Regular Article

Synthesis of Novel Pyrido[1,2-*a*]pyrimidine-3-carboxamide Derivatives and Their Anticancer Activity

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A series of novel pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives 6a–n were prepared starting from 2(1*H*) pyridone 1 via hydrolysis, de-carboxylation, selective *O*-alkylation followed by rearrangement to give pyridine-2-amine 3. Compound 3 on reaction with ethoxy methylene malonic diethyl ester (EMME) under a conventional method followed by cyclization under micro wave irradiation (MWI) conditions resulted in product 5. Compound 5 on coupling with diverse substituted aliphatic amines formed title compounds 6a–n. All the products 6a–n were screened against four human cancer cell lines and compounds 6h–k and n which showed promising anticancer activity have been identified.

Key words 2(1*H*)pyridone; *O*-alkylation; Smiles rearrangement; ethoxy methylene malonic diethyl ester (EMME); aliphatic amine; anticancer activity

Cancer is one of the most serious threats against human health in the world. Modern days human life style also promoting in increasing rate of cancer among the people. Although, many of the natural and synthetic compounds used as anticancer drugs, the development and discovery of safer anticancer agents is still a challenging task for organic chemists world over. Heterocycles are considered as an extremely important class of compounds which play a key role in health care and pharmaceutical drug design.¹⁾ Currently, a number of heterocyclic compounds are available commercially as anticancer drugs. The pyrimidine being a basic nucleus in DNA & RNA, pyrido[1,2-*a*]pyrimidine also possess diverse biological activities.²⁾ This structural scaffold is present in the tranquilizer pirenperone, the antiallergic agent ramastine, an anti-ulcerative agent and an antiasthmatic agent (Fig. 1).

Pyrimidine based compounds have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acid to their current use in the chemotherapy. Last few decades of research on pyrido pyrimidine derivatives revealed that, they had wide range of therapeutic applications such as antitumor,^{3–6)} antibacterial,^{7–9)} antifungal,^{10–13)} anti-inflammatory,¹⁴⁾ anti-allergic,¹⁵⁾ anti-diabetic,¹⁶⁾ antiviral,^{17–19)} anti-herpes²⁰⁾ and calcium channel blocking activity.^{21,22)} Many pyrimidine derivatives are used for thyroid drugs and leukemia. Fused pyrimidine derivatives are extensively used in neurology, particularly in the treatment of neurodegenerative disorders such as Parkinson's disease,²³⁾ antianxiety disorders,²⁴⁾ and depression.²⁵⁾ Recent literature also shows that the trifluoromethyl^{26,27)} group at a strategic position of an organic molecule dramatically alters the properties of the molecule in terms of lipid solubility, oxidative thermal stability thereby enhancing the transport mechanism and bio-efficacy. Similarly, amide derivatives were associated with broad spectrum of biological activities and when amides conjugates with other aliphatic, aromatic and heterocyclic ring

produces various type of biological activity. Amide derivatives synthesize conveniently by the reaction of substituted ester/acid group (–COOC₂H₅/–COOH) with different substituted amines. The highly substituted pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives have considerable chemical and pharmacological importance because of a broad range of biological activities. Based on the importance of pyrimidine derivatives, encouraged us to synthesize some new highly functionalized substituted pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives. In continuation to our efforts,^{28–30)} we designed and synthesized a series of novel trifluoromethyl substituted pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives, screened for anti cancer activity against four human cancer cell lines and promising compounds have been identified.

Chemistry

The 2-oxo-6-phenyl/(thiophen-2-yl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile 1 on hydrolysis with 50% sulfuric acid followed by de-carboxylation resulted 6-phenyl/(thiophen-2-yl)-4-(trifluoromethyl) pyridine 2(1*H*) one 2. Compound 2 on reaction with 2-chloroacetamide in dry *N,N*-dimethylformamide (DMF) using potassium carbonate as base resulted 6-phenyl/(thiophen-2-yl)-4-(trifluoromethyl)-pyridin-2-amine 3 through Smiles rearrangement. Compound 3 on further reaction with ethoxy methylene malonic diethyl ester (EMME), obtained diethyl 2-(((6-phenyl/(thiophen-2-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)methylene)malonate 4. Compound 4 was cyclized in phosphorus oxychloride to form ethyl 4-oxo-6-phenyl/(thiophen-2-yl)-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate 5 under conventional as well as under micro wave irradiation (MWI) conditions. Microwave irradiation conditions resulted high yield in low reaction times. Compound 5 was further reacted with different aliphatic amines and obtained *N*-methyl-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbox amide

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Fig. 1. Pyrido[1,2-*a*]pyrimidines Possessing Diverse Biological Activities

Chart 1

Chart 2

derivatives **6**. The sequence of reactions outlined in Charts 1 and 2 and products are tabulated in Table 1.

Results and Discussion

Anticancer Activity and Structure Activity Relationship (SAR) All the final compounds **6a-n** were screened against four human cancer cell lines such as DU145 (Prostate cancer HTB-81), A549 (Lung cancer CCL-185), SiHa (Squamous cell carcinoma HTB-35), MCF-7 (Breast cancer HTB-22) using 5-Fluorouracil as standard. IC_{50} values of the test compounds for 24 h on each cell line was calculated and presented in

Table 2. It is evident from the bioactivity assay results that, most of the test compounds have shown significant anti cancer activity on all the cell lines tested in a concentration-dependent manner. In general, compounds **6h-n** (R =thien-2-yl group at 6th position) showed good activity when compared to **6a-g** (R =phenyl group at 6th position). Among all the compounds screened, compounds **6h-k** and **n** showed promising activity. The SAR revealed that the presence of thien-2-yl group at 6th position of pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives **6h-k** considered as more potent with IC_{50} concentration $<10\mu\text{g/mL}$ on all cancer cell lines. More specifically, com-

Table 1. Preparation of Pyrido[1,2-*a*]pyrimidine-3-carboxamide Derivatives **6**

S. No.	Compd	R	R'	mp (°C)	Yield (%)
1.	6a	C ₆ H ₅	–CH ₃	191–193	91
2.	6b	C ₆ H ₅	–CH ₂ CH ₃	216–218	90
3.	6c	C ₆ H ₅	–CH ₂ CH ₂ CH ₃	198–200	85
4.	6d	C ₆ H ₅	–Cyclopentyl	178–180	81
5.	6e	C ₆ H ₅	<i>p</i> -CH ₃ –C ₆ H ₅	232–234	62
6.	6f	C ₆ H ₅	<i>p</i> -CH ₃ –C ₆ H ₅ CH ₂	252–254	60
7.	6g	C ₆ H ₅	<i>p</i> -F–C ₆ H ₅	238–240	65
8.	6h	Thien-2-yl	–CH ₃	162–164	90
9.	6i	Thien-2-yl	–CH ₂ CH ₃	191–193	92
10.	6j	Thien-2-yl	–CH ₂ CH ₂ CH ₃	222–224	88
11.	6k	Thien-2-yl	–Cyclopentyl	198–200	82
12.	6l	Thien-2-yl	<i>p</i> -CH ₃ –C ₆ H ₅	245–247	60
13.	6m	Thien-2-yl	<i>p</i> -CH ₃ –C ₆ H ₅ CH ₂	235–237	64
14.	6n	Thien-2-yl	<i>p</i> -F–C ₆ H ₅	223–225	68
15.	—	Phenyl/Thien-2-yl	Aliphatic aryl amines	No reaction	—

Table 2. *In Vitro* Anticancer Activity of Compounds **6a–n**

S. No	Test compd	IC ₅₀ values in (μM)			
		DU145	A549	SiHa	MCF-7
1	6a	— ^{a)}	86.3±0.32	92.1±0.44	—
2	6b	—	—	—	—
3	6c	19.3±0.32	22.4±0.16	25.1±0.22	18.3±0.31
4	6d	17.6±0.28	22.0±0.24	16.4±0.26	18.2±0.32
5	6e	—	—	—	—
6	6f	—	—	—	—
7	6g	10.2±0.28	—	—	8.2±0.16
8	6h	5.8±0.16	9.5±0.21	8.6±0.22	7.2±0.15
9	6i	—	3.2±0.12	5.6±0.26	6.2±0.32
10	6j	—	3.6±0.11	9.5±0.14	10.8±0.32
11	6k	5.3±0.12	7.6±0.18	8.1±0.27	10.4±0.18
12	6l	—	—	—	—
13	6m	—	16.7±0.36	15.3±0.18	19.2±0.26
14	6n	—	6.1±0.22	8.4±0.14	11.6±0.34
5-Fluorouracil (standard)		1.8±0.11	1.7±0.09	1.9±0.12	1.8±0.09

a) — indicates IC₅₀ value > 92 μg/mL. A549, Lung cancer (CCL-185); DU145, Prostate cancer (HTB-81); SiHa, Squamous cell carcinoma (HTB-35); MCF-7, Breast cancer (HTB-22).

pounds **6i** and **j** showed high activity with IC₅₀ 3.2±0.12 and 3.6±0.11 μg/mL against A549 (Lung cancer CCL-185) cell line. However, remaining compounds could not show activity up to the concentration of 92 μg/mL. The activity data is tabulated in Table 2.

Conclusion

In conclusion, a series of novel pyrido[1,2-*a*]pyrimidine-3-carboxamide derivatives **6a–n** were prepared and evaluated for cytotoxicity against four human cancer cell lines. Among all the compounds screened, the compounds **6h–k** and **n** showed promising anticancer activity against all the cell lines at micro molar concentration.

Experimental

Melting points (mp) 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 spectrophotometer using KBr optics. ¹H-NMR spectra were recorded

on Bruker AV 300 MHz in CDCl₃ and DMSO-*d*₆ using tetramethylsilane (TMS) as internal standard. Electrospray ionization (ESI) spectra were recorded on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. All high-resolution spectra were recorded on QSTARXL hybrid MS/MS system (Applied Biosystems, U.S.A.) under electrospray ionization. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60F₂₅₄; spots were visualized with UV light. Merck silica gel (60–120 mesh) was used for column chromatography.

Cytotoxicity Assay The cytotoxicity of the compounds was determined on the basis of measurement of *in vitro* growth inhibition of tumor cell lines in 96 well plates by cell-mediated reduction of tetrazolium salt to water insoluble formazan crystals using 5-fluorouracil as a standard. The cytotoxicity was assessed against a panel of four different human tumor cell lines: A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185),

DUI45 derived from human prostate cancer cells (ATCC No. HTB-81), SiHa derived from human Squamous cell carcinoma (ATCC No. HTB-35) and MCF7 derived from human breast adenocarcinoma cells (ATCC No. HTB-22) using the 3-4,5-dimethylthiazol-2-yl-2,5-diphenyltetrazolium bromide (MTT) assay.³¹⁾ The IC₅₀ values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose–response curves. IC₅₀ values (in μM) are expressed as the average of three independent experiments.

Synthesis of 6-Phenyl-4-(trifluoromethyl)pyridin-2(1H)-one (2) 2-Oxo-6-phenyl/(thiophen-2-yl)-4-(trifluoromethyl)-1,2-dihydropyridine-3-carbonitrile **1** (10 g, 0.03 mol) was slowly added to 150 mL of 50% sulfuric acid. The reaction mixture was heated with stirring for 10 h, at 148°C. The reaction mixture was allowed to cool and poured on to crushed ice. White solid was formed and filtered.

6-Phenyl-4-(trifluoromethyl)pyridine-2(1H)-one (2a) mp: 166–168°C; IR (KBr, cm^{-1}): 3358 (–NHCO–), 1639 (–NHCO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 6.60 (s, 1H, Ar-H), 6.77 (s, 1H, Ar-H), 7.49–7.54 (m, 3H, Ar-H), 7.75–7.80 (m, 2H, Ar-H), 13.40 (brs, 1H, –NHCO–); MS (ESI): m/z [(M+H)⁺]: 240. *Anal.* Calcd for $\text{C}_{12}\text{H}_8\text{F}_3\text{NO}$: C 60.26, H 3.37, N 5.86%. Found: C 60.28, H 3.35, N 5.88%.

6-Thiophen-2-yl-4-(trifluoromethyl)pyridine-2(1H)-one (2b) mp: 136–138°C; IR (KBr, cm^{-1}): 3360 (–NHCO–), 1635 (–NHCO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 7.15 (dd, 1H, $J=4.77$ Hz, Ar-H), 7.42 (dd, 1H, $J=3.61$ Hz, Ar-H), 7.65 (dd, 1H, $J=4.77$ Hz, Ar-H), 7.92 (s, 1H, Ar-H), 8.64 (s, 1H, Ar-H), 13.40 (brs, 1H, –NHCO–); MS (ESI): m/z [(M+H)⁺]: 246. *Anal.* Calcd for $\text{C}_{10}\text{H}_6\text{F}_3\text{NOS}$: C 48.98, H 2.47, N 5.71%. Found: C 48.96, H 2.46, N 5.72%.

Synthesis of 6-Phenyl/(thiophen-2-yl)-4-(trifluoromethyl)pyridin-2-amine (3) The 3-cyano-4-trifluoromethyl-6-substituted-2(1H)-pyridone **1** (2.6 mmol) was dissolved in dry acetone (50 mL). To the homogeneous solution, 2-chloroacetamide (0.243 g, 2.6 mmol), potassium carbonate (0.730 g, 5.3 mmol) and a pinch of sodium iodide (0.010 g) were added. The reaction mixture was refluxed for 6–8 h at 60°C and cooled to room temperature. The separated salt was filtered off and washed with acetone (30 mL). The total filtrate was concentrated under vacuum and the residue was treated with water. The separated white solid was filtered, dried and recrystallized from ethyl alcohol.

6-Phenyl-4-(trifluoromethyl)pyridin-2-amine (3a) mp: 109–111°C; IR (KBr, cm^{-1}): 3497 (–NHCO–), 3323, 3195 (–NH₂), 1634 (–NHCO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 4.70 (brs, 2H, NH₂), 6.61 (s, 1H, Ar-H), 7.38 (s, 1H, Ar-H), 7.46–7.51 (m, 3H, Ar-H), 7.85–7.90 (m, 2H, Ar-H); MS (EI): [(M)⁺]: 238. *Anal.* Calcd for $\text{C}_{12}\text{H}_9\text{F}_3\text{N}_2$: C 60.51, H 3.81, N 11.76%. Found: C 60.53, H 3.82, N 11.79%.

6-Thiophen-2-yl-4-(trifluoromethyl)pyridin-2-amine (3b) mp: 86–88°C; IR (KBr, cm^{-1}): 3422 (–NHCO–), 3321, 3186 (–NH₂), 1623 (–NHCO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 4.82 (brs, 2H, NH₂), 7.12 (dd, 1H, $J=4.91$ Hz, Ar-H), 7.38 (dd, 1H, $J=3.86$ Hz, Ar-H), 7.76 (dd, 1H, $J=4.91$ Hz, Ar-H), 7.91 (s, 1H, Ar-H), 8.34 (s, 1H, Ar-H); MS (ESI): m/z [(M+H)⁺]: 245. *Anal.* Calcd for $\text{C}_{10}\text{H}_7\text{F}_3\text{N}_2\text{S}$: C 48.18, H 2.89, N 11.47%. Found: C 48.19, H 2.90, N 11.46%.

Synthesis of Diethyl 2-(((6-Phenyl-4-(trifluoromethyl)pyridin-2-yl)amino)methylene)malonate (4) The 6-phenyl/(thiophen-2-yl)-4-(trifluoromethyl)pyridin-2-amine **3** (0.500 g,

0.002 mol) and diethyl 2-(ethoxymethylene)malonate (0.450 g, 0.002 mol) were taken in absolute ethanol and it was refluxed for 10 h. After completion of the reaction, ethanol was completely removed under vacuum, washed with *n*-hexane and dried to afford diethyl 2-(((6-phenyl-4-(trifluoromethyl)pyridin-2-yl)amino)methylene)malonate **4**.

Diethyl 2-(((6-Phenyl)-4-(trifluoromethyl)pyridin-2-yl)amino)methylene)malonate (4a) mp: 142–144°C; IR (KBr, cm^{-1}): 3287 (–NH–), 1715 (–NHCO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 1.39 (t, 6H, –CH₃), 4.30 (q, 4H, –CH₂–), 6.99 (s, 1H, Ar-H), 7.45–7.50 (m, 3H, Ar-H), 7.64 (s, 1H, Ar-H), 8.03–8.08 (m, 2H, Ar-H), 9.29 (d, $J=12.46$ Hz, 1H, –NCH=), 11.31 (d, $J=12.46$ Hz, 1H, –NHC=); MS (EI): [(M)⁺]: 408. *Anal.* Calcd for $\text{C}_{20}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$: C 58.82, H 4.69, N 6.86%. Found: C 58.80, H 4.71, N 6.89%.

Diethyl 2-(((6-Thiophen-2-yl)-4-(trifluoromethyl)pyridin-2-yl)amino)methylene)malonate (4b) mp: 165–167°C; IR (KBr, cm^{-1}): 3310 (–NH–), 1723 (–NHCO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 1.36 (t, 6H, –CH₃), 4.32 (q, 4H, –CH₂–), 7.02 (dd, 1H, $J=4.87$ Hz, Ar-H), 7.41 (dd, 1H, $J=3.88$ Hz, Ar-H), 7.62 (dd, 1H, $J=4.87$ Hz, Ar-H), 7.92 (s, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 9.25 (d, $J=12.42$ Hz, 1H, –NCH=), 11.32 (d, $J=12.42$ Hz, 1H, –NHC=); MS (EI): [(M+H)⁺]: 415. *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_4\text{S}$: C 52.17, H 4.13, N 6.76%. Found: C 52.18, H 4.13, N 6.78%.

Synthesis of Ethyl 4-Oxo-6-phenyl-8-(trifluoromethyl)-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (5)

Conventional Method

The diethyl 2-(((6-phenyl-4-(trifluoromethyl)pyridin-2-yl)amino)methylene)malonate **4** (0.500 g, 0.001 mol) was taken in 5 mL of phosphorus oxychloride (POCl_3), and the reaction mixture was refluxed for 4–5 h at 140°C. After completion of the reaction, the excess POCl_3 was distilled under vacuum and the residue was treated with crushed ice. Yellow color solid was formed, filtered and washed with excess water.

MWI Method

The diethyl 2-(((6-phenyl-4-(trifluoromethyl)pyridin-2-yl)amino)methylene)malonate **4** (0.500 g, 0.001 mol) and catalytic amount of POCl_3 , and this reaction mixture was maintained in MWI at 200 W, 150°C for 15 min. Initially we tried it without POCl_3 , at 100°C for 10 min and at 120°C for 15 min, however there was no progress of reaction was observed. In the presence of POCl_3 , at 120°C for 15 min, we observed 40% of yield. After completion of the reaction it was allowed to cool to room temperature, and poured into crushed ice. As a result, yellow solid was formed, collected by filtration and washed with sat. sodium bicarbonate solution for removal of POCl_3 .

Ethyl 4-Oxo-6-phenyl-8-(trifluoromethyl)-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (5a) mp: 168–170°C; IR (KBr, cm^{-1}): 1726 (–CO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 1.36 (t, 3H, –CH₃), 4.33 (q, 2H, –CH₂–), 7.06 (s, 1H, Ar-H), 7.29–7.32 (m, 2H, Ar-H), 7.42–7.45 (m, 3H, Ar-H), 7.85 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H); MS (ESI): m/z [(M+H)⁺]: 363. *Anal.* Calcd for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3$: C 59.67, H 3.62, N 7.73%. Found: C 59.69, H 3.63, N 7.70%.

Ethyl 4-Oxo-6-thiophen-2-yl-8-(trifluoromethyl)-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (5b) mp: 198–200°C; IR (KBr, cm^{-1}): 1724 (–CO–); ¹H-NMR (CDCl_3 , 300 MHz) δ : 1.36 (t, 3H, –CH₃), 4.36 (q, 2H, –CH₂–), 7.01 (dd, 1H, $J=4.91$ Hz, Ar-H), 7.10 (s, 1H, Ar-H), 7.38 (dd, 1H, $J=3.86$ Hz, Ar-H), 7.65 (dd, 1H, $J=4.91$ Hz, Ar-H), 7.89 (s, 1H, Ar-H),

8.96 (s, 1H, Ar-H); MS(ESI): m/z [(M+H)⁺]: 369. Anal. Calcd for C₁₆H₁₁F₃N₂O₃S: C 52.17, H 3.01, N 7.61%. Found: C 52.18, H 3.02, N 7.60%.

General Procedure

Synthesis of *N*-Alkyl-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6) The ethyl 4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate **5** (0.4 g, 0.001 mol) and alkyl amine (0.6 g, 0.002 mol) were taken in sealed tube, refluxed for 6 h. After completion of the reaction, the reaction mixture was allowed to cool, filtered, washed with *n*-hexane followed by water to give a yellow solid and dried.

***N*-Methyl-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6a)** mp: 191–193°C; IR (KBr, cm^{−1}): 3342 (−NHCO−), 1638 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 2.98 (d, 3H, −CH₃), 5.65 (brs, 1H, −NH−), 7.05 (s, 1H, Ar-H), 7.30–7.35 (m, 2H, Ar-H), 7.41–7.46 (m, 3H, Ar-H), 7.86 (s, 1H, Ar-H), 8.90 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 28.6, 115.4, 119.5, 122.3, 122.8, 123.1, 123.5, 125.2, 126.7, 127.1, 128.2, 129.3, 129.8, 142.1, 148.6, 158.1, 160.2; MS(ESI): m/z [(M+H)⁺]: 348. High resolution (HR)-MS m/z Calcd for C₁₇H₁₂F₃N₃O₂ [(M+H)⁺]: 348.0908, Found 348.0905.

***N*-Ethyl-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6b)** mp: 216–218°C; IR (KBr, cm^{−1}): 3340 (−NHCO−), 1635 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 1.32 (t, 3H, −CH₃), 4.32 (q, 2H, −CH₂−), 5.70 (brs, 1H, −NH−), 7.01 (s, 1H, Ar-H), 7.29–7.34 (m, 2H, Ar-H), 7.45–7.50 (m, 3H, Ar-H), 7.88 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 14.2, 29.1, 120.1, 121.2, 122.2, 122.8, 123.6, 124.7, 125.8, 126.5, 127.6, 128.4, 129.6, 130.1, 138.6, 145.4, 155.4, 159.3; MS(ESI): m/z [(M+H)⁺]: 362. HR-MS m/z Calcd for C₁₈H₁₄F₃N₃O₂ [(M+H)⁺]: 362.1010, Found 362.1007.

4-Oxo-6-phenyl-*N*-propyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6c) mp: 198–200°C; IR (KBr, cm^{−1}): 3346 (−NHCO−), 1627 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 1.08 (t, 3H, −CH₃), 1.79–1.88 (m, 2H, −CH₂−), 4.16 (t, 2H, −CH₂−), 5.71 (brs, 1H, −NH−), 7.02 (s, 1H, Ar-H), 7.30–7.35 (m, 2H, Ar-H), 7.46–7.52 (m, 3H, Ar-H), 7.89 (s, 1H, Ar-H), 8.90 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 12.1, 20.2, 42.2, 119.7, 120.3, 121.6, 122.3, 122.8, 124.2, 124.9, 125.3, 126.7, 128.3, 129.1, 135.7, 140.6, 148.8, 156.7, 159.8; MS(ESI): m/z [(M+H)⁺]: 376. HR-MS m/z Calcd for C₁₉H₁₆F₃N₃O₂ [(M+H)⁺]: 376.1220, Found 376.1223.

***N*-Cyclopentyl-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6d)** mp: 178–180°C; IR (KBr, cm^{−1}): 3341 (−NHCO−), 1626 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 1.79–1.89 (m, 4H, −CH₂−), 1.94–2.01 (m, 2H, −CH₂−), 2.28–2.36 (m, 2H, −CH₂−), 5.28–5.39 (m, 1H, =CH−), 5.68 (brs, 1H, −NH−), 7.01 (s, 1H, Ar-H), 7.29–7.35 (m, 2H, Ar-H), 7.46–7.53 (m, 3H, Ar-H), 7.90 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 21.2, 26.3, 42.6, 120.8, 121.7, 122.3, 123.5, 123.8, 124.4, 125.0, 126.1, 126.8, 127.4, 128.3, 129.5, 130.2, 137.2, 142.1, 149.4, 158.9, 160.1; MS(ESI): m/z [(M+H)⁺]: 402. HR-MS m/z Calcd for C₂₁H₁₈F₃N₃O₂ [(M+H)⁺]: 402.1380, Found 402.1383.

***N*-Benzyl-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6e)** mp: 232–234°C; IR

(KBr, cm^{−1}): 3339 (−NHCO−), 1621 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 5.65 (s, 2H, −CH₂−), 5.73 (brs, 1H, −NH−), 7.04 (s, 1H, Ar-H), 7.30–7.39 (m, 4H, Ar-H), 7.54–7.66 (m, 6H, Ar-H), 7.95 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 45.3, 119.3, 120.8, 121.5, 122.1, 122.4, 123.2, 123.5, 123.8, 124.1, 124.6, 124.9, 125.4, 126.1, 126.8, 127.2, 130.4, 132.6, 138.1, 143.2, 150.2, 159.2, 160.3; MS(ESI): m/z [(M+H)⁺]: 424. HR-MS m/z Calcd for C₂₃H₁₆F₃N₃O₂ [(M+H)⁺]: 424.1220, Found 424.1223.

***N*-(4-Methylbenzyl)-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6f)** mp: 252–254°C; IR (KBr, cm^{−1}): 3342 (−NHCO−), 1628 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 2.30 (s, 3H, −CH₃), 5.62 (s, 2H, −CH₂−), 5.72 (brs, 1H, −NH−), 7.06 (s, 1H, Ar-H), 7.29 (d, *J*=8.4 Hz, 2H, Ar-H), 7.36–7.40 (m, 3H, Ar-H), 7.44 (d, *J*=8.4 Hz, 2H, Ar-H), 7.54–7.66 (m, 2H, Ar-H), 7.94 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 25.3, 43.2, 118.5, 119.8, 121.3, 121.8, 122.2, 122.8, 123.2, 123.5, 123.9, 124.6, 125.3, 125.4, 126.2, 126.8, 127.5, 135.1, 136.3, 139.3, 142.4, 150.1, 155.8, 160.1; MS(ESI): m/z [(M+H)⁺]: 438. HR-MS m/z Calcd for C₂₄H₁₈F₃N₃O₂ [(M+H)⁺]: 438.1308, Found 438.1306.

***N*-(4-Fluorobenzyl)-4-oxo-6-phenyl-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6g)** mp: 238–240°C; IR (KBr, cm^{−1}): 3335 (−NHCO−), 1628 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 5.61 (s, 2H, −CH₂−), 5.79 (brs, 1H, −NH−), 7.02 (s, 1H, Ar-H), 7.12 (d, *J*=8.2 Hz, 2H, Ar-H), 7.34–7.38 (m, 3H, Ar-H), 7.42 (d, *J*=8.2 Hz, 2H, Ar-H), 7.52–7.53 (m, 2H, Ar-H), 7.96 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 42.3, 119.2, 120.2, 120.8, 121.3, 121.9, 122.4, 123.0, 123.4, 123.8, 124.1, 124.8, 125.4, 126.1, 126.9, 127.5, 132.2, 133.8, 140.3, 142.6, 150.6, 156.6, 161.1; MS(ESI): m/z [(M+H)⁺]: 442. HR-MS m/z Calcd for C₂₃H₁₅F₄N₃O₂ [(M+H)⁺]: 442.1121, Found 442.1123.

***N*-Methyl-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6h)** mp: 162–164°C; IR (KBr, cm^{−1}): 3348 (−NHCO−), 1638 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 3.12 (d, 3H, −CH₃), 5.52 (brs, 1H, −NH−), 7.05 (s, 1H, Ar-H), 7.32 (dd, *J*=4.90 Hz, 1H, Ar-H), 7.65 (dd, *J*=4.90 Hz, 1H, Ar-H), 7.88 (dd, *J*=3.76 Hz, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 25.6, 120.3, 120.8, 121.7, 122.3, 123.7, 124.5, 125.7, 126.7, 127.3, 130.1, 143.1, 147.6, 155.1, 160.3; MS(ESI): m/z [(M+H)⁺]: 354. HR-MS m/z Calcd for C₁₅H₁₀F₃N₃O₂S [(M+H)⁺]: 354.0471, Found 354.0474.

***N*-Ethyl-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6i)** mp: 191–193°C; IR (KBr, cm^{−1}): 3340 (−NHCO−), 1632 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 1.34 (t, 3H, −CH₃), 4.35 (q, 2H, −CH₂−), 5.50 (brs, 1H, −NH−), 7.05 (s, 1H, Ar-H), 7.33 (dd, *J*=4.34 Hz, 1H, Ar-H), 7.65 (dd, *J*=4.34 Hz, 1H, Ar-H), 7.86 (dd, *J*=3.72 Hz, 1H, Ar-H), 7.93 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H); ¹³C-NMR (CDCl₃+DMSO-*d*₆, 75 MHz) δ: 12.3, 25.2, 121.3, 122.7, 123.2, 124.7, 125.9, 126.5, 127.2, 128.7, 129.6, 132.3, 138.8, 142.1, 156.4, 159.3; MS(ESI): m/z [(M+H)⁺]: 368. HR-MS m/z Calcd for C₁₆H₁₂F₃N₃O₂S [(M+H)⁺]: 368.0636, Found 368.0633.

4-Oxo-*N*-propyl-6-(thiophen-2-yl)-8-(trifluoromethyl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (6j) mp: 222–224°C; IR (KBr, cm^{−1}): 3342 (−NHCO−), 1628 (−NHCO−); ¹H-NMR (CDCl₃+DMSO-*d*₆, 300 MHz) δ: 1.05 (t, 3H, −CH₃), 1.79–1.88

(m, 2H, $-\text{CH}_2-$), 4.18 (t, 2H, $-\text{CH}_2-$), 5.70 (brs, 1H, $-\text{NH}-$), 7.02 (s, 1H, Ar-H), 7.33 (dd, $J=4.91$ Hz, 1H, Ar-H), 7.65 (dd, $J=4.91$ Hz, 1H, Ar-H), 7.86 (dd, $J=3.77$ Hz, 1H, Ar-H), 7.89 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H); ^{13}C -NMR (CDCl_3 +DMSO- d_6 , 75 MHz) δ : 13.8, 22.1, 43.3, 120.2, 121.8, 122.4, 123.5, 124.5, 126.1, 126.8, 128.2, 130.2, 134.8, 142.4, 148.9, 155.4, 160.2; MS(ESI): m/z [(M+H) $^+$]: 382. HR-MS m/z Calcd for $\text{C}_{17}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2\text{S}$ [(M+H) $^+$]: 382.0790, Found 382.0793.

N-Cyclopentyl-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (6k) mp: 198–200°C; IR (KBr, cm^{-1}): 3345 ($-\text{NHCO}-$), 1626 ($-\text{NHCO}-$); ^1H -NMR (CDCl_3 +DMSO- d_6 , 300 MHz) δ : 1.80–1.89 (m, 4H, $-\text{CH}_2-$), 1.92–1.98 (m, 2H, $-\text{CH}_2-$), 2.30–2.38 (m, 2H, $-\text{CH}_2-$), 5.28–5.39 (m, 1H, $-\text{CH}_2-$), 5.70 (brs, 1H, $-\text{NH}-$), 7.03 (s, 1H, Ar-H), 7.33 (dd, $J=4.66$ Hz, 1H, Ar-H), 7.65 (dd, $J=4.89$ Hz, 1H, Ar-H), 7.86 (dd, $J=3.76$ Hz, 1H, Ar-H), 7.92 (s, 1H, Ar-H), 8.91 (s, 1H, Ar-H); ^{13}C -NMR (CDCl_3 +DMSO- d_6 , 75 MHz) δ : 20.3, 24.8, 43.2, 121.2, 122.4, 123.1, 123.8, 124.2, 125.5, 126.2, 126.9, 127.4, 129.4, 130.1, 135.1, 142.8, 146.4, 156.4, 159.4; MS(ESI): m/z [(M+H) $^+$]: 408. HR-MS m/z Calcd for $\text{C}_{19}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2\text{S}$ [(M+H) $^+$]: 408.0931, Found 408.0934.

N-Benzyl-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (6l) mp: 245–247°C; IR (KBr, cm^{-1}): 3340 ($-\text{NHCO}-$), 1621 ($-\text{NHCO}-$); ^1H -NMR (CDCl_3 +DMSO- d_6 , 300 MHz) δ : 5.66 (s, 2H, $-\text{CH}_2-$), 5.73 (brs, 1H, $-\text{NH}-$), 7.04 (s, 1H, Ar-H), 7.30–7.35 (m, 3H, Ar-H), 7.54–7.61 (m, 3H, Ar-H), 7.66 (dd, $J=4.91$ Hz, 1H, Ar-H), 7.90 (dd, $J=3.76$ Hz, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 8.94 (s, 1H, Ar-H); ^{13}C -NMR (CDCl_3 +DMSO- d_6 , 75 MHz) δ : 44.3, 120.2, 120.9, 121.7, 122.3, 123.1, 123.8, 124.0, 124.8, 125.1, 125.8, 126.2, 127.5, 129.2, 130.2, 131.6, 136.2, 142.7, 149.3, 155.1, 160.1; MS(ESI): m/z [(M+H) $^+$]: 430. HR-MS m/z Calcd for $\text{C}_{21}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2\text{S}$ [(M+H) $^+$]: 430.0785, Found 430.0782.

N-(4-Methylbenzyl)-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (6m) mp: 235–237°C; IR (KBr, cm^{-1}): 3338 ($-\text{NHCO}-$), 1620 ($-\text{NHCO}-$); ^1H -NMR (CDCl_3 +DMSO- d_6 , 300 MHz) δ : 2.35 (s, 3H, $-\text{CH}_3$), 5.68 (s, 2H, $-\text{CH}_2-$), 5.75 (brs, 1H, $-\text{NH}-$), 7.02 (s, 1H, Ar-H), 7.19 (dd, $J=4.91$ Hz, 1H, Ar-H), 7.29 (d, $J=8.4$ Hz, 2H, Ar-H), 7.38 (d, $J=8.4$ Hz, 2H, Ar-H), 7.66 (dd, $J=4.91$ Hz, 1H, Ar-H), 7.90 (dd, $J=3.76$ Hz, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 8.96 (s, 1H, Ar-H); ^{13}C -NMR (CDCl_3 +DMSO- d_6 , 75 MHz) δ : 23.4, 43.7, 117.8, 120.5, 121.3, 122.5, 123.3, 123.6, 124.1, 124.8, 125.2, 125.8, 126.1, 127.3, 128.5, 130.5, 133.7, 138.2, 140.1, 152.3, 156.4, 159.3; MS(ESI): m/z [(M+H) $^+$]: 444. HR-MS m/z Calcd for $\text{C}_{22}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2\text{S}$ [(M+H) $^+$]: 444.0842, Found 444.0845.

N-(4-Fluorobenzyl)-4-oxo-6-(thiophen-2-yl)-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidine-3-carboxamide (6n) mp: 223–225°C; IR (KBr, cm^{-1}): 3341 ($-\text{NHCO}-$), 1618 ($-\text{NHCO}-$); ^1H -NMR (CDCl_3 +DMSO- d_6 , 300 MHz) δ : 5.65 (s, 2H, $-\text{CH}_2-$), 5.72 (brs, 1H, $-\text{NH}-$), 7.04 (s, 1H, Ar-H), 7.18 (dd, $J=4.88$ Hz, 1H, Ar-H), 7.31 (d, $J=8.1$ Hz, 2H, Ar-H), 7.42 (d, $J=8.1$ Hz, 2H, Ar-H), 7.62 (dd, $J=4.88$ Hz, 1H, Ar-H), 7.92 (dd, $J=3.77$ Hz, 1H, Ar-H), 8.10 (s, 1H, Ar-H), 8.99 (s, 1H, Ar-H); ^{13}C -NMR (CDCl_3 +DMSO- d_6 , 75 MHz) δ : 45.6, 120.1, 121.6, 122.1, 122.8, 123.4, 123.9, 124.3, 124.9, 125.5, 126.2, 126.9, 127.5, 128.3, 130.1, 132.8, 140.7, 143.8, 150.2, 155.6, 160.4; MS(ESI): m/z [(M+H) $^+$]: 448. HR-MS m/z Calcd for $\text{C}_{21}\text{H}_{13}\text{F}_4\text{N}_3\text{O}_2\text{S}$ [(M+H) $^+$]: 448.0644, Found 448.0646.

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