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(54) **Title:** INHIBITORS OF PROTEIN KINASES

(57) **Abstract:** Compounds that inhibit protein kinases, compositions containing the compounds and methods of treating diseases using the compounds are disclosed.

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# INHIBITORS OF PROTEIN KINASES

This application claims priority to United States Provisional Parent Application Serial No. 60/749,074 , filed December 8, 2005.

## FIELD OF THE INVENTION

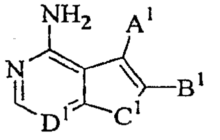
This invention pertains to compounds that inhibit protein kinases such as Aurora kinases, compositions containing the compounds and methods of treating diseases using the compounds.

## BACKGROUND OF THE INVENTION

Mitosis is a process by which a complete copy of a duplicated genome is segregated by the microtuble spindle apparatus into two daughter cells. Aurora kinases, key mitotic regulators required for genome stability, have been found to be overexpressed in human tumors. Given the central role of mitosis in the progression of maligncies, inhibitors of mitosis are expected to be useful for treating a broad range of tumors.
There is therefore an existing need in the therapeutic arts for inhibitors of Aurora kinases.

## SUMMARY OF THE INVENTION

One embodiment of this invention, therefore, pertains to compounds that inhibit Aurora kinases, the compounds having formula (I)



(I),

$A^1$ 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 $R^5$;

$R^1$ is $R^2$, $R^3$, $R^4$ or $R^5$;

$R^2$ 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;

$R^4$ 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;

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

$R^6$ is $R^7$, $R^8$ or $R^9$;

$R^7$ 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;

$R^9$ 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;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $S(O)R^{10}$, $SO_2R^{10}$, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHC(O)NHR^{10}$, $NHC(O)N(R^{10})_2$, $NR^{10}C(O)NHR^{10}$, $NR^{10}C(O)N(R^{10})_2$, $SO_2NHR^{10}$, $SO_2N(R^{10})_2$, $NHSO_2R^{10}$, $NR^1SO_2R^{10}$, $OC(O)OR^{10}$, $NHC(O)OR^{10}$ or $NR^1C(O)OR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{11A}$; $R^{11A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{12}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{12A}$; $R^{12A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{13}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{13A}$; $R^{13A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{14}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{15}$ or $NHC(O)NHR^{15}$;

$R^{15}$ is $R^{16}$, $R^{17}$ $R^{18}$;

$R^{16}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{16A}$; $R^{16A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{17}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{17A}$; $R^{17A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{18}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{18A}$; $R^{18A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$B^1$ is H, $R^{19}$, $C(O)NHR^{19}$, $C(O)N(R^{19})_2$, $NHC(O)R^{19}$, $NR^1C(O)R^{19}$, $NHC(O)NHR^{19}$, $NHC(O)N(R^{19})_2$, $NR^{19}C(O)NHR^{19}$, $NR^1C(O)N(R^{19})_2$, $SO_2NHR^{19}$, $SO_2N(R^{19})_2$, $NHSO_2R^{19}$, $NR^{19}SO_2R^{19}$, $OC(O)OR^{19}$, $NHC(O)OR^{19}$, or $NR^{19}C(O)OR^{19}$;

$R^{19}$ is $R^{20}$, $R^{21}$, $R^{22}$ or $R^{23}$;

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

$R^{21}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{21A}$; $R^{21A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{22}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{22A}$; $R^{22A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{23}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{24}$, $OR^{24}$, $SR^{24}$, $S(O)R^{24}$, $SO_2R^{24}$, $NH_2$, $NHR^{24}$, $N(R^{24})_2$, $C(O)R^{24}$, $C(O)NH_2$, $C(O)NHR^{24}$, $C(O)N(R^{24})_2$, $NHC(O)R^{24}$, $NR^{24}C(O)R^{24}$, $NHSO_2R^{24}$, $NR^{24}SO_2R^{24}$, $NHC(O)OR^{24}$, $NR^{24}C(O)OR^{24}$, $SO_2NH_2$, $SO_2NHR^{24}$, $SO_2N(R^{24})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{24}$, $NHC(O)N(R^{24})_2$, $NR^{24}C(O)N(R^{24})_2$, OH, (O), C(O)OH, CN, $NH_2$, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{24}$ is $R^{25}$, $R^{26}$, $R^{27}$,
alkyl, alkenyl or alkynyl;

$R^{25}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{25A}$; $R^{25A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{26}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{26A}$; $R^{26A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{27}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{27A}$; $R^{27A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$C^1$ is O, S, S(O), $SO_2$, NH, or N($C^2$);

$C^2$ is $R^{28}$, $R^{29}$, $R^{30}$ or $R^{31}$;

$R^{28}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{28A}$; $R^{28A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{29}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{29A}$; $R^{29A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{30}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{30A}$; $R^{30A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{31}$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^{32}$, $OR^{32}$, $SR^{32}$, $S(O)R^{32}$, $SO_2R^{32}$, $NH_2$, $NHR^{32}$, $N(R^{32})_2$, $C(O)R^{32}$, $C(O)NH_2$, $C(O)NHR^{32}$, $C(O)N(R^{32})_2$, $NHC(O)R^{32}$, $NR^{32}C(O)R^{32}$, $NHSO_2R^{32}$, $NR^{32}SO_2R^{32}$, $NHC(O)OR^{32}$, $NR^{32}C(O)OR^{32}$, $SO_2NH_2$, $SO_2NHR^{32}$, $SO_2N(R^{32})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{32}$, $NHC(O)N(R^{32})_2$, $NR^{32}C(O)N(R^{32})_2$, OH, (O), C(O)OH, CN, $NH_2$, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

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

$R^{33}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{33A}$; $R^{33A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{34}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{34A}$; $R^{34A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{35}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{35A}$; $R^{35A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$D^1$ is N, CH or C($D^2$);

$D^2$ is $R^{36}$, $R^{37}$, $R^{38}$ or $R^{39}$;

$R^{36}$ 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;

$R^{38}$ 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;

$R^{39}$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^{40}$, $OR^{40}$, $SR^{40}$, $S(O)R^{40}$, $SO_2R^{40}$, $NH_2$, $NHR^{40}$, $N(R^{40})_2$, $C(O)R^{40}$, $C(O)NH_2$, $C(O)NHR^{40}$, $C(O)N(R^{40})_2$, $NHC(O)R^{40}$, $NR^{40}C(O)R^{40}$, $NHSO_2R^{40}$, $NR^{40}SO_2R^{40}$, $NHC(O)OR^{40}$, $NR^{40}C(O)OR^{40}$, $SO_2NH_2$, $SO_2NHR^{40}$, $SO_2N(R^{40})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{40}$, $NHC(O)N(R^{40})_2$, $NR^{40}C(O)N(R^{40})_2$, OH, (O), C(O)OH, CN, $NH_2$, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{40}$ is $R^{41}$, $R^{42}$ or $R^{43}$;

$R^{41}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{41A}$; $R^{41A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{42}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{42A}$; $R^{42A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{43}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{43A}$; $R^{43A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, $OR^{44}$, $SR^{44}$, $S(O)R^{44}$, $SO_2R^{44}$, $NH_2$, $NHR^{44}$, $N(R^{44})_2$, $C(O)R^{44}$, $C(O)OR^{44}$, $C(O)NH_2$, $C(O)NHR^{44}$, $C(O)N(R^{44})_2$, $NHC(O)R^{44}$, $NR^{44}C(O)R^{44}$, $NHSO_2R^{44}$, $NR^{44}SO_2R^{44}$, $NHC(O)OR^{44}$, $NR^{44}C(O)OR^{44}$, $SO_2NH_2$, $SO_2NHR^{44}$, $SO_2N(R^{44})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{44}$, $NHC(O)N(R^{44})_2$, $NR^{44}C(O)N(R^{44})_2$, $C(N)NH_2$, $C(N)NHR^{44}$, $C(N)N(R^{44})_2$, $NHC(N)NH_2$, $NHC(N)NHR^{44}$, $NHC(N)N(R^{44})_2$, OH, (O), C(O)H, C(O)OH, $NO_2$, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{44}$ is $R^{45}$, $R^{46}$, $R^{47}$ or $R^{48}$;

$R^{45}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{45A}$; $R^{45A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{46}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{46A}$; $R^{46A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{47}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{47A}$; $R^{47A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{48}$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^{49}$, $OR^{49}$, $SR^{49}$, $S(O)R^{49}$, $SO_2R^{49}$, $NH_2$, $NHR^{49}$, $N(R^{49})_2$, $C(O)R^{49}$, $C(O)NH_2$, $C(O)NHR^{49}$, $C(O)N(R^{49})_2$, $NHC(O)R^{49}$, $NR^{49}C(O)R^{49}$, $NHSO_2R^{49}$, $NR^{49}SO_2R^{49}$, $NHC(O)OR^{49}$, $NR^{49}C(O)OR^{49}$, $SO_2NH_2$, $SO_2NHR^{49}$, $SO_2N(R^{49})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{49}$, $NHC(O)N(R^{49})_2$, $NR^{49}C(O)N(R^{49})_2$, $OP(O)(OH)_2$, $OP(O)(OH)(OR^{44})$, $OP(O)(OR^{44})_2$, OH, (O), C(O)OH, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{49}$ is $R^{50}$, $R^{51}$, $R^{52}$, alkyl, alkenyl or alkynyl;

$R^{50}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{50A}$; $R^{50A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{51}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{51A}$; $R^{51A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$R^{52}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{52A}$; $R^{52A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by $R^{45}$, $R^{46}$, $R^{47}$ and $R^{49}$ are independently unsubstituted or substituted with one or two or three of four of independently selected alkyl, alkenyl, alkynyl, OH, (O), C(O)OH, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I.

Another embodiment comprises compounds having formula (I), and therapeutically acceptable salts, prodrugs and salts of prodrugs 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 $R^5$;

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

$R^2$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^3$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^4$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

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

$R^6$ is $R^7$, $R^8$ or $R^9$;

$R^7$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^8$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^9$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $S(O)R^{10}$, $SO_2R^{10}$, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$ or $NHC(O)NHR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{12}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{13}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{14}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{15}$ or $NHC(O)NHR^{15}$;

$R^{15}$ is $R^{16}$, $R^{17}$ $R^{18}$;

$R^{16}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{17}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{18}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$B^1$ is H or $R^{19}$;

$R^{19}$ is $R^{20}$, $R^{21}$, $R^{22}$ or $R^{23}$;

$R^{20}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{21}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{22}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{23}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{24}$, $OR^{24}$, $N(R^{24})_2$, $C(O)N(R^{24})_2$, $NHC(O)R^{24}$, $NR^{24}C(O)R^{24}$;

$R^{24}$ is alkyl, alkenyl or alkynyl;

$C^1$ is O, S, S(O), $SO_2$, NH, or $N(C^2)$;

$C^2$ is $R^{28}$, $R^{29}$ or $R^{30}$;

$R^{28}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{29}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{30}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$D^1$ is N, CH or $C(D^2)$;

$D^2$ is $R^{36}$, $R^{37}$ or $R^{38}$;

$R^{36}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{37}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

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

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, $OR^{44}$, $SR^{44}$, $S(O)R^{44}$, $SO_2R^{44}$, $NH_2$, $NHR^{44}$, $N(R^{44})_2$, $C(O)R^{44}$, $C(O)OR^{44}$, $C(O)NH_2$, $C(O)NHR^{44}$, $C(O)N(R^{44})_2$, $NHC(O)R^{44}$, OH, (O), C(O)H, C(O)OH, $NO_2$, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{44}$ is $R^{45}$, $R^{46}$, $R^{47}$ or $R^{48}$;

$R^{45}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{46}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{47}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{48}$ is alkyl substituted with $OP(O)(OH)_2$;

wherein the moieties represented by $R^{45}$, $R^{46}$ and $R^{47}$ are independently unsubstituted or substituted with one or two or three of four of independently selected alkyl, alkenyl, alkynyl, OH, (O), C(O)OH, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I.

Still another embodiment comprises compounds having formula (I), and therapeutically acceptable salts, prodrugs and salts of prodrugs thereof, wherein $A^1$ is $C(O)NHR^1$ or $R^5$;

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

$R^2$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^3$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^4$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^5$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^6$, $NHC(O)NHR^6$;

$R^6$ is $R^7$, $R^8$ or $R^9$;

$R^7$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^8$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^9$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $S(O)R^{10}$, $SO_2R^{10}$, $NH_2$, $NHC(O)R^{10}$, $NHC(O)NHR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{12}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{13}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{14}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{15}$ or $NHC(O)NHR^{15}$;

$R^{15}$ is $R^{16}$, $R^{17}$ $R^{18}$;

$R^{16}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{17}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{18}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$B^1$ is H or $R^{19}$;

$R^{19}$ is $R^{20}$, $R^{21}$, $R^{22}$ or $R^{23}$;

$R^{20}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{21}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{22}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{23}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{24}$, $OR^{24}$ or $N(R^{24})_2$;

$R^{24}$ is alkyl, alkenyl or alkynyl;

$C^1$ is O, S, S(O), $SO_2$, NH, or $N(C^2)$;

$C^2$ is $R^{28}$, $R^{29}$ or $R^{30}$;

$R^{28}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{29}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{30}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$D^1$ is N, CH or $C(D^2)$;

$D^2$ is $R^{36}$, $R^{37}$ or $R^{38}$;

$R^{36}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{37}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

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

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, $OR^{44}$, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{44}$ is $R^{45}$, $R^{46}$, $R^{47}$ or $R^{48}$;

$R^{45}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{46}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{47}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{48}$ is alkyl substituted with $OP(O)(OH)_2$;

wherein the moieties represented by $R^{45}$, $R^{46}$, and $R^{47}$ are independently unsubstituted or substituted with one or two or three of four of independently selected alkyl.

Still another embodiment comprises compounds having formula (I), and therapeutically acceptable salts, prodrugs and salts of prodrugs thereof, wherein $A^1$ is $C(O)NHR^1$ or $R^5$;

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

$R^2$ is phenyl;

$R^3$ is heteroaryl;

$R^4$ is cycloalkyl or heterocycloalkyl;

$R^5$ is alkyl, alkenyl or alkynyl, each of which is substituted with $R^6$, $NHC(O)NHR^6$;

$R^6$ is $R^7$or $R^9$;

$R^7$ is phenyl;

$R^8$ is heteroaryl;

$R^9$ is heterocycloalkyl;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $SO_2R^{10}$, $NH_2$, $NHC(O)R^{10}$, $NHC(O)NHR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl;

$R^{12}$ is heteroaryl;

$R^{13}$ is cycloalkyl;

$R^{14}$ is alkylwhich is unsubstituted or substituted with $R^{16}$ or NHC(O)NHR$^{16}$;

$R^{16}$ is phenyl;

$B^1$ is H or $R^{19}$;

$R^{19}$ is $R^{21}$, $R^{22}$ or $R^{23}$;

$R^{21}$ is heteroaryl;

$R^{22}$ is heterocycloalkyl;

$R^{23}$ is alkynyl, which is unsubstituted or substituted with $R^{24}$, OR$^{24}$ or N(R$^{24}$)$_2$;

$R^{24}$ is alkyl;

$C^1$ is S or N($C^2$);

$C^2$ is $R^{30}$;

$R^{30}$ is cycloalkyl;

$D^1$ is N, CH or C($D^2$);

$D^2$ is $R^{37}$;

$R^{37}$ is heteroaryl;

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, OR$^{44}$, CN, CF$_3$, F, Cl, Br or I;

$R^{44}$ is $R^{47}$ or $R^{48}$;

$R^{47}$ is heterocycloalkyl;

$R^{48}$ is alkyl substituted with OP(O)(OH)$_2$;

wherein $R^{47}$ is unsubstituted or substituted with alkyl.

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

Still another embodiment pertains to methods of treating diseases involving overexpression or unregulation of Protein kinases in a mammal, the methods comprising administering thereto a therapeutically effective amount of a compound having formula (I).

Still another embodiment pertains to methods of treating cancer in a mammal comprising administering thereto a therapeutically effective amount of a compound having formula (I).

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).

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.

Still another embodiment pertains to methods of treating diseases involving overexpression or unregulation of protein 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 radiation.

Still another embodiment pertains to methods of treating bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, leukemia, lymphoma, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer or 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.

Still another embodiment pertains to

4-amino-N-(4-((3-toluidinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-fluoroanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide, 4-amino-N-(4-(((3-fluoro-4-methylanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((4-toluidinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((4-fluoroanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-chloro-4-fluoroanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-ethylanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-chloroanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-cyanoanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((2-fluoroanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-(trifluoromethyl)anilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((4-fluoro-3-(trifluoromethyl)anilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-methoxyanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((5-fluoro-2-methylanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((4-(trifluoromethyl)anilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((2-fluoro-5-methylanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((2-toluidinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((4-methoxyanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3,5-dimethylanilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((2-fluoro-5-(trifluoromethyl)anilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((3-chloroanilino)carbonyl)amino)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-6-(1-methyl-1H-pyrazol-4-yl)-N-(4-((3-toluidinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide

4-amino-N-(4-(((2-fluoro-5-methylanilino)carbonyl)amino)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((4-fluoro-3-(trifluoromethyl)anilino)carbonyl)amino)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((2-fluoro-5-(trifluoromethyl)anilino)carbonyl)amino)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-6-(1-methyl-1H-pyrazol-4-yl)-N-(4-(((4-(trifluoromethyl)anilino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-6-(1-methyl-1H-pyrazol-4-yl)-N-(4-phenoxyphenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-phenoxyphenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(3-methylphenoxy)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(4-chlorophenoxy)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(4-methylphenoxy)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(3-chlorophenoxy)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-6-(1-methyl-1H-pyrazol-4-yl)-N-(4-(phenylsulfanyl)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(4-methylphenoxy)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-phenoxyphenyl)-6-(1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-phenoxyphenyl)-6-(3-thienyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-6-(4-methyl-1-piperazinyl)-N-(4-((3-toluidinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-methyl-N-(4-((3-toluidinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-phenoxyphenyl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-phenoxyphenyl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-benzylphenyl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-((3-toluidinocarbonyl)amino)phenyl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-(benzoylamino)phenyl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-7-(1-methyl-1H-pyrazol-4-yl)-N-(4-((3-toluidinocarbonyl)amino)phenyl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-(benzoylamino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-7-(1-methyl-1H-pyrazol-4-yl)-N-(4-phenoxyphenyl)thieno[3,2-c]pyridine-3-carboxamide, 4-amino-7-(1-methyl-1H-pyrazol-4-yl)-N-(3-phenoxyphenyl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-benzylphenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-7-(4-(4-methyl-1-piperazinyl)cyclohexyl)-N-(4-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide,

4-amino-7-(4-(4-methyl-1-piperazinyl)cyclohexyl)-N-(3-phenoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide,

4-amino-7-(4-(4-methyl-1-piperazinyl)cyclohexyl)-N-(4-((3-toluidinocarbonyl)amino)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((4-aminophenyl)sulfanyl)phenyl)-7-(4-(4-methyl-1-piperazinyl)cyclohexyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-benzylphenyl)-7-(4-(4-methyl-1-piperazinyl)cyclohexyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide,

4-amino-7-(4-(4-methyl-1-piperazinyl)cyclohexyl)-N-(4-(phenylsulfonyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide,

4-amino-1-(4-(4-morpholinyl)cyclohexyl)-1H-pyrazolo(3,4-d)pyrimidine-3-carboxylic acid,

4-amino-1-(4-(4-morpholinyl)cyclohexyl)-N-(4-phenoxyphenyl)-1H-pyrazolo(3,4-d)pyrimidine-3-carboxamide,

N-(4-((E)-2-(4-amino-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-3-yl)ethenyl)phenyl)-N'-(3-methylphenyl)urea

7-(1-methyl-1H-pyrazol-4-yl)-3-((E)-2-(4-phenoxyphenyl)ethenyl)thieno[3,2-c]pyridin-4-amine,

3-((E)-2-(1,1'-biphenyl)-4-ylethenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridin-4-amine,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine -3-carboxamide,

4-amino-N-(4-((((3-fluorophenyl)amino)carbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-(((cyclohexylamino)carbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-((((4-methylphenyl)amino)carbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-((((2-methylphenyl)amino)carbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-((anilinocarbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-((((2-methylphenyl)amino)carbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-((((4-methylphenyl)amino)carbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide, 4-amino-N-(3-((((3-methylphenyl)amino)carbonyl)amino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-(benzoylamino)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(1-(anilinocarbonyl)piperidin-4-yl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(1-benzoylpiperidin-4-yl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

trans4-amino-N-(4-(benzoylamino)cyclohexyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

trans4-amino-N-(4-((anilinocarbonyl)amino)cyclohexyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

trans4-amino-N-(4-((((2-fluorophenyl)amino)carbonyl)amino)cyclohexyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)benzyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-((anilinocarbonyl)amino)benzyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-((1-(anilinocarbonyl)piperidin-4-yl)methyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(4-(((anilinocarbonyl)amino)methyl)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-(((anilinocarbonyl)amino)methyl)phenyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

cis-4-amino-N-(4-((anilinocarbonyl)amino)cyclohexyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

cis-4-amino-N-((1S,3R)-3-((anilinocarbonyl)amino)cyclohexyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

cis-4-amino-N-((1S,3R)-3-(anilinocarbonyl)cyclohexyl)-7-(1-methyl-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

4-amino-N-(3-(((anilinocarbonyl)amino)methyl)phenyl)-7-(1-(2-hydroxyethyl)-1H-pyrazol-4-yl)thieno[3,2-c]pyridine-3-carboxamide,

2-(4-(4-amino-3-(((3-(((anilinocarbonyl)amino)methyl)phenyl)amino)carbonyl)thieno[3,2-c]pyridin-7-yl)-1H-pyrazol-1-yl)ethyl dihydrogen phosphate,

4-amino-N-(4-((((2-fluoro-3-(trifluoromethyl)phenyl)amino)carbonyl)amino)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-6-(1-methyl-1H-pyrazol-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-6-thien-3-ylthieno[2,3-d]pyrimidine-5-carboxamide, 4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-6-morpholin-4-ylthieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((thien-3-ylamino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((cyclopentylamino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((pyridin-3-ylamino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((5-methylisoxazol-3-yl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((cyclopropylamino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((2,4-difluorophenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((3,4-difluorophenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((3-(morpholin-4-ylmethyl)phenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)cyclohexyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((3,5-dimethylisoxazol-4-yl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((1,3-thiazol-2-ylamino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-(((isoxazol-3-ylamino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(1-(anilinocarbonyl)piperidin-4-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-((anilinocarbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-6-(3-methoxyprop-1-ynyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-6-ethynylthieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-6-(thien-3-ylethynyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)phenyl)-6-(3-(dimethylamino)prop-1-ynyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((2-fluorobenzoyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((3-fluorobenzoyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide, 4-amino-N-(4-((4-fluorobenzoyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((2-methylbenzoyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((3-methylbenzoyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((3-(hydroxymethyl)phenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-(((anilinocarbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-((((2-methylphenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-(((((3-methylphenyl)amino)carbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-(((((3-fluorophenyl)amino)carbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-((((3-methylphenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-((((4-methylphenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-((((2-fluorophenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-((((3-fluorophenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-((((4-fluorophenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(3-(((((3-(trifluoromethyl)phenyl)amino)carbonyl)amino)methyl)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(5-(2-((3-fluorophenyl)amino)-2-oxoethyl)-1,3-thiazol-2-yl)thieno[2,3-d]pyrimidine-5-carboxamide,

N-(4-(2-(4-aminothieno[2,3-d]pyrimidin-5-yl)ethyl)phenyl)-N'-phenylurea,

4-amino-N-(4-((((3-(3-hydroxypropoxy)phenyl)amino)carbonyl)amino)phenyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((anilinocarbonyl)amino)benzyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((3-methylphenyl)amino)carbonyl)amino)benzyl)thieno[2,3-d]pyrimidine-5-carboxamide,

4-amino-N-(4-((((3-fluorophenyl)amino)carbonyl)amino)benzyl)thieno[2,3-d]pyrimidine-5-carboxamide

and therapeutically acceptable salts, prodrugs, salts of prodrugs and metabolites thereof.

## DETAILED DESCRIPTION OF THE INVENTION

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.

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, phenyl, spiroalkyl, spiroalkenyl, spiroheteroalkyl and spiroheteroalkenyl.

The term "cycloalkane," as used herein, means $C_3$-cycloalkane, $C_4$-cycloalkane, $C_5$-cycloalkane and $C_6$-cycloalkane.

The term "cycloalkyl," as used herein, means $C_3$-cycloalkyl, $C_4$-cycloalkyl, $C_5$-cycloalkyl and $C_6$-cycloalkyl.

The term "cycloalkene," as used herein, means $C_4$-cycloalkene, $C_5$-cycloalkene and $C_6$-cycloalkene.

The term "cycloalkenyl," as used herein, means $C_4$-cycloalkenyl, $C_5$-cycloalkenyl and $C_6$-cycloalkenyl.

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.

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

The term "heterocycloalkane," as used herein, means cycloalkane having one or two or three $CH_2$ moieties replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkane having one or two or three $CH_2$ moieties unreplaced or replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties replaced with N.

The term "heterocycloalkyl," as used herein, means cycloalkyl having one or two or three $CH_2$ moieties replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkyl having one or two or three $CH_2$ moieties unreplaced or replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties replaced with N.

The term "heterocycloalkene," as used herein, means cycloalkene having one or two or three $CH_2$ moieties replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkene having one or two or three $CH_2$ moieties unreplaced or replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties replaced with N.

The term "heterocycloalkenyl," as used herein, means cycloalkenyl having one or two or three $CH_2$ moieties replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkenyl having one or two or three $CH_2$ moieties unreplaced or replaced with independently selected O, S, S(O), $SO_2$ or NH and one or two CH moieties replaced with N.

The term "alkenyl," as used herein, means $C_2$-alkenyl, $C_3$-alkenyl, $C_4$-alkenyl, $C_5$-alkenyl and $C_6$-alkenyl.

The term "alkyl," as used herein, means $C_1$-alkyl, $C_2$-alkyl, $C_3$-alkyl, $C_4$-alkyl, $C_5$-alkyl and $C_6$-alkyl.

The term "alkynyl," as used herein, means $C_2$-alkynyl, $C_3$-alkynyl, $C_4$-alkynyl, $C_5$-alkynyl and $C_6$-alkynyl.

The term "$C_2$-alkenyl," as used herein, means ethenyl (vinyl).

The term "$C_3$-alkenyl," as used herein, means 1-propen-1-yl, 1-propen-2-yl (isopropenyl) and 1-propen-3-yl (allyl).

The term "$C_4$-alkenyl," as used herein, means 1-buten-1-yl, 1-buten-2-yl, 1,3-butadien-1-yl, 1,3-butadien-2-yl, 2-buten-1-yl, 2-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-methyl-1-propen-1-yl and 2-methyl-2-propen-1-yl.

The term "$C_5$-alkenyl," as used herein, means 2-methylene-3-buten-1-yl, 2-methylenebut-1-yl, 2-methyl-1-buten-1-yl, 2-methyl-1,3-butadien-1-yl, 2-methyl-2-buten-1-

yl, 2-methyl-3-buten-1-yl, 2-methyl-3-buten-2-yl, 3-methyl-1-buten-1-yl, 3-methyl-1-buten-2-yl, 3-methyl-1,3-butadien-1-yl, 3-methyl-1,3-butadien-2-yl, 3-methyl-2-buten-1-yl, 3-methyl-2-buten-2-yl, 3-methyl-3-buten-1-yl, 3-methyl-3-buten-2-yl, 1-penten-1-yl, 1-penten-2-yl, 1-penten-3-yl, 1,3-pentadien-1-yl, 1,3-penta-dien-2-yl, 1,3-pentadien-3-yl, 1,4-pentadien-1-yl, 1,4-pentadien-2-yl, 1,4-pentadien-3-yl, 2-penten-1-yl, 2-penten-2-yl, 2-penten-3-yl, 2,4-pentadien-1-yl, 2,4-pentadien-2-yl, 3-penten-1-yl, 3-penten-2-yl, 4-penten-1-yl and 4-penten-2-yl.

The term "$C_6$-alkenyl," as used herein, means 2,2-dimethyl-3-buten-1-yl, 2,3-dimethyl-1-buten-1-yl, 2,3-dimethyl-1,3-butadien-1-yl, 2,3-dimethyl-2-buten-1-yl, 2,3-dimethyl-3-buten-1-yl, 2,3-dimethyl-3-buten-2-yl, 3,3-dimethyl-1-buten-1-yl, 3,3-dimethyl-1-buten-2-yl, 2-ethenyl-1,3-butadien-1-yl, 2-ethenyl-2-buten-1-yl, 2-ethyl-1-buten-1-yl, 2-ethyl-1,3-butadien-1-yl, 2-ethyl-2-buten-1-yl, 2-ethyl-3-buten-1-yl, 1-hexen-1-yl, 1-hexen-2-yl, 1-hexen-3-yl, 1,3-hexadien-1-yl, 1,3-hexadien-2-yl, 1,3-hexadien-3-yl, 1,3,5-hexatrien-1-yl, 1,3,5-hexatrien-2-yl, 1,3,5-hexatrien-3-yl, 1,4-hexadien-1-yl, 1,4-hexadien-2-yl, 1,4-hexadien-3-yl, 1,5-hexadien-1-yl, 1,5-hexadien-2-yl, 1,5-hexadien-3-yl, 2-hexen-1-yl, 2-hexen-2-yl, 2-hexen-3-yl, 2,4-hexadien-1-yl, 2,4-hexadien-2-yl, 2,4-hexadien-3-yl, 2,5-hexadien-1-yl, 2,5-hexadien-2-yl, 2,5-hexadien-3-yl, 3-hexen-1-yl, 3-hexen-2-yl, 3-hexen-3-yl, 3,5-hexadien-1-yl, 3,5-hexadien-2-yl, 3,5-hexadien-3-yl, 4-hexen-1-yl, 4-hexen-2-yl, 4-hexen-3-yl, 5-hexen-1-yl, 5-hexen-2-yl, 5-hexen-3-yl, 2-methylene-3-methyl-3-buten-1-yl, 2-methylene-3-methylbut-1-yl, 2-methylene-3-penten-1-yl, 2-methylene-4-penten-1-yl, 2-methylenepent-1-yl, 2-methylenepent-3-yl, 3-methylene-1-penten-1-yl, 3-methylene-1-penten-2-yl, 3-methylenepent-1-yl, 3-methylene-1,4-pentadien-1-yl, 3-methylene-1,4-pentadien-2-yl, 3-methylene-pent-2-yl, 2-methyl-1-penten-1-yl, 2-methyl-1-penten-3-yl, 2-methyl-1,3-pentadien-1-yl, 2-methyl-1,3-pentadien-3-yl, 2-methyl-1,4-pentadien-1-yl, 2-methyl-1,4-pentadien-3-yl, 2-methyl-2-penten-1-yl, 2-methyl-2-penten-3-yl, 2-methyl-2,4-pentadien-1-yl, 2-methyl-2,4-pentadien-3-yl, 2-methyl-3-penten-1-yl, 2-methyl-3-penten-2-yl, 2-methyl-3-penten-3-yl, 2-methyl-4-penten-1-yl, 2-methyl-4-penten-2-yl, 2-methyl-4-penten-3-yl, 3-methyl-1-penten-1-yl, 3-methyl-1-penten-2-yl, 3-methyl-1,3-pentadien-1-yl, 3-methyl-1,3-pentadien-2-yl, 3-methyl-1,4-pentadien-1-yl, 3-methyl-1,4-pentadien-2-yl, 3-methyl-2-penten-1-yl, 3-methyl-2-penten-2-yl, 3-methyl-2,4-pentadien-1-yl, 3-methyl-3-penten-1-yl, 3-methyl-3-penten-2-yl, 3-methyl-4-penten-1-yl, 3-methyl-4-penten-2-yl, 3-methyl-4-penten-3-yl, 4-methyl-1-penten-1-yl, 4-methyl-1-penten-2-yl, 4-methyl-1-penten-3-yl, 4-methyl-1,3-pentadien-1-yl, 4-methyl-1,3-pentadien-2-yl, 4-methyl-1,3-pentadien-3-yl, 4-methyl-1,4-pentadien-1-yl, 4-methyl-1,4-pentadien-2-yl, 4-methyl-1,4-pentadien-3-yl, 4-methylene-2-penten-3-yl, 4-methyl-2-penten-1-yl, 4-methyl-2-penten-2-yl, 4-methyl-2-penten-3-yl, 4-methyl-2,4-pentadien-1-yl, 4-methyl-2,4-pentadien-2-yl, 4-methyl-3-penten-1-yl, 4-methyl-3-penten-2-yl, 4-methyl-3-penten-3-yl, 4-methyl-4-penten-1-yl and 4-methyl-4-penten-2-yl.

The term "$C_1$-alkyl," as used herein, means methyl.

The term "$C_2$-alkyl," as used herein, means ethyl.

The term "$C_3$-alkyl," as used herein, means prop-1-yl and prop-2-yl (isopropyl).

The term "$C_4$-alkyl," as used herein, means but-1-yl, but-2-yl, 2-methylprop-1-yl and 2-methylprop-2-yl (tert-butyl).

The term "$C_5$-alkyl," as used herein, means 2,2-dimethylprop-1-yl (neo-pentyl), 2-methylbut-1-yl, 2-methylbut-2-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, pent-1-yl, pent-2-yl and pent-3-yl.

The term "$C_6$-alkyl," as used herein, means 2,2-dimethylbut-1-yl, 2,3-dimethylbut-1-yl, 2,3-dimethylbut-2-yl, 3,3-dimethylbut-1-yl, 3,3-dimethylbut-2-yl, 2-ethylbut-1-yl, hex-1-yl, hex-2-yl, hex-3-yl, 2-methylpent-1-yl, 2-methylpent-2-yl, 2-methylpent-3-yl, 3-methylpent-1-yl, 3-methylpent-2-yl, 3-methylpent-3-yl, 4-methylpent-1-yl and 4-methylpent-2-yl.

The term "$C_2$-alkynyl," as used herein, means ethynyl (acetylenyl).

The term "$C_3$-alkynyl," as used herein, means 1-propyn-1-yl and 2-propyn-1-yl (propargyl).

The term "$C_4$-alkynyl," as used herein, means 1-butyn-1-yl, 1,3-butadiyn-1-yl, 2-butyn-1-yl, 3-butyn-1-yl and 3-butyn-2-yl.

The term "$C_5$-alkynyl," as used herein, means 2-methyl-3-butyn-1-yl, 2-methyl-3-butyn-2-yl, 3-methyl-1-butyn-1-yl, 1,3-pentadiyn-1-yl, 1,4-pentadiyn-1-yl, 1,4-pentadiyn-3-yl, 2,4-pentadiyn-1-yl, 1-pentyn-1-yl, 1-pentyn-3-yl, 2-pentyn-1-yl, 3-pentyn-1-yl, 3-pentyn-2-yl, 4-pentyn-1-yl and 4-pentyn-2-yl.

The term "$C_6$-alkynyl," as used herein, means 2,2-dimethyl-3-butyn-1-yl, 3,3-dimethyl-1-butyn-1-yl, 2-ethyl-3-butyn-1-yl, 2-ethynyl-3-butyn-1-yl, 1-hexyn-1-yl, 1-hexyn-3-yl, 1,3-hexadiyn-1-yl, 1,3,5-hexatriyn-1-yl, 1,4-hexadiyn-1-yl, 1,4-hexadiyn-3-yl, 1,5-hexadiyn-1-yl, 1,5-hexadiyn-3-yl, 2-hexyn-1-yl, 2,5-hexadiyn-1-yl, 3-hexyn-1-yl, 3-hexyn-2-yl, 3,5-hexadiyn-2-yl, 4-hexyn-1-yl, 4-hexyn-2-yl, 4-hexyn-3-yl, 5-hexyn-1-yl, 5-hexyn-2-yl, 5-hexyn-3-yl, 2-methyl-3-pentyn-1-yl, 2-methyl-3-pentyn-2-yl, 2-methyl-4-pentyn-1-yl, 2-methyl-4-pentyn-2-yl, 2-methyl-4-pentyn-3-yl, 3-methyl-1-pentyn-1-yl, 3-methyl-4-pentyn-1-yl, 3-methyl-4-pentyn-2-yl, 3-methyl-1,4-pentadiyn-1-yl, 3-methyl-1,4-pentadiyn-3-yl, 3-methyl-4-pentyn-1-yl, 3-methyl-4-pentyn-3-yl, 4-methyl-1-pentyn-1-yl and 4-methyl-2-pentyn-1-yl.

The term "$C_4$-cycloalkane," as used herein, means cyclobutane.

The term "$C_5$-cycloalkane," as used herein, means cyclopentane.

The term "$C_6$-cycloalkane," as used herein, means cyclohexane.

The term "$C_4$-cycloalkene," as used herein, means cyclobutene and 1,3-cyclobutadiene.

The term "$C_5$-cycloalkene," as used herein, means cyclopentene and 1,3-cyclopentadiene.

The term "$C_6$-cycloalkene," as used herein, means cyclohexene, 1,3-cyclohexadiene and 1,4-cyclohexadiene.

The term "$C_3$-cycloalkenyl," as used herein, means cycloprop-1-en-1-yl and cycloprop-2-en-1-yl.

The term "$C_4$-cycloalkenyl," as used herein, means cyclobut-1-en-1-yl and cyclobut-2-en-1-yl.

The term "$C_5$-cycloalkenyl," as used herein, means cyclopent-1-en-1-yl, cyclopent-2-en-1-yl, cyclopent-3-en-1-yl and cyclopenta-1,3-dien-1-yl.

The term "$C_6$-cycloalkenyl," as used herein, means cyclohex-1-en-1-yl, cyclohex-2-en-1-yl, cyclohex-3-en-1-yl, cyclohexa-1,3-dien-1-yl, cyclohexa-1,4-dien-1-yl, cyclohexa-1,5-dien-1-yl, cyclohexa-2,4-dien-1-yl and cyclohexa-2,5-dien-1-yl.

The term "$C_3$-cycloalkyl," as used herein, means cycloprop-1-yl.

The term "$C_4$-cycloalkyl," as used herein, means cyclobut-1-yl.

The term "$C_5$-cycloalkyl," as used herein, means cyclopent-1-yl.

The term "$C_6$-cycloalkyl," as used herein, means cyclohex-1-yl.

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.

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.

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.

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, camphorsufonate, 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, bucally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperintoneally 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.

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.

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 celluose, 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 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 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, 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.

Compounds having formula (I) are also expected to be useful when used with alkylating agents, angiogenesis inhibitors, antibodies, antimetabolites, antimitotics, antiproliferatives, aurora kinase 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 inhibitors, hormonal therapies, immunologicals, intercalating antibiotics, kinase inhibitors, mammalian target of rapomycin 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.

Bcr-Abl kinase inhibitors include DASATINIB® (BMS-354825), GLEEVEC® (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® (etoricoxib), BEXTRA® (valdecoxib), BMS347070, CELEBREX™ (celecoxib), COX-189 (lumiracoxib), CT-3, DERAMAXX® (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® (rofecoxib) and the like.

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

ErbB2 receptor inhibitors include CP-724-714, CI-1033 (canertinib), Herceptin® (trastuzumab), TYKERB® (lapatinib), OMNITARG® (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 bispecfic 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®, NCS-683664, PU24FCl, 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

Proteasome inhibitors include VELCADE® (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® (interferon gamma-1b), or interferon gamma-n1, combinations thereof and the like. Other agents include ALFAFERONE®, BAM-002, BEROMUN® (tasonermin), BEXXAR® (tositumomab), CamPath® (alemtuzumab), CTLA4 (cytotoxic lymphocyte antigen 4), decarbazine, denileukin, epratuzumab, GRANOCYTE® (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, 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, lentinan, sizofiran, picibanil PF-3512676 (CpG-8954), ubenimex and the like.

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

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

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 and sealed and unsealed source radiotherapy.

Additionally, compounds having formula (I) may be combined with other chemptherapeutic agents such as ABRAXANE™ (ABI-007), ABT-100 (farnesyl transferase inhibitor), ADVEXIN®, ALTOCOR® or MEVACOR® (lovastatin), 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), 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® (T4N5 liposome lotion), discodermolide, DX-8951f (exatecan mesylate), enzastaurin, EPO906, GARDASIL® (quadrivalent human papillomavirus (Types 6, 11, 16, 18) recombinant vaccine), gastrimmune, genasense, GMK (ganglioside conjugate vaccine), GVAX® (prostate cancer vaccine), halofuginone, histerelin, hydroxycarbamide, ibandronic acid, IGN-101, IL-13-PE38, IL-13-PE38QQR (cintredekin besudotox), IL-13-pseudomonas exotoxin, interferon-α, interferon-γ, JUNOVAN™ or MEPACT™ (mifamurtide), lonafarnib, 5,10-methylenetetrahydrofolate, miltefosine (hexadecylphosphocholine), NEOVASTAT®(AE-941), NEUTREXIN® (trimetrexate glucuronate), NIPENT® (pentostatin), ONCONASE® (a ribonuclease enzyme), ONCOPHAGE® (melanoma vaccine treatment), OncoVAX (IL-2 Vaccine), ORATHECIN™ (rubitecan), OSIDEM® (antibody-based cell drug), OvaRex® MAb ( murine monoclonal antibody), paditaxel, PANDIMEX™ (aglycone saponins from ginseng comprising 20(S)protopanaxadiol (aPPD) and 20(S)protopanaxatriol (aPPT)), panitumumab, PANVAC®-VF (investigational cancer vaccine), pegaspargase, PEG Interferon A, phenoxodiol, procarbazine, rebimastat, REMOVAB® (catumaxomab), REVLIMID® (lenalidomide), RSR13 (efaproxiral), SOMATULINE® LA (lanreotide), SORIATANE® (acitretin), staurosporine (Streptomyces staurospores), talabostat (PT100), TARGRETIN® (bexarotene), Taxoprexin® (DHA-paclitaxel), TELCYTA™ (TLK286), temilifene, TEMODAR® (temozolomide), tesmilifene, thalidomide, THERATOPE® (STn-KLH), thymitaq (2-amino-3,4-dihydro-6-methyl-4-oxo-5-(4-pyridylthio)quinazoline dihydrochloride), TNFerade™ (adenovector: DNA carrier containing the gene for tumor necrosis factor-α), TRACLEER® or ZAVESCA® (bosentan), tretinoin (Retin-A), tetrandrine, TRISENOX® (arsenic trioxide), VIRULIZIN®, ukrain (derivative of alkaloids from the greater celandine plant), vitaxin (anti-alphavbeta3 antibody), XCYTRIN® (motexafin gadolinium), XINLAY™ (atrasentan), XYOTAX™ (paclitaxel poliglumex), YONDELIS™ (trabectedin), ZD-6126, ZINECARD® (dexrazoxane), zometa (zolendronic acid), zorubicin and the like.

To determine the inhibitory activity of representative compounds having formula (I) to protein kinases, the following assay was used:

In 384-well v-bottom polypropylene plates (Axygen #P-384-120SQ C), 10 µL recombinant Aurora Kinase-A (AurA, Upstate #14-511, 1 nM final concentration) was mixed with 10 µL biotinylated peptide substrate (Genemed, 2 µM final concentration), and various concentrations of representative compounds (2% DMSO final) in reaction buffer (25 mM HEPES, pH 7.5, 0.5 mM DTT, 10mM $mgCl_2$ 100 µM $Na_3VO_4$, 0.075 mg/mL Triton X-100). The reaction was initiated by adding $[^{33}P]$-ATP (Perkin Elmer, 5 µM final concentration, 2mCi/umol,). The reaction was quenched after 1 hour by addition of 50 µl stop buffer (50 mM EDTA, 2M NaCl final concentration). 80 µL of the stopped reactions were transferred to 384-well streptavidin-coated FlashPlates (Perkin Elmer, #SMP410A0001PK), incubated 10 minutes at ambient temperature, washed 3 times with 0.05% Tween-20/PBS using an ELX-405 automated plate washer (BioTek) and counted on a TopCount Scintillation Plate Reader (Packard).

$IC_{50}$ values values are shown in TABLE 1.

TABLE 1

| | | | | | |
|---|---|---|---|---|---|
| 0.0001 µM | 0.0004 µM | 0.0004 µM | 0.0006 µM | 0.0008 µM | 0.0009 µM |
| 0.0011 µM | 0.0013 µM | 0.0014 µM | 0.0016 µM | 0.0016 µM | 0.0021 µM |
| 0.0021 µM | 0.0021 µM | 0.0021 µM | 0.0023 µM | 0.0025 µM | 0.0026 µM |
| 0.0028 µM | 0.0033 µM | 0.0034 µM | 0.0034 µM | 0.0037 µM | 0.0041 µM |
| 0.0041 µM | 0.0044 µM | 0.0045 µM | 0.0046 µM | 0.0047 µM | 0.0050 µM |
| 0.0053 µM | 0.0056 µM | 0.0058 µM | 0.0064 µM | 0.0064 µM | 0.0065 µM |
| 0.0066 µM | 0.0069 µM | 0.0071 µM | 0.0072 µM | 0.0086 µM | 0.0089 µM |
| 0.0099 µM | 0.0110 µM | 0.0109 µM | 0.0110 µM | 0.0113 µM | 0.0117 µM |

| | | | | | |
|---|---|---|---|---|---|
| 0.0124 µM | 0.0124 µM | 0.0135 µM | 0.0146 µM | 0.0150 µM | 0.0154 µM |
| 0.0154 µM | 0.0167 µM | 0.0180 µM | 0.0187 µM | 0.0193 µM | 0.0203 µM |
| 0.0219 µM | 0.0255 µM | 0.0257 µM | 0.0266 µM | 0.0269 µM | 0.0275 µM |
| 0.0295 µM | 0.0300 µM | 0.0316 µM | 0.0318 µM | 0.0329 µM | 0.0333 µM |
| 0.0361 µM | 0.0381 µM | 0.0392 µM | 0.0438 µM | 0.0498 µM | 0.0610 µM |
| 0.0697 µM | 0.0723 µM | 0.1003 µM | 0.1036 µM | 0.1129 µM | 0.1201 µM |
| 0.1292 µM | 0.1324 µM | 0.1471 µM | 0.1579 µM | 0.1781 µM | 0.1788 µM |
| 0.2111 µM | 0.2671 µM | 0.2819 µM | 0.3422 µM | 0.3555 µM | 0.3621 µM |
| 0.3724 µM | 0.3766 µM | 0.5762 µM | 0.6109 µM | 0.6577 µM | 0.6941 µM |
| 0.7735 µM | 0.8917µM | 0.9061µM | 1.9591 µM | | |

These data demonstrate the utility of compounds having formula (I) as inhibitors of Aurora-kinase A.

To determine the activity of other representative compounds of the invention, Active Aurora A enzyme was incubated in wells of a 384 well plate with biotinylated STK substrate-2 (Upstate), 1 mM ATP, and various concentrations of inhibitors in a Hepes buffer, pH 7.4 containing $MgCl_2$, sodium othrovanadate, and Triton X-100. After 1 hour, the reaction was stopped with EDTA and anti-phospho-STK antibody Europium Cryptate (Upstate) and SA-XL665 (Upstate) 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 $IC_{50}$'s were calculated by an exponential fit of the inhibition values with the inhibitor concentrations using Assay Explorer software.

TABLE 2

| | | | | | |
|---|---|---|---|---|---|
| 0.0011 µM | 0.0024 µM | 0.0025 µM | 0.0055 µM | 0.0063 µM | 0.0187 µM |
| 0.0423 µM | 0.0543 µM | 0.0803 µM | 0.1076 µM | 0.1210 µM | 0.14665 µM |
| 0.1886 µM | 0.1995 µM | 0.2561 µM | 0.2593 µM | 0.2844 µM | 0.6520 µM |
| 0.8258 µM | 0.9535 µM | 7.6280 µM | | | |

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

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 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, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myleogeneous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial 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, hematological cancers (leukemias such as acute lymphocytic leukemia, chronic lymphocytic leukemia and chronic myeloid leukemia) and lymphomas), hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer, lymphagioendotheliosarcoma, 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, 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, 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.

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 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 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 syatem, pediatric biphenotypic acute leukemia, pediatric Burkitts lymphoma, pediatric cancers of Ewing's family of tumors such as primitive neuroectodermal rumors, 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 psteosarcoma, pediatric rhabdoid kidney tumor, pediatric rhabdomyosarcoma, and pediatric T-cell cancers such as lymphoma and skin cancer.

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.

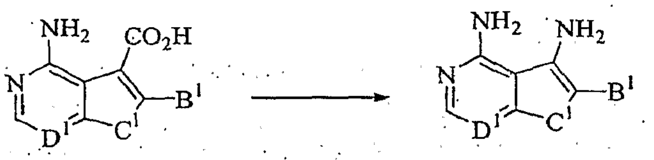
Protecting groups for C(O) and C(O)H moieties include, but are not limited to, 1,3-dioxylketal, diethylketal, dimethylketal, 1,3-dithianylketal, O-methyloxime, O-phenyloxime and the like.

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-β means a mixture of $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$ and $K_2SO_4$); AIBN means 2,2'-azobis(2-methylpropionitrile); 9-BBN means 9-borabicyclo[3.3.1]nonane; Cp means cyclopentadiene; $(DHQD)_2PHAL$ means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene; 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 means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; Fmoc means fluorenylmethoxycarbonyl; HATU means O-(7-azabenzotriazol-1-yl)-N,N'N'N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; LDA means lithium diisopropylamide; LHMDS means lithium bis(hexamethyldisilylamide); $MP\text{-}BH_3$ means macroporus triethylammonium methylpolystyrene cyanoborohydride; LAH means lithium aluminum hydride; NCS means N-chlorosuccinimide; PyBOP means benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate; 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; and $PPh_3$ means triphenylphosphine.

SCHEME 1



(1) (2)

Compounds having formula (1) can be described herein and converted to compounds having formula (2) by the former and DPPA followed by hydrolysis of the product with water. The reactions are typically conducted in solvents such as benzene, toluene, THF, mixtures thereof and the like at temperatures between about 50°C and 110°C.

Introduction of moieties represented by $A^1$ can be accomplished by reacting the compounds having formula (1), a compound having formula $H_2NR^1$ or $HN(R^1)_2$, a coupling agent and a base, with or without DMAP. Examples of coupling agents include DCC, EDCI and the like. Examples of bases include TEA, DIEA, pyridine and the like. The reactions are typically conducted in solvents such as THF, dichloromethane, DMF, DMSO, chloroform, mixtures thereof and the like at temperatures between about 0°C and 25°C.

Introduction of moieties represented by $A^1$ can also be accomplished by reacting the compounds having formula (2) and the appropriate isocyanate, carbonyl chloride, sulfonyl chloride, carbamoyl chloride. The reactions are typically conducted in solvents such as THF, ethyl acetate, dichloromethane, DMF, DMSO, chloroform, mixtures thereof and the like at temperatures between about 0°C and 110°C, depending on the reactivity of the starting materials.

The following 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.

## EXAMPLE 1A

A mixture of 5-amino-4-cyano-thiophene-3-carboxylic acid ethyl ester (2.4 g, prepared as described in Annali. di Chimica, 64, 833, 1974) in formamide (45 mL) at 170°C was stirred for 8 hours and concentrated. The concentrate was flash chromatographed on silica gel with 10-50% ethyl acetate/hexanes.

## EXAMPLE 1B

A mixture of EXAMPLE 1A (0.62 g) and $LiOH{\cdot}H_2O$ (0.54 g) in THF (54 mL), water (13 mL) and methanol (13 mL) at 80°C was stirred for 16 hours, cooled to ambient temperature and concentrated. The concentrate was taken up in water, cooled in an ice bath, stirred for 30 minutes and treated with 1N HCl until acidic, stirred for 30 minutes and filtered.

## EXAMPLE 1C

A mixture of 1-isocyanato-3-methylbenzene (0.6 mL) was added to a mixture of (4-aminophenyl)carbamic acid tert-butyl ester (1 g) in dichloromethane (48 mL) 0°C. The mixture was stirred for 30 minutes, warmed to ambient temperature, stirred for 24 hours and filtered. The filtrant was suspended in dichloromethane (80 mL), cooled in an ice bath, treated with TFA (5 mL), stirred for 15 minutes, warmed to ambient temperature, stirred for 18 hours and concentrated. The concentrate was concentrated twice from methanol and toluene.

## EXAMPLE 1D

Diisopropylethyl amine (0.3 mL) was added to a mixture of EXAMPLE 1B (0.2 g), EXAMPLE 1C (0.336 g) and HATU (0.452 g) in DMF (5.7 mL) at 0°C. The mixture was stirred for 0.5 hours, warmed to ambient temperature, stirred for for 20 hours, cooled to 0°C, diluted with water (80 mL), stirred for 1 hour and filtered. The filtrant was washed with water, dried and triturated with 2:1 dichloromethane/methanol. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (s, 1H), 8.66 (s, 1H), 8.55 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.98 (br s, 2H), 7.63 (d, 2H), 7.46 (d, 2H), 7.30 (s, 1H), 7.18 (m, 2H), 6.79 (d, 1H), 2.28 (s, 3H).

## EXAMPLE 2

This example was prepared by substituting 1-fluoro-3-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 8.89 (s, 1H), 8.76 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.02 (brs, 2H), 7.64 (d, 2H), 7.51 (s, 1H),7.47 (d, 2H), 7.30 (m, 1H), 7.12 (d, 1H), 6.78 (m, 1H).

## EXAMPLE 3

This example was prepared by substituting 1-fluoro-3-isocyanato-4-methylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 8.76 (s, 1H), 8.72 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 7.93 (s, 2H), 7.64 (d, 2H), 7.45 (m, 3H), 7.16 (m, 1H), 7.03 (d, 1H), 2.17 (s, 3H).

## EXAMPLE 4

This example was prepared by substituting 1-isocyanato-4-methylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (d, 1H), 8.62 (d, 1H), 8.51 (d, 1H), 8.37 (d, 1H) 8.32 (d, 1H), 8.00 (brs, 2H), 7.62 (d, 2H), 7.46 (d, 2H), 7.33 (d, 2H), 7.08 (d, 2H), 2.24 (m, 3H).

## EXAMPLE 5

This example was prepared by substituting 1-fluoro-4-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.66 (s, 1H), 8.68 (s, 2H), 8.37 (s, 1H), 8.32 (s, 1H), 7.92 (brs, 2H), 7.63 (d, 2H), 7.47 (d, 4H), 7.12 (t, 2H).

## EXAMPLE 6

This example was prepared by substituting 1-chloro-2-fluoro-4-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 8.86 (s, 1H), 8.79 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.07 (brs, 2H), 7.81 (d, 1H), 7.64 (d, 2H), 7.47 (d, 2H), 7.32 (m, 2H).

## EXAMPLE 7

This example was prepared by substituting 1-ethyl-3-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 8.65 (s, 1H), 8.57 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 7.63 (d, 2H), 7.46 (d, 2H), 7.24 (m, 5H), 6.82 (d, 1H), 2.58 (m, 2H), 1.18 (t, 3H).

### EXAMPLE 8

This example was prepared by substituting 1-chloro-3-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 8.87 (s, 1H), 8.78 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 7.72 (s, 1H), 7.64 (d, 2H), 7.68 (brs, 2H), 7.47 (d, 2H), 7.28 (m, 2H), 7.02 (d, 1H).

### EXAMPLE 9

This example was prepared by substituting 1-cyano-3-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 9.00 (s, 1H), 8.86 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.98 (m, 1H), 7.99 (brs, 2H), 7.66 (m, 3H), 7.46 (m, 4H).

### EXAMPLE 10

This example was prepared by substituting 1-fluoro-2-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.68 (s, 1H), 9.11 (s, 1H), 8.54 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.16 (t, 1H), 7.83 (brs, 2H), 7.66 (d, , 2H), 7.48 (d, 2H), 7.24 (m, 1H), 7.14 (t, 1H), 7.01 (m, 1H).

### EXAMPLE 11

This example was prepared by substituting 1-isocyanato-3-trifluoromethylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 9.02 (s, 1H), 8.81 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.03 (s, 1H), 8.00 (brs, 2H), 7.65 (d, 2H), 7.56 (m, 2H), 7.48 (d, 2H), 7.31 (d, 1H).

### EXAMPLE 12

This example was prepared by substituting 1-fluoro-4-isocyanato-2-trifluoromethylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 9.01 (s, 1H), 8.83 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.02 (dd, 2H), 7.98 (brs, 2H), 7.65 (d, 2H), 7.46 (m, 3H).

### EXAMPLE 13

This example was prepared by substituting 1-isocyanato-3-methoxybenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 8.66 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.02 (brs, 2H), 7.63 (d, 2H), 7.47 (d, 2H), 7.19 (s, 1H), 7.16 (d, 1H), 6.93 (d, 1H), 6.55 (d, 1H), 3.74 (s, 3H).

### EXAMPLE 14

This example was prepared by substituting 1-fluoro-3-isocyanato-4-methylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.66 (s, 1H), 9.19 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.02 (s, 3H), 7.86 (dd, 1H), 7.66 (d, 2H), 7.49 (d, 2H), 7.19 (t, 1H), 6.74 (m, 1H), 2.23 (s, 3H).

## EXAMPLE 15

This example was prepared by substituting 1-isocyanato-4-trifluoromethylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.69 (s, 1H), 9.09 (s, 1H), 8.83 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 7.88 (brs, 2H), 7.65 (m, 6H), 7.49 (d, 2H).

## EXAMPLE 16

This example was prepared by substituting 1-fluoro-2-isocyanato-4-methylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 9.09 (s, 1H), 8.47 (s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 8.00 (d, 1H), 7.81 (brs, 2H), 7.65 (d, 2H), 7.47 (d, 2H), 7.10 (m, 1H), 6.80 (s, 1H), 2.28 (s, 3H).

## EXAMPLE 17

This example was prepared by substituting 1-isocyanato-2-methylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.65 (s, 1H), 9.03 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.11 (brs, 2H), 7.89 (s, 1H), 7.84 (d, 1H), 7.64 (d, 2H), 7.48 (d, 2H), 7.15 (m, 2H), 6.94 (t, 1H), 2.25 (s, 3H).

## EXAMPLE 18

This example was prepared by substituting 1-isocyanato-4-methoxybenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.65 (s, 1H), 8.59 (s, 1H), 8.43 (s, 1H), 8.41 (s, 1H), 8.35 (s, 1H), 8.08 (brs, 2H), 7.62 (d, 2H), 7.46 (d, 2H), 7.35 (d, 2H), 6.87 (d, 2H), 3.72 (s, 3H).

## EXAMPLE 19

This example was prepared by substituting 1-isocyanato-3, 5-dimethylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 8.64 (s, 1H), 8.47 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.02 (brs, 2H), 7.63 (d, 2H), 7.46 (d, 2H), 7.07 (s, 2H), 6.61 (m, 1H), 2.23 (s, 6H).

## EXAMPLE 20

This example was prepared by substituting 1-fluoro-2-isocyanato-4-trifluoromethylbenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.69 (s, 1H), 9.21 (s, 1H), 8.88 (d, 1H), 8.64 (dd, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 8.04 (brs, 2H), 7.68 (d, 2H), 7.50 (m, 3H), 7.39 (m, 1H).

## EXAMPLE 21

This example was prepared by substituting isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 8.67 (s, 1H), 8.63 (s, 1H), 8.38 (s, 1H), 8.33 (s, 1H), 8.01 (brs, 2H), 7.63 (d, 2H), 7.46 (m, 4H), 7.28 (m, 2H), 6.97 (m, 1H).

## EXAMPLE 22A

Bromine (0.75 mL) was added dropwise to mixture of 5-amino-4-cyanothiophene-3-carboxylic acid ethyl ester (2.9 g) in dichloromethane (150 mL) at 0°C. The mixture was stirred for 1.5 hours, diluted with dichloromethane, washed with 10% $NaHSO_3$ and brine and dried ($MgSO_4$ ), filtered and concentrated.

## EXAMPLE 22B

A mixture of EXAMPLE 22A (0.2 g), 1-methyl-4-(4, 4, 5, 5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (0.368 g), $Na_2CO_3$ (0.211 g), $Pd(PPh_3)_4$ (0.05 g) in DME (4 mL) and water (2 mL) at 120°C was stirred in a sealed vial for 30 minutes in a Smith Synthesizer microwave oven (at 300W), cooled to ambient temperature and partitioned between water and ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was flash chromatographed on silica gel with 1% methanol/dichloromethane.

## EXAMPLE 22C

This example was prepared by substituting EXAMPLE 22B for 5-amino-4-cyano-thiophene-3-carboxylic acid ethyl ester in EXAMPLE 1A and EXAMPLE 1B.

## EXAMPLE 22D

This example was prepared by substituting EXAMPLE 22C and 1-chloro-3-isocyanatobenzene for EXAMPLE 1B and 1-isocyanato-3-methylbenzene in EXAMPLES 1C and 1D, respectively. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (s, 1H), 8.85 (s, 1H), 8.76 (s, 1H), 8.32 (s, 1H), 8.09 (s, 1H), 7.71 (m, 1H), 7.61 (s, 1H), 7.55 (d, 2H), 7.45 (d, 2H), 7.28 (m, 2H), 7.01 (m, 3H), 3.85 (s, 3H).

## EXAMPLE 23

This example was prepared by substituting EXAMPLE 22C for EXAMPLE 1B in EXAMPLE 1D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.61 (s, 1H), 8.66 (s, 1H), 8.54 (s, 1H), 8.32 (s, 1H), 8.08 (s, 1H), 7.60 (s, 1H), 7.53 (d, 2H), 7.44 (d, 2H), 7.29 (s, 1H), 7.22 (d, 1H), 7.15 (t, 1H), 7.00 (brs, 2H), 6.78 (d, 1H), 3.84 (s, 3H), 2.27 (s, 3H).

## EXAMPLE 24

This example was prepared by substituting EXAMPLE 22C and 1-fluoro-2-isocyanato-4-methylbenzene for EXAMPLE 1B and 1-isocyanato-3-methylbenzene in

EXAMPLES 1C and 1D, respectively. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (s, 1H), 9.08 (s, 1H), 8.44 (d, 1H), 8.33 (s, 1H), 8.08 (s, 1H), 7.99 (dd, 1H), 7.60 (m, 1H), 7.55 (m, 2H), 7.45 (m, 2H), 7.09 (dd, 1H), 7.00 (brs, 2H), 6.80 (m, 1H), 3.85 (s, 3H), 2.27 (s, 3H).

### EXAMPLE 25

This example was prepared by substituting EXAMPLE 22C and 1-fluoro-4-isocyanato-2-trifluoromethylbenzene for EXAMPLE 1B and 1-isocyanato-3-methylbenzene in EXAMPLES 1C and ID, respectively. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 9.01 (s, 1H), 8.82 (s, 1H), 8.32 (s, 1H), 8.09 (s, 1H), 8.00 (dd, 1H), 7.64 (m, 1H), 7.60 (s, 1H), 7.55 (d, 2H), 7.44 (m, 3H), 7.00 (brs, 2H), 3.85 (s, 3H).

### EXAMPLE 26

This example was prepared by substituting EXAMPLE 22C and 1-fluoro-2-isocyanato-4-trifluoromethylbenzene for EXAMPLE 1B and 1-isocyanato-3-methylbenzene in EXAMPLES 1C and 1D, respectively. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 9.21 (s, 1H), 8.87 (d, 1H), 8.63 (dd, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.59 (m, 3H), 7.48 (m, 3H), 7.39 (m, 1H), 7.02 (brs, 2H), 3.85 (s, 3H).

### EXAMPLE 27

This example was prepared by substituting EXAMPLE 22C and 1-isocyanato-4-trifluoromethylbenzene for EXAMPLE 1B and 1-isocyanato-3-methylbenzene in EXAMPLES 1C and ID, respectively. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 9.08 (s, 1H), 8.84 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.65 (m, 4H), 7.60 (s, 1H), 7.56 (d, 2H), 7.47 (d, 2H), 7.02 (brs, 2H), 3.85 (s, 3H).

### EXAMPLE 28

This example was prepared by substituting EXAMPLE 22C and 4-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.73 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.63 (t, 4H), 7.39 (t, 2H), 7.13 (t, 1H), 7.01 (m, 5H), 3.85 (s, 3H).

### EXAMPLE 29

This example was prepared by substituting 4-phenoxyphenylamine for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.76 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 7.74 (m, 2H), 7.39 (m, 2H), 7.13 (m, 1H), 7.07 (m, 2H), 7.01 (m, 2H).

### EXAMPLE 30A

A mixture of 1-fluoro-4-nitrobenzene (0.5 g), 3-methylphenol (0.383 g), 37% w/w KF-$Al_2O_3$ (0.4 g) and 18-crown-6 (0.093 g) in acetonitrile (6 mL) at reflux was stirred for 24 hours, cooled and partitioned between water and ethyl acetate. The extract was washed with water, dried ($MgSO_4$), filtered and concentrated. The concentrate was flash chromatographed on silica gel with 0-10% ethyl acetate/hexanes.

### EXAMPLE 30B

A mixture of EXAMPLE 30A (0.36 g), iron powder (0.45 g) and $NH_4Cl$ (0.086 mg) in ethanol (46 mL), THF (17 mL) and water (6 mL) at 85°C was stirred for 7 hours, cooled to ambient temperature, stirred for 18 hours, heated and filtered through diatomaceous earth (Celite®) while hot. The filtrate was concentrated and partitioned between water and ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. The concentrate was flash chromatographed on silica gel with 10% ethyl acetate/hexanes.

### EXAMPLE 30C

This example was prepared by substituting EXAMPLE 22C and 30B for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.73 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.63 (m, 3H), 7.26 (t, 1H), 7.03 (m, 2H), 6.99 (brs, 2H), 6.95 (d, 1H), 6.84 (m, 1H), 6.80 (dd, 1H), 3.85 (s, 3H), 2.29 (s, 3H).

### EXAMPLE 31

This example was prepared by substituting EXAMPLE 22C and 4-(4-chlorophenoxy)-phenylamine (prepared by substituting 4-chlorophenol for 3-methylphenol in EXAMPLE 30B) for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.76 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.66 (d, 2H), 7.61 (s, 1H), 7.42 (d, 2H), 7.08 (d, 2H), 7.03 (d, 2H), 6.98 (brs, 2H), 3.85 (s, 3H).

### EXAMPLE 32

This example was prepared by substituting EXAMPLE 22C and 4-(4-methyl-phenoxy)phenylamine (prepared by substituting 4-methylphenol for 3-methylphenol in EXAMPLE 30 B) for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.71 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.63 (s, 1H), 7.60 (brs, 2H), 7.19 (d, 2H), 6.96 (m, 6H), 3.85 (s, 3H), 2.29 (s, 3H).

### EXAMPLE 33

This example was prepared by substituting EXAMPLE 22C and 4-(3-chlorophenoxy)-phenylamine (prepared by substituting 3-chlorophenol for 3-methylphenol in EXAMPLE 30 B) for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 10.78 (s, 1H), 8.33 (s, 1H), 8.10 (s, 1H), 7.68 (d, 2H), 7.62 (s, 1H), 7.40 (t, 1H), 7.19 (m, 1H), 7.11 (d, 2H), 7.06 (t, 1H), 6.97 (m, 3H), 3.85 (s, 3H).

### EXAMPLE 34

This example was prepared by substituting EXAMPLE 22C and 4-phenylsulfanylphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.84 (s, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.67 (m, 2H), 7.59 (d, 1H), 7.38 (m, 4H), 7.28 (m, 3H), 6.96 (brs, 2H), 3.84 (s, 3H).

## EXAMPLE 35

This example was prepared by substituting 4-(4-methylphenoxy)phenylamine (prepared by substituting 4-methylphenol for 3-methylphenol in EXAMPLE 30B) for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.73 (s, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 7.96 (m, 2H), 7.71 (d, 2H), 7.19 (d, 2H), 7.01 (d, 2H), 6.91 (d, 2H), 2.29 (s, 3H).

## EXAMPLE 36

This example was prepared as described in EXAMPLES 22B and 22C by substituting 4-(4, 4, 5, 5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazole for 1-methyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazole in EXAMPLE 22B and coupling the product therefrom as described in EXAMPLE 1D by substituting 4-phenoxyphenylamine for EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.74 (s, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.70 (s, 1H), 7.65 (m, 2H), 7.38 (m, 2H), 7.13 (t, 1H), 7.03 (m, 7H).

## EXAMPLE 37

This example was prepared as described in EXAMPLES 22B and 22C by substituting 4,4,5,5-tetramethyl-2-thiophen-3-yl[1,3,2]dioxaborolane for 1-methyl-4-(4,4,5,5-tetramethyl[1.3.2]dioxaborolan-2-yl)-1H-pyrazole in EXAMPLE 22B and coupling the product therefrom as described in EXAMPLE 1D by substituting 4-phenoxyphenylamine for EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.71 (s, 1H), 8.37 (s, 1H), 7.85 (m, 1H), 7.68 (m, 1H), 7.58 (d, 2H), 7.39 (t, 2H), 7.28 (d, 1H), 7.13 (t, 2H), 7.01 (t, 5H).

## EXAMPLE 38A

A mixture of EXAMPLE 22A (0.1 g) and 1-methylpiperazine (1 mL) was stirred at 130°C for 8 hours, cooled and partitioned between water and ethyl acetate. The extract was washed with water and brine and dried ($MgSO_4$), filtered and concentrated.

## EXAMPLE 38B

This example was prepared by substituting EXAMPLE 38A for 5-amino-4-cyano-thiophene-3-carboxylic acid ethyl ester in EXAMPLES 1A-D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.60 (s, 1H), 8.65 (s, 1H), 8.56 (s, 1H), 8.20 (s, 1H), 7.64 (d, 2H), 7.50 (s, 2H), 7.46 (d, 2H), 7.30 (s, 1H), 7.23 (m, 1H), 7.15 (t, 1H), 6.79 (d, 1H), 3.12 (m, 4H), 2.43 (m, 4H), 2.28 (s, 3H), 2.18 (s, 3H).

## EXAMPLE 39A

1M borane·THF in THF (0.28 mL) was added to mixture of N-(4-(formylamino)phenyl)-N'-(3-methylphenyl)urea (0.05 g, prepared by substituting formic acid for EXAMPLE 1B in EXAMPLE 1D) in THF (2 mL) at 0°C. The mixture was stirred for 1.5 hours at ambient temperature, cooled to 0°C , treated with methanolic HCl (2 mL), stirred at reflux for 1 hour, cooled to ambient temperature and concentrated. The concentrate was reconcentrated twice from methanol then flash chromatographed on silica 5% methanol/dichloromethane.

EXAMPLE 39B

This example was prepared by substituting EXAMPLE 39A for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.70 (s, 1H), 8.57 (s, 1H), 8.31 (s, 1H), 7.37 (d, 4H), 7.35 (brs, 2H), 7.26 (s, 2H), 7.20 (d, 1H), 7.14 (m, 1H), 7.09 (d, 3H), 6.78 (d, 1H), 3.42 (s, 3H).

EXAMPLE 40A

A mixture of 3-bromothieno[3,2-c]pyridin-4-ylamine (2 g, prepared as described in WO 05/010009) and $PdCl_2$(dppf)·dichloromethane (0.715 g) in methanol (60 mL) and triethylamine (3.7 mL) in a sealed tube under CO (60 psi) was stirred at 100°C for 16 hours, cooled to ambient temperature, filtered and concentrated. The concentrate was triturated with water and filtered.

EXAMPLE 40B

A suspension of EXAMPLE 40A (0.87 g) in 9M HCl (50 mL) was heated to reflux for 18 hours, filtered hot and concentrated.

EXAMPLE 40C

This example was prepared by substituting EXAMPLE 40B and 4-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.79 (s, 1H), 8.28 (s, 1H), 7.87 (d, 1H), 7.77 (d, 2H), 7.39 (m, 2H), 7.25 (d, 1H), 7.13 (t, 1H), 7.07 (d, 2H), 7.01 (d, 2H), 6.80 (brs, 2H).

EXAMPLE 41

This example was prepared by substituting EXAMPLE 40B and 3-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.82 (s, 1H), 8.28 (s, 1H), 7.86 (d, 1H), 7.56 (d, 1H), 7.40 (m, 4H), 7.24 (d, 1H), 7.17 (t, 1H), 7.07 (d, 2H), 6.81 (d, 1H), 6.73 (brs, 2H).

EXAMPLE 42

This example was prepared by substituting EXAMPLE 40B and 4-benzylphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.69 (s, 1H), 8.25 (s, 1H), 7.86 (d, 1H), 7.66 (d, 2H), 7.24 (m, 8H), 6.78 (brs, 2H), 3.93 (s, 2H).

### EXAMPLE 43

This example was prepared by substituting EXAMPLE 40B for EXAMPLE 1B in EXAMPLE 1D. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.67 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 8.26 (s, 1H), 7.87 (d, 1H), 7.67 (d, 2H), 7.47 (d, 2H), 7.30 (s, 1H), 7.23 (m, 2H), 7.15 (t, 1H), 6.83 (s, 2H), 6.80 (d, 1H), 2.28 (s, 3H).

### EXAMPLE 44

This example was prepared by substituting EXAMPLE 40B and N-(4-aminophenyl)benzamide for EXAMPLES 1B and 1C, respectively in EXAMPLE 1D. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.76 (s, 1H), 10.28 (s, 1H), 8.29 (s, 1H), 7.98 (d, 2H), 7.88 (d, 1H), 7.81 (d, 2H), 7.74 (d, 2H), 7.56 (m, 3H), 7.26 (d, 1H), 6.83 (brs, 2H).

### EXAMPLE 45A

A mixture of EXAMPLE 40B (0.73 g) in DMF (30 mL) at ambient temperature was treated with NIS (1.42 g), stirred for 18 hours, diluted with water, treated with 10% aqueous $Na_2S_2O_3$ and filtered.

### EXAMPLE 45B

This example was prepared by substituting EXAMPLE 45A and (4-aminophenyl)carbamic acid tert-butyl ester for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. The Boc protecting group was removed by treatment of the product therefrom with TFA as described in EXAMPLE 1C.

### EXAMPLE 45C

A mixture of EXAMPLE 45B (1.93 g), 1-methyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazole (1.08 g), $PdCl_2(dppf)$ (0.19 g) and $Na_2CO_3$ (1.3 g) in DME (30 mL) and water (10 mL) at 80°C was stirred for 18 hours, cooled, treated with water and ethyl acetate and filtered.

### EXAMPLE 45D

A mixture of EXAMPLE 45C (0.03 g) in DMF (0.5 mL) at -20°C was treated with 1-isocyanato-3-methylbenzene (0.1 mL), the warmed to ambient temperature and stirred for 18 hours and filtered. The filtrant was flash chromatographed on silica gel with 0-8% methanol/dichloromethane. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.70 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 8.14 (d, 1H), 8.06 (s, 1H), 7.86 (d, 1H), 7.67 (d, 2H), 7.47 (d, 2H), 7.30 (s, 1H), 7.23 (d, 1H), 7.15 (t, 1H), 6.82 (s, 2H), 6.79 (d, 1H), 3.93 (s, 3H), 2.28 (s, 3H).

### EXAMPLE 46

This example was prepared by substituting EXAMPLE 45B and N-(4-aminophenyl)benzamide for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D then by substituting the product thereform for EXAMPLE 45B in EXAMPLE 45C. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.80 (s, 1H), 10.29 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.97 (d, 2H), 7.87 (s, 1H), 7.77 (m, 4H), 7.56 (m, 3H), 6.83 (brs, 2H), 3.93 (s, 3H).

EXAMPLE 47

This example was prepared by substituting EXAMPLE 45B and 4-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D then by substituting the product thereform for EXAMPLE 45B in EXAMPLE 45C. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.84 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.87 (s, 1H), 7.80 (d, 2H), 7.39 (m, 2H), 7.13 (t, 1H), 7.09 (d, 2H), 7.03 (d, 2H), 6.81 (brs, 2H), 3.93 (s, 3H).

EXAMPLE 48

This example was prepared by substituting EXAMPLE 45B and 3-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D then by substituting the product therefrom for EXAMPLE 45B in EXAMPLE 45C. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.85 (s, 1H), 8.35 (s, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 7.85 (s, 1H), 7.58 (d, 1H), 7.46 (m, 2H), 7.42 (d, 2H), 7.17 (t, 1H), 7.08 (d, 2H), 6.81 (m, 1H), 6.73 (brs, 2H), 3.92 (s, 3H).

EXAMPLE 49

This example was prepared by substituting EXAMPLE 45B and 4-benzylphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D then by substituting the product therefrom for EXAMPLE 45B in EXAMPLE 45C. $^1$H NMR (DMSO-$d_6$, 300 MHz) δ 10.75 (s, 1H), 8.32 (s, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 7.86 (s, 1H), 7.67 (d, 2H), 7.32-7.18 (m, 7H), 6.79 (brs, 2H), 3.94 (s, 2H), 3.93 (s, 3H).

EXAMPLE 50A

This example was prepared as described in EXAMPLE 40A and EXAMPLE 40B, except substituting 5-iodo-7-(4-(4-methyl-piperazin-1-yl)cyclohexyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamine (WO2005/74603) for 3-bromo-thieno[3,2-c]pyridin-4-ylamine in EXAMPLE 40A.

EXAMPLE 50B

This example was prepared by substituting EXAMPLE 50A and 4-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$HNMR (DMSO-$d_6$, 300MHz) δ 10.13 (s, 1H), 8.30 (s, 1H), 8.12 (s, 1H), 7.93 (brs, 2H), 7.70-7.74 (m, 1H), 7.66-7.70 (m, 1H), 7.36-7.44 (m, 2H), 7.08-7.17 (m, 1H), 6.98-7.07 (m, 4H), 4.60-4.72 (m, 1H), 3.32 (hidden, 1H), 2.48-2.59 (m, 4H), 2.33-2.48 (m, 4H), 2.15-2.23 (m, 4H), 1.96-2.15 (m, 3H), 1.74-1.85 (m, 2H), 1.53-1.68 (m, 2H).

### EXAMPLE 51

This example was prepared by substituting EXAMPLE 50A and 3-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$HNMR (DMSO-$d_6$, 300MHz) δ 10.12 (s, 1H), 8.28 (s, 1H), 8.11 (s, 1H), 7.87 (bs, 2H), 7.49-7.56 (m, 1H), 7.33-7.46 (m, 4H), 7.13-7.21 (m, 1H), 7.06-7.10 (m, 1H), 7.03-7.06 (m, 1H), 6.74-6.81 (m, 1H), 4.58-4.71 (m, 1H), 2.32-2.60 (m, 8H), 2.25-2.30 (m, 1H), 1.93-2.24 (m, 7H), 1.73-1.85 (m, 2H), 1.52-1.68 (m, 2H).

### EXAMPLE 52

This example was prepared by substituting EXAMPLE 50A for EXAMPLE 1B in EXAMPLE 1D. $^1$H NMR (DMSO-$d_6$, 300MHz) δ 10.03 (s, 1H), 8.64 (s, 49H), 8.56 (s, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 7.99 (bs, 2H), 7.59-7.63 (m, 1H), 7.56-7.59 (m, 1H), 7.45-7.48 (m, 1H), 7.42-7.45 (m, 1H), 7.31 (s, 1H), 7.20-7.26 (m, 1H), 7.15 (t, 1H), 6.79 (d, 1H), 4.59-4.72 (m, 1H), 2.37-2.51 (m, 9H), 2.28 (s, 3H), 2.20 (s, 3H), 1.96-2.16 (m, 4H), 1.74-1.86 (m, 2H), 1.53-1.68 (m, 2H).

### EXAMPLE 53

This example was prepared by substituting EXAMPLE 50A and 4-(4-aminophenylsulfanyl)phenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$HNMR(DMSO-$d_6$, 300MHz) δ 10.09 (s, 1H), 8.29 (s, 1H), 8.11 (s, 1H), 7.88 (bs, 2H), 7.59-7.63 (m, 1H), 7.56-7.59 (m, 1H), 7.17-7.21 (m, 1H), 7.14-7.17 (m, 1H), 7.08-7.11 (m, 1H), 7.05-7.08 (m, 1H), 6.81-6.83 (m, 1H), 6.79-6.81 (m, 1H), 5.47 (s, 2H), 4.58-4.71 (m, 1H), 2.56-2.70 (m, 9H), 2.20 (s, 3H), 1.94-2.16 (m, 4H), 1.73-1.85 (m, 2H), 1.52-1.67 (m, 2H).

### EXAMPLE 54

This example was prepared by substituting EXAMPLE 50A and 4-benzylphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$HNMR (DMSO-$d_6$, 300MHz) δ 10.04 (s, 1H), 8.29 (s, 1H), 8.11 (s, 1H), 7.92 (bs, 2H), 7.60-7.63 (m, 1H), 7.57-7.60 (m, 1H), 7.15-7.34 (m, 7H), 4.59-4.72 (m, 1H), 3.93 (s, 2H), 2.37-2.59 (m, 8H), 2.25-2.29 (m, 1H), 2.22 (s, 3H), 1.94-2.15 (m, 4H), 1.74-1.85 (m, 2H), 1.53-1.68 (m, 2H).

### EXAMPLE 55

This example was prepared by substituting EXAMPLE 50A and 4-benzenesulfonylphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$HNMR(DMSO-$d_6$, 300MHz) δ 10.41 (s, 1H), 8.34 (s, 1H), 8.13 (s, 1H), 7.96 (s, 5H), 7.92-7.94 (m, 1H), 7.87 (bs, 2H), 7.59-7.73 (m, 3H), 4.59-4.72 (m, 1H), 2.36-2.48 (m, 8H), 2.16-2.22 (m, 4H), 1.94-2.16 (m, 4H), 1.75-1.85 (m, 2H), 1.53-1.69 (m, 2H).

### EXAMPLE 56A

This example was prepared as described in EXAMPLES 40A and 40B by substituting 3-iodo-1-(4-morpholin-4-ylcyclohexyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine (prepared as described in WO 05/74603) for 3-bromothieno[3,2-c]pyridin-4-ylamine in EXAMPLE 40A.

### EXAMPLE 56B

This example was prepared by substituting EXAMPLE 56A and 4-phenoxyphenylamine for EXAMPLES 1B and 1C, respectively, in EXAMPLE 1D. $^1$H NMR (DMSO-$d_6$, 300MHz) δ 10.41 (s, 1H), 8.53 (s, 1H), 8.25 (s, 1H), 8.06 (bs, 1H), 7.83-7.87 (m, 1H), 7.79-7.83 (m, 1H), 7.36-7.45 (m, 2H), 7.10-7.17 (m, 1H), 6.99-7.09 (m, 4H), 4.83-4.96 (m, 1H), 3.55-3.63 (m, 4H), 2.47-2.57 (m, 4H), 2.29-2.42 (m, 1H), 2.09-2.29 (m, 2H), 1.96-2.09 (m, 4H), 1.40-1.57 (m, 2H).

### EXAMPLE 57A

This example was prepared by substituting 3-bromo-7-iodo-thieno[3,2-c]pyridin-4-ylamine (prepared as described in WO 05/10009) for EXAMPLE 45B in EXAMPLE 45C.

### EXAMPLE 57B

A mixture of 4-ethynylphenylamine (0.3 g), 4,4,5,5-tetramethyl[1,3,2]-dioxaborolane (0.56 mL) and $ZrCp_2ClH$ (0.083 g) in THF (6 mL) was stirred at 50°C for 1.5 hours and concentrated. The concentrate was flash chromatographed on silica gel with 30% ethyl acetate/hexanes.

### EXAMPLE 57C

This example was prepared by substituting EXAMPLES 57A and 57B for EXAMPLE 45B and 1-methyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazole, respectively, in EXAMPLE 45C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.92 (s, 3H) 5.32 (s, 2H) 6.01 (s, 2H) 6.57 (d, 2H) 6.86 (d, 1H) 7.27-7.42 (m, 3H) 7.60 (s, 1H) 7.85 (s, 1H) 7.99 (s, 1H) 8.11 (s, 1H).

### EXAMPLE 58A

This example was prepared by substituting EXAMPLE 57B for EXAMPLE 45C in EXAMPLE 45D.

### EXAMPLE 58B

This example was prepared by substituting EXAMPLES 57A and 58A for EXAMPLE 45B and 1-methyl-4-(4, 4, 5, 5-tetramethyl[1, 3, 2]dioxaborolan-2-yl)-1H-pyrazole, respectively, in EXAMPLE 45C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 2.28 (s, 3H) 3.93 (s, 3H) 6.08 (s, 2H) 6.80 (d, 1H) 7.00 (d, 1H) 7.16 (t, 1H) 7.20-7.27 (m, 1H) 7.31 (s, 1H) 7.44-7.54 (m, 2H) 7.54-7.68 (m, 3H) 7.73 (s, 1H) 7.86 (s, 1H) 8.01 (s, 1H) 8.12 (s, 1H) 8.62 (s, 1H) 8.79 (s, 1H).

### EXAMPLE 59

This example was prepared by substituting 1-ethynyl-4-phenoxybenzene for 4-ethynylphenylamine in EXAMPLE 57B then substituting the product therefrom and EXAMPLE 57A for 1-methyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazole and EXAMPLE 45B, respectively, in EXAMPLE 45C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.93 (s, 3H) 6.10 (s, 2H) 6.99-7.11 (m, 5H) 7.16 (t, 1H) 7.36-7.47 (m, 2H) 7.61-7.78 (m, 4H) 7.86 (s, 1H) 8.02 (s, 1H) 8.12 (s, 1H).

## EXAMPLE 60

This example was prepared by substituting EXAMPLE 57A and 2-(2-biphenyl-4-yl-vinyl)-4,4, 5,5-tetramethyl[1,3,2]dioxaborolane for EXAMPLE 45B and 1-methyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-1H-pyrazole, respectively, in EXAMPLE 45C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.93 (s, 3 H) 6.11 (s, 2 H) 7.13 (d, 1H) 7.33-7.42 (m, 1H) 7.48 (t, 2H) 7.68-7.85 (m, 8H) 7.87 (s, 1H) 8.03 (s, 1H) 8.13 (s, 1H).

EXAMPLES 61-65 were prepared following the procedures of EXAMPLE 45D and substituting the appropriate isocyanate (X) for 1-isocyanato-3-methylbenzene.

## EXAMPLE 61

X = 1-isocyanatobenzene. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.72 (s, 1H), 8.70 (s, 1H), 8.66 (s, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.87 (s, 1H), 7.67 (d, J=8.8Hz, 2H), 7.43-7.50 (m, 4H), 7.25-7.31 (m, 2H), 6.97 (t, J=7.3Hz, 1H), 6.83 (s, 2H), 3.93 (s, 3H).

## EXAMPLE 62

X = 1-fluoro-3-isocyanatobenzene. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.73 (s, 1H), 8.88 (s, 1H), 8.75 (s, 1H), 8.34 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.87 (s, 1H), 7.68 (d, J=8.8Hz, 2H), 7.44-7.53 (m, 3H), 7.31 (td, J=8.1, 6.8Hz, 1H), 7.12 (ddd, J=8.1, 2.0, 0.7Hz, 1H), 6.83 (s, 2H), 6.74-6.82 (m, 1H), 3.93 (s, 3H).

## EXAMPLE 63

X = isocyanatocyclohexane. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.65 (s, 1H), 8.35 (s, 1H), 8.31 (s, 1H), 8.13 (s, 1H), 8.05 (s, 1H), 7.86 (s, 1H), 7.59 (d, J=9.2Hz, 2H), 7.38 (d, J=9.2Hz, 2H), 6.82 (s, 2H), 6.08 (d, J=8.1Hz, 1H), 3.93 (s, 3H), 1.75-1.85 (m, 2H), 1.60-1.72 (m, 2H), 1.47-1.59 (m, 1H), 1.08-1.40 (m, 5H).

## EXAMPLE 64

X = 1-isocyanato-4-methylbenzene. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.71 (s, 1H), 8.67 (s, 1H), 8.57 (s, 1H), 8.33 (s, 1H), 8.14 (d, J=0.7Hz, 1H), 8.06 (s, 1H), 7.87 (d, J=1.0Hz, 1H), 7.66 (d, J=9.2Hz, 2H), 7.46 (d, J=9.2Hz, 2H), 7.34 (d, J=8.5Hz, 2H), 7.08 (d, J=8.5Hz, 2H), 6.83 (s, 2H), 3.93 (s, 3H), 2.24 (s, 3H).

## EXAMPLE 65

X = 1-isocyanato-2-methylbenzene. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.72 (s, 1H), 9.05 (s, 1H), 8.33 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.83-7.87 (m, 2H), 7.68 (d, J=8.8Hz, 2H), 7.48 (d, J=8.8Hz, 2H), 7.11-7.20 (m, 2H), 6.94 (td, J=7.4, 1.2Hz, 1H), 6.83 (s, 2H), 3.93 (s, 3H), 2.25 (s, 3H).

## EXAMPLE 66A

This example was prepared by substituting (3-aminophenyl)carbamic acid tert-butyl ester for (4-aminophenyl)carbamic acid tert-butyl ester in EXAMPLE 45B.

EXAMPLE 66B

This example was prepared by substituting EXAMPLE 66A and isocyanatobenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.79 (s, 1H), 8.77 (s, 1H), 8.60 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 8.07 (s, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.43-7.49 (m, 2H), 7.24-7.38 (m, 5H), 6.97 (t, J=7.3Hz, 1H), 6.80 (s, 2H), 3.93 (s, 3H).

EXAMPLE 67

This example was prepared by substituting EXAMPLE 66A and 1-isocyanato-2-methylbenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.81 (s, 1H), 9.15 (s, 1H), 8.37 (s, 1H), 8.14 (s, 1H), 8.07 (s, 1H), 8.00-8.03 (m, 1H), 7.86-7.90 (m, 3H), 7.31-7.38 (m, 1H), 7.25-7.31 (m, 2H), 7.11-7.20 (m, 2H), 6.94 (td, J=7.4, 1.2Hz, 1H), 6.80 (s, 2H), 3.93 (s, 3H), 2.26 (s, 3H).

EXAMPLE 68

This example was prepared by substituting EXAMPLE 66A and 1-isocyanato-4-methylbenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.78 (s, 1H), 8.73 (s, 1H), 8.49 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.96-7.98 (m, 1H), 7.87 (d, J=0.7Hz, 1H), 7.26-7.37 (m, 5H), 7.09 (d, J=8.5Hz, 2H), 6.80 (s, 2H), 3.93 (s, 3H), 2.24 (s, 3H).

EXAMPLE 69

This example was prepared by substituting EXAMPLE 66A for EXAMPLE 45C in EXAMPLE 45D. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.79 (s, 1H), 8.80 (s, 1H), 8.55 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.26-7.38 (m, 4H), 7.20-7.26 (m, 1H), 7.15 (t, J=7.6Hz, 1H), 6.76-6.82 (m, 3H), 3.93 (s, 3H), 2.28 (s, 3H).

EXAMPLE 70

This example was prepared by substituting EXAMPLE 45A and N-(3-aminophenyl)benzamide for EXAMPLE 1B and EXAMPLE 1C, respectively, in EXAMPLE 1D and substituting the product therefrom for EXAMPLE 45B in EXAMPLE 45C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.86 (s, 1H), 10.35 (s, 1H), 8.36-8.39 (m, 2H), 8.14 (s, 1H), 8.07 (s, 1H), 7.98 (dd, J=8.3, 1.5Hz, 2H), 7.87 (d, J=1.0Hz, 1H), 7.50-7.63 (m, 4H), 7.44-7.48 (m, 1H), 7.35 (t, J=8.0Hz, 1H), 6.82 (s, 2H), 3.93 (s, 3H).

EXAMPLE 71A

This example was prepared as described in EXAMPLE 1D bysubstituting EXAMPLE 45A and tert-butyl 4-aminopiperidine-1-carboxylate for EXAMPLE 1B and EXAMPLE 1C, respectively, and substituting the product therefrom for EXAMPLE 45B in EXAMPLE 45C. The Boc group was removed with TFA as described in EXAMPLE 1C.

EXAMPLE 71B

This example was prepared by substituting EXAMPLE 71A and isocyanatobenzene for 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.84 (d, J=7.5Hz, 1H), 8.54 (s, 1H), 8.12 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.84 (d, J=1.0Hz, 1H), 7.46 (d, J=7.8Hz, 2H), 7.23 (t, J=8.0Hz, 2H), 6.97 (s, 2H), 6.93 (t, J=7.3Hz, 1H), 3.98-4.17 (m, 3H), 3.92 (s, 3H), 2.97 (t, J=11.5Hz, 2H), 1.89 (dd, J=12.7, 3.2Hz, 2H), 1.44-1.59 (m, 2H).

## EXAMPLE 72

A mixture of EXAMPLE 71A (75 mg), benzoic acid (26 mg), HoBT (57 mg) and NMM (0.23 mL) in DMF (2 mL) at 0°C was treated with EDCI (80 mg), allowed to warm to aroom temperature, stirred for 5 hours, diluted with water and extracted with ethyl acetate. The extract was dried ($Na_2SO_4$), filtered and concentrated. The concantrate was triturated with dichloromethane, filtered and air dried. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.86 (d, J=7.5Hz, 1H), 8.12 (s, 1H), 8.11 (d, J=0.7Hz, 1H), 8.02 (s, 1H), 7.84 (d, J=1.0Hz, 1H), 7.44-7.49 (m, 3H), 7.36-7.41 (m, 2H), 6.95 (s, 2H), 4.33-4.52 (brm, 1H), 4.04-4.17 (brm, 1H), 3.92 (s, 3H), 3.52-3.71 (brm, 1H), 2.94-3.27 (brm, 2H), 1.77-2.03 (brm, 2H), 1.39-1.64 (brm, 2H).

## EXAMPLE 73A

This example was prepared by substituting tert-butyl trans-4-aminocyclohexylcarbamate for EXAMPLE 71A in EXAMPLE 72 and removing the Boc with TFA as described in EXAMPLE 1C.

## EXAMPLE 73B

This example was prepared by coupling EXAMPLES 45A and 73A as described in EXAMPLE 72 and substituting the product therefrom for EXAMPLE 45B in EXAMPLE 45C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.80 (d, J=7.8Hz, 1H), 8.27 (d, J=8.1Hz, 1H), 8.11 (s, 1H), 8.09 (s, 1H), 8.02 (s, 1H), 7.82-7.88 (m, 3H), 7.42-7.55 (m, 3H), 6.97 (s, 2H), 3.92 (s, 3H), 3.73-3.85 (brm, 2H), 1.89-2.01 (brm, 4H), 1.39-1.57 (m, 4H).

## EXAMPLE 74A

An ice cold solution of tert-butyl trans-4-aminocyclohexylcarbamate (250 mg) and isocyanatobenzene (0.11 mL) in DMF (5 mL) was treated with NMM (0.22 mL), stirred at ambient temperature for 5 hours, diluted with water and filtered. The filtrate was dissolved in dichloromethane (10 mL) and treated with TFA (1 mL). The mixture was stirred at ambient temperature for 3 hours and concentrated.

## EXAMPLE 74B

This example was prepared by coupling EXAMPLES 45A and 74A as described in EXAMPLE 72 and substituting the product therefrom for EXAMPLE 45B in EXAMPLE 45C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.77 (d, J=7.8Hz, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 8.08 (s, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.37 (d, J=7.5Hz, 2H), 7.17-7.25 (m, 2H), 6.96 (s, 2H), 6.88 (t, J=7.3Hz, 1H), 6.10 (d, J=7.5Hz, 1H), 3.92 (s, 3H), 3.74-3.87 (brm, 1H), 3.38-3.49 (brm, 1H), 1.89-1.99 (brm, 4H), 1.21-1.54 (m, 4H).

## EXAMPLE 75

This example was prepared by substituting 1-fluoro-2-isocyanatobenzene for isocyanatobenzene in EXAMPLE 74A then EXAMPLE 74B. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.77 (d, J=7.8Hz, 1H), 8.09-8.17 (m, 3H), 8.08 (s, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.16 (ddd, J=11.8, 8.1, 1.5Hz, 1H), 7.07 (t, J=7.1Hz, 1H), 6.96 (s, 2H), 6.87-6.95 (m, 1H), 6.62 (d, J=7.5Hz, 1H), 3.92 (s, 3H), 3.75-3.88 (m, 1H), 3.39-3.51 (m, 1H), 1.88-2.02 (m, 4H), 1.37-1.56 (m, 2H), 1.20-1.36 (m, 2H).

## EXAMPLE 76

This example was prepared by substituting tert-butyl 4-aminobenzylcarbamate for tert-butyl trans-4-aminocyclohexylcarbamate in EXAMPLES 74A and 74B. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.42 (t, J=5.8Hz, 1H), 8.71 (s, 1H), 8.70 (s, 1H), 8.16 (s, 1H), 8.11 (d, J=0.7Hz, 1H), 8.02 (s, 1H), 7.84 (d, J=0.7Hz, 1H), 7.41-7.47 (m, 4H), 7.24-7.31 (m, 4H), 7.02 (s, 2H), 6.92-6.99 (m, 1H), 4.45 (d, J=5.8Hz, 2H), 3.92 (s, 3H).

## EXAMPLE 77

This example was prepared by substituting tert-butyl 3-aminobenzylcarbamate for tert-butyl trans-4-aminocyclohexylcarbamate in EXAMPLES 74A and 74B. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.48 (t, J=5.9Hz, 1H), 8.68 (s, 1H), 8.62 (s, 1H), 8.19 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.84 (s, 1H), 7.36-7.47 (m, 4H), 7.23-7.30 (m, 3H), 7.03 (s, 2H), 6.93-7.01 (m, 2H), 4.49 (d, J=5.8Hz, 2H), 3.92 (s, 3H).

## EXAMPLE 78A

This example was prepared by substituting 3-bromo-7-iodothieno[3,2-c]pyridin-4-amine for EXAMPLE 45B in EXAMPLE 45C and substituting the product therefrom for 3-bromo-thieno[3,2-c]pyridn-4-ylamine in EXAMPLES 40A and 40B.

## EXAMPLE 78B

This example was prepared by coupling EXAMPLE 78A and 4-(aminomethyl)-N-phenylpiperidine-1-carboxamide (prepared by substituting tert-butyl piperidin-4-ylmethylcarbamate for tert-butyl trans-4-aminocyclohexylcarbamate in EXAMPLE 74A) as described in EXAMPLE 72. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.97 (t, J=5.6Hz, 1H), 8.45 (s, 1H), 8.12 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.84 (s, 1H), 7.45 (d, J=7.8Hz, 2H), 7.18-7.25 (m, 2H), 6.99 (s, 2H), 6.91 (t, J=7.3Hz, 1H), 4.14 (d, J=12.9Hz, 2H), 3.92 (s, 3H), 3.23 (t, J=5.9Hz, 2H), 2.79 (t, J=11.9Hz, 2H), 1.72-1.86 (m, 3H), 1.08-1.24 (m, 2H).

## EXAMPLE 79

This example was prepared by substituting 78A and tert-butyl 4-aminobenzylcarbamate for benzoic acid and 71A, respectively, in EXAMPLE 72, removing the Boc group with TFA as described in EXAMPLE 1C and substituting the product therefrom for tert-butyl trans-4-aminocyclohexylcarbamate in EXAMPLE 74A. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.78 (s, 1H), 8.53 (s, 1H), 8.35 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.86 (s, 1H), 7.71 (d, J=7.8Hz, 2H), 7.39-7.43 (m, 2H), 7.32 (d, J=8.1Hz, 2H), 7.19-7.25 (m, 2H), 6.87-6.93 (m, 1H), 6.80 (s, 2H), 6.59 (t, J=6.4Hz, 1H), 4.29 (d, J=5.8Hz, 2H), 3.93 (s, 3H).

## EXAMPLE 80

This example was prepared by substituting EXAMPLE 78A and tert-butyl 3-aminobenzylcarbamate for benzoic acid and EXAMPLE 71A, respectively, in EXAMPLE 72, removing the Boc group with TFA as described in EXAMPLE 1C and substituting the product therefrom for tert-butyl trans-4-aminocyclohexylcarbamate in EXAMPLE 74A. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.81 (s, 1H), 8.56 (s, 1H), 8.34 (s, 1H), 8.13 (d, J=0.7Hz, 1H), 8.06 (s, 1H), 7.86 (d, J=0.7Hz, 1H), 7.72-7.74 (m, 1H), 7.62-7.66 (m, 1H), 7.39-7.43 (m, 2H), 7.35 (t, J=8.0Hz, 1H), 7.18-7.25 (m, 2H), 7.10 (d, J=7.8Hz, 1H), 6.89 (t, J=7.3Hz, 1H), 6.78 (s, 2H), 6.64 (t, J=5.9Hz, 1H), 4.32 (d, J=6.4Hz, 2H), 3.93 (s, 3H).

## EXAMPLE 81A

A mixture of (1S,4S)-4-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid (245 mg) in toluene (10 mL) was treated with triethylamine (0.14 mL) and DPPA (0.22 mL), heated at 70°C for 45 minutes, cooled to ambient temperature and treated with aniline (0.18 mL). The mixture was stirred overnight at ambient temperature, diluted with ether and washed with 0.5 N HCl, saturated $NaHCO_3$, water and brine and dried ($Na_2SO_4$), filtered and concentrated. The concentrate was purified by silica gel chromatography to provide tert-butyl (1S,4S)-4-(3-phenylureido)cyclohexylcarbamate which was dissolved in dichloromethane (2 mL) and TFA (2 mL), stirred at ambient temperature for 12 hours and concentrated.

## EXAMPLE 81B

This example was prepared by substituting EXAMPLE 78A and EXAMPLE 81A for benzoic acid and EXAMPLE 71A respectively, in EXAMPLE 72. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.78 (d, J=6.8Hz, 1H), 8.41 (s, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 8.02 (s, 1H), 7.84 (s, 1H), 7.37 (d, J=7.5Hz, 2H), 7.21 (t, J=7.8Hz, 2H), 6.85-6.93 (m, 3H), 6.17 (d, J=6.8Hz, 1H), 3.92 (s, 3H), 3.83-3.90 (m, 1H), 3.66-3.73 (m, 1H), 1.62-1.79 (m, 8H).

## EXAMPLE 82

This example was prepared by substituting racemic cis-3-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid for cis-4-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid in EXAMPLES 81A and 81B. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.81 (d, J=7.8Hz, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 8.07 (s, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.37 (d, J=7.8Hz, 2H), 7.21 (t, J=7.8Hz, 2H), 6.93 (s, 2H), 6.88 (t, J=7.1Hz, 1H), 6.16 (d, J=7.8Hz, 1H), 3.91 (s, 3H), 3.78-3.94 (m, 1H), 3.47-3.62 (m, 1H), 2.11-2.20 (m, 1H), 1.73-1.92 (m, 3H), 1.00-1.48 (m, 4H).

## EXAMPLE 83A

### (±)(1R,3S)-3-amino-N-phenylcyclohexanecarboxamide

This example was prepared by substituting (±)-(1R,3S)-3-(tert-butoxycarbonylamino)cyclohexanecarboxylic acid and aniline for benzoic acid and EXAMPLE 71A respectively, in EXAMPLE 72 and removing the Boc with TFA as described in EXAMPLE 1C.

## EXAMPLE 83 B

This example was prepared by substituting EXAMPLE 78A and EXAMPLE 83A for benzoic acid and EXAMPLE 71A respectively, in EXAMPLE 72. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.91 (s, 1H), 8.85 (d, J=7.8Hz, 1H), 8.11 (s, 1H), 8.09 (s, 1H), 8.01 (s, 1H), 7.83

(s, 1H), 7.60 (d, J=7.8Hz, 2H), 7.28 (t, J=8.0Hz, 2H), 7.02 (t, J=7.3Hz, 1H), 6.95 (s, 2H), 3.91 (s, 3H), 3.83-3.97 (m, 1H), 2.00-2.09 (m, 1H), 1.77-1.96 (m, 3H), 1.13-1.61 (m, 4H).

### EXAMPLE 84A

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2 g) was added portionwise to an ice cold suspension of NaH (280 mg) in DMF (25 mL). The mixture was stirred at 0°C for 30 minutes, treated with (2-bromoethoxy)(tert-butyl)diphenylsilane (4.16 g), warmed to 50°C for 2 hours, quenched with water and extracted with ethyl acetate. The extract was dried ($Na_2SO_4$), filtered and concentrated, and the concentrate was purified by silica gel chromatography.

### EXAMPLE 84B

This example was prepared by substituting EXAMPLE 78A and tert-butyl 3-aminobenzylcarbamate for benzoic acid and EXAMPLE 71A respectively, in EXAMPLE 72.

### EXAMPLE 84C

This example was prepared by substituting EXAMPLE 84B and EXAMPLE 84A for EXAMPLE 45B and 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole in EXAMPLE 45C, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom for tert-butyl (1R,4R)-4-aminocyclohexylcarbamate in EXAMPLE 74A.

### EXAMPLE 84D

EXAMPLE 84C (0.71 g) and 1M TBAF in THF (1.8 mL) in THF (10 mL) was stirred at ambient temperature for 4 hours, diluted with water and extracted with dichloromethane and methanol. The extract, with the solid at the layer interface, was combined, concentrated and chromatographed on silica gel. The product was further purified by triturating with DMF/water/methanol. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 10.85 (s, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 8.16 (d, J=0.7Hz, 1H), 8.08 (s, 1H), 7.90 (d, J=0.7Hz, 1H), 7.71-7.74 (m, 1H), 7.64 (d, J=7.5Hz, 1H), 7.41 (dd, J=8.6, 1.2Hz, 2H), 7.35 (t, J=8.0Hz, 1H), 7.18-7.25 (m, 2H), 7.11 (d, J=7.8Hz, 1H), 6.94 (s, 2H), 6.89 (t, J=7.3Hz, 1H), 6.64 (t, J=6.1Hz, 1H), 4.95 (t, J=5.3Hz, 1H), 4.32 (d, J=6.1Hz, 2H), 4.23 (t, J=5.6Hz, 2H), 3.80 (q, J=5.1Hz, 2H).

### EXAMPLE 85A

A mixture of EXAMPLE 84D (164 mg) in dimethylacetamide (2.5 mL) was treated with $(tBuO)_2PNEt_2$ (0.31 mL) and tetrazole (132 mg), stirred at ambient temperature for 2 hours, cooled to -10°C and treated with 30% $H_2O_2$ (0.1 mL). The mixture was stirred at ambient temperature for 2.5 hours, treated with of 30% $H_2O_2$ (0.3 mL), stirred for 3 hours and partitioned between 10% $Na_2S_2O_3$ and ethyl acetate. The extract was dried ($Na_2SO_4$), filtered and concentrated, and the concentrate was purified by silica gel chromatography.

### EXAMPLE 85B

A mixture of EXAMPLE 85A (90 mg) in methanol (5 mL) was treated with 4M HCl in dioxane (0.2 mL), stirred for 1 hour, diluted with diethylether and filtered. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 11.09 (s, 1H), 8.90 (s, 1H), 8.90 (s, 2H), 8.76 (s, 1H), 8.33 (d, J=0.7Hz, 1H), 8.07 (s, 1H), 8.01 (d, J=1.0Hz, 1H), 7.63-7.68 (m, 2H), 7.35-7.47 (m, 3H), 7.13-7.28 (m, 3H), 6.89 (t, J=7.3Hz, 1H), 6.74-6.81 (m, 1H), 4.46 (t, J=5.1Hz, 2H), 4.33 (d, J=4.1Hz, 2H), 4.20-4.27 (m, 2H).

EXAMPLE 86

This example was prepared by substituting EXAMPLE 22C and 2-fluoro-1-isocyanato-3-(trifluoromethyl)benzene for EXAMPLE 1B and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLES 1C and 1D, respectively. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.65 (s, 1H,) 9.18 (s, 1H), 8.82 (d, J=2.46Hz, 1H), 8.45 (m, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.60 (m, 1H), 7.57 (d, J=8.90Hz, 2H) ,7.47 (d, J=9.21Hz, 2H), 7.35 (m, 2H), 7.00 (brs, 2H) 3.85 (s, 3H).

EXAMPLE 87

This example was prepared by substituting EXAMPLE 22C and isocyanatobenzene for EXAMPLE 1B and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLES 1C and 1D, respectively. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 8.69 (s, 1H), 8.64 (s, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.60 (s, 1H), 7.54 (d, J=9.15Hz, 2H), 7.45 (m, 4H), 7.28 (m, 2H), 7.02 (brs, 2H), 6.96 (t, J=7.32Hz, 1H), 3.85 (s, 3H).

EXAMPLE 88

This example was prepared as described in EXAMPLES 22B-C by substituting 4,4,5,5-tetramethyl-2-thiophen-3-yl-[1,3,2]dioxaborolane for 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole in EXAMPLE 22B and coupling as described in EXAMPLE 1D but substituting 1-(4-aminophenyl)-3-phenylurea for EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.58 (s, 1H), 8.66 (s, 1H), 8.61 (s, 1H), 8.36 (s, 1H), 7.83 (m, 1H), 7.67 (m, 2H), 7.45 (m, 5H), 7.27 (m, 3H), 7.07 (brs, 2H), 6.96 (t, J=7.36Hz, 1H).

EXAMPLE 89

This example was prepared by substituting morpholine for 1-methylpiperazine in EXAMPLE 38A and following the procedures of EXAMPLE 1, but substituting the product therefrom for 5-amino-4-cyano-thiophene-3-carboxylic acid ethyl ester in EXAMPLE 1A and isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.64 (s, 1H), 8.68 (s, 1H), 8.64 (s, 1H), 8.22 (s, 1H), 7.67 (d, J=8.85Hz, 2H), 7.50 (brs, 2H), 7.46 (t, J=9.15Hz, 4H), 7.28 (m, 2H), 6.97 (t, J=7.32Hz, 1H), 3.70 (m, 4H), 3.10 (m, 4H).

EXAMPLE 90

This example was prepared as described in EXAMPLE 1 by substituting 3-isocyanatothiophene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (s, 1H), 8.89 (s, 1H), 8.63 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.98 (brs, 2H), 7.63 (d, J=8.90Hz, 2H), 7.47 (d, J=8.90Hz, 2H), 7.43 (m, 1H), 7.28 (dd, J=3.07, 1.23Hz, 1H), 7.05 (dd, J=4.91, 1.23Hz, 1H).

EXAMPLE 91

This example was prepared as described in EXAMPLE 1 by substituting isocyanatocyclopentane for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.57 (s, 1H), 8.35 (s, 1H), 8.31 (s, 1H), 8.25 (s, 1H), 7.92 (brs, 2H), 7.56

(d, J=8.90Hz, 2H), 7.38 (d, J=9.21Hz, 2H), 6.11 (d, J=7.06Hz, 1H), 3.94 (m, 1H), 1.84 (m, 2H), 1.63 (m, 2H), 1.53 (m, 2H), 1.36 (m, 2H).

EXAMPLE 92

This example was prepared as described in EXAMPLE 1 by substituting 3-isocyanatopyridine for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.65 (s, 1H), 8.83 (s, 2H), 8.62 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.19 (d, J=3.38Hz, 1H), 7.95 (m, 1H), 7.96 (brs, 2H), 7.65 (d, J=8.90Hz, 2H), 7.48 (d, J=8.90Hz, 2H), 7.32 (m, 1H).

EXAMPLE 93A

This example was prepared as described in EXAMPLE 1C by substituting 1-isocyanato-4-nitrobenzene and 5-methylisoxazol-3-amine for 1-isocyanato-3-methylbenzene and (4-aminophenyl)carbamic acid tert-butyl ester, respectively, in EXAMPLE 1C.

EXAMPLE 93B

A mixture of EXAMPLE 93A (700 mg), iron powder (830 mg), $NH_4Cl$ (155 mg) in ethanol (25 mL), THF (28 mL) and water (11 mL) at 85°C was stirred for 9 hours, cooled to ambient temperature and filtered through diatomaceous earth (CELITE®) with ethanol. The filtrate was concentrated and the concentrate was purified by silica gel chromatography.

EXAMPLE 93C

This example was prepared by substituting EXAMPLE 93B for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.71 (s, 1H), 9.44 (s, 1H), 8.87 (s, 1H), 8.46 (s, 1H), 8.39 (s, 1H), 8.28 (brs, 2H), 7.65 (d, J=8.90Hz, 2H), 7.47 (d, J=9.21Hz, 2H), 6.53 (s, 1H), 2.37 (s, 3H).

EXAMPLE 94

This example was prepared as described in EXAMPLE 1 by substituting isocyanatocyclopropane for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.62 (s, 1H), 8.39 (s, 1H), 8.34 (s, 1H), 8.31 (s, 1H), 7.92 (brs, 2H), 7.56 (d, J=9.16Hz, 2H), 7.41 (d, J=9.16Hz, 2H), 6.37 (s, 1H), 2.54 (m, 1H), 0.63 (m, 2H), 0.40 (m, 2H).

EXAMPLE 95

This example was prepared as described in EXAMPLE 1 by substituting 2,4-difluoro-1-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 9.05 (s, 1H), 8.49 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 8.10 (m, 1H), 7.65 (d, J=8.54Hz, 4H), 7.47 (d, J=8.54Hz, 2H), 7.31 (t, J=8.85Hz, 1H), 7.05 (t, J=7.93Hz, 1H).

EXAMPLE 96

This example was prepared as described in EXAMPLE 1 by substituting 1,2-difluoro-4-isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.67 (s, 1H), 8.87 (s, 1H), 8.77 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.95

(brs, 2H), 7.68 (m, 1H), 7.64 (d, J=8.85Hz, 2H), 7.47 (d, J=8.85Hz, 2H), 7.34 (m, 1H), 7.12 (d, J=9.15Hz, 1H).

### EXAMPLE 97A

A mixture of 3-(morpholinomethyl)aniline (0.46 g), triethylamine (0.37 mL) and 4-nitrophenylcarbonochloridate (0.53 g) at ambient temperature was stirred for 2 hours, treated with triethylamine (0.37 mL) and tert-butyl 4-aminophenylcarbamate (0.5 g), stirred for 18 hours and partitioned between water and ethyl acetate. The extract was washed with water and brine and dried ($Na_2SO_4$), filtered and concentrated. The concentrate was purified by silica gel chromatography to provide tert-butyl 4-(3-(3-(morpholinomethyl)phenyl)ureido)phenylcarbamate, which was dissolved in dichloromethane (30 mL), cooled in an ice bath, treated with TFA (1.8 mL), stirred for 30 minutes, warmed at ambient temperature, stirred for 18 hours and concentrated with a toluene/methanol azeotrope.

### EXAMPLE 97B

This example was prepared by substituting EXAMPLE 97A for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.63 (s, 1H), 8.65 (s, 1H), 8.63 (s, 1H), 8.37 (s, 1H), 8.32 (s, 1H), 7.96 (brs, 2H), 7.63 (d, J=8.90Hz, 2H), 7.47 (d, J=8.90Hz, 3H), 7.34 (d, J=8.90Hz, 1H), 7.23 (t, J=7.67Hz, 1H), 6.92 (d, J=7.36Hz, 1H), 3.59 (m, 4H), 3.47 (s, 2H), 2.40 (s, 4H).

### EXAMPLE 98

This example was prepared by substituting EXAMPLE 74A for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.34 (brs, 1H), 8.83 (d, J=7.67Hz, 1H), 8.37 (s, 1H), 8.30 (s, 1H), 8.28 (s, 1H), 8.04 (brs, 2H), 7.37 (m, 2H), 7.21 (m, 2H), 6.88 (m, 1H), 6.08 (d, J=6.44Hz, 1H), 3.44 (brs, 1H), 1.94 (m, 4H), 1.47 (m, 2H), 1.28 (m, 2H).

### EXAMPLE 99

This example was prepared as described in EXAMPLE 93 by substituting 3,5-dimethylisoxazol-4-amine for 5-methylisoxazol-3-amine. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.66 (s, 1H), 8.84 (s, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.01 (brs, 2H), 7.70 (s, 1H), 7.61 (d, J=9.16Hz, 2H), 7.46 (d, J=8.82Hz, 2H), 2.29 (s, 3H), 2.13 (s, 3H).

### EXAMPLE 100

This example was prepared as described in EXAMPLE 93 by substituting thiazol-2-amine for 5-methylisoxazol-3-amine. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.67 (s, 1H) 10.46 (s, 1H), 8.98 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 7.98 (brs, 2H), 7.67 (d, J=8.90Hz, 2H), 7.50 (d, J=8.90Hz, 2H), 7.37 (d, J=3.68Hz, 1H), 7.11 (d, J=3.07Hz, 1H).

### EXAMPLE 101

This example was prepared as described in EXAMPLE 93 by substituting isoxazol-3-amine for 5-methylisoxazol-3-amine. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.69 (s, 1H), 9.58 (s, 1H), 8.86 (s, 1H), 8.74 (s, 1H), 8.38 (s, 1H), 8.32 (s, 1H), 7.83 (brs, 2H), 7.67 (d, J=8.24Hz, 2H), 7.48 (d, J=8.54Hz, 2H), 6.85 (s, 1H).

### EXAMPLE 102

This example was prepared as described in EXAMPLE 1 by substituting tert-butyl piperidin-4-ylcarbamate and isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.10 (brs, 1H), 8.85 (d, J=7.67Hz, 1H), 8.53 (s, 1H), 8.34 (s, 1H), 8.26 (s, 1H), 7.94 (brs, 1H), 7.46 (d, J=7.67Hz, 2H), 7.22 (m, 2H), 6.93 (t, J=7.36Hz, 1H), 4.14 (d, J=13.50Hz, 2H), 4.06 (m, 1H), 2.95 (t, J=11.66Hz, 2H), 1.88 (d, J=12.27Hz, 2H), 1.53 (m, 2H).

## EXAMPLE 103

This example was prepared as described in EXAMPLE 1 by substituting (3-aminophenyl)carbamic acid tert-butyl ester and isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 1B. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.74 (s, 1H), 8.78 (s, 1H), 8.61 (s, 1H), 8.41 (s, 1H), 8.32 (s, 1H), 8.12 (brs, 1H), 7.97 (m, 1H), 7.46 (d, J=7.63Hz, 2H), 7.34 (m, 1H), 7.29 (t, J=8.24Hz, 5H), 6.98 (t, J=7.32Hz, 1H).

## EXAMPLE 104A

A solution of EXAMPLE 1A (750 mg) in THF (34 mL) at -78°C was treated with 2M LDA in THF (5.1 mL), stirred for 2 hours, treated with iodine (855 mg) in THF (6 mL), stirred for 1 hour, warmed to and at 0°C, stirred for for 2 hours, quenched with saturated $NH_4Cl$ and extracted with ethyl acetate. The extract was washed with 10% $Na_2SO_3$ and brine and dried (MgSO4), filtered and concentrated. The concentrate was purified by silica gel chromatography.

## EXAMPLE 104B

EXAMPLE 104A (50 mg), 3-methoxyprop-1-yne (0.015 ml), $Cl_2Pd(PPh_3)_2$ (5 mg), CuI (0.8 mg), triethylamine (0.36 mL) and DMF (0.18 mL) was degassed with nitrogen, heated in a sealed tube at 60°C for 40 minutes with stirring in a Smith Synthesizer microwave oven (at 200W). The mixture was partitioned between water and dichloromethane and the extract was washed with brine and dried (MgSO4), filtered and concentrated. The concentrate and was purified by silica gel chromatography.

## EXAMPLE 104C

This example was prepared as described in EXAMPLE 1 by substituting EXAMPLE 104B for EXAMPLE 1A in EXAMPLE 1B and isocyanatobenzene for 1-isocyanato-3-methylbenzene in EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.87 (s, 1H), 8.70 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 7.47 (m, 10H), 6.97 (s, 1H), 4.38 (s, 2H), 3.22 (s, 3H).

## EXAMPLE 105

This example was prepared as described in EXAMPLE 104 by substituting ethynyltrimethylsilane for 3-methoxyprop-1-yne. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.84 (s, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 8.40 (s, 1H), 7.65 (d, J=8.90Hz, 2H), 7.47 (t, J=8.90Hz, 6H), 7.28 (t, J=8.59,Hz, 2H), 6.97 (t, J=7.36Hz, 1H), 5.08 (s, 1H).

## EXAMPLE 106

This example was prepared as described in EXAMPLE 104 by substituting 3-ethynylthiophene for 3-methoxyprop-1-yne. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.94 (s, 1H), 8.71 (s, 1H), 8.65 (s, 1H), 8.40 (s, 1H), 7.89 (m, 1H), 7.70 (d, J=8.85Hz, 2H), 7.66 (m, 1H), 7.47 (m, 6H), 7.28 (t, J=7.63Hz, 2H), 7.10 (d, J=5.19Hz, 1H), 6.97 (t, J=7.32Hz, 1H).

### EXAMPLE 107

This example was prepared as described in EXAMPLE 104 by substituting N,N-dimethylprop-2-yn-1-amine for 3-methoxyprop-1-yne. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.84 (s, 1H), 8.69 (s, 1H), 8.64 (s, 1H), 8.38 (s, 1H), 7.65 (d, J=9.21Hz, 2H), 7.46 (m, 6H), 7.27 (t, J=8.59Hz, 2H), 6.97 (t, J=7.36Hz, 1H), 3.54 (s, 2H), 2.12 (s, 6H).

### EXAMPLE 108

This example was prepared as described in EXAMPLE 1D by substituting N-(4-aminophenyl)-2-fluorobenzamide for EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.74 (s, 1H), 10.45 (s, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 8.02 (brs, 2H), 7.71 (m, 5H), 7.58 (m, 1H), 7.35 (m, 2H).

### EXAMPLE 109

This example was prepared as described in EXAMPLE 1D by substituting N-(4-aminophenyl)-3-fluorobenzamide for EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 10.36 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 7.78 (m, 8H), 7.60 (s, 1H), 7.46 (s, 1H).

### EXAMPLE 110

This example was prepared as described in EXAMPLE 1D by substituting N-(4-aminophenyl)-4-fluorobenzamide for EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.74 (s, 1H), 10.30 (s, 1H), 8.41 (s, 1H), 8.34 (s, 1H), 8.05 (m, 2H), 7.90 (brs, 2H), 7.78 (d, J=8.24Hz, 2H), 7.71 (d, J=8.24Hz, 2H), 7.37 (t, J=8.85, 8.24Hz, 1H).

### EXAMPLE 111

This example was prepared as described in EXAMPLE 1D by substituting N-(4-aminophenyl)-2-methylbenzamide for EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.70 (s, 1H), 10.30 (s, 1H), 8.40 (s, 1H), 8.32 (s, 1H), 8.01 (brs, 2H), 7.76 (d, J=8.90Hz, 2H), 7.68 (d, J=8.90Hz, 2H), 7.46 (d, J=7.67Hz, 1H), 7.39 (m, 1H), 7.30 (m, 2H), 2.40 (s, 3H).

### EXAMPLE 112

This example was prepared as described in EXAMPLE 1D by substituting N-(4-aminophenyl)-3-methylbenzamide for EXAMPLE 1C. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.71 (s, 1H), 10.22 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 8.03 (brs, 2H), 7.77 (m, 4H), 7.70 (d, J=9.21Hz, 2H), 7.40 (m, 2H), 2.41 (s, 3H).

### EXAMPLE 113A

A solution of $CaCl_2$ (104 mg) in ethanol (2.3 mL) was treated with methyl 3-(3-(4-aminophenyl)ureido)benzoate (150mg) in THF (2.3 mL) and $NaBH_4$ (71 mg), and the mixture was stirred at reflux for 18 hours, treated with $NaBH_4$ (280 mg) in 4 portions over 8 hours, cooled to ambient temperature and concentrated. The concentrate was treated with water and washed with dichloromethane. The heterogeneous water layer was filtered, and the solid was collected, washed with water and air dried.

### EXAMPLE 113B

This example was prepared as described in EXAMPLE 1D by substituting EXAMPLE 113A for EXAMPLE 1C. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.69 (s, 1H), 8.69 (s, 1H), 8.66 (s, 1H), 8.43 (s, 1H), 8.36 (s, 1H), 7.96 (brs, 2H), 7.63 (d, J=8.85Hz, 2H), 7.48 (d, J=8.85Hz, 2H), 7.43 (s, 1H), 7.32 (d, J=8.24Hz, 1H), 7.22 (t, J=7.93Hz, 1H), 6.92 (d, J=7.63Hz, 1H), 4.47 (s, 2H), 3.70 (brs, 1H).

### Example114

This example was prepared by substituting tert-butyl 3-aminobenzylcarbamate for EXAMPLE 1C in EXAMPLE 1D, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom and isocyanatobenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 8.57 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 7.97 (br s, 2H), 7.69 (s, 1H), 7.62 (d, J=7.32Hz, 1H), 7.41 (d, J=7.63Hz, 2H), 7.35 (t, J=7.63Hz, 1H), 7.22 (t, J=7.32Hz, 2H), 7.11 (d, J=7.32Hz, 1H), 6.89 (t, J=6.71Hz, 1H), 6.64 (s, 1H), 4.32 (d, J=5.19Hz, 2H).

### Example 115

This example was prepared as described in EXAMPLE 1 by substituting (3-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-2-methylbenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 1B. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.74 (s, 1H), 9.15 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 8.00 (s, 1H), 7.88 (m, 4H), 7.30 (m, 3H), 7.16 (m, 2H), 6.95 (t, J=7.32Hz, 1H), 2.26 (s, 3H).

### Example 116

This example was prepared by substituting tert-butyl 3-aminobenzylcarbamate for EXAMPLE 1C in EXAMPLE 1D, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom for EXAMPLE 45C in EXAMPLE 45D. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 8.48 (s, 1H), 8.39 (s, 1H), 8.33 (s, 1H), 7.90 (br s, 2H), 7.68 (s, 1H), 7.62 (d, J=7.93Hz, 1H), 7.35 (t, J=7.93Hz, 1H), 7.25 (s, 1H), 7.18 (d, J=7.93Hz, 1H), 7.10 (m, 2H), 6.71 (d, J=7.32Hz, 1H), 6.62 (t, J=5.80Hz, 1H), 4.32 (d, J=5.80Hz, 2H), 2.24 (s, 3H).

### Example 117

This example was prepared by substituting tert-butyl 3-aminobenzylcarbamate for EXAMPLE 1C in EXAMPLE 1D, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom and 1-fluoro-3-isocyanatobenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.75 (m, 1H), 8.84 (m, 1H), 8.39 (m, 1H), 8.32 (m, 1H), 7.98 (m, 2H), 7.68 (m, 1H), 7.62 (d, J=8.24Hz, 1H), 7.47 (d, J=12.21Hz, 1H), 7.35 (t, J=7.93Hz, 1H), 7.24 (m, 1H), 7.11 (d, J=7.63Hz, 1H), 7.05 (d, J=9.15Hz, 1H), 6.72 (m, 2H), 4.32 (d, J=6.10Hz, 2H).

### Example 118

This example was prepared as described in EXAMPLE 1 by substituting (3-aminophenyl)carbamic acid tert-butyl ester for (4-aminophenyl)carbamic acid tert-butyl ester in EXAMPLE 1B. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.74 (m, 1H), 8.77 (m, 1H), 8.55 (m, 1H), 8.41 (m, 1H), 8.33 (m, 1H), 7.97 (m, 1H), 7.75 (m, 2H), 7.29 (m, 5H), 7.16 (t, J=7.63Hz, 1H), 6.80 (d, J=7.32Hz, 1H), 2.28 (s, 3H).

### Example 119

This example was prepared as described in EXAMPLE 1 by substituting (3-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-4-methylbenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 1B. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.73 (s, 1H), 8.74 (s, 1H), 8.51 (s, 1H), 8.41 (s, 1H), 8.33 (s, 1H), 7.96 (s, 1H), 7.77 (br s, 2H), 7.30 (m, 5H), 7.09 (m, 2H), 2.24 (s, 3H).

### Example 120

This example was prepared as described in EXAMPLE 1 by substituting (3-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-2-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 1B. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 9.21 (s, 1H), 8.54 (d, J=2.14Hz, 1H), 8.41 (s, 1H) 8.33 (s, 1H), 8.17 (t, J=8.24Hz, 1H), 7.98 (s, 1H), 7.73 (br s, 2H), 7.35 (m, 1H), 7.30 (m, 2H), 7.24 (m, 1H), 7.15 (t, J=7.32Hz, 1H), 7.01 (m, 1H).

### Example 121

This example was prepared as described in EXAMPLE 1 by substituting (3-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-3-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 1B. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 8.85 (s, 2H), 8.41 (s, 1H), 8.32 (s, 1H), 7.97 (s, 1H), 7.96 (br s, 2H), 7.50 (d, J=11.90Hz, 1H), 7.36 (m, 1H), 7.29 (m, 3H), 7.12 (d, J=7.93Hz, 1H), 6.79 (t, J=6.10Hz, 1H).

### Example 122

This example was prepared as described in EXAMPLE 1 by substituting (3-aminophenyl)carbamic acid tert-butyl ester and 1-fluoro-4-isocyanatobenzene for (4-aminophenyl)carbamic acid tert-butyl ester and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 1B. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.73 (m, 1H), 8.78 (m, 1H), 8.65 (m, 1H), 8.40 (m, 1H), 8.33 (m, 1H), 7.97 (m, 1H), 7.78 (m, 2H), 7.47 (m, 2H), 7.33 (m, 1H), 7.28 (m, 2H), 7.13 (t, J=8.85Hz, 2H).

### Example 123

This example was prepared by substituting tert-butyl 3-aminobenzylcarbamate for EXAMPLE 1C in EXAMPLE 1D, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom and 1-isocyanato-3-(trifluoromethyl)benzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.75 (s, 1H), 9.04 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 7.97 (br s, 2H), 7.63 (m, 6H), 7.35 (s, 1H), 7.11 (s, 1H), 6.82 (s, 1H), 4.34 (s, 2H).

## Example 124

This example was prepared by substituting 2-(2-aminothiazol-5-yl)-N-(3-fluorophenyl)acetamide for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 12.95 (br s, 1H), 10.47 (s, 1H), 8.61 (s, 1H), 8.32 (s, 1H), 7.97 (br s, 2H), 7.61 (d, J=11.90Hz, 1H), 7.44 (s, 1H), 7.34 (m, 2H), 6.90 (t, J=6.41Hz, 1H), 3.91 (s, 2H).

## Example 125A

A solution of 4-amino-N-methoxythieno[2,3-d]pyrimidine-5-carboxamide (3 mmol) (prepared by substituting O-methylhydroxylamine for EXAMPLE 1C in EXAMPLE 1D) in THF (12 mL) was added to a suspension of LAH (235 mg) in THF (12 mL) at -78°C. The mixture was stirred for 30 minutes, treated sequentially with water (0.24 mL), 1M NaOH (0.24 mL) and water, (0.72 mL), filtered through diatomaceous earth (CELITE®) and concentrated.

## Example 125B

A solution of (4-nitrobenzyl)triphenylphosphonium bromide (1.66 g) in THF (20 mL) at 0°C was treated with 1.6M n-butyllithium in hexanes (2.2 mL), stirred for 40 minutes, treated with EXAMPLE 125A in THF (20 mL), stirred at 0°C for 3 hours and at ambient temperature for 18 hours, treated with 5% methanol in dichloromethane, washed with water and dried ($Na_2SO_4$), filtered and concentrated. The concentrate was triturated with methanol and air dried.

## Example 125C

This example was prepared as described for EXAMPLE 93B and substituting EXAMPLE 125B for EXAMPLE 93A.

## Example 125D

A mixture of EXAMPLE 125C (110 mg) and 5% Pd on carbon (50 mg) in methanol (10 mL) was shaken under hydrogen (60 psi) at 50°C for 40 hours, filtered and concentrated.

## Example 125E

This example was prepared as described for EXAMPLE 45D and substituting EXAMPLE 125D and isocyanatobenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.65 (s, 1H), 8.61 (s, 1H), 8.25 (s, 1H), 7.44 (d, J=7.98Hz, 2H), 7.35 (d, J=8.59Hz, 2H), 7.27 (t, J=7.98Hz, 2H), 7.15 (d, J=8.29Hz, 2H), 7.10 (s, 1H), 6.99 (s, 2H), 6.95 (m, 1H), 3.22 (t, J=8.29Hz, 2H), 2.90 (t, J=8.29Hz, 2H).

## Example 126

This example was prepared by substituting 1-(4-aminophenyl)-3-(3-(3-hydroxypropoxy)phenyl)urea for EXAMPLE 1C in EXAMPLE 1D. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 10.68 (s, 1H), 8.70 (s, 1H), 8.66 (s, 1H), 8.48 (br s, 1H), 8.41 (s, 1H), 8.36 (s, 1H), 7.95 (br s, 1H), 7.63 (d, J=8.85Hz, 2H), 7.47 (d, J=8.85Hz, 2H), 7.22 (m, 1H), 7.16 (t, J=8.24Hz, 1H), 6.89 (d, J=7.93Hz, 1H), 6.54 (m, 1H), 4.00 (t, J=6.41Hz, 2H), 3.56 (t, J=6.41Hz, 2H), 1.86 (m, 2H).

Example 127 This example was prepared by substituting tert-butyl 4-(aminomethyl)phenylcarbamate for EXAMPLE 1C in EXAMPLE 1D, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom and isocyanatobenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.50 (t, J=6.14Hz, 1H), 9.06 (s, 1H), 8.68 (s, 1H), 8.66 (s, 1H), 8.31 (s, 1H), 8.27 (s, 1H), 7.81 (br s, 1H), 7.43 (m, 4H), 7.27 (m, 4H), 6.96 (t, J=7.36Hz, 1H), 4.44 (d, J=5.83Hz, 2H).

### Example128

This example was prepared by substituting tert-butyl 4-(aminomethyl)phenylcarbamate for EXAMPLE 1C in EXAMPLE 1D, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom for EXAMPLE 45C in EXAMPLE 45D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.52 (t, J=5.83Hz, 1H), 9.21 (br s, 1H), 8.67 (s, 1H) 8.59 (s, 1H), 8.34 (s, 1H), 8.30 (s, 1H), 7.92 (br s, 1H), 7.43 (d, J=8.59Hz, 2H), 7.29 (d, J=5.83Hz, 2H), 7.25 (s, 1H), 7.21 (d, J=8.59Hz, 1H), 7.14 (m, 1H), 6.78 (d, J=7.98Hz, 1H), 4.44 (d, J=5.83Hz, 2H), 2.27 (s, 3H).

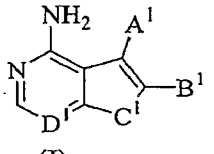
### Example129

This example was prepared by substituting tert-butyl 4-(aminomethyl)phenylcarbamate for EXAMPLE 1C in EXAMPLE 1D, removing the Boc with TFA as described in EXAMPLE 1C and substituting the product therefrom and 1-fluoro-3-isocyanatobenzene for EXAMPLE 45C and 1-isocyanato-3-methylbenzene, respectively, in EXAMPLE 45D. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.52 (t, J=5.83Hz, 1H), 9.18 (brs, 1H), 8.95 (s, 1H), 8.80 (s, 1H), 8.34 (s, 1H), 8.30 (s, 1H), 7.91 (br s, 1H), 7.49 (m, 1H), 7.43 (d, J=8.59Hz, 2H), 7.29 (m, 3H), 7.11 (m, 1H), 6.77 (s, 1H), 4.45 (d, J=5.83Hz, 2H).

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),

or a therapeutically acceptable salt 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 $R^5$;

$R^1$ is $R^2$, $R^3$, $R^4$ or $R^5$;

$R^2$ 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;

$R^4$ 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;

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

$R^6$ is $R^7$, $R^8$ or $R^9$;

$R^7$ 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;

$R^9$ 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;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $S(O)R^{10}$, $SO_2R^{10}$, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$, $NHC(O)NHR^{10}$, $NHC(O)N(R^{10})_2$, $NR^{10}C(O)NHR^{10}$, $NR^{10}C(O)N(R^{10})_2$, $SO_2NHR^{10}$, $SO_2N(R^{10})_2$, $NHSO_2R^{10}$, $NR^1SO_2R^{10}$, $OC(O)OR^{10}$, $NHC(O)OR^{10}$ or $NR^1C(O)OR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{11A}$; $R^{11A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{12}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{12A}$; $R^{12A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{13}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{13A}$; $R^{13A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{14}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{15}$ or $NHC(O)NHR^{15}$;

$R^{15}$ is $R^{16}$, $R^{17}$ $R^{18}$;

$R^{16}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{16A}$; $R^{16A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{17}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{17A}$; $R^{17A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{18}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{18A}$; $R^{18A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$B^1$ is H, $R^{19}$, $C(O)NHR^{19}$, $C(O)N(R^{19})_2$, $NHC(O)R^{19}$, $NR^1C(O)R^{19}$, $NHC(O)NHR^{19}$, $NHC(O)N(R^{19})_2$, $NR^{19}C(O)NHR^{19}$, $NR^1C(O)N(R^{19})_2$, $SO_2NHR^{19}$, $SO_2N(R^{19})_2$, $NHSO_2R^{19}$, $NR^{19}SO_2R^{19}$, $OC(O)OR^{19}$, $NHC(O)OR^{19}$, or $NR^{19}C(O)OR^{19}$;

$R^{19}$ is $R^{20}$, $R^{21}$, $R^{22}$ or $R^{23}$;

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

$R^{21}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{21A}$; $R^{21A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{22}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{22A}$; $R^{22A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{23}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{24}$, $OR^{24}$, $SR^{24}$, $S(O)R^{24}$, $SO_2R^{24}$, $NH_2$, $NHR^{24}$, $N(R^{24})_2$, $C(O)R^{24}$, $C(O)NH_2$, $C(O)NHR^{24}$, $C(O)N(R^{24})_2$, $NHC(O)R^{24}$, $NR^{24}C(O)R^{24}$, $NHSO_2R^{24}$, $NR^{24}SO_2R^{24}$, $NHC(O)OR^{24}$, $NR^{24}C(O)OR^{24}$, $SO_2NH_2$, $SO_2NHR^{24}$, $SO_2N(R^{24})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{24}$, $NHC(O)N(R^{24})_2$, $NR^{24}C(O)N(R^{24})_2$, OH, (O), C(O)OH, CN, $NH_2$, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{24}$ is $R^{25}$, $R^{26}$, $R^{27}$,
alkyl, alkenyl or alkynyl;

$R^{25}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{25A}$; $R^{25A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{26}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{26A}$; $R^{26A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{27}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{27A}$; $R^{27A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$C^1$ is O, S, S(O), $SO_2$, NH, or $N(C^2)$;

$C^2$ is $R^{28}$, $R^{29}$, $R^{30}$ or $R^{31}$;

$R^{28}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{28A}$; $R^{28A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{29}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{29A}$; $R^{29A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{30}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{30A}$; $R^{30A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{31}$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^{32}$, $OR^{32}$, $SR^{32}$, $S(O)R^{32}$, $SO_2R^{32}$, $NH_2$, $NHR^{32}$, $N(R^{32})_2$, $C(O)R^{32}$, $C(O)NH_2$, $C(O)NHR^{32}$, $C(O)N(R^{32})_2$, $NHC(O)R^{32}$, $NR^{32}C(O)R^{32}$, $NHSO_2R^{32}$, $NR^{32}SO_2R^{32}$, $NHC(O)OR^{32}$, $NR^{32}C(O)OR^{32}$, $SO_2NH_2$, $SO_2NHR^{32}$, $SO_2N(R^{32})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{32}$, $NHC(O)N(R^{32})_2$, $NR^{32}C(O)N(R^{32})_2$, OH, (O), C(O)OH, CN, $NH_2$, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

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

$R^{33}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{33A}$; $R^{33A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{34}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{34A}$; $R^{34A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{35}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{35A}$; $R^{35A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$D^1$ is N, CH or $C(D^2)$;

$D^2$ is $R^{36}$, $R^{37}$, $R^{38}$ or $R^{39}$;

$R^{36}$ 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;

$R^{38}$ 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;

$R^{39}$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^{40}$, $OR^{40}$, $SR^{40}$, $S(O)R^{40}$, $SO_2R^{40}$, $NH_2$, $NHR^{40}$, $N(R^{40})_2$, $C(O)R^{40}$, $C(O)NH_2$, $C(O)NHR^{40}$, $C(O)N(R^{40})_2$, $NHC(O)R^{40}$, $NR^{40}C(O)R^{40}$, $NHSO_2R^{40}$, $NR^{40}SO_2R^{40}$, $NHC(O)OR^{40}$, $NR^{40}C(O)OR^{40}$, $SO_2NH_2$, $SO_2NHR^{40}$, $SO_2N(R^{40})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{40}$, $NHC(O)N(R^{40})_2$, $NR^{40}C(O)N(R^{40})_2$, OH, (O), C(O)OH, CN, $NH_2$, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{40}$ is $R^{41}$, $R^{42}$ or $R^{43}$;

$R^{41}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{41A}$; $R^{41A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{42}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{42A}$; $R^{42A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{43}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{43A}$; $R^{43A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, $OR^{44}$, $SR^{44}$, $S(O)R^{44}$, $SO_2R^{44}$, $NH_2$, $NHR^{44}$, $N(R^{44})_2$, $C(O)R^{44}$, $C(O)OR^{44}$, $C(O)NH_2$, $C(O)NHR^{44}$, $C(O)N(R^{44})_2$, $NHC(O)R^{44}$, $NR^{44}C(O)R^{44}$, $NHSO_2R^{44}$, $NR^{44}SO_2R^{44}$, $NHC(O)OR^{44}$, $NR^{44}C(O)OR^{44}$, $SO_2NH_2$, $SO_2NHR^{44}$, $SO_2N(R^{44})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{44}$, $NHC(O)N(R^{44})_2$, $NR^{44}C(O)N(R^{44})_2$, $C(N)NH_2$, $C(N)NHR^{44}$, $C(N)N(R^{44})_2$, $NHC(N)NH_2$, $NHC(N)NHR^{44}$, $NHC(N)N(R^{44})_2$, OH, (O), C(O)H, C(O)OH, $NO_2$, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{44}$ is $R^{45}$, $R^{46}$, $R^{47}$ or $R^{48}$;

$R^{45}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{45A}$; $R^{45A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{46}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{46A}$; $R^{46A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{47}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{47A}$; $R^{47A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{48}$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^{49}$, $OR^{49}$, $SR^{49}$, $S(O)R^{49}$, $SO_2R^{49}$, $NH_2$, $NHR^{49}$, $N(R^{49})_2$, $C(O)R^{49}$, $C(O)NH_2$, $C(O)NHR^{49}$, $C(O)N(R^{49})_2$, $NHC(O)R^{49}$, $NR^{49}C(O)R^{49}$, $NHSO_2R^{49}$, $NR^{49}SO_2R^{49}$, $NHC(O)OR^{49}$, $NR^{49}C(O)OR^{49}$, $SO_2NH_2$, $SO_2NHR^{49}$, $SO_2N(R^{49})_2$, $NHC(O)NH_2$, $NHC(O)NHR^{49}$, $NHC(O)N(R^{49})_2$, $NR^{49}C(O)N(R^{49})_2$, $OP(O)(OH)_2$, $OP(O)(OH)(OR^{44})$, $OP(O)(OR^{44})_2$, OH, (O), C(O)OH, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{49}$ is $R^{50}$, $R^{51}$, $R^{52}$, alkyl, alkenyl or alkynyl;

$R^{50}$ is phenyl which is unfused or fused with benzene, heteroarene or $R^{50A}$; $R^{50A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

$R^{51}$ is heteroaryl which is unfused or fused with benzene, heteroarene or $R^{51A}$; $R^{51A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene; and

$R^{52}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene, heteroarene or $R^{52A}$; $R^{52A}$ is cycloalkane, cycloalkene, heterocycloalkane or heterocycloalkene;

wherein the moieties represented by $R^{45}$, $R^{46}$, $R^{47}$ and $R^{49}$ are independently unsubstituted or substituted with one or two or three of four of independently selected alkyl, alkenyl, alkynyl, OH, (O), C(O)OH, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I.

2. The compound of claim 1, or a therapeutically acceptable salt 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 $R^5$;

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

$R^2$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^3$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^4$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

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

$R^6$ is $R^7$, $R^8$ or $R^9$;

$R^7$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^8$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^9$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $S(O)R^{10}$, $SO_2R^{10}$, $NH_2$, $NHR^{10}$, $N(R^{10})_2$, $C(O)R^{10}$, $C(O)OR^{10}$, $C(O)NHR^{10}$, $C(O)N(R^{10})_2$, $NHC(O)R^{10}$, $NR^{10}C(O)R^{10}$ or $NHC(O)NHR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{12}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{13}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{14}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{15}$ or $NHC(O)NHR^{15}$;

$R^{15}$ is $R^{16}$, $R^{17}$ $R^{18}$;

$R^{16}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{17}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{18}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$B^1$ is H or $R^{19}$;

$R^{19}$ is $R^{20}$, $R^{21}$, $R^{22}$ or $R^{23}$;

$R^{20}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{21}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{22}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{23}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{24}$, $OR^{24}$, $N(R^{24})_2$, $C(O)N(R^{24})_2$, $NHC(O)R^{24}$, $NR^{24}C(O)R^{24}$;

$R^{24}$ is alkyl, alkenyl or alkynyl;

$C^1$ is O, S, S(O), $SO_2$, NH, or $N(C^2)$;

$C^2$ is $R^{28}$, $R^{29}$ or $R^{30}$;

$R^{28}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{29}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{30}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$D^1$ is N, CH or $C(D^2)$;

$D^2$ is $R^{36}$, $R^{37}$ or $R^{38}$;

$R^{36}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{37}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

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

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, $OR^{44}$, $SR^{44}$, $S(O)R^{44}$, $SO_2R^{44}$, $NH_2$, $NHR^{44}$, $N(R^{44})_2$, $C(O)R^{44}$, $C(O)OR^{44}$, $C(O)NH_2$, $C(O)NHR^{44}$, $C(O)N(R^{44})_2$, $NHC(O)R^{44}$, OH, (O), C(O)H, C(O)OH, $NO_2$, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{44}$ is $R^{45}$, $R^{46}$, $R^{47}$ or $R^{48}$;

$R^{45}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{46}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{47}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{48}$ is alkyl substituted with $OP(O)(OH)_2$;

wherein the moieties represented by $R^{45}$, $R^{46}$ and $R^{47}$ are independently unsubstituted or substituted with one or two or three of four of independently selected alkyl, alkenyl, alkynyl, OH, (O), C(O)OH, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I.

3. The compound of claim 2, or a therapeutically acceptable salt thereof, wherein $A^1$ is $C(O)NHR^1$ or $R^5$;

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

$R^2$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^3$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^4$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^5$ is alkyl, alkenyl or alkynyl, each of which is substituted with one or two of independently selected $R^6$, $NHC(O)NHR^6$;

$R^6$ is $R^7$, $R^8$ or $R^9$;

$R^7$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^8$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^9$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $S(O)R^{10}$, $SO_2R^{10}$, $NH_2$, $NHC(O)R^{10}$, $NHC(O)NHR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{12}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{13}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{14}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{15}$ or $NHC(O)NHR^{15}$;

$R^{15}$ is $R^{16}$, $R^{17}$ $R^{18}$;

$R^{16}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{17}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{18}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$B^1$ is H or $R^{19}$;

$R^{19}$ is $R^{20}$, $R^{21}$, $R^{22}$ or $R^{23}$;

$R^{20}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{21}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{22}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{23}$ is alkyl, alkenyl or alkynyl, each of which is unsubstituted or substituted with one or two of independently selected $R^{24}$, $OR^{24}$ or $N(R^{24})_2$;

$R^{24}$ is alkyl, alkenyl or alkynyl;

$C^1$ is O, S, S(O), $SO_2$, NH, or $N(C^2)$;

$C^2$ is $R^{28}$, $R^{29}$ or $R^{30}$;

$R^{28}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{29}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{30}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$D^1$ is N, CH or $C(D^2)$;

$D^2$ is $R^{36}$, $R^{37}$ or $R^{38}$;

$R^{36}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{37}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

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

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, $OR^{44}$, CN, $CF_3$, $OCF_3$, $CF_2CF_3$, F, Cl, Br or I;

$R^{44}$ is $R^{45}$, $R^{46}$, $R^{47}$ or $R^{48}$;

$R^{45}$ is phenyl which is unfused or fused with benzene or heteroarene;

$R^{46}$ is heteroaryl which is unfused or fused with benzene or heteroarene;

$R^{47}$ is cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, each of which is unfused or fused with benzene or heteroarene;

$R^{48}$ is alkyl substituted with $OP(O)(OH)_2$;

wherein the moieties represented by $R^{45}$, $R^{46}$, and $R^{47}$ are independently unsubstituted or substituted with one or two or three of four of independently selected alkyl.

4. The compound of claim 3, or a therapeutically acceptable salt thereof, wherein $A^1$ is $C(O)NHR^1$ or $R^5$;

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

$R^2$ is phenyl;

$R^3$ is heteroaryl;

$R^4$ is cycloalkyl or heterocycloalkyl;

$R^5$ is alkyl, alkenyl or alkynyl, each of which is substituted with $R^6$, $NHC(O)NHR^6$;

$R^6$ is $R^7$or $R^9$;

$R^7$ is phenyl;

$R^8$ is heteroaryl;

$R^9$ is heterocycloalkyl;

wherein the moieties represented by $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are independently substituted with one or two of independently selected $R^{10}$, $OR^{10}$, $SR^{10}$, $SO_2R^{10}$, $NH_2$, $NHC(O)R^{10}$, $NHC(O)NHR^{10}$;

$R^{10}$ is $R^{11}$, $R^{12}$, $R^{13}$ or $R^{14}$;

$R^{11}$ is phenyl;

$R^{12}$ is heteroaryl;

$R^{13}$ is cycloalkyl;

$R^{14}$ is alkylwhich is unsubstituted or substituted with $R^{16}$ or $NHC(O)NHR^{16}$;

$R^{16}$ is phenyl;

$B^1$ is H or $R^{19}$;

$R^{19}$ is $R^{21}$, $R^{22}$ or $R^{23}$;

$R^{21}$ is heteroaryl;

$R^{22}$ is heterocycloalkyl;

$R^{23}$ is alkynyl, which is unsubstituted or substituted with $R^{24}$, $OR^{24}$ or $N(R^{24})_2$;

$R^{24}$ is alkyl;

$C^1$ is S or $N(C^2)$;

$C^2$ is $R^{30}$;

$R^{30}$ is cycloalkyl;

$D^1$ is N, CH or $C(D^2)$;

$D^2$ is $R^{37}$;

$R^{37}$ is heteroaryl;

wherein each foregoing cyclic moiety is independently unsubstituted or substituted or further unsubstituted or further substituted with one or two or three or four of independently selected $R^{44}$, $OR^{44}$, CN, $CF_3$, F, Cl, Br or I;

$R^{44}$ is $R^{47}$ or $R^{48}$;

$R^{47}$ is heterocycloalkyl;

$R^{48}$ is alkyl substituted with $OP(O)(OH)_2$;

wherein $R^{47}$ is unsubstituted or substituted with alkyl.

5. A composition comprising an excipient and a therapeutically effective amount of a compound of claim 1.

6. A method of treating cancer in a mammal comprising administering thereto a therapeutically effective amount of a compound of claim 1.

7. The method of claim 6, wherein the cancer is 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.

8. A method of treating cancer in a mammal comprising administering thereto a therapeutically effective amount of a compound of claim 1 and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent, with or without radiation.

9. The method of claim 8, wherein the cancer is breast cancer, cervical cancer, colon cancer, endometrial cancer, esophageal cancer, leukemia, lymphoma, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer or thyroid cancer.