Synthesis and Antimicrobial Activity of 3-Substituted Phenyl-5-(5′-Substituted-2′-Phenylindol-3′-yl)-1,2-Diazoles and 3-Substituted Phenyl-5-(5′-Substituted-2′-Phenylindol-3′-yl)-Isoxazoles

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5-Substituted-2-phenylindol-3-carboxaldehydes **(Ia–c)** were condensed with substituted acetophenones **(IIa–h)** in ethylene glycol and catalytic amount of piperidine afforded 5-substituted-2-phenylindol-3-chalcones **(IIIa–x)**. These compounds, on reaction with hydrazine hydrate in absolute alcohol and hydroxylamine hydrochloride in alcoholic sodium hydroxide yielded 3-substituted phenyl-5-(5′-substituted-2′-phenylindol-3′-yl)-1,2-diazoles **(IVa–x)** and 3-substituted phenyl-5-(5′-substituted-2-phenylindol-3′-yl) isoxazoles **(Va–x)**, respectively. The newly sysnthesised compounds were characterised by their analytical and spectral data. All these compounds were screened for antimicrobial activity against *S. aureus*, *E. coli*, *A. niger* and *C. albicans*.

INTRODUCTION

The nitrogen heterocycles have received considerable attention in recent years due to their biological and physiological activities. Pyrazolines[1–6] represent one of the most active classes of compounds possessing a wide spectrum of biological activities. The isoxazolines have been reported to possess antidiabetic[7, 8], diuretic[9], analgesic[10, 11], anthelmintic[12], hypolipemic[13] and antimicrobial[14] activities. The biological significance of pyrazolines and isoxazolines have instilled inerest to synthesise several derivatives of these heterocylic systems containing indol nucleus. In continuation of our earlier work on the synthesis of biologically active indole derivatives[15–17], we have synthesised various pyrazolines and isoxazolines containing indole moiety and screened for their antimicrobial activity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in nujol mull Hitachi 270–50 double beam spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ on Jeol Model GSX 400 spectrophotometer using TMS as an internal standard and mass spectra on GC-LC/MS spectrophotometer.

Preparation of 5-substituted-2-phenyl indol-3-carboxaldehydes (Ia–c)

The starting compounds, 5-substituted-2-phenyl indol-3-carboxaldehydes **(Ia–c)** were prepared according to the literature method[18].

Preparation of 5-substituted-2-phenyl indol-3-chalcones (IIIa–x)[19]

5-substituted-2-phenyl indol-3-carboxaldehydes **(Ia–c)** (0.01 mol) and subs-

tituted acetophenones (**IIa–h**) (0.01 mol) were taken in ethylene glycol (15 mL). To this reaction mixture, piperidine (1 mL) was added and the resulting mixture was heated at 160–80°C for 4 h. The contents were cooled and decomposed in ice-cold water containing 1 mL of acetic acid. The yellow solid thus separated was filtered, washed thoroughly with water, dried and recrystallised from suitable solvents (Table-1).

IR: For compound (IIIr): 1620 cm^{-1} ν(C=O), 3440 cm^{-1} ν(NH) and 1600 cm^{-1} ν(C=C).

^{1}H-NMR: For compound (IIIr): 2.4 δ (s, 3H, CH_3), 12.4 δ (s, 1H, NH), and 7.3–8.2 δ (m, 12H, Ar—H, and 2H, —CH—).

Mass: For compound (IIIr): m/z-371, 373 (M^+, $C_{24}H_{18}NOCl$), 251, 253, 216, 188, 189, 119, 91 and 57.

Preparation of 3-substituted phenyl-5-(5′-substituted-2′-phenyl indol-3′-yl)-1,2-diazoles (IVa–x)

5-Substituted-2-phenyl indol-3-chalcones (**IIIa–x**) (0.005 mol) and hydrazine hydrate (99%, 0.005 mol) in absolute alcohol (20 mL) was refluxed on a water bath for 8 h, cooled to room temperature, decomposed by pouring into crushed ice. The separated product was filtered, washed with water, dried and crystallised from suitable solvent (Table-1).

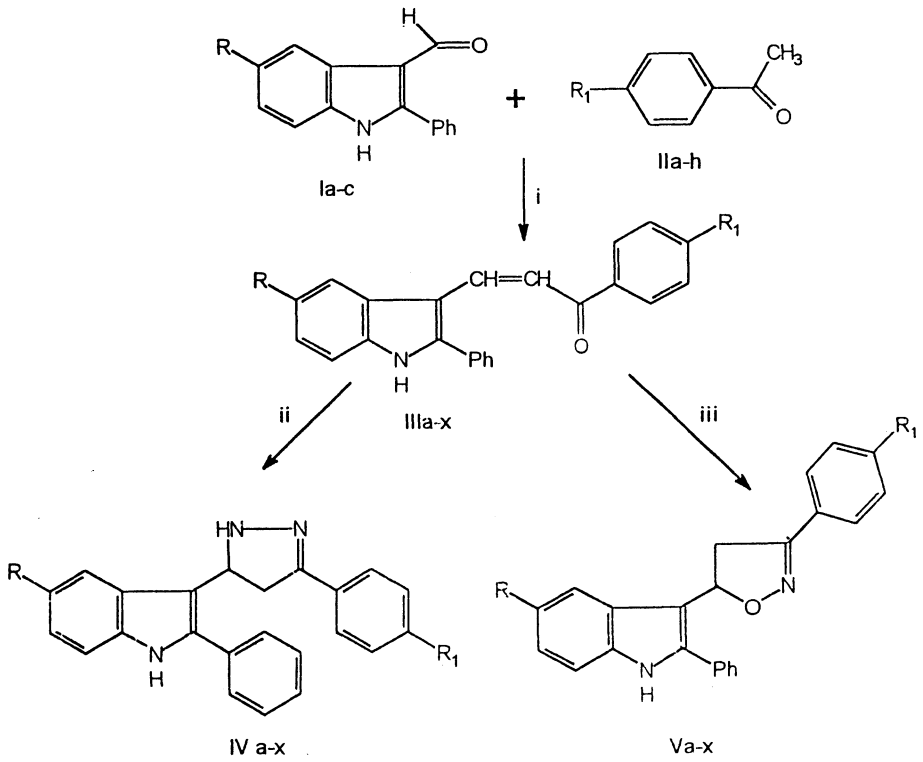
IR: For compound (IVr): 1610 cm^{-1} ν(C=N) and 3100, 3250 cm^{-1} ν(NH, NH).

^{1}H-NMR: For compound (IVr): 2.5 δ(s, 3H, CH_3), 12.2 δ (s, 1H, indole NH), 8.9 δ (s, 1H, pyrazoline NH), 3.3–3.5 δ (3H, ABX pattern —CH—CH_2— of pyrazoline ring) and 7.3–8.0 δ (m, 12H, Ar—H).

Mass: For compound (IVr): m/z-383, 385 (M^+, $C_{24}H_{20}N_3Cl$), 367, 263, 251, 253, 239, 216, 190, 119, 98 and 55.

(i) Ethylene glycol/piperidine (ii) $H_2N{\cdot}NH_2$ (99%)/EtOH (iii) $HO{\cdot}NH_2{\cdot}HCl$/ NaOH in EtOH

	R	R_1		R	R_1
a.	H	H	**m.**	CH_3	4′-NO_2
b.	H	4′-CH_3	**n.**	CH_3	4′-OH
c.	H	4′-Br	**o.**	CH_3	5′-CH_3-2′-OH
d.	H	4′-NH_2	**p.**	CH_3	5′-Cl-2′-OH
e.	H	4′-NO_2	**q.**	Cl	H
f.	H	4′-OH	**r.**	Cl	4′-CH_3
g.	H	5′-CH_3-2′-OH	**s.**	Cl	4′-Br
h.	H	5′-Cl-2′-OH	**t.**	Cl	4′-NH_2
i.	CH_3	H	**u.**	Cl	4′-NO_2
j.	CH_3	4′-CH_3	**v.**	Cl	4′-OH
k.	CH_3	4′-Br	**w.**	Cl	5′-CH_3-2′-OH
l.	CH_3	4′-NH_2	**x.**	Cl	5′-Cl-2′-OH



Preparation of 3-substituted phenyl-5-(5′-substituted-2′-phenyl indol-3′-yl)-isoxazoles (Va–x)

5-Substituted-2-phenyl indol-3-chalcones **(IIIa–x)** (0.01 mol), hydroxylamine hydrochloride (0.02 mol), NaOH (0.9 g) in ethanol (20 mL) were refluxed on a water bath for 14 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid product separated was collected by filtration, washed with water, dried and crystallised from suitable solvents (Table-1).

IR: For compound (Vr): 1610 cm^{-1} ν(C=N), 3200 cm^{-1} ν(NH) and 1230 cm^{-1} ν(C—O—C).

^{1}H-NMR: For compound (Vr): 1.5 δ (s, 3H, CH_3), 12.0 δ (s, 1H, NH), 3.4–3.7 δ (dd, 2H, CH_2), 4.2–4.4 δ (dd, 1H, —CH—) and 7.2–8.0 δ (m, 12H, Ar—H).

Mass: For compound (Vr): m/z-386, 388 (M^+, $C_{24}H_{19}N_2OCl$), 251, 253, 216, 188, 189, 119, 91 and 57.

Antimicrobial activity: Compounds **IIIa–x, IVa–x** and **Va–x** were tested for their antibacterial activity against *S. aureus* and *E. coli* and antifungal activity against *A. niger* and *C. albicans* by cup-plate method[20] at a concentration of 100 ug in DMF. Gentamycin and griseofulvin were used as standard drugs for

TABLE-1
CHARACTERISATION DATA OF THE COMPOUNDS

Compound	Substituents		Yield (%)	m.p. (°C)	m.f.	Analysis found (calcd)%		
	R	R_1				C	H	N
IIIa	H	H	40	170–71	$C_{23}H_{17}NO$	85.40 (85.45)	5.25 (5.26)	4.31 (4.33)
IIIb	H	4′-CH_3	56	81	$C_{24}H_{19}NO$	85.40 (85.46)	5.48 (5.64)	4.00 (4.15)
IIIc	H	4′-Br	60	113–14	$C_{23}H_{16}NOBr$	68.61 (68.66)	3.94 (3.98)	3.41 (3.48)
IIId	H	4′-NH_2	58	118–20	$C_{23}H_{18}N_2O$	81.62 (81.66)	5.30 (5.33)	8.22 (8.28)
IIIe	H	4′-NO_2	45	131–32	$C_{23}H_{16}N_2O_3$	74.85 (75.00)	4.30 (4.35)	7.59 (7.61)
IIIf	H	4′-OH	61	185–86	$C_{23}H_{17}NO_2$	81.40 (81.42)	5.00 (5.01)	4.10 (4.13)
IIIg	H	5′-CH_3-2′-OH	57	117–18	$C_{24}H_{19}NO_2$	81.52 (81.59)	5.36 (5.38)	3.93 (3.97)
IIIh	H	5′-Cl-2′-OH	64	124–25	$C_{23}H_{16}NO_2Cl$	73.84 (73.90)	4.30 (4.28)	3.70 (3.75)
IIIi	CH_3	H	62	178	$C_{24}H_{19}NO$	85.25 (85.46)	5.58 (5.64)	4.08 (4.15)
IIIj	CH_3	4′-CH_3	58	191–92	$C_{25}H_{21}NO$	85.41 (85.47)	5.92 (5.98)	3.90 (3.99)
IIIk	CH_3	4′-Br	44	164–65	$C_{24}H_{18}NOBr$	69.15 (69.23)	4.25 (4.33)	3.28 (3.37)
IIIl	CH_3	4′-NH_2	61	188–89	$C_{24}H_{20}N_2O$	81.68 (81.82)	5.60 (5.68)	7.98 (7.96)

Compound	Substituents		Yield (%)	m.p. (°C)	m.f.	Analysis found (calcd)%		
	R	R_1				C	H	N
IIIm	CH_3	4′-NO_2	66	173–74	$C_{24}H_{18}N_2O_3$	75.21 (75.39)	4.65 (4.71)	7.22 (7.33)
IIIn	CH_3	4′-OH	45	151–52	$C_{24}H_{19}NO_2$	81.45 (81.59)	5.25 (5.38)	3.87 (3.97)
IIIo	CH_3	5′-CH_3-2′-OH	52	171–72	$C_{25}H_{21}NO_3$	78.28 (78.33)	5.46 (5.48)	3.62 (3.66)
IIIp	CH_3	5′-Cl-2′-OH	49	183–84	$C_{24}H_{18}NO_2Cl$	74.25 (74.32)	4.58 (4.65)	3.52 (3.61)
IIIq	Cl	H	65	250–51	$C_{23}H_{16}NOCl$	77.18 (77.20)	4.40 (4.48)	3.87 (3.92)
IIIr	Cl	4′-CH_3	58	205–06	$C_{24}H_{18}NOCl$	77.43 (77.52)	4.72 (4.85)	3.65 (3.77)
IIIs	Cl	4′-Br	60	215–16	$C_{23}H_{15}NOBrCl$	63.12 (63.23)	3.22 (3.44)	3.12 (3.21)
IIIt	Cl	4′-NH_2	61	198–200	$C_{23}H_{17}N_2OCl$	74.00 (74.09)	4.58 (4.56)	7.51 (7.52)
IIIu	Cl	4′-NO_2	58	221–22	$C_{23}H_{15}N_2O_3Cl$	68.48 (68.57)	3.70 (3.73)	6.88 (6.96)
IIIv	Cl	4′-OH	61	217–18	$C_{23}H_{16}NO_2Cl$	73.81 (73.90)	4.18 (4.28)	3.65 (3.75)
IIIw	Cl	5′-CH_3-2′-OH	62	191–92	$C_{24}H_{18}NO_2Cl$	74.25 (74.32)	4.68 (4.65)	3.58 (3.61)
IIIx	Cl	5′-Cl-2′-OH	64	204–05	$C_{23}H_{15}NO_2Cl_2$	67.60 (67.65)	3.52 (3.68)	3.45 (3.43)
IVa	H	H	58	118–20	$C_{23}H_{19}N_3$	81.89 (81.90)	5.60 (5.64)	12.40 (12.46)

Compound	Substituents		Yield (%)	m.p. (°C)	m.f.	Analysis found (calcd)%		
	R	R_1				C	H	N
IVb	H	4′-CH_3	60	135–36	$C_{24}H_{21}N_3$	82.00 (82.05)	5.92 (5.98)	11.95 (11.97)
IVc	H	4′-Br	61	121–22	$C_{23}H_{18}N_3Br$	66.36 (66.35)	4.30 (4.33)	10.00 (10.10)
IVd	H	4′-NH_2	59	138–40	$C_{23}H_{20}N_4$	78.40 (78.41)	5.70 (5.68)	15.90 (15.91)
IVe	H	4′-NO_2	57	115–16	$C_{23}H_{18}N_4O_2$	72.21 (72.25)	4.72 (4.71)	14.64 (14.66)
IVf	H	4′-OH	60	118–19	$C_{23}H_{19}N_3O$	78.15 (78.19)	5.33 (5.38)	11.91 (11.90)
IVg	H	5′-CH_3-2′-OH	58	148–49	$C_{24}H_{21}N_3O$	78.44 (78.47)	5.70 (5.72)	11.40 (11.44)
IVh	H	5′-Cl-2′-OH	60	138–40	$C_{23}H_{18}N_3OCl$	71.20 (71.22)	4.63 (4.65)	10.80 (10.84)
IVi	CH_3	H	65	161–62	$C_{24}H_{21}N_3$	82.00 (82.05)	6.00 (5.98)	11.95 (11.97)
IVj	CH_3	4′-CH_3	60	200–01	$C_{25}H_{23}N_3$	82.14 (82.19)	6.28 (6.30)	11.49 (11.51)
IVk	CH_3	4′-Br	65	142–43	$C_{24}H_{20}N_3Br$	66.95 (66.98)	4.64 (4.65)	9.73 (9.77)
IVl	CH_3	4′-NH_2	58	115–17	$C_{24}H_{22}N_4$	78.68 (78.69)	6.00 (6.01)	15.32 (15.30)
IVm	CH_3	4′-NO_2	64	122–23	$C_{24}H_{20}N_4O_2$	72.70 (72.73)	5.00 (5.05)	14.12 (14.14)
IVn	CH_3	4′-OH	68	109–10	$C_{24}H_{21}N_3O$	78.45 (78.47)	5.74 (5.72)	11.36 (11.44)

Compound	Substituents		Yield (%)	m.p. (°C)	m.f.	Analysis found (calcd)%		
	R	R_1				C	H	N
IVo	CH_3	5′-CH_3-2′-OH	64	118–19	$C_{25}H_{23}N_3O$	78.70 (78.74)	6.00 (6.04)	11.01 (11.02)
IVp	CH_3	5′-Cl-2′-OH	56	131–32	$C_{24}H_{20}N_3OCl$	71.70 (71.73)	4.96 (4.98)	10.39 (10.46)
IVq	Cl	H	70	178–79	$C_{23}H_{18}N_3Cl$	74.27 (74.29)	4.83 (4.85)	11.30 (11.31)
IVr	Cl	4′-CH_3	68	125–26	$C_{24}H_{20}N_3Cl$	74.70 (74.71)	5.20 (5.19)	10.87 (10.90)
IVs	Cl	4′-Br	55	181–82	$C_{23}H_{17}N_3BrCl$	61.25 (61.27)	3.79 (3.77)	9.30 (9.32)
IVt	Cl	4′-NH_2	61	140–41	$C_{23}H_{19}N_4Cl$	71.40 (71.41)	4.88 (4.92)	14.40 (14.49)
IVu	Cl	4′-NO_2	58	161–62	$C_{23}H_{17}N_4O_2Cl$	66.28 (66.27)	4.00 (4.08)	13.44 (13.45)
IVv	Cl	4′-OH	55	155–56	$C_{23}H_{18}N_3OCl$	71.20 (71.23)	4.10 (4.65)	10.82 (10.84)
IVw	Cl	5′-CH_3-2′-OH	60	142–43	$C_{24}H_{20}N_3OCl$	71.71 (71.73)	4.96 (4. 98)	10.41 (10.46)
IVx	Cl	5′-Cl-2′-OH	65	168–69	$C_{23}H_{17}N_3OCl_2$	65.38 (65.40)	4.00 (4.03)	9.91 (9.95)
Va	H	H	48	148	$C_{23}H_{18}N_2O$	81.48 (81.66)	5.30 (5.33)	8.24 (8.28)
Vb	H	4′-CH_3	40	136	$C_{24}H_{20}N_2O$	81.57 (81.82)	5.65 (5.68)	7.87 (7.96)
Vc	H	4′-Br	52	98–99	$C_{23}H_{17}N_2OBr$	66.17 (66.19)	4.00 (4.08)	6.72 (6.71)

Compound	Substituents		Yield (%)	m.p. (°C)	m.f.	Analysis found (calcd)%		
	R	R_1				C	H	N
Vd	H	4′-NH_2	55	108–10	$C_{23}H_{19}N_3O$	78.15 (78.19)	5.36 (5.38)	11.91 (11.90)
Ve	H	4′-NO_2	48	116–17	$C_{23}H_{17}N_3O_3$	72.01 (72.06)	4.42 (4.44)	10.93 (10.97)
Vf	H	4′-OH	61	144	$C_{23}H_{18}N_2O_2$	77.95 (77.97)	5.00 (5.08)	7.89 (7.91)
Vg	H	5′-CH_3-2′-OH	60	109–10	$C_{24}H_{20}N_2O_2$	78.22 (78.26)	5.40 (5.43)	7.60 (7.61)
Vh	H	5′-Cl-2′-OH	48	111–12	$C_{23}H_{17}N_2O_2Cl$	71.00 (71.04)	4.33 (4.38)	7.19 (7.21)
Vi	CH_3	H	42	198	$C_{24}H_{20}N_2O$	81.80 (81.82)	5.65 (5.68)	7.94 (7.95)
Vj	CH_3	4′-CH_3	52	170–71	$C_{25}H_{22}N_2O$	81.97 (81.97)	6.00 (6.01)	7.64 (7.65)
Vk	CH_3	4′-Br	58	155	$C_{24}H_{19}N_2OBr$	66.80 (66.82)	4.39 (4.41)	6.49 (6.50)
Vl	CH_3	4′-NH_2	55	123–24	$C_{24}H_{21}N_3O$	78.44 (78.47)	5.70 (5.72)	11.41 (11.44)
Vm	CH_3	4′-NO_2	61	153–54	$C_{24}H_{19}N_3O_3$	72.51 (72.54)	4.76 (4.79)	10.58 (10.58)
Vn	CH_3	4′-OH	60	126–27	$C_{24}H_{20}N_2O_2$	78.24 (78.26)	5.44 (5.43)	7.60 (7.61)
Vo	CH_3	5′-CH_3-2′-OH	56	142–43	$C_{25}H_{22}N_2O_2$	78.51 (78.53)	5.74 (5.76)	7.30 (7.33)
Vp	CH_3	5′-Cl-2′-OH	48	135–36	$C_{24}H_{19}N_2O_2Cl$	71.52 (71.55)	4.70 (4.72)	6.95 (6.96)

Compound	Substituents		Yield (%)	m.p. (°C)	m.f.	Analysis found (calcd)%		
	R	R_1				C	H	N
Vq	Cl	H	39	184	$C_{23}H_{17}N_2OCl$	74.00 (74.09)	4.54 (4.56)	7.48 (7.52)
Vr	Cl	4′-CH_3	54	173	$C_{24}H_{19}N_2OCl$	74.50 (74.51)	4.93 (4.92)	7.20 (7.24)
Vs	Cl	4′-Br	61	123–24	$C_{23}H_{16}N_2OBrCl$	61.11 (61.13)	3.50 (3.54)	6.21 (6.20)
Vt	Cl	4′-NH_2	52	118–19	$C_{23}H_{18}N_3OCl$	71.20 (71.23)	4.60 (4.65)	10.81 (10.84)
Vu	Cl	4′-NO_2	49	178–79	$C_{23}H_{16}N_3O_3Cl$	66.10 (66.11)	3.82 (3.83)	10.00 (10.06)
Vv	Cl	4′-OH	54	178	$C_{23}H_{17}N_2O_2Cl$	71.00 (71.04)	4.39 (4.38)	7.19 (7.21)
Vw	Cl	5′-CH_3-2′-OH	58	156–57	$C_{24}H_{19}N_2O_2Cl$	71.50 (71.55)	4.71 (4.72)	6.94 (6.96)
Vx	Cl	5′-Cl-2′-OH	60	144–45	$C_{23}H_{16}N_2O_2Cl_2$	65.20 (65.25)	3.73 (3.78)	6.60 (6.62)

Solvents for crystallisation: For IIIa–c: Alcohol + Benzene (1 : 1); IIIe, IIIg–h and IIIm: Alcohol + Acetone (1 : 1); IIId, IIIf, IIIi–l, IIIp, IVa–x and Va–x: Alcohol, IIIn–o and IIIq–x: Benzene + Chloroform (1 : 1).

antibacterial and antifungal activity, respectively. The zone of inhibition was compared with the standard drugs after 24 h of incubation at 37°C for antibacterial activity and 48 h for antifungal activity.

Amongst the compounds tested IIIc–e, IIIo, IIIs, IIIw, IVg, IVp, IVs, IVu, Vd and Vt showed good activity against *S. aurues*. Compounds IIIk, IIIw, IVc, IVk, IVs, Vc, Vk, Vn and Vt exhibited very good activity against. *E. coli*. Compounds IIIm, IIIs, IVc, IVm, IVx, Ve, Vu and Vx showed very good activity against *A. niger*. Compounds IIIu, IIIx, IVm, IVs, Ve, Vw and Vx exhibited good activity against *C. albicans*. The activity of some of these compounds is very close to the standard drugs used. Most of the compounds are moderately active against all the organisms tested.

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