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Der Pharma Chemica, 2014, 6(2):149-154
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

An efficient synthesis and antimicrobial evaluation of N-methyl-5-substituted-1*H*-indole-2-oxo-3-((2′-acetamidothiazol-4′-yl)-carbonylmethyl hydrazones)

Lata*, Khushbu Kushwaha and Subhash C Jain

Department of Chemistry, University of Delhi, Delhi, India

ABSTRACT

*A new series of N-methyl-5-substituted-1H-indole-2-oxo-3-((2′-acetamidothiazol-4′-yl)carbonylmethyl hydrazones) (**5a-j**) were synthesized with high degree of purity and in excellent yield. The structures of new compounds were determined by analytical and spectral methods (IR, ^{1}H NMR, ^{13}C NMR, EIMS). Newly synthesized compounds were tested for their antimicrobial activity were also carried out against three Gram-positive bacteria (Staphylococcus aureus, Bacillus subtilis and Staphylococcus epidermis) and four Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi and Klebsiella pneumoniae) and against four fungi (Aspergillus niger, Aspergillus fumigatus, Aspergillus flavus and Candida albicans). Bioassay results showed that most of the synthesized compounds exhibited significant activity against Aspergillus fumigatus, Aspergillus flavus and Candida albicans. Interestingly, among all the compounds, **5c, 5g-h** and **5i** have shown activity greater than the standard drug miconazole against the fungal strain Aspergillus fumigatus in vitro.*

Keywords: 1*H*-Indol-2,3-diones, Thiazole, Acetohydrazide, Hydrazones, Antibacterial, Antifungal.

INTRODUCTION

The thiazole moiety is among the most attractive sulfur-containing motifs and forms an important constituent of many natural products such as Vitamin B_1[1], Bacillamide [2] and Epothilones [3]. It is also presence in various synthetic compounds possessing pharmaceutical properties [4,5]. The diverse physiological and biological activities possessed by thiazoles have received much attention in the recent years [6,7] in designing and developing new molecules. 2-Aminothiazole derivatives [8,9] are particularly used in medicinal chemistry [10] as they exhibit antimicrobial [11,12] and antioxidant [13] activities. Indole, on the other hand is well known bioactive precursor as it is a part of essential amino acid i.e. tryptophan and also some of the naturally occurring alkaloids [14]. Its derivatives have shown a wide variety of biological activities like antimicrobial [15-17], antiviral [18], anti-inflammatory [19] and anti-allergic [20]. Thus the molecular hybridization assumption (the coupling of two different bioactive moieties used in the development of drugs) encouraged us to design and synthesize a new series of compounds containing both 2,3-dioxoindole and thiazole moieties in a single molecular framework *via* hydrazone formation. Hydrazones served as important key intermediate for drug design, metal complexes, organo catalysis and also for the syntheses of many pharmaceutically active heterocycles [21-23]. There has been precedents in literature where of hydrazones of two different pharmaceutically moieties have been utilized to synthesize more complex molecules [24]. In view of the high status of thiazole and indole moieties in medicinal chemistry and also because of very few reports in the literature where a single molecule contain both of them [25], we herein wish to report a

simple and an efficient method for the synthesis of new indolyl-2-acetamidothiazolylhydrazones in excellent yields (**Scheme–1**).

All the newly synthesized compounds gave satisfactory elemental analysis. IR, ^{1}HNMR, ^{13}CNMR and mass spectra which were consistent with the assigned structures. All the synthesized compounds were screened for their anti-bacterial and anti-fungal activity.

MATERIALS AND METHODS

Melting points were determined on an electronic apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance (400 MHz) and ^{13}C NMR spectra were recorded on Bruker Advance (100 MHz) using tramethylsilane (TMS) as an internal standard and $CDCl_3$/$DMSOd_6$ as solvent. TOF ES+ Mass spectra (m/z) were recorded on Micromass Autospec LCTKC455. Infrared (FTIR) spectra were determined on a Perkin Elmer-2000 Spectrophotometer instrument. Elemental analyses were performed on a Perkin Elmer series 11, CHNS/O analyzer 2400. The chemicals used in this work were purchased from Mreck and were used without further purification. 2-Amino-4-(carboethoxymethyl)thiazole [26], 2-acetamido-4-(carboethoxymethyl)thiazole [27], 2-(2-acetamido-thiazol-4-yl)acetohydrazide [28], and substituted isatins [29] were synthesized according to the literature.

General procedure for preparation of N-methyl-5-substituted-1*H*-indole-2-oxo-3-((2′-acetamidothiazol-4′-yl)-carbonylmethyl hydrazones) (5a-j).
A mixture of 1*H*-indol-2,3-dione **(4a-j)** (1.0 mmol) and 2-(2-acetamido-thiazol-4-yl)acetohydrazide **(3)** (1.0 mmol) was refluxed in 20 mL of ethanol on an oil bath. Reaction was monitored by TLC. After 1-1.5 hours, the reaction mixture was allowed to cool down. The compound that separated out was filtered and dried to obtain compound **5a-j**.

1*H*-Indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethylhydrazone) (5a). Physical state: yellow solid; Yield 96%; m.p. 188-200 °C; R_f: 0.40 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3257-3163 (NH), 1723 (C=O, indole), 1664 (C=O), 1659 (C=O), 1553 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.08 (s, 1H, NH, D_2O exchangeable), 11.11 (s, 1H, NH, D_2O exchangeable), 10.81 (s, >NH, D_2O exchangeable), 8.01 (s, 1H), 7.39 (m, 1H), 7.05 (m, 2H), 6.88 (s, 1H), 4.00 (s, 2H, CH_2), 2.11 (s, 3H, $COCH_3$). ^{13}C NMR (δ, $CDCl_3$, 100 MHz): 170.1 (CO, amide), 167.2 (CO, acetyl), 163.9 (C=O, indole), 156.5 (C=N, hydrazone), 142.5, 130.1, 124.9, 120.7, 114.1, 109.7, 37.2, 21.4. MS, TOF ES+ *m/z* (%): 344.423 (M^++1), Anal. Calcd for: $C_{15}H_{13}N_5O_3S$: C, 52.47; H, 3.82; N, 20.40%. Found: C, 52.44; H, 3.80; N, 20.23%.

5-Methyl-1*H*-indole-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5b). Physical state: yellow solid; Yield 97%; m.p. 176-178 °C; R_f: 0.43 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3311-3205 (N-H), 1721 (C=O, indole), 1662 (C=O), 1650 (C=O), 1552 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.12 (s, 1H, NH, D_2O exchangeable), 11.15 (s, 1H, NH, D_2O exchangeable), 10.79 (s, >NH, D_2O exchangeable), 7.38 (s, 1H), 7.18 (d, 1H, *J*=7.3 Hz), 7.03 (d, 1H, *J*=7.3 Hz), 6.72 (s, 1H), 4.15 (s, 2H, CH_2), 2.78(s, 3H, 5-CH_3), 2.11 (s, 3H, $COCH_3$). ^{13}C NMR (δ, $CDCl_3$, 100 MHz): 169.4(CO, amide), 167.7(CO, acetyl), 162.3(C=O, indole), 157.2 (C=N, hydrazone), 142.2, 141.2, 131.3, 114.0, 109.6, 107.8, 34.3, 25.2, 21.8. MS, TOF ES+ *m/z* (%): 358.332 (M^++1), Anal. Calcd for: $C_{16}H_{15}N_5O_3S$: C, 53.77; H, 4.23; N, 19.60%. Found: C, 53.72; H, 4.19; N, 19.58%.

5-Fluoro-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5c). Yield 94%; m.p. 170-172 °C; R_f: 0.42 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3414-3244 (N-H), 1720 (C=O, indole), 1660 (C=O), 1655 (C=O), 1556 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.07 (s, 1H, NH, D_2O exchangeable), 11.29 (s, 1H, NH, D_2O exchangeable), 10.24 (s, >NH, D_2O exchangeable), 8.1 (s, 1H), 7.23 (d, 1H, *J*=7.6 Hz), 6.98 (d, 1H, *J*=7.6 Hz), 6.88 (s, 1H), 4.04 (s, 2H, CH_2), 2.09 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 172.1 (CO, amide), 168.6 (CO, acetyl), 162.2(C=O, indole), 156.9 (C=N, hydrazone), 142.8, 142.4, 140.2, 133.1, 130.5, 127.6, 121.7, 112.3, 109.6, 34.5, 22.4. MS, TOF ES+ *m/z* (%): 362.421 (M^++1), Anal. Calcd for: $C_{15}H_{12}FN_5O_3S$: C, 49.86; H, 3.35; N, 19.38%. Found: C, 49.80; H, 3.31; N, 19.33%.

5-Chloro-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5d). Yield 96%; m.p. 181-183 °C; R_f: 0.45 (96:4 chloroform: methanol, v/v); (KBr, cm^{-1}): 3310-3070 (N-H), 1720 (C=O, indole), 1659 (C=O), 1652 (C=O), 1553 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 13.03(s,1H, NH, D_2O exchangeable),

12.45 (s, 1H, NH, D_2O exchangeable), 11.88 (s, >NH, D_2O exchangeable), 7.42 (d, 1H, *J*=8.2 Hz), 7.05 (s, 1H), 6.90 (d, 1H, *J*=8.2 Hz), 6.74 (s, 1H), 4.11 (s, 2H, CH_2), 2.08 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 171.7(CO, amide), 168.3(CO, acetyl), 162.3(C=O, indole), 158.7 (C=N, hydrazone), 143.1, 142.0, 140.1, 132.8, 130.2, 127.3, 121.2, 112.2, 109.1, 34.2, 22.3. MS, TOF ES+ *m/z* (%): 378.322 (M^++1), Anal. Calcd for: $C_{15}H_{12}ClN_5O_3S$: C, 47.69; H, 3.20; N, 18.54%. Found: C, 47.60; H, 3.19; N, 18.51%.

5-Bromo-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5e). Physical state: yellow solid; Yield 96%; m.p. 189-171 °C; R_f: 0.44 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3198-3064 (N-H), 1712 (C=O, indole), 1660 (C=O), 1654 (C=O), 1555 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 13.03 (s, 1H, NH, D_2O exchangeable), 12.45 (s, 1H, NH, D_2O exchangeable), 11.88 (s, >NH, D_2O exchangeable), 7.72 (s, 1H), 7.54 (d, 1H, *J*=8.3 Hz), 7.04 (d, 1H, *J*=8.3 Hz), 6.78 (s, 1H), 4.10 (s, 2H, CH_2), 2.08 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 171.3(CO, amide), 168.1(CO, acetyl), 162.1 (C=O, indole), 157.8 (C=N, hydrazone), 141.4, 140.1, 133.7, 123.0, 121.9, 114.3, 29.0, 22.4. MS, TOF ES+ *m/z* (%): 423.435 (M^++1), Anal. Calcd for: $C_{15}H_{12}BrN_5O_3S$: C, 42.67; H, 2.86; N, 16.59%. Found: C, 42.63; H, 2.81; N, 16.50%.

1-Methyl-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5f). Physical state: yellow solid; Yield 95%; m.p. 175-177 °C; R_f: 0.44 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3482-3262 (NH), 1717 (C=O, indole), 1663 (C=O), 1657 (C=O), 1548 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.09 (s, 1H, NH, D_2O exchangeable), 12.20 (s, 1H, NH, D_2O exchangeable), 8.02 (d, 1H, *J*= 7.9), 7.46 (d, 1H, *J*= 7.9), 7.10 (m, 2H), 6.99 (s, 1H), 4.02 (s, 2H, CH_2), 3.16 (s, 3H, N-CH_3), 2.09 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 168.3(CO, amide), 162.4(CO, acetyl), 164.0(C=O, indole), 156.9 (C=N, hydrazone), 142.8, 142.5, 135.5, 125.7, 122.2, 114.5, 110.3, 109.3, 36.2, 26.0, 21.4. MS, TOF ES+ *m/z* (%): 358.314 (M^++1), Anal. Calcd for: $C_{16}H_{15}N_5O_3S$: C, 53.77; H, 4.23; N, 19.60%. Found: C, 53.71; H, 4.19; N, 19.62%.

1,5-Dimethyl-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5g). Physical state: yellow solid; Yield 94%; m.p. 182-184 °C; R_f: 0.46 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3297-2928 (N-H), 1723 (C=O, indole), 1664 (C=O), 1655 (C=O), 1554 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.09 (s, 1H, NH, D_2O exchangeable), 10.95 (s, 1H, NH, D_2O exchangeable), 8.16 (s, 1H), 7.23 (d, 1H, *J*= 7.8 Hz), 7.01 (d, 1H, *J*= 7.8 Hz), 6.80 (s, 1H), 3.92 (s, 2H, CH_2), 3.11 (s, 3H, N-CH_3), 2.77(s, 3H, 5-CH_3), 2.12(s, 3H, $COCH_3$). ^{13}C NMR (δ, $CDCl_3$, 100 MHz): 169.3(CO, amide), 167.3(CO, acetyl), 162.5(C=O, indole), 156.8 (C=N, hydrazone), 142.7, 139.7, 131.8, 114.3, 109.4, 107.3 34.6(CH_2), 26.5, 25.4, 21.8. MS, TOF ES+ *m/z* (%): 372.430 (M^++1), Anal. Calcd for: $C_{17}H_{17}N_5O_3S$: C, 54.97; H, 4.61; N, 18.86%. Found: C, 54.92; H, 4.64; N, 18.80%.

5-Fluoro-1-methyl-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5h). Physical state: yellow solid; Yield 95%; m.p. 180-182 °C; R_f: 0.45 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3260-3215 (N-H), 1719 (C=O, indole), 1663 (C=O), 1652 (C=O), 1557(C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.05 (s, 1H, NH, D_2O exchangeable), 11.10 (s, 1H, NH, D_2O exchangeable), 7.41 (s, 1H,), 7.05 (d, 1H, *J*= 7.9), 6.97 (d, 1H, *J*= 7.9), 6.89 (s, 1H), 4.10 (s, 2H, CH_2), 3.20 (s, 3H, N-CH_3), 2.09 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 169.0(CO, amide), 164.4(CO, acetyl), 160.7(C=O, indole), 156.7 (C=N, hydrazone), 140.2, 139.3, 118.91, 111.1, 124.8, 122.6, 109.0, 34.9, 26.0, 22.6. MS, TOF ES+ *m/z* (%): 376.429 (M^++1), Anal. Calcd for: $C_{16}H_{14}FN_5O_3S$: C, 51.19; H, 3.76; N, 18.66%. Found: C, 51.22; H, 3.71; N, 18.62%.

5-Chloro-1-methyl-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5i). Physical state: yellow solid; Yield 96%; m.p. 173-175 °C; R_f: 0.46 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3254-3165 (N-H), 1717 (C=O, indole), 1665 (C=O), 1656 (C=O), 1546 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.07 (s, 1H, NH, D_2O exchangeable), 11.44 (s, 1H, NH, D_2O exchangeable), 8.28 (s, 1H), 7.52 (d, 1H, *J*=8.4 Hz), 7.12 (d, 1H, *J*=8.4 Hz), 6.96 (s, 1H), 4.05 (s, 2H, CH_2), 3.16 (s. 3H, N-CH_3), 2.11 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 169.2(CO, amide), 164.8(CO, acetyl), 162.2 (C=O, indole), 157.2 (C=N, hydrazone), 142.4, 139.3, 118.42, 110.6, 124.9, 122.4, 109.4, 34.4, 26.3, 22.2. MS, TOF ES+ *m/z* (%): 392 (M^++1), Anal. Calcd for: $C_{16}H_{14}ClN_5O_3S$: C, 49.04; H, 3.60; N, 17.87%. Found: C, 49.10; H, 3.58; N, 17.88%.

5-Bromo-1-methyl-1*H*-indol-2-oxo-3-((2'-acetamidothiazol-4'-yl)carbonylmethyl hydrazone) (5j). Physical state: yellow solid; Yield 98%; m.p. 176-178 °C; R_f: 0.47 (96:4 chloroform: methanol, v/v); IR ν (KBr, cm^{-1}): 3256-3114 (N-H), 1722 (C=O, indole), 1662 (C=O), 1658 (C=O), 1544 (C=N, hydrazone). ^{1}H NMR (δ, DMSO-d_6, 400 MHz): 12.90 (s, 1H, NH, D_2O exchangeable), 12.01 (s, 1H, NH, D_2O exchangeable), 7.28 (s, 1H), 7.16 (d, 1H, *J*=8.5 Hz),

6.98 (d, 1H, *J*=8.5 Hz), 6.86 (s, 1H), 4.09 (s, 2H, CH_2), 3.15 (s, 3H, N-CH_3), 2.05 (s, 3H, $COCH_3$). ^{13}C NMR (δ, DMSO-d_6, 100 MHz): 168.8(CO, amide), 164.6(CO, acetyl), 161.1(C=O, indole), 157.4(C=N, hydrazone), 142.0, 138.8, 119.4, 112.2, 124.6, 123.3, 109.6, 34.4, 26.2, 22.4. MS, TOF ES+ *m/z* (%): 437.237 (M^++1), Anal. Calcd for: $C_{16}H_{14}BrN_5O_3S$: C, 44.05; H, 3.23; N, 16.05%. Found: C, 44.11; H, 3.19; N, 16.12%.

Antimicrobial activity assessment: Among all, compounds **5a–j** were screened for their in *vitro* antimicrobial activity to determine zone of inhibition at 100 µg/mL against three Gram-positive bacteria (*S. aureus* MTCC 096, *Bacillus subtilis* MTCC 441 and *Staphylococcus epidermis* MTCC 435), four Gram-negative bacteria (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 424, *Salmonella typhi* MTCC 733, and *Klebsiella pneumoniae* MTCC 432) as well as four fungi (*Aspergillus niger* MTCC 282, *Aspergillus fumigatus* MTCC 343, *Aspergillus flavus* MTCC 277, and *Candida albicans* MTCC 227) using Cup plate method [30, 31], where Muller-Hilton agar for bacteria and Sabouraud dextrose agar for fungi was poured on to the sterilized petri dishes (25-30 mL: each petri dish). The poured material was allowed to set (30 min.) and thereafter the 'CUPS' (08 mm diameter) was made by punching into the agar surface with a sterile cork borer and scooping out the punched part of the agar. Into these cups the test compound solution (0.1 mL) was added with the help of a micro pipette. The plates were incubated at 37 ^{0}C for 14 h for bacteria and 30 h for fungi and the results were noted. The test solution was prepared using DMSO as solvent. Clinically antimicrobial drugs Ciprofloxacin and Miconazole were used as the positive control and DMSO was used for blank. The obtained results, depicted in **Tables 1**, revealed that thiozolyl hydrazones could effectively, to some extent, inhibit the growth of all tested strains in *vitro*.

Table 1 Antimicrobial activity data of compounds 5a-j

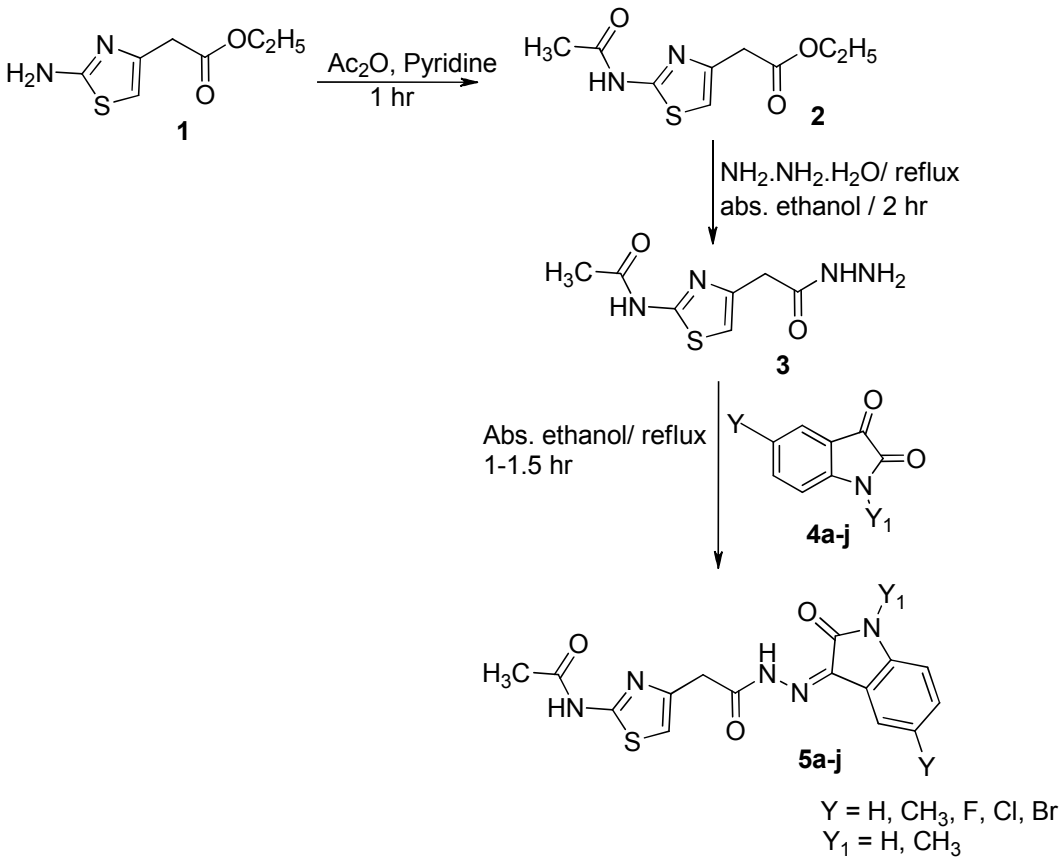
Compd.	*Sa*	*Bs*	*Se*	*Ec*	*Pa*	*St*	*Kp*	*An*	*Af*	*Afl*	*Ca*
5a	14	15	16	13	16	14	13	13	13	12	12
5b	14	14	14	15	13	14	13	14	15	14	13
5c	14	15	14	15	15	14	14	14	17	13	13
5d	13	16	13	13	13	14	13	15	14	13	11
5e	15	14	16	13	16	13	13	14	15	15	12
5f	16	15	17	13	14	14	14	14	13	15	12
5g	14	16	14	14	16	14	14	14	16	13	12
5h	14	13	14	12	15	13	13	14	16	14	14
5i	17	14	15	14	14	13	13	17	17	13	14
5j	16	14	16	14	14	14	12	12	14	14	12
Cip.	20	18	19	20	22	20	18	--	--	--	--
Mic.	--	--	--	--	--	--	--	18	15	17	19

[a] *Values represent zone of inhibition*

Sa: Staphylococcus aureus MTCC 096, Bs: Bacillus subtilis MTCC 441, Se: Staphylococcus epidermis MTCC 435, Ec: Escherichia coli MTCC 443, Pa: Pseudomonas aeruginosa MTCC 424, St: Salmonella typhi MTCC 733, Kp: Klebsiella pneumoniae MTCC 432, An: Aspergillus niger MTCC 282, Af: Aspergillus fumigatus MTCC 343, Afl: Aspergillus flavus MTCC 277, Ca: Candida albicans MTCC 227, Cip.: Ciprofloxacin, Mic.: Miconozole.

RESULTS AND DISCUSSION

The synthetic root adopted to get the target compounds are depicted in **Scheme-1**. The 2-amino-4-(carboethoxymethyl)thiazole **(1)** was reacted with acetic anhydride for 1 hr to get compound **2** and then **2** was treating with hydrazine hydrate for 2 hr to obtain compound **3**. Finally compound **3** was condensed with 1-*H*-indol-2,3-dione (**4a)** in equimolar ratio for 1 hr to obtain **5a** in a high yield. Compound (**5a)** which displayed molecular ion peak M^++1 at m/z 344.423 in TOF ES+, corresponding to the molecular formula $C_{15}H_{13}N_5O_3S$ thereby indicating that the two moieties have condensed together with the loss of a water molecule. Compound **5a** exhibited characteristic absorption band at 1664 cm^{-1} for >C=N stretching in its IR spectrum which indicated the formation of corresponding hydrazone. Further, broad absorption band at 3257-3163 cm^{-1} showed the presence of NH stretching which was also confirmed by the presence of broad singlets at δ 10.81, 11.11 and 12.08 for the D_2O exchangeable NH protons in its ^1H NMR spectrum. Further, five aromatic protons of the indole and thiazole nucleus appeared at δ 6.88 (1H), 7.05 (2H), 7.39 (1H), and 8.01 (1H). Its ^{13}C NMR spectrum, displayed all the expected peaks for amidic carbonyls, hydrazone formation and for aromatic carbons.



Scheme1. Synthetic root for the preparation of compounds 5a-j

Among all, compounds **5a–j** were screened for their in *vitro* antimicrobial activity to determine zone of inhibition at 100 µg/mL against three Gram-positive bacteria (*S. aureus*, *Bacillus subtilis* and *Staphylococcus epidermis*), four Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, and *Klebsiella pneumoniae*) as well as four fungi (*Aspergillus niger*, *Aspergillus fumigatus*, *Aspergillus flavus*, and *Candida albicans*. The obtained results, depicted in **Tables 1**, revealed that N-methyl-5-substituted-1*H*-indole-2-one-3-[(2′-acetamidothiazol-4′-yl)carbonylmethyl hydrazones (**5a-j**) could effectively, to some extent, inhibit the growth of all tested strains in *vitro*. In antibacterial studies, all the compounds tested were less active towards *E.coli*, *S.typhi* and *K. pneumonia*, as compared to other four strains of bacteria, Out of four strains of fungi, these compounds have showed significant activity against all the four strain of fungi but Interestingly, among all the compounds, **5c, 5g-h** and **5i** have shown activity greater than the reference drug miconazole against the fungal strain *Aspergillus fumigatus in vitro*. These are lead molecules and may be taken up further to develop a new pharmacophore for the future.

CONCLUSSION

In summary, we have developed a simple and an efficient approach for the synthesis of new pharmaceutically important hydrazones incorporating both indole and thiazole moieties *via* the nucleophilic addition of acetohyrazide to 2,3-dioxindoles in alcohol. The reaction can be carried out in protic solvents including alcohol, acetic acid and in the presence of either acid or base without much impact on the yield. Compounds **5a-j** were obtained in excellent yields in a short reaction time without any further purification.). The synthesized compounds were tested for their antimicrobial activity and they showed significant antibacterial and antifungal activity.

Acknowledgements
The author (Lata) acknowledge the financial support from the UGC (University Grant Commission), New Delhi and author (K.K) is thankful to CSIR (Council of Scientific and Industrial Research), New Delhi for research fellowship.

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