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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Broad-spectrum antiproliferative activity of a series of 6-(4-fluorophenyl)-5-(2-substituted pyrimidin-4-yl)imidazo [2,1-*b*]thiazole derivatives

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Abstract This article described the synthesis and in vitro antiproliferative activities a series of 6-(4-fluorophenyl)-5-(2-substituted pyrimidin-4-yl)imidazo[2,1-*b*]thiazole derivatives. The nine target compounds were tested for in vitro antitumor effect against a panel of 55 cell lines of nine different cancer types at the NCI, and their activities were compared with that of Sorafenib as a reference standard drug. Compounds **1d** and **1e** possessing terminal arylamide moiety exerted superior potencies than Sorafenib against different cancer cell lines. Both compounds were more potent than Sorafenib against UO-31 renal cancer cell line and MCF7 breast cancer cell line. Compound **1d** was also more potent than Sorafenib against COLO 205 colon cancer cell line, and compound **1e** showed higher potency than Sorafenib against OVCAR-3 ovarian cancer cell line and DU-145 prostate cancel cell line also. For instance, the IC_{50} value of compound **1e** against DU-145 prostate cancer cell line was 1.04 μM, which is threefold more potent than Sorafenib.

Keywords Antiproliferative · Biological activity · Broad-spectrum · Imidazo[2,1-*b*]thiazole

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Introduction

Cancer is one of the major leading causes of death worldwide. According to the American Cancer Society report, more than 585,720 cancer patients estimated to die, and more than 1.6 million new cancer cases were diagnosed in 2014 only in USA (http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/). More than 70 % of all cancer deaths have occurred in low- and middle-income countries. According to the World Health Organization (WHO) report, death cases because of cancer all over the globe are estimated to exceed 13 million in 2030 (http://www.who.int/mediacentre/factsheets/fs297/en/). In spite of the extensive efforts and investment in research, more efforts are required from the medicinal chemists for development of more efficient and safer anticancer agents.

Imidazo[2,1-*b*]thiazole nucleus is a very interesting scaffold in terms of chemistry and biological activity. Several reports have recently highlighted imidazo[2,1-*b*]thiazole derivatives as potential antiproliferative agents

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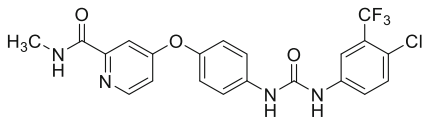


Fig. 1 Structure of Sorafenib

against several human cancer cell lines (Abdel-Maksoud *et al.*, 2015; Andreani *et al.*, 2000; Andreani *et al.*, 2005; El-Subbagh *et al.*, 2001; Gürsoy and Güzeldemirci, 2007; Park and Oh, 2010; Park *et al.*, 2011; Srimanth *et al.*, 2002). We have previously reported the activity of a series of imidazo[2,1-*b*]thiazole derivatives possessing terminal arylamide or aryl urea moiety against A375P human melanoma cell line (Park and Oh, 2010). Herein, we report their activity against a panel of 55 cancer cell line panel of nine different cancer types. The biological results of the target compounds were compared with those of Sorafenib (Fig. 1) as a reference standard drug.

Experimental

Synthesis of the target compounds

General

All melting points were obtained on a Walden Precision Apparatus Electrothermal 9300 apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectroscopy was performed using either a Bruker ARX-300, 300 MHz spectrometer or a Bruker ARX-400, 400 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA) with TMS as an internal standard. IR spectra (KBr disks) were recorded with a Bruker FT-IR instrument (Bruker Bioscience, Billerica, MA, USA). Purity of the target compounds was proven to be more than 95 % by HPLC. The chromatographic system consisting of an ACQUITY UPLC (Waters, USA) coupled with SYNAPT G2 (Waters, UK) mass spectrometer equipped with an ESI source. The HRMS was done on positive mode with Capillary: 3.1 kV, desolvation gas: 800 L/h and Extraction cone 4.0. Chromatography was performed on ACQUITY UPLC BEH C18 (1.6 µm, 2.1 × 100 mm) at 25 °C using acetonitrile and water (containing 0.1 % formic acid as mobile phase in gradient elution mode at a flow rate of 0.4 mL/min, and injection volume: 5 µL. The data acquisition was under the control of Mass Hunter workstation software. LC-MS analyses were carried out in positive ion mode by electrospray ionization (ESI) on (Waters) ACQUITY UPLC triple Quadrupole (Xevo TQD) instrument equipped with MassLynx software. The samples were dissolved in methanol diluted in spray solution (methanol/water 1:1 $^{v}/_{v}$ 0.1 % formic acid) and infused directly in combined mode with a flow rate of 0.3 mL/min. Unless otherwise noted, all solvents and reagents were commercially available and used without further purification.

6-(4-Fluorophenyl)imidazo[2,1-b]thiazole (**3**) (Ashwell *et al.*, 2005)

A solution of 2-aminothiazole (**2**, 2.37 g, 23 mmol) and α-bromo-4-fluoroacetophenone (5.0 g, 23 mmol) in ethanol (60 mL) was heated under reflux for 16 h. The mixture was concentrated to 30 mL under reduced pressure. Ice water (40 mL) was added to the remaining solution; then, 30 % ammonium hydroxide solution was added. The formed orange colored solid was filtered, washed with water, and dried overnight under vacuum at 50°C. 4.3 g of the title compound was obtained (yield 86 %). Mp 132–133°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.84–7.79 (m, 2H), 7.70 (s, 1H), 7.44 (d, 1H, $J = 3.0$ Hz), 7.12 (t, 2H, $J = 9.0$ Hz), 6.84 (d, 1H, $J = 3.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.2, 147.0, 130.3, 126.9, 126.8, 118.4, 115.7, 115.4, 112.5, 107.6; LC-MS: m/z calculated for $C_{11}H_7FN_2S$: 218, Found: 219 $(M+1)^+$.

6-(4-Fluorophenyl)-5-(2-(methylthio)pyrimidin-4-yl)imidazo[2,1-b]thiazole (**4**) A mixture of compound **3** (6.0 g, 27.6 mmol), 4-chloro-2-(methylthio)pyrimidine (10.4 g, 41.3 mmol), cesium carbonate (13.4 g, 41.3 mmol), palladium acetate (1.22 g, 5.5 mmol), and triphenylphosphine (2.896 g, 11.04 mmol) in anhydrous DMF (60 mL) was stirred at 80 °C for 12 h. The mixture was cooled to room temperature and separated between ethyl acetate (150 mL) and water (200 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer extracts were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The organic solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography. The purified title product was obtained as white solid (3.5 g, 37 %). Mp 151–152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, 1H, $J = 6.0$ Hz), 8.30 (d, 1H, $J = 6.0$ Hz), 7.67–7.62 (m, 2H), 7.22–7.16 (m, 2H), 7.02 (d, 1H, $J = 6.0$ Hz), 6.88 (d, 1H, $J = 3.0$ Hz), 2.67 (s, 3H); ^{13}C NMR (CDCl, 75 MHz) δ 172.5, 156.2, 150.0, 146.5, 131.0, 130.9, 126.7, 126.6, 118.5, 115.9, 115.6, 115.5, 115.2, 112.9, 112.4, 111.7, 107.7, 14.1; LC-MS: m/z calculated for $C_{16}H_{11}FN_4S_2$: 342. Found: 343 $(M+1)^+$.

6-(4-Fluorophenyl)-5-(2-(methylsulfonyl)pyrimidin-4-yl)imidazo[2,1-b]thiazole (**5**) To a solution of compound **4** (2.05 g, 6 mmol) in methanol (250 mL), a solution of oxone (12.3 g, 18 mmol) in water (50 mL) was added. The mixture was stirred at room temperature for 16 h. The organic solvent was evaporated under reduced pressure, the remaining aqueous solution was extracted with CH_2Cl_2

(50 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The organic solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography. 2.1 g of the title compound was obtained, yield 98 %. Mp 197–198°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.90 (d, 1H, J = 3.0 Hz), 8.55 (d, 1H, J = 6.0 Hz), 7.68–7.63 (m, 2H), 7.36 (d, 1H, J = 6.0 Hz), 7.30–7.21 (m, 2H), 7.11 (d, 1H, J = 6.0 Hz), 3.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 165.7, 157.3, 157.0, 154.2, 151.7, 131.0, 130.9, 129.9, 123.1, 119.4, 117.4, 116.4, 116.1, 114.2, 39.2; LC-MS: m/z calculated for $C_{16}H_{11}FN_4O_2S_2$: 374. Found: 375 (M+1) $^+$.

*Benzyl 2-hydroxyethylcarbamate (**7**)* (Tully *et al.*, 2006) To a stirred solution of 2-Aminoethanol (**6**, 4.94 mL, 81.86 mmol) in CH_2Cl_2 (50 mL) at 0 °C, triethylamine (22.2 mL, 159.6 mmol) was added dropwise. Benzyloxycarbonyl chloride (15.2 mL, 106.42 mmol) was added dropwise over 30 min. After completion of the addition, the mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The desired product was obtained as white solid (9.5 g, 59 %). Mp 73–75°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 5H), 5.73 (bs, 1H), 5.10 (s, 2H), 3.74 (s, 2H), 3.29 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.2, 136.4, 128.5, 128.1, 128.1, 66.8, 61.7, 43.4; LC-MS: m/z calculated for $C_{10}H_{13}NO_3$: 195, Found: 196 (M+1) $^+$.

*2-(Benzyloxycarbonylamino)ethyl methanesulfonate (**8**)* (Townsend and Basak, 1991)

To a stirred solution of compound **7** (29.7 g, 152 mmol) in CH_2Cl_2 (300 mL) at 0 °C, triethylamine (31.58 mL, 227 mmol) was added dropwise. Methanesulfonyl chloride (14.1 mL, 182 mmol) was then added dropwise to the reaction mixture over 30 min. After completion of the addition, the mixture was stirred at 0 °C for 1 h. The mixture was quenched with water (300 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The desired product was obtained (22 g, 53 %). Mp 70 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (s, 5H), 5.52 (bs, 1H), 5.11 (s, 2H), 4.28 (t, 2H, J = 6.0 Hz), 3.52 (s, 2H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 136.3, 128.5, 128.2, 128.1, 68.6, 66.9, 40.4, 37.3; LC-MS: m/z calculated for $C_{11}H_{15}NO_5S$: 273, Found: 274 (M+1) $^+$.

*Benzyl 2-azidoethylcarbamate (**9**)* A mixture of sodium azide (4.75 g, 73.2 mmol) and compound **8** (5.0 g, 18.3 mmol) in DMSO (50 mL) was stirred at 70 °C for 2 h. The mixture was allowed to cool to room temperature, quenched with water (200 mL), and then extracted with ethyl acetate (3 × 200 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The title product was obtained as a colorless oil (3.8 g, 94 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 5H), 5.11 (s, 2H), 3.41 (d, 2H, J = 6.0 Hz), 3.35 (t, 2H, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.6, 138.1, 136.5, 128.3, 127.9, 66.3, 40.5, 40.3; LC-MS: m/z calculated for $C_{10}H_{12}N_4O_2$: 220, Found: 221 (M+1) $^+$.

*Benzyl 2-aminoethylcarbamate (**10**)* Triphenylphosphine (6.7 g, 25.56 mmol) and water (15 mL) were added to a solution of compound **9** (3.8 g, 17.4 mmol) in MeOH (40 mL). The mixture was heated under reflux for 2 h. The mixture was concentrated under reduced pressure and purified by column chromatography. The target product was obtained as light brown oil (3 g, 90 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (s, 5H), 5.73 (bs, 1H), 5.08 (s, 2H), 3.19 (bs, 2H), 2.76 (bs, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.8, 136.6, 128.5, 128.0, 66.6, 43.6, 41.5; LC-MS: m/z calculated for $C_{10}H_{14}N_2O_2$: 194, Found :195 (M+1) $^+$.

*Benzyl 2-(3-phenylureido)ethylcarbamate (**11a**)* A solution of compound **10** (0.15 g, 0.772 mmol) and phenyl isocyanate (0.17 g, 0.926 mmol) in THF (5 mL) was stirred at room temperature for 2 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography. The desired product was obtained as white solid (0.2 g, 51 %). Mp 124–125°C; ^{1}H NMR (CD_3OD, 300 MHz) δ 7.70 (t, 1H, J = 3.0 Hz), 7.34–7.20 (m, 7H), 5.06 (d, 2H, J = 6.0 Hz), 3.37–3.26 (m, 4H).

Synthesis of compounds **11b**, **c** was carried out by the same procedure as described for preparation of **11a**.

11b. Yield: 60 %; mp 138–139°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, 5H), 7.18–7.14 (m, 1H), 6.99 (s, 1H), 6.78 (d, 1H, J = 9.0 Hz), 6.62 (dd, 1H, J = 2.4 and 2.4 Hz), 6.56 (bs, 1H), 5.27 (d, 1H, J = 14.1 Hz), 5.08 (s, 2H), 3.78 (s, 3H), 3.40–3.32 (m, 4H).

11c. Yield: 87 %; mp 108°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (s, 2H), 7.45 (d, 1H, J = 9.0 Hz), 7.26 (s, 5H), 5.72 (s, 1H), 5.49 (s, 1H), 5.12 (s, 1H), 5.06 (s, 2H), 3.38–3.29 (m, 4H).

*1-(2-Aminoethyl)-3-phenylurea (**12a**)* Pd/C (0.05 g) was added to a solution of compound **11a** (0.2 g, 0.52 mmol) in MeOH (10 mL). The mixture was stirred under hydrogen atmosphere at room temperature for 1 h. Pd/C was removed by Celite filter, and the filtrate was evaporated under reduced pressure. 0.08 g of the title product was obtained and used in the next step without further purification (yield 85.8 %).

Synthesis of compounds **12b**, **c** was carried out by the same procedure as described for preparation of **12a**

*Benzyl 2-benzamidoethylcarbamate (**13a**)* A mixture of compound **10** (0.15 g, 0.772 mmol), HOBt (0.23 g, 1.70 mmol), EDCI (0.37 g, 1.93 mmol), benzoic acid (0.19 g, 1.54 mmol), and TEA (0.32 mL, 2.32 mmol) in dry DMF (20 mL) was stirred at 80 °C for 8 h. The mixture was quenched with water (40 mL), then extracted with ethyl acetate (3 × 40 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The desired product was obtained as white solid (0.13 g, 56.4 %). Mp 126–128 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, 2H, J = 7.6 Hz), 7.51 (t, 1H, J = 4.0 Hz), 7.31 (s, 5H), 6.96 (bs, 1H), 5.30 (bs, 1H), 5.10 (s, 2H), 3.59 (q, 2H, J = 5.3 Hz), 3.47 (q, 2H, J = 5.6 Hz).

Synthesis of compounds **13b–f** was carried out by the same procedure as described for preparation of **13a**.

13b. Yield: 87 %; mp 139–140°C; ^{1}H-NMR (CD_3OD, 300 MHz) δ 7.71 (dd, 2H, J = 1.6 and 1.7 Hz), 7.35–7.25 (m, 7H), 5.08 (s, 2H), 3.49 (t, 2H, J = 5.9 Hz), 3.36 (t, 2H, J = 6.1 Hz).

13c. Yield: 85 %; mp 155–157°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (s, 1H), 7.32 (s, 6H), 6.94 (bs, 1H), 6.86 (d, 1H, J = 6.2 Hz), 5.25 (bs, 1H), 5.10 (s, 2H), 3.93 (s, 6H), 3.53 (t, 2H, J = 3.9 Hz), 3.48 (t, 2H, J = 3.8 Hz).

13d. Yield: 68 %; mp 153–155°C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.77 (bs, 1H), 8.18 (s, 1H), 8.13 (d, 1H, J = 7.8 Hz), 7.90 (d, 1H, J = 7.7 Hz), 7.72 (t, 1H, J = 7.5 Hz), 7.40–7.32 (m, 7H), 5.01 (s, 2H), 3.49–3.16 (m, 4H).

13e. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54 (s, 1H), 7.47 (s, 1H), 7.30 (s, 5H), 7.18 (s, 1H), 5.29 (bs, 1H), 5.09 (s, 2H), 3.85 (t, 4H, J = 4.8 Hz), 3.58 (q, 2H, J = 5.1 Hz), 3.47 (q, 2H, J = 5.3 Hz), 3.25 (t, 4H, J = 4.8 Hz).

13f. Yield: 73 %; mp 135–137°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 2H), 8.00 (bs, 1H), 7.84 (s, 1H), 7.68 (s, 1H), 7.25 (s, 5H), 7.08 (s, 1H), 5.57 (bs, 1H), 5.08 (s, 2H), 3.61 (q, 2H, J= 4.9 Hz), 3.48 (q, 2H, J= 5.3 Hz), 2.26 (s, 3H).

In addition, synthesis of compounds **14a-f** was carried out by the same procedure as described for preparation of **12a**.

*1-(2-(4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-ylamino)ethyl)-3-phenylurea (**1a**)* (Park and Oh, 2010)

A mixture of compound **5** (0.34 g, 0.92 mmol), compound **12a** (0.444 g, 2.48 mmol), and DIPEA (0.57 mL, 3.3 mmol) in DMSO (10 mL) was stirred at 80 °C for 8 h. The mixture was cooled to room temperature, quenched with water (20 mL), and then extracted with ethyl acetate (3 × 20 mL). The combined organic layer extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography. The title product was obtained as white solid (0.24 g, 56 %). Mp 140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, J = 4.4 Hz), 7.93 (d, 1H, J = 5.4 Hz), 7.56 (q, 2H, J = 4.6 Hz), 7.33 (d, 1H, J = 7.3 Hz), 7.21 (s, 4H), 7.12 (t, 2H, J = 8.4 Hz), 7.08–6.96 (m, 2H), 6.87 (d, 1H, J = 4.2 Hz), 6.41 (d, 1H, J = 5.4 Hz), 5.80 (bs, 1H), 3.58 (t, 2H, J = 5.2 Hz), 3.45 (d, 2H, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2, 157.1, 156.6, 138.6, 131.1, 131.0, 130.8, 129.1, 128.2, 123.6, 122.1, 120.8, 115.8, 115.6, 112.6, 42.1, 39.9; LC-MS: m/z calculated for $C_{24}H_{20}FN_7OS$: 473, Found: 474 $(M+1)^+$.

Synthesis of the target compounds **1b, c** and **1d–i**, was carried out by the same procedure as described for preparation of **1a**.

*1-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-3-(3-methoxyphenyl)urea (**1b**)* Yield: 68 %; mp 194–196 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.56 (s, 1H), 8.10 (d, 1H, J = 5.7 Hz), 7.63 (q, 1H, J = 4.6 Hz), 7.44 (bs, 1H), 7.30 (t, 1H, J = 8.8 Hz), 7.15–7.07 (m, 2H), 6.86 (d, 1H, J = 8.1 Hz), 6.46 (dd, 1H, J = 2.0 and 2.1 Hz), 6.31 (d, 1H, J = 5.3 Hz), 3.69 (s, 3H), 3.51–3.24 (m, 4H); LC-MS: m/z calculated for $C_{25}H_{22}FN_7O_2S$: 503, Found: 504 $(M+1)^+$.

*1-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-3-(3-(trifluoromethyl)phenyl)urea (**1c**)* Yield: 57 %; mp 146 °C; IR (KBr) [cm^{-1}]: 3333, 3116, 1663, 1497, 1444, 1333, 1165; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, 1H, J = 4.0 Hz), 7.99 (d, 1H, J = 8.0 Hz), 7.84 (dd, 1H, J = 4.0, J = 8.0 Hz), 7.70–7.58 (m, 4H), 7.14 (t, 2H, J = 8.0 Hz), 7.08 (t, 1H, J = 8.0 Hz), 6.93(d, 1H, J = 8.0 Hz), 6.48 (d, 1H, J = 8.0 Hz), 6.09 (bs, 1H), 3.67 (bs, 2H), 3.55 (t, 4H, J = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.2, 157.1, 156.9, 155.9, 152.1, 149.0, 139.5, 138.1, 131.6, 131.1, 131.0, 129.4, 122.1, 120.7, 115.9, 115.6, 112.6, 107.0,

41.9,40.0; HRMS calculated for $C_{25}H_{19}F_4N_7OS$: 541.1308, Found: 542.1389 $(M+H)^+$.

N-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)benzamide (**1d**) Yield: 60 %; mp 136 °C; IR (KBr) [cm^{-1}]: 3289, 3115, 1724, 1645, 1535, 1495, 1383, 1228; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, 1H, J = 4.0 Hz), 8.07 (d, 1H, J = 8.0 Hz), 7.71 (d, 2H, J = 4.0 Hz), 7.59 (dd, 3H, J = 4.0, J = 8.0 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.31(t, 2H, J = 8.0 Hz), 7.13 (dd, 2H, J = 4.0, J = 8.0 Hz), 6.90 (d, 1H, J = 4.0 Hz), 6.49 (d, 1H, J = 8.0 Hz), 6.05 (bs, 1H), 3.76 (bs, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 164.2, 162.7, 161.7, 157.1, 156.0, 152.1, 149.1, 134.2, 131.4, 131.1, 131.0, 128.3, 126.8, 121.9, 120.6, 115.8, 115.6, 112.7, 107.4, 41.4,40.9; HRMS calculated for $C_{24}H_{19}FN_6OS$, 458.1325 Found: 459.1491 $(M+H)^+$.

N-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-4-methoxybenzamide (**1e**) Yield: 66 %; mp 235°C; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 8.85 (bs, 1H), 8.54 (s, 1H), 8.11 (d, 1H, J = 5.1 Hz), 7.75 (d, 2H, J = 7.5 Hz), 7.62 (t, 3H, J = 6.6 Hz), 7.46 (d, 1H, J = 3.7 Hz), 7.33–7.23 (m, 3H), 6.30 (d, 1H, J = 5.3 Hz), 3.49–3.40 (m, 4H), 2.33 (s, 3H); LC-MS: m/z calculated for $C_{25}H_{21}FN_6O_2S$: 488, Found: 489 $(M+1)^+$.

N-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-3,4-dimethoxybenzamide (**1f**) Yield: 65 %; mp 208°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, J = 4.4 Hz), 8.08 (d, 1H, J = 5.3 Hz), 7.59 (q, 2H, J = 4.5 Hz), 7.40 (s, 1H), 7.37–7.29 (m, 1H), 7.12 (t, 2H, J = 8.4 Hz), 6.91 (d, 1H, J = 4.5 Hz), 6.60 (bs, 1H), 6.49 (d, 1H, J = 5.3 Hz), 5.78 (bs, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.77–3.64 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5, 162.7, 151.6, 149.1, 148.9, 131.1, 131.0, 121.8, 119.0, 115.8, 115.6, 112.7, 110.6, 109.9, 107.6, 56.0, 55.9, 41.9, 41.4; LC-MS: m/z calculated for $C_{26}H_{23}FN_6O_3S$: 518, Found: 519 $(M+1)^+$.

N-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-3-(trifluoromethyl)benzamide (**1g**) Yield: 59 %; mp 156–157°C; IR (KBr) [cm^{-1}]: 3298, 3133, 1645, 1535, 1452, 1415, 1278; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, 1H, J = 4.0 Hz), 8.07 (d, 1H, J = 8.0 Hz), 7.93 (s, 1H), 7.86 (bs, 1H), 7.69 (d, 1H, J = 8.0 Hz), 7.58 (dd, 2H, J = 4.0, J = 8.0 Hz), 7.44 (bs, 1H), 7.12 (t, 2H, J = 8.0 Hz), 6.89 (d, 1H, J = 4.0 Hz), 6.51(d, 1H, J = 8.0 Hz), 6.03 (bs, 1H), 3.77–7.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 164.2, 162.7, 161.8, 157.1, 152.2, 149.3, 135.1, 131.1, 131.0, 130.7, 130.7, 130.3, 129.0, 127.9, 123.8, 122.3, 121.9, 120.5, 115.8, 115.6, 112.6, 107.6, 41.1; HRMS calculated for $C_{25}H_{18}F_4N_6OS$, 526.1199, Found: 527.1285 $(M+H)^+$.

N-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)benzamide (**1h**) Yield: 48 %; mp 164–166°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, 1H, J = 3.2 Hz), 8.06 (d, 1H, J = 5.5 Hz), 7.62–7.54 (m, 3H), 7.29 (s, 1H), 7.15–7.09 (m, 3H), 6.91 (d, 1H, J = 4.5 Hz), 6.52 (d, 1H, J = 5.5 Hz), 5.69 (t, 1H, J = 4.5 Hz), 3.83 (t, 4H, J = 4.8 Hz), 3.77–3.72 (m, 4H), 3.21 (t, 4H, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.1, 162.7, 157.3, 156.9, 152.3, 149.5, 140.5, 138.1, 137.3, 134.4, 131.1, 130.6, 122.9, 121.9, 121.5, 120.5, 119.8, 115.8, 115.5, 114.1, 112.6, 107.7, 41.0, 13.5; LC-MS: m/z calculated for $C_{29}H_{22}F_4N_8OS$: 606, Found: 607 $(M+1)^+$.

N-(2-((4-(6-(4-Fluorophenyl)imidazo[2,1-b]thiazol-5-yl)pyrimidin-2-yl)amino)ethyl)-3-morpholino-5-(trifluoromethyl)benzamide (**1i**) Yield: 42 %; mp 155–157°C; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.50 (d, 1H, J = 4.5 Hz), 8.07 (s, 1H), 8.02 (d, 1H, J = 5.5 Hz), 7.90 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.55 (q, 2H, J = 4.6 Hz), 7.11 (t, 2H, J = 8.6 Hz), 7.02 (s, 1H), 6.91 (d, 1H, J = 4.5 Hz), 5.86 (bs, 1H), 3.78–3.76 (m, 4H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 162.7, 157.3, 157.1, 152.2, 151.6, 149.4, 136.1, 131.3, 131.1, 131.0, 122.0, 120.5, 117.4, 115.8, 115.5, 114.0, 113.2, 112.5, 107.7, 66.5, 48.3, 41.1; LC-MS: m/z calculated for $C_{29}H_{25}F_4N_7O_2S$: 611, Found: 612 $(M+1)^+$.

Antiproliferative screening of the target compounds against NCI-55 cancer cell line panel

Screening against the cancer cell lines was carried out at the National Cancer Institute (NCI), Bethesda, Maryland, USA (www.dtp.nci.nih.gov) applying the standard protocol of the NCI. The human cell lines are grown in RPMI 1640 medium containing 5 % fetal bovine serum and 2 mM $_L$-glutamine. For a typical screening experiment, cells are inoculated into 96-well microtiter plates in 100 µL at plating densities ranging from 5000 to 40,000 cells/well depending on the doubling time of individual cell lines. After cell inoculation, the microtiter plates are incubated at 37 °C, 5 % CO_2, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs. After 24 h, two plates of each cell line are fixed in situ with TCA, to represent a measurement of the cell population for each cell line at the time of drug addition (Tz). Experimental drugs are solubilized in dimethyl sulfoxide at 400-fold, the desired final maximum test concentration and stored frozen prior to use. At the time of drug addition, an aliquot of frozen concentrate is thawed and diluted to twice the desired final maximum test concentration with complete medium containing 50 µg/mL gentamicin. Additional four, tenfold or 1/2 log serial dilutions are made to provide a

total of five drug concentrations plus control. Aliquots of 100 μL of these different drug dilutions are added to the appropriate microtiter wells already containing 100 μL of medium, resulting in the required final drug concentrations. Following drug addition, the plates are incubated for an additional 48 h at 37 °C, 5 % CO_2, 95 % air, and 100 % relative humidity. For adherent cells, the assay is terminated by the addition of cold TCA. Cells are fixed in situ by the gentle addition of 50 μL of cold 50 % (w/v) TCA (final concentration, 10 % TCA) and incubated for 60 min at 4 °C. The supernatant is discarded, and the plates are washed five times with tap water and air dried. Sulforhodamine B (SRB) solution (100 μL) at 0.4 % (w/v) in 1 % acetic acid is added to each well, and plates are kept for 10 min at room temperature. After staining, unbound dye is removed by washing five times with 1 % acetic acid and the plates are air dried. Bound stain is subsequently solubilized with 10 mM trizma base, and the absorbance is read on an automated plate reader at a wavelength of 515 nm. For suspension cells, the methodology is the same except that the assay is terminated by fixing settled cells at the bottom of the wells by gently adding 50 μL of 80 % TCA (final concentration, 16 % TCA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated as:

- $[(Ti - Tz)/(C - Tz)] \times 100$ for concentrations for which $Ti \geq Tz$
- $[(Ti - Tz)/Tz] \times 100$ for concentrations for which $Ti < Tz$.

Growth inhibition of 50 % (IC_{50}) is calculated from $[(Ti - Tz)/(C - Tz)] \times 100 = 50$, which is the drug concentration resulting in a 50 % reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation.

Results and discussion

Chemistry

The intermediate mesyl compound **5** was successfully synthesized according to the pathway illustrated in Scheme 1. Upon refluxing 2-aminothiazole (**2**) with α-bromo-4-fluoroacetophenone, cyclization to 6-(4-fluorophenyl)imidazo[2,1-*b*]thiazole (**3**) occurred (Ashwell *et al.*, 2005). Heating compound **3** with 4-iodo-2-(methylthio)pyrimidine in the presence of palladium acetate, cesium carbonate, and triphenylphosphine led to a coupling reaction and formation of the methylthiopyrimidinyl compound **4**. Oxidation of the sulfide moiety of compound **4** using oxone produced the corresponding sulfonyl compound **5**.

The amino side chains used for synthesis of the target compounds **1a-i** were synthesized through the pathway illustrated in Scheme 2. Interaction of 2-aminoethanol (**6**) with benzyl chloroformate in the presence of triethylamine (TEA) produced the *N*-Boc protected compound **7** (Tully *et al.*, 2006). Reaction of compound **7** with methanesulfonyl chloride in the presence of TEA afforded the corresponding mesyl compound **8** (Townsend and Basak, 1991). Replacement of the mesyl moiety of compound **8** with azido group was done by reaction with sodium azide. Reduction of the azido group of **9** using PPh_3/H_2O afforded the corresponding amino compound **10**, which was subsequently treated with the appropriate isocyanates to produce the corresponding urea derivatives **11a–c**. Moreover, the amide derivatives **13a–f** were obtained by condensation of the amino compound **10** with the appropriate carboxylic acid derivatives using 1-hydroxybenzotriazole (HOBt), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), and TEA. Deprotection of compounds **11a–c** and **13a–f** using palladium over carbon in hydrogen atmosphere afforded the corresponding amino compounds **12a–c** and **14a–f**, respectively.

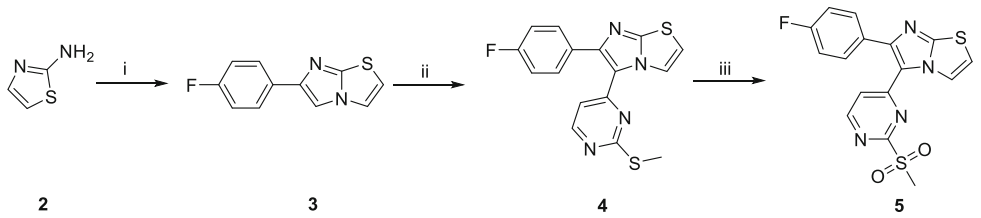
Heating compound **4** with the previously prepared reagents **12a–c** or **14a–f** in the presence of diisopropylethylamine (DIPEA) produced the target compounds **1a–c** and **1d–i**, respectively (Scheme 3) (Park and Oh, 2010). Table 1 illustrates the exact structure of every target compound.

Antiproliferative activities of the target compounds

Single-dose testing

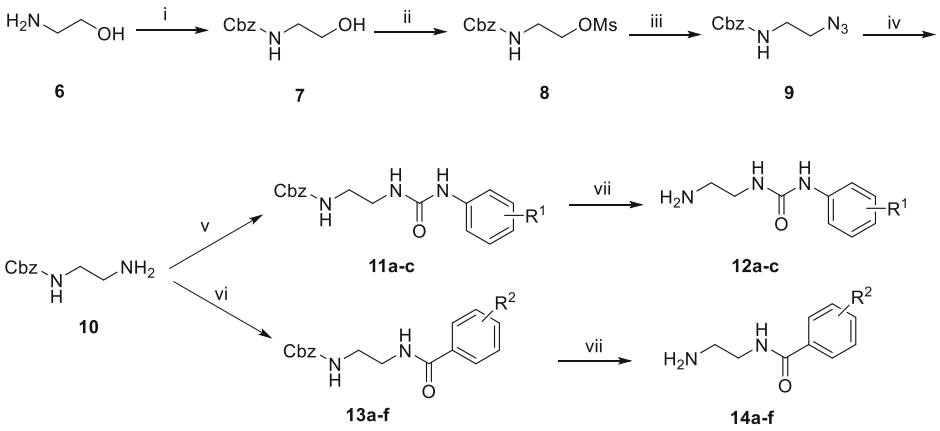
The target compounds were accepted for in vitro anticancer assay against a panel of fifty-five cancer cell line panel of nine cancer types at the National Cancer Institute (NCI), Bethesda, Maryland, USA (www.dtp.nci.nih.gov). The compounds were tested at a single-dose concentration of 10 μM, and the percentages of growth inhibition over the 55 tested cell lines were determined. The mean inhibition percentages for each of the tested compounds over the full panel of cell lines are illustrated in Fig. 2.

The results showed that compound **1d** with amide linker was more active than the corresponding urea analogue **1a**. On the contrary, the urea derivative **1c** exerted higher activity than the corresponding amide compound **1 g**. Upon comparing the mean %inhibition results of the amide compounds **1d** and **1f** with the corresponding analogues possessing sulfonamide moiety (Abdel-Maksoud *et al.*, 2015), it was found that compounds **1d** and **1f** were more



Scheme 1 Reagents and conditions: (i) α-bromo-4-fluoroacetophenone, EtOH, reflux, 16 h; (ii) 4-iodo-2-(methylthio)pyrimidine, $Pd(OAc)_2$, Cs_2CO_3, PPh_3, DMF, 80 °C, 12 h; (iii) oxone, MeOH, H_2O, rt, 16 h. (Park and Oh, 2010)

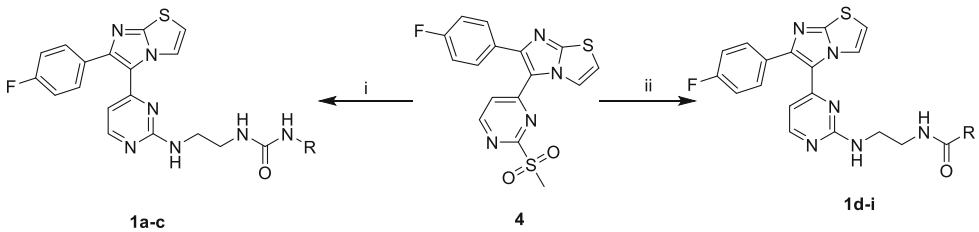
Scheme 2 Reagents and conditions: (i) benzyl chloroformate, TEA, CH_2Cl_2, 0°C; (ii) methanesulfonyl chloride, TEA, CH_2Cl_2, 0°C; (iii) NaN_3, DMSO, 70°C, 2 h; iv) PPh_3, MeOH, H_2O, reflux, 2 h; (v) appropriate aryl isocyanate, THF, rt, 2 h; (vi) appropriate benzoic acid derivative, HOBt, EDCI, TEA, DMF, 80°C, 8 h; (vii) H_2/Pd-C, MeOH, rt, 1 h. (Park and Oh, 2010)



11a, **12a**: R^1 = H
11b, **12b** : R^1= *m*-OMe
11c, **12c** : R^1 = *m*-CF_3

13a, **14a**: R^2 = H
13b, **14b** : R^2 = *p*-OMe
13c, **14c**: R^2= 3,4-dimethoxy
13d, **14d**: R^2 = *m*-CF_3
13e, **14e** : R^2 = 3-(4-methyl-*1H*-imidazol-1-yl)-5-CF_3
13f, **14f** : R^2 = 3-morpholino-5-CF_3

Scheme 3 Reagents and conditions: (i) **12a–c**, DIPEA, DMSO, 80°C, 8 h; (ii) **14a–f**, DIPEA, DMSO, 80°C, 8 h. (Park and Oh, 2010)

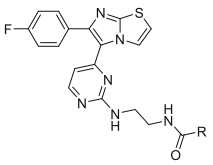


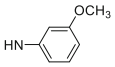
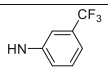
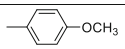
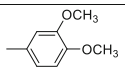
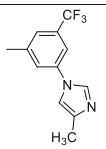
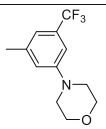
active. So the amide group may be the best spacer for the antiproliferative activity of this series of compounds. This may be rationalized that the amide group exerts the optimum affinity with the receptor site and, hence, optimum activity.

Upon studying the effect of the terminal ring substituents on the activity, it was found that *m*-(trifluoromethyl) group was the best among the urea derivatives. Among the amide derivatives, compounds **1d** and **1e** possessing phenyl and *p*-methoxyphenyl rings, respectively, showed the highest activities compared with the other derivatives. It seems that the increased bulkiness on the terminal ring such as in compounds **1f**, **1h**, and **1i** is detrimental for activity.

The importance of the fluorophenyl ring at position 6 of the imidazothiazole ring on the activity was also studied. The results of compound **1d** were compared with those of the corresponding compounds possessing 3-methoxyphenyl or 3-hydroxyphenyl moieties (Park *et al.*, 2011). It was found that the fluoro analogue **1d** was more active than *m*-methoxy or *m*-hydroxyl derivatives. So the hydrophobicity difference and/or group orientation might affect the affinity with the receptor site and, hence, antiproliferative activity.

Table 1 Structures of the target compounds **1a–i**



Compound No.	R
1a	
1b	
1c	
1d	
1e	
1f	
1g	
1h	
1i	

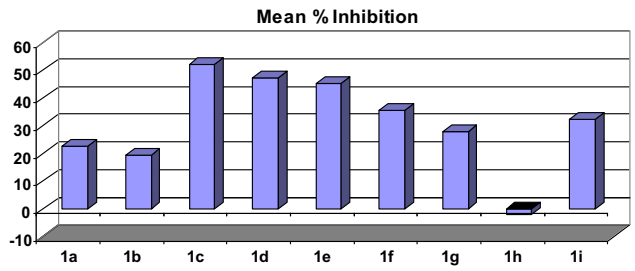


Fig. 2 Mean %inhibition values expressed by the target compounds **1a–i** at 10 μM concentration against a panel of 55 cancer cell line panel of nine different cancer types

The %inhibitions of the most active compounds **1c–e** at 10 μM concentration against each cell line of the panel are illustrated in Fig. 3. The results showed broad-spectrum antiproliferative activity of the three compounds over the nine tested cancer types. The urea compound **1c** expressed 89.49 and 88.93 % inhibitions over CCRF-CEM leukemia and TK-10 renal cancer cell lines, respectively. Compound **1d** possessing terminal benzamido moiety produced 79.98, 81.88, and 84.45 % inhibition values against NCI-H460 non-small cell lung cancer, HT29 colon cancer, and MCF7 breast cancer cell lines, respectively. And compound **1e** containing *p*-methoxybenzamido moiety exerted the highest activity against HT29 colon cancer cell line with 85.38 % inhibition.

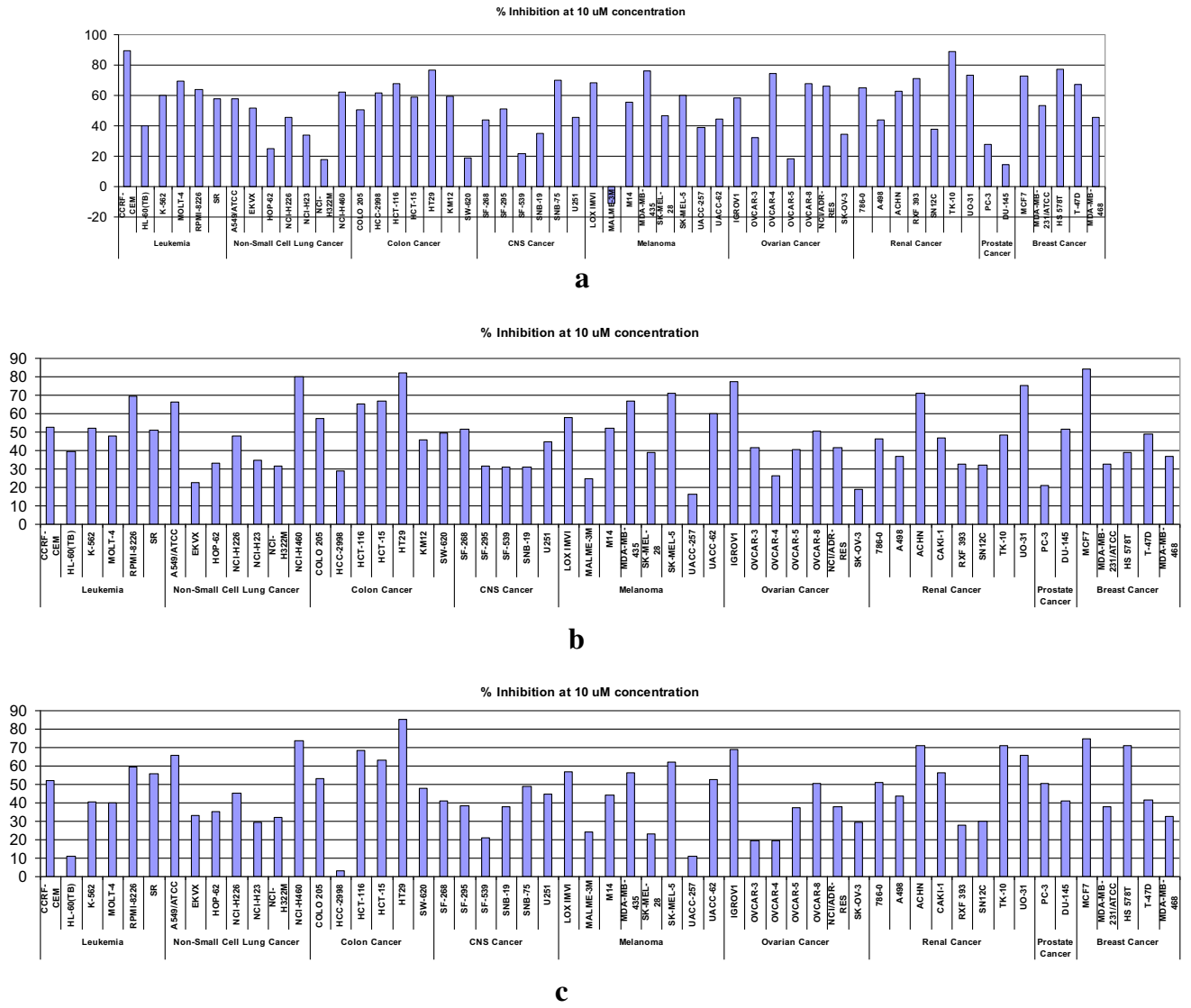


Fig. 3 The inhibition percentages exerted by compounds **1c–e** (Fig. 3a–c, respectively) at 10 μM concentration against every cancer cell line of the NCI panel

Five-dose testing

Compounds **1c–e** which showed promising results in single-dose testing were selected for further screening in 5-dose testing mode in order to determine their IC_{50} values over the 55-cell line panel. The full results are provided in the supplementary file. Table 2 illustrates the IC_{50} values of those three compounds against the most sensitive cell line of each subpanel. The results of Sorafenib as a reference standard compound were obtained from NCI data warehouse index (http://dtp.nci.nih.gov/dtpstandard/dwindex/index.jsp) and are inserted in Table 2.

Compounds **1c–e** showed high potencies, most of the results were in one-digit micromolar scale. Compound **1c** containing *m*-(trifluoromethyl)phenylurea terminal moiety was equipotent to Sorafenib against SK-MEL-5 melanoma cell line. Compound **1d** possessing terminal benzamido moiety was more potent than Sorafenib against COLO 205 colon cancer, UO-31 renal cancer, and MCF7 breast cancer cell lines. Moreover, compound **1e** with terminal *p*-methoxybenzamido moiety showed superior potency to Sorafenib against OVCAR-3 ovarian cancer, UO-31 renal cancer, DU-145 prostate cancer, and MCF7 breast cancer cell lines. The IC_{50} values of compound **1e** against those four cell lines were the lowest among all the results of compounds **1c–e** against the nine cell lines. For example, compound **1e** was 3 times more potent than Sorafenib against DU-145 prostate cancer cell line.

Table 2 IC_{50} values (μM) of compounds **1c–e** over the most sensitive cell line of each subpanel

Cell line	Compound No.			
	1c	1d	′1e	Sorafenib
CCRF-CEMa	3.14	3.83	4.75	2.00
NCI-H460b	4.50	3.28	3.55	2.51
COLO 205c	2.57	1.84	3.01	2.00
SF-295d	4.28	6.97	2.73	1.58
SK-MEL-5e	1.58	1.66	3.01	1.58
OVCAR-3f	17.70	16.20	1.24	3.16
UO-31 g	2.94	1.75	1.42	2.51
DU-145 h	11.60	12.70	1.04	3.16
MCF7i	3.73	1.43	2.00	2.51

[a] Leukemia cell line; [b] non-small cell lung cancer cell line; [c] colon cancer cell line; [d] CNS cancer cell line; [e] melanoma cell line; [f] ovarian cancer cell line; [g] renal cancer cell line; [h] prostate cancer cell line; [i] breast cancer cell line

Conclusion

A series of 6-(4-fluorophenyl)-5-(4-pyrimidinyl)imidazo[2,1-*b*]thiazole derivatives was synthesized. They were tested for in vitro antiproliferative activity over a panel of 55 cancer cell lines of nine different cancer types at the NCI. The best results were obtained from compounds **1c–e**. Those three compounds exerted broad-spectrum antiproliferative activity and high potency with IC_{50} values in one-digit micromolar scale. Compound **1e** with *p*-methoxybenzamido terminal moiety gave the highest potency. It was more potent than Sorafenib against OVCAR-3 ovarian cancer, UO-31 renal cancer, DU-145 prostate cancer, and MCF7 breast cancer cell lines. Compounds **1c–e** can be utilized as promising lead compounds for future design and synthesis of efficient anticancer agents.

The structure–activity relationship studies revealed that the *p*-fluorophenyl on position 6 of the imidazo[2,1-*b*]thiazole scaffold and the amide linker are optimal for activity of this series of compounds. The bulkiness on the terminal aryl ring was detrimental for activity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Abdel-Maksoud MS, Kim MR, El-Gamal MI, Gamal El-Din MM, Tae J, Choi HS, Lee KT, Yoo KH, Oh CH (2015) Design, synthesis, in vitro antiproliferative evaluation, and kinase inhibitory effects of a new series of imidazo[2,1-b]thiazole derivatives. Eur J Med Chem 95:453–463

Andreani A, Leoni A, Locatelli A, Morigi R, Rambaldi M, Recanatini M, Garaliene V (2000) Potential antitumor agents. part 29: synthesis and potential coanthracyclinic activity of Imidazo[2,1-b]thiazole guanylhydrazones. Bioorg Med Chem 8:2359–2366

Andreani A, Granaiola M, Leoni A, Locatelli A, Morigi R, Rambaldi M, Lenaz G, Fato R, Bergamini C, Farruggia G (2005) Potential Antitumor Agents. 37.Synthesis and Antitumor Activity of Guanylhydrazones from Imidazo[2,1-b]thiazoles and from the New Heterocyclic System Thiazolo[2',3':2,3]imidazo[4,5-c]quinolone. J Med Chem 48:3085–3089

Ashwell M, Tandon M, Lapierre JM (2005) Preparation of pyrimidinyl imidazooxazoles and imidazothiazoles as inhibitors of p38 MAP kinase. PCT Pat. Appl. WO 2006044869

El-Subbagh HI, Al-Khawad IE, El-Bendary ER, Al-Obaid AM (2001) Substituted thiazoles. IV. Synthesis and antitumor activity of new substituted imidazo[2,1-b]thiazole analogs. Saudi Pharm J 9:14–20

Gürsoy E, Güzeldemirci NU (2007) Synthesis and primary cytotoxicity evaluation of new imidazo[2,1-b]thiazole derivatives. Eur J Med Chem 42:320–326

Park JH, Oh CH (2010) Synthesis of new 6-(4-fluorophenyl)-5-(2-substituted pyrimidin-4-yl)imidazo[2,1-b]thiazole derivatives and their antiproliferative activity against melanoma cell line. Bull Korean Chem Soc 31:2854–2860

Park JH, El-Gamal MI, Lee YS, Oh CH (2011) New imidazo[2,1-b]thiazole derivatives: synthesis, in vitro anticancer evaluation, and in silico studies. Eur J Med Chem 46:5769–5777

Srimanth K, Rao VR, Krishna DR (2002) Synthesis and evaluation of anticancer activity of some imidazothiazolyl, imidazobenzothiazolyl and dihydroimidazothiazolyl coumarins. Arzneimittelforschung 52:388–392

Townsend CA, Basak A (1991) Experiments and speculations on the role of oxidative cyclization chemistry in natural product biosynthesis. Tetrahedron 47:2591–2602

Tully DC, Liu H, Chatterjee AK, Alper PB, Epple R, Williams JA, Roberts MJ, Woodmansee DH, Masick BT, Tumanut C, Li J, Spraggon G, Hornsby M, Chang J, Tuntland T, Hollenbeck T, Gordon P, Harris JL, Karanewsky DS (2006) Synthesis and SAR of arylaminoethyl amides as noncovalent inhibitors of cathepsin S: P3 cyclic ethers. Bioorg Med Chem Lett 16:5112–5117