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Oxadiazoles as bioisosteric transformations of carboxylic functionalities. Part I

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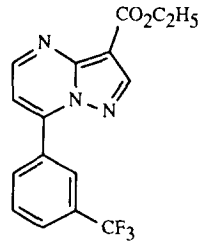
pyrazolo[1,5-*a*]pyrimidine / pyrrolo[1,2-*a*]pyrimidine / benzodiazepine receptor / 1,2,4-oxadiazole

Introduction

In this investigation of new ligands for the benzodiazepine receptor (BZR), our aim was to improve the *in vivo* efficacy of the known BZR ligand 7-(3-(trifluoromethyl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid ethyl ester **1a** (fig 1). It has been reported that compound **1a** displaces [^{3}H]-diazepam *in vitro* from BZR in the nanomolar range [1]. However, compound **1a** lacks *in vivo* activity when administered orally.

Other research groups have successfully replaced ester groups of biologically active compounds by an 1,2,4-oxadiazole moiety to obtain an improved *in vivo* efficacy [2-4]. In our investigation this approach has been applied to compound **1a** and related fused heterocyclic analogues. Consequently, a series of pyrazolo[1,5-*a*]pyrimidines has been prepared in which the ester function of **1a** has been replaced by a 1,2,4-oxadiazole moiety. Further, a series of analogous pyrrolo[1,2-*a*]pyrimidines has also been prepared.



1a

Fig 1. Structure of BZR ligand, compound **1a**.

Chemistry

By the previously described method [5], the reaction of 2-aminopyrazoles **3a** or **3b** with the appropriate 3-(dimethylamino)-1-aryl-2-propen-1-ones **2a–e** in glacial acetic acid at reflux temperature afforded the starting pyrazolo[1,5-*a*]pyrimidines **1a** and **4a–e** in 51–86% yield (scheme 1).

Treatment of the nitriles **4a–e** with hydroxylamine in aqueous ethanol at reflux temperature gave the crude amidoximes **6a–e** in 56–93% yield. According to microanalysis and ^{1}H-NMR analysis, the purity of these crude amidoximes was satisfactory for use in further reaction without purification. Heating the amidoximes **6a–e** with an acid chloride or acid anhydride in a solvent such as pyridine or acetic acid at reflux temperature afforded the 1,2,4-oxadiazole derivatives **7a–g** in 65–81% yield.

After alkaline hydrolysis of the ester **1a** the resulting acid was treated with excess thionyl chloride to give the acid chloride. Reaction of the acid chloride with 2 equivalents of acetamidoxime [6] in dry pyridine at reflux temperature afforded a low yield of the 1,2,4-oxadiazole derivative **5** after purification by column chromatography.

Reaction of **2a** with the reported 2-aminopyrroles **8a** [7] and **8b** [8] in glacial acetic acid at reflux temperature gave the pyrrolo[1,2-*a*]pyrimidines **9a** and **9b** in 71 and 16% yields respectively (scheme 2). The nitrile **9a** was converted into the 1,2,4-oxadiazole derivative **11** in low yield *via* the amidoxime **10** (scheme 2) by a procedure similar to that described above for the nitriles **4a–e**.

The 6-aryl-substituted pyrazolo[1,5-*a*]pyrimidines **13a–b** and pyrrolo[1,2-*a*]pyrimidine **14** (scheme 3)

were prepared in good yields from **3a**, **3b** and **8a**, respectively, by reaction with the previously reported [9] 3-dimethylamino-2-(3-(trifluoromethyl)phenyl)-2-propenal **12** in acetic acid at reflux temperature. As **13a** and **13b** showed *in vitro* activity on the BZR in the micromolar range, they were not reacted further to the oxadiazole derivatives.

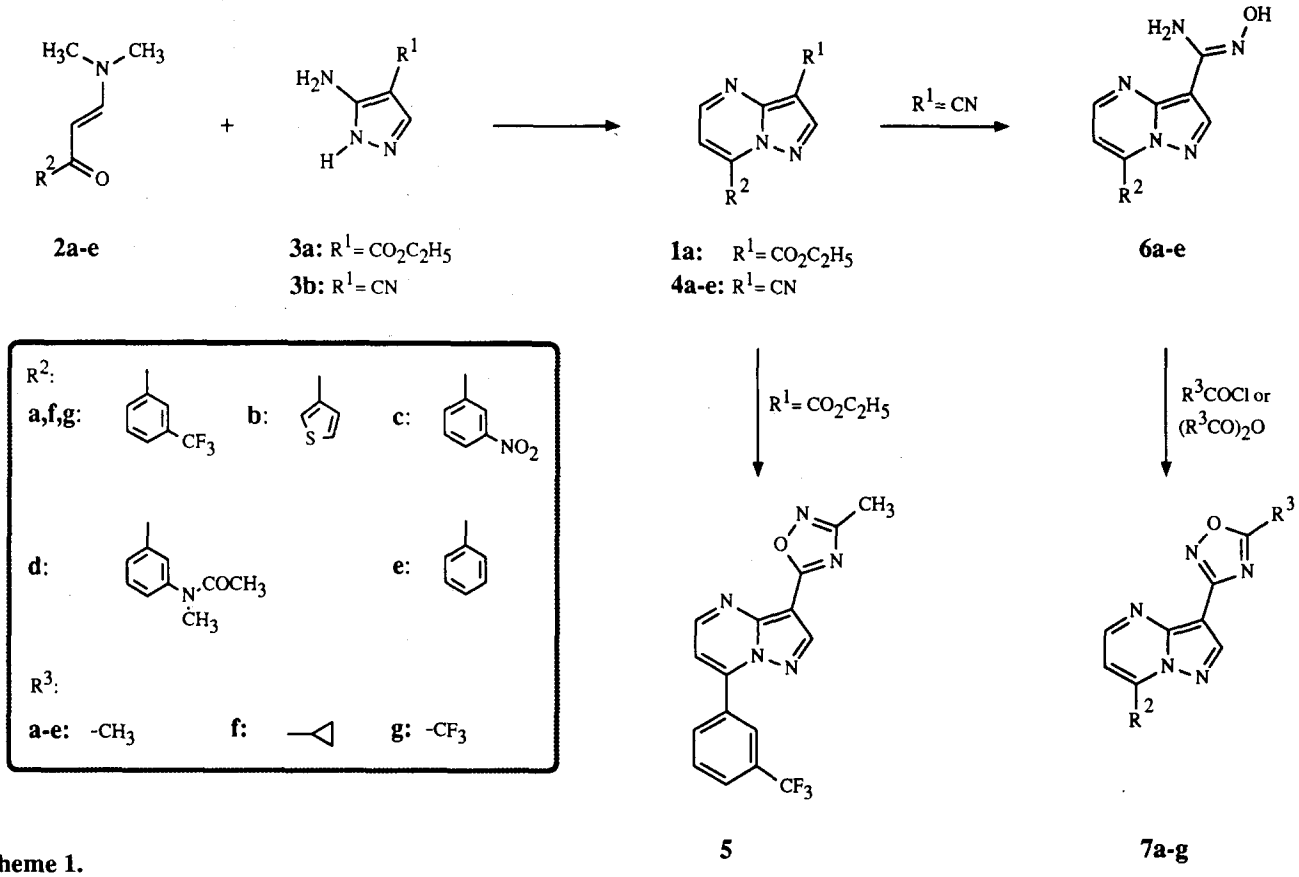
Results and Discussion

In vitro study

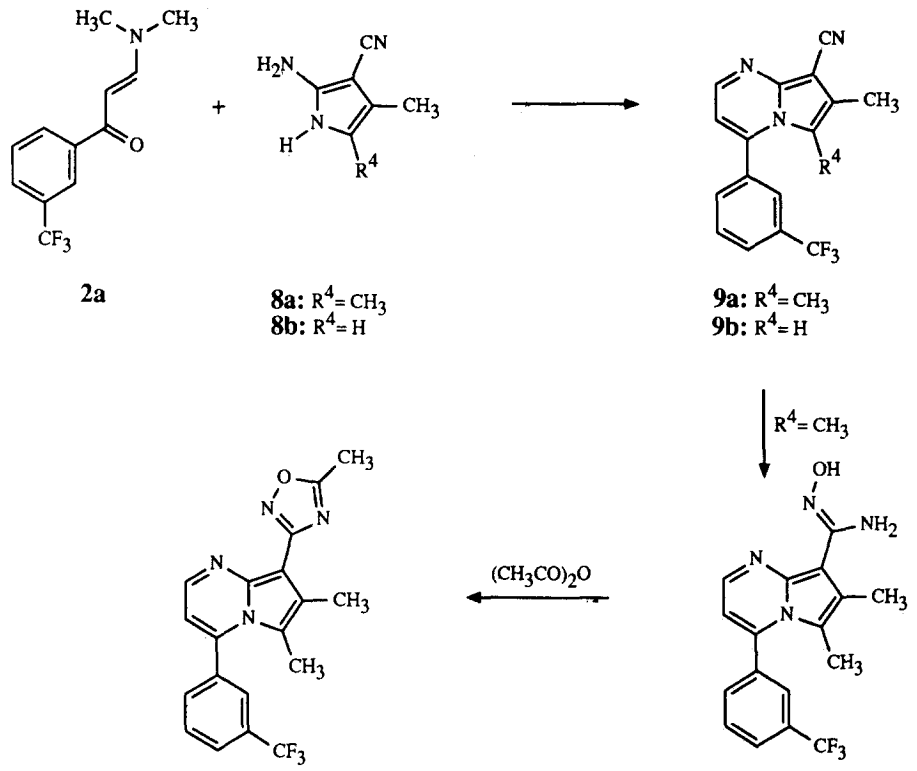
The compounds **1a**, **4a**, **5**, **6a**, **7a–g**, **9a–b**, **11** and **13a–b** were tested for their affinity on BZR using [^{3}H]-flunitrazepam as a radioligand. The result of the test performed with the present compounds is shown in table I. As it can be seen from these results, the affinity of compound **1a** is lowered considerably when the ester group is changed to an 1,2,4-oxadiazol-3-yl moiety as in compounds **7a–g**. Furthermore, when moving the 7-aryl substituent in compound **1a** to the 6-position as in **13a**, the affinity to BZR totally vanishes. However, changes in the ring system itself seem to be allowed. When the N-1 atom in compound **4a** is changed to a -CH= group as in compound **9b** only a 2-fold decrease in *in vitro* affinity is observed. However, structure **9b** is not considered as fully optimized for its affinity on BZR because of the residing 7-CH_3 group. Removal of the 7-CH_3 group in **9b** would give the highest degree of structural homology between **4a** and the desmethyl derivative of **9b**. Unfortunately we have not been able to prepare this desmethyl derivative of **9b**, which one may expect to have an increased affinity for BZR compared with **9b**.

Animal study

Due to a generally low *in vitro* affinity on BZR, only a limited number of compounds, with the highest affinity, were selected for *in vivo* testing. Compounds **1a**, **5**, **7a** and **7b** were tested for their *in vivo* affinity on BZR in NMRI mice using [^{3}H]-flunitrazepam as radioligand (table I). Furthermore, the relative



Scheme 1.



Scheme 2.

in vivo efficacy defined as the ratio ED_{50} (mg/kg)/IC_{50} (nM) was calculated and is presented in table I. As can be seen from table I no improvement in the *in vivo* affinity is observed for the tested compounds **5**, **7a** and **7b** compared with the reference compound **1a**. However, a higher bioavailability was observed for compound **7a** compared with compound **1a**, despite a lower *in vitro* and *in vivo* affinity for BZR than **1a**.

Experimental protocols

Chemistry

Melting points are uncorrected. ^{1}H-NMR spectra were obtained on a Bruker WM 400 MHz apparatus and chemical shifts (δ) are in ppm relative to tetramethylsilane. Column chromatography was performed using Merck silica gel 9385. Microanalysis were done at Novo-Nordisk A/S, supervised by R Amsler. Analyses indicated by the symbols of the elements were within ± 0.4% of theoretical values unless otherwise stated. Starting materials **3a** and **3b** were purchased from Lancaster Synthesis.

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

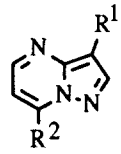
A mixture of 1-(3-(trifluoromethyl)phenyl)ethanone (25.0 g, 133 mmol) and *N,N*-dimethylformamide dimethylacetal (18.3 g, 138 mmol, 90–95%) was heated at reflux for 18 h. The reaction mixture was evaporated to dryness *in vacuo* and the residue suspended in *n*-heptane (150 ml). The solid obtained was isolated by filtration and recrystallized from cyclohexane to give 22.6 g (70%) of 3-(dimethylamino)-1-(3-(trifluoromethyl)phenyl)-2-propen-1-one **2a**; mp: 56–57°C; reported [5] mp: 60–62°C.

A mixture of **2a** (9.6 g, 39.3 mmol) and 5-amino-4-pyrazole carboxylic acid ethyl ester **3a** (6.1 g, 39.3 mmol) in acetic acid (50 ml) was heated at reflux for 8 h. The reaction mixture was poured into ice water (250 ml) and extracted with chloroform (300 ml). The organic phase was washed with a 1 N sodium hydroxide (2 x 100 ml), brine (100 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give an oil, which was dissolved in diethyl ether (100 ml). On standing a solid separated which was isolated and dried to give 11.4 g (86 %) of **1a**; mp 105–106°C, reported [5] mp 97–99°C; ^{1}H-NMR ($CDCl_3$) δ 1.45 (t, 3H); 4.48 (q, 2H); 7.12 (d, 1H); 7.74 (t, 1H); 7.86 (d, 1H); 8.24 (d, 1H); 8.26 (s, 1H); 8.62 (s, 1H); 8.86 (d, 1H). Anal $C_{16}H_{12}F_3N_3O_2$ (C, H, N).

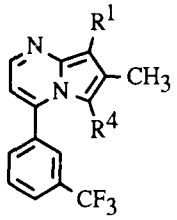
3-(3-Methyl-1,2,4-oxadiazol-5-yl)-7-(3-(trifluoromethyl)-phenyl)pyrazolo[1,5-a]pyrimidine ***5***

A mixture of **1a** (11.3 g, 34 mmol), ethanol (500 ml) and 6 N sodium hydroxide (60 ml) was heated at reflux for 4 h and then

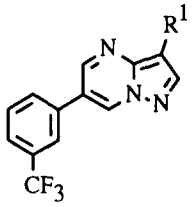
Table I. Chemical and biological data of pyrazolo[1,5-*a*]pyrimidines and pyrrolo[1,2-*a*]pyrimidines.



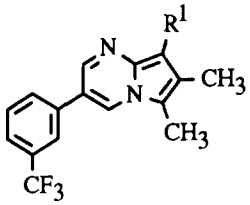
1a,4a,5,6a,7a–g



9a,b,11



13a,b



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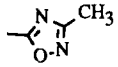
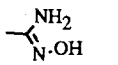
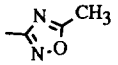
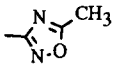
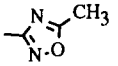
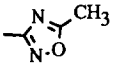
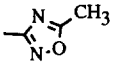
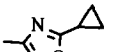
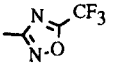
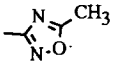
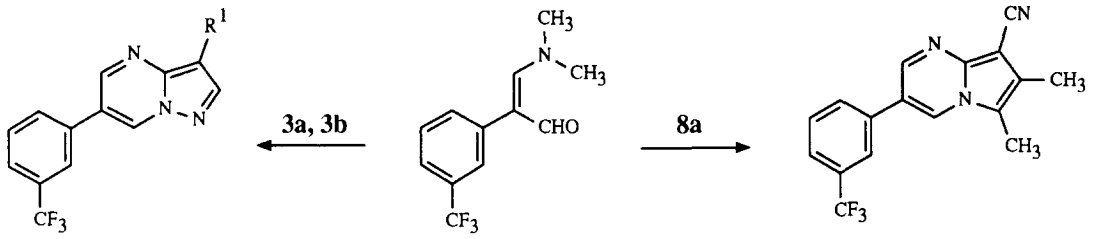
No.	R^1	R^2	R^4	mp^{0}C	*In Vitro* [^{3}H]-FNM IC_{50}(nM)[f]	*In Vivo* [^{3}H]-FNM ED_{50}(mg/kg)[g]	Relative *In Vivo* efficacy[h]
1a	$CO_2C_2H_5$	3-$CF_3C_6H_4$	-	105-106[a]	18.5±0.3	109±13	5.9
4a	CN	3-$CF_3C_6H_4$	-	140-142[b]	375±37	ND	-
5		3-$CF_3C_6H_4$	-	216[b]	316±39	>100	>0.3
6a		3-$CF_3C_6H_4$	-	235 dec[b]	15200±370	ND	-
7a		3-$CF_3C_6H_4$	-	148-150[c]	112±16	96±6	0.85
7b		3-Thienyl	-	236-237[c]	122±43	>300	>2.5
7c		3-$NO_2C_6H_4$	-	241-243[b]	1600±210	ND	-
7d		3-MeNC$_6$H$_4$ COMe	-	181-182[b]	528±30	ND	-
7e		C_6H_5	-	153-155[c]	1670±168	ND	-
7f		3-$CF_3C_6H_4$	-	139-140[c]	117±0	ND	-
7g		3-$CF_3C_6H_4$	-	162[b]	622±66	ND	-
9a	CN	-	CH_3	172-174[b]	1270±240	ND	-
9b	CN	-	H	160-161[b]	539±82	ND	-
11		-	CH_3	197-198[e]	16500±1100	ND	-
13a	$CO_2C_2H_5$	-	-	198-199[d]	>30000	ND	-
13b	CN	-	-	173-174[d]	>30000	ND	-
14	CN	-	CH_3	185-188[d]	>30000	ND	-

Crystallized from: [a]diethyl ether; [b]ethanol; [c]ethyl acetate; [d]acetic acid/water. [e]Purified on silica gel using ethyl acetate/*n*-heptane as eluent. [f]Mean ± SEM (n = 4–8). [g]Mean ± SEM (n = 2–4). [h]Defined as ED_{50} (mg/kg)/IC_{50} (nM). ND = Not Determined. Microanalysis on the following compounds showed deviations of N larger than ± 0.4% calc (found): **9b**: 13.95 (13.48); **11**: 15.05 (14.49); **13b**: 19.44 (18.79).



13a: $R^1 = CO_2C_2H_5$
13b: $R^1 = CN$

12

14

Scheme 3.

allowed to cool to room temperature. The solid was isolated, suspended in water (150 ml) and 4 N hydrochloric acid (150 ml) was added with stirring. This mixture was stirred overnight and filtered to give 5.4 g (52%) of 7-(3-(trifluoromethyl)phenyl)-3-pyrazolo[1,5-*a*]pyrimidine carboxylic acid.

A mixture of the above acid (2.0 g, 6.5 mmol) and thionyl chloride (20 ml) was stirred at room temperature for 30 min and then heated at reflux for another 30 min. Excess thionyl chloride was removed *in vacuo* to give a residue which was dissolved in dry pyridine (25 ml). Acetamidoxime [6] (0.96 g, 13.0 mmol) was added and the mixture was heated at reflux for 2.5 h and then left overnight at room temperature. The reaction mixture was poured into 2 N hydrochloric acid (200 ml) and extracted with ethyl acetate (2 x 100 ml). The combined organic extracts were washed with 1 N hydrochloric acid (2 x 100 ml), brine (100 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography using ethyl acetate as eluent to give 0.23 g (10% calculated from the acid) of **5**; mp 216°C; ^{1}H-NMR ($CDCl_3$) δ 2.54 (s, 3H); 7.22 (d, 1H); 7.78 (t, 1H); 7.91 (d, 1H); 8.30 (d, 1H); 8.32 (s, 1H); 8.80 (s, 1H); 8.94 (d, 1H). Anal $C_{16}H_{10}F_3N_5O$ (C, H, N).

7-(3-(Trifluoromethyl)phenyl)-3-pyrazolo[1,5-a]pyrimidine carbonitrile ***4a***

A mixture of **2a** (5.7 g, 23.4 mmol) and 5-amino-4-pyrazole carbonitrile **3b** (2.5 g, 23.4 mmol) in glacial acetic acid (40 ml) was heated at reflux for 18 h. The reaction mixture was poured into ice water (200 ml) and extracted with chloroform (200 ml). The organic phase was washed with 1 N sodium hydroxide (200 ml), 1 N hydrochloric acid (200 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give a solid which was recrystallized from ethanol to give 3.4 g (51%) of **4a**; mp 140–142°C; reported [5] mp 144–145°C; ^{1}H-NMR ($CDCl_3$) δ 7.30 (d, 1H); 7.84 (t, 1H); 7.99 (d, 1H); 8.34 (d, 1H); 8.47 (s, 1H); 8.54 (s, 1H); 8.91 (d, 1H). Anal $C_{14}H_7F_3N_4$ (C, H, N).

Compounds **4b–e** were prepared by a procedure similar to that described for **4a**.

7-(3-(Trifluoromethyl)phenyl)-3-pyrazolol[1,5-a]pyrimidine carboxamidoxime ***6a***

To a stirred mixture of **4a** (2.9 g, 10.1 mmol) and potassium carbonate (2.8 g, 20.0 mmol) in ethanol (40 ml) and water (4 ml), was added hydroxylamine hydrochloride (1.04 g, 15.0 mmol). The reaction mixture was heated at reflux for 2 h and then stirred overnight at room temperature. The solid formed was isolated by filtration and washed with ethanol, then suspended in water (50 ml) and stirred for 1 h. Filtration and drying in air afforded 1.4 g (44%) of **6a**; mp 235°C (decomp); ^{1}H-NMR (DMSO-d_6) 6.11 (br s, 2H); 7.51 (d, 1H); 7.96 (t, 1H); 8.10 (d, 1H); 8.48 (d, 1H); 8.56 (s, 1H); 8.60 (s, 1H); 8.72 (d, 1H); 9.54 (br s, 1H). Anal $C_{14}H_{10}F_3N_5O$ (C, H, N).

Compounds **6b–e** were prepared by a procedure similar to that described for **6a**.

3-(5-Methyl-1,2,4-oxadiazol-3-yl)-7-(3-(trifluoromethyl)-phenyl)pyrazolo[1,5-a]pyrimidine ***7a***

To a stirred mixture of **6a** (1.6 g, 5.0 mmol) in glacial acetic acid (15 ml), was added dropwise a solution of acetic anhydride (0.56 g, 5.5 mmol) in glacial acetic acid (5 ml). When the addition was complete a precipitate had formed and glacial acetic acid (10 ml) was added. The reaction mixture was heated at reflux for 1 h, cooled, poured into ice water (200 ml) and extracted with dichloromethane (100 ml). The organic phase was washed with sodium carbonate solution, dried over anhydrous potassium carbonate and the solvent evaporated *in vacuo*. The reside was purified by flash chromatography using ethyl acetate as eluent to give 1.1 g (65%) of **7a**; mp 148–150°C; ^{1}H-NMR ($CDCl_3$) δ 2.74 (s, 3H); 7.13 (d, 1H); 7.76 (t, 1H); 7.89 (d, 1H); 8.30–8.32 (m, 2H); 8.75 (s, 1H); 8.87 (d, 1H). Anal. $C_{16}H_{10}F_3N_5O$ (C, H, N).

Compounds **7b–e** were prepared by a method similar to that described above (table I) in 67-81% yield.

3-(5-Cyclopropyl-1,2,4-oxadiazol-3-yl)-7-(3-(trifluoromethyl)-phenyl)pyrazolo[1,5-a]-pyrimidine ***7f***

Cyclopropylcarboxylic acid chloride (0.78 g, 7.5 mmol) was added to a stirred solution of **6a** (2.0 g, 6.2 mmol) in pyridine (30 ml). The reaction mixture was heated at reflux for 1.5 h, cooled, poured into 2 N hydrochloric acid (240 ml) and extracted with ethyl acetate (100 ml). The organic phase was washed with 0.5 N hydrochloric acid (2 x 50 ml), brine and dried over anhydrous sulfate. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography using ethyl acetate as a eluent to give 1.6 g (70%) of **7f**; mp 139–140°C; ^{1}H-NMR ($CDCl_3$) δ 1.26–1.36 (m, 4H); 2.35 (m, 1H); 7.12 (d, 1H); 7.76 (d, 1H); 7.87 (d, 1H); 8.30–8.32 (m, 2H); 8.72 (s, 1H); 8.85 (d, 1H). Anal $C_{18}H_{12}F_3N_5O$ (C, H, N)

Compound **7g** was prepared by a method similar to that described for **7f** (table I) in 65% yield.

6,7-Dimethyl-4-(3-(trifluoromethyl)phenyl)-8-pyrrolo[1,2-a]-pyrimidine carbonitrile ***9a***

A mixture of **2a** (4.9 g, 20.0 mmol) and 2-amino-4,5-dimethyl-3-pyrrole carbonitrile **8a** [7] (2.7 g, 20.0 mmol) in glacial

acetic acid (30 ml) was heated at reflux for 2 h. The reaction mixture was poured into ice water (150 ml). The orange precipitate was isolated by filtration and recrystallized from 96% aqueous ethanol to give 4.5 g (71%) of **9a**; mp 172–174°C; ^{1}H-NMR (DMSO-d_6) δ 1.68 (s, 3H); 2.28 (s, 3H); 6.94 (d, 1H); 7.18 (t, 1H); 7.95 (d, 1H); 8.00 (d, 1H); 8.08 (s, 1H); 8.39 (d, 1H); Anal $C_{17}H_{11}F_3N_3$ (C, H, N).

*7-Methyl-4-(3-(trifluoromethyl)phenyl)-8-pyrrolo[1,2-a]pyrimidine carbonitrile **9b***
A mixture of 2-amino-4-methyl-3-pyrrole carbonitrile **8b** [8] (0.7 g, 5.8 mmol) and **2a** (1.4 g, 5.8 mmol) in absolute ethanol (25 ml) and glacial acetic acid (0.33 ml) was heated at reflux for 32 h under nitrogen. The reaction mixture was poured into ice water (80 ml) and extracted with ethyl acetate (3 x 50 ml). The combined organic phase was washed with 5% sodium bicarbonate (50 ml) and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* to give a dark oil which was dissolved into dichloromethane (125 ml) and treated with activated charcoal. The mixture was filtered and the solvent evaporated *in vacuo* to give an oil from which was flash chromatographed using dichloromethane as eluent to give 0.27 g (16%) **9b** as a solid which was recrystallized from ethanol; mp 160–161°C; ^{1}H-NMR (DMSO-d_6) δ 2.34 (s, 3H); 7.12 (d, 1H); 7.34 (s, 1H); 7.88 (t, 1H); 8.04 (d, 1H); 8.12 (d, 1H); 8.14 (s, 1H); 8.50 (d, 1H); Anal $C_{16}H_{10}F_3N_3$ (C, H, N).

*6,7-Dimethyl-8-(5-methyl-1,2,4-oxadiazol-3-yl)-4-(3-(trifluoromethyl)phenyl)pyrrolo[1,2-a]pyrimidine **11***
A mixture of **9a** (1.9 g, 6.0 mmol), ethanol (40 ml), water (4 ml) and potassium carbonate (1.7 g, 12.0 mmol) was stirred on an ice-bath. Hydroxylamine hydrochloride (0.84 g, 12.0 mmol) was added portionwise within 30 min. The reaction mixture was then heated at reflux for 18 h, which resulted in an orange precipitate. The mixture was cooled, the precipitate isolated by filtration, washed with ethanol and air-dried to give 1.35 g of crude **10** according to ^{1}H-NMR.

Crude **10** (0.85 g) was dissolved into dry ice-cooled pyridine (15 ml). When dissolution was complete the reaction mixture was allowed to come to rt and acetic anhydride (0.23 ml) was added. Stirring was continued for 0.5 h at rt and then the mixture was heated at reflux for 1.5 h and finally left overnight at rt. The reaction mixture was poured into 2 N hydrochloric acid (100 ml) and extracted with ethyl acetate (2 x 50 ml). The combined organic phase was washed with 1 N hydrochloric acid (50 ml), brine (50 ml), treated with activated charcoal and filtered. The solvent was evaporated *in vacuo* and the residue was purified by flash chromatography using ethyl acetate/*n*-heptane as eluent to give 0.4 g (18% from **9a**) of **11**; mp 197–198°C (EtOH/H_2O); ^{1}H-NMR ($CDCl_3$) δ 1.79 (s, 3H); 2.50 (s, 3H); 2.70 (s, 3H); 6.48 (d, 1H); 7.68 (m, 4H); 8.30 (d, 1H); Anal calc for $C_{19}H_{15}F_3N_4O$: C: 61.29; H: 4.06; N: 15.05; found: C: 61.50; H: 4.19; N: 14.49.

*3-Dimethylamino-2-(3-(trifluoromethyl)phenyl)-2-propenal **12***
Compound **12** was prepared similar to a previously reported method [9]. *N,N*-Dimethylformamide (54 g, 0.73 mol) was added dropwise with vigorous stirring to phosphorus oxychloride (92 g, 0.60 mol) maintaining the temperature at 28°C by intermittent cooling. Stirring was continued for 5 min after addition was complete and a solution of 3-(trifluoromethyl)phenyl acetic acid (40.8 g, 0.20 mol) in *N,N*-dimethylformamide (100 ml) was added over a period of 5 min. The mixture was stirred at 70°C for 18 h and then poured onto crushed ice (850 g) followed by neutralization with anhydrous potassium carbonate (120 g). The resulting solution was made alkaline (pH 13.5) by addition of 12 N sodium hydroxide (190 ml) at such a rate that a temperature of 50°C was maintained. After evolution of dimethylamine had ceased, the mixture was cooled and the resulting precipitate was filtered off, washed with water and air-dried to afford 46.6 g (96%) of **12**; mp 124–125°C; ^{1}H-NMR ($CDCl_3$) δ 2.86 (s, 6H); 6.88 (s, 1H); 7.42–7.54 (m, 4H); 9.12 (s, 1H); Anal $C_{12}H_{12}NF_3O$ (C, H, N).

*Ethyl 6-(3-(trifluoromethyl)phenyl)-3-pyrazolo[1,5-a]pyrimidine carboxylate **13a***
A mixture of **12** (1.57 g, 6.4 mmol) and 5-amino-4-pyrazole carboxylic acid ethyl ester **3a** (0.6 g, 3.9 mmol) in 50% acetic acid (30 ml) was heated at reflux for 15 min and then cooled to rt. The mixture was filtered and the solid was washed with 50% acetic acid, water and methanol to afford 1.15 g (89%) **13a**; mp 198–199°C; ^{1}H-NMR (DMSO-d_6) δ 1.30 (t, 3H); 4.35 (q, 2H); 7.80 (t, 1H); 8.30 (s, 1H); 8.70 (s, 1H); 9.79 (s, 1H); Anal $C_{16}H_{12}F_3N_3O$ (C, H, N).

*6-(3-(Trifluoromethyl)phenyl)-3-pyrazolo[1,5-a]pyrimidine carbonitrile **13b***
A mixture of **12** (1.6 g, 6.4 mmol) and 5-amino-4-pyrazole carbonitrile **3b** (0.6 g, 3.9 mmol) in 50% acetic acid (30 ml) was heated at reflux for 45 min and then cooled to rt. The reaction mixture was worked up as described for **13a** to give 1.03 g (93%) **13b**; mp 173–174°C; ^{1}H-NMR (DMSO-d_6) δ 7.80 (t, 1H); 7.85 (t, 1H); 8.22 (d, 1H); 8.30 (s, 1H); 8.90 (s, 1H); 9.32 (s, 1H); 9.90 (s, 1H). Anal calc for $C_{14}H_7F_3N_4$: C: 58.34; H: 2.45; N: 19.44; found: C: 58.24; H: 2.35; N: 18.79.

*6,7-Dimethyl-3-(3-(trifluoromethyl)phenyl)-8-pyrrolo[1,2-a]-pyrimidine carbonitrile **14***
A mixture of **12** (0.45 g, 1.85 mmol) and 2-amino-4,5-dimethyl-3-pyrrolecarbonitrile **8a** [7] (0.15 g, 1.1 mmol) in 50% acetic acid (10 ml) was heated under nitrogen for 15 min. The reaction mixture was cooled to rt and the solid was isolated, washed with 30% acetic acid, water, methanol and air-dried to give 0.27 g (77%) of **14**; mp 185–188°C; ^{1}H-NMR (DMSO-d_6) δ 2.36 (s, 3H); 2.50 (s, 3H); 7.76 (m, 2H); 8.15 (d, 1H); 8.22 (s, 1H); 8.78 (s, 1H); 8.98 (s, 1H). Anal calc for $C_{17}H_{12}F_3N_3$: C: 64.76; H: 3.84; N: 13.33; found: C: 64.90; H: 3.80; N: 12.92.

Pharmacology

In vitro inhibition of [^{3}H]-flunitrazepam binding
In vitro inhibition of [^{3}H]-flunitrazepam binding was performed according to general methods [10] using a final concentration of 1 nM [^{3}H]-flunitrazepam at 0°C for 40 min. The concentrations necessary for 50% inhibition (IC_{50}) are shown in table I.

In vivo inhibition of [^{3}H]-flunitrazepam binding
Inhibition of specific [^{3}H]-flunitrazepam binding in the forebrain of living NMRI mice was determined according to published method [11]. The doses of test compound used were 30 and 100 mg/kg. The doses for 50% inhibition (ED_{50}) are shown in table I.

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