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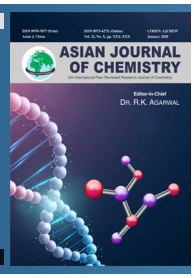

Synthesis, Characterization & Antimicrobial Activities of New Isoxazole Substituted Mannich and Schiff Bases of 5-Nitroisatin Analogs

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A sequence of new isoxazole substituted Schiff base and Mannich base of 5-nitroisatin are synthesized by a multi-step synthesis from 5-nitroisatin. Whole synthesized analogs were characterized using IR, NMR, Mass spectroscopy and microanalyses. All the Schiff and Mannich bases were tested for their antimicrobial potencies against some human pathogenic microorganism using agar well diffusion technique. The relationship between the biological activity and the functional group variation of the Schiff and Mannich bases were analyzed. Standard ciprofloxacin and ketoconazole were used to compare the antimicrobial activities of novel isatin coupled isoxazole derivatives.

Keywords: Isatin, Isoxazole, 5-Nitroisatin, Microbial activity.

INTRODUCTION

In contemporary medicine infections produced by microbes are a rising crisis and it is unavoidable to use antibiotics. In current medicine a serious and a growing phenomenon is antibiotic resistance. Pertains to pathogenic organisms in 21st century one of the well-known public health problem is antibiotic resistance. Tropical part of Africa, part of South America and Indian subcontinent are worst affected by enteric bacterial infections mortality. In the simplest cases to the 1st line antibiotics resistance were developed by drug resistant microorganisms, thus forcing the utilization of 2nd line antibiotics. In general on account of numerous advantages such as cost, availability and safety only the 1st line agents are preferred compared to 2nd line drugs, which are generally possess fewer positive risk benefit profile, wide spectrum of activity and might be costly or, in terrible conditions, unavailable locally. Thus, treatment of microbial infections remains as a challenging therapeutic problems. Therefore particularly against drug resistant bacteria and fungi it is in need of time to prepare novel group of antimicrobial drugs [1-7].

In recent years, heterocyclic compounds attained more significance because of its widespread applications and properties in the chemistry fields. Out of various known heterocyclic compounds isatin and its derivatives were identified as one of the important analog. Isatin have emerged as antimicrobial agents due to its broad *in vivo* & *in vitro* chemotherapeutic agents. For examples, 4-(4-bromophenyl)-1-(6-chloro-2-oxoindolin-3-ylidene)semicarbazide has shown a promising activity in both antibacterial and antifungal screenings. Spiro-[indole]thiadiazole derivatives showed better antimicrobial activity than standard streptomycin. 6-(4-((2,3-Dioxoindolin-1-yl)methyl)piperazin-1-yl)-1-ethyl-5-fluoro-4-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylic acid displayed five times more potent activity against *B. subtilis* than standard norfloxacin. In addition, isatins having phenyl ring with substitution at 3rd position and heterocyclic substitution at 1st position produced more active compounds with good antimicrobial activity [8-13].

Alternatively, due to its associated pharmacological and physiological properties isoxazole have gained importance. In addition, antibacterial drugs like sulphamethoxazole, sulfisoxazole and semi-synthetic penicillin such as floxacillin, diclo-

xacillin, cloxacillin and oxacillin contains isoxazole moiety [14-16].

Since, the isatin moiety seems to have various pharmacological properties, we planned to prepare derivatives with this ring system attached with isoxazole as probable antimicrobial drugs which might deliver enhanced beneficial activities. Taking into consideration the particulars as stated and as part of our initial pains to ascertain potentially active novel drugs, a variety of novel isoxazole substituted isatin derivatives (**4a-k**) were synthesized and examined for its antimicrobial potency.

EXPERIMENTAL

Using open capillaries melting points were measured and are uncorrected in melting point apparatus (Thomas Hoover). On Bruker FT-IR spectrometer, IR spectra were measured using KBr disks. At 300 MHz, ^{1}H NMR spectra was documented in $CDCl_3$ using Bruker FT-NMR spectrometer in ppm using internal standard TMS. Similarly at 125 MHz, ^{13}C NMR spectra was documented using Bruker FT-NMR spectrometer in ppm using $CDCl_3$ as standard (internal). Fast atom bombardment (FAB) positive was used to record mass spectra in JEOL-SX-102 instrument. Elemental analysis was measured on Perkin-Elmer 2400 CHN analyzer. Experimental values were compared against calculated values and found to be within the satisfactory confines (± 0.4 %). UV lamp and iodine were used as developing agent to detect the compounds. In this study, entire chemicals and reagents were obtained from Qualigens, C.D.H., E. Merck India Ltd. and S.D. Fine Chem, and used without additional purification.

Synthesis of 3-(4-acetylphenylimino)-5-nitroindolin-2-one (1): In round bottomed flask, equimolar quantities (0.01 mol) of *p*-amino acetophenone and 5-nitroisatin was dissolved in 25 mL of ethanol. For the period of 10 h in water bath, the above mixture was refluxed. The obtained mixtures were kept in room temperature for some times to cool and poured into ice-bath. The resulting mixture was kept aside in room temperature overnight. The solid settled down was filtered and dried in open. Ethanol was used to recrystallize the obtained product.

Synthesis of 3-(4-acetylphenylimino)-1-((dimethylamino)-methyl)-5-nitroindolin-2-one (2): In a beaker, 2.16 g of 3-(4-acetylphenylimino)-5-nitroindolin-2-one (**1**) (0.007 mol), 0.32 g of dimethylamine (0.007 mol), 0.3 g of formaldehyde (0.01 mol) and 25 mL ethanol were mixed. The mixture was stirred mechanically for 3 h, followed by refluxation in water bath for a period of 6 h. The resulting solutions were cooled and poured into ice cold water. The compound formed was filtered and recrystallized from alcohol.

Synthesis of 1-((dimethylamino)methyl)-5-nitro-3-(4-(3-(substituted phenyl)acryloyl)phenylimino)indolin-2-one (3a-k): To a equimolar quantities (0.003 mol) of various aromatic aldehydes and 3-(4-acetylphenylimino)-1-((dimethylamino)-methyl)-5-nitroindolin-2-one (**2**) in 25 mL ethanol, 100 mg of pellet NaoH were added and the mixture was magnetically stirred for 2 h. Latter, stirred solutions were refluxed in water bath for a period of 8 h. After refluxing, obtained solutions were poured into ice (crushed) and kept overnight in refrigerator. The solid obtained were filtered, dried and recrystallized using alcohol.

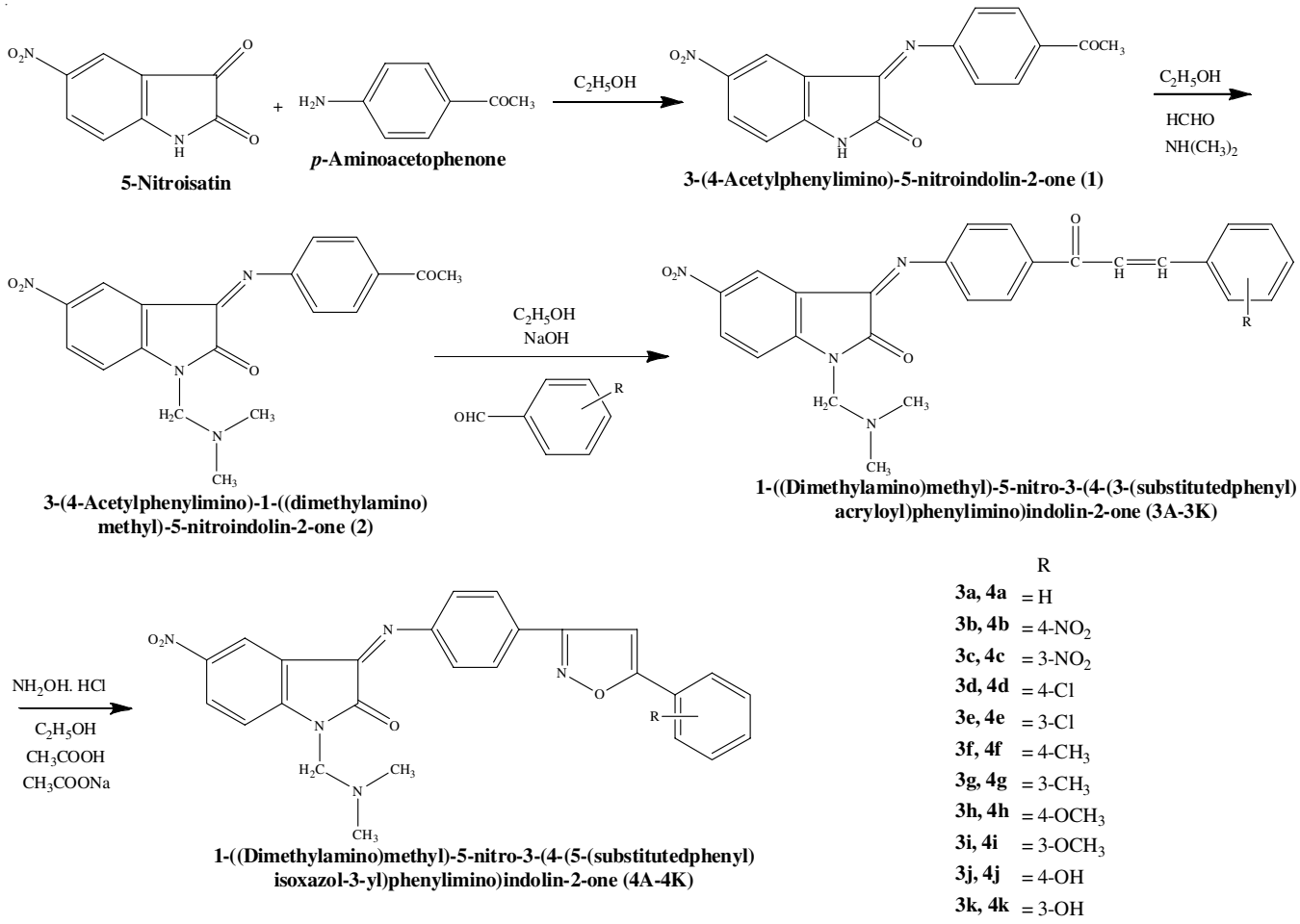
Synthesis of 1-((dimethylamino)methyl)-5-nitro-3-(4-(5-(substituted phenyl)isoxazol-3-yl)phenylimino)indolin-2-one (4a-k): To a 25 ml ethanol, 0.05 mol 1-((dimethylamino)-methyl)-5-nitro-3-(4-(3-(substituted phenyl)acryloyl)phenyl-imino)indolin-2-one (**3a-k**) was added. To this mixture, 0.05 mol of hydroxylamine hydrochloride, sodium acetate (catalytic quantity) and glacial acetic acid (catalytic quantity) were added. The resulting solutions were mixed well and refluxed for 15 h. To a ice cold water, refluxed and cooled mixture was poured and stirred vigorously. The compounds formed was filtered, dried and recrystallized from alcohol.

Antimicrobial activity: The antimicrobial activities of all the Schiff and Mannich bases were evaluated by agar streak dilution technique. The antibacterial potency of all the bases were screened against four Gram-positive bacteria (*B. cereus* ATCC 11778, *S. epidermidis* ATCC 155, *S. aureus* ATCC 9144 and *M. luteus* ATCC 4698) and thre Gram-negative bacteria (*E. coli* ATCC 25922, *P. aeruginosa* ATCC 2853 and *K. pneumoniae* ATCC 11298). The antifungal potencies of the prepared analogs are examined against two fungi (*A. fumigatus* ATCC 46645 and *A. niger* ATCC 9029). In Mueller-Hinton broth at 37 ºC bacterial strains were cultured overnight for antibacterial activity screening. Similarly, in yeast extract peptone dextrose (YEPD) agar at 30 ºC the yeast was cultured over night for antifungal activity screening. Nutrient agar was used to suspend the test strains to get 5×10^{-5} cfu/mL final density [17].

Minimum inhibitory concentration (MIC): Agar streak dilution technique was used to determine the MIC of synthesized compounds. Dimethyl formamide were employed to prepare 100 µg/mL stock solution of synthesized derivatives. To specified quantities of molten sterile agar graded quantities of synthesized derivatives were added. Title compounds incorporated medium (a specified quantity) was poured into a petridish at 40-50 ºC to give a 3-4 mm depth and permitted to solidify. Microorganism suspensions were made ready in such a way to have around 5×10^{-5} cfu/mL. Latter microorganism was applied to the petri-plates containing successively diluted test derivatives in DMF and incubated for one day and two days at 37 ºC for bacteria and fungi, respectively.

RESULTS AND DISCUSSION

The sequence of reaction leads to the synthesis of new isoxazole substituted Schiff and Mannich bases of isatins **4a-k** is outlined in **Scheme-I**. Initially by condensation reaction, 5-nitroisatin was reacted with 4-aminoacetophenone to synthesize 3-(4-acetylphenylimino)-5-nitroindolin-2-one (**1**), which particularly carried on C-3 carbonyl group of isatin nucleus selectively. Further by Mannich reaction, analog **1** were reacted with dimethylamine and formaldehyde to produce 3-(4-acetyl-phenylimino)-1-((dimethylamino)methyl)-5-nitroindolin-2-one (**2**). In next step, consequent Schiff base analogs (**3a-k**) were isolated by treating isatin Mannich base **2** in presence of NaOH with various heterocyclic or aromatic aldehydes. Lastly through simple ring closure reaction corresponding isoxazoles (**4a-k**) were obtained in presence of glacial acetic acid and sodium acetate from Schiff base derivatives (**3a-k**) by treating with hydroxylamine hydrochloride. The reactions were optimized throughout the experiment for completion and purity by TLC.



Scheme-I: Synthetic protocol of title compounds (**4a-k**)

IR, NMR, mass and microanalyses were used to confirm the chemical structure prepared analogs. Spectral data were found to be in agreement with structures assigned. All synthesized compounds characterization data are presented in Tables 1-3.

TABLE-1
IR SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS (**1, 2, 3a-k, 4a-k**)

Code	OH	NH	Ar-CH	H_3C-CH	HC=CH	C=O	C=N	C=C	NO_2	C-O-C	Cl
1	–	3372	3092	2997	–	1731	1664	1626	1540 & 1335	–	–
2	–	–	3059	2975	–	1752	1643	1638	1524 & 1347	–	–
3a	–	–	3049	2931	2864	1728	1636	1607	1517 & 1358	–	–
3b	–	–	3082	2968	2845	1760	1653	1604	1559 & 1323	–	–
3c	–	–	3013	2915	2872	1750	1658	1639	1534 & 1321	–	–
3d	–	–	3039	2952	2857	1748	1661	1620	1545 & 1356	–	–
3e	–	–	3007	2948	2825	1726	1649	1611	1543 & 1367	–	749
3f	–	–	3091	2947	2835	1750	1656	1610	1532 & 1334	–	–
3g	–	–	3064	2972	2859	1714	1653	1620	1522 & 1345	–	–
3h	–	–	3076	1989	2850	1736	1664	1605	1529 & 1313	1033	–
3i	–	–	3058	2903	2846	1709	1665	1618	1551 & 1336	1046	–
3j	3509	–	3023	2920	2848	1742	1649	1635	1534 & 1321	–	–
3k	3470	–	3085	2959	2883	1763	1647	1622	1536 & 1343	–	–
4a	–	–	3050	2975	–	1718	1654	1622	1541 & 1333	–	–
4b	–	–	3082	2954	–	1758	1631	1604	1527 & 1335	–	–
4c	–	–	3047	2939	–	1726	1623	1605	1555 & 1322	–	–
4d	–	–	3069	2976	–	1733	1649	1627	1512 & 1345	–	787
4e	–	–	3071	2948	–	1732	1640	1635	1539 & 1316	–	760
4f	–	–	3084	2992	–	1718	1653	1610	1545 & 1354	–	–
4g	–	–	3069	2951	–	1747	1632	1609	1526 & 1337	–	–
4h	–	–	3096	2963	–	1725	1646	1623	1526 & 1320	1031	–
4i	–	–	3050	2927	–	1754	1646	1628	1558 & 1345	1045	–
4j	3479	–	3073	2980	–	1749	1627	1601	1534 & 1351	–	–
4k	3482	–	3085	2944	–	1721	1639	1615	1547 & 1342	–	–

TABLE-2
NMR SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS (**1, 2, 3a-k, 4a-k**)

Code	$N(CH_3)_2$ (s, 6H)	CH_3 (s, 3H)	OCH_3 (s, 3H)	CH_2 bridge (s, 2H)	OH (s, 1H)	CH of isoxazole (s, 1H)	Ar-CH (m)		CH=CH (d, 1H)	CH=CH (d, 1H)	NH of isatin (s, 1H)
							Value	No. of H			
1	–	2.84	–		–	–	7.19-8.26	7	–	–	8.91
2	2.48	2.75	–	4.15	–	–	7.02-8.18	7	–	–	–
3a	2.46	–	–	4.30	–	–	7.05-8.21	12	8.64	8.82	–
3b	2.28	–	–	4.14	–	–	7.39-8.05	11	8.21	8.57	–
3c	2.19	–	–	4.53	–	–	6.82-7.94	11	8.37	8.55	–
3d	2.53	–	–	4.39	–	–	7.16-8.32	11	8.55	8.78	–
3e	2.60	–	–	4.26	–	–	7.13-8.17	11	8.59	8.64	–
3f	2.42	2.68	–	4.25	–	–	7.01-8.19	11	8.40	8.76	–
3g	2.54	2.75	–	4.47	–	–	7.01-8.38	11	8.84	8.90	–
3h	2.17	–	3.89	4.21	–	–	6.84-8.06	11	8.33	8.63	–
3i	2.31	–	3.70	4.54	–	–	6.97-8.15	11	8.39	8.56	–
3j	2.25	–	–	4.08	5.43	–	6.72-7.80	11	8.12	8.59	–
3k	2.47	–	–	4.32	5.54	–	7.18-8.03	11	8.46	8.71	–
4a	2.52	–	–	4.36	–	6.38	7.00-8.29	12	–	–	–
4b	2.35	–	–	4.10	–	6.67	7.16-8.43	11	–	–	–
4c	2.43	–	–	4.09	–	6.26	6.92-7.90	11	–	–	–
4d	2.59	–	–	4.35	–	6.54	6.87-7.72	11	–	–	–
4e	2.30	–	–	4.14	–	6.42	7.15-8.03	11	–	–	–
4f	2.64	2.82	–	4.48	–	6.31	7.03-7.89	11	–	–	–
4g	2.38	2.60	–	4.25	–	6.29	7.24-8.41	11	–	–	–
4h	2.26	–	3.75	4.12	–	6.50	7.18-8.14	11	–	–	–
4i	2.45	–	3.89	4.37	–	6.43	7.01-8.26	11	–	–	–
4j	2.31	–	–	4.23	5.37	6.28	7.36-8.59	11	–	–	–
4k	2.57	–	–	4.21	5.43	6.35	6.89-7.98	11	–	–	–

TABLE-3
MASS SPECTRAL & ELEMENTAL ANALYSIS DATA OF THE SYNTHESIZED COMPOUNDS (**1, 2, 3a-k, 4a-k**)

Code	Yield (%)	m.p. (°C)	m.f.	MS (EI) $[M^+; M^{+2}]$	Elemental analysis (%): Calcd. (found)		
					C	H	N
1	77	185-187	$C_{16}H_{11}N_3O_4$	309	62.14 (62.35)	3.58 (3.57)	13.59 (13.54)
2	73	219-220	$C_{19}H_{18}N_4O_4$	366	62.29 (62.43)	4.95 (4.97)	15.29 (15.24)
3a	75	165-167	$C_{26}H_{22}N_4O_4$	454	68.71 (68.48)	4.88 (4.90)	12.33 (12.37)
3b	79	179-181	$C_{26}H_{21}N_5O_6$	499	62.52 (62.68)	4.24 (4.23)	14.02 (13.98)
3c	70	190-191	$C_{26}H_{21}N_5O_6$	499	62.52 (62.71)	4.24 (4.25)	14.02 (13.97)
3d	73	153-155	$C_{26}H_{21}N_4O_4Cl$	488; 490	63.87 (64.05)	4.33 (4.34)	11.46 (11.42)
3e	71	161-163	$C_{26}H_{21}N_4O_4Cl$	488; 490	63.87 (63.69)	4.33 (4.35)	11.46 (11.49)
3f	78	204-206	$C_{27}H_{24}N_4O_4$	468	69.22 (69.03)	5.16 (5.18)	11.96 (11.99)
3g	75	157-159	$C_{27}H_{24}N_4O_4$	468	69.22 (68.99)	5.16 (5.17)	11.96 (12.00)
3h	77	198-200	$C_{27}H_{24}N_4O_5$	484	66.93 (66.75)	4.99 (4.97)	11.56 (11.54)
3i	72	182-183	$C_{27}H_{24}N_4O_5$	484	66.93 (67.12)	4.99 (4.95)	11.56 (11.50)
3j	78	186-188	$C_{26}H_{22}N_4O_5$	470	66.37 (66.54)	4.71 (4.73)	11.91 (11.95)
3k	79	174-176	$C_{26}H_{22}N_4O_5$	470	66.37 (66.61)	4.71 (4.70)	11.91 (11.88)
4a	77	238-240	$C_{26}H_{21}N_5O_4$	467	66.80 (66.59)	4.53 (4.54)	14.98 (15.02)
4b	74	206-207	$C_{26}H_{20}N_6O_6$	512	60.94 (60.73)	3.93 (3.94)	16.40 (16.45)
4c	71	262-264	$C_{26}H_{20}N_6O_6$	512	60.94 (61.10)	3.93 (3.91)	16.40 (16.36)
4d	76	224-226	$C_{26}H_{20}N_5O_4Cl$	501; 503	62.22 (62.01)	4.02 (4.04)	13.95 (13.99)
4e	70	259-261	$C_{26}H_{20}N_5O_4Cl$	501; 503	62.22 (62.04)	4.02 (4.00)	13.95 (13.98)
4f	73	247-250	$C_{27}H_{23}N_5O_4$	481	67.35 (67.53)	4.81 (4.80)	14.54 (14.49)
4g	79	213-214	$C_{27}H_{23}N_5O_4$	481	67.35 (67.60)	4.81 (4.79)	14.54 (14.48)
4h	77	232-234	$C_{27}H_{23}N_5O_5$	497	65.18 (64.95)	4.66 (4.68)	14.08 (14.13)
4i	71	265-267	$C_{27}H_{23}N_5O_5$	497	65.18 (64.98)	4.66 (4.68)	14.08 (14.11)
4j	76	251-253	$C_{26}H_{21}N_5O_5$	483	64.59 (64.81)	4.38 (4.37)	14.49 (14.43)
4k	74	227-228	$C_{26}H_{21}N_5O_5$	483	64.59 (64.85)	4.38 (4.36)	14.49 (14.44)

Antimicrobial activity: Entire title derivatives were tested for its anti-microbial potency by *in vitro* method. Against all microorganisms, MICs of all prepared derivatives were determined. In parallel experiments, ciprofloxacin and ketoconazole's MIC were also estimated with the aim of controlling test organism sensitivity. In Table-4, antimicrobial potencies of synthesized derivatives were compared effectively with that of standard drugs. Against entire tested fungi and bacteria, all

TABLE-4
MINIMUM INHIBITORY CONCENTRATION (MIC, µg/mL) OF SYNTHESIZED COMPOUNDS (**4a-k**)

Compounds	*S. aureus*	*S. epidermidis*	*M. luteus*	*B. cereus*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*	*A. niger*	*A. fumigatus*
4a	50	25	25	50	25	25	50	50	50
4b	25	6.25	12.5	6.25	12.5	6.25	6.25	25	12.5
4c	50	25	25	12.5	50	12.5	25	50	50
4d	12.5	6.25	12.5	6.25	12.5	12.5	6.25	25	12.5
4e	50	25	25	25	25	25	25	50	50
4f	25	12.5	6.25	12.5	25	12.5	12.5	25	25
4g	50	50	25	50	25	25	50	50	50
4h	25	12.5	12.5	6.25	12.5	12.5	12.5	50	50
4i	50	50	50	100	50	25	100	50	100
4j	25	12.5	12.5	12.5	25	12.5	12.5	50	25
4k	100	50	100	100	50	50	100	50	100
Ciprofloxacin	12.5	6.25	6.25	6.25	12.5	6.25	3.13	–	–
Ketoconazole	–	–	–	–	–	–	–	12.5	6.25

derivatives exhibited significant activity. Derivatives **4b** and **4d** displayed excellent antimicrobial potencies against all tested microorganisms, whereas derivatives **4a**, **4f**, **4h** and **4j** displayed moderate antimicrobial activities and remaining analogs **4c**, **4e**, **4g**, **4i** and **4k** showed weaker activities.

The present outcome exposed that the majority of synthesized compounds displayed significant antimicrobial activity. On connecting the structures of title compounds with its antimicrobial properties, it was found that the most potent antimicrobial properties displayed by derivatives **4b** and **4d** could be owing to isoxazole nucleus attached phenyl ring substituent present at *para*-position. Similarly due to the above said rationale compounds **4f**, **4h** and **4j** also displayed potent antimicrobial activities. Though other derivatives containing substituent at *meta* position to phenyl moiety joined to isoxazole ring (**4c**, **4e**, **4g**, **4i** and **4k**) didn't showed good antimicrobial (*in vitro*) potency. Moderate activity was showed by unsubstituted analog **4a**. SAR studies of prepared derivatives exposed that the analogs possessing *para* position substituent at phenyl group joined to isoxazole ring displayed greater potency than corresponding *meta*-position substituent. Additionally, it was noted that within same position electron withdrawing moiety analog displayed superior activity than electron donating group analog.

Conclusion

Briefly, a sequence of new 1-((dimethylamino)methyl)-5-nitro-3-(4-(5-(substituted phenyl)isoxazol-3-yl)phenylimino)-indolin-2-one derivatives (**4a-k**) were synthesized and characterized. Against nine different strains of microorganism by *in vitro* method these synthesized derivatives were tested for its antimicrobial potency. On the whole, *para*-substituted analogs displayed superior antimicrobial potencies than *meta*- substituted derivatives. Moreover, within same position electron withdrawing moiety analogs displayed superior activity than electron donating group analogs. Among the tested analogs, compounds **4b** and **4d** displayed highest antimicrobial activity than any other tested analogs. Hence in the future for antimicrobial drug development these derivatives can act as valuable lead.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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