HETEROCYCLES, Vol. 100, No. 3, 2020, pp. 463 - 468. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 22nd January, 2020, Accepted, 25th February, 2020, Published online, 26th February, 2020
DOI: 10.3987/COM-20-14218

NEW SYNTHESIS OF APABETALONE

Pengfei Wu, Han Wang,* Wenxin Chen, Cong Sun, Lei Gao, and Yongjun Mao

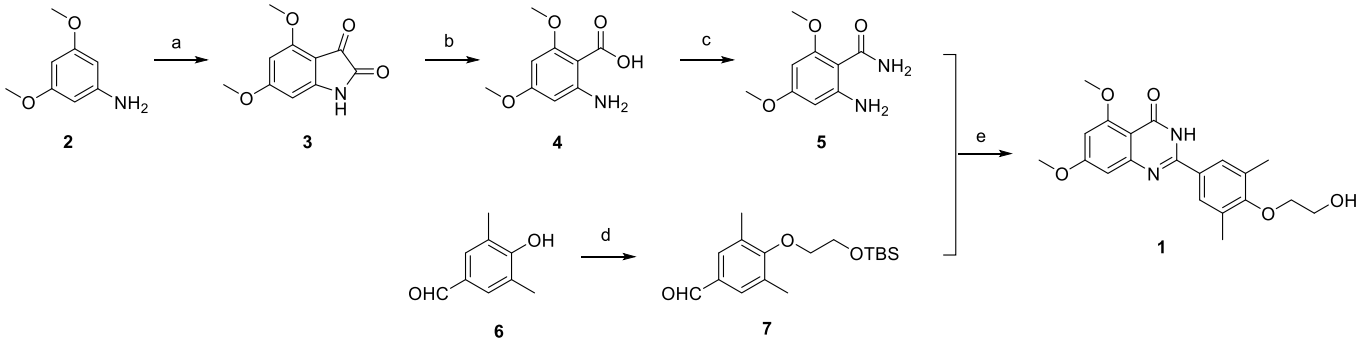
College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, Shanghai 201620, China. *Han Wang, Tel: +86 21 67791220. Fax: +86 21 67791214. E-mail: wanghan@sues.edu.cn.

Abstract – A new and convergent synthesis of apabetalone (RVX-208) is developed. The key step is to build the 2-phenylquinazolin-4(3*H*)-one main ring from 2-bromo-4,6-dimethoxybenzoic acid (**10**) and 4-(2-hydroxyethoxy)-3,5-dimethylbenzamidine hydrochloride (**15**) in 73% yield. 1-Bromo-3,5-dimethoxybenzene (**8**) and 4-hydroxy-3,5-dimethylbenzonitrile (**13**) are used as the starting materials, **1** was obtained in 49% yield from **8** over 3 steps, or 48% yield from **13** over 3 steps, including Vilsmeier-Haack formylation, oxidation, amination, Pinner amidine synthesis methods. Purification methods of the intermediates and the final product involved in the route were developed, which make it as a process of cost effective, environmental friendly, and feasible for scale-up operation.

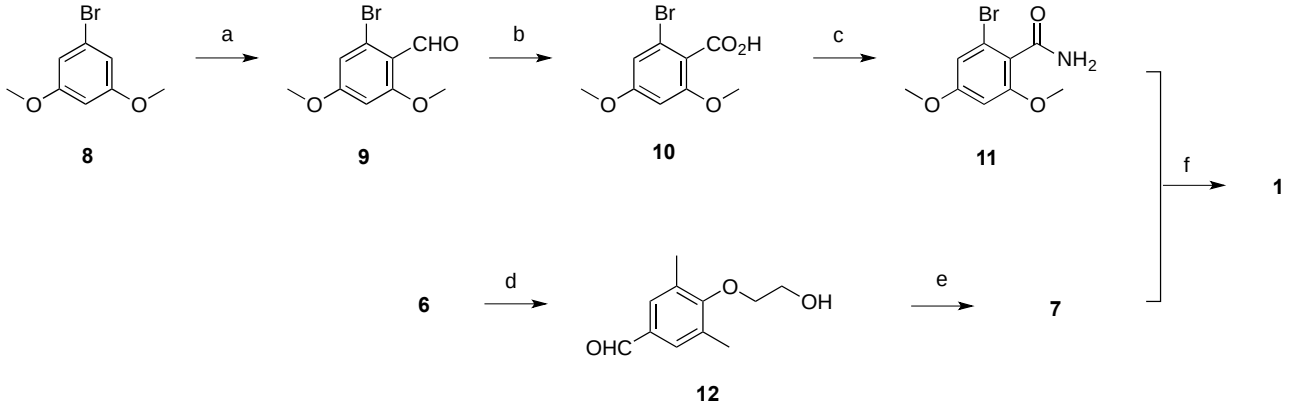
Apabetalone (**1**, RVX-208, Scheme 1), developed by Resverlogix, is a potent inhibitor of BET (bromodomain and extra-terminal) protein bromodomains.[1] It functions by removing atherosclerotic plaque via RCT (reverse cholesterol transport).[2] Apabetalone has been investigated for the treatment of diabetes, atherosclerosis, and coronary artery disease, and now in Phase III clinical research.[3]

With regard to the synthesis of apabetalone (**1**), two methods had been reported so far. The first route was reported by Wong *et al*,[4] as shown in Scheme 1. 3,5-Dimethoxyaniline (**2**) was chosen as the starting material, through cyclization, hydrolysis and amination in 23% yield over 3 steps to give the intermediate 2-amino-4,6-dimethoxybenzamide (**5**). 4-(2-((*t*-Butyldimethylsilyl)oxy)ethoxy)-3,5-dimethyl-benzaldehyde (**7**) was prepared from 4-hydroxy-3,5-dimethylbenzaldehyde (**6**) in 69% yield, which was cyclized with **5**, catalyzed by *p*-toluenesulfonamide (PTSA) and sodium hydrogen sulfite to give **1**, in 4.8% yield over 5 steps. Hydrogen peroxide is adopted in this original synthetic route, which makes the

reaction have the risk of explosion. In addition, oxalyl chloride and high temperature also make the reaction dangerous.

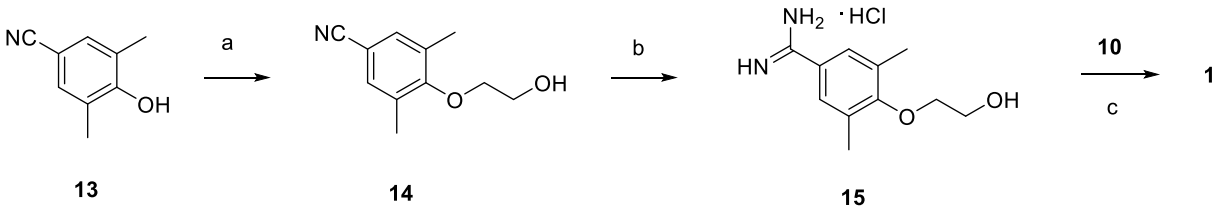


Scheme 1. Reagents and conditions: (a) i) HCl (g), Et_2O; ii) $(COCl)_2$, 170 °C, 84%; (b) NaOH, H_2O_2, 35%; (c) EDCI, HOBt, *N*-methylmorpholine, THF, NH_3 (g), rt, 77%; (d) $BrCH_2CH_2OTBS$, Cs_2CO_3, DMF, 69%; (e) $NaHSO_3$, PTSA, DMAC, 31%.



Scheme 2. Reagents and conditions: (a) $POCl_3$, DMF, 100 °C, 66%; (b) $NaClO_2$, NaH_2PO_4, *t*-BuOH, H_2O, rt, 78%; (c) EDCI, HOBt, *N*-methylmorpholine, THF, NH_3 (g), rt, 77%; (d) $ClCH_2CH_2OH$, K_2CO_3, EtOH, 94%; (e) TBSCl, DMF, 98%; (f) NH_4OH, CuI, Cs_2CO_3, *L*-proline, DMSO, 48%.

Another synthetic route **1** was reported by Liu's group,[5] as shown in Scheme 2. It was based on the Vilsmeier-Haack formylation, oxidation and amination of 1-bromo-3,5-dimethoxybenzene (**8**) to give 2-bromo-4,6-dimethoxybenzamide (**11**) in 39% yield over 3 steps. Compound **7** was prepared from **6** through two steps, using 2-chloroethanol and *t*-butylchlorodimethylsilane (TBSCl) successively, in 92% yield. Under the condition of copper iodide as catalyst and *L*-proline as ligand, compound **7** and **11** were condensed to give **1** in 48% yield. Hydrogen peroxide and oxalyl chloride were not used to make this procedure more safety than the first one. While the protective group TBS was also used so the atomic economy was poor.



Scheme 3. Reagents and conditions: (a) $ClCH_2CH_2OH$, K_2CO_3, MeCN, 80 °C, 8 h, 83%; (b) i) HCl (g), MeOH, MTBE, 10 h; ii) NH_3 (g), MeOH, rt, 12 h, 79%; (c) CuI, Cs_2CO_3, DMSO, 80 °C, 12 h, 73%.

In order to develop an efficient and practical method for preparing of apabetalone (**1**), a new and convergent synthetic route was developed successfully, as shown in Scheme 3. In given basic condition, 2-bromobenzoic acid and benzimidamide hydrochloride can be cyclized to give the 2-phenylquinazolin-4(3*H*)-one structure.[6,7] This strategy was adopted to build the 2-phenylquinazolin-4(3*H*)-one main ring for **1**. 4-Hydroxy-3,5-dimethylbenzonitrile (**13**) was chosen as the starting material, which was reacted with 2-chloroethanol under K_2CO_3/MeCN to give 4-(2-hydroxyethoxy)-3,5-dimethylbenzonitrile (**14**) in 83% yield. 4-(2-Hydroxyethoxy)-3,5-dimethylbenzimidamide hydrochloride (**15**) was obtained by the Pinner amidine synthesis method[8] in 79% yield. Another intermediate **10** was prepared from compound **8** (as shown in Scheme 2) based on Liu's method[5] in 68% isolated yield over 2 steps after modification, which was depicted in the experimental section. At the last step, **1** was obtained by reaction of compound **15** and **10** under copper iodide and cesium carbonate in DMSO at 80 °C, in 73% isolated yield, based on Fu's method.[9]

In summary, an effective and convergent synthetic route of apabetalone (**1**) was developed successfully. The key step is to build the 2-phenylquinazolin-4(3*H*)-one main ring of **1** from the 2-bromobenzoic acid **10** and the benzimidamide hydrochloride compound **15**. 1-Bromo-3,5-dimethoxybenzene (**8**) and 4-hydroxy-3,5-dimethylbenzonitrile (**13**) were used as the starting materials, **1** was obtained in 49% yield from **8** over 3 steps, or 48% yield from **13** over 3 steps, including Vilsmeier-Haack formylation, oxidation, amination, Pinner amidine synthesis methods. Purification methods of the intermediates and the final product involved in the route were developed, which make it as a process of cost effective, environmental friendly, and feasible for scale-up operation.

EXPERIMENTAL

All commercially available chemicals and solvents were used as received without any further purification. ^{1}H NMR and ^{13}C 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 uncorrected. The HPLC data

were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds was based on the areas of HPLC UV.

2-Bromo-4,6-dimethoxybenzaldehyde (9). $POCl_3$ (16.9 g, 108 mmol) was added dropwise to a mixture of 1-bromo-3,5-dimethoxybenzene (**8**) (20.0 g, 90 mmol) in DMF (35 mL) at 0~5 °C. The mixture was stirred for 30 min at room temperature, and then heated to 100 °C for 4 h. The reaction was quenched by addition to ice (100 g), and stirred at 5~20 °C for 2 h. The resulting solid was isolated by suction filtration, washed with water (20 mL × 2) and 95% EtOH (20 mL × 1), dried at 40 °C for 4 h to give **9** (19.7 g, 87%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 6.80 (d, J = 2.2 Hz, 1H), 6.45 (d, J = 2.2 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 164.6, 163.6, 127.3, 116.9, 111.6, 98.2, 56.1, 55.8. MS (ESI): *m/z* = 246.9 $[M+H]^+$. HRMS (ESI) calcd for: $C_9H_{10}BrO_3$ $[M + H]^+$ 244.9813. Found: 244.9811.

2-Bromo-4,6-dimethoxybenzoic acid (10). A mixture of compound **9** (5.0 g, 20.4 mmol) and sulfamic acid (6.9 g, 71.4 mmol) in THF (50 mL) was stirred at room temperature. A solution of sodium chlorite (6.5 g, 71.4 mmol) in water (25 mL) was added dropwise to the reaction mixture over 1 h and stirred at room temperature for another 1 h. The reaction solution was extracted with EtOAc (50 mL × 2), the combined organic solution was washed with brine (75 mL × 2). The organic solvents were concentrated under vacuum to give a yellow solid, which was dried at 40 °C for 4 h to yield **10** (4.3 g, 80%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, 1H), 6.79 (d, J = 2.1 Hz, 1H), 6.65 (d, J = 2.1 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4, 156.5, 155.6, 121.1, 119.4, 113.5, 97.2, 57.0, 56.7. MS (ESI): *m/z* = 261.0 $[M+H]^+$. HRMS (ESI) calcd for: $C_9H_{10}BrO_4$ $[M + H]^+$ 260.9762. Found: 260.9760.

HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 20 min; Mobile phase: MeOH (0.1% HCO_2H)/water = 90/10, t_R: 3.76 min, purity: 98.8%.

4-(2-Hydroxyethoxy)-3,5-dimethylbenzonitrile (14). A mixture of 4-hydroxy-3,5-dimethylbenzonitrile (**13**) (5.0 g, 34 mmol) and K_2CO_3 (14.2 g, 102 mmol) in MeCN (80 mL) was stirred at room temperature for 30 min. 2-Chloroethanol (5.5 g, 68 mmol) was added dropwise to the reaction mixture and stirred at 80 °C for 8 h. After cooled to room temperature, the solid was filtered to removed. The filtrate was extracted with EtOAc (50 mL × 2). The organic extracts were combined, washed with 1 M aqueous NaOH (50 mL × 2) and brine (50 mL × 2) respectively. The organic solvents were concentrated under vacuum to yield a light brown solid, which was crystallized from hexane (25 mL) to yield **14** (5.4 g, 83%)

as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.36 (s, 2H), 4.01–3.99 (m, 2H), 3.96–3.94 (m, 2H), 2.34 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.8, 132.6, 118.9, 106.1, 74.2, 60.4, 15.8. MS (ESI): *m/z* = 192.1 $[M+H]^+$. HRMS (ESI) calcd for: $C_{11}H_{14}NO_2$ $[M + H]^+$ 192.1025. Found: 192.1019.

4-(2-Hydroxyethoxy)-3,5-dimethylbenzamidine hydrochloride (15). A solution of compound **14** (4.0 g, 21 mmol) in methyl *t*-butyl ether (MTBE) (20 mL) and MeOH (1.35 g, 42 mmol) was stirred and cooled to 0~5 °C. Hydrogen chloride gas was burbled into the solution at 0~5 °C for 2 h, and stirred at 0~5 °C for another 8 h. The resulting solid was isolated by suction filtration, washed by MTBE (10 mL × 2) to give a white solid (4.4 g), which was dissolved directly in MeOH (20 mL) and stirred at 0~5 °C. A solution of 7 M ammonia in MeOH (4.0 mL, 28 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed under vacuum to give **15** (4.06 g, 79%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (brs, 2H), 9.19 (brs, 2H), 7.60 (s, 2H), 4.98 (t, *J* = 5.3 Hz, 1H), 3.87 (t, *J* = 4.9 Hz, 2H), 3.72 (dd, *J* = 9.6, 4.8 Hz, 2H), 2.31 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2, 160.3, 131.5, 128.8, 122.6, 74.2, 60.4, 16.2. MS (ESI): *m/z* = 209.1 $[M+H]^+$. HRMS (ESI) calcd for: $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1290. Found: 209.1287.
HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 220 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 17.5 min; Mobile phase: MeOH (0.1% TEA)/water = 70/30, t_R: 2.23 min, purity: 98.8%.

Apabetalone (1). A mixture of compound **10** (1.95 g, 7.4 mmol), **15** (2 g, 8.2 mmol), CuI (0.14 g, 0.75 mmol) and Cs_2CO_3 (4.89 g,14.8 mmol) in DMSO (15 mL) was heated and stirred at 80 °C for 12 h under nitrogen. After cooled to room temperature, the reaction mixture was quenched by the addition of 20% aqueous NH_4Cl (50 mL). The resulting solution was extracted with EtOAc (50 mL × 2), the combined organic solution was washed with brine (50 mL × 2). The organic solution was separated and removed in vacuo to give a light brown solid (2.8 g). The crude product and active carbon (0.2 g) were suspended in MeOH (12 mL), heated to reflux for 30 min. The insoluble solid was filtered through a celite pad in hot. Water 2 mL was added to the filtrate and the solution was stirred at room temperature for 2 h and at 0~5 °C for 1 h. The resulting solid was isolated by filtration, washed with 80% MeOH-H_2O (2 mL × 2), dried at 40 ºC for 4 h to give **1** (2.01 g, 73%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.90 (s, 2H), 6.74 (d, *J* = 2.3 Hz, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 4.90 (brs, 1H), 3.90 (s, 3H), 3.88–3.83 (m, 5H), 3.74 (m, 2H), 2.32 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.2, 160.1, 159.8, 158.4, 153.1, 152.5, 130.8, 128.2, 127.2, 104.6, 101.1, 97.5, 74.0, 60.4, 55.9, 55.6, 16.1. MS (ESI): *m/z* = 371.1 $[M+H]^+$. HRMS (ESI) calcd for: $C_{20}H_{23}N_2O_5$ $[M + H]^+$ 371.1607. Found: 371.1605.

HPLC Conditions: Column: Acclaim C18 (150 mm × 2.1 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.2 mg/mL; Run time: 20 min; Mobile phase: MeOH/H_2O = 80/20, t_R: 8.15 min, purity: 99.0%.

REFERENCES

1. Y. L. Khmelnitsky, V. V. Mozhaev, I. C. Cotterill, P. C. Michels, S. Boudjabi, V. Khlebnikov, M. M. Reddy, G. S. Wagner, and H. C. Hansen, *Eur. J. Med. Chem.*, 2013, **64**, 121.
2. C. Aguirre-Portoles, J. Feliu, G. Reglero, and A. R. de Molina, *Mol. Oncol.*, 2018, **12**, 1735.
3. S. Picaud, C. Wells, I. Felletar, D. Brotherton, S. Martin, P. Savitsky, B. Diez-Dacal, M. Philpott, C. Bountra, H. Lingard, O. Fedorov, S. Muller, P. E. Brennan, S. Knapp, and P. Filippakopoulos, *Proc. Natl. Acad. Sci. U S A.*, 2013, **110**, 19754.
4. N. C. W. Wong, J. E. L. Tucker, H. C. Hansen, F. S. Chiacchia, and D. McCaffrey, US 20080188467, 2008.
5. S. W. Liu, B. M. Xi, C. Li, Z. B. Liu, and L. Li, CN 108218798, 2018.
6. P. M. Scola, J. A. Campbell, N. Sin, L. Q. Sun, and X. A. Wang, WO 2005051410, 2005.
7. B. Li, L. Samp, J. Sagal, C. M. Hayward, C. Yang, and Z. J. Zhang, *J. Org. Chem.*, 2013, **78**, 1273.
8. A. W. Dox, *Org. Synth.*, 1941, Coll. Vol. **1**, 5.
9. X.-W. Liu, H. Fu, Y.-Y. Jiang, and Y.-F. Zhao, *Angew. Chem. Int. Ed.*, 2009, **48**, 348.