European Journal of Medicinal Chemistry 55 (2012) 39–48

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

Novel oxazolo[4,5-g]quinazolin-2(1H)-ones: Dual inhibitors of EGFR and Src protein tyrosine kinases

Jinsheng Lin, Wei Shen, Jingwei Xue, Juan Sun, Xue Zhang, Can Zhang*

Center of Drug Discovery, State Key Laboratory of Natural Medicines, China Pharmaceutical University, No. 24 Tongjia Xiang, Gulou District, Nanjing 210009, PR China

ARTICLE INFO

Article history:
Received 8 May 2012
Received in revised form
25 June 2012
Accepted 27 June 2012
Available online 7 July 2012

Keywords:
Protein tyrosine kinases (PTK)
Anti-tumor agents
EGFR inhibitor
Src inhibitor
Oxazolo[4,5-g]quinazolin-2(1H)-one scaffold

ABSTRACT

Quinazoline-containing derivatives are an important class of synthetic products and represent an attractive scaffold for EGFR inhibitors. A series of oxazolo[4,5-g]quinazolin-2(1H)-one derivatives were synthesized and the EGFR and Src inhibition activities were evaluated using Gefitinib as lead compound. The three most potent compounds **5y**, **5l** and **5a** each inhibited EGFR at the IC_{50} value of 61 nM, 67 nM and 78 nM. Among them, **5c** also demonstrated excellent inhibition activity against Src with the IC_{50} value of 3.1 μM. Several of these derivatives also showed good anti-proliferation effects against KB and A498 cells.

1. Introduction

Human tumors overexpress growth factor receptor tyrosine kinase enzymes of the erbB family, and this overexpression is associated with poor prognosis of the disease [1–3]. Inhibitors of growth factor signaling through these pathways, especially via erbB-1 (EGFR, HER-1) and erbB-2 (HER-2, neu), have thus been thought as potential anticancer drugs [4]. Overexpression of epidermal growth factor receptor (EGFR) plays a crucial role in mediating tumor cell growth of NSCLC and is observed as well as many other types of cancer, such as ovarian cancer, breast cancer, etc. [5–9].

There are two classes of inhibitors of EGFR: (i) monoclonal antibodies such as Cetuximab (IMC-C225) and Panitumumab (INN) which block binding of native EGF ligand to the receptor for treatment of metastatic colorectal cancer and head and neck cancer, (ii) small molecules that compete with ATP in the intracellular tyrosine kinase domain (TKD) and block activity which don't need to consider about endogenous ligand binding [10]. In recent years, the development of EGFR inhibitors focuses on ATP competitive inhibitors, and many small molecules including Gefitinib (Iressa, AstraZeneca, 1), Erlotinib (Tarceva, OSI Pharmaceuticals, 2) and Lapatinib (Tykerb, Glaxo-SmithKline, 3) etc. (Fig. 1) were approved [11–15]. These quinazoline-containing derivatives form an important class of synthetic products and represent an attractive scaffold for EGFR inhibitors. However, due to the recent findings of EGFR mutations which render the kinase resistant to Gefitinib and Erlotinib, there is an urgent need for new scaffolds to solve this tough problem [16]. A surprising dearth of chemically distinct small inhibitors is still existing despite years of intensive researches on EGFR inhibitors. Many studies have been targeted to find new structures containing 4-anilinoquinazolines as basic core which can overcome EGFR drug resistance mutations [17–19].

In order to search new promising anti-tumor agents which act similar to quinazoline-containing EGFR inhibitors, a series of 1-akyl-oxazolo[4,5-g]quinazolin-2(1H)-one derivatives were synthesized and evaluated for the EGFR inhibition activity applying Gefitinib as parent compounds. With the purpose of developing new scaffold, the 6 and 7-positon heteroatoms of quinazoline ring was condensed with carbonyl reagent to give tricyclic oxazolo[4,5-g]quinazolin-2(1H)-one on the basis of retaining the hydrophilic alkyl groups of the structure of Gefitinib. And then several different phenyl amines substituted the 8-substituted aromatic head fragment to further investigate the structure–activity relationship (SAR). Among these designed compounds, it is remarkably inspiring that the compound **5y** with new structure showed better

* Corresponding author. Tel./fax: +86 25 83271171.
E-mail addresses: zhangcan@cpu.edu.cn, zhangcancpu@yahoo.com.cn (C. Zhang).

0223-5234/$ – see front matter © 2012 Elsevier Masson SAS. All rights reserved.
http://dx.doi.org/10.1016/j.ejmech.2012.06.055

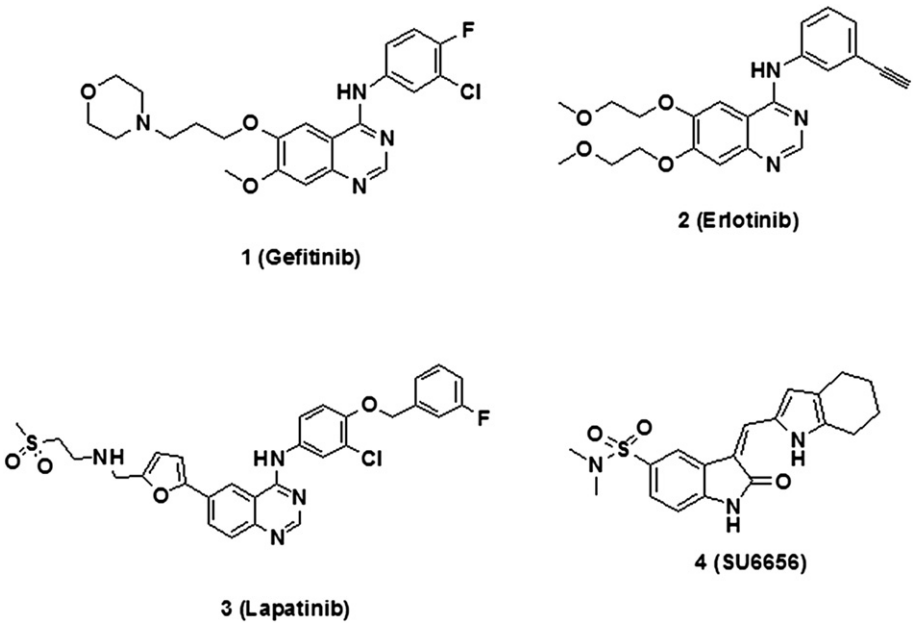


Fig. 1. The structures of Gefitinib, Erlotinib, Lapatinib and SU6656.

inhibition against EGFR compared with the parent compound (Fig. 2).

The Src inhibition activity of the designed compounds was also evaluated using SU6656 (**4**) as positive control. Several of them demonstrated moderate inhibition against Src, and among these compounds **5c** was the most potent compound for the inhibition of this kinase enzyme.

2. Results and discussion

2.1. Chemistry

The synthetic procedures were showed in Scheme 1 and Scheme 2. Nitration of compound 7 with concentrated HNO_3 gave the mixture of nitrobenzene 9 and its isomer compound 8, which were purified through column chromatography to obtain compound 9. Reduction of compound 9 with iron power in the mixture of MeOH and glacial acetic acid afforded amino benzene 10, which was further nucleophilically substituted with 1-(3-chloropropyl)morpholine in the presence of K_2CO_3 in refluxing of acetonitrile to give compound 11. Then the intramolecular condensation of compound 11 with formamidine acetate in EtOH at reflux produced oxazolo[4,5-g]quinazoline-2,8(1H,7H)-dione 12. Treatment of compound 12 with thionyl chloride using DMF as the catalyst at reflux yielded compound 13 and the final nucleophilic substitution with aniline furnish the target molecules.

2.2. Biological activities

2.2.1. In vitro inhibition activities studies of kinases

All the designed compounds were tested for effect on EGFR tyrosine kinase inhibition, as showed in Table 1. Many compounds bearing aromatic group at 8-position displayed potent inhibition activity against EGFR. Among them compounds **5a**, **5l** and **5y** inhibited EGFR at the IC_{50} values of 0.078, 0.067 and 0.061 μM respectively (summarized in Table 2). Many compounds without 8-subistituted phenyl groups showed poor EGFR inhibitory activity which further demonstrated that phenyl moiety was essential for

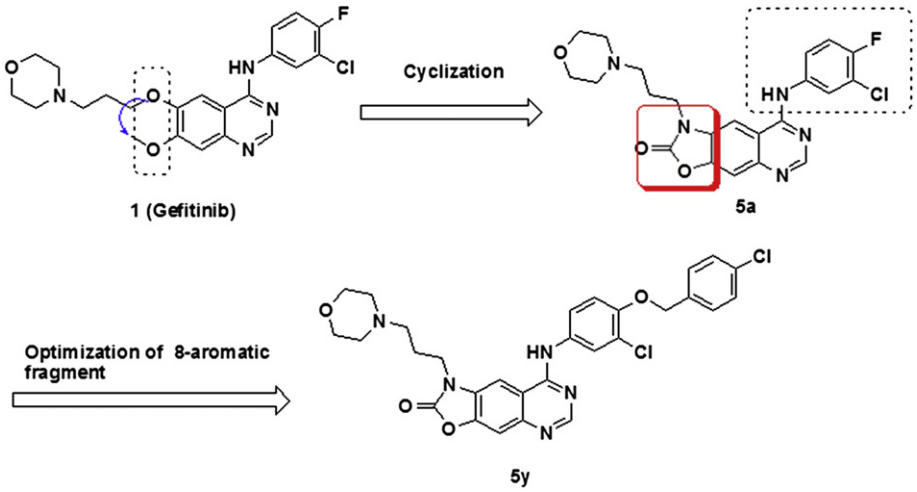
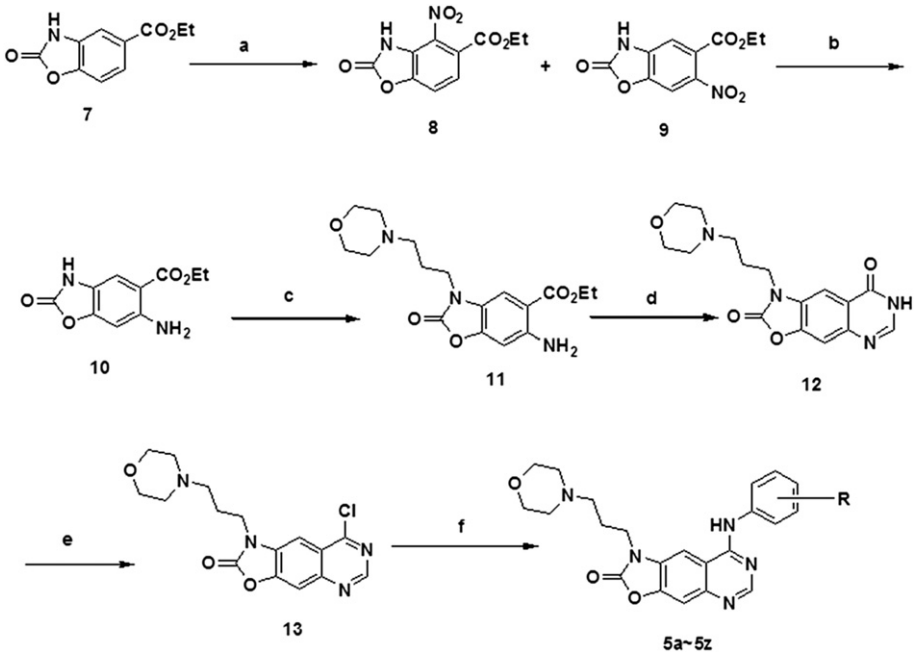


Fig. 2. The designed inhibitors of EGFR.



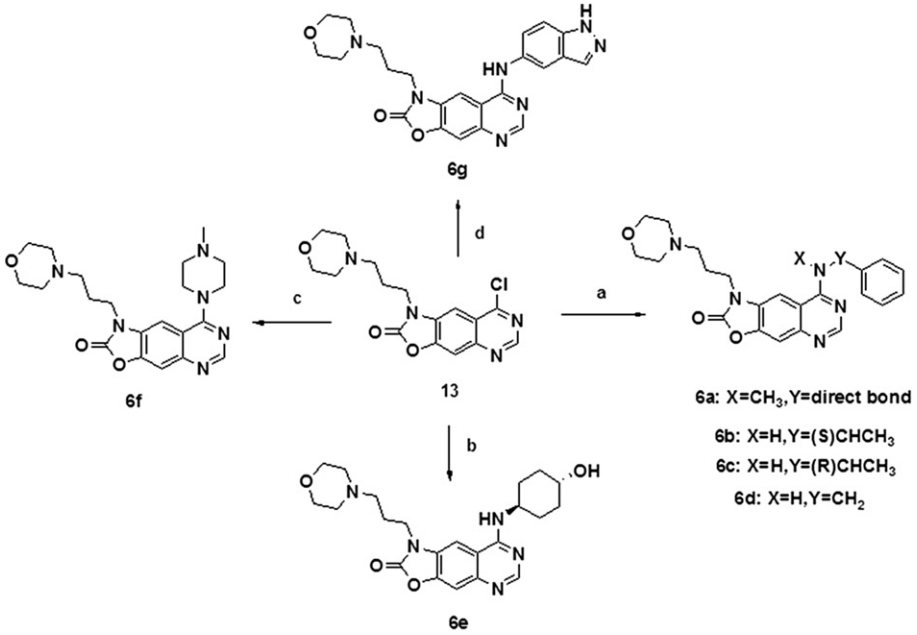
Scheme 1. Reagents and reaction conditions: (a) conc. HNO_3, 60 °C, 8 h; (b) reduced iron powder, acetic acid, MeOH, 65 °C, overnight; (c) 1-(3-chloropropyl)morpholine, acetonitrile, K_2CO_3, KI, reflux, 3 h; (d) formamidine acetate, ethanol, reflux, 24 h; (e) $SOCl_2$, DMF (cat.), reflux, 16 h; (f) aniline, i-PrOH, 60 °C to reflux, 6–24 h.

this kind of EGFR inhibitors. In comparing with other benzyl amino groups, aniline moieties directly conjugating to the 8-position increased EGFR inhibition activities, as illustrated by the more potent activities of compounds **5y**, **5l** than **6b**, **6c** and **6d**. Furthermore, although most of the designed compounds exhibited poor activities to Src, it is quite interesting to note that **5c** exhibited moderate activity to Src (IC_{50} = 3.1 μM) while the reference compound Gefitinib showed no activity (Table 3).

2.2.2. In vitro cell cytotoxicity assay

In vitro cell cytotoxicity of the 33 oxazolo[4,5-g]quinazolin-2(1H)-one derivatives was initially evaluated against KB and A498 cells by MTT assay using Gefitinib as a positive control. As shown in Table 4, some compounds exhibited good anti-proliferative activities with low μM IC_{50} values, among which compounds **5y** showed the best activities with IC_{50} values at 0.82 and 3.0 μM against KB and A498 cells, respectively. It is worthy to note that compounds **5c** only showed both moderate activities against EGFR and Src, but it exhibited promising anti-proliferative effects against KB and A498 cells.

Among the compounds synthesized, we found that replacement of the aromatic ring with other no-aromatic group at 8-position (**6e** and **6f**) resulted in significantly reduced biochemical potency against EGFR, Src, KB and A498 cells. Phenyl amines directly



Scheme 2. Reagents and reaction conditions: (a) aniline, i-PrOH, 60 °C to reflux, 10–18 h; (b) trans-4-aminocyclohexanol, i-PrOH, TEA, 50 °C, 24 h; (c) 1-methylpiperazine, i-PrOH, TEA, reflux, 12 h; (d) 1H-indazol-5-amine, i-PrOH, reflux, 13 h.

Table 1
Structures and in vitro EGFR inhibited activities of compounds with 8-subistituted phenyl groups.

Compd	R	EGFR[a] IC_{50}(μM)
5a	3-Cl-4-F	0.078
5b	3-Ethynyl	0.38
5c	4-Ethoxycarbonyl	5.8
5d	4-(SO_2NH_2)	Inactive[b]
5e	4-OCH_3	0.38
5f	3,4-Di-OCH_3	Inactive[b]
5g	4-(4-Cl-BnOCO)	Inactive[b]
5h	3,5-Di-CH_3	75
5i	3-Ethoxycarbonyl-6-OH	0.23
5j	4-OH	Inactive[b]
5k	4-OC_2H_5	1.4
5l	4-CH_3	0.067
5m	4-(4-Cl-BnO)	0.99
5n	4-Cl	Inactive[b]
5o	4-BnO	0.14
5p	2-CH_3	Inactive[b]
5q	2-OH	30
5r	3,4-Di-F	0.57
5s	3-Isopropoxyl	3.0
5t	3-Acetyl	6.8
5u	4-[(3-CH_3-4-OCH_2CF_3)–Pyr.-2-CH_2O]	7.8
5v	4-CH_3CONH	Inactive[b]
5w	3-[(3-CH_3-4-OCH_2CF_3)–Pyr.-2-CH_2O]	0.099
5x	4-(2-Pyr.CH_2O)	1.7
5y	3-Cl-4-(4-Cl-BnO)	0.061
5z	4-Tert-butyl	79
Gefitinib		0.072

[a] Data shown are from triplicate experiments.
[b] Inactive at >100 μM.

conjugating to the 8-position in comparing with other benzyl amines contributed more to the cytotoxicity and inhibition against kinases, as it was suggested by the results of compounds **5l**, **5y** and **6b**, **6c**, **6d**; whereas some compounds bearing other aromatic ring such as benzoheterocycle at the 8-position also showed obvious EGFR inhibition and cytotoxicity to KB and A498 cells, for example, compound **6g** was found to be active at 18.5 and 18.7 μM; and **6g** also showed high inhibition to EGFR with the IC_{50} value of 0.12 μM; introducing methyl group, halogen or alkoxyl group into the m- or p-position on the 8-postion aniline ring contributed to the increase of biochemical activity, while o-substitution resulted in a significant loss of potency (such as **5p** and **5q**). This probably arises from the augmentation of steric interactions between the o-substituent groups and the oxazolo[4,5-g]quinazolin-2(1H)-ones core which force the aniline ring to adopt a less optimal geometry in the binding pocket. The kinase inhibition activities and cytotoxicities would reduced or even disappear after adopting highly hydrophilic moiety such as sulphonylamino, acetyl and acetylamino group to 8-postion phenyl ring as the illustration of **5d**, **5t** and **5v**.

2.3. Molecular docking study

Docking study was carried out for the target compounds into EGFR using Discovery Studio version 2.5.5 and Glide version 7.3, Tripos Inc and Molegro virtual docker version 2007. The crystal

Table 2
In vitro EGFR inhibited activities of compounds with non-phenyl 8-subistituted amine groups.

Compd	EGFR[a] IC_{50} (μM)	Compd	EGFR[a] IC_{50} (μM)
6a	7.2	**6b**	3.7
6c	4.5	**6d**	65
6e	Inactive[b]	**6f**	Inactive[b]
6g	0.12	Gefitinib	0.072

[a] Data shown are from triplicate experiments.
[b] Inactive at >100 μM.

Table 3
In vitro Src inhibited activities of compounds with 8-subistituted phenyl groups.

Compd	Src[a] IC_{50} (μM)	Compd	Src[a] IC_{50} (μM)
5c	3.1	**5j**	66
5l	7.5		
Gefitinib	Inactive[b]	SU6656	0.073

[a] Data shown are from triplicate experiments.
[b] Inactive at >100 μM.

Table 4
Cellular anti-proliferative data for the selected compounds.

Compd	Cell inhibition IC_{50}[a] (μM)		Compd	Cell inhibition IC_{50}[a] (μM)	
	KB[b]	A498[c]		KB[b]	A498[c]
5a	6.5	32	**5c**	6.0	8.8
5i	8.1	15.7	**5m**	37.1	7.4
5o	37.6	14.8	**5w**	16.0	35.3
5y	0.82	3.0	**6g**	18.5	18.7
Gefitinib	2.8	8.6			

[a] IC_{50} values are reported as means of at least three determinations.
[b] KB cells is a cell line derived from a human carcinoma of the nasopharynx that overexpresses both EGFR and Src.
[c] A498 cells is a renal cell carcinoma (RCC) cell line that overexpresses both EGFR and Src.

structures of the enzyme with Lapatinib (ID: 1XKK) and Gefitinib (ID: 1M17) were obtained from protein data bank PDB.

Since it is found that Gefitinib mimic ATP and the ATP binding site is sandwiched between the lobes where ATP forms critical hydrogen bonding interactions to the hinge region, the binding of ATP itself involves two important hydrogen bonding interactions between the purine base of ATP and the kinase backbone between amino acids Gln767 and Met769 and the quinazoline ring of Gefitinib have two nitrogen atoms that act as hydrogen bond acceptors [20]. The kinase or catalytic domain consists of an N-terminal lobe, which consists mainly of β-strands but contains one α-helix and C helix. The C-terminal lobe is mainly α-helical, and a short strand termed the hinge region connects the two lobes.

Compound **5a** was initially docked to the EGFR active site cavity based on the structure of the Gefitinib DEP-in enzyme complex (EGFR; PDB ID: 1M17) and the resulting structure of the active site

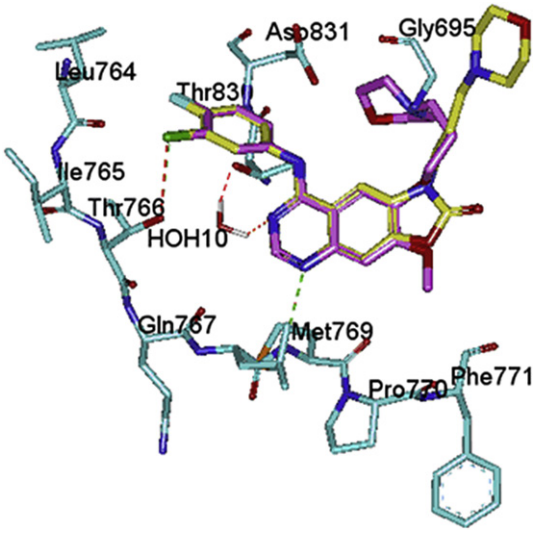


Fig. 3. Docking model of compounds' enzyme complex. Gefitinib (purple), **5a** (yellow) docked into the catalytic gorge of EGFR (PDB ID: 1M17). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was shown in Fig. 3. The most likely conformations of the ligand were selected based on the calculated docking score for the bonding strength.

It was found that **5a** forms hydrogen binding interactions in the hinge region between the N5 nitrogen and the backbone NH of Met769, N7 nitrogen and the side-chain OH of Thr 830 via a bridging water molecule which is similar to Gefitinib. But it was disappointed to find that **5y** was poorly docked into EGFR active conformation. As **5y** showed promising activity against EGFR, we hypothesized there may be exist another mechanism. So we docked **5y** into the inactive conformation of EGFR with the ligand of Lapatinib (PDB ID: 1XKK), and it was excited to see that **5y** fit well in the DEP-out form of the enzyme (Fig. 4).

These docking studies had revealed that the oxazolo[4,5-g]quinazolin-2(1H)-one ring binds to a narrow hydrophobic pocket in the N-terminal domain of EGFR where N5 of the quinazoline ring interacts with the backbone NH of Met 793 via a hydrogen bond, and similarly, a water molecule-mediated hydrogen bonding interaction was observed between the N7 of the quinazoline ring and the Thr 854 side chain, and it was glad to see that a water molecule-mediated hydrogen bonding interaction also was observed between carbonyl oxygen atom at C2 of the oxazolo[4,5-g]quinazolin-2(1H)-one core and the backbone NH of Cys 797. The aniline moiety lies in a deep hydrophobic pocket, which located at the same position of the 3′-chloro-4′-(3-fluorobenzyl)oxy moiety of Lapatinib. All of these demonstrated that compound **5y** worked similarly as Lapatinib (Fig. 5).

3. Conclusions

In summary, a series of new oxazolo[4,5-g]quinazolin-2(1H)-one derivatives were synthesized and subjected to pharmacological evaluation. The results showed that most of oxazolo[4,5-g]quinazolin-2(1H)-one derivatives possessed moderate to high EGFR inhibition activities. Protein tyrosine kinase inhibitions assay

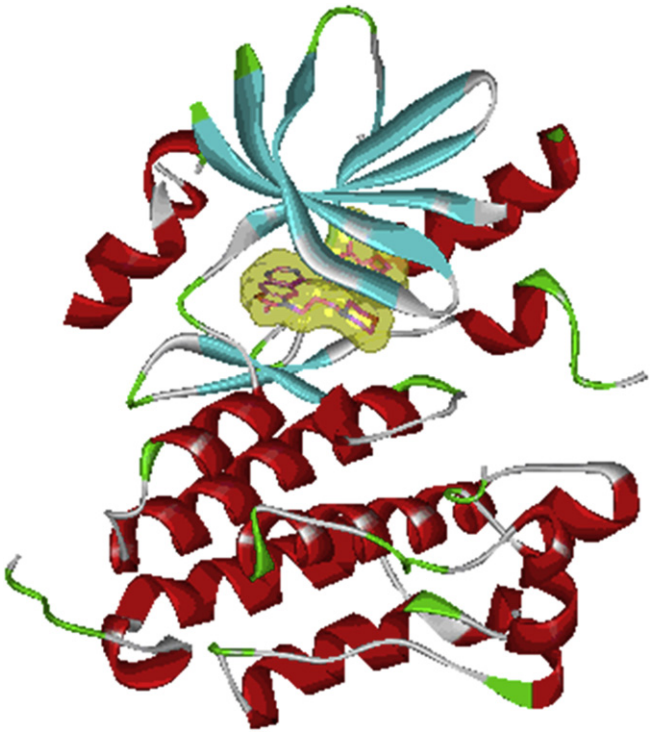


Fig. 4. Ribbon model of the X-ray of crystal structure of **5y** bond to the ATP binding domain of EGFR DEP-out conformation (PDB ID: 1XKK).

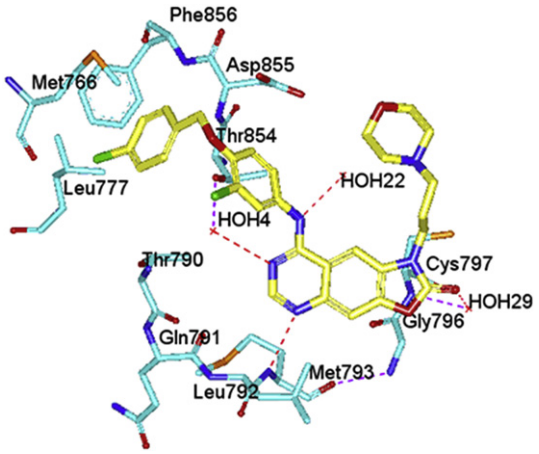


Fig. 5. Binding model of **5y** to ATP binding site of EGFR DEP-out conformation (PDB ID: 1XKK).

indicated that most of these derivatives were good inhibitors with a range of 2.2–6.4 μM, which inhibited EGF mediated phosphorylation of EGFR. Src inhibition activity of these compounds was also evaluated, but only two compounds showed moderate inhibition activity against it. These derivatives exhibited high potencies of anti-proliferation activities against KB and A498 cells, among them four tested compounds exhibited more potent inhibitive activities than the reference compounds Gefitinib. It is worthy to note that compound **5y** showed high inhibitory activities against EGFR with an IC_{50} value of 0.061 μM. These findings presented herein showed the potential of building oxazolo[4,5-g]quinazolin-2(1H)-one scaffold and adopting the hydrophilic side-chain 3-morpholinopropoxyl group at its 1-position for EGFR small molecule inhibitors.

4. Experimental sections

4.1. Chemistry: general procedures

All commercially available starting materials, reagents and solvents were used without further purification unless otherwise stated. Melting points were determined with an Electro thermal melting point apparatus, and are uncorrected. High-resolution mass spectra (HRMS) were recorded on QSTAR XL Hybrid MS/MS mass spectrometer. Infrared (IR) spectra were recorded on Thermo FTIR spectrometer (KBr disks). ^{1}H NMR and ^{13}C NMR spectra on a Bruker AV 300 or 500 MHz spectrometer were recorded in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in δ (ppm) units relative to the internal standard tetramethylsilane (TMS). The reaction conditions were not optimized for reaction yields. All oxygen-sensitive or moisture-sensitive reactions were run under nitrogen atmosphere. All the reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel G plates at 254 nm under a UV lamp using ethyl hexane/acetate or DCM/MeOH as eluent. Column chromatography separations were obtained on silica gel (200–300 mesh).

4.1.1. Ethyl 6-nitro-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carboxylate (**9**)

Compound **7** (103.5 g, 0.500 mol) was added portionwise to 500 ml conc. HNO_3 at the temperature of 0–5 °C. The mixture was heated to 60 °C and stirred for 8 h at this temperature, after the starting material was completely consumed. Then the solution was poured to 2.5 l cold water. The resulting precipitate was filtered and washed with chill water, dried, and the crude product was purified by silica gel column chromatography with petroleum ether/acetate

(4/1, v/v) as mobile phase to give compound 9 (88.3 g, yield, 70%) and the by-product compound 8 (34.0 g, yield, 27%) as a pale yellow solid. Compound 9: Mp: 162–164 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.60 (1H, bs), 8.16 (1H, s), 4.30 (2H, q, J = 6.9 Hz), 1.29 (3H, t, J = 6.9 Hz); IR (film, cm^{-1}): 3289, 3062, 2990, 1788, 1712, 1626, 1540, 1477, 1372, 1292, 1247, 1104, 929, 893, 651.

Compound **8**: Mp: 173–175 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.78 (1H, bs), 7.70 (1H, d, J = 8.7 Hz), 7.42 (1H, d, J = 8.7 Hz), 4.31 (2H, q, J = 7.1 Hz), 1.27 (3H, t, J = 7.1 Hz); IR (cm^{-1}): 3196, 2995, 2360, 1786, 1728, 1641, 1540, 1477, 1356, 1314, 1266, 1190, 1021, 945, 833, 740.

4.1.2. Ethyl 6-amino-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carboxylate (**10**)

A mixture of compound 9 (88.3 g, 0.35 mol), reduced iron power (60.8 g, 1.08 mol), acetic acid (600 ml) in 2 l CH_3OH was mechanically stirred at reflux for 3 h. After cooled to room temperature, this mixture was added aqueous ammonia until the PH was adjusted to 10. The mixture was filtered and the solid was washed with hot CH_3OH (500 ml). The solvent was removed from filtrate and the resulting solid was extracted with boiling acetone (600 ml) and filtered. The acetone extracts were concentrated in vacuo. The residue was recrystallized from EtOAc (300 ml) to 71.5 g (yield, 92%) of compound 10 as light brown solid. The compound was used without further purification: Mp: 173–175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.63 (1H, bs), 7.57 (1H, s), 6.53 (1H, s), 4.35(2H, q, J = 7.0 Hz), 1.39 (3H, t, J = 7.0 Hz); IR (film, cm^{-1}): 3459, 3351, 3255, 2991, 1775, 1665, 1583, 1426, 1279, 1229, 1126, 1077, 929, 866, 706.

4.1.3. Ethyl 6-amino-3-(3-morpholinopropyl)-2-oxo-2,3-dihydrobenzo[d]oxazole-5-carboxylate (**11**)

K_2CO_3 (24.8 g, 180 mmol), KI (0.75 g, 4.5 mmol) and 4-(3-chloropropyl) morpholine (16.2 g, 99 mmol) were added successively to a solution of the compound 10 (20 g, 90.0 mmol) in acetonitrile (250 ml) and the mixture was stirred at 70 °C for 3 h. The mixture was poured to water (500 ml) and the aqueous phase was extracted with EtOAc (3 × 400 ml). The organic solution was washed with water follow by saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated to afford the compound 11 (30.5 g, yield, 97%), which was used to the next reaction without further purification. Mp: 126–128 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.45 (1H, s), 6.71 (1H, s), 4.28 (2H, q, J = 7.1 Hz), 3.79 (2H, t, J = 3.8 Hz), 3.53 (4H, t, J = 4.3 Hz), 2.28 (6H, m), 1.81 (2H, p, J = 7.3 Hz), 1.32 (3H, t, J = 7.1 Hz); IR (film, cm^{-1}): 3498, 3379, 3052, 2945, 2856, 2815, 1777, 1688, 1580, 1491, 1431, 1369, 1269, 1233,1117, 1064, 955, 871, 734.

4.1.4. 1-(3-Morpholinopropyl)oxazolo[4,5-g]quinazoline-2,8(1H,7H)-dione (**12**)

A solution of compound 11 (30.5 g, 87.3 mmol) and formamidine acetate (10.9 g, 104.8 mmol) in ethanol (120 ml) was heated at reflux for 24 h under the protection of N_2. The mixture was cooled to room temperature and filtered, then the solid was washed with EtOH (50 ml) and water (40 ml), and dried to give compound 12 as white power (23.1 g, yield, 80%); Mp: 218–219 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.25 (1H, bs), 8.05 (1H, s), 7.94 (1H, s), 7.59 (1H, s), 3.98 (2H, t, J = 6.4 Hz), 3.49 (4H, t, J = 4.4 Hz), 2.31 (2H, t, J = 3.5 Hz), 2.23 (4H, m), 1.88 (2H, p, J = 6.9 Hz); IR (film, cm^{-1}): 3496, 3159, 3011, 2871, 2810, 1780, 1658, 1589, 1487, 1368, 1270, 1116, 1067, 967, 912, 877, 788, 745.

4.1.5. 8-Chloro-1-(3-morpholinopropyl)oxazolo[4,5-g]quinazolin-2(1H)-one (**13**)

Compound 12 (23.1 g, 69.8 mmol) was added to thionyl chloride (180 ml) with magnetic stirring, then DMF (1.0 ml) was slowly added dropwise and the reaction flask was heated to reflux for 16 h. Most of the excess of thionyl chloride and DMF was then removed under reduced pressure and the yellow residue was purified by silica gel column chromatography with DCM/MeOH (60/1, v/v) as mobile phase to give compound 13 (20.0 g, yield, 82%); Mp: 150–152 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.98 (1H, s), 7.98 (1H, s), 7.90 (1H, s), 4.07 (2H, t, J = 6.4 Hz), 3.46 (4H, t, J = 4.1 Hz), 2.37 (2H, t, J = 6.4 Hz), 2.25 (4H, m), 1.93 (2H, p, J = 7.1 Hz); IR (film, cm^{-1}): 3075, 2947, 1799, 1604, 1567, 1481, 1443, 1350, 1258, 1109, 1071, 1021, 956, 809, 746, 682.

4.2. General procedure for the synthesis of oxazolo[4,5-g]quinazolin-2(1H)-one derivatives (**5a**–**5z**, **6a**–**6g**)

4.2.1. 8-(3-Chloro-4-fluorophenylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g]quinazolin-2(1H)-one (**5a**)

3-Chloro-4-fluoroaniline (172 mg, 1.18 mmol) was added to a solution of compound 13 (373 mg, 1.07 mmol) in isopropanol (10 ml) and stirred at reflux for 8 h. The mixture was cooled to room temperature and filtered, then the solid was washed with chill isopropanol (5 ml), treated with aqueous $NaHCO_3$ (10 ml) and extracted with EtOAc/MeOH (20:1, 30 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel with DCM–MeOH (50/1, v/v) gave 416 mg (yield, 85%) of the title compound as white solid: Mp: 248–250 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{22}H_{22}ClFN_5O_3$ $(M + H)^+$, 458.1390; found, 458.1388; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.73 (1H, s), 7.95 (1H, dd, J = 2.6 Hz, 6.4 Hz), 7.54 (1H, m), 7.31 (1H, s), 7.22 (1H, d, J = 4.2 Hz), 7.19 (1H, m), 4.05 (2H, t, J = 6.7 Hz), 3.64 (4H, t, J = 4.4 Hz), 2.47 (2H, t, J = 6.6 Hz), 2.41 (4H, m), 2.05 (2H, p, J = 6.7 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ:156.82, 154.27, 152.75, 152.33, 147.08, 146.43,136.38, 131.21, 123.61, 122.45, 122.40, 116.58, 116.43, 111.51, 106.48, 100.12, 65.90, 55.49, 53.24, 40.91, 22.82.

4.2.2. 8-(3-Ethynylphenylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g]quinazolin-2(1H)-one (**5b**)

White solid, 372 mg, yield, 81%; Mp: 240–243 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{24}H_{23}N_5O_3$ $(M + H)^+$, 430.1874; found, 430.1871; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.66 (1H, bs), 8.57 (1H, s), 8.26 (1H, s), 8.01 (1H, s), 7.91 (1H, d, J = 8.2 Hz), 7.68 (1H, s), 7.43 (1H, t, J = 7.8 Hz), 7.25 (1H, t, J = 7.6 Hz), 4.20 (2H, s), 4.00 (2H, t, J = 6.4 Hz), 3.40 (4H, m), 2.39 (2H, m), 2.44 (4H, m), 2.05 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ:156.94, 153.57, 152.86, 147.13, 146.43, 139.42,131.21, 128.88, 126.66, 124.90, 122.68, 121.76, 111.65, 106.47, 100.26, 83.32, 80.54, 65.92, 55.50, 53.25, 40.92, 22.84.

4.2.3. Ethyl 4-(1-(3-morpholinopropyl)-2-oxo-1,2-dihydrooxazolo[4,5-g]quinazolin-8-ylamino)benzoate (**5c**)

White solid, 313 mg, yield, 75%; Mp: 234–237 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{25}H_{28}N_5O_5$ $(M + H)^+$, 478.2085; found, 478.2094; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.86 (1H, bs), 8.63 (1H, s), 8.29 (1H, s), 8.06 (2H, d, J = 8.8 Hz), 8.00 (2H, d, J = 8.8 Hz), 7.71 (1H, s), 4.32 (2H, q, J = 7.0 Hz), 4.01 (2H, t, J = 6.4 Hz), 3.40 (4H, t, J = 4.4 Hz), 2.38 (2H, t, J = 6.6 Hz), 2.23 (4H, m), 2.01 (2H, p, J = 6.5 Hz), 1.34 (3H, t, J = 7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 165.33, 156.68, 153.56, 152.67, 147.32, 146.54, 143.81,131.36, 129.77, 124.02, 120.78, 111.89, 106.51, 100.26, 65.93, 60.34, 55.50, 53.27, 40.92, 22.84, 14.17.

4.2.4. 4-(1-(3-Morpholinopropyl)-2-oxo-1,2-dihydrooxazolo[4,5-g]quinazolin-8-ylamino)benzenesulfonamide (**5d**)

White solid, 404 mg, yield, 78%; Mp: 273–275 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{22}H_{25}N_6O_5S$ $(M + H)^+$, 485.1602; found, 485.1609; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.88 (1H, bs), 8.62 (1H, s), 8.29 (1H, s), 8.05 (2H, d, J = 8.6 Hz), 7.86 (2H, d, J = 8.6 Hz), 7.72 (1H, s), 4.01 (2H, t, J = 6.2 Hz), 3.40 (4H, m), 2.39 (2H, m), 2.24 (4H, m), 2.01 (2H,

p, J = 7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:156.89, 153.62, 152.76, 147.33, 146.61, 142.34, 138.35, 131.42, 126.34, 121.41, 111.84, 106.52, 106.35, 65.91, 55.48, 53.27, 40.95, 22.83.

*4.2.5. 8-(4-Methoxyphenylamino)-1-(3-morpholinopropyl)oxazolo [4,5-g]quinazolin-2(1H)-one (**5e**)*

White solid, 423 mg, yield, 87%; Mp: 222–225 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{23}H_{26}N_5O_4$ (M + H)$^+$, 436.1979; found, 436.1987; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.54 (1H, bs), 8.44 (1H, s), 8.22 (1H, s), 7.65 (2H, d, J = 8.6 Hz), 7.62 (1H, s), 7.00 (2H, d, J = 8.6 Hz), 3.97 (2H, t, J = 6.6 Hz), 3.78 (3H, s), 3.40 (4H, t, J = 4.5 Hz), 2.38 (2H, t, J = 6.6 Hz), 2.23 (4H, m), 2.01 (2H, p, J = 6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:157.37, 155.92, 153.62, 153.23, 146.93, 146.20, 131.80, 130.87, 124.44, 113.68, 111.53, 106.34, 100.33, 65.96, 55.54, 55.19, 53.28, 40.89, 22.91.

*4.2.6. 8-(3,4-Dimethoxyphenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5f**)*

White solid, 448 mg, yield, 90%; Mp: 245–247 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{24}H_{28}N_5O_5$ (M + H)$^+$, 466.2085; found, 466.2090; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.53 (1H, bs), 8.47 (1H, s), 8.24 (1H, s), 7.63 (1H, s), 7.39 (1H, d, J = 2.3 Hz), 7.31 (1H, dd, J = 2.3 Hz, 8.7 Hz), 7.00 (1H, d, J = 8.7 Hz), 3.98 (2H, t, J = 6.4 Hz), 3.79 (3H, s), 3.78 (3H, s), 3.41 (4H, t, J = 4.2 Hz), 2.38 (2H, t, J = 6.6 Hz), 2.23 (4H, m), 2.01 (2H, p, J = 6.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:157.36, 153.54, 153.22, 148.47, 146.96, 146.24, 145.60, 132.24, 130.94, 115.22, 111.82, 111.59, 108.17, 106.39, 100.36, 65.95, 55.74, 55.60, 55.51, 53.28, 40.90, 22.88.

*4.2.7. 4-Chlorobenzyl 4-(1-(3-morpholinopropyl)-2-oxo-1,2-dihydrooxazolo[4,5-g]quinazolin-8-ylamino)benzoate (**5g**)*

White solid, 497 mg, yield, 81%; Mp: 309–310 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{30}H_{29}ClN_5O_5$ (M + H)$^+$, 574.1852; found, 574.1857; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.91 (1H, bs), 8.63 (1H, s), 8.30 (1H, s), 8.08 (2H, d, J = 8.5 Hz), 7.31 (2H, d, J = 8.5 Hz), 7.71 (1H, s), 7.52 (2H, d, J = 8.2 Hz), 7.48 (2H, d, J = 8.2 Hz), 5.35 (2H, s), 4.00 (2H, t, J = 6.6 Hz), 3.39 (4H, m), 2.38 (2H, t, J = 6.6 Hz), 2.22 (4H, m), 2.00 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ:165.75, 156.73, 153.60, 152.69, 147.34, 146.54, 146.24, 144.36, 135.33, 132.65, 131.37, 130.00, 129.78, 128.47, 123.40, 120.89, 112.06, 106.51, 100.42, 65.94, 65.06, 55.50, 53.28, 40.93, 22.86.

*4.2.8. 8-(3,5-Dimethylphenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5h**)*

White solid, 389 mg, yield, 84%; Mp: 232–234 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{24}H_{28}N_5O_3$ (M + H)$^+$, 434.2187; found, 434.2194; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.46 (1H, bs), 8.52 (1H, s), 8.26 (1H, s), 7.64 (1H, s), 7.44 (2H, s), 6.80 (1H, s), 3.99 (2H, t, J = 6.5 Hz), 3.40 (4H,m), 2.31 (6H, s), 2.24 (4H, m), 2.00 (2H, p, J = 6.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:157.17, 153.64, 153.14, 147.04, 146.31, 138.88, 137.42, 131.06, 125.38, 125.31, 120.16, 111.66, 106.42, 100.35, 65.93, 55.56, 53.27, 40.94, 22.84, 21.03.

*4.2.9. Ethyl 4-hydroxy-3-(1-(3-morpholinopropyl)-2-oxo-1,2-dihydrooxazolo[4,5-g]quinazolin-8-ylamino)benzoate (**5i**)*

White solid, 470 mg, yield, 89%; Mp: 323–325 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{25}H_{28}N_5O_6$ (M + H)$^+$, 494.2034; found, 494.2038; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.70 (1H, bs), 9.53 (1H, bs), 8.37 (1H, bs), 8.42 (1H, s), 8.25 (1H, s), 8.08 (1H, d, J = 1.9 Hz), 7.76 (1H, dd, J = 1.9 Hz, 8.5 Hz), 7.66 (1H, s), 7.06 (1H, d, J = 8.5 Hz), 4.28 (2H, q, J = 7.1 Hz), 3.98 (2H, t, J = 6.4 Hz), 3.42 (4H, m), 2.39 (2H, t, J = 6.5 Hz), 2.26 (4H, m), 2.00 (2H, p, J = 6.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:165.38, 158.15, 156.36, 153.66, 153.09, 146.90, 146.41, 131.05, 128.65, 128.65, 128.21, 126.64, 120.59, 116.30, 106.35, 100.72, 65.98, 60.25, 55.54, 53.29, 40.93, 22.95, 14.23.

*4.2.10. 8-(4-Hydroxyphenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5j**)*

White solid, 392 mg, yield, 87%; Mp: 260–263 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{22}H_{24}N_5O_4$ (M + H)$^+$, 422.1823; found, 422.1830; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.47 (1H, bs), 9.33 (1H, bs), 8.42 (1H, s), 8.22 (1H, s), 7.60 (1H, s), 7.48 (2H, d, J = 8.4 Hz), 6.81 (2H, d, J = 8.4 Hz), 3.97 (2H, t, J = 6.4 Hz), 3.41 (4H, m), 2.38 (2H, t, J = 6.5 Hz), 2.24 (4H, m), 1.99 (2H, p, J = 6.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:157.51, 154.20, 153.65, 153.35, 146.89, 146.17, 130.83, 130.16, 124.95, 114.99, 111.52, 106.33, 100.41, 65.96, 55.55, 53.29, 40.91, 22.90.

*4.2.11. 8-(4-Ethoxyphenylamino)-1-(3-morpholinopropyl)oxazolo [4,5-g]quinazolin-2(1H)-one (**5k**)*

White solid, 437 mg, yield, 91%; Mp: 254–257 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{24}H_{28}N_5O_4$ (M + H)$^+$, 450.2136; found, 422.2143; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.53 (1H, bs), 8.45 (1H, s), 8.22 (1H, s), 7.63 (2H, d, J = 8.8 Hz), 7.62 (1H, s), 6.98 (2H, d, J = 8.8 Hz), 4.05 (2H, q, J = 6.9 Hz), 3.97 (2H, t, J = 6.4 Hz), 3.41 (4H, m), 2.38 (2H, t, J = 6.4 Hz), 2.24 (4H, m), 2.00 (2H, p, J = 6.4 Hz), 1.35 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:157.37, 155.17, 153.64, 153.25, 146.95, 146.23, 131.67, 130.92, 124.54, 124.43, 114.20, 111.54, 106.38, 100.37, 65.95, 55.53, 53.28, 40.90, 22.88, 14.66.

*4.2.12. 8-(p-Toluidino)-1-(3-morpholinopropyl)oxazolo[4,5-g] quinazolin-2(1H)-one (**5l**)*

White solid, 381 mg, yield, 85%; Mp: 212–216 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{22}H_{24}N_5O_4$ (M + H)$^+$, 420.2030; found, 420.2030; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.53 (1H, bs), 8.46 (1H, s), 8.23 (1H, s), 7.64 (1H, s), 7.63 (2H, d, J = 7.7 Hz), 7.20 (2H, d, J = 7.7 Hz), 3.96 (2H, t, J = 5.8 Hz), 3.38 (4H, m), 2.36 (2H, t, J = 6.1 Hz), 2.30 (3H, s), 2.21 (4H, m), 1.98 (2H, p, J = 6.1 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ:157.24, 153.62, 153.13, 147.02, 146.28, 136.43, 132.84, 131.00, 128.87, 122.66, 111.63, 106.40, 100.39, 65.94, 55.52, 53.27, 40.90, 22.88, 20.47.

*4.2.13. 8-(4-(4-Chlorobenzyloxy)phenylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g]quinazolin-2(1H)-one (**5m**)*

White solid, 502 mg, yield, 86%; Mp: 335–338 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{29}H_{29}ClN_5O_4$ (M + H)$^+$, 546.1903; found, 546.1903; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.53 (1H, bs), 8.46 (1H, s), 8.23 (1H, s), 7.66 (1H, s), 7.64 (2H, d, J = 8.8 Hz), 7.51 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.8 Hz), 5.14 (2H, s), 3.99 (2H, t, J = 6.4 Hz), 3.42 (4H, m), 2.39 (2H, t, J = 6.3 Hz), 2.25 (4H, m), 2.01 (2H, p, J = 6.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:157.33, 154.70, 153.61, 153.20, 146.95, 146.23, 136.19, 132.29, 132.51, 130.92, 129.38, 128.35, 124.46, 114.70, 111.52, 106.37, 100.36, 68.53, 65.92, 55.50, 53.26, 40.89, 22.87.

*4.2.14. 8-(4-Chlorophenylamino)-1-(3-morpholinopropyl)oxazolo [4,5-g]quinazolin-2(1H)-one (**5n**)*

White solid, 390 mg, yield, 83%; Mp: 221–223 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{22}H_{23}ClN_5O_3$ (M + H)$^+$, 440.1484; found, 440.1477; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.69 (1H, bs), 8.53 (1H, s), 8.23 (1H, s), 7.86 (2H, d, J = 8.8 Hz), 7.65 (1H, s), 7.45 (2H, d, J = 8.8 Hz), 3.98 (2H, t, J = 6.5 Hz), 3.40 (4H, t, J = 4.2 Hz), 2.37 (2H, t, J = 6.5 Hz), 2.22 (4H, m), 1.99 (2H, p, J = 6.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:156.96, 153.61, 152.89, 147.13, 146.42, 138.32, 131.18, 128.31, 127.14, 123.79, 111.79, 106.46, 100.38, 65.93, 55.50, 53.27, 40.92, 22.86.

*4.2.15. 8-(4-(Benzyloxy)phenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5o**)*

White solid, 477 mg, yield, 87%; Mp: 279–282 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{29}H_{30}N_5O_4$ (M + H)$^+$, 512.2292; found, 513.2283; ^{1}H NMR (300 MHz, DMSO-d_6) δ:9.57 (1H, bs), 8.45 (1H, s), 8.23 (1H, s),

7.63 (1H, s), 7.33–7.49 (5H, m), 7.07 (2H, d, $J = 8.8$ Hz), 5.13 (2H, s), 3.98 (2H, t, $J = 6.4$ Hz), 3.40 (4H, t, $J = 4.3$ Hz), 2.38 (2H, t, $J = 6.5$ Hz), 2.23 (4H, m), 2.00 (2H, p, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:157.37, 154.96, 153.64, 153.24, 146.96, 146.25, 137.14, 132.01, 130.95, 128.37, 127.74, 127.61, 124.52, 114.69,111.54,106.39, 100.37, 69.39, 65.94, 55.53, 53.28, 40.91, 22.88.

4.2.16. 8-(o-Toluidino)-1-(3-morpholinopropyl)oxazolo[4,5-g] quinazolin-2(1H)-one (**5p**)

White solid, 363 mg, yield, 81%; Mp: 230–232 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{23}H_{26}N_5O_3$ $(M + H)^+$, 420.2030; found, 420.2030; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.55 (1H, bs), 8.34 (1H, s), 8.22 (1H, s), 7.63 (1H, s), 7.33 (2H, m), 7.25 (2H, m), 3.96 (2H, t, $J = 6.6$ Hz), 3.41 (4H, m), 2.39 (2H, p, $J = 5.8$ Hz), 2.26 (4H, m), 2.18 (3H, s), 2.00 (2H, t, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:158.36, 153.64, 153.52, 146.90, 146.30, 137.07, 134.96, 131.00, 130.45, 127.62, 126.38, 126.25, 111.30, 106.33, 100.57, 65.93, 55.49, 53.24, 40.91, 22.89, 17.93.

4.2.17. 8-(2-Hydroxyphenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5q**)

White solid, 383 mg, yield, 85%; Mp: 255–257 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{22}H_{24}N_5O_4$ $(M + H)^+$, 422.1823; found, 422.1820; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.70 (1H, bs), 9.38 (1H, bs), 8.40 (1H, s), 7.64 (1H, s), 7.49 (1H, d, $J = 7.7$ Hz), 7.11 (1H, t, $J = 8.1$ Hz), 6.98 (1H, d, $J = 8.1$ Hz), 6.87 (1H, t, $J = 7.7$ Hz), 3.99 (2H, t, $J = 6.5$ Hz), 3.41 (4H, m), 2.39 (2H, p, $J = 5.8$ Hz), 2.26 (4H, m), 2.00 (2H, t, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:158.15, 153.64, 153.18, 151.53, 146.86, 130.96, 127.26, 126.52, 125.96, 118.92, 111.65, 106.32, 100.76, 65.91, 55.54, 53.28, 40.92, 22.97.

4.2.18. 8-(3,4-Difluorophenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5r**)

White solid, 387 mg, yield, 82%; Mp: 250–254 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{22}H_{22}F_2N_5O_3$ $(M + H)^+$, 442.1685; found, 442.1677; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.71 (1H, bs), 8.56 (1H, s), 8.19 (1H, s), 8.06 (1H, m), 7.66 (1H, s), 7.58 (1H, m), 7.47 (2H, dd, $J = 9.3$ Hz, 10.1 Hz), 3.98 (2H, t, $J = 6.4$ Hz), 3.40 (4H, m), 2.38 (2H, t, $J = 6.4$ Hz), 2.23 (4H, m), 1.88 (2H, p, $J = 5.6$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:156.84, 153.57, 152.75, 149.70, 147.76, 147.11, 146.46, 144.45, 136.20, 131.24, 118.39, 117.06, 116.92, 111.56, 111.34, 111.17, 106.50, 100.15, 65.93, 55.49, 53.26, 40.92, 22.85.

4.2.19. 8-(3-Isopropoxyphenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5s**)

White solid, 416 mg, yield, 84%; Mp: 259–262 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{25}H_{30}F_2N_5O_4$ $(M + H)^+$, 464.2292; found, 464.2285; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.53 (1H, bs), 8.54 (1H, s), 8.24 (1H, s), 7.65 (1H, s), 7.50 (1H, s), 7.36 (1H, d, $J = 8.6$ Hz), 7.29 (1H, t, $J = 8.1$ Hz), 6.71 (1H, d, $J = 8.6$ Hz), 4.62 (1H, m), 3.99 (2H, t, $J = 6.4$ Hz), 3.41 (4H, m), 2.38 (2H, t, $J = 6.5$ Hz), 2.23 (4H, m), 2.00 (2H, p, $J = 6.5$ Hz), 1.31(6H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ:157.55, 157.07, 153.60, 152.99, 147.09, 146.34, 140.28, 131.12, 129.12, 114.34, 111.71, 110.01, 106.44, 100.33, 69.20, 65.92, 55.45, 53.25, 40.00, 22.86, 21.83.

4.2.20. 8-(3-Acetylphenylamino)-1-(3-morpholinopropyl)oxazolo [4,5-g]quinazolin-2(1H)-one (**5t**)

White solid, 373 mg, yield, 78%; Mp: 275–278 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{24}H_{26}N_5O_4$ $(M + H)^+$, 448.1979; found, 448.1982; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.79 (1H, bs), 8.56 (1H, s), 8.32 (1H, s), 8.27 (1H, s), 8.23 (1H, d, $J = 7.9$ Hz), 7.77 (1H, d, $J = 7.6$ Hz), 7.68 (1H, s), 7.58 (1H, t, $J = 7.9$ Hz), 4.00 (2H, t, $J = 6.2$ Hz), 3.40 (4H, m), 2.63 (3H, s), 2.39 (2H, t, $J = 6.3$ Hz), 2.23 (4H, m), 2.01 (2H, p, $J = 6.3$ Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ:197.67, 157.06, 153.60, 152.88, 147.17, 146.46, 139.61, 137.18, 131.24, 128.84, 126.78, 123.70, 121.20, 111.68, 106.49, 100.32, 65.92, 55.52, 53.27, 40.94, 26.73, 22.83.

4.2.21. 8-(4-((3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl) methoxy)phenylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g] quinazolin-2(1H)-one (**5u**)

White solid, 567 mg, yield, 85%; Mp: 357–360 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{31}H_{32}F_3N_6O_5$ $(M + H)^+$, 625.2381; found, 625.2370; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.55 (1H, bs), 8.44 (1H, s), 8.23 (1H, s), 7.63 (1H, s), 7.62 (2H, d, $J = 8.3$ Hz), 7.16 (1H, d, $J = 5.6$ Hz), 7.09 (2H, d, $J = 8.7$ Hz), 5.21 (2H, s), 4.92 (2H, q, $J = 8.7$ Hz), 3.98 (2H, t, $J = 6.0$ Hz), 3.41 (4H, m), 2.38 (2H, t, $J = 6.1$ Hz), 2.25 (7H, m), 2.00 (2H, p, $J = 6.4$ Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 161.35, 157.39, 155.38, 154.99, 153.62, 153.21, 147.60, 146.94, 146.25, 132.09, 130.94, 124.52, 122.64, 114.62, 111.53, 107.56, 106.38, 100.37, 70.44, 65.92, 64.60, 55.49, 53.25, 40.89, 22.87, 9.98.

4.2.22. N-(4-(1-(3-morpholinopropyl)-2-oxo-1,2-dihydrooxazolo [4,5-g]quinazolin-8-ylamino)phenyl)acetamide (**5v**)

White solid, 430 mg, yield, 87%; Mp: 308–310 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{24}H_{27}N_6O_4$ $(M + H)^+$, 463.2088; found, 463.2084; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.94 (1H, bs), 9.58 (1H, bs), 8.48 (1H, s), 8.24 (1H, s), 7.70 (2H, d, $J = 8.7$ Hz), 7.63 (1H, s), 7.62 (2H, d, $J = 8.7$ Hz), 5.21 (2H, s), 3.98 (2H, t, $J = 6.0$ Hz), 3.41 (4H, m), 2.38 (2H, t, $J = 6.1$ Hz), 2.24 (4H, m), 2.06 (3H, s), 2.00 (2H, p, $J = 6.4$ Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ:167.96, 157.19, 153.62, 153.14, 147.01, 146.27, 135.44, 134.01, 130.98, 123.11, 119.07, 111.59, 106.38, 100.37, 65.93, 55.52, 53.26, 40.91, 23.85, 22.87.

4.2.23. 8-(3-((3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl) methoxy)phenylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g] quinazolin-2(1H)-one (**5w**)

White solid, 568 mg, yield, 85%; Mp: 356–357 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{31}H_{32}F_2N_6O_5$ $(M + H)^+$, 625.2381; found, 625.2372; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.63 (1H, bs), 8.51 (1H, s), 8.32 (2H, d, $J = 8.3$ Hz), 8.02 (1H, d, $J = 8.3$ Hz), 7.63 (2H, d, $J = 8.7$ Hz), 7.35 (1H, s), 7.14 (2H, d, $J = 8.7$ Hz), 6.84 (1H, s), 5.20 (2H, s), 4.91 (2H, q, $J = 8.7$ Hz), 3.98 (2H, t, $J = 6.0$ Hz), 3.47 (4H, m), 3.38 (2H, m), 2.39 (2H, t, $J = 6.1$ Hz), 2.27 (7H, m), 2.01 (2H, p, $J = 6.4$ Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 161.35, 158.51, 157.10, 153.62, 152.97, 147.65, 147.10, 146.37, 144.52, 140.32, 131.15, 129.13, 121.30, 114.99, 111.75, 109.66, 109.17, 107.56, 106.81, 106.44, 104.35, 100.46, 70.26, 65.99, 64.38, 55.49, 54.88, 53.26, 40.92, 23.23, 22.87, 9.92.

4.2.24. 1-(3-Morpholinopropyl)-8-(4-(pyridin-2-ylmethoxy) phenylamino)oxazolo[4,5-g]quinazolin-2(1H)-one (**5x**)

White solid, 482 mg, yield, 88%; Mp: 332–335 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{28}H_{29}N_6O_4$ $(M + H)^+$, 513.2245; found, 513.2235; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.55 (1H, bs), 8.55 (1H, d, $J = 4.2$ Hz), 8.34 (1H, s), 8.22 (1H, s), 7.80 (2H, dt, $J = 7.8$ Hz, 5.2 Hz), 7.63 (1H, s), 7.48 (1H, d, $J = 7.8$ Hz), 7.31 (1H, t, $J = 5.2$ Hz), 6.73 (2H, d, $J = 8.8$ Hz), 6.52 (1H, d, $J = 8.8$ Hz), 5.13 (2H, s), 3.99 (2H, t, $J = 6.4$ Hz), 3.40 (4H, t, $J = 4.3$ Hz), 2.38 (2H, t, $J = 6.4$ Hz), 2.23 (4H, m), 2.00 (2H, p, $J = 6.5$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:167.96, 161.35, 157.45, 155.38, 154.99, 148.88, 142.71, 136.74, 132.09, 130.94, 122.65, 121.40, 115.60, 115.03, 111.53, 107.56, 106.38, 100.37, 70.89, 65.93, 55.52, 53.26, 40.91, 23.85, 22.87.

4.2.25. 8-(4-(4-Chlorobenzyloxy)-3-chlorophenylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g]quinazolin-2(1H)-one (**5y**)

White solid, 539 mg, yield, 87%; Mp: 339–340 °C; HRMS, ESI$^+$, m/z: Calcd for $C_{29}H_{28}Cl_2N_5O_4$ $(M + H)^+$, 580.1513; found, 580.1511; ^{1}H NMR (500 MHz, DMSO-d_6) δ:9.58 (1H, bs), 8.52 (1H, s), 8.19 (1H, s), 7.96 (1H, d, $J = 2.1$ Hz), 7.70 (1H, dd, $J = 8.9$ Hz, 2.1 Hz), 7.64 (1H, s), 7.52 (2H, d, $J = 8.4$ Hz), 7.48 (2H, d, $J = 8.4$ Hz), 7.28 (1H, d, $J = 8.9$ Hz), 5.23 (2H, s), 3.98 (2H, m), 3.41 (4H, m), 2.38 (2H, t, $J = 6.4$ Hz), 2.24 (4H, m), 2.00 (2H, p, $J = 6.4$ Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ:157.00, 153.59, 152.99, 149.69, 147.01, 146.35, 135.68,

133.07, 132.47, 131.09, 129.24, 128.43, 124.08, 122.26, 121.07, 114.36, 111.52, 106.46, 100.22, 69.44, 65.99, 55.52, 53.27, 53.12, 40.92, 30.66, 22.85.

4.2.26. 8-(4-tert-Butylphenylamino)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**5z**)

White solid, 414 mg, yield, 84%; Mp: 285–287 °C; HRMS, ESI^+, *m/z*: Calcd for $C_{26}H_{32}N_5O_3$ $(M + H)^+$, 462.2500; found, 462.2503; ^1H NMR (500 MHz, DMSO-d_6) δ:9.63 (1H, bs), 8.48 (1H, s), 8.28 (1H, s), 7.70 (2H, d, $J = 6.8$ Hz), 7.65 (1H, s), 7.43 (2H, d, $J = 6.8$ Hz), 3.99 (2H, t, $J = 6.1$ Hz), 3.40 (4H, m), 2.38 (2H, t, $J = 6.1$ Hz), 2.24 (4H, m), 2.00 (2H, p, $J = 6.4$ Hz), 1.32 (9H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ:167.96, 157.19, 153.62, 153.14, 147.01, 146.27, 135.44, 134.01, 130.98, 123.11, 119.07, 111.59, 106.38, 100.37, 65.93, 55.52, 53.26, 40.91, 23.85, 22.87.

4.2.27. 8-(Methyl(phenyl)amino)-1-(3-morpholinopropyl)oxazolo [4,5-g]quinazolin-2(1H)-one (**6a**)

N-methylbenzenamine (95.4 mg, 0.89 mmol) was added to a solution of compound 13 (300 mg, 1.07 mmol) in isopropanol (10 ml) and stirred at 50 °C for 24 h. The mixture was cooled to room temperature and concentrated in vacuo, then the residue was treated with aqueous $NaHCO_3$ (10 ml) and extracted with EtOAc/MeOH (20:1, 30 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel with DCM–MeOH (90/1,v/v) gave 282 mg (yield, 63%) of the title compound as pale yellow solid: Mp: 218–221 °C; HRMS, ESI^+, *m/z*: Calcd for $C_{23}H_{26}ClN_5O_3$ $(M + H)^+$, 420.2030; found, 420.2041; ^1H NMR (500 MHz, DMSO-d_6) δ: 8.61 (1H, s), 8.50 (1H, s), 7.80 (1H, d, $J = 7.7$ Hz), 7.69 (1H, s), 7.44 (2H, t, $J = 7.7$ Hz), 7.21 (1H, d, $J = 7.4$ Hz), 4.00 (2H, t, $J = 6.6$ Hz), 3.39 (4H, m), 2.78 (3H, s), 2.38 (2H, t, $J = 6.6$ Hz), 2.22 (4H, m), 2.00 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ:160.80, 153.43, 152.81, 148.58, 148.11, 145.56, 130.08, 129.58, 126.22, 125.55, 112.83, 106.64, 102.92, 65.94, 55.52, 53.22, 41.92, 40.54, 22.10.

4.2.28. (S)-1-(3-morpholinopropyl)-8-(1-phenylethylamino) oxazolo[4,5-g]quinazolin-2(1H)-one (**6b**)

(S)-1-phenylethanamine (155 mg, 1.28 mmol) and TEA (216 mg, 2.14 mmol) was added to a solution of compound 13 (300 mg, 1.07 mmol) in isopropanol (10 ml) and stirred at 55 °C for 24 h. The mixture was cooled to room temperature and concentrated in vacuo, the residue was treated with aqueous $NaHCO_3$ (12 ml) and extracted with EtOAc/MeOH (20:1, 30 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel with DCM–MeOH (120/1,v/v) gave 357 mg (yield, 70%) of the title compound as pale yellow solid: Mp: 261–265 °C; HRMS, ESI^+, *m/z*: Calcd for $C_{24}H_{28}N_5O_3$ $(M + H)^+$, 434.2187; found, 434.2182; ^1H NMR (300 MHz, DMSO-d_6) δ:8.37 (1H, s), 8.27 (1H, d, $J = 7.7$ Hz), 8.22 (1H, s), 7.57 (1H, s), 7.46 (2H, d, $J = 7.4$ Hz), 7.34 (2H, d, $J = 7.4$ Hz), 7.24 (1H, t, $J = 7.2$ Hz), 5.65 (1H, p, $J = 7.2$ Hz), 3.99 (2H, t, $J = 6.3$ Hz), 3.41 (4H, m), 2.39 (2H, t, $J = 6.3$ Hz), 2.25 (4H, m), 2.01 (2H, p, $J = 6.4$ Hz), 1.65 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 160.22, 153.57, 152.05, 146.70, 145.37, 144.13, 131.24, 119.14, 106.66, 104.37, 101.70, 65.98, 54.87, 53.12, 40.29, 23.21.

4.2.29. (R)-1-(3-morpholinopropyl)-8-(1-phenylethylamino) oxazolo[4,5-g]quinazolin-2(1H)-one (**6c**)

(R)-1-phenylethanamine (155 mg, 1.28 mmol) and TEA (216 mg, 2.14 mmol) was added to a solution of compound 13 (300 mg, 1.07 mmol) in isopropanol (10 ml) and stirred at 55 °C for 26 h. The mixture was cooled to room temperature and concentrated in vacuo, the residue was treated with aqueous $NaHCO_3$ (15 ml) and extracted with EtOAc/MeOH (20:1, 30 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel with DCM–MeOH (120/1,v/v) gave 348 mg (yield, 75%) of the title compound as pale yellow solid: Mp: 264–267 °C; HRMS, ESI^+, *m/z*: Calcd for $C_{24}H_{28}N_5O_3$ $(M + H)^+$, 434.2187; found, 434.2184; ^1H NMR (300 MHz, DMSO-d_6) δ:8.37 (1H, s), 8.27 (1H, d, $J = 7.7$ Hz), 8.22 (1H, s), 7.57 (1H, s), 7.46 (2H, d, $J = 7.4$ Hz), 7.34 (2H, d, $J = 7.4$ Hz), 7.24 (1H, t, $J = 7.2$ Hz), 5.65 (1H, p, $J = 7.2$ Hz), 3.99 (2H, t, $J = 6.3$ Hz), 3.41 (4H, m), 2.39 (2H, t, $J = 6.3$ Hz), 2.25 (4H, m), 2.01 (2H, p, $J = 6.3$ Hz), 1.65 (3H, d, $J = 7.0$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 159.47, 153.30, 152.04, 148.44, 148.32, 144.13, 134.36, 120.79, 106.66, 104.37, 101.66, 66.00, 55.04, 53.17, 40.63, 22.90.

4.2.30. 8-(Benzylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g] quinazolin-2(1H)-one (**6d**)

White solid, 314 mg, yield, 70%; Mp: 217–220 °C; HRMS, ESI^+, *m/z*: Calcd for $C_{23}H_{26}N_5O_3$ $(M + H)^+$, 420.2030; found, 420.2028; ^1H NMR (500 MHz, DMSO-d_6) δ: 8.61 (1H, t, $J = 5.8$ Hz), 8.40 (1H, s), 8.07 (1H, s), 7.57 (1H, s), 7.38 (2H, d, $J = 7.4$ Hz), 7.32 (2H, t, $J = 7.4$ Hz), 7.25 (1H, t, $J = 7.2$ Hz), 4.83 (2H, d, $J = 5.8$ Hz), 3.92 (2H, t, $J = 6.6$ Hz), 3.37 (2H, t, $J = 4.4$ Hz), 2.36 (2H, t, $J = 6.6$ Hz), 2.22 (4H, m), 1.96 (2H, p, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:159.44, 157.18, 153.58, 153.07, 147.12, 146.37, 138.97, 130.91, 128.41, 123.77, 122.62, 111.64, 106.42, 100.23, 65.94, 59.81, 55.51, 53.27, 40.90, 22.88.

4.2.31. 8-(trans-4-Hydroxycyclohexylamino)-1-(3-morpholinopropyl)oxazolo[4,5-g]quinazolin-2(1H)-one (**6e**)

Trans-4-aminocyclohexanol (148 mg, 1.28 mmol) and TEA (150 mg, 2.14 mmol) was added to a solution of compound 13 (300 mg, 1.07 mmol) in isopropanol (12 ml) and stirred at 60 °C for 24 h. The mixture was cooled to room temperature and concentrated in vacuo, the residue was treated with aqueous $NaHCO_3$ (10 ml) and extracted with EtOAc/MeOH (20:1, 30 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel with DCM–MeOH (90/1,v/v) gave 361 mg (yield, 79%) of the title compound as pale yellow solid: Mp: 312–315 °C; HRMS, ESI^+, *m/z*: Calcd for $C_{22}H_{30}N_5O_4$ $(M + H)^+$, 428.2292; found, 428.2295; ^1H NMR (500 MHz, DMSO-d_6) δ:8.70 (1H, s), 7.80 (1H, s), 7.74 (1H, s), 4.14 (1H, s), 4.00 (2H, t, $J = 6.4$ Hz), 3.52 (4H, t, $J = 4.2$ Hz), 2.33 (2H, t, $J = 6.3$ Hz), 2.26 (4H, m), 2.00 (2H, p, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ:165.61, 159.43, 153.45, 153.26, 152.57, 152.00, 148.36, 148.27, 147.64, 147.03, 134.26, 132.23, 120.73, 112.49, 106.61, 106.06, 106.38, 101.58, 100.19, 66.00, 65.86, 55.01, 54.77, 54.15, 53.16, 53.12, 40.59, 40.33, 22.19, 22.91.

4.2.32. 8-(4-Methylpiperazin-1-yl)-1-(3-morpholinopropyl) oxazolo[4,5-g]quinazolin-2(1H)-one (**6f**)

1-Methylpiperazine (118 mg, 1.18 mmol) and TEA (324 mg, 3.21 mmol) was added to a solution of compound 13 (300 mg, 1.07 mmol) in isopropanol (10 ml) and stirred for 10 h under reflux. The mixture was cooled to room temperature and concentrated in vacuo. Chromatography of the residue on silica gel with DCM–MeOH (20/1,v/v) gave 357 mg (yield, 81%) of the title compound as pale yellow solid: Mp: >370 °C; HRMS, ESI^+, *m/z*: Calcd for $C_{21}H_{29}N_6O_3$ $(M + H)^+$, 413.2296; found, 413.2305; ^1H NMR (500 MHz, DMSO-d_6) δ: 8.61 (1H, s), 7.70 (1H, s), 7.56 (1H, s), 4.03 (2H, t, $J = 6.5$ Hz), 3.71 (4H, m), 3.48 (4H, m), 2.64 (4H, m), 2.35 (2H, m), 2.32 (3H, s), 2.25 (4H, m), 1.91 (2H, p, $J = 6.4$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.78, 153.57, 152.27, 148.60, 146.36, 130.83, 112.99, 106.64, 102.18, 65.88, 55.13, 53.98, 53.92, 53.73, 53.25, 53.13,48.92, 48.74, 44.96, 40.43, 22.96.

4.2.33. 8-(1H-indazol-5-ylamino)-1-(3-morpholinopropyl)oxazolo [4,5-g]quinazolin-2(1H)-one (**6g**)

1H-indazol-5-amine (171 mg, 1.28 mmol) was added to a solution of compound 13 (300 mg, 1.07 mmol) in isopropanol (15 ml)

and stirred at reflux for 13 h. The mixture was cooled to room temperature and filtered, the solid was washed with chill isopropanol (5 ml), the residue was treated with aqueous $NaHCO_3$ (10 ml) and extracted with EtOAc/MeOH (20:1, 30 ml). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel with DCM–MeOH (70/1,v/v) gave 395 mg (yield, 83%) of the title compound as white solid: Mp: 346–348 °C; HRMS, ESI$^+$, *m/z*: Calcd for $C_{23}H_{24}N_7O_3$ $(M + H)^+$, 446.1935; found, 446.1939; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.69 (1H, s), 8.47 (1H, s), 8.27 (1H, s), 8.16 (1H, s), 8.05 (1H, s), 7.93 (1H, s), 7.64 (1H, d, J = 8.8 Hz), 7.63 (1H, s), 7.58 (1H, t, J = 8.8 Hz), 3.99 (2H, t, J = 6.6 Hz), 3.41 (4H, m), 2.39 (2H, t, J = 6.3 Hz), 2.25 (4H, m), 2.01 (2H, p, J = 6.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 157.67, 153.65, 153.28, 146.95, 146.26, 144.05, 137.41, 133.39, 131.26, 130.96, 123.84, 122.76, 114.01, 113.94, 111.60, 109.86, 106.91, 104.35, 100.44, 65.99, 55.54, 53.28, 53.13, 40.93, 23.23, 22.91.

Acknowledgments

We would like to thank Professor Tao Lu and Ms. Yanmin Zhang for docking study. This study is financially supported by 111 Project from the Ministry of Education of China and the State Administration of Foreign Expert Affairs of China (No. 111-2-07).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejmech.2012.06.055. These data include MOL files and InChiKeys of the most important compounds described in this article.

References

[1] M.A. Lemmon, The EGF receptor family as therapeutic targets in breast cancer, Breast Dis. 18 (2003) 33–43.
[2] K.K. Ang, N.H. Andratschke, L. Milas, Epidermal growth factor receptor and response of head-and-neck carcinoma to therapy, Int. J. Radiat. Oncol. Biol. Phys. 58 (2004) 959–965.
[3] A.P. Meert, B. Martin, M. Paesmans, T. Berghmans, C. Mascaux, J.M. Verdebout, P. Delmotte, J.J. Lafitte, J.P. Sculier, The role of HER-2/neu expression on the survival of patients with lung cancer: a systematic review of the literature, Br. J. Cancer 89 (2003) 959–965.
[4] S.R. Klutchko, H. Zhou, R.T. Winters, T.P. Tran, A.J. Bridges, Tyrosine kinase inhibitors. 19. 6-Alkynamides of 4-anilinoquinazolines and 4-anilinopyrido [3,4-d]pyrimidines as irreversible Inhibitors of the erbB family of tyrosine kinase receptors, J. Med. Chem. 49 (2006) 1475–1485.
[5] F.R. Hirsch, M.V. Garcia, P.A. Bunn Jr., M.V. Dimaria, R. Veve, R.M. Bremmes, A.E. Baron, C. Zeng, W.A. Franklin, Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis, J. Clin. Oncol. 21 (2003) 3798–3807.
[6] N.E. Hynes, H.A. Lane, ERBB receptors and cancer: the complexity of targeted inhibitors, Nat. Rev. Cancer 5 (2005) 341–354.
[7] J. Mendelsohn, J. Baselga, Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer, J. Clin. Oncol. 21 (2003) 2787–2799.
[8] C.M. Rocha-Lima, H.P. Soares, L.E. Raez, R. Singal, EGFR targeting of solid tumors, Cancer Control 14 (2007) 295–304.
[9] E. Balius, C. Robert, Quantitative prediction of fold resistance for inhibitors of EGFR, Biochemistry 48 (2009) 8435–8448.
[10] D.W. Fry, Mechanism of action of erbB tyrosine kinase inhibitors, Exp. Cell Res. 284 (2003) 131–139.
[11] L. Alexander, Protein kinase inhibitors as a therapeutic modality, Acc. Chem. Res. 36 (2003) 462–469.
[12] J.B. Smaill, H.D. Showalter, H.R. Zhou, A.J. Bridges, D.J. McNamara, Tyrosine kinase inhibitors. 18. 6-Substituted 4-anilinoquinazolines and 4-anilinopyrido [3,4-d]pyrimidines as soluble, irreversible inhibitors of the epidermal growth factor receptor, J. Med. Chem. 44 (2001) 429–440.
[13] M. Ranson, L.A. Hammond, D. Ferry, M. Kris, A. Tullo, P.I. Murray, V. Miller, S. Averbuch, J. Ochs, C. Morris, A. Feyereislova, H. Swaisland, E.K. Rowinsky, ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial, J. Clin. Oncol. 20 (2002) 2240–2250.
[14] F. Ciardiello, G. Tortora, A novel approach in the treatment of cancer: targeting the epidermal growth factor receptor, Clin. Cancer Res. 7 (2001) 2958–2970.
[15] X. Wenle, R.J. Mullin, B.R. Keith, L.H. Liu, H.D. Ma, W. Rusnak, G. Owens, K.J. Alligood, N.L. Spector, Anti-tumor activity of GW-572016: a dual tyrosine kinase inhibitor blocks EGF activation of EGFR/erbB2 and downstream Erk1/2 and AKT pathways, Oncogene 21 (2002) 6255–6263.
[16] O. Cruz-López, A. Conejo-García, M.C. Núñez, M. Kimatrai, M.E. García-Rubiño, F. Morales, V. Gómez-Pérez, J.M. Campos, Novel substituted quinazolines for potent EGFR tyrosine kinase inhibitors, Curr. Med. Chem. 18 (2011) 943–963.
[17] D.D. Li, P.C. Lv, H. Zhang, H.J. Zhang, Y.P. Hou, K. Liu, Y.H. Ye, H.L. Zhu, The combination of 4-anilinoquinazoline and cinnamic acid: a novel mode of binding to the epidermal growth factor receptor tyrosine kinase, Bioorg. Med. Chem. 19 (2011) 5012–5022.
[18] P. Ballard, B. Barlaam, R.H. Bradbury, A. Dishington, L.F. Hennequin, D.M. Kickinson, I.M. Hollinsworth, J.G. Kettle, T. Klinowska, D.J. Ogilvie, S.E. Pearson, J.S. Scott, A. Suleman, R. Whittaker, E.J. Williams, R. Wood, L. Wright, Neutral 5-substituted 4-anilinoquinazolines as potent, orally active inhibitors of erbB2 receptor tyrosine kinase, Bioorg. Med. Chem. Lett. 17 (2007) 6326–6329.
[19] B. Barlaam, P. Ballard, R.H. Bradbury, R. Ducray, H. Germain, D.M. Kickinson, K. Hudson, J.G. Kettle, T.K. linowska, F. Magnien, D.J. Ogilvie, A. Olivier, S.E. Pearson, J.S. Scott, A. Suleman, C.B. Trigwell, M. Vautier, R.D. Whittaker, R. Wood, A new series of neutral 5-substituted 4-anilinoquinazolines as potent, orally active inhibitors of erbB2 receptor tyrosine kinase, Bioorg. Med. Chem. Lett. 18 (2008) 674–678.
[20] J.J. Liao, Molecular recognition of protein kinase binding pockets for design of potent and selective kinase inhibitors, J. Med. Chem. 50 (2007) 409–424.