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New and Practical Synthesis of Gedatolisib

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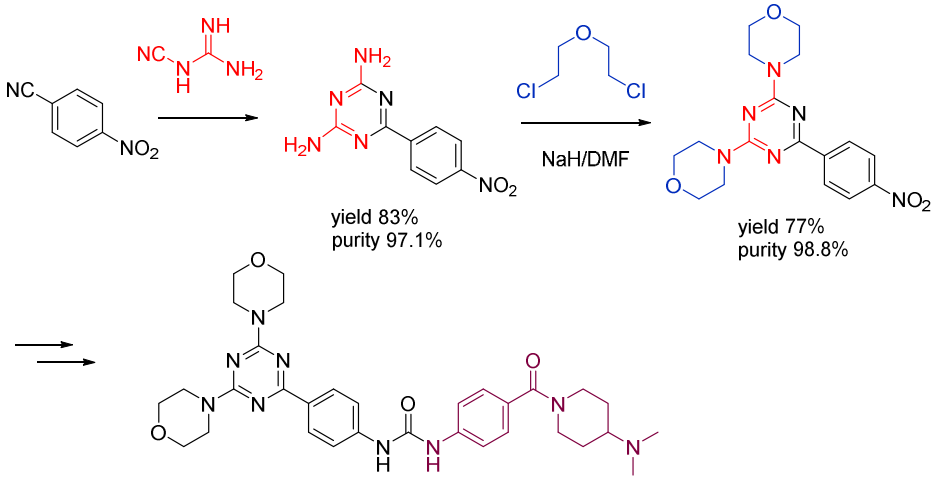
SYNOPSIS TOC

New and Practical Synthesis of Gedatolisib



ABSTRACT

A new, practical and convergent synthetic route of gedatolisib, an antitumor agent, is developed on a hectogram scale which avoids the Pd coupling method. The key step is adopting 6-(4-nitrophenyl)-1,3,5-triazine-2,4-diamine and 2,2'-dichlorodiethyl ether to prepare the key 4,4'-(6-(4-nitrophenyl)-1,3,5-triazine-2,4-diyl)dimorpholine in 77% yield and 98.8% purity. Gedatolisib is obtained in 48.6% yield over five simple steps and 99.3% purity (HPLC). Purification methods of the intermediates and the final product involved in the route are given.

Key Words Gedatolisib, Antitumor agent, New route, Organic process, Hectogram scale.

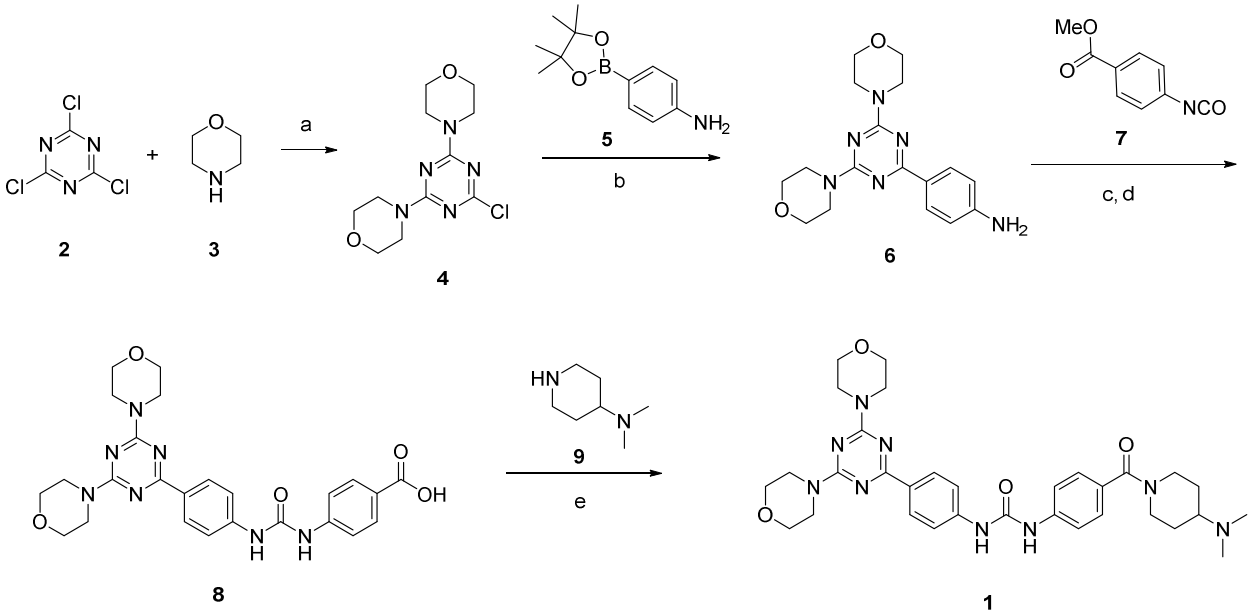
INTRODUCTION

Gedatolisib (**1**, Scheme 1), also known as PKI-587 and PF-05212384, is an agent targeting the phosphatidylinositol 3 kinase (PI3K) and mammalian target of rapamycin (mTOR) in the PI3K/mTOR signaling pathway, that inhibits PI3K-α, β, γ, δ isoforms and mTOR with IC_{50} of 0.4, 6.0, 5.4, 6.0 and 1.6 nM respectively, with potential antitumor activity.[1, 2] It was developed by Pfizer for the treatment of acute myeloid leukemia which is now in phase III clinical study.[3]

The synthetic routes of gedatolisib were developed and reported so far, [4–6] which adopted almost the same method, as shown in Scheme 1. Cyanuric chloride and morpholine were reacted at basic condition to give 4,4'-(6-chloro-1,3,5-triazine-2,4-diyl)dimorpholine (**4**) in 64% yield, which was coupled with 4-aminophenylboronic acid pinacol ester (**5**), catalyzed by 5 mol% $Pd(PPh_3)_4$, to give 4-(4,6-dimorpholino-1,3,5-triazin-2-yl)aniline (**6**) in 88% yield on a 30 g scale. The subsequent steps included addition with 4-isocyanatobenzoate (**7**), esterolysis and amidation,

the title compound **1** was obtained in 37% yield over five steps (from compound **2**) on a 45 g scale. The intermediates in this route, such as compound **5** and **7**, were also needed to prepare. This procedure gave a Pd residue > 20 ppm, which is not conform to API preparation.[6]

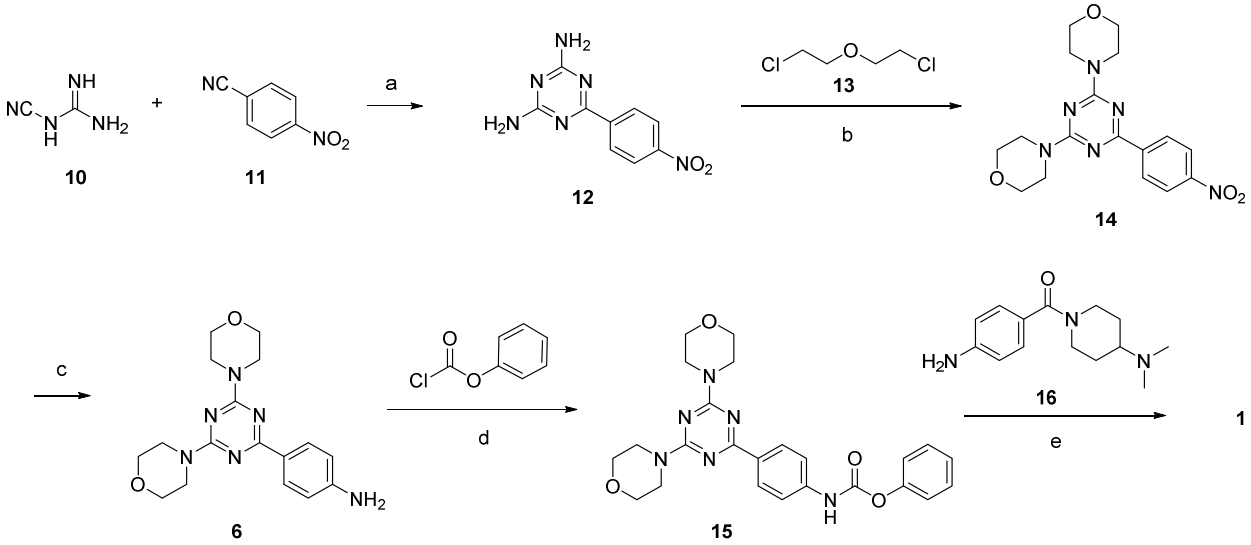
Scheme 1. Reported synthetic route of 1[a]



[a]Reagents and conditions: (a) TEA, acetone, –10°C to 0°C, 64%; (b) 5 mol% $Pd(PPh_3)_4$, Na_2CO_3, DME, reflux, 5 h, 88%; (c) CH_2Cl_2, rt, 5 h, 90%; (d) LiOH, H_2O, THF, MeOH, reflux, 2 h, 92%; (e) CDI, DMAP, THF, 50°C, 18 h, then DMAC, 17 h, 80%.

In order to develop a practical and commercial process of preparing gedatolisib, a new synthetic route was designed and studied, in order to avoid the Pd coupling method. The key step is adopting 6-(4-nitrophenyl)-1,3,5-triazine-2,4-diamine (**12**) and 2,2'-dichlorodiethyl ether (**13**) to prepare the key intermediate 4,4'-(6-(4-nitrophenyl)-1,3,5-triazine-2,4-diyl)dimorpholine (**14**), which is depicted in Scheme 2.

Scheme 2. Improved synthetic route of 1[a]



[a]Reagents and conditions: (a) KOH, EtOH, reflux, 3 h, 83%; (b) NaH, DMF, 65°C, 2 h, 77%; (c) H_2, Ni, THF, rt, 12 h, 95%; (d) pyridine, CH_2Cl_2, 0°C, 3 h, 91%; (e) DMSO, 65°C, 3 h, 88%.

RESULTS AND DISCUSSION

Starting from dicyandiamide and 4-nitrobenzonitrile, 6-(4-nitrophenyl)-1,3,5-triazine-2,4-diamine (**12**) was prepared by adopting the method described by Simons,[7] with 83% isolated yield and > 97% purity (HPLC) without extra purification operation. The reaction optimization conditions are depicted in Table 1, including solvents, reaction temperature, and the molar ratio of base (KOH). The experiment results indicated that KOH was more like a catalyst since 0.4 eq of KOH given the best yield. Enhancing the molar ratio of KOH will consume more dicyandiamide to complete the reaction, while the isolated yield was reduced since side product was given. The reaction temperature was another determination factor since the reaction was not complete at 60°C, and the yield was more than 80% at 78°C. While side products were given

when the reaction was carried out at 120°C. In consideration of the solvents, DME (1,2-dimethoxyethane) and EtOH were selected and the latter gave better results. The best reaction condition was established as the item 8 in Table 1.

Table 1 Modification of the preparing 12[a, b]

Item	Solvent	**10** : **11** : KOH (mol)	T (°C)	time (h)	Yield %
1	DME	1.1 : 1	60	4	/
2	DME	1.1 : 1 : 0.1	90	4	<10% (TLC)
3	DME	1.1 : 1 : 0.5	90	4	48.8%
4	DME	1.1 : 1 : 0.5	120	4	49.6%
5	DME	1.1 : 1 : 1	90	4	Side product
6	EtOH	1.1 : 1 : 0.5	60	4	<40% (TLC)
7	EtOH	1.1 : 1 : 0.5	78	4	81%
8	EtOH	1.1 : 1 : 0.4	78	3	83%
9	EtOH	1.5 : 1 : 1	78	3	Low isolated yield

[a]Reactions were performed with **10** (22–30 mmol) and **11** (20 mmol) in solvents (20 vol of **10**). [b]All reactions were run in one-pot.

Under NaH (60% mineral oil dispersion)/DMF (*N*, *N*-dimethylformamide) condition,[8] compound **12** reacted with 2,2'-dichlorodiethyl ether to give the key dimorpholine intermediate **14** in 77% yield after modification, as shown in Table 2. During the conditions optimization, we selected TEA (triethylamine), K_2CO_3 and NaH as the base and adopted DMF, DMAC (dimethylacetamide), *o*-dichlorobenzene, diglyme, *n*-butanol as the solvents, respectively. This reactions were carried in different conditions. The experimental results shown that TEA or K_2CO_3 were too weak to give product, while NaH/DMF would give better yield. In order to reduce the mole ratio of 2,2'-dichlorodiethyl ether and NaH to substrate **12**, and more crucially to reduce the risk of operating NaH, the modification was carried out by adding the solution of **12** and **13** in DMF to NaH/DMF suspension at 65°C *via* peristaltic pump, **14** was obtained in 77% isolated yield with 98.8% purity (HPLC). During the optimization, we found that mixing the

materials together (one-pot operation), the mole ratio of compound **12** : **13** : NaH was 1 : 4 : 9 at least to convert the materials while the isolated yield was only around 40%. What's more, foam generated obviously when the reaction temperature reached to 50°C.

Table 2 Modification of the reaction of 12 to 14[a, b]

Item	Solvent	**12** : **13** : Base (mol)	Catalyst	T (°C)	time (h)	Yield %
1	DMF	1 : 4 : 9 (Et_3N)	NaI	60–90	4	/
2	DMF	1 : 4 : 5 (K_2CO_3)	NaI	60–110	4	/
3	DMF	1 : 4 : 9 (NaH)	NaI	60	4	41%
4	DMAC	1 : 4 : 9 (NaH)	/	60	4	35%
5	*o*-dichlorobenzene	1 : 4 : 9 (NaH)	/	60–140	4	/
6	diglyme	1 : 4 : 9 (NaH)	/	60–120	4	<20% (TLC)
7	*n*-butanol	1 : 4 : 9 (NaH)	/	60–110	4	<20% (TLC)
9	DMF	1 : 2.2 : 4.2 (NaH)	/	65	3	~30% (TLC)
10	DMF	1 : 2.2 : 4.2 (NaH)	/	65	2	77%[c]

[a]Reactions were performed with 6-(4-nitrophenyl)-1,3,5-triazine-2,4-diamine **12** (25 mmol), 2,2'-dichlorodiethyl ether and NaH (60%) under a argon atmosphere. [b]Unless otherwise noted, all reactions were run in one-pot. [c]This item was carried out by adding **12** and **13** solution to NaH/DMF suspension at 65°C through peristaltic pump.

Comparatively to the one-pot operation, the reaction materials **12** and **13** were dissolved in DMF at 65°C and added *via* peristaltic pump to the NaH/DMF suspension over 2 h. The flow speed is set up to 4 mL/min, a solution of **12** (80.0 g, 0.35 mol) and **13** (112.5 g, 0.79 mol) in DMF (400 mL, flask B) was added to the suspension of 60% NaH over mineral oil (60 g, 1.5 mol) in 300 mL DMF (flask A) at 65°C. To investigate the safety of this step, the reaction calorimetry, the gas evolution rate and the volumetric measurement data were detected. The reaction calorimetry data was tested based on the experimental results from oxygen bomb calorimeter (HR-15, Shanghai Testing Instrument Co.). The combustion heat of compound **12** and **14** were calculated respectively based on Eq. 1 (corrected by benzoic acid to get the parameter K) and the Reynolds temperature correction curves were obtained and depicted in

Figure 1 to 3. Since the molar combustion heat of 2,2'-dichlorodiethyl ether **13** (–2502.7 kJ/mol), H_2 (–285.8 kJ/mol) and NaH (–282.5 kJ/mol) are known (as shown in Table 3),[9] so we can calculate the reaction calorimetry of the reaction of **12** to **14** is –1753.1 kJ/mol, as shown in Eq. 2.

$$Q_vW - 1400G = -K\Delta T \qquad (1)$$

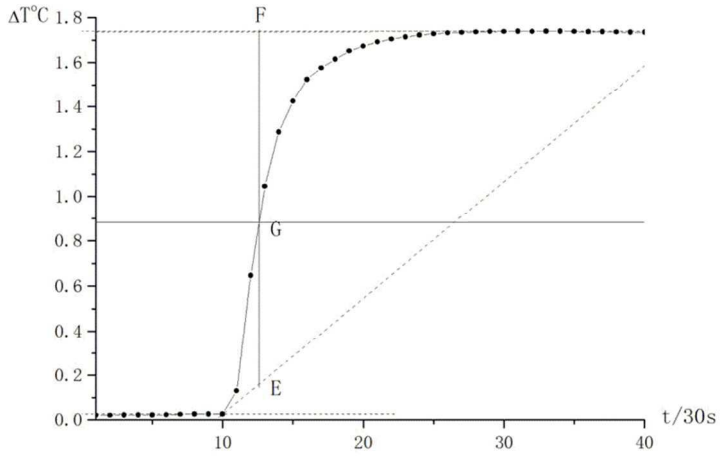


Figure 1. The Reynolds temperature correction curve of benzoic acid.

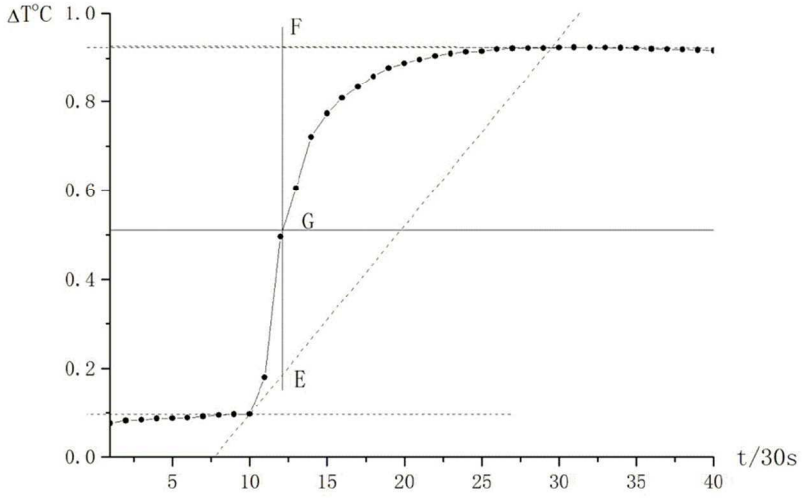


Figure 2. The Reynolds temperature correction curve of compound **12**.

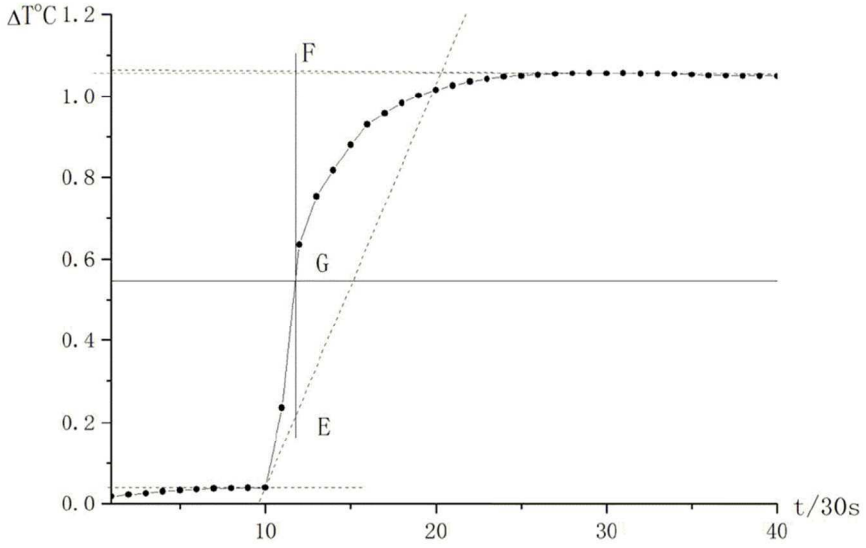


Figure 3. The Reynolds temperature correction curve of compound **14**.

Table 3 The molar combustion heat of the related compounds [a, b]

Compounds	$\Delta_C H_m^\theta$ (kJ/mol)
12	-4512.3 [a]
13	-2502.7 [b]
14	-7751.3 [a]
NaH	-282.5 [b]
NaCl	0 [b]
H_2	-285.8 [b]

[a]The molar combustion heat data was calculated based on the experimental results from oxygen bomb calorimeter. [b]The molar combustion heat data was reported.

$$\begin{aligned}\Delta_r H_m^\theta &= -\sum_B V_B \, \Delta_C H_m^\theta(B) \\ &= \left[\Delta_C H_m^\theta(\mathbf{12}) + 2 \times \Delta_C H_m^\theta(\mathbf{13}) + 4 \times \Delta_C H_m^\theta(\mathrm{NaH})\right] \\ &\quad - \left[\Delta_C H_m^\theta(\mathbf{14}) + 4 \times \Delta_C H_m^\theta(\mathrm{NaCl}) + 4 \times \Delta_C H_m^\theta(H_2)\right] \\ &= (-4512.3 + 2 \times -2502.7 + 4 \times -282.5) - (-7751.3 + 4 \times -285.8) \\ &= -1753.1 \ \mathrm{kJ/mol}\end{aligned} \quad (2)$$

The above reaction was carried out in a flask with mark to measure the reactant volume, and the gas evolution rate was detected by float flowmeter (DK800-4F, Changfa Instrument Co., China). The volumetric measurement data was depicted in Figure 4, which shown that there was no volume violent change in the flask A so the reaction was controllable.

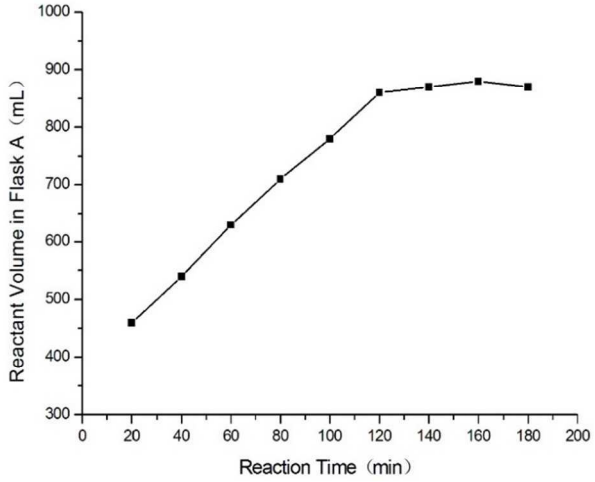


Figure 4. Volumetric measurement for **12** to **14** in flask A.

The gas evolution rate was shown in Figure 5. From the diagram we can see that during the material charging from Flask B to A (20–120 min), the gas evolution rate was between 2.7–4.0 L/20 min. While the evolution rate declined sharply after the charging, which indicated that the reaction was complete.

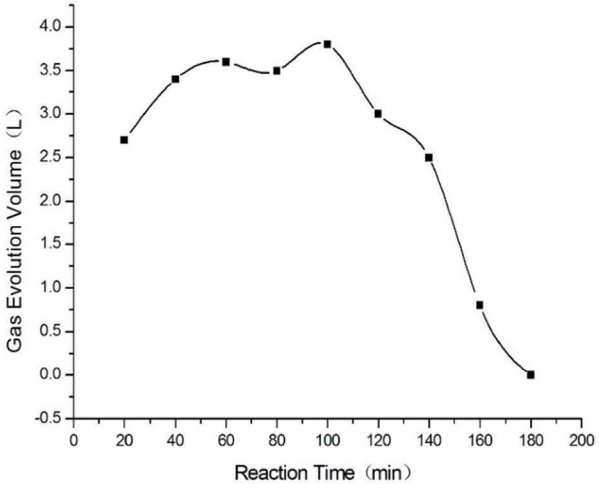


Figure 5. Gas evolution rate for **12** to **14**.

Treated compound **14** at H_2/Raney Ni condition at room temperature to give 4-(4,6-dimorpholino-1,3,5-triazin-2-yl)aniline (**6**) in 96% yield, with 98.8% purity (HPLC). Many methods are effectual for nitro-compounds reduction and catalytic hydrogenation is a clean and convenient way. With regard to this step, no more conditions were optimized besides adoption MeOH and EtOH as the solvents in view of cost. While material **14** and product **6** have poor solubility in alcohol solvents so THF (tetrahydrofuran) was chosen as the solvent.

The aniline compound **6** was reacted with phenyl carbonochloridate to give the phenyl carbamate intermediate **15** in 91% yield. In order to establish the urea part of the final product, the phenylcarbamate group was introduced as the leaving group. Firstly, an one-pot method was tried by treating compound **6**, **16** and triphosgene in acetonitrile while the experiment failed. Methyl chloroformate was also used to instead of phenyl carbonochloridate, while the subsequent reaction with compound **16** given bad results.

The title gedatolisib (**1**) was obtained by treating compound **15** with (4-aminophenyl)(4-

(dimethylamino)piperidin-1-yl)methanone (**16**) in DMSO with 88% yield and 99.3% purity (HPLC). Compound **16** can be prepared based on Gopalsamy's method in good yield.[10] So the urea formation of gedatolisib using amide **16** and **15** is a more convergent approach than the reported synthesis. There were no more conditions optimization about last step since the related published methods was simple and practical.[11] Most of the work was focus on the purification method. Finally the crude product of **1** was stirred and heated in EtOAc-EtOH (1:1 vol) and the product can be purified up to standard.

CONCLUSION

A new and practical synthetic route of gedatolisib (**1**) is designed and developed on a hectogram scale which avoid the Pd coupling method. The key step is adopting 1,3,5-triazine-2,4-diamine compound **12** and dichlorodiethyl ether **13** to prepare the key intermediate 4,4'-(6-(4-nitrophenyl)-1,3,5-triazine-2,4-diyl)dimorpholine (**14**) in ~80% yield and > 98% purity. Several modifications are carried out in this step and the optimal condition is established. The title compound **1** is obtained in 48.6% yield over five simple steps (calculated from 4-nitrobenzonitrile) and 99.3% purity (HPLC). Purification methods of the intermediates and the final product involved in the route are also given, which make this process environmentally friendly, cost-effective, and feasible for scale-up operation.

EXPERIMENTAL SECTION

General. All commercially available chemicals and solvents were used as received without any further purification. ^{1}H NMR spectra were recorded on a Bruker UltraShield 400 Plus spectrometer using TMS as an internal standard. Mass spectra were obtained from a Finnigan

MAT-95/711 spectrometer. The HPLC data were acquired using a Waters 2487 UV/Visible Detector and Waters 515 Binary HPLC Pump. The purity of the compounds were based on the areas of HPLC UV.

6-(4-Nitrophenyl)-1,3,5-triazine-2,4-diamine (12). KOH (17.0 g, 0.30 mmol) was added and stirred in ethanol (1 L) to give a solution. Then dicyanodiamide (71.0 g, 0.84 mol) and 4-nitrobenzonitrile (112.5 g, 0.76 mol) were added into the solution and heated to reflux for 3 h. The resulting solution was cooled to room temperature and filtrated, washed with ethanol (150 mL × 2), and dried at atmospheric pressure (50°C, 4 h) to give product **12** (146.4 g, 83%) as a white solid. ^{1}H NMR(400 MHz, DMSO-d_6): δ 6.92 (brs, 4H), 8.34 (d, J = 8.8 Hz, 2H), 8.45 (d, J = 8.8 Hz, 2H). HPLC conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 220 nm; Flow rate: 1.0 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 20 min; Mobile phase A: water; Mobile phase B: MeOH/TEA = 100:0.1; Gradient program: time (min): 20; % of mobile phase A: 20; % of mobile phase B: 80; t_R = 4.299 min, purity: 97.10%.

4,4'-(6-(4-Nnitrophenyl)-1,3,5-triazine-2,4-diyl)dimorpholine (14). Flask A: A suspension of NaH (60% mineral oil dispersion, 60.0 g, 1.5 mol) and DMF (300 mL) was stirred and heated to 65^{o}C under argon.

Flask B: A mixture of 1,3,5-triazine-2,4-diamine **12** (80.0 g, 0.35 mol) and dichlorodiethyl ether **13** (112.5 g, 0.79 mol) in DMF (400 mL) was stirred and heated to 65^{o}C under argon to give a solution.

The solution in Flask B was added to Flask A through a peristaltic pump, setting the flow speed at 4 mL/min until complete (~2 h). The reaction mixture was stirred at 65^{o}C for another 1 h. Around 400 mL DMF was recovered under vacuum and the residue was poured into ice water

(1.5 L) and stirred for 1 h. The resulting solid was filtered, washed with ethanol (200 mL × 2), and dried at ordinary pressure (50°C, 4 h) to give a brown solid crude **14** (130 g), which was stirred and heated in EtOH (400 mL) to reflux for 1 h, cooled to room temperature. The resulting solid was filtered, washed with ethanol (200 mL × 2), and dried at atmospheric pressure (50°C, 4 h) to give **14** (100.2 g, 77%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (m, 8H), 3.95 (m, 8H), 8.27 (d, J = 8.0 Hz, 2H), 8.53 (d, J = 8.0 Hz, 2H). ESI-MS (*m/z*) 372.3 (M + H). HPLC conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 20 min; Mobile phase A: water; Mobile phase B: MeOH/TEA = 100:0.1; Gradient program: time (min): 20; % of mobile phase A: 10; % of mobile phase B: 90; t_R = 5.131 min, purity: 98.85%.

4-(4,6-Dimorpholino-1,3,5-triazin-2-yl)aniline (6). A suspension of dimorpholine **14** (93.0 g, 0.25 mol), Raney Ni (wet, 30 g) and THF (1 L) was stirred under H_2 bag at room temperature for 12 h. The resulting mixture was filtered through a Celite pad and the filter cake was washed by THF (100 mL × 2). The combined filtrate was concentrated under vacuum to give a light brown solid, which was stirred and heated in 50% THF-H_2O (200 mL) to 50°C for 1 h, cooled to room temperature. The resulting solid was filtered, washed with 50% THF-H_2O (70 mL × 2), and dried at atmospheric pressure (45°C, 4 h) to give **6** (81.2 g, 95%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.64 (m, 8H), 3.78 (m, 8H), 5.70 (s, 2H), 6.57 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H). ESI-MS (*m/z*) 343.0 (M + H). HPLC conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 20 min; Mobile phase A: water; Mobile phase B: MeOH/TEA = 100:0.1; Gradient

program: time (min): 20; % of mobile phase A: 10; % of mobile phase B: 90; t_R = 5.595 min, purity: 98.82%.

Phenyl (4-(4,6-dimorpholino-1,3,5-triazin-2-yl)phenyl)carbamate (15). A solution of compound **6** (82.1 g, 0.24 mol), pyridine (28.4 g, 0.36 mol) in CH_2Cl_2 (600 mL) was stirred and cooled at an ice-water bath to ~5°C. A solution of phenyl carbonochloridate (41.3 g, 0.26 mol) in CH_2Cl_2 (120 mL) was added dropwise into the mixture over 1 h and stirred at 5°C for another 2 h. The reaction solution was washed with water (400 mL × 3), dried over anhydrous Na_2SO_4. The organic solution was filtered and concentrated under vacuum to give the crude carbamate product **15** (109 g) as a light yellow solid, which was stirred and heated in EtOAc-Hexane (1:1 vol) (240 mL) to 60°C for 1 h, cooled to room temperature. The resulting solid was filtered, washed with EtOAc-Hexane (1:1 vol) (80 mL × 2), and dried at atmospheric pressure (45°C, 4 h) to give **15** (100.9 g, 91%) as an off-white solid. ^{1}H NMR (400MHz, $CDCl_3$): δ 3.75–3.83 (m, 8H), 3.94 (brs, 8H), 7.16 (s, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.28 (m, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.55 (d, J = 9.6 Hz, 2H), 8.40 (d, J = 8.4 Hz, 2H). ESI-MS (*m/z*) 463.1 (M + H).

Gedatolisib (1). A solution of compound **15** (94.4 g, 0.204 mol) and (4-aminophenyl)(4-(dimethylamino)piperidin-1-yl)methanone **16** (55.5 g, 0.224 mol) in DMSO (550 mL) was stirred and heated to 65°C for 3 h. The reaction mixture was cooled to room temperature and poured into ice water (1.4 L) and stirred for 1 h. The resulting solid was filtrated and dried at 45°C for 4 h to give the crude **1** (125 g) as a light yellow solid, which was stirred and heated in EtOAc-EtOH (1:1 vol) (350 mL) to 70°C for 2 h, cooled to room temperature. The resulting solid was filtered, washed with EtOAc-EtOH (1:1 vol) (80 mL × 2), and dried at atmospheric pressure (45°C, 4 h) to give **1** (110.5 g, 88%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-

d_6): δ 1.46 (brs, 2H), 1.89 (brs, 2H), 2.29 (s, 6H), 2.94 (brs, 2H), 3.76 (m, 8H), 3.89 (m, 8H), 7.09 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 8.28 (s, 1H), 8.31 (d, J = 8.6 Hz, 2H), 8.48 (s, 1H). ESI-MS (*m/z*) 615.9 (M+H). HPLC conditions: Column: Agilent Eclipse XDB-C18 (250 mm × 4.6 mm × 5 μm); Detection: 254 nm; Flow rate: 0.8 mL/min; Temperature: 30 °C; Injection load: 1 μL; Solvent: MeOH; Concentration: 0.5 mg/mL; Run time: 20 min; Mobile phase A: water; Mobile phase B: MeOH/TEA = 100:0.1; Gradient program: time (min): 20; % of mobile phase A: 10; % of mobile phase B: 90; t_R = 2.598 min, purity: 99.34%.

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