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Synthesis, Characterization and Evaluation of Antifungal and Antibacterial Activities of Some Quinazoline Derivatives

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ABSTRACT

Present work includes synthesis of 2-{[2-(piperazin-1-yl)quinazolin-4-yl]amino}ethan-1-ol (IV) , N2, N4-di p-tolylquinazoline-2,4- diamine (V) and N2, N4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) which are quinazoline derivatives and out of these three quinazoline derivatives N2, N4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) have shown "antifungal activity" against fungus "Aspergillus flavus" and "antibacterial activity" against bacteria "Pseudomonas". At first 2- amino benzoic acid react with urea at temperature 130 ºC to 140ºC to gives Quinazolin-2,4-diol (I) which on further reaction with phosphorus oxychloride at 150 ºC for 24 hr. to gives second product 2,4-dichloroquinazoline (II). Then 2-4-dichloroquinazoline (II) reacts with 2-aminoethan-1-ol and piperazine to gives 2-{[2-(piperazin-1-yl)quinazolin-4-yl]amino}ethan-1-ol (IV) and when p-toluidine react with 2-4-dichloroquinazoline (II) to gives N2, N4-di p-tolylquinazoline-2,4- diamine (V) and again this 2,4-dichloroquinazoline (II) react with p-chloroanline to gives N2, N4-bis(4-chlorophenyl) quinazoline-2,4-diamine (VI) which characterized by I. R., 1HNMR and 13CNMR.

Keywords : Quinazoline Derivative, Antifungal Activity, Antibacterial Activity, N2, N4-Di P-Tolylquinazoline-2, 4-Diamine, N2, N4-Bis (4-Chlorophenyl) Quinazoline-2, 4-Diamine, Quinazolin-2, 4-Diol, 2,4--Dichloroquinazoline

I. INTRODUCTION

Quinazoline is N-containing heterocyclic compound, till date many researcher have synthesized many derivatives of Quinazoline and all these derivatives have shown different pharmacological activities like anti-bacterial [3], antimicrobial [4], anti-inflammation [6], antifungal [8], anti-hypertension [10], anti-oxidation [12] analgesia [13], anticonvulsant [14], antimalarial [15], anti-tumor [16], anti-tuberculosis [17], anti-HIV activity [18] 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 (quinazolineorpyrido [2, 3-d] pyrimidine ring), selected as the central fragment that can act as a scaffold to carry two functionalized branches at 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. We have synthesized derivatives of Quinazoline which are 2-{[2-(piperazin-1-yl)quinazolin-4-yl]amino}ethan-1-ol (IV) , N^2, N^4-di p-tolylquinazoline-2,4- diamine (V) and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) In first derivative that is 2-{[2-(piperazin-1-yl)quinazolin-4-yl]amino}ethan-1-ol (IV) we have substituted second and fourth position of quinazoline by piperazine and aminoethan-1-ol respectively while in second derivative that is N^2, N^4-di p-tolylquinazoline-2,4- diamine (V) by p-toluidine and in third derivative N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) by p-chloroaniline. For synthesis of Quinazoline derivatives we have used piperazine, aminoethan-1-ol, p-toluidine and p-chloroaniline because individually they shows important pharmacological and other activities therefore at the time of synthesis we expected that after synthesis of these quinazoline derivatives they will be show some pharmacological activities and after evaluation of biological activities of these synthesized derivatives of quinazoline, result is that N^2, N^4-bis(4-

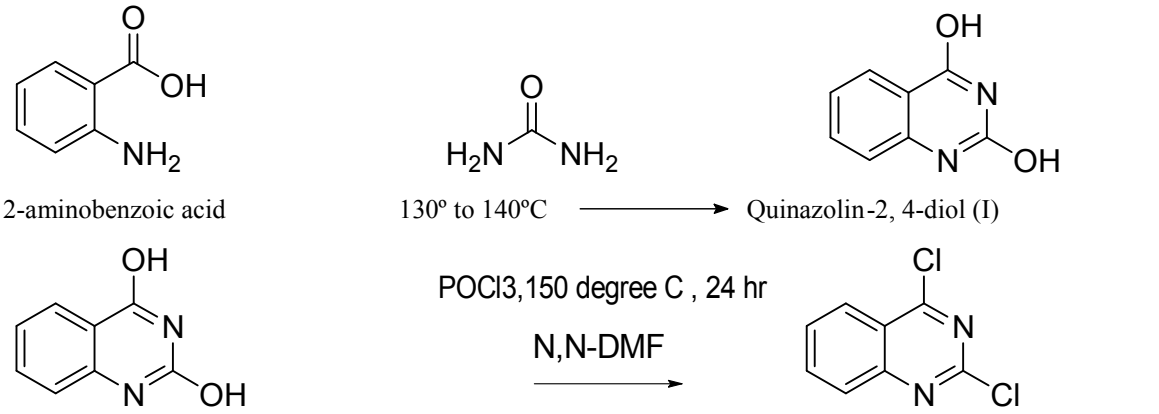
chlorophenyl)quinazoline-2,4-diamine (VI) have shown "antifungal activity" against fungus "Aspergillus flavus" and "antibacterial activity" against bacteria " Pseudomonas".

II. RESULT AND DISCUSSION

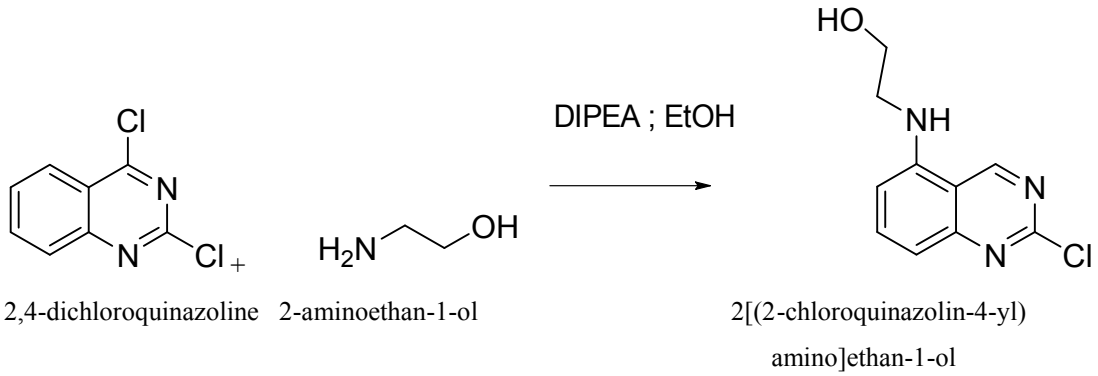
Target molecules which synthesized are 2-{[2-(piperazin-1-yl)quinazolin-4-yl]amino}ethan-1-ol (IV), N^2, N^4 - di p-tolylquinazoline-2,4- diamine (V) and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI). At first 2- amino benzoic acid react with urea at temperature 130 ºC to 140ºC to gives Quinazolin-2,4-diol (I) which on further reaction with phosphorus oxychloride at 150 ºC for 24 hr. to gives second product 2,4-dichloroquinazoline (II). Then 2-4-dichloroquinazoline (II) reacts with aminoethan-1-ol and piperazine to gives 2-{[2-(piperazin-1-yl)quinazolin-4-yl]amino}ethan-1-ol (IV) and when p-toluidine react with 2-4-dichloroquinazoline (II) to gives N^2, N^4-di p-tolylquinazoline-2,4- diamine (V) and again this 2,4-dichloroquinazoline (II) react with p-chloroanline to gives N^2, N^4-bis(4-chlorophenyl) quinazoline-2,4-diamine (VI) which characterized by I. R., ^{1}HNMR and ^{13}CNMR. Out of these derivatives of quinazoline N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) have shown "antifungal activity" against fungus "Aspergillus flavus" and "antibacterial activity" against bacteria " Pseudomonas".

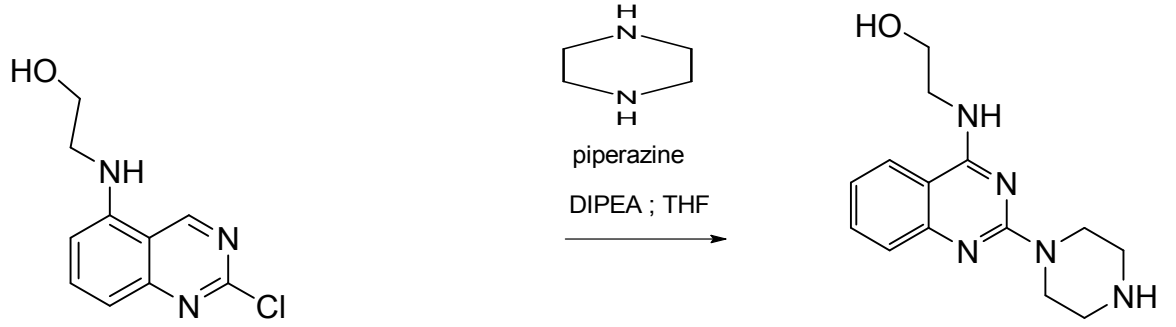
Present trends are to synthesize a large variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods therefore we have introduced piperazine, aminoethan-1-ol, p-toluidine and p-chloroaniline groups at second and fouth position of quinazoline because all these four groups have important pharmacological and other activities and have synthesized derivatives of quinazoline and tested for antifungal and antibacterial activities and we have got successful result according to our expectation.

Scheme 1.

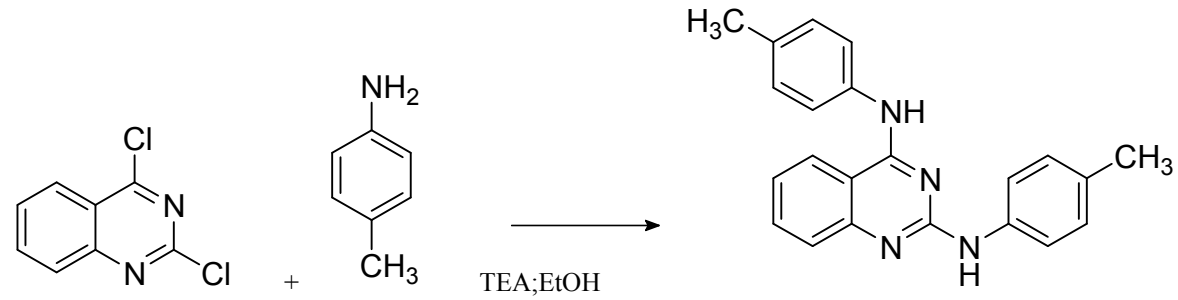


Scheme – II

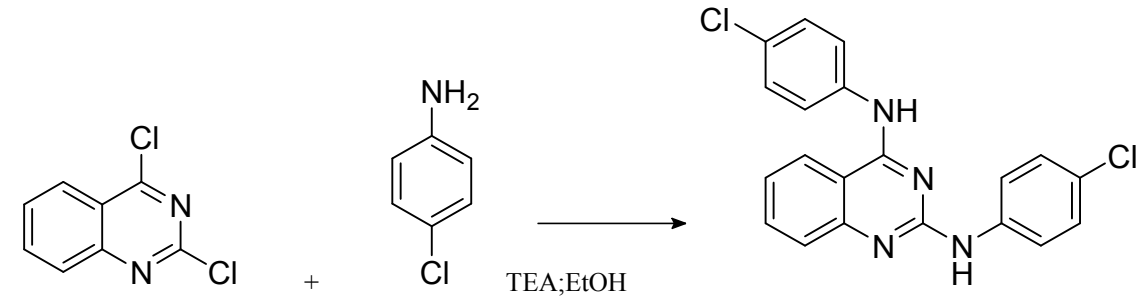




2[(2-chloroquinazolin-4-yl)amino]ethan-1-ol 2-{[2-piperazin-1-yl)quinazolin-4-yl] amino}ethan-1-ol **Scheme – III**



2,4-dichlorouinazoline P-toluidine 70ºC , 5 hr N^2,N^4-di p-tolylquinazoline-2,4- diamine (V)



2,4-dichloroquinazoline P-chloroaniline 70ºC , 5 hr N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine(VI)

III. EXPERIMENTAL

Anthranilic acid, Urea, phosphorus oxychloride, N, N-dimethyl formamide, Triethyl amine, diisopropyl ethyl amine, 2-aminoethan-1-ol, piperazine, p-toluidine,P-Chloroaniline, ethanol 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. ^{1}H-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.

Synthesis and characterization of Quinazolin-2, 4-diol (I) [25] : 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 140ºC using an air condenser for 3h. The melted reaction mixture was poured into sodium hydroxide (1000 mL, 1N) solution and any insoluble material removed by filtration. The mixture was then acidified with HCl (2 N), to yield 2,4-dihydroxy quinazoline as a white precipitate which was collected by filtration and dried. Yield 70%; m. p. >250ºC.

IR max cm^{-1}: 3428 (OH, broad), 3079 (Ar C-H), 1604 (C=N), **^{1}H NMR (DMSO-d^6) δ ppm**: 7.56 (t, 2H, Ar-H), 7.98 (d, 1H, Ar-H), 9.19 (s, 1H, Ar-H), 7.17 (t, 1H), 9.16 (1H, S), **^{13} CNMR (DMSO-d^6) (δ/ppm)**: 121.11 (Ar C-H), 115.39 (Ar C-H), 142.59 (Ar C-H), 135.02 (Ar C-H),

163.98 (Ar C-OH), 155.69 (Ar C-OH), 108.35 (Ar C), 151.2 (Ar C)

Synthesis and characterization of 2, 4-dichloroquinazoline (II) [20] : A mixture quinazolin-2, 4-diol (6.0 milimole), POCl3 (5 ml) and N, N-DMF (catalytic amount) was stirred and heated for 150°C under reflux for 24 h. The solvents were removed under vacuum then 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 and compound obtained used for further analysis.

IR max cm^{-1}: 755 (C-Cl), 3029 (Ar C-H), 1625 (C=N), **^{1}H NMR (CDCl3-d^{1}) δ ppm**: 7.18 (m, IH), 7.61 (m, 2H), 7.87 (d, I H), **^{13}C NMR (CDCl3-d^{1}) (δ/ppm)**: 115.35 (Ar C), 122.33 (Ar C), 126.96 (Ar C), 134.97 (Ar C), 14.90 (Ar C), 150.31 (Ar C), 162.85 (Ar C)

Synthesis[20] and characterization of 2-[2-chloroquinazolin-4-yl) amino] ethan-1-ol (III) : Taken 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. Added to it (for 1 g sample required 10 ml ethanol) ethanol & DIPEA (3 eq.) at 0ºC then stir for 6 hr. The progress of reaction checked by TLC. After completion of reaction, distilled out it completely then added dichloromethane to it & washed with water. The Organic layer dried over sodium sulphate & concentrated to obtain off white solid. The obtained off white solid purified by hexane, dried it, weighed it & used for further analysis & reaction.

^{1}H NMR (CDCl3-d1) δ ppm : 3.66 (1 H, s), 3.61 (2H, t), 3.58 (2H, t), 8.25 (1 H, s), 8.28 (1H, d), 7.78 (1 H, t), 7.59(1H, t), 7.80 (1H, d).
^{13}C NMR (CDCl3-d1) (δ/ppm) : 161.73 (Ar C), 157.4 (Ar C), 150.65 (Ar C), 134.00(Ar CH), 127.01 (Ar CH), 126.43(Ar CH), 114.09 (Ar C-), 59.22 (aliphatic CH_2), 44.07 (aliphatic CH_2)

IV. Synthesis of 2-{[2-(piperazin-1-yl)quinazolin-4-yl] amino} ethan-1-ol (IV)
Taken 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. Added to it THF & DIPEA at 0ºC & then reaction mixture heated at 80ºC for 16 hr. The progress of reaction was checked by TLC. After completion of reaction diluted it with ethyl acetate & washed with water. The organic layer dried over sodium sulphate & concentrated to obtain white solid which is purified by hexane washing. Dried it, washed it & used for further analysis & reaction.
^{1}HNMR (400MHz, DMSO-d1) δ ppm: 5.04 (1H, s), 1.05 (1H, s), 8.11 (1H, s), 2.99 (4H, t), 2.88 (4H, t), 7.50 (1H, d), 7.30 (1H, m), 7.29 (1H, m), 7.08 (1H, t), 3.67 (2H, t), 3.56 (2H, t)
^{13}C NMR (CDCl3-d1) (δ/ppm): 160.12 (quinazoline C), 160.04 (quinazoline C), 158.53 (quinazoline C), 110.8 (quinazoline C), 125.05 (quinazoline CH), 132.31 (quinazoline CH), 132.4 (quinazoline CH), 123.04 (quinazoline CH), 59.17 (aliphatic CH_2), 43.59 (aliphatic CH_2), 43.00 (aliphatic CH_2), 41.93(aliphatic CH_2)

Synthesis and characterization of N^2,N^4-di p-tolylquinazoline-2,4- diamine (V) [20] : A mixture of 5 (5.0 mmol), the respective Toluidine (12 mmol), equimolecular amounts of triethylamine, and ethanol (15 mL) was heated at 70ºC for 5 h with stirring. The solvent was removed under vacuum and chloroform was added in solution and extracted with water. Product precipitated out in water layer because it is insoluble in water as well as in chloroform. Water layer washed with chloroform and filtered. Obtained water insoluble product dried, purified and characterized by using IR, ^{1}HNMR and ^{13}CNMR
IR max cm^{-1}: 3300 (-NH), 1616 (-C=N), **^{1}H NMR (DMSO-d6) δ ppm** : 7.99 (1H, s), 8.51(1H, d), 7.84 (2H, d), 7.62 (1H, d), 6.27 (1H, s), 7.58 (2H, d), 7.52(2H, d), 7.43 (2H, d) 7.38 (2H, d), 2.5 (6H, s), **^{13}C NMR (DMSO-d6) (δ/ppm)**: 46.33(aliphatic C), 103.06 (quinazoline C), 115.05 (quinazoline C), 125.12 (Ar C), 126.71 (quinazoline C), 129.67 (quinazoline C), 137.06 (quinazoline C), 174.68 (Ar C), 180.18 (Ar C), 180.99 (quinazoline C), 182.77 (quinazoline C), 183.04 (quinazoline C), 188.31 (quinazoline C)

Synthesis and characterization of N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) [20] : A mixture of 5 (5.0 mmol), the respective p-chloroaniline (12 mmol), equimolecular amounts of triethylamine, and ethanol (15 mL) was heated at 70ºC for 5 h with stirring. The solvent was removed under vacuum and chloroform was added in solution and extracted with water. Product

precipitate out in water layer because it is insoluble in water as well as chloroform. Water layer washed with chloroform and filter. Obtained water insoluble product dried, purified and characterized by using IR, ^{1}HNMR and ^{13}CNMR

IR max cm^{-1}: 750 (C-Cl), 3015(Ar C-H), 1615 (C=N), 3360 (-NH), **^{1}HNMR (400MHz, DMSO-d1) δ ppm :** 8.03 (1 H, d), 8.17 (2H, t), 8.01 (2H, d), 7.66 (1 H, t), 7.62 (2H, d), 7.49 (1 H, s), 7.25 (1H, s), 7.08 (2H, d), 6.60 (2H, d), **^{13}C NMR (CDCl3-d1) (δ/ppm)**: 109.56 (quinazoline CH), 116.26 (quinazoline CH), 119.5 (Ar-C), 121.99 (quinazoline CH), 124.22 (quinazoline CH), 125.44 (Ar-CH), 126.40 (Ar-C), 127.92(Ar-C), 129.12 (Ar- CH), 128.99 (Ar-C), 130.51 (quinaoline-C), 131.57 (quinazoline-C), 134.53 (quinazoline-C)

Antifungal studies :

The newly synthesized compounds were screened and tested for their antifungal activity against "Aspergillus flavus" in DMSO solvent by well plate method. Sterile N.A. and P.D.A. plates were inoculated with Aspergillus flavus and make well with sterile cork borer. And then loaded 20 microliter of compound N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) solution (0.01 g in 1 ml DMSO solvent) then this plate was dried by placing in an incubator at 37°C for 1 hr., prepared each well was labeled. The temperature was controlled and maintained at 37°C for 24 hr. The Inhibition zone were measured and compared with the controls. Zone diameter: 4 mm.

Antibacterial :

The newly prepared compounds were screened for their "antibacterial activity" against "Psedomonas aerogenosa" in DMSO by well plate method. Sterile N.A. and P.D.A. plates were inoculated with "Psedomonas aerogenosa". Made a well with sterile cork borer. Loaded 20 microlitre of compound N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) solution (0.01 g in 10 ml DMSO solvent) then this plate was dried by placing in an incubator at 37°C for 1 hr, wells were made and each well was labeled. A control was also prepared in and maintained at 37°C for 1 day. Inhibition zone were measured and compared with the controls.

Zone diameter : 2 mm

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IV. CONCLUSION

We have synthesized 2-{[2-(piperazin-1-yl)quinazolin-4-yl]amino}ethan-1-ol (IV) , N^2, N^4-di p-tolylquinazoline-2,4- diamine (V) and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) and out of these quinazoline derivatives N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (VI) have shown "antifungal activity" against fungus "Aspergillus flavus" and "antibacterial activity" against bacteria " Pseudomonas" and all these compounds will be tested for various biological activities like anti-cancer, anti-inflammation, anti-bacterial, analgesia, anti-virus, anti-cytotoxic, anti-spasm, anti-tuberculosis, anti-oxidation, antimalarial, anti-hypertension, anti-obesity, anti-psychotic, anti-diabetes, etc.

V. REFERENCES

[1]. Joshi N. and Goyal Anju (2011) Microwave assisted one-pot Total synthesis of some natural Quinazoline alkaloids-a review,International Journal of Pharmaceutical Erudition; www.pharmaerudition.org,Aug. 2011,1(2),1 -9 1

[2]. Dewick,P. M. (1997) Medicinal Natural Products: A Biosynthetic Approach Pub: Willey & Sons p-376.)

[3]. Nagar,A. A.,Patel,A.,Rajesh K.S.,Danao,K. R. and Rathi,L.G.(2013) Solvent Free One Pot Microwave Synthesis of Quinazolin 4-(3H)-One derivatives with their Antibacterial and Antifungal Activity PHARMAGENE Vol:1 Issue:1 (genesisjournals.org Received on: 22-12-2012 Modified on: 15-01-2013 Accepted on: 26-02-2013)

[4]. Gautam S,Mishra D,Singh R and Pal DK (2012) Synthesis of some novel 4,6-disubstituted derivatives and evaluation of their antimicrobial activity,International Journal of Pharmaceutical,Chemical and Biological

Sciences,ijpcbs 2012,2(1),97-103 sucheta et al. ISSN: 2249-9504

[5]. Doshi H,Bhatt M,Thakkar S,Ray(2012) A synthesis,characterizations and biological screening of tetrahydro-quinazoline analogues American Journal of Organic Chemistry 2012,2(5): 122-126 ,Doi: 10.5923/j.ajoc.20120205.03

[6]. Mohamed M. S. ,Kamel M. M. ,Kassem E. M .M.,Abotaleb khedr N ,m. and Ahmed M. f.(2011) Synthesis,Biological Evaluation and Molecular Docking of Quinazoline-4(1h)-one Derivatives as Anti-inflammatory and Analgesic Agents,Acta Poloniae Pharmaceutical Drug Research,Vol. 68 No. 5 pp. 665ñ675,2011

[7]. Sinha N. K.,Asnani A. J.,Dravyakar B. R(2013).,A Novel Approach Towards Development Of Quinazoline Derivatives In Pain Management Asain journal of pharmaceutical and clinical research Vol 6,Suppl 3,2013 ISSN-0974-2441(Sinha N. K.,Asnani A. J.,Dravyakar B. R(2013).,A Novel Approach Towards Development Of Quinazoline Derivatives In Pain Management Asain journal of pharmaceutical and clinical research Vol. 6,Suppl 3,2013 ISSN-0974-2441

[8]. Vashi R.T.,Shelat C. D. & Patel H(2010),Synthesis and Antifungal Activity of 6-bromo-2[(4-(2,3-dichlorophenyl)) piperazine-1-yl)methyl]-3-[8-hydroxyquinoline -5-yl]-3-quinazolin -4-one Ligand and its Transition Metal Chelates International Journal of Applied Biology and Pharmaceutical Technology. Volume: I: Issue-3: Nov-Dec -2010 ISSN 0976-4550

[9]. Vijai and P.R.,Suresh K. K.,Sivakumar R.,Sam Solomon W.D. and Jayaveera K.N. (2009)Synthesis of Quinazoline Derivatives and their Biological Activities Asian Journal of Chemistry Vol. 21,No. 9 (2009)

[10]. Patel H. U.,Patel R. S.,Patel C. N,(2013) Synthesis and Antihypertensive Activity of Some Quinazoline Derivatives,Journal of Applied Pharmaceutical Science Vol. 3 (03),pp. 171-174,March,2013

[11]. Mohamed,Y. A. ,El-galil,A.,Amrb,C.,Mohamed,S.F.,Abdalla,M. M.,Al-omar,M. and Shfik,S. H. (2012),Cytotoxicity and anti-HIV evaluations of some new synthesized quinazoline and thioxopyrimidine derivatives using 4-(thiophen-2-yl)3,4,5,6tetrahydrobenzo[h]quinazoline-2(1H)-thione as synthon YAJ. Chem. Sci. Vol. 124,No. 3,May 2012,pp. 693–702.

[12]. Al-Omar,M.A.,El-Azab,A. S.,El-Obeid,H.A. and Abdel Hamide,S.G.,(2006) J. Saudi Chem.Soc.,2006,10,1131

[13]. Sinha N. K.,Asnani A. J.,Dravyakar B. R(2013).,A Novel Approach Towards Development Of Quinazoline Derivatives In Pain Management Asain journal of pharmaceutical and clinical research Vol 6, ISSN-0974-2441

[14]. Mukherjee D,Mukhopadhyay A.,Shridhara K. B,Shridhara A.M.,Rao K.S.(2014) Synthesis,Characterization And Anticonvulsant Activity Of Substituted 4-Chloro-2-(4-Piperazin-1-Yl) Quinazolines International Journal of Pharmacy and Pharmaceutical Sciences,ISSN-0975-1491 Vol 6,Issue 5,2014

[15]. Sen D,Banerjee A,Ghosh A. K,and Chatterjee T. K (2010) Synthesis and Antimalarial Evaluation of Some 4-Quinazolinone Derivatives Based On Febrifugine Journal of Advanced Pharmacological Technology and Research J. Adv Pharm Technol Res. 2010Oct-Dec; 1(4): 401–405.doi: 10.4103/0110-5558.76439

[16]. El-Azab A. S.,Al-Omar M. A.,Abdel-Aziz A .A.-M.,Abdel-Aziz N. I. El-Sayed M. A.-A.,Aleisa A. M.,Sayed-Ahmed M. M. ,Abdel-Hamide S. G(2010) Design,Synthesis And Biological Evaluation Of Novel Quinazoline Derivatives As Potential Antitumor Agents: Molecular Docking Study European Journal of Medicinal Chemistry journal,June 2010

[17]. Srivastav M. K. And Shantakumar S. M. (2013),Design and Synthesis of Novel 2-Trichloromethyl-4-Substituted Quinazoline Derivatives as Anti-tubercular Agents Chem Sci Trans.,2013,2(3),1056-1062 Chemical Science Transactions DOI:10.7598/cst2013.490 ISSN/E-ISSN: 2278-3458/2278-3318 ,January 2013.

[18]. Pandeya SN,Sriram D,Nath G,Clercq E D. Synthesis antibacterial antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin derivatives with 3-amino-2-

methylmercaptoquinazolin-4(3H)-one. Pharmaceutical Acta Helvetiae. 1999; 74: 11–17

[19]. Nagwa M A G,Hanan H G,Riham M Y,Nehad A E S. Synthesis and antitumor activity of some 2,3-disubstituted quinazolin-4(3H)-ones and 4,6-disubstituted-1,2,3,4- tetrahydroquinazolin-2H-ones. European Journal of Medicinal Chemistry. 2010; 45:6058-6067.

[20]. Maria Font a,Alvaro GonzAlez a,Juan Antonio Palop b,Carmen Sanmartin b a Section de Modelizacion Molecular,Dpto de Quimica OrgAnica Pharmaceutical,Facultad de Farmacia,Universidad de Navarra,Irunlarrea 1,E-31008 Pamplona,Spain b Seccion de Synthesis,Dpto de Quimica OrgAnica y Farmacéutica,Facultad de Farmacia,Universidad de Navarra,Irunlarrea 1, E-31008,Pamplona,Spain

[21]. Juan J. Marugan,a,Wei Zhenga,Omid Motabara,b,Noel Southalla,Ehud Goldinb,Wendy Westbroekb,Barbara K. Stubblefieldb,Ellen Sidranskyb,Ronald A. Aungstc,Wendy A. Leaa,Anton Simeonova,William Leistera,and Christopher P. Austina,Evaluation of Quinazoline Analogues as Glucocerebrosidase Inhibitors with Chaperone Activity,J. Med. Chem. 2011,54,1033–1058 1033 DOI: 10.1021/jm1008902

[22]. Giorgi-Renault,S.,Renault J.,Baron M.,Gebel-Servolles,P.,Delic,J.,Cros S. C.,Heterocyclic quinones XIII. Dimerization in the series of 5,8-quinazolinediones: Synthesis and anti-tumor effects of bis (4-amino-5,8-quinazolinediones),Chem. Pharm. Bull.,36 (10),3933-3947 (1988)

[23]. P. A. Mason and Gillian Sturman Some pharmacological properties of piperazine,Br. J. Pharmac. (1972),44,169-176.

[24]. Prabhakar V1,Sudhakar BK2,Ravindranath LK2,Latha J3 and Venkateshwarlu B4 ,Synthesis,Characterization and biological evaluation of Quinazoline Dervatives as Novel Anti-microbial agents.

[25]. K. M. Durgade A.A.Kale1 Synthesis,Characterization of 2-{[2-(Piperazin-1-yl) quinazolin4-yl] Amino} ethan-1-ol Quinolone Derivatives International Journal of Scientific & Engineering Research,Volume 8,Issue 1,January-2017 1148 ISSN 2229-5518 IJSER©2017. http://www.ijser.org