HL **ISSN: 2231 – 3087(print) / 2230 – 9632(Online)**
http://heteroletters.org **Vol. 2: (4), 2012, 467-478**

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)

Dr.Piyush V Patel*, Dr.Narendra Joshi, Dharmesh P Panchal

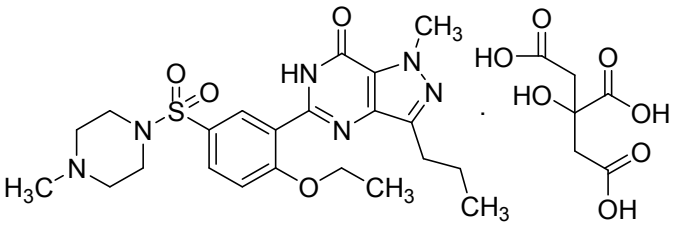
Amoli Organics Pvt. Ltd. Plot No.422, 432, Village-Luna, Taluka-Padra.Baroda-391440.
Corresponding author: Phone: + 91-9978904978,E-mail:piyush.patel@amoliindia.com

Abstract:
Sildenafil citrate (1), a substituted pyrazole derivative, is a Viagra drug was made by a group of pharmaceutical chemists at Pfizer's research facility in England. It was studied to aid in hypertension or high blood pressure, and angina pectoris which is a symptom of heart disease. An improved cost-effective and impurity-free process for Sildenafil citrate (1) suitable for large-scale production is described here by addressing various process development issues. A comparative account on commercial and medicinal chemistry routes for the synthesis of Sildenafil citrate. The discovery of an impotence prescription drug came about by accident. Sildenafil Citrate was first tested for the treatment of heart disease. During testing the results for the treatment of heart disease were not favorable. But something interesting happened. Many of the patients experienced an erection .Testing for the treatment of heart disease failed. However, because of phenomenon of the erections that the male patients were experiencing, extensive testing for the treatment of erectile dysfunction continued. When results proved that in fact Sildenafil Citrate had close to an 80% success rate, the necessary steps were taken to get the drug approved for the treatment of erectile dysfunction by the FDA. Sildenafil citrate is a drug used to treat erectile dysfunction. It is sold as Viagra and Revatio as well as under other brand names. The drug became available in 1998 and has been used among men for erectile dysfunction as well as some other types of medical problems such as pulmonary hypertension and altitude sickness. Sildenafil can also be used for non medical reasons as well.

Keywords: Sildenafil Citrate Impurity, Viagra drug, Pyrazole derivative

Introduction:

Male erectile dysfunction (MED), the persistent inability to achieve or maintain an erection for satisfactory sexual performance is common and important medical problem.[I, II] According to a random community –based sampled study, over half of men at 40 to 70 years of age suffered from erectile dysfunction.[III-V] Ten percent of the respondents claimed complete dysfunction, while 25% and 17 % were diagnosed as moderate and minimal dysfunction, respectably.



Sildenafil citrate (1)

Recent development of sildenafil citrate (Viagra) as an orally effective agent for the treatment of male erectile dysfunction[VI, VII] (MED) has spurred significant interest in the discovery of additional phosphodiesterase type 5 (PDE5) inhibitors. Sildenafil citrate is a potent reversible and selective PDE5 inhibitor that blocks cGMP hydrolysis effectively(Ki=3nM).PDE5 is the predominant cGMP –hydrolyzing enzyme present in the corpus cavernosum (the smooth muscle in the penis) which helps to control the vascular tone under normal conditions from the cavernosal nerve upon sexual stimulation. This activates soluble guanylyl cyclase in the corpus cavernosum causing an increase in intracellular cGMP, which is normally hydrolyzed by PDE5.Inhibition of PDE5elevates levels of the cyclic nucleotide, leading to enhanced relaxation of smooth muscle, increased arterial inflow, venous congestion, and ultimately resulting in improved penile erection in men with erectile dysfunction. Despite the efficacy of sildenafil as a treatment of MED, there are some notable drawbacks associated with its use. Clinically, significant adverse effects such as headache (16%), facial flushing (10%), dyspepsia (7%), and visual disturbances (3%) have been reported, and their incidence is dose –depend. Certain of these side effects are thought to be due to non-specific inhibition of other PDEs, specially PDE1 and PDE6.

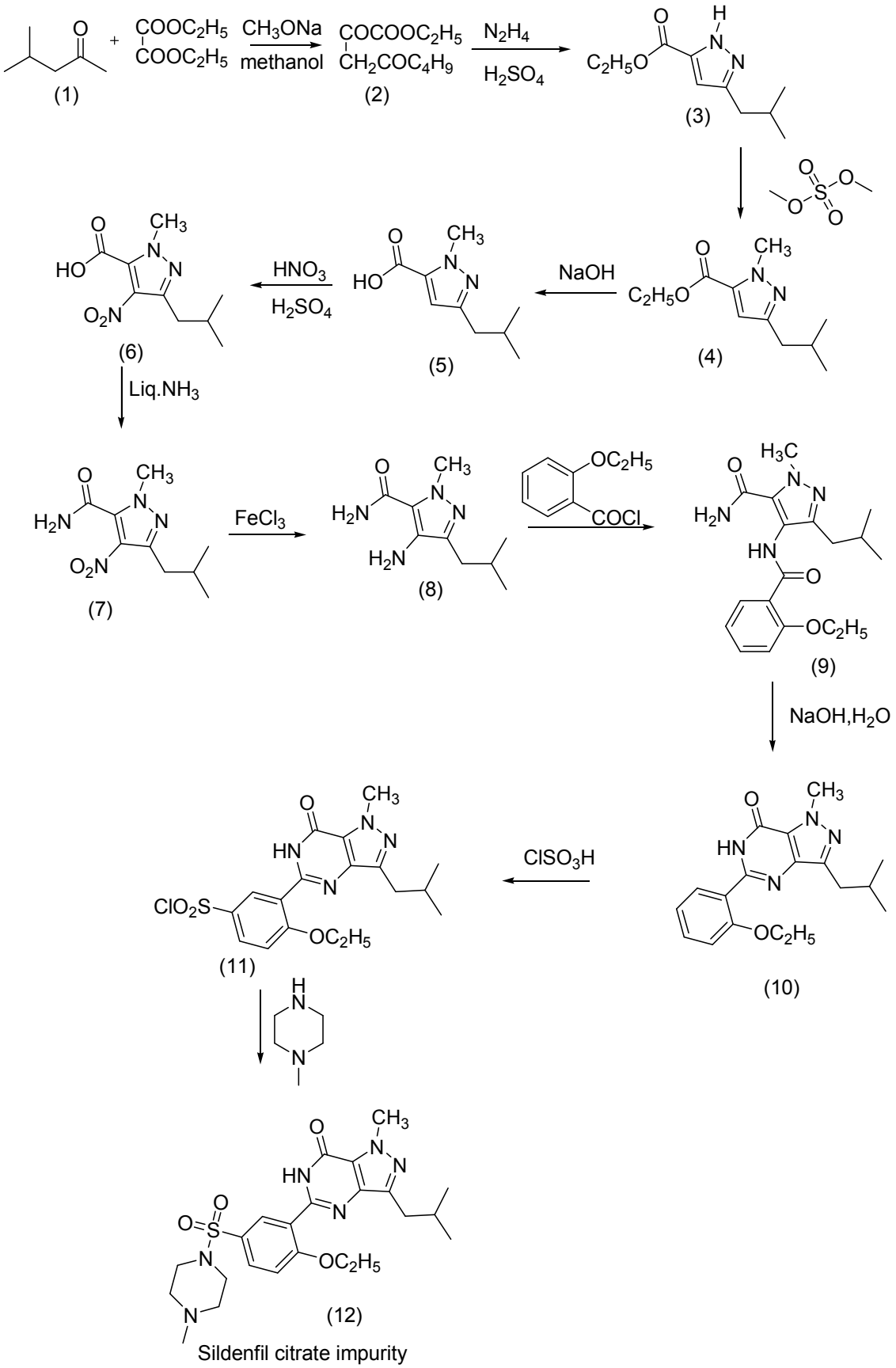
Therefore, in order to eliminate above drawbacks, various compounds as analogues of sildenafil with improved selectivity against PDEs are reported, which are either isolated from plants as natural products like papaverine[VIII-,X],dehydroepiandrosterone, yohimbine, l-citrulline[(N_5-aminocarbonyl)-l-], Pyrano-isoflavone, Berberine prostaglandinE1, forskolin[XI-XV], furost-5-ene-3, 22, 26-triol, Macardine, N-benzyl-5-oxo-6E, 8E-octadeca dieneamide[XVI-XX], Panaxsapogenin,[XXI]or synthesized by various groups around the globe. In almost all previous syntheses to search for more selective PDEs inhibitors follow a synthetic pathway described by Terrett et al that carry some draw backs including the use of environmentally banned chemicals lengthy pathway long reaction time, tedious reaction workup involvement of conventional heating cost effect etc commercially these kinds of compounds are produced by the Pfizer's commercial synthesis. A comparative account on the advantages and disadvantages of both synthetic processes is outlined in the following phrases.

The commercial synthesis[XXIII] generates 9 kg (10 L) of organic waste per kilogram sildenafil compared with the industry norm[XXIV] of 25-100 kg. Waste production is being reduced by various time by time discoveries of new designed, convergent, synthetic routes, like cyclization reaction as the final step (Scheme 10) which eliminates the purification operations. Subsequent careful chemical development and thorough solvent recovery optimized the environmental performance. Achievement includes a nine-fold yield increase from the pyrazole 76 to sildenafil citrate. The amount of organic and aqueous waste is reduced 15 and 5 fold eliminating 4000 tones and 3900 tones of organic and aqueous waste, respectively. In addition, the elimination of

highly volatile solvent such as dichloromethane, ether, acetone and methanol also makes a substantial reduction to atmospheric pollution. A tin chloride (toxic heavy metal) reduction was replaced by an environmentally benign catalytic hydrogenation reaction. Hydrogen peroxide (a worker safety issue and fire hazard) was eliminated. Three chemical steps were combined, using a single solvent that was recovered. Through innovative chemistry, including a new bond forming sequence, waste elimination, solvent reductions strategies and yield maximization of the desired reaction pathway have demonstrated significant green chemistry innovations for an important pharmaceutical agent. The direct pollution prevention, which benefits to society are substantial, noteworthy with additional benefits of safety.

Reaction Scheme:

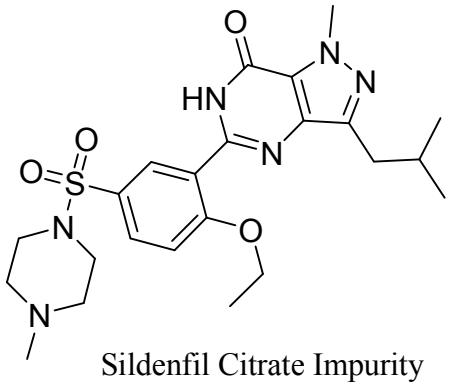
Synthetic of Sildenfil citrate impurity



Sildenfil citrate impurity

The present research provides an impurity of Sildenafil Citrate, designated Compound 1.

Compound 1, or 5-(2-ethoxy-5-((4-methylpiperazin-1-yl) sulfonyl) phenyl)-3-isobutyl-1-methyl-1H-pyrazolo [4, 3-d] pyrimidin-7(6H)-one, has the following chemical structure:



Sildenfil Citrate Impurity

Formula 1

Compound 1 has the following 1H NMR (400 MHz, DMSO) δ (ppm) 8.00, 3.06, 3.06, 2.37, 2.37, 7.91, 7.34, 8.39, 4.09, 3.85, 2.26, 2.51, 1.82, 1.32, 0.81, 0.91. 13C NMR (400 MHz, DMSO) δ (ppm) 147.1, 136.2, 104.2, 131.4, 157.1, 157.3, 159.2, 48.5, 48.5, 56.2, 56.2, 106.6, 127.1, 111.8, 119.5, 64.6, 40.1, 46.6, 33.4, 27.5, 14.8, 22.8, 22.8. Mass (m/z) 488.22 (100%), 489.22 (28.0%), 490.22 (6.1%), 490.23 (3.1%), 491.22 (1.2%)

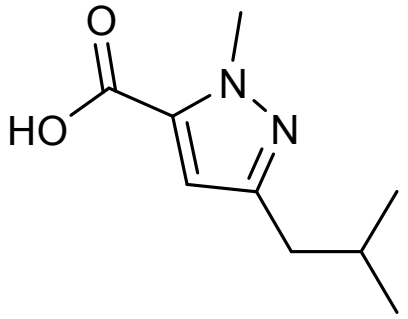
In another aspect, the research encompasses a process for synthesizing Compound 1. The structure of compound 1 is determined by structural analysis of both the synthesized compound and the compound isolated from the preparation of Sildenafil citrate. A Sildenafil citrate impurity prepared by an independent chemical synthesis is indistinguishable from that isolated from the reaction mixture containing Sildenafil citrate. By increasing the reaction time of the preparation of Sildenafil citrate significantly after the reaction is finished, it is possible to receive relatively large amounts of this impurity.

Compound 1 was synthesized by reacting 4-methylpentan-2-one and diethyl oxalate as the key starting materials.

The process comprises:

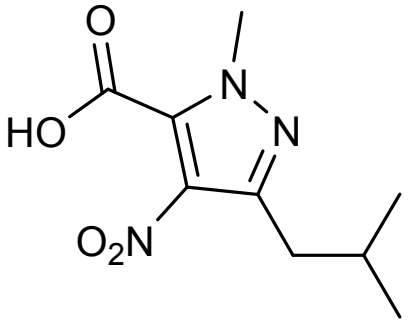
(a) combining 4-methylpentan-2-one and diethyl oxalate in a solvent with sodium methoxide to give ethyl 2, 4-dioxo-octanoate which was then further reacted with
(b) diamine in the presence of strong acid, to give ethyl 3-isobutyl-1H-pyrazole-5-carboxylate.
(c) Dimethyl sulfate was added to the reaction followed by a base to give carboxylic acid.
(d) Nitration of the reaction was carried out with nitric acid in presence of sulfuric acid to form nitropyrazole
(e) And addition of liquid ammonia resulted in pyrazole carboxamide.
(f) Reduction with ferric chloride gave amino pyrazole.
(g) To this, 2-ethoxy benzoyl chloride was added to give pyrazole-5-carboxamide

(h) And aq NaOH was added to form 5-(2-ethoxyphenyl)-3-isobutyl-1-methyl-1H-pyrazolo [4, 3-d] pyrimidin-7(6H)-one.
(i) Addition of chlrosulphonic acid gave 4-ethoxy-3-(3-isobutyl-1-methyl-7-oxo-6, 7-dihydro-1H-pyrazolo [4, 3-d] pyrimidin-5-yl) benzene-1-sulfonyl chloride
(j) Which was then reacted with 1-methyl piperazine to give the Sildenafil citrate impurity 5- (2-ethoxy-5- (4- methylpiperazine - 1 – yl sulfonyl) phenyl) – 3 – isobutyl – 1 – methyl - 1H –pyrazolo [4, 3-d] pyrimidin-7(6H)-one.



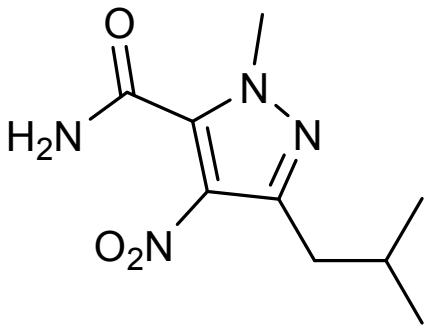
Formula 6

The solvent used in step (a) can be methanol, ethanol, propanol, butanol and the likes, but best results were found in methanol as solvent. The cyclization of ethyl 2, 4-dioxo-octanoate was carried out in the presence of strong acid like sulphuric acid to give ethyl 3-isobutyl-1H-pyrazole-5-carboxylate. The base used for hydrolysis in step (c) was NaOH and the product formed, 3-isobutyl-1-methyl-1H-pyrazole-5-carboxylic acid was first diluted with water and then acidified with concentrated hydrochloric acid. Pale brown crystals of compound of formula 6 were obtained by crystallization



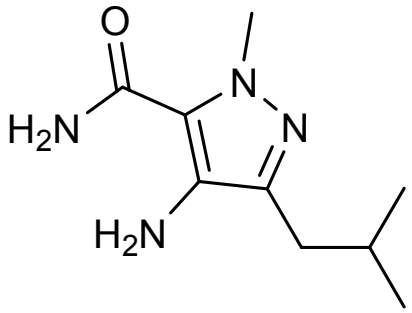
Formula 7

The nitration of the product of step (c) was carried out with concentrated nitric acid in the presence of concentrated sulfuric acid and the mixture was heated at 60°C overnight. The mixture was cooled to room temperature and poured onto ice and filtered to extract the white solid of nitropyrazole compound of Formula 7.



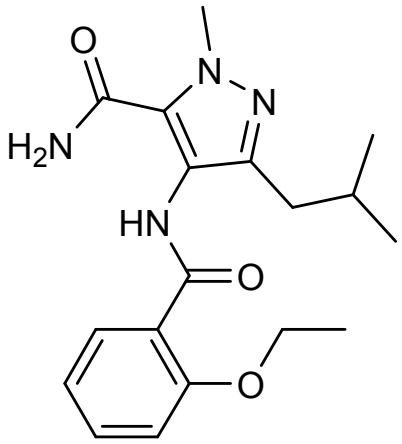
Formula 8

Nitropyrazole was then reacted with thionyl chloride to give an oily residue that was dissolved in acetone and poured onto a mixture of ice and concentrated ammonium hydroxide solution to give the pale yellow solid of pyrazole carboxamide compound of Formula 8.



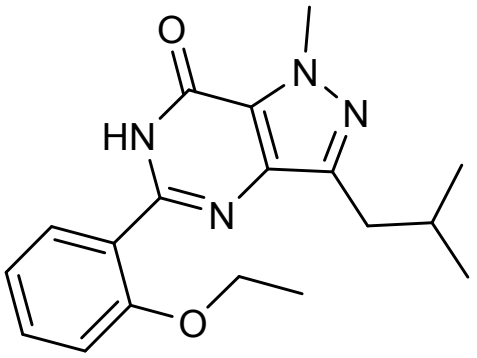
Formula 9

The compound 8 formed was reduced with stannous chloride dihydrate or ferric chloride in ethanol, the mixture was refluxed for 2-3 hrs. It was then cooled to room temperature and basified to pH 9 with 2N NaOH. The off white solid of aminopyrazole was extracted by vacuum evaporation in DCM.



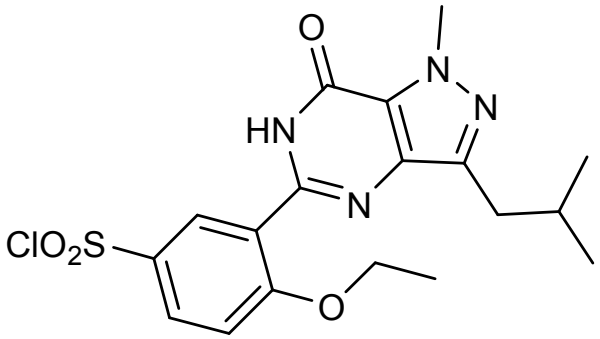
Formula 10

Aminopyrazole thus obtained was reacted with 2-ethoxy benzoyl chloride in a suitable solvent such as DCM and 4-diethylaminopyridine and triethylamine in DCM at low temperature of 0°C. The mixture was allowed to warm to room temperature (25-30°C) and stirred thoroughly. The solvent was evaporated under vacuum and the residue was dissolved in a mixture of DCM and methanol. The solution was washed with 1N hydrochloric acid, dried and evaporated under vacuum. The crude material formed was again eluted with DCM and methanol to give a pink colored solid that was recrystallized from ethyl acetate to give compound of Formula 10.



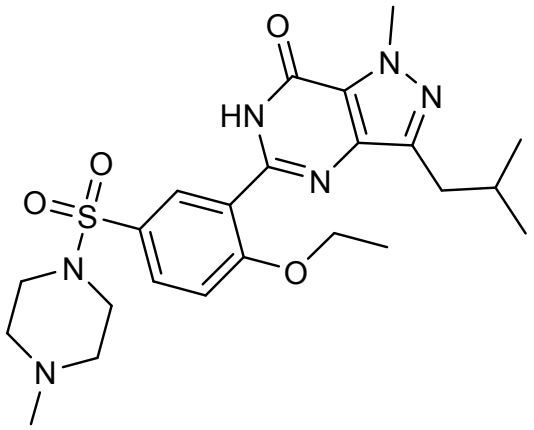
Formula 11

The crystallized compound 10 was hydrolyzed in the presence of sodium hydroxide and hydrogen peroxide solution in water. Ethanol was added and the mixture was refluxed for 2-3 hrs. The mixture was then cooled and evaporated under vacuum. The residue was treated with 2N hydrochloric acid with external cooling and extracted with DCM. The organic extracts were washed with aq sodium carbonate and dried under vacuum. The crude compound was chromatographed and triturated with ether to give colorless compound of Formula 11.



Formula 12

Compound of Formula 11 is then potion wise added to chlorosulphonic acid at 0°C in a nitrogen atmosphere and stirred thoroughly or 10-12 hours. The mixture is then added to ice water and extracted with DCM and methanol and vacuum dried to give white solid of compound of Formula 12.



Formula 1

N methyl piperazine in ethanol was added to compound of Formula 12 and stirred thoroughly for 20-24 hrs and then vacuum dried to give a crude product. The crude was then partitioned between ethyl acetate and water and recrystallized from ethyl acetate or dimethylformamide to give off the white powder of the Sildenafil citrate impurity.

Synthesis Process:

3-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (1-5)

Charge 400.0 ml of methanol at room temperature under nitrogen atmosphere and cool the reaction to 5-15^{0}C then charge sodium methoxide drop wise slowly at 5-15^{0}C and stir for 15 mints check the moisture it should be below 0.5 % then raise the temperature of reaction mass to 25-30^{0}C and then charge the mixture of methyl isobutyl ketone (30.0 gm,) and diethyl oxalate during 2 hrs at 25-30^{0}C.maintain the reaction mass for 12 hrs at 25-30^{0}C.after then raise the reaction mass temperature to 40-45^{0}C and maintain it for 4 hrs at 40-45^{0}C.cool the reaction mass to 25-30^{0}C.
Take 200.0 ml methanol at 25-30^{0}C and charge hydrazine hydrate slowly during 1 hrs in 60 at 25-30^{0}C.add conc. sulphuric acid under vigorous stirring below at 50^{0}C then cool the reaction mass to 25-30^{0}C add above reaction mass solution to this reaction mass in 15-20mints at 25-30^{0}C. raise the reaction temperature to 60-65^{0}C and maintain it for 4 hrs at 60-65^{0}C after then filter the reaction mass and washed it with methanol. Distilled filter ml at atmospherically at 70^{0}C. Completely. Charge the water into residue and stir for 15 mints then charge 400.0 ml MDC and stir for 15 mints separate the layer take organic layer and distilled out organic layer atmospherically up to 60^{0}C and remove traces of MDC by vacuum. Cool the residue to 20-25^{0}C and add dimethyl sulphate during 2hrs at 20-25^{0}C. raise the temperature 80^{0}C and maintain at 80-85^{0}C for 8 hrs after then charge 600.0 ml water at 80-85^{0}C and slowly cool to RT then add 6N aqueous sodium hydroxide solution (50 ml, 0.30 mol) to the reaction mass slowly at 25-30^{0}C . The mixture was heated to 80° C. for 2 hours then diluted with water (50 ml) an acidified with concentrated hydrochloric acid (25 ml). Filtration gave the carboxylic acid as pale brown crystals

3-butyl-1-methyl-4-nitro-1H-pyrazole-5-carboxylic acid (6)

3-butyl-1-methyl-1H-pyrazole-5-carboxylic acid (12.1 g, 0.075 mol) was added portion wise to a mixture of conc. sulphuric acid 98% (13 ml) and fuming nitric acid (11 ml), keeping the temperature below 60° C.

After the addition, the mixture was heated at 60° C. overnight and then cooled to room temperature before being poured onto ice; filtration then gave the nitropyrazole as a white solid

3-butyl-1-methyl-4-nitro-1H-pyrazole-5-carboxamide (7)

3-butyl-1-methyl-4-nitro-1H-pyrazole-5-carboxylic acid (11.3 g, 0.053 mol) was added to thionyl chloride (50 ml) and the resulting mixture heated under reflux for 3 hours. The reaction mixture was then cooled and excess thionyl chloride removed by evaporation under vacuum. The oily residue was dissolved in acetone (50 ml) and the solution cautiously added to a mixture of ice (50 g) and concentrated aqueous ammonium hydroxide solution (50 ml). The precipitate was collected by filtration to provide the pyrazolecarboxamide as a pale yellow solid

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

3-butyl-1-methyl-4-nitro-1H-pyrazole-5-carboxamide (3.45 g, 16.2 mmol) and stannous chloride dihydrate (18.4 g, 81 mmol) were suspended in ethanol and the mixture heated under reflux for 2 hours. The resulting solution was cooled to room temperature, basified to pH 9 by the addition of 2N aqueous sodium hydroxide solution and extracted with dichloromethane (3×150 ml). The organic extracts were combined, dried ($MgSO_4$) and evaporated under vacuum. Trituration of the residue with ether gave the aminopyrazole as an off-white solid

3-butyl-4-(2-ethoxybenzamido)-1-methyl-1H-pyrazole-5-carboxamide (9)

A solution of 2-ethoxybenzoyl chloride (6.1 g, 33.0 mmol) in dichloromethane (50 ml) was added to a stirred solution of 4-amino-3-butyl-1-methyl-1H-pyrazole-5-carboxamide (3.0 g, 16.4 mmol), 4-dimethylaminopyridine (0.02 g, 0.164 mmol) and triethylamine (3.34 g. 33.0 mmol) in dichloromethane (50 ml) at 0° C. The resulting mixture was allowed to warm to room temperature and stirred for a further 2 hours. The solvent was evaporated under vacuum, the residue dissolved in a 19:1 mixture of dichloromethane and methanol (250 ml), and then the solution washed with 1N hydrochloric acid (100 ml), dried ($MgSO_4$) and evaporated under vacuum. The crude material was chromatographed on silica gel (200 g), eluting with a 97:3 mixture of dichloromethane and methanol, to give a pink solid; crystallization from ethyl acetate-hexane gave the pyrazole-5-carboxamide as a pale pink solid

3-butyl-5-(2-ethoxyphenyl)-1-methyl-1H-pyrazolo [4, 3-d] pyrimidin-7(6H)-one (10)
4-(2-Ethoxybenzamido)-1-methyl-3-n-propylpyrazole-5-carboxamide (30.0 g, 0.676 mol) was added portion wise to a solution of sodium hydroxide (54 g, 1.35 mol) and 30% hydrogen peroxide solution (224 ml) in water (2000 ml). Ethanol (700 ml) was added and the resulting mixture heated under reflux for 2.5 hours, cooled, then evaporated under vacuum. The resulting solid was treated with 2N hydrochloric acid (380 ml), with external cooling, and the mixture was extracted with dichloromethane (1×700 ml, 3×200 ml). The combined organic extracts were washed successively with saturated aqueous sodium carbonate solution (3×400 ml) and brine (300 ml), then dried ($Na_2 SO_4$) and evaporated under vacuum. Chromatography of the residue on silica gel (1000 g), using a methanol in dichloromethane elution gradient (0-1% methanol), followed by triturating of the crude product with ether (300 ml), gave the title compound as a colorless solid
3-(3-butyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxybenzene-1-sulfonyl chloride (11)
3-butyl-5-(2-ethoxyphenyl)-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one (25.0 gm 32.1 mmol) was added protionwise to chlrosulphonic acid (25 ml) at 0^0C under a nitrogen atmosphere after being stirred overnight the reaction solution was cautiously added to ice-water(150 ml) and the aqueous mixture extracted with a 9:1 mixture of dichloromethane and methanol(4 x 100 ml) the

combined extract were dried and evaporated under vacuum to give the required suphonyl chloride as a white solid.

5-(2-ethoxy-5-((4-methylpiperazin-1-yl) sulfonyl) phenyl)-3-isobutyl-1-methyl-1H-pyrazolo[4,3-d]pyrimidin-7(6H)-one (12) (Sildenafil Citrate Impurity).

A solution of 3-(3-butyl-1-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-4-ethoxybenzene-1-sulfonyl chloride (15.1 gm,0.0007 mol) and N-methylpiperazine (32 ml 0.0046 mol) in ethanol was stirred at room temperature for 22 hrs the solution was evaporated under vacuum and the residue partitioned between ethyl acetate and water the fine precipitate was filtered off washed with water then ethyl acetate and crystallized from ethyl acetate/DMF to give the title compound as an off white powder.

Experimental Analysis

All the melting points are taken in an open capillary and uncorrected. The IR spectra was recorded with KBr pellets on Per kin-Elmer 783 Spectrophotometer and H1-NMR spectra on a In strum DPX 300 MHz using solvent DMSO-d6 Purity of the compounds in addition to elemental analysis was checked by TLC.

Table 1 THE ANALYTICAL DATA OF THE SILDENAFIL IMPURITY

Comp. No.	Molecular Formula	Molecular Weight	Melting Point ^{0}C	% Yield	Elemental Analysis % theoretical (Practical)				
					C	H	N	O	S
5.	$C_9H_{14}N_2O_2$	182.22	160-162	76	59.32(59.45)	7.74(7.78)	15.37(15.33)	17.56(17.54)	-
6.	$C_9H_{13}N_3O_4$	227.22	133-135	72	47.57(47.48)	5.77(5.79)	18.49(18.47)	28.17(28.16)	-
7.	$C_9H_{14}N_4O_3$	227.11	146-148	81	47.78(47.79)	6.24(6.29)	24.77(24.80)	21.22(21.25)	-
8.	$C_9H_{16}N_4O$	196.25	105-107	86	55.08(55.10)	8.22(8.25)	28.55(28.54)	8.15(8.22)	-
9.	$C_{18}H_{24}N_4O_3$	344.18	153-155	75	62.77(62.78)	7.02(7.04)	16.27(16.25)	13.94(13.95)	-
10.	$C_{18}H_{22}N_4O_2$	326.39	150-152	83	66.24(66.23)	6.79(6.82)	17.17(17.16)	9.80(9.85)	-
11.	$C_{18}H_{21}N_4O_4ClS$	424.9	160-164	89	50.88(50.86)	4.98(4.96)	13.19(13.21)	15.06(15.04)	7.55(7.52)
12.	$C_{23}H_{32}N_6O_4S$	488.6	168-170	79	56.54(56.55)	6.60(6.58)	17.20(17.22)	13.10(13.11)	6..56(6.54)

Acknowledgements:

The author is thankful to Dr.Narendra Joshi for motivating my work and also thankful to Dharmesh Panchal for helping me in my work. Authors are also thankful to Amoli Pharma Pvt Ltd for providing research facilities they are also grateful to SECART LAB for screening the synthetically compounds.

References

I. Anastasas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice;* Oxford University Press: New York, 1988.

II. Constable, D. J. C.; Curzons, A. D.; Cunningham, V. L. *Green Chem.* **2002,** *4,* 521–527. Doi:10.1039/b206169b

III. Trost, B. M. *Science* **1991,** *254,* 1471.

IV. Trost, B. M. *Acc. Chem. Res.* **2002,** *35,* 695–705. doi:10.1021/ ar010068z

V. Sheldon, R. A. *Chem. Ind. (London)* **1992,** 903–906.

VI. Sheldon, R. A. *CHEMTECH* **1994,** 38–47.
VII. Sheldon, R. A. *J. Chem. Technol. Biotechnol.* **1997,** *68,* 381.doi:10.1002/(SICI)1097-4660(199704)68:4<381:: AIDJCTB620-3.0.CO;2-3
VIII. Sheldon, R. A. *Chem. Ind. (London)* **1997,** 12–15.
IX. Dunn, P. J.; Galvin, S.; Hettenbach, K. *Green Chem.* **2004,** *6,* 43–48. doi:10.1039/b312329d
X. Hungerbühler, K. *Ind. Eng. Chem. Res.* **1998,** *37,* 3395–3413.doi:10.1021/ie9708539
XI. Hungerbühler, K. *Ind. Eng. Chem. Res.* **2000,** *37,* 960–972.
XII. Hudlicky, T.; Frey, D. A.; Koroniak, L.; Claeboe, C. D.; Brammer, L. E. *Green Chem.* **1999,** 57–59. Doi:10.1039/a901397k
XIII. Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001,** *3,* 1–6. Doi: 10.1039/b007871i
XIV. Berkoff, C. E.; Kamholz, K.; Rivard, D. E.; Wellman, G.; Winicov, H. *CHEMTECH* **1986,** 552–559.
XV. Anastasas, P. T.; Lankey, R. L. *Green Chem.* **2000,** *2,* 289–295.doi:10.1039/b005650m
XVI. Herrchen, M.; Klein, W. *Pure Appl. Chem.* **2000,** *72,* 1247–1252.
XVII. *Clean Technology for the Manufacture of Speciality Chemical;* Lancaster, M.; Hoyle, W., Eds.; the Royal Society of Chemistry: Cambridge, 2001; pp 1–5.
XVIII. Green Chemistry Program of the U.S. Environmental Protection Agency. http://www.epa.gov/gcc/ (accessed Jan 9, 2008).
XIX. Constable, D. J. C.; Curzons, A. D.; Freitas dos Santos, L. M.; Geen, G. R.; Hannah, R. E.; Hayler, J. D.; Kitteringham, J.; McGuire, M. A.; Richardson, J. E.; Smith, P.; Webb, R. L.; Yu, M. *Green Chem.* **2001,** *3,* 7–9. Doi:10.1039/b007875l
XX. Andreos, J. *Org. Process Res. Dev.* **2009,** *9,* 149–163. Doi: 10.1021/ op049803n
XXI. Andreos, J. *Org. Process Res. Dev.* **2005,** *9,* 404–431. Doi: 10.1021/op050014v
XXII. The hazard warning symbols can be found on the containers of the Chemicals, in chemical catalogues or on the internet.
XXIII. Gowda, D. C.; Mahesh, B. *Synth. Commun.* **2010,** *30,* 3639.
XXIV. Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2011,** *66,* 3235–3237. Doi: 10.1021/ jo001796n

Received on August 7, 2012.