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SYNTHESIS AND MOLECULAR DOCKING STUDIES OF ANTIDIABETIC ACTIVITY OF 2-AMINOBENZOTHIAZOLE DERIVATIVES

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ABSTRACT
The 2-aminobenzothiazole derivatives were synthesised and evaluated for their antidiabetic activity. The substituted 2-amino benzothiazole derivatives were synthesised by reaction of substituted anilines with ammonium thiocyanate. All the synthesized compounds were characterized on the basis of their IR, ^{1}HNMR and mass spectroscopy. The antidiabetic activity of the titled compounds 2b(R=4-Br), 2d(R=3-Br), 2e(R=2-Cl) exhibited highly significant and comparable antidiabetic activity is determined through Molecular docking by using docking software ArgusLab. The present molecular docking studies of novel 2-aminobenzothiazole derivatives as inhibitors of p56(dok-2) for diabetes. The protein file of p56(dok-2) [PDB code: 2DLW] was taken from the protein data bank. The derivatives of 2-aminobenzothiazole have shown best ligand pose energy between -8.0282 kcal/mol to -10.082 kcal/ mol. Among them 6-chlorobenzo[d]thiazol-2-amine has shown best ligand pose like -10.082kcal/mol. Pymol software was used to view the structure and calculating the length of hydrogen bond.

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INTRODUCTION

The high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). The diabetes can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack[1]. The non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes is a metabolic disorder that is characterized by high blood glucose in the context

of insulin resistance and relative insulin deficiency.[2] .Diabetes is often initially managed by increasing exercise and dietary modification. DOK proteins are enzymatically inert adaptor or scaffolding proteins. They provide a docking platform for the assembly of multimolecular signaling complexes.. Docking protein 2 is a protein that in humans is encoded by the *DOK2* gene [3]. A 56-kDa tyrosine phosphorylated protein, p56(dok-2) (Dok-2), from p210(bcr-abl) expressing cells. The human dok-2 cDNA encodes a 412-amino acid protein with a predicted N-terminal pleckstrin homology domain as well as several other features of a signaling molecule, including 13 potential tyrosine phosphorylation sites, six PXXP motifs, and the ability to bind to p120(RasGAP). Dok-2 was shown to be 35% identical to p62 (dok-1), a recently identified RasGAP binding protein[4,5]. More recently a variety of substituted 2-amino benzothiazole derivatives have emerged as potent antidiabetic agents. In view of these data we have undertaken the synthesis and antidiabetic evaluation of 2-amino benzothiazole derivatives represented in Fig. No.01. All the synthesized compounds were characterized on the basis of their physical properties, IR, 1HNMR spectral data and Mass spectroscopy [6,7]. The physical data of titled compounds are summarized in Table No.01.

Scheme: Derivatives of benzo[d]thiazol-2-amines (Refer Fig. No. 01)

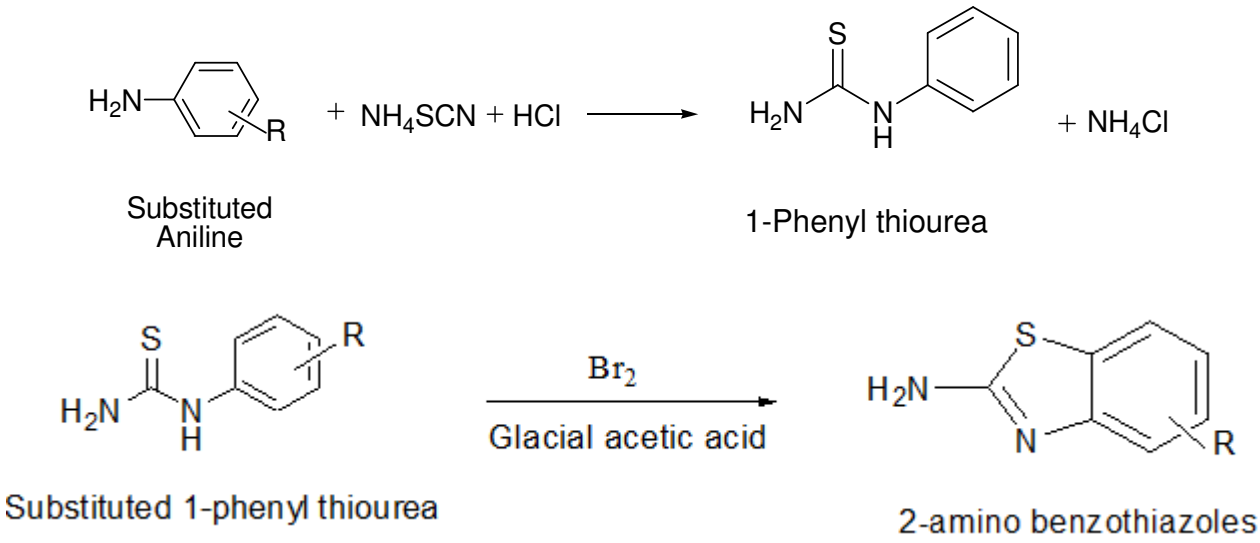


Fig. No. 01.Scheme: Derivatives of benzo[d]thiazol-2-amines

Table I. Characterization data of compounds (2a-2e) (Refer Table No.01)

Comp	R	Yield (%)	M.P. (°C)	R f	Mol. Formula
2a	4-NO_2	77%	198-200°c	0.5	$C_7H_5N_3O_2S$
2b	4-Br	75%	200-203°c	0.28	C_7H_5 Br N_2S
2c	P-Cl	84%	193-195°c	0.61	C_7H_5 ClN_2S
2d	3-Br	76%	165-170°c	0.37	$C_7H_5BrN_2S$
2e	0-Cl	73%	175-180°c	0.5	$C_7H_5ClN_2S$

Table No.01.Characterization data of compounds (2a-2e)

MATERIALS & METHODS:

The melting points were carried out in open capillary tube and were uncorrected. Thin layer Chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapour. IR spectra of compounds were scanned on Shimadzu IR spectrophotometer using KBr disc and expressed in cm-1. 1H NMR spectra were recorded in DMSO on BRUKER (300MHz) spectrometer using TMS as an internal standard (chemical shifts in δ, ppm).

General procedure:

(1) Synthesis of substituted 1-phenyl urea:

Equimolar quantities aniline, substituted aniline (0.02mol), and ammonium thiocyanate (1.5g, 0.02mol) were dissolved in ethanol containing 2ml of Conc. Hydrochloric acid taken in round bottom flask. It was allowed to stand for 30minutes.

(2) Synthesis of 2-amino Benzothiazole derivatives*:*

A mixture of derivative bromine in glacial acetic acid (2.7ml, 0.05mol) was added and the reaction mixture was refluxed for 1hr. Then, it was cooled in ice-water mixture. The precipitate obtained, strained well, filtered washed with cold water and dried. The crude product was recrystallised from rectified spirit. This is a cyclisation reaction.

Molecular modeling (docking) studies:

The structure of the enzyme tyrosine phosphorylated p56(dok-2) with the PDB ID 2DLW was retrieved from the protein data bank. It is a repository for the 3-D structural data of large biological molecules, such as proteins and nucleic acids. After obtaining the structure from protein data bank, the possible binding sites of docking protein 2 were searched using Q-site Finder. These include pockets located on protein surfaces ana voids buried in the interior of proteins. Q-site Finder includes a graphical user interface, fiexible interactive visualization, as well as n-the-fly calculation for user uploaded structures.

The inhibitor and target protein was geometrically optimized and docked using the docking engine Argus Dock. (http://www.arguslab.com).Arguslab consists of a user interface that supports OpenGL graphics display of molecule structures and runs quantum mechanical calculations using the Argus computer server.

RESULTS AND DISCUSSION:

The structured based drug design for the target P56 (dok-2) involved in diabetes is as follows. The potential active site amino acids were predicted using Q-site finder .Among the 10 active sites predicted, pocket 1 found to be the best active site which contains 27 amino acids. The Fig. No. 02 shows the active site of the target protein which has the surface area of 10044 cubic angstroms and volume of 1107 cubic angstroms. Thus the protein was targeted against pocket 1.

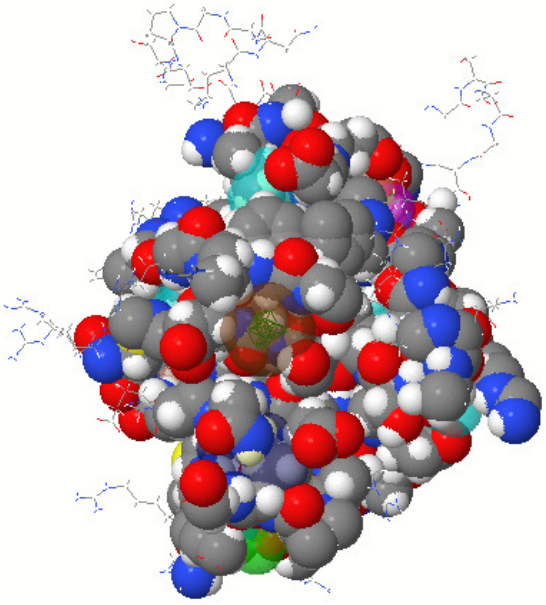
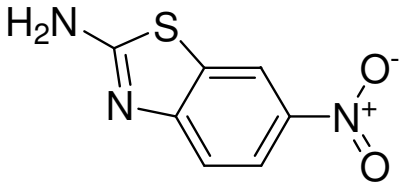
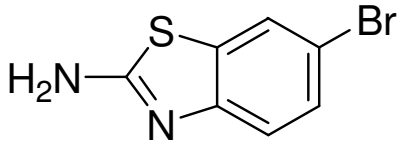


Fig. No. 02: active site of P-56(dok-2)

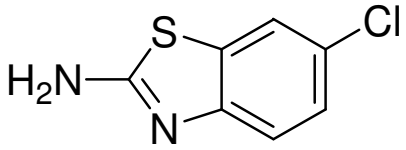
Given the three-dimensional structure of a target receptor molecule usually a protein, chemical compounds having potential affinity it are designed rationally, with the aid of computational methods. Fig. No. 03 shows the structure of inhibitors target against the p56 (dok-2) protein.



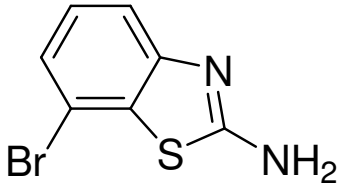
Compound -2a
6-nitrobenzo[d]thiazol-2-amine



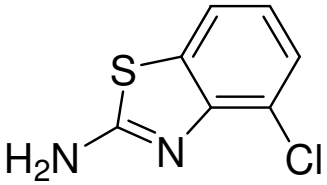
Compound -2b
6-bromobenzo[d]thiazol-2-amine



Compound -2d
6-chlorobenzo[d]thiazol-2-amine



Compound -2f
4-bromo benzo[d]thiazol-2-amine



Compound -2g
4-chlorobenzo[d]thiazol-2-amine

Fig. No. 03:The structure of inhibitors target against the p56 (dok-2) protein

The target protein and compounds were geometrically optimized. All the five compounds were docked against active site of the target protein using Argus lab which gives an insight into the binding modes for the various compounds. Out of the 5 compounds analyzed i.e. compound 2a, compound 2b, compound 2c,compound 2d,compound 2e. The Binding Energy Of 2-Amino Benzothiazole Derivatives was shown in table 2.

S.No	Name of the drugs	Binding Energy	Hydrogen bonds
1	**2A**	-8.0282	1
2	**2B**	-9.769	1
3	**2C**	-8.20434	1
4	**2D**	-10.082	1
5	**2E**	-9.03418	1

Table No.02. Binding Energy of 2-Amino Benzothiazole Derivatives

Compound 2d showed highest affinity towards DOK-2 compared to other compounds. This creates a strong hypothesis that the effects of complex formation by DOK-2 and Compound 2d contribute towards combating against diabetes. Fig. No. 04 shows the hydrogen bonding interaction between the compound 2d and target molecule.

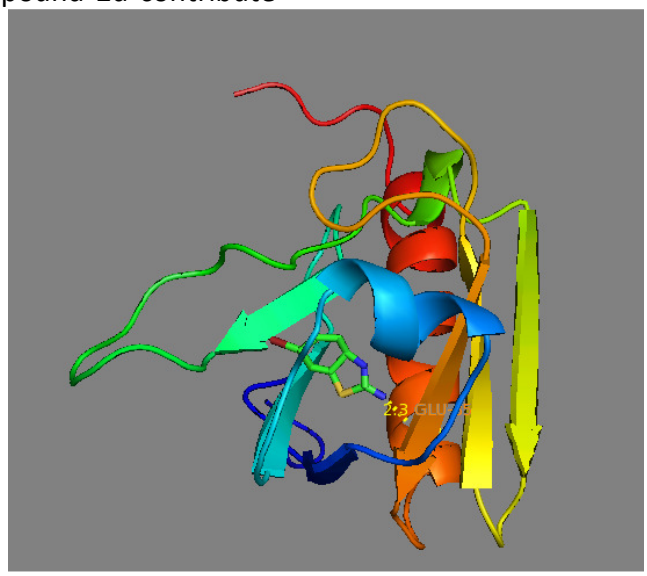


Fig. No. 04: The hydrogen bonding interaction between the compound 2d and target molecule.

CONCLUSION:

The substituted 2-amino benzothiazole derivatives are synthesized and determined for their antidiabetic activity. The substituted dervatives were synthesised by reaction of substituted anilines with ammonium thiocyanate. Thin layer Chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapour.the Rf value of the compounds are represented in these research. All the synthesized compounds were characterized on the basis of their IR, ^{1}HNMR and mass spectroscopy. The substituted 2-amino benzothiazole derivatives were docked with DOK-2 protein by using argus lab to get best hits. 2d showed the highest affinity towards DOK-2 than other compounds. This creates a strong hypothesis that the effect of complex formation by DOK-2 and substituted 2-amino benzothiazole derivatives represents the hydrogen bonding interaction between the 2d and target molecule. Thus we can conclude that the compounds having substituted 2-amino benzothiazole derivatives could act as a best drug for the treatment of Diabetes.

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