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ORIGINAL PAPER

A new route for the synthesis of Palbociclib

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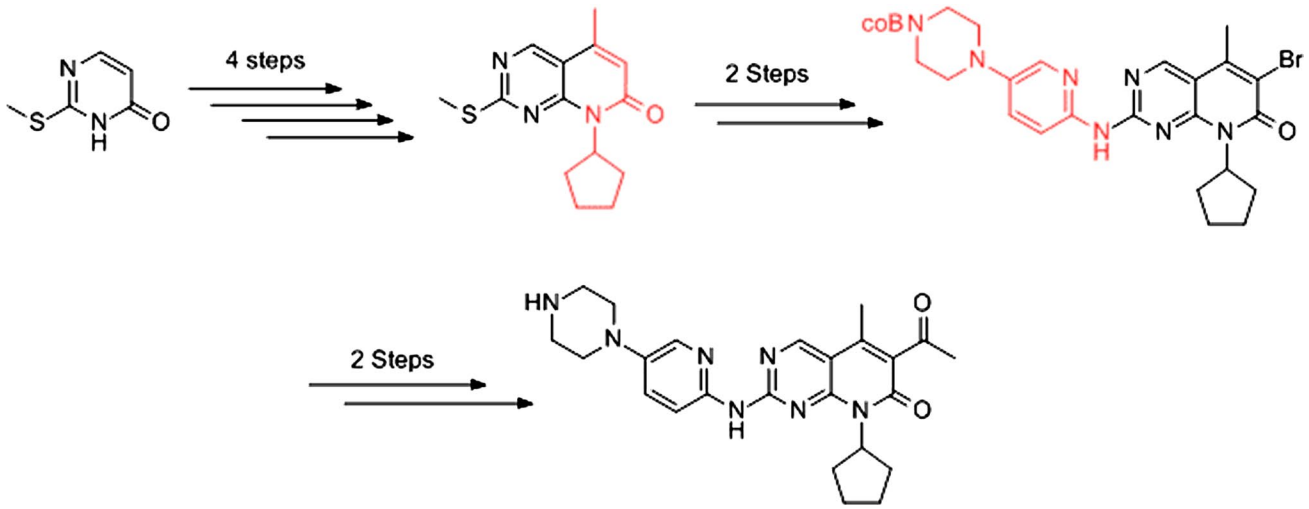
Abstract
In this paper, a novel synthetic method for Palbociclib was reported. It was synthesized in eight steps from 2-(methylthio) pyrimidin-4-(3H)-one with approximately 10% overall yield. This protocol started material 2-(methylthio) pyrimidin-4-(3H)-one, involved nucleophilic substitution by thionyl chloride, bromination, nucleophilic substitution by cyclopentylamine, a one pot-two step method (Heck reaction, ring close sequence), oxidation and bromination, cross-coupling reaction, Heck reaction, aqueous workup to afford Palbociclib. This synthetic route used inexpensive raw material and reagents, involved readily controllable reaction conditions and reduced environmental hazards.

Graphic abstract
Synthesis of Palbociclib, a small molecule CDK inhibitor, starting from 2-(methylthio) pyrimidin-4-(3H)-one by 8 steps reaction. This method afforded the Palbociclib in 10% yield.



Keywords CDK · CDK inhibitor · Palbociclib · Synthesis

Introduction

Cyclin-dependent kinases (CDKs) are heterodimeric proteins that comprise of a catalytic subunit (Cdk) and a member of a family of regulatory subunits (cyclins). (Malumbres and Barbacid 2005; Harper and Adams 2001). Cyclin-dependent kinases (CDKs) can regulate the cell cycle and thus control transcriptional process, which is important pathway for cell cycle regulatory machinery. CDKs 1, 2, 4, 6, and 7 are important drivers of the cell cycle, resulting in division of a cell into two identical daughter cells by highly orchestrated series of events (Malumbres et al. 2009; Diaz-Moralli et al. 2013). Incorrect regulation of cyclin-dependent kinases (CDKs) will lead to uncontrolled cell division and

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metastasis, and then cause cancer. (Gupta et al. 2016; Bollard et al. 2017). Palbociclib (**1**) (Fig. 1) (also IBRANCE) is an effective anti-proliferative agent against Rb-positive tumor cells in retinoblastoma, which inhibits Ser780/Ser795 phosphorylation on Rb protein to induce G1 arrest (Kim and Scott 2017; Fry et al. 2004). In February 2015, the United States Food and Drug Administration (FDA) approved Palbociclib as a first selective inhibitor of the CDK4/6 for marketing. It was approved for using in combination with letrozole as initial endocrine-based therapy for metastatic disease in postmenopausal women with HR-positive, HER2-negative breast cancer, and combination with fulvestrant in women with HR-positive, HER2-negative advanced breast cancer with disease progression following endocrine (Rocca et al. 2017; Konecny 2016).

Palbociclib was first synthesized by Pfizer in 2005, involved substitution reaction, a series of redox reactions, Wittig-Horner reaction, bromination reaction, cross-coupling reaction, Stille reaction, Boc deprotection procedure, and hydrolysis reaction. The starting material 4-chloro-2-methylthio-pyrimidine-5-carboxylic acid ethyl ester (**2**) was expensive and the synthesis process required eleven-step sequence (Scheme 1) (Toogood et al. 2005; VanderWel et al. 2005). According to this procedure to prepare Palbociclib would encountered problems that required optimization of the original synthetic procedures. In a two-step reduction–oxidation sequence employing lithium aluminum hydride followed by manganese (IV) to convert ester **3** to aldehyde **5**, this step required an ultra-low temperature (− 78 °C) and isolation of air and water to add reducing agent ($LiAlH_4$). It also required strict conditions to use Grignard reagents to convert aldehyde **5** to alcohols **6** and to use NaH in Wittig-Horner reaction to synthesize methyl sulfides **8**. These represented difficulties if carried out on a large scale. In summary, this synthetic route was fairly labor intensive, not only required harsh conditions but also used expensive and unstable reagents. In addition, the method had a long route and a low yield (3–4%), not suitable for industrialization.

An alternative way for the preparation of Palbociclib has been reported in relatively high yield from

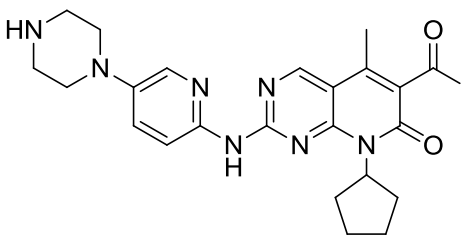

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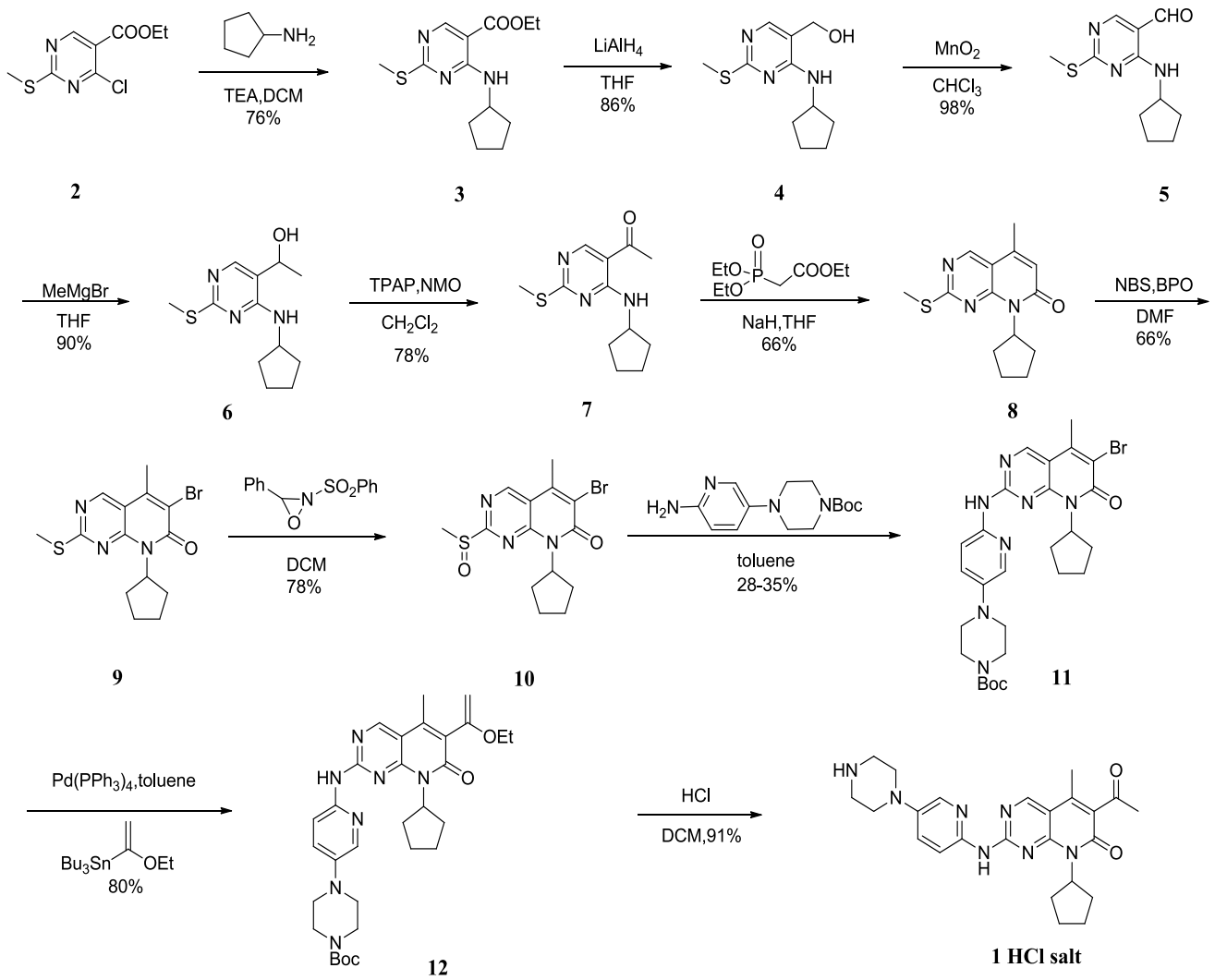
Fig. 1 Palbociclib

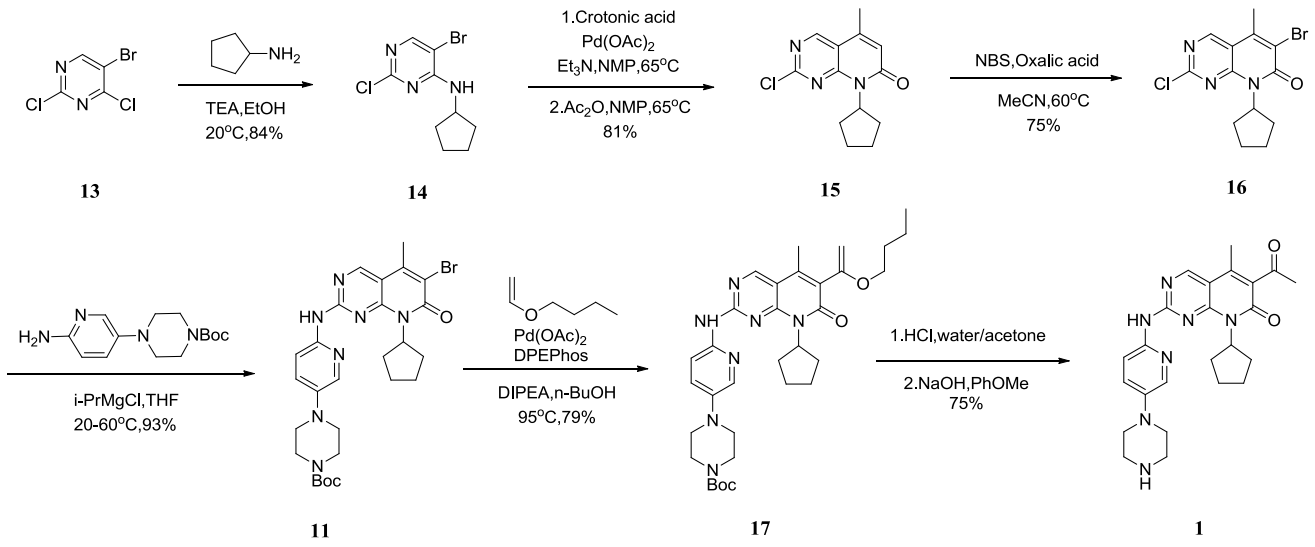
5-bromo-2,4-dichloropyrimidine (**13**) by six-step reaction (Scheme 2) (Duan et al. 2016; Maloney et al. 2016; Chekal et al. 2016). It also required the transformation of 5-bromo-2,4-dichloropyrimidine (**13**) into intermediate **11**. In displacement of the chlorine of intermediate **13** to give intermediate **14**, the presence of chlorine at the 2 and 4 positions selectively affected the reaction yield and separation. The use of the high boiling point solvent NMP in the Heck reaction increased the difficulty in post-reaction processing, resulting in difficulty in separating the purified product. Overall, this procedure shortened the reaction step to six-step and achieved a relatively high yield. However, the cost of this method was the higher, not only used the palladium catalyst twice, but also used raw materials expensive.

Another route investigated employed a convergent palladium-catalyzed amination reaction (Scheme 3) (Nathel et al. 2014). Intermediate **18** was readily available by reaction of intermediate **16** (Scheme 2) with a methanol solution of ammonia. Hence, this method could share starting materials with the Scheme 2 but involved different intermediates. While the amino compound **18** readily underwent a Heck reaction to produce intermediate **19** compared with intermediate **11**, the use of two palladium-catalyzed steps increased the accumulation of palladium in the process, which increased the difficulties to remove residual metals from the process (Carpino 2000). These problems also restricted large-scale synthesis of Palbociclib and this procedure did not develop further.

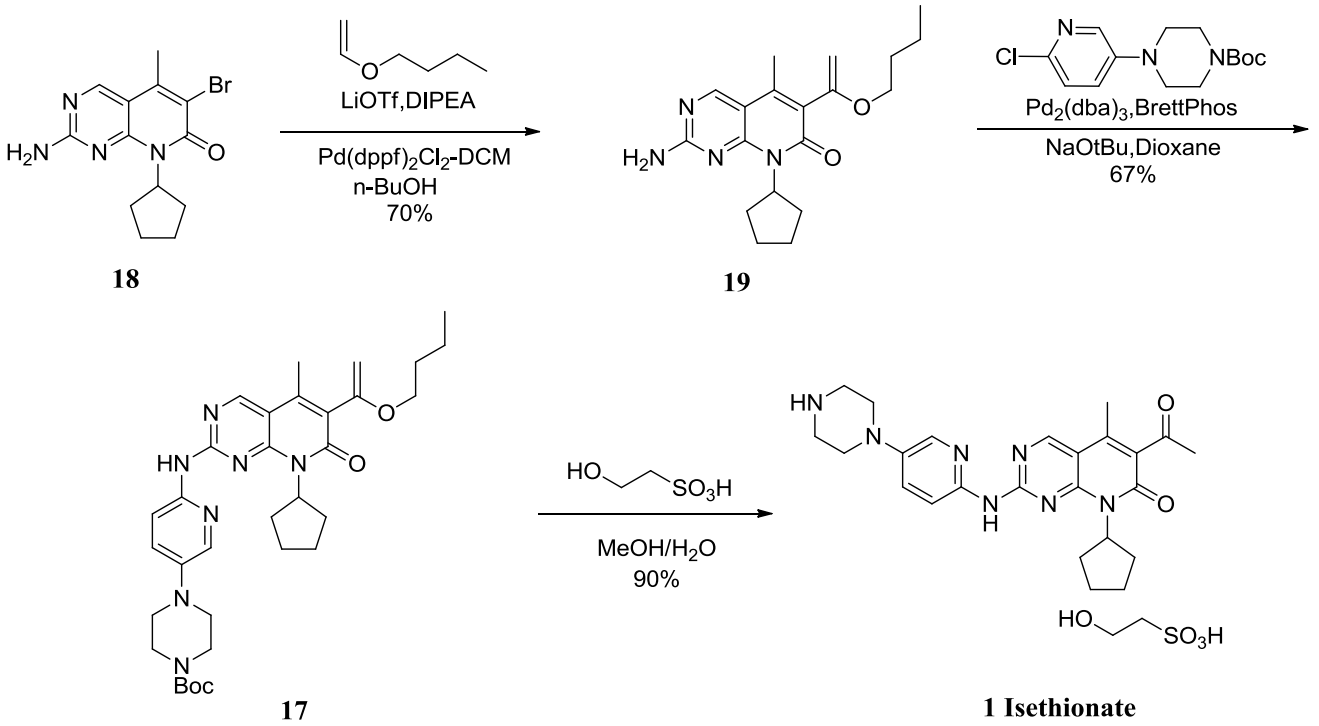
Hence, we designed a novel route for the synthesis of Palbociclib using an economic starting material 2-(methylthio) pyrimidin-4-(3H)-one (**20**) and involving eight-step reaction (Scheme 4). In the present procedure, it required the transformation of 2-(methylthio) pyrimidin-4-(3H)-one (**20**) into intermediate **10**. In the key synthetic reaction, the intermediate **8** was formed by two-step heck reaction-ring close sequence employing crotonic acid followed by acetic anhydride. After oxidizing the 2-position methylthio group while introducing bromine, intermediate **8** afforded intermediate **10**. This strategy could also assist in developing a facile route for preparing 6-bromo-8-cyclopentyl-5-methyl-2-(methylsulfinyl) pyrido[2,3-d] pyrimidin-7(8H) (**10**). The next steps could share intermediate but involve different reagents with previous route. After cross-coupling reaction, Heck reaction, aqueous workup, intermediate **11** gave Palbociclib. Overall, this method offered a route based on good yields, with low cost, readily controllable reaction conditions and reduced environmental hazards.



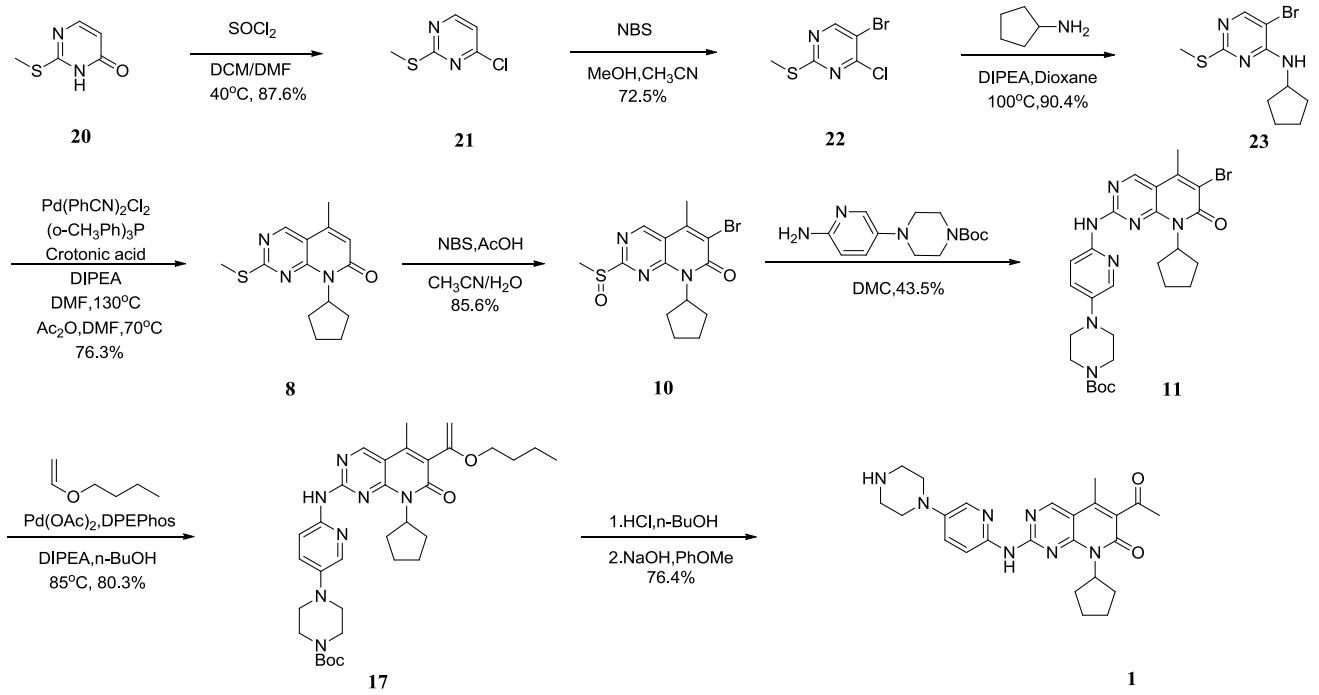
Scheme 1 The first synthetic strategy for the preparation of Palbociclib



Scheme 2 The second synthetic strategy for the preparation of Palbociclib



Scheme 3 The third synthetic strategy for the preparation of Palbociclib



Scheme 4 The new synthetic strategy for the preparation of the Palbociclib

Experimental

Materials and instruments

The solvents, reagents and materials were commercially available and were used without further purification unless otherwise noted. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (GF-254, Qingdao Ocean Chemical Company, China). Silica gel column chromatography (CC) (200–300 mesh, Qingdao Marine chemical industry corporation, China). Melting points were determined on a YRT-3 drug melting point meter and were uncorrected. NMR spectra were recorded on a Bruker Avance DPX-300 MHz/500 MHz instrument in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference and the chemical shifts (δ) were reported in parts per million (ppm). High resolution mass spectra (HRMS) were obtained from Agilent 1100 LC/MS Spectrometry Services.

Synthesis of 4-chloro-2-(methylthio) pyrimidine (21)

To a solution of 2-methylthio-4-ketopyrimidine (**20**, 10 g, 70.3 mmol) in DCM (20 mL) and DMF (10 mL) mixed solution, thionyl chloride (3.07 mL, 42.2 mmol) solution was slowly added dropwise while heating. After addition, the reaction mixture was stirred at 40 °C for 3 h. After quenching with saturated $NaHCO_3$ the solution was adjusted to a neutral pH and the solution was extracted three times with DCM. The organic phases were washed with saturated $NaHCO_3$ solution and saturated NaCl solution and dried over anhydrous Na_2SO_4. After filtering to remove the anhydrous Na_2SO_4, the solution was distilled at 40 °C to remove solvents under atmospheric pressure to give the product **21** (Katritzky et al. 1989; Davey et al. 2007). Yellow oil; yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, $J = 5.2$ Hz, 1H), 6.99 (d, $J = 5.2$ Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 161.0, 158.0, 116.4, 14.3; HRMS ($[M+H]^+$): *m/z* calcd for $[(C_5H_5ClN_2S)+H]^+$: 160.99404; found 160.99335.

Synthesis of 4-chloro-5-bromo-2-(methylthio) pyrimidine (22)

To a solution of 4-chloro-2-(methylthio)-pyrimidine (**21**, 9.90 g, 61.6 mmol) in MeOH (28 mL) and MeCN (20 mL) mixed solution, NBS (13.16 g, 73.9 mmol) was added (2×6.58 g). After the additions, the reaction mixture was stirred at room temperature. After quenching with saturated Na_2SO_3 solution, the solution was extracted with DCM and saturated $NaHCO_3$ solution three times. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by passing the organic extract through a silica gel column using PE/EA (25:1) to give the product **22** (Elliott 1981). White solid; yield 73%; m.p. 48.5–50.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 2.55 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 159.5, 114.1, 14.7; HRMS ($[M+H]^+$): *m/z* calcd for $[(C_5H_4BrClN_2S)+H]^+$: 240.90254, found: 240.90203.

Synthesis of 5-bromo-*N*-cyclopentyl-2-(methylthio) pyrimidin-4-amine (23)

To a solution of 4-chloro-5-bromo-2-(methylthio) pyrimidine (**22**, 10.70 g, 44.8 mmol) in dioxane (40 mL), DIPEA (14.77 mL, 89.4 mmol) and cyclopentylamine (5.56 mL, 67.0 mmol) were added into the solution. After completion of the addition, the reaction mixture was stirred at 100 °C for 4 h. After quenching with water, the solution was extracted with ethyl acetate and saturated $NaHCO_3$ solution three times. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by passing the organic extract through a silica gel column using PE/EA (15:1) to give the product **23** (patent WO2004065378). Yellow oil; yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H), 5.24 (s, 1H), 4.42-4.33 (m, 1H), 2.48 (s, 3H), 2.12–2.06 (m, 2H), 1.77–1.62 (m, 4H), 1.51–1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 157.1, 154.8, 99.8, 52.9, 33.2, 23.8, 14.4; HRMS ($[M+Na]^+$): *m/z* calcd for $[(C_{10}H_{14}BrN_3S)+Na]^+$: 311.99690, found 311.99651.

Synthesis of 8-cyclopentyl-5-methyl-2-(methylthio) pyrido[2,3-d] pyrimidin-7(8H)-one (8)

To a solution of 5-bromo-*N*-cyclopentyl-2-(methylthio) pyrimidin-4-amine (**23**, 11.64 g, 40.4 mmol) and crotonic acid (5.22 g, 60.6 mmol) in DMF (100 mL), DIPEA (28.14 mL, 166.4 mmol) were added. Then palladium dibenzylcarbonitrile (465 mg, 1.2 mmol) and tri-o-tolylphosphorus (860 mg, 3.0 mmol) were added under a nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred at 130 °C for 24 h under nitrogen protection. After 24 h, acetic anhydride (25 mL) was added and the solution was stirred at 70 °C for 4 h. Then the mixture was cooled, diluted with MTBE (100 mL) and then extracted with NH_4Cl, $NaHCO_3$ and water. The organic phases were combined, dried $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by passing the organic extract through a silica gel column using PE/EA (15:1) to give the product **8** (Toogood et al. 2005; VanderWel et al. 2005). Gray white solid; yield 76%; m.p. 201.2–202.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H), 6.41 (s, 1H), 5.97–5.82 (m, 1H), 2.61 (s, 3H), 2.36 (m, 5H), 2.06 (s, 2H), 1.87 (s, 2H), 1.69 (d, $J = 10.3$ Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 163.0, 154.1, 144.0, 122.0, 111.0, 53.8, 28.4, 25.8, 17.2, 14.5; HRMS ($[M+Na]^+$): *m/z* calcd for $[(C_{14}H_{17}N_3OS)+Na]^+$: 298.09903, found 298.09853.

Synthesis of 6-bromo-8-cyclopentyl-5-methyl-2-(methylsulfinyl) pyrido[2,3-d] pyrimidin-7(8H)-one (10)

To a solution of 8-cyclopentyl-5-methyl-2-(methylthio) pyrido[2,3-d] pyrimidin-7(8H)-one (**8**, 8.49 g, 14.7 mmol) in MeCN (100 mL), acetic acid (177 µL, 3.1 mmol), H_2O (580 µL, 32.1 mmol) and NBS (17.22 g, 96.8 mmol) were added. After completion of the addition, the reaction mixture was stirred at room temperature for 8 h. After quenching with water (70 mL), the solution was stirred for 10 min, filtered. The filter cake was washed with water to obtain a white solid. After purification by recrystallization with ethanol (50 mL), the product was dried in vacuo to give the product **10** (Toogood et al. 2005; VanderWel et al. 2005). White solid; yield 86%; m.p. 158.3–160.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 6.12–5.96 (m, 1H), 2.97 (s, 3H), 2.69 (s, 3H), 2.24–2.06 (m, 4H), 1.92 (d, $J=9.8$ Hz, 2H), 1.72–1.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.41, 160.68, 157.91, 156.66, 145.22, 126.59, 116.88, 58.30, 42.89, 31.30, 31.20, 28.60, 21.04; HRMS ($[M+Na]^+$): *m/z* calcd for $[(C_{14}H_{16}BrN_3O_2S)+Na]^+$: 394.00243, found 394.00248.

Synthesis of *tert*-butyl 4-(6-((6-bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d] pyrimidin-2-yl) amino) pyridin-3-yl) piperazine-1-carboxylate (11)

To a solution of 6-bromo-8-cyclopentyl-5-methyl-2-(methylsulfinyl) pyrido[2,3-d] pyrimidin-7(8H)-one (**10**, 9.80 g, 26.4 mmol) in dimethyl carbonate (100 mL), *tert*-butyl 4-(6-aminopyridin-3-yl) piperazine-1-carboxylate (11.02 g, 39.6 mmol) was added under a nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred at 110 °C for 25 h under nitrogen protection. After 25 h, the reaction solution was cooled to room temperature, diluted with water and then extracted with dichloromethane and saturated $NaHCO_3$ solution. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by passing the organic extract through a silica gel column using DCM/MeOH (40:1) to give the product **11** (Toogood et al. 2005; VanderWel et al. 2005; Duan et al. 2016). Yellow solid; yield 47%; m.p. > 250 °C; 1H NMR (300 MHz, CDCl3) δ 8.82 (s, 1H), 8.43 (s, 1H), 8.21 (d, $J=9.0$ Hz, 1H), 8.04 (d, $J=2.5$ Hz, 1H), 7.35 (dd, $J=9.1$, 2.8 Hz, 1H), 5.99 (p, $J=8.7$ Hz, 1H), 3.68–3.55 (m, 4H), 3.20–3.04 (m, 4H), 2.61 (s, 3H), 2.40–2.22 (m, 2H), 2.13 (t, $J=9.6$ Hz, 2H), 1.95–1.84 (m, 2H), 1.74–1.64 (m, 2H), 1.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.05, 157.84, 156.40, 154.96, 154.77, 145.59, 143.64, 143.49, 136.80, 127.04, 117.62, 113.67, 108.20, 80.26, 77.16, 55.29, 49.90, 43.62, 28.58, 28.44, 26.16, 18.19; HRMS ($[M+H]^+$): *m/z* calcd for $[(C_{27}H_{34}BrN_7O_3)+H]^+$: 586.19651, found 586.19626.

Synthesis of *tert*-butyl 4-(6-((6-(1-butoxyvinyl)-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d] pyrimidin-2-yl) amino) pyridin-3-yl) piperazine-1-carboxylate (17)

To a solution of *tert*-butyl 4-(6-((6-bromo-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d] pyrimidin-2-yl) amino) pyridin-3-yl) piperazine-1-carboxylate (**11**, 6.71 g, 11.5 mmol) in *n*-butanol (67 mL), *n*-butyl vinyl ether (4.86 mL, 34.4 mmol), and diisopropylethylamine (4.80 mL, 27.6 mmol) was added. Then palladium acetate (52.5 mg, 0.23 mmol) and bis(2-diphenylphosphinophenyl) ether (154 mg, 0.28 mmol) were added under a nitrogen atmosphere. After completion of the addition, the reaction mixture was stirred at 85 °C overnight under nitrogen protection. Then the mixture was cooled to 80 °C, and water (10.5 mL) and *n*-butanol (20 mL) were added. Then the mixture was stirred for 0.5 h and then quickly filtered. Water (24.5 mL, 3.5 vol) and 1,2-diaminopropane (2.96 mL, 34.4 mmol) were added and stirred at 70 °C for 0.5 h. The aqueous phase was removed, the organic phase was programmed to cool to room temperature and a large amount of yellow solid precipitated. The solids were filtered and washed twice with *n*-butanol (7 mL) and three times with methyl *t*-butyl ether (7 mL). The product was dried in vacuo to give the product **17** (Maloney et al. 2016). Yellow solid; yield 80%; ^{1}H NMR (500 MHz, DMSO-d6) δ 9.89 (s, 1H), 8.86 (s, 1H), 8.06 (s, 1H), 7.90 (d, $J=9.0$ Hz, 1H), 7.48 (d, $J=11.4$ Hz, 1H), 5.82 (t, $J=8.7$ Hz, 1H), 4.47 (s, 1H), 4.05 (s, 1H), 3.77 (t, $J=6.2$ Hz, 2H), 3.48 (s, 4H), 3.11 (s, 4H), 2.37 (s, 3H), 2.23 (s, 2H), 1.90 (s, 2H), 1.74 (s, 2H), 1.64–1.60 (m, 3H), 1.43 (s, 9H), 1.39-1.35 (m, 1H), 0.91 (t, $J=7.3$ Hz, 2H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 160.96, 158.22, 157.33, 155.26, 154.68, 153.76, 145.03, 143.06, 142.58, 136.03, 125.81, 125.45, 114.69, 106.66, 87.83, 78.95, 66.85, 52.91, 48.55, 39.52, 30.35, 28.00, 27.48, 25.04, 18.81, 14.42, 13.56; HRMS ($[M+H]^+$): *m/z* calcd for $[(C_{33}H_{45}N_7O_4)+H]^+$:604.36091, found 604.36086.

Synthesis of 6-acetyl-8-cyclopentyl-5-methyl-2-((5-(piperazin-1-yl) pyridin-2-yl) amino) pyrido[2,3-d] pyrimidin-7(8H)-one (Palbociclib, 1)

To a solution of *tert*-butyl 4-(6-((6-(1-butoxyvinyl)-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-d] pyrimidin-2-yl) amino) pyridin-3-yl) piperazine-1-carboxylate

(**17**, 5.57 g, 9.22 mmol) in water (50.5 mL) and *n*-butanol (60.0 mL), hydrochloric acid solution (36 wt%, 0.93 g, 9.22 mmol) was added when the mixture was heated to 70 °C. The mixture was stirred for 6 h. Upon reaction completion, anisole (45.5 mL, 45.27 g, 41.8 mmol) was added followed by sodium hydroxide solution (50 wt%, 0.15 g, 1.87 mmol), and the mixture was stirred for 2 h. The aqueous phase was removed, and the organic phase was washed twice with water (250 mL) before being distilled atmospherically to an end temperature of 120 °C. After cooling, the solution was placed in refrigerator overnight. A large amount of yellow solid was precipitated, suction filtered. And the solid was washed with *n*-butanol and dried in vacuo to give product **1** (Toogood et al. 2005; VanderWel et al. 2005; Duan et al. 2016; Chekal et al. 2016). Yellow solid; yield 76%; m.p. 199.3-201.5 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.00 (s, 1H), 8.94 (s, 1H), 8.03 (d, $J = 2.6$ Hz, 1H), 7.83 (d, $J = 9.0$ Hz, 1H), 7.43 (dd, $J = 9.0$, 2.8 Hz, 1H), 5.88–5.74 (m, 1H), 3.10–3.02 (m, 4H), 2.89–2.81 (m, 4H), 2.42 (s, 3H), 2.31 (s, 3H), 2.27–2.17 (m, 2H), 1.88 (s, 2H), 1.77 (d, $J = 9.9$ Hz, 2H), 1.63–1.53 (m, 2H), 1.24 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 202.32, 160.71, 158.54, 158.17, 154.72, 144.08, 144.04, 142.00, 135.28, 129.00, 124.51, 115.16, 106.49, 52.86, 49.38, 45.35, 39.52, 31.22, 27.48, 25.00, 13.53; HRMS ($[M+H]^+$): *m/z* calcd for $[(C_{24}H_{29}N_7O_2)+H]^+$: 448.24553, found 448.24585.

Results and discussion

Our novel eight-step synthesis of Palbociclib was shown in Scheme 4. Starting material **20** was commercially available, inexpensive and readily prepared from thiouracil by methylation reaction. The reaction between the reactants was readily controllable, generated by conventional heating and stirring operations in common solvent. The determining step in the route was the procedure for synthesizing intermediate **8** and intermediate **11**.

In a previous report, intermediate **8** was obtained by the Wittig-Horner reaction with $(EtO)_2P(O)CHXCO_2Et$ (Scheme 1). This process involved a complex operating procedure and relatively long reaction route. Hence, we inspired by Scheme 2 to adopt the strategy of Heck reaction and amidation ring closure reaction. After nucleophilic substitution by thionyl chloride, bromination, nucleophilic substitution by cyclopentylamine, starting material **20** gave intermediate **23**. Then intermediate **23** was reacted sequentially, in one pot, with crotonic acid and acetic anhydride to convert to intermediate **8**. Heck reaction is a coupling reaction of an unsaturated halogenated hydrocarbon with an olefin to form a substituted olefin using a strong base with palladium catalysis and nitrogen protection. Heck reaction commonly used divalent palladium compounds as catalyst and monodentate phospine agents as ligand (Mizoroki et al. 1971; Heck and Nolley 1972). However, initial attempts to obtain compound **8** from **23** through reactions with crotonic acid were not successful with $Pd(OAc)_2$ as catalyst, PPh_3 as ligand and TEA as base. Then, screening the combination of ligand and base of this reaction system, including TEA and $(o\text{-}CH_3Ph)_3P$, DIPEA and PPh_3, DIPEA and $(o\text{-}CH_3Ph)_3P$, K_2CO_3 and PPh_3, K_2CO_3 and $(o\text{-}CH_3Ph)_3P$, gave an unsatisfactory result (no reaction) with $Pd(OAc)_2$ as catalyst. In further attempts to synthesize intermediate **8**, we changed the palladium catalyst and also screened the combination of ligand and base. When using $Pd(PhCN)_2Cl_2$ as catalyst, $(o\text{-}CH_3Ph)_3P$ as ligand and DIPEA as base successfully gave rise to product. This one pot-two step method (Heck reaction, ring close sequence) achieved 76% yield.

In the present procedure, the 2-position oxidation of methylthio and the introduction of bromine could be completed in one step. The literature confirmed that aromatic sulfides are oxidized cleanly to sulfoxides in aqueous media when treated with *N*-bromosuccinimide (Harville and Reed 1968; Carpino and Williams 1974; Surendra et al. 2005). Hence, intermediate **8** converted to intermediate **10** with the transformation of two functional groups. This method not only avoided long reaction times and hazardous reagents, but also shortened the reaction steps and increased the yield of the intermediate **10**.

Attempts to the cross-coupling reaction between intermediate **10** and *tert*-butyl 4-(6-aminopyridin-3-yl) piperazine-1-carboxylate encountered a certain resistance. Initial attempt to the cross-coupling reaction was carried out in toluene at 110 °C. This method only achieved a yield of 26%. Considering the production of sulfinic acid at the end of the reaction, the base including Et_3N, K_2CO_3, K_3PO_4 was added to the reaction system. However, this operation did not improve the yield. And obtained intermediate **11** from intermediate **10** through reactions with *tert*-butyl 4-(6-aminopyridin-3-yl) piperazine-1-carboxylate was not successful, when K_2CO_3, K_3PO_4 as base. The further attempts to synthesize intermediate **11** used different polarity solvents including toluene, dimethyl carbonate, THF, dioxane and acetonitrile. We found that got a slightly better yield with dimethyl carbonate as solvents.

Conclusions

In summary, we demonstrated a facile route to synthesize Palbociclib starting from commercial 2-methylthio-4-ketopyrimidine (**20**). A practical chromatography-free method of post-processing to purify 4-chloro-2-(methylthio) pyrimidine (**21**), 6-bromo-8-cyclopentyl-5-methyl-2-(methylsulfinyl) pyrido[2,3-d] pyrimidin-7(8H) (**10**), tert-butyl 4-(6-((6-(1-butoxyvinyl)-8-cyclopentyl-5-methyl-

7-oxo-7,8-dihydropyrido[2,3-d] pyrimidin-2-yl) amino) pyridin-3-yl) piperazine-1-carboxylate (**17**) and 6-acetyl-8-cyclopentyl-5-methyl-2-((5-(piperazin-1-yl) pyridin-2-yl) amino) pyrido[2,3-d] pyrimidin-7(8H)-one (**Palbociclib**, **1**) was offered, which was suitable for large-scale manufacture. This strategy also developed a facile route for preparing 6-bromo-8-cyclopentyl-5-methyl-2-(methylsulfinyl) pyrido[2,3-d] pyrimidin-7(8H) (**10**). The advantages of this developed synthetic strategy included improved overall yield, inexpensive starting materials, readily controllable and cleaner reaction conditions. This procedure has potential for scale-up in production.

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