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Mannich Synthesis Under Ionic Liquid $[Et_3NH][HSO_4]$ Catalysis

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Abstract *: Ionic liquid $[Et_3NH][HSO_4]$ was found to be a particularly efficient catalyst for the synthesis of β-amino carbonyl pyrimidines through the Mannich condensation reaction of substituted pyrimidin-2(1H)-ones, cyclohexanone and 4-fluro/chlorobenzaldehyde under ultrasonic irradiation at room temperature. The present methodology offers several advantages such as excellent yields, simple procedure and mild conditions.*
Keywords*: Pyrimidine, Ionic Liquid, Mannich Reaction, Ultrasound, Green chemistry*

I. Introduction

A pyrimidine heterocycle is present in numerous natural products as well as synthetic pharmacophores with biological activities[1].Substituted pyrimidines, particularly with amino-groups at 2 and 4 positions, are known pharmacophores for several structure-based drug design approaches in medicinal chemistry[2] . Mannich reaction is one of the most important C-C bond forming reactions in organic synthesis for the preparation of secondary and tertiary amine derivatives[3] . Various drugs derived from Mannich bases have proved to be more effective and less toxic than their parent compounds. Mannich bases also find utility in polymers and dispersants in lubricating oil[4].

Conventional catalysts for the classical Mannich reaction[5] of aldehydes, ketone and amines involve mainly Lewis acids[6],Bronsted acids [7] and Lewis bases[8]. A variety of other catalysts, like $Zn(OTf)_2$[9], $ZrOCl_2.8H_2O$[10], DBS[11], SDS–HCl[12], $Bi(OTf)_3.4H_2O$[13], ionic liquids[14] and recently $NbCl_5$[15] have also been found to catalyze this reaction.

Some of these methods suffer from certain drawbacks such as hazardous organic solvents, high cost, long reaction time, low selectivity, and excessive amounts of base. Therefore, the development of facile and environmentally benign methods for the synthesis of Mannich reaction is necessary.

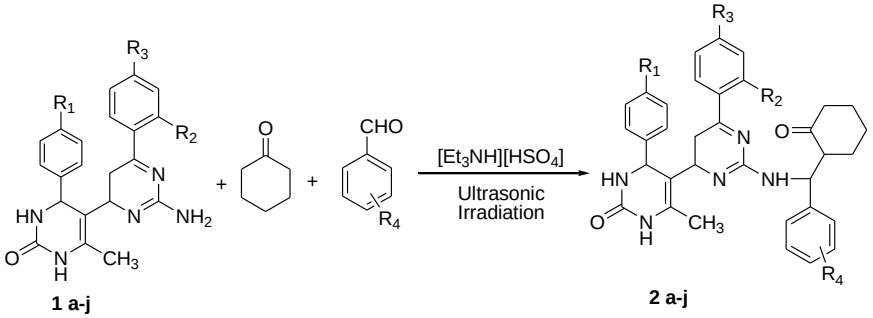
Ultrasound irradiation has increasingly been used in organic synthesis in the past three decades. Compared with traditional methods, this method is more convenient and easily controlled. A large number of organic reactions have been carried out in higher yields, shorter reaction times, and milder conditions under ultrasound irradiation[16].

When liquids are irradiated with high-intensity ultrasound irradiation, acoustic cavitations (the formation, growth, and implosive collapse of the bubbles) provide the primary mechanism for sonochemical effects. During cavitation, bubble collapse produces intense local heating, high pressures and extremely rapid cooling rates[17].

We present herein, an evaluation of the use of IL and ultrasound, in this protocol under room temperature without any added catalyst, to accelerate the reaction. The choice of ionic liquids(Triethylamine sulfate $[Et_3NH][HSO_4]$) was dictated by it being the most widely used, and therefore the most widely available. The presented protocol is simple and high-yielding; it also reduces environmental pollution.

II. Results and Discussion

Scheme 1



1 a-j **2 a-j**

2.1. Effect of IL concentration:

Initially, efforts were made towards catalytic evaluation of [Et_3NH][HSO_4] ionic liquid towards the synthesis of Mannich bases **2a-j**. In an initial endeavor, a reaction was carried out conventionally using 1 equivalent each of 5-(2-amino-4, 5-dihydro-6- phenylpyrimidin-4-yl)-3, 4-dihydro- 6-methyl-4-phenylpyrimidin-2(1H)-one (**1a**), cyclohexanone and 4-flurobenzaldehyde under reflux in methanol for 6-8 hours. This synthetic approach resulted in formation of **2a** with 40% yield. Additional reflux time and lower yields prompted us to explore better options. The same reaction when carried out under the catalysis of ILs, was completed in two hours resulting in formation of **2a** in 70% yield

To further improve the yield and to optimize the reaction conditions, the same reaction was carried out with different proportions of [Et_3NH][HSO_4] ionic liquid. An increase in the quantity of ILs from 0.25mol% to 1mol% increased the turbidity of the reaction mixture. The yield of compound **2a**, when 0.25%, 0.5%, 0.75% and 1% were used to catalyze the reaction of Mannich base synthesis, were revealed to be 70%, 83%, 72%, and 75% respectively.

2.2. Effect of ultrasonic irradiation time and ultrasonic frequency:

We initiated catalytic evaluation of [Et_3NH][HSO_4] ionic liquid 0.5mol%, ILs towards the synthesis of Mannich bases **2a-j** under ultrasound irradiation at 50 kHz for 55 min at room temp: compound **2a** was formed in83% yield. This dramatic conversion and outstanding output prompted us to establish the reaction conditions at 50 kHz for 55 min under ultrasound irradiation. Further, to study the scope and limit of the reaction, the reaction time was minimized till maximum yield of respective product could be achieved.

The Mannich reaction was performed at 20, 50, 80 and 100 kHz. The yields for the reactions at 20, 50, 80 and 100 kHz were 60%, 83%, 71% and 59% respectively. Surprisingly, higher efficiency of the reaction was observed at 50 kHz with 83% output. Boost in yields were observed at 50 kHz, further increase in frequency up to 100 kHz diminished the efficiency of the reaction with minimal output (Table 1). In addition, identical results were obtained when the reaction was carried out for long hours.

Table 1: Yield of compound **2a–j** under ultrasound irradiation for 55-75min

Entry	Compound	Yield[a,b]			
		20 kHz	50 kHz	80 kHz	100 kHz
1	**2a**	60	83	71	59
2	**2b**	69	83	61	59
3	**2c**	61	85	52	50
4	**2d**	60	88	65	50
5	**2e**	58	90	75	40
6	**2f**	40	90	76	71
7	**2g**	55	78	65	60
8	**2h**	52	75	64	59
9	**2i**	60	88	76	62
10	**2j**	62	89	69	57

[a] Isolated yield.

[b] Reaction conditions:, (0.005 mol) 5-(2-amino-4, 5-dihydro-6- phenylpyrimidin-4-yl)-3, 4- dihydro- 6-methyl-4-phenylpyrimidin-2(1H)-one (**1a**), (0.005 mol) cyclohexanone and (0.005 mol) 4-flurobenzaldehyde,[Et_3NH][HSO_4] ionic liquid 0.5mol% at ultrasonic frequencies of 20–100 kHz, the ultrasonic power was kept at 100 W for 55-75 min, at room temp.

Our observations on ultrasound irradiation inducing a remarkable acceleration in reactions and also decreasing the reaction times prompted us to further optimize experimental conditions at ambient temperature. A synthesis of **2a** was used as a standard reaction; a mixture of all required reactants was sonicated at 50 kHz to obtain maximum product conversion. The reaction time and yield of **2a** did not change from further changes in irradiation power; therefore, 100 W of ultrasonic irradiation was sufficient to effect optimal conversions. Various changes suggested that the best yield for **2a** could also be achieved by ultrasonic irradiation i.e. 50 kHz for 55 min at room temperature and 100 W. More significantly, the isolation of products was simplified: pure **2a** was obtained directly, requiring no column chromatography.

The reaction conditions were set at optimal concentration of [Et_3NH][HSO_4] ionic liquid: Dosage/0.5% mole, temperature: room temp and time: 55 ± 25 minutes with frequency: 50 kHz (Table 2).

Table 2: Catalytic activity evaluation for Mannich reaction with respect to time at 50 kHz

S.N	Entry	Time (minutes)	Isolated Yield (%)
1.	**2a**	55	83
2.	**2b**	59	83
3.	**2c**	61	85
4.	**2d**	56	88
5.	**2e**	69	90
6.	**2f**	75	90
7.	**2g**	65	78
8.	**2h**	59	75
9.	**2i**	71	88
10.	**2j**	70	89

The purity of the compounds was monitored by TLC and the structures of all the derivatives **2a-j** were supported by spectral data. The IR, ^{1}HNMR, ^{13}CNMR, Mass spectra and elemental analytical data are in agreement with the proposed structures. Physical and analytical data of the synthesized compounds are reported in Table 3.

Table3: Synthesis of substituted 5-(2-((phenyl)(2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2a-j**) promoted by ultrasound irradiation at 50kHz

Entry	Compd.	R_1	R_2	R_3	R_4	Yield[a/b](%)	m.p. (^{O}C)	Mol. Formula
1	**2a**	H	H	H	4F	40/83	123	$C_{34}H_{34}N_5O_2F$
2	**2b**	H	H	OCH_3	2Cl	39/83	117	$C_{35}H_{36}N_5O_3Cl$
3	**2c**	H	H	Cl	2Cl	45/85	127	$C_{34}H_{33}N_5O_2Cl_2$
4	**2d**	OCH_3	H	H	4F	35/88	161	$C_{35}H_{36}N_5O_3F$
5	**2e**	OCH_3	H	OCH_3	4F	52/90	118	$C_{36}H_{38}N_5O_4F$
6	**2f**	OCH_3	H	Cl	4F	49/90	140	$C_{35}H_{35}N_5O_3ClF$
7	**2g**	OH	H	OCH_3	4F	41/78	138	$C_{35}H_{36}N_5O_4F$
8	**2h**	OH	Cl	H	4F	37/75	145	$C_{34}H_{33}N_5O_3ClF$
9	**2i**	Cl	H	OCH_3	4F	43/88	112	$C_{35}H_{35}N_5O_3ClF$
10	**2j**	Cl	Cl	H	4F	42/89	107	$C_{34}H_{32}N_5O_2Cl_2F$

[a] : Isolated yield by conventional method.
[b]: Isolated yield by catalysis of [Et_3NH][HSO_4] ionic liquid under ultrasound irradiation.

2.3. Compound Characterization:

The IR spectra of compounds 2a-j showed a peak at 3098-3150 cm^{-1} due to –NH function. A sharp band was observed at 1680-1720 cm^{-1} corresponding to the carbonyl (-C=O) function derived from cyclohexanone structure.

A molecule with two chiral centers will have 4 stereomers comprising of diastereomeric and enantiomeric pairs. The four stereomers have the following configurations at the carbogenic center: RR, SS and RS, SR. Conventional organic synthesis without chiral catalysts always results in racemic mixtures. For a non-diastereoselective reaction the pairs of racemates ie [RR + SS] and [RS + SR] can be separated by column. Enantiomers cannot be differentiated by NMR whereas the diastereomers show variations in coupling constants sufficient to permit differentiation. In a racemate of enantiomers the protons on the adjoining chiral centres will have a cis- relationship while in the diastereomer racemate the adjoining protons should have a trans-relationship. The cis coupling constant is generally smaller than that of the trans coupling constant.

In our study the ^{1}HNMR spectrum of 2a showed characteristic doublet at δ 2.73-2.76 with J =10.88 Hz for the vicinal proton C28 coupled with the C35 proton of cyclohexanone at cis position. There was no evidence of a vicinal proton at trans position suggesting a possible preponderance of one set of enantiomers over the diastereomers in the racemic isolates.

The ^{1}H NMR spectra of compounds 2a-j displayed an additional signal at 3.00-3.75 ppm due to the –NH linkage derived from aminopyrimidine moiety with aldehyde and cyclohexanone, while the signal due the –NH_2 group of aminopyrimidine structure did not appear. The singlet for –OCH_3 observed at 3.86-3.96 ppm integrated for three protons in ^{1}H NMR spectra of compounds 2b, 2d-f, 2g and2i. The ^{1}H NMR spectra of compounds 2g and 2h revealed singlets at 10.39 ppm and 10.40 ppm integrating for a single proton of –OH group respectively. The signal at aliphatic region integrating for 9 protons indicated the presence of a

cyclohexanone ring attached to an –NH group of aminopyrimidine appended with an aldehyde moiety. All compounds supported these stereo-chemical evidences.

The ^{13}C NMR of compound 2ashowed the peak at δ 15.1, 23.7, 24.2, 24.8, 35.4, 36.5, 40.6, 50.2, 56, 58.6, 114.6, 124.5, 127.1, 128.2, 129.4, 129.8, 130.9, 134.3, 136.7, 143.6, 150.7, 160.3, 163.6, 164.3, 210.6 ppm. The compounds 2a-j revealed peaks at 210.5-212.1 suggesting the presence of -C=O of cyclohexanone ring. The mass of 2a m/z = 563 (M^+) confirmed the structure. The compounds 2a-j gave satisfactory elemental analysis. The physicochemical data is depicted in Table 3**.**

III. Experimental

3.1 General

Melting points were determined by open capillary method and are uncorrected. All solvents were distilled and dried prior to use. TLC was performed on silica gel G. ^{1}HNMR and ^{13}CNMR spectra were recorded in DMSO-d_6/$CDCl_3$ solutions on a Brucker AC 400 (MHz) instrument and ^{13}CNMR spectra were recorded in $CDCl_3$on Varian mercury 300 instrument. Chemical shifts are reported in ppm using TMS as internal standard. IR spectra were obtained on a Perkin Elmer 1800 spectrophotometer using KBr discs and Mass spectra were measured with Shimadzu gas chromatograph. Elemental analyses were performed on a Perkin Elmer 2400 instrument. The reactions were carried out with a high-intensity ultrasonic probe (Misonix, XL sonifier, 1.13-cm-diameter Ti horn, 20–100 kHz, 100 W/cm^2).

3.2 General procedure for the preparation of Mannich reactions 2a-j.

General procedure for the preparation of 5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (2a)

Conventional Method:

To a well stirred solution of (0.005 mol) 5-(2-amino-4, 5-dihydro-6- phenylpyrimidin-4-yl)-3, 4-dihydro- 6-methyl-4-phenylpyrimidin-2(1H)-one (1a), (0.005 mol) cyclohexanone and (0.005 mol) 4-flurobenzaldehyde in methanol (10ml), HCl was added so that the pH of the reaction was maintained at 5-6. The reaction mixture was allowed to stir for a brief while, followed by 6-8 hrs reflux. At the end of the reaction, the mixture was treated with ice cold water. The products of 5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (2a) was separated by filtration and purified by recrystallization from ethanol.

Non-Conventional Method:

Ionic Liquid: To a well stirred mixture of (0.005 mol) 5-(2-amino-4, 5-dihydro-6- phenylpyrimidin-4-yl)-3, 4- dihydro- 6-methyl-4-phenylpyrimidin-2(1H)-one **(1a)**, (0.005 mol) cyclohexanone and (0.005 mol) 4-flurobenzaldehyde, the quaternary ammonium ionic liquids (Triethylamine sulfate [Et_3NH][HSO_4]) (1%). The reaction mixture was allowed to stir for some time and refluxed for 2-3 hr. The progress of reaction was monitored by TLC. At the end of the reaction, the mixture was treated with ice cold water. The products of 5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one **(2a)** was separated by filtration and purified by recrystallization from ethanol.

Ultrasound Irradiation

The quaternary ammonium ionic liquids (Triethylamine sulfate [Et_3NH][HSO_4]) (0.5%) was added drop wise at room temperature to a well stirred solution of (0.005 mol) 5-(2-amino-4, 5-dihydro-6-phenylpyrimidin-4-yl)-3, 4- dihydro- 6-methyl-4-phenylpyrimidin-2(1H)-one (**1a**), (0.005 mol) cyclohexanone and (0.005 mol) 4-flurobenzaldehyde; The reaction mixture was allowed to stir for some time, followed by continuous irradiation by ultrasound wave (50kHz) at room temperature for few minutes. The progress of reaction was monitored by TLC. At the end of the reaction, the mixture was treated with ice cold water. The products of 5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**2a**) was separated by filtration and purified by recrystallization from ethanol, yield 83%.; similarly the series of compounds has been synthesized.

5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-6 methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one **(2a)**

Yield: 83%; m.p.: 123^{o}C; IR (KBr): 3250 (-NH), 1747 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ 1.24-1.87 (m, 9H, cyclohexanone), 2.03 (s, 3H, Ar-CH_3), 2.73-2.76 (d, 1H, *J* = 10.88Hz, -CH), 3.47 (s, 1H, -NH), 5.08 (s, 1H, -CH), 6.71 (s, 1H, Ar-CH), 6.82-6.85 (d, 2H, *J* = 12.96 Hz, Ar-CH_2), 6.88-7.06 (m, 12H, Ar-H), 7.10 (s, 2H, -NH), 7.21 (s, 2H, Ar-CH); ^{13}CNMR (75MHz, $CDCl_3$): δ 15.1, 23.7, 24.2, 24.8, 35.4, 36.5, 40.6, 50.2, 56, 58.6, 114.6, 124.5, 127.1, 128.2, 129.4, 129.8, 130.9, 134.3, 136.7, 143.6, 150.7, 160.3, 163.6, 164.3, 210.6; GC/MS: m/z 563 (M^+). Anal. Calcd. for $C_{34}H_{34}N_5O_2F$: C, 72.44; H, 6.08; N, 12.43. Found: C, 72.32; H, 5.93; N, 12.35 %.

5-(2-((2-chlorophenyl)(2-oxocyclohexyl)methylamino)-6-(4-methoxyphenyl)-4,5-dihydro pyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one **(2b)**
Yield: 83%; m.p.: 117°C; IR (KBr): 3245 (-NH), 1749 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ 1.25-1.79 (m, 9H, cylcohexanone), 2.12 (s, 3H, Ar-CH_3), 2.79-2.81 (d, 1H, *J* = 10.2 Hz, -CH), 3.52 (s, 1H,-NH), 3.92 (s, 3H, -OCH_3), 5.02 (s, 1H, -CH), 6.64 (s, 1H, Ar-CH), 6.65-6.67 (d, 2H, *J* = 8.44 Hz, Ar-CH_2), 6.87-7.33 (m, 15H, Ar-H, -NH,); ^{13}CNMR (75MHz, $CDCl_3$): δ 14.8, 24.2, 24.7, 25.1, 34.8, 36.6, 40.5, 41.1, 114.1, 115.3, 124.1, 126.2, 126.5, 128.4, 129.3, 129.8, 133.6, 140.3, 143.2, 150.5, 163.1, 164.7, 211.2; GC/MS: m/z 609 (M^+). Anal. Calcd. for $C_{35}H_{36}N_5O_3Cl$: C, 68.89; H, 5.94; N, 11.48. Found: C, 68.76; H, 5.81; N, 11.32 %.

5-(6-(4-chlorophenyl)-2-((2-chlorophenyl)(2-oxocyclohexyl)methylamino)-4,5-dihydro pyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one **(2c)**
Yield: 85%; m.p.: 127°C; IR (KBr): 3252 (-NH), 1744 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ 1.25-1.96 (m, 9H, cyclohexanone), 2.11 (s, 3H, Ar-CH_3), 2.62-2.64 (d, 1H,*J* = 9.80 Hz, -CH), 3.06 (s, 1H, -NH), 5.06 (s, 1H, -CH), 6.92-7.04 (m, 3H, Ar-CH_2, Ar-CH), 7.10-7.57 (m, 14H, Ar-H, -NH); ^{13}CNMR (75MHz, $CDCl_3$) δ 15.2, 24.3, 24.7, 25.3, 35.1, 36.7, 40.5, 41.3, 55.1, 58.1, 115.1, 124.2, 126.6, 127.3, 128.1, 128.3, 129.2, 130.1, 132, 133.6, 136.3, 140.3, 143.5, 150.4, 162.5, 164.5, 210.5; GC/MS: m/z 613 (M^+). Anal. Calcd. for $C_{34}H_{33}N_5O_2Cl_2$: C, 66.44; H, 5.42; N, 11.41. Found: C, 66.31; H, 5.34; N, 11.29 %.

5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(2d)**
Yield: 88%; m.p.: 161°C; IR (KBr): 3246 (-NH), 1748 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ δ 1.24-1.88 (m, 9H, cyclohexanone), 2.07 (s, 3H, Ar-CH_3), 2.79-2.82 (d, 1H, *J* = 10.12 Hz, -CH), 3.17(s, 1H, -NH), 3.89 (s, 3H, -OCH_3), 4.93 (s, 1H, -CH), 6.65-7.29 (m, 18H, Ar-CH, Ar-CH_2, -NH); ^{13}CNMR (75MHz, $CDCl_3$) : δ 14.6, 24.2, 24.6, 25.2, 35.6, 36.4, 41.2, 50.1, 55.1, 55.9, 58.1, 114.1, 114.7, 123.9, 127.9, 129.2, 129.6, 130.8, 134.3, 135.7, 135.4, 150.5, 158.6, 160.2, 163.1, 165.3, 110.9; GC/MS: m/z593 (M^+). Anal. Calcd. for $C_{35}H_{36}N_5O_3F$: C, 70.82; H, 6.10; N, 11.80. Found: C, 70.68; H, 6.01; N, 11.69 %.

5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-(4-methoxyphenyl)-4,5-dihydro pyrimidin-4-yl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(2e)**
Yield: 90%; m.p.: 118°C; IR(KBr): 3251 (-NH), 1749 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ δ 1.26-1.91 (m, 9H, cyclohexanone), 2.02 (s, 3H, Ar-CH_3), 2.78-2.80 (d, 1H, *J* = 10.00 Hz, -CH), 3.02 (s, 1H, -NH), 3.92 (s, 3H, -OCH_3), 3.96 (s, 3H, -OCH_3), 4.93 (s, 1H, -CH), 6.57 (s, 1H, Ar-CH), 6.66-7.52 (m, 16H, Ar-CH_2, Ar-H, -NH); ^{13}CNMR (75MHz, $CDCl_3$) : δ 14.8, 24.2, 24.5, 25.2, 35.2, 36.6, 41.3, 50.1, 55.1, 55.8, 58.2, 114.3, 115.4, 124.6, 126.4, 128.1, 130, 134.6, 136.1, 150.4, 158.4, 160.4, 163.3, 164.5, 210.8; GC/MS: m/z 623 (M^+). Anal. Calcd. for $C_{36}H_{38}N_5O_4F$: C, 69.32; H, 6.14; N, 11.23. Found: C, 69.19; H, 6.07; N, 11.12 %.

5-(6-(4-chlorophenyl)-2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-4,5-dihydro pyrimidin-4-yl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(2f)**
Yield: 90%; m.p.: 140°C; IR (KBr): 3245 (-NH), 1747 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ δ 1.18-1.60 (m, 9H, cyclohexanone), 2.08 (s, 3H, Ar-CH_3), 2.85-2.87 (d, 1H, *J* = 10.20 Hz, -CH), 3.75 (s, 1H, -NH), 3.80 (s, 3H, -OCH_3), 5.08 (s, 1H, -CH), 6.80-6.91 (m, 3H, Ar-CH, Ar-CH_2), 7.02-7.70 (m, 14H, Ar-H, -NH); ^{13}CNMR (75MHz, $CDCl_3$) : δ 15.4, 24.1, 24.8, 25.2, 35.1, 36.2, 41.5, 50.2, 54.8, 55.9, 57.9, 114.2, 115.2, 124.2, 128.1, 129.3, 129.7, 130.5, 131.8, 135.4, 136.3, 137.2, 150.3, 159.1, 160.6, 163.3, 164.4, 110.5; GC/MS: m/z 627 (M^+). Anal. Calcd. for $C_{35}H_{35}N_5O_3ClF$: C, 66.92; H, 5.62; N, 11.14. Found: C, 66.78; H, 5.46; N, 11.02 %.

5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-(4-methoxyphenyl)-4,5-dihydro pyrimidin-4-yl)-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(2g)**
Yield: 78%; m.p.: 138°C; IR (KBr): 3247 (-NH), 1755 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ 1.34-1.82 (m, 9H, cyclohexanone), 1.97 (s, 3H, Ar-CH_3), 2.54-2.56 (d, 1H, 10.02 Hz, -CH), 3.02 (s, 1H, -NH,), 3.89 (s, 3H, -OCH_3), 4.95 (s, 1H, -CH), 6.97 (s, 1H, Ar-CH), 7.06-7.56 (m, 17H, Ar-CH_2, Ar-H, -NH), 10.39 (s, 1H, -OH); ^{13}CNMR (75MHz, $CDCl_3$) : δ 14.3, 23.6, 24.4, 24.6, 34.6, 36.2, 41.7, 49.5, 54.4, 56.2, 57.4, 114.8, 115.6, 124.1, 126.6, 128.1, 128.4, 129.9, 131.9, 134.2, 136.4, 150.3, 156.1, 160.2, 163.3, 164.2, 212.1; GC/MS: m/z 609 (M^+). Anal. Calcd. for $C_{35}H_{36}N_5O_4F$: C, 68.92; H, 5.91; N, 11.48. Found: C, 68.88; H, 5.87; N, 11.56 %.

5-(6-(2-chlorophenyl)-2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-4,5-dihydro pyrimidin-4-yl)-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(2h)**
Yield: 75%; m.p.: 145°C; IR (KBr): 3250 (-NH), 1751 cm^{-1}(C=O); ^{1}HNMR (400MHz, $CDCl_3$): δ δ 1.32-1.81 (m, 9H, cyclohexanone), 1.95 (s, 3H, Ar-CH_3), 2.52-2.54 (d, 1H, *J* = 10.04Hz, -CH), 3.02 (s, 1H, -NH,), 4.94 (s, 1H, -CH), 6.98 (s, 1H, Ar-CH), 7.07-7.57 (m, 17H, Ar-CH_2, Ar-H, -NH), 10.40 (s, 1H, -OH); ^{13}CNMR (75MHz, $CDCl_3$) : δ 14.4, 23.5, 24.2, 24.6, 34.5, 36.2, 41.1, 49.3, 54.6, 57.8, 115.3, 124, 126.6, 128, 128.8, 129.7, 130.5, 132.2, 134.1, 135.7, 136.9, 150.4, 158.2, 160.1, 163.3, 164.4, 211.3; GC/MS: m/z 614 (M^+). Anal. Calcd. for $C_{34}H_{33}N_5O_3ClF$: C, 66.51; H, 5.42; N, 11.40. Found: C, 66.38; H, 5.47; N, 11.56 %.

4-(4-chlorophenyl)-5-(2-((4-fluorophenyl)(2-oxocyclohexyl)methylamino)-6-(4-methoxy phenyl)-4,5-dihydropyrimidin-4-yl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(2i)**
Yield: 88%; m.p.: 112°C; IR (KBr): 3247 (-NH), 1755 cm^{-1}(C=O); ^{1}HNMR (400MHz, DMSO-d_6): δ 1.09-1.78 (m, 9H, cyclohexanone), 2.12 (s, 3H, Ar-CH_3), 2.71-2.73 (d, 1H, *J* = 10.00 Hz, -CH), 3.39 (s, 1H, -NH), 3.86 (s,

3H, -OCH_3), 4.99 (s, 1H, -CH), 6.88-7.72 (m, 17H, Ar-CH_2, Ar-CH, Ar-H, -NH); ^{13}CNMR (75MHz, $CDCl_3$) : δ 14.9, 23.7, 24.2, 25.1, 34.3, 36.7, 41, 50.3, 54.6, 55.9, 58.1, 114.3, 115.2, 124.3, 127.4, 128.3, 129.5, 129.9, 132.1, 136.2, 137.7, 140.8, 150.7, 160.3, 163.2, 164.8, 210.7; GC/MS: m/z 627 (M^+). Anal. Calcd. for $C_{35}H_{35}N_5O_3ClF$: C, 66.96; H, 5.61; N, 11.13. Found: C, 66.85; H, 5.58; N, 11.17 %.

4-(4-chlorophenyl)-5-(6-(2-chlorophenyl)-2-((4-fluorophenyl)(2-oxocyclohexyl)methyl amino)-4,5 dihydropyrimidin-4-yl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one **(2j)**

Yield: 89%; m.p.: 107^{o}C; IR (KBr): 3249 (-NH), 1753 cm^{-1}(C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08-1.76 (m, 9H, cyclohexanone), 2.12 (s, 3H, Ar-CH_3), 2.71-2.73 (d, 1H, *J* = 9.96 Hz, -CH), 3.39 (s, 1H, -NH), 4.99 (s, 1H, -CH), 6.87-7.71 (m, 17H, Ar-CH_2, Ar-CH, Ar-H, -NH); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 14.8, 23.7, 24.3, 25.2, 34.2, 36.5, 41.1, 50.2, 54.6, 56.3, 114.5, 124.3, 127.1, 128.3, 129.1, 129.5, 130.8, 132.1, 134.3, 136.2, 137.3, 140.8, 150.7, 160.4, 163.1, 164.9, 210.8; GC/MS: m/z 631 (M^+). Anal. Calcd. for $C_{34}H_{32}N_5O_2Cl_2F$: C, 64.56; H, 5.11; N, 11.08. Found: C, 64.45; H, 4.98; N, 11.17 %.

IV. Conclusion

In summary, simple, convenient and efficient procedures for the syntheses of substituted 5-(2-((R)-(4-fluoro/chlorophenyl)((R)-2-oxocyclohexyl)methylamino)-6-phenyl-4,5-dihydropyrimidin-4-yl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-ones in the presence of catalytic amount of ionic liquid [Et_3NH][HSO_4] under ultrasonic irradiation at room temperature have been developed. The salient features of this protocol are improved yields, cleaner reactions, simple work-up and very short reaction times: the synthesis of Mannich reaction with promising bioactivity promises to be environmentally benign.

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