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Synthesis of Novel Amide-Functionalized Imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones and Their Biological Evaluation as Anticancer Agents

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Abstract—A series of novel amide-functionalized imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones were synthesized by propargylation of the key intermediate 2-amino-6-(trifluoromethyl)pyrimidin-4(3*H*)-one, followed by cyclization and amide functionalization. All synthesized compounds were evaluated for their anticancer activity against different human cancer cell lines, and most of them showed a good activity. In particular, pyrrolidine-derived imidazo[1,2-*a*]pyrimidine showed excellent anticancer activity against HeLa cell line.

Keywords: imidazo[1,2-*a*]pyrimidine, propargylation, trifluoromethyl pyrimidone, anticancer activity

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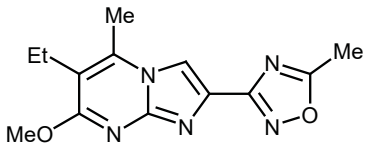
INTRODUCTION

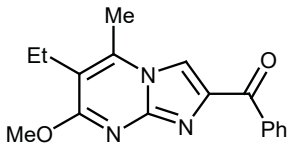
Cancer is a multifaceted disease that represents one of the leading causes of mortality in developed countries. Worldwide, one in eight deaths is due to cancer, and it is the second most common cause of death in the US, exceeded by heart diseases [1]. Chemotherapy is the mainstay for cancer treatment; however, the use of available chemotherapeutics is often limited due to undesirable side effects. It is important to identify new agents and new targets for the treatment of cancer.

Nitrogen-containing heterocyclic compounds featured prominently in early studies of chemistry, and they have received a great deal of attention in the literature due to their role as active pharmacophores of historical significance. Especially, pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in the chemotherapy of AIDS. For instance, pyrimethamine [2], and trimethoprim [3] are powerful antimalarial drugs, minoxidil [4] is used as antihypertensive, and sulfadiazine [5] is one of the chemotherapeutics containing a pyrimidine moiety.

The imidazo[1,2-*a*]pyrimidine nucleus is present in many biologically active compounds, and derivatives based thereon have been found to possess anxiolytic (Fig. 1) [6], cardiovascular [7], analgesic [8], antihypertensive [9], and neuroleptic [10, 11] activities. The



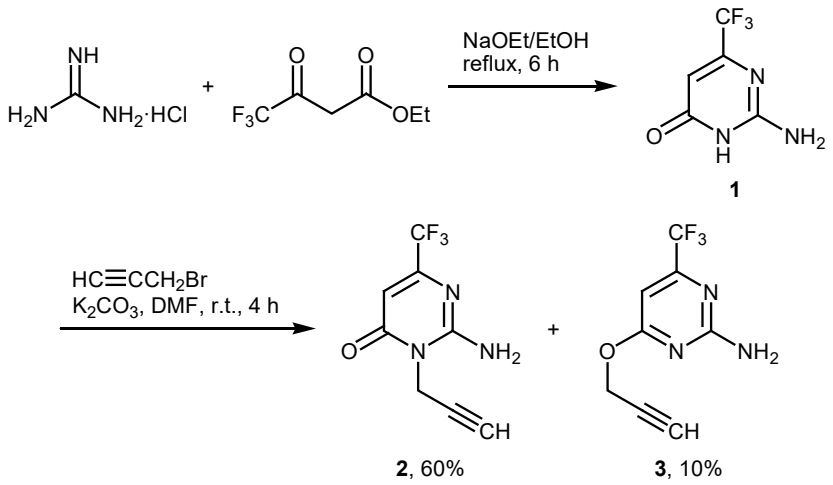
Fasiplon (RU 33203)
(anxiolytic)



Divaplon (RU 32698)
(anxiolytic & anticonvulsant)

Fig. 1. Imidazo[1,2-*a*]pyrimidine-based bioactive compounds.

Scheme 1.



structure of imidazo[1,2-*a*]pyrimidine is related to the purine ring system, and anti-inflammatory [12], insecticidal, acaricidal, and nematocidal activities [13] of imidazo[1,2-*a*]pyrimidine derivatives have been reported. Based on the importance of these moieties, herein we describe the synthesis of amide-functionalized imidazo[1,2-*a*]pyrimidines and their anticancer activity against four human cancer cell lines.

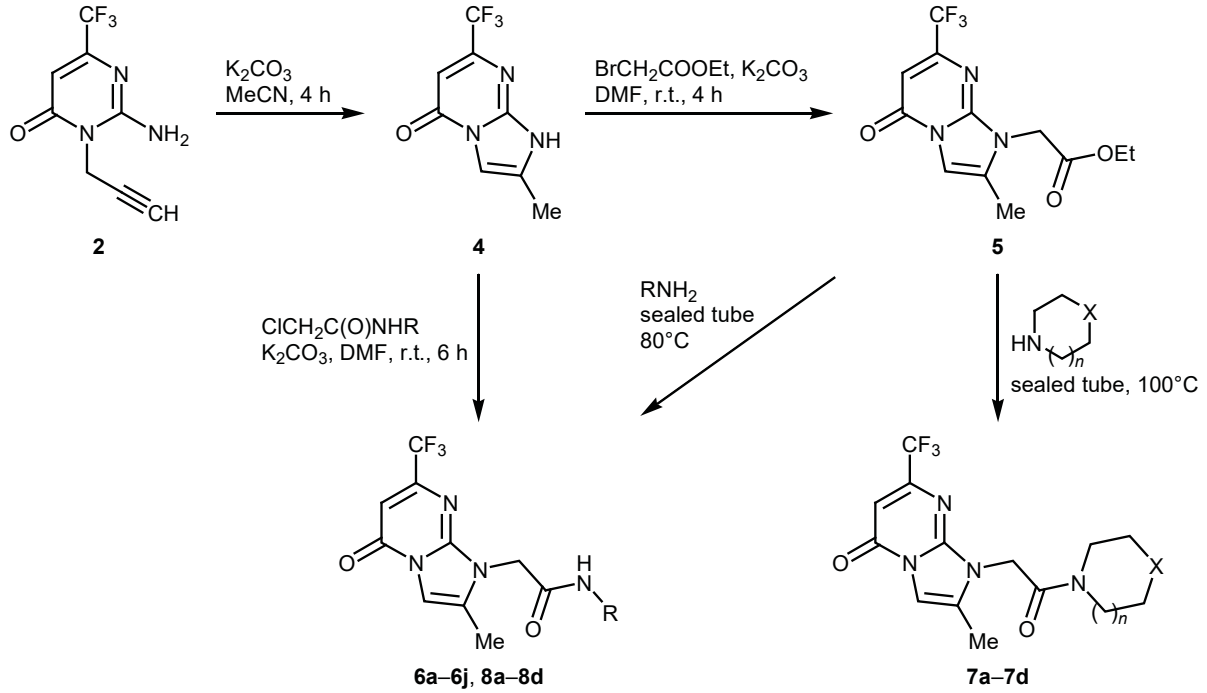
RESULTS AND DISCUSSION

2-Amino-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**1**) was synthesized by well known method [14, 15] from ethyl 4,4,4-trifluoro-3-oxobutanoate and guanidine hydrochloride. Compound **1** reacted with propargyl bromide in the presence of a base, resulting in the formation of two regioisomers, i.e., *N*-propargyl derivative **2** (60%) and *O*-propargyl analog **3** (10%) (Scheme 1). Both regioisomers were isolated in the pure state by column chromatography and were identified on the basis of their ^{1}H NMR spectra, which showed a singlet at δ 4.83 ppm due to NCH_2 group of **2** or at δ 5.01 ppm for OCH_2 group of **3**. Compound **2** underwent cyclization in acetonitrile in the presence of potassium carbonate to give imidazo[1,2-*a*]-pyrimidine **4**.

Compound **4** was used as a precursor to obtain final compounds functionalized with an acetamide moiety. For this purpose, it was reacted with ethyl bromoacetate in DMF using potassium carbonate as a base to produce exclusively ester **5**. Compound **5** was then reacted with various primary aliphatic amines and cyclic secondary amines under different conditions to afford acetamide derivatives **6** and **7**, respectively. *N*-Aryl acetamides **8a**–**8d** were synthesized as follows. Initially, we prepared the corresponding 2-chloro-*N*-arylacetamides by reacting chloroacetyl chloride with substituted anilines in dimethylformamide. Finally, the alkylation of compound **4** with these 2-chloro-*N*-arylacetamides in DMF in the presence of potassium carbonate as a base at room temperature gave target imidazopyrimidinylacetamides **8a**–**8d**. The synthetic sequence is outlined in Scheme 2.

Biological activity. The anticancer activity of compounds **6a**–**6j**, **7a**–**7d**, and **8a**–**8d** was evaluated against four human cancer cell lines, namely MCF7 human breast cancer (ATCC no. HTB-22), A549 human pancreatic cancer (ATCC no. CRL-1469), HeLa human cervical cancer (ATCC no. CCL-2), and MDA-MB-231 human breast cancer (ATCC no. HTB-26). 5-Fluorouracil and dimethyl sulfoxide were used as positive and negative controls, respectively. All tested compounds showed a good activity against the selected cancer cell lines, and their IC_{50} values are collected in Table 1. Most of the synthesized compounds exhibited promising anticancer activity with IC_{50} values ranging between 2.6 and 25.1 μg/mL. Compounds **7a** and **8b** turned out to be potent against human cervical cancer cell line (HeLa) and human pancreatic cancer cell line (A549) with IC_{50} values of 2.3 and 2.6 μg/mL. Compounds **6c**, **6e**, and **7c** exhibited promising activity against human pancreatic cancer cell line (A549) with IC_{50} values of 4.8, 4.8, and 4.3 μg/mL, respectively. Compounds **6c**–**6f** and **6i** were active against human breast cancer cell line MCF7 with IC_{50} values of 5.4, 5.1, 5.5, 5.1, and 5.7 μg/mL, respectively. Compounds **6d**, **6g**, and **8c** showed good activity against human cervical cancer cell line. Compounds **6a**, **6h**, **6i**, and **7b** showed good activity against MDA-MB-231 with IC_{50} values of 5.3, 6.0, 6.1, and 6.6 μg/mL, respectively.

Scheme 2.



6, R = Me (**a**), Et (**b**), Pr (**c**), $H_2NCH_2CH_2$ (**d**), $HOCH_2CH_2$ (**e**), *cyclo*-C_3H_5 (**f**), *cyclo*-C_5H_9 (**g**), *cyclo*-C_6H_{11} (**h**), 2-(morpholin-4-yl)ethyl (**i**), $PhCH_2$ (**j**); **7**, n = 0, X = CH_2 (**a**), n = 1, X = CH_2 (**b**), n = 1, X = O (**c**), n = 1, X = NMe (**d**); **8**, R = 3-ClC_6H_4 (**a**), 3-$MeOC_6H_4$ (**b**), 3-FC_6H_4 (**c**), 4-FC_6H_4 (**d**).

The structure–activity relationship analysis revealed that compound **6c** with a propyl group in the acetamide moiety showed promising anticancer activity; the activity of *N*-ethyl analog **6b** was lower, and it further decreased in going to *N*-methyl derivative **6a**. Amides **6d** and **6e** bearing a polar group on the amide nitrogen atom were more active than simple *N*-alkyl amides **6a**–**6c**. The presence of a pyrrolidine group in **7a** and methoxy group on the phenyl ring in **8b** favored their enhanced activity against human cervical cancer cell line (HeLa) and human pancreatic cancer cell line (A549) with IC_{50} values of 2.3 and 2.6 μg/mL, respectively. Compounds **7a** and **8b** are thus considered to be most potent among the other tested compounds.

EXPERIMENTAL

The melting points were measured in open glass capillaries on a Casia-Siamia (VMP-AM) melting point apparatus and are uncorrected. The IR spectra were recorded in KBr on a Perkin Elmer FTIR 240C spectrophotometer using KBr optics. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 300 spectrometer at 300 and 75 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The high-resolution mass spectra (electrospray ionization) were run on a determined by using a Bruker microTOF-Q II HRMS/MS instrument. The progress of reactions was monitored by thin-layer chromatography (TLC) on precoated silica gel 60 F254 plates; spots were visualized with UV light. Merck silica gel (60–120 mesh) was used for column chromatography.

Ethyl 2-[2-methyl-5-oxo-7-(trifluoromethyl)-imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetate (5). 2-Methyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**4**), 100 mg, 0.46 mmol) was dissolved in DMF (5 mL), potassium carbonate (0.28 mmol) was added, and ethyl 2-bromoacetate (0.51 mmol) was then slowly added. The mixture was stirred at room temperature for 4 h. After completion of the reaction, the mixture was poured onto crushed ice, and the precipitate was filtered off and dried. Yield 89%, white powder, mp 110–114°C. IR spectrum, ν, cm^{-1}: 1656 (C=O), 1589 (C=N), 1287 (C–F). ^1H NMR spectrum, δ, ppm: 1.28 t (3H, J = 7.17 Hz, Me), 2.39 s (3H, CH_3), 4.24 q (2H, J = 7.17 Hz, OCH_2), 4.99 s (2H, NCH_2), 6.34 s (1H, H_{arom}), 7.45 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 9.3, 13.5, 42.8, 61.9, 97.4, 103.7, 117.5 q (J = 274.1 Hz), 128.9, 146.4, 151.1 q (J = 34.3 Hz), 156.4, 166.1. Mass spectrum: m/z 304.0909 $[M + H]^+$. Calculated for $C_{12}H_{12}F_3N_3O_3$: M + H 304.0903.

Table 1. Anticancer activity of compounds **6a**–**6j**, **7a**–**7d**, and **8a**–**8d**[a]

Compound no.	IC_{50},[b] μg/mL			
	MCF7	A549	HeLa	MDA-MB-231
6a	10.6±0.17	9.2±0.59	10.9±0.8	5.3±0.11
6b	10.4±0.76	22.8±0.62	10.6±0.98	15.3±0.27
6c	5.4±0.29	4.8±0.91	25.1±0.16	7.7±0.02
6d	5.1±0.67	9.2±0.87	5.5±0.30	18.1±0.89
6e	5.5±0.63	4.8±0.97	9.3±0.45	9.7±0.73
6f	5.1±0.38	9.5±0.37	16.2±0.36	9.8±0.92
6g	6.2±0.77	9.5±0.88	6.7±0.85	14.2±0.78
6h	10.0±0.84	7.6±0.91	11.7±0.82	6.0±0.19
6i	5.7±0.52	5.4±0.98	10.2±0.38	6.1±0.56
6j	11.5±0.74	5.9±0.84	7.5±0.64	18.0±0.02
7a	12.5±0.66	11.8±0.44	2.3±0.63	7.7±0.20
7b	6.7±0.95	5.1±0.15	12.9±0.4	6.6±0.51
7c	7.1±0.95	4.3±0.66	13.8±0.78	17.6±0.06
7d	11.3±0.71	13.3±0.48	15.7±0.17	14.3±0.65
8a	6.4±0.613	11.0±0.96	8.3±0.042	17.4±0.71
8b	13.6±0.11	2.6±0.32	15.3±0.59	20.6±0.66
8c	11.5±0.6	9.0±0.18	6.9±0.32	8.5±0.72
8d	13.7±0.69	11.1±0.23	13.6±0.31	16.9±0.19
5-Fluorouracil	1.4±0.09	1.3±0.11	1.3±0.14	1.8±0.07

[a] Exponentially growing cells were treated with the test compounds at different concentrations for 48 h, and cell growth inhibition was determined by using MTT assay.
[b] Mean ± SE of three individual observations.

Amide-functionalized imidazo[1,2-*a*]pyrimidine derivatives 6a–6j and 7a–7d (*general procedure***).** A mixture of ethyl 2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetate (**4**, 0.33 mmol) and excess amine (1.6 mmol) was heated at 50–100°C in a sealed tube for 10–12 h. After completion of the reaction (TLC), the tube was cooled to room temperature and opened, the mixture was quenched with crushed ice, and the solid product was filtered off, washed with excess water, and dried.

***N*-Methyl-2-[2-methyl-5-oxo-7-(trifluoromethyl)-imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6a).** Yield 89%, white powder, mp >250°C. IR spectrum, ν, cm^{-1}: 3437 (N–H), 1656 (C=O), 1588 (C=N), 1287 (C–F). ^{1}H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 2.70 d (3H, NCH_3), 4.72 s (2H, NCH_2), 6.21 s (1H, H_{arom}), 7.34 s (1H, H_{arom}), 7.93 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 9.3, 25.6, 44.2, 96.2, 103.7, 121.2 q (J = 274.4 Hz), 130.7, 146.4, 149.6 q (J = 35.1 Hz), 156, 165.8. Mass spectrum: *m*/*z* 289.0908 $[M + H]^+$. Calculated for $C_{11}H_{11}F_3N_4O_2$: M + H 289.0907.

***N*-Ethyl-2-[2-methyl-5-oxo-7-(trifluoromethyl)-imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6b).** Yield 86%, white powder, mp 242–246°C. IR spectrum, ν, cm^{-1}: 3292 (N–H), 1655 (C=O), 1593 (C=N), 1284 (C–F). ^{1}H NMR spectrum, δ, ppm: 1.15 t (3H, J = 7.5 4 Hz, $CH_2C\mathbf{H}_3$), 2.38 s (3H, CH_3), 3.01 q (2H, NCH_2), 4.81 s (2H, NCH_2), 6.30 s (1H, H_{arom}), 7.65 s (1H, H_{arom}), 8.11 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 8.5, 13.2, 32.9, 43.2, 95.4, 102.4, 129.1, 145.5, 155.2, 163.9. Mass spectrum: *m*/*z* 303.1072 $[M + H]^+$. Calculated for $C_{12}H_{13}F_3N_4O_2$: M + H 303.1069.

2-[2-Methyl-5-oxo-7-(trifluoromethyl)imidazo-[1,2-*a*]pyrimidin-1(5*H*)-yl]-*N*-propylacetamide (6c).

Yield 79%, white powder, mp 230–234°C. IR spectrum, ν, cm^{-1}: 3289 (N–H), 1658 (C=O), 1590 (C=N), 1284 (C–F). ^1H NMR spectrum, δ, ppm: 0.92 t (3H, J = 7.41 Hz, CH_2CH_3), 1.50–1.58 m (2H, CH_2), 2.38 s (3H, CH_3), 3.18 q (2H, J = 6.35 Hz, NCH_2), 4.82 s (2H, NCH_2), 6.31 s (1H, H_{arom}), 7.57 s (1H, H_{arom}), 8.01 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 9.2, 10.6, 21.7, 40.5, 43.9, 96.4, 103.08, 129.6, 146.1, 150.5, 156.1, 164.7. Mass spectrum: *m*/*z* 317.1226 $[M + H]^+$. Calculated for $C_{13}H_{15}F_3N_4O_2$: M + H 317.1225.

***N*-(2-Aminoethyl)-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6d).** Yield 73%, white powder, mp 222–226°C. IR spectrum, ν, cm^{-1}: 3382, 3361 (NH_2), 3289 (N–H), 1661 (C=O), 1591 (C=N), 1285 (C–F). ^1H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 3.35–3.40 m (2H, CH_2), 3.62–3.67 m (2H, CH_2), 4.87 s (2H, NCH_2), 6.33 s (1H, H_{arom}), 7.33 s (1H, H_{arom}), 7.43 s (2H, NH_2), 8.08 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 8.02, 40.3, 42.7, 58.2, 94.8, 102.02, 118.5, 128.1, 128.9, 163.9. Mass spectrum: *m*/*z* 319.1015 $[M + H]^+$. Calculated for $C_{12}H_{13}F_3N_4O_3$: M + H 319.1018.

***N*-(2-Hydroxyethyl)-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6e).** Yield 68%, white powder, mp 160–164°C. IR spectrum, ν, cm^{-1}: 3440 (O–H), 3290 (N–H), 1664 (C=O), 1585 (C=N), 1286 (C–F). ^1H NMR spectrum, δ, ppm: 2.38 s (3H, CH_3), 2.87 t (2H, J = 5.85 Hz, NH_2), 3.33–3.40 m (2H, CH_2), 4.86 s (2H, NCH_2), 6.33 s (1H, H_{arom}), 7.43 s (1H, H_{arom}), 8.35 s (1H, NH). Mass spectrum: *m*/*z* 318.1175 $[M + H]^+$. Calculated for $C_{12}H_{14}F_3N_5O_2$: M + H 318.1178.

***N*-Cyclopropyl-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6f).** Yield 83%, white powder, mp >250°C. IR spectrum, ν, cm^{-1}: 3288 (N–H), 1661 (C=O), 1589 (C=N), 1287 (C–F). ^1H NMR spectrum, δ, ppm: 0.53 m (2H, CH_2), 0.70–0.75 m (2H, CH_2), 2.37 s (3H, CH_3), 2.69–2.76 m (1H, CH), 4.77 s (2H, NCH_2), 6.31 s (1H, H_{arom}), 7.41 s (1H, H_{arom}), 7.55 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 5.5, 9.3, 22.3, 44.3, 96.1, 103.7, 121.4 q (J = 274.1 Hz), 130.9, 146.4, 149.8 q (J = 33.7 Hz), 155.9, 166.4. Mass spectrum: *m*/*z* 315.1075 $[M + H]^+$. Calculated for $C_{13}H_{13}F_3N_4O_2$: M + H 315.1069.

***N*-Cyclopentyl-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6g).** Yield 82%, white powder, mp >250°C. IR spectrum, ν, cm^{-1}: 3289 (N–H), 1659 (C=O), 1586 (C=N), 1286 (C–F). ^1H NMR spectrum, δ, ppm: 0.38 m (2H, CH_2), 0.61 m (2H, CH_2), 2.13 s (3H, CH_3), 2.27–2.44 m (4H, CH_2), 3.63–3.77 m (1H, CH), 4.60 s (2H, NCH_2), 6.20 s (1H, H_{arom}), 7.47 s (1H, H_{arom}), 8.37 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 5.7, 9.5, 22.5, 44.4, 96.4, 103.9, 121.4 q (J = 272.2 Hz), 131.2, 146.6, 150.05 q (J = 34.1 Hz), 156.3, 166.8. Mass spectrum: *m*/*z* 343.1384 $[M + H]^+$. Calculated for $C_{15}H_{17}F_3N_4O_2$: M + H 343.1382.

***N*-Cyclohexyl-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6h).** Yield 78%, white powder, mp 225–229°C. IR spectrum, ν, cm^{-1}: 3287 (N–H), 1657 (C=O), 1588 (C=N), 1285 (C–F). ^1H NMR spectrum, δ, ppm: 1.13–1.42 m (6H, CH_2), 1.69–1.79 m (2H, CH_2), 1.82–1.91 m (2H, CH_2), 2.37 s (3H, CH_3), 3.62–3.75 m (1H, CH), 4.80 s (2H, NCH_2), 6.30 s (1H, H_{arom}), 7.42 s (1H, H_{arom}), 7.97 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 9.07, 23.8, 24.5, 31.7, 43.8, 47.7, 96.1, 102.8, 129.5, 142.9, 145.9, 155.9, 163.5. Mass spectrum: *m*/*z* 357.1543 $[M + H]^+$. Calculated for $C_{16}H_{19}F_3N_4O_2$: M + H 357.1538.

2-[2-Methyl-5-oxo-7-(trifluoromethyl)imidazo-[1,2-*a*]pyrimidin-1(5*H*)-yl]-*N*-[2-(morpholin-4-yl)-ethyl]acetamide (6i). Yield 72%, white powder, mp 181–185°C. IR spectrum, ν, cm^{-1}: 3303 (N–H), 1677 (C=O), 1589 (C=N), 1284 (C–F). ^1H NMR spectrum, δ, ppm: 2.16 s (3H, CH_3), 2.35–2.41 m (4H, NCH_2), 2.43–2.49 m (4H, OCH_2), 3.32–3.39 m (2H, CH_2), 3.66 t (2H, J = 4.53 Hz, CH_2), 4.85 s (2H, NCH_2), 6.30 s (1H, H_{arom}), 7.45 s (1H, H_{arom}), 8.02–8.09 br.s (1H, NH). Mass spectrum: *m*/*z* 388.1597 $[M + H]^+$. Calculated for $C_{16}H_{20}F_3N_5O_3$: M + H 388.1596.

***N*-Benzyl-2-[2-methyl-5-oxo-7-(trifluoromethyl)-imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamide (6j).** Yield 65%, white powder, mp 145–149°C. IR spectrum, ν, cm^{-1}: 3278 (N–H), 1670 (C=O), 1583 (C=N), 1283 (C–F). ^1H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 4.44 d (2H, J = 5.47 Hz, CH_2), 4.87 s (2H, NCH_2), 6.34 s (1H, H_{arom}), 7.24–7.37 m (5H, H_{arom}), 7.42 s (1H, H_{arom}), 8.55–8.62 br.s (1H, NH). Mass spectrum: *m*/*z* 365 365.1229 $[M + H]^+$. Calculated for $C_{17}H_{15}F_3N_4O_2$: M + H 365.1225.

2-Methyl-1-[2-oxo-2-(pyrrolidin-1-yl)ethyl]-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (7a). Yield 58%, white powder, mp 204–206°C. IR spectrum, ν, cm^{-1}: 1655 (C=O), 1589 (C=N), 1278 (C–F). ^1H NMR spectrum, δ, ppm: 1.87–1.98 m (2H, CH_2), 2.03–2.14 m (2H, CH_2), 2.37 s (3H, CH_3), 3.48 t (2H, J = 6.60 Hz, CH_2), 3.69 t (2H, J = 6.60 Hz, CH_2),

4.97 s (2H, NCH_2), 6.28 s (1H, H_{arom}), 7.45 s (1H, H_{arom}). Mass spectrum: *m*/*z* 329.1220 $[M + H]^+$. Calculated for $C_{14}H_{15}F_3N_4O_2$: *M* + H 329.1225.

2-Methyl-1-[2-oxo-2-(piperidin-1-yl)ethyl]-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (7b). Yield 55%, white powder, mp 183–187°C. IR spectrum, ν, cm^{-1}: 1657 (C=O), 1591 (C=N), 1281 (C–F). ^1H NMR spectrum, δ, ppm: 1.59–1.75 m (6H, CH_2), 2.35 s (3H, CH_3), 3.54–3.61 m (4H, CH), 4.92 s (2H, NCH_2), 6.39 s (1H, H_{arom}), 7.41 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 8.6, 22.6, 24.7, 42.8, 44.5, 44.9, 95.6, 102.4, 120.2 q (*J* = 273.5 Hz), 129.4, 145.5, 149.6 q (*J* = 32.9), 155.4, 162.1. Mass spectrum: *m*/*z* 343.1385 $[M + H]^+$. Calculated for $C_{15}H_{17}F_3N_4O_2$: *M* + H 343.1382.

2-Methyl-1-[2-(morpholin-4-yl)-2-oxoethyl]-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (7c). Yield 84%, white powder, mp 246–250°C. IR spectrum, ν, cm^{-1}: 1657 (C=O), 1591 (C=N), 1281 (C–F). ^1H NMR spectrum, δ, ppm: 2.28 s (3H, CH_3), 3.25–3.30 m (4H, NCH_2), 3.52–3.57 m (4H, OCH_2), 4.82 s (2H, NCH_2), 6.21 s (1H, H_{arom}), 7.37 s (1H, H_{arom}). Mass spectrum: *m*/*z* 345.1181 $[M + H]^+$. Calculated for $C_{14}H_{15}F_3N_4O_3$: *M* + H 345.1175.

2-Methyl-1-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (7d). Yield 60%, white powder, mp 120–124°C. IR spectrum, ν, cm^{-1}: 1664 (C=O), 1586 (C=N), 1281 (C–F). ^1H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 2.36 s (3H, NCH_3), 2.43 t (2H, *J* = 4.91 Hz, NCH_2), 2.54 t (2H, *J* = 4.91 Hz, NCH_2), 3.62–3.71 m (4H, NCH_2), 5.02 s (2H, NCH_2), 6.33 s (1H, H_{arom}), 7.51 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 8.4, 40.7, 41.9, 43.4, 44.4, 52.9, 53.4, 95.5, 102.3, 129.4, 145.4, 149.6, 155.2, 162.4. Mass spectrum: *m*/*z* 358.1497 $[M + H]^+$. Calculated for $C_{15}H_{18}F_3N_5O_2$: *M* + H.

***N*-Aryl-2-[2-methyl-5-oxo-7-(trifluoromethyl)-imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]acetamides 8a–8d (*general procedure*).** Potassium carbonate (0.28 mmol) was added to a solution of 2-methyl-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**4**, 100 mg, 0.461 mmol) in DMF (5 mL), and the corresponding *N*-arylchloroacetamide (0.51 mmol) was then slowly added. The mixture was stirred at room temperature for 4 h and poured onto crushed ice, and the precipitate was filtered and dried.

***N*-(3-Chlorophenyl)-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]-acetamide (8a).** Yield 89%, white powder, mp 168–172°C. IR spectrum, ν, cm^{-1}: 1664 (C=O), 1586 (C=N), 1281 (C–F). ^1H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 5.07 s (2H, NCH_2), 6.35 s (1H, H_{arom}), 7.15 d (1H, *J* = 7.74 Hz, H_{arom}), 7.33–7.46 m (2H, H_{arom}), 7.68 s (1H, H_{arom}), 7.77 s (1H, H_{arom}), 10.72 s (1H, NH). Mass spectrum: *m*/*z* 385.0677 $[M + H]^+$. Calculated for $C_{16}H_{12}ClF_3N_4O_2$: *M* + H 385.0679.

***N*-(3-Methoxyphenyl)-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]-acetamide (8b).** Yield 86%, white powder, mp 151–155°C. IR spectrum, ν, cm^{-1}: 1664 (C=O), 1586 (C=N), 1281 (C–F). ^1H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 3.71 s (3H, OCH_3), 5.04 s (2H, NCH_2), 6.27 s (1H, H_{arom}), 6.62 d (1H, *J* = 8.49 Hz, H_{arom}), 7.06–7.10 m (2H, H_{arom}), 7.18 t (1H, *J* = 8.49 Hz, H_{arom}), 7.27 s (1H, H_{arom}), 10.46 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 7.5, 42.9, 52.8, 94.4, 101.7, 103.1, 107.3, 109.4, 118.8 q (*J* = 274.5 Hz), 127.4, 128.8, 137.3, 144.6, 147.7 q (*J* = 34.6 Hz), 153.9, 157.5, 162.1. Mass spectrum: *m*/*z* 381.1177 $[M + H]^+$. Calculated for $C_{17}H_{15}F_3N_4O_3$: *M* + H 381.1175.

***N*-(3-Fluorophenyl)-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]-acetamide (8c).** Yield 85%, white powder, mp 156–160°C. IR spectrum, ν, cm^{-1}: 1664 (C=O), 1586 (C=N), 1281 (C–F). ^1H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 5.06 s (2H, NCH_2), 6.35 s (1H, H_{arom}), 6.93 t (1H, *J* = 8.49 Hz, H_{arom}), 7.25–7.44 m (2H, H_{arom}), 7.54 m (1H, H_{arom}), 7.68 s (1H, H_{arom}), 10.76 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 9.4, 44.9, 96.4, 103.8, 106.1 d (*J* = 26.40 Hz), 110.3 d (*J* = 20.35 Hz), 115.0, 120.09 q (*J* = 275.09 Hz), 130.5, 131.1, 139.7, 146.5, 149.6 q (*J* = 34.11 Hz), 155.9, 161.8, 164.6. Mass spectrum: *m*/*z* 369.0976 $[M + H]^+$. Calculated for $C_{16}H_{12}F_4N_4O_2$: *M* + H 369.0975.

***N*-(4-Fluorophenyl)-2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]-acetamide (8d).** Yield 88%, white powder, mp 145–149°C. IR spectrum, ν, cm^{-1}: 1664 (C=O), 1586 (C=N), 1281 (C–F). ^1H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 5.01 s (2H, NCH_2), 6.21 s (1H, H_{arom}), 6.90–7.01 m (2H, H_{arom}), 7.48–7.58 m (2H, H_{arom}), 7.89 s (1H, H_{arom}), 10.41 s (1H, NH). Mass spectrum: *m*/*z* 369.0976 $[M + H]^+$. Calculated for $C_{16}H_{12}F_4N_4O_2$: *M* + H 369.0975.

CONCLUSIONS

A series of new N-substituted 2-[2-methyl-5-oxo-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidin-1(5*H*)-yl]-acetamides have been synthesized, and their in vitro anticancer activity against some human cancer cell lines has been evaluated. Among the synthesized

compounds, *N*-(2-hydroxyethyl), *N*-[2-(morpholin-4-yl)ethyl], and *N*,*N*-pentamethylene derivatives showed potent anticancer activities in comparison with standard drugs, and the other compounds showed good activity against four tumor cell lines. Studies aimed at improving the biological activity of the imidazo-[1,2-*a*]pyrimidine scaffold are underway

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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