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Synthesis and Anticancer Activity of Novel Thiazole-5-Carboxamide Derivatives

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Abstract: A series of novel 2-phenyl-4-trifluoromethyl thiazole-5-carboxamide derivatives have been synthesized and evaluated for their anticancer activity against A-549, Bel7402, and HCT-8 cell lines. Among the tested compounds, highest activity (48%) was achieved with the 4-chloro-2-methylphenyl amido substituted thiazole containing the 2-chlorophenyl group on the two position of the heterocyclic ring. Other structurally similar compounds displayed moderate activity. The key intermediates have been fully characterized.

Keywords: thiazole; amide; synthesis; antitumour

1. Introduction

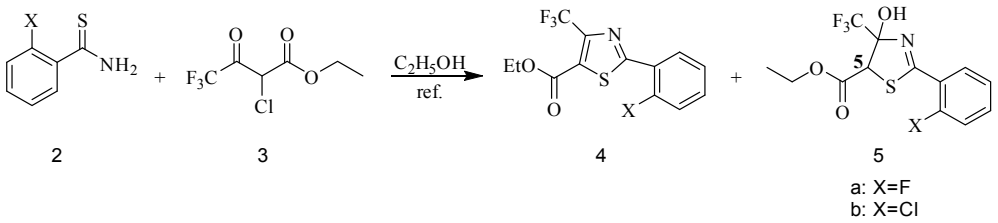
Substituted thiazole compounds play an important role in nature and have a diverse range of biological effects such as antitumor [1–3] antibacterial [4], antimicrobial [5], anti-viability [6], anti-inflammatory [7], Syk inhibitor [8], antiviral [9], antiproliferative [10], and anticandidal activity [11]. In past decades, amide containing heterocycles are reported as a class of compounds displaying extensive biological activities, which consist of a large number of natural and synthetic products and are extremely versatile building blocks for the manufacture of bioactive compounds in pharmaceutical drug design and agrochemical industry [12–18]. We noticed that most optimizations focused on the pyridine [19], pyrazole [20], piperazine [21] and oxadiazole [22] heterocycles, but the thiazole ring, as an active moiety widely used in pesticides and medicine, has not been fully reported. For example, phthalic diamides [23] and anthranilic diamides [24] were reported by Nihon Nohyaku (Tokyto, Japan), Bayer CropScience (Monheim, Genmany) and DuPont (Delaware, USA), respectively.

In view of all these facts and as continuation of our research on bioactive compounds [25–37], the promising bioactive diversity of this class of heteroaryl compounds encourage us to synthesize and biologically evaluate a series of novel structural variants of 2-phenyl-4-trifluoromethyl thiazole-5-carboxamide derivatives and related intermediates. Their antitumor activity was tested in A-549 lung cancer cell lines, Bel7402 liver cancer cell lines and HCT-8 intestine cancer cell lines.

2. Results and Discussion

2.1. Synthesis

Surprisingly, in the synthesis process of **4** (Scheme 1), an unprecedented structure **5** was obtained at the same time. To identify their structures, the single crystal of **4b** (Figure 1) and **5b** (Figure 1) were recrystallized. The possible mechanism of intermediate **4** is shown in Scheme 2.



Scheme 1. Synthetic pathway for the preparation of **4** and **5**.

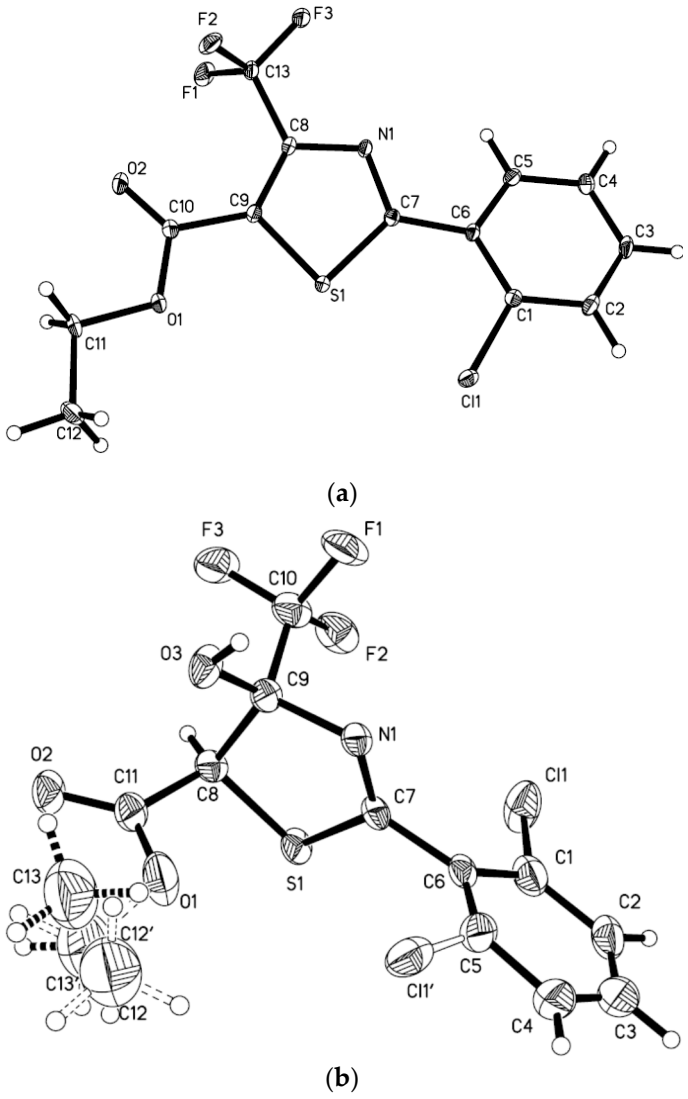
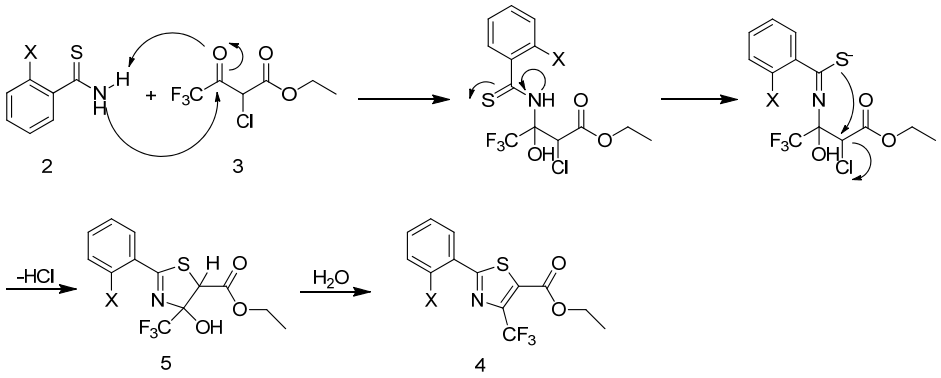


Figure 1. The crystal structure of **4b** (**a**) and **5b** (**b**).



Scheme 2. The possible mechanism to afford **4**.

Due to the incomplete dehydration to form the thiazole ring, the yield of **4** was low (**4a**: 39.5%, **4b**: 56.2%). The yield could not be significantly improved by extending the reaction time or increasing the reaction temperature (using DMF (Dimethyl Formamide) as solvent, when T > 120 °C, **5** would disappear in 1 h, which was accompanied by the decomposition of **4a**, reducing the yield down to 30%). Compared with the yield using trifluoroacetyl ethyl acetate and substituted bentiamine (<40%) in our experiments, a much better yield (81.5%) using acetyl ethyl acetate and bentiamine was reported by relevant literature [38], which probably results from the strong electron withdrawing properties of the CF_3 moiety. However, under the same condition, by-product **5** could also be hydrolyzed to get the key intermediate **5** in yield of 50%. After by-product **5** hydrolyzed under basic conditions, the acidification process with dilute hydrochloric acid might promote the dehydration reaction of **5**. Therefore, **4** and **5** could be hydrolyzed together to get **6**, avoiding the need for separation.

Based on the above mechanism, we analyzed the transformation process: When **2** and **3** were reflexed in EtOH directly, the formation of HCl would make the reaction system acidic, dehydrating a portion of product **5** to obtain compound **4**. However, due to the strong electron withdrawing effect of the CF_3 moiety, coupled with the weak acidity of the reaction system, the transformation would not be complete. Therefore, we propose that, in the synthesis of compounds **4**, the HCl gas could be introduced into the system to facilitate the generation of the thiazole ring.

The final amide derivatives **7** (Scheme 4) and **8** (Scheme 5) were produced by reaction of the acyl chloride of **6** with appropriate arylamines at room temperature in dichloromethane. The reaction to produce compounds 7 and 8 required *N*,*N*-diisopropylethylamine as a base to give acceptable yields. In addition, pyridine, triethylamine and some inorganic bases (Na_2CO_3, K_2CO_3, $NaHCO_3$) were trialed and gave decreased yields. Inorganic bases were not suitable for the organic reaction system used.

2.2. Anticancer Activities

The anticancer results of title compounds are listed in Table 1, 5-fluorouracil was used as controls. As shown in Table 1, some of the title compounds showed good inhibitory against A-549 at a concentration of 5 μg/mL, such as compound **8c** (48%) and **8f** (40%), which is a little lower than that of control, while some of them exhibited low activity against A-549. Furthermore, compound **7d** and **7f** can increase the A-549 cell growth. All the title compounds exhibited no inhibition or low inhibitor effect against Bel7402 and HCT-8. Only compound **7f** (40%) displayed moderate inhibitory against HCT-8.

Table 1. The anticancer activity of title compounds at 5 μg/mL (%, inhibitory).

No.	A-549	Bel7402	HCT-8
7a	36	10	2
7b	24	0	19
7c	16	0	−7
7d	−2	6	−5
7e	4	9	17
7f	−19	12	40
8a	27	6	1
8b	27	22	2
8c	48	5	28
8d	37	16	8
8f	40	16	2
5-Fluorouracil	57	75	79

3. Experimental Section

3.1. Instruments

Chemicals and solvents were procured from commercial sourced in analytical grade purity. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. Thin-layer chromatography (TLC) was carried out on aluminium-supported silica gel plates (Merck 60F 254) (Darmstadt, Genmany) with visualization of components by UV light (254 nm). Column chromatography was carried out on silica gel (Merck 230–400 mesh) (Darmstadt, Genmany). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). All chemical shifts are reported in δ (ppm) using TMS (Tetramethylsilane) as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer (Waltham, MA, USA).

3.2. Synthesis

3.2.1. Preparation of **1**

To a suspension of benzoic acid (40 mmol) in CH_2Cl_2 (50 mL) was added oxalyl chloride (120 mmol), two drops of DMF followed by stirring at room temperature for 12 h. After the reaction was complete and the solvent was evaporated under vacuo and the residue added into ammonia solution to obtain **1**. Compound **1a** (2-fluorobenzamide): white solid (88%); m.p. 111–112 °C. Compound **1b** (2-chlorobenzamide): white solid (95%); m.p. 111–112 °C (140–142 °C) [39].

3.2.2. Preparation of **2** [40]

To a solution of THF (100 mL) was added **1** (20 mmol), Lawesson's Reagent (20 mmol) and refluxed for 3 h under the nitrogen protection. After the reaction was complete, THF was evaporated under vacuo. The crude residue was purified by column chromatography (EtOAc/ Petroleum ether) to get **2**. Compound **2a** (2-fluorobenzothioamide): yellow solid (93%); m.p. 80–81 °C (83 °C) [41]. Compound **2b** (2-chlorobenzothioamide): yellow solid (82%); m.p. 56–59 °C.

3.2.3. Preparation of **3** [42]

To a solution of CCl_4 (100 mL) was added ethyl 4,4,4-trifluoro-3-oxobutanoate (0.2 mmol), SO_2Cl_2 (0.24 mmol), the solution was heated at reflux for 24 h. After the reaction was complete, CCl_4 was evaporated under vacuo. The residual liquid was distilled under reduced pressure, collecting 60–62/20 mmHg fraction to get **3**. Compound **3** (ethyl 2-chloro-4,4,4-trifluoro-3-oxobutanoate):

transparent liquid (66%); m.p. 60–62/20 mmHg (67–71/35 mmHg) [43]. Compound **2b** (2-chlorobenzothioamide): White solid (82%); m.p. 56–59 °C.

3.2.4. Preparation of **4** [44]

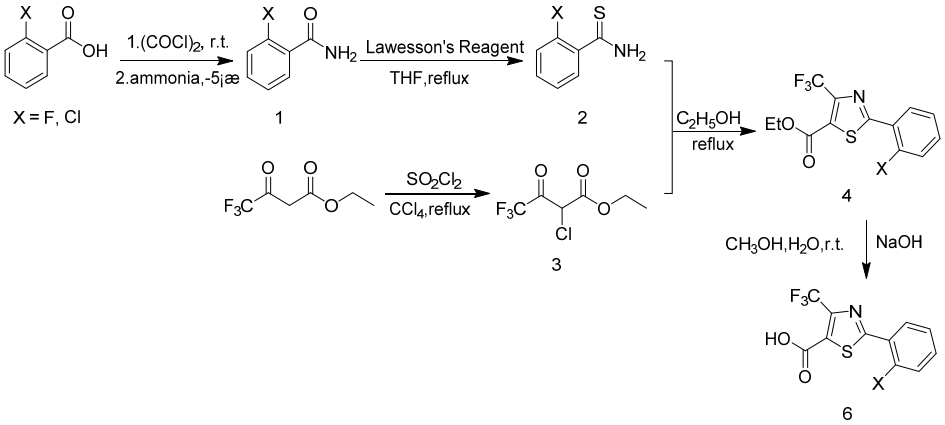
To a solution of **2** (35 mmol) in EtOH (100 mL) was added **3** (35 mmol) and refluxed for 24 h. After the reaction was complete, the solvent was evaporated under vacuo. The residue was allowed to stand until white needle like crystals precipitated, then the solution filtered to isolate compound **4**.

Ethyl 2-(2-fluorophenyl)-4-(trifluoromethyl)thiazole-5-carboxylate (**4a**) White solid (40%); m.p. 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 4.43 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 7.23–7.27 (m, 1H, Ar–H), 7.30–7.34 (m, 1H, Ar–H), 7.48–7.54 (m, 1H, Ar–H), 8.37–8.41 (m, 1H, Ar–H).

Ethyl 2-(2-chlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxylate (**4b**) White solid (56%); m.p. 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.42 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 4.43 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 7.43–7.45 (m, 2H, Ar–H), 7.53–7.55 (m, 1H, Ar–H), 8.42–8.44 (m, 1H, Ar–H).

3.2.5. Preparation of **6** (Scheme 3)

To a solution of **4** (10 mmol) in MeOH (50 mL) and distilled water (10 mL) was added NaOH (12 mmol) and stirred at room temperature for 12 h. After the reaction was complete, the solvent was evaporated *in vacuo* followed by the addition of water (50 mL) and the pH was adjusted to 1.5 with diluted hydrochloric acid (2 mol/L). After stirring for 30 min, the mixture was filtered to isolate compound **6**.



Scheme 3. Synthetic strategy of intermediates **6**.

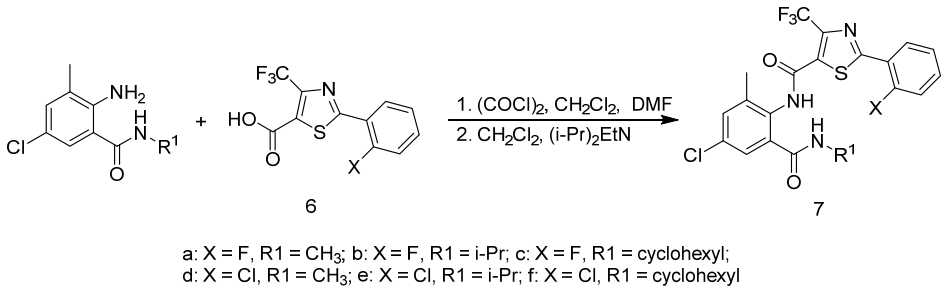
2-(2-Fluorophenyl)-4-(trifluoromethyl) thiazole-5-carboxylic acid (**6a**) White solid (71%); m.p. > 190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.41–7.53 (m, 2H, Ar–H), 7.64–7.68 (m, 1H, Ar–H), 8.22–8.26 (m, 1H, Ar–H), 14.43 (br, 1H, COOH).

2-(2-chlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxylic acid (**6b**) White solid (84%); m.p. > 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.54–7.64 (m, 2H, Ar–H), 7.70–7.72 (m, 1H, Ar–H).

3.2.6. Synthesis of Target Compounds (**7a**–**f**)

To a suspension of **6** (1 mmol) and oxalyl chloride (3 mmol) in CH_2Cl_2 (20 mL) was added two drops of DMF and stirred at room temperature for 6 h. After the reaction was complete by TLC, the solution was evaporated *in vacuo* to get the crude residue. The crude residue was dissolved in CH_2Cl_2, then was slowly added into a solution of *o*-amino-benzamide (1.2 mmol) in CH_2Cl_2 (20 mL). After stirring for 20 min, the solution was neutralized using (*i*-Pr)$_2$EtN (1 mmol). After the reaction was complete, a great quantity of white solid was precipitated and 20 mL distilled water was added.

After thorough stirring, the mixture was filtered to get the white solid, which was washed with CH_2Cl_2 (10 mL) and distilled water (10 mL) to obtain **7** (Scheme 4).



Scheme 4. Synthetic strategy of target compounds **7**.

N-(4-chloro-2-methyl-6-(methylcarbamoyl)phenyl)-2-(2-fluorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**7a**) White solid (48%); m.p. 256–259 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.26 (s, 3H, CH_3), 2.73 (d, J = 4.4 Hz, 3H, CH_3NH), 7.41–7.71 (m, 5H, Ar–H), 8.25–8.29 (m, 1H, Ar–H), 8.40 (br, 1H, $NHCH_3$), 10.55 (br, 1H, NH). Anal. Calculated for $C_{20}H_{14}ClF_4N_3O_2S$: C 50.72, H 3.47, N 8.90; found: C 50.91, H 2.99, N 8.91.

N-(4-chloro-2-(iso-propylcarbamoyl)-6-methylphenyl)-2-(2-fluorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**7b**) White solid (38%); m.p. 280–284 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (d, J = 6.4 Hz, 6H, $CH(CH_3)_2$), 2.24 (s, 3H, CH_3), 3.94–4.01 (m, 1H, $CH(CH_3)_2$), 7.34–7.55 (m, 4H, Ar–H), 7.64–7.69 (m, 1H, Ar–H), 8.23–8.27 (m, 1H, Ar–H), 8.31–8.33 (m, 1H, $NHCH(CH_3)_2$), 10.53 (br, 1H, NH). Anal. Calculated for $C_{22}H_{18}ClF_4N_3O_2S$: C 53.37, H 4.10, N 8.60; found: C 52.86, H 3.63, N 8.41.

N-(4-chloro-2-(cyclohexylcarbamoyl)-6-methylphenyl)-2-(2-fluorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**7c**) White solid (68%); m.p. 157–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.21–1.84 (m, 10H, cyclohexyl-H), 2.24 (s, 3H, CH_3), 3.62–3.67 (m, 1H, CH), 7.32–7.33 (m, 1H, Ar–H), 7.42–7.56 (m, 3H, Ar–H), 7.64–7.69 (m, 1H, Ar–H), 8.23–8.27 (m, 1H, Ar–H), 8.31 (d, J = 7.6 Hz, 1H, NHCH), 10.53 (br, 1H, NH). Anal. Calculated for $C_{25}H_{22}ClF_4N_3O_2S$: C 55.44, H 3.86, N 7.93; found: C 55.61, H 4.11, N 7.78.

N-(4-chloro-2-methyl-6-(methylcarbamoyl)phenyl)-2-(2-chlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**7d**) White solid (81%); m.p. 247–249 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.24 (s, 3H, CH_3), 2.71 (d, J = 4.4 Hz, 3H, $NHCH_3$), 7.37–7.75 (m, 5H, Ar–H), 8.23–8.36 (m, 2H, Ar–H), 8.24 (br, 1H, NHCH), 10.58 (br, 1H, NH). Anal. Calculated for $C_{20}H_{14}Cl_2F_3N_3O_2S$: C 49.05, H 3.39, N 8.59; found: C 49.19, H 2.89, N 8.61.

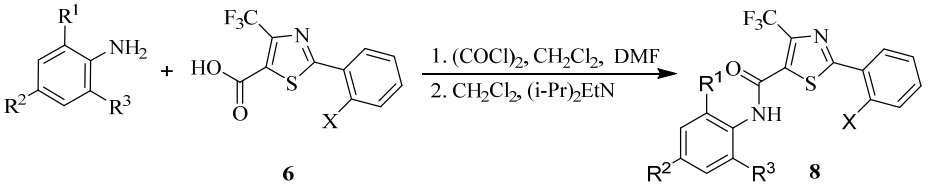
N-(4-chloro-2-(iso-propylcarbamoyl)-6-methylphenyl)-2-(2-chlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**7e**) White solid (91%); m.p. 277–280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12 (d, J = 6.4 Hz, 6H, $CH(CH_3)_2$), 2.24 (s, 3H, CH_3), 3.92–4.01 (m, 1H, $CH(CH_3)_2$), 7.33–7.34 (m, 1H, Ar–H), 7.51–7.62 (m, 3H, Ar–H), 7.72–7.74 (m, 1H, Ar–H), 8.23–8.26 (m, 1H, Ar–H), 8.31 (br, 1H, NHCH), 10.56 (br, 1H, NH). Anal. Calculated for $C_{22}H_{18}Cl_2F_3N_3O_2S$:C 50.92, H 3.90, N 7.98; found: C 51.17, H 3.51, N 8.14.

N-(4-chloro-2-(cyclohexylcarbamoyl)-6-methylphenyl)-2-(2-chlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**7f**) White solid (67%); m.p. 279–281 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.12–1.88 (m, 10H, cyclohexyl-H), 2.26 (s, 3H, CH3), 3.66–3.68 (m, 1H, CH), 7.32–7.77 (m, 5 H, Ar-H), 8.27–8.29 (m, 1H, Ar–H), 8.32 (d, J = 7.6 Hz, 1H, NHCH), 10.53 (br, 1H, NH); Anal. Calculated for $C_{25}H_{22}Cl_2F_3N_3O_2S$: C 54.36, H 3.65, N 7.57; found: C 53.96, H 3.99, N 7.55.

3.2.7. Synthesis of Target Compounds (**8a**–**g**)

To a suspension of **6** (1 mmol) and oxalyl chloride (3 mmol) in CH_2Cl_2 was added two drops of DMF and stirred at room temperature for 6 h. After the reaction was complete, the solution was evaporated *in vacuo* to get the crude residue. The crude residue was dissolved in CH_2Cl_2, then was slowly added into a solution of o-amino-benzamide (1.2 mmol) in CH_2Cl_2. After stirring for 20 min, the acid binding agent (i-Pr)$_2$EtN (1 mmol) was added and kept stirring in room temperature for 12 h.

After the reaction was complete, the solution was added 20 mL CH_2Cl_2. Combined organic layers were washed with dilute hydrochloric acid (20 mL), saturated Na_2CO_3 solution (20 mL) and saturated NaCl solution (20 mL) respectively, dried with anhydrous Na_2SO_4. The mixture was filtered under reduced pressure, the filtrate was evaporated under vacuo. The crude residue was purified by column chromatography to get compounds **8** (Scheme 5).



a: X = F, R^1 = CH_3, R^2 = Cl, R^3 = H; b: X = F, R^1 = Cl, R^2 = Cl, R^3 = H;
c: X = Cl, R^1 = CH_3, R^2 = Cl, R^3 = H; d: X = Cl, R^1 = Cl, R^2 = Cl, R^3 = H;
e: X = Cl, R^1 = CF_3, R^2 = R^3 = H; f: X = Cl, R^1 = Cl, R^2 = Cl, R^3 = Cl;
g: X = Cl, R^1 = Cl, R^2 = Cl, R^3 = Br

Scheme 5. Synthetic strategy of target compounds **8**.

N-(4-chloro-2-methylphenyl)-2-(2-fluorophenyl)-4-(trifluoromethyl) thiazole-5-carboxamide (**8a**) White solid (69%); m.p. 226–227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.24 (s, 3H, CH_3), 7.29–7.32 (m, 1H, Ar–H), 7.39–7.56 (m, 4H, Ar–H), 7.65–7.69 (m, 1H, Ar–H), 8.23–8.27 (m, 1H, Ar–H), 10.55 (br, 1H, NH). Anal. Calculated for $C_{18}H_{11}ClF_4N_2OS$: C 51.61, H 3.21, N 6.79; found: C 52.12, H 2.67, N 6.75. IR (KBr, v_{max}) cm^{-1}: 3249 (N–H stretch); 3026~3121 (aliphatic C–H stretch); 1633 (C=O stretch); 1436~1548(aromatic and thiazole C=C stretch); 1126(C–S stretch).

N-(2,4-dichlorophenyl)-2-(2-fluorophenyl)-4-(trifluoromethyl) thiazole-5-carboxamide (**8b**) White solid (58%); m.p. 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.43–7.56 (m, 3H, Ar-H), 7.65–7.76 (m, 3H, Ar–H), 8.24–8.28 (m, 1H, Ar–H), 10.87 (br, 1H, NH). Anal. Calculated for $C_{17}H_8C_{l2}F_4N_2OS$: C 46.85, H 2.36, N 6.21; found: C 46.91, H 1.85, N 6.44.

N-(4-chloro-2-methylphenyl)-2-(2-chlorophenyl)-4-(trifluoromethyl) thiazole-5-carboxamide (**8c**) Yellow solid (44%); m.p. 228–229 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.25 (s, 3H, CH_3), 7.30–7.49 (m, 3H, Ar–H), 7.59–7.65 (m, 2H, Ar–H), 7.73–7.75 (m, 1H, Ar–H), 8.25–8.27 (m, 1H, Ar–H), 10.59 (br, 1H, NH). Anal. Calculated for $C_{18}H_{11}C_{l2}F_3N_2OS$: C 49.91, H 2.87, N 6.59; found: C 50.13, H 2.57, N 6.50.

2-(2-Chlorophenyl)-N-(2,4-dichlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**8d**) White solid (65%); m.p. 204–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.493–7.52 (m, 1H, Ar–H), 7.56-7.64 (m, 2H, Ar–H), 7.69–7.76 (m, 3H, Ar–H), 8.25–8.27 (m, 1H, Ar–H), 10.90 (br, 1H, NH). Anal. Calculated for $C_{17}H_8Cl_3F_3N_2OS$: C 45.02, H 2.09, N 6.29; found: C 45.21, H 1.79, N 6.20.

2-(2-Chlorophenyl)-4-(trifluoromethyl)-N-(2-(trifluoromethyl)phenyl)thiazole-5-carboxamide (**8e**) White solid (68%); m.p. 158–160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.56–7.65 (m, 4H, Ar–H), 7.73–7.83 (m, 4H, Ar–H), 10.92 (br, 1H, NH). Anal. Calculated for $C_{18}H_9ClF_6N_2OS$: C 47.67, H 2.51, N 6.39; found: C 47.96, H 2.01, N 6.21.

2-(2-Chlorophenyl)-N-(2,4,6-trichlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**8f**) White solid (58%); m.p. 120–122 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.56–7.66 (m, 2H, Ar–H), 7.88 (s, 2H, Ar–H), 7.75–7.77 (m, 1H, Ar–H), 8.29–8.31 (m, 1H, Ar–H), 11.18 (br, 1H, NH). Anal. Calculated for $C_{17}H_7Cl_4F_3N_2OS$: C 42.19, H 1.78, N 5.49; found: C 42.00, H 1.45, N 5.76.

N-(2-bromo-4,6-dichlorophenyl)-2-(2-chlorophenyl)-4-(trifluoromethyl)thiazole-5-carboxamide (**8g**) White solid (60%); m.p. 250–251 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.59–7.67(m, 2H, Ar-H), 7.75–7.77 (m, 1H, Ar–H), 7.91 (d, *J* = 2.4 Hz, 1H, Ar–H), 7.98 (d, *J* = 2.4 Hz, 1H, Ar–H), 8.29–8.31 (m, 1H, Ar–H), 11.17 (br, 1H, NH). Anal. Calculated for $C_{17}H_7BrCl_3F_3N_2OS$: C 38.15, H 1.81, N 5.03; found: C 38.48, H 1.33, N 5.28.

3.3. Anticancer Activity

Three different human cancer cell lines, A-549, Bel7402 and HCT-8, were obtained from the National Center for Pharmaceutical Screening, Institute of Materia Medica (Beijing, China), and cultured on RPMI1640 medium at 37 °C in a humidified atmosphere with 5% CO_2 for 24 h. All cells to be tested in the following assays had a passage number of 3–6.

For the drug treatment experiments, the cancer cells were treated with the compounds (predissolved in DMSO) at 5 μg/mL for a period of three days. At the end of the drug treatment period, MTT (4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-*H*-tetrazolium bromide) solution (150 μL, 0.5 mg/mL) in PBS (PBS without MTT as the blank) was fed to each well of the culture plate. After 4 h incubation, the formazan crystal formed in the well was dissolved with 150 μL of DMSO for optical density reading at 544 nm.

4. Conclusions

Some interesting amide derivatives containing thiazole moiety were designed and synthesized. Their structures were confirmed by NMR and elemental analysis. The primary bioassay showed some of them exhibited moderate anticancer activities.

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