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HIGHLY STEREOSELECTIVE SYNTHESIS OF *ANTI*-TETRAHYDROPYRIMIDINE DERIVATIVES UNDER MICROWAVE HEATING

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Abstract –New [3+3] heterocyclization has been established for the synthesis of *anti*-tetrahydropyrimidine derivatives. The reaction was conducted by reacting readily available and inexpensive starting materials, such as 4-arylidene-2-phenyloxazol-5(4*H*)-ones, and aryl amidines, under solvent-free condition and microwave irradiation. During the reaction processes, the selective construction of *anti*-tetrahydropyrimidine skeleton and two amide functions were readily achieved *via* TEA-catalyzed ring-opening of oxazoles in a one-pot operation; in the meanwhile, lactone was converted into corresponding lactam in an intermolecular manner.

INTRODUCTION

The pyrimidines and their derivatives have been utilized as important heterocyclic building blocks in a wide array of synthetic and industrial applications. They are integral parts of genetic materials of DNA and RNA as nucleotides and nucleosides, but also play critical roles in biomedical and pharmaceutical research.[1] Hydropyrimidines belong to pyrimidine family exhibiting a broad range of biological activities, such as *anti*-viral, *anti*-tumor, *anti*-bacterial and *anti*-inflammatory activities.[2] In addition, they are also

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Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

served as mitotic kinesin Eg5 motor protein inhibitors,[3] α-adrenergic antagonists,[4] calcium channel blockers,[5] as well as potent HIV gp-120-CD4 inhibitors.[6] Furthermore, 2-aryl substituted hydropyrimidine scaffold was reported to display a range of interesting pharmacological properties such as *anti*-hepatitis B replication activity[7] and Rho-associated kinase isoform 1 (ROCK1) inhibitor.[8] Accordingly, many powerful methodologies for the synthesis of these heterocycles have been developed, and the majority of these methods involve Biginelli reaction of *β*-keto esters (Figure 1, Type **A**),[9] perhydropyrimidines formation from 1,3-oxazol-5-ones (Figure 1, Type **B**)[10] and palladium-catalyzed cross-coupling (Figure 1, Type **C**).[11] To the best of our knowledge, an efficient construction of *anti*-tetrahydropyrimidine skeleton of type **D** substituted at multiple sites with very high stereoselectivities has not been documented so far.

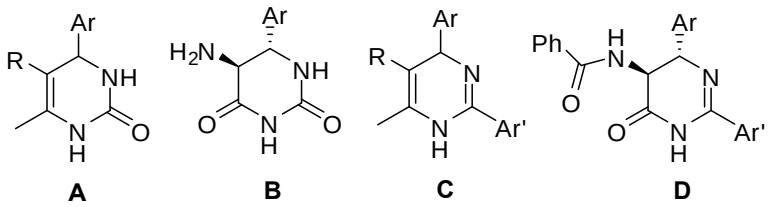
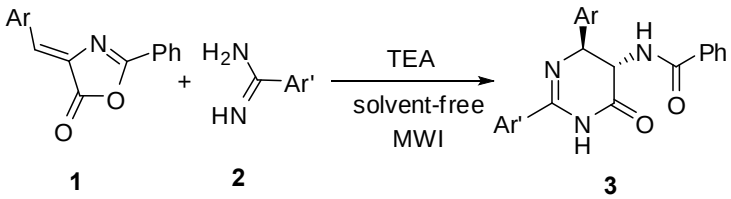


Figure 1. The structurally diverse hydropyrimidines

Amidines and related compounds possessing 1,3-binucleophilic centers are versatile synthetic intermediates in organic chemistry.[12] They are frequently applied in the preparation of pyrimidine derivatives.[12,13] Many pyrimidines have been synthesized by the reactions of amidines, aldehydes, and appropriate ketones via various methods.[13] Very recently, our group has developed several reactions that can offer easy access to useful functionalized multiple ring structures of chemical and pharmaceutical interest.[14] As part of our continuing interest in the development of new reaction in heterocyclic compounds,[14,15] In this paper, we would like to report a new route to a set of *anti*-tetrahydropyrimidine derivatives with two aryl and one amide groups residing in 2-, 4- and 5-positions, respectively (Figure 1, Type **D**). This reaction was achieved by using readily available 4-arylidene-2-phenyloxazol-5(4*H*)-ones **1** and aryl amidines **2** under solvent-free condition and microwave heating shown in Scheme 1.



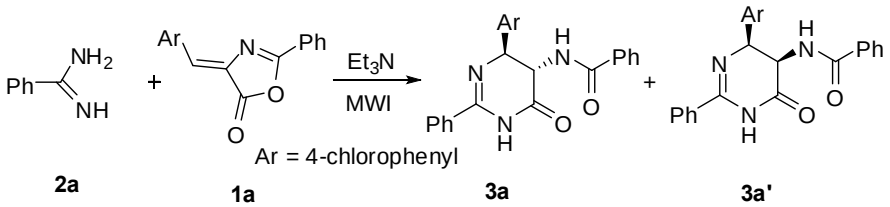
Scheme 1. Synthesis of *anti*-tetrahydropyrimidine derivatives

RESULTS AND DISCUSSION

We have planned to link two biologically important nuclei, tetrahydropyrimidine and amides, to generate a new series of compounds, pyrimidine analogues, using [3+3] heterocyclization of 4-arylidene-2-phenyloxazol-5(4*H*)-ones **1** and aryl amidines **2**. It should be known that the amido function is synthetically and pharmacologically readily manipulable and important. Tetrahydropyrimidine scaffolds incorporating the amide (–NH-C=O) function is seldom reported and is not accessible through any one of known synthetic routes although they appear as attractive scaffolds to be utilized for exploiting chemical diversity and generating a drug-like library to screen for lead candidates. In addition, 4-arylidene-2-phenyloxazol-5(4*H*)-ones are versatile and readily obtainable reagents, and their chemistry has received considerable attention in recent years.[16]

We started this research by subjecting a preformed 4-arylidene-2-phenyloxazol-5(4*H*)-ones **1a** to the reaction with benzimidamide **2a** in various solvents at 80 °C under microwave irradiation using triethylamine (TEA) as a base catalyst. The results of extensive solvent screening and optimization are shown in Table 1. Triethylamine (TEA)-catalyzed two-component reaction in organic solvents such as ethanol, CH_2Cl_2, and glycol gave the desired *anti*-tetrahydropyrimidine **3a** as a single isomer in low yields without observation of *syn*-tetrahydropyrimidine **3a'** (Table 1, entries 1-4). In another case, when DMF was used as the solvent, the reaction proceeded more efficiently, and *anti*-product **3a** was obtained in 60% chemical yield. To our satisfaction, 73% yield of *anti*-tetrahydropyrimidine **3a** was achieved under solvent-free condition. Subsequently, the reaction catalyzed by TEA was performed and repeated many times at different temperatures in sealed vessels under solvent-free condition and microwave irradiation for 20 min. The highest yield of *anti*-tetrahydropyrimidine **3a** (80%) as a single isomer was obtained when the reaction temperature was increased to 100 °C.

The structural elucidation and the attribution of stereoselectivity were unequivocally determined by NMR spectroscopic analysis. The *anti* and *syn* isomers were identified by coupling constants (*J*) of vicinal protons adjacent to aryl and NH in their ^{1}H-NMR spectra. The coupling constants *J* of *anti* isomer is higher than that of corresponding *syn* one (Scheme 2).[17] ^{1}H-NMR spectrum of **3a** showed a doublet at δ 5.05 due to CH and coupling constant J = 13.6 Hz (Figure 2); it indicated that compounds **3** were in *anti*-configuration because of steric hindrance between the aryl substituent and vicinal amido group.



Scheme 2. The optimized reactions for the synthesis of **3a**

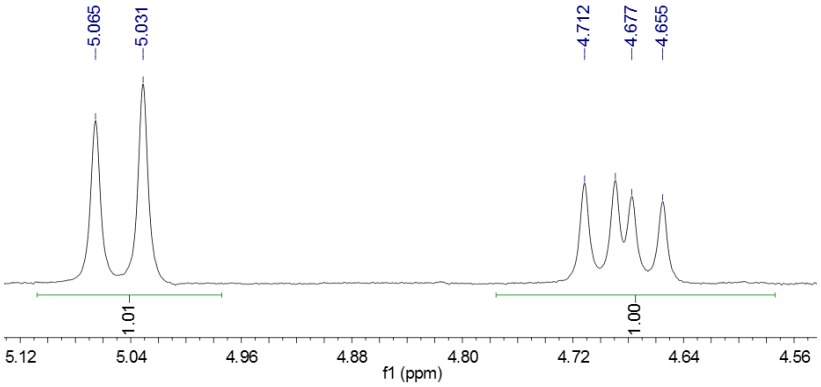


Figure 2. Determination of *anti*-configuration of products **3a**

Table 1. Results of optimization for synthesis of **3a**

Entry	Solvent	T/°C	Time/min	**3a**:**3a'**	Yield (%)
1	EtOH	80	20	>100:1	35
2	ethylene glycol	80	20	>100:1	20
3	DMF	80	20	>100:1	60
4	CH_2Cl_2	80	20	>100:1	28
5	solvent-free	80	20	>100:1	73
6	solvent-free	100	20	>100:1	80

Table 2. Synthesis of *anti*-tetrahydropyrimidines **3** under MW

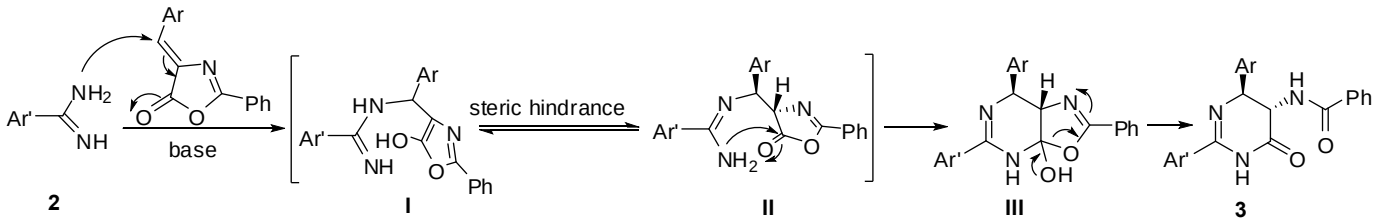
Entry	**3**	Ar	Amidine **2**	Time/min	Yield/%
1	**3a**	4-Chlorophenyl (**1a**)	Phenyl (**2a**)	20	80
2	**3b**	4-Bromophenyl (**1b**)	Phenyl (**2a**)	18	82
3	**3c**	4-Fluorophenyl (**1c**)	Phenyl (**2a**)	17	75
4	**3d**	Phenyl (**1d**)	Phenyl (**2a**)	20	76
5	**3e**	4-Methoxyphenyl (**1e**)	Phenyl (**2a**)	22	81
6	**3f**	4-Methylphenyl (**1f**)	Phenyl (**2a**)	23	80
7	**3g**	4-Chlorophenyl (**1a**)	4-Bromophenyl (**2b**)	20	76
8	**3h**	4-Methoxyphenyl(**1e**)	4-Bromophenyl (**2b**)	25	80
9	**3i**	4-Methylphenyl (**1f**)	4-Bromophenyl (**2b**)	23	75
10	**3j**	3,4,5-Trimethoxyphenyl (**1g**)	4-Bromophenyl (**2b**)	24	78
11	**3k**	4-Bromophenyl (**1b**)	4-Chlorophenyl (**2c**)	19	76
12	**3l**	Phenyl (**1d**)	4-Chlorophenyl (**2c**)	25	80

13	**3m**	4-Methoxyphenyl (**1e**)	4-Chlorophenyl (**2c**)	22	86
14	**3n**	3,4,5-Trimethoxyphenyl (**1g**)	4-Chlorophenyl (**2c**)	23	71
15	**3o**	4-Chlorophenyl (**1a**)	Pyridin-3-yl (**2d**)	23	72
16	**3p**	4-Fluorophenyl (**1c**)	Pyridin-3-yl (**2d**)	18	77
17	**3q**	4-Methoxyphenyl (**1e**)	Pyridin-3-yl (**2d**)	25	73
18	**3r**	4-Methylphenyl (**1f**)	Pyridin-3-yl (**2d**)	21	80
19	**3s**	3,4,5-Trimethoxyphenyl (**1g**)	Pyridin-3-yl (**2d**)	20	70
20	**3t**	4-Methoxyphenyl (**1e**)	Pyridin-4-yl (**2d**)	28	81
21	**3u**	4-Methylphenyl(**1f**)	Pyridin-4-yl (**2d**)	25	75

With this result in hand, we studied the scope of this new methodology. Using the optimized reaction conditions, a variety of structurally diverse 4-arylidene-2-phenyloxazol-5(4*H*)-ones were investigated, and a series of new multi-functionalized *anti*-tetrahydropyrimidine **3** were afforded in good yields. As shown in Table 2 that we sought for the oxazol-5(4*H*)-one substrate scope, benzimidamide **2a** was then used as model substrates (Table 2). The results indicated that oxazol-5(4*H*)-one bearing different substituents including electron-withdrawing (such as chloro, bromo or fluoro) and electron-donating groups (such as methyl, or methoxy) on the aromatic rings were suitable for the synthesis of compound **3**. Subsequently, the aryl amidine scope of this transformation was next investigated (Table 2). Several different aryl amidines were compared and substituents with 4-bromophenyl **2b**, 4-chlorophenyl **2c**, pyridin-3-yl **2d**, or pyridin-4-yl **2e** groups were found to be suitable for this reaction. The results exhibit the scope and generality of the new reaction with respect to a range of oxazol-5(4*H*)-one and aryl amidine substrates. Furthermore, functional groups like bromide and chloride were well tolerated. These functional groups provide ample opportunity for further functional group manipulations, for example, by modern cross-coupling reactions.

Similar to our previous process,[14,15] the present reaction also showed the following attractive characteristics: (1) fast reaction rates which enable the reaction to be completed within 17-28 min; (2) high atom utilization; (3) the convenient work-up which only needs simple filtration since products directly precipitate out when the reaction system is neutralized with diluted hydrochloric acid and then poured into cold water; (4) readily available starting materials of aryl amidines and preformed oxazol-5(4*H*)-ones. Moreover, during these processes, the selective construction of *anti*-tetrahydropyrimidine skeleton and two amide functions were readily achieved accompanied by ring-opening of oxazoles *via* TEA-catalyzed reaction in a one-pot operation, and lactone was converted into corresponding lactam in a one-pot and intermolecular manner.

On the basis of the above results, possible mechanism has been proposed for the formation of *anti*-tetrahydropyrimidine derivatives **3** as shown in scheme 3. Firstly, Michael addition between 4-arylidene-2-phenyloxazol-5(4*H*)-ones **1** and benzamidine **2** furnishes the intermediate **I**, which subsequently isomerizes to form intermediate **II**. Next, the intermediate **II** undergoes intramolecular nucleophilic addition (**II** to **III**) and elimination (**III** to **3**) to afford the final product **3**.



Scheme 4. The proposed mechanism for *anti*-pyrimidines **3**

In conclusion, we have developed TEA-catalyzed domino heterocyclization for stereoselective synthesis of *anti*-tetrahydropyrimidine with concomitant formation of two amide functions in one-pot manner. The reaction proceeds by [3+3] heterocyclization obtaining *anti*-tetrahydropyrimidines in good yields, showing that the synthetic route allows us to assemble building blocks of tetrahydropyrimidine derivatives with a wide diversity in substituents. The ready accessibility of inexpensive starting materials, the broad compatibility of oxazol-5(4*H*)-one and aryl-amidine substrates, and the generality of this process make the reaction highly valuable in view of synthetic and medical importance of heterocycles of this type. Features of this strategy include mild condition, convenient one-pot operation, short reaction periods of 17-28 min, and excellent stereoselectivities.

EXPERIMENTAL

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shift (δ) given in ppm relative to TMS as internal standard [(s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet), coupling constant (Hz)]. HRMS (ESI) was determined by using microTOF-Q Ⅱ HRMS/MS instrument (BRUKER).

Synthesis of Products 3 under Microwave Irradiation

In a 10 mL reaction vial, 4-(4-chlorophenyl)-2-phenyloxazol-5(4*H*)-one (**1a**, 1 mmol), benzamidine (**2a**, 1.1 mmol) and triethylamine (1.0 mzL) were mixed and stirred at room temperature for 3 min. Then the mixture was heated for a given min at 100 °C under microwave irradiation. Upon completion, monitored

by TLC, the reaction mixture was cooled to room temperature. The resulting suspension was neutralized with diluted hydrochloric acid solution and then poured into cold water (50 mL). The crude solid product was collected by Büchner filtration and washed with H_2O and acetone. The solid was purified by recrystallization form acetone to give the pure product **3a**.

***N*-(4-(4-Chlorophenyl)-1,4,5,6-tetrahydro-6-oxo-2-phenylpyrimidin-5-yl)benzamide (3a)**

White solid, mp 251-253 °C; IR (KBr): 3280, 1720, 1539, 1490, 1290, 1001, 820 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.14 (s, 1H, NH), 8.72 (d, J = 8.8 Hz, 1H, NH), 7.93 (d, J = 7.2 Hz, 2H, ArH), 7.75 (d, J = 7.2 Hz, 2H, ArH), 7.56-7.53 (m, 2H, ArH), 7.59-7.45 (m, 6H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 5.05 (d, J = 13.6 Hz, 1H, CH), 4.68 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 169.8, 166.1, 151.7, 140.7, 133.0, 131.6, 131.4, 131.0, 129.7, 128.2, 127.8, 127.3, 127.1, 60.8, 52.5; HRMS (ESI) *m/z*: calc. For $C_{23}H_{18}ClN_3NaO_2$: 426.0985 $[M+Na]^+$, found: 426.0985.

***N*-(4-(4-Bromophenyl)-1,4,5,6-tetrahydro-6-oxo-2-phenylpyrimidin-5-yl)benzamide (3b)**

White solid, mp 259-261 °C; IR (KBr): 3280, 2913, 1720, 1538, 1365, 1011, 816 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.15 (s, 1H, NH), 8.71 (d, J = 8.8 Hz, 1H, NH), 7.93 (d, J = 7.6 Hz, 2H, ArH), 7.76 (d, J = 1.2 Hz, 1H, ArH), 7.74 (t, J = 2.0 Hz, 1H, ArH), 7.56-7.52 (m, 3H, ArH), 7.51-7.45 (m, 5H, ArH), 7.40 (d, J = 8.4 Hz, 2H, ArH), 5.03 (d, J = 14.0 Hz, 1H, CH), 4.67(dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 166.1, 133.8, 133.0, 131.4, 131.0, 130.7, 130.1, 128.3, 128.2, 127.3, 127.1, 120.2, 52.4; HRMS (ESI) *m/z*: calc. For $C_{23}H_{18}BrN_3NaO_2$: 472.0457 $[M+Na]^+$, found: 472.0457 $[M+Na]^+$.

***N*-(4-(4-Fluorophenyl)-1,4,5,6-tetrahydro-6-oxo-2-phenylpyrimidin-5-yl)benzamide (3c)**

White solid, mp 255-257 °C; IR (KBr): 3305, 1720, 1509, 1459, 1399, 1222, 831 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.13 (s, 1H, NH), 8.70 (d, J = 8.8 Hz, 1H, NH), 7.93 (d, J = 7.6 Hz, 2H, ArH), 7.75 (s, 1H, ArH), 7.73 (t, J = 1.2 Hz, 1H, ArH), 7.54-7.42 (m, 2H, ArH), 7.48-7.44 (m, 6H, ArH),7.16 (t, J = 8.8 Hz, 2H, ArH), 5.04 (d, J = 14.0 Hz, 1H, CH), 4.68 (dd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, 1H, CH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 169.9, 166.1, 137.8, 133.0, 131.0, 129.7, 128.2, 127.0, 114.6, 114.4, 60.7, 52.6; HRMS (ESI) *m/z*: calc. For $C_{23}H_{18}FN_3NaO_2$: 410.1281 $[M+Na]^+$, found: 410.1282.

***N*-(1,4,5,6-Tetrahydro-6-oxo-2,4-diphenylpyrimidin-5-yl)benzamide (3d)**

White solid, mp 249-251 °C; IR (KBr): 3286, 1719, 1541, 1312, 1288,1001, 852 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.12 (s, 1H, NH), 8.70 (d, J = 8.8 Hz, 1H, NH), 7.92 (d, J = 7.2 Hz, 2H, ArH), 7.73 (d, J = 7.2 Hz, 2H, ArH), 7.56-7.49 (m, 3H, ArH), 7.45 (t, J = 8.4 Hz, 5H, ArH), 7.29 (t, J = 7.2 Hz, 2H, ArH),7.22 (t, J = 7.2 Hz, 1H, ArH), 5.04 (d, J = 13.6 Hz, 1H, CH), 4.69 (dd, J_1 = 13.6 Hz, J_2

= 8.8 Hz, 1H, CH); HRMS (ESI) *m/z*: calc. for $C_{23}H_{19}N_3NaO_2$: 392.1375$[M+Na]^+$, found: 392.1375.

***N*-(1,4,5,6-Tetrahydro-4-(4-methoxyphenyl)-6-oxo-2-phenylpyrimidin-5-yl)benzamide (3e)**

White solid, mp 277-279 °C; IR (KBr): 3309, 1720, 1541, 1458, 1234, 1038, 825 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.09 (s, 1H, NH), 8.67 (d, J = 8.8 Hz, 1H, NH), 7.92 (d, J = 7.6 Hz, 2H, ArH), 7.75 (d, J = 7.2 Hz, 2H, ArH), 7.54-7.51 (m, 2H, ArH), 7.49-7.44 (m, 4H, ArH), 7.35 (d, J = 7.6 Hz, 2H, ArH), 6.84 (d, J = 8.4 Hz ,2H, ArH), 4.98 (d, J = 14.0 Hz, 1H, CH), 4.65 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH), 3.69 (s, 3H, OCH_3); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 170.0, 133.1, 131.3, 128.8, 128.2, 127.2, 127.1, 113.2, 60.8, 54.9; HRMS (ESI) *m/z*: calc. For $C_{24}H_{21}N_3NaO_3$: 422.1481 $[M+Na]^+$, found: 422.1470.

***N*-(1,4,5,6-Tetrahydro-6-oxo-2-phenyl-4-*p*-tolylpyrimidin-5-yl)benzamide (3f)**

White solid, mp 265-267 °C; IR (KBr): 3287, 3110, 1731, 1542, 1369, 1283, 1283, 1011, 814 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.10 (s, 1H, NH), 8.68 (d, J = 8.8 Hz, 1H, NH), 7.92 (d, J = 7.2 Hz, 2H, ArH), 7.75 (d, J = 7.2 Hz, 2H, ArH), 7.56-7.51 (m, 2H, ArH), 7.49-7.44 (m, 4H, ArH), 7.31 (d, J = 8.0 Hz, 2H, ArH), 7.09 (d, J = 7.6 Hz, 2H, ArH), 5.01 (d, J = 14.0 Hz, 1H, CH), 4.65 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH), 2.24 (s, 3H, CH_3); HRMS (ESI) *m/z*: calc. For $C_{24}H_{21}N_3NaO_2$: 406.1531 $[M+Na]^+$, found: 406.1531.

***N*-(2-(4-Bromophenyl)-4-(4-chlorophenyl)-1,4,5,6-tetrahydro-6-oxopyrimidin-5-yl)benzamide (3g)**

White solid, mp 257-259 °C; IR (KBr): 3301, 1719, 1542, 1492, 1371, 1011, 834, 820 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.19 (s, 1H, NH), 8.72 (d, J = 8.8 Hz, 1H, NH), 7.87 (d, J = 8.4 Hz, 2H, ArH), 7.75 (d, J = 7.2 Hz, 2H, ArH) 7.69 (d, J = 8.4 Hz, 2H, ArH), 7.54(t, J = 7.2 Hz, 1H, ArH), 7.49-7.45 (m, 4H, ArH), 7.36 (d, J = 8.4 Hz, 2H, ArH), 5.04 (d, J = 14.0 Hz, 1H, CH), 4.71 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 166.1, 133.8, 133.2, 131.4, 131.2, 129.7, 128.3, 127.6, 127.1, 79.1, 52.3; HRMS (ESI) *m/z*: calc. for $C_{23}H_{17}BrClN_3NaO_2$: 506.0064 $[M+Na]^+$, found: 506.0064.

***N*-(2-(4-Bromophenyl)-1,4,5,6-tetrahydro-4-(4-methoxyphenyl)-6-oxopyrimidin-5-yl)benzamide (3h)**

White solid, mp 260-262 °C; IR (KBr): 3315, 3133, 1718, 1512, 1370, 1288, 1036, 824 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.14 (s, 1H, NH), 8.67 (d, J = 8.8 Hz, 1H, NH), 7.87 (d, J = 8.4 Hz, 2H, ArH), 7.74 (d, J = 7.2 Hz, 2H, ArH), 7.68 (d, J = 8.4 Hz, 2H, ArH), 7.53 (t, J = 7.2 Hz, 1H, ArH), 7.46 (t, J = 7.6 Hz, 2H, ArH), 7.34 (d, J = 8.4 Hz, 2H, ArH), 6.85 (d, J = 8.4 Hz, 2H, ArH), 4.97 (d, J = 13.6 Hz, 1H, CH), 4.67 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H, CH), 3.69 (s, 3H, OCH_3);HRMS (ESI) *m/z*: calc. for $C_{24}H_{20}BrN_3NaO_3$: 502.0563 $[M+Na]^+$, found: 502.0569.

***N*-(2-(4-Bromophenyl)-1,4,5,6-tetrahydro-6-oxo-4-*p*-tolylpyrimidin-5-yl)benzamide (3i)**

White solid, mp 260-262 °C; IR (KBr): 3308, 1719, 1542, 1371, 1245, 1073, 835, 814 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.15 (s, 1H, NH), 8.69 (d, J = 9.2 Hz, 1H, NH), 7.87 (d, J = 8.0 Hz, 2H, ArH), 7.75 (d, J = 7.2 Hz, 2H, ArH), 7.68 (d, J = 8.4 Hz, 2H, ArH), 7.53 (t, J = 7.2 Hz, 1H, ArH), 7.46 (t, J = 7.2 Hz, 2H, ArH), 7.32 (d, J = 7.6 Hz, 2H, ArH), 7.10 (d, J = 8.0 Hz, 2H, ArH), 5.00 (d, J = 9.6 Hz, 1H, CH), 4.68 (dd, J_1 = 13.2 Hz, J_2 = 9.2 Hz, 1H, CH), 2.25 (s, 3H, CH_3); HRMS (ESI) *m/z*: calc. for $C_{24}H_{20}BrN_3NaO_2$: 486.0614 $[M+Na]^+$, found: 486.0613.

***N*-(2-(4-Bromophenyl)-1,4,5,6-tetrahydro-4-(3,4,5-trimethoxyphenyl)-6-oxopyrimidin-5-yl)benzamide (3j)**

White solid, mp 263-264 °C; IR (KBr): 3262, 2997, 1720, 1551, 1372, 1242, 1133, 1009, 834 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.15 (s, 1H, NH), 8.79 (d, J = 8.8 Hz,1H, NH), 8.87 (d, J = 8.4 Hz, 2H, ArH), 7.77 (d, J = 7.2 Hz, 2H, ArH), 7.69 (d, J = 8.8 Hz, 2H, ArH), 7.54 (t, J = 7.2 Hz, 1H, ArH), 7.46 (t, J = 7.6 Hz, 2H, ArH), 6.74 (s, 2H, ArH), 4.99 (d, J = 14.0 Hz, 1H, CH), 4.68 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH), 3.66 (s, 6H, OCH_3), 3.60 (s, 3H, OCH_3); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 169.8, 166.1, 152.3, 150.6, 137.0, 136.4, 133.9, 132.3, 131.4, 131.2, 129.4, 128.2, 127.1, 124.6, 105.2, 61.4, 59.8, 55.6, 52.4; HRMS (ESI) *m/z*: calc. for $C_{26}H_{24}BrN_3NaO_5$: 562.0775 $[M+Na]^+$, found: 562.0774.

***N*-(4-(4-Bromophenyl)-2-(4-chlorophenyl)-1,4,5,6-tetrahydro-6-oxopyrimidin-5-yl)benzamide (3k)**

White solid, mp 293-295 °C; IR (KBr): 3300, 1720, 1542, 1367, 1286, 1073, 838 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.21 (s, 1H, NH), 8.88 (d, J = 8.8 Hz,1H, NH), 7.95 (d, J = 7.6 Hz, 2H, ArH), 7.79 (d, J = 7.2 Hz, 2H, ArH), 7.54 (t, J = 8.4 Hz, 3H, ArH), 7.50-7.42 (m, 6H, ArH), 5.12 (d, J = 13.6 Hz, 1H, CH), 4.68 (dd, J_1 = 13.2 Hz, J_2 = 8.8 Hz, 1H, CH); HRMS (ESI) *m/z*: calc. for $C_{23}H_{17}BrClN_3NaO_2$: 506.0064 $[M+Na]^+$, found: 506.0064.

***N*-(2-(4-Chlorophenyl)-1,4,5,6-tetrahydro-6-oxo-4-phenylpyrimidin-5-yl)benzamide (3l)**

White solid, mp 261-263 °C; IR (KBr): 3306, 1718, 1541, 1456, 1287, 1015, 840 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.18 (s, 1H, NH), 8.70 (d, J = 8.8 Hz,1H, NH), 7.94 (d, J = 8.4 Hz, 2H, ArH), 7.73 (d, J = 7.2 Hz, 2H, ArH), 7.56-7.51 (m, 3H, ArH), 7.47-7.42 (m, 4H, ArH), 7.29 (t, J = 7.2 Hz, 2H, ArH), 7.23-7.20 (m, 1H. ArH), 5.04 (d, J = 13.6 Hz, 1H, CH), 4.70 (dd, J_1 = 13.2 Hz, J_2 = 8.8 Hz, 1H, CH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 166.1, 141.4, 133.9, 131.9, 131.3, 129.2, 128.3, 128.2, 127.8, 127.1, 61.4, 52.5; HRMS (ESI) *m/z*: calc. for $C_{23}H_{18}ClN_3NaO_2$: 426.0985 $[M+Na]^+$, found: 426.0986.

***N*-(2-(4-Chlorophenyl)-1,4,5,6-tetrahydro-4-(4-methoxyphenyl)-6-oxopyrimidin-5-yl)benzamide (3m)**

White solid, mp 277-279 °C; IR (KBr): 3313, 2932, 1718, 1512, 1464, 1370, 1038, 824 cm^{-1}; ^1H NMR

(400MHz, DMSO-d_6) (δ, ppm): 11.14 (s, 1H, NH), 8.67 (d, J = 8.8 Hz,1H, NH), 7.86 (d, J = 8.8 Hz, 2H, ArH), 7.74 (d, J = 7.2 Hz, 2H, ArH), 768 (d, J = 8.4 Hz, 2H, ArH), 7.55-7.51 (m, 1H, ArH), 7.46 (t, J = 7.6 Hz, 2H, ArH), 7.34 (d, J = 8.8 Hz, 2H, ArH), 6.85 (d, J = 8.4 Hz, 2H, ArH), 4.97 (d, J = 13.6 Hz, 1H, CH), 4.66 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH), 3.69 (s, 3H, ArH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 166.1, 133.9, 132.3, 131.3, 131.2, 129.4, 128.8, 128.2, 127.1, 113.2, 54.9, 52.6; HRMS (ESI) *m/z*: calc. for $C_{24}H_{20}ClN_3NaO_3$: 456.1091 $[M+Na]^+$, found: 456.1089.

***N*-(2-(4-Chlorophenyl)-1,4,5,6-tetrahydro-4-(3,4,5-trimethoxyphenyl)-6-oxopyrimidin-5-yl)benzamide (3n)**

White solid, mp 253-254 °C; IR (KBr): 3263, 2997, 1721, 1551, 1372, 1132, 1004, 834 cm^{-1}; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.16 (s, 1H, NH), 8.86 (d, J = 8.4 Hz, 1H, NH), 7.96 (d, J = 8.0 Hz, 2H, ArH), 7.83 (d, J = 7.6 Hz, 2H, ArH), 7.56-7.52 (m, 3H, ArH), 7.46 (t, J = 7.6 Hz, 2H, ArH), 6.79 (s, 2H, ArH), 5.08 (d,J = 13.6 Hz, 1H, CH), 4.68 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H, CH), 3.67 (s, 6H, OCH_3), 3.59 (s, 3H, OCH_3); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 166.1, 152.2, 133.9, 131.3, 129.2, 128.3, 128.2, 127.1, 105.2, 99.4, 59.8, 55.8, 55.2; HRMS (ESI) *m/z*: calc. for $C_{26}H_{24}ClN_3NaO_5$: 516.1302 $[M+Na]^+$, found: 516.1302.

***N*-(4-(4-Chlorophenyl)-1,4,5,6-tetrahydro-6-oxo-2-(pyridin-3-yl)pyrimidin-5-yl)benzamide (3o)**

White soild mp 269-270 °C; IR (KBr): 3281, 1720, 1647, 1543, 1489, 1292, 820 cm^{-1}; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.31 (s, 1H, NH), 9.07 (s, 1H, ArH), 8.74 (d, J = 11.6 Hz, 2H, ArH), 8.26 (d, J = 7.6 Hz, 1H, NH), 7.76 (d, J = 7.2 Hz, 2H, ArH), 7.56-7.47 (m, 6H, ArH), 7.37 (d, J = 8.8 Hz, 2H, ArH), 5.08 (d, J = 13.6 Hz, 1H, CH), 4.75 (dd, J_1 = 13.2 Hz, J_2 = 9.6 Hz, 1H, CH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 169.7, 166.2, 151.5, 150.3, 148.3, 140.5, 129.7, 128.9, 128.3, 127.8, 127.1, 123.2, 60.9, 52.4; HRMS (ESI) m/z: calc. for $C_{22}H_{17}ClN_4O_2$: 403.0961 $[M-H]^+$, found: 403.0960.

***N*-(4-(4-Fluorophenyl)-1,4,5,6-tetrahydro-6-oxo-2-(pyridin-3-yl)pyrimidin-5-yl)benzamide (3p)**

White soild mp 270-271 °C; IR (KBr): 3280, 3073, 2898, 2778, 1736, 1648, 1543, 1222, 857, 823 cm^{-1}; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.25 (s, 1H, NH), 9.07 (s, 1H, ArH), 8.71 (d, J = 4.0 Hz, 2H, ArH), 8.26 (d, J = 7.6 Hz, 1H, NH), 7.74 (d, J = 7.2 Hz, 2H, ArH), 7.55-7.45 (m, 6H, ArH), 7.12 (t, J = 8.8 Hz, 2H, ArH), 5.07 (d, J = 14.0 Hz, 1H, CH), 4.74 (dd, J_1 = 13.2 Hz, J_2 = 9.2 Hz, 1H, CH); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 166.1, 151.5, 148.3, 131.4, 129.8, 129.7, 128.9, 128.3, 127.1, 123.2, 114.7, 114.4, 52.5; HRMS (ESI) m/z: calc. for $C_{22}H_{16}FN_4O_2$: 387.1257 $[M-H]^+$, found: 387.1269.

***N*-(1,4,5,6-Tetrahydro-4-(4-methoxyphenyl)-6-oxo-2-(pyridin-3-yl)pyrimidin-5-yl)benzamide (3q)**

White soild mp 268-269 °C; IR (KBr): 3278, 1721, 1650, 1515, 1473, 1241, 1180, 829 cm^{-1}; ^{1}H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.26(s, 1H, NH), 9.05 (s, 1H, ArH), 8.70 (d, J = 9.2 Hz, 2H, ArH), 8.25 (d, J = 7.6 Hz, 1H, NH), 7.75 (d, J = 8.0 Hz, 2H, ArH), 7.55-7.45 (m, 4H, ArH), 7.35 (d, J = 8.4 Hz,

2H,ArH), 6.85 (d, J = 8.8 Hz, 2H, ArH), 5.01 (d, J = 13.6 Hz, 1H, CH), 4.70 (dd, J_1 = 14.0 Hz, J_2 = 8.8 Hz, 1H, CH), 3.69 (s, 3H, OCH_3); HRMS (ESI) m/z: calc. for $C_{23}H_{19}N_4O_3$: 399.1456 $[M-H]^+$, found: 399.1456.

***N*-(1,4,5,6-Tetrahydro-6-oxo-2-(pyridin-3-yl)-4-*p*-tolylpyrimidin-5-yl)benzamide (3r)**

White soild mp 260-261 °C; IR (KBr): 3277, 3066. 2091, 1733, 1648, 1543, 1292, 1102, 813 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.24 (s, 1H, NH), 9.07 (s, 1H, ArH), 8.71 (d, J = 5.6 Hz, 2H, ArH), 8.26 (d, J = 7.6 Hz, 1H, NH), 7.76 (d, J = 7.2 Hz, 2H, ArH), 7.55-7.44 (m, 4H, ArH), 7.33 (d, J = 7.6 Hz, 2H,ArH), 7.10 (d, J = 7.6 Hz, 2H, ArH), 5.04 (d, J = 13.6 Hz, 1H, CH), 4.73 (dd, J_1 = 13.2 Hz, J_2 = 9.2 Hz, 1H, CH), 2.24 (s, 3H, CH_3); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm): 166.1, 151.5, 148.3, 131.3, 128.9, 128.4, 128.2, 127.7, 127.1, 123.2, 52.5, 20.6; HRMS (ESI) m/z: calc. for $C_{22}H_{17}N_4NaO_2$: 369.1351 $[M-H]^+$, found: 369.1350.

***N*-(1,4,5,6-Tetrahydro-4-(3,4,5-trimethoxyphenyl)-6-oxo-2-(pyridin-3-yl)pyrimidin-5-yl)benzamide (3s)**

White soild mp 264-265 °C; IR (KBr): 3277, 2899, 1723, 1650, 1311, 1278, 843 cm^{-1}; ^1H NMR (400MHz, DMSO-d_6) (δ, ppm): 11.24 (s, 1H, NH), 9.08 (s, 1H, ArH), 8.70 (d, J = 9.2 Hz, 2H, ArH), 8.27 (d, J = 7.6 Hz, 1H, NH), 7.77 (d, J = 7.2 Hz, 2H, ArH), 7.56-7.46 (m, 4H, ArH), 6.75 (s, 2H, ArH), 5.04 (d, J = 14.0 Hz, 1H, CH), 4.71 (dd, J_1 = 13.6 Hz, J_2 = 9.2 Hz, 1H, CH), 3.67 (s, 6H, OCH_3), 3.60 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm): 169.9, 166.2, 152.3, 151.5, 149.9, 148.4, 136.4, 135.0, 133.9, 131.4, 128.9, 128.2, 127.1, 123.3, 105.2, 61.4, 59.8, 55.6, 52.5; HRMS (ESI) m/z: calc. for $C_{25}H_{23}N_4O_5$: 459.1668 $[M-H]^+$, found: 459.1648.

***N*-(1,4,5,6-Tetrahydro-4-(4-methoxyphenyl)-6-oxo-2-(pyridin-4-yl)pyrimidin-5-yl)benzamide (3t)**

White soild mp 262-263 °C; IR (KBr): 3312, 3153, 2840, 1721, 1649, 1510, 1241, 815 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) (δ, ppm): 11.28 (s, 1H, NH), 8.71 (s, 2H, ArH), 8.69 (d, J = 5.2 Hz, 1H, NH), 7.86 (d, J = 5.2 Hz, 2H, ArH), 7.75 (d, J = 7.6 Hz, 2H, ArH), 7.53 (t, J = 7.2 Hz, 1H, ArH), 7.46 (t, J = 7.2 Hz, 2H, ArH), 7.34 (d, J = 7.6 Hz, 2H, ArH), 6.85 (d, J = 8.4 Hz, 2H, ArH), 5.03 (d, J = 13.6 Hz, 1H, CH), 4.69 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH), 3.69 (s, 3H, OCH_3); HRMS (ESI) m/z: calc. for $C_{23}H_{19}N_4O_3$: 399.1456 $[M-H]^+$, found: 399.1456.

***N*-(1,4,5,6-Tetrahydro-6-oxo-2-(pyridin-4-yl)-4-*p*-tolylpyrimidin-5-yl)benzamide (3u)**

White soild mp 272-273 °C; IR (KBr): 3276, 3113, 1731, 1653, 1542, 1287, 1066, 816 cm^{-1}; ^1H NMR (400MHz, DMSO) (δ, ppm): 11.28 (s, 1H, NH), 8.72 (s, 2H, ArH), 8.70 (d, J = 5.2 Hz, 1H, NH), 7.86 (d, J = 4.4 Hz, 2H, ArH), 7.75 (d, J = 8.0 Hz, 2H, ArH), 7.53 (t, J = 7.6 Hz, 1H, ArH), 7.46 (t, J = 7.2 Hz, 2H, ArH), 7.32 (d, J = 7.6 Hz, 2H, ArH), 7.10 (d, J = 7.6 Hz, 2H, ArH), 5.05 (d, J = 13.6 Hz, 1H, CH), 4.71 (dd, J_1 = 13.6 Hz, J_2 = 8.8 Hz, 1H, CH), 2.24 (s, 3H, CH_3); ^{13}C NMR (100MHz, DMSO-d_6) (δ, ppm):

166.1, 149.9, 140.3, 138.3, 131.3, 128.2, 127.1, 121.3, 61.3, 52.4, 20.6; HRMS (ESI) m/z: calc. for $C_{23}H_{19}N_4O_2$: 383.1507 $[M-H]^+$, found: 383.1506.

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