MICROWAVE ASSISTED SYNTHESIS OF 2-AMINOTHIAZOLE DERIVATIVES

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Abstract

Thiazole is a good pharmacophore nucleus due to its various pharmaceutical applications. Its derivatives have a wide range of biological activities such as antioxidant, analgesic, and antimicrobial including antibacterial, antifungal, antimalarial, anticancer, antiallergic, antihypertensive, anti-inflammatory, and antipsychotic. A series of novel 2-aminothiazole derivatives were synthesized by microwave assisted method as a green chemistry approach and were characterized by spectral methods and elemental analysis. The antioxidant potential of the derivatives was determined by using molecular docking against two different oxidoreductase protein (PDB: 2CDU and 3NM8). Compound 3a and 3d shows the stronger binding affinity to the targeted protein. The synthesised drug was pharmacologically evaluated for the antioxidant activity using ascorbic acid as a reference drug. Compound 3a shows highest inhibition.

Key Words:Thiazole, Microwave assisted synthesis,antioxidant, in silico activity,Molecular docking.

Introduction:

During the past decades, the synthesis of thiazoles and analogues has gained interest due to their broad range of biological and pharmaceutical properties. Microwave-assisted organic synthesis of heterocyclic compounds has become an effective technique for generating new heterocyclic scaffolds useful for drug discovery.(Baba et al., 2018)Thiazole, or 1,3-thiazole, is a heterocyclic compound that contains both sulfur and nitrogen; the term 'thiazole' also refers to a large family of derivatives.(Kamoutsis et al., 2021; Narender et al., 2007)The thiazole ring is notable as a component of the vitamin thiamine (B1). Thiazoles belong to the azole's family of heterocycles, which also includes imidazoles and oxazoles.(Dharmacon, 2017; Petrou et al., 2021) Thaizole undergoes various chemical reaction like electrophilic substitution, nucleophilic substitution condensation and coupling reaction. (Lingaraju et al., 2012; Tang et al., 2016; Wang et al., 2018) Thiazole synthesis by various method(Kiran et al., 2020) like Cu-catalyzed oxidative method(Wang et al., 2018), Solid phase synthesis(Sanz-Cervera et al., 2009),Solvent-Free Approach(Facchinetti et al., 2016), copper(I)-catalyzed 1,3-dipolar cycloadditionof terminal alkynes(Miura et al., 2015) and one potthree-component synthesis(Chinnaraja & Rajalakshmi, 2015; De Andrade & De Mattos, 2018; Fu et al., 2019) was reported. Thiazole possess various pharmacological activities like such as anti-bacterial (Mamidala et al., 2021), anti-human immunodeficiency virus type 1 (HIV-1)(Chimirri et al., 1998), antihypertensive(Bagheri et al., 2004), anti-inflammatory, anti-tubercular(Kesicki et al., 2016), antiviral and anticancer activities.(Gomha et al., 2017)

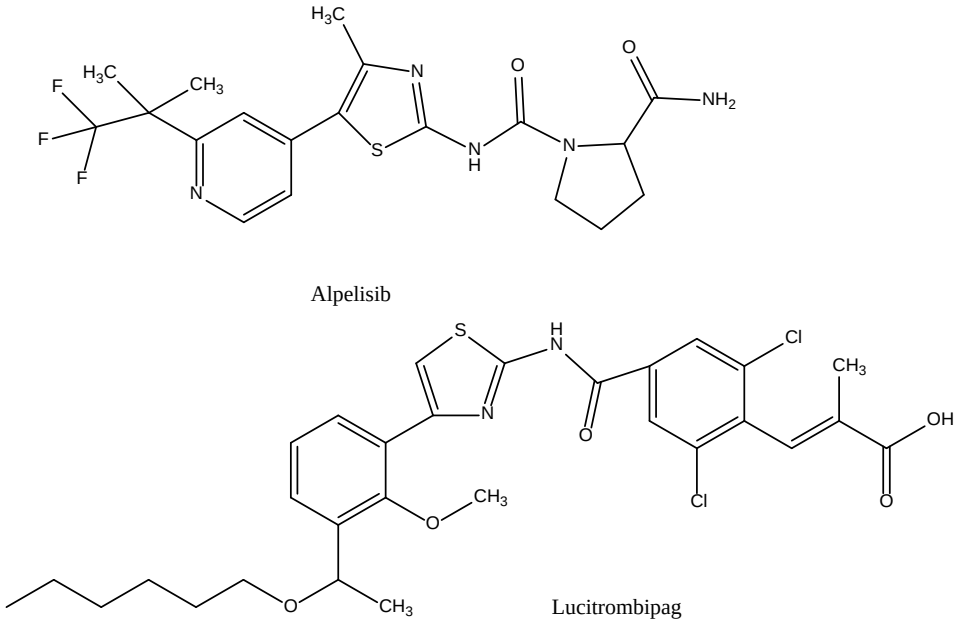
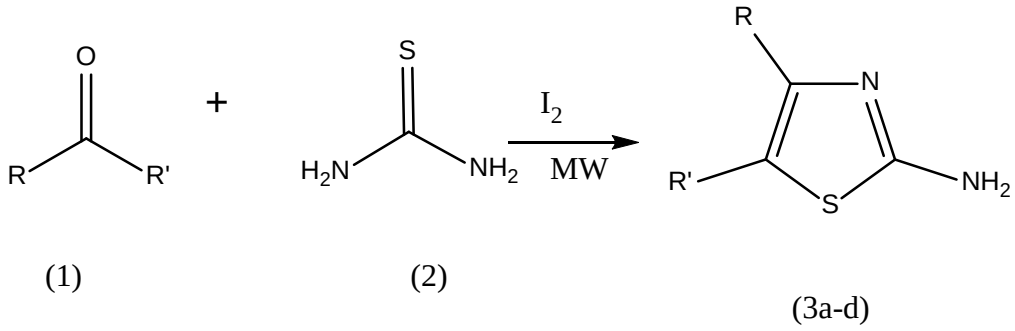


Figure 1. Structures of thiazole-bearing drugs recently approved by the FDA

Experimental Work:



(1) (2) (3a-d)

Figure 2: Scheme for synthesis of 2-aminothiazole derivatives

General procedure for synthesis of 2-aminothiazole derivatives (Chinnaraja & Rajalakshmi, 2015; Karamthulla et al., 2014)

Chemicals were procured from local vender. Chemicals were of laboratory grade and used as such. The completion of reaction was monitored by TLC. 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.

Conventional method:

Substituted ketone (1) (0.01M), thiourea (2) (0.02M), iodine 0.01M) were refluxed for 8-10 hrs. Reaction was confirmed by TLC. After cooling reaction mixture was poured in ice. Precipitate was filtered and dried. Product (3a-d) was recrystallized by using ethanol.

Microwave assisted synthesis:

Substituted ketone (1) (0.01M), thiourea (2) (0.02M), iodine (0.01M) were taken in a microwave flask and subjected to microwave irradiation at 170 W to 5 – 15 min.Reaction confirmation was doneby TLC. After cooling reaction mixture was poured in ice. Precipitate was filtered and dried. Product (3a-d) was recrystallized using ethanol.

***In-silico* analysis:**

The physicochemical properties were determined using online chemical property calculator Molinspiration (http://www.molinspiration.com). Further ADME and toxicity study completed using PreADMET server (http://preadmet.bmdrc.org/) and SwissADME (http://www.swissadme.ch).

Molecular docking:

Based on literature survey, oxidoreductase protein molecules was used as target molecule for docking study. The 3D structure of target proteins (2CDU and 3NM8)(Da Silva Costa et al., 2018; Irfan et al., 2021) was obtained from protein data bank pdb (www.rcsb.org). The docking compatible structures of synthesised thiazole derivatives (ligand) was first drawn in chem draw (Patil & Amrutkar, 2021)which then converted in open babel 3.1.1. (O'Boyle et al., 2011) The active domain of protein molecule was determined used Pymol software. The target paroteins were prepared for docking in Autodock tool 1.5.7 by removing water, heteroatom and adding charges.(Allouche, 2012) The ligand structure was docked on active domain and post docking analysis was performed in discovery studio 3.5. visualizer (DS visualizer).(BIOVIA DS, 2017)

Antioxidant activity:

The antioxidant activity of all the synthesised compounds was assessed using the DPPH (1, 1diphenyl-2-picrylhydrazyl) test in this study.(de Torre et al., 2019; Sehwag & Das, 2013) To make the solution, 2 mg of DPPH was dissolved in 100 mL of Methanol.(Surana et al., 2013) 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 the dark. The radical scavenging ability was determined at 15, 30 and 45 minutes using UV-visible spectrophotometer. The activity, was determined by the proportion of scavenging activity derived using the equation:

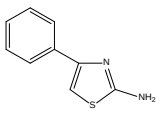
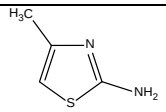
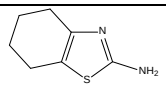
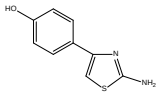
$$Scavenging\ Activity = \frac{(\mathrm{A}\ control - \mathrm{A}\ Sample)}{\mathrm{A}\ control} \mathrm{X}\ 100$$

Where $\mathrm{A}_{\mathrm{control}}$ is the absorbance of the blank (DPPH alone) and $\mathrm{A}_{\mathrm{Sample}}$ the absorbance of the tested solution

Result and discussion:

Due to the fascinating chemistry and biology of thiazoles; these compounds continue to attract, the synthetic and medicinal organic chemists for further research. The present work deals with synthesis of novel 2-amino thiazoles by conventional and by using green chemistry approach of using microwave condensation methods. The compound obtained in good yield and high purity by microwave irradiation as compare to conventional method. This indicate that the green method of synthesis was efficient and effective in obtaining desired product. Table 1 summarises the physical data of synthesised compounds. Compound 3d obtained in highest yield.

Table no .1: Physical parameters of 2-Aminothiazole Derivatives

Sr. no	Comp	structure	IUPAC	M.P. (°C)	%Yield		MW	Molecular formula	Crystal shape
					Conventional	Microwave			
1	3a		2-amino-4-phenyl thiazole	210	14.20	29.46	176	$C_9H_8N_2S$	Fine powder
2	3b		2-amino-4-methyl thiazole	48	24.56	34.82	114	$C_4H_6N_2S$	Needle shape
3	3c		2-amino-4,5,6,7-tetrahydr o benzothiazole	132	25.68	34.82	154	$C_7H_{10}N_2S$	Needle shape
4	3d		P-Hydroxy Acetophenone	50	64.58	61.45	136	4-(OH)C_6H_4 $COCH_3$.	Fine powder

In-silico studies:

Physicochemical properties characterize the compounds in absorption, distribution and partly in excretion (ADE). During the last two decades some of these properties were believed to be the most important in ADE, like acidity/basicity, lipophilicity, hydrogen bond donor/acceptor capabilities and molecular size-related properties.(Patil & Pharm, n.d.) There are different parameters for the representation of these properties, like pKa, 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. (Clark & Roe,

2010)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.(Sliwoski et al., 2014)The *In-sillico* activity tells that all compound follows Lipinski rule with no violation as given in table 2.

Table 2: Physicochemical Parameter and druglikeness of 2-amino thiazole derivative

Compound name / 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

The ADME and toxicity studies summarised in Table 3 shows that the compound are substrate for cytochrome enzyme, possess mutagenicity and moderate carcinogenicity. The synthesised 2- amino thiazole derivatives has significant pharmacokinetics like high protein binding, negligible concentration in brain and low skin permeability.

Table 3: ADME and Toxicity study of 2-amino thiazole derivative

Compound code / 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

Docking study:

The bonding and non-bonding interaction of synthesised 2-amino thiazole derivatives with oxidoreductase protein molecule was studied by using molecular docking. The 2-amino thiazole derivatives shows -3.62 to -6.64 kcal/mol binding affinity as compare to standard ascorbic acid with -3.61kcal/mol binding affinity against Tyrosinaseoxidoreductase enzyme (PDB:3NM8). Ala40A, Gly43A, Ala44A, Glu141A, Gly143A, Ala44B, Ala45B, Lys47B, Phe48B and Tyr267B are amino acid present in active domain and involve in binding with ligand.The amino acid present in active domain interact with derivatives through Vander Waal, Conventional Hydrogen bond, Pi-Sulfur, Alkyl Pi-alkyl and Pi-Pi- stacked interaction. Compound 3d shows lowest docking score -6.64 kcal/mol. (Table 04)

All synthesised derivatives also possess 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. Vander Wall,Conventional Hydrogen bond, Pi-Sigma, Pi-Pi- stacked, Amide-Pi-stacked, Alkyl and Pi-Alkyl are the bonding interaction of amino acid Ile155, Gly156, Ser157,Ile160, Cys242, Ile243 and Gly244 present in active domain of NADPH Oxidase with the standard and synthesised derivatives.(Table 04) Compound 3a and 3d shows the highest binding affinity over the standard drug.

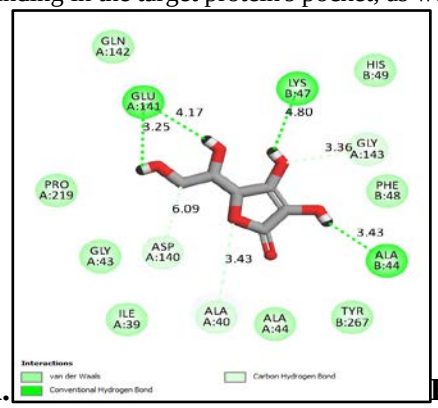
Table No 04: Binding affinity and interaction of 2- amino thiazole derivatives and reference with target protein (3NM8 and 2CDU)

Tyrosinaseoxidoreductase enzyme (**PDB:3NM8**)							
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
Reference (Ascorbic acid)	-3.61	21.28	2.27mM	04	Glu141A (3.25, 4.17) Ala44B (3.43), Lys47B(4.80)	Vander 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 uM	01	Ala 44B (3.13)	Vander 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)	Vander 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 uM	03	His49B(2.16, 2.22, 4.50)	Vander 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 uM	03	Ala40A(3.64), His49B(3.52), Gly143A(3.71,3.93)	Vander 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	-4.73	50.71	342.50uM	07	Gly158B(3.26),	Vander Waal,	Ile155, Gly156, Ser157, Gly158,

acid					Tyr159(4.79), Ile160(3.43), Tyr188(4.89, 4.99), Cys242(3.95, 4.46)	Conventional Hydrogen bond,	Tyr159, Ile160, Gly161, Tyr188, CYs242, Ile243, Gly244
3a	-5.68	58.19	69.03 uM (micromolar)	02	Ile178(4.71), Asp179 (2.98)	Vander 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 uM (micromolar)	03	Thr118B (3.58), Gly244 (2.76,3.21)	Vander 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 uM (micromolar)	01	Gly244B (2.87)	Vander 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 uM (micromolar)	01	Leu241B (5.00)	Vander 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

FIGURE LEGENDS:

Docking images of ligand with molecular target protein. The 2D (2 Dimentional) interaction (A) with Amino acid in the active site of target along with type of interaction. The 3D interaction (B) depicts the ligand's binding in the target protein's pocket, as well as the bonding distance.

A. 

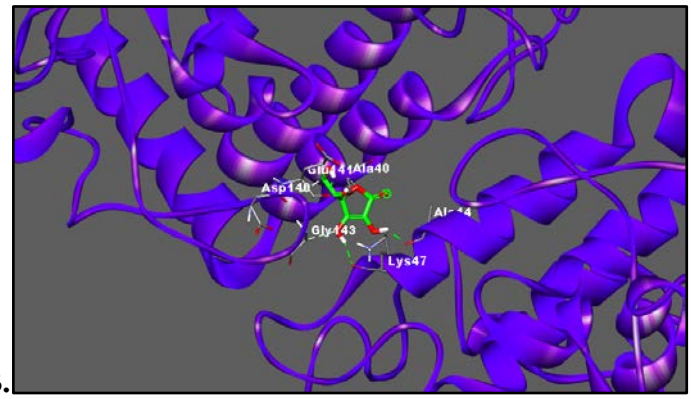
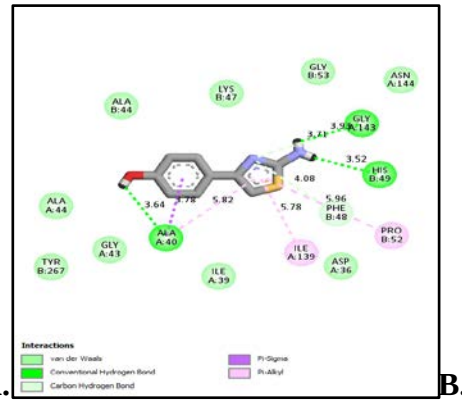
B. 

Figure 3: A: 2D interaction of standard (Ascorbic acid) with Tyrosinaseoxidoreductase enzyme (PDB:3NM8)

B: 3D interaction of standard (Ascorbic acid) with Tyrosinaseoxidoreductase enzyme (PDB:3NM8)

A. 

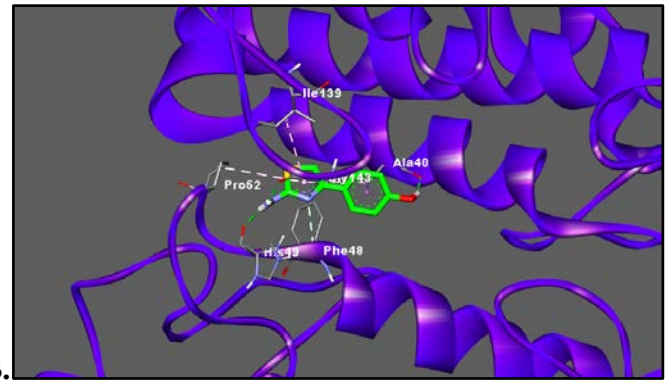
B. 

Figure 4: A: 2D interaction of Compound 3d with Tyrosinaseoxidoreductase enzyme (PDB:3NM8)

B: 3D interaction of Compound 3d with Tyrosinaseoxidoreductase enzyme (PDB:3NM8)

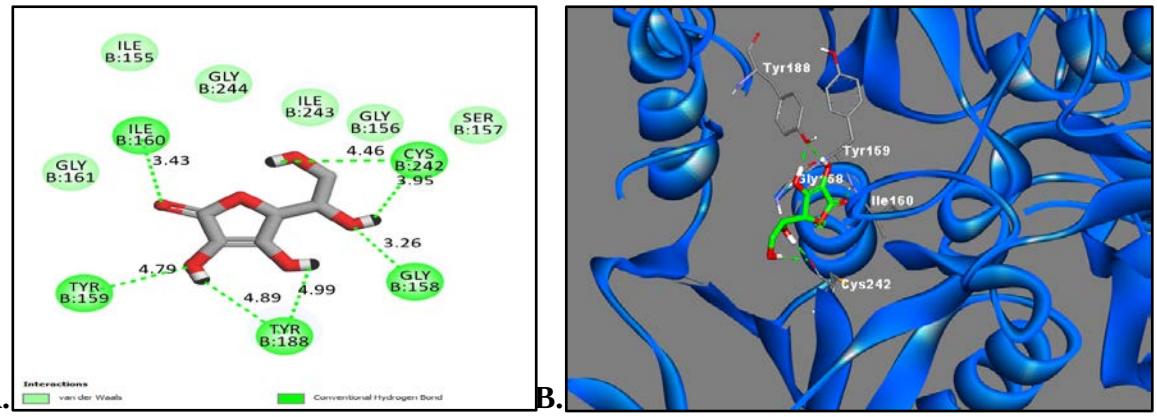


Figure 5: A: 2D interaction of standard (Ascorbic acid) with NADPH Oxidase (PDB: 2CDU)
B: 3D interaction of standard (Ascorbic acid) with NADPH Oxidase (PDB: 2CDU)

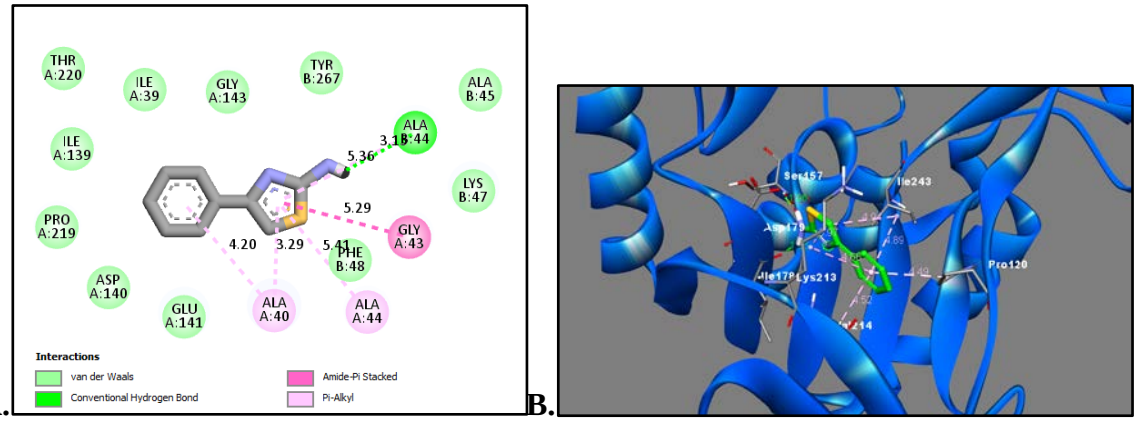


Figure 6: A: 2D interaction of Compound 3a with NADPH Oxidase (PDB: 2CDU)
B: 3D interaction of Compound 3a with NADPH Oxidase (PDB: 2CDU)

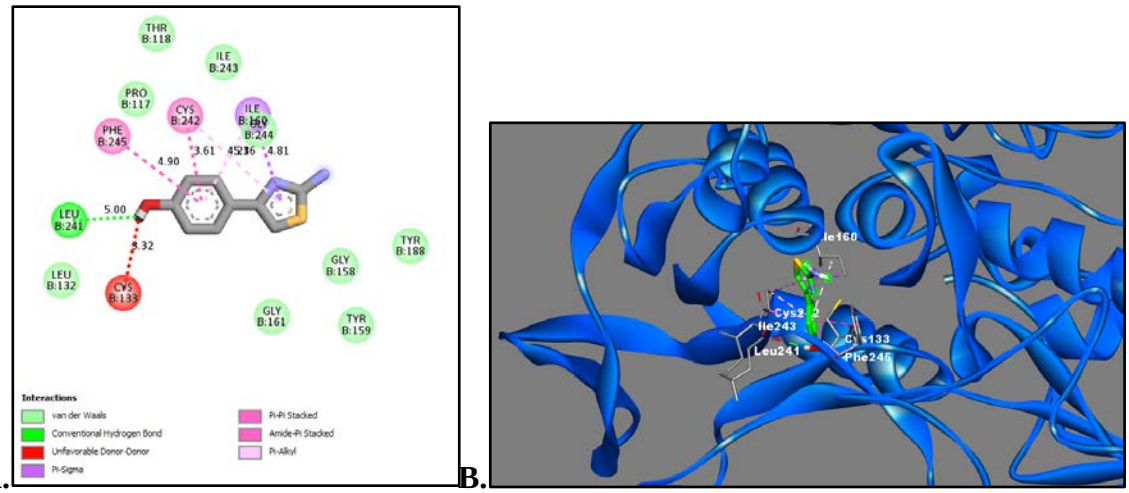


Figure 7: A: 2D interaction of Compound 3d with NADPH Oxidase (PDB: 2CDU)
B: 3D interaction of Compound 3d with NADPH Oxidase (PDB: 2CDU)

Antioxidant activity:

The biological evaluation of synthesized derivative 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 as shown in Table 4 and diagrammatically presented as bar diagrams in Figure 3. All synthesised derivatives has substantial antioxidant potential as compared to standard ascorbic acid. Compound 3a shows highest antioxidant scavenging activity among the synthesised derivatives.

Table No. 05: Percentage of inhibition of DPPH by 2-amino thiazole derivative

Sample Id (Conc)	Percent inhibition		
	After 15 min.	After 30 min.	After 45 min.
Std (50)	22	24.33	32.66
Std (100)	29.5	33.5	33.91
3a(50)	66.25	67	68.83
3a (75)	22.08	31.5	32.25
3a (100)	63.16	63.41	64
3b(50)	37.83	38.66	49
3b (75)	28.5	29.33	32.75
3b (100)	26	33.25	33.25
3c(50)	18.75	33.25	41.33
3c (75)	25.5	23.58	29.66
3c (100)	3.583	32.41	5
3d(50)	15.166	17.66	22.41
3d (75)	23	24.83	29.08
3d (100)	14.33	16.5	18.75
Control	1.2	--	--

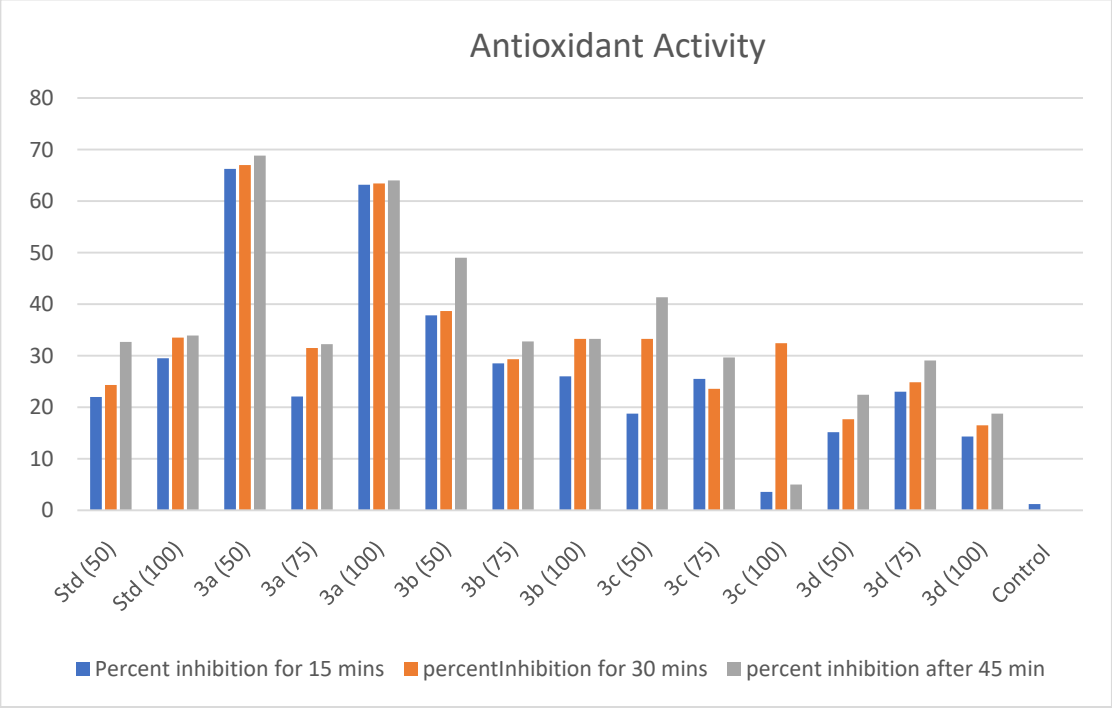


Figure 8: Antioxidant activity of 2-amino thiazole derivatives by DPPH method.

CONCLUSION:

The present research work indicate that green chemistry approach, use of microwave synthesis optimises time, energy in synthesis of 2-aminothiazole derivatives as well as the product obtained was high purity in better yield. The in-silico finding shows that compound has best possible physicochemical properties suitable for administration. Docking study illustrate that compound 3a and 3d has lowest binding score that suggest highest binding affinity towards the oxidoreductase enzyme and their potency as antioxidant compound. The compound has moderate antioxidant activity. The compound 3a showing the highest potential. The study conclude that 2-amino thiazole has antioxidant potential as compare to standard which can be further improved by modifying the substituents on 4- position of thiazole ring.

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