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# United States Patent [19]

**Maduskuie, Jr. et al.**

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[54] **N-(AMIDINOPHENYL) CYCLOUREA ANALOGS AS FACTOR XA INHIBITORS**

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[73] Assignee: **DuPont Pharmaceuticals Company**, Wilmington, Del.

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**Related U.S. Application Data**

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[51] **Int. Cl.**[6] ..... **A61K 31/55**; C07D 243/10; C07D 487/04

[52] **U.S. Cl.** ..... **514/221**; 540/500; 540/502; 540/503

[58] **Field of Search** ..... 514/221; 540/500, 540/502, 503

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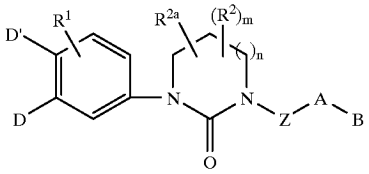
[57] **ABSTRACT**

The present application describes N-(amidinophenyl) cyclourea analogs of formula I:

I




which are useful as inhibitors of factor Xa.

**20 Claims, No Drawings**

# N-(AMIDINOPHENYL) CYCLOUREA ANALOGS AS FACTOR XA INHIBITORS

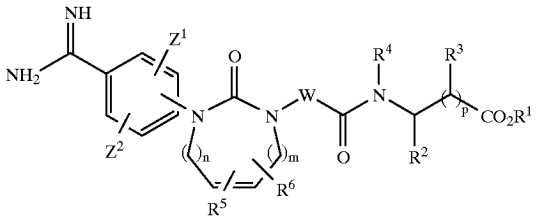
This application claims benefit of provisional application 60/015684 filed Apr. 17, 1996.

## FIELD OF THE INVENTION

This invention relates generally to N-(amidinophenyl) cyclourea analogs which are inhibitors of factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

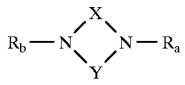
## BACKGROUND OF THE INVENTION

Bovy et al, U.S. Pat. No. 5,430,043 describe phenyl amidines of the formula:



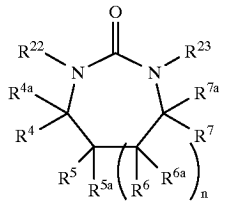
which are reported to be platelet aggregation inhibitors. However, no mention is made of inhibiting Factor Xa.

Himmelsbach et al, CA 2,105,934, address cyclic ureas of the formula:



wherein, among the multitude of choices, X may be a carbonyl, Y may be an $C_{2-4}$ alkylene, $R_a$ may be A—B—C— and $R_b$ may be —D—E—F. Group F is selected from —$CO_2$R, phosphono, tetrazolyl, and $R_8$CO—O—$CHR_9$—O—CO—. The compounds described by the above formula are alleged to have aggregation inhibiting and/or fibrinogen binding properties. Factor Xa inhibiting is not discussed.

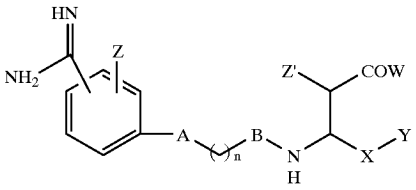
Lam et al, WO 94/19329, report cyclic carbonyls which may be cyclic ureas of the formula:



wherein at least one of $R^4$, $R^{4a}$, $R^7$, and $R^{7a}$ is other than hydrogen. Compounds of this sort are said to be useful as HIV protease inhibitors. N-(Amidinophenyl)cycloureas are not suggested as factor Xa inhibitors.

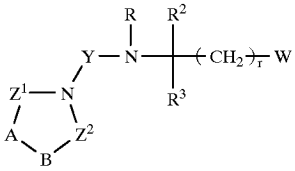
Currie et al, WO 96/36639, set forth amidine derivatives of the formula:





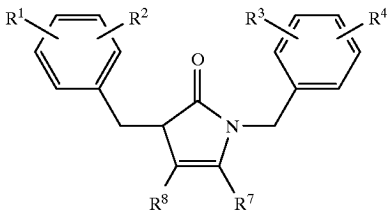
wherein A may be a 6-membered cyclic urea, which may be useful as anti-platelet aggregation inhibitors. However, Y is nitrate, nitrite, or a nitric oxide donating group. The present compounds, in contrast, do not contain the nitric oxide donating groups of WO 96/36639.

Klinger et al, WO 94/21607, illustrate heterocyclic compounds of the formula:



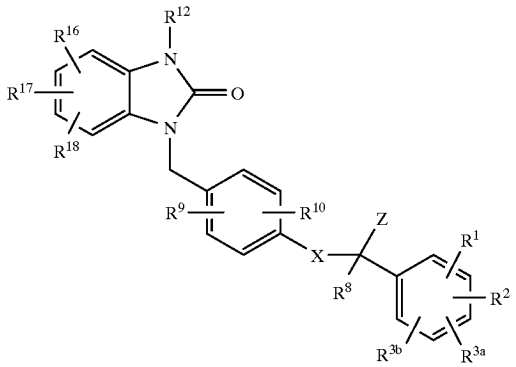
wherein, upon judicious selection of variables, $Z^1$ may be a carbonyl, A may be $NR^1$, $R^1$ may be an amidino-substituted phenyl, and B and $Z^2$ may each be $CH_2$. However, the present compounds do not include the right-side chain shown above.

Mohan et al, WO 96/38421, describe N,N-di(arylmethyl) cyclic urea derivatives of the formula:



wherein $R^7$ and $R^8$ may combine to form a benzene ring and the double bond shown may be absent, which may be useful as Factor Xa inhibitors. These compounds are preferably bis-amidino substituted. However, the presently claimed compounds are neither bis-benzyl nor bis-amidino substituted.

Chakravarty et al, WO 95/03044, discuss benzimidazoles substituted with phenoxyphenylacetic acid dervatives of the formula:



wherein $R^{12}$ may be a substituted aryl group. But, this reference does not consider amidino-phenyl groups. Furthermore, the present compounds do not contain the above variable Z, which is defined as a carbonyl, sulfonyl, or phosphoryl group.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, $Ca^{2+}$ and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: *Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. Thromb. Res.* 1979, 15, 617–629), inhibition of factor Xa may be more efficient that inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

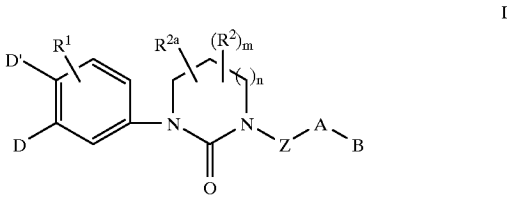
## SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel N-(amidinophenyl)cyclourea factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

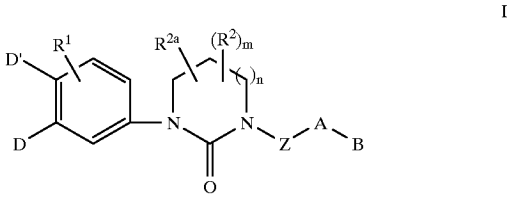
These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):



or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, $R^1$, $R^2$, m and n are defined below, are effective factor Xa inhibitors.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides novel compounds of formula I:



or stereoisomers or pharmaceutically acceptable salt forms thereof, wherein;

one of D and D' is selected from CN, $C(=NR^{11})NR^{12}R^{13}$, $NHC(=NR^{11})NR^{12}R^{13}$, $NR^{12}CH(=NR^{11})$, $C(O)NR^{12}R^{13}$, and $(CH_2)_rNR^{12}R^{13}$ and the other is H;

$R^1$ is selected from H, $(CH_2)_rOR^3$, halo, $C_{1-4}$ alkyl, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNR^4SO_2R^5$;

$R^2$ is selected from H, =O, $C_{1-4}$ alkyl substituted with 0, 1, or 2 $R^7$, $C_{2-6}$ alkenyl substituted with 0, 1, or 2 $R^7$, $(CH_2)_rOR^3$, $(CH_2)_rC(O)R^4$, $(CH_2)_rOC(O)R^4$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rNR^3C(O)R^4$, $(CH_2)_rSO_2R^5$, $(CH_2)_rNR^3SO_2R^5$, $C_{3-10}$ carbocyclic residue substituted with 0–2 $R^6$; and, 5–10 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^6$;

$R^{2a}$ is absent;

alternatively, $R^2$ and $R^{2a}$ may be present on adjacent carbon atoms and combine to form a benzene ring substituted with 0–2 $R^{10}$ or a 5–6 membered aromatic heterocycle containing 0–2 heteratoms selected from the group consisting of N, O, and S and substituted with 0–2 $R^{10a}$;

$R^3$ and $R^{3'}$ are independently selected from H, $C_{1-4}$ alkyl, benzyl and phenyl;

$R^3$ and $R^{3'}$ may be taken together to form a 5 or 6 membered ring substituted with 0–2 $R^6$;

$R^4$ and $R^{4'}$ are independently selected from H, $OR^3$, $C_{1-4}$ alkyl, phenyl and $NR^3R^{3'}$;

$R^5$ is selected from $C_{1-4}$ alkyl, phenyl and $NR^3R^{3'}$;

Z is selected from a bond, $C_{1-4}$ alkylene, $(CH_2)_rO(CH_2)_r$, $(CH_2)_2NR^3(CH_2)_r$, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)O(CH_2)_r$, $(CH_2)_2OC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)O(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_2NR^3SO_2(CH_2)_r$, and $(CH_2)_2NR^3SO_2NR^3(CH_2)_r$;

A is selected from:
$C_{3-10}$ carbocyclic residue substituted with 0–2 $R^6$, and 5–10 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^6$;

B is selected from:
X—Y, $NR^3R^{3'}$, $C(O)NR^3R^{3'}$, $SO_2NR^3R^{3'}$,
benzyl substituted with 0–2 $R^6$,
$C_{3-10}$ carbocyclic residue substituted with 0–2 $R^6$, and 5–10 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^6$;

X is selected from $C_{1-4}$ alkylene, —C(O)—, —C(O)$CR^3R^{3'}$, —$CR^3R^{3'}$C(O)—, —C(O)O—, —C(O)$OCR^3R^{3'}$—, —$CR^3R^{3'}$C(O)O—, —OC(O)—, —OC(O)$CR^3R^{3'}$—, —$CR^3R^{3'}$OC(O)—, —$S(O)_p$—, —$S(O)_pCR^3R^{3'}$—, —$CR^3R^{3'}S(O)_p$—, —$S(O)_2NR^3$—, —$NR^3S(O)_2$—, —$NR^3S(O)_2CR^3R^{3'}$—, —$CR^3R^{3'}S(O)_2NR^3$—, —$NR^3S(O)_2NR^3$—, —C(O)$NR^3$—, —$NR^3$C(O)—, —C(O)$NR^3CR^3R^{3'}$—, —$NR^3C(O)CR^3R^{3'}$—, —$CR^3R^{3'}C(O)NR^3$—, —$CR^3R^{3'}NR^3C(O)$—, —$NR^3$C(O)O—, —$OC(O)NR^3$—, —$NR^3C(O)NR^3$—, —$NR^3$—, —$NR^3CR^3R^{3'}$—, —$CR^3R^{3'}NR^3$—, O, —$CR^3R^{3'}O$—, —$OCR^3R^{3'}$—, S, —$CR^3R^{3'}S$—, and —$SCR^3R^{3'}$—;

Y is selected from:
$C_{1-4}$ alkyl substituted with 0–2 $R^6$
$C_{3-10}$ carbocyclic residue substituted with 0–2 $R^6$, and 5–10 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^6$;

$R^6$ is selected from H, OH, $CF_3$, $(CH_2)_nOR^3$, halo, $C_{1-4}$ alkyl, CN, $NO_2$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3'}$, $NR^3C(O)NR^3R^{3'}$, $SO_2NR^3R^{3'}$, $NR^3SO_2NR^3R^{3'}$, $NR^3SO_2$—$C_{1-4}$ alkyl, $SO_2$-phenyl, and $NR^3SO_2R^8$;

$R^7$ is selected from:
$C_{3-10}$ carbocyclic residue substituted with 0–2 $R^6$; and, 5–10 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^6$;

$R^8$ is selected from:
$C_{3-10}$ carbocyclic residue substituted with 0–2 $R^9$; and, 5–10 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^9$;

$R^9$ is selected from H, OH, $(CH_2)_nOR^3$, halo, $C_{1-4}$ alkyl, CN, $NO_2$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3'}$, $NR^3C(O)NR^3R^{3'}$, $SO_2NR^3R^{3'}$, $NR^3SO_2NR^3R^{3'}$, and $NR^3SO_2$—$C_{1-4}$ alkyl;

$R^{10}$ is selected from H, $OR^3$, halo, $C_{1-4}$ alkyl, CN, $NO_2$, $NR^3R^{3'}$, $NR^3C(O)R^{3'}$, $NR^3C(O)OR^{3'}$, $NR^3SO_2$-phenyl, and $NR^3SO_2$—$C_{1-4}$ alkyl;

$R^{10a}$ if a substituent on nitrogen is selected from H and $C_{1-4}$ alkyl;

$R^{10a}$ if a substituent on carbon is selected from H, $C_{1-4}$ alkyl, $NR^3R^{3'}$, $NR^3C(O)R^{3'}$, $NR^3C(O)OR^{3'}$, $NR^3SO_2$-phenyl, and $NR^3SO_2$—$C_{1-4}$ alkyl;

$R^{11}$ is selected from H, OH, $C_{1-6}$ alkyl, $C_{1-6}$ alkylcarbonyl, $C_{1-6}$ alkoxy, $C_{1-4}$ alkoxycarbonyl, $C_{6-10}$ aryloxy, $C_{6-10}$ aryloxycarbonyl, $C_{6-10}$ arylmethylcarbonyl, $C_{1-4}$ alkylcarbonyloxy $C_{1-4}$ alkoxycarbonyl, $C_{6-10}$ arylcarbonyloxy $C_{1-4}$ alkoxycarbonyl, $C_{1-6}$ alkylaminocarbonyl, phenylaminocarbonyl, and phenyl $C_{1-4}$ alkoxycarbonyl;

$R^{12}$ is selected from H, $C_{1-6}$ alkyl and $(CH_2)_n$-phenyl;

$R^{13}$ is selected from H, $C_{1-6}$ alkyl and $(CH_2)_n$-phenyl;

n is selected from 0, 1, 2, and 3;

m is selected from 0 and 1;

p is selected from 0, 1, and 2;

q is selected from 1, 2, 3, 4, and 5; and

r is selected from 0, 1, and 2.

[2] In a preferred embodiment, the present invention provides compounds of formula I wherein:

D is $C(=NH)NH_2$;

D' is H;

$R^1$ is selected from H, $(CH_2)_rOR^3$, halo, $(CH_2)_rNR^4R^{4'}$, $(CH_2)_rCO_2H$, $(CH_2)_rC(=O)R^4$, $(CH_2)_rNR^4C(=O)R^4$, $(CH_2)_rSO_2R^5$, and $(CH_2)_rNHSO_2R^5$;

$R^2$ is selected from H, =O, $(CH_2)_rOR^3$, $(CH_2)_rC(O)R^4$, $(CH_2)_rOC(O)R^4$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rNR^3C(O)R^4$, $(CH_2)_rSO_2R^5$, $(CH_2)_rNR^3SO_2R^5$, $C_{3-10}$ carbocyclic residue substituted with 0–2 $R^6$; and, 5–10 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^6$;

$R^4$ and $R^{4'}$ are independently selected from H, $OR^3$, $C_{1-4}$ alkyl, and $NR^3R^{3'}$;

$R^5$ is selected from $C_{1-4}$ alkyl and $NR^3R^{3'}$;

Z is selected from a bond, $C_{1-4}$ alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2OC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)O(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, $(CH_2)_rS(O)_p(CH_2)_r$, $(CH_2)_rSO_2NR^3(CH_2)_r$, $(CH_2)_2NR^3SO_2(CH_2)_r$, and $(CH_2)_2NR^3SO_2NR^3(CH_2)_r$; and,

X is selected from $C_{1-4}$ alkylene, —C(O)—, —C(O)$CR^3R^{3'}$, —$CR^3R^{3'}$C(O)—, —C(O)O—, —C(O)$OCR^3R^{3'}$, —$CR^3R^{3'}$C(O)O—, —OC(O)—, —OC(O)$CR^3R^{3'}$, —$CR^3R^{3'}$OC(O)—, —$S(O)_p$—, —$S(O)_pCR^3R^{3'}$—, —$CR^3R^{3'}S(O)_p$—, —$S(O)_2NR^3$—, —C(O)$NR^3$—, —$NR^3$C(O)—, —$NR^3C(O)NR^3$—, —$NR^3$C(O)O—, —$OC(O)NR^3$—, —$NR^3C(O)NR^3$—, —$NR^3$—, —$NR^3CR^3R^{3'}$—, —$CR^3R^{3'}NR^3$—, O, —$CR^3R^{3'}O$—, and —$OCR^3R^{3'}$—.

[3] In a more preferred embodiment, the present invention provides compounds of formula I wherein:

$R^1$ is selected from H, $OR^3$, $(CH_2)OR^3$, halo, $NR^4R^{4'}$, $(CH_2)NR^4R^{4'}$, $C(=O)R^4$, $(CH_2)C(=O)R^4$, $NHC(=O)R^4$, $(CH_2)NHC(=O)R^4$, $SO_2R^5$, $(CH_2)SO_2R^5$, $NHSO_2R^5$, and $(CH_2)NHSO_2R^5$;

$R^2$ is selected from H, =O, $OR^3$, $C(O)R^4$, $(CH_2)C(O)R^4$, $OC(O)R^4$, $NR^4R^{4'}$, $NR^3C(O)R^4$, and $NR^4SO_2R^5$;

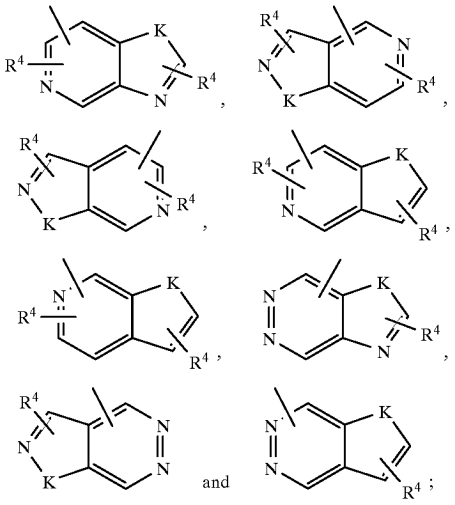
A is selected from:
$C_{5-6}$ carbocyclic residue substituted with 0–1 $R^6$, and 5–6 membered heterocyclic system containing from 1–2 heteroatoms selected from the group consisting of N and O substituted with 0–1 $R^6$;

B is selected from: Y, X—Y, and $NR^2R^{2a}$;

Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0–2 $R^{4a}$;
phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazole, thiadiazole, triazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, benzofuran,

benzothiofuran, indole, benzoxazole, benzthiazole, indazole, benzisoxazole, benzisothiazole, isoindazole, and benzothiadiazole;

Y may also be selected from the following bicyclic heteroaryl ring systems:



and



K is selected from O, S, NH, and N;

X is selected from —$CH_2$—, —C(O)—, —C(O)$CHR^3$—, —$CHR^3$C(O)—, —$S(O)_p$—, —$S(O)_pCR^3R^{3'}$—, —$CHR^3S(O)_p$—, —$S(O)_2NR^3$—, —C(O)$NR^3$—, —$NR^3$C(O)—, —$NR^3$—, —$NR^3CHR^3$—, and —$CHR^3NR^3$;

$R^6$ is selected from H, OH, $CF_3$, $(CH_2)_nOR^3$, halo, $C_{1-4}$ alkyl, CN, $NO_2$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3'}$, $SO_2NR^3R^{3'}$, $SO_2$-phenyl, $NR^3SO_2$—$C_{1-4}$ alkyl, and $NR^3SO_2R^8$;

$R^8$ is selected from:

$C_{5-6}$ carbocyclic residue substituted with 0–2 $R^9$; and,

5–6 membered heterocyclic system containing from 1–3 heteroatoms selected from the group consisting of N, O, and S substituted with 0–2 $R^9$;

$R^9$ is selected from H, OH, $(CH_2)_nOR^3$, halo, $C_{1-4}$ alkyl, CN, $NO_2$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3'}$, $NR^3C(O)NR^3R^{3'}$, $SO_2NR^3R^{3'}$, $NR^3SO_2NR^3R^{3'}$, and $NR^3SO_2$—$C_{1-4}$ alkyl; and,

p is 2.

[4] In an even more preferred embodiment, the present invention provides compounds of formula I wherein:

Z is selected from a bond, $C_{1-4}$ alkylene, $(CH_2)_rC(O)(CH_2)_r$, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$, and $(CH_2)_rS(CH_2)_r$;

X is selected from —$CH_2$—, —C(O)—, —C(O)$CHR^3$—, —$CHR^3$C(O)—, —$S(O)_p$—, —$S(O)_pCR^3R^{3'}$—, —$CHR^3S(O)_p$—, —$S(O)_2NR^3$—, —C(O)$NR^3$—, and —$NR^3$C(O)—;

$R^6$ is selected from H, OH, $CF_3$, $(CH_2)_nOR^3$, halo, $C_{1-4}$ alkyl, CN, $NO_2$, $(CH_2)_rNR^3R^{3'}$, $(CH_2)_rC(O)R^3$, $NR^3C(O)R^{3'}$, $SO_2NR^3R^{3'}$, $SO_2$-phenyl, and $NR^3SO_2$—$C_{1-4}$ alkyl;

m is 1; and,

r is selected from 0 and 1.

[5] In a further preferred embodiment, the present invention provides compounds of formula I wherein:

$R^3$ and $R^{3'}$ are independently selected from H and $C_{1-4}$ alkyl;

Z is selected from a bond, $C_{1-4}$ alkylene, $(CH_2)_rC(O)NR^3(CH_2)_r$, $(CH_2)_2NR^3C(O)(CH_2)_r$, and $(CH_2)_2NR^3C(O)NR^3(CH_2)_r$;

A is selected from phenyl substituted with 0–1 $R^6$ and a 6 membered heterocyclic system containing 1 N and 0–1 O atoms and substituted with 0–1 $R^6$;

X is selected from —$CH_2$—, —$S(O)_p$—, —$S(O)_pCR^3R^{3'}$—, —$S(O)_2NR^3$—, —C(O)$NR^3$—, and;

Y is selected from phenyl, i-propyl, quinolynyl, thiadizolyl, benzothiadiazolyl, thiophenyl, pyridyl, cyclohexyl, and naphthyl, each of which is substituted with 0–2 $R^6$; and,

n is selected from 0, 1, and 2.

[6] In an even further preferred embodiment, the present invention provides compounds of formula I wherein:

$R^3$ and $R^{3'}$ are independently selected from H and methyl;

Z is selected from a bond, $CH_2$, —$CH_2CH_2$—, —$CH_2CH_2CH_2$— and —$CH_2CH_2CH_2CH_2$—;

A is selected from phenyl substituted with 0–1 $R^6$, and piperidinyl substituted with 0–1 $R^6$; and,

n is 2.

[7] In a particularly preferred embodiment, the present invention provides compounds selected from:

N-(3-amidinophenyl)-N'-((4-((2-sulphonamido)phenyl)phenyl)methyl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-benzylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-2-yl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-3-yl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(picolin-4-yl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(a-phenethyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((phenyl)methane)sulfonyl)-piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(phenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(quinolin-8-yl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(2-fluorophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(4-acetamidophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(2-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(3-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-(4-aminophenyl)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((2-aminophenyl)methane)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((2-acetamido-phenyl)methane)sulfonylpiperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((thiophen-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-chlorothiophen-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((5-carbomethoxythiophen-2-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((benzo-2,1,3-thiadiazo-4-yl)sulfonyl)piperidin-4-yl)cycloheptylurea;

N-(3-amidinophenyl)-N'-(1-((cyclohexyl)sulfamido)piperidin-4-yl)cycloheptylurea;

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