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NEW AND CONVERGENT SYNTHESIS OF AZD 4547

Lehao Bu, Han Wang,* Wenxin Chen, Lei Gao, Cong Sun, and Yongjun Mao

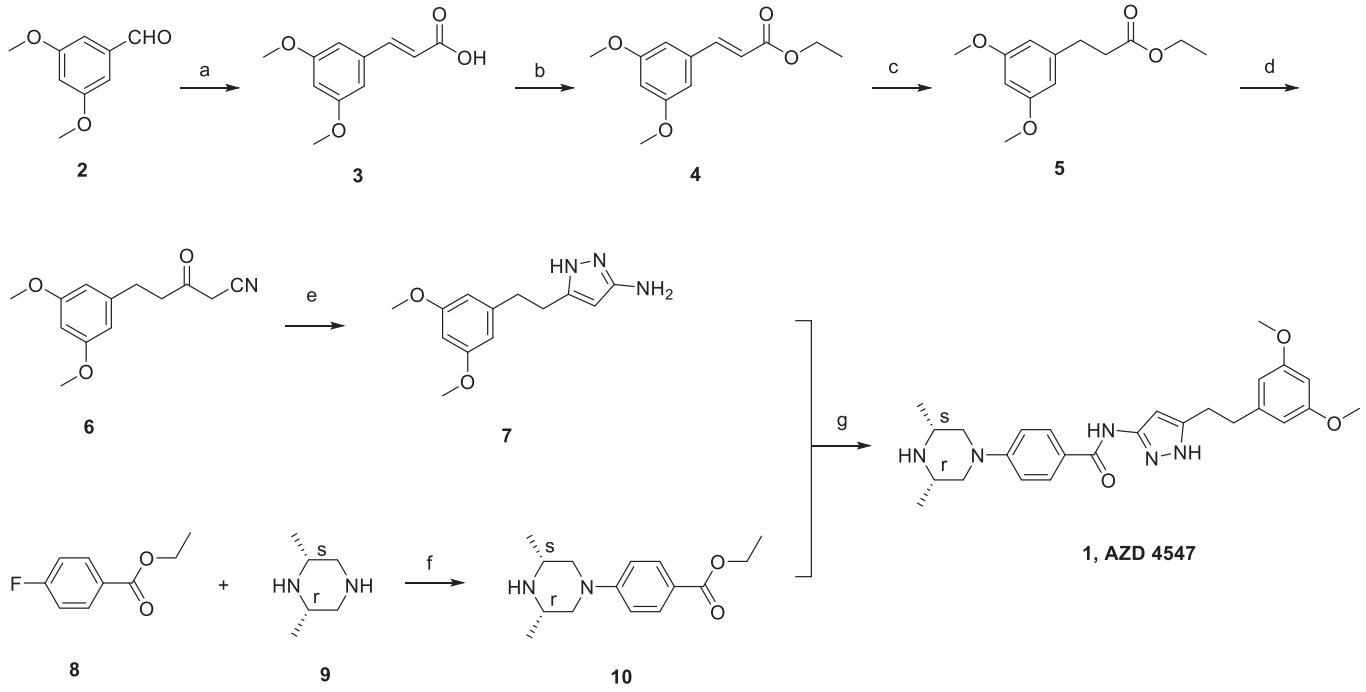
College of Chemistry and Chemical Engineering, Shanghai University of Engineering Science, Shanghai 201620, China. *Han Wang, Tel: +86 21 67791220. Fax: +86 21 67791214. E-mail: wanghan@sues.edu.cn

Abstract – A practical and convergent synthetic route of AZD 4547 was developed successfully. The intermediate 5-(3,5-dimethoxyphenylethyl)-1*H*-pyrazol-3-amine (**7**) was prepared from 3,5-dimethoxybenzaldehyde through 6 simple steps in 52.3% yield. Another intermediate 4-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzoic acid (**14**) was synthesized from ethyl 4-fluorobenzoate and (2*R*,6*S*)-2,6-dimethylpiperazine in 62% yield over 2 steps. Finally, AZD 4547 was obtained from **7** and **14** in 73% yield and 99.1% purity. Purification methods of the intermediates and the final product involved in the route were developed.

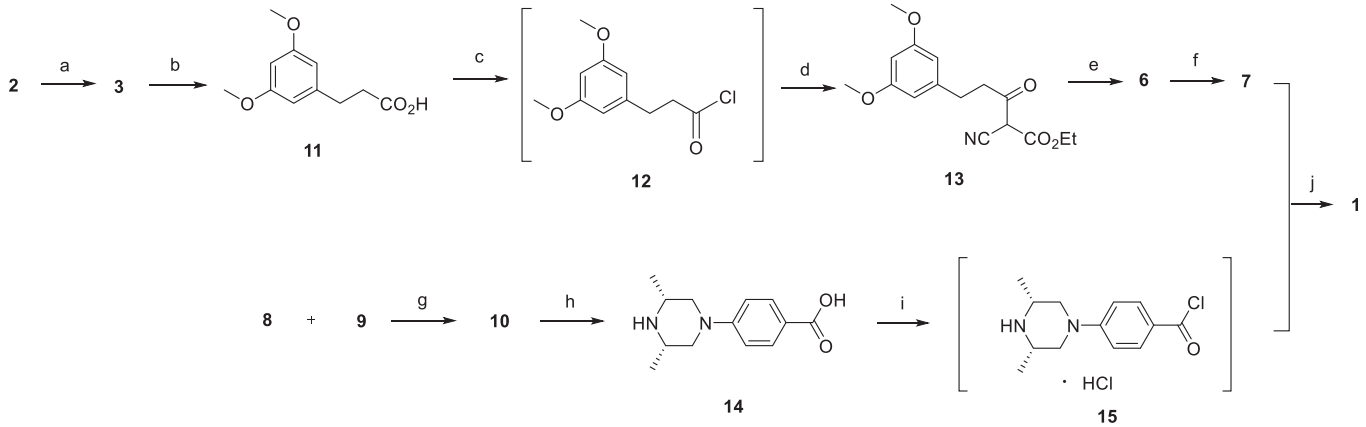
AZD 4547 (**1**, Scheme 1) is a selective FGFR (fibroblast growth factor receptor) inhibitor, which can be used for cure gastric cancer, esophageal cancer, breast cancer and non-small cell lung cancer (NSCLC) with high expression of FGFR.[1] It was developed by AstraZeneca and is currently in Phase II clinical research.[2]

The reported synthetic method for the preparation of AZD 4547 was shown in Scheme 1.[3–5] Using 3,5-dimethoxybenzaldehyde (**2**) as the starting material, 3-(3,5-dimethoxyphenyl)propionic acid ethyl ester (**5**) was synthesized by aldol condensation, esterification, hydrogenation reduction respectively, in 66% overall yield. Compound **5** was reacted with acetonitrile to form 5-(3,5-dimethoxyphenyl)3-oxo-pentanenitrile (**6**) in the presence of sodium hydride, which was cyclized with hydrazine hydrate to give 5-(3,5-dimethoxyphenylethyl)-1*H*-pyrazol-3-amine (**7**) in 42% yield over two steps. Ethyl 4-fluorobenzoate (**8**) reacted with (2*R*,6*S*)-2,6-dimethylpiperazine (**9**) to give ethyl 4-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzoate (**10**) in 72% isolated yield. At the last step, compound **7** reacted with **10** by catalytic reaction of trimethylaluminum to form AZD 4547 (**1**) in 50% yield. The total yield of the

final product **1** was only 10% over 7 steps (from **2**), and dangerous reagents, such as sodium hydride and trimethylaluminum were used, which was not suitable for scale-up.



Scheme 1. Reagents and conditions: (a) malonic acid, pyridine, piperidine, reflux, 3 h, 85%; (b) *p*-TsOH, EtOH, reflux, 12 h, 79%; (c) H_2, Pd/C, EtOAc, rt, 6 h, 99%; (d) NaH, MeCN, toluene, reflux, 18 h, 44%; (e) $NH_2NH_2 \cdot H_2O$, EtOH, reflux, 24 h, 95%; (f) DMSO, 120 °C, 20 h, 72%; (g) $AlMe_3$, toluene, 60 °C, 18 h, 50.2%.



Scheme 2. Reagents and conditions: (a) malonic acid, pyridine, piperidine, 100 °C, 1 h, 94.5%; (b) H_2, Pd/C, THF, 25 °C, 15 h, 95%; (c) $(COCl)_2$, DMF (cat.), CH_2Cl_2 , rt, 4 h; (d) $NCCH_2CO_2Et$, NaOEt, EtOH, 0 °C, 2 h, 72%; (e) DMSO-H_2O, 110 °C, 0.5 h, 81%; (f) $NH_2NH_2 \cdot H_2O$, EtOH, 80 °C, 20 h, 94%; (g) K_2CO_3, DMSO, 100 °C, 8 h, 81%; (h) NaOH, EtOH, 70 °C, 3 h, 76%; (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2, rt, 3 h; (j) TEA, DCM, −10~0 °C, 2 h, 73%.

In order to develop a practical method for preparing of AZD 4547 (**1**), a new, efficient and convergent synthetic route was developed successfully, as shown in Scheme 2. 3,5-Dimethoxybenzaldehyde (**2**) and malonic acid were used as the starting materials, gone through aldol condensation and hydrogenation reduction to give 3-(3,5-dimethoxyphenyl)propionic acid (**11**) in 94.5% isolated yield. **11** was chloridized by oxalyl chloride to obtain the acyl chloride **12**, which was directly reacted with ethyl cyanoacetate and sodium ethoxide to give the key intermediate ethyl 2-cyano-5-(3,5-dimethoxyphenyl)-3-oxopentanoate (**13**) in 72% isolated yield.[6] Compound **13** was heated in DMSO-H_2O solution to give 5-(3,5-dimethoxyphenyl)-3-oxopentanenitrile (**6**) in 81% isolated yield. Compound **6** was reacted with hydrazine hydrate to give 5-(3,5-dimethoxyphenylethyl)-1*H*-pyrazol-3-amine (**7**) in 94% isolated yield.

Ethyl 4-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzoate (**10**) was prepared using the reported method in 81% yield after modification,[3] which was hydrolyzed to give 4-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzoic acid (**14**) under basic conditions in 76% yield. Compound **14** was reacted with oxalyl chloride to give the acyl chloride hydrochloride **15**, which was directly condensed with compound **7** to give the final compound **1** in 73% isolated yield. Since there are reactive amino groups in compounds **7** and **15**, it could give over acylated by-products. The reaction condition should be controlled at low temperature (–5~0 ºC) and keep compound **7** excessive (compound **15** was added to **7** over 1 h), which will give a good reaction result.

In summary, an effective, practical, convergent synthetic route of AZD 4547 was developed successfully. Commercially available chemicals including 3,5-dimethoxybenzaldehyde, malonic acid, ethyl cyanoacetate, dimethyl sulfoxide were used as the staring materials. The intermediate 5-(3,5-dimethoxyphenylethyl)-1*H*-pyrazol-3-amine (**7**) was prepared from 3,5-dimethoxybenzaldehyde (**2**) through six simple steps in 52.3% yield. Another intermediate 4-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzoic acid (**14**) was synthesized from ethyl 4-fluorobenzoate (**8**) and (2*R*,6*S*)-2,6-dimethyl-piperazine (**9**) in 62% yield over 2 steps. Finally, AZD 4547 was obtained from **7** and **14** in 73% yield and 99.1% purity. 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.

3-(3,5-Dimethoxyphenyl)acrylic acid (3). 3,5-Dimethoxybenzaldehyde (50.0 g, 0.3 mol) was added to a stirred suspension of malonic acid（38.0 g, 0.36 mol）and piperidine (15.0 mL) in pyridine (150.0 mL). The mixture was stirred at 100 ºC for 1 h. After cooled to room temperature, the reaction mixture was added to chilled water (300 mL), stirred and acidified to pH 2–3 with HCl, the resulting solid was collected by suction filtration, washed with H_2O (100 mL × 2), dried at 40 ºC for 6 h to afford **3** (59.2 g, 94.5%) as a white solid; mp 173.2−174.5 ºC (Lit.[7] 174 ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (s, 1H), 7.52 (d, J = 16.0 Hz, 1H), 6.87 (d, J = 2.2 Hz, 2H), 6.61–6.50 (m, 2H), 3.78 (s, 6H). MS (ESI): m/z = 211.1 $[M+H]^+$.

3-(3,5-Dimethoxyphenyl)propionic acid (11). A suspension of compound **3** (30.0 g, 0.144 mol) and Pd-C (5% wet, 1.5 g) in THF (180 mL) was stirred under hydrogen atmosphere at room temperature for 15 h. The reaction mixture was then filtered through a celite pad, the filter cake was washed by THF (40 mL × 2). The combined filtrate was concentrated under vaccum, the resulting solid was collected, dried at 45 ºC for 4 h to give **11** (28.8 g, 95%) as an off-white solid; mp 59.6−60.8 ºC (Lit.[8] 59−61 ºC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (brs, 1H), 6.40–6.39 (m, 2H), 6.32–6.30 (m, 1H), 3.71 (s, 6H), 2.75 (t, J = 7.6 Hz, 2H), 2.51 (t, J = 7.6 Hz, 2H). MS (ESI): m/z = 211.1 $[M+H]^+$.

Ethyl 2-cyano-5-(3,5-dimethoxyphenyl)-3-oxopentanoate (13). $(COCl)_2$ (14.5 g, 0.114 mol) and DMF (0.55 g, 7.5 mmol) were added respectively to a mixture of **11** (20.0 g, 95.1 mmol) in CH_2Cl_2 (100 mL) at 5–10 ºC, and the mixture was stirred at room temperature for 4 h to form a homogeneous solution. The solvent was removed under vaccum to give 3-(3,5-dimethoxyphenyl)propionyl chloride (**12**) as a light-yellow liquid.

A suspension of NaOEt (12.9 g, 0.19 mol) in anhydrous EtOH (150 mL) was stirred at 40–50 ºC for 1 h to get a solution, then $NCCH_2CO_2Et$ (16.2 g, 0.143 mol) was added to the solution. The resulting white suspension was heated to reflux for another 0.5 h and then cooled to –5~0 ºC and treated dropwise with **12** (95.1 mmol) in THF (150 mL) over 2 h, keeping the reaction temperature below 0 ºC. The reaction mixture was then added to chilled water (600 mL), stirred and acidified to pH 2–3 with HCl. The resulting solid was collected by suction filtration, washed with H_2O (30 mL × 2), dried at 30 ºC for 8 h to give a light yellow solid, which was recrystallized from 90% MeOH-H_2O (50 mL) to give **13** (11.5 g, 72.0%) as an off-white solid; mp 46.0−48.3 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.74 (s, 1H), 6.40–6.39

(m, 2H), 6.36–6.35 (m, 1H), 4.35 (q, J = 8.0 Hz, 2H), 3.80 (s, 6H), 2.96 (s, 4H), 1.38 (t, J = 8.0 Hz, 3H). MS (ESI): m/z = 306.1 $[M+H]^+$.

5-(3,5-Dimethoxyphenyl)-3-oxopentanenitrile (6). A mixture of **13** (8.04 g, 0.26 mol), DMSO (40 mL) and H_2O (0.8 mL) was heated at 100–110 ºC for 0.5 h. Then the brown solution was cooled to around 50 ºC, poured into chilled water (80 mL), and stirred for 1 h. The resulting precipitate was collected by suction filtration, washed with H_2O (15 mL × 2), dried at 40 ºC for 4 h to give **6** (4.98 g, 81%) as yellow solid; mp 65.1−67.2 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 3H), 3.82 (s, 6H), 3.43 (s, 2H), 2.99–2.90 (m, 4H). MS (ESI): m/z = 234.1 $[M+H]^+$, 256.1 $[M+Na]^+$.

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: 30 min; Mobile phase: MeOH/water = 80/20, t_R: 10.18 min, purity: 98.5%.

5-(3,5-Dimethoxyphenylethyl)-1*H*-pyrazol-3-amine (7). Compound **6** (2.78 g, 11.9 mmol) was added to a stirred suspension of EtOH (25 mL) and hydrazine hydrate (0.89 g, 17.8 mmol) at 80 ºC. The resulting solution was stirred for 20 h. The reaction mixture was then cooled to room temperature and added to chilled water (60 mL), and stirred for 1 h. The resulting solid was collected by suction filtration, dried at 40 ºC for 6 h to give **7** (2.79 g, 94%) as a light yellow solid; mp 143.3−144.7 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (brs, 1H), 6.39–6.38 (m, 2H), 6.32–6.30 (m, 1H), 5.20 (s, 1H), 4.43 (brs, 2H), 3.71 (s, 6H), 2.82–2.63 (m, 4H). MS (ESI): m/z = 248.1 $[M+H]^+$.

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: 30 min; Mobile phase: MeOH/water = 80/20, t_R: 5.29 min, purity: 98.8%.

Ethyl 4-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzoate (10). A mixture of ethyl 4-fluorobenzoate (**8**) (10.0 g, 60 mmol), (2*R*,6*S*)-2,6-dimethylpiperazine (**9**) (7.8 g, 68 mmol) and K_2CO_3 (8.3 g, 60 mmol) in DMSO (70 mL) was stirred at 100 ºC for 8 h. After cooled to room temperature, the reaction mixture was added to chilled water (200 mL), and stirred for 1 h. The resulting solid was collected by suction filtration, dried at 45 ºC for 6 h to afford **10** (12.8 g, 81%) as an off-white solid; mp 183.0−184.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 4.30 (q, J = 8.0 Hz, 2H), 3.64–3.61 (m, 2H), 2.96–2.93 (m, 2H), 2.38–2.32 (m, 2H), 1.63 (brs, 1H), 1.34 (t, J = 8.0 Hz, 3H), 1.21 (d, J = 6.4 Hz, 6H). MS (ESI): m/z = 263.2 $[M+H]^+$.

4-((3*S*,5*R*)-3,5-Dimethylpiperazin-1-yl)benzoic acid (14). Compound **10** (11.2 g, 43.0 mmol) was added to a stirred suspension of NaOH (1.90 g, 47.2 mmol) and EtOH (35 mL). The reaction mixture was stirred at 70 ºC for 3 h. After cooled to room temperature, the reaction solution was then added to chilled water (90 mL), stirred and acidified to pH 6–7 with HCl, the resulting solid was collected by suction filtration, dried at 45 ºC for 3 h to afford **14** (7.7 g, 76%) as an off-white solid; mp 202.1−204.0 ºC. ^{1}H NMR (400 MHz, D_2O) δ 7.78 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 2H), 3.89–3.85 (m, 2H), 3.41–3.40 (m, 2H), 2.77–2.71 (m, 2H), 1.30 (d, J = 8.0 Hz, 6H). MS (ESI): *m/z* = $[M+H]^+$.

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: 25 min; Mobile phase: MeOH/water = 80/20, t_R: 2.49 min, purity: 97.2%.

AZD 4547 (1). $(COCl)_2$ (3.6 g, 28.3 mol) and DMF (0.1 g, 1.9 mmol) were added respectively to a mixture of **14** (4.5 g, 19.1 mmol) in CH_2Cl_2 (50 mL) at room temperature and the mixture was stirred for 4 h to form a homogeneous solution. The solvent was removed to give 4-((3*S*,5*R*)-3,5-dimethylpiperazin-1-yl)benzoyl chloride hydrochloride (**15**).

Compound **7** (4.82 g, 19.0 mmol) was added to a stirred solution of TEA (2.2 g, 21.4 mmol) and DCM (40 mL) at –5~0 ºC and stirred for 30 min. A solution of **15** (19.1 mmol) in DCM (30 mL) was added to this solution over 1 h, keeping the reaction temperature below 0 ºC. The reaction mixture was stirred at 0~5 ºC for another 1 h and then added to chilled water (60 mL). The organic layer was separated, washed with water (30 mL × 2). The solvent was removed and give a light-yellow solid. The crude product was recrystallized from 95% EtOH-H_2O (40 mL), dried at 45 ºC for 4 h to afford **1** (6.4 g, 73%) as a white solid; mp 191.4−194.0 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (brs,1H), 10.42 (s,1H), 7.94 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.42 (m, 3H), 6.32 (m, 1H), 4.03–3.99 (m, 2H), 3.72 (s, 6H), 3.28 (m, 2H), 2.87 (s, 4H), 2.79–2.73 (m, 2H), 1.31 (s, 6H). MS (ESI): *m/z* = 464.3 $[M+H]^+$. HRMS (ESI) calcd for: $C_{26}H_{33}N_5O_3$ $[M + H]^+$ 464.2662, Found: 464.2651.

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: 15 min; Mobile phase: MeOH/water = 80/20, t_R: 3.53 min, purity: 99.1%.

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