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Original article

Design and synthesis of novel 4-benzothiazole amino quinazolines Dasatinib derivatives as potential anti-tumor agents

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ABSTRACT

Three series of novel 4-benzothiazole amino quinazolines Dasatinib derivatives have been designed and synthesized. The entire target compounds were investigated for their *in vitro* cytotoxic activity by the MTT-based assay against 6 human cancer cell lines. Compared with the parental Dasatinib, most of the new compounds, especially 2, 4, 6-trimethylaniline series (**3**), demonstrated significant inhibitory activities against six cell lines. Furthermore, the target compounds were screened for Src and Abl kinase inhibitory activity. Among them, **1a**, **1f** and **3a**–**3f** are more potential dual Src/Abl kinase inhibitors. Thus they may be promising lead compounds to be developed as an alternative for current Dasatinib therapy or for Imatinib-resistant patients, potentially via simultaneously blocking multiple RTK signaling pathways.

1. Introduction

Chronic myeloid leukemia (CML) is a hematopoietic stem cell cancer that arises following a reciprocal genetic translocation between chromosomes 9 and 22 [1], resulting in the short Philadelphia (Ph) chromosome carrying the Bcr-Abl (Breakpoint cluster region-Abelson leukemia) oncogene [2–4]. The understanding of the central role played by Bcr-Abl in the pathogenesis of CML gave birth to the so-called "targeted therapy" [5]. In 2001, Imatinib (Gleevec™, Fig. 1), a potent Bcr-Abl inhibitor, was approved for the treatment of CML serves as validation of the concept that therapeutic agents targeting cancer-specific pathways can offer significative improvements over traditional chemotherapeutic agents [6]. Imatinib is now considered as a first-line therapy for the majority of CML cases due to its high efficacy and relatively mild side effects [7].

However, the initial enthusiasm generated by the high response rate to this drug has been dampened by the development of resistance, accounting for 16% in newly diagnosed chronic phase CML and more than 50% in more advanced stages [8]. Mutations in the kinase domain of Bcr-Abl are the major mechanism of acquired Imatinib resistance [9–11]. To date, at least 50 different point mutations that encode distinct single amino acid substitutions have been identified in CML patients who are resistant to Imatinib [12]. Despite the fact that the targeted therapy era started as a hunt for selective kinase inhibitors [13], the aim has recently changed to the identification of compounds acting on multiple targets in order to overcome the drug resistance often connected to the activation of alternative signaling pathways [14,15].

Several studies have provided a rationale for the use of dual Src/Abl kinase inhibitors to overcome Imatinib resistance [16–18], overexpression of Src family kinases (SFK) has been implicated in Bcr-Abl mediated leukemogenesis, particularly the induction of B-cell acute lymphoblastic leukemia (B-ALL), and also in CML disease progression [19]. Moreover, inhibition of overexpressed Src was proven to be very effective in treating a number of tumors such as colon, breast, pancreas, lung, liver, brain, and bladder cancers [20–25]. Taken together, since Src shares significant sequence homology and remarkable structural resemblance with the active form of Abl, several Src inhibitors showed potent Bcr-Abl inhibitory activity and were successfully used as second generation antileukemia drugs [26–28]. An important step forward has been made with the approval of Dasatinib (Sprycel™, Fig. 1), a multi-targeted tyrosine kinase inhibitor, active against 14 of the 15 clinically relevant Imatinib resistant mutants [29]. Acquired resistance is becoming a

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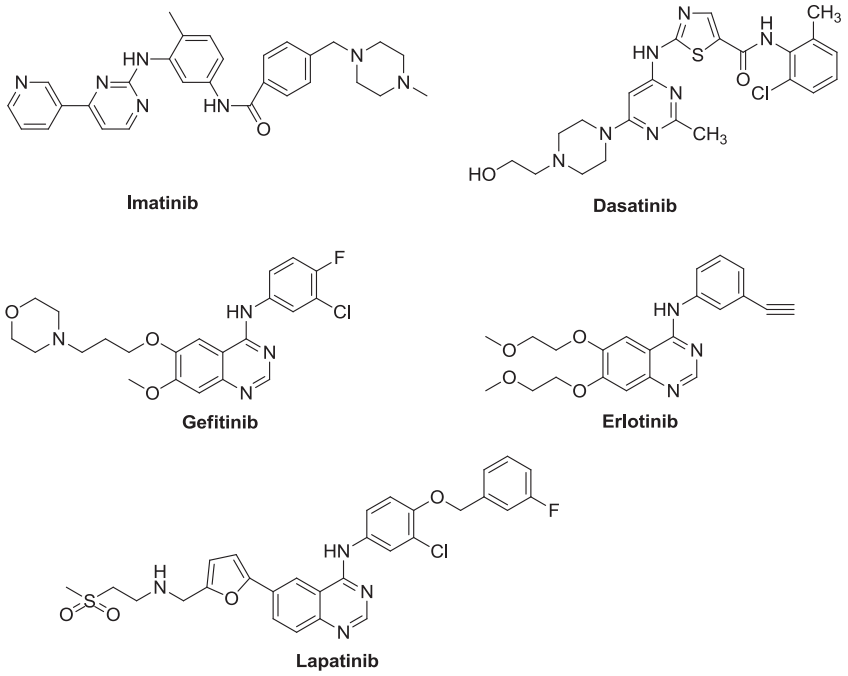


Fig. 1. Chemical structure of Imatinib, Dasatinib, Gefitinib, Erlotinib and Lapatinib.

common issue in targeted therapy of malignant diseases and, as a consequence, there is a growing interest in developing novel TK inhibitors able to target Imatinib-resistant form of CML [30,31].

Gefitinib (Iressa™), Erlotinib (Tarceva™) and Lapatinib (Tykerb™) (Fig. 1), are three selective EGFR inhibitors approved by the FDA in 2003, 2004 and 2007 respectively, for locally advanced or metastatic tumor therapy [32–34]. They possessed the common pharmacophore: 4-anilino quinazoline moiety. On the basis of our previous work [35–37], according to structure–activity relationship (SAR) analysis of the leading compound Dasatinib [38–40], as well as the basic drug design principals of ring-addition and combination, we have devised and synthesized novel 4-benzothiazole amino quinazolines derivatives (Fig. 2): (1) replacement of thiazole ring with benzothiazole; (2) replacement pyrimidine with quinazoline, methoxy group at position 6 and various secondary amino-substituted propoxy side chains at position 7 of the quinazoline nucleus; and (3) various substituted phenylamines were also investigated. Our objective was to determine whether these compounds favor greater inhibition of cell proliferation and higher induction of cell death.

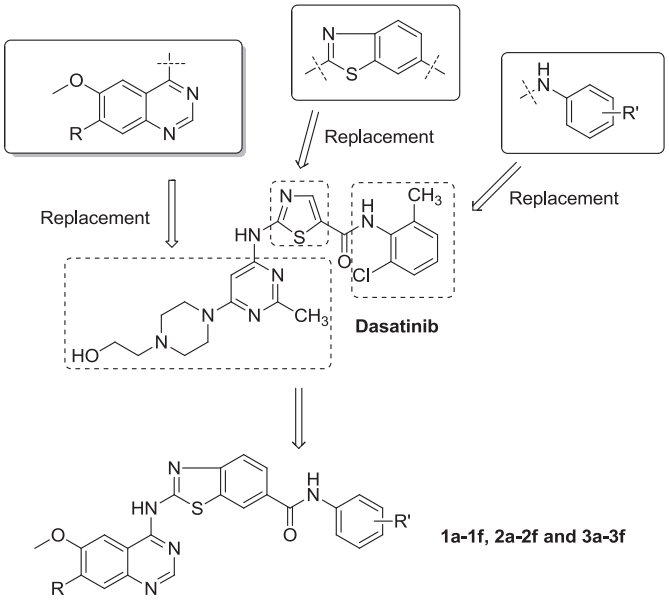


Fig. 2. A design for Dasatinib derivatives.

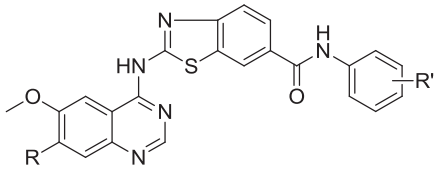
2. Chemistry

As summarized in Table 1, up to 18 compounds (**1a**–**1f**, **2a**–**2f** and **3a**–**3f**) were synthesized. The synthetic routes were illustrated in Schemes 1 and 2.

Synthesis of the key intermediates **10a**–**10c** of the target compounds is shown in Scheme 1. The benzo[d]thiazole ring on compound **5** was assembled via coupling of ethyl 4-aminobenzoate **4** with potassium thiocyanate and copper sulfate in methanol with a yield of 79%. The amino group of obtained **5** was protected by Boc Anhydride to give **6**, which was hydrolyzed by NaOH in THF (Tetrahydrofuran) to generate **7** in 91% yield. Compound **7** was treated with oxalyl chloride and condensed with various substituted phenylamine to produce **9a**–**9c**. The key intermediates **10a**–**10c** were finally obtained by de-protection of **9a**–**9c** with TFA (trifluoroacetic acid) in dichloromethane in high yields.

Methyl 4-hydroxy-3-methoxybenzoate **11** as starting material was alkylated with 1-bromo-3-chloropropane to give **12** in 94% yield. Nitration of **12** with nitric acid in acetic acid afforded **13**, which was then reduced by powdered iron in acetic acid to give **14** in satisfactory yield (80%). In contrast, catalytic hydrogenation using Raney/Ni or 5% Pd/C gave incomplete conversions, even after a long reaction time. Cyclization of **14** with formamidine acetate gave **15** in 95% yield. The next step was nucleophilic displacement of the chlorine atom with different aliphatic amines to yield the corresponding compounds **16a**–**16f**, which were chloridized with thionyl chloride to give **17a**–**17f**. Aminolysis of **17a**–**17f** was performed using intermediates **10a**–**10c** to afford the corresponding target compounds **1a**–**1f**, **2a**–**2f** and **3a**–**3f** (Scheme 2).

Table 1
Structure of compounds **1a**–**1f**, **2a**–**2f** and **3a**–**3f**



1a-1f, 2a-2f and 3a-3f

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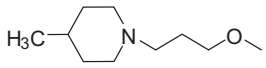
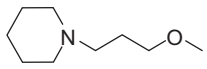
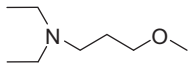
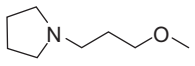
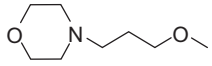
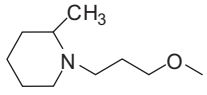
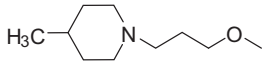
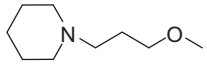
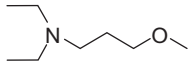
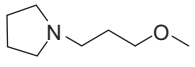
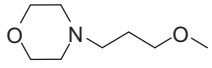
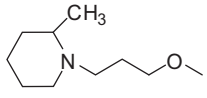
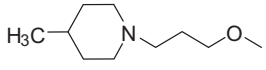
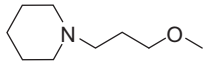
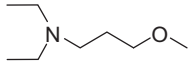
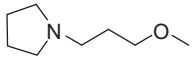
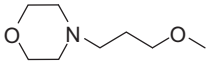
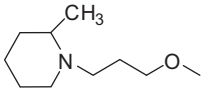
Compd	R′	R	Mp (°C)	Yields (%)
1a	2-Cl, 6-Me		139–140	28.5
1b	2-Cl, 6-Me		132–134	30.8
1c	2-Cl, 6-Me		128–129	29.7
1d	2-Cl, 6-Me		143–144	28.2
1e	2-Cl, 6-Me		148–149	32.3
1f	2-Cl, 6-Me		144–145	27.7
2a	2,6-*di*-Me		137–138	29.5
2b	2,6-*di*-Me		136–137	31.0
2c	2,6-*di*-Me		133–134	32.5
2d	2,6-*di*-Me		154–155	30.0
2e	2,6-*di*-Me		147–148	28.4
2f	2,6-*di*-Me		144–145	32.7
3a	2,4,6-*tri*-Me		127–128	26.4
3b	2,4,6-*tri*-Me		134–135	31.1
3c	2,4,6-*tri*-Me		131–132	32.6
3d	2,4,6-*tri*-Me		147–148	30.2

Table 1 (*continued*)

Compd	R′	R	Mp (°C)	Yields (%)
3e	2,4,6-*tri*-Me		151–152	28.6
3f	2,4,6-*tri*-Me		143–145	31.2

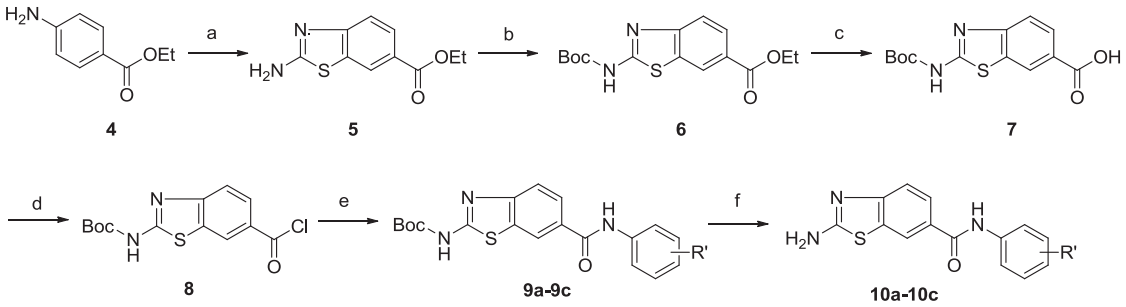
3. Results and discussion

3.1. In vitro cytotoxic activity of the target compounds

All the 18 newly synthesized Dasatinib derivatives (**1a**–**1f**, **2a**–**2f** and **3a**–**3f**) were investigated for their *in vitro* cytotoxic activity by the MTT-based assay using Dasatinib as a positive control against six human cancer cell lines, representing different tumor types, namely human colon cancer cell lines (HCT-116 and DLD1), human chronic myeloid leukemia cell line (K562), human acute monocytic myeloid leukemia cell line (U937) and human lung cancer cell lines (A549 and NCI-H661). These compounds were assayed for their anti-proliferative activity indicated by IC_{50} values, which were calculated by linear regression analysis of the concentration–response curves obtained for each compound.

Table 2 outlines the SAR observed with the different quinazoline moieties modification at the C2 amine of the benzothiazole nucleus. Almost all the 2, 4, 6-trimethylaniline series (**3**) compounds demonstrated potent anti-proliferation effects with IC_{50} values less than Dasatinib in 6 cell lines except for **3b** and **3e**, it is worth pointing out that the most significant inhibition was achieved for compound **3f**. Compared with series (**3**), the 2-chloro-6-methylaniline series (**1**) compounds displayed lower inhibition activity in 6 cell lines. While in the 2, 6-dimethylaniline series (**2**), most of the compounds demonstrated evident anti-proliferation effects of leukemia cell lines (K562 and U937), but very poor anti-proliferation effects of solid tumor cell lines (HCT-116, DLD1, A549 and NCI-H661).

It is noticeable that compounds **1f** and **3f** with 2-methylpiperidine substitution displayed the most strongly cytotoxic activity in their respective series, while the piperidine substituted **1b** and **3b** showed lower cytotoxic activity. According to the previous studies of molecular docking and preferred conformation analysis [35,41], we speculated that conformational restriction of methyl group in piperidine would help to form appropriate angle by amino quinazolines ring and benzothiazole ring, this was more conducive for aniline ring to reside in the active binding site, meanwhile the nitrogen of 2-methylpiperidine form hydrogen bond to the hinge region, all of which would help to improve the anti-proliferation activity. In addition, the morpholine substituted compounds **1e** and **2e** almost showed poorest cytotoxic activity in their respective series, which may be induced by the electro negativity of the oxygen atoms by our conjecture. Besides these factors, the structure difference among these compounds in each series was the basic side chain at position 7 of quinazoline nucleus, which was reported to affect the pharmacokinetic properties and solubility of compound *in vivo* [42,43]. The introduction of the basic side chains was to increase the volume of distribution at steady state (V_{dss}), and thus increased the observed half-life and a long terminal half-life was desirable in terms of increasing drug exposure and ultimately efficacy. Moreover, previous SAR studies of the binding of in the reversible amino quinazolines EGFR inhibitors



Scheme 1. Synthetic route for the preparation of the compounds **10a**–**10c**. Reagents and conditions: (a) KSCN, $CuSO_4.5H_2O$, CH_3OH, reflux, 6 h, 79%; (b) $(Boc)_2O$, DMAP, THF, rt, 16 h, 86%; (c) NaOH, THF, rt, 12 h, 91%; (d) $(COCl)_2$, cat. DMF, THF, 10 °C, 6 h; (e) substituted phenylamine, Et_3N, THF, rt, 2 h, 83–87%; (f) TFA, CH_2Cl_2, rt, 2 h, 95–97%.

suggested a binding mode whereby 7-position side chains reside in a large, mostly lipophilic ATP binding pocket toward the solvent [44], so there was tolerance for substitution at the 7-position with cationic side chains. As cytotoxicity assay was carried out *in vitro*, the inhibitory effect variance among these compounds could be attributed to the hydrophobicity and permeability changes resulting from different basic side chains.

Coincidentally, the benzothiazole derivatives in this article displayed the equivalent antiproliferative activity against K562 and U937 cell lines compared with our previous report about benzothiophene amino quinazolines derivatives [36]. And the SAR of the basic side chains were similar, 2-methylpiperidine compounds demonstrated the most strongly cytotoxic activity, while the morpholine compounds showed poor cytotoxic activity.

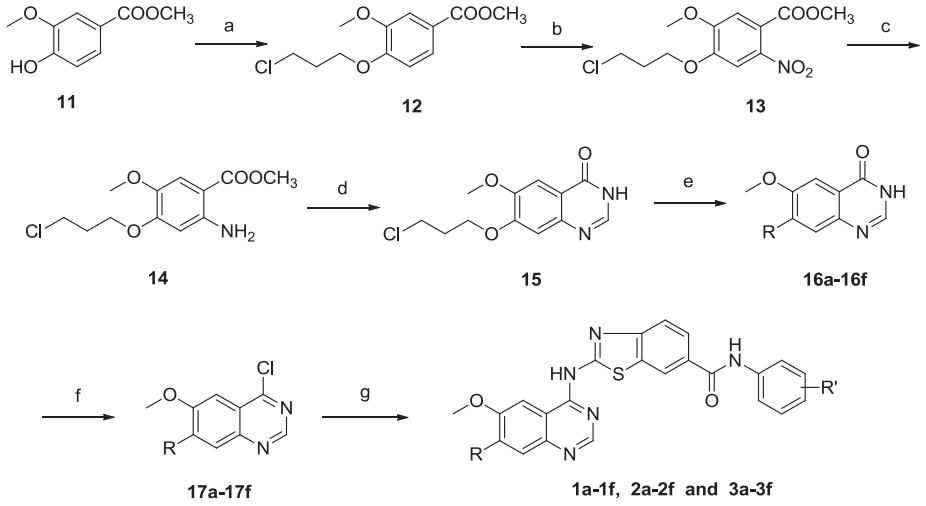
3.2. Kinase inhibitory activity

As Gefitinib with quinazoline nucleus is a selective EGFR inhibitor, so we firstly determined the EGFR inhibitory activity of these analogues using an EGFR Kinase Assay Kit. As also shown in Table 2, the inhibitory potency of the new compounds is much lower than that of Gefitinib and Erlotinib, which indicates that these compounds are no longer specific EGFR tyrosine kinase inhibitors.

Dasatinib, initially designed and synthesized for Src inhibition, was subsequently found to possess potent Abl inhibitory activity as well. In order to study the mechanism of action of the new synthesized compounds, all compounds were preliminarily tested in a cell-free assay to evaluate their affinity toward Src and Abl enzymes using Dasatinib as a reference compound. As also shown in Table 2, almost all the 2,4,6-trimethylaniline series (**3**) and the 2-chloro-6-methylaniline series (**1**) derivatives, with the exception of **1e**, have significant dual Src/Abl kinase inhibitory activity. In addition, the test result of enzyme is consistent with former antiproliferative assay. Those compounds such as **1a**, **1f** and **3a**–**3f** with stronger cytotoxicity also show better dual Src/Abl kinase inhibitory potency. Taken the biological data together, we could preliminarily arrive at the conclusion that part of the target compounds are potential dual Src/Abl kinase inhibitors. Thus they may be promising lead compounds to be developed as an alternative for current Dasatinib therapy or for Imatinib-resistant patients, potentially via simultaneously blocking multiple RTK signaling pathways. However, we also noticed that all compounds have decreasing inhibitory potency in both kinases compared to Dasatinib. Therefore, we are currently carrying out more experiments to access inhibitory activity on other RTKs, hoping to confirm the exact target(s) and details on the mechanism of action.

4. Conclusion

In our study, using Dasatinib as a leading compound, three series of 18 novel 4-benzothiazole amino quinazolines derivatives have been designed and synthesized. The entire target compounds were investigated for their *in vitro* cytotoxic activity by the MTT-



Scheme 2. Synthetic route for the preparation of the target compounds **1a**–**1f**, **2a**–**2f** and **3a**–**3f**. Reagents and conditions: (a) K_2CO_3, $ClCH_2CH_2CH_2Br$, DMF, 2 h, 70 °C, 94%; (b) HNO_3, AcOH, Ac_2O, 2 h, 55 °C, 94%; (c) Fe, AcOH, $CH_3COOC_2H_5$, N_2, 6 h, 50 °C, 80%; (d) formamidine acetate, EtOH, 6 h, reflux, 95%; (e) HNR_1, KI, DMF, 6 h, 70 °C, 94–97%; (f) $SOCl_2$, cat. DMF, 1 h, reflux, 77–87%; (g) **10a**–**10c**, NaH, THF, 12 h, rt, 26–51%.

Table 2
In vitro cytotoxic activity in different cell lines and enzyme inhibition activity of target compounds **1a**–**1f**, **2a**–**2f** and **3a**–**3f**.

Compd	Cytotoxicity in different cell lines (IC_{50} μmol/L)[a,b]						Enzyme inhibition (%)[a,c,d]		
	HCT-116	DLD1	K562	U937	A549	NCI-H661	EGFR	SRC	ABL
1a	9.1	11.3	8.3	9.2	9.7	7.9	23.7	67.4	56.2
1b	23.4	14.7	12.5	8.6	12.8	13.8	28.7	83.3	49.9
1c	13.2	11.7	9.6	7.3	10.6	11.2	46.8	68.2	67.1
1d	63.8	60.7	13.3	19.9	38.6	45.5	15.6	55.7	78.7
1e	>100	>100	16.4	22.6	75.2	>100	10.4	34.3	43.7
1f	7.2	6.7	6.8	7.0	6.7	5.3	53.6	78.9	71.1
2a	>100	>100	15.8	11.2	89.7	72.3	13.3	56.5	54.2
2b	>100	>100	13.7	14.7	>100	>100	17.3	43.4	39.0
2c	>100	>100	28.4	23.7	>100	66.5	10.5	53.6	50.0
2d	>100	>100	15.7	18.9	83.8	>100	21.2	39.9	34.3
2e	>100	>100	>100	19.2	>100	>100	9.9	28.7	41.7
2f	>100	>100	12.3	10.8	75.7	84.4	25.4	49.0	49.2
3a	6.9	7.0	5.9	5.6	5.4	7.7	36.3	78.6	68.2
3b	16.9	24.5	9.3	12.2	10.3	10.0	37.9	69.7	81.6
3c	7.5	6.8	6.8	4.3	5.7	7.3	25.4	65.3	76.3
3d	5.8	5.9	4.3	4.6	8.9	9.6	48.7	91.8	82.3
3e	5.6	5.8	20.0	24.2	16.3	18.4	45.1	80.6	76.5
3f	5.6	5.7	3.5	3.6	5.8	8.8	65.8	89.2	79.8
Dasatinib	5.3	4.6	11.9	12.2	8.2	7.8	NT	98.1	96.7
Gefitinib	NT	NT	NT	NT	NT	NT	98.5	NT	NT
Erlotinib	NT	NT	NT	NT	NT	NT	95.7	NT	NT

NT, no test.
[a] Values are averages of three independent experiments, SD < 10%.
[b] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control.
[c] Values are averages of two independent experiments, SD < 10%.
[d] Compounds tested at a concentration of 10 μM.

based assay against 6 human cancer cell lines (HCT-116, DLD1, K562, U937, A549 and NCI-H661). Compared with the parental Dasatinib, most of the new compounds, especially 2,4,6-trimethylaniline series (**3**), demonstrated significant inhibitory activities against six cell lines. Furthermore, the target compounds were screened for Src and Abl kinase inhibitory activity. Among them, **1a**, **1f** and **3a**–**3f** are more potential dual Src/Abl kinase inhibitors. Thus they may be promising lead compounds to be developed as an alternative for current Dasatinib therapy or for Imatinib-resistant patients, potentially via simultaneously blocking multiple RTK signaling pathways.

5. Experimental protocols

5.1. Synthesis

All reagents were purchased from commercial sources and used without further purification. Melting points were measured on an RY-1 hot-stage microscope, and the thermometer was uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker-ACF 300/500 spectrometer; chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS), used as an internal standard. Mass spectra (MS) were obtained from Agilent 1100LC/MS Spectrometry Services. IR spectra were run on FI-IR Spectrometer (Perkin–Elmer). Elementary analyses were performed on Elementar Vario EL III instrument. All compounds were routinely checked by TLC with silica gel GF-254 glass plates and viewed under UV light at 254 nm.

5.1.1. Ethyl 2-aminobenzo[d]thiazole-6-carboxylate (*5*)

To methanol (800 mL) were added ethyl 4-aminobenzoate **4** (49.5 g, 0.3 mol), KSCN (291 g, 3 mol) and $CuSO_4 \cdot 5H_2O$ (275 g, 1.5 mol). The mixture was heated to reflux by mechanical stir for 6 h. After cooling to room temperature, the precipitate was filtered, about 2/3 of the filtrate was evaporated under reduced pressure. Water (600 mL) was added, the precipitate obtained was filtered and added to 2 N NaOH solution (500 mL), stirred for 10 min at room temperature. The precipitate was filtered, washed with water and dried to get **5** (52.6 g, 79%) as white powder, mp: 242–243 °C ([45], mp, 241–242 °C).

5.1.2. Ethyl 2-(tert-butoxycarbonyl)benzo[d]thiazole-6-carboxylate (*6*)

To THF (500 mL) were added compound **5** (22.2 g, 0.1 mol) and DMAP (1.22 g, 0.01 mol), when all had dissolved, diteutyl dicarbonate (26.2 g, 0.12 mol) in THF (150 mL) was added slowly by dripping at 0 °C. The mixture was stirred at room temperature for 16 h, about 3/4 of the solvent was evaporated under reduced pressure, the precipitate obtained was filtered, washed with THF and dried to yield **6** (27.6 g, 86%) as white powder, mp > 300 °C [46]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.34 (t, J = 7.1 Hz, 3H, $OCH_2\underline{CH_3}$), 1.52 (s, 9H, 3 × CH_3), 4.33 (q, J = 7.1 Hz, 2H, CH_2O), 7.74 (d, J = 8.4 Hz, 1H, Ar–H), 7.97 (d, J = 8.5 Hz, 1H, Ar–H), 8.58 (s, 1H, Ar–H), 12.01 (br, 1H, –NH–Boc).

5.1.3. 2-(tert-Butoxycarbonyl)benzo[d]thiazole-6-carboxylic acid (*7*)

Compound **6** (25.8 g, 0.08 mol) was added to THF (200 mL) and 2 N NaOH solution (500 mL). The mixture was stirred at room temperature for 12 h. After THF was evaporated under reduced pressure, the water layer was cooled to 0 °C, the pH adjusted to 1 with 10% HCl. The precipitate obtained was filtered, washed with water and dried to yield **7** (21.5 g, 91%) as white solid, mp > 300 °C [46].

5.1.4. General process for the synthesis of the compounds *9a*–*9c*

Compound **7** (9.6 g, 32 mmol) and DMF (2 mL) were dissolved in THF (200 mL), to this solution was added slowly oxalyl chloride (3.2 mL, 38.4 mmol) in THF (50 mL) by dripping at 0 °C. The mixture was stirred for 6 h at 10 °C. After cooling to 0 °C, to the react solution were added different substituted phenylamine (38.4 mmol) and triethylamine (7.12 mL, 64 mmol), and the mixture was stirred for 2 h at room temperature. The precipitate obtained was filtered and the filtrate was evaporated under reduced pressure to get crude

product, which was added to water (200 mL) and stirred for 30 min at room temperature, the precipitate was filtered, washed with water and dried to yield the compounds **9a**–**9c**.

Compounds **9a**–**9c** were characterized as follows.

*5.1.4.1. tert-Butyl 6-((2-chloro-6-methylphenyl)carbamoyl)benzo[d] thiazol- 2-yl carbamate (**9a**).* White solid, yield: 84%, mp: 254–256 °C [46]. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 1.53 (s, 9H, 3 × CH_3), 2.23 (s, 3H, Ar–CH_3), 7.24–7.30 (m, 2H, Ar–H), 7.40 (d, J = 7.7 Hz, 1H, Ar–H), 7.78 (d, J = 8.5 Hz, 1H, Ar–H), 8.05 (d, J = 8.4 Hz, 1H, Ar–H), 8.58 (s, 1H, Ar–H), 10.02 (s, 1H, –NH–CO–), 11.95 (br, 1H, –NH–Boc).

*5.1.4.2. tert-Butyl 6-((2,6-dimethylphenyl)carbamoyl)benzo[d]thiazol-2-ylcarbamate (**9b**).* White solid, yield: 83%, mp: 193–194 °C [46]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.53 (s, 9H, 3 × CH_3), 2.20 (s, 6H, 2 × Ar–CH_3), 7.13 (s, 3H, Ar–H), 7.77 (d, J = 8.5 Hz, 1H, Ar–H), 8.04 (d, J = 8.5 Hz, 1H, Ar–H), 8.58 (s, 1H, Ar–H), 9.78 (s, 1H, –NH–CO–), 11.96 (br, 1H, –NH–Boc).

*5.1.4.3. tert-Butyl 6-(mesitylcarbamoyl)benzo[d]thiazol-2-ylcarbamate (**9c**).* White solid, yield: 87%, mp > 300 °C [46]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.53 (s, 9H, 3 × CH_3), 2.12 (s, 6H, 2 × Ar–CH_3), 2.25 (s, 3H, Ar–CH_3), 7.13 (s, 2H, Ar–H), 7.77 (d, J = 8.5 Hz, 1H, Ar–H), 8.04 (d, J = 8.5 Hz, 1H, Ar–H), 8.58 (s, 1H, Ar–H), 9.66 (s, 1H, –NH–CO–), 11.96 (br, 1H, –NH-Boc).

*5.1.5. General process for the synthesis of the compounds **10a**–**10c***

Compounds **9a**–**9c** (23.9 mmol) was dissolved in TFA (30 mL) and CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 2 h, and the solvent was evaporated under reduced pressure. Then the pH adjusted to 14 with 1 N NaOH at 0 °C, the precipitate obtained was filtered, washed with water and dried to yield **10a**–**10c** as white solid.

Compounds **10a**–**10c** were characterized as follows.

*5.1.5.1. 2-Amino-N-(2-chloro-6-methylphenyl)benzo[d]thiazole-6-carboxamide (**10a**).* White powder, yield: 96%, mp: 211–212 °C [38]. ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 2.23 (s, 3H, Ar–CH_3), 7.22–7.30 (m, 2H, Ar–H), 7.39 (d, J = 7.2 Hz, 1H, Ar–H), 7.47 (d, J = 8.4 Hz, 1H, Ar–H), 7.78 (s, 2H, NH_2), 7.96 (d, J = 8.4 Hz, 1H, Ar–H), 8.37 (s, 1H, Ar–H), 9.92 (s, 1H, –NH–CO–).

*5.1.5.2. 2-Amino-N-(2,6-dimethylphenyl)benzo[d]thiazole-6-carboxamide (**10b**).* White solid, yield: 95%, mp: 240–241 °C [46]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.19 (s, 6H, 2 × Ar–CH_3), 7.11 (s, 3H, Ar–H), 7.41 (d, J = 8.4 Hz, 1H, Ar–H), 7.78 (s, 2H, NH_2), 7.90 (d, J = 8.4 Hz, 1H, Ar–H), 8.31 (s, 1H, Ar–H), 9.62 (s, 1H, –NH–CO–).

*5.1.5.3. 2-Amino-N-mesitylbenzo[d]thiazole-6-carboxamide (**10c**).* White solid, yield: 97%, mp: 270–271 °C [46]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.13 (s, 6H, 2 × Ar–CH_3), 2.25 (s, 3H, Ar–CH_3), 6.91 (s, 2H, Ar–H), 7.40 (d, J = 8.4 Hz, 1H, Ar–H), 7.77 (s, 2H, NH_2), 7.88 (d, J = 8.4 Hz, 1H, Ar–H), 8.29 (s, 1H, Ar–H), 9.53 (s, 1H, –NH–CO–).

*5.1.6. Methyl 4-(3-chloropropoxy)-3-methoxybenzoate (**12**)*

A mixture of methyl 4-hydroxy-3-methoxybenzoate (91 g, 0.5 mol), 1-bromo-3-chloropropane (94.5 g, 0.6 mol), and K_2CO_3 (103.5 g, 0.75 mol) in DMF (300 mL) was heated at 70 °C for 2 h. The mixture was cooled to room temperature, then poured slowly into ice water (4 L) while stirring constantly. The precipitate obtained was filtered, washed with cold water and dried to yield **12** (121 g, 94%) as white powder, mp: 99–100 °C ([47], mp: 98–99 °C).

*5.1.7. Methyl 4-(3-chloropropoxy)-5-methoxy-2-nitrobenzoate (**13**)*

HNO_3 (90 mL, 65–68%) was added dropwise at 0–5 °C to a solution of **12** (120 g, 0.47 mol) in a mixture of CH_3COOH (400 mL) and Ac_2O (100 mL). This mixture was stirred at room temperature for 0.5 h and heated at 55 °C for 2 h, then slowly poured into ice water (4 L) and extracted with ethyl acetate (4 × 300 mL). The combined organic layer was washed with saturated sodium bicarbonate (3 × 200 mL) and brine (2 × 100 mL) and dried with Na_2SO_4. The ethyl acetate was evaporated under reduced pressure to yield a yellow oil that solidified after standing in a refrigerator for 12 h and was then recrystallized from ethyl acetate/petroleum ether to afford the product **13** (133.5 g, 94%) as light yellow crystals, mp: 66–68 °C ([47], mp: 63–64 °C).

*5.1.8. Methyl 2-amino-4-(3-chloropropoxy)-5-methoxybenzoate (**14**)*

Powdered iron (50 g, 0.89 mol) was added to CH_3COOH (500 mL). The resulting suspension was stirred for 15 min at 50 °C under an atmosphere of N_2, and a solution of **13** (90.0 g, 0.30 mol) in ethyl acetate (300 mL) was added dropwise. The mixture was stirred for another 6 h at 75 °C. The catalyst was filtered, and the filtrate was slowly poured into water (4 L) and extracted with ethyl acetate (4 × 300 mL). The organic phase was washed with a saturated solution of sodium carbonate (2 × 200 mL) and brine (2 × 100 mL) and then dried with Na_2SO_4. The solvent was removed under vacuum and the brown solid residue was recrystallized from ethyl acetate/petroleum ether to give the product **14** (65.3 g, 80%) as almost white solid, mp: 97–98 °C ([47], mp: 98–99 °C).

*5.1.9. 7-(3-Chloropropoxy)-6-methoxyquinazolin-4(3H)-one (**15**)*

A solution of **14** (52 g, 0.19 mol) and formamidine acetate (52 g, 0.40 mol) in ethanol (400 mL) was heated at reflux for 6 h. The mixture was allowed to stand in the refrigerator overnight. The precipitate was then collected by filtration, washed with cold ethanol and dried to give **15** (48.5 g, 95%) as a white powder, mp: 218–219 °C ([47], mp: 259 °C).

*5.1.10. General process for the synthesis of the compounds **16a**–**16f***

Compound **15** (8 g, 29.8 mmol) and KI (0.5 g, 3 mmol) were added to the solution of HNR_1 (200 mmol) in DMF (150 mL). The solution was stirred at 70 °C for 6 h. The solvent was then removed under reduced pressure and the residue washed with water, and then dried to afford **16a**–**16f**.

Compounds **16a**–**16f** were characterized as follows.

*5.1.10.1. 6-Methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinazolin-4(3H)-one (**16a**).* White powder, yield: 94%, mp: 195–196 °C [47].

*5.1.10.2. 6-Methoxy-7-(3-(piperidin-1-yl)propoxy)quinazolin-4(3H)-one (**16b**).* White solid, yield: 95%, mp: 217–218 °C ([48], mp: 218–219 °C).

*5.1.10.3. 7-(3-(Diethylamino)propoxy)-6-methoxyquinazolin-4(3H)-one (**16c**).* White solid, yield: 97%, mp: 203–204 °C [49].

*5.1.10.4. 6-Methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazolin-4(3H)-one (**16d**).* White solid, yield: 96%, mp: 181–182 °C [50].

*5.1.10.5. 6-Methoxy-7-(3-morpholinopropoxy)quinazolin-4(3H)-one (**16e**).* White solid, yield: 97%, mp: 214–215 °C [51]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.88–1.97 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.35–2.51 (m, 6H, 3 × CH_2N), 3.57 (t, J = 4.6 Hz, 4H, 2 × morpholine-CH_2), 3.87 (s, 3H, OCH_3), 4.15 (t, J = 6.4 Hz, 2H, CH_2O), 7.12 (s, 1H, Ar–H), 7.44 (s, 1H, Ar–H), 7.97 (s, 1H, Ar–H).

*5.1.10.6. 6-Methoxy-7-(3-(2-methylpiperidin-1-yl)propoxy)quinazolin-4(3H)-one (**16f**).* White solid, yield: 95%, mp: 201–202 °C [47].

*5.1.11. General process for the synthesis of the compounds **17a**–**17f***

Compounds **16a**–**16f** (18.1 mmol) was added to thionyl chloride (120 mL) with magnetic stirring. DMF (10 mL) was then slowly added dropwise and the mixture was heated to reflux for 1 h. Most of the excess of thionyl chloride was then removed under reduced pressure and the residue was dissolved in dichloromethane (200 mL), washed with a saturated solution of sodium carbonate (3 × 100 mL) and water (2 × 100 mL), and dried with Na_2SO_4. The dichloromethane was then removed under reduced pressure to give a powder, which was recrystalized from ethyl acetate to give the product **17a**–**17f**.

Compounds **17a**–**17f** were characterized as follows.

*5.1.11.1. 4-Chloro-6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy)quinazoline (**17a**).* White solid, yield: 84%, mp: 105–106 °C [52]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.92 (d, J = 6.2 Hz, 3H, piperidine-CH_3), 1.17–1.38 (m, 3H, piperidine-CH_2 and piperidine-CH), 1.60–1.65 (m, 2H, piperidine-CH_2), 1.90–1.98 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.10–2.14 (m, 2H, CH_2N), 2.51–2.55 (m, 2H, CH_2N), 2.87–2.91 (m, 2H, CH_2N), 4.04 (s, 3H, OCH_3), 4.26 (t, J = 6.7 Hz, 2H, CH_2O), 7.34 (s, 1H, Ar–H), 7.37 (s, 1H, Ar–H), 8.85 (s, 1H, Ar–H).

*5.1.11.2. 4-Chloro-6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinazoline (**17b**).* Light yellow solid, yield: 82%, mp: 198–199 °C [48]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.43–1.46 (m, 2H, piperidine-CH_2), 1.54–1.60 (m, 4H, 2 × piperidine-CH_2), 2.06–2.15 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.29–2.53 (m, 6H, 3 × CH_2N), 4.04 (s, 3H, OCH_3), 4.26 (t, J = 6.6 Hz, 2H, CH_2O), 7.34 (s, 1H, Ar–H), 7.36 (s, 1H, Ar–H), 8.84 (s, 1H, Ar–H).

*5.1.11.3. 3-(4-Chloro-6-methoxyquinazolin-7-yloxy)-N, N-diethylpropan-1-amine (**17c**).* Light yellow solid, yield: 77%, mp: 86–87 °C [49]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.01–1.06 (m, 6H, 2 × $\underline{CH_3}CH_2N$), 2.03–2.13 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.53–2.69 (m, 6H, 3 × CH_2N), 4.04 (s, 3H, OCH_3), 4.26 (t, J = 6.5 Hz, 2H, CH_2O), 7.33 (s, 1H, Ar–H), 7.36 (s, 1H, Ar–H), 8.84 (s, 1H, Ar–H).

*5.1.11.4. 4-Chloro-6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazoline (**17d**).* Light yellow solid, yield: 85%, mp: 194–195 °C [53]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.04 (m, 4H, 2 × pyrolidine-CH_2), 2.40–2.45 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 3.02–3.13 (m, 6H, 3 × CH_2N), 4.03 (s, 3H, OCH_3), 4.29 (t, J = 6.2 Hz, 2H, CH_2O), 7.30 (s, 1H, Ar–H), 7.36 (s, 1H, Ar–H), 8.85 (s, 1H, Ar–H).

*5.1.11.5. 4-Chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (**17e**).* White solid, yield: 80%, mp: 178–179 °C [54]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.10–2.15 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.49–2.60 (m, 6H, 3 × CH_2N), 3.72 (t, J = 4.5 Hz, 4H, 2 × morpholine-CH_2), 4.04 (s, 3H, OCH_3), 4.28 (t, J = 6.5 Hz, 2H, CH_2O), 7.34 (s, 1H, Ar–H), 7.37 (s, 1H, Ar–H), 8.85 (s, 1H, Ar–H).

*5.1.11.6. 4-Chloro-6-methoxy-7-(3-(2-methylpiperidin-1-yl)propoxy)quinazoline (**17f**).* White solid, yield: 87%, mp: 106–107 °C [49]. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 1.06 (d, J = 6.2 Hz, 3H, piperidine-CH_3), 1.27–1.31 (m, 2H, piperidine-CH_2), 1.54–1.67 (m, 4H, 2 × piperidine-CH_2), 2.06–2.11 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.10 (t, J = 10.1 Hz, 1H, C*H*HN), 2.30–2.31 (m, 1H, CHN), 2.52 (quint, J = 10.0 Hz, 1H, CH*H*N), 2.87–2.93 (m, 2H, CH_2N), 4.05 (s, 3H, OCH_3), 4.21–4.29 (m, 2H, CH_2O), 7.34 (s, 1H, Ar–H), 7.38 (s, 1H, Ar–H), 8.85 (s, 1H, Ar–H).

*5.1.12. General process for the synthesis of the compounds **1a**–**1f**, **2a**–**2f** and **3a**–**3f***

A solution of compounds **10a**, **10b** or **10c** (2 mmol) and NaH (10 mmol) in anhydrous tetrahydrofuran (50 mL) was stirred for 3 h at room temperature, then compound **17a**–**17f** (2 mmol) was added and stirred for another 12 h at room temperature. CH_3COOH (1 mL) was added to quench the reaction, the solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (100 mL), washed with a saturated solution of sodium bicarbonate (3 × 50 mL) and brine (2 × 50 mL), and dried with Na_2SO_4. The solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel, eluting with ethyl acetate: triethylamine: methanol (40:2:1) to afford the final product.

Compounds **1a**–**1f**, **2a**–**2f** and **3a**–**3f** were characterized as follows.

*5.1.12.1. N-(2-chloro-6-methylphenyl)-2-(6-methoxy-7-(3-(4-methylpiperidin-1-yl) propoxy)quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**1a**).* Light yellow solid, yield: 29%. Mp: 139–140 °C. IR (KBr, cm^{-1}): 3288.68, 2942.71, 2804.97, 1636.77, 1617.92, 1594.81, 1560.41, 1499.38, 1478.26, 1457.11, 1424.37, 1370.01, 1282.77, 1233.13, 841.28, 757.99; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 0.89 (d, J = 6.4 Hz, 3H, piperidine-CH_3), 1.12–1.20 (m, 2H, piperidine-CH_2), 1.28–1.35 (m, 1H, piperidine-CH), 1.57 (d, J = 11.3 Hz, 2H, piperidine-CH_2), 1.85–1.93 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 1.95–1.99 (m, 2H, CH_2N), 2.22 (s, 3H, Ar–CH_3), 2.42–2.46 (m, 2H, CH_2N), 2.84 (d, J = 11.3 Hz, 2H, CH_2N), 3.83 (s, 3H, OCH_3), 4.29 (t, J = 6.3 Hz, 2H, CH_2O), 6.67 (d, J = 8.5 Hz, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.22–7.30 (m, 2H, Ar–H), 7.38–7.41 (m, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 7.78 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.92 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.93 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 18.19, 21.78, 25.99, 30.35, 33.97, 53.44, 54.49, 56.03, 67.54, 101.95, 107.15, 110.33, 117.48, 121.67, 123.89, 126.16, 126.92, 128.04, 128.94, 132.28, 134.02, 138.60, 142.25, 150.76, 151.04, 153.58, 154.47, 156.13, 157.72, 164.20; ESI-MS m/z: 631.2 $[M + H]^+$, 629.2 $[M - H]^-$, 665.2 $[M + Cl]^-$; Anal. calcd for $C_{33}H_{35}ClN_6O_3S$ (%): C, 62.79; H, 5.59; N, 13.31. Found: C, 62.42; H, 5.72; N, 13.17.

*5.1.12.2. N-(2-chloro-6-methylphenyl)-2-(6-methoxy-7-(3-(piperidin-1-yl)propoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**1b**).* Light yellow solid, yield: 31%. Mp: 132–134 °C. IR (KBr, cm^{-1}): 3417.42, 2934.63, 1658.72, 1650.78, 1619.88, 1594.73, 1574.09, 1500.05, 1479.67, 1453.87, 1424.69, 1370.65, 1328.52, 1283.05, 1233.68, 1206.57, 1143.67, 847.34, 770.42; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.38–1.39 (m, 2H, piperidine-CH_2), 1.49–1.51 (m, 4H, 2 × piperidine-CH_2), 1.92–2.01 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.22 (s, 3H, Ar–$CH_3$), 2.34–2.51 (m, 6H, 3 × CH_2N), 3.83 (s, 3H, OCH_3), 4.29 (t, J = 6.3 Hz, 2H, CH_2O), 6.67 (d, J = 8.5 Hz, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.25–7.33 (m, 2H, Ar–H), 7.38–7.41 (m, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 7.78 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.92 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.94 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 18.19, 24.09, 25.57, 25.88, 54.07, 54.88, 56.04, 67.55, 101.95, 107.16, 110.34, 117.49, 121.67, 123.90, 126.17, 126.93, 128.05, 128.94, 132.29, 134.02, 138.60, 142.26, 150.77, 151.05, 153.59, 154.48, 156.13, 157.73, 164.20; ESI-MS m/z: 617.2 $[M + H]^+$, 615.2 $[M - H]^-$; Anal. calcd for $C_{32}H_{33}ClN_6O_3S \cdot 3/4H_2O$ (%): C, 60.94; H, 5.51; N, 13.33. Found: C, 60.91; H, 5.76; N, 13.36.

*5.1.12.3. N-(2-chloro-6-methylphenyl)-2-(7-(3-(diethylamino)propoxy)-6-methoxyquinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**1c**).* Light yellow solid, yield: 30%. Mp: 128–129 °C. IR (KBr, cm^{-1}): 3269.43, 2967.71, 1618.11, 1594.88, 1574.69, 1499.96, 1479.49, 1453.66, 1424.80, 1370.51, 1329.01, 1283.20, 1233.71, 1205.48, 1183.17, 1140.93, 1093.86, 847.05; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 0.91–0.98 (m, 6H, 2 × $\underline{CH_3}CH_2N$), 1.88–1.97 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.22 (s, 3H, Ar–$\underline{CH_3}$), 2.43–2.58 (m, 6H,

3 × CH_2N), 3.83 (s, 3H, OCH_3), 4.30 (t, J = 6.3 Hz, 2H, CH_2O), 6.68 (d, J = 8.5 Hz, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.22–7.30 (m, 2H, Ar–H), 7.38–7.41 (m, 1H, Ar–H), 7.52 (s, 1H, Ar–H), 7.78 (dd, J_1 = 1.4 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.92 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.94 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 11.79, 18.19, 26.18, 46.43, 48.38, 56.05, 67.35, 101.93, 107.08, 110.35, 117.48, 121.66, 123.89, 126.16, 126.93, 128.03, 128.93, 132.28, 134.02, 138.60, 142.26, 150.77, 151.07, 153.58, 154.47, 156.17, 157.73, 164.20; ESI-MS m/z: 605.2 $[M + H]^+$, 603.2 $[M - H]^-$; Anal. calcd for $C_{31}H_{33}ClN_6O_3S \cdot 3/4H_2O$ (%): C, 60.18; H, 5.62; N, 13.58. Found: C, 60.30; H, 5.81; N, 13.68.

*5.1.12.4. N-(2-chloro-6-methylphenyl)-2-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**1d**).* Light yellow solid, yield: 28%. Mp: 143–144 °C. IR (KBr, cm^{-1}): 3257.32, 2958.96, 2798.93, 1617.77, 1594.60, 1576.03, 1499.39, 1479.62, 1453.80, 1424.39, 1370.45, 1329.11, 1283.17, 1233.15, 1205.60, 1139.65, 1098.04, 847.12, 756.87; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.68–1.71 (m, 4H, 2 × pyrolidine-CH_2), 1.95–2.04 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.22 (s, 3H, Ar–CH_3), 2.46–2.51 (m, 4H, 2 × CH_2N), 2.58 (t, J = 7.0 Hz, 2H, CH_2N), 3.83 (s, 3H, OCH_3), 4.31 (t, J = 6.4 Hz, 2H, CH_2O), 6.67 (d, J = 8.4 Hz, 1H, Ar–H), 7.11 (s, 1H, Ar–H), 7.22–7.31 (m, 2H, Ar–H), 7.38-7.41 (m, 1H, Ar–H), 7.54 (s, 1H, Ar–H), 7.79 (dd, J_1 = 1.4 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.92 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.94 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 18.19, 23.10, 27.76, 52.00, 53.57, 56.04, 67.46, 101.94, 107.16, 110.33, 117.49, 121.67, 123.90, 126.16, 126.92, 128.03, 128.93, 132.28, 134.02, 138.60, 142.25, 150.76, 151.03, 153.59, 154.47, 156.12, 157.72, 164.20; ESI-MS m/z: 603.2 $[M + H]^+$, 625.2 $[M + Na]^+$, 601.2 $[M - H]^-$, 637.1 $[M + Cl]^-$; Anal. calcd for $C_{31}H_{31}ClN_6O_3S \cdot 3/4H_2O$ (%): C, 60.38; H, 5.31; N, 13.63. Found: C, 60.37; H, 5.57; N, 13.57.

*5.1.12.5. N-(2-chloro-6-methylphenyl)-2-(6-methoxy-7-(3-morpholinopropoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**1e**).* Light yellow solid, yield: 32%. Mp: 148–149 °C. IR (KBr, cm^{-1}): 3263.35, 2955.87, 2811.74, 1618.19, 1594.46, 1499.41, 1478.99, 1452.43, 1424.49, 1370.19, 1282.90, 1233.23, 1205.42, 1114.88, 848.40, 758.72; ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 1.97–2.02 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.22 (s, 3H, Ar–CH_3), 2.35–2.50 (m, 6H, 3 × CH_2N), 3.59 (t, J = 4.5 Hz, 4H, 2 × morpholine-CH_2), 3.83 (s, 3H, OCH_3), 4.31 (t, J = 6.2 Hz, 2H, CH_2O), 6.68 (d, J = 8.5 Hz, 1H, Ar–H), 7.11 (s, 1H, Ar–H), 7.23–7.28 (m, 2H, Ar–H), 7.38–7.40 (m, 1H, Ar–H), 7.55 (s, 1H, Ar–H), 7.78 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.92 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.93 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 18.14, 25.44, 53.29, 54.57, 56.01, 66.16, 67.39, 101.96, 107.17, 110.30, 117.47, 121.62, 123.85, 126.14, 126.87, 127.98, 128.89, 132.26, 133.99, 138.57, 142.22, 150.73, 151.03, 153.54, 154.46, 156.09, 157.70, 164.18; ESI-MS m/z: 619.2 $[M + H]^+$, 641.2 $[M + Na]^+$, 657.2 $[M + K]^+$, 617.2 $[M - H]^-$, 653.1 $[M + Cl]^-$; Anal. calcd for $C_{31}H_{31}ClN_6O_4S \cdot 1/2H_2O$ (%): C, 59.28; H, 5.13; N, 13.38. Found: C, 59.15; H, 5.45; N, 13.35.

*5.1.12.6. N-(2-chloro-6-methylphenyl)-2-(6-methoxy-7-(3-(2-methylpiperidin-1-yl) propoxy)quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**1f**).* Light yellow solid, yield: 28%. Mp: 144–145 °C. IR (KBr, cm^{-1}): 3270.17, 2927.35, 1618.32, 1594.55, 1574.34, 1499.26, 1480.21, 1453.73, 1423.70, 1369.69, 1281.52, 1232.19, 1204.55, 845.20, 755.52; ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 0.99 (d, J = 5.7 Hz, 3H, piperidine-CH_3), 1.18–1.23 (m, 2H, piperidine-CH_2), 1.42–1.46 (m, 1H, piperidine-C*H*H), 1.52–1.57 (m, 3H, piperidine-CH*H* and piperidine-CH_2), 1.92–1.94 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.10 (t, J = 9.7 Hz, 1H, C*H*HN), 2.22 (s, 3H, Ar–CH_3), 2.26–2.27 (m, 1H, CHN), 2.38 (quint, J = 9.7 Hz, 1H, CH*H*N), 2.80–2.85 (m, 2H, CH_2N), 3.83 (s, 3H, OCH_3), 4.29 (t, J = 6.3 Hz, 2H, CH_2O), 6.67 (d, J = 8.4 Hz, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.23–7.29 (m, 2H, Ar–H), 7.38–7.40 (m, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 7.78 (dd, J_1 = 1.5 Hz, J_2 = 8.4 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.91 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.92 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 18.14, 18.43, 23.37, 25.18, 25.74, 34.15, 49.42, 51.45, 55.23, 56.03, 67.48, 101.95, 107.12, 110.30, 117.45, 121.62, 123.85, 126.13, 126.87, 127.97, 128.89, 132.26, 134.00, 138.57, 142.22, 150.75, 151.07, 153.54, 154.46, 156.15, 157.69, 164.17; ESI-MS m/z: 631.2 $[M + H]^+$, 629.2 $[M - H]^-$, 665.2 $[M + Cl]^-$; Anal. calcd for $C_{33}H_{35}ClN_6O_3S \cdot 3/4H_2O$ (%): C, 61.48; H, 5.71; N, 13.04; Found: C, 61.74; H, 6.12; N, 13.15.

*5.1.12.7. N-(2, 6-dimethylphenyl)-2-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**2a**).* Light yellow solid, yield: 30%. Mp: 137–138 °C. IR (KBr, cm^{-1}): 3272.95, 2949.47, 1618.12, 1594.76, 1576.87, 1499.36, 1480.24, 1454.43, 1424.26, 1370.03, 1281.76, 1232.57, 1204.66, 1137.90, 767.21; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 0.89 (d, J = 6.4 Hz, 3H, piperidine-CH_3), 1.12-1.19 (m, 2H, piperidine-CH_2), 1.31 (br, 1H, piperidine-CH), 1.57 (d, J = 11.1 Hz, 2H, piperidine-CH_2), 1.85–1.92 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 1.95-1.99 (m, 2H, CH_2N), 2.17 (s, 6H, 2 × Ar-CH_3), 2.42–2.46 (m, 2H, CH_2N), 2.84 (d, J = 11.1 Hz, 2H, CH_2N), 3.83 (s, 3H, OCH_3), 4.29 (t, J = 6.2 Hz, 2H, CH_2O), 6.66 (d, J = 8.4 Hz, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.11 (s, 3H, Ar–H), 7.53 (s, 1H, Ar–H), 7.77 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.68 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 18.02, 21.82, 26.00, 30.37, 33.98, 53.47, 54.52, 56.05, 67.56, 101.97, 107.16, 110.35, 117.51, 121.59, 123.84, 126.04, 126.60, 127.68, 128.61, 135.32, 135.58, 142.07, 150.77, 151.04, 153.62, 154.53, 156.13, 157.77, 164.07; ESI-MS m/z: 611.3 $[M + H]^+$, 633.2 $[M + Na]^+$, 609.3 $[M - H]^-$, 645.2 $[M + Cl]^-$; Anal. calcd for $C_{34}H_{38}N_6O_3S \cdot H_2O$ (%): C, 64.94; H, 6.41; N, 13.37. Found: C, 65.16; H, 6.80; N, 13.48.

*5.1.12.8. N-(2,6-dimethylphenyl)-2-(6-methoxy-7-(3-(piperidin-1-yl) propoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**2b**).* Light yellow solid, yield: 31%. Mp: 136–137 °C. IR (KBr, cm^{-1}): 3269.00, 2933.08, 2852.40, 1618.11, 1594.76, 1575.38, 1499.47, 1480.51, 1454.04, 1424.50, 1370.33, 1327.63, 1282.30, 1232.86, 1205.51, 1141.17, 845.20, 768.33; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.38–1.40 (m, 2H, piperidine-CH_2), 1.50–1.53 (m, 4H, 2 × piperidine-CH_2), 1.96–2.02 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.17 (s, 6H, 2 × Ar–CH_3), 2.37–2.47 (m, 6H, 3 × CH_2N), 3.83 (s, 3H, OCH_3), 4.30 (t, J = 6.3 Hz, 2H, CH_2O), 6.66 (d, J = 8.5 Hz, 1H, Ar–H), 7.10 (s, 1H, Ar–H), 7.11 (s, 3H, Ar–H), 7.54 (s, 1H, Ar–H), 7.77 (dd, J_1 = 1.4 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.68 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 18.00, 24.01, 25.49, 25.80, 54.03, 54.85, 56.04, 67.53, 101.98, 107.17, 110.32, 117.50, 121.57, 123.81, 126.03, 126.58, 127.66, 128.62, 135.31, 135.57, 142.05, 150.76, 151.04, 153.60, 154.53, 156.12, 157.76, 164.06; ESI-MS m/z: 597.3 $[M + H]^+$, 619.2 $[M + Na]^+$, 595.2 $[M - H]^-$, 631.2 $[M + Cl]^-$; Anal. calcd for $C_{33}H_{36}N_6O_3S \cdot 3/4H_2O$ (%): C, 64.95; H, 6.19; N, 13.77. Found: C, 64.79; H, 6.64; N, 13.69.

*5.1.12.9. 2-(7-(3-(Diethylamino)propoxy)-6-methoxyquinazolin-4-ylamino)-N- (2,6-dimethylphenyl)benzo[d]thiazole-6-carboxamide (**2c**).* Light yellow solid, yield: 33%. Mp: 133–134 °C. IR (KBr, cm^{-1}): 3268.35, 2966.93, 2818.15, 1618.05, 1594.74, 1575.36, 1499.34, 1480.31, 1424.46, 1370.36, 1328.56, 1282.40, 1232.89, 1204.61, 1140.33, 1093.66, 1036.29, 883.02, 846.70, 767.83, 714.24, 648.69; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 0.92–0.98 (m, 6H, 2 × $\underline{CH_3}CH_2N$), 1.88-1.99 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.17 (s, 6H, 2 × Ar–CH_3), 2.44-2.59 (m, 6H, 3 × CH_2N), 3.83 (s, 3H, OCH_3), 4.30 (t, J = 6.3 Hz, 2H, CH_2O), 6.66 (d, J = 8.5 Hz, 1H, Ar–H), 7.10 (s, 1H,

Ar–H), 7.11 (s, 3H, Ar–H), 7.52 (s, 1H, Ar–H), 7.78 (dd, $J_1 = 1.7$ Hz, $J_2 = 8.5$ Hz, 1H, Ar–H), 8.17 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.19 (s, 1H, Ar–H), 9.68 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 11.78, 17.99, 26.16, 46.43, 48.38, 56.05, 67.35, 101.96, 107.09, 110.33, 117.49, 121.55, 123.81, 126.02, 126.57, 127.65, 128.60, 135.30, 135.56, 142.05, 150.76, 151.06, 153.58, 154.51, 156.16, 157.75, 164.06; ESI-MS *m/z*: 585.2 $[M + H]^+$, 583.3 $[M - H]^-$, 619.2 $[M + Cl]^-$; Anal. calcd for $C_{32}H_{36}N_6O_3S \cdot 3/4H_2O$ (%): C, 64.25; H, 6.32; N, 14.05. Found: C, 64.40; H, 6.46; N, 13.97.

*5.1.12.10. N-(2,6-dimethylphenyl)-2-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**2d**).* Light yellow solid, yield: 30%. Mp: 154–155 °C. IR (KBr, cm^{-1}): 3260.14, 2955.87, 2795.73, 1617.77, 1594.60, 1576.03, 1499.39, 1479.62, 1453.80, 1424.39, 1370.45, 1283.17, 1233.15, 1205.60, 845.20, 752.31, 569.75; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.69–1.72 (m, 4H, 2 × pyrolidine-CH_2), 1.96–2.05 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.17 (s, 6H, 2 × Ar–CH_3), 2.50–2.60 (m, 6H, 3 × $CH_2\underline{N}$), 3.83 (s, 3H, OCH_3), 4.32 (t, $J = 6.3$ Hz, 2H, CH_2O), 6.66 (d, $J = 8.4$ Hz, 1H, Ar–H), 7.11 (s, 4H, Ar–H), 7.54 (s, 1H, Ar–H), 7.77 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.5$ Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.68 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 14.04, 17.99, 23.08, 27.67, 51.99, 53.57, 56.04, 67.53, 101.96, 107.17, 110.32, 117.50, 121.56, 123.81, 126.02, 126.58, 127.65, 128.61, 135.30, 135.56, 142.05, 150.75, 151.02, 153.60, 154.52, 156.10, 157.75, 164.05; ESI-MS *m/z*: 583.2 $[M + H]^+$, 581.2 $[M - H]^-$, 617.2 $[M + Cl]^-$; Anal. calcd for $C_{32}H_{34}N_6O_3S \cdot H_2O$ (%): C, 63.98; H, 6.04; N, 13.99. Found: C, 64.04; H, 6.12; N, 13.80.

*5.1.12.11. N-(2,6-dimethylphenyl)-2-(6-methoxy-7-(3-morpholinopropoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**2e**).* Light yellow solid, yield: 28%. Mp: 147–148 °C. IR (KBr, cm^{-1}): 3265.44, 2954.46, 2850.18, 2805.34, 1617.79, 1594.60, 1575.45, 1499.20, 1480.51, 1456.06, 1424.15, 1370.30, 1327.95, 1282.15, 1232.74, 1205.06, 1184.52, 1139.97, 1115.22, 841.99, 745.91; ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 1.97–2.02 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.17 (s, 6H, 2 × Ar–CH_3), 2.39–2.51 (m, 6H, 3 × $CH_2\underline{N}$), 3.59 (t, $J = 4.6$ Hz, 4H, 2 × morpholine-CH_2), 3.83 (s, 3H, OCH_3), 4.31 (t, $J = 6.3$ Hz, 2H, CH_2O), 6.66 (d, $J = 8.4$ Hz, 1H, Ar–H), 7.11 (s, 4H, Ar–H), 7.54 (s, 1H, Ar–H), 7.78 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.5$ Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.67 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 17.93, 25.43, 53.29, 54.56, 56.00, 66.15, 67.38, 101.97, 107.16, 110.27, 117.46, 121.50, 123.76, 125.97, 126.51, 127.60, 128.60, 135.27, 135.52, 142.00, 150.72, 151.01, 153.54, 154.50, 156.08, 157.70, 164.01; ESI-MS *m/z*: 599.2 $[M + H]^+$, 597.2 $[M - H]^-$, 633.2 $[M + Cl]^-$; Anal. calcd for $C_{32}H_{34}N_6O_4S \cdot 3/4H_2O$ (%): C, 62.78; H, 5.84; N, 13.73. Found: C, 62.89; H, 5.85; N, 13.70.

*5.1.12.12. N-(2,6-dimethylphenyl)-2-(6-methoxy-7-(3-(2-methylpiperidin-1-yl) propoxy)quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**2f**).* Light yellow solid, yield: 33%. Mp: 144–145 °C. IR (KBr, cm^{-1}): 3270.17, 2927.35, 1618.32, 1594.55, 1574.34, 1499.26, 1480.21, 1453.73, 1423.70, 1369.69, 1281.52, 1232.19, 1204.55, 838.79, 758.72; ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 0.99 (d, $J = 6.0$ Hz, 3H, piperidine-CH_3), 1.18–1.26 (m, 2H, piperidine-CH_2), 1.42–1.45 (m, 1H, piperidine-C*H*H), 1.52–1.59 (m, 3H, piperidine-CH*H* and piperidine-CH_2), 1.92–1.96 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.10 (t, $J = 9.7$ Hz, 1H, C*H*HN), 2.17 (s, 6H, 2 × Ar–CH_3), 2.27–2.28 (m, 1H, CHN), 2.37 (quint, $J = 9.7$ Hz, 1H, CH*H*N), 2.80–2.85 (m, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 4.29 (t, $J = 6.2$ Hz, 2H, CH_2O), 6.66 (d, $J = 8.4$ Hz, 1H, Ar–H), 7.10 (s, 4H, Ar–H), 7.53 (s, 1H, Ar–H), 7.77 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.5$ Hz, 1H, Ar–H), 8.17 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.19 (s, 1H, Ar–H), 9.67 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 17.93, 18.44, 23.37, 25.18, 25.73, 34.15, 49.41, 51.44, 55.22, 56.02, 67.47, 101.96, 107.11, 110.27, 117.44, 121.49, 123.75, 125.97, 126.51, 127.59, 128.60, 135.27, 135.52, 142.00, 150.74, 151.05, 153.52, 154.48, 156.13, 157.70, 164.01; ESI-MS *m/z*: 611.3 $[M + H]^+$, 609.3 $[M - H]^-$, 645.2 $[M + Cl]^-$; Anal. calcd for $C_{34}H_{38}N_6O_3S \cdot 3/4H_2O$ (%): C, 65.41; H, 6.38; N, 13.46. Found: C, 65.41; H, 6.42; N, 13.64.

*5.1.12.13. N-mesityl-2-(6-methoxy-7-(3-(4-methylpiperidin-1-yl)propoxy) quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**3a**).* Light yellow solid, yield: 26%. Mp: 127–128 °C. IR (KBr, cm^{-1}): 3266.65, 2946.86, 2919.54, 1617.76, 1595.37, 1575.74, 1499.56, 1454.19, 1424.25, 1369.46, 1281.93, 1233.01, 1205.71, 1184.13, 848.40, 749.11; ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 0.88 (d, $J = 6.4$ Hz, 3H, piperidine-CH_3), 1.13–1.18 (m, 2H, piperidine-CH_2), 1.31 (br, 1H, piperidine-CH), 1.57 (d, $J = 11.1$ Hz, 2H, piperidine-CH_2), 1.86–1.90 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 1.96–2.00 (m, 2H, CH_2N), 2.12 (s, 6H, 2 × Ar–CH_3), 2.25 (s, 3H, Ar–CH_3), 2.41–2.45 (m, 2H, CH_2N), 2.84 (d, $J = 11.1$ Hz, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 4.29 (t, $J = 6.3$ Hz, 2H, CH_2O), 6.65 (d, $J = 8.5$ Hz, 1H, Ar–H), 6.92 (s, 2H, Ar–H), 7.10 (s, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 7.76 (dd, $J_1 = 1.5$ Hz, $J_2 = 8.5$ Hz, 1H, Ar–H), 8.16 (s, 1H, Ar–H), 8.89 (s, 1H, –NH–), 9.19 (s, 1H, Ar–H), 9.58 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 125 MHz) δ (ppm): 17.85, 20.42, 21.72, 26.09, 30.31, 33.96, 53.39, 54.45, 55.99, 67.52, 101.96, 107.13, 110.24, 117.44, 121.46, 123.71, 125.95, 128.19, 128.69, 132.62, 135.17, 135.45, 141.94, 150.72, 151.02, 153.52, 154.49, 156.10, 157.69, 164.07; ESI-MS *m/z*: 625.3 $[M + H]^+$, 647.2 $[M + Na]^+$, 623.3 $[M - H]^-$, 659.2 $[M + Cl]^-$; Anal. calcd for $C_{35}H_{40}N_6O_3S \cdot 3/4H_2O$ (%): C, 65.86; H, 6.55; N, 13.17; Found: C, 65.89; H, 6.81; N, 12.96.

*5.1.12.14. N-mesityl-2-(6-methoxy-7-(3-(piperidin-1-yl)propoxy)quinazolin-4- ylamino)benzo[d]thiazole-6-carboxamide (**3b**).* Light yellow solid, yield: 31%. Mp: 134–135 °C. IR (KBr, cm^{-1}): 3261.18, 2932.59, 2852.74, 1616.29, 1566.24, 1499.02, 1453.76, 1423.86, 1369.78, 1311.46, 1266.71, 1232.84, 1205.44, 1139.45, 1094.76, 1035.89, 943.55, 882.79, 847.38, 786.30, 759.16, 710.18, 648.45, 563.52; ^{1}H NMR (DMSO-d_6, 500 MHz) δ (ppm): 1.38–1.40 (m, 2H, piperidine-CH_2), 1.49–1.53 (m, 4H, 2 × piperidine-CH_2), 1.93–2.00 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.12 (s, 6H, 2 × Ar–CH_3), 2.25 (s, 3H, Ar–CH_3), 2.35–2.49 (m, 6H, 3 × CH_2N), 3.83 (s, 3H, OCH_3), 4.29 (t, $J = 6.3$ Hz, 2H, CH_2O), 6.65 (d, $J = 8.4$ Hz, 1H, Ar–H), 6.91 (s, 2H, Ar–H), 7.10 (s, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 7.76 (dd, $J_1 = 1.4$ Hz, $J_2 = 8.5$ Hz, 1H, Ar–H), 8.17 (s, 1H, Ar–H), 8.89 (s, 1H, –NH–), 9.19 (s, 1H, Ar–H), 9.58 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 17.91, 20.48, 24.07, 25.55, 25.86, 54.06, 54.87, 56.03, 67.55, 101.96, 107.16, 110.30, 117.49, 121.54, 123.77, 126.00, 128.26, 128.70, 132.66, 135.21, 135.51, 141.99, 150.78, 151.04, 153.59, 154.52, 156.12, 157.75, 164.11; ESI-MS *m/z*: 611.3 $[M + H]^+$, 609.2 $[M - H]^-$, 645.2 $[M + Cl]^-$; Anal. calcd for $C_{34}H_{38}N_6O_3S \cdot H_2O$ (%): C, 64.94; H, 6.41; N, 13.37; found: C, 65.06; H, 6.53; N, 13.24.

*5.1.12.15. 2-(7-(3-(Diethylamino)propoxy)-6-methoxyquinazolin-4-ylamino)-N-mesitylbenzo[d]thiazole-6-carboxamide (**3c**).* Light yellow solid, yield: 33%. Mp: 131–132 °C. IR (KBr, cm^{-1}): 3263.35, 2965.89, 1616.77, 1595.15, 1575.24, 1499.13, 1454.13, 1423.49, 1369.35, 1327.75, 1311.47, 1282.31, 1232.41, 1203.79, 1138.17, 847.56, 758.72; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 0.93–0.99 (m, 6H, 2 × $\underline{CH_3}CH_2N$), 1.88–1.99 (m, 2H, –CH_2–$\underline{CH_2}$–CH_2–), 2.12 (s, 6H, 2 × Ar–CH_3), 2.25 (s, 3H, Ar–CH_3), 2.43–2.59 (m, 6H, 3 × CH_2N), 3.83 (s, 3H, OCH_3), 4.30 (t, $J = 6.3$ Hz, 2H, CH_2O), 6.66 (d, $J = 8.5$ Hz, 1H, Ar–H), 6.93 (s, 2H, Ar–H), 7.10 (s, 1H, Ar–H), 7.52 (s, 1H, Ar–H), 7.77 (dd, $J_1 = 1.7$ Hz, $J_2 = 8.5$ Hz, 1H, Ar–H), 8.17 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.59 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 11.80, 17.91, 20.47, 26.19, 46.43, 48.39, 56.03, 67.34, 101.95, 107.07, 110.31, 117.48, 121.52, 123.76, 125.99,

128.24, 128.69, 132.66, 135.21, 135.50, 141.99, 150.76, 151.05, 153.57, 154.51, 156.16, 157.75, 164.10; ESI-MS *m/z*: 599.3 $[M + H]^+$, 597.3 $[M - H]^-$, 633.2 $[M + Cl]^-$; Anal. calcd for $C_{33}H_{38}N_6O_3S \cdot 3/4H_2O$ (%): C, 64.74; H, 6.50; N, 13.73; found: C, 64.92; H, 6.63; N, 13.65.

*5.1.12.16. N-mesityl-2-(6-methoxy-7-(3-(pyrrolidin-1-yl)propoxy)quinazolin-4- ylamino)benzo[d]thiazole-6-carboxamide (**3d**).* Light yellow solid, yield: 30%. Mp: 147–148 °C. IR (KBr, cm^{-1}): 3260.63, 2957.78, 2792.53, 1617.32, 1595.18, 1575,70, 1498.99, 1454.15, 1423.52, 1369.80, 1328.01, 1311.59, 1282.23, 1232.52, 1204.70, 1137.28, 1093.72, 1035.95, 847.73, 758.47; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.68–1.70 (m, 4H, 2 × pyrolidine-CH_2), 1.97–2.04 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.12 (s, 6H, 2 × Ar–$CH_3$), 2.25 (s, 3H, Ar–$CH_3$), 2.44–2.60 (m, 6H, 3 × CH_2N), 3.83 (s, 3H, OCH_3), 4.31 (t, J = 6.3 Hz, 2H, CH_2O), 6.65 (d, J = 8.5 Hz, 1H, Ar–H), 6.92 (s, 2H, Ar–H), 7.10 (s, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 7.76 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.17 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.19 (s, 1H, Ar–H), 9.60 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 17.92, 20.48, 23.10, 27.78, 52.01, 53.57, 56.03, 67.46, 101.96, 107.16, 110.30, 117.49, 121.53, 123.77, 126.00, 128.25, 128.70, 132.66, 135.21, 135.51, 141.99, 150.75, 151.02, 153.59, 154.52, 156.12, 157.74, 164.11; ESI-MS m/z: 597.3 $[M + H]^+$, 595.3 $[M - H]^-$, 631.2 $[M + Cl]^-$; Anal. calcd for $C_{33}H_{36}N_6O_3S \cdot H_2O$ (%): C, 64.47; H, 6.23; N, 13.67; found: C, 64.48; H, 6.20; N, 13.68.

*5.1.12.17. N-mesityl-2-(6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-ylamino)benzo[d]thiazole-6-carboxamide (**3e**).* Light yellow solid, yield: 29%. Mp: 151–152 °C. IR (KBr, cm^{-1}): 3256.94, 2959.07, 2853.38, 1616.56, 1595.05, 1575.38, 1498.83, 1455.15, 1423.51, 1369.94, 1310.97, 1282.06, 1232.60, 1204.71, 1139.14, 1115.08, 848.01, 749.11; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 1.95–2.03 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.12 (s, 6H, 2 × Ar–$CH_3$), 2.25 (s, 3H, Ar–$CH_3$), 2.37–2.51 (m, 6H, 3 × CH_2N), 3.59 (t, J = 4.5 Hz, 4H, 2 × morpholine-CH_2), 3.83 (s, 3H, OCH_3), 4.31 (t, J = 6.3 Hz, 2H, CH_2O), 6.65 (d, J = 8.5 Hz, 1H, Ar–H), 6.92 (s, 2H, Ar–H), 7.10 (s, 2H, Ar–H), 7.54 (s, 1H, Ar–H), 7.76 (dd, J_1 = 1.6 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.17 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.20 (s, 1H, Ar–H), 9.59 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 17.91, 20.48, 25.47, 53.32, 54.60, 56.02, 66.18, 67.40, 101.97, 107.17, 110.30, 117.50, 121.52, 123.76, 125.99, 128.24, 128.69, 132.65, 135.21, 135.50, 141.98, 150.74, 151.01, 153.58, 154.52, 156.09, 157.74, 164.10; ESI-MS *m/z*: 613.2 $[M + H]^+$, 635.2 $[M + Na]^+$, 611.2 $[M - H]^-$, 647.2 $[M + Cl]^-$; Anal. calcd for $C_{33}H_{36}N_6O_4S \cdot 1/8H_2O$ (%): C, 64.45; H, 5.94; N, 13.67; found: C, 64.37; H, 5.99; N, 13.48.

*5.1.12.18. N-mesityl-2-(6-methoxy-7-(3-(2-methylpiperidin-1-yl) propoxy)quinazolin- 4-ylamino)benzo[d]thiazole-6-carboxamide (**3f**).* Light yellow solid, yield: 31%. Mp: 143–145 °C. IR (KBr, cm^{-1}): 3256.94, 2927.72, 2843.77, 1617.82, 1595.47, 1576.53, 1498.91, 1423.60, 1369.70, 1327.69, 1311.62, 1281.69, 1232.69, 1204.68, 1183.90, 1138.09, 848.26, 758.72; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 0.99 (d, J = 6.0 Hz, 3H, piperidine-CH_3), 1.15–1.26 (m, 2H, piperidine-CH_2), 1.42–1.60 (m, 4H, 2 × piperidine-CH_2), 1.88–1.97 (m, 2H, $-CH_2-\underline{CH_2}-CH_2-$), 2.07–2.12 (m, 7H, C*H*HN and 2 × Ar–CH_3), 2.25–2.27(m, 4H, Ar–CH_3 and CHN), 2.36 (q, J = 9.6 Hz, 1H, CH*H*N), 2.79–2.88 (m, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 4.28 (t, J = 6.2 Hz, 2H, CH_2O), 6.65 (d, J = 8.5 Hz, 1H, Ar–H), 6.92 (s, 2H, Ar–H), 7.10 (s, 1H, Ar–H), 7.53 (s, 1H, Ar–H), 7.76 (dd, J_1 = 1.7 Hz, J_2 = 8.5 Hz, 1H, Ar–H), 8.16 (s, 1H, Ar–H), 8.90 (s, 1H, –NH–), 9.19 (s, 1H, Ar–H), 9.59 (s, 1H, –NH–CO–); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 17.90, 18.52, 20.47, 23.43, 25.15, 25.77, 34.20, 49.44, 51.49, 55.26, 56.04, 67.49, 101.96, 107.12, 110.30, 117.48, 121.51, 123.76, 125.99, 128.24, 128.68, 132.65, 135.20, 135.50, 141.99, 150.76, 151.05, 153.57, 154.51, 156.14, 157.74, 164.10; ESI-MS *m/z*: 625.3 $[M + H]^+$, 623.3 $[M - H]^-$, 659.2 $[M + Cl]^-$; Anal. calcd for $C_{35}H_{40}N_6O_3S \cdot 1/8H_2O$ (%): C, 67.04; H, 6.47; N, 13.40; found: C, 67.04; H, 6.60; N, 13.26.

5.2. Biological evaluation

5.2.1. In vitro cytotoxic activity against 6 human cancer cell lines

All of the target compounds were determined against human colon cancer cell lines (HCT-116 and DLD1), human chronic myeloid leukemia cell line (K562), human acute monocytic myeloid leukemia cell line (U937) and human lung cancer cell lines (A549 and NCI-H661). 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 [55]. Briefly, the tumor 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% CO_2 for 4 h. The test compound was then added, and the cells were incubated at 37 °C with 5% CO_2 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.

5.2.2. In vitro kinase assays

In vitro kinase inhibitory ability was determined using the HTScan EGFR Kinase Assay Kit (Cell Signaling Technology), Recombinant human Src Kinase Assay Kit (Upstate Biotechnology) and Recombinant human Abl Kinase Assay Kit (Upstate Biotechnology), following the manufacturer's instructions.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.03.013.

References

[1] A. Quintas-Cardama, J. Cortes, Molecular biology of bcr-abl1-positive chronic myeloid leukemia, Blood 113 (2009) 1619–1630.
[2] P.C. Nowell, D.A. Hungerford, Minute chromosome in human chronic Granulocytic leukemia, Science 132 (1960) 1497, 1497.
[3] J.D. Rowley, Letter: a new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining, Nature 243 (1973) 290–293.
[4] J. Groffen, J.R. Stephenson, N. Heisterkamp, A. Deklein, C.R. Bartram, G. Grosveld, Philadelphia chromosomal breakpoints are clustered within a limited region, Bcr, on chromosome-22, Cell 36 (1984) 93–99.
[5] F. Palandri, L. Lacobucci, F. Castagnetti, N. Testoni, A. Poerio, M. Amabile, M. Breccia, T. Intermesoli, F. Luliano, G. Rege-Cambrin, M. Tiribelli, M. Miglino, F. Pane, G. Saglio, G. Martinelli, G. Rosti, M. Baccarani, CML, front-line treatment of Philadelphia positive chronic myeloid leukemia with imatinib and interferon-alpha: 5-year outcome, Haematol-Hematol J. 93 (2008) 770–774.
[6] T. Schindler, W. Bornmann, P. Pellicena, W.T. Miller, B. Clarkson, J. Kuriyan, Structural mechanism for STI-571 inhibition of Abelson tyrosine kinase, Science 289 (2000) 1938–1942.
[7] B.J. Druker, C.L. Sawyers, H. Kantarjian, D.J. Resta, S.F. Reese, J.M. Ford, R. Capdeville, M. Talpaz, Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the philadelphia chromosome, New Engl. J. Med. 344 (2001) 1038–1042.
[8] B.J. Druker, F. Guilhot, S.G. O'Brien, I. Gathmann, H. Kantarjian, N. Gattermann, M.W.N. Deininger, R.T. Silver, J.M. Goldman, R.M. Stone, F. Cervantes, A. Hochhaus, B.L. Powell, J.L. Gabrilove, P. Rousselot, J. Reiffers, J.J. Cornelissen, T. Hughes, H. Agis, T. Fischer, G. Verhoef, J. Shepherd, G. Saglio, A. Gratwohl,

J.L. Nielsen, J.P. Radich, B. Simonsson, K. Taylor, M. Baccarani, C. So, L. Letvak, R.A. Larson, Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia, New Engl. J. Med. 355 (2006) 2408–2417.
[9] N.P. Shah, C. Tran, F.Y. Lee, P. Chen, D. Norris, C.L. Sawyers, Overriding imatinib resistance with a novel ABL kinase inhibitor, Science 305 (2004) 399–401.
[10] A. Quintas-Cardama, J. Cortes, Therapeutic options against BCR-ABL1 T315I-positive chronic myelogenous leukemia, Clin. Cancer Res. 14 (2008) 4392–4399.
[11] F. Lee, A. Fandi, M. Voi, Overcoming kinase resistance in chronic myeloid leukemia, Int. J. Biochem. Cell. B 40 (2008) 334–343.
[12] G. Noronha, J.G. Cao, C.P. Chow, E. Dneprovskaia, R.M. Fine, J. Hood, X.S. Kang, B. Klebansky, D. Lohse, C.C. Mak, A. McPherson, M.S.S. Palanki, V.P. Pathak, J. Renick, R. Soll, B.Q. Zeng, Inhibitors of ABL and the ABL-T315I mutation, Curr. Top. Med. Chem. 8 (2008) 905–921.
[13] C. Sawyers, Targeted cancer therapy, Nature 432 (2004) 294–297.
[14] A. Petrelli, S. Giordano, From single- to multi-target drugs in cancer therapy: when aspecificity becomes an advantage, Curr. Med. Chem. 15 (2008) 422–432.
[15] Z.A. Knight, H. Lin, K.M. Shokat, Targeting the cancer kinome through polypharmacology, Nat. Rev. Cancer 10 (2010) 130–137.
[16] F.X. Mahon, S. Hayette, V. Lagarde, F. Belloc, B. Turcq, F. Nicolini, C. Belanger, P.W. Manley, C. Leroy, G. Etienne, S. Roche, J.M. Pasquet, Evidence that resistance to Nilotinib may Be due to BCR-ABL, Pgp, or Src kinase overexpression, Cancer Res. 68 (2008) 9809–9816.
[17] S. Schenone, F. Manetti, M. Botta, Last findings on dual inhibitors of abl and SRC tyrosine-kinases, Mini Rev. Med. Chem. 7 (2007) 191–201.
[18] H.M. Kantarjian, F. Giles, A. Quintas-Cardama, J. Cortes, Important therapeutic targets in chronic myelogenous leukemia, Clin. Cancer Res. 13 (2007) 1089–1097.
[19] Y.G. Hu, Y.H. Liu, S. Pelletier, E. Buchdunger, M. Warmuth, D. Fabbro, M. Hallek, R.A. Van Etten, S.G. Li, Requirement of Src kinases Lyn, Hck and Fgr for BCR-ABL1-induced B-lymphoblastic leukemia but not chronic myeloid leukemia, Nat. Genet. 36 (2004) 453–461.
[20] S.I. Park, A.N. Shah, J. Zhang, G.E. Gallick, Regulation of angiogenesis and vascular permeability by Src family kinases: opportunities for therapeutic treatment of solid tumors, Expert Opin. Ther. Targets 11 (2007) 1207–1217.
[21] J.M. Summy, G.E. Gallick, Treatment for advanced tumors: Src reclaims center stage, Clin. Cancer Res. 12 (2006) 1398–1401.
[22] T. Chen, J.A. George, C.C. Taylor, Src tyrosine kinase as a chemotherapeutic target: is there a clinical case? Anticancer Drugs 17 (2006) 123–131.
[23] R.H. Alvarez, H.M. Kantarjian, J.E. Cortes, The role of Src in solid and hematologic malignancies - development of new-generation Src inhibitors, Cancer 107 (2006) 1918–1929.
[24] A.Y. Tsygankov, S.K. Shore, Src: regulation, role in human carcinogenesis and pharmacological inhibitors, Curr. Pharm. Des. 10 (2004) 1745–1756.
[25] T.J. Yeatman, A renaissance for SRC, Nat. Rev. Cancer 4 (2004) 470–480.
[26] S. Danhauser-Riedl, M. Warmuth, B.J. Druker, B. Emmerich, M. Hallek, Activation of Src kinases p53/56lyn and p59hck by p210bcr/abl in myeloid cells, Cancer Res. 56 (1996) 3589–3596.
[27] M. Warmuth, R. Damoiseaux, Y. Liu, D. Fabbro, N. Gray, SRC family kinases: potential targets for the treatment of human cancer and leukemia, Curr. Pharm. Des. 9 (2003) 2043–2059.
[28] S.G. Li, Src-family kinases in the development and therapy of Philadelphia chromosome-positive chronic myeloid leukemia and acute lymphoblastic leukemia, Leuk. Lymphoma. 49 (2008) 19–26.
[29] J.S. Tokarski, J.A. Newitt, C.Y.J. Chang, J.D. Cheng, M. Wittekind, S.E. Kiefer, K. Kish, F.Y.F. Lee, R. Borzillerri, L.J. Lombardo, D.L. Xie, Y.Q. Zhang, H.E. Klei, The structure of dasatinib (BMS-354825) bound to activated ABL kinase domain elucidates its inhibitory activity against imatinib-resistant ABL mutants, Cancer Res. 66 (2006) 5790–5797.
[30] T. Tauchi, K. Ohyashiki, The second generation of BCR-ABL tyrosine kinase inhibitors, Int. J. Hematol. 83 (2006) 294–300.
[31] J. Cortes, Overcoming drug resistance in chronic myeloid leukemia, Curr. Opin. Hematol. 13 (2006) 79–86.
[32] M.H. Cohen, G.A. Williams, R. Sridhara, G. Chen, R. Pazdur, FDA drug approval summary: Gefitinib (ZD1839) (Iressa (R)) tablets, Oncologist 8 (2003) 303–306.
[33] M.H. Cohen, J.R. Johnson, Y.F. Chen, R. Sridhara, R. Pazdur, FDA drug approval summary: Erlotinib (Tarceva (R)) tablets, Oncologist 10 (2005) 461–466.
[34] M.G. Kris, R.B. Natale, R.S. Herbst, T.J. Lynch Jr., D. Prager, C.P. Belani, J.H. Schiller, K. Kelly, H. Spiridonidis, A. Sandler, K.S. Albain, D. Cella, M.K. Wolf, S.D. Averbuch, J.J. Ochs, A.C. Kay, Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial, JAMA 290 (2003) 2149–2158.
[35] M. Sun, Y. Zheng, H. Wei, J. Chen, M. Ji, QSAR studies on 4-anilino-3-quinolinecarbonitriles as Src kinase inhibitors using robust PCA and both linear and nonlinear models, J. Enzym. Inhib. Med. Chem. 24 (2009) 1109–1116.
[36] J. Cai, S.N. Zhang, M. Zheng, X.Q. Wu, J.Q. Chen, M. Ji, Design, synthesis, and in vitro antiproliferative activity of novel Dasatinib derivatives, Bioorg. Med. Chem. Lett. 22 (2012) 806–810.
[37] X.Q. Wu, M.D. Li, Y. Qu, W.H. Tang, Y.G. Zheng, J.Q. Lian, M. Ji, L. Xu, Design and synthesis of novel Gefitinib analogues with improved anti-tumor activity, Bioorgan Med. Chem. 18 (2010) 3812–3822.
[38] J. Das, R.V. Moquin, J. Lin, C.J. Liu, A.M. Doweyko, H.F. DeFex, Q. Fang, S.H. Pang, S. Pitt, D.R. Shen, G.L. Schieven, J.C. Barrish, J. Wityak, Discovery of 2-amino-heteroaryl-benzothiazole-6-anilides as potent p56(lck) inhibitors, Bioorg. Med. Chem. Lett. 13 (2003) 2587–2590.
[39] C. Ping, D. Norris, J. Das, S.H. Spergel, J. Wityak, L. Leith, R.L. Zhao, B.C. Chen, S. Pitt, S.H. Pang, R.S. Ding, R. Zhang, H.F. De Fex, A.M. Doweyko, K.W. McIntyre, D.J. Shuster, K. Behnia, G.L. Schieven, J.C. Barrish, Discovery of novel 2-(aminoheteroaryl)-thiazole-5-carboxamides as potent and orally active Src-family kinase p56(Lck) inhibitors, Bioorg. Med. Chem. Lett. 14 (2004) 6061–6066.
[40] J. Das, P. Chen, D. Norris, R. Padmanabha, J. Lin, R.V. Moquin, Z.Q. Shen, L.S. Cook, A.M. Doweyko, S. Pitt, S.H. Pang, D.R. Shen, Q. Fang, H.F. de Fex, K.W. McIntyre, D.J. Shuster, K.M. Gillooly, K. Behnia, G.L. Schieven, J. Wityak, J.C. Barrish, 2-aminothiazole as a novel kinase inhibitor template. Structure–activity relationship studies toward the discovery of N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl)]-2-methyl-4-pyrimidinyl]amino)]-1,3-thiazole-5-carboxamide (Dasatinib, BMS-354825) as a potent pan-Src kinase inhibitor, J. Med. Chem. 49 (2006) 6819–6832.
[41] Y.G. Zheng, X.Q. Wu, B. Xue, M.D. Li, M. Ji, Design, synthesis, docking and antitumor activity of Quinazolino [3, 4-a] thieno [3, 2-d] pyrimidin-8-one derivatives, Chem. Biol. Drug Des. 76 (2010) 285–290.
[42] P. Ballard, R.H. Bradbury, C.S. Harris, L.F.A. Hennequin, M. Hickinson, J.G. Kettle, J. Kendrew, T. Klinowska, D.J. Ogilvie, S.E. Pearson, E.J. Williams, I. Wilson, Inhibitors of epidermal growth factor receptor tyrosine kinase: optimisation of potency and in vivo pharmacokinetics, Bioorg. Med. Chem. Lett. 16 (2006) 4908–4912.
[43] Y.M. Zhang, S. Cockerill, S.B. Guntrip, D. Rusnak, K. Smith, D. Vanderwall, E. Wood, K. Lackey, Synthesis and SAR of potent EGFR/erbB2 dual inhibitors, Bioorg. Med. Chem. Lett. 14 (2004) 111–114.
[44] J.B. Smaill, G.W. Rewcastle, J.A. Loo, K.D. Greis, O.H. Chan, E.L. Reyner, E. Lipka, H.D.H. Showalter, P.W. Vincent, W.L. Elliott, W.A. Denny, Tyrosine kinase inhibitors. 17. Irreversible inhibitors of the epidermal growth factor receptor: 4-(phenylamino)quinazoline- and 4-(phenylamino)pyrido[3,2-d]pyrimidine-6-acrylamides bearing additional solubilizing functions, J. Med. Chem. 43 (2000) 1380–1397.
[45] V. Bellavita, L. Santamaria, New derivatives of benzothiazole. I. Synthesis, Boll Soc. Ital. Biol. Sper. 27 (1951) 296–297.
[46] J. Das, J. Lin, R.V. Moquin, Z.Q. Shen, S.H. Spergel, J. Wityak, A.M. Doweyko, H.F. DeFex, Q. Fang, S.H. Pang, S. Pitt, D.R. Shen, G.L. Schieven, J.C. Barrish, Molecular design, synthesis, and structure-activity relationships leading to the potent and selective P56(lck) inhibitor BMS-243117, Bioorg. Med. Chem. Lett. 13 (2003) 2145–2149.
[47] S. Nishino, K. Hirotsu, H. Shima, T. Harada, H. Oda, T. Takahashi, S. Suzuki, Preparation of quinazolin-4-one derivative useful as pharmaceutical and agrochemical intermediates comprises reacting anthranilic acid derivative with formic acid derivative in presence of ammonium carboxylate, WO2003064399-A (2003).
[48] P. Knesl, D. Roseling, U. Jordis, Improved synthesis of substituted 6,7-dihydroxy-4-quinazolineamines: tandutinib, erlotinib and gefitinib, Molecules 11 (2006) 286–297.
[49] M. Ji, M. Sun, X. Wu, New 2-(4-aminoquinazolinyl)benzo(d)thiazole derivative used for inhibiting effect on multiplication of tumor cells, preferably for treating colon cancer, CN101701018-A, 2010.
[50] N.C. Moore, K. Oldham, Use of quinazoline derivatives in the manufacture of a medicament for the prevention or treatment of T cell mediated diseases or medical conditions such as autoimmune diseases, WO2003045943-A, 2003.
[51] A. Telliez, M. Desroses, N. Pommery, O. Briand, A. Farce, G. Laconcle, A. Lemoine, P. Depreux, J.P. Henichart, Derivatives of iressa, a specific epidermal growth factor receptor inhibitor, are powerful apoptosis inducers in PC3 prostatic cancer cells, ChemMedChem 2 (2007) 318–332.
[52] P. Ple, F.H. Jung, P.P.J.F. Henri, New quinazoline derivatives are platelet-derived growth factor inhibitors useful to treat cell proliferative disorders and disease states associated with angiogenesis and/or vascular permeability, e.g. neoplastic disorder, WO2006040520-A1, 2006.
[53] S. Tasler, O. Muller, T. Wieber, T. Herz, S. Pegoraro, W. Saeb, M. Lang, R. Krauss, F. Totzke, U. Zirrgiebel, J.E. Ehlert, M.H.G. Kubbutat, C. Schachtele, Substituted 2-arylbenzothiazoles as kinase inhibitors: hit-to-lead optimization, Bioorgan Med. Chem. 17 (2009) 6728–6737.
[54] P.A. Ple, T.P. Green, L.F. Hennequin, J. Curwen, M. Fennell, J. Allen, C. Lambert-van der Brempt, G. Costello, Discovery of a new class of anilinoquinazoline inhibitors with high affinity and specificity for the tyrosine kinase domain of c-Src, J. Med. Chem. 47 (2004) 871–887.
[55] M.V. Berridge, P.M. Herst, A.S. Tan, Tetrazolium dyes as tools in cell biology: new insights into their cellular reduction, Biotechnol. Ann. Rev. 11 (2005) 127–152.