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A NEW AND PRACTICAL SYNTHESIS OF TIVOZANIB

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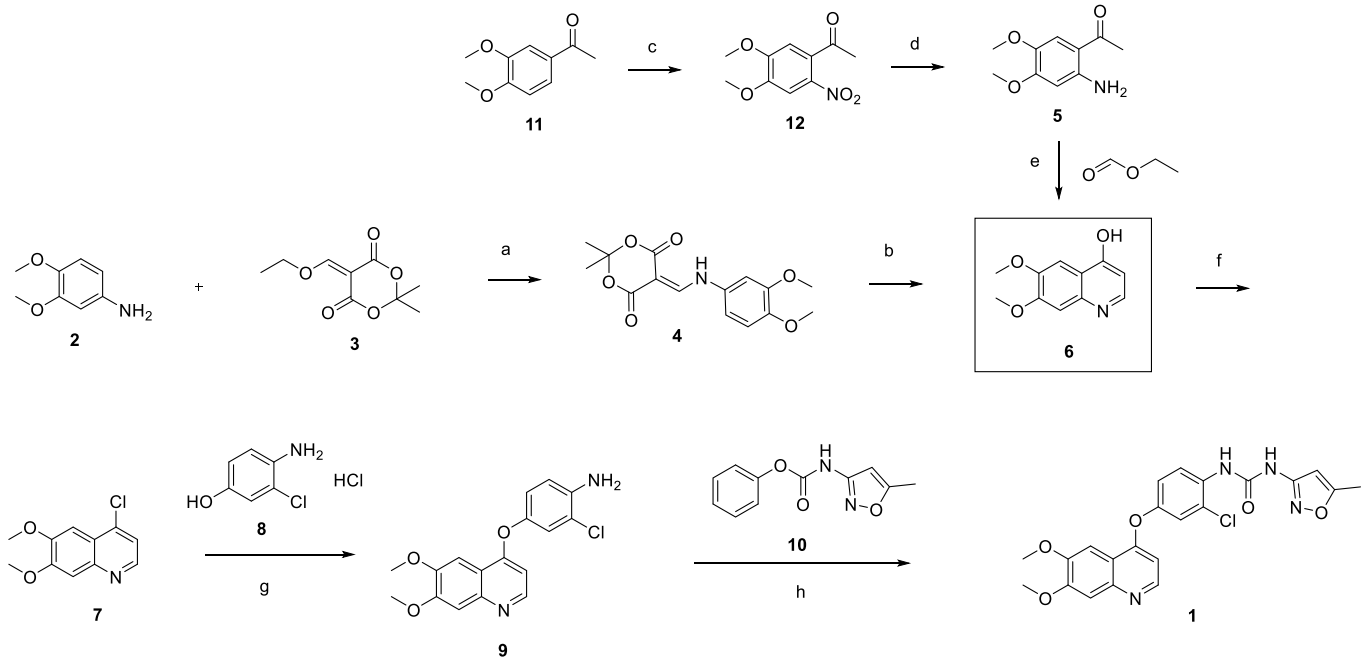
Abstract – New and improved synthetic route of tivozanib is described on a hectogram scale. An reduction cyclization process to prepare the key intermediate 6,7-dimethoxyquinolin-4-ol from the 3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one compound at H_2/Ni condition is adopted in good result. Commercially available materials, simple reaction and operation are used, including nitration, condensation, hydrogenation, chlorination and so on, to give the final product in 28.7% yield over six steps and 98.9% purity (HPLC).

Tivozanib (**1**) (formerly as AV-951, KRN-951, Scheme 1), which is a potent and selective VEGFR inhibitor, blocks the VEGFR-1, -2, and-3 tyrosine kinases at picomolar concentrations.[1] It completed a trial investigation for the treatment of renal cell carcinomas.[2] It was developed by AVEO Pharmaceuticals and now in Phase III clinical study in Third Line advanced RCC patients.[3]

A couple of synthetic routes of tivozanib were developed so far.[4–6] 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. The common work to prepare **6** was based on the Gould-Jacobs methodology,[4] that the Meldrum's acid derivative **4** was heated with Dowtherm A at 230 ºC for several minutes to give **6**. This method is brief and short while the main problem is that the high reaction temperature leads to a messy and tedious operation. What's more, Dowtherm A is high boiling point solvent which is difficult to recover, it's harmful to environment and also cause allergy to the operation people based on our own experience. Alternatively, 1-(2-aminophenyl)ethan-1-one **5** reacted with ethyl formate at strong alkaline conditions can give the intermediate **6** in 55% yield.[5] Generally, MeONa or *t*-BuONa and anhydrous solvents are used in the reaction, and the overall yield is not unsatisfactory.

4-Chloro-6,7-dimethoxyquinoline (**7**) was then reacted successively with 4-amino-3-chlorophenol

hydrochloride (**8**) and phenyl (5-methylisoxazol-3-yl)carbamate (**10**) to give the final product tivozanib (**1**) in around 60% yield over the last three steps.[6]



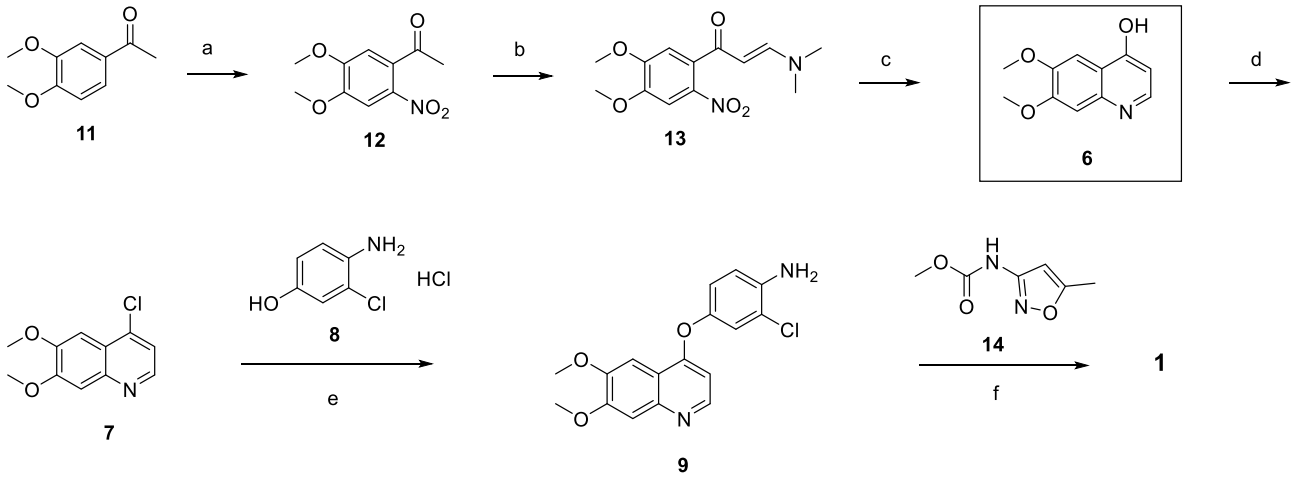
Scheme 1. Reagents and conditions: (a) EtOH, rt~–20 ºC; (b) PhOPh, 230 ºC, 95%; (c) $NaNO_2$, HNO_3, 90%; (d) Fe, HOAc, 81%; (e) *t*-BuONa, dioxane, 55%; (f) $POCl_3$, toluene; (g) NaH, DMSO, 0~110 ºC, 75%; (h) DMAC, pyridine, 0 ºC~rt, 86%.

In order to develop a practical and commercial process of preparing tivozanib, a new and practical synthetic route was developed, as shown in Scheme 2. Since reduction cyclization method is a good process for preparation of 4-hydroxyquinoline-3-carbonitrile compounds,[7] it 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**).[8]

Commercially available 1-(3,4-dimethoxyphenyl)ethan-1-one (**11**) was nitrated in HOAc/HNO_3 system to give 1-(4,5-dimethoxy-2-nitrophenyl)ethan-1-one (**12**) in 86% isolated yield, which was then reacted with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in toluene to obtain 3-(dimethylamino)-1-(2-nitrophenyl)prop-2-en-1-one (**13**) in 79% yield.[9] 6,7-Dimethoxyquinolin-4-ol (**6**) was obtained by treating compound **13** in H_2/Ni condition at room temperature in 89% yield and 99.1% purity (HPLC) after purification. Compound **6** was chlorinated by $POCl_3$ to give 4-chloroquinoline **7** in 78% yield.

Compound **7** was then reacted with 4-amino-3-chlorophenol hydrochloride (**8**) at *t*-BuOK/DMAC condition to give 2-chloro-4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (**9**) in 77% isolated yield. Methyl (5-methylisoxazol-3-yl)carbamate (**14**) was prepared from methyl chloroformate and 5-methylisoxazol-3-amine. At the last step, aniline compound **9** reacted with compound **14**, catalyzed by pyridine to give

the final product tivozanib (**1**), which was purified by recrystallization in EtOH/EtOAc in 79% yield and 98.9% purity (HPLC).



Scheme 2. Reagents and conditions: (a) HOAc, HNO_3, 60 ºC, 3 h, 86%; (b) DMF-DMA, toluene, 110 ºC, reflux, 4 h, 79%; (c) H_2, Ni, THF, rt, 6 h, 89%; (d) $POCl_3$, 100 ºC, 78%; (e) *t*-BuOK, DMAC, 5 ºC–115 ºC, 5 h, 77%; (f) DMAC, pyridine, 10 ºC–80 ºC, 5 h, 79%.

In summary, we have developed a new and practical synthetic route of tivozanib (**1**) on a hectogram scale, especially adopting a reduction cyclization process to prepare the key intermediate 6,7-dimethoxyquinolin-4-ol (**6**) from 1-(4,5-dimethoxy-2-nitrophenyl)-3-(dimethylamino)prop-2-en-1-one (**13**) at H_2/Ni condition in good result. Commercially available 1-(3,4-dimethoxyphenyl)ethan-1-one (**11**) was used as the starting material, through nitration, condensation, hydrogenation, chlorination and so on, to give the final product **1** in 28.7% yield over six steps and 98.9% purity (HPLC). Purification methods of the intermediates involved in the route were also given.

EXPERIMENTAL

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 from a Finnigan MAT-95/711 spectrometer. Melting points were measured on a Shenguang WRS-1B melting point apparatus and are uncorrected. The HPLC data were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds were based on the areas of HPLC UV. HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 30 ºC; Injection load: 1 μL; Solvent: MeOH; Run time: 15 min; Mobile phase: MeOH/water = 90/10.

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), HOAc (1.5 L) was stirred and heated to 60 ºC. When the solid dissolved, 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 formed was filtered off and washed with cold water (600 mL × 2), dried at 60 ºC for 4 h to give crude product **12** (210 g). The crude **12** (210 g) was stirred and heated with EtOAc : petroleum ether = 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 ether = 1:1 (v:v) (100 mL × 2), dried at 50 ºC for 4 h to afford **12** (193.7 g, 86%) as a yellow solid; mp 131.3−133.1 ºC (Lit.[10] 130−132 ºC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.52 (s, 3H), 3.90 (s, 3H), 3.93(s, 3H), 7.23 (s, 1H), 7.64 (s, 1H). MS (ESI): *m/z* = 226.1 [M + H]$^+$, 473.2 [2M + Na]$^+$.

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 ºC for 4 h to afford **13** (157.1 g, 79%) as a yellow solid; mp 140.5−143.1 ºC (Lit.[11] 142−145 ºC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.87 (br s, 3H), 3.10 (br s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 5.23 (br s, 1H), 6.86 (s, 1H), 7.60 (s, 1H). MS (ESI): *m/z* = 281.2 [M + H]$^+$, 561.3 [2M + H]$^+$, 583.2 [2M + Na]$^+$.

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 by THF and added to the reaction solution. The reaction mixture was stirred under 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 ºC for 4 h to afford **6** (62.1 g, 89 %) as a grey solid; mp 222.0−224.2 ºC (Lit.[12] 224−225 ºC). ^{1}H NMR (400 MHz, 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). MS (ESI): *m/z* = 206.2 [M + H]$^+$, 411.2 [2M + H]$^+$, 433.2 [2M + Na]$^+$.

HPLC: 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 ºC 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 filtrated, washed with H_2O (50 mL × 2), and dried at 55 ºC for 4 h to give **7** (41.8 g, 78%) as a light brown solid; mp 130.2−131.4 ºC (Lit.[13] 130−131 ºC). ^{1}H NMR (400 MHz, 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). MS (ESI): m/z = 223.2 $[M + H]^+$, 245.2 $[M + Na]^+$.

2-Chloro-4-((6,7-dimethoxyquinolin-4-yl)oxy)aniline (9). A solution of 4-amino-3-chlorophenol hydrochloride **8** (10.0 g, 0.06 mol) and dimethylacetamide (40 mL) was stirred in an ice-water bath. *t*-BuOK (15.5 g, 0.14 mol) was added and the reaction mixture was stirred at the temperature for 1.5 h. Then 4-chloro-6,7-dimethoxyquinoline **7** (9.4 g, 0.04 mol) was added to the resulting solution, and heated to 115 ºC for another 5 h. After cooled to room temperature, the reaction mixture was then added to water (100 mL) and MeOH (100 mL), and stirred for 3 h. The resulting solid was collected by suction filtration, washed with H_2O (50 mL × 3), and dried at 50 ºC for 5 h to give **9** (10.2 g, 77%) as a faint yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.93 (s, 3H), 3.94 (s, 3H), 5.43 (s, 2H), 6.43 (d, J = 5.2 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.99 (dd, J = 2.4, 8.8 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.38 (s, 1H), 7.49 (s, 1H), 8.45 (d, J = 5.2 Hz, 1H). MS (ESI): m/z = 331.1 $[M + H]^+$.

Tivozanib (1). A solution of 5-methylisoxazol-3-amine (5.3 g, 0.054 mol) and pyridine (17.2 g, 0.22 mol) in dimethylacetamide (30 mL) was stirred and cooled in an ice-water bath. Methyl chloroformate (5.1 g, 0.054 mol) was added slowly and keeping the reaction temperature below 10 ºC. The reaction mixture was stirred at the ambient temperature for another 2 h to give the methyl (5-methylisoxazol-3-yl)carbamate (**14**).

Then 2-cholo-4-((6,7-dimethoxyquinolin-4-yl)oxy)-aniline **9** (12.0 g, 0.036 mol) was added and the reaction mixture was stirred at 80 ºC for 5 h. The reaction suspension was cooled to room temperature and added into water (300 mL) and MeOH (100 mL) and stirred for 30 min. The resulting solid was filtered, washed with water (50 mL × 2), and dried at 50 ºC to give the crude product **1**, which was taken up in EtOAc : EtOH = 1:1 (v:v) (60 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 ºC for 3 h to afford **1** (12.9 g, 79%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.35 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 6.52 (d, J = 5.2 Hz, 1H), 6.57 (d, J = 8.8 Hz, 1H), 7.28 (dd, J = 2.4, 8.8 Hz, 1H), 7.42 (s, 1H), 7.49 (s, 1H), 7.51 (d, J = 2.4 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.51 (d, J = 5.2 Hz, 1H), 9.02 (s, 1H), 10.42 (s, 1H). ESI-MS (m/z) 455.1 $[M+H]^+$.

HPLC: t_R: 5.446 min, purity: 98.9%.

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