yellow needle crystals, mp 142–143°. *Anal.* ($C_{10}H_8N_2O$) C, H, N.

Ethyl *p*-N-[2-(3-Methylquinoxalinyl)methylene]aminobenzoate (9b).—The aldehyde **8b** (3.0 g, 0.017 mole) and ethyl *p*-aminobenzoate (3.0 g, 0.018 mole) were refluxed in C_6H_6 (50 ml) for 15 hr, using a Dean–Stark H_2O trap to remove the H_2O formed. The solution was evaporated to dryness under reduced pressure. The residue was dissolved, using a small amount of EtOAc, and cooled to give fine yellow crystals which were collected (0.7 g, 50%) and recrystallized from EtOAc to give yellow needle crystals, mp 123–124°. *Anal.* ($C_{19}H_{17}N_3O_2$) C, H, N.

Ethyl *p*-N-[2-(3-Methylquinoxalinyl)methyl]aminobenzoate (10b).—The Schiff base **9b** (0.35 g, 1.1 mmoles) was suspended in absolute MeOH (20 ml) and cooled in an ice bath. To the suspension, $NaBH_4$ (0.083 g, 2.2 mmoles) was added in small portions within 30 min with stirring. The solution became clear after half of the $NaBH_4$ had been added and the desired product started to precipitate toward the end of the addition. The mixture was stirred at room temperature for another 3–4 hr. H_2O (10 ml) was added and the crystals were collected (0.32 g, 91%). For analysis the sample was recrystallized from MeOH to give white needle crystals, mp 143–144°. *Anal.* ($C_{19}H_{19}N_3O_2$) C, H, N.

Ethyl *p*-N-[2-(3-Methyl-1,2,3,4-tetrahydroquinoxalinyl)methyl]aminobenzoate (11b).—PtO_2 (0.5 g) was prereduced in HOAc (20 ml) in a microhydrogenation unit and a solution of **10b** (0.5 g, 1.57 mmoles) in HOAc (10 ml) was added. The solution was hydrogenated until 2 equiv of H_2 had been absorbed (*ca.* 20 min). The catalyst was removed by filtration and the solvent was removed by lyophilization. The oily residue was dissolved in Et_2O (15 ml), washed with 5% NaOH aqueous solution and H_2O, and dried (Na_2SO_4). The solution was evaporated to 5 ml and was found to contain three major components by tlc. The separation was carried out in a preparative tlc plate (Al_2O_3, Brinkman, 20 × 20 cm, 1.5 mm thick, petroleum ether–EtOAc 5:1) by multiple-development technique to give 0.2 g (40%) of the desired product as pale yellow flakes after vacuum drying at room temperature. It could not be purified by recrystallization and softened when heated to 50–52°. The ditosylate was prepared according to the general method, mp 196–197°. *Anal.* ($C_{38}H_{34}N_3O_6S_2$) C, H, N.

Ethyl *p*-N-[2-(3-Methyl)quinoxalinyl)methyl]-N-thyminyl-aminobenzoate (22).—The secondary amine **10b** (0.57 g, 1.57 mmoles), 5-bromomethyluracil (0.32 g, 1.57 mmoles), Na_2CO_3 (0.16 g, 1.57 mmoles), and a catalytic amount of NaI were refluxed in dry THF (50 ml) for 14 hr. The solution was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 20 ml of hot MeOH. The white precipitate was collected after cooling and recrystallized from MeOH to give 0.3 g (43%) of white fine crystals, mp 216–217 dec. *Anal.* ($C_{24}H_{23}N_5O_4$) C, H, N.

2-*p*-Carbethoxyphenyl-3-(5′-uracil)-9-methylhexahydroimidazo[1,5-*a*]quinoxaline (23).—The amine **11b** (0.18 g, 0.55 mmole) and 5-formyluracil (0.07 g, 0.55 mmole) were refluxed in 30 ml of absolute MeOH under N_2 for 27 hr. The solution was evaporated to small volume and cooled overnight. The precipitate was collected (0.16 g, 70%) and recrystallized from MeOH–EtOH solvent to give pale yellow fine crystals, mp 237–238°. *Anal.* ($C_{24}H_{25}N_5O_4$) C, H, N.

Acknowledgment.—The authors wish to acknowledge the assistance of Professor James D. McChesney during the absence of M. P. M., Mrs. Wen Ho, Mrs. Richard Wiersema, and Mrs. Phyllis Shaffer for the biological studies, and Mr. James Haug for technical assistance.

Irreversible Enzyme Inhibitors. CLXVI.[1,2] Active-Site-Directed Irreversible Inhibitors of Dihydrofolic Reductase Derived from 2,4-Diamino-5-(3,4-dichlorophenyl)pyrimidine with 6 Substituents and Some Factors in Their Cell Wall Transport

B. R. BAKER AND NICOLAAS M. J. VERMEULEN[3]

Department of Chemistry, University of California at Santa Barbara, Santa Barbara, California 93106

Received August 14, 1969

Fourteen 6-substituted derivatives of 2,4-diamino-5-(3,4-dichlorophenyl)pyrimidine were synthesized for comparison with the 6-methyl derivative (**1d**) (used as a standard) as reversible inhibitors of L1210 dihydrofolic reductase and for kill of L1210 cell culture; the best compounds were the 6-phenylbutyl (**5**) and 6-(α-naphthylethyl) (**6**) derivatives. However, **5** and **6** were still 100- and 300-fold less effective then the 6-methyl derivative (**1d**) against L1210 cell culture. Even less effective were the 6-phenoxymethyl (**2**) and 6-phenethyl (**3**) derivatives. In order to determine the effect of an SO_2F moiety, three of these 6-substituted pyrimidines were converted to irreversible inhibitors. The 6-(*p*-fluorosulfonyl)phenethyl (**17**) derivative was an excellent irreversible inhibitor of L1210 dihydrofolic reductase which also showed good specificity with no irreversible inhibition of the enzyme from mouse liver; however, **17** was no more effective than the parent **3** against L1210 cell culture. As previously noted in another series of compounds, the SO_2F moiety slows the rate of cell wall penetration, but increases the effect on the target enzyme when the molecule is an active-site-directed irreversible inhibitor.

Among the numerous active-site-directed irreversible inhibitors[4] of dihydrofolic reductase from L1210 mouse leukemia, a few showed specificity with a low amount of inactivation of the enzyme from normal liver, spleen, and intestine of the mouse; among these selective compounds was **1a**.[5,6] Although **1a** was a reasonably specific irreversible inhibitor for the L1210 enzyme, its reversible inhibition of the L1210/DF8 enzyme of $I_{50} = 6K_i = 0.82\ \mu M$ was considered to be too high to be useful *in vivo*.[5] Therefore a series of compounds re-

(1) This work was generously supported by Grant CA-08695 from the National Cancer Institute, U. S. Publich Health Service.

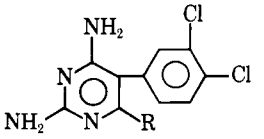
(2) (a) For the previous paper of this series see B. R. Baker and M. Cory, *J. Med. Chem.*, **12**, 1053 (1969). (b) For the previous paper on this enzyme see B. R. Baker, E. E. Janson, and N. M. J. Vermeulen, *ibid.*, **12**, 898 (1969).

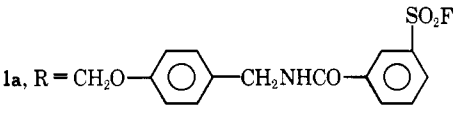
(3) N. M. J. V. wishes to thank the Council of Scientific and Industrial Research, Republic of South Africa, for a tuition fellowship.

(4) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley and Sons, Inc., New York, N. Y., 1967.

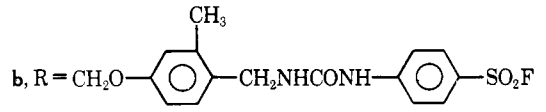
(5) B. R. Baker, G. J. Lourens, R. B. Meyer, Jr., and N. M. J. Vermeulen, *J. Med. Chem.*, **12**, 67 (1969), paper CXXXIII of this series.

(6) B. R. Baker and P. C. Huang, *ibid.*, **11**, 639 (1968), paper CXX of this series.

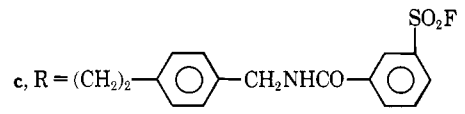




1a, R = CH_2O–CH_2NHCO–



b, R = CH_2O–$CH_2NHCONH$–



c, R = $(CH_2)_2$–CH_2NHCO–

d, R = CH_3

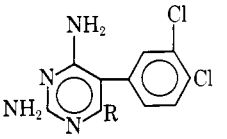
lated to **1a** with varying bridges to the SO_2F moiety were synthesized and evaluated.[5,7-13] A number were found to have $I_{50} = 6\ K_i < 0.1\ \mu M$ in the desired range; for example, **1b** and **1c**[11] had $I_{50} = 0.086$ and $0.025\ \mu M$, respectively.

Most of these compounds have now been measured for their ability to kill L1210 cells in culture;[14] as a first approximation these data can be related to the ability of the compounds to penetrate the L1210 cell wall.[2b,15] The concentrations for 50% cell kill (ED_{50}) by **1a–c** were 4, 0.5, and 0.9 μM, respectively. As a second approximation, differences in I_{50} between compounds can be normalized by comparing ED_{50}/I_{50} ratios;[15] **1a–c** had ED_{50}/I_{50} ratios of 5, 6, and 36, respectively. These ratios are poor when compared to the pyrimethamine analog **1d** with R = Me that is used as a standard;[2b] **1d** had $I_{50} = 0.01\ \mu M$, $ED_{50} = 2 \times 10^{-5}\ \mu M$ and $ED_{50}/I_{50} = 0.002$.[15]

Since **1a–c** and related irreversible inhibitors showed such poor transport compared to **1d**, studies were initiated to determine which parts of these large 6 substituents were detrimental to transport. The results are the subject of this paper.

Placement of a phenoxy group on the 6-methyl of **1d** gave **2** which was fivefold less effective as a reversible inhibitor of dihydrofolic reductase, but 4×10^5 times less effective than **1d** in cell culture (Table I); when the normalized ED_{50}/I_{50} ratios were compared, **2** was 100,000-fold less effective than the standard, **1d**. Comparison of the parent **2** and the irreversible inhibitor **1a** derived from it showed that **1a** was only 20-fold more effective than **2**; thus the poor transport of **1a** is readily accounted for by the phenoxy substitution on the 6-methyl group of **1d**. Similarly, the relatively poor inhibition of L1210 cell culture by **1c** is readily accounted for by the comparison of **1c** with **3** and **1d**; the loss is due to the 15,000-fold loss between **1c** and **3**.

TABLE I
INHIBITION OF L1210 DIHYDROFOLIC REDUCTASE AND L1210 CELL CULTURE BY



No.	R	I_{50},[a,b] μM	ED_{50},[c] μM	ED_{50}/I_{50}
1a	*p*-$CH_2OC_6H_4CH_2NHCOC_6H_4SO_2F$-*m*	0.82[d]	4	5
1b	4-CH_2O-2-$MeC_6H_3CH_2NHCONHC_6H_4SO_2F$-*p*	0.086[e]	0.5	6
1c	*p*-$(CH_2)_2C_6H_4CH_2NHCOC_6H_4SO_2F$-*m*	0.025[f]	0.9	36
1d[g]	CH_3	0.010	2×10^{-5}	0.002
2	$CH_2OC_6H_5$	0.047	8	200
3	$(CH_2)_2C_6H_5$	0.032	1	30
4	$(CH_2)_3C_6H_5$	0.030	0.4	10
5	$(CH_2)_4C_6H_5$	0.020	0.003	0.2
6	$(CH_2)_2C_{10}H_7$-α	0.080	0.05	0.6
7	$(CH_2)_2C_{10}H_7$-β	0.22	0.6	3
8	*p*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_5$	0.15	0.3	2
9	$CH_2OC_{10}H_7$-α	0.028	0.7	30
10	$CH_2OC_{10}H_7$-β	0.060	7	100
11	$CH{=}CHC_6H_5$	0.027	7	300
12	$CH{=}CHCH_2C_6H_5$	0.020	0.7	40
13	$(CH{=}CH)_2C_6H_5$	0.091	0.9	10
14	$CH{=}CHC_{10}H_7$-α	0.039	9	200
15	$CH{=}CHC_{10}H_7$-β	0.12	0.9	8

[a] The technical assistance of Diane Shea with these assays is acknowledged. [b] I_{50} = concentration for 50% inhibition of mouse liver dihydrofolic reductase when assayed with 6 μM dihydrofolate and 0.15 M KCl in pH 7.4 Tris buffer as previously described;[5] little difference is seen in reversible inhibition of the enzyme from L1210/DF8 and mouse liver. [c] Concentration for 50% kill of L1210 cell culture. [d] Data from ref 5 on L1210 enzyme. [e] Data from ref 12 on L1210 enzyme. [f] Data from ref 11 on L1210 enzyme. [g] Data from ref 15.

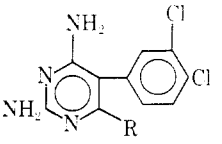
Studies were then made to see what large groups could be placed on the 6-methyl group of **1d** that would give good transport characteristics, but would also allow building an irreversible inhibitor. As the phenyl group was increased in distance from two CH_2 (**3**) to three CH_2 (**4**) or four CH_2 (**5**), the ED_{50}/I_{50} became more effective in a ratio of 30, 10, 0.2, respectively; that is, the 6-phenylbutylpyrimidine (**5**) was 300-fold more effective against L1210 cell culture than the 6-phenethylpyrimidine (**3**).

Conversion of the 6-phenethyl group of **3** to a 6-(α-naphthylethyl)pyrimidine (**6**) increased transport effectiveness by a factor of 50-fold over **3**; the corresponding 6-(β-naphthylethyl)pyrimidine (**7**) was only twofold more effective than **3** in cell culture and tenfold more effective when normalized by comparison of ED_{50}/I_{50}. Similar trends were seen when the phenoxymethyl moiety of **2** was converted to α-naphthyloxymethyl (**9**) or β-naphthyloxymethyl (**10**).

Placement of a phenylethyl group on the *para* posi-

(7) B. R. Baker and N. M. J. Vermeulen, *J. Med. Chem.*, **12**, 74 (1969), paper CXXXIV of this series.
(8) B. R. Baker and N. M. J. Vermeulen, *ibid.*, **12**, 79 (1969), paper CXXXV of this series.
(9) B. R. Baker and N. M. J. Vermeulen, *ibid.*, **12**, 82 (1969), paper CXXXVI of this series.
(10) B. R. Baker and N. M. J. Vermeulen, *ibid.*, **12**, 86 (1969), paper CXXXVII of this series.
(11) B. R. Baker and N. M. J. Vermeulen, *ibid.*, **12**, 89 (1969), paper CXXXVIII of this series.
(12) B. R. Baker and N. M. J. Vermeulen, *ibid.*, **12**, 680 (1969), paper CLIVII of this series.
(13) B. R. Baker and N. M. J. Vermeulen, *ibid.*, **12**, 684 (1969), paper CLIVIII of this series.
(14) We wish to thank Dr. Florence White for these results obtained by Dr. Philip Himmelfarb of Arthur D. Little, Inc.
(15) For a more detailed discussion see B. R. Baker and R. B. Meyer, Jr., *J. Med. Chem.*, **12**, 688 (1969), paper CLIV of this series.

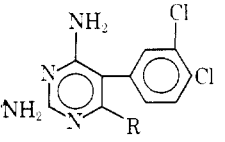
Table II
Inhibition[a] of Dihydrofolic Reductase by



No.	R	Enzyme source	I_{50},[b] μM	Inhib, μM	Time, min	% inactvn[d]	ED_{50},[c] μM	ED_{50}/I_{50}
16	$CH_2OC_6H_4SO_2F$-*p*	L1210/DF8	0.021	0.10	60	43	1	50
		Liver		0.10	60	8		
17	$(CH_2)_2C_6H_4SO_2F$-*p*	L1210/DF8		0.08	2, 30	89, 89	0.6	20[e]
		Liver	0.040	0.12	60	0		
18	$CH{=}CHC_6H_4SO_2F$-*p*	L1210/DF8		0.24	60	33	98	800
		Liver	0.12	0.36	60	5		
19	*p*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_4SO_2F$-*p*	L1210/DF8	0.046	0.16	2, 4	97, 99	2	50[e]
				0.046	60	84		
		Liver		0.16	60	52		
				0.046	60	5		
20	*p*-$CH{=}CHC_6H_4CH{=}CHC_6H_4SO_2F$-*p*	L1210/DF8		0.60	60	36	4	10
		Liver	0.30	0.90	60	20		
21	*p*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_4SO_2F$-*m*	L1210/DF8	0.036	0.072	60	92	0.1	3
		Liver		0.11	60	67		
22	*m*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_4SO_2F$-*p*	L1210/DF8	0.024	0.05	60	82	0.9	40
		Liver		0.07	60	6		
23	*m*-$CH{=}CHC_6H_4CH{=}CHC_6H_4SO_2F$-*p*	L1210/DF8	0.31	0.62	60	69		
		Liver		0.62	60	0		

[a–c] See corresponding footnotes in Table I. [d] Enzyme incubated with inhibitor at 37° in pH 7.4 Tris buffer containing 60 μM TPNH, then the remaining enzyme was assayed as previously described.[5] [e] From a six-point time study.[5]

Table III
Physical Properties of



No.	R	Method	Yield, %	Mp, °C	Formula
2	$CH_2OC_6H_5$	A	50[a]	175–177	$C_{17}H_{14}Cl_2N_4O$
3	$(CH_2)_2C_6H_5$	C	85[b]	194–195	$C_{18}H_{16}Cl_2N_4$
4	$(CH_2)_3C_6H_5$	C	55[a]	251–254 dec	$C_{19}H_{18}Cl_2N_4 \cdot 0.5H_2SO_4$
5	$(CH_2)_4C_6H_5$	C	60[c]	248–250	$C_{20}H_{20}Cl_2N_4 \cdot 0.5H_2SO_4$
6	$(CH_2)_2C_{10}H_7$-α	C	48[b]	196–200	$C_{22}H_{18}Cl_2N_4$
7	$(CH_2)_2C_{10}H_7$-β	C	69[d]	180–182	$C_{22}H_{18}Cl_2N_4$
8	*p*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_5$	C	28[b]	>265 dec	$C_{26}H_{24}Cl_2N_4 \cdot 0.5H_2SO_4 \cdot 0.5H_2O$
9	$CH_2OC_{10}H_7$-α	A	63[e]	167–169	$C_{21}H_{16}Cl_2N_4O$
10	$CH_2OC_{10}H_7$-β	A	50[b]	158–160	$C_{21}H_{16}Cl_2N_4O$
11	$CH{=}CHC_6H_5$	B	45[a]	244–245	$C_{18}H_{14}Cl_2N_4$
12	$CH{=}CHCH_2C_6H_5$	B	32[a]	>198 dec	$C_{19}H_{16}Cl_2N_4 \cdot 0.5H_2SO_4$
13	$(CH{=}CH)_2C_6H_5$	B	63[f]	>189	$C_{20}H_{16}Cl_2N_4 \cdot 0.5H_2SO_4 \cdot 0.5EtOH$
14	$CH{=}CHC_{10}H_7$-α	B	45[e]	245–248	$C_{22}H_{16}Cl_2N_4$
15	$CH{=}CHC_{10}H_7$-β	B	69[d]	171–199	$C_{22}H_{16}Cl_2N_4$
29a	*p*-$CH{=}CHC_6H_4CHO$-*p*	D	46[c]	>300 dec	$C_{19}H_{14}Cl_2N_4O \cdot 0.5H_2SO_4 \cdot 0.5H_2O$
29b	*p*-$CH{=}CHC_6H_4CHO$-*m*	D	52[g]	>300 dec	$C_{19}H_{14}Cl_2N_4O \cdot 0.5H_2SO_4$
30a	*p*-$CH{=}CHC_6H_4CH{=}CHC_6H_5$	B	77[b]	>290 dec	$C_{26}H_{20}Cl_2N_4$

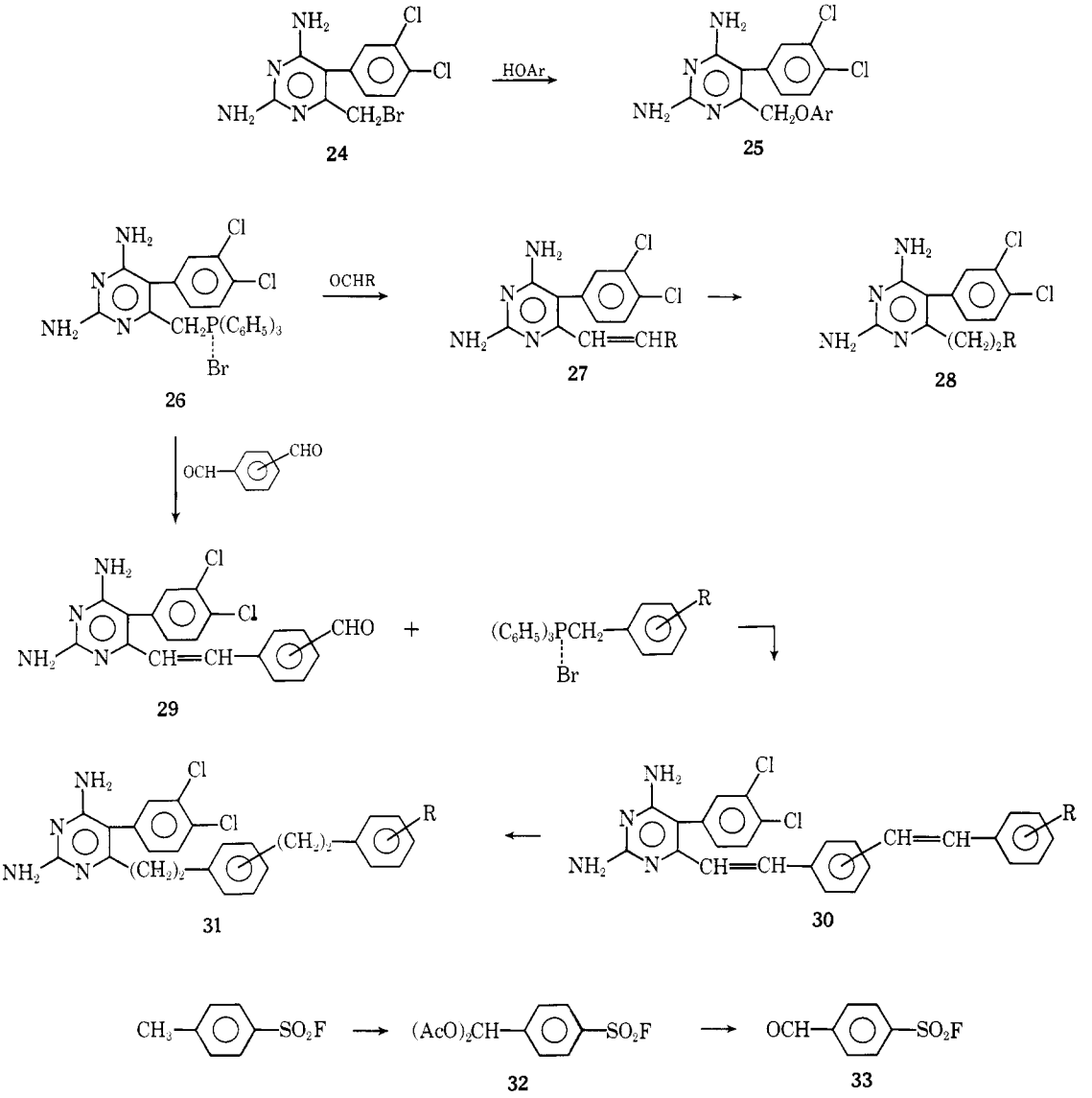
[a] Recrystallized from EtOH. [b] Recrystallized from EtOH–H_2O. [c] Recrystallized from MeOEtOH–H_2O. [d] Recrystallized from EtOH–H_2O, then from EtOH. [e] Recrystallized from EtOH–THF. [f] Recrystallized from MeOEtOH–EtOH. [g] Recrystallized from MeOEtOH.

tion of the 6-phenethyl group of **3** gave **8**; the latter was only threefold better in inhibiting L1210 cell culture than the parent **3** and 15-fold better when ED_{50}/I_{50} ratios were compared.

The vinyl intermediates in the synthesis of **3–7** were **11–15**, respectively. In each case, the vinyl intermediate was less effectively transported than the corresponding reduction product, the biggest difference being 300-fold between **6** and **14** and the smallest difference being between **7** and **15**; thus, decreasing the conformational flexibility of the 6 side chain led to poorer transport characteristics.

In order to determine the effect on transport of conversion to an irreversible inhibitor, three of the compounds (**2**, **3**, **8**) in Table I were selected mainly on the basis of ease of synthesis; results are listed in Table

SCHEME I



24 25 26 27 28 29 30 31 32 33

II. The fluorosulfonylphenoxymethyl derivative (**16**) was a rather poor irreversible inhibitor of the dihydrofolic reductase from L1210 mouse leukemia; **16** was fourfold more effective than the parent **2** when their ED_{50}/I_{50} ratios were compared. In contrast, the fluorosulfonylphenethyl derivative (**17**) was an excellent irreversible inhibitor of L1210 dihydrofolic reductase with good specificity; that is, **17** showed no inactivation of the mouse liver enzyme. Even though **17** was an excellent irreversible inhibitor it was essentially no more effective than its parent **3** against L1210 cell culture. These results with **16** and **17** support the previous experience with the SO_2F moiety;[2b] that is, the SO_2F moiety decreases rate of transport but increases the effect on the target inside the cell when it is part of an active-site-directed irreversible inhibitor.[4]

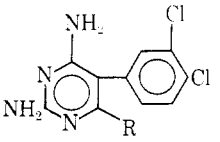
When **8** was converted to the SO_2F derivative, the resultant **19** was an excellent irreversible inhibitor of L1210 dihydrofolic reductase; however, transport was greatly decreased by a factor of >25. Therefore the terminal fluorosulfonylphenethyl group of **19** was moved to the *meta* position to give **22**. The latter was also an excellent irreversible inhibitor of L1210 dihydrofolic reductase with good specificity; however, transport of both **19** and **22** were still poor. When the SO_2F group of **19** was moved to the *meta* position, the resultant **21** was an excellent irreversible inhibitor and cell wall transport was about 20-fold more effective; in fact **21** was the most effective compound against L1210 cell culture in Table II.

It seems unlikely that other members of this series of 6-substituted pyrimidines would give more effective SO_2F derivatives against L1210 cell culture. Therefore the more potent **5** and **6** were not converted to their SO_2F derivatives since they would be much more laborious to synthesize than compounds previously shown to be highly effective against L1210 in cell culture.[2b]

Chemistry.—The compounds in Tables I and II were synthesized by appropriate modification of routes previously used.[7,9] Condensation of **24**[16] with the appropriate phenol gave inhibitors which can be generalized by structure **25** (Scheme I). Wittig reaction of **26**[9] with the appropriate aldehyde and 1,5-

(16) B. R. Baker, P. C. Huang, and R. B. Meyer, Jr., *J. Med. Chem.*, **11**, 475 (1968), paper CXVI of this series.

Table IV
Physical Properties of



No.	R	Method	Yield, %	Mp, °C	Formula[a]
16	$CH_2OC_6H_4SO_2F$-*p*	A[b]	64[c]	210–213	$C_{17}H_{13}Cl_2FN_4O_3S$
17	$(CH_2)_2C_6H_4SO_2F$-*p*	C[d]	54[e]	178–181	$C_{18}H_{15}Cl_2FN_4O_2S$
18	$CH{=}CHC_6H_4SO_2F$-*p*	B[d]	69[e]	266–268	$C_{18}H_{13}Cl_2FN_4O_2S$
19	*p*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_4SO_2F$-*p*	C[d]	62[f]	220–222 dec	$C_{26}H_{23}Cl_2FN_4O_2S\cdot 0.5H_2SO_4$
20	*p*-$CH{=}CHC_6H_4CH{=}CHC_6H_4SO_2F$-*p*	B[d]	41[f]	270–275	$C_{26}H_{19}Cl_2FN_4O_2S$
21	*p*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_4SO_2F$-*m*	C[g]	80[e]	203–205 dec	$C_{26}H_{23}Cl_2FN_4O_2S\cdot 0.5H_2SO_4$
22	*m*-$(CH_2)_2C_6H_4(CH_2)_2C_6H_4SO_2F$-*p*	C[d]	64[f]	>150 dec	$C_{26}H_{23}Cl_2FN_4O_2S\cdot 0.5H_2SO_4$
23	*m*-$CH{=}CHC_6H_4CH{=}CHC_6H_4SO_2F$-*p*	B[d]	54[h]	222–226	$C_{26}H_{19}Cl_2FN_4O_2S$
30b	*p*-$CH{=}CHC_6H_4CH{=}CHC_6H_4SO_2F$-*m*	B[g]	40[i]	>299 dec	$C_{26}H_{19}Cl_2N_4O_2S\cdot 0.5H_2SO_4\cdot H_2O$

[a] All compounds gave analyses for C, H, F within 0.4% of theory. [b] For starting 4-fluorosulfonylphenol see W. Steinkopf, *J. Prakt. Chem.*, **117**, 1 (1927). [c] Recrystallized from EtOH–H_2O. [d] For starting 4-fluorosulfonylbenzyltriphenylphosphonium bromide see B. R. Baker and G. J. Lourens, *J. Med. Chem.*, **11**, 666 (1968). [e] Recrystallized from EtOH–THF. [f] Recrystallized from *i*-PrOH–THF. [g] For starting 3-fluorosulfonylbenzyltriphenylphosphonium bromide see ref 2b. [h] Recrystallized from MeOEtOH. [i] Recrystallized from EtOH.

diazabicyclo[4.3.0]nonene[17] (DBN) as the base gave inhibitors with general structure **27**; hydrogenation of **27** with PtO_2 catalyst gave inhibitors of type **28**.

Wittig reaction of **26** with a sixfold excess of terephthalaldehyde or isophthalaldehyde and DBN[17] gave intermediates **29** which were isolated as the hemisulfate. A second Wittig reaction of **29** with the appropriate benzyltriphenylphosphonium bromide and DBN[17] gave **30**, which on catalytic reduction with PtO_2 catalyst gave inhibitors of type **31**.

p-Fluorosulfonylbenzaldehyde[18] **33** was synthesized by oxidation of *p*-fluorosulfonyltoluene *via* the diacetate **32**.

Experimental Section

All analytical samples had proper uv and ir spectra and moved as a single spot on Brinkmann silica gel GF; each gave combustion values for C, H, or N and F within 0.4% of theoretical. Melting points were taken in capillary tubes on a Mel-Temp block and are uncorrected.

***p*-Fluorosulfonylbenzal diacetate (32)**[18] was synthesized according to the general method of Nishimura.[19] Recrystallization from EtOH gave 40% yield, mp 70–71°. *Anal.* ($C_{11}H_{11}FO_6S$) C, H, F.

***p*-Fluorosulfonylbenzaldehyde (33).**[18]—A mixture of 10 g (34 mmoles) of **32**, 10 ml of C_2H_5OH, 30 ml of H_2O, and 35 ml of 12 *N* HCl was refluxed for 4 hr. The cooled reaction was filtered and the solid washed with cold H_2O. Two recrystallizations from Et_2O gave 3.6 g (56%) of white crystals, mp 58–60°. *Anal.* ($C_7H_5FO_3S$) C, H.

Method A has been previously described.[2]

Method B. 2,4-Diamino-5-(3,4-dichlorophenyl)-6-styrylpyrimidine (11).—To a stirred solution of 1.2 g (2 mmoles) of **26** and 0.21 g (2 mmoles) of benzaldehyde in 20 ml of DMF protected from moisture was added 0.25 g (2 mmoles) of 1,5-diazabicyclo[4,3,0]nonene.[17] After 16 hr at ambient temperature the mixture was diluted with 20 ml of H_2O. The light yellow product was collected on a filter and washed with H_2O. Recrystallization from EtOH with the aid of decolorizing carbon gave 0.32 g (45%), mp 244–245°. See Tables III and IV for additional data and other compounds prepared by this method.

Method C. 2,4-Diamino-5-(3,4-dichlorophenyl)-6-(phenethyl)-pyrimidine (3).—A mixture of 210 mg (0.59 mmole) of **11** and 100 ml of MeOEtOH was shaken with H_2 at 2–3 atm in the presence of 60 mg of PtO_2 for 3 hr when reduction was complete. The filtered solution was evaporated *in vacuo*. Recrystallization from EtOH–H_2O gave 180 mg (85%) of white crystals, mp 194–195°. See Tables III and IV for additional data and other compounds prepared by this method.

Method D. 2,4-Diamino-5-(3,4-dichlorophenyl)-6-(*p*-formylstyryl)pyrimidine (29a).—To a stirred solution of 2.4 g (4 mmoles) of **26** and 3.2 g (24 mmoles) of 1,4-phthalaldehyde in 35 ml of DMF protected from moisture was added dropwise 0.50 g (4 mmoles) of 1,5-diazabicyclo[4,3,0]nonene[17] in 5 ml of DMF. After being stirred at room temperature for 20 hr, the mixture was added to a cold solution of 50 ml of 2 *N* H_2SO_4. The precipitate was collected and washed with H_2O. The yellow solid was leached with 30 ml of boiling EtOH to remove excess 1,4-phthalaldehyde. Recrystallization from MeOEtOH–H_2O gave 0.80 g (46%) mp >300°. See Table III for additional data.

(17) H. Oediger, H. Kabbe, F. Möller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

(18) This compound was first synthesized in this laboratory by G. J. Lourens, Ph.D. Thesis, University of California at Santa Barbara, 1968.

(19) T. Nishimura, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 713.