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Synthesis, Characterization and Biological Evaluation of Some Novel Pyrrolopyrimidine Analogues

SANJAY P. TAJANE[1], GANAPAVARAPU VEERA RAGHAVA SHARMA[1], SUSHILKUMAR DHANMANE[2,*] and GANGA GORE[3]

[1]Department of Chemistry, GITAM Deemed to be University, Vishakhapatnam-530045, India
[2]Department of Chemistry, Fergusson College, Pune-411004, India
[3]Department of Chemistry, Dapoli Urban Bank Sr. Science College, Dapoli-415712, India

*Corresponding author: E-mail: sushorganic@gmail.com

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The evidences over drug resistance, narrow spectrum and side effects of commercially available antimicrobials intended present study to carry out synthesis and antimicrobial evaluation of some novel pyrrolopyrimidine analogues. Current study involved synthesis of some novel 4-[2-(substituted benzylidene)hydrazinyl]-7*H*-pyrrolo[2,3-*d*]pyrimidines (**2a-j**) followed by evaluation of their antimicrobial potential against bacterial and fungal strains. The synthesis of new pyrrolopyrimidine analogues **2a-j**, was carried out in two distinct stages. In first step, azo compound 4-hydrazinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine was synthesized by reacting hydrazine hydrate with 4-chloropyrrolopyrimidine, whereas in second step, novel imino analogues of 4-hydrazinyl-7*H*-pyrrolo[2,3-*d*]pyrimidines (**2a-j**) were synthesized by treating with various substituted benzaldehydes. All the synthesized compounds were subjected to characterization based on IR, ^{1}H NMR and CHN analysis data. The synthesized compounds were also evaluated for their antibacterial and antifungal potential using disc diffusion method. Results of present study revealed that tested compounds possess significant inhibitory potential against tested bacterial and fungal strains. Present study concludes that novel compounds **2a-j** possess high antibacterial and antifungal potential, however they must be further evaluated preclinically and clinically for their therapeutic significance.

Keywords: Pyralopyrimidinehydrazide, Hydrazine hydrate, Dimethyl formamide, Potassium carbonate.

INTRODUCTION

The evidences over drug resistance, narrow spectrum, and side effects of commercially available antimicrobials to treat various types of bacterial, fungal, and viral infections motivates the investigators to invent new heterocyclic antimicrobials [1]. Facts suggest that pyrrolopyrimidine as an important heterocyclic system as possess various pharmacological properties such as antibacterial [2,3], antimycobacterial [4,5], anti-inflammatory [5,6], antifungal [7,8], antitumor [8,9], antiproliferative [10,11], antiviral [12], muscarinic antagonist [13, 14] and anticancer [13,15]. Several biologically active drugs, including vemurafenib, pexidartinib, plexxikon, famitinib, peficitinib, antalarmin, *etc*. are known to possess pyrrolopyridines in their chemical structure [16].

Given the preceding, we set out to develop and synthesize pyrrolo[2,3-*b*]pyrimidines with the substituted benzaldehyde group at a biologically active position. Synthesis of novel compounds with some fundamental structural properties with known physiologically active molecules is crucial to hunt new leads in drug development programs. Literary facts suggest that biological potential is affected by nature and position of the substituents [17,18]. Several studies indicated that incorporation of aromatic, heteroaromatic, halogen, hydrazide and imino groups in the organic agents improve the antimicrobial potential, widens the antimicrobial spectrum, encounters the drug resistance and reduces the side effects of antimicrobial drugs [19-22].

In light of potential applications of heteroaromatics with fused ring systems or substituted with halogens, hydrazides and imino groups [23-26], present study was designed to carry out the synthesis and antimicrobial evaluation of some novel pyrrolopyrimidine analogues. Present study describes the synthesis and characterization of novel 4-hydrazinyl-7*H*-pyrrolo-

[2,3-*d*]pyrimidine analogues, followed by evaluation of their antimicrobial and antifungal activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Candida albicans*.

EXPERIMENTAL

All the chemicals used were of the highest possible purity and were of the analytical reagent grade (AR). They comprised 2/3/4-iodobenzaldehyde, 3,4/3,5-diiodobenzaldehyde, 2,3/2,4/3,4/3,5-dibromobenzaldehyde, 4-chloro-7*H*-pyrrolo[2,3-*d*]-pyrimidine and hydrazine hydrate. Melting points were measured using open capillary tube method and are uncorrected. Characterization of synthesized compounds was done using IR spectra on Jasco FTIR spectrometer at ranging from 4000-400 cm^{-1}; and proton magnetic resonance spectra recorded on Bruker DPX 300 using DMSO as solvent, on δ value scale in ppm with TMS as standard. Purity of synthesized compounds and reactions were monitored by TLC experiment using aluminum sheets and silica gel 60 F_{254} (Merck, India) with methanol: acetone (9.5:0.5) solvent mixture in SPRECTROLINE® CM-26 UV viewing chamber [27,28].

Synthesis of 4-[2-(substituted benzylidene)hydrazinyl]-7*H*-pyrrolo[2,3-*d*]pyrimidines (2a-j): Compounds **2a-j** were synthesized as per the standard protocol with minor modification [29,30], briefly a mixture of 4-hydrazinyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine (0.01 mol) and 2-iodobenzaldehyde (0.01 mol) in ethanol were refluxed for 7 h at 60-70 ºC. The resultant crude was filtered, washed with ethanol and diethyl ether and finally vacuum dried to offer pure compound **2a**. Following the similar protocol, other compounds **2b-j** were also synthesized (**Scheme-I**).

4-[2-(2-Iodobenzylidene)hydrazinyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidine (2a): White crystals, yield: 76.98 %; m.p.: 195 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3365 (N-H), 3065 (=C-H), 1592 (C=N), 1486, 1447 (C=C), 578 (C-I); ^{1}H NMR (DMSO-d_6, δ ppm): 12.90 (s, 1H, NH), 8.36 (s, 1H, NH-Ar), 8.57 (s, 1H, N=CH), 7.56-8.01 (m, 6H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5I$: C, 42.99 (42.78); H, 2.78 (2.70); N, 19.28 (19.15); I, 34.94 (34.47).

4-[2-(3-Iodobenzylidene)hydrazinyl]-7H-pyrrolo[2,3-*d*]-pyrimidine (2b): White crystals, yield: 77.62 %, m.p.: 199 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3360 (NH), 3065 (=C-H), 1592 (C=N), 1485, 1448 (C=C), 523 (C-I); ^{1}H NMR (DMSO-d_6, δ ppm): 12.91 (s, 1H, NH), 8.36 (s, 1H, NH-Ar), 8.57 (s, 1H, N=CH), 7.56-8.01 (m, 6H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5I$: C, 42.99 (42.93); H, 2.78 (2.73); N, 19.28 (19.25); I, 34.94 (34.87).

4-[2-(4-Iodobenzylidene)hydrazinyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidine (2c): White crystals, yield: 79.88%, m.p.: 201 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3368 (N-H), 3064 (=C-H), 1591 (C=N), 1483, 1444 (C=C), 485 (C-I); ^{1}H NMR (DMSO-d_6, δ ppm): 12.86 (s, 1H, NH), 8.35 (s, 1H, NH-Ar), 8.57 (s, 1H, N=CH), 7.56-8.00 (m, 6H Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5I$: C, 42.99 (42.95); H, 2.78 (2.75); N, 19.28 (19.25); I, 34.94 (34.89).

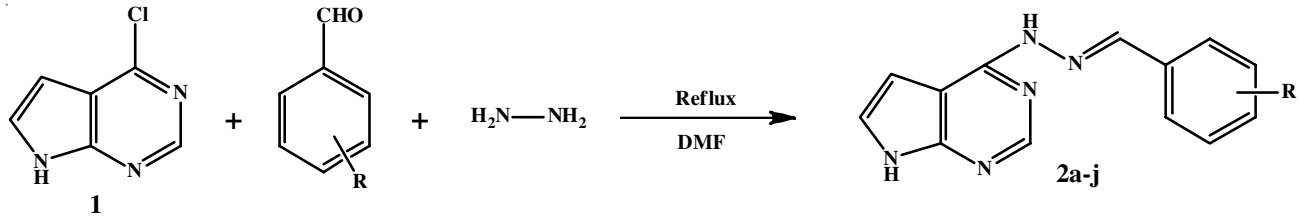
4-[2-(3,4-Diiodobenzylidene)hydrazinyl]-7*H*-pyrrolo-[2,3-*d*]pyrimidine (2d): White crystals, yield: 76.97 %, m.p.: 206 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3373 (N-H), 3061 (=C-H), 1589 (C=N), 1482, 1449 (C=C), 488 (C-I); ^{1}H NMR (DMSO-d_6, δ ppm): 12.86 (s, 1H, NH), 8.33 (s, 1H, NH-Ar), 8.55 (s, 1H, N=CH), 7.56-8.13 (m, 6H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5I_2$: C, 31.93 (31.90); H, 1.85 (1.81); N, 14.32 (14.28); I, 51.90 (51.83).

4-[2-(3,5-Diiodobenzylidene)hydrazinyl]-7*H*-pyrrolo-[2,3-*d*]pyrimidine (2e): White crystals, yield: 81.06 %, m.p.: 210 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3398 (N-H), 3063 (=C-H), 1588 (C=N), 1491, 1451 (C=C), 487 (C-I); 1H-NMR (DMSO-d6, ppm) ?: 12.89 (s, 1H, NH), 8.36 (s, 1H, NH-Ar), 8.56 (s, 1H, N=CH), 7.56-8.00 (m, 5H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5I_2$: C 31.93 (31.88), H 1.85 (1.84), N 14.32 (14.25), I, 51.90 (51.86).

4-[2-(2,3-Dibromobenzylidene)hydrazinyl]-7*H*-pyrrolo-[2,3-*d*]pyrimidine (2f): White crystals, yield: 80.71, m.p.: 205 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3369 (N-H), 3067 (=C-H), 1592 (C=N), 1487, 1449 (C=C), 649 (C-Br); ^{1}H NMR (DMSO-d_6, δ ppm): 12.86 (s, 1H, NH), 8.33 (s, 1H, NH), 8.55 (s, 1H, N=CH), 7.56-8.13 (m, 5H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5Br_2$: C, 39.52 (38.90); H, 2.30 (2.21); N, 17.73 (17.29); Br, 40.45 (40.41).

4-[2-(2,4-Dibromobenzylidene)hydrazinyl]-7*H*-pyrrolo-[2,3-*d*]pyrimidine (2g): White crystals, yield: 76.99 %, m.p.: 209 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3373 (N-H), 3069 (=C-H), 1590 (C=N), 1489, 1451 (C=C), 642 (C-Br); ^{1}H NMR (DMSO-d_6, δ ppm): 12.86 (s, 1H, NH), 8.33 (s, 1H, NH-Ar), 8.55 (s, 1H, N=CH), 7.560-8.131 (m, 5H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5Br_2$: C, 39.52 (39.50); H, 2.30 (2.26); N, 17.73 (17.26); Br, 40.45 (40.44).

4-[2-(2,5-Dibromobenzylidene)hydrazinyl]-7*H*-pyrrolo-[2,3-*d*]pyrimidine (2h): White crystals, yield: 73.22 %, m.p.: 211 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3376 (NH), 3064 (=C-H), 1587 (C=N), 1490, 1452 (C=C), 648 (C-Br); ^{1}H NMR (DMSO-d_6, δ ppm): 12.98 (s, 1H, NH), 8.33 (s, 1H, NH-Ar), 8.55 (s, 1H, N=CH), 7.562-8.132 (m, 5H, Ar-H); Anal. calcd. (found) % for



where, R = 2-iodo (2a); 3-iodo (2b); 4-iodo (2c); 3,5-diiodo (2d); 3,4-diiodo (2e); 2,3-dibromo (2f); 3,5-dibromo (2g); 2,4-dibromo (2h); 3,4-dibromo (2i); 3,5-dibromo (2j)

Scheme-I: Synthesis of novel 4-hydrazinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine derivatives

$C_5H_{10}N_5Br_2$: C, 39.52 (39.48); H, 2.30 (2.29); N, 17.73 (17.70); Br, 40.45 (40.40).

4-[2-(3,4-Dibromobenzylidene)hydrazinyl]-7*H*-pyrrolo[2,3-*d*]pyrimidine (i): White crystals, yield: 74.68 %, m.p.: 213 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3370 (N-H), 3071 (=C-H), 1589 (C=N), 1492, 1455 (C=C), 650 (C-Br); ^{1}H NMR (DMSO-d_6, δ ppm): 12.98 (s, 1H, NH), 8.33 (s, 1H, NH-Ar), 8.55 (s, 1H, N=CH), 7.56-8.13 (m, 5H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5Br_2$: C, 39.52 (39.49); H, 2.30 (2.22); N, 17.73 (17.72); Br 40.45 (40.44).

4-[2-(3,5-Dibromobenzylidene)hydrazinyl]-7*H*-pyrrolo-[2,3-*d*]pyrimidine (2j): White crystals, yield: 79.90 %, m.p.: 211 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3374 (NH), 3066 (-CH=), 1589 (C=N), 1490, 1458 (C=C), 648 (C-Br); ^{1}H NMR (DMSO-d_6, δ ppm): 12.86 (s, 1H, -NH), 8.33 (s, 1H, NH-Ar), 8.55 (s, 1H, N=CH), 7.56-8.13 (m, 5H, Ar-H); Anal. calcd. (found) % for $C_5H_{10}N_5Br_2$: C, 39.52 (39.51); H, 2.30 (2.26); N, 17.73 (17.25); Br, 40.45 (40.43).

Antibacterial activity: All the synthesized compounds **2a-j** were evaluated for their antibacterial potential by cup plate method using standard protocol [31]. Briefly, all the synthesized compounds **2a-j** were screened for antibacterial activity against freshly cultured strains of against *S. aureus* (MCC-2408), *B. subtilis* (MCC-2010), *P. aeruginosa* (MCC-2080) and *E. coli* (MCC-2412) using Mueller-Hinton agar media using cup plate method. The media were autoclaved for 15 min at 10 pounds per square inch pressure. Each microbial strain was cultured by swabbing 20 mL of Mueller-Hinton agar media into a Petri plate. For next 15 min, the medium was allowed to absorb the culture and the cultivation process was continued. Wells with 6 mm diameter were created on the agar plates using sterile borer. Next 100 µL of each test compounds were reconstituted in DMSO were introduced to the previously inoculated plates. The plates were kept at a temperature of 37 ºC for 24 h. The zone of inhibition for each test compound was recorded using streptomycin as positive control and DMSO as negative control. The procedure was repeated in triplicate and the efficiency of the streptomycin antibiotic served as a point of comparison in this study.

Antifungal activity: All the synthesized compounds **2a-j** were also evaluated for their antifungal potential against freshly cultured strains of *C. albicans* and *S. cerevisiae* using cup-plate method by cup plate method using standard protocol [32]. Media were autoclaved for 15 min at 10 pounds per square inch pressure. Each microbial strain was cultured by swabbing 20 mL of Mueller-Hinton agar media into a Petri plate. For next 15 min, the medium was allowed to absorb the culture and the cultivation process was continued. Wells with 6 mm diameter were created on the agar plates using sterile borer. Next 100 µL of each test compounds were reconstituted in DMSO were introduced to the previously inoculated plates. The plates were kept at a temperature of 37 ºC for three days. The zone of inhibition for each test compound was recorded using fluconazole as positive control and DMSO as negative control. The procedure was repeated in triplicate and the efficiency of fluconazole served as a point of comparison in this study.

RESULTS AND DISCUSSION

The problems of drug resistance, narrow spectrum and side effects associated with commercially available antimicrobials to treat various types of bacterial, fungal and viral infections on one hand; and the potential applications of heterocycles with fused ring systems or substituted with halogens, hydrazides and imino groups emphasizes the need for for present study to carry out the synthesis and antimicrobial evaluation of some novel pyrrolopyrimidine analogues. Present study presented 4-[2-(substituted benzylidene)hydrazinyl]-7*H*-pyrrolo[2,3-*d*]-pyrimidines (**2a-j**) using one pot multicomponent reaction.

One-pot multicomponent reactions have emerged as an attractive methodology for the synthesis of diverse organic molecules with varying substitution patterns, owing to their inherent simplicity and rapidity. This makes them an extremely attractive new way in synthesis [33]. The condensation process of 4-hydrazinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine was key step in synthesizing the newly prepared 4-hydrazinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine derivatives. For this, 4-hydrazinyl-7*H*-pyrrolo-[2,3-*d*]pyrimidine dissolved in ethanol was added to halo benzaldehyde derivatives dissolved in ethanol. The resulting mixture was agitated under reflux for approximately 7 h at temperature ranged between 60-70 ºC. During this reaction a solid crude was separated, which was then dried in a vacuum after being filtered, recrystallized, washed multiple times with ethanol and diethyl ether and finally dried out [29]. The purity of synthesized compounds **2a-j** was assessed based on the sharp melting point, single spot TLC pattern and elemental analysis.

The structures of newly synthesized compounds **2a-j** were confirmed based on the FTIR and ^{1}H NMR data. The newly synthesized compounds **2a-j** were characterized based on the spectral data and supported with literature data [22]. The stretching vibration across the 33983360 cm^{-1} range was found FTIR spectra of new synthesized compounds **2a-j**. This stretching vibration is one of the numerous low-intensity absorption peaks correlating to N-H stretching [34,35]. Compounds **2a**, **2b** and **2j** each exhibited distinctive absorption bands in their individual IR spectra at 578, 523, and 485 cm^{-1} due to *ortho*, *meta* and *para*-iodo groups on the aromatic ring, respectively [34]. The presence of characteristic FTIR band at 1592-1587 cm^{-1} for C=N stretching. The ^{1}H NMR signal at δ 8.55-8.57 ppm confirmed structure of new synthesized compounds **2a-j**. The results of characterization data of compounds **2a-j** synthesized in this study were also found to be in agreement with the results of the other studies especially for the hydrazide and imino groups [27,28,30,36].

Antimicrobial activity: The new synthesized compounds **2a-j** were subjected to evaluation of their antibacterial and antifungal potential against Gram-positive/negative bacterial strains and fungal strains using cup plate method (Table-1). Study revealed that compounds **2c**, **2f**, **2h** and **2j** exhibited highest activity, however the antibacterial activity against *E. coli* was observed for compounds **2a**, **2b**, **2c** and **2d** but not for compound **2e**. The *E. coli* inhibition activity of new synthesized compounds was significantly increased when the iodo group was changed.

TABLE-1
ANTIMICROBIAL ACTIVITY-SENSITIVITY TESTING OF COMPOUNDS **2a-j**

Compounds	Zone of inhibition (mm)					
	Antibacterial activity				Antifungal activity	
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*C. albicans*	*S. cerevisiae*
2a	19	16	17	11	14	15
2b	18	16	16	14	12	13
2c	24	24	20	19	21	22
2d	15	14	12	13	18	19
2e	10	12	11	5	12	10
2f	24	24	21	24	18	17
2g	11	10	14	22	22	22
2h	24	24	24	24	17	17
2i	19	13	23	21	12	12
2j	24	24	20	24	21	22
Streptomycin	25	25	25	25	–	–
Fluconazole	–	–	–	–	24	24

Compounds **2c**, **2e**, **2f** and **2j** were all quite active against *P. aeruginosa*; however, compounds **2h** and **2i** were extremely active against this particular strain of bacteria [37]. Compounds **2a**, **2b** and **2j** exhibited substantial antimicrobial activity when tested against *S. aureus*. Compounds **2d** and **2f** showed promising action against *C. albicans* during the experiment. After switching out the iodo group for a bromo group, the antifungal activity against *C. albicans* improved significantly. Compounds **2c**, **2e** and **2j** were among the effective chemicals against *S. cerevisiae*. The results of the present study were also found to be in agreement with the results of other studies [37,38].

Conclusion

A straightforward multicomponent, one-pot synthesis for novel pyrrolopyrimidine analogues (**2a-j**) has been synthesized using starting materials that are easily accessible. As part of our research on halo-substituted benzaldehyde ring systems and attempts to identify novel lead compounds by compiling pyrazole and pyrimidine heterocycles, compounds **2c**, **2f**, **2h**, and **2g** show potential activity against bacterial strains, and compounds **2c**, **2g** and **2j** show potential activity against fungal strains when compared with commercially standard. The structure activity association demonstrates that adding electron-donating iodo or bromo groups as a substituent improves an agent's ability to fight bacteria and fungi. The outcomes of the current research endeavors aimed at optimizing the efficacy of the leadership framework will establish the basis for our continuous investigation. Present study concludes that novel pyrrolopyrimidine analogues (**2a-j**) possess high antibacterial and antifungal potential, wowever, it is necessary to conduct further preclinical and clinical evaluations in order to determine their therapeutic importance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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