

Side-Chain Analogues of 8-(4-Amino-1-methylbutylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline

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Received April 13, 1983

Six side chain analogs of the highly active antimalarial agent 8-(4-amino-1-methylbutylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline (I) were prepared and evaluated for blood and tissue schizonticidal activity. Although most examples were markedly superior to primaquine none was superior to the parent compound I.

J. Heterocyclic Chem., **21**, 33 (1984).

We have previously reported the preparation of a series of 5-aryloxy-4-methylprimaquine analogs which possessed a surprisingly high level of both blood and tissue schizonticidal activity [1]. We presently wish to report the preparation of a series of side chain analogues of one of the more active examples, 8-(4-amino-4-methylbutylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline (I), in an attempt to further increase the antimalarial activity of this class of compounds.

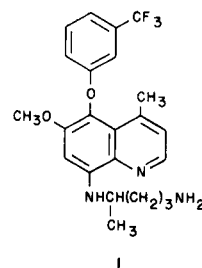
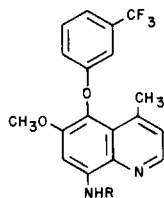


Table I

Physical Properties



| Compound No. | R | Mp, °C Solvent | Yield, % | Empirical Formula | Analysis, % | | | |
|--------------|--|---------------------------|----------|--|-------------|------|-------|-------|
| | | | | | C | H | N | F |
| 1 | -CH(CH ₃)(CH ₂) ₄ NPh _t | [a] | 40 [b] | C ₃₂ H ₃₀ F ₃ N ₃ O ₄ | | | | |
| 2 | -(CH ₂) ₃ CH(NPh _t)(CH ₃) | 122-124 Ethanol | 79 [b] | C ₃₁ H ₂₈ F ₃ N ₃ O ₄ | 66.07 | 5.01 | 7.46 | |
| 3 | -(CH ₂) ₄ CH(NPh _t)(CH ₃) | 110-111 Ethanol | 57 [b] | C ₃₂ H ₃₀ F ₃ N ₃ O ₄ | 66.54 | 5.24 | 7.27 | |
| 4 | -CH(C ₂ H ₅)(CH ₂) ₃ NPh _t | 185-187 [c] 2-Propanol | 40 [b] | C ₃₂ H ₃₁ ClF ₃ N ₃ O ₄ | 62.59 | 5.09 | 6.84 | 9.28 |
| 5 | -CH(CH ₃)(CH ₂) ₄ NH ₂ | ~ 85 [d] | 52 [e] | C ₂₄ H ₃₁ F ₃ N ₃ O ₆ P [f] | 52.84 | 5.73 | 7.70 | 10.45 |
| 6 | -(CH ₂) ₃ CH(CH ₃)NH ₂ | 177-179 | 53 [e] | C ₂₅ H ₂₉ F ₃ N ₃ O ₄ [g] | 52.59 | 5.93 | 7.44 | 10.10 |
| 7 | -(CH ₂) ₄ CH(CH ₃)NH ₂ | 149-151 Ethanol | 75 [e] | C ₂₆ H ₃₃ F ₃ N ₃ O ₅ [h] | 60.97 | 5.95 | 8.53 | 11.57 |
| 8 | -CH(C ₂ H ₅)(CH ₂) ₃ NH ₂ | 137-139 Acetonitrile | 60 [e] | C ₂₈ H ₃₄ F ₃ N ₃ O ₆ [i] | 61.07 | 6.34 | 8.01 | 10.87 |
| 9 | -CH(CH ₃)(CH ₂) ₃ NHCH(CH ₃) ₂ | 145-147.5 Acetonitrile | 81 [j] | C ₃₀ H ₃₈ F ₃ N ₃ O ₆ [i] | 59.27 | 6.37 | 8.08 | 11.00 |
| 10 | -CH(CH ₃)(CH ₂) ₃ NH-(1-ethyl-3-piperidyl) [k] | | 72 [j] | C ₃₀ H ₃₉ F ₃ N ₄ O ₂ | 59.46 | 6.06 | 7.43 | 10.08 |
| | | | | | 60.61 | 6.48 | 9.48 | 7.23 |
| | | | | | 66.16 | 7.22 | 10.29 | |
| | | | | | 66.15 | 6.99 | 10.49 | |

[a] Oil, not analyzed. [b] From 8-aminoquinoline. [c] Hydrochloride salt. [d] Indefinite melting point. [e] From phthalimido intermediate. [f] Phosphate salt. [g] Hemisuccinate salt. [h] Hemisuccinate hydrate. [i] Succinate salt. [j] From compound I. [k] Free base, mixture of two diastereoisomers.

Table II
Antimalarial Activity Data

| Compound No. [a] | <i>P. berghei</i> (Rane Mouse) [b], mg/kg, ΔMST (day), 5 mice | | | | | | <i>P. cynomolgi</i> (Rhesus) [c], mg/kg (salt)/day (× 7) | | | | | |
|------------------|---|----|----------|----|-------|--------|--|-------|------|------|-------|-----|
| | 5 | 10 | 20 | 40 | 80 | 160 | 320 | 640 | 10 | 1.0 | 0.316 | 0.1 |
| 5 | I | I | 13.0 (A) | 4C | 4C | 5C | 5C | 5C | | 3/3C | I | I |
| 6 | | I | 4C | 5C | 3C,2T | 5T | 5T | 5T | | 2/2C | 2/4C | I |
| 7 | 13 (A) | 3C | 5C | 5C | 4C | 4C | 5T | 5T | | 2/2C | I | I |
| 8 | I | 3C | 5C | 5C | 5C | 5C | 5C | 3C,2T | | 2/2C | 1/2C | I |
| 9 | | | | I | I | | 5 | 5T | 1/1C | 3/3C | 1/2C | I |
| 10 | | | I | I | I | I | 9.6 (A) | 4C | 1/1C | 1/1C | 1/1C | I |
| Primaquine [d] | | | | I | I | 16 (A) | 2T | 5T | | 1/2C | I | I |
| I [e] | 1C | 3C | 5C | 5C | 5C | 5C | 5C | 1C,4T | | 2/2C | 2/2C | I |

[a] For structures see Table I. [b] See reference [3], A = Active, C = Cure, T = Toxic, I = Inactive; administration Procedure sc. [c] See reference [4], C = Cure, I = Inactive, administration procedure p.o. [d] Administered as the diphosphate salt. [e] Administered as the succinate salt.

Chemistry.

The six side chain analogs of I [5-10] are listed in Table I. Target compounds **5-8** were prepared *via* condensation of 8-amino-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline [1] with the appropriate phthalimido-protected amino alkyl halide as described earlier [2]. Removal of the phthalimide protection with hydrazine hydrate involved standard procedures [2]. Target compounds **9** and **10** were prepared *via* condensation of I with acetone and *N*-ethyl-3-piperidone respectively under reductive amination conditions.

Biological Activity.

Compounds **5-10** were evaluated for blood schizonticidal activity against *P. berghei* in mice [3] and for tissue schizonticidal (radical curative) activity against *P. cynomolgi* in the Rhesus monkey [4]. The data are listed in Table II. The activity data for primaquine and compound I have been included for the purpose of comparison. Three analogs were superior to primaquine in terms of both blood and tissue schizonticidal activity; however, none was superior to compound I. The data indicate, therefore, that the 4-amino-1-methylbutylamino side chain appears to be optimal.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 237B spectrometer. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis, Indiana. The nmr spectra were determined on a Varian Model T60A spectrometer. Ethanol used in this work was specially denatured grade 3A alcohol (90% ethanol, 5% 2-propanol and 5% methanol, v/v). Commercial Raney nickel was purchased from W. R. Grace Co. (No. 30). Silica gel was purchased from EM Labs (70-230 mesh).

6-Methoxy-4-methyl-8-[(5-phthalimido-1-methylpentyl)amino]-5-(3-trifluoromethylphenoxy)quinoline (1).

A mixture of 8-amino-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline (10.0 g, 0.029 mole), 5-iodo-1-phthalimido-hexane [2] (14.0 g, 0.039 mole), sodium bicarbonate (5.0 g, 0.06 mole) and ethanol (30 ml) was stirred and heated under reflux for 48 hours. The reaction mixture was poured into chloroform (75 ml) and washed successively with 5% potassium hydroxide (25 ml) and water. After drying (potassium carbonate), the solution was filtered and the filtrate was stripped of solvent to give a dark oil. Partial purification was obtained by chromatography on silica gel (250 g) with benzene. Re-chromatography on silica gel (750 g) with chloroform afforded the title compound as an orange oil, 6.7 g (40%) which was used in the hydrazinolysis reaction without further purification.

6-Methoxy-4-methyl-8-(4-phthalimido-1-pentylamino)-5-(3-trifluoromethylphenoxy)quinoline (2).

A solution of 8-amino-6-methoxy-4-methyl-8-(3-trifluoromethylphenoxy)quinoline (5.26 g, 15 mmoles), 1-iodo-4-phthalimidopentane (supplied by WRAIR, 5.26 g, 15 moles) in 2-ethoxyethanol (25 ml) was heated at 110° for 1.5 hours after which time an additional 7.5 mmoles of iodo-phthalimidopentane and triethylamine were added. After stirring 1.5 hours an additional 7.5 mmoles of each reagent was added. After stirring an additional 4.5 hours the reaction mixture was diluted with dichloromethane and the organic layer was washed with water (× 3). After drying (potassium carbonate) the organic layer was concentrated to dryness and the residue was chromatographed over a silica gel column (33 mm × 500 m). Elution with chloroform afforded the intermediate phthalimide (6.65 g, 79%) which could be crystallized from ethanol to give mp 122-123.4°.

Anal. Calcd. for C₃₁H₂₈F₃N₃O₄ (563.6): C, 66.07; H, 5.01; N, 7.46. Found: C, 66.37; H, 4.97; N, 7.46.

6-Methoxy-4-methyl-8-(5-phthalimido-1-hexylamino)-5-(3-trifluoromethylphenoxy)quinoline (3).

The title compound was prepared *via* the procedure described above for the preparation of **2**. The yield of the phthalimide intermediate was 57%, mp 109.5-111° (eff, ethanol).

Anal. Calcd. for C₃₂H₃₀F₃N₃O₄ (577.6): C, 66.54; H, 5.24; N, 7.27. Found: C, 66.38; H, 5.04; N, 7.33.

6-Methoxy-4-methyl-8-(4-phthalimido-1-ethylbutylamino)-5-(3-trifluoromethylphenoxy)quinoline Hydrochloride (4).

A solution of 8-amino-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline [1] (10 g, 29 mmoles), 4-iodo-1-phthalimido-hexane (IPH, 10 g, 28 mmoles), triethylamine (TEA, 4.5 cc) and 2-ethoxyethanol (10 ml) were heated at 115° for 2 ½ hours. One equivalent of IPH and TEA was added and the solution was heated at 115° an additional 2 ½ hours. One-half equivalent each of IPH and TEA was added and the reaction mixture

was heated five hours longer. The reaction mixture was diluted with chloroform and washed with water ($\times 3$). The organic layer was dried (potassium carbonate) and concentrated to dryness *in vacuo*. The oily residue was combined with that obtained from another 8.5 g run and chromatographed over a silica gel column (EM Labs). Elution with chloroform and collection of the fast-moving yellow band afforded the desired phthalimide intermediate (ca. 12 g) contaminated with some IPH. The slower moving material, ca. a 1/1 mixture of product and starting 8-aminoquinoline, was then collected and recycled with IPH and TEA as described above. An additional 7 g of crude product was obtained. The crude material from both runs was combined, dissolved in hot isopropyl alcohol and acidified with 2.7 N hydrogen chloride-2-propanol to afford pure phthalimide hydrochloride, 13.2 g (40%), mp 185-187°.

Anal. Calcd. for $C_{22}H_{31}F_3ClN_3O_4$: C, 62.59; H, 5.09; F, 9.28; N, 6.84. Found: C, 62.64; H, 5.02; F, 9.07; N, 6.71.

8-(5-Amino-1-methylpentylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline Phosphate (5).

A mixture of 1 (6.7 g, 0.012 mole), 95% aqueous hydrazine (1.9 g, 0.06 mole) and ethanol (100 ml) was heated under reflux for 4 hours. Water (50 ml) was added and the ethanol was distilled *in vacuo*. Aqueous potassium hydroxide (4 g in 20 ml water) was added and the mixture was extracted with ether (3×30 ml). The combined ether extract was washed with water (50 ml), dried (potassium carbonate), filtered and the filtrate was evaporated to give an oil, 4.1 g (77%). An additional 5.9 g of the title free base was prepared to give a total of 10.0 g for conversion to the phosphate salt. The above 10.0 g of amine was dissolved in ethanol (68 ml) and treated with 1 M phosphoric acid in ethanol (20.2 ml, 0.9 equivalent). The solution was filtered and the filtrate was diluted with ether (300 ml). The resulting yellow solid (9.6 g) was collected and washed with ether (2×50 ml). Recrystallization from ethanol-methanol-ether (200 ml-50 ml-50 ml) gave the phosphate salt as yellow powder, 8.2 g (52%), mp $> 85^\circ$ (indefinite).

Anal. Calcd. for $C_{24}H_{28}F_3N_3O_2 \cdot H_3PO_4$ (545.5): C, 52.84; H, 5.73; F, 10.45; N, 7.70. Found: C, 52.59; H, 5.93; F, 10.10; N, 7.44.

8-(4-Amino-1-pentylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline Hemisuccinate (6).

Phthalimide [2] (7.5 g, 14.8 mmoles) was heated at reflux with hydrazine hydrate (75%, 2.2 ml) in ethanol (125 ml) for nine hours as described for 5. The crude oily free base was dissolved in methanol and a solution of succinic acid (1.75 g, 14.8 mmoles) in methanol (10 ml) was added. The solution was concentrated to dryness and the solid residue was crystallized from acetonitrile (100 ml) to yield the succinate salt (5.2 g), mp 125-127° (eff). Recrystallization from ethanol gave 3.9 g (53%), mp 177-178.5°.

Anal. Calcd. for $C_{23}H_{26}F_3N_3O_2 \cdot 1/2C_4H_6O_4$ (492.5): C, 60.97; H, 5.93; F, 11.57; N, 8.53. Found: C, 61.07; H, 5.95; F, 11.47; N, 8.60.

8-(5-Amino-1-hexylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline Hemisuccinate Hydrate (7).

The phthalimide intermediate [3] (10 g, 17.3 mmoles) was converted to the target diamine as described for 5. The yield was 75%, mp 149-151° (ethanol, dried *in vacuo* at 78°).

Anal. Calcd. for $C_{24}H_{28}F_3N_3O_2 \cdot 0.5C_4H_6O_4 \cdot H_2O$ (524.6): C, 59.53; H, 6.34; F, 10.87; N, 8.01. Found: C, 59.27; H, 6.37; F, 11.0; N, 8.08.

Anal. (block dried at 130°) Calcd. for $C_{24}H_{28}F_3N_3O_2 \cdot 0.5C_4H_6O_4$: C, 61.65; H, 6.17; N, 8.30. Found: C, 61.39; H, 5.93; N, 8.30.

8-(4-Amino-1-ethylbutylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline Succinate (8).

Phthalimide [4] in dichloromethane was converted to the free base with dilute aqueous ammonium hydroxide. After drying and concentrating the organic layer, the residual oil was heated in ethanol (125 cc) containing 75% hydrazine hydrate (4.0 ml). Additional hydrazine hydrate was added after three hours (2 ml) and after 4 1/2 hours (1 ml). The reaction was heated an additional two hours and the reaction mixture was concentrated *in vacuo*. The residue was shaken with 20% aqueous

potassium hydroxide and ether and the ether was removed *in vacuo*. The base (7.5 g) was dissolved in ether (100 ml) and the solution was added to a solution of succinic acid (2.0 g) in ether (325 ml). The slurry was stirred for 3.5 hours and filtered to yield the title compound (8.7 g, 72%), mp 107-110° (eff), with shrinking at 103°. This material was recrystallized from acetonitrile (140 ml) and filtered after 48 hours to give pure title compound (7.5 g, 60%) mp 137-139° (eff), shrinks 135°.

Anal. Calcd. for $C_{24}H_{28}F_3N_3O_2 \cdot C_4H_6O_4$ (565.6): C, 59.46; H, 6.06; F, 10.08; N, 7.43. Found: C, 59.58; H, 5.90; F, 9.80; N, 7.63.

8-(4-Isopropylamino-1-methylbutylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline Succinate (9).

A solution of 8-(4-amino-1-methylbutylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline [1] (4.7 g, 10.8 mmoles) in ethanol (60 ml) containing acetone (1.8 ml), prerduced platinum oxide (0.6 g) and molecular sieves (3A) was reduced on a Parr apparatus at 45 psig for 5 hours. An additional quantity of acetone (0.9 ml) was added and the reduction was continued an additional 18 hours. The catalyst and molecular sieves were filtered (celite) and the solvent was removed *in vacuo*. The residue was dissolved in acetonitrile (50 ml) and succinic acid (1.35 g, 1 mole equivalent) was added with stirring. After cooling in the refrigerator overnight and the solid was filtered to yield the title compound (5.8 g, 91%), mp 143-146°. Recrystallization from acetonitrile (75 ml) afforded 5.2 g (81%), mp 145-147°.

Anal. Calcd. for $C_{30}H_{38}F_3N_3O_4$: C, 60.70; H, 6.45; F, 7.08; N, 9.60. Found: C, 60.61; H, 6.48; F, 7.23; N, 9.48.

8-[4-(1-Ethyl-3-piperidylamino)-1-methylbutylamino]-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline (10).

A solution of 8-(4-amino-1-methylbutylamino)-6-methoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinoline [1] (9.6 g, 22 mmoles) in ethanol (200 ml) containing triethylamine (1.8 ml), *N*-ethyl-3-piperidone hydrochloride (12 g, 73 mmoles) and platinum oxide (1 g) was reduced at 45 psig for 20 hours. The catalyst was filtered through celite and the filtrate was concentrated under reduced pressure. The residue was shaken with ether and aqueous potassium hydroxide. The ether layer was washed with water, dried (potassium carbonate) and concentrated. The oily residue (15 g) was chromatographed over silica gel eluting first with chloroform to remove a faster moving impurity and then with chloroform-water (20:1). The product fractions were collected and after concentration the title compound, 8.6 g (72%) was obtained as an oil. The material was chromatographically homogeneous but attempts to prepare a crystalline salt were not successful presumably due to the existence of two diastereoisomers.

Anal. Calcd. for $C_{30}H_{39}F_3N_4O_2$: C, 66.16; H, 7.22; N, 10.29. Found: C, 66.15; H, 6.99; N, 10.49.

Acknowledgement.

This work was supported by the U. S. Army Medical Research and Development Command under Contract DADA17-69-C-9065. This is contribution No. 1582 from the Army Research Program on Antiparasitic Drugs. The advice and timely suggestions of Drs. T. R. Sweeney and R. E. Strube, of the Walter Reed Army Institute of Research are gratefully acknowledged. Mouse testing was performed by Dr. Arba L. Ager of the Rane Laboratory, University of Miami, Florida. Monkey testing was performed by David E. Davidson, Jr. VMD, Ph.D., F. Chapple, DVM, and J. Brown, DVM of the Armed Forces Institute of Medical Services, Bangkok, Thailand.

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