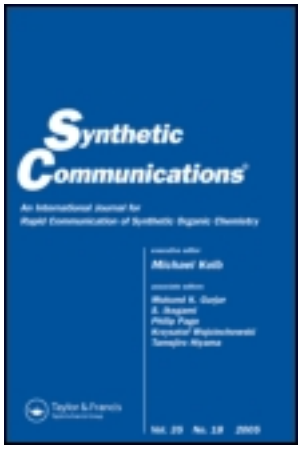

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SYNTHESIS OF SUBSTITUTED QUINAZOLINES: APPLICATION TO THE SYNTHESIS OF VERUBULIN

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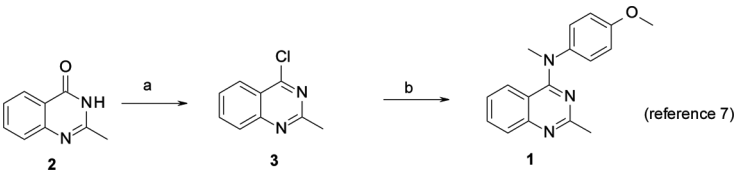
GRAPHICAL ABSTRACT



Abstract *Through newly adapted methodology, 2-methyl-3*H*-quinazolin-4-one was activated using a number of methods followed by displacement to afford 4-aminoquinazolines. The most useful of these processes utilize the p-toluenesulfonate ester or I_2/PPh_3 activation. Using this methodology, the anticancer vascular targeting clinical candidate verubulin (**1**) was synthesized in a highly efficient manner.*

Keywords 4-Aminoquinazoline; I_2 PPh_3; quinazolin-4-one; *p*-toluenesulfonate ester

INTRODUCTION

4-Aminoquinazolines are ubiquitous structures in medicinal chemistry. In addition to their use as antirheumatic cytokine-suppressing agents,[1] adenosine A_3 receptor ligands,[2] and vanilloid 1 receptor antagonists,[3] they provide a scaffold for the presentation of hydrogen bond donors and acceptors suitable for kinase inhibition. U.S. Food and Drug Administration–approved non–small cell lung cancer therapeutics gefitinib and erlotinib are 4-aminoquinazoline inhibitors of epidermal growth factor receptor (EGFR).[4] Similar compounds have been described as inhibitors of platelet derived growth factors phosphorylation[5] and c-Src.[6]

As part of our efforts to identify new cancer treatments, we examined the synthesis of 4-amino substituted quinazoline compounds such as verubulin (Azixa, MPC-6827, **1**).[7] As published previously, **1** is a very potent inhibitor of β-tubulin that interacts at or near the cholchicine binding site.[8] Compound **1** has also been shown to act as a vascular targeting agent that is highly efficacious against a number

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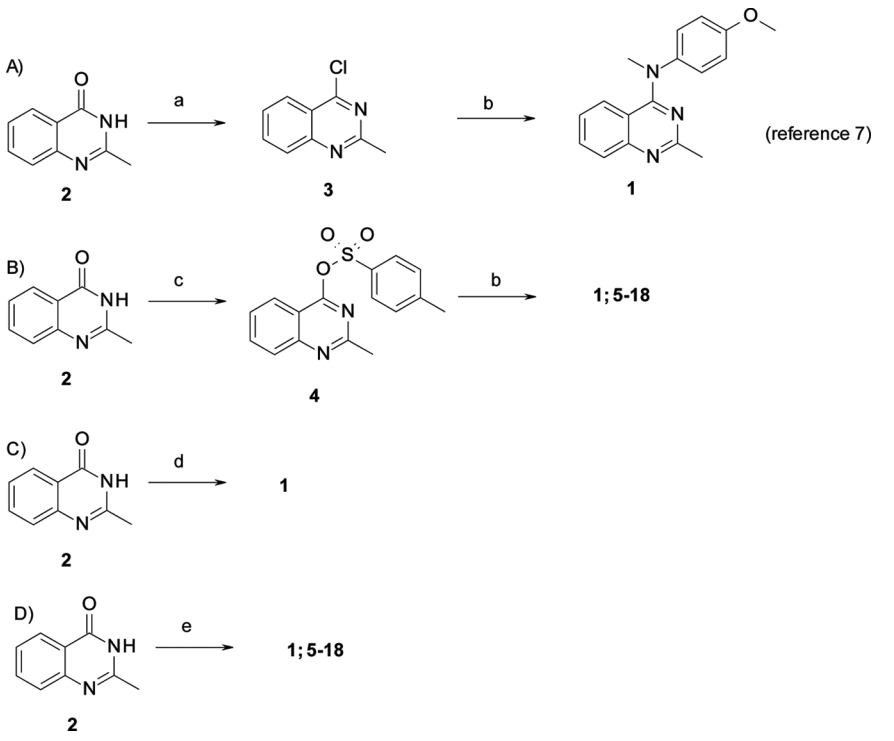
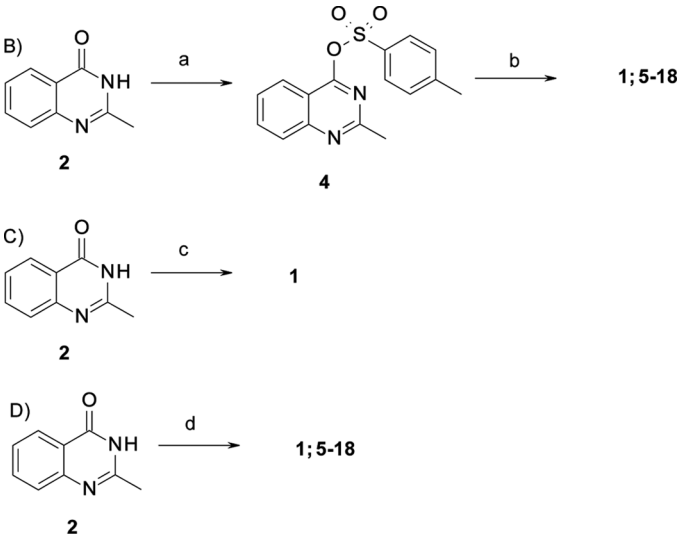
of cancer cell lines in mouse xenograft studies.[9] Recently completed phase II clinical trials have shown that **1** is safe and well tolerated when coadministered with carboplatin in patients with recurrent/refractory glioblasoma multiforme[10a] and when coadministered with temozolomide in patients with metastatic melanoma.[10b]

Via more classical synthetic methodology, **1** has been synthesized by activation of 2-methyl-3*H*-quinazolin-4-one (**2**) as chloride **3** by treatment with $POCl_3$ (Scheme 1A).[7] Subsequent reaction of 4-chloroquinazoline **3** with *N*-methyl-*p*-anisidine gave **1**. This route has several drawbacks: chloride **3** is quite difficult to work with, has a very foul odor, and is not stable to prolonged storage. Literature has shown that similar heterocycles, such as 4-hydroxypyrimidines, can be substituted through activation as their sulfonate esters.[11] Subsequent displacement of the sulfonate ester with a variety of nucleophiles gives the desired substitution products in good yield. It was envisioned that this methodology could be expanded to the synthesis of **1**, resulting in good yield and with the added benefit of eliminating the problematic chloride **3** from the synthetic route.

As outlined in Scheme 1B, treatment of quinazolinone **2** with *p*-toluenesulfonyl chloride, triethylamine, and a catalytic amount of dimethylaminopyridine (DMAP) in CH_2Cl_2 resulted in activated quinazoline sulfonate ester **4** in 91% yield. The sulfonate ester **4** was found to be stable to both silica-gel chromatography and room temperature storage for several months. Treatment of **4** with *N*-methyl-*p*-anisidine



Scheme 1. Reagents: (a) $POCl_3$; (b) *N*-methyl-*p*-anisidine, 2-PrOH/CH_2Cl_2 (c) TsCl, Et_3N, DMAP, CH_2Cl_2; (d) coupling agent, DIEA, DMF; and (e) I_2, PPh_3, DIEA, $PhCH_3$.



Scheme 2. Reagents: (a) TsCl, Et_3N, DMAP, CH_2Cl_2; (b) *N*-methyl-*p*-anisidine, 2-PrOH/CH_2Cl_2; (c) coupling agent, DIEA, DMF; and (d) I_2, PPh_3, DIEA, $PhCH_3$.

in 2-propanol, with CH_2Cl_2 added for solubility, resulted in displacement of the sulfonate, yielding **1** in >99% yield.

We next explored the scope of this reaction: sulfonate ester **4** was allowed to react under conditions analogous to those used for the synthesis of **1**. As 4-aminoquinazolines are a common medicinal chemistry building block, a range of primary aliphatic and aromatic amines were investigated, as were secondary amines of varying size and electronics (Table 1, conditions B). With the notable exception of extremely hindered derivatives, all amines studied reacted in a near-quantitative fashion when performed on a 0.5 mmol scale and as judged by high-performance liquid chromatoraphy–mass spectrometry (HPLC-MS) using Ph_2O as an internal standard. Reactions with both diisopropylamine and diphenylamine resulted in recovery of sulfonate **4** along with hydrolysis product **2** without any evidence of product by HPLC-MS. The synthesis of **1** by this method was also performed on a 3.1-g (10-mmol) scale with 99% isolated yield. This result demonstrates that the synthesis of **1** via the sulfonate ester route is amenable to multigram synthesis, while benefiting from both the reduced price of *p*-toluenesulfonyl chloride ($20–30/kg vs. $60–70/kg for phosphorus oxychloride) and the stoichiometric vs. solvent quantities.

Other synthetic methods of synthesizing 4-aminoquinazolines were also examined. The peptide coupling reagent benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) has been used to synthesize 4-aminopurines and 4-aminoquinazolines,[12] and consequently we attempted the synthesis of **1** utilizing a range of peptide coupling conditions (Scheme 1C). Contrary to literature reports utilizing 4-hydroxyquinazoline,[12] only a small amount (<10%) of product was observed by HPLC-MS, and none was isolated with BOP when the reaction was conducted using N,N-diisopropylethylamine (DIEA) ($^iPr_2NEt$) in dimethylformamide (DMF) at 60 °C (Table 2). The use of AcCN as solvent and

Table 1. Scope of amine displacement reactions

Compound	Amine	Conditions (% conversion[a])		
		B	**D1**	**D2**
1	*N*-Methyl-*p*-anisidine	99+	64	99+
5	4-OMePh	99+	2	87
6	4-MePh	99+	26	36
7	3-MePh	99+	22	30
8	2-MePh	99+	99+	82
9	Ph	99+	40	45
10	4-ClPh	99+	99+	99+
11	4-NO_2Ph	86	99+	99+
12	4-Aminopyridine	75[b]	50	79
13	$MeNH_2$-HCl	99+	0	5[c]
14	Me_2NH-HCl	99+	0	99+[c]
15	Morpholine	99+	99+	99+
16	n-$BuNH_2$	99+	0	0
17	*i*-Pr_2NH	0	0	0
18	Ph_2NH	0	0	0

Notes. Conditions B: **4**, R^1R^2NH (1.2 equiv.), 10:1 IPA/CH_2Cl_2, rt, 1 h. Conditions D1: **2**, R^1R^2NH (1.2 equiv.), I_2 (1.2 equiv.), PPh_3 (1.2 equiv.), DIEA (2 equiv.), $PhCH_3$, 60 °C, 19 h. Conditions D2: R^1R^2NH (5 equiv.), I_2 (3.6 equiv.), PPh_3 (3.8 equiv.), DIEA (5.8 equiv.), CH_2Cl_2, rt, 19 h.

[a]Conversion determined by HPLC using Ph_2O as an internal standard (Ref. 12c).

[b]Conversion complete at 4 h. by HPLC.

[c]11.6 equiv. DIEA used.

1,3-diazabicyclo[5.4.0]undec-7-ene (DBU) as base improved the conversion, but only when the reaction was run at reflux. Much better results were obtained with (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), O-(7-azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HATU), O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HBTU), O-(6-chlorobenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate (HCTU), and O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TBTU) (Table 2, entries 2–6). The major by-product of each reaction was the dimethylamine adduct that was clearly observed by HPLC-MS. This likely resulted from the decomposition of DMF under the reaction conditions as reported by others.[11c] As seen previously,[12] an analog of hydroxybenzotriazole was required for the reaction to proceed as the use of bromotripyrrolidinophosphonium hexafluorophosphate (PyBrop) yielded no product. In many cases, it was difficult to chromatographically separate **1** from coupling reagent by-products, and the isolated yields were significantly lower than the >80% conversion observed by HPLC-MS for entries 4–8.

Carbodiimide reagents N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDCI) and dicyclohexylcarbodiimide (DIC), in the presence or absence of 1-hydroxybenzotriazole hydrate (HOBt), bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl), 1,1-carbonyldiimidazole (CDI), and tetraethyl pyrophosphate (TEPP) gave no evidence of product formation by HPLC-MS even after 7 days at 60 °C (Table 2, entries 8–14). The formation of an activated adduct was not seen when HOBt was added in the cases utilizing carbodiimides, suggesting that a

Table 2. Peptide coupling methods

Entry	Coupling method[a]	Isolated yield (%)
1	BOP	0
2	BOP[b]	0
3	BOP[c]	56[d]
4	PyBOP	47
5	HATU	30
6	HBTU	51
7	HCTU	86
8	TBTU	25
9	PyBrop	0
10	BOP-Cl	0
11	DIC	0
12	EDCI	0
13	DIC/HOBt (1:1)	0
14	EDCI/HOBt (1:1)	0
15	CDI	0
16	TEPP[e]	0
17	I_2/PPh_3/DIEA[f]	54

[a]*N*-Methyl-*p*-anisidine (1.2 equiv.), coupling reagent (1.2 equiv), DIEA (2 equiv), DMF, 60 °C.

[b]*N*-Methyl-*p*-anisidine (1.5 equiv.), BOP (3 equiv), DBU (2 equiv), AcCN, 60 °C (Ref. 12c).

[c]*N*-Methyl-*p*-anisidine (1.5 equiv.), BOP (3 equiv), DBU (2 equiv), AcCN, reflux.

[d]Conversion determined by HPLC using Ph_2O as an internal standard (Ref. 12c).

[e]*N*-Methyl-*p*-anisidine (1.2 equiv.), TEPP (1.2 equiv), $PhCH_3$, 110 °C.

[f]*N*-Methyl-*p*-anisidine (1.2 equiv.), I_2 (1.2 equiv), PPh_3 (1.2 equiv), DIEA (2 equiv), $PhCH_3$, 60 °C.

more reactive phosphonium or uronium intermediate is required for quinazolinone addition. No evidence of N^3 alkylation was observed in the cases of HATU and HBTU, as has been reported with quinazolinones unsubstituted at C^2 in the presence of DBU in AcCN.[13]

Lastly, the formation of **1** was attempted utilizing the Appel combination of triphenylphosphine and I_2 to couple quinazolinone **2** with *N*-methyl-*p*-anisidine (Scheme 1D). This method has been described previously for functionalizing hydroxypurines, but with the use of a large excess of both incoming amine and I_2/PPh_3.[14] The advantages of this reaction are its simplicity and its cost: only one step is required for the synthesis of **1** from **2** as compared with two steps via the sulfonate; the cost of PPh_3/I_2 (<\$0.10/g) is trivial compared to coupling reagents such as PyBOP and HCTU (~\$1.00/g).

Using only a slight excess of incoming amine and I_2/PPh_3, the reaction proceeded cleanly and in moderate yield to form **1**, 65% conversion by HPLC using Ph_2O as an internal standard and 54% isolated yield on a 0.5-mmol scale. The reaction was performed with the same panel of amines as the sulfonate ester reaction, and the results are shown in Table 1 (conditions D1). The reaction was much less predictable than the sulfonate ester displacement, showing widely varying conversion for the tested anilines with little trend in regards to sterics or electronics. Most aliphatic amines were completely unreactive under these conditions, as was the sterically congested and electron-poor diphenylamine.

An increase in conversion to **1** was observed when the equivalents of all reagents other than the 2-methyl-4-hydroxyquinazoline were increased to coincide with those described by Lin and Robins[14] and the solvent changed from toluene to CH_2Cl_2 (Table 1, conditions D2). While dramatically greater conversion was noted in the cases of *N*-methyl-*p*-anisidine, *p*-anisidine, and dimethylamine hydrochloride, in most cases the effect was small. These moderate increases in conversion seen in most cases upon the change from conditions D1 to conditions D2 are mitigated by the small amount by total mass of desired product that must be purified from a mixture of various by-products.

We next attempted to gauge this procedure's potential on a multigram scale by repeating it on a 3.2-g (20-mmol) scale. We felt that the increased conversion provided by the Lin protocol was not enough in the case of **1** to compensate for the difficulty in purification it would entail on a large scale, and consequently only small excesses of reagents were used. A workup with 10% aqueous $Na_2S_2O_3$ was found to be useful in removing residual base and iodine from the reaction mixture, but once this workup is done the product was more easily purified by column chromatography, resulting in a 45% isolated yield.

In conclusion, several alternative syntheses of **1** have been identified that obviate the use of unstable and difficult-to-handle 2-methyl-4-chloroquinazoline (**3**). Several peptide coupling reagents affect the transformation, although the previously reported reagent BOP resulted in very low product yields. Synthesis of **1** via the formation and subsequent amine displacement of toluene sulfonate ester **4** proceeded in good yield on a multigram scale. On similar scale, the one-step formation of **1** from quinazolinone **2** utilizing I_2/PPh_3/DIEA also gave a moderate yield. In most cases, only a small excess of I_2/PPh_3 was needed for the reaction to proceed well. Both the sulfonate displacement and I_2/PPh_3 methods were shown to work with moderate to good yields on amines with a variety of steric and electronic requirements, suggesting the use of these procedures as general methods to generate 4-aminoquinazolines.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 400 MHz. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS, 0.00 ppm), and *J* coupling constants are reported in hertz. HPLC-MS were run in the electrospray ionization (ESI) mode using an Xterra MS C18 (Waters) 4.6 mm × 50 mm 5 u column; HPLC purity was performed using a 4.6 mm × 150 mm Xterra C18 5 u column. Both HPLC-MS and HPLC were reverse phase with an AcCN/H_2O (0.01% v/v TFA) gradient and a flow rate of 0.5 mL/min. Medium-pressure liquid chromatography (MPLC) purifications were performed using an Isco RF system utilizing a hexane/EtOAc gradient. Compounds **1**,[7b] **5**,[7b] 6–11,[15] **12**,[16] **13**,[17] **14**,[18] and **16**[11c] have been previously reported.

Method B

(2-Methylquinazolin-4-yl)4-methylbenzenesulfonate (4). *p*-Toluenesulfonyl chloride (2 equiv) was added to quinazolinone **2**, Et_3N (2 equiv), and DMAP (0.01

equiv) in CH_2Cl_2, and the solution was stirred at rt overnight. The solution was washed with saturated $NaHCO_3$, dried with Na_2SO_4, and concentrated. The resulting solid was purified by MPLC, isolated as 3:1 mixture of rotamers, and gave 91% yield as a mixture. ^{1}H NMR (DMSO-d_6) δ 8.17 (d, $J = 7.7$ Hz, 0.75 H), 8.14 (d, $J = 7.7$ Hz, 0.25 H), 7.96 (t, $J = 7.7$ Hz, 0.75 H), 7.90 (t, $J = 7.7$ Hz, 0.25 H), 7.69 (d, $J = 7.7$ Hz, 0.75 H), 7.64 (t, $J = 7.7$ Hz, 0.75 H), 7.59 (t, $J = 7.7$ Hz, 0.25 H), 7.55 (d, $J = 7.7$ Hz, 0.25 H), 7.47 (d, $J = 7.7$ Hz, 2H), 7.11 (d, $J = 7.7$ Hz, 2H), 2.80 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (CD_3OD) δ 170.0, 164.6, 142.1, 141.5, 140.3, 137.1, 135.6, 129.7, 129.2, 128.4, 127.8, 127.7, 127.5, 125.5, 124.6, 22.8, 22.0, 19.9, 18.3. HRMS calculated for $C_{16}H_{14}N_sO_3S$ ($M + H^+$) 315.07979; found 315.07967.

4-Aminoquinazoline 1,5–18. A solution of **4** in IPA/CH_2Cl_2 (approx. 10:1) was added to the appropriate amine (1.2 equiv.), and the reaction was stirred or shaken at ambient temperatures while being monitored by HPLC-MS or HPLC. Upon complete reaction, a portion of the mixture was removed and purified by MPLC. Compounds **10** and **11** precipitated from solution as TsOH salts and were isolated by filtration.

Method C

DIEA (2 equiv) was added to quinazolinone **2**, aniline (1.2 equiv), and coupling reagent (1.2 equiv) in DMF, and the solution stirred or shaken at 60 °C for 16–18 h. The reaction mixture was concentrated and purified by MPLC.

Method D

DIEA (2 equiv) was added to quinazolinone **2**, aniline (1.1 equiv), I_2 (1.2 equiv), and PPh_3 (1.2 equiv), and the was reaction stirred or shaken at 60 °C for 16–18 h. Upon completion of the reaction, a portion of the mixture was removed and purified by MPLC. On a large scale (10 mmol), the reaction mixture was worked up by diluting it in EtOAc, washing it with 10% aqueous $Na_2S_2O_3$, drying it with Na_2SO_4, and MPLC purification.

4-(2-Methylquinazolin-4-yl)morpholine (15). ^{1}H NMR (DMSO-d_6) δ 7.98 (d, $J = 8.0$ Hz, 1H), 7.81–7.71 (m, 2H), 7.47 (t, $J = 8.0$ Hz, 1H), 3.79 (t, $J = 4.7$ Hz, 4H), 3.67 (t, $J = 4.7$ Hz, 4H), 2.54 (s, 3H). ^{13}C NMR (CD_3OD) δ 164.6, 162.9, 151.3, 132.7, 126.1, 125.0, 124.8, 114.0, 66.4, 49.9, 24.3. HRMS calculated for $C_{13}H_{16}N_3O$ ($M + H^+$), 230.1288; found 230.1276.

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