Anthelmintic 2-(5-Nitro-2-thienyl)-4-(substituted amino)quinazolines

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As part of a continuing program directed toward the development of new and novel anthelmintic agents,[1] a series of 2-(5-nitro-2-thienyl)-4-(substituted amino)quinazolines was synthesized.

The general method for the preparation of the amino compounds **6–24** involves displacement of the activated 4-Cl atom in 4-chloro-2-(5-nitro-2-thienyl)quinazolines **5a** or **5b** by a variety of amines in DMF solution. The synthesis of **5a** and **5b** involves the reaction of 5-nitro-2-thiophenecarboxaldehyde (**1**) with an anthranilamide (**2a** or **2b**) in acidic EtOH. The resulting dihydroquinazolinone (**3a** or **3b**) is oxidized to the corresponding quinazolinone (**4a** or **4b**) with *p*-benzoquinone. Chlorination of the quinazolinones with PCl_5 in $POCl_3$ results in the formation of **5a** or **5b** in moderate yield. The syntheses of **5a** and **5b** and **6–24** are outlined in Scheme I.

The 2-(5-nitro-2-thienyl)-4-(substituted amino)quinazolines **6–24** are shown in Table I.

Scheme I

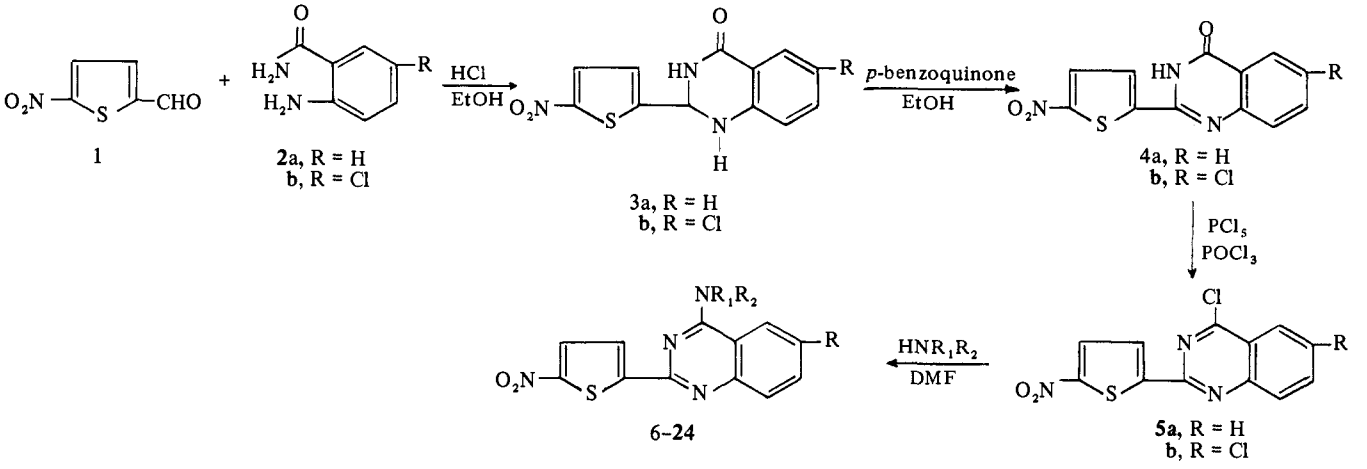
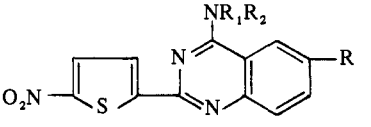
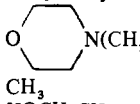


Table I



No.	R_1	R_2	R	Mp, °C	Yield, %	Recrystn solvent[b]	Formula[c]	Anthelmintic testing *in vivo* Per cent reductions[a] *A. suum*	*S. obvelata*
6	*N*-Hydroxyethyl piperazino		H	283–284	62	A/B	$C_{18}H_{19}N_5O_3S \cdot 2HCl \cdot 0.5H_2O$	89	100
7		H	H	202–204	69	C/D	$C_{19}H_{21}N_5O_3S$	98	99
8	CH_3	NH_2	H	195–196	75	C/D	$C_{13}H_{11}N_5O_2S$	47	74
9	$HOCH_2CH_2$	$HOCH_2CH_2$	H	175–178	67	D/E	$C_{16}H_{16}N_4O_4S$	82	100
10	$HOCH_2CH_2$	$HOCH_2CH_2$	Cl	168–170	81	F	$C_{16}H_{15}ClN_4O_4S$	68	100
11	$HOCH_2CH_2$	C_2H_5	H	158–160	75	C/D	$C_{16}H_{16}N_4O_3S$	79	99
12	$HOCH_2CH_2$	$CH_3(CH_2)_2$	H	137–139	76	A/E	$C_{18}H_{20}N_4O_3S$	96[d]	99[d]
13	$HOCH_2CH_2$	NH_2	H	192–194	86	C/D	$C_{14}H_{13}N_5O_3S$	83	100
14	$HOCH_2CH_2$	$CH_3CHOHCH_2$	H	158–160	50	G	$C_{17}H_{18}N_4O_4S$	94	100
15	$HOCH_2CH_2$	$HOCH_2CH_2CH_2$	H	166–168	75	A	$C_{17}H_{18}N_4O_4S$	99	100
16	$CH_3CHOHCH_2$	$CH_3CHOHCH_2$	H	159–161	86	A	$C_{18}H_{20}N_4O_4S$	96	100
17	$HOCH_2CH_2$	H	H	213–215	83	A	$C_{14}H_{12}N_4O_3S$	90	100
18	$HOCH_2CHOHCH_2$	H	H	212–213	100	H	$C_{15}H_{14}N_4O_4S$	73	100
19	$HOCH_2CHOHCH_2$	H	Cl	212–214	62	C/D/E	$C_{15}H_{13}ClN_4O_4S$	54	98
20	$CH_3CHOHCH_2$	H	H	200–202	82	D/E	$C_{15}H_{14}N_4O_3S$	47	99
21	$HO(CH_2)_3$	H	H	175–177	82	D/E	$C_{15}H_{14}N_4O_3S$	73	21
22	$CH_3CHOHCH_2CH_2$	H	H	155–156	59	C/E	$C_{16}H_{16}N_4O_3S$	28	49
23	$HO(CH_2)_4$	H	H	171–173	93	C/D	$C_{16}H_{16}N_4O_3S$	76	84
24	$H(OCH_2CH_2)_2O(CH_2)_3$	H	H	83–85	80	A/E	$C_{19}H_{22}N_4O_5S$	87[d]	99[d]
Tetramisole								99	73
Bunamidine								11	*e*

[a] Dosed at 100 mg/kg (bid for 5 days) to groups of 5 mice. [b] A = 95% EtOH; B = concd HCl; C = MeOH; D = DMF; E = H_2O; F = CH_3NO_2; G = *i*-PrOH; H = EtOAc. [c] All compds were analyzed for C, H, N. Anal. results were within ±0.4% of the calcd values. [d] Dosed at 300 mg/kg (bid for 5 days). [e] Inactive at highest level tested.

Table II. Titration of Anthelmintic Activity of 17

	Dose,[a] mg/kg	Percentage reduction		
		A. suum	*S. obvelata*	*H. nana*[b]
	300	92	100	100
	100	90	100	100
	50	84	100	100
	25	72	99	100
	12.5	26	54	35
Tetramisole	300	Toxic		
	100	99	73	Inactive
	50	100	Inactive	
	25	100		
	12.5	53		
Bunamidine	300	Toxic		
	100	11	Inactive	100
	50	Inactive		59
	25			30
	12.5			13

[a] *A. suum* and *S. obvelata* infected mice were dosed twice a day for 5 days. [b] *H. nana*–taeniacidal activity was detd by use of *H. nana* as described previously by Culbertson[4] using modified techniques of Steward[5] and Standen.[6] In addn, on the 13th day of infection, to the end of testing, the mice were given hydrocortisone (USP–microfine, Merck & Co., Inc., Rahway, N. J.) at the rate of 25 mg/l. in their drinking water to prevent natural worm elimination. Medication was administered twice a day for 3 days (days 18 to 20 inclusive of the infection). Necropsy was performed on infection day 22 and worm counts were made by pressing the small intesting between glass plates and scanning at X7 magnification.

Anthelmintic Testing. The anthelmintic activity of the compounds prepared in this work and of the comparison drugs tetramisole and bunamidine are shown in Table I.[2,3] The most active compounds are those bearing a hydroxyalkylamino substituent in the 4 position. However, no real structure-activity trends are apparent among the hydroxyalkylamino-substituted quinazolines. By normal titration of activity, the most consistently active compound of the series against the two helminthic parasites is **17**. A titration of its anthelmintic activity against *Ascaris suum* and *Syphacia obvelata* and also against the tapeworm *Hymenolepis nana* is shown in Table II. The activities of the reference drugs are also included in the table for comparison purposes.

Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected.

2,3-Dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3a). A soln of 5-nitro-2-thiophenecarboxaldehyde (157 g, 1.0 mole) in EtOH (1 l.) was warmed on a steam bath and treated with concd HCl (20 ml). A warm soln of anthranilamide (136 g, 1.0 mole) in EtOH (500 ml) was added with rapid stirring. The stirred reaction mixt was heated under reflux for 1 hr, then chilled in ice, and filtered. After thorough washing with cold aq EtOH and air drying, the product weighed 227 g (83%). An analytical sample was obtd as yellow needles, mp 219–221°, following several recrystns from EtOH (charcoal). *Anal.* ($C_{12}H_9N_3O_3S$) C, H, N.

6-Chloro-2,3-dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3b) was prepd as described for 3a, using 2-amino-5-chlorobenzamide. The crude yield was 67%. Analytically pure product was obtd by recrystn from EtOH, mp 196–198°. *Anal.* ($C_{12}H_8ClN_3O_3S$) C, H, N.

2-(5-Nitro-2-thienyl)quinazolin-4(3*H*)-one (4a). A mixt of 3a (245 g, 0.89 mole) and *p*-benzoquinone (120 g, 1.1 moles) in EtOH (1.5 l.) and DMF (600 ml) was refluxed with stirring for 6 hr. After chilling, the product was removed by filtration and washed thoroughly with EtOH, then Et_2O. The crude yellow product weighed 160 g (66%). Recrystn from aq DMF provided an analytical sample as yellow needles, mp 350–351°. *Anal.* ($C_{12}H_7N_3O_3S$) C, H, N.

6-Chloro-2-(5-nitro-2-thienyl)quinazolin-4(3*H*)-one (4b) was prepd in 71% yield from 3b according to the procedure described for 4a. The crude product was recrystd from DMF to give yellow needles, mp 349–351°. *Anal.* ($C_{12}H_6ClN_3O_3S$) C, H, N.

4-Chloro-2-(5-nitro-2-thienyl)quinazoline (5a). A mixt of 4a (68 g, 0.25 mole) and PCl_5 (68 g, 0.33 mole) in $POCl_3$ (500 ml) was refluxed with stirring until all the material went into soln. The reaction mixt was heated for an addnl 15 min and then cooled, and the pptd product was removed by filtration. After thoroughly washing with hexane and drying, the product weighed 65 g (89%). Recrystn from $MeNO_2$ gave yellow crystals, mp 187–189°. *Anal.* ($C_{12}H_6ClN_3O_3S$) C, H, N.

4,6-Dichloro-2-(5-nitro-2-thienyl)quinazoline (5b) was prepd in 87% yield from 4b as described for 5a. Recrystn from $MeNO_2$ gave pure material, mp 167–169°. *Anal.* ($C_{12}H_5Cl_2N_3O_3S$) C, H, N.

4-(2-Hydroxyethylamino)-2-(5-nitro-2-thienyl)quinazoline (17). A mixt of 5a (50 g, 0.17 mole) and ethanolamine (24 g, 0.40 mole) in DMF (500 ml) was heated on a steam bath with stirring for 5 hr. After treatment with charcoal, the hot soln was filtered, and the filtrate poured onto ice. The pptd product weighed 45 g (83%) and was recrystd from EtOH to give an analytical sample as yellow crystals.

The remaining compds in Table I were prepd in a similar manner from 5a or 5b and the appropriately substituted amine or hydrazine.

Biological Method. *A. suum.* The method was described previously.[1] *S. obvelata.* Natural infections of this parasite were used for drug activity evaluation. The groups of mice used for the *A. suum* tests were concomitantly observed for *S. obvelata.* Worm counts were made by removal of the mouse caecum, splitting it open in a small dish containing 10 ml of physiological saline and incubating at 37° for 1 hr. Each dish was then filled with 10–20 ml of saturated $ZnSO_4$ soln and the worms floating on the surface were counted at X7 magnification by use of a "stereozoom" microscope (Bausch and Lomb).

Compd effectiveness was detd as a percentage reduction in the manner described previously.[1]

Acknowledgment. The authors are grateful to Miss Yvonne Miller, Mr. James Sheffer, Mr. D. Richard Anthony, Jr., and Mr. Frederick Abbott for the preparation of chemical intermediates and to Mr. Stephen Ashton and Mr. Edward Scholz, Jr., for their assistance in the biological testing. Microanalyses were performed by Mr. Marvin Tefft and Mr. Grant Gustin.

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Effects of *S*-(+)- and *R*-(−)-3,4,Dimethoxyphenylisopropylamines in the Rat

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While much information is available about the structure-activity relationships of one-ring psychotomimetics related to mescaline,[1] no data on the relative potency of optical isomers has been reported. Since a cross-tolerance exists between LSD and mescaline-type compounds, it has been suggested that they act *via* the same mechanism. Both compounds are β-arylethylamine derivatives. While most litera-

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