Research Article

SYNTHESIS, CHARACTERIZATION AND PHARMACOLOGICAL ACTIVITY OF NOVEL 1-(3'-SUBSTITUTED PHENYL-5'-IMINO-ARYL PYRIMIDINE)-3-(SUBSTITUTED PHENYL)-5-(SUBSTITUTED PHENYL)-2-PYRAZOLINE ANALOGUES

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ABSTRACT

A series of novel 1-(3'-substituted phenyl-5'-imino-aryl pyrimidine)-3-(substituted phenyl)-5-(substituted phenyl)-2-pyrazoline analogues 2(a-i) have been synthesized by refluxing amino pyrimidine embedded 1,3,5-trisubstituted-2-pyrazolines 1 with different aromatic aldehydes and characterized by elemental analysis, FTIR, NMR (¹H, ¹³C) and Mass spectrometry. All compounds have been screened for their antibacterial activities against *Bacillus subtilis*, *Streptococcus aureus*: gram positive strain, *Pseudomonas aeruginosa*, *Escherichia coli*: gram negative strain and antifungal activities against *Aspergillus niger* comparable to reference standard ciprofloxacin and fluconazole by agar-well diffusion method. 2a, 2d, 2f, 2g, 2i showed good antibacterial activity compared to the standard drug ciprofloxacin. 2b, 2c, 2d, 2e, 2f displayed moderate antifungal activity compared to the standard drug fluconazole. All compounds exhibited high activity for *Streptococcus aureus* and moderate to high activity against *Pseudomonas aeruginosa* and *Bacillus subtilis*.

Keywords: 2-pyrazoline, Pyrimidine, Schiff bases, antibacterial, antifungal

INTRODUCTION

The rapid development of pathogen resistance to most of the known antibiotics has become a pressing problem worldwide¹. To conflict the resistant strains, the synthesis of new antibacterial agents is a vital need, which prove to be lead scaffolds. Under these prospective, the search for molecule with increased biological activities, we tried to design molecule by combining different pharmacophores in one structure. The development of new chemotherapeutic Schiff bases is now attracting the attention of medicinal chemists². Schiff bases, the condensation product of primary amine and active carbonyl groups, represents valuable intermediates in organic synthesis³. Schiff bases acquired broad spectrum of biological activities like antibacterial⁴, antifungal⁵, anti-inflammatory⁶, anti-proliferative⁷, anti-tubercular⁸ and anti-convulsant⁹. Biocidal activities of Schiff bases have been well established and attributed to the toxophoric C=N linkage in them¹⁰.

N-containing compounds become remarkable due to their valuable biological properties. 2-pyrazoline, five membered heterocyclic molecule with two adjacent nitrogen atoms possess a broad spectrum of biological activity such as antitumor¹¹, anti-depressant¹², anti-epileptic¹³, anti-cancer¹⁴, analgesic¹⁵, anti-proliferative¹⁶, anti-inflammatory¹⁷, anti-oxidant¹⁸, cytotoxic¹⁹ and insecticidal²⁰ properties. The six membered heterocyclic molecule pyrimidine showed anti-viral²¹, anti-pyretic²², anti-hypertensive²³, anti-proliferative²⁴, anti-bacterial²⁵, analgesic²⁶

and anti-nociceptive²⁷ effects. Many pyrimidine derivatives are reported to possess anti-malarial, anti-leishmanial²⁸ and CNS depressant properties²⁹.

On the basis of literature survey our main aim is to design mutual pro-drugs which contain 2-pyrazoline, pyrimidine and Schiff base nuclei to produce synergistic anti-microbial activity. This prompted us to synthesize a series of novel Schiff bases of pyrimidine-pyrazoline hybrid and study their inhibitory effect against selected bacterial and fungal strains.

MATERIALS & METHODS

All the chemicals and solvents of Sigma Aldrich were AR grade and used without further purification. Melting Points were determined in open glass capillaries in an electrical melting point apparatus and are uncorrected. Purity was checked by thin layer chromatography on silica gel G plates using UV light as visualizing agent. IR spectra were recorded on FTIR spectrophotometer Shimadzu 8201 PC (4000-400 cm⁻¹) using KBr pallet technique. ¹H and ¹³C NMR spectra were recorded on Bruker Avance-II 400 MHz NMR spectrometer using DMSO-*d*₆ as a solvent and tetra methyl silane as internal standard. Mass spectra were recorded on Waters, Q-TOF, Micromass (LC-MS spectrometer) and Elemental analyser used for CHN analysis. All the synthesized compounds were screened for their antibacterial and antifungal activity using agar-well diffusion method.

GENERAL PROCEDURE FOR SYNTHESIS OF PHARMACOLOGY COMPOUNDS

1) Synthesis of 1-(3'-substituted phenyl-5'-amino pyrimidine)-3-(substituted phenyl)-5-(substituted phenyl)-2-pyrazolines (1) : Equimolar quantity of 1- (substituted chalcone)-3-(substituted phenyl)-5-(substituted phenyl)-2-pyrazoline (0.01 mole), guanidine carbonate (0.01 mole) and NaOH (0.01 mole) was dissolved in DMF (40 ml). The reaction mixture was stirred and refluxed for 5 hours then poured onto crushed ice. The product was washed with cold water and purified by re-crystallization from suitable solvent.

2) Synthesis of 1-(3'-substituted phenyl-5'-imino-aryl pyrimidine)-3-(substituted phenyl)-5-(substituted phenyl)-2-pyrazoline [2(a-i)] : A mixture of 1-(3'-substituted phenyl-5'-amino pyrimidine)-3-(substituted phenyl)-5-(substituted phenyl)-2-pyrazolines **1** (0.01 mole) and different aldehydes (0.01 mole) were dissolved in ethanol containing one drop of concentrated Sulphuric acid and refluxed for 3 to 5 hours in water bath. The reaction was monitored by TLC. It was then cooled and added to ice cold water. The precipitated solid obtained was filtered, washed with water and recrystallized from ethanol. Physicochemical characterization and Spectral data of synthesized compounds were shown in table 1 and 2 respectively.

Evaluation of antimicrobial activity: All the synthesized compounds were evaluated for their antibacterial activity against *Bacillus subtilis*, *Streptococcus aureus*: gram positive strain, *Pseudomonas aeruginosa*, *Escherichia coli*: gram negative strain and antifungal activity against *Aspergillus niger* using agar-well diffusion method³⁰⁻³¹. The preparation of nutrient broth, subculture and agar medium were done as per standard procedure. Muller-Hinton and potato-dextrose- agar medium were used for bacterial and fungal culture respectively. Each petri dish was inoculated with one bacterial or fungal culture by spreading the suspension of the organism with a sterile glass rod with a bended tip. Wells of 10mm diameter were made at equal distances using sterile cork borer and a specific volume of the synthesized compound were placed in them, by using sterile pipettes. All the compounds and standard were tested at 200 µg dose level and DMSO used as a control. Petri dishes were incubated at 37°C for 24 hour and at 28°C for 48 hour for bacterial and fungal activity respectively. The compound diffuses through agar around its well and produces a clear zone of inhibition. After appropriate incubation the diameter of zone of inhibition of each well was measured. Duplicate were maintained and the average values were calculated for estimating the degree of activity of the antimicrobial substances.

Scheme 1

Where,

	R ₁	R ₂	R ₃	R ₄
2a	4-NO ₂	4-OH	2,4-(Cl) ₂	4-OH
2b	4-NO ₂	4-OH	2,4-(Cl) ₂	3-NO ₂
2c	4-NO ₂	4-OH	2,4-(Cl) ₂	4N(CH ₃) ₂
2d	4-NO ₂	4N(CH ₃) ₂	4N(CH ₃) ₂	4-OH
2e	4-NO ₂	4N(CH ₃) ₂	4N(CH ₃) ₂	3-NO ₂
2f	4-NO ₂	4N(CH ₃) ₂	4N(CH ₃) ₂	4N(CH ₃) ₂
2g	4-OH	H	4-N-(CH ₃) ₂	4-OH
2h	4-OH	H	4-N-(CH ₃) ₂	3-NO ₂
2i	4-OH	H	4-N(CH ₃) ₂	4N(CH ₃) ₂

Table 1: Physicochemical characterization data of compound 2(a-i)

Compound ID	Molecular Formula	M.P (°C)	Yield (%)	Analysis		
				C %	H %	N %
2a	C ₃₂ H ₂₂ N ₆ O ₄ Cl ₂	152	67	61.44 (61.46)	3.52 (3.50)	13.44 (13.46)
2b	C ₃₂ H ₂₁ N ₇ O ₅ Cl ₂	124	71	58.72 (58.75)	3.21 (3.18)	14.99 (14.96)
2c	C ₃₄ H ₂₇ N ₇ O ₃ Cl ₂	146	68	62.58 (62.60)	4.14 (4.10)	15.03 (15.09)
2d	C ₃₆ H ₃₄ N ₈ O ₃	168	67	69.01 (69.05)	5.43 (5.44)	17.89 (17.92)
2e	C ₃₆ H ₃₃ N ₈ O ₄	112	87	65.95 (65.98)	5.04 (5.08)	19.24 (19.28)
2f	C ₃₈ H ₃₉ N ₈ O ₂	126	78	69.83 (69.86)	5.97 (5.94)	19.30 (19.35)
2g	C ₃₄ H ₃₀ N ₆ O ₂	141	69	73.65 (73.68)	5.42 (5.46)	15.16 (15.19)
2h	C ₃₄ H ₂₉ N ₇ O ₃	129	65	69.98 (70.01)	4.97 (5.03)	16.81 (16.84)
2i	C ₃₆ H ₃₅ N ₇ O	138	70	74.36 (74.40)	6.02 (5.98)	16.87 (16.92)

Table 2: Spectral Data of compound 2(a-i)

Compound ID	IR (KBr, $\gamma_{\max}$, cm ⁻¹)	¹ H NMR (DMSO) 400 MHz, δ ppm	¹³ C NMR (DMSO) 100 MHz, δ ppm	Mass Spectra (m/z), (M ⁺)
2a	3235.16 (Ar-OH); 3049.71, 2192.11 (Ar-H); 2822.16, 2720.18 (C-H); 1662.55, 1604.19 (C=N); 1552.48 (C=C); 1539.72, 1370.69 (Ar-NO ₂); 728.52 (C-Cl)	9.40 (s, 1H, -OH); 8.55 (s, 1H, -N=CH-); 6.68-8.22 (m, 16H, Ar-H); 5.63 (dd, 1H, C ₅ pyrazoline); 3.66 (dd, 1H, C _{4cis} pyrazoline); 3.22 (dd, 1H, C _{4trans} pyrazoline)	170.12, 164.90, 163.40, 157.81, 151.76, 115.98 – 158.50, 93.76, 59.02, 41.99	624
2b	3242.63 (Ar-OH); 3050.16, 2916.77 (Ar-H); 2861.02, 2714.10 (C-H); 1660.18, 1602.32 (C=N); 1552.60 (C=C); 729.13 (C-Cl); 1542.12, 1368.15 (Ar-NO ₂);	9.60 (s, 1H, -OH); 8.84 (s, 1H, -N=CH-); 6.70-8.34 (m, 16H, Ar-H); 5.60 (dd, 1H, C ₅ pyrazoline); 3.61 (dd, 1H, C _{4cis} pyrazoline); 3.17 (dd, 1H, C _{4trans} pyrazoline)	169.57, 164.88, 163.58, 157.69, 151.80, 115.99 – 157.75, 93.66, 58.88, 42.38	653
2c	3239.02 (Ar-OH); 3048.27, 2920.31 (Ar-H); 862.11, 2739.60 (C-H); 1660.19, 1603.28 (C=N); 1552.72 (C=C); 1536.29, 1372.69 (Ar-NO ₂); 728.71 (C-Cl)	9.24 (s, 1H, -OH); 8.48 (s, 1H, -N=CH-); 6.69-8.22 (m, 16H, Ar-H); 5.62 (dd, 1H, C ₅ pyrazoline); 3.65 (dd, 1H, C _{4cis} pyrazoline); 3.25 (dd, 1H, C _{4trans} pyrazoline); 3.04 (s, 6H, -N(CH ₃) ₂)	170.03, 164.88, 163.44, 157.70, 151.881, 110.20 – 157.75, 94.12, 59.07, 42.63, 40.44	651
2d	3231.51 (Ar-OH); 3048.18, 2918.20 (Ar-H); 2872.30, 2719.21 (C-H); 1661.91, 1602.78 (C=N); 1552.48 (C=C); 1536.42, 1372.55 (Ar-NO ₂);	9.28 (s, 1H, -OH); 8.54 (s, 1H, -N=CH-); 6.74-8.20 (m, 17H, Ar-H); 5.65 (dd, 1H, C ₅ pyrazoline); 3.66 (dd, 1H, C _{4cis} pyrazoline); 3.24 (dd, 1H, C _{4trans} pyrazoline); 3.05 (s, 12H, -N(CH ₃) ₂)	169.17, 164.44, 164.21, 158.47, 110.76 – 156.08, 151.98, 93.77, 58.76, 42.44, 40.41	626
2e	3049.28, 2908.22 (Ar-H); 2880.61, 2742.81 (C-H); 1661.72, 1601.89 (C=N); 1552.60 (C=C); 1532.38, 1366.14 (Ar-NO ₂);	8.66 (s, 1H, -N=CH-); 6.88-8.53 (m, 16H, Ar-H); 5.63 (dd, 1H, C ₅ pyrazoline); 3.65 (dd, 1H, C _{4cis} pyrazoline); 3.23 (dd, 1H, C _{4trans} pyrazoline); 3.05 (s, 12H, -N(CH ₃) ₂)	169.57, 164.48, 164.18, 158.12, 151.95, 110.22 – 151.89, 94.02, 58.60, 42.70, 40.48	655
2f	3044.62, 2922.17 (Ar-H); 2823.72, 2729.64 (C-H); 1661.78, 1603.45 (C=N); 1551.68 (C=C); 1540.19, 1372.28 (Ar-NO ₂);	8.50 (s, 1H, -N=CH-); 6.72-8.24 (m, 17H, Ar-H); 5.66 (dd, 1H, C ₅ pyrazoline); 3.61 (dd, 1H, C _{4cis} pyrazoline); 3.24 (dd, 1H, C _{4trans} pyrazoline); 3.04 (s, 18H, -N(CH ₃) ₂)	170.02, 164.44, 164.09, 158.22, 151.98, 110.28 – 151.47, 93.98, 58.76, 41.98, 40.40	653
2g	3242.52 (Ar-OH); 3052.16, 2917.28 (Ar-H); 1831.41, 2725.70 (C-H); 1661.52, 1601.91 (C=N); 1555.40 (C=C);	8.92 (s, 1H, -OH); 8.65 (s, 1H, -N=CH-); 6.80-8.10 (m, 18H, Ar-H); 5.63 (dd, 1H, C ₅ pyrazoline); 3.69 (dd, 1H, C _{4cis} pyrazoline);	169.25, 164.55, 164.02, 157.78, 110.22 – 156.08, 152.10, 93.70, 58.76,	554

		3.22(dd,1H,C _{4trans} pyrazoline); 3.03 (s,12H,-N(CH ₃) ₂);	42.60, 40.33	
2h	3244.19 (Ar-OH) ; 3061.02,2917.11(Ar-H) 2832.61,2731.08 (C-H) 1662.19,1604.28 (C=N); 1552.16 (C=C); 1532.81,1365.89 (Ar-NO ₂);	8.90 (s,1H,-OH); 8.41 (s,1H,-N=CH-); 6.84-8.41 (m,18H,Ar-H); 5.65 (dd,1H,C ₅ pyrazoline); 3.68 (dd,1H,C _{4cis} pyrazoline); 3.22(dd,1H,C _{4trans} pyrazoline); 3.03 (s,12H,-N(CH ₃) ₂);	168.98, 164.50, 163.99, 157.80, 110.20 – 159.48, 152.20, 93.80, 58.60, 42.69, 40.25	583
2i	3240.27 (Ar-OH) ; 3048.82,2909.10 (Ar-H) 2823.15,2719.61 (C-H) ; 1662.24,1605.31 (C=N); 1551.80 (C=C); 1530.79,1372.19 (Ar-NO ₂);	8.81 (s,1H,-OH); 8.36 (s,1H,-N=CH-); 6.79-8.22 (m,18H,Ar-H); 5.63 (dd,1H,C ₅ pyrazoline); 3.66 (dd,1H,C _{4cis} pyrazoline); 3.23(dd,1H,C _{4trans} pyrazoline); 3.04 (s,12H,-N(CH ₃) ₂);	169.20, 164.53, 163.98, 157.82, 110.20 – 159.84, 152.18, 93.78, 58.84, 42.70, 40.30	581

Table 3: The *In Vitro* antimicrobial activity of compound, 2(a-i)

SNo	Derivative	Diameter of zone of inhibition (mm) for organism				
		Bacterial Strains				Fungal strains
		Gram negative		Gram positive		
		<i>Escherichia coli</i>	<i>Pseudomonas Aeruginosa</i>	<i>Streptococcus Aurius</i>	<i>Bacillus Subtilis</i>	
1	2a	20	19	24	17	12
2	2b	19	17	23	16	13
3	2c	20	18	23	17	13
4	2d	18	20	22	19	14
5	2e	17	19	20	16	13
6	2f	18	20	21	18	14
7	2g	12	22	24	19	12
8	2h	12	21	22	18	11
9	2i	13	24	23	20	12
10	Ciprofloxacin	48	49	40	40	--
11	Fluconazole	--	--	--	--	41

RESULT AND DISCUSSION

Chemistry: The general methods employed for the synthesis of desired Schiff bases 2(a-i) incorporated with pyrimidine and pyrazoline nuclei were outlined in Scheme 1. The precursor chalcones were synthesized with good yields by Claisen-schmidt condensation reaction of different aromatic aldehydes and acetophenones, in presence of 40% NaOH in ethanol. The chalcones were cyclised into N-acetyl-2 pyrazoline derivatives by reacting with hydrazine hydrate and glacial acetic acid. N-substituted chalcones-2-pyrazoline were synthesized by condensation of N-acetyl-2 pyrazoline with substituted benzaldehydes in ethanolic sodium hydroxide solution. 1-[(3'-substituted phenyl)-5'-(amino pyrimidine)]-3-substituted phenyl-5-substituted phenyl-2-pyrazole 1 were obtained by cyclising N-substituted chalcone-2 pyrazoline with guanidine carbonate in DMF. The targeted analogues 1-[(3'-substituted phenyl)-5'-(imino aryl pyrimidine)-3-(substituted phenyl)-5-(substituted phenyl)-2-pyrazolines 2(a-i) were obtained with good yield by refluxing 1 with different aromatic aldehydes in presence of concentrated sulphuric acid. The synthesized compound were characterized by elemental analysis, IR, NMR(¹H and ¹³C) and Mass spectrometry. The physicochemical characterization data of synthesized compounds were given in Table 1.

The IR spectra of compounds 2(a-i) showed strong absorption band in the range of 1660-1663 cm⁻¹ attributed to (HC=N) vibration characteristics of imine groups which are not present in compound 1. The absence of band in the range of 3400-3550 cm⁻¹ confirms the conversion of primary amino (-NH₂) group into azomethine in the product 2(a-i). The different absorption bands appeared in the region 1550-1560cm⁻¹ (for C=C),

3242cm⁻¹ (for Ar-OH), 3049cm⁻¹ (for Ar-H), 1532.38 and 1366.14 cm⁻¹ (for Ar-NO₂) groups.

The ¹H NMR spectrum of compounds 2(a-i) showed a singlet between δ 8.5-8.9ppm due to proton of imine group (N=CH) and multiplet between δ 6.68-8.53ppm due to aromatic proton (Ar-H). The different signals obtained in the range of δ 3-6 ppm represent the presence of different protons present in the pyrazoline and pyrimidine ring. The absence of singlet in the range of δ 4-5ppm indicates the absence of NH₂ proton. The ¹³C NMR spectra were consistent with the ¹H NMR spectra. The aryl carbon and azomethine carbon of all the Schiff bases exhibited peaks in the region of δ168-172 ppm and δ110-160 ppm respectively. Peaks in the region of 152, 42, 58 and 164, 93, 158, 164 ppm were assigned to C₃, C₄ and C₅ of pyrazoline and C₁, C₂, C₃, C₅ of pyrimidine nuclei δ 40-41 ppm was observed for N-(CH₃)₂ carbon. The mass spectra showed the expected peaks. In case of 2d the molecular ion peak observed at (m/z), 626 (M⁺) which matches with its molecular formula C₃₆H₃₄N₈O₃.

PHARMACOLOGY

Antibacterial and Antifungal Activity : The Schiff bases 2(a-i) were screened for their antibacterial activity *Bacillus subtilis*, *Streptococcus aureus*: gram positive strain, *Pseudomonas aeruginosa*, *Escherichia coli*: gram negative strain and antifungal activities against *Aspergillus niger* by agar well diffusion method. Standard ciprofloxacin and fluconazole were also tested under similar conditions for comparison. Results are represented in Table 3.

All compounds showed high activity against *Streptococcus aureus*. 2a, 2d, 2e, 2f, 2g, 2h, 2i showed high activity against

Pseudomonas aeruginosa and 2b, 2c showed moderate activity. 2a, 2b, 2c showed high activity for *Escherichia coli* and others showed poor to moderate activity. 2d, 2h, 2i exhibit good activity against *Bacillus subtilis*. All compounds showed poor to moderate activity against *Aspergillus niger*. The results showed moderate to high activity of 2(a-i) for selected micro-organisms.

CONCLUSION

In this work, different Schiff bases incorporated with pyrimidine and pyrazoline nuclei were synthesized with good yields and characterized by elemental and spectral data. The antimicrobial activity results inferred that the compounds 2(a-i) were more active for bacterial strains than fungal strains. The compounds were highly active for *Pseudomonas aeruginosa* and *Streptococcus aureus*. All are poor to moderately active for *Aspergillus niger*. 2a, 2b, 2c, 2d, 2e, 2f showed good activity for bacterial strains than fungal strain. Unsubstituted phenyl ring show lower activity than substituted. Chloro substituted ring show high activity. Further work needs to be carried out to investigate the structure activity relationship.

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