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Synthesis and structure–activity relationship of tetrahydropyrazolopyrimidine derivatives—A novel structural class of potent calcium-sensing receptor antagonists

Masato Yoshida *, Akira Mori, Atsuhiro Inaba, Masahiro Oka, Haruhiko Makino, Masashi Yamaguchi, Hisashi Fujita, Tomohiro Kawamoto, Mika Goto, Hiroyuki Kimura, Atsuo Baba, Tsuneo Yasuma

Pharmaceutical Research Division, Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi-2-chome, Yodogawa-ku, Osaka 532-8686, Japan

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ABSTRACT

A series of novel tetrahydropyrazolopyrimidine derivatives containing an adamantyl group were synthesized and evaluated as potential calcium-sensing receptor (CaSR) antagonists. After chemical modification of **9a**, which was identified as a hit compound in a random screening of CaSR antagonist assay, 7,7-dimethyl derivative **16c** was found to be the most active compound of this new series (IC_{50} = 10 nM). We report the synthesis of this series and their biological activities and structure–activity relationship.

1. Introduction

Osteoporosis is a common, serious disease in which bone density is reduced.[1] Low bone density can lead to fractures and significant health problems. Worldwide, 100–200 million people are at risk of osteoporotic fractures.[2,3] Currently available therapies such as estrogen, raloxifene,[4] calcitonin, and bisphosphonate[5,6] therapies prevent further bone loss by inhibiting bone resorption, and maintain the required bone density, thus reducing fracture risk by 40–50%. Patients with significantly advanced osteoporosis, however, require alternative, more effective therapies for better outcomes. The current list of anabolic agents in development includes fluoride,[7] IGF-1,[8] statins,[9] and parathyroid hormone (PTH).[10–12] PTH is an 84-amino acid peptide produced by the parathyroid glands that regulates calcium homeostasis through actions on the kidney and bone. Clinical trials on recombinant hPTH-(1–34) (called Teriparatide) have been completed, and this drug has reached the market as the first bone anabolic agent. However, Teriparatide must be administered parenterally. An orally active anabolic agent can provide a valuable alternative for treating osteoporosis.

PTH secretion from the parathyroid glands is closely regulated by the seven-transmembrane-spanning extracellular calcium-sensing receptor (CaSR),[13] a G-protein-coupled receptor (GPCR) that is expressed at high levels on parathyroid cells. CaSR is predominantly expressed on the surface of parathyroid cells and responds to small changes in the concentration of circulating Ca^{2+}, thus leading to PTH regulation. The receptor is negatively coupled to PTH secretion; therefore, increasing the concentration of extracellular Ca^{2+} leads to inhibition of PTH secretion. It has been proposed that an antagonist of CaSR (a calcilytic) can mimic a state of hypocalcemia and stimulate PTH secretion.[14] Since it is well established that a transient increase in plasma PTH through daily injection of hormone potently stimulates bone formation in several species, including humans, stimulation of endogenous PTH secretion through antagonism of CaSR is anticipated to produce a similar anabolic effect on bone.

Recently, some small organic molecules were discovered to be calcilytic compounds: NPS-2143 (**1**), PHD-401 (**2**), quinazolin-4(3*H*)-one derivative (**3**), and quinazoline-2(1*H*)-thione derivative (**4**) (Fig. 1).[14–19] NPS-2143 elicits a three to fourfold increase in the plasma PTH level when administered orally.[18] When administered together with an antiresorptive agent (estradiol), NPS-2143 causes an increase in trabecular bone volume and bone mineral density in osteopenic rats. These findings show that calcilytics can be developed as a novel class of anabolic agents for the treatment of osteoporosis. In order to identify alternative and proprietary structural class of calcilytics, we conducted a high-throughput screening that involved a GTP-binding assay for CaSR. This led to the identification of the tetrahydropyrazolopyrimidine derivative containing an adamantyl group, **9a**—whose structure is completely different from those of known calcilytics—as a lead compound with an

* Corresponding author. Tel.: +81 6 6308 9081; fax: +81 6 6300 6306.
E-mail address: Yoshida_Masato@takeda.co.jp (M. Yoshida).

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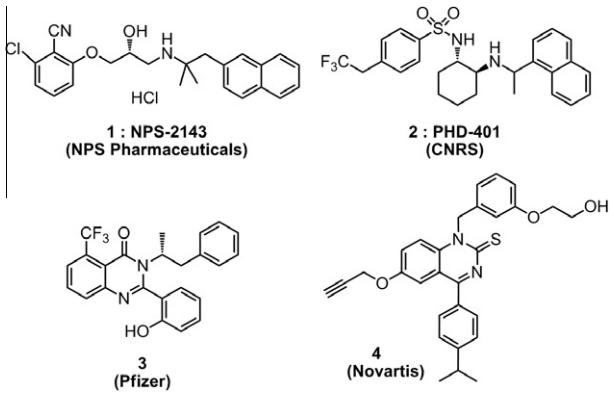


Figure 1. Calcilytic compounds.

IC_{50} = 40 nM. In this report, we describe the synthesis and preliminary structure–activity relationship of these new calcilytic congeners.

2. Chemistry

The hit compound, **9a**; 5,7-substituted analogue **9b–l**; and the ester analogue **10** were synthesized via the route shown in *N*-methyl analogue Scheme 1. Condensation of commercially available aminopyrazole **5** with various diketones in acetic acid gave the pyrazolopyrimidines **6a–l**. Reduction of the pyrimidine ring with sodium borohydride ($NaBH_4$) gave only *cis* isomer of tetrahydropyrazolopyrimidines **7a–l**, and subsequent hydrolysis with potassium hydroxide (KOH) gave carboxylic acids **8a–l**. The carboxylic acids were condensed with 1-adamantylamine to give **9a**–**l**, and with 1-adamantanol to give the ester analogue **10**. *N*-methyl analogue **11** was prepared by alkylation of **9a** by using sodium hydride and methyl iodide.

The synthesis of 5-unsubstituted analogue **16a** and 7-unsubstituted analogue **16b** was accomplished as outlined in Scheme 2. Intermediates **12a** and **12b** were obtained by condensation of aminopyrazole **5** with ethyl 4,4,4-trifluoroacetoacetate and ethyl benzoylacetate, respectively.[20,21] After treatment of **12a–b** with phosphorus oxychloride ($POCl_3$) to form the pyrimidine ring, the pyrimidine ring was reduced with 10% Pd–C under a hydrogen atmosphere, and tetrahydropyrazolopyrimidines **14a–b** were obtained. Subsequent hydrolysis with KOH gave the carboxylic acids 15a–**b**. Finally, the carboxylic acids were reacted with 1-adamantylamine to give **16a** and **16b**, respectively. The synthesis of 7,7-dimethyl analogue **16c** is also described in Scheme 2. Treatment of 2-aminopyrazole **5** with 3-methyl-1-phenylbut-2-en-1-one in trifluoroacetic acid (TFA) gave the dihydropyrazolopyrimidine **12c**. Reduction of the dihydropyrimidine ring with 10% Pd–C under hydrogen atmosphere gave tetrahydropyrazolopyrimidine **14c**, and subsequent hydrolysis with KOH gave carboxylic acid **15c**. Finally, condensation reactions performed using 2-(1*H*-7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HATU) as a coupling reagent gave **16c**. 7,7-Dimethyl dihydropyrazolopyrimidine derivative **12e** was also prepared from ethyl ester **12c** under the same conditions as those employed for the preparation of **16**.

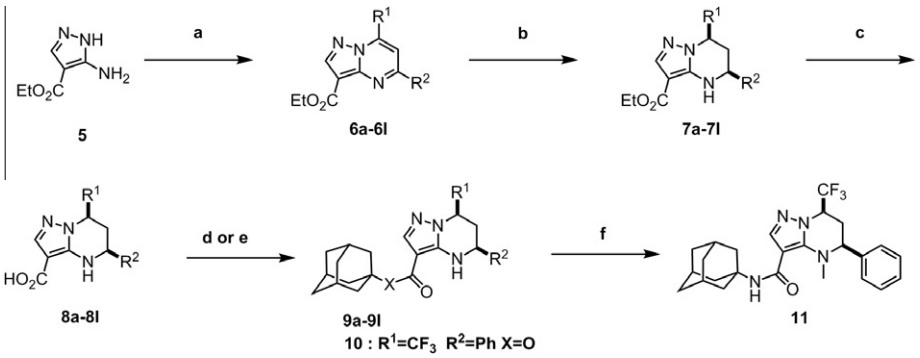
Reverse amide **23** was prepared as shown in Scheme 3. After condensation of aminopyrazole **17** with 4,4,4-trifluoro-1-phenylbutane-1,3-dione in acetic acid, formylation via the Vilsmeier reagent was performed to yield aldehyde **18**. Subsequently, oxidation of **18** with $NaClO_2$ gave carboxylic acid **19a**. The carboxylic acid was then converted into amine **20** by Curtius rearrangement and removal of the Boc group. Finally, condensation with 1-adamantane carboxylic acid and subsequent reduction with $NaBH_4$ gave the reverse amide **23**. Amine analogue **25** was synthesized from aldehyde **18** by reductive amination using sodium cyanoborohydride, and the reaction of carboxylic acid **19a** with 1-adamantylamine gave pyrazolopyrimidine derivative **19b**.

3. Results and discussion

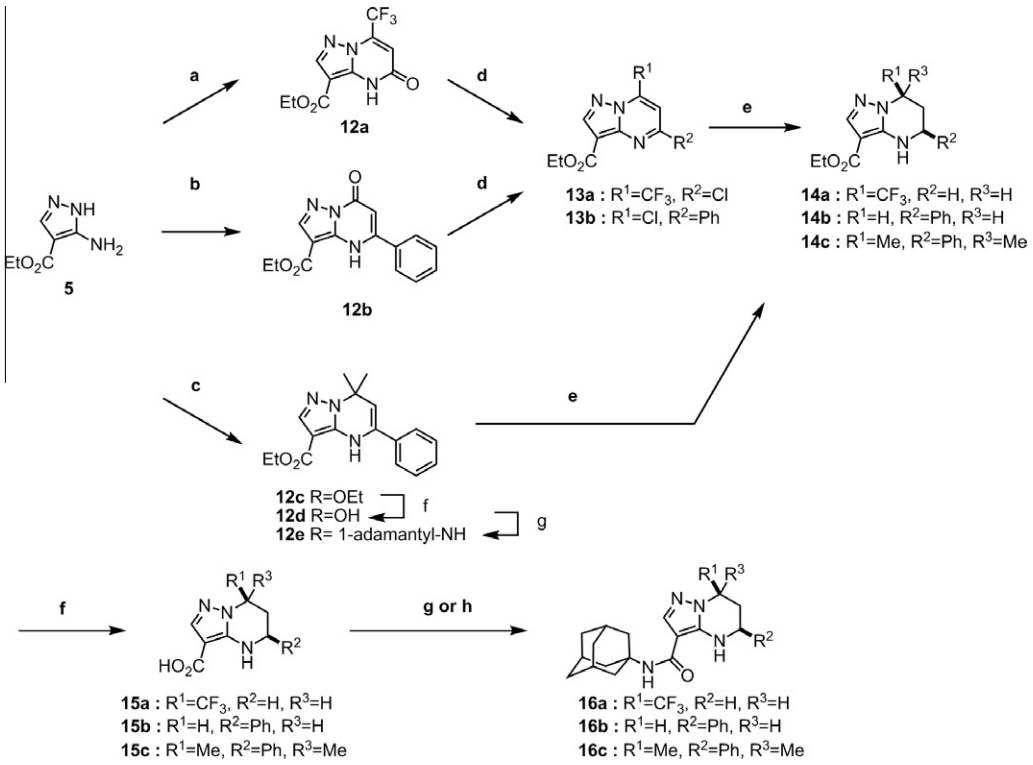
The antagonistic activity of the synthesized compounds was evaluated by performing a GTP-binding assay, in which the membrane fractions were prepared from CaSR-expressing CHO cells.

We initially prepared several adamantyl analogues in the 5-phenyl-7-trifluoromethyl series to investigate the effect of a carbamoyl linker at the 3-position and an NH group at the 4-position (Table 1). Although ester analogue **10** showed moderate activity, with an IC_{50} = 97 nM, the reverse amide **23** and the amine analogue **25** showed low activity. *N*-Methyl analogue **11** also showed weak activity. These results indicated that antagonistic activity was influenced by the intramolecular hydrogen bond interaction between the carbonyl group at the 3-position and the NH group at the 4-position.

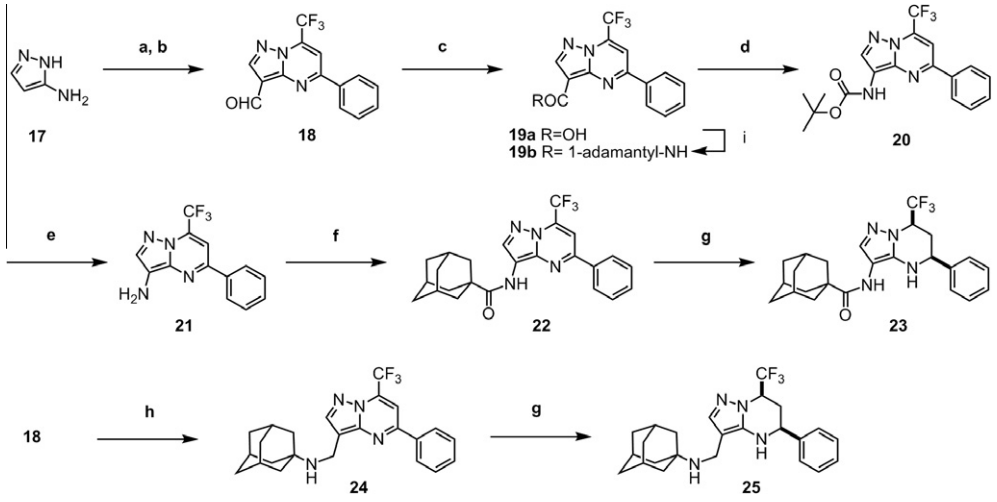
We then focused on the steric and electronic effect of the substitution at the 5- and the 7-positions of the lead compound **9a** on the antagonistic activity to CaSR (Table 2). First, the structure–activity relationship (SAR) of the substituent on the phenyl ring at the 5-position of **9a**–**f** was evaluated. The activity of the molecule following introduction of a chloro group (**9d**), methoxy group (**9e**), or ethyl group (**9f**) at the para-position of the phenyl ring was lower than that of the unsubstituted phenyl group **9a**. Substitution with a chlorine atom at the ortho- or meta-position (**9b** and **9c**) was tolerated. Second, we focused on the replacement of phenyl ring at the 5-position with several aromatic and alkyl



Scheme 1. Reagents and conditions: (a) $R^1COCH_2COR^2$, AcOH; (b) $NaBH_4$, THF–EtOH; (c) aqueous KOH, THF–EtOH; (d) 1-adamantylamine, WSC, HOBt, DMF; (e) 1-adamantanol, Bu_3P, ADDP, THF; (f) NaH, MeI, DMF.



Scheme 2. Reagents and conditions: (a) (1) $CF_3COCH_2CO_2Et$, AcOH; (2) TFA; (b) $PhCOCH_2CO_2Et$, AcOH; (c) $Me_2C{=}CHCOPh$, TFA, dimethoxyethanol; (d) $POCl_3$; (e) H_2, 10% Pd–C; (f) aqueous KOH, THF–EtOH; (g) 1-adamantylamine, WSC, HOBt, DMF; (h) 1-adamantylamine, HATU, *i*Pr_2EtN, DMF.



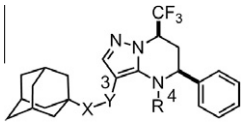
Scheme 3. Reagents and conditions: (a) CF_3COCH_2COPh, AcOH; (b) $POCl_3$; (c) $NaClO_2$, $NaHPO_4$, $CH_3CH{=}C(CH_3)_2$, dioxane–H_2O; (d) DPPA, Et_3N, *t*BuOH; (e) 4 N HCl in AcOEt; (f) 1-adamantane carboxylic acid, WSC, HOBt, Et_3N, DMF; (g) $NaBH_4$, THF–EtOH; (h) 1-adamantylamine, $NaBH_3CN$, THF–EtOH; (i) 1-adamantylamine, WSC, HOBt, DMAP, DMF.

groups. Although the 2-furanyl derivative **9g** showed moderate activity, with an IC_{50} = 400 nM, the 3-pyridiyl derivative **9h** and *tert*-butyl analogue **9i** were less active than **9a**. Furthermore, the analogue without any substituent (**16a**) also had weak activity. These results suggested that an unsubstituted phenyl ring is the most favorable group at the 5-position.

Next, we explored the modification of the substituent at the 7-position. Replacement of the trifluoromethyl group with a phenyl group resulted in weak activity (**9j**, IC_{50} = 700 nM), and the unsubstituted compound **16b** showed a remarkably lower activity. The activity of the methyl analogue **9k** (IC_{50} = 76 nM) was the same as that observed for compound **9a**. Additionally, the 5-methyl-7-phenyl derivative **9l**—a switched substitution derivative of **9k**—showed reduced activity. Therefore, the 7,7-dimethyl derivative **16c** was prepared in order to reduce the number of chiral centers. As a result of the introduction of dimethyl group at the 7-position, compound **16c** (IC_{50} = 10 nM) showed a fourfold higher activity than compound **9a**. These results indicated that the 7,7-dimethyl group had suitable bulkiness and lipophilicity at the 7-position.

Finally, we examined the effect of conversion of the tetrahydropyrazolopyrimidine ring. Ring conversion of **16c** to form 7,7-dimethyl dihydropyrimidine **12e** (IC_{50} = 580 nM) resulted in

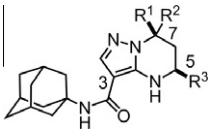
Table 1
SAR summary for the 3- and 4-positions of the adamantyl analogues on GTP-binding assay



Compd	X	Y	R	IC_{50}[a] (nm)
9a	NH	CO	H	40
10	O	CO	H	97
11	NH	CO	Me	>10,000
23	CO	NH	H	>10,000
25	NH	CH_2	H	>10,000

[a] IC_{50} values shown are means of duplicate measurement.

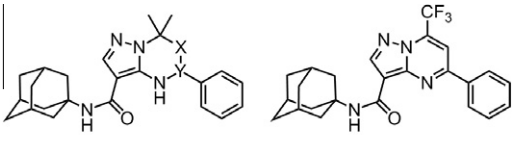
Table 2
SAR summary for the 5- and 7-positions of the adamantyl analogues on GTP-binding assay



Compd	R^1	R^2	R^3	IC_{50}[a] (nm)
9a	CF_3	H	Ph	40
9b	CF_3	H	2-Cl-Ph	110
9c	CF_3	H	3-Cl-Ph	320
9d	CF_3	H	4-Cl-Ph	>10,000
9e	CF_3	H	4-MeO-Ph	>10,000
9f	CF_3	H	4-Et-Ph	>10,000
9g	CF_3	H	2-Furanyl	400
9h	CF_3	H	3-Pyridinyl	>10,000
9i	CF_3	H	*t*Bu	>10,000
9j	Ph	H	Ph	700
9k	Me	H	Ph	76
9l	Ph	H	Me	>10,000
16a	CF_3	H	H	>10,000
16b	H	H	Ph	5300
16c	Me	Me	Ph	10

[a] See corresponding footnotes in Table 1.

Table 3
SAR summary for adamantyl analogues on GTP-binding assay



12e, 16c **19b**

Compd	X–Y	IC_{50}[a] (nm)
12e	CH=C	580
16c	CH_2CH	10
19b	—	>10,000

[a] See corresponding footnotes in Table 1.

reduced activity (Table 3). Furthermore, the pyrazolopyrimidine **19b** showed markedly lower potency. These results also suggested that intramolecular hydrogen bond interaction between the carbonyl group at the 3-position and the NH group at the 4-position was essential for antagonistic activity and important to fix the orientation of two hydrophobic moieties (Fig. 2, hydrophobic moieties A and B).

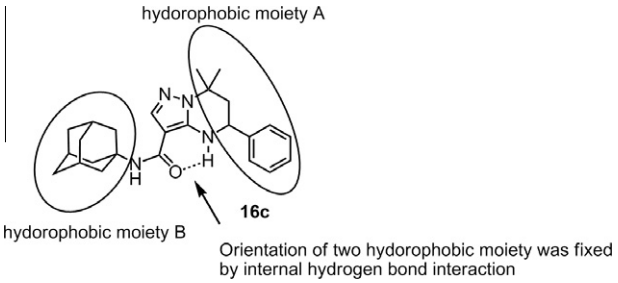


Figure 2. Structure of compound **16c**.

Table 4
Pharmacokinetic parameters of **16c** in rats

	Pharmacokinetics parameters[a,b,c]	
	With 0.5% MC suspension	With solubilized reagent[d]
C_{max} (μg/mL)	0.064 ± 0.042	0.237 ± 0.006
T_{max} (h)	1.30 ± 0.60	0.67 ± 0.29
AUC (μg h/mL)	0.591 ± 0.511	1.268 ± 0.516
MRT (h)	4.65 ± 1.44	4.48 ± 0.57

[a] Studies conducted in male SD rats, 8 W.
[b] 10 mg/kg oral administration.
[c] Mean ± SD (n = 3).
[d] DMA 7.5%, HCO 50.5.0%, TC 51.5%, D.W. 86%.

On the basis of the in vitro antagonistic activities, we selected **16c** and examined its pharmacokinetic profile in rats. The C_{max} and AUC value for the dosing of **16c** with a solubilized reagent was 0.24 μg/mL and 1.27 μg h/mL, respectively, representing a two to fourfold increase in exposure when compared to the dosing with a methylcellulose suspension (Table 4). This result indicated that good solubility is needed to improve the pharmacokinetic profile of tetrahydropyrazolopyrimidine derivatives. We are continuing a further optimization study based on **16c**, with special focus on the substitution of the adamantyl group at the 3-position of the tetrahydropyrazolopyrimidine. The results of this detailed study will be reported in the near future.

4. Conclusion

In this study, our in-house screening for a new structural class of calcilytics revealed a novel lead compound **9a**, which possesses a tetrahydropyrazolopyrimidine scaffold. To clarify the SAR of these proprietary calcilytics, we optimized the 3-, 4-, 5-, and 7-positions of the tetrahydropyrazolopyrimidine. Our studies indicated that intramolecular hydrogen bond interaction between the carbonyl group at the 3-position and the NH group at the 4-position was essential for antagonistic activity. Among all the compounds prepared, 7,7-dimethyl derivatives **16c** showed the most potent in vitro antagonistic activity and exhibited the exposure after oral administration. The excellent in vitro potency of this series warrants further studies on the development of more advanced analogues for the treatment of osteoporosis.

5. Experimental

5.1. Chemistry

Melting points were determined on a Yanagimoto micromelting point apparatus or BÜCHI B-545 and uncorrected. ^{1}H NMR spectra of deuteriochloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6) solution (internal standard tetramethylsilan (TMS), δ 0) were recorded on a Varian Gemini-200, Mercury-300 or Bruker AVANCE-

300. Reactions were followed by TLC on Silica Gel 60 F 254 precoated TLC plates (E. Merck) or NH TLC plates (Fuji Silysia Chemical Ltd). Column chromatography was performed with WAKO gel 300 using the indicated eluents. Elemental analysis (C, H, N) were carried out by the Analytical Department of Takeda Chemical Industries.

5.1.1. Ethyl 5-phenyl-7-(trifluoromethyl)-pyrazolo[1,5-*a*] pyrimidine-3-carboxylate (6a)

A mixture of ethyl 5-amino-1*H*-pyrazole-4-carboxylate **5** (5.0 g, 32.2 mmol) and 4,4,4-trifluoro-1-phenyl-1,3-butanedione (7.0 g, 32.4 mmol) in acetic acid (100 mL) was refluxed for 4 h. The mixture was cooled to room temperature and concentrated, and the resulting crystals was collected by filtration to give **6a** (8.63 g, 79%) as yellow crystals: mp 111–113 °C; ^{1}H NMR ($CDCl_3$): δ 1.47 (3H, t, J = 7.0 Hz), 4.47 (2H, q, J = 7.0 Hz), 7.54–7.61 (3H, m), 7.80 (1H, s), 8.23–8.28 (2H, m), 8.68 (1H, s). Anal. Calcd for $C_{16}H_{12}N_3O_2F_3$: C, 57.32; H, 3.61; N, 12.53. Found: C, 57.22; H, 3.73; N, 12.55.

5.1.2. Ethyl 5-(2-chlorophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6b)

Compound **6b** was prepared in a manner similar to that described for **6a**. Yield 34%, mp 112–113 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (3H, t, J = 7.2 Hz), 4.44 (2H, q, J = 7.2 Hz), 7.43–7.56 (3H, m), 7.85 (1H, s), 7.86–7.91 (1H, m), 8.71 (1H, s). Anal. Calcd for $C_{16}H_{11}N_3O_2ClF_3$: C, 51.98; H, 3.00; N, 11.37. Found: C, 52.00; H, 2.88; N, 11.37.

5.1.3. Ethyl 5-(3-chlorophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6c)

Compound **6c** was prepared in a manner similar to that described for **6a**. Yield 27%, mp 107–109 °C. ^{1}H NMR ($CDCl_3$): δ 1.48 (3H, t, J = 7.2 Hz), 4.47 (2H, q, J = 7.2 Hz), 7.49–7.58 (2H, m), 7.76 (1H, s), 8.10–8.13 (1H, m), 8.26–8.27 (1H, m), 8.70 (1H, s). Anal. Calcd for $C_{16}H_{11}N_3O_2ClF_3$: C, 51.98; H, 3.00; N, 11.37. Found: C, 51.80; H, 2.85; N, 10.99.

5.1.4. Ethyl 5-(4-chlorophenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6d)

Compound **6d** was prepared in a manner similar to that described for **6a**. Yield 62%, mp 165–166 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (3H, t, J = 7.2 Hz), 4.47 (2H, q, J = 7.2 Hz), 7.55 (2H, d, J = 8.88 Hz), 7.75 (1H, s), 8.21 (2H, d, J = 8.8 Hz), 8.68 (1H, s).

5.1.5. Ethyl 5-(4-methoxyphenyl)-7-(trifluoromethyl) pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6e)

Compound **6e** was prepared in a manner similar to that described for **6a**. Yield 50%, ^{1}H NMR ($CDCl_3$): δ 1.47 (3H, t, J = 7.0 Hz), 3.92 (3H, s), 4.46 (2H, q, J = 4.8 Hz), 7.06 (2H, d, J = 6.0 Hz), 7.73 (1H, s), 8.23 (2H, d, J = 6.0 Hz), 8.63 (1H, s).

5.1.6. Ethyl 5-(4-ethyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carb-oxylate (6f)

Compound **6f** was prepared in a manner similar to that described for **6a**. Yield 34%, ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, J = 7.6 Hz), 1.47 (3H, t, J = 7.2 Hz), 2.76 (2H, q, J = 7.6 Hz), 4.46 (2H, q, J = 7.2 Hz), 7.39 (2H, d, J = 8.4 Hz), 8.18 (2H, d, J = 8.4 Hz), 8.66 (1H, s).

5.1.7. Ethyl 5-(2-furanyl)-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxy-late (6g)

Compound **6g** was prepared in a manner similar to that described for **6a**. Yield 52%, ^{1}H NMR ($CDCl_3$): δ 1.45 (3H, t, J = 7.2 Hz), 4.45 (2H, q, J = 7.2 Hz), 6.69 (1H, dd, J = 3.8, 1.8 Hz), 7.54 (1H, dd, J = 3.8, 0.8 Hz), 7.71 (1H, dd, J = 1.8, 0.6 Hz), 7.75 (1H, s), 8.63 (1H, s). Anal. Calcd for $C_{14}H_{10}N_3O_3F_3$: C, 51.70; H, 3.10; N, 12.92. Found: C, 51.63; H, 3.03; N, 12.93.

5.1.8. Ethyl 7-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6k) and Ethyl 5-Methyl-7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (6l)

Compounds **6k–l** were prepared in a manner similar to that described for **6a**. These regioisomers were purified by column chromatography on silica gel eluted with EtOAc–hexane (1:1). **6k**: yield 15%, mp 124.9–125.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.47 (3H, t, J = 7.2 Hz), 2.89 (3H, d, J = 0.6 Hz), 4.45 (2H, q, J = 7.2 Hz), 7.35 (1H, d, J = 0.6 Hz), 7.49–7.55 (3H, m), 8.21–8.25 (2H, m), 8.59 (1H, s). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.23; H, 5.31; N, 14.97. **6l**: yield 37%, mp 119.9–121.4 °C. ^{1}H NMR ($CDCl_3$): δ 1.43 (3H, t, J = 7.2 Hz), 2.78 (3H, s), 4.43 (2H, q, J = 7.2 Hz), 6.94 (1H, s), 7.56–7.60 (3H, m), 7.95–7.99 (2H, m), 8.52 (1H, s). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.14; H, 5.47; N, 15.09.

5.1.9. Ethyl 5-phenyl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyri-midine-3-carboxylate (7a)

To a solution of **6a** (3.51 g, 10.3 mmol) in MeOH was added $NaBH_4$ (1.4 g, 3.70 mmol) at room temperature. The whole was stirred at the same temperature for 5 h, quenched with saturated citric acid solution, concentrated in vacuo, and extracted with EtOAc. The extract was successively washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and then concentrated to give the title compound (1.73 g, 49%) as colorless oil: ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, J = 6.8 Hz), 2.28–2.46 (1H, m), 2.50–2.61 (1H, m), 4.25 (2H, q, J = 6.8 Hz), 4.58 (1H, dd, J = 11.4, 3.4 Hz), 4.85 (1H, ddd, J = 3.4, 3.0, 2.6 Hz), 6.15 (1H, s), 7.34–7.48 (5H, m), 7.74 (1H, s).

5.1.10. Ethyl 5-(2-chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (7b)

Compound **7b** was prepared in a manner similar to that described for **7a**. Yield 70%. ^{1}H NMR ($CDCl_3$): δ 1.34 (3H, t, J = 7.2 Hz), 2.14–2.32 (1H, m), 2.66–2.78 (1H, m), 4.27 (2H, q, J = 7.0 Hz), 4.81–4.97 (1H, m), 5.07 (1H, dd, J = 11.4, 3.0 Hz), 6.11 (1H, s), 7.28–7.46 (3H, m), 7.66–7.70 (1H, m), 7.75 (1H, s).

5.1.11. Ethyl 5-(3-chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (7c)

Compound **7c** was prepared in a manner similar to that described for **7a**. Yield 87%. ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, t, J = 7.0 Hz), 2.26–2.44 (1H m), 2.50–2.61 (1H, m), 4.26 (2H, q, J = 7.0 Hz), 4.57 (1H, dd, J = 11.6, 3.0 Hz), 4.76–4.93 (1H, m), 6.16 (1H, s), 7.29–7.46 (4H, m), 7.74 (1H, s).

5.1.12. Ethyl 5-(4-chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (7d)

Compound **7d** was prepared in a manner similar to that described for **7a**. Yield 81%. ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, J = 7.2 Hz), 2.24–2.42 (1H, m), 2.48–2.58 (1H, m), 4.25 (2H, q, J = 7.2 Hz), 4.57 (1H, dd, J = 11.2, 2.8 Hz), 4.76–4.99 (1H, m), 6.13 (1H, br s), 7.40 (4H, m), 7.74 (1H, s).

5.1.13. Ethyl 5-(4-methoxyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (7e)

Compound **7e** was prepared in a manner similar to that described for **7a**. Yield 63%, mp 105–109 °C. ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, J = 7.2 Hz), 2.25–2.43 (1H, m), 2.47–2.56 (1H, m), 3.83 (3H, s), 4.25 (2H, q, J = 7.2 Hz), 4.53 (1H, dd, J = 11.2, 2.8 Hz), 4.75–4.92 (1H, m), 6.08 (1H, br s), 6.89–6.97 (2H, m), 7.33–7.39 (2H, m), 7.73 (1H, s). Anal. Calcd for C17H18N3O3F3: C, 55.27; H, 5.01; N, 11.11. Found: C, 55.20; H, 4.81; N, 10.85.

5.1.14. Ethyl 5-(4-ethyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxylate (7f)

Compound **7f** was prepared in a manner similar to that described for **7a**. Yield 73%. ^{1}H NMR ($CDCl_3$): δ 1.26 (3H, t, J = 7.6 Hz), 1.32 (3H, t, J = 7.0 Hz), 2.26–2.45 (1H, m), 2.48–2.60 (1H, m), 2.68 (2H, q, J = 7.4 Hz), 4.25 (2H, q, J = 7.4 Hz), 4.55 (1H, dd, J = 11.2, 2.8 Hz), 4.75–4.89 (1H, m), 6.11 (1H, br s), 7.25 (2H, d, J = 8.4 Hz), 7.36 (2H, d, J = 8.0 Hz), 7.73 (1H, s).

5.1.15. Ethyl 5-(2-furanyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-3-carboxylate (7g)

Compound **7g** was prepared in a manner similar to that described for **7a**. Yield 88%, mp 85.9–86.0 °C. ^{1}H NMR ($CDCl_3$): δ 1.34 (3H, t, J = 7.2 Hz), 2.48–2.72 (4H, m), 4.27 (2H, q, J = 7.0 Hz), 4.68–4.88 (2H, m), 6.23 (1H, br s), 6.36–6.41 (2H, m, J = 7.2 Hz), 7.44 (1H, dd, J = 1.0 Hz), 7.72 (1H, s). Anal. Calcd for $C_{14}H_{14}N_3O_3F_3$: C, 51.07; H, 4.29; N, 12.76. Found: C, 51.13; H, 4.26; N, 12.99.

5.1.16. Ethyl 7-methyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (7k)

Compound **7k** was prepared in a manner similar to that described for **7a**. Yield 96%. ^{1}H NMR ($CDCl_3$): δ 1.31 (3H, t, J = 6.9 Hz), 1.60 (3H, d, J = 6.3 Hz), 1.95–2.07 (1H, m), 2.30–2.37 (1H, m), 4.24 (2H, q, J = 10.8 Hz), 4.22–4.38 (1H, m), 4.58 (1H, dd, J = 11.1, 3.0 Hz), 5.95 (1H, br s), 7.32–7.45 (5H, m), 7.65 (1H, s).

5.1.17. Ethyl 5-methyl-7-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (7l)

Compound **7l** was prepared in a manner similar to that described for **7a**. Yield 78%, ^{1}H NMR ($CDCl_3$): δ 1.34 (3H, t, J = 7.0 Hz), 1.92–2.10 (1H, m), 2.30–2.41 (1H, m), 3.65–3.78 (1H, m), 4.27 (2H, q, J = 7.0 Hz), 5.17 (1H, dd, J = 11.4, 5.2 Hz), 5.79 (1H, br s), 7.18–7.42 (5H, m), 7.59 (1H, s).

5.1.18. 5-Phenyl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (8a)

A mixture of **7a** (2.2 g, 6.5 mmol), 1.5 N KOH solution (14 mL, 21 mmol) in EtOH (20 mL) was stirred at 60 °C for 12 h, acidified with saturated citric acid solution, and the precipitated solid was collected by filtration, which was washed with water and IPE to give the title compound (1.59 g, 76%) as colorless prisms, mp 202–204 °C; ^{1}H NMR ($CDCl_3$): δ 2.31–2.44 (1H, m), 2.50–2.59 (1H, m), 4.59 (1H, dd, J = 11.4, 3.0 Hz), 4.79 (1H, m), 6.10 (1H, s), 7.20–7.26 (5H, m), 7.78 (1H, s). Anal. Calcd for $C_{14}H_{12}F_3N_3O_2$: C, 54.02; H, 3.89; N, 13.50. Found: C, 54.05; H, 3.82; N, 13.67.

5.1.19. 5-(2-Chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-3-carboxylic acid (8b)

Compound **8b** was prepared in a manner similar to that described for **8a**. Yield 88%, mp 177–179 °C. ^{1}H NMR (DMSO-d_6): δ 2.09–2.17 (1H, m), 2.54–2.65 (1H, m), 5.02–5.08 (1H, m), 5.33–5.44 (1H, m), 6.76 (1H, br s), 7.32–7.52 (3H, m), 7.59–7.63 (1H, m), 7.64 (1H, s). Anal. Calcd for $C_{14}H_{11}N_3O_2ClF_3$: C, 48.68; H, 3.21; N, 12.15. Found: C, 48.73; H, 2.97; N, 12.19.

5.1.20. 5-(3-Chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-3-carboxylic acid (8c)

Compound **8c** was prepared in a manner similar to that described for **8a**. Yield 51%, mp 194–195 °C. ^{1}H NMR (DMSO-d_6): δ 1.99–2.33 (1H, m), 2.50–2.60 (1H, m), 4.68–5.75 (1H, m), 5.17–5.31 (1H, m), 6.74 (1H, br s), 7.36–7.50 (4H, m), 7.62 (1H, s). Anal. Calcd for $C_{14}H_{11}N_3O_2ClF_3$: C, 48.68; H, 3.21; N, 12.15. Found: C, 48.63; H, 2.99; N, 12.05.

5.1.21. 5-(4-Chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-3-carboxylic acid (8d)

Compound **8d** was prepared in a manner similar to that described for **8a**. Yield 83%, mp 186–187 °C. ^{1}H NMR ($CDCl_3$): δ 2.25–2.43 (1H, m), 2.50–2.60 (1H, m), 4.59 (1H, dd, J = 10.8, 2.8 Hz), 4.79–4.90 (1H, m), 6.07 (1H, br s), 7.36–7.45 (4H, m), 7.78 (1H, s). Anal. Calcd for $C_{14}H_{11}N_3O_2ClF_3$: C, 48.68; H, 3.21; N, 12.15. Found: C, 48.53; H, 3.09; N, 11.98.

5.1.22. 5-(4-Methoxyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-3-carboxylic acid (8e)

Compound **8e** was prepared in a manner similar to that described for **8a**. Yield 91%, mp 154.5–155.1 °C. ^{1}H NMR ($CDCl_3$): δ 2.25–2.43 (1H, m), 2.45–2.60 (1H, m), 3.83 (3H, s), 4.50–4.58 (1H, m), 4.78–4.89 (1H, m), 6.03 (1H, br s), 6.94 (2H, d, J = 8.4 Hz), 7.35 (2H, d, J = 8.8 Hz), 7.77 (1H, s). Anal. Calcd for $C_{15}H_{14}N_3O_3F_3{\cdot}0.3H_2O$: C, 51.97; H, 4.24; N, 12.12. Found: C, 51.95; H, 4.31; N, 12.13.

5.1.23. 5-(4-Ethyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-3-carboxylic acid (8f)

Compound **8f** was prepared in a manner similar to that described for **8a**. Yield 74%, mp 165–168 °C. ^{1}H NMR ($CDCl_3$): δ 1.25 (3H, t, J = 7.5 Hz), 2.26–2.45 (1H, m), 2.48–2.60 (1H, m), 2.68 (2H, q, J = 7.6 Hz), 4.56 (2H, dd, J = 11.6, 2.8 Hz), 4.75–4.90 (1H, m), 6.06 (1H, br s), 7.25 (2H, d, J = 8.6 Hz), 7.35 (2H, d, J = 8.0 Hz), 7.77 (1H, s). Anal. Calcd for $C_{16}H_{16}N_3O_2F_3$: C, 56.64; H, 4.75; N, 12.38. Found: C, 56.62; H, 4.98; N, 12.56.

5.1.24. 5-(2-Furanyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimi-dine-3-carboxylic acid (8g)

Compound **8g** was prepared in a manner similar to that described for **8a**. Yield 92%, mp 156–157 °C; ^{1}H NMR ($CDCl_3$): δ 2.50–2.72 (4H, m), 4.71–4.91 (2H, m), 6.19 (1H, br s), 6.38–6.43 (2H, m), 7.45 (1H, dd, J = 1.8, 1.0 Hz), 7.78 (1H, s). Anal. Calcd for $C_{12}H_{10}N_3O_3F_3$: C, 47.85; H, 3.35; N, 13.95. Found: C, 47.99; H, 3.44; N, 13.86.

5.1.25. 7-Methyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxyli-c acid (8k)

Compound **8k** was prepared in a manner similar to that described for **8a**. Yield 83%, mp 165–167 °C. ^{1}H NMR ($CDCl_3$): δ 1.60 (3H, d. J = 6.3 Hz), 1.94–2.06 (1H, m), 2.30–2.37 (1H, m), 4.26–4.36 (1H, m), 4.58 (1H, dd, J = 11.1, 3.0 Hz), 5.91 (1H, br s), 7.32–7.42 (5H, m), 7.69 (1H, s). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.28; H, 6.13; N, 16.36.

5.1.26. 5-Methyl-7-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxyli-c acid (8l)

Compound **8l** was prepared in a manner similar to that described for **8a**. Yield 92%, mp 159.2–159.3 °C. ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, t, J = 6.2 Hz), 1.93–2.11 (1H, m), 2.33–2.42 (1H, m), 3.69–3.80 (1H, m), 5.18 (1H, dd, J = 11.2, 5.0 Hz), 5.79 (1H, br s), 7.19–7.43 (5H, m), 7.66 (1H, s). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.10; H, 5.90; N, 16.00.

5.1.27. *N*-(1-Adamantyl)-5-phenyl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxamide (9a)

A mixture of **8a** (0.35 g, 1.12 mmol), 1-adamantylamine (0.17 g, 1.12 mmol), WSC (0.24 g, 1.25 mmol), HOBt (0.25 g, 0.56 mmol) and DMF (10 mL) was stirred at room temperature for 3 h, and concentrated to dryness. The residue was dissolved in EtOAc, and the organic layer was successively washed with aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and then concentrated. The residue was chromatographed on silica gel using EtOAc–hexane (1:2) to give **9a** (1.34 g, 73%) as colorless crystals: mp 210–212 °C; ^{1}H

NMR ($CDCl_3$): δ 1.70 (6H, br s), 2.08 (9H, br s), 2.15–2.37 (1H, m), 2.62–2.70 (1H, m), 4.82–4.93 (1H, m), 5.02 (1H, dd, J = 11.7, 2.4 Hz), 5.23 (1H, br s), 6.63 (1H, br s), 7.20–7.26 (5H, s), 7.47 (1H, s). Anal. Calcd for $C_{24}H_{27}F_3N_4O$: C, 64.85; H, 6.12; N, 12.60. Found: C, 64.69; H, 6.05; N, 12.59.

5.1.28. *N*-(1-Adamantyl)-5-(2-chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (9b)

Compound **9b** was prepared in a manner similar to that described for **9a**. Yield 58%, mp 256–257 °C. ^{1}H NMR ($CDCl_3$): δ 1.70 (6H, br s), 2.08 (9H, br s), 2.15–2.37 (1H, m), 2.62–2.70 (1H, m), 4.82–4.93 (1H, m), 5.02 (1H, dd, J = 11.7, 2.4 Hz), 5.23 (1H, br s), 6.63 (1H, br s), 7.28–7.41 (3H, m), 7.47 (1H, s), 7.72 (1H, dd, J = 7.2 Hz). Anal. Calcd for $C_{24}H_{26}N_4OClF_3$: C, 60.90; H, 5.47; N, 11.70. Found: C, 60.22; H, 5.50; N, 11.54.

5.1.29. *N*-(1-Adamantyl)-5-(3-chlorophenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (9c)

Compound **9c** was prepared in a manner similar to that described for **9a**. Yield 61%, mp 246–247 °C. ^{1}H NMR ($CDCl_3$): δ 1.70 (6H, s), 2.05–2.10 (9H, m), 2.30–2.42 (1H, m), 2.47–2.55 (1H, m), 4.50 (1H, dd, J = 11.4, 2.7 Hz), 4.78–4.89 (1H, m), 5.23 (1H, br s), 6.69 (1H, br s), 7.30–7.37 (3H, m), 7.46 (2H, s). Anal. Calcd for $C_{24}H_{26}N_4OClF_3$: C, 60.19; H, 5.47; N, 11.70. Found: C, 60.90; H, 5.53; N, 11.65.

5.1.30. *N*-(1-Adamantyl)-5-(4-methoxyphenyl)-7-(trifluoromethyl)-4, 5,6,7-tetrahyd-ropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (9e)

Compound **9e** was prepared in a manner similar to that described for **9a**. Yield 34%, mp 241–243 °C. ^{1}H NMR ($CDCl_3$): δ 1.69 (6H, s), 2.05–2.09 (9H, m), 2.29–2.51 (2H, m), 3.82 (3H, s), 4.47 (1H, dd, J = 7.8, 2.0 Hz), 4.79–4.88 (1H, m), 5.21 (1H, br s), 6.61 (1H, br s), 6.90 (2H, d, J = 5.8 Hz), 7.34 (2H, d, J = 5.8 Hz), 7.45 (1H, s). Anal. Calcd for $C_{25}H_{29}N_4O_2F_3$: C, 63.28; H, 6.16; N, 11.81. Found: C, 63.13; H, 6.36; N, 11.77.

5.1.31. *N*-(1-Adamantyl)-5-(2-furanyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydropyra-zolo[1,5-*a*]pyrimidine-3-carboxamide (9g)

Compound **9g** was prepared in a manner similar to that described for **9a**. Yield 67%, mp 230–231 °C; ^{1}H NMR ($CDCl_3$): δ 1.70 (6H, br s), 2.08 (9H, br s), 2.53–2.64 (2H, m), 4.66 (1H, dd, J = 9.2, 5.0 Hz), 4.72–4.89 (1H, m), 5.21 (1H, br s), 6.34–6.37 (2H, m), 6.74 (br s), 7.39–7.40 (1H, m), 7.44 (1H, s). Anal. Calcd for $C_{22}H_{25}N_4O_2F_3{\cdot}0.2$EtOAc: C, 60.57; H, 5.93; N, 12.39. Found: C, 60.39; H, 6.17; N, 12.25.

5.1.32. *N*-(1-Adamantyl)-5-pyridin-3-yl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyra-zolo[1,5-*a*]pyrimidine-3-carboxamide (9h)

Compound **9h** was prepared in a manner similar to that described for **6–9a**. Yield 17% in four steps. ^{1}H NMR ($CDCl_3$): δ 1.69 (6H, br s), 2.01–2.16 (9H, m), 2.32–2.59 (2H, m), 4.58 (1H, dd, J = 11.6, 2.84 Hz), 4.76–4.93 (1H, m), 5.23 (1H, s), 6.70 (1H, d, J = 1.5 Hz), 7.34 (1H, dd, J = 8.0, 5.3 Hz), 7.47 (1H, s), 7.84 (1H, dt, J = 8.0, 2.1 Hz), 8.58–8.68 (2H, m).

5.1.33. *N*-(1-Adamantyl)-5-*tert*-butyl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazo-lo-[1,5-*a*]pyrimidine-3-carboxamide (9i)

Compound **9i** was prepared in a manner similar to that described for **9a**. Yield 70%. ^{1}H NMR ($CDCl_3$): δ 1.05 (9H, s), 1.70 (6H, s), 2.00–2.40 (10H, m), 2.95–3.20 (2H, m), 4.60–4.65 (1H, m), 5.20 (1H, s), 6.50 (1H, s), 7.40 (1H, s).

5.1.34. *N*-(1-Adamantyl)-5,7-diphenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxamide (9j)

Compound **9j** was prepared in a manner similar to that described for **9a**. Yield 39%. ^{1}H NMR ($CDCl_3$): δ 1.70 (6H, s), 2.08 (9H, s), 2.40–2.60 (2H, m), 4.60–4.65 (1H, m), 5.20–5.40 (2H, m), 6.60 (1H, s), 7.20–7.50 (10H, m).

5.1.35. General procedure of compound 9 using HTOS method

1-Adamantylamine (24 mg, 0.19 mmol) was added to a suspension of compound **8** (0.05 g, 0.16 mmol), WSC (37 mg, 0.19 mmol), HOBt (29 mg, 0.19 mmol), and DMAP (23 mg, 0.19 mmol) in DMF (1.5 mL). The reaction mixture was stirred at room temperature for 14 h, diluted with DCM (0.5 mL) and std aq $NaHCO_3$ solution (0.5 mL), and then separated using PHASE-SEP filtration syringe. The organic layer was concentrated and loaded onto preparative HPLC (Gilson 215 system).

5.1.36. *N*-(1-Adamantyl)-5-(4-chlorophenyl)-7-(trifluoromethyl)-4, 5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (9d)

MS(ESI, m/z) 475, $(M+H)^+$.

5.1.37. *N*-(1-Adamantyl)-5-(4-ethyphenyl)-7-(trifluoromethyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (9f)

MS(ESI, m/z) 469, $(M+H)^+$.

5.1.38. *N*-(1-Adamantyl)-7-methyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyr-imidine-3-carboxamide (9k)

MS(ESI, m/z) 387, $(M+H)^+$.

5.1.39. *N*-(1-Adamantyl)-5-methyl-7-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyri-midine-3-carboxamide (9l)

MS(ESI, m/z) 387, $(M+H)^+$.

5.1.40. 1-Adamantyl-5-phenyl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]-pyrimidine-3-carboxylate (10)

To a mixture of **8a** (0.50 g, 1.61 mmol), 1-adamantanol (0.32 g, 2.10 mmol) and Bu_3P (0.42 g, 2.10 mmol) in THF (200 mL) was added ADDP (0.53 g, 2.10 mmol) at 0 °C under Ar atmosphere. The whole was stirred at room temperature for 24 h. The reaction mixture was poured into H_2O and extracted with EtOAc. The extract was washed successively with 1 N HCl, aq $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc–hexane (1:1) to give **10** as crystals (0.30 g, 42%): mp 128–129 °C; ^{1}H NMR ($CDCl_3$): δ 1.67 (6H, s), 2.18 (9H, s), 2.35–2.53 (2H, m), 4.56 (1H, dd, J = 11.4, 2.7 Hz), 4.83–4.90 (1H, m), 6.13 (1H, s), 7.38–7.46 (5H, m), 7.66 (1H, s). Anal. Calcd for $C_{24}H_{26}N_3O_2F_3$: C, 64.71; H, 5.88; N, 9.43. Found: C, 64.82; H, 5.90; N, 9.30.

5.1.41. *N*-(1-Adamantyl)-4-methyl-7-trifluoromethyl-4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimidine-3-carboxamide (11)

To a solution of **9a** (0.06 g, 0.13 mmol) in DMF (5 mL) was added NaH (0.089 g, 2.22 mmol) with ice-water cooling. After stirred for 30 min, iodomethane (60 μL) was added thereto, and the mixture was stirred at room temperature for 12 h, and concentrated in vacuo. The residue was chromatographed on silica gel with EtOAc–hexane (1:2) to give **11** (0.035 g, 58%) as colorless needles: ^{1}H NMR ($CDCl_3$): δ 1.70 (6H, m), 2.08 (9H, m), 2.46 (2H, m), 2.81 (3H, s), 4.21 (1H, dd, J = 12.0, 3.4 Hz), 4.81 (1H, septet, J = 5.6 Hz), 5.59 (1H, s), 7.38–7.41 (5H, m), 7.60 (1H, s).

5.1.42. Ethyl 5-oxo-7-(trifluoromethyl)-4,5-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxy-late (12a)

A mixture of **5** (31.0 g, 0.20 mol) ethyl trifluoroacetoacetate (40.6 g, 0.22 mol) in AcOH (50 mL) was refluxed for 3 h, and concentrated in vacuo. The residue was diluted with aqueous $NaHCO_3$, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give the hydrate. The residue was dissolved in TFA (120 mL), and the mixture was refluxed for 24 h, and concentrated in vacuo. The residue was poured into ice-water, neutralized with $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$ and then concentrated to afford solid (14.3 g, 26%): ^{1}H NMR ($CDCl_3$): δ 1.40 (3H, t, J = 7.0 Hz), 4.39 (2H, q, J = 7.2 Hz), 6.58 (1H, s), 8.12 (1H, s), 9.90 (1H, br s).

5.1.43. Ethyl 5-chloro-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxyla-te (13a)

A mixture of **12a** (0.14 g, 0.5 mmol) and $POCl_3$ (1.65 g, 10.8 mmol) was refluxed overnight. After cooling, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by preparative TLC using EtOAc–hexane (1:5) to give **13a** (0.10 g, 68%) as colorless crystals, mp 121.4–121.5 °C; ^{1}H NMR ($CDCl_3$): δ 1.43 (3H, t, J = 7.2 Hz), 4.45 (2H, q, J = 7.2 Hz), 7.34 (1H, s), 8.67 (1H, s). Anal. Calcd for $C_{10}H_7N_3O_2ClF_3$: C, 40.90; H, 2.40; N, 14.21. Found: C, 41.04; H, 2.42; N, 14.25.

5.1.44. Ethyl 7-trifluoromethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-car-boxylate (14a)

A mixture of **13a** (3.52 g, 12.0 mmol) and 10% Pd–C (1.00 g) in EtOH–THF (100 mL–20 mL) was stirred at room temperature under hydrogen atmosphere (5 kgf/cm^2) for 2 h. After the catalyst was filtered off, the filtrate was concentrated in vacuo to obtain the title compound (3.10 g, 98%) as colorless prisms, mp 183–185 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J = 7.2 Hz), 2.20–2.55 (2H, m), 4.33 (2H, q, J = 7.2 Hz), 4.52 (2H, t, J = 5.4 Hz), 4.75 (1H, dd, J = 7.6, 1.8 Hz), 6.63 (1H, br s), 7.28–7.32 (2H, m), 7.38–7.44 (3H, m), 7.95 (1H, s). Anal. Calcd for $C_{10}H_{12}N_3O_2F_3$: C, 45.63; H, 4.60; N, 15.96. Found: C, 45.56; H, 4.40; N, 15.94.

5.1.45. 7-Trifluoromethyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (15a)

A mixture of **14a** (2.60 g, 9.88 mmol), KOH (1.30 g, 23.2 mmol), water (10 mL), EtOH (10 mL) and THF (10 mL) was stirred at 50 °C for 5 h, concentrated in vacuo, acidified with aqueous citric acid and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and then concentrated to obtain crystals, which was recrystallized from EtOAc–IPE to give **15a** (2.18 g, 94%) as colorless prisms, mp 162.6–162.7 °C. ^{1}H NMR (DMSO-d_6): δ 2.05–2.34 (2H, m), 3.09–3.23 (1H, m), 3.30–3.45 (1H, m), 4.97–5.11 (1H, m), 6.79 (1H, br s), 7.39 (1H, s). Anal. Calcd for $C_8H_8N_3O_2F_3$: C, 40.86; H, 3.43; N, 7.87. Found: C, 40.96; H, 3.21; N, 17.79.

5.1.46. *N*-(1-Adamantyl)-7-trifluoromethyl-4,5,6,7-tetrahydro-pyrazolo[1,5-*a*]pyrim-idine-3-carboxamide (16a)

A mixture of **15a** (1.17 g, 4.98 mmol), 1-adamantylamine (0.75 g, 4.96 mmol), WSC (1.14 g, 5.95 mmol), HOBt (0.91 g, 5.98 mmol) and DMF (30 mL) was stirred at room temperature for 20 h, concentrated in vacuo, diluted with aqueous $NaHCO_3$, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and then concentrated. The residue was chromatographed on silica gel using EtOAc–hexane (1:4) to give **16a** (1.34 g, 73%) as an amorphous solid: ^{1}H NMR ($CDCl_3$): δ 1.71 (6H, s), 2.02–2.15 (9H, m), 2.16–2.32 (1H, m), 2.32–2.47 (1H, m), 3.32–3.54 (2H, m), 4.61–4.83 (1H, m), 5.16 (1H, s), 6.61 (1H, s), 7.39 (1H, s).

5.1.47. Ethyl 7-oxo-5-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (12b)

A mixture of **5** (14.38 g, 85.5 mmol), ethyl 3-oxo-3-phenylpropanoate (16.43 g, 85.5 mmol) and AcOH (100 mL) was refluxed for 10 h, concentrated in vacuo to afford **12b** (16.0 g, 66%) as a solid, which was used for the next step without further purification: ^{1}H NMR (DMSO-d_6): δ 1.31 (3H, t, J = 7.2 Hz), 4.20 (2H, q, J = 7.2 Hz), 6.18 (1H, s), 7.21 (1H, br s), 7.39–7.47 (3H, m), 8.05–8.10 (3H, m).

5.1.48. Ethyl 7-Chloro-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (13b)

A mixture of **12b** (6.35 g, 22.4 mmol) and $POCl_3$ (34.0 g, 0.22 mol) was refluxed for 2 h, and concentrated in vacuo. The residue was poured into cold water and extracted with EtOAc. The extract was successively washed with water and brine, dried over $MgSO_4$, and then concentrated. The residue was chromatographed on silica gel using EtOAc–hexane (1:6–1:3) as eluent to give **13b** (2.46 g, 36%) as a light yellow solid: ^{1}H NMR (DMSO-d_6): δ 1.31 (3H, t, J = 7.0 Hz), 4.20 (2H, q, J = 7.0 Hz), 6.17 (1H, s), 7.38–7.49 (3H, m), 8.03–8.11 (3H, m).

5.1.49. Ethyl 5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate (14b)

A mixture of **13b** (1.0 g, 3.31 mmol) and 10% Pd–C (0.43 g) in EtOH–THF (100–50 mL) was stirred at room temperature under hydrogen atmosphere (5 kgf/cm^2) for 3 h. After the catalyst was filtered off, the filtrate was concentrated in vacuo to obtain **14b** (2.99 g, 100%) as colorless crystals, mp 183–185 °C; ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, t, J = 7.2 Hz), 2.20–2.55 (2H, m), 4.33 (2H, q, J = 7.2 Hz), 4.52 (2H, t, J = 5.4 Hz), 4.75 (1H, dd, J = 7.6, 1.8 Hz), 6.63 (1H, br s), 7.28–7.32 (2H, m), 7.38–7.44 (3H, m), 7.95 (1H, s).

5.1.50. *N*-(1-Adamantyl)-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carboxyamide (16b)

A mixture of **14b** (0.80 g, 2.95 mmol), KOH (0.47 g, 8.38 mmol), EtOH (20 mL), THF (10 mL) and water (20 mL) was stirred at 50 °C for 3 h, followed by addition of KOH (0.17 g, 3.03 mmol). The resulting mixture was stirred at 80 °C for 12 h, and concentrated in vacuo. The residue was acidified by aq citric acid solution, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and then concentrated to obtain 5-phenyl-4,5,6,7-tetra-hydropyrazolo[1,5-*a*]-pyrimidine-3-carboxylic acid **15b** (0.36 g, 50%) as a solid: A mixture of **15b** (0.36 g, 1.48 mmol), 1-adamantylamine (0.22 g, 1.46 mmol), WSC (0.32 g, 1.67 mmol), HOBt (0.25 g, 1.64 mmol), DMAP (0.20 g, 1.64 mmol) and DMF (10 mL) was stirred at room temperature for 20 h, and concentrated in vacuo. The residue was diluted with aqueous $NaHCO_3$, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and then concentrated in vacuo to afford crystals, which was recrystallized from EtOAc–IPE to give **16b** (0.05 g, 9%) as colorless prisms, mp 142–143 °C; ^{1}H NMR ($CDCl_3$): δ 1.70 (6H, s), 2.08 (9H, s), 2.22–2.36 (2H, m), 3.98–4.23 (2H, m), 4.54 (1H, t, J = 6.2 Hz), 5.18 (1H, s), 6.49 (1H, s), 7.28–7.43 (5H, m). Anal. Calcd for $C_{23}H_{28}N_4O{\cdot}0.2H_2O$: C, 72.68; H, 7.53; N, 14.73. Found: C, 72.43; H, 7.38; N, 5.06.

5.1.51. Ethyl 7,7-Dimethyl-5-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbo-xylate (12c)

A mixture of **5** (43.0 g, 27.7 mmol), 3-methyl-1-phenyl-2-buten-1-one (49.82 g, 30.9 mmol), TFA (3.16 g, 27.7 mmol) and 2-methoxyethanol (250 mL) was refluxed overnight. After cooling, the mixture was concentrated in vacuo, and diluted with EtOAc. The mixture was washed with aqueous $NaHCO_3$, water and brine,

dried over $MgSO_4$, and then concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc–hexane (1:4) as an eluent to give **12c** (32.0 g, 62%) as a colorless oil: ^1H NMR ($CDCl_3$): δ 1.32 (3H, t, J = 7.0 Hz), 1.72 (6H, s), 4.30 (2H, q, J = 7.0 Hz), 4.93 (1H, d, J = 2.2 Hz), 7.32–7.52 (6H, m), 7.73 (1H, s).

5.1.52. 7,7-Dimethyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine-3-carb-oxylic acid (15c)

A mixture of **12c** (2.20 g, 7.40 mmol) and 10% Pd–C (1.0 g) in THF–MeOH (50 mL–50 mL) was stirred for 2 h under the hydrogen atmosphere (balloon pressure). After the insoluble materials were filtered off, the residue was concentrated in vacuo to give ethyl 7,7-dimethyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidi-ne 3-carboxylate **14c** as a colorless oil. The ester **14c** was dissolved in EtOH (50 mL), and 1 N NaOH (25 mL, 25 mmol) was added thereto. The resulting mixture was stirred at 80 °C for 14 h, concentrated in vacuo. The residue was acidified with citric acid solution, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and then concentrated to afford a solid, which was recrystallized from EtOAc–hexane to give **15c** (0.84 g, 42%) as colorless prisms: mp 156–157 °C; ^1H NMR ($CDCl_3$): δ 1.57 (3H, s), 1.63 (3H, s), 2.04–2.18 (2H, m), 4.63 (1H, dd, J = 10.2, 5.1 Hz), 5.99 (1H, s), 7.32–7.42 (5H, m), 7.68 (1H, s).

5.1.53. *N*-(1-Adamantyl)-7,7-dimethyl-5-phenyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrimidine-3-carboxamide (16c)

A mixture of **15c** (0.50 g, 1.84 mmol), HATU (1.05 g, 2.76 mmol), and iPr$_2$NEt (0.48 g, 3.68 mmol) in DMF (4 mL) was stirred at room temperature for 1 h, followed by an addition of 1-adamantanamine (0.42 g, 2.76 mmol). The whole was stirred at 50 °C overnight, and concentrated in vacuo. The residue was diluted with EtOAc, washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc–hexane (1:1) to give crystals. Recrystallization from EtOAc–hexane afforded **16c** (0.58 g, 78%) as colorless prisms: mp 238–239 °C; ^1H NMR ($CDCl_3$): δ 1.55 (3H, s), 1.62 (3H, s), 1.69 (6H, s), 2.07–2.24 (11H, m), 4.58 (1H, dd, J = 11.2, 3.6 Hz), 5.17 (1H, s), 6.53 (1H, s), 7.29–7.45 (6H, s). Anal. Calcd for $C_{25}H_{32}N_4O$: C, 74.22; H, 7.97; N, 13.35. Found: C, 74.07; H, 8.24; N, 13.64.

5.1.54. *N*-(1-Adamantyl)-7,7-dimethyl-5-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimid-ine-3-carboxamide (12e)

A mixture of **12c** (350 mg, 1.18 mmol) and 1 N NaOH solution (2.35 mL, 2.35 mmol) in EtOH (5 mL) was stirred at 70 °C for 3 h, neutralized with 1 N HCl and the solvent was concentrated in vacuo. The residue was diluted with CHCl3 and brine. The organic layer separated was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give **12d** as solid (170 mg, 54%). A mixture of **12d** (150 mg, 0.56 mmol), HATU (0.25 g, 0.67 mmol), and iPr$_2$NEt (0.16 g, 1.23 mmol) in DMF (3 mL) was stirred at room temperature for 1 h, followed by an addition of 1-adamantanamine (0.10 g, 0.67 mmol). After stirring at the same temperature for 16 h, the reaction mixture was poured into water and extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc–hexane (2:1) to give **12e** (0.10 g, 45%) as crystals: mp 235–236 °C; ^1H NMR ($CDCl_3$): δ 1.56 (6H, s), 1.74 (6H, s), 2.13–2.18 (9H, m), 3.14 (2H, s), 7.53–7.56 (3H, m), 7.74 (1H, s), 7.98–8.03 (3H, m).

5.1.55. 5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde (18)

A mixture of **17** (4.8 g, 57.8 mmol) and 4,4,4-trifluoro-1-phenyl-1.3-butane dione (12.6 g, 58.3 mmol) in AcOH (200 mL) was refluxed for 3 h, and concentrated in vacuo. The residue was neutralized with aqueous $NaHCO_3$ and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was crystallized from EtOAc–hexane to give 5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine as pale yellow crystals (13.2 g, 86%), mp 106–107 °C; ^1H NMR ($CDCl_3$): δ 6.89 (1H, d, J = 2.4 Hz), 7.52–7.58 (3H, m), 7.64 (1H, s), 8.10–8.15 (2H, m), 8.27 (1H, d, J = 2.2 Hz). Anal. Calcd for $C_{13}H_8N_3F_3$: C, 59.32; H, 3.06; N, 15.96. Found: C, 59.13; H, 2.77; N, 15.88. $POCl_3$ (2 mL) was added dropwise to DMF (5 mL) with ice cooling. After stirring at room temperature for 1 h, 5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (1.32 g, 5.00 mmol) was added thereto in small portions. The mixture was stirred at room temperature for 1 h and at 80 °C for 4 h, cooled, diluted with ice, basified with 1 N NaOH, and extracted with hexane–EtOAc (1:10). The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting precipitate was collected by filtration to give **18** as colorless crystals (0.93 g, 64%): mp 146–147 °C; ^1H NMR ($CDCl_3$): δ 7.57–7.65 (3H, m), 7.85 (1H, m), 8.21–8.26 (2H, m), 8.71 (1H, s), 10.46 (1H, s). Anal. Calcd for $C_{14}H_8N_3OF_3$: C, 57.74; H, 2.77; N, 14.43. Found: C, 57.79; H, 2.66; N, 14.55.

5.1.56. 5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (19a)

A solution of 80% $NaClO_2$ (2.71 g, 30.0 mmol), NaH_2PO_4 (2.0 g, 16.7 mmol) in H_2O (10 mL) was added to a stirred mixture of **18** (0.87 g, 2.99 mmol), 2-methyl-2-butene (5 mL) and dioxane (20 mL) with ice cooling. The mixture was stirred at room temperature for 5 h, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting precipitate was collected by filtration to give **19a** as pale yellow crystals (0.86 g, 93%), mp 250–251 °C. ^1H NMR ($CDCl_3$): δ 7.58–7.66 (3H, m), 7.84 (1H, s), 8.17–8.22 (2H, m), 8.77 (1H, s). Anal. Calcd for $C_{14}H_8N_3O_2F_3$: C, 54.73; H, 2.62; N, 13.68. Found: C, 54.64; H, 2.53; N, 13.41.

5.1.57. *N*-(1-Adamantyl)-5-phenyl-7-(trifluoromethyl)pyrazolo [1,5-*a*]pyrimidine-3-carboxamide (19b)

A mixture of **19a** (0.31 g, 1.0 mmol), 1-adamantylamine (0.17 g, 1.1 mmol), WSC (0.23 g, 1.2 mmol), HOBt (0.15 g, 1.1 mmol) and DMAP (0.12 g, 1.0 mmol) in DMF (5 mL) was stirred at room temperature overnight, diluted with water and extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, and then concentrated to give crystals. Recrystallization from EtOAc–hexane afforded **19b** (0.35 g, 79%) as pale yellow crystals; ^1H NMR ($CDCl_3$): δ 1.72–1.82 (6H, m), 2.17 (3H, s), 2.23 (6H, s), 7.61–7.63 (3H, m), 7.73 (1H, s), 7.88 (1H, br s), 8.11–8.14 (2H, m), 8.75 (1H, s). Anal. Calcd for $C_{24}H_{23}F_3N_4O$: C, 65.44; H, 5.26; N, 12.72. Found: C, 65.17; H, 5.31; N, 12.48.

5.1.58. *tert*-Butyl 5-phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-ylcarba-mate (20)

A mixture of **19a** (1.54 g, 5.0 mmol), DPPA (1.51 g, 5.5 mmol), Et_3N (0.56 g, 5.5 mmol) and *tert*-BuOH (10 mL) was refluxed for 3 h, and concentrated in vacuo. The residue was partitioned between EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc–hexane (1:5) to give **20** as pale yellow crystals (0.75 g, 40%): mp 133–134 °C; ^1H NMR ($CDCl_3$): δ 1.58 (9H, s), 6.94 (1H, br s), 7.51–7.58 (4H, m), 8.08–8.13 (2H, m), 8.70 (1H, br s). Anal. Calcd for $C_{18}H_{17}N_4O_2F_3$: C, 57.14; H, 4.53; N, 14.81. Found: C, 57.21; H, 4.43; N, 14.82.

5.1.59. 5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-amine (21)

Four molar HCl in EtOAc (15 ml, 60.0 mmol) was added dropwise to a solution of **20** (0.57 g, 1.51 mmol) in EtOAc (30 ml) at 0 °C. The mixture was stirred at room temperature for 3 h, and then

stirred at 60 °C for 3 h. The resulting precipitate was collected by filtration to give **21** as pale yellow crystals (0.45 g, 95%), mp 160–165 °C; ^{1}H NMR ($CDCl_3$): δ 7.61–7.66 (3H, m), 8.25 (1H, m), 8.38–8.42 (2H, m), 8.45 (1H, s), 9.00–11.00 (2H, br s).

5.1.60. *N*-[5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-yl]adamantine-1-carboxamide (22)

Et_3N (0.21 g, 2.08 mmol) was added dropwise to a stirred mixture of **21** (0.44 g, 1.58 mmol), 1-adamantane carboxylic acid (0.30 g, 1.68 mmol), HOBt (0.23 g, 1.68 mmol) and WSC (0.32 g, 1.68 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred at room temperature for 2.5 days, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc–hexane (1:5) to give **22** as orange crystals (0.43 g, 70%), mp 257–259 °C; ^{1}H NMR ($CDCl_3$): δ 1.73–1.93 (6H, m), 2.07–2.16 (9H, m), 7.54–7.61 (4H, m), 7.90 (1H, br s), 8.08–8.15 (2H, m), 9.00 (1H, s). Anal. Calcd for $C_{24}H_{23}N_4OF_3$: C, 65.44; H, 5.26; N, 12.72. Found: C, 65.74; H, 5.03; N, 12.36.

5.1.61. *N*-[5-Phenyl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidi-ne-3-yl]-adamantane-1-carboxamide (23)

$NaBH_4$ (91 mg, 2.41 mmol) was added portion to a stirred solution of **22** (0.35 g, 0.79 mmol) in THF–EtOH (3 mL–3 mL) at 0 °C. The mixture was stirred at room temperature for 3 h, diluted with ice, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc–hexane (1:2) to give **23** as colorless crystals (0.24 g, 66%), mp 209–211 °C; ^{1}H NMR ($CDCl_3$): δ 1.67–1.78 (6H, m), 1.90 (6H, d, J = 2.7 Hz), 2.07 (3H, br s), 2.44–2.51 (1H, s), 4.52 (1H, d, J = 11.4 Hz), 4.80–4.91 (1H, m), 5.78 (1H, br s), 7.06 (1H, br s), 7.30 (1H, s), 7.32–7.46 (5H, m). Anal. Calcd for $C_{24}H_{27}N_4OF_3{\cdot}0.5H_2O$: C, 63.56; H, 6.22; N, 12.35. Found: C, 63.71; H, 5.99; N, 12.39.

5.1.62. *N*-{[5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-yl]methyl}ad-amantan-1-amine (24)

A mixture of **18** (0.61 g, 2.09 mmol), 1-adamantane amine (0.32 g, 2.12 mmol) and one drop of AcOH in THF–MeOH (4 mL–2 mL) was stirred at room temperature for 1.5 h. Then, $NaBH_3CN$ was added thereto. The whole was stirred at room temperature overnight, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with EtOAc. The product was recrystallized from EtOAc–hexane to give **24** as pale yellow crystals (0.52 g, 58%), mp 144–145 °C; ^{1}H NMR ($CDCl_3$): δ 1.69–1.75 (6H, m), 1.80–1.82 (6H, m), 2.14 (3H, s), 4.13 (2H, s), 7.54–7.57 (3H, m), 7.60 (1H, s), 8.11–8.16 (2H, m), 8.27 (1H, s). Anal. Calcd for $C_{24}H_{25}N_4F_3$: C, 67.59; H, 5.91; N, 13.14. Found: C, 67.50; H, 5.66; N, 13.15.

5.1.63. *N*-{[5-Phenyl-7-(trifluoromethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimi-dine-3-yl]-methyl}adamantan-1-amine (25)

$NaBH_4$ (57 mg, 1.51 mmol) was added portion to a stirred solution of **24** (0.22 g, 0.52 mmol) in THF–EtOH (1 mL–1 mL) at 0 °C. The mixture was stirred at room temperature for 15 h, diluted with ice, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on SiO_2 with $CHCl_3$–MeOH (10:1) to give **25** as colorless crystals (40 mg, 17%), mp 169–171 °C; ^{1}H NMR ($CDCl_3$): δ 1.66 (6H, s), 1.85 (6H, s), 2.11 (3H, s), 2.19–2.31 (1H, m), 2.45–2.60 (1H, m), 3.73 (2H, dd, J = 17.4, 13.4 Hz), 4.54–4.60 (1H, m), 4.98–5.10 (1H, m), 6.26 (1H, br s), 7.32–7.52 (6H, m). Anal. Calcd for $C_{24}H_{29}N_4F_3{\cdot}1.5H_2O$: C, 63.00; H, 7.05; N, 12.25. Found: C, 62.87; H, 6.72; N, 12.07.

5.2. Biology

5.2.1. GTPγS binding assay

The GTPγS binding activity was measured as follows. The CaR-expressing cell membrane was incubated with test compounds for 10 min. The assays were carried out at room temperature for an hour in a reaction solution mixture containing 20 mM HEPES (pH 7.4), 100 mM NaCl, 1 mM $MgCl_2$, 167 μg/mL DTT, 5 μM guanosine 5′-diphosphate, 0.4 nM [35S]-guanosine 5′-(γ-thio) triphosphate ([35S]-GTPγS) and 6 mM $CaCl_2$. The mixture was filtrated through a GF/C filter. After washing fourth with 300 μL of Phosphate-Buffered Saline, radioactivity of the filter was measured using a Top-count scintillation counter. Data from GTPγS binding assays for antagonists were analyzed with the use of the Prism program (GraphPad Software, Inc). IC_{50} values were determined through nonlinear regression analysis performed with Prism.

5.2.2. Plasma concentration in rats

Compound **16c** was administered orally to nonfasted Crl: CD(SD) rats (male, 8 weeks old, n = 3) at a dose of 10 mg/kg in 0.5% methylcellulose suspension or solubilized reagent. At 0.25, 0.5, 1, 2, 4, 8, and 24 h after oral administration, blood samples were collected, and then immediately centrifuged to obtain the plasma fraction. The plasma samples were deproteinized with acetonitrile. After centrifugation, the supernatant obtained was diluted with 0.01 mol/L ammonium acetate and centrifuged again. The compound concentration in the supernatant was measured by high performance LC system (SHIMADZU, Kyoto, Japan) consisting of a binary solvent manager (LC-10AD$_{vp}$), sample organizer (SCL-10AD$_{vp}$), sample manager (SIL-10A$_{vp}$) and column oven (CTO-10AC). The HPLC conditions were as follows: column, L-column ODS (4.6 mm × 250 mm) from Chemicals Evaluation and Research Institute (Tokyo, Japan); mobile phase, (A) 0.01 mol/L ammonium acetate/(B) acetonitrile = 3:7; flow rate, 1.0 mL/min; column temperature, 40 °C; wavelength, 260 nm.

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