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Synthesis of Schiff Base Indolyl-1,3,4-Oxadiazole, Thiazolidinone and Azetidinone as Efficient Antimicrobial, Antioxidant, Antituberculosis and Anticancer Agents

Vaijinath A. Verma[1,✉], Anand R. Saundane[2] and Rajkumar S. Meti[3]

Asian Journal of Organic & Medicinal Chemistry

Volume: 4 Year: 2019
Issue: 2 Month: April–June
pp: 77–88
DOI: https://doi.org/10.14233/ajomc.2019.AJOMC-P

Received: 10 January 2019
Accepted: 28 March 2019
Published: 29 June 2019

ABSTRACT

The present investigation was under-taken to synthesize the Schiff base indole derivatives bearing of 1,3,4-oxadiazole thiazolidinone and azetidinone moieties. New series of 5-(5-substituted-3-phenyl-1*H*-indol-2-yl)-*N*-[(5-substituted-2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amines and screened their biological activities. Compound **4a** showed excellent antibacterial and radical scavenging activities. Compound **5a** revealed efficient to antifungal activity. In addition, compound **4a** was found to be most active against H37Rv strain *Mycobacterium tuberculosis*. In case of anticancer activity methoxy compounds **4e** and **6e** against all the three tumor cell lines manifested remarkable cytotoxic activity. Compounds **4e**, **5e** and **6e** have shown strong ferrous ions (Fe^{3+}) reducing antioxidant power (FRAP) among the compounds screened. Compound **5b** showed more potent of metal chelating on Fe^{2+} ions activity at all concentrations.

KEYWORDS

Indole, Oxadiazole, Azetidinone, Thiazolidinone, Microbial activities.

INTRODUCTION

Cancer is one the horrendous diseases which cause unrestrained onto genesis of group of cell. It remains an imply treat to human beings and intensifying causes of death [1-3]. The basic effectuate of cancer is due to the spectacular free radicals and reactive oxygen species (ROS). These are ions or molecules that have a single unpaired electron in their outermost shell of electrons. It is possible to endogenous free radical reaction, initiated by ionizing radiation, resulting to in increased metabolic activity and caused damage to cell structure, nucleic acids, membrane lipids, proteins purine and pyrimidine bases of DNA biomolecule, thus leading to mutation [4-7]. Many studies have suggested that anticancer role to detoxify ROS pull down in cancer cells, resulting intromission of programmed cell death or counter-regulation promoted ROS dismantle in normal cells by antioxidant mechanism [8]. The predominate reactive oxygen species generated in cell metabolism exogenous factors include superoxide anion radical ($HO^{-\bullet}$), hydrogen peroxide (H_2O_2), singlet ($^1O_2$) and hydroxyl radical ($HO^{\bullet}$).These free radical have essential roles in cell in signaling apoptosis and gene expre-

Author affiliations:

[1]Department of Chemistry, S.S. Margol College of Arts, Science and Commerce, Shahabad-585228, India
[2]Department of Post-Graduate Studies and Research in Chemistry, Gulbarga University, Kalaburagi-585106, India
[2]Department of Biochemistry, Mangalore University, P.G. Centre Chikka Aluvara, Kodagu-571232, India

✉To whom correspondence to be addressed:

Fax: +91 8474 204472
Tel: +91 8474 204473
E-mail: drvermachem@gmail.com

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ssion resulting diseases like cancer. The antioxidant molecules can balance ROS by neutralizing defenses to remove the toxic agents [9]. Meanwhile, tuberculosis is still endemic and a major public health impact. This disease is caused by *Mycobacterium tuberculosis* mainly affects the lungs (pulmonary). Mycobacterial cell wall components may induce nitric oxide production and reactive oxygen species, both concerned in carcinogenesis [10]. According to global tuberculosis report World Health Organization-2018, tuberculosis (TB) is one of the top 10 causes of death. Globally, the best estimate is that 10 million people (range, 9.0-11.1 million) developed TB disease in 2017: 5.8 million men, 3.2 million women and 1.0 million children and caused an estimated 1.3 million deaths were cases in Worldwide. The spread of anti-TB resistant is a major threat to global TB control. These strains are now entrenched in most countries and spreading at an alarming rate. Multidrug resistant (MDR) TB isolates are resistant to isoniazid (INH) and rifampicin, the two frontline drugs for TB treatment, and have been detected in every country surveyed. New anti-TB compounds must overcome the issues with current treatments, The development of this novel regimen will require a robust drug development pipeline, as well as an improved drug development process to advance the new therapeutic candidates. On the other hand,the emergence and spread of antimicrobial resistance led to an increase in morbidity and mortality and has become a worldwide public health issue. Antimicrobial resistance refers to microorganism that has developed the ability to inactivate, exclude or lethal mechanism of the antimicrobial agents [11]. The compounds bearing indole nucleus moieties play an important role in diverse to exhibit versatile range of biological activities *i.e.*, antibacterial [12,13], antifungal [14,15], antitumor [16,17], antiviral [18,19], antioxidant [20] and so forth. Understanding that incorparion of 1,3,4-oxadiazole thiazolidinones and azetidinones derivatives, which includes anticonvulsant [21], tuberculostic [22], analgesic and ulcerogenicity [23], antibacterial, antifungal, diuretic [24], antimiotic [25], anti-inflammatory [26] and anti-HIV [27].

As part of interest in the synthesis of heterocyclic compounds that have been explored for developing biologically important molecules, thiazolidinones [28-30] and azetidinones [31-35] derivatives are the important classes displaying an important role in medicinal chemistry. Meanwhile, several derivatives of 4-thiazolidinone and 2-azetidinone have been studied extensively because of their ready accessibility, diverse chemical reactivity and various pharmacological properties. Adjudicating the literature, the variety result due to modification of a classical molecule that result into a more effective molecule embodied with a wider perspective in medicine citations, focus was made in this area. Prompted by these results and in continuation of our research work in the synthesis of biologically important heterocyclic compounds, herein we have focused mainly on synthesis 5-(5-substituted-3-phenyl-1*H*-indol-2-yl)-*N*-[(5-substituted-2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amines. All the synthesized compounds were evaluated their *in vitro* antimicrobial, antioxidant, antituberculosis and anticancer activities. So far, it has contemplated to synthesize the indole derivatives bearing three known bioactive moieties such as 1,3,4-oxadiazole, thiazolidinone and azetidinone.

EXPERIMENTAL

All the reagents were obtained commercially and used by further purification. Melting points were determined by an open capillary method and are uncorrected. Purity of the compounds were checked by TLC using silica gel-G coated aluminium plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. The IR (KBr) spectra were recorded using a Perkin-Elmer Spectrum on FT-IR spectrometer. The ^{1}H NMR (DMSO) spectra were recorded using Marcy Plus (Varian 400 MHz) and the chemical shifts were expressed in ppm (δ scale) and ^{13}C NMR (125 MHz, DMSO) spectra recorded on Bruker NMR. Mass spectra were recorded using an ILS-CHU-C-41-VBV4 MS mass spectrometer. Elemental analysis was carried out using Flash EA 1112 series elemental analyzer.

General procedure for synthesis 5-substitued-3-phenyl-1*H*-indole-2-carbohydrazide (1a-c): These compounds were synthesized by the reported literature method [36].

5-(5-substituted-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (2a-c): 5-Substitued-3-phenyl-1*H*-indole-2-carbohydrazides **(1a-c)** (0.01 mol) and cyanogen bromide (0.01mol) in EtOH were refluxed with stirring for 90 min [37]. The reaction mixture was then cooled and neutralized by sodium bicarbonate solution. The product separated was filtered, dried and recrystallized in ethanol to afford pure **2a-c**.

5-(5-Chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (2a): Yield: 85 %; m.p.: 262-263 °C; IR (KBr, ν_{max}, cm^{-1}): 3454 (indole NH), 3136 (NH_2), 1615 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.20 (s, 1H, indole NH), 7.00-8.00 (m, 8H, Ar-H), 6.60 (s, 2H, NH_2), Anal. cald. for $C_{16}H_{11}N_4OCl$: C, 61.86; H, 3.58; N, 18.05; Found: C, 61.84; H, 3.57; N, 18.03 %.

5-(5-Methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (2b): Yield: 75 %; m.p.: 243-244 °C; IR (KBr, ν_{max}, cm^{-1}): 3245 (indole NH), 3095 (NH_2), 1620 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.60 (s, 1H, indole NH), 7.15-8.20 (m, 8H, Ar-H), 6.50 (s, 2H, NH_2), 3.35 (s, 3H, OCH_3); Anal. cald. for $C_{17}H_{14}N_4O_2$: C, 66.67; H, 4.61: N, 18.29; Found: C, 66.66; H, 4.62; N, 18.30 %.

5-(5-Methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (2c): Yield: 79 %; m.p.: 232-233 °C. IR (KBr, ν_{max}, cm^{-1}): 3400 (indole NH), 3109 (NH_2), 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.10 (s, 1H, indole NH), 6.50-7.95 (m, 9H, Ar-H), 6.40 (s, 2H, NH_2), 2.55 (s, 3H, CH_3); Anal. cald. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30; Found: C, 70.37; H, 4.88; N, 19.31 %.

5-[(5-Substituted-2-phenyl-1*H*-indol-3-yl)methylene]-N-(5-substituted-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amines (3a-i): A solution of compound **2a-c** (0.01 mol) and 5-substituted-2-phenylindole-3-carboxyaldehydes (0.01 mol) in 1,4-dioxane (40 mL) containing glacial acetic acid (2 mL) was refluxed for 8 h [38]. The excess of solvent was removed under reduced pressure. The reaction mixture was cooled to room temperature and poured into ice-cold water. The separated product was filtered, washed thoroughly with cold water, dried and recrystallized from ethanol.

5-[(5-Chloro-2-phenyl-1*H*-indol-3-yl)methylene]-N-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (3a): Yield: 77 %; m.p.: 248-249 °C IR (KBr, ν_{max}, cm^{-1}): 3440, 3210 (indole-NH), 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm):

12.60 (s, 1H, indole NH), 12.20 (s, 1H, indole NH), 8.75 (s, 1H, N=CH), 7.10-8.10 (m, 16H, Ar-H); Anal. cald. for $C_{31}H_{19}N_5OCl_2$: C, 60.54; H, 4.56; N, 12.54; Found: C, 60.55; H, 4.58; N, 12.59 %.

5-[(5-Chloro-2-phenyl-1*H*-indol-3-yl)methylene]-N-(5-methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (3b): Yield: 81 %; m.p.: 239-240 °C; IR (KBr, ν_{max}, cm^{-1}): 3436, 3260 (indole-NH), 1615 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.50 (s, 1H, indole NH), 12.10 (s, 1H, indole NH), 8.59 (s, 1H, N=CH), 7.00-8.12 (m, 16H, Ar-H).), 3.30 (s, 3H, OCH_3); Anal. cald. for $C_{32}H_{22}N_5O_2Cl$: C, 70.65; H, 4.08; N, 12.87; Found: C, 70.66; H, 4.10; N, 12.85 %.

5-[(5-Chloro-2-phenyl-1*H*-indol-3-yl)methylene]-N-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (3c): Yield: 78 %: m.p.: 219-220 °C: IR (KBr, ν_{max}, cm^{-1}): 3300, 3185 (indole-NH), 1623 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.30 (s, 1H, indole NH), 11.75 (s, 1H, indole NH), 8.70 (s, 1H, N=CH), 6.80-8.05 (m, 16H, Ar-H); Anal. cald. for $C_{32}H_{22}N_5OCl$: C, 72.79; H, 4.20; N, 13.26; Found C, 72.80; H, 4.27; N, 13.24 %.

5-(5-Chloro-3-phenyl-1*H*-indol-2-yl)-N-[(5-methyl-2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amine (3d): Yield: 81 %; m.p.: 233-234 °C; IR (KBr, ν_{max}, cm^{-1}): 3345, 3190 (indole-NH), 1605 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.55 (s, 1H, indole NH), 12.15 (s, 1H, indole NH), 8.69 (s, 1H, N=CH), 6.85-8.00 (m, 16H, Ar-H), 2.30 (s, 3H, CH_3); Anal. cald. for $C_{32}H_{22}N_5OCl$: C, 72.79; H, 4.20; N, 13.26; Found: C, 72.81; H, 4.23; N, 13.24 %.

5-(5-Methoxy-3-phenyl-1*H*-indol-2-yl)-N-[(5-methyl-2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amine (3e): Yield: 82 %; m.p.: 212-213 °C; IR (KBr, ν_{max}, cm^{-1}): 3423, 3200 (indole-NH), 1600 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.60 (s, 1H, indole NH), 12.25 (s, 1H, indole NH), 8.78 (s, 1H, N=CH), 6.80-7.95 (m, 16H, Ar-H), 3.37 (s, 3H, OCH_3), 2.33 (s, 3H, CH_3); Anal. cald. for $C_{33}H_{23}N_5O$: C, 77.87; H, 4.70; N, 14.09; Fund: C, 77.85; H, 4.74; N, 14.10 %.

5-[(5-Methyl-2-phenyl-1*H*-indol-3-yl)methylene]-N-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amine (3f): Yield: 80 %; m.p.: 208-209 °C; IR (KBr, ν_{max}, cm^{-1}): 3440, 3250 (indole-NH), 1620 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.00 (s, 1H, indole NH), 11.85 (s, 1H, indole NH), 8.64 (s, 1H, N=CH), 7.00-8.10 (m, 16H, Ar-H), 2.65 (s, 3H, CH_3), 2.40 (s, 3H, CH_3); Anal. cald. for $C_{32}H_{23}N_5O$: C, 78.09; H, 4.96; N, 13.80; Found: C, 78.12; H, 4.07; N, 13.84 %.

5-(5-Chloro-3-phenyl-1*H*-indol-2-yl)-N-[(2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amine (3g): Yield: 75 %; m.p.: 198-199 °C; IR (KBr, ν_{max}, cm^{-1}): 3436, 3260 (indole-NH), 1615 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.20 (s, 1H, indole NH), 11.60 (s, 1H, indole NH), 8.50 (s, 1H, N=CH), 7.00-7.95 (m, 17H, Ar-H); ^{13}C NMR (DMSO-d_6, 125 MHz, δ): 160.3, 158.2, 156.4, 142.5, 134.9, 134.0, 133.0, 132.1, 130.3, 129.3, 128.5, 127.2, 126.8, 126.1, 125.8, 124.3, 123.0, 122.6, 122.1, 121.6, 121.4, 119.8, 119.5, 15.4; MS (EI): *m/z*, 513 [M^+] 514 [M^++2]; Anal. cald. for $C_{31}H_{20}N_5OCl$: C, 72.44; H, 3.92; N, 13.63; Found: C, 72.46, H, 3.93; N, 13.65 %.

5-(5-Methoxy-3-phenyl-1*H*-indol-2-yl)-N-[(2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amine (3h): Yield: 76 %; m.p.: 182-183 °C; IR (KBr, ν_{max}, cm^{-1}): 3423, 3265 (indole-NH), 1620 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.45 (s, 1H, indole NH), 12.05 (s, 1H, indole NH), 8.78 (s, 1H, N=CH), 7.10-8.20 (m, 17H, Ar-H), 3.65 (s, 3H, OCH_3); Anal. cald. for $C_{32}H_{23}N_5O_2$: C, 75.43; H, 4.55; N, 13.74; Found: C, 75.47; H, 4.58; N, 13.79 %.

5-(5-Methyl-3-phenyl-1*H*-indol-2-yl)-N-[(2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amine (3i): Yield: 78 %; m.p. 191-192 °C; IR (KBr, ν_{max}, cm^{-1}): 3438, 3242 (indole-NH), 1609 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.10 (s, 1H, indole NH), 11.90 (s, 1H, indole NH), 8.79 (s, 1H, N=CH), 6.75-7.90 (m, 18H, Ar-H), 2.41 (s, 3H, CH_3); Anal. cald. for $C_{32}H_{23}N_5O$: C, 77.87; H, 4.70; N, 14.19; Found: C, 77.89; H, 4.72; N, 14.20 %.

2-(5-Substituted-2-phenyl-1*H*-indol-3-yl)-3-[5-(5-substituted-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]thiazolidin-4-ones (4a-i): A mixture of compounds 5-[(5-substituted-2-phenyl-1*H*-indol-3-yl)methylene]-N-(5-substituted-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amines (**3a-i**) (0.05 mol) and thioglycolic acid (0.05 mol) in methanol (100 mL) containing a pinch of anhydrous $ZnCl_2$ was kept four days at room temperature and the mixture was refluxed for 10 h on water bath, distilled off, poured into ice-cold water, filtered and recrystallized from ethanol.

2-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-3-[5-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]thiazolidin-4-one (4a): Yield: 73 %; m.p.: 212-213 °C; IR (KBr, ν_{max}, cm^{-1}): 3441, 3318 (indole NH), 1679 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 12.60 (s, 1H, indole NH), 12.30 (s, 1H, indole NH), 6.95-8.00 (m, 16H, Ar-H), 6.81 (d, 1H, N-CH), 3.72 (d, 2H, CH_2CO); Anal. cald. for $C_{33}H_{21}N_5O_2SCl_2$: C, 63.67; H, 3.40; N, 11.25; Found: C, 63.65; H, 3.44; N, 11.29 %.

2-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-3-[5-(5-methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]thiazolidin-4-one (4b): Yield: 73 %; m.p.: 196-197 °C; IR (KBr, ν_{max}, cm^{-1}): 3430, 3259 (indole NH), 1685 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 12.50 (s, 1H, indole NH), (s, 1H, indole NH), 12.05 (s, 1H, indole NH), 7.00-8.10 (m, 16H, Ar-H), 6.83 (d, 1H, N-CH), 4.75 (3, 2H, CH_2CO), 3.40 (s, 3H, OCH_3); Anal. cald. for $C_{34}H_{24}N_5O_2$ SCl: C, 66.07; H, 3.91; N, 11.33; Found: C, 66.06; H, 3.94; N, 11.35 %.

2-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-3-[5-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]thiazolidin-4-one (4c): Yield: 67 %; m.p.: 198-199 °C; IR (KBr, ν_{max}, cm^{-1}): 3412, 3298 (indole NH), 1685 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 12.35 (s, 1H, indole NH), 11.80 (s, 1H, indole NH), 6.70-8.10 (m, 16H, Ar-H), 6.55 (d, 1H, N-CH), 3.73 (d, 2H, CH_2CO); Anal. cald. for $C_{34}H_{24}N_5O_2SCl$: C, 67.82; H, 4.02; N, 11.63; Found: C, 67.86; H, 4.05; N, 11.65 %.

3-[5-(5-Chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-2-(5-methyl-2-phenyl-1*H*-indol-3-yl)thiazolidin-4-one (4d): Yield: 71 %; m.p.: 193-194 °C; IR (KBr, ν_{max}, cm^{-1}): 3405, 3300 (indole NH), 1695 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.10 (s, 1H, indole NH), 11.90 (s, 1H, indole NH), 7.10-8.10 (m, 16H, Ar-H), 6.83 (d, 1H, N-CH), 3.77 (d, 2H, CH_2CO), 2.32 (s, 3H, CH_3); Anal. cald. for $C_{34}H_{24}N_5O_2SCl$: C, 67.82; H, 4.02; N, 11.63; Found: C, 72.81; H, 4.03; N, 11.64 %.

3-[5-(5-Methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-2-(5-methyl-2-phenyl-1*H*-indol-3-yl)thiazolidin-4-

one (4e): Yield: 68 %; m.p.: 189-190 °C; IR (KBr, ν_{max}, cm^{-1}): 3400, 3309 (indole NH), 1665 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 12.45 (s, 1H, indole NH), 12.00 (s, 1H, indole NH), 7.00-8.00 (m, 16H, Ar-H), 6.87 (d, 1H, N-CH), 3.72 (d, 1H, CH_2CO), 3.34 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3); Anal. cald. for $C_{35}H_{27}N_5O_3S$: C, 70.33; H, 4.55; N, 11.72; Found: C, 70.35; H, 4.55; N, 11.75 %.

2-(5-Methyl-2-phenyl-1*H*-indol-3-yl)-3-[5-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]thiazolidin-4-one (4f): Yield: 69 %; m.p.: 200-201 °C; IR (KBr, ν_{max}, cm^{-1}): 3438, 3300 (indole NH), 1650 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 12.55 (s, 1H, indole NH), 12.20 (s, 1H, indole NH), 6.85-7.90 (m, 12H, Ar-H), 6.25 (d, 1H, N-CH), 4.75 (d, 2H, CH_2CO), 2.50 (s, 3H, CH_3), 2.36 (s, 3H, CH_3); Anal. cald. for $C_{35}H_{27}N_5O_2S$: C, 72.27; H, 4.68; N, 12.04; Found: C, 72.30; H, 4.70; N, 12.05 %.

3-[5-(5-Chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-2-(2-phenyl-1*H*-indol-3-yl)thiazolidin-4-one (4g): Yield: 65 %; m.p.: 196-197 °C; IR (KBr, ν_{max}, cm^{-1}): 3441, 3318 (indole NH), 1679 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): IR (KBr, ν_{max}, cm^{-1}): 12.20 (s, 1H, indole NH), 12.00 (s, 1H, indole NH), 6.95-7.90 (m, 17H, Ar-H), 6.81 (d, 1H, N-CH), 4.22 (d, 2H, CH_2CO); ^{13}C NMR (DMSO-d_6, 125 MHz, δ): 168.5, 159.2, 154.5, 143.9, 135.0, 134.1, 133.0, 132.8, 131.1, 130.1, 127.8, 127.6, 126.8, 126.3, 125.4, 125.1, 123.0, 122.8, 122.0, 121.8, 120.0, 119.0, 55.9, 35.2, 15.5; MS (EI): *m/z*: 587 [M^+], 589 [M^++2]; Anal. cald. for $C_{33}H_{22}N_5O_2SCl$: C, 67.40; H, 3.77; N, 11.91; Found: C, 67.46; H, 3.83; N, 11.95 %.

3-[5-(5-methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-2-(2-phenyl-1*H*-indol-3-yl)thiazolidin-4-one (4h): Yield: 68 %; m.p.: 201-202 °C; IR (KBr, ν_{max}, cm^{-1}): 3412, 3250 (NH), 1682 (C=O), 1595 (C=N) 3395, 3285 (indole NH), 1670 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 12.55 (s, 1H, indole NH), 12.20 (s, 1H, indole NH), 7.10-8.10 (m, 17H, Ar-H), 6.35 (d, 1H, N-CH), 3.36 (s, 3H, OCH_3), 6.70 (d, 2H, CH_2CO); Anal. cald. for $C_{34}H_{25}N_5O_3S$: C, 69.97; H, 4.32; N, 12.00; Found: C, 69.93; H, 4.38; N, 12.04 %.

3-[5-(5-Methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-2-(2-phenyl-1*H*-indol-3-yl)thiazolidin-4-one (4i): Yield: 69 %; m.p.: 191-192 °C; IR (KBr, ν_{max}, cm^{-1}): 3425, 3365 (indole NH), 1695 (C=O); ^1H NMR ($CDCl_3$) δ (ppm): 12.55 (s, 1H, indole NH), 12.20 (s, 1H, indole NH), 7.00-8.20 (m, 18H, Ar-H), 6.50 (d, 1H, N-CH), 3.73 (d, 2H, CH_2CO), 2.39 (s, 3H, CH_3Anal. cald. for $C_{34}H_{25}N_5O_2S$: C, 71.94; H, 4.44; N, 12.34; Found: C, 71.95; H, 4.45; N, 12.36 %.

3-Chloro-4-(5-substituted-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-substituted-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]azetidin-2-ones (5a-i): To a stirred solution of 5-[(5-substituted-2-phenyl-1*H*-indol-3-yl)methylene]-N-(5-substituted-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amines (**3a-i**) (0.02 mol) in 1,4-dioxane (100 mL), chloroacetyl chloride (0.04 mol) was added drop-wise at 0-5 °C in presence of triethyl amine (0.04 mol). The reaction mixture was constantly for 6 h and the precipitated amine hydrochloride was filtered off. The filtrate was refluxed for 12 h and the separated solid was recrystallized in alcohol to furnish compounds (**5a-i)**.

3-Chloro-4-(5-chloro-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-azetidin-2-one (5a): Yield: 65 %; m.p.: 224-225 °C; IR (KBr, ν_{max}, cm^{-1}): 3430, 3335 (indole NH), 1680 (C=O), 1610 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.60 (s, 1H, indole NH), 12.05 (s, 1H, indole NH), 7.00-8.15 (m, 16H, 2Ar-H), 6.25 (d, 1H, N-CH), 4.80 (d, 1H, CHCO); Anal. cald. for $C_{33}H_{20}N_5O_2Cl_3$: C, 63.43; H, 3.23; N, 11.21; Found: C, 63.45; H, 3.28; N, 11.29 %.

3-Chloro-4-(5-chloro-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]azetidin-2-one (5b): Yield: 67 %; m.p.: 200-201 °C; IR (KBr, ν_{max}, cm^{-1}): 3415, 3150 (indole NH), 1670 (C=O), 1615 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.50 (s, 1H, indole NH), 12.05 (s, 1H, indole NH), 7.30-8.18 (m, 16H, Ar-H), 6.02 (d, 1H, N-CH), 4.80 (d, 1H, CHCO), 3.30 (s, 3H, OCH_3); Anal. cald. for $C_{34}H_{23}N_5O_3Cl_2$: C, 65.81; H, 3.74; N, 11.29; Found: C, 65.86; H, 3.76; N, 11.26 %.

3-Chloro-4-(5-chloro-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-azetidin-2-one (5c): Yield: 60 %; m.p.: 223-224 °C; IR (KBr, ν_{max}, cm^{-1}): 3415, 3250 (NH), 3420, 3150 (indole NH), 1695 (C=O), 1620 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.30 (s, 1H, indole NH), 11.95 (s, 1H, indole NH), 7.10-8.10 (m, 16H, Ar-H), 6.10 (d, 1H, N-CH), 4.80 (d, 1H, CHCO), 2.45 (s, 3H, CH_3); Anal. cald. for $C_{34}H_{24}N_5O_2Cl_2$: C, 67.56; H, 3.84; N, 11.59; Found: C, 67.57; H, 3.86; N, 11.60 %

3-Chloro-1-[5-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)-azetidin-2-one (5d): Yield: 67 %; m.p.: 187-188 °C; IR (KBr, ν_{max}, cm^{-1}): 3350, 3215 (indole NH), 1690 (C=O), 1620 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.40 (s, 1H, indole NH), 12.10 (s, 1H, indole NH), 6.75-8.00 (m, 16H, Ar-H), 6.20 (d, 1H, N-CH), 5.80 (d, 1H, CHCO), 2.40 (s, 3H, CH_3); Anal. cald. for $C_{34}H_{23}N_5O_2Cl_2$: C, 67.56; H, 3.84; N, 11.59; Found: C, 67.58; H, 3.85; N, 11.60 %.

3-Chloro-1-[5-(5-methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)azetidin-2-one (5e): Yield: 69 %; m.p.: 193-194 °C; IR (KBr, ν_{max}, cm^{-1})3460, 3245 (indole NH), 1655 (C=O), 1690 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.10 (s, 1H, indole NH), 11.95 (s, 1H, indole NH), 7.00-8.10 (m, 16H, Ar-H), 6.75 (d, 1H, N-CH), 4.85 (d, 1H, CHCO), 3.30 (s, 3H, OCH_3), 2.75 (s, 3H, CH_3); Anal. cald. for $C_{35}H_{26}N_5O_2Cl$: C, 70.05; H, 4.37; N, 11.67; C, 70.08; H, 4.39; N, 11.70 %.

3-Chloro-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-azetidin-2-one (5f): Yield: 70 %; m.p.: 184-185 °C; IR (KBr, ν_{max}, cm^{-1}): 3350, 3270 (indole NH), 1700 (C=O), 1621 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.45 (s, 1H, indole NH), 12.10 (s, 1H, indole NH), 7.10-8.20 (m, 17H, Ar-H), 6.85 (d, 1H, N-CH), 4.75 (d, 1H, CHCO), 3.55 (s, 3H, CH_3), 2.37 (s, 3H, CH_3); Anal. cald. for $C_{35}H_{26}N_5O_2Cl$: C, 71.97; H, 4.49; N, 11.99; Found: C, 71.99; H, 4.52; N, 12.00 %.

3-Chloro-1-[5-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-4-(2-phenyl-1*H*-indol-3-yl)azetidin-2-one (5g): Yield: 65 %; m.p.: >172-173 °C; IR (KBr, ν_{max}, cm^{-1}): 3415, 3220 (indole NH), 1715 (C=O), 1610 (C=N); ^1H NMR ($CDCl_3$) δ (ppm): 12.50 (s, 1H, indole NH), 12.20 (s, 1H, indole NH), 7.00-8.00 (m, 17H, Ar-H), 6.20 (d, 1H, N-CH), 5.81 (d,

1H, CHCO); Anal. cald. for $C_{33}H_{21}N_5O_2Cl_2$: C, 67.13; H, 3.58; N, 11.86 (; Found: C, 67.15; H, 3.60; N, 11.90 %.

3-Chloro-1-[5-(5-methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-4-(2-phenyl-1*H*-indol-3-yl)azetidin-2-one (5h): Yield: 61 %; m.p.: 172-173 °C; IR (KBr, ν_{max}, cm^{-1}): 3345, 3325 (indole NH), 1720 (C=O), 1600 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.20 (s, 1H, indole NH), 11.73 (s, 1H, indole NH), 6.80-8.14 (m, 17H, Ar-H), 6.28 (d, 1H, N-CH), 5.87 (d, 1H, CHCO) 3.31 (s, 3H, OCH_3); Anal. cald. for $C_{34}H_{24}N_5O_3Cl$: C, 69.68; H, 4.13; N, 11.95; Found: C, 69.72; H, 4.15; N, 11.99 %.

3-Chloro-1-[5-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-4- (2-phenyl-1*H*-indol-3-yl)azetidin-2-one (5i): Yield: 63 %; m.p.: 171-172 °C; IR (KBr, ν_{max}, cm^{-1}): 3420, 3355 (indole NH), 1660 (C=O), 1600 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.30 (s, 1H, indole NH), 11.85 (s, 1H, indole NH), 7.05-8.05 (m, 18H, Ar-H), 6.70 (d, 1H, N-CH), 5.73 (d, 1H, CHCO), 2.34 (s, 3H, CH_3); Anal. cald. for $C_{33}H_{23}N_5O_2Cl$: C, 71.64; H, 4.24; N, 12.26; Found: C, 71.66; H, 4.30; N, 12.28 %.

4-(5-Substituted-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-substituted-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenylazetidin-2-one (6a-i): To a solution of Schiff base **(4a-i)** (0.02 mol) in dry benzene (50 mL), phenyl acetyl chloride (0.02 mol) was added in presence of triethyl amine (0.04 mol). The reaction mixture was constantly stirred refluxed for 3 h. The precipitated amine hydrochloride was filtered off, washed with dry benzene and petroleum ether (40:60) to remove unreacted Schiff's base and recrystallized from ethanol to afford comopunds **(6a-i)**.

4-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenylazetidin-2-one (6a): Yield: 62 %; m.p.: 178-179 °C; IR (KBr, ν_{max}, cm^{-1}): 3400, 3330 (indole NH), 1720 (C=O), 1620 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.50 (s, 1H, indole NH), 12.05 (s, 1H, indole NH), 7.10-8.10 (m, 21H, Ar-H), 6.75 (d, 1H, N-CH), 6.10 (d, 1H, CHCO); Anal. cald. for $C_{39}H_{25}N_5O_2Cl_2$: C, 70.27; H, 3.78; N, 10.51; Found: C, 70.25; H, 3.80; N, 11.52 %.

4-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenylazetidin-2-one (6b): Yield: 65 %; m.p.: 165-166 °C; IR (KBr, ν_{max}, cm^{-1}): 3445, 3227 (indole NH), 1670 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.15 (s, 1H, indole NH), 11.56 (s, 1H, indole NH), 6.90-8.00 (m, 21H, Ar-H), 6.60 (d, 1H, N-CH), 6.21 (d, 1H, CHCO), 3.67 (s 3H, OCH_3); Anal. cald. for $C_{40}H_{28}N_5O_3Cl$: C, 72.56; H, 4.26; N, 10.58; Found: C, 72.60; H, 4.28; N, 10.60 %.

4-(5-Chloro-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenylazetidin-2-one (6c): Yield: 60 %; m.p.: 179-180 °C; IR (KBr, ν_{max}, cm^{-1}): 3260, 3140 (indole NH), 1645 (C=O), 1600 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.35 (s, 1H, indole NH), 11.60 (s, 1H, indole NH), 7.10-8.20 (m, 21H, Ar-H), 6.70 (d, 1H, N-CH), 6.00 (d, 1H, CHCO), 2.37 (s, 3H, CH_3); Anal. cald. for $C_{49}H_{28}N_5O_2Cl$: C, 74.35; H, 4.37; N, 10.84; Found: C, 74.37; H, 4.40; N, 10.88 %.

1-[5-(5-Chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)-3-phenylazetidin-2-one (6d): Yield: 61 %; m.p.: 182-183 °C; IR (KBr, ν_{max}, cm^{-1}): 3300, 3250 (indole NH), 1655 (C=O), 1609 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.20 (s, 1H, indole NH), 11.30 (s, 1H, indole NH), 7.20-8.20 (m, 21H, Ar-H), 6.85 (d, 1H, N-CH), 6.20 (d, 1H, CHCO), 2.75 (s, 3H, CH_3); Anal. cald. for $C_{40}H_{28}N_5O_2Cl$: C, 74.35; H, 4.37: N, 10.84; Found: C, 74.39; H, 4.40; N, 10.86 %.

1-[5-(5-Methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-4-(5-methyl-2-phenyl-1*H*-indol-3-yl)-3-phenylazetidin-2-one (6e): Yield: 72 %; m.p.: 159-160 °C; IR (KBr, ν_{max}, cm^{-1}): 3250, 3185 (indole NH), 1675 (C=O), 1615 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 11.95 (s, 1H, indole NH), 11.50 (s, 1H, indole NH), 7.00-8.10 (m, 21H, Ar-H), 6.90 (d, 1H, N-CH), 6.15 (d, 1H, CHCO), 3.67 (s, 3H, OCH_3), 2.80 (s 3H, CH_3); Anal. cald. for $C_{41}H_{31}N_5O_2$: C, 76.74; H, 4.87; N, 10.91; Found: C, 76.76; H, 4.90; N, 10.95 %.

4-(5-Methyl-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenylazetidin-2-one (6f): Yield: 70 %; m.p.: 154-155 °C; IR (KBr, ν_{max}, cm^{-1}): 3444, 3300 (indole NH), 1650 (C=O), 1610 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.15 (s, 1H, indole NH), 11.75 (s, 1H, indole NH), 6.95-8.00 (m, 21H, Ar-H), 6.50 (d, 1H, N-CH), 5.90 (d, 1H, CHCO), 2.35 (s, 3H, CH_3), 2.43 (s, 3H, CH_3); Anal. cald. for $C_{41}H_{31}N_5O_2$: C, 78.70; H, 4.99; N, 11.19; Found: C, 78.73; H, 5.02; N, 11.18 %

1-[5-(5-Chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenyl-4-(2-phenyl-1*H*-indol-3-yl)azetidin-2-one (6g): Yield: 68 %; m.p.: 152-153 °C; IR (KBr, ν_{max}, cm^{-1}): 3441, 3324 (indole NH), 1680 (C=O), 1601 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.30 (s, 1H, indole NH), 11.65 (s, 1H, indole NH), 7.00-8.20 (m, 22H, Ar-H), 6.50 (d, 1H, N-CH), 6.00 (d, 1H, CHCO); ^{13}C NMR (DMSO-d_6, 125 MHz, δ): 167.2, 159.3, 156.4, 144.6, 134.8, 133.9, 133.2, 131.5, 131.3, 130.2, 129.9, 129.8, 129.4, 128.1, 127.5, 127.0, 126.8, 125.9, 125.1, 123.9, 123.4, 122.3, 122.0, 121.5, 120.1, 120.0 64.5, 63.1, 15.9; MS (EI): *m/z*: 632 [M^+] 634 [M^++2]; Anal. cald. for $C_{39}H_{26}N_5O_2Cl$: C, 74.10; H, 4.15; N, 11.08; Found: C, 74.15; H, 4.19: N, 11.10 %

1-[5-(5-Methoxy-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenyl-4-(2-phenyl-1*H*-indol-3-yl)azetidin-2-one (6h): Yield: 65 %; m.p.: 162-163 °C; IR (KBr, ν_{max}, cm^{-1}): 3405, 3295 (indole NH), 1705 (C=O), 1618 C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.00 (s, 1H, indole NH), 11.55 (s, 1H, indole NH), 7.70-8.15 (m, 22H, Ar-H), 6.79 (d, 1H, N-CH), 6.20 (d, 1H, CHCO), 3.70 (s, 3H, OCH_3; Anal. cald. for $C_{40}H_{29}N_5O_3$: C, 76.54; H, 4.66; N, 11.16; Found: C, 76.66; H, 4.67; N, 11.18 %.

1-[5-(5-Methyl-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]-3-phenyl-4-(2-phenyl-1*H*-indol-3-yl)azetidin-2-one (6i): Yield: 64 %; m.p.: 167-168 °C; IR (KBr, ν_{max}, cm^{-1}): 3430, 3345 (indole NH), 1680 (C=O), 1601 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 12.45 (s, 1H, indole NH), 12.00 (s, 1H, indole NH), 7.10-8.10 (m, 23H, Ar-H), 6.90 (d, 1H, N-CH), 6.00 (d, 1H, CHCO), 2.42 (s, 3H, CH_3); Anal. cald. for $C_{40}H_{29}N_5O_2$: C, 78.54; H, 4.78; N, 11.45; Found: C, 78.57; H, 4.79; N, 11.47 %.

Biological evaluation

Antimicrobial activity: The antimicrobial screening the synthesized compounds was tested against four bacteria and four fungal species using culture medium in a sterilized boro-

silicate test tubes and different bacterial strains incubated at 10^6 bacilli/mL concentration by the broth dilution method [39-41] (concentrations 50, 25, 12.5, 6.25, 3.12 and 1.5 µg/mL), respectively. The optical density is measured at a wavelength of 655 nm of each sample and compared with ciprofloxin and fluconazole as standard drugs for antibacterial and antifungal activities, respectively. The precise MIC values were obtained from the lowest concentration of the test compound. The bacterial and fungal growth were completely inhibited at this concentration.

Antioxidant activity: 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity (RSA) was tested in methanolic solution at concentrations 25, 50, 75 and 100 µg/mL containing freshly prepared DPPH solution (0.004 % w/v) according to the reported method [42].

Ferric ion (Fe^{3+}) reducing antioxidant power (FRAP): The reducing power of the synthesized compounds was determined according to the literature method [42] using BHA, TBHQ and ascorbic acid as standards. Different concentrations of samples (25, 50, 75 and 100 µg/mL) in DMSO (1 mL) were mixed with phosphate buffer (2.5 mL, 0.2 M, pH = 6.6) and potassium ferricyanide (2.5 mL, 1 %).

Ferrous (Fe^{2+}) ion metal chelating activity: Chelating activity of ferrous ions by the synthesized compounds and BHA, TBHQ and ascorbic acid as standards was estimated by the reported earlier method [43] with test samples concentrations of 25, 50, 75 and 100 µg/mL.

Antituberculosis activity: Anti-tuberculosis activity of synthesized compounds was tested against *M. tuberculosis* (ATCC 27294) H37RV using alamar blue reagent. Serial diluted solutions (100, 50, 25, 12.5, 6.25, 3.12, 1.5 and 0.8 µg/mL) of the test compounds in dimethyl formamide (DMF), rifampicin (1.0 µg/mL) as a positive control and DMF as negative control were used to determine the activity according to the literature MABA method [44,45].

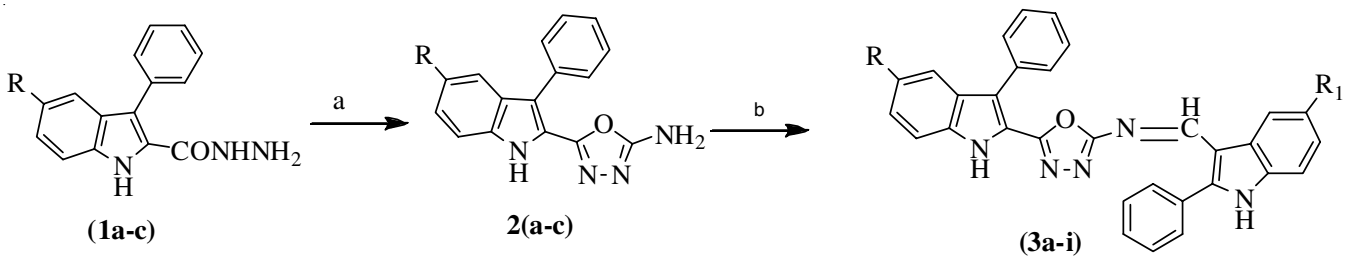
Anticancer activity: The anticancer activity of synthesized compounds was tested against three different human cancer cell lines including MCF-7 (breast carcinoma), A-549 (lung carcinoma) and HeLa (Cervical carcinoma) cancer cell lines. The synthesized compounds were diluted in DMSO at various concentrations (10, 5, 2.5 and 1.25 µg/mL) and assessed using 3-(4, 5-dimethyl-2-yl-2, 5-diphenyl tetrazolium bromide (MTT assay) [46]. Anticancer activity was determined for cells treated various concentrations of the tested compounds, the untreated cells (negative control) and doxorubicin (positive control). A statistical significance was tested between sample and negative control using independent t-test by SPSS 12 program. The concentration of test compounds required to kill 50 % of cell population (IC_{50}) were determined by non-linear regression analysis. Cytotoxic activity was expressed as the mean IC_{50} of three independent experiments.

RESULTS AND DISCUSSION

Synthesis of target compounds were achieved according to the steps illustrated in **Schemes I** and **III** and plausible mechanistic pathway in Schemes **II** and **IV**. 5-Substituted 3-phenyl-1*H*-indole-2-carbohydrazides (**1a-c**) were synthesized from the prepared precursors [36]. Compounds **1a-c** were subjected to cyclocondensation with cyanogen bromide in ethanol under reflux to afford 5-(5-substituted 3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-amines (**2a-c**) [37]. Compounds (**2a-c**) upon heterocyclization with 5-substituted 2-phenyl-3-carboxaldehydes [38] in presence of 1,4-dioxane yielded 5-(5-substituted-3-phenyl-1*H*-indol-2-yl)-*N*-[(5-substituted-2-phenyl-1*H*-indol-3-yl)methylene]-1,3,4-oxadiazol-2-amines (**3a-i**). The compounds **3a-i** when subjected to cyclocondensation with commercially available reagents such as thioglycolic acid, chloro acetylchloride and phenyl acetylchloride gave 2-(5-substituted 2-phenyl-1*H*-indol-3-yl)-3-[5-(5-substituted 3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]thiazolidin-4-ones (**4a-i**), 3-chloro-4-(5-substituted 2-phenyl-1*H*-indol-3-yl)-1-[5-(5-substituted3-phenyl-1H-indol-2-yl)-1,3,4-oxadiazol-2-yl]azetidin-2-ones (**5a-i**) and 4-(5-substituted 2-phenyl-1*H*-indol-3-yl)-1-(5-(5-substituted 3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl)-3-phenylazetidin-2-ones (**6a-i**), respectively, in high yield. Progess of the reactions were checked by TLC using silica gel-G coated aluminium plates (Merck). All the new compounds were characterized by IR, NMR ^1H and ^{13}C, mass spectra and elemental analysis.

Antibacterial activity: All the synthesized compounds were screened for *in vitro* antimicrobial activities against *Escherichia coli* (NCIM 2065), *Klebsiella pneumoniae* (NCIM 5082), *Staphylococcus aureus* (NCIM 2079) and *Bacillus subtilis* (NCIM 2063). For antifungal studies, *Aspergillus niger* (NCIM 548), *Aspergillus oryzae* (NCIM 643), *Candidia albicans* (NCIM 3102) and *Pencillium chrysogenum* (NCIM 738) by broth dilution method and results are summarized in Table-1.

Antibacterial screening revealed that compound **4a** was found to exhibit strong activity with MIC values 12(1.5)/15(1.5)

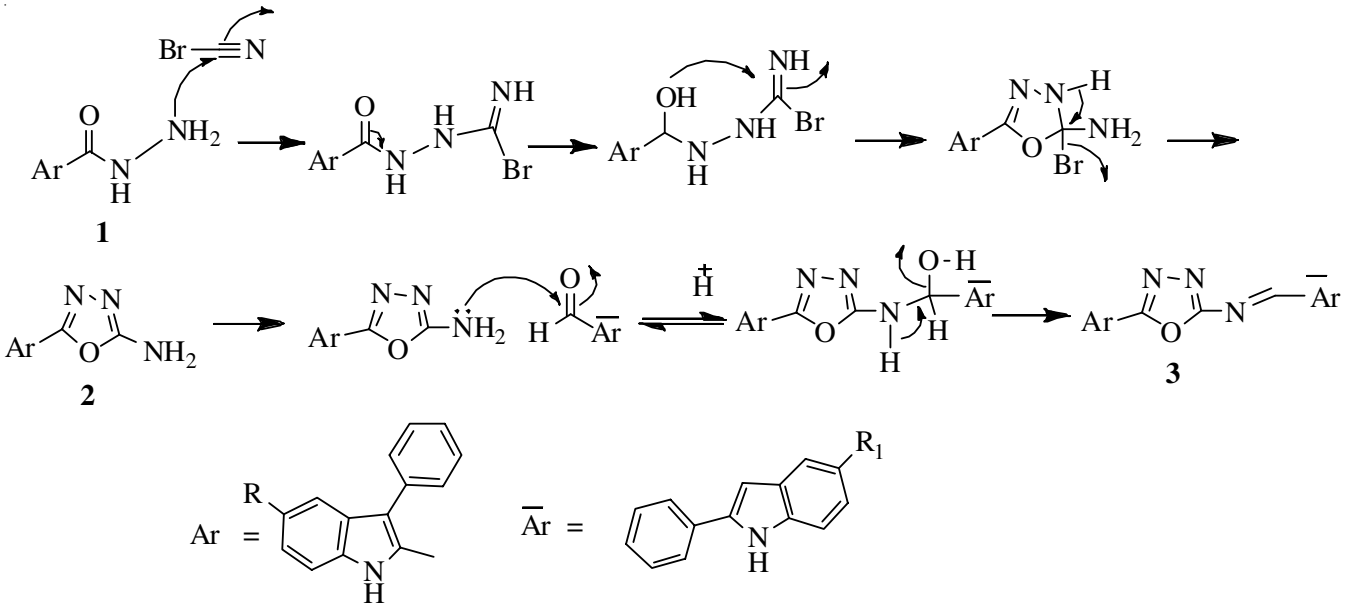


(1a-c) **2(a-c)** **(3a-i)**

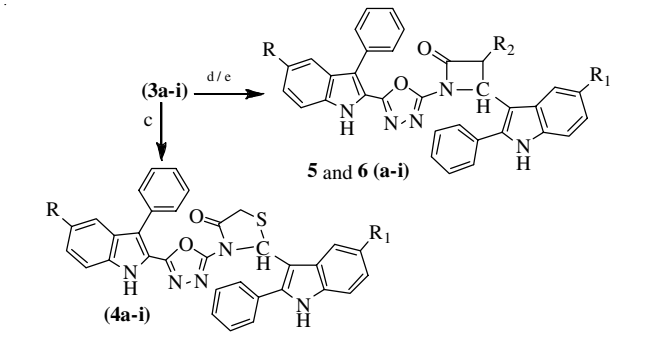
R = Cl(**a**), OCH_3(**b**), CH_3(**c**).

Reagents and conditions: (a) CNBr; EtOH; reflux, 90 min;
(b) 5-Substituted-2-phenyl-3-carboxaldehydes, 1,4-dioxane, reflux, 8 h

Scheme-I



Scheme-II: Plausible mechanistic pathway for the compounds **2** and **3**



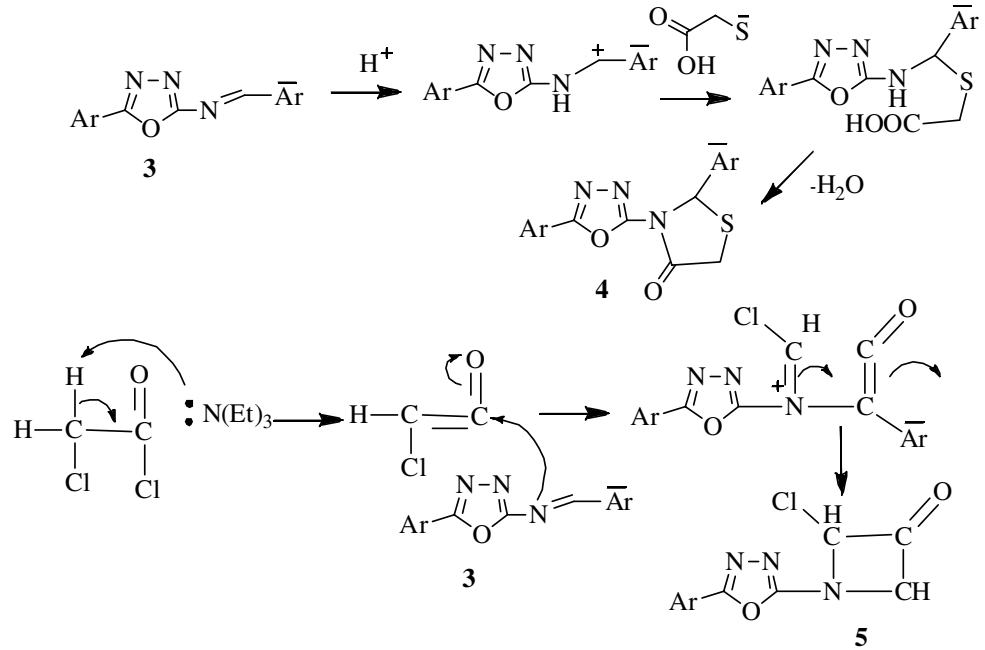
R= Cl, (**a**, **d**, **g**), OCH_3, (**b**, **e**, **h**), CH_3(**c**, **f, i**);R_1= Cl (**a-c**), CH_3 (**d-f**), H (**g-i**); R_2 = Cl, Ph

Reagents and conditions:
(c) $HSCH_2COOH$, MeOH, $ZnCl_2$, reflux, 10h;
(d/e) R_2CH_2COCl/Et_3N; $C_4H_8O_2$ /C_6H_6 ; reflux, 6h/3h

Scheme-III

against *E. coli*, *K. pneumoniae*, respectively, and compound **5a** demonstrated potent activity against *S. aureus*, *B. subtilis*. MIC values 16(1.5) 17(1.5) were almost equivalent to standard drug. The inhibitory activity of the compounds **4d**, **5e** and **6a** against *E. coli* was notable. Compounds **4d**, **5a**, **5b**, **5c**, **6a** and **6d** exhibited great activity against *K. pneumoniae*. Compounds **4b**, **4g**, **5a**, **5h** and **6a** showed relatively good inhibitory effect on *S. aureus*. Further, compounds **6g**, **5c**, **5d**, **5g**, **6a** and **6d** displayed high activity against *B. subtilis*.

Antifungal activity: The antifungal activity results showed that compound **5a** displayed excellent activity against *A. niger*, *A. oryzae*, *C. albicans* and *P. chrysogenum*. The activity were better than standard drug fluconazole. Compound **6a** with replacement of chloro at 2-azetidinone ring with phenyl (R_2) seems to display decreased antifungal activity, suggesting that



Scheme-IV: Plausible mechanistic pathway for the compounds **4** and **5**

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF TARGET SYNTHESIZED COMPOUNDS

Compounds	Minimum inhibitory concentration (MIC µg/mL)[a]							
	Antibacterial activity				Antifungal activity			
	E. coli	*K. pneumonia*	*S. aureus*	*B. subtilis*	*A. niger*	*A. oryzae*	*C. albicans*	*P. chrysogenum*
3a	18 (12.5)	21 (12.5)	17 12.5)	13 (25)	21 (25)	19 (50)	20 (25)	24 (3.12)
3b	18 (50)	20 (50)	20 (50)	17 (50)	23 (25)	17 (3.12)	22 (25)	27 (50)
3c	13 (50)	18 (50)	19 (25)	11 (50)	16 (25)	12 (25)	21 (25)	–
3d	19 (25)	19 (50)	21 (25)	16 (50)	23 (3.12)	16 (25)	14 (25)	21 (50)
3e	17 (25)	20 (25)	11 (25)	12 (50)	19 (25)	21 (25)	20 (25)	18 (25)
3f	16 (25)	21 (25)	10 (25)	19 (50)	23 (12.5)	17 (12.5)	20 (25)	19 (12.5)
3g	21 (25)	19 (50)	15 (25)	17 (50)	18 (25)	21 (25)	24 (25)	22 (25)
3h	16 (25)	–	18 (50)	10 (50)	23 (50)	26 (12.5)	20 (25)	22 (25)
3i	14 (25)	22 (25)	–	–	18 (50)	21 (25)	17 (25)	18 (25)
4a	12 (1.5)	15 (1.5)	20 (3.12)	18 (3.12)	23 (1.5)	14 (1.5)	12 (1.5)	18 (3.12)
4b	19 (6.25)	22 (12.5)	10 (6.25)	27 (6.25)	18 (3.5)	20 (3.12)	21 (3.12)	14 (6.25)
4c	22 (25)	17 (12.5)	15 (12.5)	17 (6.25)	13 (12.5)	15 (25)	08 (25)	18 (6.25)
4d	19 (6.25)	19 (3.12)	10 (6.25)	18 (6.25)	07 (50)	17 (12.5)	11 (3.12)	14 (1.5)
4e	21 (6.25)	17 (12.5)	15 (6.25)	24 (6.25)	11 (50)	13 (12.5)	09 (50)	10 (12.5)
4f	24 (6.25)	18 (12.5)	11 (12.5)	23 (6.25)	16 (12.5)	17 (6.25	10 (25)	11 (12.5)
4g	20 (6.25)	17 (12.5)	16 (6.25)	19 (3.12)	20 (25)	22 (12.5)	16 (12.5)	18 (12.5)
4h	17 (6.25)	19 (6.25)	21 (12.5)	14 (6.25)	14 (25)	15 (12.5)	10 (12.5)	12 (12.5
4i	22 (6.25)	23 (12.5)	–	17 (6.25)	14 (50)	16 (25)	11 (25)	14 (12.5)
5a	14 (3.12)	20 (3.12)	16 (1.5)	17 (1.5)	15 (1.5)	10 (1.5)	13 (1.5)	12 (1.5)
5b	17 (6.25)	21 (6.25)	20 (3.12)	19 (3.12)	15 (6.25)	19 (12.5)	16 (12.5)	16 (6.25)
5c	18 (6.25)	20 (6.25)	22 (3.12)	21 (3.12)	10 (25)	17 (12.5)	15 (1.5)	11 (12.5)
5d	17 (6.25)	19 (6.25)	18 (12.5)	19 (6.25)	16 (3.12)	18 (3.12)	20 (3.12)	18 (1.5)
5e	20 (6.25)	15 (12.5)	13 (6.25)	17 (6.25)	12 (25)	18 (12.5)	20 (12.5)	17 (12.5)
5f	17 (6.25)	21 (12.5)	19 (12.5)	12 (25)	19 (25)	19 (50)	11 (25)	14 (12.5)
5g	22 (6.25)	17 (12.5)	23 (12.5)	25 (3.12)	21 (12.5)	23 (50)	17 (3.12)	18 (12.5)
5h	18 (6.25)	22 (6.25)	15 (25)	19 (25)	19 (50)	21 (50)	19 (50)	18 (12.5)
5i	18 (6.25)	22 (12.5)	17 (12.5)	19 (6.35)	17 (50)	24 (50)	11 (50)	–
6a	18 (6.25)	18 (3.12)	17 (6.26)	19 (3.6.25)	15 (3.12)	17 (3.12)	12 (3.12)	14 (1.5)
6b	19 (6.25)	17 (6.25)	11 (12.5)	13 (6.25)	16 (6.25)	15 (12.5	10 (12.5)	11 (6.25)
6c	–	20 (6.25)	12 (12.5)	14 (6.25)	17 (12.5)	18 (12.5)	14 (12.5)	14 (12.5)
6d	21 (6.25)	20 (12.5)	13 (12.5)	14 (6.25)	20 (12.5)	13 (12.5)	19 (12.5)	21 (12.5)
6e	16 (6.25)	22 (3.15)	17 (12.5)	19 (6.25)	17 (12.5)	17 (12.5)	12 (50)	14 (25)
6f	21 (6.25)	22 (12.5)	13 (12.5)	13 (6.25)	18 (12.5)	20 (25)	19 (12.5)	14 (25)
6g	22 (12.5)	18 (12.5)	21 (12.5)	18 (6.25)	13 (12.5)	21 (25)	18 (50)	18 (12.5)
6h	16 (12.5)	20 (25)	11 (12.5)	25 (6.25)	17 (25)	23 (25)	21 (25)	11 (50)
6i	25 (25)	–	–	25 (12.5)	11 (25)	25 (50)	19 (25)	–
Ciprofloxin	12 (1.5)	12 (1.5)	15 (1.5)	17 (1.5)	–	–	–	–
Fluconazole	–	–	–	–	16 (1.5)	19 (1.5)	18 (1.5)	15 (1.5)

[a]A each values are the mean of three independent experiments, MIC the lowest concentration of drug which entirely inhibited bacterial growth. Ciprofloxin was used as standard for antibacterial activity, MIC values are given in brackets. (–) showed no antibacterial/antifungal activity, Diameters of inhibition zone was measured in mm.

some steric hindrance must be present of chloro-substituent on azetidinone ring plays important role in antifugal activity. Compound **4a** showed potent activity against *A. niger* while compounds **4a** and **6a** exhibited good activity against *A. oryzae* and *C. albicans* whereas, compound **5a** showed good activity against *P. chrysogenum*.

Antioxidant activity: *in vitro* Antioxidant activity of the synthesized compounds including intermediates **3-6(a-i)** were evaluated by DPPH free radical indicates their free radical scavenging ability. Compound **4a** showed excellent radical scavenging activity at all concentrations (70.12, 78.56, 80.18 and 87.54 % at 25, 50, 75 and 100 µg/mL),whereas compounds **5a** and **6a** were found to scavenge 80.34, 79.54 at 100 µg/mL, respectively. Compounds which contain the electron releasing group showed moderate interaction with DPPH in all concentrations.

Ferric ion (Fe^{3+}) reducing antioxidant power (FRAP) activity: The synthesized compounds **3-6a-i** were evaluated for ferric ion (Fe^{3+}) reducing antioxidant power (FRAP) activity by observing their interaction with Fe^{3+} cations as the standard drugs BHA, TBHQ and ascorbic acid. Screening results pointed that all the new indolyl moieties were most active FRAP antioxidant agents. It is observed that introduction of OCH_3(R) and CH_3 (R_1) on indolyl-1, 3,4-oxadiazole, thiazolidinone and azetidinone (**4e**, **5e** and **6e**) were found that possessed excellent activity at all concentrations. Compounds **3e**, **3g**, **3h**, **4f**, **4g**, **4i**, **5f**, **5h**, **6f**, **6h** and **6i** exhibited promising activity at 25 and 75 µg/mL, whereas compounds **3f**, **4h**, **4i**, **5f**, **5h**, **5i**, **6f**, **6h** and **6i** exhibited good activity at 100 µg/mL concentrations.

Metal chelating activiy: The transition metal ion Fe^{2+} attributes the ability to prevail the formation of free radicals by gain or loss of electrons. Consequently, ferrous (Fe^{2+}) ions

have been noted to be most potent pro-oxidant among various kinds of transition metal Fe^{2+} which retards metal-catalyzed oxidation and thus protect against oxidative damage. In Fe^{2+} ions are expected to participate in HO^- generating Fenton type reactions. The chelating effect of ferrous ions (Fe^{2+}) by newly synthesized indolyl-1,3, 4-oxadiazole, thiazolidinone and azetidinone moieties (3-6) indicated that by replacement of methoxy and chloro substitutions at C-5 of indole ring (compound **5b**: 63.41, 70.14, 83.32, 89.42 %) exhibited more potent in chelating activityat 25, 50,75 100 µg/mL concentrations, respectively. The values of metal chelating effect followed order **4b** ≥ **4e** > **3e** ≥ **5e** > **6e** > **6b** at 25 µg/mL concentration, **6e** > **3f** > **4e** > **3e** ≥ **6b** > **3b** ≥ **5e** > **4b** at 50 µg/mL concentration, **3a** > **3e** > **3b** > **4e** ≥ **6b** ≥ **5e** > **4e** at 75 µg/mL concentration, **3d** > **3g** > **4e** > **6e** > **3a** ≥ **5a** > **6b** > **5a** ≥ **3a** > **3b** > **3e** > **4b** at 100 µg/mL concentration.

Antituberculosis activity: The selected compounds **3a-c** and **4-6a-i** were tested for *in vitro* anti-tuberculosis (Anti-TB) activity against H37Rv strain *M. tuberculosis* (ATCC 27294) with rifampicin as the standard drug and DMF as negative control. Compounds **4g**, **5a**, **5g** and **6a** started activity at 50-1.5 µg/mL. Compounds **3a** and **6d** exhibited activity with concentrations of 25-0.8 µg/mL. Compounds **5d**, **6c** and **6g** demonstrated good activity at 3.12-1.5 µg/mL. Rest of the test compounds exhibited moderate to less activity. The best results were obtained for indolyl-1,3,4-oxadiazole, thiazolidinone **4a** (R,R_1-chloro) substituted demonstrated the highest anti-tuberculosis activity (MIC = 100-0.8 µg/mL). Compounds **3c**, **4e**, **4f**, **4h**, **4i**, **5e**, **5h**, **5i**, **6h** and **6i** which bear electron donating OCH_3 and CH_3 on indole ring did not show activities. The results are shown in Table-2.

Anticancer activity: Indolyl-1,3,4-oxadiazole, thiazolidinone and azetidinone newly synthesized moieties **4-6a-i** were evaluated of their *in vitro* anticancer activity against three human cancer cell lines: MCF-7 (breast carcinoma), A549 (lung carcinoma) and HeLa (cervical carcinoma) using MTT assay with doxorubicin as standard drug. Compound **4e** exhibited most significant cytotoxic effect against all the three cell lines, MFC-7 (IC_{50} µM, 0.45), A-589 (IC_{50} µM, 0.53) and HeLa (IC_{50} µM, 0.52), relatively better than reference drug. Compound **6e** exhibited effective cytotoxicity against MFC-7(IC_{50} µM, 0.61) A-589 (IC_{50} µM, 0.78) and HeLa (IC_{50} µM, 0.85). By replacement of chloro group by phenyl ring substituent (R_2) at azetidinone ring potent activity was exhibited. However, compounds **4f** and **6f** with methyl substitution at R and R_1 on indole were less active as compared to compounds **4e** and **6e** with a methoxy and methyl substitution at R and R_1, respectively. Compounds **4h**, **4i**, **6h** and **6i** expressed enhanced activity, whereas compounds **4b**, **4c**, **4d** and **5e** were found to be moderate and rest of the compound were very poor, further compounds **4a**, **5a**, **5b**, **5g** and **6a** did not display any anticancer activity. The results as MIC_{50} values are presented in Table-3.

Structure-activity relationship: In terms of structure-activity relationship (SAR), it is interesting to point out that thiazolidinone with the electron withdrawing substituted compounds were more effective on Gram-negative bacteria. Compound **5a** containing Cl group on the azetidinone analogues instead of thiazolidinone displayed good antibacterial activity against Gram-positive bacteria. Furthermore, analyses have revealed that the presence of electron withdrawing chloro group on indolyl-oxadiazole-thiazolidinone encourages enhanced activity, whereas replacement of electron donating OCH_3, CH_3 and H groups do not show any antibacterial activity. In case of antifungal activity, electron withdrawing chloro group on indolyl-oxadiazole-azetidinone moiety enhance activity of the synthesized compound 3-chloro-4-(5-chloro-2-phenyl-1*H*-indol-3-yl)-1-[5-(5-chloro-3-phenyl-1*H*-indol-2-yl)-1,3,4-oxadiazol-2-yl]azetidin-2-one (**5a**) against *A. niger*, *A. oryzae*, *C. albicans* and *P. chrysogenum*. In consideration of SAR, it seems that the presence of chloro substituted (R, R_1) on indole ring displayed relatively better antimicrobial activities. This may be due to lipophilic nature of chloro group with improvement in physico-chemical properties for the increased activity, these changes can be speculated in the afforded biological activities. This property is useful to a compound to diffuse through biological membrane and reach its site of action. For this reason, lipophilicity was found to be directly related to antimicrobial activity.

The presence of electron withdrawing Cl group as substituent on indole rings had a prominent impact on the radical scavenging activity (RSA). The electron withdrawing effect may be due to polarization of π-electrons of indole ring which increase the acidity of conjugated indole-NH. In view of the precedent of ferric reducing antioxidant activity, the results clearly signify the incorporation of electron-releasingsubstitutes on indolyl-

TABLE-2
ANTITUBERCULOSIS ACTIVITY AGAINST
M. tuberculosis OF COMPOUNDS **3**(**a-c**) AND **4-6**(**a-i**)

Compd.	Minimum inhibitory concentration, MIC_{50} (µg/mL)							
	100	50	25	12.5	6.25	3.12	1.5	0.8
3a	S	S	R	R	R	R	R	R
3b	S	S	S	S	S	S	R	R
3c	S	S	S	S	S	S	S	S
4a	R	R	R	R	R	R	R	R
4b	S	S	S	S	S	R	R	R
4c	S	S	S	S	R	R	R	R
4d	S	S	S	S	S	S	S	R
4e	S	S	S	S	S	S	S	S
4f	S	S	S	S	S	S	S	S
4g	S	R	R	R	R	R	R	S
4h	S	S	S	S	S	S	S	S
4i	S	S	S	S	S	S	S	S
5a	S	R	R	R	R	R	R	S
5b	S	S	S	S	S	R	R	S
5c	S	S	S	S	R	R	R	R
5d	S	S	S	S	S	R	R	S
5e	S	S	S	S	S	S	S	S
5f	S	S	S	S	S	S	S	R
5g	S	R	R	R	R	R	R	R
5h	S	S	S	S	S	S	S	S
5i	S	S	S	S	S	S	S	S
6a	S	R	R	R	R	R	R	S
6b	S	S	S	S	S	S	R	S
6c	S	S	S	S	S	R	R	R
6d	S	S	S	R	R	R	R	R
6e	S	S	S	S	S	S	S	S
6f	S	S	S	S	S	S	R	R
6g	S	S	S	S	S	R	R	R
6h	S	S	S	S	S	S	S	S
6i	S	S	S	S	S	S	S	S

R = Resistant, S = Sensitive

TABLE-3
ANTICANCER ACTIVITY AGAINST THREE CANCER CELL LINES OF COMPOUNDS **4-6(a-i)**

Compounds	R	R_1	R_2	MIC_{50} (μM)		
				MFC-7 (Breast carcinoma)	A-589 (Lung carcinoma)	HeLa (Cervical carcinoma)
4a	Cl	Cl	–	No activity	No activity	> 10
4b	OCH_3	Cl	–	4.45	6.25	7.42
4c	CH_3	Cl	–	5.56	4.69	3.52
4d	Cl	CH_3	–	4.52	6.42	7.49
4e	OCH_3	CH_3	–	0.45	0.53	0.52
4f	CH_3	CH_3	–	4.64	3.34	2.18
4g	Cl	H	–	No activity	5.62	No activity
4h	OCH_3	H	–	1.54	1.78	1.56
4i	CH_3	H	–	1.82	1.85	1.80
5a	Cl	Cl	Cl	> 10	No activity	No activity
5b	OCH_3	Cl	Cl	No activity	No activity	No activity
5c	CH_3	Cl	Cl	No activity	> 10	No activity
5d	Cl	CH_3	Cl	No activity	No activity	No activity
5e	OCH_3	CH_3	Cl	3.82	5.73	2.93
5f	CH_3	CH_3	Cl	3.51	4.80	No activity
5g	Cl	H	Cl	No activity	No activity	No activity
5h	OCH_3	H	Cl	> 10	> 10	> 10
5i	CH_3	H	Cl	> 10	> 10	> 10
6a	Cl	Cl	Ph	No activity	No activity	No activity
6b	OCH_3	Cl	Ph	> 10	> 10	> 10
6c	CH_3	Cl	Ph	> 10	> 10	> 10
6d	Cl	CH_3	Ph	> 10	> 10	> 10
6e	OCH_3	CH_3	Ph	0.61	0.78	0.85
6f	CH_3	CH_3	Ph	2.45	2.12	2.6
6g	Cl	H	Ph	No activity	No activity	No activity
6h	OCH_3	H	Ph	1.93	1.32	1.58
6i	CH_3	H	Ph	1.89	1.69	No activity
Doxorubicin	–	–	–	0.58	0.72	0.89

oxadiazole-azetidinone amplified FRAP activity. Accordingly, anti-tuberculosis investigation reveals the effects of (R,R_1-chloro) substitution designs on indoles with oxadiazole, thiazolidinone scaffolds, as the lipophilic nature of compounds plays a key role in varying the efficaciousness of activity, whereas in the chelating effect of ferrous ions (Fe^{2+}) electron withdrawng and the electron donating groups on indole ring showed excellent activity with the except for compound **5b**. The higher antioxidant activities of these compounds may be attributed to the presence of indole rings. Anticancer study manifested that the introduction of electron donating groups would lead to more potent compounds than those with the electron withdrawing groups. It clearly suggests that steric hindrance attributes methoxy group as more potent anticancer agents. The structure-activity relationship of synthesized moieties are summerized in Fig. 1 with respect to electron withdrawing or donating conduct.

Conclusion

In summary, the study reports the synthesis of indolyl-1, 3,4-oxadiazole, thiazolidinone and azetidinone and their biological activities. Among synthesized compounds, **4a** having indolyl-oxadiazole-thiazolidinone moieties exhibited great

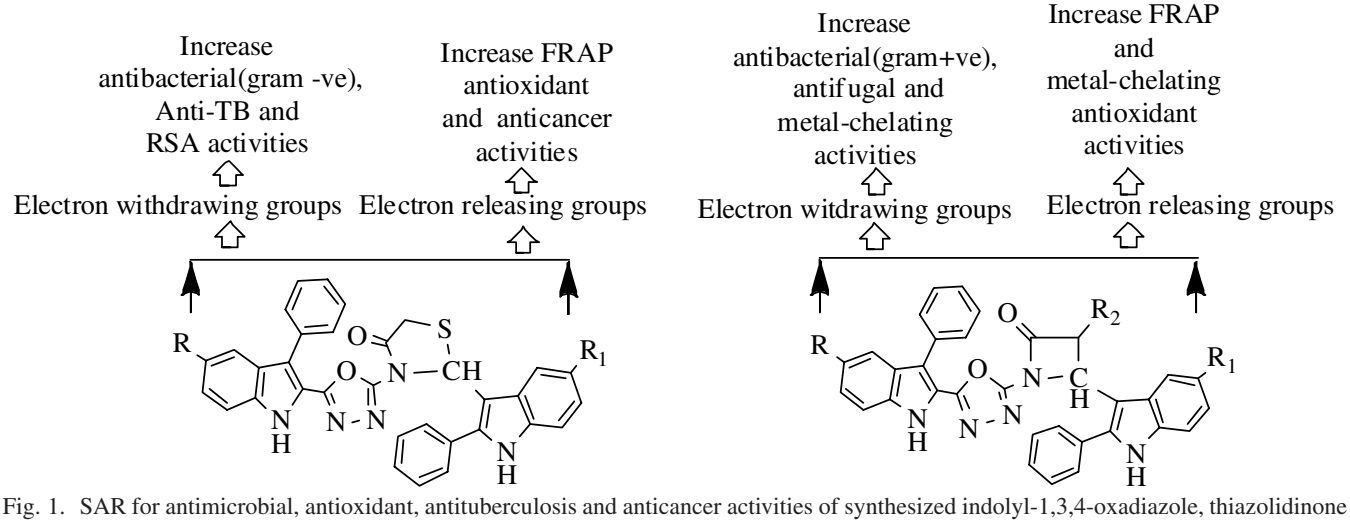


Fig. 1. SAR for antimicrobial, antioxidant, antituberculosis and anticancer activities of synthesized indolyl-1,3,4-oxadiazole, thiazolidinone and azetidinone derivatives

antibacterial activity against *E. coli* and *K. pneumoniae*, excellent radical scavenging and anti-tuberculosis (anti-TB) activity against H37Rv strain *M. tuberculosis* at all concentrations, whereas compound **5a** having indolyl-oxadiazole-azetidinone presents the highest activity against *S. aureus*, *B. subtilis* and antifungal activities. Anticancer results indicate that compound **4e** was the most effective againstanticancer against all the three cell lines, MFC-7(IC_{50} µM, 0.45), A-589 (IC_{50} µM, 0.53) and HeLa (IC_{50} µM, 0.52), relatively more potent than the standard drug doxorubicin. Compounds **4e**, **5e** and **6e** were found that possessed excellent FRAP and compound **5b** showed better metal-chelating activities at all concentrations.However, further investigation is needed in order to gain insight into the mechanism of action of examined compounds.

ACKNOWLEDGEMENTS

The authors are grateful to The Director, National Collection of Industrial Microorganisms (NCIM), National Chemical Laboratory (NCL), The Director, National Centre for Cell Science (NCCS), Pune, India, for providing test materials and the Director, IIT Madras, Chennai, India, for providing spectral data.

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