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Original article

1,3-dihydro-2H-indol-2-ones derivatives: Design, Synthesis, *in vitro* antibacterial, antifungal and antitubercular study

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ABSTRACT

1,3-dihydro-2H-indol-2-ones derivatives are reported to exhibit a wide variety of biodynamic activities such as antituberculer, anti HIV, fungicidal, antibacterial, anticonvulsant. These valid observations led us to synthesize some new indole-2-one derivative. Thus, herein we report synthesis of various 5-substituted-3-[{5-(6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4 tetrahydro pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl}imino]-1,3-dihydro-2H-indol-2-one derivatives **4a**–**l** using one pot multicomponent–Biginelli reaction via $CaCl_2$ catalyst. Structures and purity of these compounds were confirmed by elemental, IR, (^{1}H & ^{13}C) NMR and Mass spectral analysis. Newly synthesized compounds were also tested for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H_{37}Rv, *in vitro* antibacterial activity against selected human pathogens viz. *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Staphylococcus aureus*, *Staphylococcus pyogenus*, *Bacillus subtilis* and antifungal activity against *Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus* strains.

1. Introduction

Drug discovery and development is a very laborious and costly process involving synthesis and screening of diverse organic compounds. In this regard, multicomponent reactions (MCRs) are of increasing importance in the field of medicinal chemistry [1–3]. Currently, attention is put on speed, diversity, and efficiency in the drug discovery process [4]. MCRs can provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques. The search and discovery for new MCRs on one hand [5], and the full exploitation of already known multicomponent reactions on the other hand, are therefore of considerable current interest. In 1893, Pietro Biginelli has reported on the acid-catalyzed cyclo-condensation reaction of ethylacetoacetate, benzaldehyde and urea. The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of conc. HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling the reaction mixture was identified correctly by Biginelli as dihydropyrimidin-2-one [6]. The scope of this reaction was gradually extended by the variation of all three building blocks, allowing access to a large number of multi-functionalized dihydropyrimidines of medicinal use [3b,7–10]. Dihydropyrimidines show a diverse range of biological activities. They are known to possess activities such as antiviral (nitractin) [11], anticancer [12], antibacterial [13], analgesic and anti-inflammatory [13], as well as efficacy as calcium channel modulators and α1a-antagonists [14]. Thus development of methodologies for efficient lead structure identification and for pharmacophore variation of dihydropyrimidines motif has always attracted the attention of pharmaceutical industry [15]. Furthermore, certain compounds bearing 1,3-dihydro-2H-indol-2-ones nucleus is used as a versatile lead molecule for designing potential antivirals [16], antituberculars [17], anticonvulsants [18] and anti-tumor therapeutic activities [19]. While, Schiff bases of 1,3-dihydro-2H-indol-2-ones and its derivatives were reported for antibacterial [20], antifungal [20], anti-HIV [21], anticonvulsant activities [22] and GAL3 receptor antagonists [23].

Prompted by the biological properties of dihydropyrimidines and 1,3-dihydro-2H-indol-2-ones nucleus, they were incorporated with thiadiazoles [24] and schiff bases were synthesized. Moreover, in the design of new drugs, the development of hybrid molecules through the combination of different pharmacophores in one frame may lead to compounds with interesting dual biological profiles, which is being reflected in present work.

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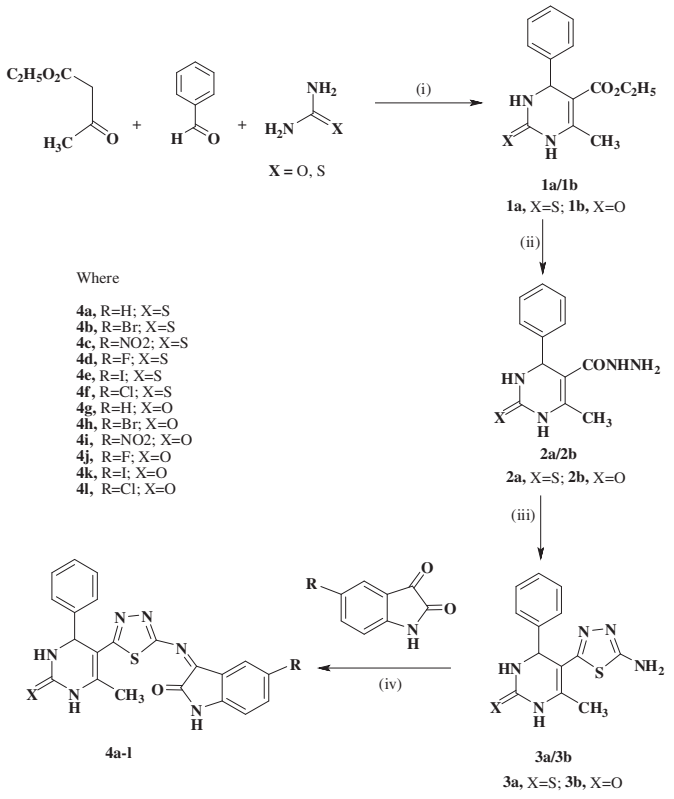
2. Chemistry

Several improved procedures have been reported to carry out Biginelli's reactions using Lewis acid catalyst as well as protic acid under classical reflux [25]. Other studies have focused on the use of ionic liquids [26], microwave irradiation [27], combinatorial techniques [28], use of boron compounds [29], Trimethylsilyl chloride (TMSCl) [30] and heterogeneous catalysts viz. as tangstophosphoric acid [31], zeolite [32a,b], montmorillonite [33], ion-exchange resins [34], and the also use of silica sulfuric acid [35], Poly(p-phenylene ethynylene) (PPE) [36] etc. To the best of our knowledge there have been relatively few reports available for one-pot synthesis of dihydropyrimidinones using $CaCl_2$ [37] as catalyst. And in recent years, the development of more economical and environmental friendly conversion processes is gaining interest in the chemical community. Thus, herein, we report an efficient, practical, environmentally benign and high yielding method for Biginelli three component, one-pot synthesis of tetrahydropyrimidinones using $CaCl_2$ [38] as catalyst for preparation of compound **1a**/**1b**.

The synthesis of title compound **4a**–**l** is outlined in Scheme 1. In a typical experimental procedure a solution of β-ketoester, aldehyde and urea/thiourea in ethanol was heated under reflux in the presence of catalystic amount of $CaCl_2$ to give ethyl 6-methyl-4-phenyl-2-(oxo/thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1a**/**1b**, followed by reaction with hydrazine hydrate in ethanol to give 6-methyl-4-phenyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **2a/2b**. Treatment of 6-methyl-4-phenyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **2a/2b** with ammonium thiocyanate in acidic medium afforded 6-methyl-2-(oxo/thioxo)-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonyl hydrazine-carbothioamide, which on heterocyclisation in presence of conc. H_2SO_4 gave 5-(5-amino-1,3,4-thiadiazol-2-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one/thione **3a/3b**. Finally, compounds **3a/3b** on condensation with various 5-substituted indoline-2,3-dione in acidic medium afforded the title compound 5-substituted-3-[{5-(6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4 tetrahydro pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl}imino]-1,3-dihydro-2H-indol-2-one **4a**–**l**. The purity of compounds was checked by TLC. The structure of all the synthesized compounds was established by IR, (^{1}H & ^{13}C) NMR and Mass spectral analysis. The result of elemental analysis of the synthesized compounds was in agreement with theoretical values.



Scheme 1. Reaction Conditions. i) $CaCl_2/C_2H_5OH$, reflux, 2 h; ii) $NH_2NH_2.H_2O/C_2H_5OH$, conc. H_2SO_4, reflux, 3 h; iii) 1 N HCl, NH_4SCN, 8–10 h; conc. H_2SO_4, room temp., 2 h iv) CH_3OH/glacial CH_3COOH, reflux, 45 min.

3. Biological activity

3.1. in vitro evaluation of antimicrobial and antituberculosis activity

The MICs of synthesized compounds were carried out by broth microdilution method as described by Rattan [39]. Antibacterial activity was screened against *Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688), *Klebsiella pneumonia* (MTCC-109), *Salmonella typhi* (MTCC-98), *Staphylococcus aureus* (MTCC-96), *Staphylococcus pyogenus* (MTCC-442) and *Bacillus subtilis* (MTCC-441). Gentamycin, Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species C. albicans (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323). Nystatin and Griseofulvin was used as a standard antifungal agent. The antimicrobial screening data are shown in Tables 1 and 2.

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against known drugs. Mueller–Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains.

Table 1
Antibacterial Activity (Minimal Inhibition Concentration, MICs, μg/mL).

Entry	R	X	E.c. MTCC 443	P.a MTCC 1688	Kl.pn. MTCC 109	S.ty MTCC 98	S.a. MTCC 96	S.py. MTCC 442	B.s. MTCC 441
4a	H	S	500	200	200	200	200	200	200
4b	Br	S	200	200	200	250	100	100	100
4c	NO_2	S	62.5	100	100	100	100	200	100
4d	F	S	62.5	62.5	100	100	62.5	100	100
4e	I	S	250	250	200	250	200	200	200
4f	Cl	S	200	100	200	200	200	200	100
4g	H	O	500	250	250	250	500	500	500
4h	Br	O	250	250	200	250	100	100	100
4i	NO_2	O	62.5	100	200	200	200	250	200
4j	F	O	100	62.5	100	100	62.5	100	100
4k	I	O	250	250	250	250	250	200	250
4l	Cl	O	100	200	200	200	200	200	200
Gentamycin			0.05	1	0.05	1	0.25	0.5	0.5
Ampicillin			100	100	100	100	250	100	100
Chloramphenicol			50	50	50	50	50	50	50
Ciprofloxacin			25	25	25	25	50	50	50
Norfloxacin			10	10	10	10	10	10	10

E.c. = *E. coli* (MTCC-443); P.a. = *P. aeruginosa* (MTCC-1688); Kl.pn. = *Kl. pneumoniae* (MTCC-109); S.ty. = *S. typhi* (MTCC-98); S.a. = *S. aureus* (MTCC-96); S.py. = *S. pyogenus* (MTCC-442); B.s. = *B. subtilis* (MTCC-441).

Table 2
Antifungal Activity (Minimal Fungicidal Concentration, MICs, μg/mL).

Entry	*C. albicans*	*A. niger*	*A. clavatus*
	MTCC 227	MTCC 282	MTCC 1323
4a	>1000	500	500
4b	500	500	500
4c	250	100	250
4d	100	100	100
4e	>1000	>1000	>1000
4f	500	500	500
4g	250	250	250
4h	500	500	>1000
4i	250	250	500
4j	100	100	200
4k	>1000	>1000	>1000
4l	>1000	500	500
Nystatin	100	100	100
Greseofulvin	500	100	100

in vitro antituberculosis activity of all the newly synthesized compounds against Mycobacterium tuberculosis H37Rv strain was determined by using Lowenstein–Jensen medium (conventional method) as described by Rattan [39] and the observed MIC of compounds are presented in Table 3.

4. Results and discussion

4.1. Analytical results

A series of 1,3-dihydro-2H-indol-2-ones derivatives has been synthesized in good yields by using the synthetic route as outlined in Scheme 1. IR, (^{1}H & ^{13}C) NMR and mass spectral data are in well agreement with the proposed structures of all newly synthesized compounds.

Here, in novel synthetic research work, an effort has been made to undertake the synthesis of **1a/1b** ethyl 6-methyl-4-phenyl-2-(oxo/thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylate via Biginelli's reaction through one step process. Purity and yield of compounds **1a/1b** was excellent without any tedious workup procedure and also mass spectrum gives molecular ion peak at m/z 260.3 for **1a** and m/z 276.2 for **1b** respectively. And IR spectrum displayed stretching vibration at 1735, 1700 and 1652 cm^{-1} for ethyl ester ($COOC_2H_5$) and secondary amine (NH) functional groups, while ^{1}H NMR spectrum showed singlet of amine at δ 2.24, 7.20 and13.53 multiplet of aromatic ring at δ 7.15–7.42, singlet of single proton of cyclized heterocyclic ring at range δ 5.05 and triplet-quartet patterns of ethyl chain is recorded at δ 1.15 (t, 3H, J = 7.0) & 3.78 (q, 2H, J = 7.1) ppm which proved the synthetic nucleus **1a/1b**. Formation of 6-methyl-4-phenyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide **2a/2b** showed broad stretching bands around 3200 & 3420 cm^{-1} for NH_2 and NH, in ^{1}H NMR spectrum a singlet at δ 4.80, 8.90 ppm for **2a** & δ 4.87, 8.93 ppm for **2b** were accounted for NH_2 and NH, while triplet-quatert pattern of ethyl chain vanished. Also disappearance of these NH and NH_2 signals in **3a/3b** with ^{1}H NMR proved that the ring closure is resulted in the formation of 1,3,4-thiadiazole ring from **2a/2b**. Which is further evident from IR spectra, which displayed broad stretching vibration at 3084 cm^{-1} due to the aromatic ring (ArH) and absorption band at 1579 cm^{-1} due to C=N group while at 1063 cm^{-1} is due to thiadiazole ring. Condensation of compounds **3a/3b** with various 5-substituted indoline-2,3-dione produces the final 1,3-dihydro-3H-indol-3-one derivatives **4a**–**l**. Position & numbers of protons have been recorded in ^{1}H NMR spectrum, which favors multiplet of aromatic protons at δ 7.00–8.90, while range for proton of iminebase (–CH=) is observed between δ 4.54–4.59. The ^{13}C NMR and Mass spectral data of compound **4a**–**l** is given in the experimental section.

Table 3
Antitubercular Activity (Minimal Inhibition Concentration, MICs, μg/mL).

Entry	*M. tuberculosis* H37Rv	% Inhibition
	MTCC – 200	
4a	500	98
4b	250	98
4c	62.5	99
4d	25	99
4e	1000	98
4f	62.5	99
4g	1000	98
4h	500	98
4i	62.5	99
4j	50	99
4k	1000	98
4l	100	98
Rifampicin	40	98
Isoniazid	0.20	99

4.2. Biological results

The literature survey revealed that introduction of electron-withdrawing groups at positions 5, 6, and 7 greatly increased activity from that of 1,3-dihydro-2H-indol-2-one, with substitution at the 5th position being most favorable. This is not surprising, as C–5 substitution has previously been associated with increased biological activity for a range of indole-based compounds [40,41] and the presence of substituted aromatic ring at 3rd position has been reported to be associated with antimicrobial properties [42,43]. The various substituent at 3rd position of the isatin which were reported, were various substituted phenyl ring moieties [44,45] heterocyclic rings [46–48] and aliphatic system [49]. These observations led to the conception that a series of some different novel schiff bases of 5-(5-amino-1,3,4-thiadiazol-2-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(H)-one/thione using different 5-substituted indoline-2,3-dione.

From *in vitro* antibacterial activity data, it is confirmed that compounds containing strong electron withdrawing (fluorine group) i.e. **4d** & **4j** exhibited excellent activity against all microbial strains, while compounds **4b** & **4h** exhibited comparable activity against gram positive strains, while compound **4c** & **4i** are found to be highly active against gram negative strains as compared to standard antibiotic ampicillin.

From *in vitro* antifungal activity data, it is found that compound **4d** & **4f** is displaying highest activity against all fungal strains, while compounds **4c** & **4i** are showing somewhat less activity compare to compounds **4d** & **4i**. But overall, all the compounds have displayed significant antibacterial and antifungal activity. In general, the order of antibacterial activity of the substituents at the 5th position of 1H-indole-2,3-diones is F > NO_2>Br > Cl > H=I and also due to presence of sulphur atom at position–2 in the compounds **4a**–**f** is responsible for better activity compared to oxygen atom (at position–2) for compounds **4g**–**l**. The *in vitro* antibacterial and antifungal screening results are summarized in Tables 1 and 2.

The encouraging results from the antibacterial and antifungal studies impelled us to go for preliminary screening of synthesized compounds against *M. tuberculosis* H_{37}Rv, which is summarized in Table 3. Compound **4j** containing 5-flouro substituent on indolone ring with oxygen atom on tetrahydropyrimidine nucleus showed better activity (50 μg/ml) and compounds **4c**, **4f** and **4i** showed good activity (50–62.5 μg/ml) which is attributed due to 5-nitro, 5-chloro substituents of 2-thioxo-tetrahydropyrimidine indolone nucleus and 5-nitro substituents of 2-oxo-tetrahydropyrimidine

indolone nucleus respectively, where as compound **4d** which is having inductively electron withdrawing but mesomerically electron releasing sulphur atom with 5-flouro substituent on indolone ring showed better activity (25 μg/ml) compared to other analoges. Thus, further developmental studies to acquire more information about structure-activity relationships are in progress in our laboratories.

5. Experimental section

5.1. Chemistry

All the melting points were taken in open capillaries and are uncorrected. The purity of compounds was checked routinely by TLC (0.5 mm thickness) using silica gel-G coated aluminium plates (Merck) and spots were visualized by exposing the dry plates in iodine vapours. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. IR spectra (ν_{max} in cm^{-1}) were recorded on Shimadzu FTIR spectrophotometer using KBr technique. ^1H & ^{13}C NMR spectra on a Bruker's WM 400 FT MHz NMR instrument using DMSO-d_6 as solvent and TMS as internal reference (chemical shifts in δ ppm). The elemental analysis (C, H, and N) of compounds was performed on Carlo Erba − 1108 elemental analyzer.

5.1.1. General procedure

5.1.1.1. Preparation of ethyl 6-methyl-4-phenyl-2-(oxo/thioxo)-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***1a/1b*** *[37].* Title compounds **1a/1b** was prepared using reported procedure [32b,37] with minor modifications. Urea/thiourea (0.5 mol), ethylacetoacetate (0.75 mol) and benzaldehyde (0.75 mol) were mixed in ethanol (25 ml). Catalytic amount of $CaCl_2$ (0.020 mol) was added to the reaction mixture and was refluxed for 2 h. White/yellowish precipitates was obtained during reflux. The progress of reaction was monitored by TLC. After completion of reaction, the stirring was stopped, and the reaction mass was cooled and treated with crushed ice. Almost pure product obtained as white/cream solid was filtered and dried. And further crystallized using methanol: water (60: 40), yield: **1a**, 85% & **1b**, 90%, mp: **1a**, 201 °C & **1b**, 218 °C.

5.1.1.2. Preparation of 6-methyl-4-phenyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide ***2a/2b***. **1a/1b** (0.01 mol) in ethanol (20 ml), hydrazine hydrate (0.01 mol) was added followed by the addition of a catalytic amount of conc. H_2SO_4 and allowed to stir for 3 h at 75 °C. Yellowish precipitates were obtained during reflux. A progress of reaction was monitored using TLC. After completion of reaction, crude mass was allowed to cool and poured on crushed ice. Product obtained as yellowish precipitate, was filtered and dried. Purification was done by crystallization using ethanol.

Spectral data of **2a**: Yellowish solid, yield 82%; mp 190 °C; MS: m/z $[247.05]^+$; IR [ν_{max}, cm^{-1}, KBr]: ^1H- NMR [400 MHz, δ, ppm, DMSO-d6] 2.37 (3H, s, $-CH_3$), 4.80 (2H, s, $-NH_2$), 5.40 (1H, s, −CH═), 6.51, 8.90 (1H × 2, s, −NH), 7.11–7.39 (5H, m, aromatic). ^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 17.90 (C1), 58.87 (C4), 115.10–146.90 (C3,C7,C8,C9,C10,C11,C12), 152.62 (C2), 154.73 (C5), 167.56 (C6). Anal. Calcd. for $C_{12}H_{14}N_4O_2$ (246.27): C, 58.53; H, 5.73; N, 22.75. Found: C, 58.21; H, 5.52; N, 22.39%.

Spectral data of **2b**: Yellowish solid, yield 85%; mp 195 °C; MS: m/z $[263.45]^+$; IR [ν_{max}, cm^{-1}, KBr]: ^1H- NMR [400 MHz, δ, ppm, DMSO-d_6] 1.89, 4.87, 8.93,11.96 (1H × 4, s, −NH), 2.30 (3H, s, $-CH_3$), 5.46 (1H, s, −CH═), 7.20–7.42 (5H, m, aromatic). ^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 17.60 (C_1), 60.40 (C_4), 110.34–148.13 (C_3,C_7,C_8,C_9,C_{10},C_{11},C_{12}), 162.12 (C_2), 167.42 (C_6), 176.29 (C_5). Anal. Calcd. for $C_{12}H_{14}N_4OS$ (262.33): C, 54.94; H, 5.38; N, 21.36. Found: C, 54.71; H, 5.01; N, 21.00%.

5.1.1.3. Preparation of 5-(5-amino-1, 3, 4-thiadiazol-2-yl)-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2 (1H)-one/thione ***3a/3b***. Title compound **3a/3b** is obtained using reported procedure using 1 N HCl, ammonium thiocynate and conc. H_2SO_4 [50].

Spectral data for **3a**: Pale yellow solid, yield 72%; mp 165–167 °C; MS: m/z $[288.05]^+$; ^1H- NMR [400 MHz, δ, ppm, DMSO-d_6] 8.90, 5.90 (1H × 2, s, −NH), 7.56 (2H, s, $-NH_2$), 6.99–7.36 (4H, m, aromatic), 5.65 (1H, s, −CH═),1.98 (3H, s, $-CH_3$). ^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 17.20 (C_1), 109.12–145.06 (C_2,C_5,C_8,C_9,C_{10},C_{11},C_{12},C_{13}), 157.70 (C_6), 162.28 (C_7), 170.16 (C_4). Anal. Calcd. for $C_{13}H_{13}N_5OS$ (287.34): C, 54.34; H, 4.56; N, 24.37; Found: C, 54.28; H, 4.21; N, 24.07%.

Spectral data for **3b**: Dark yellow solid, yield 65%; mp 150–152 °C; MS: m/z $[304.15]^+$; ^1H- NMR [400 MHz, δ, ppm, DMSO-d6] 1.90, 11.50 (1H × 2, s, −NH), 2.16 (3H, s, $-CH_3$), 5.25 (1H, s, −CH═), 6.96 (2H, s, $-NH_2$), 7.05–7.40 (4H, m, aromatic). ^{13}C-NMR [100 MHz, δ, ppm, DMSO-d_6]: 16.80 (C_1), 110.56–141.08 (C_2,C_5,C_8,C_9,C_{10},C_{11},C_{12},C_{13}), 157.30 (C_6), 160.17 (C_7), 173.52 (C_4). Anal. Calcd. for $C_{13}H_{13}N_5S_2$ (303.41): C, 51.46; H, 4.32; N, 23.08; Found: C, 51.12; H, 3.91; N, 22.74%.

5.1.1.4. Preparation of 5-substituted-3-[{5-(6-methyl-2-oxo/thioxo-4-phenyl-1,2,3,4 tetrahydro pyrimidin-5-yl)-1,3,4-thiadiazol-2-yl} imino]-1,3-dihydro-2H-indol-2-one ***4a–l***. Compounds **3a/3b** (0.01 mol) and 5-substituted indoline-2,3-dione (0.01 mol) were dissolved in methanol(10 mL) in presence of catalytic amount of glacial acetic acid and reflux for 45 min. A progress of reaction was monitored using TLC. After completion of reaction, crude mass was allowed to cool and poured on crushed ice. Final product obtained was filtered, washed with cold ether (20–30 ml), dried and purified by crystallization in THF:water (60:40).

The compounds **4a–l** were prepared in the same fashion using appropriate 5-substituted indoline-2,3-diones and **3a/3b** (Scheme 1).

5.1.1.4.1. 3-{[5-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4a***. Grey solid, Yield 70%, mp.210–212 °C; MS: m/z $[432.08]^+$; IR [ν_{max}, cm^{-1}, KBr]: 3459, 3088, 2970 (C–H, aromatic), 3331, 3167 (NH), 1724 (C═O), 1633 (C═N, iminebase), 1660 (C═S), 1467 (C–H, aliphatic), 1463 (C═C, aromatic), 1377 (C═N), 1273, 1185 (C–S–C), 725, 759, 695, 662 (C–H, deformation). ^1H- NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.05, 8.00, 13.76 (1H × 3, s, NH), 2.26 (3H, s, CH_3), 4.59 (1H, s, −CH =), 7.23–7.86 (9H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d_6]: 16.74 (C_{31}), 62.92 (C_{17}), 117.11 (C_{11}), 119.20–132.15 (C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 140.60 (C_{10}), 143.22 (C_{24}), 150.30 (C_8), 156.60 (C_2), 158.27 (C_5), 164.90 (C_7), 173.70 (C_{19}). Anal. Calcd. for $C_{21}H_{16}N_6OS_2$ (432.52): C, 58.31; H, 3.73; N, 19.43. Found: C, 58.03; H, 3.22; N, 18.90%.

5.1.1.4.2. 5-bromo-3-{[5-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4b***. Yellowish solid, Yield 72%, mp. 199–200 °C; MS: m/z $[511.99]^+$; IR [ν_{max}, cm^{-1}, KBr]: 3447, 3078, 2988 (C–H, aromatic), 3344, 3167 (NH), 1739 (C═O), 1466 (C–H, aliphatic), 1460 (C═C, aromatic), 1366 (C═N), 1283, 1185 (C–S–C), 1658 (C═S), 1643 (C═N, iminebase), 733, 759, 688, 662 (C–H, deformation), 610 (C–Br). ^1H- NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.23, 8.24, 13.73 (1H × 3, s, NH), 2.25 (3H, s, CH_3), 4.55 (1H, s, −CH =), 7.15–8.15 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d_6]: 16.94 (C_{31}), 63.92 (C_{17}), 117.60–133.15 (C_{11},C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 140.10 (C_{10}), 143.72 (C_{24}), 149.90 (C_8), 156.90 (C_2), 158.35 (C_5), 162.30 (C_7), 173.65 (C_{19}). Anal. Calcd. for $C_{21}H_{15}BrN_6OS_2$ (511.42): C, 49.32; H, 2.96; N, 16.43. Found: C, 49.12; H, 3.74; N, 16.08%.

5.1.1.4.3. 3-{[5-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-5-nitro-1,3-dihydro-2H-indol-2-one ***4c***. Yellow solid, Yield 74%, mp. 202–204 °C; MS: m/z

[477.07]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3454, 3098, 2980 (C–H, aromatic), 3334, 3177 (NH), 1729 (C=O), 1668 (C=S), 1623 (C=N, iminebase), 1574 (N=O), 1468 (C=C, aromatic), 1450 (C–H, aliphatic), 1283, 1195 (C–S–C), 1371 (C=N), 723, 749, 690, 652 (C–H, deformation). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d6]: 2.07, 8.33, 13.70 (1H × 3, s, NH), 2.27 (3H, s, CH_3), 4.54 (1H, s, –CH =), 7.25–8.51 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 16.80 (C_{31}), 65.35 (C_{17}), 117.95 (C_{11}), 122.50–144.15 (C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26}, C_{27},C_{28},C_{29}), 143.34 (C_{24}), 147.95 (C_{10}), 150.55 (C_8), 155.63 (C_2), 159.12 (C_5), 164.20 (C_7), 174.15 (C_{19}). Anal. Calcd. for $C_{21}H_{15}N_7O_3S_2$ (477.52): C, 52.82; H, 3.17; N, 20.53. Found: C, 52.33; H, 3.02; N, 20.13%.

5.1.1.4.4. 5-fluoro-3-{[5-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4d***. Yellowish solid, Yield 78%, mp. 205–206 °C; MS: m/z [550.07]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3465, 3105, 2970 (C–H, aromatic), 3345, 3187 (NH), 1734 (C=O), 1658 (C=S), 1623 (C=N, iminebase), 1468 (C–H, aliphatic), 1448 (C=C, aromatic), 1371 (C=N), 1321 (C–F), 1268, 1205 (C–S–C), 723, 757, 690, 655 (C–H, deformation). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.23 (3H, s, CH_3), 2.34, 8.18, 13.74 (1H × 3, s, NH), 4.57 (1H, s, –CH=), 7.28–8.10 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 16.30 (C_{31}), 65.05 (C_{17}), 111.06–142.68 (C_{11},C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 145.33 (C_{24}), 150.13 (C_8), 153.95 (C_{10}), 155.23 (C_2), 157.98 (C_5), 164.25 (C_7), 174.15 (C_{19}). Anal. Calcd. for $C_{21}H_{15}FN_6OS_2$ (450.51): C, 55.99; H, 3.36; N, 18.65. Found: C, 55.86; H, 3.12; N, 18.43%.

5.1.1.4.5. 5-iodo-3-{[5-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4e***. Cream solid, Yield 70%, mp. 215–218 °C; MS: m/z [557.98]$^+$; IR [ν_{max}, cm-1, KBr]: 3454, 3088, 2980 (C–H, aromatic), 3334, 3163 (NH), 1739 (C=O), 1668 (C=S), 1633 (C=N, iminebase), 1478 (C=C, aromatic), 1463 (C–H, aliphatic), 1370 (C=N), 1264, 1185 (C–S–C), 733, 749, 685, 652 (C–H, deformation), 550 (C–I). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.05, 8.43, 13.72 (1H × 3, s, NH), 2.25 (3H, s, CH_3), 4.56 (1H, s, –CH=), 7.24–8.16 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 15.60 (C_{31}), 59.95 (C_{17}), 91.66–138.18 (C_{11}, C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 140.95 (C_{10}), 143.33 (C_{24}), 150.53 (C_8), 155.30 (C_2), 158.46 (C_5), 163.35 (C_7), 173.85 (C_{19}). Anal. Calcd. for $C_{21}H_{15}IN_6OS_2$ (558.42): C, 45.17; H, 2.71; N, 15.05. Found: C, 44.90; H, 2.58; N, 14.80%.

5.1.1.4.6. 5-chloro-3-{[5-(6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4f***. Pale yellow solid, Yield 70%, mp. 210–212 °C; MS: m/z [466.04]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3444, 3098, 2969 (C–H, aromatic), 3350, 3177 (NH), 1735 (C=O), 1643 (C=N, iminebase), 1659 (C=S), 1478 (C=C, aromatic), 1465 (C–H, aliphatic), 1378 (C=N), 1267, 1205 (C–S–C), 728, 765, 687, 662 (C–H, deformation), 715 (C–Cl). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.27 (3H, s, CH_3), 2.42, 8.16, 13.77 (1H × 3, s, NH), 4.55 (1H, s, –CH=), 7.22–7.83 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 16.55 (C_{31}), 59.90 (C_{17}), 92.00–137.05 (C_{11},C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 141.30 (C_{10}), 143.10 (C_{24}), 150.40 (C_8), 155.48 (C_2), 159.10 (C5), 164.60 (C7), 174.10 (C19). Anal. Calcd. for $C_{21}H_{15}ClN_6OS_2$ (466.97): C, 54.01; H, 3.24; N, 18.00. Found: C, 53.83; H, 3.01; N, 17.82%.

5.1.1.4.7. 3-{[5-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4g***. Yellow solid, Yield 74%, mp. 214–216 °C; MS: m/z [416.11]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3334, 2912 (NH), 3154, 2988, 2840 (C–H, aromatic), 1701, 1729 (C=O), 1623 (C=N, iminebase), 1478 (C=C, aromatic), 1450 (C–H, aliphatic), 1371 (C=N), 1283, 1195 (C–S–C), 741, 759, 678, (C–H, deformation). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.28 (3H, s, CH_3), 4.57 (1H, s, –CH=), 6.13, 8.08 (1H × 3, s, NH), 7.25–7.89 (9H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 15.74 (C_{31}), 60.92 (C_{17}), 120.10–131.15 (C_{11}, C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 141.60 (C_{10}), 142.72 (C_{24}), 151.30 (C_8), 152.05 (C_{19}), 155.20 (C_2), 157.85 (C_5), 162.90 (C_7), Anal. Calcd. for $C_{21}H_{16}N_6O_2S$ (477.52): C, 60.56; H, 3.87; N, 20.18. Found: C, 60.10; H, 3.42; N, 20.03%.

5.1.1.4.8. 5-bromo-3-{[5-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4h***. Orange solid, Yield 79%, mp. 250–252 °C; MS: m/z [494.02]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3174, 2969, 2880 (C–H, aromatic), 1712, 1724 (C=O), 1633 (C=N, iminebase), 1478 (C–H, aliphatic), 1448 (C=C, aromatic), 1263, 1205 (C–S–C), 1377 (C=N), 743, 769, 670, (C–H, deformation), 630 (C–Br). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.25 (3H, s, CH_3), 4.55 (1H, s, –CH=), 6.15, 8.28 (1H × 3, s, NH), 7.22–8.14 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 15.10 (C_{31}), 60.15 (C_{17}), 118.40–133.95 (C_{11},C_{12},C_{13},C_{14},C_{15},C_{16}, C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 141.22 (C_{10}), 142.68 (C_{24}), 151.45 (C_{19}), 152.90 (C_8), 155.80 (C_2), 158.52 (C_5), 163.40 (C_7). Anal. Calcd. for $C_{21}H_{15}BrN_6O_2S$ (495.35): C, 50.92; H, 3.05; N, 16.97. Found: C, 50.71; H, 2.82; N, 16.58%.

5.1.1.4.9. 3-{[5-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-5-nitro-1,3-dihydro-2H-indol-2-one ***4i***. Yellow color, Yield 75%, mp. 253–254 °C; MS: m/z [461.09]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3318, 2945 (NH), 3129, 2989, 2855 (C–H, aromatic), 1720, 1749 (C=O), 1630 (C=N, iminebase), 1574 (N=O), 1454 (C–H, aliphatic), 1448 (C=C, aromatic), 1368 (C=N), 1273, 1175 (C–S–C), 723, 769, 690, (C–H, deformation). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.25 (3H, s, CH_3), 4.55 (1H, s, –CH=), 5.93, 8.03 (1H × 3, s, NH), 7.20–8.56 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 15.00 (C_{31}), 58.95 (C_{17}), 117.60 (C_{11}), 123.76–144.58 (C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{24},C_{25},C_{26},C_{27},C_{28},C_{29}), 148.95 (C_{10}), 150.05 (C_{19}), 151.35 (C_8), 155.90 (C_2), 158.68 (C_5), 163.50 (C_7). Anal. Calcd. for $C_{21}H_{15}N_7O_4S$ (461.45): C, 54.66; H, 3.28; N, 21.25. Found: C, 54.13; H, 2.82; N, 21.10%.

5.1.1.4.10. 5-fluoro-3-{[5-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4j***. Cream color, Yield 78%, mp. 214–216 °C; MS: m/z [435.10]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3244, 2922 (NH), 3115, 2979, 2852 (C–H, aromatic), 1724, 1701 (C=O), 1647 (C=N, iminebase), 1473 (C–H, aliphatic), 1453 (C=C, aromatic), 1368 (C=N), 1313 (C–F), 1290, 1222 (C–S–C), 782, 758, 699, (C–H, deformation). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.27 (3H, s, CH_3), 4.57 (1H, s, –CH=), 5.92, 8.26 (1H × 3, s, NH), 7.22–7.86 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 15.85 (C_{31}), 57.05 (C_{17}), 110.18–146.88 (C_{11},C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{24},C_{25},C_{26},C_{27},C_{28},C_{29}), 150.28 (C_{19}), 151.43 (C_8), 154.60 (C_{10}), 155.37 (C_2), 158.48 (C_5), 163.58 (C_7). Anal. Calcd. for $C_{21}H_{15}FN_6O_2S$ (434.35): C, 58.06; H, 3.48; N, 19.34. Found: C, 57.86; H, 3.26; N, 19.03%.

5.1.1.4.11. 5-iodo-3-{[5-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4k***. Reddish pink color, Yield 70%, mp. 218–220 °C; MS: m/z [442.45]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3332, 2922 (NH), 3154, 2998, 2890 (C–H, aromatic), 1729, 1749 (C=O), 1643 (C=N, iminebase), 1472 (C–H, aliphatic), 1468 (C=C, aromatic), 1371 (C=N), 1293, 1176 (C–S–C), 743, 749, 670, (C–H, deformation), 556 (C–I). ^{1}H-NMR [400 MHz, δ, ppm, DMSO-d$_6$]: 2.26 (3H, s, CH_3), 4.55 (1H, s, –CH=), 6.15, 8.15 (1H × 3, s, NH), 7.24–8.08 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d$_6$]: 16.15 (C_{31}), 58.70 (C_{17}), 91.80–137.58 (C_{11},C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 141.42 (C_{10}), 143.52 (C_{24}), 150.10 (C_8), 155.28 (C_2), 158.90 (C_5), 163.55 (C_7), 173.85 (C_{19}). Anal. Calcd. for $C_{21}H_{15}IN_6O_2S$ (542.35): C, 46.51; H, 2.79; N, 15.50. Found: C, 46.27; H, 2.58; N, 15.26%.

5.1.1.4.12. 5-chloro-3-{[5-(6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-yl]imino}-1,3-dihydro-2H-indol-2-one ***4l***. Reddish color, Yield 70%, mp. 225–227 °C; MS: m/z [450.07]$^+$; IR [ν_{max}, cm^{-1}, KBr]: 3334, 2936 (NH), 3174, 3018, 2867 (C–H, aromatic), 1730, 1749 (C=O), 1619 (C=N, iminebase), 1470 (C=C, aromatic), 1448 (C–H, aliphatic), 1359 (C=N), 1276, 1195

(C–S–C), 733, 759, 690, (C–H, deformation), 710 (C–Cl). ^{1}H- NMR [400 MHz, δ, ppm, DMSO-d_6]: 2.25 (3H, s, CH_3), 4.54 (1H, s, –CH=), 6.13, 8.22 (1H × 3, s, NH), 7.25–7.85 (8H, m, Ar–H). ^{13}C NMR [100 MHz, δ, ppm, DMSO-d_6]: 15.05 (C_{31}), 59.05 (C_{17}), 91.80–137.18 (C_{11},C_{12},C_{13},C_{14},C_{15},C_{16},C_{21},C_{25},C_{26},C_{27},C_{28},C_{29}), 141.10 (C_{10}), 143.30 (C_{24}), 150.70 (C_8), 151.90 (C_{19}), 155.28 (C_2), 157.98 (C_5), 164.88 (C_7). Anal. Calcd. for $C_{21}H_{15}ClN_6OS_2$ (542.35): C, 54.01; H, 3.24; N, 18.00. Found: C, 53.78; H, 3.08; N, 17.95%.

5.2. Biological activity

5.2.1. in vitro evaluation of antimicrobial activity

The antibacterial screening results are summarized in Tables 1 and 2 The MICs of synthesized compounds were carried out by broth Microdilution method. DMSO was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful (1 loop) evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was subcultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test included a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 μg/ml concentration, as a stock solution. In primary screening 500, 250 and 125 μg/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 μg/ml concentrations. The highest dilution showing at least 99% inhibition is taken as MIC (Table 1).

5.2.2. in vitro evaluation of antitubercular activity

Drug susceptibility and determination of MIC of the test compounds against M. tuberculosis H37Rv were performed by Lowenstein–Jensen (LJ) MIC method [29–32] where primary 1000, 500, 250, and secondary 200, 100, 62.5, 50, 25, 12.5, 6.25, 3.25 μg/ml dilutions of each test compound were added liquid Lowenstein–Jensen Medium and then media were sterilized by inspissation method. A culture of M. tuberculosis H37Rv growing on Lowenstein–Jensen Medium was harvested in 0.85% saline in bijou bottles. All test compound make first stock solution of 2000 μg/ml concentration of compounds was prepared in DMSO. These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* H37Rv (5×10^4 bacilli per tube). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 12, 22, and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* H37Rv. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC concentration of test compound. The standard strain M. tuberculosis H37Rv was tested with known drug rifampicin and isoniazid. The results of *in vitro* antitubercular activity are summarized in Table 3.

6. Conclusion

Tetrahydropyrimidinyl-1,3,4-thiadiazolylimino-1,3-dihydro-2H-indol-2-ones derivatives **4a–l** were synthesized and characterized for their structure elucidation. Various chemical and spectral data supported the structures of newly synthesized compounds. The Biginelli's reaction for preparation of tetrahydropyrimidinones derivatives **1a/1b** was efficiently carried out using $CaCl_2$ as catalyst. Compounds **4d** and **4j** showed significant antibacterial and antifungal activity. While the compound **4d** displayed promising antitubercular activity compared to standards. Thus, present library model can be used to design the new ligand of this class for their antimicrobial and antitubercular activity.

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