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Research Article

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Synthesis of novel pyrimido-[5, 4-d] pyrimidines by sequential nucleophillic substitution reaction

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ABSTRACT

Novel heterocyclic compound containing pyrimido-pyrimidine moiety have been synthesized by the reaction of 2,4,6,8-tetrachloropyrimido[5,4-d]pyrimidine (DBMY-2) with sequential nucleophillic substitutions of Piperazine, diethanolamine, diethanolamine and ethanolamine in the pattern of C-4,C-8,C-2 and C-6 respectively. The use of low temperature, relatively dilute solution, and careful addition of amine nuleophile can control the critical steps, which have been characterized by using IR and 1H NMR and mass spectral data.

Keywords: pyrimido-pyrimidine, Piperazine, Amino alcohols. Sequentialnucleophillic substitution.

INTRODUCTION

It is an object of this invention to provide new heterocyclic compound. This invention relates to new pyrimido-pyrimidine derivative, its preparation and characterization. Upon further study of the specification and appended claims, further objects and advantages of this invention will become those skilled in the art. Pyrimido-pyrimidine derivatives exhibit various types of physiological activity and enter into medicinal products and this determines the great attention that has been paid to the synthesis of new compounds of this series [1-5].

The pyrimido-pyrimidine derivatives drew a lot of attention on various pharmacological activities because of their structural similarity to Purines. Like anti-microbial [4-5], antidiabetic, antioxidant [6] and antitumor [7-9]. Pyrimido-pyrimidines have been drawn as promising structural units in the field of medicinal chemistry. To this end we have investigated how to control the substitution chemistry of 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine (DBMY-2) [10]. 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 a diverse array of novel compounds.

DBMY-2 is the classical precursor of 2, 4, 6, 8-tetrasubstituted pyrimido [5, 4-d] pyrimidines, the substitution pattern can be described in scheme-1. The pattern of substitution is the typical outcome of two stepwise substitution reactions of DBMY-2, employing an excess of nucleophile in each step. [11, 12] 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 of DBMY-2 with an excess of piperazine at ambient temperature led to the formation of 4,8-bis(Piperazine)-2,6- dichloropyrimido[5,4-d]pyrimidine 6a(scheme-1). Further reaction of this compound with an excess of ethanolamine (2-aminoethanol) at 120°C gave 4,8-bis(piperazino)-2,6-bis(2 hydroxyethylamino)pyrimido[5,4-d]pyrimidine 6b (Scheme 1).

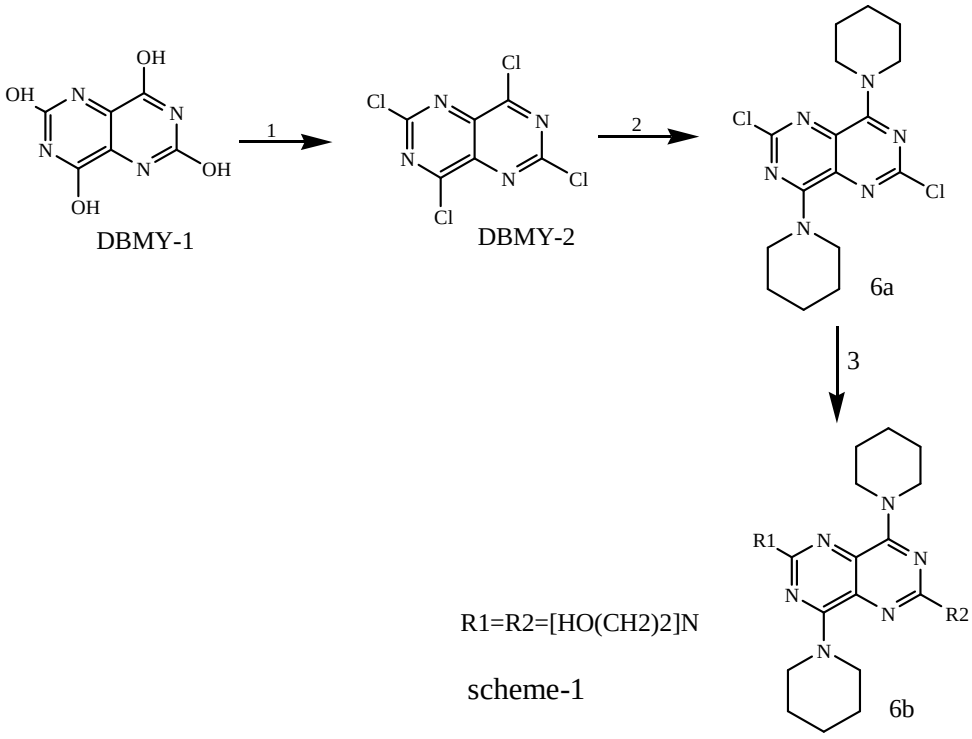
The observed regioselectivity relates to the ability to delocalise the negative charge arising from attack of a nucleophile at C-2/C 6 or C-4/ C-8. Attack at C-4/C-8 gives a species in which negative charge on nitrogen can be delocalised into an adjacent C=N bond, whereas attack at C-2/C-6 does not permit this stabilising interaction.

The reactions of 4,8-bis(piperazine)-2,6-dichloropyrimido-[5,4-d]pyrimidine with nucleophiles can be carried out in a stepwise fashion to afford 4,8-bis(Piperazine)-2,6-disubstituted pyrimido[5,4-d]pyrimidines, with different substituent's at C-2 and C-6, i.e. an scheme-2, substitution pattern Furthermore, we have found that the reaction of DBMY-2 with Piperazine can be controlled to give the mono-substituted product, 4-piperazine-2,6,8-trichloropyrimido[5,4-d]pyrimidine, in acceptable yield. This compound served as a valuable starting material for the preparation of 2, 4, 6, 8-tetrasubstituted pyrimido [5, 4-d] pyrimidine. The structure of tetra substituted pyrimido [5, 4-d] pyrimidines described herein were validated by spectroscopic characterisation.

EXPERIMENTAL SECTION

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. IR spectra in KBr pellets were recorded Perkin-Elmer Spectrum 100 FT IR spectrometer (400 MHZ) in DMSO-d6 /CDCl3 using TMS as an internal standard (chemical shifts are expressed in ppm). The homogeneity of the compounds was checked on silica gel–G coated plates, Hexane, ethyl acetate, Chloroform and methanol as the eluent and observed in UV lamp, iodine vapours or KMnO4 spray as developing agents. The synthesised compound gave good elemental analysis.

Scheme -1



scheme-1

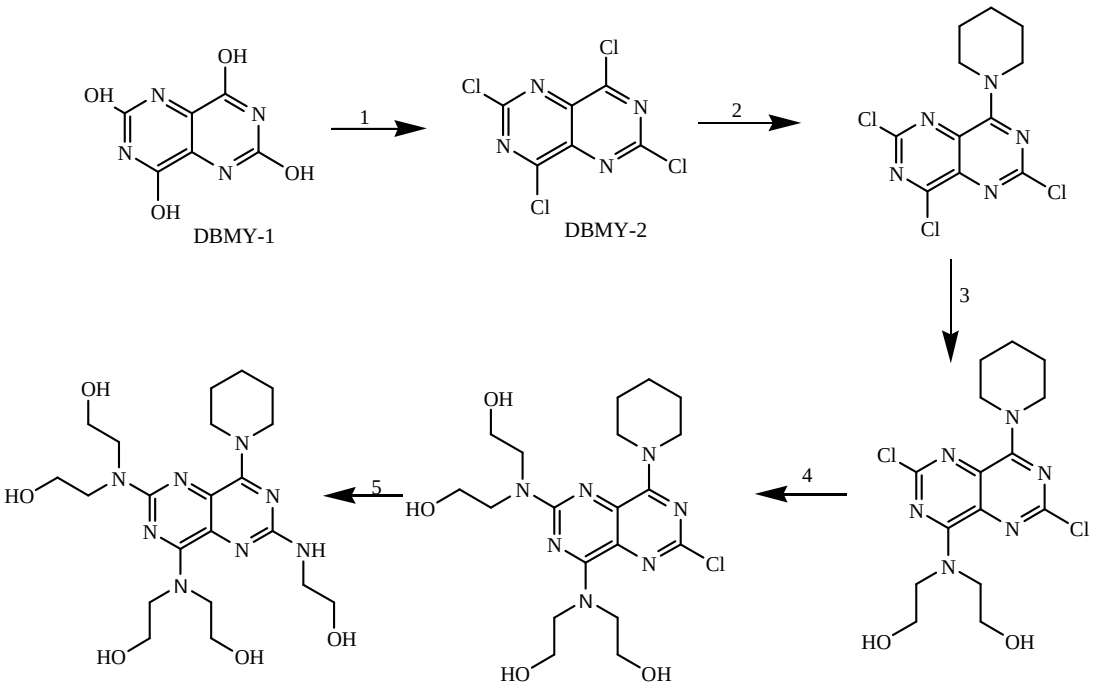
Step-1; Synthesis of 2, 4, 6, 8-tetrachloropyrimido [5, 4-d] pyrimidine. (DBMY-2)

To an aqueous solution of sodium hydroxide(0.1M, 200ml)was added 1,5-dihydropyrimido[5,4d]pyrimidine-2,4,6,8-(3H,-7H)-tetrone (DBMY-1) (2g,10 mmol), and the mixture was boiled for 20 min. after addition of H2O (159ml), the solution was filtered hot and was cooled to give the disodium salt as light yellow needles, which were collected and dried. (1.86g, 78%). The finely powdered disodium salt (3g, 12.5 mmol) was added to a solution of PCl_5 (15g, 72 mmol) in $pocl_3$(125 ml, 1.34 mol) with stirring. The mixture was heated under reflux for 8 h, and excess $pocl_3$ was removed under reduced pressure. The yellow-brown residue was carefully added to ice-water (50-6- g) and the solids were collected by filtration, washed with H_2O until acid free. And dried over KOH at 100°c. To afford tetrachloropyrimido pyrimidine DBMY-2 as yellow solid; 13c NMR 141.9, 157.8, 165.8: MS m/z 268.12.

Step-2; Synthesis of4, 8-bis (piperazine)-2, 6- dichloropyrimido[5,4-d]pyrimidine.
To DBMY-2 (2.0g, 7.40 mmol) in dry THF (50–60 ml) stirred under N2 at 25°C, was added an appropriate piperazine (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+]. 1H NMR (CDCl3): 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-3; Synthesis of 4, 8-bis (Piperazine)-2, 6-bis (2-dihydroxyethylamino) pyrimido-[5, 4-d] pyrimidine.
The 4, 8- bis (Piperazine)-2, 6-dichloropyrimido [5, 4-d] pyrimidine (0.10 g, 0.24 mmol) under nitrogen added diethanolamine (2 ml) and heated at 80–120°C for 1–3 days. After cooling the solution, water (20 ml) was added and an extraction was performed using ethyl acetate (100 ml). The organic solvent was dried (Na_2SO_4), and removed in vacuum. The crude solid was recrystallised from ethyl acetate, producing the title compound as yellow crystals (0.08 g, 73%); mp 215–219°C, LC-MS: m/z 504.63 [M+]. 1H NMR ($CDCl_3$): δ 1.58-1.62 (12H, m,-CH2-); δ 2.90-3.16 (8H, m,-CH2-); δ 3.68-3.92 (8H, m,-CH2-); δ 4.28-4.62 (8H, m,-CH2-); Anal. Calcd for $C_{24}H_{40}N_8O_4$: C, 57.12: H, 7.99: N, 22.2. Found: C, 57.60: H, 8.22: N, 22.72.



scheme-2

Scheme-2; sequential nucleophillic substitutions.

Step-2; Synthesis of 4-piperazine-2, 6, 8- trichloropyrimido [5, 4-d] pyrimidine.
To DBMY-2 (010 g,0.37 mmol) and potassium carbonate (010g, 0.74 mmol) in THF (6 ml) , stirred under nitrogen at -78°c, was added Piperazine (0.04 g, 0.42 mmol)in THF(6 ml) drop wise from a syringe at a rate of 1 ml per minute . a cloudy yellow solution was obtained which 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 glass, triturate with diethyl ether, filtration and dry under vacuum to gave the yellow colored solid, which was used without further purification (0.09g, 75%).

Step-3; Synthesis of 8-(dihydroxyethylamino)-2, 6-dichloro-4-piperazinepyrimido-[5, 4-d] pyrimidine.
To a stirred solution of step-2 (0.30 g, 0.88 mmol) in dry THF (12ml) under nitrogen at 0°c was added appropriate dihydroxyethanolamine (>2.0 mol equiv. 33%,0.8 ml) in THF (12 ml) over a 10 min period. Precipitate formed and suspension was left to stir for 10-30min. reaction was monitored by TLC and LCMS shows m/z 387.8 confirms mano substituted of dihydroxyethylamino at C-8. This was used without further purification.

Step-4; Synthesis of 8, 2-bis (dihydroxyethylamine)-6-chloro-4-piperazine pyrimido-[5, 4-d] pyrimidine.
Continuation of step-3, to the reaction mixture added appropriate dihydroxyethanolamine (>2.0 mol equiv. 33%, 0.8 ml) in THF (12 ml) over a 10 min period. Stirred for 30 min. water (20 ml) was added and THF was removed in vacuum. Purification of crude product by extracting with ethyl acetate, followed by chromatography by ethyl acetate; hexane as eluent, 10; 90, gave the title compound as a white powder. (0.21 g, 68%); LC-MS: m/z 456.25 [M+]. 1H NMR (DMSO): δ 1.52-1.56 (6H, m,-CH2-); δ 2.48-2.62 (4H, m,-CH2-); δ 3.38-3.62 (8H, m,-CH2-); δ 3.92-4.22 (8H, m,-CH2-); Anal. Calcd for $C_{19}H_{30}ClN_7O_4$: C, 50.05: H, 6.63: N, 21.50. Found: C, 51.20: H, 6.22: N, 22.02.

Step-4; Synthesis of 8, 2-bis (dihydroxyethylamino)-6-ethanolamine-4-piperazine pyrimido-[5, 4-d] pyrimidine.
To the appropriate step-4 (0.20 g, 0.63 mmol) in 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 concentrated taken for purification by Column chromatography, recrystalisation from ethyl acetate, gave a title compound as a white solid (0.15g, 78%). Mp 97-98 oc. LC-MS: m/z 481.26 [M+]. 1H NMR (CdCl3): δ 1.42-1.68 (6H, m,-CH2-); δ 3.40-3.82 (22H, m,-CH2-); δ 4.13 (3H, m,-CH2-); δ 4.6-4.8 (8H, m,-CH2-); δ 7.2-7.40 (3H, m,-CH2-, NH2-). Anal. Calcd for $C_{21}H_{36}N_8O_5$: C, 52.49: H, 7.55: N, 23.32. Found: C, 52.80: H, 7.32: N, 23.52.

RESULTS AND DISCUSSION

The synthesised new pyrimido-pyrimidines further studied for characterisation of IR, NMR and Mass. To study their structure and to optimize.

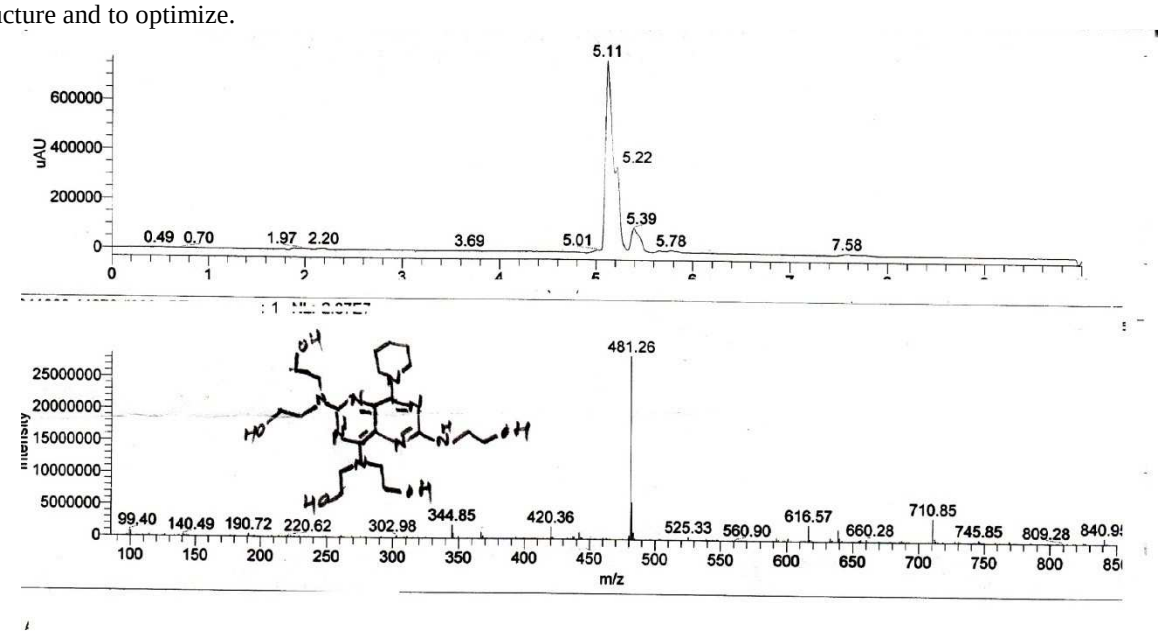


Fig.no 1 mass spectrum of 2-bis (dihydroxyethylamino)-6-ethanolamine-4-piperazine pyrimido-[5, 4-d] pyrimidine. (M/z):481.26 corresponding to molecular ion peak.

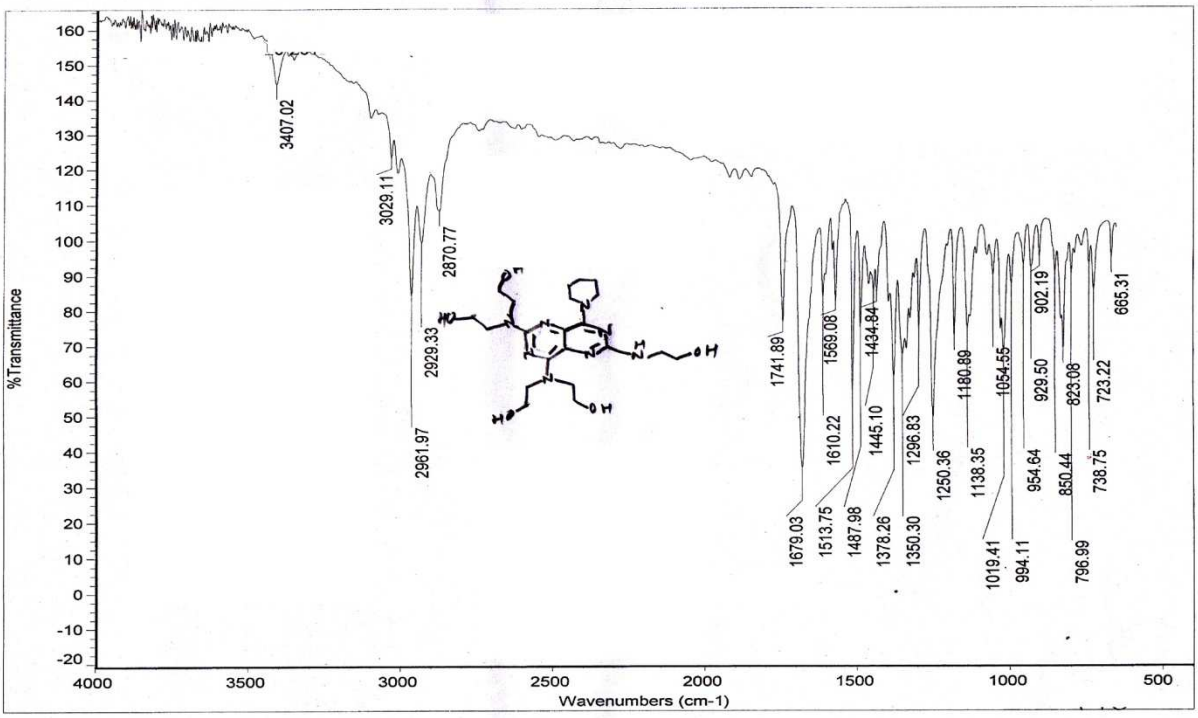


Fig. no 2: IR spectrum of 2-bis (dihydroxyethylamino)-6-ethanolamine-4-piperazine pyrimido-[5, 4-d] pyrimidine.

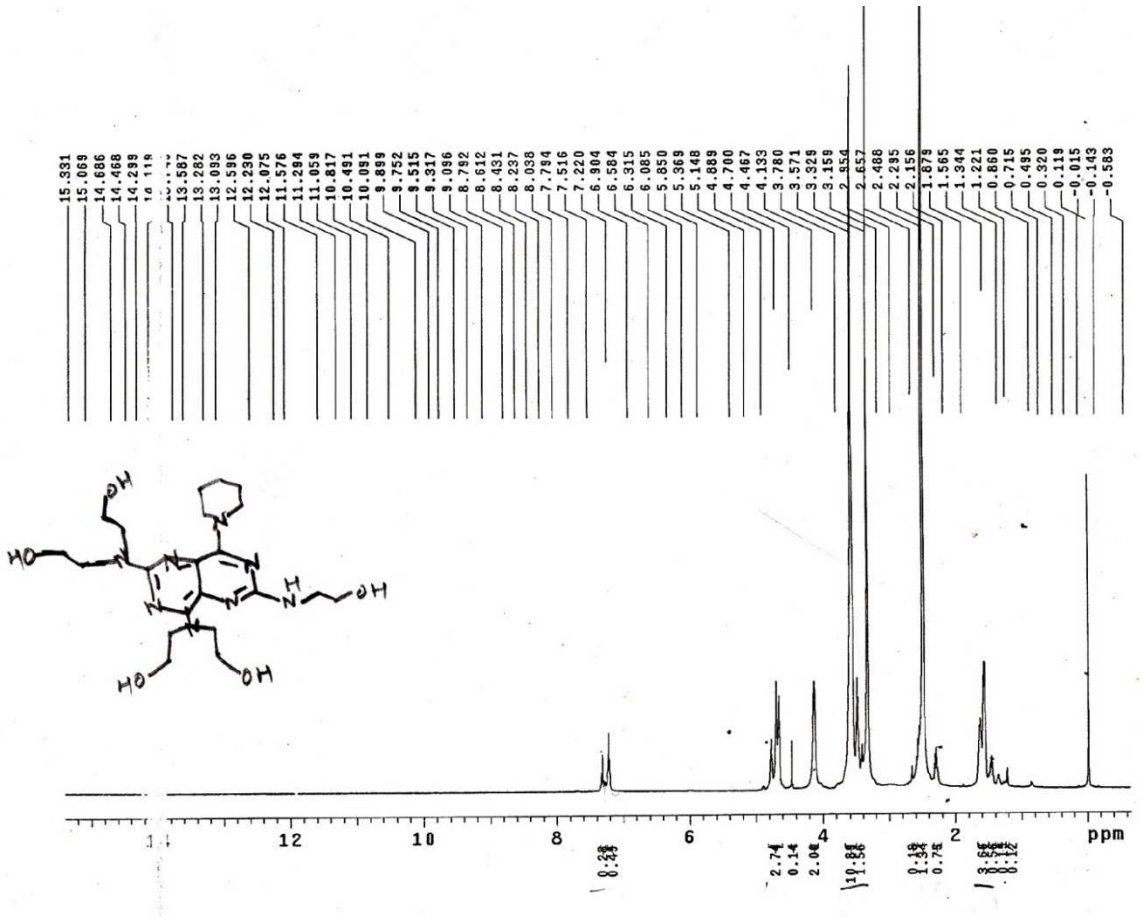


Fig.no 3: 1HNMR of 2-bis (dihydroxyethylamino)-6-ethanolamine-4-piperazine pyrimido-[5, 4-d] Pyrimidine

CONCLUSION

The work described in this paper has shown how reactions of 2,4,6,8-tetrachloropyrimido[5,4-d]pyrimidine with nucleophiles can be controlled to give structurally characterised tetra substituted pyrimido[5,4-d]pyrimidines. The methodology described in this paper should facilitate the design of pyrimido [5, 4-d] pyrimidine analogues. Furthermore, this indicate how combinatorial approaches could be used for the development of biologically active compounds based on the pyrimido [5, 4-d] pyrimidine scaffold.

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