group of the bases to the azarine formed from photolysis.

This is the most definitive data to date to suggest the aromatic azides are useful photoaffinity labeling agents for DNA. Further studies are needed to determine (1) the relative reactivity of light-activated 3-azidoamsacrine with different bases and base sequences and (2) whether the reactivity is indiscriminate enough to give a similar probability of reaction at each DNA binding site and, thereby, allow a study of the sequence specificity of binding of 3-azidoamsacrine to DNA.

Acknowledgment. This research was supported by NIH Grants GM29175, CA40228, and AI27152. We thank Constance G. Moynihan for excellent technical assistance.

Preparation of Triazolo[1,5-*c*]pyrimidines as Potential Antiasthma Agents

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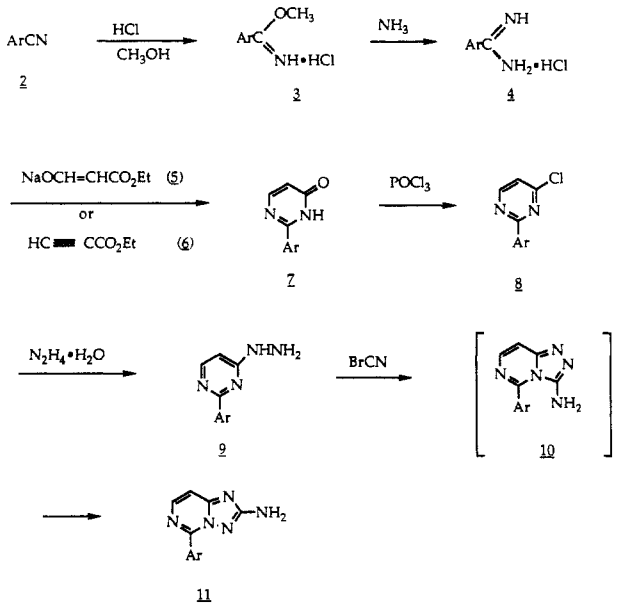
Received March 13, 1989

With the use of the human basophil histamine release assay, 5-aryl-2-amino[1,2,4]triazolo[1,5-*c*]pyrimidines were found to be active as mediator release inhibitors. These compounds were prepared by reacting arylamidines with sodium ethyl formylacetate or with ethyl propiolate to give pyrimidinones. Treatment with phosphorus oxychloride gave a chloropyrimidine, which was converted to a hydrazinopyrimidine with hydrazine. Cyclization, using cyanogen bromide, gave the triazolo[1,5-*c*]pyrimidines, after a Dimroth rearrangement. Following a structure–activity evaluation, the 5-[3-(trifluoromethyl)phenyl]-2-amino (**8-10**), 5-(3-bromophenyl)-2-amino (**8-13**), 5-[3-(difluoromethoxy)-phenyl]-2-amino (**8-11**), and 5-(4-pyridinyl)-2-amino (**6-7**) compounds were found to have the best activity. They were chosen for further pharmacological and toxicological study.

It has been pointed out by Reed[1] that in the past 10 years there was a 4-fold increase in the number of prescriptions written for obstructive lung diseases, while the rate of hospitalization for asthma has increased at almost the same rate. In addition, the death rate for asthma has not decreased. The implication of these results is that current methods of asthma treatment are inadequate. Most therapies treat the symptoms of the disease and it would be an improvement to treat asthma prophylactically. One of the few prophylactic drugs currently available is disodium cromoglycate[2] (DSCG) which must be taken by inhalation. However, the method of taking DSCG may result in lack of patient compliance and limits its usefulness. One approach to the treatment of asthma would be to prevent the release of mediators of anaphylaxis from mast cells and basophils[3] by an oral medication, since it is believed that the release of mediators, such as histamine, leukotrienes, PAF, and others, precipitate the bronchoconstruction of asthma and the inflammation of allergic attacks.

In searching for antiasthmatic compounds, the rat mast cell has been used as a screen[4] and also as an evaluation model.[5] It has been concluded that rat mast cells differ in their pharmacology from human mast cells,[6] thus rat mast cells are not ideal models for asthma. Obviously the best method to study mediator release with would be the human mast cell, since it is believed that the reaction of an antigen with IgE on the mast cell surface triggers the release of mediators. However, since human mast cells are not available in quantities for screening, a good substitute is the readily available human basophil. Like the mast cell, the basophil has on its surface IgE, which reacts with antigens. Release of mediators from this cell has been used to confirm active compounds found by the rat passive cutaneous anaphylaxis (PCA) test,[7] but to the best of our

Scheme I



(1) Reed, C. E. *J. Allergy Clin. Immunol.* **1986**, *77*, 537.
(2) Cairus, H.; Cox, D.; Gould, K. J.; Ingall, A. H.; Suschitzky, J. L. *J. Med. Chem.* **1985**, *28*, 1832.
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(4) Loev, B.; Jones, H.; Brown, R. E.; Huang, F.-c.; Khandwala, A.; Leibowitz, M. J.; Sonnino-Goldman, P. *J. Med. Chem.* **1985**, *28*, 24. Musser, J. H.; Jones, H.; Sciortino, S.; Bailey, K.; Coutts, S. M.; Khandwala, A.; Sonnino-Goldman, P.; Leibowitz, M.; Wolf, P.; Neiss, E. S. *J. Med. Chem.* **1985**, *28*, 1255.
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(6) Peters, S. P.; Schulman, E. S.; MacGlashan, D. W.; Schleimer, R. P.; Newball, H. H.; Lichtenstein, L. M. *J. Allergy Clin. Immunol.* **1982**, *69*, 150.

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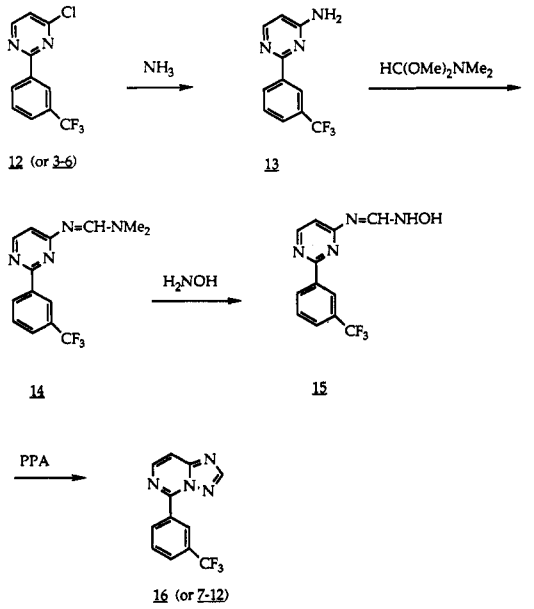
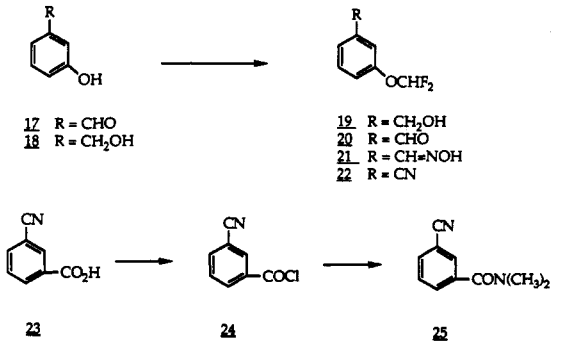
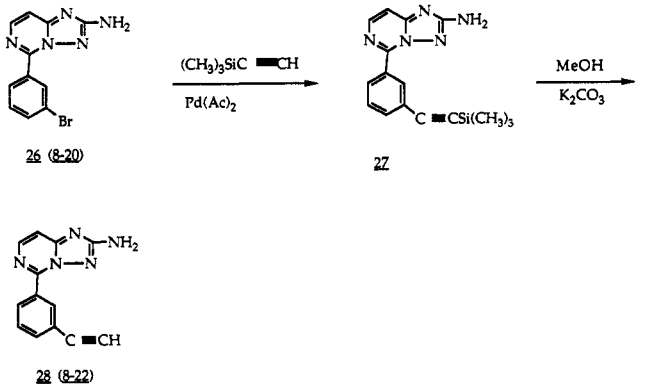
Scheme II



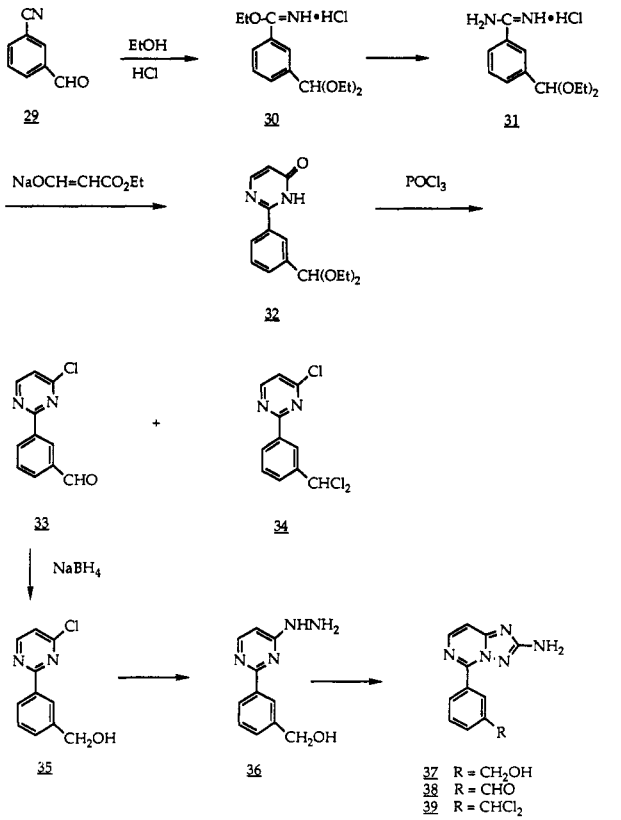
Scheme III



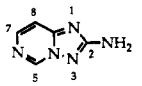
Scheme IV



Scheme V



knowledge, the human basophil has not been used as a primary screen by groups other than our own.[8] Using the basophil asthma model, developed by Lichtenstein,[9] as a routine screen, we found activity in a series of 2-amino-5-aryl- and -5-heteroaryltriazolo[1,5-*c*]pyrimidines (1).



1

Chemistry

The general synthesis of 2-amino-5-substituted-triazolo[1,5-*c*]pyrimidines is shown in Scheme I. Nitriles **2** were converted to amidines **4** via a Pinner reaction,[10] with the exception of the pyridine derivatives. In those cases the nitrile was reacted with sodium methoxide to give **3** as the free base, followed by reflux with ammonium chloride to form amidine **4**.[11]

The amidines were reacted with ethyl formylacetate sodium salt **5**[12] to give pyrimidinones **7**. Since **5** had to be prepared from ethyl formate, ethyl acetate, and sodium methoxide in a tedious reaction and since **5** was not stable to lengthy storage, an alternate synthesis using commercially available, indefinitely stable, ethyl propiolate (**6**) was developed. Phosphorus oxychloride converted **7** to **8** which on treatment with hydrazine hydrate gave hydrazinopyrimidines (**9**). Cyclization with cyanogen bromide of **9** gave **11** presumably via Dimroth rearrangement of **10**.

In general, the rearrangement was so facile that intermediates of type **10** were not isolated. In one case, however, where Ar = 3-nitrophenyl, the intermediate was isolated and characterized by ^{1}H NMR (see Experimental Section). From the large differences in the ^{1}H NMR of the two isomers, it was determined that only isomer **11** was usually obtained. These results agree with those reported by Miller and Rose.[13] In addition, we prepared **16** by the method of Stanovnik–Tišler[14] (Scheme II), which does not

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(8) Paul, R.; Brockman, J. A.; Hallett, W. A.; Hanifin, J. W.; Tarrant, M. E.; Torley, L. W.; Callahan, F. M.; Fabio, P. F.; Johnson, B. D.; Lenhard, R. H.; Schaub, R. E.; Wissner, A. *J. Med. Chem.* **1985**, *28*, 1704.
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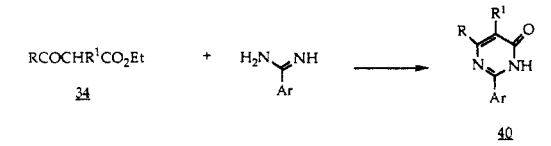
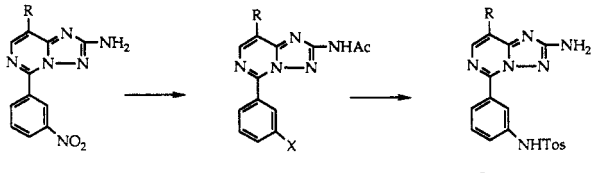
(10) Pinner, A.; Klein, F. *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1889.
(11) Schaeffer, F. C.; Peters, G. H. *J. Org. Chem.* **1965**, *36*, 412.
(12) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 3638. Moffatt, J. S. *J. Chem. Soc.* **1950**, 1603.
(13) Miller, G. W.; Rose, F. L. *J. Chem. Soc.* **1963**, 5642.

Scheme VI



Scheme VII



involve a rearrangement. The ^{1}H NMR of **16** resembled that of **11** rather than that of **10**.

Finally an X-ray structure determination (Molecular Structure Corp., College Station, TX) of 2-amino-5-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*c*]pyrimidine (Table VIII, entry 2, or **8-2**) proved the assigned structure to be correct.

Two nitriles were prepared by the method of Scheme III. Reduction of **17** ($NaBH_4$) to **18**, reaction with Freon 22 ($CHClF_2$) to **19**, reoxidation (CrO_3) to **20** followed by oxime formation (**21**), and dehydration gave **22**. For compound **25**, **23** was converted to the acid chloride with thionyl chloride then treated with dimethylamine to give amide **25**.

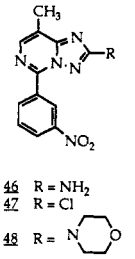
Using palladium chemistry,[15] bromo phenyl analogue **26** was converted to acetylene **28** (Scheme IV).

Scheme V shows the preparation of the 3′-aldehyde derivative. 3-Cyanobenzaldehyde on conversion to the imino ether simultaneously formed acetal **30**. Then reaction with ammonia gave amidine **31**, which was cyclized to **32** with sodium ethyl formylacetate. Using phosphorus oxychloride on **32** gave two products, the major one being deprotected aldehyde **33** and a minor product, **34**, from the conversion of the aldehyde to the dichloromethyl group. After a failed attempt to react **33** with hydrazine followed by hydrolysis of the resulting Schiff base, **33** was reduced to **35** with sodium borohydride under carefully controlled conditions to avoid loss of chlorine. Routine conversion of **36** to **37** with cyanogen bromide ensued, followed by reoxidation of **37** to **38** using (diethylamino)pyridinium chlorochromate. In a separate synthesis **34** was converted to its triazolopyrimidine **39** by the method of Scheme I.

If the amidines were condensed with ethyl acetoacetate,[13] disubstituted pyrimidines **40** were obtained, which were transformed, as in Scheme I, to give 7,8-substituted triazolopyrimidines.

Various substitutions on the phenyl ring required special preparations. In Scheme VII is shown the preparation of 3-tosylamino compound **45**. Nitro compound **41** was prepared as in Scheme I, then acetylated to **42**. Hydrogenation gave **43**, which, upon tosylation (**44**) and hydrolysis, gave **45**.

A Sandmeyer reaction was used to convert amino compound **46** to chloro compound **47**. Reaction with morpholine then gave **48**.



The replacement of a simple aryl moiety with pyridine in **2** (Scheme I) proved to be difficult. Instead of the Pinner method, the procedure of Schaeffer and Peters[11] (10% $NaOCH_3$ followed by reflux in ammonium chloride) was utilized to prepare the required amidines **4** from nitriles **2**. Conversion to hydrazines **9** from the nitriles was routine. Unfortunately, treatment of 4-hydrazino-2-(3-pyridinyl)pyrimidine (**9**) with cyanogen bromide afforded only minor amounts of 5-(4-pyridinyl)[1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (**6-4**). With the exception of ortho pyridinyl analogue **6-3**, the yields for the pyridinyl analogue were poor (<30%). However, if the pyridinyl nitrogen was protected by formation of the *N*-oxide, the Dimroth rearrangement of the desired hydrazine proceeded smoothly. The *N*-oxide was removed from the final product with sodium dithionite.

Structure–Activity Relationships

Initial screening of the triazolo[1,5-*c*]pyrimidines was carried out in the human basophil assay[2] at a 48 μM concentration. Histamine release was measured after antigen challenge by the method of Siraganian.[16]

If a test compound produced at least a 50% inhibition of release, it was considered active and an IC_{50} was determined. Further synthetic efforts were guided to a great degree by the basophil assay. Subsequently compounds were evaluated in the mouse PCA[17] assay for in vivo activity, to further distinguish compounds with similar basophil activities.

Intermediates used to prepare the triazolo[1,5-*c*]pyrimidines are listed in Tables I–IV. Table V shows compounds which were substituted in the 7- and/or 8-position. All 7-substituted analogues were inactive. Only two of the 8-methyl compounds, **5-1** and **5-5**, retained some activity and it was reduced from that of their 8-H equivalents **8-9** and **8-10**, respectively.

Table VI shows the 5-heterocyclic substituted triazolo-[1,5-*c*]pyrimidines. Of the four active compounds, **6-8** had toxicity (during a PCA assay, the mice died). The other three, **6-4**, **6-7**, and **6-9** fluoresced, while interfered with the histamine analysis. Basophil values were arrived at by subtracting the absorption of the compound from the total histamine value. While only modest activity was found in the basophil, compounds **6-4** and **6-7** were active in the PCA assay, which made them interesting.

Triazolopyrimidines with the 2-position substituted by moieties other than NH_2 are shown on Table VII. Replacing the 2-amino group by a hydrogen (**7-7**) or chlorine atom (**7-15**) caused all activity to be lost. Disubstituting the 2-amino group also removed activity (**7-16**, **7-6**, **7-4**, and **7-9**). Monoalkylation of the 2-nitrogen generally reduced or eliminated activity (compare **7-10**, **7-2**, and **7-5** to **8-10**).

(14) Polanc, S.; Verček, B.; Šek, B.; Stanovnik, B.; Tišler, M. *J. Org. Chem.* **1974**, *39*, 2143.
(15) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. *J. Org. Chem.* **1981**, *46*, 2280.
(16) Siraganian, R. P. *J. Allergy Clin. Immunol.* **1976**, *57*, 525. Siraganian, R. P.; Hook, W. A. *J. Immunol.* **1977**, *119*, 2078.
(17) Friedman, H. In *Animal and Clinical Pharmacologic Techniques in Drug Evolution*; Siegler, P. E., Moyer, J. H., Eds.; Yearbook Medical Publisher: New York, 1967; Vol. II, pp 548–568.

Table I. Amidines

$RC(=NH)NH_2 \cdot HCl$

	substituents	synth method	% yield[a]	mp, °C	recryst solvent	starting nitrile	molecular formula	analyses
1-1	4-$C_6H_4CO_2Et$	A	54	208–211 dec[b]	EtOH	COM	$C_{10}H_{13}ClN_2O_2$	
1-2	2-pyridinyl	B	94	*c*		COM	$C_6H_7N_3 \cdot HCl$	
1-3	4-C_6H_4F	A	84	*d*		COM	$C_7H_7FN_2 \cdot HCl$	
1-4	3-$C_6H_4CF_3$	A	64	180–186[e]	CH_3CN	COM	$C_8H_7F_3N_2 \cdot HCl$	
1-5	2-thiophenyl	A	20	102–104[f]	DMSO–$CHCl_3$	COM	$C_5H_6N_2S \cdot {}^1/_8H_2O$	C, H, N, S
1-6	4-pyridinyl	B	68	236–242[g]	EtOH	COM	$C_6H_7N_3 \cdot HCl$	
1-7	CH_2-3-$C_6H_4CF_3$	A	46	198–203	EtOH–Et_2O	COM	$C_9H_9F_3N_2 \cdot HCl$	C, H, N, F, Cl
1-8	3-C_6H_4Br	A	95	141–143.5[e]		COM	$C_7H_8BrClN_2$	
1-9	3-Me,2-pyridinyl	B	74	193–196	EtOH	*h*	$C_7H_{10}ClN_3$	
1-10	3-$C_6H_4CO_2Et$	A	75	190–192.5[i]	EtOH–Et_2O	COM	$C_{10}H_{13}ClN_2O_2$	
1-11	3,3-$C_6H_3(CF_3)_2$	A	66[j]	101–103	$CHCl_3$	COM	$C_9H_6F_6N_2$	C, H, N, F
1-12	2-C_6H_4F	A	72			COM	$C_7H_7FN_2 \cdot HCl$	
1-13	3-pyridinyl	B		*c*, *k*		COM	$C_7H_7N_3 \cdot HCl$	
1-14	3-C_6H_4Cl	A	66			COM	$C_7H_7ClN_2 \cdot HCl$	
1-15	4-$C_6H_4CF_3$	A	55			COM	$C_8H_7F_3N_2 \cdot HCl$	
1-16	3-C_6H_4F	A	65			COM	$C_7H_7FN_2 \cdot HCl$	
1-17	3-$C_6H_4CH(OEt)_2$	A				COM[l]	$C_{12}H_{18}N_2O_2 \cdot HCl$	
1-18	3,3-$C_6H_3Cl_2$	A	99			COM	$C_7H_6Cl_2N_2 \cdot HCl$	
1-19	3-$C_6H_4CH_3$	A				COM	$C_8H_{10}N_2 \cdot HCl$	
1-20	3-$C_6H_4CONMe_2$	C, A	55[m]				$C_{10}H_{13}N_3O \cdot HCl$	
1-21	3-$C_6H_4OCHF_2$	D, E, A	52				$C_8H_8F_2N_2O \cdot HCl$	
1-22	3-Me, 4-pyridinyl	B				*n*	$C_7H_9N_2 \cdot HCl$	

[a] Amidines were generally used crude in the next reaction. [b] DiGangi, F. E.; Gisvold, O. *J. Am. Pharm. Assoc.* **1949**, *38*, 154 (mp 207–208 °C). [c] Schaeffer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *19*, 412. [d] Fanta, P. E.; Hedman, E. A. *J. Am. Chem. Soc.* **1956**, *78*, 1434. [e] Baker, B. R.; Cory, M. *J. Med. Chem.* **1969**, *12*, 1049 (reported as the TsOH salt). [f] Freudenberg, K.; Eichel, H.; Leutert, F. *Ber. Dtsch. Chem. Ges.* **1932**, *65B*, 1183 (mp 176 °C). [g] Gardner, T. S.; Wenis, E.; Lee, J. *J. Org. Chem.* **1954**, *19*, 753 (mp 242–244 °C). [h] Feely, W. E.; Evanega, G.; Beavers, E. M. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, 269. [i] Tanizawa, K.; Ishii, S.; Kanaoka, Y. *Chem. Pharm. Bull. (Jpn.)* **1970**, *18*, 2247 (mp 199–201 °C). [j] The reaction of the imino ether and NH_3 took 12 days at 0 °C. [k] Barber, H. J.; Slack, R. *J. Am. Chem. Soc.* **1944**, *66*, 1607. [l] Used 3-cyanobenzaldehyde. [m] The imino ether was formed in EtOH and HCl(g). It was isolated by concentration under vacuum. [n] Ochiai, E.; Suzuki, I. *Pharm. Bull. (Jpn.)* **1954**, *2*, 147.

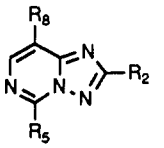
Reduction of basophil activity was also noted when a compound was N-acylated; compare **7-3** to **8-10**, **7-11** to **5-1**, and **7-13** to **8-9**. The one exception was **7-17** (compare to **8-7**).

Table VIII shows the effects of various substituents on the 5-phenyl ring. In general meta electron-withdrawing groups were active (**8-3**, **8-5**, **8-6**, **8-7**, **8-8**, **8-9**, **8-10**, **8-11**, **8-13**, **8-18**, and **8-19**). Exceptions to this rule were **8-4** and **8-12**. In the first, the zwitterionic nature of the molecule probably made it too insoluble for the aqueous test system.

A possible explanation for the lack of activity of *m*-fluoro compound **8-12** is that there is a minimum steric requirement for the meta position that the fluorine does not fill. Electron-withdrawing groups in both meta positions increased the activity in one case (**8-17**) and eliminated it in a second case (**8-16**); compare to **8-10** and **8-8**.

Electron-donating groups in the meta position were generally inactive (**5-2**, **7-12**, **7-14**, **7-19**, and **8-15**), with *m*-methyl (**8-14**) being an exception. There are several interesting comparisons of the effects of electron induction and withdrawal. When inactive alcohol **8-15** was oxidized to aldehyde **8-19**, it became highly active. Reduction of active *m*-nitro compound **5-1** gave inactive amine **5-2**. An attempt to recover the activity by tosylating the *m*-amine did not work with 8-methyl compound **5-11**. When there was a proton in the 8-position, *m*-toslyamino **8-7** was as active as the equivalent nitro compound **8-9**. There was not enough material to reduce **8-9**, but tosylating inactive **7-14** gave active **7-17**. Lack of success with the Pinner reaction on ortho substituted nitriles permitted the synthesis of only one ortho substituted final product (**8-2**) which was inactive. Para substituted compounds gave erratic results. For instance, *p*-fluoro compound **8-20** was more active than **8-12**, while **8-6** and **8-10** were more active than **8-22** and **8-21**. Moving the phenyl ring away from the heterocycle by a methylene group on an active compound (**8-23**) eliminated the activity (**8-10**).

Chart I



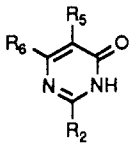
	R_f	BASO IC_{50}	substitution 5	2	7	8
6-4	0.02	18	4-pyridinyl	NH_2		
7-11	0.03	I	3-$C_6H_4NH_2$	NHAc		Me
8-1	0.03	I	3-$C_6H_4CO_2H$	NH_2		
7-13	0.04	I	3-$C_6H_4NO_2$	NHAc		
8-16	0.06	I	3-$C_6H_4CH_2OH$	NH_2		
6-9	0.06	2.5	3-Me, 4-pyridinyl	NH_2		
8-9	0.13	3.8	3-$C_6H_4NO_2$	NH_2		
8-19	0.15	0.7	3-C_6H_4CHO	NH_2		
8-23	0.22	3.4	3-$C_6H_4OCHF_2$	NH_2		
8-2	0.25	2.2	3-$C_6H_4CF_3$	NH_2		
8-20	0.25	3.7	3-C_6H_4Br	NH_2		
8-8	0.25	4.3	3-C_6H_4Cl	NH_2		
8-22	0.25	12.6	3-C_6H_4CCH	NH_2		
7-18	0.31	10.2	3-$C_6H_4CF_3$	NHMe		
8-17	0.46	0.7	3-$C_6H_4(CF_3)_2$	NH_2		
7-9	0.46	I	3-$C_6H_4CF_3$	NHMeAc		
7-7	0.52	I	3-$C_6H_4CF_3$	$N(Me)_2$		
5-9	0.53	I	3-$C_6H_4CF_3$	NH_2	Pr	

Finally, unsubstituted phenyl compound **8-1**, which had been reported as a bronchodilator,[18] had no activity in the basophil at 48 μM, our cutoff point, and was inactive to borderline even at a dose of 128 μM.

During the course of developing a thin-layer chromotographic system, preparatory to some high-pressure liquid chromotography studies, an interesting correlation of R_f value to activity in the basophil system was observed. The R_f values were determined by running the samples on the

(18) Miller, G. W.; Rose, F. L. GB 859,287, 1961.

Table II. Pyrimidones



	substituents			synth	%		recryst	starting	molecular
	2	5	6	method	yield	mp, °C	solvent	material	formula[a]
2-1	4-$C_6H_4CO_2Et$			F	26	270–320	EtOH	1-1	$C_{13}H_{12}N_2O_3 \cdot {}^1/_8H_2O$
2-2	2-C_6H_4F			F	16	195–198	HOAc–H_2O	1-12	$C_{10}H_7FN_2O \cdot {}^1/_8H_2O$
2-3	3-pyridinyl			G	29	188–191	EtOAc–$CHCl_3$	1-13	$C_9H_7N_3O$[b]
2-4	3-$C_6H_4CF_3$			G	75	180–183	Me_2CO	1-4	$C_{11}H_7F_3N_2O \cdot {}^1/_2H_2O$
2-5	3-C_6H_4Cl			G	36	208–210	EtOH	1-14	$C_{10}H_7ClN_2O$[c]
2-6	4-C_6H_4F			G	32	215–217	EtOH	1-3	$C_{10}H_7FN_2O$
2-7	Ph	Me		G	65	201–203.5	EtOH	COM	$C_{11}H_{10}N_2O$
2-8	3-$C_6H_4NO_2$	Me		d	58	320–323	EtOH	COM	$C_{11}H_9N_3O_3 \cdot {}^1/_{16}H_2O$
2-9	3-$C_6H_4CF_3$		Me	e	64	211–217	MeOH	1-4	$C_{12}H_9F_3N_2O$
2-10	3-$C_6H_4CF_3$	Pr	Me	e	26	198.5–201	Me_2CO	1-4	$C_{15}H_{15}F_3N_2O$
2-11	3-$C_6H_4CF_3$		CF_3	e	44	198.5–201	Me_2CO	1-4	$C_{12}H_6F_6N_2O$
2-12	3-$C_6H_4CF_3$	Me		d	52	210–212	MeOH	1-4	$C_{12}H_9F_3N_2O \cdot {}^1/_8H_2O$
2-13	3-$C_6H_4CF_3$		Pr	e	43	118–124	EtOH	1-4	$C_{14}H_{13}F_3N_2O$
2-14	4-$C_6H_4CF_3$			G	58	257.5–258	MeOH	1-15	$C_{11}H_7F_3N_2O$
2-15	4-$C_6H_4CF_3$		Me	e	57	229–231.5	MeOH	1-15	$C_{12}H_9F_3N_2O$
2-16	4-$C_6H_4CF_3$	Me		d	52	283–289.5	DMF	1-15	$C_{12}H_9F_3N_2O$
2-17	3-$C_6H_4NO_2$			G	30	284–286	DMF	COM	$C_{10}H_7N_3O_3$
2-18	2-thiophenyl			G	9	252–254	EtOH boil	1-5	$C_8H_6N_2OS$
2-19	2-pyridinyl[f]			G	31	134–138	CH_2Cl_2-hex.	1-2	$C_9H_7N_3O \cdot {}^1/_8H_2O$
2-20	4-pyridinyl			G	31	195–205	EtOAc	1-6	$C_9H_7N_3O \cdot {}^1/_4H_2O$
2-21	3-C_6H_4F			G	25	181–183	EtOH	1-16	$C_{10}H_7FN_2O$
2-22	3-$C_6H_4CH(OEt)_2$			G	27	126–128	EtOH	1-17	$C_{15}H_{18}N_2O_3$
2-23	CH_2-3-$C_6H_4CF_3$			G	27	106–108	CH_2Cl_2-hex.	1-7	$C_{12}H_9F_3N_2O$
2-24	3,5-$C_6H_3Cl_2$			F	16	268–270	EtOH	1-18	$C_{10}H_6Cl_2N_2O \cdot {}^3/_8HCl$[g]
2-25	3-$C_6H_4CH_3$			G	27	148–149.5	MeOH-EtOH	1-19	$C_{11}H_{10}N_2O \cdot {}^1/_4H_2O$
2-26	3-Me, 2-pyridinyl			G	20	85–89	CH_2Cl_2	1-9	$C_{10}H_9N_3O$
2-27	3,5-$C_6H_3(CF_3)_2$			G	68	232–234	PHMe-hex.	1-11	$C_{12}H_6F_6N_2O \cdot {}^1/_8H_2O$[h]
2-28	3-$C_6H_4CONMe_2$			F	31	163–165	EtOH	1-20	$C_{13}H_{13}N_3O_2$
2-29	3-$C_6H_4OCHF_2$			G	42	187–189	EtOH	1-21	$C_{11}H_8F_2N_2O_2$
2-30	3-$C_6H_4CO_2Et$			F	28	174–176	EtOH	1-10	$C_{13}H_{12}N_2O_3$
2-31	3-C_6H_4Br			F	69	207–208	EtOH	1-8	$C_{10}H_7BrN_2O$
2-32	3-Me, 4-pyridinyl			G	50	186–189	CH_2Cl_2-hex.	1-22	$C_{10}H_9N_3O \cdot {}^1/_8H_2O$

[a] Analyses were within ±0.4% for each element (except O) unless otherwise noted. [b] Anal. Calcd: C, 62.42; N, 24.27. Found: C, 60.49; N, 22.79. [c] MS M^+ Calcd: 231. Found: 231. [d] Used NaOCH=C(Me)CO_2Et: Wislicenus, W. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2934. [e] Method of ref 8. [f] Kirino, O.; Yoshida, R.; Sumida, S. *Agric. Biol. Chem.* **1982**, *25*, 837. [g] MS M^+ Calcd: 241. Found: 240 and 242. [h] MS M^+ Calcd: 308. Found: 308.

same silica gel plate and eluting it twice with ethyl acetate/hexane 1:1 (Chart I). Unfortunately this correlation was discovered as our synthetic efforts were ending and we had no opportunity to explore it further.

To test our underlying assumption that the measurement of histamine release was a measurement of total mediator release, the radioimmunoassay of Lichtenstein et al.[19] for leukotriene C_4 was used with compound **8-2**. With a single blood sample from one donor, an IC_{50} for histamine was determined to be 3.3 ± 0.9 μM (n = 6), while the IC_{50} for LTC_4 was 2.5 ± 0.6 μM (n = 6).

For a compound to be useful as a drug, in vitro activity is obviously not enough. Thus, the compounds found most active in the basophil screen was evaluated in an in vivo test, the mouse PCA. Only compounds active in both systems were considered for further evaluation (Table IX).

Conclusion

The most active compounds in the basophil which also had activity in an in vivo test (i.e. PCA) were **8-10**, **8-13**, and **8-11**. Compound **8-17**, while highly active, showed toxicity in the mouse PCA. In addition, compounds **6-4** and **6-7**, while not as active in the basophil assay, had enough in vivo activity to make at least one of them worth pursuing. Thus **8-10**, **8-13**, **8-11**, and **6-7** were chosen for further pharmacological and toxicological study.

Experimental Section

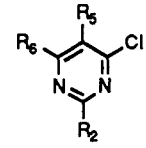
Melting points were taken on a Mel-Temp block and are uncorrected. The instruments for spectra were as follows: ^1H and ^{13}C nuclear magnetic resonance, Varian FT 80; ultraviolet, Hewlett-Packard 4050A; infrared, Nicolet 7199; mass, Finnigan-MAT CH7. Compounds without references were commercially available. Column chromatography was carried out by evaporating a MeOH solution of impure material onto a small amount of silica gel. The dried gel was placed on top of a wet (CCl_4) silica gel column. Then the column was eluted with $CHCl_3$ followed by 1% increments of MeOH to 10% MeOH/$CHCl_3$. TLC was carried out on silica gel plates using MeOH/$CHCl_3$ (1:3, 1:9, or 1:19) unless otherwise specified.

Mouse PCA Test.[17] **(a) Preparation of Immunoglobulin G (IgG).** Female Swiss Webster mice were immunized by intraperitoneal (ip) injection of 10 mg of ovalbumin in 0.5 mL of saline/Fruend's complete adjuvant. The mice were boosted with this antigen preparation 1 and 2 weeks later. Forty days after the original immunization, the mice were sacrificed by decapitation, and the serum was collected. The sera were pooled, heated at 56 °C for 4 h, and titered to obtain a 2-h PCA lesion slightly greater than 1 cm in diameter upon challenge with 0.1 mg DNP-ovalbumin.

(b) Preparation of Immunoglobulin E (IgE) Serum. Female B6 × D2F1 mice (Jackson Laboratories) were given an ip injection of 0.5 mL of saline with 1 μg of dinitrophenylated ovalbumin and 1 mg of aluminum hydroxide gel (Wyeth Am-

(19) MacGlashan, D. W.; Peters, S. P.; Warner, J.; Leichtenstein, L. M. *J. Immunol.* **1986**, *136*, 2231.

Table III. Chloropyrimidines



	substituents 2	5	6	% yield	synth method	mp, °C	recryst solvent	starting material	molecular formula[a]
3-1	3-C_6H_4CHO			10	H	136–138	Et_2O	2-22	$C_{11}H_7ClN_2O$
3-2	CH_2-3-$C_6H_4CF_3$			78	H	oil		2-23	
3-3	3-$C_6H_4CH_2OH$			99	J	91–93	chromat	3-1	$C_{11}H_9ClN_2O$
3-4	2-C_6H_4F			88	H	83–85	pet. ether	2-2	$C_{10}H_6ClFN_2$
3-5	3-pyridinyl			74	H	87–89	$CHCl_3$–hex.	2-3	$C_9H_6ClN_3$
3-6	3-$C_6H_4CF_3$			93	H	96–98.5	cyhex	2-4	$C_{11}H_6ClF_3N_2$
3-7	3-C_6H_4Cl			64	H	130–133[b]		2-5	
3-8	4-C_6H_4F			99	H	99–101	EtOH	2-6	$C_{10}H_6ClFN_2$
3-9	Ph	Me		95	H	91–92[c]	hex.	2-7	$C_{11}H_9ClN_2$
3-10	3-$C_6H_4NO_2$	Me		42	H	161–163	$CHCl_3$–cyhex	2-8	$C_{11}H_8ClN_3O_2$
3-11	3-$C_6H_4CF_3$		Me	89	H	59–61	hex.	2-9	$C_{12}H_8ClF_3N_2$
3-12	3-$C_6H_4CF_3$	Me		96	H	98–100.5	hex.	2-12	$C_{12}H_8ClF_3N_2$
3-13	3-$C_6H_4CF_3$	Pr	Me	87	H	68.5–70	hex.	2-10	$C_{15}H_{14}ClF_3N_2$
3-14	3-$C_6H_4NO_2$			77	H	156–158	EtOH	2-17	$C_{10}H_6ClN_3O_2$
3-15	4-$C_6H_4CF_3$			94	H	98–100	hex.	2-14	$C_{11}H_6ClF_3N_2$
3-16	4-$C_6H_4CF_3$		Me	97	H	65–67	hex.	2-15	$C_{12}H_8ClF_3N_2$
3-17	4-$C_6H_4CF_3$	Me		87	H	110–114	hex.	2-16	$C_{12}H_8ClF_3N_2$
3-18	2-thiophenyl			83	H	136–139	$CHCl_3$	2-18	$C_8H_5ClN_2S$
3-19	2-pyridinyl			94	H	87–89	$CHCl_3$	2-19	$C_9H_6ClN_3$
3-20	4-pyridinyl			89	H	115–116[d]	CH_2Cl_2–hex.	2-20	$C_9H_6ClN_3$
3-21	3-C_6H_4F			64	H	110–112	EtOAc	2-21	$C_{10}H_6ClFN_2$
3-22	3,5-$C_6H_3Cl_2$			82	H	63–66	chromat	2-24	$C_{10}H_5Cl_3N_2 \cdot {}^3/_8HCl$
3-23	3-Me, 2-pyridinyl			99	H	95–98	$CHCl_3$	2-26	$C_{10}H_8ClN_3$
3-24	3-$C_6H_4CHCl_2$			90	H	46–48	Et_2O–hex.	2-22	$C_{11}H_7Cl_3N_2 \cdot {}^1/_8H_2O$
3-25	3,5-$C_6H_3(CF_3)_2$			59	H	24–26	chromat	2-27	$C_{12}H_5ClF_6N_2 \cdot {}^1/_8H_2O$
3-26	3-$C_6H_4OCHF_2$			72	H	54–55	$CHCl_3$–hex.	2-29	$C_{11}H_7ClF_2N_2O \cdot {}^1/_2H_2O$
3-27	4-$C_6H_4CO_2Et$			71	H	94–96.5	hex.	2-1	$C_{13}H_{11}ClN_2O_2$
3-28	3-$C_6H_4CO_2Et$			84	H	87–89	hex.	2-30	$C_{13}H_{11}ClN_2O_2$
3-29	3-C_6H_4Br			53	H	124.5–126	hex.	2-31	$C_{10}H_6BrClN_2$
3-30	3-Me, 4-pyridinyl			78	H	89–90	CH_2Cl_2–hex.	2-32	$C_{10}H_8ClN_3$
3-31	3-$C_6H_4CF_3$		CF_3		H	oil		2-11	
3-32	3-$C_6H_4CF_3$		Pr		H	oil		2-13	
3-33	3-$C_6H_4CH_3$			50	H	74–75[b]		2-25	
3-34	3-$C_6H_4CONMe_2$			99	H	oil		2-28	
3-35	4-pyridinyl *N*-oxide			95	I	165 dec[e]	CH_2Cl_2–hex.	3-20	$C_9H_6N_3ClO$

[a] See footnote *a* of Table II. [b] Crude, used as such. [c] van Meeteren, H. W.; van der Plas, H. C. *Tetrahedron Lett.* **1966**, 4517. [d] Lesher, G. Y.; Singh, B.; Mielens, Z. E. *J. Med. Chem.* **1982**, *25*, 837 (mp 130–132 °C). [e] Only a sample was recrystallized for analysis.

phogel). One and 2 months later, the mice were boosted with the same antigen preparation. One week after the second boost, the mice were sacrificed by decapitation, and the serum was collected. The sera were pooled and titered to obtain a 48-h PCA lesion slightly greater than 1 cm in diameter.

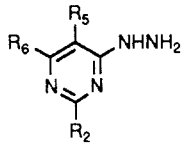
(c) Passive Cutaneous Anaphylaxis Test. At −50 h (relative to antigen challenge at 0 time), 50 μL of mouse IgE serum or mouse monoclonal IgE was injected intradermally (id) in the left side of the mouse posterior to the axilla at the level of the diaphragm. At −2 h, 50 μL of mouse IgE against ovalbumin was injected id on the right side of the mouse. In some experiments histamine disphosphate (5 μg) was injected id on the opposite side of the animal from the IgE injection site at the time of antigen injection.

At 1 h prior to antigen challenge, the control animals received an ip injection of 0.5 mL of a 0.05% solution of (carboxymethyl)cellulose in saline. For drug-treated animals the drug was dissolved or suspended (if necessary using a Heat Systems Model C3 sonicator) in the (carboxymethyl)cellulose solution and administered ip (total volume 0.5 mL) at −1 h. The usual dose was 50 mg/kg. At zero time, the mice were anesthetized with ethyl ether, and 0.5 mL of saline containing 0.1 mg of DNP-ovalbumin and 2.5 mg of Evans blue dye (Fisher Scientific Company) was injected into the tail vein.

At +15 min, the mice were sacrificed by cervical dislocation, the dorsal skin was removed, and the blue PCA spots were examined on the inside surface. The largest and smallest diameters of the lesion and a qualitative estimate of intensity of color were recorded. The mean of the products of diameters (area) for mice in a given treatment group was compared with that of the control group. IgE and IgG lesions were analyzed independently. If the area for a treatment group was significantly smaller than the lesion area for the control group ($p < 0.05$ for two-tailed Student's t test) for either IgE or IgE lesion, the compound was considered active. If the compound inhibited the IgE lesion with minimal effects on the histamine lesion, the compound was considered active. If the histamine lesion was inhibited the compound was examined in other assays to determine if it had antihistamine activity.

Basophil Mediator Release. Blood (100 mL) was drawn from volunteers with a sensitivity to known antigens or to anti-IgE by collection in heparinized Vacutainer tubes. The blood was mixed with buffer-containing saline, dextran, and dextrose to yield a final concentration of 6 mg/mL dextrose and 12 mg/mL dextran. The mixture was allowed to separate into two layers into a sharp interface developed. The supernatant was removed and transferred to a polycarbonate centrifuge tube. The supernatant was centrifuged at 100 *g* for 8 min at 4 °C and the resulting cell pellet was resuspended in buffer and washed twice by recentrifugation with fresh buffer. The pellet resulting after the final centrifugation was resuspended in approximately 65 mL of buffer containing 25 mM PIPES, 110 mM NaCl, 5 mM KCl, 0.6 mM $CaCl_2$, 1.0 mM $MgCl_2$, and 0.03% HSA, pH 7.4. A 1-mL aliquot of cells in buffer was then added to tubes containing 0.2-mL aliquots of the drug of interest or control buffer and preincubated at 37 °C for 10 min. The antigen or anti-IgE in a 10-μL volume was added to each tube with mixing (concentration of antigen varied with individual donors and was individually adjusted for maximal effect–anti-IgE was adjusted to give a 10 μg/mL final concentration) and incu-

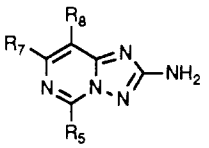
Table IV. Hydrazinopyrimidines



	substituents			%		recryst	starting	molecular
	2	5	6	yield[a]	mp, °C	solvent	material	formula[b]
4-1	3-$C_6H_4CH_2OH$			79	154–156	EtOH	3-3	$C_{11}H_{12}N_4O$
4-2	4-$C_6H_4CO_2Et$			66	161–163	*c*	3-27	*d*
4-3	3-$C_6H_4CF_3$[e]			81	115–117	EtOAc–hex.	3-6	$C_{11}H_9F_3N_4$
4-4	2-C_6H_4F			94	oil		3-4	*d*
4-5	3-C_6H_4Cl[e]			86	122–124	Et_2O–hex.	3-27	$C_{10}H_9ClN_4$
4-6	4-C_6H_4F[e]			90	130–133	EtOH	3-8	$C_{10}H_9FN_4 \cdot {}^1/_8H_2O$[f]
4-7	3-pyridinyl			71	107–108		3-5	$C_9H_9N_5$
4-8	Ph	Me		96	192–196	MeOH	3-9	$C_{11}H_{12}N_4$
4-9	3-$C_6H_4NO_2$	Me		97	208–210	$CHCl_3$–cyhex	3-10	$C_{11}H_{11}N_5O_2$
4-10	3-$C_6H_4CF_3$		Me	92	141–143.5	EtOAc	3-11	$C_{12}H_{11}F_3N_4$
4-11	3-$C_6H_4NO_2$			67	208–209	MeOH–EtOH	3-14	$C_{10}H_9N_5O_2$
4-12	3-$C_6H_4CF_3$	Me		85	193–195	EtOAc	3-12	$C_{12}H_{11}F_3N_4$
4-13	3-$C_6H_4CF_3$	Pr	Me	82	198–199	EtOAc	3-13	$C_{15}H_{17}F_3N_4$
4-14	3-$C_6H_4CF_3$		Pr	85	78–79.5	cyhex	3-32	$C_{14}H_{15}F_3N_4$
4-15	3-$C_6H_4CF_3$		CF_3	54	183–185.5	MeOH	3-31	$C_{12}H_8F_6N_4$
4-16	4-$C_6H_4CF_3$			94	110–113	PHMe	3-15	$C_{11}H_9F_3N_4$
4-17	4-$C_6H_4CF_3$		Me	94	135.5–138	PHMe	3-16	$C_{12}H_{11}F_3N_4$
4-18	4-$C_6H_4CF_3$	Me		83	243–247	PHMe	3-17	$C_{12}H_{11}F_3N_4$
4-19	2-thiophenyl			77	136–139	$CHCl_3$–hex.	3-18	$C_8H_8N_4S$
4-20	2-pyridinyl			76	108–110	CH_2Cl_2–hex.	3-19	$C_9H_9N_5 \cdot {}^3/_8H_2O$
4-21	4-pyridinyl			80	208–212	EtOH	3-20	$C_9H_9N_5$
4-22	3-C_6H_4F			87	130–131	MeOH–H_2O	3-21	$C_{10}H_9FN_4$
4-23	CH_2-3-$C_6H_4CF_3$			67	oil		3-2	$C_{12}H_{11}F_3N_4$
4-24	3,5-$C_6H_3Cl_2$			55	210–212	EtOH	3-22	$C_{10}H_8Cl_2N_4$
4-25	3-$C_6H_4CH_3$			58	102–103	EtOH	3-33	$C_{11}H_{12}N_4 \cdot {}^1/_8EtOH$
4-26	3-Me, 2-pyridinyl			66	108–112	CH_2Cl_2–hex.	3-23	$C_{10}H_{11}N_5 \cdot {}^5/_8H_2O$
4-27	3-C_6H_4Br			78	136–138	EtOH	3-29	$C_{10}H_9BrN_4$
4-28	3,5-$C_6H_3(CF_3)_2$			81	111–112	$CHCl_3$–hex.	3-25	$C_{12}H_8F_6N_4 \cdot {}^3/_{16}H_2O$[g]
4-29	3-$C_6H_4OCHF_2$			70	75–76.5	$CHCl_3$–hex.	3-26	$C_{11}H_{10}F_2N_4O$
4-30	3-$C_6H_4CONMe_2$			94	165–167.5	EtOH	3-34	$C_{13}H_{15}N_5O$
4-31	3-Me, 4-pyridinyl			94	185–186		3-30	$C_{10}H_{11}N_5$
4-32	3-$C_6H_4CHCl_2$			32	gum		3-24	*d*
4-33	3-$C_6H_4CO_2Et$				171–173	*c*	3-28	*d*
4-34	pyridinyl *N*-oxide			92	225 dec		3-35	$C_9H_9N_5O$

[a] Prepared by method K. [b] See footnote *a* of Table II. [c] Crystallized from the reaction and was used immediately to avoid polymerization. [d] Not analyzed. [e] Hardy, R. A., Jr.; Baker, J. S.; Quinones, N. Q. US 4,269,980 (22 May 1981). [f] MS M^+ Calcd: 204. Found: 204. [g] MS M^+ Calcd: 322. Found: 322.

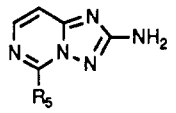
Table V. 7- and 8-Substituted Triazolo[1,5-*c*]pyrimidines



	substituents				synth	%		recryst	starting	molecular
	5	7	8	baso[a]	method	yield	mp, °C	solvent	material	formula[b]
theophylline				309 ± 55 (17)						
disodium chromoglycate				1000						
5-1	3-$C_6H_4NO_2$		Me	8.7 ± 2.7 (2)	L	88	240–242	DMF	4-9	$C_{12}H_{10}N_6O_2 \cdot {}^1/_4H_2O$ (c)
5-2	3-$C_6H_4NH_2$		Me	I	W	82	197–199	EtOH	5-1	$C_{12}H_{12}N_6$
5-3	Ph		Me	I	L	78	188–191	$CHCl_3$	4-8	$C_{12}H_{11}N_5$
5-4	3-$C_6H_4CF_3$	Me	Pr	I	L	99	181–181.5	EtOH–Et_3N	4-13	$C_{16}H_{16}F_3N_5$
5-5	3-$C_6H_4CF_3$		Me	5.6 ± 0.01 (2)	L	83	179–180.5	EtOH	4-12	$C_{13}H_{10}F_3N_5 \cdot {}^1/_8H_2O$
5-6	3-$C_6H_4CF_3$	Me		I	L	55	186.5–189	EtOH	4-10	$C_{13}H_{10}F_3N_5$
5-7	3-$C_6H_4CF_3$	CF_3		I	L	79	212–213	EtOH	4-15	$C_{13}H_7F_6N_5$
5-8	4-$C_6H_4CF_3$		Me	I	L	84	219–223	EtOH	4-18	$C_{13}H_{10}F_3N_5$
5-9	3-$C_6H_4CF_3$	Pr		I	L	89	131–132	EtOH–Mecyhex	4-14	$C_{15}H_{14}F_3N_5$
5-10	4-$C_6H_4CF_3$	Me		I	L	69	167–170.5	EtOH	4-17	$C_{13}H_{10}F_3N_5$
5-11	3-C_6H_4NHTos		Me	I	T	17	188–190	EtOAc–EtOH	7-18	$C_{19}H_{18}N_6O_2S$

[a] IC_{50} in μM as means ± SEM. The numbers in parentheses indicate the number of dose responses carried out. Inactivity (I) is defined as inactive at 48 μM. [b] See footnote *a* of Table II. [c] MS M^+ Calcd: 270. Found: 270.

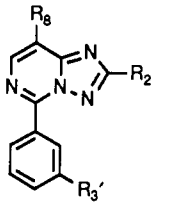
Table VI. 5-Heterocyclic Triazolo[1,5-c]pyrimidines



	5-substituents	baso[a]	synth method	% yield	mp, °C	recryst solvent	starting material	molecular formula[b]	MS (M^+) calcd	MS (M^+) fnd
6-1	2-thiophenyl	I	L	84	169–172	$CHCl_3$–hex.	4-19	$C_9H_7N_5S \cdot {}^1/_8H_2O$	217	217
6-2	2-pyridinyl	I	L	65	187–189	chromat	4-20	$C_{10}H_8N_6$		
6-3	3-Me, 2-pyridinyl	I	L	15	185–190	MeOH–Et_2O	4-26	$C_{11}H_{10}N_6 \cdot {}^1/_8H_2O$	226	226
6-4	3-pyridinyl	14 ± 2.5 (8)	L	30	228–231	chromat	4-7	$C_{10}H_8N_6 \cdot {}^1/_8H_2O$	212	212
6-5	3-pyridinyl Me^+I^-	I	EE	77	260–270 dec	EtOH	6-4	$C_{11}H_{11}IN_6 \cdot {}^5/_8H_2O$		*c*
6-6	3-pyridinyl *N*-oxide	I	I	46	233–236	CH_2Cl_2	6-4	$C_{10}H_8N_6O \cdot {}^5/_8H_2O$	228	228
6-7	4-pyridinyl	18 ± 3 (12)	HH	58	>250 dec		6-8	$C_{10}H_8N_6 \cdot {}^3/_8H_2O$	212	212
6-8	4-pyridinyl *N*-oxide	5.6 ± 2.3 (2)	L	80	274–277 dec	EtOH	4-34	$C_{10}H_8N_6O \cdot {}^1/_8H_2O$	228	228
6-9	3-Me, 4-pyridinyl	2.5 ± 1.4 (2)	L	10	132–134	MeOH	4-31	$C_{11}H_{10}N_6 \cdot {}^1/_8H_2O$	226	226

[a] IC_{50} in μM. I = inactive at 48 μM. [b] See footnote *a* of Table II. [c] Decomposes on mass spectra to 212 + 142 (CH_3I).

Table VII. 2-Substituted Triazolo[1,5-c]pyrimidines



	substituents 2	substituents 3′	substituents 8	baso[a]	synth method	% yield	mp, °C	recryst solvent	starting material	molecular formula[b]
7-1	$NHCH_2\overline{CHOCH_2}$	CF_3		I	S[c]	18	144–146	EtOAc	7-3	$C_{15}H_{12}F_3N_5O$
7-2	$NHCH_2CHOHCH_2Cl$	CF_3		9.3 ± 1.4 (2)	V	43	141–142	MeOH	7-1	$C_{15}H_{13}ClF_3N_5O$
7-3	$NHCOCH_3$	CF_3		20.0 ± 10.7 (2)	R	96	221–222.5	EtOH	8-10	$C_{14}H_{10}F_3N_5O$
7-4	$NMeCOCH_3$	CF_3		I	S	76	122.5–124.5	CCl_4	7-3	$C_{15}H_{12}F_3N_5O$
7-5	NHMe	CF_3		10.2 ± 7.4 (3)	T	61	177.5–179	EtOAc	7-4	$C_{13}H_{10}F_3N_5$
7-6	$N(Me)_2$	CF_3		I	U	43	104–105	chrom + hex.	7-5	$C_{14}H_{12}F_3N_5$
7-7	H	CF_3		I	Q	61	99–101	cyhex	15	$C_{12}H_7F_3N_4$
7-8	$N{=}CHNMe_2$	CF_3		I	O	78	164–165	$PHCH_3$	8-10	$C_{15}H_{13}F_3N_6$
7-9	$NAcCH_2CO_2Et$	CF_3		I	S	69	97–98	cyhex	7-3	$C_{18}H_{16}F_3N_5O_3$
7-10	$NHCH_2CO_2Et$	CF_3		I	T	38	170.5–172.5	EtOAc	7-9	$C_{16}H_{14}F_3N_5O_2$
7-11	$NHCOCH_3$	NO_2	Me	11.0 ± 4.2 (2)	R	75	245–247	EtOH	5-1	$C_{14}H_{12}N_6O_3$
7-12	$NHCOCH_3$	NH_2	Me	I	W	27	243–245	EtOH	7-11	$C_{14}H_{14}N_6O$
7-13	$NHCOCH_3$	NO_2		I	R	69	280–283	DMF	8-9	$C_{13}H_{10}N_6O_3$
7-14	$NHCOCH_3$	NH_2		I	W	72	250–254	EtOAc–Me_2CO	7-13	$C_{13}H_{12}N_6O \cdot {}^3/_8H_2O$[d]
7-15	Cl	NO_2	Me	I	CC	43	188–190	EtOH	5-1	$C_{12}H_8ClN_5O_2$
7-16	morpholine	NO_2	Me	I	DD	20	210–213	EtOH	7-15	$C_{16}H_{16}N_6O_3 \cdot {}^1/_8H_2O$[e]
7-17	$NHCOCH_3$	NHTos		1.6 ± 1.5 (2)	X	32	208–211	EtOAc–EtOH	7-14	$C_{20}H_{18}N_6O_3S$
7-18	$NHCOCH_3$	NHTos	Me	51.8 ± 17.5 (2)	X	60	218–220	Et_2O	7-12	$C_{21}H_{20}N_6O_3S$
7-19	NHMe	NHMe	Me	I	FF	7	169–170.5	chrom + EtOAc	5-2	$C_{14}H_{16}N_6$

[a] IC_{50} in μM. I = inactive at 48 μM. [b] See footnote *a* of Table II. [c] After alkylating 7-3 with epichlorohydrin, the acetyl group came off during aqueous workup. [d] MS M^+ Calcd: 268. Found: 268. [e] MS M^+ Calcd: 340. Found: 340.

bated at 37 °C with gentle shaking for 1 h. All experiments were carried out in triplicate with controls run in sextuplicate.

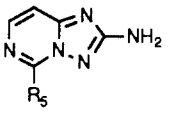
Following the release reaction, the leukocytes were removed by centrifugation at 1500 rpm for 10 min at 4 °C, and 1-mL aliquots were removed and added to polyethylene tubes. Then 0.2 mL of 8% $HClO_4$ was added to these fractions, and the samples were centrifuged at 2000 rpm for 10 min to remove protein precipitate. Blanks had cells and all reagents except antigen or anti-IgE. Aliquots of cells in the same reaction volume were lysed by treatment with $HClO_4$ to evaluate total histamine content. Histamine content was determined by automated fluorometric assay using a Technicon autoanalyzer as described by Siraganian.[8]

Values of percent histamine release obtained at different concentrations of compound were used to calculate an IC_{50} by computer-calculated linear regression. These IC_{50} values, obtained for individual donors, were then utilized for calculations of the mean ● SEM as reported in the tables.

Method A, 4-(Trifluoromethyl)benzimidamide Hydrochloride (1-15). A solution of 98.08 g (0.574 mol) of *p*-(trifluoromethyl)benzonitrile, 27.8 mL (22.0 g, 0.688 mol) of MeOH, and 1.2 L of Et_2O was saturated with HCl at 3–4 °C in an ice bath. After several days in a refrigerator, 107.8 g of white needles, mp 179–185 °C, were collected. The imino ether thus obtained was suspended in 400 mL of EtOH, cooled in an ice bath, and saturated with NH_3. After 4 days at 0 °C, the precipitated NH_4Cl was filtered off and the filtrate was concentrated under vacuum. The residue crystallized to leave 70.9 g (55%) of damp, solid amidine hydrochloride, which was used without further purification.

Method B, 3-Pyridinecarboximidamide Monohydrochloride (1-13). 3-Cyanopyridine (52 g, 0.5 mol) was dissolved in MeOH (500 mL). Powdered NaOMe (2.7 g, 50 mmol) was added in one portion. The solution was stirred overnight at room temperature. After adding NH_4Cl (30 g, 0.56 mol), the mixture was heated at reflux for 4 h and then cooled. The solvent was removed in vacuo. Absolute EtOH (600 mL) was added and the mixture was heated to reflux. After 15 min, the solids were filtered off and the mixture was allowed to cool to room temperature and stand overnight. Additional inorganic salts were filtered off, and the reaction mixture was concentrated to approximately $^1/_2$ volume and filtered to afford 7.0 g of product (mp 186–188 °C).

Table VIII. 5-Phenyl-Substituted Aminotriazolo[1,5-c]pyrimidines



	5-substituents	baso[a]	synth method	% yield	mp, °C	recryst solvent	starting material	molecular formula[b]	MS (M^+) calcd	MS (M^+) fnd
8-1	Ph (c)	I	L					$C_{11}H_9N_5$		
8-2	2-C_6H_4F	I	L	50	164–166	EtOH	4-4	$C_{11}H_8FN_5$		
8-3	3-$C_6H_4CON(Me)_2$	3.5 (1)	L	47	213.5–215.5	EtOH	4-30	$C_{14}H_{14}N_6O$		
8-4	3-C_6H_4COOH	I	GG	25	340–342	EtOH	8-15	$C_{12}H_9N_9O_2 \cdot {}^1/_4H_2O$	255	255
8-5	3-$C_6H_4C{\equiv}CH$	12.6 ± 2.1 (2)	Y	26	170–172	$CHCl_3$–cyhex	8-13	$C_{13}H_9N_5 \cdot {}^1/_4H_2O$	235	235
8-6	3-$C_6H_4CO_2Et$	11.5 ± 0.37 (2)	L	9	124.5–127	EtOH	4-33	$C_{14}H_{13}N_5O_2 \cdot {}^1/_8EtOH$		
8-7	3-C_6H_4NHTos	1.5 ± 1.4 (2)	T	27	197–200	EtOAc–cyhex	7-17	$C_{18}H_{16}N_6O_2S \cdot {}^1/_4H_2O$	380	380
8-8	3-C_6H_4Cl	4.3 ± 3.5 (2)	L	63	192–194	EtOH	4-5	$C_{11}H_8ClN_5$		
8-9	3-$C_6H_4NO_2$	3.8 ± 0.74 (2)	L	56	267–269	DMF	4-11	$C_{11}H_8N_6O_2$		
8-10	3-$C_6H_4CF_3$	2.2 ± 0.42 (21)	L	68	125.5–128	$CHCl_3$–hex.	4-3	$C_{12}H_8F_3N_5$		
8-11	3-$C_6H_4OCHF_2$	3.4 ± 2.2 (8)	L	59	115–117	$CHCl_3$–hex.	4-29	$C_{12}H_9F_2N_5O \cdot {}^1/_8H_2O$	277	277
8-12	3-C_6H_4F	I	L	67	162–164	EtOH	4-22	$C_{11}H_8FN_5$		
8-13	3-C_6H_4Br	3.7 ± 0.93 (17)	L	76	175–177	EtOH	4-27	$C_{11}H_8BrN_5$		
8-14	3-$C_6H_4CH_3$	5.5 ± 3.2 (2)	L	21	125–126	CH_2Cl_2–hex.	4-25	$C_{12}H_{11}N_5$		
8-15	3-$C_6H_4CH_2OH$	I	L	36	180–182	EtOH–Et_2O	4-1	$C_{12}H_{11}N_5O \cdot {}^1/_2H_2O$	241	241
8-16	3,5-$C_6H_3Cl_2$	I	L	55	231–233	MeOH–10% aq K_2CO_3	4-24	$C_{11}H_7Cl_2N_5$		
8-17	3,5-$C_6H_3(CF_3)_2$	0.7 ± 0.45 (4)	L	49	172–173.5	CH_3CN	4-28	$C_{13}H_7F_6N_5 \cdot {}^1/_4H_2O$	347	347
8-18	3-$C_6H_4CHCl_2$	1.0 ± 0.56 (4)	L	10	145–148	$CHCl_3$–hex.	4-32	$C_{12}H_9Cl_2N_5$		
8-19	3-C_6H_4CHO	0.7 ± 0.41 (3)	BB	23	211 dec	EtOAc	8-15	$C_{12}H_9N_5O \cdot {}^1/_4H_2O$	239	239
8-20	4-C_6H_4F	31.3 ± 0.7 (2)	L	48	215–subl	EtOH	4-6	$C_{11}H_8FN_5 \cdot {}^5/_8H_2O$	229	229
8-21	4-$C_6H_4CF_3$	I	L	52	177–178.5	EtOH	4-16	$C_{12}H_8F_3N_5$		
8-22	4-$C_6H_4CO_2Et$	16.5 (1)	L	29	180.5–181.5	$CHCl_3$–hex.	4-2	$C_{14}H_{13}N_5O_2$		
8-23	CH_2-3-$C_6H_4CF_3$	I	L	60	144–145	CH_2Cl_2–hex.	4-23	$C_{13}H_{10}F_3N_5$		

[a] IC_{50} in μM. I = inactive at 48 μM. [b] See footnote a of Table II. [c] Reference 18.

Table IX. Mouse PCA Activity

compound	ED_{50} (after 1 h, po),[a] mg/kg
theophylline	140 ± 25 (2)
6-4	14 ± 6 (6)
6-7	14 ± 6 (4)
8-2	218 ± 35 (5)
8-10	166 ± 28 (4)
8-11	138 ± 37 (4)
8-13	142 ± 62 (7)
8-20	178 ± 37 (5)
8-23	178 ± 37 (5)

[a] Number of determinations in parentheses.

Concentration of the filtrate again to $^1/_2$ its volume afforded an additional 25.0 g of product (mp 184–188 °C), followed by a third crop of 12.6 g (mp 184–188 °C) for a total of 44.6 g (57%) of 3-pyridinecarboximidamide (**1-13**), lit.[6] mp 190 °C.

Method C, 3-Cyano-*N*,*N*-dimethylbenzamide (25). A mixture of 85.22 g (0.579 mol) of *m*-cyanobenzoic acid (**23**), 400 mL of PhMe, 4.48 mL (4.23 g, 0.0579 mol) of DMF,[20] and 44.4 mL (72.3 g, 0.608 mol) of $SOCl_2$ was gently heated on a steam bath for 2 h until a solution formed and gas evolution ceased. The cooled reaction solution was added to a stirred solution of 250 mL (2.2 m) of 40% aqueous dimethylamine and 100 mL of H_2O, with caution. At intervals, 2–3 mL of concentrated aqueous KOH was added. After the addition was completed, the mixture was stirred for several hours. Then the layers were separated and the organic layer was washed with H_2O. The organic layer was next evaporated to dryness. Recrystallization from 300 mL of EtOH and subsequent concentration of the mother liquors to obtain a second fraction gave a total of 82.11 g (82%) of amide **25**, mp 85–88 °C (**1-23**). Anal. ($C_{10}H_{10}N_2O$) C, H, N.

Method D, 3-(Difluoromethoxy)benzaldehyde (20). 3-Hydroxybenzaldehyde (116 g, 0.950 mol) was dissolved in 3 L of 2-PrOH and 24.0 g (0.615 mol) of $NaBH_4$ was added. After stirring over a weekend, 535 g (9.6 mol) of KOH was added portionwise, with stirring, until most of it dissolved (2.5 h). Then chlorodifluoromethane (Freon 22) was bubbled into the reaction, with vigorous stirring, at such a rate that a temperature of 55–60 °C was maintained. When the exotherm had subsided, the reaction was stopped. Removal of the solvent under vacuum left a residue which was partitioned between water and ether. The organic phase was washed with 6N HCl, dried (Na_2SO_4), and concentrated to produce 111 g of a brown oil. Short-path distillation of the oil gave 88.6 g (53%) of colorless liquid, bp 95–100 °C (3.3 mm). Repetition of this reaction gave a total of 168.3 g (0.965 mol) of 3-(difluoromethoxy)benzyl alcohol (**19**), which was dissolved in 200 mL of CH_2Cl_2 and added to a stirred slurry of 313 g (1.45 mol) of pyridinium chlorochromate in 2 L of CH_2Cl_2. After stirring overnight, the CH_2Cl_2 was decanted and passed through a hydrous magnesium silicate pad. The reaction residue was washed with 700 mL of CH_2Cl_2, which was used to wash the pad. Concentration of the filtrate under vacuum left an oil, which was purified by a short-path distillation to give 114.7 g (69%) of aldehyde **20**, bp 80–90 °C (0.3 mm). ^1H NMR showed the presence of a difluoromethyl group: ^1H NMR ($CDCl_3$) δ 6.58 (t, 1 H, J = 72 Hz, one band hidden, $OCHF_2$), 7.20–7.80 (m, 4 H, Ph-H), 9.86 (s, 1 H, CHO). Anal. ($C_8H_6F_2O_2 \cdot {}^1/_8H_2O$) C, H, N.

Method E, 3-(Difluoromethoxy)benzonitrile (22). Hydroxylamine hydrochloride (184 g, 2.63 mol) and 3-difluoromethoxybenzaldehyde (**20**) were stirred with 1100 mL of H_2O and 850 mL of EtOH until a solution formed. Next, 735 mL (3.7 mol) of 5 N NaOH was added and the reaction mixture was brought to a gentle boil for 10 min. After cooling, most of the EtOH was removed on a rotary evaporator. The residual solution was adjusted to pH 7 with concentrated HCl. Extraction into $CHCl_3$ of the yellow oil, followed by drying ($MgSO_4$) and concentration under vacuum, left 100 g (99%) of a yellow oil, **21**.

After combining some oxime from another reaction, 132.8 g (0.710 mol) of oxime **21** was dissolved in 640 mL of sieve-dried THF and 121.0 g (0.780 mol) of *N*,*N*′-carbonyldiimidazole was added. Using a water bath to keep the initial exotherm and effervescence under control, the solution was permitted to stir overnight at room temperature. The solvent was removed under vacuum and the residue was stirred with 350 mL of H_2O while the pH was adjusted to 3 with concentrated HCl. The product was extracted into Et_2O, dried (Na_2SO_4), and concentrated under

(20) Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653.

vacuum to 120 g of oil. Distillation gave 112.4 g (93%) of a colorless oil, **22**, bp 85–95 °C (0.4 mm), which had one spot on TLC and integrated corrected on ^{1}H NMR: ^{1}H NMR ($CDCl_3$) δ 6.57 (t, 1 H, J = 72 Hz), 7.30–7.60 (m, 4 H, Ph-H).

Method F, 2-(3-Bromophenyl)-4(1*H*)-pyrimidinone (2-31). To 64.28 g (0.2730 mol) of crude 3-bromobenzimidamide hydrochloride (**1-8**) was added concentrated aqueous KOH and the resulting oil was extracted with three 100-mL portions of $CHCl_3$. The combined extracts were dried (Na_2SO_4) and concentrated under vacuum to an oil which crystallized. Upon dissolving the crystals (51.60 g, 0.2592 mol) in 500 mL of EtOH, 29 mL (28.1 g, 0.29 mol) of ethyl propiolate was added. After a 10 °C exotherm, the solution was warmed to 60 °C and a previously prepared solution of 16.8 g (0.3 mol) of KOH in 400 mL of EtOH (warmed to speed dissolving) was added dropwise over 1 h. Refluxing the solution for 2.5 h gave a dark brown color. Then the reaction solution was concentrated under vacuum and the residue was taken up in H_2O. Adjusting the pH to 4–5 with concentrated HCl gave a precipitate which was collected and pressed dry with a rubber dam. Air-drying left 99.1 g, mp 176–191 °C. The product was recrystallized from EtOH to give 23.81 g of tan crystals, mp 200–202 °C. Fractional recrystallization of the mother liquor residue gave a total of 23.25 g more of product, mp 180–192 °C (69%). A sample of the second crop was dissolved in $CHCl_3$ and passed through a pad of hydrous magnesium silicate. After evaporation of the solvent, the residue was recrystallized from EtOH to give an analytical sample of **2-31**, mp 207–208 °C (anal. in Table II).

Method G, 2-[3-(Trifluoromethyl)phenyl]-4(1*H*)-pyrimidinone (2-4). The title compound was prepared from **1-4** and the sodium salt of ethyl formyl acetate by the methods described by Gabriel and by Moffatt.[12]

Method H, 4-Chloro-2-[4-(trifluoromethyl)phenyl]pyrimidine (3-15). Applying heat to a mixture of 12.99 g (0.05408 mol) of 2-[4-(trifluoromethyl)phenyl]-4(1*H*)-pyrimidinone (**2-14**) and 65 mL of $POCl_3$ gave a solution which was refluxed for 3 h. Upon concentration of the reaction under vacuum, the oily residue was poured onto ice and stirred vigorously. After standing 1 h, the product was collected as a solid (16.21 g), mp 95–99 °C. Recrystallization from hexane gave 13.09 g (94%) of **3-15**, mp 98–100 °C (anal. in Table III).

Method I, 4-Chloro-2-(4-pyridinyl)pyridine 1-Oxide (3-35). 4-Chloro-2-(4-pyridinyl)pyrimidine (**3-20**, 9.58 g, 50 mmol) was dissolved in CH_2Cl_2 (500 mL). *m*-Chloroperbenzoic acid (18.18 g, 90 mmol) was added and the reaction mixture was stirred for 24 h at room temperature under a $CaCl_2$ drying tube. The mixture was diluted with CH_2Cl_2 (500 mL) and then washed successively with 10% Na_2SO_3 (2 × 75 mL) and with saturated aqueous $NaHCO_3$ (2 × 75 mL), dried ($MgSO_4$), filtered, and then concentrated to afford 10.1 g (100%) of >95% pure product, which was carried on to the next step without further purification.

An analytical sample was prepared by recrystallizing 210 mg of crude product with CH_2Cl_2/hexane to afford 115 mg of pure product, mp 165 °C dec (anal. in Table III).

Method J, 3-(4-Chloro-2-pyrimidinyl)benzenemethanol (3-3). 3-(4-Chloro-2-pyrimidinyl)benzaldehyde (**3-1**, 1.00 g, 4.56 mmol) was placed in 230 mL of 2-PrOH, and 0.32 g (9.4 mmol) of freshly ground $NaBH_4$ pellets was added. The mixture was stirred in a room temperature H_2O bath until the reaction was completed (3 h, TLC). Excess borohydride was destroyed with 6 N HCl, followed by neutralization with aqueous $NaHCO_3$. The solvent was removed under vacuum and the residue was partitioned between EtOAc and H_2O. After drying of the organic phase (Na_2SO_4) and concentration of it under vacuum, 1.1 g of oil remained which eventually crystallized, mp 112–118 °C. A sample was chromatographed (TLC, silica, $CHCl_3$) for analysis, mp 91–93 °C (anal. in Table III).

Method K, 4-Hydrazino-2-[4-(trifluoromethyl)phenyl]pyrimidine (4-16). Mixing 10.79 g (0.04172 mol) of 4-chloro-2-[4-(trifluoromethyl)phenyl]pyrimidine (**3-15**), 41 mL of EtOH, and 40.5 mL (41.8 g, 0.835 mol) of hydrazine hydrate gave a solution which was gently refluxed for 1 h. The reaction was poured into 700 mL of H_2O and cooled to 0 °C, giving 10.1 g of a solid, mp 80–90 °C. Recrystallization from 60 mL of PhMe yielded 9.37 g of hydrazine **4-16**, mp 110–113 °C. Concentration of the mother liquors and recrystallization of the precipitate gave a second crop, 0.64 g (94%) of product, mp 110–112 °C (anal. in Table IV).

Method L, 2-Amino-5-[4-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*c*]pyrimidine (8-21). A mixture of 9.64 g (0.0379 mol) of 4-hydrazino-2-[4-(trifluoromethyl)phenyl]pyrimidine (**4-16**), 150 mL of MeOH, and 6.82 g (0.0645 mol) of cyanogen bromide was heated under reflux for 4 h. To the cooled reaction solution was added, with stirring, 30 mL of 13% aqueous $KHCO_3$ and the subsequent mixture was permitted to evaporate. Diluting the residue with 300 mL of H_2O gave 11.07 g of a tacky solid, mp 113–165 °C. Two recrystallizations from MeOH gave 3.50 g of yellow crystals, mp 177–178.5 °C. The mother liquor concentrate was recrystallized from PhMe and again from MeOH to give an additional 1.97 g (52%), mp 176–178.5 °C (anal. in Table VIII).

Method M, 5-(3-Nitrophenyl)[1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (8-9) and 5-(3-Nitrophenyl)[1,2,4]triazolo[4,3-*c*]pyrimidin-3-amine (10, Ar = 3-$NO_2C_6H_4$). A mixture of 7.10 g (0.0308 mol) of 4-hydrazino-2-(3-nitrophenyl)pyrimidine (**4-11**), 5.75 g (0.0540 mol) of cyanogen bromide, and 1.2 L of MeOH was brought to a boil on a steam bath. After 5 min of boiling, a small amount of undissolved solid, A, remained, which was collected. Boiling of the filtrate was continued in an Erlenmeyer flask for 3 h, to a volume of 600 mL. After cooling overnight to room temperature, a second solid, B, was collected. The filtrate was boiled down to 125 mL and cooled, giving a third solid, identical by mp and TLC ($CHCl_3$/MeOH, 9:1) with A, which was then combined with A: A, 4.8 g, mp 262–265 °C, R_f 0.25; B, 1.5 g, mp 268–272 °C, R_f 0.5. Recrystallization of A from DMF gave 2.6 g of the desired [1,5-*c*] isomer **8-9**: mp 267–269 °C; MS M^+ = 256.0729, Δ = 2.1 mmu.

Recrystallization of B gave 0.90 g of unrearranged 5-(3-nitrophenyl)[1,2,4]triazolo[4,3-*c*]pyrimidin-3-amine (**10**, Ar = 3-$NO_2C_6H_4$): mp 281–284 °C; MS M^+ = 256.0715, Δ = 2.1 mmu. Anal. ($C_{11}H_8N_6O_2 \cdot {}^1/_8H_2O$) C, H, N.

The ^{1}H NMR spectrum for isomers A and B allowed assignment of structures based on the following reasoning. Protons in the 2- and 6-position on the phenyl ring of A were shifted downfield to δ 9.50 and δ 8.92, respectively, verus δ ~8.8 for both 2 and 6 phenyl protons in isomer B. Since the NH_2 moiety in isomer A (rearranged) had no crowding effects on the planarity, the entire system was flat and in conjugation, allowing hetero nitrogens at 4 and 6 to deshield the 2 and 6 phenyl protons. In isomer B (unrearranged) the crowding from the NH_2 moiety distorts the planarity of the molecule and no conjugated deshielding was observed for the 2 and 6 phenyl protons.

Method N, 2-[3-(Trifluoromethyl)phenyl]-4-pyrimidinamine (13). A mixture of 12.49 g (0.0483 mol) of 4-chloro-2-[3-(trifluoromethyl)phenyl]pyrimidine (**3-6**) and 120 mL of EtOH was placed into an open bomb and cooled to −30 °C in a dry ice/acetone bath. After saturating the mixture with NH_3, the bomb was sealed and heated to 142–169 °C for 10 h. The reaction mixture was evaporated and the residue was taken up in $CHCl_3$. After washing with aqueous $KHCO_3$, the organic layer was dried and evaporated to a solid. Recrystallization from Et_2O/hexane gave 6.86 g of a solid, mp 79–81 °C. Recrystallization of the mother liquor residue from CCl_4 gave a second crop of **13** (4.21 g), mp 79.5–81 °C (96%). Anal. ($C_{11}H_8F_3N_3$) C, H, F, N.

Method O, *N*,*N*-Dimethyl-*N*′-[2-[3-(trifluoromethyl)phenyl]-4-pyrimidinyl]methanimidamide (14). A solution of 10.28 g (0.0430 mol) of 2-[3-(trifluoromethyl)phenyl]-4-pyrimidinamine (**13**) in 61 mL (54.7 g, 0.46 mol) of *N*,*N*-dimethylformamide dimethyl acetal was heated on a steam bath for 45 min. The reaction solution was concentrated under vacuum and the residue was recrystallized from MeOH to give 9.02 g of product, mp 99.5–101.5 °C. A second crop was obtained from the mother liquors (2.24 g), mp 100–101.5 °C (89%). Anal. ($C_{14}H_{13}F_3N_3$) C, H, F, N.

Method P, *N*-Hydroxy-*N*′-[2-[3-(trifluoromethyl)phenyl]-4-pyrimidinyl]methanimidamide (15). To a stirred solution of 3.68 g (0.0531 mol) of hydroxylamine hydrochloride in 85 mL of MeOH was added 10.40 g (0.0354 mol) of *N*,*N*-dimethyl-*N*′-[2-[3-(trifluoromethyl)phenyl]-4-pyrimidinyl]-methanimidamide (**14**). A clear solution resulted, which gave a precipitate in 2 min. After stirring at room temperature for 20 min, the mixture was cooled to 0 °C and the precipitate was collected. Recrystallization from EtOAc gave a first crop of 7.76

g, mp 164–166 °C. Concentration of the mother liquor gave a second crop of 3.20 g, mp 159–162.5 °C. Anal. ($C_{12}H_9F_3N_4O \cdot {}^1/_4H_2O$) C, H, F, N.

Method Q, 5-[3-(Trifluoromethyl)phenyl][1,2,4]triazolo-[1,5-*c*]pyrimidine (7-7). A 11.61 g (0.04050 mol) portion of *N*-hydroxy-*N'*-[2-[3-(trifluoromethyl)phenyl]-4-pyrimidinyl]-methanimidamide (**15**) and 360 mL of polyphosphoric acid were mixed, and the mixture was heated at 100 °C, with stirring, for 2.5 h. The reaction was poured onto ice and neutralized first with concentrated aqueous KOH, then solid K_2CO_3. The product (8.35 g) was collected and air-dried, mp 89–98 °C. This solid was twice recrystallized from cyclohexane, some of the insoluble material being filtered off to get 2.25 g of product, mp 81–94 °C. Further recrystallization from EtOH gave 1.30 g of product, mp 99.5–101.5 °C. A second crop was obtained from the mother liquors (0.22 g, 61%), mp 101–103 °C (anal. in Table VII).

Method R, *N*-[5-[3-(Trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (7-3). After refluxing of a solution of 15.37 g (0.05509 mol) of 2-amino-5-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*c*]pyrimidine (**8-10**), 33 mL of HoAc, and 33 mL (35.6 g, 0.35 mol) of Ac_2O for 1.5 h, the reaction was cooled to room temperature. The product crystallized out and was collected. Next the product was triturated with Et_2O and washed with Et_2O, EtOH, and again with Et_2O. After air-drying, 16.43 g of white, fluffy crystals, mp 221–222.5 °C, of **7-3** was obtained. Recrystallization of the wash residues from EtOH gave an additional 0.57 g, mp 215–218.5 °C (96%) (anal. in Table VII).

Method S, *N*-Methyl-*N*-[5-[3-(trifluoromethyl)phenyl]-[1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (7-4). A mixture of 8.00 g (0.0249 mol) of *N*-[5-[3-(trifluoromethyl)-phenyl][1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (**7-3**), 75 mL of sieve-dried (3A) DMF and 1.31 g (0.0274 mol) of 50% NaH/oil was stirred until the effervescence stopped and a dark brown solution resulted (1.5 h). Then 3.10 mL (7.07 g, 0.0498 mol) of MeI was added, discharging the color with a mild exotherm. After 0.5 h, the mixture was heated on a steam bath for 10 min, giving a saltlike precipitate.

A few milliliters of EtOH was added to decompose any excess hydride and the reaction mixture was distributed between $CHCl_3$ and H_2O, the pH of the H_2O layer being adjusted to 8. After separation, the organic layer was dried (Na_2SO_4) and evaporated to a crystalline residue. Recrystallization from CCl_4, with filtration of the hot solution through a pad of hydrous magnesium silicate, gave 4.62 g of **7-9**, mp 122.5–124 °C. A second crop was obtained by recrystallizing the mother liquor residue from MeOH (1.72 g), mp 123–124.5 °C (76%) (anal. in Table VII).

Method T, *N*-Methyl-5-[3-(trifluoromethyl)phenyl]-[1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (7-5). *N*-Methyl-*N*-[5-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (**7-4**, 3.35 g, 0.0100 mol) was dissolved in 100 mL of THF, and 50 mL of EtOH, and 4.15 ML (0.025 mol) of 6 N HCl. After standing at room temperature for 7 days, aqueous $KHCO_3$ was added and the mixture was permitted to evaporate. The residue was triturated with aqueous $KHCO_3$ and collected (3.21 g), mp 158–166 °C. Recrystallization from 40 mL of EtOAc gave 1.80 g of light yellow crystals, mp 177.5–179 °C. Upon concentration, the mother liquors gave a second crop, which was recrystallized from EtOAc (0.27 g), mp 177–178 °C (61%) (anal. in Table VII).

Method U, *N*,*N*-Dimethyl-5-[3-(trifluoromethyl)-phenyl][1,2,4]triazolo[1,5-*c*]pyrimidinamine (7-6). To a mixture of 0.308 g (0.00105 mol) of *N*-methyl-5-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (**7-5**) and 0.60 g (0.0013 mol) of 50% NaH/oil was added 5 mL of DMF. A dark red color formed, and the solids were dissolved. After 15 min, 0.10 mL (0.23 g, 0.0016 mol) of MeI was added. As the color did not discharge, the solution was heated on a steam bath until it was colorless (30 min). On concentration, the residue crystallized. Trituration with H_2O left 0.339 g of solid, which was purified by preparative TLC on silica gel ($MeOH/CHCl_3$ 1:19). Recrystallization of the main band from 50 mL of hexane, boiled down to 10 mL, gave 0.138 g (43%) of white crystals, mp 104–105 °C (anal. in Table VII).

Method V, 1-Chloro-3-[[5-[3-(trifluoromethyl)phenyl]-[1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]amino]-2-propanol (7-2). A solution of 1.43 g (0.00426 mol) of *N*-(oxiranylmethyl)-5-[3-(trifluoromethyl)phenyl][1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (**7-1**) in 10 mL of THF was treated with 2 mL of 6 N HCl. The clear solution was permitted to stand for 3.25 h. After neutralization of the reaction with aqueous $KHCO_3$, the solvent was removed under vacuum at 35 °C and the part-crystalline residue was taken up in $CHCl_3$ with warming. A small amount of H_2O was separated and the $CHCl_3$ was dried (Na_2SO_4) and concentrated under vacuum. Recrystallization of this residue from MeOH gave 0.45 g of white crystals, mp 141–142 °C. Concentration of the mother liquor gave a second crop (0.24 g, 43%), mp 140–140.5 °C (anal. in Table VII). TLC of the crude reaction mixture showed only traces of other products and no glycol could be isolated. ^1H NMR before and after deuterium exchange showed that the chlorine was in the terminal position: ^1H NMR (Me_2SO-d_6) δ 3.30–3.50 (m, 2, CH_2N), 3.60 (dd, 1 H, J = 5.2 and 11.2 Hz, CH_2Cl), 3.72 (dd, 1 H, J = 4.0 and 11.2 Hz, CH_2Cl), 3.97 (m, 1 H, CHOH, pattern simplified after exchange of OH), 5.35 (d, 1 H, J = 5.3 Hz, OH exchanges), 7.20 (t, 1 H, J = 5.8 Hz NH), 7.48 (d, 1 H, J = 6.4 Hz, H-5), 7.82 (t, 1 H, J = 7.9 Hz, H-5-Ph), 7.96 (d, 1 H, J = 7.9 Hz, H-4-Ph), 8.26 (d, 1 H, J = 6.4 Hz, H-6), 8.87 (d, 1 H, J = 7.9 Hz, H-6-Ph), 8.97 (s, 1 H, H-2-Ph). MS M^+ = 371.

Method W, *N*-[5-(3-Aminophenyl)-8-methyl[1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (7-12). A partial solution of 620 mg (1.95 mmol) of *N*-[8-methyl-5-(3-nitrophenyl)[1,2,4]-triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (**7-11**) in 240 mL of EtOH with 500 mg of 10% Pd on C was hydrogenated at 45 °C and 50 lbs in a Parr apparatus for 30 h. The catalyst was filtered off and thoroughly washed with EtOH. Concentrating the filtrate gave 400 mg of a beige solid. Two recrystallizations from EtOH produced 150 mg (27%) of light yellow crystals, mp 249–251 °C (anal. in Table VII).

Method X, *N*-[8-Methyl-5-[3-[(4-methylphenyl)-sulfonyl]phenyl][1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (7-18). A solution of 282 mg (1.0 mmol) of *N*-[5-(3-aminophenyl)-8-methyl[1,2,4]triazolo[1,5-*c*]pyrimidin-2-yl]acetamide (**7-12**) in 100 mL of pyridine was stirred and treated with 315 mg (1.65 mmol) of *p*-toluenesulfonyl chloride. After standing overnight, the reaction was heated on a steam bath for 0.5 h. After concentration of the reaction under vacuum, the residue was washed with Et_2O, giving 150 mg (60%) of product. A sample was recrystallized from EtOAc/cyclohexane for analysis, giving white crystals, mp 215–218 °C (anal. in Table VII).

Method Y, 5-(3-Ethynylphenyl)[1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (8-5). A suspension of 2.0 g (6.9 mmol) of 5-(3-bromophenyl)[1,2,4]triazolo[1,5-*c*]pyrimidin-2-amine (**8-13**) in 45 mL of Et_3N was flushed with argon for 15 min. Then 0.034 g of $Pd(OAc)_2$ and 0.068 g of $P(Ph)_3$ followed by 1.52 mL (1.06 g, 10.8 mmol) of ethynyltrimethylsilane were added. The mixture was stirred and heated under reflux for 20 h. After cooling and evaporation of the reaction, the residue was taken up in $CHCl_3$ and washed with aqueous $KHCO_3$, dried (Na_2SO_4), and evaporated to give 2.0 g of a brown glass, primarily one spot on TLC. The glass was deprotected by dissolving it in 50 mL of MeOH, adding 200 mg of K_2CO_3, and stirring the mixture overnight. Evaporation of the solution was followed by taking up the residue in 100 mL of $CHCl_3$ and washing with aqueous $KHCO_3$. The organic layer was separated, dried (Na_2SO_4), and filtered through a pad of hydrous magnesium silicate. Evaporation of the filtrate left 1.0 g of solid. Recrystallization of the solid from $CHCl_3$/cyclohexane gave 425 mg (26%) of beige crystals, mp 170–172 °C (anal. in Table VIII).

Method Z, 3-(4-Chloro-2-pyrimidinyl)benzaldehyde (3-1) and 4-Chloro-2-[3-(dichloromethyl)phenyl]pyrimidine (3-24). Overnight heating of 5.30 g (0.0193 mol) of 2-[3-(diethoxymethyl)phenyl]-4(1*H*)-pyrimidinone (**2-22**) in 30 mL of $POCl_3$ on a steam bath gave a solution. After concentration under vacuum, the solid residue was taken up in $CHCl_3$ and passed through a hydrous magnesium silicate pad. Evaporation left 3.1 g of solid showing two spots on TLC ($CHCl_3$). Trituration with Et_2O and evaporation gave 400 mg of substance A, mp 136–138 °C, plus Et_2O-insoluble substance B, 3.0 g (90%), mp 46–48 °C. Substance A was shown by analysis, IR, and ^1H NMR to be **3-24** (anal. in Table III). In the same fashion, B was shown to be **3-1** (anal. in Table III).

Method AA, 3-(4-Chloro-2-pyrimidinyl)benzenemethanol (3-3). 3-(4-Chloro-2-pyrimidinyl)benzaldehyde (**3-1**, 1.00 g, 4.56 mmol) was placed in 230 mL of 2-PrOH and 0.32 g (9.4 mmol) of freshly ground $NaBH_4$ pellets was added. The mixture was stirred in a room temperature water bath until the reaction was completed (3 h, TLC). Excess $NaBH_4$ was destroyed with 6 N HCl, which was then neutralized with aqueous $NaHCO_3$. The solvent was removed under vacuum and the residue was partitioned between EtOAc and H_2O. After drying of the organic phase (Na_2SO_4) and concentration of it under vacuum, 1.1 g of oil remained, which eventually crystallized, mp 112–118 °C. A sample was chromatographed (silica, $CHCl_3$) for analysis, mp 91–93 °C (anal. in Table III).

Method BB, 3-(2-Amino[1,2,4]triazolo[1,5-c]pyrimidin-5-yl)benzaldehyde (8-19). A mixture of 1.00 g (4.00 mmol) of 3-(2-amino[1,2,4]triazolo[1,5-c]pyrimidin-5-yl]benzenemethanol (**8-15**), 100 mL of $CHCl_3$, and 4.15 g (16.0 mmol) of freshly prepared (dimethylamino)pyridinium chlorochromate[21] was stirred at ambient temperature for 4 days. The reaction mixture was filtered and the filtrate was passed through a 3-cm pad of silica gel. Only a trace of product was in the first filtrate. Washing the pad with 2% MeOH/$CHCl_3$ gave, on evaporation, 400 mg of fairly pure product. A third washing, again with 2% MeOH/$CHCl_3$, eluted 200 mg of 1:1 product and starting material. Recrystallization of the product fraction from EtOAc gave 225 mg (23%) of **8-19**, mp 211 °C (anal. in Table VIII).

Method CC, 2-Chloro-8-methyl-5-(3-nitrophenyl)[1,2,4]triazolo[1,5-c]pyrimidine (7-15). After heating of 4.06 g (0.0150 mol) of 2-amino-8-methyl-5-(3-nitrophenyl)[1,2,4]triazolo[1,5-c]pyrimidine (**5-1**) in 150 mL of concentrated HCl to boiling, a little insoluble material was filtered off and the filtrate was cooled to −40 °C. Next, 1.10 g (0.0160 mol) of $NaNO_2$ in 30 mL of H_2O was added dropwise with stirring over a few minutes. The reaction mixture was stirred at −40 °C for 1.5 h, then 4.50 g (0.0264 mol) of cupric chloride dihydrate in 50 mL of H_2O was added dropwise and the reaction was stirred for 10 min more. After allowing the reaction to slowly come to room temperature overnight, it was poured into 160 mL of H_2O and neutralized with solid $KHCO_3$. Extraction of the reaction with three 300-mL portions of EtOAc, combining, and drying (Na_2SO_4) the extracts gave, on evaporation, a solid. Recrystallization of the solid from EtOH gave 1.9 g (43%) of light yellow crystals, mp 188–190 °C (anal. in Table VII).

Method DD, 8-Methyl-2-(4-morpholinyl)-5-(3-nitrophenyl)[1,2,4]triazolo[1,5-c]pyrimidine (7-16). 2-Chloro-8-methyl-5-(3-nitrophenyl)[1,2,4]triazolo[1,5-*d*]pyrimidine (**7-15**, 1.00 mg, 0.345 mmol) was added to 20 mL of morpholine and refluxed overnight. After cooling, the reaction was concentrated under vacuum to give a light yellow solid. Recrystallization from EtOH gave 30 mg (20%) of beige crystals, mp 210–213 °C (anal. in Table VII).

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Method EE, 3-(2-Amino[1,2,4]triazolo[1,5-c]pyrimidin-5-yl)-1-methylpyridinium Iodide (6-5). Upon refluxing of a solution of 50 mg (0.24 mmol) of 5-(3-pyridinyl)[1,2,4]triazolo[1,5-c]pyrimidin-2-amine (**6-4**), 10 mL of EtOH, and 1 mL (16 mmol) of MeI for 0.5 h, a precipitate appeared. Reflux was continued for an additional 2 h and then the solid was collected. After washing with EtOH and then Et_2O, the product was air-dried to leave 47 mg of **6-5** (77%), mp 260–270 °C dec (anal. in Table VI).

Method FF, *N*,8-Dimethyl-5-[3-(methylamino)phenyl][1,2,4]triazolo[1,5-c]pyrimidin-2-amine (7-19). A solution of 1.1 g (4.6 mmol) of 5-(3-aminophenyl)-8-methyl[1,2,4]triazolo[1,5-c]pyrimidin-2-amine (**5-2**), 40 mL of triethyl orthoformate, and 2 drops of trifluoroacetic acid was refluxed for 4 h and then concentrated under vacuum. The residual yellow gum was immediately dissolved in EtOH at 0 °C and 460 mg (12.1 mmol) of $NaBH_4$ was added. Next, the reaction was slowly (15 min) brought to reflux for 3 h. After evaporation of the solvent, the residue was distributed between EtOAc and H_2O. The organic phase was dried (Na_2SO_4) and concentrated under vacuum to a yellow oil. Chromatography, on preparative TLC plates (silica gel, EtOAc) gave 170 mg of product, which was recrystallized from EtOAc to give 90 mg (7%) of **7-19**, mp 169–170.5 °C (anal. in Table VII).

Method GG, 3-(2-Amino[1,2,4]triazolo[1,5-c]pyrimidin-5-yl)benzoic Acid (8-4). 3-(2-Amino[1,2,4]triazolo[1,5-c]pyrimidin-5-yl)benzenemethanol (**8-15**, 200 mg, 6.80 mmol) was dissolved in 150 mL of Me_2CO and ~5 mL of Jones reagent[22] was added dropwise with stirring. After 1 h, the excess reagent was destroyed with a few milliliters of 2-PrOH and stirred for 0.5 h more. The mixture was dried by adding $MgSO_4$ and then was filtered through a pad of hydrous magnesium silicate. When the filtrate had evaporated, 100 mg of a crystalline residue remained. Recrystallization from EtOH/10% DMF gave 50 mg of gray crystals (25%) mp 340–342 °C (anal. in Table VIII).

Method HH, 5-(4-Pyridinyl)[1,2,4]triazolo[1,5-c]pyrimidin-2-amine (6-7). To 17.5 L of water was added 100.8 g of Na_2HPO_4 and 61.84 g of NaH_2PO_4 to form a buffer. Then, 96.7 g (0.42 mol) of 5-(4-pyridinyl)[1,2,4]triazolo[1,5-c]pyrimidin-2-amine *pyridine*-1-oxide (**6-8**) and 369 g (2.12 mol) of sodium dithionite were added. The suspension was heated to 94 °C and stirred for 45 min until all the starting material had disappeared. After cooling to room temperature overnight, the crystalline product was collected, washed with water, and air-dried to afford 52 g (58%) of product **6-7**, mp >250 °C dec (anal. in Table VI).

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