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SYNTHESIS AND ANTITUBERCULAR ACTIVITY OF NOVEL 6,7,8,9-TETRAHYDRO-5*H*-5-(2'-HYDROXYPHENYL)-2-(4'-SUBSTITUTED BENZYLIDENE)THIAZOLO[2,3-*B*]QUINAZOLIN-3-PHENYLHYDRAZONES

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In this study, 8 novel 6,7,8,9-tetrahydro-5H-5-(2'-hydroxyphenyl)-2-(4'-substituted benzylidene) thiazolo[2,3-b]quinazolin-3-phenylhydrazones ***5a–h*** *derivatives were synthesised and tested for antituberculosis activity. During our investigation in the area of antituberculosis activity, we have identified the 6,7,8,9-tetrahydro-5H-5-(2'-hydroxyphenyl)thiazolo[2,3-b]quinazolin-3-phenylhydra zones* **4** *as the lead compound. Structures of the title compounds were determined by analytical and spectral methods. Antituberculosis activities of the synthesised compounds were screened in vitro using BACTEC 460 Radiometric System against Mycobacterium tuberculosis H37Rv at 6.25 µg/mL. The highest inhibition observed with the synthesised compounds is 6,7,8,9-tetrahydro-5H-5-(2'-hydroxyphenyl)-2-(4'-fluorobenzylidene)thiazolo[2,3-b]quinazolin-3 phenylhydrazones* ***5f.***

Keywords: *Thiazoloquinazoline, Thiazoloquinazoline phenylhydrazones, Aromatic aldehydes substitution, Benzylidene thiazoloquinazoline phenylhydrazones antitubercular activity*

INTRODUCTION

Tuberculosis (TB) is an ancient disease that remains a significant global health problem. According to a recent report compiled by the World Health Organization (WHO), the total number of new TB cases worldwide in 2007 had risen to approximately 9.2 million (World Health Organization 2007). No novel antituberculosis drugs have been introduced into clinical practice over the past four decades. Only within the last few years have several promising drug candidates emerged (Nayyar and Jain 2005; Laughon 2007). Therefore, the development of new drugs with activity against multi drug resistant (MDR) TB, extensively drug-resistant (XDR) TB, and latent TB is a priority task. It is well known that the hydrazone group plays an important role for the antimicrobial activity. Furthermore, a number of hydrazide hydrazone derivatives have been claimed to possess interesting antituberculosis activities (Küçükgüzel *et al.* 1999; Cocco *et al.* 1999; Kocyigit and Rollas 2002; Karali *et al.* 2002; Rando *et al.* 2002; Patole *et al.* 2003; Maccari, Ottana and Vigorita 2005) and compounds that contain thiourea structure also show antituberculosis activity (Buu-Hoi, Xuong and Nam 1955; Doub *et al.* 1958; Riccieri, Porcelli and Castellani Pastoris

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1967; Winkelmann, Wagner and Hilmer 1969; Wisterowicz, Foks and Janowiec 1989). On the other hand, literature surveys show that thiazolinyl hydrazones exhibit antitubercular (Taniyama, Tanaka and Uchida 1954) and antimicrobial (Habib and Khalil 1984) activities. The previously reported works on the synthesis of 4-thiazolinyl arylidene hydrazones (Gursoy and Ates 1978; Gursoy, Karali and Outk 1992; Karah, Terzioglu and Gursoy 1998; Karali *et al.* 1998; Gursoy and Karali 2000), indicated that cyclohexyl substitution on 3-position of the thiazoline led to the highest antituberculosis activity. These observation led to the conception that a novel series of 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-substituted enzylidene)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazones derivatives were synthesised using different aromatic aldehydes and their chemical structure were confirmed by IR, ^{1}H-NMR, mass spectroscopy and elemental analysis. The main objective of the present study is to investigate the antituberculosis activity of different substitute of thiazolo quinazoline derivatives.

Structure–activity Relationship Study

In an on-going research work, we have synthesised thiazolo quinazoline linked with phenyl hydrazine. These newly synthesised Schiff bases when screened for antitubercular activities against the H37Rv strain, compound 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxy phenyl)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazones **4** exhibited better antitubercular activity. Having confirmed incorporation of the activity of compound **4**, we embarked on a hit-to-lead exploration program focusing on the 2-position of thiazole nucleus. The 2-position was modified with differently substituted aromatic aldehydes such as 4-hydroxy, 4-methoxy, 4-methyl, 3,4-dimethyl, 4-dimethylamino, 4-fluoro, 4-chloro and 4-bromo benzaldehydes. Thus our aim was to explore structural activity relationship (SAR) trends and to find out the lead for further optimisation.

METHODS

Synthetic starting material, reagents and solvents were of analytical grade that were purchased from Aldrich Chemical Co. (Hyderabad, India), Merck Chemical Co. (Mumbai, India) and Acros Organics (Mumbai, India), and were dried when necessary.

General Procedures

The synthesis of starting compound 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)thiazolo [2,3-*b*]quinazolin 3(2*H*)-one **3**, was done by adding equimolar quantities (0.039 mol) of cyclohexanone and salicylaldehyde into a beaker, to this 20 mL of 10% sodium hydroxide solution was added to make the solution alkaline; this was shaken and kept aside for 2 hours. The solid thus obtained, was filtered, washed with water and recrystallised from absolute ethanol.

A mixture of 2-hydroxybenzylidene cyclohexanone ring **1** (0.039 mol), thiourea (0.03 mol) and potassium hydroxide (2.5 g) in ethanol (100 mL) was heated under reflux for 3 hours. The reaction mixture was concentrated to half of its volume, diluted with water, then acidified with dilute acetic acid and kept overnight. The solid thus obtained, was filtered, washed with water and recrystallised from ethanol to give

4-hydroxyphenyl-3,4,5,6,7,8-hexahydroquinazolin-2-thione **2**. The chloro acetic acid (0.096 mol) was melted on a water bath and thione (0.009 mol) was added to it portion wise to maintain its homogeneity. The homogeneous mixture was further heated on a water bath for 30 min and kept overnight. The solid thus obtained was washed with water until neutralised and crystallised from ethanol to give 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)thiazolo[2,3-*b*]quinazolin-3(2*H*)-one **3** (Sharma, Kumar and Pujari 1991).

A mixture of compound **3** (0.002 mol)**,** treated with phenyl hydrazine (0.002 mol), anhydrous sodium acetate (0.002 mol) and glacial acetic acid (10 mL) were dissolved in 10 mL of warm ethanol and refluxed for 30 min. After standing for approximately 24 hours at room temperature, the product were separated by filtration, vaccum dried and recrystallised from warm ethanol to yield 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl) thiazolo[2,3-*b*]quinazolin-3-phenylhydrazones **4.**

Equimolar quantities (0.002. mol) of compound **4** clubbed with substituted benzaldehyde and anhydrous sodium acetate in glacial acetic acid (10 mL) was heated under reflux for 4 hours. The reaction mixture was kept overnight and the solid, thus separated, was filtered, washed with water and recrystallised from ethanol to furnish of 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'substituted benzylidene)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazones **(5a–h).** The spectral data IR, ^{1}H NMR, mass spectroscopy and elemental analyses were used to ascertain the structures of all the compounds.

^{1}H NMR spectra were recorded for all the target compounds. The ^{1}H NMR spectra were recorded for the representative key intermediate **3,** the 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)thiazolo[2,3-*b*]quinazolin-3-one. Yield: 71%; m.p. 153°C–155°C; IR (KBr, cm^{-1}): 3402 (phenolic OH), 3046 (Ar-CH), 1719 (C=O), 1462 (C=C) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 6.61–6.89 (m, 4H, Ar-H), 5.71 (s, 1H,–CH) 9.91 (s, 1H, Ar-OH), 3.76 (s, 2H,-CH_2) 1.6–2.42 (m, 8H, CH_2, CH_2, CH_2, CH_2). EI-MS *m/z* (M+): 300 (calcd for $C_{16}H_{16}N_2O_2S$; 300.38). Anal. calcd for $C_{16}H_{16}N_2O_2S$; C, 63.98; H, 5.37; N, 9.32. Found: C, 63.81; H, 5.28; N, 9.43.

4. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3467 (O-H), 3064 (Ar-CH), 1541 (C=C), 1610 (C=N), 1333 (N-H bending), 3378 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.74 (s, 1H, H-2', Ar-OH), 6.98–7.36 (m, 9H, Ar-H), 7.12 (s, 1H, N-H), 5.82 (s, 1H, H-5), 2.97 (s, 2H, thiazole), 1.59–2.47 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 390 (M+); (calcd for $C_{22}H_{22}N_4OS$;390.5). Anal. calcd for $C_{22}H_{22}N_4OS$; C, 67.67; H, 5.68; N, 14.32. Found: C, 67.56; H, 5.59; N, 14.43.

5a. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-hydroxybenzylidene)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3415 (O-H), 3060 (Ar-CH), 1534 (C=C), 1619 (C=N), 1312 (N-H bending), 3310 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.74 (s, 1H, H-2', Ar-OH), 7.78 (s, 1H, N-H), 6.98–7.36 (m, 13H, Ar-H), 6.53 (s, 1H, =CH), 5.82 (s, 1H, H-5), 5.12 (s, 1H, H-4'', Ar-OH), 1.59–2.47 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 494 (M+); (calcd for $C_{29}H_{26}N_4O_2S$; 494.18). Anal. calcd for $C_{29}H_{26}N_4O_2S$; C, 70.42; H, 5.30. N, 11.33. Found: C, 70.12; H, 5.02; N, 11.54.

5b. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-methoxybenzylidene)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3464 (O-H), 3027 (Ar-CH), 1494 (C=C), 1626 (C=N), 1306 (N-H bending), 3396 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.87 (s, 1H, H-2', Ar-OH), 7.26 (s, 1H, N-H), 6.72–7.23 (m, 13H, Ar-H), 6.36 (s, 1H, =CH), 5.62 (s, 1H, H-5), 3.78 (s, 3H, $-OCH_3$), 1.46–2.42 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 508 (M+); (calcd for $C_{30}H_{28}N_4O_2S$; 508.63). Anal. calcd for $C_{30}H_{28}N_4O_2S$; C, 70.84; H, 5.55; N, 11.02. Found: C, 70.75; H, 5.46; N, 11.21.

5c. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-methylbenzylidene)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3438 (O-H), 3024 (Ar-CH), 1412 (C=C), 1632 (C=N), 1322 (N-H bending), 3310 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.82 (s, 1H, H-2', Ar-OH), 7.69 (s, 1H, N-H), 6.69–7.24 (m, 13H, Ar-H), 6.28 (s, 1H, =CH), 5.72 (s, 1H, H-5), 2.28 (s, 3H, $-CH_3$), 1.36–2.41 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 492 (M+); (calcd for $C_{30}H_{28}N_4OS$; 492.63). Anal. calcd for $C_{30}H_{28}N_4OS$; C, 73.14; H, 5.73; N, 11.37. Found: C, 73.26; H, 5.57; N, 11.19.

5d. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(3',4'-dimethylbenzylidene)thiazolo [2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3429 (O-H), 3019 (Ar-CH), 1413 (C=C), 1648 (C=N), 1334 (N-H bending), 3313 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.93 (s, 1H, H-2', Ar-OH), 7.62 (s, 1H, N-H), 6.79–7.24 (m, 12H, Ar-H), 6.26 (s, 1H, =CH), 5.74 (s, 1H, H-5), 2.34 (s, 6H, $-CH_3$), 1.36–2.41 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 506 (M+); (calcd for $C_{31}H_{30}N_4OS$; 506.66). Anal. calcd for $C_{31}H_{30}N_4OS$; C, 73.49; H, 5.97; N, 11.06. Found: C, 73.28; H, 5.82; N, 11.18.

5e. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-nitrodimethylbenzylidene)thiazolo [2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3441 (O-H), 3035 (Ar-CH), 1417 (C=C), 1653 (C=N), 1336 (N-H bending), 3376 (N-H stretching) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.86 (s, 1H, H-2', Ar-OH), 7.89 (s, 1H, N-H), 6.72–7.23 (m, 13H, Ar-H), 6.46 (s, 1H, =CH), 5.74 (s, 1H, H-5), 2.28 (s, 6H, $-CH_3$), 1.39–2.43 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 521 (M+); (calcd for $C_{31}H_{31}N_5OS$; 521.68). Anal. calcd for $C_{31}H_{31}N_5OS$; C, 71.37; H, 5.99; N, 13.42. Found: C, 71.49; H, 5.86; N, 13.31.

5f. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-fluorobenzylidene)thiazolo[2,3-*b*] quinazolin-3-phenylhydrazone

IR: 3449 (O-H), 3026 (Ar-CH), 1524 (C=C), 1639 (C=N), 1316 (N-H bending), 3319 (N-H stretching), 821 (C-F) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.96 (s, 1H, H-2', Ar-OH), 7.34 (s, 1H, N-H), 6.74–7.32 (m, 13H, Ar-H), 6.23 (s, 1H, =CH), 5.84 (s, 1H, H-5), 1.24–2.32 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 496 (M+); (calcd for $C_{29}H_{25}FN_4OS$; 496.6). Anal. calcd for $C_{29}H_{25}FN_4OS$; C, 70.14; H, 5.07; N, 11.28. Found: C, 70.25; H, 5.19; N, 11.10.

5g. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-chlorobenzylidene)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3446 (O-H), 3013 (Ar-CH), 1526 (C=C), 1646 (C=N), 1348 (N-H bending), 3336 (N-H stretching), 824 (C-Cl) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.74 (s, 1H, H-2', Ar-OH), 7.31 (s, 1H, N-H), 6.71–7.33 (m, 13H, Ar-H), 6.24 (s, 1H, =CH), 5.86 (s, 1H, H-5), 1.21–2.31 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 515 (M+2); (calcd for $C_{29}H_{25}ClN_4OS$; 513.05). Anal. calcd for $C_{29}H_{25}ClN_4OS$; C, 67.89; H, 4.91; N, 10.92. Found: C, 6759; H, 4.72; N, 10.74.

5h. 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)-2-(4'-bromobenzylidene)thiazolo[2,3-*b*]quinazolin-3-phenylhydrazone

IR: 3447 (O-H), 3021 (Ar-CH), 1519 (C=C), 1641 (C=N), 1327 (N-H bending), 3352 (N-H stretching), 818 (C-Br) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 9.81 (s, 1H, H-2', Ar-OH), 7.79 (s, 1H, N-H), 6.81–7.36 (m, 13H, Ar-H), 6.49 (s, 1H, =CH), 5.84 (s, 1H, H-5), 1.29–2.34 (m, 8H, 4 × CH_2); EI-MS (*m/z*): 559 (M+2); (calcd for $C_{29}H_{25}BrN_4OS$; 557.5). Anal. calcd for $C_{29}H_{25}BrN_4OS$; C, 62.48; H, 4.52; N, 10.05. Found: C, 62.52; H, 4.18; N, 10.26.

Biological Activity

Antituberculosis activities of the synthesised compounds were screened in vitro using BACTEC 460 radiometric system against *M. tuberculosis* H37Rv at 6.25µg/mL. Primary antituberculosis activity screening results of these compounds are shown in Table 1.

BACTEC Radiometric Method of Susceptibility Testing

Inocula for susceptibility testing were either from a positive BACTEC isolation vial with a growth index (GI) of 500 or more, or a suspension of organisms isolated earlier on a conventional medium. The culture was well mixed with a syringe and 0.1 mL of a positive BACTEC culture was added to each of the vials containing the test drugs. (0.25 µg/mL rifampicin). A control vial was inoculated with 1:100 dilution of the culture. A suspension equivalent to a McFarland No. 1 standard was prepared in the same manner as a BACTEC positive vial, when growth from a solid medium was used. Each vial was tested immediately on a BACTEC instrument to provide CO_2 in the headspace. The vials were incubated at 37°C and tested daily with a BACTEC instrument. When the GI in the control reads at least 30, the increase in GI (ΔGI) from the previous day in the control was compared with that in the drug vial (Lennette *et al.* 1985; Inderland and Lorion 1986). The following formula was used to interpret results:

ΔGI control > ΔGI drug = susceptible
ΔGI control < ΔGI drug = resistant

RESULTS

Chemistry

The series of heterocycles **5a–h** was synthesised by reacting ketone **3** with appropriate phenyl hydrazine and aromatic aldehydes in the presence of anhydrous sodium acetate and glacial acetic acid as presented in Figure 1. The IR, ^{1}H-NMR, mass spectroscopy and elemental analysis for the new compounds are in accordance with the assigned structures. The IR spectrum of compound **3** showed stretching bands of keto group at 1715–1740 cm^{-1}. Azomethine **4,** stretching and bending NH bands of thiazoloquinazoline moiety appear at 3300–3400 cm^{-1} and 1300–1350 cm^{-1} respectively.

The absence of keto group absorption at 1715–1740 cm^{-1} and appearance of a strong intensity band in the IR spectra of compound **4** in the range of 1610–1655 cm^{-1} attributable to C=N provides a strong evidence for the condensation and also confirms the formation of the azomethine **4.** The ^{1}H NMR spectra of thiazolo quinazoline and their corresponding derivatives have been recorded in $CDCl_3$. In this **5a–h** NH signal of thiazolo[2, 3-*b*]quinazolin-3-phenylhydrazones moiety appear at 7.78 (s), 7.26 (s), 7.69 (s), 7.62 (s), 7.89 (s), 7.34 (s) 7.31 (s), 7.79 (s) ppm, respectively. The position and presence of NH signal in the ^{1}H NMR spectra of final compounds conforms the secondary NH proton in thiazolo quinazoline moiety. This clearly envisages that thiazole-3-one moiety involved in thiazolo(2,3-b)quinazolin-3-phenylhydrazone formation. All these observed facts clearly demonstrate that the 3rd position of keto group in thiazole ring is converted in to a secondary amino group as indicated in Figure 1 and conforms the proposed structure **(5a–h).**

Experimental Section

The melting points were taken in open capillary tube and are uncorrected. IR spectra were recorded with KBr pellets (ABB Bomem FT-IR spectrometer MB 104 ABB Limited, Bangaluru, India). Proton (^{1}H) NMR spectra (Bruker 400 NMR spectrometer, Mumbai, India) were recorded with TMS as internal references. Mass spectral data were recorded with a quadrupole mass spectrometer (Shimadzu GC MS QP 5000, Chennai, India), and microanalyses were performed using *aV*ario EL V300 elemental analyser (Elemental Analysensysteme, *GmbH,* Chennai, India). The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E. Merck) using ethyl acetate: benzene (1:3) and visualised in UV chamber. IR, ^{1}H NMR, mass spectral datas and elemental analyses were consistent with the assigned structures.

Antitubercular Activity

The encouraging results from the compound **4** antitubercular activity prompted us to opt for screening of the titled compounds. The antitubercular activity data are mentioned in Table 1.

At the commencement of this screening study, compound **4** displayed better activity and showed >95% inhibition at 6.25 µg/mL concentration. This result encouraged us to consider compound6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)thiazolo[2,3-*b*] quinazolin-3-phenylh yd razones **4** (Fig. 2) as our lead molecule. Subsequent structural

modifications were carried out for lead optimisation. The fifth step towards lead optimisation was the incorporation of different substituted aromatic aldehydes groups. The structural modification resulted in substantial improvement in activity. More than 96% inhibition at 6.25 µg/mL concentration was noticed. Enhancement in activity indicates that this modification is a step up towards synthesis of a pharmacophore.

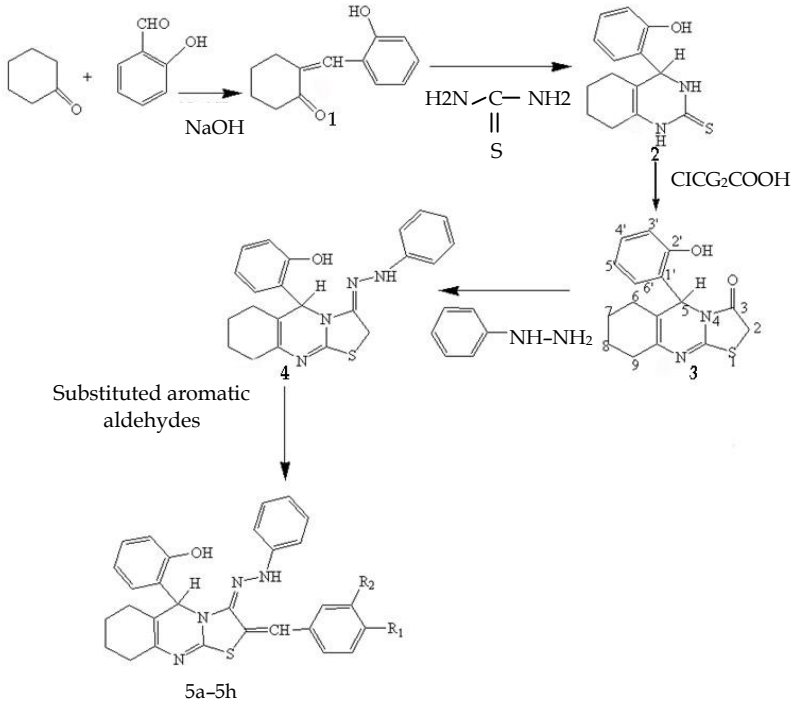

Fig. 1: 6,7,8,9,-tetrahydro-5h-5-(2'-hydroxyphenyl)-2-(4'-substituted benzylidene)thiazolo [2,3-b]quinazolin-3-phenylhydrazones**.**

Notes:

	R_1	R_2
5a	-OH	-H
5b	$-OCH_3$	-H
5c	$-CH_3$	-H
5d	$-CH_3$	$-CH_3$
5e	$-N(CH_3)_2$	-H
5f	-F	-H
5g	-CI	-H
5h	-Br	-H

Table 1: Antitubercular activity of compounds **5a–5f.**

Compound	R	R_1	MIC (μg/mL)	% inhibition
4	–	–	> 6.25	95
5a	-OH	-H	> 6.25	74
5b	$-OCH_3$	-H	> 6.25	79
5c	$-CH_3$	-H	> 6.25	68
5d	$-CH_3$	$-CH_3$	> 6.25	–
5e	$-N(CH_3)_2$	-H	> 6.25	–
5f	-F	-H	> 6.25	96
5g	-Cl	-H	> 6.25	96
5h	-Br	-H	> 6.25	96
Rifampcin	–	–	0.015–0.125	97

Note: MIC: Minimum intibitory concentration

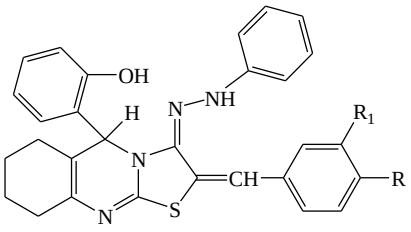

Fig. 2: 6,7,8,9-tetrahydro-5*H*-5-(2'-hydroxyphenyl)thiazolo[2,3-*b*]quinazolin-3-phenyl hydrazones **4**.

DISCUSSION

Biological Activity

On the basis of the BACTEC radiometric method using lead optimisation projects, this study has demonstrated that the method used results in significantly higher antitubercular activity. A previous study by Maccari, Ottana and Vigorita (2005) found that hydrazide hydrazone derivatives have been claimed to possess interesting antituberculosis activities. Another study on one data set containing thiazolinyl hydrazones derivatives suggested that the compounds have promising antituberculosis activities (Gursoy and Karali 2000). On the basis of biological data, improvement in biological activity was observed with increase in electronegativity of substituents. To study the influence of electronic effects on the biological activities, we introduced electron withdrawing and donating groups at 3- and 4- positions on the aromatic ring. Different analogues with electron withdrawing groups e.g. fluorine, chlorine and bromine and donating groups like hydroxy, methoxy and methyl were synthesised. These analogues were evaluated for

antitubercular activity. In majority of the cases, compounds having electronegative atoms like fluorine, chlorine and bromine **(5f–h)** exhibited good activity i.e. >96% inhibition at 6.25 µg/mL concentration. The 4-hydroxy and 4-methoxy substituents had moderate inhibition with 74% and 79% respectively.

CONCLUSION

In the present investigation, for the first time, we synthesised a series of novel thiazoloquinazoline moieties and their antituberculosis activity assayed. The results showed that the compounds had potential antituberculosis activity. In future reports we shall describe our investigations of the substitution chemistry of these tricyclic heterocycles.

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