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Short communication

6-(3-Fluoroanilino)-9-(substituted-benzyl)-2-trifluoromethyl-9*H*-purines with antirhinovirus activity

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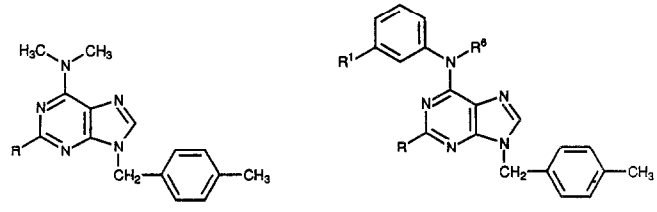
Summary — A series of 6-(3-fluoroanilino)-9-(substituted-benzyl)-2-trifluoromethylpurines was synthesized and tested for antirhinovirus activity. Most of the compounds were prepared by alkylation of a 6-anilino-2-trifluoromethylpurine with a benzyl halide or by amination of a 6-chloro-9-benzylpurine with an aniline. Compounds with a variety of *para*-benzyl substituents had activity against rhinovirus serotype 1B. The 6-(3-fluoroanilino)-9-(3-fluorobenzyl)-2-trifluoromethylpurine **15** had good activity (IC_{50}s = 0.4–13 μM) against 80% of the 47 serotypes tested, but pharmacokinetic studies indicated poor oral bioavailability.

Résumé — 6-(3-fluoroanilino)-9-(substituted-benzyl)-2-trifluorométhyl-9*H*-purines à activité antirhinovirus. *Une série de 6-(3-fluoroanilino)-9-(benzyl-substitué)-2-trifluorométhylpurines a été synthétisée et essayée pour leur activité antirhinovirus. La plupart des composés ont été préparés par alkylation d'une 6-anilino-2-trifluorométhylpurine avec un halogénure de benzyle ou par amination d'une 6-chloro-9-benzylpurine par une aniline. Les composés diversement substitués en* para *du benzyle ont une activité contre le rhinovirus sérotype 1B. La 6-(3-fluoroanilino)-9-(3-fluorobenzyl)-2-trifluorométhylpurine **15** présente une bonne activité (IC_{50}s = 0,4 à 13 μM) vis-à-vis de 80% des 47 sérotypes essayés, mais les études pharmacocinétiques ont révélé une pauvre biodisponibilité orale.*

benzylpurine / purine / trifluoromethylpurine / antiviral / rhinovirus

Introduction

In vitro activity against rhinovirus has been reported for many different types of compounds [1, 2], but none has consistently exhibited significant clinical efficacy [2, 3]. We have previously reported the *in vitro* antirhinovirus activity of a series of 9-benzyl-6-dimethylamino purines [4–7]. Two of the most active compounds are the 2-chloro (**1**) and 2-trifluoromethyl (**2**) 9-benzylpurines, which have IC_{50} values of 0.08 μM and 0.03 μM, respectively, against rhinovirus serotype 1B [5–7]. Structure–activity studies show that optimum activity against serotype 1B is associated with a dimethylamino group at the 6-position [8], but none of these analogues has a uniform profile of potent antirhinovirus serotype activity [5–8]. To develop an agent with a broader spectrum of rhinovirus serotype activity, a series of analogues of the 6-anilino-2-chloropurine **3a** was studied [9]. The *meta*-F analogue **3b** had the most uniform profile of antirhinovirus activity, but the compound had poor oral bioavailability in an animal model [9]. As an extension of this work, a series of analogues of **4** were prepared where the benzyl substituents were varied amongst a set with well-spread physicochemical properties [10, 11]. The synthesis and antirhinovirus structure–activity relationships of these new compounds are reported herein.



1; R = Cl
2; R = CF_3

3a; R = Cl, R^1 = H, R^6 = H
3b; R = Cl, R^1 = F, R^6 = H
4; R = CF_3, R^1 = H, R^6 = CH_3

Scheme 1.

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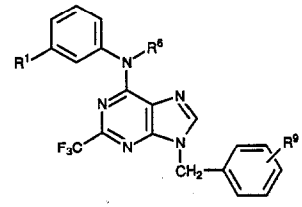
Table I. Physical properties of 6-anilino-2-trifluoromethylpurines.

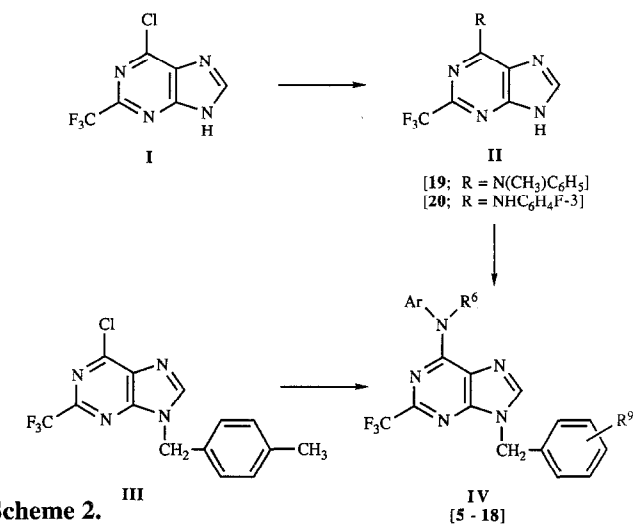


Cmpd	*R^1*	*R^6*	*R^9*	*Method*	*Yield (%)*	*mp (°C)*	*Formula[a]*
5	H	H	4-CH_3	A[b,c]	52[d]	149-150	$C_{20}H_{16}F_3N_5$
6	H	CH_3	H	B	34[e]	88-89	$C_{20}H_{16}F_3N_5$
7	F	H	4-CH_3	C	38[f]	122-124	$C_{20}H_{15}F_4N_5$
8	F	H	4-F	D	73[d]	150-152	$C_{19}H_{12}F_5N_5$
9	F	H	4-CF_3	D	63[d]	163-165	$C_{20}H_{12}F_7N_5$
10	F	H	4-$N(CH_3)_2$	G[g]	41[d]	134-136	$C_{21}H_{18}F_4N_6$
11	F	H	4-$NHCOCH_3$	H[h]	51[d]	217-219	$C_{21}H_{16}F_4N_6O$[i]
12	F	H	4-NH_2	E	61[j]	220-223	$C_{19}H_{14}F_4N_6$
13	F	H	4-CN	D	48[d]	191-193	$C_{20}H_{12}F_4N_6$
14	F	H	4-NO_2	D	57	198-200[d]	$C_{19}H_{12}F_4N_6O_2$
15	F	H	3-F	D	59[k]	126-129	$C_{19}H_{12}F_5N_5$
16	F	H	2-F	D[l]	74[k]	128-131	$C_{19}H_{12}F_5N_5$
17	F	CH_3	3-F	F	43[e]	78-82	$C_{20}H_{14}F_5N_5$
18	F	CH_2CH_3	3-F	F[l]	46[e]	100-102	$C_{21}H_{16}F_5N_5$

[a]All compounds were analyzed for C, H, N; [b]A: see preparation of compound **16** in reference [8]; [c]The reaction was done at ambient temperature instead of at reflux; [d]Recrystallized from hexane–ethyl acetate; [e]Recrystallized from pentane; [f]Recrystallized from hexane; [g]G: see Method E in reference [7]; [h]H: see preparation of **24** in reference [7]; [i]Characterized as acetate salt; [j]Recrystallized from ethanol-water; [k]Recrystallized from cyclohexane–ethyl acetate; [l]The reaction was carried out in dimethylsulfoxide instead of dimethylformamide

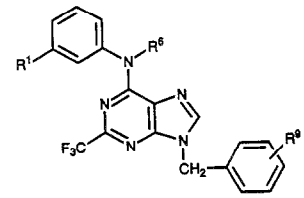
Chemistry

Most of the compounds in table I were prepared by alkylation of the 6-anilinopurine **II** with a benzyl halide or by amination of **III** with an aniline (scheme 2). Amination of **I** with *N*-methylaniline or 3-fluoroaniline gave purines **II** (**19** and **20**). Alkylation of **19** with benzyl bromide gave **6** in 34% yield; alkylation of **20** with the appropriate benzyl halide provided **8**, **9** and **13–16** in 48 to 74% yields. Anilinopurines **5** and **7** were prepared by amination of **III** with the appropriate aniline [8]. The 4-aminobenzylpurine **12** was prepared by reduction of **14** with palladium and hydrogen. The primary amine of **12** was selectively methylated by Borch reductive alkylation to give **10** or acetylated with acetic anhydride to give **11** [7]. Alkylation of **15** with methyl iodide or ethyl iodide provided **17** or **18**, respectively.



Scheme 2.

Table II. Activity of 6-anilino-2-trifluoromethylpurines against rhinovirus serotypes 1B, 2, 4 and 5.



				IC_{50}, μM[a]			
Cmpd	R^1	R^6	R^9	*1 B*	*2*	*4*	*5*
4	H	CH_3	4-CH_3	1.9	2.7	5.1	> 8
5	H	H	4-CH_3	2.3	NT	NT	NT
6	H	CH_3	H	2.3	NT	NT	NT
7	F	H	4-CH_3	1.7	2.6	180[b]	190[b]
8	F	H	4-F	0.9	6.7	13	32[b]
9	F	H	4-CF_3	3.5	43	40	> 40
10	F	H	4-$N(CH_3)_2$	76	130[b]	110[b]	> 80
11	F	H	4-$NHCOCH_3$	0.4	300[b]	45	> 80
12	F	H	4-NH_2	0.4	11	19	> 40
13	F	H	4-CN	2.7	68	> 100	190[b]
14	F	H	4-NO_2	1.5	16.4	> 100	> 100
15	F	H	3-F	0.43	2.2	2.6	13
16	F	H	2-F	3.9	5.1	> 20	> 20
17	F	CH_3	3-F	0.9	5.7	(38)[c]	(18)[c]
18	F	CH_2CH_3	3-F	17[b]	21[b]	(38)[c]	11[b]
4', 6-dichloroflavan (683C77)				0.007	0.04	> 10	> 100

[a]The numbers are the 50% inhibitory concentration (IC_{50}) measured as described in reference [4]. In several cases the exact IC_{50} was not determined and is denoted as greater than (>) the concentration. NT = not tested; [b]The IC_{50} was estimated by extrapolation; [c]Percent inhibition of plaque formation at 10 μM

Biological results and discussion

The compounds in table II were tested initially in a plaque inhibition assay using monolayers of M-HeLa cells [4]. The 50% inhibitory concentration (IC_{50}) was measured with the plaque reduction assay. For several compounds the IC_{50} is reported as 1) greater than (>) a concentration, or 2) the percent inhibition at a concentration is given in parentheses; the value could not be quantitated due to limited solubility.

The 6-(*N*-methylanilino) purine **4** had activity against serotype 1B with an IC_{50} of 1.9 μM. Neither removal of the *N*-methyl substituent to give **5** nor removal of the benzyl 4-CH_3 substituent as in **6** had a significant effect on activity.

To study the effect of different benzyl substituents on activity, analogues of **5** with a *meta*-F substituent in the anilino moiety were studied. The *meta*-F substituent did not have a detrimental effect on activity as **3a** and **3b** have similar IC_{50}s against serotype 1B [9]; the activities of **5** and **7** against serotype 1B were also similar. Furthermore, a fluoroanilinopurine might be less susceptible to metabolic hydroxylation, a consideration in planning *in vivo* experiments.

Analogues with a variety of *para*-benzyl substituents had, with 1 exception, IC_{50}s against serotype 1B that ranged over 10-fold. The CH_3 (**7**), CF_3 (**9**), CN (**13**) and NO_2 (**14**) analogues had comparable IC_{50}s (1.5 to 3.5 μM), suggesting that *para* substituents of diverse lipophilicity and electronic properties were

tolerated. The 2 most active compounds were **11** (4-$NHCOCH_3$) and **12** (4-NH_2), which had IC_{50}s of 0.4 μM. The $NHCOCH_3$ and NH_2 substituted compounds are able to hydrogen bond through donation, a property unique amongst the R9 substituents in this set of compounds. The activity of **12** was lost when the amine was methylated; dimethylamine **10** was 190-fold less active than **12**. This large decrease in activity may also have been due to limited bulk tolerance for the $N(CH_3)_2$ in space that was not in the plane of the aryl ring. Of the *para* substituents on compounds **7**–**14**, only **10** has a shape that must project bulk out of the plane of the ring, which may result in an unfavorable interaction.

The fluorinated benzylpurines **8**, **15** and **16** had IC_{50}s ranging from 0.43–3.9 μM. The *meta*-F analog **15** was most active. Substitution of the anilino nitrogen with methyl to give **17** did not affect activity, but the *N*-ethyl analogue **18** was 40-fold less active.

Compounds **7** to **18** were also tested against serotypes 2, 4 and 5. We felt that these serotypes could give an indication of breadth of serotype activity, without testing against 19 or more serotypes as was done earlier [5–7]. For most compounds the activities varied over a wide range; many IC_{50}s were 40 μM or greater. Only the *meta*-F analogue **15** was active against all 4 serotypes with IC_{50}s of 13 μM or less. Against types 1B, 2, 4 and 5, compound **15** had IC_{50}s of 0.43, 2.2, 2.6 and 13 μM, respectively. Compound **15** was tested against 43 other rhinovirus serotypes (table III). None was more sensitive than type 1B, although 80% of these serotypes tested were sensitive with IC_{50}s of 13 μM or less.

Since **15** was active against a high percentage of serotypes it was deemed worthy of further evaluation *in vivo*. Since an animal model of rhinovirus infection was not available, preliminary pharmacokinetic studies with **15** were performed in dogs to obtain information on its *in vivo* properties. Compound **15** had an elimination half-life of 24 min following intravenous dosing of 5 mg/kg with a peak plasma concentration of 10.5 μg/ml. However, after oral administration of 5 mg/kg of **15**, a peak plasma level of 60 ng/ml at 0.5 h declined to 20 ng/ml by 3 h postdose. Thus, following oral dosing of **15** plasma concentrations were very low, which indicated poor oral bioavailability.

Conclusion

The synthesis and antirhinovirus evaluation of this set of 6-anilino-2-trifluoromethylpurines has led to the discovery of compound **15** with good activity (IC_{50}s = 0.4 to 13 μM) against 80% of the 47 serotypes tested. However, secondary evaluation revealed *in vivo* properties of **15** incompatible with further drug development.

Table III. Activity of **15** against 47 rhinovirus serotypes[a].

Serotype	*IC_{50}, μM*	*Serotype*	*IC_{50}, μM*
1A	1.3	25	1.2
1B	0.43	26	3[b]
2	2.2	27	> 5
3	5.6[b]	28	4.7[b]
4	2.6	29	12[b]
5	13	30	(17)[d]
6	(21)[c]	31	5.4[b]
7	1.9	32	5.7[b]
8	3.7	34	3.0
9	1.4	35	9.7[b]
10	3.3	36	3.9[b]
11	1.2	38	1.0
12	4.4	39	12[b]
13	55[b]	40	> 2.5
14	7[b]	41	5.6[b]
16	1.4[b]	43	6.3[b]
18	4.3	45	4.1
19	3.6	47	1.7
20	11[b]	50	3.8
21	50[b]	53	6.6[b]
22	2.3	54	(27)[c]
23	1.1	58	4.2
24	1.9	79	25[b]
		86	(38)[d]

[a]The non-bracketed numbers are the 50% inhibitory concentration (IC_{50}) measured as described in reference [4]. In a few cases the exact IC_{50} was not determined; the activity is denoted as greater than (>) the concentration or as percent inhibition at the footnoted concentration; [b]IC_{50} estimated by extrapolation; [c]Percent inhibition at 2.5 μM; [d]Percent inhibition at 5 μM.

Experimental protocols

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 XL-100-15-FT or Varian FT-80A spectrometer using Me_4Si as an internal standard. UV absorption spectra were measured on a Cary 118 UV-vis spectrophotometer. 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 micron MK6F plates of silica gel (SG) with a fluorescent indicator. Preparative flash chromatography [12] was performed on silica gel 60 (40–63 μM, E Merck No 9385). The analytical samples

gave combustion values for C, H and N within 0.4% of theoretical. Elemental analyses were performed by Atlantic Microlab, Inc.

*Method B. 9-Benzyl-6-(*N*-methylanilino)-2-trifluoromethyl-9*H*-purine* ***6***

A mixture of **19** (0.500 g, 1.70 mmol), anhydrous potassium carbonate (0.282 g, 2.04 mmol), benzyl bromide (0.24 ml, 2.04 mmol) and dry dimethylformamide (20 ml) was stirred at ambient temperature for 2 h. The reaction mixture was poured into ice water (100 ml), and the pH of the mixture was adjusted to 4.5 with acetic acid. The mixture was extracted with ether (2 X 75 ml), the combined ether extract was washed with water (2 X 100 ml) and dried (sodium sulfate). The solution was concentrated under reduced pressure, and the resultant oil was dissolved in ethyl acetate. Silica gel 60 (5 g) was added to the solution, and the mixture was spin evaporated *in vacuo*. The residual solids were introduced on a column (3.5 cm X 16 cm) of silica gel 60 wetted with ethyl acetate–hexane (1:3). The column was eluted with ethyl acetate–hexane (1:3) using the flash chromatography technique. Fractions containing the highest R_f, major component were combined and spin evaporated *in vacuo* to give 0.579 g (89%) of **6** as an oil. The oil was dissolved in 2 ml of methanol, and the solution was allowed to evaporate. The residual solids were collected and recrystallized from pentane to give 0.221 g (34%) of analytically pure material, mp 88–89°C; UV λ_{max} (10% EtOH in 0.1 N HCl) 294 nm, UV λ_{max} (10% EtOH in 0.1 N NaOH and H_2O) 289 nm; NMR (DMSO–d_6) δ 8.36 (s, 1H, purine H-8), 7.38-7.31 (m, 10H, ArH), 5.41 (s, 2H, CH_2Ar), 3.80 (s, 3H, NCH_3). Anal $C_{20}H_{16}F_3N_5$ (C, H, N).

*Method C. 6-(3-Fluoroanilino)-9-(4-methylbenzyl)-2-trifluoromethyl-9*H*-purine* **7**

A mixture of 6-chloro-9-(4-methylbenzyl)-2-trifluoromethyl-9*H*-purine [6, 13] (3.86 g, 11.8 mmol), 3-fluoroaniline (3.35 g, 29.5 mmol), ethanol (75 ml) and water (30 ml) was refluxed with stirring for 64 h. Additional 3-fluoroaniline (1.34 g, 12.1 mmol) was added, and the reaction was refluxed for 24 h. The volatiles were removed by spin evaporation *in vacuo*, and the residual solids were partitioned between ethyl acetate–water (125/100 ml). The phases were separated, and the aqueous portion was extracted with ethyl acetate (100 ml). The combined ethyl acetate extracts were washed with 1 N hydrochloric acid (2 X 100 ml) and dried over sodium sulfate. The solution was concentrated under reduced pressure. The resultant oil was dissolved in ethyl acetate, and silica gel 60 (15 g) was added to the solution. This mixture was spin evaporated *in vacuo*, and the residual solid was introduced on a column (5 cm X 18 cm) of silica gel 60 wetted with ethyl acetate–hexane (2:3). The column was eluted with ethyl acetate–hexane (2:3) using the flash chromatography technique. The fractions containing the lowest R_f, major component were combined and spin evaporated *in vacuo* to give an oil, which slowly crystal-lized to give **7**. Recrystallization from hexane gave 1.78 g (38%) of analytically pure material, mp 122–124°C; UV λ_{max} (10% EtOH in 0.1 N HCl) 301 nm, UV λ_{max} (10% EtOH in 0.1 N NaOH and H_2O) 302 nm; NMR (DMSO–d_6) δ 10.62 (br s, 1H, NH), 8.63 (s, 1H, purine H-8), 8.05–6.88 (complex m, 8H, ArH), 5.45 (s, 2H, CH_2Ar), 2.26 (s, 3H, CH_3). Anal $C_{20}H_{15}F_4N_5$ (C, H, N).

*Method D. 6-(3-Fluoroanilino)-9-(4-fluorobenzyl)-2-trifluoromethyl-9*H*-purine* ***8***

A mixture of **20** (2.00 g, 6.73 mmol), 4-fluorobenzyl chloride (1.26 g, 8.75 mmol), anhydrous potassium carbonate (1.21 g, 8.75 mmol) and dry dimethylformamide was stirred at ambient temperature for 18 h. The reaction mixture was poured into ice water (100 ml), and the pH of the mixture was adjusted to 5 with acetic acid. The mixture was extracted with ether (3 X 100 ml), and the combined ether extract was washed with 1 N sodium hydroxide (100 ml) and saturated brine (100 ml) and dried over sodium sulfate. The organic phase was concentrated under reduced pressure, and the resultant solid was dissolved in ethyl acetate (150 ml). Silica gel 60 (20 g) was added to the solution, and the mixture was spin evaporated *in vacuo*. The residual solids were introduced on a column (5 cm X 18 cm) of silica gel 60 wetted with ethyl acetate. The column was eluted with ethyl acetate using the flash chromatography technique. The fractions containing the highest R_f, major component were combined and spin evaporated *in vacuo* to give 2.29 g (84%) of **8** as a solid. Recrystallization from hexane-ethyl acetate gave 2.00 g (73%) of analytically pure **8**, mp 150–152°C; UV λ_{max} (10% EtOH in 0.1 N HCl, 0.1 N NaOH and H_2O) 302 nm; NMR (DMSO–d_6) δ 10.63 (br s, 1H, NH), 8.65 (s, 1H, purine H-8), 8.05–6.88 (complex m, 8H, ArH), 5.49 (s, 2H, CH_2Ar). Anal $C_{19}H_{12}F_5N_5$ (C, H, N).

*Method E. 9-(4-Aminobenzyl)-6-(3-fluoroanilino)-2-trifluoromethyl-9*H*-purine* ***12***

A mixture of **14** (3.66 g, 8.47 mmol), acetic acid (100 ml) and methanol (20 ml) was warmed on a steam bath to achieve dissolution. Palladium on carbon (5%) (1.00 g) was added, and the mixture was shaken in the presence of hydrogen at 2–3 atm for 1 h. The reaction mixture was filtered through a pad of Celite, and the pad was washed with methanol (75 ml). The filtrate was spin evaporated *in vacuo* to give 3.58 g of crude **12**. Recrystallization of 1.50 g of crude **12** from ethanol–water gave 0.913 g (61%) of analytically pure material, mp 220–223°C; UV λ_{max} (10% EtOH in 0.1 N HCl) 301 nm, UV λ_{max} (10% EtOH in H_2O) 300 nm, UV λ_{max} (10% EtOH in 0.1 N NaOH) 301 nm; NMR (DMSO–d_6) δ 10.59 (br s, 1H, NH), 8.56 (s, 1H, purine H-8), 8.06–6.47 (complex m, 8H, ArH), 5.28 (s, 2H, CH_2Ar), 5.12 (s, 2H, NH_2). Anal $C_{19}H_{14}F_4N_6$ (C, H, N).

*Method F. 9-(3-Fluorobenzyl)-6-(3-fluoro-*N*-methylanilino)-2-trifluoromethyl-9*H*-purine* ***17***

A mixture of **15** (1.00 g, 2.47 mmol), methyl iodide (2.10 g, 14.8 mmol), anhydrous potassium carbonate (1.02 g, 7.41 mmol) and dry dimethylformamide (10 ml) was stirred at ambient temperature for 18 h. The reaction mixture was poured into ice water (100 ml) and extracted with ether (3 X 40 ml). The combined ether extract was dried with sodium sulfate. The organic phase was evaporated on a hot water bath, followed by spin evaporation *in vacuo* to give a yellow oil. The oil was dissolved in dichloromethane (50 ml) and adsorbed to silica gel 60 (7.5 g) by spin evaporation *in vacuo*. The residual solids were introduced on a column (7.5 cm X 22 cm) of silica gel 60 wetted with ethyl acetate–hexane (2:3). The column was eluted with ethyl acetate–hexane (2:3) using the flash chromatography technique. The fractions containing the highest R_f, major component were combined and spin evaporated *in vacuo* to give 0.874 g (85%) of **17** as an oil. Crystallization from pentane gave 0.445 g (43%) of analytically pure **17**, mp 78–82°C; UV λ_{max} (9.5% EtOH in 0.1 N HCl) 295 nm, UV λ_{max} (9.5% EtOH in 0.1 N NaOH) 300 nm; NMR (DMSO–d_6) δ 8.41 (s, 1H, purine H-8), 7.42-7.12 (m, 8H, Ar), 5.46 (s, 2H, CH_2Ar), 3.81 (s, 3H, NCH_3). Anal $C_{20}H_{14}F_5N_5$ (C, H, N).

*6-(*N*-Methylanilino)-2-trifluoromethyl-9*H*-purine (****19****)*

A solution of 6-chloro-2-trifluoromethyl-9*H*-purine [14]

(1.50 g, 6.74 mmol), *N*-methylaniline (3.61 g, 33.7 mmol), triethylamine (2.05 g, 20.2 mmol) and ethanol (25 ml) was heated at 108°C in a stainless steel reactor for 18 h. The reactor was cooled on ice. Ethanol (200 ml) and silica gel 60 (20 g) were added to the reaction. This mixture was spin evaporated *in vacuo*, and the residual solids were introduced on a column (5 cm X 16 cm) of silica gel 60 wetted with dichloromethane. The column was eluted with methanol-dichloromethane (3:97) using the flash chromatography technique. The fractions containing the 2nd highest R_f, major component were combined and spin evaporated *in vacuo* to give 1.34 g (68%) of **19** as a solid residue. Recrystallization of this solid from ethyl acetate–hexane gave 0.790 g (40%) of analytically pure material, mp 218–219°C; UV λ_{max} (10% EtOH in 0.1 N HCl) 292 nm, UV λ_{max} (10% EtOH in H_2O) 290 nm, UV λ_{max} (10% EtOH in 0.1 N NaOH) 301 nm; NMR (DMSO–d_6) δ 8.22 (s, 1H, purine H-8), 7.46–7.34 (complex m, 5H, ArH), 3.81 (s, 3H, NCH_3). Anal $C_{13}H_{10}F_3N_5$ (C, H, N).

*6-(3-Fluoroanilino)-2-trifluoromethyl-9*H*-purine (**20**)*
This compound was prepared on a 4.5-mmol scale from 6-chloro-2-trifluoromethyl-9*H*-purine [14] and 3-fluoroaniline as described for preparation of **19** to give 0.41 g (31%). Recrystallization from hexane–ethyl acetate gave the analytical sample, mp 300–302°C; UV λ_{max} (10% EtOH in 0.1 N HCl and H_2O) 301 nm, UV λ_{max} (10% EtOH in 0.1 N NaOH) 304 nm; NMR (DMSO–d_6) δ 10.48 (br s, 1H, ArNH), 8.54 (s, 1H, purine H-8), 8.10-6.77 (complex m, 4H, ArH). Anal $C_{12}H_7F_4N_5$ (C, H, N).

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References

1 Kelley JL (1984) *Annu Rep Med Chem* 19, 117-126
2 Ahmad ALM, Tyrrell DAJ (1986) *Antiviral Res* 6, 241-252
3 Al-Nakib W, Higgins PG, Barrow GI, Tyrrell DAJ, Andries K, Bussche GV, Taylor N, Janssen PAJ (1989) *Antimicrob Agents Chemother* 33, 522-525
4 Kelley JL, Miller CA, Selway JWT, Schaeffer HJ (1988) *Eur J Med Chem* 23, 319-323
5 Kelley JL, Linn JA, Krochmal MP, Selway JWT (1988) *J Med Chem* 31, 2001-2004
6 Kelley JL, Linn JA, Selway JWT (1989) *J Med Chem* 32, 218-224
7 Kelley JL, Linn JA, Selway JWT (1989) *J Med Chem* 32, 1757-1763
8 Kelley JL, Linn JA, Selway JWT (1990) *Eur J Med Chem* 25, 131–135
9 Kelley JL, Linn JA, Selway JWT (1990) *J Med Chem* 33, 1360–1363
10 Wootton R, Cranfield R, Sheppey GC, Goodford PJ (1975) *J Med Chem* 18, 607-613
11 Craig PN (1971) *J Med Chem* 14, 680-684
12 Still WC, Kahn M, Mitra A (1978) *J Org Chem* 43, 2923-2925
13 Kelley JL, Linn JA (1986) *J Org Chem* 51, 5435-5436
14 Nagano H, Inoue S, Saggiomo AJ, Nodiff EA (1964) *J Med Chem* 7, 215-220