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Note

Synthesis of *N*-3(4-(4-chlorophenyl thiazole-2-yl)-(2-(amino)methyl)-quinazoline-4(3*H*)-one and their derivatives for antitubercular activity

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A new series of *N*-3[4-(4-chlorophenyl thiazole-2-yl)-2-amino methyl] quinazoline-4(3*H*)-one and their derivatives are synthesized. The structures of the title compounds are confirmed on the basis of IR and ^{1}H NMR. The compounds are screened for their antitubercular activity, using $H_{37}Rv$ strain on L J medium. All the compounds have showed moderate to promising antitubercular activity.

Keywords: Mycobacterial activity, quinazolones, antitubercular, antitumour, antifungal, antithrombic, anticonvulsant

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Research programs for the discovery of new antimicrobial drug for improving the evaluation criteria are under way in many laboratories. In addition, knowledge of specific constituents of the mycobacterial cell and their biochemical role has advanced considerably in the recent years and may permit a more rational approach to the design of new drug acting on specific targets. Also recent improvements in the knowledge of the mechanism of action of the available drug in the biochemical mechanism of resistance to them may be used as a basis for designing new and better weapons to fight the mycobacterial diseases.

The quinazolines and quinazolones when selectively functionalized act as building blocks for the preparation of numerous biological active compounds. The quinazolines are found to exhibit antithrombic[1], antifungal[2], antitubercular[3], antitumour[4] and anticonvulsant[5] activities. In the light of above facts we have synthesized some new quinazolones and their derivatives (**Scheme I**), and screened them for antitubercular activities.

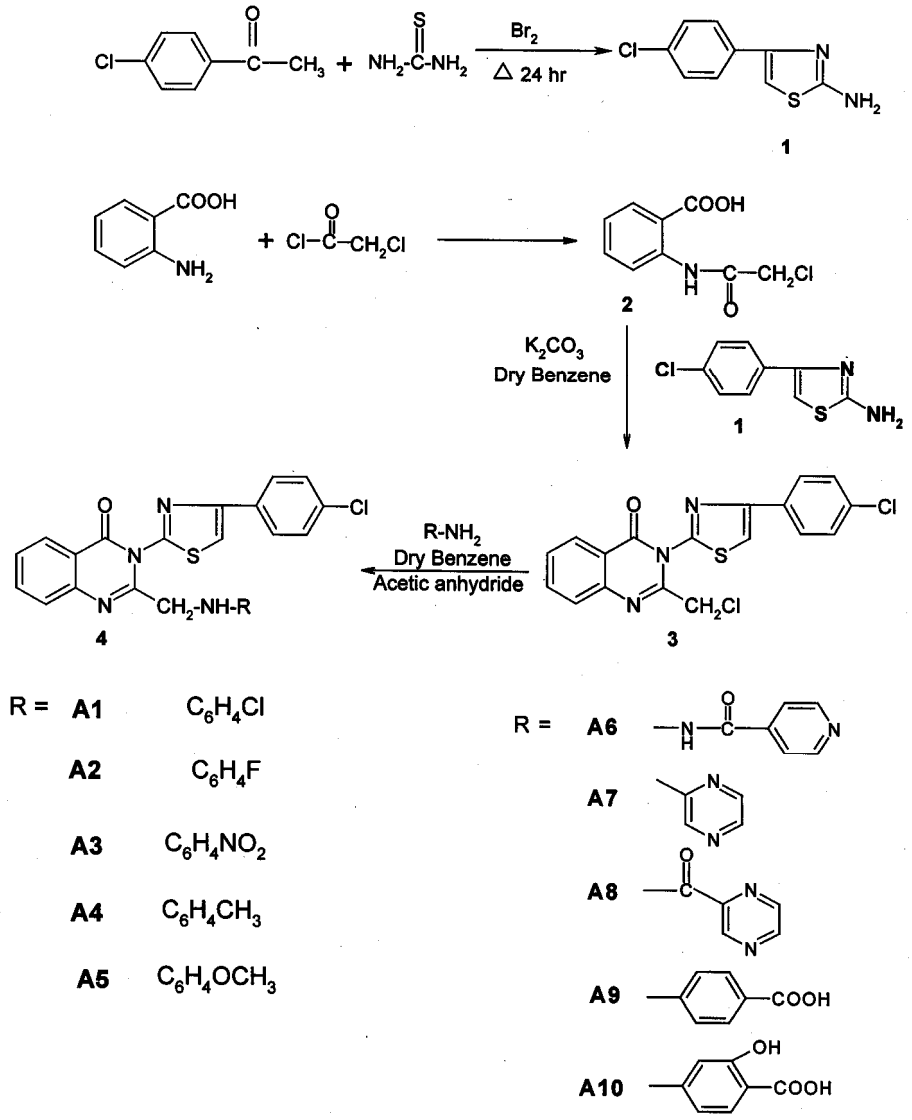
Experimental Section

All the melting points reported are uncorrected. The IR spectra were recorded on a NICOLET FTIR spectrometer and ^{1}H NMR spectra (DMSO-d_6) recorded on a VXRO-300 MHz using TMS as internal standard.

General synthesis of 2-amino-4-chloro phenyl-thiazole 1(ref. 7). A mixture consisting of *p*-chloro-acetophenone (0.1 mole), thiourea (0.2 mole), in 100 mL of ethanol and bromine (0.2 mole) was added drop-wise. After the complete addition of bromine reaction mixture was heated on a water-bath for over-night, and water was added to it and again heated until most of the solid had gone into solution. The reaction mixture was filtered while hot. The filtrate was cooled and made alkaline with ammonium hydroxide to obtain 2-amino-4-chlorophenythiazole, was filtered, washed with alcohol and dried over P_2O_5. It was purified by crystallization from ethanol as colorless needles. m.p.98-103 ºC. Yield 85%. IR (KBr): 3392, 3276 (NH_2), 2949, 2846 (CH of thiazole), 1473 (Ar C=C), 1400 (C=N), 1074, 1191 (C-S), 731 (Ar str) cm^{-1}.

General procedure for synthesis of *N*-chloro-acetyl anthranilic acid 2(ref. 8). In a 250 mL round bottom flask 6.5 g (0.06 mole) of anthranillic acid was dissolved in 100 mL of benzene with two or three drops of pyridine and 4 mL (0.06 mole) of chloroacetyl chloride was added in dry benzene under the cold condition and refluxed it for 4 hr, cooled and filtered, The solid was purified by recrystallization from acetone-ethanol mixture (1:1). Yield 72%, m.p.169ºC. IR (KBr): 3500, (OH str), 3300, (NH str) 3010 (C-H Ar str), 2960 (C-H alkyl str), 1680 (C=O), 1587 (C=C Ar str) cm^{-1}.

General procedure for synthesis of 2-chloro-methyl 3-(4-(4-chlorophenyl)thiazol-2-yl) quina-zoline 4(3*H*)–one 3(ref.9). *N*-Chloroacetyl anthra-nilic acid **2** 2.14 g, 0.01 mole was refluxed for 20 hr with 1.98 g (0.01 mole) of 4-chlorophenyl thiazole **1** in the presence of 10 g of K_2CO_3 in 100 mL of dry ethanol under anhydrous condition. The reaction mixture was filtered and ethanol extract was



Scheme I

evaporated. The residue washed thoroughly with boiling water and recrystallized from acetone:ethanol mixture (1:1) to yield 57.5%, m.p.195 ºC. IR (KBr): 3126, (C-H Ar str), 2959, (C-H alkyl str), 1660 (C=O), 1610, (C=N str), 1525 (C-N str of quinazoline), 1191 (C-S), 731 (Ar Str), 691 (C-S-C str) cm^{-1}.

General procedure for the synthesis of *N*-3-(4-(4–chlorophenyl)thiazol-2-yl)-(2-(amino)methyl)-quinazoline-4(3*H*)-one derivatives 4. 2-Chloro-methyl-3-[4-(4-chlorophenyl)thiazol-2-yl]quinazo-line-4(3H)-one **3** and respective amine (0.01 mole) were refluxed in 4 mL of dry pyridine and 20 mL of acetic anhydride for 4 hr. The excess solvent was distilled off. The mixture was cooled and poured onto crushed ice. The product was filtered and purified by recrystallization from ethanol. IR (KBr): 3400, (N-H str), 3030 (C-H Ar str), 2959, (C-H alkyl str), 1660 (C=O), 1610, (C=N str), 1525 (C-N str of quinazoline), 1191 (C-S), 731 (Ar str), 691 (C-S-C str) cm^{-1}. Physical and spectral data are given in **Table I**.

Anti-tubercular activity

The antitubercular screening was carried out by Lowenstain–Jensen egg medium (L J Medium) as described by Watt[6] against $H_{37}Rv$ strain. L J Medium containing standard drug as well as control L J Medium was also inoculated with mycobacterium tuberculosis of $H_{37}Rv$ strain. The medium inoculated was incubated for 37°C for 6 weeks. At the end of 6 weeks readings were taken. (**Table II**).

Table I—Characterization data of compounds **A1-A10**

Compd	Mol. Formula	m.p. °C	Yield (%)	Calcd (Found) % C	H	N	^{1}H NMR (DMSO-d_6)
A1	$C_{24}H_{16}Cl_2N_4OS$	55	52.00%	60.13 (60.36	03.36 03.29	11.69 11.96)	1.72, 2H, (s), CH_2, 5.08, 1H, (s), NH, 6.7 -7.7. 12H, (m), aryl H, 7.2, 1H, thiazole
A2	$C_{24}H_{16}ClFN_4OS$	210	60.50%	62.27 (62.48	03.48 03.39	12.10 11.96)	
A3	$C_{24}H_{16}ClN_5O_3S$	123	54.50%	58.80 (58.96	03.29 03.16	14.29 14.11)	1.2, 2H, (s), CH_2, 4.4, 1H (s), NH, 7.3, 1H, thiazole, 6.6 – 8.1, 12 H(m), aryl H
A4	$C_{25}H_{19}ClN_4OS$	139	52.50%	65.50 (65.73	04.17 04.01	12.21 12.30)	1.6, 5H, (s), CH_2, CH_3, 4.9, 1H, (s), NH, 6.7- 7.7, 12H, (m), aryl H, 7.2, 1H, thiazole
A5	$C_{25}H_{19}ClN_4O_2S$	156	57.10%	63.20 (63.42	04.03 03.82	11.80 1159)	1.70, 5H, (s), CH_2, CH_3, 5.03, 1H, (s), NH, 6.7 - 8.1, 8H, (m), aryl H, 7.28, 1H, thiazole, 3.6, 3H, (s), OCH_3
A6	$C_{24}H_{17}ClN_6O_2S$	85	65.30%	58.90 (58.64	03.50 03.38	17.19 17.12)	
A7	$C_{22}H_{15}ClN_6OS$	151	56.50%	59.12 (59.37	03.38 03.14	18.80 18.53)	1.70, 2H, (s), CH_2, 5.04, 1H, (s), NH, 6.7-7.8, 8H, (m), aryl H, 7.2, 1H, thiazole 8.82-9.0, 3H, pyrazine,
A8	$C_{23}H_{15}ClN_6O_2S$	180	48.25%	58.17 (58.51	03.18 03.11	17.70 (17.48)	1.26, 2H, (s), CH_2, 5.9, 1H, (s), NH, 7.2, 8H, (m), aryl H, 7.6-8.7, 1H, thiazole, 9.43, 3H, pyrazine
A9	$C_{25}H_{17}ClN_4O_3S$	147	47.00%	61.40 (61.26	03.50 03.27	11.46 11.30)	
A10	$C_{25}H_{17}ClN_4O_4S$	123	60.20%	59.40 (59.28	03.39 03.13	11.10 11.08)	1.27, 2H,(s),CH_2, 3.5, 1H,(s),NH, 2.6, 1H,(s),OH, 6.7-7.7, 11H, (m), aryl-H, 7.2, 1H, thiazole

Table II—Antitubercular activity

Compd	10 mcg /mL	50 mcg /mL	100 µg /mL
A1	+ +	+ -	- -
A2	+ +	+ -	- -
A3	+ -	- -	- -
A4	+ -	- -	- -
A5	+ +	+ +	+ -
A6	- -	- -	- -
A7	+ -	- -	- -
A8	- -	- -	- -
A9	+ +	+ +	+ +
A10	+ +	- -	- -
Streptomycin	- -	- -	- -

+ + : Denotes the growth
+ - : Denotes the growth less than 20 colonies
- - : Denotes no growth

Result and Discussion

The compounds were synthesized as per **Scheme I**. Chloroacetophenone was reacted with thiourea in presence of bromine for 24 hr to get compound **1**. Anthranillic acid was treated with chloroacetyl-chloride to get the intermediate **2**. Further, it was refluxed with 4-chlorophenyl thiazole **1,** for 20 hr, in anhydrous condition in presence of K_2CO_3 in 100 mL dry ethanol. 2-chloromethyl 3-(4-(4-chlorophenyl)-thiazol-2-yl) quinazoline 4(3*H*) –one **3** was treated with substituted anilines and amino compounds to get compound **4**.

The synthesized compounds were screened for antitubercular activity using $H_{37}Rv$ strain. Compounds **A6**, **A8** and **A10** showed maximum antitubercular activity. Compounds **A3, A4** and **A7** showed moderate antitubercular activity. Compounds **A1, A2** and **A5** have not showed any significant anti-tubercular activity. Compound **A9** did not exhibit any antitubercular activity. Streptomycin was used as the standard. The incorporation of INH, pyrazinamide and *p*-amino salicylic acid with quinazolones (**A6, A8, A10**) has enhanced the activity.

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