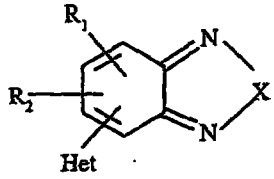
BENZOTHIADIAZOLES AND DERIVATIVES

The present invention relates to novel benzothiadiazoles and derivatives, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides a compound of formula I



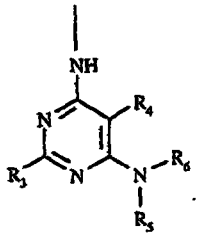
I

wherein

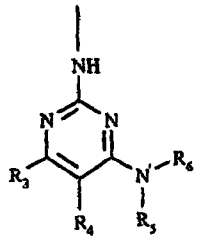
X is O, S, N-CH_3, CH=CH or CAlk = CAlk, where the Alk independently are (C_{1-4})alkyl,

R_1 and R_2 independently, are hydrogen, halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy or trifluoromethyl, and

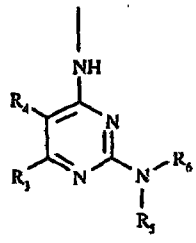
Het is a radical having one of the formulae (a) to (p) below:



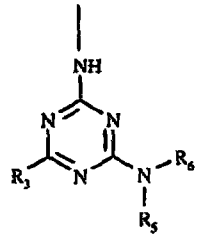
(a)



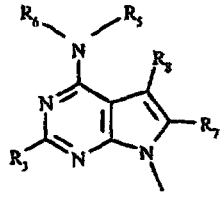
(b)



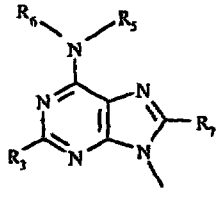
(c)



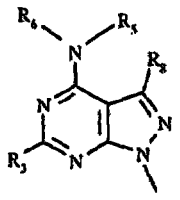
(d)



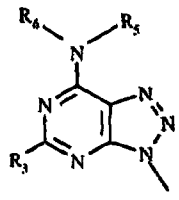
(e)



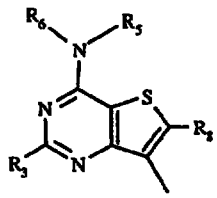
(f)



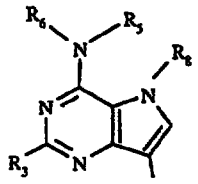
(g)



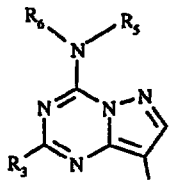
(h)



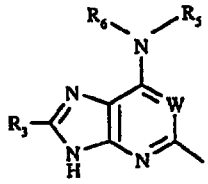
(i)



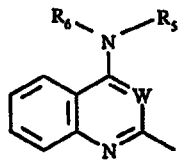
(j)



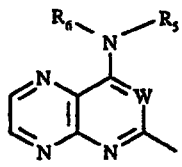
(k)



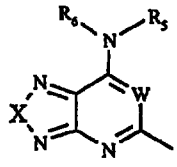
(l)



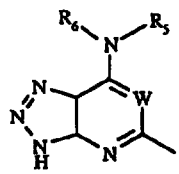
(m)



(n)



(o)



(p)

wherein

R_3 and R_8, independently, are hydrogen or (C_{1-4})alkyl,

R_4 is hydrogen, halogen, (C_{1-4})alkyl, cyano, nitro, formyl or (C_{1-4})alkylcarbonyl,

R_5 and R_6, independently, are hydrogen, (C_{1-7})alkyl, (C_{3-7})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl (C_{1-4})alkyl, (C_{1-4})alkoxy(C_{2-5})alkyl or benzyl,

R_7 is hydrogen, hydroxy, (C_{1-4})alkyl or (C_{1-4})alkoxy,

W is N, C-CN, C-NO_2, C-COH or C-CO-Alk where Alk is as defined above, and

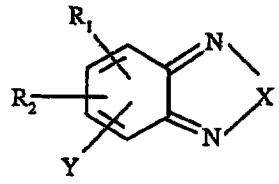
X is as defined above,

in free base or acid addition salt form.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

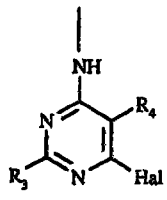
The radical Het is preferably located on a carbon atom which is adjacent to the heterocyclic moiety in formula I. Preferably Het is of formula (a) to (k), particularly of formula (a).

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, whereby a compound of formula II

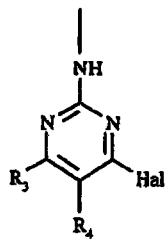


II

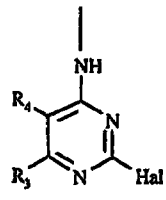
wherein X, R_1 and R_2 are as defined above and Y is a radical having one of the formulae (a') to (p') below:



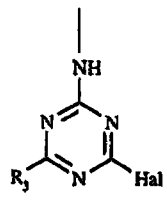
(a')



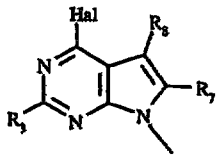
(b')



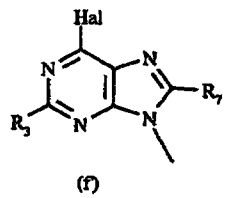
(c')



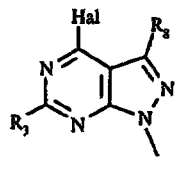
(d')



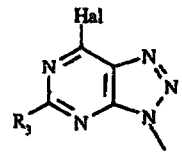
(e')



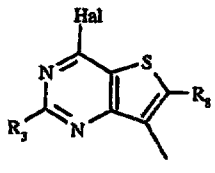
(f')



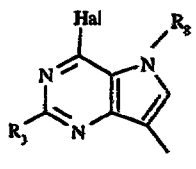
(g')



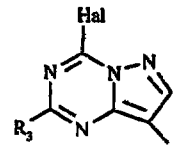
(h')



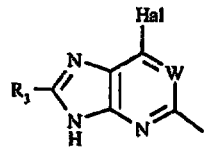
(i')



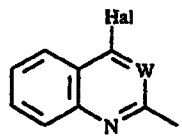
(j')

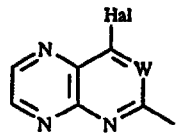


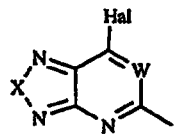
(k')

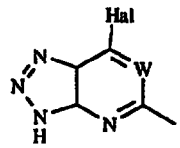


(l')

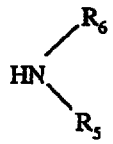

(m')


(n')


(o')


(p')

wherein R_3 to R_8, W and X are as defined above and Hal is halogen, is reacted with a compound of formula III


III

wherein R_5 and R_6 are as defined above, and the resulting compound is recovered in free base form or in acid addition salt form.

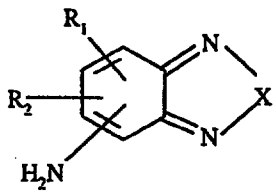
The reaction may be effected in known manner, e.g. as described in Example 1. Hal is preferably chlorine, bromine or iodine, particularly chlorine.

Working up of the reaction mixtures obtained according to the above process and purification of the compounds thus obtained may be carried out in accordance to known procedures.

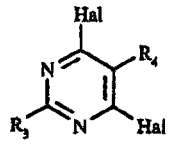
Acid addition salts may be produced in known manner from the free base forms and vice-versa. Suitable pharmaceutically acceptable acid addition salts for use in accordance with the present invention include for example the hydrochloride, the hydrogen maleate, the hydrogen fumarate and the hydrogen malonate.

The starting materials of formula II may be obtained as follows:

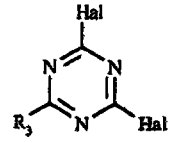
Compounds of formula II wherein Y is a radical having one of the formulae (a') and (d'), may be obtained by reacting a compound of formula IV


IV

wherein X, R_1 and R_2 are as defined above, with a compound of formula Va or Vd



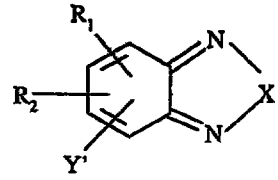
Va



Vd

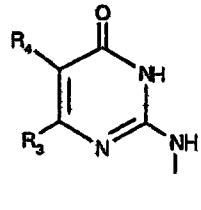
wherein R_3 and R_4 are as defined above and the Hal independently are halogen.

Compounds of formula II wherein Y is a radical having one of the formulae (b'), (c') and (e') to (l') may be obtained by reaction of $POCl_3$ with a compound of formula VI

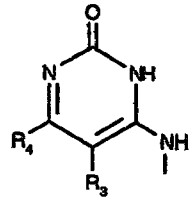


VI

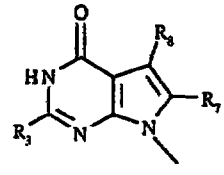
wherein Y' is a radical having one of the formulae (b"), (c") and (e") to (l") below



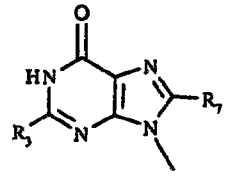
(b")



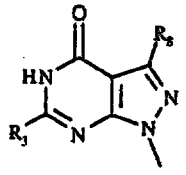
(c")



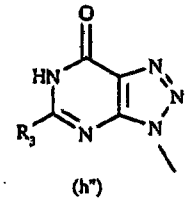
(e")



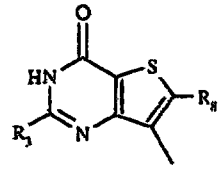
(f")



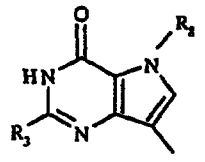
(g")



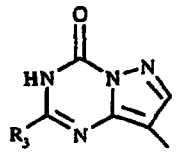
(h")



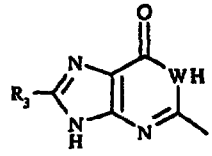
(i")



(j")



(k")



(l")

wherein R_3, R_4, R_7, R_8 and W are as defined above.

All the above mentioned reactions are conventional.

The compounds of formulae III, IV, Va, Vd and VI are know or may be obtained from known compounds, using conventional procedures.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro using corticotropine releasing factor (CRF) receptor expressing cell cultures, and in animals, and are therefore useful as pharmaceuticals.

In particular the agents of the invention bind to CRF receptors. More particularly they exhibit antagonistic activity at CRF_1 receptors, as determined in vitro in the following assay:

Chinese hamster ovary (CHO) cells expressing human recombinant CRF_1 (Chen et al., Proc Natl Acad Sci USA 90, 8967-8971, 1993) are propagated in Dulbecco's modified Eagle medium supplemented with 10% foetal calf serum, non-essential aminoacids, 100U/ml penicillin, 100 mg/l streptomycin and 1 g/l geneticin (G418). For cyclic AMP determinations, cells are grown to confluence in 24-multiwell plates. Stimulation of cyclic AMP accumulation by CRF (human/rat form) is measured in intact cells, using the [^{3}H]adenine labelling technique, as described previously (Schoeffter et al., Neuropharmacology 36, 429-437, 1997). Concentration-response curves for CRF are constructed in the presence of putative antagonists (10 μM) or vehicle (dimethyl sulfoxide 1% vol). K_B values are calculated from the rightward shifts of the control curve, according to the formula: K_B = [antagonist, M]/concentration-ratio-1), where the concentration-ratio designates the ratio of CRF EC_{50} value in the presence/CRF EC_{50} value in the absence, of antagonist [Furchgott, In: catecholamines (edited by Blaschko H and Muscholl E) pp. 283-335. Springer, Berlin, 1972].

In this test, the agents of the invention show CRF_1 antagonistic activity with Kb CRF_1 values of about 1 to 500 nM.

The agents according to the invention are therefore useful in the treatment of any state with increased endogenous level of CRF or in which the HPA (hypothalamic pituitary axis) is disregulated, or of various diseases induced or facilitated by CRF, including inflammatory disorders, such as arthritis, asthma and allergies; anxiety including generalized anxiety; phobic and panic attacks; depression; fatigue syndrome; headache; pain, e.g. inflammatory or neuropathic pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as senile dementia, Alzheimer's disease and Parkinson's disease; stroke and head trauma; epilepsy; gastrointestinal diseases; eating and body weight disorders such as obesity and anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; sleeping disorders; hormonal disregulations; skin disorders; stress-induced psychotic episodes; fertility problems; sexual dysfunctions and pre-term birth.

The utility of the agents of the invention in the above indicated diseases could be confirmed in a range of standard tests:

For example the anxiolytic activity of the agents of the invention could be confirmed in the mouse elevated plus-maze [see for example Rodgers R.J., Behavioural Pharmacology 8: 477-496 (1997) where the relevance of the elevated plus-maze is discussed on p. 486; for the method, see Rodgers R.J. et al. Ethology and Psychopharmacology (Eds SJ Cooper and CA Hendrie), pp 9-44 (1994), J. Wiley, Chichester]. In this test, the agents of the invention show anxiolytic-like effects on administration of 0.1 to 30 mg/kg p.o.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 100, preferably from about 0.5 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from yout 1 to about 500, preferably from about 1 to about 300 mg of an agent of the invention,

conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

For the above-mentioned indications a preferred compound is the compound of Example 1 below. In the above-described binding test said compound exhibits CRF_1 antagonistic activity with a Kb CRF_1 of 36 nM. In the above-described elevated plus-maze, doses of 0.1 to 10 mg/kg p.o. (with a maximum at 3mg/kg) significantly affect the anxiety-related behavioural parameters. In contrast to the standard chlordiazepoxide, parameters related to motor stimulation are not affected, which indicates that the observed anxiolytic effects are not attributable to a general motor stimulation.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of diseases induced or facilitated by CRF, such as these indicated above.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from 0.25 to about 25 mg of a compound according to the invention.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above.

In still a further aspect the present invention provides a method for the treatment of any condition mentioned above, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention. The temperatures are given in degrees Celsius and are uncorrected.

Example 1: 5,7-dimethyl-4-[2,5-dimethyl-6-(di-n-propyl)-amino-pyrimidin-4-yl]-amino-2,1,3-benzothiadiazole

A solution of 4-(4-chloro-2,5-dimethyl-pyrimidin-6-yl)-amino-5,7-dimethyl-2,1,3-benzothiadiazole (3.5 g) and di-n-propylamine (5.35 ml) in abs. n-methylpyrrolidone (35 ml) is stirred at 157° in a sealed vessel for 96 hours. The reaction is monitored using thin layer chromatography. The reaction mixture is cooled, 50 ml water are added and the aqueous phase is extracted twice with methyl-t-butylether (2x200 ml). The organic phase is dried, evaporated and chromatographically separated on silicagel using cyclohexane/methyl-t-butylethan (5:1). The appropriate fraction is evaporated and the residue recrystallised from methanol to give the title product. Mp = 117-119°.

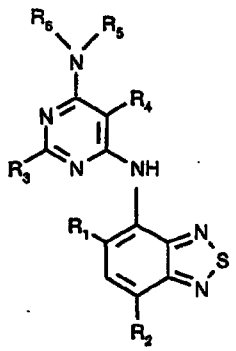
The starting material 4-(4-chloro-2,5-dimethyl-pyrimidin-6-yl)-amino-5,7-dimethyl-2,1,3-benzothiadiazole is produced as follows:
4,6-Dimethyl-2,1,3-benzothiadiazole (7.7 g) is disolved in conc. sulphuric acid (20 ml), cooled under stirring to 0-5° and nitric acid (2.5 ml; d = 1.52) is added dropwise. The clear solution is poured on ice, the so obtained precipitate is filtered off and washed with water. The resulting 5,7-dimethyl-4-nitro-2,1,3-benzothiadiazole is recrystallized from cyclohexane. Mp = 105-106°.

5,7-Dimethyl-4-nitro-2,1,3-benzothiadiazole (20 g) is warmed to ebullition in water (2.2 l) and ethanol (2.2 l) and sodium dithionite is added portionwise (strongly exothermic reaction). The reaction mixture is immediately cooled in an ice bath and extracted with ethyl acetate. The organic phase is concentrated by evaporation and the residue recrystallised in water to give 4-amino-5,7-dimethyl-2,1,3-benzothiadiazole. Mp = 113-114°.

4-Amino-5,7-dimethyl-2,1,3-benzothiadiazole (4 g) is added in portions to a 55%-dispersion of sodium hydride (2.72 g) in abs. tetrahydrofuran (50 ml) under an argon atmosphere. The mixture is stirred at 25-30° for 3 hours, then a solution os 4,5-dichloro-2,5-dimethyl-pyrimidine (4 g) in abs. tetrahydrofuran (20 ml) is added in drops at 5° during 30 minutes. The reaction mixture is stirred at room temperature for 16 further hours, then ice water is carefully added. The resulting precipitate is washed with water and a few methanol. After recrystallisation from methanol or cyclohexane, 4-(4-chloro-2,5-dimethyl-pyrimidin-6-yl)-amino-5,7-dimethyl-2,1,3-benzothiadiazole is obtained. Mp = 174-177°.

The following compounds of formula I are prepared analogously to example 1:

a) Compounds of formula

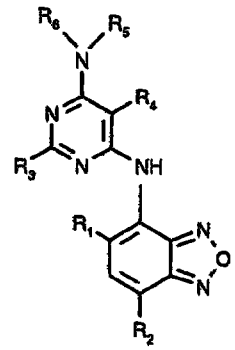


Ex.	R_1	R_2	R_3	R_4	R_5	R_6	Mp
2	Me	Me	Me	Me	n-Propyl	-CH_2-Cyclopropyl	120-121°
3	Me	Me	Me	H	n-Propyl	-CH_2-Cyclopropyl	124-127° *
4	Me	Me	Me	H	n-Propyl	n-Propyl	177-179° *
5	Me	Me	Me	Cl	n-Propyl	n-Propyl	106-108°
6	Me	Me	Me	Cl	n-Propyl	-CH_2-Cyclopropyl	111-113°
7	Me	Me	Me	Me	n-Propyl	Et	101-102°
8	Me	Me	Me	Me	n-Butyl	Et	83-84°
9	Me	Me	Me	Me	-$CH_2CH_2OCH_3$	-$CH_2CH_2OCH_3$	70-73°
10	Me	Me	Me	Me	-CH_2-$CH(CH_3)$-CH_3	-CH_2-$CH(CH_3)$-CH_3	104-105°
11	Me	Me	Me	Me	3-Pentyl	H	113-115°
12	Me	Me	Me	Me	2-Butyl	H	88°
13	Me	Me	Me	CN	n-Propyl	n-Propyl	171-173°
14	Me	Me	Me	CN	n-Propyl	-CH_2-Cyclopropyl	165-167°
15	Cl	Cl	Me	Me	Me	Et	116°
16	Cl	Cl	Me	Me	Me	n-Butyl	105°
17	Cl	Cl	Me	Me	Et	Et	189-193° *
18	Cl	Cl	Me	Me	Et	n-Propyl	107°
19	Cl	Cl	Me	Me	Et	n-Butyl	101°

20	Cl	Cl	Me	Me	n-Propyl	n-Propyl	118-121°
21	Cl	Cl	Me	Me	n-Propyl	-CH_2-Cyclopropyl	120-123°
22	Cl	Cl	Me	Me	n-Butyl	n-Butyl	56°
23	Cl	Cl	Me	Me	Allyl	Allyl	112°
24	Cl	Cl	Me	Me	H	Benzyl	126°
25	Cl	Cl	Me	Me	Me	Benzyl	138°
26	Me	Cl	Me	Me	n-Propyl	n-Propyl	102-104°
27	Me	Cl	Me	Me	n-Propyl	-CH_2-Cyclopropyl	131-132°
28	Cl	Me	Me	Me	n-Propyl	-CH_2-Cyclopropyl	110-112°
29	Cl	Me	Me	Me	n-Propyl	n-Propyl	112-114°
30	Cl	H	Me	Me	n-Propyl	n-Propyl	77-80°
31	Me	H	Me	Me	n-Propyl	n-Propyl	95-98°

Me = Methyl; Et = ethyl; *: Fumarate

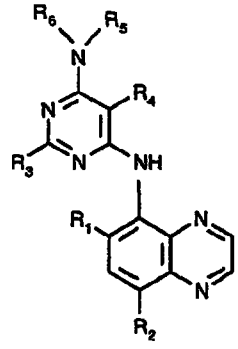
b) Compounds of formula



Ex.	R_1	R_2	R_3	R_4	R_5	R_6	Mp
32	Me	Me	Me	Me	n-Propyl	n-Propyl	123°
33	Cl	Me	Me	Me	n-Propyl	n-Propyl	100°
34	Me	Me	Me	Me	n-Propyl	-CH_2-Cyclopropyl	105°
35	Cl	Me	Me	Me	n-Propyl	-CH_2-Cyclopropyl	86°
36	Me	Me	Me	Me	n-Propyl	Et	102°
37	Me	Me	Me	Me	n-Butyl	Et	71°

Me = Methyl; Et = Ethyl

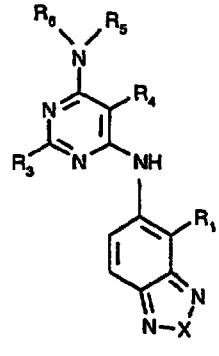
c) Compounds of formula



Ex.	R_1	R_2	R_3	R_4	R_5	R_6	Mp
38	Me	Me	Me	Me	n-Propyl	n-Propyl	94-96°
39	Cl	Cl	Me	Me	n-Propyl	n-Propyl	126-128°
40	Cl	Me	Me	Me	n-Propyl	n-Propyl	107-109°
41	Cl	Me	Me	Me	n-Propyl	-CH_2-Cyclopropyl	115-117°
42	Me	Me	Me	Me	n-Propyl	-CH_2-Cyclopropyl	105-106°
43	Cl	Cl	Me	Me	n-Propyl	-CH_2-Cyclopropyl	126-127°
44	Cl	Cl	Me	Me	Et	n-Propyl	120-123°
45	Me	Me	Me	Me	Et	n-Propyl	109-110°
46	Cl	Cl	Me	Me	Et	n-Butyl	117-119°
47	Me	Me	Me	Me	Et	n-Butyl	106-107°

Me = Methyl; Et = Ethyl

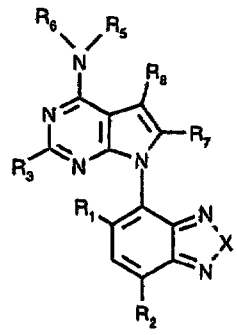
d) Compounds of formula



Ex.	X	R_1	R_3	R_4	R_5	R_6	Mp
48	S	Cl	Me	Me	Et	n-Butyl	85°
49	S	Cl	Me	Me	n-Propyl	-CH_2-Cyclopropyl	84°
50	CH=CH	Br	Me	Me	Et	n-Butyl	110°
51	CH=CH	Br	Me	Me	n-Propyl	-CH_2-Cyclopropyl	135°

Me = Methyl; Et = Ethyl

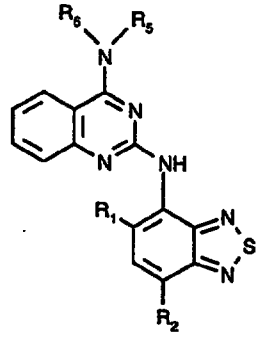
e) Compounds of formula



Ex.	X	R_1	R_2	R_3	R_5	R_6	R_7	R_8	Mp
52	S	Me	Me	Me	Et	n-Butyl	Me	Me	90-92°
53	CH=CH	Me	Me	Me	Et	n-Butyl	Me	Me	106-108°
54	S	Me	Me	Me	n-Propyl	n-Propyl	Me	Me	126-128°
55	CH=CH	Me	Me	Me	n-Propyl	n-Propyl	Me	Me	156-158°
56	S	Cl	Me	Me	n-Propyl	n-Propyl	Me	Me	135-136°
57	CH=CH	Cl	Me	Me	n-Propyl	n-Propyl	Me	Me	130-131°
58	S	Cl	Me	Me	Et	n-Butyl	Me	Me	90-92°
59	CH=CH	Cl	Me	Me	Et	n-Butyl	Me	Me	177-178°

Me = Methyl; Et = Ethyl

f) The compound of formula

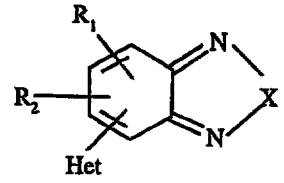


Ex.	R_1	R_2	R_5	R_6	Mp
60	Me	Me	n-Propyl	-CH_2-Cyclopropyl	234-237° *

Me = Methyl; *: Fumarate

CLAIMS:

1. A compound of formula I



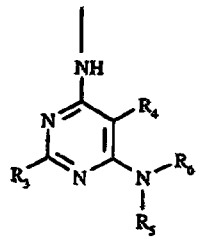
I

wherein

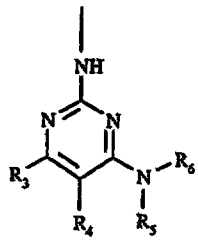
X is O, S, N-CH_3, CH=CH or CAlk = CAlk, where the Alk independently are (C_{1-4})alkyl,

R_1 and R_2 independently, are hydrogen, halogen, (C_{1-4})alkyl, (C_{1-4})alkoxy or trifluoromethyl, and

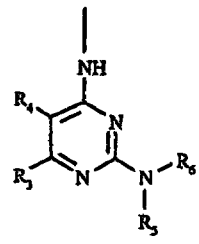
Het is a radical having one of the formulae (a) to (p) below:



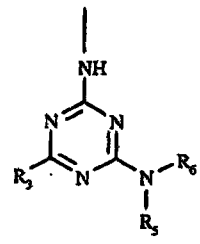
(a)



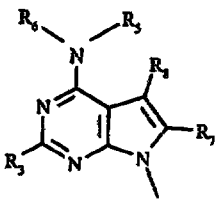
(b)



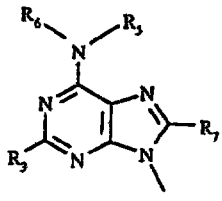
(c)



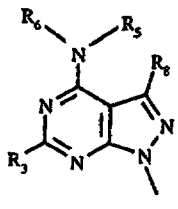
(d)



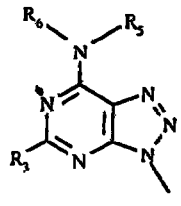
(e)



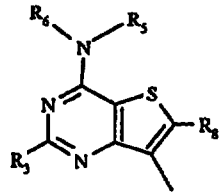
(f)



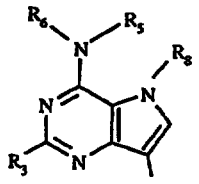
(g)



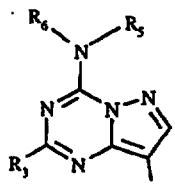
(h)



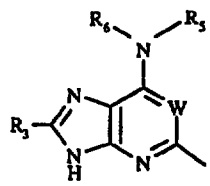
(i)



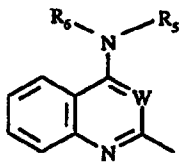
(j)



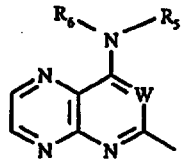
(k)



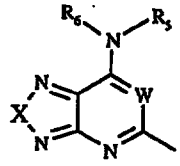
(l)



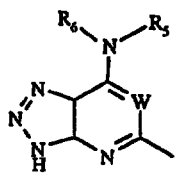
(m)



(n)



(o)



(p)

wherein

R_3 and R_8, independently, are hydrogen or (C_{1-4})alkyl,

R_4 is hydrogen, (C_{1-4})alkyl, cyano, nitro, formyl or (C_{1-4})alkylcarbonyl,

R_5 and R_6, independently, are hydrogen, (C_{1-7})alkyl, (C_{3-7})alkenyl, (C_{3-7})cycloalkyl, (C_{3-7})cycloalkyl (C_{1-4})alkyl, (C_{1-4})alkoxy(C_{2-5})alkyl or benzyl,

R_7 is hydrogen, hydroxy, (C_{1-4})alkyl or (C_{1-4})alkoxy,

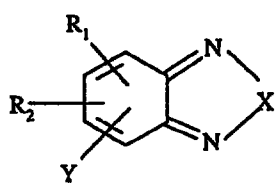
W is N, C-CN, C-NO_2, C-COH or C-CO-Alk where Alk is as defined above, and

X is as defined above,

in free base or acid addition salt form.

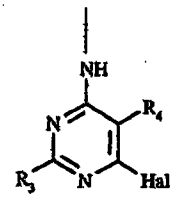
2. 5,7-Dimethyl-4-[2,5-dimethyl-6-(di-n-propyl)-amino-pyrimidin-4-yl]amino-2,1,3-benzothiazole in free base or acid addition salt form.

3. A process for the preparation of a compound of formula I as defined in claim 1, or a salt thereof, which includes the step of reacting a compound of formula II

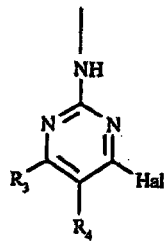


II

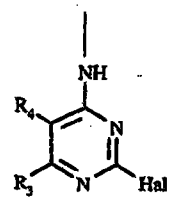
wherein X, R_1 and R_2 are as defined in claim 1 and Y is a radical having one of the formulae (a') to (p') below:



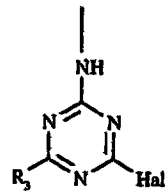
(a')



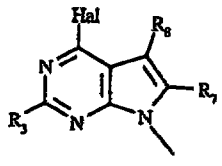
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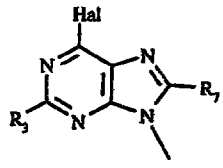
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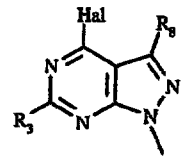
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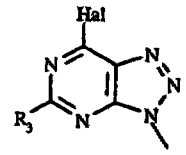
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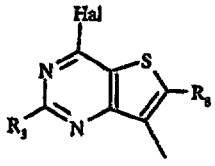
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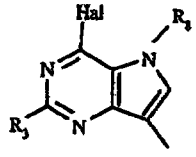
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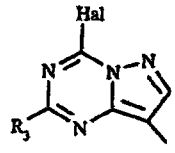
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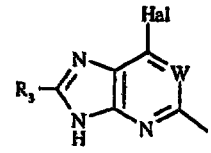
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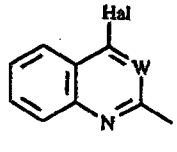
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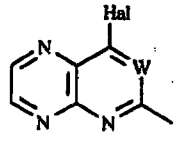
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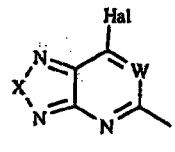
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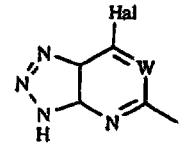
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(n')

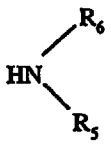


(o')



(p')

wherein R_3 to R_8, W and X are as defined in claim 1 and Hal is halogen, with a compound of formula III



III

wherein R_5 and R_6 are as defined in claim 1, and recovering the thus obtained compound of formula I in free base or acid addition salt form.

4. A compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

5. A compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of any state with increased endogenous level of CRF or in which the HPA is disregulated, or of a disease induced or faciliated by CRF.

6. A pharmaceutical composition comprising a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

7. The use of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, as a pharmaceutical for the treatment of any state with increased endogenous level of CRF or in which the HPA is disregulated, or of a disease induced or faciliated by CRF.

8. The use of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of any state with increased endogenous level of CRF or in which the HPA is disregulated, or of a disease induced or faciliated by CRF.

9. A method for the treatment of any state with increased endogenous level of CRF or in which the HPA is disregulated, or of a disease induced or faciliated by CRF in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of claim 1 or 2 in free base or pharmaceutically acceptable acid addition salt form.