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Synthesis and Characterization of 4-Amino-quinazoline Derivatives

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Four 4-amino-quinazoline compounds, including 7-[3-(2-methoxyphenoxy)propoxy]-*N'*-(3-chlorophenyl)-6-methoxyquinazolin-4-amine, 7-[3-(4-methoxyphenoxy)propoxy]-*N'*-(3-chlorophenyl)-6-methoxyquinazolin-4-amine, 2-[3-{4-(3-chlorophenylamino)-6- methoxy-quinazolin-7-yloxy}propoxy]benzaldehyde, 4-[3-{4-(3-chlorophenylamino)-6-methoxyquinazolin-7-yloxy}propoxy]benzaldehyde, were synthesized from *N'*-[5-(3- chloropropoxy)-2-cyano-4-methoxyphen-yl]-*N,N*-dimethylformamidine by cyclization and etheration. The yields of the compounds **IIIa-d** were 70.3, 71.0, 45.5 and 50.2 %, respectively. Their structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.

Keywords: 4-Amino-quinazoline, Quinazoline derivatives.

INTRODUCTION

The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases (RTKs) is recognized as a key mediator of cancer progression[1-4]. The HER tyrosine kinase family consists of four structurally related cellular receptors *i.e.*, the epidermal growth factor receptor (EGFR; HER1), HER2 (ErbB2), HER3 (ErbB3) and HER4[2,5]. Therefore, dysregulation of the EGFR signaling pathway may contribute to malignant transformation and over expression of HER1 and HER2 is frequently observed in several solid tumors[6]. Accordingly, the EGFR family is a major target of anticancer agents[7].

Several small-molecule inhibitors of EGFR tyrosine kinases have been developed (Fig. 1). The first class of EGFR-targeting therapeutic agents includes the Her-1 specific inhibitors, 1 (Gefitinib)[8] and 2 (Erlotinib)[9], for treatment of non-small cell lung cancer. However, the drug's resistance to Her-1 specific inhibitors has been clinically observed[10]. The second class includes the Her-1/Her-2 dual inhibitor, 3 (Lapatinib)[11], for treatment of Her-2-positive breast cancer. The third class includes the EGFR irreversible inhibitors, 4(HKI-272)[12,13] and 5 (CI-1033)[14]. The chemical structure of these compounds Gefitinib, Erlotinib, Lapatinib, HKI-272 and CI-1033 are shown in Fig. 1.

The halogen atoms in the benzene ring of 4-phenylamino were retained[15-18], while some heterocyclic fragments were introduced at the end of 6 or 7 position[19-24] in the synthesis of many 4-phenylamino-quinazolines compounds. The 1,2,4-triazolo[1,5-a]quinazolines[25] and thiazolo[2,3-b]quinazolines[26] were synthesized in recent years. In this paper, 4 compounds (**IIIa-IIId**) of 4-amino-quinazoline derivatives were synthesized by retaining the parent ring structure of 4-(3'-chlorophenyl)amino-quinazoline and introducing an aryl group at the end of the phenoxypropoxy. There structures were determined by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. Synthetic routes and chemical structures of the compounds **IIIa-IIId** are shown in Fig. 2.

EXPERIMENTAL

The melting points of synthesized compounds were recorded using X-4 digital microscopy melting point instrument that was uncorrected before use. IR spectra were recorded on Bruker VECTOR22 infrared spectrometer in the range 4000-400 cm^{-1} in KBr pellets. PMR spectra were recorded on JEOL-ECX 500MHz NMR spectrometer with TMS as an internal standard using $CDCl_3$ and DMSO-d_6 as a solvent. The mass spectra and elemental analysis were recorded on Agilent 1100 MSD-Trap-VL mass spectrometer and Elementar Vario-III elemental analyzer, respectively. The purity of the compounds was checked on silica gel-G plates by TLC with layer thickness of 3 mm. All chemicals used were of AR grade (China make) and not purified before use.

(*E*)-*N'*-[5-(3-chloropropoxy)-2-cyano-4-methoxyphenyl]-*N,N*-dimethylformamidine (**I**) and 7-(3-chloropropoxy)-*N*-(3-chlorophenyl)-6-methoxyquinazolin-4-amine (**II**) were synthesized according to the reported methods[17,18], respectively.

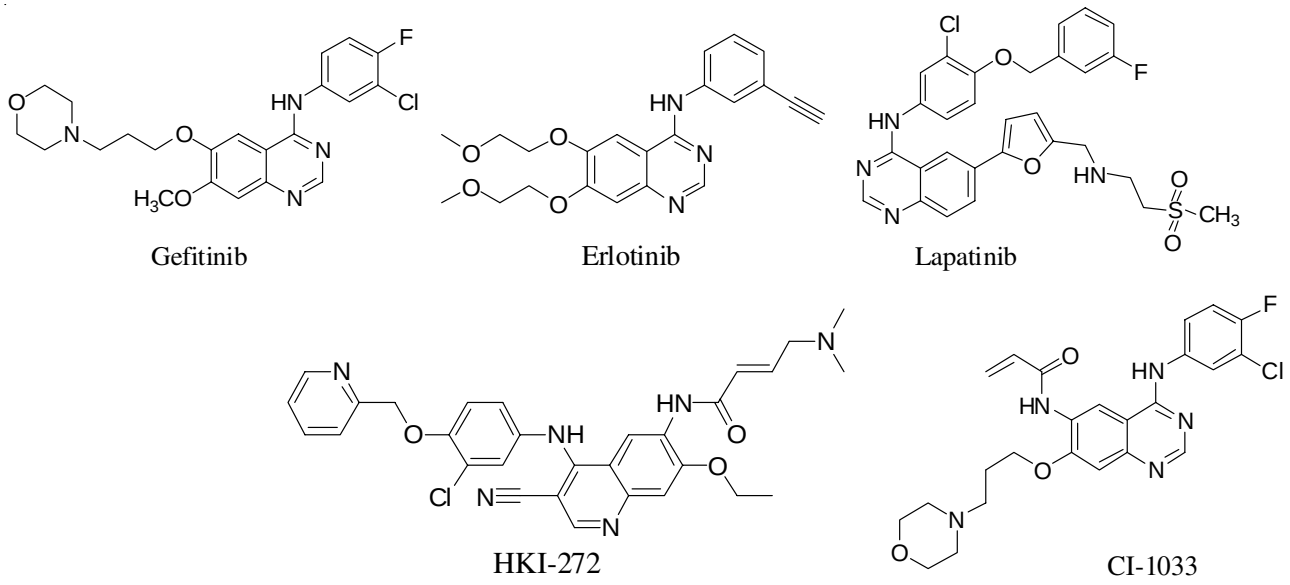
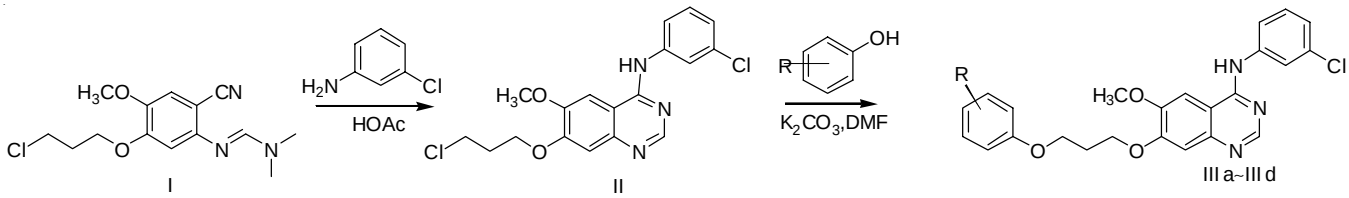


Fig. 1. Chemical structure of compounds Gefitinib, Erlotinib, Lapatinib, HKI-272 and CI-1033



III a:R=2-OCH_3; III b:R=4-OCH_3; III c:R=2-CHO; III d:R=4-CHO

Fig. 2. Synthetic routes and chemical structures of compounds **IIIa-IIId**

Synthesis and characterization of compounds IIIa: 0.50 g of *N*-(3-chlorophenyl)-7-(3-chloropropoxy)-6-methoxy-quinazoline-4-amine, 0.18 g 2-methoxyphenol, 15 mL DMF and 1 g K_2CO_3 were reacted at 85 °C for 10 h. The compound of **IIIa** was obtained by standing, precipitation and purification with thin-layer chromatographic separation. The compounds of **IIIb-IIId** were also synthesized by using the similar method. The physical characteristics of the synthesized compounds **IIIa-d** were given in Table-1.

Compound IIIa: ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.24-2.27 (m, 2H, -$CH_2CH_2CH_2$-), 3.75 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3), 4.14-4.17 (t, *J* = 6.3 Hz, 2H, -OCH_2-), 4.30-4.33 (t, *J* = 6.3 Hz, 2H, -OCH_2), 6.86-6.92 (m, 2H, HAr), 6.95-6.97 (m, 1H, HAr), 7.01-7.03 (m, 1H, HAr), 7.13-7.15 (d, *J* = 8.0 Hz, 1H, HAr), 7.24 (s, 1H, HAr), 7.39-7.42 (t, *J* = 8.3 Hz, 1H, HAr), 7. 90-7.91 (d, *J* = 8.0 Hz, 1H, HAr), 8.01 (s, 1H, HAr), 8.12 (s, 1H, HAr), 8.53 (s, 1H, -CH=), 9.84 (brs, 1H, -NH-); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 29.1, 56.0, 57.0, 65.5, 65.7, 102.9, 108.4, 109.6, 112.8, 114.2, 120.7, 121.3, 121.7, 121.7, 123.1, 130.5, 133.2, 141.8, 147.6, 148.5, 149.6, 149.7, 153.2, 154.1, 156.6; IR (KBr, ν_{max}, cm^{-1}): 3446, 2958, 1625, 1521, 1458, 1246, 1222, 1124, 1026, 850, 788, 740.

Compound IIIb: ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.22-2.25 (m, 2H, -$CH_2CH_2CH_2$-), 3.69 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 4.09-4.12 (t, *J* = 6.3 Hz, 2H, -OCH_2-), 4.30-4.32 (t, *J* = 6.3 Hz, 2H, -OCH_2-), 6.84-6.86 (m, 2H, HAr), 6.90-6.92 (m, 2H, HAr), 7.14-7.16 (d, *J* = 8.0 Hz, 1H, HAr), 7.25 (s, 1H, HAr), 7.40-7.44 (t, *J* = 8.3 Hz, 1H, HAr), 7.82-7.84 (m, 2H, HAr), 8.05 (s, 1H, HAr), 8.53 (s, 1H, -CH=), 9.56 (s, 1H, -NH-); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 29.0, 55.8, 56.8, 65.1, 65.7, 102.4, 108.4, 109.5, 115.1, 115.9, 120.6, 121.7, 123.2, 130.6, 133.2, 141.7, 147.6, 149.6, 152.9, 153.1, 153.9, 154.1, 156.5; IR (KBr, ν_{max}, cm^{-1}): 3442, 2918, 2846, 1621, 1506, 1450, 1429, 1234, 1207, 1145, 991, 823.

Compound IIIc: ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.34-2.36 (m, 2H, -$CH_2CH_2CH_2$-), 3.99 (s, 3H, -OCH_3), 4.33-4.35 (t, *J* = 5.7 Hz, 2H, -OCH_2-), 4.38-4.40 (t, *J* = 5.7 Hz, 2H,-OCH_2-), 7.06-7.09 (t, *J* = 7.5 Hz, 1H, HAr), 7.12-7.14 (d, *J* = 8.0 Hz, 1H, HAr), 7.27 (s, 1H, HAr), 7.29 (s, 1H, HAr), 7.38-7.41 (t, *J* = 7.5 Hz, 1H, HAr), 7.64-7.68 (t, *J* = 8.0 Hz, 1H, HAr), 7.69-7.71 (d, *J* = 8.0 Hz, 1H, HAr), 7.90-7.92 (d, *J* = 8.0 Hz, 1H, HAr), 8.03 (s, 1H, HAr), 8.12 (s, 1H, HAr), 8.52 (s, 1H, -CH=), 9.90 (s, 1H, -NH-),10.45 (s, 1H, -CHO); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 28.8, 57.1, 65.8, 66.0, 102.8, 108.4, 109.7, 113.9, 120.8, 121.2, 121.7, 123.0, 124.8, 128.1, 130.4, 133.1, 137.0, 141.9, 147.6, 149.5, 153.1, 154.0, 156.7, 161.4, 190.1; IR (KBr, ν_{max}, cm^{-1}): 3444, 2954, 1653, 1622, 1598, 1427, 1250, 1217, 1138, 846, 761.

Compound IIId: ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.29-2.34 (m, 2H, -$CH_2CH_2CH_2$-), 4.0 (s, 3H, -OCH_3), 4.29-4.32 (t, *J* = 6.3 Hz, 2H, -OCH_2-), 4.32-4.35 (t, *J* = 6.3 Hz, 2H, -OCH_2), 7.12-7.14 (d, *J* = 8.6 Hz, 1H, HAr), 7.17 (s, 1H, HAr), 7.19 (s, 1H, HAr), 7.25 (s, 1H, HAr), 7.38-7.41 (t, *J* = 8.3 Hz, 1H, HAr), 7.87 (s, 1H, HAr), 7.89 (s, 1H, HAr), 7.93-7.94 (d, *J* = 9.2 Hz, 1H, HAr), 8.08 (s, 1H, HAr), 8.14-8.15 (m, 1H, HAr), 8.52 (s, 1H, -CH=), 9.88 (s, 1H, -NH-), 9.96 (s, 1H, -CHO); ^{13}C NMR (DMSO-d_6, 125 MHz) δ: 28.8, 57.2, 65.4, 65.6, 103.2, 108.4, 109.7, 115.5, 120.8, 121.8, 123.0, 130.2,

TABLE-1
PHYSICAL CHARACTERISTICS OF THE SYNTHESIZED COMPOUNDS **IIIa-d**

Comp. No.	m.f.	m.p. (°C)	Yield (%)	Colour	Found (%) (calcd.)			Mass (*m/z*)	
					C	H	N	$[M]^+$	$[M+H]^+$
IIIa	$C_{25}H_{24}N_3O_4Cl$	115-116	70.3	Light yellow	64.45(64.44)	5.21(5.19)	9.00(9.02)	465.15	466.3
IIIb	$C_{25}H_{24}N_3O_4Cl$	80-81	71.0	Yellow	64.45(64.44)	5.18(5.19)	8.99(9.02)	465.15	466.2
IIIc	$C_{25}H_{22}N_3O_4Cl$	201-202	45.5	Yellow	64.71(64.72)	4.80(4.78)	9.05(9.06)	463.13	464.2
IIId	$C_{25}H_{22}N_3O_4Cl$	125-127	50.2	Light yellow	64.73(64.72)	4.81(4.78)	9.05(9.06)	463.13	464.2

130.4, 132.4, 133.1, 141.9, 147.5, 149.5, 153.1, 154.0, 156.7, 164.0, 191.9; IR (KBr, ν_{max}, cm^{-1}): 3444, 2960, 1668, 1624, 1600, 1575, 1508, 1419, 1398, 1263, 1163, 615, 545.

RESULTS AND DISCUSSION

The structures of synthesized compounds were identified on the basis the IR, ^{1}H NMR, ^{13}C NMR, MS spectral and elemental analysis data. The spectral values support the expected structures.

In IR spectrum characteristic absorption peak of N-H stretching vibration was observed at 3444 cm^{-1}. The absorption peak of C=N stretching vibration was found from 1621 to 1625 cm^{-1} and the obvious aromatic ring skeleton vibration peak could be seen from 1400 to 1620 cm^{-1}.

It could be seen from the MS spectra that obvious excimer ionic peaks were appeared in all target compounds.

In ^{1}H NMR spectrum, the peak of -CH=N and N-H in the compounds **IIIa-d** appeared at d = 8.53, 9.88-9.90 ppm, respectively. The peak of -CH=O in the compounds **IIIc** and **IIId** appeared at d = 10.45, 9.96 ppm, respectively. The *m* peak of -CH_2 CH_2CH_2- in the compounds **IIIa-d** appeared from 2.22 to 2.34 ppm. The peak of -CH_2 CH_2CH_2- in the compounds **IIIa-d** was typical *t* peak.

In ^{13}C NMR spectrum, the peak of -CH=O in the compounds **IIIc-d** appeared at d = 190.09, 191.88 ppm, respectively. The peak of the middle methylene carbon among 3 methylene groups in the compounds **IIIa-d** was between 28.76-29.06.

Conclusion

In summary, different derivatives of 4-(3′-chlorophenylamino)-6-methoxy-7- substituted quinazoline were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.

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