Full Paper

Synthesis of Novel Thiazolyl-Pyrimidines and Their Anticancer Activity *in Vitro*

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A series of novel compounds **7–43** were prepared *via* the condensation of enaminones **4a–h** and the guanidines carbonate **6a–f**. The structures of these newly synthesized compounds were confirmed by ^{1}H-NMR, MS, EA and IR. All the compounds were tested for their cytotoxic activity *in vitro* against human cancer cell lines including Ishikawa, A549, BEL-7404, SPC-A-01 and SGC-7901. Most of them showed moderate cytotoxic against the tested cell lines. Among them, the most potent compounds **9** and **30** exhibited more efficient activity against Ishikawa, A549.

Keywords: Anticancer activity / Pyrimidine / Thiazole

Received: August 22, 2010; Revised: November 25, 2010; Accepted: November 30, 2010

DOI 10.1002/ardp.201000238

Introduction

The cyclin-dependent kinases (CDKs) are key regulators of progression through the various stages of the eukaryotic cell cycle [1, 2]. It has been shown that overexpression and/or loss of function of key proteins implicated in the chain of events upstream and downstream of the CDKs leads to tumorigenesis and neoplastic transformation [3]. Campbell McInnes firstly reported use of computational methods to elucidate the characteristics of selectivity and derive the structural basis for specific, high-affinity binding of inhibitors to the CDK4 active site. The findings showed that 2-anilino-4-thiazol-5-yl) pyrimidine pharmacophore are potent and highly selective ATP antagonists of CDK4/cyclin D1 [4]. 2-Anilino-4-(thiazol-5-yl) pyrimidine, also including a thiazole and a pyrimidine structure, showed good biological activities and a series of analogs by the modification of the structure were synthesized [5–8]. For example (Figure 1), the studies of Wang et al. showed that the anticancer effects of lead compound **CYC116** (K_i values of 8.0 and 9.2 nM for aurora A and B, respectively) were shown to emanate from cell death following mitotic failure and increased polyploidy as a consequence of cellular inhibition of aurora A and B kinases [9]. **CYC116** is currently undergoing phase I clinical evaluation in cancer patients [10, 11].

These facts prompted us to design a new series of thiazole derivatives in order to find more potential antitumor compounds, and to carry out a structure-activity relationship study. The present work is an extension of our ongoing efforts towards the development of new aminothiazole derivatives and their biological activities [12, 13]. Accordingly, we attempt to investigate whether introduction of arylamino group into **CYC116** with retaining the thiazole and pyrimidine could enhance their anticancer activities or not. Here, we describe the synthesis and the cytotoxic activity *in vitro* against human cancer cell lines of this novel class of compounds.

Result and Discussion

{4-[4-Methyl-2-(methyl-aryl amino)-thiazol-5-yl]-pyrimidine-2-yl}-arylamines were synthesized (Scheme 1) by the general pyrimidine condensation of Bredereck [14]. *N*-substituted thioureas **1a–h** were prepared by known methods in high yields [15, 16]. Treatment of acetylacetone with NCS (*N*-chlorosuccinimide) in carbon tetrachloride under reflux for 5 h resulted in 3-chloro-acetylacetone **2**. The aminothiazole **3a–h** were prepared by thioureas **1a–h** and **2** refluxing in methanol *via* the method of Hantzsch [17] and were converted to the

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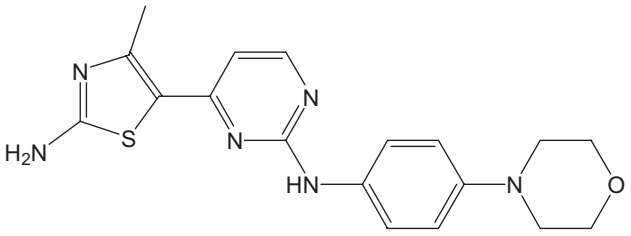


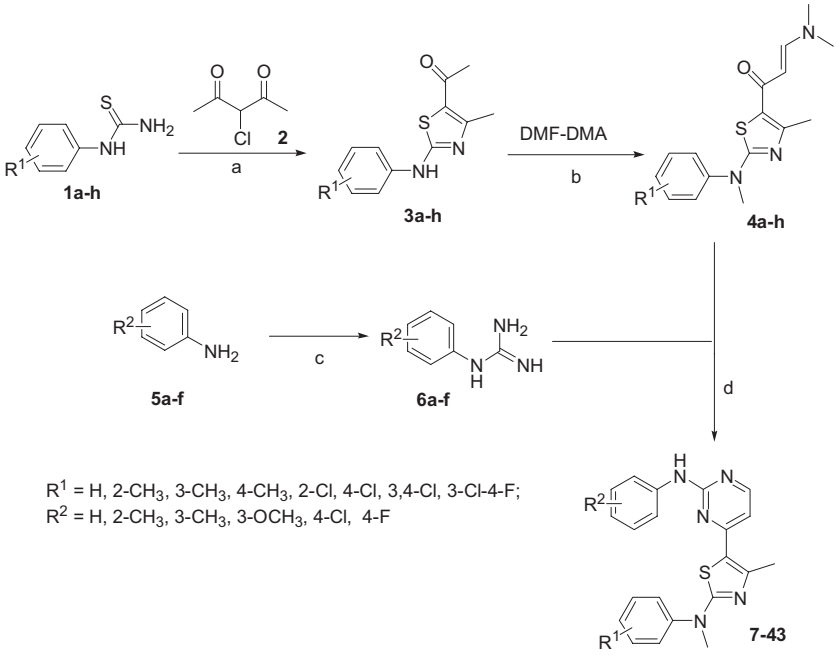
Figure 1. The structure of CYC116.

enaminones **4a–h** by heating in *N*,*N*-dimethyl formamide dimethyl acetal (DMF-DMA) and *N*,*N*-dimethyl formamide (DMF). The aniline guanidines carbonate **6a–f** were derived from the corresponding anilines **5a–f** by treatment of hydrochloride with cyanamide [18]. Enaminones **4a–h** were then condensed to the desired thiazolyl-pyrimidines at elevated temperature catalyzed by sodium hydroxide in 2-methoxyethanol with guanidines carbonate **6a–f**. It is interesting that according to the approach methods of Wang et al. isolation of the structure of thiazolyl-pyrimidine is aryl-methylamino group at the thiazole C2 position and not arylamino group that been reported[19]. The structures of synthesized compounds **7–43** were determined by ^{1}H-NMR, MS, EA and IR.

A preliminary evaluation of the cytotoxic activity of all the target compounds was performed by MTT assays *in vitro* against several human cancer cell lines including endometrial adenocarcinoma cell Ishikawa, human lung cancer cell A549, human liver cancer cell BEL-7404, human lung cancer cell SPC-A-01 and human gastric cancer cell SGC-7901. Cisplatin was employed as a positive control in the assay. The results are summarized in Table 1.

As shown in Table 1, most of the tested compounds showed moderate to potent cytotoxic activity against Ishikawa, A549, BEL-7404, SPC-A-01 and SGC-7901. It was noteworthy that the cytotoxic effects were more pronounced against Ishikawa cell compared with the others, displayed higher activities (e.g. **9**, **14**, **22**, **31** and **33** with IC_{50} 1.42–3.87 μM) in comparison with cisplatin (IC_{50} 15.67 μM). Comparing the results of compounds 7–11 with the same R^1 substituent (R^1 = H) but different R^2, it could be found that compound **9** (R^2 = 3-Cl) showed strong cytotoxic activity efficient against Ishikawa, A549 and BEL-7404 cell with IC_{50} values of 1.99, 2.99 and 8.25 μM, respectively. Moreover, compound **14** (R^2 = 3-Cl) has better activities among compounds **12–16** (R^1 = 4-CH_3), and **21** (R^2 = 4-F) has better activities among **17–21** (R^1 = 3-CH_3), and **22** (R^2 = H) have better activities among **22–24** (R^1 = 2-CH_3). The result implied that the R^1 groups such as H, CH_3 and the R^2 group such as Cl may be positive to enhance the inhibitory activities.

On the other hand, comparing the activities among **25–29**, **33–36** and **34–48** with the same R^1 such as Cl, 3,4-Cl, 3-Cl-4-F but different R^2, the results revealed that the compounds such as **28** (R^2 = 3-OCH_3), **30** (R^2 = H), **31** (R^2 = 3-CH_3), **32** (R^2 = 3-Cl), **33** (R^2 = 3-OCH_3), **35** (R^2 = 3-CH_3) and **42** (R^2 = 3-Cl) were beneficial for the inhibitory activities. The most potent compound **30** exhibited significant activity against Ishikawa, A549 and SGC-7901 with IC_{50} values of



Scheme 1. Synthesis route of compounds **7–43**. Reagents and conditions: (a): Methanol, reflux; (b): DMF-DMA, DMF, N_2, 90°C; (c): Conc. HCl, 50% aq. cyanamide, 27% aq. sodium carbonate, r.t. to 85°C; (d): 2-Methoxyethanol, NaOH, N_2, 110°C.

Table 1. *In-vitro* cytotoxic activity of compounds **7–43** against human cancer cell lines.

Compds.	Substituent		Cell lines (IC_{50}, μM)[a,b]				
	R^1	R^2	Ishikawa	A549	BEL-7404	SPC-A-01	SGC-7901
7	H	H	>268	>268	>268	>268	>268
8	H	3-CH_3	21.03	82.66	13.75	42.69	18.60
9	H	3-Cl	1.99	2.90	8.25	46.11	11.24
10	H	3-OCH_3	>248	>248	>248	>248	>248
11	H	4-F	>256	>256	>256	104.25	>256
12	4-CH_3	H	60.96	>258	112.79	>258	117.78
13	4-CH_3	3-CH_3	26.81	>249	31.15	>249	25.16
14	4-CH_3	3-Cl	1.85	10.75	17.46	34.38	3.65
15	4-CH_3	3-OCH_3	22.18	>240	50.58	>240	40.74
16	4-CH_3	4-F	>247	>247	>247	>247	>247
17	3-CH_3	H	26.95	19.22	29.20	99.53	67.60
18	3-CH_3	3-CH_3	15.29	90.17	133.94	>249	128.93
19	3-CH_3	3-Cl	29.28	142.51	110.70	100.90	89.42
20	3-CH_3	3-OCH_3	43.07	41.08	81.77	57.65	124.44
21	3-CH_3	4-F	10.54	23.38	42.86	37.01	21.14
22	2-CH_3	H	1.81	10.72	13.13	61.16	24.86
23	2-CH_3	3-CH_3	4.21	21.60	43.87	104.36	39.98
24	2-CH_3	3-Cl	16.30	26.95	75.28	70.20	36.04
25	4-Cl	H	48.27	17.99	79.93	>245	11.95
26	4-Cl	3-CH_3	>238	>238	>238	>238	>238
27	4-Cl	3-Cl	>226	>226	>226	>266	92.96
28	4-Cl	3-OCH_3	24.16	19.82	17.87	36.55	58.38
29	4-Cl	4-F	>235	141.93	120.73	130.58	119.06
30	2-Cl	H	7.98	1.52	5.06	6.26	12.64
31	2-Cl	3-CH_3	3.87	11.48	22.16	26.33	39.50
32	2-Cl	3-Cl	4.95	7.44	13.42	33.78	11.58
33	2-Cl	3-OCH_3	1.42	4.73	16.43	21.62	12.73
34	3,4-Cl	H	146	>226	36.04	76.90	12.62
35	3,4-Cl	3-CH_3	9.85	74.80	90.20	135.96	60.50
36	3,4-Cl	2-CH_3	81.84	132.68	>219	>219	>219
37	3,4-Cl	3-Cl	111.44	61.76	36.43	106.57	30.51
38	3,4-Cl	3-OCH_3	88.52	89.68	>212	>212	>212
39	3-Cl-4-F	H	19.65	34.45	>235	>235	158
40	3-Cl-4-F	3-CH_3	30.15	76.50	48.33	103.09	38.52
41	3-Cl-4-F	2-CH_3	122.18	98.61	160.52	218.93	130.22
42	3-Cl-4-F	3-Cl	5.10	56.83	19.59	37.87	8.51
43	3-Cl-4-F	3-OCH_3	>220	>220	>220	>220	49.37
Cisplatin			15.67	34.83	8.07	3.73	30.1

[a] IC_{50}, compound concentration required to inhibit tumor cell proliferation by 50%.[b] Values are the mean of three experiments.

7.98, 1.52 and 12.64 μM, respectively, which is 2-, 23-, and 2.4-fold more potent than that of cisplatin. Moreover, comparing the activities of compounds **30–33** with the same R^1 (R^1 = 2-Cl) and different R^2 (R^2 = H, 3-CH_3, 3-Cl, 3-OCH_3), these all exhibited significant cytotoxic activity against all of the tested cell lines. In addition, when the *ortho*-methyl group of **22–24** was replaced by the *ortho*-chloro group of **30–32**, it could be found that the *ortho*-chloro group could obviously increase the cytotoxic activity. So the better substituent R^1 may be 2-Cl moiety and positive to enhance the activities.

Furthermore, in order to investigate the effects of the position of substituents R^1 on the anticancer activity, comparing the compounds with the same R^2 and the different R^1 such as R^2 = H (**12**, **17** and **22**) or R^2 = 3-OCH_3 (**28**, **38** and **43**) or R^2 = 3-CH_3 (**13**, **18** and **23**) or R^2 = 3-CH_3 (**26**, **31** and **35**), it showed IC_{50} values decreased in the sequence of *ortho*-, *meta*- and *para*-position. Therefore, it inferred that cytotoxic activity correlate with the presence of position of electron-adopting group on the benzene ring and whether further studies of other electron-adopting groups such as CF_3, NO_2, etc., could enhance their anticancer activities or not are under way.

In conclusion, a series of novel compounds **7–43** were prepared and some of them showed high or moderate cytotoxic against human cancer cell lines. Among them, the most potent compound **9** and **30** exhibited significant activity

against Ishikawa, A549. The preliminary structure-activity relationships showed the position of electron-adopting group R^1 on the benzene ring was related to cytotoxic inhibitory effect.

Experimental

Melting points were taken on X-4 apparatus and are uncorrected (Shanghai Optical instrument, China). IR spectra (KBr pellets) were obtained on a Bruker TENSOR27 spectrometer (Bruker Optics, Germany). ^{1}H NMR spectra were recorded on a Bruker ADVANCE spectrometer operating at 400 MHz or a Bruker AVANCE III spectrometer at 500 MHz using TMS as the internal standard in $CDCl_3$ (Bruker). MS spectra were recorded on an HP5989B instrument (Agilent, USA). Elemental analyses were performed on a Flash EA1112 Elemental analyzer (CE, ThermoFingnigan). Reagents and solvents were purchased from SinoPharm Chemical Reagent Co., Ltd and were used without further purification. The process of the reaction was monitored by thin layer chromatography (TLC).

Chemistry

The compounds **1a–h** and 2-chloro-acetylacetone **2** were synthesized according to the known method [15, 16, 20]. The compounds **3a–h** were prepared by the Hantsch's method [17]. The aniline guanidines carbonates **6** were prepared according to [18].

*General method for synthesis of compounds **4a–h***

A solution of 2-phenylamino-4-methyl-5-acetyl-thiazole **3a** (2.32 g, 10 mmol) and *N*,*N*-dimethylformamide dimethylacetal (3.57 g, 30 mmol) in DMF (20 mL) was heated at 90°C under N_2 for 14 h (EtOAc/toluene, 1:2, monitored by TLC). The reaction mixture was cooled and poured into ice-water with stirring, then stood overnight in refrigerator. When crude product separated out as a dark solid or oil, it was filtered and washed liberally with H_2O, then purified by preparative layer chromatography, eluting with toluene/ethyl acetate (2:1) to afford the title compound **4a** as a light-yellow solid. Compounds **4b–h** were also prepared by the procedure described above.

*3-Dimethylamino-1-[4-methyl-2-(methyl-phenyl-amino)-thiazol-5-yl]-propenone **4a***

Yield 38.5%. M.p. 53–55°C. IR: ν_{max} (KBr) cm^{-1}: 3442, 2919, 2804, 1638, 1551, 1496, 1433, 1366, 1322. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 7.63 (d, 1H, J = 12 Hz, =CH), 7.46–7.38 (m, 4H, Ar-H), 7.32–7.27 (m, 1H, Ar-H), 5.21 (d, 1H, J = 12 Hz, =CH), 3.54 (s, 3H, CH_3), 2.94 (brs, 6H, 2 CH_3), 2.63 (s, 3 H, CH_3). EIMS *m*/*z* (%): 301 (M^+, 40), 284 (10), 257 (78), 231 (19), 203 (12), 195 (17), 151 (100), 136 (47), 106 (17), 98 (61), 91 (14), 82 (11), 77 (20), 70 (12), 55 (25).

*3-Dimethylamino-1-[4-methyl-2-(methyl-o-tolyl-amino)-thiazol-5-yl]-propenone **4b***

Yield 61.7%. M.p. 73–75°C. IR: ν_{max} (KBr) cm^{-1}: 3424, 2920, 2804, 1632, 1503, 1433, 1367, 1319. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 7.61 (d, 1H, J = 12 Hz, =CH), 7.35–7.28 (m, 3H, Ar-H), 7.25–7.18 (m, 1H, Ar-H), 5.16 (d, 1H, J = 12 Hz, =CH), 3.45 (s, 3H, CH_3), 2.91 (brs, 6H, 2 CH_3), 2.63 (s, 3H, CH_3), 2.25 (s, 3H, CH_3). EIMS *m*/*z* (%): 315 (M^+, 23), 298 (9), 271 (75), 245 (13), 217 (8), 195 (17), 151 (100), 144 (21), 136 (45), 121 (23), 105 (15), 98 (55), 91 (23), 82 (11), 69 (12), 55 (28).

*3-Dimethylamino-1-[4-methyl-2-(methyl-m-tolyl-amino)-thiazol-5-yl]-propenone **4c***

Yield 56.4%. M.p. 187–190°C. IR: ν_{max} (KBr) cm^{-1}: 3357, 2965, 2931, 2804, 1634, 1571, 1513, 1488, 1459, 1414, 1366, 1313. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 7.70 (d, 1H, J = 12.4 Hz, =CH), 7.27–7.24 (m, 1H, Ar-H), 7.14 (t, J = 9.4 Hz, 2H, Ar-H), 6.93 (d, 1H, J = 7.6 Hz, Ar-H), 5.33 (d, 1H, J = 12 Hz, =CH), 3.52 (s, 3H, CH_3), 2.99 (brs, 6H, 2 CH_3), 2.61 (s, 3H, CH_3), 2.37 (s, 3H, CH_3). EIMS *m*/*z* (%): 315 (M^+, 31), 300 (10), 271 (20), 257 (59), 231 (11), 195 (11), 151 (100), 136 (36), 98 (56), 91 (18), 60 (12), 55 (37).

*3-Dimethylamino-1-[4-methyl-2-(methyl-p-tolyl-amino)-thiazol-5-yl]-propenone **4d***

Yield 68.6%. M.p. 48–51°C. IR: ν_{max} (KBr) cm^{-1}: 3359, 3236, 2930, 2804, 1624, 1520, 1435, 1415, 1363, 1316. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 7.62 (d, 1H, J = 12 Hz, =CH), 7.27 (d, 2H, J = 5.6 Hz, Ar-H), 7.24 (d, 2H, J = 5.6 Hz, Ar-H), 5.20 (d, 1H, J = 12 Hz, =CH), 3.51 (s, 3H, CH_3), 2.93 (brs, 6H, 2 CH_3), 2.63 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). EIMS *m*/*z* (%): 315 (M^+, 45), 298 (10), 271 (83), 245 (15), 217 (8), 195 (20), 151 (100), 144 (19), 136 (48), 121 (20), 105 (11), 98 (51), 91 (20), 82 (10), 69 (10), 55 (26).

*3-Dimethylamino-1-{2-[(2-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-propenone **4e***

Yield 41%. M.p. 50–52°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 2922, 2803, 1638, 1552, 1503, 1433, 1366, 1316. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 7.62 (d, 1H, J = 12.4 Hz, =CH), 7.55–7.53 (m, 1H, Ar-H), 7.44–7.41 (m, 1H, Ar-H), 7.39–7.35 (m, 2H, Ar-H), 5.19 (d, 1H, J = 12.4 Hz, =CH), 3.47 (s, 3H, CH_3), 2.94 (brs, 6H, 2 CH_3), 2.63 (s, 3H, CH_3). EIMS *m*/*z* (%): 335 (M^+, 26), 318 (10), 300 (43), 291 (67), 265 (20), 255 (11), 203 (26), 165 (14), 151 (64), 136 (100), 113 (23), 98 (81), 82 (13), 70 (18), 55 (35).

*3-Dimethylamino-1-{2-[(4-chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-propenone **4f***

Yield 60.9%. M.p. 111–113°C. IR: ν_{max} (KBr) cm^{-1}: 3426, 2918, 2812, 1634, 1547, 1490, 1434, 1400, 1363, 1340, 1316. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 7.64 (d, 1H, J = 12.4 Hz, =CH), 7.39 (d, J = 8.8 Hz, 2H, Ar-H), 7.35 (d, J = 8.8 Hz, 2H, Ar-H), 5.22 (d, 1H, J = 12.4 Hz, =CH), 3.51 (s, 3H, CH_3), 2.95 (brs, 6H, 2 CH_3), 2.62 (s, 3H, CH_3). EIMS *m*/*z* (%): 335 (M^+, 35), 318 (8), 291 (70), 265 (14), 195 (26), 166 (16), 151 (100), 136 (55), 125 (10), 111 (10), 98 (60), 82 (12), 70 (16), 55 (35).

*3-Dimethylamino-1-{2-[(3,4-dichloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-propenone **4g***

Yield 50%. M.p. 115–117°C. IR: ν_{max} (KBr) cm^{-1}: 3435, 3270, 3069, 2903, 2802, 1635, 1545, 1486, 1438, 1410, 1353, 1324. ^{1}H-NMR ($CDCl_3$, TMS, 500 MHz, δ ppm): 7.69 (d, 1H, J = 12 Hz, =CH), 7.53 (d, J = 3 Hz, 1H, Ar-H), 7.49 (d, J = 8.5 Hz, 1H, Ar-H), 7.31 (dd, J_1 = 3.0 Hz, J_2 = 2.5 Hz, 1H, Ar-H), 5.25 (d, J = 11.5 Hz, 1H, =CH), 3.53 (s, 3H, CH_3), 2.97 (brs, 6H, 2 CH_3), 2.63 (s, 3H, CH_3). EIMS *m*/*z* (%): 369 ($[M - H]^+$, 9), 355 (6), 325 (44), 195 (16), 177 (13), 151 (100), 136 (45), 98 (8).

3-Dimethylamino-1-{2-[(3-dichloro-4-fluoro–phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-propenone ***4h***

Yield 72.3%. M.p. 95–97°C. IR: ν_{max} (KBr) cm^{-1}: 3439, 3030, 2908, 2808, 1640, 1549, 1496, 1434, 1417, 1363, 1331, 1311. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 7.65 (d, 1H, J = 12 Hz, =CH), 7.46 (dd, J_1 = 2.8 Hz, J_2 = 2.4 Hz, 1H, Ar-H), 7.32–7.28 (m, 1H, Ar-H), 7.19 (t, J = 8.8 Hz, 1H, Ar-H), 5.23 (d, 1H, J = 12 Hz, =CH), 3.49 (s, 3H, CH_3), 2.97 (brs, 6H, 2 CH_3), 2.61 (s, 3H, CH_3). EIMS m/z (%): 355 (M^+, 32), 336 (9), 309 (67), 283 (13), 195 (24), 184 (9), 162 (16), 151 (100), 136 (57), 129 (10), 98 (70), 82 (13), 70 (22), 55 (34).

General method for preparation of compounds ***7–43***

A mixture of 3-dimethylamino-1-[4-methyl-2-(methyl-phenyl-amino)-thiazol-5-yl]-propenone (1.51 g, 5 mmol) and NaOH (0.2 g, 5 mmol) in 2-methoxylethanol (20 mL) was treated with *N*-phenyl-guanidine carbonate (1.48 g, 7.5 mmol). The reaction mixture was heated at 110°C under N_2 for 21 h. After concentration, the residue was filtered and washed liberally with ethanol and water. Recrystallization from acetone afforded the title compound **7** as light-yellow needle crystals. Compounds **8–43** were also prepared by the procedure described above.

{4-[2-(Phenyl-methyl-amino)-4-methyl-thiazol-5-yl}-pyrimidin-2-yl}-phenylamine ***7***

Yield 60.6%. M.p. 214–217°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3257, 3189, 3042, 1618, 1598, 1580, 1486, 1448, 1402, 1340. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (d, 1H, J = 4.8 Hz, Py-H), 7.58 (d, 2H, J = 7.6 Hz, Ar-H), 7.47–7.45 (m, 3H, Ar-H), 7.39–7.34 (m, 1H, Ar-H), 7.28–7.24 (m, 2H, Ar-H), 7.01–6.99 (m, 2H, Ar-H), 6.81 (d, 1H, J = 5.2 Hz, Py-H), 3.58 (s, 3H, CH_3), 2.61 (s, 3H, CH_3). EIMS m/z (%): 373 (M^+, 100), 358 (8), 281 (13), 240 (12), 208 (14), 186 (14), 77 (12). Anal. calcd. for $C_{21}H_{19}N_5S$: C, 67.53; H, 5.13; N, 18.75; Found: C, 67.37; H, 5.22; N, 18.65.

{4-[2-(Phenyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-m-tolyl-amine ***8***

Yield 4%. M.p. 160–163°C. IR: ν_{max} (KBr) cm^{-1}: 3420, 3268, 3160, 3088, 2980, 1625, 1589, 1525, 1493, 1469, 1395, 1296. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.26 (d, 1H, J = 5.6 Hz, Py-H), 7.64 (s, 1H, Ar-H), 7.48–7.42 (m, 3H, Ar-H), 7.38–7.31 (m, 1H, Ar-H), 7.17–7.11 (m, 3H, Ar-H), 6.82 (d, 1H, J = 5.2 Hz, Py-H), 6.79 (m*, 1H, Ar-H), 3.58 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.21 (s, 3H, CH_3) (* overlapped with Py-H). EIMS m/z (%): 387 (M^+, 100), 372 (9), 295 (15), 254 (9), 222 (14). Anal. calcd. for $C_{22}H_{21}N_5S$: C, 68.19; H, 5.46; N, 18.07; Found: C, 68.26; H, 5.25; N, 18.11.

{4-[2-(Phenyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(3-chloro-phenyl)-amine ***9***

Yield 19.7%. M.p. 204–207°C. IR: ν_{max} (KBr) cm^{-1}: 3426, 3268, 3184, 3110, 1598, 1575, 1531, 1490, 1421, 1410, 1365, 1333. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.27 (d, 1H, J = 5.6 Hz, Py-H), 8.03 (s, 1H, NH), 7.49–7.39 (m, 4H, Ar-H), 7.35–7.29 (m, 2H, Ar-H), 7.15–7.14 (m, 2H, Ar-H), 6.94 (d, 1H, J = 4.0 Hz, Ar-H), 6.86 (d, 1H, J = 5.2 Hz, Py-H), 3.58 (s, 3H, CH_3), 2.61 (s, 3H, CH_3). EIMS m/z (%): 407 (M^+, 100), 315 (29), 303 (15), 274 (8), 242 (10), 207 (20), 186 (9), 164 (11), 91 (7), 77 (7). Anal. calcd. for $C_{21}H_{18}ClN_5S$: C, 61.83; H, 4.45; N, 17.17; Found: C, 61.75; H, 4.33; N, 17.03.

{4-[2-(Phenyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(3-methoxy-phenyl)-amine ***10***

Yield 63.6%. M.p. 174–177°C. IR: ν_{max} (KBr) cm^{-1}: 3274, 3204, 3005, 1596, 1582, 1537, 1494, 1463, 1428, 1340, 1368, 1335. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (s, 1H, J = 4.4 Hz, Py-H), 7.51–7.35 (m, 5H, Ar-H), 7.14 (t, 1H, J = 8.0 Hz, Ar-H), 7.06 (s, 1H, Ar-H), 6.88 (d, 1H, J = 8.0 Hz, Ar-H), 6.84 (d, 1H, J = 5.2 Hz, Py-H), 6.54 (d, 1H, J = 8.0 Hz, Ar-H), 3.64 (s, 3H, OCH_3), 3.57 (s, 3H, CH_3), 2.60 (s, 3H, CH_3). EIMS m/z (%): 403 (M^+, 100), 388 (8), 311 (9), 256 (10), 238 (9), 129 (10), 105 (8), 97 (10), 83 (10), 73 (17), 57 (21). Anal. calcd. for $C_{22}H_{21}N_5OS$: C, 65.49; H, 5.25; N, 17.36; Found: C, 65.42; H, 5.34; N, 17.30.

{4-[2-(Phenyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(4-fluoro-phenyl)-amine ***11***

Yield 45.2%. M.p. 211–213°C. IR: ν_{max} (KBr) cm^{-1}: 3433, 3260, 3049, 2920, 1622, 1574, 1541, 1507, 1488, 1425, 1405, 1366, 1335. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.23 (brs, 1H, Py-H), 7.48–6.95 (m, 9H, Ar-H), 6.81 (brs, 1H, Py-H), 3.58 (s, 3H, CH_3), 3.60 (s, 3H, CH_3). EIMS m/z (%): 391 (M^+, 100), 299 (16), 226 (13), 97 (9), 83 (13), 71 (16), 57 (25). Anal. calcd. for $C_{21}H_{18}FN_5S$: C, 64.43; H, 4.63; N, 17.89; Found: C, 64.41; H, 4.79; N, 17.94.

{4-[2-(p-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-phenyl-amine ***12***

Yield 34.5%. M.p. 191–194°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3261, 3040, 1618, 1580, 1540, 1513, 1488, 1447, 1340. ^{1}H-NMR ($CDCl_3$, TMS, 500 MHz, δ ppm): 8.26 (d, 1H, J = 5.5 Hz, Py-H), 7.57 (d, 2H, J = 8 Hz, Ar-H), 7.31–7.24 (m, 5H, Ar-H), 7.06 (s, 1H, Ar-H), 6.99 (t, 1H, J = 7.5 Hz, Ar-H), 6.79 (d, 1H, J = 5.0 Hz, Py-H), 3.54 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). EIMS m/z (%): 387 (M^+, 100), 372 (8), 281 (12), 240 (10), 208 (12), 193 (14), 105 (8), 91 (8), 77 (9). Anal. calcd. for $C_{22}H_{21}N_5S$: C, 68.19; H, 5.46; N, 18.07. Found: C, 68.32; H, 5.33; N, 18.15.

{4-[2-(p-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-m-tolyl-amine ***13***

Yield 22.8%. M.p. 183–185°C. IR: ν_{max} (KBr) cm^{-1}: 3417, 3269, 3202, 3066, 3034, 1601, 1563, 1539, 1492, 1428, 1400, 1367, 1335. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.25 (d, 1H, J = 4.8 Hz, Py-H), 7.69 (s, 1H, Ar-H), 7.33–7.25 (m, 4H, Ar-H), 7.19–7.11 (m, 2H, Ar-H), 6.86 (m*, 1H, Ar-H), 6.79 (brs, 1H, Py-H), 3.53 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 2.19 (s, 3H, CH_3) (* overlapped with Py-H). EIMS m/z (%): 401 (M^+, 100), 386 (8), 295 (19), 254 (8), 222 (12). Anal. calcd. for $C_{23}H_{23}N_5S$: C, 68.80; H, 5.77; N, 17.44; Found: C, 68.94; H, 5.91; N, 17.21.

{4-[2-(p-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(3-chloro-phenyl)-amine ***14***

Yield 36.9%. M.p. 206–208°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3267, 2920, 1607, 1576, 1531, 1495, 1425, 1400, 1368, 1334. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.27 (d, 1H, J = 5.2 Hz, Py-H), 8.06 (s, 1H, NH), 7.31–7.27 (m, 3H, Ar-H), 7.21–7.10 (m, 4H, Ar-H), 6.94 (d, 1H, J = 7.2 Hz, Ar-H), 6.85 (d, 1H, J = 5.6 Hz, Py-H), 3.55 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). EIMS m/z (%): 421 (M^+, 100), 406 (8), 388 (5), 315 (27), 303 (12), 207 (10). Anal. calcd. for $C_{22}H_{20}ClN_5S$: C, 62.62; H, 4.78; N, 16.60; Found: C, 62.78; H, 4.57; N, 16.65.

{4-[2-(p-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(3-methoxy-phenyl)-amine **15**

Yield 46.7%. M.p. 180–183°C. IR: ν_{max} (KBr) cm^{-1}: 3460, 3280, 3207, 3132, 3076, 3013, 1620, 1584, 1553, 1529, 1501, 1464, 1445, 1422, 1407, 1376, 1361, 1318. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.27 (s, 1H, J = 4.8 Hz, Py-H), 7.53 (s, 1H, Ar-H), 7.29–7.07 (m, 5H, Ar-H), 6.87 (d, 1H, J = 8.0 Hz, Ar-H), 6.83 (d, 1H, J = 5.2 Hz, Py-H), 6.54 (d, 1H, J = 8.0 Hz, Ar-H), 3.64 (s, 3H, OCH_3), 3.54 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). EIMS *m/z* (%): 417 (M^+, 100), 402 (7), 311 (12), 105 (9), 91 (10), 73 (12), 57 (17). Anal. calcd. for $C_{23}H_{23}N_5OS$: C, 66.16; H, 5.55; N, 16.77; Found: C, 66.23; H, 5.69; N, 16.96.

{4-[2-(p-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(4-fluoro-phenyl)-amine **16**

Yield 67.6%. M.p. 215–218°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3260, 3216, 3041, 1621, 1574, 1541, 1506, 1488, 1424, 1402, 1366, 1337. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.24 (s, 1H, J = 5.2 Hz, Py-H), 7.52–7.49 (m, 2H, Ar-H), 7.31–7.28 (m, 3H, Ar-H), 6.96–6.93 (m, 3H, Ar-H), 6.79 (s, 1H, J = 5.2 Hz, Py-H), 3.54 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). EIMS *m/z* (%): 405 (M^+, 100), 391 (13), 299 (16), 226 (13), 105 (10), 91 (9). Anal. calcd. for $C_{22}H_{20}FN_5S$: C, 65.16; H, 4.97; N, 17.27; Found: C, 65.39; H, 4.83; N, 17.42

{4-[2-(m-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-phenyl-amine **17**

Yield 8.2%. M.p. 170–173°C. IR: ν_{max} (KBr) cm^{-1}: 3422, 3265, 3188, 3032, 1644, 1605, 1580, 1536, 1496, 1445, 1369, 1339. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.27 (d, 1H, J = 5.2 Hz, Py-H), 7.58 (d, 2H, J = 8.0 Hz, Ar-H), 7.35 (t, 1H, J = 7.6 Hz, Ar-H), 7.28–7.22 (m, 4H, Ar-H), 7.15 (d, 1H, J = 8.0 Hz, Ar-H), 7.00 (t, 1H, J = 7.4 Hz, Ar-H), 6.81 (d, 1H, J = 5.6 Hz, Py-H), 3.56 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). EIMS *m/z* (%): 387 (M^+, 100), 372 (6), 281 (17), 269 (7), 208 (13). Anal. calcd. for $C_{22}H_{21}N_5S$: C, 68.19; H, 5.46; N, 18.07; Found: C, 68.35; H, 5.31; N, 18.15.

{4-[2-(m-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-m-tolyl-amine **18**

Yield 14.6%. M.p. 165–167°C. IR: ν_{max} (KBr) cm^{-1}: 3424, 3267, 3054, 1599, 1579, 1558, 1428, 1398, 1369, 1339. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.26 (d, 1H, J = 5.6 Hz, Py-H), 7.63 (s, 1H, Ar-H), 7.34 (t, 1H, J = 8.0 Hz, Ar-H), 7.22 (d, 2H, J = 6.4 Hz, Ar-H), 7.18–7.11 (m, 3H, Ar-H), 7.08 (s, 1H, Ar-H), 6.81 (d, 1H, J = 5.6 Hz, Py-H), 3.56 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). EIMS *m/z* (%): 401 (M^+, 100), 386 (9), 269 (11), 256 (14), 237 (12), 222 (10). Anal. calcd. for $C_{23}H_{23}N_5S$: C, 68.80; H, 5.77; N, 17.44; Found: C, 68.61; H, 5.65; N, 17.65.

{4-[2-(m-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(3-chloro-phenyl)-amine **19**

Yield 41.2%. M.p. 173–175°C. IR: ν_{max} (KBr) cm^{-1}: 3431, 3264, 3182, 3105, 1607, 1575, 1532, 1497, 1424, 1332. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (brs, 1H, Py-H), 8.01 (s, 1H, NH), 7.35 (s, 1H, Ar-H), 7.26–7.12 (m, 6H, Ar-H), 6.94 (s, 1H, Ar-H), 6.86 (brs, 1H, Py-H), 3.56 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). EIMS *m/z* (%): 421 (M^+, 100), 406 (5), 315 (16), 274 (8), 242 (9), 209 (14), 193 (23), 178 (10), 164 (10), 120 (10), 105 (18), 91 (18). Anal. calcd. for $C_{22}H_{20}ClN_5S$: C, 62.62; H, 4.78; N, 16.60; Found: C, 62.85; H, 4.99; N, 16.55.

{4-[2-(m-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(3-methoxy-phenyl)-amine **20**

Yield 55.1%. M.p. 183–184°C. IR: ν_{max} (KBr) cm^{-1}: 3272, 3208, 3191, 3119, 3047, 3005, 1953, 1582, 1566, 1538, 1503, 1457, 1428, 1399, 1371, 1333. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.27 (s, 1H, J = 5.2 Hz, Py-H), 7.51 (s, 1H, NH), 7.35 (t, 1H, J = 7.6 Hz, Ar-H), 7.21–7.12 (m, 4H, Ar-H), 7.06 (s, 1H, Ar-H), 6.89 (d, 1H, J = 8.0 Hz, Ar-H), 6.84 (d, 1H, J = 5.2 Hz, Py-H), 6.54 (d, 1H, J = 8.4 Hz, Ar-H), 3.64 (s, 3H, OCH_3), 3.55 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). EIMS *m/z* (%): 417 (M^+, 100), 402 (8), 311 (10), 270 (9), 238 (8), 208 (9), 91 (8). Anal. calcd. for $C_{23}H_{23}N_5OS$: C, 66.16; H, 5.55; N, 16.77; Found: C, 66.41; H, 5.35; N, 16.65.

{4-[2-(m-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(4-fluoro-phenyl)-amine **21**

Yield 43.8%. M.p. 152–153°C. IR: ν_{max} (KBr) cm^{-1}: 3454, 3280, 3219, 3124, 3056, 1619, 1588, 1557, 1536, 1505, 1463, 1417, 1365, 1340, 1317. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.25 (s, 1H, J = 3.2 Hz, Py-H), 7.50 (m*, 1H, Ar-H), 7.37–7.33 (m, 1H, Ar-H), 7.23–7.15 (m, 3H, Ar-H), 7.00–6.93 (m, 3H, Ar-H), 6.80 (s, 1H, J = 3.6 Hz, Py-H), 3.56 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.41 (s, 3H, CH_3) (* overlapped with NH). EIMS *m/z* (%): 405 (M^+, 100), 390 (8), 299 (14), 226 (12). Anal. calcd. for $C_{22}H_{20}FN_5S$: C, 65.16; H, 4.97; N, 17.27; Found: C, 65.29; H, 4.86; N, 17.23.

{4-[2-(o-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-phenyl-amine **22**

Yield 40%. M.p. 181–183°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3266, 3193, 3110, 3047, 1612, 1583, 1539, 1497, 1447, 1370, 1340, 1323. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.25 (d, 1H, J = 5.2 Hz, Py-H), 7.55 (d, 2H, J = 8.0 Hz, Ar-H), 7.38–7.27 (m, 4H, Ar-H), 7.25–7.21 (m, 2H, Ar-H), 6.98 (t, 1H, J = 7.4 Hz, Ar-H), 6.93 (s, 1H, NH), 6.78 (d, 1H, J = 5.2 Hz, Py-H), 3.49 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). EIMS *m/z* (%): 387 (M^+, 100), 372 (35), 354 (16), 263 (50), 256 (8), 235 (8), 208 (14), 194 (8), 185 (13), 171 (8), 146 (13), 129 (11), 118 (23), 91 (17), 77 (33), 65 (17), 55 (22). Anal. calcd. for $C_{22}H_{21}N_5S$: C, 68.19; H, 5.46; N, 18.07; Found: C, 68.35; H, 5.63; N, 18.28.

{4-[2-(o-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-m-tolyl-amine **23**

Yield 58.5%. M.p. 182–185°C. IR: ν_{max} (KBr) cm^{-1}: 3424, 3268, 3201, 1601, 1581, 1561, 1542, 1509, 1423, 1368, 1337. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.24 (d, 1H, J = 5.2 Hz, Py-H), 7.65 (s, 1H, Ar-H), 7.36–7.27 (m, 4H, Ar-H), 7.13–7.09 (m, 2H, Ar-H), 6.92 (s, 1H, Ar-H), 6.79 (d, 1H, J = 5.6 Hz, Py-H), 3.49 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). EIMS *m/z* (%): 401 (M^+, 100), 386 (28), 368 (17), 283 (9), 222 (8), 129 (10), 118 (8), 98 (11), 91 (15), 83 (12), 73 (21), 65 (10), 57 (28). Anal. calcd. for $C_{23}H_{23}N_5S$: C, 68.80; H, 5.77; N, 17.44; Found: C, 68.72; H, 5.65; N, 17.58.

{4-[2-(o-Tolyl-methyl-amino)-4-methyl-thiazol-5-y}-pyrimidin-2-yl}-(3-chloro-phenyl)-amine **24**

Yield 38.7%. M.p. 195–198°C. IR: ν_{max} (KBr) cm^{-1}: 3422, 3265, 3183, 3101, 3067, 3016, 1599, 1575, 1561, 1525, 1422, 1367, 1336. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.26 (d, 1H,

J = 5.2 Hz, Py-H), 8.01 (s, 1H, NH), 7.35–7.28 (m, 4H, Ar-H), 7.15–7.07 (m, 3H, Ar-H), 6.91 (d, 1H, J = 6.0 Hz, Ar-H), 6.83 (d, 1H, J = 5.6 Hz, Py-H), 3.50 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). EIMS m/z (%): 421 (M^+, 100), 406 (32), 388 (15), 303 (13), 284 (18), 256 (14), 241 (10), 213 (10), 185 (14), 171 (11), 157 (8), 129 (28), 118 (10), 105 (15), 97 (18), 83 (21), 73 (60), 55 (53). Anal. calcd. for $C_{22}H_{20}ClN_5S$: C, 62.62; H, 4.78; N, 16.60; Found: C, 62.36; H, 4.62; N, 16.51.

(4-{2-[(4-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-phenyl-amine ***25***

Yield 23.2%. M.p. 203–205°C. IR: ν_{max} (KBr) cm^{-1}: 3426, 3258, 3188, 3044, 1617, 1571, 1541, 1488, 1447, 1403, 1367, 1341. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (d, 1H, J = 5.2 Hz, Py-H), 7.58 (d, 2H, J = 7.6 Hz, Ar-H), 7.44–7.36 (m, 4H, Ar-H), 7.32–7.29 (m, 2H, Ar-H), 7.03 (t, 1H, J = 7.2 Hz, Ar-H), 6.83 (d, 1H, J = 5.6 Hz, Py-H), 3.55 (s, 3H, CH_3), 2.60 (s, 3H, CH_3). EIMS m/z (%): 407 (M^+, 100), 392 (9), 372 (5), 281 (35), 267 (7), 240 (14), 208 (27). Anal. calcd. for $C_{21}H_{18}ClN_5S$: C, 61.83; H, 4.45; N, 17.17; Found: C, 61.75; H, 4.35; N, 17.29.

(4-{2-[(4-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-m-tolyl-amine ***26***

Yield 17.5%. M.p. 205–208°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3280, 1601, 1580, 1561, 1539, 1490, 1425, 1401, 1368, 1336. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.27 (d, 1H, J = 5.6 Hz, Py-H), 7.65 (s, 1H, Ar-H), 7.40 (dd, 4H, J_1 = 8.8 Hz, J_2 = 8.8 Hz, Ar-H), 7.15 (d, 3H, J = 4.8 Hz, Ar-H), 6.83 (d, 1H, J = 5.6 Hz, Py-H), 3.55 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). EIMS m/z (%): 421 (M^+, 100), 406 (10), 295 (23), 254 (11), 222 (17), 207 (10). Anal. calcd. for $C_{22}H_{20}ClN_5S$: C, 62.62; H, 4.78; N, 16.60; Found: C, 62.79; H, 4.67; N, 16.51.

(4-{2-[(4-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-chloro-phenyl)-amine ***27***

Yield 50.1%. M.p. 226–229°C. IR: ν_{max} (KBr) cm^{-1}: 3424, 3266, 3184, 3109, 1614, 1595, 1575, 1532, 1486, 1424, 1365, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.18 (d, 1H, J = 5.2 Hz, Py-H), 8.06 (s, 1H, NH), 7.44–7.34 (m, 4H, Ar-H), 7.17–7.02 (m, 4H, Ar-H), 6.89 (d, 1H, J = 5.6 Hz, Py-H), 3.58 (s, 3H, CH_3), 2.63 (s, 3H, CH_3). EIMS m/z (%): 441 (M^+, 100), 406 (8), 315 (66), 303 (15), 274 (13), 242 (16), 207 (28), 202 (11), 164 (11), 125 (11), 75 (8). Anal. calcd. for $C_{21}H_{17}Cl_2N_5S$: C, 57.02; H, 3.87; N, 15.83; Found: C, 57.21; H, 3.73; N, 15.95.

(4-{2-[(4-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-methoxy-phenyl)-amine ***28***

Yield 60%. M.p. 180–183°C. IR: ν_{max} (KBr) cm^{-1}: 3419, 3280, 3197, 3121, 3067, 3053, 1598, 1583, 1561, 1537, 1491, 1456, 1429, 1401, 1369, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (s, 1H, J = 4.4 Hz, Py-H), 7.49 (s, 1H, NH), 7.40 (dd, 4H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, Ar-H), 7.16 (t, 2H, J = 8.0 Hz, Ar-H), 6.92 (d, 1H, J = 7.6 Hz, Ar-H), 6.85 (d, 1H, J = 4.8 Hz, Py-H), 6.57 (d, 1H, J = 8.0 Hz, Ar-H), 3.71 (s, 3H, OCH_3), 3.54 (s, 3H, CH_3), 2.59 (s, 3H, CH_3). EIMS m/z (%): 437 (M^+, 100), 422 (8), 403 (10), 311 (10), 284 (9), 270 (9), 256 (9), 238 (10), 185 (9), 129 (17), 111 (14), 97 (20), 83 (21), 73 (33), 55 (48). Anal. calcd. for $C_{22}H_{20}ClN_5OS$: C, 60.34; H, 4.60; N, 15.99; Found: C, 60.52; H, 4.71; N, 15.87.

(4-{2-[(4-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(4-fluoro-phenyl)-amine ***29***

Yield 69.3%. M.p. 216–217°C. IR: ν_{max} (KBr) cm^{-1}: 3423, 3264, 3222, 3050, 1625, 1578, 1539, 1493, 1427, 1399, 1369, 1337. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.25 (s, 1H, J = 5.2 Hz, Py-H), 7.53–7.50 (m, 2H, Ar-H), 7.40 (dd, 4H, J_1 = 8.4 Hz, J_2 = 8.8 Hz, Ar-H), 7.16 (s, 1H, NH), 6.98 (t, 2H, J = 8.4 Hz, Ar-H), 6.81 (s, 1H, J = 5.2 Hz, Py-H), 3.55 (s, 3H, CH_3), 2.59 (s, 3H, CH_3). EIMS m/z (%): 425 (M^+, 100), 299 (22), 258 (10), 226 (19), 212 (9), 111 (8), 95 (9), 83 (8), 57 (8). Anal. calcd. for $C_{21}H_{17}ClFN_5S$: C, 59.22; H, 4.02; N, 16.44; Found: C, 59.36; H, 4.13; N, 16.62.

(4-{2-[(2-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-phenyl-amine ***30***

Yield 40.8%. M.p. 168–170°C. IR: ν_{max} (KBr) cm^{-1}: 3416, 3267, 3192, 3115, 3059, 3034, 2927, 2860, 1934, 1934, 1611, 1580, 1537, 1499, 1434, 1402, 1370, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.27 (s, 1H, J = 5.2 Hz, Py-H), 7.58–7.54 (m, 3H, Ar-H), 7.46–7.45 (m, 1H, Ar-H), 7.41–7.39 (m, 2H, Ar-H), 7.24–7.22 (m, 1H, Ar-H), 7.02–6.97 (m, 2H, Ar-H), 6.80 (d, 1H, J = 5.2 Hz, Py-H), 3.51 (s, 3H, CH_3), 2.61 (s, 3H, CH_3). EIMS m/z (%): 407 (M^+, 91), 372 (100), 240 (12), 238 (8), 208 (20), 186 (44), 77 (19). Anal. calcd. for $C_{21}H_{18}ClN_5S$: C, 61.83; H, 4.45; N, 17.17; Found: C, 61.79; H, 4.63; N, 17.11.

(4-{2-[(2-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-m-tolyl-amine ***31***

Yield 56.7%. M.p. 189–191°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3269, 3200, 3068, 1925, 1752, 1601, 1580, 1563, 1541, 1505, 1423, 1401, 1367, 1336. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.23 (brs, 1H, Py-H), 7.64 (s, 1H, NH), 7.58–7.56 (m, 1H, Ar-H), 7.45–7.39 (m, 3H, Ar-H), 7.22–7.12 (m, 3H, Ar-H), 6.81 (d, 1H, J = 5.6 Hz, Py-H), 6.79 (m*, 1H, Ar-H), 3.52 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 2.17 (s, 3H, CH_3) (* overlapped with Py-H). EIMS m/z (%): 421 (M^+, 100), 406 (11), 386 (90), 254 (10), 222 (13), 207 (9), 193 (15), 186 (33), 129 (12), 111 (10), 91 (13), 73 (19), 57 (23). Anal. calcd. for $C_{22}H_{20}ClN_5S$: C, 62.62; H, 4.78; N, 16.60; Found: C, 62.71; H, 4.64; N, 16.37.

(4-{2-[(2-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-chloro-phenyl)-amine ***32***

Yield 53%. M.p. 195–198°C. IR: ν_{max} (KBr) cm^{-1}: 3417, 3261, 3180, 3067, 3005, 1815, 1747, 1608, 1576, 1503, 1419, 1368, 1536. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (s, 1H, J = 5.2 Hz, Py-H), 8.03 (s, 1H, NH), 7.57–7.55 (m, 1H, Ar-H), 7.47–7.45 (m, 1H, Ar-H), 7.39–7.38 (m, 2H, Ar-H), 7.16–7.08 (m, 3H, Ar-H), 6.92 (d, 1H, J = 7.2 Hz, Ar-H), 6.86 (d, 1H, J = 5.6 Hz, Py-H), 3.52 (s, 3H, CH_3), 2.62 (s, 3H, CH_3). EIMS m/z (%): 441 (M^+, 67), 406 (100), 331 (10), 296 (13), 256 (11), 207 (13), 186 (35), 164 (9), 129 (15), 111 (16), 97 (14), 85 (15), 73 (32), 57 (35). Anal. calcd. for $C_{21}H_{17}Cl_2N_5S$: C, 57.02; H, 3.87; N, 15.83; Found: C, 57.15; H, 3.95; N, 15.79.

(4-{2-[(2-Chloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-methoxy-phenyl)-amine ***33***

Yield 43.6%. M.p. 165–167°C. IR: ν_{max} (KBr) cm^{-1}: 3424, 3282, 3212, 3114, 3012, 1585, 1538, 1503, 1462, 1424, 1399, 1368, 1337. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (brs, 1H, Py-H), 7.57–6.85 (m, 8H, Ar-H), 6.52 (brs,1H, Py-H), 3.64 (s, 3H, OCH_3), 3.50 (s, 3H, CH_3), 2.61 (s, 3H, CH_3). EIMS m/z (%): 437 (M^+, 100), 402 (72), 256 (11), 201 (12), 185 (16), 129 (13), 111 (12), 97 (18), 83 (17), 73

(29), 57 (42). Anal. calcd. for $C_{22}H_{20}ClN_5OS$: C, 60.34; H, 4.60; N, 15.99; Found: C, 60.39; H, 4.53; N, 15.83.

(4-{2-[(3,4-Dichloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-phenyl-amine ***34***

Yield 20.4%. M.p. 178–179°C. IR: ν_{max}(KBr) cm^{-1}: 3425, 3276, 3116, 3067, 3047, 1613, 1580, 1553, 1496, 1427, 1402, 1365, 1344. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.29 (d, 1H, J = 5.2 Hz, Py-H), 7.61–7.59 (m, 3H, Ar-H), 7.51 (d, 1H, J = 8.4 Hz, Ar-H), 7.34–7.29 (m, 3H, Ar-H), 7.04 (t, 1H, J = 7.4 Hz, Ar-H), 6.84 (d, 1H, J = 5.6 Hz, Py-H), 3.55 (s, 3H, CH_3), 2.60 (s, 3H, CH_3). EIMS m/z (%): 441 (M^+, 100), 426 (9), 281 (18), 256 (17), 240 (17), 221 (9), 208 (27), 185 (11), 171 (10), 129 (23), 111 (11), 97 (18), 83 (20), 73 (53), 55 (47). Anal. calcd. for $C_{21}H_{17}Cl_2N_5S$: C, 57.02; H, 3.87; N, 15.83; Found: C, 57.21; H, 3.71; N, 15.97.

(4-{2-[(3,4-Dichloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-m-tolyl-amine ***35***

Yield 15%. M.p. 199–200°C. IR: ν_{max} (KBr) cm^{-1}: 3424, 3266, 3201, 3067, 1601, 1581, 1563, 1541, 1496, 1425, 1401, 1368, 1336. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.30 (d, 1H, J = 5.2 Hz, Py-H), 7.61 (s, 1H, Ar-H), 7.57 (d, 1H, J = 2.8 Hz, Ar-H), 7.51 (d, 1H, J = 8.8 Hz, Ar-H), 7.33 (dd, 1H, J_1 = 2.4 Hz, J_2 = 2.4 Hz, Ar-H), 7.23–7.15 (m, 2H, Ar-H), 7.04 (s, 1H, Ar-H), 6.84 (d, 1H, J = 5.6 Hz, Py-H), 3.54 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.27 (s, 3H, CH_3). EIMS m/z (%): 455 (M^+, 100), 440 (9), 295 (11), 256 (12), 222 (13), 213 (9), 185 (10), 171 (8), 129 (19), 111 (9), 97 (16), 85 (19), 73 (41), 65 (8), 57 (48). Anal. calcd. for $C_{22}H_{19}Cl_2N_5S$: C, 57.90; H, 4.20; N, 15.35; Found: C, 57.81; H, 4.22; N, 15.19.

(4-{2-[(3,4-Dichloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-o-tolyl-amine ***36***

Yield 13.6%. M.p. 159–161°C. IR: ν_{max}(KBr) cm^{-1}: 3430, 3239, 3186, 3036, 1541, 1483, 1450, 1400, 1368, 1339. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.29 (d, 1H, J = 5.6 Hz, Py-H), 7.98 (d, 1H, J = 8.0 Hz, Ar-H), 7.57 (d, 1H, J = 2.4 Hz, Ar-H), 7.50 (d, 1H, J = 8.8 Hz, Ar-H), 7.32 (dd, 1H, J_1 = 2.4 Hz, J_2 = 3.2 Hz, Ar-H), 7.22–7.18 (m, 2H, Ar-H), 7.02 (t, 1H, J = 7.6 Hz, Ar-H), 6.81 (d, 1H, J = 5.6 Hz, Py-H), 6.78 (brs, 1H, NH), 3.54 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). EIMS m/z (%): 455 (M^+, 73), 440 (9), 401 (15), 281 (12), 256 (25), 222 (24), 213 (19), 199 (8), 185 (17), 171 (18), 157 (15), 143 (10), 129 (39), 115 (15), 97 (27), 83 (30), 73 (89), 55 (81). Anal. calcd. for $C_{22}H_{19}Cl_2N_5S$: C, 57.90; H, 4.20; N, 15.35; Found: C, 58.02; H, 4.37; N, 15.43.

(4-{2-[(3,4-Dichloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-chloro-phenyl)-amine ***37***

Yield 17.2%. M.p. 215–217°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3265, 3184, 3106, 3007, 1620, 1574, 1531, 1487, 1460, 1364, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.30 (d, 1H, J = 5.2 Hz, Py-H), 8.05 (s, 1H, NH), 7.56 (d, 1H, J = 2.4 Hz, Ar-H), 7.51 (d, 1H, J = 8.8 Hz, Ar-H), 7.34 (dd, 1H, J_1 = 2.4 Hz, J_2 = 2.4 Hz, Ar-H), 7.22–7.16 (m, 3H, Ar-H), 7.00–6.97 (m, 1H, Ar-H), 6.89 (d, 1H, J = 5.6 Hz, Py-H), 3.55 (s, 3H, CH_3), 2.60 (s, 3H, CH_3). EIMS m/z (%): 475 (M^+, 95), 455 (12), 315 (24), 284 (8), 274 (11), 242 (13), 220 (11), 207 (16), 185 (8), 171 (10), 157 (9), 129 (30), 111 (24), 97 (25), 83 (26), 73 (69), 55 (67). Anal. calcd. for $C_{21}H_{16}Cl_3N_5S$: C, 52.90; H, 3.38; N, 14.69; Found: C, 52.77; H, 3.31; N, 14.73.

(4-{2-[(3,4-Dichloro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-methoxy-phenyl)-amine ***38***

Yield 41.6%. M.p. 184–186°C. IR: ν_{max} (KBr) cm^{-1}: 3384, 3261, 3054, 3016, 1699, 1627, 1574, 1543, 1503, 1460, 1430, 1407, 1370, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.32 (d, 1H, J = 5.6 Hz, Py-H), 7.56 (d, 1H, J = 2.4 Hz, Ar-H), 7.51 (d, 1H, J = 8.4 Hz, Ar-H), 7.46 (t, 1H, J = 2.2 Hz, Ar-H), 7.33 (dd, 1H, J_1 = 2.8 Hz, J_2 = 2.4 Hz, Ar-H), 7.19 (t, 1H, J = 8.4 Hz, Ar-H), 7.02 (brs, 1H, NH), 6.97 (dd, 1H, J_1 = 1.2 Hz, J_2 = 1.6 Hz, Ar-H), 6.86 (d, 1H, J = 5.6 Hz, Py-H), 6.58 (dd, 1H, J_1 = 2.0 Hz, J_2 = 2.0 Hz, Ar-H), 3.75 (s, 3H, OCH_3), 3.54 (s, 3H, CH_3), 2.59 (s, 3H, CH_3). EIMS m/z (%): 471 (M^+, 100), 456 (10), 440 (7), 311 (10), 270 (9), 256 (15), 238 (12), 213 (10), 185 (10), 171 (8), 129 (17), 111 (10), 97 (15), 83 (16), 73 (42), 55 (39). Anal. calcd. for $C_{22}H_{19}Cl_2N_5OS$: C, 55.94; H, 4.05; N, 14.83; Found: C, 55.76; H, 4.31; N, 14.75.

(4-{2-[(3-Chloro-4-fluoro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-phenyl-amine ***39***

Yield 14.9%. M.p. 176–178°C. IR: ν_{max} (KBr) cm^{-1}: 3442, 3284, 2923, 1618, 1580, 1540, 1491, 1448, 1402, 1368, 1341. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.30 (d, 1H, J = 5.6 Hz, Py-H), 7.59 (d, 2H, J = 8.0 Hz, Ar-H), 7.52 (dd, 1H, J_1 = 2.8 Hz, J_2 = 2.8 Hz, Ar-H), 7.35–7.20 (m, 3H, Ar-H), 7.08–7.01 (m, 2H, Ar-H), 6.83 (d, 1H, J = 5.6 Hz, Py-H), 3.53 (s, 3H, CH_3), 2.59 (s, 3H, CH_3). EIMS m/z (%): 425 (M^+, 100), 410 (8), 281 (13), 240 (14), 208 (20), 170 (7), 143 (8), 129 (10), 77 (14), 60 (10). Anal. calcd. for $C_{21}H_{17}ClFN_5S$: C, 59.22; H, 4.02; N, 16.44; Found: C, 59.26; H, 4.17; N, 16.64.

(4-{2-[(3-Chloro-4-fluoro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-m-tolyl-amine ***40***

Yield 23%. M.p. 182–184°C. IR: ν_{max} (KBr) cm^{-1}: 3424, 3474, 3201, 3069, 1601, 1581, 1563, 1540, 1493, 1423, 1401, 1367, 1336. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.29 (d, 1H, J = 5.2 Hz, Py-H), 7.61 (s, 1H, Ar-H), 7.50 (dd, 1H, J_1 = 2.4 Hz, J_2 = 2.0 Hz, Ar-H), 7.35–7.32 (m, 1H, Ar-H), 7.24–7.14 (m, 3H, Ar-H), 7.01 (s, 1H, Ar-H), 6.83 (d, 1H, J = 5.2 Hz, Py-H), 3.53 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.26 (s, 3H, CH_3). EIMS m/z (%): 439 (M^+, 100), 424 (10), 295 (10), 256 (11), 222 (12), 213 (10), 185 (8), 129 (17), 97 (12), 83 (13), 73 (34), 65 (8), 57 (31). Anal. calcd. for $C_{22}H_{19}ClFN_5S$: C, 60.06; H, 4.35; N, 15.92; Found: C, 59.92; H, 4.23; N, 15.75.

(4-{2-[(3-Chloro-4-fluoro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-o-tolyl-amine ***41***

Yield 16.3%. M.p. 159–161°C. IR: ν_{max} (KBr) cm^{-1}: 3442, 3238, 3185, 3037, 1601, 1562, 1542, 1500, 1484, 1453, 1428, 1401, 1367, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.28 (d, 1H, J = 5.6 Hz, Py-H), 7.98 (d, 1H, J = 8.0 Hz, Ar-H), 7.50 (dd, 1H, J = 2.80 Hz, Ar-H), 7.34–7.30 (m, 1H, Ar-H), 7.24–7.16 (m, 3H, Ar-H), 7.01 (t, 1H, J = 7.2 Hz, Ar-H), 6.80 (d, 1H, J = 5.2 Hz, Py-H), 6.75 (brs, 1H, NH), 3.52 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 2.31 (s, 3H, CH_3). EIMS m/z (%): 439 (M^+, 100), 424 (10), 284 (15), 256 (15), 222 (19), 207 (12), 185 (11), 171 (8), 157 (11), 143 (9), 129 (27), 111 (8), 97 (15), 83 (18), 73 (44), 60 (43). Anal. calcd. for $C_{22}H_{19}ClFN_5S$: C, 60.06; H, 4.35; N, 15.92; Found: C, 60.13; H, 4.28; N, 15.99.

(4-{2-[(3-Chloro-4-fluoro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-chloro-phenyl)-amine ***42***

Yield 14.1%. M.p. 196–198°C. IR: ν_{max} (KBr) cm^{-1}: 3422, 3268, 3186, 3112, 1617, 1576, 1532, 1490, 1460, 1421, 1364, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.31 (d, 1H, $J = 5.2$ Hz, Py-H), 8.04 (s, 1H, NH), 7.49 (d, 1H, $J = 5.6$ Hz, Ar-H), 7.33 (brs, 1H, Ar-H), 7.23–7.11 (m, 4H, Ar-H), 6.97 (d, 1H, $J = 6.8$ Hz, Ar-H), 6.88 (d, 1H, $J = 5.2$ Hz, Py-H), 3.54 (s, 3H, CH_3), 2.60 (s, 3H, CH_3). EIMS *m/z* (%): 459 (M^+, 100), 315 (20), 274 (9), 242 (10), 207 (12), 129 (12), 111 (13), 97 (10), 83 (11), 71 (16), 57 (22). Anal. calcd. for $C_{21}H_{16}ClFN_5S$: C, 54.79; H, 3.50; N, 15.21; Found: C, 54.62; H, 3.41; N, 15.35.

(4-{2-[(3-Chloro-4-fluoro-phenyl)-methyl-amino]-4-methyl-thiazol-5-yl}-pyrimidin-2-yl)-(3-methoxy-phenyl)-amine ***43***

Yield 5.5%. M.p. 181–183°C. IR: ν_{max} (KBr) cm^{-1}: 3425, 3279, 3213, 3119, 3066, 1584, 1538, 1498, 1459, 1427, 1398, 1368, 1338. ^{1}H-NMR ($CDCl_3$, TMS, 400 MHz, δ ppm): 8.31 (brs, 1H, Py-H), 7.47 (d, 2H, $J = 14.4$ Hz, Ar-H), 7.32–7.17 (m, 2H, Ar-H), 7.04 (s, 1H, Ar-H), 6.96 (d, 1H, $J = 5.6$ Hz, Ar-H), 6.85 (s, 1H, Ar-H), 6.57 (d, 1H, $J = 5.2$ Hz, Py-H), 3.74 (s, 3H, OCH_3), 3.52 (s, 3H, CH_3), 2.59 (s, 3H, CH_3). EIMS *m/z* (%): 455 (M^+, 100), 311 (8), 270 (8), 238 (9), 227 (8), 129 (10), 97 (8), 83 (8), 73 (13), 57 (18). Anal. calcd. for $C_{22}H_{19}ClFN_5S$: C, 57.95; H, 4.20; N, 15.36; Found: C, 57.92; H, 4.23; N, 15.15.

Biological Assays

The tumor cell lines (Ishikawa, A549, BEL-7404, SPC-A-01 and SGC-7901) were obtained from Shanghai Institutes for Biological Sciences of Chinese Academy of Sciences.

Cytotoxicity Assay

The cytotoxic activities of compounds **7–43** was evaluated against human cell lines by the MTT method [21]. MTT solution (10.0 μL/well) in RPMI-1640 (Sigma, St. Louis, MO, USA) was added after cells were treated with drug for 72 h, and cells were incubated for a further 3 h at 37°C. The purple formazan crystals were dissolved in 150 μL DMSO. After 5 min, the plates were read on an automated microplate spectrophotometer (Bio-Tek Instruments, Winooski, VT, USA) at 570 nm. Assays were performed in triplicate in three independent experiments. The concentration required for 50% inhibition of cell viability (IC_{50}) was calculated using the software, Dose-Effect Analysis with Microcomputers'. The tumor cell line panel consisted of Ishikawa, A549, BEL-7404, SPC-A-01 and SGC-7901. In all of these experiments, three replicate wells were used to determine each point.

We are grateful for the Natural Science Foundation of Ningbo City (grant No. 2009A610185) for financial support and Nantong Center for Disease Control and Prevention, Jiangsu, PR China for drug screening.

The authors have declared no conflict of interest.

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