8-Amino-3-benzyl-1,2,4-triazolo[4,3-*a*]pyrazines. Synthesis and Anticonvulsant Activity

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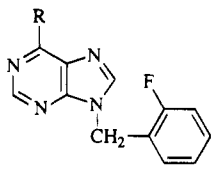
Eleven substituted 8-amino-3-benzyl-1,2,4-triazolo[4,3-*a*]pyrazines were synthesized and tested for anticonvulsant activity against maximal electroshock-induced seizures (MES) in rats. The compounds were prepared in four stages from the phenylacetonitriles **I**. The intermediate (2,2,2-triethoxyethyl)benzenes **III** were condensed with 2-chloro-3-hydrazinopyrazine (**IV**) to provide the 3-benzyl-8-chloro-1,2,4-triazolo[4,3-*a*]pyrazines **V**. The latter were converted to the 8-amine targets **VI** with methylamine or ammonia. Several compounds exhibited potent activity against MES; the 3-(2-fluorobenzyl)-8-(methylamino) and 3-(2,6-difluorobenzyl)-8-(methylamino) congeners (**4** and **12**) exhibited the best anticonvulsant activity with oral ED_{50}s of 3 mg/kg. The 1,2,4-triazolo[4,3-*a*]pyrazine ring system serves as a bioisostere of the purine ring for anticonvulsant activity; however, these agents exhibit less propensity to cause emesis.

Introduction

Although several antiepileptic drugs are used in the treatment of epilepsy, many patients fail to experience satisfactory seizure control with them, or they do so at the expense of significant side effects.[1,2] Because new, improved antiepileptic drugs are needed, a program was initiated to discover and develop candidate antiepileptic agents with improved properties.[3-7] Purine **1** [9-(2-fluorobenzyl)-6-(methylamino)-9*H*-purine, 78U79], which is an orally active anticonvulsant agent with potent activity against maximal electroshock-induced seizures (MES) in rats and mice, emerged from this program.[5-7] Structure–activity relationship studies showed that optimum activity was associated with a 9-(2-fluorobenzyl) and 6-(alkylamino) substitution pattern.[6,7] If the 3-nitrogen of **1** was replaced with carbon, the resultant 3-deazapurine also was very active as an anticonvulsant agent.[8] Isosteric replacement of the imidazole ring



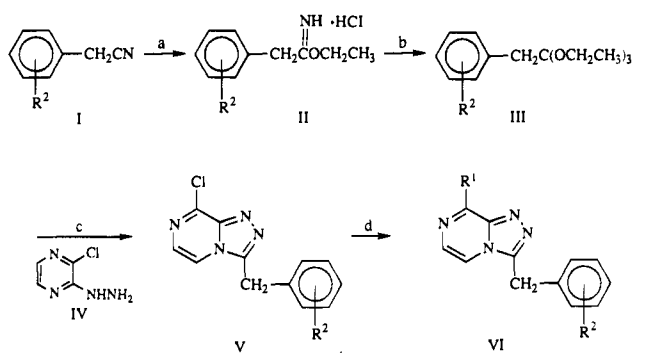
1, R = $NHCH_3$
2, R = NH_2

atoms of **1** to give the pyrrolo[2,3-*d*]-, pyrazolo[3,4-*d*]-, and triazolo[4,5-*d*]pyrimidine analogues resulted in agents with less activity against MES.[9] We have extended our structure–activity relationship studies of **1** to the 1,2,4-triazolo[4,3-*a*]pyrazine ring system. The synthesis and pharmacological activity of these compounds are reported herein.

Chemistry

The 1,2,4-triazolo[4,3-*a*]pyrazines **3–13** (Table 1) were synthesized from the appropriate phenylacetonitriles as outlined in Scheme 1. The intermediate ethyl phenylacetimidates **II** (Table 2) were prepared from nitriles **I** with HCl in EtOH at 0 °C in high yields.[10] Reaction of **II** with absolute EtOH provided the (2,2,2-triethoxyethyl)benzenes **III** in high yields as relatively pure oils. Condensation of 2-chloro-3-hydrazinopyrazine (**IV**),[11] which was prepared from aminoacetaldehyde diethylacetal in four stages,[11,12] with **III** in refluxing xylene gave the 8-chloro-1,2,4-triazolo[4,3-*a*]pyrazines **V** in 62–77% yield.[13] Displacement of the 8-chloro substituent with 40% aqueous $MeNH_2$ or NH_3-saturated MeOH gave compounds **3–13** as free bases. The hydrochlorides were formed with ethereal HCl in EtOH.

Scheme 1[a]



[a] (a) EtOH, HCl; (b) EtOH; (c) **III**, xylene; (d) EtOH, $MeNH_2$ or MeOH, NH_3, 120 °C.

Biological Results and Discussion

The compounds in Table 3 were evaluated for anticonvulsant activity in the maximal electroshock-induced seizure (MES) test in Wistar male rats obtained from Charles River as described previously.[4] The compounds were tested initially at 25 mg/kg ip. If activity was high, an ED_{50} was determined and the compound was tested orally.

The 9-(2-fluorobenzyl)purine **1** is a potent anticonvulsant with an ip ED_{50} of 1.7 mg/kg and an oral ED_{50}

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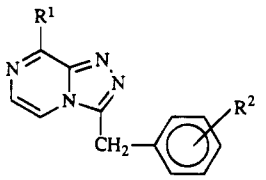
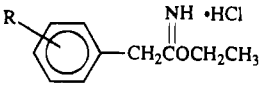
Table 1. Physical Properties of 1,2,4-Triazolo[4,3-*a*]pyrazines



no.	R^1	R^2	method	yield, %	mp, °C	formula[a]
3	$NHCH_3$	H	D	57[b]	178–180	$C_{13}H_{13}N_5$
3[a]	$NHCH_3$	H	E	90[d]	280–282 (dec)	$C_{13}H_{13}N_5$·HCl
4	$NHCH_3$	2-F	D	66[e]	165–167	$C_{13}H_{12}FN_5$
4[c]	$NHCH_3$	2-F	E	83[d]	292–295 (dec)	$C_{13}H_{12}FN_5$·HCl
5	NH_2	2-F	F	41[f]	289–292 (dec)	$C_{12}H_{10}FN_5$
5[c]	NH_2	2-F	E	54[d]	286–289 (dec)	$C_{12}H_{10}FN_5$·HCl
6	$NHCH_3$	3-F	D	82[g]	167–168	$C_{13}H_{12}FN_5$
6[c]	$NHCH_3$	3-F	E	89[d]	>250	$C_{13}H_{12}FN_5$·HCl
7	NH_2	3-F	F	84[h]	>250	$C_{12}H_{10}FN_5$
7[c]	NH_2	3-F	E	94[d]	>250	$C_{12}H_{10}FN_5$·HCl·$^1/_2H_2O$
8	$NHCH_3$	4-F	D	82[g]	199–201	$C_{13}H_{12}FN_5$
8[c]	$NHCH_3$	4-F	E	97[d]	>250	$C_{13}H_{12}FN_5$·HCl
9	NH_2	4-F	F	70[h]	>250	$C_{12}H_{10}FN_5$
9[c]	NH_2	4-F	E	65[i]	>250	$C_{12}H_{10}FN_5$·2HCl
10	$NHCH_3$	2,5-F_2	D	78[g]	192–194	$C_{13}H_{11}F_2N_5$
10[c]	$NHCH_3$	2,5-F_2	E	98[d]	>250	$C_{13}H_{11}F_2N_5$·HCl
11	NH_2	2,5-F_2	F	75[g]	>250	$C_{12}H_9F_2N_5$
11[c]	NH_2	2,5-F_2	E	89[d]	>250	$C_{12}H_9F_2N_5$·HCl
12	$NHCH_3$	2,6-F_2	D	86[g]	205–207	$C_{13}H_{11}F_2N_5$
12[c]	$NHCH_3$	2,6-F_2	E	94[c,d]	>250	$C_{13}H_{11}F_2N_5$·HCl
13	NH_2	2,6-F_2	F	82[g]	>250	$C_{12}H_9F_2N_5$
13[c]	NH_2	2,6-F_2	E	92[d]	>250	$C_{12}H_9F_2N_5$·HCl
14	Cl	H	B,C	66	161–162[b]	$C_{12}H_9ClN_4$
15	Cl	2-F	B,C	70	126–127[b]	$C_{12}H_8ClFN_4$
16	Cl	3-F	B,C	63[h]	156–157	$C_{12}H_8ClFN_4$
17	Cl	4-F	B,C	77[h]	117–118	$C_{12}H_8ClFN_4$
18	Cl	2,5-F_2	B,C	62[h]	123–124	$C_{12}H_7ClF_2N_4$
19	Cl	2,6-F_2	B,C	63[h]	152–154	$C_{12}H_7ClF_2N_4$

[a] All compounds were analyzed for C, H, and N. [b] Recrystallized from EtOH–H_2O. [c] Hydrochloride salt. [d] Recrystallized from EtOH–Et_2O. [e] Recrystallized from EtOAc–hexane. [f] Recrystallized from MeOH. [g] Isolated pure from the reaction mixture. [h] Recrystallized from EtOH. [i] Freeze-dried.

Table 2. Physical Properties of Acetimidates



no.	R	method	yield, %	mp, °C	formula[a]
20	H	A	89	89–91[b]	$C_{10}H_{13}NO$·HCl
21	2-F	A	91	96–99	$C_{10}H_{12}FNO$·HCl
22	3-F	A	94		$C_{10}H_{12}FNO$·HCl
23	4-F	A	98	*c*	$C_{10}H_{12}FNO$·HCl
24	2,5-F_2	A	98		$C_{10}H_{11}F_2NO$·HCl·0.15H_2O
25	2,6-F_2	A	90	108–109 (dec)	$C_{10}H_{11}F_2NO$·HCl

[a] All compounds were analyzed for C, H, and N. [b] This compound was reported by: Hill, A. J.; Rabinowitz, I. *J. Am. Chem. Soc.* **1926**, *48*, 732. [c] This compound was reported by: Huang, Z.; Liu, Z. *Synthesis* **1987**, 357.

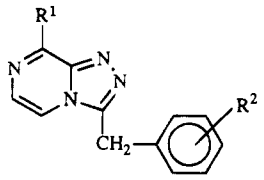
= 2.5 mg/kg in rats (Table 3).[5,7] The 6-amino analogue **2** is several fold less active by both routes of administration. Replacement of the pure ring with the 1,2,4-triazolo[4,3-*a*]pyrazine ring system to give **4** resulted in a compound with excellent activity against MES. Triazolopyrazine **4** has an oral ED_{50} = 3 mg/kg, and the 8-amino analogue **5** is 2–3-fold less active.

The presence and position of a fluorine substituent has a very significant impact on activity. The des-fluoro compound **3** is 5-fold less active than **4** via the oral route of administration. The *m*-fluoro analogue **6** is over 6-fold less active po, and the ip ED_{50} of *p*-fluoro **8** is 25 mg/kg. Amongst these monofluoro-substituted 3-benzyltriazolopyrazines, the *o*-fluoro-substituted analogue has the best anticonvulsant activity.

The 2,5-difluoro and 2,6-difluoro analogues of **4** and **5** are also active against MES (see **10**–**13**). The 2,6-difluoro substitution pattern imparts potent activity comparable to that of **4**; the 8-(methylamino) analogue **12** is very active with a po ED_{50} of 3 mg/kg. This activity trend is very similar to that observed for the purine series.[7] For example, the ranked order of potency for these triazolopyrazines is **4** (2-F) ≃ **12** (2,6-F_2) > **10** (2,5-F_2) > **3** (H) ≃ **6** (3-F) ≫ **8** (4-F). The order for the purines is the same: **1** (2-F) ≃ (2,6-F_2) > (2,5-F_2) > (H) ≃ (3-F) ≫ (4-F).[7] Thus the 1,2,4-triazolo[4,3-*a*]pyrazine ring system serves as an excellent bioisostere of the purine ring with these anticonvulsant agents.

The purine and 1,2,4-triazolo[4,5-*a*]pyrazine ring systems give compounds with similar physicochemical

Table 3. Anticonvulsant Activity of 1,2,4-Triazolo[4,3-*a*]pyrazines against Maximal Electroshock-Induced Seizures (MES)[a]



no.	R^1	R^2	MES ED_{50},[b,c] mg/kg ip	MES ED_{50},[b,c] mg/kg po
1[d]			1.7 ± 0.4	2.5 ± 0.2
2[e]			4.5 ± 1.0	12.0 ± 0.4
3	$NHCH_3$	H	6 ± 3	16 ± 2
4	$NHCH_3$	2-F	5 ± 2	2.6 ± 0.8
5	NH_2	2-F	9 ± 2	8.0 ± 0.6
6	$NHCH_3$	3-F	4	20 ± 2
7	NH_2	3-F	>25[f]	
8	$NHCH_3$	4-F	25	
9	NH_2	4-F	>25[g]	
10	$NHCH_3$	2,5-F_2	4	10 ± 2
11	NH_2	2,5-F_2	7 ± 2	20 ± 2
12	$NHCH_3$	2,6-F_2	2	3 ± 2
13	NH_2	2,6-F_2	4 ± 2	7 ± 3
phenytoin[d]			10 ± 2	20 ± 3

[a] The compounds were tested for their ability to protect Wistar male rats against maximal electroshock-induced seizures as described in ref 4. The ED_{50} was the dose needed to protect 50% of the animals against the hind-limb extensor component and was calculated by the method of: Miller, L. C.; Tainter, M. L. *Proc. Soc. Exp. Biol. Med.* **1944**, *57*, 261. [b] The compounds were administered as solutions or fine dispersions in water or 0.5% methylcellulose. Samples that were not completely soluble were micronized to enhance the uniformity of sample delivery. [c] Where ED_{50} values are presented with a standard error, a minimum of 12 animals were used per dose level with four doses per compound. ED_{50} values without standard error were determined by using three doses of compound with six animals per point. [d] MES data from refs 5 and 7. [e] MES data from ref 7. [f] 33% protection at 25 mg/kg. [g] 16% protection at 25 mg/kg.

properties. The dissociation constants of the two types of compounds are almost identical; the pK_a of **1** is 3.88 (±0.02),[9] and that of **4** is 4.02 (±0.02). Compound lipophilicity is similar with measured log Ps of 1.86 (±0.04)[9] for **1** and 1.56 (±0.05) for **4**. Thus, transposition of the nitrogen and carbon atoms of purine **1** to give triazolopyrazine **4** does not significantly change the degree of ionization or lipophilicity of the molecule.

The activity profile in rodents of purine **1** suggests it would be useful in the treatment of seizure disorders in humans.[5] However, the compound causes dose-related occurrences of nausea and emesis in some humans, and it causes very significant emesis in a dog-emesis model.[9,14] Compound **4**, tested in the dog-emesis model did not produce emesis when administered iv at 7.5 mg/kg nor po at 40 mg/kg. Thus, although **4** has physicochemical properties and anticonvulsant activity similar to pure **1**, it possesses less propensity to cause emesis. If the absence of nausea and emesis translates to the human subject, then this class of anticonvulsant agents may be useful in the treatment of seizure disorders for which phenytoin is presently indicated.

Experimental Section

Melting points were taken in capillary tubes on a Mel-Temp block or a Thomas-Hoover Unimelt and are uncorrected. NMR spectra were recorded on a Varian FT-80A, a Varian XL-100-15-FT, a Varian XL-200, or a Varian XL-300 spectrometer with Me_4Si as an internal standard. Mass spectra (~50 eV) were obtained from Oneida Research Services, Whitesboro, NY, using a Finnegan 4500 TFQ mass spectrometer. Each analytical sample had spectral data compatible with its assigned structure and moved as a single spot on TLC. TLCs were developed on Whatman 200 μm MK6F plates of silica gel with fluorescent indicator. Preparative flash chromatography[15] was performed on silica gel 60 (40–63 μm, E. Merck No. 9385). The analytical samples gave combustion values for C, H, N within 0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab, Inc.

Method A. Ethyl 2-(2-fluorophenyl)acetimidate hydrochloride (21). Dry HCl gas (29.8 g, 0.817 mol) was bubbled through a solution of (2-fluorophenyl)acetonitrile (100 g, 0.743 mol) in absolute EtOH (37.6 g, 0.817 mol) at 0 °C. After uptake of HCl was complete, the reaction was kept at 0 °C for 48 h. The solid was triturated under Et_2O (3 × 200 mL), and the white solid was collected by suction filtration. The product was dried for 3 days under vacuum in a dessicator containing NaOH pellets and P_2O_5 to give 148 g (91%) of **21**: mp 96–99 °C; NMR (DMSO-d_6) δ 11.58 (br s, 2 H, NH_2), 7.50–6.95 (m, 4 H, ArH), 4.40 (q, 2 H, OCH_2), 4.06 (s, 2 H, CH_2), 1.24 (t, 3 H, CH_3); MS *m/e* 181 (M^+), 162 ($M^+ - F$), 153 ($M^+ - C_2H_4$), 136 ($M^+ - OEt$), 109 ($C_7H_6F^+$). Anal. ($C_{10}H_{13}ClFNO$) C, H, N.

Method B. 1-Fluoro-2-(2,2,2-triethoxyethyl)benzene (III). A mixture of **21** (34.4 g, 0.158 mol) and absolute EtOH (50 mL) was stirred at ambient temperature for 18 h. Et_2O (50 mL) was added to the mixture, and the solids were removed by suction filtration. The solids were rinsed with Et_2O (2 × 25 mL), and the combined filtrates were spin-evaporated *in vacuo* to give 34.7 g (86%) of product as a semisolid oil: NMR (DMSO-d_6) δ 7.7–6.7 (m, 4 H, ArH), 3.48 (q, 6 H, OCH_2), 3.03 (s, 2 H, CH_2), 1.03 (t, 9 H, CH_3).

Method C. 8-Chloro-3-(2-fluorobenzyl)-1,2,4-triazolo[4,3-*a*]pyrazine (15). A mixture of 2-chloro-3-hydrazinopyrazine[11] (8.51 g, 58.9 mmol), 1-fluoro-2-(2,2,2-triethoxyethyl)benzene (34.7 g, 135 mmol), and dry xylene (125 mL) was refluxed with stirring for 3 h. The solvent was removed by spin evaporation *in vacuo*. The solid residue was triturated in Et_2O (200 mL), and the solid was collected by suction filtration. The solid was rinsed with Et_2O and dried with aspirator suction to give 14.9 g (96%) of crude **15**. One gram of **15** was recrystallized from EtOH–H_2O to give 0.697 g of analytically pure material: mp 126–127 °C; NMR (DMSO-d_6) δ 8.58 (d, 1 H, J = 4.7 Hz, pyrazine H), 7.79 (d, 1 H, J = 4.7 Hz, pyrazine H), 7.40–7.09 (m, 4 H, ArH), 4.60 (s, 2 H, CH_2); MS *m/e* 262 (M^+), 261 ($M^+ - 1$), 243 ($M^+ - F$), 227 ($M^+ - Cl$), 109 ($C_7H_6F^+$). Anal. ($C_{12}H_8ClFN_4$) C, H, N.

Method D. 3-(2-Fluorobenzyl)-8-(methylamino)-1,2,4-triazolo[4,3-*a*]pyrazine (4). Aqueous methylamine (40%; 50 mL) was added to a mixture of **15** (4.00 g, 15.2 mmol) and EtOH (60 mL) and stirred for 1.5 h. The mixture was suction-filtered, and the solid was dried to give 3.31 g (85%) of crude **4**. Recrystallization of the solid from EtOAc–hexane gave 2.57 g (66%) of **4** as the free base: mp 165–167 °C. Anal. ($C_{13}H_{12}FN_5$) C, H, N.

Method E. 3-(2-Fluorobenzyl)-8-(methylamino)-1,2,4-triazolo[4,3-*a*]pyrazine (4) Hydrochloride. The free base of **4** (2.45 g) was dissolved in warm EtOH (175 mL), and ethereal HCl was added to the solution to afford a precipitate. The solid was collected by suction filtration to give 2.31 g (94%) of **4**·HCl as analytically pure material: mp 292–295 °C (dec); NMR (DMSO-d_6) δ 10.07 (br s, 1 H, NH), 7.83 (d, 1 H, J = 5.4 Hz, pyrazine H), 7.40–7.12 (m, 5 H, ArH and pyrazine H), 4.53 (s, 2 H, CH_2), 3.07 (s, 3 H, CH_3); MS *m/e* 257 (M^+), 229 ($(M + 1) - CH_2NH^+$), 121 ($C_8H_6F^+$), 109 ($C_7H_6F^+$). Anal. ($C_{13}H_{13}ClFN_5$) C, H, N.

Method F. 8-Amino-3-(2-fluorobenzyl)-1,2,4-triazolo[4,3-*a*]pyrazine (5). Liquid NH_3 (35 mL) was condensed into a mixture of **15** (2.50 g, 9.52 mmol) and dry MeOH (60 mL) at −78 °C. The mixture was heated at 120 °C for 22 h in a stainless steel vessel. After evaporation of the NH_3, the solids were collected by suction filtration. Four recrystallizations from MeOH gave 0.954 g (41%) of **5** as the analytically pure

free base: mp 289–292 °C (dec); NMR (DMSO-d_6) δ 7.61 (d, 1 H, J = 4.8 Hz, pyrazine H), 7.46 (br s, 2 H, NH_2), 7.40–7.10 (m, 4 H, ArH), 7.20 (d, 1 H, J = 4.8 Hz, pyrazine H), 4.46 (s, 2 H, CH_2); MS m/e 243 (M^+), 224 ($M^+ - F$), 108 ($C_7H_5F^+$). Anal. ($C_{12}H_{10}FN_5$) C, H, N.

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