Substituted Thiosemicarbazido/Semicarbazido Quinolines as Possible Antimalarials

Suman Mehrotra, Jayanti P. Barthwal, Bhagwan R. Pandey (1), Krishna P. Bhargava, and Surendra S. Parmar

Jawahar Lal Nehru Laboratories of Molecular Biology, Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow, 226003, India
and Department of Physiology, University of North Dakota, School of Medicine, Grand Forks, North Dakota 58202, U.S.A.

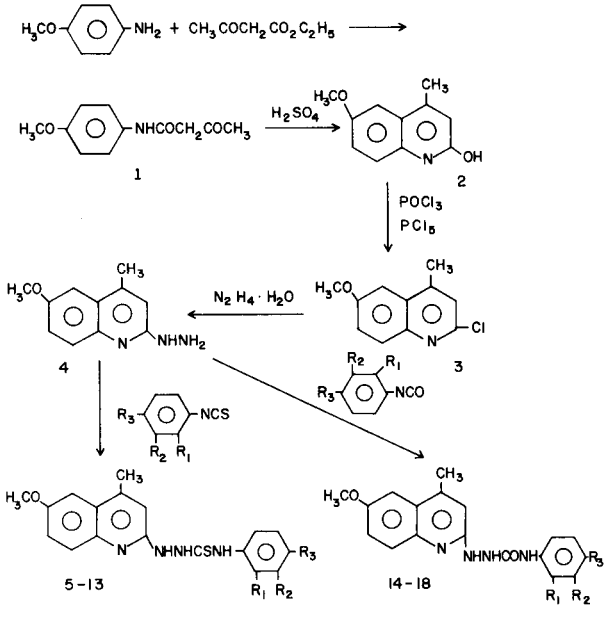
Received April 4, 1980

Several 2-aryl substituted thiosemicarbazido-4-methyl-6-methoxyquinolines and 2-aryl substituted semicarbazido 4-methyl-6-methoxyquinolines were synthesized and evaluated for their antimalarial activity in mice infected with *Plasmodium berghei*. Two of these substituted quinolines were found to exhibit 50% clearance in a dose of 500 mg./kg. administered intraperitoneally for 5 days.

J. Heterocyclic Chem., **17**, 1213 (1980).

Quinine, which contains 6-methoxyquinoline moiety, was the first alkaloid isolated from chinchona bark which possessed therapeutic usage as an antimalarial compound (2). Several synthetic compounds possessing quinoline moiety included pamaquine, chloroquine, and primaquine which were subsequently introduced for the treatment of malaria (2). These observations prompted synthesis of some 2-(4-arylthiosemicarbazido)-4-methyl-6-methoxyquinolines and 2-(4-arylsemicarbazido)-4-methyl-6-methoxyquinolines which were evaluated for their antimalarial activity. Various steps involved in the syntheses of these substituted quinolines are outlined in Scheme I.

The reaction of 4-methoxyaniline with ethyl acetoacetate yielded 4-methoxyacetoacetanilide (**1**) which was cyclized into 2-hydroxy-4-methyl-6-methoxyquinoline (**2**) in the presence of sulfuric acid. The compound **2**, on treatment with phosphorus pentachloride and phosphorus oxychloride, resulted in the formation of 2-chloro-4-methyl-6-methoxyquinoline (**3**). The chloro group of **3** was replaced by hydrazino group by refluxing **3** in the



Scheme I

Table I

Physical Constants of 2-(4-Arylthiosemicarbazido/arylsemicarbazido)-4-methyl-6-methoxyquinolines

Compound No.	R_1	R_2	R_3	Melting Points	Molecular Formula	Yield %	Analysis Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
5	H	H	H	268	$C_{18}H_{18}N_4OS$	72	65.80	5.40	16.50	65.65	5.29	16.30
6	H	F	H	352	$C_{18}H_{17}FN_4OS$	65	61.01	4.80	15.80	61.36	4.62	15.60
7	H	H	F	316	$C_{18}H_{17}FN_4OS$	75	61.01	4.80	15.80	60.82	4.94	15.70
8	OCH_3	H	H	288	$C_{19}H_{20}N_4O_2S$	68	61.90	5.40	15.10	61.74	5.54	14.90
9	H	H	OCH_3	304	$C_{19}H_{20}N_4O_2S$	70	61.90	5.40	15.10	61.82	5.62	14.89
10	CH_3	H	H	290	$C_{19}H_{20}N_4OS$	78	64.70	5.60	15.90	64.86	5.58	15.60
11	H	H	CH_3	310	$C_{19}H_{20}N_4OS$	62	64.70	5.60	15.90	64.91	5.54	15.80
12	H	H	Cl	306	$C_{18}H_{17}ClN_4OS$	77	57.90	4.50	15.03	57.76	4.32	14.90
13	H	Cl	H	314	$C_{18}H_{17}ClN_4OS$	76	57.90	4.50	15.03	58.12	4.39	14.88
14	H	H	H	174	$C_{18}H_{18}N_4O_2$	66	67.08	5.50	17.30	66.86	5.38	17.15
15	OCH_3	H	H	170	$C_{19}H_{20}N_4O_3$	70	64.70	5.65	15.90	64.58	5.45	15.78
16	H	H	Br	278	$C_{18}H_{17}BrN_4O_2$	72	54.00	4.25	11.47	53.86	4.38	11.33
17	H	H	OCH_3	202	$C_{19}H_{20}N_4O_3$	69	64.70	5.60	15.90	64.86	5.88	15.75
18	H	Cl	H	168	$C_{18}H_{17}ClN_4O_2$	78	60.50	4.70	15.68	60.74	4.54	15.42

0022-152X/80/061213-02$02.25

presence of hydrazine hydrate. The 2-hydrazino-4-methyl-6-methoxyquinoline (**4**), thus obtained, was converted into various 2-(4-arylthiosemicarbazido)-4-methyl-6-methoxyquinolines (**5-13**) and 2-(4-arylsemicarbazido)-4-methyl-6-methoxyquinolines (**14-18**) by refluxing with appropriate arylisothiocyanates or arylisocyanates.

All 2-(4-arylthiosemicarbazido)-4-methyl-6-methoxyquinolines (**5-13**) and 2-(4-arylsemicarbazido)-4-methyl-6-methoxyquinolines (**14-18**) were screened for their antimalarial activity against erythrocytic stages of *Plasmodium berghei* in mice at a dose at 150 mg./kg. None of these substituted quinolines showed any antimalarial activity at this dose. However, compound **15** and **16** exhibited 50% activity at a dose of 500 mg./kg. The approximate LD_{50} values of these compounds (**5-18**) were determined in mice and were found to be in the range of 1000 mg./kg. to >1000 mg./kg. These values reflected the low toxicity of these substituted quinolines.

EXPERIMENTAL

The melting points of these compounds were taken in open capillary tubes with partial immersion thermometer and are corrected.

4-Methoxyacetoacetanilide (**1**).

Freshly crystallized 4-methoxyaniline (0.74 mole) was added over a period of 30 minutes to ethyl acetoacetate (3.1 mole) at 160°. The mixture was held at this temperature for 30 minutes and was cooled overnight at 0°. The crude product which separated out was filtered, washed with hexane and recrystallized from ethanol, m.p. 115° (reported m.p. 115-116°) (3).

2-Hydroxy-4-methyl-6-methoxyquinoline (**2**).

4-Methoxyacetoacetanilide (0.57 mole) was added to 80 ml. of concentrated sulfuric acid over a period of 30 minutes. The temperature of the reaction mixture was maintained below 35°. The mixture was then heated with stirring to approximately 90° at which point vigorous gas evolution took place. After the reaction subsided, the temperature was maintained at 95° for 1 hour. The reaction mixture was then poured with stirring into 450 ml. of ice cold water. The solid product thus obtained was filtered, washed with water and then suspended in 200 ml. of ice-water. The suspension was treated with ammonium hydroxide until the solution became neutral. The crude product thus obtained was filtered, washed with water, and recrystallized from methanol, m.p. 273° (reported m.p. 273-274°) (3).

2-Chloro-4-methyl-6-methoxyquinoline (**3**).

A mixture of **2** (0.026 mole), phosphorus pentachloride (0.026 mole) and phosphorus oxychloride (0.065 mole) was heated under reflux for 2 hours. The reaction mixture was cooled, stirred with 215 ml. of ice-water and allowed to stand overnight. The solid mass which separated out was collected by filtration and recrystallized from ethanol, m.p. 143° (reported m.p. 143.5-144.5°) (3).

2-Hydrazino-4-methyl-6-methoxyquinoline (**4**).

Ethanolic solution of **3** (0.01 mole) was refluxed with excess of hydrazine hydrate for 16 hours. Excess of ethanol was distilled off under reduced pressure and the solid thus separated out was filtered, washed with water, and recrystallized from ethanol, m.p. 184°.

Anal. Calcd. for $C_{11}H_{11}N_3O$: C, 65.34; H, 5.94; N, 20.79; Found: C, 65.20; H, 5.88; N, 20.82.

2-(4-Arylthiosemicarbazido)-4-methyl-6-methoxyquinolines (**5-13**).

Equimolar quantities of **4** (0.01 mole) and suitable aryl isothiocyanates (0.01 mole) were refluxed in dry benzene for 4 hours. Removal of the excess of benzene under reduced pressure gave solid product which was recrystallized from dimethylformamide. These compounds (**5-13**) were characterized by their sharp melting points and elemental analyses (Table I).

2-(4-Arylsemicarbazido)-4-methyl-6-methoxyquinolines (**14-18**).

A mixture of **4** (0.01 mole) and appropriate arylisocyanates (0.01 mole) in dry benzene was refluxed on water bath for 4 hours. The excess of solvent was removed under reduced pressure. The crude product thus obtained was collected by filtration and recrystallized from dimethylformamide. The various substituted quinolines (**14-18**) were characterized by their sharp melting points and elemental analyses (Table I).

Determination of Antimalarial Activity.

The adult albino, mice kept on an *ad lib* diet, of either sex weighing 20-25 g. were used in groups of five in the present study. The animals were infected with an intraperitoneal injection of *Plasmodium berghei* (approximately one million parasites).

The test compounds (**5-18**) were suspended in peanut oil and were given intraperitoneally at a dose of 150 mg./kg. prior to the infection and continued for four consecutive days and parasitaemia was recorded in the fourth day by the method of Rane (4).

Approximate LD_{50}.

The approximate LD_{50} values of these compounds (**5-18**) were determined by intraperitoneal administration in albino mice of either sex weighing 20-25 g. by following the method reported earlier (5).

Acknowledgement.

The authors wish to express their thanks to Dr. Nitya Nand, Director Central Research Institute, Lucknow for providing facilities for microanalysis and screening of compounds for their antimalarial activity. Grateful acknowledgement is made to the Indian Council of Medical Research, New Delhi for providing Junior Research Fellowship to Miss S. Mehrotra and Dr. Earl J. Freise, Director of Research and Program Development at the University of North Dakota for providing some research support for these investigations.

REFERENCES AND NOTES

(1) Present address: Department of Chemicals and Pharmaceuticals, Council of Science and Environment, Lucknow 226001, India.

(2) The Merck Index, Edited by M. Windholz, Merck and Co. Inc., Rahway, N.J., pages 7583, 6810, 7546, and 2143 (1976).

(3) L. C. March, W. A. Romanchick, G. S. Bajwa and M. M. Joullic, *J. Med. Chem.*, **18**, 337 (1973).

(4) Rane test for blood schizonatal screening with *P. Berghei* Chemotherapy of Malaria and Resist to antimalarials, W. H. O. Tech. Report Series No. 529, Geneva (1973).

(5) C. C. Smith, *J. Pharmacol. Exp. Therap.*, **100**, 408 (1950).