# A novel and efficient synthesis of anti-cancer agent, mereletinib

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A convenient route for the synthesis of a third-generation epidermal growth factor receptor inhibitor, mereletinib (AZD9291) using starting materials that are commercially available has been achieved through reactions that are readily conducted under mild conditions. Importantly, a 5 g scale synthesis was also accomplished and this method could therefore be useful in the synthesis of similar drugs.

**Keywords:** irreversible inhibitor, non-small-cell lung cancer, AZD9291, epidermal growth factor receptor, mereletinib, 3-(pyrimidin-4-yl)indole

In the clinic, patients suffering from non-small-cell lung cancer (NSCLC) with activating mutations have been treated with epidermal growth factor receptor (EGFR) inhibitors for many years.[1-6] As reversible small-molecule ATP analogues,[7-10] the first-generation gefitinib and the second-generation erlotinib (Fig. 1) were originally designed to inhibit the tyrosine kinase (TK) activity of wild-type EGFR. Both of these TK inhibitors (TKI) were found to be most effective in patients with advanced NSCLC during their clinical development. However, both are associated with side effects such as skin rash and diarrhoea that are due to the inhibition of wild-type EGFR in skin and gastrointestinal organs. Mereletinib (AZD9291) (Fig. 1) is a novel oral, potent and selective third-generation irreversible inhibitor of both EGFR-sensitising (EGFRm+) and T790M-resistance mutations with selectivity over the wild type form of the receptor.[11-13] This mono-anilino–pyrimidine compound is structurally distinct from other third-generation EGFR TKIs and offers a pharmacologically differentiated profile from those of an earlier generation. As a result FDA granted AZD9291 Breakthrough Therapy Designation last year.

The synthesis of mereletinib has been a challenging and costly task due to the high temperature and inefficient, impractical synthetic routes. There are two synthetic methods documented for the synthesis of AZD9291. The first one uses acryloyl chloride as the acrylating reagent and gave a low yield (32%).[11] The second requires a very high temperature and the reduction of a nitro group by Fe/ammonium chloride which is environmentally hazardous, and moreover is an inefficient process.[14]

We now describe the development of a novel, highly efficient method for the preparation of AZD9291 **1** starting from readily available starting materials.

## Results and discussion

Our plan for the synthesis of **1** is shown in Scheme 1. Retrosynthetically, **1** can be broken into two fragments, 3-(2-chloro-pyrimidin-4-yl)-1-methyl-1*H*-indole **2** and the trisubstituted *N*-aryl-acrylamide **3**. We synthesised fragment **2** by the reported method,[11,14] so the focus was on establishing an efficient method to prepare the trisubstituted *N*-aryl-acrylamide **3**. Our synthesis of **3** began with reduction of the nitro group of the commercially available 4-fluoro-2-methoxy-1-nitro-benzene **4** to yield an amine, nitration of which gave **5** in 93% yield (Scheme 2). We found that N1,N1,N2-trimethylethane-1,2-diamine failed to react with the amine **5** under the reported reaction conditions.[11] As is well known electron-donating substituents decrease the reactivity of nucleophilic aromatic substitution.[15-17] Since the Boc-protected amino group is a moderate to weak electron-donating group compared with the amino group, the amine **5** was Boc-protected with di-*t*-butyl pyrocarbonate to give **6** in 98% yield. Gratifyingly, the reaction of **6** with N1,N1,N2-trimethylethane-1,2-diamine under mild conditions displaced the fluoro group to give **7** in quantitative yield. Catalytic reduction of the intermediate **7** with hydrogen over Pd/C gave a quantitative yield of the corresponding amine, a light yellow compound, acylation of which with acryloyl chloride gave the corresponding intermediate **8** in

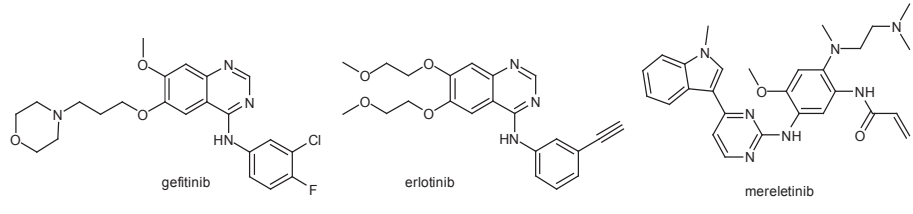
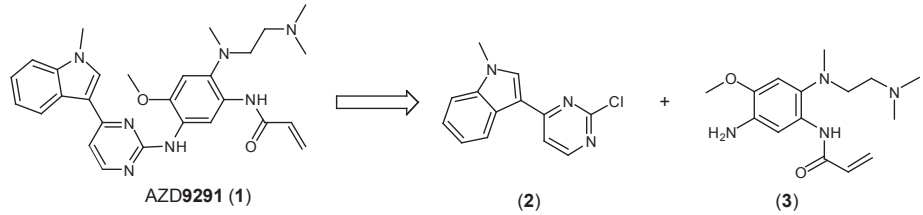



**Fig 1.**




**Scheme 1**

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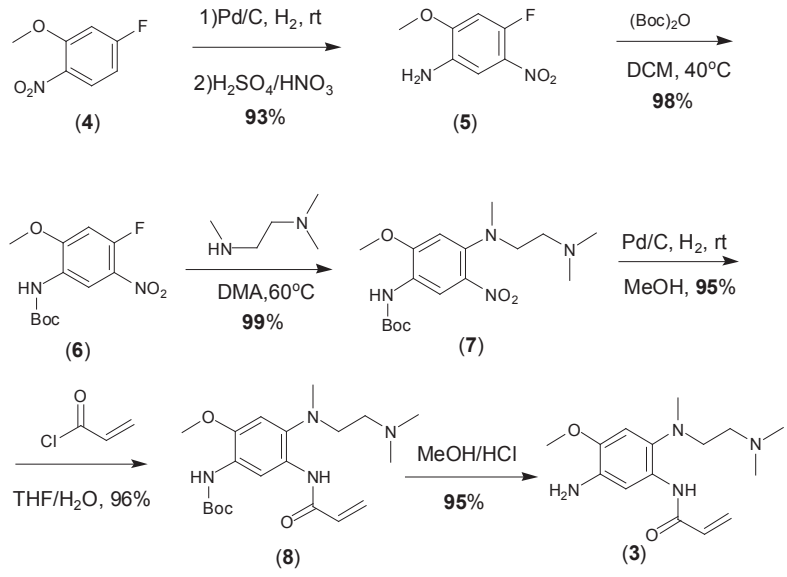


**Scheme 2**

excellent yield. The Boc-protected 5-amino group of **8** resisted a Michael reaction due to its decreased nucleophilicity, and so de-protection of the Boc-group of **8** with 2N HCl/MeOH gave the desired salt of target compound **3** in 95% yield. In a final step, the indolyl-2-pyrazoyl chloride **2** reacted with the trisubstituted *N*-aryl-acrylamide **3** in butanol in the presence of 4-methylbenzenesulfonic acid under very mild conditions (40°C/2.5 h) and, conveniently, cooling the reaction mixture to 0 °C produced crystalline **3** (AZD9291) in 92% yield.

To further evaluate the synthetic potential of this protocol, gram-scale reactions were performed under the optimized reaction conditions. Gratifyingly, the reactions proceeded smoothly to give the corresponding products in 90% isolated yields. Because AZD9291 is a solid, it was isolated in high yield without chromatography. The overall yield was 75% from 3-(2-chloropyrimidin-4-yl)-1*H*-indole. Finally, there was good agreement between the $^1$H NMR spectra at 400 MHz of AZD9291 in $CDCl_3$ and previously reported spectral data.[11,14]

## Experimental

All reagents including analytical-grade solvents were purchased from Sigma–Aldrich (USA), Aladdin (China), or Sinopharm Chemical Reagent (China) and used without further purification. Melting points are uncorrected. NMR spectra were obtained on a Bruker 400 MHz spectrometer ($^1$H NMR at 400 Hz, $^{13}$C NMR at 100 Hz) in $CDCl_3$ or DMSO-$d_6$ using TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. Mass spectra (MS) were obtained from Finnigan (USA) MAT-95 Spectrometry Services. The synthesised compounds were obtained as detailed below. Silica gel (200–300 μm) for flash chromatography was purchased from Qingdao Haiyang Chemical (China).

*Synthesis of 3-(2-Chloropyrimidin-4-yl)-1-methylindole (**2**)*

This compound was prepared by the procedure of Finlay *et al.*[11] A suspension of 2,4-dichloropyrimidine (5.0 g, 33.6 mmol) and aluminum chloride (1.83 mL, 33.6 mmol) in DME (1,2-dimethoxyethane) (50 mL) was stirred at ambient temperature for 15 min. To this was added 1-methylindole (4.29 mL, 33.6 mmol), and the mixture was heated at 80 °C for 2–4 h. The cooled reaction mixture was added dropwise to vigorously stirring water (300 mL) over 20 min. Upon complete addition, the mixture was stirred for 30 min, filtered and the solid washed with water (250 mL). The crude product was purified by flash silica chromatography, eluting with DCM. Pure fractions were evaporated to dryness to afford 3-(2-chloropyrimidin-4-yl)-1-methylindole (5.08 g, 62%) as a white solid. m.p. 201°C dec. (acetonitrile/water);$^1$H NMR ($CDCl_3$) δ 8.45 (m, 2H), 8.35 (m, 1H), 7.37–7.95 (m, 4H), 3.89 (s, 3H); MS calcd for $C_{13}H_{10}ClN_3$ $[M]^+$ 243.1; found: 244.1

*4-Fluoro-2-methoxy-5-nitro-phenylamine* (**5**): 4-Fluoro-2-methoxy-aniline (12.0g, 85.0 mmol) was added to cooled concentrated $H_2SO_4$ (80 mL).[14] The mixture was stirred at 0–10°C for 15–30 min. $KNO_3$ (8.6g, 85.0 mmol) was added to the mixture. The resulting mixture was stirred at 0–5°C for 1–2 h and then poured into ice/water. The mixture was neutralised with concentrated $NH_4OH$. The resulting solid was filtered off and dried under vacuum. A suspension of crude product and Pd/C (0.35g, 0.3%) in methanol (200 mL) was stirred under one atm hydrogen at room temperature for 2–3 h. Filtration of the Pd/C was effected through celite and the solid cake washed with methanol. The combined solvents were evaporated under reduced pressure. The corresponding amine was used in the next step without further purification.

*(4-Fluoro-2-methoxy-5-nitro-phenyl)-carbamic acid t-butyl ester* (**6**): A solution of 4-fluoro-2-methoxy-5-nitroaniline (8.0g, 43.0 mmol) in DCM (dichloromethane) (100 mL) was cooled to 0–5°C in an ice/water bath. $Boc_2O$ (9.4g, 43.0 mmol) in DCM (30 mL) was added to the mixture slowly. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated to dryness under reduced pressure. The crude product was purified by flash silica chromatography, with gradient 10–40% EtOAc in hexane to yield intermediate (**6**) (12.0 g, 42.1 mmol, 98%) as a yellow solid. m.p. 88–90 °C (EtOAc /hexane); $^1$H NMR ($CDCl_3$) δ 8.91 (br, 1H), 6.99 (s, 1H), 6.72 (d, *J*=12.0, 1H), 4.0 (s, 3H), 1.567 (s, 9H); $^{13}$C NMR ($CDCl_3$) δ 153.5, 152.6, 152.5,152.2, 150.9, 124.7, 124.7, 114.7, 100.0, 99.7, 56.8, 28.3, 7.9; IR 3432, 2985, 1723, 1536, 1485, 1158. MS calcd for $C_{12}H_{15}FN_2O_5$ $[M-H]^-$ 285.0887; found: 285.0865

*{4-[(2-Dimethylamino-ethyl)-methyl-amino]-2-methoxy-5-nitro-phenyl}-carbamic acid t-butyl ester* (**7**): N1,N1,N2-Trimethylethane-1,2-diamine (2.7 g, 27.0 mmol) was added to a solution of (4-fluoro-2-methoxy-5-nitro-phenyl)-carbamic acid *t*-butyl ester (6.3g, 22.0 mmol) and DIPEA (*N,N*-Diisopropylethylamine) (3.82 mL, 22.0 mmol) in DMA (*N,N*-Dimethylacetamide) (100 mL). The mixture was heated to 60 °C and stirred at this temperature for 2h. Water (200 mL) was added to the reaction mixture, which was then extracted with DCM (50 mL*3). The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to give **7** as an orange solid (7.9 g, 97%); m.p. 92–94 °C (DCM). $^1$H NMR (DMSO) δ 8.12 (m, 2H), 6.74 (s, 1H), 3.90 (s, 3H), 3.21 (m, 2H), 2.81 (s, 3H), 2.44 (m, 2H), 2.14 (s, 6H), 1.45 (s, 9H); $^{13}$C NMR (DMSO) δ 153.5, 144.9, 132.1, 120.0, 102.4, 79.8, 56.8, 56.7, 53.1, 45.9, 40.8, 40.6,

40.4, 28.5, 27.9; IR 3441, 2979, 2359, 1708, 1546, 1162; MS calcd for $C_{17}H_{28}N_4O_5$ $[M+H]^+$ 369.2132; found: 369.2136. The crude product was used in the next step without further purification.

*N-{5-Amino-2-[(2-dimethylamino-ethyl)-methyl-amino]-4-methoxy-phenyl}-acrylamide* (**3**): Acryloyl chloride (20 mL, 1M in THF, 20.0 mmol) was added dropwise to intermediate **7** (7.3 g, 19.8 mmol) and DIPEA (3.82 mL, 22.0 mmol) in THF (100 mL) cooled to 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was extracted with DCM (100 mL*2) and the organic extract was washed sequentially with saturated $NaHCO_3$ (50 mL), water (50 mL), and saturated brine (50 mL). The organic layer was evaporated to afford the crude product which was purified by flash silica chromatography, through the gradient elution 0–10% MeOH in DCM to yield {5-acryloylamino-4-[(2-dimethylamino-ethyl)-methyl-amino]-2-methoxy-phenyl}-carbamic acid *t*-butyl ester as a brown oil. This was dissolved in cooled 3N/MeOH (100mL), and the mixture stirred at room temperature for 20 h. The solvent was removed and the residue neutralised with saturated $NaHCO_3$ aqueous, and then extracted with DCM. The crude product was purified by flash silica chromatography, with gradient elution 0–10% MeOH in DCM to yield the intermediate **3** (5.04g, 87%) as a brown oil. $^1$H NMR ($CDCl_3$); δ 10.03 (br, 1H), 7.99 (s, 1H), 6.69 (s, 1H), 6.39 (m, 2H), 5.68 (m, 1H), 3.83 (s, 3H), 3.78 (br, 2H), 2.89 (m, 2H), 2.67(s, 6H), 2.30(m, 2H); $^{13}$C NMR ($CDCl_3$); δ 163.3, 143.6, 133. 9, 132.4, 132.3, 129.9, 125.9, 107.1, 105.2, 57.2, 55.8, 45.15, 44.2; IR 3452, 3342, 2935, 2823, 1670, 1526, 1207; MS calcd for $C_{15}H_{24}N_4O_2$ $[M+H]^+$ 293.1972; found: 293.1973.

*N-[2-(2-Dimethylaminoethylmethylamino)-4-methoxy-5-[[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino]phenyl]prop-2-enamide*. (AZD**9291**): 4-Methylbenzenesulfonic acid hydrate (6.5 g, 34.2 mmol) was added in one portion to 3-(2-chloropyrimidin-4-yl)-1-methylindole **2** (4.2 g, 17.1 mmol) and intermediate **3** (5.0 g, 17.1 mmol) in n-butanol (80 mL). The resulting mixture was stirred at 40 °C for 2.5 h. The mixture was cooled to 0–5°C and stirred at this temperature for 1–2h. The precipitate was collected by filtration, washed with *n*-butanol (20 mL), and dried under vacuum to afford AZD9291 as a yellow solid. The yellow solid was triturated with MeCN to give a solid which was collected by filtration and dried under vacuum to give AZD9291 (7.8 g,15.7 mmol, 92%) as a yellow solid. $^1$H NMR ($CDCl_3$) δ 10.19 (br, 1H), 9.88 (s, 1H), 9.13(s, 1H), 8.40(d, 1H), 8.08(t, 1H), 7.75(s, 1H), 7.42 (t, 1H), 7.27 (m, 1H), 6.81 (s, 1H), 6.47 (m, 1H), 5.73 (m, 2H), 4.02(s, 3H), 3.91(s, 3H) , 2.92(m, 2H) , 2.73(s, 3H) , 2.31(s, 8H); MS calcd for $C_{28}H_{33}N_7O_2$ $[M+H]^+$ 499.27; found: 500.3

We are grateful for financial support from the National Basic Research Program of China (No. 2011CB933503 and No.2013AA032205).

*Received 16 April 2015; accepted 14 May 2015*
*Paper 1503316 doi: 10.3184/174751915X14320297505570*
*Published online: 4 June 2015*

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