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Synthesis And Antimicrobial Activity Of Di(Subsitituted Phenyl)-2 Pyrazoline Derivatives

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Abstract: In the present study synthesis and antimicrobial activity of di(subsitituted phenyl)-2 pyrazoline derivatives was done. A total of nine compound were synthesised, out of which product 3g was further elucidated for structure by IR, ^{1}HNMR. Standard cup-plate technique was done for Antimicrobial activity using Ciprofloxacin, Fluconazole and Amphotericin B as standard for comparison of Zone of inhibition for the prepared compound.
Key Words: pyrazoline derivatives, Antimicrobial activity, Standard cup-plate technique.

Introduction:

In the past centuries combating against microbial infections has resulted in synthesis of a wide variety of antibiotics & antifungal agent. Synthetic medicinal chemistry has made possible mass production of drugs of very high reproducibility with short period of time. An important aspect of medicinal chemistry has been to establish a relationship between chemical structure and biological activity. As more information is gained as to causative factors of different disease, the move will be from empirical approach to the rational design of new drugs.[1]

In drug designing programs an essential component of the search for new leads is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of presence of critical structural features. Certain small heterocyclic molecules act as highly functionalized scaffolds and are known pharmacophores of a number of biologically active and medicinally useful molecules.

Electron-rich nitrogen heterocycles like pyrazine, pyridine, imidiazole, piperidine, thiazolidine, are found to possess various diversified activities viz antibacterial antifungal, antimycobacterial[3]. Introducing a pyrazolidine ring in a place of the β-lactam ring (in penicillins and cephalosporins result in enhanced activity[4] A second nitrogen in the five–membered ring also influences the antibacterial or pharmacokinetic properties.[5] 2-Pyrazoline derivatives have been reported in the literature to exhibit various pharmacological activities such as antimicrobial[6], anti-inflammatory[7] and anti hypertensive[8].

Materials and Methods:

All reagents were used as purchased from commercial suppliers without further purification. Melting points were determined by using an Electrothermal melting point apparatus and were uncorrected. The purity and homogeneity of the synthesized compounds was routinely ascertained by thin layer chromatography, using Silica gel G as an adsorbent. For 1,3-di(substituted -phenyl) prop-2-en-1-one derivatives the solvent system used was benzene : methanol (5: 5 v/v) and for 1-Thiocarbylamine -3,5-di(substituted phenyl)-2-

pyrazoline derivatives solvent system used was benzene: ethyl acetate (9 : 1 v/v). For 1-(4-methyl–thiazol-2-yl)-3,5-di(subsitituted phenyl)-2 pyrazoline solvent system used was hexane: ethyl

acetate (5 : 5 v/v). Iodine vapour chamber was used for locating spots. Rf values for compounds were calculated. UV absorbtion maxima of compounds synthesized was carried out in methanol (HPLC grade, 1mg/100ml). The solutions were scanned on U.V Spectrophotometer Shimadzu 1700 Kyoto, Japan, in the region 200-400 nm and λmax values for synthesized compounds were noted.

The IR absorption spectra of the compounds were recorded on Shimadzu 210, spectrophotometer by using liquid film forming method.

General procedure for the synthesis of the compounds

1-Thiocarbamoyl -3,5-di(substituted phenyl)-2-pyrazolines were synthesized by adding to a suspension of 1, 3-di(substituted-phenyl) prop-2-en-1-one derivatives (0.01 mol) and sodium hydroxide (1 g, 0.025 mol) in ethanol (50 ml). The mixture was refluxed for 8 h. The products were poured into crushed ice and the solid mass which separated out was filtered, dried and crystallized from ethanol.[6]

For synthesis of 1-(4-methyl –thiazol-2-yl)-3,5-di(subsitituted phenyl)-2 pyrazoline**.** To a suspension of compounds (0.01 mol) in ethanol (15 ml) chloroacetone (0.01 mol) were added and heated to reflux for 1 h. After cooling, the precipitate was collected by suction filtration and crystallized from ethanol.

Results And Discussion

In the present work different 1-Thiocarbamoyl -3,5-di(substituted phenyl)-2-pyrazoline was prepared by reacting 3-di(substituted-phenyl) prop-2-en- 1-one with thiosemicarbazide. The condensation of 1-Thiocarbamoyl -3,5-di(substituted phenyl)-2-pyrazoline with chloroacetone resulted in the formation of 1-(4-methyl –thiazol-2-yl)-3,5-di(substituted phenyl)-2 pyrazoline derivatives In this present work, a new compounds was synthesized. Thus, starting from the 1-[Thiocarbamoyl -3,5-di(substituted phenyl)]-2-pyrazoline was obtained of through treatment with thiosemicarbazide. Final compound was obtained by reacting 1-(4-methyl –thiazol-2-yl)-3,5-di(substituted phenyl)-2 pyrazoline with choloacetone in ethanol in the presence of NaOH .

The homogeneity and the purity of the synthesized compound was confirmed by sharp melting points and thin layer chromatography. The U.V. absorption spectra of the compound show absorption between 200-400 nm (methanol).The I. R. spectrums of synthesized compound showed characteristic band of C=N stretching in the range of 1590-1530 cm-1 and C-N stretching of pyrazoline ring in the range of 1080-1020 cm-1 which confirmed the structure of synthesized compound (**figure 1).** The chemical structure of synthesized compound was further confirmed by 1H NMR spectra. The 1H NMR spectrum of synthesized compound showed characteristic ABX system due to geminal-vicinal multiple coupling between 4-CH2 and 5-CH protons of pyrazoline ring. The high field doublet–doublet at δ 3.08 - 3.16 and δ 3.8-3.9 due to HA and HB respectively of C4 protons and low field doublet-doublet at δ 5.3-5.4 due to HX at C5 are characteristic signals due to vicinal coupling with the two magnetically non equivalent protons of the methylene group at position 4 of the pyrazoline ring. The C-5–proton of thiazole was observed as a singlet between δ 6.7-6.85. Thearomatic proton appeared as multiplet at δ 6.8-7.9. Antimicrobial activity were recorded as the Percentage Zone of Inhibition, is the area in cm which showed the inhibition the growth of tested microorganisms. The compound tested illustrated significant anti-bacterial and antifungal activity when compared with reference drugs (**figure 2).** Antimicrobial screening of synthesized compounds was done by agar well diffusion method. The results show that synthesized compound possesses mild to moderate antibacterial activity and very promising antifungal activity (figure 3). Compound was found to have good antibacterial and antifungal activity. From the observation of their structures it is assumed that the activity increases with presence of –NH2 on benzene ring, while it is lowered down with the presence of other groups.

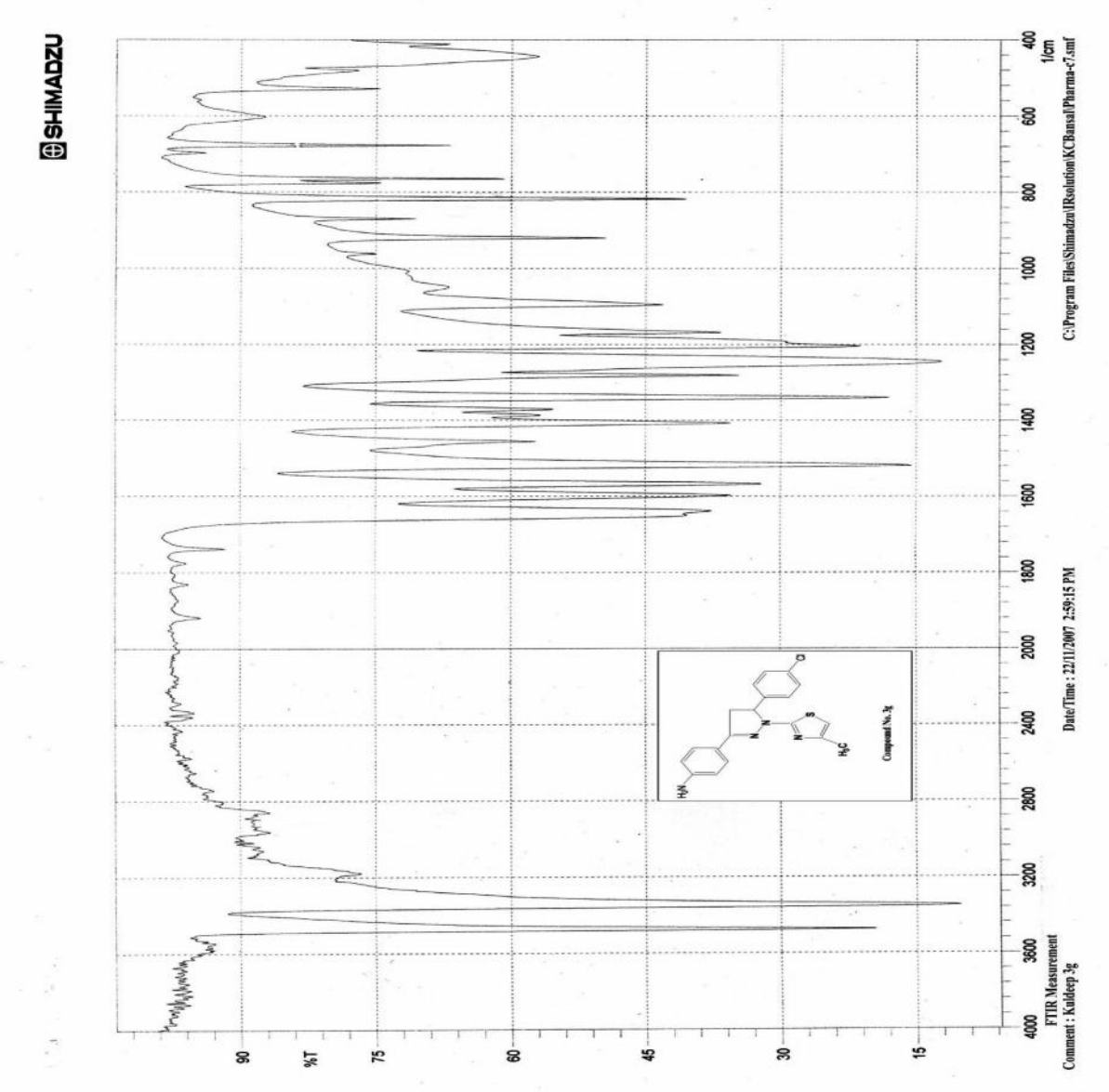


Figure 1: IR Spectrum of Prepared Compound (3g)

Table No 1: Assignment of IR absorption spectra of compound

Compound No.	Assignment of Spectra	
	Wave Number in cm^{-1}	**Interpretations**
3g	1575 -1565 1060-1040 1355-1345 3120-3010	C=N stretching C^5-N^1 stretching C=S stretching C-H aromatic stretching

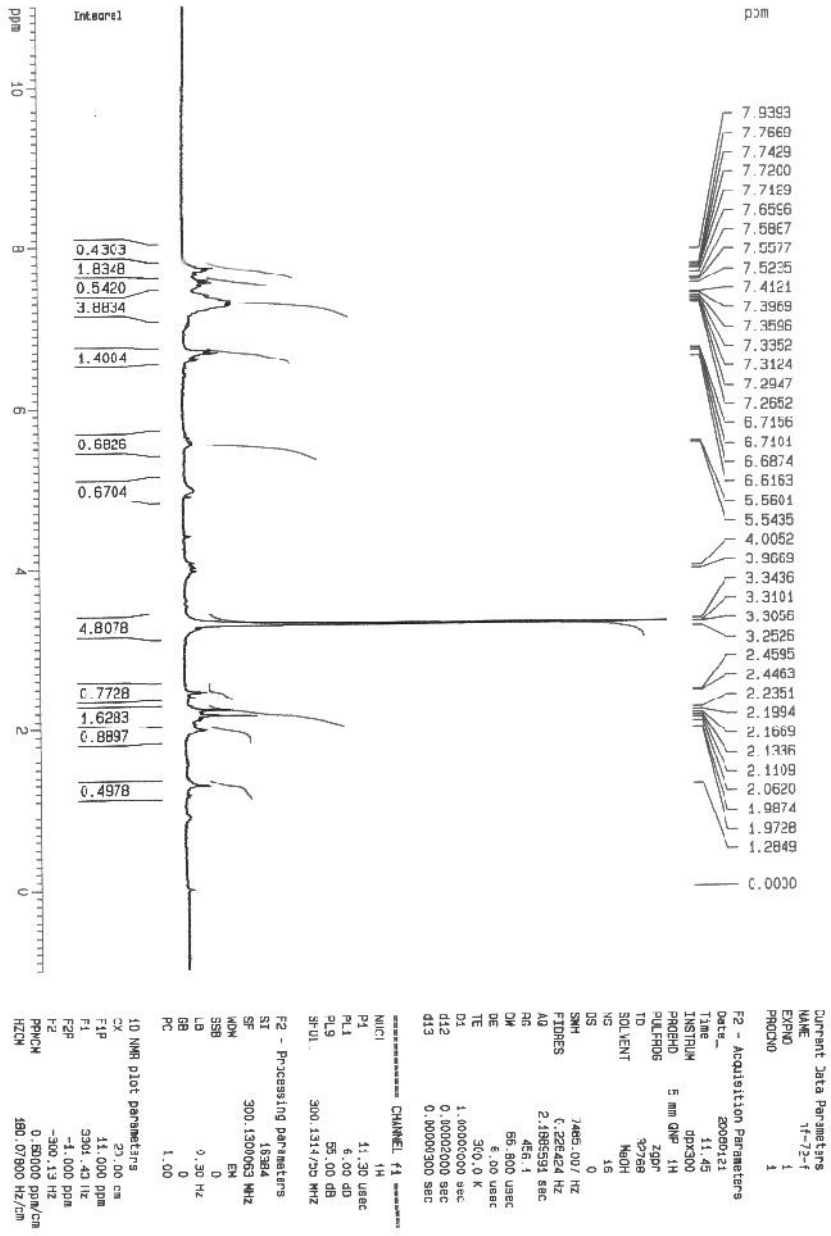
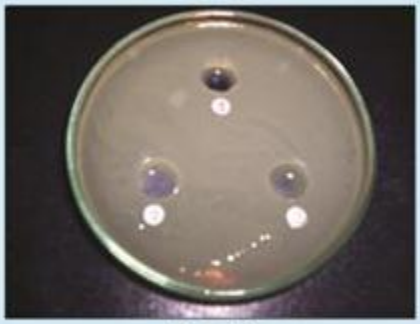


Figure 2: [1]HNMR spectra of synthesized compound

Table No 2: Interpretation of [1]HNMR spectra of synthesized compound

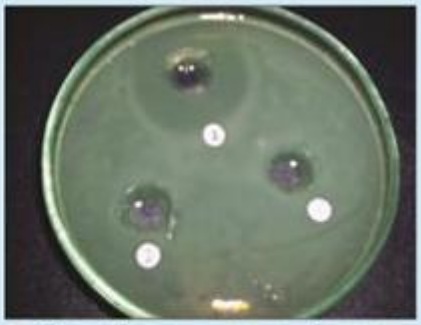
Compound No.	Chemical shift in δ(ppm)	Interpretation s=singlet, dd=doublet, t=tiplet, m=multiplet	
3g	3.15	1H,dd,H_A	(C_4 proton of pyrazoline)
	3.93	1H, dd,H_B	(C_4 proton of pyrazoline)
	5.34	1H,dd ,H_X	(C_5 proton of pyrazoline)
	6.78	1H, s	(C-5'proton of thiazole)
	7.54	8H,m	(Aromatic proton)

E.coli
(3g)



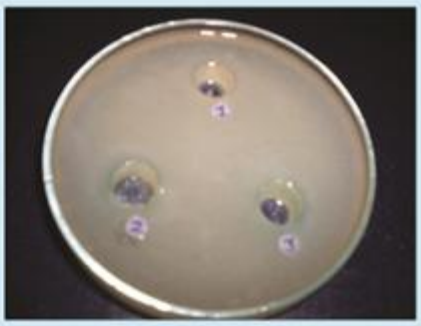
E.coli
(standard)

Pseudomonas aeruginosa
(3g)



Pseudomonas aeruginosa
(standard)

Proteus mirabilis
(3g)



Proteus mirabilis
(standard)

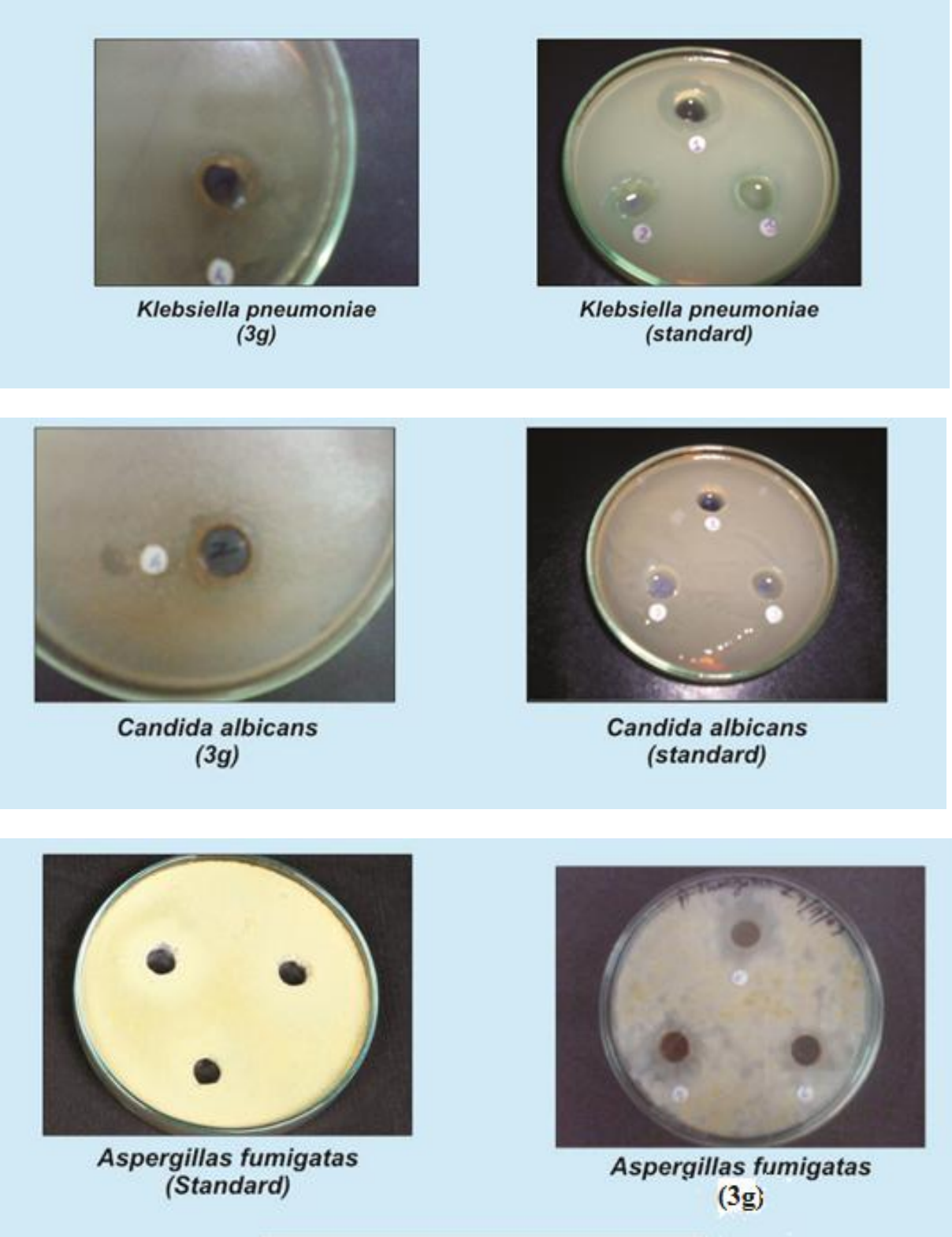


Figure 3: Antibacterial Study of prepared Compound (3g) by using standard Cup-Plate technique

Table No. 3 *In Vitro* Antibacterial Activity of the synthesized compound

Compound no	*E.coli*		*Pseudomonas aeruginosa*		*Proteus mirabilis*		*Klebsiella pneumoniae*	
	Z.O.I	**% Inhi**	**Z.O.I**	**% Inhi**	**Z.O.I**	**% Inhi**	**Z.O.I**	**% Inhi**
3g	8	34	10	33	9	45	7	32
Standard (Ciprofloxacin)	23	100	30	100	20	100	22	100

Table No.4 *In Vitro* Antifungal Activity of the synthesized compound

Compounds No.	*Candida albicans*		*Aspergillas fumigatus*	
	Zone of Inhibition	**% Inhibition**	**Zone of Inhibition**	**% Inhibition**
3g	31	155	23	190
Standard (Flouconazole)	10	100	12	100
Amphotericin B	20	100	12	100

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