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Synthesis, Characterization and Biological Evaluation of N^2, N^4-dip-tolylquinazoline-2,4-Diamine and N^2, N^4-bis(4-chlorophenyl) quinazoline2,4diamineQuinazoline Derivatives

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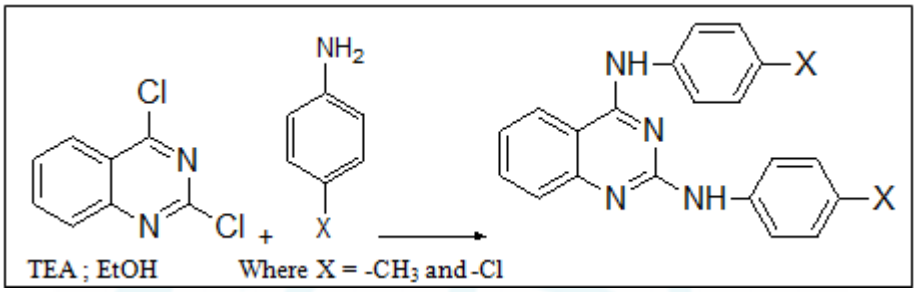


Abstract: ***Present work includes synthesis of N^2, N^4-di p-tolylquinazoline-2, 4- diamine and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine which are quinazoline derivatives and out of these two N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV) have shown "antifungal activity" against Aspergillusflavus. At first 2- amino benzoic acid react with urea attemperature 130 ºC to 140ºC to gives Quinazoli-2,4-diol (I) which on further reaction with $POCl_3$ at 150 ºC for 24 hr. to gives second product 2,4-dichloroquinazoline (II). Then 2-4-dichloroquinazoline (II) react with p-toluidine to gives N^2, N^4-di p-tolylquinazoline-2,4- diamine (III)and again this 2,4-dichloroquinazoline (II) react with p-chloroanline to gives N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV) which characterized by I. R., ^{1}HNMR and ^{13}CNMR.***

Keywords: Quinazoline derivative, Antifungal activity, N^2, N^4-di p-tolylquinazoline-2,4- diamine, N^2, N^4-bis(4-chlorophenyl) quinazoline-2,4-diamine, Quinazolin-2,4-diol, 2,4-dichloroquinazoline

1. Introduction

Quinazoline is heterocyclic compound. Derivatives of quinazoline are called quinazolines. Quinazoline is 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-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.

First of all we have synthesized Quinazoline-2,4-diol (I) from 2-amino benzoic acid and urea then again this formed quinazoline-2,4-diol treated with $POCl_3$ in presence of N,N-dimethyl formamide to gives 2,4-dichloroquinazoline (II). From this 2,4-dichloroquinazoline (II) we have synthesized our target molecules N^2, N^4-di p-tolylquinazoline-2,4-diamine (III) and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV) by reacting 2,4-dichloroquinazoline with p-toluidine and p-chloroaniline in presence of triethylamine simultaneously.

The target molecules which we have synthesized that is N^2, N^4-di p-tolylquinazoline-2,4- diamine and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine. Out of these two N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV) have shown "antifungal activity" against Aspergillusflavus.

2. Result and Discussion

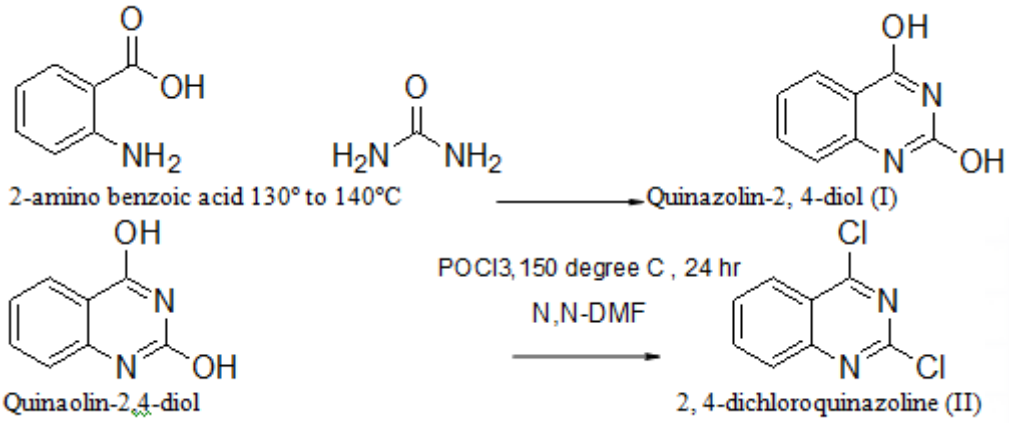
Target molecules which synthesized are of N^2, N^4 - di p-tolylquinazoline-2,4- diamine (III) and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV). Those target

molecules obtained by reacting2-amino benzoic acid with urea to give Quinazolin-2,4-diol (I) which on further reaction with phosphorus oxychloride to gives 2,4-dichloroquinazoline (II). This formed 2,4-dichoroquinazoline react with Toluidine and 4-chloroaniline simultaneously to gives of N^2, N^4 - di p-tolylquinazoline-2,4- diamine (III) and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV) respectively.

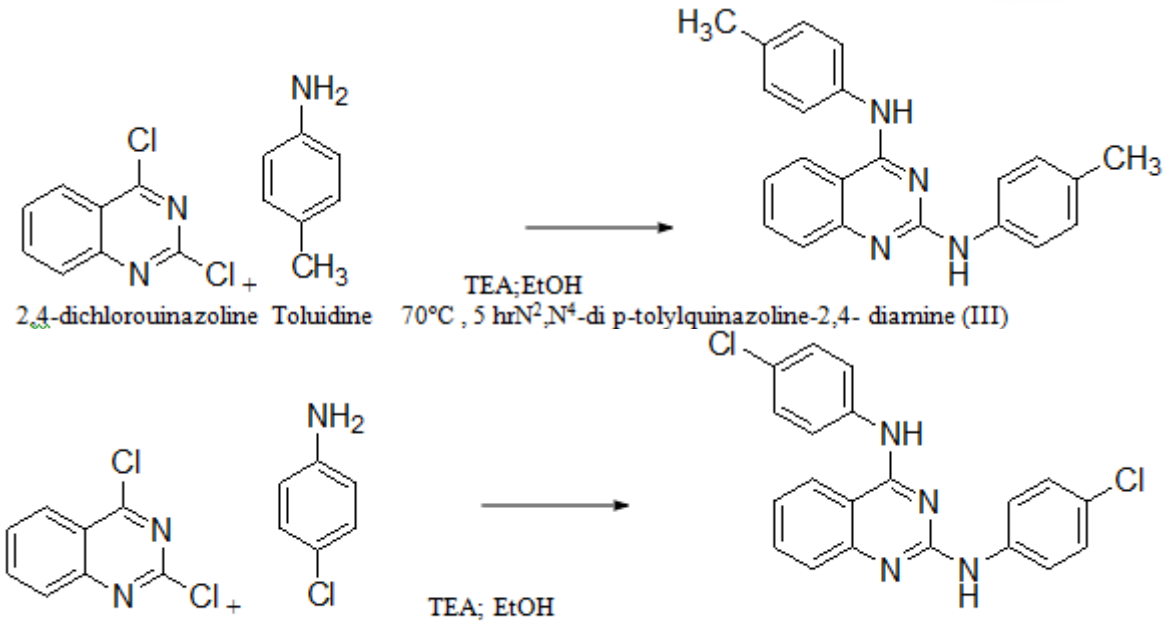
The synthesized compounds N^2, N^4 - di p-tolylquinazoline-2,4- diamine (III) and N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV) have tested against fungus " Aspergillusflavus" then N^2, N^4-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV) have shown "antifungal activity" against Aspergillusflavus.

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.

Scheme - I



Scheme – II



3. Conclusion

We have synthesized compounds N^2, N^4- di p-tolylquinazoline-2,4- diamine (III) and N^2, N^4-bis (4-chlorophenyl) quinazoline-2,4-diamine (IV) and they have tested against fungus " Aspergillusflavus" then N^2, N^4-bis(4-chlorophenyl) quinazoline-2,4-diamine (IV) have shown "antifungal activity" against "Aspergillusflavus" 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.

4. Experimental

Anthranilic acid, Urea, phosphorus oxychloride, N, N-dimethyl formamide, Triethyl amine, 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.

Synthesisand 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 and characterizationof N^{2},N^{4}-di p-tolylquinazoline-2,4- diamine(III)[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 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}:**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)

Synthesisand characterization of N^{2}, N^{4}-bis(4-chlorophenyl)quinazoline-2,4-diamine (IV)[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)

5. Antifungal Studies

The newly synthesized compounds were screened and tested for their antifungal activity against Aspergillusflavusin DMSO solvent by well plate method. Sterile N.A. and P.D.A. plates were inoculated with Aspergillusflavus and make well with sterile cork borer. And then loaded 20 microlitre of compound 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

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