Journal of Applied Sciences 4 (2): 302-307, 2004
ISSN 1607-8926

Synthesis of Certain New 6-Iodoquinazolines as Potential Antitubercular Agents

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Abstract: In the present study 2-(4-Chlorophenyl)-6-iodo-3, 4-dihydroquinazolin-4-one 3 was prepared by the reaction of 2-(4-chlorophenyl)-6-iodo-4*H*-3,1-benzoxazin-4-one 2 with formamide. Treatment of 3 with phosphorus penta sulfide yielded the thione derivative 4. Alkylation of 3 and 4 with certain alkylhalides gave the target compounds. The structure of the new compounds was confirmed by ^{1}H NMR, IR and MS. Some of the new compounds were screened for antitubercular activity, the 4-alkylthio derivatives were active while the 4-alkyloxy derivatives were inactive.

Key words: Quinazoline, alkylthioquinazoline, antimycobacterial activity

INTRODUCTION

It was reported that quinazolines have an interesting antimicrobial activity against different species of pathogenic Gram positive bacteria, Gram negative bacteria and Fungi[1-5]. In the course of the research for potential antitubercular agents, an important relationship was found between the structure and antitubercular effect.

Waisser *et al.*[6] supposed that the alkylthio group bound to an electron deficient carbon atom was identified as a possible pharmacophore of antitubercular activity. This hypothesis was confirmed for a number of compounds containing this structural moiety, such as 2-alkylthiobenzothiazoles[7], 1-aryl-5-alkylthio-1, 2, 3, 4-tetrazoles[8] and 4-alkylthioquinazolines[9-12].

The aim of this work was to study the validity of this hypothesis for some iodoquinazoline derivatives. So it was necessary to prepare some 4-alkyloxy and 4-alkylthioquinazoline derivatives and to assess their activity against various strains of mycobacteria.

MATERIALS AND METHODS

Interaction of 5-iodoanthranilic acid with 4-chlorobenzoylchloride in dimethylformamide yielded N-(4-chlorobenzoyl)-5-iodoanthranilic acid 1, which was subsequently cyclized to the benzoxazine derivative 2 by heating with acetic anhydride. Condensation of 2 with formamide yielded the target quinazoline derivative 3, which was reacted with phosphorus penta sulphide in dry pyridine to yield the thione derivative 4. Reaction of compound 4 with certain alkyl halide in acetone in the presence of potassium carbonate yielded the corresponding 4-S-alkylderivatives 5a-I (Scheme 1, Table 1 and 2). In the same way 6a-I (Scheme 2, Table 3 and 4) were obtained by the reaction of 3 with the same alkyl halide. The products were obtained in a pure from in case of compounds 6b-g, while alkylation of compound 3 by methyl iodide or bromoactonitrile under the same reaction conditions, afforded a mixture of the *O*- and *N*- (6a:4-methoxy and 6j:3-methyl, 6i:4-cyanomethoxy and 6k:3-cyanomethyl) quinazoline derivatives which were separated by column chromatography using chloroform: *n*-hexane (1:1). {6j separated from the column was found to be the same as that obtained by boiling the benzoxazine 1 with *N*-methylformamide). However compounds 5a-I were obtained in a pure form on alkylating the precursor 4 under the same conditions.

These results suggests that the ratio of *O* (4-position) to *N* (3-position) alkylation in case of compound 3 is greatly affected by the steric and electronic factors of the 2-substituent in the quinazoline ring and the nature of the entering alkyl group which is in accordance with Hori *et al.*[13]. comments, where the relatively small CH_3 and the highly reactive CH_2CN groups entered equally in both positions which didn't happen in case of larger or branched alkyl groups.

Chemistry: Melting points (°C) were determined on a Koffler apparatus and are uncorrected. IR spectra were obtained on a Pye Unicam SP 1200 spectrophotometer using KBr wafer technique (υ, cm^{-1}). ^{1}H NMR spectra were recorded on a varian Gimine 200-MHZ, Brucker AC

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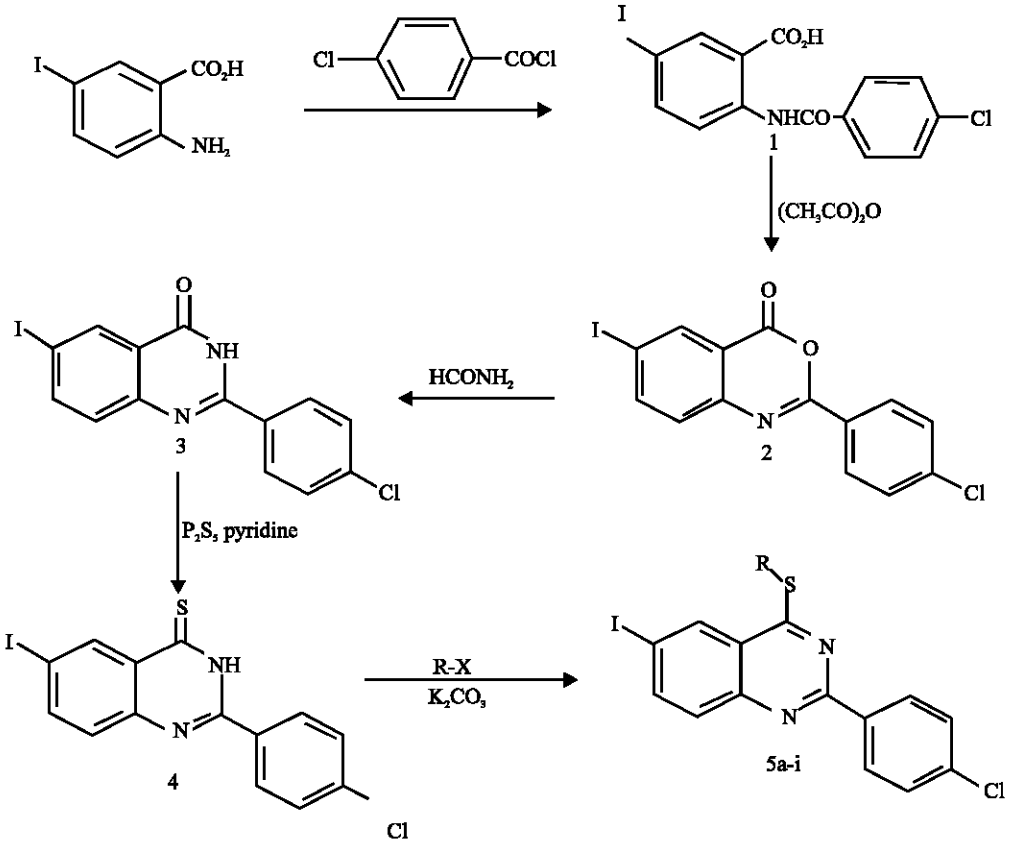
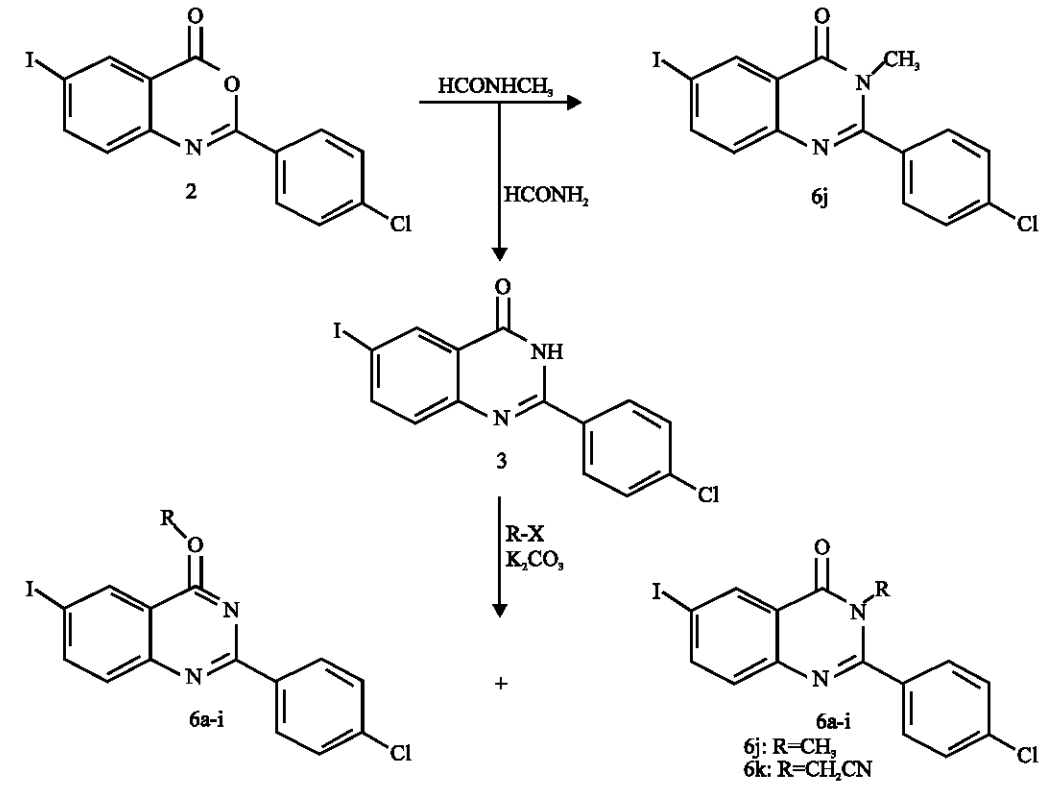


Scheme 1



Scheme 2

Table 1: Yield percentages, melting points, molecular formulae and microanalytical data for compounds 5(a-l)

Comp. No.	R	Yield%	M.P°C	Mol. Formula	Analysis	Calcd.	Found
5a	CH_3	85	183-5	$C_{15}H_{10}ClIN_2S$	C:	43.66	43.8
					H:	2.44	2.8
					N:	6.79	7.0
					S:	7.77	7.8
5b	C_2H_5	83	187-9	$C_{16}H_{12}ClIN_2S$	C:	45.04	45.1
					H:	2.83	3.0
					N:	6.57	6.6
					S:	7.51	7.8
5c	C_3H_7(*n*)	85	165-7	$C_{17}H_{14}ClIN_2S$	C:	46.33	46.0
					H:	3.20	3.5
					N:	6.36	6.5
					S:	7.28	7.5
5d	C_3H_7(*iso*)	86	162-4	$C_{17}H_{14}ClIN_2S$	C:	46.33	46.1
					H:	3.20	3.6
					N:	6.36	6.6
					S:	7.28	7.6
5e	C_4H_9(*n*)	87	135-7	$C_{18}H_{16}ClIN_2S$	C:	47.54	47.9
					H:	3.55	3.2
					N:	6.16	6.3
					S:	7.05	7.3
5f	C_4H_9(*iso*)	87	131-3	$C_{18}H_{16}ClIN_2S$	C:	47.54	47.6
					H:	3.55	3.3
					N:	6.16	6.4
					S:	7.05	7.3
5g	CH_2=CH-CH_2	82	180-2	$C_{17}H_{12}ClIN_2S$	C:	46.54	46.6
					H:	2.76	2.6
					N:	6.39	6.4
					S:	7.31	7.7
5h	$C_6H_5CH_2$	90	205-7	$C_{21}H_{14}ClIN_2S$	C:	51.60	51.9
					H:	2.89	2.8
					N:	5.73	5.8
					S:	6.56	6.7
5i	CH_2CN	80	222-4	$C_{16}H_9ClIN_3S$	C:	43.91	43.9
					H:	2.05	2.1
					N:	9.67	9.9
					S:	7.33	7.7

Table 2: ^{1}H NMR ($CDCl_3$, δ, ppm) data of compounds 5b, 5d, 5e and 5f

Comp. No.	δ, ppm
5b	1.2-1.3 (t, 3H, CH_2CH_3), 3.01-3.02 (q, 2H, SCH_2), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*)
5d	1.2-1.3 (d, 6H, $2CH_3$), 3.01-3.02 (m, 1H, S*CH*), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*).
5e	1.0-1.1 (t, 3H, CH_3), 1.3-1.4 (m, 2H, CH_3CH_2), 1.7-1.8 (m, CH_2CH_2S), 3.0-3.1 (t, 2H, CH_2CH_2S), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*).
5f	3.1 (d,2H, SCH_2) 3.9-4.0 (q, 2H, CH=CH_2), 4.3-4.4(m, 1H,C*H*=CH_2), 7.4-8.2 (m, 7H, Ar-*H* and quinazoline-*H*).

200-MHZ and Brucker MAX 400-MHZ using TMS as an internal standard with chemical shift (δ) expressed in ppm, the mass spectra were determined using MP model MS-5988 at 70 eV. The reactions and the purity of all compounds were checked by TLC using chloroform-n-hexane(9:1) as eluent.

***N*-(4-Chlorobenzoyl)-5-iodoanthranilic acid 1:** 4-Chlorobenzoyl chloride (8.75 g, 0.05 mol) was added dropwise to a stirred solution of 5-iodoanthranilic acid (13.15 g, 0.05 mol) in dimethylformamide (70 ml) and the reaction mixture was stirred at room temperature for 2 h. Water (100 ml) was then added with stirring and the separated solid was washed with water, dried and crystallized from ethanol. M.P.: 266-8°C. Yield: 16 g (80%). IR: 3300-2500 (OH), 1730(C=O). ^{1}H NMR (CD_3OD): δ 7.5-8.5 (m, 7H, Ar-*H*), 9.9 (bs, 1H, N*H*CO), 10.2 (s, 1H, O*H*). Analysis for $C_{14}H_9ClINO_3$: % Calc. (Found); C 41.87 (42.1), H 2.26 (1.9), N 3.49 (3.1).

2-(4-Chlorophenyl)-6-iodo-4*H*-3,1-benzoxazin-4-one2: A mixture of *N*-(4-chlorobenzoyl)-5-iodoanthranilic acid 1 (4.01 g, 0.01 mol) and acetic anhydride (10 ml) was heated under reflux for 3 h. Excess acetic anhydride was evaporated under reduced pressure and the obtained solid was crystallized from ethanol. M.P.: 185-7°C. Yield: 3.1 g (78%). IR: 1750 (C=O). ^{1}H NMR ($CDCl_3$): δ 7.2-8.5 (m, 7H, Ar-*H* and quinazoline-*H*). Ms: m/z (Rel. Int.): 383 (M^+ 73.7%), 385 (M^++2, 18.28%). Analysis for $C_{14}H_7ClINO_2$: % Calc. (Found); C 43.84 (44.1), H 1.84 (1.6), N 3.65 (3.8).

2-(4-Chlorophenyl)-6-iodo-3,4-dihdroquinazolin-4-one3 A mixture of 2-(4-chlorophenyl)-6-iodo-4*H*-3,1-benzoxazin-

Table 3: Yield percentages, melting points, molecular formulae and microanalytical data of compounds 6(a-I)

Comp. No.	R	Yield %	M.P °C	Mol. Formula	Analysis	Calcd.	Found
6a	CH_3	70	185-7	$C_{15}H_{10}ClIN_2O$	C:	45.43	45.8
					H:	2.54	2.8
					N:	7.06	7.2
6b	C_2H_5	75	197-9	$C_{16}H_{12}ClIN_2O$	C:	46.80	47.0
					H:	2.95	3.0
					N:	6.82	6.6
6c	C_3H_7(*n*)	75	140-2	$C_{17}H_{14}ClIN_2O$	C:	48.08	48.0
					H:	3.32	3.5
					N:	6.60	6.5
6d	C_3H_7(*iso*)	70	162-4	$C_{17}H_{14}ClIN_2O$	C:	48.08	48.4
					H:	3.32	3.6
					N:	6.60	6.6
6e	C_4H_9(*n*)	75	125-7	$C_{18}H_{16}ClIN_2O$	C:	49.28	48.9
					H:	3.68	4.0
					N:	6.39	6.3
6f	C_4H_9(*iso*)	75	133-5	$C_{18}H_{16}ClIN_2O$	C:	49.28	49.0
					H:	3.68	4.1
					N:	6.39	6.7
6g	CH_2=CH-CH_2	70	155-7	$C_{17}H_{12}ClIN_2O$	C:	48.31	48.6
					H:	2.86	2.6
					N:	6.63	6.4
6h	$C_6H_5CH_2$	75	145-7	$C_{21}H_{14}ClIN_2O$	C:	53.36	53.1
					H:	2.99	2.8
					N:	5.93	5.8
6i	CH_2CN	70	202-4	$C_{16}H_9ClIN_3O$	C:	45.58	45.9
					H:	2.15	2.1
					N:	9.97	9.9

Table 4: ^{1}H NMR ($CDCl_3$, δ, ppm) data of compounds 6a, 6b, 6d, 6e and 6f

Comp. No.	δ, ppm
6a	3.8 (s, 3H, OCH_3), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*)
6b	1.3-1.4 (t, 3H, CH_2CH_3), 4.0-4.1 (q, 2H, OCH_2), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*)
6d	1.3-1.4 (d, 6H, 2CH_3), 3.7-3.9 (m, 1H, OC*H*), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*).
6e	0.9-1.1 (t, 3H, CH_3), 1.3-1.4 (m, 2H, CH_3CH_2), 1.7-1.8 (m, CH_2CH_2O), 4.0-4.1 (t, 2H, CH_2CH_2O), 7.3-8.2 (m, 7H, Ar-*H* and quinazoline-*H*).
6f	4.7 (d,2H, OCH_2) 4.9-5.1 (q, 2H, CH=CH_2), 5.3-5.4(m, 1H,C*H*=CH_2), 7.4-8.2 (m, 7H, Ar-*H* and quinazoline-*H*)

4-one 2 (1.15 g, 0.003 mol) and formamide (10 ml) was heated under reflux for 2 h. On cooling, the separated solid was washed with water and crystallized from acetic acid. M.P.: > 300°C. Yield: 0.65 g (56.6%). IR: 3150 (NH), 1680 (C=O), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 7.2-8.3 (m, 7H, Ar-*H* and quinazoline-*H*), 12.7 (bs, 1H, N*H*). Ms: m/z (Rel. Int.); 382 (M^+ 73.44%), 384 (M^++2, 16.31%). Analysis for $C_{14}H_8ClIN_2O$: % Calc. (Found); C 43.95 (44.1), H 2.11 (2.5), N 7.32 (7.5).

2-(4-Chlorophenyl)-6-iodo-3,4-dihdroquinazolin-4-thione 4: Phosphorus penta sulfide (6.93 g, 0.031 mol) was added to a solution of 2-(4-chlorophenyl)-6-iodo-3,4-dihydroquinazolin-4-one 3 (11.79 g, 0.03 mol) in dry pyridine (100 ml) and the mixture was heated under reflux for 6 h. On cooling, the mixture was poured onto crushed ice and the obtained solid was washed with water, dried and crystallized from acetic acid. M.P. > 300°C. Yield: 6.2 g, (86%), IR: 3150 (NH), 1620 (C=N), 1450 (C=S). ^{1}H NMR (DMSO-d_6): δ 7.2-8.3 (m, 7H, Ar-*H* and quinazoline-*H*), 12.7 (bs, 1H, N*H*). Ms: m/z (Rel. Int.); 398 (M^+ 67.57%), 400 (M^++2, 17.14%). Analysis for $C_{14}H_8ClIN_2S$: % Calc. (Found); C 42.18 (42.1), H 2.02 (2.4), S 8.04 (8.4), N 7.03 (7.2).

General procedure for the synthesis of the compounds 2(4-chlorophenyl)-4-alkylthio-6-iodoquinazolines 5(a-I) and 2(4-chlorophenyl)-4-alkyloxy-6-iodo-quinazolines 6(a-I): A mixture of 2-(4-chlorophenyl)-6-iodo-3, 4-dihdroquinazolin-4-thione 4 or 4-one 3 (0.003 mol), the appropriate alkyl halide (0.0031 mol) and anhydrous potassium carbonate (2 g) in dry acetone (20 ml), was heated under reflux for 3 h and the reaction mixture was filtered while hot. The filtrate was evaporated under vacuum and the separated solid was washed with water and crystallized from ethanol to yield compounds 5a-I (Table 1 and 2) and 6a-I (Table 3 and 4).

2-(4-Chlorophenyl)-3-methyl-6-iodo-3,4-dihydro-quinazolin-4-thione 5j: A mixture of 2-(4-Chlorophenyl)-3-methyl-6-iodo-3,4-dihydroquinazolin-4-one 6j (1.19 g, 0.003 mol) and phosphorus penta sulfide (0.693 g, 0.0031 mol) in dry pyridine (10 ml) was heated under reflux for 2 h. On cooling, the separated solid was filtered,

Table 5: Antimycobacterial activity (MIC, μg/ml) of 4-alkylthioquinzoline derivatives 5a-I (INH= isoniazide)

		Compound 5								
Mycobacterium	INH	a	b	c	d	e	f	g	h	I
M.T.CNCTC.TBC.1/47	4	200	200	100	150	>200	200	100	50	50
M.T.CNCTC.M.235/80	500	>200	200	150	150	200	100	100	100	100
M.T.CNCTC.M.187/73	60	200	100	100	150	200	100	100	100	50
M.A.CNCTC.M.66/72	250	>200	100	150	150	200	150	100	100	100
M.A.D 5/93	62	>200	150	150	150	200	100	100	100	50
M.A.CNCTC.My.80/72	125	>200	200	150	150	200	100	100	100	100
M.I. D.39/93	250	>200	150	150	150	200	100	100	100	100
M.I. D.38/92	62	>200	150	150	150	200	100	100	100	50

washed with water and crystallized from ethanol. M.P.: >300°C. Yield: 0.86 g (70.0%). IR: 1620 (C=N), 1450(C=S). ^{1}H NMR (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 7.2-8.3 (m, 7H, Ar-*H* and quinazoline-*H*). Ms: m/z (Rel. Int.): 412 (M^+ 73.44%), 414 (M^++2, 25.31%). Analysis for $C_{15}H_{10}ClIN_2S$: % Calc. (Found); C 43.66 (44.0), H 2.44 (2.5), N 6.79 (7.1), S 7.77 (7.4).

2-(4-Chlorophenyl)-3-methyl-6-iodo-3,4-dihydro-quinazolin-4-one 6j: A mixture of 2-(4-chlorophenyl)-6-iodo-4*H*-3,1-benzoxazin-4-one 1 (1.15 g, 0.003 mol) and N-methylformamide (10 ml) was heated under reflux for 2 h. On cooling, the separated solid was filtered, washed with water and crystallized from ethanol. M.P.: > 300°C. Yield: 0.6 g (50.4%). IR: 1680 (C=O), 1620 (C=N). ^{1}H NMR (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 7.3-8.2(m, 7H, Ar-*H* and quinazoline-*H*). Analysis for $C_{15}H_{10}ClIN_2O$: % Calc. (Found); C 45.43 (45.1), H 2.54 (2.5), N 7.06 (7.4).

Microbiology: The in *vitro* antimycobacterial activity[14] of the prepared compounds against, *Mycobacterium tuberculosis CNCTC TBC 1/47, Mycobacterium kansaii CNCTC My 235/80, Mycobacterium fortuitum CNCTC My 187/73, Mycobacterium avium CNCTC My 66/72, Mycobacterium avium D 5/93, Mycobacterium avium CNCTC 80/72, Mycobacterium intracellular D 39/93 and Mycobacterium intracellular D 38/92* was determined by adding the compounds to the media as dimethylsulfoxide solutions. The compounds were tested in 200, 100, 50, 25, 12.5, 6 μg ml^{-1} concentration. The minimum inhibitory concentrations (MICs) of the compounds were determined after incubation at 37°C for 14 days. MIC values were the lowest concentration of a substance, at which the inhibition of the growth of mycobacterium occurred (Table 5).

RESULTS AND DISCUSSION

Some of the prepared compounds were subjected to antitubercular activity screening and the results are summarized in Table 5. As a result of this evaluation, a few conclusions could be made. The 4-alkyloxyquinazoline derivatives were much less active than the corresponding derivatives bearing the thio moiety. In case of the alkylthio derivatives with an unbranched alkyl in the molecule, the activity increases from methyl to ethyl and is nearly the same in case of propyl and butyl. Branching of the chain leads also to antitubercular compounds but branching on the α-carbon increases the activity than that on the β-carbon atom (4-isopropyl is more active than the 4-isobutyl derivative). Important antitubercular activity was found in case of compounds with the benzylthio and cyanomethylthioquinazoline derivatives which showed activities comparable to the reference drug isoniazide.

The results represent a further confirmation of the hypothesis that the alkylthio group bound to an electron-deficient carbon atom is a pharmacophore of antitubercular activity, as the results fall well in line with it.

ACKNOWLEDGMENT

The authors are grateful to Dr. Hasan Samaha, Assoc. Prof. of Microbiology, Faculty of Pharmacy, Al-Azhar University for carrying out the antitubercular testing.

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