European Journal of Medicinal Chemistry 45 (2010) 2299–2306

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Design, synthesis, and *in vitro* antitumor evaluation of novel diaryl ureas derivatives

Min Sun [a], Xiaoqing Wu [a,b], Junqing Chen [a], Jin Cai [a], Meng Cao [a], Min Ji [a,*]

[a] Pharmaceutical Engineering Institute, School of Chemistry & Chemical Engineering, Southeast University, Nanjing 210096, PR China
[b] Department of Radiation Oncology, University of Michigan Comprehensive Cancer Center, Ann Arbor, MI 48109, USA

ARTICLE INFO

Article history:
Received 18 November 2009
Received in revised form
31 January 2010
Accepted 1 February 2010
Available online 6 February 2010

Keywords:
Diaryl ureas
Antitumor activity
A549
MDA-MB-231

ABSTRACT

Two series of novel diaryl ureas have been designed and synthesized, with their *in vitro* antitumor effect screened on human non-small cell lung cancer (NSCLC) cell line A549 and human breast cancer cell line MDA-MB-231. Some target compounds demonstrated significant inhibitory activities against both cell lines. Compared to contrast drug Sorafenib, **1b**, **1d**, **1f**, **1i** were found to demonstrate more potent antitumor activities. The structures of all the newly synthesized compounds were determined by ^{1}H, ^{13}C NMR, MS, IR and elementary analysis.

1. Introduction

The relative mortality rate caused by cancer is still very high in the developed countries, accounting for more than 20% of all deaths. Among the various types of malignant tumors, Lung cancer is the most commonly diagnosed cancer, while breast cancer causes the second leading deaths in women [1]. Although chemotherapy is the mainstay of cancer therapy, the use of available chemotherapeutics is often limited mainly due to undesirable side effects and a limited choice of available anticancer drugs. This clearly underlies the urgent need of developing novel chemotherapeutic agents with more potent antitumor activities [2].

Small molecule kinase inhibitors (including urea-based compounds) have just begun to meet the high expectations of early 1990s, and hold great potential as novel therapeutics in cancer treatment [3]. After the first report in 1996, the potentiality of diaryl urea compounds has been focused by a large number of publications and patent applications because of their unique binding mode and kinase inhibition profile [4]. Following the successful marketing of Sorafenib (BAY 43-9006) [5] and those currently undergoing clinical trials including ABT-869 (Phase II) [6], KRN-951 (Phase II) [7], the interest in designing and developing novel diaryl urea compounds with more potent antitumor activities has been greatly highlighted.

Sorafenib, approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced renal cell carcinoma (RCC) [5] and unresectable hepatocellular carcinoma (HCC) [8] in December 2005 and November 2007 respectively, is a diaryl urea small molecule inhibitor of several kinases involved in tumour proliferation and tumour angiogenesis including Raf, VEGFR and PDGFR [5]. At present, clinical phase III and phase II efficacy trials are being conducted for this drug against lung [9] and breast cancer [10]. Recently, efforts targeting for potent analogs of sorafenib have been the focus of many studies [11–13]. Based on sorafenib as the leading compound, we have devised and synthesized two series of diaryl urea compounds containing thiazole ring and imidazole ring respectively through intramolecular cyclization of the formamide group on the pyridine ring, with the aim of obtaining agents displaying more potent antitumor activities. The antitumor effect of all the newly synthesized compounds on the *in vitro* growth of two cell lines, namely human non-small cell lung cancer (NSCLC) cell line A549 and human breast cancer cell line MDA-MB-231, was evaluated. Apparent growth inhibition was observed for most of the compounds, with **1b**, **1d**, **1f**, **1i** and **1b**, **1d**, **1i** demonstrating more potent activities against A549 and MDA-MB-231 as compared to sorafenib, respectively. Furthermore, some structure–activity relationships have also been established.

* Corresponding author. Tel.: +86 25 83272349; fax: +86 25 86636901.
E-mail address: jimin@seu.edu.cn (M. Ji).

0223-5234/$ – see front matter © 2010 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2010.02.005

2. Chemistry

The preparation of two series target compounds is illustrated in Scheme 1, where the same starting material **3** is utilized. The thiazole ring on compound (**6**) was assembled via coupling of α-haloacetal and thiobenzamide precursors (Hantzsch synthesis). The thioamide precursor was readily prepared from the corresponding nitrile. Thus, addition of 2 equiv. of sodium hydrogen sulfide and 1 equiv. magnesium chloride to a concentrated solution of 4-methoxybenzonitrile (**3**) in DMF readily afforded the 4-methoxybenzothioamide (**4**) with a yield of 90% without handing of hazardous hydrogen sulfide [14]. 2-(4-Methoxyphenyl)thiazole (**6**) was readily formed when stoichiometric amounts of the thioamides were reacted with bromoacetaldehyde diethyl acetal in hot ethanol [15]. Convenient treatment of the reaction mixtures mentioned above finally gave pure compound (**6**) in high-yield.

The imidazole ring on compound (**7**) was obtained via dehydrogenation of the corresponding imidazoline (**5**) using potassium permanganate supported on alumina under mild conditions at room temperature [16]. The imidazoline was prepared by the method reported in our previous study [17], which was a high-yield one-pot reaction of the corresponding nitrile (**3**) with ethylenediamine in the presence of sodium hydrosulfide as catalyst. A plausible explanation is that sodium hydrosulfide reacts with the nitrile grove to produce a thioamide. The thioamide then reacts with ethylenediamine, which upon eliminates ammonia and hydrogen sulfide and produces the 2-imidazoline.

It is reported that the heterocyclic-substituted anisoles (**6**,**7**) could be cleaved to the corresponding phenols (**8**,**9**) with either HBr/AcOH or BBr_3/Et_2O [18]. On many occasions, the heterocyclic ring was cleaved during this procedure in this study, suggesting that carefully controlled conditions had to be developed. In this case, we found that reasonable yields of phenol could only be achieved by using HBr/AcOH procedure. Compounds (**8**,**9**) were reacted with 1-chloro-4-nitrobenzene by S_NAr reaction to produce compounds (**10**,**11**), the nitro group of which was then reduced with hydrogen by using Raney Ni as catalyst to produce the key intermediates (**12**,**13**), which were reacted with different aromatic amines in the present of *N*,*N*′-Carbonyldiimidazole (CDI) [19] to produce the desired series of diaryl ureas derivatives (**1a**–**1k**, **2a**–**2k**).

The chemical structures of the compounds were confirmed by ^1H, ^{13}C NMR, MS, IR spectra and elementary analysis and the results are presented in Section 6.

3. Biological evaluation

Preliminary cytotoxic activity of these diaryl ureas derivatives (**1a**–**1k**, **2a**–**2k**) on A549, MDA-MB-231 cell lines was investigated *in vitro*. The cell viability was determined by the MTT-based assay using cell proliferation reagent WST-8, a reagent solution prepared as an aqueous solution containing 5 mM WST-8 (Sigma), 0.2 mM 1-methoxyphenazinium salt (Sigma) and 150 mM NaCl [20]. Briefly, the tumour cell lines in RPMI1640 medium with 10% fetal bovine serum were plated in 96-well microtiter plates (5.0×10^3 cells/well), and allowed to adhere at 37 °C with 5% CO2 for 4 h. The test compound was then added, and the cells were incubated at 37 °C with 5% CO2 for 72 h later. Subsequently, cell growth medium was removed, and WST-8 was added to each well for another incubation of 1.5 h at 37 °C. Absorbance was finally measured with a plate reader at 450 nm with correction at 650 nm. The results were expressed as the percentage of absorbance of treated wells versus that of vehicle control. IC_{50}, the drug concentration causing 50% growth inhibition, was calculated via sigmoid curve fitting using GraphPad Prism 5.0.

Table 1
In vitro cytotoxic activity of target compounds against A549 and MDA-MB-231 cells in concentration 10 μM.

Compound	Growth inhibition percentage of cancer cell line (%)	
	A549	MDA-MB-231
1a	17.74	32.53
1b	77.64	69.63
1c	NT	NT
1d	77.10	72.77
1e	71.50	64.13
1f	76.42	71.75
1g	15.57	22.75
1h	75.52	60.41
1i	81.72	72.78
1j	37.27	43.94
1k	6.78	10.98
2a	8.86	47.57
2b	67.94	38.06
2c	7.09	11.39
2d	12.44	3.36
2e	29.98	28.12
2f	63.27	26.55
2g	24.64	49.32
2h	22.32	32.29
2i	44.09	−13.55
2j	14.57	4.20
2k	2.34	−1.46
Sorafenib	81.23	79.61

NT: no test.

4. Result and discussion

The *in vitro* growth inhibition activities of the newly synthesized diaryl urea compounds **1a**–**1k** and **2a**–**2k** against cancer cell lines A549 and MDA-MB-231 were first evaluated by the MTT-based assay using sorafenib as a positive control at the concentration of 10 μM. As shown in Table 1, compounds **1b**, **1d**–**1f**, **1h**, **1i** demonstrated evident anti-proliferation effects with inhibition percentages higher than 70% and 64% for A549 and MDA-MB-231 respectively. It is worth pointing out that significant inhibition was achieved for compound **1i** with an inhibition percentage higher than 80%. Compounds **2b** and **2f** were relatively less potent, which only displayed a inhibition percentage around 65% for A549.

After a close inspection, we found that **6** out of the **8** compounds showing potent cytotoxic activities belong to thiazoles, while only 2 compounds belong to imidazoles. Moreover, the cytotoxic effect of series 2 compounds was also consistently lower than that of series 1. Evidenced by the lower log *P* value that indicates hydrophobicity

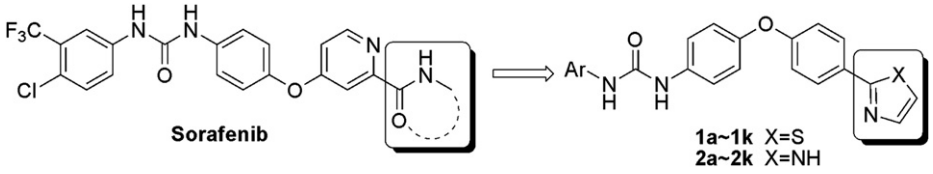


Fig. 1. A design for synthesis of sorafenib analogs (**1a**–**1k** and **2a**–**2k**).

Table 2
Cytotoxic activity (IC_{50} values) of targeted compounds against A549 and MDA-MB-231 cells *in vitro*.

Compound	IC_{50}[a](μM)	
	A549	MDA-MB-231
1b	3.81	6.06
1d	3.89	6.87
1e	5.56	9.55
1f	4.98	8.66
1h	7.04	8.90
1i	2.71	4.19
2b	7.09	NT
2f	10.52	NT
Sorafenib	5.21	7.62

NT: no test.
[a] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control.

for series 2 compounds, we proposed that the lower cytotoxicities of these compounds could be attributed to the relatively poor membrane permeability of them, since the cytotoxic screening was carried out *in vitro* and the intake of compounds from medium formed the basis of cytotoxicity effects.

The cytotoxicities of the resulting diaryl urea derivatives appeared to be related to the electronic effect of the substituent group on the benzene ring that connects with the urea group. It has been observed from Table 1 that most of the derivatives with strong electron-absorbing substituent groups such as nitro and especially trifluoromethyl, have significantly higher cytotoxicities than those with electron-donating groups or with no substitution. Moreover, the effect of halogen substitution on cytotoxic activities in the presence of strong electron-absorbing substituent groups in the *meta* position of benzene ring has also been evaluated. We found that the introduction of different halogen substituents could improve cytotoxicities to various extents. Generally, compounds with chloro substituted at *para* position were more cytotoxic than those with fluoro substitution and those with chloro substituted at *ortho* position. Furthermore, compounds with bromo substitution at *meta* position demonstrated the most strong cytotoxic activities.

The 8 compounds that demonstrated evident growth inhibition activities have been further assayed for their antitumor potency indicated by IC_{50} values, which were calculated by linear regression analysis of the concentration–response curves obtained for each compound. It is evident from Table 2 that one third of the newly synthesized derivatives demonstrated apparent inhibitory activities against both cell lines. Compared to contrast drug Sorafenib, **1b**, **1d**, **1f**, **1i** were found to be more potent antitumor activities.

5. Conclusion

We have synthesized two series of novel diaryl urea derivatives and tested for their antitumor activities on A549 and MDA-MB-231 cell lines. Preliminary anti-tumorigenic activities indicated that one third of the newly synthesized derivatives displayed significant inhibitory activities against both cell lines. Moreover, compounds **1b**, **1d**, **1f**, **1i** demonstrated more potent antitumor activities when compared to contrast drug Sorafenib. From the structure–activity relationships we may conclude that compounds containing thiazole ring demonstrated significantly better cytotoxic activities than those with imidazole ring. In general, activity is driven by the presence of a substituent at the *meta* position relative to the amine. Most noteworthy was the electronic effect of substituents, such as trifluoromethyl, which led to a significant improvement in activity. Moreover, the addition of a halogen atom at benzene ring further increased cytotoxic activity. This study may provide valuable information for further designing and developing antitumor agents with potent activities.

6. Experimental protocols

Melting points were determined on an RY-1 hot-stage microscope, and the thermometer was uncorrected. Infrared spectra were recorded in a Nicolet Impact 410 spectrophotometer. ^1H, ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300/500 MHz instrument in $CDCl_3$ or DMSO, and chemical shifts (δ) were reported in parts per million (ppm) relative to TMS as an internal standard. Mass spectra were recorded on Aglient 1100 LC-MS. Elementary analyses were performed on Elementar Vario EL III instrument. All reactions were monitored by TLC on silica gel 60F-254 glass plates (E.Merk).

6.1. Synthesis of 4-methoxybenzothioamide (*4*)

To a slurry consisting of 70% sodium hydrosulfide hydrate (60 g, 0.75 mol) and magnesium chloride hexahydrate (76 g, 0.375 mol) in 500 mL of DMF was added 4-methoxybenzonitrile (50 g, 0.375 mol) in one portion, and the mixture was stirred at room temperature for 8 h. The resulting green slurry was poured into 1 L of water, and the resulting precipitates were collected by filtration. The crude product was resuspended in 1 N HCl and stirred for 30 min, then filtered and washed with water to give compound **4** (56.2 g, 90%) as a yellow solid, mp 149–151 °C.

6.2. Synthesis of 2-(4-methoxyphenyl)thiazole (*6*)

Compound **4** (20 g, 0.12 mol) and bromoacetaldehyde diethyl acetal (18.6 mL, 0.12 mol) were first dissolved in 500 mL ethanol. After reflux of the above mixture for 10 h, the resulting mixture was cooled to room temperature, and then distilled under reduced pressure. The residue was added into water, and the aqueous layer was extracted with ethyl acetate (3×100 mL). The combined ethyl acetate extracts were washed with water (80 mL) and brine (80 mL) respectively, and then dried with anhydrous Na_2SO_4. When the solvent was evaporated, the yield of yellow oil compound **6** was 16.5 g (72%). ^1H NMR($CDCl_3$, 300 MHz) δ(ppm): 3.83 (s, 3H, $-OCH_3$), 6.93–6.96 (m, 2H, Ar-H), 7.23 (d, $J = 3.30$ Hz, 1H, Ar-H), 7.79 (d, $J = 3.29$ Hz, 1H, Ar-H), 7.88–7.91 (m, 2H, Ar-H).

6.3. Synthesis of 2-(4-methoxyphenyl)imidazoline (*5*)

A mixture of 4-methoxybenzonitrile (40 g, 0.3 mol), 70% sodium hydrosulfide hydrate (1.7 g, 0.03 mol) and ethylenediamine (300 mL) was refluxed with stirring for 2 h. The resulting mixture was poured into ice water, and the aqueous layer was extracted with CH_2Cl_2 (3×250 mL). The combined CH_2Cl_2 extracts were washed with water (200 mL) and brine (200 mL) respectively, and then dried with anhydrous Na_2SO_4. After the solvent was evaporated, the yield of the white solid compound **5** was 47.5 g (90%), mp 138–139 °C. ^1H NMR($CDCl_3$, 300 MHz) δ(ppm): 3.74 (s, 4H, $2CH_2$), 3.83 (s, 3H, CH_3O), 4.94 (br s, 1H, NH), 6.89 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.72 (d, $J = 8.8$ Hz, 2H, Ar-H); ESI-MS m/z: 177.1$[M+H]^+$; Anal. Calcd for $C_{10}H_{12}N_2O$ (%): C 68.16, H 6.86, N 15.90; Found: 67.89, H 6.88, N 16.04.

6.4. Synthesis of 2-(4-methoxyphenyl)imidazole (*7*)

Compound **5** (8.8 g, 0.05 mol) was first dissolved in 500 mL acetonitrile, with potassium permanganate (23.7 g, 0.15 mol) and alumina (30.6 g, 0.3 mol) added into the solution in batch. After

stirring the resulting mixture at room temperature for 3 h, Ethanol (25 mL) was added to reduce excess oxidant. The mixture was then filtered and the solid material was washed with acetonitrile (500 mL). The filtrate was evaporated and the resulting crude material was purified by column chromatography on alumina to afford the pure compound **7** (5.1 g, 59%) as a yellow solid, mp 152–154 °C. ^{1}H NMR($CDCl_3$, 500 MHz) δ(ppm): 3.85 (s, 3H, CH_3O), 5.92 (br s, 2H, imidazole CH═CH), 6.93 (dd, $J = 1.98$, 6.89 Hz, 2H, Ar-H), 7.78 (dd, $J = 2.01$, 6.83 Hz, 2H, Ar-H).

6.5. Synthesis of 4-(thiazol-2-yl)phenol (**8**) and 4-(imidazol-2-yl)phenol (**9**)

The compound **6** (11.5 g, 60.2 mmol) was dissolved in 40% HBr (250 mL) and acetic acid (60 mL), and the mixture was refluxed for 24 h. The resulting mixture was cooled to room temperature, and then distilled under reduced pressure. The saturated $NaHCO_3$ solution was slowly dropped into the residue with an ice-bath, and set to pH = 8. The resulting precipitates were collected by filtration and washed with water to give compound **8** (10.1 g, 95%) as an off-white solid, mp 162–164 °C.

Compound **9**. Yield 83%, brown solid, mp 225–227 °C. ^{1}H NMR(DMSO-d_6, 500 MHz) δ(ppm): 6.81 (dd, $J = 1.91$, 6.74 Hz, 2H, Ar-H), 7.03 (br s, 2H, imidazole CH═CH), 7.74 (dd, $J = 1.91$, 6.74 Hz, 2H, Ar-H), 9.62 (s, 1H, OH), 12.18 (br s, 1H, imidazole-NH).

6.6. Synthesis of 2-[4-(4-nitrophenoxy)phenyl]thiazole (**10**) and 2-[4-(4-nitrophenoxy) phenyl]imidazole (**11**)

The compound **8** (5 g, 28.2 mmol), 1-chloro-4-nitrobenzene (4.5 g, 28.2 mmol) and K_2CO_3 (7.8 g, 56.4 mmol) were dissolved in DMF (150 mL), with the mixture refluxed with stirring for 3 h. The resulting mixture was cooled to room temperature, and then poured into ice water. The precipitates were collected by filtration and washed with water to give compound **10** (7.9 g, 94%) as a yellow solid, mp 109–111 °C. ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.07–7.11 (m, 2H, Ar-H), 7.15–7.18 (m, 2H, Ar-H), 7.36 (d, $J = 3.28$ Hz, 1H, Ar-H), 7.88 (d, $J = 3.24$ Hz, 1H, Ar-H), 8.03–8.06 (m, 2H, Ar-H), 8.23–8.26 (m, 2H, Ar-H).

Compound **11**. Yield 64%, yellow solid, mp 204–246 °C. ^{1}H NMR(DMSO-d_6, 500 MHz) δ(ppm): 7.17 (br s, 2H, imidazole CH═CH), 7.19 (dd, $J = 2.20$, 7.05 Hz, 2H, Ar-H), 7.27 (dd, $J = 2.05$, 6.70 Hz, 2H, Ar-H), 8.03 (dd, $J = 2.05$, 6.70 Hz, 2H, Ar-H), 8.27 (dd, $J = 2.20$, 7.05 Hz, 2H, Ar-H), 12.52 (br s, 1H, imidazole-NH).

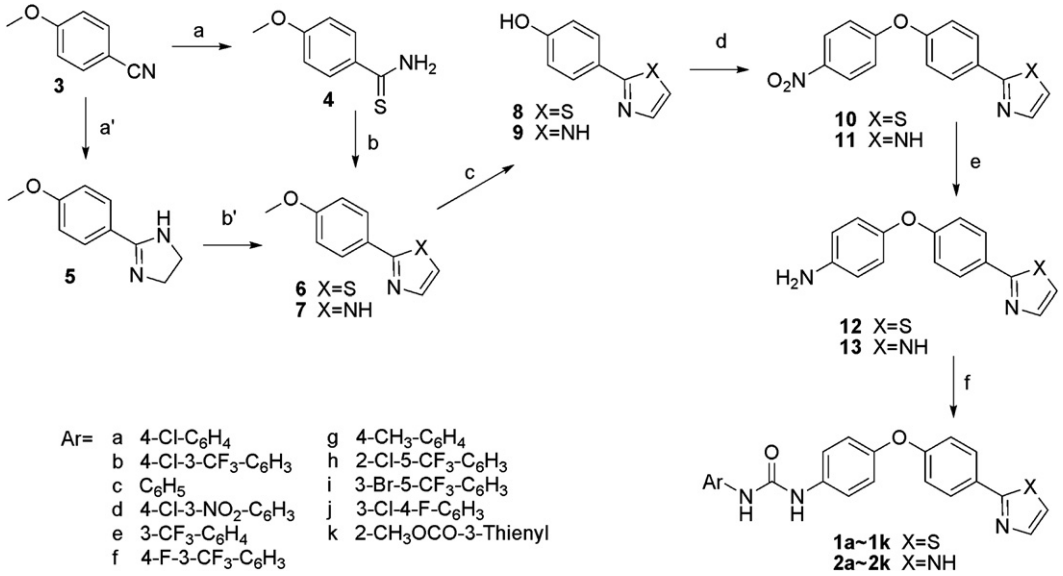
6.7. Synthesis of 4-[4-(thiazol-2-yl)phenoxy]aniline (**12**) and 4-[4-(imidazol-2-yl) phenoxy]aniline (**13**)

A mixture of compound **10** (5 g, 17.8 mmol), ethanol (200 mL), and Raney Ni (5 g) was placed in the 500 mL flask, and then pumped in hydrogen at atmospheric pressure and ambient temperature. After 24 h, the mixture was filtered and the solid material was washed with ethanol (50 mL). The filtrate was evaporated, and the resulting crude material was purified by recrystallisation with ethanol to afford compound **12** (3.9 g, 89%) as a yellow solid, mp 75–77 °C.

Compound **13**. Yield 87%, yellow solid. ^{1}H NMR($CDCl_3$, 300 MHz) δ(ppm): 3.88 (br s, 2H, NH_2), 6.61–6.78 (m, 4H, Ar-H), 6.81–6.86 (m, 2H, Ar-H), 6.98 (d, $J = 8.44$ Hz, 1H, Ar-H), 7.03–7.05 (m, 1H, Ar-H), 7.12–7.17 (m, 1H, Ar-H), 7.30–7.35 (m, 1H, Ar-H).

6.8. General process for the synthesis of compound **1a–1k** and **2a–2k**

A solution of compound **12** or **13** (2 mmol) in anhydrous tetrahydrofuran (40 mL) was stirred under N_2 at room temperature during addition of *N*,*N*′-carbonyldiimidazole (CDI) (6 mmol). The contents were stirred for 6 h, and then treated with dropwise addition of different aromatic amines (2.1 mmol) in anhydrous tetrahydrofuran (10 mL). A solution formed, followed by precipitation of an off-white solid. The mixture was refluxed for 3 h. The resulting mixture was cooled to room temperature, and then distilled under reduced pressure. Water (50 mL) was added to removal excess CDI, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined ethyl acetate extracts were washed with water (30 mL) and brine (30 mL) respectively, and then dried with anhydrous Na_2SO_4. After the filtrate was evaporated, the resulting crude material was purified by column



Scheme 1. Synthetic route for the preparation of the target compounds **1a–1k** and **2a–2k**. Reagents and conditions: (a) 70% NaSH, $MgCl_2 \cdot 6H_2O$, DMF, rt, 8 h, 90% of **4**; (a′) $H_2NCH_2CH_2NH_2$, 70% NaSH, reflux, 2 h, 90% of **5**; (b) bromoacetaldehyde diethyl acetal, EtOH, reflux, 10 h, 72% of **6**; (b′) $KMnO_4/Al_2O_3$, CH_3CN, rt, 3 h, 59% of **7**; (c) HBr/AcOH, reflux, 24 h, 95% of **8** and 83% of **9**; (d) 1-chloro-4-nitrobenzene, K_2CO_3, DMF, reflux, 3 h, 94% of **10** and 64% of **11**; (e) H_2, Raney Ni, EtOH, rt, 12 h, 89% of **12** and 87% of **13**; (f) CDI, THF, reflux, 3.5 h.

chromatography (silica gel 60, mesh size 200–300, ethyl acetate/petroleum ether, v/v) to afford the compounds **1a**–**1k** and **2a**–**2k** Fig. 1.

Compounds **1a**–**1k** and **2a**–**2k** were characterized as follows.

*6.8.1. 1-(4-Chlorophenyl)-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl}urea (**1a**)*

Off-white solid, yield: 51%, mp 192–193 °C; IR(KBr, cm^{-1}): 3299.56, 1639.92, 1602.54, 1567.16, 1505.39, 1492.54, 1482.64, 1255.82, 1236.06, 829.78; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.01–7.06 (m, 4H, Ar-H), 7.28–7.31 (m, 2H, Ar-H), 7.44–7.50 (m, 4H, Ar-H), 7.70 (d, $J = 3.26$ Hz, 1H, Ar-H), 7.85 (d, $J = 3.26$ Hz, 1H, Ar-H), 7.90–7.93 (m, 2H, Ar-H), 8.73 (s, 1H, –NHCONH–), 8.78 (s, 1H, –NHCONH–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ(ppm): 117.77, 119.73, 119.79, 120.16, 120.22, 125.39, 127.85, 128.00, 128.52, 136.05, 138.70, 143.60, 150.04, 152.49, 159.35; ESI-MS *m*/*z*: 422.2$[M + H]^+$.

*6.8.2. 1-[4-Chloro-3-(trifluoromethyl)phenyl]-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl} urea (**1b**)*

White solid, yield: 53%, mp 135–136 °C; IR(KBr, cm^{-1}): 3304.98, 1645.91, 1601.07, 1556.23, 1501.78, 1415.30, 1251.96, 1175.09, 1139.86, 823.38; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.04–7.11 (m, 4H, Ar-H), 7.51–7.54 (m, 2H, Ar-H), 7.59–7.67 (m, 2H, Ar-H), 7.73 (d, $J = 3.26$ Hz, 1H, Ar-H), 7.88 (d, $J = 3.25$ Hz, 1H, Ar-H), 7.92–7.97 (m, 2H, Ar-H), 8.11 (d, $J = 2.27$ Hz, 1H, Ar-H), 8.87 (s, 1H, –NHCONH–), 9.14 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 125 MHz) δ(ppm): 117.61, 118.17, 119.77, 120.32, 121.75, 127.67, 127.96, 128.69, 136.27, 139.63, 143.60, 149.68, 152.53, 159.40, 166.54; ESI-MS *m*/*z*: 490.0$[M + H]^+$.

*6.8.3. 1-Phenyl-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl}urea (**1c**)*

White solid, yield: 48%, mp 198–199 °C; IR(KBr, cm^{-1}): 3221.00, 1642.70, 1594.66, 1559.43, 1498.58, 1482.56, 1408.90, 1300.00, 1229.54, 829.18; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm): 6.97 (t, $J = 14.67$ Hz, 1H, Ar-H), 7.03–7.10 (m, 4H, Ar-H), 7.25–7.31 (m, 2H, Ar-H), 7.44–7.48 (m, 2H, Ar-H), 7.50–7.54 (m, 2H, Ar-H), 7.73 (d, $J = 3.26$ Hz, 1H, Ar-H), 7.88 (d, $J = 3.26$ Hz, 1H, Ar-H), 7.92–7.96 (m, 2H, Ar-H), 8.65 (s, 1H, –NHCONH–), 8.71 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 125 MHz) δ(ppm): 116.72, 116.76, 117.73, 119.80, 120.25, 120.47, 122,22, 123.00, 127.77, 127.98, 131.91, 135.67, 139.33, 143.61, 150.17, 152.42, 159.27, 166.52; HRMS (ESI) *m*/*z*: Calcd for $C_{22}H_{17}N_3O_2S$ $[M + H]^+$ 388.1041, Found 388.1095; Anal. Calcd for $C_{22}H_{17}N_3O_2S \cdot 1/2H_2O$ (%): C 66.65, H 4.58, N 10.60; Found: C 66.97, H 4.68, N 10.25.

*6.8.4. 1-(4-Chloro-3-nitrophenyl)-3-{4-[4-(thiazol-2-yl)phenoxy]-phenyl}urea (**1d**)*

Yellow solid, yield: 50%, mp 179–180 °C; IR(KBr, cm^{-1}): 3340.21, 1658.47, 1595.71, 1556.38, 1531.36, 1504.66, 1480.92, 1343.74, 1305.38, 1245.74, 1228.95, 1198.38, 833.55; ^1H NMR(DMSO-d_6, 500 MHz) δ(ppm): 7.04–7.09 (m, 4H, Ar-H), 7.52–7.54 (m, 2H, Ar-H), 7.64–7.65 (m, 2H, Ar-H), 7.72 (d, $J = 3.25$ Hz, 1H, Ar-H), 7.88 (d, $J = 3.24$ Hz, 1H, Ar-H), 7.93–7.95 (m, 2H, Ar-H), 8.31 (t, $J = 2.66$ Hz, 1H, Ar-H), 8.65 (s, 1H, –NHCONH–), 8.71 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 114.20, 116.57, 117.73, 119.72, 120.17, 120.47, 123,01, 127.77, 127.93, 131.65, 135.49, 139.81, 143.56, 147.41, 150.27, 152.25, 159.19, 166.48; ESI-MS *m*/*z*: 465.0$[M - H]^-$; Anal. Calcd for $C_{22}H_{15}ClN_4O_4S \cdot 1/4H_2O$ (%): C 56.05, H 3.31, N 11.89; Found: C 56.04, H 3.31, N 12.09.

*6.8.5. 1-{4-[4-(Thiazol-2-yl)phenoxy]phenyl}-3-[3-(trifluoromethyl)phenyl]urea (**1e**)*

White solid, yield: 59%, mp 193–194 °C; IR(KBr, cm^{-1}): 3308.76, 1636.55, 1603.26, 1568.96, 1507.51, 1491.29, 1480.86, 1344.36, 1299.73, 1246.44, 1168.78, 1145.09, 1127.20, 1066.19, 701.49, 630.03; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.04–7.12 (m, 4H, Ar-H), 7.31 (d, $J = 7.52$ Hz, 1H, Ar-H), 7.49–7.61 (m, 4H, Ar-H), 7.73 (d, $J = 3.25$ Hz, 1H, Ar-H), 7.89 (d, $J = 3.25$ Hz, 1H, Ar-H), 7.93–7.97 (m, 2H, Ar-H), 8.03 (s, 1H, Ar-H), 8.85 (s, 1H, –NHCONH–), 9.04 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 114.08, 114.13, 117.68, 119.71, 120.19, 120.28, 121.75, 127.74, 127.93, 129.75, 135.80, 140.51, 143.55, 150.05, 152.48, 159.26, 166.50; HRMS (ESI) *m*/*z*: Calcd for $C_{23}H_{16}F_3N_3O_2S$ $[M + H]^+$ 456.0951, Found 456.0981; Anal. Calcd for $C_{23}H_{16}F_3N_3O_2S$ (%): C 60.65, H 3.54, N 9.23; Found: C 60.99, H 3.44, N 9.43.

*6.8.6. 1-[4-Fluoro-3-(trifluoromethyl)phenyl]-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl} urea (**1f**)*

White solid, yield: 53%, mp 187–188 °C; IR(KBr, cm^{-1}): 3309.82, 1654.45, 1608.70, 1556.61, 1503.03, 1482.04, 1425.52, 1408.85, 1336.62, 1301.00, 1251.83, 1219.65, 1162.36, 1130.68, 1052.54, 840.33, 631.22; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.03–7.11 (m, 4H, Ar-H), 7.43 (t, $J = 19.51$ Hz, 1H, Ar-H), 7.50–7.55 (m, 2H, Ar-H), 7.63–7.68 (m, 2H, Ar-H), 7.73 (d, $J = 3.26$ Hz, 1H, Ar-H), 7.88 (d, $J = 3.26$ Hz, 1H, Ar-H), 7.92–7.97 (m, 2H, Ar-H), 8.11 (dd, $J = 2.66$, 6.47 Hz, 1H, Ar-H), 8.83 (s, 1H, –NHCONH–), 9.01 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 115.90, 115.96, 117.17, 117.45, 117.66, 119.58, 120.02, 120.32, 127.73, 127.85, 135.67, 136.42, 136.45, 143.45, 150.10, 152.49, 159.15, 166.42; ESI-MS *m*/*z*: 474.1$[M + H]^+$; Anal. Calcd for $C_{23}H_{15}F_4N_3O_2S$ (%): C 58.35, H 3.19, N 8.88; Found: C 58.73, H 3.15, N 9.01.

*6.8.7. 1-{4-[4-(Thiazol-2-yl)phenoxy]phenyl}-3-p-tolylurea (**1g**)*

White solid, yield: 57%, mp 223–224 °C; IR(KBr, cm^{-1}): 3301.42, 1640.85, 1604.07, 1568.54, 1505.35, 1482.05, 1241.24, 829.88; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm): 2.22 (s, 3H, Ar-CH_3), 7.00–7.07 (m, 6H, Ar-H), 7.32 (d, $J = 8.39$ Hz, 2H, Ar-H), 7.46–7.50 (m, 2H, Ar-H), 7.70 (d, $J = 3.24$ Hz, 1H, Ar-H), 7.85 (d, $J = 3.25$ Hz, 1H, Ar-H), 7.89–7.93 (m, 2H, Ar-H), 8.51 (s, 1H, –NHCONH–), 8.64 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 20.16, 117.66, 118.36, 119.63, 119.88, 120.15, 127.74, 127.93, 129.01, 130.60, 136.32, 137.03, 143.53, 149.76, 152.57, 159.36, 166.53; ESI-MS *m*/*z*: 402.1$[M + H]^+$; Anal. Calcd for $C_{23}H_{19}N_3O_2S$ (%): C 68.81, H 4.77, N 10.47; Found: C 68.51, H 4.71, N 10.50.

*6.8.8. 1-[2-Chloro-5-(trifluoromethyl)phenyl]-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl} urea (**1h**)*

Off-white solid, yield: 44%, mp 199–200 °C; IR(KBr, cm^{-1}): 3301.42, 1640.85, 1604.07, 1568.54, 1505.35, 1482.05, 1241.24, 829.88; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm) 3301.69, 1649.79, 1600.71, 1559.83, 1500.86, 1482.60, 1409.07, 1301.75, 1221.39, 1166.59, 832.22; ^1H NMR($CDCl_3$, 500 MHz) δ(ppm): 6.99–7.03 (m, 4H, Ar-H), 7.19 (dd, $J = 1.94$, 8.40 Hz, 1H, Ar-H), 7.32 (d, $J = 3.3$ Hz, 1H, Ar-H), 7.34–7.38 (m, 2H, Ar-H), 7.39 (d, $J = 8.36$ Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.61 (br, 1H, –NHCONH–), 7.85 (d, $J = 3.3$ Hz, 1H, Ar-H), 7.89–7.92 (m, 2H, Ar-H), 8.59 (d, $J = 1.8$ Hz, 1H, –NHCONH–); ^{13}C NMR($CDCl_3$, 75 MHz) δ(ppm): 118.13, 118.52, 118.80, 120.07, 120.61, 123.64, 128.38, 128.43, 129.50, 133.53, 136.05, 143.42, 152.85, 159.51, 168.34; ESI-MS *m*/*z*: 490.0$[M + H]^+$.

*6.8.9. 1-[3-Bromo-5-(trifluoromethyl)phenyl]-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl} urea (**1i**)*

White solid, yield: 53%, mp 208–209 °C; IR(KBr, cm^{-1}): 3308.19, 1648.13, 1591.86, 1560.61, 1505.80, 1483.14, 1457.47, 1333.43, 1304.51, 1244.41, 1224.77, 1171.24, 1129.79, 836.43, 694.40; ^1H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.05–7.10 (m, 4H, Ar-H), 7.51–7.55 (m, 3H, Ar-H), 7.73 (d, $J = 3.22$ Hz, 1H, Ar-H), 7.89 (d, $J = 3.17$ Hz, 1H, Ar-H), 7.94–7.97 (m, 3H, Ar-H), 8.98 (s, 1H,

–NHCONH–), 9.20 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 113.37, 117.75, 119.83, 120.25, 120.60, 122.25, 123.99, 127.78, 127.99, 135.56, 142.18, 143.62, 150.26, 152.33, 159.25, 166.51; ESI-MS *m/z*: 533.9[M + H]$^+$; Anal. Calcd for $C_{23}H_{15}BrF_3N_3O_2S$ (%): C 51.70, H 2.83, N 7.86; Found: C 51.71, H 3.07, N 7.91.

*6.8.10. 1-(3-Chloro-4-fluorophenyl)-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl}urea (**1j**)*

White solid, yield: 49%, mp 171–172 °C; IR(KBr, cm^{-1}): 3317.79, 1656.72, 1590.98, 1551.63, 1505.30, 1482.61, 1431.45, 1332.55, 1271.33, 1228.65, 1177.00, 1115.63, 1081.77, 854.80; ^{1}H NMR(DMSO-d_6, 500 MHz) δ(ppm): 7.04–7.09 (m, 4H, Ar-H), 7.32–7.34 (m, 2H, Ar-H), 7.51–7.53 (m, 2H, Ar-H), 7.73 (d, *J* = 3.24 Hz, 1H, Ar-H), 7.80–7.82 (m, 1H, Ar-H), 7.88 (d, *J* = 3.24 Hz, 1H, Ar-H), 7.93–7.95 (m, 2H, Ar-H), 8.82 (s, 1H, –NHCONH–), 8.87 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 116.65, 116.94, 117.68, 118.45, 118.54, 119.50, 119.82, 120.21, 120.31, 127.72, 127.99, 135.95, 143.63, 149.94, 152.51, 159.34, 166.53; ESI-MS *m/z*: 438.2[M − H]$^-$.

*6.8.11. 1-[Methyl (thien-3-yl)-2-carboxylate]-3-{4-[4-(thiazol-2-yl)phenoxy]phenyl} urea (**1k**)*

White solid, yield: 45%, mp 201–202 °C; IR(KBr, cm^{-1}): 3295.37, 1704.96, 1672.94, 1575.54, 1555.56, 1503.65, 1487.32, 1445.77, 1424.25, 1309.16, 1281.95, 1260.52, 1230.60, 1199.96, 829.18, 771.53; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 3.87 (s, 3H, OCH_3), 7.05–7.12 (m, 4H, Ar-H), 7.59 (d, *J* = 8.60 Hz, 2H, Ar-H), 7.73 (d, *J* = 3.02 Hz, 1H, Ar-H), 7.86 (d, *J* = 5.43 Hz, 1H, Ar-H), 7.89 (d, *J* = 3.05 Hz, 1H, Ar-H), 7.95 (d, *J* = 8.45 Hz, 2H, Ar-H), 8.02 (d, *J* = 5.39 Hz, 1H, Ar-H), 9.61 (s, 1H, –NHCONH–), 10.10 (s, 1H, –NHCONH–); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 51.77, 106.97, 117.74, 119.80, 120.26, 120.34, 121.80, 127.77, 127.99, 132.59, 135.93, 143.63, 145.61, 150.16, 151.28, 159.31, 163.64, 166.55; ESI-MS *m/z*: 452.1[M + H]$^+$, 450.1[M − H]$^-$; Anal. Calcd for $C_{22}H_{17}N_3O_4S_2$ (%): C 58.52, H 3.79, N 9.31; Found: C 58.38, H 3.75, N 8.89.

*6.8.12. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-(4-chlorophenyl)urea (**2a**)*

White solid, yield: 50%, mp >300 °C; IR(KBr, cm^{-1}): 3301.01, 1637.62, 1601.06, 1560.24, 1534.88, 1502.11, 1227.83, 1199.76, 834.24; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.00–7.10 (m, 5H, Ar-H), 7.32 (d, *J* = 8.45 Hz, 3H, Ar-H), 7.49 (d, *J* = 8.51 Hz, 4H, Ar-H), 7.91 (d, *J* = 8.31 Hz, 2H, Ar-H), 8.73 (s, 1H, –NHCONH–), 8.80 (s, 1H, –NHCONH–), 12.42 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 125 MHz) δ(ppm): 117.68, 119.71, 119.84, 119.91, 120.10, 125.30, 125.78, 126.49, 128.58, 135.70, 138.75, 145.24, 150.56, 152.52, 157.48; ESI-MS *m/z*: 405.2[M + H]$^+$, 403.0[M − H]$^-$; Anal. Calcd for $C_{22}H_{17}ClN_4O_2$ (%): C 65.27, H 4.23, N 13.84; Found: C 65.52, H 4.37, N 13.99.

*6.8.13. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-[4-chloro-3-(trifluoromethyl) phenyl]urea (**2b**)*

White solid, yield: 51%, mp 228–230 °C; IR(KBr, cm^{-1}): 3353.02, 1696.68, 1609.32, 1556.15, 1503.60, 1486.32, 1331.99, 1307.48, 1245.86, 1227.30, 1201.72, 1170.06, 1144.27, 1125.94, 833.99; ^{1}H NMR(DMSO-d_6, 500 MHz) δ(ppm): 7.02–7.06 (m, 4H, Ar-H), 7.10 (s, 2H, Ar-H), 7.50–7.52 (m, 2H, Ar-H), 7.60–7.66 (m, 2H, Ar-H), 7.91–7.93 (m, 2H, Ar-H), 8.11 (d, *J* = 2.50 Hz, 1H, Ar-H), 7.92–7.97 (m, 2H, Ar-H), 8.85 (s, 1H, –NHCONH–), 9.13 (s, 1H, –NHCONH–), 12.39 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 116.68, 116.75, 116.83, 117.71, 119.76, 120.45, 122.16, 122.97, 124.55, 125.81, 126.43, 131.88, 135.23, 139.34, 145.16, 150.83, 152.42, 157.30; ESI-MS *m/z*: 473.1[M + H]$^+$, 471.0[M − H]$^-$; Anal. Calcd for $C_{23}H_{16}ClF_3N_4O_2$ (%): C 58.42, H 3.41, N 11.85; Found: C 58.52, H 3.74, N 11.57.

*6.8.14. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-phenylurea (**2c**)*

White solid, yield: 52%, mp 234–235 °C; IR(KBr, cm^{-1}): 3300.65, 1639.72, 1602.59, 1595.47, 1567.92, 1504.13, 1445.06, 1257.98, 1233.22, 834.82; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 6.94–7.05 (m, 5H, Ar-H), 7.10 (s, 2H, Ar-H), 7.25–7.34 (m, 2H, Ar-H), 7.44–7.51 (m, 4H, Ar-H), 7.91 (d, *J* = 8.60 Hz, 1H, Ar-H), 8.64 (s, 1H, –NHCONH–), 8.69 (s, 1H, –NHCONH–), 12.42 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 125 MHz) δ(ppm): 117.63, 118.19, 119.94, 121.77, 125.71, 126.49, 128.74, 135.92, 139.71, 145.23, 150.39, 152.61, 157.55; ESI-MS *m/z*: 371.1[M + H]$^+$, 369.1[M − H]$^-$; Anal. Calcd for $C_{22}H_{18}N_4O_2 \cdot 1/2H_2O$ (%): C 69.64, H 5.05, N 14.77; Found: C 69.92, H 4.99, N 14.75.

*6.8.15. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-(4-chloro-3-nitrophenyl)urea (**2d**)*

Yellow solid, yield: 40%, mp 161–162 °C; IR(KBr, cm^{-1}): 3321.00, 2356.94, 1659.11, 1599.96, 1537.41, 1502.69, 1341.29, 1306.32, 1225.96, 1199.03, 1101.18, 855.63, 835.21, 668.99; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.01–7.06 (m, 4H, Ar-H), 7.14 (s, 2H, Ar-H), 7.49–7.52 (m, 2H, Ar-H), 7.64–7.65 (m, 2H, Ar-H), 7.90–7.94 (m, 2H, Ar-H), 8.31 (t, *J* = 2.72 Hz, 1H, Ar-H), 8.90 (s, 1H, –NHCONH–), 9.34 (s, 1H, –NHCONH–), 12.23 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 114.14, 116.53, 117.72, 119.82, 120.42, 122.75, 122,97, 125.26, 126.57, 131.69, 135.16, 139.86, 145.03, 147.41, 150.78, 152.29, 157.47; ESI-MS *m/z*: 450.1[M + H]$^+$, 448.0[M − H]$^-$; Anal. Calcd for $C_{22}H_16ClN_5O_4$ (%): C 58.74, H 3.59, N 15.57; Found: C 58.99, H 3.79, N 15.15.

*6.8.16. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-[3-(trifluoromethyl)phenyl]urea (**2e**)*

White solid, yield: 53%, mp >300 °C; IR(KBr, cm^{-1}): 3307.15, 1634.53, 1616.12, 1600.58, 1567.16, 1506.05, 1491.08, 1344.00, 1245.15, 1170.13, 1129.19, 854.80; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.03–7.07 (m, 4H, Ar-H), 7.11 (s, 2H, Ar-H), 7.31 (d, *J* = 7.48 Hz, 2H, Ar-H), 7.49–7.62 (m, 4H, Ar-H), 7.94 (d, *J* = 8.68 Hz, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 8.83 (s, 1H, –NHCONH–), 9.05 (s, 1H, –NHCONH–), 12.42 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 125 MHz) δ(ppm): 114.15, 117.73, 117.99, 119.83, 120.35, 121.79, 125.86, 126.50, 129.82, 135.47, 140.63, 145.26, 150.80, 152.60, 157.43; ESI-MS *m/z*: 439.1[M + H]$^+$, 437.0[M − H]$^-$, 473.0[M + Cl]$^-$; Anal. Calcd for $C_{23}H_{17}F_3N_4O_2$ (%): C 63.01, H 3.91, N 12.78; Found: C 63.03, H 3.75, N 13.09.

*6.8.17. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-[4-fluoro-3-(trifluoromethyl) phenyl]urea (**2f**)*

White solid, yield: 64%, mp 231–232 °C; IR(KBr, cm^{-1}): 3307.33, 1629.51, 1563.29, 1504.09, 1330.00, 1298.91, 1251.14, 1237.30, 1170.08, 1150.89, 1120.83, 1108.27, 1055.33, 829.68; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.01–7.07 (m, 4H, Ar-H), 7.10 (s, 2H, Ar-H), 7.42 (t, *J* = 19.58 Hz, 1H, Ar-H), 7.50 (d, *J* = 8.91 Hz, 2H, Ar-H), 7.64–7.66 (m, 1H, Ar-H), 7.92 (d, *J* = 8.73 Hz, 2H, Ar-H), 8.01 (dd, *J* = 2.47, 6.38 Hz, 1H, Ar-H), 8.82 (s, 1H, –NHCONH–), 9.02 (s, 1H, –NHCONH–), 12.43 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 115.89, 115.95, 117.29, 117.58, 117.68, 119.76, 120.36, 124.08, 124.19, 125.77, 126.43, 135.38, 136.54, 136.58, 145.16, 150.73, 152.60, 157.34; ESI-MS *m/z*: 457.2[M + H]$^+$, 455.0[M − H]$^-$, 491.1[M + Cl]$^-$; Anal. Calcd for $C_{23}H_{16}F_4N_4O_2$ (%): C 60.53, H 3.53, N 12.28; Found: C 61.05, H 3.60, N 12.60.

*6.8.18. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-p-tolylurea (**2g**)*

White solid, yield: 54%, mp >300 °C; IR(KBr, cm^{-1}): 3300.95, 1639.09, 1599.92, 1565.27, 1502.58, 1231.24, 1199.41, 834.31; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 2.24 (s, 3H, Ar-CH_3), 7.00–7.09

(m, 8H, Ar-H), 7.34 (d, $J = 8.31$ Hz, 2H, Ar-H), 7.48 (d, $J = 8.90$ Hz, 2H, Ar-H), 7.91 (d, $J = 8.72$ Hz, 2H, Ar-H), 8.53 (s, 1H, –NHCONH–), 8.64 (s, 1H, –NHCONH–), 12.39 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 20.19, 117.54, 118.16, 118.24, 119.79, 119.80, 125.66, 126.39, 129.02, 130.51, 135.92, 137.03, 145.15, 150.24, 152.56, 157.44; ESI-MS m/z: 385.2$[M + H]^+$, 383.1$[M - H]^-$, 419.1$[M + Cl]^-$; Anal. Calcd for $C_{23}H_{20}N_4O_2$ (%): C 71.86, H 5.24, N 14.57; Found: C 71.50, H 5.35, N 14.33.

*6.8.19. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-[2-chloro-5-(trifluoromethyl) phenyl]urea (**2h**)*

White solid, yield: 41%, mp >300 °C; IR(KBr, cm^{-1}): 3263.35, 1689.47, 1588.34, 1566.06, 1532.83, 1504.55, 1431.56, 1335.73, 1263.64, 1248.48, 1228.74, 1168.66, 1127.39, 1100.55, 1081.42, 1064.87, 832.80, 733.09; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.02–7.10 (m, 6H, Ar-H), 7.36 (dd, $J = 1.76$, 8.41 Hz, 1H, Ar-H), 7.52 (d, $J = 8.94$ Hz, 2H, Ar-H), 7.71 (d, $J = 8.29$ Hz, 1H, Ar-H), 7.92 (d, $J = 8.73$ Hz, 2H, Ar-H), 8.59 (s, 1H, Ar-H), 8.65 (d, $J = 1.85$ Hz, 1H, –NHCONH–), 9.59 (d, $J = 1.8$ Hz, 1H, –NHCONH–), 12.42 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 116.70, 117.84, 119.20, 119.88, 120.21, 125.27, 125.91, 126.50, 130.31, 135.07, 136.98, 151.05, 152.08, 157.29; ESI-MS m/z: 473.1$[M + H]^+$, 471.0$[M - H]^-$.

*6.8.20. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-[3-bromo-5-(trifluoromethyl) phenyl]urea (**2i**)*

White solid, yield: 58%, mp >300 °C; IR(KBr, cm^{-1}): 3250.53, 1693.43, 1593.45, 1553.19, 1503.52, 1458.43, 1336.10, 1304.75, 1243.02, 1223.97, 1172.52, 1132.78, 1100.03, 855.20, 694.57; ^{1}H NMR(DMSO-d_6, 300 MHz) δ(ppm): 7.00–7.07 (m, 4H, Ar-H), 7.10 (s, 2H, Ar-H), 7.48–7.54 (m, 3H, Ar-H), 7.88–7.96 (m, 4H, Ar-H), 8.94 (s, 1H, –NHCONH–), 9.18 (s, 1H, –NHCONH–), 12.40 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 113.37, 113.40, 117.75, 119.71, 120.31, 120.36, 120.60, 122.20, 123.95, 125.86, 126.43, 135.08, 142.19, 145.16, 150.97, 152.32, 157.25; ESI-MS m/z: 517.1$[M + H]^+$; Anal. Calcd for $C_{23}H_{16}BrF_3N_4O_2$ (%): C 53.40, H 3.12, N 10.83; Found: C 53.36, H 3.24, N 10.92.

*6.8.21. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-(3-chloro-4-fluorophenyl)urea (**2j**)*

White solid, yield: 45%, mp >300 °C; IR(KBr, cm^{-1}): 3295.08, 1638.90, 1603.50, 1560.98, 1500.06, 1234.89, 1213.23, 835.04; ^{1}H NMR(DMSO-d_6, 500 MHz) δ(ppm): 7.00–7.05 (m, 4H, Ar-H), 7.09 (s, 2H, Ar-H), 7.30–7.33 (m, 2H, Ar-H), 7.48–7.50 (m, 2H, Ar-H), 7.79–7.80 (m, 1H, Ar-H), 7.90–7.92 (m, 2H, Ar-H), 8.76 (s, 1H, –NHCONH–), 8.84 (s, 1H, –NHCONH–), 12.38 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 116.65, 116.94, 117.72, 118.48, 118.56, 119.55, 119.85, 120.27, 125.84, 126.48, 135.54, 137.01, 137.05, 145.22, 150.70, 152.56, 157.41; ESI-MS m/z: 423.1$[M + H]^+$, 421.0$[M - H]^-$; Anal. Calcd for $C_{22}H_{16}ClFN_4O_2$ (%): C 62.49, H 3.81, N 13.25; Found: C 62.42, H 3.98, N 13.03.

*6.8.22. 1-{4-[4-(1H-Imidazol-2-yl)phenoxy]phenyl}-3-[methyl (thien-3-yl)-2-carboxylate]urea (**2k**)*

White solid, yield: 40%, mp >300 °C; IR(KBr, cm^{-1}): 3311.39, 1685.99, 1672.17, 1575.40, 1546.85, 1508.77, 1442.77, 1417.36, 1307.84, 1263.34, 1234.24, 1095.03, 855.21; ^{1}H NMR(DMSO-d_6, 500 MHz) δ(ppm): 3.85 (s, 3H, OCH_3), 7.02–7.06 (m, 4H, Ar-H), 7.09 (s, 2H, Ar-H), 7.53–7.55 (m, 2H, Ar-H), 7.85 (d, $J = 5.47$ Hz, 1H, Ar-H), 7.91–7.92 (m, 2H, Ar-H), 8.00 (d, $J = 5.48$ Hz, 1H, Ar-H), 9.57 (s, 1H, –NHCONH–), 10.03 (s, 1H, –NHCONH–), 12.39 (br, 1H, imidazole-NH); ^{13}C NMR(DMSO-d_6, 75 MHz) δ(ppm): 51.71, 106.94, 117.73, 119.80, 120.26, 121.76, 125.82, 126.43, 132.52, 135.43, 145.16, 145.57, 150.85, 151.26, 159.29, 163.58; ESI-MS m/z: 435.1$[M + H]^+$, 432.9$[M - H]^-$, 469.0$[M + Cl]^-$; Anal. Calcd for $C_{22}H_{18}N_4O_4S$ (%): C 60.82, H 4.18, N 12.90; Found: C 60.79, H 4.38, N 12.58.

Acknowledgments

We are grateful for the project (BE2009639) supported by the Technology Supporting Programme of Jiangsu.

References

[1] R.A. Smith, V. Cokkinides, O.W. Brawley, CA Cancer J. Clin. 59 (2009) 27–41.
[2] V.R. Solomon, C. Hua, H. Lee, Bioorg. Med. Chem. 17 (2009) 7585–7592.
[3] E.A. Sausville, Anticancer Drug Des. 15 (2000) 1–2.
[4] J. Dumas, R.A. Smith, T.B. Lowinger, Curr. Opin. Drug Discov. Devel. 7 (2004) 600–616.
[5] S. Wilhelm, C. Carter, M. Lynch, T. Lowinger, J. Dumas, R.A. Smith, B. Schwartz, R. Simantov, S. Kelley, Nat. Rev. Drug Discov. 5 (2006) 835–844.
[6] Y. Dai, K. Hartandi, Z. Ji, A.A. Ahmed, D.H. Albert, J.L. Bauch, J.J. Bouska, P.F. Bousquet, G.A. Cunha, K.B. Glaser, C.M. Harris, D. Hickman, J. Guo, J. Li, P.A. Marcotte, K.C. Marsh, M.D. Moskey, R.L. Martin, A.M. Olson, D.J. Osterling, L.J. Pease, N.B. Soni, K.D. Stewart, V.S. Stoll, P. Tapang, D.R. Reuter, S.K. Davidsen, M.R. Michaelides, J. Med. Chem. 50 (2007) 1584–1597.
[7] K. Nakamura, E. Taguchi, T. Miura, A. Yamamoto, K. Takahashi, F. Bichat, N. Guilbaud, K. Hasegawa, K. Kubo, Y. Fujiwara, R. Suzuki, K. Kubo, M. Shibuya, T. Isae, Cancer Res. 18 (2006) 9134–9142.
[8] H.C. Spangenberg, R. Thimme, H.E. Blum, Nat. Rev. Gastroenterol. Hepatol. 6 (2009) 423–432.
[9] A. Rossi, P. Maione, M.L. Ferrara, P.C. Sacco, C. Schettino, M.A. Bareschino, C. Gridelli, Curr. Med. Chem. 16 (2009) 3919–3930.
[10] V. Roy, E.A. Perez, Breast Cancer Res. Treat. 116 (2009) 31–38.
[11] M.H. Potashman, J. Bready, A. Coxon, T.M. DeMelfi Jr., L. DiPietro, N. Doerr, D. Elbaum, J. Estrada, P. Gallant, J. Germain, Y. Gu, J.C. Harmange, S.A. Kaufman, R. Kendall, J.L. Kim, G.N. Kumar, A.M. Long, S. Neervannan, V.F. Patel, A. Polverino, P. Rose, S. Plas, D. Whittington, R. Zanon, H. Zhao, J. Med. Chem. 50 (2007) 4351–4373.
[12] S. Ramurthy, S. Subramanian, M. Aikawa, P. Amiri, A. Costales, J. Dove, S. Fong, J.M. Jansen, B. Levine, S. Ma, C.M. McBride, J. Michaelian, T. Pick, D.J. Poon, S. Girish, C.M. Shafer, D. Stuart, L. Sung, P.A. Renhowe, J. Med. Chem. 51 (2008) 7049–7052.
[13] D. Ménard, I. Niculescu-Duvaz, H.P. Dijkstra, D. Niculescu-Duvaz, B.M. Suijkerbuijk, A. Zambon, A. Nourry, E. Roman, L. Davies, H.A. Manne, F. Friedlos, R. Kirk, S. Whittaker, A. Gill, R.D. Taylor, R. Marais, C.J. Springer, J. Med. Chem. 52 (2009) 3881–3891.
[14] A. Manaka, M. Sato, Synth. Commun. 35 (2005) 761–764.
[15] J.W. Pavlik, P. Tongcharoensirikul, N.P. Bird, A. Colin Day, J.A. Barltrop, J. Am. Chem. Soc. 116 (1994) 2292–2300.
[16] M. Abdollahi-Alibeik, I. Mohammadpoor-Baltork, M.A. Zolfigol, Bioorg. Med. Chem. Lett. 14 (2004) 6079–6082.
[17] M. Sun, H.T. Wei, D. Li, Y.G. Zheng, J. Cai, M. Ji, Synth. Commun. 38 (2008) 3151–3158.
[18] H. Jones, M.W. Fordice, R.B. Greenwald, J. Hannah, A. Jacobs, W.V. Ruyle, G.L. Walford, T.Y. Shen, J. Med. Chem. 21 (1978) 1100–1104.
[19] D. Bankston, J. Dumas, R. Natero, B. Riedl, M.K. Monahan, R. Sibley, Org. Process Res. Dev. 6 (2002) 777–781.
[20] M.V. Berridge, A.S. Tan, P.M. Herst, Biotechnol. Annu. Rev. 11 (2005) 127–152.

Web references

[1] http://caonline.amcancersoc.org/cgi/content/full/59/1/27.
[2] http://www.sciencedirect.com/science?_ob=ArticleListURL&;_method=list&_ArticleListID=1096436340&_sort=r&view=c&_acct=C000056919&_version=1&_urlVersion=0&_userid=2324995&md5=87dc68849777d0db8945bf2ebeeeb6f8.
[3] http://chinesesites.library.ingentaconnect.com/content/cog/antcan/2000/00000015/00000001/art00001.
[4] http://www.biomedcentral.com/1367-6733/7/600.
[5] http://www.nature.com/nrd/journal/v5/n10/abs/nrd2130.html.
[6] http://pubs.acs.org/doi/abs/10.1021/jm061280h?journalCode=jmcmar&quickLinkVolume=50&quickLinkPage=1584&volume=50.
[7] http://cancerres.aacrjournals.org/cgi/content/abstract/66/18/9134.
[8] http://www.nature.com/nrgastro/journal/v6/n7/abs/nrgastro.2009.86.html.
[9] http://chinesesites.library.ingentaconnect.com/content/ben/cmc/2009/00000016/00000030/art00001.
[10] http://www.springerlink.com/content/q8m61r8467p38138/?p=8059bbb57ea946d4aa67999266a65535&;pi=2.
[11] http://pubs.acs.org/doi/abs/10.1021/jm070034i?journalCode=jmcmar&quickLinkVolume=50&quickLinkPage=4351&volume=50.
[12] http://pubs.acs.org/doi/abs/10.1021/jm801050k?journalCode=jmcmar&quickLinkVolume=51&quickLinkPage=7049&volume=51.
[13] http://pubs.acs.org/doi/abs/10.1021/jm900242c?journalCode=jmcmar&quickLinkVolume=52&quickLinkPage=3881&volume=52.
[14] http://www.informaworld.com/smpp/content~db=all~content=a713733841.
[15] http://pubs.acs.org/doi/abs/10.1021/ja00085a008?journalCode=jacsat&quickLinkVolume=116&quickLinkPage=2292&volume=116.

[16] http://www.sciencedirect.com/science?_ob=ArticleListURL&;_method=list&_ArticleListID=1096471209&view=c&_acct=C000056919&_version=1&_urlVersion=0&_userid=2324995&md5=e9072fa8b85f76509bbcf4fc62bb3c94.
[17] http://www.informaworld.com/smpp/content~db=all~content=a902365749.
[18] http://pubs.acs.org/doi/abs/10.1021/jm00209a002?journalCode=jmcmar&quickLinkVolume=21&quickLinkPage=1100&volume=21.
[19] http://pubs.acs.org/doi/abs/10.1021/op020205n?journalCode=oprdfk&quickLinkVolume=6&quickLinkPage=777&volume=6.
[20] http://www.sciencedirect.com/science?_ob=ArticleListURL&;_method=list&_ArticleListID=10964741748_sort=r&view=c&_acct=C000056919&_version=1&_urlVersion=0&_userid=2324995&md5=99aa493a083cd14eb0d2dcff0f0543a5.