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Synthesis of Some New *3H*-quinazolin-4-One Derivatives as Potential Antitubercular Agents

A. Omar Al-Deeb and Ahmed M. Alafeefy

Department of Pharmaceutical Chemistry, College of Pharmacy,
King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

Abstract: A series of 21 new 2-alkylthio-6-iodo-3-substituted-quinazolin-4-one derivatives was prepared and screened for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$, using the radiometric BACTEC 460-TB methodology. Active compounds were also screened by serial dilution to assess toxicity to a VERO cell line. The results indicate that compounds 5, 14 and 16 showed 96%, 97% and 94% GI, respectively, at a concentration of 6.25. The IC_{50} for these 3 compounds, respectively, was found to be 8.522, 2.589 and 23.167. Unfortunately, the overall results indicate that they were weakly active with a low selectivity index as indicated by there cytotoxic effects.

Key words: Antitubercular · Mycobacterium · Synthesis · 3*H*-Quinazolin-4-one

INTRODUCTION

Tuberculosis (TB) is one of the oldest and most pervasive diseases in history [1,2]. According to alarming data from the World Health Organization (WHO), TB has spread to every corner of the globe. As much as one-third of the world's population is currently infected and more than 5000 people die from TB everyday [3]. It is estimated that between 2002 and 2020, approximately 1000 million people will be newly infected, over 150 million people will develop diseases and 36 million will die of TB if proper control measures are not established [4].

The Directly Observed Treatment, short-course (DOTS) strategy, constitutes the cornerstone of the current protocol for control of TB. However, the three key drugs, isoniazide, pyrazinamide and rifampicin, used in the regimen are potentially hepatotoxic and may lead to drug-associated hepatitis [5].

Despite the undoubted success of DOTS strategy, the emergence of multi drug resistant strains, recurrently isolated from patient's sputum, darken the future. Furthermore, one of the main causes for the prevalence of TB is synergy with Human Immunodeficiency Virus (HIV) epidemic where 31% of new TB cases were attributable to HIV co-infection [6].

From the chemotherapeutic point of view, there are two sources of new chemical entities.The first is the extraordinary diversity provided by natural products. The second results from the design of new or the modernization of synthetic transformations.

Although many compounds are in clinical trials, it is astonishing that with this background, there have been no new drugs registered to treat TB in the last 40 years. This reflects the inherent difficulties in discovery and clinical testing of new agents and the lack of pharmaceutical industry research in this area [7].

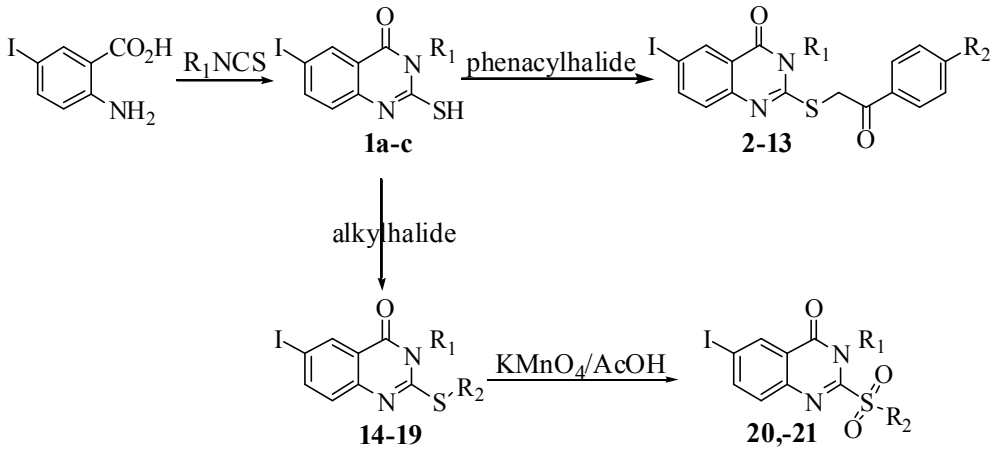
It was reported that 3*H*-quinazolin-4-one derivatives have interesting antimicrobial activity against different species of Gram positive bacteria, Gram negative bacteria and pathogenic Fungi [8-11]. It was also reported that 2 and/ or 4-substituted thioquinazoline derivatives were identified as a possible pharmacophore for antitubercular activity [12-15].

In the quest for biologically potent anti-tubercular agents, as pharmaceutical chemists, we have designed, synthesized and screened some2-alkylthio-6-iodo-3-substituted-quinazolin-4-one derivatives to mimic those reported as potential antitubercular agents [12-15] according to Scheme 1.

MATERIALS AND METHODS

Chemistry: Melting points (°C, uncorrected) were determined in open capillaries on a Gallenkemp melting point apparatus (Sanyo Gallenkemp, Southborough, UK) and were uncorrected. Precoated silica gel plates (silica gel 0.25 mm, 60G F254; Merck, Germany) were used for

Corresponding Author: Ahmed Mahmoud Alafeefy, Pharmaceutical Chemistry Department, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh-11451, Saudi Arabia



2: R_1= allyl, R_2=H; **3:**R_1=benzyl, R_2=H; **4:** R_1=phenyl, R_2=H;
5:R_1=allyl, R_2=Br; **6:**R_1=benzyl, R_2=Br; **7:**R_1=phenyl, R_2=Br;
8:R_1=allyl, R_2=Cl; **9:**R_1=benzyl, R_2=Cl; **10:**R_1=phenyl, R_2=Cl;
11:R_1=allyl, R_2=NO_2; **12:**R_1=benzyl, R_2=NO_2; **13:**R_1=phenyl, R_2=NO_2;
14: R_1=R_2= allyl; **15:** R_1= allyl, R_2= benzyl;**16:**R_1= benzyl, R_2= allyl;
17: R_1=R_2=benzyl;**18:**R_1= phenyl, R_2= allyl; **19:**R_1= phenyl, R_2= benzyl;
20:R_1=R_2=benzyl;**21:**R_1=phenyl, R_2=benzyl.

Scheme 1:

thin layer chromatography. Dichloromethane /methanol (9.5: 0.5) was used as a developing solvent system and the spots were visualized by ultraviolet light and/or iodine. Infra red spectra were recorded in KBr discs using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). ^{1}H NMR spectra were recorded on Bruker AC-500 Ultra Shield NMR spectrometer (Bruker, Flawil, Switzerland, δppm) at 500 MHz for ^{1}H and 125 MHz for ^{13}C, using TMS as internal Standard and peak multiplicities are designed as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Electron impact Mass Spectra were recorded on a Shimadzu GC-MS-QP 5000 instrument (Shimadzu, Tokyo, Japan). Elemental analyses were performed on Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany) and were less than 0.4% of theoretical values.

Synthesis of 6-Iodo-2-Nercapto-3-Substituted-3*H*-Quinazolin-4-Ones 1a-c: A mixture of 5-iodoanthranilic acid (2.63 g, 0.01 mol), the appropriate isothiocyanate derivative (0.011 mol) and triethylamine (1 mL) in absolute ethanol (30 mL) was heated under reflux for 3 hrs. The reaction mixture was left to cool and the solvent was removed under reduced pressure. The obtained solid was then washed with petroleum ether, dried and crystallized.

2-Alkylthio-3-Substituted-6-Iodo-3*H*-Quinazolin-4-Ones 2-19: A mixture of 2-thioxoquinazoline derivative 1a-c (0.01 mol), the appropriate alkyl halide (0.01 mol) and anhydrous potassium carbonate (1g) in 2-propanol (30 mL) was heated under reflux for 5 hrs. After cooling, the solvent was removed under vacuum and the separated solid was filtered, washed with water, dried and crystallized.

2.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.61 (s, 2H, CH_2S), 4.70 (d, 2H, CH_2N), 5.13-5.17 (d, 2H, =CH_2), 5.88 (m, 1H, =CH), 7.20-8.29 (m, 8H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38 (CH_2S), 44 (CH_2N), 96, 119, 125, 127, 130, 135, 137, 139, 144, 148, 156, 164, 196. MS *m/z* (Rel. Int.): 463 [M^+ + 1, 0.25], 462 [M^+, 1.30]. Anal. Calcd for $C_{19}H_{15}IN_2O_2S$ (462.32): C, 49.35; H, 3.27; N, 6.06. Found: C, 49.26; H, 3.49; N, 5.92.

3.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.08 (s, 2H, CH_2N), 4.49 (s, 2H, CH_2S), 7.11-8.12 (m, 13H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38 (CH_2S), 45 (CH_2N), 96, 125, 127, 130, 132, 136, 139, 145, 149, 156, 165, 198. MS *m/z* (Rel. Int.): 513 [M^+ + 1, 2.85], 512 [M^+, 11.66]. Anal. Calcd for $C_{23}H_{17}IN_2O_2S$ (512.36): C, 53.92; H, 3.34; N, 5.47. Found: C, 53.97; H, 3.58; N, 5.64.

4.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.15 (s, 2H, CH_2S), 7.12-8.29 (m, 13H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38, 96, 125, 127, 130, 132, 136, 139, 145, 149, 156, 165, 196. MS *m/z* (Rel. Int.): 498 (*m/z* M^+). Anal. Calcd for $C_{22}H_{15}IN_2O_2S$ (498.34): C, 53.02; H, 3.03; N, 5.62. Found: C, 53.15; H, 3.11; N, 5.59.

5.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.66 (s, 2H, CH_2S), δ 4.84 (d, 2H, CH_2N), 5.21-5.25 (d, 2H), 5.99 (m, 1H, =CH), 7.25-8.21 (m, 7H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38, 44, 96, 120, 125, 127, 130, 134, 137, 139, 145, 149, 156, 163, 197. MS *m/z* (Rel. Int.): 543 [M^+ + 2, 2.1], 541 [M^+, 2.06]. Anal. Calcd for $C_{19}H_{14}BrIN_2O_2S$ (541.20): C, 42.17; H, 2.61; N, 5.18. Found: C, 42.02; H, 2.79; N, 4.93.

6.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.42 (s, 2H, CH_2N), δ 4.83 (s, 2H, CH_2S), 7.25-8.18 (m, 12H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38 (CH_2S), 45 (CH_2N), 96, 125, 127, 128, 129, 133, 137, 139, 143, 145, 149, 156, 165, 196. MS *m/z* (Rel. Int.): 593 [M^+ + 2, 3.0], 591 [M^+, 3.11]. Anal. Calcd for $C_{23}H_{16}BrIN_2O_2S$ (591.26): C, 46.72; H, 2.73; N, 4.74. Found: C, 46.93; H, 2.99; N, 4.86.

7.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.12 (s, 2H, CH_2S), 7.11-8.23 (m, 12H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 39, 96, 125, 126, 130, 132, 134, 136, 139, 145, 149, 164, 166, 197. MS *m/z* (Rel. Int.): 579 [M^+ + 2, 1.83], 577 [M^+, 1.80]. Anal. Calcd for $C_{22}H_{14}BrIN_2O_2S$ (577.23): C, 45.78; H, 2.44; N, 4.80. Found: C, 45.97; H, 2.36; N, 5.13.

8.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.69 (s, 2H, CH_2S), δ 4.85 (d, 2H, CH_2N), 5.21-5.25 (d, 2H), 5.99 (m, 1H, =CH), 7.25-8.21 (m, 7H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38, 44, 96, 119, 125, 127, 130, 133, 137, 139, 142, 145, 149, 156, 164, 197. MS *m/z* (Rel. Int.): 498 [M^+ + 2, 1.14], 496 [M^+, 3.26]. Anal. Calcd for $C_{19}H_{14}ClIN_2O_2S$ (496.75): C, 54.94; H, 2.84; N, 5.64. Found: C, 55.20; H, 3.05; N, 5.77.

9.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.33 (s, 2H, CH_2N), δ 4.75 (s, 2H, CH_2N), 7.11-8.18 (m, 12H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38 (CH_2S), 45 (CH_2N), 96, 125, 127, 130, 131, 133, 136, 138, 141, 144, 145, 149, 156, 165, 196. MS *m/z* (Rel. Int.): 498 [M^+ + 2, 4.71], 496 [M^+, 13.60]. Anal. Calcd for $C_{23}H_{16}ClIN_2O_2S$ (546.81): C, 50.52; H, 2.95; N, 5.12. Found: C, 50.36; H, 2.71; N, 5.48.

10.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.04 (s, 2H, CH_2S), 7.12-8.20 (m, 12H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 39 (CH_2S), 96, 124, 126, 128, 131, 134, 137, 139, 143, 145, 149, 164, 166, 197. MS *m/z* (Rel. Int.): 534 (M^+ + 2, 0.86), 532 (M^+, 2.59). Anal. Calcd for $C_{22}H_{14}ClIN_2O_2S$ (532.78): C, 49.60; H, 2.65; N, 5.26. Found: C, 49.37; H, 2.81; N, 5.09.

11.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.54 (s, 2H, CH_2S), δ 4.91 (d, 2H, CH_2N), 5.11-5.18 (d, 2H), 5.88 (m, 1H, =CH), 7.25-8.28 (m, 7H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38 (CH_2S), 44 (CH_2N), 96, 120, 125, 127, 131, 136, 138, 145, 148, 155, 157, 164, 165, 197. MS *m/z* (Rel. Int.): 508 (M^+ + 1, 1.6), 507 (M^+, 7.5). Anal. Calcd for $C_{19}H_{14}IN_3O_4S$ (507.30): C, 44.98; H, 2.78; N, 8.28. Found: C, 45.26; H, 3.01; N, 7.95.

12.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.27 (s, 2H, CH_2N), δ 4.88 (s, 2H, CH_2S), 7.13-8.20 (m, 12H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38 (CH_2S), 45 (CH_2N), 96, 125, 127, 129, 131, 133, 139, 144, 145, 148, 155, 156, 164, 197. MS *m/z* (Rel. Int.): 558 (M^+ + 1, 3.5), 557 (M^+, 18.0). Anal. Calcd. for $C_{23}H_{16}IN_3O_4S$ (557.36): C, 49.56; H, 2.89; N, 7.54. Found: C, 49.30; H, 2.71; N, 7.26.

13.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.95 (s, 2H, CH_2S), 7.23-8.27 (m, 12H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 38, 97, 124, 125, 128, 130, 131, 135, 138, 145, 148, 155, 163, 165, 197. MS *m/z*: 544 (M^+ + 1, 6.15), 543 (M^+, 34.0). Anal. Calcd. for $C_{22}H_{14}IN_3O_4S$ (543.33): C, 48.63; H, 2.60; N, 7.73. Found: C, 48.70; H, 2.52; N, 7.96.

14.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.49 (d, 2H, CH_2S), 3.90 (d, 2H, CH_2N), 5.11-5.17 (m, 4H), 5.83-5.92 (m, 2H), 7.25-8.28 (m, 3H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 33, 45, 97, 120, 121, 126, 128, 137, 138, 140, 146, 150, 157, 165. MS *m/z* (Rel. Int.): 385 (M^+ + 1, 2.5), 384 (M^+, 8.7). Anal. Calcd for $C_{14}H_{13}IN_2OS$ (384.24): C, 43.76; H, 3.41; N, 7.29. Found: C, 43.55; H, 3.17; N, 7.02.

15.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.88 (s, 2H, CH_2S), 4.34 (d, 2H, CH_2N), 5.12-5.16 (d, 2H, CH_2), 5.86-5.90 (m, 1H, CH), 7.25-8.31 (m, 8H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 40 (CH_2S), 45 (CH_2N), 97, 121, 125, 126, 129, 131, 137, 140, 143, 146, 150, 166. MS *m/z* (Rel. Int.): 435 (M^+ + 1, 1.3), 434 (M^+, 4.9). Anal. Calcd for $C_{18}H_{15}IN_2OS$ (434.29): C, 49.78; H, 3.48; N, 6.45. Found: C, 49.75; H, 3.25; N, 6.62.

16.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.58 (d, 2H, CH_2S), 4.65 (s, 2H, CH_2N), 5.11-5.15 (d, 2H, CH_2) 5.88-5.90 (m, 1H, CH), 7.31-8.24 (m, 8H, ArH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34 (CH_2S), 45 (CH_2N), 96, 120, 125, 127, 129 132, 136, 140, 144, 149, 156, 164. MS *m/z* (Rel. Int.): 435 [M^+ + 1, 1.8], 434 [M^+, 10.15]. Anal. Calcd for $C_{18}H_{15}IN_2OS$ (434.29): C, 49.78; H, 3.48; N, 6.45. Found: C, 49.70; H, 3.24; N, 6.67.

17.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.84 (s, 2H, CH_2S), 4.44 (s, 2H, CH_2N), 7.18-8.28(m, 13H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 40, 44, 96, 125, 127, 130, 131, 133, 138, 142, 144, 145, 148, 156, 164. MS *m/z*

(Rel. Int.): 485 (M^+ + 1, 5.2), 484 (M^+, 23.9). Anal. Calcd for $C_{22}H_{17}IN_2OS$ (484.35): C, 54.55; H, 3.54; N, 5.78. Found: C, 54.70; H, 3.66; N, 6.01.

18.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.70 (d, 2H, CH_2S), 5.06-5.13 (m, 2H, =CH_2), 5.88-5.93 (m, 1H, =CH) 7.16-8.29 (m, 8H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 34, 96, 120, 124, 125, 127, 131, 134, 137, 140, 144, 148, 163, 165. MS *m/z* (Rel. Int.): 421 (M^+ + 1, 3.51), 420 (M^+, 17.04). Anal. Calcd for $C_{17}H_{13}IN_2OS$ (420.27): C, 48.58; H, 3.12; N, 6.67. Found: C, 48.81; H, 3.35; N, 6.99.

19.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.03 (s, 2H, CH_2S), 7.22-8.18(m, 13H, ArH). ^{13}C NMR($CDCl_3$, 75 MHz): δ 40, 96, 124, 125, 127, 129, 132, 135, 138, 141, 144, 149, 162, 165. MS *m/z* (Rel. Int.): 471 (M^+ + 1, 3.11), 470 (M^+, 14.97). Anal. Calcd for $C_{21}H_{15}IN_2OS$ (470.33): C, 53.63; H, 3.21; N, 5.96. Found: C, 53.58; H, 3.02; N, 5.88.

2.3-Substituted-2-benzylsulphonyl-6-iodo-3*H*-quinazolin-4-one 20, 21.: To a solution of 17 or 19 (0.005 mol) in 50% acetic acid (30 ml), potassium permanganate(0.8 g, 0.005 mol) in 10 ml water was added. The reaction mixture was stirred at room temperature for 2 hours. The solvents was removed under reduced pressure and the obtained solid was filtered, dried and crystallized.

20.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.38 (s, 2H, CH_2N), 4.69 (s, 2H, CH_2S), 7.18-8.28 (m, 13H, ArH). ^{13}C NMR($CDCl_3$, (75 MHz): δ 45 (CH_2N), 51 (CH_2S), 96, 125, 127, 128, 129, 131, 135, 138, 144, 145, 148, 164, 165. MS *m/z* (Rel. Int.): 517 (M^++1, 5.2), 516 (M^+, 22.5). Anal. Calcd. for $C_{22}H_{17}IN_2O_3S$ (516.35): C, 51.17; H, 3.32; N, 5.43. Found: C, 51.18; H, 3.50; N, 5.66.

21.: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.60 (s, 2H, CH_2S), 7.20-8.25 (m, 13H, ArH). ^{13}C NMR($CDCl_3$, (75 MHz): δ 51 (CH_2S), 96, 124, 125, 128, 131, 135, 138, 145, 148, 164, 166. MS *m/z* (Rel. Int.): 503 (M^+ + 1, 13.7), 502 (M^+, 57.9). Anal. Calcd. for $C_{21}H_{15}IN_2O_3S$ (502.32): C, 50.21; H, 3.01; N, 5.58. Found: C, 49.97; H, 2.92; N, 6.82.

Evaluation of Antitubercular Activity: Primary screening was conducted at 6.25 µg/ml against *Mycobacterium tuberculosis* strain H_{37}Rv (ATCC 27294) in BACTEC 12B medium using a broth microdilution assay, the Microplate Alamar Blue Assay (MABA) [16]. Compounds exhibiting fluorescence were tested in the BACTEC 460 Radiometric System [17]. Compounds showing =90% inhibition in the primary screening (i.e., minimum inhibitory concentration, MIC < 6.25 µg/ml) were considered active and then retested at lower concentrations to determine their actual MIC using MABA. The MIC is defined as the lowest concentration effecting a reduction in fluorescence of 99% relative to the controls.

Compounds were also tested for cytotoxicity (IC_{50}) in VERO cell line at a concentration equal to and greater than the MIC for *M. tuberculosis* strain H_{37}RV. After 72 h exposure, viability was assessed on the basis of cellular conversion of MTT into a formazan product using the Promega Cell Titer 96 Non-radio-active Cell Proliferation assay.

RESULTS AND DISCUSSION

Chemistry: In the present work twenty one new compounds were prepared according to the synthetic strategy depicted in Scheme 1. 5-Iodo anthranilic acid was allowed to react with allyl, benzyl and phenyl isothiocyanates to produce the 2-thioxo-3-substituted-6-iodo-3*H*-quinazolin-4-ones 1a-c adopting reported procedures [18].

The 2-thioxo function of 1a-c was then alkylated with some selected á-halo ketones as well as some alkyl halides to afford the corresponding S-alkylthioether derivatives 2-19. Oxidation of the thioether derivatives 17 and 19 using potassium permanganate afforded the corresponding sulfonyl analogues 20 and 21 (Scheme 1, Table 1).

The structure of the synthesized intermediates and final products was confirmed by elemental analyses (C, H, N), IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry.

In the IR spectra, a significant stretching band due to 3*H*-quinazolin-4-one carbonyl group was observed around 1670 cm^{-1} in all compounds.Compounds 2-13 showed an additional strong band around 1710 due to the ketonic carbonyl. The IR spectrum of compounds 20 and 21 exhibited strong band around 1300 and 1150 cm^{-1} due to the sulfonyl group in addition to the common pattern of the 3*H*-quinazolin-4-one backbone. In the ^{1}H-NMR spectra, the signal due to the allyl protons, present at position 2 and/ or 3, in compounds 2, 5, 8, 11, 14-16 and 18, appeared as multiplet around 3.77-4.28 ppm (CH_2), 5.0-5.20 ppm (=CH_2) and 5.88-6.02 ppm (=C*H*). In compounds 3, 6, 9, 12, 15-17 and 19-21 containing benzyl group at position 2 and/ or 3, the CH_2 protons appeared at around 3.84-4.34 ppm as singlet. All the other aromatic protons were observed in the expected regions. Mass spectra of target compounds showed the major fragment in agreement with their proposed molecular formula.

Table 1: Physicochemical data of compounds 2-21 and results of the first screening

Cpd	R_1	R_2	Molecular formula (MW)	Yield[a](%)	M.P[b] ([i]C)	MIC(µg/mL)[c]	GI(%)[d]
2	Allyl	H	$C_{19}H_{15}IN_2O_2S$ (462.30)	78	216-18	> 6.25	64
3	Benzyl	H	$C_{23}H_{17}IN_2O_2S$ (512.36)	75	228-30	> 6.25	60
4	Phenyl	H	$C_{22}H_{15}IN_2O_2S$ (498.34)	68	223-25	> 6.25	28
5	Allyl	Br	$C_{19}H_{14}BrIN_2O_2S$ (541.20)	80	260-62	< 6.25	96
6	Benzyl	Br	$C_{23}H_{16}BrIN_2O_2S$ (591.26)	73	255-257	> 6.25	74
7	Phenyl	Br	$C_{22}H_{14}BrIN_2O_2S$ (577.23)	70	253-55	> 6.25	66
8	Allyl	Cl	$C_{19}H_{14}ClIN_2O_2S$ (496.75)	75	240-42	> 6.25	28
9	Benzyl	Cl	$C_{23}H_{16}ClIN_2O_2S$ (546.81)	77	254-56	> 6.25	37
10	Phenyl	Cl	$C_{22}H_{14}ClIN_2O_2S$ (498.34)	75	250-52	> 6.25	66
11	Allyl	NO_2	$C_{19}H_{14}IN_3O_4S$ (507.30)	60	198-91	> 6.25	31
12	Benzyl	NO_2	$C_{23}H_{16}IN_3O_4S$ (557.36)	60	197-99	> 6.25	42
13	Phenyl	NO_2	$C_{22}H_{14}IN_3O_4S$ (543.33)	55	192-94	> 6.25	30
14	Allyl	Allyl	$C_{14}H_{13}IN_2OS$ (384.24)	80	167-69	< 6.25	97
15	Allyl	Benzyl	$C_{18}H_{15}IN_2OS$ (434.29)	76	183-85	> 6.25	81
16	Benzyl	Allyl	$C_{18}H_{15}IN_2OS$ (434.29)	75	183-85	< 6.25	94
17	Benzyl	Benzyl	$C_{22}H_{17}IN_2OS$ (484.35)	75	205-07	> 6.25	52
18	Phenyl	Allyl	$C_{17}H_{13}IN_2OS$ (420.27)	70	165-67	> 6.25	39
19	Phenyl	Benzyl	$C_{21}H_{15}IN_2OS$ (470.33)	66	185-87	> 6.25	43
20	Benzyl	Benzyl	$C_{22}H_{17}IN_2O_3S$ (516.35)	70	293-95	> 6.25	0
21	Phenyl	Benzyl	$C_{21}H_{15}IN_2O_3S$ (502.32)	70	284-86	> 6.25	0

[a)]The developing solvent system used is CH_2Cl_2: CH_3OH (9.5:0.5). [b)] The crystallization solvent is ethanol. [c)] MIC of Rifampin: 0.125 µg/mL versus $H_{37}Rv$ strain of *M. tuberculosis* (97% inhibition).

[d)]Growth inhibition of virulent $H_{37}Rv$ strain of *M. tuberculosis*. According to TAACF program compounds effecting < 90% inhibition are considered inactive.

Table 2: *In-vitro* results of second level cytotoxicity antitubercular assay for compounds demonstrating > 90% inhibition

Compound ID	Drug Units	IC90	IC50	Activity
5	µg/mL	47.378	8.522	weakly Active
14	µg/mL	12.381	2.589	weakly Active
16	µg/mL	60.019	23.167	weakly Active

Antitubercular Activity: *In vitro* evaluation of the antitubercular activity of the target compounds was carried out at the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF) screening program for the discovery of novel drugs for treatment of tuberculosis. Under the direction of the US National Institute of Allergy and Infectious Disease (NIAID), Southern Research Institute coordinates the overall program. The purpose of the screening program is to provide a resource whereby new experimental compounds can be tested for their capacity to inhibit the growth of virulent *Mycobacterium tuberculosis*.

Compounds 5, 14 and 16 showed notable antitubercular activity with growth inhibition of 96, 97 and 94%, respectively, at a concentration of 6.25 µg/ml. As can be inferred from Table 1. These three compounds, with MIC < 6.25 µg/ml, were then tested for cytotoxicity (IC_{50}) in VERO cells and the results are reported in Table 2, unfortunately they showed very low selectivity index. However, compound 14 could be considered as an interesting lead for future optimization. Other compounds showed varying growth inhibition degrees between 81-28%. But, most of the tested compounds revealed no or weak inhibitory activity against the tested strain. The poor solubility of the compounds might be a limiting factor; therefore, work is in progress to build up more hydrophilic candidates.

SAR observation showed that, an electron withdrawing group on the sulphur atom at position 2 in addition to an allyl and/or benzyl moiety at position 3 has a positive impact on the antitubercular activity.

CONCLUSION

The results obtained, although somewhat low, encourages us to make further research for better

derivatives that might show more promising activity, for the derivatives presented in this work needs future derivatization and evaluation to achieve our hopeful goal.

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