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SYNTHESIS AND STUDIES MOLECULAR DOCKING OF SOME NEW 2-[(2*Z*)-2-BENZYLIDENEHYDRAZINYL]QUINOXALINE DERIVATIVES.

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ABSTRACT

o-Phenylenediamine reacts with Glyoxylic acid to form quinoxalin-2-ol (1), on reacts with POCl3, gives 2-chloroquinoxaline (2). On reaction with hydrazinehydrate , gives 2-[(2Z)-2-benzylidenehydrazinyl] quinoxaline (3), on condensation with different aromatic aldehydes gives Derivatives. and These newly synthesized compounds were docked within the active site of Mycobacterium tuberculosis glutamine synthetase MtGS (PDB ID: 2BVC). The results of this docking study revealed that the new compounds might exhibit good anti-tb activity. The structure of new compounds was demonstrated by elemental analysis, IR, ^{1}H NMR spectra and mass spectra.

KEYWORDS

Quinoxalines, molecular docking , hydrazinehydrate.

INTRODUCTION:

Quinoxalines or benzopyrazines are heterocyclic compounds that present designed properties for commercial and/or academic applications as dyes, drugs or pharmacological tools.1,2 Methodologies to obtain quinoxaline compounds regioselectively are rarely reported in literature, thus regioselective and multi-gram methodologies to obtain those derivatives are desirable to explore the entire potential of these scaffolds.[1] Further more these newly synthesized compounds were docked within the active site of Mycobacterium tuberculosis glutamine synthetase MtGS (PDB ID: 2BVC). The results of this docking study revealed that the new compounds might exhibit good anti-tb activity.

EXPERIMENTAL SECTION:

the coupling constant values (*J*) are given in Hz. Signal multiplicities are represented by: s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet) and br (broad signal). FTIR spectra were obtained using a Thermo Scientific Nicolet's Avatar iS10 spectrometer equipped with smart endurance diamond ATR unit for direct measurements. Mass spectra were obtained from a TLC-MS (thin layer chromatography) interface CAMAG in negative mode and from a Hewlette Packard HP 5973 mass selective detector (70 eV). Melting points were determined using a MP70 Mettler Toledo and are uncorrected. The purity of compounds was determined by high-performance liquid chromatography (HPLC, Merck Hitachi L-6200 intelligent pump, Merck Hitachi AS-2000 auto sampler, Merck Hitachi L-4250 UV-Vis detector) using a Zorbax® Eclipse XDB C8 column (5 mm), employing a gradient of 0.01 M KH2PO4 (pH 2.3) and methanol as solvent system with a flow rate of 1.5 mL min-1 and detection at 230 and 254 nm.

Procedure for synthesis of quinoxalin-2-ol (1),

A solution of *o*-phenylenediamine (**1**) (10.0 g, 93 mmol) in methanol (100 mL) was slowly added to an ice bath cooled solution of glycoxilic acid monohydrate (10.2 g, 111 mmol) in methanol (120 mL) and the mixture was kept at room temperature for 1 h after addition of the *o*-phenylenediamine solution. 12.0 g of a white crystalline solid were obtained after filtration and washing with water. Yield 89%; mp 269-270 ºC (lit. 268-270 ºC);4 ATR/FTIR n / cm-1 3302, 1682, 1638, 898, 753;

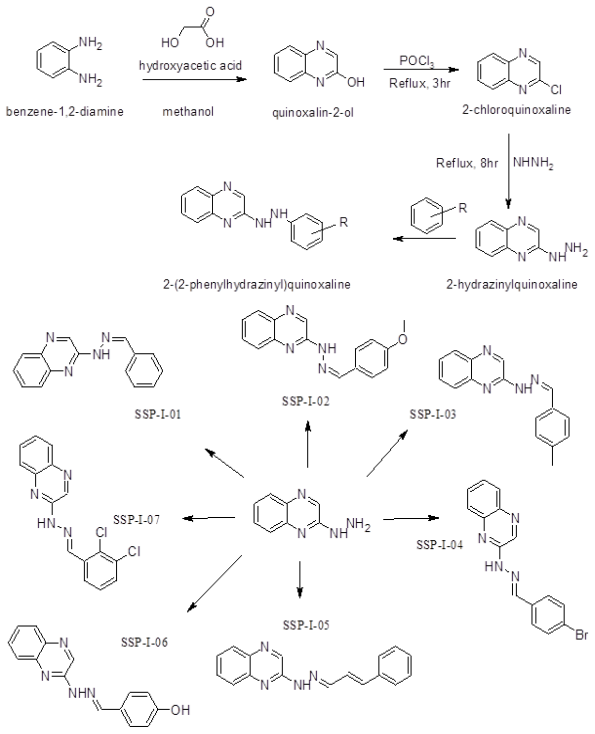
Procedure for the synthesis of 2-chloroquinoxaline (2).

In a round bottom flask, a mixture quinoxalin-2-ol (**1**) (12.73 g, 67 mmol) in 20 mL of phosphoryl chloride (POCl3) was refluxed for 3 h. Then, the mixture was slowly poured into a stirred mixture of ice and water. The precipitate was filtrated and washed with water to obtain 13.43 g of a red/cherry solid. Yield 96%; mp 183-186 °C (lit. 185-189 °C);5 ATR/FTIR n / cm-1 3092, 3048, 1682, 1525, 1350, 740;

Procedure for the synthesis of 2-[(2*Z*)-2-benzylidenehydrazinyl] quinoxaline(3)

To the solution of 2-[(2*Z*)-2-benzylidenehydrazinyl] quinoxaline (3) (3gm, 0.015 mol) in ethanol (10 ml), (0.935ml,0.015 mol) hydrazine hydrate 99% was added at room temperature and the reaction mixture was refluxed for 8h. Then reaction was monitored by TLC using Cyclohexane and Ethylacetate in the ratio 1:3. Rf value 0.42. Reaction mixture was allowed to cool at bellow 10°C temperature resultant solid was filtered, dried and recrystallized from ethanol. Yield 93%; mp 171-173 °C (lit. 167-169 ºC);13 ATR/FTIR n / cm-1 3389, 3077, 2928, 1615, 1538, 1509, 1338, 741; 1H NMR (200 MHz, DMSO-*d*6) d 8.50 (t, 2H, *J* 6.0, NH and H3), 8.27 (d, 1H, *J* 2.0, H8), 8.05 (dd, 1H, *J* 2.0, 9.0, H6), 7.96 (d, 1H, *J* 8.0, H5), 7.36 (d, 2H, *J* 8.0, H3'), 6.91 (d, 2H, *J* 8.0, H4'), 4.56 (d, 2H, *J* 6.0, CH2), 3.73 (s, 3H, OCH3). 13C NMR (50 MHz, DMSO-*d*6) d 158.4, 152.8, 147.5, 143.6, 141.4, 139.3, 130.4, 129.9, 129.2, 120.9, 116.8, 113.8, 55.1, 43.3; DEPT-135 (50 MHz, DMSO-*d*6) d 143.6, 129.9, 129.2, 120.9, 116.8, 113.8, 55.1, 43.3; ESI-MS 309.3;

SCHEME



Procedure Of Molecular Docking

The crystal structure of Mycobacterium tuberculosis glutamine synthetase MtGS (PDB ID: 2BVC) was downloaded from Protein Data Bank. The structure is complex with magnesium, adenosine-5'-diphosphate (ADP) and L-methionine-s-sulfoximine phosphate MSO-P [1]. The protein structure is prepared in discovery studio 3.2 by addition of hydrogen, removal of water molecule and existing ligand

molecule. The chemical structure were drawn in marvin sketch and engery minimised in discovery studio 3.2.

ADMET property of each molecule was predicted by swiss ADMET tool which is online tool. Binding site of target protein molecule was predicted using PDBsum. Protein-ligand docking studies were performed using the Autodock 4.2 . In docking stimulations, each ligand was kept flexible but the amino acid residues of the enzyme were held rigid. For the simulation runs default parameter values were taken. The selection of atoms in the active site within 1 Å of original ligands was chosen as default.

Structure Of Target Protein

The crystal structure of glutamine synthetase (MtGS) in complex with inhibitor has been retrived from PDB (PDB ID: 4PYG). This protein catalyzes the ligation of glutamate and ammonia to form glutamine by hydrolysis of ATP. MtGS play important role in nitrogen metabolism in bacteria. In crystalline state, MtGS is in a complex with magnesium, ADP and L-methionine-s-sulfoximine phosphate MSO-P consisting of six subunits that onstitute a hexameric ring. The enzyme composed of six chain (A,B,C,D,E,F) with molecular weight 33.22 kD.

Binding Site Determination

The binding site information of TG2 structure was predicted by performing PDBsum and literature evidences PubMed. Active site of contain five amino acid especially on chain A. Glu 133, Gly 272, His 276, Arg 329, Arg 347,Arg 368.

ADME/T studies of ligand

The compounds which are labeled as druglike resemble the existing drug molecules and exhibit the following property cut-off values. The compounds exceeding the cut-off values tend to have solubility and permeability problems which would lead to poor oral bioavailabity. In addition to the rule of five there are other properties which help in distinguishing drug and non drug-like compounds.

Docking Result

Table.1

	Molecule	Binding energy	Inhibition constant	Total internal energy	Interaction with amino acid
Scheme 1	Ref	-3.71	1.92	-0.33	ARG59,ARG189,GLY184
	SSP-I-1	-5.24	144.19	-1.48	--
	SSP-I-2	-6.17	30.02	-0.61	LYS265,TYR153
	SSP-I-3	-5.05	200.02	-1.42	GLU366, HIS278
	SSP-I-4	-5.49	2.78	-1.02	TYR153,PHE262
	SSP-I-5	-4.95	236.0	-1.43	
	SSP-I-6	-5.22	150.05	-0.91	SER 372,TYR178

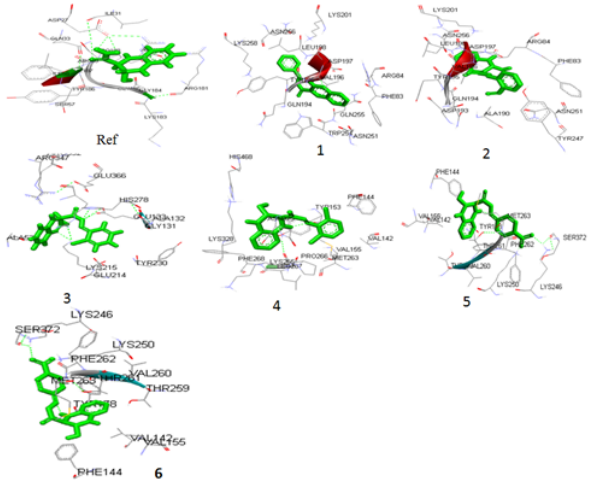


Figure 1. Docking Interaction Of Receptor And Ligands With Respect To Scheme.

CONCLUSION

All the compounds were synthesized with high purity and In this present, *in-silico* study various bioinformatics tools were used for docking the anti TB drug with the 3D structure of protein target Mycobacterium tuberculosis glutamine synthetase MtGS.

The results of this study revealed that these molecules especially and show potential inhibition of TG2 and thus can be implicated for treatment of lung cancer.

The combined approach of ADME and docking used in this study, helps in expressing the binding affinity of drug on the target protein well and also validates as potential candidates for second generation drug target discovery.

Development of effective and selective inhibitors of TB will make possible for better treatment for TB, which may ultimately lead to effective clinical treatments against same. Further *in-vitro* studies could be undertaken to validate the present study.

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