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Synthesis And Biological Evaluation of β – Amino Carbonyl Pyrimidines Under Ionic Liquid $[Et_3NH][HSO_4]$ Catalysis

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ABSTRACT

For searching newly synthesized β – Amino Carbonyl pyrimidines as new and efficient antimicrobial agents. They were tested for in vitro antibacterial (*E.coli, P. aeruginonasa, S. aureus)* and antifungal (*C. albicans)* activity against Standard drugs. Ionic liquid $[Et_3NH][HSO_4]$ was found to be a particularly efficient catalyst for the synthesis of β-amino carbonyl pyrimidin activies through the Mannich condensation reaction of substituted pyrimidin-2(1H)-ones, cyclohexanone and 4-fluro/chlorobenzaldehyde. The present methodology offers several advantages such as excellent yields, simple procedure and mild conditions. The structures of 2a-j were confirmed by IR, NMR, and Mass analysis. Antimicrobial activity was tested at different level of concentrations. Majority of newly synthesized compounds shows pronounced antibacterial and antifungal activity.

Keywords: Pyrimidine, Ionic Liquid, Mannich Reaction, Green chemistry, Antibacterial and Antifungal activity.

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

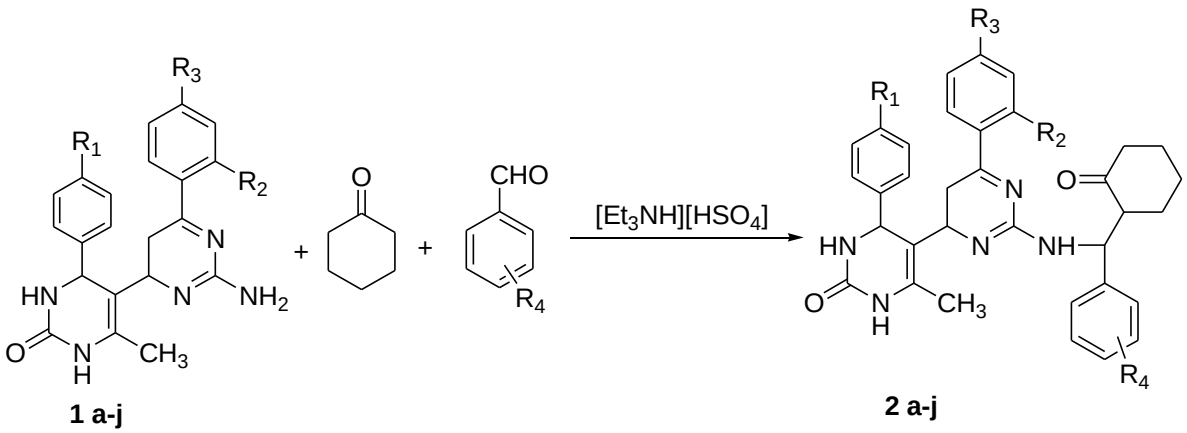
polymers and dispersants in lubricating oil [4]. Mannich bases exhibit a wide variety of interesting biological activities such as Nitric oxide inhibitor [5]**,** Antimicrobial activity [6]**,** Antimalarial Activity [7]**,** Anticancer agents [8]**,** Antitubercular [9]**,** etc.

Conventional catalysts for the classical Mannich reaction [10] of aldehydes, ketone and amines involve mainly Lewis acids [11]**,** Bronsted acids [12] and Lewis bases [13]. A variety of other catalysts, like $Zn(OTf)_2$[14], $ZrOCl2.8H_2O$[15], ionic liquids[16] and recently $NbCl_5$[17] have also been found to catalyze this reaction.

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

In continuation of our research on Ionic Liqiuds [18]. In the present study, an evaluation of the use of ionic liquids to accelerate the reaction by reducing time. 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. All newly synthesized compounds were tested for in vitro antibacterial and antifungal activity against Standard drugs.

RESULT AND DISCUSSION



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

Scheme 1

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 81% 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%, 81%, 72%, and 75% respectively.

Our observations by using IL inducing a remarkable acceleration in reactions and also decreasing the reaction times prompted us to further optimize experimental conditions at ambient temperature.

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 1.

Table 1: 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)

Entry	Compd.	R_1	R_2	R_3	R_4	Yield[a/b](%)	m.p. (^OC)	Mol. Formula
1	2a	H	H	H	4F	40/81	123	$C_{34}H_{34}N_5O_2F$
2	2b	H	H	OCH_3	2Cl	39/81	117	$C_{35}H_{36}N_5O_3Cl$
3	2c	H	H	Cl	2Cl	45/83	127	$C_{34}H_{33}N_5O_2Cl_2$
4	2d	OCH_3	H	H	4F	35/86	161	$C_{35}H_{36}N_5O_3F$
5	2e	OCH_3	H	OCH_3	4F	52/88	118	$C_{36}H_{38}N_5O_4F$
6	2f	OCH_3	H	Cl	4F	49/88	140	$C_{35}H_{35}N_5O_3ClF$
7	2g	OH	H	OCH_3	4F	41/76	138	$C_{35}H_{36}N_5O_4F$
8	2h	OH	Cl	H	4F	37/73	145	$C_{34}H_{33}N_5O_3ClF$
9	2i	Cl	H	OCH_3	4F	43/86	112	$C_{35}H_{35}N_5O_3ClF$
10	2j	Cl	Cl	H	4F	42/87	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..

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.

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 and 2i. 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 2a showed 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 1**.**

In vitro anti-bacterial and anti-fungal activity

All the newly synthesized compounds 2a-j were screened *in vitro* for their antibacterial and antifungal agents against Gram –ve bacteria [*E.coli* (ATCC 25922), *P. aeruginonasa* (ATCC 27853)], Gram +ve bacteria [*S. aureus* (ATCC 25923)] and *C.* albicans (clinically isolated) as antifungal agents. The cytotoxicity of all scaffolds was compared with ampicillin for antibacterial study and fluconazole for antifungal study. The antimicrobial screening was carried out at different levels of concentration (25, 50, 100 ug/mL) in solvent DMSO. It was found that, *P. aeruginonasa* displayed high resistance to maximum scaffolds and showed moderate zones of inhibition. However *E.coli, S. aureus* and *C. albicans* showed sensitivity to all the scaffolds and had medium to high zone of inhibition. The inhibitory effects of compounds 2a-j against these organisms are depicted in table 2. The results were compared with Ampicillin and Fluconazole as standard drugs.

Table 2: Anti-bacterial and anti-fungal activities of compounds 2 a-j.

No. Compd.	Microbial									Fungal		
	Escherichia coli			*Pseudomonas aeruginonasa*			*Staphylococcus aureus*			*Candida albicans*		
	100ug	50ug	25ug	100ug	50ug	25ug	100ug	50ug	25ug	100ug	50ug	25ug
2a	11	10	8	-	-	-	12	10	-	12	10	-
2b	12	10	8	-	-	-	11	10	9	12	10	-
2c	11	10	8	-	-	-	12	10	9	12	10	9
2d	11	10	8	-	-	-	12	11	9	11	9	-
2e	11	10	-	-	-	-	11	10	9	11	10	9
2f	12	11	8	-	-	-	11	11	9	10	9	-
2g	11	10	-	-	-	-	10	10	9	10	9	-
2h	12	10	8	-	-	-	12	11	10	12	10	9
2i	11	10	8	-	-	-	11	10	9	11	10	-
2j	11	10	8	-	-	-	11	10	9	12	10	9
Ampicillin	18	15	12	13	-	-	32	29	24	-	-	-
Fluconazole	-	-	-	-	-	-	-	-	-	33	30	11

Structure-activity relationship

Our hybrid molecule may be considered as a template scaffold in which one can insert substituent at different positions to enhance the specificity towards microorganisms thereby manifesting antibacterial and antifungal activities.

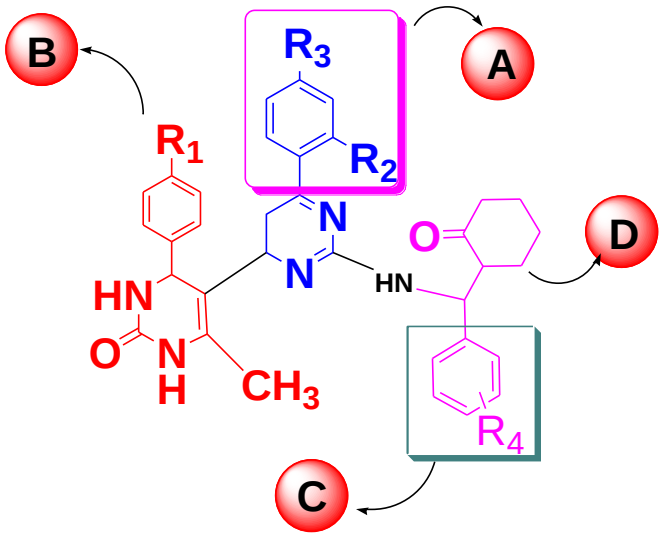


Fig. 1 Structure-activity relationship

Our hybrid molecules possesses (Fig. 1) ring A and ring B as substituted aromatic ring skeleton at C-2 and C-4 position. Ring C derived from substituted aromatic aldehyde and ring D possess β–carbonyl cyclohexanone subunit.

Compounds 2b, 2f and 2h were found to be active compounds among the rest of the compounds against the microbial strain of *Escherichia coli*. However the other compounds show moderate activity against *S. aureus* and other microorganisms.

The compounds 2b, 2f and 2h displayed maximum activity for *Escherichia coli* at 100 ug/ml due to -OCH_3 substitution on ring A and ring B at para position and -F substitution at para position of ring C which enhanced the synergistic effects leading to compounds having excellent activity.

It is also interesting to note that the compounds 2d, 2f, and 2h exhibit moderate activity against *S. aureus*, at 50 ug/ml. Other compounds exhibited moderate activity against fungi and bacteria due to presence of –OCH_3, -Cl at ring A and –OCH_3, -Cl, -OH and -F substituents at ring B and ring C irrespective of their inductive effects.

EXPERIMENTAL

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.

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 $[Et_3NH][HSO_4]$) (0.5 %). 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. Yield 81%.; 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: 81%; m.p.: 123ºC; 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: 81%; m.p.: 117ºC; 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: 83%; m.p.: 127ºC; 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: 86%; m.p.: 161ºC; 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: 88%; m.p.: 118ºC; 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: 88%; m.p.: 140ºC; 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: 76%; m.p.: 138ºC; 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: 73%; m.p.: 145ºC; 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: 86%; 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: 87%; m.p.: 107°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 %.

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] 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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