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Novel Synthesis of Differentially Substituted 5,7-Dialkoxyquinazolin-4-ones

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Abstract: The preparation of 7-ethoxy-5-fluoroquinazolin-4-one, starting from 3,5-difluorophenol, is described. Further reaction with alkoxide then gives differentially substituted 5,7-dialkoxyquinazolin-4-ones.

Keywords: Anthranilic acid, 2-aminobenzonitrile, 5,7-dialkoxyquinazolin-4-ones, 5,7-difluoroquinazolin-4-one

Pharmaceutical interest in 4-anilinoquinazolines has increased considerably over the past decade, due mainly to the discovery that these compounds are potent and selective inhibitors of many protein kinases implicated in proliferative diseases.[1] Much of the earlier work focused on variation of the solubilizing side chain at C-6 and/or C-7 of the quinazoline core and resulted in the discovery and subsequent regulatory approval of the EGF receptor tyrosine kinase inhibitors gefitinib[2] and erlotinib[1] (Fig. 1) for the treatment of non-small cell lung cancer.

As part of our more recent work on inhibitors of the EGFR[3] and c-Src[4] family of kinases, we have investigated switching the quinazoline C-6 substituent to the C-5 position. In this article, we describe a regioselective and highly versatile route to differentially substituted 5,7-dialkoxyquinazolin-4-ones as precursors to the desired 4-anilino-5,7-dialkoxyquinazolines.

Quinazolinones **1** with identical C-5 and C-7 alkoxy substituents are readily prepared from symmetrically disubstituted anilines via the

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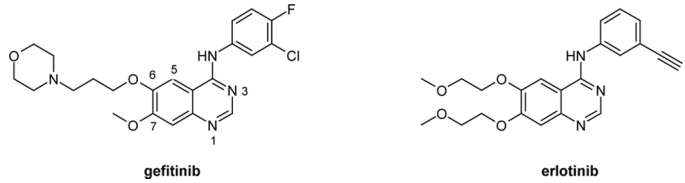
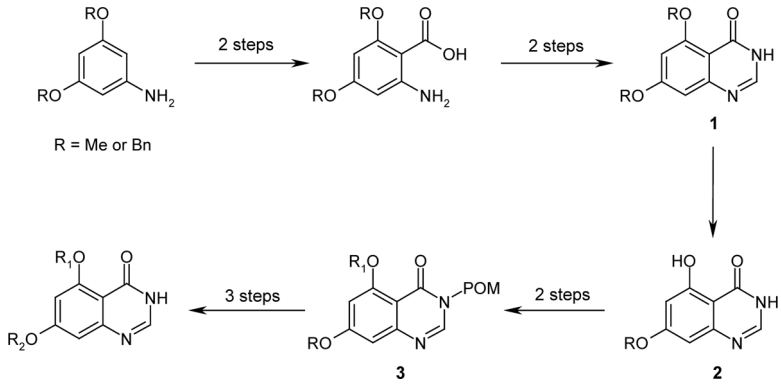


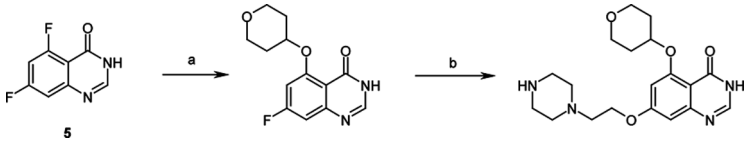
Figure 1.

corresponding isatins and anthranilic acids as outlined in Scheme 1.[5] The C-5 alkoxy group can be selectively deprotected by treatment with magnesium bromide or pyridine hydrochloride in pyridine to give **2**, which, after POM protection of the quinazolinone N-3, can be further elaborated by Mitsunobu or direct alkylation. Additionally, homologation at C-7 can then be achieved by deprotection of the C-7 benzyl group in **3** followed by alkylation of the resulting 7-hydroxyquinazolinone, thereby enabling sequential functionalization of the C-5 and C-7 positions.

The use of 5,7-difluoroquinazolin-4-one **5** also allows differing functionalities to be introduced, this time through selective S_NAr displacements of the reactive fluorine leaving groups (Scheme 2).[5] Here the 5-fluorine is much more reactive than the 7-fluorine and can be displaced selectively by alkoxides at room temperature in a few minutes. However, because of the differing reactivities of the two fluorines, the C-5 substituent again has to be introduced before the C-7. A further limitation of this approach is that the more forcing conditions required for the second displacement reaction[6] can lead to displacement of the first introduced alkoxide group (particularly when this group is methoxide) in competition with displacement of the 7-fluorine, resulting in scrambling of the two groups.



Scheme 1.



Scheme 2. Reagents and conditions: (a) 4-hydroxytetrahydropyran, NaH, DMF, 20 °C, 30 min.; (b) 2-piperazin-1-ylethanol, t-BuOK, THF, reflux, 15 h.

Although these methodologies allow introduction of a range of C-7 substituents subsequent to functionalization of C-5, we also sought a route that would enable variation of the C-5 substituent at a later stage of the synthesis. An ideal intermediate for carrying out such a variation would be a 5-fluoro-7-alkoxyquinazolinone **6** (Fig. 2) in which the C-7 substituent has been introduced first.

Such compounds are not described in the literature and for reasons described previously cannot be synthesized from 5,7-difluoroquinazolin-4-one. We envisaged an alternative approach involving synthesis of the quinazolinone ring with the required fluoro and alkoxy substituents already in place. Historically, quinazolinones have been prepared by the Neimentowski reaction of anthranilic acids[7] (Scheme 1), and we were aware of one attempt to prepare the required fluoro-methoxyanthranilic acid starting from 3-fluoro-5-methoxyaniline. However, Friedel–Crafts acylation of this compound with oxalyl chloride gives only the undesired regioisomeric isatin (Scheme 3).[8]

As reported by Roth and Tai,[9] it is also possible to form quinazolinone rings from 2-aminobenzonitriles by reaction with formic acid, and a suitably substituted aminobenzonitrile should thus give access to our desired fluoroalkoxyquinazolinone **6**. As shown in Scheme 4, we discovered we could access such an aminobenzonitrile starting from 3,5-difluorophenol. 3,5-Difluorophenol was first converted to benzonitrile **7** using standard functional group manipulations. Reaction with ammonia at high temperature gives aminobenzonitrile **8**,[10] which cyclizes in formic acid to give the desired 7-ethoxy-5-fluoroquinazolin-4-one **9** in good yield. Displacement of the 5-fluorine with alkoxide then takes place cleanly and under mild conditions to give a 5,7-disubstituted quinazolinone **10** in

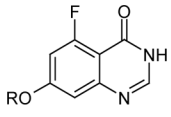
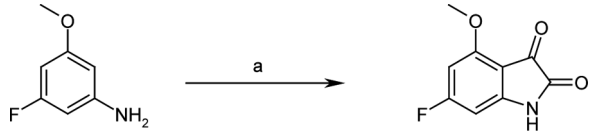
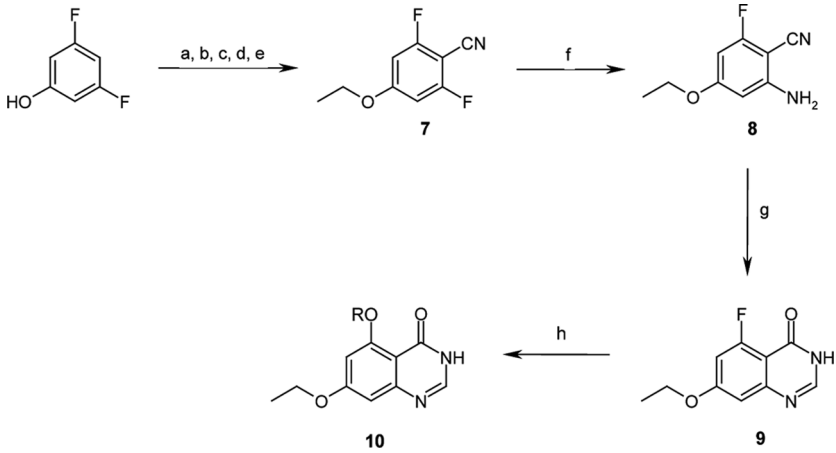


Figure 2.



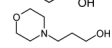
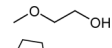
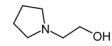
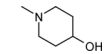
Scheme 3. Reagents: (a) oxalyl chloride.

which the 7-substituent has been introduced first. As illustrated in Table 1, quinazolinone **9** can thus be used to introduce a range of C-5 substituents in high yield while keeping the C-7 substituent constant.



Scheme 4. Regants and conditions: (a) Et_2SO_4, K_2CO_3, DMF, 80 °C; (b) n-BuLi, THF, CO_2; (c) $(COCl)_2$, DCM; (d) NH_3(aq.), THF; (e) Cl_3CCOCl, Et_3N, DCM; (f) NH_3(EtOH), 150 °C; (g) HCO_2H, c.H_2SO_4 (cat.), 100 °C; (h) ROH, NaH, DMF, 60 °C.

Table 1. Reaction of fluoroquinazolinone **9** with alkoxides derived from alcohol ROH and sodium hydride in DMF

Entry	Alcohol ROH	Yield (%)
a		77
b		90
c		73
d		79
e		76

In summary, we have introduced a new intermediate that allows the preparation of differentially substituted 5,7-dialkoxyquinazolinones and provides an alternative sequence to previously used methods. This methodology complements existing strategies and increases the synthetic scope of the anilinoquinazoline class of receptor tyrosine kinase inhibitors.

EXPERIMENTAL

^{1}H NMR spectra were recorded at 400 MHz on a Bruker DPX-400 spectrometer. LCMS were performed using a Waters 2890/ZMD micromass system. HRMS were recorded on a Thermo LTQ FT or a Waters GCT Premier system. All solvents (anhydr. where appropriate) and reagents were used as received.

1-Ethoxy-3,5-difluorobenzene

Diethyl sulfate (13.1 ml, 0.10 mol) was added to a stirred mixture of 3,5-difluorophenol (13.0 g, 0.10 mol) and potassium carbonate (20.9 g, 0.15 mol) in DMF (200 ml). The mixture was heated at 80 °C for 1.5 h. before adding further diethyl sulfate (3.3 ml, 25 mmol) and potassium carbonate (5.2 g, 37.5 mmol). After heating for a further 2 h, the mixture was cooled to room temperature, poured into water, and extracted twice with diethyl ether. The combined extracts were washed with water, dried over magnesium sulfate, and evaporated to a pale yellow oil (13.6 g, 86% yield).

^{1}H NMR (400.132 MHz, DMSO) 6.77–6.65 (m, 3H, ArH), 4.06 (q, $J = 7.0$ Hz, 2H, OCH_2), 1.32 (t, $J = 7.0$ Hz, 3H, CH_3). MS (+ve EI): 158 (M^+).

4-Ethoxy-2,6-difluorobenzoic acid

n-Butyl lithium (13.5 ml of a 1.6 M solution in hexanes, 21.6 mmol) was added dropwise to a stirred solution of 1-ethoxy-3,5-difluorobenzene (3.42 g, 21.6 mmol) in THF (30 ml) at −78 °C under an atmosphere of nitrogen. The mixture was stirred at −78 °C for 2 h. before adding excess carbon dioxide (solid, as pellets), then allowed to warm slowly to room temperature. The resulting solution was poured into water, made basic by the addition of aqueous sodium hydroxide, and extracted with diethyl ether. The aqueous layer was separated, acidified with dilute hydrochloric acid, and extracted twice with diethyl ether. The combined extracts were washed with water, dried over magnesium sulfate, and evaporated to a colorless solid (3.87 g, 89% yield).

^{1}H NMR (400.132 MHz, DMSO) 13.36 (br s, 1H, CO_2H), 6.79 (d, $J = 10.4$ Hz, 2H, ArH), 4.11 (q, $J = 7.0$ Hz, 2H, OCH_2), 1.33 (t, $J = 7.0$ Hz, 3H, CH_3). MS (+ve CI): 203 $(M + H)^+$.

4-Ethoxy-2,6-difluorobenzamide

Oxalyl chloride (3.17 ml, 36.4 mmol) was added dropwise to a stirred suspension of 4-ethoxy-2,6-difluorobenzoic acid (3.5 g, 17.3 mmol) and DMF (5 drops) in dichloromethane (50 ml). The resulting solution was stirred at room temperature for 4 h, then evaporated. The residue was dissolved in THF (20 ml) and added dropwise to a vigorously stirred 35% aqueous solution of ammonia (60 ml). After cooling the reaction in icewater for 1.5 h, the resulting colorless solid was filtered, washed with ice-cold water, and dried under vacuum (3.23 g, 93% yield).

^{1}H NMR (400.132 MHz, DMSO) 7.91 (s) and 7.65 (s, 2H, $CONH_2$), 6.74 (d, $J = 9.9$ Hz, 2H, ArH), 4.08 (q, $J = 7.0$ Hz, 2H, OCH_2), 1.32 (t, $J = 7.0$ Hz, 3H, CH_3). MS (+ve EI): 201 (M^+).

4-Ethoxy-2,6-difluorobenzonitrile (7)

Trichloroacetyl chloride (1.94 ml, 17.4 mmol) was added dropwise at 0–5 °C to a stirred suspension of 4-ethoxy-2,6-difluorobenzamide (3.18 g, 15.8 mmol) and triethylamine (4.44 ml, 31.6 mmol) in dichloromethane (25 ml). The mixture was stirred at 0–5 °C for 5 min, then washed successively with water, dilute hydrochloric acid, dilute sodium hydroxide, dilute hydrochloric acid, and water. It was then dried over magnesium sulfate and evaporated to a pale yellow solid (2.56 g, 89% yield).

^{1}H NMR (400.132 MHz, DMSO) 7.05 (d, $J = 10.2$ Hz, 2H, ArH), 4.17 (q, $J = 7.0$ Hz, 2H, OCH_2), 1.34 (t, $J = 7.0$ Hz, 3H, CH_3). LCMS (+ve CI): 184 $(M + H)^+$. HRMS (EI) calcd. for $C_9H_7F_2NO$ 183.0496; found 183.0481.

2-Amino-4-ethoxy-6-fluorobenzonitrile (8)

A solution of 4-ethoxy-2,6-difluorobenzonitrile (8.0 g, 44 mmol) in a saturated solution of ammonia in ethanol (270 ml) was heated at 150 °C in an autoclave for 16 h. The resulting solution was evaporated, and the residue was taken up in dichloromethane and washed with water. The organic solution was separated, dried over magnesium sulfate, concentrated, and purified by chromatography on silica using dichloromethane as eluent to give a colorless solid (6.07 g, 77% yield).

^{1}H NMR (400.132 MHz, DMSO) 6.32 (s, 2H, NH_2), 6.14–6.11 (m, 2H, ArH), 3.99 (q, $J = 7.0$ Hz, 2H, OCH_2), 1.30 (t, $J = 7.0$ Hz, 3H,

CH_3). MS (+ve EI): 180 (M^+). HRMS (ES) calcd. for $C_9H_9FN_2O$ (M + H) 181.07717; found 181.07716.

7-Ethoxy-5-fluoroquinazolin-4(3H)-one (9)

2-Amino-4-ethoxy-6-fluorobenzonitrile (2.5 g, 13.9 mmol) was added portionwise over 20 min to a stirred mixture of formic acid (20 ml) and conc. sulfuric acid (5 drops) heated at 100 °C. The mixture was heated at 100 °C for a further 5 h, then cooled to room temperature and quenched in icewater (80 ml). The resulting colorless solid was filtered, washed with water followed by diethyl ether, and then dried under vacuum (2.02 g, 70% yield).

^{1}H NMR (400.132 MHz, DMSO) 12.06 (br s, 1H, NH), 8.01 (s, 1H, ArH), 6.91 (d, $J = 2.8$ Hz, 1H, ArH), 6.87 (dd, $J = 12.7$, 2.8 Hz, 1H, ArH), 4.17 (q, $J = 7.0$ Hz, 2H, OCH_2), 1.36 (t, $J = 7.0$ Hz, 3H, CH_3). LCMS (+ve CI): 209 $(M + H)^+$. HRMS (ES) calcd. for $C_{10}H_9FN_2O_2$ (M + H) 209.07208; found 209.07210.

7-Ethoxy-5-(tetrahydro-2*H*-pyran-4-yloxy)quinazolin-4(3*H*)-one (10a)

Sodium hydride (93 mg of a 60% dispn. in oil, 2.31 mmol) was suspended in DMF (2 ml), then 4-hydroxytetrahydropyran (117 mg, 1.15 mmol) was added dropwise over 5 min. The resulting mixture was stirred 20 min before adding 7-ethoxy-5-fluoroquinazolin-4(3H)-one (160 mg, 0.77 mmol). The reaction was stirred at room temperature for 30 min, then heated to 60 °C for a further 30 min before cooling to room temperature and quenching in dilute aqueous ammonium chloride solution to give a pale yellow solid. It was filtered, washed with water followed by diethyl ether, and then dried (172 mg, 77% yield).

^{1}H NMR (399.902 MHz, DMSO) 11.7 (br s, 1H, NH), 7.90 (s, 1H, ArH), 6.66 (d, $J = 2.0$ Hz, 1H, ArH), 6.61 (d, $J = 1.9$ Hz, 1H, ArH), 4.77–4.70 (m, 1H, OCH), 4.14 (q, $J = 6.9$ Hz, 2H, $ArOCH_2$), 3.94–3.89 (m, 2H, OCH_2), 3.53–3.48 (m, 2H, OCH_2), 1.99–1.88 (m, 2H, CH_2), 1.73–1.62 (m, 2H, CH_2), 1.36 (t, $J = 7.0$ Hz, 3H, CH_3). LCMS (+ve CI): 291 $(M + H)^+$. HRMS (ES) calcd. for $C_{15}H_{18}N_2O_4$ (M + H) 291.13393; found 291.13394.

7-Ethoxy-5-(3-morpholin-4-ylpropoxy)quinazolin-4(3*H*)-one (10b)

Compounds **10b–e** were prepared in the same manner as described previously.

^{1}H NMR (399.902 MHz, DMSO) 11.74 (br s, 1H, NH), 7.96 (s, 1H, ArH), 6.69 (d, $J = 2.3$ Hz, 1H, ArH), 6.58 (d, $J = 2.3$ Hz, 1H, ArH), 4.19 (q, $J = 7.0$ Hz, 2H, $ArOCH_2$), 4.13 (t, $J = 6.1$ Hz, 2H, $ArOCH_2$), 3.66 (m, 4H, OCH_2), 2.70–2.59 (m, 2H, NCH_2), 2.55–2.41 (m, 4H, NCH_2), 1.98 (quintet, $J = 6.4$ Hz, 2H, CH_2), 1.41 (t, $J = 7.0$ Hz, 3H, CH_3). LCMS (+ve CI): 334 $(M + H)^+$. HRMS (ES) calcd. for $C_{17}H_{23}N_3O_4$ (M + H) 334.17613; found 334.17618.

7-Ethoxy-5-(2-methoxyethoxy)quinazolin-4(3*H*)-one (10c)

^{1}H NMR (399.902 MHz, DMSO) 11.7 (br s, 1H, NH), 7.90 (s, 1H, ArH), 6.65 (d, $J = 2.3$ Hz, 1H, ArH), 6.54 (d, $J = 2.3$ Hz, 1H, ArH), 4.16 (m, 4H, OCH_2), 3.71 (m, 2H, OCH_2), 3.37 (s, 3H, OCH_3), 1.37 (t, $J = 6.9$ Hz, Hz, 3H, CH_3). LCMS (+ve CI): 265 $(M + H)^+$. HRMS (ES) calcd. for $C_{13}H_{16}N_2O_4$ (M + H) 265.11828; found 265.11826.

7-Ethoxy-5-(2-pyrrolidin-1-ylethoxy)quinazolin-4(3*H*)-one (10d)

^{1}H NMR (399.902 MHz, DMSO) 11.64 (br s, 1H, NH), 7.90 (s, 1H, ArH), 6.64 (d, $J = 2.3$ Hz, 1H, ArH), 6.54 (d, $J = 2.3$ Hz, 1H, ArH), 4.17–4.12 (m, 4H, OCH_2), 2.85 (t, $J = 6.0$ Hz, 2H, NCH_2), 2.62–2.56 (m, 4H, NCH_2), 1.68 (m, 4H, CH_2CH_2), 1.37 (t, $J = 7.0$ Hz, 3H, CH_3). LCMS (+ve CI): 304 $(M + H)^+$. HRMS (ES) calcd. for $C_{16}H_{22}N_3O_3$ (M + H) 304.16557; found 304.16556.

7-Ethoxy-5-[(1-methylpiperidin-4-yl)oxy]quinazolin-4(3*H*)-one (10e)

^{1}H NMR (399.902 MHz, DMSO) 11.57 (br s, 1H, NH), 7.89 (s, 1H, ArH), 6.65 (d, $J = 2.4$ Hz, 1H, ArH), 6.56 (d, $J = 2.3$ Hz, 1H, ArH), 4.53–4.47 (m, 1H, OCH), 4.14 (q, $J = 7.0$ Hz, 2H, $ArOCH_2$), 2.68–2.63 (m, 2H, NCH_2), 2.26–2.18 (m, 2H, NCH_2), 2.19 (s, 3H, NCH_3), 1.93–1.86 (m, 2H, CH_2), 1.77–1.69 (m, 2H, CH_2), 1.36 (t, $J = 7.0$ Hz, 3H, CH_3). LCMS (+ve CI): 304 $(M + H)^+$. HRMS (ES) calcd. for $C_{16}H_{22}N_3O_3$ (M + H) 304.16557; found 304.16553.

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