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Research Article

SYNTHESIS AND CHARACTERIZATION OF DIPYRIDAMOLE IMPURITIES BY SEQUENTIAL NUCLEOPHYLLIC SUBSTITUTION REACTION

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ABSTRACT

Dipyridamole is used as drug for the treatment to inhibits blood clot formation and causes blood vessel dilation when given at high doses over a short time by inhibiting the phosphodiesterase enzymes that normally break down cAMP by increasing cellular cAMP levels and blocking the platelet aggregation response to ADP and cGMP. Presence of higher level of related substances or impurities may have harmful effect on body, hence needed to be identified, synthesised & characterised for safer use of the medicine. During process optimization of Dipyridamole drug, impurities were observed. These related substances or impurities were synthesised, characterized and proposed structures we reconfirmed by chemical synthesis. Dipyridamole impurities containing pyrimido-pyrimidine have been synthesized by the reaction of 2,4,6,8-tetrachloropyrimido[5,4-d]pyrimidine with sequential nucleophilic substitutions of piperidine, diethanolamine and ethanolamine in the pattern of C-4, C-8, C-2 and C-6 respectively³. Which have been characterized by using LCMS, ¹H NMR and HPLC analysis.

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INTRODUCTION

Dipyridamole is used as drug for the treatment to inhibits blood clot formation, It is used to dilate blood vessels (Boehringer Ingelheim Pharmaceuticals, Inc. 2016) in people with peripheral arterial disease and coronary artery disease and it has been shown to lower pulmonary hypertension without significant drop of systemic blood pressure (Brown DG *et al*, 2015; Dixon BS *et al* 2009; Derendorf H *et al*, 2005). The safety of a drug product is not only dependent on the toxicological properties of the active drug substance or API (De Schryver EL *et al*, 2007; Sprigg N *et al*, 2008), but also on the impurities formed during the various chemical transformations. Therefore, identification, quantification, and control of impurities in the drug substance and drug product are important parts of drug development for obtaining marketing approval (S.J. Ingale *et al*, 2011; Brown D.G *et al*, 2015). As per the guidelines recommended by ICH, the acceptable level for a known or Unknown impurity or related substances is less than 0.2% in a drug substance. To meet the stringent regulatory requirements, it is more challenging for pharma industry to identify the impurities which are formed in very small quantities in a drug substance. Since most of the time it is very difficult to identify and control impurities within acceptable levels in the process, extra purification steps may then be necessary thereby making the process less competitive (V.S. Tegeli *et al*, 2011; B. Misra *et al*, 2015). The syntheses of impurities are not described in the literature which makes it even more difficult for the organic chemist who must then design a synthesis, which is time consuming. The development of a drug substance is incomplete without the identification of an impurity profile involved in the process. In our study we explored the identification, synthesis and characterization of impurities found in the preparation of dipyridamole. This study will be of immense help for the pharma industry to understand the potential impurities in dipyridamole synthesis and thereby obtain the pure compound (FA Attaby *et al*, 1995; SS Ghabrial *et al*, 1996; S Ranjit Pada *et al*, 2012). The object of this invention to provide novel synthetic route with high purity of dipyridamole impurities containing pyrimidopyrimidine nucleus, upon further study of the specification and appended claims, Pyrimidopyrimidines have been drawn as promising structural units in the field of medicinal chemistry. Pyrimido-pyrimidine derivatives exhibit various types of physiological activity and enter medicinal products and this determines the great attention that has been paid to the synthesis of new compounds of this series. The pyrimido-pyrimidine derivatives drew a lot of attention on various pharmacological activities because of their structural similarity to Purines, like anti-

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microbial (SS Ghabrial *et al*, 1994; M. Suresh *et al*, 2010), antidiabetic, antioxidant (R Ghahremanzadeh *et al*, 2008) and antitumor (NA Devi *et al*, 1998; Osama Mohamed Ahmed *et al*, 2011; M Samir *et al*, 2011).

To this end we have investigated how to control the substitution chemistry of 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine. Besides enabling the synthesis of individual purine mimetics, a better knowledge of the chemistry of 2, 4, 6,8-tetrachloropyrimido [5, 4-d] pyrimidines would provide an opportunity for parallel or combinatorial syntheses of adverse array of novel compounds. 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine is the classical precursor, the pattern of substitution is the typical outcome of two stepwise substitution reactions of 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine, employing an excess of nucleophile in each step. This is because the rates of substitution greatly favour the C-4 and C-8 positions over C-2 and C-6. For example, treatment 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine with an excess of piperidine at ambient temperature led to the formation of 4,8-bis(Piperidine)-2,6- dichloropyrimido [5,4-d] pyrimidine (Yogesh D. Bomme Gowda *et al*, 2012). However, no synthetic details have been reported. In this context, the present study describes identification, synthesis and characterization of dipyridamole impurities.

MATERIALS AND METHODS

Thin layer chromatography was used to monitor the completion of the reaction and homogeneity of the synthesised compound. Melting points were determined using a manual Buchi electro thermal apparatus (range 0-300°C) in open capillary tubes and uncorrected.

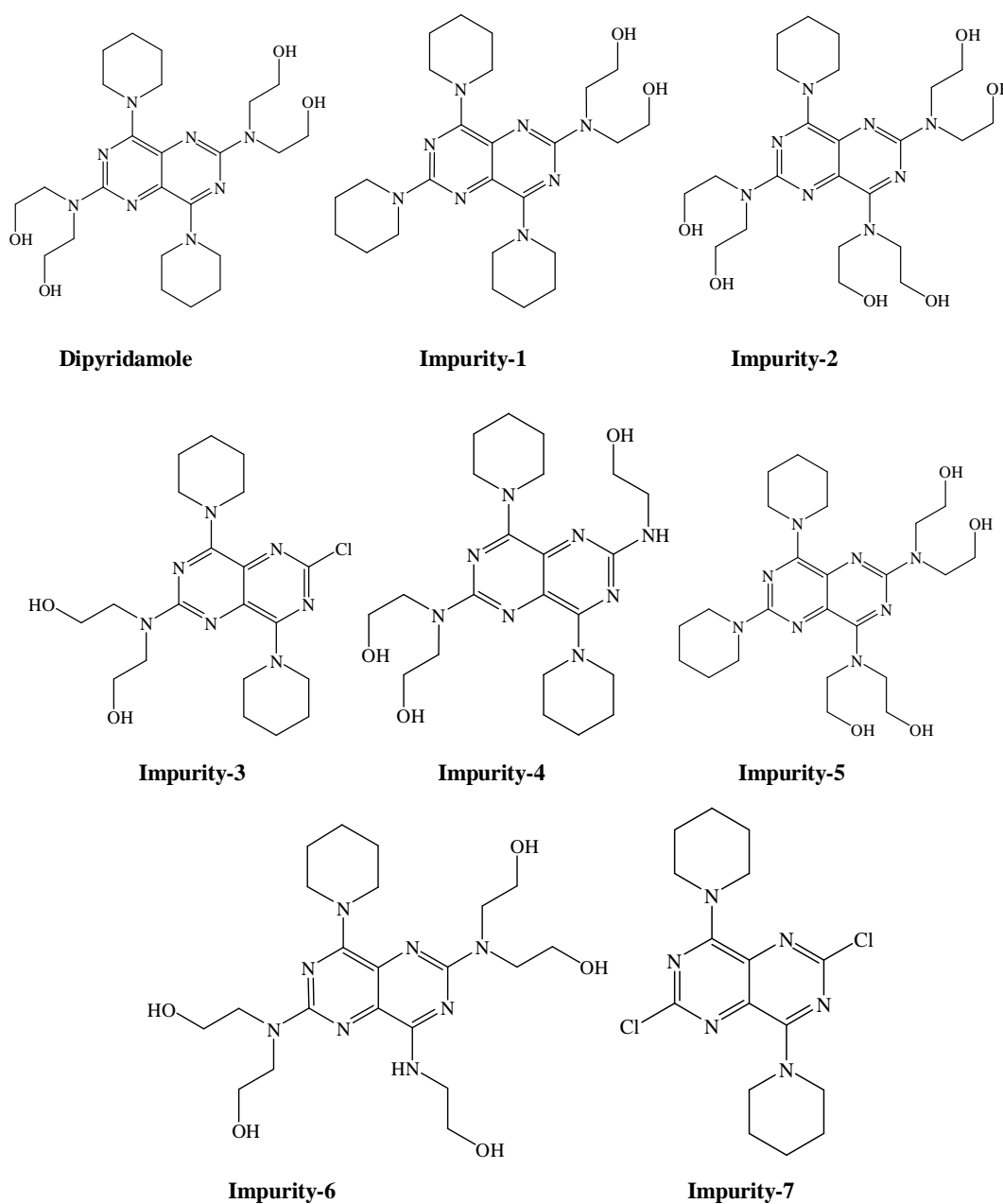
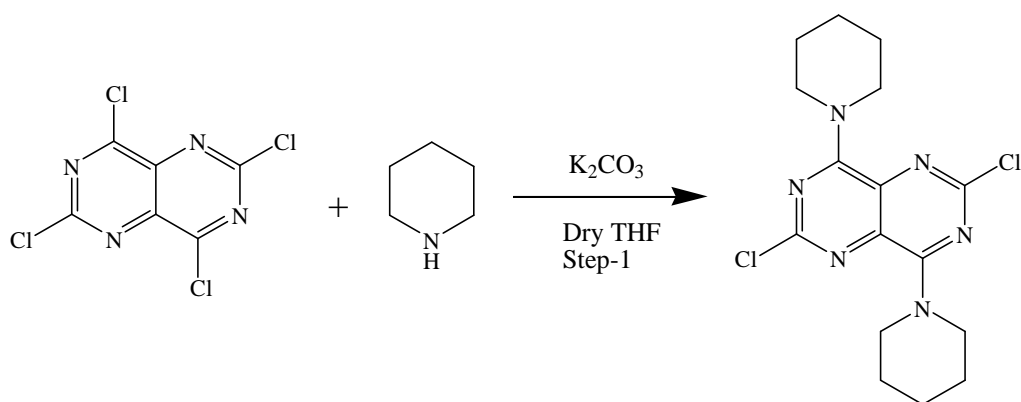
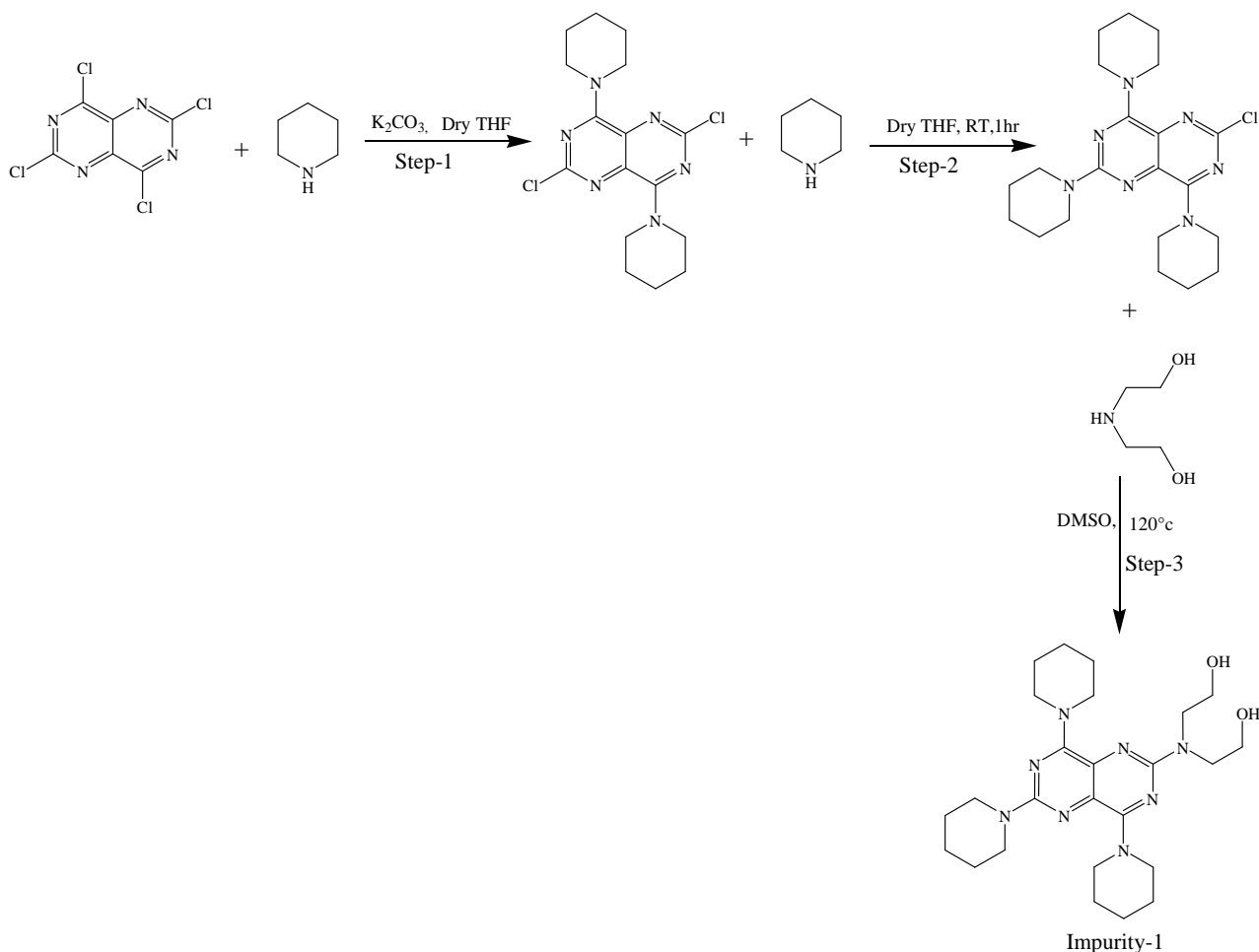


Figure 1 Dipyridamole and its related impurities

Mass spectra were obtained using MS- Agilent technologies- 6130 Quadrupole LC/MS. ¹H-NMR spectra were recorded on Agilent varien 3.2 version,400 MHz in DMSO-d6 /CDCl3 with TMS as an internal standard, yields mentioned are from unoptimized reaction condition of isolated pure product. The homogeneity of the compounds was checked on silica gel coated plates, hexane, ethyl acetate and chloroform as the eluent and observed in UV lamp, iodine vapours or KMnO₄ spray as developing agents. All the synthesised compounds gave satisfactory elemental analysis.

RESULTS AND DISCUSSION

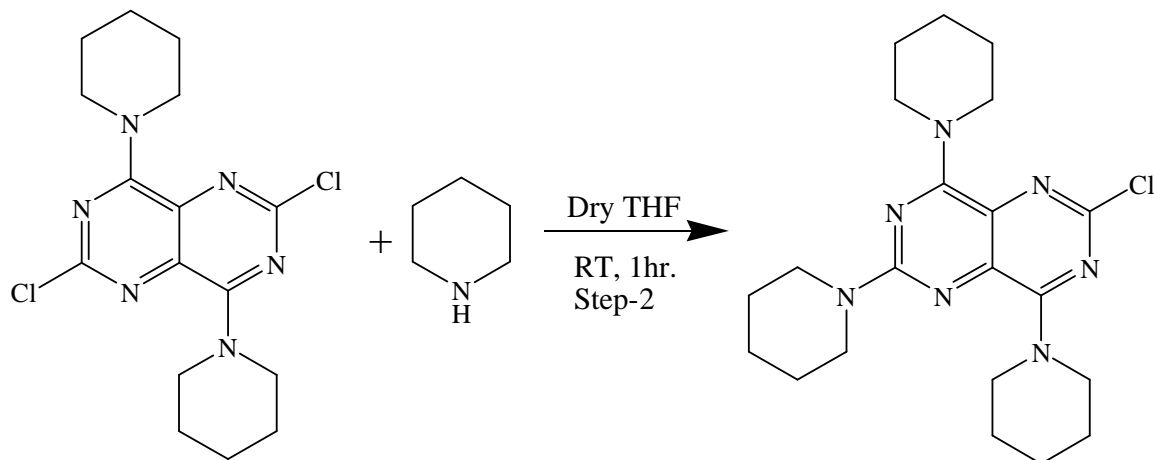
Scheme-1: Synthesis of impurity-1 or impurity A as per EP monograph



To 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine (2.0g, 7.40 mmol) in dry THF (50–60ml) stirred under nitrogen atmosphere at 25°C, was added an appropriate piperidine (3.23g,3.24ml,29.60mmol),2.40 equiv. potassium carbonate. The resulting suspension was agitated for 20 min. Addition of water (80 ml) precipitated the product. The solid was filtered off, washed with water and dried. The resulting product was recrystallised from hot ethyl acetate gave the title compound as fine yellow solid. (2.20g,74%); mp 202-

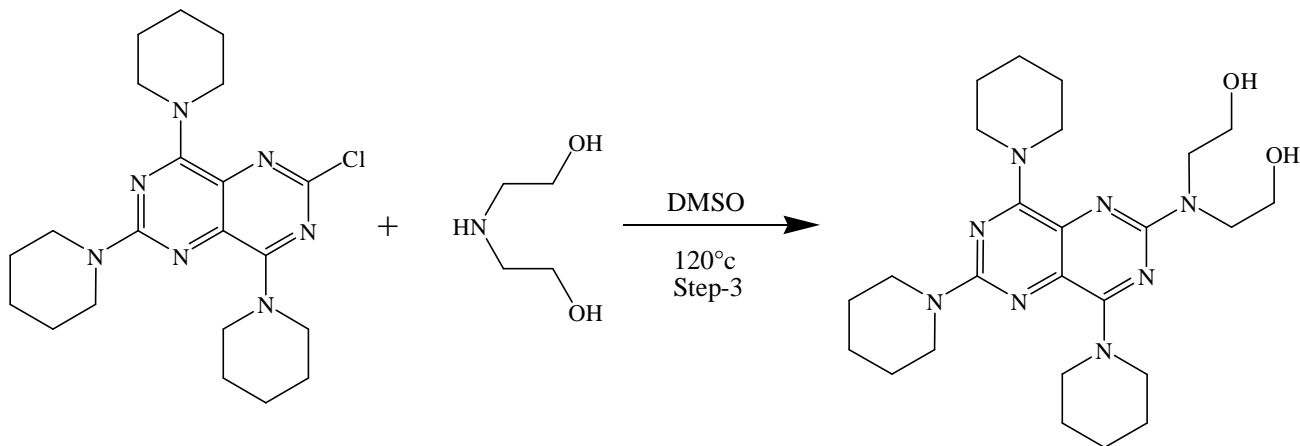
206°C, LC-MS: m/z 367.25 [M+1]. ¹H NMR (CDCl₃): δ 1.58-1.62 (12H, m, -CH₂-); δ 2.90-3.16 (8H, m, -CH₂-). Anal. Calcd for C₁₆H₂₀C₁₂N₆: C, 52.32; H, 5.49; N, 22.88. Found: C, 52.00; H, 5.72; N, 22.62.

Step-2; Synthesis of 2-chloro-4,6,8-tri(piperidin-1-yl)pyrimido[5,4-d]pyrimidine



The 4, 8- bis Piperidine-2, 6-dichloropyrimido [5, 4-d] pyrimidine (0.20 g, 0.24 mmol) dissolved in dry THF under nitrogen, piperidine was added slowly dropwise, the reaction mixture was stirred for 1 hr at room temperature, water (10ml) was added and stirred for 30 minutes, solid was precipitated washed with excess of water to get 99% of solid crystals (0.25 g.). The product was confirmed by LC-MS: m/z 416.2.

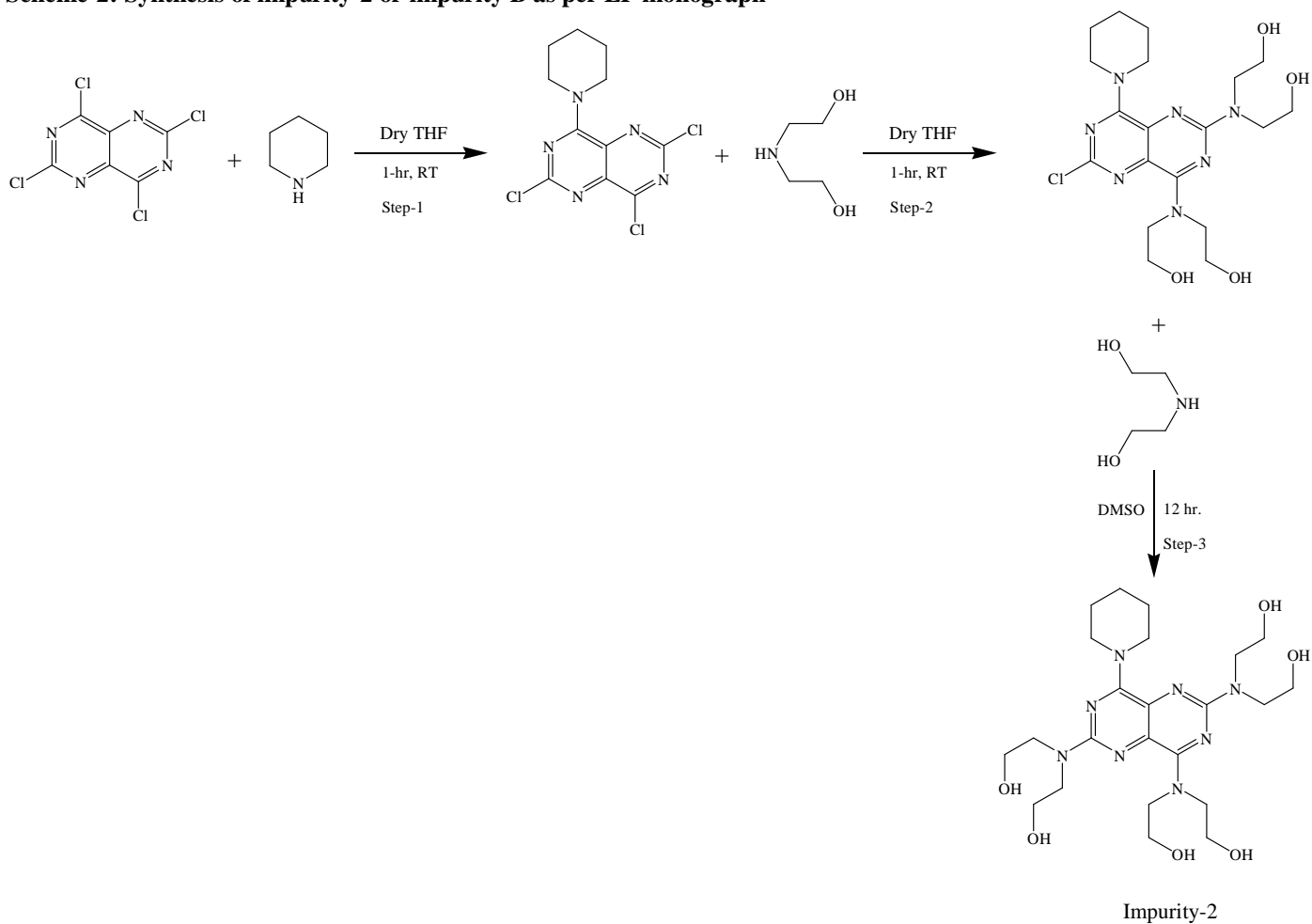
Step-3; Synthesis of 2,2'-[[4,6,8-Tri(piperidin-1-yl)pyrimido[5,4-d]pyrimidin-2-yl]nitrilo] diethanol



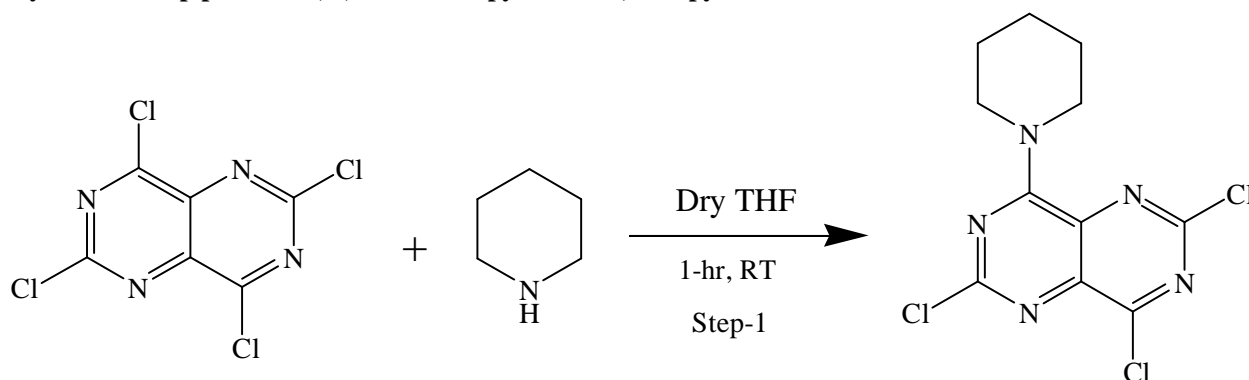
Impurity-1

To the step-2, product: 2-chloro-4,6,8-tri(piperidin-1-yl) pyrimido[5,4-d] pyrimidine (0.20 g, 0.24 mmol) dissolved in DMSO, added diethanolamine dropwise at RT, temperature raised to 120° C for 3-4 hours, reaction was monitored by TLC, reaction mixture was cooled to 50°C, acetone and water 50:50 was added, stirred for 1 hr at room temperature, solid was precipitated, filtered off the reaction mixture, the solid was washed with water followed by hexane and ethyl acetate 60:40 twice to get yellow solid product. (0.2g 99%); mp 202-206°C, LC-MS: m/z 485.4 [M+1]. ¹H NMR (DMSO- d₆): δ 1.58-1.80 (30H, m, -CH₂-); δ 3.30-4.04 (8H, m, -CH₂-). Anal. Calcd for C₂₅H₄₀N₈O₂: C, 61.96; H, 8.32; N, 23.12; O, 6.60 Found: C, 62.00; H, 8.50; N, 24.05; O, 6.45.

Scheme-2: Synthesis of impurity-2 or impurity B as per EP monograph

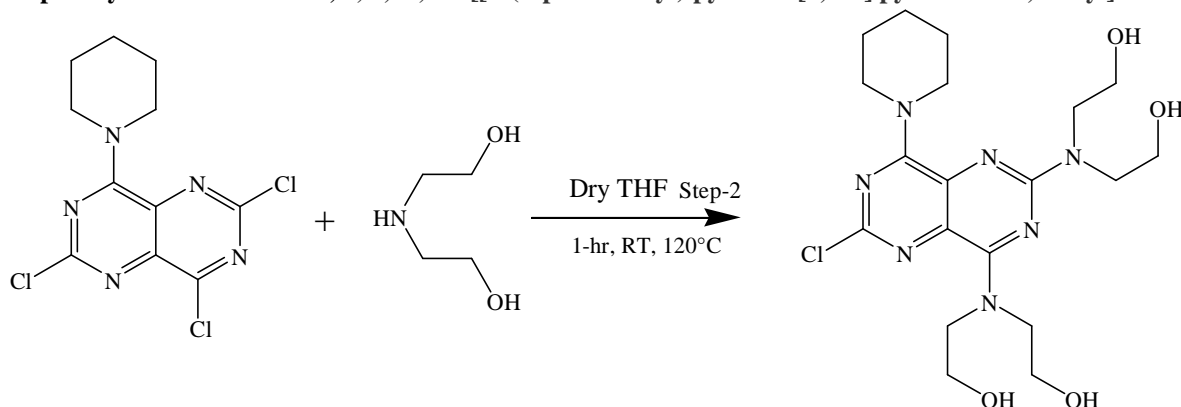


Step-1: Synthesis of 8-piperidine-2, 4, 6- trichloropyrimido [5, 4-d] pyrimidine



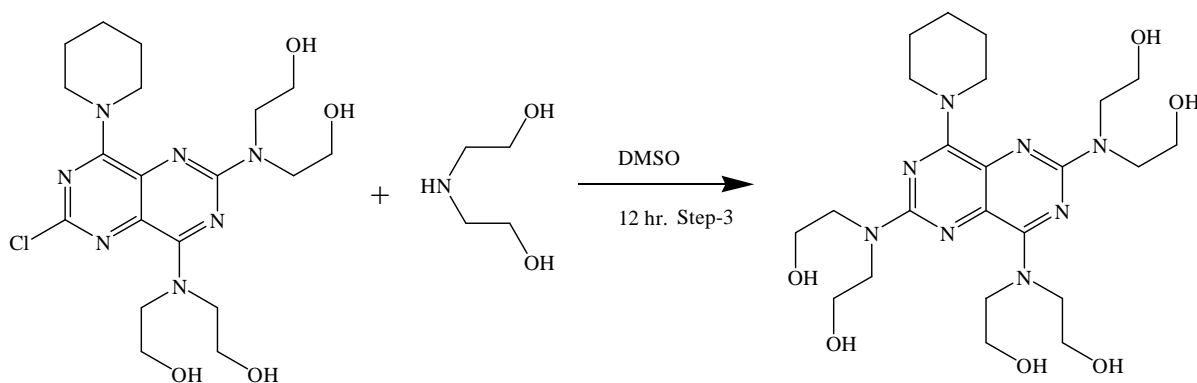
To 2,4,6,8,tetra chloro pyrimido[5,4-d]pyrimidine(1.0 g,0.37 mmol) and potassium carbonate (1.0g, 0.74 mmol) in THF (60 ml), stirred under nitrogen at -78°C , piperidine was added (0.40 g, 0.42 mmol) in THF (60 ml) drop wise from a syringe at a rate of 1 ml per minute. A cloudy yellow solution was obtained and it was allowed to warm up for 10 min. addition of an excess of water gave fine yellow precipitate which was extracted with ethyl acetate. After drying of organic extract over sodium sulphate, removal of the solvent gave a yellow cake, triturate with diethyl ether, filtration and dry under vacuum to give the yellow coloured solid, which was used without further purification (0.90g, 78%). The product formation was confirmed by TLC and LCMS analysis.

Step-2: Synthesis of 6-chloro, 2,2',2'',2'''-[[8-(Piperidin-1-yl) pyrimido[5,4-d] pyrimidine-2,4-diiyl] diinitrilo]hexaethanol.



To the step-1 product, 8-piperidine-2, 4, 6- trichloropyrimido [5, 4-d] pyrimidine. (0.5 g,0.50mmol) dissolved in DMSO at room temperature, dropwise added diethanolamine (0.5 g, 3.0mmol) and heated to 120°C for 1 hr.the reaction mixture was cooled to 50°C added 50ml of water and acetone. The formed solid was washed with hexane 3-4 times followed by ethyl acetate, which was used without further purification (0.60g, 80%).

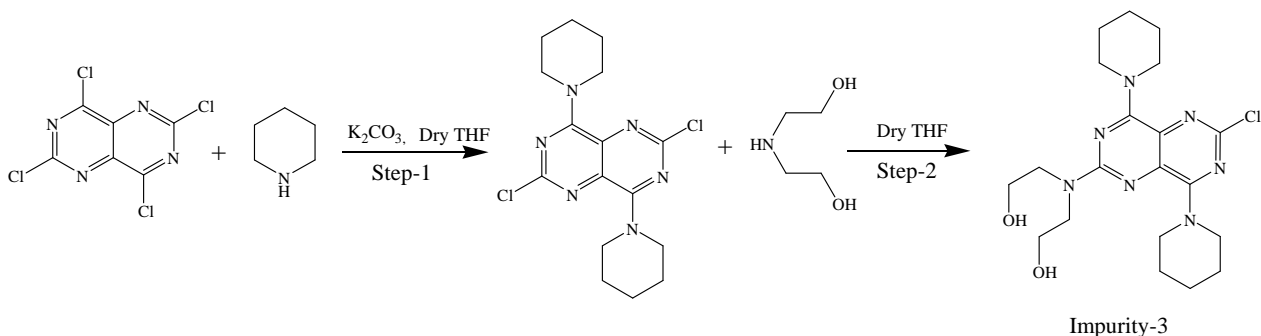
Step-3: Synthesis of 2,2',2'',2''',2''''-[[8-(piperidin-1-yl) pyrimido[5,4-d] pyrimidine-2,4,6-triyl]trinitrilo]hexaethanol



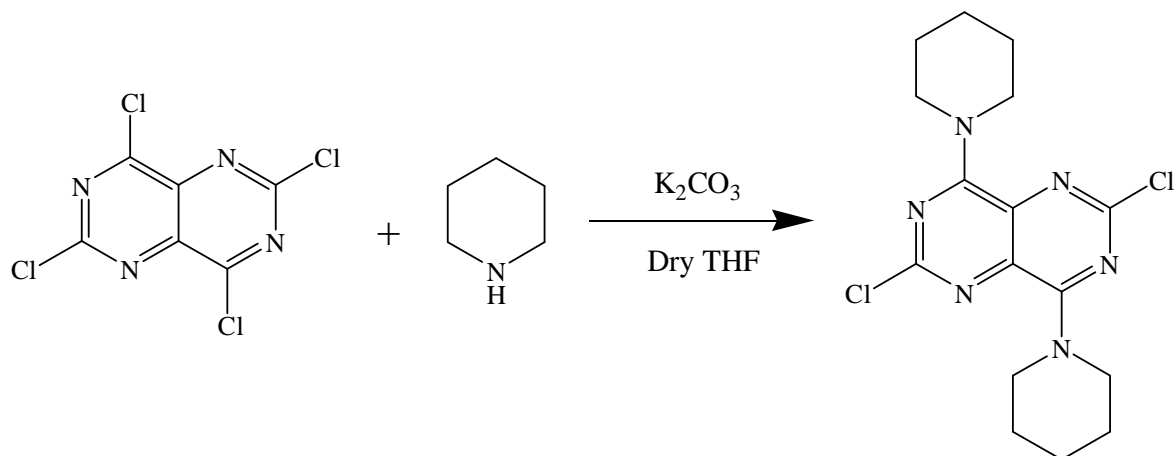
Impurity-2

To the step-2 product,6-chloro, 2,2',2'',2'''-[[8-(Piperidin-1-yl) pyrimido[5,4-d] pyrimidine-2,4-diiyl] diinitrilo] hexaethanol (0.5 g,0.45mmol) dissolved in DMSO at room temperature, dropwise added diethanolamine (0.2 g,1.5mmol) and heated to 120°C for 12 hrs. the reaction mixture was cooled to 50°C added 50ml of water stirred for 50 min at 50°C. Reaction mixture was washed with hexane 3-4 times followed by ethyl acetate twice to get yellow solid, (0.4g 95%); mp 202-206°c, LC-MS: m/z 525.3 [M+1]. 1H NMR (DMSO-d6): δ 1.59-2.49 (8H, m, -CH2-); δ 3.56-3.70 (28H, m,-CH2-). Anal. Calcd for C₂₃H₄₀N₈O₆: C, 52.66; H, 7.69; N, 21.36; O, 18.30 Found: C, 52.50; H, 7.98; N, 21.63.O, 18.80.

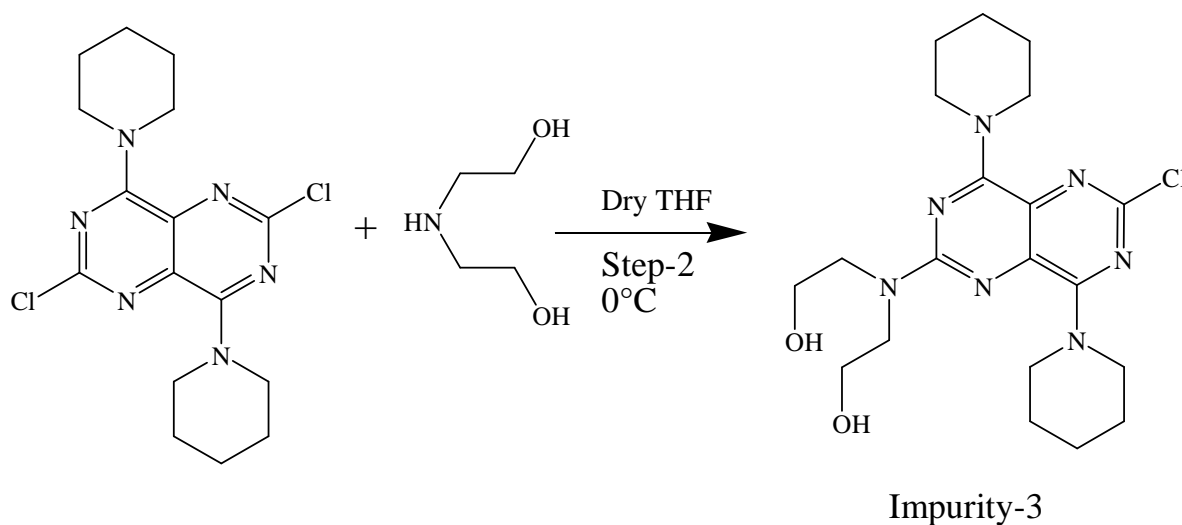
Scheme-3: Synthesis of impurity-3 or impurity C as per EP monograph



Impurity-3

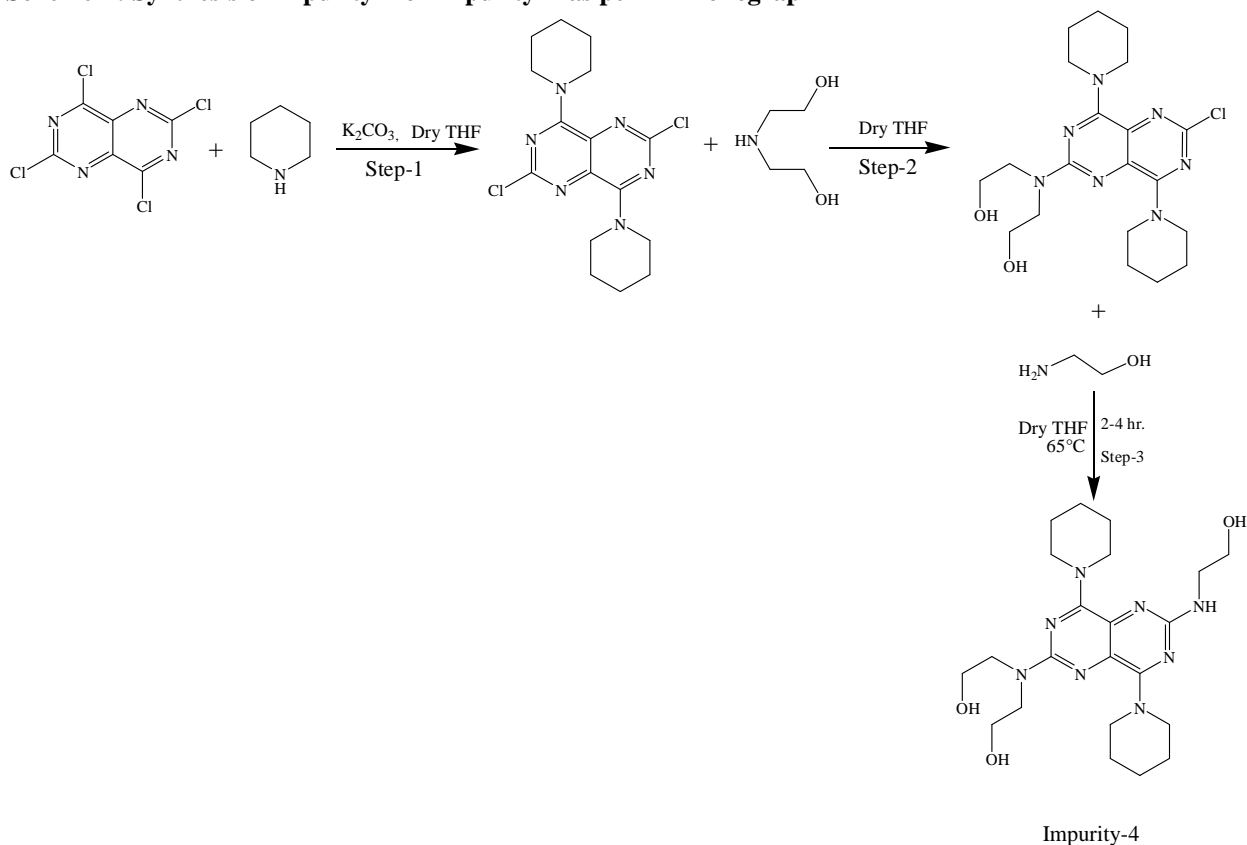
Step-1; Synthesis of 4, 8-bis (piperidine)-2, 6- dichloropyrimido[5,4-d] pyrimidine

To 4,8-bis(Piperidine)-2,6- dichloropyrimido [5,4-d] pyrimidine (2.0g, 7.40 mmol) in dry THF (50–60ml) stirred under N_2 at $25^\circ C$, was added an appropriate piperidine (3.23g,3.24ml,29.60mmol),2.40 equiv. potassium carbonate. The resulting suspension was agitated for 20 min. Addition of water (80 ml) precipitated the product. The solid was filtered off, washed with water and dried. The resulting product was recrystallised from hot ethyl acetate gave the title compound as fine yellow solid. (2.20g,74%); mp $202-206^\circ c$, LC-MS: m/z 367.25 [M+1]. 1H NMR ($CDCl_3$): δ 1.58-1.62 (12H, m, -CH₂-); δ 2.90-3.16 (8H, m, -CH₂-). Anal. Calcd for $C_{16}H_{20}Cl_2N_6$: C, 52.32; H, 5.49; N, 22.88. Found: C, 52.00; H, 5.72; N, 22.62.

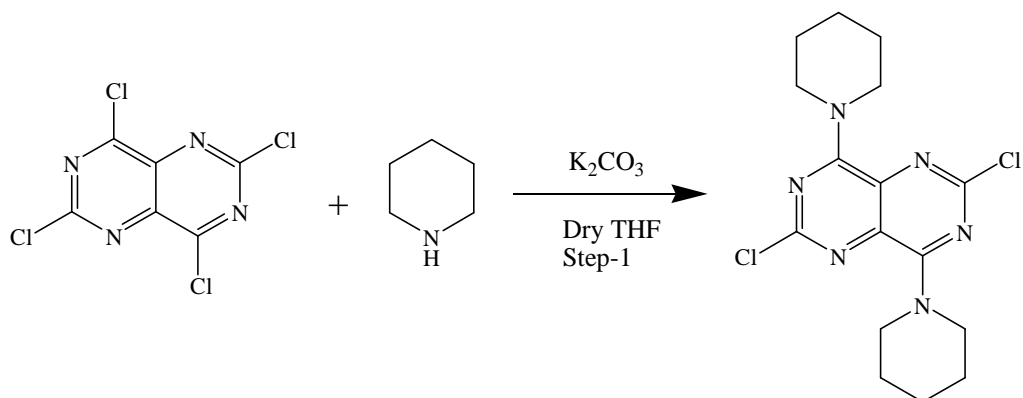
Step-2; Synthesis of 2,2'-[[2-Chloro-4,8-di(piperidin-1-yl) pyrimido[5,4-d]pyrimidin-6-yl]nitrilo] diethanol.

To a stirred solution of step-1 product, 4, 8-bis (piperidine)-2, 6- dichloropyrimido[5,4-d] pyrimidine (0.30 g, 0.88 mmol) in dry THF (12ml) under nitrogen at $0^\circ c$ was added appropriate dihydroxy ethanolamine (>2.0 mol equiv. 33%,0.8 ml) in THF (12 ml) over a 10min period. Precipitate formed and suspension was left to stir for 10-30min. reaction was monitored by TLC, reaction mixture was cooled and 10 volumes of water was added to precipitate the product, filtered off, washed with hexane to get yellow solid. (2.20g,74%); mp $202-206^\circ c$, LC-MS: m/z 436.2 [M+1]. 1H NMR ($DMSO-d_6$): δ 1.58-1.64 (20H, m, -CH₂-); δ 3.6 (8H, m, -CH₂-). Anal. Calcd for $C_{20}H_{30}ClN_7O_2$: C, 55.10; H, 6.94; Cl, 8.13; N, 22.49; O, 7.34 Found: C, 55.50; H, 7.25; Cl, 7.98; N, 22.56; O, 7.20.

Scheme-4: Synthesis of impurity-4 or impurity D as per EP monograph

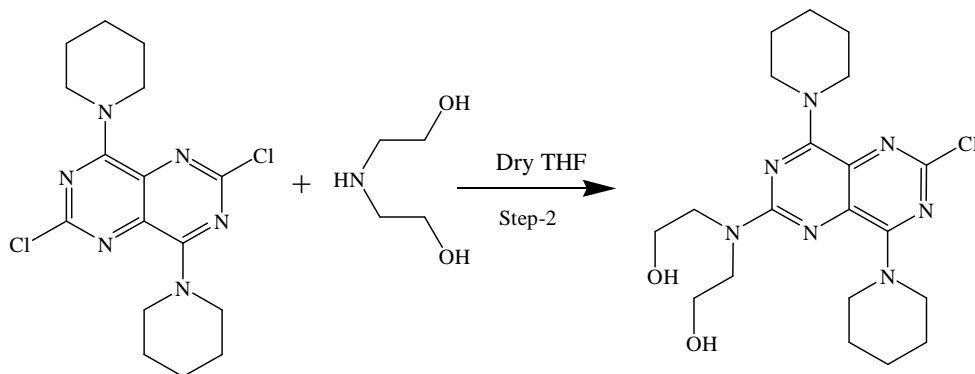


Step-1; Synthesis of 4, 8-bis (piperidine)-2, 6- dichloropyrimido[5,4-d] pyrimidine.



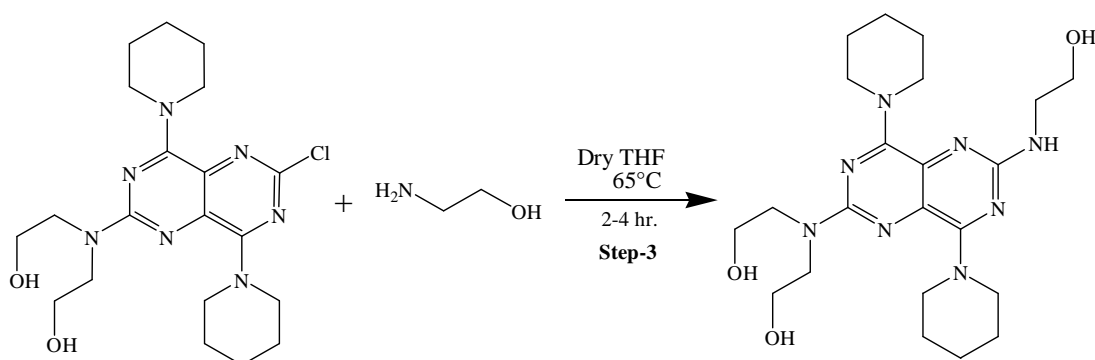
To 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine (2.0g, 7.40 mmol) in dry THF (50–60ml) stirred under nitrogen atmosphere at 25°C, was added an appropriate piperidine (3.23g,3.24ml,29.60mmol),2.40 equiv. potassium carbonate. The resulting suspension was agitated for 20 min. Addition of water (80 ml) precipitated the product. The solid was filtered off, washed with water and dried. The resulting product was recrystallised from hot ethyl acetate gave the title compound as fine yellow solid. (2.20g, 74%); mp 202-206°C, LC-MS: m/z 367.25 [M+1]. ¹H NMR (CDCl₃): δ 1.58-1.62 (12H, m, -CH₂-); δ 2.90-3.16 (8H, m, -CH₂-). Anal. Calcd for C₁₆H₂₀C₁₂N₆: C, 52.32; H, 5.49; N, 22.88. Found: C, 52.00; H, 5.72; N, 22.62.

Step-2; Synthesis of 2,2'-[[2-Chloro-4,8-di(piperidin-1-yl) pyrimido[5,4-d] pyrimidin-6-yl] nitrilo] diethanol



To a stirred solution of step-1 product, 4, 8-bis (piperidine)-2, 6- dichloropyrimido[5,4-d] pyrimidine (0.30 g, 0.88 mmol) in dry THF (12ml) under nitrogen at 0°C was added appropriate dihydroxy ethanolamine (>2.0 mol equiv. 33%, 0.8 ml) in THF (12 ml) over a 10min period. Precipitate formed and suspension was left to stir for 10-30min. reaction was monitored by TLC, reaction mixture was cooled and 10 volumes of water was added to precipitate the product, filtered off, washed with hexane to get yellow solid. (2.20g, 74%); mp 202-206°C, LC-MS: m/z 436.2 [M+1]. ¹H NMR (DMSO-d₆): δ 1.58-1.64 (20H, m, -CH₂-); δ 3.6 (8H, m, -CH₂-). Anal. Calcd for C₂₀H₃₀ClN₇O₂: C, 55.10; H, 6.94; Cl, 8.13; N, 22.49; O, 7.34 Found: C, 55.50; H, 7.25; Cl, 7.98; N, 22.56; O, 7.20.

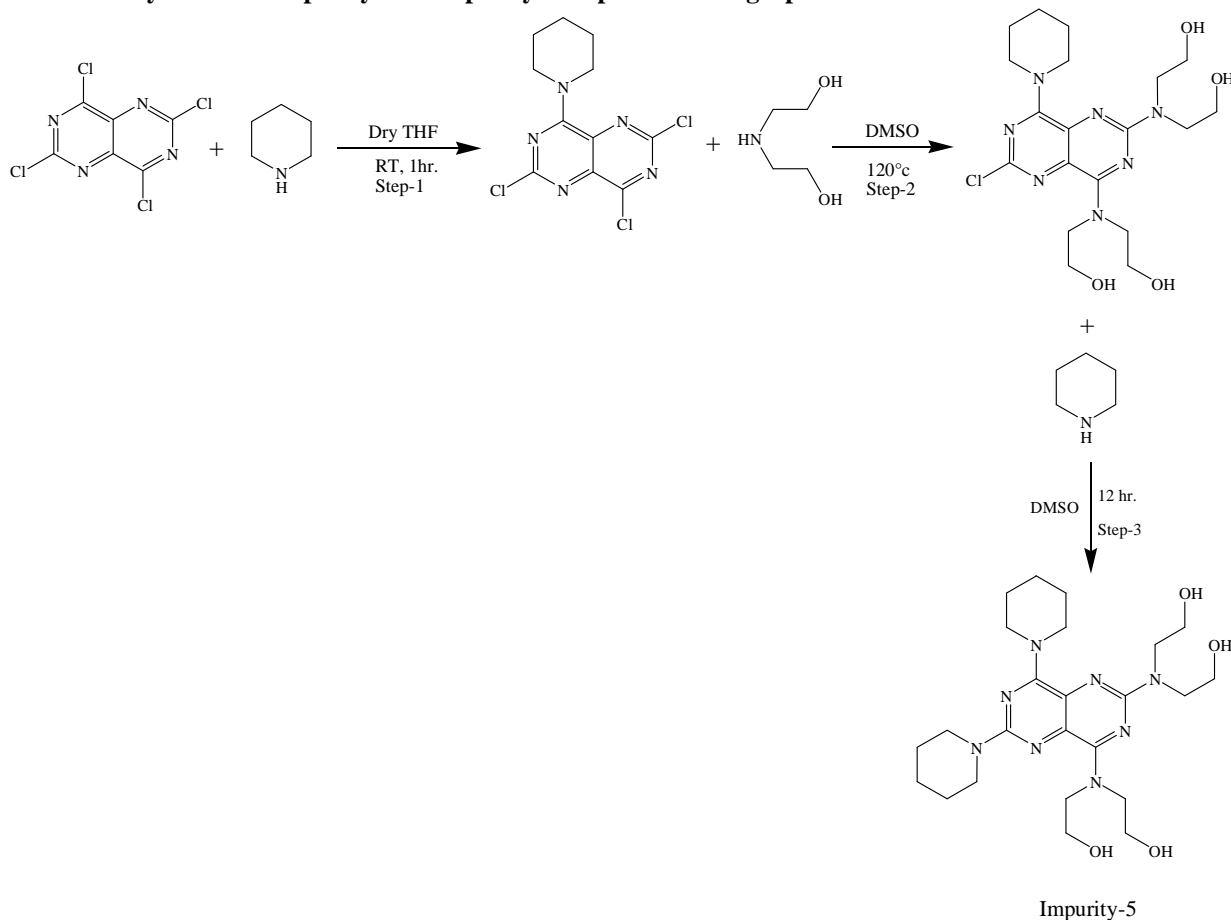
Step-3; Synthesis of 2,2'-[[2-(2-Hydroxyethyl) amino-4,8-di(piperidin-1-yl)pyrimido[5,4-d]pyrimidin-6-yl]nitrilo]diethanol



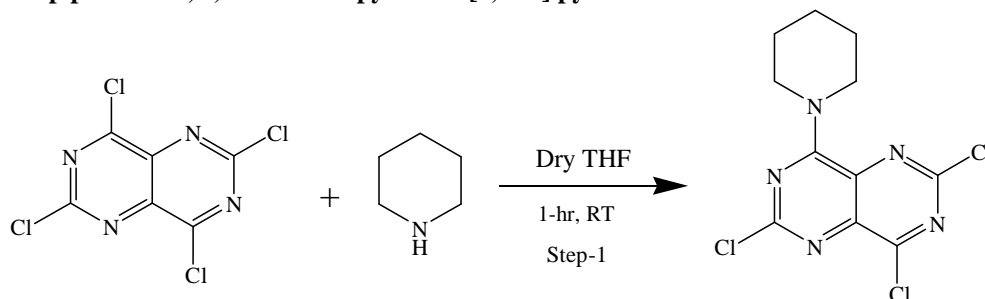
Impurity-4

To the appropriate step-4 (0.20 g, 0.63 mmol) in dry THF (5–12 ml) under nitrogen was added ethanolamine (5 ml). The resultant yellow solution was heated at 65°C for 2–4 h. The suspension was cooled and water (50 ml) was added, precipitating the product. The resultant mixture was filtered, to give an off-white solid which was retained. The filtrate was extracted with ethyl acetate and the organic layer was washed with water, dried (Na₂SO₄), filtered and recrystallised from ethyl acetate, gave a title compound as a white solid (0.15g, 78%). mp 202-206°C, LC-MS: m/z 461.3 [M+1]. ¹H NMR (DMSO-d₆): δ 1.59 (12H, m, -CH₂-); δ 3.5-3.58 (8H, m, -CH₂-); δ 4.0-4.6 (12H, m, -CH₂-); δ 4.5 (1H, s, -NH-). Anal. Calcd for C₂₂H₃₆N₈O₃: C, 57.37; H, 7.88; N, 24.33; O, 10.42 Found: C, 56.98; H, 7.65; N, 24.88; O, 9.98.

Scheme-5: Synthesis of impurity-5 or impurity E as per EP monograph.

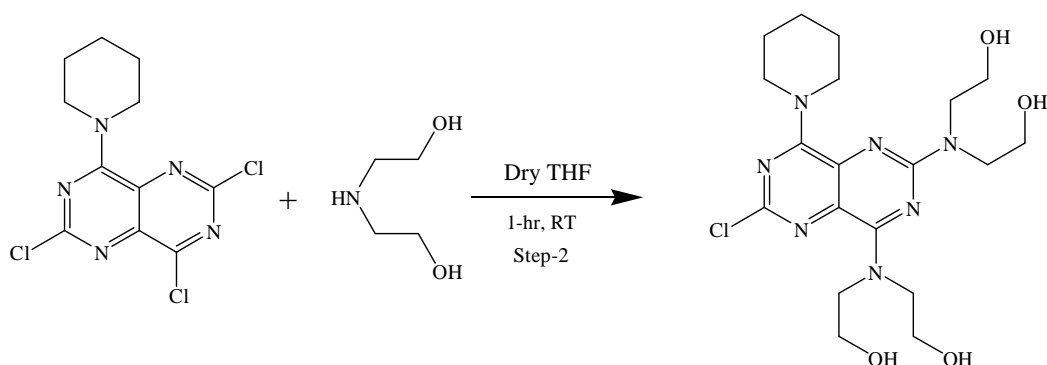


Step-1: Synthesis of 8-piperidine-2, 4, 6- trichloropyrimido [5, 4-d] pyrimidine.



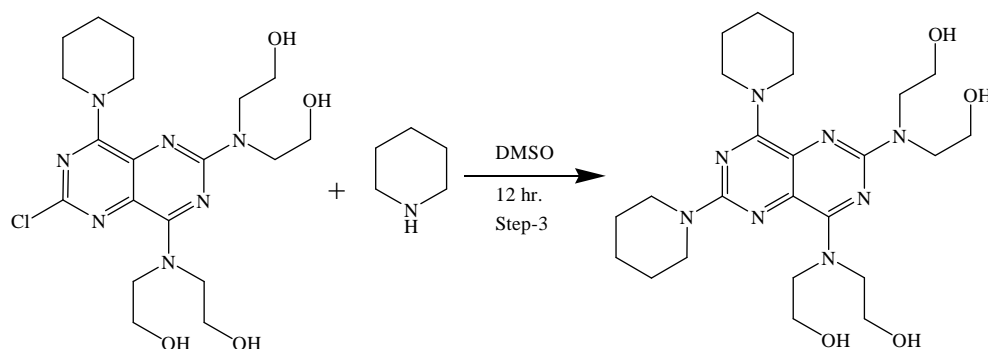
To 2,4,6,8, tetra chloro pyrimido[5,4-d] pyrimidine (1.0 g, 0.37 mmol) and potassium carbonate (1.0g, 0.74 mmol) in THF (60 ml), stirred under nitrogen at -78°C , piperidine was added (0.40 g, 0.42 mmol) in THF(60 ml) drop wise from a syringe at a rate of 1 ml per minute. a cloudy yellow solution was obtained and it was allowed to warm up for 10 min. addition of an excess of water gave fine yellow precipitate which was extracted with ethyl acetate. After drying of organic extract over sodium sulphate, removal of the solvent gave a yellow cake, triturate with diethyl ether, filtration and dry under vacuum to give the yellow coloured solid, which was used without further purification (0.90g, 78%). The product formation was confirmed by TLC and LCMS analysis.

Step-2: Synthesis of 6-chloro,2,4-di (di(2-hydroxyethyl) amino)-8-di(piperidin-1-yl)-pyrimido [5,4-d] pyrimidine.



To the step-1 product, 8-piperidine-2, 4, 6- trichloropyrimido [5, 4-d] pyrimidine (0.5 g, 0.50mmol) dissolved in DMSO at room temperature, dropwise added diethanolamine (0.5 g, 3.0mmol) and heated to 120°C for 1 hr. the reaction mixture was cooled to 50°C added 50ml of water and acetone. The formed solid was washed with hexane 3-4 times followed by ethyl acetate, which was used without further purification (0.60g, 80%).

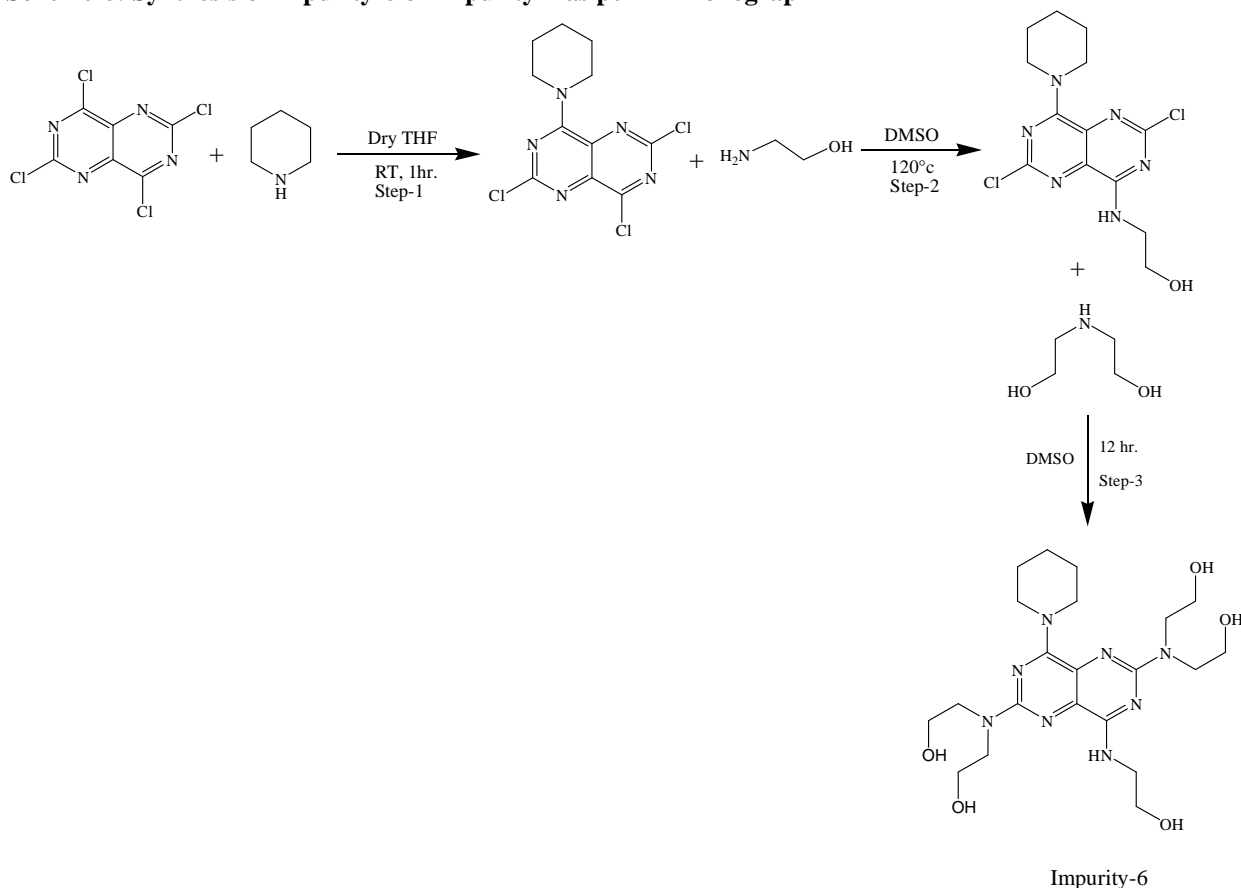
Step-3: Synthesis of 2,4-Di[di(2-hydroxyethyl)amino]-6,8-di(piperidin-1-yl)-pyrimido[5,4-d] pyrimidine



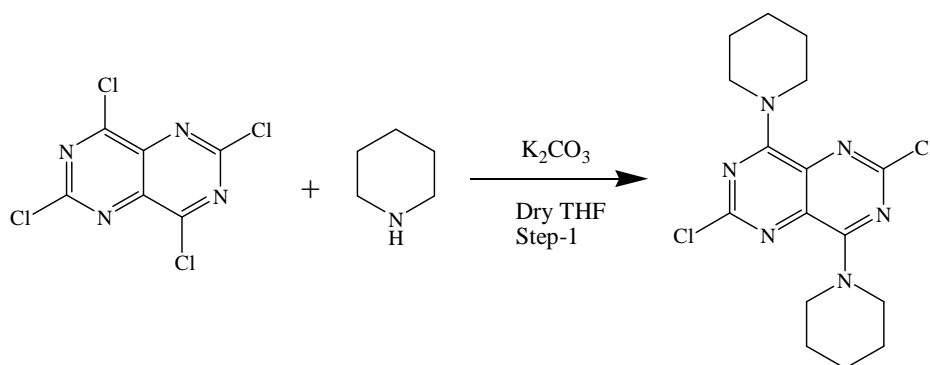
Impurity-5

To the step-2, product: Synthesis of 6-chloro,2,4-di [di(2-hydroxyethyl) amino]-8-di(piperidin-1-yl)-pyrimido [5,4-d] pyrimidine (0.20 g, 0.24 mmol) dissolved in DMSO, added diethanolamine dropwise at RT, temperature raised to 120° C for 12 hours, reaction was monitored by TLC, reaction mixture was cooled to 50°C, acetone and water 50:50 was added, stirred for 1 hr at room temperature, solid was precipitated, filtered off the reaction mixture, the solid was washed with water followed by hexane and ethyl acetate 60:40 twice to get yellow solid product. (0.2g 99%); mp 202-206°C, LC-MS: m/z 505.62 [M+1]. ¹H NMR (DMSO- d₆): δ 1.48-1.60 (12H, m, -CH₂-); δ 3.50-3.68 (16H, m, -CH₂-); δ 4.0-4.7 (12H, m, -CH₂-). Anal. Calcd for C₂₄H₄₀N₈O₄: C, 57.12; H, 7.99; N, 22.21; O, 12.68 Found: C, 56.84; H, 7.45; N, 23.50; O, 12.77.

Scheme-6: Synthesis of impurity-6 or impurity F as per EP monograph

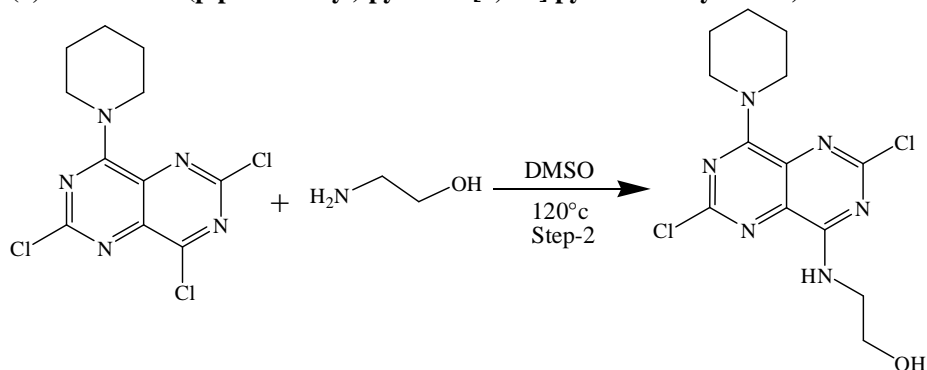


Step-1; Synthesis of 4, 8-bis (piperidine)-2, 6- dichloropyrimido[5,4-d] pyrimidine



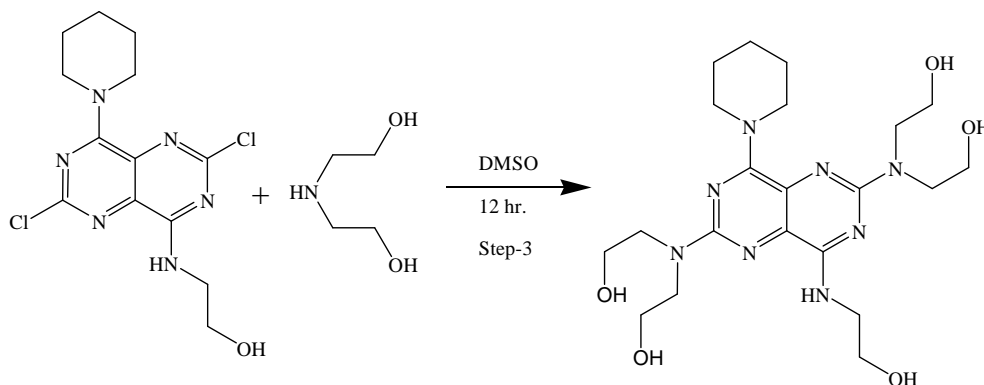
To 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine (2.0g, 7.40 mmol) in dry THF (50–60ml) stirred under nitrogen atmosphere at 25°C, was added an appropriate piperidine (3.23g, 3.24ml, 29.60mmol), 2.40 equiv. potassium carbonate. The resulting suspension was agitated for 20 min. Addition of water (80 ml) precipitated the product. The solid was filtered off, washed with water and dried. The resulting product was recrystallised from hot ethyl acetate gave the title compound as fine yellow solid. (2.20g, 74%); mp 202–206°C, LC-MS: m/z 367.25 [M+1]. ¹H NMR (CDCl₃): δ 1.58–1.62 (12H, m, -CH₂-); δ 2.90–3.16 (8H, m, -CH₂-). Anal. Calcd for C₁₆H₂₀C₁₂N₆: C, 52.32; H, 5.49; N, 22.88. Found: C, 52.00; H, 5.72; N, 22.62.

Step-2: synthesis of 2-(2,6-dichloro-8-(piperidin-1-yl) pyrimido[5,4-d] pyrimidin-8-ylamino) ethanol.



To the step-1 product, 4-piperidine-2, 6, 8- trichloropyrimido [5, 4-d] pyrimidine. (0.5g,0.50mmol) dissolved in DMSO at room temperature, dropwise added ethanolamine (0.3g, 1.5mmol) and heated to 120°C for 1 hr. the reaction mixture was cooled to 50°C added 50ml of water and acetone. The formed solid was washed with hexane 3-4 times followed by ethyl acetate, which was used without further purification (0.48g, 80%).

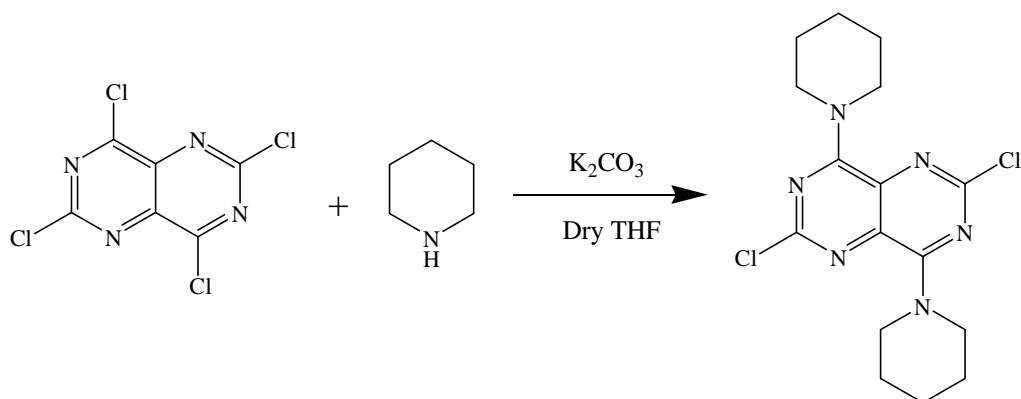
Step-3: synthesis of 2,6-di[di(2-hydroxyethyl) amino]-4-(2-hydroxyethyl)amino-8-(piperidin-1-yl)-pyrimido[5,4-d] pyrimidine.



Impurity-6

To the step-2 product, 2-(2,6-dichloro-4-(piperidin-1-yl) pyrimido[5,4-d] pyrimidin-8-ylamino) ethanol. (0.25g,0.40mmol) dissolved in DMSO at room temperature, dropwise added diethanolamine (0.3g, 3.5mmol) and heated to 120°C for 12 hrs. the reaction mixture was cooled to 50°C added 50ml of water stirred for 50 min at 50°C. Reaction mixture was washed with hexane 3-4 times followed by ethyl acetate twice to get yellow solid, (0.4g 95%); mp 202-206°C, LC-MS: m/z 481.6 [M+1]. 1H NMR (DMSO-d6): δ 1.58-1.65 (6H, m, -CH2-); δ 3.40-3.62 (14H, m, -CH2-); δ 4.62-4.75 (10H, m, -CH2-); δ 4.14(1H, s, -NH-). Anal. Calcd for C₂₁H₃₆N₈O₅: C, 52.49; H, 7.55; N, 23.32; O, 16.65 Found: C, 52.32; H, 7.05; N, 20.82; O, 16.86.

Scheme-6: Synthesis of 4, 8-bis (piperidine)-2, 6- dichloropyrimido[5,4-d] pyrimidine.



To 2,4,6,8-tetrachloropyrimido[5,4-d] pyrimidine (2.0g, 7.40 mmol) in dry THF (50–60ml) stirred under N₂ at 25°C, was added an appropriate piperidine (3.23g,3.24ml,29.60mmol),2.40 equiv. potassium carbonate. The resulting suspension was agitated for 20 min. Addition of water (80 ml) precipitated the product. The solid was filtered off, washed with water and dried. The resulting product was recrystallised from hot ethyl acetate gave the title compound as fine yellow solid. (2.20g,74%); mp 202-206°C, LC-MS:

m/z 367.25 [M+1]. ¹H NMR (CDCl₃): δ 1.58-1.62 (12H, m, -CH₂-); δ 2.90-3.16 (8H, m, -CH₂-). Anal. Calcd for C₁₆H₂₀C₁₂N₆: C, 52.32; H, 5.49; N, 22.88. Found: C, 52.00; H, 5.72; N, 22.62.

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CONCLUSION

For the better understanding of the synthetic pathway of an active pharmaceutical ingredient (API) it is necessary to identify all the impurities formed/anticipated. In this regard, we have synthesized and characterized different potential process-related impurities of dipyridamole.

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