Accepted Manuscript

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PII: S0960-894X(17)30159-2
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.02.027
Reference: BMCL 24699

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 26 December 2016
Revised Date: 10 February 2017
Accepted Date: 14 February 2017

Please cite this article as: Zhang, Y., Zhang, Y., Liu, J., Chen, L., Zhao, L., Li, B., Wang, W., Synthesis and in vitro biological evaluation of novel quinazoline derivatives, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.02.027

Synthesis and in vitro biological evaluation of novel quinazoline derivatives

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Abstract: A series of novel 4-arylamino-6-(5-substituted furan-2-yl)quinazoline derivatives were designed, synthesized and evaluated on biological activities in vitro. Compound **2a**, **3a** and **3c** exhibited highly anti-proliferation activities on all tested tumor cell lines including SW480, A549, A431 and NCI-H1975 cells. Especially, compound **2a** not only exhibited strong anti-proliferation activities against the tumor cell lines which expressed wild type or mutant $EGFR^{L858R/T790M}$, but also showed the most potent inhibitory activity toward wild type EGFR (IC_{50} = 5.06 nM). The result of docking with EGFR suggested the binding mode of **2a** was similar to that of lapatinib. While Western-blot analyses showed **2a** obviously inhibited the activation of EGFR, Akt and Erk1/2 in lung cancer cells at indicated concentration. It is believed that this work would be very useful for developing a new series of TKIs targeting EGFR.

Keywords: 4-arylamino-6-(5-substituted furan-2-yl)quinazoline, EGFR, tyrosine kinase inhibitors, anti-proliferation

Several quinazoline derivatives as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), for example gefitinib, erlotinib and lapatinib, have been approved for the cancer treatment by the US Food and Drug Administration (FDA).[1-4] Gefitinib and erlotinib as the first-generation EGFR inhibitors were highly effective in the treatment of lung-cancer patients with activated EGFR mutations, which occurred in the kinase domain of the *EGFR* gene with deletions in exon 19 or point mutation of L858R in exon 21.[5-7] Unfortunately, patients harboring the *mut*EGFR (T790M) were reported to develop resistance to these drugs.[5, 8, 9] Replacement of the threonine with methionine leads to steric repulsion of the first- and second-generation inhibitors (afatinib and dacomitinib) and results in a slightly different binding geometry, which accounts for the loss of inhibitory activity both in vitro and in vivo.[10] Lapatinib, a dual inhibitor of the EGFR and human epidermal growth factor receptor 2 (HER2), was approved in 2007 for the treatment of breast cancer.[4, 11-14] However, a mandatory black-box warning was released in 2008 because of lapatinib-related hepatotoxicity in clinical trials and post-marketing surveillance.[15]

Nazartinib, osimertinib and rociletinib as the third-generation EGFR inhibitors were designed to avoid the steric interference caused by Met790. These inhibitors bind with EGFR in a covalent form through the alkylation of EGFR at Cys797 at the lip of the ATP-binding site.[10] However, the effective treatment of patients that harbor the EGFR-T790M drug resistance mutation is limited by the emergence of new drug resistances.[16] C797S is a recently discovered resistance mutation in the kinase domain of EGFR.[9] This mutation prevents the covalent bond formation with third-generation inhibitors and reduces their efficacy.[17] Thus there is an urgent demand for new EGFR inhibitors that effectively treats various cancers.

Herein, we report the design, synthesis, and biological evaluation of some novel quinazoline

derivatives. Based on the importance of quinazoline moiety for its anticancer activity, and referring to the structure characteristics of gefitinib, erlotinib and lapatinib, we chose 4-arylamino-6-(furan-2-yl)quinazoline as a core structure, 3 classes of new quinazoline derivatives (11 compounds) were designed through assignment different R^1 and R^2 as shown in Figure 1 and Table 1. The Lipinski parameters of these virtual compounds were predicted by Sybyl 2.1. The results showed the most of these compounds are match the conditions of Lipinski rule. Thereby they were synthesized and evaluated on bioactivity in vitro.

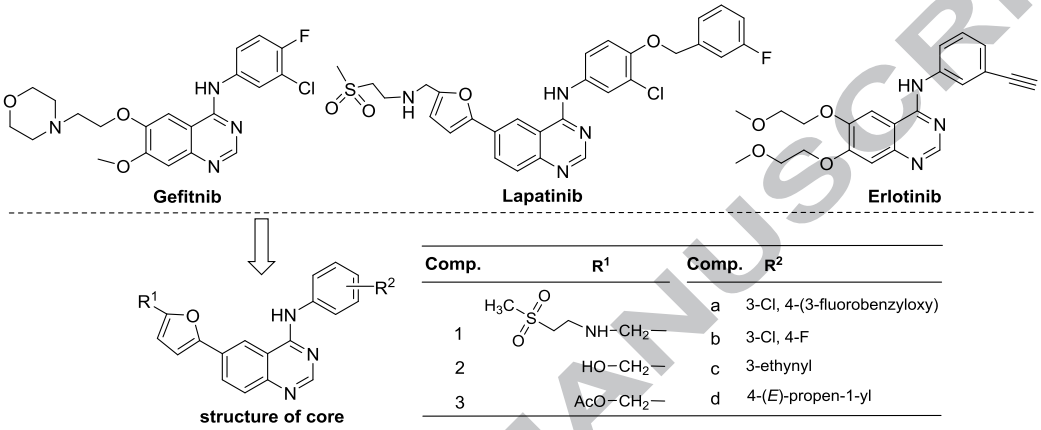
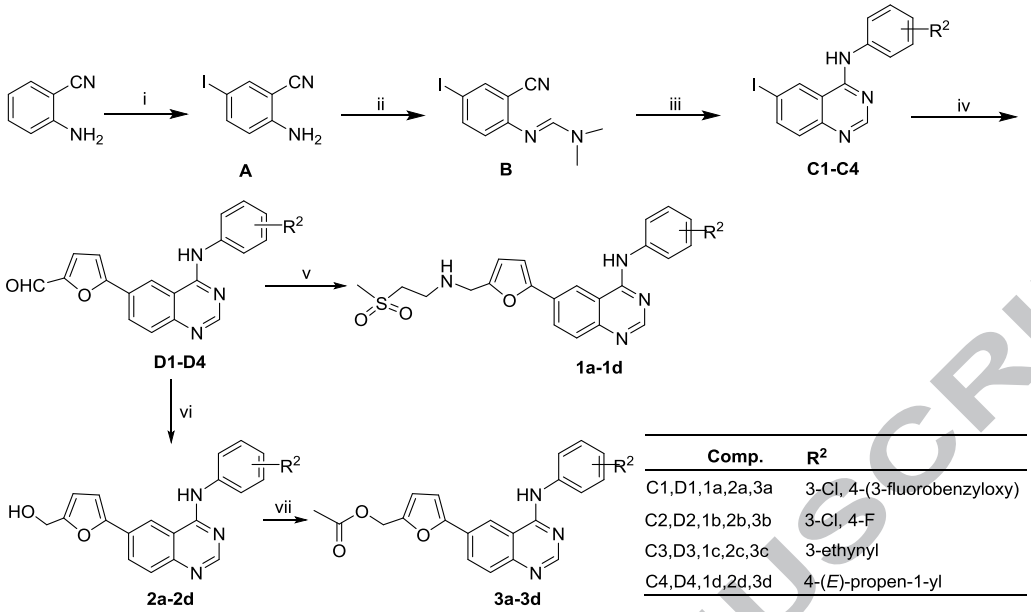


Figure 1. Design of new quinazoline derivatives

The synthetic route of the target compounds is showed in Scheme 1. We herein chose 2-aminobenzonitrile as starting material to synthesize these 4-arylamino-6-(5-substituted furan-2-yl)quinazoline derivatives. Firstly, 2-Amino-5-iodobenzonitrile (**A**) was prepared in 92.6% yield from starting material by using the system of ammonium iodide and hydrogen peroxide in the presence of acetic acid.[18] After the procedures, the reaction of **A** with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) yielded *N'*-(2-cyano-4-iodophenyl)-*N*,*N*-dimethyl formamidine (**B**) in 89.3%. Dimroth rearrangement was used to form quinazoline core.[19] When **B** was mixed respectively with four substituted anilines such as 3-chloro-4-((3-fluorobenzyl)oxy)aniline, 3-chloro-4-fluoroaniline, 3-ethynylaniline and 4-(*E*)-(propen-1-yl)aniline in acetate acid at 125~130 °C for 15 min, four 4-arylamino-6-iodoquinazolines (**C1-C4**) were obtained in 84.3~92.5% yield. Then, Suzuki coupling reaction of **C** and 5-formylfuran-2-yl boronic acid gave key intermediates 4-arylamino-6-(5-formylfuran-2-yl)quinazolines (**D**) catalyzed by Pd/C. These key intermediates were sequentially transformed to compound **1** through the reductive amination with 2-(methylsulfonyl)ethylamine hydrochloride, and to compound **2** by reducing with $NaBH_4$. Finally, compound **3** was prepared by the acetylation of **2** in acetic anhydride. The structures of **1**, **2** and **3** were identified by NMR, IR and HRMS (see Supplementary material).



Comp.	R^2
C1,D1,1a,2a,3a	3-Cl, 4-(3-fluorobenzyloxy)
C2,D2,1b,2b,3b	3-Cl, 4-F
C3,D3,1c,2c,3c	3-ethynyl
C4,D4,1d,2d,3d	4-(*E*)-propen-1-yl

Scheme 1. Synthetic route of the target compounds **1**-**3**. Reagents and conditions. i. NH_4I-H_2O_2, r.t. 12 h, 92.6%; ii. DMF-DMA, 35 °C, 0.5 h, 89.3%; iii. R^2-aniline, 125~130 °C, 15 min, 84.3~92.5%; iv. 5-formylfuran-2-yl boronic acid, Pd/C, 50 °C, 0.5 h, 57.2~83.4%; v. 2-(methylsulfonyl)ethylamine ·HCl, $NaBH_3CN$, 0 °C, 2 h, 78.1~82.6%; vi. $NaBH_4$, 0 °C, 4 h, 90.3~94.6%; vii. Ac_2O, $NaOAc{\cdot}3H_2O$, r.t. 0.5 h, 84.7~89.6%.

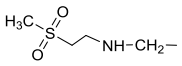
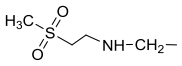
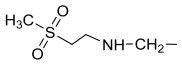
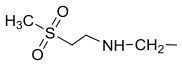
The anti-proliferation activities of these new compounds were evaluated by MTT assay[20-22] against four human tumor cell lines including SW480, A549, A431 and NCI-H1975. Clinical drugs, lapatinib and gefitinib, were used as reference compounds. The results indicated that most of the synthesized compounds exhibited good anti-proliferation activities in the dose-response. Their IG_{50} values were listed in Table 1. Except **2b** and **2c**, all compounds exhibited the anti-proliferation activities against human colon cancer cell line SW480. Especially, the IG_{50} of **2a** (5.58 μM) and **3a** (5.18 μM) were lower than that of lapatinib (12.58 μM) and gefitinib (12.50 μM). Compound **1b**, **1d**, **2b**, **2c** and **3b** nearly did not have anti-proliferation activities against human non-small-cell lung cancer (NSCLC) cell line A549 which harboring wild type EGFR ($EGFR^{WT}$), but the IG_{50} of **2a**, **3a** and **3c** were 7.35, 5.49 and 4.05 μM, respectively, which showed **2a**, **3a** and **3c** possessed high activities against A549 cells. We then assessed the inhibitory efficacy of these compounds on the drug-resistant NSCLC cell line H1975, which harbors EGFR-L858R/T790M double mutants. Except **1d**, **2b** and **2c**, the whole series displayed inhibitory effect on H1975 cells. Particularly, compound **2a**, **3a** and **3c** exhibited excellent inhibitory effect on H1975 cells (IG_{50} values of 3.01, 6.78 and 5.40 μM, respectively), their activities were even higher than that of gefitinib and lapatinb. This demonstrated these compounds had high potential for targeting the acquired T790M drug resistance mutation of EGFR. Whilst the high active **1a**, **2a** and **3a** suggested that 3-fluorobenzyloxy and Cl as synergia groups in 4- and 3-position of phenylamino can obviously increase the activity of inhibitors against H1975 cells. Overall the activities of synthesized compounds, compound **2a**, **3a** and **3c** represented highly single-digit micromole anti-proliferation activities on all tested tumor cell lines. Meanwhile, it is worth noting that all synthesized compounds displayed a moderate to excellent inhibitory effect on human skin squamous cancer cell line A431 with abnormally high expressing EGFR. Especially, three compounds attached ethynyl in 3-position of phenylamino moiety including **1c**, **2c** and **3c** showed low IG_{50} (5.78, 3.21 and 1.28 μM, respectively) and high activities. The fact implied 3-ethynyl in phenylamino moiety was a key active group on A431 cells. On the other hand, the broadly activities of

the whole series on A431 cells also implied the inhibitory effect of these compounds with quinazoline core may result from the suppression of EGFR.

To further prove this proposal, the inhibitory activities of compounds **1b**, **1c**, **2a** and **2c** to EGFR were tested by ELISA method. Reference compounds lapatinib and gefitinib were also tested under the same condition. The result indicated all tested compounds possessed the inhibitory effect against $EGFR^{WT}$ (see Table 1). Moreover compound **2a** showed remarkably higher activity (IC_{50} = 5.06 nM) than EGFR and HER2 inhibitor lapatinib (IC_{50} = 27.06 nM), and similar activity compared with EGFR inhibitor gefitinib (IC_{50} = 3.22 nM). These suggested that **2a** was a high active $EGFR^{WT}$ inhibitor.

Table 1.

Biological evaluation of synthesized novel quinazoline derivatives in *vitro.*

Compound.	R^1	R^2	IG_{50} (μM)*				IC_{50} (nM)*
			SW480	A549	NCI-H1975	A431	$EGFR^{WT}$
lapatinib, **1a**		3-Cl, 4-(3-fluorobenzyloxy)	12.58±1.35	14.90±1.21	9.08±5.82	4.80±0.71	27.06±3.77
1b		3-Cl, 4-F	60.59±0.83	> 100	83.61±21.91	39.34±8.94	23.99±3.30
1c		3-ethynyl	13.38±0.25	11.35±2.22	14.92±0.68	5.78±0.80	34.16±4.81
1d		4-(*E*)-propen-1-yl	56.34±3.03	84.50±13.12	> 100	37.56±2.79	N.D.
2a	HO−CH_2−	3-Cl, 4-(3-fluorobenzyloxy)	5.58±1.43	7.35±1.42	3.01±1.07	3.64±0.51	5.06±1.92
2b	HO−CH_2−	3-Cl, 4-F	> 100	> 100	>100	3.91±1.23	N.D.
2c	HO−CH_2−	3-ethynyl	> 100	> 100	>100	3.21±0.94	15.69±4.96
2d	HO−CH_2−	4-(*E*)-propen-1-yl	51.25±11.76	38.24±20.27	37.93±5.18	21.43±1.45	N.D.
3a	AcO−CH_2−	3-Cl, 4-(3-fluorobenzyloxy)	5.18±0.99	5.49±1.54	6.78±1.98	8.33±1.29	N.D
3b	AcO−CH_2−	3-Cl, 4-F	43.18±7.09	> 100	54.13±16.79	10.75±1.85	N.D
3c	AcO−CH_2−	3-ethynyl	14.97±3.61	4.05±0.67	5.40±0.08	1.28±0.04	N.D
3d	AcO−CH_2−	4-(*E*)-propen-1-yl	11.18±1.62	20.61±9.38	40.85±1.63	5.53±0.51	N.D
gefitinib			12.50±0.28	21.17±0.47	12.70±2.98	4.45±0.25	3.22±1.48

*IG_{50} and IC_{50} values were presented in mean ± SD obtained from three independent determinations. N.D. indicated not determination.

Furthermore, molecular docking of **2a** to ATP binding site of EGFR kinase was performed using Surflex-Dock module of SYBYL-X 2.1. Here the EGFR/lapatinib complex crystal structure (1xkk.pdb)[23] was selected as the binding model due to the similarity of core structure between **2a** and lapatinib. To check the consistency, the original ligand lapatinib was docked back into the optimized receptor protein. The calculated root-mean-square deviation (RMSD) between the best docked pose and the observed X-ray crystallographic conformation of lapatinib was 1.053 Å. This suggested the established docking mode is reliable.[24, 25] The docking results showed compound **2a** and the control ligand lapatinib were in similar binding mode as shown in Figure 2. The N1 atom in **2a** was hydrogen-bonded to the main chain NH of the hinge region Met793, and the length of hydrogen bond

was 1.924 Å, which was a little bit longer than that of lapatinib (1.908 Å). While the residue Thr790 was directly involved in hydrogen bonding with the F atom of 4-(3-fluorobenzyloxy) group of **2a** or lapatinib, and the distance of hydrogen bond of **2a** was 2.622 Å, and a little shorter than that of lapatinib (2.676 Å). These changes should be corresponding to their different inhibitory activity on EGFR.

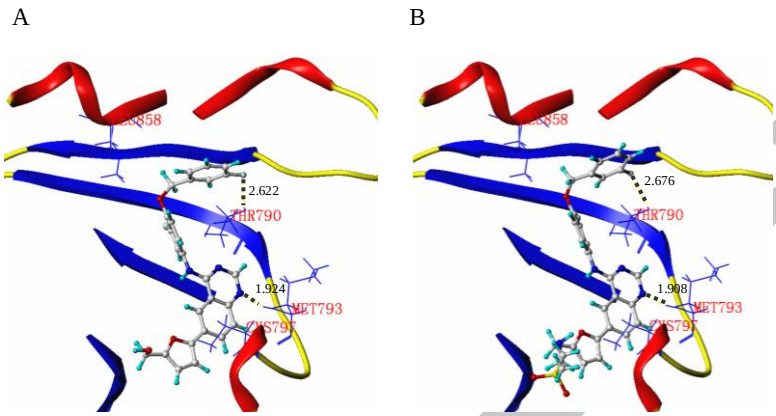


Figure 2. The binding modes of EGFR and compounds **2a** (A) or lapatinib (B) docked by the Surflex-Dock program. The hydrogen bonds were illustrated as black dashed lines (length unit in Å).

Finally, in order to further investigate the anti-proliferative mechanism of compound **2a** against cancer cells, we examined the effects of **2a** on the activation of EGFR, namely phosphorylation of EGFR (p-EGFR), and the activation of downstream signaling proteins in human lung cancer cell lines A549 and NCI-H1975 by Western Bolt analyses. As shown in Figure 3A, similar to lapatinib, the activated EGFR (p-Tyr/EGFR or p-EGFR) in A549 cells ($EGFR^{WT}$) was obviously decreased when the concentration of **2a** was even in 1 μM. The activation levels of downstream proteins p-Akt and p-Erk1/2 were also dramatically down-regulated, especially the amount of p-Akt was still significantly decreased when the concentration of **2a** was in 1 μM, while the total proteins of EGFR, Akt, Erk and GAPDH remained almost at the same level in A549 cells under different conditions. These results indicated the inhibition of the activation of EGFR, Akt and Erk1/2 played a crucial role in the anti-proliferation of compound **2a** on A549 cells. Whilst it was revealed the exertion of anti-proliferation of **2a** might mainly go through EGFR downstream signaling pathways Akt and Erk1/2 on A549 cells. Although compound **2a** also exhibited an excellent anti-proliferation activity (IG_{50} = 3.01 μM) (see Table 1) and lower the amount of p-Tyr/EGFR or p-EGFR on NCI-H1975 cells (see Figure 3B), the levels of p-Erk1/2 and p-Akt were only down-regulated slightly in NCI-H1975 cells at high concentration of **2a** (50 μM). This suggested the anti-proliferation mechanism of **2a** on NCI-H1975 cells might undergo different downstream signaling pathways comparing with that of **2a** on A549 cells.

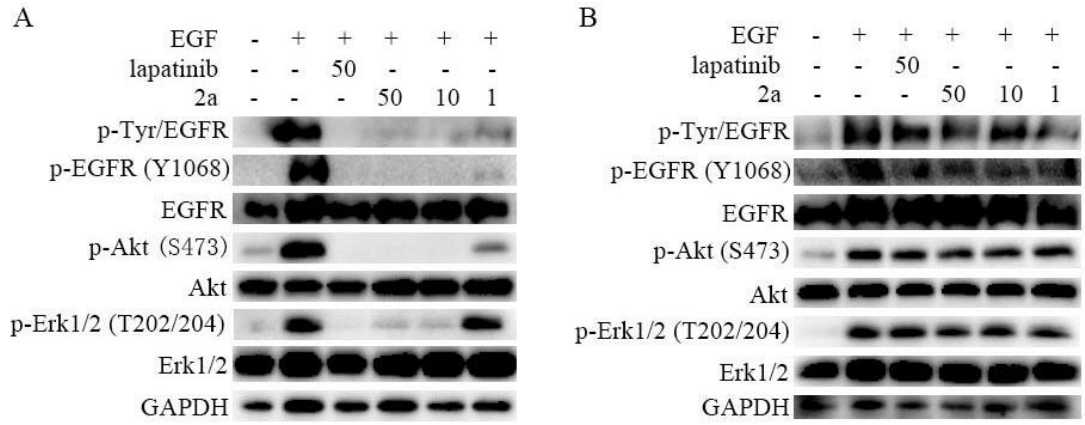


Figure 3. Western-blot analyses of **2a** in A549 (A) and NCI-H1975 (B) human lung cancer cell lines. Cells were cultured in the presence of different concentrations of **2a** or lapatinb (μM) for 2 h and stimulated with 50 nM EGF for 10min, then harvested. Whole-cell lysate was assayed for total EGFR, Akt and Erk1/2, as well as p-Tyr/EGFR, p-EGFR, p-Akt and p-Erk1/2 by immunoblotting. A representative anti-GAPDH immunoblot was showed as loading control.

In conclusion, a series of novel 4-arylamino-6-(5-substituted furan-2-yl)quinazoline derivatives were designed, synthesized and evaluated on biological activities in vitro. Most of synthesized compounds have potency of inhibition against four tumor cell lines (SW480, A549, A431 and NCI-H1975). Compound **2a**, **3a** and **3c** exhibited highly single-digit micromole anti-proliferation activities on all tested tumor cell lines. Especially, **2a** not only demonstrated strong anti-proliferation activities against the tumor cells which expressed wild type or mutant EGFR (with the IG_{50} values in the range of 3.01 - 7.35 μM), but also showed the most potent inhibitory activity toward $EGFR^{WT}$ (IC_{50} = 5.06 nM). The molecular docking showed **2a** formed two hydrogen bonds with $EGFR^{WT}$, and binded in similar pose comparing with lapatinib in activity pocket. In addition, compound **2a** inhibited EGF-induced EGFR activation in the human lung cancer A549 and NCI-H1975 cell lines. However, EGF-induced EGFR downstream phosphorylation proteins, such as p-Akt and p-Erk1/2, displayed different levels on two cell lines under indicated concentration of **2a**, which indicated that **2a** interacted with the signaling pathways in different manner in A549 and NCI-H1975 cells.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Grant number 21272144), and the Fundamental Research Funds for the Central Universities of Shaanxi Normal University (grant number X2015YB06).

Supplementary material

Supplementary data associated with this article can be found, in the online version, at

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Graphical abstract