

# Convenient Synthesis and Characterization of Novel 4-[2-Ethoxy-5-(4-Methyl-1-Piperazinesulphonyl)Benzamido]-3-Isobutyl-1-Methyl-1H-Pyrazole-5-Carboxamide: Key Precursor for Isobutyl Sildenafil

Jiali Sun<sup>1, a</sup>, Zheng Guo<sup>1, b</sup>, Shengxuan Qi<sup>1, c</sup>, and Yan Zhang<sup>1, d</sup>

<sup>1</sup>School of Materials Design and Engineering, Beijing Institute of Fashion Technology, Beijing, 100029, China

<sup>a</sup> sunjiali2020@126.com, <sup>b</sup> 116283119@qq.com, <sup>c</sup> 1797050065@qq.com, <sup>d</sup> clyzhy@bift.edu.cn

**Abstract.** This work presents a rational synthesis of 4-[2-Ethoxy-5-(4-Methyl-1-Piperazinesulphonyl)benzamido]-3-Isobutyl-1-Methyl-1H-Pyrazole-5-Carboxamide (13) by condensation of 4-amino-3-isobutyl-1-methyl-1H-pyrazole-5-carboxamide (8) with 2-ethoxy-5-(4-methyl-1-piperazinesulphonyl)benzoyl chloride (12) with an overall yield of 37.4 %. The preparative details of all intermediates and Isobutyl Sildenafil were discussed step by step. The structures of key intermediate 13 and Sildenafil impurity A were characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR and HR-MS analysis. It provides a convenient approach in good yield for Sildenafil impurity A in a convergent way with easy manipulations and scale up.

**Keywords:** Key Intermediates; Synthesis; Nonlinear Route; Isobutyl Sildenafil.

## 1. Introduction

Sildenafil, a substituted pyrazole derivative, was initiated the U.S. market in 1998 as new drug for male erectile dysfunction (MED)[1,2]. The chemical name is 1-[4-Ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-n-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulphonyl]-4-methylpiperazine). Since it is used for oral consumption, its quality and safety should be ensured. Some adverse effects such as headache, facial flushing and visual disturbances have been reported [3]. Part of these side effects are deemed to be associated with the poor-quality problem. Drug quality maybe depends not only on the adopted procedures, but also on the raw materials reagents, solvents, side reaction products, intermediates and degradation products. In the past two decades, 66 sildenafil-like compounds or impurities have been recognized in 'all-natural' herbal recipe or meal supplements[4]. These compounds generally exhibit only small structural differences compared to the original sildenafil. Due to these structural similarities, it is expected that these analogues would exhibit similar activities in human bodies. In most instances, however, the presence of analogues in medicine, especially in an unapproved potion, could bring a great risk to public health[5]. In order to ensure the quality of medicines, the impurities should be structurally determined and well assayed before wide applications.

The preparation of sildenafil was originally disclosed by Pfizer Inc with several steps, and an improved process was then published[6,7]. Sildenafil Impurity A was isolated from the preparations of Sildenafil and listed as an impurity. This new analogue possesses an isobutyl group instead of the propyl part in original Sildenafil, and was named as Isobutyl Sildenafil or Sildenafil impurity A. To our knowledge, Sildenafil Impurity A was prepared in reported references following a multiple linear steps from 4-methylpentan-2-one described by Dr. Piyush V Patel [8]. However, this linear route (Figure 1) had some obvious drawbacks as a practical synthetic route due to the following weakness. 1) It was a linear 11 steps; 2) in step 7, FeCl<sub>3</sub> or SnCl<sub>2</sub> was used as reduction reagents, which would resulted in solid waste and will be hard for purification and workup; 3) the cyclization in step 9 with sodium hydroxide/hydrogen peroxide/water would expect a moderate yield. Ambati. V. Raghava Reddy [9] also reported the synthesis of sildenafil butyl analogue as the same linear route (figure 1) by simple improved modifications. From the known syntheses to Sildenafil, the nonlinear commercial route described in the reference [7] is a safe and convergent synthesis with

high yield. So our recent studies presented an alternate routes for the synthesis of the key intermediate 13, which followed subsequently by dehydration reaction to Isobutyl Sildenafil according the nonlinear commercial route of Sildenafil [7,10,11] outlined in figure 2. The main focus of our efforts was endeavor to develop an efficient and convenient process.

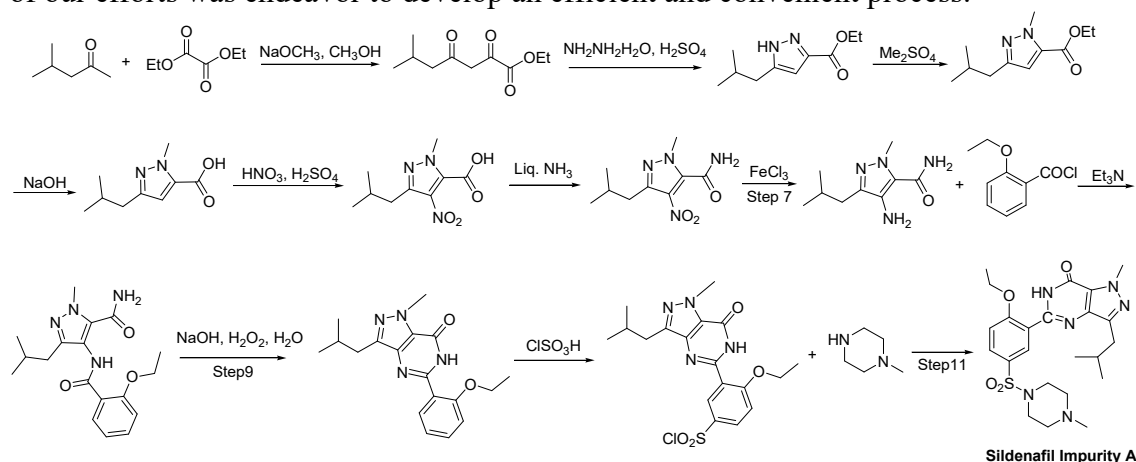


Fig. 1 The synthesis of sildenafil butyl analogue as the linear route

## 2. Results and Discussion

According to a precedential synthesis to Sildenafil, we anticipated convergent coupling of aminopyrazole 8 with acid chloride 12 to give key intermediate 13 of Isobutyl Sildenafil (Figure 2). So the main problem was to develop a simple procedure for the synthesis of the aminopyrazole 8. Some methods which can reach this goal have been reported in some literatures [12, 13].

In this paper, as outlined in our synthetic plan (Figure 2), the preparation of the isobutyl pyrazole 8 began from the inexpensive starting material 4-methyl-pentan-2-one and diethyl oxalate with the seven steps conversion with total high yield of 44.0 %. The purification of intermediates was simple and practicable. Using 4-methyl-pentan-2-one and diethyl oxalate as the raw material, ethyl 6-methyl-2,4-dioxoheptanoate 2 was obtained by the classic Claisen condensation in ethanol with sodium ethoxide. Pyrazole ring formation via cyclization of heptanoate 2 with hydrazine hydrate in acetic acid to afford the corresponding pyrazole 3 has been carried out conveniently in a single step in near-quantitative yield. Compound 3 was first methylated at N<sub>1</sub> position and was then treated with NaOH/EtOH. The methylation before saponification reaction is very important since the free acid may be methylated again by Me<sub>2</sub>SO<sub>4</sub>. A light yellow solid of carboxylic acid 5 was obtained by filtration in good yield. The nitration of the compound 5 was conducted with fuming HNO<sub>3</sub> (95%) in concentrated sulphuric acid at 65°C for 10 h. The reaction temperature should be controlled carefully to avoid the decarboxylation of carboxylic acid over 120°C. After reaction the cold water was carefully added to the cooled mixture. The compound 6 was produced by filtration and another part of product 6 was obtained by extraction with CH<sub>2</sub>Cl<sub>2</sub> from aqueous phase in an overall yield of 80.8 %. Since carboxylic acids are not reactive towards ammonia, so nitropyrazole 6 have to be transformed to acid halide with thionyl chloride in toluene at 55°C for 6 h. The addition of catalytic quantity of dimethylformamide(DMF) enhances the reactivity by forming a Vilsmeier intermediate. The created acid chloride was poured into a concentrated ammonia solution (28.0 %) to provide a pale yellow solid of carboxamide 7 in excellent yield. Heterogeneous hydrogenation of compound 7 using the catalyst of 5% palladium on charcoal in ethyl acetate in the presence of 4 atm hydrogen pressure at 50°C for 4.5 h leaves no residues to yield a violet solid 8 with the yield of 97.4 %, which could be used directly in the next coupling step. The structure of 8 was confirmed by <sup>1</sup>H NMR spectra that showed the amino signal at δ 7.48 ppm, and also <sup>13</sup>C NMR spectra which showed the only one C=O signal at δ 161.85 ppm.

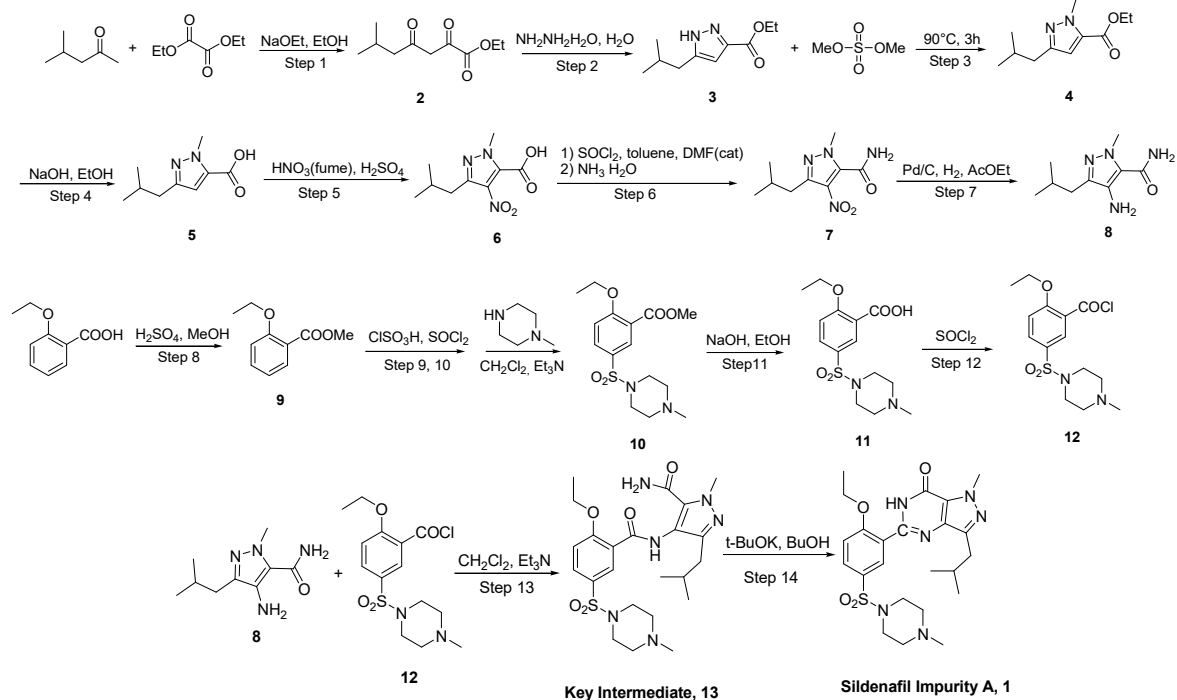


Fig. 2 The nonlinear commercial route for synthesis of Isobutyl Sildenafil

The intermediate 12 was synthesized from commercially available 2-ethoxybenzoic acid in five-step chemical transformations with high yield. In this method, 2-ethoxybenzoic acid methyl ester 9 was chlorosulfonated at the contraposition of the ethoxyl group using chlorosulfonic acid ( $\text{HSO}_3\text{Cl}$ ) in the presence of  $\text{SOCl}_2$  to ensure maximum conversion [14]. For simplicity and efficiency, the intermediate sulfonyl chloride was dissolved in  $\text{CH}_2\text{Cl}_2$  and was coupled to N-methyl piperazine with excess amounts of  $(\text{CH}_3\text{CH}_2)_3\text{N}$ . The resultant ester 10 was hydrolyzed and then conducted using thionyl chloride in toluene to give compound 12 which was used directly in the following reaction.

Aminopyrazole 8 was coupled with acid chloride 12 in  $\text{CH}_2\text{Cl}_2$  in the presence of  $(\text{CH}_3\text{CH}_2)_3\text{N}$  at low temperature and then stirred thoroughly at R.T. for 60 h. After evaporation of the solution, a normal water-based workup in EtOAc yielded the crude residue which was recrystallized out of  $\text{CH}_3\text{OH}/\text{H}_2\text{O}$  to afford a white solid with the yield of 72.5%. The structure of this new intermediate was confirmed by  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and HR-MS data. The  $^1\text{H-NMR}$  spectra showed additional different peaks of protons 9.62 ppm for  $-\text{CONH}-$ , and appeared five peaks at  $\delta$  2.89 ppm (broad s, 4 H), 2.36 ppm (m, 6 H), 2.15 ppm (s, 3 H), 1.93 ppm (m, 1H) and 0.88 ppm (d, 6 H) for hydrogen signals of isobutyl group and N-methyl piperazine. Furthermore the carbon peaks in the  $^{13}\text{C}$  NMR spectra at  $\delta$  166.4 and 160.44 ppm verifies the structures of the key intermediate 13. In the HR-MS (ESI),  $m/z$  507.23704 with the formula  $\text{C}_{23}\text{H}_{35}\text{N}_6\text{O}_5\text{S}$  provided further support to the structures of this compound. The resulting coupled product 13 was then cyclized smoothly in tert-butyl alcohol in presence of potassium tert-butoxide into the target Sildenafil impurity A. The last step involves only water soluble solvents and the final product precipitates from water solution with the pH 7. No further purification is necessary and an off-white solid 1 was clinical quality detected by HPLC analysis. The  $^1\text{H-NMR}$  spectra showed additional broad singlet at  $\delta$  12.16 ppm for amide proton as to be expected, due to the aromatic and heteroaromatic system in this compound, and HR-MS spectra revealed the formula of  $\text{C}_{23}\text{H}_{32}\text{N}_6\text{O}_4\text{S}$ .

### 3. Experimental Section

All NMR spectra were recorded on a Bruker Avance II 500 MHz spectrometer (Bruker, Germany) in  $\text{DMSO-}d_6$  or  $\text{CDCl}_3$  solutions with TMS as internal reference. HR-MS spectra was

conducted on a Bruker APEX IV mass spectrometer. Melting points were measured on a WRS-1B melting point apparatus (China). An analytical HPLC (Agilent 1200, United States) was run with the Symmetry C18, 210 × 4.6 mm column at 290nm. All reagents used were analytical grade and were used without further purification. Reaction progress was monitored by thin-layer chromatography (TLC).

3-isobutyl-1-methyl-1H-pyrazole-5-carboxylic acid (5).

Sodium ethoxide (NaOEt, 7.48 g, 0.11 mol) was dissolved in 150 mL anhydrous alcohol (EtOH) at -20°C to give a solution. To the solution were added 4-Methyl-pentan-2-one (10.0 g, 0.1 mol) and diethyl oxalate (14.6 g, 0.1 mol) sequentially at -20°C. The obtained admixture was stirred for 1 h at 0°C and then overnight at ambient temperature. The reaction mixture was concentrated under vacuum. To the obtained residue was added diluted HCl (2 mol/L, 120 mL). The generated mixture was extracted with dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>, 3 × 120 mL). And the CH<sub>2</sub>Cl<sub>2</sub> layers were washed with water, dried with anhydrous MgSO<sub>4</sub> and filtered. The solvent was distilled to afford product 2 as a colorless oil (17.8 g, 89.0 %). To a solution of compound 2 (20.0 g, 0.1 mol) in 100 mL of acetic acid at 0 °C was slowly added hydrazine hydrate (80.0 %, 6.88 g, 0.11 mol) in 30 minutes. The generated mixture was heated under reflux. After the consumption of compound 2, the mixture was cooled in an ice bath and the solvent was removed under vacuum to afford a residual oil. To the obtained oil was added saturated NaHCO<sub>3</sub> solution (100 mL). The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×80 mL), and the combined CH<sub>2</sub>Cl<sub>2</sub> phase was washed with H<sub>2</sub>O. The solvent was distilled to afford compound 3 as a white solid (18.8 g, 96.0 %). A mixture of product 3 (19.6 g, 0.1 mol) and Me<sub>2</sub>SO<sub>4</sub> (13.9 g, 0.11 mol) were heated to 90°C for 3 h in a 250 ml three-necked flask. Then the mixture was cooled and diluted with CH<sub>2</sub>Cl<sub>2</sub> (300 mL), and washing was performed sequentially with H<sub>2</sub>O (2 × 250 mL). The CH<sub>2</sub>Cl<sub>2</sub> was evaporated to produce a colorless oil 4 (14.8 g, 70.5 %). To a solution of intermediate 4 (21.0 g, 0.1 mol) in ethanol (200 mL) was added 10 % aqueous NaOH solution (60 mL) with constant stirring, and the admixture was heated to 80°C for 2 h. The CH<sub>3</sub>CH<sub>2</sub>OH was distilled off in vacuo and the residue was diluted with H<sub>2</sub>O (80 mL) and acidified with 5 mol/L HCl (150 mL) to pH 2. The product was collected by filtration, and then dried to give a light yellow solid (17.3 g, 95.1 %) as desired compound 5, R<sub>f</sub> 0.3 (DCM-MeOH, 10:1). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 12.30 (br. s, 1H, OH), 6.75 (s, 1H, CH), 4.18 (s, 3H, CH<sub>3</sub>), 2.53 (d, 2 H, CH<sub>2</sub>, J = 7.0 Hz), 1.88-1.99 (m, 1 H, CH), 0.96 (d, 6 H, 2CH<sub>3</sub>, J = 6.5 Hz) [8]. <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 163.45, 150.95, 132.64, 111.34, 39.08, 36.74, 28.86, 22.30. HR-MS(ESI): m/z = 183.11248 (M+H)<sup>+</sup>, C<sub>9</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>. Calculated: (M+H)<sup>+</sup> 183.11248.

4-amino-3-isobutyl-1-methyl-1H-pyrazole-5-carboxamide (8).

A suspension of carboxylic acid (5) (5.46 g, 0.030 mol) in concentrated H<sub>2</sub>SO<sub>4</sub> (18mL) was heated at 55 °C. To the above mixture was added a mixture of fuming HNO<sub>3</sub> (1.8 mL) in concentrated H<sub>2</sub>SO<sub>4</sub> (98 %, 3 mL) dropwise while keeping the reaction temperature at 50-55 °C. The admixture was then heated to 65 °C for 10 h, cooled to ambient temperature, and then carefully poured into icy water (150 mL). During the process, the temperature was maintained below 25°C. A lot of precipitate was filtered to give compound 6. The generated filtrate was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×80 mL). The CH<sub>2</sub>Cl<sub>2</sub> phases were washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and distilled to yield another batch of compound 6 (5.5 g, 80.8 %). To a suspension of compound 6 (5.70 g, 0.025 mol) in toluene (50 mL), was added thionyl chloride (20 mL), followed by addition of a catalytic quantity of dimethylformamide (0.1 mL). The obtained mixture was heated to 55°C for 6 h. The mixture was distilled under pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL). Concentrated cold ammonia solution (28.0 %, 30 mL) was added to the above mixture. The resulting solution was maintained at ambient temperature for 1 h. H<sub>2</sub>O (50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL) were added. The CH<sub>2</sub>Cl<sub>2</sub> phase was separated, washed with water and dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and condensed under pressure to afford a pale yellow solid as desired compound 7 (5.5 g, 97.5 %). The nitropyrazole 7 (5.0 g, 0.022 mol) was suspended in EtOAc (50 mL), and 4.8 g of 5% palladium on charcoal was added. The admixture was heated to 50°C under 4 atm hydrogen pressure for 4 h. The reaction mixture was cooled. The catalyst was filtered out and washed with EtOAc to give an ethyl acetate solutions. The

solution was dried over anhydrous  $\text{MgSO}_4$ , filtered and condensed to give a white powder as compound 8 (4.2 g, 97.4 %).  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$  7.48 (s, 2H,  $\text{NH}_2$ ), 4.10 (s, 2H,  $\text{NH}_2$ ), 3.87 (s, 3H,  $\text{CH}_3$ ), 2.34 (d, 2H,  $\text{CH}_2$ ,  $J = 7.0$  Hz), 1.82-2.00 (m, 1 H, CH), 0.88 (d, 6H,  $2\text{CH}_3$ ,  $J = 6.5$  Hz) [8].  $^{13}\text{C}$  NMR ( $d_6$ -DMSO):  $\delta$  161.85, 140.26, 129.26, 123.90, 38.84, 33.46, 27.61, 22.23. HR-MS(ESI):  $m/z = 197.13948$  ( $\text{M}+\text{H}$ ) $^+$ ,  $\text{C}_9\text{H}_{17}\text{N}_4\text{O}$ . Calculated: ( $\text{M}+\text{H}$ ) $^+$  197.13969.

2-ethoxy-5-(4-methyl-1-piperazinesulphonyl)benzoyl chloride (12).

2-ethoxybenzoic acid methyl ester (9) was prepared from 2-ethoxybenzoic acid as colorless oil (17.9 g, 99.4%). compound 9 (1.8 g, 0.10 mol) was added portionwise to a solution of chlorosulphonic acid (4.5 mL) and thionyl chloride (2 mL) whilst keeping the temperature at  $0^\circ\text{C}$ . After stirring for 1 h at  $50^\circ\text{C}$ , the mixture was cooled to ambient temperature, and then carefully poured into icy water (60 mL). The aqueous phase was extracted with EtOAc ( $2 \times 80$  mL). The EtOAc layers were dried and distilled to yield desired sulphonyl chloride as an off-white solid. The above sulphonyl chloride (1.12 g, 0.004 mol) was dissolved in 30 mL of  $\text{CH}_2\text{Cl}_2$ . To the solution were added a quantity of triethylamine (2 mL) and N-methyl piperazine (0.50 g, 0.005 mol). The admixture was stirred at ambient temperature for 1 h, and the solution was evaporated under pressure until all solvent had been removed. The remains was dissolved in  $\text{CH}_2\text{Cl}_2$  (80 mL) and washing was performed with saturated  $\text{NaHCO}_3$  solution (80 mL) and  $\text{H}_2\text{O}$  (80 mL) in turn. The  $\text{CH}_2\text{Cl}_2$  phase was separated, dried and condensed under pressure to afford a colorless oil as desired compound 10 (1.2 g, 87.7 %). A solution of ester 10 (3.42 g, 0.01 mol) was hydrolyzed as procedure of compound 5 in ethanol (40 mL) with 10 mL of 10 % aqueous NaOH solution to give a pale yellow solid 11 (3.2 g, 97.5 %).  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$  7.89 (s, 1H, ArH), 7.80 (dd, 1H, ArH,  $J_1 = 9.0$  Hz,  $J_2 = 2.0$  Hz), 7.34 (d, 1H, ArH,  $J = 8.5$  Hz), 4.20 (q, 2H,  $\text{CH}_2$ ,  $J = 7.0$  Hz), 2.97 (br. s, 4H,  $2\text{CH}_2$ ), 2.63 (br. s, 4H,  $2\text{CH}_2$ ), 2.31 (s, 3H,  $\text{CH}_3$ ), 1.35 (t, 3 H,  $\text{CH}_3$ ,  $J = 7.0$  Hz)[7]. HR-MS(ESI):  $m/z = 329.11574$  ( $\text{M}+\text{H}$ ) $^+$ ,  $\text{C}_{14}\text{H}_{21}\text{N}_2\text{O}_5\text{S}$ . Calculated: ( $\text{M}+\text{H}$ ) $^+$  329.11657. To a suspension of carboxylic acid 11 (3.28 g, 0.01 mol) in toluene (40 mL), were added thionyl chloride (15mL) and a quantity of dimethylformamide (2 drops). The solution was heated to  $55^\circ\text{C}$  for 6 h. The mixture was distilled under reduced pressure. The residue was used directly in the next step as benzoyl chloride (12).

4-[2-Ethoxy-5-(4-Methyl-1-Piperazinesulphonyl)benzamido]-3-Isobutyl-1-Methyl-1H-Pyrazole-5-Carboxamide (13).

The aminopyrazole 8 (5.9 g, 0.03 mol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (150 mL), triethylamine (20 mL) was added and stirred for 0.5h. To the above solution was added a solution of benzoyl chloride 12 (10.4 g, 0.03 mol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) and resulted mixture was stirred for 60 h at ambient temperature. Thin-layer chromatography (TLC) monitoring indicated most of aminopyrazole 8 was consumed and a new spot was formed. After evaporation of organic solvent, the residue was redissolved in EtOAc (80 mL) and washed with saturated  $\text{NaHCO}_3$  solution and  $\text{H}_2\text{O}$  (80 mL). The EtOAc phase was separated, dried and condensed under reduced pressure to afford a residue which was recrystallized out of methanol/water to give a white solid (11.0 g, 72.5 %). mp  $178.5\text{-}181.7^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $d_6$ -DMSO):  $\delta$ : 9.62 (br. s, 1H, NH), 7.85 (s, 1H, ArH), 7.83 (s, 2H,  $\text{NH}_2$ ), 7.43 (d, 1H, ArH,  $J = 8.0$  Hz), 7.30 (s, 1H, ArH), 4.32 (q, 2H,  $\text{CH}_2$ ,  $J = 6.5$  Hz), 3.93 (s, 3H,  $\text{CH}_3$ ), 2.89 (br. s, 4 H,  $\text{CH}_2$ ), 2.36-2.38 (m, 6 H,  $\text{CH}_2$ ), 2.15 (s, 3 H,  $\text{CH}_3$ ), 1.88-1.96 (m, 1H, CH), 1.42 (t, 3 H,  $\text{CH}_3$ ,  $J = 7.0$  Hz), 0.88 (d, 6 H,  $2\text{CH}_3$ ,  $J = 6.5$  Hz).  $^{13}\text{C}$  NMR ( $d_6$ -DMSO):  $\delta$  164.40, 160.44, 159.07, 145.97, 132.24, 131.72, 129.09, 126.30, 124.66, 116.10, 113.45, 65.04, 53.34, 45.55, 45.11, 38.64, 34.45, 27.28, 22.32, 14.16. HR-MS(ESI):  $m/z = 507.23704$  ( $\text{M}+\text{H}$ ) $^+$ ,  $\text{C}_{23}\text{H}_{35}\text{N}_6\text{O}_5\text{S}$ . Calculated: ( $\text{M}+\text{H}$ ) $^+$  507.23842.

5-[2-Ethoxy-5-((4-methylpiperazin-1-yl)sulphonyl)phenyl]-3-isobutyl-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one (1).

The above product 13 (12.65 g, 0.025 mol) was suspended in  $(\text{CH}_3)_3\text{COH}$  (65 mL), and  $(\text{CH}_3)_3\text{COK}$  (3.36 g, 0.03 mol) added. The resulted mixture was refluxed for 16 h. Thin-layer chromatography (TLC) indicated that pyrazolecarboxamide 13 was consumed completely. The mixture was cooled to ambient temperature, 70 mL of  $\text{H}_2\text{O}$  was added and the resulting solution

was filtered into a flask. Then a solution of concentrated HCl (2.3 mL) in H<sub>2</sub>O (60 mL) was added slowly to above mixture. The precipitated crude product was granulated at pH 7 between 0°C and 5°C for 2 h. The pure Sildenafil Impurity A was gathered by filtration, washed with H<sub>2</sub>O and dried under reduced pressure to give an off-white solid (11.25 g, 92.2 %). mp 164.5-167.4°C [lit.[8] mp 168-170°C]; <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO): δ 12.17 (br. s, 1H, NH), 7.82-7.84 (m, 2H, ArH), 7.36 (d, 1H, ArH, J = 8.0 Hz), 4.18 (q, 2H, CH<sub>2</sub>, J = 6.5 Hz), 4.14 (s, 3H, CH<sub>3</sub>), 2.88 (broad s, 4 H, CH<sub>2</sub>), 2.76 (d, 2 H, CH<sub>2</sub>, J = 8.0 Hz), 2.35 (br. s, 4 H, CH<sub>2</sub>), 2.15 (s, 3 H, CH<sub>3</sub>), 1.69-1.77 (m, 1H, CH), 1.32 (t, 3 H, CH<sub>3</sub>, J = 7.0 Hz), 0.94 (d, 6 H, 2CH<sub>3</sub>, J = 6.5 Hz). HR-MS(ESI): m/z = 489.22724 (M+H)<sup>+</sup>, C<sub>23</sub>H<sub>33</sub>N<sub>6</sub>O<sub>4</sub>S. Calculated: (M+H)<sup>+</sup> 489.22785.

#### 4. Acknowledgments

The authors want to thank the financial support from the Scientific and Technological Project of Beijing Municipal Education Commission (Project no. KM201810012007), the Special funds of high-level teachers of Beijing Institute of Fashion Technology (Project no. BIFTXZ201904) and the Beijing Institute of Fashion Technology Graduate Student Innovation Project (Project no. X2023-048)

#### References

- [1] Gong Binbin, Ma Ming, Xie Wenjie, et al. Direct comparison of tadalafil with sildenafil for the treatment of erectile dysfunction: a systematic review and meta-analysis. *International Urology and Nephrology*, 2017, 49(10): 1731–1740.
- [2] Haroldo A. Flores Toque, Fernanda B. M. Priviero, Cleber E. Teixeira, et al. Synthesis and pharmacological evaluations of sildenafil analogues for treatment of erectile dysfunction. *Journal of Medicinal Chemistry*, 2008, 51(9), 2807-2815.
- [3] Morales A, Gingell C, Collins M, et al. Clinical safety of oral sildenafil citrate (VIAGRA) in the treatment of erectile dysfunction. *International Journal of Impotence Research*, 1998, 10(2), 69-73.
- [4] Kee Chee Leong, Koh Hwee Ling, Bloodworth Bosco Chen, et al. Structural elucidation of propoxyphenyl isobutyl sildenafil, adulterant in a health supplement using high-resolution Orbitrap mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis*, 2014, 98: 153-159.
- [5] Lee Ji Hyun, Park Han Na, Park Ok Rim, et al. Screening of illegal sexual enhancement supplements and counterfeit drugs sold in the online and offline markets between 2014 and 2017. *Forensic Science International*, 2019, 298: 10-19.
- [6] Bell Andrew S, Brown David, Terret Nicholas K, Pyrazolopyrimidinone antianginal agent. EP0463756 B1, 1995 (corresponding to US5250534 A).
- [7] David J. Dale, Peter J Dunn, Clare Golightly, et al. The Chemical Development of the Commercial Route to Sildenafil: A Case History. *Organic Process Research & Development*, 2000, 4(1): 17-22.
- [8] Patel P V, Joshi N and Panchal D P. Process for preparation of 5-(2-ethoxy-5-((4-methylpiperazin-1-yl)sulfonyl)phenyl)-3-isobutyl-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one (sildenafil citrate impurity). *Heterocyclic Letters*, 2012, 2: 467–478.
- [9] Ambati V Raghava Reddy, Garaga Srinivas, Chandiran Takshinamoorthy, et al. A Facile, Improved Synthesis of Sildenafil and Its Analogues. *Scientia Pharmaceutica*, 2016, 84(3), 447-455.
- [10] Shi Jingbo, Tang Wenjian, Qi Xing Bao, et al. Novel pyrazole-5-carboxamide and pyrazole-pyrimidine derivatives: synthesis and anticancer activity. *European Journal of Medicinal Chemistry*, 2015, 90: 889-896.
- [11] Kumar I V S, Ramanjaneyulua G S, Bindub V H. Synthesis of Sildenafil citrate and process related impurities. *Letters in Organic Chemistry*, 2011, 8: 668–673.

- [12] Zhao Yan Fang, Zhai Xin, Chen Jiao Yue, et al. Syntheses and Vasodilatory Activities of New Pyrazolo[4,3-d] pyrimidin -7-ones. *Chemical Research in Chinese Universities*, 2006, 22(4): 468-473.
- [13] Si Weijie, Wang Xiaobin, Chen Min, et al. Design, synthesis, antifungal activity and 3D-QSAR study of novel pyrazole carboxamide and niacinamide derivatives containing benzimidazole moiety. *New Journal of Chemistry*, 2019,43(7), 3000-3010.
- [14] Amjad M. Qandil. Synthesis and Spectroscopic Analysis of Novel 1H-Benzo[d]imidazolylphenylsulfonylpiperazines. *Pharmaceuticals*, 2012, 5(9), 460-468.