Research Article on Synthesis, Characterization, Molecular Docking and Biological Evaluation of 6-Methoxy-Benzothiazol-2-Yl-Amide Derivatives

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Abstract **- Benzothiazole is a privileged fused heterocyclic moiety, has attracted synthetic and medicinal chemists for good reasons. It is a valuable scaffold that possesses diverse biological activities, such as antimicrobial, antitubercular, antitumor, antimalarial, anticonvulsant, anthelmintic, analgesic and anti-inflammatory activity and other miscellaneous activities which makes benzothiazole an interesting molecule for the researchers to work on. Six derivatives of 6-methoxy-benzothiazol-2-yl-amide derivatives were subjected to *in silico* docking studies with the help of N-Myristoyltransferase (PDB ID:1ZAP). 2-amino-6-methoxy benzothiazole reacted with acid chlorides, to obtain a final product 6-methoxy-benzothiazol-2-yl-amide derivatives. The newly synthesized derivatives are characterized by using IR, ^{1}H NMR and Mass spectral data. From the docking results the compounds showed moderate to good activity which was comparable to that of the standard Fluconazole drug.**

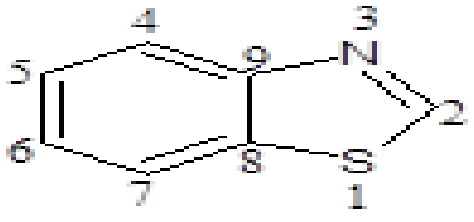
Index Terms **- Benzothiazoles, 2-amino-6-methoxy benzothiazole, Fluconazole and N-Myristoyltransferase.**

I.INTRODUCTION

Heterocyclic compounds are the major class of organic substrates that contain at least two different types of atoms in the ring. The mixed rings without any carbon atoms are inorganic heterocyclics and ring with one or more carbon atoms and heteroatoms (Nitrogen, Oxygen & Sulphur) are organic heterocyclics. The presence of heteroatom gives heterocyclic compounds many significant physical and chemical properties. Heterocycles are abundant in natural and are of great importance to human life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and pigments. Thus, these derivatives have attracted considerable attentions in the design of biologically active molecules. The nitrogen containing heterocyclics are synthetically challenging models for a number of physiologically active natural products. Modern society is dependent on synthetic heterocycles for many purposes such as drugs, pesticides, dyes, plastics, cosmetics, information storage, solvents, antioxidants, and vulcanization accelerators [1].

Heterocycles have widespread therapeutic uses such as antibacterial, antifungal, antimycobacterial, trypanocidal, anti-HIV, antileishmanial, genotoxic, antitubercular, antimalarial, herbicidal, analgesic, anti-inflammatory, muscle relaxants, anticonvulsant, anticancer, lipid peroxidation inhibitors, hypnotics, antidepressant, antitumoral, antihelmintic and insecticidal activities. Heterocyclic rings like pyrrole (1), thiazole (2), imidazole (3), triazole (4), pyridine (5), pyridazine (6), pyrimidine (7), pyrazine (8)[2].

Benzothiazole is a privileged bicyclic ring system. It contains a benzene ring fused to a thiazole ring. Thiazole ring is a five-member ring consists of one nitrogen and one sulphur atom in the ring. The small and simple benzothiazole nucleus is present in compounds involved in research aimed at evaluating new products that possess interesting biological activities like- antimicrobial, antitubercular, antitumor, antimalarial, anticonvulsant, anthelmintic, analgesic and anti-inflammatory activity [3



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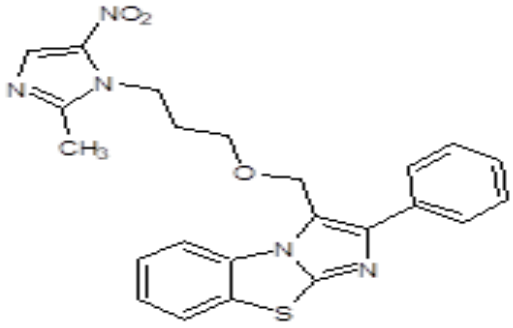
In this research, we analysed the properties by using *in silico* docking studies and we synthesized the 6-methoxy benzothiazol-2-yl-amide derivatives with the best protein binding interactions by using AUTODOCK vina. The synthesized compounds are characterized by using melting point, TLC, IR, H^1NMR and MASS spectral data.

II.LITERATURE REVIEW

Literature related for the Docking studies of Benzothiazoles:

Swetha Kameswari Maddili *et al.*, (2018) have synthesized Azoalkyl ether imidazo[2,1-b] benzothiazoles (2) and tested for antibacterial activity and structure were docked against *S. aureus gyrase* DNA (PDB ID: 2XCS). The result obtained showed good docking score was -9.338 for the compound below and it showed interactions with MET 1121, AGP 1083, SER 1084[4].



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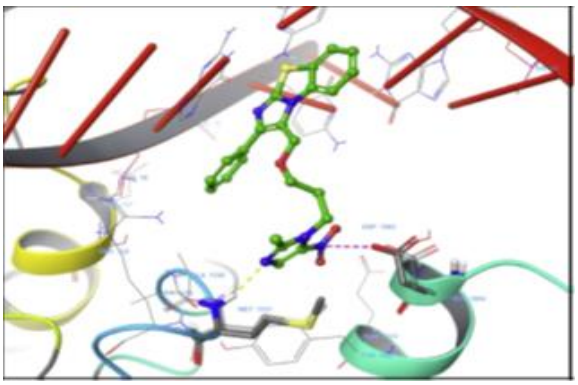
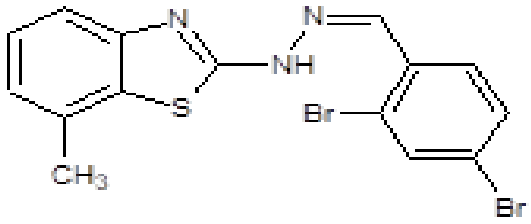


Fig.1. The binding mode of Azoalkyl ether imidazo[2,1-b] benzothiazoles and *S. aureus gyrase* DNA supramolecular complex

Hua-Li Qin *et al.*, (2017) synthesized 2-[(2Z)-2-(2,4-dibromobenzylidene) hydrazinyl]-7-methyl-1, 3-benzothiazole (3) and tested for anti-inflammatory activity and structure were docked against COX-2 (PDB ID: 1PXX). It is a most potent ligand gave docking score −8.90 and showed hydrophobic interaction with Arg 120, Tyr 385 and Tyr 387[5].



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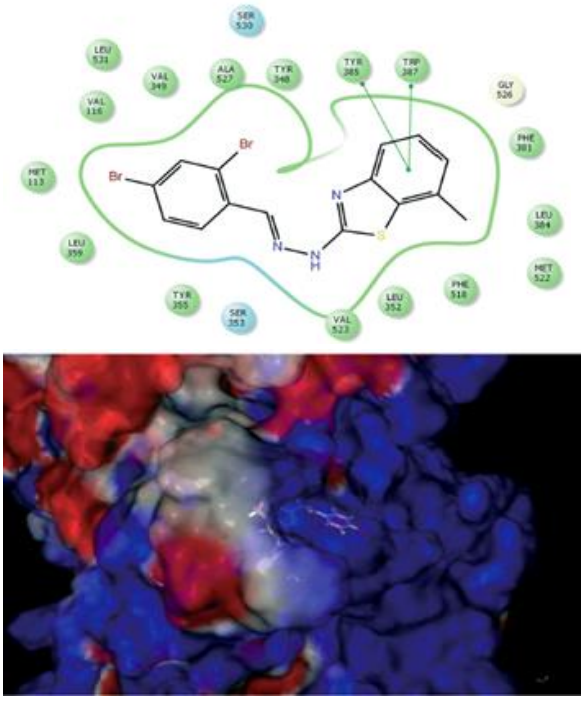
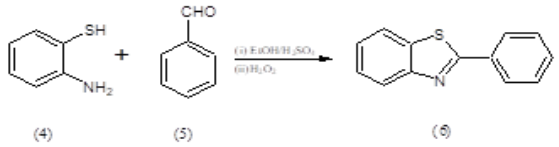


Fig.2. Molecular interaction and Electrostatic surface representation of COX-2 enzyme with 2-[(2Z)-2-(2,4-dibromobenzylidene) hydrazinyl]-7-methyl-1,3-benzothiazole depicting the best docking configuration.

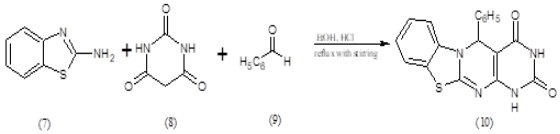
Literature related for the synthesis of Benzothiazoles:

Murshida Karim *et al.*, (2019) worked on the synthesis of 2-Aryl Benzothiazoles (6) by reacting 2-aminothiophenol (4), aldehydes or substituted aldehydes (5) and a minimum amount of ethanol were mixed in a pestle in an open mortar with thoroughly ground. To it, few drops of dil. HCl was added and ground the mixture for 2-3 minutes. Then H_2O_2 was added to the mixture and ground the mixture for 20 minutes. The reaction was monitored by TLC. The

product was washed with distilled H_2O and was recrystallized with alcohol [6].

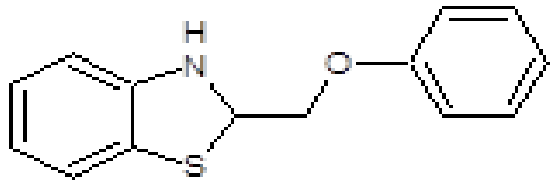


Talavara Venkatesh *et al*., (2018) have reported synthesis of Novel 5-Phenyl-1,5-dihydro-2H-benzo [4,5] thiazolo[3,2-a]pyrimido[4,5-d]pyrimidine-2,4(3H)-dione (10) by dissolving 2-aminobenzothiazoles (7), barbituric acid (8), benzaldehydes (9) and 2-3 drops of HCl in ethanol was refluxed with constant stirring for about 8 h. After completion of the reaction, the reaction mixture was poured into the crushed ice with vigorous stirring and the solid residue separated was filtered, dried, and recrystallized using ethanol [7].



Literature related for the Biological activity of Benzothiazoles:

Bo Luo *et al*, (2016) have synthesized 2-(aryloxymethyl) benzothiazole (11) and tested for antifungal activity which inhibited the growth of *F. solani* with IC50 of 4.34–17.61 μg/mL, which were stronger than that of the positive control, hymexazol (IC50 of 38.92 μg/mL). 2-(aryloxymethyl) benzothiazole was the most potent inhibitor (IC50 of 4.34 μg/mL) against *F. Solani*, which was about nine times more potent than hymexazol [8].



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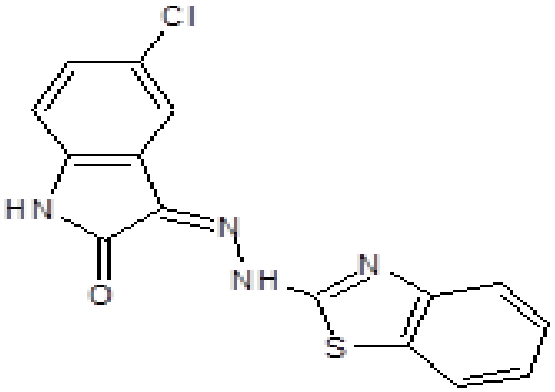
Rupinder K. Gill *et al*., (2015) synthesized (3Z)-3-[2-(1,3-benzothiazol-2-yl) hydrazinylidene]-5-chloro-1,3-dihydro-2H-indol-2-one (12) for anthelmintic activity against *Eudrilus eugeinae* and *Megascoplex Konkanensis* have shown the most potent activity comparable to standard drug albendazole in *in vitro* assay [9].



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III. EXPERIMENTAL METHODOLOGY

All the materials used in the research project were procured from SD Fine chemicals and AVRA labs, Hyderabad.

In silico studies:

The term '*in silico'* is used to define experimentation performed by computers and is related to the more commonly known biological terms *in vivo* and *in vitro*. It defines the use of data in the creation of computational models or simulations that can be used to make predictions, suggest hypotheses, and ultimately provide discoveries or advances in medicine and therapeutics.

In silico studies for the title compounds was done by using softwares like Molinspiration, Osiris, pkCSM and Autodock vina.

The Molinspiration tool was used in order to predict the physical properties of the title compounds. The properties are supposed to align with the Lipinski rule of five i.e., a molecule cannot have more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors, molecular mass of less than 500 daltons and a partition coefficient less than 5[10,11].

Osiris property calculator was used to predict toxicity prediction, partition coefficient, aqueous solubility, druglikeness and drug score of the title compounds. The structures of the compounds were drawn, the properties were automatically calculated, and the results were usually colour coded [12].

pkCSM is a novel method for predicting and optimizing small-molecule pharmacokinetic and toxicity properties which relies on distance-based graph signatures. While chemical modifications and

drug carriers can improve a compounds ADMET properties, pkCSM provides a rapid and easy method to for early evaluation of compounds [13].

Autodock are a set of automated docking tools which were designed in order to calculate the interactions of a ligand molecule on the protein molecule. The protein molecule i.e., N-myristoyltransferase (Nmt) enzyme (PDB ID: 1ZAP) was downloaded from the rcsb protein data bank. The ligand molecules were drawn by using chemsketch and were converted into pdb form by using Open babel software. The pdb formats of the ligand and the protein molecule was converted into pdbqt format by using autodockvina software. The grid box dimensions were adjusted into the active site of N-myristoyltransferase (Nmt) with the center of the grid box at x = 6.48, y = 29.457, z = 4.532 and the size of the grid box was x = 40, y = 40 and z = 40. The docking was then proceeded by using command prompt and the results were obtained in the form of a log file and a pdbqt output file. These files were later analysed by using Autodock vina. About the protein: N-myristoyltransferase (Nmt) is a monomeric enzyme that catalyzes the transfer of the fatty acid myristate from myristoyl-CoA to the N-terminal glycine residue of a variety of eukaryotic and viral proteins. Genetic and biochemical studies have established that Nmt is an attractive target for antifungal drugs [14].

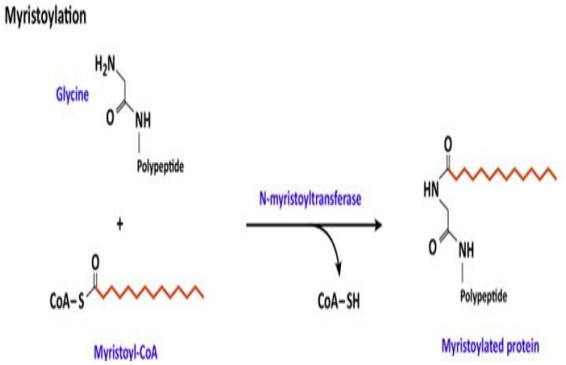


Fig.3. Pathway of Myristoylation

NMT gene is essential for vegetative growth and survival of *Candida albicans* and *Cryptococcus neoformans. Candida albicans.* Nmt has 451 amino acids residues and Human Nmt has 496 amino acids. Clear differences in the peptide-substrate specificity between fungal and humans Nmts have been exploited and Nmt has been identified as a potential chemotherapeutic target for antifungal agents. This enzyme has a PDB ID of 1ZAP in RCSB protein data bank. The molecule has two chains, chain A and chain B. The experimental data for the protein is given as follows.

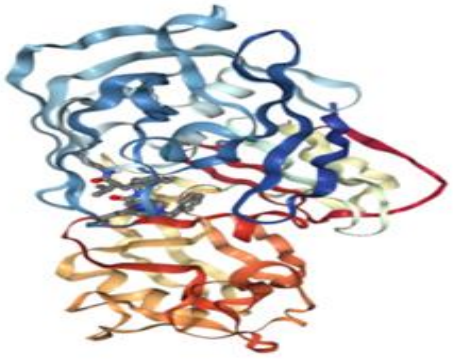
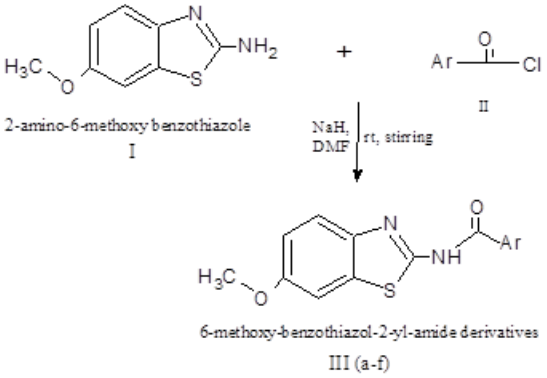
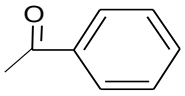
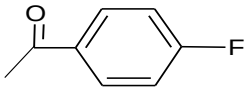
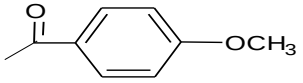
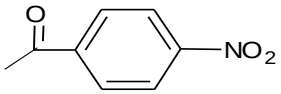
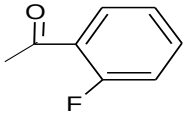
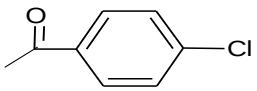


Fig.4. Crystal structure of Secreted aspartic protease from Candida albicans (PDB ID: 1ZAP)

SCHEME



Compound	Ar
III (a)	
III (b)	
III (c)	
III (d)	
III (e)	
III (f)	

Experimental Procedures

General procedure for synthesis of 6-methoxy-benzothiazol-2-yl-amide derivatives:

2-amino-6-methoxy benzothiazole (1gm, 0.005mol) dissolved in DMF (0.37ml, 0.005mol) and NaH (0.16ml, 0.006mol) was added slowly and the mixture was stirred vigorously for 5 min at room temperature. To the resulting solution, benzoyl chloride (0.75ml, 0.005mol) in (2ml, 0.027mol) of DMF was added, and the mixture was stirred for 3-4 h at room temperature and the completion of reaction was monitored by TLC. The reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was washed with brine (saturated Nacl) two times and dried over $MgSO_4$. After filtration and concentration, the crude product was purified by recrystallization to afford the desired amide.

IV.RESULTS AND DISCUSSION

In silico studies

Molinspiration, Osiris and pkcsm

All the six derivatives of 6-methoxy benzothiazol-2-yl-amidewere analysed by using MOLINSPIRATION and OSIRIS in order to calculate the molecular properties, the Toxicity of the molecules and the pharmacokinetics properties (ADMET).

Table.1. Physical properties of 6-methoxy benzothiazol-2-yl-amide derivatives using Molinspiration

Compound	IUPAC name	Log P	TPSA	Mol wt	nON	nOHNH	nrotb
III (a)	N-(6-Methoxybenzo[d]thiazol-2-yl) benzamide	3.42	51.22	284.39	4	1	3
III (b)	4-Fluoro-N-(6-methoxy-benzothiazol-2-yl) benzamide	3.58	51.22	302.33	4	1	3
III (c)	4-Methoxy-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	3.48	60.46	314.37	5	1	4
III (d)	N-(6-Methoxy-benzothiazol-2-yl)-4-nitrobenzamide	3.38	97.05	329.34	5	1	4
III (e)	2-Fluoro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	3.53	51.22	302.33	4	1	3
III (f)	4-Chloro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	4.10	51.22	318.79	4	1	3

The log P value or the partition coefficient for a drug molecule affects its absorption and solubility. If a compound has higher log P value it is considered as a hydrophobic molecule and if the logP value is less it is considered as a hydrophilic molecule. An ideal drug molecule should contain moderate logP value. All the compounds that were analysed have moderate logP value.

TPSA or Topological Polar Surface Area is the total surface area of a drug molecule that allows the drug to permeate into the cells. The TPSA should be less than 140 sq. angstroms to enter into the cells and the TPSA should be less than 90 sq. angstroms to cross the blood brain barrier. All the designed compounds were found to have TPSA of less than 90 sq. angstroms.

According to Lipinski's rule of five, a drug molecule must have molecular weight less than 500 daltons so that the drug molecule can be easily transported through the membranes by passive transport. All the title compounds show less than 500 daltons of molecular weight.

They should have less than or equal to 10 Hydrogen bond donors (nON) so that the molecule can interact with the active site of the target protein. All the proposed compounds have shown the number of hydrogen bonds to be less than 10.

The number of rotational bonds in a molecule gives an impression about the stability of the molecule. The number of rotational bonds should be less than or equal to 8 in order to be highly stable. The title compounds have rotational bonds in the range of 4 and thus are concluded to be stable molecule.

Table.2. Drug likeness and toxicity calculation of 6-methoxy benzothiazol-2-yl-amide derivatives using OSIRIS property calculator.

Compound	IUPAC name	Log S	Drug score	Drug likeliness	Toxicity risk
III (a)	N-(6-Methoxybenzo[d]thiazol-2-yl) benzamide	-4.11	0.42	2.03	None
III (b)	4-Fluoro-N-(6-methoxy-benzothiazol-2-yl) benzamide	-4.26	0.39	1.66	None

III (c)	4-Methoxy-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	-4.16	0.42	2.25	None
III (d)	N-(6-Methoxy-benzothiazol-2-yl)-4-nitrobenzamide	-4.14	0.22	2.44	None
III (e)	2-Fluoro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	-4.26	0.35	0.58	None
III (f)	4-Chloro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	-4.70	0.37	3.99	None

Log S corresponds to the aqueous solubility of a compound. Prevailingly, most of the drugs that are present have a logS value above -4 and below +4. If the drug solubility is less, there are minimum chances for the drug to be absorbed into the tissues. Therefore, it is preferred to have a moderate solubility for the drug molecules. All the compounds (III a-f**)** showed logS value lesser than -4.

Drug score of a molecule is based on the fragments of the molecules that have already present and valuated. These fragment scores must not have any negative value, thus corresponding to the drug molecules that are already present. The drug scores for compounds III a, III b, III c, III d III e, and III f were positive.

Drug likeness of a compound is based on the fragment comparison of the drug molecule with the pre knowledge of the standard compounds. The drug likeness of the compound can give values between 1.0 (no risk), 0.8 (moderate risk) and 0.6 (high risk) that reveal the toxicity and risk that the compound may cause. Compounds III a to III f have shown drug likeness score in between 1 to 0.8.

Mutagenicity was also calculated by OSIRIS property calculator. The compounds III a - III f have showed no mutagenic properties and hence were further evaluated by Ligand Flexible Docking.

Table.3. Prediction of ADMET properties of 6-methoxy benzothiazol-2-yl-amide derivatives using pkCSM

Compound	IUPAC name	Property	Model Name	Predicted Value
III (a)	N-(6-Methoxybenzo[d]thiazol-2-yl)benzamide	Absorption	Water solubility Intestinal absorption (human)	-3.781 (log mol/L) 93.553 (%Absorbed)
		Distribution	VDss (human) Fraction unbound (human)	-0.085 (log L/kg) 0.063 (Fu)
		Metabolism	CYP2D6substrate CYP3A4 substrate	No Yes
		Excretion	Total Clearance	0.196(log ml/min/kg)
		Toxicity	AMES toxicity Max.tolerated dose (human)	No 0.412 (log mg/kg/day)

Compound	IUPAC name	Property	Model Name	Predicted Value
III (b)	4-Fluoro-N-(6-methoxy-benzothiazol-2-yl) benzamide	Absorption	Water solubility Intestinal absorption (human)	-4.24 (log mol/L) 90.825 (%Absorbed)
		Distribution	VDss (human) Fraction unbound (human)	-0.294 (log L/kg) 0.025 (Fu)
		Metabolism	CYP2D6substrate CYP3A4 substrate	No Yes
		Excretion	Total Clearance	0.054 (log ml/min/kg)
		Toxicity	AMES toxicity Max.tolerated dose (human)	No 0.557 (log mg/kg/day)

Compound	IUPAC name	Property	Model Name	Predicted Value
III (c)	4-Methoxy-N-(6-methoxy-1,3-benzothiazol-2-yl)benzamide	Absorption	Water solubility Intestinal absorption (human)	-4.301 (log mol/L) 91.855 (%Absorbed)

	Distribution	VDss (human) Fraction unbound (human)	-0.285 (log L/kg) 0.012 (Fu)
	Metabolism	CYP2D6substrate CYP3A4 substrate	No Yes
	Excretion	Total Clearance	0.231(log ml/min/kg)
	Toxicity	AMES toxicity Max.tolerated dose (human)	No 0.637 (log mg/kg/day)

Compound	IUPAC name	Property	Model Name	Predicted Value
III (d)	N-(6-Methoxy-benzothiazol-2-yl)-4-nitrobenzamide	Absorption	Water solubility Intestinal absorption (human)	-4.53 (log mol/L) 90.409 (%Absorbed)
		Distribution	VDss (human) Fraction unbound (human)	-0.323 (log L/kg) 0 (Fu)
		Metabolism	CYP2D6substrate CYP3A4 substrate	No Yes
		Excretion	Total Clearance	0.219(log ml/min/kg)
		Toxicity	AMES toxicity Max.tolerated dose (human)	No 0.26 (log mg/kg/day)

Compound	IUPAC name	Property	Model Name	Predicted Value
III (e)	2-Fluoro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	Absorption	Water solubility Intestinal absorption (human)	-4.353 (log mol/L) 90.588 (%Absorbed)
		Distribution	VDss (human) Fraction unbound (human)	-0.352 (log L/kg) 0.022 (Fu)
		Metabolism	CYP2D6substrate CYP3A4 substrate	No Yes
		Excretion	Total Clearance	0.254(log ml/min/kg)
		Toxicity	AMES toxicity Max.tolerated dose (human)	No 0.548 (log mg/kg/day)

Compound	IUPAC name	Property	Model Name	Predicted Value
III (f)	4-Chloro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide	Absorption	Water solubility Intestinal absorption (human)	-4.551 (log mol/L) 89.922 (%Absorbed)
		Distribution	VDss (human) Fraction unbound (human)	-0.132 (log L/kg) 0.006 (Fu)
		Metabolism	CYP2D6substrate CYP3A4 substrate	No Yes
		Excretion	Total Clearance	0.072(log ml/min/kg)
		Toxicity	AMES toxicity Max.tolerated dose (human)	No 0.573 (log mg/kg/day)

All six compounds are evaluated for its drug likeliness and toxicity properties. All compounds were found to be better pharmacokinetic properties, and they have shown well absorption properties from human intestine and dose is uniformly distributed in blood plasma. These compounds do not show any mutagenic properties.

Molecular docking

After thorough screening six molecules were found to be non-mutagenic so these compounds were docked by using AUTODOCK vina software. The protein used was N-Myristoyltransferase (PDB ID:1ZAP). The docking site or active site was selected, and a grid box was laid out to specify the region.

The Amino acids present in the active site of the protein were found to be Thr 222, Ile 305, Thr 13, Val 12, Tyr 84, Ile 30, Ile 123, Gly 85, Asp 218, Asp 32 and Gly 34. Hydrogen bonds as well as non-bonded interactions were found between the various compounds and the active site of N-Myristoyltransferase protein.

Fluconazole was taken as the standard drug and docking was performed at the same active site. Nine conformations were identified and docked on the protein. The highest docking score was -6.2 Kcal/mol and various conformations of the fluconazole molecule showed 2 Hydrogen bonds with THR 6 and GLY 103, hydrophobic interactions with VAL 5, PHE 101 and GLY 102 and hydrophilic interactions with ASP 17 and THR 19 (Fig.8).

Docking interactions for compound III (a) forms 2 hydrogen bond with ASN 323 and TYR 128, hydrophobic interaction with LYS 129 and hydrophilic interactions with THR 130, and ASP 191 (Fig.9). The best docking score for this compound was found to be -6.1.

Docking interactions for compound III (b) forms 1 hydrogen bond with GLY 295, hydrophobic interaction with ILE 223 and hydrophilic interactions with ASN 247 and ASN 249 (Fig.10). -6.2 was the best docking score for this molecule.

Docking interactions for compound III (c) forms 1 hydrogen bond with GLN 295, hydrophobic interactions with LEU 297, ILE 223 (Fig.11) and hydrophilic interactions with ASN 249, GLN 295, ASP 299 and ASN 247. The best docking score was -6.1.

Docking interactions for compound III (d) forms 1 hydrogen bond with SER 180, hydrophobic interactions with PRO 162, TYR 332 and PRO 275 and hydrophilic interactions with LYS 331, GLN 329 (Fig.12). The highest docking score for this compound was found to be -6.3.

The compound III (e) showed 1 hydrogen bond with ASP 299, hydrophobic interaction with ILE 223 and hydrophilic interaction with GLN 295 (Fig.13). The best docking score for the compound was -6.4.

Docking interactions for compound III (f) forms 1 hydrogen bond with SER 118, and hydrophilic interactions with GLN 48 and ASP 86 (Fig.14). The docking score for this compound was found to be -5.8.

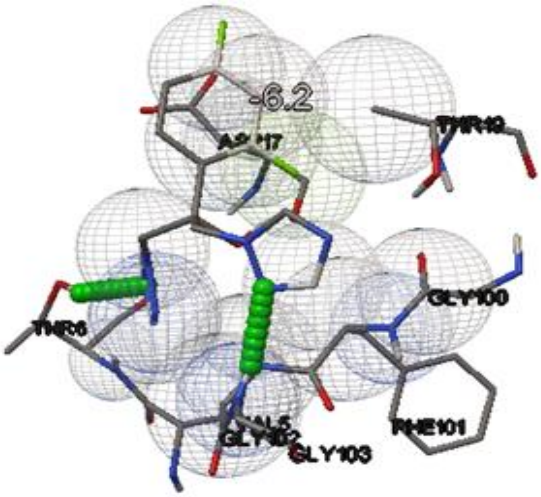


Fig.5. Interactions of Fluconazole with active site of N-Myristoyltransferase protein

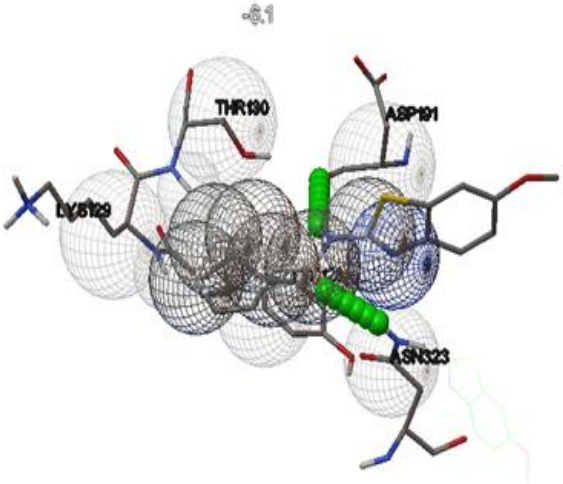


Fig.6. Hydrophobic and Hydrophilic Interactions of compound III (a) with active site 1ZAP

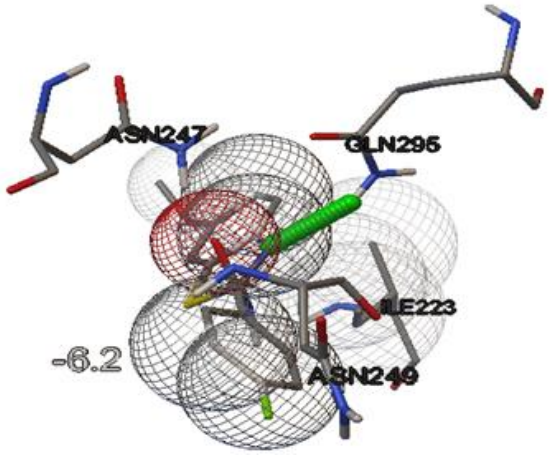


Fig.7. Hydrophobic and Hydrophilic Interactions of compound III (b) with active site 1ZAP

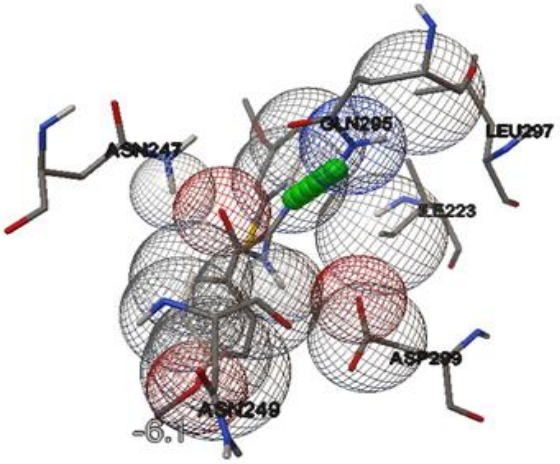


Fig.8. Hydrophobic and Hydrophilic Interactions of compound III (c) with active site 1ZAP

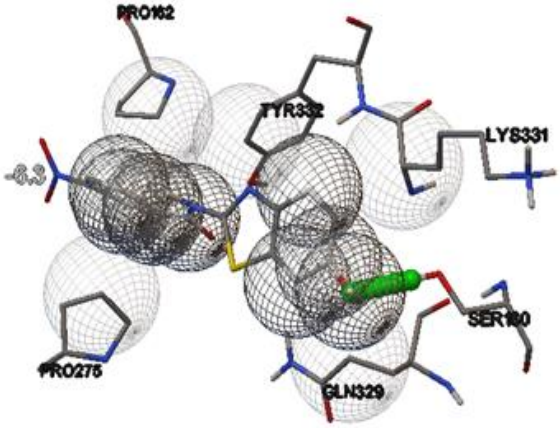


Fig.9. Hydrophobic and Hydrophilic Interactions of compound III (d) with active site 1ZAP

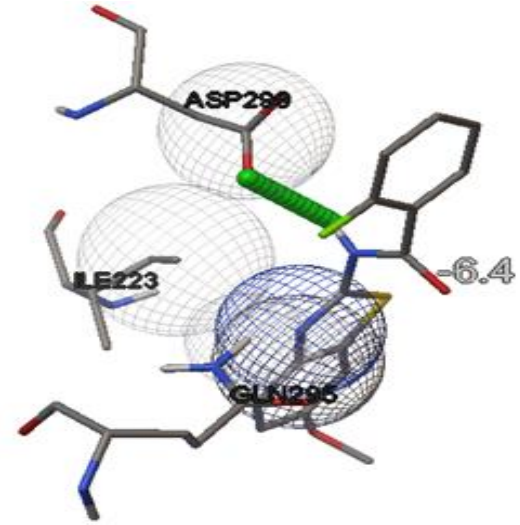


Fig.10. Hydrophobic and Hydrophilic Interactions of compound III (e) with active site 1ZAP

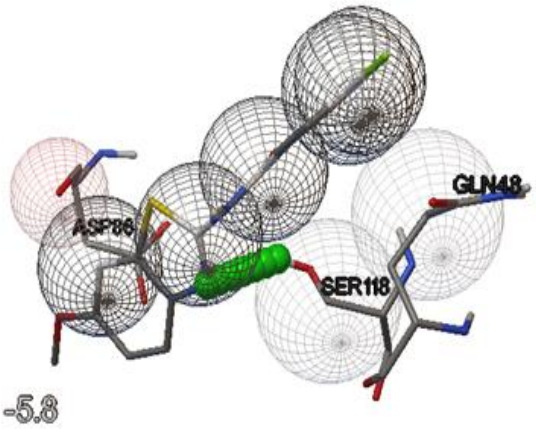


Fig.11. Hydrophobic and Hydrophilic Interactions of compound III (f) with active site 1ZAP

Table.4. Docking score and Hydrogen bond interactions of 6-methoxy benzothiazol-2-yl-amide derivatives and Fluconazole

Compound	Docking score	Hydrogen bond interactions
III a	-6.1	ASN 323, TYR 128
III b	-6.2	GLY 295
III c	-6.1	GLN 295
III d	-6.3	SER 180
III e	-6.4	ASP 299
III f	-5.8	SER 118
Fluconazole	-6.2	THR 6, GLY 103

The hydrophilic docking interactions were found to be with Sulphur and nitrogen in Thiazole ring, whereas the hydrophobic interactions were observed with Carbon atoms in thiazole and benzene ring. When there was an electron donating group (oxygen) substituted as side chain with benzene and other substituents are fluorine and chlorine showed hydrophilic interactions and hydrophobic interactions with the Carbons of benzene.

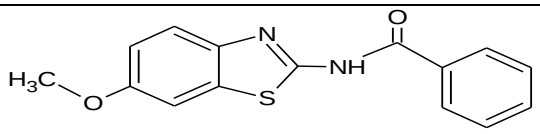
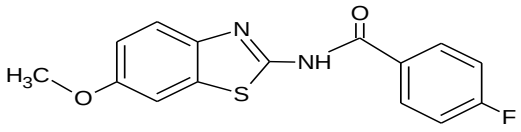
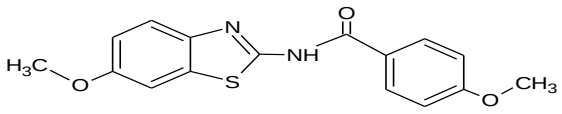
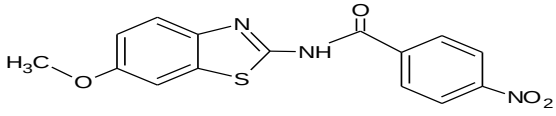
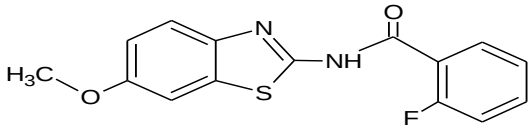
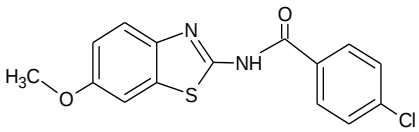
Chemistry and spectral data

After performing an evaluation of the molecular properties and molecular docking studies, six derivatives of 6-methoxy benzothiazol-2-yl-amide have been synthesized. The completion of the reaction was confirmed by TLC. All the compounds were purified by recrystallization. The compounds were identified by using physical data and were characterized by using spectral data.

Table.5. Physical data of 6-methoxy benzothiazol-2-yl-amide derivatives

Compound	Ar	Name of the derivative & Molecular Formula	Mol Wt	Physical State	Melting point ˚C	Yield %	Rf value Hexane: Ethyl acetate (5:5)
III (a)	Benzoyl chloride	N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide $C_{15}H_{12}N_2O_2S$	140.57	Pale brown powder	70-110˚C	80%	0.78 cm
III (b)	4-fluoro benzoyl chloride	4-fluoro-*N*-(6-methoxy-1,3-benzothiazol-2-yl) benzamide $C_{15}H_{11}FN_2O_2S$	144.58	Cream powder	150-156˚C	75%	0.52 cm
III (c)	4-methoxy benzoyl chloride	4-methoxy-*N*-(6-methoxy-1,3-benzothiazol-2-yl) benzamide $C_{16}H_{14}N_2O_3S$	170.6	Cream powder	130-164˚C	78%	0.9 cm
III (d)	4-nitro benzoyl chloride	*N*-(6-methoxy-1,3-benzothiazol-2-yl)-4-nitrobenzamide $C_{15}H_{11}N_3O_4S$	291.30	Yellow powder	216-230˚C	69%	0.64 cm

Table.6. Spectral data of 6-methoxy benzothiazol-2-yl-amide derivatives

Compound	Molecular structure	(IR) υmax(KBr/cm-1)
III (a)		-NH=3309.85 cm^{-1} C-N(St) = 1325.10 cm^{-1} C = O(St) =1654.92 cm^{-1} C = C(St)=1508.33 cm^{-1} C-S=707.88 cm^{-1}
III (b)		-NH =3385.07 cm^{-1} C- N(St) = 1276.88 cm^{-1} C = O(St) = 1645.28 cm^{-1} C = C(St) = 1548.84 cm^{-1} C-F = 1178.51 cm^{-1} C-S – 709.80cm^{-1} C=N – 1604.77cm^{-1}
III (c)		-NH =3431.36 cm^{-1} C- N(St) = 1261.45cm^{-1} C = O(St) = 1685.79 cm^{-1} C = C(St) = 1465.90 cm^{-1} C-O(St) = 1026.13cm^{-1}
III (d)		-NH =3367.71 cm^{-1} C- N(St) = 1458.18 cm^{-1} C = O(St) = 1697.36 cm^{-1} C = C(St) = 1541.12 cm^{-1} C-S = 717.52cm^{-1} C=N = 1606.70cm^{-1} NO_2 = 1350.17cm^{-1}
III (e)		-NH = 3298.78 cm^{-1} C- N(St) = 1271.09cm^{-1} C = O(St) = 1635.22 cm^{-1} C = C(St) = 1506.41 cm^{-1} C-F = 1216.80 cm^{-1}
III (f)		-NH = 3278.93 cm^{-1} C- N(St) = 1267.52cm^{-1} C = O(St) = 1701.22 cm^{-1} C = C(St) = 1575.85 cm^{-1} C-Cl = 1740.02 cm^{-1}

The compounds III a – III f were synthesized with a percentage yield of 70-80%. The IR, H^1NMR and the MASS spectral data confirm the formation of 6-methoxy benzothiazol-2-yl-amide derivatives.

V.CONCLUSION

In the present work we have performed *insilico* studies for the various derivatives of 6-methoxy enzothiazole-2-yl-amide which includes molecular property calculations, assessment of toxicity, pkCSM and molecular docking studies. The results were analysed and the compounds screened accordingly. All compounds obeying the Lipinski rule of 5. They exhibited good ADMET properties. The molecular docking results showed that all the six compounds that were screened showed a very good binding affinity which was similar to that of the standard fluconazole. Compound 2-Fluoro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide showed highest binding affinity -6.4 with the N-Myristoyltransferase protein which was more than that of the Fluconazole binding affinity -6.2. So, the benzothiazole derivatives showed good interactions with the N-Myristoyltransferase protein. All the six compounds are evaluated for inhibitory activity of N-Myristoyltransferase protein and the compound 2-Fluoro-N-(6-methoxy-1,3-benzothiazol-2-yl) benzamide (III e) shows highest inhibitory activity towards N-Myristoyltransferase protein. The synthesis of a series of functional derivatives of various 6-methoxy enzothiazole-2-yl-amide was done and characterized by TLC, IR and H^1NMR and MASS spectral analysis.

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