Res Chem Intermed
DOI 10.1007/s11164-015-1939-z

An improved synthesis of sunitinib malate via a solvent-free decarboxylation process

Ge Meng[1] · Chunyan Liu[1] · Shidong Qin[1] · Mengshu Dong[2] · Xiaomi Wei[1] · Meilin Zheng[1] · Liwen Qin[1] · Huihui Wang[1] · Xiaoshuang He[1] · Zhiguo Zhang[1]

Received: 23 October 2014 / Accepted: 27 January 2015
© Springer Science+Business Media Dordrecht 2015

Abstract To search for an economical and convenient synthesis of sunitinib and its malate salt, optimization of a scalable synthetic route was explored by designing a standard experimental protocol on laboratory scale using commercially available materials including acetyl ethyl acetate, 4-fluoroaniline, and N^1,N^1-diethylethane-1,2-diamine. The optimal conditions were established based on investigating the main reaction steps, including cyclization, hydrolysis, decarboxylation, formylation, and condensation, giving optimized yields for each step of 94.4, 97.6, 98.5, 97.1, 91.0, 86.3, 85.5, 88.2, 99.1, 97.3, and 58.7 %, respectively. The synthesis process of 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid as the important intermediate was significantly improved by using solvent-free decarboxylation instead of the traditional process in a high-boiling-point solvent. The subsequent formylation was conducted directly using the dichloromethane solution of the crude product from decarboxylation, leading to an almost quantitative combined yield of these two steps. The overall yields of sunitinib and its salt using the optimal synthesis process were 67.3 and 40.0 % based on acetyl ethyl acetate. The obtained data could be used as reference for future industrialization, especially for avoiding expensive solvents and reducing reaction time.

Electronic supplementary material The online version of this article (doi:10.1007/s11164-015-1939-z) contains supplementary material, which is available to authorized users.

✉ Ge Meng
mengge@mail.xjtu.edu.cn

[1] School of Pharmacy, Health Science Center, Xi'an Jiaotong University, Xi'an 710061, Shaanxi, People's Republic of China

[2] School of Software Engineering, Xi'an Jiaotong University, Xi'an 710049, Shaanxi, People's Republic of China

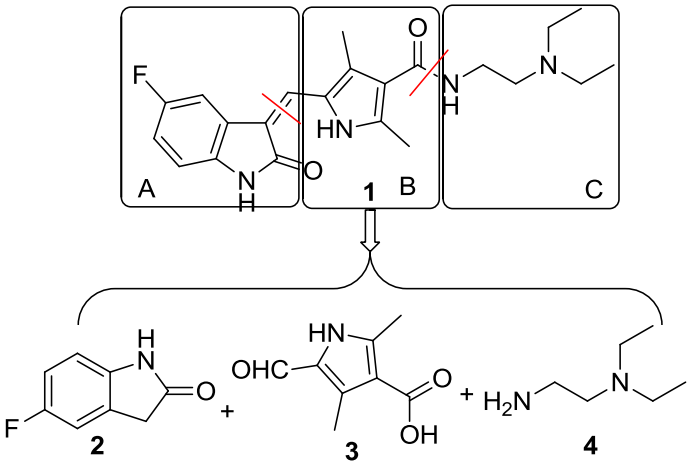
Published online: 05 May 2015

Keywords Sunitinib · SU11248 · Sutent · Synthesis · Optimization · Solvent-free · Standard design

Introduction

Sunitinib (**1**, SU11248, Sutent®, Sugen-Pfizer [1], Scheme 1) was approved by the Food and Drug Administration (FDA) in 2006 for treatment of renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST), and other tumors resistant to imatinib [2]. The basis for its antitumor effect is multikinase inhibition, targeting a variety of kinases [1] including vascular endothelial growth factor receptor (VEGFR)-1 [1], VEGFR-2 [2], platelet-derived growth factor receptor β (PDGFRβ), and FMS-like tyrosine kinase 3 (FLT3) [3] involved in mutated forms of acute leukemia [3]. Having three hydrogen-bond donors and two hydrogen-bond acceptors, sunitinib with molecular weight of 398.5 shows a clogP value of 5.2 [2], nicely satisfying Lipinski's four "rules of five" [4]. These good characteristics make **1** a very promising molecule in many regards, such as for clinical use [2], for synthetic improvements [5, 6], for use as a positron emission tomography (PET) tracer [7], analytically [8], and for the design and synthesis of its derivatives [9].

The structure of **1** can be divided into three portions: A, B, and C (Scheme 1). The 5-fluoroindolin-2-one ring (A) is connected to a substituted pyrrole ring (B) with an attached amino side-chain (C). Retrosynthetic analysis of **1** indicated that synthesis methods for building the target molecule could be divided into the following three categories: "A + (B + C)" [6, 10], "B + A + C," and "(A + B) + C" [6]. All three approaches involve the use of three main materials, namely 5-fluoroindolin-2-one (**2**), 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (**3**) and its derivatives, and N^1,N^1-diethylethane-1,2-diamine (**4**). Since compound **4** is commercially available and synthesis of **2** can be easily achieved



Scheme 1 Retrosynthetic analysis of sunitinib (**1**)

by traditional Sandmeyer isatin synthesis reaction, improvement of the synthesis of **3** has become the crucial element for the synthesis of **1** (Scheme 1).

Although there have been many reports on synthesis of **1** in literature [5, 9], the methods involved share various shortcomings, such as long production period, high production price, tedious manipulations, and expensive reagents and solvents. Therefore, there is an urgent need to develop an optimized protocol suitable for possible industrial application. To enhance the yield and decrease the price of the product, it is still necessary to develop an efficient method to achieve **1** as well as the related intermediates based on the "A + (B + C)" strategy, which seems to be the most favorable for industrialization when comparing the different features of all possible synthetic routes [11].

In this work, we developed a new, efficient solvent-free process to provide the important intermediate **8** in high yield. The product of this process could be used directly in the subsequent step, simplifying the workups during the purification process. The combined yield of these two sequential steps was almost quantitative, greatly benefiting the overall yield of **1**. The reaction time is greatly shortened via use of a rapid decarboxylation process under solvent-free conditions, and expensive high-boiling-point solvents are omitted.

Moreover, other reaction conditions were also modified using a standard design method; this work can be summarized as follows: The yield of the intermediate **6** was improved by strictly controlling the temperature in the addition process of sodium nitrite and zinc powder during the Knorr reaction. The best condition for synthesis of intermediate **7** was optimized by exploring the mole ratio, base concentration, and reaction temperature. For the synthesis method of the building block **10** (B + C), workups for eliminating the main side-product 1,3-dicyclohexylurea (DCU) were explored to enhance the yield of **10**. The synthesis of **2** was optimized via using a short, direct route from intermediate **13**. Finally, different solvents and catalysts were investigated to establish the best conditions to synthesize **1**. The transformation methods from sunitinib to its malate salt were also investigated and optimized in this work.

Results and discussion

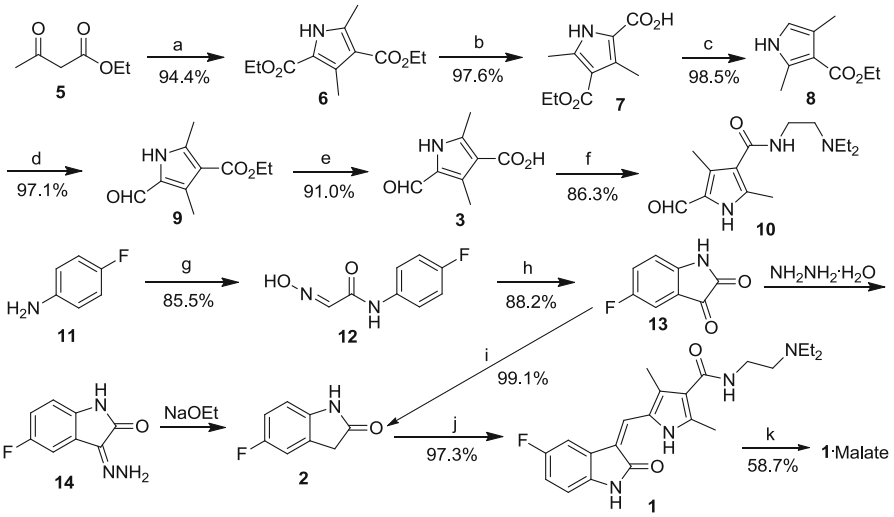
The main important synthons of **1** are parts A and B, i.e., the 5-fluoroindolin-2-one (**2**) and pyrrole part (**3**), respectively. The synthesis of part A included Sandmeyer isonitrosoacetanilide isatin and Wolff–Kishner–Huangminglong reaction. The synthesis of part B included Knorr reaction, monohydrolyzation, decarboxylation, Vilsmeier–Haack (V–H) reaction, and hydrolyzation, which were explored one by one to search for good conditions to achieve higher yield and a convenient process for each unit reaction. The results are discussed below.

For the synthesis of the substituted pyrrole part intermediates, diethyl-3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**6**) was first obtained via Knorr reaction from acetyl acetate ethyl ester (**5**). Monohydrolyzation of **6** provided 4-(ethoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**7**) as the intermediate. Direct heating of **7** under N_2 atmosphere provided ethyl 2,4-dimethyl-1*H*-pyrrole-3-

carboxylate (**8**). Formylation of **8** via Vilsmeier–Haack reaction gave ethyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**9**). Further hydrolyzation of **9** in basic condition produced 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (**3**) as the important intermediate to **1** (Scheme 2).

Compound **8** is usually obtained by heating in a suitable solvent with high boiling point, such as dimethylformamide (DMF), triethyl phosphate (TEP). All these methods share the shortcomings of difficult recovery and removal of the higher-boiling-point solvent, tedious workups, as well as low yield. To solve this problem, we used a solvent-free process to achieve this purpose successfully with a very high yield to afford **8** from **7**, which has not been reported before. Besides, ethyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**9**) could also be obtained from **7** via a sequential semi-one-pot reaction without further purification of **8**, offering a quantitative yield for the combination of these two reaction steps (Scheme 2).

During the synthesis process of diethyl-3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**6**), it should be noted that keeping the temperature between 0 and 10 °C was crucial for a rapid and clean reaction. Portionwise addition of zinc powder was also necessary to keep the temperature between 25 and 30 °C to prevent the evolution of a large amount of hydrogen gas in a very short time, which could result in an uncontrollable boiling reaction. Mechanical stirring should be adopted in large-scale processing for better mixing effect.



Scheme 2 Synthesis route for sunitinib (**1**) malate via "A + (B + C)" method. Reagents and conditions: (*a*) (i) $NaNO_2$, AcOH, 0–10 °C; (ii) AcOH, Zn, 25–30 °C, reflux for 1 h; (*b*) (i) KOH, 50–60 °C, (ii) ice-water, HCl (2.0 mol/L), pH 4; (*c*) 200–202 °C, solvent-free; (*d*) DMF/$POCl_3$ with DCM at 0 °C, reflux, 1.5 h, 40–41 °C and then NaOH, reflux, 0.5 h; (*e*) Reflux, 82–83 °C, NaOH, 4.5 h, HCl (2.0 mol/L), pH 2; (*f*) DMF (anhy.), 0 °C, DCC/DCM, DMAP, *N*,*N*-diethylethylenediamine (**4**), r.t., 59 h, citric acid (5.0 %), NaOH, $NaHCO_3$; (*g*) $CCl_3CH(OH)_2$, Na_2SO_4, $NH_2OH{\cdot}HCl$, HCl (conc.), 65 °C, 2 h; (*h*) H_2SO_4 (conc.), 50 °C, 75 °C, 20 min; (*i*) NH_2NH_2 (80 %), 140 °C, 6 h, HCl (2.0 mol/L), pH 2; (*j*) Compound **10**, toluene/piperidine, reflux, 3 h; (*k*) Malic acid, MeOH, CH_3CN

Regarding synthesis of 4-(ethoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**7**), the reported method is reflux of **6** in ethanol and sodium hydroxide. Double hydrolyzation of the diethyl ester might also occur in this basic condition [12]. The results of standard experimental design indicated that the mole ratio of **6** to KOH, concentration of the base in water, stirring method, temperature, and reaction time were crucial factors determining the final yield and quality of **7** (Table 1).

The best mole ratio of diethyl-3,5-dimethyl-1*H*-pyrrole-2,4-dicarboxylate (**6**) to potassium hydroxide to achieve **7** was 2:5 (Table 1). The best basic concentration was 0.83 mol/L with mechanical stirring. The best reaction temperature was 50–60 °C with shorter reaction time of 10 h (entry 8).

For the decarboxylation process from 4-(ethoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**7**) to synthesize ethyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**8**), the available reported method is reflux of **7** in a solvent with high boiling point, such as triethyl phosphate (TEP) [13], *N*,*N*-dimethylformamide (DMF) [14]. Since TEP is very difficult to evaporate because of its high boiling point (216 °C), the related workups usually require an extraction and then column chromatography. The extracted liquid is liable to emulsify and then exhibit a very dark color, leading to a tedious separation process that is almost impossible to manipulate. The yield is also very low (less than 50 %). The reaction via reflux of **7** in DMF might last more than 1 day (30 h). The workup manipulations also require an extraction and column chromatography, resulting in relatively low yield. Therefore, the shortcomings of both method 1 and 2 are only too obvious for use in possible industrial applications. Although the product from method 3 was very dark, after being decolorized with active carbon, the product could be used directly in the next step of V–H formylation. Sufficiently high product purity was obtained by simply dissolving in absolute dichloromethane to elevate the overall yield of sunitinib significantly. On the other hand, dissolving the product **8** in dichloromethane for direct use in the subsequent formylation offers potential for large-scale processing as the dissolution process would be helpful for collecting **8** spread on the surfaces of the walls of a reaction container.

Method 3 was the best among the three tested decarboxylation processes. The solvent-free condition offers many advantages over the other two methods due to the shorter reaction time, energy efficiency, easy manipulation and workups, as well as high yield (98.0 %) (Table 2).

During the process of synthesizing ethyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**9**), it was crucial to control the reaction temperature below 0 °C using a salt-ice bath to avoid formation of dark-colored polymers leading to subsequent tedious workups. Evaporation under vacuum after completion was also necessary to eliminate dichloromethane and DMF, ensuring that the subsequent reaction system was homogeneous after addition of aqueous sodium hydroxide solution to ensure complete hydroxylation. Otherwise, the reaction system might get bumped, since the possibility of formation of a heterogeneous system is not favorable for large-scale synthesis processing, resulting in expensive economic loss.

Since both **9** and 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (**3**) share a common aldehyde group in 5-position of the pyrrole skeleton, which might be

Table 1 Yield of compound **7** for different reaction conditions

Entry	**6**:KOH (mol:mol)	C_{base} (mol/L)	Stirring method	Temperature	Time (h)	Yield (%)	M.p. (°C)	Notes
1	2:5	1.67	Magnetic	Refluxing	1.5	88.1	189–191	Many side-products formed[a]
2	2:4	1.33	Magnetic	Refluxing	1.5	90.5	173–175	Many side-products formed;[a] compound **3** did not fully react
3	2:5	1.25	Magnetic	50–60 °C	36.5	52.4	185–188	Fully reacted
4	2:4	1.00	Magnetic	50–60 °C	36.5	73.8	187–189	Small amount of compound **3** did not fully react
5	2:5	1.25	Magnetic	65–70 °C	24	66.7	[b]	Reaction completed
6	2:6	1.2	Magnetic	65–70 °C	10	66.4	185–188	Double-hydrolyzed product also formed
7	2:7	1.4	Magnetic	65–70 °C	10	68.7	191–195	Double-hydrolyzed product also formed
8	2:5	0.83	Mechanical	50–60 °C	10	97.6	169–170	Almost no side-products formed
9	2:5	2.50	Magnetic	50–60 °C	5.3	83.3	173–176	Many side-products formed[a]
10	2:5	3.03	Magnetic	50–60 °C	5.3	88.1	178–180	Many side-products formed[a]
11	2:5	2.00	Magnetic	50–60 °C	6	88.1	178–181	Few side-products formed[a]
12	2:5	1.52	Magnetic	50–60 °C	6	92.9	172–174	Few side-products formed[a]
13	2:5	1.00	Magnetic	50–60 °C	7.3	92.9	174–176	Few side-products formed[a]
14	2:5	1.28	Magnetic	50–60 °C	7.3	97.6	177–178	Few side-products formed[a]

[a] Side-products were shown by thin-layer chromatography (TLC) analysis

[b] The compound turned gray at 200 °C, and black and gray at 215 °C, then began to sublime slowly

Table 2 Yield of compound **8** for different reaction conditions

Method	Reaction condition	Reaction temperature (°C)	Time	Yield (%)	M.p. (°C)
Method 1	Using TEP (b.p. 216 °C)	170–180	1.5 h	47.6	71–72
Method 2	Using DMF (b.p. 153 °C)	164–170	30 h	68.4	73–74
Method 3	Solvent-free condition	200–202	5 min	98.0	73–74

oxidized, the process for synthesis of **3** should be done under N_2 atmosphere. Double hydrolyzation, as in the reaction of the substrate **6**, cannot occur, as there is only one ethyl ester group in **9**. Therefore, simply refluxing in aqueous sodium hydroxide might be an easy way to achieve **3**.

For synthesis of *N*-(2-(diethylamino)ethyl)-5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (**10**), attempting to transform acid **3** to its acid chloride before reacting with **4** could not provide the desired amide **10**. The reaction via DCC condensation should be conducted in anhydrous condition. The DCU formed from DCC is usually difficult to remove, as all the reported methods do not work very well, especially for full elimination of side-products [13]. Although the amide formation reaction could not happen at r.t. without a catalyst, attempting to react at r.t. with DMAP catalyst worked very well for both a small amount and in a large-scale reaction. Elimination of DCU was successfully achieved by the procedures designed in the following. The residue was washed with a large amount of aqueous citric acid solution (5.0 %) to ensure **10** entered the aqueous phase completely, with monitoring of the organic layer sample by TLC analysis. The aqueous layer was adjusted to pH 8 using aqueous sodium bicarbonate and sodium hydroxide solution, which was extracted with dichloromethane to give the organic phase, concentrated under vacuum to give the desired product **10** as pale-yellow solid.

Many methods to synthesize the intermediate *N*-(4-fluorophenyl)-2-(hydroxyimino)acetamide (**12**) have been reported, among which the Sandmeyer isonitrosoacetanilide isatin synthesis remains the best choice [15]. The reaction was explored in terms of the mole ratio of the main materials, reaction temperature, and time (Table 3).

During the cyclization process from **12** to **13** in H_2SO_4 (conc.), the temperature should be controlled strictly around 75 °C. The reaction cannot occur below 50 °C. Too many side-products were produced above 80 °C according to TLC analysis. Adjusting pH of 2–4 could be an efficient way to purify **13**, although crude **13** could be used directly in the next step.

Synthesis of 5-fluoroindolin-2-one (**2**) could be achieved by two different methods. Refluxing **13** in hydrazine hydrate (80 %) afforded 5-fluoro-3-hydrazonoindolin-2-one (**14**) in high yield, which reacted with sodium ethoxide to give **2** with very low yield. On the other hand, direct reflux of **13** in hydrazine hydrate (80 %) for a relatively long time provided **2** via Wolff–Kishner–Huangminglong reaction. Although the reaction time was very long, the workups were relatively simple with elevated yield compared with the two-step method. Based on the

Table 3 Yield of compound **12** for different conditions

Method	Mole ratio[a]	Reaction conditions	Notes
Method I	1.1:21.8:1:3	Reflux for 3 min	Large amounts of sodium sulfate left in the residue; product was not very pure, as shown by a m.p. different from literature
Method II	1.1:18.3:1:3	React at 65 °C for 2 h	Large amounts of sodium sulfate left in the residue; the product purified from recrystallization showed a m.p. in agreement with literature
Method III	1.1:11.2:1:3.2	React at 60–70 °C for 2 h	No sodium sulfate left in the residue; the product was not very pure, as shown by a m.p. different from literature
Method IV	1:10.6:1:3.3	Reflux for 3 min	No sodium sulfate left in the residue; the product was not very pure, as shown by a m.p. different from literature

[a] Mole ratio refers to the ratio of chloral hydrate/anhydrous sodium sulfate/4-fluoroaniline/hydroxylamine hydrochloride

Table 4 Yield of compound **2** under different conditions

Method	Reaction temperature (°C)	Reaction time (h)	Notes
Method I	140	8	Many black impurities in the yellow product **2**
Method II	140	6	Yellow product **2** was pure, as shown by TLC analysis
Method III	145	6	Many black impurities in the yellow product **2**
Method IV	120	6	Reaction not complete, as shown by TLC analysis

superior one-step method, the effects of temperature and reaction time on the yield of **2** were investigated by a standard design (Table 4).

The suitable reaction time for synthesis of **2** should be no more than 6 h. Some black side-products were produced when the reaction proceeded for more than 8 h, which might decrease the yield. The suitable temperature range should be 130–140 °C. The reaction cannot complete below 120 °C. The higher the temperature, the blacker the color of the side-products (Table 4).

The traditional Knoevenagel reaction was used for the final condensation between **2** and **10** to provide (*Z*)-*N*-(2-(diethylamino)ethyl)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1*H*-pyrrole-3-carboxamide (**1**, sunitinib). It was established by our research group that slight excess of 5-fluoroindolin-2-one should be used during the condensation process to facilitate the final workups to purify the product **1**. The effects of different solvents and catalysts as well as reaction time on the yield of the final product were investigated (Table 5). The high, sharp m.p. (222–223 °C) of the obtained product **1** indicated that the product was very pure, showing a different polymorphic form to the original form reported in literature (195–197 °C).

It was clearly seen that toluene could be used as the best solvent to achieve the highest yield without using column chromatography as the purification method.

Table 5 Yield of compound **1** under different conditions

Method	Solvent	Catalyst	Time (h)	Yield (%)	M.p. (°C)
Method I	Absolute ethanol[a]	Triethylamine (pK_a 11.02)	2	62.9	223–224
Method II	Absolute ethanol[a]	Piperidine (pK_a 11.12)	3	85.7	224–225
Method III	Toluene	Piperidine (pK_a 11.12)	3	97.3	222–223

[a] When ethanol was used as solvent, the product **1** might dissolve in ethanol. Purification of the product requires column chromatography, which is not suitable for industrial purposes

Since **1** is insoluble in toluene, there was almost no product **1** left after filtration except for unreacted **2**. The purification could be easily manipulated by simply washing with cold solvent. The results indicate that piperidine was better than triethylamine as an organic basic catalyst.

Since ether is not a suitable solvent for industrial purposes [16], two different methods using other solvent systems were investigated for the saltification process of sunitinib (**1**) with malic acid. The results showed that methanol and acetonitrile were superior to ethanol for higher yield and simple workups.

Experimental

All materials were obtained from commercial suppliers and used as received. Melting points were taken on an X-1 digital melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nicolet FT-IR 360 spectrophotometer. ^{1}H nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AM-300 (400 MHz) spectrometer with tetramethylsilane (TMS) as internal standard; chemical shifts are reported in δ. Mass spectra were measured on a HP5988A instrument by direct inlet at 70 eV.

General procedures for the target molecule and intermediates

*Diethyl-3,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (**6**)* Ethyl 3-oxobutanoate (**5**, 30.0 mL, 236.0 mmol) and acetic acid (60.0 mL) were mixed in a flask. The mixture was cooled down to 0–10 °C with an ice-water bath, and then aqueous solution of sodium nitrite (12.0 mL, 9.8 mol/L) was added under stirring in 30 min, while keeping the temperature below 10 °C. The reaction mixture was allowed to rise to r.t. for 2.5 h before adding zinc powder (15.4 g, 236.0 mmol) portionwise. The temperature should be kept between 25 and 30 °C during the process of zinc addition. The reaction mixture was then heated to reflux for 1.0 h, until the reaction was completed according to TLC monitoring. The mixture was then poured into ice-water (400 mL) to form large amounts of yellow solids. After cooling in a refrigerator for 2–3 h to allow complete precipitation, the solids were collected by filtration and washed with ice-water, and dried under vacuum to provide the yellow solids as the crude product **6** (6.70 g, 94.4 %), which was recrystallized from

ethanol to afford the pure product **6** with yield of 93.0 % [12], m.p. 133–134 °C (*lit.* 135–136 °C [17, 18]), yield 60.0 % (*lit.* [13]). $R_f = 0.20$ (eluent: petroleum ether/ethyl acetate, v/v = 20:1, three times), $R_f = 0.27$ (eluent: chloroform/methanol, v/v = 10:1). ^{1}H NMR ($CDCl_3$), δ: 1.35–1.39 (m, 6H, $2CH_3$), 2.52 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 4.27–4.35 (m, 4H, $2CH_2$), 9.23 (s, 1H, N*H*-pyrrole).

*4-(Ethoxycarbonyl)-3,5-dimethyl-1H-pyrrole-2-carboxylic acid (**7**)* Compound **6** (0.48 g, 2.0 mmol) was added into a flask equipped with a stirrer, a thermometer, and a condenser; absolute ethanol (3.0 mL) was added into the flask until partially dissolving. Aqueous solution (6.0 mL) of potassium hydroxide (0.28 g, 5.0 mmol) was added under mechanical stirring, being kept at 50–60 °C for 10 h with monitoring by TLC (eluent: chloroform/methanol, v/v = 10:1) until reaction completion. The reaction was then stopped by cooling down to r.t. The reaction mixture was poured into ice-water (20 mL) to form an aqueous solution. A small amount of insoluble substance was filtered under vacuum and was washed with water (20 mL). The combined aqueous layers were adjusted with hydrochloride (2 mol/L) to pH 4 to afford some white precipitates, which were collected via filtering and washing with ice-water to provide **7** (0.41 g, 97.6 %), m.p. 169–170 °C (*lit.* 235–236 °C [13]), yield 85.3 % (*lit.* [13]). $R_f = 0.41$ (eluent: chloroform/methanol, v/v = 10:1). ^{1}H NMR (DMSO-d_6) δ: 1.25 (t, 3H, $J = 7.2$ Hz, CH_3), 2.38 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.15 (q, 2H, $J = 7.2$ Hz, CH_2), 11.70 (s, 1H, N*H*-pyrrole), 12.34 (s, 1H, COO*H*).

*Ethyl 2,4-dimethyl-1H-pyrrole-3-carboxylate (**8**)* 4-(Ethoxycarbonyl)-3,5-dimethyl-1*H*-pyrrole-2-carboxylic acid (**7**, 5.0 g, 25.0 mmol) was heated in a flask to 200–210 °C with an oil bath for 12 min. The reactant gradually melted with accompanying production of carbon dioxide. The heating was removed when there was no more gas evolving. The reaction was allowed to cool down to r.t. and then dried under vacuum to afford **8** as a pale-gray solid (3.90 g, 98.5 %), m.p. 75–76 °C (*lit.* 74–76 °C [17]), yield 90.0 % (*lit.* [13]). $R_f = 0.73$ (eluent: chloroform/methanol, v/v = 10:1).

*Ethyl 5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxylate (**9**)* Anhydrous DMF (2.0 mL, 24.4 mmol) in a dry flask was precooled to 0 °C with a salt-ice bath, into which a solution of $POCl_3$ (3.60 mL, 39.1 mmol) in anhydrous dichloromethane (8.2 mL) was added slowly dropwise. The temperature should be kept below 3 °C during the whole addition process. The reaction mixture was stirred for 0.5 h using an ice-bath before dropwise addition of solution of ethyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**8**) in anhydrous dichloromethane (10.0 mL, 2.27 mol/L). The mixture was heated under reflux for 1.5 h before evaporating the excess dichloromethane from the system. Aqueous sodium hydroxide (52.0 mL, 2.81 mol/L) was then added before further reflux for 0.5 h. While cooling to r.t., a large amount of pale-gray solid appeared from the system. The solid was filtrated and washed with a small amount of cold water, and dried under vacuum to afford **9** (4.5 g, 100 %), m.p. 163–164 °C (*lit.* 166–167 °C [19]), yield 91.5 % (*lit.* [13]). $R_f = 0.71$ (eluent: chloroform/methanol, v/v = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$)

δ: 10.71 (s, 1H, C*H*O), 9.61 (s, 1H, pyrrole-1-*H*), 4.31 (q, 2H, CH_3CH_2O), 2.58 (m, 6H, 2 × (CH_3)), 1.38 (t, 3H, J = 8.0 Hz, CH_3CH_2O).

*5-Formyl-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (**3**)* To a three-necked flask equipped with a thermometer, ethyl 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**9**, 1.17 g, 6.0 mmol) and methanol (6.0 mL) were added with stirring, to which was added solution of sodium hydroxide (1.20 g) in water (10 mL). The reaction mixture was kept under reflux at 82–83 °C for 4.5 h under nitrogen atmosphere. The mixture was then cooled down to r.t. before being added into ice-water (20 mL). The obtained mixture was extracted with dichloromethane (12 mL). The organic layer was then washed with water (15 mL × 3) until there was no absorption under ultraviolet (UV) light. The aqueous layers were combined before being acidified with hydrochloride (2.0 mol/L) to pH 2 until many precipitates appeared from the mixture. The yellowish solids were obtained via filtrating under vacuum, washing with water, and drying under vacuum to provide **3** (0.91 g, 91 %), m.p. >250 °C (sublimes and decomposes) (*lit.* 275–277 °C [13]), yield 90.0 % (*lit.* [13]). R_f = 0.28 (eluent: chloroform/methanol, v/v = 10:1 or petroleum ether/ethyl acetate, v/v = 10:1). Electrospray ionization (EI) mass spectroscopy (MS) *m*/*z* (%): 167.1 ($[M]^+$, 100), 138.1 (20), 121.1 (60). ^{1}H NMR (DMSO-d_6) δ: 1.35 (t, 3H, J = 7.3 Hz, CH_3), 2.53 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 4.29 (q, 2H, J = 7.3 Hz, CH_2), 7.24 (s, 1H, pyrrole-1-N*H*), 9.97 (s, 1H, C*H*O).

*N-(2-(Diethylamino)ethyl)-5-formyl-2,4-dimethyl-1H-pyrrole-3-carboxamide (**10**)* To a three-necked flask equipped with a thermometer, 5-formyl-2,4-dimethyl-1*H*-pyrrole-3-carboxylic acid (**3**, 5.50 g, 32.7 mmol) and anhydrous DMF (13.1 mL) were added while being cooled down to 0 °C with an ice-salt bath. To the above mixture was added dropwise a solution of dicyclohexylcarbodiimide (DCC, 10.13 g, 49.0 mmol) in dichloromethane (78.4 mL) under stirring while keeping the reaction temperature between 0 and 2 °C, to which were then added at r.t. 4-dimethylaminopyridine (DMAP, 1.65 g) and N^1,N^1-diethylethane-1,2-diamine (**4**, 5.03 mL, 35.9 mmol). The reaction mixture was then allowed to react at r.t. for 59 h with TLC monitoring (eluent: chloroform/methanol, v/v = 5:1). The filtrate obtained from filtration was added with water, which was extracted with dichloromethane (15 mL × 3). The organic layers were combined, washed with saturated brine (65.7 mL), then dried over anhydrous sodium sulfate. The filtrate was concentrated to give some solids, which were dissolved in a small amount of dichloromethane (5.0 mL). The obtained organic phase was washed with aqueous citric acid solution (5.0 %, 330 mL × 3) until there was no product in the organic layer (as monitored by TLC). The reason was that the weak basic product **10** could form a water-soluble salt with citric acid. The aqueous phase was then basified with saturated aqueous sodium hydroxide solution and a large amount of aqueous sodium bicarbonate solution to pH 8, which was then extracted with dichloromethane (330 mL × 3). The combined organic layers were combined and concentrated to provide brownish-red oily liquid. Further purification could be achieved with stepwise column chromatography with petroleum ether/ethyl acetate eluent (v/v = 3:1 to 1:1) to provide **10** as yellowish solid (8.11 g, 86.3 %), m.p. 153–154 °C

(*lit.* 177–181 °C [13]), yield 42.5 % (*lit.* [13]). $R_f = 0.60$ (eluent: chloroform/methanol, v/v = 5:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.85 (s, 1H, N*H*), 9.54 (s, 1H, C*H*O), 7.36–7.38 (t, 1H, CON*H*), 3.24–3.29 (m, 2H, NHCH_2), 2.50–2.56 (m, 6H, 3 × (N–CH_2)), 2.32 (s, 3H, 4-CH_3), 2.37 (s, 3H, 2-CH_3), 0.95–0.99 (t, 6H, 2 × (CH_3)).

*N-(4-Fluorophenyl)-2-(hydroxyimino)acetamide (**12**)* To a three-necked flask equipped with a thermometer were added chloral hydrate (4.55 g, 27.5 mmol) and water (120 mL) with stirring until chloral hydrate dissolved completely. Sodium sulfate (65.0 g, 457.7 mmol) was added into the mixture with full stirring, to which was added 4-fluoroaniline (**11**, 2.43 mL, 25.0 mmol) until the mixture was milky white. Hydroxylamine hydrochloride (5.20 g, 75.0 mmol) was added to the mixture. After the solution became clear, hydrochloride (conc., 1.1 mL) was then added at r.t. with stirring. The reaction mixture was heated under 65 °C for 2 h. The solution turned milky white with precipitation of white crystals, which were collected by filtration and washing with water. Yellow powders containing white and granular-like solids were obtained after drying under vacuum. The solid was dissolved in ethyl acetate, which was filtered to eliminate the insoluble inorganic sodium sulfate. The filtration was stood overnight until some crystals precipitated from the solution system. Pale-yellow crystal was obtained by filtering and drying as the desired product **12** (3.15 g), m.p. 161–164 °C (*lit.* 160 °C [15], 158–159 °C [20]), yield 87.9 % (*lit.* [21]). Small amount of hexane (about 1.0 mL) was added into the filtration until another portion of **12** was obtained as yellow solids (0.74 g), m.p. 158–160 °C. The total amount of **12** thus reached 3.89 g with yield of 85.5 %. $R_f = 0.56$ (eluent: chloroform/methanol, v/v = 10:1).

*5-Fluoroindoline-2,3-dione (**13**)* To a flask equipped with a thermometer, sulfuric acid (conc., 3.26 mL) was added under 50 °C in a water bath. *N*-(4-fluorophenyl)-2-(hydroxyimino)acetamide (**12**, 0.75 g, 4.11 mmol) was added portionwise to the mixture under stirring. The reaction mixture was heated to 75 °C for 20 min, then cooled down to r.t. before being poured into ice-water (10 mL). The mixture was kept in an ice bath for 1 h; the precipitated brownish solid was collected by filtration. The filter cake was washed with water until pH 7 to provide **13** as brownish solid (0.60 g, 88.2 %), m.p. 223–226 °C (*lit.* 228–229 °C [13]), yield 92.6 % (*lit.* [21]). $R_f = 0.52$ (eluent: chloroform/methanol, v/v = 20:1). ^{1}H NMR (DMSO-d_6) δ: 6.89–6.93 (m, 1H, aryl-6-*H*), 7.39-7.49 (m, 2H, aryl-4,7-*H*), 11.05 (s, 1H, N*H*-indole).

*5-Fluoroindolin-2-one (**2**)* To a flask equipped with a thermometer were added 5-fluoroisatin (**13**, 4.60 g, 27.9 mmol), hydrazine hydrate (80 %, 19.3 mL, 386 mmol), and water (19.3 mL) with full stirring. The reaction mixture was kept at 140 °C in an oil bath for 6 h before cooling down to r.t., to which was added hydrochloride (2.0 mol/L) to pH 2. The reaction mixture was stirred at r.t. for 12 h. Brownish-gray solid was obtained by filtering under vacuum and washing with water as the first portion of compound **2** (2.59 g), m.p. 131–133 °C. Some solid was recovered from the filtration via extracting with ethyl acetate (30 mL × 3) then evaporating to give the second portion of compound **2** (1.58 g), m.p. 134–135 °C

(*lit.* 134–135 °C [21]). The total amount of **2** was 4.17 g with yield of 99.1 % (*lit.* yield 80.8 % [21]). $R_f = 0.51$ (eluent: petroleum ether/ethyl acetate, v/v = 3:1). ^{1}H NMR (DMSO-d_6) δ: 3.49 (s, 2H, 3-CH_2), 6.76–6.79 (m, 1H, aryl-6-*H*), 6.96–7.01 (m, 1H, aryl-4-*H*), 7.08–7.10 (m, 1H, aryl-7-*H*), 10.36 (s, 1H, N*H*-indole).

*(Z)-N-(2-(Diethylamino)ethyl)-5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carboxamide (**1**, sunitinib)* To a flask equipped with a condenser were added **10** (0.50 g, 1.89 mmol), **2** (0.32 g, 2.08 mmol), and toluene (8.0 mL). The mixture was stirred to be fully dissolved before addition of a drop of piperidine with stirring. The mixture was heated to reflux for 3 h before cooling down with an ice-bath. The precipitates were collected by filtration. The filter cake was washed with petroleum ether and dried under vacuum to give the free base of the desired target molecule **1** as orange–yellow solid (0.73 g, 97.3 %), m.p. 222–223 °C (*lit.* 195–197 °C [13]), yield 90.0 % (*lit.* [13]). $R_f = 0.24$ (eluent: chloroform/methanol, v/v = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.69 (s, 1H, N*H*-pyrrole), 10.90 (s, 1H, N*H*-indole), 7.75–7.78 (m, 1H, CON*H*), 7.72 (s, 1H, alkenyl-*H*), 7.43–7.46 (m, 1H, aryl-7-*H*), 6.90–6.95 (m, 1H, aryl-4-*H*), 6.83–6.86 (m, 1H, aryl-6-*H*), 3.26–3.31 (m, 2H, NHCH_2), 2.51–2.57 (m, 6H, 3 × (N-CH_2)), 2.43 (s, 3H, pyrrole-2-CH_3), 2.44 (s, 3H, pyrrole-4-CH_3), 0.96–1.00 (t, 6H, 2 × (CH_3)); EI MS *m*/*z* (%): 398.1 ([M]$^+$, 5), 326.1 (2), 283.0 (4), 149.1 (8), 86.1 (100); the purity of sunitinib was 99.5 %.

*Sunitinib malate (**1**·malate)* To a flask were added sunitinib (**1**, 0.131 g, 0.331 mmol) and methanol (20.0 mL) with stirring, to which was added (2*S*)-hydroxysuccinic acid (0.047 g, 0.351 mmol) under stirring. The solid dissolved rapidly to afford clear pale-yellow solution. The methanol was evaporated under vacuum. The residue was added with acetonitrile (5.0 mL) and kept stirring under refluxing for 10 min. Yellow precipitates were obtained via filtration under vacuum to provide sunitinib malate (**1**·malate, 0.103 g, 58.7 %) as orange–yellow crystals, m.p. 200–201 °C (*lit.* 196 °C [21]), yield 86.0 % (*lit.* [21]). ^{1}H NMR (DMSO-d_6) δ: 1.19 (t, 6H, 2 × (CH_3)), 2.45 (s, 3H, pyrrole-2-CH_3), 2.47 (s, 3H, pyrrole-4-CH_3), 3.07–3.09 (m, 6H, 3 × (N-CH_2)), 3.54 (m, 2H, NHCH_2), 4.10 (q, 1H, malic acid-CH), 6.84–6.87 (m, 1H, aryl-6-*H*), 6.92–6.95 (m, 1H, aryl-4-*H*), 7.75 (s, 1H, aryl-7-*H*), 7.77 (m, 1H, alkenyl-*H*), 7.79 (dd, 1H, CON*H*), 10.94 (s, 1H, N*H*-indole), 13.75 (s, 1H, N*H*-pyrrole); the purity of sunitinib malate was 98.2 %.

Conclusions

Sunitinib malate was synthesized from commercially available materials through an 11-step reaction synthetic route with improved overall yield of 40.0 % (based on **5**). The best conditions for each reaction of the synthesis route were established via the designed investigational research. The synthesis of the important intermediate **3** was significantly improved by using a solvent-free decarboxylation process. By avoiding expensive solvents, these processes with shorter reaction time might be beneficial for possible industrial purposes. Direct use of intermediate **8** in the formylation

process without purification enhanced the yield of the intermediate **9** as well as the overall yield of the final product **1**.

Acknowledgments The authors would like to thank the Returned Overseas Chinese Scholars, State Education Ministry (SRF for ROCS, SEM), P.R. China (JWSL 20101561) and Technology Research and Development Program of China, International Cooperation (2013KW31-04) for financial support. The research work has also been sponsored by the National Undergraduate Innovative Experiment Program (2012).

References

1. F. Musumeci, M. Radi, C. Brullo, S. Schenone, J. Med. Chem. **55**(24), 10797–10822 (2012)
2. R. Roskoski Jr, Biochem. Biophys. Res. Commun. **356**(2), 323–328 (2007)
3. S. Schenone, C. Brullo, M. Botta, Curr. Med. Chem. **15**(29), 3113–3132 (2008)
4. C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, Adv. Drug Del. Rev. **46**(1–3), 3–26 (2001)
5. J.M. Manley, M.J. Kalman, B.G. Conway, C.C. Ball, J.L. Havens, R. Vaidyanathan, J. Org. Chem. **68**(16), 6447–6450 (2003)
6. L. Sun, C. Liang, S. Shirazian, Y. Zhou, T. Miller, J. Cui, J.Y. Fukuda, J.-Y. Chu, A. Nematalla, X. Wang, H. Chen, A. Sistla, T.C. Luu, F. Tang, J. Wei, C. Tang, J. Med. Chem. **46**(7), 1116–1119 (2003)
7. J.Q. Wang, K.D. Miller, G.W. Sledge, Q.H. Zheng, Bioorg. Med. Chem. Lett. **15**(19), 4380–4384 (2005)
8. K. Sidoryk, M. Malinska, K. Bankowski, M. Kubiszewski, M. Laszcz, M. Bodziachowska-Panfil, M. Kossykowska, T. Giller, A. Kutner, K. Wozniak, J. Pharm. Sci. **102**(2), 706–716 (2013)
9. K. Lv, L.L. Wang, M.L. Liu, X.B. Zhou, S.Y. Fan, H.Y. Liu, Z.B. Zheng, S. Li, Bioorg. Med. Chem. Lett. **21**(10), 3062–3065 (2011)
10. R. Vaidyanathan, V.G. Kalthod, D.P. Ngo, J.M. Manley, S.P. Lapekas, J. Org. Chem. **69**(7), 2565–2568 (2004)
11. Z. Fang, P. Wei, Z. Yang, Chin. J. Pharm. **38**(11), 822–824 (2007)
12. G. Meng, M.-L. Zheng, M. Wang, Org. Prep. Proced. Int. **43**(3), 308–311 (2011)
13. B. Liu, R. Lin, J. Liao, Z. Li, K. Chen, Chin. J. Pharm. **38**(8), 539–542 (2007)
14. Z. Fang, Z. Yang, S. Bao, W. Wang, P. Wei, Huaxue Shiji **32**(1), 82–84 (2010)
15. V.Q. Yen, N.P. Buu-Hoi, N.D. Xuong, J. Org. Chem. **23**(12), 1858–1861 (1958)
16. K. Lv, Y. Du, D. Zhao, Z. Zheng, S. Li, Chinese. J. Med. Chem. **19**(2), 116–119 (2009)
17. R.A. Schnettler, R.C. Dage, J.M. Grisar, U.S. Patent 4560700, 24 Dec 1985
18. J.V. Cooney, E.J. Beal, R.N. Hazlett, Org. Prep. Proced. Int. **15**(4), 292–295 (1983)
19. P. Tang, T.A. Miller, X. Li, L. Sun, C.C. Wei, S. Shirazian, C. Liang, T. Vojkovsky, A.S. Nematala, M. Hawley, ed. WO (US, 2002)
20. K.C. Joshi, V.N. Pathak, S.K. Jain, Pharmazie **35**(11), 677–679 (1980)
21. X. Dong, F. Zhou, R. Wen, Chinese. J. Med. Chem. **18**(1), 28–31 (2008)