*Heterocyclic Letters*
*Vol. 14| No.1|121-129|Nov-Jan|2024*
*ISSN : (print) 2231–3087 / (online) 2230-9632*
*CODEN: HLEEAI*
*http://heteroletters.org*

# A CLEAN AND EFFICIENT SYNTHESIS OF PYRIMIDO[4,5-*B*]QUINOLINE AND PYRIDO[2,3-*D*]PYMIDINE UNDER SONICATION USING FE(DS)$_3$ AS LEWIS ACID-SURFACTANT-COMBINED CATALYST

**Aakash Singh[a], SunitaYadav[b], and Ruby Singh[b,*]**

[a]*Department of Applied Sciences and Humanities, Dr. Shakuntla Mishra National Rehabilitation University, Lucknow, 226017, Uttar Pradesh, India.*
[b]*Department of Chemistry, School of Basic Sciences, Jaipur National University, Jaipur, 302017, Rajasthan, India*
*****E-mail address: drrubychem@yahoo.com*

**ABSTRACT**: The present work explores an ultrasound-assisted efficient synthesis of two biologically potent fused scaffolds *i.e.*, pyrimido[4,5-*b*]quinolines and pyrido[2,3-*d*]pymidines *via* multi-component reaction of 1,3-dimethyl-6-amino-uracil, cyclic ketones and substituted aldehydes using Fe(DS)$_3$ as Lewis acid-surfactant-combined catalyst in aqueous medium. The described procedure is environmentally benign and offers several advantages such as very simple work-up, mild reaction conditions and reusability of catalyst.
**KEYWORDS**:Pyrimido[4,5-*b*]quinoline,Pyrido[2,3-*d*]pymidine,Ultrasound,Environmentally benign.

## 1. INTRODUCTION

Heterocyclic compounds have gained vast significance in human life because of their diversity of applications. Nitrogen containing heterocycles have received unique attention in pharmaceutical chemistry, due to their wide medicinal utility[i]. Pyrimidine derivatives are well known for their biological activities[ii] and numerous pyrimidine and uracil-based compounds have found application in medicine and therapeutics as used in the chemotherapy of cancer[iii] and against HIV and viral diseases[iv]. Heterocycles with two or more heterocyclic moieties are called as amalgamated or fused heterocycles and these heterocycles is the traditional divisions of heterocyclic chemistry and cover both biologically and industrially applications.

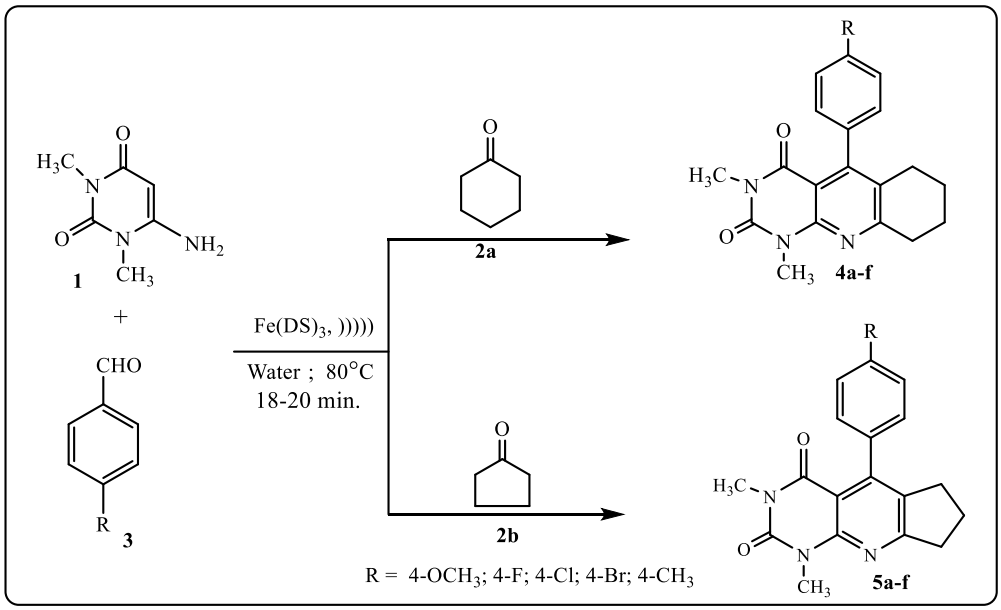
In recent years, significant attention has been focused on the synthesis of diverse fused pyrimidine derivatives, but herein we focused our attention only on two fused systems *i.e.*, pyrimido[4,5-*b*]quinoline and pyrido[2,3-*d*]pyrimidines due to their significant biological interest. Pyrimido[4,5-*b*]quinoline is one of the important class of heterocyclic moiety that possesses biological properties such as analgesic[v], antiviral[vi], anti-inflammatory[vii], antimicrobial [viii], antifungal[ix] and anticancer activity[x]. Likewise pyrido[2,3-d]pyrimidine derivatives are also reported as calcium channel antagonists[xi], tyrosine kinase inhibitors[xii] and also used in acute diarrhea treatment[xiii].

Various substituted pyrimido[4,5-*b*]quinolines and pyrido[2,3-*d*]pyrimidines have been synthesized by diverse procedures using different catalyst and reaction conditions [xiv] and it

was found that the substituted 6-amino-uracils are important synthon required for annulations of pyrimidine ring onto other heterocyclic rings to form fused derivatives.

The reported procedures for synthesis of these fused pyrimidine systems required use of expensive and toxic transition metals, volatile organic solvents, corrosive reagents, non-recoverable catalysts and harsh reaction conditions is some limitations that make these procedures less suitable. Therefore, it is urgently necessary to expand procedures that are more economically feasible and environmentally friendly for the synthesis of pyrido[2,3-d]pyrimidines and pyrido[2,3-*d*]pyrimidines.

Hence, in continuation of our efforts toward the development of one-pot, eco-compatible and viable protocols for synthesis of biologically active heterocycles[xv-xvii], herein we developed a straightforward convergent three component one-pot synthesis for two pyrimidine fused system such as pyrimido[4,5-*b*]quinolines**4a-f** and pyrido[2,3-*d*]pyrimidines **5a-f** in water using Sodium Dodecyl Sulphate ($Fe(DS)_3$) as a Lewis acid surfactant combined catalyst under sonication (scheme-1).




**Scheme-1:** Multicomponent synthesis of ofpyrimido[4,5-*b*]quinoline-2,4-diones (**4a-f**)andpyrido[2,3-*d*]pymidine-2,4-diones (**5a-f**)**.**

## 2. EXPERIMENTAL SECTION

Analytical grade solvents and commercially available reagents were used without further purification. The melting points of all compounds were determined on a Digital melting point apparatus. The purity of compounds was checked on thin layers of silica Gel-G coated glass plates using benzene: ethyl acetate (8:2) as eluent. IR spectra were recorded on a Shimadzu FT IR–8400S spectrophotometer using KBr pellets. $^1H$ and $^{13}C$ NMR spectra were recorded in deuterium solvent (DMSO-$d_6$) on a Jeol Resonance at 400 MHz. Chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The Mass spectra of representative compounds were obtained using JEOL SX-102 spectrometer at 70 eV. Elemental analyses were carried out on a Euro–E 3000 CHN Elemental analyzer**.**

## 3. GENERAL PROCEDURE FOR SYNTHESIS OF PYRIMIDO[4,5-*B*]QUINOLINES (4a-f) AND PYRIDO[2,3-*D*]PYRIMIDINES (5a-f).

A mixture of 6-amino-1,3-dimethyluracil **1** (1 mmol), cyclohexanone **2a**/cyclopentanone **2b** (1 mmol), benzaldehyde **3** (1 mmol) and 10 mol % of $Fe(DS)_3$ was taken in 25 ml of tap water in a flask. Then, the mixture was sonicated for appropriate time at amplitude of 50% (power 50 W) with 12 mm probe. At the end of reaction confirmed by TLC, the crude solid compound was filtered and washed with solvent (water and ethanol) and then crystallized to obtained pure corresponding product. In order to recover the catalyst, $H_2O$ was evaporated under reduced pressure, and the resulting solid was washed with diethyl ether, and dried under reduced pressure. All Synthesized compounds were characterized on the basis of IR, NMR and Mass spectral data.

## 4. ANALYTICAL DISCUSSION

**5-(4-Methoxy-phenyl)-1,3-dimethyl-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-dione** (**4a**): IR (KBr): 2960, 1704 $cm^{-1}$; $^1$H NMR : δ 1.95-2.12 (m, 4H, $CH_2$), 2.39-2.50 (m, 4H, $CH_2$), 3.27(s, 6H, N-$CH_3$), 3.69 (s, 3H, O-$CH_3$), 6.70-6.94 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 21.23, 26.59, 30.08, 31.24, 35.80, 52.41, 119.12, 120.81, 126.17, 128.27, 129.44, 129.81, 129.94, 130.21, 132.69, 135.03, 138.97, 148.36, 162.49, 169.78 ppm; MS (m/z): 352$[M+H]^+$ ; Anal. calcd. for $C_{20}H_{21}N_3O_3$:C 68.36, H 6.02, N 11.96 %. Found: C 64.56, H 6.05, N 11.91 %.

**5-(4-Chloro-phenyl)-1,3-dimethyl-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-dione** (**4b**): IR (KBr): 2962, 1705 $cm^{-1}$; $^1$H NMR: δ 1.92-2.24 (m, 4H, $CH_2$), 2.40-2.49 (m, 4H, $CH_2$), 3.24 (s, 6H, N-$CH_3$), 6.65-6.89 (m, 4H, Ar-H) ppm; $^{13}$C NMR : δ 21.32, 26.54, 30.11, 31.26, 35.08, 119.21, 120.78, 126.15, 128.23, 129.46, 129.84, 129.86, 130.12, 132.59, 135.30, 138.79, 148.30, 162.41, 169.87 ppm; Anal. calcd. for $C_{19}H_{18}ClN_3O_2$ :C 64.14; H 5.10; N 11.81 %. Found: C 64.34, H 5.06, N 11.86 %.

**5-(4-Bromo-phenyl)-1,3-dimethyl-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-dione (4c):** IR (KBr): 2962, 1708 $cm^{-1}$; $^1$H NMR: δ 1.89-2.22 (m, 4H, $CH_2$), 2.35-2.42 (m, 4H, $CH_2$), 3.28 (s, 6H, N-$CH_3$), 6.52-6.92 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 21.28, 26.45, 30.65, 31.31, 35.10, 118.21, 121.78, 124.15, 128.30, 129.41, 129.89, 130.12, 130.46, 132.59, 135.03, 138.59, 148.34, 162.46, 169.89 ppm; Anal. calcd. for $C_{19}H_{18}BrN_3O_2$ :C 57.01, H 4.53, N 10.50 %. Found: C 57.21, H 4.56, N 11.45 %.

**5-(4-Nitro-phenyl)-1,3-dimethyl-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-dione (4d):** IR (KBr): 2962, 1705 $cm^{-1}$; $^1$H NMR : δ 1.92-2.25 (m, 4H, $CH_2$), 2.38-2.40 (m, 4H, $CH_2$), 3.31 (s, 6H, N-$CH_3$), 6.55-6.89 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 21.22, 26.39, 30.56, 31.24, 35.15, 118.29, 121.71, 124.20, 128.31, 129.46, 129.80, 130.21, 130.43, 132.95, 135.16, 138.58, 148.24, 162.56, 169.81 ppm; Anal. calcd. for $C_{19}H_{18}N_4O_4$ :C 62.29, H 4.95, N 15.29 %. Found: C 62.49, H 4.93, N 15.34 %.

**5-(4-Methyl-phenyl)-1,3-dimethyl-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4--(1*H*,3*H*)-dione (4e):** IR (KBr): 2962, 1706 $cm^{-1}$; $^1$H NMR: δ 1.88-2.15 (m, 4H, $CH_2$), 2.27 (s, 3H, $CH_3$), 2.29-2.36 (m, 4H, $CH_2$), 3.34 (s, 6H, N-$CH_3$), 6.54-6.84 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 21.19, 22.53, 26.29, 30.50, 31.21, 35.18, 118.31, 121.70, 124.21, 128.37, 129.40, 129.89, 130.25, 130.34, 132.59, 135.20, 138.68, 148.14, 162.66, 169.97 ppm; Anal. calcd. for $C_{20}H_{21}N_3O_2$ :C 71.62; H 6.31; N 12.53 %. Found: C 71.82, H 6.34, N 12.58 %.

**5-(4-Fluoro-phenyl)-1,3-dimethyl-6,7,8,9-tetrahydro-1*H*-pyrimido[4,5-*b*]quinoline-2,4-(1*H*,3*H*)-dione (4f):** IR (KBr): 2960, 1703 $cm^{-1}$;$^1$H NMR : δ 1.88-2.20 (m, 4H, $CH_2$), 2.23-2.38 (m, 4H, $CH_2$), 3.36 (s, 6H, N-$CH_3$), 6.49-6.78 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 21.2426.31, 30.55, 31.19, 35.24, 118.32, 121.71, 124.28, 128.36, 129.47, 129.86, 130.22, 130.31, 132.52, 135.35, 138.86, 148.41, 162.69, 169.85 ppm; MS (m/z): 340$[M+H]^+$ ; Anal. calcd. for $C_{19}H_{18}FN_3O_2$ :C 67.24, H 5.35, N 12.38 %. Found: C 67.44, H 5.38, N 12.43 %.

**5-(4-Fluorophenyl)-1,3-dimethyl-1,6,7,8-tetrahydro-2*H*-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidine-2,4-(3*H*)-dione**(**5a**): IR (KBr): 2970, 1703 $cm^{-1}$; $^1$H NMR : δ 2.24 (m, 2H, $CH_2$), 2.41-2.56 (m, 4H, $CH_2$), 3.27 (s, 6H, N-$CH_3$), 6.34-6.89 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 22.22, 30.14, 31.26, 35.65, 119.21, 120.63, 126.12, 128.65, 129.48, 129.84, 130.36, 132.78, 135.42, 138.41, 148.23, 162.87, 169.82 ppm; Anal. calcd. for $C_{18}H_{16}FN_3O_2$:C 66.45; H 4.96; N 12.92 %. Found: C 66.65, H 4.92, N 12.97 %.

**5-(4-Chlorophenyl)-1,3-dimethyl-1,6,7,8-tetrahydro-2*H*-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidine-2,4(3*H*)-dione**(**5b**): IR (KBr): 2975, 1709 $cm^{-1}$; $^1$H NMR :δ 2.26 (m, 2H, $CH_2$), 2.44-2.61 (m, 4H, $CH_2$), 3.25 (s, 6H, N-$CH_3$), 6.34-6.86 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 22.20, 30.15, 31.43, 35.68, 119.13, 120.76, 126.11, 128.25, 129.39, 129.90, 130.25, 132.97, 135.33, 138.74, 148.32, 162.57, 169.89 ppm; Anal. calcd. for $C_{18}H_{16}ClN_3O_2$ :C 63.25; H 4.72; N 12.29 %. Found: C 63.45, H 4.77, N 12.24 %.

**5-(4-Bromophenyl)-1,3-dimethyl-1,6,7,8-tetrahydro-2*H*-cyclopenta[5,6]pyrido[2,3-d]pyrimidine-2,4(3*H*)-dione** (**5c**):IR (KBr): 2975, 1705 $cm^{-1}$; $^1$H NMR: δ 2.28 (m, 2H, $CH_2$), 2.42-2.58 (m, 4H, $CH_2$), 3.23 (s, 6H, N-$CH_3$), 6.32-6.84 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 22.27, 30.18, 31.39, 35.65, 119.24, 120.67, 126.10, 128.52, 129.46, 129.98, 130.35, 132.87, 135.23, 138.47, 148.23, 162.57, 169.76 ppm; MS (m/z): 387$[M+H]^+$; Anal. calcd. For $C_{18}H_{16}BrN_3O_2$ :C 55.97; H 4.18; N 10.88 %. Found: C 55.77, H 4.15, N 10.83 %.

**5-(4-Methoxyphenyl)-1,3-dimethyl-1,6,7,8-tetrahydro-2*H*-cyclopenta[5,6]pyrido[2,3-d]pyrimidine-2,4(3*H*)-dione** (**5d**): IR (KBr): 2979, 1704 $cm^{-1}$; $^1$H NMR : δ 2.21 (m, 2H, $CH_2$), 2.39-2.59 (m, 4H, $CH_2$), 3.28 (s, 6H, N-$CH_3$), 3.59 (s, 3H, O-$CH_3$), 6.22-6.90 (m, 4H, Ar-H) ppm; $^{13}$C NMR : δ 21.28, 30.09, 31.34, 35.79, 52.14, 119.21, 120.88, 126.15, 128.28, 129.41, 129.86, 130.21, 132.95, 135.31, 138.79, 148.38, 162.58, 169.84 ppm; Anal. calcd. for $C_{19}H_{19}N_3O_3$ :C 67.64; H 5.68; N 12.46 %. Found: C 67.84, H 5.65, N 12.51 %.

**5-(4-Methylphenyl)-1,3-dimethyl-1,6,7,8-tetrahydro-2*H*-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidine-2,4(3*H*)-dione** (**5e**): IR (KBr): 2978, 1704 $cm^{-1}$;$^1$H NMR: δ 2.23 (m, 2H, $CH_2$), 2.32-2.61(m, 4H, $CH_2$), 2.68 (s, 3H, $CH_3$), 3.25 (s, 6H, N-$CH_3$), 6.37-6.85 (m, 4H, Ar-H) ppm; $^{13}$C NMR : δ 21.24, 22.55, 30.14, 31.46, 35.72, 119.31, 120.85, 126.21, 128.32, 129.48, 129.79, 130.31, 132.85, 135.21, 138.69, 148.48, 162.68, 169.84 ppm; Anal. calcd. for $C_{19}H_{19}N_3O_2$:C 71.01; H 5.96; N 13.08 %. Found: C 71.21, H 5.93, N 13.03 %.

**5-(4-Nitrophenyl)-1,3-dimethyl-1,6,7,8-tetrahydro-2*H*-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidine-2,4(3*H*)-dione** (**5f**): IR (KBr): 2978, 1704 $cm^{-1}$; $^1$H NMR: δ 2.27 (m, 2H, $CH_2$), 2.47-2.59 (m, 4H, $CH_2$), 3.22 (s, 6H, N-$CH_3$), 6.43-6.98 (m, 4H, Ar-H) ppm; $^{13}$C NMR: δ 22.19, 30.41, 31.62, 35.56, 119.12, 120.36, 126.21, 128.56, 129.84, 129.94, 130.63, 132.87, 135.24, 138.14, 148.32, 162.78, 169.83 ppm; Anal. calcd. for $C_{18}H_{16}N_4O_4$:C 61.36; H 4.58; N 15.90 %. Found: C 61.56, H 4.55, N 15.95 %.

## 5. RESULTS AND DISCUSSION

Sodium Dodecyl SulphateFe(DS)$_3$has been prepared by literature method[xviii]. In order to optimization of reaction conditions and to find out the best catalyst and solvent, we have carried out long screening experiments using various catalyst and solvents under sonication.

Sonochemistry means the use of ultrasonic irradiation in chemical synthesis is a safe and green chemical nontraditional approach and recently attracted the attention of scientist [xix]. In comparison to traditional approach it offers many advantages such as easy operation, convenient and easily controlled and handled. Chemical reaction under sonication completed in shorter time with high yield under mild reaction conditions. The acceleration of reaction rate under sonication can be explained by the phenomenon of acoustic cavitation and due to this a very high temperature and pressure generated instantly in reaction mixture which leads the formation of product with instance reaction rate [xx-xxi].

For present investigation 1, 3-dimethyl-6-amino-uracil **1**, cyclohexanone **2a** and4-methoxy benzaldehyde **3** have been chosen as a model reaction. Initially, the model reaction has been carried out under ultrasonic irradiation without using any catalyst in aqueous medium, but present reaction was failed to occur even after 60 min. irradiation (table-1, entry-1). Then reaction was carried out in aqueous medium using various catalysts such as *p*-TSA, boric acid, $ZnCl_2$, $MgCl_2$, sulfamic acid, $FeCl_3$ and surfactant SDS (table-1, entry-2-8). The results obtained from the (table-1), we find that the Lewis acid catalyst worked efficiently than Bronsted catalysts and out of other Lewis acids catalyst the $FeCl_3$ was found good but not best. The yield of product is also moderate using sodium docecyl sulfate (SDS) as surfactant. Further, to improve the yield of product **4a** under eco-friendly conditions using water as solvent, we have carried out the present reaction using Fe(DS)$_3$ as LASC catalyst under sonication. The results obtained using Fe(DS)$_3$ are very encouraging and excellent yield of product was obtained in shorter reaction time (entry-9). It is relevant to state that the addition of Fe(DS)$_3$ changed the initially floating reaction mass into a homogeneous mixture, which on during sonication becomes turbid emulsion.

**Table -1:** Optimization of reaction conditions under sonication for the synthesis of 5-(4-methoxy-phenyl)-1,3-dimethyl-6,7,8,9-tetrahydro-1H-pyrimido[4,5-b]quinoline-2,4-(1H,3H)-dione **4a**[a].

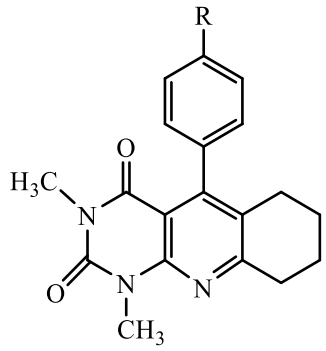
| S.No | Catalyst (mol %) | Solvent | Time (Min) | Yield (%)* |
|---|---|---|---|---|
| 1 | No catalyst | $H_2O$ | 60 min | 00 |
| 2 | *p*-TSA (10 mol %) | $H_2O$ | 40 min | 48 |
| 3 | Boric acid (10 mol %) | $H_2O$ | 40 min | 35 |
| 4 | Sulphamic acid (10 mol %) | $H_2O$ | 40 min | 40 |
| 5 | SDA (10 mol %) | $H_2O$ | 40 min | 55 |
| 6 | $MgCl_2$ (10 mol %) | $H_2O$ | 40 min | 48 |
| 7 | $ZnCl_2$ (10 mol %) | $H_2O$ | 40 min | 50 |
| 8 | $FeCl_3$ (10 mol %) | $H_2O$ | 40 min | 66 |
| 9 | Fe(DS)$_3$(10 mol %) | $H_2O$ | 20 min | 90 |
| 10 | Fe(DS)$_3$ (10 mol %) | 1,4-dioxane | 20 min | 70 |
| 11 | Fe(DS)$_3$ (10 mol %) | Acetonitrile | 20 min | 72 |
| 12 | Fe(DS)$_3$ (10 mol %) | $CH_2Cl_2$ | 20 min | 75 |
| 13 | Fe(DS)$_3$ (5 mol %) | $H_2O$ | 20 min | 70 |
| 14 | Fe(DS)$_3$ (15 mol %) | $H_2O$ | 20 min | 90(89,87,86,85)[b] |

[a]3-dimethyl-6-amino-uracil**1**(1mmol), cyclohexanone **2a**(1mmol), and4-methoxy benzaldehyde **3** (1mmol).
[b] Yields of the consequent runs.

After that, to check the effect of solvent the model reaction was also performed in various organic solvents such as 1,4-dioxane, $CH_3CN$ and $CHCl_2$ (table-1, entries 10-12) under sonication in presence of $Fe(DS)_3$ as catalyst. The results showed that using water as solvent best results were found as compared to other tested solvents which make this strategy further greener and suitable. The role of solvents under sonication is playing an important role as $I_{max}$ (maximum cavitation intensity) and $T_{Imax}$(the temperature at $I_{max}$ is reached) of any solvent have a profound effect on sonochemical reactivity for water $I_{max}$ is 100), the $I_{max}$ of water is responsible for the increase in the reaction rate as compared to the other solvents for which $I_{max}$ is lower [xxii-xxiii]. The effect of $Fe(DS)_3$ amount was also checked by changing the loading amount to 5%, 10%, and 15%, it was observed that 10 mol % of $Fe(DS)_3$ provided the upper limit yield (table-1, entry13-14). Furthermore, after the completion of the reaction, the catalyst was easily recovered and reused. Recovered $Fe(DS)_3$ used for several times for the model reaction under optimize reaction conditions and it was observed that the catalytic activity of $Fe(DS)_3$ was not lost even after five runs there is no notable change observed in yield (table-1, entry14).

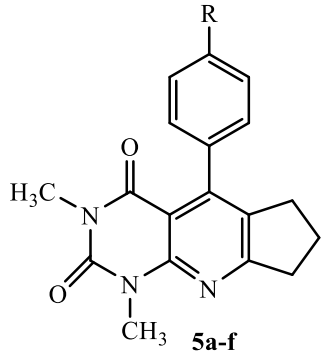
After optimization of reaction conditions and to estimate the scope and generality of the protocol the reaction has been carried out with diverse type of substituted aldehydes for synthesis of various pyrimido[4,5-*b*]quinoline (**4a-f**). The results are presented in table-3. Further, to extend our work we have also used cyclopentanone**2b** as cyclic ketone in place of cyclohexanone to obtained pyrido[2,3-*d*]pyrimidine derivatives **5a-f** (Table-4).

**Table-3:** Preparation of pyrimido[4,5-*b*]quinolines**4a-f** hybrids under optimized conditions

|  **4a-f** | **Products** | **R** | **Yield*** **(%)** | **Mp (°C)** |
|---|---|---|---|---|
| | **4a** | 4-$OCH_3$ | 90 | 350-352 |
| | **4b** | 4-Cl | 89 | 310-312 |
| | **4c** | 4-Br | 89 | 290-292 |
| | **4d** | 4-$NO_2$ | 89 | 270-272 |
| | **4e** | 4-$CH_3$ | 88 | 276-278 |
| | **4f** | 4-F | 90 | 340-342 |

*Isolated yields. All products formed in 18-20 min. irradiations under sonocator.

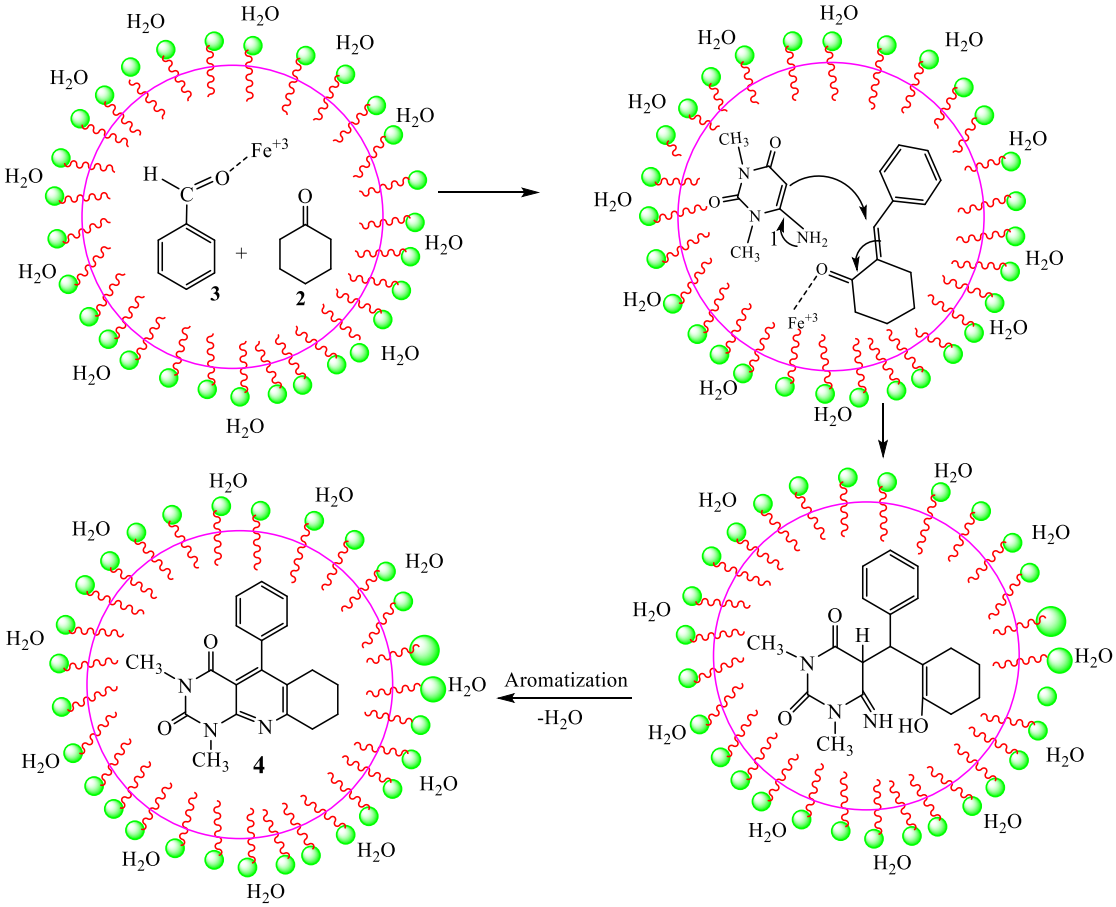
**Table-4:** Preparation of pyrido[2,3-*d*]pyrimidines (**5a-f**) hybrids under optimized conditions

|  **5a-f** | **Products** | **R** | **Yield* (%)** | **Mp (°C)** |
|---|---|---|---|---|
| | **5a** | 4-$OCH_3$ | 85 | 259-261°C |
| | **5b** | 4-Cl | 87 | 262-264 |
| | **5c** | 4-Br | 88 | 252-254 |
| | **5d** | 4-$NO_2$ | 87 | 228-230 |
| | **5e** | 4-$CH_3$ | 88 | 248-250 |
| | **5f** | 4-F | 90 | 333-335 |

*Isolated yields. All products formed in 18-20 min. irradiations under sonicator.

**Plausible mechanism**

The proposed mechanism for synthesis of pyrimido[4,5-*b*]quinolines**4a-f**andpyrido[2,3-*d*]pyrimidines **5a-f** have been presented in scheme-2. The organic part of surfactant in $Fe(DS)_3$ form micelles in aqueous medium with hydrophilic side outside and hydrophobic side inner side. The organic substrate 6-amino-1,3-dimethyluracil **1**, cyclic ketones **2** and aldehyde **3** are forced into the hydrophobic core and hydrophobic force compressed the reactants together in a tiny space. During the reaction $Fe^{+3}$ ions coordinate with carbonyl carbon and entered in hydrophobic core and act as Lewis acid catalyst to catalyze the reaction. Entry-9 in table-1 clearly justified that presence and catalytic behavior of $Fe^{+3}$ ions. The Lewis acidity of $Fe^{+3}$ is not found sufficient to catalyze the present reaction due to water labile character of $FeCl_3$ (table-1, entry-8). The mechanism of the reaction involves, Knoevenagel condensation, Michael addition, and then intra molecular cyclization catalyzed by $Fe^{3+}$ ions (Scheme 2).




**Scheme 2:** Plausible mechanism for synthesis ofpyrimido[4,5-*b*]quinolines (**4a-f**).

## 6. CONCLUSIONS

In conclusion, we have developed a novel, efficient and eco-friendly synthetic strategy for the synthesis of biologically potent fused systems pyrimido[4-5-*b*]quinolines and pyrido[2,3-*d*]pyrimidines from three component reaction of 6-amino-1,3-dimethyluracil, substitutedbenzaldehydes and cyclic ketones using Lewis acid-surfactant-combined catalyst ($Fe(DS)_3$ in aqueous medium under sonicationin shorter reaction timewithhigh yields. Use of wateras a reaction medium and sonication rendered this procedure cost-effective and environmentally benign.

7. **ACKNOWLEDGEMENTS**

Dr. Shakuntla Mishra National Rehabilitation University, Lucknow, and Jaipur National University, Jaipur are thankful to for providing experimental and financial support. We are also thankful to MNIT, Jaipur for the data collections.

8. **REFERENCES**

i Heravi M. M.; Zadsirjan V.; Prescribed drugs containing nitrogen heterocycles: an overview; RSC Adv.; 2020, 10, 44247- 44311.

ii Kumar S.; Narasimhan B.; Therapeutic potential of heterocyclic pyrimidine scaffolds; Chemistry Central Journal.; 2018, **12**(1), 1-29.

iii Heidelberger C., in Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicine, ed. J. F. Holland, E. Frei; Lea and Febiger, Philadelphia; 1984, 801–824.

iv Baba M.; Tanaka H.; De Clercq E.; Pauwels R.; Balzarini J.; Schols D.; Nakashima H.; Perno C. F.; Walker R. T.; Miyasaka T.; Highly specific inhibition of human immunodeficiency virus type 1 by a novel 6-substituted acyclouridine derivative; Biochem. Biophys. Res. Commutt.; 1989, **165**, 1375-1381.

v El-Gazzar A. R. B.; Hafez, H. N.; Synthesis of 4-substituted pyrido [2, 3-d] pyrimidin-4 (1H)-one as analgesic and anti-inflammatory agents; Bioorg. Med. Chem. Lett.; 2009, **19**(13), 3392-3397.

vi Satasia S. P.; Kalaria P. N.; Raval D. K.; Catalytic regioselective synthesis of pyrazole based pyrido [2, 3-d] pyrimidine-diones and their biological evaluation; Org. Biomol. Chem.; 2014, **12**(11), 1751-1758.

vii Hayallah A. M.; Abdel-Hamid, M. K.; Design and synthesis of new pyrido [2, 3-d] pyrimidine-1,4-dione derivatives as anti-inflammatory agents; Der. Pharm. Chem., 2014, **6**, 45-57.

viii Gangjee A.; Namjoshi O. A.; Raghavan S.; Queener S. F.; Kisliuk R. L.; Cody V.; Design, synthesis, and molecular modeling of novel pyrido [2, 3-d] pyrimidine analogues as antifolates; application of Buchwald–Hartwig aminations of heterocycles.; J. Med. Chem.; 2013, **56**(11), 4422-4441.

ix Farghaly, T. A.; Hassaneen, H. M.; Synthesis of pyrido [2, 3-d][1, 2, 4] triazolo [4, 3-a] pyrimidin-5-ones as potential antimicrobial agents; Arch. Pharm. Res.; 2013, **36**, 564-572.

x Gineinah M. M.; Nasr, M. N.; Badr S. M., El-Husseiny W. M.; Synthesis and antitumor activity of new pyrido [2, 3-d] pyrimidine derivatives; Med. Chem. Res.; 2013, **22**, 3943-3952

xi Pastor A.; Alajarin R.; Vaquero J. J.; Alvarez-Builla, J.; de Casa-Juana M.F.; Sunkel C.; Priego J. G.; Fonseca I.; Sanz-Aparicio J.;. Synthesis and structure of new pyrido [2, 3-d] pyrimidine derivatives with calcium channel antagonist activity; Tetrahedron, 1994, **50**(27), 8085-8098.

xii Thompson A. M.; Bridges A. J.; Fry D. W.; Kraker A. J.; Denny W. A.; Tyrosine kinase inhibitors. 7. 7-Amino-4-(phenylamino)-and 7-amino-4-[(phenylmethyl) amino] pyrido [4,3-d] pyrimidines: a new class of inhibitors of the tyrosine kinase activity of the epidermal growth factor receptor; J. Med. Chem.; 1995, **38**(19), 3780-3788.

xiii Kots A.Y.; Choi B. K.; Estrella-Jimenez M. E.;Warren C.A.; Gilbertson S. R.; Guerrant, R. L.; Murad F.; Pyridopyrimidine derivatives as inhibitors of cyclic

nucleotide synthesis: Application for treatment of diarrhea; PNAS; 2008, **105**(24), 8440-8445.

xiv Ziarani G. M.; Nasab N.H.; Lashgari N.; Synthesis of heterocyclic scaffolds through 6-aminouracil-involved multicomponent reactions; RSC Advances; 2016, **6**(45), 38827-38848.

xv Bhardwaj D.; Dhawan K.; Singh R.; On water greener synthesis of pyrido [2, 3-d] pyrimidines using Ag-$TiO_2$ nanocomposite catalyst under sonication; J. Iran. Chem. Soc.; 2022, **19**(3), 1003-1013.

xvi Singh R.; Singh, A.; Bhardwaj D.; Selective and Solvent-Free Synthesis of Isoxazole-Containing Spiro-Thiazolidinones Using $TiO_2$-$SO_3H$ as Solid Catalyst; Chemistry Select; 2019, **4**(33), 9600-9607.

xvii Singh R.; Saini M. R.; Bhardwaj D.; Singh, A.; An expedient synthesis of new imino-thiazolidinone grafted dispiro-pyrrolidine-oxindole/indeno hybrids via a multicomponent [3+2] cycloaddition reaction in a deep eutectic solvent; New J. Chem.; 2020, **44**(19), 7923-7931.

xviii Pradhan K.; Paul S.; Das A. R.; Fe $(DS)_3$, an efficient Lewis acid-surfactant-combined catalyst (LASC) for the one pot synthesis of chromeno [4, 3-b] chromene derivatives by assembling the basic building blocks; Tetrahedron Lett.; 2013, **54**(24), 3105-3110.

xix Mason T. J.; Ultrasound in synthetic organic chemistry; Chem. Soc. Rev.; 1997, **26**(6), 443-451.

xx Banerjee, B.; Recent developments on ultrasound assisted catalyst-free organic synthesis. Ultrason. Sonochem.; 2017, **35**, 1-14.

xxi Fonseca S. F.; Padilha N. B.; Thuro, S.; Roehr, J. A.; Savegnag, L.; de Souza M.N.; Fronza M. G.; Collare, T.; Bus, J.; Seixas F. K.; Alves, D.; Ultrasound-promoted copper-catalyzed synthesis of bis-arylselanyl chrysin derivatives with boosted antioxidant and anticancer activities. Ultrason. Sonochem.; 2017, **39**, 827-836.

xxii Mason, T. J.; Theory. Applications and uses of ultrasound in chemistry. Sonochemistry. 1988.

xxiii Mason, T. J.; Sonochemistry and sonoprocessing: the link, the trends and (probably) the future; Ultrason. Sonochem. 2003; 10(4-5), 175-179.

Received on August 24, 2023.