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Research Article

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Synthesis of Some Schiff's Base Analogues of Pyrimidine and Evaluation of Antimicrobial Efficacy

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ABSTRACT

Pyrimidine constitutes an important class of heterocycles in drug discovery and is very well known for their pharmacological activities. Pyrimidines and their derivatives possess biological and pharmacological activities such as antibacterial, antifungal, anti-inflammatory, analgesic, anticonvulsant, antitubercular, anti-cancer, etc. properties. Azomethines are the compounds, which contain –HC=N- group. These compounds are known as Schiff" base to honor Hugo Schiff, who synthesized these compounds first. Schiff" bases, an important group of compounds, play a vital role in pharmaceutical as well as in clinical fields. Schiff"s bases containing Pyrimidine derivatives have attracted attention of medicinal chemistry for both with regard to heterocyclic chemistry and the pharmacological activities associated with them, inspired us to synthesize Methyl-2-[2-(arylidine)hydrazinyl]-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carboxylate by reaction of methyl-4-(4-fluorophenyl)-2-hydrazinyl-6-isopropylpyeimidine-5-carboxylate with various substituted benzaldehydes in presence of catalytic amount of acetic acid using ethanol as a solvent. The synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H-NMR and Mass spectral studies and in vitro antimicrobial activities were evaluated. Antimicrobial data revealed that among all the compounds screened, many compounds were found to have promising antimicrobial activity.

Keywords: Pyrimidine; Schiff' base; Aldehydes; Antimicrobial activities

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INTRODUCTION

Hybrid molecules, an emerging trend containing two or more structural domains, acting on same or different targets have been reported to exhibit diverse pharmacological activities [1] Pyrimidines, refers to a six membered heterocyclic system analogous to benzene having two nitrogen atoms at 1- and 3-position, are widely found in nature as they are vital components of nucleic acids, i.e., DNA and RNA. Pyrimidine and its derivatives demonstrate a diverse array of biological and pharmacological activities including anticonvulsant, antibacterial, antifungal, etc. properties. This broad spectrum of biochemical targets has been facilitated by the synthetic versatility of pyrimidine, which has allowed the generation of a large number of structurally diverse derivatives including analogues derived from substitution of the aryl rind, and/or derivatisation of the pyrimidine nitrogen. Pyrimidines are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds and as raw materials for drug synthesis [2-9]. Schiff's Bases, the class of organic compounds containing the azomethine (-HC=N-) group in their structure, are also called imine compounds. Schiff' bases have been found to be potent drug in pharmaceutical industries and possess a wide spectrum of biological activity [10-15]. Due to the various biological activities of pyrimidines and Schiff' bases, synergistic activity was expected upon attaching these two moieties. In this contex, Methyl-2-[2-(arylidine)hydrazinyl]-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carboxylate derivatives have been synthesized.

EXPERIMENTAL SECTION

All melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a FTIR - 8400 spectrophotometer. H NMR spectra recorded on a Bruker 300 MHz spectrometer with DMSO as a solvent and tetra methyl silane (TMS) as internal standard. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as *s* (singlet), *d* (doublet) and *m* (multiplate). Thin Layer Chromatography (TLC) analytical separation was conducted with Silica Gel 60 F-254 (Merck) plates of 0.25 mm thickness eluted with Hexanes : Ethyl acetate (7 : 3 v/v) and visualized with UV (254 nm) or iodine to check the purity of the synthesised compounds.

The antimicrobial activity was assayed by using the microtitre broth dilution method by measuring the zone of inhibition in mm. All the compounds were screened in vitro for their antimicrobial activities against varieties of bacterial strains such *Staphylococcus aureus, Escherichia coli, Bacillus megaterium, Pseudomonas aeruginosa fungi Aspergillus niger and Aspergillus flavus* at various concentration. Standard drugs like Streptomycin, Ampicillin and Nystatin were used for comparison purpose (Table 1 and Chart 1). General Procedure for the synthesis of compounds (3) and KLDa are as under (Figure 1).

Preparation of methyl 4-(4-fluorophenyl)-2-hydrazinyl-6-isopropylpyrimidine-5-carboxylate (3)

Methyl 4-(4-fluorophenyl)-2-hydroxy-6-isopropylpyrimidine-5-carboxylate (0.01 mol, 2.9 gm) was taken and added $POCl_3$ (10 ml) at 0-5°C, heated this mixture at 70-80°C on water bath for 5-6 hrs. The completion of reaction was monitored by TLC. After completion of reaction the reaction mass was cooled at room temperature and poured slowly in ice water with stirring. The product was filtered, washed with sodium bicarbonate solution and dried. Taking this product (2) (methyl-2-chloro-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carboxylate) (0.01 mol, 3.08 gm), added neat hydrazine hydrate (12 ml) and heated at 80-85°C on water bath for 7-8 hrs. After completion of the reaction, the reaction mass was cooled at room temperature and poured into ice water. The product was filtered and washed with water and dried. Yield: 75%, m.p. - 120°C.

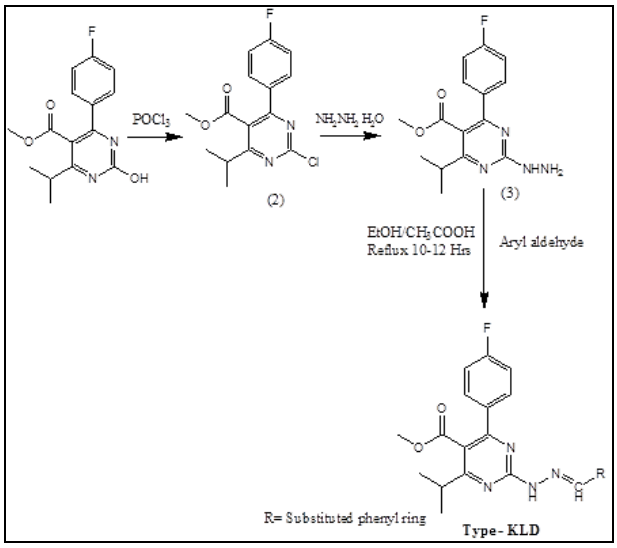

Figure 1: Procedure for the synthesis of compounds (KLDa)

Preparation of methyl 4-(4-fluorophenyl)-6-isopropyl-2-(2-(4-nitrobenzylidene) hydrazinyl) pyrimidine - 5-carboxylate (KLDa)

A mixture of 4-(4-fluorophenyl)-2-hydrazinyl-6-isopropylpyrimidine-5-carboxylate (0.304 gm, 0.001 mol) in ethanol (20 ml) was added to a solution of 4-nitro benzaldehyde (0.23 gm, 0.0015 mol) in ethanol, added glacial acetic acid (1.5 ml) as a catalyst. The reaction mass was refluxed for 8-10 hrs, the solvent was removed and residue was poured into ice cold water and solid mass so obtained was isolated, dried and purified by recrystallization from methanol. Yield: 58%, m.p.- 98°C [$C_{22}H_{20}FN_5O_4$; found: C-60.44, H-4.69, N-16.14; calculated: C-60.41, H-4.61, N-16.01%]. Similarly, other Methyl-2-(2-(arylidine) hydrazinyl)-4-(4-fluorophenyl)-6-isopropyl pyrimidine-5-carboxylate were prepared. The physical constants are recorded in Table 2.

Compound (KLDa) IR (KBr, cm^{-1}): 3201 (N-H bonded str.), 1713 (-C=O ester str.) 1647 (-C=N- azomethine str..), 1511 (Nitro group str.), 1462 (aromatic ring -C=C- str), 1152 (isopropyl –C-H str.); ^{1}H NMR (DMSO – d_6, δ, ppm): 1.98-2.5 (6H, d, Isopropyl), 3.6 (3H, s, ester –OCH_3), 2.5 (1H, m, -CH-), 7.3-8.3 (8H, s, Phenyl ring), 11.9 (1H, s, Sec. Amine),; Mass m/z = 438.4.

RESULTS AND DISCUSSION

Antibacterial Activity

When the synthesized compounds (KLD a-j) were tested aginst gram-positive bacteria, compound KLD b [Ar= 2-NO_2-C_6H_4] was found to exhibit excellent activity against *B. subtilis* as compared to the standard drug ampicillin. However compound KLD e [Ar=4-Cl-C_6H_4] was found to possess significant activity and compounds KLD d and KLD f were found to have good activity against the same bacterial strain. On other hand the synthesized compounds were found have less toxic activity against *S. aureus* than that of against *B. subtilis.* Compounds LKD b, KLD d, KLD e, KLD f, KLD g and KLD h were found to possess good to moderate activity against *S. aureus* as compared to the standard drug ampicillin. Compounds KLD a, KLD c, KLD i and KLD j were found to have the least toxic effect on both the gram-positive bacteria. When the same set of synthesized compound were tested against gram-negative bacteria, compounds KLD b [Ar=2-NO_2-C_6H_4] and KLD j [Ar=3-OH-C_6H_4] were found to possess significant activity as compared to the standard drug streptomycin. However compound KLD d, KLD e, KLD f were found to have good activity as compared to the standard drug. Compound KLD c, KLD g, KLD h and KLD i was found to have the least toxic effect on the gram-negative bacterial strain.

Antifungal Activity

The antifungal tests were performed against two different fungal strains *A. niger and A. flavus,* where nystatin was used as a standard drug. The antifungal property of the synthesized compounds (KLD a-j) was found to be less effective as compared to the bacterial strains. The compounds KLD b [Ar= 2-NO_2-C_6H_4] and KLD e [Ar = 4-Cl-C_6H_4] were found to exhibit excellent activity as compared to the standard drug. However compounds KLD a, KLD d and KLD f were found to have moderate activity as compared to the standard drug. Compounds KLD c, KLD g, KLD h, KLD i and KLD j were the least toxic against both the fungal strains.

Table 1: Antibacterial and antifungal activity data of compounds (KLD a-j)

Compounds	Minimum Inhibitory Concentration (MIC) in µg/ml					
	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	B. subtilis	***S. aureus***	***E. coli***	***P.aeruginosa***	***A. niger***	***A. flavus***
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
KLD a	1000	1000	500	1000	500	1000
KLD b	125	250	250	250	250	**125**
KLD c	1000	1000	1000	1000	1000	1000
KLD d	500	500	500	500	1000	500
KLD e	250	500	500	500	250	250
KLD f	500	500	500	500	500	500
KLD g	1000	500	1000	1000	1000	1000
KLD h	1000	500	1000	1000	1000	1000
KLD i	1000	1000	1000	1000	1000	1000
KLD j	1000	1000	250	500	1000	1000

Table 2: Characterisation data of compound (KLD a-j)

No	R Substitution	Molecular Formula	M.P. (°C)	Nitrogen %	
				Calcd	Found
KLD a	4-NO_2-C_6H_4	$C_{22}H_{20}FN_5O_4$	98°C	16.01	16.14
KLD b	2-NO_2-C_6H_4	$C_{22}H_{20}FN_5O_4$	135°C	16.01	16.09
KLD c	4-$N(CH_3)_2$-C_6H_4	$C_{24}H_{26}FN_5O_2$	195°C	16.08	16.02
KLD d	C_6H_5	$C_{22}H_{21}FN_4O_2$	175°C	14.28	14.22
KLD e	4-ClC_6H_4	$C_{22}H_{20}ClFN_4O_2$	200°C	13.12	13.09
KLD f	4-OH-3-OCH_3-C_6H_3	$C_{23}H_{23}FN_4O_4$	100°C	12.78	12.69
KLD g	2,4,5-$(OCH_3)_3$ -C_6H_2	$C_{25}H_{27}FN_4O_5$	78°C	11.61	11.57
KLD h	3,4,5-$(OCH_3)_3$ -C_6H_2	$C_{25}H_{27}FN_4O_5$	97°C	11.61	11.63
KLD i	2,5-$(OCH_3)_2$-C_6H_3	$C_{24}H_{25}FN_4O_4$	106°C	12.38	12.43
KLD j	3-OH-C_6H_4	$C_{22}H_{21}FN_4O_3$	140°C	13.72	13.7

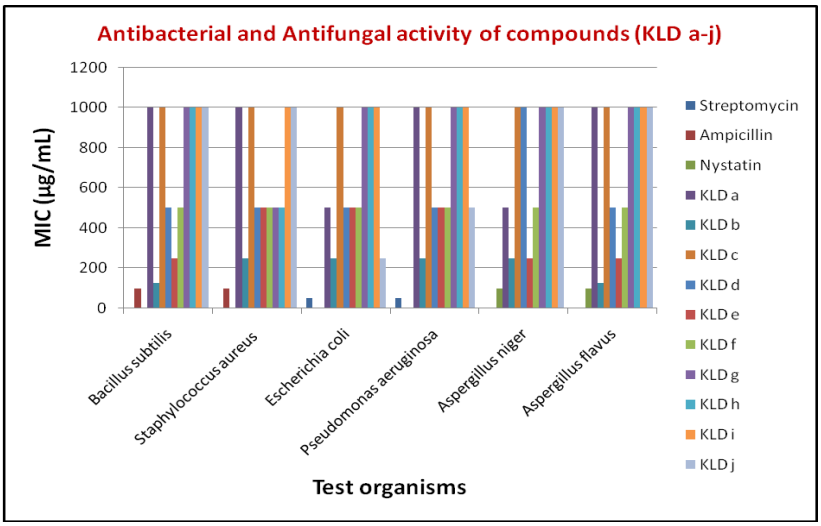

Chart 1: Antibacterial and antifungal activity data of compounds (KLD a-j)

CONCLUSION

The present study leads to a convenient synthetic method for the synthesis of new compounds which shows significant antibacterial and antifungal activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically useful products.

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