

Synthesis, Characterization of 2-{{2-(Piperazin-1-yl) quinazolin-4-yl} Amino} ethan-1-ol Quinolone Derivatives

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Abstract Present work includes synthesis of quinazolin-2, 4-diol from 2-amino benzoic acid and NN Dimethyl formamide. Further conversion of quinazolin-2, 4-diol into 2,4-dichloroquinazoline, to substitute chlorine which at fourth position of quinazoline ring by 2-aminoethan-1-ol in which polar hydroxyl group present at the end of the chain and tried to replace chlorine group which at second position of quinazoline ring by piperazine which having important pharmacological properties. 2,4-dichloroquinazoline further converted into 2-[(2-chloroquinazolin-4-yl) amino]ethan-1-ol This further converted in to 2-{{2-(piperazin-1-yl)quinazolin-4-yl}amino}ethan-1-ol form different compounds referred as I to IV(Scheme-1). In future compound (IV) can be treated with Derivatives of benzoic acid(2,4-dichlorobenzoic acid / 2,4-difluorobenzoic acid/4-cyanobenzoic acid / 4-methoxybenzoic acid / 4-hydroxybenzoic acid) to obtain novel derivatives In present work we have achieved substantially good yields and purity of 2-{{2-(piperazin-1-yl)quinazolin-4-yl}amino}ethan-1-ol. The target molecule which was synthesized containing Quinazoline ring substituted at position 2 by piperazine ring and 4 position by 2-aminoethan-1-ol because quinazoline derivative have wide and distinct bio pharmacological activity and substituted piperazine and 2-aminoethan-1-ol also having pharmacological property individually which is taken under investigation.

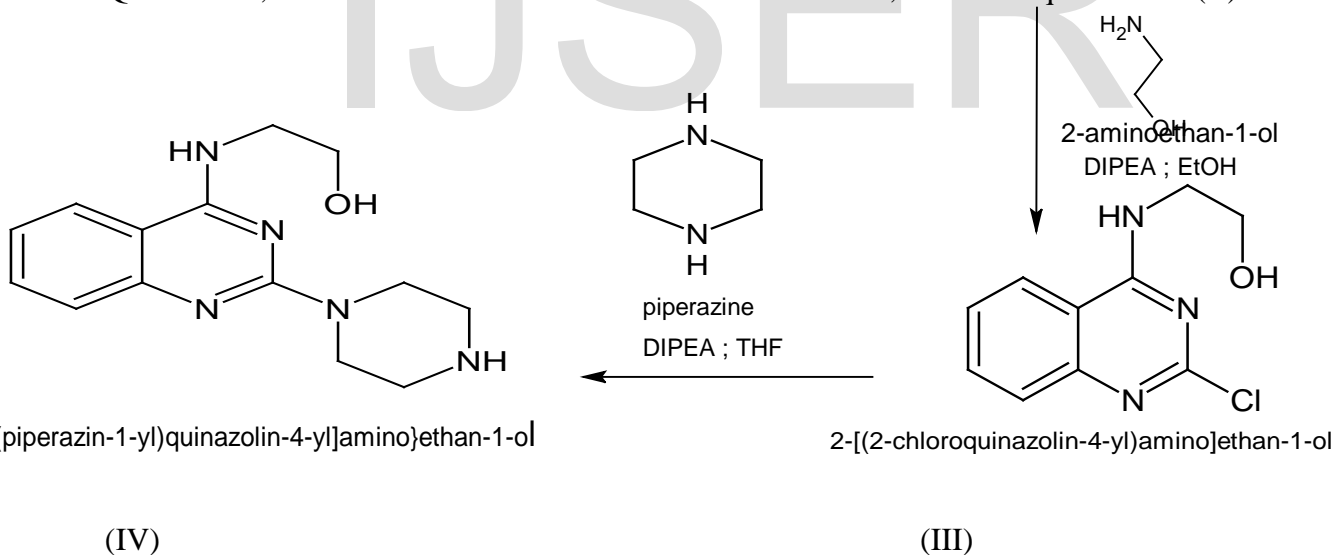
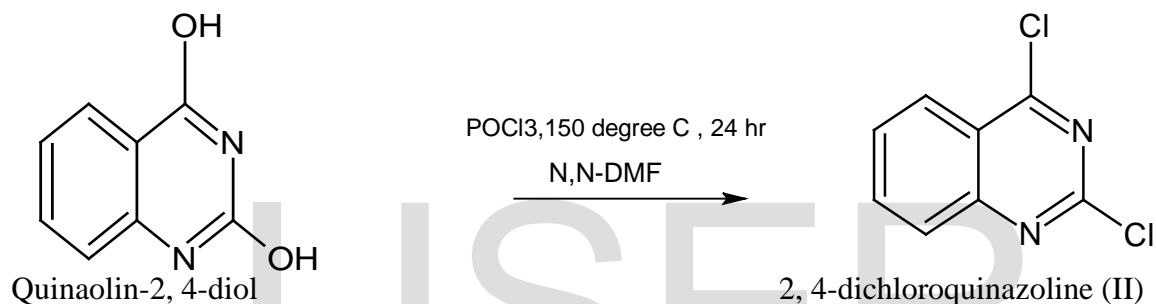
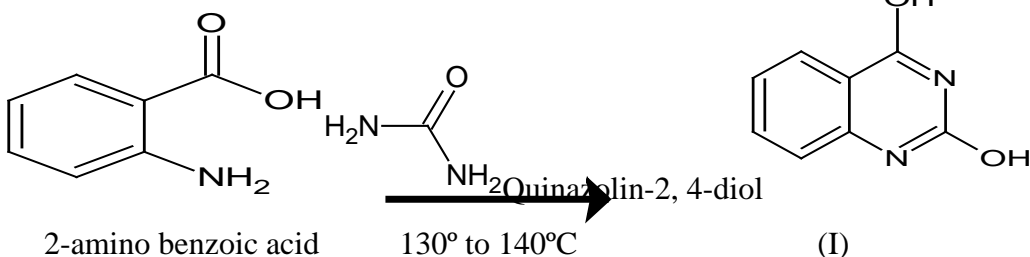
Introduction

Quinazoline is a heterocyclic yellow solid. It is isomeric with other naphthyridines including quinoxaline, phthalazine and cinnoline. Derivatives of quinazoline are called quinazolines. And

it has been used as an anti-malarial agent and in cancer treatment. Quinazoline derivatives as quinazolinones showed activity against murine P388 Leukemia, increased by dimerization. doxazosinmesylate. Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer, anti-inflammation, anti-bacterial, analgesia, anti-virus, anti-cytotoxin, anti-spasm, anti-tuberculosis, anti-oxidation, antimalarial, anti-hypertension, anti-obesity, anti-psychotic, anti-diabetes, etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. And the potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored. This process involved the construction of a starting general structure with a planar heterocyclic ring (quinazoline or pyrido [2, 3-d] pyrimidine ring), selected as the central fragment that can act as a scaffold to carry two functionalized branches in positions 2 and 4, which are equivalent or different with the aim of evaluating the possible influence of the symmetry/asymmetry on the target activity. The selected starting ring systems are involved in numerous biological activities mainly concerning cancer with action mechanisms related to folate metabolism inhibition, topoisomerase inhibition, the inhibition of diverse tyrosine kinases and apoptosis induction. Piperazines are a broad class of chemical compounds with many important pharmacological properties. Piperazine and substituted piperazine nuclei had constituted an attractive pharmacological scaffold present in various potent marketed drugs. The incorporation of piperazine is an important synthetic strategy in drug discovery due to its easy modifiability, proper alkalinity, water solubility, the capacity to form hydrogen bonds and adjustment of molecular physicochemical properties. This di-nitrogen moiety has been an inseparable component of plethora of drugs. Present work includes converted quinazolin-2, 4-diol into 2, 4-dichloroquinazoline and we are trying to substitute chlorine which at fourth position of quinazoline ring by 2-aminoethan-1-ol in which polar hydroxyl group present at the end of the chain and we are trying to replace chlorine group which at second position of quinazoline ring by piperazine which having important pharmacological properties. And after attachment of piperazine at 2 position of quinazoline, we are trying to use free nitrogen of piperazine which is

attached to quinazoline ring to react with derivatives of benzoic acid to form different compounds. And these formed products may be play vital role as a drug.

Experimental(Scheme-I)

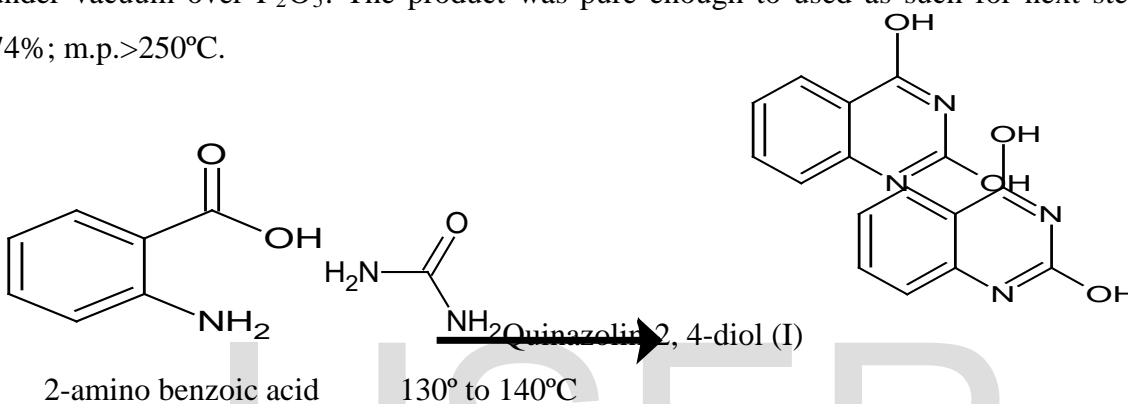


Chemicals and Instrument

Anthranilic acid, Urea, phosphorus aminoethan oxychloride, N, N- dimethyl formamide, 2-1-ol, diisopropyl ethyl amine, ethanol, piperazine, and tetrahydrofuran obtained from local dealer.. Analytical TLC was performed on Silica plates- GF254 (Merck) with visualization by UV or in iodine. Melting points were determined by using thiels tube. 1H-NMR (in CDCl₃ / DMSO-d₆)

spectra were recorded using Bruker -400 with TMS as internal standard. ^{13}C were recorded by using DMSO solvent. All the chemicals used were of Laboratory grade.

I. Synthesis and characterization of Quinazolin-2, 4-diol (I) A mixture of Anthranilic acid (50g, 0.36 mol) and urea (109 g, 1.82 mol) in a round bottom flask equipped with mechanical stirrer was heated without solvent at 135 to 140°C using an air condenser for 3h. The melted reaction mixture was poured into crushed ice (500 ml) with continuous stirring for 30 min. The solid so formed was filtered through Buchner funnel, washed with water (3X100 mL) and dried under vacuum over P_2O_5 . The product was pure enough to used as such for next step. Yield 74%; m.p.>250°C.



^1H NMR (DMSO- d_6) δ ppm: 7.15 (t, 2H, Ar-H), 7.6 (t, 1H, Ar-H), 7.85 (d, 1H, Ar-H), 11.05(1H, S), 11.1 (1H, S).

^{13}C NMR (DMSO- d_6) (δ /ppm):

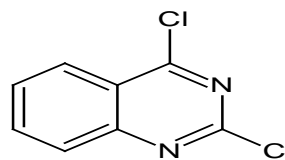
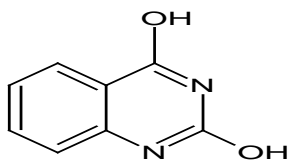
120 (Ar C-H), 125.6 (Ar C-H), 133.5(Ar C-H), 126.6(Ar C-H), 185(Ar C-OH), 187(Ar C-OH), 110(Ar C), 151 (Ar C).

IR (KBr, ν/cm^{-1}):

3428 (OH, broad), 3079 (Ar C-H), 1604 (C=N)

II. Synthesis and characterization of 2, 4-dichloroquinazoline (II)

A mixture quinazolin-2, 4-diol (6.0 mmol), POCl_3 (5 mL) and N, N-DMF (catalytic amount) was stirred and heated under reflux for 48 h. The solvents were removed under vacuum and cold water (0°C, 25 mL) and chloroform (25 mL) were added. The organic layer was washed with water (3X20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum .



POCl₃; N, N-DMF



Quinazolin-2, 4-diol (I)

2, 4-dichloroquinazoline (II)

¹H NMR (CDCl₃-d₁) δ ppm

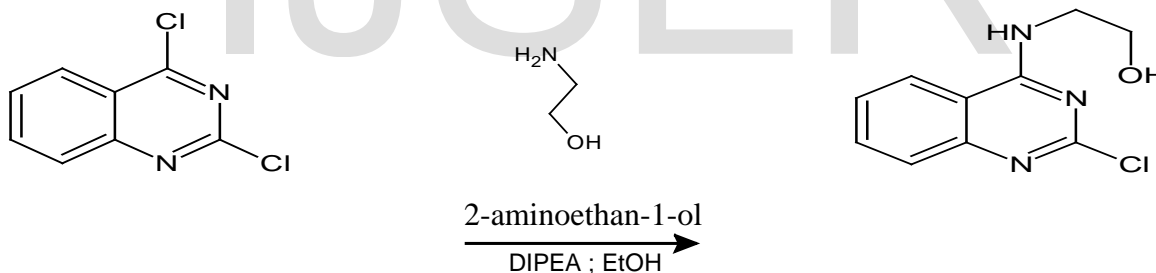
8.30-8.20 (d, 1H), 8.10-8.00 (m, 2H), 7.80-7.70 (d, 1H)

¹³C NMR (CDCl₃-d₁) (δ/ppm): 120(Ar C), 125 (Ar C), 128.6 (Ar C), 136.5(Ar C), 151 (Ar C), 157(Ar C), 161.3(Ar C-).

IR (KBr, ν/cm⁻¹):755 (C-Cl), 3040 (Ar C-H), 1619 (C=N);

III. Synthesis and characterization of 2-[2-chloroquinazolin-4-yl] amino] ethan-1-ol(III)

Take mixture of 1 eq. of 2, 4-Dichloroquinazoline & 1.2 eq. of 2-aminoethan-1-ol in 100 ml two necked round bottom flask with appropriate requirement. Add to it (for 1 g sample required 10 ml ethanol) ethanol & DIPEA (3 eq.) at 0°C then stir for 6 hr. The progress of reaction check by TLC. After completion of reaction, distill out it completely then add Dichloromethane to it & wash with water. The Organic layer dried over sodium sulphate & concentrated to obtain off white solid. The obtained off white solid purified by hexane, dry it, weight it & used for further analysis & reaction.



2, 4-dichloroquinazoline

2-[(2-chloroquinazolin-4-yl) amino] ethan-1- ol (III)

¹H NMR (400MHz, DMSO-d₆) δ

M.P.188°C; Yield: 84%;

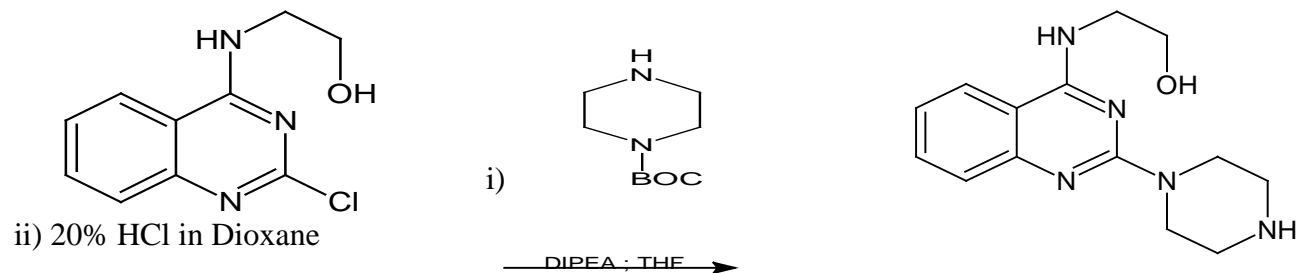
IRmax cm⁻¹: 3028.52 (Ar-CH); 1476.56 (Ar C=C); 1678.02 (HC=N);756.15(C-Cl)

¹H NMR 8.73(s,1H),8.26(d,J=7.6Hz,1H),7.77(t,J=7.2Hz,1H),7.60(d,J=8.0Hz,1H),7.51(t,J=7.6Hz,1H),4.83(t,J=4.2Hz, 1H), 3.64-3.56 (m, 4H)

IV. Synthesis of 2-[[2-(piperazin-1-yl)quinazolin-4-yl] amino} ethan-1-ol(IV)

Take mixture of 1 eq. of 2-[(2-Chloroquinazoline-4-yl) amino] ethan-1-ol & Piperazine (1.2 eq.) in 100 ml two necked round bottom flask as per requirement. Add to it THF & DIPEA at 0°C & then reaction mixture heated at 80°C for 16 hr. The progress of reaction was checked by TLC.

After completion of reaction dilute it with ethyl acetate & wash with water. The organic layer dry over sodium sulphate & concentrated to obtain white solid which is purified by hexane washing. Dry it, wash it & use for further analysis & reaction.



2-[(2-chloroquinazolin-4-yl)
amino] ethan-1-ol

2-[[2-(piperazin-1-yl)
quinazolin-4-yl] amino] ethan-1-ol (4)

M.P.167°C; Yield: 82%;

IRmax cm-1: 3034.00 (Ar-CH); 1510.50 (Ar C=C); 1710.00 (HC=N);¹HNMR (DMSO D6):
 δ =8.1(1H,d,quinazoline aromatic CH); 7.7-7.75 (2H,m,quinazoline aromatic CH); 7.71
(1H,m,quinazoline aromatic); 3.20 (4H, m, piperazine CH₂); 2.54 (4H, m, piperazine CH₂);
2.4(3H, s,-CH₃)

¹³CNMR: 45.1(1C,-CH₃) 50.1-51.6 (4C, piperazine -CH₂); 118.2(1C, quinazoline aromatic
CH); 126-140(4C, quinazoline aromatic CH); 151.0(1C, C-N); 151.6(1C,quinazolineC-N);
180.0(1C,quinazoline N=CN);

Result and Discussion

Spectral Analysis

Fig. 1 ^1H NMR of quinazolin-2, 4-diol (I)

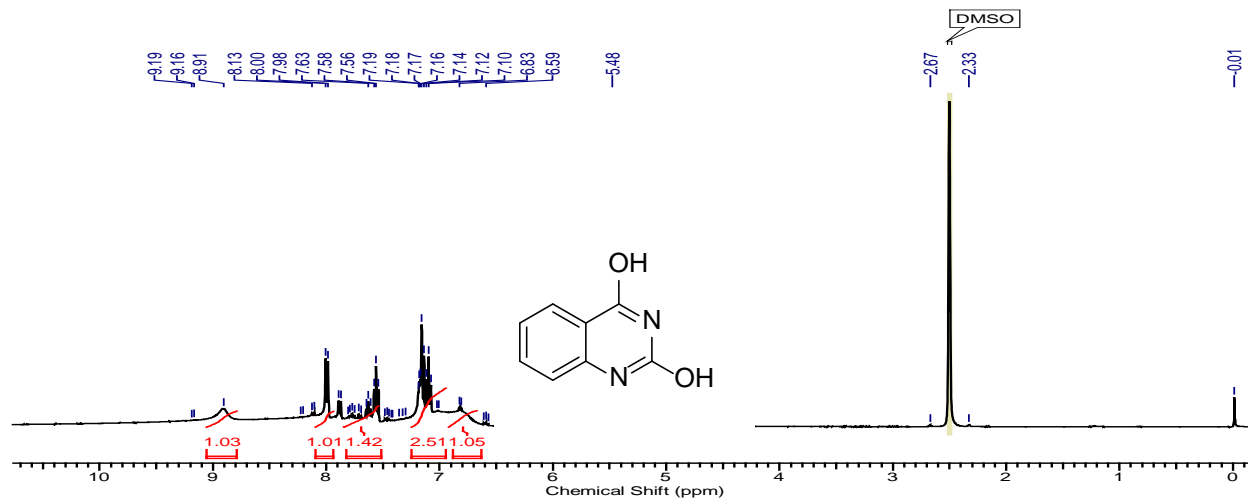


Fig. 2 ^{13}C NMR of quinazolin-2, 4-diol (I)

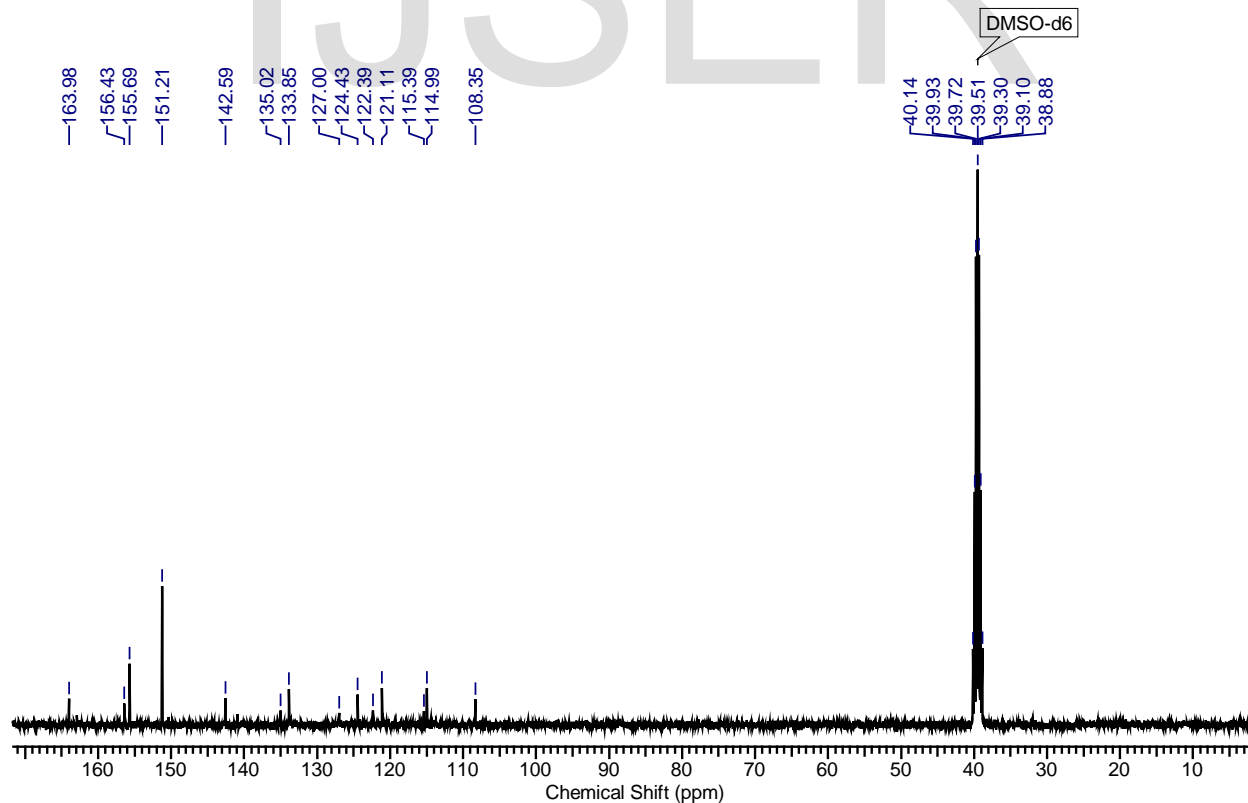


Fig. 3 ^1H NMR of 2, 4-dichloroquinazoline (II)

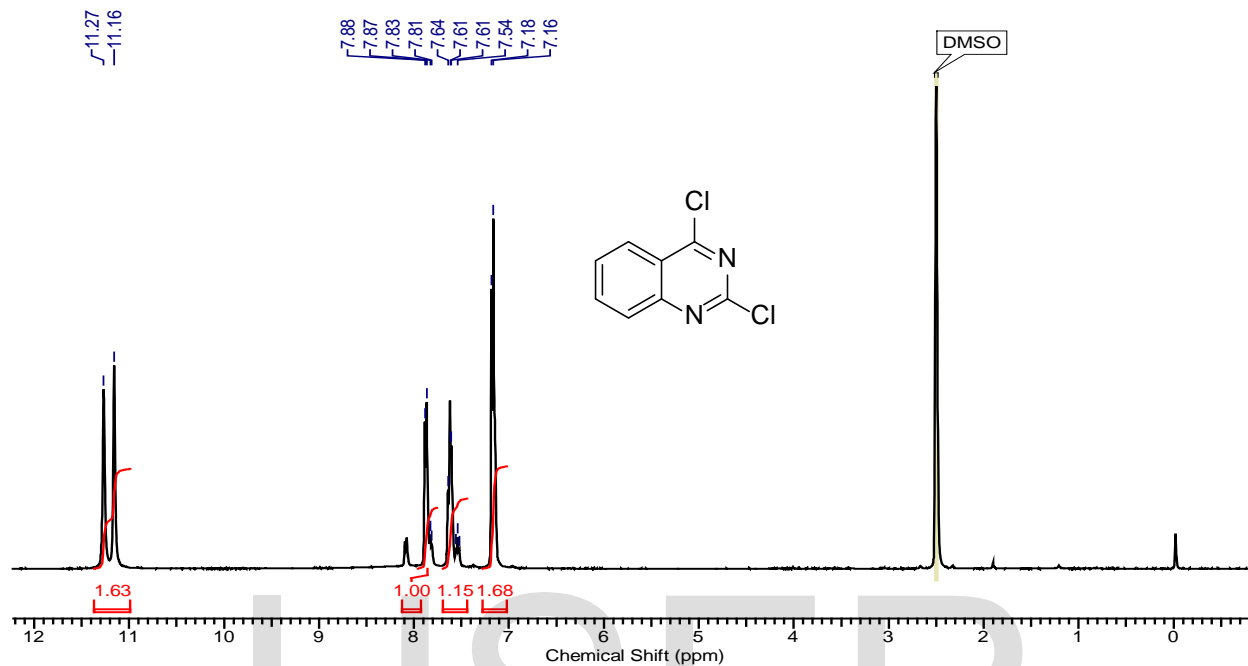


Fig. 4 ^{13}C NMR of 2, 4-dichloroquinazoline (II)

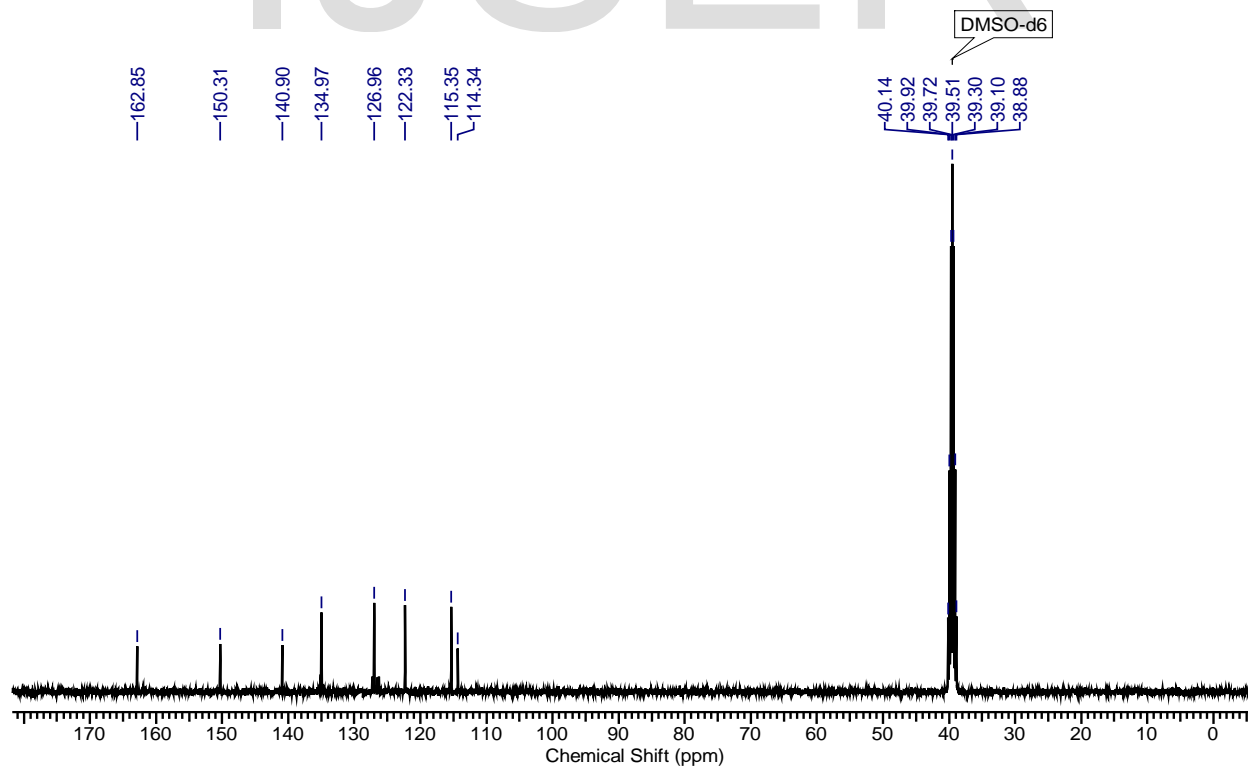


Fig. 5 ^1H NMR of 2-[2-chloroquinazolin-4-yl] amino] ethan-1-ol (III)

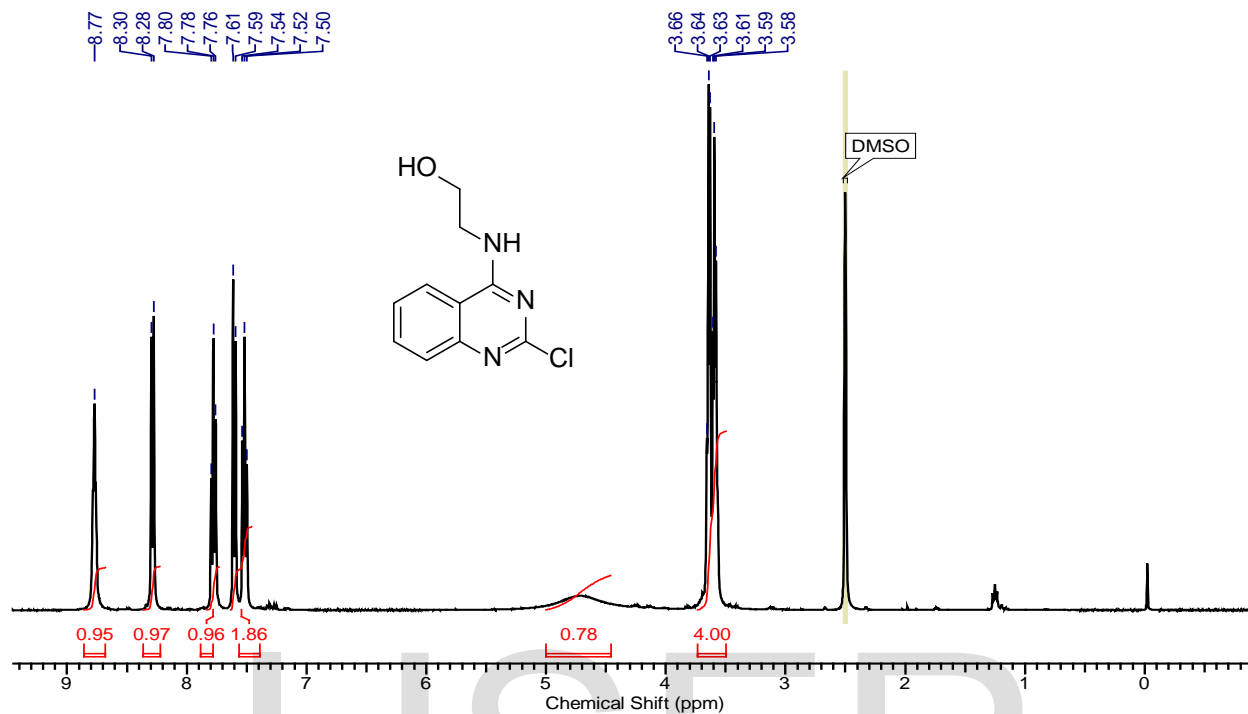


Fig. 6 ^{13}C NMR of 2-[2-chloroquinazolin-4-yl] amino]ethan-1-ol (III)

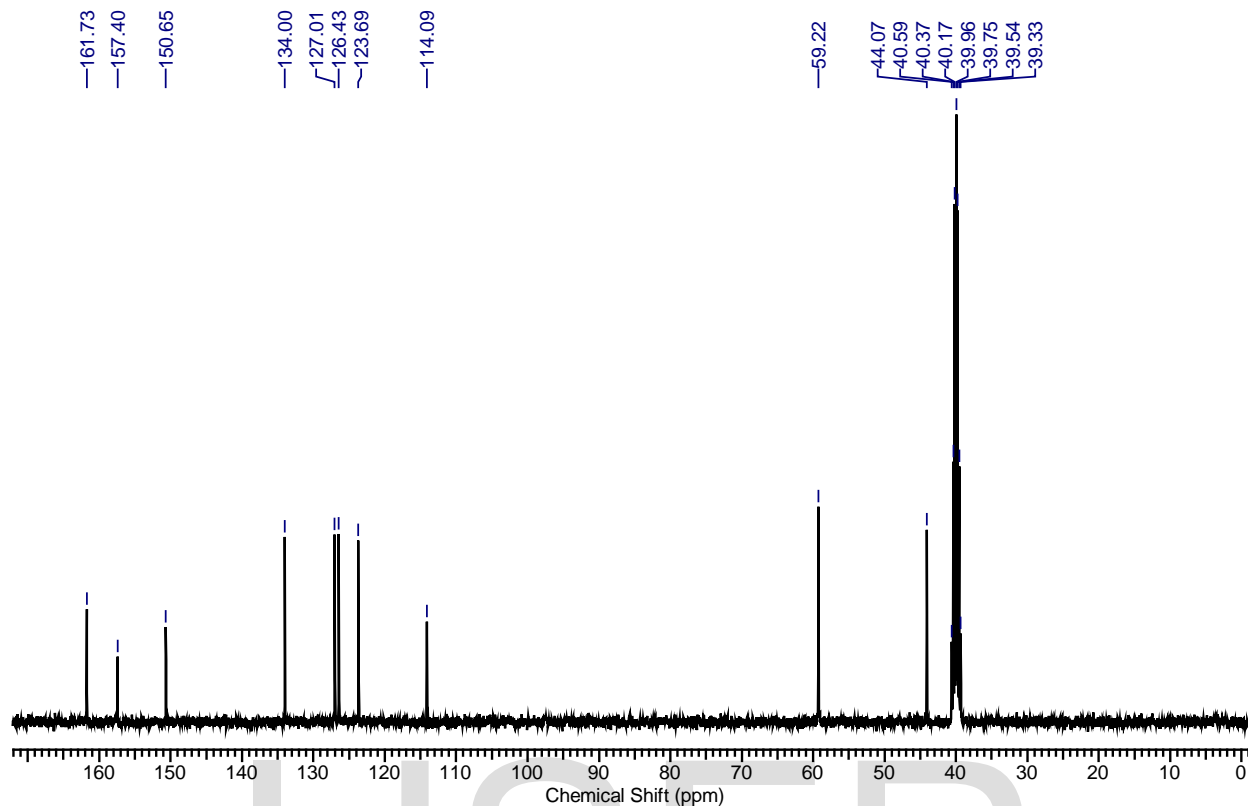


Fig. 7 ^{13}C NMR of 2-[[2-(piperazin-1-yl)quinazolin-4-yl] amino]ethan-1-ol (IV)

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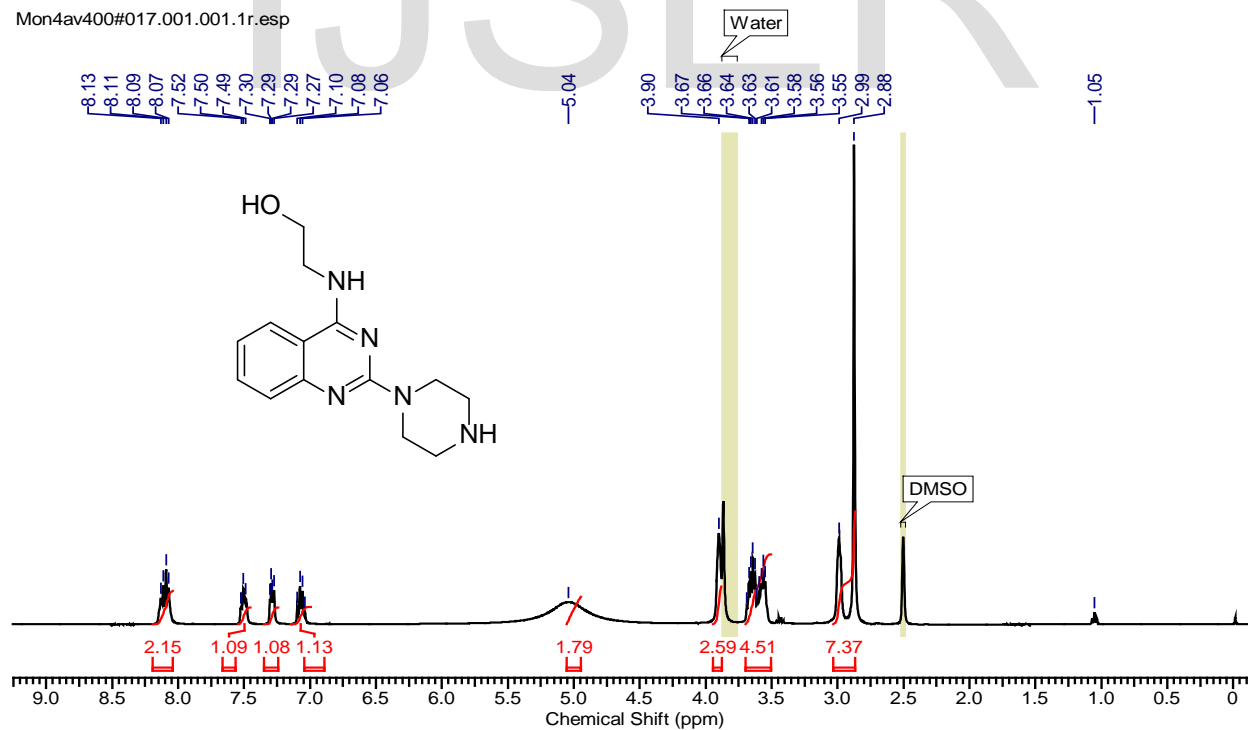
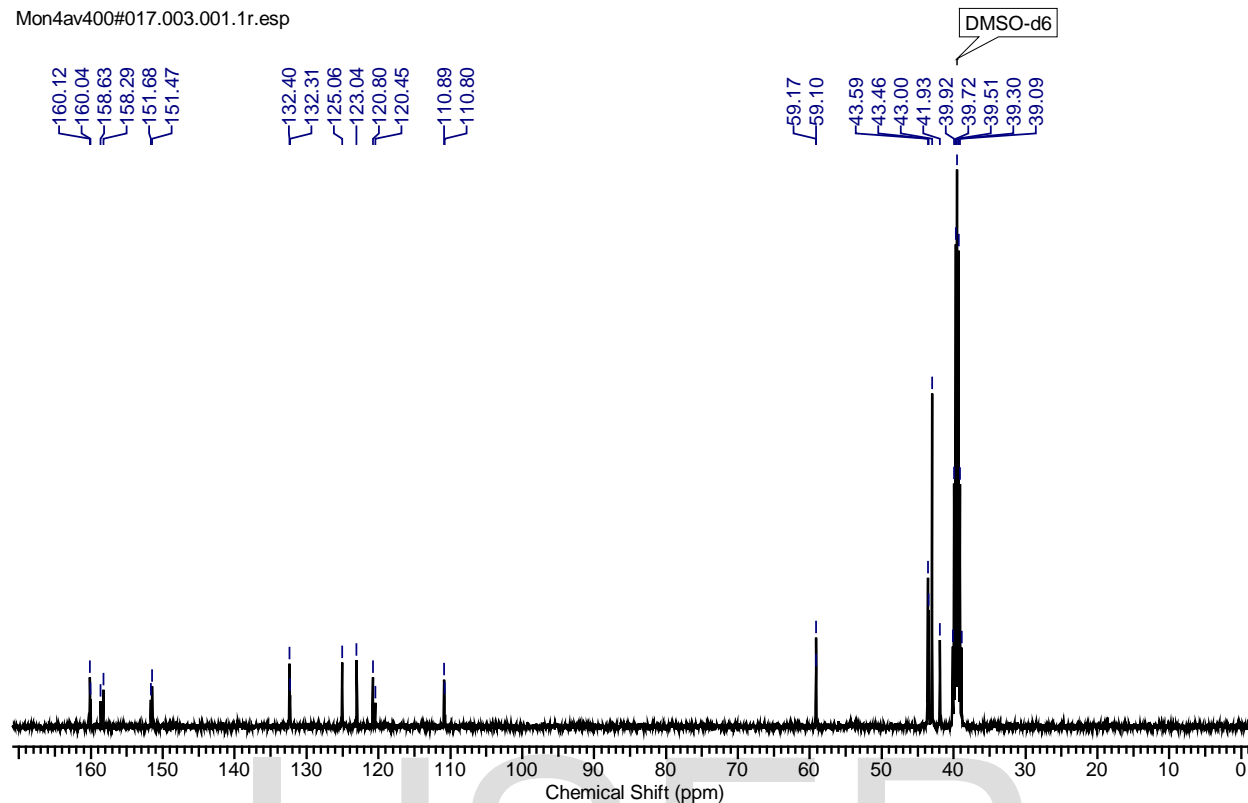


Fig. 8 ^1H NMR of 2-[[2-(piperazin-1-yl)quinazolin-4-yl] amino]ethan-1-ol (IV)

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Quinazoline derivatives, is N-containing heterocyclic compounds, have been universally distinguished and known for their biological activities and many therapeutic activities, including anti-cancer, anti-inflammation, anti-bacterial, analgesia, anti-virus, anti-cytotoxin, anti-spasm, anti-tuberculosis, anti-oxidation, antimalarial, anti-hypertension, anti-obesity, anti-psychotic, anti-diabetes, etc. Present trends are to synthesize a large variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. Present work deals with the to synthesize new derivatives of Quinazoline marked as Compound (I to IV) as per the scheme -I and the compounds synthesized will be characterized separately by different spectral methods including elemental analysis, IR, ^1H NMR, ^{13}C NMR, etc. All these compounds will be tested for various biological activities like anti-cancer, anti-inflammation, anti-bacterial, and analgesia, anti-virus, anti-cytotoxin, anti-spasm, anti-tuberculosis, anti-oxidation, antimalarial, anti-hypertension, anti-obesity, anti-psychotic, anti-diabetes, etc.

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