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Preliminary communication

Convenient synthesis of novel 4-substitutedamino-5-trifluoromethyl–2,7-disubstituted pyrido[2,3-*d*] pyrimidines and their antibacterial activity ☆

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Abstract

Novel pyrido[2,3-*d*]pyrimidines **4** have been synthesised starting from 2-amino-4-trifluoromethyl-6-substituted nicotinonitriles **1** via imine formation, selective amination followed by Dimroth rearrangement. Compound **4** were screened against Gram +ve and –ve bacteria in vitro. Compounds **4h** and **4d** showed significant activity against all species of Gram positive bacteria and moderate activity against Gram negative bacteria. N-2,4 difluorophenyl compounds **4l** and **4m** were the least active among all the compounds. All the compounds were inactive against *Pseudomonas aeruginosa* at the maximum concentration of 200 μg ml^{-1}.

Keywords: Pyrido[2,3-*d*]pyrimidines; Imino-ether; Dimroth rearrangement; Aminolysis; Antibacterial; Ciprofloxacin

1. Introduction

The pyrido [2,3-*d*] pyrimidine ring system is present in a number of biologically active organic compounds which includes antitumour [1], antibacterial [2] and anticonvulsant agents [3]. Pyrido[2,3-*d*] pyrimidines also have antipyretic [4], analgesic [5] and CNS depressant activity [6]. More specifically pyrido [2,3-*d*] pyrimidines were considered as inhibitors of *Pneumocystis carinii* (pc), *Toxoplasma gondii* (tg) of tumour cell lines in culture [7] and some have anticytokinin activity [8]. The activity is mainly due to inhibition of dihydrofolate reductase (DHFR) [9,10].

The synthesis of pyrido[2,3-*d*] pyrimidines is mainly by two ways i.e. annulation of pyrimidine ring over pyridine or vice versa [11]. 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 [12] to synthesise novel heterocycles, we report here a convenient synthesis of 4-substituted amino-5-trifluoromethyl-2,7-disubstituted pyrido[2,3-*d*]pyrimidines **4**, starting from 2-amino-4-trifluoromethyl-6-substituted nicotinonitriles **1** via imine formation, selective amination followed by Dimroth rearrangement and their in vitro antibacterial activity.

2. Chemistry

The 2-amino-4-trifluoromethyl-6-substituted nicotinonitriles [13] **1** were reacted with triethylorthoformate/triethylorthoacetate in presence of catalytic amount of acetic acid at 140 °C gave iminoethers **2** in sufficiently good yields. The rate of reaction and yields of products formed are found to be independent of substituents used in pyridine ring. The geometry of the iminoethers **2** has not been determined due to limited data on these compounds [14,15]. The reaction is schematically drawn in Scheme 1.

The compounds **2** were further reacted with aliphatic/aromatic primary amines and obtained 4-substituted amino-5-trifluoromethyl-2,7-disubstituted pyrido [2,3-*d*] pyrimidines, **4** in high yields. In case of aliphatic amines, the reaction was carried out at room temperature in aqueous medium as the rate of reaction being fast and with aromatic amines the reaction was

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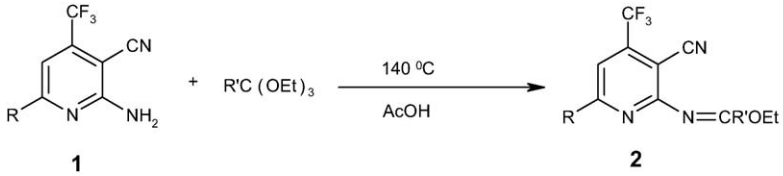


compounds	R	R'
2a	C_6H_5	H
2b	C_6H_5	CH_3
2c	p-CH_3-C_6H_4	H
2d	p-Cl-C_6H_4	H

Scheme 1.

carried out at 110 °C. The yields of the products with aliphatic amines is comparatively higher than with aromatic amines. The sequence of reactions is mainly selective aminolysis of compounds **2**, followed by the spontaneous cyclisation to less stable intermediate **3** which further undergoes Dimroth rearrangement [16–18] to give the more stable isomer **4** (Scheme 2). More specifically nicotinonitriles **2** on reaction with ethylamine/ammonia solution resulted an intermediate product **3** which was converted into **4** by refluxing in ethanolic amine solution. However other amines gave the stable isomer **4** directly at room temperature.

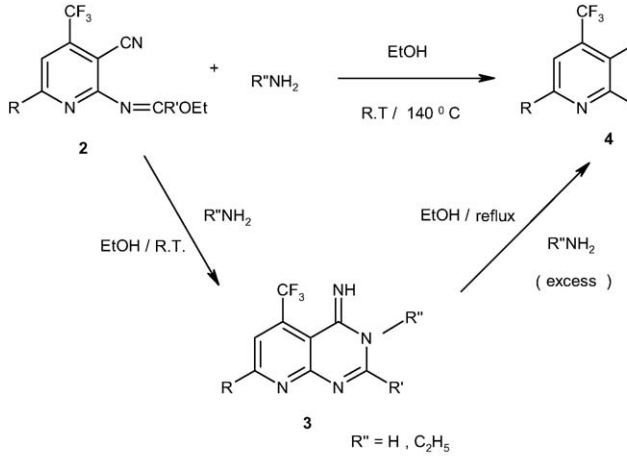
3. In vitro antibacterial assays

Six bacterial test organisms such as *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), and *Pseudomonas aeruginosa* (MTCC 741), *Klebsiella aerogenes* (MTCC 39), *Bacillus sphaericus* (MTCC 511), *Chromobacterium violaceum* (MTCC 2656) were selected and obtained from the Institute of Microbial Technology, Chandigarh. Cultures of test organisms were maintained on nutrient agar slants and were subcultured in Petri dishes prior to testing. The media used was nutrient agar, nutrient broth procured from Himedia Laboratories, Mumbai.

The minimum inhibitory concentration (MIC) was determined by broth dilution method [19].

4. Results and discussion

Compounds **4a**, **b**, **d**, **e**, **f**, **h**, **i** and **4k**–**o** were screened for their in vitro antibacterial activity. The antibacterial activity were tested against Gram positive (*B. subtilis*, *B. sphaericus*, *S. aureus*) and Gram negative (*P. aeruginosa*, *K. aerogenes*, *C. violaceum*) bacteria. Compounds **4d** and **4h** showed significant activity against all species of Gram positive bacteria and moderate activity against Gram negative bacteria. Enhanced



compounds	R	R'	R"
4a	C_6H_5	H	H
4b	C_6H_5	CH_3	H
4c	p-CH_3- C_6H_4	H	H
4d	p-Cl- C_6H_4	H	H
4e	C_6H_5	H	C_2H_5
4f	C_6H_5	H	CH_3
4g	C_6H_5	CH_3	C_2H_5
4h	C_6H_5	CH_3	CH_3
4i	C_6H_5	H	Ph
4j	C_6H_5	H	Cyclopropyl
4k	C_6H_5	CH_3	Cyclopropyl
4 l	C_6H_5	H	2,4 - difluorophenyl
4 m	C_6H_5	CH_3	2,4 - difluorophenyl
4n	C_6H_5	CH_3	m- CF3 -phenyl
4o	C_6H_5	H	m- CF3 -phenyl

Scheme 2.

activity was observed as in the case of **4h** by replacing H with CH_3 on C-2 and NH_2. Compound **4b** having methyl on C-2 and NH_2 exhibited activity against *B. sphaericus* and moderate activity against all other tested microorganisms. Compounds **4e** and **4k** were active against *B. subtilis*. The N-phenyl compound **4i** exhibited activity against *B. subtilis*. The N-m-CF_3-phenyl analogue **4n** showed significant to moderate activity against all the tested microorganisms whereas the N-2,4-difluorophenyl compounds **4l** and **4m** were the least active among the screened compounds. All the compounds were inactive against *P. aeruginosa* at the maximum concentration of 200 μg ml^{-1}. In conclusion the 4-amino and N-methyl amino compounds **4d** and **4h** were the most active among the screened compounds. In case of N-phenyl and N-substituted phenyl compounds, N-m-CF_3 substituted compound **4n** showed significant activity. The MIC values of the compounds were compared with commercial antibiotic (ciprofloxacin). The details of compounds and their activity against various microorganisms tabulated in Table 1.

5. Experimental

Melting points were recorded on Casia-siamia (VMP-AM) melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer FT-IR 240-C spectro photometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini varian 200 MHz, Bruker AV 300 MHz and Unity 400 MHz spectro meter in $CDCl_3$ using TMS as an internal standard. Electron impact (EI) and chemical ionisation mass spectra were recorded on a VG 7070 H instrument at 70 ev. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F_{254} (mesh); Spots were visualised with UV light. Merck silica gel (100–200 mesh) was used for chromatography. CHN analyses were recorded on a Vario EL analyser.

5.1. Ethyl-3-cyano-6-substituted-4-(trifluoromethyl)pyridin-2-ylimidoformate/ethanamidoate (2): general procedure

The 2-amino-4-trifluoromethyl-6-substituted nicotinonitriles **1** (11.4 mmol) was taken in excess of triethylorthoformate/triethylorthoacetate (8 ml) along with catalytic amount of acetic acid and heated at 140 °C for 6 h. The resulting dark brown solution was allowed to cool to room temperature and evaporated in vacuo to give a brown coloured solid residue. To the residue n-hexane was added and separated solid is filtered, washed with n-hexane. The crude product was dried and purified through column using 60–120 mesh silica gel and the desired product was eluted using 10% $CHCl_3$ in hexane solvent mixture.

*5.1.1. Ethyl N-[3-cyano-6-phenyl-4-(trifluoromethyl)-2-pyridyl]iminoformate (**2a**)*

Yield 90%; m.p. 116 °C; IR (KBr): 2250 (CN), 1640 (N–C), 1230 (C–O) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, t, $J = 8.2$ Hz, CH_3), 4.5 (2H, quartet, $J = 9.6$ Hz, CH_2), 7.5 (3H, m, Ar-H), 7.8 (1H, s, H-C(5), Ar-H), 8.1(2H, m, Ar-H), 8.7 (1H, s, CH); EIMS, *m/z*: 319 (M^+), 290 (M – 29). Anal. Calcd. for $C_{16}H_{12}F_3N_3O$: C, 60.18; H, 3.78; N, 13.16. Found: C, 60.25; H, 3.86; N, 13.23.

*5.1.2. 1-Ethyl N-1-[3-cyano-6-phenyl-4-(trifluoromethyl)-2-pyridyl]ethanimidate (**2b**)*

Yield 85%; m.p. 93 °C; IR (KBr): 2246 (CN), 1644 (N–C), 1232 (C–O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.4 (3H, t, $J = 8.2$ Hz, $OCH_2\underline{CH_3}$), 2.1 (3H, s), 4.4 (2H, quartet, $J = 9.6$ Hz, CH_2), 7.5 (3H, m, Ar-H), 7.7 (1H, s, (C)-5 Ar-H), 8.1(2H, m, Ar-H); EIMS, *m/z*: 333 (M^+), 304 (M – 29). Anal. Calcd. for $C_{17}H_{14}F_3N_3O$: C, 61.26; H, 4.23; N, 12.60. Found: C, 61.18; H, 4.32; N, 12.55.

*5.1.3. Ethyl N-[3-cyano-6-(4-methylphenyl)-4-(trifluoromethyl)-2-pyridyl]iminoformate (**2c**)*

Yield 88%; m.p. 152 °C; IR (KBr): 2252 (CN), 1642 (N–C), 1226 (C–O) cm^{-1}. ^{1}H NMR(300 MHz, $CDCl_3$): δ 1.5 (3H, t, $J = 8.2$ Hz, $OCH_2\underline{CH_3}$), 2.4 (3H, s, CH3), 4.6 (2H, quartet, $J = 9.6$ Hz, CH_2), 7.3 (2H, m, Ar-H), 7.8 (1H, s, H- C-(5), Ar-H), 7.9 (2H, d, $J = 14$ Hz, Ar-H), 8.65 (1H, s, CH); EIMS, *m/z*: 333 (M^+), 290 (M – 29). Anal. Calcd. for $C_{17}H_{14}F_3N_3O$: C, 61.26; H, 4.23; N, 12.60. Found: C, 60.18; H, 4.31; N, 12.55.

Table 1
MIC (in μg ml^{-1}) values of novel 4-substituted amino-5-trifluoromethyl-2,7-disubstituted pyrido[2,3-d]pyrimidines

Compounds	Microorganisms					
	Gram positive			Gram negative		
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
4a	25	25	25	–	50	25
4b	25	3.25	25	–	50	25
4d	6.25	3.25	6.25	–	25	12.5
4e	12.5	25	25	–	25	50
4f	25	12.5	50	–	12.5	25
4h	1.25	3.25	1.25	–	25	25
4i	6.25	25	25	–	50	25
4k	12.5	25	25	–	25	12.5
4l	25	25	25	–	25	25
4m	25	25	50	–	25	50
4n	50	6.25	12.5	–	12.5	50
4o	25	25	50	–	25	25
Ciprofloxacin	0.78	0.78	0.39	0.78	0.78	0.39

*5.1.4. Ethyl N-[6-(4-chlorophenyl)-3-cyano-4-(trifluoromethyl)-2-pyridyl]iminoformate (**2d**)*

Yield 80%; m.p. 160 °C; IR (KBr): 2248 (CN), 1645 (N–C), 1232 (C–O) cm^{-1}. ^1H NMR(300 MHz, $CDCl_3$): δ 1.5 (3H, t, $J = 8.2$ Hz,), 4.6 (2H, quartet, $J = 9.6$ Hz, CH_2), 7.5 (2H, d, Ar-H), 7.8 (1H, s, H- C-(5), Ar-H), 8.0 (2H, d, $J = 14$ Hz, Ar-H), 8.7 (1H, s, CH); EIMS, *m/z*: 353 (M^+), (40%), 355 ($M^+ + 2$), (14%). Anal. Calcd. for $C_{16}H_{11}F_3N_3OCl$: C, 54.32; H, 3.13; N, 11.87. Found: C, 54.27; H, 3.22; N, 11.75.

*5.2. 3-Substituted-2-methyl-7-phenyl-5-(trifluoromethyl)pyrido [2,3-d]pyrimidin-4(3H)-imine (**3**): general procedure*

Compound **2** (0.5 g, 1.57 mmol) was dissolved in ethanolic solution (10 ml) of ammonia/ethylamine (5 ml), and was stirred at room temperature for 3 h, during which time solid separated out from the solution. Ethanol was removed under vacuum. The crude product residue was purified by column using 60–120 mesh silica gel and the desired product was eluted with 10% $CHCl_3$ in hexane mixture.

*5.2.1. 2-Methyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4(3H)-imine (**3a**)*

Yield 76%; m.p. 248 °C; IR (KBr): 3450 (N–H), 1645 (C=N), 1354 (N–C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.6 (3H, s, CH_3), 6.6 (1H, br, s, NH), 7.5–7.6 (3H, m, Ar-H), 8.15 (1H, s, Ar-H), 8.2–8.3 (2H, m, Ar-H). EIMS, *m/z*: 304 (M^+). Anal. Calcd. for $C_{15}H_{11}F_3N_4$: C, 59.21; H, 3.64; N, 18.41. Found: C, 57.15; H, 3.55; N, 18.53.

*5.2.2. 3-Ethyl-2-methyl-7-phenyl-5-(trifluoromethyl)pyrido [2,3-d]pyrimidin-4(3H)-imine (**3b**)*

Yield 81%; m.p. 82 °C; IR (KBr): 3456 (N–H), 1655 (C=N), 1350 (N–C) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.45 (3H, t, $NCH_2\underline{CH_3}$), 2.65 (3H, s, CH_3), 4.2 (2H, qt, CH_2), 7.45–7.55 (3H, m, Ar-H), 7.95 (1H, s, Ar-H), 8.15–8.2 (2H, m, Ar-H). EIMS, *m/z*: 332 (M^+). Anal. Calcd. for $C_{17}H_{15}F_3N_4$: C, 61.44; H, 4.54; N, 16.85. Found: C, 61.52; H, 4.61; N, 16.96.

*5.3. 2,7-Disubstituted-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4-amine (**4**): general procedure*

Compound **2** (0.8 g, 2.5 mmol) was dissolved in ethanolic solution of the corresponding amine (10 ml, and was stirred at room temperature for 3 h, during which time solid separated out from the solution. In case of substituted anilines, the reaction was carried out at 110 °C for 6 h. Ethanol or aniline was removed under vacuum. The crude product residue was purified by column using 60–120 mesh silica gel and the desired product was eluted with 20% $CHCl_3$ in hexane mixture.

*5.3.1. 7-Phenyl-5-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-amine (**4a**)*

Yield 85%; m.p. 222 °C; IR (KBr): 3350, 3400 (NH_2), 1350 (C–N) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.3 (2H, br, s, NH_2), 7.4–7.6 (3H, m, Ar-H), 8.2–8.4 (2H + 1H, m, Ar-H), 8.8 (1H, s, CH). EIMS, *m/z*: 290 (M^+), 221 ($M^+ - 69$). Anal. Calcd. for $C_{14}H_9F_3N_4$: C, 57.93; H, 3.12; N, 19.30. Found: C, 57.88; H, 3.22; N, 19.42.

*5.3.2. 2-Methyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4-amine (**4b**)*

Yield 82%; m.p. 230 °C; IR (KBr): 3355, 3440 (NH_2), 1354 (C–N) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.6 (3H, s), 6.1 (2H, br, s, NH_2), 7.5–7.6 (3H, m, Ar-H), 8.2 (1H, s, Ar-H), 8.3–8.4 (2H, m, Ar-H). EIMS, *m/z*: 304 (M^+). Anal. Calcd. for $C_{15}H_{11}F_3N_4$: C, 59.21; H, 3.64; N, 18.41. Found: C, 57.15; H, 3.55; N, 18.53.

*5.3.3. 7-(4-Methylphenyl)-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4-amine (**4c**)*

Yield 78%; m.p. 242 °C; IR (KBr): 3350, 3400 (NH_2), 1350 (C–N) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.5 (3H, s), 5.5 (2H, br, s, NH_2), 7.3–7.4 (2H, m, Ar-H), 8.2–8.3 (2H + 1H), m, Ar-H), 8.8 (1H, s, CH). EIMS, *m/z*: 304 (M^+). Anal. Calcd. for $C_{15}H_{11}F_3N_4$: C, 59.21; H, 3.64; N, 18.41. Found: C, 59.33; H, 3.72; N, 18.38.

*5.3.4. 7-(4-Chlorophenyl)-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4-amine (**4d**)*

Yield 70%; m.p. 252 °C; IR (KBr): 3350, 3445 (NH_2), 1350 (C–N) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 5.5 (2H, brs, NH_2), 7.3–7.4 (2H, m, Ar-H), 8.2–8.3 ((2H + 1H), m, Ar-H), 8.8 (1H, s, CH). EIMS, *m/z*: 324 (M^+), (50%), 326 ($M^+ + 2$), (17%). Anal. Calcd. for $C_{14}H_8F_3N_4Cl$: C, 51.78; H, 2.48; N, 17.25. Found: C, 51.65; H, 2.55; N, 17.38.

*5.3.5. N-ethyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4-amine (**4e**)*

Yield 80%; m.p. 88 °C; IR (KBr): 3450 (N–H), 1360 (C–N) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.3 (3H, t, CH_3), 3.6–3.7 (2H, m, CH_2), 6.1 (1H, br, s, NH_2), 7.4–7.5 (3H, m, Ar-H), 8.1 (1H, s, Ar-H), 8.2–8.3 (2H, m, Ar-H), 8.7 (1H, s, CH). EIMS, *m/z*: 318 (M^+). Anal. Calcd. for $C_{16}H_{13}F_3N_4$: C, 60.37; H, 4.11; N, 17.60. Found: C, 60.44; H, 4.25; N, 17.52.

*5.3.6. N-methyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4-amine (**4f**)*

Yield 86%; m.p. 150 °C; IR (KBr): 3452 (N–H), 1360 (C–N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.2 (3H, d, CH_3), 6.2 (1H, br, s, NH), 7.5–7.6 (3H, m, Ar-H), 8.1 (1H, s, Ar-H), 8.2–8.3 (2H, m, Ar-H), 8.8 (1H, s, CH). EIMS, *m/z*: 304 (M^+). Anal. Calcd. for $C_{15}H_{11}F_3N_4$: C, 59.21; H, 3.64; N, 18.41. Found: C, 59.33; H, 3.55; N, 18.38.

*5.3.7. N-ethyl-2-methyl-7-phenyl-5-(trifluoromethyl)pyrido [2,3-d]pyrimidin-4-amine (**4g**)*

Yield 78%; m.p. 97 °C; IR (KBr): 3456 (N–H), 1365 (C–N) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.4 (3H, t, $NHCH_2\underline{CH_3}$), 2.7 (3H, s, CH_3), 3.7–3.8 (2H, m, CH_2), 6.1 (1H, br, s, NH), 7.5–7.6 (3H, m, Ar-H), 8.1 (1H, s, Ar-H), 8.3–8.4 (2H, m, Ar-

H). EIMS, *m/z*: 332 (M^+). Anal. Calcd. for $C_{17}H_{15}F_3N_4$: C, 61.44; H, 4.54; N, 16.85. Found: C, 61.52; H, 4.61; N, 16.96.

*5.3.8. N-methyl-2-methyl-7-phenyl-5-(trifluoromethyl)pyrido [2,3-d]pyrimidin-4-amine (**4h**)*

Yield 84%; m.p. 124 °C; IR (KBr): 3458 (N–H), 1362 (C–N) cm^{-1}. ^1H NMR(300 MHz, $CDCl_3$): δ 2.7 (3H, s, CH_3), 3.2 (3H, d, $NHCH_3$), 6.2 (1H, br, s, NH), 7.5–7.6 (3H, m, Ar-H), 8.1 (1H, s, Ar-H), 8.2–8.3 (2H, m, Ar-H). EIMS, *m/z*: 319 (M^+). Anal. Calcd. for $C_{16}H_{13}F_3N_4$: C, 60.37; H, 4.11; N, 17.60. Found: C, 60.44; H, 4.25; N, 17.52.

*5.3.9. 2-Methyl-N,7-diphenyl-5-(trifluoromethyl)pyrido[2,3-d] pyrimidin-4-amine (**4i**)*

Yield 78%; m.p. 136 °C; IR (KBr): 3450 (N–H), 1360 (C–N) cm^{-1}. ^1H NMR(200 MHz, $CDCl_3$): δ 2.7 (3H, s, CH_3), 7.45 (2H, t, $J = 13$ Hz, Ar-H) 7.5–7.6 (3H, m, Ar-H), 7.7 (3H, m, Ar-H), 7.8 (1H, br, s, NH), 8.2 (1H, s, Ar-H), 8.3 (2H, m, Ar-H). EIMS, *m/z*: 380 (M^+). Anal. Calcd. for $C_{21}H_{15}F_3N_4$: C, 66.37; H, 3.97; N, 14.72. Found: C, 66.44; H, 3.88; N, 14.66.

*5.3.10. N-cyclopropyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-amine (**4j**)*

Yield 75%; m.p. 87 °C; IR (KBr): 3445 (N–H), 1360 (C–N) cm^{-1}. ^1H NMR(200 MHz, $CDCl_3$): δ 0.6 (2H, d, $J = 2.5$ Hz, CH_2), 0.9 (2H, d, $J = 5.2$ Hz, CH_2), 3.1 (1H, m, CH), 6.2(1H, br, s, NH), 7.5–7.6 (3H, m, Ar-H), 8.1–8.3 (3H, m, Ar-H), 8.7 (1H, s, CH). EIMS, *m/z*: 330 (M^+). Anal. Calcd. for $C_{17}H_{13}F_3N_4$: C, 61.81; H, 3.96; N, 16.96. Found: C, 61.72; H, 3.88; N, 16.84.

*5.3.11. N-cyclopropyl-2-methyl-7-phenyl-5-(trifluoromethyl) pyrido[2,3-d]pyrimidin-4-amine (**4k**)*

Yield: 85%; m.p. 96 °C; IR (KBr) ν: 3345 (N–H), 1345 (C–N), 1154 (C–F) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.7 (3H, s, CH_3), 0.7 (2H, d, $J = 2.2$ Hz, CH_2), 0.9 (2H, d, $J = 5.3$ Hz, CH_2), 3.1 (1H, m, CH), 6.2 (1H, br, s, NH), 7.6 (3H, m, Ar-H), 8.1 (1H, s, Ar-H), 8.2–8.3 (2H, m, Ar-H); LSIMS, *m/z*: 344 (M^+), 329 ($M^+ - CH_3$); Anal. Calcd. for $C_{18}H_{15}N_4F_3$: C, 62.78; H, 4.39; N, 16.27. Found: C, 62.65; H, 4.44; N, 16.33.

*5.3.12. N-(2,4-difluorophenyl)-2-methyl-7-phenyl-5-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-amine (**4l**)*

Yield: 80%; mp.: 140 °C; IR (KBr) ν: 3360 (N–H), 1350 (C–N), 1150 (C–F) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.6 (3H, s, CH_3), 6.95 (2H, m, Ar-H), 7.55 (3H, m, Ar-H), 8.2 (1H, s, Ar-H), 8.3 (2H, m, Ar-H), 8.55 (1H, m, Ar-H); LSIMS, *m/z*: 417 ($M^+ + 1$); Anal. Calcd. for $C_{21}H_{13}F_5N_4$: C, 60.58; H, 3.14; N, 13.45. Found: C, 60.66; H, 3.22; N, 13.52.

*5.3.13. N-(2,4-difluorophenyl)-7-phenyl-5-(trifluoromethyl) pyrido[2,3-d]pyrimidin-4-amine (**4m**)*

Yield: 76%; m.p. 152 °C; IR (KBr) ν: 3385 (N–H), 1346 (C–N), 1156 (C–F) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.05 (2H, m, Ar-H), 7.55–7.6 (3H, m, Ar-H), 8.15 (1H, s, Ar-H), 8.3 (2H, m, Ar-H), 8.55 (1H, m, Ar-H); 8.85 (1H, s, CH); LSIMS, *m/z*: 431 ($M^+ + 1$); Anal. Calcd. for $C_{20}H_{11}N_4F_5$: C, 59.70; H, 2.75; N, 13.92. Found: C, 59.66; H, 2.62; N, 13.88.

*5.3.14. 2-Methyl-7-phenyl-5-(trifluoromethyl)-N-[3-trifluoromethyl)phenyl]pyrido[2,3-d]pyrimidin-4-amine (**4n**)*

Yield: 82%; m.p. 129 °C; IR (KBr) ν: 3370 (N–H), 1348 (C–N), 1152 (C–F) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.7 (3H, s, CH_3), 7.3–7.5 (5H, m, Ar-H), 7.8–7.9 (1H + 1H, m, Ar-H), 8.1 (1H, s, Ar-H), 8.3 (2H, m, Ar-H); LSIMS, *m/z*: 449 ($M^+ + 1$); Anal. Calcd. for $C_{22}H_{14}N_4F_6$: C, 58.93; H, 3.14; N, 12.49. Found: C, 58.85; H, 3.22; N, 12.56.

*5.3.15. 7-Phenyl-5-(trifluoromethyl)-N-[3-(trifluoromethyl) phenyl]pyrido[2,3-d]pyrimidin-4-amine (**4o**)*

Yield: 80%; m.p. 176 °C; IR (KBr) ν: 3550 (N–H), 1350 (C–N), 1100 (C–F) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.5 (1H, d, $J = 17.5$ Hz, Ar-H); 7.6 (4H, m, Ar-H), 7.85 (1H, d, $J = 17.5$ Hz, Ar-H), 8.1 (1H, s, Ar-H), 8.3–8.4 (3H, m, Ar-H), 8.9 (1H, s, CH); LSIMS, *m/z*: 435 ($M^+ + 1$); Anal. Calcd. for $C_{21}H_{12}F_6N_4$: C, 58.07; H, 2.78; N, 12.89. Found: C, 58.15; H, 2.65; N, 12.77.

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