3-Benzothiazole Derivatives -Green synthesis, Insilico Screening, ADMET Prediction and Evaluation of Invitro Anthelmintic agents.

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ABSTRACT:

The present study is an attempt to explore the anthelmintic activity with novel 3- benzothiazole derivatives. Intestinal worms increase your risk for anaemia and intestinal blockages, as well as malnutrition, So 3-benzothiazole derivatives are designed to kill or expel infesting helminths . In-silico design of novel analogues were carried out using discovery studio, pyrex, pymol , ChemSketch 12.0. Molinspiration software will be used to analyse 'Lipinski Rule of Five' and drug likeness properties. Five derivatives (B3,B10,B13,B14,B15) (Tab-02) which obeyed rule of five and having desired physic-chemical properties were synthesized under green synthesis by microwave irradiation method in ethanol by two step process. After the completion of reaction in each step, the compounds will isolate, recrystallize by using suitable solvents, and purified by TLC and column chromatography. Analogues will characterize by FT-IR, H^1NMR, ^{13}C NMR and Mass Spectroscopy. The Biological evaluation will be carried and the results will be compared, Among this the compound B10 and B15 in concentration 30,60,80 and 100mg/ml showed paralysis of worms within 1 and 2 min and death within 3 and 4 min depending on the concentration. More time was taken by compound B3,B13,B14 concentrations 30,60,80, and 100mg/ml, showed paralysis of worms within 6 to 7 min and death within 10 to 12 min.(Tab-04)

INTRODUCTION:

Benzothiazole is an important class of pharmaceutical drug that possesses many attractive biological activities. It has anthelmintic [1,2], anti- tuberculosis [3], , anti-inflammatory [4,5,6] , anticancer [7,8,9, 17] antiproliferative [10,16], antimalarial [11] hypoglycemic[12,13,14] antioxidant [15,16] anti-bacterial [17] , and antiviral [18,19,20] properties. The literature survey had demonstrated that benzothiazole derivatives are very reactive, so it has been utilized for development of Nitrogen containing mixes. Furthermore, benzothiazole can be found in a variety of natural goods, metabolic products of fungus and primitive marine creatures etc. Because of their importance in industry, agriculture, and biological activity, In this study, It was aimed to synthesize novel compounds bearing 3 benzothiazole derivatives as a backbone that had anthelmintic activities. Mechanisms of activity were aimed to be revealed by docking studies. Herein, we describe the successful design and synthesis of five new compounds commonly known as 3- Benzothiazole derivatives. These derivatives (B3,B10,B13,B14,B15) were fully characterized by FTIR, ^{1}H NMR ^{13}C NMR and mass spectra . All reported compounds were evaluated for their anthelmintic activity . These compounds will be further evaluated computationally for their

ADMET (*Absorption,distribution, Metabolism, Excretion and Toxicity*) profile. The scaffolds which show good interaction with the target and ADMET profiles will be taken up as the lead molecule for further synthesis.

1. EXPERIMENT SECTION:

MATERIALS AND METHODS:

All the chemicals utilized in this study were obtained from vasa chemicals Malleshwaram, Bangalore. FTIR spectra were recorded on ABB Bomem FTLA 2000-102 FTIR instrument involving KBr pellets in the 400-4000 cm-1. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300 (300 MHz) and Bruker 600MHz. The compound relocations are given in parts per million (ppm) involving TMS as interior norm at 300 and 75 MHz separately.

GENERAL PROCEDURE FOR THE SYNTHESIS OF BENZOTHIAZOLE DERIVATIVES:

The scaffolds (B3, B10, B13, B14, and B15) that exhibit good insilico docking findings were created and their FT-IR, $^{1}HNMR$, ^{13}C NMR, and mass spectra were analyzed.

Additionally, the substance's anthelmintic action has been examined. Compound A was created by heating (300-350 W) an equimolar combination of benzothiazole, acetaldehyde, and acetamide (1mmol) in a microwave 10-15 minutes. Equimolar amounts of primary amines (Tab-01) (1.0mmol) and formaldehyde (1.05 mmol) in ethanol (3 ml) were introduced to a pyrex reaction tank along with compound A(1.1mmol). After that, the reaction vessel was put inside the Emrys Optimizer and heated to 80°C using a microwave for 15 minutes.

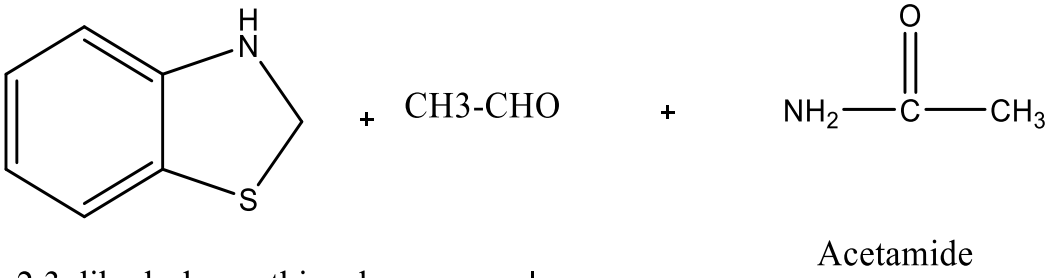
After the reaction mixture had cooled to room temperature, it was quenched with 15 ml of water. Ethyl acetate was used to remove the reaction mixture's raw materials. In order to obtain the pure product, the combined general experimental approach organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and refined by column chromatography on silica gel using petroleum ether/ethyl acetate. Melting point and TLC (n-hexane: ethyl acetate in a 7:3 ratio) were used to complete the reaction.

2. BIOLOGICAL ACTIVITY:

Healthy adult Indian earthworm (*P. posthuma*; Annelida; Megascolecidae) were collected from Microbial Resources Division, Gandhi Krushi VijnanaKendra (GKVK), Government of Karnataka, Bengaluru. Earthworms in moist soil were washed with normal saline and used for the study. The earthworms 3-5 cm in length and 0.1-0.2 cm width were used due to its anatomical and physiological resemblance with the

intestinalroundworm parasites of human beings.

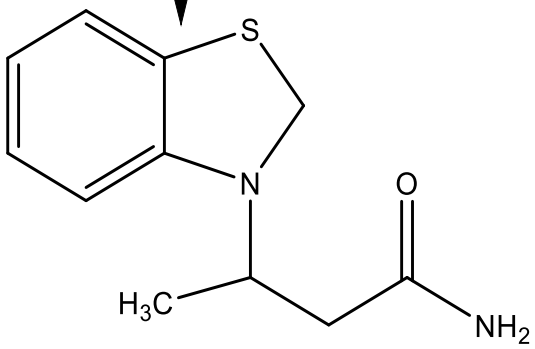
3.SCHEME:



2,3 dihydrobenzothiazole

Acetamide

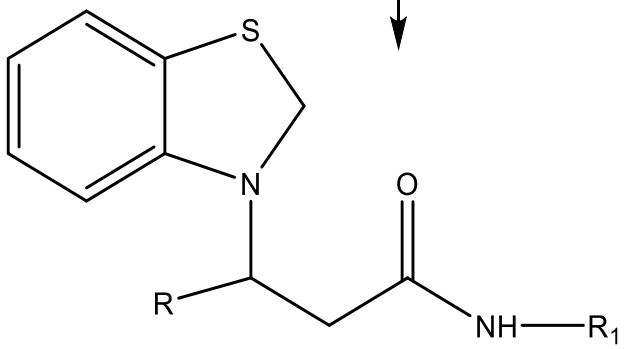
Ethanol



3-(benzo[*d*]thiazol-3(2*H*)-yl)butanamide

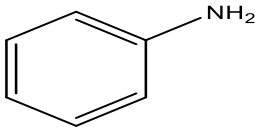
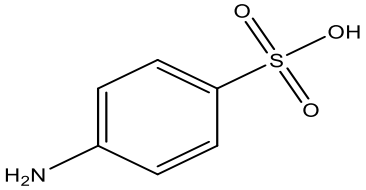
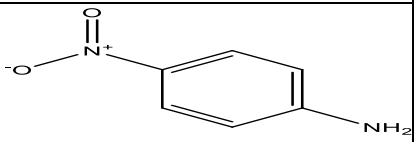
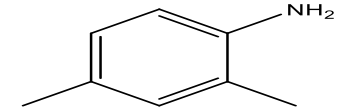
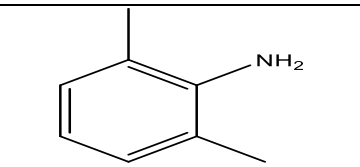
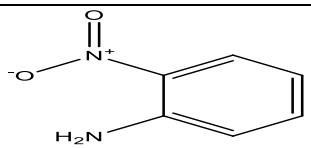
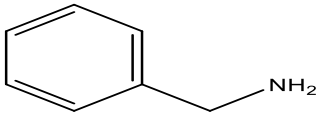
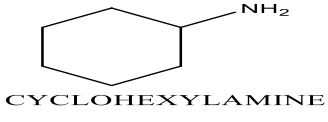
COMPOUND A

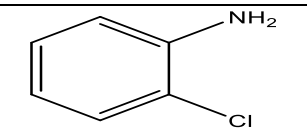
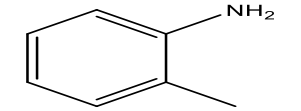
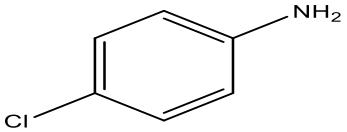
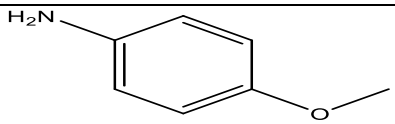
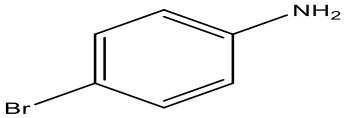
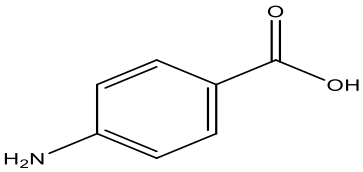
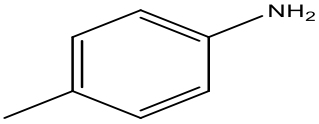
formaldehyde/amines



COMPOUND B(1-15)

Table-01 List of aromatic primary amines used in the synthesis

Sl No	Compounds	R1	structure
1	B1	Aniline	 ANILINE
2	B2	Sulphanilic acid	 SULPHANILIC ACID
3	B3	Para nitro aniline	 PARA-NITRO ANILINE
4	B4	2.4 Dimethyl aniline	 2,4,DIMETHYL ANILINE
5	B5	2,6 Dimethyl aniline	 2,6,DIMETHYL ANILINE
6	B6	2-nitro aniline	 2-NITRO ANILINE
7	B7	Benzyl amine	 benzyl amine
8	B8	Cyclohexyl amine	 CYCLOHEXYLAMINE

9	B9	2-Chloro aniline	 2-CHLORO ANILINE
10	B10	o-toludine	 ORTHO-TOLUIDINE
11	B11	4-chloro aniline	 4-CHLORO ANILINE
12	B12	Para anisidine	 PARA ANISIDINE
13	B13	4-Bromo aniline	 4-bromo aniline
14	B14	4-Amino benzoic acid	 4-AMINO BENZOIC ACID
15	B15	p -toludine	 PARA-TOLUIDINE

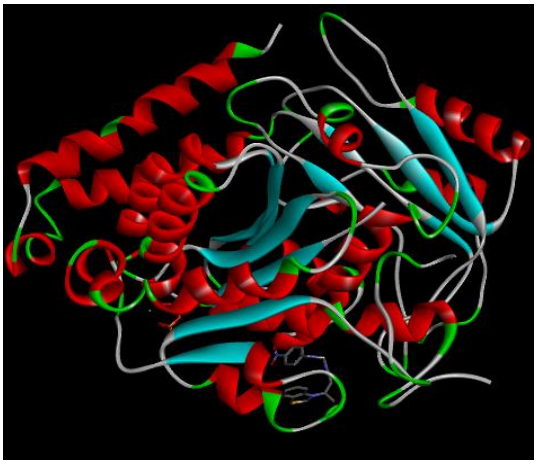
4.MOLECULAR DOCKING [21,22,23,24]

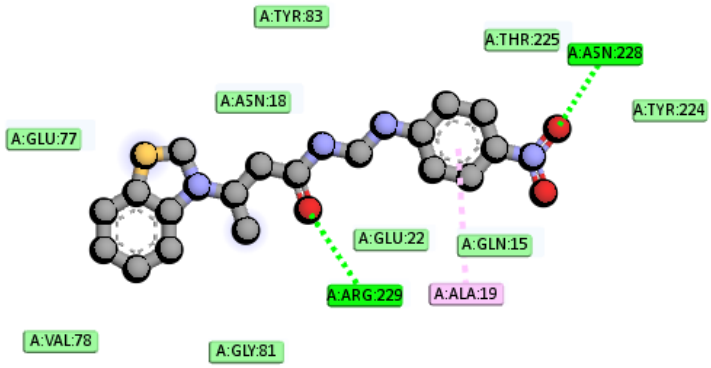
A library of compounds having potent activities in their structure will be generatedon the computer and evaluated for their rigid/flexible docking with key enzyme tubulin – colchicine.The benzothiazole derivatives were designed and the structure was analyzed using ChemDraw Ultra 6.0. 3D co-ordinates were prepared using PRODRUG server. Theprotein structure file (1SA0 for tubulin) was taken from PDB (www.rcsb.org/pdb) Different substituted with heterocyclic rings will be subjected to docking studies to

analyze the ligand target interaction..Suitable poses and binding interactions for specific protein/ receptor sites will be studied by the use of drug design software *discovery studio*. Before the docking analysis, ligands were prepared from the optimized Compounds and saved in pdb file format using spartan,14 .The 3D Compound of tubulin – colchicine was downloaded from the protein bank (with pdb (ID:1SAO).The enzyme was prepared with help of discovery studio visualizer for the docking analysis.in the course of the preparation, hydrogen was added. water molecule, heteroatoms and co-ligands were eliminated from the crystal Compound saved in pbd file. The docking of the ligands to the active site of rhodoquinone was achieved with the help of pyrex soft ware using Autodock vina. After successful docking protocol, reformation of the complexes (ligand-receptor) for further investigation was also achieved utilizing chimera software. Discovery studio visualizer and pyMOL were used to investigate the interactions of the complexes

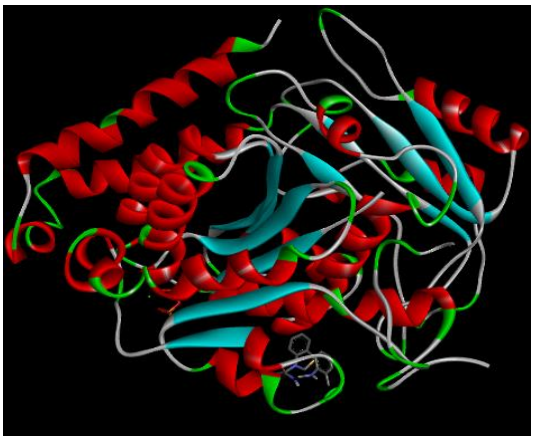
Table -02 DOCKING AND GLIDE SCORE OF 1SAO(B1-B15)

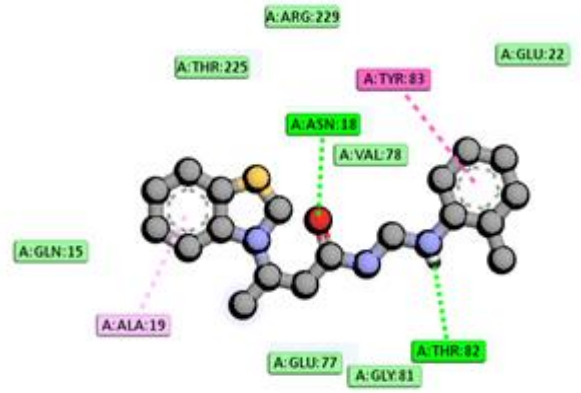
Sl. No	Compounds	(PDB id: 1SAO)	Interaction of amino acids
1.	Compound B1	-5.9	Tyr,Glu,Arg,Asn
2.	Compound B2	-5.9	Asp.Gln,Val,Asn
3.	Compound B3	-6.4	Asn,Arg,Ala
4.	Compound B4	-5.6	Val,Tyr,Ala,Asn
5.	Compound B5	-5.6	Glu,Asn,Gly
6.	Compound B6	-4.6	Ala,Asn,Glu
7.	Compound B7	-5.7	Thr,Asn,Ala
8.	Compound B8	-5.6	Val,Thr,Pro,Cys
9.	Compound B9	-4.9	Glu,Arg,Tyr,Asn
10.	Compound B10	-6.3	Asn,Tyr,Thr
11.	Compound B11	-5.3	Arg,Asn,Glu
12.	Compound B12	-5.8	Arg,Asn,Tyr,Ala
13.	Compound B13	-6.7	pro ,Leu,Tyr,Ala,Thr
14.	Compound B14	-6.9	Ala,Glu,Arg,Asn
15.	Compound B15	-6.5	Thr,Tyr,Arg,Leu,pro,Ala



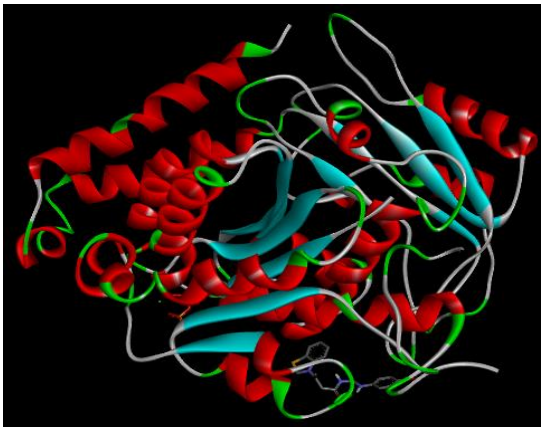


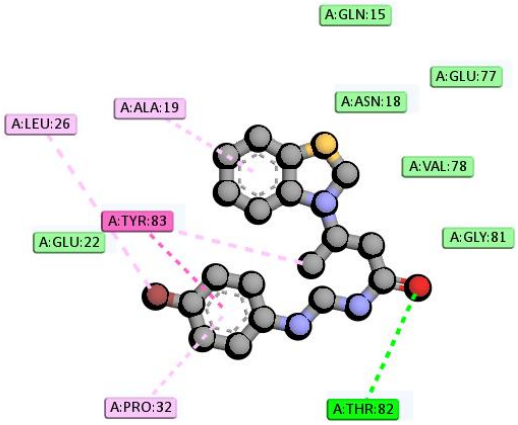
COMPOUND B3



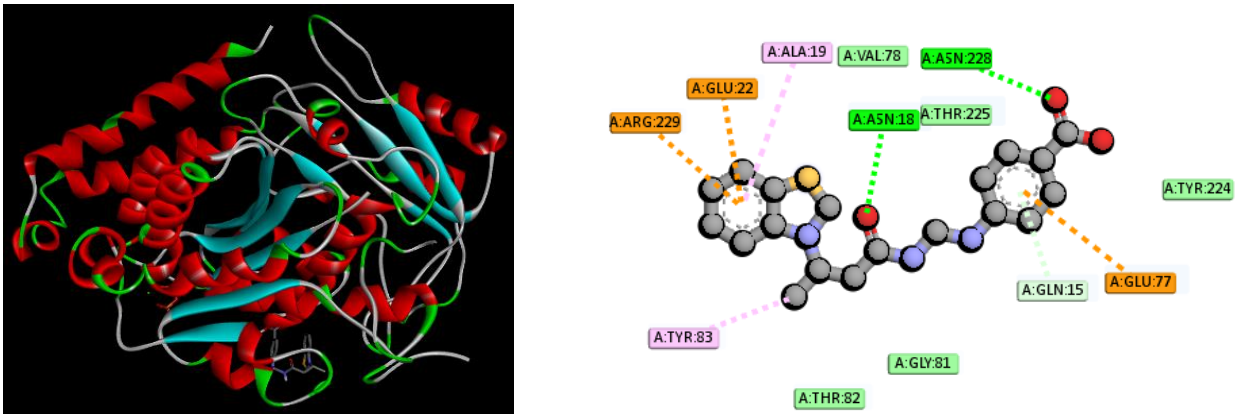


COMPOUND B10

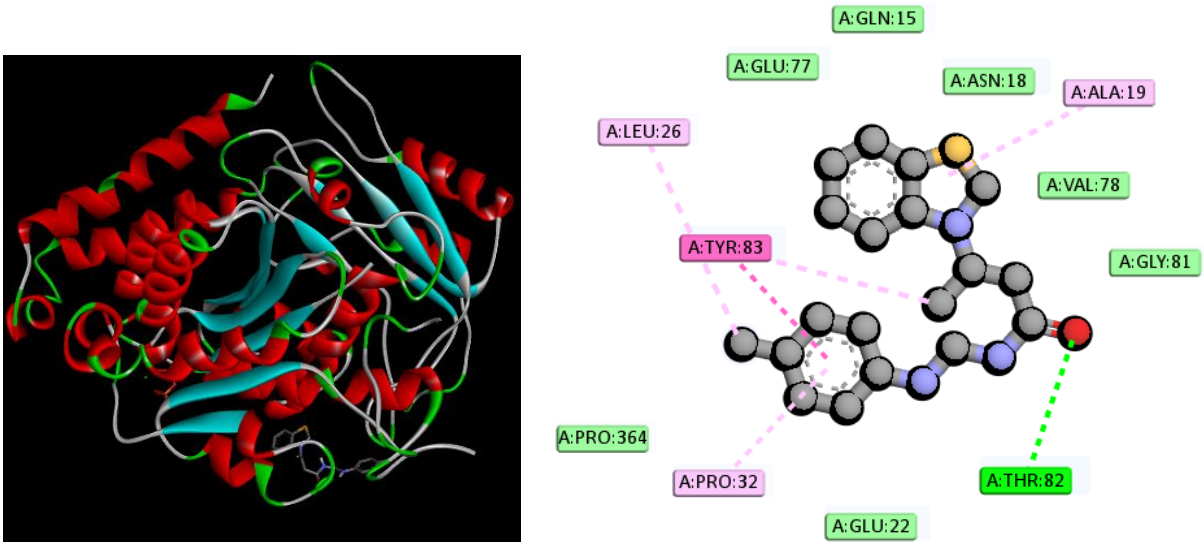




COMPOUND B13



COMPOUND B14



COMPOUND B15

5. RESULT AND DISCUSSION: The synthesized compounds were structurally elucidated using FTIR ,^{1}H NMR, ^{13}C NMR and MASS. The spectral details of the synthesized compounds were given below.

3-(benzo[d]thiazole − 3(2H) − yl)N − (((4 − nitrophenyl)amino)methyl)butanamide:

(Compound B3)

Yellow colour, M.P 142ºC ,Yield 83%,Mol Formula: $C_{18}H_{20}N_4O_3S$, Mol Wt: 372.4, Elemental Analysis C,58.05;H,5.41:N,15.04;O,12.89;S8.61 . FTIR (KBR,cm^{-1}) 1655, 1550 and 1350 cm-1. ^{1}H NMR(500.13MHz,CDCl3, δ, ppm) (NH) 6.94 (CH2) 4.85,(CH)6.63 , ^{13}C NMR (100.61MHz,CDCl3, δ, ppm) (CH2)51.2,(CH)135.7(C)136.3, *m/z* 372.13. (BASE PEAK) 373.13, 374.12

3-(benzo[d]thiazole − 3(2H) − yl)N − ((O − tolylamino)methyl)butanamide:

(Compound B10)

Whitish yellow colour, M.P .158ºC ,Yield 81%, Mol Formula: $C_{19}H_{23}N_3OS$, Mol Wt: 341.16, Elemental Analysis C,66.83;H,6.79:N,12.31;O,4.69,S;9.39 FTIR(KBR,cm^{-1}) 1680, 3000,3050 cm-1 ^{1}HNMR, (500.13 MHz,CDCl3, δ, ppm) (NH) 5.80 (CH2) 4.85, (CH) 7.05 ^{13}C NMR, (100.61MHz,CDCl3, δ, ppm) (CH2) 51.2 (C) 125.1 (CH) 135.7, *m/z* 341.16(BASE PEAK) 342.16,343.15.

3-(benzo[d]thiazole − 3(2H) − yl)N − (((4 − Bromophenyl)amino)methyl)butanamide:

(Compound B13)

Slight Yellow crystals, M.P .180ºC ,Yield 88%, Mol Formula: $C_{18}H_{20}BrN_3OS$, Mol Wt: 405.05, Elemental Analysis C,53.21;H,4.96:N,19.66;O,3.94;S,7.89, FTIR (KBR,cm^{-1}) 1697, 1075 cm-1 ^{1}HNMR, (500.13MHz,CDCl3, δ, ppm) (NH) 6.34 (CH_2) 4.85, (CH) 7.05 (CH_3) 1.24 ^{13}C NMR, (100.61MHz,CDCl3, δ, ppm) (CH_2) 51.2 (C) 125.1,(C) In benzene 151.7 (CH) 135.7 Benzene , *m/z* 401.2(BASE PEAK) 407.05, 408.05

4-(((3-(benzo[d]thiazole − 3(2H) − yl)butanamide)methyl)amino)benzoic acid:

(Compound B14)

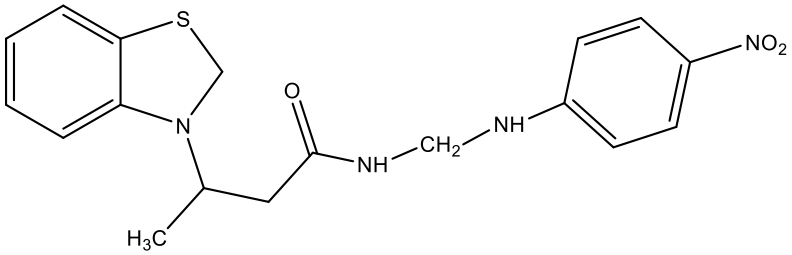
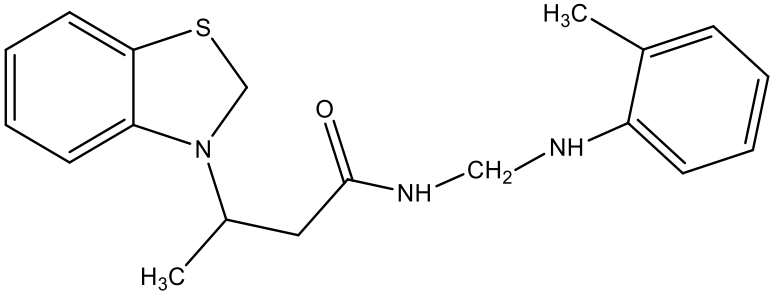
Yellow crystals, M.P .198ºC ,Yield 84%, Mol Formula: $C_{19}H_{21}N_3O_3S$, Mol Wt: 371.13, Elemental Analysis C,61.44;H,5.70:N,11.31; O,12.92,S;12.63. FTIR(KBR,cm^{-1}) 1655, 2500,3500 cm^{-1}, ^{1}HNMR, (500.13MHz,CDCl3, δ, ppm) (OH) 12.71 (NH) 6.34 (CH_2) 4.85, (CH_2) methylene 4.85 (CH) 7.05 ^{13}C NMR, (100.61MHz,CDCl3, δ, ppm) (CH_2) 51.2 (C) 125.1, (CH) 135.7 Benzene , *m/z* 371.13(BASE PEAK) 372.13, 373.13.

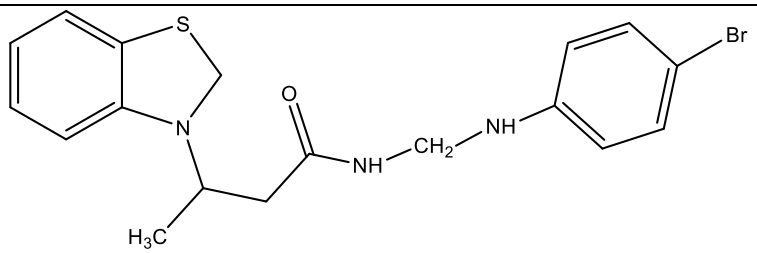
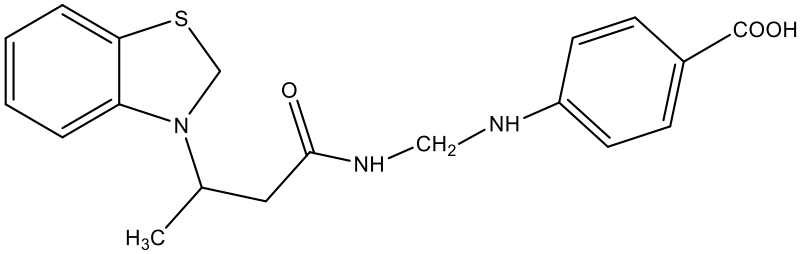
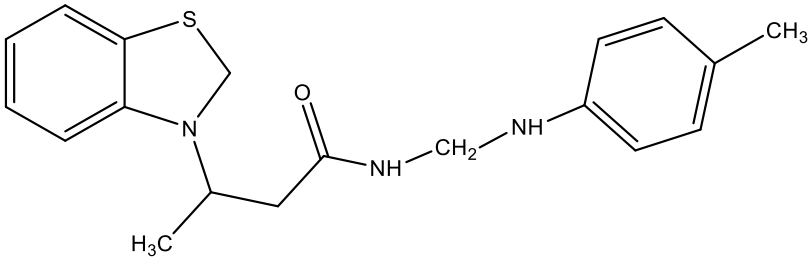
3-(benzo[d]thiazole − 3(2H) − yl)N − ((p − tolylamino)methyl)butanamide:

(Compound B15)

Yellowish brown, M.P .190ºC ,Yield 85%, Mol Formula: $C_{19}H_{23}N_3OS$, Mol Wt: 341.47, Elemental Analysis C,66.83;H,6.79:N,12.31;O,4.69;S,9.39, IR(KBR,cm^{-1}) 1695, 3000,3050 cm^{-1}, ^{1}HNMR, (500.13MHz,CDCl3, δ, ppm) (NH) 6.34 (CH_2) 4.85, (CH_2) methylene(CH) 4.85 (CH_3) 1.24 ^{13}C NMR, (100.61MHz,CDCl3, δ, ppm), (CH_2) 51.2 (C) 125.1, (CH) 135.7, *m/z* 341.16(BASE PEAK) 342.16,343.15.

TABLE 03-SYNTHESIZED COMPOUNDS:

Comp	Structures	Reaction time(Min)	Yield(%	M.P (ºC)
B 3	 3-(benzo[*d*]thiazol-3(2*H*)-yl)-*N*-(((4-nitrophenyl)amino)methyl)butanamide	15min	83	142
B10	 3-(benzo[*d*]thiazol-3(2*H*)-yl)-*N*-((*o*-tolylamino)methyl)butanamide	14min	81	158

B13	 3-(benzo[*d*]thiazol-3(2*H*)-yl)-*N*-(((4-bromophenyl)amino)methyl)butanamide	15min	88	180
B14	 4-(((3-(benzo[*d*]thiazol-3(2*H*)-yl)butanamido)methyl)amino)benzoic acid	14min	84	198
B15	 3-(benzo[*d*]thiazol-3(2*H*)-yl)-*N*-((*p*-tolylamino)methyl)butanamide	15min	85	190

6. IN VITRO ANTHELMINTIC ACTIVITY:

The benzothiazole derivatives was suspended in Tween 80 (0.1 %) in normal saline at concentration of 30mg/ml, 60mg/ml , 80mg/ml & 100mg/ml was used to examine the time of paralysis (Pt) and Death (Dt). The selected earthworms are categorized into 11 groups of 6 each viz., control group treated with 2% Tween 80 in distilled water, 9 Test groups treated with concentrations of 30mg/ml, 60mg/ml , 80mg/ml& 100mg/ml of each benzothiazole derivatives and standard group treated with 10mg/ml concentration of Albendazole as standard. Earthworms are treated with volume of 10ml of each concentration of standard, controland test solutions respectively. The time taken for Paralysis (Pt) and

Death (Dt) was noted. Observations were made for the time (in minutes) taken to paralysis and death of individual worms up to 4 h of the test period. Paralysis was said to occur when the wormsdid not revive even in normal saline. Death was concluded when the worms lost their motility followed by fading away of their body color.

Table-04 Anthelmintic Activity

Conc (Mg/ml)	Comp B3		Comp B10		Comp B13		Comp B14		Comp B15		Std drug ALBENDAZOLE	
	Paralysis(mean±SD) (Min)	Death (mean±SD) (Min)	Paralysis(mean ±SD) (Min)	Death (mean±SD) (Min)	Paralysis (mean±SD) (Min)	Death (mean±S D) (Min)	Paralysis (mean±SD) (Min)	Death(mean±SD) (Min)	Paralysis(mean±SD) (Min)	Death (mean±SD) (Min)	Paralysis(mean ±SD) (Min)	Death(mean±SD) (Min)
30	6.19±0.13	13.74±0.66	2.06± 0.09	4.28± 0.12	7.77± 0.42	12.92±1.27	7.22± 0.22	3.12±0.11	2.06± 0.09	4.38± 0.19	15.2± 0.58	34.18± 0.83
60	5.40±0.02	13.53 ±0.66	1.52± 0.12	3.12± 0.11	7.22± 0.22	13.2± 1.31	11.66 ±1.42	3.64±0.11	1.54± 0.18	4.12± 0.11	14.11± 0.50	33.10± 0.97
80	5.02±0.21	11.66±1.42	1.29. ± 0.40	3.84± 0.11	6.62± 0.13	11.32±0.32	3.84± 0.11	1.52±0.12	1.49± 0.43	3.64±0.11	14.24± 0.14	27.8±0.71
100	4.72±0.09	10.06±1.52	1.27± 0.42	3.26± 0.19	6.08± 0.22	10.28±0.11	1.49±0.43	6.08±0.22	1.27± 0.42	2.84±0.11	15.16±0.09	27.18± 0.54

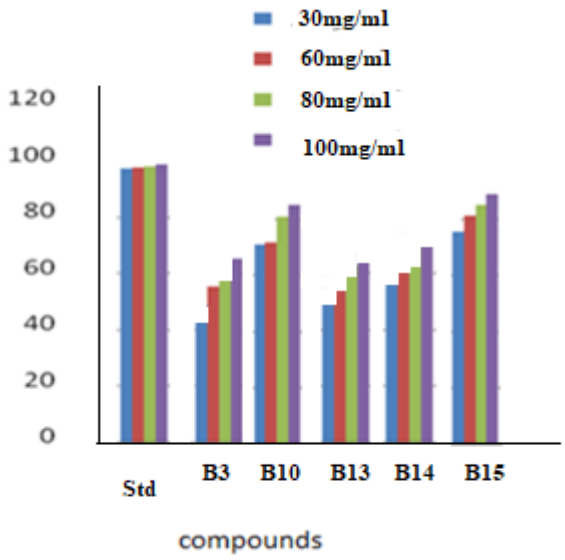


Table-05 ADMET STUDIES:

Molecules	MW	HBD	HBA	QPlog Po/W	GI absorbtion	% Human Oral Absorption	Rule of Five
Acceptable range	130.0 - 725.0	0 - 6	2 - 20	-2.0 – 1.2	High/Low	> 80% is high	Maximum is 4
Compound B1	327.44 g/mol	2	1	-5.15 cm/s	High	69.67	0
Compound B2	407.51 g/mol	3	4	-6.53 cm/s	High	132.42	0
Compound B3	372.44 g/mol	2	3	-5.54 cm/s	High	115.49	0
Compound B4	355.50 g/mol	2	1	-4.80 cm/s	High	69.67	0
Compound B5	355.50 g/mol	2	1	-4.80 cm/s	High	69.67	0
Compound B6	372.44 g/mol	2	3	-5.54 cm/s	High	115.49	0
Compound B7	341.47 g/mol	2	2	-6.06 cm/s	High	69.67	0
Compound B8	333.49 g/mol	2	2	-5.39 cm/s	High	69.67	0
Compound B9	361.89 g/mol	2	1	-4.91 cm/s	High	69.67	0
Compound B10	341.47 g/mol	2	1	-4.97 cm/s	High	69.67	0
Compound B11	361.89 g/mol	2	1	-4.91 cm/s	High	69.67	0

Compound B12	357.47 g/mol	2	2	-5.35 cm/s	High	78.90	0
Compound B13	406.34 g/mol	2	1	-5.14 cm/s	High	69.67	0
Compound B14	371.45 g/mol	3	3	-5.75 cm/s	High	371.45 g/mol	0
Compound B15	341.47 g/mol	2	1	-4.97 cm/s	High	69.67	0

7. RESULT AND DISCUSSION:

All the synthesized compounds (B3,B10,B13,B14,B15) were evaluated for their anthelmintic activities . Here, we summarized the current state of research on the docking and synthesizing new molecule. The main aim of this study is to docking of different derivatives and highest score has been synthesized. The synthesized molecule has been characterized and anthelmintic studies has been carried out. the compound B10 and B15 in concentration 30,60,80 and 100mg/ml showed paralysis of worms within 1 and 2 min and death within 3 and 4 min depending on the concentration. More time was taken by compound B3,B13,B14 concentrations 30,60,80, and 100mg/ml, showed paralysis of worms within 6 to 7 min and death within 10 to 12 min.(Tab-04)

8. CONCLUSION:

According to data obtained from the present study, benzothiazole derivatives were found to be an effective invitro anthelmintic activity .we compared to standard anthelmintic compounds such as Albendazole respectively. The results showed that the methyl substituted in 2^{nd} and 3^{rd} position imparted more anthelmintic activity, more over nitro, bromo and acid function group shows no significant activity. Based on the discussion above, these Benzothiazole analogs could be considered as useful templates for further development to obtain more potent anthelmintic activity. Benzothiazole derivatives could be very useful for the virtual screening in the development of anticancer agents.

9. REFERENCES:

1. Rajareddy A, Srinivas Murthy M. Synthesis, characterization, and anthelmintic activity of novel benzothiazole derivatives containing indole moieties. Asian J Pharm Clin Res. 2019;12(3):321-5.
2. Jayachandran E, Jagtap VA, Sreenivasa GM. Anthelmintic activity of newly synthesized moieties of fluoro benzothiazole Schiff's bases. Research Journalof Pharmaceutical, Biological and Chemical Sciences. 2011;2(1):510-5.
3. Bhat M, Belagali SL. Synthesis, In-Vitro and In-Silico Studies of Benzothiazole Azo-Ester Derivatives as Anti-TB Agents. Anti-Infective Agents. 2020 Mar 1;18(1):15-23.
4. Kumar A, Shakya AK, Siddiqui HH. Synthesis and anti-inflammatory activity of some novel 2-aminobenzothiazole derivatives. Indian J Heterocycl Chem. 2016 Jan 1;25:243-49.
5. Verma AK, Martin A, Singh Sr AK. Synthesis, Characterization and evaluation of Anti-inflammatory and Analgesic activity of Benzothiazole derivatives. Indian Journal of Pharmaceutical and Biological Research. 2014 Jul 1;2(3):84.
6. Pattan SR, Pujar VD, Dighe NS, Musmade DS, Hiremath SN, Shinde HV, Laware RB. Synthesis and anti-inflammatory activity of 2-amino substituted benzothiazoles. Asian Journal of Research in Chemistry. 2010;3(1):113-5.
7. Deepthy C, Pappachen LK, Prathap M, Miao JS, Jilsha G. In silico drug design andmolecular docking studies of some novel benzothiazole derivatives as anti-cancer and anti-inflammatory agents. Int J Pharm Pharm Sci. 2014;6(2):203-8.
8. Pappachen LK, Zachariah SM, Chandran D. Insilico design, synthesis and characterization of some novel benzothiazole derivatives as anti-cancer agents. Asian Journal of Pharmaceutical and Clinical Research. 2017 Apr 1:150-5.
9. Havrylyuk D, Mosula L, Zimenkovsky B, Vasylenko O, Gzella A, Lesyk R. Synthesis and anticancer activity evaluation of 4-thiazolidinones containing benzothiazole moiety. European Journal of Medicinal Chemistry. 2010 Nov 1;45(11):5012-21.
10. Ćaleta I, Grdiša M, Mrvoš-Sermek D, Cetina M, Tralić-Kulenović V, Pavelić K, Karminski-Zamola G. Synthesis, crystal structure and antiproliferative evaluation of some new substituted benzothiazoles and styrylbenzothiazoles. Il Farmaco. 2004 Apr 1;59(4):297-305.
11. Thakkar SS, Thakor P, Ray A, Doshi H, Thakkar VR. Benzothiazole analogues: Synthesis,

characterization, MO calculations with PM6 and DFT, in silico studies and in vitro antimalarial as DHFR inhibitors and antimicrobial activities. Bioorganic & Medicinal Chemistry. 2017 Oct 15;25(20):5396-406.

12. Meltzer-Mats E, Babai-Shani G, Pasternak L, Uritsky N, Getter T, Viskind O, Eckel J, Cerasi E, Senderowitz H, Sasson S, Gruzman A. Synthesis and mechanism of hypoglycemic activity of benzothiazole derivatives. Journal of medicinal chemistry. 2013 Jul 11;56(13):5335-50.
13. Mariappan G, Prabhat P, Sutharson L, Banerjee J, Patangia U, Nath S. Synthesis and antidiabetic evaluation of benzothiazole derivatives. Journal of the Korean Chemical Society. 2012;56(2):251-6.
14. Ullah S, Mirza S, Salar U, Hussain S, Javaid K, Khan KM, Khalil R, Ul-Haq Z, Perveen S, Choudhary MI. 2-Mercapto benzothiazole derivatives: As potential leads for the diabetic management. Medicinal Chemistry. 2020 Sep 1;16(6):826-40.
15. Djuidje EN, Barbari R, Baldisserotto A, Durini E, Sciabica S, Balzarini J, Liekens S, Vertuani S, Manfredini S. benzothiazole derivatives as multifunctional antioxidant agents for skin damage: Structure–activity relationship of a scaffold bearing a five-membered ring system. Antioxidants. 2022 Feb 17;11(2):407.
16. Barbari R, Tupini C, Durini E, Gallerani E, Nicoli F, Lampronti I, Baldisserotto A, Manfredini S. Design, Synthesis and Evaluation of New Multifunctional Benzothiazoles as Photoprotective, Antioxidant and Antiproliferative Agents. Molecules. 2022 Dec 29;28(1):287.
17. Racané L, Ptiček L, Fajdetić G, Tralić-Kulenović V, Klobučar M, Pavelić SK, Perić M, Paljetak HČ, Verbanac D, Starčević K. Green synthesis and biological evaluation of 6-substituted-2-(2-hydroxy/methoxy phenyl) benzothiazole derivatives as potential antioxidant, antibacterial and antitumor agents. Bioorganic chemistry. 2020 Jan 1;95:103537.
18. Azzam RA, Osman RR, Elgemeie GH. Efficient synthesis and docking studies of novel benzothiazole-based pyrimidinesulfonamide scaffolds as new antiviral agents and Hsp90α inhibitors. ACS omega. 2020 Jan 9;5(3):1640-55.
19. Ke S, Wei Y, Yang Z, Wang K, Liang Y, Shi L. Novel cycloalkylthiophene–imine derivatives bearing benzothiazole scaffold: Synthesis, characterization and antiviral activity evaluation. Bioorganic & medicinal chemistry letters. 2013 Sep 15;23(18):5131-4.
20. Asiri YI, Alsayari A, Muhsinah AB, Mabkhot YN, Hassan MZ. Benzothiazoles as potential antiviral agents. Journal of Pharmacy and Pharmacology. 2020 Nov;72(11):1459-80.

21. Morsy MA, Ali EM, Kandeel M, Venugopala KN, Nair AB, Greish K, El-Daly M. Screening and molecular docking of novel benzothiazole derivatives as potential antimicrobial agents. Antibiotics. 2020 Apr 29;9(5):221.
22. Anuse DG, Mali SN, Thorat BR, Yamgar RS, Chaudhari HK. Synthesis, SAR, in silico appraisal and anti-microbial study of substituted 2-aminobenzothiazoles derivatives. Current Computer-Aided Drug Design. 2020 Dec 1;16(6):802-13.
23. Luo B, Li D, Zhang AL, Gao JM. Synthesis, antifungal activities and molecular docking studies of benzoxazole and benzothiazole derivatives. Molecules. 2018 Sep 25;23(10):2457.
24. Ugwu DI, Okoro UC, Ukoha PO, Gupta A, Okafor SN. Novel anti-inflammatory and analgesic agents: synthesis, molecular docking and in vivo studies. Journal of enzyme inhibition and medicinal chemistry. 2018 Jan 1;33(1):405-15.