2860, 1726, 1458, 1435, 1410, 1380, 1365, 1315, 1225, 1210, 1170, 1155, 1118, 1100, 1048, 1028, 975, 925, 860, 825 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 5.42 (m, 2 H, -CH=CH-), 4.71 (dd, 1 H, J_{HF} = 37 Hz, J_{HH} = 10 Hz, -CH=CF-), 4.18 (m, 1 H), 4.09 (dt, 1 H, J_{HF} = 17 Hz, J_{HH} = 7 Hz, =CFCHOH-), 3.96 (m, 1 H), 3.68 (s, 3 H), 2.82 (td, 1 H), 2.00-2.60 (m, 7 H), 1.20-1.80 (m, 12 H), 0.88 (br t, 3 H). Anal. ($C_{21}H_{35}FO_5$) C, H.

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Anticoccidial Derivatives of 6-Azauracil. 3. Synthesis, High Activity, and Short Plasma Half-life of 1-Phenyl-6-azauracils Containing Sulfonamide Substituents[1]

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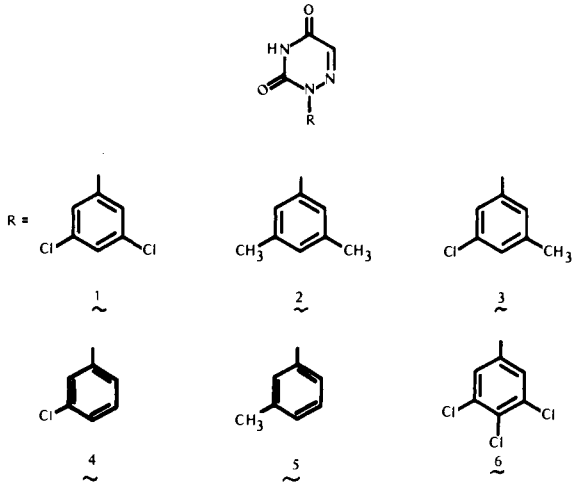
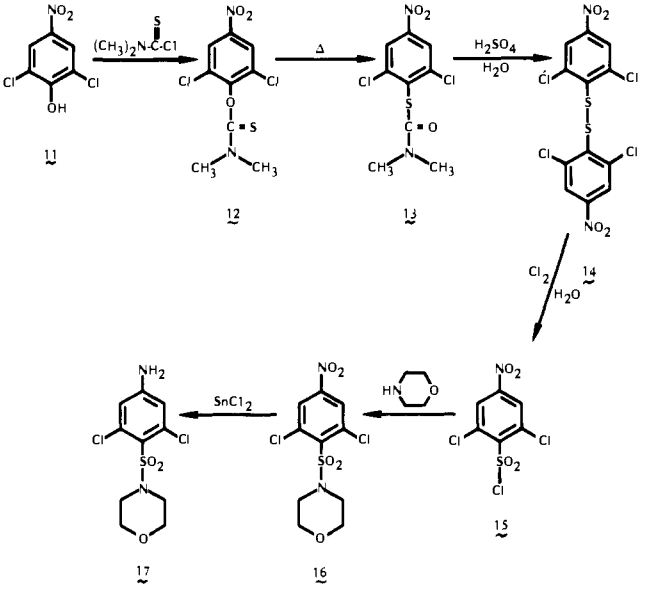
A series of 1-phenyl-6-azauracils containing sulfonamide substituents was prepared. In contrast to previous 1-phenyl-6-azauracils, some of these sulfonamides combine high activity against *Eimeria tenella* infections in chickens with a very rapid rate of clearance from plasma. Most active was 1-[3'-chloro-5'-methyl-4'-(morpholinylsulfonyl)phenyl]-6-azauracil, with a minimum effective concentration in feed of about 10 ppm.

We had previously discovered that the attachment of suitably substituted phenyl rings to the 1 position of 6-azauracil produces potent anticoccidial agents, for example 1.[2] As activity increased among these 1-phenyl-6-azauracils, so did the plasma half-life in chickens, but persistence of the drug in the body of food animals is obviously undesirable. The very potent compound 1 had an extremely long plasma half-life (160 h). Retention of the substitution pattern but replacement of the chlorine atoms by methyl groups gave 2, which was cleared more rapidly from plasma. Rapid clearance was, however, achieved at a considerable sacrifice of potency. To a degree, a combination of the two desirable properties was accomplished in 3, which was intermediate in both potency and plasma clearance time. Monosubstituted compounds 4 and 5 were markedly less potent.



It was suspected that the electronegative character of the chloro substituents made an important contribution to the potency of 1, while their lipophilicity contributed to its slow clearance. The 3,5-substitution pattern in the phenyl ring was critical to maximum activity, yet in certain compounds, e.g., 6, a 4-substituent could be added without loss of potency; it seemed reasonable, then, to seek an electron-withdrawing 4-substituent with a low degree of hydrophobic character. Attached to 1, such a group might facilitate clearance, or incorporated into 2, it might enhance potency.

Scheme I



The sulfonamide group seemed like an attractive possibility, since it has one of the lowest recorded π values,[3]

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(1) This work was presented in part at the 179th National Meeting of the American Chemical Society. See "Abstracts of Papers", 179th Meeting of the American Chemical Society, Houston, Texas, March 1980, American Chemical Society, Washington, D.C., 1980, Abstract MEDI 050.

(2) M. W. Miller, B. L. Mylari, H. L. Howes, Jr., J. E. Lynch, M. J. Lynch, and R. C. Koch, *J. Med. Chem.*, 22, 1483 (1979).
(3) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, 86, 5175 (1964).

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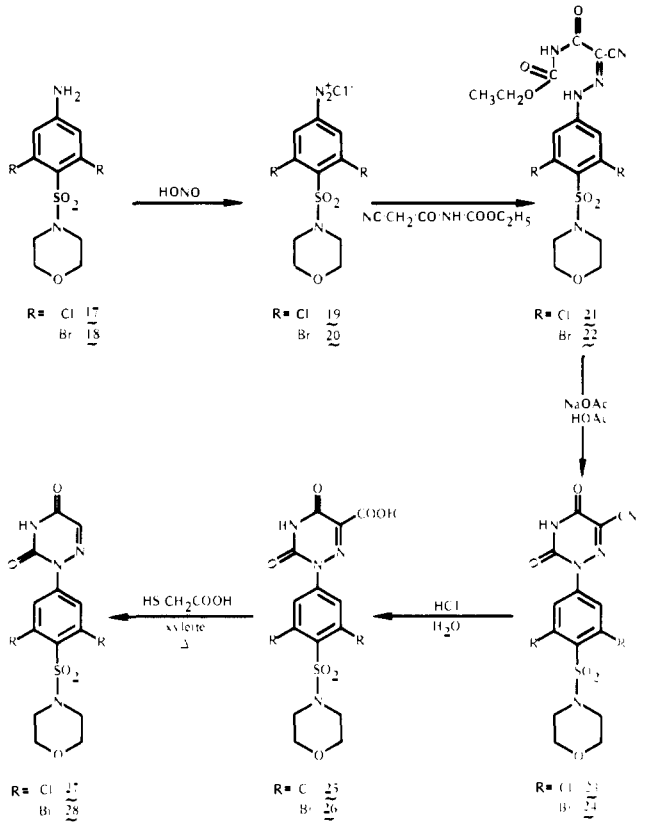
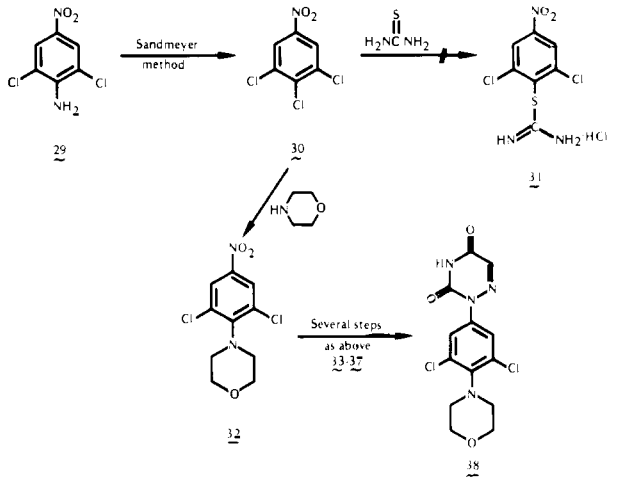
Scheme II

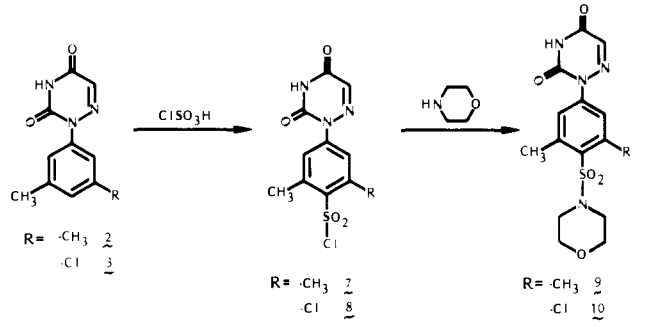


Scheme III



combined with a high para σ value[4] and group dipole moment.[5] Sulfonamides tend to have short plasma half-lives, as attested by the extensive research that has been devoted to modifications of the sulfanilamide structure in order to obtain long-acting drugs.[6] Moreover, if **1**, **2**, or **3** could be chlorosulfonated selectively in the 4′ position, a useful intermediate would be obtained from which a variety of sulfonamides could be derived.

Chemistry. Treatment of **2** with chlorosulfonic acid did indeed give **7** in good yield. Similarly, **3** was chlorosulfonated in the 4′ position to form a useful intermediate, **8**. Without recrystallization, these sulfonyl chlorides could be treated with amines to form sulfonamides; for instance, reaction with morpholine afforded **9** and **10**. The monosubstituted phenyl analogues **4** and **5** furnished the corresponding sulfonamides in a like manner. In contrast



to **2**, it was found that **1** could not be chlorosulfonated, even with catalysts and forcing conditions; consequently, an alternate route was devised. Starting from 2,6-dichloro-4-nitrophenol (**11**), it was possible to prepare the aniline **17** in six high-yield steps (Scheme I). Using this aniline, the dichloro analogue **27** of **9** and **10** was prepared by a modification of the Slouka procedure[7] described in the preceding paper of this series.[2] The even more hindered dibromo analogue **28** was prepared in a similar fashion (Scheme II). The value of the Newman technique[10] in the conversion of hindered phenols to thiophenols (**12** to **13**) is illustrated by the failure of conventional methods to accomplish the same end. For example, while the activated 4-chloro atom of **30** can be displaced selectively by some reagents, such as morpholine in the synthesis of **32**, attempted conversion to a thiophenol by way of the isothiouronium salt **31** was unsuccessful (Scheme III).

Results and Discussion

The phenylazauracil derivatives prepared by the procedures described above are listed in Table I, together with their anticoccidial potency. The minimum effective concentrations (MEC's), given in parts per million (ppm), were determined by a modification by Chappel et al.,[8] of the screening method published by Lynch,[9] using *Eimeria tenella* infections in Leghorn cockerels. As is apparent from the table, many of the sulfonamides were active against these infections. In general, those derived from morpholine were the most active. The morpholine sulfonamide **27** retained about an eighth of the activity of the corresponding 1-phenyl-6-azauracil which does not contain a substituent in the 4′ position (compound **1**). As in the parent 1-phenyl-6-azauracil series, chloro or methyl substituents in the meta positions were more conducive to activity than hydrogen. In contrast to our experience in the parent series, however, replacement of one or both meta chlorine substituents in **27** by methyl enhanced activity, resulting in the most potent members of the sulfonamide series, **9** and **10**. Furthermore, these sulfonamides were less well absorbed and had much shorter plasma half-lives than the corresponding 1-phenyl-6-aza-

(4) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(5) A. L. McClellan, "Tables of Experimental Dipole Moments", W. H. Freeman, San Francisco, CA, 1963.
(6) R. G. Shepherd, in "Medicinal Chemistry", Part 1, 3rd ed., A. Burger, Ed., Wiley-Interscience, New York, 1970, pp 288–295.
(7) J. Slouka, *Monatsh. Chem.*, **96**, 134 (1965).
(8) L. R. Chappel, H. L. Howes, and J. E. Lynch, *J. Parasitol.*, **60**, 415 (1974).
(9) J. E. Lynch, *Am. J. Vet. Res.*, **22**, 324 (1961).
(10) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).
(11) J. J. Rash and M. J. Lynch, *Drug Metab. Dispos.*, 4, 59 (1976).
(12) M. K. Bezzubets and V. S. Rozina, *Zh. Prikl. Khim. (Leningrad)*, **21**, 1152–1161 (1948).

uracils devoid of sulfonamide groups (Table II). Our objective of combining in one drug the high potency attained in the 1-phenyl-6-azauracil series with a rapid clearance time was therefore realized for *E. tenella*, the coccidial species used in our primary screen.

The minimum effective concentration range of 10–15 ppm by weight in feed reached by **9** and **10** against *E. tenella* did not, however, hold up across the entire spectrum of important *Eimeria* species, as shown in Table III. Levels two- to sixfold higher were required, for example, to control *E. acervulina*. It is noteworthy that the structurally related nonsulfonamide **38** did not show this specificity.

The high potencies demonstrated in the *E. tenella* infections are not easy to explain in view of the low blood levels and rapid clearance times characteristic of these compounds relative to those of other 1-phenyl-6-azauracils described in this series of publications. Some of these levels and times are compared in Table II. The sulfonamides **9**, **10**, **49**, and **76** were all more potent than would have been predicted from the relationship between the potency of 1-phenyl-6-azauracils and their plasma half-lives that was described in the preceding paper;[2] for instance, **9** and **76** had plasma half-lives comparable to those of the 3,5-dichloro-4-methoxyphenyl analogue (1.5–2 h), and yet they were 8–16 times as potent. A high *intrinsic* potency against *E. tenella* seems indicated.

Experimental Section

Melting points were determined on a calibrated Kofler hot stage microscope. Solvents used were analytical reagent grade and, where pertinent, were protected from water by storage over molecular sieves. Mass spectra were obtained with Hitachi Model RMU-6E. Nuclear magnetic resonance spectra were obtained for selected compounds with Perkin-Elmer/Hitachi Model R-20. Thin-layer chromatography was performed with Uniplate (Analtech) precoated TLC plates (Silica Gel GF, 250 μm) in a variety of solvent systems.

Method A. 2-[3,5-Dimethyl-4-(chlorosulfonyl)phenyl]-*as*-triazine-3,5(2*H*,4*H*)-dione (7). At room temperature, 3.5 g (0.016 mol) of **2** was added to 50 mL of chlorosulfonic acid. The mixture was heated at 75 °C for 135 min, then cooled, and poured slowly with stirring into 500 mL of ice–water. After 20 min, the solid that separated was removed by filtration, washed three times with H_2O, and dried at reduced pressure to yield 4.3 g (85%), mp 188–190 °C. The NMR spectrum showed a singlet for the two aromatic protons, in agreement with the assigned substitution pattern: NMR [$(CD_3)_2SO$] δ 2.78 (s, 6 H, $2CH_3$), 7.62 (s, H, C_6 H), 7.68 (s, 2 H, aromatic).

In a similar manner, **4** was converted to 2-[3-chloro-4-(chlorosulfonyl)phenyl]-*as*-triazine-3,5(2*H*,4*H*)-dione (**51**) in 83% yield, mp 198–200 °C. The aromatic proton signals of the NMR spectrum were consistent with a structure having the chlorosulfonyl function either ortho or para to the triazine ring. The chemical shift of the triazine C-6 proton was the same in both the starting material and the chlorosulfonyl product; the latter observation supports the assigned para-substituted structure: NMR [$(CD_3)_2SO$] δ 7.48 [q, 1 H (C-6′), aromatic, $J_{H_6',H_5'}$ = 8 Hz, $J_{H_6',H_2'}$ = 3 Hz], 7.56 [d, 1 H (C-2′), aromatic, J = 3 Hz], 7.67 [s, 1 H (C-6)], 8.0 [d, 1 H (C-5′), aromatic, J = 8 Hz].

2-[3,5-Dimethyl-4-(morpholinylsulfonyl)phenyl]-*as*-triazine-3,5(2*H*,4*H*)-dione (9). To a solution of 462 mg (1.4 mmol) of **7** in 10 mL dry tetrahydrofuran was added dropwise, with stirring, 500 mg (5.7 mmol) of freshly distilled morpholine. After 3 h of refluxing, the mixture was cooled and poured into 100 mL of ice-cold 6 N HCl. After stirring for 90 min, the solid present was removed by filtration. The dry product (293 mg, 57%), mp 196–197 °C, was recrystallized from 95% EtOH. Pure **9** consisted of white crystals, mp 199–200 °C. Anal. ($C_{15}H_{18}N_4O_5S$) C, H, N.

Method B. *O*-(2,6-Dichloro-4-nitrophenyl) Dimethylthiocarbamate (12). To a solution of 20.8 g (0.10 mol) of 2,6-dichloro-4-nitrophenol in 200 mL of dimethylformamide was added 3.95 g (0.10 mol) of 61.5% sodium hydride in mineral oil over a 30-min period with stirring and cooling. The mixture was then warmed to 40 °C until H_2 evolution stopped. The solution was cooled to 5 °C and 16.0 g (0.13 mol) of dimethylthiocarbamoyl chloride was added in one portion with stirring. During 40 min, the temperature was raised to 70 °C. The reaction mixture was stirred into 1100 mL of 4% NaOH solution. After 20 min, the solid which separated was removed by filtration, washed with H_2O, and dried. The yield was 24.49 g (83%) of crude product, mp 134–139 °C.

***S*-(2,6-Dichloro-4-nitrophenyl) Dimethylthiocarbamate (13).** A 23.5-g (0.083 mol) sample of **12** was heated at 175–180 °C for 10 min. After 5 min the solid had melted completely, but then it crystallized again, and TLC indicated complete transformation to a new product. The solid was crushed, slurried with refluxing MeOH, removed by filtration, and dried. The crude yield was 21.5 g (91.5%), mp 216–218 °C.

Bis(2,6-dichloro-4-nitrophenyl) Disulfide (14). To a mixture of 200 mL of concentrated H_2SO_4 and 20 mL of H_2O in a 500-mL flask was added 20.5 g (0.069 mol) of **13**. The solution was warmed on a steam bath for 25 min and then poured onto 1 L of crushed ice with stirring. The solid that separated was collected by filtration and washed with H_2O. The yield of crude product was 12.7 g (83%), mp 164–166 °C.

2,6-Dichloro-4-nitrobenzenesulfonyl Chloride (15). A 12-g (0.027 mol) sample of **14** was suspended in H_2O and chlorine gas was added through a gas-dispersion tube to the stirred suspension for 3.5 h. The mixture was filtered, and the solid was collected, washed with H_2O, and dried. The crude product weighed 5.62 g (72% yield), mp 93–94 °C.

3,5-Dichloro-4-(morpholinylsulfonyl)nitrobenzene (16). To a stirred slurry of 5.7 g (0.018 mol) of **15** in 150 mL of ether was added dropwise 15.0 g (0.170 mol) of morpholine in 50 mL of ether. After the mixture stirred for 3 h at reflux, the solid present was removed by filtration and washed with 6 N HCl. The crude yellow crystalline product weighed 2.64 g, mp 169–170 °C. It was characterized by MS.

3,5-Dichloro-4-(morpholinylsulfonyl)aniline (17). A solution of 6.6 g (0.29 mol) of $SnCl_2{\cdot}2H_2O$ in 13 mL of concentrated HCl was added to a stirred slurry of 2.5 g (0.0073 mol) of **16**. After 1.25 h of reflux, the mixture was poured into 100 mL of H_2O with stirring. After 3 h, the solid was separated by filtration and washed with H_2O. An aqueous suspension was made alkaline with 30% NaOH solution and then extracted with $CHCl_3$. After drying over Na_2SO_4, removal of solvent yielded 1.6 g (73% yield) of white crystals, mp 170–171 °C. This aniline was characterized (MS) and used in the synthesis of **27** by way of the following procedures. In a similar manner, 3,5-dichloro-4-*N*-morpholinylnitrobenzene (**32**) was converted to 3,5-dichloro-4-*N*-morpholinylaniline (**33**) in 59% yield, mp 175–176 °C.

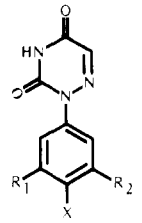
3,5-Dichloro-4-(morpholinylsulfonyl)benzenediazonium Chloride (19). A stirred mixture of 1.6 g (5.1 mmol) of **17** and 35 mL of 6 N HCl was warmed and then cooled to 0–5 °C while 450 mg (7 mmol) of $NaNO_2$ in 5 mL of H_2O was added dropwise during 10 min.

3,5-Dichloro-4-*N*-morpholinylbenzenediazonium Nitrate (34). A mixture of 4.8 g (0.027 mol) of **33** with 60 mL of 85% H_3PO_4 was heated to 70 °C to effect solution. After the mixture cooled to 0–5 °C, 20 mL of chilled 70% HNO_3 was added. Then 20 mL of a cold aqueous solution of 1.6 g (0.024 mol) of $NaNO_2$ was added during 20 min.

Ethyl *N*-[[[Cyano(3,5-dichloro-4-morpholinylsulfonyl)-hydrazinylidene]methyl]carbonyl]carbamate (21). A mixture of 2 g (0.013 mol) of *N*-cyanoacetylurethane, 10 mL of pyridine, and 200 mL of H_2O was stirred gently at 15–20 °C while the solution of diazonium salt **19** was added dropwise during 20 min. After 16 h at ambient temperature, the solid was collected, washed with H_2O, and dried (60 °C at 24 mmHg for 20 h). The product weighed 2.23 g (87% yield), mp 184–187 °C. In a similar manner, **34** was converted to ethyl *N*-[[[(cyano(3,5-dichloro-4-*N*-morpholinylphenyl)hydrazinylidene]methyl]carbonyl]carbamate (**35**), mp 302–306 °C, homogeneous by TLC and MS.

2-[3,5-Dichloro-4-(morpholinylsulfonyl)phenyl]-3,5-(2*H*,4*H*)-dioxo-*as*-triazine-6-carboxylic Acid (25). A mixture of 2.2 g (4.6 mmol) of **21**, 50 mL of acetic acid, and 1.0 g (12 mmol) of anhydrous sodium acetate was refluxed and stirred for 7 h.

Table I. 2-Phenyl-*as*-triazine-3,5(2*H*,4*H*)-diones (1-Phenyl-6-azauracils) and Their Activities vs. *Eimeria tenella* Infections[a]

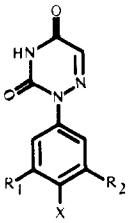


no.	R_1	R_2	X	mol formula[b]	mp, °C	MEC,[c] ppm
1	Cl	Cl	H	*d*		4
2	Me	Me	H	*d*		30
3	Cl	Me	H	*d*		15
4	Cl	H	H	*d*		120
5	Me	H	H	$C_{10}H_9N_3O_2$ [d]	134-136	>120
6	Cl	Cl	Cl	*d*		4
7	Me	Me	SO_2Cl	$C_{11}H_{10}ClN_3O_4S$ [e,f]	188-190	250
8	Cl	Me	SO_2Cl	$C_{10}H_7Cl_2N_3O_4S$ [f]	98	
9	Me	Me	SO_2-morpholin-4-yl	$C_{15}H_{18}N_4O_5S$	200	15
10	Cl	Me	SO_2-morpholin-4-yl	$C_{14}H_{15}ClN_4O_5S$	168-170	10
27	Cl	Cl	SO_2-morpholin-4-yl	$C_{13}H_{12}Cl_2N_4O_5S$ [g]	208-210	30
28	Br	Br	SO_2-morpholin-4-yl	$C_{13}H_{12}Br_2N_4O_5S$ [g]	212-214	>30
38	Cl	Cl	morpholin-4-yl	$C_{13}H_{12}Cl_2N_4O_3$ [h]	231-233	15
39	H	H	H	$C_9H_7N_3O_2$ [d]	209-210	500
40	H	H	SO_2Cl	$C_9H_5ClN_3O_4S$ [f]	193-195	>250
41	H	H	$SO_2NHC(Me)_2CH_2C(Me)_3$	$C_{17}H_{24}N_4O_4S$ [e]	208-209	>120
42	H	H	$SO_2NHC_6H_4$-(4-SO_2NH_2)	$C_{15}H_{13}N_5O_6S_2$	233-236	500
43	H	H	SO_2-piperidin-1-yl	$C_{14}H_{16}N_4O_4S$	282-284	250
44	H	H	SO_2-morpholin-4-yl	$C_{13}H_{14}N_4O_5S$	264	>250
45	Me	H	SO_2Cl	$C_{10}H_8ClN_3O_4S$ [f]	188-190	
46	Me	H	$SO_2N(Me)$(allyl)	$C_{14}H_{16}N_4O_4S$	130-133	120
47	Me	H	$SO_2N(Me)$(cyclopentyl)	$C_{16}H_{20}N_4O_4S$	192-193	>120
48	Me	H	$SO_2N(Et)$(*i*-Pr)	$C_{15}H_{20}N_4O_4S$	175-177	500
49	Me	H	SO_2-morpholin-4-yl	$C_{14}H_{16}N_4O_5S$	243-244	15-30
50	Me	H	SO_2-1-CHO-piperazin-4-yl	$C_{15}H_{17}N_5O_5S$	278-280	500
51	Cl	H	SO_2Cl	$C_9H_5Cl_2N_3O_4S$ [f]	198-200	
52	Cl	H	SO_2NH_2	$C_9H_7ClN_4O_4S$	305-308	>120
53	Cl	H	$SO_2NHCH_2C_6H_4$-(2-Cl)	$C_{16}H_{12}Cl_2N_4O_4S$	220-221	>250
54	Cl	H	$SO_2NHC_6F_5$	$C_{15}H_6ClF_5N_4O_4S$	179-180	>60
55	Cl	H	SO_2NH-cyclohexyl	$C_{15}H_{17}ClN_4O_4S$	183	>500
56	Cl	H	SO_2NH-cyclooctyl	$C_{17}H_{21}ClN_4O_4S$	230-232	>250
57	Cl	H	$SO_2NHC_6H_4$-(3-Cl)	$C_{15}H_{10}Cl_2N_4O_4S$	243-244	>500
58	Cl	H	$SO_2NHC_6H_3$-(3-Cl-4-Me)	$C_{16}H_{12}Cl_2N_4O_4S$ [e]	203	>250
59	Cl	H	$SO_2NHC_6H_3$-(3-Cl-5-Me)	$C_{16}H_{12}Cl_2N_4O_4S$	257	>250
60	Cl	H	$SO_2N(Me)_2$	$C_{11}H_{11}ClN_4O_4S$	214	250
61	Cl	H	$SO_2N(Me)$(Et)	$C_{12}H_{13}ClN_4O_4S$	180	120
62	Cl	H	$SO_2N(Me)$(*n*-Pr)	$C_{13}H_{15}ClN_4O_4S$	169-170	250
63	Cl	H	$SO_2N(Me)$(allyl)	$C_{13}H_{13}ClN_4O_4S$	148-149	60
64	Cl	H	$SO_2N(Me)$(cyclopentyl)	$C_{15}H_{17}ClN_4O_4S$	194-195	>120
65	Cl	H	$SO_2N(Me)(CH_2CH_2OH)$	$C_{12}H_{13}ClN_4O_5S$	199-200	>120
66	Cl	H	$SO_2N(n\text{-}Bu)(CH_2CN)$	$C_{15}H_{16}ClN_5O_4S$	161-162	>120
67	Cl	H	$SO_2N[CH_2CH(OEt)_2]_2$	$C_{21}H_{31}ClN_4O_8S$	104-105	250
68	Cl	H	$SO_2N(Me)$(Ph)	$C_{16}H_{13}ClN_4O_4S$	189-190	>250
69	Cl	H	$SO_2N(Me)[CH_2C_6H_4$-(4-Cl)]	$C_{17}H_{14}Cl_2N_4O_4S$	234-235	500
70	Cl	H	$SO_2N(n\text{-}Pr)_2$	$C_{15}H_{19}ClN_4O_4S$	165-166	>250
71	Cl	H	$SO_2N(allyl)_2$	$C_{15}H_{15}ClN_4O_4S$	120-121	250
72	Cl	H	$SO_2N(CH_2C_6H_5)_2$	$C_{23}H_{19}ClN_4O_4S$	226	>250
73	Cl	H	$SO_2N(Me)(CH_2C_6H_5)$	$C_{17}H_{15}ClN_4O_4S$	203-204	60-120
74	Cl	H	SO_2-thiazolidin-3-yl	$C_{12}H_{11}ClN_4O_4S_2$	207-208	>120
75	Cl	H	SO_2-4-OH-piperidin-1-yl	$C_{14}H_{15}ClN_4O_5S$	232-233	>250
76	Cl	H	SO_2-morpholin-4-yl	$C_{13}H_{13}ClN_4O_5S$	227-228	30
77	Cl	H	SO_2-1-COOEt-piperazinyl	$C_{16}H_{18}ClN_5O_6S$	195-196	>250
78	Cl	H	SO_2-pyrrolidin-1-yl	$C_{13}H_{13}ClN_4O_4S$	225	250
79	Cl	H	SO_2-piperidin-1-yl	$C_{14}H_{15}ClN_4O_4S$	170-175	250
80	Cl	H	SO_2-4-(=O)-piperidin-1-yl	$C_{14}H_{13}ClN_4O_5S$	195-197	>250
81	Cl	H	SO_2-(4-$C_6H_5CH_2$)piperidinyl	$C_{21}H_{21}ClN_4O_4S$	171-172	>250
82	Cl	H	SO_2-thiamorpholin-4-yl	$C_{13}H_{13}ClN_4O_4S_2$	216-217	60
83	Cl	Me	$SO_2N(Me)_2$	$C_{12}H_{13}ClN_4O_4S$	223-224	60
84	Cl	Me	$SO_2N(Et)_2$	$C_{14}H_{17}ClN_4O_4S$	183-184	250
85	Cl	Me	SO_2-thiamorpholinyl	$C_{14}H_{15}ClN_4O_4S_2$	178-180	120
86	Me	Me	$SO_2NHC_6H_4$-(4-OMe)	$C_{18}H_{18}N_4O_5S$	195-196	>250
87	Me	Me	$SO_2N(Me)_2$	$C_{13}H_{16}N_4O_4S$	232-234	60
88	Me	Me	$SO_2N(Me)$(*n*-Pr)	$C_{15}H_{20}N_4O_4S$	189-191	120
89	Me	Me	$SO_2N(CH_2CH_2OMe)_2$	$C_{17}H_{24}N_4O_6S$	131	250
90	Me	Me	$SO_2N(Me)(CH_2C_6H_5)$	$C_{19}H_{20}N_4O_4S$	172-174	60
91	Me	Me	SO_2-pyrrolidin-1-yl	$C_{15}H_{18}N_4O_4S$	196-198	60

Footnotes to Table I

[a] Unless otherwise noted, the compounds of this table were prepared as in method A described under Experimental Section. [b] Except where noted, elemental analysis or mass spectral analysis and thin-layer chromatography were used to confirm desired product and establish purity. [c] MEC values are expressed as the minimum amounts (parts per million by weight in feed mixtures) of drugs required to prevent formation of detectable disease lesions. [d] Prepared by method of previous paper.[2] [e] Solvated form: 7·0.5H_2O, 41·MeOH, 58·EtOH. [f] Intermediate; identity established by NMR and by characterization of products. [g] Prepared as in method B. [h] Prepared as in method C.

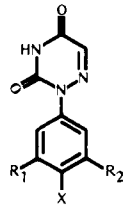
Table II. Plasma Levels and Half-lives of Phenylazauracils



no.	R_1	R_2	X	plasma levels,[a] mcg/mL: in young cockerels[c]	plasma levels,[a] mcg/mL: in older birds[d]	$t_{1/2}$,[b] h: in young cockerels[c]	$t_{1/2}$,[b] h: in older birds[d]	MEC, ppm
1	Cl	Cl	H	14.5	24.3	56	150	4
2	Me	Me	H	8.1	22.4	6	12	30
3	Cl	Me	H		21.7		20	15
4	Cl	Cl	Cl		22.5		120	4
9	Me	Me	SO_2-morpholin-4-yl	0.95		1.5		15
10	Cl	Me	SO_2-morpholin-4-yl	0.38		1.0		10
49	Me	H	SO_2-morpholin-4-yl	3.1		1.1		15-30
76	Cl	H	SO_2-morpholin-4-yl	1.9		2.1		30
e	H	H	H			8		500
e	Cl	Cl	OMe			2		250

[a] Measured 3 h after oral administration of 4-5 mg/kg body weight. [b] Plasma half-lives ($t_{1/2}$) were determined by the method described by Rash and Lynch.[11] [c] Around 10 days old. [d] Around 9-10 weeks old. [e] Reference 2.

Table III. Variations in the Vulnerability of *Eimeria* Species to Selected Phenylazauracils



No.	R_1	R_2	X	Organisms[a]/MEC (ppm): *E.t.*	*E.a.*	*E.b.*	*E.m.*	*E.n.*
9	Me	Me	SO_2-morpholin-4-yl	15	50	30-60		15-30
10	Cl	Me	"	10	60			
27	Cl	Cl	"	15	30			
49	Me	H	"	15-30	30			
76	Cl	H	"	30	120			
38	Cl	Cl	morpholin-4-yl	15-30	15-30		15	

[a] *E.t., Eimeria tenella; E.a., E. acervulina; E.b., E. brunetti; E.m., Eimeria maxima; E.n., E. necatrix.*

Then, 20 mL of concentrated HCl was added and refluxing continued for 1.5 h. The mixture was cooled and the solid that separated was collected, washed with H_2O, and dried. The yield was 1.345 g (62% from **19**). In the same way, **35** was converted to 2-(3,5-dichloro-4-morpholinylphenyl)-3,5(2*H*,4*H*)-dioxo-*as*-triazine-6-carboxylic acid (**37**). The yield was 58% from **35**.

2-[3,5-Dichloro-4-(morpholinylsulfonyl)phenyl]-*as*-triazine-3,5(2*H*,4*H*)-dione (27). A mixture of 1.3 g (2.9 mmol) of **25** and 3 mL of thioglycolic acid was heated at 165 °C for 2 h. Then, 6 mL of saturated $NaHCO_3$ solution and 5 mL of H_2O were added at room temperature. After the solution stirred for 1 h, the solid was collected, washed with H_2O, and dried. The crude product was crushed and slurried with 50 mL of refluxing EtOH, and the insoluble material was removed by hot filtration. The EtOH solution was treated with activated charcoal (Darco) and concentrated to 30 mL. The crystals that separated were dried. The yield was 745 mg (68%), mp 208–210 °C. Anal. ($C_{13}H_{12}Cl_2N_4O_5S$) C, H, N. In the same manner, **37** was decarboxylated to 2-(3,5-dichloro-4-morpholinylphenyl)-*as*-triazine-3,5-(2*H*,4*H*)-dione (**38**), mp 231–233 °C. Anal. ($C_{13}H_{12}Cl_2N_4O_3$) C, H, N.

Method C. 3,4,5-Trichloronitrobenzene (30). A mixture of 2 L of concentrated HCl, 800 mL of acetic acid, and 544 mL of concentrated H_2SO_4 was cooled and stirred gently while 75.9 g (1.1 mol) of $NaNO_2$ followed by 207 g (1.0 mol) of 2,6-dichloro-4-nitroaniline were added. Then, 200 g (2 mol) of Cu_2Cl_2 was added. After 0.5 h, the mixture was heated at 80 °C for 0.5 h. The reaction mixture was added to an equal volume of ice–water and the solid was collected. The crude, oily solid was taken up in 1 L of $CHCl_3$, and the solution was washed twice with H_2O, once with 10% NaOH, twice with H_2O again, then dried thoroughly over Na_2SO_4. After treatment with activated charcoal (Darco), the solvent was removed, leaving an oil. Stirring with hexane caused crystallization. The dried product weighed 106 g (47% yield), mp 65–67 °C, lit.[12] 68–69 °C.

3,5-Dichloro-4-*N*-morpholinylnitrobenzene (32). To a stirred solution of 20.0 g (0.885 mol) of **30** in 40 mL of dry dimethylformamide was added 7.7 g (0.885 mol) of freshly distilled morpholine. The mixture was refluxed under N_2 for 43 h, cooled, and poured into 500 mL of 6 N HCl. The solid that separated was collected and recrystallized from 95% EtOH with a Darco treatment. The yield was 10.10 g (42%) of colorless crystals, mp 116–118 °C, homogeneous by TLC.

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