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Comparative studies on conventional and microwave-assisted synthesis of novel indole derivatives and their antimicrobial activities

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ABSTRACT

The 2, 5-disubstituted Indole 3-carboxaldehydes (**1a-e**) on crossed aldol condensation reaction with 2-acetoacetamido-pyridine (**2**) yields (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamides (**3a-e**). The (E)-2-((5', 2'-disubstituted-1H-indol-3-yl) methylene)-3-oxo-N-(pyridine-2''-yl) butanamides (**3a-e**) undergoes cyclocondensation reaction with hydrazine hydrate in the presence of glacial acetic acid in ethanol yields 1-acetyl-5-(5', 2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)-1H-pyrazole-4-carboxamides (**4a-e**) and with hydroxyl amine hydrochloride in the presence of potassium hydroxide yields 5-(5', 2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl) isoxazole-4-carboxamides (**5a-e**). These Indole derivatives were synthesized under conventional and microwave assisted conditions and found evidently that Microwave irradiation method reduces time of reactions, improves the yields and reproducibility over conventional method. The structures of the products thus obtained are confirmed by their analytical and spectroscopic analysis. Newly synthesized compounds (**3a-e**), (**4a-e**) and (**5a-e**) were evaluated for *In-vitro* antimicrobial activities against various microbial strains and most of the molecules have displayed significant antimicrobial activities.

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KEYWORDS

Carboxamido pyridines;
2, 5-disubstituted indoles;
Green chemistry;
Isoxazoles;
Microwave assisted
organic synthesis (MAOS);
Pyrazolines.

INTRODUCTION

Indole and its derivatives occupied a unique place in the chemistry of nitrogen heterocyclic compounds because of their varied biodynamic properties^[1-4]. In recent years, there are increasing numbers of reports on the synthesis of Indole analogs for their agrochemical anthelmintic activity and COX-II enzyme inhibitory activity^[5,6]. Pyrazoline and isoxazole derivatives are of great interest, because of their biological and pharmacological activities. Several pyrazoline derivatives are

found to have antiproteolytic^[7], antifungal^[8], chemotherapeutic^[9] and various industrial applications^[10]. A number of substituted isoxazole derivatives are reported to possess anti-inflammatory^[11], sedative and antiviral^[12-14] activities. In addition, green chemistry momentum is gaining in the field of organic synthesis; emphasis is on devising new methods of synthesizing potentially important bioactive molecules in eco-friendly environment^[15]. Microwave assisted reactions with short reaction times are becoming more popular for organic chemists^[16,17], due to user and eco-friendly nature, and synthesis can

be performed on a preparative scale^[18,19]. In continuation of our interest on synthesis of bioactive Indole analogs^[20,21] and green chemistry^[22], we have employed synthesis of novel Indolyl pyrazolins and isoxazoles containing carbaxamido pyridine using conventional and microwave irradiation methods. The comparison study of both the methods and benefits associated with the microwave assisted organic synthesis have been studied. All newly synthesized Indole analogs subjected to antimicrobial activities against various microbial strains.

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr on Perkin-Elmer Spectrum-one FTIR Spectrophotometer (ν max in cm^{-1}) and ^1H NMR spectra on a DSX 300 MHz FTNMR Spectrometer (Chemical shift in δ ppm down field from TMS as an internal reference). The Mass spectra were recorded on LC-MSD-Trap-SL instruments and Microwave reactions are carried out in BPL-700T560W multimode domestic microwave oven.

Method A: Conventional

General procedure for synthesis of (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamides (3a-e)

A mixture of 3-Oxo-N-(Pyridin-2-yl) butanamide (**2**) (0.01 mol) and an 2,5-disubstituted-1H-indole-3-carboxaldehyde (**1a-e**) (0.01 mol) was fused for 10–15 min under oil bath and the resulting mass was cooled and crystallized from ethanol to yield (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamide (**3a-e**)

General procedure for synthesis of 1-acetyl-5-(5', 2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)-1H-pyrazole-4-carboxamides (4a-e)

A mixture of (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamide (**3a-e**) (0.005 mol), hydrazine hydrate (0.035 mol) in glacial acetic acid (10mL) in ethanol (50mL) were refluxed for 480-540 min. The resulting solution was concentrated, cooled and poured over ice water. The yellow

product separated was filtered, washed and then crystallized from suitable solvent to yield 1-acetyl-5-(5', 2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)-1H-pyrazole-4-carboxamide (**4a-e**)

General procedure for synthesis of 5-(5', 2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyrido-2-yl)isoxazole-4-carboxamides (5a-e)

The mixture of (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamide (**3a-e**) (0.005 mol), hydroxylamine hydrochloride (0.005 mol), ethanol (50 mL) and potassium hydroxide (0.005 mol) were refluxed for 720-750 min. The resulting mixture was concentrated, cooled and poured in to ice water. The deep yellow compound obtained was filtered, washed and crystallized from suitable solvent to yield 5-(5', 2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyrido-2-yl)isoxazole-4-carboxamide (**5a-e**).

Method B: Microwave assisted organic synthesis (MAOS)

General procedure for synthesis of (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamides (3a-e)

A mixture of 3-Oxo-N-(Pyridin-2-yl) butanamide (**2**) (0.01 mol) and 2,5-disubstituted-1H-indole-3-carboxaldehyde (**1a-e**) (0.01 mol) were introduced in to open borosil glass vessel and then placed in a domestic microwave oven (BPL-700T) and zapped the contents for 2–4 min at 560 watts with microwave irradiation. Upon completion of reaction (monitored by TLC). The resulting mass was cooled and crystallized from suitable solvent to yield (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamide (**3a-e**).

General procedure for synthesis of 1-acetyl-5-(5', 2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)-1H-pyrazole-4-carboxamides (4a-e)

A mixture of (E)-2-((5', 2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl) butanamide (**3a-e**) (0.005 mol), hydrazine hydrate (0.035 mol) in presence of Glacial acetic acid (10mL) in ethanol (50mL) were introduced in to open borosil glass vessel. This

5,2-disubstituted indole-3-carboxaldehydes (**1a-d**) were prepared according to the literature procedures^[23,24]. The condensation of 2-acetoacetamidopyridine (**2**) with 2,5-disubstituted-1H-indole-3-carboxaldehyde (**1a-e**) is performed under neat reaction condition to afford compound (E)-2-((5',2'-disubstituted-1H-indol-3-yl) methylene)-3-oxo-N-(pyridine-2''-yl)butanamide (**3a-e**). As monitor by TLC, reaction under thermal condition completes in 10 to 15 minutes but in microwave irradiation furnished only 3.20 to 3.22 minutes with increased yield, this is carried out in open borosil vessel using BPL-700T domestic microwave oven with 560 watts microwave irradiation. The obtained products (**3a-e**) was characterized by analytical and spectral analysis. Differences found in reaction time and yields of the mol-

ecules (**3a-e**) with respect to conventional and microwave irradiation method with characterization data are depicted in TABLE 1 & 2. Further cyclocondensation of compounds (**3a-e**) were conducted with the nitrogen nucleophiles hydrazine hydrate in the presence of acetic acid and with hydroxylaminehydrochloride in the presence of potassium hydroxide in ethanol to obtain 1-acetyl-5-(5',2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)-1H-pyrazole-4-carboxamides (**4a-e**) and 5-(5',2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)isoxazole-4-carboxamides (**5a-e**) respectively. These reactions were carried out at elevated temperature conventionally and 560 watts microwave irradiation using BPL-700T domestic microwave oven. The completion of reactions was at 480

TABLE 2 : Characterization data of (E)-2-((5', 2'-disubstituted-1H-indol-3-yl) methylene)-3-oxo-N-(pyridine-2''-yl) butanamides (3a-e)

Comp. No.	Substituents R (R')	M.P. (°C)	Elemental analysis Found (%) (calcd)			Spectral data (IR (KBr) ν_{max} in cm^{-1} / ¹ HNMR (DMSO) in δ / Mass in m/z)
			C	H	N	
3a	Cl (Ph)	270	69.28 (69.31)	4.34 (4.36)	10.06 (10.10)	3163 (NH), 3055 (Amide NH), 1627/1581 (C=O/C=O); 2.5(s, 3H, -CH ₃), 6.2(s, 1H, Ar-CH), 6.9-7.9(m, 12H, ArH), 9.4(s, 1H, Amide NH). 11.8(s, 1H, Indole NH).
3b	CH ₃ (Ph)	184	75.90 (75.93)	5.32 (5.35)	10.61 (10.63)	2858(NH), 2731(NH), 1765(CO), 1654(CO). 2.24(s, 3H, -CH ₃), 2.4(s, 3H, Ar-CH ₃), 6.5(d, 1H, Ar-CH), 6.5-7.8(m, 12H, ArH) 8.2(s, 1H, Amide NH). 11.3(s, 1H, Indole NH).
3c	H (Ph)	210	75.53 (75.57)	5.00 (5.02)	11.01 (11.02)	3117(NH), 3063(NH), 1633(CO), 1579(CO). 2.3(s, 3H, -CH ₃), 6.5(d, 1H, Ar-CH), 6.8-7.9(m, 13H, ArH) 9.4(s, 1H, Amide NH). 11.8(s, 1H, Indole NH).
3d	H (Me)	280	71.44 (71.46)	5.35 (5.37)	13.14 (13.16)	3253(NH), 3043(NH), 1678(CO), 1595(CO), 2.3(s, 3H, -CH ₃), 2.34(s, 3H, Ar-CH ₃), 6.7(d, 1H, Ar-CH), 6.8-7.9(m, 8H, ArH) 8.8(s, 1H, Amide NH). 11.6(s, 1H, Indole NH).
3e	H (H)	180	70.82 (70.81)	4.94 (4.95)	13.74 (13.76)	2818(NH), 2739(NH), 1635(CO), 1515 (CO); 2.31(s, 3H, -CH ₃), 2.34(s, 3H, Ar-CH ₃), 6.7(d, 1H, Ar-CH), 6.8-7.9(m, 9H, ArH) 8.4(s, 1H, Amide NH). 11.4(s, 1H, Indole NH).

TABLE 3 : Characterization data of 1-acetyl-5-(5',2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)-1H-pyrazole-4-carboxamide (4a-e) and 5-(5',2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl) isoxazole-4-carboxamides (5a-e).

Cpd. No.	Substituents R (R')	M.P. (°C)	Elemental analysis Found (%) (calcd)			Spectral data (IR (KBr) ν_{max} in cm^{-1} / ¹ HNMR (DMSO) in δ / Mass in m/z)
			C	H	N	
4a	Cl (Ph)	195	66.15 (66.17)	4.68 (4.70)	14.80 (14.84)	3008(NH), 2923 (NH), 1651 (CO), 1578 (CO); 2.4 δ (s, 3H, CH ₃), 3 δ (s, 3H, CH ₃), 3.2 δ (d, 1H, CO-CH), 6.7 δ (d, 1H, Ar-CH), 7.2-8.4 δ (m, 12H, ArH), 9.0 δ (s, 1H, CONH), 10.0 δ (s, 1H, Indole NH); 471 (M+1) (18%), 473 (M+2) (4.5%)
4b	CH ₃ (Ph)	170	71.80 (71.82)	5.52 (5.58)	15.48 (15.51)	3116(NH), 2919(NH), 1719(CO), 1695(CO), 1553 (C=N); 2.1 δ (s, 3H, N-COCH ₃), 2 δ (s, 3H, Pyr-CH ₃), 2.2 δ (s, 3H, Indole-CH ₃), 3.4 δ (d, 1H, CO-CH), 6.6 δ (d, 1H, Ar-CH), 7.2-8.4 δ (m, 12H, ArH), 10.4 δ (s, 1H, NH), 10.0 δ (s, 1H, CONH)

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Cpd. No.	Substituents R (R')	M.P. (°C)	Elemental analysis Found (%) (calcd)			Spectral data (IR (KBr) ν_{\max} in cm^{-1} / ^1H NMR (DMSO) in δ / Mass in m/z)
			C	H	N	
4c	H (Ph)	225	71.32 (71.38)	5.29 (5.30)	16.00 (16.01)	3207(NH), 3065(NH), 1651(CO), 1615(CO), 1455(C=N); 2.14 δ (s, 3H, N-COCH ₃), 1.9 δ (s, 3H, Pyr-CH ₃), 3.2 δ (d, 1H, CO-CH), 6.3 δ (d, 1H, Ar-CH), 7-8.5 δ (m, 13H, ArH), 11.4 δ (s, 1H, NH), 10.0 δ (s, 1H, CONH)
4d	H (Me)	285	67.15 (67.18)	5.63 (5.64)	18.62 (18.65)	3043(NH), 2913(NH), 1696(CO), 1600(CO); 2.2 δ (s, 3H, N-COCH ₃); 2 δ (s, 3H, Pyr-CH ₃), 2.2 δ (s, 3H, Indole-CH ₃), 3.6 δ (d, 1H, CO-CH), 6.6 δ (d, 1H, Ar-CH), 7.4-8.0 δ (m, 7H, ArH), 11.5 δ (s, 1H, IndoleNH), 10.2 δ (s, 1H, CONH)
4e	H (H)	188	66.44 (66.47)	5.27 (5.30)	19.33 (19.38)	3318(NH), 3053(NH), 1675(CO), 1463(C=N), 1259(-O-); 2.0 δ (s, 3H, N-COCH ₃), 1.9 δ (s, 3H, Pyr-CH ₃), 3.3 δ (d, 1H, CO-CH), 5.6 δ (d, 1H, Ar-CH), 7.4-8.2 δ (m, 9H, ArH), 11.4 δ (s, 1H, IndoleNH), 10.6 δ (s, 1H, CONH)
5a	Cl (Ph)	188	66.76 (66.90)	4.45 (4.44)	12.88 (13.00)	3240 (indole NH), 3055 (amide NH), 1666 (C=O), 1550 (C=N) and 1149(-O-); 3.3 δ (s, 3H, CH ₃), 4.3 δ (d, 1H, COCH), 6.2 δ (d, 1H, Ar-CH), 6.9-7.9 δ (m, 12H, ArH), 11.8 δ (s, 1H, IndoleNH). 9.7 δ (s, 1H, CONH); 430 (M+) (2%), 432 (M+2) (0.6%), 227 (100%)
5b	CH ₃ (Ph)	195	73.12 (73.15)	5.39 (5.40)	13.63 (13.65)	3431(NH), 3032(NH), 1603(CO), 1315(-O-); 2.8 δ (s, 3H, CH ₃), 2.3 δ (s, 3H, Indole-CH ₃), 3.3 δ (d, 1H, COCH) 5.8 δ (d, 1H, Ar-CH) 7.0-7.9 δ (m, 12H, ArH), 10.8 δ (s, 1H, CONH). 11.2 δ (s, 1H, NH)
5c	H (Ph)	238	72.69 (72.71)	6.06 (5.08)	14.10 (14.13)	3435(NH), 3169(NH), 1617(CO), 1452(C=N); 3.2 δ (s, 3H, CH ₃), 4.4 δ (d, 1H, COCH), 5.3 δ (d, 1H, Ar-CH), 6.8-7.9 δ (m, 13H, ArH), 10.8 δ (s, 1H, CONH). 11.2 δ (s, 1H, IndoleNH)
5d	H (Me)	185	68.22 (68.25)	5.40 (5.43)	16.74 (16.76)	3356(NH), 2919(NH), 1675(CO), 1459(C=N), 1259(-O-), 2.28 (s, 3H, Indole-CH ₃), 3.3 δ (s, 3H, CH ₃), 4.4 δ (d, 1H, COCH), 4.7 δ (d, 1H, Ar-CH) 6.8-7.9 δ (m, 8H, ArH) 10.6 δ (s, 1H, CONH). 10.8 δ (s, 1H, IndoleNH)
5e	H (H)	255	67.45 (67.49)	5.00 (5.03)	17.46 (17.49)	3389(NH), 2963(NH), 1599(CO), 1434(C=N), 1100(-O-), 3.2 δ (s, 3H, CH ₃), 4.2 δ (d, 1H, COCH) 4.4 δ (d, 1H, Ar-CH) 6.5-8.1 δ (m, 9H, ArH) 10.6 δ (s, 1H, CONH). 10.9 δ (s, 1H, NH)

to 720 minutes in conventional heating and 3.10 to 3.40 min microwave irradiation with increments in yield of the product (TABLE 1).

The comparison studies of conventional and microwave assisted organic synthesis of novel Indole derivatives with respect to reaction time and yield of the products are listed in TABLE 1. Synthesized remaining compounds of the series (4a-e) and (5a-e) are characterized with their spectral and analytical reports and are tabulated in TABLE 3. The reactions of compounds (4a-e) and (5a-e) are remarkably influenced by the microwave irradiation than conventional heating in respect of reaction time and yield. Microwave irradiation method is evidently proved that it consumes very less reaction time, excellent improvement in yields and improved reproducibility.

ANTIMICROBIAL ASSAY

The antibacterial activities of compounds (3a-e), (4a-e) and (5a-e) were carried out using Cup-plate diffusion method^[25] and antibacterial species used are two Gram negative species *Escherichia coli*, *Pseudomonas aeruginosa* and two Gram positive species *Bacillus subtilis*, *Staphylococcus aureus*. Four fungal strains *Aspergillus niger*, *Penicillium chrysogenum*, *Aspergillus flavus*, *Aspergillus fumigatus* are used for antifungal activity. Solution of each compound at a concentration of 100 μg /0.1 mL in DMF was prepared and the inhibition zone diameter in centimeter (IZD) was used as the criterion for measure the microbial activity. Gentamycin, Ciprofloxacin were used as bacterial standards and Fluconazole,

Greseofulvin were used as fungal standards for references to evaluate the efficacy of the tested compounds under the same conditions. Dimethyl farmamide used as control and solvent to prepare compound solutions as 10 mg per 10 mL. The results are depicted in TABLE 4. Compounds (3a), (3c), (3d), (3e), (4b), (4e), (5a), (5b), (5c) and (5e) have shown significant activities to-

TABLE 4 : In vitro antimicrobial assay of newly synthesized (3a-e), (4a-e) and (5a-e) compounds

Comp's. (R,R')	Zone of inhibition in mm							
	Antibacterial activity			Antifungal activity				
	<i>E.coli</i>	<i>P.aeruginosa</i>	<i>S.aureus</i>	<i>B.subtilis</i>	<i>A.niger</i>	<i>P.chrysogonium</i>	<i>A.flavus</i>	<i>A.fumigatus</i>
3a (Cl,Ph)	17	16	15	22	15	14	10	17
3b (Me,Ph)	16	14	16	16	17	10	10	16
3c (H,Ph)	17	15	12	13	21	12	18	12
3d (H,Me)	18	16	13	21	18	10	10	10
3e (H,H)	15	17	14	14	11	10	11	22
4a (Cl,Ph)	16	14	12	17	12	10	12	10
4b (Me,Ph)	17	18	17	14	11	13	17	10
4c (H,Ph)	17	14	17	15	14	12	10	10
4d (H,Me)	18	13	14	14	14	15	11	10
4e (H,H)	17	19	16	19	10	12	25	12
5a (Cl,Ph)	21	22	14	23	17	15	19	15
5b (Me,Ph)	14	19	17	16	10	16	14	11
5c (H,Ph)	14	14	17	16	16	13	13	16
5d (H,Me)	15	15	15	15	10	11	13	10
5e (H,H)	17	18	14	12	15	13	11	10
Gentamicin	18	18	21	23	-	-	-	-
Ciprofloxacin	19	20	19	24	-	-	-	-
Fluconazole	-	-	-	-	18	15	23	18
Greseofulvin	-	-	-	-	20	18	18	16
DMF(Ctrl)	08	08	08	08	08	08	08	08

ward various bacterial strains and compounds (3c), (3d), (4b), (4e), and (5a) have displayed highest activities towards various fungal strains and remaining compounds are moderate to weekly active.

CONCLUSION

Compound (E)-2-((5',2'-disubstituted-1H-indol-3-yl)methylene)-3-oxo-N-(pyridine-2''-yl)

butanamides (3a-e) and their cyclocondensed product 1-acetyl-5-(5',2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)-1H-pyrazole-4-carboxamides (4a-e) and 5-(5',2'-disubstituted-1H-indol-3-yl)-4,5-dihydro-3-methyl-N-(pyridine-2-yl)isoxazole-4-carboxamide (5a-e) were synthesized under conventional and microwave-assisted conditions. Then comparison studies of both the methods have been carried out and found evidently that microwave-assisted synthesis reduces reaction time from hours to minutes and also improves the yields of the product. The products obtained were characterized by using analytical and spectral analysis. Synthesized compounds (3a-e), (4a-e) and (5a-e) series were screened for *in-vitro* antimicrobial activities using cup-plate diffusion method and compounds (5a), (3c), (3e) and (4e) displayed significantly active in comparison with standard used in antimicrobial assay.

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