One pot synthesis of tetrahydroquinoline-5-thiones and evaluation of their antimicrobial activities

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One-pot syntheses of various tetrahydroquinoline-5-thiones are reported. The antimicrobial activity of the obtained products against various types of bacteria was estimated.

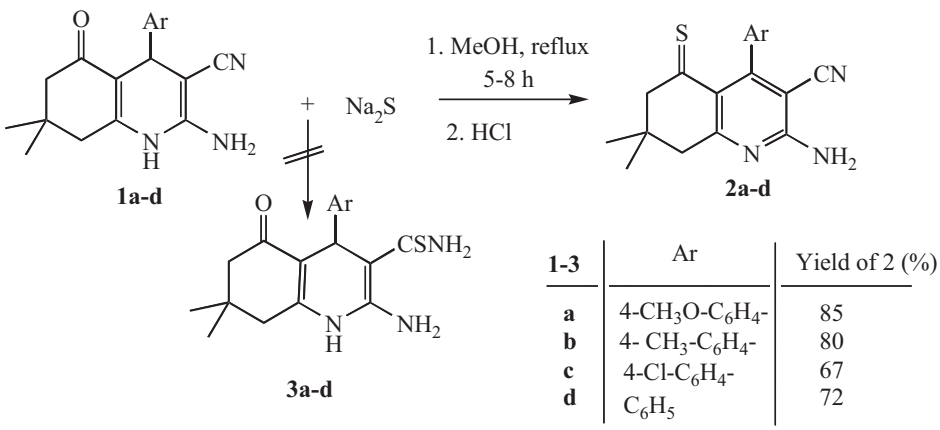
Keywords**:** dihydropyridines, tetrahydroquinoline-5-thiones, antimicrobial activity

The oxidation of 1,4-dihydropyridines (1,4-DHPs) to the corresponding pyridines occurs initially during the first pass metabolism in the liver.[1] A variety of reagents has been utilised for this oxidative conversion: nitric acid,[2] manganese dioxide–bentonite clay,[3] chromium trioxide,[4,5] potassium permanganate,[6] pyridinium chlorochromate,[7] ceric ammonium nitrate (CAN),[8] clayfen,[9] bismuth trinitrate,[10] and ruthenium trichloride.[11] However, most of these reactions require an extended period of time for completion, utilise strong oxidants in large excess, and give only modest yields of the products. Varma[12] demonstrated that solid state oxidation of 1,4-DHPs using elemental sulfur yields the dehydro derivatives, whatever the 4-substituent is. Bagley reported that substituted arene- or heteroarene-carbonitriles can be converted into the corresponding thioamides, when treated with sodium sulfide solution in methanol at reflux.[13] Subsequently, we have applied those conditions to 2-amino-4-aryl-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **1a**–**d**, and we described the results herein. We also tested the activity of the obtained products as antimicrobial compounds. Having been interested in the synthesis of pyridines that carry heterocyclic substituents for some time,[14] we now report the preparation of tetrahydroquinoline-5-thiones by a novel, efficient and facile procedure.

Results and discussion

The reaction of compounds **1a**–**d** with sodium sulfide in refluxing aqueous methanol (Scheme 1), followed by treatment of the aqueous layer with a few drops of concentrated hydrochloric acid (until pH=7), afforded the corresponding tetrahydroquinoline-5-thiones **2a**–**d** in good yields (Scheme 1).

The formation of compounds **2a**–**d** is emphasised by the precedence of the activity of sulfur atom in the oxidation under acidic conditions.[15,16] The structures of **2a**–**d** were confirmed by spectroscopic data and elemental analyses. EI-MS gave molecular ion peaks related to the molecular weight of the suggested structures. The ^{1}H NMR, ^{13}C NMR and IR spectra of **2a**–**d** generally were consistent with the suggested structures. The IR spectra of **2a**–**d** generally exhibited absorption bands at ν = 1200–1170 and 1322–1312 (C=S), 2220–2210 (CN), and 3240–3200 cm^{-1} (NH_2). For example, in compound **2a** these appeared at ν = 1170, 1320, 2212, and 3240 cm^{-1} respectively. In ^{1}H NMR spectra, compounds **2a**–**d** lack the characteristic dihydropyridine- NH and 4-CH signals (δ = 11.00–12.00 and 4.20–4.80 respectively)[17] found in the starting materials **1a**–**d**. Three singlets were observed at δ = 6.10–6.30 (broadened), 3.22–3.10, and 1.06–0.97 ppm corresponding to the NH_2, 8-CH_2 and CH_3 protons, respectively. Distinctive δ' values of the ^{1}H NMR spectrum of compound **2a** are as shown in Fig. 1. As an example, the ^{13}C NMR spectrum of **2a** (see also Fig. 1) revealed distinctive signals at δ = 182.0, 164.0, 160.0, 143.0, 128.0, 126.0 and 99.0 assignable to C-5, C-8a, Ar-C-4', C-2, C–4, C-4a and C-3, respectively (Fig. 1). In the case of **2c**, the ^{1}H NMR spectrum revealed the NH_2-protons as a broad singlet at δ = 6.22 ppm, whereas the protons in the *p*-chlorophenyl ring resonated as two double-doublets, each for two protons, at δ = 7.22 and 7.03 ppm (J = 8.0, 1.2 Hz). The ^{13}C NMR spectrum of **2c** showed the thione group at δ = 182.8 along with C-4, C-2 and nitrile at δ = 138.6, 126.8 and 113.5 ppm, respectively. The carbon signals of all substitutes of compounds **2a**–**d** were completely recognised from their ^{13}C NMR spectra (see the Experimental). For example, compound



1-3	Ar	Yield of 2 (%)
a	4-CH_3O-C_6H_4-	85
b	4- CH_3-C_6H_4-	80
c	4-Cl-C_6H_4-	67
d	C_6H_5	72

Scheme 1 Synthesis of tetrahydrquinoline-5-thiones **2a–d.**

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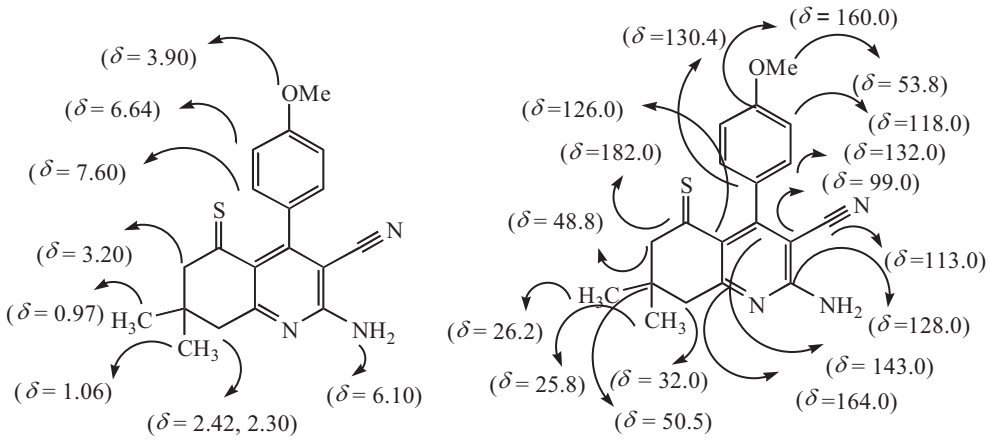

Fig. 1 Disctinctive δ's values of compound **2a**.

2b has carbon signals at δ = 182.6 (C-5), 163.6 (C-8a), 142.0 (C-4), 134.0 (ArC-4'), 130.8 (2 ArCH, CH-2', -6'), 128.6 (ArC-1'), 127.6 (C-2), 126.8 (C-4a), 126.2 (2 ArCH, CH-3', -5'), 113.4 (CN), 99.4 (C-3), 50.2 (C-7), 48.4 (C-6), 34.2 (CH_3), 32.2 (C-8), 26.0 (CH_3), 25.6 (CH_3).

The synthesised compounds were tested for their antibacterial activity by adopting (Cup–plate method)[18,19] the agar well diffusion technique. The following bacterial cultures were used for anti-bacterial activity studies: *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli,* and *Klebsiella pneumoniae.* From Table 1 it is evident that the newly synthesised compounds **2a–d** have no antibacterial activity against *S. aureus* and *B. subtillus* (Gram positive) while they have antimicrobial activity against *E.coli* and *K. pneumoniae* (Gram negative). Also, it was noted that compounds **2a–d** are more potent against *E.coli* and *K. pneumoniae* than the standard drug Ciprofloxacin with MIC ranged from 6.25 to 12.5 and 6.25 to 20 μg/ml respectively. Compound **2a** showed more antimicrobial activity than **2b, 2c,** or **2d**, against either *E.coli* or *K. pneumoniae.*

In conclusion, we have developed simple, rapid and practical method for sulfurisation and oxidation of 1,4-dihydropyridinones to thienopyridines. Thienopyridines are proved to be effective antimicrobial gram negative bacteria.

Experimental

General

All melting points were recorded on a Gallenkamp apparatus. ^{1}H NMR (400.134 MHz) and ^{13}C NMR (100.6 MHz) spectra were measured in DMSO-d_6, on a Bruker AM 400 spectrometer. Chemical shifts are expressed in δ, and coupling constants are expressed in Hz. Elemental analyses were carried at the Cairo Microanalysis Centre of Ca iro University. The IR spectra were run on a Shimadzu 470 spectrometer using KBr pellets; absorption frequencies are expressed in cm^{-1}. All the microorganisms used were obtained from the laboratory stock of the Department of Microbiology; Faculty of Pharmacy, El-Minia University. Ciprofloxacin was used as the standard drug. Nutrient agar was poured onto the sterilised Petri dishes (20–25 ml: each petri dish). The poured material was allowed to set (1–1.5 h) and thereafter the 'CUPS' (10 mm diameter) was made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups the test compound solution was added *via* a sterile syringe. The plates were incubated at 37°C for 48 h and the results were noted. A solvent control (DMF) was also run. Further dilutions of the compounds and standard drug in the test medium were prepared at the quantities of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 μg/ml. The minimum inhibitory concentrations (MIC) were determined using the two-fold serial dilution technique.[19,20]

Starting materials

Dihydropyridines **1a–d** were prepared according to ref. 17.

Table 1 Minimum inhibitory concentration of the tested compounds **2a–d**

Compound	Minimum inhibitory concentration in μg/ml			
	S. aureus	*B. subtillus*	*E. coli*	*K. pneumoniae*
Ciprofloxacin	50	50	25	25
2a	0	0	6.25	6.25
2b	0	0	12.5	20
2c	0	0	12.5	12.5
2d	0	0	6.25	12.5

Synthesis of 2-amino-4-aryl-7,7-dimethyl-5-thioxo-5,6,7,8-tetrahydroquinoline-3-carbonitriles (**2a–d**)

General procedure

A mixture of **1a–d** (1 mmol) and sodium sulfide (2.0 mmol, 0.16 g) in methanol (50 ml) was heated at reflux for 5–8 h. The precipitate formed was filtered off and a few drops of concentrated hydrochloric acid were added to the clear solution till pH = 7. The solid material formed was collected by filtration and purified by recrystallisation to give products **2a–d**.

2-Amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-thioxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile **(2a):** Pale orange crystals (0.29 g, 85%), m.p. 320–322°C (ethanol). ^{1}H NMR: δ = 7.60 (dd, 2 H, ArH, *J* = 8.2, 1.2 Hz), 6.64 (dd, 2 H, ArH, *J* = 8.2, 1.2 Hz), 6.10 (br s, 2 H, NH_2), 3.90 (s, 3 H, OCH_3), 3.20 (s, 2 H, 6-CH_2), 2.42 (d, 1 H, 8-H, *J* = 16.1 Hz), 2.30 (d, 1 H, 8'-H, *J* = 16.1 Hz), 1.06 (s, 3 H, CH_3); 0.97 (s, 3 H, CH_3). ^{13}C NMR: δ = 182.0 (C-5), 164.0 (C-8a), 160.0 (ArC-4'), 143.0 (C-4), 132.0 (ArCH-2',6'), 130.4 (ArC-1'), 128.0 (C-2), 126.0 (C-4a), 118.0 (ArCH-3',5'), 113.0 (CN), 99.0 (C-3), 53.8 (OCH_3), 50.5 (C-7), 48.8 (C-6), 32.0 (C-8), 26.2 (CH_3), 25.8 (CH_3). IR: ν = 3240 (m, NH_2), 3030-2980 (m, ArCH), 2970–2765 (m, aliph-CH), 2212 (m, CN), 1610 (s, C=N), 1595 (m, C=C), 1320, 1170 (s, C=S). MS (70 eV), *m/z* (%) = 337 [M$^+$] (100), 322 (18), 306 (36), 290 (28), 264 (18), 250 (30), 234 (16), 229 (28), 108 (60), 77 (34). Anal. Calcd. for $C_{19}H_{19}N_3OS$ (337.45): C, 67.63; H, 5.68; N, 12.45; S, 9.50. Found: C, 67.58; H, 5.64; N, 12.50; S, 9.59.

2-Amino-4-(4-methylphenyl)-7,7-dimethyl-5-thioxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile **(2b):** Yellow crystals (0.26 g, 80%), m.p. 311–313°C (acetone). ^{1}H NMR: δ = 7.50–7.28 (m, 4 H, ArH), 6.30 (br s, 2 H, NH_2), 3.22 (s, 2 H, 6-CH_2), 2.40 (d, 1 H, 8-H, *J* = 15.9 Hz), 2.34 (s, 3 H, CH_3Ar), 2.30 (d, 1 H, 8'-H, *J* = 15.9 Hz), 1.10 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3). ^{13}C NMR: δ = 182.6 (C-5), 163.6 (C-8a), 142.0 (C-4), 134.0 (ArC-4'), 130.8 (ArCH-2',6'), 128.6 (ArC-1'), 127.6 (C-2), 126.8 (C-4a), 126.2 (ArCH-3',-5'), 113.4 (CN), 99.4 (C-3), 50.2 (C-7), 48.4 (C-6), 34.2 (CH_3), 32.2 (C-8), 26.0 (CH_3), 25.6 (CH_3). IR (KBr): ν = 3210 (m, NH_2), 3050–2990 (m, ArCH), 2972–2770 (m, aliph-CH), 2210 (m, CN), 1612 (s, C=N), 1560 (s, C=C), 1318, 1175 (s, C=S). MS (70 eV), *m/z* (%) = 321 [M$^+$] (100), 304 (32), 288 (32), 264 (22), 250 (28), 234 (20), 229 (30), 91 (56), 77 (30). Anal. Calcd for $C_{19}H_{19}N_3S$ (321.44): C, 70.99; H, 5.96; N, 13.07; S, 9.98. Found: C, 70.85; H, 5.90; N, 13.11; S, 9.90.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-thioxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile **(2c):** Yellow crystals (0.23 g, 67%), m.p. 350–352°C (EtOH). ^{1}H NMR: δ = 7.22 (d, 2 H, ArH, *J* = 8.0, 1.2 Hz), 7.03 (dd, 2 H, ArH, *J* = 8.0, 1.2 Hz), 6.22 (br s, 2 H, NH_2), 3.18 (s, 2 H, 6-CH_2), 2.38 (d, 1 H, 8-H, *J* = 15.9 Hz), 2.20 (d, 1 H, 8'-H, *J* = 15.9 Hz), 1.20 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3). ^{13}C NMR: δ = 182.8 (C-5), 166.2 (C-8a), 138.6 (C-4), 128.8 (ArC-1'), 128.0 (ArC-1'), 128.6 (C-4a) 126.8 (C-2), 126.1 (ArC-4'), 125.4 (ArCH,-3',5'), 123.2 (ArCH-2',6'), 113.5 (CN), 99.6 (C-3), 51.0 (C-7), 48.4 (C-6), 31.6 (C-8), 27.0 (CH_3), 26.0 (CH_3). IR (KBr): ν = 3200 (m, NH_2), 3040-2980 (ArCH), 2220 (m, CN), 1600 (s, C=N), 1587 (s, C=C), 1312, 1180 (m, C=S). MS (70 eV), *m/z* (%) = 341 [M^+] (100), 339 (34), 322 (18), 324 (14), 308 (40), 306 (36), 290 (28), 264 (18), 262 (24), 250 (30), 234 (16), 229 (28), 115 (52), 113 (60), 77 (34). Anal. Calcd for $C_{18}H_{16}ClN_3S$ (341.86): C, 63.24; H, 4.72; Cl, 10.37; N, 12.29; S, 9.38. Found: C, 63.21; H, 4.69; Cl, 10.66; N, 12.32; S, 8.40.

2-Amino-4-phenyl-7,7-dimethyl-5-thioxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile **(2d):** Yellow crystals (0.22 g, 72%), m.p. 330–332°C (acetone). ^{1}H NMR: δ = 7.40–7.00 (m, 5 H, Ar-H), 6.30 (br s, 2 H, NH_2), 3.10 (s, 2 H, 6-CH_2), 2.40 (d, 1 H, 8-H, *J* = 16.0 Hz), 2.20 (d, 1 H, 8'-H, *J* = 16.0 Hz), 1.10 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3). ^{13}C NMR: δ = 184.0 (C-5), 163.5 (C-8a), 144.0 (C-2), 139.6 (C-4), 134.8 (ArC-1'), 129.7 (C-4a), 128.6 (ArCH-3',5'), 127.2 (ArCH-2',6'), 126.2 (Ar*p*-CH), 113.4 (CN), 98.2 (C-3), 51.4 (C-7), 50.0 (C-6), 32.4 (C-8), 26.8 (CH_3), 26.0 (CH_3). IR (KBr): ν = 3228 (m, NH_2), 3026–2968 (Ar-CH), 2218 (m, CN), 1612 (s, C=N), 1590 (s, C=C), 1322, 1170 (m, C=S). MS (70 eV), *m/z* (%) = 307 [M^+] (100), 290 (26), 262 (22), 248 (28), 234 (20), 229 (26), 77 (54). Anal. Calcd. for $C_{18}H_{17}N_3S$ (307.41): C, 70.33; H, 5.57; N, 13.67; S, 10.43. Found: C, 70.29; H, 5.50; N, 13.62; S, 10.40.

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