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ARTICLE

In silico Study, Molecular Docking and Synthesis of 2-Amino thiazole Derivatives using Green Chemistry Approach as Antioxidant Agent

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ABSTRACT

A series of novel 2-aminothiazole derivatives were synthesized by microwave assisted method as a green chemistry approach and characterized by spectral techniques and elemental analysis. The antioxidant potential of the derivatives was determined by using molecular docking against two different oxidoreductase protein (PDB: 2CDU and 3NM8). Compounds **3a** and **3d** show the stronger binding affinity to the target protein. The synthesized drug was pharmacologically evaluated for the antioxidant activity using ascorbic acid as a reference drug, where compound **3a** showed the highest inhibition.

KEYWORDS

Thiazole, Microwave assisted synthesis, Antioxidant, *in silico* activity, Molecular docking.

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INTRODUCTION

During the past decades, the synthesis of thiazoles and analogues has gained interest due to their broad range of biological and pharmaceutical properties [1,2]. Microwave-assisted organic synthesis of heterocyclic compounds has become an effective technique for generating new heterocyclic scaffolds useful for drug discovery [3]. Thiazole or 1,3-thiazole is a heterocyclic compound which contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives [4,5]. The thiazole ring is notable as a component of vitamin thiamine (B_1). Thiazoles belong to the azole's family of heterocycles, which also includes imidazoles and oxazoles [6,7].

Thaizole undergoes various chemical reaction like electrophilic substitution, nucleophilic substitution condensation and coupling reaction [8-10]. Synthesis of thiazole/s can be accompained by various method [11] like Cu-catalyzed oxidative method [10], solid phase synthesis [12], solvent-free approach [13], copper(I)-catalyzed 1,3-dipolar cycloaddition of terminal alkynes [14] and one pot three-component synthesis [15-17] was reported. Thiazole possess various pharmacological activities like such as antibacterial [18], anti-human immunodeficiency virus type 1 (HIV-1) [19], antihypertensive [20], antitubercular, anti-inflammatory [21], antiviral and anticancer activities [22].

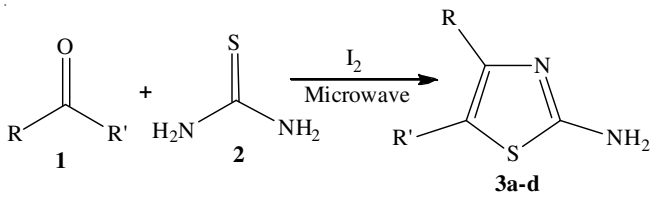
EXPERIMENTAL

Chemicals were procured from the well-known commercial sources. Chemicals were of laboratory grade and used as such. Pre-coated aluminium silica gel plates was used as stationary phase and diethyl ether and ethyl acetate (8:2) used as mobile phase. The visualization was carried out in UV-Florescence cabinet.

General procedure for synthesis of 2-aminothiazole derivatives

Conventional method: Substituted ketone (**1**) (0.01 M), thiourea (**2**) (0.02 M), iodine (0.01 M) were refluxed for 8-10 h. Reaction was confirmed by TLC. After cooling reaction mixture was poured in ice-cold bath. The product was filtered, dried and recrystallized from absolute ethanol [15,23].

Microwave assisted synthesis: Substituted ketone (**1**) (0.01 M), thiourea (**2**) (0.02 M), iodine (0.01 M) were taken in a microwave flask and subjected to microwave irradiation at 170 W to 5-15 min. Reaction confirmation was done by TLC. After cooling, the reaction mixture was poured in ice-cold bath. The product was filtered, dried and recrystallized from absolute ethanol (**Scheme-I**).



Scheme-I: Synthesis of 2-aminothiazole derivatives

***In silico* analysis:** The physico-chemical properties were determined using online chemical property calculator Molinspiration (http://www.molinspiration.com). Further ADME and toxicity studies were performed using PreADMET server (http://preadmet.bmdrc.org/) and SwissADME (http://www.swissadme.ch), repectively.

Molecular docking studies: The oxidoreductase protein molecule was used as target molecule for docking study. The 3D structure of target proteins (2CDU and 3NM8) [24,25] was obtained from protein data bank pdb (www.rcsb.org). The docking compatible structures of synthesized thiazole derivatives (ligand) was first drawn in chemdraw [26], which then converted in open babel 3.1.1. [27]. The active domain of protein molecule was determined used Pymol software. The target proteins were prepared for docking in Autodock tool 1.5.7 by removing water, heteroatom and adding charges [28]. The ligand structure was docked on active domain and post docking analysis was performed in discovery studio 3.5. visualizer (DS visualizer) [29].

Antioxidant activity: The antioxidant activity of all the synthesized compounds was assessed using DPPH (1,1-diphenyl-2-picrylhydrazyl) assay in this study [30,31]. To make the solution, 2 mg of DPPH was dissolved in 100 mL of methanol [32]. On the other hand, concentrations of both ligands and ascorbic acid (positive control) ranging from 25 to 100 g/mL were produced. For antioxidant activity study, 2 mL of DPPH with 2 mL of each ligand was combined and incubated them in dark. The radical scavenging ability was determined at 15, 30 and 45 min using UV-visible spectrophotometer. The activity, was determined by the proportion of scavenging activity derived using eqn. 1:

$$\text{Scavenging activity } (\%) = \frac{A_{Control} - A_{Sample}}{A_{control}} \times 100$$

where $A_{Control}$ is the absorbance of the blank (DPPH alone) and A_{Sample} the absorbance of the tested solution.

RESULTS AND DISCUSSION

Present work reported with the synthesis of novel 2-aminothiazoles by conventional method as well as by green chemistry approach of using microwave condensation methods. The compounds were obtained in good yield and high purity by microwave irradiation in comparison to conventional method. This indicates that the green synthesis is efficient and effective in obtaining desired product. Table-1 summarises the physical data of synthesized compounds.

***In silico* studies:** The physico-chemical properties of the synthesized compounds in absorption, distribution and partly in excretion (ADE) were conducted. There are different parameters for the representation of these properties, like pK_a, log P and log D or polar surface area (PSA) and molar refractivity (MR), all of them are to model the behaviour of the compound in solutions and in crossing different barriers [33]. Traditionally, most of these parameters have been measured and even though the experimental techniques are continuously developed, due to the increased capacity of chemical synthesis the prediction tools have got more and more importance. *In silico* ADME-PK (absorption, distribution, metabolism, excretion and pharmacokinetics) is the use of computer modeling to understand structure-property relationships [34]. The *in silico* activity data confirmed that all the synthesized compounds follows the Lipinski's rule of 5 with no violation (Table-2).

The ADME and toxicity data are summarized in Table-3, which show that all the compounds are substrate for cytochrome enzyme, possess mutagenicity and moderate carcinogenicity. Synthesized 2-aminothiazole derivatives (**3a-d**) has significant pharmacokinetics like high protein binding, negligible concentration in brain and low skin permeability.

Docking studies: The bonding and non-bonding interaction of synthesized 2-aminothiazole derivatives (**3a-d**) with oxidoreductase protein molecule was studied by using molecular docking. 2-Aminothiazole derivatives shows -3.62 to -6.64 kcal/mol binding affinity as compared to standard ascorbic acid with -3.61 kcal/mol binding affinity against tyrosinase oxidoreductase enzyme (PDB:3NM8). Ala40A, Gly43A, Ala44A, Glu141A, Gly143A, Ala44B, Ala45B, Lys47B, Phe48B and Tyr267B are amino acid present in active domain and involved in the binding with ligand (Figs. 1 and 2). Compound **3d** shows the lowest docking score of -6.64 kcal/mol (Table-4).

All the synthesized 2-aminothiazole derivatives (**3a-d**) also possess a high affinity to bind with NADPH oxidase (PDB: 2CDU) with the binding affinities -5.20 to -5.79 kcal/mol as compared to standard ascorbic acid -4.73 kcal/mol. Van der Waal, conventional hydrogen bond, pi-sigma, pi-pi-stacked, amide-pi-stacked, alkyl and pi-alkyl are the bonding interaction

TABLE-1
PHYSICAL PARAMETERS OF 2-AMINOTHIAZOLE DERIVATIVES

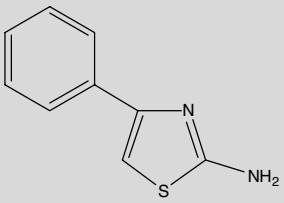
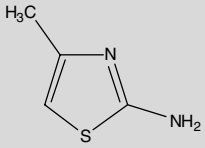
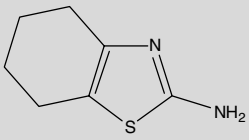
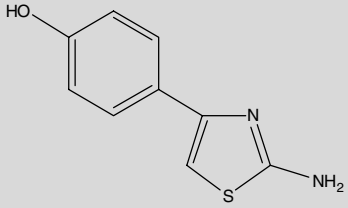
Compound	Nomenclature	m.p. (°C)	Yield (%)		m.w.	m.f.	Crystal shape
			Conven-tional	Micro-wave			
 **3a**	2-Amino-4-phenyl thiazole	210	14.20	29.46	176	$C_9H_8N_2S$	Fine powder
 **3b**	2-Amino-4-methyl thiazole	48	24.56	34.82	114	$C_4H_6N_2S$	Needle shape
 **3c**	2-Amino-4, 5, 6, 7-tetrahydr o benzothiazole	132	25.68	34.82	154	$C_7H_{10}N_2S$	Needle shape
 **3d**	*p*-Hydroxy acetophenone	50	64.58	61.45	136	4-(OH)$C_6H_4COCH_3$	Fine powder

TABLE-2
PHYSICO-CHEMICAL PARAMETER AND DRUG LIKENESS OF 2-AMINO THIAZOLE DERIVATIVE

Parameter	**3a**	**3b**	**3c**	**3d**
Log P	2.15	0.70	1.71	1.88
TPSA	38.91	38.91	38.91	59.14
natoms	12	7	10	13
MW	176.24	114.17	154.24	192.24
nON	2	2	2	3
nOHNH	2	2	2	3
nviolation	0	0	0	0
nrotb	1	0	0	1
Volume	153.30	98.45	138.25	161.31
Lipinski	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation	Yes, 0 violation
Ghose	Yes	No, 3 violations;	No, 1 violation;	Yes
Bioavailability score	0.55	0.55	0.55	0.55

TABLE-3
ADME AND TOXICITY STUDY OF 2-AMINO THIAZOLE DERIVATIVE

Parameter	**3a**	**3b**	**3c**	**3d**
Blood brain barrier	1.06493	0.416813	0.803984	0.850342
CaCo2	20.647	8.53843	2.76645	4.7453
Cytochrome inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor
Skin permeability	-2.13693	-3.77822	-3.41972	-3 0323
Plasma proteins binding	84.12996	88.895160	100.000	84.12996
Ames test	Mutagen	Mutagen	Mutagen	Mutagen
Carcino mouse	Positive	Negative	Positive	Positive
Carsino rat	Negative	Positive	Negative	Positive
hERG inhibition	Medium risk	Medium risk	Medium risk	Medium risk

TABLE-4
BINDING AFFINITY AND INTERACTION OF 2-AMINO THIAZOLE DERIVATIVES AND REFERENCE WITH TARGET PROTEIN (3NM8 AND 2CDU)

Comp.	Binding energy (kcal/mol)	RMSD	Inhibition constant (Ki)	No. of H-bond (drug enzyme)	Amino acid Involved in Interaction	Type of interaction	Amino acids
Tyrosinaseoxidoreductase enzyme (**PDB:3NM8**)							
Ascorbic acid	-3.61	21.28	2.27 mM	04	Glu141A (3.25, 4.17), Ala44B (3.43), Lys47B (4.80)	van der Waal, conventional hydrogen bond, carbon-hydrogen bond	Ile39A, Ala40A, Gly43A, Ala44A, Asp140A, Glu141A, Gln142A, Gly143A, Pro219A, Ala44B, Lys47B, Phe48B, His49B, Tyr267B.
3a	-5.74	21.26	62.06 µM	01	Ala 44B (3.13)	van der Waal, conventional hydrogen bond, amide-Pi-stacked, Pi-alkyl	Ile39A, Ala40A, Gly43A, Ala44A, Ile139A, Asp140A, Glu141A, Gly143A, Pro219A, Thr220A, Ala44B, Ala45B, Lys47B, Phe48B, Tyr267B.
3b	-3.62	22.15	2.21 mM	02	Ala40A (3.71), Tyr267B (5.38)	van der Waal, conventional hydrogen bond, Pi-sulfur, Alkyl Pi-alkyl	Ala40A, Trp41A, Gly43A, Ala44A, Glu141A, Gln142A, Gly143A, Ala44B, Lys47B, Phe48B, Tyr267B.
3c	-5.87	24.99	50.18 µM	03	His49B (2.16, 2.22, 4.50)	van der Waal, conventional hydrogen bond, Pi-Pi- stacked, alkyl Pi-alkyl	Asp36A, Ile39A, Ala40A, Ile139A, Gly143A, Lys47B, Phe48B, His49B, Pro52B
3d	-6.64	21.47	13.69 µM	03	Ala40A (3.64), His49B (3.52), Gly143A (3.71, 3.93)	van der Waal, conventional hydrogen bond, carbon-hydrogen bond	Asp36A, Ile39A, Ala40A, Gly43A, Ala44A, Ile139A, Gly143A, Asn144A, Ala44B, Lys47B, Phe48B, His49B, Pro52B, Gly53A Tyr267B
NADPH oxidase (**PDB: 2CDU**)							
Ascorbic acid	-4.73	50.71	342.50 µM	07	Gly158B (3.26), Tyr159 (4.79), Ile160 (3.43), Tyr188 (4.89, 4.99), Cys242 (3.95, 4.46)	van der Waal, conventional hydrogen bond,	Ile155, Gly156, Ser157, Gly158, Tyr159, Ile160, Gly161, Tyr188, CYs242, Ile243, Gly244
3a	-5.68	58.19	69.03 µM	02	Ile178 (4.71), Asp179 (2.98)	van der Waal, conventional hydrogen bond, unfavourable donor-donor, alkyl	Pro120, Ile122, Ile155, Gly156, Ser157, Ile178, Asp179, Gly180, Lys213, Val214, Ile243
3b	-5.20	57.30	153.49 µM	03	Thr118B (3.58), Gly244 (2.76, 3.21)	van der Waal, conventional hydrogen bond, Pi-Pi-stacked, alkyl, Pi-alkyl	Pro117, Thr118, Val119, Leu132, Cys133, Ile160, Leu241, Cys242, Ile243, Gly244, Phe245
3c	-5.50	56.25	92.43 µM	01	Gly244B (2.87)	van der Waal, conventional hydrogen bond, sulfur-X, alkyl, Pi-alkyl	Pro117, Thr118, Val119, Leu132, Cys133, Ile160, Leu241, Cys242, Ile243, Gly244, Phe245
3d	-5.79	25.76	56.56 µM	01	Leu241B (5.00)	van der Waal, conventional hydrogen bond, Pi-sigma, Pi-Pi-stacked, amide-Pi-stacked, alkyl, Pi-alkyl	Pro117, Thr118, Leu132, Cys133, Gly158, Tyr159, Ile160, Gly161, Tyr188, Leu241, Cys242, Ile243, Gly244, Phe245

of amino acid Ile155, Gly156, Ser157, Ile160, Cys242, Ile243 and Gly244 present in active domain of NADPH Oxidase with the standard (Fig. 3) and synthesized derivatives (Table-4). Compounds **3a** and **3d** showed the highest binding affinity over the standard drug (Figs. 4 and 5).

Antioxidant activity: The biological evaluation of synthesized 2-aminothiazole derivatives (**3a-d**) for the antioxidant activity was carried out by the well-known DPPH method with ascorbic acid as standard. Antioxident activity was assessed by measuring UV absorbance then calculated percent inhibition and compared with the standard drug. All the synthesized derivatives has substantial antioxidant potential as compared to standard ascorbic acid (Table-5). Compound **3a** shows the highest antioxidant scavenging activity among the synthesized derivatives.

Conclusion

Present research work indicates that the green chemistry approach, use of microwave synthesis optimizes time, energy in synthesis of 2-aminothiazole derivatives (**3a-d**) as well as the product obtained was high purity in better yield. The *in silico* finding shows that 2-aminothiazole derivatives (**3a-d**) has best possible physico-chemical properties suitable for administration. Docking studies illustrated that compounds **3a** and **3d**

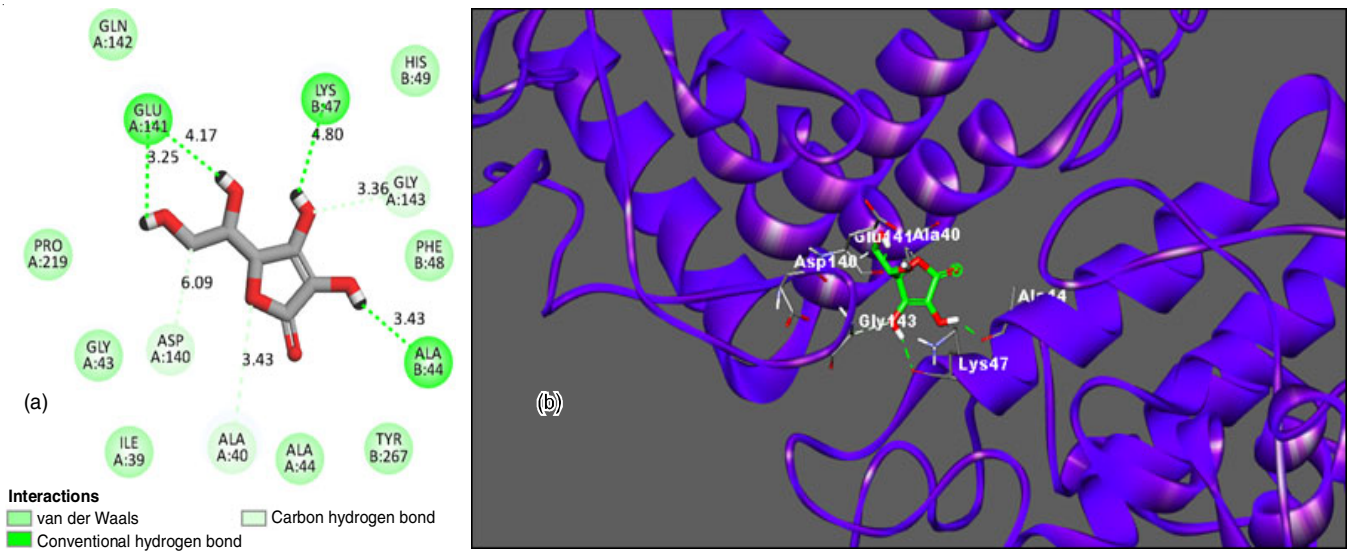


Fig. 1. 2D (a) and 3D (b) interaction of of standard (ascorbic acid with tyrosinaseoxidoreductase enzyme (PDB:3NM8)

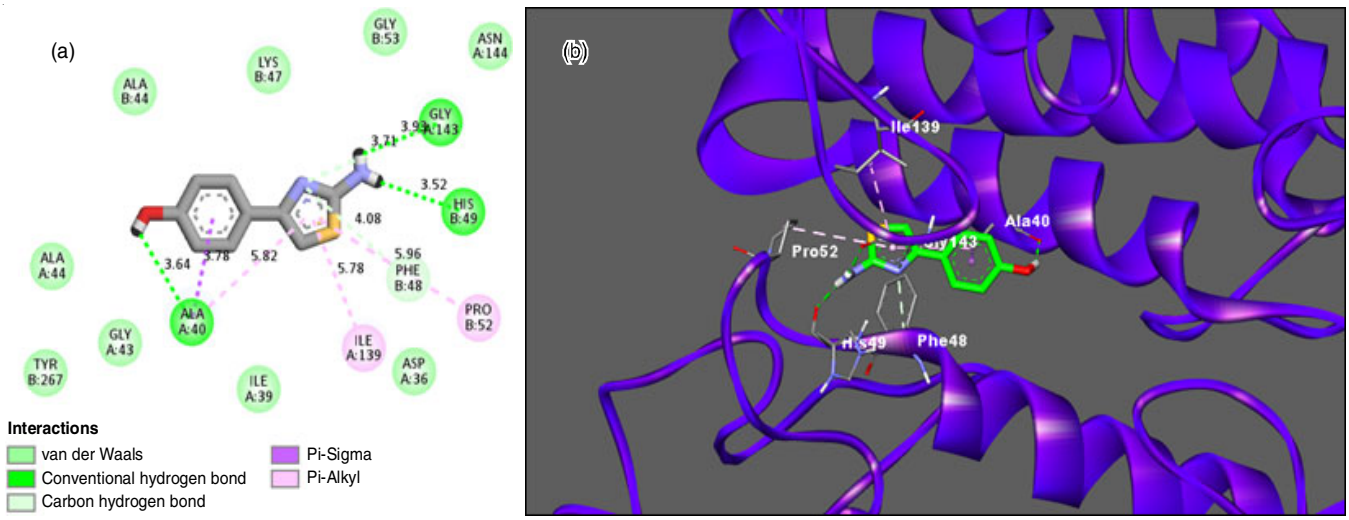


Fig. 2. 2D (a) and 3D (b) interaction of compound **3d** with ryrosinaseoxidoreductase enzyme (PDB:3NM8)

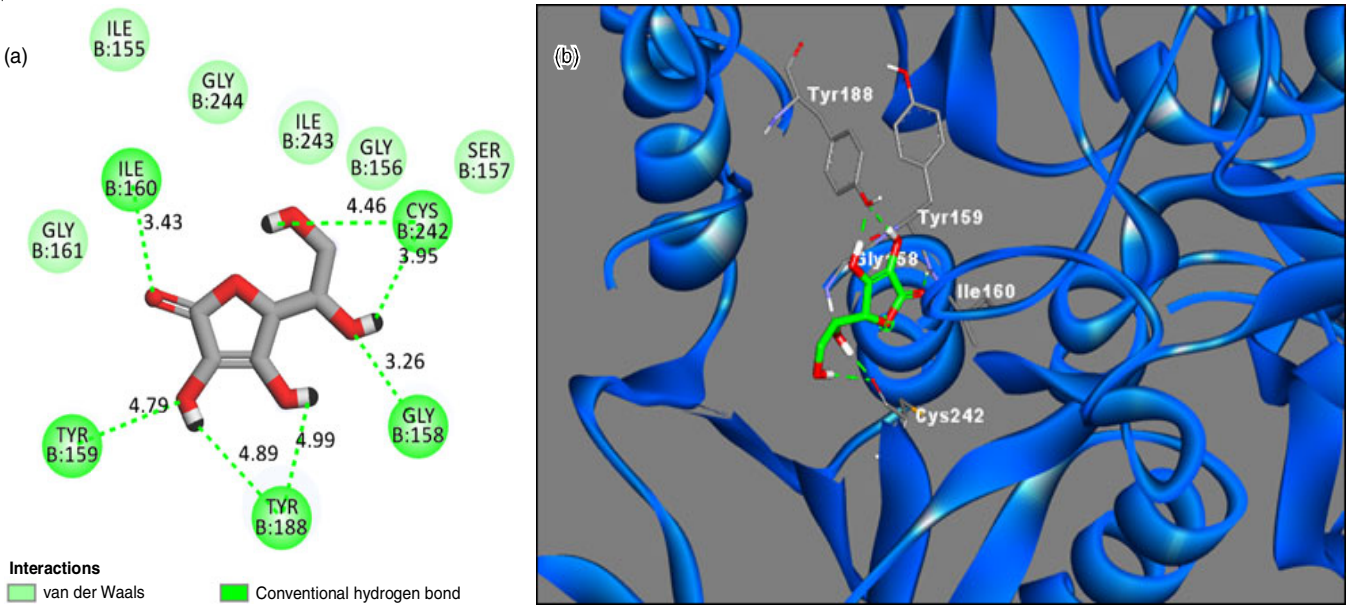


Fig. 3. 2D (a) and 3D (b) interaction of standard (ascorbic acid) with NADPH oxidase (PDB: 2CDU)

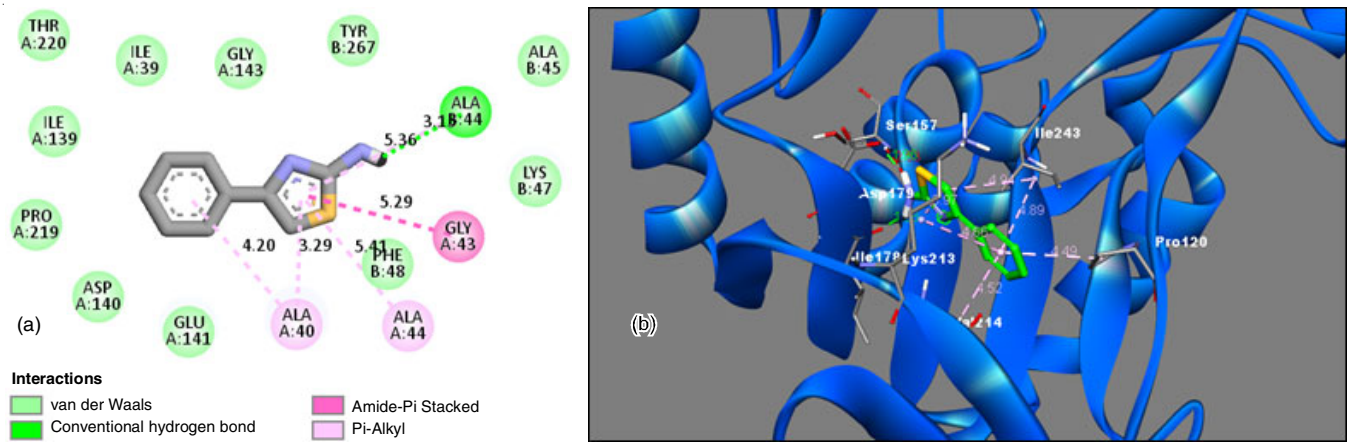


Fig. 4. 2D (a) and 3D (b) interaction of compound **3a** with NADPH oxidase (PDB: 2CDU)

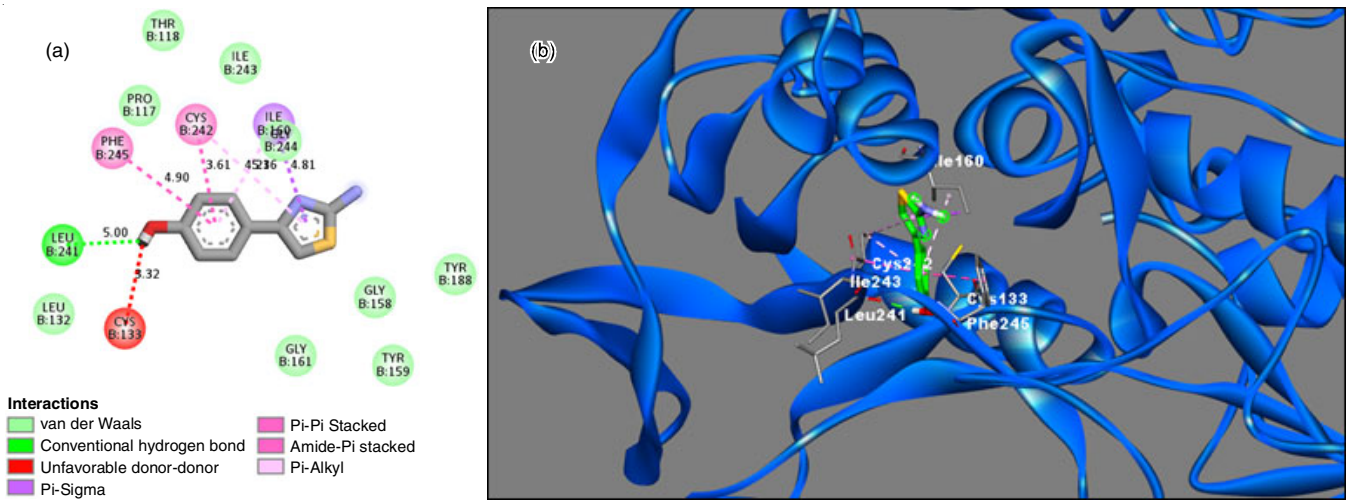


Fig. 5. 2D (a) and 3D (b) interaction of compound **3d** with NADPH oxidase (PDB: 2CDU)

TABLE-5
PERCENTAGE OF INHIBITION OF
DPPH BY 2-AMINO THIAZOLE DERIVATIVE

Compd.	Conc.	Inhibition (%)		
		After 15 min	After 30 min	After 45 min
Std.	50	22.00	24.33	32.66
	100	29.50	33.50	33.91
3a	50	66.25	67.00	68.83
	75	22.08	31.50	32.25
	100	63.16	63.41	64.00
3b	50	37.83	38.66	49.00
	75	28.50	29.33	32.75
	100	26.00	33.25	33.25
3c	50	18.75	33.25	41.33
	75	25.50	23.58	29.66
	100	3.583	32.41	5.00
3d	50	15.166	17.66	22.41
	75	23.00	24.83	29.08
	100	14.33	16.50	18.75
Control		1.2	–	–

has lowest binding score that suggest highest binding affinity towards the oxidoreductase enzyme and their potency as anti-oxidant compound. The compound has moderate antioxidant activity. It is concluded that 2-aminothiazoles has antioxidant potential as compared to standard (ascorbic acid), which can be further improved by modify the substituents on 4-position of thiazole ring.

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