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Synthesis and Antimicrobial Activity of 3-(3-Phenylsulphonamidophenyl)-5-aryl-2-pyrazolines

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New 1-isonicontinoyl/carboxamido-3-(3-phenylsulphonamido phenyl)-5-aryl pyrazoline (**2a–e/3a–e**) have been synthesized by the action of isonicontinic acid hydrazide/semicarbazide hydrochloride with 1-(3-phenylsulphonamidophenyl)-3-aryl prop-2-ene-1-ones (**1a–e**) in pyridine medium. The synthesized compounds have been characterized by elemental analysis, IR and NMR spectral analysis and screened for antimicrobial activity.

Key Words: Synthesis, Pyrazoline, Antimirobial activity.

INTRODUCTION

Synthesis and characterization of pyrazoline derivatives has been a developing field within the realm of heterocyclic chemistry for the past several decades because of their ready accessibility through synthesis, wide range of chemical reactivity and broad spectrum of biological activity[1, 2]. Pyrazoline derivatives have been found to be bactericidal[3], fungicidal[4], insecticidal[5] agents. Survey of literature in the recent past reveals that some pyrazoline derivatives possess cerebroprotective effect[6] and antidepressant activity[7]. Ozawa *et al.*[8] reported the synthesis of some pyrazoline derivatives which are effective for killing the houseflies on contact. Hussain *et al.*[9] reported the hypoglycemic activity of pyrazolines with phenylsulphonamidoaryl moiety at C-3 which causes up to 25% decrease in blood sugar at 250 mg/kg dose. Pyrazolines with substituted phenylsulphonamidophenyl group at C-3 in pyrazoline nucleus have been found to possess broad spectrum of antimicrobial activity[10–15] which is comparable with that of the standard antibiotics like ampicillin, chloromycetin, norfloxacin and grisoefulvin.

Findings from our laboratory and elsewhere reveal that pyrazolines can be synthesized by action of hydrazine/substituted hydrazine with substituted prop-2-en-1-ones in different solvents[17–18] like ethanol, acetic acid, DMF, pyridine etc. In view of the biological importance of pyrazolines with phenylsul phonamidophenyl moiety at C-3, it was thought of interest to extend this work to the study of changes in the biological profile brought about by variations in one or more chemical functions in the related compounds.

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In our search for new antimicrobial agents, we herein present the synthesis of 1-substituted-3,5-diarylopyrazolines in which N-1 of pyrazoline cycle was linked to isonicotinoyl/carboxamido residue. The structures of the synthesized compounds have been confirmed by elemental analysis and IR and NMR spectral analysis. All the synthesized compounds were tested for their antimicrobial activity by a paper-disc method towards the strains of *S. aureus, E. coli, P. mirabilis and P. aeruginosa.*

EXPERIMENTAL

All the melting points were taken in open capillary in silicon oil bath and are uncorrected. Purity of the compounds was checked by TLC on silica gel G. IR spectra were recorded on a Nicolet-Impact 400 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Brucker AC300 FNMR spectrometer (300 MHz), using TMS as an internal standard. Microanalysis of nitrogen was obtained on Coleman 29-N analyzer.

1-(3-phenylsulphonamidophenyl)-3-phenyl-prop-2-en-1-one(1a)

To a mixture of 3-phenylsulphonamidoacetophenone (2.75 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) in ethanol (25 mL), 40% aq. NaOH (6 mL) was added dropwise with constant stirring. The reaction mixture was kept overnight at room temperature and then acidified with 50% HCl. The resulting solid was filtered, dried and crystallized from ethanol to obtain the compound **1a**, yield 70%, m.p. 174°C.

IR (ν_{max})(cm^{-1}): 3167 ν(NH), 1650 ν(C=O), 1575 ν(C=C), 1329 and 1155 ν(SO_2 asymm. and symm.). ^{1}H NMR (δ ppm): 7.2–8.0 (m, 16H, 14 Ar—H + CH=CH), 10.8 (s, 1H, SO_2NH).

1-(3-Phenylsulphonamidophenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (b)

To a mixture of 3-phenylsulphonamido acetophenone (2.75 g, 0.01 mol) and 4-methoxybenzaldehyde (1.36 g, 0.01 mol) in ethanol (25 mL), 40% aq. NaOH (6 mL) was added dropwise with constant stirring. The reaction mixture was kept overnight at room temperature and then acidified with 50% HCl. The resulting solid was filtered, dried & crystallized from ethanol to obtain the compound **1b**, yield 72%, m.p. 176°C.

IR (ν_{max}) (cm^{-1}): 3203 ν(NH), 1649 ν(C=O), 1605 ν(C=C), 1356 & 1175 ν(SO_2 asymm and symm). ^{1}H NMR (δ ppm): 3.8 (s, 3H, —OCH_3), 7.33 (d, 1H, =CH—Ar, J = 15 Hz), 7.95 (d, 1H, =CH—C=O, J = 15 Hz), 7.2–8.0 (m, 13H, Ar—H), 10.8 (s, 1H, SO_2NH).

Similarly compounds **1c–e** of the series were prepared and their physical data are recorded in Table-1.

1-isonicotinoyl-3-(3-phenylsulphonamidophenyl)-5-phenyl-2-pyrazoline (2a)

1-(3-phenylsulphonamidophenyl)-3-phenyl-prop-2-ene-1-one **(1a)** (3.63 g, 0.01 mol) and isonicotinic acid hydrazide (2.72 g, 0.02 mol) in pyridine (20 mL) were refluxed for 8 h. The reaction mixture was cooled and neutralized by 50% HCl. The solid obtained was filtered, washed with water, dried and crystallized from acetic acid to obtain compound **2a**, yield 65%, m.p. 168°C.

IR (ν_{max}) (cm^{-1}): 3170 ν(NH), 1569 ν(C=N), 1339 and 1152 ν(SO_2 *asymm.* and symm.). ^1H NMR (δ ppm): 3.04 (dd, 1H, H_A of pyrazoline, J_{AB} = 13.68 and J_{AX} = 4.60 Hz), 3.74 (dd, 1H, H_B of pyrazoline, J_{AB} = 13.68 and J_{BX} = 6.68 Hz), 5.52 (dd, 1H, H_X of pyrazoline, J_{AX} = 4.60 Hz and J_{BX} = 6.68), 7.2–8.0 (m, 18H, 18Ar—H), 10.6 (s, 1H, SO_2NH).

1-Isonicotinoyl-3-(3-phenylsulphonamidophenyl)-5-(4-methoxyphenyl)-2-pyrazoline (2b)

1-(3-phenylsulphonamidophenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one **(1b)** (3.93 g, 0.01 mol) and isonicotinic acid hydrazide (2.72 g, 0.02 mol) in pyridine (20 mL) were refluxed for 8 h. The reaction mixture was cooled and neutralized by 50% HCl. The solid obtained was filtered, washed with water, dried and crystallized from acetic acid to obtain compound **2b**, yield 60%, m.p. 164°C.

IR (ν_{max}) (cm^{-1}): 3216 ν(NH), 1562 ν(C=N), 1346 & 1160 ν(SO_2 asymm & symm.). ^1H NMR (δ ppm): 3.82 (s, 3H, —OCH_3), 2.99 (dd, 1H, H_A of pyrazoline, J_{AB} = 13.96 and J_{AX} = 4.45 Hz), 3.68 (dd, 1H, H_B of pyrazoline, J_{AB} = 13.96 and J_{BX} = 6.72 Hz), 5.47 (dd, 1H, H_X of pyrazoline, J_{AX} = 4.45 and J_{BX} = 6.72 Hz), 7.2–8.0 (m, 17H, 17Ar—H), 10.7 (s, 1H, SO_2NH).

Similarly compounds **2c–e** of the series were prepared and their physical data are recorded in Table-1.

TABLE-1
PHYSICAL DATA OF THE SYNTHESIZED COMPOUNDS

Compd.	R^1	R^2	Yield (%)	m.p. (°C)	m.f.	% N	
						Found	(Calcd.)
1a	H	H	70[a]	174	$C_{21}H_{17}SNO_3$	3.80	(3.85)
1b	H	OCH_3	72[a]	176	$C_{22}H_{19}SNO_4$	3.50	(3.56)
1c	H	$N(CH_3)_2$	74[c]	204	$C_{23}H_{22}SN_2O_3$	6.82	(6.89)
1d	H	OH	70[a]	156	$C_{21}H_{17}SNO_4$	3.61	(3.69)
1e	OCH_3	OH	65[a]	173	$C_{22}H_{19}SNO_5$	3.40	(3.42)
2a	H	H	65[b]	168	$C_{27}H_{22}SN_4O_3$	11.02	(11.61)
2b	H	OCH_3	60[b]	164	$C_{28}H_{24}SN_4O_4$	10.54	(10.93)
2c	H	$N(CH_3)_2$	52[b]	150	$C_{29}H_{27}SN_5O_3$	12.96	(13.33)
2d	H	OH	60[a]	180	$C_{27}H_{22}SN_4O_4$	11.00	(11.24)
2e	OCH_3	OH	58[a]	132	$C_{28}H_{24}SN_4O_5$	10.05	(10.60)
3a	H	H	62[b]	161	$C_{22}H_{20}SN_4O_3$	12.96	(13.33)
3b	H	OCH_3	62[b]	225	$C_{23}H_{22}SN_4O_4$	12.06	(12.44)
3c	H	$N(CH_3)_2$	58[b]	218	$C_{24}H_{25}SN_5O_3$	14.99	(15.11)
3d	H	OH	65[a]	160	$C_{22}H_{20}SN_4O_4$	12.50	(12.84)
3e	OCH_3	OH	68[a]	120	$C_{23}H_{22}SN_4O_5$	11.68	(12.01)

Solvent for crystallization: a = ethanol, b = acetic acid and c = ethanol + acetic acid

1-Carboxamido-3-(3-phenylsulphonamidophenyl)-5-phenyl-2-pyrazoline (3a)

1-(3-phenylsulphonamidophenyl)-3-phenyl-phenyl-prop-2-en-1-one **(1a)** (3.63 g, 0.01 mol) and semicarbazide hydrochloride (2.24 g, 0.02 mol) in pyridine (20 mL) were refluxed for 8 h. The reaction mixture was cooled and neutralized by 50% HCl. The solid obtained was filtered, washed with water, dried and crystallized from acetic acid to obtain compound **3a**, yield 62%, m.p. 161°C.

IR (ν_{max}) (cm^{-1}): 3550 cm^{-1} $\nu(NH_2)$, 3249 ν(NH), 1513 ν(C=N), 1336 and 1159 $\nu(SO_2$ asymm. and symm.). ^1H NMR (δ ppm): 3.02 (dd, 1H, H_A of pyrazoline, J_{AB} = 13.68 and J_{AX} = 4.6 Hz), 3.62 (dd, 1H, H_B of pyrazoline, J_{AB} = 13.68 and J_{BX} = 6.68 Hz), 5.52 (dd, 1H, H_X of pyrazoline, J_{AX} = 4.5 Hz and J_{BX} = 6.68 Hz), 7.2–8.0 (m, 14H, 14 Ar—H), 8.09 (s, 2H, NH_2), 9.31 (s, 1H, SO_2NH).

1-Carboxamido-3-(3-phenylsulphonamidophenyl)-5-(4-methoxyphenyl)-2-pyrazoline (3b)

1-(3-phenylsulphonamidophenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one **(1b)** (3.93 g, 0.01 mol) and semicarbazide hydrochloride (2.24 g, 0.02 mol) in pyridine (20 mL) were refluxed for 8 h. The reaction mixture was cooled and neutralized by 50% HCl. The solid obtained was filtered, washed with water, dried and crystallized from acetic acid to obtain compound **3b**, yield 62%, m.p. 225°C.

IR (ν_{max}) (cm^{-1}): 3553 $\nu(NH_2)$, 1513 ν(C=N), 1346 and 1160 $\nu(SO_2$ asymm. and symm.), 1262 (Ar—O—C).

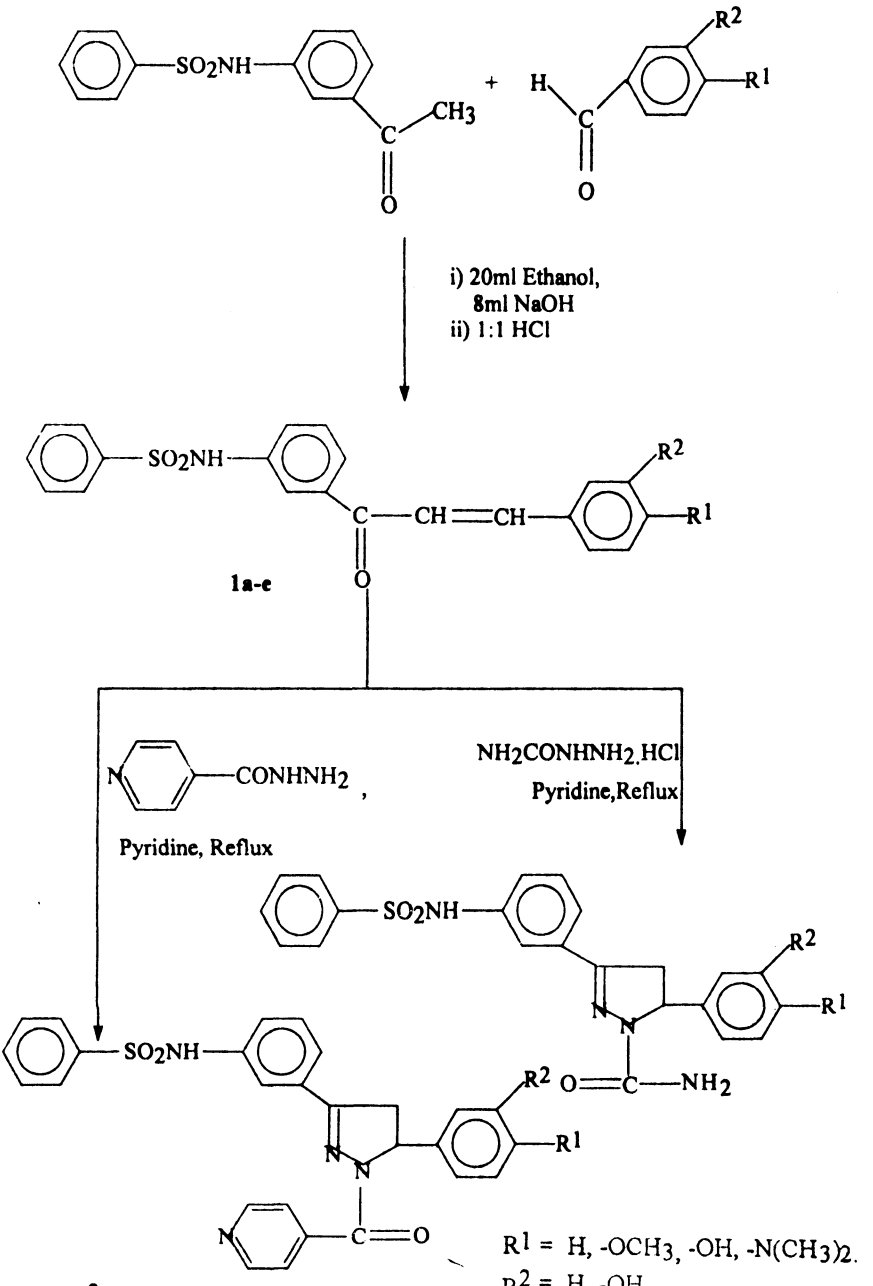
^1H NMR (δ ppm): 3.8 (s, 3H, —OCH_3), 3.05 (dd, 1H, H_A of pyrazoline, J_{AB} = 13.70 and J_{AX} = 4.68 Hz), 3.72 (dd, 1H, H_B of pyrazoline, J_{AB} = 13.70 and J_{BX} = 6.70 Hz), 5.50 (dd, 1H, H_X of pyrazoline, J_{AX} = 4.68 Hz and J_{BX} = 6.70), 7.2–8.0 (m, 13H, 13Ar—H), 8.09 (s, 2H, NH_2), 10.6 (s, 1H, SO_2NH).

Similarly compounds **3c–e** of the series were prepared and their physical data are recorded in Table-1.

RESULTS AND DISCUSSION

Structures of the synthesized compounds have been elucidated by elemental analysis, IR & ^1H NMR analysis. IR spectra showed absorption band around 1600–1500 cm^{-1} which is a characteristic of C=N stretch of pyrazoline. In ^1H NMR, H_A, H_B and H_X of pyrazoline ring were seen as doublet of doublet at 2.99–3.05, 3.62–3.78 and 5.4–5.6 ppm respectively. The protons of the aromatic ring and methoxy group were observed at expected chemical shift and integral value.

Synthesized compounds have been screened for their antimicrobial activities against the strains of *S. aureus, E. coli, P. mirabilias and P. aeruginosa* at a concentration of 100 μg/mL. The maximum activity was found in **2e, 2d, 3a, 3b, 3e** for *E. coli* and **2e, 3c, 3d, 3e** for *P. mirabilis*. Most of the compounds were found moderately active against *S. aureus* and resistant against *P. aeruginosa*. Antimicrobial data are listed in Table-2.


SO2NH
CH3
C
O
+
H
C
O
R2
R1
i) 20ml Ethanol,
8ml NaOH
ii) 1:1 HCl
SO2NH
C
CH
CH
O
R2
R1
1a-e
N
CONHNH2
,
Pyridine, Reflux
NH2CONHNH2.HCl
Pyridine,Reflux
SO2NH
SO2NH
N
N
R2
R1
R2
O
C
NH2
R1
N
N
C
O
2a-e
R1 = H, -OCH3, -OH, -N(CH3)2.
R2 = H, -OH .

Scheme

TABLE-2
ANTIMICROBIAL DATA OF THE SYNTHESIZED COMPOUNDS

Compound	*S. aureus*	*E. coli*	*P. mirabilis*	*P. aeruginosa*
1a	6	9	R	6.5
1b	6	R	11	R
1c	6	R	R	R
1d	6	7	R	R
1e	6	9	R	R
2a	R	R	R	R
2b	R	R	R	R
2c	R	R	R	R
2d	7	11	7	R
2e	6.5	10	10	R
3a	6.5	10	R	R
3b	6.5	10	R	R
3c	6.5	7	10	7
3d	6	R	11	R
3e	7.5	10	9	R

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