Synthesis of 4-amino-5-cyano-2, 6-Disubstituted Pyrimidines as a Potential Antifilarial DNA Topoisomerase II Inhibitors

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Abstract: A novel series of 4-amino-5-cyano-2, 6-disubstituted pyrimidines have been synthesized and evaluated for their *in vitro* antifilarial DNA topoisomerase II activity against filarial parasite *Setaria Cervi*. In particular compounds bearing 4-chloro-phenyl substitutent at position-6, exhibited strong inhibition at 40 µg/mL and 5 µg/mL concentration. The present study based on the biological results obtained, suggests that the nature of substitutent at position-4 in the phenyl ring directly affects DNA topoisomerase II inhibitory activity. Most of the compounds have shown better topoisomerase II inhibitory activity than the standard antifilarial drug (DEC) and the topoisomerase II inhibitors (Novobiocin, Nalidixic acid).

Key Words: Pyrimidine, antifilarial, topoisomerase II, knoevenagel condensation.

1. INTRODUCTION

Lymphatic filariasis, a vector born parasitic disease continues to be a worsening problem in the developing world and around 120 million people are infected worldwide [1]. Current filariasis control strategies are not entirely successful and filarial infection is on the rise. In the absence of antifilarial vaccines, Chemotherapy remains the mainstay for the treatment of the disease [2]. The age old drug diethylcarbamazine (DEC) removes almost all the microfilariae from blood stream but has lethal side effects [3]. Ivermectin, a semi synthetic drug is highly effective in reducing microfilariae but it does not completely kill the adult filarial worms [4]. So there is a need to develop new antifilarial agents that can kill all the stages in the life cycle of causative filariae. DNA topoisomerase II of the filarial parasite *Setaria cervi* has been identified as a target for the development of new antifilarial compounds [5,6]. DNA topoisomerase II is an essential enzyme which has an important role in DNA replication, repair and transcription. The presence of ATP- dependent DNA topoisomerase II activity in the filarial parasite has been demonstrated in our laboratory [7,8].

Surprisingly, this newly discovered biochemical target has not been extensively explored for the development of new antifilarial agents, although bacterial DNA topoisomerase II inhibitors, particularly quinolone antibacterials have shown an ability to inhibit this enzyme in filarial parasite [9]. There are only few reports that described DNA topoisomerase II inhibitory activity which include the chemical classes such as glycosylated amino esters [10], Coumarins [11] and Ruthenium (II) poly- pyridyl and pyridyl- azine complexes [12].

Earlier our research group has discovered quinolones as a new class of antifilarial agents. Among them, the most potent macrofilaricidal compounds exhibited DNA topoisomerase II activity at 10µg/ml concentration [13]. Aminopyrimidines have been reported for broad range of biological activities like analgesic [14] and non- nucleoside HIV-1 reverse transcriptase [15] inhibitory activity. We had previously synthesized the new trisubstituted pyrimidine derivatives and identified them as novel antifilarial topoisomerase II inhibitors [16]. In extension of this work, a new series of 4-amino-5-cyano-2, 6-disubstituted pyrimidines was synthesized which showed promising DNA topoisomerase II inhibitory activity against filarial parasite *Setaria cervi*.

2. CHEMISTRY

The pyrimidine derivatives (**6-26**) were synthesized according to the synthetic route outlined in Scheme **1**. Knoevenagel condensation reaction was carried out between the different aldehydes (**1**) and malononitrle (**2**) in the presence of piperidine in ethanol to yield the corresponding benzylidine malononitriles (**3a-d**). Compounds (**3a-d)** were cyclised with S-methylisothiourea sulfate in the presence of K_2CO_3 in methanol to give 2-thiomethyl-4-amino-5-cyano-6-aryl pyrimidines (**4a-d**) according to the reported procedure with slight modification [17,18]. Compounds (**4a-d**) were further oxidized to corresponding sulfones (**5a-d**) in the presence of m-chloroperoxybenzoic acid. The sulfones (**5a-d**) were subjected to nucleophilic substitution with different amines at refluxing methanol to yield the targeted compounds (**6-26**).

3. BIOLOGICAL ACTIVITY

3.1. Material and Methods

DNA topoisomerase was partially purified from the filarial parasite *Setaria Cervi* according to the slightly modified method as given in reference [19]. Filarial parasite were homogenized in nuclei isolation buffer (NIB) (2.5mM potassium phosphate buffer, pH 7.0; 2mM $MgCl_2$, 0.1mM EDTA;

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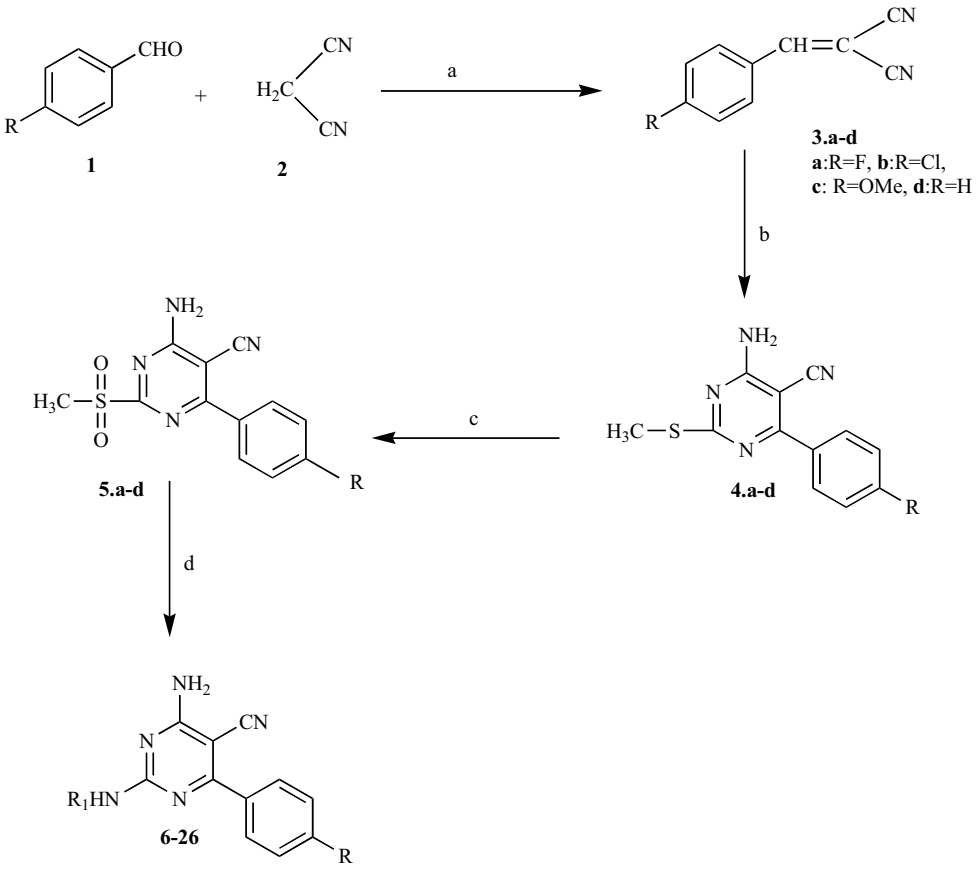


Scheme 1. Reagents and conditions: (a) piperidine, ethanol, rt; (b) S-methylisothiourea Sulfate, K_2CO_3, methanol, reflux, 5h; (c) m-CPBA, DCM, O ^oC-rt; (d)different amines, methanol, reflux.

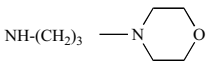
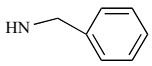
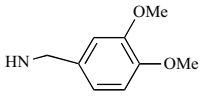
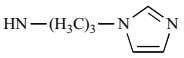
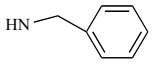
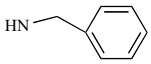
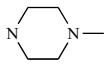
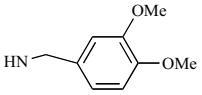
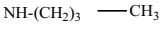
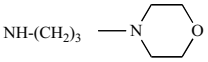
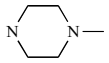
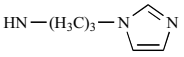
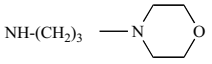
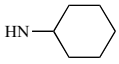
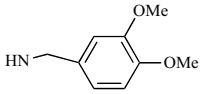
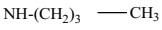
1mM EGTA; 1mM DTT and 1mM PMSF) and centrifuged at 3000g for 10 min at 4 ^oC. The pellet was washed with NIB and resuspended in NIB solution containing 4mM EDTA; 0.35 % (v/v) Triton x-100 and 0.375 M NaCl. The suspension was gently agitated for 15 min on ice and polyethylene glycol (9%, w/v) was added.The mixture was kept on ice for 1h with occasional shaking and centrifuged at 10,000g for 30 min and 1,05,000g for 1h.

Topoisomerase activity was estimated by monitoring the relaxation of super coiled pBR322 DNA as reported previously [19]. Assay mixture (20µL) contained 50 mM Tris – HCl, (pH 7.5); 50mM KCl; 1mM $MgCl_2$; 1mM ATP; 0.1mM EDTA; 0.5 mM DTT; 30µg/ml BSA; 0.25 µg pBR322 DNA and enzyme protein. The reaction mixture was incubated at 37 ^0C for 30 min and 5µL stop buffer (0.25%, bromophenol blue, 1M sucrose, 1mM EDTA, 0.5% SDS) was added. The entire reaction mixture was loaded on 1% agarose gel and elcetrophoresed in 40mM Tris-acetate buffer, Ph 8.3, 1mM EDTA at 20V for 20 h. The gel was stained with ethidium bromide (0.5 µg/ml) and photographed in GDS 7500 UVP (Ultra Violet Products, UK) transilluminator.The effect of inhibitors on the enzyme activity was measured by incubating enzyme with inhibitor for 10 min at 37 ^oC and staring the reaction with the addition of pBR322 DNA.The percent inhibition was measured by micro densitometry of the gel with GEL BASE/GEL BLOT PROGEL analysis software program (Ultra Violet Products, UK).

4. RESULTS AND DISCUSSION

All the synthesized compounds were evaluated for their *in vitro* topoisomerase II inhibitory activity against filarial parasite *Setaria cervi*. The inhibitory activities of all the evaluated pyrimidine derivatives are shown in Table **2** including the standard antifialrial drug (DEC) and the topoisomerase II inhibitors (Novobiocin, and Nalidixic acid) and the inhibitory effect of compounds towards topoisomerase II enzyme were evaluated by gel electrophoresis as shown in Fig. (**1**). Six compounds (**6-11**) bearing 4-fluoro-phenyl substitutent at position-6 exhibited 90% inhibition at 40 µg/mL concentration and 50-60% inhibition at 5 µg/mL concentration. Five compounds (**12-16**) having 4-chloro-phenyl substitutent at position-6 showed 90-95% inhibition at 40 µg/mL concentration and at 5 µg/mL concentration, these compounds have 70-80 % inhibitory activity. Surprisingly, compounds (**17, 18**) bearing 4-chloro-phenyl substitutent with the aminobenzyl and the 3-imidazol-1-yl-propylamine at position-2 respectively showed weak inhibition. It is interesting to note that the compounds having 4-chloro-phenyl substitutent are more potent than the compounds with 4-fluorophenyl group. When there was 4-methoxy-phenyl substituent at position-6 in pyrimidines (**19-24**), there was 30-85% inhibitory activity at 40 µg/mL concentration and no inhibition at 5 µg/mL concentration. So introduction of 4-methoxy group in the phenyl ring resulted significant reduction of inhibitory activity as compared to the compounds having 4-

Table1. All the New Synthesized Compounds (6-26)

Compound No.	R	R_1	Compound No.	R	R_1
6	F		**17**	Cl	
7	F		**18**	Cl	
8	F		**19**	OMe	
9	F		**20**	OMe	
10	F		**21**	OMe	
11	F		**22**	OMe	
12	Cl		**23**	OMe	
13	Cl		**24**	OMe	
14	Cl		**25**	H	
15	Cl		**26**	H	
16	Cl				

chloro or 4-fluoro group in the phenyl ring. So it is evident that the electron withdrawing group in the phenyl ring has some role in enhancing the topo II inhibitory activity while electron donating group has adverse effect on the inhibitory activity. The compounds (**25, 26**) bearing phenyl with no substitution showed 50% and 60% inhibition at 40 µg/mL concentration respectively, whereas there was no inhibition at 5 µg/mL concentration. There was no significant effect of varying concentration from 5 µg/mL to 1 µg/mL on the inhibitory activity of the compounds. Only two compounds (**7, 11**) exhibited largest variation in their inhibitory activity from 5 µg/mL to 1 µg/mL concentration while rest of the compounds (**6, 8, 9, 10, 12, 13, 14, 15, 16**) showed almost similar inhibitory activity. Comparing the results of the all the evaluated compounds with the standards (DEC, Novobiocin and Nalidixic acid) we found that compounds (**6-16**) have shown 50-80% inhibition while the standard drugs exhibited no inhibition at 5 µg/mL concentration. From the point of structure activity relationship in all the evaluated pyrimidine derivatives, the results obtained reveal that the difference in activity is due to the nature of substitutent on the aromatic phenyl ring while there is no significant effect of varying amines at position-2 in the pyrimidines.

5. CONCLUSION

We have synthesized and evaluated a new series of pyrimidine derivatives as potential antifialrial DNA II topoisomerase inhibitors. Based on the present study, we conclude that the compounds bearing 4-chloro phenyl substitutent at position 6 are more potent than the standard antifialrial drug (DEC) and the topoisomerase II inhibitors (Novobiocin, Nalidixic acid).The careful structural optimization of this class of compounds can lead to the development of promising agents for the treatment of filarial infection.

6. EXPERIMENTAL SECTION

IR spectra were recorded on Beckman Aculab-10, Perkin Elmer 881 and FTIR 8210 PC, Scimadzu spectrophotometers either on KBr discs or in neat. Nuclear Magnetic Resonance (NMR) spectra were recorded on either Bruker Avance DRX-300 MHz or Bruker DPX 200 FT spectrometers using TMS as an internal reference. FAB mass spectra were recorded on JEOL SX 102/DA 6000 mass spectrometer using Argon/ Xenon (6 KV, 10 mA) as the FAB gas. Chemical analysis was carried out on Carlo-Erba-1108 instrument. The melting

Table 2. Topoisomerase II Inhibitory Activity Against Filarial Parasite *Setaria Cervi*

S. No	Compound	% Inhibition at Different Concentrations*		
		40 µg/mL	5 µg/mL	1 µg/mL
1	**6**	90	60	50
2	**7**	90	50	35
3	**8**	90	50	45
4	**9**	90	50	50
5	**10**	90	60	50
6	**11**	90	60	35
7	**12**	90	80	70
8	**13**	95	80	75
9	**14**	90	80	75
10	**15**	90	75	75
11	**16**	90	70	70
12	**17**	30	NI	ND
13	**18**	60	NI	ND
14	**19**	50	NI	ND
15	**20**	40	NI	ND
16	**21**	30	NI	ND
17	**22**	85	NI	ND
18	**23**	85	NI	ND
19	**24**	85	NI	ND
29	**25**	50	NI	ND
21	**26**	60	NI	ND
22	**DEC(antifilarial)**	45	NI	ND
23	**Novobiocin**	80	NI	ND
24	**Nalidixic acid**	80	NI	ND

NI: No inhibition, ND: Not done, Compounds which did not shows inhibition at 5 µg/mL

* The values are mean of three experiments.

points were recorded on an electrically heated melting point apparatus and are uncorrected.

6.1. General Procedure for the Synthesis of Benzylidine Malononitriles (3a-d)

A reaction mixture of different benzaldehyde (1.0 equiv), piperidine (two drops) and malononitrile (1.1 equiv) in ethanol (20 mL) was stirred at room temp for 30 min. During the course of the reaction, the product was precipitated and filtered. Crude product was crystallized from methanol to afford the pure compound (**3a-d**).

6.1.1. 2-(4-Fluoro-benzylidene)-malononitrile (3a)

Yield: 95 %; mp 196-198°C; MS: 173 (M+1); IR (KBr) 2213, 1649, 1533, 1252 cm^{-1}; ^1H NMR: (200 MHz): δ (ppm) 7.96 (dd, 2H, J =8.84, 5.20 Hz, Ar-H), 7.76 (s, 1H, CH), 7.27 (t, 2H, J = 8.80 Ar-H); Anal. Calcd for $C_{10}H_5FN_2$: C, 69.77; H, 2.93; N, 16.27. Found: C, 69.85; H, 3.05; N, 16.15.

6.1.2. 2-(4-Chloro-benzylidene)-malononitrile (3b)

Yield: 92 %; mp: 195- 197°C; MS: 187 (M+1); IR (KBr) 2215, 1642, 1535, 1253 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.99(d, 2H, J = 8.48, Ar-H), 7.78(s, 1H, CH), 7.56 (d, 2H, J = 8.48 Hz, Ar-H); Anal. Calcd for $C_{10}H_5ClN_2$: C, 63.68; H, 2.67; N, 14.85. Found: C, 63.85; H, 2.73; N, 14.68

6.1.3. 2-(4-Methoxy-benzylidene)-malononitrile (3c)

Yield: 90 %; mp: 202- 204°C; MS: 185 (M+1); IR (KBr) 2209, 1635, 1521, 1249 cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ

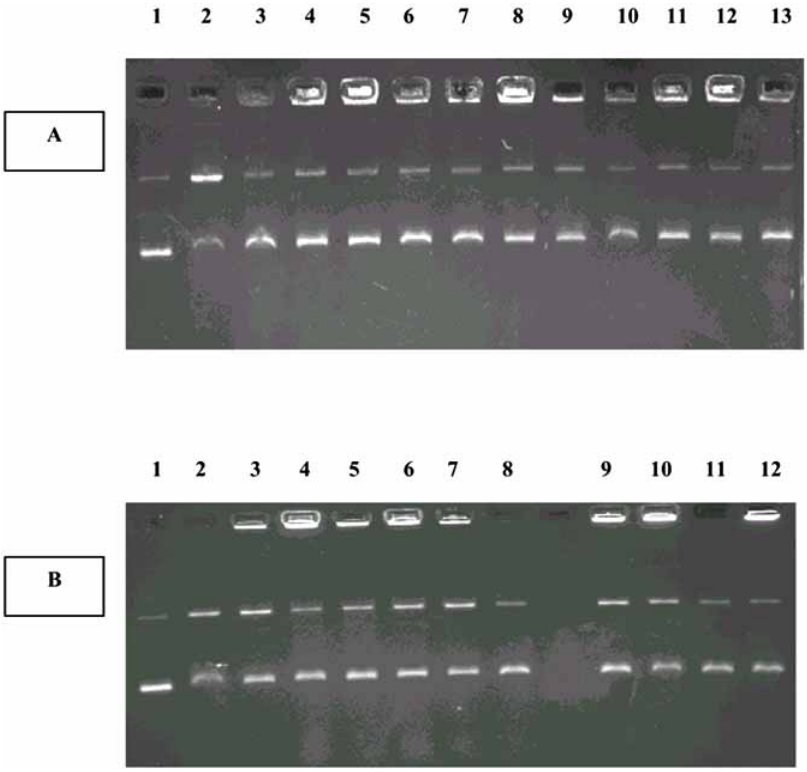


Fig (1): Effect of 4-amino-5-cyano-2, 6-disubstituted pyrimidines (**6-26**) at 40 µg/ml on topo II mediated supercoiled pBR 322 relaxation, In panel **A**, Lane 1: Supercoiled pBR 322 alone; Lane 2: pBR 322 DNA + enzyme protein; Lane 3- 13: pBR 322 DNA + enzyme protein + compound 6- 16; In panel **B**, Lane 1: Supercoiled pBR 322 alone; Lane 2: pBR 322 DNA + enzyme protein: Lane 3-12: pBR 322 DNA + enzyme protein + compound compound 17-26.

(ppm) 8.02 (d, 2H, J = 8.83 Hz, Ar-H), 7.75(s, 1H, CH), 7.05 (d, 2H, J = 8.84 Hz.Ar-H); Anal. Calcd for $C_{11}H_8N_2O$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.89; H, 4.25; N, 15.37.

6.1.4. 2-Benzylidene-malononitrile (3d)

Yield: 85 %; mp:191- 193°C; MS: 155 (M+1); IR (KBr) 2211, 1637, 1529, 1247 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.76(s, 1H, CH), 7.57(dd, 2H, J = 7.74 Hz, Ar-H), 7.32(t, 2H, J = 7.62 Hz,Ar-H), 7.02(t, 1H, J = 7.65 Hz, Ar-H); Anal. Calcd for $C_{10}H_6N_2$: C, 77.91; H, 3.92; N, 18.17. Found: C, 78.03; H, 3.84; N: 18.35.

6.2. General Procedure for the Synthesis of 2-thiomethyl Pyrimidines (4a-d)

A reaction mixture of different benzylidine malononitriles (3a-d, 1.0 equiv), S-methylisothiourea Sulfate (2.0 equiv) and K_2CO_3 (2.5 equiv) in methanol (50 mL) was refluxed for 5h.The solvent was removed from the reaction mixture under reduced pressure and the resulting residue was dissolved in chloroform (100 mL),washed with water (2 x 30 mL).The solution was dried over anhydrous Na_2SO_4 and concentrated.The crude product was purified through column chromatography on silica gel using chloroform/methanol (100:2) to afford the pure compound (**4a-d**).

6.2.1. 4-Amino-6-(4-fluoro-phenyl)-2-methylsulfanyl-pyrimidine-5-carbonitrile (4a)

Yield: 65 %; mp: 205- 207°C; MS: 261 (M+1); IR (KBr) 3388, 3211, 2216, 1660, 1531, 1330 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 8.03 (dd, 2H, J = 8.70, 5.3 Hz, Ar-H), 7.23 (t, 2H, J= 8.69, Ar-H), 5.71 (bs, 2H, NH_2), 2.57 (s, 3H, SCH_3); Anal. Calcd for $C_{12}H_9FN_4S$: C, 55.37; H, 3.49; N, 21.52; S, 12.32. Found: C, 55.12; H, 3.65; N, 21.32; S: 12.48.

6.2.2. 4-Amino-6-(4-chloro-phenyl)-2-methylsulfanyl-pyrimidine-5-carbonitrile (4b)

Yield: 67%; mp: 200- 202°C; MS: 277 (M+1); IR (KBr) 3389, 3212, 2217, 1663, 1521 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.02(d, 2H, J=8.52 Hz, Ar-H), 7.52 (d, 2H, J = 8.52 Hz, Ar-H), 5.64 (bs, 2H, NH_2), 2.58 (s, 3H, SCH_3); Anal. Calc. for $C_{12}H_9ClN_4S$: C, 52.08; H, 3.28; N, 20.24; S, 11.59. Found: C, 52.23; H, 3.38; N, 20.13; S, 11.32.

6.2.3. 4-Amino-6-(4-methoxy-phenyl)-2-methylsulfanyl-pyrimidine-5-carbonitrile (4c)

Yield: 56%; mp: 205 – 207°C; MS: 273 (M+1); IR (KBr) 3388, 3219, 2215, 1661, 1518, 1311 cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ (ppm) 8.07 (d, 2H, J = 8.82 Hz, Ar-H),7.03 (d, 2H, J = 8.84 Hz, Ar-H), 5.61 (bs, 2H, NH_2), 3.88 (s, 3H, OCH_3), 2.57 (s, 3H, SCH_3); Anal. Calc. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57; S, 11.77; Found: C, 57.18; H, 4.34; N, 20.73; S, 11.91.

6.2.4. 4-Amino-2-methylsulfanyl-6-phenyl-pyrimidine-5-carbonitrile (4d)

Yield: 48%; mp: 201- 203°C; MS: 243 (M+1); IR (KBr) 3387, 3212, 2214, 1656, 1522, 1310 cm^{-1}; ^1H NMR ($CDCl_3$,

300MHz): δ (ppm) 7.98-7.95 (m, 2H, Ar-H), 7.52- 7.48 (m, 3H, Ar-H), 5.35 (Bs, 2H, NH_2), 2.56 (s, 3H, SCH_3); Anal. Calcd for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.12; S, 13.23. Found: C, 59.69; H, 4.23; N, 23.36; S, 13.47.

6.3. General Procedure for the Synthesis of Sulfones (5a-d)

To an ice cold solution of compound (4a-d, 1.0 equiv) in dry CH_2Cl_2 (50 mL) was added m-CPBA (2.5 equiv) dissolved in dry CH_2Cl_2 (10 mL) drop wise with the help of dropping funnel. After addition of m-CPBA, the reaction was allowed to stir at room temp for 1 hour. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with aqueous 10% $NaHCO_3$ solution (3 × 30 mL), water (2 x 30 mL), dried over anhydrous Na_2SO_4.The solution was concentrated and crystallized with chloroform-hexane to obtain compound (**5a-d**).

6.3.1. 4-Amino-6-(4-fluoro-phenyl)-2-methanesulfonyl-pyrimidine-5-carbonitrile (5a)

Yield: 85%; mp: 208-210°C; MS: 293 (M+1); IR (KBr) 3385, 3215, 2215, 1662, 1531, 1350, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) = 8.12 (dd, 2H, J = 8.65 Hz, Ar-H), 7.26 (t, 2H, J = 8.64 Hz, Ar-H), 5.78 (bs, 2H, NH_2), 3.37 (s, 3H, SCH_3); Anal. Calcd for $C_{12}H_9FN_4O_2S$: C, 49.31; H, 3.10; N, 19.17; S, 10.97; Found: C, 49.24; H, 3.21; N, 19.02; S, 11.18.

6.3.2. 4-Amino-6-(4-chloro-phenyl)-2-methanesulfonyl-pyrimidine-5carbonitrile (5b)

Yield: 82%; mp: 206- 208°C; MS: 309 (M+1); IR (KBr) 3386, 3210, 2218, 1663, 1519, 1353, 1149 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.04 (d, 2H, J = 8.51 Hz, Ar-H), 7.53 (d, 2H, J = 8.51 Hz, Ar-H), 7.53 (d, 2H, J = 8.51 Hz, Ar-H), 5.65 (bs, 2H, NH_2), 3.35 (s, 3H, SCH_3); Anal. Calc. for $C_{12}H_9ClN_4O_2S$: C, 46.68; H, 2.94; N, 18.15; S, 10.39. Found: C, 46.85; H, 3.02; N, 18.11; S, 10.26

6.3.3. 4-Amino-2-methanesulfonyl-6-(4-methoxy-phenyl)-pyrimidine-5-carbonitrile (5c)

Yield: 74%; mp: 208- 210°C; MS: 305 (M+1); IR (KBr) 3389, 3211, 2218, 1657, 1519, 1350, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ (ppm) 8.09 (d, 2H, J = 8.84 Hz, Ar-H), 7.04 (d, 2H, J = 8.85 Hz, Ar-H), 5.65 (bs, 2H, NH_2), 3.88(s, 3H, OCH_3), 3.32 (s, 3H, SCH_3); Anal. Calcd for $C_{13}H_{12}N_4O_3S$: C, 51.31; H, 3.97; N, 18.41; S, 10.54. Found: C, 51.09; H, 4.08; N, 18.30; S, 10.65.

6.3.4. 4-Amino-2-methanesulfonyl-6-phenyl-pyrimidine-5-carbonitrile (5d)

Yield: 68 %; mp: 205- 207°C; MS: 275 (M+1); IR (KBr) 3389, 3211, 2215, 1659, 1519, 1354, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.99- 7.94 (m, 2H, Ar-H), 7.53- 7.49 (m, 3H, Ar-H), 5.36 (bs, 2H, NH_2), 3.28(s, 3H, SCH_3); Anal. Calcd for $C_{12}H_{10}N_4O_2S$: C, 52.54; H, 3.67; N, 20.43; S, 11.69. Found: C, 52.79; H, 3.59; N, 20.31; S, 11.73.

6.4. General Procedure for the Synthesis of Compound (6-25)

The solution of compound (5a-d, 1.0 equiv) and different amines (1.5 equiv) in dry THF (25 mL) was refluxed for 3 hours. The solvent was removed under reduced pressure and the resultant residue was dissolved in chloroform (50 mL).The organic phase was washed with water (3 x 20 mL) dried over anhydrous Na_2SO_4.The solution was concentrated and purified with column chromatography using chloroform/methanol (100:2) to afford the compound (**6-26**).

6.4.1. 4-Amino-6-(4-fluoro-phenyl)-2-(3-morpholin-4-yl-propylamino)-pyrimidine-5-carbonitrile (6)

Yield: 90%; mp: 168- 170°C; MS: 357 (M+1); IR (KBr) 3389, 3211, 2210, 1675, 1547, 1308 cm^{-1}; ^1H NMR ($CDCl_3$,300MHz): δ (ppm) 7.99 (dd, 2H, J= 8.76,5.37 Hz, Ar-H),7.17 (t,2H,J=8.72 Ar-H), 6.36 (bs,1H,NH), 5.42 (bs, 2H, NH_2), 3.76 (t,4H,J=4.64 Hz, OCH_2),3.53 (t,2H, J=6.52 Hz,CH_2), 2.53-2.48 (m, 6H, CH_2), 1.80 (quint,2H,J=6.52 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.64, 167.21, 166.51, 163.46, 134.67, 132.20, 119.12, 117.21, 116.92, 77.86, 68.52, 58.88, 55.30, 27.19; Anal. Calcd for $C_{18}H_{21}FN_6O$: C, 60.66; H, 5.94; N, 23.58. Found: C, 60.49; H, 5.71; N, 23.39.

6.4.2. 4-Amino-2-(3, 4-dimethoxy-benzylamino)-6-(4-fluoro-phenyl)-pyrimidine-5-carbonitrile (7)

Yield: 88%; mp: 173- 175°C; MS: 380 (M+1); IR (KBr) 3380, 3212, 2215, 1665, 1551, 1312 cm^{-1}; ^1H NMR ($CDCl_3$,300MHz): δ (ppm) = 7.92 (dd, 2H, J=8.72, 5.42 Hz, Ar-H), 7.18 (t, 2H, J=8.72, Ar-H), 6.91-6.84 (m, 3H,Ar-H), 5.72 (bs, IH, NH), 5.47 (bs, 2H, NH_2), 4.59 (s, 2H, CH_2), 3.89 (s, 6H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.41, 164.56, 163.99, 161.03, 160.84, 148.12, 147.34, 132.43, 131.23, 130.86, 129.71, 129.56, 129.43, 118.53, 116.07, 113.88, 113.60, 110.62, 53.97, 53.88, 43.12; Anal. Calcd for $C_{20}H_{18}FN_5O_2$: C, 63.32; H, 4.78; N, 18.46. Found: C, 63.53; H, 4.51; N, 18.28.

6.4.3. 4-Amino-6-(4-fluoro-phenyl)-2-morpholin-4-yl-pyrimidine-5-carbonitrile (8)

Yield: 92%; mp: 169- 172°C; MS: 300 (M+1); IR (KBr) 3385, 3213, 2217, 1663, 1546, 1311 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.92 (dd, 2H, J-= 8.68, 5.42 Hz, Ar-H), 7.20 (t, 2H, J= 8.67 Hz, Ar-H), 5.36 (bs, 2H, NH_2), 4.06 (t, 4H, J=5.04 Hz, CH_2), 3.78 (t, 4H, J=4.47 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.78, 166.22, 165.06, 161.29, 160.41, 133.88, 131.16, 130.99, 118.13, 115.84, 115.41, 66.32, 44.11; Anal. Calcd for $C_{15}H_{14}FN_5O$: C, 60.19; H, 4.71; N, 23.40. Found: C, 60.45; H, 4.92; N, 23.22.

6.4.4. 4-Amino-2-benzylamino-6-(4-fluoro-phenyl)-pyrimidine-5-carbonitrile (9)

Yield: 85%; mp: 178- 180°C; MS: 320 (M+1); IR (KBr) 3390, 3214, 2218, 1659, 1553, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.07 (dd, 2H, J= 8.65, 5.36 Hz, Ar-H), 7.42-7.30 (m, 5H, Ar-H), 7.24 (t, 2H, J= 8.66Hz, Ar-H), 5.71 (bs, 1H, NH), 5.47 (bs, 2H, NH_2), 4.67 (s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.59, 164.60, 164.01, 160.96, 138.88, 138.49, 132.44, 129.57, 129.45, 128.84, 126.98, 126.18, 125.52, 116.02, 113.89, 43.23; Anal. Calcd for $C_{18}H_{14}FN_5$: C, 67.70; H, 4.42; N, 21.93. Found: C, 67.48; H, 4.69; N, 21.76.

6.4.5. 4-Amino-6-(4-fluoro-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carbonitrile (10)

Yield: 89%; mp: 174- 176°C; MS: 313 (M+1); IR (KBr) 3387, 3211, 2217, 1664, 1553, 1313 cm^{-1}; ^1H NMR ($CDCl_3$,

300MHz): δ (ppm) 7.98 (dd, 2H, J= 8.85, 5.43 Hz, Ar-H), 7.18 (t, 2H,J=8.85 Hz, Ar-H), 5.34 (bs, 2H, NH_2), 3.95 (t, 4H, J= 5.2 Hz, CH_2), 2.47 (t, 4H,J= 5.2 Hz,, CH_2), 2.34 (s,3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.20, 164.38, 164.09, 161.09, 159.19, 132.64, 129.65, 129.53, 116.25, 113.96, 113.67, 53.38, 44.11, 42.11; Anal. Calcd for $C_{16}H_{17}FN_6$: C, 61.53; H, 5.49; N, 26.91. Found: C, 61.83; H, 5.24; N, 26.69.

6.4.6. 4-Amino-2-butylamino-6-(4-fluoro-phenyl)-pyrimidine-5-carbonitrile (11)

Yield: 81%; mp: 144- 146°C; MS: 286 (M+1); IR (KBr) 3385, 3209, 2216, 1665, 1551, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.04 (dd, 2H, J= 8.86, 5.36 Hz, Ar-H), 7.17 (dd, 2H, J=8.65 Hz, Ar-H), 5.43 (bs, 1H, NH), 5.22 (bs, 2H, NH_2), 3.43 (t, 2H, J=7.12 Hz, CH_2), 1.62 (quint,2H, J=7.12 Hz, CH_2), 1.46 (sext, 2H, J= 7.47 Hz, CH_2), 0.98 (t, 3H, J=7.29 Hz,CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.34, 164.58, 164.30, 163.85, 160.95, 132.69, 132.53, 129.64, 129.51, 116.18, 113.84, 113.56, 39.32, 30.46, 18.54, 11.97; Anal. Calcd for $C_{15}H_{16}FN_5$: C, 63.14; H, 5.65; N, 24.55. Found: C, 63.57; H, 5.73; N, 24.37.

6.4.7. 4-Amino-6-(4-chloro-phenyl)-2-(4-methyl-piperazin-1-yl)-pyrimidine-5-carbonitrile (12)

Yield: 92%; mp: 162- 165°C; MS: 329 (M+1); IR (KBr) 3386, 3211, 2218, 1663, 1547 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.97 (d, 2H, J = 8.72 Hz, Ar-H), 7.49 (d, 2H, J = 8.72 Hz, Ar-H), 5.39 (bs, 2H, NH_2), 3.93 (t, 4H, J = 5.42 Hz, CH_2), 2.45 (t, 4H, J = 5.42 Hz, CH_2), 2.31 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.92, 165.34, 164.52, 160.92, 136.85, 135.47, 130.67, 129.12, 118.16, 52.85, 43.37, 41.65; Anal. Calcd for $C_{16}H_{17}ClN_6$: C, 58.45; H, 5.21; N, 25.56. Found: C, 58.62; H, 5.04; N, 25.13.

6.4.8. 4-Amino-6-(4-chloro-phenyl)-2-(3-morpholin-4-yl-propylamino)-pyrimidine-5-carbonitrile (13)

Yield: 86%; mp:166-168°C; MS: 373 (M+1); IR (KBr) 3387, 3211, 2216, 1661, 1552 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.93 (dd, 2H, J= 8.62 Hz, Ar-H), 7.48 (t, 2H, J= 8.63 Hz, Ar-H), 6.4 (bs,1H, NH), 5.42 (bs, 2H, NH_2), 3.76 (t, 4H, J= 4.56 Hz, CH_2), 3.48 (t, 2H, J= 6.99 Hz, CH_2), 2.52-2.48 (m, 6H, N-CH_2),1.80 (quint, 2H, J=6.39 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.13, 165.79, 165.15, 162.13, 136.88, 135.75, 130.06, 128.85, 118.46, 67.19, 57.26, 53.95, 40.57, 25.84; Anal. Calcd for $C_{18}H_{21}ClN_6O$: C, 57.98; H, 5.68; N, 22.54. Found: C, 57.63; H, 5.35; N, 22.78.

6.4.9. 4-Amino-6-(4-chloro-phenyl)-2-(3,4-dimethoxy-benzylamino)-pyrimidine-5-carbonitrile (14)

Yield: 78%; mp: 203- 205°C; MS: 396 (M+1); IR (KBr) 3389, 3211, 2215, 1670, 1554, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.87 (d, 2H, J=8.52, Ar-H), 7.48 (d, 2H, J = 8.52,Ar-H), 6.91-6.83 (m, 3H, Ar-H), 5.75 (bs, 1H, NH), 5.49 (bs, 2H, NH_2), 4.64 (s, 2H, CH_2), 3.89 (s, 6H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.23, 165.33, 164.88, 161.97, 148.91, 148.08, 136.25, 135.45, 132.88, 132.42, 130.40, 128.71, 119.91, 118.16, 112.01, 55.88, 44.01; Anal. Calcd for $C_{20}H_{18}ClN_5O_2$: C, 60.68; H, 4.58; N, 17.69. Found: C, 60.83; H, 4.37; N, 17.95.

6.4.10. 4-Amino-6-(4-chloro-phenyl)-2-morpholin-4-yl-pyrimidine-5-carbonitrile (15)

Yield: 82%; mp: 210- 212°C; MS: 316 (M+1); IR (KBr) 3388, 3212, 2216, 1665, 1556 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.93 (d, 2H, J =8.55, Ar-H), 7.47 (d, 2H, J=8.58, Ar-H), 5.37 (bs, 2H, NH_2), 4.05 (t, 4H, J=5.1 Hz, CH_2), 3.76 (t, 4H, J= 5.1 Hz. CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.17, 165.12, 164.37, 160.83, 137.43, 135.67, 130.20, 129.06, 118.06, 67.12, 44.52; Anal. Calcd for $C_{15}H_{14}ClN_5O$: C, 57.06; H, 4.47; N, 22.18. Found: C, 57.32; H, 4.29; N, 22.01.

6.4.11. 4-Amino-2-butylamino-6-(4-chloro-phenyl)-pyrimidine-5-carbonitrile (16)

Yield: 87%; mp: 134- 136°C; MS: 302 (M+1); IR (KBr) 3388, 3213, 2217, 1661, 1530 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.98 (d, 2H, J =8.52Hz, Ar-H), 7.48 (d, 2H, J= 8.52 Hz), 5.73 (bs,1H, NH), 5.32 (bs, 2H, NH_2), 3.43 (t, 2H, J=7.14, CH_2), 1.62 (quint, 2H, J=7.41, CH_2), 1.45 (sext, 2H, J = 7.8, CH_2), 0.99 (t, 3H, J= 7.26, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.27, 164.54, 163.80, 160.96, 135.06, 134.54, 129.07, 127.25, 116.04, 53.10, 39.34, 30.45, 18.55, 11.96; Anal. Calcd for $C_{15}H_{16}ClN_5$: C, 59.70; H, 5.34; N, 23.21.Found: C, 59.87; H, 5.53; N, 23.45.

6.4.12. 4-Amino-2-benzylamino-6-(4-chloro-phenyl)-pyrimidine-5-carbonitrile (17)

Yield: 80%; mp: 194 - 196°C; MS: 336(M+1); IR (KBr): 3387, 3212, 2215, 1662, 1638, 1547, 1308 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.98 (d, 2H, J = 8.64, Ar-H), 7.48 ((d, 2H, J = 8.62 Hz, Ar-H), 7.39-7.30 (m, 5H, Ar-H), 5.83 (bs, 1H, NH), 5.59 (bs, 2H, NH_2), 4.72(s, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.27, 165.38, 164.92, 161.92, 140.55, 136.24, 135.49, 130.41, 128.71, 128.57, 127.64, 127.02, 118.14, 44.35; Anal. Calcd for $C_{18}H_{14}ClN_5$: C, 64.38; H, 4.20; N, 20.86. Found: C, 64.18; H, 4.02; N, 20.59.

6.4.13. 4-Amino-6-(4-chloro-phenyl)-2-(3-imidazol-1-yl-propylamino)-pyrimidine-5-carbonitrile (18)

Yield: 78%; mp: 135- 137°C; MS: 354 (M+1); IR (KBr) 3386, 3211, 2216, 1665, 1542, 1315 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.01 (s, 1H, Imidazole-H), 7.76 (d, 2H, J= 8.5 Hz, Ar-H), 7.46 (d, 2H, J=8.5 Hz, Ar-H), 7.04 (d, 1H, J= 4.5 Hz, Imidazole-H), 6.94 (d, 1H, J= 4.5 Hz, Imidazole-H), 5.90 (bs, 1H, NH), 5.52 (bs, 2H, NH_2), 4.05 (t, 2H, J= 6.6 Hz, CH_2), 3.38 (t, 2H, J= 6.8 Hz, CH_2), 2.06 (quint, 2H, J = 6.6 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.10, 165.40, 164.74, 162.04, 137.66, 136.23, 135.43, 131.92, 130.39, 128.52, 119.78, 118.18, 44.16, 38.13, 30.69; Anal. Calcd for $C_{17}H_{16}ClN_7$: C, 57.71; H, 4.56; N, 27.71. Found: C, 57.89; H, 4.78; N, 27.93.

6.4.14. 4-Amino-2-benzylamino-6-(4-methoxy-phenyl)-pyrimidine-5-carbonitrile (19)

Yield: 81%; mp: 176- 178°C; MS: 332 (M+1); IR (KBr) 3387, 3212, 2213, 1659, 1545, 1310 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.99 (d, 2H, J= 8.82 Hz, Ar-H), 7.39-7.29 (m, 5H, Ar-H), 7.01 (d, 2H, J= 8.82 Hz, Ar-H), 5.85 (bs, IH, NH), 5.43 (bs, 2H, NH_2), 4.72 (s, 2H, CH_2), 3.88 (s,3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.01, 169.16,

168.52, 165.05, 142.47, 133.51, 132.73, 131.91, 130.82, 130.53, 122.04, 117.10, 58.82, 48.31; Anal. Calcd for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 69.12; H, 5.37; N, 21.31.

6.4.15. 4-Amino-6-(4-methoxy-phenyl)-2-morpholin-4-yl-pyrimidine-5-carbonitrile (20)

Yield: 85%; mp: 213 – 215°C; MS: 312 (M+1); IR (KBr) 3387, 3212, 2216, 1661, 1518, 1313 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.01 (d, 2H, J=8.88 Hz, Ar-H), 7.01 (d, 2H, J = 8.87 Hz, Ar-H), 5.33 (bs, 2H, NH_2), 3.92 (t, 4H, J = 5.04 Hz, CH_2), 3.88 (s, 3H, OCH_3), 3.76 (t, 4H, J = 5.04 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.58, 165.53, 162.20, 160.83, 133.32, 130.54, 129.67, 118.99, 114.13, 67.15, 55.76, 44.86; Anal. Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.45; H, 5.76; N, 22.18.

6.4.16. 4-Amino-2-(3,4-dimethoxy-benzylamino)-6-(4-methoxy-phenyl)-pyrimidine-5-carbonitrile (21)

Yield: 75%; mp: 208 – 210°C; MS: 392 (M+1); IR (KBr) 3388, 3213, 2219, 1663, 1520, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.03 (d, 2H, J= 8.84, Ar-H), 7.01 (d, 2H, J = 8.82, Hz, Ar-H), 6.91-6.83 (m, 3H, Ar-H), 5.71 (bs, 1H, NH), 5.43 (bs, 2H, NH_2), 4.64 (s, 2H, OCH_3), 3.89 (s, 9H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.65, 165.19, 161.96, 161.32, 148.85, 147.97, 132.54, 130.12, 129.75, 119.85, 118.64, 113.64, 111.88, 111.74, 55.86, 55.47, 44.24; Anal. Calcd for $C_{19}H_{17}N_5O$: C, 68.87; H, 5.17; N, 21.13. Found: C, 68.69; H, 5.12; N, 21.47.

6.4.17. 4-Amino-6-(4-methoxy-phenyl)-2-(3-morpholin-4-yl-propylamino)-pyrimidine-5-carbonitrile (22)

Yield: 83%; mp: 158 – 160°C; MS: 369 (M+1); IR (KBr) 3389, 3211, 2217, 1665, 1519, 1316 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.01 (d, 2H, J= 8.82 Hz, Ar-H), 7.01 (d, 2H, J = 8.83 Hz, Ar-H), 6.32 (bs, 1H, NH), 5.41 (bs, 2H, NH_2), 3.88 (s, 3H, OCH_3), 3.76 (t, 4H, J= 4.47 Hz, CH_2), 3.62 (t, 2H, J = 6.48, CH_2), 2.53-2.49 (m, 6H, CH_2), 1.82 (quint, 2H, J= 6.54 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.87, 166.01, 165.85, 162.21, 130.43, 129.49, 118.92, 114.23, 67.34, 57.42, 55.82, 54.09, 40.79, 26.03; Anal. Calcd for $C_{19}H_{24}N_6O_2$: C, 61.94; H, 6.57; N, 22.81. Found: C, 61.72; H, 6.42; N, 22.98.

6.4.18. 4-Amino-2-(3-imidazol-1-yl-propylamino)-6-(4-methoxy-phenyl)-pyrimidine-5-carbonitrile (23)

Yield: 88%; mp: 140 – 142°C; MS: 350 (M+1); IR (KBr) 3387, 3210, 2216, 1664, 1522, 1410, 1318 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.91 (d, 2H, J= 9.5 Hz, Ar-H), 7.56 (s, 1H, Imidazole-H), 7.09 (d, 1H, J= 4.42 Hz, Imidazole-H), 7.05 (d, 2H, J = 9.5 Hz, Ar-H), 6.94 (d, 1H, J = 4.42 Hz, Imidazole-H), 5.65 (bs, 1H, NH), 5.41 (bs, 2H, NH_2), 3.88 (s, 3H, OCH_3), 4.02 (t, 2H, J = 6.6 Hz, CH_2), 3.42 (t, 2H, J = 6.8 Hz, CH_2), 2.14 (quint, 2H, J = 6.8 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.17, 165.63, 162.03, 161.29, 137.32, 130.05, 129.56, 128.68, 119.27, 118.65, 113.54, 55.37, 44.24, 37.92, 30.77; Anal. Calcd for $C_{18}H_{19}N_7O$: C, 61.88; H, 5.48; N, 28.06. Found: C, 61.69; H, 5.62; N, 28.23.

6.4.19. 4-Amino-2-cyclohexylamino-6-(4-methoxy-phenyl)-pyrimidine-5-carbonitrile (24)

Yield: 78%; mp:120 – 122°C; MS: 324 (M+1); IR (KBr) 3388, 3211, 2215, 1659, 1516, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 8.09 (d, 2H, J = 8.31 Hz, Ar-H), 7.01 (d, 2H, J = 8.31 Hz, Ar-H), 5.65 (bs, 1H, NH), 5.38 (bs, 2H, NH_2), 3.88 (s, 3H, OCH_3), 3.83-3.77 (m, 1H, N-CH), 2.12-2.07 (m, 2H, CH_2), 1.79-1.22 (m, 2H, CH_2), 1.47-1.36 (m, 2H, CH_2), 1.29-1.22 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.35, 165.89, 162.56, 160.29, 130.12, 129.32, 118.63, 114.12, 54.12, 33.56, 27.65, 22.72; Anal. Calcd for $C_{18}H_{21}N_5O$: C, 66.85; H, 6.55; N, 21.66. Found: C, 66.63; H, 6.45; N, 21.82.

6.4.20. 4-Amino-6-phenyl-2-pyrrolidin-1-yl- pyrimidine-5-carbonitrile (25)

Yield: 85%; mp: 204 – 206°C; MS: 266 (M+1); IR (KBr) 3389, 3211, 2216, 1661, 15178, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.99-7.96 (m, 2H, Ar-H), 7.55-7.45 (m, 3H, Ar-H), 5.34 (bs, 2H, NH_2), 3.72 (t, 2H, J = 6.41 Hz, CH_2), 3.58 (t, 2H, J = 6.41 Hz, CH_2), 1.99 (t, 4H, J= 6.42 Hz, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.05, 165.21, 159.69, 137.58, 131.10, 128.88, 128.81, 119.07, 47.32, 47.17, 25.74; Anal. Calcd for $C_{15}H_{15}N_5$: C, 67.90; H, 5.70; N, 26.40. Found: C, 68.11; H, 5.61; N, 26.49.

6.4.21. 4-Amino-6-phenyl-2-piperidin-1-yl-pyrimidine-5-carbonitrile (26)

Yield: 82%; mp: 160 – 162°C; MS: 280 (M+1); IR (KBr) 3389, 3213, 2218, 1617, 1658, 1517, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 300MHz): δ (ppm) 7.97-7.95 (m, 2H, Ar-H), 7.46-7.42 (m, 3H, Ar-H), 5.39 (bs, 2H, NH_2), 3.98-3.89 (m, 4H, CH_2), 1.73-1.64 (m, 6H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.16, 165.42, 160.73, 137.66, 131.09, 128.89, 128.80, 45.26, 26.32, 25.18; Anal. Calcd for $C_{16}H_{17}N_5$: C, 68.79; H, 6.13; N, 25.07. Found: C, 68.58; H, 6.04; N, 25.19.

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