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ORIGINAL PAPER

Novel method for the synthesis of lenvatinib using 4-nitrophenyl cyclopropylcarbamate and their pharmaceutical salts

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Abstract
4-Nitrophenyl cyclopropylcarbamate was deployed as a novel synthon for the synthesis of anticancer drug lenvatinib. 4-Nitrophenyl cyclopropylcarbamate was prepared by the reaction of 4-nitrophenyl chloroformate and cyclopropyl amine in acetonitrile at room temperature. Furthermore, lenvatinib was synthesized by reacting 4-(4-amino-3-chlorophenoxy)-7-methoxyquinoline-6-carboxamide with 4-nitrophenyl cyclopropylcarbamate in good yields. Apart from the synthesis of lenvatinib, citrate, phosphate, malate and oxalate salts of lenvatinib were also reported in good yields.

Keywords Synthesis · Process · Lenvatinib · Salts · Analysis

Introduction

Cancer is one of the leading death causing disease globally. According to World Health Organization (WHO) the cancer patients will increases to 27.5 million by 2040. Lenvatinib is an anticancer drug used for the treatment of thyroid cancer and also acts as a kinase inhibitor against VEGFR1, VEGFR2 and VEGFR3 (Zschäbitz and Grüllich 2018).

Lenvatinib inhibits effectively in the tumor progression by preventing phosphorylation and subsequent activation of many tyrosine kinases taking part in tumor cell proliferation and neo-angiogenesis. (Scott et al. 2015) Lenvatinib was approved for medical use in the United States from 2016 for the treatment of advanced renal cell carcinoma. FDA approved lenvatinib for the treatment of patients with advanced endometrial carcinoma along with pembrolizuma. (Makker et al. 2020).

On the other hand, it is important to develop high quality, commercially viable and cost-efficient methods for an existing active pharmaceutical ingredients (API). Many researchers from academic as well as industry have focused to develop commercially viable novel methods for the new and existing API molecules. In this regard, we plan to develop a novel method for the synthesis of lenvatinib which is an important anticancer compound (Fig. 1).

After thorough literature review, several synthetic methods were reported for the synthesis of lenvatinib which were shown in Scheme 1. (Matsushima et al. 2005; Sakaguchi et al. 2006; Funahashi et al. 2007; Naito et al. 2006; Nakamura et al. 2016; Gang 2015; Flick et al. 2015; Casar 2020).

Lenvatinib synthesis was shown in Scheme 1 using different approaches. We are using 4-nitrophenyl cyclopropyl carbamate as unsymmetrical reactive carbamate for the synthesis of lenvatinib. Most of the lenvatinib synthesis were reported using 1-(2-chloro-4-hydroxyphenyl)-3-cyclopropyl urea as an intermediate which is prepared by the reaction of 3-chloro-4-aminophenol and cyclopropyl amine using phenylchloroformate or carbonyldiimidazole. In the same way lenvatinib was synthesized by the reaction of 4-(4-amino-3-chlorophenoxy)-7-methoxy-6-quinolinecarboxamide and cyclopropyl amine using phenylchloroformate or

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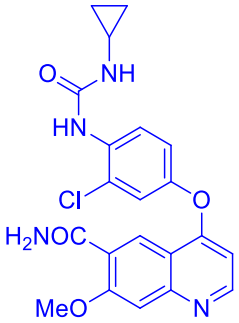
Fig. 1 Structure of lenvatinib **1**

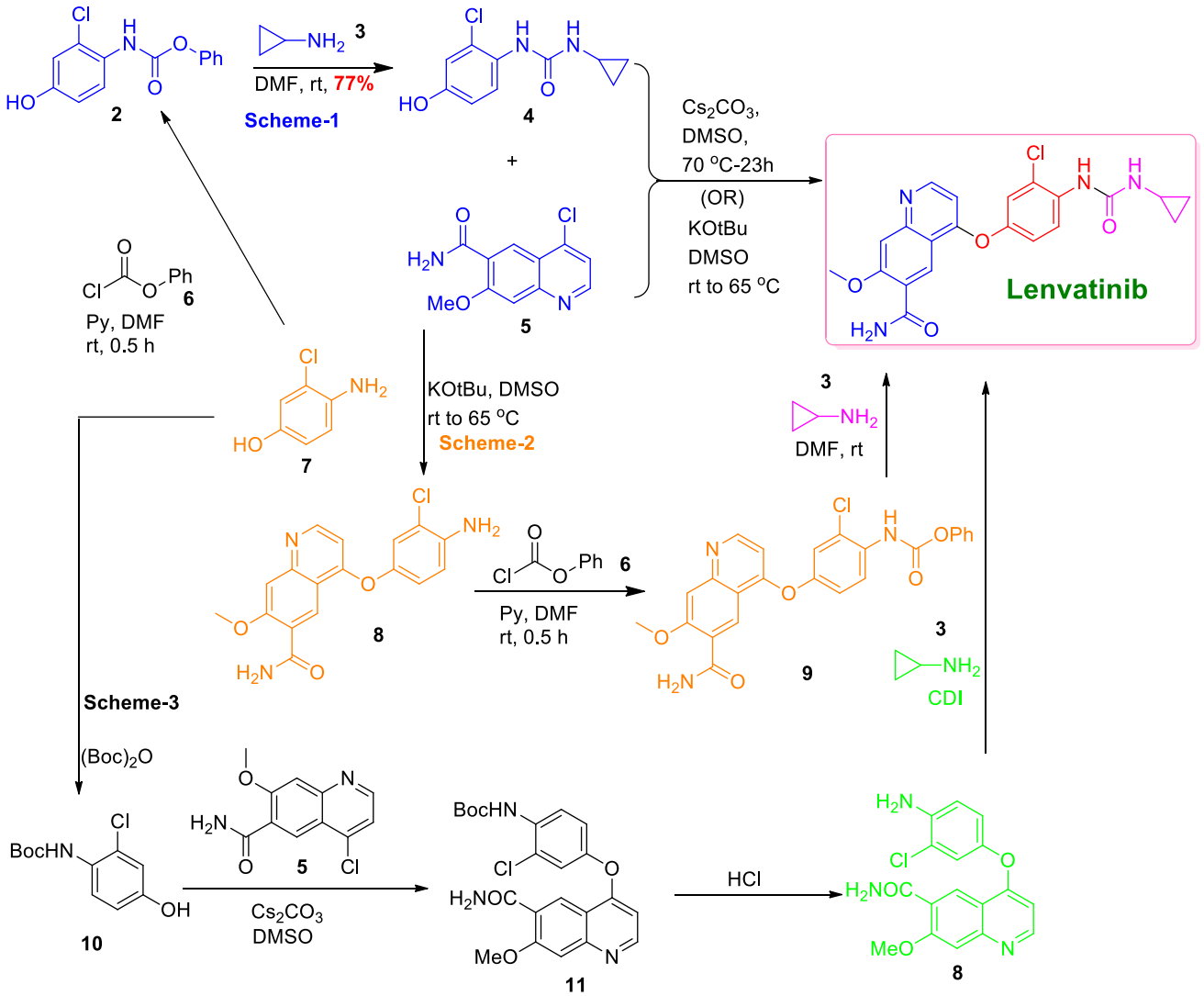


carbonyldiimidazole. (Reddy et al. 2017; Oruganti et al. 2017; Gang 2015).

Due to continuous efforts in the development of API and API impurities (Gudisela et al. 2018; Rapolu et al. 2018; Rapolu et al. 2019a, b) by our team, we wish to report a novel method for the synthesis of lenvatinib using 4-nitrophenyl cyclopropylcarbamate as a novel intermediate. Previously several researchers used 4-nitrophenyl cyclopropylcarbamate for the construction of cyclopropylurea in the literature. (Thomas et al. 2007; Harry et al. 2013; Michael et al. 2003; Rapolu et al. 2019a, b). The importance of the present study is to synthesize lenvatinib using novel process followed by the preparation of different lenvatinib salts which are having novel polymorphism. All the synthesized compounds were characterized using ^{1}H NMR, ^{13}C NMR, Mass spectra and HPLC method.

Experimental procedure

Solvents and reagents obtained from commercial sources were used without any further purification. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$, DMSO-d_6 on a Varian



Scheme 1 Literature known synthetic schemes of lenvatinib **1**

Mercury spectrometer using TMS as an internal standard. The mass spectrum (70 eV) was recorded on an HP 5989 A LC–MS spectrometer. TLC analyses were performed on Merck silica gel 60 F_{254} plates. HPLC was performed using waters 2695 model pump and 2996 PDA detector. YMC C-18 column (4.6 × 150 mm, 5 µ) analytical column and a mobile phase containing water and methanol in a ration 30:70 isocratic systems was used to separate the lenvatinib peak. PXRD was performed on Bruker D8 advance instrument.

Preparation of 4-nitrophenyl cyclopropylcarbamate (12)

To a stirred solution of 4-nitrophenyl chloroformate **13** (88.0 g, 0.436 mol) in acetonitrile (1000 mL) cyclopropyl amine **3** (25.0 g, 0.437 mol) was added at 0–5 °C over a period of 50–60 min. The reaction mixture was warmed to room temperature and stirred for 24–26 h. After completion of the starting material (Checked by TLC), the reaction mixture was filtered and washed with dichloromethane (100 mL). The filtrate was evaporated under reduced pressure to obtain solid compound. The solid compound was slurried in hexane (2 × 500 mL), filtered and washed with hexane (2 × 100 mL). The wet cake was dried to obtain 4-nitrophenyl cyclopropylcarbamate **12** (73.7 g, 76%) as an off white solid.

Off white solid: mp: 203–206 °C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.29–8.20 (m, 3H), 7.40 (dd, J = 7.1, 2.0 Hz, 2H), 2.62–2.56 (m, 1H), 0.69–0.64 (m, 2H), 0.52–0.50 (m, 2H). Mass (m/z): Calculated-222.25, Found-223.4 $(M+H)^+$.

Preparation of 4-(4-amino-3-chlorophenoxy)-7-methoxyquinoline-6-carboxamide (8)

To a stirred solution of 4-chloro-7-methoxyquinoline-6-carboxamide **5** (50 g, 0.211 mol) in DMSO (250 mL) 4-amino-3-chloro phenol **7** (42.5 g, 0.296 mol) was added at room temperature. After 5–10 min, KOH (35.5 g, 0.633 mol) in 70 mL water was added drop wise over a period of 30–40 min at room temperature. The reaction mixture was warmed to 70–80 °C and stirred at the same temperature for 12–13 h. After consumption of starting material, the reaction was cooled to room temperature and water (500 mL) was added to obtain the solid. The contents were stirred for 60 min at room temperature, filtered, washed with water (150 mL) and dried to afford 4-(4-amino-3-chlorophenoxy)-7-methoxyquinoline-6-carboxamide **8** (54 g, 84%) as light brown solid.

Light brown solid: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.27 (s, 1H), 8.64 (d, J = 5.3 Hz, 1H), 7.79 (brs, 1H), 7.52 (s, 1H), 7.13 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 8.6, 2.6 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 6.46 (1 d, J = 5.3 Hz, 1H), 5.95 (brs, 1H), 4.12 (s, 3H), 4.11 (s, 2H); Mass (m/z): Calculated-343.0, Found-343.9 (M + H) + .

Preparation of lenvatinib (4-(3-chloro-4-(3-cyclopropylureido)phenoxy)-7-methoxy quinoline-6-carboxamide) (1)

To a stirred solution of 4-(4-amino-3-chlorophenoxy)-7-methoxyquinoline-6-carboxamide **4** (50 g, 0.145 mol) in acetonitrile (500 mL) 4-nitrophenyl cyclopropylcarbamate **10** (63 g, 0.278 mol) was added, followed by pyridine (34.5 g, 0.434 mol) at room temperature. The reaction mixture was heated to 80–85 °C and stirred at the same temperature for 13 h. Another lot 4-nitrophenyl cyclopropylcarbamate **10** (10 g, 0.044 mol) was added and stirred for 7–8 h at 80–85 °C. The reaction mixture was cooled to room temperature and filtered. The obtained solid was washed with acetonitrile (100 mL) and crude solid was dissolved in methanol: DCM (1:1, 1560 mL). The solution was warmed to 40–45 °C, carbon (25 g) was added and stirred for 1 h at the same temperature. After filtering the reaction mass, the filtrate was evaporated under vacuum below 40 °C to furnish crude. The crude was slurried in acetone (250 mL) and filtered to furnish lenvatinib **1** (4-(3-chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide) (45.7 g, 74%).

HPLC purity: 98.27%.Off white solid; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.67 (d, J = 5.2 Hz, 1H), 8.66 (s, 1H), 8.28 (d, J = 9.1 Hz, 1H), 7.99 (s, 1H), 7.85 (s, 1H), 7.74 (s, 1H), 7.52 (s, 1H), 7.50 (d, J = 2.8 Hz, 1H), 7.25 (dd, J = 9.1, 2.8 Hz, 1H), 7.21 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 5.2 Hz, 1H), 4.04 (s, 3H), 2.62–2.56 (m, 1H), 0.70–0.64 (m, 2H), 0.46–0.40 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 165.7, 162.2, 161.3, 158.4, 155.5, 152.7, 150.5, 147.4, 134.7, 125.3, 124.8, 122.1, 121.9, 121.8, 120.3, 11.4, 107.0,103.1, 56.2, 22.3, 6.2. Mass (m/z): Calculated-426.85, Found-427.74 $(M+H)^+$

Purification of lenvatinib

Using DMSO-IPA

To a stirred solution of lenvatinib **1** (32 g, crude) in DMSO (640 mL) IPA (1600 mL) was added drop wise at 40–45 °C. The suspension was cooled to room temperature and stirred for 15–16 h. The suspension was filtered and the solid was washed with water (50 mL) followed by acetone (100 mL). The wet cake was dried at 50 °C under vacuum to obtain lenvatinib **1** (23 g, 72%) with 99.54% HPLC purity.

Using DMSO-acetone

To a stirred solution of lenvatinib **1** (7 g, crude) in DMSO (140 mL) acetone (420 mL) was added dropwise at 40–45 °C. The suspension was cooled to room temperature and stirred for 6 days. The suspension was filtered and the solid was washed with water (20 mL) followed by acetone (20 mL). The wet cake was dried at 50 °C under vacuum to obtain lenvatinib **1** (1.7 g, 24%) with 99.55% HPLC purity.

Preparation of lenvatinib mesylate

(4-(3-Chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide methanesulfonate

To a stirred suspension of 4-(3-chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide **1** (5 g, 0.011 mol.) in IPA (50 mL) MSA (1.1 g, 0.011 mol.) was added at room temperature. The reaction mixture was heated to 80–85 °C and stirred at the same temperature for 7–8 h. The reaction mass was cooled to room temperature and stirred for 15–18 h. The suspension was filtered, washed with IPA (10 mL) and dried to yield lenvatinib mesylate **12** (4-(3-chloro-4-(3-cyclopropylureido)phenoxy)-7-methoxyquinoline-6-carboxamide methane sulfonate) (5 g, 82%) as an off white solid.

Off white solid: mp: 226.5–231.0 °C, LOD: 0.3%;^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.98 (d, J = 6.5 Hz, 1H), 8.73 (s, 1H), 8.37 (d, J = 9.1 Hz, 1H), 8.07 (s, 1H), 7.97 (broad, 1H), 7.91 (brs, 1H), 7.64 (s, 2H), 7.36 (d, J = 9.1, 2.8 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 6.95 (d, J = 6.5 Hz, 1H), 4.09 (s, 3H), 2.62–2.56 (m, 1H), 2.35 (s, 3H), 0.71–0.60 (m, 2H), 0.47–0.41 (m, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): 165.7, 161.5, 158.0, 155.4, 153.2, 151.5, 147.5, 134.5, 124.9, 124.6, 121.8, 121.7, 120.3, 114.3, 107.8, 102.9, 101.5, 56.1, 22.3, 6.2. Mass (m/z): Calculated-426.85, Found-427.20 $(M + H)^+$, HPLC purity: 95.19%; TGA (Method: Ramp 5.00 °C/min to 300.00 °C, Equilibrate at 30.00 °C): (30.00 °C–120.00 °C): 0.26%; DSC (Method: Ramp 5.00 °C/min to 300.00 °C, Equilibrate at 30.00 °C): 225.8–229.3 °C.

Process for lenvatinib (L)-malate

4-(3-Chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide (*S*)-2-hydroxysuccinate (15)

To a stirred suspension of 4-(3-chloro-4-(3-cyclopropylureido)phenoxy)-7-methoxyquinoline-6-carboxamide **1** (4 g, 0.009 mol) in acetone (120 mL) (L)-malic acid (1.5 g, 0.011 mol) was added at room temperature. The reaction mixture was heated to 60–65 °C and stirred for 6–7 h at the same temperature. The suspension was cooled to room temperature and stirred for 18–20 h. The suspension was filtered, washed with acetone (15 mL) and dried to give lenvatinib (L)-malate (4-(3-chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide (*S*)-2-hydroxysuccinate) **15** (5 g, 95%) as an off white solid.

Off white solid: mp: 157.5–161.0 °C; LOD: 0.9%; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.33 (broad, 1H), 8.67 (s, 1H), 8.66 (s, 1H), 8.27 (d, J = 9.1 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.51 (s, 1H), 7.48 (d, J = 3.0 Hz, 1H), 7.24 (dd, J = 9.0, 2.5 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.53 (d, J = 5.2 Hz, 1H), 4.28–4.23 (m, 1H), 4.03 (s, 3H), 2.64–2.56 (m, 2H), 2.57–2.40 (m, 1H), 0.70–0.64 (m, 2H), 0.46–0.40 (m, 2H); Mass (m/z): 426.9$(M + H)^+$. HPLC purity: 99.63%; Assay by HPLC: 73.2%; TGA (Method: Ramp 5.00 °C/min to 300.00 °C, Equlibrate at 30.00 °C):(30.00 °C–100.00 °C):2.69%; DSC (Method: Ramp 5.00 °C/min to 300.00 °C, Equlibrate at 30.00 °C):157.2–160.46 °C; XRD: 4.012, 7.329, 8.125, 9.369, 10.840, 12.382, 14.285, 14.797, 15.514, 16.518, 18.048, 18.552, 18.928, 19.920, 19.866, 20.586, 21.481, 22.733, 22.986, 23.461, 24.043, 24.930, 25.864, 26.963, 27.861, 28.629, 29.030, 29.793, 30.552, 31.448, 33.917, 35.035, 36.275, 38.523.

Process for lenvatinib oxalate

4-(3-Chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide oxalate (16)

To a stirred suspension of 4-(3-chloro-4-(3-cyclopropylureido)phenoxy)-7-methoxyquinoline-6-carboxamide 1 (5 g, 0.011 mol) in acetone (200 mL) oxalic acid (1.27 g, 0.014 mol) was added at room temperature. The reaction mixture was heated to 60–65 °C and stirred for 6–7 h at the same temperature. The suspension was cooled to room temperature and stirred for 15–16 h. The suspension was filtered, washed with acetone (30 mL) and dried to yield lenvatinib oxalate **16**(4-(3-chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide oxalate) (5.8 g, 96%) as an light brown solid.

Light brown solid: mp:170.0–173.2 °C; LOD:0.06%; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.71–8.68 (m, 1H), 8.67 (s, 1H), 8.28 (d, J = 9.1 Hz, 1H), 7.99 (s, 1H), 7.85 (s, 1H), 7.73 (s, 1H), 7.52 (s, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.25 (dd, J = 9.5, 3.0 Hz, 1H), 7.19 (d, J = 3.0 Hz, 1H), 6.55 (d, J = 5.3 Hz, 1H), 4.03 (s, 3H), 2.61–2.56 (m, 1H), 0.70–0.64 (m, 2H), 0.46–0.40 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 165.7, 162.2, 161.3, 158.4, 155.5, 152.7, 150.5, 147.4, 134.7, 125.3, 124.8, 122.1, 121.9, 121.8, 120.3, 114.4, 107.0, 103.1, 56.2, 22.3, 6.2., Mass (m/z): Calculated-426.85, Found-427.15$(M + H)^+$; HPLC purity: 99.26%. Assay by HPLC: 77.1%; TGA (Method: Ramp 5.00 °C/min to

300.00 °C, Equilibrate at 30.00 °C):30.00 °C–120.00 °C: 3.46%,120.0–155.0 °C:3.12%, 155–200 °C:21.79%; DSC (Method: Ramp 5.00 °C/min to 300.00 °C, Equilibrate at 30.00 °C):171.89 °C–188.71 °C(melting with decompose); XRD: 3.495, 5.483, 8.034, 10.527, 11.105, 16.699, 18.047, 20.145, 24.016, 25.881, 27.109, 27.156, 28.642, 29.313.

Process for lenvatinib phosphate

4-(3-Chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide phosphate (17)

To a stirred suspension of 4-(3-chloro-4-(3-cyclopropylureido)phenoxy)-7-methoxyquinoline-6-carboxamide **1** (5 g, 0.011 mol) in IPA (200 mL) phosphoric acid (1.37 g, 0.013 mol) was added at room temperature. The reaction mixture was heated to 80–85 °C and stirred at the same temperature for 4–5 h. The suspension was cooled to room temperature and stirred for 15–16 h. The suspension was filtered, washed with IPA (20 mL) and dried to obtain lenvatinib phosphate(4-(3-chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide phosphate) **17** (5.0 g, 82%) as an off white solid.

Off white solid: mp: 191.5–193.0 °C; LOD: 1.80%; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.67 (m, 1H), 8.66 (s, 1H), 8.27 (d, J = 9.0 Hz, 1H), 7.98 (s, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.52 (s, 1H), 7.49 (d, J = 3.0 Hz, 1H), 7.24 (dd, J = 9.0, 2.5 Hz, 1H), 7.19 (d, J = 3.0 Hz, 1H), 6.53 (d, J = 5.2 Hz, 1H), 4.03 (s, 3H), 2.62–2.56 (m, 1H), 0.69–0.64 (m, 2H), 0.45–0.40 (m, 2H); Mass(m/z): Calculated: 426.15, Found: 426.9(M + H)$^{+}$; HPLC purity: 99.57%; Assay by HPLC: 72.7%; TGA (Method: Ramp 5.00 °C/min to 300.00 °C, Equilibrate at 30.00 °C):120.0 °C:2.69%, 180.0 °C:10.42%, 230.0 °C:4.07%; DSC (Method: Ramp 5.00 °C/min to 300.00 °C, Equlibrate at 30.00 °C):185.8–192.9 °C; XRD: 3.154, 4.030, 4.469, 6.151, 6.099, 6.633, 9.715, 10.269, 11.020, 12.268, 12.490, 13.936, 16.456, 16.896, 17.004, 17.145, 18.976, 19.461, 19.944, 20.892, 21.609, 23.199, 23.496, 26.634, 27.575, 28.200, 28.729, 29.327.

Process for lenvatinib citrate

4-(3-Chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide 2-hydroxypropane-1,2,3-tricarboxylate (18)

To a stirred suspension of 4-(3-chloro-4-(3-cyclopropylureido)phenoxy)-7-methoxyquinoline-6-carboxamide **1** (5 g, 0.011 mol) in acetone (200 mL) citric acid (2.7 g, 0.014 mol) was added at room temperature. The reaction mixture was heated to 60–65 °C and stirred for 6–7 h at the same temperature. The suspension was cooled to room temperature and stirred for 15–16 h. The suspension was filtered, washed with acetone (20 mL) and dried to furnish lenvatinib citrate (4-(3-chloro-4-(3-cyclopropylureido) phenoxy)-7-methoxyquinoline-6-carboxamide-2-hydroxy propane-1,2,3-tricarboxylate) **18** (6 g, 83%) as an off white solid.

Off white solid: mp: 161.5–164.0 °C; LOD: 0.25%; ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.21 (broad, 1H), 8.67 (s, 1H), 8.66 (s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.71 (s, 1H), 7.50 (s, 1H), 7.49 (d, J = 3.0 Hz, 1H), 7.24 (dd, J = 9.0, 2.5 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.53 (d, J = 5.3 Hz, 1H), 4.03 (s, 3H), 2.73, 2.64 (q, J = 15.5 Hz, 4H), 2.61–2.56 (m, 1H), 0.70–0.64 (m, 2H), 0.46–0.40 (m, 2H); Mass (m/z): Calculated-426.1, Found-426.9(M + H)$^{+}$; HPLC purity: 99.78%; TGA (Method: Ramp 5.00 °C/min to 300.00 °C, Equilibrate at 30.00 °C):120.0 °C: 1.92%,150.0 °C: 14.29%, 200.0 °C: 14.75%; DSC (Method: Ramp 5.00 °C/min to 300.00 °C, Equilibrate at 30.00 °C):150.94–160.2 °C; XRD: 3.993, 5.475, 6.827, 8.268, 10.301, 11.667, 12.480, 13.139, 13.654, 14.697, 14.931, 15.505, 16.827, 17.137, 17.880, 17.976, 18.525, 19.063, 20.128, 20.908, 22.468, 23.222, 23.453, 24.187, 24.699, 26.035, 26.748, 27.099, 27.232, 27.850, 28.859, 29.687, 30.929, 31.423, 32.983, 34.894, 35.485, 38.962, 39.010.

Results and discussion

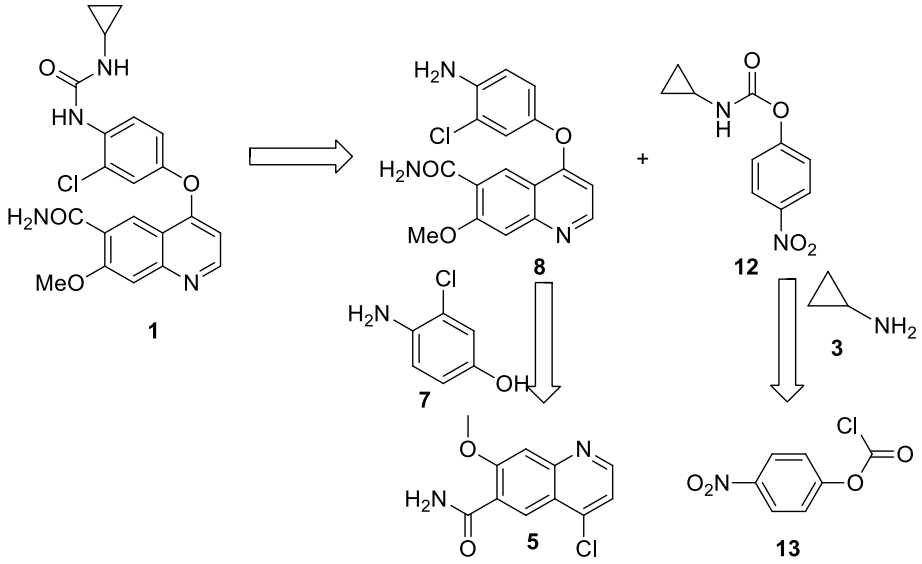
After thorough literature analysis, following retrosynthetic analysis of lenvatinib was proposed (Scheme 2).

After going through the retrosynthetic route we proceeded to use 4-nitrophenyl cyclopropylcarbamate **12** as a key starting material for the synthesis of lenvatinib. 4-Nitrophenyl cyclopropylcarbamate **12** which is a good leaving group can be used for the synthesis of lenvatinib. It was prepared by the reaction of 4-nitrophenyl chloroformate **14** with cyclopropyl amine **3**.

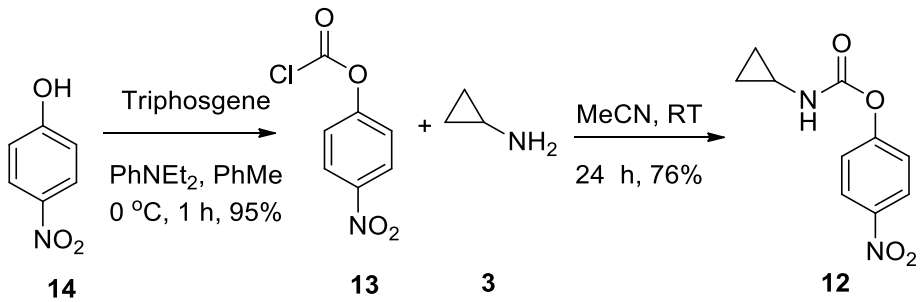
The key starting material, 4-nitrophenyl cyclopropylcarbamate **12** was prepared starting from commercially available 4-nitrophenol. 4-Nitrophenol **14** on reaction with triphosgene in toluene at 0–5 °C for 1–2 h afforded Compound **13** in 95% yield. (Onozuka et al. 2011) (Scheme 3).

After synthesizing 4-nitrophenyl chloroformate **13**, we focused on the synthesis of 4-nitrophenyl cyclopropylcarbamate **12** which was synthesized by the reaction of 4-nitrophenyl chloroformate **13** and cyclopropyl amine **3**. To optimise this reaction, we conducted a preliminary reaction using literature procedure between 4-nitrophenyl chloroformate and cyclopropyl amine in THF using diisopropylethyl amine as a base at room temperature. Only 10% of the desired product **12** was formed at room temperature. (Arcari et al. 2007).

Scheme 2 Retrosynthetic analysis of lenvatinib **1**



Scheme 3 Preparation of 4-nitrophenyl cyclopropylcarbamate **12**



To optimize the reaction conditions for the synthesis of 4-nitrophenyl cyclopropyl carbamate **12**, we tried the reaction with different bases such as TEA, DIPA, Pyridine, NaOH, K_2CO_3 and found there is no improvement in the yield of the reaction. When the reaction was tried without using any base in DCM we observed an improvement in the formation of the desired product with 57% yield. The same reaction when performed in acetonitrile at room temperature for 24 h the yield of the desired product was increased to 76% yield (Table 1).

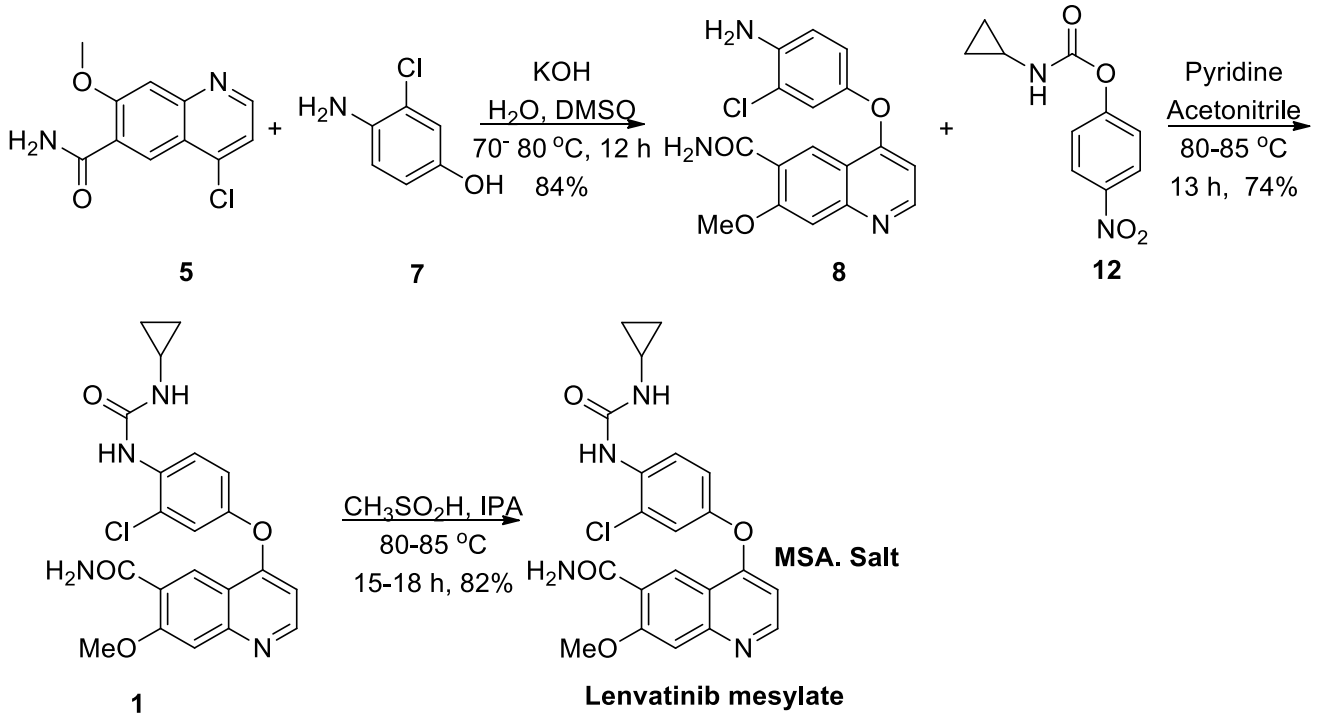
After the synthesis of Compound **12**, we started to optimize the reaction between Compound **7** and Compound **5** to get Compound **8**. By following the literature references we screened the reaction using different bases such as cesium carbonate, potassium carbonate, sodium hydride, potassium tertiary butoxide and potassium hydroxide. In all the above bases potassium hydroxide was effective in DMSO by giving 84% of Compound **8** at 70–80 °C for 12–14 h. (Nakamura et al. 2016; Reddy et al. 2019) (Scheme 4).

Now we focused on the optimization of critical reaction between Compound **8** and Compound **12** which is the novel reaction for the synthesis of lenvatinib **1**. The reaction was screened using different bases such as cesium carbonate, TEA, pyridine, DIPEA, DIPA and KOH. In most of the bases the reaction was either incomplete or formation of by-products was observed. Among all the above bases TEA and pyridine were effective in getting the final compound in good yield. Better yields were obtained when the reaction was

Table 1 Optimization of reaction conditions for the synthesis of 4-nitrophenyl cyclopropylcarbamate 12

Entry	Base	Solvent	Time/temperature (h/RT)	Yield (isolated) (%)
1	DIPEA	THF	12	10
2	TEA	THF	12	16
3	DIPA	THF	12	18
4	Pyridine	THF	12	26
5	NaOH	DCM	12	6
6	K_2CO_3	DCM	12	11
7	No base	DCM	12	57
8	No base	MeCN	24	76[a]

[a]Reaction conditions. Compound **13** (0.436 mol.) in acetonitrile (12 vol.), cyclopropylamine 3 (0.437 mol.), 0–5 °C, 1 h then 30–35 °C, 24–26 h



Scheme 4 Synthesis of lenvatinib

Table 2 Optimization of reaction conditions for the synthesis of Compound **1**

Entry	Base	Solvent	Yield
1	Cs_2CO_3	DCM	32
2	TEA	DCM	56
3	Pyridine	DCM	64
4	DIPEA	DCM	43
5	DIPA	DCM	37
6	KOH	DCM	28
7	TEA	Acetonitrile	62
8	Pyridine	Acetonitrile	74

Reaction conditions. Compound **5** (0.211 mol.), Compound **7** (0.296 mol.), in DMSO (5 vol.), KOH (0.633 mol.), 70–80 °C, 12–13 h

performed in acetonitrile using pyridine as base at 80–85 °C for 13 h. The isolated yield of lenvatinib was 74% (Table 2).

The solubility of lenvatinib base **1** was poor in water and most of the organic solvents. To get pure form of lenvatinib, purification was attempted under several conditions. Most of the common solvents like DCM, MeOH, IPA, DMF and DMSO didn't increase the purity of the lenvatinib. (Zheng et al. 2020) Finally, purification was tried with a mixture of solvents using DMSO (or) DMF as one of the solvents. Excellent purity of lenvatinib was achieved when the purification was performed using a mixture of DMSO-IPA (1:2.5) (or) DMSO-acetone (1:4).

To increase the solubility of lenvatinib, we converted the free base into its mesylate salt using methane sulfonic acid in IPA (or) methanol. During the preparation of mesylate salt we used one equivalent of methane sulfonic acid which controls the formation of mutagenic alkyl-sulfonate impurities. (Snodin and Teasdale 2015; Snodin et al. 2019).

After the synthesis of mesylate salt of lenvatinib, we focused on the preparation of different salts of lenvatinib. After thorough screening we synthesized four different salts of lenvatinib, i.e., lenvatinib (L)-malate **15**, lenvatinib oxalate **16**, lenvatinib phosphate **17**, lenvatinib citrate **18.** (Fig. 2).

Lenvatinib (L)-malate **15**, lenvatinib oxalate **16** are novel salts and lenvatinib phosphate **17**, lenvatinib citrate **18** are novel polymorphic forms when compared with the literature references.

Lenvatinib phosphate **17** which is a novel polymorphic form having characteristic values 9.7, 11.0, 20.8, 21.6 and 26.6 are different from the reported values 8.1; 11.3; 20.3; 21.5 and 25.8. (Zvatora et al. 2017) Differential Scanning Calorimetry (DSC) was used to measure the melting point of the synthesized salt. The melting point obtained is 185.8–192.9 °C which is different from the reported value 178 °C. The above two techniques confirm the formation of novel polymorph of lenvatinib phosphate salt.

Lenvatinib citrate **18** which is also having novel polymorphic form having characteristic peak values 12.4, 19.0, 22.4 and 29.6 in comparison with the reported values 12.3; 18.9; 21.6 and 29.3. (Zvatora et al. 2017) DSC

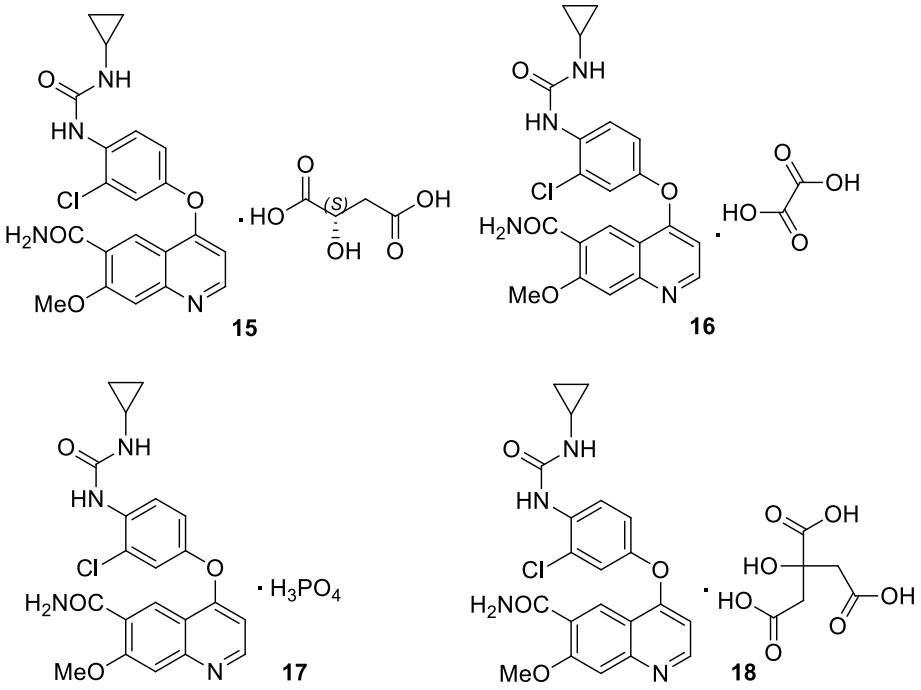


Fig. 2 Structures of novel salts of lenvatinib

thermogram is showing the melting point at 150.9–160.2 which is different from the reported value 227.7–270.0. It confirms the formation of novel citrate salt of lenvatinib.

After synthesizing the citrate and phosphate salts we also synthesized malate **15**, oxalate **16.** These two salts are novel and have high solubility in water compared with citrate and phosphate slats. All the salts were confirmed by their analysis using ^{1}H NMR, PXRD and DSC.

Conclusion

In conclusion, we reported a novel and practically viable process for the synthesis of lenvatinib using 4-nitrophenyl cyclopropylcarbamate. 4-Nitrophenyl cyclopropylcarbamate was identified as a novel intermediate for the synthesis of lenvatinib. This process is scalable with good to excellent yields. Four different salts of lenvatinib were synthesized, analyzed and found that citrate and phosphate salts are having novel polymorphism and other two salts are novel.

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Compliance with ethical standards

Conflict of interest No conflict of interest.

References

Arcari JT, Bhattacharya SK, Brosius AD, Luzzio MJ, Nelson KL, Pan G, Southers JA, Wishka DG, Xiao J (2007) Pyrimidine derivatives for the treatment of abnormal cell growth. WO 2007/072158 A2

Flick AC, Ding HX, Leverett CA, Kyne RE, Liu KKC, Fink SJ, O'Donnell CJ (2017) Synthetic approaches to the new drugs approved during 2015. J Med Chem 60(15):6480–6515. https://doi.org/10.1021/acs.jmedchem.7b00010

Funahashi Y, Tsuruoka A, Matsukura M, Haneda T, Fukuda Y, Kamata J, Takahashi K, Matsushima T, Miyazaki K, Nomoto KI, Watanabe T, Obaishi H, Yamaguchi A, Suzuki S, Nakamura K, Mimura F, Yamamoto Y, Matsui J, Matsui K, Yoshiba T, Suzuki Y, Arimoto I (2007) Nitrogen-containing aromatic derivatives. US 7253286 B2

Gang C (2015) Preparation method of lenvatinib. CN104876864A

Gudisela MR, Bommu P, Navuluri S, Mulakayala N (2018) Synthesis and characterization of potential impurities of dolutegravir: a HIV drug. Chem Sel 3:7152–7155. https://doi.org/10.1002/slct.201800948

Harry F, Monique Bodil VN, Chi-Kit W (2013) Derivatives of 4-hydroxy-1,2,3,4-tetrahedronaphtalen-1yl urea and their use in the treatment of inter alia, diseases of the respiratory treat. WO/2013/083206 A1

Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, Romeo M, Bratos R, Brose MS, DiSimone C, Messing M, Stepan DE, Dutcus CE, Wu J, Schmidt EV, Orlowski R, Sachdev P, Shumaker R, Herraez AC (2020) Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol. https://doi.org/10.1200/JCO.19.02627

Matsushima T, Nakamura T, Yoshizawa K, Kamada A, Ayata Y, Suzuki N, Arimoto I, Sakaguchi T, Gotoda M (2005) Crystal of salt of 4-(3-chloro-4-(cyclopropylamino carbonyl)amino-phenoxy)-7-methoxy-6-quinolinecarboxamide or of solvate thereof and processes for producing these. WO2005063713 A1

Michael JR, Shen-Chu CR, George WM, Hon-Wah M (2003) Isoindole-imide compounds, compositions, and uses thereof. US 20030096841 A1

Naito T, Yoshizawa K (2006) Urea derivative and process for preparing the same. US 7683172

Nakamura T, Abe T, Miyashita Y, Kuroda H, Ayata Y, Akao A (2016) High-Purity Quinoline Derivative And Method For Manufacturing Same. WO2016031841

Onozuka T, Satake S, Tanaka M, Washizaki K (2011) Method for producing 4-nitrophenyl chloroformate. JP2011001330A

Oruganti S, Kandagatla B (2017) Improved process for the preparation of lenvatinib using dimethylformamide as a solvent. Indian Pat. Appl. 201641011188

Rapolu RK, Chavali M, Mulakayala N, Raju VVNKVP (2018) An alternate and scalable process for the synthesis of temozolomide. Heterocycl Lett 8:325–331

Rapolu RK, Areveli S, Raju VVNKVP, Srinivasu N, Mulakayala N (2019) An efficient synthesis of darunavir substantially free from impurities: synthesis and characterization of novel impurities. Chem Sel 4:4422–4427. https://doi.org/10.1002/slct.201803825

Rapolu RK, Chavali M, Raju VVNKVP, Mulakayala N (2019) Novel and environmentally friendly synthesis of pimavanserin (5-HT2A receptor). Asian J Chem 31:723–726

Reddy NVS, Kapoor A, Nath A, Prasad M (2017) Crystalline forms of salts of lenvatinib. WO2017221214A1

Reddy AAK, Bhalerao D, Mahapatra T, Venkateswarlu M, Reddy JR, Elati RC (2019) Process for the preparation of lenvatinib or its salts thereof. WO 2019092625 A1

Sakaguchi T, Tsuruoka A (2006) Amorphous salt of 4-(3-chloro-4-(cyclopropylamino carbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide and process for producing the same. WO2006137474 A1

Scott LJ (2015) Lenvatinib: first global approval. Drugs 75(5):553–560. https://doi.org/10.1007/s40265-015-0383-0

Snodin DJ (2019) Elusive impurities—evidence versus hypothesis. Technical and regulatory update on alkyl sulfonates in sulfonic acid salts. Org Process Res Dev 19(11):1465

Snodin D, Teasdale A (2015) Mutagenic alkyl-sulfonate impurities in sulfonic acid salts: reviewing the evidence and challenging regulatory perceptions. Org Process Res Dev 19(11):1465

Thomas AJ, Kumar BS, Douglas BA, Joseph LM, Louise LK, Gonghua P, Alfred Jr. SJ, Gregory WD, Jun X (2007) Pyrimidine derivatives for the treatment of abnormal cell growth and their preparation WO/2007/072158 A2

Zdenko Č (2020) Synthetic approaches to contemporary drugs that contain the cyclopropyl moiety. Synthesis 52(09):1315–1345

Zheng Z, Hou B, Cheng X, Liu W, Huang X, Bao Y, Wang T, Wanga Z, Hao H (2020) The mechanism of solvent-mediated desolvation transformation of lenvatinib mesylate from dimethyl sulfoxide solvate to form D. Acta Cryst. B76:343–352

Zschäbitz S, Grüllich C (2018) Lenvantinib: a tyrosine kinase inhibitor of VEGFR 1–3, FGFR 1–4, PDGFRα, KIT and RET. Recent Results Cancer Res. 211:187–198. https://doi.org/10.1007/978-3-319-91442-8_13

Zvatora P, Dammer O, Krejcik L, Lehnert P (2017) Salts of lenvatinib. WO2017186197A1