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Hydroxyapatite/$ZnCl_2$ nano-flakes: an efficient catalyst for the synthesis of 2-arylbenzothiazoles with molecular docking and anti-oxidant evaluation

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ABSTRACT

Synthesis of 2-substituted benzothiazole derivatives using $ZnCl_2$ nano-flakes supported on nano-hydroxyapatite as a catalyst. Has been achieved by one-pot reaction of 1 mole of aromatic heterocyclic aldehydes with 1 mole of 2-aminothiophenol under solvent – free condition. The adopted reaction has many characteristics: fast, efficacious, eco-friendly and short time $ZnCl_2$/HAp catalyst was synthesized and identified using X-ray diffraction, Scanning Electron Microscopy, and Fourier transforms infrared. The obtained results explained the formation of nano-crystalline sheets over the hydroxyapatite nano-matrix. The molecular docking validation as transpeptidase and 14 α-demethylase enzyme inhibitors explains that there are five for the synthesized compounds that give good energy score values. Also, the anti-oxidant study showed that four 2-benzothiazoles of the synthesized compounds gave promised ABTS (Inhibition %) compared with ascorbic acid.

Keywords: *Aldehydes; HAp/$ZnCl_2$; Anti-oxidant; Molecular docking; FTIR.*

1. INTRODUCTION

Hydroxyapatite (HAp; $Ca_{10}(PO_4)_6(OH)_2$) is a highly abundant, natural material, being the major component of teeth and bones. In addition, it is easy to get because it can be extracted from animal bones, egg-shells, wood and algae. HAp was used as catalyst supports for the following advantages: (a) limitations of reduced mass transfer related to the absence of structural porosity, (b) adsorption capacity and ion-exchange ability, and (c) Acidity of surface is low, this decrease any side reactions arising from the support itself. All these physicochemical properties of HAp encourage us to focus on the use of the HAp matrix in the metal nanoparticles stabilization. The reduction of the HAp matrix particles size from the microcrystalline to the nanocrystalline regime (from >1 μm to <100 nm) was performed in anticipation of improved activity due to a higher external surface area. This has been demonstrated in the use of HAp-supported Lewis acids in organic synthesis, and more recently in Michael's addition reaction. Herein, the first time the use of nano flakes of $ZnCl_2$ supported on nano crystalline HAp, as a highly effective, cheap, reusable and stable solid catalyst for the synthesis of benzothiazoles [1, 2]. Benzothiazole derivatives as an example of bicyclic ring containing one nitrogen and one sulfur atom in the thiazole ring fused with benzene ring [3] Benzothiazoles have attracted a great attention of many researchers in recent times, because of their important uses. Benzothiazoles are the key structure of many drugs, natural products. Various activities were shown by benzothiazoles in biological and pharmaceutical fields as antitumor, antiglutamate, antimicrobial, antidiabetic, anticonvulsant, anti-inflammatory, antihypertensives, antivirals, antihistaminics, antifungals, anticancers, and antibacterial. [4-6] The most useful protocols for the synthesis of benzothiazoles are acidic cyclocondensation of 2-aminothiophenol with acyl chloride [7,8] esters [9] aldehydes [8,10] carboxylic acids [11,12] and nitriles [13,14]. Oxidative cyclo-dehydrogenations of o-aminothiophenol with aldehydes using several oxidative reagents such as nitrobenzene, DDQ, [15] $NaHSO_3$(aq), benzofuroxan [9] tetracyanoethylene [16] MnO_2 [17] 1,4benzoquinone [12] $Pb(OAc)_4$ [13] and Oxone [18] have been used for the synthesis benzothiazoles. However, most of these methods have many drawbacks as harsh conditions of difficult work-up, long reaction times and expensive catalysts. Recently, some deficiencies have been found in the synthesis of benzothiazoles, where high temperature and microwave radiation were used in metal free procedures through the interaction of o-aminothiophenol/anilines with aryl ketones [14] or alkyl amines [19,20]. Thus, we're aiming in this study to prepare some benzothiazoles with high efficiency avoiding the disadvantages suffered previously.

2. MATERIALS AND METHODS

2.1. Catalyst preparation.

Hydroxyapatite (HAp) was synthesized using egg residuals as discussed elsewhere [21].

2.2. Catalyst characterizations.

2.2.1. Fourier transform infrared spectra (FTIR).

Fourier transform infrared absorption spectra were recorded for 32 runs for all samples within the spectral range extended from 4000 to 400 cm^{-1} and 2 cm^{-1} spectral resolution using Therom Fisher-Nicolet *is*10 single beam spectrophotometer. All measurements were recorded at ambient room temperature. Recorded spectra were corrected for background and dark current noises using Omnic 8 computer program. KBr disc technique was used, at which, 1:100 sample to KBr was used to obtain clear homogenous disks of diameter 1cm under pressure up to 5 tons/cm^2.

2.2.2. X-ray Diffraction (XRD).

Internal arrangement of atoms within the prepared matrices were examined using XRD diffractogram pattern recorded via computerized PA analytical X'Pert PRO X-ray machine occupied with Cu Kα line operating at 45 kV–40 mA within the Bragg's angle (2θ) ranging between 5 and 70° and wavelength λ = 1.540 Å peak maxima located at Bragg angle used to recognize crystalline phases within the material structure.

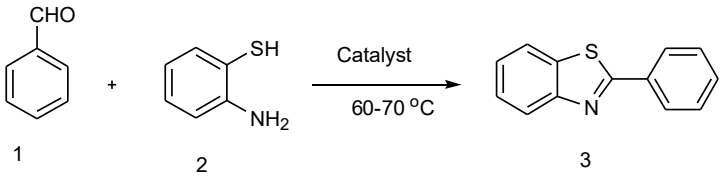
2.2.3. Scanning electron microscopy (SEM) and energy dispersive X-ray (EDAX).

Morphology and surface nature were examined using scanning electron microscope (SEM) type Quanta 250FEG linked to EDX unit operating with accelerating potential 30 kV and magnification up to $x10^6$. All samples were coated with a thin layer of gold to minimize the effect of charge.

2.3. Organic reaction and structure elucidation.

2.3.1. Organic reaction.

Towards our aim to discover new catalyst and examine it's catalytic reactivity in organic reactions [22-25]. Initially, we started by the reaction optimization through checked a range of catalysts for the synthesis of 2-substitutes benzothiazoles under solvent-free conditions Scheme 1. Traditional catalysts showed moderate catalytic activities (table 1, entries 1-5). Ultimately, the use of HAp/$ZnCl_2$ afforded a significant rate increase with 95% yield at 60-70 ℃ for 15 min (table 1, entry 6). The reaction was extended and investigated using various aromatic and heterocyclic aldehydes scheme 3. We observed that the reactions provided the corresponding products in good – highly yields (65-95%) (table 2, entries 1-12).

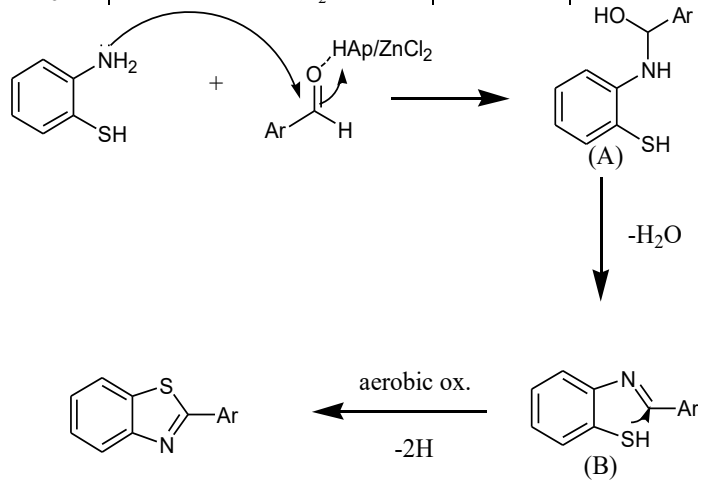


Scheme 1. Synthesis of 2-phenylbenzothiazole and reaction optimization.

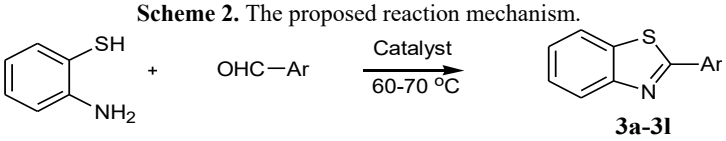
Proposed Mechanism would be presumably the activation of the carbonyl group of the aldehyde by the catalyst. The mechanism started by nucleophilic attack from amino group towards activated aldehyde carbonyl and this form intermediate **A** and this was followed by dehydration to give the imine **B**. After that, the SH group in the intermediate **B** attached the imine group then subsequently underwent aromatization through aerobic oxidation under the reaction conditions to form the desired products. The reaction mechanism for the hydroxyapatite/zinc chloride catalyzed synthesis of 2-substitutes benzothiazoles (**3a-3l**) was discussed in (Scheme 2).

Table 1. Reaction optimization.

Entry	Catalyst	Time	Yield %
1	Sm_2O_3/SiO_2	3.0 hr	65
2	Silica	3.5 hr	70
3	$ZnCl_2/SiO_2$	2.0 hr	70
4	V_2O_5/SiO_2	4.0 hr	80
5	Sm_2O_3/SiO_2 in Nano scale	1.0 hr	85
6	HAP/$ZnCl_2$	15.0 min	95



Scheme 2. The proposed reaction mechanism.



3a-3l

Scheme 3. Preparation of various 2-substituted benzothiazoles.

Examples of spectral data:

Entry 4

4-Benzothiazol-2-yl-2-methoxy-phenol

IR (KBr): ύ = 3437 (OH) cm^{-1},1620 (C=N) cm^{-1} , ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09-7.39 (m,4H.Ar), 7.38 (d, J = 8 Hz, 1H), 7.28 (S,1H) 7.03 (d, J=8 H_Z ,1H) 6.12 (S,1H) ,4.05(S,3H)ppm; ^{13}C-NMR (100 MHz, DMSO) δ = 168.37 (C=N), 148.79 (C-N) ,147.01(C-OH) , 134.48(C-S) , 126.42 (C=C) , 125.77-122.03 (4C-Ar) , 121.55 (CH=C) , 114.77 (CH-C-OH) , 109.45 (CH-C-OMe) , 56,31 (CH_3 –O) MS (EI) m/z=257$[M]^+$, Anal. calcd. for $C_{14}H_{11}NO_2S$, C, 65.35; H, 4.41; N, 5.44; O, 12.44; S, 12.46. Found: C,65.30; H,4.27; N,5.38.

Entry 9

2-Benzo[1,3]dioxol-5-yl-benzothiazole

IR (KBr): ύ = 1615 (C=N) cm^{-1}, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.03(d, J=8 H_Z ,1H), 7.87 (d, J=8 , 1H) , 7.62 (m, 2H) , 7,24(S , 1H) , 6.89 (d , J=8 H_Z ,2H) , 6.04 (S,1H) ppm; ^{13}C-NMR (100 MHz, DMSO) δ = 167.68 (C=N) ,153.57 (C-N) ,148.36-147.69 (2C-O) ,145.62 (C-S) , 134.56 (C-C=N) , 162.35-122.79 (4C-Ar) , 121.48 (C=C) , 113.66 (C-C) 107.51 (C=C) , 100.66 (CH_2-C-O). MS (EI) m/z=255$[M]^+$. Anal. Calad. For $C_{14}H_9NO_2S$. C, 65.87; H, 3.55; N,5.49; O, 12.53; S, 12.56.Found C, 65.77; H, 3.49; N,5.41.

Table 2. Synthesis of benzothiazoles using various aldehydes.

Entry	Product	Ar	Time (min.)	Yield (%)	M.p. (°C) Found/reported
1	**3a**	Phenyl	15	95	112/112-114 [29]
2	**3b**	4-MeO-phenyl	30	80	120/120-122 [30]
3	**3c**	1, 2, 3, Trimethoxy-phenyl	90	67	136
4	**3d**	3-methoxy-4 hydroxy phenyl	10	80	140
5	**3e**	4- fluoro-phenyl	15	90	100/99-100 [6]
6	**3f**	4- chloro-phenyl	20	85	119/117-119 [6]
7	**3g**	3- chloro-phenyl	25	90	83
8	**3h**	4-nitro-phenyl	30	75	195-196[31]
9	**3i**	Benzo[1,3] dioxole	20	80	115

Entry	Product	Ar	Time (min.)	Yield (%)	M.p. (°C) Found/reported
10	**3j**	3-pyridyl	25	65	118
11	**3k**	3-indolyl	40	80	183
12	**3l**	5-methyl-2-furyl	15	85	100

3. RESULTS

3.1. Fourier transform infrared spectra (FTIR).

Hydroxyapatite $Ca_{10}(PO4)_6(OH)_2$ (HAp) can be considered as the most vital and important mineral phase in almost hard tissues of vertebrates as it forms the mineral part of teeth and bones. Biological HAp typically has a calcium deficiency and permanently replaced with carbonate partner via direct substitution and charge compensation. Substitution groups usually provoke distinguish variations within different characteristic constraints including lattice parameters, relative crystallinity combined with crystal symmetry and thermal stability. In addition to other physical characteristics such as morphology, solubility, physical, chemical and biological characteristics.

HAp is characterized by the presence of specific characteristic chemical groups that are indicated via FTIR vibrational spectroscopy. FTIR spectra of the studied HAp before and after adding $ZnCl_2$ are shown in Figure (1) and the specific functional groups which characterize non-stoichiometric HAp (PO43-, OH-, CO_3^{2-}, as well as HPO_4^{2-}) are attributed according to their positions.

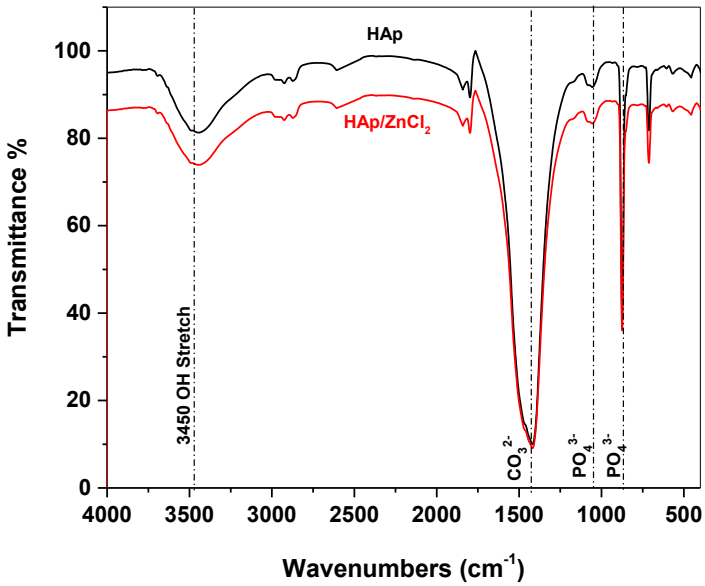


Figure 1. FTIR transmission spectra of studied hydroxyapettite in combination witha sample that contain.

3.2. XRD experimental data.

Figure (2) reveals X-ray diffraction analysis of studied hydroxyapettite and other sample combined with ZnCl catalyst to study the type of interaction thought between variable constituents. Obtained data compared with XRD libraries to identify possible phases. Pure HAp sample was shown to contain two major phases mainly consists of hydroxylapattite $[Ca_5(PO_4)_3OH]$ and residue of calcite $[CaCO_3]$ (JCPDS card No. 9–0432 and 33-0268) respectively. Samples that contain ZnCl contains additional phase of calcium zinc hydroxide hydrate in expense of the two previous phases. Whereas, the band at about 2θ = 30° was noticed to be intensified and new sharp peaks at 15, 40 and 45° as correlated with the new phase was also shown.

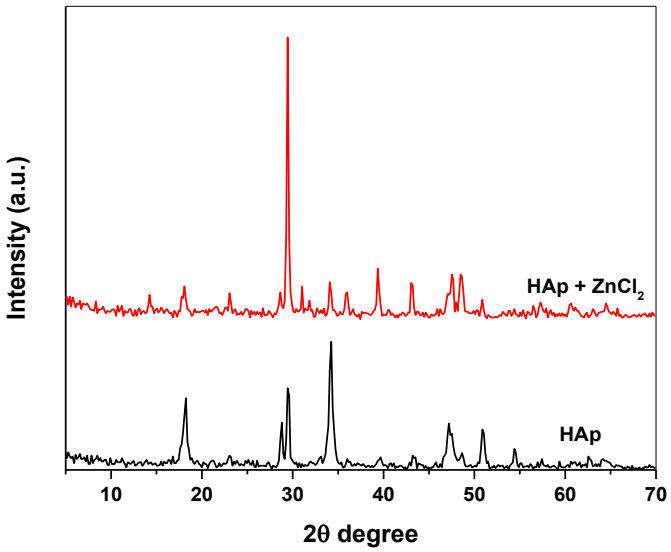


Figure 2. X-ray diffraction scans of hydroxyapattite in combination with a sample that contain fraction of $ZnCl_2$.

3.3. SEM analysis.

Figure (3) shows scanning electron micrographs, energy dispersive X-ray (EDX), and mapping of the studied hydroxyapettite and other sample combined with $ZnCl_2$ catalyst. The measurement was performed to ensure the homogeneity of the sample before and after adding $ZnCl_2$ in addition to their chemical composition.

The prepared catalyst shows a formation of flakes or platelet- like structure lie in the nanoscale range in their dimension that leads to an increase in the surface area. The increase in surface area of the flakes may result in reducing the reaction time via promoting higher surface area of the catalyst.

3.3. Molecular docking part.

3.3.1. Drug-receptor interaction.

The biochemistry of the bacteria cell wall needs about 30 enzymes and the most important one is the transpeptidase enzyme. Most of the antibiotics like penicillin series work on inhibition of the final cross link step by inhibiting the transpeptidase. The following calculation from molecular docking software explains the ligands-enzyme interaction between the synthesized compounds **3a-3i** and transpeptidase. The following table and figures explained that the most promised data of Energy score validation.

The building up of the fungal cell membrane consists of multi-steps but the most important step is the Ergosterol Biosynthesis. The lanosterol is converted to ergosterol by 14 α-demethylase enzyme. The previous molecular docking studied the ligands-enzyme interaction between the synthesized compounds **3a-l** and 14 α-demethylase. The E-score values reflect the efficacy of ligand-enzyme antagonist. The following data and figures explained the promised selected E-score values data. The energy score of compounds **3b, 3c, 3d, 3g** and **3i** are -5.68, -5.86, -5.98, -5.72 and -5.99 respectively.

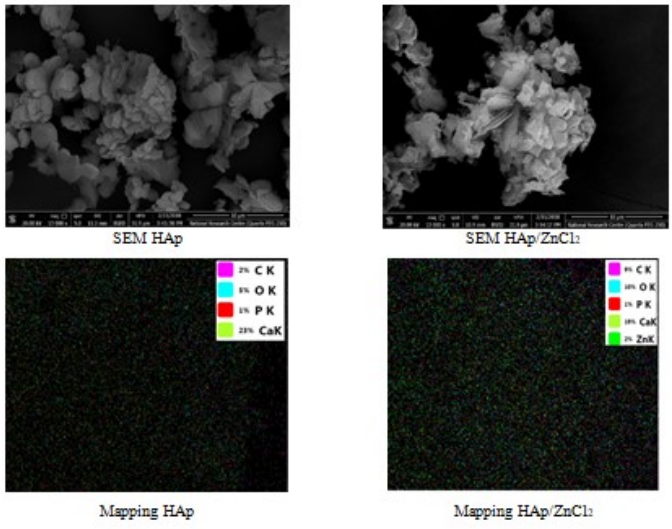


Figure 3. Scanning electron micrographs, energy dispersive X-ray (EDX).

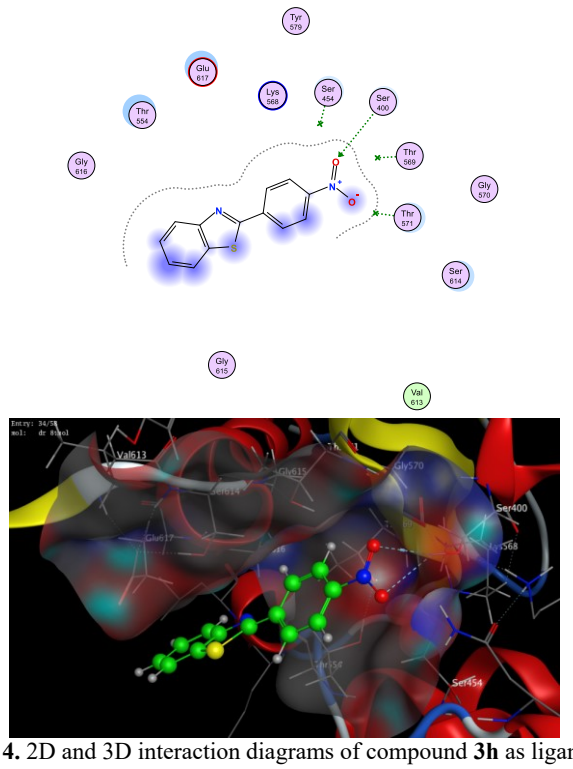


Figure 4. 2D and 3D interaction diagrams of compound **3h** as ligand with transpeptidase.

Compound	3b	3c	3h	3i	3k
E-score	-5.23	-5.52	-5.23	-5.28	-5.28

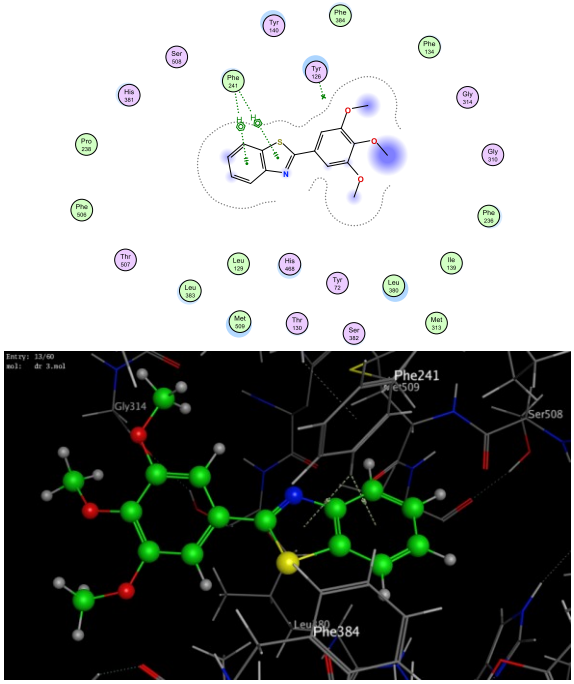


Figure 5. 2D and 3D interaction diagrams of compound **3c** as ligand with 14 α-demethylase.

3.3.2 Pharmacophore.

The selection of benzothiazoles (**3a-3i**) to build a pharmacophore for potential 14 α-demethylase inhibitors and transpeptidase inhibitors was based on their high potency superposition of **3c** generated a pharmacophore with aromatic center (Aro), H-bond acceptor (Acc, Acc2), with H-bond donar projection (Don), and hydrophobic (hyd) (Fig 4, 5 and 6).

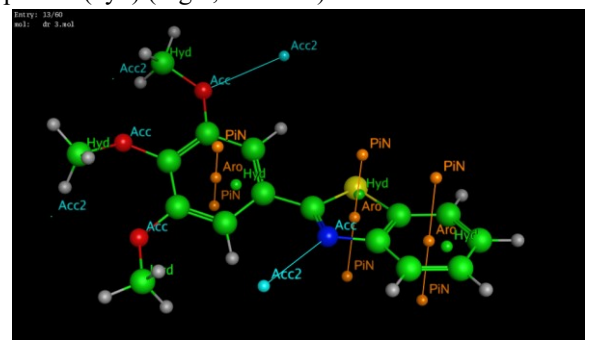


Figure 6. 3D pharmacophore structure of **3c** simulated to active site in 14 α-demethylase.

3.4. Experimental.

- On the bases of the standard docking protocol using MOE 2015.10 software.
- The proteins in mdb file downloaded from the PDB (protein data bank) the PDB codes: 1EW8, 4ZTK and 4LXJ

3.4.1. Biological activity.

All compounds were tested for the antioxidant activity using ATBS method where compounds **3g**, **3h** and **3j** showed good activities. On the other hand, compounds **3k** and **3l** showed moderate activities while **3d** compound activity showed high antioxidant activity.

Some compounds gave good results as (**3g-3h** and **3j**) of values 55.1, 54.3 and 62.6 as the 3g has the Cl atom located in a meta position, and **3h** has nitro group in a para position. While **3j** has a pyridine containing lone pair of electrons on their nitrogen atom.

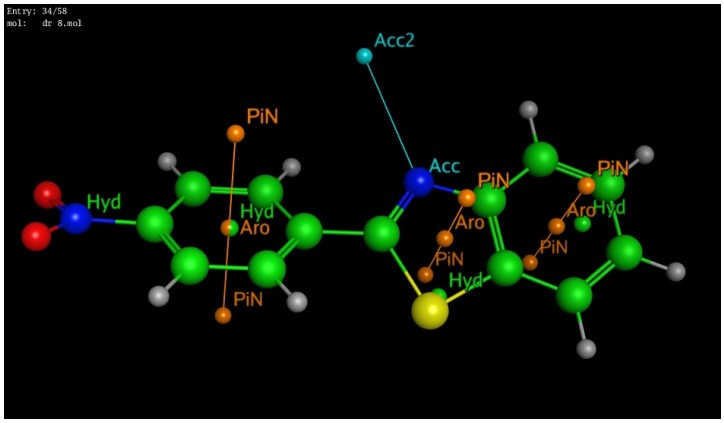


Figure 7. 3D pharmacophore structure of **3h** simulated to active site in transpeptidase.

Table 3. Anti-oxidant test by ATBS method.

Entry	Compounds	Absorbance of samples	% inhibition
	Control of ABTS	0.492	0
	Ascorbic-acid	0.053	89.2%
1	3a	0.399	18.9%
2	3b	0.410	19.6%
3	3c	0.337	31.5%
4	3d	0.056	88.6%
5	3e	0.337	31.5%
6	3f	0.429	12.8%
7	3g	0.221	55.1%
8	3h	0.225	54.3%
9	3i	0.382	25.1%
10	3j	0.189	61.6%
11	3k	0.293	40.4%
12	3l	0.321	34.7%

5. CONCLUSIONS

2-substituted benzothiazole derivatives were synthesized using $ZnCl_2$ nano-flakes supported on nano-hydroxyapatite as a catalyst under solvent–free condition. $ZnCl_2$/HAp catalyst was synthesized and identified. The molecular docking validation as transpeptidase and 14 α-demethylase enzyme inhibitors explains that there are five for the synthesized compounds that give good energy score values. Also, the anti-oxidant study showed that four 2-benzothiazoles of the synthesized compounds gave promised ABTS (Inhibition %) compared with ascorbic acid (Table 3).

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