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Green Chemistry Protocol for the Synthesis and Antimycobacterial Activity of Multicomponent Biginelli Condensation Catalyzed by Surfactant in Aqueous Media

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ABSTRACT

Background and Objective: A Simple, Green and efficient procedure for the synthesis of 4-aryl-3, 4-dihydropyrimidine-2(1*H*)-ones/thione (Biginelli reaction) from 1, 3-dicarbonyl compound, substituted aldehydes and urea/thiourea in the presence of Sodium Dodecyl Sulphate (SDS), a novel catalyst has been introduced in this study. **Materials and Methods:** The structures of these compounds have been confirmed on the basis of their physical and spectral (IR, ^{1}HNMR and Mass) data. The dihydropyrimidinone derivatives were evaluated for their *in vitro* antimycobacterial activity against H_{37}Rv strain by using alamar blue dye method. **Results:** The synthesized compounds were purified by column chromatography. All the reactions were monitored by TLC and the derivatives were supported by spectral data. The products are obtained in good yield under conventional and domestic microwave methods. All the synthesized compounds exhibited promising activity (MIC: 6.25-100 μg mL^{-1}) against *Mycobacterium tuberculosis* H_{37}Rv. **Conclusion:** A novel method which is eco-friendly, cost effective, solvent free was developed for the synthesis of dihydropyrimidines under conventional and domestic microwave methods. Using these methods, compounds were produced in high yield. Among 12 compounds screened, IVf found to be most potent with MIC: 6.25 μg mL^{-1} with least minimal toxicity some of them were found to possess significant activity, when compared to standard drugs(Streptomycin and Pyrazinamide).

Key words: Dihydropyrimidinone, sodium dodecyl sulphate, urea, antimycobacterial activity

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INTRODUCTION

At the beginning of new century, organic solvent free reactions have attracted considerable interest due to increasing awareness about environmental problems in chemical research and industry[1]. Water is safe, cheap and environmentally benign in comparison with organic solvents[2]. Using water as reaction media led to the discovery of organic reactions like Claisen condensation[3], Aldol condensation[4], Diels-alder[5], Benzoin condensation[6], Mannich[7] and Micheal addition reactions[8]. The surfactant used in water can make organic substances soluble or form colloidal dispersions with great stability in water. Surfactants have been used as good catalyst in various organic reactions[9, 10].

Dihydropyrimidinones (DHPM) have exhibited important biological and pharmacological properties as the integral backbone of several calcium channel blockers[11], antihypertensive[12], anti-tumor[13], α1-adrenergic antagonist[14], antimycobacterial[15] and anti-inflammatory[16] activities. Several alkaloids isolated from marine sources also exhibit interesting biological activities, molecular structures of which contain the dihydropyrimidinone moiety[17]. Tuberculosis (TB) is by far the most frequently encountered mycobacterial disease in the world[18]. However, there are numerous

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examples of nitrogen containing heterocycles being used to treat TB, for example Clofazimine, Isoniazid and Pyrazinamide[19].

Several synthetic methods have been reported for the synthesis of DHPM derivatives, but still they have limitations like long reaction time, less yield and costly chemicals/catalysts. Therefore, their synthesis has been the focus of great interest for organic and medicinal chemists. To enhance the efficiency of the Biginelli reaction, various catalysts and reaction conditions have been studied[20-22]. From the literature survey, there are no reports using sodium dodecyl sulphate (SDS) was reported as catalyst for classical Biginelli reaction. The catalytic activity of SDS as is notable and it is low cost, commercially easily available for the synthesis of Biginelli products and also environmentally benign process. Here, the capacity of SDS was reported as potential catalyst for the one pot synthesis of DHPMs and evaluated for their *in vitro* antimycobacterial activity using standard protocol.

MATERIALS AND METHODS

All chemicals used were of analytical grade and commercially available from Merck, Mumbai. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh) (Merck, Mumbai) and spots were visualized under UV light (254 nm). Melting points were detected in open capillaries using Bachi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer RX1-FTIR and ^{1}H NMR spectra on a JEOL 400 spectrometer using internal standard as TMS. Mass spectra were recorded on JEOL DX 300 in E1 ionization method at 70 ev. The elemental analyses of the compounds were recorded using Perkin–Elmer series 2400 analyzer.

Chemistry

General procedure:

Synthesis of 4-(substituted phenyl-)-3,4-dihydropyrimidine-2-(1H)-ones/thiones (IVa-IVl)

Conventional method: To a mixture of β-ketoester (0.01 mol, I), aldehyde (0.01 mol, II), urea or thiourea (0.01 mol, III) and sodium dodecyl sulphate (10 %w/v in water) was heated under reflux for 4-5 h with magnetic stirring as shown in Fig. 1. The completion of the reaction was monitored by TLC. After cooling to room temperature, the reaction mixture was poured into 100 mL of cold water and stirred for 5 min. The separated solid was filtered under suction, washed with cold water and then recrystallized from ethanol to afford the pure product.

Micro-wave irradiation method: To a mixture of β-ketoester (0.01 mol, I), aldehyde (0.01 mol, II), urea or thiourea (0.01 mol, III) and Sodium dodecyl sulphate (10% w/v in water) was subjected to microwave irradiation at 220 W for 5-6 min. The completion of the reaction was monitored by TLC. After cooling to room temperature, the reaction mixture was poured into 100 mL of cold water and stirred for 5 min. The separated solid was filtered under suction, washed with cold water and then recrystallized from ethanol to afford the pure product.

The physical properties of the synthesized compounds were shown in Table 1.

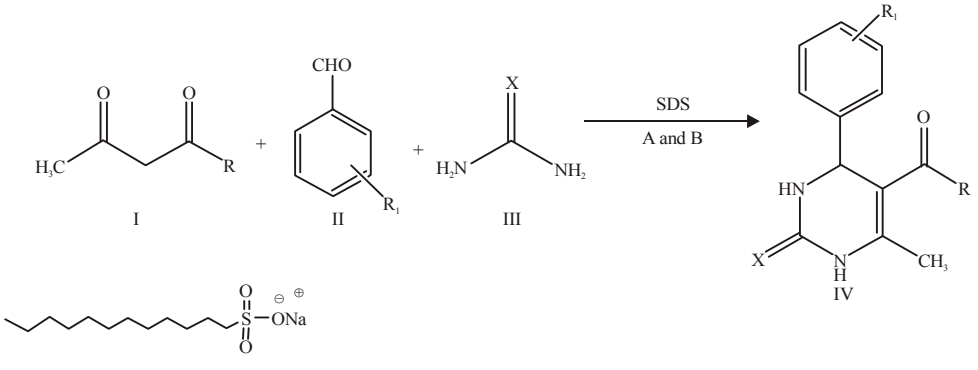

Fig. 1: Scheme of compound synthesis, sodium dodecyl sulphate (SDS), X: O,S, R: -CH3, -OC2H5, R1: -H, 4-OCH3, 4-OH, 2-OH, 4-Cl, -4-NO_2, A: Conventional method, B: Microwave irradiation method

Table 1: Physical data of the synthesized DHPM derivatives (IVa-IV_l)

Compounds code	R	R_1	X	Yield (%)		M.P(°C)	
				Conventional method	Microwave method	Found	Reported[23]
IV_a	C_6H_5	CH_3	O	92	95	229-232	233-235
IV_b	C_6H_5	OC_2H_5	O	90	96	203-205	201-202
IV_c	4-OCH_3 C_6H_4	OC_2H_5	O	87	89	199-201	200-201
IV_d	4-OHC_6H_4	OC_2H_5	O	89	92	226-229	222-229
IV_e	2-OH-C_6H_4	OC_2H_5	O	90	94	199-201	201-202
IV_f	4-ClC_6H_4	OC_2H_5	O	91	95	209-211	212-214
IV_g	4-$NO_2C_6H_4$	OC_2H_5	O	90	93	206-208	207-209
IV_h	C_6H_5	OC_2H_5	S	92	96	208-210	204-206
IV_i	C_6H_5	CH_3	S	91	95	216-218	219-220
IV_j	4-(OCH_3)-C_6H_4	CH_3	O	92	96	165-168	167-169
IV_k	4-ClC_6H_4	OC_2H_5	S	92	95	190-192	192-194
IV_l	4-OH C_6H_4	OC_2H_5	S	86	88	227-228	--

Spectral data of synthesized compounds

5-(acetyl)-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-one(IV_a): IR (KBr) cm^{-1}: 3241(N-H), 3095 (C-H, Ar), 1713 (C = O); ^{1}H-NMR (DMSO-d_6) ppm: δ2.1 (3H, s, -CH_3), 2.29 (3H, s, -CH_3), 5.26 (1H, s, H of pyrimidine ring), 7.24 (5H, m, Ar-H) 7.82 (1H, s, -NH), 9.17 (1H, s, -NH). Mass (ESI-MS): m/z 231 (M+1). Elemental analysis: For $C_{13}H_{14}N_2O_2$ Calculated 67.81% C, 6.12% H, 12.16% N; Found 67.82% C, 6.08% H, 12.17% N.

5-(ethoxycarbonyl)-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-one (IV_b): IR (KBr) cm^{-1}: 3249 (N-H), 3073 (C-H, Ar), 1738 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.04 (3H, t, -OCH_2CH_3), 2.23 (3H, s, -CH_3), 3.95 (2H, q, -OCH_2CH_3), 5.19 (1H, s, H of pyrimidine ring), 7.15 (5H, m, Ar-H), 7.77 (1H, s, NH), 9.85(1H, s, -NH). Mass (ESI-MS): m/z 261 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_3$ Calculated 64.61% C, 6.19% H, 10.76% N; Found 64.61% C, 6.15% H, 10.76% N.

5-(carboethoxy)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (IV_c): IR(KBr) cm^{-1}: 3246 (N-H), 3042 (C-H, Ar), 1709 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.04(3H, t, -OCH_2CH_3), 2.23 (3H, s, -CH_3), 3.79 (3H, s, -OCH_3), 3.94 (2H, q, -OCH_2CH_3), 5.15 (1H, s, H of pyrimidine ring), 6.97(4H, m, Ar-H), 7.75 (1H, s, -NH), 9.73(1H, s, -NH). Mass (ESI-MS): m/z 291 (M+1). Elemental analysis: For $C_{15}H_{18}N_2O_4$ Calculated 62.06% C, 6.25% H, 9.65% N; Found 62.06% C, 6.20% H, 9.65% N.

5-(carboethoxy)-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one(IV_d): IR (KBr) cm^{-1}: 3290 (N-H), 3092 (C-H, Ar), 1690 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.03(3H, t, OCH_2CH_3), 2.22 (3H, s, -CH_3), 3.94 (2H, q, -OCH_2CH_3), 5.12 (1H, s, H of pyrimidine ring), 6.61(4H,m,Ar-H), 7.73(1H, s, -NH), 8.86 (1H, s, -NH), 9.76 (1H, s, -OH). Mass (ESI-MS): m/z 277 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_4$ Calculated 60.86% C, 5.83% H, 10.04% N; Found 60.86% C, 5.79% H, 10.14% N.

5-(ethoxycarbonyl)-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one(IV_e): IR (KBr) cm^{-1}: 3224 (N-H), 3084 (C-H, Ar), 1748 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.04(3H, t, -OCH_2CH_3), 2.23 (3H, s, -CH_3), 3.95 (2H, q, -OCH_2CH_3), 5.15 (1H, s, H of pyrimidine ring), 6.74 (4H, m, Ar-H), 7.76 (1H, s, -NH), 8.27 (1H, s, -NH), 9.73 (1H, s, -OH). Mass (ESI-MS): m/z 277 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_4$ Calculated 60.86% C, 5.83% H, 10.04% N; Found 60.86% C, 5.79% H, 10.14% N.

5-(carboethoxy)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (IV_f): IR(KBr)cm^{-1}: 3242 (N-H), 3095 (C-H, Ar), 1723 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.04 (3H, s, -OCH_2CH_3), 2.24 (3H, s, -CH_3), 3.21 (2H, q, -CH_2CH_3), 5.21 (1H, s, H of pyrimidine ring), 7.16 (4H, m, Ar-H), 8.51 (1H, s, -NH), 9.46 (1H, s, -NH). Mass (ESI-MS): m/z 295 (M+1). Elemental analysis: For $C_{14}H_{15}N_2O_3Cl$ Calculated 57.05% C, 5.13% H, 9.50% N; Found 57.14% C, 5.10% H, 9.52% N.

5-(ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (IV_g): IR (KBr) cm^{-1}: 3274 (N-H), 3052 (C-H, Ar), 1758 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.06(3H, t, -OCH_2CH_3), 2.26 (3H, s, -CH_3), 3.95 (2H, q, -OCH_2CH_3), 5.23 (1H, s, H of pyrimidine ring), 7.47 (m, 4H, Ar-H), 7.84 (1H, s, -NH), 9.35 (1H, s, -NH). Mass (ESI-MS): m/z 306 (M+1). Elemental analysis: For $C_{14}H_{15}N_3O_5$ Calculated 55.08% C, 4.95% H, 13.76% N; Found 55.08% C, 4.91% H, 13.77% N.

5-(ethoxycarbonyl)-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (IV_h): IR (KBr) cm^{-1}: 3265 (N-H), 3086 (C-H, Ar), 1742 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.12(3H, t, -OCH_2CH_3), 2.31 (3H, s, CH_3), 4.01(2H, q, -OCH_2CH_3), 5.22 (1H, s, H of pyrimidine ring), 7.29 (5H, m, Ar-H), 9.61 (1H, s, -NH), 10.27 (1H, s, -NH). Mass (ESI-MS): m/z 277 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_2S$ Calculated 60.84% C, 5.83% H, 10.14% N; Found 60.86% C, 5.79% H, 10.14% N.

5-(Acetyl)-4-phenyl-6-methyl-3,4-dihydropyrimidine-2(1H)-thione(IV_i): IR (KBr) cm^{-1}: 3283 (N-H), 3099 (C-H, Ar), 1715 (C = O).^{1}H-NMR (DMSO-d_6) ppm: δ1.90 (3H, s, -CH_3), 2.02 (3H, s, -CH_3), 5.07 (1H, s, H of pyrimidine ring), 7.06 (5H, m, Ar-H), 9.51 (1H, s, -NH), 10.05 (1H, s, -NH). Mass (ESI-MS): m/z 247 (M+1). Elemental analysis: For $C_{13}H_{14}N_2OS$ Calculated 67.81% C, 6.12% H, 12.16% N; Found 67.82% C, 6.08% H, 12.17% N.

5-(acetyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-one (IV_j): IR (KBr) cm^{-1}: 3213 (N-H), 3057 (C-H, Ar), 1715 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ2.06 (3H,s, CH_3), 2.27 (3H, s, CH_3), 3.71 (3H, s, -OCH_3), 5.24 (1H, s, H of pyrimidine ring), 6.86 (4H, m, Ar-H), 7.7 (1H, s, -NH), 9.10 (1H, s, -NH). Mass (ESI-MS): m/z 258 (M+1). Elemental analysis: For $C_{13}H_{14}N_2O_2$ Calculated 63.38% C, 5.72% H, 11.37% N; Found 63.41% C, 5.69% H, 11.38% N.

5-(ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)-thione (IV_k): IR (KBr) cm^{-1}: 3204 (N-H), 3080 (C-H, Ar), 1698 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ0.97 (t, 3H, -OCH_2CH_3), 2.21 (3H, s, CH_3), 3.82 (2H, q, -OCH_2CH_3), 5.43 (1H, s, H of pyrimidine ring), 7.31 (m, 4H, Ar-H), 7.96 (1H, s, -NH), 8.81 (1H, s, -NH). Mass (ESI-MS): m/z 279 (M+1). Elemental analysis: For $C_{14}H_{15}N_2O_2SCl$ Calculated 60.32% C, 5.42% H, 10.05% N; Found 60.43% C, 5.39% H, 10.07% N.

5-(ethoxycarbonyl)-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidine-2(1H)thione(IV_l): IR (KBr) cm^{-1}: 3422 (O-H), 3219 (N-H), 3074 (C-H, Ar), 1672 (C = O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.14 (t, 3H, -OCH_2CH_3), 2.28 (3H, s,-CH_3), 3.97 (2H, q, -OCH_2CH_3), 5.18 (1H, s, H of pyrimidine ring), 6.84 (4H, m, Ar-H), 7.67 (1H, s, -NH), 9.18 (1H, s, -NH), 9.87 (1H, s, OH). Mass (ESI-MS): m/z 293 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_3S$ Calculated 57.52% C, 5.51% H, 9.58% N; Found 57.53% C, 5.47% H, 9.58% N.

Biological activity: The *in vitro* anti mycobacterial activities of compounds (IVa-IVl) were evaluated against *M. tuberculosis* H_{37}Rv strain using Micro plate Alamar Blue assay (MABA)[24]. Briefly, 200 μL of sterile deionised water was added to all outer perimeter wells of sterile 96 well plates to minimize evaporation of medium in the test wells during incubation. The 96 plates received 100 μL of the Middle brook 7H9 broth and a serial dilution of compounds (IVa-IVl) were made directly on plate. The final drug concentrations tested were 100 to 0.8 μg mL^{-1} and standards pyrazinamide 3.125 μg mL^{-1} and streptomycin 6.25 μg mL^{-1}. Plates were covered and sealed with parafilm and incubated at 37°C for five days. After this time, 25 μL freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue colour in the well was interpreted as no bacterial growth and pink colour was scored as growth. The MIC (Minimal Inhibition Concentration) was defined as the lowest drug concentration which prevented a color change from blue to pink.

RESULTS AND DISCUSSION

Chemistry: The 4-(substituted phenyl-)-3, 4-dihydropyrimidine-2-(1H)-ones/thiones (IVa-IVl) were prepared using one pot Biginelli reaction using sodium dodecyl sulphate as catalyst and water as solvent as depicted in Fig. 1. The mechanism of Biginelli reaction is shown in Fig. 2 and it involves the formation of an N-acyliminium ion intermediate from the aldehyde and urea component. Interception of the iminium ion by β-ketoester, possibly through its enol tautomer produces an open-chain ureide which subsequently cyclization and dehydration to dihydropyrimidinones (IV). The reactions proceeded with good yields and compounds were obtained as solids. The synthesized compounds were purified by column chromatography. All the reactions were monitored by TLC and the derivatives were supported by spectral data. The IR spectra of the compound IVa showed the absorption bands at 3241,2985 and 1713 cm^{-1} due to presence of -NH, Ar-H and C = O groups respectively. ^{1}H NMR spectra shows signals at δ2.29 (s, -$COCH_3$), 7.24 (m, Ar-H), 7.82 and 9.12 (br, -NH). Mass spectra the base peak is shown as M+1 peak and also characteristic of all the remaining derivatives.

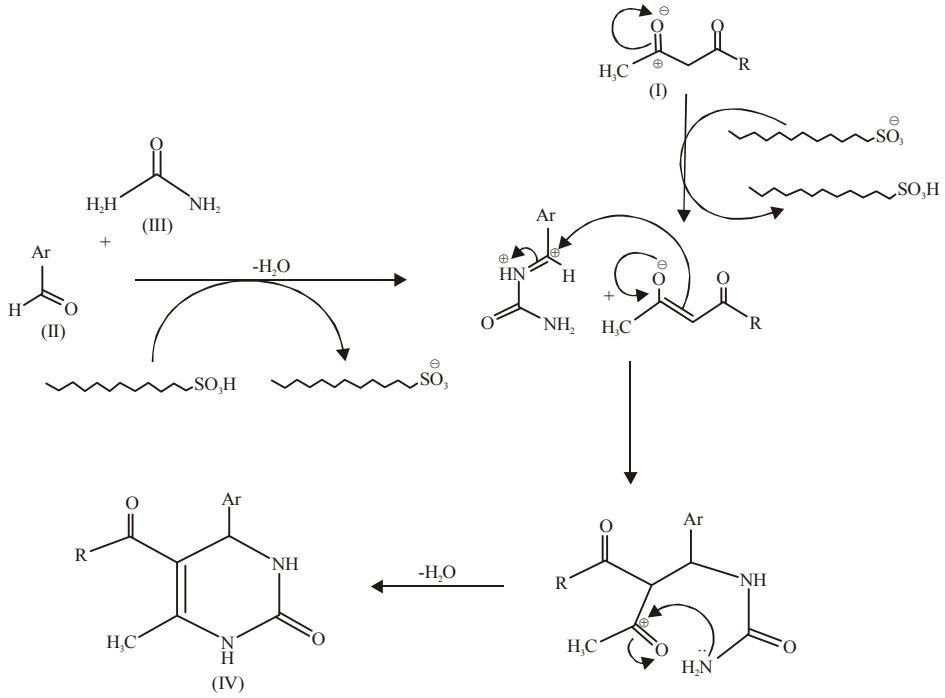

Fig. 2: Mechanism of Biginelli reaction

Table 2: *In vitro* evaluation of the antimycobacterial activity DHPM IVa-IV_l

Compounds	MIC (μg mL^{-1})[a] (*M. tuberculosis* H_{37}Rv)
IVa	100.00
IVb	100.00
IVc	12.50
IVd	12.50
IVe	50.00
IVf	6.25
IVg	25.00
IVh	100.00
IVi	100.00
IV_j	50.00
IV_k	12.50
IV_l	25.50
Streptomycin	6.25
Pyrazinamide	3.125

[a]MIC defined as the lowest concentration, which prevented a color change from blue to pink

Antimycobacterial activity: All the synthesized compounds were evaluated for their *in vitro* antimycobacterial activity against *M. tuberculosis* H_{37}Rv strain. All compounds exhibited significant antimycobacterial activity and were dose dependent. The MIC values of all the compounds were shown in Table 2. From the structure activity relationship, the compounds bearing C-4 phenyl group in DHPMs (IVa, IVb, IVh and IVi) do not show any significant activity, were as 4-methoxyphenyl, 4-hydroxyphenyl and 4-chlorophenyl substituents (IVc, IVd and IVk) showed moderate activity with an MIC values of 12.5 μg mL^{-1} but 4-chlorophenyl substituent (IVf) in DHPMs showed potent antimycobacterial activity at an MIC value of 6.25 μg mL^{-1} and were comparable with standard drugs Pyrazinamide (3.125 μg mL^{-1}) and Streptomycin (6.25 μg mL^{-1}) respectively. Among 12 compounds screened, IVf bearing electron withdrawing groups on phenyl ring found to be most potent with MIC: 6.25 μg mL^{-1} with least minimal toxicity.

CONCLUSIONS

A highly convenient procedure for the synthesis of 4-aryl-3, 4-dihydropyrimidine derivatives catalyzed by SDS in aqueous media under two experimental methods has been reported. This method has several advantages like less toxic, less expensive, high yields and eco-friendly. The yields of synthesized compounds were found to be more under microwave irradiation method then conventional method. The synthesized compounds were evaluated for their antimycobacterial activity using MABA. Among the tested compounds IV_f showed excellent activity with an MIC value of 6.25 μg mL^{-1} and were comparable with standards. These studies were utilized for designing novel synthetic routes for the preparation of pyrimidine scaffold.

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