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Synthesis and Antimycobacterial Activity Evaluation of Isatin-derived 3-[(4-aryl-2-thiazolyl])hydrazone]-1H-indol-2,3-diones

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ABSTRACT

A series of 3-[(4-aryl-2-thiazolyl)hydrazone]-1*H*-indol-2,3-dione derivatives (**2a-f**) were designed and synthesized using isatin as starting material. The obtained thiazole compounds were screened to investigate their antituberculosis activity against *Mycobacterum tuberculosis* H37RV (ATCC 27294). Among them, two compounds **2c** and **2d** were displayed antitubercular potential two-fold greater than standard drugs.

Keywords: Isatin, Indole, Thiazole, Antimycobacterial activity

INTRODUCTION

Tuberculosis (TB) is an airborne infectious disease persisting with high mortality which is caused by mycobacterium, *Mycobacterium tuberculosis*. Each year, over 12 million peple suffer from the disease accompanied with 1.4 million death circumstances. Emergence of multidrug resistance against existing chemotherapeutic applications has led to find out a solution to this alarming increase of TB infections. Accordingly, Therefore, there is an intensive study to develop new, more effective antituberculotic agents[1-5].

Indoles, especially 1*H*-indole-2,3-dione (isatin) are the most prevalent heterocyclic scaffolds which have a broad spectra of medical applications such as anti-HIV, antiviral, anti-tumor, antifungal, antiangiogenic, anti-convulsant, and antiparkinsonian activity[6-8]. In particular, antituberculotic activity of various indole derivatives[9-14] and isatin derivatives[15-22] have attracted attention. The syn-

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thetic feasibility and extensive use of this scaffold have led to medicinal chemists to this ring which has also stemmed from the interest in the biological and pharmacological properties[23,24].

In the other hand, thiazole ring is another important structure which have enhanced lipid solubility which is easily metabolized by routine biochemical reactions. Thiazole derivatives have well established with antituberculosis effects in many studies[25-30]. Studies combined these two rings, thiazole and isatin have also been reported[31,32].

In this work, based on isatin structure we have designed and synthesized new 3-[(4-aryl-2-thiazolyl)hydrazone]-1*H*-indol-2,3-dione derivatives. Six final compounds were screened for their antituberculotic activity, against *M. tuberculosis*. Log *P* values for the compounds were calculated, virtually and the biological results have been evaluated compared to standard drugs, isoniazid and rifampicin.

METHODOLOGY

Chemistry

Melting points were determined using a MP90 digital melting point apparatus (Mettler Toledo, OH) and were uncorrected. Spectroscopic data were recorded on the following instruments: a Bruker Tensor 27 IR spectrophotometer; a ^{1}H NMR (nuclear magnetic resonance) Bruker DPX- 300 FT-NMR spectrometer, ^{13}C NMR, Bruker DPX 75 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA); M+1 peaks were determined by Shimadzu LC/MS ITTOF system (Shimadzu, Tokyo, Japan).

Synthesis of 1H-Indole-2,3-dione-3-thiosemicarbazone (1)

0.02 mol of isatin, 0.02 mol of thiosemicarbazide and catalytic amount of acetic acid were refluxed in ethanol for 6 hours. After the end of the reaction was controlled by TLC, the reaction mixture was allowed to cool to room temprature and obtained precipitate was filtrated. The raw product was crystallised from ethanol.

Synthesis of 3-[(4-aryl-2-thiazolyl)hydrazone]-1H-indol-2,3-dione derivatives (2a-f)

3 mmol of gained intermediate (**1**) and appropriate α-bromoarylethanone derivative (3 mmol) were stirred in ethanol at room temprature. After the reaction was ended, the mixture was filtrated with excess ethanol and recrystallised from ethanol.

3-[[4-(2-Hydroxyphenyl)-2-thiazolyl]hydrazone]-1H-indol-2,3-dione (2a)

68 % yield; mp 310 °C. IR ν_{max} (cm^{-1}): 3250 (NH), 3136 (OH), 1691 (C=O), 1616-1454 (C=C, C=N), 1386-981 (C-O, C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 6.84-6.97 (m, 3H, Ar-H), 7.09 (t, J=7.38 Hz, 1H, Ar-H), 7.17 (t, J=7.35 Hz,

1H, Ar-H), 7.34 (t, J=7.99 Hz, 1H, Ar-H), 7.53 (d, J=7.67 Hz, 1H, Ar-H), 7.68 (s, 1H, thiazole C_5-H), 7.92 (d, J=8.30 Hz, 1H, Ar-H), 10.54 (s, 1H, OH), 11.23 (s, 1H, NH), 13.53 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 109.00, 111.48, 116.95, 119.61, 119.95, 120.31, 121.78, 122.84, 128.51, 129.41, 130.95, 132.57, 141.79, 148.52, 155.48, 163.42, 165.68. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}N_4O_2S$ 337.37; found 337.08.

3-[[4-(3-Hydroxyphenyl)-2-thiazolyl]hydrazone]-1H-indol-2,3-dione (2b)

72 % yield; mp 316 °C. IR ν_{max} (cm^{-1}): 3161 (OH, NH), 1695 (C=O), 1616-1431 (C=C, C=N), 1346-987 (C-O, C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 6.71-6.74 (m, 1H, Ar-H), 6.97 (d, J=7.76 Hz, 1H, Ar-H), 7.09 (t, J=7.47 Hz, 1H, Ar-H), 7.21 (t, J=8.05 Hz, 2H, Ar-H), 7.31-7.37 (m, 2H, Ar-H), 7.53-7.54 (m, 2H, Ar-H and thiazole C_5-H), 9.48 (s, 1H, OH), 11.25 (s, 1H, NH), 13.35 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 107.13, 111.53, 113.09, 115.47, 116.96, 120.21, 120.32, 122.88, 130.16, 130.94, 132.48, 135.68, 141.74, 151.61, 158.11, 163.68, 166.25. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}N_4O_2S$ 337.37; found 337.07.

3-[[4-(4-Hydroxyphenyl)-2-thiazolyl]hydrazone]-1H-indol-2,3-dione (2c)

69 % yield; mp 285 °C. IR ν_{max} (cm^{-1}): 3165 (OH, NH), 1691 (C=O), 1612-1463 (C=C, C=N), 1327-987 (C-O, C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 6.79-6.86 (m, 3H, Ar-H), 6.96 (d, J=8.00 Hz, 1H, Ar-H), 7.08 (t, J=7.62 Hz, 1H, Ar-H), 7.34 (s, 1H, thiazole C_5-H), 7.53 (d, J=7.62 Hz, 1H, Ar-H), 7.71 (d, J=8.20 Hz, 2H, Ar-H), 9.60 (s, 1H, OH), 11.24 (s, 1H, NH), 13.32 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 104.21, 110.15, 111.51, 115.85, 116.02, 120.25, 121.73, 122.85, 125.81, 127.62, 130.85, 132.28, 141.68, 151.85, 157.87, 163.67, 166.19. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{17}H_{12}N_4O_2S$ 337.37; found 337.07.

3-[[4-(2-Pyridyl)-2-thiazolyl]hydrazone]-1H-indol-2,3-dione (2d)

65 % yield; mp 298 °C. IR ν_{max} (cm^{-1}): 3124 (NH), 1683 (C=O), 1616-1464 (C=C, C=N), 1344-987 (C-O, C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 6.97 (d, J=8.80 Hz, 1H, Ar-H), 7.09 (t, J=7.54 Hz, 1H, Ar-H), 7.32-7.37 (m, 2H, Ar-H), 7.55 (d, J=7.96 Hz, 1H, Ar-H), 7.81 (s, 1H, thiazole C_5-H), 7.88 (t, J=7.96 Hz, 1H, Ar-H), 7.95-7.98 (m, 1H, Ar-H), 8.60 (d, J=4.28 Hz, 1H, Ar-H), 11.26 (s, 1H, NH), 13.36 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 111.02, 111.55, 120.17, 120.39, 120.54, 120.77, 122.91, 123.50, 131.04, 137.85, 141.82, 149.93, 152.10, 163.66, 166.90. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{11}N_5OS$ 322.36; found 322.07.

3-[[4-(3-Pyridyl)-2-thiazolyl]hydrazone]-1H-indol-2,3-dione (2e)

69 % yield; mp 318 °C. IR ν_{max} (cm^{-1}): 3298 (NH), 1666 (C=O), 1616-1462 (C=C, C=N), 1357-988 (C-O, C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 6.91 (d,

J=8.86 Hz, 1H, Ar-H), 7.06 (t, J=8.23 Hz, 1H, Ar-H), 7.31 (t, J=8.23 Hz, 1H, Ar-H), 7.48 (d, J=7.32 Hz, 1H, Ar-H), 7.90-7.95 (m, 1H, Ar-H), 8.04 (s, 1H, thiazole C_5-H), 8.75-8.79 (m, 2H, Ar-H), 9.25-9.26 (m, 1H, Ar-H), 11.25 (s, 1H, NH), 13.34 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 110.62, 111.56, 111.93, 119.97, 120.42, 120.25, 121.94, 122.89, 126.43, 126.86, 131.18, 132.44, 133.25, 139.82, 141.49, 141.91, 143.16, 143.31, 146.04, 163.57, 167.50. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{11}N_5OS$ 322.36; found 322.07.

3-[[4-(4-Pyridyl)-2-thiazolyl]hydrazone]-1H-indol-2,3-dione (2f)

67 % yield; mp 297 °C. IR ν_{max} (cm^{-1}): 3156 (NH), 1684 (C=O), 1620-1466 (C=C, C=N), 1346-985 (C-O, C-N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 6.91 (d, J=7.64 Hz, 1H, Ar-H), 7.05 (t, J=7.64 Hz, 1H, Ar-H), 7.30 (t, J=7.64 Hz, 1H, Ar-H), 7.48 (d, J=8.06 Hz, 1H, Ar-H), 7.76-7.80 (m, 2H, Ar-H), 7.92 (s, 1H, thiazole C_5-H), 8.58 (d, J=5.82 Hz, 2H, Ar-H), 11.23 (s, 1H, NH), 13.31 (s, 1H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ 110.07, 110.40, 111.50, 111.57, 120.08, 120.15, 120.38, 121.81, 122.82, 126.36, 131.02, 131.26, 132.88, 141.07, 149.05, 150.55, 163.59, 166.99. HRMS (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{11}N_5OS$ 322.36; found 322.07.

Microplate Alamar Blue Assay (MABA)

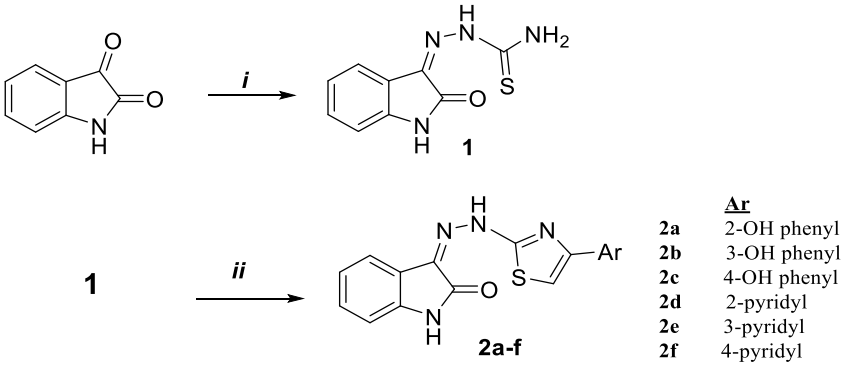
M. tuberculosis H37RV (ATCC 27294), was obtained from the American Type Culture Collection (ATCC). The microorganism was cultured at ATCC® Medium 1395: Middlebrook 7H9 broth with ADC enrichment at a temperature of 37°C for 10 day. The turbidity of the cultures was adjusted to McFarland standard no. 1. Rifampicin and isoniazid were used as standard drugs. Plates (Corning) were incubated at 37°C in 5% CO_2 for 7 days which were added freshly prepared 1:1 mixture of Alamar Blue reagent (1:10 dilution, Invitrogen, 156703SA)) and 10% Tween 80 and then plates were reincubated at 37°C for 24h. After color change from blue to pink the reagent mixture was added to all the wells of the microplate. The results were expressed as MIC (at which all bacteria were inhibited)[33].

RESULTS AND DISCUSSION

Chemistry

Novel 3-[(4-aryl-2-thiazolyl])hydrazone]-1*H*-indol-2,3-dione derivatives (**2a-f**) were synthesized in this study. Six compounds were obtained starting from isatin by nucleophilic addition and cyclization reactions in order, as can be seen **Scheme 1**. 1*H*-Indole-2,3-dione-3-thiosemicarbazone (**1**), the intermediate product was previously obtained molecule which was reported with a melting point of 240-241 °C in literature[34]. The structures of the final compounds were elucidated with spectroscopic techniques. In the IR spectra of the compounds, characteristic bands at 3124-3298 cm^{-1} and 1666-1695 cm^{-1} were observed belong to N-H and C=O bonds, respectively. In the ^{1}H NMR spectra, thiazole C_5-H proton was detected at 7.34-8.04 ppm whereas cyclic amide (lactam) proton

of indole ring was determined at 11.23-11.26 ppm. All other peaks were seen at aromatic region and between ppm 6.71-9.26 ppm. In ^{13}C NMR spectra of the compounds, carbonyl carbon was resonated at about 165.68-167.50 ppm and other carbons were observed at 104.21-163.68 ppm. MS data was also confirmed molecular weights of the compounds.



Scheme 1: Synthesis of the compounds (**2a-f**). Reagents: (i) thiosemicarbazide, catalytic amount of acetic acid, ethanol, reflux, 6h; (ii) α-bromoarylethanone, ethanol, rt.

Antitubercular activity

The antimycobacterial activity of six final compounds (**2a-f**) were investigated against *Mycobacterum tuberculosis* H37RV (ATCC 27294) compared with standard drugs isoniazid and rifampin. Minumum inhibitor concentrations (MIC) of tested compounds were found in between 15.63-500 μg/mL whereas MIC was calculated as 31.25 μg/mL for standard drugs. Compounds **2c** with 4-hydroxyphenyl moiety and **2d** with 2-pyridyl moiety displayed significant activity which were determined as the most active compounds (MIC=15.63 μg/mL) even if higher than positive controls. Besides, compound **2e** showed half potential to standard drugs with MIC=62.50 μg/mL. The rest of the compounds did not exhibit remarkable antitubercular activity.

Mycobacterium tuberculosis is known with lipid wrapped cell wall which most of the antibiotics unable to penetrate[35]. It is reported that the lipophilicity is closely associated with antimycobacterial potential of molecules[36]. Log *P* values of the synthesized compounds were predicted using Molinspiration-Calculation of Molecular Properties and Bioactivity Score toolkit[37] and compared with activity results. When MIC values and lipophilic character of the compounds (calculated log *P*) were compared, there is no distinct relationship; however, molecules **2c** and **2d** possess the lowest MIC values with average log *P* values. Accordingly, it could be declared that 3-[(4-aryl-2-thiazolyl)hydrazone]-1*H*-indol-2,3-dione derivatives (**2a-f**) did not show correlative values between log *P* and antituberculotic effects of the compounds.

Table 1: Antitubercular activities against *M. tuberculosis* H37RV (ATCC 27294) and log P predictions of compounds **2a-f**

Compounds	MIC (μg/mL)	Log P[a]
2a	250	2.89
2b	125	2.89
2c	15.63	2.92
2d	15.63	2.94
2e	62.50	3.52
2f	500	3.54
Isoniazid	31.25	-
Rifampin	31.25	-

[a]Calculated by http://www.molinspiration.com/.

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