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Il Farmaco 55 (2000) 725–729

IL FARMACO

Quinazoline derivatives with antitubercular activity

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Received 26 April 2000; accepted 12 September 2000

Abstract

4-Quinazolinol was prepared by the reaction of anthranilic acid and formamide. The hydroxy group was converted into the thiol function by treatment with phosphorus(V)sulfide, and the subsequent alkylation of the thiol group was carried out with alkylhalides under the conditions of phase-transfer catalysis. The structure of the substances was confirmed by ^{1}H, ^{13}C NMR, IR, and MS. Most of the synthesized compounds exhibited antimycobacterial activity against the strains of *Mycobacterium tuberculosis*, *Mycobacerium avium*, *Mycobacterium fortuitum*, *Mycobacterium kansasii* and *Mycobacterium intracellulare*. 4-(S-Butylthio)quinazoline (**3c**) was even more active than isoniazide against atypical strains of mycobacteria.

Keywords: Quinazoline; Alkylthioquinazoline; Antimycobacterial activity

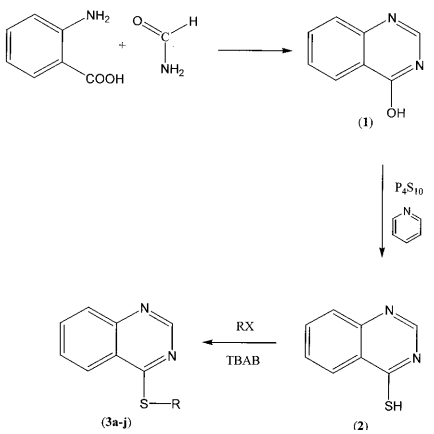
1. Introduction

In the course of the research into potential antitubercular agents, an important relationship was found between the structure and antitubercular effect, as the alkylthio group bound to an electron-deficient carbon atom was identified as a possible pharmacophore of antitubercular activity [1]. This hypothesis was confirmed for a number of compounds containing this structural moiety, such as 2-alkylthiobenzothiazoles [2–4], 1-aryl-5-alkylthio-1.2.3.4-tetrazoles [5,6], substituted 4-alkylthiopyridine-4-carbothioamides and 4-carbonitriles, and substituted 2-alkylthiopyridine-4-carbothioamides and 4-carbonitriles [7]. The aim of this work was to verify the validity of the above hypothesis for the derivatives of quinazoline. It was thus necessary to prepare a set of derivatives of 4-alkylthioquinazoline, and to assess their activity against various strains of mycobacteria.

2. Chemistry

The precursor of the target compounds, 4-quinazolinol (**1**) was prepared by the condensation of formamide with anthranilic acid [8] (Scheme 1).

In the following step, the hydroxy group in position 4 of the quinazoline skeleton was converted into the thiomoiety by the treatment of **1** with phospho-



Scheme 1. TBAB: tetrabutylammonium bromide.

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0014-827X/00/$ - see front matter
PII: S0014-827X(00)00100-2

rus(V)sulfide in anhydrous pyridine, which yielded compound **2**.

To prepare 4-alkylthioquinazolines, two alkylation methods were chosen: alkylation under the conditions of classical nucleophilic substitution, and under the conditions of phase-transfer catalysis. Comparison of both methods showed that better results were obtained with the use of phase-transfer catalysts. The target compounds (**3a**–**j**) were thus obtained by the reaction of 4-quinazolinethiole and the appropriate alkylhalide in a two-phase medium with tetrabutylammonium bromide as a catalyst.

The structures of the prepared compounds were confirmed by spectral methods (IR, ^{1}H, ^{13}C NMR and MS).

3. Experimental

3.1. Chemistry

The melting points of the substances were determined on a Koffler apparatus and are uncorrected. IR spectra were obtained on a Nicolet Impact 400 spectrometer in KBr pellets or in chloroform. The ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at ambient temperature on a Varian Mercury–Vx BB 300 spectrometer operating at 300 MHz. Chemical shifts were recorded as δ values in parts per million (ppm), and were indirectly referenced to tetramethylsilane via the solvent signal (7.26 for ^{1}H and 77.0 for ^{13}C). Multiplicities are given together with the coupling constants (in Hz). Mass spectra of all substances were measured on a MAGNUM FINNIGAN MAT spectrometer with low resolution.

The reactions and the purity of all compounds was checked by TLC (Silufol $UV_{254/366}$, Kavalier, Votice, Czech Republic) in petrolether–ethylacetate (8:2) using UV detection and iodine vapours.

3.2. General procedure for the synthesis of the compounds

3.2.1. 4-Quinazolinol (*1*)

A mixture of formamide (7.5 g, 170 mmol) and anthranilic acid (13.7 g, 100 mmol) was stirred at 120–125°C for 4 h. The crude product was then filtered off, and recrystallized from ethanol. Yield 47%, m.p. 214–7°C; literature: m.p. 215.5–216.5°C [8].

3.2.2. 4-Quinazolinthiol (*2*)

Phosphorus(V)sulfide (28.65 g, 128 mmol) was added to a solution of 4-quinazolinol (18.5 g, 126.7 mmol) in anhydrous pyridine (200 ml), and the mixture was heated at reflux for 20 h. The reaction mixture was then poured onto ice, and the resultant precipitate was dissolved in aqueous KOH. Acidification of the solution with acetic acid afforded the product crystals, which were filtered off and dried. Yield 93%, m.p. 300–2°C; literature: m.p. 311–312°C [9].

3.2.3. 4-Alkylthioquinazolines (*3a–j*)

The appropriate alkylhalide (1.1 mol. eq.), 1 M KOH (15 ml), and tetrabutylammonium bromide (200 mg) were added to a suspension of 4-quinazolinethiol (1 g, 6 mmol) in cyclohexane (15 ml), and the mixture was heated at reflux for 12–40 h. The crude product was purified by column chromatography (silica gel Merck, mobile phase petrolether–ethylacetate 9:1). The data of the prepared 4-alkylthioquinazolines (**3a**–**j**) are summarized in Table 1.

*3.2.3.1. 4-Ethylthioquinazoline (**3a**).* IR (KBr) 1258(m), 1323(s), 1333(s), 1487(s), 1544(s), 1564(s), 1911(w), 2489(w), 2932(m), 2977(m). LRMS: 190 (M+), 162 (–C_2H_5), 129 (–S–C_2H_5), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91s (H2), 7.96d 1H $J = 8.24$ (H5), 7.86d 1H $J = 8.24$ (H8), 7.77–7.69m 1H (H7), 7.50–7.41m 1H (H6), 3.29q 2H $J = 14.69$, 7.42 (CH_2), 1.38t 3H $J = 7.42$ Hz (CH_3).

^{13}C NMR δ 171.3, 153.4, 147.7, 133.3, 128.6, 127.0, 123.8, 123.7, 23.8, 14.1.

*3.2.3.2. 4-Propylthioquinazoline (**3b**).* IR (KBr) 1259(m), 1323(s), 1333(s), 1486(s), 1544(s), 1564(s), 1911(w), 2487(w), 2935(m), 2969(m). LRMS: 205 (M+), 162 (–C_3H_7), 129 (–S–C_3H_7), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96s (H2), 8.07ddd 1H $J = 8.24$, 1.37, 0.55 (H5), 7.92d 1H $J = 8.24$ (H8), 7.85–7.77m 1H (H7), 7.58–7.50m 1H (H6), 3.34t 2H $J = 7.42$ (CH_2), 1.88–1.74m 2H (CH_2), 1.08t 3H $J =$ 7.42 Hz (CH_3).

^{13}C NMR δ 171.7, 153.5, 147.8, 133.5, 128.7, 127.1, 124.0, 123.9, 31.4, 22.4, 13.5.

*3.2.3.3. 4-Butylthioquinazoline (**3c**).* IR ($CHCl_3$) 1259(m), 1323(s), 1333(s), 1487(s), 1543(s), 1565(s), 2934(m), 2963(m). LRMS: 218 (M+), 162 (–C_4H_9), 129 (–S–C_4H_9), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92s (H2), 8.01d 1H $J = 8.24$ (H5), 7.88d 1H $J = 8.24$ (H8), 7.80–7.71m 1H (H7), 7.53–7.44m 1H (H6), 3.31t 2H $J = 7.42$ (CH_2), 1.79–1.66m 2H (CH_2), 1.55–1.37 2H (CH_2), 0.92t 3H $J = 7.42$ Hz (CH_3).

^{13}C NMR δ 171.5, 153.4, 147.7, 133.3, 128.6, 127.0, 123.9, 123.7, 30.9, 23.1, 22.0, 13.6.

*3.2.3.4. 4-Hexylthioquinazoline (**3d**).* IR ($CHCl_3$) 1258(m), 1323(s), 1333(s), 1487(s), 1543(s), 1565(s), 1911(w), 2486(w), 2931(m), 2960(m). LRMS: 247 (M+), 162 (–C_6H_{13}), 129 (–S–C_6H_{13}), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94s (H2), 8.03d 1H $J = 8.24$ (H5), 7.89d 1H $J = 8.24$ (H8), 7.77dt 1H $J =$ 8.24, 1.37 (H7), 7.55dt 1H $J = 8.24$, 1.37 (H6), 3.32t 2H $J = 7.42$ (CH_2), 1.83–1.68m 2H (CH_2), 1.53–1.38m 2H (CH_2), 1.37–1.19m 2H (CH_2), 0.86t 3H $J = 7.42$ Hz (CH_3).

^{13}C NMR δ 171.6, 153.4, 147.8, 133.4, 128.6, 127.0, 123.9, 123.8, 31.3, 29.4, 28.8, 28.6, 22.4, 13.9.

*3.2.3.5. 4-Cetylthioquinazoline (**3e**).* IR (KBr) 1279(m), 1323(s), 1333(s), 1487(s), 1543(s), 1565(s), 2927(m), 2956(m). LRMS: 386 (M +), 162 (–$C_{16}H_{33}$), 129 (–S–$C_{16}H_{33}$), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97s (H2), 8.09ddd 1H $J = 8.24$, 1.38, 0.55 (H5), 7.96d 1H $J = 8.24$ (H8), 7.83dt 1H $J = 8.24$, 1.38 (H7), 7.57dt 1H $J = 8.24$, 1.38 (H6), 3.37t 2H $J = 7.41$ (CH_2), 1.88–1.72m 2H (CH_2), 1.56–1.20m 26H (CH_2), 0.87t 3H $J = 7.41$ Hz (CH_3).

^{13}C NMR δ 172.0, 153.4, 147.6, 133.6, 128.6, 127.2, 124.0, 123.9, 34.0, 32.8, 31.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 28.9, 28.8, 28.2, 22.7, 14.1.

*3.2.3.6. 4-Benzylthioquinazoline (**3f**).* IR (KBr) 1259(m), 1322(s), 1333(s), 1495(s), 1545(s), 1565(s), 1910(w), 2933(m), 2983(m). LRMS: 252 (M +), 162 (–C_7H_7), 129 (–S–C_7H_7), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02s (H2), 8.05ddd 1H $J = 8.24$, 1.37, 0.55 (H5), 7.96d 1H $J = 8.24$ (H8), 7.83dt 1H $J = 8.24$, 1.37 (H7), 7.55dt 1H $J = 8.24$, 1.37 Hz (H6), 7.42–7.22m 5H (H2′, H3′, H4′, H5′, H6′).

^{13}C NMR δ 172.8, 153.4, 147.9, 136.8, 133.7, 129.1, 128.6, 128.4, 127.4, 127.3, 123.7, 123.6, 33.7.

*3.2.3.7. 4-Phenethylthioquinazoline (**3g**).* IR ($CHCl_3$) 1259(m), 1322(s), 1333(s), 1487(s), 1544(s), 1565(s), 2984(m). LRMS: 266 (M +), 162 (–C_8H_9), 129 (–S–C_8H_9), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02s (H2), 8.07ddd 1H $J = 8.24$, 0.82, 0.55 (H5), 7.97d 1H $J = 8.24$ (H8), 7.88–7.81m 1H (H7), 7.60–7.53m 1H (H6), 7.39–7.18m 5H (H2′, H3′, H4′, H5′, H6′), 3.63t 2H $J = 7.42$ (CH_2), 3.11t 2H $J = 7.42$ Hz (CH_2).

^{13}C NMR δ 171.3, 153.5, 147.8, 140.0, 133.6, 128.7, 128.6, 128.4, 127.2, 126.5, 124.0, 123.9, 35.3, 30.8.

*3.2.3.8. 4-Allylthioquinazoline (**3h**).* IR ($CHCl_3$) 1259(m), 1323(s), 1333(s), 1486(s), 1545(s), 1564(s), 1910(w), 2487(w), 2932(m), 2984(m). LRMS: 202 (M +), 162 (–C_3H_5), 129 (–S–C_3H_5), 75 (C_6H_4).

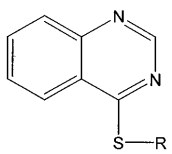
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99s (H2), 8.08ddd 1H $J = 8.52$, 1.38, 0.55 (H5), 7.96d 1H $J = 8.52$ (H8), 7.84dt 1H $J = 8.52$, 1.38 (H7), 7.58dt 1H $J = 8.52$, 1.38 (H6), 6.12–5.95m 1H (CH), 5.40ddd 1H $J = 17.03$, 2.74, 1.37 (CH_2), 5.19ddd 1H $J = 10.17$, 2.20, 1.1 (CH_2), 4.06dd 2H $J = 6.87$, 1.1 Hz (CH_2).

^{13}C NMR δ 170.8, 153.4, 147.9, 133.7, 132.7, 128.7, 127.3, 123.9, 123.8, 118.6, 32.2.

*3.2.3.9. 4-Isopropylthioquinazoline (**3i**).* IR ($CHCl_3$) 1258(m), 1323(s), 1333(s), 1487(s), 1542(s), 1565(s), 2466(w), 2935(m), 2969(m). LRMS: 204 (M +), 162 (–C_3H_7), 129 (–S–C_3H_7), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91s (H2), 7.97–7.92m 1H (H5), 7.85d 1H $J = 8.52$ (H8), 7.75–7.68m 1H (H7), 7.48–7.40m 1H (H6), 4.32–4.17m 1H (CH), 1.43d 6H $J = 7.14$ Hz (CH_3).

Table 1
Characteristics of the compounds



Comp.	*R*	M.p. (°C)	M.p. (°C)	Yield (%)	Molecular formula	MW
3a	C_2H_5	32–34	33–34 [10]	75	$C_{10}H_{10}N_2S$	190.27
3b	C_3H_7	33–35		75	$C_{11}H_{12}N_2S$	204.29
3c	C_4H_9	oil		80	$C_{12}H_{14}N_2S$	218.32
3d	C_6H_{13}	oil		74	$C_{14}H_{18}N_2S$	246.37
3e	$C_{16}H_{33}$	31–33		70	$C_{24}H_{38}N_2S$	386.64
3f	$CH_2C_6H_5$	89–91	103–4 [11]	80	$C_{15}H_{12}N_2S$	252.33
3g	$CH_2CH_2C_6H_5$	oil		78	$C_{16}H_{14}N_2S$	264.36
3h	$CH_2CH=CH_2$	oil	oil [a] [12]	80	$C_{11}H_9N_2S$	201.27
3i	$CH(CH_3)_2$	oil		83	$C_{11}H_{12}N_2S$	204.29
3j	$CH_2CH(CH_3)_2$	oil		64	$C_{12}H_{14}N_2S$	218.32

[a] B.p. 150°C [7,8].

Table 2
Antimycobacterial activity (MIC, μmol/l) of 4-alkylthioquinazolines (INH = isoniazide)

Mycobacterium	INH	Comp.									
		a	**b**	**c**	**d**	**e**	**f**	**g**	**h**	**i**	**j**
M. tuberculosis CNCTC TBC 1/47	4	125	250	63	125	500	63	63	250	125	125
M. kansasii CNCTC My 235/80	500	125	250	63	500	>1000	125	125	250	250	125
M. fortuitum CNCTC My 187/73	60	125	63	63	63	>1000	63	63	250	125	125
M. avium CNCTC My 66/72	250	125	63	32	63	>1000	125	32	250	32	63
M. avium D 5/93	62	500	125	32	63	>1000	63	63	250	63	125
M. avium CNCTC My 80/72	125	500	250	32	125	>1000	63	63	>1000	125	250
M. intracellulare D 39/93	250	63	125	32	125	>1000	63	32	500	63	125
M. intracellulare D 38/92	62	>1000	125	32	125	>1000	63	32	250	63	125

^{13}C NMR δ 171.5, 153.4, 147.8, 133.3, 128.6, 126.9, 123.7, 123.7, 34.9, 22.7.

*3.2.3.10. 4-Isobutylthioquinazoline (**3j**).* IR ($CHCl_3$) 1258(m), 1321(s), 1333(s), 1486(s), 1543(s), 1565(s), 1911(w), 2483(w), 2929(m), 2964(m). LRMS: 218 (M +), 162 ($-C_4H_9$), 129 ($-S-C_4H_9$), 75 (C_6H_4).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95s (H2), 8.10d 1H $J = 8.24$ (H5), 7.93d 1H $J = 8.24$ (H8), 7.81dt 1H $J =$ 8.24, 1.37 (H7), 7.55dt 1H $J = 8.24$, 1.37 (H6), 3.29d 2H $J = 6.60$ (CH_2), 2.13–1.97m 1H (CH), 1.08d 6H $J = 6.60$ Hz (CH_3).

^{13}C NMR δ 171.8, 153.4, 147.8, 133.5, 128.7, 127.2, 124.0, 123.9, 37.8, 28.3, 22.0.

3.3. Microbiology

To evaluate the antimycobacterial activity of the substances in vitro, the following strains were used: *Mycobacterium tuberculosis* CNCTC TBC 1/47, *Mycobacterium kansasii* CNCTC My 235/80, *Mycobacterium fortuitum* CNCTC My 187/73, *Mycobacterium avium* CNCTC My 66/72, *Mycobacterium avium* D 5/93, *Mycobacterium avium* CNCTC My 80/72, *Mycobacterium intracellulare* D 39/93 and *Mycobacterium intracellulare* D 38/92.

The antimycobacterial activities of the compounds against these strains were determined in the Šula semisynthetic medium (SEVAC, Prague). The compounds were added to the medium in dimethylsulfoxide solutions. The following concentrations were used: 1000, 500, 250, 125, 62 and 31 mmol/l. Minimum inhibitory concentrations (MICs) were determined after incubation at 37°C for 14 days. MIC was the lowest concentration of a substance, at which the inhibition of the growth of mycobacteria occurred.

4. Results and discussion

In the course of this work, we prepared ten compounds with different substituents at position 4 of the quinazoline skeleton, out of which seven had not been described in the literature as yet. The structures of the substances were corroborated by IR, MS, ^{1}H and ^{13}C NMR spectra. The IR spectra of the quinazoline derivatives showed characteristic C–H_{arom} vibrations in the range of 3079–3045 cm^{-1}, C–H_{alif} in the range of 2977–2855 cm^{-1}, and the bands of C–C and C–N bonds of aromatic cycles in the range of 1565–1486 cm^{-1}. A molecular fragment at m/z 129 corresponding to the quinazoline skeleton, and molecular fragments indicative of the individual alkyl and alkylthio groups were evident in the mass spectra. The structures of the compounds were also confirmed by NMR. In the ^{1}H NMR spectra, the signal of H2 appeared as a singlet in the range of 9.02–8.90 ppm, H5 and H8 were observed mostly as doublets in the range of 8.10–7.96 and 7.96–7.89 ppm, and H7 and H6 mostly as triplets in the range of 7.88–7.69 ppm and 7.60–7.41 ppm. The spectra also contained the signals of the substituents attached to sulphur in position 4.

The compounds were subjected to antitubercular activity assays, and the results are summarized in Table 2. As a result of this evaluation, a few conclusions could be made.

In case of derivatives with an unbranched alkyl in the molecule, the activity depends on the length of this chain, with a maximum for a four-carbon residue. Further lengthening of the chain leads to a decrease of activity and cetylderivative was very poorly active. Branching of the chain leads to antitubercular compounds as well: branching on the α-carbon as opposed to branching on the β-carbon increases the activity. When an unsaturated alkyl is bound to sulphur in position 4, the antitubercular activity decreases. Important antitubercular activity was found in the case of compounds with the benzylthio and 2-phenylethylthio groups in position 4; the latter was the second most active substance of the series. The most active derivative of the set was 4-butylthioquinazoline. Its activity, especially against atypical strains of mycobacteria, was

much higher as compared to the activity of the clinically used antitubercular isoniazide.

This study thus represents a further confirmation of the hypothesis of the alkylthio group bound to an electron-deficient carbon atom being a pharmacophore of antitubercular activity, as the results fall well in line with it.

Acknowledgements

This study was supported by the Ministry of Education of the Czech Republic, (Project CEZ J 13/98: 111600001, and Project Nos. VS97124 and LB98233).

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