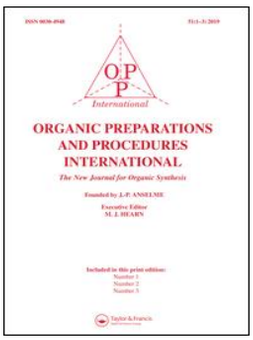

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OPPI BRIEF

A New Synthesis of Cabozantinib

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Cabozantinib (**1**, *Scheme 1*) marketed as *Cometriq*® is a small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2.[1] It was developed by Exelixis Inc. and was approved by the U.S. FDA in 2012 for medullary thyroid cancer and advanced renal cell carcinoma in people who have received prior anti-angiogenic therapy.[2]

Two synthetic routes of *cabozantinib* have been developed so far.[3–10] With regard to preparation of the key intermediate 6,7-dimethoxyquinolin-4-ol (**6**), there are two kinds of approaches, as shown in *Scheme 1*. A common route to prepare **6** is based on Gould-Jacobs methodology,[3,4] in which the Meldrum's acid derivative **4** is heated with Dowtherm A at $> 230\,^{\circ}C$ for several hours to give **6**. This method is short, but the main problem is that the high reaction temperature leads to a complex and tedious procedure. Dowtherm A is a high boiling solvent which is difficult to recover, is harmful to the environment and may cause allergic reactions in workers, an effect which we have seen in our own experience.

Alternatively, 1-(2-aminophenyl)ethan-1-one **5** reacts with ethyl formate under strong alkaline conditions to give the intermediate **6** in 55% yield.[5,6] Generally, MeONa or ^{t}-BuONa and anhydrous solvents are used in the reaction. We consider the overall yield to be unsatisfactory.

4-Chloro-6,7-dimethoxyquinoline (**7**) was then reacted successively with 4-aminophenol (**8**) and 1-((4-fluorophenyl)carbamoyl)cyclopropane-1-carbonyl chloride (**10**)[7] to give the final product *cabozantinib* (**1**) in about 60% over-all yield from compound **6**.[8–10]

We developed a new and practical synthetic route, as shown in *Scheme 2*. A reduction cyclization process was adopted to prepare the key 6,7-dimethoxyquinolin-4-ol (**6**) from 1-(4,5-dimethoxy-2-nitrophenyl)-3-(dimethylamino) prop-2-en-1-one (**13**).[11]

Commercially available 1-(3,4-dimethoxyphenyl)ethan-1-one (**11**) was nitrated in $HOAc/HNO_3$ to give 1-(4,5-dimethoxy-2-nitrophenyl)ethan-1-one (**12**) in 86% isolated yield. Compound **12** was then reacted with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) in toluene to obtain **13** in 79% yield.[12] Through nucleophilic substitution

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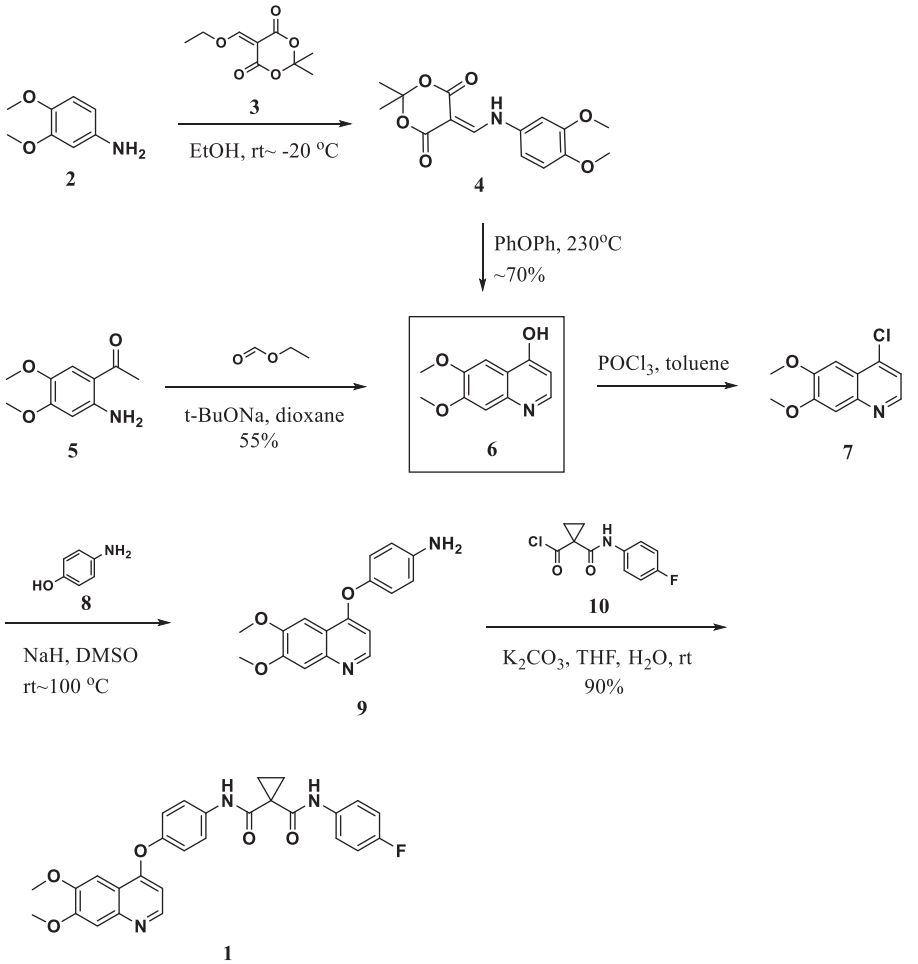
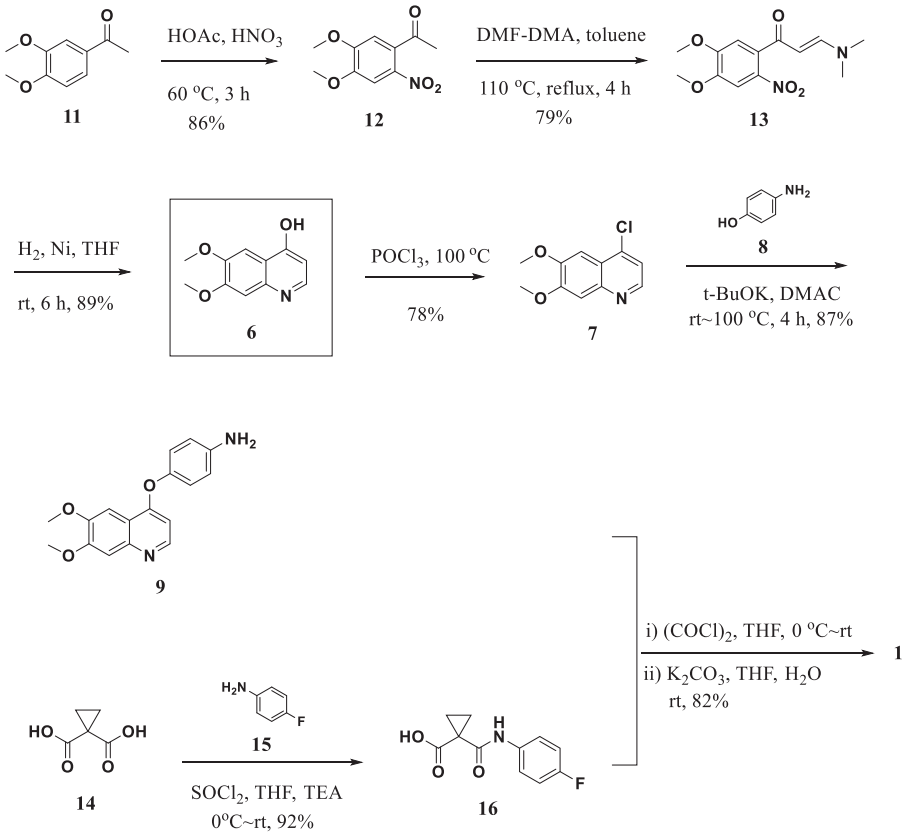


Scheme 1

reactions, DMF-DMA can react with benzophenone, 3-oxo-3-phenylpropanenitrile, or 3-oxo-3-phenylpropanoate compounds to give the 3-(dimethylamino)-1-prop-2-en-1-one intermediates for preparation of 4-hydroxyquinoline compounds.[13,14] Since DMF-DMA has higher reactivity, in general the reaction temperature is lower and the isolated yield is higher than if using ortho-formate.[15,16] Compound **6** was then obtained by treating compound **13** with H_2/Ni at room temperature in 89% yield and 99.1% purity (HPLC) after purification. Compound **6** was subsequently chlorinated by $POCl_3$ to give 4-chloroquinoline **7** in 78% yield.

Compound **7** was then reacted with 4-aminophenol (**8**) in ^{t}-BuOK/DMAC to give 4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (**9**) in 87% isolated yield.[7] 1-((4-Fluorophenyl)carbamoyl) cyclopropane-1-carboxylic acid (**16**) was prepared in high yield by reaction of cyclopropane-1,1-dicarboxylic (**14**) with $SOCl_2$ and 4-fluoroaniline (**15**) successively.[8] Compound **16** was then treated with $(COCl)_2$, followed by compound **9** in K_2CO_3/THF/H_2O to give cabozantinib (**1**).[9] Compound **1** was purified by heating and stirring in 50% EtOH/EtOAc in 82% overall yield and $>$ 99.0% purity (HPLC).



Scheme 2

In summary, we have developed a new and practical synthetic route of *cabozantinib* (**1**), adopting a reduction cyclization process to prepare the key 4-hydroxyquinoline compound **6** from **13**. Commercially available **11** was used as the starting material. The final product **1** was obtained in 31% yield over seven steps and > 99% purity (HPLC).

The reduction cyclization method was developed[13–16] in recent years and we also expanded its application for the preparation of *bosutinib*[17,18] and *tivozanib*.[19,20] During the design and synthesis of *cabozantinib*, the key intermediate **6** was obtained through this method. Common and inexpensive regents and mild reaction conditions are used in the new route, in order to simplify the operation, enhance the overall yield, and decrease the preparation cost; as a result the new process is efficient, practical, and suitable for commercial manufacture.

Experimental Section

All commercially available chemicals and solvents were used as received without any further purification. ^{1}H NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained on a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Shenguang

WRS-1B melting point apparatus and are uncorrected. The HPLC results were generated using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump.

1-(4,5-Dimethoxy-2-nitrophenyl)ethan-1-one (12)

A mixture of 1-(3,4-dimethoxyphenyl)ethan-1-one **11** (180 g, 1.0 mol) and HOAc (1.5 L) was stirred and heated to 60 °C to give a clear solution. 65% HNO_3 (110 mL, 1.5 mol) was added over 30 min and the mixture was stirred for another 3 h to give a yellow solution. The reaction mixture was poured slowly into ice-water (5 L) while stirring constantly. The yellow solid that formed was filtered off and washed with cold water (600 mL × 2), dried at 60 °C for 4 h to give crude product **12** (210 g). The crude **12** (210 g) was stirred and heated with EtOAc: petroleum = 1:1 (v:v) (800 mL) at reflux for 2 h then cooled to room temperature, the resulting solid was filtered off and washed with EtOAc: petroleum = 1:1 (v:v) (100 mL × 2), dried at 50 °C for 4 h to afford **12** (193.7 g, 86%) as a yellow solid, mp 131.3 – 133.1 °C (lit mp[21] 130 – 132 °C). ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 3H), 3.90 (s, 3H), 3.93(s, 3H), 7.23 (s, 1H), 7.64 (s, 1H). ESI-MS (*m/z*): 226.1 $(M+H)^+$, 473.2 $(2M+Na)^+$.

Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92. Found : C, 53.42; H, 4.89.

1-(4,5-Dimethoxy-2-nitrophenyl)-3-(dimethylamino) prop-2-en-1-one (13)

A solution of **12** (160.0 g, 0.71 mol), DMF-DMA (119.2 g, 1.0 mol) and toluene (1.5 L) was stirred and heated to reflux for 4 h, then cooled to room temperature. The resulting yellow solid was filtered, washed with toluene (150 mL × 2) and dried at 60 °C for 4 h to afford **13** (157.1 g, 79%) as a yellow solid, mp 140.5 – 143.1 °C (lit mp[22] 142 – 145 °C). ^{1}H NMR ($CDCl_3$): δ 2.87 (br s, 3H), 3.10 (br s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.86 (s, 1H), 7.60 (s, 1H). ESI-MS (*m/z*): 281.2 $(M+H)^+$, 561.3 $(2M+H)^+$, 583.2 $(2M+Na)^+$.

Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75. Found : C, 55.93; H, 5.80.

6,7-Dimethoxyquinolin-4-ol (6)

Compound **13** (95.3 g, 0.34 mol) was stirred and dissolved in THF (1.1 L) at room temperature. Raney Ni (wet, 30 g) was washed with THF and added to the reaction solution. The reaction mixture was stirred under a hydrogen balloon at atmospheric pressure for 6 h to give a light-yellow solution. The resulting mixture was filtered through a *Celite* pad, the filter cake was washed by THF (100 mL × 2). The combined filtrate was concentrated to give the crude product **6** as a light yellow solid, which was stirred and heated with EtOAc: EtOH = 1:1 (v:v) (250 mL) at reflux for 2 h then cooled to room temperature; the resulting solid was filtered off and washed with EtOAc: EtOH = 1:1 (v:v) (50 mL × 2), dried at 50 °C for 4 h to afford **6** (62.1 g, 89%) as a grey solid, mp 222.0 – 224.2 °C (lit mp [23] 224 – 225 °C). ^{1}H NMR (DMSO-d_6): δ 3.68 (s, 3H), 3.72 (s, 3H), 5.68 (d, J = 12.0 Hz, 1H), 6.26 (s, 1H), 6.83 (s, 2H), 7.17 (s, 1H), 7.53 (d, J = 12.0 Hz, 1H). ESI-MS (*m/z*): 206.2 $(M+H)^+$, 411.2 $(2M+H)^+$, 433.2 $(2M+Na)^+$.

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found : C, 64.51; H, 5.46.

HPLC Conditions— Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL;

Solvent: methanol; Run time: 15 min; Mobile phase: methanol/water = 90/10, t_R: 3.527 min, purity: 99.093%.

4-Chloro-6,7-dimethoxyquinoline (7)

A solution of **6** (50 g, 0.24 mol) in $POCl_3$ (400 mL) was stirred at 100 °C for 6 h. Most of the solvent was recovered under vacuum. The residue was added slowly to cooled water (500 mL) and adjusted with 10% K_2CO_3 to pH ~ 9, and stirred for another 1 h. The resulting solid was filtered, washed with H_2O (50 mL × 2), and dried at 55 °C for 4 h to give **7** (41.8 g, 78%) as a light brown solid, mp 130.2 – 131.4 °C (lit mp[24] 130 – 131 °C). ^{1}H NMR (DMSO-d_6): δ 3.96 (s, 3H), 3.97 (s, 3H), 7.35 (s, 1H), 7.44(s, 1H), 7.54 (d, J = 5.2 Hz, 1H), 8.61 (d, J = 5.2 Hz, 1H). ESI-MS (*m/z*): 223.2 $(M+H)^+$, 245.2 $(M+Na)^+$.

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51. Found : C, 59.20; H, 4.46.

4-((6,7-Dimethoxyquinolin-4-yl)oxy)aniline (9)

Compound **7** (16.0 g, 0.071 mol) and 4-aminophenol **8** (11.0 g, 0.10 mol) were added to dimethylacetamide (200 mL), and stirred for 10 min at room temperature; then a solution of *t*-BuOK (9.68 g, 0.09 mol) in dimethylacetamide (20 mL) was added slowly such that the reaction temperature kept at or below 25 °C; the reaction mixture was then stirred at 100 °C for another 4 h, then cooled to room temperature, and poured slowly into water (400 mL) while stirring constantly. The solid formed was filtered off and washed with cold water (50 mL × 2), dried at 60 °C for 4 h to afford **9** (18.4 g, 87%) as a light tan solid, mp 140 °C (dec.). ^{1}H NMR (DMSO-d_6): δ3 .93 (s, 3H), 3.94 (s, 3H), 5.16 (s, 2H), 6.37 (d, J = 5.2 Hz, 1H), 6.67 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.37 (s, 1H), 7.51 (s, 1H), 8.43 (d, J = 5.2 Hz, 1H). ESI-MS (*m/z*): 297.8 $(M+Na)^+$.

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44. Found : C, 68.79; H, 5.49.

1-((4-Fluorophenyl)carbamoyl)cyclopropane-1-carboxylic acid (16)

A suspension of cyclopropane-1,1-dicarboxylic acid **14** (10.0 g, 0.08 mol) in THF (56 mL) was stirred in an ice-water bath and triethylamine (7.79 g, 0.08 mol) was added slowly to keep the reaction temperature below 10 °C. $SOCl_2$ (9.16 g, 0.08 mol) was added slowly to the reaction mixture to keep the reaction temperature below 8 °C. When the addition was complete, the mixture was stirred below 5 °C for another 1 h.

4-Fluoroaniline **15** (7.77 g, 0.07 mol) in THF (20 mL) was added to the reaction solution slowly to keep the reaction temperature below 8 °C, and stirred on the ice-water bath for another 3 h. The reaction solution was then diluted with ethyl acetate (100 mL) and water (100 mL), stirred at room temperature for 30 min. The organic phase was separated, washed with water (80 mL) and brine (80 mL). The solution was concentrated under vacuum to give the solid, dried at 50 °C for 4 h to give the product **16** as a cream solid (9.2 g, 92%). ^{1}H NMR (DMSO-d_6): δ 1.41 (s, 4H), 7.14 (t, J = 8.8 Hz, 2H), 7.61 (dd, J = 4.8, 8.8 Hz, 2H), 10.57 (s, 1H).

Anal. Calcd for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52. Found : C, 59.30; H, 4.45.

Cabozantinib (1)

A stirred suspension of **16** (10.3 g, 0.043 mol) and DMF (0.3 mL, 0.004 mol) in THF (50 mL) was cooled in an ice-water bath. Oxalyl chloride (4.7 mL, 0.055 mol) was added slowly to the suspension to keep the reaction temperature below 10 °C. When the addition was complete, the reaction mixture was stirred at room temperature for another 2 h. The solution was concentrated under vacuum to give 1-((4-fluorophenyl) carbamoyl)cyclopropane-1-carbonyl chloride (**10**) as a light yellow soild, which was used directly at the next step.

To a stirred suspension of **9** (8.4 g, 0.028 mol) in THF (80 mL) was added a solution of K_2CO_3 (8.3 g, 0.06 mol) in water (40 mL). The mixture was stirred at room temperature for 2 h. Then the carbonyl chloride **10** (0.043 mol) was added at room temperature and the reaction solution was stirred for 3 h. The stirring was stopped and the phases of the mixture were allowed to separate. The lower aqueous phase was removed and discarded. To the remaining upper organic phase was added water (100 mL). Then the mixture was stirred at 15 °C for 10 h. The solid was precipitated. The product was filtered and washed with a mixture of 2:1 (v/v) water/THF (20 mL × 2). The crude product was dried at 60 °C for 4 h. The dried product was then taken up in EtOAc: EtOH = 1:1 (v:v) (50 mL) and heated to reflux for 30 min, then cooled to room temperature for 1 h, the resulting solid was filtered off and washed with EtOAc (20 mL × 2), dried at 50 °C for 3 h to afford **1** (11.5 g, 82%) as an off-white solid. ^{1}H NMR (DMSO-d_6): δ 1.48 (s, 4H), 3.94 (s, 3H), 3.95 (s, 3H), 6.42 (d, $J = 5.2$ Hz, 1H), 6.67 (d, $J = 9.2$ Hz, 1H), 6.93 (d, $J = 9.2$ Hz, 1H), 7.16 (t, $J = 8.8$ Hz, 2H), 7.23 (d, $J = 9.6$ Hz, 2H), 7.39 (s, 1H), 7.51 (s, 1H), 7.65 (dd, $J = 4.8$, 8.8 Hz, 2H), 7.77 (d, $J = 9.6$ Hz, 2H), 8.47 (d, $J = 5.2$ Hz, 1H), 10.07 (s, 1H), 10.20 (s, 1H). ESI-MS (*m/z*): 502.2 $(M + H)^+$.

Anal. Calcd for $C_{28}H_{24}FN_3O_5$: C, 67.06; H, 4.82. Found : C, 67.25; H, 4.78.

HPLC Conditions— Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: methanol; Run time: 15 min; Mobile phase: methanol/water = 90/10, t_R: 4.143 min, purity: 99.1%.

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