Bioorganic & Medicinal Chemistry 19 (2011) 5432–5445

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

6,7-Dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidines and their derivatives as novel corticotropin-releasing factor 1 receptor antagonists

Tetsuji Saito *, Tetsuo Obitsu, Takashi Kondo, Toshiaki Matsui, Yuuki Nagao, Kensuke Kusumi, Naoya Matsumura, Sonoko Ueno, Akihiro Kishi, Seishi Katsumata, Yoshifumi Kagamiishi, Hisao Nakai, Masaaki Toda

Minase Research Institute, Ono Pharmaceutical Co., Ltd, 3-1-1 Sakurai, Shimamoto, Mishima, Osaka 618-8585, Japan

ARTICLE INFO

Article history:
Received 3 July 2011
Revised 23 July 2011
Accepted 25 July 2011
Available online 31 July 2011

Keywords:
Corticotrophin-releasing factor 1 receptor
Antagonist

ABSTRACT

To identify an orally active corticotropin-releasing factor 1 receptor antagonist, a series of 6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidines and their derivatives were designed, synthesized and evaluated. An in vitro study followed by in vivo and pharmacokinetic studies of these heterotricyclic compounds led us to the discovery of an orally active CRF1 receptor antagonist. The results of a structure–activity relationship study are presented.

1. Introduction

The majority of research on the therapeutic utility of corticotropin-releasing factor (CRF) receptor antagonists has focused on treatment of stress-related disorders such as anxiety and depression.[1–4] Thus, CRF, a 41-amino acid peptide first isolated in 1981,[5] is considered to be one of the principal regulators of the hypothalamic–pituitary–adrenal (HPA) axis, which coordinates the endocrine, behavioral, and autonomic responses to stress. CRF and its receptors play a key role in mediating the body's response to stress, and have provided compelling targets for novel pharmacological approaches to treating depression, anxiety and stress disorders.[6–8] It is well known that CRF exerts its biological functions through binding to type-1(CRF_1) and type-2 (CRF_2) receptors.[9] Major industry efforts have identified potent and selective antagonists for the CRF_1 receptor, as summarized in recent reviews.[10–12] Since the report of antidepressant activity of one of these, R121919, in an open-label, phase 2 trial conducted in depressed patients,[13,14] very few clinical results[8] with CRF_1 antagonists have been published. However, recent advances in CRF neurobiology have further validated this target.[15–17]

The design and synthesis of non-peptidic small molecule CRF_1 antagonists continues to be an active area of research. The key features found in several known classes of CRF_1 antagonists are an aromatic heterocyclic core (monocyclic, bicyclic, or tricyclic) that includes an sp^2 nitrogen acting as a hydrogen bond acceptor; an aryl ring in an orthogonal orientation to the core ring, which is minimally substituted in the *ortho*- and *para*-positions; a halide or small alkyl group *ortho* to the sp^2 nitrogen of the aromatic heterocyclic core; and a branched, lipophilic group, with limited tolerance for polar functional groups, *para* to the sp^2 nitrogen of the heterocyclic core. Many potent, small molecule CRF_1 antagonists from a variety of chemical classes have been reported since the disclosure of the CRF_1 antagonist CP-154,526 **1** in 1996 and 1997.[18,19] Among the variety of chemotypes, representative bicyclic core antagonists **1**, **2a–b**,[20] **3**,[21] and **4**[22] are shown in Figure 1. This report will focus on the discovery of novel CRF_1 antagonists, specifically the aromatic heterotricyclic core antagonists **7a** and **7b** (Scheme 1), which were designed based on the bicyclic core antagonists **2a** and **2b**, respectively.

As shown in Scheme 1, representative chemotypes containing tricyclic cores have been designed based on the bicyclic core structures **2a** and 2**b**. Cyclization '*a*' resulted in the pyrrole- and pyrazole-based compounds **5a–b** and others.[23–31] Cyclization '*b*' resulted in structure **6**, which was reported to show potent CRF_1 receptor binding.[32] Cyclization '*c*' resulted in novel structures as illustrated by **7a–b**, the biological profiles of which have not been reported yet. In this paper, the discovery and biological evaluation of a series of aromatic heterotricyclic core CRF_1 antagonists is reported.

2. Chemistry

Synthesis of the test compounds listed in Tables 1–5 is outlined in Schemes 2–6. Key intermediates **35a–g** were prepared as

* Corresponding author. Tel.: +81 75 961 1151; fax: +81 75 962 9314.
E-mail address: te.saitou@ono.co.jp (T. Saito).

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.07.055

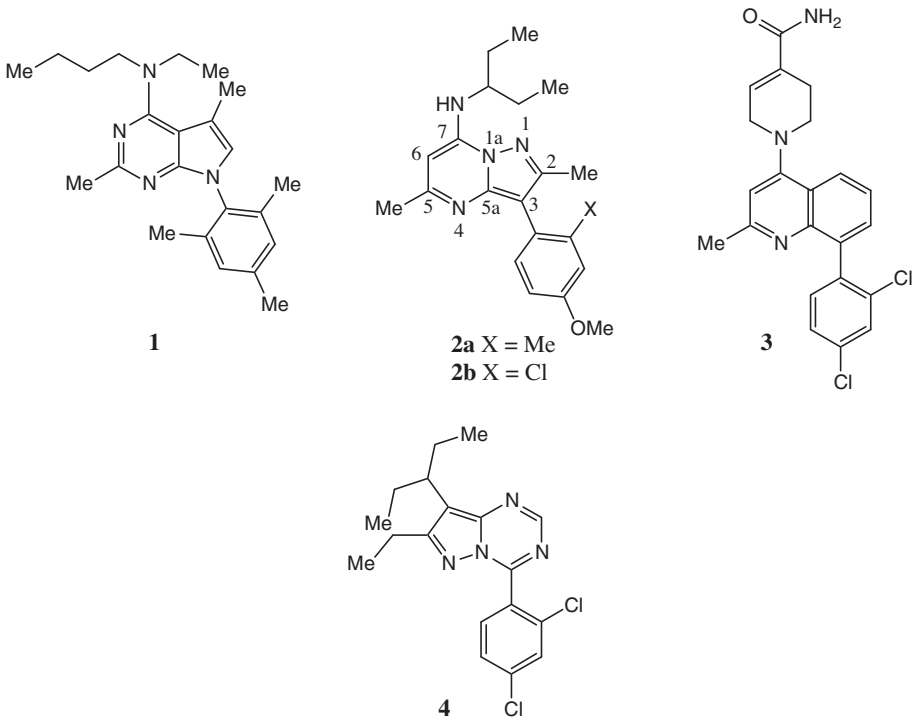
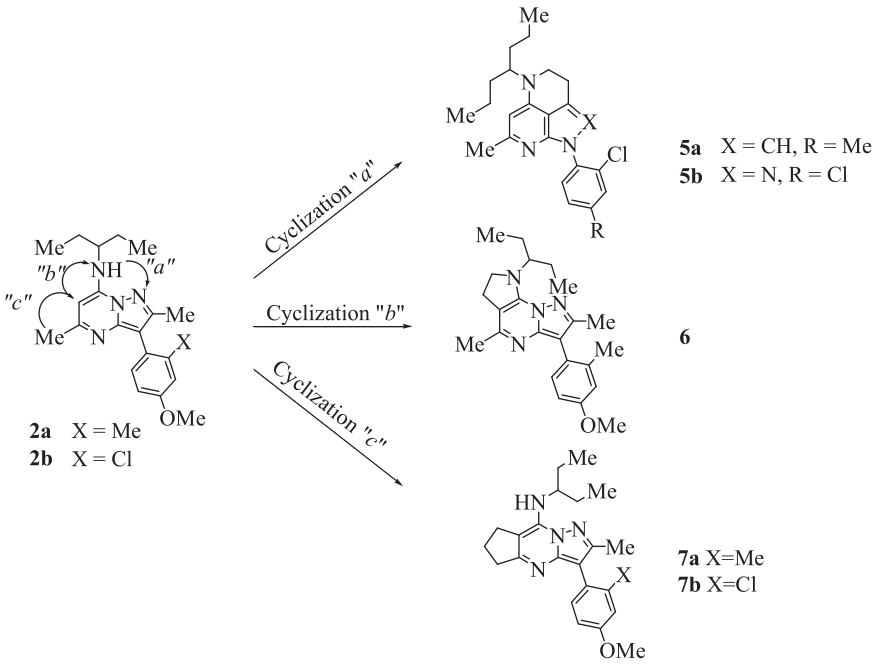


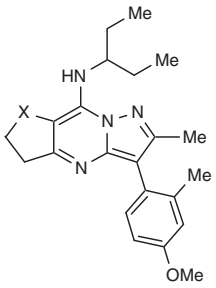
Figure 1. CRF_1 receptor antagonists containing bicyclic cores.



Scheme 1. Molecular design of CRF_1 receptor antagonists containing tricyclic cores.

described in Scheme 2. Condensation reaction of benzyl nitriles **32** and **33** with an optional ethyl ester in the presence of base afforded enolate anions of β-keto nitriles (**34a–g)**. Cyclization reaction of **34a–g** with hydrazine hydrate provided the 5-aminopyrazoles **35a–g**.[33] Synthesis of **7a–b**, **8a–b**, **9–10**, **11a–b**, **12**, **18–28** and **30** is outlined in Scheme 3a–e. Coupling reaction of 5-amino-3-methyl-4-phenylpyrazole (**35b**) and cyclic β-keto esters (**36a–d**) in acetic acid under reflux temperature followed by chlorination with phosphorous oxychloride afforded **37a–d**. Aminolysis of **37a–d** with 1-ethylpropylamine resulted in **7a**, **8a**, and **9–10**, respectively (Scheme 3a). Cyclization reaction of **35b** 5-amino-3-methyl-4-arylpyrazoles possessing an optionally substituted aryl group and β-keto esters (**38a–b**) followed by treatment with phosphorous oxychloride afforded **39a** and **39b**, aminolysis of which with 2-ethylpropylamine provided **11a** and **12**, respectively (Scheme 3b). Compound **30** was synthesized from **35g** (Scheme 3c) using a β-keto ester (**40)** instead of **36a–d** and **38a–b**, according to the procedure (Scheme 3a–b) described above. Compounds **7b**,

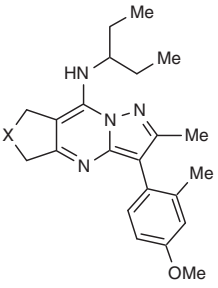
Table 1
Effect of the fused cyclic structure on the activity profiles



Compd	X	Binding affinity IC_{50} (nM) Human	Antagonist activity EC_{50} (nM) Human
7a	CH_2	37	170
8a	O	31	640
9	S	80	NT[a]
10	NH	170	NT[a]

[a] Not tested.

Table 2
Effect of the fused cyclic structure on the activity profiles



Compd	X	Binding affinity IC_{50} (nM) Human	Antagonist activity EC_{50} (nM) Human
7a	CH_2	37	70
11a	O	35	75
12	S	37	150

8b, and **11b** were synthesized from **35g** (Scheme 3d) using **36a–b** and **38b** as β-keto esters according to the procedures described above. Compounds **18–28** were prepared from an optional 5-aminopyazole[20] (Scheme 3e) using **36a** as a β-keto ester according to the procedure described above.

As shown in Scheme 4, compounds **13–17** were synthesized from 5-aminopyrazoles **35a** and **35c–f** (Scheme 2), respectively, using **36a** as a cyclic β-keto ester according to the procedure described above. Another tricyclic core analog **31** was prepared as outlined in Scheme 5. Coupling reaction of cyclic β-enaminoketonitrile **43**[34] with 5-amino-4-arylpyrazole **35g** afforded an aminoheterotricyclic core structure, **44**, N-alkylation of which with 3-bromopentane in *N*,*N*-dimethylformamide in the presence of tetra-*n*-butyl ammonium iodide afforded **31**. Synthesis of **29** is described in Scheme 6. Demethylation of **7b** with boron tribromide in dichloromethane provided **45**. Difluoromethylation of phenol **48** with chlorodifluoromethane under basic condition afforded **29**.[35]

3. Results and discussion

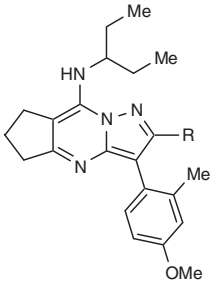
The compounds listed in Tables 1–5 were first tested for their binding affinity to human CRF_1 receptor and antagonist activity in a CRF-stimulated adenylate cyclase assay.[36] One of the leading compounds with higher receptor binding and antagonist activity was then evaluated for an in vitro activity and subjected to an in vivo pharmacokinetic study in rats. Anxiolytic efficacy was also assessed in the rat elevated plus-maze model.[37–39]

As shown in Table 1, compounds **7a**, **8a**, **9**, and **10**, which possess 6,7-dihydrocyclopentapyrazolopyrimidine, 2,3-dihydrofuropyrazolopyrimidine, 2,3-dihydropyrazolothienopyrimidine and 2,3-dihydropyrazolopyrrolopyrimidine cores, respectively, showed moderate binding affinity. As reported previously,[40,41] the newly attached cyclopenta moiety seemed to be very sensitive to bulkiness while compound **7a** still exhibited equipotent activity with the chemical lead **2a**, which showed potent binding affinity (K_i = 1.0 ± 02 nM)[42] and antagonist activity (IC_{50} = 10 ± 0.01 nM).[42] Fine tuning of its bulkiness and polarity by introducing a heteroatom into the cyclopenta moiety was predicted to result in an interesting investigation. Thus, replacement of one of the carbon atoms of the fused carbocyclic five-membered ring with a more hydrophilic hetero atom such as oxygen, sulfur and nitrogen afforded **8a**, **9** and **10**, respectively, with a tendency for decreased binding affinity and/or antagonist activity. Compound **8a** exhibited unexpectedly reduced antagonist activity given its potent binding affinity. Table 2 shows the activity profiles of compounds **11a**, and **12**, which possess 5*H*,7*H*-furo[3,4-*d*]pyrazolopyrimidine, and 5*H*,7*H*-pyrazolo[1,5*a*]thienopyrimidine. Compounds **11a** and **12**, which contain more Lewis basic heteroatoms O and S than the corresponding isomers **8a** and **9**, respectively, tended to show equipotent to slightly less potent binding affinity. Accordingly, the more Lewis basic property of the ether and the sulfide moieties of **11a** and **12** were found to be more beneficial relative to the corresponding moieties of **8a** and **9**, respectively, especially in effort to improve antagonist activity of **11b**. Transformation of the bicyclic core of the known antagonists (**2a–b**, Fig. 1) into the tricyclic core led us to readjustment of the size and/or polarity of the methyl residue attached to the pyrazole moiety of the tricyclic core.

The effect of the substituent attached to the pyrazole moiety on activity profiles was investigated and the results are summarized in Table 3. Removal of the methyl group from the pyrazole moiety of **7a** afforded the unsubstituted pyrazole analog **13** with a 6.5-fold reduction in binding affinity, while replacement of the methyl group with an ethyl group and cyclobutyl group afforded **14** and **15**, respectively, with reduced binding affinity. Replacement of the methyl group of **7a** with a trifluoromethyl group afforded **16** with nearly equipotent binding affinity. Replacement of the methyl group of **7a** with a methylthiomethyl group provided **17** with reduced binding affinity. As a result, the methyl group was found to be the most optimized substituent among the substituents tested, in terms of both bulkiness and hydrophobicity.

The tricyclic core was predicted to require another optimal aryl structure different from the one required by the parent bicyclic core. Based on the above-mentioned prediction, the effect of the substituents of the aryl ring on activity profiles was investigated. Among 2-methylphenyl analogs (**7a**, **18–21**), the 2,4-disubstituted phenyl analogs **7a** and **18–20** tended to show relatively stronger binding affinities than the 2,5-disubstituted phenyl analog **21**. The 4-methoxyphenyl analogs **22–25** were tested to determine binding affinity and antagonist activity. Among the tested analogs, the 2,6-dimethyl-4-methoxyphenyl analog **23**, the 2-chloro-4-methoxyphenyl analog **7b** and the 2,5-dimethyl-4-methoxyphenyl analog **22** showed potent binding affinity and antagonist activity. The 2-methylthio-4-methoxyphenyl analog **24** showed moderate

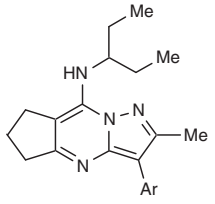
Table 3
Effect of the substituent on the pyrazole moiety on activity profiles

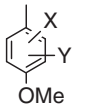
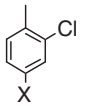


Compd	R	Binding affinity IC_{50} (nM)	Antagonist activity EC_{50} (nM)
		Human	Human
13	H	240	NT[a]
7a	Me	37	170
14	Et	97	NT[a]
15		490	NT[a]
16	CF_3	59	NT[a]
17	CH_2SMe	620	NT[a]

[a] Not tested.

Table 4
Effect of the substituent on the aryl ring on the activity profiles

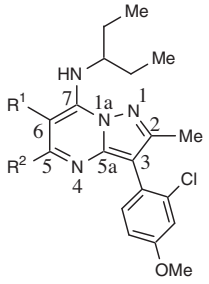


Compd	Ar	X and/or Y	Binding affinity IC_{50} (nM) Human	Antagonist activity EC_{50} (nM) Human
7a		4-OMe	37	170
18		4-Me	72	920
19		4-F	93	NT[a]
20		4-NMe_2	38	NT[a]
21		5-Me	820	NT[a]
22		2,5-Dimethyl	22	47
23		2,6-Dimethyl	9	80
7b		2-Cl	4	40
24		2-SMe	49	NT[a]
25		3-OMe	600	NT[a]
27		4-OMe	4 (7)[b]	40 (40)[c]
29		4-OEt	71	NT[a]
7b		4-OCF_3	15	NT[a]
26		4-Cl	37	200
28		4-$OCHF_2$	3	200

[a] Not tested.
[b] Binding assay for rat CRF.
[c] cAMP assay for rat.

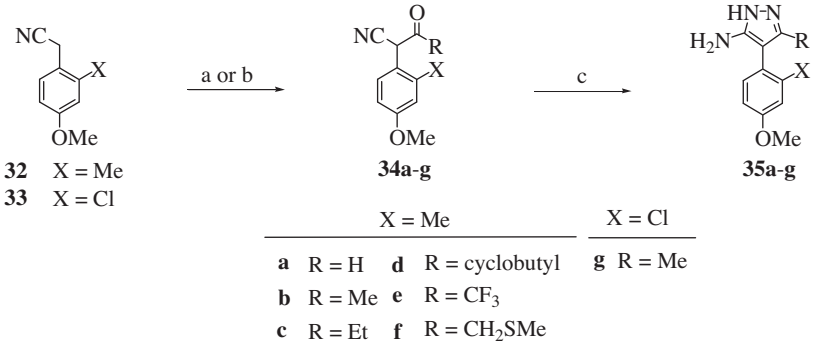
binding affinity. The 3,4-dimethoxyphenyl analog **25** showed relatively weaker binding affinity (IC_{50} = 600 nM) because the aryl ring was unsuitably oriented to the core ring. Based on the results described above, further optimization of the 2-chloro-4-substituted phenyl moiety, which was found to be the most optimal among those tested, was carried out. This screening led us to the discovery of the 2-chloro-4-difluoromethoxy analog **29**, which exhibited very potent binding affinity (IC_{50} = 3 nM) but only weak antagonist activity (IC_{50} = 200 nM). Analogs **26**–**28**, which exhibited moderate to weak binding affinity, were also discovered. Compounds **28** and

Table 5
SAR of 2-chloro-4-methoxyphenyl analogs



Compd	R^1, R^2	Binding affinity IC_{50} (nM) Human	Antagonist activity EC_{50} (nM) Human
2b	R^1 = H, R^2 = Me	6[a]	31[a]
30	R^1 = R^2 = Me	49[a]	100[a]
7b		4	40
8b		7	4
11b		22	66
31		84	8

[a] In-house data.

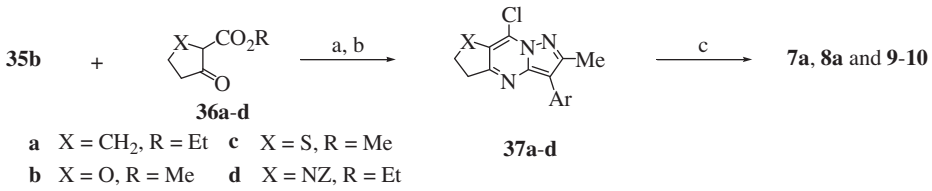


Scheme 2. Synthesis of intermediates **35a–g**. Reagents: (a) NaOEt, RCO_2Et, reflux; (b) Na, ethyl acetate, reflux; (c) $NH_2NH_2{\cdot}H_2O$, acetic acid/toluene, reflux.

29 showed equipotent antagonist activity, although their binding affinities differed by more than 10 times. Among the tested compounds, the 2-chloro-4-methoxyphenyl moiety of **7b** was found to be the most optimized aryl moiety in terms of both binding affinity and antagonist activity.

A study of the structure–activity relationships of the 5-methyl bicyclic core analogs **2a–b**, the 5,6-dimethyl bicyclic core analog **30** and the tricyclic core analog **7b** was conducted as shown in Table 5. First, replacement of the 2-methyl-4-methoxyphenyl moiety of **2a** with a 2-chloro-4-methoxyphenyl moiety afforded **2b** with very strong binding affinity and antagonist activity, while introduction of another methyl residue into the 6-position of the bicyclic core provided **30** with significant loss of these activities. Accordingly, introduction of an alkyl group into the 6-position is not beneficial while the loss of activity was recovered in the tricyclic core antagonist **7b**. Based on this result, the 6-position of the bicyclic core system was found to be one of the very sensitive positions for these small molecules to interact with the CRF receptor. While it is difficult to clarify the SAR between the bicyclic core **30** and the tricyclic core **7b**, the intramolecular steric hindrance of the 6-methyl of **30** may be slightly alleviated by forming the tricyclic core system **7b**. Second, fine readjustment of the physicochemical properties of **7b** was also carried out as described in Table 5. Replacement of the aliphatic carbon atom of the newly fused ring with ether oxygen is considered to lower the *c*-log *P* value of the highly lipophilic **7b**. Thus, introduction of ether oxygen into the newly fused five-membered ring of **7b** afforded the three isomers **8b**, **11b** and **31**, all of which possess a 2-chloro-4-methoxyphenyl group as an optimized aryl moiety. The isomer **8b** exhibited increased binding affinity and antagonist activity, while **11b** and **31** showed decreased binding affinity relative to **7b**. The isomer **11b** exhibited nearly equipotent antagonist activity relative to **7b**, while **31** showed unexpectedly strong antagonist activity for its decreased binding affinity. As a result, the structural fine tuning described above resulted in discovery of **8b** as the most optimized structure in the in vitro tests. Compounds **2b** and **7b**

a) Synthesis of **7a**, **8a** and **9**-**10**



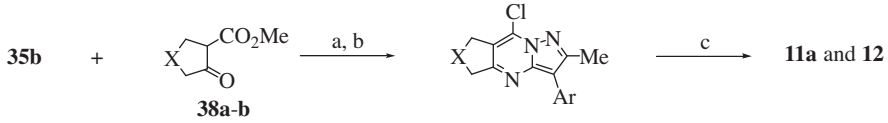
36a-d

a X = CH_2, R = Et **c** X = S, R = Me

b X = O, R = Me **d** X = NZ, R = Et

37a-d

b) Synthesis of **11a** and **12**



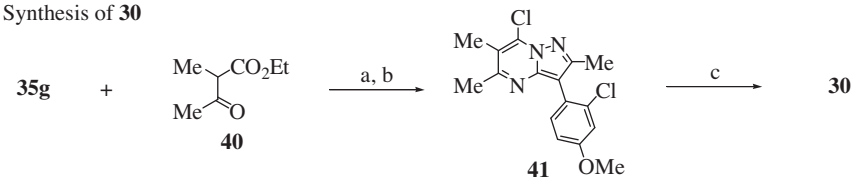
38a-b

a X = O

b X = S

39a-b

c) Synthesis of **30**



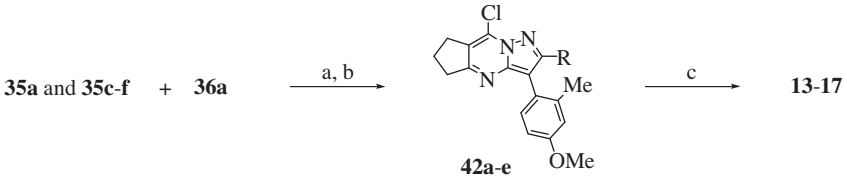
40

41

d) Synthesis of **7b**, **8b** and **11b**

e) Synthesis of **18**-**28**

Scheme 3. Synthesis of **7a–b**, **8a–b**, **9–10**, **11a–b**, **12**, **18–28** and **30**. Reagents: (a) acetic acid, reflux; (b) $POCl_3$, *N*,*N*-diethylaniline, toluene, reflux; (c) 1-ethylpropylamine, isopropyl alcohol, 90 °C.



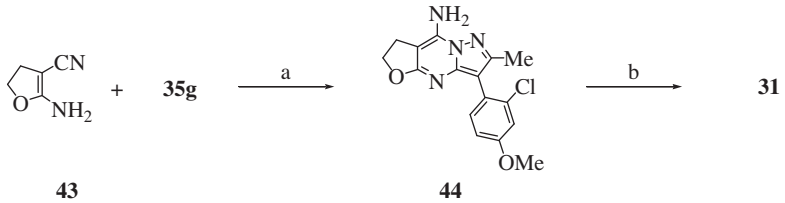
42a-e

a R = H **d** R = CF_3

b R = Et **e** R = CH_2SMe

c R = cyclobutyl

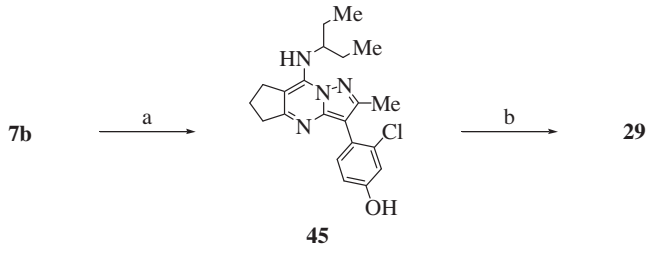
Scheme 4. Synthesis of **13–17**. Reagents: (a) acetic acid, reflux; (b) $POCl_3$, *N*,*N*-diethylaniline, toluene, reflux; (c) 1-ethylpropylamine, isopropyl alcohol, 90 °C.



43

44

Scheme 5. Synthesis of **31**. Reagents: (a) pyridine, reflux; (b) 3-bromopentane, NaH, tetra-*n*-butylammonium iodide, DMF, 50–70 °C.



Scheme 6. Synthesis of **29**. Reagents: (a) BBr_3, CH_2Cl_2, −50–0 °C; (b) $ClCHF_2$, NaOH, THF, H_2O, 70 °C.

showed equipotency in both the binding affinity and antagonist activity while **7a** showed less potency relative to **2a** (in-house data). Based on the data, replacement of the 2-methyl-4-methoxyphenyl moiety of **7a** with 2-chloro-4-methoxyphenyl moiety was estimated to contribute for the increased potency although the effect was found to reach the ceiling as illustrated by the results obtained for **2a**, **2b**, and **7b**. Thus, 2-chloro-4-methoxyphenyl moiety was considered to have more contribution to the increased binding affinity than 2-methyl-4-methoxy moiety as illustrated by the potency of their receptor binding: **7a** < **7b** and **8a** < **8b**. Hydrophilic moiety such as the ether moieties also considered to be one of the important factors influencing in vitro activities. Hydrophilicity and Lewis basicity of the ether function, both of which are expected to be higher in **11a** and **11b** relative to **8a** and **8b** because of the more delocalization of the lone pairs of the ether oxygen of **8a** and **8b**. As a result, the more hydrophilic and more Lewis basic ether oxygen is presumed to have more chances to result in an irrelevant interaction with off-targets. Such an unfavorable effect may result in the unexpected SAR of **11a** and **11b**, which showed equipotency in the in vitro assay. In evaluation of antagonist activity, it may be relatively more difficult to get exact activity in such a cell-based assay, that is, influenced during evaluation process starting from the addition of the test compound to the assay system till measurement of the released cAMP. For such a reason, antagonist activity sometimes does not show EC_{50} values expected from the corresponding binding assay. Thus, weaker antagonist activity for the corresponding binding affinity is usually explained by protein-binding while stronger antagonist activity for the corresponding binding affinity as illustrated by **31** may suggest the plausible existence of other mechanism of inhibiting cAMP release. Compound **31** showed weaker binding affinity relative to **7b** and **8b**. Based on the result, the ether oxygen in **31**, which corresponds to the methyl substituent in the reported bicyclic core system such as **2b**, was considered to give a negative effect to the binding affinity while the ether oxygen in **8b** was regarded as a linker, which could be replaced with the methylene moiety without reduction of the binding affinity as illustrated by **7b**.

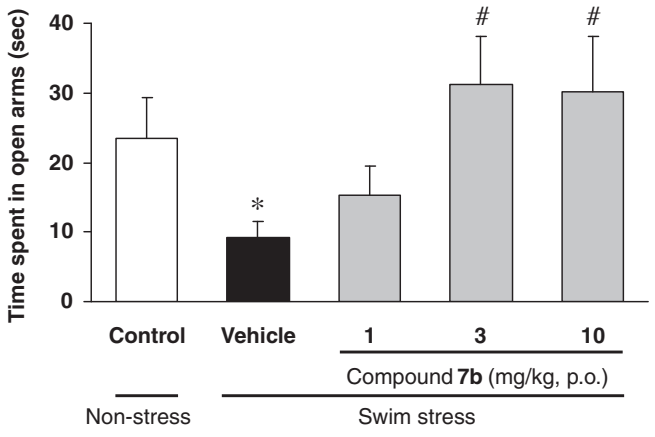


Figure 2. Effect of compound **7b** in the rat elevated plus-maze test in swim stress-loaded rats. Each column represents mean ± standard errors of 16 rats. $^{\#}p$ <0.05 versus control group (*t*-test). $^{*}p$ <0.05 versus vehicle group (Dunnett test).

Table 6
Pharmacokinetic parameters of compound **7b**

Parameter	iv	po
Dose (mg/kg)	0.3	3
$AUC_{infinity}$ (ng h/ml)	278	608
T_{max} (h)		1.0
C_{max} (ng/mL)		87.1
CL_{total} (ml/min/kg)	18	
$T_{1/2}$ (h)	4.7	7.8
V_{ss} (ml/kg)	1780	
F (%)		22

n = 4.

3.1. In vivo study of one of the representative compounds

The anxiolytic efficacy of compound **7b**, which showed good binding affinity to rat brain membranes (IC_{50} = 7 nM) and good antagonist activity in a cyclic AMP assay (EC_{50} = 40 nM), was assessed using the rat elevated plus-maze test (Fig. 2). Vehicle-treated animals spent significantly less time in the open arms ($p < 0.05$) relative to control animals. Pretreatment with compound **7b** at doses of 3 and 10 mg/kg significantly increased the time spent in open arms (p = 0.023 and 0.032, respectively) relative to vehicle-treated animals.

3.2. Rat pharmacokinetic study

Pharmacokinetic data for compound **7b** were investigated after administration of single doses to rats (Table 6). Intravenous administration of compound **7b** to rats (0.3 mg/kg, n = 4) resulted in detectable plasma levels ($T_{1/2}$ = 4.7 h), while oral administration of **7b** to rats (3 mg/kg, n = 4) resulted in a $T_{1/2}$ of 7.8 h. The AUC value of **7b** was 278 ng h/ml after intravenous administration versus 608 ng h/ml after oral administration. The steady state volume of distribution (V_{ss}) was calculated to be 1780 ml/kg indicating that this compound showed good distribution to tissues. Systemic clearance was 18 ml/min/kg. The C_{max} value after oral dosing was 87.1 ng/ml while the T_{max} value was 1.0 h. Bioavailability of **7b** was 22%. *Kp* value (brain content of **7b**/plasma concentration of **7b**) was 0.4 (1.0 h after oral dosing).

4. Conclusion

For the purpose of finding an orally active CRF_1 receptor antagonist, a series of heterotricyclic derivatives were designed, synthesized and evaluated. After substantial chemical modification and evaluation, the unsubstituted carbocyclic analogs **7a**–**b**, and the oxa-analogs **8a–b**, **11a**–**b** and **31** were identified as CRF_1 antagonists possessing potent to moderate in vitro activity. In particular, the 2-chloro-4-methoxyphenyl analogs **7b**, **8b** and **31** exhibited potent in vitro activity. Among them, **7b** was found to show orally effective CRF_1 antagonist activity.

5. Experimental

5.1. Chemistry

5.1.1. General procedures

Analytical samples were homogeneous as confirmed by TLC, and afforded spectroscopic results consistent with the assigned

structures. Proton nuclear magnetic resonance spectra (^{1}H NMR) were taken on a Varian Mercury 300 spectrometer using deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) as the solvent. Fast atom bombardment (FAB-MS, HRMS) and electron ionization (EI) mass spectra were obtained on a JEOL JMS-DX303HF spectrometer. Atmospheric pressure chemical ionization (APCI) mass spectra were determined on a HITACHI MI200H spectrometer. Infrared spectra (IR) were measured in a Perkin-Elmer FT-IR 1760X spectrometer. Melting points and results of elemental analyzes were uncorrected. Column chromatography was carried out on silica gel [Merck Silica gel 60 (0.063–0.200 mm), Wako gel C-200, or Fuji Silysia FL60D]. Thin layer chromatography was performed on silica gel (Merck TLC or HPTLC plates, Silica gel 60 F254). The following abbreviations for solvents and reagents are used diethyl ether (Et_2O), *N*,*N*-dimethylformamide (DMF), ethyl acetate (EtOAc), acetic acid (AcOH), methanol (MeOH), dichloromethane (CH_2Cl_2), chloroform ($CHCl_3$), *tert*-butylmethyl ether (*t*-BuOMe), sodium hydride (NaH), tetrahydrofuran (THF).

5.1.2. 2-(2-Methyl-4-methoxyphenyl)-3-oxo-butyronitrile (34b)

To a stirred solution of **32** (5.0 g, 31 mmol) in EtOAc (70 mL) was portionwisely added sodium (929 mg) at room temperature and the reaction mixture was allowed to be heated at reflux. After being stirred over night, the reaction mixture was cooled to room temperature. The precipitates were collected by filtration and then dissolved in water. The solution was acidified with 2 N HCl (pH 5–6) and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over $MgSO_4$ and evaporated to give **34b** (5.38 g, 85% yield) as a pale yellow oil, which was used for the next reaction without further purification. TLC R_f = 0.65 (EtOAc/hexane, 1:1), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 1H), 6.85–6.75 (m, 2H), 4.75 (s, 1H), 3.81 (s, 3H), 2.33 (s, 3H), 2.22 (s, 3H).

5.1.3. 2-(4-Methoxy-2-methylphenyl)-3-oxo-propionitrile (34a)

A reddish yellow oil; TLC R_f = 0.45 (MeOH/$CHCl_3$, 1:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 3.0 Hz, 1H), 6.77 (dd, J = 3.0, 8.4 Hz, 1H), 3.82 (s, 3H), 2.27 (s, 3H).

5.1.4. 2-(4-Methoxy-2-methylphenyl)-3-oxo-pentanenitrile (34c)

A brown oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 1H), 6.79 (m, 2H), 4.76 (s, 1H), 3.81 (s, 3H), 2.54 (m, 2H), 2.32 (s, 3H), 1.05 (t, J = 6.9 Hz, 3H).

5.1.5. 3-Cyclobutyl-2-(4-methoxy-2-methylphenyl)-3-oxo-propionitrile (34d)

A yellow oil; TLC R_f = 0.75 (EtOAc/benzene, 1:5) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.1 Hz, 1H), 6.78 (m, 2H), 4.73 (s, 1H), 3.80 (s, 3H), 3.40 (m, 1H), 2.38–1.77 (m, 9H).

5.1.6. 4,4,4-Trifluoro-2-(4-methoxy-2-methylphenyl)-3-oxo-butyronitrile (34e)

A pale yellow oil; TLC R_f = 0.61 (MeOH/$CHCl_3$, 1:20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 1H),6.84 (d, J = 3.0 Hz, 1H), 6.78 (dd, J = 3.0, 8.4 Hz, 1H), 3.83 (s, 3H), 2.16 (s, 3H).

5.1.7. 2-(2-Chloro-4-methoxyphenyl)-3-oxo-butyronitrile (34g)

TLC R_f = 0.13 (EtOAc/hexane, 1:3); ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 8.4, 2.4 Hz, 1H), 5.11 (s, 1H), 3.83 (s, 3H), 2.29 (s, 3H).

5.1.8. 4-(2-Methyl-4-methoxyphenyl)-3-methyl-1*H*-pyrazol-5-amine (35b)

To a stirred solution of **34b** (5.38 g, 26.5 mmol) in toluene (95 mL) were added AcOH (5.16 mL, 90.1 mmol) and hydrazine monohydrate (2.92 mL, 59.6 mmol) at room temperature and the reaction mixture was allowed to be heated at reflux and stirred for 3 h. The reaction mixture was cooled and evaporated. The resulting residue was dissolved in 2 N HCl aq and washed with hexane/EtOAc (3:1). By adding ammonium hydroxide solution (28%), pH value of the solution was adjusted to 11. The solution was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give **35b** (5.15 g, 90% yield) as a yellow oil, which was used for the next reaction without further purification. TLC R_f = 0.4 (AcOH/MeOH/$CHCl_3$, 1:4:15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 3 Hz, 1H), 6.77 (dd, J = 8.4, Hz, 1H), 3.82 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H).

5.1.9. 4-(4-Methoxy-2-methylphenyl)-2*H*-pyrazol-3-ylamine (35a)

A reddish yellow oil:TLC R_f = 0.45 (MeOH/$CHCl_3$, 1:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 3.0 Hz, 1H), 6.77 (dd, J = 3.0, 8.4 Hz, 1H), 3.82 (s, 3H), 2.27 (s, 3H).

5.1.10. 5-Ethyl-4-(4-methoxy-2-methylphenyl)-2*H*-pyrazol-3-ylamine (35c)

A brown oil; MS (MALDI, Pos) m/z 232 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 2.7 Hz, 1H), 6.76 (dd, J = 8.7, 2.7 Hz, 1H), 3.82 (s, 3H), 2.45 (dq, J = 3.3, 7.5 Hz, 2H), 2.18 (s, 3H), 1.11 (t, J = 7.5 Hz, 3H).

5.1.11. 5-Cyclobutyl-4-(4-methoxy-2-methylphenyl)-2*H*-pyrazol-3-ylamine (35d)

A yellow oil; MS (MALDI, Pos) m/z 258 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 2.7 Hz, 1H), 6.75 (dd, J = 8.4, 2.7 Hz, 1H), 3.82 (s, 3H), 3.32 (m, 1H), 2.22–1.72 (m, 9H).

5.1.12. 4-(4-Methoxy-2-methylphenyl)-5-trifluoromethyl-2*H*-pyrazol-3-ylamine (35e)

A pale yellow oil; TLC R_f = 0.61 (MeOH/$CHCl_3$, 1/20); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 1H),6.84 (d, J = 3.0 Hz, 1H), 6.78 (dd, J = 3.0, 8.4 Hz, 1H), 3.83 (s, 3H), 2.16 (s, 3H).

5.1.13. 4-(4-Methoxy-2-methylphenyl)-5-methylsulfanylmethyl-2*H*-pyrazol-3-ylamine (35f)

TLC R_f = 0.40 (MeOH/CH_2Cl_2, 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 2.7 Hz, 1H), 6.77 (dd, J = 8.4, 2.7 Hz, 1H), 3.82 (s, 3H), 3.51 (d, J = 13.5 Hz, 1H), 3.46 (d, J = 13.5 Hz, 2H), 2.19 (s, 3H), 1.98 (s, 3H).

5.1.14. 4-(2-Chloro-4-methoxyphenyl)-5-methyl-2*H*-pyrazol-3-ylamine (35g)

A pale yellow powder; TLC R_f = 0.26 (MeOH /CH_2Cl_2, 1:9); ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.19 (d, J = 8.7 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 8.7, 2.4 Hz, 1H), 3.83 (s, 3H), 2.13 (s, 3H).

5.1.15. 3-(4-Methoxy-2-methylphenyl)-2-methyl-6,7-dihydro-5*H*-1,4,8*a*-triaza-*s*-indacen-8-ol

To a stirred solution of **35b** (3.0 g, 13.8 mmol) in AcOH (20 mL) was added ethyl 2-oxocyclopentanecarboxylate (2.37 g, 15.2 mmol) at room temperature and the reaction mixture was allowed to be heated at reflux and stirred for 3 h. The reaction mixture was cooled to room temperature and diluted with Et_2O/hexane (1:3). The precipitates were collected by filtration to give 3-(2-methyl-4-methoxyphenyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-ol (3.88 g, 91% yield) as an off-white powder, which was used for the next reaction without further purification. TLC R_f = 0.47 (MeOH/$CHCl_3$, 1:10); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.90 (br s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 3.0 Hz, 1H), 6.83

(dd, J = 8.0, 3.0 Hz, 1H), 3.78 (s, 3H), 2.81 (t, J = 7.5 Hz, 2H), 2.66 (t, J = 7.5 Hz, 2H), 2.07 (s, 3H), 2.05 (s, 3H), 2.03 (m, 2H).

5.1.16. 8-Chloro-3-(4-methoxy-2-methylphenyl)-2-methyl-6,7-dihydro-5*H*-1,4,8*a*-triaza-*s*-indacene (37a)

To a stirred suspension of 3-(2-methyl-4-methoxyphenyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-ol (3.88 g, 12.6 mmol) in toluene (40 mL) were added diethylaniline (2.4 mL, 15.1 mmol) and phosphorus oxychloride (6.1 mL, 65.3 mmol) at room temperature and the reaction mixture was allowed to be heated at reflux and stirred for 5 h. The reaction mixture was cooled to room temperature, poured into ice-water, stirred for 20 min and extracted with EtOAc. The combined organic layers were washed with water, $NaHCO_3$ aq, brine, dried over $MgSO_4$ and evaporated to give **37a** (3.73 g, 91% yield) as a yellow powder. TLC R_f = 0.42 (EtOAc/hexane, 1:2); MS (APCI, Pos) m/z 328 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 2.4, 8.4 Hz, 1H), 3.83 (s, 3H), 3.05 (m, 4H), 2.40 (s, 3H), 2.23 (m, 2H), 2.15 (s, 3H).

5.1.17. 8-Chloro-5-(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1-oxa-4,7,7a-triaza-*s*-indacene (37b)

TLC R_f = 0.55 (EtOAc/hexane, 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 2.7 Hz, 1H), 6.81 (dd, J = 8.1, 2.7 Hz, 1H), 4.82 (t, J = 8.4 Hz, 2H), 3.83 (s, 3H), 3.40 (t, J = 8.4 Hz, 1H), 2.38 (s, 3H), 2.15 (s, 3H).

5.1.18. 8-Chloro-5-(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1-thia-4,7,7a-triaza-*s*-indacene (37c)

TLC R_f = 0.38 (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 2.5 Hz, 1H), 6.82 (dd, J = 8.5, 2.5 Hz, 1H), 3.84 (s, 3H), 3.50–3.38 (m, 4H), 2.38 (s, 3H), 2.15 (s, 3H).

5.1.19. 8-Chloro-5-(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1*H*-1,4,7,7a-tetraaza-*s*-indacene (37d)

TLC R_f = 0.31 (EtOAc/hexane, 1:3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 3.0 Hz, 1H), 6.83 (dd, J = 3.0, 8.4 Hz, 1H), 4.45 (m, 2H), 3.84 (s, 3H), 3.27 (m, 2H), 2.41 (s, 3H), 2.14 (s, 3H).

5.1.20. 8-Chloro-3-(4-methoxy-2-methylphenyl)-2-methyl-5*H*,7*H*-6-oxa-1,4,8a-triaza-*s*-indacene (39a)

TLC R_f = 0.31 (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.83 (dd, J = 8.5, 2.5 Hz, 1H), 5.21 (s, 2H), 5.01 (s, 2H), 3.84 (s, 3H), 2.43 (s, 3H), 2.15 (s, 3H).

5.1.21. 8-Chloro-3-(4-methoxy-2-methylphenyl)-2-methyl-5*H*,7*H*-6-thia-1,4,8a-triaza-*s*-indacene (39b)

A yellow solid; TLC R_f = 0.42 (EtOAc/hexane, 1:2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 3.0 Hz, 1H), 6.82 (dd, J = 8.5, 3.0 Hz, 1H), 4.28–4.22 (m, 4H), 3.84 (s, 3H), 2.42 (s, 3H), 2.14 (s, 3H).

5.1.22. 7-Chloro-3-(4-methoxy-2-methylphenyl)-2,5,6-trimethyl-pyrazolo[1,5-*a*]pyrimidine (41)

A yellow oil; R_f = 0.67 (EtOAc/hexane = 1/2); MS (APCI, Pos) 335 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 2.7 Hz, 1H), 6.91 (dd, J = 8.4, 2.7 Hz, 1H), 3.85 (s, 3H), 2.55 (s, 3H), 2.44 (s, 3H), 2.42 (s, 3H).

5.1.23. 8-Chloro-3-(4-methoxy-2-methylphenyl)-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacene (42a)

A yellow powder; TLC R_f = 0.42 (EtOAc/hexane, 1:3); ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.39 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 2.7 Hz, 1H), 6.83 (dd, J = 2.7, 8.1 Hz, 1H), 3.83 (s, 3H), 3.09 (t, J = 7.8 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 2.33 (s, 3H), 2.26 (m, 2H).

5.1.24. 8-Chloro-2-ethyl-3-(4-methoxy-2-methylphenyl)-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacene (42b)

TLC R_f = 0.89 (EtOAc/hexane, 1:1); MS (MALDI, Pos) m/z 342 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H), 3.83 (s, 3H), 3.04 (m, 4H), 2.77 (m, 2H), 2.22 (m, 2H), 2.13 (s, 3H), 1.18 (t, J = 7.8 Hz, 3H).

5.1.25. 8-Chloro-2-cyclobutyl-3-(4-methoxy-2-methylphenyl)-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacene (42c)

A solid; MS (MALDI, Pos) m/z 368 $(M+H)^+$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 2.7 Hz, 1H), 6.79 (dd, J = 8.4, 2.7 Hz, 1H), 3.83 (s, 3H), 3.60 (m, 1H), 3.05 (t, J = 5.7 Hz, 2H), 3.03 (t, J = 6.3 Hz, 2H), 2.44 (m, 2H), 2.22 (m, 4H), 2.11 (s, 3H), 1.92 (m, 2H).

5.1.26. 8-Chloro-3-(4-methoxy-2-methylphenyl)-2-trifluoromethyl-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacene (42d)

An ivory powder; TLC R_f = 0.37 (EtOAc/hexane, 1:3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 1H), 6.86 (d, J = 2.7 Hz, 1H), 6.80 (dd, J = 2.7, 8.7 Hz, 1H), 3.83 (s, 3H), 3.11 (t, J = 6.9 Hz, 2H), 3.09 (t, J = 7.8 Hz, 2H), 2.28 (m, 2H), 2.11 (s, 3H).

5.1.27. 8-Chloro-3-(4-methoxy-2-methylphenyl)-2-methylsulfanylmethyl-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacene (42e)

TLC R_f = 0.40 (EtOAc/hexane, 1:3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.1 Hz, 1H), 6.87 (d, J = 2.7 Hz, 1H), 6.81 (dd, J = 8.1, 2.7 Hz, 1H), 3.84 (d, J = 13.5 Hz, 1H), 3.83 (s, 3H), 3.71 (d, J = 13.5 Hz, 2H), 3.06 (t, J = 7.5 Hz, 2H), 3.04 (t, J = 7.5 Hz, 2H), 2.23 (m, 2H), 2.15 (s, 3H), 2.09 (s, 3H).

5.1.28. (1-Ethyl-propyl)-[3-(4-methoxy-2-methylphenyl)-2-methyl-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacen-8-yl]-amine (7a)

To a stirred solution of **37a** (1.0 g, 3.0 mmol) in 2-propanol (10 mL) was added 1-ethylpropylamine (1.78 mL, 15.3 mmol) at room temperature and the reaction mixture was allowed to be heated at 90 °C and stirred for 4 h. The reaction mixture was evaporated. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:3) to yield **7a** (1.16 g, 100% yield) as a white powder. TLC R_f = 0.57 (EtOAc/hexane, 1/1); MS (APCI, Pos) m/z 379 $(M+H)^+$; FABHRMS calcd for $C_{23}H_{30}N_4O$: 379.2498. Found: 379.2495;^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.78 (dd, J = 8.4, 2.7 Hz, 1H), 6.22 (d, J = 10.5 Hz, 1H), 3.82 (s, 3H), 3.79 (m, 1H), 3.08 (t, J = 7.2 Hz, 2H), 2.89 (t, J = 7.8 Hz, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 2.13 (m, 2H), 1.72 (m, 4H), 1.02 (m, 6H); IR (KBr) 3361, 2960, 2933, 1625, 1557, 1509, 1467, 1305, 1235, 1165, 1011, 845 cm^{-1}; mp 156–157 °C.

5.1.29. (1-Ethyl-propyl)-[5-(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1-oxa-4,7,7a-triaza-*s*-indacen-8-yl]-amine (8a)

The title compound was synthesized from **35b** as a white powder according to the same manner as described for the preparation of **7a** from **35b** using **36b** instead of **36a**. TLC R_f = 0.43 (EtOAc/hexane, 1:2); MS (APCI, Pos) m/z 381 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{29}N_4O_2$: 381.2291. Found: 381.2286; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (br s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.7 Hz, 1H), 6.82 (dd, J = 8.4, 2.7 Hz, 1H), 4.76 (t, J = 9.0 Hz, 2H), 4.30 (m, 1H), 3.83 (s, 3H), 3.74 (t, J = 9.0 Hz, 2H), 2.34 (s, 3H), 2.19 (s, 3H), 1.90–1.70 (m, 4H), 1.04 (m, 6H); IR (KBr) 3434, 2925, 1657, 1604, 1493, 1453, 1320, 1240, 1029, 756, 698 cm^{-1}.

5.1.30. (1-Ethyl-propyl)-[5-(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1-thia-4,7,7a-triaza-*s*-indacen-8-yl]-amine (9)

The title compound was synthesized from **35b** as a white powder according to the same manner as described for the preparation of **7a** from **35b** using **36c** instead of **36a**. TLC R_f = 0.40 (EtOAc/hexane, 1:2); MS (APCI, Pos) *m*/*z* 397 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{29}N_4OS$: 397.2062. Found: 397.2071; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 6.85 (d, *J* = 3.0 Hz, 1H), 6.79 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.17 (d, *J* = 10.0 Hz, 1H), 3.99 (m, 1H), 3.82 (s, 3H), 3.36–3.20 (m, 4H), 2.30 (s, 3H), 2.18 (s, 3H), 1.82–1.56 (m 4H), 1.03 (t, *J* = 7.5 Hz, 6H); IR (KBr) 3339, 2962, 2930, 1619, 1558, 1504, 1469, 1314, 1290, 1237, 1006 cm^{-1}.

5.1.31. (1-Ethyl-propyl)-[5-(4-methoxy-2-methylphenyl)-6-methyl-2,3-dihydro-1*H*-1,4,7,7a-tetraaza-*s*-indacen-8-yl]-amine (10)

The title compound was synthesized from **35b** as a viscous oil according to the same manner as described for the preparation of **7a** from **35b** using **36d** instead of **36a**. TLC R_f = 0.37 (EtOAc/hexane, 1:1); MS (APCI, Pos) *m*/*z* 380 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{30}N_5O$: 380.2450. Found: 380.2440; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.78 (dd, *J* = 2.7, 8.4 Hz, 1H), 5.86 (d, *J* = 10.5 Hz, 1H), 4.07 (m, 1H), 3.82 (s, 3H), 3.58 (t, *J* = 8.1 Hz, 2H), 3.06 (t, *J* = 8.1 Hz, 2H), 2.30 (s, 3H), 2.19 (s, 3H), 1.52–1.82 (m, 4H), 1.01 (m, 6H) ; IR (neat) 3348, 2963, 1638, 1557, 1512, 1464, 1314, 1236, 1161, 1054, 732 cm^{-1}.

5.1.32. (1-Ethyl-propyl)-[3-(4-methoxy-2-chlorophenyl)-2-methyl-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacen-8-yl]-amine (7b)

The title compound was synthesized from **36a** as a white powder according to the same manner as described for the preparation of **7a** from **36a** using **35g** instead of **35b**. TLC R_f = 0.45 (EtOAc /hexane, 1:2); MS (APCI, Pos) *m*/*z* 399 $(M+H)^+$; ^1H NMR(300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 1H), 7.05 (d, *J* = 2.7 Hz, 1H), 6.88 (dd, *J* = 2.7, 8.4 Hz, 1H), 6.22 (br d, *J* = 10.5 Hz, 1H), 3.82 (s, 3H), 3.80 (m, 1H), 3.08 (t, *J* = 7.2 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 2.14 (m, 2H), 1.52–1.82 (m, 4H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.36, 13.74, 23.65, 28.76, 29.33, 34.70, 55.59, 55.86, 97.42, 104.91, 113.04, 114.91, 124.05, 133.62, 135.44, 142.69, 146.92, 151.23, 159.14, 168.62; Anal. Calcd for $C_{22}H_{27}ClN_4O$; C, 66.24; H, 6.82; N, 14.04. Found: C, 66.11; H, 6.76; N, 14.15; IR (KBr) 33351, 2962, 1622, 1557, 1508, 1473, 1368, 1321, 1271, 1231, 1135, 1061, 1040, 1008, 875, 819, 611 cm^{-1}; mp 148–149 °C.

5.1.33. 5-(2-Chloro-4-methoxyphenyl)-*N*-(1-ethylpropyl)-6-methyl-2,3-dihydrofuro[3,2-*d*]pyrazolo[1,5-*a*]pyrimidin-9-amine (8b)

The title compound was synthesized from **35g** as a white powder according to the same manner as described for the preparation of **7a** from **35b** using **36b** instead of **36a**. TLC R_f = 0.46 (EtOAc/hexane, 1:1); MS (APCI, Pos) *m*/*z* 401 $(M+H)^+$; FABHRMS calcd for $C_{21}H_{26}ClN_4O_2$:401.1744. Found: 401.1746; ^1H NMR (300 MHz, DMSO-d_6) δ 7.30 (d, *J* = 8.42 Hz, 1H), 7.06 (d, *J* = 2.56 Hz, 1H), 6.88 (dd, *J* = 8.42, 2.56 Hz, 1H), 5.76 (d, *J* = 10.06 Hz, 1H), 4.61 (t, *J* = 8.60 Hz, 2H), 4.02–4.18 (m, 1H), 3.83 (s, 3H), 3.26 (t, *J* = 8.60 Hz, 2H), 2.35 (s, 3H), 1.50–1.80 (m, 4H), 1.00 (t, *J* = 7.41 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.35, 13.73, 28.87, 32.40, 55.60, 56.47, 70.71, 104.97, 113.10, 114.96, 123.89, 124.72, 133.11, 133.54, 135.46, 145.00, 151.17, 154.19, 159.26; IR (KBr) 1029, 1060, 1080, 1136, 1227, 1261, 1290, 1317, 1409, 1516, 1567, 1653, 2876, 2926, 2965, 3360 cm^{-1}; mp 149–150 °C.

5.1.34. 3-(2,4-Dimethylphenyl)-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (18)

The title compound was synthesized from **36a** as a white powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**.

TLC R_f = 0.50 (EtOAc/benzene, 1:10); MS (MALDI, Pos) *m*/*z* 363 $(M+H)^+$; FABHRMS calcd for $C_{23}H_{31}N_4$: 363.2549. Found: 363.2571; ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.5 Hz, 1H), 7.11 (br s, 1H), 7.03 (m, 1H), 6.21 (d, *J* = 10.8 Hz, 1H), 3.80 (m, 1H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 2.31 (s, 3H), 2.18 (s, 3H), 2.13 (m, 2H), 1.56–1.82 (m, 4H), 1.02 (m, 6H); IR (KBr) 3447, 2961, 1624, 1560, 1459, 1317, 1281, 1013 cm^{-1}.

5.1.35. *N*-(1-Ethylpropyl)-3-(4-fluoro-2-methylphenyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (19)

The title compound was synthesized from **36a** as a white powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**.

TLC R_f = 0.44 (EtOAc/hexane, 1:3); MS (MALDI, Pos) *m*/*z* 367 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{28}FN_4$: 367.2298. Found: 367.2284; ^1H NMR (300 MHz, DMSO-d_6) δ 7.34–7.24 (m, 2H), 7.20–7.10 (m, 1H), 4.03–3.85 (m, 1H), 3.14 (br t, *J* = 8.1 Hz, 2H), 2.95 (br t, *J* = 8.1 Hz, 2H), 2.25 (s, 3H), 2.25–2.10 (m) and 2.12 (s) total 5H, 1.85–1.60 (m, 4H), 0.95–0.85 (m, 6H); IR (KBr) 2967, 1645, 1593, 1543, 1460, 1357, 1325, 1255, 1154, 1129 cm^{-1}; mp 126.5–131.5 °C.

5.1.36. 3-[4-(Dimethylamino)-2-methylphenyl]-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (20)

The title compound was synthesized from **36a** as a white powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**.

TLC R_f = 0.17 (EtOAc/hexane, 1:3); MS (APCI, Pos) *m*/*z* 392 $(M+H)^+$; FABHRMS calcd for $C_{24}H_{34}N_5$: 392.2814. Found: 392.2825; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 2.7 Hz, 1H), 6.64 (dd, *J* = 8.1, 2.7 Hz, 1H), 6.19 (d, *J* = 10.2 Hz, 1H), 3.80 (m, 1H), 3.08 (t, *J* = 7.5 Hz, 2H), 2.95 (s, 6H), 2.89 (t, *J* = 7.5 Hz, 2H), 2.32 (s, 3H), 2.18 (s, 3H), 2.18–2.08 (m, 2H), 1.80–1.56 (m, 4H), 1.01 (br s, 6H); IR (KBr) 3340, 2965, 1624, 1562, 1515, 1478, 1348, 1320, 1273, 1134, 1011, 841, 806 cm^{-1}.

5.1.37. 3-(2,5-Dimethylphenyl)-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (21)

The title compound was synthesized from **36a** as a white powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **36b**.

TLC R_f = 0.54 (acetone/benzene, 1:10); MS (MALDI, Pos) *m*/*z* 363 $(M+H)^+$; FABHRMS calcd for $C_{23}H_{31}N_4$: 363.2549. Found: 363.2557; ^1H NMR(300 MHz, $CDCl_3$) δ 7.31 (br d, *J* = 10.2 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.15 (br dd, *J* = 1.2, 7.5 Hz, 1H), 7.01 (br s, 1H), 3.99 (m, 1H), 3.49 (t, *J* = 7.5 Hz, 2H), 3.14 (t, *J* = 6.9 Hz, 2H), 2.35 (s, 3H), 2.32 (s, 3H), 2.29 (m, 2H), 2.18 (s, 3H), 1.64–1.94 (m, 4H), 1.07 (t, *J* = 7.5 Hz, 6H), 1.06 (t, *J* = 7.2 Hz, 6H); IR (KBr) 3444, 2964, 1644, 1593, 1460, 1354 cm^{-1}.

5.1.38. *N*-(1-Ethylpropyl)-3-(4-methoxy-2,5-dimethylphenyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (22)

The title compound was synthesized from **36a** as an ivory powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-

1*H*-pyrazol-5-amine instead of **35b**. TLC R_f = 0.43 (EtOAc/benzene, 1:10); MS (MALDI, Pos) *m*/*z* 393 $(M+H)^+$; FABHRMS calcd for $C_{24}H_{33}N_4O$: 393.2654. Found: 393.2668; ^{1}H NMR(300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.76 (s, 1H), 6.20 (d, *J* = 10.5 Hz, 1H), 3.84 (s, 3H), 3.82 (m, 1H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 2.19 (6.9 Hz, 3H), 2.17 (s, 3H), 2.14 (m, 2H), 1.01 (m, 6H); IR (KBr) 3345, 2965, 1625, 1559, 1511, 1469, 1318, 1233, 1109 cm^{-1}.

5.1.39. *N*-(1-Ethylpropyl)-3-(4-methoxy-2,6-dimethylphenyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (23)

The title compound was synthesized from **36a** as an ivory powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**. TLC R_f = 0.33 (EtOAc/benzene, 1:10); MS (APCI, Pos) *m*/*z* 393 $(M+H)^+$; FABHRMS calcd for $C_{24}H_{33}N_4O$: 393.2654. Found: 393.2650; ^{1}H NMR(300 MHz, $CDCl_3$) δ 6.68 (s, 2H), 6.21 (d, *J* = 10.5 Hz, 1H), 3.81 (m, 1H), 3.80 (s, 3H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.19 (s, 3H), 2.13 (m, 2H), 2.04 (s, 6H), 1.55–1.83 (m, 4H), 1.03 (t, *J* = 7.5 Hz, 6H); IR (KBr) 3337, 2966, 1620, 1557, 1498, 1466, 1321, 1274, 1146, 1068, 1011 cm^{-1}.

5.1.40. *N*-(1-Ethylpropyl)-3-[4-methoxy-2-(methylsulfanyl)phenyl]-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (24)

The title compound was synthesized from **36a** as a white powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**. TLC R_f = 0.10 (EtOAc/hexane, 1:3); MS (APCI, Pos) 411 $(M+H)^+$; FABHRMS calcd for $C_{23}H_{31}N_4OS$:411.2219. Found: 411.2212; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.26–7.16 (m, 1H), 6.83 (m, 1H), 6.84–6.76 (m, 1H), 3.97 (m, 1H), 3.86 (s, 3H), 3.48 (m, 2H), 3.12 (m, 2H), 2.44 (s, 3H), 2.33 (s, 3H), 2.28 (m, 2H), 1.95–1.44 (m, 4H), 1.11–0.99 (m, 6H); IR (KBr) 3412, 3276, 2967, 1645, 1596, 1462, 1360, 1325, 1288, 1239, 1037 cm^{-1}.

5.1.41. 3-(3,4-Dimethoxyphenyl)-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (25)

The title compound was synthesized from **36a** as an off-white powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**. TLC R_f = 0.56 (EtOAc/hexane, 1:1); MS (APCI, Pos) 395 $(M+H)^+$; FABHRMS calcd for $C_{23}H_{31}N_4O_2$: 395.2447. Found: 395.243; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 2.1 Hz, 1H), 7.19 (dd, *J* = 2.1, 8.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.20 (br d, *J* = 10.5 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.80 (m, 1H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.55 (s, 3H), 2.16 (m, 2H), 1.53–1.81 (m, 4H), 1.00 (t, *J* = 7.2 Hz, 6H); IR (KBr) 3457, 2955, 1621, 1571, 1552, 1463, 1254, 1220, 1142, 1029 cm^{-1}.

5.1.42. 3-(2-Chloro-4-ethoxyphenyl)-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (26)

The title compound was synthesized from **36a** as an ivory powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**. TLC R_f = 0.49 (EtOAc/hexane, 1:2); MS (APCI, Pos) 413$(M+H)^+$; FABHRMS calcd for $C_{23}H_{30}ClN_4O$: 413.2108. Found: 413.2114; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.95 (dd, *J* = 2.4, 8.7 Hz,1H), 4.07 (m, 2H), 3.99 (m, 1H), 3.34–3.65 (m, 2H), 3.13 (t, *J* = 7.8 Hz, 2H), 2.35 (s, 3H), 2.29 (m, 2H), 1.42 (t, *J* = 6.9 Hz, 3H), 1.06 (t, *J* = 7.5 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); IR (KBr) 3428, 2968, 1650, 1596, 1548, 1462, 1325, 1287, 1227, 1060 cm^{-1}.

5.1.43. 3-[2-Chloro-4-(trifluoromethoxy)phenyl]-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (27)

The title compound was synthesized from **36a** as a colorless powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**. TLC R_f = 0.52 (EtOAc/hexane, 1:3); MS (MALDI, Pos) 453 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{25}ClF_3N_4O$: 453.1669. Found: 453.1663; ^{1}H NMR (300 MHz, Pyridine-d_5 0.5 mL $CDCl_3$ 0.1 mL) δ 7.71 (d, *J* = 8.4 Hz, 1H), 7.57 (m, 1H), 7.28 (m, 1H), 6.77 (d, *J* = 10.5 Hz, 1H), 3.74 (m, 1H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.46 (s, 3H), 1.98 (m, 2H), 1.64–1.48 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 6H); IR (KBr) 3425, 3320, 2969, 1804, 1637, 1599, 1544, 1460, 1360, 1281, 1224, 1153 cm^{-1}.

5.1.44. 3-(2,4-Dichlorophenyl)-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (28)

The title compound was synthesized from **36a** as an ivory powder according to the same manner as described for the preparation of **7a** from **36a** using an optional 4-phenyl-3-methyl-1*H*-pyrazol-5-amine instead of **35b**. TLC R_f = 0.50 (EtOAc/hexane, 1:2); MS (MALDI, Pos) *m*/*z* 403 $(M+H)^+$; FABHRMS calcd for $C_{21}H_{25}Cl_2N_4$: 403.1456. Found: 403.1443 ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.0 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.23 (d, *J* = 10.5 Hz, 1H), 3.81 (m, 1H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 2.15 (m, 2H), 1.82–1.55 (m 4H), 1.01 (t, *J* = 7.5 Hz, 6H); IR (KBr) 3315, 2957, 1626, 1562, 1500, 1463, 1377, 1320, 1280, 1094, 1069 cm^{-1}.

5.1.45. *N*-(1-Ethylpropyl)-3-(4-methoxy-2-methylphenyl)-2-methyl-5*H*,7*H*-furo[3,4-*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (11a)

The title compound was synthesized from **35b** as an ivory powder according to the same manner as described for the preparation of **7a** from **35b** using **38a** instead of **36a**. TLC R_f = 0.33 (EtOAc/hexane, 1:2); MS (MALDI, Pos) *m*/*z* 381 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{29}N_4O_2$: 381.2291. Found: 381.2288; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.32 (d, *J* = 10.0 Hz, 1H), 5.29 (s, 2H), 4.90 (br s, 2H), 3.82 (s, 3H), 3.24 (m, 1H), 2.33 (s, 3H), 2.18 (s, 3H), 1.84–1.56 (m 4H), 1.02 (t, *J* = 7.5 Hz, 6H) ; IR (KBr) 3344, 2960, 2873, 1632, 1581, 1514, 1467, 1326, 1304, 1234, 1056 cm^{-1}.

5.1.46. *N*-(1-Ethylpropyl)-3-(4-methoxy-2-methylphenyl)-2-methyl-5*H*,7*H*-pyrazolo[1,5-*a*]thieno[3,4-*d*]pyrimidin-8-amine (12)

The title compound was synthesized from **35b** as a yellow amorphous solid according to the same manner as described for the preparation of **7a** from **35b** using **38b** instead of **36a**. TLC R_f = 0.51 (EtOAc/hexane, 1:2); MS (MALDI, Pos) *m*/*z* 397 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{29}N_4OS$: 397.2062. Found: 397.2061; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1H), 6.79 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.44 (m, 1H), 4.32 (br s, 2H), 4.14 (br s, 2H), 3.82 (s, 3H), 3.76 (m, 1H), 2.32 (s, 3H), 2.18 (s, 3H), 1.84–1.57 (m 4H), 1.03 (t, *J* = 7.0 Hz, 6H); IR (KBr) 3331, 2963, 1616, 1557, 1506, 1466, 1319, 1237 cm^{-1}.

5.1.47. 3-(2-Chloro-4-methoxyphenyl)-*N*-(1-ethylpropyl)-2-methyl-5*H*,7*H*-furo[3,4-*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (11b)

The title compound was synthesized from **35g** as a white solid according to the same manner as described for the preparation of **7a** from **38b** using **36b** instead of **36a**. TLC R_f = 0.41 (EtOAc/benzene, 1:4); MS (APCI, Pos) *m*/*z* 401 $(M+H)^+$; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.30 (d, J = 8.52 Hz, 1H), 7.06 (d, J = 2.75 Hz, 1H), 6.89 (dd, J = 8.52, 2.75 Hz, 1H), 6.34 (d, J = 10.71 Hz, 1H), 5.29 (s, 2H), 4.92 (s, 2H), 3.83 (s, 3H), 3.23 (m, 1H), 2.36 (s, 3H), 1.70 (m, 4H), 1.02 (t, J = 7.42 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.29, 13.62, 28.68, 55.56, 56.86, 70.80, 72.58, 93.43, 105.71, 113.18, 115.07, 123.50, 133.55, 135.51, 141.50, 152.45, 152.47, 159.50, 163.41; Anal. Calcd for $C_{21}H_{25}ClN_4O_2$; C, 62.92; H, 6.29; N, 13.97. Found: C, 63.11; H, 6.23; N, 14.04; mp 138–139 °C.

5.1.48. *N*-(1-Ethylpropyl)-3-(4-methoxy-2-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (13)

The title compound was synthesized from **36a** as an off-white powder according to the same manner as described for the preparation of **7a** from **36a** using **35a** instead of **35b**. TLC R_f = 0.46 (EtOAc/hexane, 1:3); MS (FAB, Pos) m/z 365 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{29}N_4O$: 365.2341. Found: 365.2318; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.25 (m, 1H), 8.31 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 6.95 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 2.4, 8.1 Hz, 1H), 3.99 (m, 1H), 3.78 (s, 3H), 3.15 (m, 2H), 3.02 (t, J = 7.8 Hz, 2H), 2.20 (s, 3H), 2.18 (m, 2H), 1.60–1.88 (m, 4H), 0.89 (t, J = 7.5 Hz, 6H); IR (KBr) 3421, 2966, 1646, 1596, 1459, 1361, 1241, 1189, 1037 cm^{-1}.

5.1.49. 2-Ethyl-*N*-(1-ethylpropyl)-3-(4-methoxy-2-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (14)

The title compound was synthesized from **36a** according to the same manner as described for the preparation of **7a** from **36a** using **35c** instead of **35b**. TLC R_f = 0.59 (EtOAc/benzene, 1:5) ; MS (MALDI, Pos) m/z 393 $(M+H)^+$; FABHRMS calcd for $C_{24}H_{33}N_4O$: 393.2654. Found: 393.2646; H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 2.7 Hz, 1H), 6.77 (dd, J = 8.1, 2.7 Hz, 1H), 6.27 (d, J = 10.5 Hz, 1H), 3.82 (s, 3H), 3.80 (m, 1H), 3.08 (t, J = 7.5 Hz, 2H), 2.89 (t, J = 7.8 Hz, 2H), 2.67 (m, 2H), 2.17 (s, 3H), 2.13 (m, 2H), 1.81–1.52 (m, 4H), 1.16 (t, J = 7.2 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H), 1.01 (t, J = 7.8 Hz, 3H); IR (neat) 2963, 1623, 1557, 1508, 1459, 1275, 1235, 1160 cm^{-1}.

5.1.50. 2-Cyclobutyl-*N*-(1-ethylpropyl)-3-(4-methoxy-2-methylphenyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (15)

The title compound was synthesized from **36a** as an off-white powder according to the same manner as described for the preparation of **7a** from **36a** using **35d** instead of **35b**. TLC R_f = 0.62 (EtOAc/benzene, 1:5); MS (MALDI, Pos) m/z 419 $(M+H)^+$; FABHRMS calcd for $C_{26}H_{35}N_4O$: 419.2811. Found: 419.2835; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 2.7 Hz, 1H), 6.75 (dd, J = 8.1, 2.7 Hz, 1H), 6.35 (d, J = 10.5 Hz, 1H), 3.82 (s, 3H), 3.81 (m, 1H), 3.53 (m, 1H), 3.08 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 7.8 Hz, 2H), 2.41 (m, 2H), 2.28–2.06 (m, 4H), 2.15 (s, 3H), 2.01–1.58 (m, 6H), 1.05 (t, J = 7.5 Hz, 3H), 1.02 (t, J = 7.8 Hz, 3H); IR (neat) 2963, 1623, 1556, 1508, 1465, 1276, 1238, 1160 cm^{-1}.

5.1.51. *N*-(1-Ethylpropyl)-3-(4-methoxy-2-methylphenyl)-2-(trifluoromethyl)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (16)

The title compound was synthesized from **36a** as a white powder according to the same manner as described for the preparation of **7a** from **36a** using **35e** instead of **35b**. TLC R_f = 0.42 (EtOAc/hexane, 1:3); MS (APCI, Pos) m/z 433 $(M+H)^+$; FABHRMS calcd for $C_{23}H_{28}F_3N_4O$: 433.2215. Found: 433.2223; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (br d, J = 10.2 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 2.4, 8.7 Hz, 1H), 4.04 (m, 1H), 3.83 (s, 3H), 3.56 (m, 2H), 3.20 (m, 2H), 2.33 (m, 2H), 2.19 (s, 3H), 1.70–2.22 (m, 4H), 1.08 (m, 6H); IR (KBr) 3428, 2968, 1650, 1597, 1507, 1461, 1363, 1242, 1180, 1134 cm^{-1}.

5.1.52. *N*-(1-Ethylpropyl)-3-(4-methoxy-2-methylphenyl)-2-[(methylsulfanyl)methyl]-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine hydrochloride (17)

A colorless powder. TLC R_f = 0.31 (EtOAc/hexane, 1:3); MS (MALDI, Pos) m/z 425 $(M+H)^+$; FABHRMS calcd for $C_{24}H_{33}N_4OS$: 425.2375. Found: 425.2383; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (br d, J = 10.8 Hz, 1H), 7.16 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 2.4 Hz, 1H), 6.80 (dd, J = 8.4, 2.4 Hz, 1H), 4.00 (br s, 1H), 3.83 (s, 3H), 3.70 (d, J = 13.5 Hz, 1H), 3.60 (d, J = 13.5 Hz, 1H), 3.50 (m, 2H), 3.14 (t, J = 7.2 Hz, 2H), 2.29 (m, 2H), 2.32 (s, 3H), 2.04 (s, 3H), 1.95–1.65 (m, 4H), 1.07 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.5 Hz, 3H); IR (KBr) 2964, 1644, 1591, 1543, 1459, 1359, 1307, 1237, 1043 cm^{-1}.

5.1.53. 3-(2-Chloro-4-methoxyphenyl)-*N*-(1-ethylpropyl)-2,5,6-trimethylpyrazolo[1,5-*a*]pyrimidin-7-amine (30)

The title compound was synthesized from **35g** as a white powder according to the same manner as described for the preparation of **7a** from **35g** using **41** instead of **36a**.

TLC R_f = 0.43 (EtOAc/hexane, 1:3); MS (APCI, Pos) 387 $(M+H)^+$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.52 Hz, 1H), 7.05 (d, J = 2.47 Hz, 1H), 6.88 (dd, J = 8.52, 2.75 Hz, 1H), 5.98 (d, J = 10.44 Hz, 1H), 3.89 (m, 1H), 3.83 (s, 3H), 2.46 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H), 1.67 (m, 4H), 0.99 (t, J = 7.42 Hz, 6H); Anal. Calcd for $C_{21}H_{27}ClN_4O$; C, 65.19; H, 7.03; N, 14.48. Found: C, 65.30; H, 7.06; N, 14.47; mp 117–119 °C.

5.1.54. 3-(2-Chloro-4-methoxyphenyl)-2-methyl-6,7-dihydrofuro[2,3-*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (44)

A solution of **43** (700 mg, 6.3 mmol) and 38 g in pyridine (0.9 mL) was heated up to reflux temperature and stirred for 14 h. The solvent was removed by evaporation. The resulting residue was purified by column chromatography on silica gel (MeOH/CH_2Cl_2, 1:10) to give **44** (756 mg, 36% yield) as an ivory powder. TLC R_f = 0.40 (MeOH/CH_2Cl_2, 1:9); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.01 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.5, 2.6 Hz, 1H), 5.47 (s, 2H), 4.68 (m, 2H), 3.80 (s, 3H), 3.11 (t, J = 8.2 Hz, 2H), 2.32 (s, 3H).

5.1.55. 3-(2-Chloro-4-methoxyphenyl)-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydrofuro[2,3-*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (31)

To a stirred solution of **44** (200 mg, 0.60 mmol) in DMF (3.0 mL) was added NaH (26 mg, 0.67 mmol , 60% in mineral oil) and tetrabutylammoniun iodide (catalytic amount) at ambient temperature under argon atmosphere. After 1.5 h, the reaction mixture was allowed to be heated at 50 °C for 1 h, then at 80 °C for 22 h. The reaction mixture was cooled to ambient temperature and diluted with hexane/EtOAc (1:1). The organic layer was washed with brine and dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using Et_2O/hexane (1:2–1:3) to give **31** (36 mg, 15% yield) as an ivory powder. TLC R_f = 0.67 (EtOAc/hexane, 1:1) ; MS (APCI, Pos) m/z 401 $(M+H)^+$; FABHRMS calcd for $C_{21}H_{26}ClN_4O_2$: 401.1744. Found: 401.1743; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.01 (d, J = 2.6 Hz, 1H), 6.84 (dd, J = 8.5, 2.6 Hz, 1H), 6.18 (d, J = 10.8 Hz, 1H), 4.62 (m, 2H), 3.81 (s, 3H), 3.60 (m, 1H), 3.34 (t, J = 8.2 Hz, 2H), 2.30 (s, 3H), 1.68 (m, 4H), 1.01 (m, 6H); mp 139–141 °C.

5.1.56. 3-Chloro-4-[8-(1-ethylpropylamino)-2-methyl-6,7-dihydro-5*H*-1,4,8a-triaza-*s*-indacen-3-yl]-phenol (45)

To a stirred solution of **7b** (1.0 g, 2.5 mmol) in CH_2Cl_2 was added BBr_3 (7.5 mL, 7.5 mmol, 1.0 M CH_2Cl_2 solution) at −50 °C under argon atmosphere and allowed to be warmed at 0 °C. After being stirred for 5.5 h, the reaction mixture was quenched with $NaHCO_3$ aq

and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The resulting residue was purified by column chromatography on silica gel to yield **45** (730 mg, 76% yield) as an ivory solid. TLC R_f = 0.31 (EtOAc/hexane, 1:2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.43 (br s, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 6.50 (dd, J = 8.3, 2.5 Hz, 1H), 6.42 (d, J = 10.4 Hz, 1H), 3.85 (m 1H), 3.12 (t, J = 7.1 Hz, 2H), 3.00 (t, J = 7.9 Hz, 2H), 2.30 (s, 3H), 2.20 (tt, J = 8.9, 7.3 Hz, 2H), 1.76 (m, 2H), 1.66 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H).

5.1.57. 3-[2-Chloro-4-(difluoromethoxy)phenyl]-*N*-(1-ethylpropyl)-2-methyl-6,7-dihydro-5*H*-cyclopenta[*d*]pyrazolo[1,5-*a*]pyrimidin-8-amine (29)

In a three-neck flask (50 mL) equipped with a condenser (dry-ice), a gas-inlet tube, and a magnetic stirring bar, NaOH (310 mg, 7.8 mmol) was added to a solution of **45** (600 mg, 1.6 mmol) in a mixture of THF (11.0 mL) and H_2O (0.7 mL) at room temperature. The reaction mixture was stirred under the continuous flow of ClF_2CH for 3 h at reflux temperature. The resulting mixture was cooled and extracted with *t*-BuOMe. The organic layer was washed with water, brine, dried over $MgSO_4$ and evaporated. The resulting residue was purified by column chromatography on silica gel to yield **29** (380 mg, 56% yield) as a white solid. TLC R_f = 0.49 (EtOAc/hexane, 1:2); MS (APCI, Pos) 435 $(M+H)^+$; FABHRMS calcd for $C_{22}H_{26}ClF_2N_4O$: 435.1763. Found: 435.1744; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.09 (dd, J = 8.4, 2.4 Hz, 1H), 6.52 (t, J = 73.5 Hz, 1H), 6.24 (d, J = 10.5 Hz, 1H), 3.81 (m, 1H), 3.09 (m, 2H), 2.91 (m, 2H), 2.35 (s, 3H), 2.15 (m, 2H), 1.82–1.54 (m, 4H), 1.02 (t, J = 7.5 Hz, 6H); IR (KBr) 3343, 2962, 2875, 1625, 1558, 1503, 1391, 1322, 1271, 1221, 1132, 1036 cm^{-1}.

5.1.58. 3-Oxo-pyrrolidine-1,2-dicarboxylic acid 1-benzyl ester 2-ethyl ester (36d)

The titled compound was prepared as detailed in the literature.[43]

TLC R_f = 0.40 (EtOAc/hexane 1:2); ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.23–7.44 (m, 5H), 5.06–5.28 (m, 2H), 4.61 and 4.56 (s, total 1H), 3.80–4.33 (m, 4H), 2.70 (t, J = 7.5 Hz, 2H),1.30 and 1.16 (t, J = 7.2 Hz, total 3H).

5.2. Biology

5.2.1. Membrane preparations

CHO-K1 cells expressing CRF receptor type 1 were washed with phosphate buffered saline (PBS), scraped and pelleted by centrifugation. Cell pellets were homogenized with binding assay buffer (50 mmol/l Tris–HCl buffer containing 10 mmol/l MgCl , 2 mmol/l EDTA, and 10 TIU/L aprotinin) and centrifuged at 10,000 g for 15 min at 4 °C. The pellet was suspended in the assay buffer, and used as crude membrane preparations for binding studies. Protein concentration was determined according to Bradford, 1976.

5.2.2. Binding assay

Binding assays for ^{125}I human/rat CRF were done according to reported method (De Souza, 1987; Grigoriadis et al., 1996) but with slight modification. The reaction was initiated by incubating 49 μl of membrane preparations with 50 μl of 0.5 nmol/l ^{125}I human/rat CRF and 1 μl of test compound (1–10,000 nmol/l). The reaction mixture was incubated for 2 h at room temperature, and terminated by centrifugation at 15,000 g for 10 min, and pellet was washed with PBS containing with 0.01% Triton X-100. The radioactivity was measured in a γ-counter. Nonspecific bindings were determined in the presence of unlabeled 1 μmol/l human/rat CRF. Specific binding was determined by subtracting nonspecific binding from total binding. Concentration of the test compound that caused 50% inhibition of specific radiolabeled ligand binding (IC_{50} values) was determined from each concentration–response curve.

5.2.3. cAMP assay

CHO-K1 cells expressing CRF receptor type 1 dispersed at 1×10^4 cells/well in 96-well plates were incubated overnight. The culture medium was removed, the cells were washed twice with F-12 nutrient mixture, and then 178 μl of assay medium (F12 nutrient mixture containing 1 mmol/l 3-isobutyl-1-methylxanthine, a phosphodiesterase inhibitor) was added. After incubation for 10 min at 37 °C, cells were treated with 2 μl of test compound (1–10,000 nmol/l) and 20 μl of assay medium containing 10 nmol/l CRF. After the treated cells were incubated for 15 min at 37 °C, supernatants were aspirated, and cells were immediately chilled to terminate further reactions. cAMP formed in the cells was determined using a cAMP enzyme immunoassay system.

The cAMP level under respective treatments was determined by mean of corresponding two wells of the blank group from that of treatment group. Concentration of the test compound that caused 50% inhibition of cAMP production (IC_{50} values) was determined from each concentration–response curve.

5.2.4. Elevated plus-maze test in swim stress-loaded rats

5.2.4.1. Animals. Male Sprague–Dawley rats weighing 230–280 g (Charles River, Japan) were used. Rats were accommodated for more than a week in a room at 24 ± 2 °C, 55 ± 15% relative humidity with controlled 12 h dark–light cycles (alternating 12 h cycles with illumination from fluorescent light: 08:00–20:00 h) and were allowed free access to food and water. They were housed in groups of five or six rats per cage until experiments. All experimental procedures were approved by the Animal Care and Use Committee of Ono Pharmaceutical Co. Ltd and conducted in accordance with the 'Guidelines on the Use of Experimental animals'.

5.2.4.2. Elevated plus-maze test in rats, swim stress induced anxiety-like behavior. The elevated plus-maze apparatus was made of Plexiglas and consisted of four arms (50 cm long × 10 cm wide): two had 40 cm high walls (closed arms), and two had no walls (open arms). The maze was elevated to a height of 50 cm. In the experiments of swim stress paradigm, rats were forced to swim for 90 s in a pool (40 × 30 × 38 cm) filled with water (depth of 25 cm) maintained at 22 ± 2 °C prior to the elevated plus-maze test. In non-stress conditions, the rats in the control group were not subjected to forced swim stress. After forced swim stress for 90 s, rats were removed from the pool and dried with a paper towel. For testing, rats were placed individually onto the center of the maze facing a closed arm and behavior was recorded for 5 min with a video camera. The images were analyzed using a computerized behavior tracking and analysis system (EthoVision Version 3.0, Noldus Information Technology). The primary measures were the time spent in open arms and the number of entries in open arms.

Experiments were performed 1 h after oral administration of vehicle (0.5% MC (w/v)), test compounds (1, 3, and 10 m/kg).

5.2.4.3. Data and statistical analysis. The results of the elevated plus-maze test were expressed as mean ± S.E. values. Comparisons between the vehicle and control groups were performed using the *t*-test, while differences between the vehicle and test compound groups were compared with the Dunnett test. Probabilities of <5% (p <0.05) were considered statistically significant.

5.3. Single dose rat pharmacokinetic study of 7b

Single dose pharmacokinetics of **7b** was studied in rats. Formulation for intravenous injection was prepared using saline containing 30% HP-β-CD (w/v). Formulation for oral dosing was prepared using saline containing 0.5% MC (w/v). Test compounds (0.3 mg/kg) were dosed intravenously to the fasted male rats ($n = 4$). Test compounds (3 mg/kg) were dosed orally to the fasted male rats ($n = 4$). After dosing, blood samples (250 μl) were collected from the jugular vein using a heparinized syringe at the selected time points (iv: pre-dosing, 2, 5, 15, 30 min and 1, 2, 3, 4, 8, 24, 48, 72 h; po: 1, 2, 4, 6, 8, 24, 48, 72 h, respectively). The blood samples were ice-chilled and then centrifuged at 12,000 rpm for 2 min at room temperature to obtain plasma, which was preserved at −70 °C in a freezer. The AUC, C_{max}, T_{max}, $T_{1/2}$, V_{ss} and CL were obtained by measuring the time course of the plasma concentration of the test compounds. Bioavailability (F) was calculated according to the following equation:

$$F(\%) = (AUC_{po}/D_{po})/AUC_{iv}/D_{iv}) \times 100$$

AUC_{po}: AUC after oral dosing; AUC_{iv}: AUC after intravenous dosing; D_{po}: Dosage of oral administration; D_{iv}: Dosage of intravenous administration.

References and notes

1. Holsboer, F.; Ising, M. *Eur. J. Pharmacol.* **2008**, *583*, 350.
2. Hemley, C. F.; McCluskey, A.; Keller, P. A. *Curr. Drug Targets* **2007**, *8*, 105.
3. Zoumakis, E.; Rice, K. C.; Gold, P. W.; Chrousos, G. P. *Ann. N.Y. Acad. Sci.* **2006**, *1083*, 239.
4. Ising, M.; Hosboer, F. *Exp. Clin. Psychopharmacol.* **2007**, *15*, 519.
5. Vale, W.; Speiss, J.; Rivier, C. *Science* **1981**, *213*, 1394.
6. Kehne, J. H.; De Lombaert, S. *Curr. Drug Targets CNS Neurol. Disorders* **2002**, *1*, 467.
7. De Souza, E.;Grigoriadis, D.E., In *Neuropsychopharmacology; The Fifth Generation of Williams & Wilkins*, Philadelphia; 2002.
8. Dzierba, C. D.; Hartz, R. A.; Bronson, J. J. *Annu. Rep. Med. Chem.* **2008**, *43*, 3.
9. Stckler, T.; Dautzenberg, F. M. *CNS Neurol. Disord. Drug Targets* **2006**, *5*, 147.
10. Gilligan, P. J.; Li, Y.-W. *Curr. Opin. Drug Discov Devel.* **2004**, *7*, 487.
11. Chen, C. *Curr. Med. Chem.* **2006**, *13*, 1261.
12. Gilligan, P. J. *Expert Opin. Ther. Patents* **2006**, *16*, 913.
13. Zolbel, A. W.; Nichel, T.; Kunzel, H. E.; Ackl, N. *J. Psychiatr. Res.* **2000**, *34*, 171.
14. Binneman, B.; Feltner, D.; Kolluri, S.; Shi, Y.; Qiu, R.; Stiger, T. *Am. J. Psychiatry* **2008**, *165*, 617.
15. Strome, E. M.; Wheler, G. H.; Higley, J. D.; Loriaux, D. L.; Soumi, S. J.; Doudet, D. J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 15749.
16. Roche, M.; Commons, K. G.; Peoples, A.; Valentino, R. J. *J. Neurosci.* **2003**, *23*, 970.
17. Bakshi, V. P.; Smith-roe, S.; Newman, S. M.; Grigoriadis, D. E.; Kalin, N. H. *J. Neurosci.* **2002**, *22*, 2926.
18. Schulz, D. W.; Mansbach, R. S.; Sprouse, J.; Braselton, J. P.; Collins, J.; Corman, M.; Dunaiskis, A.; Faraci, S.; Schmidt, A. W.; Seeger, T.; Seymour, P.; Tingley, F. D.; Winston, E. N.; Chen, Y. L.; Heym, J. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10477.
19. Chen, Y. L.; Mansbach, R. S.; Winter, S. M.; Brooks, E.; Collins, J.; Corman, M. L.; Dunaiskis, A. R.; Faraci, W. S.; Gallaschun, R. J.; Schmidt, A.; Schulz, D. W. *J. Med. Chem.* **1997**, *40*, 1749.
20. Gilligan, P. J.; Baldauf, C.; Cocuzza, A.; Chidester, D.; Zaczek, R.; Fitzgerald, L. W.; McElroy, J. F.; Smith, M. A.; Shen, H.-S. L.; Saye, J. A.; Christ, D.; Trainor, G.; Robertson, D. W.; Hartig, P. *Bioorg. Med. Chem.* **2000**, *8*, 181.
21. Chaki, S.; Nakazato, A.; Kennis, L.; Nakamura, M.; Mackie, C.; Sugiura, M.; Vinken, P.; Ashton, D.; Langlois, X.; Steckler, T. *Eur. J. Pharmacol.* **2004**, *485*, 145.
22. Gilligan, P. J.; Folmer, B. K.; Hartz, R. A.; Koch, S.; Nanda, K. K.; Andreuski, S.; Fitzgerald, L.; Miller, K.; Marshall, W. J. *Bioorg. Med. Chem.* **2003**, *11*, 4093.
23. Dyck, B.; Grigoriadis, D. E.; Gross, R. S.; Guo, Z.; Haddach, M.; Marinkovic, D.; McCarthy, J. R.; Moorjani, M.; Regan, C. F.; Saunders, J.; Schwaebe, M. K.; Szabo, T.; Williams, J. P.; Zhang, X.; Bozigian, H.; Chen, T. K. *J. Med. Chem.* **2005**, *48*, 4100.
24. Guo, Z.; Tellew, J. E.; Gross, R. S.; Dyck, B.; Grey, J.; Haddach, M.; Kiankarimi, M.; Lanier, M.; Li, B.-F.; Luo, Z.; McCarthy, J. R.; Saunders, J.; Sullivan, R.; Zhang, X.; Zamani-Kord, S.; Grigoriadis, D. E.; Crowe, P. D.; Chen, T. K.; Williams, J. P. *J. Med. Chem.* **2005**, *48*, 5104.
25. Gross, R. S.; Guo, Z.; Dyck, B.; Coon, T.; Huang, C. Q.; Lowe, R. F.; Marinkovic, D.; Moorjani, M.; Nelson, J.; Zamani-Kord, S.; Grigoriadis, D. E.; Hoare, S. R. J.; Crowe, P. D.; Bu, J. H.; Haddach, M.; McCarthy, J.; Saunders, J.; Sullivan, R.; Chen, T.; Williams, J. P. *Med. Chem.* **2005**, *48*, 5780.
26. Han, X.; Pin, S. S.; Burris, K.; Fung, L. K.; Huang, S.; Taber, M. T.; Zhang, J.; Dubowchik, G. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4029.
27. Han, X.; Civiello, R.; Pin, S. S.; Burris, K.; Balanda, L. A.; Knipe, J.; Ren, S.; Fiedler, T.; Browman, K. E.; Macci, R.; Taber, M. T.; Zhang, J.; Dubowchik, G. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2026.
28. Gentile, G.; Di Fabio, R.; Pavone, F.; Sabbatini, F. M.; St-Denis, Y.; Zampori, M. G.; Vitulli, G.; Worby, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5218.
29. St-Denis, Y.; Di Fabio, R.; Bernasconi, G.; Castiglioni, E.; Conati, S.; Fazzolari, E.; Gentile, G.; Ghirlanda, D.; Marchionni, C.; Messina, F.; Micheli, F.; Pavone, F.; Pasqarello, A.; Sabbatini, F. M.; Zampori, M. G.; Arban, R.; Vitulli, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3713.
30. Nakazato, A.; Okubo, T.; Nozawa, D.; Tamita T.; Kennis, L.E.J., *PCT Publication* WO 2005/066178.
31. Luo, Z.; Tellew J.E.; Williams, J., *PCT Publication* WO 2005/063749.
32. Hibi S.; Hoshino Y.; Yoshiuchi T.; Shin K.; Kikuchi K. et al, WO200142247.
33. He, L.; Gilligan, P. J.; Zaczek, R.; Fitzgerald, L. W.; McElroy, J.; Shen, H.-S. L.; Saye, J. A.; Kalin, N. H.; Shelton, S.; Christ, D.; Trainor, G.; Hartig, P. *J. Med. Chem.* **2000**, *43*, 449.
34. Matsuda, T.; Yamazaki, M., et al *Chem. Pharm. Bull.* **1985**, *33*, 937.
35. Miller, T. G.; Thanassi, J. W. *J. Org. Chem.* **1960**, *25*, 2009.
36. Battaglia, G.; Webster, E. L.; De Souza, E. B. *Synapse* **1987**, *1*, 572.
37. McElroy, J. F.; Ward, K.; Zeller, K. L.; Jones, K. W.; Gilligan, P. L.; He, L.; Lelas, S. *Psychopharmacology* **2002**, *165*, 86.
38. Li, Y.-W.; Hill, G.; Wong, H.; Kelly, N.; Ward, K.; Pierdomenico, M.; Ren, S.; Gilligan, P.; Grossman, S.; Trainor, G.; Taub, R.; McElroy, J.; Zaczek, R. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 86.
39. Li, Y.-W.; Fitzgerald, L.; Wong, H.; Lelas, S.; Zhang, G.; Lindner, M. D.; Wallace, T.; McElroy; Lodge, N. J.; Gilligan, P. J.; Zaczek, R. *CNS Drug Rev.* **2005**, *11*, 21.
40. Chen, C.; Wilcoxen, K. M.; Huang, C. Q.; McCarthy, J. R.; Chen, T.; Grigoriadis, D. E. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3669.
41. Hartz, R. A.; Nanda, K. K.; Ingalls, C. L.; Ahuja, V. T.; Molski, T. F.; Zhang, G.; Wong, H.; Peng, Y.; Kelley, M.; Lodge, N. J.; Zaczek, R.; Gilligan, P. J.; Trainor, G. L. *J. Med. Chem.* **2004**, *47*, 4741.
42. Gilligan, P. J.; Baldauf, C.; Cocuzza, A.; Chidester, D.; Zaczek, R.; Fitzgerald, L. W.; McElroy, J.; Smith, M. A.; Shen, H.-S. L.; Saye, J. A.; Christ, D.; Trainor, G.; Robertson, D. W.; Hartig, P. *Bioorg. Med. Chem.* **2000**, *8*, 181.
43. Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.