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ARTICLE

# An Efficient And Catalytically Free Chemical Transformation of Pyrimidin-2(1*H*)-one to 2-(*N*-Arylamino)pyrimidines and their *in vitro* Cytotoxicity Evaluation

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## ABSTRACT

With the aim to develop an efficient strategy to synthesize pyrimidine derivatives bearing diversely substituted amines involves four step linear protocols started with Biginelli multi-component reaction leading to dihydropyrimidines which passing throug multistep sequantial process containing oxidation, chlorination and catalytically free transformation of pyrimidin-2(1*H*)-one to 2-(*N*-arylamino)pyrimidines, were evaluated for cytotoxicity study against human cancer lines HCT-116, Hep-G2 and QG-56. Compound **4j** exhibit significant anticancer activity showed against: human hepato carcinoma (Hep-G2) and human colon carcinoma (HCT-116) serve as a excellent lead molecule for the generation of various promising targets.

## KEYWORDS

Biginelli Multi-component reaction, Dihydropyrimidine, Pyrimidin-2(1*H*)-one, 2-(*N*-Arylamino)pyrimidines.

## INTRODUCTION

2-Aminopyrimidine is an important structural motif utilized in a wide number of applications such as medicinal and natural products [1]. The heterocyclic guanidine moiety is structurally resemble unit, consequently it has been widely utilized as a drug like scaffold in the medicinal chemistry [1-7]. The most promising targets are derivatives containing an aromatic ring system at the 4th position and an electron-withdrawing groups such as an amide and ester or at 5th position of pyrimidine ring system (**Scheme-I**) [2-5]. Numerous 2-aminopyrimidines of such types shows significant biological activities, such as kinease 3 (GSK3), UDP-glucose-glycogen glucosyltransferase, N-type calcium channels [4] and rhoassociated protein kinease 1 [2,3]. Remarkably, 2-amino-pyrimidine scaffold is found to be important precursor in the synthesis of drug like molecules such as the potent anticancer drug Gleevec (tyrosine kinase inhibitor) [7] and rosuvastatin: the hypocholesterolemic agent (HMG-CoA reductase inhibitor)$_x$ [5,6] (Fig. 1).

The most common and generalize route to synthesize 2-aminopyrimidine heterocycles by condensation mechanism of arylidine with selective guanidine or resemble nitrogen containing scaffolds [8]. However, this approach is of limited use for the efficient synthesis of molecule libraries in a combina-

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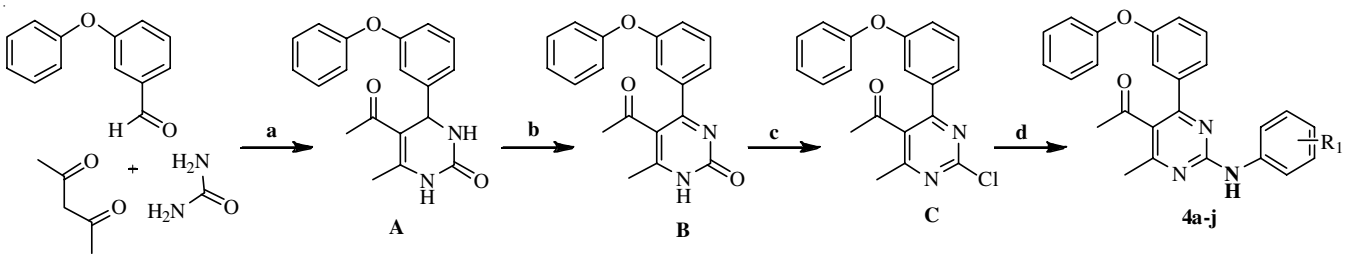



**Reagents and conditions**; (a) Ethanol, conc. HCl, reflux, 3 h, (b) $HNO_3$ (60%) 0 °C, 30 min, (c) N,N-dimethylaniline, $POCl_3$, reflux, 12 h, (d) Arylamine, ethanol, reflux, 2-5 h

**Scheme-I:** Synthesis of 2-amino-pyrmidine *via* Biginelli condensation

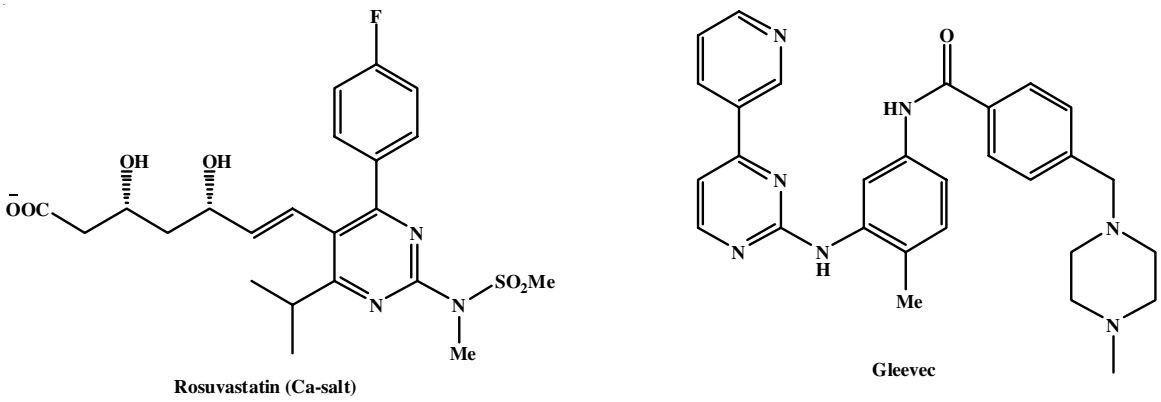



Fig. 1. Drug molecules containing 2-aminopyrimidine structural motif

torial synthesis because of the limited accessibility of guanidine like building blocks. The most précising way is to generate 2-amino group of pyrimidine by replacement of a good leaving group at the 2nd position of primidines (such as chloride) with a secondary amine or primary amine [5,9,10]. From the stand point of library diversity and combinatorial chemistry, 2nd approach is clearly the preferred option.

In current context, a facile and efficient protocol is developed for the synthesis of 2-amino-pyrimidines with utilizing highly functionalize pyrimidine motif obtained through a multi-component (MCR) Biginelli synthetic approach [11] using diversely substituted α-ketoesters, urea and aldehydes as starting materials. In order to synthesize small library of molecules stated with dihydropyrimidine-2-one building block A is converted to a pyrimidine-2-one B, which subsequently converted into 2-chloropyrimidine C, can be displaced with diversely substituted nucleophiles leading to the desired target **4a-j**. With the view of previously published approaches related to the synthesis of 2-aminopyrimidines [5,10], present strategy allows for extensive variety in all building blocks and all step in the four step sequence has been illustrated to operate under conventional conditions [12].

## EXPERIMENTAL

All research chemicals were purchased from Sigma-Aldrich and used as such for the reactions. Solvents were dried (except laboratory grade) and purified according to standard method when it necessary. The reactions were monitored by pre-coated silica gel $GF_{254}$ plates (thin-layer chromatography) from E. Merck Co. and molecules visualized by UV exposure. The determination of melting points had been carried out by open capillaries and are uncorrected. The IR spectra were recorded on IR spectrophotometer (Nicolet Impact 410 FTIR) using KBr pellets. $^1H$ and $^{13}C$ NMR spectra were recorded on FT NMR spectrometer (Bruker 300-MHz FTNMR) in $CDCl_3$ and DMSO-$d_6$ with TMS act as internal standard. Mass spectrum analysis was recorded on Thermo-Finnigan-MAT, Bremen (Model MAT8200) spectrometer and CHN analysis was carried out using Heraus CHN rapid analyzer.

**Synthesis of 1-(2-((3-chloro-4-fluorophenyl)amino)-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4a):** A mixture of 1-(2-chloro-4-methyl-6-(4-phenoxyphenyl)-pyrimidin-5-yl)ethan-1-one (0.5 g, 1.47 mmol) and 3-chloro-4-flouroaniline (0.71 g, 1.47 mmol) was dissolved in ethanol (12 mL) under catalytically free reaction conditions and refluxed for 3 h. The reaction progress was monitored by TLC. The resulting reaction mass allowed to cool at room temperature and the solid mass obtained was filtered out, washed with *n*-hexane to affording desired product with yellow solid. The product was crystallized in ethanol. Yield 78%; m.p.: 122-124 ºC; $^1H$ NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 7.08-7.10 (d, $J$ = 8.0 Hz, Ar-1H), 7.14 (s, Ar-1H), 7.18-7.22 (t, $J$ = 8 Hz, Ar- 1H), 7.25-7.26 (d,Ar-1H), 7.28-7.35 (m, Ar-2H); 7.42-7.46 (t, Ar- 2H), 7.55-7.59 (t, Ar-1H), 7.71-7.73 (m, Ar-1H), 8.10-8.12 (dd, Ar-1H), 10.22 (s, -NH). $^{13}C$ NMR (100 MHz, DMSO-$d_6$) δ: 20.99, 22.35, 31.65, 55.07, 105.62, 118.9, 125.3, 126.7, 128.06, 128.15, 128.63, 130.01, 131.09, 134.67, 140.30, 158.4, 161.4, 162.4, 163.4; IR (KBr, $\nu_{max}$, $cm^{-1}$): 2964, 1691, 1626, 1537, 1485, 1261, 858, 798. Anal. calcd. (found) % for $C_{25}H_{19}N_3O_2ClF$: C, 67.04 (67.18); H, 4.28 (4.24); N, 9.38 (9.35).

**Synthesis of 1-(4-methyl-6-(4-phenoxyphenyl)-2- (phenylamino)pyrimidin-5-yl)ethan-1-one (4b):** Aniline reacted with 1-(2-chloro-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)-

ethan-1-one as described above to give compound **4b** as pale yellow solid, yield 82%; m.p.: 116-118 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 7.10-7.13 (m, Ar-4H), 7.12-7.27 (m, Ar-3H), 7.29-7.32 (m, Ar-2H), 7.42-7.46 (t, Ar-2H), 7.54-7.56 (t, Ar-1H); 7.80-7.82 (d, *J* = 8.2 Hz, Ar-2H), 10.15 (s, -NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 20.99, 22.35, 31.65, 55.07, 105.62, 118.9, 125.3, 126.7, 128.06, 128.15, 128.63, 130.01, 131.09, 134.67, 140.30, 158.4, 161.4, 162.4, 163.4; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2961, 2333, 1770, 1620, 1529, 1469, 813, 709. Anal. calcd. (found) % for $C_{25}H_{21}N_3O_2$: C, 75.93 (75.96); H, 5.35 (5.51); N, 10.63 (10.66).

**Synthesis of 1-(2-((4-chlorophenyl)amino)-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4c):** 4-Chloroaniline reacted with 1-(2-chloro-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one as described above to give compound **4c** as light yellow solid, yield 71%; m.p.: 103-105 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 7.06-7.08 (d, *J* = 8.6 Hz, Ar-2H), 7.18-7.20 (m, Ar-3H), 7.25-7.27 (d, *J* = 8.0 Hz, Ar-2H), 7.42- 7.46 (m, Ar-2H), 7.51-7.54 (m, Ar-3H); 10.15 (s, -NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.8, 29.3, 117.6, 118.0, 118.9, 122.1, 124.9, 127.2, 128.4, 129.6, 137.0, 157.0, 162.0, 162.6, 166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2961, 2351, 1691, 1643, 1527, 1238, 707, 835. Anal. calcd. (found) % for $C_{25}H_{20}N_3O_2Cl$: C, 69.85 (69.95); H, 4.69 (4.78); N, 9.77 (9.86).

**Synthesis of 1-(2-((2,4-dichlorophenyl)amino)-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4d):** 2,4-Dichloroaniline reacted with 1-(2-chloro-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one as described above to give compound **4d** as yellow solid, yield 76%; m.p.: 112-114 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 7.06-7.09 (m, Ar-3H), 7.18-7.21 (t, Ar-1H), 7.25-7.27 (d, *J* = 8.0 Hz, Ar-2H), 7.42-7.45 (m, Ar-2H), 7.51-7.53 (d, *J* = 8.3 Hz, Ar-2H); 7.58 (s, Ar-H); 10.20 (s, -NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.8, 29.3, 117.6, 118.0, 118.9, 119.1, 121.8, 122.1, 124.9, 125.7, 126.6, 127.2, 127.7, 128.4, 131.2, 134.4, 157.0, 162.6, 166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2968, 2351, 1768, 1643, 1527, 1491, 1232, 868, 711. Anal. calcd. (found) % for $C_{25}H_{19}N_3O_2Cl_2$: C, 66.67 (66.90); H, 4.12 (4.43); N, 9.05 (9.18).

**Synthesis of 1-(2-((4-methoxyphenyl)amino)-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4e):** 4-Methoxyaniline reacted with 1-(2-chloro-4-methyl-6-(4- phenoxyphenyl)pyrimidin-5-yl)ethan-1-one as described above to give compound **4e** as brown solid, yield 78%, m.p.: 107-109 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 3.81 (s, 3H); 6.93-6.95 (d, Ar-2H); 7.06-7.08 (d, *J* = 8.0 Hz, Ar-2H), 7.18-7.21 (t, Ar-1H), 7.25-7.27 (d, *J* = 8.6 Hz, Ar-2H), 7.42-7.45 (m, Ar-2H), 7.51-7.53 (d, Ar-2H); 7.64-7.66 (d, Ar-2H); 10.15 (s, -NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.8, 29.3, 55.8, 115.1, 117.6, 118.0, 118.9, 121.7,121.8, 127.2, 127.7, 128.4, 131.2, 134.4, 153.3, 157.0, 162.6,166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2958, 1680, 1625, 1542,1476, 1268, 864, 795. Anal. calcd. (found) % for $C_{26}H_{23}N_3O_3$: C, 73.39 (73.45); H, 5.45 (5.49); N, 9.88 (9.94).

**Synthesis of 1-(2-((4-methylphenyl)amino)-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4f):** 4-Methylaniline reacted with 1-(2-chloro-4-methyl-6-(4-phenoxyphenyl)-pyrimidin-5-yl)ethan-1-one as described above to give compound **4f** as pale yellow solid, yield 84%; m.p.: 125-127 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.32 (s, 3H), 2.38 (s, 3H), 7.06-7.09 (m, Ar-4H), 7.18-7.21 (t, Ar-1H), 7.25-7.27 (d, *J* = 8.0 Hz, Ar- 2H), 7.37-7.39 (d, *J* = 8.4 Hz, Ar-2H), 7.42-7.45 (m, Ar-2H), 7.51-7.53 (d, Ar-2H); 10.19 (s, -NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.3, 21.8, 29.3, 117.6, 118.0, 118.9, 120.3, 121.7, 121.8, 124.9, 127.2, 127.7, 128.4, 129.8, 131.2, 135.9, 153.3, 157.0, 162.6, 166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2970, 2368, 1691, 1579, 1485, 1201, 1263, 1101, 848, 798, 692. Anal. calcd. (found) % for $C_{26}H_{23}N_3O_2$: C, 76.26 (76.32); H, 5.66 (5.79); N, 10.26 (10.35).

**Synthesis of 1-(2-((2-chlorophenyl)amino)-4-methyl- 6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4g):** 2- Chloroaniline reacted with 1-(2-chloro-4-methyl-6-(4- phenoxyphenyl)-pyrimidin-5-yl)ethan-1-one as described above to give compound **4g** as light yellow solid, yield 67%; m.p.: 118-120 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 6.75-6.79 (m, Ar-1H), 7.17-7.20 (m, Ar-5H), 7.40-7.42 (m, Ar-5H), 7.62-7.64 (d, *J* = 8.0 Hz, Ar-2H), 10.18 (s, -NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.8, 29.2, 117.6, 118.0, 118.9, 121.10, 122.2, 122.9, 124.9, 127.2, 128.4, 130.6, 137.3, 157.0, 162.6, 166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2968, 2350, 1695, 1644, 1529, 1230, 715, 851. Anal. calcd. (found) % for $C_{25}H_{20}N_3O_2Cl$: C, 69.85 (69.94); H, 4.69 (4.74); N, 9.77 (9.88).

**Synthesis of 1-(2-((3-fluorophenyl)amino)-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4h):** 3-Fluoroaniline reacted with 1-(2-chloro-4-methyl-6-(4-phenoxyphenyl)-pyrimidin-5-yl)ethan-1-one as above to give compound **4h** as dark yellow solid, yield 63 %; m.p.: 126-128 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 6.62-6.65 (m, Ar-1H), 7.14-7.18 (m, Ar-5H), 7.25-7.27 (d, Ar-2H), 7.40-7.43 (m, Ar-2H), 7.62-7.64 (d, *J* = 8.4 Hz, Ar-2H); 7.76 (s, Ar-H); 10.18 (s, -NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.8, 29.3, 104.6, 110.5, 115.4, 117.6, 118.0, 118.9, 119.1, 121.8, 122.1, 124.9, 127.2, 127.7, 131.2, 144.7, 157.0, 162.6, 166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2962, 2358, 1760, 1647, 1521, 1488, 1235, 1178, 830. Anal. calcd. (found) % for $C_{25}H_{20}N_3O_2F$: C, 72.63 (72.70); H, 4.88 (4.93); N, 10.16 (10.18).

**Synthesis of 1-(2-((4-bromophenyl)amino)-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one (4i):** 4- Bromoaniline reacted with 1-(2-chloro-4-methyl-6-(4- phenoxyphenyl)-pyrimidin-5-yl)ethan-1-one as described above to give compound **4i** as yellow solid, yield 75%; m.p.: 107-109 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 7.01-7.03 (d, *J* = 8.2 Hz, Ar-2H), 7.14- 7.18 (m, Ar-5H), 7.35-7.37 (d, *J* = 8.0 Hz, Ar-2H), 7.41-7.43 (m, Ar-2H), 7.52-7.54 (d, *J* = 8.2 Hz, Ar-2H); 10.18 (s, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.8, 29.3, 116.6, 118.2, 118.9, 122.8, 124.9, 127.2, 128.4, 129.6, 132.4, 137.7, 157.0, 162.0, 162.6, 166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2970, 2354, 1690, 1645, 1521, 1232, 731. Anal. calcd. (found) % for $C_{25}H_{20}N_3O_2Br$: C, 63.30 (63.54); H, 4.25 (4.34); N, 8.86 (8.87).

**Synthesis of 1-(4-methyl-2-((4-nitrophenyl)amino)-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethanone (4j):** 4-Nitroaniline reacted with 1-(2-chloro-4-methyl-6-(4-phenoxyphenyl)pyrimidin-5-yl)ethan-1-one as described above to give

compound **4j** as dark yellow solid, yield 62%; m.p.: 85-87 ºC; $^1$H NMR (400 MHz, DMSO-$d_6$) δ: 2.05 (s, 3H), 2.38 (s, 3H), 6.89-6.91 (d, *J* = 8.2 Hz, Ar-2H), 7.14-7.18 (m, Ar-5H), 7.41-7.43 (m, Ar-2H), 7.62-7.64 (d, *J* = 8.6 Hz, Ar-2H); 7.89-7.91 (d, *J* = 8.4 Hz, Ar-2H); 10.19 (s, - NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ: 21.8, 29.3, 117.6, 118.9, 119.2, 121.8, 124.7, 124.9, 128.4, 129.6, 137.9, 145.0, 157.0, 162.6, 166.8, 169.1, 199.8; IR (KBr, $\nu_{max}$, cm$^{-1}$): 2965, 2358, 1690, 1647, 1520, 1234, 707, 812. Anal. calcd. (found) % for $C_{25}H_{20}N_4O_4$: C, 69.17 (69.25); H, 4.58 (4.71); N, 12.72 (12.80).

## RESULTS AND DISCUSSION

**Optimization of reaction conditions for the synthesis of Pyrimidine-2-one A to B:** The synthetic strategy derived in **Scheme-I** commenced with dihydropyrimidine-2-one (DHPM) A which transformed into the 2-(*N*-arylamino)pyrimidines constructed by 2-chloropyrimidine precursor. The outlined multicomponent synthesis involving reaction of urea with β-ketoester and an aromatic aldehyde building block, a plethora of synthetic strategy is reported in the literature [11], including the utilization of microwave synthesis [13]. With the view of previously reported methods concerning the use of an expensive catalyst such Lewis acid like Yb(OTf)$_3$ [11], we utilized conc. HCl as an inexpensive mediator of Biginelli synthesis [14]. Gratifyingly, a 85% yield of dihydropyrimidine-2-one (DHPM) A was obtained by heating (reflux, 3-6 h) of a mixture of ethylacetoacetate, aromatic aldehyde and urea (1:1:1.2) in methanol solvent.

The same protocol also optimized under microwave irradiation using 10 mol % Yb(OTf)$_3$ as catalyst [15] and with a run using conc. HCl, significantly the conventional method using conc. HCl much favourable then microwave upon considering availability and yield [15].

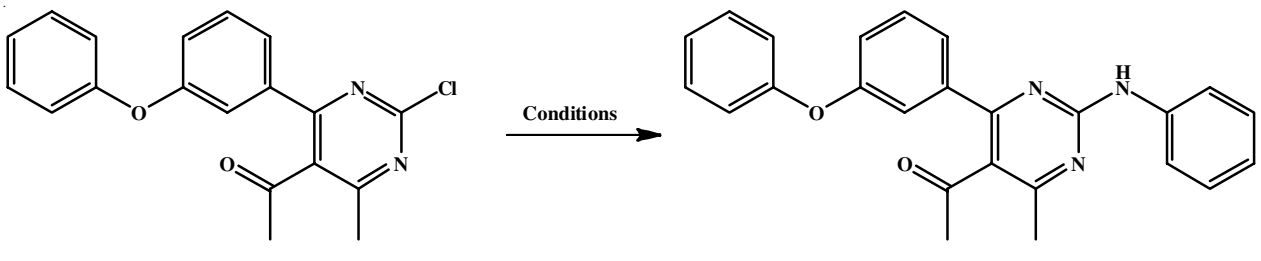
The various protocols were investigated for the aromatization of dihyropyrimidine motifs (A to B). Up to all, the most promising route carried out considering product yield and purity of the compounds with the use of cerium ammonium nitrate (CAN) in DCM or activated $MnO_2$ as a cyclizing agent but both strategy are quite unused because either it takes longer time (10-18 h) at room temperature or the controlled microwave condition required at 100-120 ºC. The successful results with fully conversation typically achieved in the later case, within less than 30 min by using of conc. $HNO_3$ at 0 ºC under stirred reaction conditions, showed similar purity profiles and yield of isolated product B in a 82% yield. The same protocol also optimized under microwave irradiation of pyrimidine-2-one (**2a**) with 5 equiv. of $MnO_2$ in anhydrous dichloromethane under sealed vessel reaction conditions at 120 ºC for 15 min [16]. Upon considering workup and general applicability, it was decided to use of conc. $HNO_3$ for all subsequent studies. The chlorination of oxidized products B were carried out using routine protocol using $POCl_3$ in the presence of *N*,*N*-dimethylaniline as a base under reflux condition for 12 h. The product was isolated from reaction mixture with the yield of 92%.

**Displacement of chlorine group in pyrimidine 4a with nucleophiles:** Few methods are reported for the displacement of chlorine group at 2nd position in pyrimidines with nucleophiles [5,10]. Of our particular interest in the elaborating the scope of this important transformation, would create considerable diversity at 2nd position of pyrimidine cores. So, in the contrast we have examined the transformation of substrate C with diverse nitrogen containing nucleophiles. In order to explore the better reaction condition, we optimized the effect of reaction parameters such as solvent, temperature and catalyst on the coupling reaction of aromatic amine with 2-chloro pyrimidinylethanones C for that 2-chloro pyrimidinylethanone C and aniline took as the model reaction (**Scheme-II**). Present investigations started with the use of primary aromatic amines treated with substrate C in the presence of THF/$K_2CO_3$ at 140 ºC affording moderate yield with 67%. The same protocol was used under microwave gives poor yield of 45%. On the basis of earlier reports in the literature [17,18], same subtract was utilize with THF/$CS_2CO_3$, DMF /$CS_2CO_3$ and DMF/$K_2CO_3$ gives moderate to good yield. Moreover the another protocol was applied using catalytically free condition in the presence of ethanol as a solvent media afforded good yield of 82-88% (**4a-j**) (Table-1). So, it is quite reliable to use of catalytically free conditions in the presence of ethanol to produce 2-aminopyrimidines. The simple conventional method proved applicable for the conversion of C into **4a-j** with utilizing a variety of different substrates.

**Biological activity:** 2-Aminopyrimidine analogues **4a-j** synthesized compounds were screened for *in vitro* cytotoxicity

TABLE-1
DIFFERENT OPTIMIZED CONDITIONS FOR THE CONVERSION OF C INTO **4a-j** UNDER DIFFERENT REACTION PARAMETERS

| Entry | Solvent/ catalyst | Temp. (°C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | THF/$K_2CO_3$ | 60-70 | 6 | 67 |
| 2 | THF/$K_2CO_3$ | Microwave/reflux | 15 min | 45 |
| 3 | THF | 60-70 | 5 | 54 |
| 4 | THF/$CS_2CO_3$ | 60-70 | 4 | 71 |
| 5 | DMF/$CS_2CO_3$ | 120-140 | 6 | 58 |
| 6 | DMF/$K_2CO_3$ | 110-120 | 8 | 55 |
| 7 | DMF | 120-140 | 8 | 52 |
| 8 | Ethanol | 60-80 | 3 | 82 |




**C** **4b**

**Scheme-II:** Model reaction condition

studies on three selected human tumor cell lines HCT-116, Hep-G2 and QG- 56 using the standard MTT assay [19,20]. Inhibitory concentration ($IC_{50}$) was represented in micro molar per milliliter (μM/mL) concentrations of synthesized 2-amino-pyrimidine derivatives. The nitro group containing pyrimidines exhibited significant cytotoxicity than other compounds. All the compounds **4a-j** shows anticancer activity with $IC_{50}$ values ranging from < 5.0 to 100 μM/mL, while the positive control, adriamycin demonstrated the $IC_{50}$ in the ranging from < 2.5 μM/mL to 5.0 μM/mL (Table-2). The most promising anti-cancer activity showed by the compound derived from 4-nitro-aniline **4j** against human colon carcinoma (HCT-116) and human hepato carcinoma (Hep-G2).

TABLE-2
CYTOTOXICITY EVALUATION OF PYRIMIDINES AGAINST THREE CARCINOMA CELL LINES ($IC_{50}$ μM/mL)[a]

| Compounds | Cytotoxicity ($IC_{50}$) | | |
|---|---|---|---|
| | Hep-G2[b] | HCT-116[c] | QG-56[d] |
| **4a** | 50 | 25 | 50 |
| **4b** | 100 | 100 | 100 |
| **4c** | 100 | 100 | 100 |
| **4d** | 25 | 50 | 100 |
| **4e** | 50 | 50 | 100 |
| **4f** | 100 | 50 | 50 |
| **4g** | 50 | 50 | 100 |
| **4h** | 100 | 100 | 100 |
| **4i** | 50 | 100 | 100 |
| **4j** | 5.0 | 12.5 | 25 |
| Adriamycin[e] | 2.5 | 5.0 | 5.0 |

[a]$IC_{50}$ = Concentration of drug that decreases the cell viability by 50% compared to non-treated control cells. [b]HeP-G2 = Human hepato carcinoma. [c]HCT-116 = Human colon carcinoma. [d]QG-56 = Human lung carcinoma. [e]Control drug

## Conclusion

In summary, a facile and efficient protocols have been established to elaborate 2-amino-pyrimidines, are excellent precursor useful in generation of wide verity pyrimidine building blocks would be amenable to build-up new substituted 2-amino-pyrimidines scaffolds with potential medicinal applications. Of our particular interest, the transformation required simple reaction conditions, shorten reaction time with increasing reaction yields and easiest way to scale up in large scale synthesis without passing through tedious process of workup or column purification.

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