# Synthesis of several new quinazolin-4-amines containing *p*-toluenesulfonate moiety

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A series of novel quinazolin-4-amine derivatives containing *p*-toluenesulfonate moiety have been synthesised through the reaction of 4-chloro-7-methoxyquinazolin-6-yl acetate with substituted anilines in toluene solution at 90 °C. Further treatment of the synthesised compound with ammonium hydroxide gave the corresponding substituted quinazoline derivatives which were subsequently processed through the sulfonyl reaction into quinazolin-4-amines containing *p*-toluenesulfonate moiety in DMF. Their structures were established by elemental analysis, IR and $^1$H NMR spectra.

**Keywords:** quinazolin-4-amine, *p*-toluenesulfonate, heterocycles, synthesis

Substituted quinazolines are important and useful skeletons in organic synthesis and medicine chemistry.[1] Quinazolines and related fused heterocycles have been found to possess significant pharmacological activities.[2] Quinazoline derivatives have been utilised extensively in medicinal chemistry due to its privileged structure that shows various pharmacological activities, such as antibacterial,[3] antihypertensive,[4] anti-inflammatory,[5] antifungal,[6] anticonvulsant[7] and anticancer activities[8–10] among others. This scaffold has been identified as new class of cancer chemotherapeutic agents acting as potent inhibitors for epidermal growth factor receptor (EGFR).[11,12]

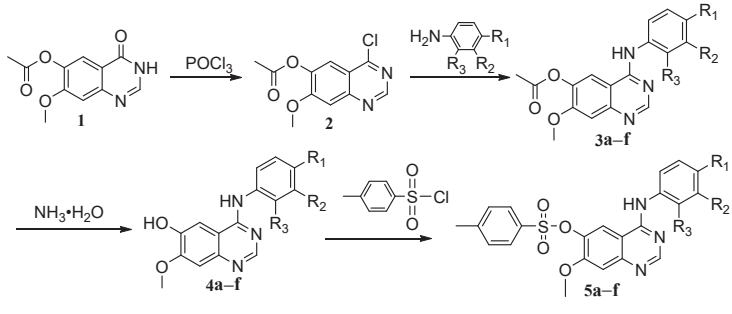
Our interest in fused quinazoline heterocycles is due to their known biological activity reported in the literature.[11] In order to find novel antitumor bioactive compounds, several new kind of quinazoline derivatives have been synthesised in our laboratory.[13] We now report the synthesis a series of quinazolin-4-amines by a four-step method.

## Results and discussion

The synthetic methods for compounds **5a**–**f** are outlined in Scheme 1. The substituted quinazolin-4-amine derivatives have been synthesised starting from compound **1**. Upon refluxing with freshly distilled phosphoryl chloride ($POCl_3$) in presence of triethylamine ($Et_3N$), compound **1** yielded the corresponding key 4-chloro intermediates **2**, which were used without purification. Reaction of **2** with the substituted anilines in a molar ratio 1:1.1, in toluene under reflux gave the desired compounds **3a**–**f** at 90 °C. Compounds **3a**–**f** were converted into **4a**–**f** by reaction with ammonium hydroxide (28%) in methanol solution at room temperature for 12 h with a high yield. Finally **5a**–**f** were prepared by reaction with *p*-toluenesulfonyl chloride in DMF at 90 °C for 12 h. Compounds **5a**–**f** were appropriately established by spectroscopic and analytical methods. IR shows the peak at about 3500–3600 cm$^{-1}$ results from the stretching vibration of aromatic amino in all products. $^1$H NMR data were consistent with structures **5a**–**f**, for example, the $^1$H NMR spectrum for compound **5f** exhibits a sharp singlet at 2.43 and another singlet at 3.57 ppm, corresponding to the methyl proton at benzene ring and to the methoxy proton at quinazoline ring, respectively. Aromatic protons resonate as multiples at δ 7.17–8.46. The presence of these signals agrees with the proposed structure reaction route.

## Conclusion

In summary, we have prepared several new quinazolin-4-amines containing *p*-toluenesulfonate moiety **5a**–**f**. The structure elucidation of these compounds was achieved using IR, $^1$H NMR and elemental analyses. These new compounds like all other biologically active heterocyclic compounds may be good candidates for investigating their pharmaceutical properties in biological systems. These studies are currently in progress in our laboratory and will be published in due course.




| Comp. | a | b | c | d | e | f |
|---|---|---|---|---|---|---|
| $R_1$ | Cl | Cl | H | $OCH_3$ | Cl | F |
| $R_2$ | H | F | $OCH_3$ | H | Cl | H |
| $R_3$ | H | H | H | H | F | F |

**Scheme 1**

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## Experimental

Unless specified otherwise, all starting materials and reagents were obtained from commercial supplies without further purification. All melting points were taken on a Beijing Taike X-4 microscopy melting point apparatus and were uncorrected. $^1$H NMR spectra were recorded on a Bruker Biospin 400 MHz instrument using TMS as the internal standard. All chemical shifts are reported in ppm. IR spectra were recorded on a Bruker Platinum ART Tensor II FTIR spectrometer. Elemental analysis of the newly synthesised compounds was carried out on Carlo Erba 1108 analyser and are found within the range of theoretical value. Compound **1** was synthesised according to reported procedures.[14]

*Synthesis of 4-chloro-7-methoxyquinazolin-6-yl acetate* (**2**): A mixture of **1** (1.0 g, 4.27 mmol), triethylamine (1.2 mL, 8.66 mmol) and phosphorus oxychloride (1.2 mL, 13.11 mmol) in toluene (15 mL) was heated to 80 °C for 4 h, which directly to the next step reaction without purification.

*Synthesis of 7-methoxy-4-(substituted anilines)quinazolin-6-yl acetate* (**3a**–**f**)*; general procedure*

A mixture of substituted anilines (4.70 mmol) in toluene (25 mL) was added to the above reaction solution, followed by stirring for 3 h. Upon completion of the reaction, the resulting mixture was cooled to 20 °C. The solid thus obtained was filtered under a reduced pressure and washed with toluene (20 mL). Isopropanol (18 mL) was added to the solid, which was then stirred for 5 h. The resulting solid was filtered and washed with isopropanol (10 mL). The solid was dried at 50 °C in the oven to afford **3a**–**f** as white powder.

*4-[(4-chlorophenyl)amino]-7-methoxyquinazolin-6-yl acetate* (**3a**) Yield 92.0%; m.p. 201–203 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3285 (NH), 1771 (C=O), 1460, 1266; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.39 (s, 3H, $CH_3$), 4.01 (s, 3H, $OCH_3$), 7.54–7.57 (m, 2H, ArH), 7.62 (s, 1H, ArH), 7.78–7.81 (m, 2H, ArH), 8.94 (d, *J* = 2.8 Hz, 2H, ArH), 11.79 (d, *J* = 2.0 Hz, 1H, NH); Anal. calcd for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; N, 12.22; found: C, 59.45; H, 4.18; N, 12.29%.

*4-[(4-chloro-3-fluorophenyl)amino]-7-methoxyquinazolin-6-yl acetate* (**3b**): Yield 93.2%; m.p. 220–222 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 1776 (C=O), 1471, 1455, 1257; $^1$H NMR (DMSO-$d_6$, 400 MHz):δ 2.38 (s, 3H, $CH_3$), 4.00 (s, 3H, $OCH_3$), 7.52–7.77 (m, 1H, ArH), 7.78 (s, 1H, ArH), 7.79–7.81 (m, 1H, ArH), 8.08–8.10 (m, 1H, ArH), 8.93 (s, 1H, ArH), 8.97 (s, 1H, ArH), 11.75 (s, 1H, NH); Anal. calcd for $C_{17}H_{13}ClFN_3O_3$: C, 56.44; H, 3.62; N, 11.62; found: C, 56.49; H, 3.68; N, 11.69%.

*7-methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-yl acetate* (**3c**): Yield 91.1%; m.p. 227–229 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 1771 (C=O), 1456, 1218, 1204; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.39 (s, 3H, $CH_3$), 3.79 (s, 3H, $OCH_3$), 4.01 (d, *J* = 5.2 Hz, 3H, $OCH_3$), 6.90–6.95 (m, 1H, ArH), 7.32–7.38 (m, 2H, ArH), 7.39–7.42 (m, 1H, ArH), 7.58 (s, 1H, ArH), 8.83 (s, 1H, ArH), 8.923 (s, 1H, ArH), 11.49 (s, 1H, NH); Anal. calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; found: C, 63.77; H, 5.09; N, 12.45%.

*7-methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl acetate* (**3d**): Yield 96.6%; m.p. 253–255 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3381 (NH), 1771 (C=O), 1508, 1469, 1282; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.39 (d, *J* = 4.0 Hz, 3H, $CH_3$), 3.80 (d, *J* = 0.8 Hz, 3H, $OCH_3$), 3.99 (s, 3H, $OCH_3$), 3.01–3.04 (m, 2H, ArH), 7. 90 (d, *J* = 4.0 Hz, 2H, ArH), 7.61 (d, *J* = 2, 1H, ArH), 8.86 (s, 2H, ArH), 11.61 (s, 1H, NH); Anal. calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; found: C, 63.73; H, 5.08; N, 12.44%.

*4-[(3,4-dichloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl acetate* (**3e**): Yield 94.0%; m.p. 211–213 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.38 (s, 3H, $CH_3$), 4.01 (s, 3H, $OCH_3$), 7.57–7.69 (m, 3H, ArH), 8.76 (s, 1H, ArH), 8.92 (s, 1H, ArH); Anal. calcd for $C_{17}H_{12}Cl_2FN_3O_3$: C, 51.54; H, 3.05; N, 10.61; found: C, 51.59; H, 3.09; N, 10.68%.

*4-[(2,4-difluorophenyl)amino]-7-methoxyquinazolin-6-yl acetate* (**3f**): Yield 94.3%; m.p. 216–218 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 2978, 2945, ($CH_3$), 1766 (C=O), 1474, 1396, 1035; Anal. calcd for $C_{17}H_{13}F_2N_3O_3$: C, 59.13; H, 3.79; N, 12.17; found: C, 59.19; H, 3.84; N, 12.25%.

*Synthesis of 7-methoxy-4-(substituted anilines)quinazolin-6-ol* (**4a**–**f**)*; general procedure*

7-methoxy-4-(substituted anilines)quinazolin-6-yl acetate (30 mmol) (**3a**–**f**) was admixed with methanol (100 mL). The mixture was cooled to 10 °C, added with an ammonia solution (45 g), and stirred for 5 hours at 20 °C. The solid thus obtained was filtered and washed with a mixed solvent of methanol (20 mL) and water (20 mL). The resulting solid was dried at 50 °C in an oven to afford **4a**–**f** as white powder.

*4-[(4-chlorophenyl)amino]-7-methoxyquinazolin-6-ol* (**4a**): Yield 67.3%; m.p. 252–254 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3378 (NH), 3356 (OH), 1455, 1274; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.98 (s, 3H, $OCH_3$), 7.21 (s, 1H, ArH), 7.38–7.42 (m, 2H, ArH), 7.84 (s, 1H, ArH), 7.92–7.96 (m, 2H, ArH), 8.47 (d, *J* = 4.8 Hz, 1H, ArH), 9.48 (s, 1H, NH); Anal. calcd for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93; found: C, 59.76; H, 4.03; N, 13.98%.

*4-[(4-chloro-3-fluorophenyl)amino]-7-methoxyquinazolin-6-ol* (**4b**): Yield 69.0%; m.p. > 260 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3382 (OH), 1470, 1245; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.98 (s, 3H, $OCH_3$), 7.21 (d, *J* = 5.2 Hz, 1H, ArH), 7.41 (t, *J* = 9.2 Hz, 1H, ArH), 7.79 (s, 1H, ArH), 8.22 (dd, *J* = 2.4 Hz, *J* = 6.8 Hz, 1H, ArH), 8.48 (s, 1H, ArH), 9.49 (s, 1H, NH); Anal. calcd for $C_{15}H_{11}ClFN_3O_2$: C, 56.35; H, 3.47; N, 13.14; found: C, 56.39; H, 3.48; N, 13.17%.

*7-methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-ol* (**4c**): Yield 97.0%; m.p. 246–248 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3306 (OH), 1466, 1271; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.77 (s, 3H, $OCH_3$), 6.65 (s, 1H, ArH), 7.21 (s, 1H, ArH), 7.25 (s, 1H, ArH), 7.51 (s, 1H, ArH), 7.57 (s, 1H, ArH), 7.82 (s, 1H, ArH), 8.46 (s, 1H, ArH), 9.31 (s, 1H, OH), 9.647(s, 1H, NH); Anal. calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13; found: C, 64.67; H, 5.17; N, 14.19%.

*7-methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-ol* (**4d**): Yield 76.5%; m.p. 261–263 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3337 (OH), 1510, 1472, 1225; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.97 (s, 3H, $OCH_3$), 6.93–6.96 (m, 2H, ArH), 7.17 (s, 1H, ArH), 7.68 (d, *J* = 2.4 Hz, 1H, ArH), 7.70–7.71 (m, 1H, ArH), 7.78 (s, 1H, ArH), 8.36 (s, 1H, ArH), 9.26 (s, 1H, NH); Anal. calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13; found: C, 64.71; H, 5.16; N, 14.19%.

*4-[(3,4-dichloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-ol* (**4e**): Yield 88.4%; m.p. > 260 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3460 (OH), 1495, 1207; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 3.97 (s, 3H, $OCH_3$), 7.21 (s, 1H, ArH), 7.52–7.62 (m, 2H, ArH), 7.68 (s, 1H, ArH), 8.35 (s, 1H, ArH), 9.57 (br, 2H, NH and OH); Anal. calcd for $C_{15}H_{10}Cl_2FN_3O_2$: C, 50.87; H, 2.85; N, 11.86; found: C, 50.94; H, 2.90; N, 11.91%.

*4-((2,4-difluorophenyl)amino)-7-methoxyquinazolin-6-ol* (**4f**): Yield 90.0%; m.p. 260–262 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3225 (OH), 1510, 1137; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 4.03 (s, 3H, $OCH_3$), 7.10–7.12 (d, *J* = 8.0 Hz, 1H, ArH), 7.31 (s, 1H, ArH), 7.49–7.51 (d, *J* = 8.0 Hz, 2H, ArH), 7.90 (s, 1H, ArH), 8.80 (s, 1H, ArH); Anal. calcd for $C_{15}H_{11}F_2N_3O_2$: C, 59.41; H, 3.66; N, 13.86; found: C, 59.48; H, 3.69; N, 13.93%.

*Synthesis of 7-methoxy-4-(substituted anilines)quinazolin-6-toluenesulfonate* (**5a**–**f**)*; general procedure*

A mixture of the appropriate 7-methoxy-4-(substituted aniline) quinazolin-6-ol (3.0 mmol) **4a**–**f**, $K_2CO_3$ (3.0 mmol) and 4-toluenesulfonyl chloride (3.0 mmol) in 50 mL dry *N,N*-Dimethylformamide (DMF) was stirred at 90 °C for 5 h. The reaction mixture was diluted with water (100 mL), extracted by ethyl acetate (100 mL × 3), and dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude product, which was purified by column chromatography to afford **5a**–**f** as white powder.

*4-[(4-chlorophenyl)amino]-7-methoxyquinazolin-6-yl 4-methylbenzenesulfonate* (**5a**): Yield 60.9%; m.p. 251–252 °C; IR ($\nu_{max}$, cm$^{-1}$) KBr: 3425 (NH), 1419, 1391, 1237, 1213, 762; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.43 (s, 3H, $CH_3$), 3.55 (s, 3H, $OCH_3$), 7.210(s, 1H, ArH), 7.44–7.48 (m, 4H, ArH), 7.74 (d, *J* = 7.6 Hz, 2H, ArH), 7.89 (d, *J* = 8.8 Hz, 2H, ArH), 8.57 (s, 2H, ArH), 9.89 (s, 1H, NH); Anal. calcd for $C_{22}H_{18}ClN_3O_4S$: C, 57.96; H, 3.98; N, 9.22; found: C, 58.01; H, 4.07; N, 9.28.

*4-[(4-chloro-3-fluorophenyl)amino]-7-methoxyquinazolin-6-yl 4-methylbenzenesulfonate* (**5b**): Yield 54.6%; m.p. 228–229 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 3599 (NH), 1496, 1447, 1365; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.43 (s, 3H, $CH_3$), 3.55 (s, 3H, $OCH_3$), 7.21 (s, 1H, ArH), 7.42–7.48 (m, 3H, ArH), 7.73–7.78 (m, 2H, ArH), 7.79–7.83 (m, 1H, ArH), 8.15–8.17 (m, 1H, ArH), 8.54 (s, 1H, ArH), 8.59 (s, 1H, ArH), 9.90 (s, 1H, NH); Anal. calcd for $C_{22}H_{17}ClFN_3O_4S$: C, 55.76; H, 3.62; N, 8.87; found: C, 55.80; H, 3.69; N, 8.95%.

*7-methoxy-4-[(3-methoxyphenyl)amino]quinazolin-6-yl 4-methylbenzenesulfonate* (**5c**): Yield 46.1%; m.p. 113–115 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 3421 (NH), 1532, 1484, 1191, 820; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.43 (s, 3H, $CH_3$), 3.55 (s, 3H, $OCH_3$), 3.79 (s, 3H, $OCH_3$), 6.72–6.74 (m, 1H, ArH), 7.21 (s, 1H, ArH), 7.31 (s, 1H, ArH), 7.46–7.512 (m, 4H, ArH), 7.74 (d, *J* = 8.4 Hz, 2H, ArH), 8.58 (d, *J* = 8.0 Hz, 2H, ArH), 9.77 (s, 1H, NH); Anal. calcd for $C_{23}H_{21}N_3O_5S$: C, 61.18; H, 4.69; N, 9.31; found: C, 61.24; H, 4.77; N, 9.41%.

*7-methoxy-4-[(4-methoxyphenyl)amino]quinazolin-6-yl 4-methylbenzenesulfonate* (**5d**): Yield 52.0%; m.p. 219–221 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 3556 (NH), 1507, 1471, 1456, 1276, 826; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.43 (s, 3H, $CH_3$), 3.54 (s, 3H, $OCH_3$), 3.78 (s, 3H, $OCH_3$), 6.98 (d, *J* = 8.8 Hz, 2H, ArH), 7.17 (s, 1H, ArH), 7.47 (d, *J* = 8.0 Hz, 2H, ArH), 7.66 (d, *J* = 8.8 Hz, 2H, ArH), 7.74 (d, *J* = 8.0 Hz, 2H, ArH), 8.48 (s, 1H, ArH), 8.54 (s, 1H, ArH), 9.75 (s, 1H, NH); Anal. calcd for $C_{23}H_{21}N_3O_5S$: C, 61.18; H, 4.69; N, 9.31; found: C, 61.24; H, 4.79; N, 9.38%.

*4-[(3,4-dichloro-2-fluorophenyl)amino]-7-methoxyquinazolin-6-yl 4-methylbenzenesulfonate* (**5e**): Yield 48.8%; m.p. 230–231 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 3622 (NH), 1524, 1466, 1389, 810; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.44 (s, 3H, $CH_3$), 3.59 (s, 3H, $OCH_3$), 7.25 (s, 1H, ArH), 7.48 (d, *J* = 8.0 Hz, 2H, ArH), 7.59 (s, 2H, ArH), 7.76 (d, *J* = 8.0 Hz, 2H, ArH), 8.46 (s, 1H, ArH), 8.50 (s, 1H, ArH), 10.08 (s, 1H, NH); Anal. calcd for $C_{22}H_{16}Cl_2FN_3O_4S$: C, 51.98; H, 3.17; N, 8.27; found: C, 52.09; H, 3.26; N, 8.34%.

*4-[(2,4-difluorophenyl)amino]-7-methoxyquinazolin-6-yl 4-methylbenzenesulfonate* (**5f**): Yield 43.8%; m.p. 196–197 °C; IR ($\nu_{max}$, $cm^{-1}$) KBr: 3569 (NH), 3476 (NH), 1507, 1294, 807; $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.43 (s, 3H, $CH_3$), 3.57 (s, 3H, $OCH_3$), 7.17 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.34–7.56 (m, 4H, ArH), 7.75 (d, *J* = 8.0 Hz, 2H, ArH), 8.44–8.46 (d, *J* = 8.0 Hz, 2H, ArH), 9.87 (s, 1H, NH); Anal. calcd for $C_{22}H_{17}F_2N_3O_4S$: C, 57.76; H, 3.75; N, 9.19; found: C, 57.88; H, 3.78; N, 9.25%.

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## Electronic Supplementary Information

The ESI {IR and $^1$H NMR} is available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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