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New Synthetic Route to Tucatinib

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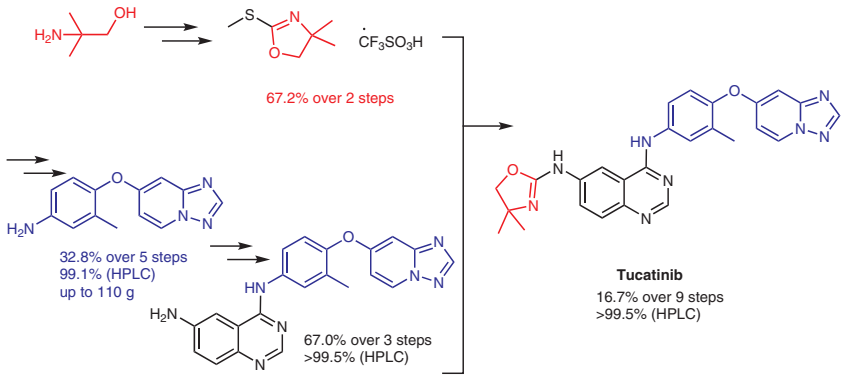

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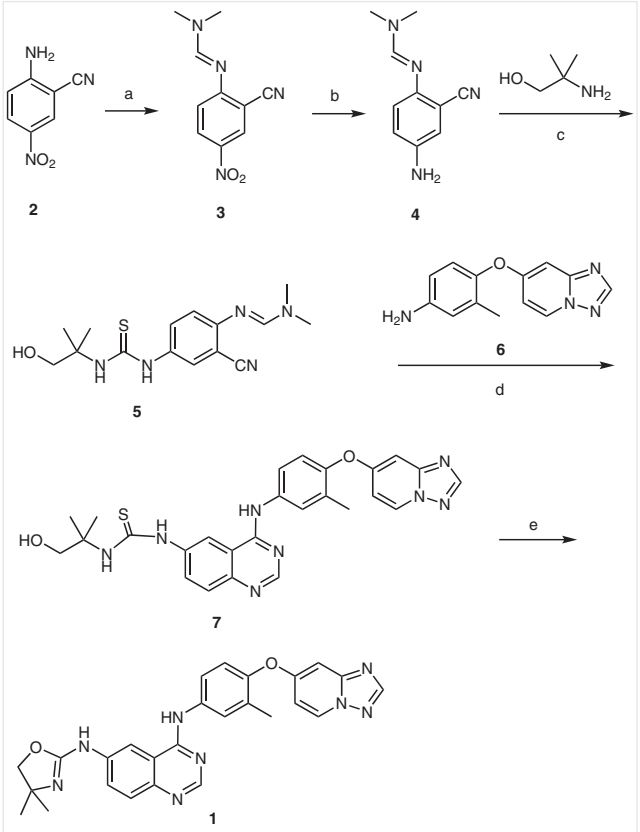
Abstract A new and improved synthetic route to tucatinib is described that involves three key intermediates. The first of these, 4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylaniline, was prepared on a 100 g scale in 33% yield over five steps and 99% purity. Next, N^4-(4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)quinazoline-4,6-diamine was isolated in 67% yield over three steps and >99% purity. Then, 4,4-dimethyl-2-(methylthio)-4,5-dihydrooxazoletrifluoromethanesulfonate was prepared under mild conditions in 67% yield over two steps. Finally, tucatinib was obtained in 17% yield over nine steps and in >99% purity (HPLC). Purification methods used to isolate the product and the intermediates involved in the route are also reported.

Key Words tucatinib, irbinitinib, new route, synthetic process

Tucatinib (**1**; Scheme 1), which is also named irbinitinib, ARRY-380 or ONT-380, is an orally administered inhibitor of human epidermal growth factor receptor tyrosine kinase ErbB-2 (also called HER2) with potential antineoplastic activity.[1] It was developed by Array BioPharma Inc. and is now in Phase II clinical study for the treatment of HER2$^+$ breast cancers.[2]

The reported synthetic routes to **1** were developed by Array BioPharma Inc.[3] on a milligram scale, as shown in Scheme 1. 2-Amino-5-nitrobenzonitrile (**2**) and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) reacted to give *N*′-(2-cyano-4-nitrophenyl)-*N*,*N*-dimethylformamidine (**3**) in 87% isolated yield. The aniline compound **4** was obtained in good yield through catalytic hydrogenation of **3**. Upon treatment with 2-amino-2-methyl-1-propanol and 1,1′-(thiocarbonyl)-diimidazole (TCDI) at –10 °C for 16 hours, the thiourea compound **5** was obtained in 34% yield, which was purified by column chromatography, and then cyclized with 4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylaniline (**6**) to give the 4-phenylaminequinazolin compound **7** in 60% yield. Finally, **7** was treated with NaOH and *p*-TsCl at room temperature to give tucatinib on a milligram scale (no yield data reported) after purification by column chromatography. This route is suitable for medicinal

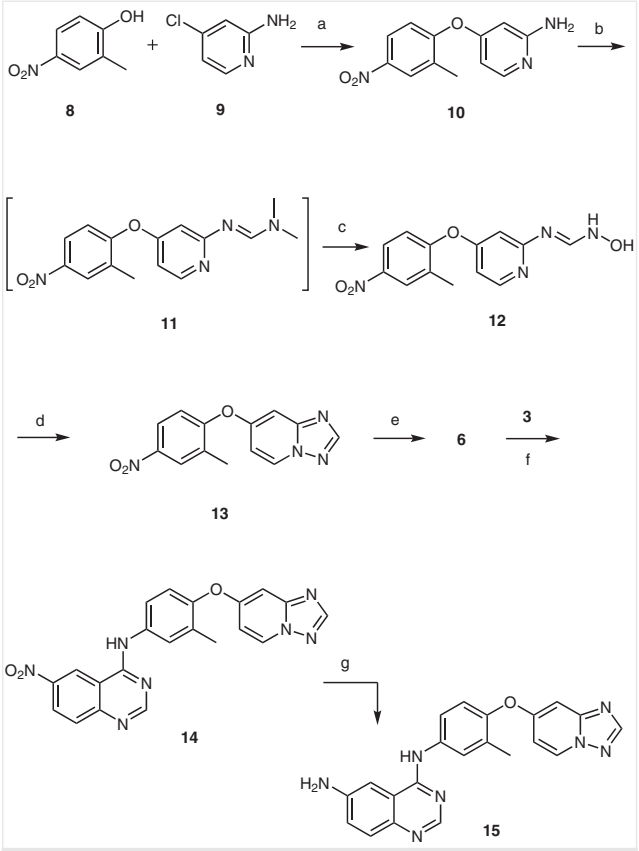


Scheme 1 *Reagents and conditions*: (a) DMF-DMA, 100 °C, 2 h, 87%; (b) H_2, 10% Pd/C, cyclohexene, MeOH, 10 h, 90%; (c) TCDI, THF, –10 °C, 16 h, 34%; (d) AcOH, *i*PrOAc, r.t., 16 h, 62%; (e) NaOH, *p*-TsCl, THF, r.t., 3 h.

chemistry research but is not fit for scale-up preparation of tucatinib.

To develop a practical process for preparing tucatinib, a new, convergent synthetic route was designed, as shown in Scheme 2 and Scheme 3. Three key intermediates were prepared: compound **6**, the quinazoline-4,6-diamine compound **15**, and the methylthio-4,5-dihydrooxazole compound **17**.

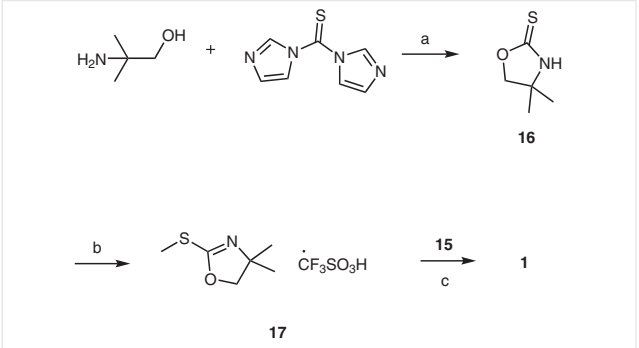
With regard to compound **6**, to date there is no reported synthetic method available. This intermediate was prepared on a 100 gram scale in high purity, based on the reported synthesis of the nitrobenzene compound **13** after optimization.[3,4] 2-Methyl-4-nitrophenol (**8**) and 4-chloropyridin-2-amine (**9**) were used as starting materials to give 4-(2-methyl-4-nitrophenoxy)pyridine-2-amine (**10**) in 64% isolated yield, which was relatively low for a process route (Scheme 2). We think the yield was reduced during the work-up preparation when using active charcoal and when THF was used for recrystallization. We did not identify any clear impurities by TLC or HPLC analysis. Certainly, this step should be optimized in the future; however, since the synthesis of compound **10** is not the key step in the synthesis of tucatinib, we have not yet optimized the conditions to increase the isolated yield of this step. Compound **10** was reacted with DMF-DMA and hydroxylamine hydrochloride in EtOH to obtain the *N*-hydroxyformimidamide compound **12** in 81% yield. The latter was treated with trifluoroacetic acid anhydride (TFAA) to give triazolo[1,5-*a*]pyridine **13** in around 70% yield. Compound **6** was obtained in 93% yield and 99.1% purity, through a catalytic hydrogenation reaction of **13**.



Scheme 2 *Reagents and conditions*: (a) NMP, DIPEA, 150 °C, 48 h, 64%; (b) (i) EtOH, DMF-DMA, 75 °C, 3 h; (ii) $NH_2OH{\cdot}HCl$, 50 °C, 3 h, 81%; (d) THF, TFAA, 20–25 °C, 68%; (e) H_2, Pd/C, THF, 40 °C, 15 h, 93%; (f) AcOH, 85 °C, 2 h, 83%; (g) H_2, Pd/C, r.t., 5 h, 92%.

2-Amino-5-nitrobenzonitrile (**2**) was reacted with DMF-DMA to give compound **3** in 88% isolated yield based on the reported method.[3] The subsequent ring-forming reaction was carried out by treating **6** and **3** in acetic acid solution to give **14** in 83% yield and 99% purity (Scheme 2). Compound **15** was obtained in 92% yield and 99.5% purity, through catalytic hydrogenation of **14** under H_2, Pd/C, THF at room temperature. During the catalytic hydrogenation reaction of compound **13** to **6** and **14** to **15**, a hydrogen gas balloon was used to conduct the reaction. No over-reduced impurities have yet been found, presumably because the hydrogen pressure was relatively low.

The methylthio-4,5-dihydrooxazole compound **17** was prepared based one the reported method after optimization.[5,6] 2-Amino-2-methyl-1-propanol and 1,1′-(thiocarbonyl)-diimidazole (TCDI) was cyclized in CH_2Cl_2 to give 4,4-dimethyloxazolidine-2-thione (**16**) in 83% isolated yield, which was then reacted with methyl trifluoromethanesulfonate to give compound **17** in 81% isolated yield (Scheme 3). Compound **16** is relatively stable and it can be stored at 4 °C for a couple of weeks, whereas compound **17** was used immediately in the next step after it was produced. We found that compound **17** decomposed after one week at room temperature, but it can be stored at –18 °C for two weeks under argon without deterioration.



Scheme 3 *Reagents and conditions*: (a) CH_2Cl_2, r.t., 17 h, 83%; (b) $CF_3SO_2OCH_3$, r.t., 15 h, 81%; (c) DMF, Cs_2CO_3, 125 °C, 20 h, 76%.

Finally, compounds **17** and **15** were coupled in Cs_2CO_3/DMF solution at 125 °C for 20 hours to give the final compound **1**, in 76% yield and >99% purity after recrystallization (Scheme 3). Methyl mercaptan can be generated during the preparation of compound **1** from **15** and **17**. To

date, we have carried out the reaction in a simple fuming hood and have not developed exhaust gas absorption methods. The final product was purified by recrystallization and no strong odor was retained in the final product.

In summary, a new and practical synthetic route to tucatinib (**1**) has been developed. Firstly, the 4-([1,2,4]triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylaniline (**6**) was prepared on a 100 gram scale in 33% yield over five steps, and with 99% purity. Secondly, the triazolo[1,5-*a*]pyridine compound **15** was prepared from **6** in 67% yield over three steps, and with >99% purity. Thirdly, the methylthio-4,5-dihydrooxazole trifluoromethanesulfonate compound **17** was prepared under mild conditions in 67% yield over two steps. Finally, **1** was obtained by reaction of **15** and **17** in 76% yield and >99% purity. Purification methods for the product and the intermediates involved in the route were also described.

All commercially available materials and solvents were used as received without further purification. The equipment was used directly after drying in an air-dry oven. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained with a Finnigan MAT-95/711 spectrometer. Melting points were measured with a Shenguang WRS-1B melting point apparatus and are uncorrected. Generally, TLC was used to monitor the progress of the reactions in the experiments. HPLC data were acquired with a Waters 2487 UV/Vis Detector and Waters 515 Binary HPLC Pump. The purities of the compounds were based on the peak areas in the HPLC UV traces.

4-(2-Methyl-4-nitrophenoxy)pyridin-2-amine (10)

To a 10 L reactor was added *N*-methyl pyrrolidone (NMP) (2 kg), diisopropylethylamine (DIPEA) (670 g, 5.2 mol), 2-methyl-4-nitrophenol (**8**) (400 g, 2.6 mol) and 4-chloro-2-aminopyridine (**9**) (340 g, 2.6 mol), and the resulting solution was stirred at 150 °C for 48 h. The reaction solution was cooled to r.t., poured into H_2O (8 kg) and stirred for 2 h. The resulting solid was collected by suction filtration, washed with H_2O (2 × 600 g), and dried at 45 °C for 6 h to give a brown solid (680 g). The crude product and active charcoal (70 g) were suspended in THF (3 kg) and heated to reflux for 2 h. The solids were removed by hot filtration and the filtrate was concentrated to around 1 kg, and stirred at r.t. for 12 h. The resulting solid was collected by suction filtration, washed with THF (2 × 180 g), and dried at 45 °C for 12 h to give the product **10** (405 g, 64%) as an off-white solid.[3]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29 (d, *J* = 2.6 Hz, 1 H), 8.14 (dd, *J* = 8.9, 2.8 Hz, 1 H), 7.88 (d, *J* = 5.8 Hz, 1 H), 7.23 (d, *J* = 8.9 Hz, 1 H), 6.21 (dd, *J* = 5.8, 2.2 Hz, 1 H), 6.10 (s, 2 H), 5.90 (d, *J* = 2.1 Hz, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.1, 95.1, 102.8, 120.9, 123.8, 127.2, 131.8, 144.2, 150.5, 158.5, 162.3, 164.0.

MS (ESI): *m*/*z* = 246.1 [M + H]$^+$.

Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.90; H, 4.50; N, 17.06.

N-Hydroxy-*N*′-(4-(2-methyl-4-nitrophenoxy)pyridin-2-yl)formimidamide (12)

To a solution of **10** (390 g, 1.59 mol) in EtOH (2 kg) was added DMF-DMA (210 g, 1.75 mol) and the reaction solution was stirred and heated to 75 °C for 3 h. The resulting solution was cooled to 40 °C, then hydroxylamine hydrochloride (130 g, 1.9 mol) was added to the reactant and the resulting solution was stirred and heated to 50 °C for another 3 h. A yellow solid formed during this time. The reaction suspension was cooled to r.t. and the resulting yellow solid was collected by suction filtration, washed with EtOH (2 × 80 g), and dried at 45 °C for 6 h to give **12** (370 g, 81%) as a light-tan solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.08 (s, 1 H), 9.37 (d, *J* = 9.9 Hz, 1 H), 8.33 (d, *J* = 2.3 Hz, 1 H), 8.16 (dd, *J* = 8.9, 2.6 Hz, 1 H), 8.10 (d, *J* = 5.8 Hz, 1 H), 7.82 (d, *J* = 9.9 Hz, 1 H), 7.32 (d, *J* = 10.6 Hz, 1 H), 6.61 (*d*, *J* = 2.1 Hz, 1 H), 6.55 (dd, *J* = 5.8, 2.2 Hz, 1 H), 2.28 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.1, 97.8, 106.5, 121.6, 123.9, 127.3, 132.2, 135.9, 144.7, 150.2, 155.2, 157.9, 164.6.

MS (ESI): *m*/*z* = 289.1 [M + H]$^+$.

Anal. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44. Found: C, 54.29; H, 4.18; N, 19.52.

7-(2-Methyl-4-nitrophenoxy)-[1,2,4]triazolo[1,5-*a*]pyridine (13)

A suspension of compound **12** (220 g, 0.77 mol) in anhydrous THF (1.3 kg) was stirred and cooled to 5 °C, TFAA (170 g, 0.80 mol) was slowly added to the reactant while maintaining the reaction temperature below 15 °C. The reaction suspension was stirred at 20–25 °C for another 5 h to give a clear solution. The solvents were removed under reduced pressure to give a yellow oil, then EtOAc (1.2 kg) was added to the residue to give a solution. The organic layer was washed with H_2O (2 × 1 kg) and saturated $NaHCO_3$ (1 × 1 kg). The solvents were removed under reduced pressure to obtain a light-yellow oil. MeOH (650 g) and active charcoal (20 g) were added to the oil and the mixture was stirred and heated to reflux for 1 h. The solids were removed by hot filtration and the filtrate was stirred at r.t. for 12 h. The resulting solid was collected by suction filtration, washed with MeOH (2 × 80 g), and dried at 45 °C for 12 h to give the product **13** (142 g, 68%) as a yellow solid.[4]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.02 (d, *J* = 7.4 Hz, 1 H), 8.46 (s, 1 H), 8.33 (d, *J* = 2.4 Hz, 1 H), 8.13 (dd, *J* = 8.9, 2.7 Hz, 1 H), 7.30 (d, *J* = 9.0 Hz, 1 H), 7.27 (d, *J* = 2.4 Hz, 1 H), 7.10 (dd, *J* = 7.4, 2.5 Hz, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.1, 101.9, 108.9, 120.2, 123.9, 127.4, 131.4, 131.5, 144.4, 151.2, 154.9, 157.9, 158.6.

MS (ESI): *m*/*z* = 271.1 [M + H]$^+$.

Anal. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73. Found: C, 57.90; H, 3.70; N, 20.81.

4-([1,2,4]Triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylaniline (6)

A suspension of **13** (135 g, 0.5 mol) and Pd/C (5% wet, 7 g) in THF (1.2 kg) was stirred under hydrogen atmosphere at 40 °C for 15 h to give a clear brown solution. The reaction mixture was then filtered through a Celite pad, the filter cake was washed with THF (1 × 80 g). The combined filtrate was concentrated to give a yellow oil. MeOH (160 g) was added to the crude product and the mixture was stirred at 50 °C to give a clear solution, then H_2O (200 g) was added slowly to the solution and the mixture was stirred at r.t. for 12 h. The resulting solid was collected by suction filtration, washed with MeOH (2 × 80 g), and dried at 45 °C for 12 h to give **6** (112 g, 93%) as an off-white solid; mp 155.5–160.0 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.87 (d, *J* = 7.4 Hz, 1 H), 8.34 (s, 1 H), 6.95 (dd, *J* = 7.4, 2.1 Hz, 1 H), 6.82 (d, *J* = 8.5 Hz, 1 H), 6.63 (d, *J* = 2.1 Hz, 1 H), 6.54 (s, 1 H), 6.50 (d, *J* = 8.4 Hz, 1 H), 5.11 (s, 2 H), 1.99 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.1, 96.9, 107.6, 113.2, 116.7, 122.3, 130.5, 130.6, 142.1, 147.3, 151.7, 154.9, 161.1.

MS (ESI): m/z = 241.0 $[M + H]^+$.

Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.78; H, 5.06; N, 23.27.

HPLC Conditions: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 1.0 mL/min; Temperature: 35 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 20 min; Mobile phase: MeOH/H_2O = 80:20; t_R: 4.088 min, purity: 99.13%.

N-(4-([1,2,4]Triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)-6-nitroquinazolin-4-amine (14)

N′-(2-Cyano-4-nitrophenyl)-*N*,*N*-dimethylformimidamide (**3**) was prepared based on the reported method as a red solid in 88% isolated yield.[3]

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.48 (d, J = 2.4 Hz, 1 H), 8.29–8.26 (m, 2 H), 7.38 (d, J = 9.2 Hz, 1 H), 3.17 (s, 3 H), 3.09 (s, 3 H).

MS (ESI): m/z = 219.1 $[M + H]^+$.

HPLC Conditions: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 45 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 30 min; Mobile phase: MeOH/H_2O = 80:20; t_R: 5.289 min, purity: 98.82%.

A stirred suspension of compound **3** (26.2 g, 0.12 mol) and **6** (29.0 g, 0.12 mol) in acetic acid (250 g) was stirred and heated to 85 °C for 2 h to give a light-yellow suspension. The solvent was partially distilled under reduced pressure, and then poured into H_2O (120 g) and stirred at 0–5 °C for 1 h. The resulting solid was collected by suction filtration, washed with H_2O (2 × 50 g), and dried at 45 °C for 12 h to give **14** (41.2 g, 83%) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1 H), 9.69 (s, 1 H), 8.95 (d, J = 7.5 Hz, 1 H), 8.75 (s, 1 H), 8.57 (dd, J = 9.2, 2.2 Hz, 1 H), 8.39 (s, 1 H), 7.95 (d, J = 9.2 Hz, 1 H), 7.86 (d, J = 11.5 Hz, 2 H), 7.25 (d, J = 8.5 Hz, 1 H), 7.04 (dd, J = 7.5, 2.5 Hz, 1 H), 6.84 (d, J = 2.4 Hz, 1 H), 2.22 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.3, 98.3, 107.9, 114.8, 121.2, 121.6, 122.6, 126.2, 127.0, 129.9, 130.4, 130.9, 136.6, 144.9, 148.7, 151.6, 153.5, 155.1, 158.1, 159.1, 159.9.

MS (ESI): m/z = 414.1 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{15}N_7O_3$: C, 61.01; H, 3.66; N, 23.72. Found: C, 61.22; H, 3.62; N, 23.81.

HPLC Conditions: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 1.0 mL/min; Temperature: 35 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 40 min; Mobile phase: MeOH/H_2O = 70:30; t_R: 23.30 min, purity: 99.47%.

N^4-(4-([1,2,4]Triazolo[1,5-*a*]pyridin-7-yloxy)-3-methylphenyl)quinazoline-4,6-diamine (15)

A suspension of **14** (32.0 g, 0.077 mol) and Pd/C (5% wet, 1.8 g) in THF (240 g) was stirred under hydrogen atmosphere at r.t. for 5 h to give a clear brown solution. The reaction mixture was then filtered through a Celite pad, the filter cake was washed with THF (2 × 40 g). The combined filtrate was concentrated to around 70 g, the residue was poured into H_2O (120 g) and stirred at r.t. for 2 h. The resulting solid was collected by suction filtration, washed with H_2O (2 × 30 g), and dried at 45 °C for 12 h to give **15** (27.6 g, 92%) as a yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.38 (d, J = 13.8 Hz, 1 H), 8.93 (d, J = 7.4 Hz, 1 H), 8.38 (s, 1 H), 8.36 (s, 1 H), 7.90 (d, J = 2.1 Hz, 1 H), 7.85 (dd, J = 8.7, 2.3 Hz, 1 H), 7.54 (t, J = 8.1 Hz, 1 H), 7.38 (d, J = 2.2 Hz, 1 H), 7.26 (dd, J = 8.9, 2.2 Hz, 1 H), 7.18 (d, J = 8.7 Hz, 1 H), 7.03 (dd, J = 7.5, 2.6 Hz, 1 H), 6.79 (d, J = 2.4 Hz, 1 H), 5.59 (s, 2 H), 2.19 (d, J = 5.5 Hz, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.3, 98.3, 107.8, 107.9, 121.3, 121.6, 122.7, 126.3, 127.1, 129.9, 130.5, 130.9, 136.5, 145.0, 148.7, 151.7, 153.5, 155.5, 158.1, 159.2, 159.9.

MS (ESI): m/z = 384.1 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{17}N_7O$: C, 65.79; H, 4.47; N, 25.57. Found: C, 65.60; H, 4.49; N, 25.49.

HPLC Conditions: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 1.0 mL/min; Temperature: 35 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 40 min; Mobile phase: MeOH/H_2O = 70:30; t_R: 6.475 min, purity: 99.90%.

4,4-Dimethyloxazolidine-2-thione (16)

To a stirred solution of 2-amino-2-methyl-1-propanol (13.4 g, 0.15 mol) in CH_2Cl_2 (200 g) was slowly added a solution of 1,1′-(thiocarbonyl)diimidazole (26.7 g, 0.15 mol) in CH_2Cl_2 (260 g), maintaining the reaction temperature below 25 °C. The resulting solution was stirred at r.t. for 17 h. The reaction solution was washed with H_2O (2 × 150 g) and the solvent was removed under reduced pressure to give **16** (16.3 g, 83%) as a white solid,[5] which was used directly in the next step without purification, or should be stored below 4 °C for no more than two weeks under argon atmosphere.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.05 (br. s, 1 H), 4.27 (s, 2 H), 1.26 (s, 6 H).

4,4-Dimethyl-2-(methylthio)-4,5-dihydrooxazole Trifluoromethanesulfonate (17)

To a stirred solution of **16** (13.1 g, 0.1 mol) in CH_2Cl_2 (200 g) was slowly added methyl trifluoromethanesulfonate (18.0 g, 0.11 mol), maintaining the reaction temperature below 25 °C. The resulting solution was stirred at r.t. for 15 h. The reaction solution was diluted with *tert*-butyl methyl ether (400 g) and stirred at 0–5 °C for 2 h. The resulting solid was collected by suction filtration, washed with *t*-butyl methyl ether (2 × 20 g), and dried under vacuum at r.t. for 6 h to give **17** (23.9 g, 81%) as a white solid,[6] which was used directly in the next step, or should be stored below –18 °C for no more than two weeks under argon atmosphere.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.56 (s, 2 H), 2.61 (s, 3 H), 1.39 (s, 6 H).

Tucatinib (1)

Cs_2CO_3 (26.5 g, 0.082 mol) was added in portions to a suspension of **17** (16.2 g, 0.055 mol) in DMF (70 g) at r.t. and the solution was stirred for 1 h. Compound **15** (16.9 g, 0.044 mol) was added to the reactant and the resulting mixture was stirred at 125 °C for 20 h. The reaction solution was cooled to r.t. and poured into ice H_2O (300 g), then stirred at r.t. for 1 h. The resulting solid was collected by suction filtration, washed with H_2O (2 × 20 g), and dried at 45 °C for 6 h to give a light-yellow solid (21 g). The crude product and active charcoal (4 g) were suspended in EtOAc (80 g) and heated to reflux for 1 h. The solids were removed by hot filtration and the filtrate was concentrated to around 50 g. Heptane (40 g) was added slowly to the warm solution and the mixture was stirred at r.t. for 12 h. The resulting solid was

collected by suction filtration, washed with heptane (2 × 15 g), and dried at 45 °C for 12 h to give **1** (16.1 g, 76%) as a white solid;[3] mp 251.2–254.7 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.58 (s, 1 H), 8.94 (d, J = 7.5 Hz, 1 H), 8.50 (s, 1 H), 8.38 (s, 1 H), 8.03 (br. s, 1 H), 7.92 (s, 1 H), 7.87 (d, J = 8.5 Hz, 1 H), 7.67 (d, J = 8.5 Hz, 1 H), 7.59–7.41 (m, 1 H), 7.20 (d, J = 8.7 Hz, 1 H), 7.03 (dd, J = 7.5, 2.6 Hz, 1 H), 6.80 (d, J = 2.3 Hz, 1 H), 4.08 (s, 2 H), 2.19 (s, 3 H), 1.29 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 16.3, 27.5, 78.1, 97.9, 107.8, 116.2, 121.6, 121.9, 125.4, 128.5, 130.2, 130.8, 137.9, 145.9, 147.7, 151.7, 152.6, 155.1, 157.4, 160.2.

MS (ESI): m/z = 481.2 $[M + H]^+$.

Anal. Calcd for $C_{26}H_{24}N_8O_2$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.84; H, 5.06; N, 23.25.

HPLC Conditions: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 1.0 mL/min; Temperature: 35 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 40 min; Mobile phase: MeOH/H_2O = 70:30; t_R: 7.563 min, purity: 99.9%.

References

(1) Dinkel, V.; Anderson, D.; Winski, S.; Winkler, J.; Koch, K.; Lee, P. A. *Cancer Res.* **2014**, *72*, 852.
(2) Lee, P.; Anderson, D.; Bouhana, K.; Garrus, J.; Napier, C.; Avrustkaya, A.; White, A.; Pheneger, T.; Winkler, J. *Cancer Res.* **2014**, *69*, 5104.
(3) Lyssikatos, J. P.; Marmsater, F. P.; Zhao, Q.; Greschuk, J. M. PCT Int. Appl WO 2007059257, **2007**.
(4) Tsou, H. R.; Mamuya, N.; Johnson, B. D.; Reich, M. F.; Gruber, B. C.; Ye, F.; Nilakantan, R.; Shen, R.; Discafani, C.; DeBlanc, R. *J. Med. Chem.* **2001**, *44*, 2719.
(5) Matsushima, T.; Shirotori, S.; Takahashi, K.; Kamada, A.; Wakasugi, K.; Sakaguchi, T. US Pat. Appl. Publ US 20080319188, **2008**.
(6) Allen, J. R.; Hitchcock, S. A.; Turner, W. W. Jr.; Liu, B. PCT Int. Appl WO 2004094382, **2004**.