DESIGN, SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF SOME NOVEL 3-(4-SUBSTITUTED PHENYL)-2-(2-SUBSTITUTED-*1H*-INDOL-3-YL)-3, 4-DIHYDROIMIDAZO [4, 5-*B*] INDOLES

[1]S. M. Basavarajaiah, [2]K. N. Sheshandrakumara, [3]N. R. Sudharshan, [4]B. Lokesh
[1]Assistant Professor, [2, 3 and 4] Research Students
[1]P. G. Department of Chemistry,
[1]Vijaya College, R.V. Road, Basavanagudi, Bengaluru-560004, INDIA

Abstract: A series of some novel 3-(4-substituted phenyl)-2-(2-substituted-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indoles (5a-l) derivatives were prepared by the condensation of compounds containing 2-substituted-1*H*-indole-3-carbaldehydes (1a-c) and 4-substituted anilines (2a-d) to give respective 4-substituted-*N*-[(*E*)-(2-substituted -1*H*-indol-3-yl) methylidene] anilines (3a-l), which was further reacted with isatin (4) and ammonium acetate in the presence of glacial acetic acid. All the synthesized compounds were characterized by using spectral data like IR, ^{1}H NMR, FAB-Mass & Elemental analysis. All the synthesized compounds screened for their antimicrobial activity. Compounds 5b, 5c, 5g, 5j and 5k showed good activity against all the tested pathogens.

IndexTerms **–** Indole, Isatin, Indolo-imidazole, Antibacterial activity, Antifungal activity, Antitubercular activity.

I. INTRODUCTION

Tuberculosis (TB), an infection of *Mycobacterium tuberculosis*, still remains the leading cause of worldwide death among infectious diseases. One-third of the population is infected with *M. Tuberculosis* and the World Health Organization (WHO) estimates that within the next 20 years about 30 million people will be infected with the bacillus. Active disease following new infection, as well as reactivation of latent tuberculosis, is particularly prevalent in individuals with compromised immune systems, such as those that are HIV positive. Duration of the treatment of cases is very prolonged especially when caused by resistant bacteria [1].

Since last few decades, there is tremendous growth of research in the synthesis of nitrogen containing heterocyclic derivatives because of their utility in various applications, such as pharmaceuticals, propellants, explosives, pyrotechnics and especially in chemotherapy [2]. A largenumber of ring systems containing indole have been exhibited a wide variety of biological activities including anti-inflammatory [3], antiproliferative activity [4], sedatives [5], anti-anxiety [6], antioxidant & antimicrobial activities [7], anticonvulsant agents [8], antimalarial activity [9] and COX-2 inhibitors [10]. Many indolo-imadazole were reported in the literature have been found to possess bactericidal and fungicidal activities [11-14].

Since many years our studies have been focused on the search for new antibacterial agents [15-22] and in light of above findings, in the present work we synthesized a new series of some 3-(4-substitutedphenyl)-2-(2-substituted-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indoles **(5a-l)** having indole and indoloimidazole moieties in their structure with the hope getting compound with more potent antimicrobial activity by making use of bases 4-substituted-*N*-[(*E*)-(2-substituted -1*H*-indol-3-yl) methylidene] anilines (**3a-l**), isatin (**4**) and ammonium acetate in presence of glacial acetic acid (**Scheme 1**).

II. EXPERIMENTAL

2.1 General Procedures

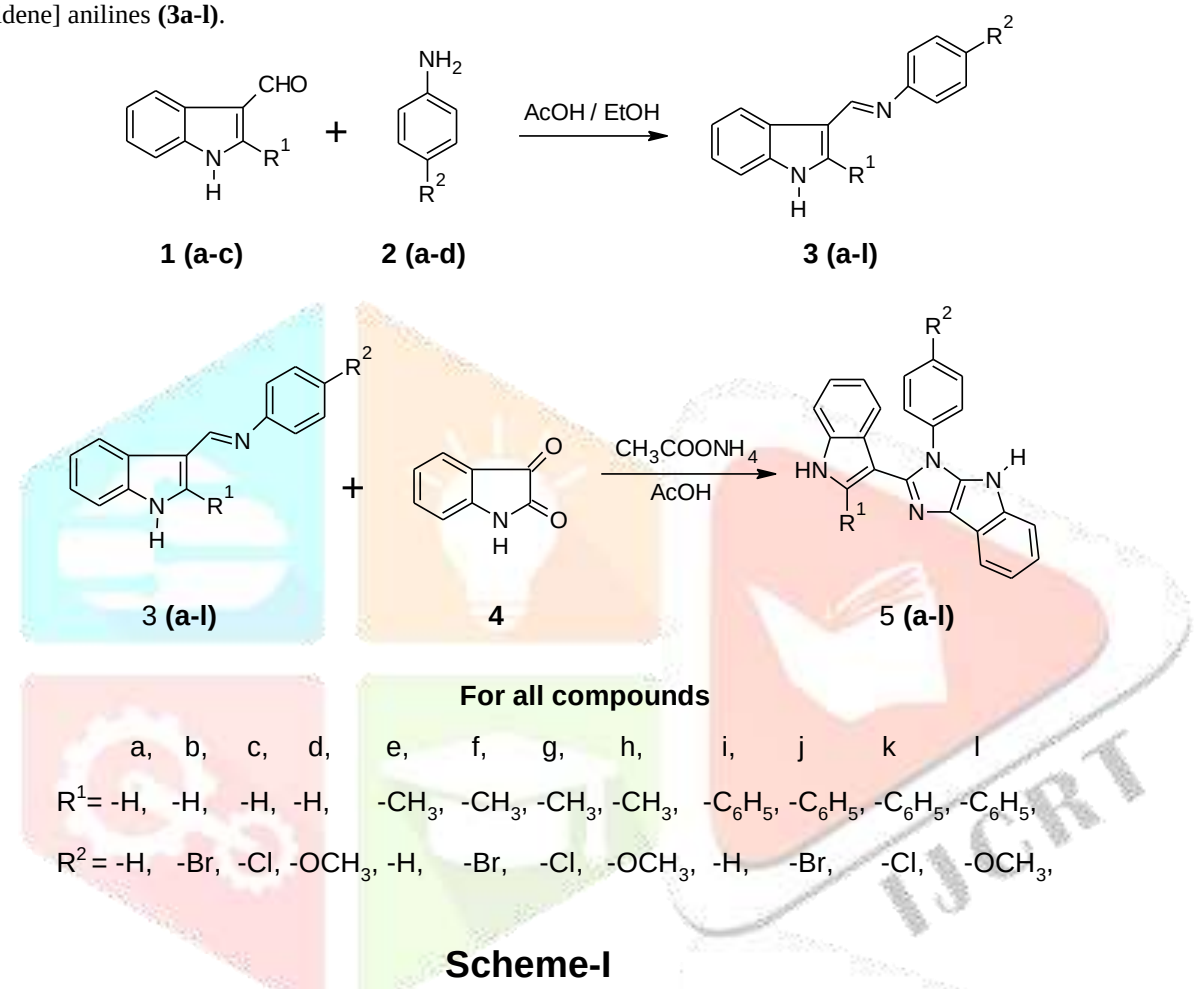
Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr discs (ν_{max} in cm^{-1}) on Perkin- Elmer FT-IR (Spectrum ONE) spectrophotometer, ^{1}H NMR spectra on a Bruker AMX (400 MHz) spectrophotometer using DMSO-d_6 as solvent using TMS as an internal standard (chemical shifts in δ) and mass spectra on a mass spectrometer JEOL sx-102 (FAB) instrument. Compounds were checked for their purity by TLC on silica gel 60G F254 plates and iodine vapours were used as visualizing agent. Elemental analysis carried out using Flash EA1112 series elemental analyzer.

2.2. Materials and Methods:

The starting materials 4-substituted-*N*-[(*E*)-(2-substituted-1*H*-indol-3-yl) methylidene] anilines (**3a-l**) was prepared according reported method [23] and were confirmed by physical and IR spectral data.

General procedure for the preparation of 4-substituted-*N*-[(*E*)-(2-substituted -1*H*-indol-3-yl) methylidene] anilines (3a-l):

2-Substituted-1*H*-indole-3-carbaldehyde (**1a-c**) (0.001 mol), 4-substituted anilines (**2a-d**) (0.001 mol) and a catalytic amount of glacial acetic acid were taken in ethanol (20 ml) and refluxed for 8 h on water bath. The resulting solids were filtered, washed with little alcohol, dried and purified by crystallization from 1, 4-dioxane to get 4-substituted-*N*-[(*E*)-(2-substituted -1*H*-indol-3-yl) methylidene] anilines **(3a-l)**.



Scheme-I

Fig-1: Various steps involved in the synthesis of title compounds 5 (a-l).

General procedure for the preparation of 3-(4-substituted phenyl)-2-(2-substituted-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indoles (5a-l):

Isatin **(4)** (0.001 M) and ammonium acetate (0.0015 M) were transferred into a round bottom flask containing the 4-substituted-*N*-[(*E*)-(2-substituted -1*H*-indol-3-yl) methylidene] anilines **(3a-l)** (0.001 M) and glacial acetic acid. The reaction mixture was constantly stirred and refluxed on thermostatically controlled heating plate with magnetic stirrer for about 10-12 hours. The completion of the reaction was monitored through TLC. The reaction mixture was poured into 250 ml of water contained in a beaker to remove ammonium acetate and acetic acid and it was filtered, dried in hot air oven and product was recrystallized by ethyl acetate to get 3-(4-substituted phenyl)-2-(2-substituted-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indoles **(5a-l)**.

3-Phenyl-2-(*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole (5a): Light brown crystals, Yield 82%, m. p. 221 ^{0}C; IR (KBr) in cm^{-1}: 3295, 3302, 1622 (NH, NH and C=N). ^{1}H NMR in δ: 6.69-8.15 (m, 14H, ArH), 10.31 (s, 1H, NH) and 10.51 (s, 1H, NH). FAB-MS m/z (in %): 349 (M+1). Anal. Requires for $C_{23}H_{16}N_4$: C, 79.29; H, 4.63; N, 16.08 %. Found: C, 79.35; H, 4.60; N, 16.04 %.

3-(4-Bromo phenyl)-2-(*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole (5b): Brown crystals, Yield 87%, m. p. 257 ^{0}C; IR (KBr) in cm^{-1}: 3304, 3349, 1630 (NH, NH and C=N). ^{1}H NMR in δ: 6.71-8.05 (m, 13H, ArH), 10.35 (s, 1H, NH) and 10.82 (s, 1H, NH). FAB-MS m/z (in %): 427.30. Anal. Requires for $C_{23}H_{15}BrN_4$: C, 64.65; H, 3.54; N, 13.11%. Found: C, 64.61; H, 3.61; N, 13.08 %.

3-(4-Chloro phenyl)-2-(*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole (5c): Light brown crystals, Yield 82%, m. p. 189 ^{0}C; IR (KBr) in cm^{-1}: 3291, 3341, 1634 (NH, NH and C=N). ^{1}H NMR in δ: 6.85-8.22 (m, 13H, ArH), 10.74 (s, 1H, NH) and 10.91 (s, 1H, NH). FAB-MS m/z (in %): 382.85. Anal. Requires for $C_{23}H_{15}ClN_4$: C, 72.16; H, 3.95; N, 14.63 %. Found: C, 72.15; H, 4.01; N, 14.74 %.

3-(4-Methoxy phenyl)-2-(*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5d): Light brown crystals, Yield 78%, m. p. 281^{0}C; IR (KBr) in cm^{-1}: 3281, 3332, 1625 (NH, NH and C=N). ^{1}H NMR in δ: 4.24 (s, 3H, OCH_3), 6.69-8.15 (m, 13H, ArH), 10.38 (s, 1H, NH) and 10.78 (s, 1H, NH). FAB-MS m/z (in %): 378.43. Anal. Requires for $C_{24}H_{18}N_4O$: C, 76.17; H, 4.79; N, 14.81%. Found: C, 76.22; H, 4.75; N, 14.82 %.

3-Phenyl-2-(2-methyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5e): Color crystals, Yield 89%, m. p. 274 ^{0}C; IR (KBr) in cm^{-1}: 3301, 3356, 1614 (NH, NH and C=N). ^{1}H NMR in δ: 1.21 (s, 3H, CH_3), 6.79-8.05 (m, 13H, ArH), 10.47 (s, 1H, NH) and 10.89 (s, 1H, NH). FAB-MS m/z (in %): 362.43. Anal. Requires for $C_{24}H_{18}N_4$: C, 79.54; H, 5.01; N, 15.46 %. Found: C, 79.35; H, 4.60; N, 16.04 %.

3-(4-Bromo phenyl)-2-(2-methyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5f): Light yellow crystals, Yield 84%, m. p. 204 ^{0}C; IR (KBr) in cm^{-1}: 3324, 3359, 1628 (NH, NH and C=N). ^{1}H NMR in δ: 1.28 (s, 3H, CH_3), 6.91-8.01 (m, 12H, ArH), 10.34 (s, 1H, NH) and 10.75 (s, 1H, NH). FAB-MS m/z (in %): 441.32. Anal. Requires for $C_{24}H_{17}BrN_4$: C, 65.32; H, 3.88; N, 12.70 %. Found: C, 65.35; H, 3.94; N, 12.67%.

3-(4-Chloro phenyl)-2-(2-methyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5g): Brown crystals, Yield 68%, m. p. 189 ^{0}C; IR (KBr) in cm^{-1}: 3315, 3373, 1628 (NH, NH and C=N). ^{1}H NMR in d: 1.30 (s, 3H, CH_3), 6.94-8.12 (m, 12H, ArH), 10.11 (s, 1H, NH) and 10.68 (s, 1H, NH). FAB-MS m/z (in %): 396.87. Anal. Requires for $C_{24}H_{17}ClN_4$: C, 72.63; H, 4.32; N, 14.12 %. Found: C, 72.65; H, 4.29; N, 14.18 %.

3-(4-Methoxy phenyl)-2-(2-methyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5h): Colorless crystals, Yield 79%, m. p. 174 ^{0}C; IR (KBr) in cm^{-1}: 3321, 3372, 1624 (NH, NH and C=N). ^{1}H NMR in δ: 1.01 (s, 3H, CH_3), 3.8 (s, 3H, CH_3), 6.91-7.98 (m, 12H, ArH), 10.51 (s, 1H, NH) and 10.94 (s, 1H, NH). FAB-MS m/z (in %): 362.43. Anal. Requires for $C_{25}H_{20}N_4O$: C, 76.51; H, 5.14; N, 14.28%. Found: C, 76.59; H, 5.19; N, 14.24 %.

3-(Phenyl)-2-(2-phenyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5i): Light brown crystals, Yield 85%, m. p. 201 ^{0}C; IR (KBr) in cm^{-1}: 3291, 3374, 1629 (NH, NH and C=N). ^{1}H NMR in δ: 6.79-8.38 (m, 18H, ArH), 10.42 (s, 1H, NH) and 10.95 (s, 1H, NH). FAB-MS m/z (in %): 424.50. Anal. Requires for $C_{29}H_{20}N_4$: C, 82.05; H, 4.75; N, 13.20 %. Found: C, 82.08; H, 4.69; N, 13.09 %.

3-(4-Bromo phenyl)-2-(2-phenyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5j): Light brown crystals, Yield 85%, m. p. 295 ^{0}C; IR (KBr) in cm^{-1}: 3242, 3381, 1619 (NH, NH and C=N). ^{1}H NMR in δ: 6.81-8.42 (m, 17H, ArH), 10.51 (s, 1H, NH) and 10.91 (s, 1H, NH). FAB-MS m/z (in %): 503.39. Anal. Requires for $C_{29}H_{19}BrN_4$: C, 69.19; H, 3.80; N, 11.13 %. Found: C, 69.14; H, 3.85; N, 11.08 %.

3-(4-Chloro phenyl)-2-(2-phenyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5k): Pale yellow crystals, Yield 87%, m. p. 267 ^{0}C; IR (KBr) in cm^{-1}: 3264, 3354, 1627 (NH, NH and C=N). ^{1}H NMR in δ: 6.59-8.12 (m, 17H, ArH), 10.49 (s, 1H, NH) and 10.81 (s, 1H, NH). FAB-MS m/z (in %): 458.94. Anal. Requires for $C_{29}H_{19}ClN_4$: C, 75.89; H, 4.17; N, 12.21 %. Found: C, 75.84; H, 4.19; N, 12.24 %.

3-(4-Methoxy phenyl)-2-(2-phenyl-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indole(5l): Colorless crystals, Yield 91%, m. p. 259 ^{0}C; IR (KBr) in cm^{-1}: 3242, 3385, 1634 (NH, NH and C=N). ^{1}H NMR in δ: 6.56-8.21 (m, 17H, ArH), 10.34 (s, 1H, NH) and 10.91 (s, 1H, NH). FAB-MS m/z (in %): 454.52. Anal. Requires for $C_{30}H_{22}N_4O$: C, 79.27; H, 4.88; N, 12.33 %. Found: C, 79.18; H, 4.79; N, 12.36 %.

2.3 ANTIMICROBIAL ACTIVITY

2.3.1. Antibacterial and antifungal activity [24]

The *in vitro* biological screening of the compounds was undertaken against the bacteria *S. aureus* (MTCC 3160) and *E. coli* (MTCC 46), fungi *A. niger* (MTCC1881) and *A. flaus* (1883) by cup-plate method using nutrient agar as medium. Then holes of 6 mm diameter were punched carefully using a sterile cork borer and these were filled with test solutions (5 & 10 mg/ml in DMF) and DMF used as control. The plates were incubated at 37^{0}C for 24 h in case of antibacterial activity and 72 h in case of antifungal activity. The diameter of the zone of inhibition for all the test compounds was measured and the results were compared with the standard drug Gentamycin for antibacterial activity and Nystatin for antifungal activity at the same concentration (5 and 10 mg/ml in DMF) as that test drugs and tabulated in **Table 1**.

2.3.2. Anti-tuberculosis activity [16]

Invitro antituberculosis testing was carried out against the human virulent strain *Mycobacterium tuberculosis* ($H37R_v$) by the method of disperse culture technique using Kirchner's medium method containing Tween-80. To sterile Kichner disperse medium (4.5 ml) dispersed in borosilicate test tube (150 x 20 mm), was added 0.5 ml of sterile normal bovine serum, inactivated by heating at 56^{0}C for 30 min.

The compounds under test were dissolved in DMF and added in the form of solution in such a way as to give final concentrations of 100, 50, 25, 12.5, 6.25, 3.12 and 1.56 µg/ml, the inoculums consisted of 0.1 ml of standard suspension of *M. tuberculosis* ($H37R_v$) containing 10^6 bacilli /ml. The tubes were incubated at 37^{0}C for eight days and then examined for the presence or absence of the

growth of the test organism. The lowest concentration that showed no visible growth was taken as an end point. The minimum inhibition concentration for all the test compounds was measured and the results were compared with the standard drug control tube with streptomycin and tube without any drug was kept for comparison i.e. only DMF and results were tabulated in **Table 1**.

III. RESULTS AND DISCUSSION

3.1. Chemistry

The various Schiff bases **(3a-l)** were prepared according to the procedure reported by our group [21]. These compounds **(3a-l)** when reacted with isatin **(4)** and sodium acetate in acetic acid afforded 3-(4-substitutedphenyl)-2-(2-substituted-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indoles **(5a-l)**in a good yield. Compound **5a** in its IR spectrum showed absorption bands at 1622, 3295 and 3302 cm^{-1} due to imidazole -C=N- and two indole NH functions respectively. A multiplet and two singlets were observed at 6.69-8.15 and 10.31 & 10.51δ in its ^1H NMR spectrum of compound **5a** were due to the thirteen aromatic protons and two protons of indole NH protons respectively. Mass spectrum of compound **5a** exhibited molecular ion peak M+1 at 349 (72%), which corresponds to its molecular weight. All these data proves the formation of compound **5a** from compound **4a**.

3.2. Antimicrobial activity

3.2.1. Antibacterial and antifungal activity

The results showed that the compounds **5b, 5c, 5g, 5j** and **5k** showed good activity and compounds **5d, 5f, 5h** and **5l** exhibited moderate activity against *S. aureus* when compared to that of standard drug Gentamycin. Compounds **5b, 5c, 5g, 5j** and **5k** showed good activity and compounds **5f, 5h** and **5l**exhibited moderate activity when compared to that of standard drug Gentamycin against *E .coli*. Compounds **5b, 5c, 5g, 5j** and **5k** showed good activity and compounds **5d, 5f, 5h** and **5l**exhibited moderate activity when compared to that of standard drug Nystatin against *A. Niger*. Compounds **5b, 5c, 5g, 5j** and **5k**showed good activity and compounds **5d, 5f** and **5h** exhibited moderate activity when compared to that of standard drug Nystatin against *A. flaus*. Rest of the compounds showed less activity against all the microorganisms tested. Under these conditions control *N*, *N*-dimethylformamide did not show any antimicrobial activity (**Table 1**).

3.2.2. Anti-tuberculosis activity

The results showed that the compounds **5b, 5c, 5g, 5j** and **5k** inhibited the growth of mycobacterium at concentration 6.5 μg/ml. Compounds **5d, 5f, 5h** and **5l** exhibited moderate activity when compared to that of standard drug Streptomycin against *M. tuberculosis*. Rest of the compounds tested showed less activity against the *M. tuberculosis*. Under these conditions standard Streptomycin was sensitive at concentration 6.25 μg/ml and control *N, N*-dimethylformamide did not show any antituberculosis activity (**Table 1**).

IV. CONCLUSIONS

The synthesis of the target novel compounds 3-(4-substituted phenyl)-2-(2-substituted-*1H*-indol-3-yl)-3, 4-dihydroimidazo [4, 5-*b*] indoles **(5a-l)** were achieved according to the steps indicated in **Scheme I**. These reactions are simple, easily carried under normal reaction conditions and these systems are novel and hitherto unknown.

All the newly synthesized compounds (**5a-l**) were tested for their antibacterial activity against *S. aureus,* & *E. coli* and antifungal activity against *A. niger* & *A. flavus.* Compounds **5b, 5c, 5g, 5j** and **5k** showed good activity against the above microorganisms tested when compared with those of standards Gentamycin and Nystatin which were used at the same concentration (5 and 10 mg/ml in DMF) as that of test drugs. All the newly synthesized compounds (**5a-l**) were tested for their antituberculosis activity against *M. tuberculosis.* Compounds **5b, 5c, 5g, 5j** and **5k** showed good activity when compared with standard drug Streptomycin.

Table 1. Antimicrobial activity of newly synthesized compounds 5(a-l).

Compds	Zone of inhibition in mm*								Anti-TB activity in MIC (μg / ml)
	Antibacterial activity				Antifungal activity				
	S. aureus		*E. coli*		*A. niger*		*A. flaus*		
	5 mg/ml	10 mg/ml	5 mg/ml	10 mg/ml	5 mg/ml	10 mg/ml	5 mg/ml	10 mg/ml	
5a	12	14	10	12	09	10	10	13	50
5b	17	18	17	18	18	19	17	18	6.25
5c	18	19	18	18	18	18	16	17	6.25
5d	14	15	13	14	14	15	15	16	12.50
5e	14	14	11	13	12	13	09	12	50
5f	15	16	13	15	13	15	14	16	12.50
5g	18	18	17	18	16	17	17	18	6.25
5h	16	16	15	16	13	15	16	16	12.50
5i	13	14	11	12	10	11	11	13	50
5j	17	18	18	17	15	17	17	18	6.25
5k	16	19	17	18	16	17	16	17	6.25

5l	15	16	14	15	13	16	12	14	12.50
Gentamycin	16	18	16	17	-	-	-	-	-
Nystatin	-	-	-	-	17	18	16	18	-
Streptomycin	-	-	-	-	-	-	-	-	6.25
Control (DMF)	-	-	-	-	-	-	-	-	-

*Diameter of well (bore size) - 6 mm,

V. ACKNOWLEDGEMENT

The authors gratefully acknowledged financial support from the University Grant Commission, India under minor research project (2029-MRP/15-16/KABA057/UGC-SWRO). The authors are thankful to the Directors, SIF IISc, Bengaluru for spectral data. Authors are also grateful to The Principal and Coordinator, P.G. Department of Chemistry, Vijaya College, R.V. Road, Basavanagudi, Bengaluru-5600004 for providing laboratory facilities.

REFERENCES

[1]. Ozlen, G. Nalan, T. Gultaze, C. and Aydin, S. 2006. Synthesis and biological evaluation of new 5-methyl-*N*-(3-oxo-1-thia- 4-azaspiro [4. 5] -dec-4-yl) -3-phenyl-1*H*-indole-2-carboxamide derivatives. *ARKIVOC*, 12: 98-110.

[2]. Yatin, J. M. Arun, M. I. Shridhar, M. Shrikrishna, I. and Hoong, K. F. 2013. Synthesis and antimicrobial activities of some novel 1, 2, 4-triazole derivatives. *Arabian J. Chem.*, 6: 177–181.

[3]. Preeti, R. Srivastava, S. K. and Ashok, K. 2004. Synthesis and anti-inflammatory activity of heterocyclic indole derivatives, *Euro. J. Med. Chem.*, 39(5): 449-452.

[4]. Narayana, B. Ashalatha, B.V. Vijaya Raj, K. K. and Sarojini, B. K. 2009. Synthesis and studies on antimicrobial, anti-inflammatory and antiproliferative activities of heterocycles derived from 4-/5-/6-7/-nitro/5-fluoro/chloro/bromoindole-2-carbohydrazides, *Indian J. Chem.*, 48B: 1794-1805.

[5]. Sudo, G. Z. Sudo, L. B. Gabriel, D. Mendes, T. C. F. Ribeiro, N. M. Pinto, A. C. Trachez, M. M. and Sudo, R. R. 2007. Sedative-hypnotic profile of novel isatin ketals. *Pharma. Biochem. Behaviour*, 86: 678-85.

[6]. Athina, G. Eugeni, B. John, D. Wim, D. Dmitrii, F. Irina, G. Valentina, K. Alexey, L. Fliur, M. Guenadiy, M. Vladimir, P. Serghei, P. Victor, S. Alla, S. Eugenia, S. Natalia, T. Liudmila, V. and Tatiana, V. 2004. Design, synthesis, computational and biological evaluation of new anxiolytics, *Bioorg. Med. Chem.*, 12: 6559-6568.

[7]. Saundane, A. R. Manjunatha, Y. Prabhaker, W. and Vaijanatha, K. 2010. Synthesis, antioxidant and antimicrobial evaluation of thiazolidinone, azetidinone encompassing indolylthienopyrimidines, *J. Chem. Sci.*, 124(2): 469-481.

[8]. Adel, H. Mandour, Eslam R. E. Kamel, H. S. and Mohamed, A. M. 2010, Synthesis, anti-inflammatory, analgesic and anticonvulsant activities of 1, 8-dihydro-1-aryl-8-alkyl pyrazolo(3, 4-b) indoles, Acta Pharm., 60: 73-88.

[9]. Schuck, D. C. Jordao, A. K. Nakabashi, M. Cunha, A. C. Ferreira, V. F. and Garcia, C. R. 2014. Synthetic indole and melatonin derivatives exhibit antimalarial activity on the cell cycle of the human malaria parasite plasmodium falciparum, *Euro. J. Med. Chem.*, 6(78): 375-382.

[10]. Asit, K.C. Sanjeev, and G. Rajkumar Pradeep, J. 2010. Progress in COX-2 inhibitors: A journey so far, *Curr. Med. Chem.*, 17(15): 1563-1593.

[11]. Nitin Kumar. Munirajan, S. and Prabu M. 2007. Pharmacological evaluation of some indoloimidazoles, *Asian J. Chem.*, 19(5): 4124-4126.

[12]. Kumar, N. Sharma, P. K. Garg, and V. K. Singh, P. 2011. Synthesis and anticonvulsant activity of novel substituted phenyl indoloimidazole derivatives. *Current Research in Chemistry*, 3: 114-120.

[13]. Biradar, J. S. Praveen, S. M. Sasidhar, B. S. Parveen, R. 2008. One pot synthesis of substituted imidazoles containing indole and antimicrobial activities, *Org. Chem. Ind. J.*, 4(6-8): 408-411.

[14]. Biradar, J. S. Sasidhar, B. S. and Praveen, S. M. 2012. One-pot, solvent free synthesis of 2, 5-disubstituted indolylimidazoles by microwave radiation, *Der Pharma Chemica*, 4(1): 437-441.

[15]. Basavarajaiah, S. M. and Mruthyunjayaswamy, B. H. M. 2009. Synthesis and antimicrobial activity of some new 5-substituted-*N*1 [(1*E*)-(2-hydroxyquinolin-3yl) methylene] -3-phenyl-1*H*-indole-2-carbohydrazide, *Heterocyclic Comm*., 15(3): 217-224.

[16]. Basavarajaiah, S. M. and Mruthyunjayaswamy, B. H. M. 2009. Synthesis and Antimicrobial Activity of Some 5-Substituted-3-phenyl-*N*b-(Substituted-2-oxo-2*H*-pyrano [2, 3-*b*] quinoline-3-carbonyl)-1*H*-indole-2-carboxyhydrazide.*Chem Pharma Bull*. 57(6): 557-560.

[17]. Mruthyunjayaswamy, B. H. M. and Basavarajaiah, S. M. 2009. Synthesis and antimicrobial activity of novel ethyl-5-(ethoxy carbonyl)-4-methylthiazol-2-yl-carbmate compounds. *Indian J. Chem.*, 48B: 1274-1278.

[18]. Basavarajaiah, S. M. and Mruthyunjayaswamy, B. H. M. 2010. Synthesis and anti-microbial activity of (*Z*) -4-(4-substituted-thiazol-2-yl) -1-(2-oxoindolin-3-ylidene) semicarbzide and its derivatives. *Indian J. Chem.*, 49B: 1117-1126.

[19]. Mruthyunjayaswamy, B. H. M. Shanthaveerappa, B. K. and Basavarajaiah, S. M. 2010, Synthesis and antimicrobial activity of 5-substituted-2-phenyl-3-(o-carboethoxyphenyl) iminomethyl indoles and their derivatives. *J. Indian Chem. Soc.*, 87(9): 1109-1115.

[20]. Basavarajaiah, S. M. and Mruthyunjayaswamy, B. H. M. 2016. Synthesis and antimicrobial activity of novel 5-substituted-*N*-(substituted-*2H*-[1,3]oxazino[6,5-b]quinolin-3(*4H*)-yl)-3-phenyl-*1H*-indole-2-carboxamides, *Indian J. Chem.*, 55B: 1511-1519.

[21]. Sheshandrakumar, K. N. Srividya, J. Narayanaswamy, B. J., Umesha, K., Basavarajaiah S. M., Synthesis and evaluation of biological activity of some new 3, 7-substituted 2*h*-pyrano/thiopyrano[2, 3-*b*] quinolin-2-ones, *Indian J. of Hetero. Chem.*, **2017**, 27(3), 281-288.

[22].Basavarajaiah, S. M. and Mruthyunjayaswamy, B. H. M. 2018. Synthesis and antimicrobial activity of some 5-chloro-3-phenyl-*1H*-indole-2-carbonyl azide derivatives, *Indian J. Chem.*, 57B: 390-399.

[23]. Mruthunjayaswamy B. H. M. and Shanthaveerappa B. K. 1998. Synthesis and pharmacological evaluation of 3, 5-disubstituted indole-2-[*Nβ*(substituted benzopyran-2-one-3-carboxyl)] carboxy hydrazides and *2H-3*- (various substituted indol-3' -yl) methyl-l , 3-benzothiazoles. *Indian J. Heterocyclic Chem.*, 8: 31-38.

[24]. Nagesh, G. Y. Mahadev, D. U. and Mruthunjayaswamy B. H. M. 2016. Synthesis, characterization, mass spectral fragmentation, thermal study and biological evaluation of new Schiff base ligand and its metal(II) complexes derived from 4-(diethylamino) salicylaldehyde and thiazole moiety. *Eur. J. Chem.*, 7(1): 56-68.