 by substituting tert-butyl 3-aminobenzylcarbamate for tert-butyl 4-aminobenzylcarbamate in 37A and 1-fluoro-3-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 37B. <sup>4</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ 4.32 (d, J=5.22 Hz, 2H) 6.62-6.81 (m, 2H) 7.01-7.13 (m, 2H) 7.18-7.37 (m, 2H) 7.48 (d, J=11.97 Hz, 1H) 7.55-7.71 (m, 3H) 7.75 (s, 1H) 7.95 (s, 1H) 8.22 (s, 1H) 8.85 (s, 1H) 9.92 (s, 1H) 10.17 (s, 1H).

40

## EXAMPLE 40

This example was prepared as described in EXAMPLE 37 by substituting tert-butyl 3-aminobenzylcarbamate for tert-butyl 4-aminobenzylcarbamate in 37A and

isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 37B. <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 4.32 (d, J=5.80 Hz, 2H) 6.63 (t, J=5.65 Hz, 1H) 6.89 (t, J=7.17 Hz, 1H) 7.08 (d, J=7.32 Hz, 1H) 7.22 (t, J=7.63 Hz, 2H) 7.26-7.47 (m, 3H) 7.53-7.78 (m, 4H) 7.94 (s, 1H) 8.19 (s, 1H) 8.56 (s, 1H) 9.92 (s, 1H) 10.16 (s, 1H).

5

## EXAMPLE 41

4-amino-N-(3-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

10

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-trifluoromethyl-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.34 (d, J=5.55 Hz, 2 H) 6.84 (t, J=5.95 Hz, 1 H) 7.10 (d, J=7.54 Hz, 1 H) 7.34 (t, J=7.93 Hz, 1 H) 7.49 - 7.76 (m, 7 H) 7.82 (d, J=2.78 Hz, 1 H) 8.01 (s, 1 H) 8.50 (s, 1 H) 9.05 (s, 1 H) 10.24 (s, 2 H). MS(ESI(+)) m/e 470 (M+H)<sup>+</sup>.

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20

## EXAMPLE 42

4-amino-N-(3-(((3,4-difluorophenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

25

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 1, 2-difluoromethyl-4-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.32 (d, J=5.55 Hz, 2 H) 6.77 (t, J=5.75 Hz, 1 H) 6.94 - 7.17 (m, 2 H) 7.20 - 7.45 (m, 2 H) 7.51 - 7.75 (m, 4 H) 7.82 (d, J=3.17 Hz, 1 H) 8.02 (s, 1 H) 8.52 (s, 1 H) 8.85 (s, 1 H) 10.24 (s, 2 H). MS(ESI(+)) m/e 438 (M+H)<sup>+</sup>.

30

## EXAMPLE 43

4-amino-N-(3-(((4-chloro-2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

35

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-chloro-2-fluoro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.33 (d, J=5.95 Hz, 2 H) 7.03 - 7.24 (m, 3 H) 7.28 - 7.48 (m, 2 H) 7.53 - 7.73 (m, 3 H) 7.79 (d, J=3.17

40

Hz, 1 H) 7.98 (s, 1 H) 8.17 (t,  $J=8.92$  Hz, 1 H) 8.35 (s, 1 H) 8.51 (d,  $J=2.38$  Hz, 1 H) 10.07 (s, 1 H) 10.20 (s, 1 H). MS(ESI(+)) m/e 454 (M+H)<sup>+</sup>

## EXAMPLE 44

5 4-amino-N-(3-((((3-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 3-chloro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.32 (d,  $J=5.95$  Hz, 2 H) 6.77 (t,  $J=5.95$  Hz, 1 H) 6.85 - 7.00 (m, 1 H) 7.02 - 7.44 (m, 4 H) 7.52 - 7.75 (m, 4 H) 7.82 (d,  $J=3.17$  Hz, 1 H) 8.01 (s, 1 H) 8.48 (s, 1 H) 8.82 (s, 1 H) 10.23 (s, 2 H) MS(ESI(+)) m/e 436 (M+H)<sup>+</sup>

15

## EXAMPLE 45

4-amino-N-(3-((((4-methylphenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

20 The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 1-isocyanato-4-methylbenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 2.21 (s, 3 H) 4.31 (d,  $J=5.55$  Hz, 2 H) 6.58 (t,  $J=5.75$  Hz, 1 H) 6.93 - 7.15 (m, 3 H) 7.21 - 7.40 (m, 3 H) 7.52 - 7.74 (m, 3 H) 7.81 (d,  $J=3.17$  Hz, 1 H) 8.01 (s, 1 H) 8.44 (s, 1 H) 8.48 (s, 1 H) 10.23 (s, 2 H). MS(ESI(+)) m/e 416 (M+H)<sup>+</sup>

25

## EXAMPLE 46

30 4-amino-N-(3-((((4-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-chloro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.32 (d,  $J=5.76$  Hz, 2 H) 6.70 (t,  $J=5.76$  Hz, 1 H) 7.09 (d,  $J=7.46$  Hz, 1 H) 7.18 - 7.51 (m, 5 H) 7.54 - 7.75 (m, 3 H) 7.81 (d,  $J=3.05$  Hz, 1 H) 8.01 (s, 1 H) 8.48 (d,  $J=2.03$  Hz, 1 H) 8.74 (s, 1 H) 10.22 (s, 2 H). MS(ESI(+)) m/e 436 (M+H)<sup>+</sup>

35

## EXAMPLE 47

40 4-amino-N-(3-((((4-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide



The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-fluoro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.32 (d, *J*=5.76 Hz, 2 H) 6.64 (t, *J*=5.93 Hz, 1 H) 6.97 - 7.15 (m, 3 H) 7.26 - 7.47 (m, 3 H) 7.57 - 7.71 (m, 3 H) 7.82 (d, *J*=3.05 Hz, 1 H) 8.01 (s, 1 H) 8.49 (s, 1 H) 8.61 (s, 1 H) 10.23 (s, 2 H). MS(ESI(+)) m/e 420 (M+H)<sup>+</sup>.

10 EXAMPLE 48

4-amino-N-(3-(((pyridin-3-ylamino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 3-isocyanatopyridine for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.36 (d, *J*=5.76 Hz, 2 H) 7.10 (d, *J*=8.14 Hz, 1 H) 7.21 - 7.49 (m, 2 H) 7.51 - 7.88 (m, 5 H) 7.99 (s, 1 H) 8.14 - 8.31 (m, 1 H) 8.39 (d, *J*=5.09 Hz, 2 H) 9.01 (d, *J*=2.37 Hz, 1 H) 9.58 (s, 1 H) 10.07 (s, 1 H) 10.20 (s, 1 H). MS(ESI(+)) m/e 403 (M+H)<sup>+</sup>.

EXAMPLE 49

4-amino-N-(3-(((4-(difluoromethoxy)phenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-difluoromethoxy-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 4.31 (d, *J*=5.76 Hz, 2 H) 6.66 (t, *J*=5.93 Hz, 1 H) 6.84 (s, 1 H) 6.98 - 7.20 (m, 3 H) 7.19 - 7.86 (m, 7 H) 7.94 (s, 1 H) 8.23 (s, 1 H) 8.68 (s, 1 H) 9.93 (s, 1 H) 10.17 (s, 1 H) MS(ESI(+)) m/e 468(M+H)<sup>+</sup>.

35 EXAMPLE 50

4-amino-N-(3-(((2,4-difluorophenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-carboxamide

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 2,4-difluoro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.33 (d, *J*=5.76

Hz, 2 H) 6.86 - 7.13 (m, 3 H) 7.14 - 7.43 (m, 2 H) 7.56 - 7.82 (m, 4 H) 7.94 (s, 1 H)  
7.95 - 8.14 (m, 1 H) 8.21 (s, 1 H) 8.36 (d,  $J=2.03$  Hz, 1 H) 9.92 (d,  $J=5.09$  Hz, 1 H)  
10.16 (s, 1 H). MS(ESI(+)) m/e 438(M+H)<sup>+</sup>

5

## EXAMPLE 51

4-amino-N-(3-((((2,5-  
difluorophenyl)amino)carbonyl)amino)methyl)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-  
carboxamide

The title compound was prepared by substituting tert-butyl 3-  
10 (aminomethyl)phenylcarbamate and 1,4-difluoro-2-isocyanatobenzene for (4-  
aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene,  
respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 12D as  
described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 4.34 (d,  $J=5.76$   
Hz, 2 H) 6.52 - 6.83 (m, 1 H) 6.97 - 7.44 (m, 4 H) 7.54 - 7.82 (m, 4 H) 7.94 (s, 1 H)  
15 8.00 - 8.11 (m, 1 H) 8.20 (s, 1 H) 8.63 (s, 1 H) 9.91 (s, 1 H) 10.16 (s, 1 H).  
MS(ESI(+)) m/e 438(M+H)<sup>+</sup>

## EXAMPLE 52

20 4-amino-N-(4-((((4-chloro-2-  
fluorophenyl)amino)carbonyl)amino)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-5-  
carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by  
substituting 4-chloro-2-fluoro-1-isocyanatobenzene for 1-fluoro-3-isocyanatobenzene  
in EXAMPLE 1G and EXAMPLE 12D for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H  
25 NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 7.23 (d,  $J=9.16$  Hz, 1 H) 7.36 - 7.68 (m, 6 H) 7.75  
(d,  $J=3.05$  Hz, 1 H) 7.93 (s, 1 H) 8.19 (t,  $J=8.82$  Hz, 2 H) 8.62 (s, 1 H) 9.08 (s, 1 H)  
9.97 (s, 1 H) 10.09 (s, 1 H). MS(ESI(+)) m/e 440(M+H)<sup>+</sup>

## EXAMPLE 53

30 4-amino-N-(4-((((4-  
(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)pyrrolo(2,1-f)(1,2,4)triazine-  
5-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by  
substituting 4-trifluoromethyl-1-isocyanatobenzene for 1-fluoro-3-isocyanatobenzene  
35 in EXAMPLE 1G and EXAMPLE 12D for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H  
NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 7.41 - 7.72 (m, 9 H) 7.75 (d,  $J=3.05$  Hz, 1 H) 7.94  
(s, 1 H) 8.17 (s, 1 H) 8.80 (s, 1 H) 9.08 (s, 1 H) 9.98 (s, 1 H) 10.09 (s, 1 H).  
MS(ESI(+)) m/e 456(M+H)<sup>+</sup>

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## EXAMPLE 54

8-amino-3-cyclopropyl-N-(4-((((3-  
fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

## EXAMPLE 54A

8-amino-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxylic acid

The title compound was prepared as described in EXAMPLES 1A-1F, by substituting cyclopropanecarboxylic acid for acetic acid in 1A.

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## EXAMPLE 54B

8-amino-3-cyclopropyl-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1H, except substituting EXAMPLE 54A for EXAMPLE 1F. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.87 - 1.28 (m, 4 H) 2.19 - 2.45 (m, 1 H) 6.60 - 6.91 (m, 1 H) 7.04 - 7.59 (m, 7 H) 7.58 - 7.90 (m, 3 H) 8.74 (s, 1 H) 8.90 (s, 1 H) 9.21 (s, 1 H) 9.96 (s, 1 H). MS(ESI(+)) m/e 446(M+H)<sup>+</sup>.

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## EXAMPLE 55

8-amino-N-(4-((anilino)carbonyl)amino)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting isocyanatobenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.87 - 1.32 (m, 4 H) 2.15 - 2.42 (m, 1 H) 6.96 (t, J=7.29 Hz, 1 H) 7.11 - 7.59 (m, 8 H) 7.59 - 7.86 (m, 3 H) 8.64 (d, J=2.03 Hz, 2 H) 9.17 (s, 1 H) 9.94 (s, 1 H). MS(ESI(+)) m/e 428(M+H)<sup>+</sup>.

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## EXAMPLE 56

8-amino-3-cyclopropyl-N-(4-(((3-methylphenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-3-methylbenzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.85 - 1.41 (m, 4 H) 2.28 (s, 3 H) 2.29 - 2.45 (m, 1 H) 6.78 (d, J=7.14 Hz, 1 H) 7.00 - 7.54 (m, 7 H) 7.59 - 7.85 (m, 3 H) 8.57 (s, 1 H) 8.64 (s, 1 H) 9.15 (s, 1 H) 9.94 (s, 1 H). MS(ESI(+)) m/e 442(M+H)<sup>+</sup>.

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## EXAMPLE 57

8-amino-3-cyclopropyl-N-(4-(((2-fluoro-5-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting 1-fluoro-2-isocyanato-4-(trifluoromethyl)benzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.84 - 1.29 (m, 4 H) 2.16 - 2.45 (m, 1 H) 7.20 (d, J=3.73 Hz, 1 H) 7.30 - 7.64 (m, 5 H) 7.66 - 8.03 (m, 3 H) 8.63

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(dd,  $J=7.29, 2.20$  Hz, 1 H) 8.87 (d,  $J=2.71$  Hz, 1 H) 9.16 (s, 2 H) 9.98 (s, 1 H).  
MS(ESI(+)) m/e 514(M+H)<sup>+</sup>

## EXAMPLE 58

5 8-amino-3-cyclopropyl-N-(4-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-4-(trifluoromethyl)benzene for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in  
10 EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 1.01 - 1.33 (m, 4 H) 2.46 - 2.62 (m, 1 H) 7.22 (d,  $J=5.52$  Hz, 1 H) 7.50 (d,  $J=8.90$  Hz, 2 H) 7.56 - 7.81 (m, 6 H) 7.99 (d,  $J=5.83$  Hz, 1 H) 8.99 (s, 1 H) 9.24 (s, 2 H) 10.33 (s, 1 H) 10.92 (s, 1 H). MS(ESI(+)) m/e 496(M+H)<sup>+</sup>

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## EXAMPLE 59

8-amino-3-cyclopropyl-N-(3-(((pyridin-3-ylamino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting 3-isocyanatopyridine for 1-fluoro-3-isocyanatobenzene in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>) δ ppm 1.16 (s, 4 H) 2.22 - 2.43 (m, 1 H) 6.93 - 8.01 (m, 9 H) 8.20 (s, 1 H) 8.64 (s, 1 H) 9.01 (d,  $J=19.03$  Hz, 2 H) 10.14 (s, 2 H). MS(ESI(+)) m/e 429(M+H)<sup>+</sup>.

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## EXAMPLE 60

8-amino-3-cyclopropyl-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)-3-methylphenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting tert-butyl 4-amino-3-methylphenylcarbamate for (4-aminophenyl)carbamic acid tert-butyl ester in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 1.01 - 1.15 (m, 4 H) 2.26 (s, 3 H) 2.29 - 2.41 (m, 1 H) 6.63 - 6.85 (m, 1 H) 7.10 (d,  $J=7.54$  Hz, 1 H) 7.20 (d,  $J=4.76$  Hz, 1 H) 7.24 - 7.36 (m, 1 H) 7.46 - 7.62 (m, 2 H) 7.62 - 7.76 (m, 3 H) 7.98 (s, 1 H) 9.17 (s, 1 H) 9.90 (s, 1 H). MS(ESI(+)) m/e 460(M+H)<sup>+</sup>

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## EXAMPLE 61

8-amino-3-cyclopropyl-N-(4-(((2-fluorophenyl)amino)carbonyl)amino)-3-methylphenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting 1-fluoro-2-isocyanatobenzene and tert-butyl 4-amino-3-methylphenylcarbamate for 1-fluoro-3-isocyanatobenzene and (4-aminophenyl)carbamic acid tert-butyl ester, respectively in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-

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d<sub>6</sub>) δ pm 0.98 - 1.30 (m, 4 H) 2.10 - 2.37 (m, 4 H) 6.88 - 7.34 (m, 4 H) 7.52 - 7.70 (m, 2 H) 7.75 - 7.90 (m, 1 H) 7.93 - 8.06 (m, 1 H) 8.11 - 8.27 (m, 1 H) 8.28 - 8.49 (m, 1 H) 8.71 - 9.26 (m, 2 H) 10.24 (s, 1 H) 10.77 (s, 1 H). MS(ESI(+)) m/e 460(M+H)<sup>+</sup>.

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## EXAMPLE 62

8-amino-3-cyclopropyl-N-(3-methyl-4-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting 1-isocyanato-4-trifluoromethylbenzene and tert-butyl 4-amino-3-methylphenylcarbamate for 1-fluoro-3-isocyanatobenzene and (4-aminophenyl)carbamic acid tert-butyl ester, respectively in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.96 - 1.30 (m, 4 H) 2.04 - 2.37 (m, 4 H) 7.02 - 7.34 (m, 1 H) 7.51 - 7.83 (m, 7 H) 7.89 - 8.04 (m, 1 H) 8.13 (s, 1 H) 9.11 (s, 1 H) 9.44 (s, 1 H) 10.27 (s, 1 H) 10.84 (s, 1 H). MS(ESI(+)) m/e 510(M+H)<sup>+</sup>.

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## EXAMPLE 63

8-amino-3-cyclopropyl-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLES 1G-1H by substituting (3-aminophenyl)carbamic acid tert-butyl ester for (4-aminophenyl)carbamic acid tert-butyl ester in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.80 - 1.26 (m, 4 H) 2.14 - 2.45 (m, 1 H) 6.50 - 6.87 (m, 1 H) 7.05 - 7.60 (m, 8 H) 7.74 (d, *J*=4.75 Hz, 1 H) 8.00 (s, 1 H) 8.83 (d, *J*=3.05 Hz, 2 H) 9.15 (s, 1 H) 9.96 (s, 1 H). MS(ESI(+)) m/e 446(M+H)<sup>+</sup>.

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## EXAMPLE 64

8-amino-3-cyclopropyl-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate for (4-aminophenyl)carbamic acid tert-butyl ester in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.86 - 1.28 (m, 4 H) 2.16 - 2.44 (m, 1 H) 4.31 (d, *J*=5.76 Hz, 2 H) 6.47 - 6.90 (m, 2 H) 6.94 - 7.55 (m, 7 H) 7.57 - 7.97 (m, 3 H) 8.82 (s, 1 H) 9.16 (s, 1 H) 10.01 (s, 1 H). MS(ESI(+)) m/e 460(M+H)<sup>+</sup>.

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## EXAMPLE 65

8-amino-N-(3-(((4-chloro-2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide

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The title compound was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-chloro-2-fluoro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G and EXAMPLE 54A for  
5 EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.58 - 1.50 (m, 4 H) 2.17 - 2.43 (m, 1 H) 4.33 (d, *J*=5.76 Hz, 2 H) 6.89 - 7.53 (m, 7 H) 7.59 - 7.90 (m, 3 H) 8.18 (t, *J*=8.98 Hz, 1 H) 8.52 (d, *J*=2.03 Hz, 1 H) 9.12 (s, 1 H) 10.02 (s, 1 H). MS(ESI(+)) m/e 494(M+H)<sup>+</sup>.

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## EXAMPLE 66

8-amino-N-(3-(((anilincarbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and isocyanatobenzene for  
15 (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.84 - 1.33 (m, 4 H) 2.14 - 2.44 (m, 1 H) 4.31 (d, *J*=5.76 Hz, 2 H) 6.62 (t, *J*=5.93 Hz, 1 H) 6.89 (t, *J*=7.46 Hz, 1 H) 7.07 (d, *J*=7.80 Hz, 1 H) 7.15 - 7.53 (m, 7 H) 7.54 - 8.00 (m, 3 H) 8.54 (s, 1 H) 9.06 (s, 1 H)  
20 10.00 (s, 1 H). MS(ESI(+)) m/e 442(M+H)<sup>+</sup>.

## EXAMPLE 67

8-amino-3-cyclopropyl-N-(3-(((3,4-difluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide  
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The title compound was prepared as described in EXAMPLE 1G-H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 3,4-difluoro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G and EXAMPLE 54A for  
30 EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.82 - 1.41 (m, 4 H) 2.21 - 2.44 (m, 1 H) 4.31 (d, *J*=5.76 Hz, 2 H) 6.73 (t, *J*=5.93 Hz, 1 H) 6.90 - 7.13 (m, 1 H) 7.14 - 7.46 (m, 5 H) 7.50 - 7.95 (m, 4 H) 8.81 (s, 1 H) 9.20 (s, 1 H) 10.00 (s, 1 H). MS(ESI(+)) m/e 478(M+H)<sup>+</sup>.

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## EXAMPLE 68

8-amino-3-cyclopropyl-N-(3-(((2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

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## EXAMPLE 68A

8-amino-N-(3-(aminomethyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as a bis-trifluoroacetate salt by first substituting tert-butyl 3-aminobenzylcarbamate and EXAMPLE 54A for EXAMPLES 1G and EXAMPLE 1F respectively, in EXAMPLE 1H, followed by removing the NBoc protecting group by treatment with TFA as described in EXAMPLE 1G.

5 MS(ESI(+)) m/e 323(M+H)<sup>+</sup>

#### EXAMPLE 68B

8-amino-3-cyclopropyl-N-(3-(((2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

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The title compound was prepared as described in EXAMPLE 37B by substituting 1-fluoro-2-isocyanatobenzene and EXAMPLE 68A for 1-isocyanato-3-methylbenzene and EXAMPLE 37A, respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 1.13 - 1.41 (m, 4 H) 2.36 - 2.63 (m, 1 H) 4.34 (d, *J*=5.52 Hz, 2 H) 6.94 (s, 1 H) 7.01 - 7.29 (m, 5 H) 7.37 (t, *J*=7.67 Hz, 1 H) 7.57 - 7.85 (m, 2 H) 7.99 (d, *J*=5.52 Hz, 1 H) 8.06 - 8.28 (m, 1 H) 8.39 (d, *J*=1.84 Hz, 1 H) 9.26 (s, 1 H) 10.39 (s, 1 H) 10.83 (s, 1 H)

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MS(ESI(+)) m/e 460(M+H)<sup>+</sup>

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#### EXAMPLE 69

8-amino-3-cyclopropyl-N-(3-(((4-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

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The title compound was prepared as described in EXAMPLE 37B by substituting 1-fluoro-4-isocyanatobenzene and EXAMPLE 68A for 1-isocyanato-3-methylbenzene and EXAMPLE 37A, respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 1.07 - 1.36 (m, 4 H) 2.38 - 2.60 (m, 1 H) 4.32 (d, *J*=5.83 Hz, 2 H) 6.73 (t, *J*=5.68 Hz, 1 H) 6.94 - 7.56 (m, 7 H) 7.58 - 7.89 (m, 2 H) 7.99 (d, *J*=5.83 Hz, 1 H) 8.68 (s, 1 H) 9.33 (s, 1 H) 10.37 (s, 1 H) 10.82 (s, 1 H). MS(ESI(+)) m/e 460(M+H)<sup>+</sup>

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#### EXAMPLE 70

8-amino-N-(3-(((3-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide

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The title compound was prepared as described in EXAMPLE 37B by substituting 1-chloro-3-isocyanatobenzene and EXAMPLE 68A for 1-isocyanato-3-methylbenzene and EXAMPLE 37A, respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 1.13 - 1.33 (m, 4 H) 2.31 - 2.49 (m, 1 H) 4.32 (d, *J*=5.83 Hz, 2 H) 6.82 (t, *J*=6.14 Hz, 1 H) 6.89 - 7.01 (m, 1 H) 7.06 - 7.27 (m, 4 H) 7.36 (t, *J*=7.83 Hz, 1 H) 7.52 - 7.86 (m, 3 H) 7.97 (d, *J*=5.52 Hz, 1 H) 8.86 (s, 1 H) 9.09 (s, 1 H) 10.35 (s, 1 H) 10.69 (s, 1 H). MS(ESI(+)) m/e 476(M+H)<sup>+</sup>

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#### EXAMPLE 71

8-amino-N-(3-((((4-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLE 37B by substituting 1-chloro-4-isocyanatobenzene and EXAMPLE 68A for 1-isocyanato-3-methylbenzene and EXAMPLE 37A, respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.99 - 1.41 (m, 4 H) 2.24 - 2.48 (m, 1 H) 4.32 (d, *J*=5.76 Hz, 2 H) 6.74 (t, *J*=5.76 Hz, 1 H) 7.03 - 7.56 (m, 7 H) 7.59 - 7.85 (m, 2 H) 8.00 (d, *J*=5.76 Hz, 1 H) 8.78 (s, 1 H) 9.24 (s, 1 H) 10.40 (s, 1 H) 10.86 (s, 1 H) MS(ESI(+)) m/e 476(M+H)<sup>+</sup>

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## EXAMPLE 72

8-amino-3-cyclopropyl-N-(4-(((pyridin-3-ylamino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLE 37B by substituting 3-isocyanatopyridine and EXAMPLE 68A for 1-isocyanato-3-methylbenzene and EXAMPLE 37A, respectively. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.79 - 1.39 (m, 4 H) 2.17 - 2.43 (m, 1 H) 4.33 (d, *J*=5.83 Hz, 2 H) 6.80 (t, *J*=5.83 Hz, 1 H) 6.95 - 7.56 (m, 5 H) 7.57 - 7.84 (m, 3 H) 7.82 - 8.00 (m, 1 H) 8.12 (d, *J*=3.68 Hz, 1 H) 8.55 (d, *J*=2.15 Hz, 1 H) 8.77 (s, 1 H) 9.05 (s, 1 H) 10.00 (s, 1 H) MS(ESI(+)) m/e 443(M+H)<sup>+</sup>

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## EXAMPLE 73

8-amino-3-cyclopropyl-N-(3-(((phenylsulfonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

A solution of EXAMPLE 68A (0.102 g) in DMF 3mL was treated with triethylamine (0.112 ml, 0.800 mmol) and benzenesulfonyl chloride (0.026 ml, 0.200 mmol), stirred at room temperature overnight then diluted with water and extracted with ethyl acetate. The extract was washed (brine), dried (MgSO<sub>4</sub>), concentrated to dryness and purified by preparative HPLC. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 1.01 - 1.29 (m, 4 H) 2.34 - 2.58 (m, 1 H) 3.98 (d, *J*=5.95 Hz, 2 H) 7.04 (d, *J*=7.54 Hz, 1 H) 7.19 - 7.36 (m, 2 H) 7.48 - 7.69 (m, 4 H) 7.72 (s, 1 H) 7.77 - 7.91 (m, 2 H) 7.98 (d, *J*=5.55 Hz, 1 H) 8.18 (t, *J*=6.35 Hz, 1 H) 9.08 (s, 1 H) 10.32 (s, 1 H) 10.69 (s, 1 H). MS(ESI(+)) m/e 463(M+H)<sup>+</sup>

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## EXAMPLE 74

8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(3-((((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

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## EXAMPLE 74A

Ethyl 3-(8-chloro-1-iodoimidazo[1,5-a]pyrazin-3-yl)propanoate

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The title compound was prepared as described in EXAMPLES 1A-1C, except substituting 4-ethoxy-4-oxobutanoic acid for acetic acid in EXAMPLE 1A. MS(ESI(+)) m/e 380(M+H)<sup>+</sup>



## EXAMPLE 74B

3-(8-chloro-1-iodoimidazo[1,5-a]pyrazin-3-yl)propanoic acid

5 A solution of EXAMPLE 74A (1.96 g) in tetrahydrofuran (5mL) and ethanol (1mL) was treated with 2N LiOH (5.16 ml), stirred at room temperature for 3 hours and then neutralized to pH 3-4 with 3N HCl. The mixture was extracted with ethyl acetate. The extract was washed (brine), dried (MgSO<sub>4</sub>) and concentrated to dryness to give the title compound. MS(ESI(+)) m/e 352(M+H)<sup>+</sup>

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## EXAMPLE 74C

3-(8-amino-1-iodoimidazo[1,5-a]pyrazin-3-yl)-N-ethyl-N-(2-hydroxyethyl)propanamide

15 A mixture of EXAMPLE 74B (1.3 g), 2-(ethylamino)ethanol (0.363 g), 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (0.78 g), 1-hydroxybenzotriazole hydrate (0.623 g), and N-methylmorpholine (0.748 g) in 5 mL DMF was stirred at room temperature for 10 hours. The reaction mixture was extracted with ethyl acetate 3 times and the combined extracts were washed (brine), dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by flash chromatography with 0-4% methanol/CH<sub>2</sub>Cl<sub>2</sub> to afford 3-(8-(1H-benzo(d)(1,2,3)triazol-1-yloxy)-1-iodoimidazo[1,5-a]pyrazin-3-yl)-N-ethyl-N-(2-hydroxyethyl)propanamide. MS(ESI(+)) m/e 522(M+H)<sup>+</sup> This product was placed in a high pressure tube with 20 7N ammonia (15 ml) in methanol, heated at 60C overnight then concentrated to dryness. The residue was purified by flash column with 0-10% methanol/CH<sub>2</sub>Cl<sub>2</sub> to give the title compound. MS(ESI(+)) m/e 404(M+H)<sup>+</sup>

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## EXAMPLE 74D

8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)imidazo[1,5-a]pyrazine-1-carboxylic acid

30 The title compound was prepared as described in EXAMPLES 1E-1F, substituting EXAMPLE 74C for EXAMPLE 1D in EXAMPLE 1E.

## EXAMPLE 74E

35 8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(3-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-trifluoromethyl-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 74D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.70 - 1.45 (m, 3 H) 2.86 - 3.15 (m, 2 H) 3.09 - 3.92 (m, 8 H) 4.34 (d, J=6.14 Hz, 2 H) 6.86 (t, J=5.68 Hz, 1 H) 7.12 - 7.27 (m, 2 H) 7.37 (t, J=7.83 Hz, 1 H) 7.52 - 7.71 (m, 5 H) 7.77 (s, 1

H) 7.89 (t,  $J=5.83$  Hz, 1 H) 9.06 (s, 2 H) 10.45 (d,  $J=7.37$  Hz, 1 H) 10.74 (s, 1 H).  
MS(ESI(+)) m/e 613(M+H)<sup>+</sup>

## EXAMPLE 75

5 8-amino-N-(3-((((4-chloro-2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 4-chloro-2-fluoro-1-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene,  
10 respectively in EXAMPLE 1G, then reacting the product with EXAMPLE 74D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.73 - 1.40 (m, 3 H) 2.84 - 3.89 (m, 10 H) 4.26 - 4.45 (m, 2 H) 4.86 (s, 1 H) 7.00 - 7.54 (m, 6 H) 7.55 - 7.97 (m, 3 H) 8.17 (t,  $J=8.82$  Hz, 1 H) 8.52 (d,  $J=2.37$  Hz, 1 H) 9.04 (s, 1 H) 10.47 (d,  $J=5.43$  Hz, 1 H) 10.70 (s, 1 H). MS(ESI(+)) m/e 597(M+H)<sup>+</sup>

15

## EXAMPLE 76

8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(3-((((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

20 The title compound was prepared by substituting tert-butyl 3-(aminomethyl)phenylcarbamate for (4-aminophenyl)carbamic acid tert-butyl ester in EXAMPLE 1G, then reacting the product with EXAMPLE 74D as described in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.84 - 1.30 (m, 3 H) 2.82 - 4.00 (m, 10 H) 4.27 - 4.42 (m, 2 H) 4.87 (s, 1 H) 6.53 - 6.87 (m, 2 H) 6.96 - 7.56 (m, 6  
25 H) 7.59 - 8.01 (m, 3 H) 8.87 (s, 1 H) 9.12 (s, 1 H) 10.47 (d,  $J=5.43$  Hz, 1 H) 10.76 (s, 1 H). MS(ESI(+)) m/e 563(M+H)<sup>+</sup>

## EXAMPLE 77

30 8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(4-((((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

The title compound was prepared as described in EXAMPLE 1H by substituting EXAMPLE 74D for EXAMPLE 1F. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.73 - 1.33 (m, 3 H) 2.82 - 4.08 (m, 10 H) 4.97 (s, 1 H) 6.59 - 6.88 (m, 1 H) 7.02 - 7.40 (m, 3 H) 7.42 - 7.60 (m, 3 H) 7.60 - 7.84 (m, 2 H) 7.83 - 8.09 (m, 1 H) 8.84 (s,  
35 1 H) 8.97 (s, 2 H) 10.44 (d,  $J=2.71$  Hz, 1 H) 10.84 (s, 1 H). MS(ESI(+)) m/e 549(M+H)<sup>+</sup>

## EXAMPLE 78

40 8-amino-3-cyclopropyl-N-(3-((((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide

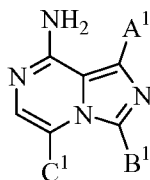
The title compound was prepared as described in EXAMPLES 1G-1H by substituting tert-butyl 3-(aminomethyl)phenylcarbamate and 1-isocyanato-4-

trifluoromethyl-benzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene, respectively in EXAMPLE 1G and EXAMPLE 54A for EXAMPLE 1F in EXAMPLE 1H. <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ ppm 0.89 - 1.28 (m, 4 H) 2.17 - 2.42 (m, 1 H) 4.33 (d, *J*=5.55 Hz, 2 H) 6.81 (t, *J*=5.75 Hz, 1 H) 7.08 (d, *J*=7.93 Hz, 1 H) 7.20 (d, *J*=5.16 Hz, 1 H) 7.32 (t, *J*=7.93 Hz, 1 H) 7.45 - 7.93 (m, 7 H) 9.02 (s, 1 H) 10.01 (s, 1 H). MS(ESI(+)) m/e 510(M+H)<sup>+</sup>.

The foregoing is meant to illustrate the invention but not to limit it. Variations and changes obvious to one skilled in the art are intended to be within the scope of the invention as defined in the claims.

WE CLAIM:

1. A compound having Formula I



(I),

- 5 or a therapeutically acceptable salt thereof, wherein

A<sup>1</sup> is C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup> or R<sup>5</sup>;

10

B<sup>1</sup> and C<sup>1</sup> are independently H, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup> or R<sup>5</sup>; wherein

15

R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup>;

R<sup>2</sup> is phenyl which is unfused or fused with benzene, heteroarene or R<sup>2A</sup>; R<sup>2A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

20

R<sup>3</sup> is heteroaryl which is unfused or fused with benzene, heteroarene or R<sup>3A</sup>; R<sup>3A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

25

R<sup>4</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or R<sup>4A</sup>; R<sup>4A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

30

R<sup>5</sup> is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected R<sup>6</sup>, OR<sup>6</sup>, SR<sup>6</sup>, S(O)R<sup>6</sup>, SO<sub>2</sub>R<sup>6</sup>, NH<sub>2</sub>, NHR<sup>6</sup>, N(R<sup>6</sup>)<sub>2</sub>, C(O)R<sup>6</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>6</sup>, C(O)N(R<sup>6</sup>)<sub>2</sub>, NHC(O)R<sup>6</sup>, NR<sup>6</sup>C(O)R<sup>6</sup>, NHSO<sub>2</sub>R<sup>6</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>6</sup>, NHC(O)OR<sup>6</sup>, NR<sup>6</sup>C(O)OR<sup>6</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>6</sup>, SO<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub>, NHC(O)NH<sub>2</sub>, NHC(O)R<sup>6</sup>, NHC(O)N(R<sup>6</sup>)<sub>2</sub>, NR<sup>6</sup>C(O)N(R<sup>6</sup>)<sub>2</sub>, OH, (O), C(O)OH, CN, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

35

R<sup>6</sup> is R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, or R<sup>9A</sup>;

$R^7$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{7A}$ ;  $R^{7A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

40  $R^8$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{8A}$ ;  $R^{8A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^9$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{9A}$ ;  $R^{9A}$  is cycloalkane,  
45 cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{9A}$  is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $SO_2NH_2$ ,  $NHC(O)NH_2$ ,  $OH$ ,  $(O)$ ,  $C(O)OH$ ,  $CN$ ,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

50

wherein each foregoing cyclic moiety is independently unsubstituted or substituted with one or two or three or four or five of independently selected  $R^{30}$ ,  $OR^{30}$ ,  $OCH_2R^{30}$ ,  $SR^{30}$ ,  $S(O)R^{30}$ ,  $SO_2R^{30}$ ,  $C(O)R^{30}$ ,  $CO(O)R^{30}$ ,  $OC(O)R^{30}$ ,  $OC(O)OR^{30}$ ,  $NO_2$ ,  $NH_2$ ,  $NHR^{30}$ ,  $N(R^{30})_2$ ,  $C(O)NH_2$ ,  $C(O)NHR^{30}$ ,  $C(O)N(R^{30})_2$ ,  $NHC(O)R^{30}$ ,  $NHC(O)NHR^{30}$ ,  
55  $NHC(O)N(R^{30})_2$ ,  $NR^{30}C(O)NHR^{30}$ ,  $NR^{30}C(O)N(R^{30})_2$ ,  $C(O)NHOH$ ,  $C(O)NHOR^{30}$ ,  $C(O)NHOSO_2R^{30}$ ,  $C(O)NR^{30}SO_2R^{30}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{30}$ ,  $SO_2N(R^{30})_2$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $C(O)H$ ,  $C(O)OH$ ,  $C(N)NH_2$ ,  $C(N)NHR^{30}$ ,  $C(N)N(R^{30})_2$ ,  $CNOH$ ,  $CNOCH_3$ ,  $OH$ ,  $(O)$ ,  $N_3$ ,  $CF_3$ ,  $CF_2CF_3$ ,  $OCF_3$ ,  $OCF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

60  $R^{30}$  is  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$  or  $R^{34}$ ;

$R^{31}$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{31A}$ ;  $R^{31A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

65  $R^{32}$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{32A}$ ;  $R^{32A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{33}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{33A}$ ;  $R^{33A}$  is cycloalkane,  
70 cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{34}$  is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $R^{35}$ ,  $OR^{35}$ ,  $SR^{35}$ ,  $S(O)R^{35}$ ,  $SO_2R^{35}$ ,  $NH_2$ ,  $NHR^{35}$ ,  $N(R^{35})_2$ ,  $C(O)R^{35}$ ,  $C(O)NH_2$ ,  $C(O)NHR^{35}$ ,  $C(O)N(R^{35})_2$ ,  $NHC(O)R^{35}$ ,  
75  $NR^{35}C(O)R^{35}$ ,  $NHSO_2R^{35}$ ,  $NR^{35}SO_2R^{35}$ ,  $NHC(O)OR^{35}$ ,  $NR^{35}C(O)OR^{35}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{35}$ ,  $SO_2N(R^{35})_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{35}$ ,  $NHC(O)R^{35}$ ,  $NHC(O)N(R^{35})_2$ ,  $NR^{35}C(O)N(R^{35})_2$ ,  $OH$ ,  $(O)$ ,  $C(O)OH$ ,  $CN$ ,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

R<sup>35</sup> is R<sup>36</sup>, R<sup>37</sup>, R<sup>38</sup> or R<sup>39</sup>;

80

R<sup>36</sup> is phenyl which is unfused or fused with benzene, heteroarene or R<sup>36A</sup>; R<sup>36A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>37</sup> is heteroaryl which is unfused or fused with benzene, heteroarene or R<sup>37A</sup>;  
85 R<sup>37A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

R<sup>38</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or R<sup>38A</sup>; R<sup>38A</sup> is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

90

R<sup>39</sup> is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with R<sup>40</sup>;

R<sup>40</sup> is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl;

95

wherein the moieties represented by R<sup>31</sup>, R<sup>32</sup>, R<sup>33</sup>, R<sup>36</sup>, R<sup>37</sup> and R<sup>38</sup> are independently unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I, OH, (O)OH, NO<sub>2</sub>, NH<sub>2</sub>, CF<sub>3</sub>, OH, R<sup>45</sup>, OR<sup>45</sup>, SR<sup>45</sup>, S(O)R<sup>45</sup>, SO<sub>2</sub>R<sup>45</sup>, C(O)NHR<sup>45</sup>, C(O)N(R<sup>45</sup>)<sub>2</sub>, NHC(O)R<sup>45</sup>, NR<sup>45</sup>C(O)R<sup>45</sup>, NHC(O)NHR<sup>45</sup>,  
100 NHC(O)N(R<sup>45</sup>)<sub>2</sub>, NR<sup>45</sup>C(O)NHR<sup>45</sup>, NR<sup>45</sup>C(O)N(R<sup>45</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>45</sup>, SO<sub>2</sub>N(R<sup>45</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>45</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>45</sup>, OC(O)OR<sup>45</sup>, NHC(O)OR<sup>45</sup> or NR<sup>45</sup>C(O)OR<sup>45</sup>;

R<sup>45</sup> is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected R<sup>50</sup>, F, Cl, Br, I, OH, C(O)OH, NO<sub>2</sub> or NH<sub>2</sub>;  
105 and

R<sup>50</sup> is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl.

2. The compound of claim 1 wherein

110 A<sup>1</sup> is C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup> or R<sup>5</sup>;

115 B<sup>1</sup> and C<sup>1</sup> are independently H, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NHSO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup> or R<sup>5</sup>; wherein

$R^1$  is  $R^2$ ,  $R^3$  or  $R^4$ ;

120

$R^2$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{2A}$ ;  $R^{2A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^3$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{3A}$ ;  $R^{3A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

125

$R^4$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{4A}$ ;  $R^{4A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

130

$R^5$  is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $R^6$ ,  $OR^6$ ,  $SR^6$ ,  $S(O)R^6$ ,  $SO_2R^6$ ,  $NH_2$ ,  $NHR^6$ ,  $N(R^6)_2$ ,  $C(O)R^6$ ,  $C(O)NH_2$ ,  $C(O)NHR^6$ ,  $C(O)N(R^6)_2$ ,  $NHC(O)R^6$ ,  $NR^6C(O)R^6$ ,  $NHSO_2R^6$ ,  $NR^6SO_2R^6$ ,  $NHC(O)OR^6$ ,  $NR^6C(O)OR^6$ ,  $SO_2NH_2$ ,  $SO_2NHR^6$ ,  $SO_2N(R^6)_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)R^6$ ,  $NHC(O)N(R^6)_2$ ,  $NR^6C(O)N(R^6)_2$ ,  $OH$ ,  $(O)$ ,  $C(O)OH$ ,  $CN$ ,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

135

$R^6$  is  $R^7$ ,  $R^8$ ,  $R^9$ , or  $R^{9A}$ ;

$R^7$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{7A}$ ;  $R^{7A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

140

$R^8$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{8A}$ ;  $R^{8A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

145

$R^9$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{9A}$ ;  $R^{9A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{9A}$  is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $NH_2$ ,  $C(O)NH_2$ ,  $SO_2NH_2$ ,  $NHC(O)NH_2$ ,  $OH$ ,  $(O)$ ,  $C(O)OH$ ,  $CN$ ,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

150

wherein each foregoing cyclic moiety is independently unsubstituted or substituted with one or two or three or four or five of independently selected  $R^{30}$ ,  $NHC(O)R^{30}$ ,  $NHC(O)NHR^{30}$ ,  $F$ ,  $Cl$ ,  $Br$  or  $I$ ;

155

$R^{30}$  is  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$  or  $R^{34}$ ;

160  $R^{31}$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{31A}$ ;  $R^{31A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{32}$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{32A}$ ;  $R^{32A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

165

$R^{33}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{33A}$ ;  $R^{33A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

170

$R^{34}$  is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $R^{35}$ ,  $OR^{35}$ ,  $SR^{35}$ ,  $S(O)R^{35}$ ,  $SO_2R^{35}$ ,  $NH_2$ ,  $NHR^{35}$ ,  $N(R^{35})_2$ ,  $C(O)R^{35}$ ,  $C(O)NH_2$ ,  $C(O)NHR^{35}$ ,  $C(O)N(R^{35})_2$ ,  $NHC(O)R^{35}$ ,  $NR^{35}C(O)R^{35}$ ,  $NHSO_2R^{35}$ ,  $NR^{35}SO_2R^{35}$ ,  $NHC(O)OR^{35}$ ,  $NR^{35}C(O)OR^{35}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{35}$ ,  $SO_2N(R^{35})_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{35}$ ,  $NHC(O)R^{35}$ ,  $NHC(O)N(R^{35})_2$ ,  $NR^{35}C(O)N(R^{35})_2$ , OH, (O), C(O)OH, CN,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

175

$R^{35}$  is  $R^{36}$ ,  $R^{37}$ ,  $R^{38}$  or  $R^{39}$ ;

180  $R^{36}$  is phenyl which is unfused or fused with benzene, heteroarene or  $R^{36A}$ ;  $R^{36A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{37}$  is heteroaryl which is unfused or fused with benzene, heteroarene or  $R^{37A}$ ;  $R^{37A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

185

$R^{38}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or  $R^{38A}$ ;  $R^{38A}$  is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

190  $R^{39}$  is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with  $R^{40}$ ;

$R^{40}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl;

195 wherein the moieties represented by  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$ ,  $R^{36}$ ,  $R^{37}$  and  $R^{38}$  are independently unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I,  $CF_3$ ,  $R^{45}$ ; and

200  $R^{45}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I, OH, C(O)OH,  $NO_2$  or  $NH_2$ .



3. The compound of claim 2 wherein

A<sup>1</sup> is C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>, NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>,  
NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>, SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>,  
NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup> or R<sup>5</sup>;

205

B<sup>1</sup> and C<sup>1</sup> are independently H, C(O)NHR<sup>1</sup>, C(O)N(R<sup>1</sup>)<sub>2</sub>, NHC(O)R<sup>1</sup>,  
NR<sup>1</sup>C(O)R<sup>1</sup>, NHC(O)NHR<sup>1</sup>, NHC(O)N(R<sup>1</sup>)<sub>2</sub>, NR<sup>1</sup>C(O)NHR<sup>1</sup>, NR<sup>1</sup>C(O)N(R<sup>1</sup>)<sub>2</sub>,  
SO<sub>2</sub>NHR<sup>1</sup>, SO<sub>2</sub>N(R<sup>1</sup>)<sub>2</sub>, NH<sub>2</sub>SO<sub>2</sub>R<sup>1</sup>, NR<sup>1</sup>SO<sub>2</sub>R<sup>1</sup>, OC(O)OR<sup>1</sup>, NHC(O)OR<sup>1</sup>, NR<sup>1</sup>C(O)OR<sup>1</sup>  
or R<sup>5</sup>; wherein

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R<sup>1</sup> is R<sup>2</sup>, R<sup>3</sup> or R<sup>4</sup>;

R<sup>2</sup> is phenyl;

215

R<sup>3</sup> is heteroaryl;

R<sup>4</sup> is cycloalkyl;

220

R<sup>5</sup> is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with  
one, two, three, four or five of independently selected R<sup>6</sup>, OR<sup>6</sup>, SR<sup>6</sup>, S(O)R<sup>6</sup>, SO<sub>2</sub>R<sup>6</sup>, NH<sub>2</sub>,  
NHR<sup>6</sup>, N(R<sup>6</sup>)<sub>2</sub>, C(O)R<sup>6</sup>, C(O)NH<sub>2</sub>, C(O)NHR<sup>6</sup>, C(O)N(R<sup>6</sup>)<sub>2</sub>, NHC(O)R<sup>6</sup>, NR<sup>6</sup>C(O)R<sup>6</sup>,  
NH<sub>2</sub>SO<sub>2</sub>R<sup>6</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>6</sup>, NHC(O)OR<sup>6</sup>, NR<sup>6</sup>C(O)OR<sup>6</sup>, SO<sub>2</sub>NH<sub>2</sub>, SO<sub>2</sub>NHR<sup>6</sup>, SO<sub>2</sub>N(R<sup>6</sup>)<sub>2</sub>,  
NHC(O)NH<sub>2</sub>, NHC(O)R<sup>6</sup>, NHC(O)N(R<sup>6</sup>)<sub>2</sub>, NR<sup>6</sup>C(O)N(R<sup>6</sup>)<sub>2</sub>, OH, (O), C(O)OH, CN, CF<sub>3</sub>,  
OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

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R<sup>6</sup> is R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, or R<sup>9A</sup>;

R<sup>7</sup> is phenyl;

230

R<sup>8</sup> is heteroaryl;

R<sup>9</sup> is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

235

R<sup>9A</sup> is alkyl, alkenyl, or alkynyl, each of which is unsubstituted or substituted with  
one, two, three, four or five of independently selected NH<sub>2</sub>, C(O)NH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>,  
NHC(O)NH<sub>2</sub>, OH, (O), C(O)OH, CN, CF<sub>3</sub>, OCF<sub>3</sub>, CF<sub>2</sub>CF<sub>3</sub>, F, Cl, Br or I;

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wherein each foregoing cyclic moiety is independently unsubstituted or substituted  
with one or two or three or four or five of independently selected R<sup>30</sup>, NHC(O)R<sup>30</sup>,  
NHC(O)NHR<sup>30</sup>, F, Cl, Br or I;

$R^{30}$  is  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$  or  $R^{34}$ ;

$R^{31}$  is phenyl;

245

$R^{32}$  is heteroaryl;

$R^{33}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

250

$R^{34}$  is alkyl, alkenyl, or alkenyl, each of which is unsubstituted or substituted with one, two, three, four or five of independently selected  $R^{35}$ ,  $OR^{35}$ ,  $SR^{35}$ ,  $S(O)R^{35}$ ,  $SO_2R^{35}$ ,  $NH_2$ ,  $NHR^{35}$ ,  $N(R^{35})_2$ ,  $C(O)R^{35}$ ,  $C(O)NH_2$ ,  $C(O)NHR^{35}$ ,  $C(O)N(R^{35})_2$ ,  $NHC(O)R^{35}$ ,  $NR^{35}C(O)R^{35}$ ,  $NHSO_2R^{35}$ ,  $NR^{35}SO_2R^{35}$ ,  $NHC(O)OR^{35}$ ,  $NR^{35}C(O)OR^{35}$ ,  $SO_2NH_2$ ,  $SO_2NHR^{35}$ ,  $SO_2N(R^{35})_2$ ,  $NHC(O)NH_2$ ,  $NHC(O)NHR^{35}$ ,  $NHC(O)R^{35}$ ,  $NHC(O)N(R^{35})_2$ ,  $NR^{35}C(O)N(R^{35})_2$ , OH, (O), C(O)OH, CN,  $CF_3$ ,  $OCF_3$ ,  $CF_2CF_3$ , F, Cl, Br or I;

255

$R^{35}$  is  $R^{36}$ ,  $R^{37}$ ,  $R^{38}$  or  $R^{39}$ ;

$R^{36}$  is phenyl;

260

$R^{37}$  is heteroaryl;

$R^{38}$  is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl;

265

$R^{39}$  is alkyl, alkenyl or alkenyl, each of which is unsubstituted or substituted with  $R^{40}$ ;

$R^{40}$  is phenyl, heteroaryl, cycloalkyl, cycloalkenyl or heterocycloalkyl;

270

wherein the moieties represented by  $R^{31}$ ,  $R^{32}$ ,  $R^{33}$ ,  $R^{36}$ ,  $R^{37}$  and  $R^{38}$  are independently unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I,  $CF_3$ ,  $R^{45}$ ; and

275

$R^{45}$  is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I, OH, C(O)OH,  $NO_2$  or  $NH_2$ .

4. The compound of claim 3 wherein

$A^1$  is  $C(O)NHR^1$ ;

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$B^1$  and  $C^1$  are independently H or  $R^1$ ; wherein

$R^1$  is  $R^2$  or  $R^4$ ;

- 285  $R^2$  is phenyl;
- $R^4$  is cycloalkyl;
- 290  $R^5$  is alkyl, each of which is unsubstituted or substituted with  $C(O)NHR^6$ , F, Cl, Br or I;
- $R^6$  is  $R^{9A}$ ;
- $R^{9A}$  is alkyl, which is unsubstituted or substituted with OH, F, Cl, Br or I;
- 295 wherein each foregoing cyclic moiety is independently unsubstituted or substituted with one or two or three or four or five of independently selected  $R^{30}$ ,  $NHC(O)R^{30}$ ,  $NHC(O)NHR^{30}$ , F, Cl, Br or I;
- 300  $R^{30}$  is  $R^{31}$ ,  $R^{32}$ , or  $R^{34}$ ;
- $R^{31}$  is phenyl;
- $R^{32}$  is heteroaryl;
- 305  $R^{34}$  is alkyl, each of which is unsubstituted or substituted with  $NHSO_2R^{35}$ ,  $NHC(O)NHR^{35}$ , F, Cl, Br, or I;
- $R^{35}$  is  $R^{36}$ , or  $R^{37}$ ;
- 310  $R^{36}$  is phenyl;
- $R^{37}$  is heteroaryl;
- 315 wherein the moieties represented by  $R^{31}$  and  $R^{36}$  are independently unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I,  $CF_3$ ,  $R^{45}$ ; and
- $R^{45}$  is alkyl, which is unsubstituted or substituted with one or two or three of independently selected F, Cl, Br, I, or OH.
- 320 5. A compound of claim 4, which is  
8-amino-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

325 8-amino-N-(4-((anilincarbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

8-amino-N-(4-(benzoylamino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

330

8-amino-3-methyl-N-(4-(((3-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide,

335 8-amino-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

8-amino-N-(3-(((anilincarbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

340

8-amino-N-(3-(((2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

345 8-amino-N-(3-(((4-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

8-amino-3-methyl-N-(3-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide,

350

8-amino-N-(4-(((3-(2-hydroxyethyl)phenyl)amino)carbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide,

355 8-amino-N-(4-(((4-(2-hydroxyethyl)phenyl)amino)carbonyl)amino)phenyl)-3-methylimidazo[1,5-a]pyrazine-1-carboxamide

8-amino-3-cyclopropyl-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

360 8-amino-N-(4-((anilincarbonyl)amino)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(4-(((3-methylphenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

- 365 8-amino-3-cyclopropyl-N-(4-(((2-fluoro-5-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 370 8-amino-3-cyclopropyl-N-(4-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 375 8-amino-3-cyclopropyl-N-(3-(((pyridin-3-ylamino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 8-amino-3-cyclopropyl-N-(4-(((3-fluorophenyl)amino)carbonyl)amino)-3-methylphenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 380 8-amino-3-cyclopropyl-N-(4-(((2-fluorophenyl)amino)carbonyl)amino)-3-methylphenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 385 8-amino-3-cyclopropyl-N-(3-methyl-4-(((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 8-amino-3-cyclopropyl-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 390 8-amino-3-cyclopropyl-N-(3-(((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 395 8-amino-N-(3-(((4-chloro-2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide;
- 8-amino-N-(3-(((anilino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide;
- 400 8-amino-3-cyclopropyl-N-(3-(((3,4-difluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;
- 405 8-amino-3-cyclopropyl-N-(3-(((2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(3-((((4-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

410

8-amino-N-(3-((((3-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-N-(3-((((4-chlorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-cyclopropylimidazo[1,5-a]pyrazine-1-carboxamide;

415

8-amino-3-cyclopropyl-N-(4-((pyridin-3-ylamino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-cyclopropyl-N-(3-(((phenylsulfonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

420

8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(3-((((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

425

8-amino-N-(3-((((4-chloro-2-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)imidazo[1,5-a]pyrazine-1-carboxamide;

430

8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(3-((((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

8-amino-3-(3-(ethyl(2-hydroxyethyl)amino)-3-oxopropyl)-N-(4-((((3-fluorophenyl)amino)carbonyl)amino)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

435

8-amino-3-cyclopropyl-N-(3-((((4-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)imidazo[1,5-a]pyrazine-1-carboxamide;

440

or a therapeutically acceptable salt thereof.

6. A composition comprising an excipient and a therapeutically effective amount of a compound having Formula I.

7. A method of treating bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer or thyroid cancer in a mammal, the method comprising administering thereto a therapeutically effective amount
- 5 of a compound having Formula I.

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/US2008/063189

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C07D487/04 A61K31/4985 A61P35/00 A61K31/53

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)  
C07D A61K A61P

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 practical, search terms used)

EPO-Internal, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/041712 A (SCHERING CORP [US]; PARUCH KAMIL [US]; GUZI TIMOTHY J [US]; DWYER MICH) 12 April 2007 (2007-04-12) claims	1-7
X	WO 2005/097800 A (OSI PHARM INC [US]; ARNOLD LEE D [US]; CESARIO CARA [US]; COATE HEATHE) 20 October 2005 (2005-10-20) the whole document	1-7
X	WO 2005/037836 A (OSI PHARM INC [US]; BECK PATRICIA ANNE [US]; CESARIO CARA [US]; COX MA) 28 April 2005 (2005-04-28) the whole document	1-7

Further documents are listed in the continuation of Box C.

See patent family annex.

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
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- \* & \* document member of the same patent family

Date of the actual completion of the international search

7 August 2008

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2008/063189

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2007/064993 A (OSI PHARM. INC [US]; CREW ANDREW PHILIP [US]; DONG HAN-QING [US]; MULVI) 7 June 2007 (2007-06-07) the whole document -----	1-4,6,7
X,P	WO 2007/087395 A2 (OSI PHARMACEUTICALS, INC., USA) 2 August 2007 (2007-08-02) the whole document -----	1-4,6,7
X,P	WO 2007/061737 A2 (USA) 31 May 2007 (2007-05-31) the whole document -----	1-4,6,7
X,P	WO 2007/106503 A2 (OSI PHARMACEUTICALS, INC., USA) 20 September 2007 (2007-09-20) the whole document -----	1-4,6,7

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2008/063189

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2007041712	A	12-04-2007	AR 056206 A1	26-09-2007
			AU 2006299338 A1	12-04-2007
			CA 2624882 A1	12-04-2007
			EP 1931676 A1	18-06-2008
WO 2005097800	A	20-10-2005	AR 048518 A1	03-05-2006
			AU 2005230818 A1	20-10-2005
			BR PI0509576 A	29-05-2007
			CA 2561950 A1	20-10-2005
			CN 1960993 A	09-05-2007
			EP 1740591 A1	10-01-2007
			JP 2007531754 T	08-11-2007
			KR 20070008669 A	17-01-2007
			WO 2005037836	A
BR PI0415395 A	12-12-2006			
CA 2542481 A1	28-04-2005			
CN 1898240 A	17-01-2007			
EP 1675860 A2	05-07-2006			
JP 2007509060 T	12-04-2007			
KR 20060086987 A	01-08-2006			
SG 132683 A1	28-06-2007			
WO 2007064993	A	07-06-2007	AR 057960 A1	26-12-2007
			US 2007149521 A1	28-06-2007
WO 2007087395	A2	02-08-2007	AR 059187 A1	12-03-2008
WO 2007061737	A2	31-05-2007	AR 056884 A1	31-10-2007
			AU 2006316605 A1	31-05-2007
			EP 1951724 A2	06-08-2008
WO 2007106503	A2	20-09-2007	US 2007280928 A1	06-12-2007