

One-pot reductive cyclization to antitumor quinazoline precursors

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Abstract

A highly efficient and versatile synthetic approach to the central core of anti-cancer quinazolinone derivatives is reported. Intermolecular reductive *N*-heterocyclizations of various 2-nitrobenzoic acid derivatives with formamide were catalyzed by indium(III) or bismuth(III) salts to yield the title compounds in high yields and excellent purities. In the present one-pot sequence, the aryl nitro group is apparently reduced by formamide decomposition product carbon monoxide and the resultant anthranilic acid derivative proceeds to Niementowski cyclocondensation to form quinazolinones. The transformation is robust for diverse substituents on the aryl group and In(III) counterions, and is also compatible with *N*-alkyl formamides but not dimethylformamide.

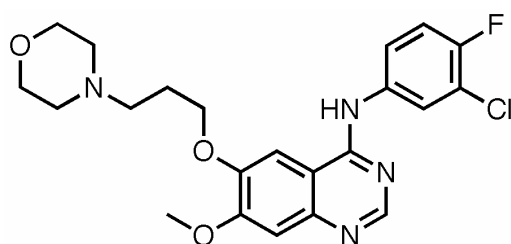
Keywords: Indium(III) acetate, nitro reduction, reductive heterocyclization, quinazolinone, cancer therapeutics

Introduction

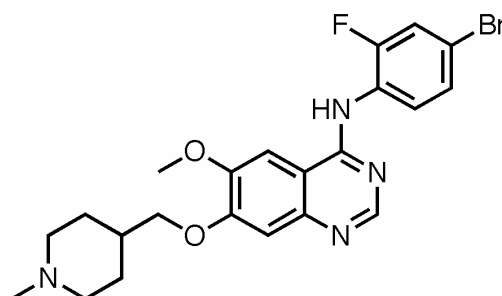
Quinazoline and its derivatives are a class of heteroaromatic compounds that have drawn much attention because of their biological and pharmaceutical activities including a wide range of antitumor activity.¹⁻⁴ Anilinoquinazolines in particular are potent inhibitors of Growth Factor Receptor (GFR) tyrosine kinases and have found clinical applications in Epidermal and Vascular Endothelial GFR targets (Figure 1).⁵⁻⁷ Among other pharmacological activities, quinazoline derivatives show remarkable antimicrobial properties against microorganisms associated with death in patients carrying immunocompromised diseases.⁸ We recently embarked on a program to synthesize anilinoquinazoline analogs as experimental cancer therapeutics. The preparation of

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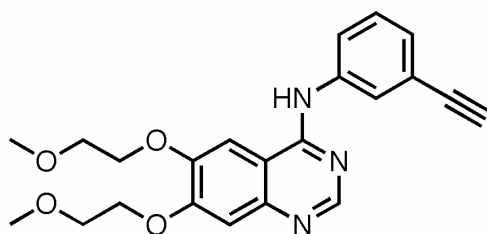
such targets proceeds via the intermediacy of 4(3*H*)-quinazolinone, which is also active against microorganisms.⁹⁻¹⁰ Here, we describe a streamlined and highly efficacious entry into the quinazolinone derivatives via a novel reductive heterocyclization mediated by indium(III) and bismuth(III) acetates.



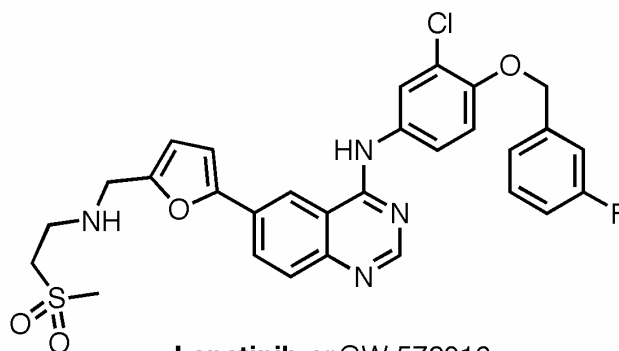
Gefitinib or ZD-1839
(**Iressa**®; AstraZeneca)



Vandetanib or ZD-6474
(**Zactima**®; AstraZeneca)



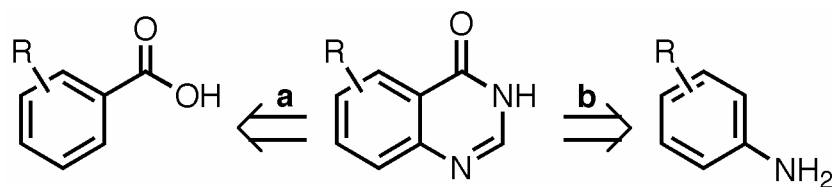
Erlotinib or OSI-774
(**Tarceva**®; Genentech/OSIP)



Lapatinib or GW-572016
(**Tykerb**®; GlaxoSmithKline)

Figure 1. Growth Factor Receptor tyrosine kinase-targeting anti-cancer drugs.

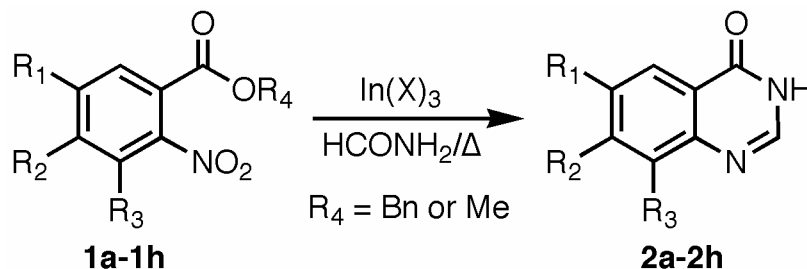
The syntheses of quinazolinone derivatives has been accomplished by cyclocondensation of formamide with anthranilic acid derivatives (Scheme 1, route **a**) or the less common Friedel-Crafts annulation of aminoaryl substrates (Scheme 1, route **b**).¹¹ Variations of the former transformation typically proceed via a two-step sequence¹¹⁻¹² beginning with reduction of 2-nitrobenzoate to the amino analog followed by conventional Niementowski^{11a} cyclization with formamide to elaborate the quinazolinone framework. The overall yield of this route is reduced by the modest efficiencies of the reduction (Zn/acetic acid, SnCl₂/HCl, or catalytic hydrogenation) and cyclocondensation steps, and the purifications required after each stage. In the present report, the reduction and Niementowski cyclization steps occur in a single pot without added reducing agents to provide quinazolinone products in excellent yields and purities.



Scheme 1. Approaches to the quinazolinone framework.

Results and Discussion

Our studies required the preparation of 7-benzyloxy-6-methoxy-4(3*H*)-quinazolinone (**2b**),¹³ which had been previously formed from the reduction of benzyl 4-benzyloxy-5-methoxy-2-nitrobenzoate (**1b**) in Zn/HOAc followed by cyclocondensation with formamide (150 °C/10 h). In our hands, the sequence gave a modest overall yield (42% from **1b**) due to the appreciable formation of byproducts at each step and the careful chromatographic isolations required to purify materials. Subsequent one-pot experiments that employed **1b** and formamide in the presence of indium(III) acetate (1 equiv, 150 °C/5 h) yielded a single product according to the TLC and ¹H-NMR analysis (Scheme 2). After filtration of the crude product through a plug of silica gel (ethyl acetate) **2b** was obtained in high yield (87%, Entry 2; Table 1). Likewise, 4(3*H*)-quinazolinone (**2a**) was obtained in 89% yield (Entry 1) from benzyl 2-nitrobenzoate (**1a**). The purity of crude materials from the one-pot reactions in all examples in Table 1 obviated the need for chromatographic separations.¹³⁻¹⁴



Scheme 2. Quinazolinone preparation by reductive heterocyclization.

Cognizant that a diverse set of substituted quinazolinone analogs have been employed in medicinal studies, a preliminary examination of the generality of this sequence was undertaken. The transformation was compatible with alkoxy, chloro, and thiomethyl substituents on the fused aryl ring (Entry 2–8; Table 1), each of which provided products that are intermediates in the syntheses of therapeutic analogs.⁵⁻⁷ For example, **2b** is the precursor to cancer drugs ZD6474 (Vandetanib, developed by AstraZeneca under the trade name Zactima®)¹⁵ and ZD4190 (currently under clinical trials; AstraZeneca),¹⁶ while **2c** is the precursor for the potent lung

cancer drug ZD1839 (Gefitinib, developed by AstraZeneca under the trade name Iressa®).¹⁷ A comparison of the yields of this streamlined sequence with reported cyclocondensations (from anthranilic acids) are presented in the Table 1 (reported yields do not include the nitro group reductions as they are not typically reported).

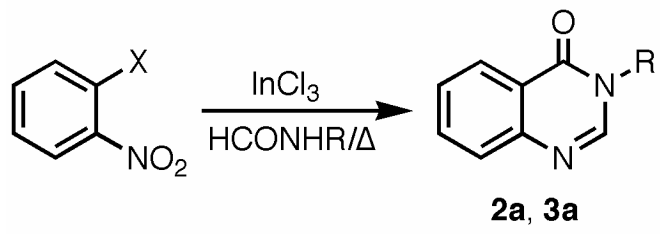
Table 1. Synthesis of 4(3*H*)-quinazolinone derivatives from corresponding alkyl esters^a

Entry	Substrate ^b	R ¹	R ²	R ³	Product ^b	Yield ^c	Lit. Yield ^d	Mp (Lit.) °C
1	1a	H	H	H	2a	89	59 ^e	214 (215) ^e
2	1b	OMe	OBn	H	2b	87 (83) ^f	60 ^g	258 (–) ^h
3	1c	OBn	OMe	H	2c	83	65 ^g	252 (–) ^h
4	1d	OMe	OMe	H	2d	78	65 ^e	262 (264) ^e
5	1e	OMe	H	OMe	2e	71	37 ^e	281 (280–282) ^e
6	1f	OMe	OMe	OMe	2f	75	77 ⁱ	229 (231) ^j
7	1g	Cl	H	H	2g	79	68 ^e	264 (265–267) ^e
8	1h	SMc	H	H	2h	73	92 ^e	201 (203–204) ^e

^a All reactions were performed in the presence of 100 mol% catalyst at 150 °C and were completed within 5 hours according to TLC and ¹H-NMR analyses. ^bSee Scheme 2 for the positions of R¹, R², and R³ on substrates and products. ^cIsolated yields after silica gel filtration and crystallization. ^dThe yields reported are for Niementowski cyclization only. ^eReference 14. ^fYield of the reaction with 100 mol% Bi(OAc)₃ in place of In(OAc)₃. ^gYields we obtained after following the procedure in Reference 13. ^hThese compounds were previously reported without melting points (reference 13). ⁱYield from microwave assisted reaction (reference 12b). ^jReference 12b.

The use of other 2-nitrocarboxylic acid derivatives was also examined. Thus, methyl 2-nitrobenzoate, 2-nitrobenzoic acid, 2-nitrobenzamide, and 2-nitrocyanobenzene each cleanly gave product upon exposure to formamide and In(III) chloride (Table 2; 150 °C/5 h).

Table 2. Reactions of carboxylic acid and formamide derivatives

	R	X	Product	Yield
	H	CO ₂ H	2a	94
	H	CONH ₂	2a	81
	H	CN	2a	91
	CH ₃	CO ₂ H	3a	78
	CH ₃	CONH ₂	3a	71
	CH ₃	CN	3a	73

The transformation was compatible with indium(III) chloride and triflate salts, as well as bismuth(III) acetate but did not occur with the acetates of Zn^{+2} , Fe^{+3} , Sc^{+3} , Yb^{+3} , and Ni^{+2} . A full equivalent of In(III) or Bi(III) salt was required for the complete conversion. The transformation did not proceed in the absence of salt even after extended heating. Only a small amount of **2a** was formed when methyl 2-nitrobenzoate and formamide were reacted with 20 mol% of $\text{In}(\text{OAc})_3$ or InCl_3 (150 °C), even after 5 days.

Several observations and experiments yielded mechanistic insights for this transformation. The reaction is likely to proceed via nitro group reduction followed by typical Niementowski cyclocondensation (Scheme 3), however the reagents used in this transformation include no obvious reductant. Carbon monoxide has been previously employed in transition metal complex¹⁸ or selenium¹⁹ catalyzed aryl nitro group reductions to anilines and is also a known byproduct of formamide thermal decomposition²⁰ at 197 °C^{20a} or at 230 °C.^{20b} To test for the decomposition of formamide under the present conditions, methyl benzoate was heated with formamide (150 °C, 5 h) in the presence and absence of $\text{In}(\text{OAc})_3$. The observation of the quantitative formation of benzamide in the In(III) containing preparation and the lack of benzamide in the reaction not containing In(III) indicates that the metal salt catalyzes the formamide decomposition at these lower temperatures. Also, the nitro group reduction under these conditions was further examined by exposing nitrobenzene to In(III) salts (chloride or acetate, *N*-methylformamide, 150 °C, 10 h). The quantitative formation of aniline was observed (¹H NMR), indicating the reductive potential of these conditions. In all In(III)- and Bi(III)-promoted transformations a brown, organic-insoluble solid was also recovered in place of the original white salt. An experiment in which metal salts InCl_3 , $\text{In}(\text{OAc})_3$, and $\text{Bi}(\text{OAc})_3$ were independently heated in formamide (150 °C, 10 h) also induced the conversion of the white metal salts to dark materials (dark gray beads in the case of the bismuth salt), which suggests that CO reduces the metal(III) cation concurrently in this transformation. This was confirmed by the observation that the beads obtained from $\text{Bi}(\text{OAc})_3$ were capable of conducting electric current. Several experiments examined the possibility that a reduced amount of formamide might selectively reduce the aryl nitro group without effecting metal cation reduction, which would enable the development of a conversion using a catalytic quantity of metal salt. Preparations with reduced amounts of formamide (3 or 6 equiv; 1.0 equiv InCl_3) generated dark salts and trace amounts of quinazoline, indicating that the metal cation and aryl nitro groups are reduced at similar rates.

Acros (Geel, Belgium) Chemical Companies and used without purification. All the metal salts were purchased with 99% or better purity.

Substrate preparation. Benzyl 2-nitrobenzoate (**1a**) and benzyl 5-chloro-2-nitrobenzoate (**1g**) were prepared from 2-nitrobenzoic acid and 5-chloro-2-nitrobenzoic acid, respectively. Benzyl 5-thiomethoxy-2-nitrobenzoate (**1h**) was prepared from **1g** using literature procedure.¹⁴ Benzyl 4-benzyloxy-5-methoxy-2-nitrobenzoate (**1b**; from vanillic acid), benzyl 5-benzyloxy-4-methoxy-2-nitrobenzoate (**1c**; from isovanillic acid), benzyl 4,5-dimethoxy-2-nitrobenzoate (**1d**; from vanillic acid), and benzyl 3,5-dimethoxy-2-nitrobenzoate (**1e**; from 3,5-dimethoxybenzoic acid), were prepared according to the literature procedure.¹³

Typical procedure for the synthesis of 4(3*H*)-quinazolinone derivative (**2**) in single-step reaction

The mixture of the corresponding 2-nitrobenzoic acid derivative **1** (1.0 mmol) and formamide (1.6 mL, 40 mmol) was heated at 150 °C in the presence of indium (III) salt (1.0 mmol) and monitored by TLC. After the completion of the reaction (average time: 5 h), the mixture was poured into ice-cold water and stirred for additional 30 min. The resulting precipitate was filtered, washed with water, and passed through a 1-cm silica gel plug using neat ethyl acetate to remove any unwanted insoluble particles. After solvent removal, the resulting solid was crystallized with methanol to yield crystalline **2** in good yield.

4(3*H*)-Quinazolinone (2a). This was obtained from **1a** in 89% yield as crystalline solid; mp: 214 °C (Lit. 215 °C)¹⁴; IR ($\nu_{\max}$, cm⁻¹): 3134, 1695, 1601; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.50 (dt, 1H, *J* = 8.5, 1.0 Hz), 7.67 (d, 1H, *J* = 8.5 Hz), 7.81 (dt, 1H, *J* = 8.5, 1.5 Hz), 8.09 (s, 1H), 8.13 (dd, 1H, *J* = 8.5, 1.5 Hz), 12.24 (br s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 122.5, 125.7, 126.6, 127.1, 134.2, 145.2, 148.5, 160.6.

7-Benzyloxy-6-methoxy-4(3*H*)-quinazolinone (2b). This was obtained from **1b** in 87% yield as crystalline solid; mp: 258 °C; IR ($\nu_{\max}$, cm⁻¹): 2909, 1639, 1607; ¹H NMR (500 MHz, DMSO-*d*₆): δ 3.95 (s, 3H), 5.29 (s, 2H), 7.24 (s, 1H), 7.36 (t, 1H, *J* = 7.5 Hz), 7.43 (t, 2H, *J* = 7.5 Hz), 7.49 (t, 3H, *J* = 7.5 Hz), 8.01 (s, 1H), 12.19 (br s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 55.7, 70.0, 105.1, 109.3, 115.7, 127.9, 128.1, 128.5, 136.3, 143.8, 144.6, 148.7, 153.3, 160.1.

6-Benzyloxy-7-methoxy-4(3*H*)-quinazolinone (2c). This was obtained from **1c** in 83% yield as crystalline solid; mp: 252 °C; IR ($\nu_{\max}$, cm⁻¹): 2911, 1671, 1610; ¹H NMR (500 MHz, DMSO-*d*₆): δ 3.97 (s, 3H), 5.24 (s, 2H), 7.18 (s, 1H), 7.38 (t, 1H, *J* = 7.0 Hz), 7.40 (t, 2H, *J* = 7.0 Hz), 7.45 (d, 2H, *J* = 7.0 Hz), 7.54 (s, 1H), 7.98 (s, 1H), 12.21 (br s, 1H); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 56.0, 69.9, 106.5, 108.2, 115.5, 127.8, 127.9, 128.4, 136.5, 143.9, 145.0, 147.4, 154.7, 160.0.

6,7-Dimethoxy-4(3*H*)-quinazolinone (2d). This was obtained from **1d** in 78% yield as crystalline solid; mp: 262 °C (Lit. 264 °C)¹⁴; IR ($\nu_{\max}$, cm⁻¹): 2922, 1674, 1615; ¹H NMR (500 MHz, DMSO-*d*₆): δ 3.86 (s, 3H), 3.90 (s, 3H), 7.13 (s, 1H), 7.44 (s, 1H), 7.98 (s, 1H), 12.19 (br

s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 55.6, 55.9, 104.8, 107.9, 115.5, 143.7, 144.7, 148.4, 154.3, 159.9.

6,8-Dimethoxy-4(3H)-quinazolinone (2e). This was obtained from **1e** in 71% yield as crystalline solid; mp: 281 °C (Lit. 280–282 °C)¹⁴; IR (ν_{max} , cm^{-1}): 2937, 1667, 1607; ^1H NMR (500 MHz, DMSO- d_6): δ 3.85 (s, 3H), 3.87 (s, 3H), 6.93 (d, 1H, $J = 3.0$ Hz), 7.07 (d, 1H, $J = 3.0$ Hz), 7.91 (s, 1H), 12.28 (br s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 55.5, 56.0, 96.5, 104.9, 123.9, 134.8, 141.5, 155.6, 158.1, 160.2.

5,6,7-Trimethoxy-4(3H)-quinazolinone (2f). This was obtained from **1f** in 75% yield as crystalline solid; mp: 229 °C (Lit. 231 °C)^{12b}; IR (ν_{max} , cm^{-1}): 2838, 1674, 1599; ^1H NMR (500 MHz, DMSO- d_6): δ 3.81 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 7.42 (s, 1H), 8.01 (s, 1H), 12.21 (br s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 55.9, 60.8, 61.8, 101.1, 118.6, 138.3, 142.7, 146.9, 147.5, 151.9, 159.9.

6-Chloro-4(3H)-quinazolinone (2g). This was obtained from **1g** in 79% yield as crystalline solid; mp: 264 °C (Lit. 265–267 °C)¹⁴; IR (ν_{max} , cm^{-1}): 2847, 1679, 1604; ^1H NMR (500 MHz, DMSO- d_6): δ 7.69 (d, 1H, $J = 8.5$ Hz), 7.84 (dd, 1H, $J = 8.5, 2.5$ Hz), 8.05 (d, 1H, $J = 2.5$ Hz), 8.12 (s, 1H), 12.42 (br s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 123.7, 124.7, 129.4, 130.9, 134.3, 145.8, 147.3, 159.6.

6-Thiomethoxy-4(3H)-quinazolinone (2h). This was obtained from **1h** in 73% yield as crystalline solid; mp: 252 °C (Lit. 203–204 °C)¹⁴; IR (ν_{max} , cm^{-1}): 2850, 1682, 1605; ^1H NMR (500 MHz, DMSO- d_6): δ 3.35 (s, 3H), 7.70 (d, 1H, $J = 8.5$ Hz), 7.84 (dd, 1H, $J = 8.5, 2.5$ Hz), 8.06 (d, 1H, $J = 2.5$ Hz), 8.13 (s, 1H), 12.51 (br s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 40.1, 124.4, 125.4, 130.1, 131.7, 135.1, 146.5, 148.2, 160.4.

3-Methyl-4(3H)-quinazolinone (3a). A mixture of 1.0 mmol of starting material (2-nitrobenzoic acid, methyl 2-nitrobenzoate, 2-nitrobenzamide, or 2-nitrocyanobenzene) and *N*-methylformamide (1.5 mL, 25 mmol) was heated at 150 °C in the presence of indium (III) chloride (0.22 g, 1.0 mmol) and monitored by TLC. After the completion of the reaction (average time: 10 h), the mixture was poured into ice-cold water (10 mL) and EtOAc (10 mL), the organic layer was separated, and the aqueous phase was further extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO_4 , and filtered. The solvent was evaporated *in vacuo* and the remaining solid was passed through a silica gel column (EtOAc/hexanes, 1:1) to yield **3a** as white solid, mp: 103 °C (Lit. 105 °C)²¹; IR (ν_{max} , cm^{-1}): 2923, 1665, 1608; ^1H NMR (500 MHz, DMSO- d_6): δ 3.49 (s, 3H), 7.54 (t, 1H, $J = 7.5$ Hz), 7.68 (d, 1H, $J = 7.5$ Hz), 7.81 (t, 1H, $J = 7.5$ Hz), 8.16 (d, 1H, $J = 7.5$ Hz), 8.37 (s, 1H); ^{13}C NMR (75 MHz, DMSO- d_6): δ 33.6, 121.3, 125.7, 126.8, 126.9, 133.9, 147.9, 148.3, 160.5.

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