Synthesis and Antibacterial Activity of a New Series of 2,3,5,7-Substituted-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one Derivatives

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A new series of 2,3,5,7-substituted-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one derivatives were prepared from 2-amino-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides. The key intermediate 2-amino-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides were synthesized from 2-bromo-*N*,6-disubstituted phenyl-4-(trifluoromethyl or methyl)nicotinamides as well as from ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) coupling of 2-amino-4,6-substituted nicotinic acid and substituted arylamines. All the synthesized compounds were screened for antibacterial activity against Gram +ve and Gram −ve bacteria. Compound 7c showed better antibacterial activity against Gram +ve and Gram −ve bacteria.

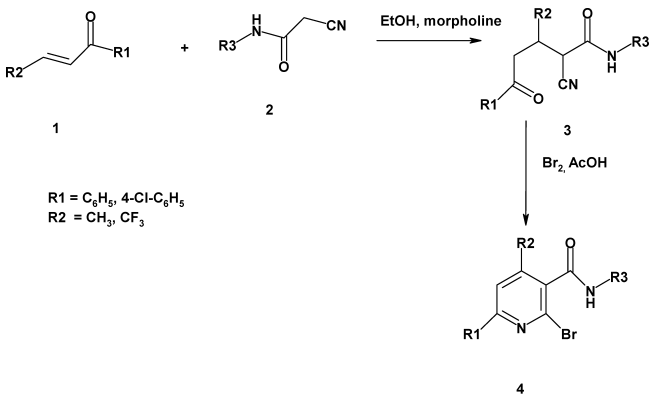
Key words pyrido[2,3]pyrimidin-4(3*H*)-one; *N*-substituted nicotinamide; antibacterial activity; 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide; triethylorthopropionate

Pyrido[2,3-*d*]pyrimidine ring system is present in a number of biologically active compounds which includes, antibacterial,[1—3] antitumor,[4] antipyretic,[5] analgesic,[6] antihistaminic,[7—9] phosphodiesterase-4 (PDE4) inhibitor,[10] adenosine kinase inhibitor,[11] tyrosine kinase inhibitor[12] and diuretic[13,14] activities. More specifically pyrido[2,3-*d*]pyrimidines were considered as inhibitors of *Pneumocystis carinii*, *Toxoplasma gondii* of tumor cells in culture this activity is mainly due to inhibition of dihydrofolate reductase (DHFR) enzyme.[15—19]

The synthesis of pyrido[2,3-*d*]pyrimidines is mainly by two ways *i.e.,* annulation of pyrimidine ring over pyridine or *vice versa*.[20] The wide range of activity profile of pyrido[2,3-*d*]pyrimidines given insight to probe into synthesis of novel analogues and to study their antibacterial activity. Moreover trifluoromethyl substituted compounds are supposed to have enhanced activity due to high lipid solubility. Thus in continuation of our efforts to synthesize novel heterocycles,[21—24] we report here a convenient synthesis of 2-substituted-3-(4-substituted phenyl)-7-(substituted phenyl)-5-(trifluoromethyl or methyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **7** from 2-bromo-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamide **4** *via* 2-amino-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides **5** and their *in vitro* antibacterial activity.

Chemistry 2-Cyano-*N*-substituted phenyl-5-oxo-5-substituted phenyl-3-(trifluoromethyl or methyl)pentanamide analogues **3** were synthesized from condensation of 1,4-disubstituted but-2-en-1-ones **1** with 2-cyano-*N*-(substituted phenyl)acetamides **2a**—**j** in the presence of a catalytic amounts of morpholine as a basic catalyst, afforded the corresponding compounds **3a**—**j** in good yields. The structure of the latter was established through spectroscopic (IR, ^{1}H-NMR and MS) as well as elemental analyses data. Addition of bromine to pentamides **3a**—**j** in glacial acetic acid at 70—80 °C gave directly the 2-bromo-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides **4a**—**j** in good yields (Chart 1). The structure of **4a**—**j** was determined through spectroscopic (IR, ^{1}H-NMR, and MS) and elemental analyses. The IR spectra of the compounds showed disappearance of cyano (–CN–) peak in the range of 2225—2218 cm^{-1} and disappearance of ketone (C=O) peak in the range of 1730—1715 cm^{-1} indicate the cyclization of ketone and cyano group to form compound **4**. ^{1}H-NMR spectra showed the disappearance of the signals at the range of δ 4.92 to 3.64 ppm due to aliphatic protons and it showed the signal around δ 8.80 ppm due to pyridine (C-5) proton. The mass spectra exhibited the molecular ion peaks corresponding to the molecular weight of the compounds which further confirmed the formation of compound **4**.

Reaction of 2-bromo-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides **4a**—**j** with aromatic amine (aniline) in pyridine gave two products **5** and **6** (Chart



1 2 3 4

	R_1	R_2	R_3
a.	C_6H_5	CF_3	4-ClC_6H_4
b.	C_6H_5	CH_3	4-IC_6H_4
c.	4-ClC_6H_4	CF_3	4-FC_6H_4
d.	4-ClC_6H_4	CF_3	4-$CH_3C_6H_4$
e.	C_6H_5	CF_3	4-$CF_3C_6H_4$
f.	4-ClC_6H_4	CF_3	2-$CH_3OC_6H_4$
g.	C_6H_5	CF_3	4-$CH_3SC_6H_4$
h.	C_6H_5	CH_3	2-$CH_3C_6H_4$
i.	4-ClC_6H_4	CF_3	3,5-$(CH_3)_2C_6H_3$
j.	C_6H_5	CH_3	3,4-$(CH_3O)_2C_6H_3$

Chart 1

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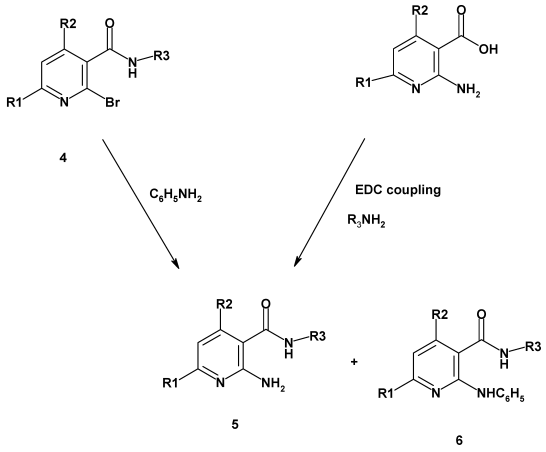
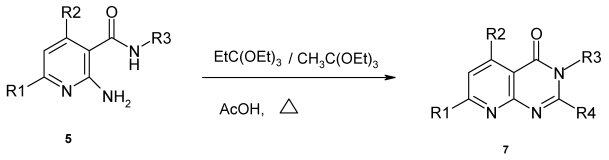


	R_1	R_2	R_3
a.	C_6H_5	CF_3	4-ClC_6H_4
b.	C_6H_5	CH_3	4-IC_6H_4
c.	4-ClC_6H_4	CF_3	4-FC_6H_4
d.	4-ClC_6H_4	CF_3	4-$CH_3C_6H_4$
e.	C_6H_5	CF_3	4-$CF_3C_6H_4$
f.	4-ClC_6H_4	CF_3	2-$CH_3OC_6H_4$
g.	C_6H_5	CF_3	4-$CH_3SC_6H_4$
h.	C_6H_5	CH_3	2-$CH_3C_6H_4$
i.	4-ClC_6H_4	CF_3	3,5-$(CH_3)_2C_6H_3$
j.	C_6H_5	CH_3	3, 4-$(CH_3O)_2C_6H_3$

Chart 2

2) which were separated and purified by column chromatography using silica gel (60—120 mesh) and the desired product was eluted with ethyl acetate–*n*-hexane as mobile phase. The structures of which were characterized as 2-amino-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamide **5** and 2-(substituted amino)-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamide **6** based on spectroscopic (IR, ^{1}H-NMR, and MS) and elemental analyses data.

Formation of **5** probably took place through iminoform isomerization originated from the primary aromatic amines under the basic reaction conditions (pyridine reflux), which *via* hydrolysis 'due to unavoidable moisture' liberated ammonia. The latter due to aromatic nucleophilic substitution with the used starting compound 2-bromo-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides **4** gave finally, the 2-amino-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides **5**. Simultaneously compounds **5** were synthesized from the 2-amino-4,6-substituted nicotinic acid and substituted arylamines through EDC (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide) coupling.[25,26] It has been noticed that, the yields of **5a**—**j** (39—25%) were greater in case of aromatic amine substituted with deactivating moiety compared with the cases, when the amines were substituted with electron-donating or activating functions. This observation supports the role of substituent attached with the used aromatic amine in deriving the reaction mechanistic route toward the product **5** formation, which coincides with the role of substitution favoring the imino-form process isomerization during the reaction course. Eventually, it could be concluded that, the opportunity of 5 formation under the described basic reaction conditions appeared greater when the used primary aromatic amine substituted with deactivating moieties. Formation of **5** during the reaction course seems similar to what was previously reported about



	R_1	R_2	R_3	R_4
a.	C_6H_5	CF_3	4-ClC_6H_4	C_2H_5
b.	C_6H_5	CH_3	4-IC_6H_4	C_2H_5
c.	4-ClC_6H_4	CF_3	4-FC_6H_4	C_2H_5
d.	4-ClC_6H_4	CF_3	4-$CH_3C_6H_4$	C_2H_5
e.	C_6H_5	CF_3	4-$CF_3C_6H_4$	C_2H_5
f.	4-ClC_6H_4	CF_3	2-$CH_3OC_6H_4$	C_2H_5
g.	C_6H_5	CF_3	4-$CH_3SC_6H_4$	C_2H_5
h.	C_6H_5	CH_3	2-$CH_3C_6H_4$	C_2H_5
i.	4-ClC_6H_4	CF_3	3,5-$(CH_3)_2C_6H_3$	C_2H_5
j.	C_6H_5	CH_3	3,4-$(CH_3O)_2C_6H_3$	C_2H_5
k.	4-ClC_6H_4	CF_3	4-FC_6H_4	CH_3
l.	4-ClC_6H_4	CF_3	4-$CH_3C_6H_4$	CH_3
m.	4-ClC_6H_4	CF_3	2-$CH_3OC_6H_4$	CH_3
n.	C_6H_5	CH_3	2-$CH_3C_6H_4$	CH_3
o.	4-ClC_6H_4	CF_3	3,5-$(CH_3)_2C_6H_3$	CH_3
p.	C_6H_5	CH_3	3,4-($CH_3O)_2C_6H_3$	CH_3

Chart 3

the yielding of 2-amino-3-pyridinecarbonitrile derivatives through the reaction of 2-bromo analogues with primary amino acid (glycine or alanine) in pyridine.[27] It was assumed in the latter reaction that, the mechanistic pathway proceeded analogously to the famous ninhydrin reaction with α-amino acids where the amino acids isomerized to the corresponding imino-acid forms under the effect of applied reaction conditions.[28] Then, upon hydrolysis, due to unavoidable moisture, ammonia was liberated which in turn interacted with 2-bromo-3-pyridinecarbonitriles giving the 2-amino derivatives. Another observation was also reported about the formation of 2-aminonicotinate esters through the reaction of 2-bromonicotinates with primary aromatic amines under similar reaction conditions.[29]

Pyrido[2,3-*d*]pyrimidines were prepared by reaction of 2-aminonicotinamide and triethylorthoformate.[30—33] In this note we are reporting facile synthesis and antibacterial activity of *N*-substituted pyrido[2,3-*d*]pyrimidines. The reaction of 2-amino-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamides **5** with triethylorthoacetate or triethylorthopropionate in the presence of catalytic amounts of glacial acetic acid gave 2,3,7-substituted-5-(trifluromethyl or methyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones **7a**—**p** in good yields (Chart 3). The structure of compounds **7** was determined through spectroscopic (IR, ^{1}H-NMR and MS) as well as elemental analyses. IR spectra of the compounds were showed the disappearance of the peaks pertaining to primary and secondary amine groups in the range of 3400—3250 cm^{-1}. Disappearance of ^{1}H-NMR amino signals (primary and secondary) around δ 6.18 ppm and δ 10.32 ppm and mass spectra exhibited molecular ion peaks corresponding to the molecular weight of the compounds which further confirmed the formation of compounds **7**. The elemental analyses showed that all the newly synthesized compounds were having the purity within $\pm$0.4% of the theoretical values.

Antibacterial Activity (*in Vitro*) Six bacterial test organisms such as *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), *Bacillus sphaericus* (MTCC 511), *Escherichia coli* (MTCC 722), *Chromobacterium violaceum* (MTCC 2656) and *Klebsiella pneumoniae* (MTCC 109) were

Table 1. MIC (in μg/ml) Values of 2,3,5,7-Substituted-pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones (**7a**—**p**)

Compounds	Microorganigms					
	Gram positive			Gram negative		
	B. subtilis	*S. aureus*	*B. sphaericus*	*E. coli*	*C. violaceum*	*K. pneumoniae*
7a	3.25	3.25	1.25	6.25	25.00	12.50
7b	12.50	25.00	50.00	6.25	—	12.50
7c	1.25	1.25	3.25	3.25	1.25	1.25
7d	1.25	6.25	3.25	12.50	25.00	12.50
7e	1.25	3.25	6.25	12.50	25.00	3.25
7f	1.25	6.25	12.50	12.50	50.00	50.00
7g	6.25	12.50	1.25	25.00	—	1.25
7h	25.00	25.00	50.00	1.50	—	12.50
7i	3.25	6.25	3.25	1.25	—	3.25
7j	25.00	25.00	12.50	3.25	—	3.25
7k	1.25	3.25	3.25	1.25	25.00	6.25
7l	12.5	12.25	12.25	12.50	—	50.00
7m	12.50	12.50	25.00	25.00	—	50.00
7n	25.00	12.50	50.00	1.25	25.00	12.50
7o	6.25	6.25	3.25	6.25	3.25	1.25
7p	25.00	25.00	12.50	6.25	6.25	6.25
Ciprofloxacin	0.78	0.39	0.78	0.39	0.39	0.78

selected and obtained from the Institute of Microbial Technology, Chandigarh. Cultures of test organisms were maintained on nutrient agar slants and were sub cultured in petri dishes prior to testing. The media used was nutrient agar, nutrient broth procured from Himedia Laboratories, Mumbai.

Results and Discussions

All the synthesized compounds were evaluated for the antimicrobial activity against various Gram +ve (*Bacillus subtilis*, *Staphylococcus aureus* and *Bacillus sphaericus*) and Gram −ve (*Escherichia coli*, *Chromobacterium violaceum* and *Klebsiella pneumoniae*). Among all the compounds, compounds having the chloro and fluoro substitutions exhibited better activity compared to other compounds. Compound **7c**, **7e**, and **7k** showed better activity against both Gram +ve and Gram −ve bacteria. Antibacterial activity of compounds **7c**, **d**, **e**, **f** and **k** were comparable with standard (ciprofloxacine) against *B. subtilis*. Compounds **7a** and **7g** exhibited better activity against Gram +ve (*B. sphaericus*) than Gram −ve bacteria which are comparable with standard. Compounds **7d** and **7f** showed better activity against *B. subtilis*. Compounds **7b**, **7l**, **7m** and **7p** exhibited moderate activity against both Gram +ve and Gram −ve bacteria. Compounds **7c**, **g** and **o** were exhibited comparable activity that of standard against *K. pneumonia*. Compounds **7b**, **7g**, **7h**, **7i**, **7j**, **7l** and **7m** were inactive against Gram −ve bacteria (*C. violaceum*) at the concentration of 100 μg/ml, only **7c** showed better activity against *C. violaceum*. Compound **7o** showed comparable activity to that of standard against *K. pneumoniae*. Compounds **7h** and **7n** exhibited better activity against *Escherichia coli*. Introduction of chlorosubstitution at 7th position of pyridopyrimidine ring found to be increased antibacterial activity. Replacement of methyl group with trifluoromethyl group at 5th position showed better antibacterial activity. Exchange of electron-releasing substitution with electron-withdrawing substitution at *N*-phenyl leads to the better antibacterial activity. Replacement of ethyl group with methyl group at 2nd-position showed decreased antibacterial activity. As all the compounds exhibited antibacterial activity against both Gram +ve and Gram −ve bacteria under study, it indicates that this basic moiety can be a potential scaffold for the antibacterial agents.

Experimental

Melting points were recorded on Casiaa siamea (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectrophotometer using KBr optics. ^{1}H-NMR spectra were recorded on Gemini Varian 400 MHz spectrometer in DMSO-d_6 using TMS as an internal standard. Electron impact and chemical ionization mass spectra were recorded on a VG 7070 H instrument at 70 eV. CHN analyses were recorded on a Vario EL analyzer and were within $\pm$0.4% of the theoretical values. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh), spots were visualized with UV light. Merck silicagel (100—200 mesh) was used for chromatography. The starting compounds **1a**—**j**[34] and **2a**—**j**[35] were prepared according to the previously reported procedures. All solvents were dried and freshly distilled prior to use according to standard procedures. All the chemicals used were of analytical grade and commercially available.

Synthesis of 2-Cyano-*N*-subsituted phenyl-5-oxo-5-substituted phenyl-3-(trifluoromethyl or methyl)pentanamides (3a—j) A mixture of equimolar amounts of 1-(4-chlorophenyl)-4,4,4-trifluorobut-2-en-1-one (10 mmol) [4,4,4-trifluoro-1-phenyl-2-en-1-one (in case of **3a**, **e** and **g**) or 1-phenyl-but-2-en-1-one (in case of **3b**, **h** and **j**) and the corresponding 2-cyano-*N*-(substituted phenyl)acetamides **2a**—**j** (10 mmol) in absolute ethanol (20 ml) containing morpholine (3—5 drops) as a basic catalyst was boiled under reflux for 24 h. The reaction mixture was evaporated until dryness under reduced pressure and the remaining residue was triturated with methanol (5 ml). So, the separated solid was collected and crystallized from ethyl acetate–*n*-hexane mixture.

N-(4-Chlorophenyl)-2-cyano-5-oxo-5-phenyl-3-(trifluoromethyl)pentanamide (**3a**): Yield: 79 %, mp 203 °C; IR (KBr) cm^{-1}: 3302, 2220, 1720, 1685, 1600, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.64 (1H, dd, upfield H of $\underline{CH_2}CH$, J=5.3, 17.5 Hz), 3.76 (1H, dd, downfield H of $\underline{CH_2}CH$, J=8.5, 17.5 Hz), 4.33 (1H, d, CH), 4.92 (1H, m, $CF_3\underline{CH}$), 7.23—7.99 (9H, m, Ar-H), 10.43 (1H, s, br, NH). EI-MS *m*/*z*: 396 (M^++2), 394 (M^+). *Anal.* Calcd for $C_{19}H_{14}ClF_3N_2O_2$ (394.77): C, 57.81; H, 3.57; N, 7.10. Found: C, 57.53; H, 3.54; N, 7.17.

2-Cyano-*N*-(4-iodophenyl)-3-methyl-5-oxo-5-phenylpentanamide (**3b**): Yield: 83%, mp 224 °C; IR (KBr) cm^{-1}: 3300, 2222, 1722, 1680, 1600, 1532. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.12 (3H, d, CH_3), 3.25 (1H, dd, upfield H of $\underline{CH_2}CH$, J=5.6, 17.8 Hz), 3.52 (1H, dd, downfield H of $\underline{CH_2}CH$, J=8.8, 17.2 Hz), 4.23—4.29 (2H, m, $CH_2\underline{CH}$+$CH_2CH\underline{CH}$), 7.23—7.99 (9H, m, Ar-H), 10.22 (1H, s, br, NH). EI-MS *m*/*z*: 434 (M^++2), 432 (M^+).

Anal. Calcd for $C_{19}H_{17}IN_2O_2$ (432.25): C, 52.79; H, 3.96; N, 6.48. Found: C, 53.04; H, 4.13; N, 6.72.

5-(4-Chlorophenyl)-2-cyano-*N*-(4-fluorophenyl)-5-oxo-3-(trifluoromethyl)pentanamide (**3c**): Yield: 88%, mp 184 °C; IR (KBr) cm^{-1}: 3308, 2220, 1728, 1680, 1658, 1610, 1522. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.52 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.5, 17.5 Hz), 3.78 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.8, 17.5 Hz), 4.34 (1H, d, CH), 4.94 (1H, m, $CF_3\underline{CH}$), 7.23—7.99 (8H, m, Ar-H), 10.06 (1H, s, br, NH). EI-MS *m*/*z*: 414 (M^++2), 412 (M^+). *Anal.* Calcd for $C_{19}H_{13}ClF_4N_2O_2$ (412.76): C, 55.29; H, 3.17; N, 6.79. Found: C, 55.48; H, 3.22; N, 6.99.

5-(4-Chlorophenyl)-2-cyano-5-oxo-*N*-*p*-tolyl-3-(trifluoromethyl)pentanamide (**3d**): Yield: 73%, mp 194 °C; IR (KBr) cm^{-1}: 3302, 2220, 1718, 1678, 1610, 1522. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.23 (3H, s, CH_3), 3.54 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.6, 17.4 Hz), 3.81 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.5, 17.4 Hz), 4.33 (1H, d, CH), 5.01 (1H, m, $CF_3\underline{CH}$), 7.23—7.86 (8H, m, Ar-H), 10.14 (1H, s, br, NH). EI-MS *m*/*z*: 410 (M^++2), 408 (M^+). *Anal.* Calcd for $C_{20}H_{16}ClF_3N_2O_2$ (408.80): C, 58.76; H, 3.94; N, 6.85. Found: C, 58.42; H, 3.83; N, 6.98.

2-Cyano-5-oxo-5-phenyl-3-(trifluoromethyl)-*N*-[4-(trifluoromethyl)-phenyl]pentanamide (**3e**): Yield: 88%, mp 204 °C; IR (KBr) cm^{-1}: 3300, 2224, 1730, 1689, 1604, 1548. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.44 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.4, 17.7 Hz), 3.78 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.6, 17.7 Hz), 4.33 (1H, d, CH), 4.92 (1H, m, $CF_3\underline{CH}$), 7.23—7.99 (9H, m, Ar-H), 10.41 (1H, s, br, NH). EI-MS *m*/*z*: 430 (M^++2), 428 (M^+); *Anal.* Calcd for $C_{20}H_{14}F_6N_2O_2$ (428.32): C, 56.08; H, 3.29; N, 6.54. Found: C, 56.22; H, 3.24; N, 6.61.

5-(4-Chlorophenyl)-2-cyano-*N*-(2-methoxyphenyl)-5-oxo-3-(trifluoromethyl)pentanamide (**3f**): Yield: 93%, mp 179 °C; IR (KBr) cm^{-1}: 3302, 2222, 1723, 1685, 1601, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.64 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.3, 17.5 Hz), 3.76 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.5, 17.5 Hz), 3.84 (3H, s, OCH_3), 4.33 (1H, d, CH), 4.92 (1H, m, $CF_3\underline{CH}$), 7.23—7.99 (8H, m, Ar-H), 10.43 (1H, s, br, NH). EI-MS *m*/*z*: 426 (M^++2), 424 (M^+). *Anal.* Calcd for $C_{20}H_{16}ClF_3N_2O_3$ (424.80): C, 56.55; H, 3.80; N, 6.59. Found: C, 56.62; H, 3.87; N, 6.65.

2-Cyano-*N*-[(4-methylthio)phenyl]-5-oxo-5-phenyl-3-(trifluoromethyl)-pentanamide (**3g**): Yield: 86%, mp 221 °C; IR (KBr) cm^{-1}: 3306, 2218, 1728, 1685, 1601, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.62 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.3, 17.5 Hz), 3.72 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.5, 17.5 Hz), 3.76 (3H, s, SCH_3), 4.32 (1H, d, CH), 4.94 (1H, m, $CF_3\underline{CH}$), 7.23—7.99 (9H, m, Ar-H), 10.39 (1H, s, br, NH). EI-MS *m*/*z*: 408 (M^++2), 406 (M^+). *Anal.* Calcd for $C_{20}H_{17}F_3N_2O_2S$ (406.42): C, 59.10; H, 4.22; N, 6.89. Found: C, 59.18; H, 4.14; N, 7.04.

2-Cyano-3-methyl-5-oxo-5-phenyl-*N*-*o*-tolylpentanamide (**3h**): Yield: 92%, mp 175 °C; IR (KBr) cm^{-1}: 3302, 2220, 1721, 1678, 1610, 1522. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.24 (3H, d, CH_3), 3.54 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.6, 17.4 Hz), 3.81 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.5, 17.4 Hz), 4.23 (1H, m, CH), 4.31 (1H, d, CH), 7.23—7.86 (9H, m, Ar-H), 10.10 (1H, s, br, NH). EI-MS *m*/*z*: 320 (M^+). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$ (320.38): C, 74.98; H, 6.29; N, 8.74. Found: C, 74.82; H, 6.37; N, 8.88.

5-(4-Chlorophenyl)-2-cyano-*N*-(3,5-dimethylphenyl)-5-oxo-3-(trifluoromethyl)pentanamide (**3i**): Yield: 81%, mp 184 °C; IR (KBr) cm^{-1}: 3302, 2220, 1712, 1678, 1610, 1522. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.28 (6H, s, CH_3), 3.54 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.6, 17.4 Hz), 3.81 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.5, 17.4 Hz), 4.33 (1H, d, CH), 5.01 (1H, m, $CF_3\underline{CH}$), 7.23—7.86 (7H, m, Ar-H), 10.14 (1H, s, br, NH). EI-MS *m*/*z*: 424 (M^++2), 422 (M^+). *Anal.* Calcd for $C_{21}H_{18}ClF_3N_2O_2$ (422.82): C, 59.65; H, 4.29; N, 6.63. Found: C, 59.83; H, 4.57; N, 6.52.

2-Cyano-*N*-(3,4-dimethoxyphenyl)-3-methyl-5-oxo-5-phenylpentanamide (**3j**): Yield: 83%, mp 224 °C; IR (KBr) cm^{-1}: 3302, 2220, 1720, 1678, 1610, 1522. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.22 (3H, d, CH_3), 3.52 (1H, dd, upfield H of $\underline{CH_2}$CH, J=5.6, 17.4 Hz), 3.79 (1H, dd, downfield H of $\underline{CH_2}$CH, J=8.5, 17.4 Hz), 3.89 (6H, s, OCH_3), 4.23 (1H, m, CH), 4.31 (1H, d, CH), 7.23—7.86 (8H, m, Ar-H), 10.12 (1H, s, br, NH). EI-MS *m*/*z*: 366 (M^+). *Anal.* Calcd for $C_{21}H_{22}N_2O_4$ (366.41): C, 68.84; H, 6.05; N, 7.65. Found: C, 68.62; H, 6.17; N, 7.73.

Synthesis of 2-Bromo-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamide (4a—j) To a solution of the appropriate **3a**—**j** (10 mmol) in glacial acetic acid (30 ml), heated at 70—80 °C, a solution of bromine (11 mmol) in glacial acetic acid (10 ml) was added dropwise while stirring, at such a rate maintaining the same temperature for 30 min. After complete addition, stirring was continued for 4 h at the same temperature. The separated solid was collected and purified by column chromatography using silica gel (60—120 mesh) and the desired product was eluted with ethyl acetate–*n*-hexane as mobile phase.

2-Bromo-*N*-(4-chlorophenyl)-6-phenyl-4-(trifluoromethyl)nicotinamide (**4a**): Yield: 81%, mp 220 °C; IR (KBr) cm^{-1}: 3272, 3246, 1658, 1600, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.12—7.52 (7H, m, Ar-H), 8.16—8.18 (2H, m, Ar-H), 8.84 (1H, s, pyr. H-5), 10.62 (1H, s, br, NH). EI-MS *m*/*z*: 458 (M^++4), 456 (M^++2), 454 (M^+). *Anal.* Calcd for $C_{19}H_{11}BrClF_3N_2O$ (455.65): C, 50.08; H, 2.43; N, 6.15. Found: C, 50.23; H, 2.21; N, 6.22.

2-Bromo-*N*-(4-iodophenyl)-4-methyl-6-phenylnicotinamide (**4b**): Yield: 88%, mp 205 °C; IR (KBr) cm^{-1}: 3278, 1660, 1602, 1539. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.23 (3H, s, CH_3), 7.13—7.54 (7H, m, Ar-H), 7.74 (1H, s, pyr. H-5), 8.14—8.19 (2H, m, Ar-H), 10.43 (1H, s, br, NH). EI-MS *m*/*z*: 494(M^++2), 492 (M^+). *Anal.* Calcd for $C_{19}H_{14}BrIN_2O$ (493.13): C, 50.08; H, 2.43; N, 6.15. Found: C, 50.21; H, 2.24; N, 6.22.

2-Bromo-6-(4-chlorophenyl)-*N*-(4-fluorophenyl)-4-(trifluoromethyl)-nicotinamide (**4c**): Yield; 82%, mp 212 °C; IR (KBr) cm^{-1}: 3280, 1662, 1602, 1540. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 6.96 (2H, d, J=8.4 Hz, Ar-H), 7.43 (2H, d, J=8.4 Hz, Ar-H), 7.76 (2H, d, J=8.4 Hz, Ar-H), 8.02 (2H, d, J=8.3 Hz, Ar-H), 8.79 (1H, s, pyr. H-5), 10.41 (1H, s, br, NH). EI-MS *m*/*z*: 476 (M^++4), 474 (M^++2), 472 (M^+). *Anal.* Calcd for $C_{19}H_{10}BrClF_4N_2O$ (473.64): C, 48.18; H, 2.13; N, 5.91. Found: C, 48.23; H, 2.21; N, 5.74.

2-Bromo-6-(4-chlorophenyl)-*N*-*p*-tolyl-4-(trifluoromethyl)nicotinamide (**4d**): Yield: 78%, mp 194 °C; IR (KBr) cm^{-1}: 3284, 1660, 1612, 1540. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.14 (3H, s, CH_3), 7.21—7.37 (4H, m, Ar-H), 7.54 (2H, d, J=8.3 Hz, Ar-H), 7.96 (2H, d, J=8.5 Hz, Ar-H), 8.81 (1H, s, pyr. H-5), 10.41 (1H, s, br, NH). EI-MS *m*/*z*: 472 (M^+++4), 470 (M^++2), 468 (M^+). *Anal.* Calcd for $C_{20}H_{13}BrClF_3N_2O$ (469.68): C, 51.14; H, 2.79; N, 5.96. Found: C, 50.96; H, 2.83; N, 5.84.

2-Bromo-6-phenyl-4-(trifluoromethyl)-*N*-[4-(trifluoromethyl)phenyl]-nicotinamide (**4e**): Yield: 91%, mp 199 °C; IR (KBr) cm^{-1}: 3270, 3240, 1660, 1600, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.22—7.46 (7H, m, Ar-H), 8.26—8.29 (2H, m, Ar-H), 8.83 (1H, s, pyr. H-5), 10.54 (1H, s, br, NH). EI-MS *m*/*z*: 490 (M^++2), 488 (M^+). *Anal.* Calcd for $C_{20}H_{11}BrF_6N_2O$ (489.21): C, 49.10; H, 2.27; N, 5.73. Found: C, 49.23; H, 1.98; N, 5.82.

2-Bromo-6-(4-chlorophenyl)-*N*-(2-methoxyphenyl)-4-(trifluoromethyl)-nicotinamide (**4f**): Yield: 73%, mp 224 °C; IR (KBr) cm^{-1}: 3272, 3242, 1662, 1600, 1544. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.26 (3H, s, OCH_3), 7.16 (2H, m, Ar-H), 7.24 (1H, dd, J=1.8, 7.9 Hz, Ar-H), 7.42 (1H, dd, J=4.5, 7.8 Hz, Ar-H), 7.53 (2H, d, J=8.4 Hz, Ar-H), 7.96 (2H, d, J=8.4 Hz, Ar-H), 8.81 (1H, s, pyr. H-5), 10.46 (1H, s, br, NH). EI-MS *m*/*z*: 488 (M^++4), 486 (M^++2), 484 (M^+). *Anal.* Calcd for $C_{20}H_{13}BrClF_3N_2O_2$ (485.68): C, 49.46; H, 2.70; N, 5.77. Found: C, 49.55; H, 2.79; N, 5.82.

2-Bromo-*N*-[4-(methylthio)phenyl]-6-phenyl-4-(trifluoromethyl)nicotinamide (**4g**): Yield: 86%, mp 206 °C; IR (KBr) cm^{-1}: 3270, 3240, 1660, 1600, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.42 (3H, s, SCH_3), 7.23—7.45 (7H, m, Ar-H), 8.26—8.29 (2H, m, Ar-H), 8.81 (1H, s, pyr. H-5), 10.52 (1H, s, br, NH). EI-MS *m*/*z*: 470 (M^++4), 468 (M^++2), 466 (M^+). *Anal.* Calcd for $C_{20}H_{14}BrF_3N_2OS$ (467.30): C, 51.40; H, 3.02; N, 5.99. Found: C, 51.23; H, 3.06; N, 6.34.

2-Bromo-4-methyl-6-phenyl-*N*-o-tolylnicotinamide (**4h**): Yield: 83%, mp 224 °C; IR (KBr) cm^{-1}: 3274, 1662, 1602, 1540. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.13 (3H, s, CH_3), 2.22 (3H, s, CH_3), 7.13—7.54 (9H, m, Ar-H), 7.74 (1H, s, pyr. H-5), 10.43 (1H, s, br, NH). EI-MS *m*/*z*: 384 (M^++4), 382 (M^++2), 380 (M^+). *Anal.* Calcd for $C_{20}H_{17}BrN_2O$ (381.26): C, 63.00; H, 4.49; N, 7.35. Found: C, 63.33; H, 4.25; N, 7.69.

2-Bromo-6-(4-chlorophenyl)-*N*-(3,5-dimethylphenyl)-4-(trifluoromethyl)-nicotinamide (**4i**): Yield: 79%, mp 194 °C; IR (KBr) cm^{-1}: 3280, 1664, 1610, 1540. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.24 (6H, s, CH_3), 7.22—7.39 (3H, m, Ar-H), 7.54 (2H, d, J=8.3 Hz, Ar-H), 7.96 (2H, d, J=8.5 Hz, Ar-H), 8.81 (1H, s, pyr. H-5), 10.41 (1H, s, NH). EI-MS *m*/*z*: 486 (M^++4), 484 (M^++2), 482 (M^+). *Anal.* Calcd for $C_{21}H_{15}BrClF_3N_2O$ (483.71): C, 52.14; H, 3.13; N, 5.79. Found: C, 52.36; H, 3.23; N, 5.66.

2-Bromo-*N*-(3,4-dimethoxyphenyl)-4-methyl-6-phenylnicotinamide (**4j**): Yield: 85%, mp 214 °C; IR (KBr) cm^{-1}: 3274, 1662, 1602, 1540. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.14 (3H, s, CH_3), 3.82 (6H, s, OCH_3),6.98—7.02 (3H, m, Ar-H), 7.39—7.44 (5H, m, Ar-H), 7.72 (1H, s, pyr. H-5), 10.40 (1H, s, br, NH). EI-MS *m*/*z*: 430 (M^++4), 428 (M^++2), 426 (M^+). *Anal.* Calcd for $C_{21}H_{19}BrN_2O_3$ (427.29): C, 57.98; H, 4.38; N, 6.76. Found: C, 57.84; H, 4.25; N, 6.83.

Synthesis of 2-Amino-*N*,6-substituted phenyl-4-(trifluoromethyl or methyl)nicotinamide 5a—j and *N*,6-substituted phenyl-2-(phenylamino)-4-(trifluoromethyl or methyl)nicotinamide 6a—j. Method A Solution of **4a**—**j** (10 mmol) and primary aromatic amine (aniline) (20 mmol) in pyridine (40 ml) was boiled under reflux for 3 d. The solid sep-

arated upon pouring the reaction mixture into water (400 ml) and acidification with dil HCl (5%), was collected and washed with water. Then, it was purified by column chromatography using silica gel (60—120 mesh) and the desired product was eluted with ethyl acetate–*n*-hexane as mobile phase. The resulted products were characterized as **5a**—**j** and **6a**—**j**.

Method B A mixture of 2-amino-4,6-substituted nicotinic acid (10 mmol), substituted arylamine (10 mmol), *N*-hydroxybenzotriazole (HOBt, 4 mmol) and EDC (12 mmol) in freshly distilled DCM (80 ml) was allowed to stir at room temperature for 24 h. The reaction mixture was successively washed with water (20 ml), 10% NaOH (20 ml), water (20 ml), brine (20 ml) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to get dryness and the product was purified by column chromatography using ethyl acetate–*n*-hexane as mobile phase.

2-Amino-*N*-(4-chlorophenyl)-6-phenyl-4-(trifluoromethyl) nicotinamide (**5a**): Yield: method A: 28% and method B: 65%, mp 189 °C; IR (KBr) cm^{-1}: 3490, 3393, 3249, 1650, 1600, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 6.18 (2H, s, br, NH_2), 7.23—7.56 (7H, m, Ar-H), 8.10—8.16 (2H, m, Ar-H), 8.81 (1H, s, pyr. H-5), 10.32 (1H s, br, NH). EI-MS *m*/*z*: 393 (M^++2), 391 (M^+). *Anal.* Calcd for $C_{19}H_{13}ClF_3N_3O$ (391.77): C, 58.25; H, 3.34; N, 10.73. Found: C, 58.32; H, 3.28; N, 10.89.

2-Amino-*N*-(4-iodophenyl)-4-methyl-6-phenylnicotinamide (**5b**): Yield: method A: 25% and method B: 57%, mp 176 °C; IR (KBr) cm^{-1}: 3486, 3390, 3250, 1653, 1603, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.19 (3H, s, CH_3), 6.20 (2H, s, br, NH_2), 7.15—7.94 (7H, m, Ar-H), 7.72 (1H, s, pyr. H-5), 8.15—8.21 (2H, m, Ar-H), 10.38 (1H, s, br, NH). EI-MS *m*/*z*: 431 (M^++2), 429 (M^+). *Anal.* Calcd for $C_{19}H_{16}IN_3O$ (429.25): C, 53.16; H, 3.76; N, 9.79. Found: C, 53.27; H, 3.92; N, 9.91.

2-Amino-6-(4-chlorophenyl)-*N*-(4-fluorophenyl)-4-(trifluoromethyl)nicotinamide (**5c**): Yield: method A: 39% and method B: 68%, mp 212 °C; IR (KBr) cm^{-1}: 3491, 3386, 3252, 1646, 1599, 1538. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 6.22 (2H, s, br, NH_2), 6.89 (2H, d, J=8.5 Hz, Ar-H), 7.40 (2H, d, J=8.3 Hz, Ar-H), 7.73 (2H, d, J=8.3 Hz, Ar-H), 8.08 (2H, d, J=8.3 Hz, Ar-H), 8.81 (1H, s, pyr. H-5), 10.38 (1H, s, br, NH). EI-MS *m*/*z*: 411 (M^++2), 409 (M^+). *Anal.* Calcd for $C_{19}H_{12}ClF_4N_3O$ (409.76): C, 55.69; H, 2.95; N, 10.25. Found: C, 55.86; H, 2.98; N, 10.58.

2-Amino-6-(4-chlorophenyl)-*N*-*p*-tolyl-4-(trifluoromethyl)nicotinamide (**5d**): Yield: method A: 36% and method B: 65%, mp 220 °C; IR (KBr) cm^{-1}: 3494, 3381, 3262, 1649, 1597, 1541. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.12 (3H, s, CH_3), 6.24 (2H, s, br, NH_2), 7.19—7.42 (4H, m, Ar-H), 7.51 (2H, d, J=8.4 Hz, Ar-H), 7.94 (2H, d, J=8.5 Hz, Ar-H), 8.80 (1H, s, pyr. H-5), 10.31 (1H, s, br, NH). EI-MS *m*/*z*: 407 (M^++2), 405 (M^+). *Anal.* Calcd for $C_{20}H_{15}ClF_3N_3O$ (405.80): C, 59.20; H, 3.73; N, 10.35. Found: C, 59.43; H, 3.64; N, 10.59.

2-Amino-6-phenyl-4-(trifluoromethyl)-*N*-[4-(trifluoromethyl)phenyl]-nicotinamide (**5e**): Yield: method A: 32% and method B: 72%, mp 208 °C; IR (KBr) cm^{-1}: 3490, 3378, 3260, 1653, 1599, 1544. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 6.21 (2H, s, br, NH_2), 7.21—7.49 (7H, m, Ar-H), 8.23—8.26 (2H, m, Ar-H), 8.81 (1H, s, pyr. H-5), 10.31 (1H, s, br, NH). EI-MS *m*/*z*: 425 (M^+). *Anal.* Calcd for $C_{20}H_{13}F_6N_3O$ (425.32): C, 56.43; H, 3.08; N, 9.88. Found: C, 56.29; H, 2.94; N, 9.98.

2-Amino-6-(4-chlorophenyl)-*N*-(2-methoxyphenyl)-4-(trifluoromethyl)-nicotinamide (**5f**): Yield: method A: 36% and method B: 69%, mp 202 °C; IR (KBr) cm^{-1}: 3494, 3382, 3262, 1646, 1602, 1542. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.26 (3H, s, OCH_3), 6.23 (2H, s, br, NH_2), 7.14 (2H, m, Ar-H), 7.26 (1H, dd, J=1.6, 7.8 Hz, Ar-H), 7.41 (1H, dd, J=4.6, 7.6 Hz, Ar-H), 7.55 (2H, d, J=8.5 Hz, Ar-H), 7.93 (2H, d, J=8.3Hz, Ar-H), 8.80 (1H, s, pyr. H-5), 10.31 (1H, s, br, NH); EI-MS *m*/*z*: 423 (M^++2), 421 (M^+). *Anal.* Calcd for $C_{20}H_{15}ClF_3N_3O_2$ (421.8): C, 56.95; H, 3.58; N, 9.96. Found: C, 57.15; H, 3.72; N, 9.88.

2-Amino-*N*-[4-(methylthio)phenyl]-6-phenyl-4-(trifluoromethyl)nicotinamide (**5g**): Yield: method A: 27% and method B: 69%, mp 181 °C; IR (KBr) cm^{-1}: 3492, 3378, 3260, 2250,1650, 1602, 1541. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.39 (3H, s, SCH_3), 6.15 (2H, s, br, NH_2), 7.22—7.45 (7H m, Ar-H), 8.22—8.28 (2H, m, Ar-H), 8.78 (1H, s, pyr. H-5), 10.30 (1H, s, br, NH). EI-MS *m*/*z*: 405 (M^++2), 403 (M^+). *Anal.* Calcd for $C_{20}H_{16}F_3N_3OS$ (403.42): C, 59.54; H, 4.00; N, 10.42. Found: C, 59.24; H, 4.26; N, 10.22.

2-Amino-4-methyl-6-phenyl-*N*-o-tolyl nicotinamide (**5h**): Yield: method A: 37% and method B: 52%, mp 172 °C; IR (KBr) cm^{-1}: 3498, 3382, 3256, 1648, 1602, 1546. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.96 (3H, s, CH_3), 2.19 (3H, s, CH_3), 6.18 (2H, s, br, NH_2), 7.15—7.54 (9H, m, Ar-H), 7.69 (1H, s, pyr. H-5), 10.29 (1H, s, br, NH). EI-MS *m*/*z*: 317 (M^+). *Anal.* Calcd for $C_{20}H_{19}N_3O$ (317.38): C, 75.69; H, 6.03; N, 13.24. Found: C, 75.61; H, 6.29; N, 13.12.

2-Amino-6-(4-chlorophenyl)-*N*-(3,5-dimethylphenyl)-4-(trifluoromethyl)-nicotinamide (**5i**): Yield: method A: 30% and method B: 50%, mp 218 °C; IR (KBr) cm^{-1}: 3498, 3382, 3256, 1648, 1602, 1546. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.21 (6H, s, CH_3), 6.16 (2H, s, br, NH_2), 7.22—7.41 (3H, m, Ar-H), 7.53 (2H, d, J=8.3 Hz, Ar-H), 7.94 (2H, d, J=8.5 Hz, Ar-H), 8.80 (1H, s, pyr. H-5), 10.32 (1H, s, br, NH). EI-MS *m*/*z*: 421 (M^++2), 419(M^+). *Anal.* Calcd for $C_{21}H_{17}ClF_3N_3O$ (419.82): C, 60.08; H, 4.08; N, 10.01. Found: C, 60.21; H, 4.28; N, 10.06.

2-Amino-*N*-(3,4-dimethoxyphenyl)-4-methyl-6-phenylnicotinamide (**5j**): Yield: method A: 38% and method B: 70%, mp 172 °C; IR (KBr) cm^{-1}: 3498, 3382, 3256, 1648, 1602, 1546. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.12 (3H, s, CH_3), 3.84 (6H, s, OCH_3), 6.19 (2H, s, br, NH_2), 6.98—7.27 (3H, m, Ar-H), 7.39—7.44 (5H, m, Ar-H), 7.72 (1H, s, pyr. H-5), 10.40 (1H, s, br, NH). EI-MS *m*/*z*: 363 (M^+). *Anal.* Calcd for $C_{21}H_{21}N_3O_3$ (363.41): C, 69.41; H, 5.82; N,11.56. Found: C, 69.64; H, 5.75; N, 11.43.

N-(4-Chlorophenyl)-6-phenyl-2-(phenylamino)-4-(trifluoromethyl)nicotinamide (**6a**): Yield: 68%, mp 198 °C; IR (KBr) cm^{-1}: 3390, 1662, 1610, 1551, 1270, 710. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.18—7.52 (12H, m, Ar-H), 8.12—8.18 (2H, m, Ar-H), 8.83 (1H, s, pyr. H-5), 9. 43 (2H, s, NH). EI-MS *m*/*z*: 469 (M^++2), 467 (M^+). *Anal.* Calcd for $C_{25}H_{17}ClF_3N_3O$ (467.87): C, 64.18; H, 3.66; N, 8.98. Found: C, 64.42; H, 3.58; N, 8.84.

N-(4-Iodophenyl)-4-methyl-6-phenyl-2-(phenylamino)nicotinamide (**6b**): Yield: 74%, mp 194 °C; IR (KBr) cm^{-1}: 3384, 1653, 1614, 1555, 1265, 705. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.22 (3H, s, CH_3), 7.19—7.94 (12H, m, Ar-H), 7.74 (1H, s, pyr. H-5), 8.15—8.21 (2H, m, Ar-H), 9.42 (2H, s, NH). EI-MS *m*/*z*: 505 (M^+). *Anal.* Calcd for $C_{25}H_{20}IN_3O$ (505.35): C, 59.42; H, 3.99; N, 8.32. Found: C, 59.24; H, 3.82; N, 8.29.

6-(4-Chlorophenyl)-*N*-(4-fluorophenyl)-2-(phenylamino)-4-(trifluoromethyl)nicotinamide (**6c**): Yield: 50%, mp 230 °C; IR (KBr) cm^{-1}: 3384, 1653, 1614, 1555, 1265, 705. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 6.86 (2H, d, J=8.5 Hz, Ar-H), 7.21—7.24 (5H, m, Ar-H), 7.40 (2H, d, J=8.3 Hz, Ar-H), 7.73 (2H, d, J=8.3 Hz, Ar-H), 8.09 (2H, d, J=8.3 Hz, Ar-H), 8.82 (1H, s, pyr. H-5), 9.46 (2H, s, NH). EI-MS *m*/*z*: 487 (M^++2), 485 (M^+). *Anal.* Calcd for $C_{25}H_{16}ClF_4N_3O$ (485.86): C, 61.80; H, 3.32; N, 8.65. Found: C, 61.96; H, 3.21; N, 8.52.

6-(4-Chlorophenyl)-2-(phenylamino)-*N*-*p*-tolyl-4-(trifluoromethyl)nicotinamide (**6d**): Yield: 62%, mp 236 °C; IR (KBr) cm^{-1}: 3360, 1663, 1614, 1555, 1254, 712. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.14 (3H, s, CH_3), 7.19—7.42 (9H, m, Ar-H), 7.51 (2H, d, J=8.4 Hz, Ar-H), 7.94 (2H, d, J=8.5 Hz, Ar-H), 8.80 (1H, s, pyr. H-5), 9.43 (2H, s, NH). EI-MS *m*/*z*: 483 (M^++2), 481 (M^+). *Anal.* Calcd for $C_{26}H_{19}ClF_3N_3O$ (481.89): C, 64.80; H, 3.97; N, 8.72. Found: C, 64.82; H, 4.13; N, 8.62.

6-Phenyl-2-(phenylamino)-4-(trifluoromethyl)-*N*-[4-(trifluoromethyl)-phenyl]nicotinamide (**6e**): Yield: 62%, mp 224 °C; IR (KBr) cm^{-1} : 3362, 1672, 1621, 1552, 1250, 710. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.19—7.49 (12H, m, Ar-H), 8.21—8.28 (2H, m, Ar-H), 8.79 (1H, s, pyr. H-5), 9.45 (2H, s, NH). EI-MS *m*/*z*: 501 (M^+). *Anal.* Calcd for $C_{26}H_{17}F_6N_3O$ (501.42): C, 62.28; H, 3.42; N, 8.38 Found: C, 62.41; H, 3.54; N, 8.18.

6-(4-Chlorophenyl)-*N*-(2-methoxyphenyl)-2-(phenylamino)-4-(trifluoromethyl)nicotinamide (**6f**): Yield: 60%, mp 218 °C; IR (KBr) cm^{-1}: 3352, 1668, 1612, 1552, 1258, 706. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.27 (3H, s, OCH_3), 7.14—7.19 (7H, m, Ar-H), 7.25 (1H, dd, J=1.6, 7.8 Hz, Ar-H), 7.40 (1H, dd, J=4.6, 7.6 Hz, Ar-H), 7.54 (2H, d, J=8.5 Hz, Ar-H), 7.91 (2H, d, J=8.3Hz, Ar-H), 8.79 (1H, s, pyr. H-5), 9.59 (2H, s, NH). EI-MS *m*/*z*: 499 (M^++2), 497 (M^+). *Anal.* Calcd for $C_{26}H_{19}ClF_3N_3O_2$ (497.89): C, 62.72; H, 3.85; N, 8.44. Found: C, 62.62; H, 3.72; N, 8.26.

N-[4-(Methylthio)phenyl]-6-phenyl-2-(phenylamino)-4-(trifluoromethyl)-nicotinamide (**6g**): Yield: 71%, mp 210 °C; IR (KBr) cm^{-1}: 3352, 2254, 1668, 1612, 1552, 1258. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.37 (3H, s, SCH_3), 7.19—7.45 (12H, m, Ar-H), 8.22—8.28 (2H, m, Ar-H), 8.76 (1H, s, pyr. H-5), 9.46 (2H, s, NH). EI-MS *m*/*z*: 481 (M^++2), 479 (M^+). *Anal.* Calcd for $C_{26}H_{20}F_3N_3OS$ (479.51): C, 65.12; H, 4.20; N, 8.76. Found: C, 65.33; H, 4.51; N, 8.81.

2-Amino-4-methyl-6-phenyl-*N*-o-tolyl nicotinamide (**6h**): Yield: 61%, mp 184 °C; IR (KBr) cm^{-1}: 3364, 1671, 1622, 1555. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.24 (3H, s, CH_3), 2.22 (3H, s, CH_3), 7.15—7.54 (14H, m, Ar-H), 7.65 (1H, s, pyr. H-5), 9.49 (2H, s, NH). EI-MS *m*/*z*: 393 (M^+). *Anal.* Calcd for $C_{26}H_{23}N_3O$ (393.48): C, 79.36; H, 5.89; N, 10.68. Found: C, 79.49; H, 6.01; N, 10.41.

2-Amino-6-(4-chlorophenyl)-*N*-(3,5-dimethylphenyl)-4-(trifluoromethyl)-nicotinamide (**6i**): Yield: 69%, mp 221 °C; IR (KBr) cm^{-1}: 3362, 1659, 1625, 1555, 1268, 752. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.19 (6H, s, CH_3), 7.24—7.41 (8H, m, Ar-H), 7.53 (2H, d, J=8.3 Hz, Ar-H), 7.93 (2H, d, J=8.5 Hz, Ar-H), 8.79 (1H, s, pyr. H-5), 9.41 (2H, s, NH). EI-MS *m*/*z*: 497 (M^++2), 495(M^+). *Anal.* Calcd for $C_{27}H_{21}ClF_3N_3O$ (495.92): C, 65.39; H,

4.27; N, 8.47. Found: C, 65.54; H, 4.58; N, 8.69.

2-Amino-*N*-(3,4-dimethoxyphenyl)-4-methyl-6-phenylnicotinamide (**6j**): Yield: 60%, mp 202 °C; IR (KBr) : 3352, 1675, 1622, 1555 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.14 (3H, s, CH_3), 3.85 (6H, s, OCH_3), 6.98—7.27 (3H, m, Ar-H), 7.39—7.44 (10H, m, Ar-H), 7.72 (1H, s, pyr. H-5), 9.42 (2H, s, NH). EI-MS *m*/*z*: 439 (M^+). *Anal.* Calcd for $C_{27}H_{25}N_3O_3$ (439.50): C, 73.78; H, 5.73; N, 9.56. Found: C, 73.52; H, 5.83; N, 9.67.

2,3,7-Substituted-5-(trifluoromethyl or mrthyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one. General Procedure To a solution or slurry of the substituted 2-aminonicotinamide (10 mmol) in triethylorthopropionate (80 mmol) [or triethyl orthoacetaqte (80 mmol) in case of **k**—**p**] was added glacial acetic acid (20 mmol). The mixture was heated to 90 °C for 7 h at which time the HPLC analysis revealed full consumption of starting material. The mixture was diluted with aq 1 M HCl (10 ml) and stirred for 20 min. The reaction mixture was made basic by the addition of concd NH_4OH and extracted with dichloromethane (5×15 ml). The organic layers were combined, dried, filtered and concentrated *in vacuo*. Silica gel chromatography of the crude material (hexane–ethylacetate, 30 : 70) afforded the desired substituted pyrido[2,3-*d*]pyrimidines.

3-[4-Chlorophenyl]-2-ethyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7a**): Yield: 80%, mp 331 °C; IR (KBr) cm^{-1}: 3070, 2996, 1678, 1600, 1425, 1270, 750. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.24 (3H, t, J=7.6 Hz, CH_3), 2.42 (2H, q, J=8.5 Hz, CH_2), 7.24 (5H, m, Ar-H), 7.44 (2H, d, J=8.6 Hz, Ar-H), 7.98 (2H, d, J=8.6 Hz, Ar-H), 8.92 (1H, s, H-6). EI-MS *m*/*z*: 431 (M^++2), 429 (M^+). *Anal.* Calcd for $C_{22}H_{15}ClF_3N_3O$ (429.82): C, 61.48; H, 3.52; N, 9.78. Found: C, 61.72; H, 3.22; N, 9.94.

2-Ethyl-3-[4-iodophenyl]-5-methyl-7-phenyl pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7b**): Yield: 78%, mp 315 °C; IR (KBr) cm^{-1}: 3062, 2986, 1674, 1606, 1432. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.26 (3H, t, J=7.4 Hz, CH_3), 1.92 (3H, s, CH_3), 2.88 (2H, q, J=8.2 Hz, CH_2), 7.26 (5H, m, Ar-H), 7.42 (2H, d, J=8.4 Hz, Ar-H), 7.81 (1H, s, H-6), 7.98 (2H, d, J=8.2 Hz, Ar-H). EI-MS *m*/*z*: 467 (M^+). *Anal.* Calcd for $C_{22}H_{18}IN_3O$ (467.05): C, 56.54; H, 3.88; N, 8.99. Found: C, 56.72; H, 3.84; N, 9.06.

7-(4-Chlorophenyl)-2-ethyl-3-(4-fluorophenyl)-5-(trifluoromethyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7c**): Yield: 92%, mp 306 °C; IR (KBr) cm^{-1}: 3068, 2998, 1675, 1603, 1422, 1268, 768. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.19 (3H, t, J=7.8 Hz, CH_3), 2.52 (2H, q, J=8.3 Hz, CH_2), 6.98 (2H, d, J=8.5 Hz, Ar-H), 7.42 (2H, d, J=8.3 Hz, Ar-H), 7.78 (2H, d, J=8.5 Hz, Ar-H), 8.02 (2H, d, J=8.3 Hz, Ar-H), 8.82 (1H, s, H-6). EI-MS *m*/*z*: 449 (M^++2), 447 (M^+). *Anal.* Calcd for $C_{22}H_{14}ClF_4N_3O$ (447.08): C, 59.01; H, 3.15; N, 9.38. Found: C, 59.08; H, 3.22; N, 9.56.

7-(4-Chlorophenyl)-2-ethyl-3-*p*-tolyl-5-(trifluoromethyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7d**): Yield: 94%, mp 312 °C; IR (KBr) cm^{-1}: 3068, 2988, 1678, 1603, 1422, 1269, 778. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.22 (3H, t, J=7.6 Hz, CH_3), 1.56 (3H, s, CH_3), 2.42 (2H, q, J=8.5 Hz, CH_2), 7.24—7.36 (4H, m, Ar-H), 7.52 (2H, d, J=8.3 Hz, Ar-H), 7.98 (2H, d, J=8.5 Hz, Ar-H), 8.79 (1H, s, H-6). EI-MS *m*/*z*: 445 (M^++2), 443 (M^+). *Anal.* Calcd for $C_{23}H_{17}ClF_3N_3O$ (443.1): C, 62.24; H, 3.86; N, 9.47. Found: C, 62.48; H, 4.04; N, 9.56.

2-Ethyl-7-phenyl-5-(trifluoromethyl)-3-[4-(trifluoromethyl)phenyl]-pyrido[2,3-*d*]pyrimidin-4[3*H*]-one (**7e**): Yield: 86%, mp 321 °C; IR (KBr) cm^{-1}: 3068, 2990, 1676, 1603, 1422, 1270, 778. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.22 (3H, t, J=7.6 Hz, CH_3), 2.42 (2H, q, J=8.5 Hz, CH_2), 7.24—7.28 (3H, m, Ar-H), 7.52 (2H, d, J=8.6 Hz, Ar-H), 7.72 (2H, d, J=8.6 Hz, Ar-H), 7.98 (2H, d, J=8.5 Hz, Ar-H), 8.81 (1H, s, H-6). EI-MS *m*/*z*: 465 (M^++2), 463 (M^+). *Anal.* Calcd for $C_{23}H_{15}ClF_6N_3O$ (463.11): C, 59.62; H, 3.26; N, 9.07. Found: C, 59.83; H, 3.24; N, 9.26.

7-(4-Chlorophenyl)-2-ethyl-3-(2-methoxyphenyl)-5-(trifluoromethyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7f**): Yield: 75%, mp 290 °C; IR (KBr) cm^{-1}: 2978, 2844, 1678, 1586, 1492, 1248, 788. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.30 (3H, t, J=7.3 Hz, CH_3), 2.45 (2H, q, J=8.4 Hz, CH_2), 3.76 (3H, s, OCH_3), 7.14 (2H, m, Ar-H), 7.22 (1H, dd, J=1.8, 7.9 Hz, Ar-H), 7.44 (1H, dd, J=4.5, 7.8 Hz, Ar-H), 7.52 (2H, d, J=8.4 Hz, Ar-H), 7.98 (2H, d, J=8.4 Hz, Ar-H), 8.82 (1H, s, H-6). EI-MS *m*/*z*: 461 (M^++2), 459 (M^+). *Anal.* Calcd for $C_{23}H_{17}ClF_3N_3O_2$ (459.1): C, 60.07; H, 3.73; N, 9.14. Found: C, 59.88; H, 4.04; N, 9.22.

2-Ethyl-3[4-(methylthio)phenyl]-7-phenyl-5-(trifluoromethyl)pyrido[2,3-*d*]pyrimidin-4[3*H*]-one (**7g**): Yield: 79%, mp 318 °C; IR (KBr) cm^{-1}: 3060, 2990, 2254, 1686, 1574, 1422, 1270, 708. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.22 (3H, t, J=7.6 Hz, CH_3), 2.22 (2H, q, J=8.5 Hz, CH_2), 2.56 (3H, s, SCH_3), 7.12 (2H, d, J=8.4 Hz, Ar-H), 7.24—7.31 (3H, m, Ar-H), 7.52 (2H, d, J=8.5 Hz, Ar-H), 7.98 (2H, d, J=8.5 Hz, Ar-H), 8.82 (1H, s, H-6). EI-MS *m*/*z*: 442 (M^++2), 441 (M^+). *Anal.* Calcd for $C_{23}H_{18}ClF_3N_3O$ S (441.11): C, 62.57; H, 4.11; N, 9.52. Found: C, 62.42; H, 3.92; N, 9.68.

2-Ethyl-5-methyl-7-phenyl-3-o-tolyl pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7h**): Yield: 82%, mp 280 °C; IR (KBr) cm^{-1}: 3054, 2978, 1681, 1586, 1492, 1248, 788. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.19 (3H, t, J=7.4 Hz, CH_3), 2.16 (3H, s, CH_3), 2.22 (2H, q, J=8.4 Hz, CH_2), 2.49 (3H, s, CH_3), 7.24—7.44 (9H, m, Ar-H), 7.82 (1H, s, H-6). EI-MS *m*/*z*: 355 (M^+). *Anal.* Calcd for $C_{23}H_{21}N_3O$ (355.17): C, 77.77; H, 5.96; N, 11.82. Found: C, 77.94; H, 5.84; N, 12.02.

7-(4-Chlorophenyl)-3-(3,5-dimethylphenyl)-2-ethyl-5-(trifluoromethyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7i**): Yield: 92%, mp 288 °C; IR (KBr) cm^{-1}: 3068, 2988, 1683, 1603, 1422, 1270, 708. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.21 (3H, t, J=7.3 Hz, CH_3), 2.15 (6H, s, CH_3), 2.32 (2H, q, J=8.4 Hz, CH_2), 7.07 (2H, s, Ar-H), 7.18 (1H, s, Ar-H), 7.42 (2H, d, J=8.5 Hz, Ar-H), 7.98 (2H, d, J=8.5 Hz, Ar-H), 8.82 (1H, s, H-6). EI-MS *m*/*z*: 459(M^++2), 457 (M^+). *Anal.* Calcd for $C_{24}H_{19}ClF_3N_3O$ (457.88): C, 62.96; H, 4.18; N, 9.18. Found: C, 63.25; H, 3.94; N, 8.92.

3-(3,4-Dimethoxyphenyl)-2-ethyl-5-methyl-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7j**): Yield: 84%, mp 296 °C; IR (KBr) cm^{-1}: 2978, 2844, 1681, 1586, 1492. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.21 (3H, t, J=7.5 Hz, CH_3), 1.99 (3H, s, CH_3), 2.20 (2H, q, J=8.3 Hz, CH_2), 3.86 (6H, s, OCH_3), 6.98—7.02 (3H, m, Ar-H), 7.39—7.44 (5H, m, Ar-H), 7.80 (1H, s, H-6). EI-MS *m*/*z*: 401 (M^+). *Anal.* Calcd for $C_{24}H_{23}N_3O_3$ (401.17): C, 71.80; H, 5.77; N, 10.47. Found: C, 71.94; H, 5.54; N, 10.39.

7-(4-Chlorophenyl)-3-(4-fluorophenyl)-2-methyl-5-(trifluoromethyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7k**): Yield: 90%, mp 300 °C; IR (KBr) cm^{-1}: 3068, 2998, 1675, 1603, 1422, 1270, 768. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.19 (3H, s, CH_3), 6.98 (2H, d, J=8.5 Hz, Ar-H), 7.42 (2H, d, J=8.3 Hz, Ar-H), 7.78 (2H, d, J=8.5 Hz, Ar-H), 8.02 (2H, d, J=8.3 Hz, Ar-H), 8.82 (1H, s, H-6). EI-MS *m*/*z*: 435 (M^++2), 433 (M^+). *Anal.* Calcd for $C_{21}H_{12}ClF_4N_3O$ (433.06): C, 58.14; H, 2.79; N, 9.69. Found: C, 58.28; H, 2.83; N, 9.56.

7-(4-Chlorophenyl)-2-methyl-3-*p*-tolyl-5-(trifluoromethyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7l**): Yield: 96%, mp 310 °C; IR (KBr) cm^{-1}: 3068, 2988, 1678, 1603, 1422, 1270, 778. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.12 (3H, s, CH_3), 2.26 (3H, s, CH_3), 7.24—7.36 (4H, m, Ar-H), 7.52 (2H, d, J=8.3 Hz, Ar-H), 7.98 (2H, d, J=8.5 Hz, Ar-H), 8.79 (1H, s, H-6). EI-MS *m*/*z*: 431 (M^++2), 429 (M^+). *Anal.* Calcd for $C_{22}H_{15}ClF_3N_3O$ (429.09): C, 61.48; H, 3.52; N, 9.78. Found: C, 61.66; H, 3.44; N, 9.62.

7-(4-Chlorophenyl)-3-(2-methoxyphenyl)-2-methyl-5-(trifluoromethyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7m**): Yield: 81%, mp 282 °C; IR (KBr) cm^{-1}: 2978, 2844, 1678, 1586, 1492, 1248, 788. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.23 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 7.14 (2H, m, Ar-H), 7.22 (1H, dd, J=1.8, 7.9 Hz, Ar-H), 7.44 (1H, dd, J=4.5, 7.8 Hz, Ar-H), 7.52 (2H, d, J=8.4 Hz, Ar-H), 7.98 (2H, d, J=8.4 Hz, Ar-H), 8.82 (1H, s, H-6). EI-MS *m*/*z*: 447 (M^++2), 445 (M^+). *Anal.* Calcd for $C_{22}H_{15}ClF_3N_3O_2$ (445.08): C, 59.27; H, 3.39; N, 9.43. Found: C, 58.98; H, 3.48; N, 9.63.

2,5-Dimethyl-7-phenyl-3-*o*-tolyl pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7n**): Yield: 84%, mp 272 °C; IR (KBr) cm^{-1}: 3054, 2978, 1681, 1586, 1492. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.13 (3H, s, CH_3), 2.26 (3H, s, CH_3), 2.29 (3H, s, CH_3), 7.24—7.44 (9H, m, Ar-H), 7.82 (1H, s, H-6). EI-MS *m*/*z*: 341 (M^+). *Anal.* Calcd for $C_{22}H_{19}N_3O$ (341.15): C, 77.40; H, 5.61; N, 12.31. Found: C, 77.54; H, 5.84; N, 12.63.

7-(4-Chlorophenyl)-3-(3,5-dimethylphenyl)-2-methyl-5-(trifluoromethyl)-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7o**): Yield: 90%, mp 272 °C; IR (KBr) cm^{-1}: 3068, 2988, 1683, 1603, 1422, 1270, 708. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.16 (6H, s, CH_3), 2.22 (3H, s, CH_3), 7.07(2H, s, Ar-H), 7.18 (1H, s, Ar-H), 7.42 (2H, d, J=8.5 Hz, Ar-H), 7.98 (2H, d, J=8.5 Hz, Ar-H), 8.82 (1H, s, H-6). EI-MS *m*/*z*: 445 (M^++2), 443 (M^+). *Anal.* Calcd for $C_{23}H_{17}ClF_3N_3O$ (443.1): C, 62.24; H, 3.86; N, 10.78. Found: C, 61.93; H, 3.62; N, 10.65.

3-(3,4-Dimethoxyphenyl)-2,5-dimethyl-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**7p**): Yield: 88%, mp 288 °C; IR (KBr) cm^{-1}: 2978, 2844, 1681, 1586, 1492. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.20 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.86 (6H, s, OCH_3), 6.98—7.02 (3H, m, Ar-H), 7.39—7.44 (5H, m, Ar-H), 7.80 (1H, s, H-6). EI-MS *m*/*z*: 387 (M^+). *Anal.* Calcd for $C_{23}H_{21}N_3O_3$ (387.16): C, 71.30; H, 5.46; N, 10.85. Found: C, 71.53; H, 5.54; N, 10.67.

Antibacterial Activity (*in Vitro*) All the test compounds was assayed *in vitro* for antibacterial activity against different strains of Gram-negative [*Escherichia coli* (MTCC 722), *Chromobacterium violaceum* (MTCC 2656) and *Klebsiella pneumoniae* (MTCC 109)], Gram-positive [*Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96) and *Bacillus sphaericus* (MTCC 511)] bacteria using standard protocol.[36] The minimum inhibitory concentration (MIC) was determined by the test tube dilution technique using ciprofloxacin as standard. The stock solution (1 mg/ml) of test compounds was prepared in DMSO. The stock solution was sterilised by passing

through a 0.2 mm polycarbonate sterile membrane (Nuclepore) filters. Further the serial dilution of test compounds was carried out and the following concentration was used: 100, 50, 25, 12.5, 6.25, 3.25, 1.25 μg/ml. Test compounds at various concentrations were added to culture medium in a sterilised borosilicate test tube and different bacterial strains were inoculated at 106 bacilli/ml concentration. The tubes were incubated at 37 °C for 24 h and then examined for the presence or absence of growth of the test organisms. All experiments were performed in triplicate. The MIC values were obtained from the lowest concentration of the test compound where the tubes remained clear, indicated that the bacterial growth was completely inhibited at this concentration. The MIC values were expressed in μg/ml and the results were tabulated (Table 1).

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