Asian Journal of Chemistry; Vol. 34, No. 4 (2022), 907-911

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2022.23644

Microwave Irradiated Eco-friendly Synthesis of Pyrimidine Derivatives as Potential Antitubercular Agents

KRISHNA CHANDRA PANDA[1,*], BERA VENKATA VARAHA RAVI KUMAR[1], BISWA MOHAN SAHOO[1], BIMAL KRISHNA BANIK[2] and ABHISHEK TIWARI[3]

[1]Roland Institute of Pharmaceutical Sciences, (Affiliated to Biju Patnaik University of Technology, Rourkela), Berhampur-760010, India
[2]Department of Mathematics and Natural Sciences, College of Sciences and Human Studies, Prince Mohammad Bin Fahd University, Al Khobar 31952, Kingdom of Saudi Arabia
[3]Faculty of Pharmacy, IFTM University, Moradabad-244102, India

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

Received: 30 November 2021; *Accepted*: 29 December 2021; *Published online*: 10 March 2022; AJC-20732

The microwave irradiation method is applied for the efficient synthesis of pyrimidine derivatives. The synthetic protocol involves Knoevenagel condensation followed by Michael addition reaction and cyclization of equimolar quantities of aromatic aldehydes, ethyl cyanoacetate and guanidine in the presence of ethanolic NaOH solution to produce corresponding pyrimidine derivatives. The reaction mixture was allowed to reflux under microwave radiation at power level-2 for 7-12 min. The microwave heating technique offers a cleaner reaction with a shorter reaction time and improved product yield as compared to conventional synthesis. The newly synthesized compounds were characterized by their FT-IR, ^{1}H NMR and LC-MS spectral data. All the synthesized pyrimidine derivatives were evaluated *in vitro* for their antitubercular activity *in vitro* by using the luciferase reporter phage (LRP) assay method. The antimycobacterial activity was determined in terms of the percent reduction in the relative light unit (RLU). The test compounds exhibited promising antitubercular activity against *Mycobacterium tuberculosis* H37Rv and clinical isolates, S, H, R and E resistant *M. tuberculosis* in comparison with the standard drug (isoniazid).

Keywords: Microwave synthesis, Pyrimidine, Antitubercular activity, Luciferase, Isoniazid.

INTRODUCTION

Heterocyclic compounds play a major role to produce diverse biologically active compounds during the drug development process [1]. The heterocyclic moiety provides the opportunity to design target molecules with suitable therapeutic potentials [2]. Hence, nitrogen containing heterocyclic compounds like pyrimidines have received significant attention due to their wide spectrum of biological activities such as anticancer, antitubercular, anthelmintic, antidiabetic, antihypertensive, anticonvulsant, antibacterial, antifungal, anti-Alzheimer, antiviral, analgesic, anti-inflammatory activities, *etc*. [3-7]. Pyrimidine is a six-membered heterocyclic compound that contains two nitrogen atoms present at positions 1 and 3 of the ring system.

Various drugs used clinically that contain pyrimidine scaffold include sulphamidine (antibacterial), cyprodinil (antifungal), fluorouracil (antineoplastic), propylthiouracil (antithyroid), azacitidine (antineoplastic), enazadrem (antipsoriatic), *etc*. [8-10]. Ceritinib was identified as a potential antitubercular agent that contains a pyrimidine nucleus in its chemical structure (Fig. 1) [11]. Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, which remains a serious health problem worldwide [12]. The treatment of TB with first-line antitubercular drugs like isoniazid, rifampicin, pyrazinamide, ethambutol and their combination therapy requires 6-9 months to complete dose but that result in several side effects [13]. So, the development of new drugs containing pyrimidine moiety with improved therapeutic strategies is needed to improve the potential of drug treatment of TB [14].

In present work, the microwave irradiated synthetic technique is applied to synthesize pyrimidine derivatives [15]. All the reactions were performed under optimized reaction

This is an open access journal, and articles are distributed under the terms of the Attribution 4.0 International (CC BY 4.0) License. This license lets others distribute, remix, tweak, and build upon your work, even commercially, as long as they credit the author for the original creation. You must give appropriate credit, provide a link to the license, and indicate if changes were made.

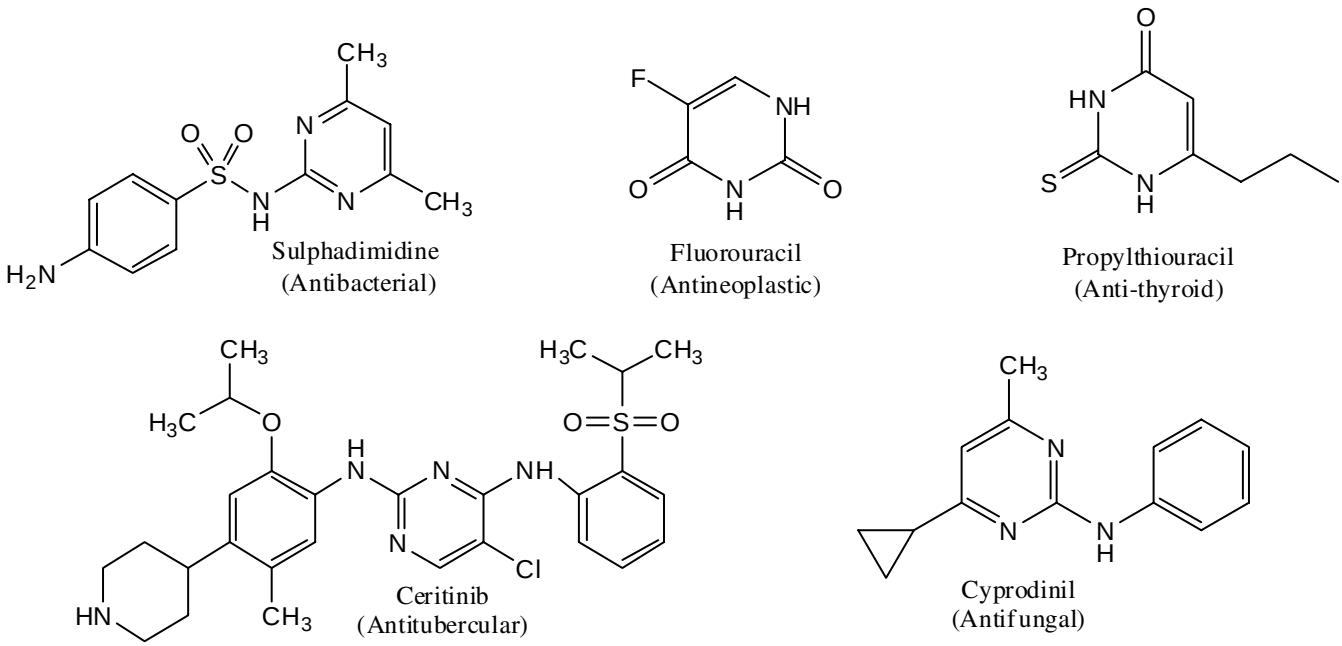


Fig. 1. Structures of drugs with pyrimidine moiety

conditions. Microwave-induced synthetic protocol is mainly considered an environment-friendly process that affords cleaner products with higher yield, selectivity, reduced reaction period, efficient rate of the reaction and also reduces the environmental pollution [16-18].

Thus, the synthesis of pyrimidine derivatives is carried under microwave irradiation by reacting the equimolar mixture of ethyl cyanoacetate, aryl aldehydes and guanidine [19]. The formation of the pyrimidine derivatives involves the sequential reaction mechanism such as Knoevenagel condensation of ethyl cyanoacetate with aryl aldehydes followed by Michael addition of guanidine and intramolecular cyclization in presence of ethanolic NaOH solution [20]. The characterization of newly synthesized compounds is carried out by spectral data of FT-IR, ^{1}H NMR and LC-MS. The titled compounds are subjected to *in vitro* screening for their antitubercular activity [21].

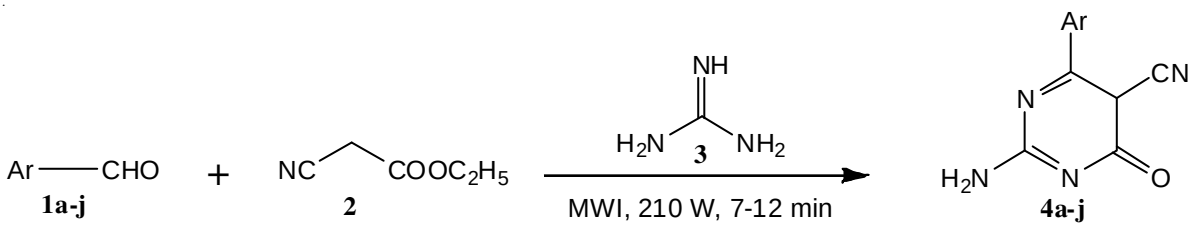
EXPERIMENTAL

The reagents, chemicals and solvents used for the current experimental work were of commercial grade. The melting points of the synthesized compounds were determined by the open capillary tube method and are found uncorrected. TLC was monitored to check the purity of the synthesized compounds and also to determine the completion of the reaction. Ethyl acetate and *n*-hexane were used as mobile phase. The IR spectra of the titled compounds were recorded on FT-IR Spectrophotometer, model IR Affinity-1 (SHIMADZU) using KBr powder. ^{1}H NMR spectra of the selected compounds were recorded on FT NMR spectrometer; model Advance-II (Bruker), (400 MHz) using tetramethylsilane (TMS) as an internal standard. Mass spectral data was obtained by using electrospray ionization (ESI) techniques.

General synthesis of pyrimidine derivatives (4a-j): An equimolar mixture of aryl aldehydes (**1a-j**), ethyl cyanoacetate (**2**) and guanidine (**3**) in ethanolic NaOH solution was allowed to reflux under microwave irradiation at power level-2 (210 W) for 7-12 min. The completion of the reaction was checked by TLC. After completion of the reaction, the reaction mixture was poured into ice-cold water to get pyrimidine derivatives (**4a-j**) as solid product (**Scheme-I**).

2-Amino-4-oxo-6-phenyl-4,5-dihydropyrimidine-5-carbonitrile (4a): White solid; yield 65% (conventional), 74% (microwave); m.p.: 170-172 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3422 (-NH_2), 3018 (C-H, Ar), 2200 (-CN), 1660 (-C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.8-7.4 (m, 5H, aromatic-H), 8.47 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 134.0, 129.2, 128.9, 131.1, 128.9, 129.2; MS (ESI), *m/z* (%): 212.21 [M+1]; Anal. calcd. (found) % for $C_{11}H_8N_4O$: C, 62.26 (62.23); H, 3.80 (3.78); N, 26.40 (26.38); O, 7.54 (7.52).

2-Amino-4-oxo-6-*p*-tolyl-4,5-dihydropyrimidine-5-carbonitrile (4b): White solid; yield 69% (conventional), 74% (microwave); m.p.: 172-174 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3327.27



Scheme-I: Synthesis of pyrimidine derivatives (**4a-j**)

($-NH_2$), 3026 (C-H, Ar), 2960 (C-H aliphatic), 2190 (-CN), 1663 (-C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.40 (s, 3H, $-CH_3$), 7.10-7.21 (m, 4H, aromatic-H), 9.98 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 131.0, 129.1, 140.7, 129.1, 129.2, 129.2, 24.3; MS(ESI), *m/z* (%): 226.23 [M+1]; Anal. calcd. (found) % for $C_{12}H_{10}N_4O$: C, 63.71 (63.70); H, 4.46 (4.44); N, 24.76 (24.74); O, 7.07 (7.04).

2-Amino-6-(4-methoxyphenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4c): White solid; yield 58% (conventional), 67% (microwave); m.p.: 180-183 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3423 ($-NH_2$), 3034 (C-H, Ar), 2856 ($-OCH_3$), 2220 (-CN), 1668 (-C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.42 (s, 3H, $-OCH_3$), 7.09-7.44 (m, 4H, aromatic-H), 8.20 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 126.3, 130.2, 114.4, 163.0, 114.4, 130.2, 55.2; MS (ESI), *m/z* (%): 242.23 [M+1]; Anal. calcd. (found) % for $C_{12}H_{10}N_4O_2$: C, 59.50 (59.48); H, 4.16 (4.14); N, 23.13 (23.12); O, 13.21 (13.20).

2-Amino-6-(2-nitrophenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4d): Yellow solid; yield 65% (conventional), 73% (microwave); m.p.: 162-164 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3323 ($-NH_2$), 2974 (C-H, Ar), 1687 (-CO), 2226 (-CN), 1573, 1344 (Ar-NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33-7.42 (m, 4H, aromatic-H), 8.26 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 32.7, 164.6, 115.3, 126.3, 148.9, 121.2, 132.0, 135.0, 130.1; MS(ESI), *m/z* (%): 285.43 [M+1]; Anal. calcd. (found) % for $C_{11}H_7N_5O_3$: C, 53.10 (53.08); H, 8.71 (8.70); N, 25.33 (25.32); O, 12.86 (12.84).

2-Amino-6-(4-nitrophenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4e): Yellow solid; yield 72% (conventional), 84% (microwave); m.p.: 160-162 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3363 ($-NH_2$), 2987 (C-H, Ar), 2226 (-CN), 1738 (-C=O), 1575, 1342 (Ar-NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36-7.50 (m, 4H, aromatic-H), 8.42 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 140.3, 130.1, 121.2, 150.7, 121.2, 130.1; MS(ESI), *m/z* (%): 285.43 [M+1]; Anal. calcd. (found) % for $C_{11}H_7N_5O_3$: C, 53.10 (53.08); H, 8.71 (8.70); N, 25.33 (25.32); O, 12.86 (12.84).

2-Amino-6-(4-fluorophenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4f): Brown solid; yield 67% (conventional), 78% (microwave); m.p.: 156-158 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3427 ($-NH_2$), 2967 (C-H, Ar), 2208 (-CN), 1693 (-C=O), 1080 (C-F); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.26-7.46 (m, 4H, aromatic-H), 8.26 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 129.6, 130.8, 115.6, 165.2, 115.6, 130.8; MS(ESI), *m/z* (%): 230.2 [M+1]; Anal. calcd. (found) % for $C_{11}H_7N_4OF$: C, 59.73 (59.70); H, 3.42 (3.40); N, 25.33 (25.32); O, 7.23 (7.21); F 4.29 (4.27).

2-Amino-6-(4-hydroxyphenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4g): White solid; yield 54% (conventional), 68% (microwave); m.p.: 154-157 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3480 (-OH), 3463 ($-NH_2$), 2974 (C-H, Ar), 2216 (-CN), 1683 (-C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49-7.57 (m, 4H, aromatic-H), 8.16 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 126.6, 130.6, 116.0, 160.8, 116.0, 130.6; MS(ESI), *m/z* (%): 252.4 [M+1]; Anal. calcd. (found) % for $C_{11}H_8N_4O_2$: C, 56.87 (56.85); H, 8.68 (8.66); N, 24.12 (24.10); O, 10.33 (10.32).

2-Amino-6-(2-chlorophenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4h): White solid; yield 62% (conventional), 76% (microwave); m.p.: 166-169 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3363 ($-NH_2$), 2994 (C-H, Ar), 2238 (-CN), 1685 (-C=O), 786 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.05-7.33 (m, 4H, aromatic-H), 8.32 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 137.2, 134.0, 129.0, 132.5, 127.0, 130.6; MS(ESI), *m/z* (%): 246.65 [M+1], 248.65 [M+2]; Anal. calcd. (found) % for $C_{11}H_7N_4OCl$: C, 57.59 (57.58); H, 3.29 (3.28); N, 24.42 (24.40); Cl, 7.73 (7.72); O, 6.97 (6.95).

2-Amino-6-(4-chlorophenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4i): White solid; yield 66% (conventional), 72% (microwave); m.p.: 174-177 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3342 ($-NH_2$), 2979 (C-H, Ar), 2228 (-CN), 1681 (-C=O), 798 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.9-7.3 (m, 4H, aromatic-H), 8.30 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.7, 164.6, 115.3, 132.1, 130.6, 129.0, 136.6, 129.0, 130.6; MS(ESI), *m/z* (%): 246.65 [M+1], 248.65 [M+2]; Anal. calcd. (found) % for $C_{11}H_7N_4OCl$: C, 57.59 (57.58); H, 3.29 (3.28); N, 24.42 (24.40); Cl, 7.73 (7.72); O, 6.97 (6.95).

2-Amino-6-(2,3-dichlorophenyl)-4-oxo-4,5-dihydropyrimidine-5-carbonitrile (4j): White solid; yield 57% (conventional), 65% (microwave); m.p.: 166-169 ºC; FT-IR (KBr, ν_{max}, cm^{-1}): 3415 ($-NH_2$), 2979 (C-H, Ar), 2242 (-CN), 1668 (-C=O), 834 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.27-7.91 (m, 4H, aromatic-H), 8.56 (s, 2H, NH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163, 200, 33.2, 164.6, 115.3, 138.6, 130.9, 133.5, 132.6, 128.4, 128.7; MS(ESI), *m/z* (%): 279.99 [M+1], 281.1 [M+2]; Anal. calcd. (found) % for $C_{11}H_6N_4OCl_2$: C, 47.04 (47.02); H, 2.15 (2.14); N, 19.93 (19.92); Cl, 25.22 (25.20); O, 5.69 (5.67).

Antitubercular activity: All the newly synthesized pyrimidine derivatives were evaluated for antimycobacterial activity *in vitro* against *M. tuberculosis* H37Rv and clinical isolates such as S, H, R and E resistant strains. In the case of antimycobacterial activity, the percentage reduction in relative light units (RLU) was calculated by using luciferase reporter phage (LRP) assay using isoniazid as a standard drug [22]. The compounds as considered to be antimycobacterial agents, if a 50% reduction in the relative light unit was observed when compared to the control. The RLU was measured by using a luminometer [23].

Luciferase reporter phage (LRP) assay: Approximately 50 µL bacterial suspension equivalent to McFarland's No. 2 standard was added to 400 mL of G7H9 with and without the test compounds. For each sample, two drug-free controls and two drug concentrations were prepared and this setup was incubated at 37 ºC for 72 h. After incubation, 50 mL of high titer LRP (phAE129) and 400 mL of 0.1 M $CaCl_2$were added to all the vials and this setup was incubated at 37 ºC for 4 h. After incubation, 100 mL of mixture was taken from each tube into a luminometer cuvette and an equal amount of working D-luciferin solution (0.3 mM in 0.05 M sodium citrate buffer, pH 4.5) was added. The percentage reduction in the RLU was

calculated for each test compound in comparison with the control. DMSO (1%) was used as solvent control [24].

$$RLU\ (\%) = \frac{RLU_{Control} - RLU_{Test}}{RLU_{Control}} \times 100$$

RESULTS AND DISCUSSION

In current study, a series of pyrimidine derivatives (**4a-j**) were synthesized by reacting the equimolar mixture of aromatic aldehydes, ethyl cyanoacetate and guanidine under microwave irradiation. With the help of microwave irradiation, the rate of chemical reaction was enhanced with a high product yield as compared to conventional synthesis (Table-1). Hence, ethyl cyanoacetate undergoes Knoevenagel condensation reaction with aryl aldehydes followed by Michael addition reaction of guanidine and intramolecular cyclization in presence of ethanolic NaOH solution. Due to microwave synthesis, the yield of the finished product was improved (65-84%). The melting points of the newly synthesized compounds were determined by the open capillary tube method and were found to be in the range of 154-183 ºC. The purity of the compounds was monitored by TLC using *n*-hexane and ethyl acetate (70:30) as mobile phase.

TABLE-1
OPTIMIZATION STUDY ON REACTION TIME AND PRODUCT YIELD

Compd. No.	Ar	R_f	Conventional synthesis		Microwave synthesis	
			RT (h)	Yield (%)	RT (min)	Yield (%)
4a	C_6H_5-	0.54	2	65	6	74
4b	4-CH_3 C_6H_4-	0.67	4	69	8	74
4c	4-OCH_3 C_6H_4-	0.65	3	58	7	67
4d	2-NO_2 C_6H_4-	0.56	2	65	10	73
4e	4-NO_2 C_6H_4-	0.58	4	72	9	84
4f	4-F C_6H_4-	0.52	3	67	12	78
4g	4-OH C_6H_4-	0.56	2	54	7	68
4h	2-Cl C_6H_4-	0.58	4	62	11	76
4i	4-Cl C_6H_4-	0.54	3	66	9	72
4j	2,3-Cl_2 C_6H_3-	0.59	4	57	12	65

In the FTIR studies, the stretching vibrations in the range of 1290-1346, 1422-1568, 1576-1620, 1674-1736, 2190-2318, 3034-3124 and 3487-3546 cm^{-1} indicates the presence of -OCH_3, -C=C, -C=N,C=O, -CN, Ar-CH and -NH, respectively. Further, the IR spectrum of the nitro group (-NO_2) exhibited absorption with λ_{max} at 1620-1546 and 1440-1360 cm^{-1}. Similarly, pyrimidine derivatives substituted with halogens exhibited the IR absorption bands in the region 1426-1024 and 837-647 cm^{-1} which corresponds to C-F *str.* and C-Cl *str.* respectively. Whereas the presence of Ar-OH is confirmed by IR absorption bands in the region of 3640-3235 cm^{-1} and the C-H stretching in case of –CH_3 exhibited at 2945-2857 cm^{-1}. The chemical shift (δ ppm) in the range of 7.14-8.47 indicates the presence of aromatic proton (Ar-H) and was observed as a multiplet. Similarly, the ^1H NMR spectrum of –NH_2 was observed as a singlet at δ 8.58. The mass spectra of the pyrimidine derivative exhibited a molecular ion peak that corresponds to their molecular formula. Compounds **4b, 4c, 4d, 4e**, showed molecular ion peaks at *m/z* 226.06, 242.04 and 257.06 respectively.

The synthesized compounds such as **4d**, **4e**, **4f**, **4h**, **4i** and **4j** were found to be active against *M. tuberculosis* H37Rv at a concentration of 50 µg/mL. Similarly, compounds **4f**, **4g**, **4h**, **4i** and **4j** exhibited antitubercular activity at a concentration of 100 µg/mL. Whereas compounds **4d**, **4i**, **4j** displayed promising activity against clinical isolate S, H, R and E resistance of *M. tuberculosis* at a concentration of 50 µg/mL. But, the tested compounds like **4d, 4e, 4g, 4i** and **4j** displayed potential activity against resistant strains at a concentration of 100 µg/mL as compared to isoniazid (Table-2).

TABLE-2
ANTITUBERCULAR ACTIVITY OF THE TITLE COMPOUNDS (**4a-j**)

Compd. No.	Reduction in RLU (%)			
	M. tuberculosis H37Rv		Clinical isolate: S, H, R and E resistant *M. tuberculosis*	
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
4a	41.62	47.48	43.62	47.76
4b	44.46	48.64	44.37	49.83
4c	44.85	51.68	38.76	47.24
4d	62.47	66.82	51.62	56.64
4e	54.76	58.46	43.35	54.85
4f	61.45	67.84	40.78	47.43
4g	47.65	53.76	48.87	52.66
4h	50.36	62.73	38.84	42.77
4i	52.67	57.86	54.87	58.48
4j	56.84	61.68	56.64	61.46
Isoniazid	81.57		84.58	

SAR study: The structure-activity relationship (SAR) study of pyrimidine derivatives is mainly focused on the screening results obtained from the biological activity. The promising antitubercular activity of the pyrimidine derivatives may be due to the presence of the type of substituents and their position on the aryl ring (hydrophobic domain). The presence of pyrimidine scaffold potentiates the activity. Similarly, the presence of an aryl ring on pyrimidine pharmacophore augments the lipophilicity of the designed molecule. The presence of electron-withdrawing groups including nitro, chloro, fluoro, hydroxy, methoxy on aryl ring of pyrimidine derivatives exhibit better antitubercular activity as compared to other derivatives (Fig. 2) [25].

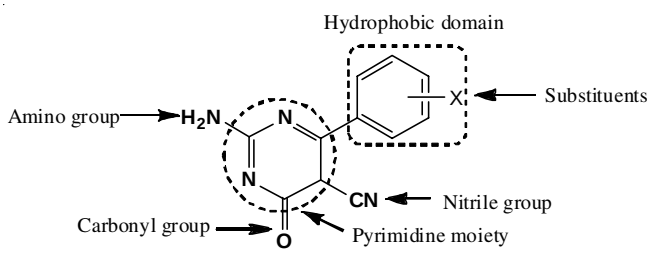


Fig. 2. SAR study of pyrimidine derivatives

Conclusion

A microwave irradiated eco-friendly approach was applied for the synthesis of pyrimidine derivatives. The equimolar

mixture of aryl aldehydes, ethyl cyanoacetate and guanidine was allowed to react in the presence of ethanolic NaOH solution under microwave irradiation. The newly synthesized compounds were evaluated for their antitubercular activity *in vitro* by using the LRP assay method. Most of the tested compounds exhibited significant activity as compared to standard drugs. It was observed that the promising biological activity is due to the presence of electron-withdrawing groups at *para* positions on the aryl ring of pyrimidine derivatives. Hence, it can be concluded that this new series of pyrimidine derivatives certainly holds a greater promise in designing the potential antitubercular agent in the future.

ACKNOWLEDGEMENTS

The authors are thankful to Roland Institute of Pharmaceutical Sciences, Berhampur, India for providing the necessary facilities to carry out the research activities.

CONFLICT OF INTEREST

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

REFERENCES

1. N. Kerru, L. Gummidi, S. Maddila, K.K. Gangu and S.B. Jonnalagadda, *Molecules*, **25**, 1909 (2020); https://doi.org/10.3390/molecules25081909
2. A.K. Dhingra, B. Chopra, J.S. Dua and D.N. Prasad, Antiinflamm. Antiallergy Agents Med. Chem., 16, 136 (2017); https://doi.org/10.2174/1871523017666180126150901
3. M.M. Heravi and V. Zadsirjan, *RSC Adv*., 10, 44247 (2020); https://doi.org/10.1039/D0RA09198G
4. P.J. Jainey and K.I. Bhat, *Indian J. Heterocycl. Chem.*, **20**, 309 (2011).
5. M.C. Sanu, J. Joseph, D. Chacko, B. Vinod and P.A. Daisy, *Int. J. Pharm. Sci. Rev. Res*., **69**, 64 (2021); https://doi.org/10.47583/ijpsrr.2021.v69i02.010
6. A. De, S. Sarkar and A. Majee, *Chem. Heterocycl. Comp*., **57**, 410 (2021); https://doi.org/10.1007/s10593-021-02917-3
7. A.L. Alanzy, D.A. Bakhotm and R.M. Abdel-Rahman, *Int. J. Org. Chem*., **10**, 39 (2020); https://doi.org/10.4236/ijoc.2020.102003
8. S. Kumar and B. Narasimhan, *Chem. Central J.*, **12**, 38 (2018); https://doi.org/10.1186/s13065-018-0406-5
9. T.P. Selvam, C.R. James, P.V. Dniandev and S.K. Valzita, *Res. Pharm.*, **2**, 1 (2012).
10. I.M. Lagoja, *Chem. Biodivers.*, **2**, 1 (2005); https://doi.org/10.1002/cbdv.200490173
11. J. Zhuang and S. Ma, *ChemMedChem*, **15**, 1875 (2020); https://doi.org/10.1002/cmdc.202000378
12. J. Morgan, R. Haritakul and P.A. Keller, *Bioorg. Med. Chem. Lett.*, **13**, 1755 (2003); https://doi.org/10.1016/S0960-894X(03)00241-5
13. C.J. Queval, R. Brosch and R. Simeone, *Front. Microbiol.*, **8**, 2284 (2017); https://doi.org/10.3389/fmicb.2017.02284
14. V.J. Faldu, V.K. Gothalia and V.H. Shah, *Indian J. Chem.*, **54B**, 391 (2015).
15. M. Kidwai, K. Singhal and S. Kukreja, *Z. Naturforsch. B*, **62**, 732 (2007); https://doi.org/10.1515/znb-2007-0518
16. A.K. Mahato, B.M. Sahoo, B.K. Banik and B.C. Mohanta, *J. Indian Chem. Soc.*, **95**, 1327 (2018).
17. B.M. Sahoo, B.V.V. Ravi Kumar, J. Panda and S.C. Dinda, *J. Nanopart.*, **2013**, 780786 (2013); https://doi.org/10.1155/2013/780786
18. C.O. Kappe, *Angew. Chem. Int. Ed.*, **43**, 6250 (2004); https://doi.org/10.1002/anie.200400655
19. M. De Rosa, J. Gising, L.R. Odell and M. Larhed, *Ups. J. Med. Sci.*, **119**, 181 (2014); https://doi.org/10.3109/03009734.2014.899655
20. M. Gaba and N. Dhingra, *Indian J. Pharm. Educ. Res.*, **45**, 175 (2011).
21. R. Gedye, R. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett.*, **27**, 279 (1986); https://doi.org/10.1016/S0040-4039(00)83996-9
22. A. Rattan, A. Kalia and N. Ahmad, *Emerg. Infect. Dis.*, **4**, 195 (1998); https://doi.org/10.3201/eid0402.980207
23. S. Anbarasu, K. Revathy, M. Radhakrishnan, P. Krupakar, J. Joseph and V. Kuma, *Biosci. Biotechnol. Res. Commun.*, **13**, 1236 (2020); https://doi.org/10.21786/bbrc/13.3/39
24. N. Banaiee, M. Bobadilla-del-Valle, S. Bardarov Jr., P.F. Riska, P.M. Small, A. Ponce-de-Leon, W.R. Jacobs Jr., G.F. Hatfull and J. Sifuentes-Osornio, *J. Clin. Microbiol.*, **39**, 3883 (2001); https://doi.org/10.1128/JCM.39.11.3883-3888.2001
25. Y. Pore, B. Kuchekar, M. Bhatia and K. Ingale, *Dig. J. Nanomater. Biostruct.*, **4**, 373 (2009).