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DESIGN AND SYNTHESIS OF SOME BENZTHAIZOLE ANALOGS AS A_{2A} RECEPTOR ANTAGONIST

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ABSTRACT

BACKGROUND

The A_{2A} receptor is expressed in the brain, where it has important roles in the regulation of glutamate and dopamine release, making it a potential therapeutic target for the treatment of conditions such as insomnia, pain, depression, drug addiction and Parkinson's disease

METHOD

Molecular Modelling Study with respect to Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. On the basis of docking study, some compounds are Proceed to synthesize.

RESULT

Molecular docking studies of designed A_{2A} receptor antagonist was validated on the basis of docking score obtained by re-docking of co-crystallized ligand of A_{2A} receptor (PDB ID: 3EML) as well as all synthesized compound was validated by spectral analysis.

INTRODUCTION

The A_{2A} receptor is expressed in the brain, where it has important roles in the regulation of glutamate and dopamine release, making it a potential therapeutic target for the treatment of conditions such as insomnia, pain, depression, drug addiction and Parkinson's disease [1,2]. As a rule, dead neurons in the adult central nervous system (CNS) are not replaced, nor can their terminals regenerate when their axons are interrupted, therefore any pathological process causing neuronal death generally has irreversible consequences. At first sight, this appears to be very unpromising territory for pharmacological intervention, and indeed drug therapy is currently very limited. Nevertheless, the incidence and social impact of neurodegenerative brain disorders in ageing populations has resulted in a massive research effort in recent years.

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized pathologically by a marked loss of dopaminergic nigrostriatal neurons and clinically by disabling movement disorders[3]. It occurs mainly in the elderly and patients walk with a characteristic shuffling gait. They find it hard to start, and once in progress they cannot quickly stop or change direction. PD is commonly associated with dementia, probably because the degenerative process is not confined to the basal ganglia but also affects other parts of the brain. Parkinson's disease often occurs with no obvious underlying cause, but it may be the result of cerebral ischemia, viral encephalitis or other types of pathological damage. Possible aspects to treat the Parkinson disease are- MAO-B inhibitors (e.g. selegiline), drugs that release dopamine (e.g. amantadine), muscarinic acetylcholine receptor antagonists (e.g. benztropine)(see fig.1)[4] .At present the mainstay for the treatment of PD relies on dopamine replacement therapy with the dopamine precursor l-DOPA. Although this approach provides considerable symptomatic relief in the early stages of this disease. Drugs

that target the mechanism of neuronal cell death and therefore delay or even halt the progression of this disease may offer improved therapeutic approaches for the treatment of PD. Attempts to develop neuroprotective agents have focused on identifying compounds that protect against the degenerative processes associated with exposure to the neurotoxin[5,6].

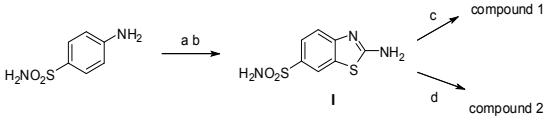
METHOD

MOLECULAR MODELLING STUDY

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex(see fig.2). Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example functions. The associations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced (e.g., agonism v/s antagonism). Therefore docking is useful for predicting both the strength and type type of signal produced (e.g., agonism v/s antagonism). Therefore docking is useful for predicting both the strength and type of signal produced [7]. Docking studies are performed on substituted benzthiazole analogs by using Glide 5.0 version software installed in a single machine running on a 1.85 GHz Pentium 4 processor with 1GB RAM and 120 GB Hard Disk with Red Hat Linux Enterprise version 5.0 as the Operating System [R].Ligand structures were built, optimized and saved in ***.mae*** format. By using the ***LIGPREP*** utility of ***Glide***, these structures were geometry optimized by using the Optimized Potentials for Liquid Simulations-2005 (OPLS-2005) force field with the steepest descent followed by truncated Newton conjugate gradient protocol. Partial atomic charges were computed using the OPLS-2005 force field [8,9].

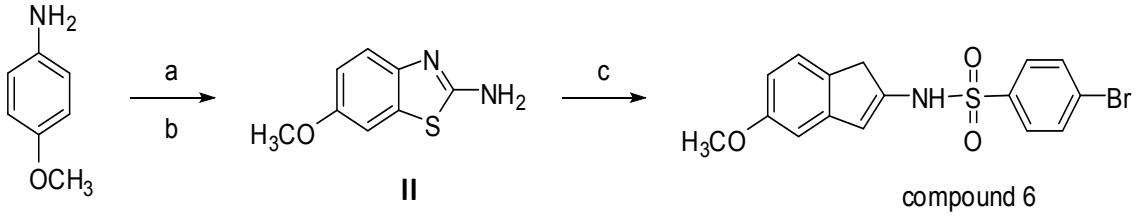
Protein Preparation Wizard of Schrodinger Inc. has been used to prepare protein. The protein with **PDB ID: 3EML** was taken from the structure of A_{2A} complex filed in the Brookhaven Protein Data Bank. After deleting water, which was followed by assigning charge and protonation state, finally energy minimization was done using OPLS2005 force field. All docking calculations were performed using the "Standard Precision" (XP) mode of Glide Program 5.0 (An application of SCRODINGER`s MAESTRO 8.0). A grid was prepared with the centre defined by the co-crystallized ligand. The docking of Co-crystallized ligand ***ZM241385*** (ZMA) which were extracted previously from ***A_{2A}*** receptor complex PDB ID ***3MEL*** was performed to test the reliability and reproducibility of the docking protocol for our study. This served as validation of the docking protocol. After the validation of the docking methods using ***ZM241385*** (ZMA), all the substituted Benzthiazole analogs 1 to 21 were docked into the same coordinates of the crystal structure(refer table 1and table 2 for designed benzthiazole analogs.). The docked 3D-structures of substituted Benzthiazole derivatives were scored. [10-12].

SYNTHETIC STUDY



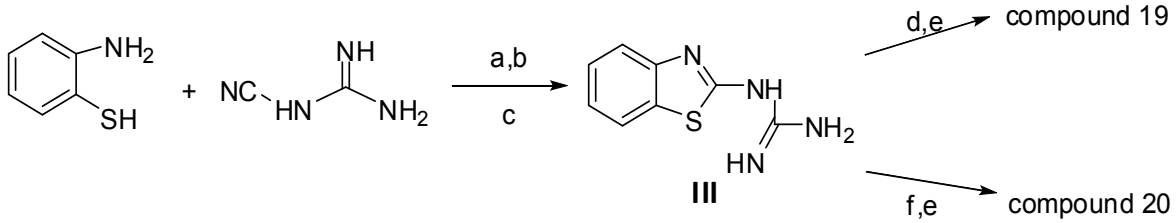
Scheme 1: a=potassium thiocyanate, b=glacial acetic acid, c= 4-ethylbenzene-1-sulfonyl chloride, d= 2-methylbenzene-1-sulfonyl chloride.

6-sulfamido-2-amino-1, 3-benzthiazole **(I)** were suitably proceed as intermediate to synthesized COMPOUND 1 and COMPOUND 2. (As shown in scheme 1).



Scheme2: a= potassium thiocyanate, b=glacial acetic acid, c= 4-bromobenzene-1-sulfonyl chloride.

6-methoxy-2-aminobenzthiazole **(II)** were suitably proceed as intermediate to synthesized COMPOUND 6. (As shown in scheme 2).



Scheme 3: d= 2-methyl-benzene sulfonylchloride, e= pyridine, f=4-methyl-3-nitrobenzene sulfonylchloride.

N-1, 3-benzthiazole-2-guanidine **(III)** were suitably proceed as intermediate to synthesized COMPOUND 19 and COMPOUND 20. (As shown in scheme 3).

Synthesis of 6-sulfamido-2-amino-1,3-benzthiazole (I) : Sulfanilamide (5.17.gm; 0.03 moles), glacial acetic acid (45 ml), and potassium-thiocyanate (11.6 gm; 0.12 moles) were stirred at 19 °C for 20 minutes, and then a solution of bromine (1.5 ml; 0.03 moles) in glacial acetic acid was added over 20 min; during this addition, the temperature rose up to 35 °C. The reaction mixture was stirred for 20 hours in room temperature, then reaction mixture was poured into cold water (500 ml), made alkaline with 50 % aqueous ammonia and precipitated solids are filtered out, dried and recrystallized from dry ethanol.

Synthesis of 6- sulfamido-2-(4-ethyl-benzene-sulfonyl)amino-1,3benzthiazole: (COMPOUND 1) : A mixture of 2-amino-1,3-benzthiazole-6-sulfonamide (2.29 gm; 0.01 moles) with pyridine and 4-ethyl-benzene-sulfonyl chloride (2.18 gm / 1.67 ml / 0.01 moles) were taken in conical flask, heated in water bath near about 80 °C for 30 minutes. This reaction mixture poured into ice cold water. It is then basified with K_2CO_3 (potassium carbonate). Precipitated products were filtered out recrystallized from dry ethanol [15, 16].

Synthesis of 6-sulfamido-2-(2-methyl-benzene-sulfonyl)amino-1,3-benzthiazole (COMPOUND3) : A mixture of 2-amino-1,3-benzthiazole-6-sulfonamide (2.29 gm; 0.01 moles)with pyridine and 2-methyl benzene-sulfonyl chloride (2.05 gm / 1.52 ml / 0.01moles)were taken in conical flask, heated in water bath near about 80 °C for 30 minutes. This reaction mixture poured into ice cold water. It is then basified with K_2CO_3 (potassium carbonate). Precipitated products were filtered out recrystallized in dry ethanol [15, 16].

Synthesis of 6-methoxy-2-aminobenzthiazole (II): 4-Methoxy aniline (3.7 gm; 0.03 moles), glacial acetic acid (45 ml), and potassium-thiocyanate (11.6 gm; 0.12 moles) were stirred at 19 °C for 20 minutes, and then a solution of bromine (1.5 ml; 0.03 moles) in glacial acetic acid was added over 20 min; during this addition, the temperature rose up to 35 °C. The

reaction mixture was stirred for 20 hours in room temperature, then reaction mixture was poured into cold water (500 ml) , made alkaline with 50 % aqueous ammonia and precipitated solids are filtered out dried and recrystallized.

Synthesis of 4-bromo-N-(6-methoxybenz[d]thiazol-2-yl) benzene Sulphonamide (COMPOUND 6): A mixture of 6-methoxy-2-benzthiazolamine (1.80 gm; 0.01 moles) with pyridine and p-bromo-benzene-sulfonyl chloride (2.55 gm / 1.42 ml / 0.01 moles) were taken in conical flask, heated in water bath near about 80 °C for 30 minutes. This reaction mixture poured into ice cold water. It is then basified with $NaHCO_3$. Precipitated product was filtered out and recrystallized from dry ethanol [17].

Synthesis of N-1, 3-benzthiazole-2-guanidine (III): 1.25 gm (1.068 ml) of 2-mercapto aniline was dissolved in 2 ml of conc. HCl & boiled for dissolved completely. In that solution added 0.01 moles of cyanoguanidine (0.84 gm) & that is hydrochloric salt of the base, m.p. 212 ^{o}c. Then the hydrochloric salt refluxed for 2.5 hrs. The reaction was monitored by TLC. The product which was obtained 1,3-benzthiazol-2-ylguanidine is added in 50 % NaOH (equimolar) solution for neutralization & to form free base i.e. N-1,3 benzthiazol-2-ylguanidine.

Synthesis of N-[(1, 3-benzthiazole-2-yl amino){imino}methyl]–2-Methyl-benzene sulphonamide (compound 19) : A mixture of N-1,3-benzthiazole-2-guanidine (1.92 gm; 0.01 moles) with pyridine and 2-methyl benzene-sulfonyl chloride (1.90 gm / 1.42 ml / 0.01moles)were taken in conical flask, heated in water bath near about 80 °C for 30 minutes. This reaction mixture poured into ice cold water. It is then basified with NaHCO3. Precipitated products were filtered out recrystallized from dry ethanol.

Synthesis of N-[(1, 3-benzthiazole-2-yl amino){imino}methyl]–4-methyl-3-nitro-benzene sulphonamide(compound 20) : A mixture of N-1,3-benzthiazole-2-guanidine (1.92 gm; 0.01 moles) with pyridine and 4-methyl-3-nitro-benzene-sulfonyl chloride (2.37 gm / 1.75 ml / 0.01 moles) were taken in conical flask, heated in water bath near about 80 °C for 30 minutes. This reaction mixture poured into ice cold water. It is then basified with NaHCO3. Precipitated products were filtered out recrystallized in dry ethanol [19].

RESULT & DISCUSSIONS

MOLECULAR DOCKING STUDIES OF DESIGNED A_{2A} RECEPTOR ANTAGONIST

ZMA binding pockets

The co-crystallized ligand ZM241385 (ZMA) has been split from the core of the protein and re-docked in the crystallized protein. The glide score of the co crystallized ligand is **-6.20**.A recently performed assessment of blind predictions of adenosine A_{2A}receptor (AA2AR) structure in complex with ZM241385 (ZMA) antagonist provided a first example of unbiased evaluation of the current modelling algorithms on a GPCR target with 30% sequence identity to the closest structural template. In structures, (see fig. 3) the bicyclic triazolotriazine core of

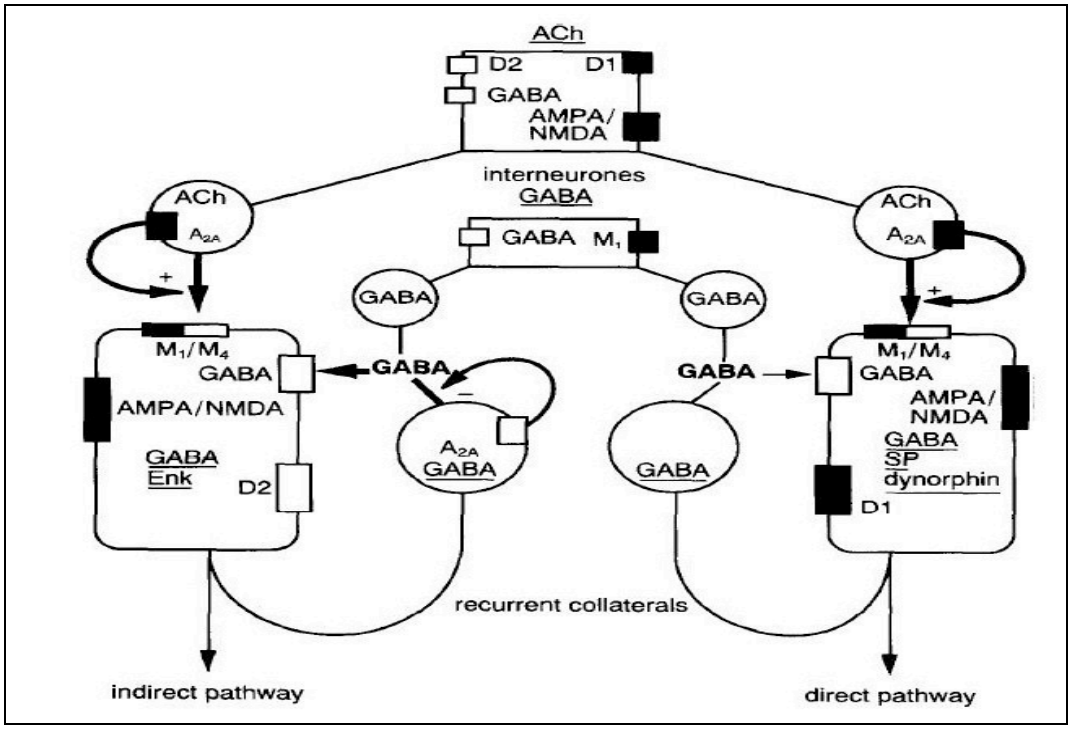


Fig. 1: Role of A_{2A} in Parkinson disease.

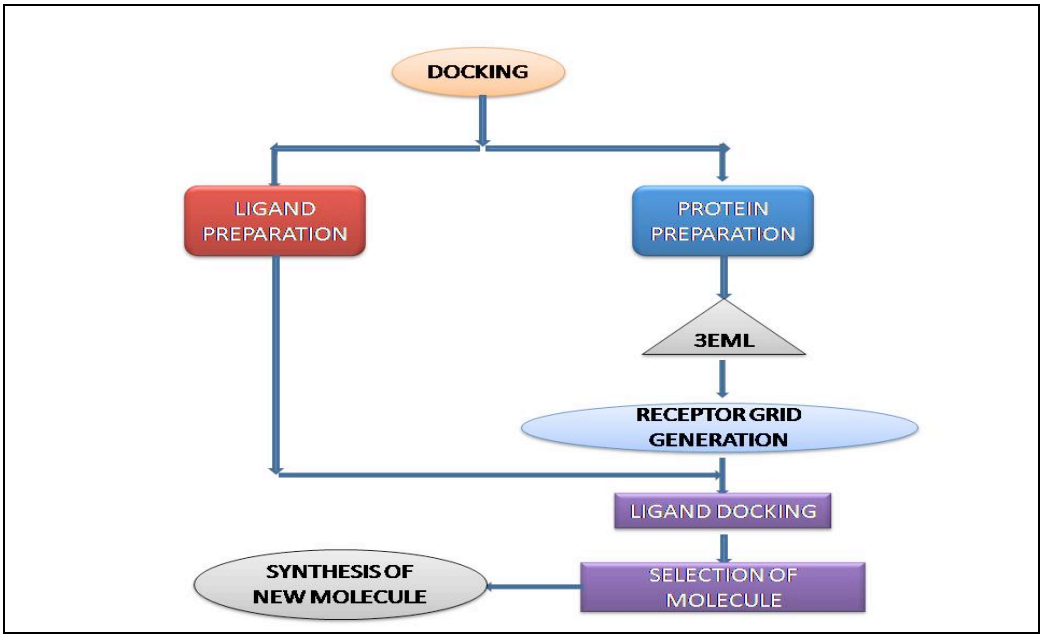


Fig. 2: flowchart showing docking protocol.

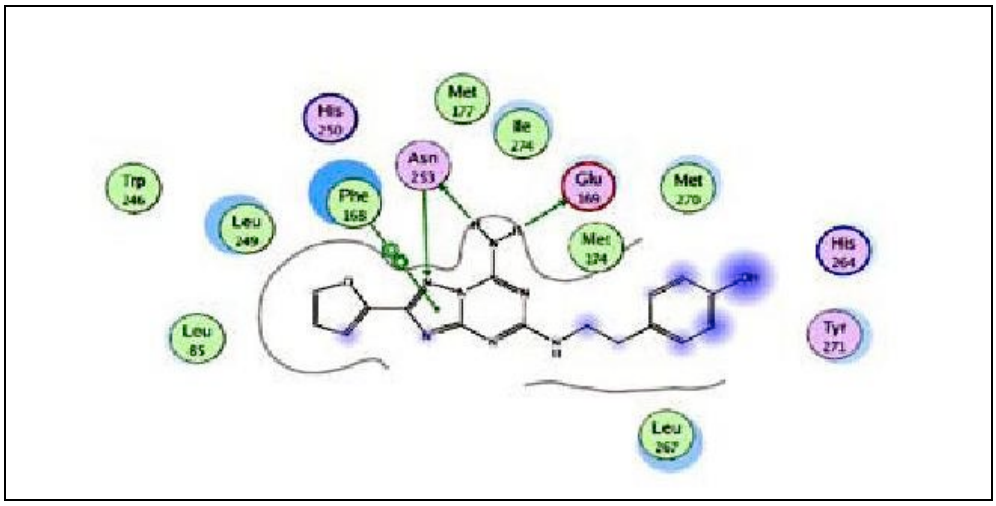


Fig.3: Crystallographic view of 3eml after re-docking of co-crystallized ligand ZM241385 (ZMA)

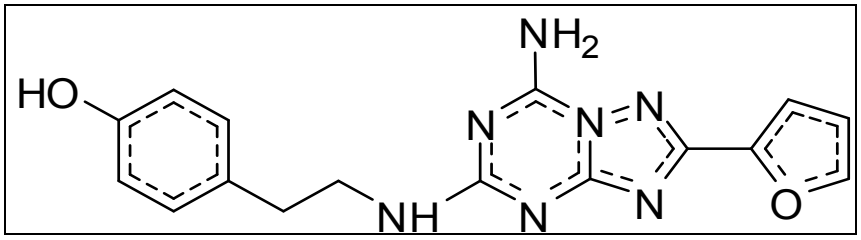


Fig. 4: CO-CRSTALLIZED LIGAND (ZMA) with docking score = -6.20

COMPOUND NAME	R	Ar	DOCKING SCORE
COMPOUND	—SO_2—NH_2	1-ethyl-4-methylbenzene	-7.17
COMPOUND	—SO_2—NH_2	o-xylene	-7.32
COMPOUND	—SO_2—NH_2	*N*-*p*-tolylacetamide	-6.83
COMPOUND	—SO_2—NH_2	1,2-dimethoxy-4-methylbenzene	-6.64
COMPOUND	—SO_2—NH_2	1-chloro-4-methylbenzene	-6.20
COMPOUND	—OCH_3	1-bromo-4-methylbenzene	-7.15
COMPOUND	—OCH_3	1,2,3,5-tetramethylbenzene	-5.72
COMPOUND	—OCH_3	1-ethyl-4-methylbenzene	-5.18
COMPOUND	—OCH_3	*m*-xylene	-6.23
COMPOUND	—OCH_3	2-chloro-1-methyl-4-nitrobenzene	-6.45
COMPOUND	—OCH_3	1-chloro-4-methylbenzene	-6.13
COMPOUND	—OCH_3	1-bromo-4-methylbenzene	-6.66
COMPOUND	—H	*p*-xylene	-5.83
COMPOUND	—H	1-methylpiperazine	-5.27
COMPOUND	—H	1-(3-methoxyphenyl)-4-methylpiperazine	-4.90
COMPOUND	—Cl	—H	-5.97
COMPOUND	—Cl	—Cl	-6.66
COMPOUND	—Cl	—Br	-6.72

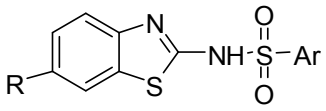
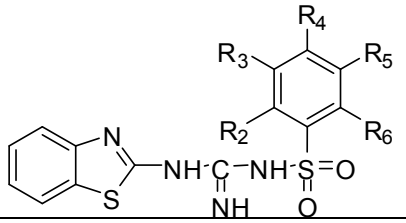


Table 1: showing docking score of series 1 compounds



COMPOUND NAME	R	DOCKING SCORE
COMPOUND 19	$R_2 = CH_3$	-7.00
COMPOUND 20	$R_3 = CH_3$ $R_4 = NO_2$	-7 .91
COMPOUND 21	$R_2 = R_4 = R_6 = CH_3$	-3.71

Table 2: showing docking score of series 2 compounds

the ligand is anchored by an aromatic stacking interaction with Phe168, aliphatic hydrophobic interactions with Ile274, Met177, Ile252, Met270 and Met174 and a hydrogen bonding interaction with Asn253. Furthermore, Glu169 interacts with the exocyclic amino group, and the phenolic hydroxyl group forms a hydrogen bonding interaction with a water molecule. Also, the phenyl ring (this moiety appears to be mobile within the reference

receptor) forms hydrophobic interactions with Leu267, Leu167, Tyr271 and His264. The furan ring is hydrogen-bonded to Asn253 and located in the hydrophobic pocket formed by His250, Leu85, Val84, and Leu249. Additionally, the furan ring is roughly 3.3A° away from the highly conserved Trp246.All the designed benzthiazole analogs was compare with co crystallized ligand (***ZMA***) in term of docking score and binding mode. Top scorers were collected for each molecule with the best docked score value associated with a favourable binding conformation compare to the co-crystallised ligand being consider as having favourable binding. The values of the dock score all performers are shown in table 1and table 2. The compounds with best docking score are planned to synthesized [21,22].

Validation of synthesized compound

6-sulfamido-2-amino-1,3-benzthiazole(I): To synthesize compound 1 and compound 2, **I** was synthesized as intermediate, in scheme 1. Yield: 60 %, Melting Point: 240 - 242°C, IR spectral data (KBr): 3427.62 cm-1: N-H str.(1° amine); 3329.25, 3242.45 cm-1: N-H str. (2° amine); 1311.64 cm-1: Aromatic NH_2;1247.99-1143.83cm-1 SO_2NHR; 678.94 cm-1 : C-S str.

6-sulfamido-2-(4-ethyl-benzene-sulfonyl)amino-1,3-benzthiazole (COMPOUND 1) :Intermediate **I** was suitably treated to synthesize compound 1, in scheme 1. Yield: 30.20%, Melting Point: 144 to 145 °C, NMR spectral data 1H NMR: (300 MHz, DMSO): M 8.5(b, NH_2), M7.845-8.114(s, 1H, benzthiazole), M7.405-7.646(d, 1H, Ar.), M2.500(s, 2H, CH_2), M3.333(s, 1H, C-NH).

6-sulfamido-2-(2-methyl-benzene-sulfonyl)amino-1,3-benzthiazole (COMPOUND3) :Intermediate **I** was suitably treated to synthesize compound 3, in scheme 1. Yield: 41.70% , Melting Point: 141 - 142 °C, IR spectral data(KBr): 2978.19 cm-1: Ar. C-H str.; 3049.56 cm-1:C-H str.; 1317.43 cm-1 -1153.47 cm-1:asymmetric str. (SO_2NH_2); 2868.24 cm-1:methyl C-H str.; 1597.11 cm-1 - 1492.95cm-1 : C=C ring str.; 709.83 cm-1: C-S str.NMR spectral data 1H NMR (300 MHz, DMSO): M 7.787-7.814(d, 1H,benzthiazole at C4 and C6),7.740(s, 1H, benzthiazole at C5), 7.387-7.413(d, 1H, Ar.), 3.314(s, 1H, C-NH),2.352 (s, CH_3), 8.34(b, N-H).

6-methoxy-2-aminobenzthiazole (II): To synthesize compound 6, **II** was synthesized as intermediate, in scheme 2. Yield: 42.60%, Melting Point: 140-145°C, IR spectral data(KBr): 3389.04 cm-1: aromatic primary amine; 1548.89 cm-1 : C-O stretch.; 1465.95 CH3- O-R (strong); 1338.64 cm-1 : Ar. C-H bending; 711.76 cm-1: C-S str.

4-bromo-N-(6-methoxybenz[d]thiazol-2-yl) benzene Sulphonamide (COMPOUND 6): Intermediate **II** was suitably treated to synthesize compound 2, in scheme 2. Yield: 36%, Melting Point: 171-173 °C, IR spectral data(KBr): 3099.71cm-1: Ar. C-H str.; 2835.45 cm -1 : methyl C-H str.; 1269.20 cm-1: C-O-C asymmetric str.; 1178.55 cm -1 : C-O-C symmetric str.; 1145.75 cm-1 : S(=O)2 asymmetric str.; 960.58 cm-1: Ar. Bromine. NMR spectral data 1H NMR : (300 MHz, DMSO): M 7.465- 7.518(d, 1H, benzthiazole at C4 and C7), 6.789-6.978(m, 1H, benzthiazole at C5 and C6), 7.005-7.212(t, 1H, Ar.), 3.730-3.762(d, 1H, C-NH), 3.31(s, 3H, OCH3).

N-1,3-benzthiazole-2-guanidine (III) : To synthesize compound 19 and compound 20, **III** was synthesized as intermediate, in scheme 3.Yield: 44.22%, Melting Point: 157°C, IR

spectral data (KBr): 3446.91 cm-1: NH str. (in primary amine); 3186.51 cm-1: sec. N-H str.; 1641.48 cm-1: C-N (str. imines group); 1253.77 cm-1: C-N (str. in aliphatic proton); 1157.33 cm-1 C-N (str. In aromatic proton); 657.75 cm-1: C-S str.

N-[(1, 3-benzthiazole-2-yl amino){imino} methyl]–2-Methyl-benzene sulphonamide (compound 19) : Intermediate **III** was suitably treated to synthesize compound 19 in scheme 3.Yield: 46.10%, Melting Point: 135-140°C, IR spectral data (KBr): 3292.60 cm-1: N-H str. (2° amine); 3076.56 cm-1: Ar. C-H str.; 2800.73 cm-1: methyl C-H str.;1618.33 cm-1 : C-N (str. imines group); 1519.96cm-1–1442.80 cm-1 : C=C and C=N str.; 1213.27cm-1 : S(=O)2 asymmetric str.; 1153.47 cm-1 :S(=O)2 symmetric str.; 709.83 cm-1 : C-S str. NMR spectral data 1H NMR : (300 MHz, DMSO): M 7.785-7.809(d,1H, benzthiazole at C4 and C7), 7.559-7.7372(m, 1H, benzthiazole at C 5 and C6), 7.313-7.415(m, 1H, Ar.), 3.329(b, 1H, C-NH), 2.500(s, 1H, C=NH), 2.287-2.609(s, 3H, CH3), 1.232(s, 1H, S-NH).

N-[(1,3-benzthiazole-2-yl amino){imino}methyl]–4-methyl-3-nitro-benzene sulphonamide(compound 20) : Intermediate **III** was suitably treated to synthesize compound 20 in scheme 3.Yield: 51% Melting Point: 197-199 ^{o}C, IR spectral data (KBr): 3315.34 cm-1: N-H str.(2^{o} amine); 3134.43 cm-1 : sec. N-H str.; 2964.69 cm-1: methyl CH str.; 1612.54 cm-1 : C-N (str. imines group); 1526.74 cm-1 : asymmetric (aq. NO_2) N=O str.; 1350.22 cm-1 : symmetric (aq. NO_2) N=O str.; 1217.12 cm-1 : S(=O)2 asymmetric str.;1136.11 cm-1 : S(=O)2 symmetric str.; 758.05 cm-1 : C-S str.NMR spectral data 1H NMR : (300 MHz, DMSO): M 7.974- 8.001(d, 1H, benzthiazole at C4 and C7),7.464-7.505(m, 1H, benzthiazole at C5 andC6), 8.312(brs. 1H, Ar.), 8.102-8.107(d, 1H,Ar.), 3.338(brs., 1H, C-NH), 2.500-2.516(t,1H, S-NH), 2.5(s, 3H, CH_3).

The 3D crystal structure of A2A adenosine receptor (pdb code-3eml) wasdownloaded from protein data bank. The co-crystallized ligand ZM241385 has been split from the core of the protein and re-docked in the crystallized protein. The glide score of the co-crystallized ligand is -6.20 and the RMSD values is 0.6. Benzothiazole nucleus which are heterocyclic sulphonamides, heterocyclic guanidine and heterocyclic methoxy derivatives are synthesized and werecharacterized by melting point, Rf, FT-IR, MASS and NMR spectra.

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