Asian Journal of Chemistry; Vol. 35, No. 9 (2023), 2210-2214

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2023.28100

Microwave-Assisted Synthesis and Antimicrobial Profiling of New Pyrrolo-Pyrimidine Analogues

HANDE BHAUSAHEB and GAVALI LAXMAN*

Chem Research Lab, Karmveer Bhaurao Patil College, Vashi, Navi Mumbai-400703, India

*Corresponding author: E-mail: laxmanvg70@gmail.com

Received: 4 June 2023; *Accepted*: 25 July 2023; *Published online*: 31 August 2023; AJC-21366

Present study intended for the development of microbial resistance of existing antimicrobials to synthesize some new antimicrobials. This study involved a microwave assisted synthesis of some new 4-aminopyrrolo[2,3-*d*]pyrimidine analogues (**2a-h**), which were synthesized *via* condensation of substituted benzaldehydes and 4-aminopyrrolo[2,3-*d*]pyrimidine. All the compounds were characterized (using elemental analysis and IR, ^{1}H NMR spectrometry) and evaluated for their antibacterial (against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa)* and antifungal (against *C. albicans* and *S. cerevisiae*) potential by determining the zone of inhibition using disk diffusion method. The antibacterial activity of compounds **2a-h** revealed that compounds **2c**, **2e** and **2f** against *E. coli*, **2d** against *S. aureus*, **2f** against *B. subtilis* and **2d** against *P. aeruginosa* exhibited maximum inhibitory activity. Whereas antifungal activity of compounds **2a-h** revealed that compound **2g** (against *C. albicans)* and **2b** and **2e** (against *S. cerevisiae*) exhibited maximum antimicrobial activity (zone of inhibition). The high antibacterial and antifungal potential of newly synthesized compounds supports their potential application as antibacterial and antifungal agents, however the synthesized compounds must be additionally investigated for the *in vivo* and clinical studies.

Keywords: 4-Aminopyrrolo[2,3-*d*]pyrimidine, Substituted benzaldehydes, Antibacterial activity, Antifungal activity.

INTRODUCTION

Emergence of resistance to conventional antimicrobials due to their massive use in the treatment of various infections makes investigators to continuously search for new antifungal and antibacterial entities [1]. Facts suggest that incorporation of heterocyclic groups into the organic moieties enhances their antimicrobial potential [2]. Fused pyrimidines are an interesting class of heterocycles, which are extensively explored by chemists due to their massive pharmacological profile [3]. Initial studies followed by exhaustive investigation with prime focus on the pharmacological spectrum of purines and its analogues, in particular deaza analogues, pyrrolo[2,3-*d*]pyrimidines and pyrrolo[3,2-*d*]pyrimidines [4]. Pyrrolo[2,3-*d*]pyrimidine analogues attributed to their strong antibacterial and antifungal properties always attracts the researchers attention [5]. The pyrrolopyrimidines development began in 1970s, such that initially synthesis of pyrrolopyrimidines involving monocyclic pyrimidines as the key substrate occurred in 1974 [6]. Later, based on pyrrole derivatives and modifications in skeleton of bicyclic pyrimidines, various synthetic strategies were developed. Likewise, simultaneously more simplified approaches involving substituted pyrimidines were developed that employed highly reactive reagents such as acetals of acid amides and amines [7].

Evidence suggest pyrrolopyrimidine antibiotics to inhibit microbial DNA topoisomerases GyrB and ParE and thymidylate monophosphate kinase (TMPK) the key enzymes essential for DNA synthesis, thereby act as bactericidal agents [8]. Recently, azomethine analogues attributed to their antimicrobial activities have become a subject of interest for many chemists [9,10]. Sindhu *et al.* [11] highlighted the synthesis of some new imines using pyrrolo-pyrimidine. Hence based on the literary evidences over microbial resistance offered by commercially available antibiotics, the high antimicrobial potential of pyrrolo-pyridines and azomethines, intended present study to perform the synthesis of new pyrrolo[2,3-*d*]pyrimidine analogues, followed by evaluation of their antibacterial (against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa*) and antifungal (against *C. albicans* and *S. cerevisiae*) potential by determining the zone of inhibition using disk diffusion method.

EXPERIMENTAL

In current study, the chemicals to synthesize new pyrrolo-pyridine analogues (NPPAs) were obtained from Merck KGaA, Sigma-Aldrich, HmbG® Chemicals and Friendemann Schmidt Chemicals. The NPPAs ^{1}H NMR spectral data were recorded by Bruker, DPX 300 spectrometer on δ value scale in ppm using tetramethylsilane and DMSO as solvent. In ^{1}H NMR signal representation the terms 's' for singlet and 'brs' for broad signal were used. The NPPAs IR spectral data were recorded using Alpha-P Bruker FT-IR Spectrometer at wavelength ranged between 4000 to 400 cm^{-1}. For the elemental analysis of NPPAs Perkin Elmer 240 B and 240 C instruments were used. The microwave synthesis was performed in an Anton Paar Mono-wave 300 microwave synthesizer. The melting points of the pyrrolo-pyrimidines analogues was recorded in open capillary using SMP11 Analogue apparatus and are uncorrected. Reaction moni-toring was done by TLC using silica gel 60 F_{254} in Sprec-troline® CM-26 UV chamber and solvent system of methanol: chloroform (9.5:0.5).

General procedure for synthesis of *N*-(substituted benzylidene)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2a-h): The NPPAs **2-h** were synthesized as per the standard procedure given in the literature with some minor modification [12-15]. Briefly, a reaction mixture of equimolar concentration of 4-amino-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1**) and nitro benzaldehyde in 10 mL glass vial sealed with septum was placed at 100 ºC in microwave synthesis reactor, with gradual increase in power of irradiation from 180 W maintained at 600 rpm for 1-5 min. The reaction mixture after quenching with water (10 mL), was allowed to cool and further extracted with ethyl acetate. The organic layer was evaporated over anhydrous Mg_2SO_4 and the crude was purified by silica gel column chromatography using petroleum ether and acetone (10:1 v:v) as eluent to obtain pure NPPA **2a**. Using similar experimental protocol, other compounds **2b-h** were also synthesized (**Scheme-I**).

***N*-(2-Nitrobenzylidene)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2a):** Pale yellow solid; yield 79.68%, m.p. 185 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3356 (NH), 3064 (=C-H), 1562 (C=N), 1495, 1437 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 7.28-8.19 (m, 5H, aromatic-H), 8.72 (s, 1H, pyrimidine-H), 9.17 (s, 1H, N=CH), 9.96 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{13}H_9N_5O_2$ (267.24): C, 58.43 (58.12); H, 3.39 (3.37); N, 26.21 (26.09); O, 11.97 (11.21).

N-(3-Nitrobenzylidene)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2b): Yellow solid; yield 84.54%, m.p. 188 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3352 (NH), 3061 (=C-H), 1559 (C=N), 1492, 1435 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 7.90-8.51 (m, 5H, aromatic-H), 8.57 (s, 1H, pyrimidine-H), 8.89 (s, 1H, N=CH), 9.96 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{13}H_9N_5O_2$ (267.24): C, 58.43 (58.19); H, 3.39 (3.33); N, 26.21 (26.18); O, 11.97 (11.90).

***N*-(4-Nitrobenzylidene)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2c):** Pale brown solid; yield: 81.74%, m.p. 183 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3354 (NH), 3063 (=C-H), 1560 (C=N), 1487, 1452 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 7.24-8.40 (m, 5H, aromatic-H), 8.80 (s, 1H, pyrimidine-H), 8.85 (s, 1H, N=CH), 9.91 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{13}H_9N_5O_2$ (*m.w.* 267.24): C, 58.43 (58.19); H, 3.39 (3.33); N, 26.21 (26.18); O, 11.97 (11.90).

***N*-Benzylidene-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2d):** White solid; yield: 80.79%, m.p. 180 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3358 (NH), 3059 (=C-H), 1552 (C=N), 1481, 1455 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 6.89-8.37 (m, 6H, aromatic-H), 8.42 (s, 1H, pyrimidine-H), 9.80 (s, 1H, N=CH), 9.91 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{13}H_9N_5O_2$ (*m.w.* 222.25): C, 70.26 (70.19); H, 4.54 (4.53); N, 25.21 (25.17).

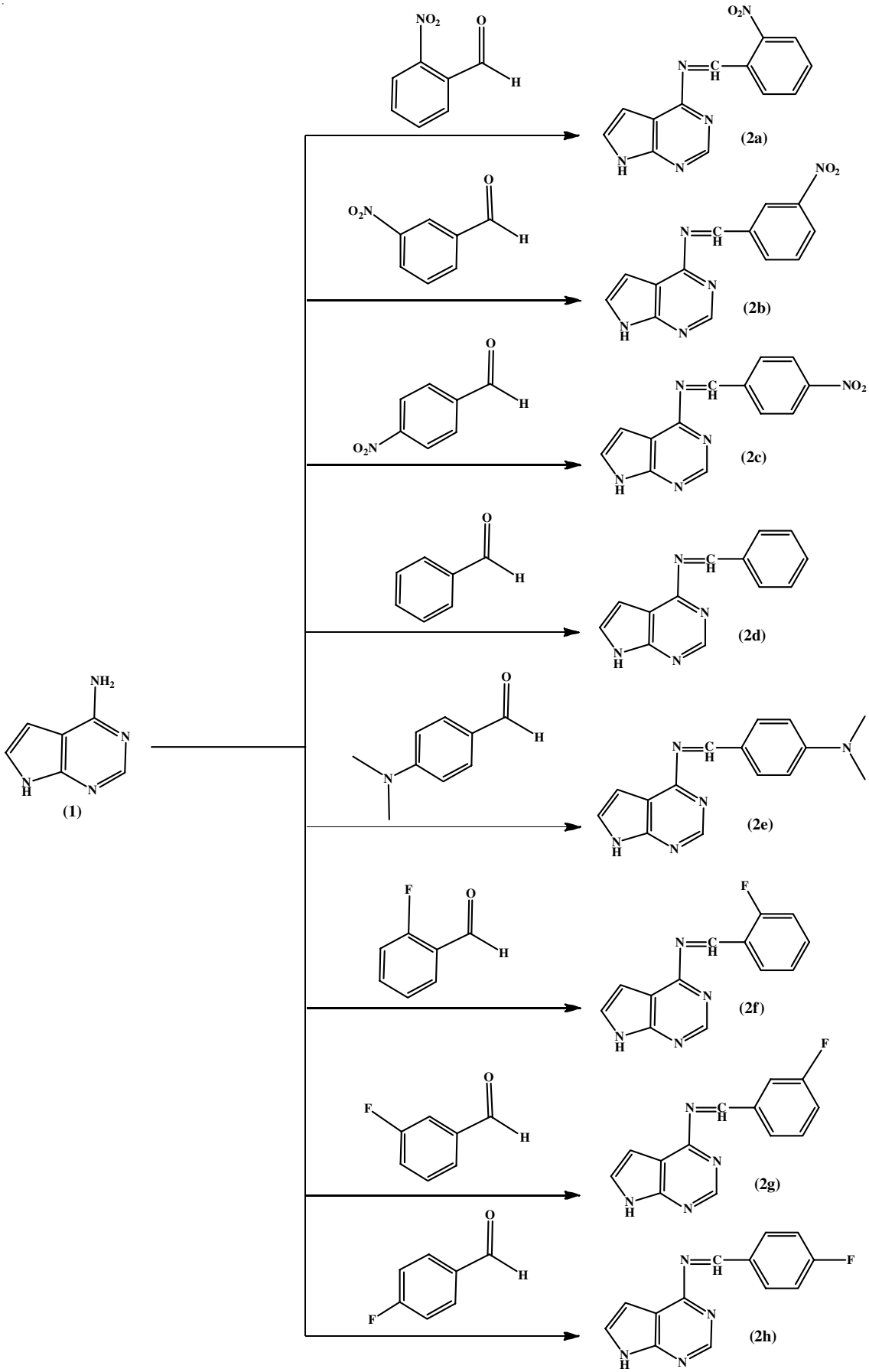
***N*-(4-(Dimethylamino)benzylidene)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-amine (2e):** White solid; yield: 76.44%, m.p. 189 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3358 (NH), 3063 (=C-H), 2924 (C-H), 1555 (C=N), 1479, 1452 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 3.35 (s, 6H, $N(CH_3)_2$), 6.69-7.99 (m, 5H, aromatic-H), 8.57 (s, 1H, pyrimidine-H), 8.78 (s, 1H, N=CH), 9.98 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{15}H_{15}N_5$ (*m.w.* 265.31): C, 67.90 (67.89); H, 5.70 (5.59); N, 26.40 (26.37).

***N*-(2-Fluorobenzylidene)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2f):** White solid; yield 80.22%, m.p. 179 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3364 (NH), 3065 (=C-H), 1555 (C=N), 1481, 1457 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 7.21-8.03 (m, 5H, aromatic-H), 8.56 (s, 1H, pyrimidine-H), 8.78 (s, 1H, N=CH), 9.96 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{15}H_{15}N_5$ (*m.w.* 240.24): C, 64.99 (64.91); H, 3.78 (3.72); N, 23.23 (23.18); F, 7.91 (7.83).

***N*-(3-Fluorobenzylidene)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2g):** White solid; yield: 78.97%, m.p. 181 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3363 (NH), 3062 (=C-H), 1554 (C=N), 1479, 1459 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 7.24-8.04 (m, 5H, aromatic-H), 8.72 (s, 1H, pyrimidine-H), 8.74 (s, 1H, N=CH), 9.94 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{15}H_{15}N_5$ (*m.w.* 240.24): C, 64.99 (64.83); H, 3.78 (3.74); N, 23.23 (23.19); F, 7.91 (7.86).

***N*-(4-Fluorobenzylidene)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine (2h):** White solid; yield: 79.64%, m.p. 187 ºC; FTIR (KBr, ν_{max}, cm^{-1}): 3361 (NH), 3060 (=C-H), 1552 (C=N), 1480, 1461 (C=C); ^{1}H NMR (DMSO-d_6, ppm) δ: 7.71-8.12 (m, 5H, aromatic-H), 8.66 (s, 1H, pyrimidine-H), 8.65 (s, 1H, N=CH), 9.92 (brs, 1H, NH, D_2O-exchangeable); Anal. calcd. (found) % for $C_{15}H_{15}N_5$ (*m.w.* 240.24): C, 64.99 (64.95); H, 3.78 (3.76); N, 23.23 (23.03); F, 7.91 (7.86).

Antibacterial activity: The synthesized NPPAs **2a-h** were evaluated for their antibacterial potential against the freshly cultured bacterial strains of *S. aureus* (MCC 2010), *B. subtilis* (MCC 2010), *E. coli* (MCC 2412) and *P. aeruginosa* (MCC 2080) by disk diffusion method over Mueller-Hinton plates using sterile nutrient agar media [16]. For the study NPPAs **2a-h** were dissolved in 1 mL of 1% DMSO and bacterial strains were allowed to grow to log phase overnight with constant shaking at 37 ºC. Bacterial cultures were spread on the Mueller-Hinton (MH) plates agar media with 4 mm of depth. Next, discs with 1 mm thick and 6 mm diameters impregnated with 100 µg/mL solution of compounds **2a-h** in 1% DMSO, 50 µg/mL of strep-tomycin (positive standard) and 1% DMSO (negative control)



Scheme-I: Synthesis of substituted benzaldehyde derivatives of the 4-aminopyrrolo[2,3-*d*]pyrimidine form

were placed firmly over MH plates agar surface. The plates were incubated for 24 h at 37 ºC and same experimental protocol was repeated in triplicate. After 24 h incubation, the zone of inhibition of compound **2a-h** was measured on mm scale.

Antifungal activity: The synthesized NPPAs **2a-h** were also investigated for their antifungal potential against freshly cultured fungal strains of *Candida albicans* (MCC 1439) and *S. cerevisiae* (MCC1033) by disk diffusion method over Mueller-Hinton plates using sterile Sabouraud's agar media [17]. For the study NPPAs **2a-h** were dissolved in 1 mL of 1% DMSO and next discs with 1 mm thick and 6 mm diameters impregnated with 100 µg/mL solution of compounds **2a-h** in 1% DMSO, 50 µg/mL of fluconazole (positive standard) and 1% DMSO (negative control) were placed over MH plates agar surface. Finally, the plates were incubated for 72 h at 37 ºC and the same experimental protocol was repeated in triplicate. After 72 h incubation, the zone of inhibition of compounds **2a-h** was measured in mm.

RESULTS AND DISCUSSION

The facts over microbial resistance to commercially available antimicrobials, related side effects and high antimicrobial potential of azomethines and heterocycles especially pyrrolo pyrimidines emphasizes the need for new synthesis of new analogues of pyrrolo-pyrimidines [18-20]. The scheme for synthesis of NPPAs was based on the standard protocols given in the literature [16,21] and offered all NPPAs in good yield.

Microwave assisted synthesis (MAS) enhances the rate of organic reactions based on superheating of solvent [22]. In present study, various azomethine analogues of pyrrolo-pyrimidine (**2a-h**) were synthesized by treatment of 4-aminopyrrolo[2,3-*d*]-pyrimidine with various aromatic aldehydes following Schiff's reaction under microwave assisted conditions [23]. The purifying process of the resulting NPPAs involved recrystallization using methanol and activated charcoal. Purity of all NPPAs **2a-h** was determined based on their melting point, pattern of single spot-on TLC plates and percentage of elemental analysis. The elemental analysis of NPPAs revealed that in all the synthesized compounds **2a-h**, the elements C, H and N were within the ± 0.4% of theoretical range. Structures of NPPAs were elucidated and confirmed based on the FT-IR and ^{1}H NMR spectrometric data and has also been supported with literary evidences [12,18,24]. The presence of characteristic FTIR bands ranging from 3364-3356 cm^{-1} attributed to the N-H stretching and FTIR bands ranging from 1564-1562 cm^{-1} ascribed to C=N stretching. The ^{1}H NMR signals at δ value ranging from 8.57-9.80 ppm corresponding to N=CH protons confirmed the structure of newly synthesized NPPAs **2a-h**. The characterization data of all the synthesized NPPAs compounds in the present study were also matched and found to be in agreement with the results of the other studies [25,26].

Biological activity: The synthesized NPPAs **2a-h** were further evaluated for their *in vitro* their antibacterial potential against the freshly cultured bacterial strains of *S. aureus* (MCC 2010), *B. subtilis* (MCC 2010), *E. coli* (MCC 2412) and *P. aeruginosa* (MCC 2080) by disk diffusion method in triplicate following the standard protocol [16]. The zone of inhibition obtained as result of *in vitro* testing NPPAs **2a-h** against different strains is presented in Table-1. It is revealed that all NPPAs exhibit significant antibacterial activity against *S. aureus*, *B. subtilis*, *E. coli* and *P. aeruginosa* with zone of inhibition ranging from 13 to 21 mm, according to the antibacterial screening results. Additionally, all NPPAs were found to exhibit more antibacterial potential against *S. aureus* when compared with streptomycin (18-21 mm). Also, among all NPPAs, the NPPAs **2c**, **2e** and **2f** (against *E. coli)*, **2d** (against *S. aureus)*, **2f** (against *B. subtilis)* and NPPA **2d** (against *P. aeruginosa*) exhibited the maximum inhibitory activity.

The synthesized NPPAs **2a-h** when investigated for their antifungal potential against *C. albicans* (MCC 1439) and *S. cerevisiae* (MCC1033) by disk diffusion method in triplicate [17], the results showed that all the synthesized compounds had nearly 2.5 times the potency (9-15 mm) compared to the common fluconazole and were active against the two fungi namely: *C. albicans* (MCC1439) and *S. cerevisiae* (MCC1033). The antifungal activity of NPPAs **2a-h** revealed that NPPA **2g** against *C. albicans* and NPPAs **2b** and **2e** against *S. cerevisiae* exhibited maximum activity. The data for zone of inhibition, obtained as result of *in vitro* testing NPPAs **2a-h** against different strains is presented in Table-1.

The high antibacterial and antifungal potential of new synthesized NPPAs **2a-h** supports their potential application as antibacterial and antifungal agents; however the synthesized

TABLE-1
ANTIBACTERIAL AND ANTIFUNGAL STUDIES OF COMPOUNDS **2a-h**

Compound	Zone of inhibition (mm)					
	Antibacterial activity				Antifungal activity	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*S. cerevisiae*
2a	19	16	13	19	9	16
2b	20	13	18	15	17	21
2c	18	15	21	19	18	19
2d	21	15	20	20	15	14
2e	20	16	21	16	19	21
2f	19	21	21	15	20	12
2g	20	20	19	17	21	13
2h	19	20	18	20	18	18
Streptomycin	15	22	21	14	–	–
Fluconazole	–	–	–	–	15	13

compounds must be additionally investigated for the *in vivo* and clinical studies.

Conclusion

The present study involved successful microwave assisted synthesis of *N*-(substituted benzylidene)-7*H*-pyrrolo[2,3-*d*]-pyrimidin-4-amine **(2a-h)** from 4-amino-pyrrolo[2,3-*d*]-pyrimidine, *via* Schiff's reaction. The structures of synthesized NPPAs **2a-h** were further confirmed based on the single spot TLC, sharp melting point, IR and NMR spectrometry data. Present study concludes that all synthesized NPPAs **2a-h** exhibit significant antibacterial and antifungal activities and among all synthesized NPPAs, the NPPAs having nitro, fluoro and dimethyl amino groups at *ortho*, *meta*- and *para*-position of benzene ring impart strong antimicrobial activity. Current study recommends synthesized NPPAs as effective antimicrobial agents against. However, additional *in vivo* and clinical studies are required to further establish the safety and efficacy of the synthesized NPPAs to be established as an effective antimicrobial agents for the treatment of various bacterial and fungal infections.

ACKNOWLEDGEMENTS

The authors are thankful to the Karmveer Bhausaheb Patil College, Vashi, Navi Mumbai, India, for providing the necessary research facilities to successfully complete this research.

CONFLICT OF INTEREST

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

REFERENCES

1. E. S. Fondjo, A.S. Njoya, J.D. Tamokou, G. Doungmo and B.N. Lenta, P.F.W. Simon, A. Tsopmo, J.R. Kuiate, *BMC Chem.,* **16**, 8 (2022); https://doi.org/10.1186/s13065-022-00801-5
2. M. Aatif, M.A. Raza, K. Javed, S.M. Nashre-ul-Islam, M. Farhan and M.W. Alam, Antibiotics, 11, 1750 (2022); https://doi.org/10.3390/antibiotics11121750
3. V.S. Dinakaran, B. Bomma and K.K. Srinivasan, *Der Pharm. Chem.,* **4**, 255 (2012); https://doi.org/10.1016/j.ejmech.2018.08.023
4. R. Glushkov and O. Sizova, *Pharm. Chem. J.*, **20**, 415 (1986); https://doi.org/10.1007/BF00758338
5. K.M. Hilmy, M.M. Khalifa, M.A. Hawata and R.M. Keshk, *Eur. J. Med. Chem*., **45**, 5243 (2010); https://doi.org/10.1016/j.ejmech.2010.08.043
6. S. Pathania and R.K. Rawal, *Eur. J. Med. Chem*., **157**, 503 (2018); https://doi.org/10.1016/j.ejmech.2018.08.023
7. A. Kadushkin, A. Sokolova, N. Solov'eva and V. Granik, *Pharm. Chem. J.*, **28,** 792 (1994); https://doi.org/10.1007/BF02218707
8. C.E. Olsen, F.H. Blindheim, C.K. Søgaard, L.M. Røst, A.H. Singleton, O.E.T. Bergum, P. Bruheim, M. Otterlei, E. Sundby and H. Hoff, *Antibiotics*, **11**, 984 (2022); https://doi.org/10.3390/antibiotics11080984
9. J. Ceramella, D. Iacopetta, A. Catalano, F. Cirillo, R. Lappano and M.S. Sinicropi, *Antibiotics*, **11**, 191 (2022); https://doi.org/10.3390/antibiotics11020191
10. A. Kajal, S. Bala, S. Kamboj, N. Sharma and V. Saini, *J. Catalysts*, **2013**, 893512 (2013); https://doi.org/10.1155/2013/893512
11. Y. Sindhu, C.J. Athira, M.S. Sujamol, R.S. Joseyphus and K. Mohanan, *Synth. React. Inorg. Met*., **43**, 226 (2013); https://doi.org/10.1080/15533174.2012.740711
12. S.H. Rohane, V.K. Redasani, N.K. Fuloria and S. Fuloria, *Indian J. Chem*., **62B**, 551 (2023); https://doi.org/10.56042/ijc.v62i6.2507
13. A. Ansari, A. Ali and M. Asif, *New J. Chem*., **42**, 184 (2018); https://doi.org/10.1039/C7NJ03742B
14. O.J. Jesumoroti, R.M. Beteck, A. Jordaan, D.F. Warner, L.J. Legoabe, *Mol. Divers*., **27**, 753 (2023); https://doi.org/10.1007/s11030-022-10453-1
15. S.H. Rohane, A.J. Chauhan, N.K. Fuloria and S. Fuloria, *Arab. J. Chem.,* **13**, 4495 (2020); https://doi.org/10.1016/j.arabjc.2019.09.004
16. S. Chigurupati, N.K. Fuloria, S. Fuloria, S. Karupiah, R. Veerasamy, A.R. Nemala, L.J. Yi, A.X. Ilan and S.A.A. Shah, *Trop. J. Pharm. Res.* **15**, 821 (2016); https://doi.org/10.4314/tjpr.v15i4.22
17. N.K. Fuloria, V. Singh, M. Shaharyar and M. Ali, *Molecules*, **14**, 1898 (2009); https://doi.org/10.3390/molecules14051898
18. S. Vazirimehr, A. Davoodnia, S.A. Beyramabadi and M.N. Moghaddam, N.T. Hoseini, *Z. fur Naturforsch. B*, **72**, 481 (2017); https://doi.org/10.1515/znb-2017-0004
19. C. Oussama, M. Fatma, A. Fatma, C. Fakher and T. Mohamed, *Heterocycl. Commmun*., **21**, 191 (2015); https://doi.org/10.1515/hc-2015-0066
20. M.S. El-Gaby, A.M. Gaber, A.A. Atalla and K.A.A.A. Wahab, *Il Farmaco*, **57**, 613 (2002); https://doi.org/10.1016/S0014-827X(00)00079-3
21. A.A. Al-Mutairi, H.N. Hafez, A.B.A. El-Gazzar and M.Y.A. Mohamed, *Molecules*, **27**, 1246 (2022); https://doi.org/10.3390/molecules27041246
22. K. Mayo, E.H. Nearhoof and J.J. Kiddle, *Org. Lett*., **4**, 1567 (2022); https://doi.org/10.1021/ol025789s
23. S.S. Khaidir, H. Bahron, A.M. Tajuddin and K. Ramasamy, *J. Sustain. Sci. Manag*., **17**, 32 (2022); https://doi.org/10.46754/jssm.2022.4.003
24. F. Naaz, F. Ahmad, B. Ahmad, L. Yuba, R. Pokharel, N.K. Fuloria, S. Fuloria, M. Ravichandran, L. Pattabhiraman, S. Shafi and M. ShaharYar, *Bioorg. Chem*., **95**, 103519 (2021); https://doi.org/10.1016/j.bioorg.2019.103519
25. N.K. Fuloria, V. Singh, M.S. Yar and M. Ali, *Acta Pol. Pharm*., **66**, 371 (2009).
26. A.I. Sayed, Y.E. Mansour, M.A. Ali, O. Aly, Z.M. Khoder, A.M. Said, S.S. Fatahala and R.H.A. El-Hameed, *J. Enzyme Inhib. Med. Chem.,* **37**, 1821 (2022); https://doi.org/10.1080/14756366.2022.2090546