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## Benzothiazole Derivatives as Potential Antimalarial Drug

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### ABSTRACT

*Plasmodium berghei* is transmitted by *Anopheles* mosquitoes and it infects the liver after being injected into the bloodstream by a bite of an infected female mosquito. We have reported the synthesis of benzothiazole derivatives (compound 3a-b) by condensing 2-aminothiophenol with different aromatic aldehydes in polyethylene glycol-400 and the progress of the reaction was monitored using thin-layer chromatography, with dichloromethane and n-hexane used as a developing solvent in the ratio of 2:1. The synthesized compound was characterized by <sup>13</sup>C-Nuclear Magnetic Resonance and <sup>1</sup>H- Nuclear Magnetic Resonance. The acute toxicity of the synthesized compound was evaluated and found to be less

toxic. The antimalarial activity of the compound was also studied in-vitro using albino mice and the result showed that the compound has significant antimalarial activity against *Plasmodium berghei*.

**Keywords:** Synthesis; Benzothiazole; Haematological assay; Antimalarial; Parasitama

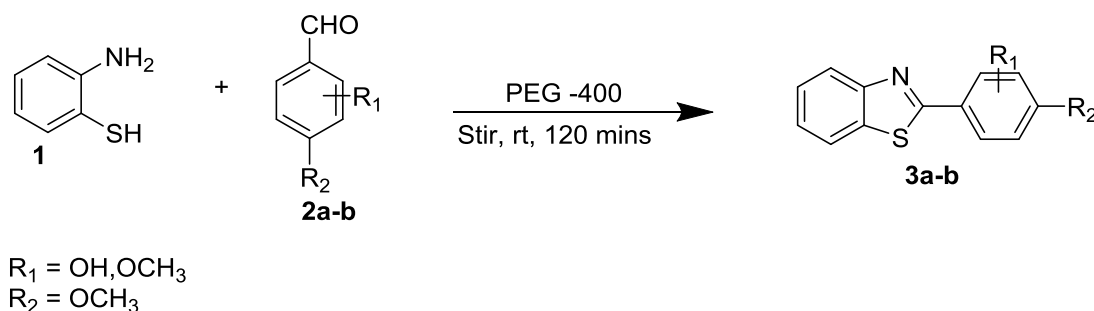
## INTRODUCTION

Malaria is one of the dangerous diseases in the world, as well as a major cause of morbidity and mortality in people living in tropical countries [1]. It is a life-threatening disease caused by *Plasmodium* species parasites transmitted to humans through infectious bites of female *Anopheles* mosquitoes [2]. Malaria is endemic in more than 90 countries, affecting approximately 40% of the world's population [3]. Malaria remains one of the major public health problems and a major cause of illness, hospitalizations, and deaths in Nigeria. Research shows that Nigeria is a malaria-endemic area where 97% of the Nigerian population is at risk of contracting malaria [4-7]. Several antimalarial drugs have been synthesized for the treatment and prevention of the disease but the development of resistance by the parasites has led to the inefficiency of some of these drugs. Therefore, it is essential to find novel antimalarial drug which has high pharmacological effectiveness instead of what is obtainable presently. Benzo-thiazoles analogues are of interest due to their potential activity against malarial and microbial infections [8].

Benzothiazole are classes of organic compound characterized with the basic skeleton (C<sub>7</sub>H<sub>5</sub>NS). They belong to the family of bicyclic heterocyclic compounds having benzene nucleus fused with five-membered ring comprising nitrogen and sulfur atoms. 2-substituted benzothiazole has emerge in its usage as a core structure in the diversified therapeutically applications. The study of structure-activity relationship interestingly reveals that change of the structure of substituent group at C-2 position commonly results to change of its bioactivity [9]. Benzothiazole and their Schiff bases are very important biological compound with reference to various biological activities such as antimicrobial [10-14], anticancer [15-18], anti-helminthic [19], anti-diabetic activities [20], anti-tubercular [21-22], anti-malaria [23], anticonvulsant [24-25], analgesic [26], anti-inflammatory [27], antitumor [28] anti-viral [29-30], anti-oxidant [31], anti-glutamate and anti-parkinsonism [32], muscle relaxant activities [33], neuroprotective [34], inhibitors of several enzymes [35]. With increase in the number of malaria cases recorded worldwide, especially in Africa, and due to the resistance of these parasites to malaria drugs, there is need to synthesize new compounds with antimalarial activity that will not only suppress the parasite but serve as a curative drug and other promising gateway to other future discoveries.

## METHODOLOGY

2-aminothiophenol (16mmol) was reacted with different benzealdehyde (16 mmol,) in polyethylene glycol-400 (20ml). The mixture was stirred using a magnetic stirrer at room temperature for 120 minutes and a solution with a yellow color was obtained. The progress of the reaction was monitored using TLC. Dichloromethane and n-hexane were used as the developing solvent in the ratio of 2:1. Upon completion of the reaction, the mixture was poured into ice and then extracted with 50ml of diethyl ether. The mixture was poured into a separating funnel and shook for proper extraction and then the two phases were separated. The ethereal extracted was collected in a beaker and heated to obtain the crude product which was purified by recrystallization using ethanol as solvent.



**Scheme 1: General synthetic approach of the benzothiazole derivatives**

**Determination of Acute toxicity of benzothiazole derivatives (3a-b)**

The oral acute toxicity of the Benzothiazole derivatives was estimated in albino mice as described by Lorke (1983).

A total of 12 mice weighing (12.89 – 17.94 g) were used for the study. The experiment was conducted in two phases. The first phase was for 10, 100 and 1000 mg/kg while the second phase was for 1600, 2900, and 5000 mg/kg orally administered. The animals were starved for 18 hours before administration of the test sample. In the first phase, three groups of three (3) animals each received 10, 100, and 1000 mg/kg respectively. The animals were monitored for 24 hours for behavioral changes and death. None of the animal died in the first groups. So, the second phase was introduced. The animals for each group received 1600, 2900, and 5000 mg/kg respectively and were monitored as in the first phase.

**Determination of Antimalarial activity of benzothiazole derivatives (3a-b)**

*Plasmodium berghei* was used to test for the antimalarial activity of benzothiazole derivatives (3a-b). The parasites were sustained through weekly blood passage from infected mice to uninfected mice kept in the laboratory.

A total of 20 mice weighing between 11.77- 14.37 g were used for the study.

The animals were fed with standard rats' chow and tap water. The 20 mice were grouped into four groups of five (5) animals each. Group A and B are for the test sample, received 200 and 400 mg/kg respectively. Groups C and D were for the positive control (Standard drugs- Artemether & Lumefantrine 4 mg/kg) and negative control (water) respectively.

Their blood samples were collected at this stage and the hematological indices (HB, RBC and PCV) were analyzed to obtain their baseline values. All the animals were passaged with *Plasmodium berghei* and left for 72 hours for the development of a full malarial parasite load. At the end of the 72 hours, their blood samples were collected. An EDTA bottle containing EDTA was used to store the blood sample for various hematological assays.

After 72 hours, drug administration started. The mice in groups A & B received 200 mg/kg and 400 mg/kg of compound (3a-b) respectively while groups C and D received 4 mg/kg of (Artemether & Lumefantrine) and (water) respectively daily for 3 days. On day four, their blood samples were collected and analyzed for the effectiveness of the treatment.

**Collection of the Blood samples**

The blood samples were collected in two different ways for the experiment. Inserting a heparinized hematocrit capillary tube through the retro-plexus vein (ocular puncture) of the rats and collecting the blood samples into a bottle containing EDTA. Cutting the tips of the rat tails with sharp scissors and collecting their blood samples on a slide.

**Determination of Parasitemia count of the blood samples**

A thin blood film was prepared with the blood obtained from the rats' tails, fixed with methanol, air-dried, and stained with Giemsa. The stain was washed with water and allowed to air dry. This was followed by viewing the slides in a microscope to count the damaged cells.

**Determination of Packed Cell Volume (PCV)**

A hematocrit capillary tube was filled with blood obtained from the retro-plexus vein by placing one of the open ends of the tube in the blood bottle and tilting it at an angle of about 30°C. One end of the filled capillary tube was sealed with a plastercine and the tube was allowed to centrifuged for 20 minutes at 300 rpm in a hematocrit centrifuge. A hematocrit reader was used to read off the length of the packed cell in percentage.

**RESULT AND DISCUSSION****Table 1:** Physiochemical properties of benzothiazole derivatives (3a-b)

Compound	R <sub>1</sub>	R <sub>2</sub>	Molecular formulae	Molecular weight(g/mol)	Melting point	% Yield	Rf value
3a	OH	OCH <sub>3</sub>	C <sub>14</sub> H <sub>11</sub> O <sub>2</sub> NS	257	156-160	84.1	0.67
3b	OCH <sub>3</sub>	OCH <sub>3</sub>	C <sub>15</sub> H <sub>13</sub> O <sub>2</sub> NS	271	118-120	69.4	0.64

**Interpretation of spectral for compound (3a-b)****<sup>1</sup>H NMR spectrum of 2-(3-hydroxyl-4-methoxyphenyl) benzothiazole (3a)**

The proton at C<sub>1</sub> is assigned the peak δ8.10, the protons at C<sub>2</sub> and C<sub>3</sub> are both assigned the peak δ8.08δ8.09 is the proton at C<sub>4</sub>, δ7.98 is assigned to the proton at C<sub>9</sub>, δ9.54 is assigned to the proton attached to the O of the hydroxyl group. The proton at C<sub>12</sub> is assigned the peak δ7.09, the proton attached to C<sub>13</sub> is assigned the peak δ7.98 and δ3.81 is assigned to the protons at C<sub>14</sub>.

**<sup>13</sup>C NMR spectrum of 2-(3-hydroxyl-4-methoxyphenyl) benzothiazole (3a)**

The four aromatic carbons, C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub> are assigned the peaks  $\delta$ 122.6, 125.5,  $\delta$ 126.1 and  $\delta$ 122.8 respectively. C<sub>5</sub> is assigned the peak  $\delta$ 134.6, C<sub>6</sub> is assigned the peak  $\delta$ 154.1, C<sub>7</sub> is assigned the peak  $\delta$ 167.74 and C<sub>8</sub> is assigned the peak  $\delta$ 126.9. The peak  $\delta$ 112.8 is assigned to C<sub>9</sub>,  $\delta$ 147.4 is assigned to C<sub>10</sub>,  $\delta$ 151.1 is assigned to C<sub>11</sub> and  $\delta$ 114.0 is assigned to C<sub>12</sub>. C<sub>13</sub> is assigned the peak  $\delta$ 119.5 and the methoxy carbon, C<sub>14</sub> is assigned the peak  $\delta$ 56.1.

#### <sup>1</sup>H NMR spectrum of 2-(2, 4-dimethoxyphenyl) benzothiazole (3b)

The proton at C<sub>1</sub> is assigned the peak  $\delta$ 8.23 the protons at C<sub>2</sub> and C<sub>3</sub> are both assigned the peak  $\delta$ 7.55,  $\delta$ 8.12 is assigned to the proton at C<sub>4</sub>,  $\delta$ 6.34 is assigned to the proton at C<sub>10</sub>,  $\delta$ 6.39 is assigned to the proton at C<sub>12</sub>. The proton at C<sub>13</sub> is assigned the peak  $\delta$ 7.26, the proton attached to the both methoxy group are assigned the peak  $\delta$ 3.73.

#### <sup>13</sup>C NMR spectrum of 2-(2, 4-dimethoxyphenyl) benzothiazole (3b)

The four aromatic carbons, C<sub>1</sub>, C<sub>2</sub>, C<sub>3</sub>, C<sub>4</sub> are assigned the peaks  $\delta$ 122.1, 125.1,  $\delta$ 125.8 and  $\delta$ 122.7 respectively. C<sub>5</sub> is assigned the peak  $\delta$ 133.9, C<sub>6</sub> is assigned the peak  $\delta$ 153.5, C<sub>7</sub> is assigned the peak  $\delta$ 171.4 and C<sub>8</sub> is assigned the peak  $\delta$ 114.4. The peak  $\delta$ 161.5 is assigned to C<sub>9</sub>,  $\delta$ 100.2 is assigned to C<sub>10</sub>,  $\delta$ 163.0 is assigned to C<sub>11</sub> and  $\delta$ 106.9 is assigned to C<sub>12</sub>. C<sub>13</sub> is assigned the peak  $\delta$ 129.0, the methoxy carbon, C<sub>14</sub> is assigned the peak  $\delta$ 56.3, and the methoxy carbon, C<sub>15</sub> is assigned the peak  $\delta$ 56.0.

#### Antimalarial and Hematological indices of the Mice induced with *Plasmodium Berghei*

##### Baseline analysis

**Table 2:** Baseline values of the hematological indices of mice

Sample	Hb	PCV	RBC
A1 200 Mg/kg	14.4500±.21794	44.7500±1.03078	44.7500±1.03078
B1 200 mg/kg	14.6250±.13769	44.5000±1.50000	4.1650±.03524
A 400 mg/kg	14.6250±.13769	43.7500±.47871	4.2075±.05907
B 400 mg/kg	14.4750±.10308	44.0000±.70711	4.1050±.08723
Art/Lum 4 mg/kg	14.5000±.12910	43.2500±.85391	4.2900±.13934
NC 10 ml/kg	14.4750±.10308	43.5000±1.25831	4.1925±.05105

There is no statistical difference between the negative control and the test sample/positive control of the haematological parameters. This analysis is to establish the baseline or the normal haematological indexes before the animal were infected with *Plasmodium berghei*

**Table 3:** After *Plasmodium* Induction analysis and values obtained after inoculation

Sample	Hb	PCV	RBC	Parasthemia count
A1 200 Mg/kg	12.35±.19365	36.25±.75000	3.5200±.13832	36.0±2.82843
B1 200 mg/kg	12.50±.24833	35.75±1.10868	3.5250±.05439	35.0±2.73861
A 400 mg/kg	12.22±.30104	36.00±1.08012	3.5425±.21336	34.5±2.72336
B 400 mg/kg	12.63±.2561	35.50±1.32288	3.5125±.11324	34.0±.70711
Art/Lum 4 mg/kg	12.580±.2	35.75±1.54785	3.7450±.08382	33.8±3.11916
NC 10 ml/kg	12.45±.22500	36.25±1.03078	3.6350±.15516	35.0±2.67706

There is no statistical difference between the negative control and the test sample/positive control of the haematological parameters. This analysis is to observe the effect of the *plasmodium* on haematological indexes before treatment ensues.

**Table 4:** After Treatment values obtained after treatment

Sample	Hb	PCV	RBC	Parasthemia count
A1 200 Mg/kg	13.95±.06455*	41.00±.91287*	4.2050±.03379*	3.5000±.86603*
B1 200 mg/kg	14.08±.13769*	41.75±1.10868*	4.1850±.07489*	3.0000±.40825*
A 400 mg/kg	12.58±.55132*	34.25±1.9311*	3.4850±.25194*	3.0000±.40825*
B 400 mg/kg	13.88±.17017*	39.50±1.55456*	4.0550±.04555*	1.7500±.25000*
Art/Lum 4 mg/kg	14.18±.08539*	41.00±.91287*	4.1025±.01887*	1.2500±.47871*
NC 10 ml/kg	12.48±.22500	36.25±1.03078	3.6350±.15516	35.0002±.67706

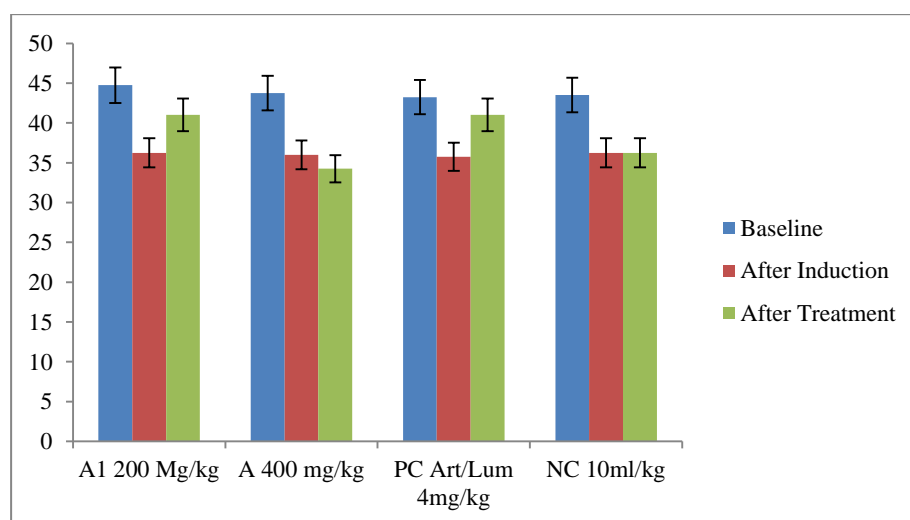
\*The mean difference is significant at the 0.05 level.

The result showed that all the haematological parameters decreases with increasing dosage except the parasthemia count which has a dose dependent statistically significant improvement for the test samples (200 and 400 mg/kg) and the standard when compared with the negative control group.

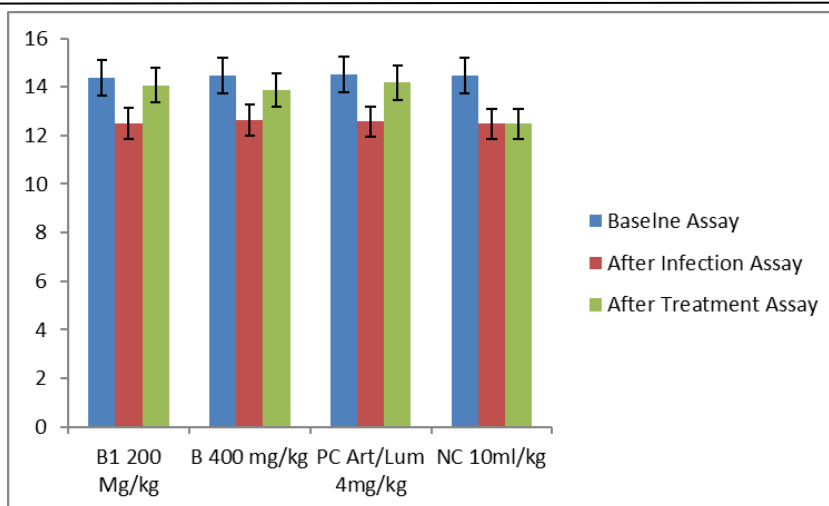
#### Summary of the effect of Compound (3a-b) on Hemoglobin concentration

**Table 5:** Effect of compound (3a-b) on the Hemoglobin concentration of mice induced with *Plasmodium berghei*

Compound/dosage	Hb 1(Baseline)	Hb 2(After induction)	Hb 3(After treatment)	D	%D
A1 200 mg/kg	14.45	12.35	13.95	1.6	11.47
B1 200 Mg/kg	14.37	12.5	14.08	1.58	11.22
A 400 mg/kg	14.62	12.22	12.58	0.36	2.86
B 400 mg/kg	14.47	12.63	13.88	1.25	9
Art/Lum 4 mg/kg	15.5	12.58	14.18	1.6	11.28
NC 10 ml/kg	14.47	12.45	12.48	0.03	0.24



**Figure 1:** Graph representing the effect of 2-(3-hydroxy, 4-methoxyphenyl) benzothiazole (3a) on the Hemoglobin Concentration

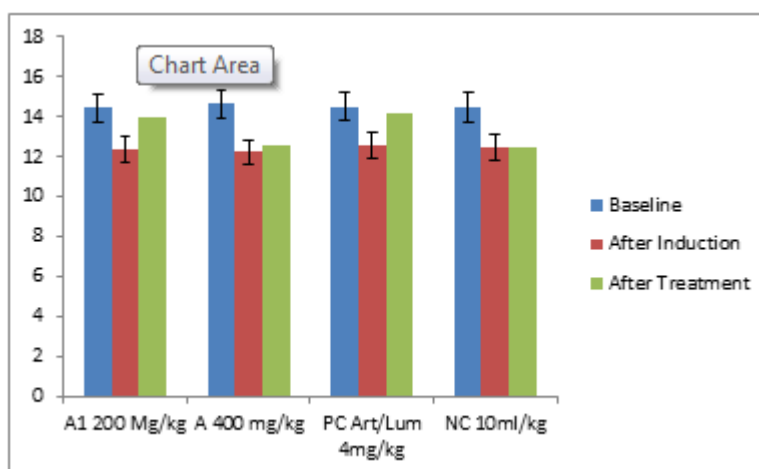


**Figure 2:** Graph representing the effect of 2-(2,4-dimethoxyphenyl)benzothiazole (3b) on the Hemoglobin Concentration of mice induced with *Plasmodium berghei*

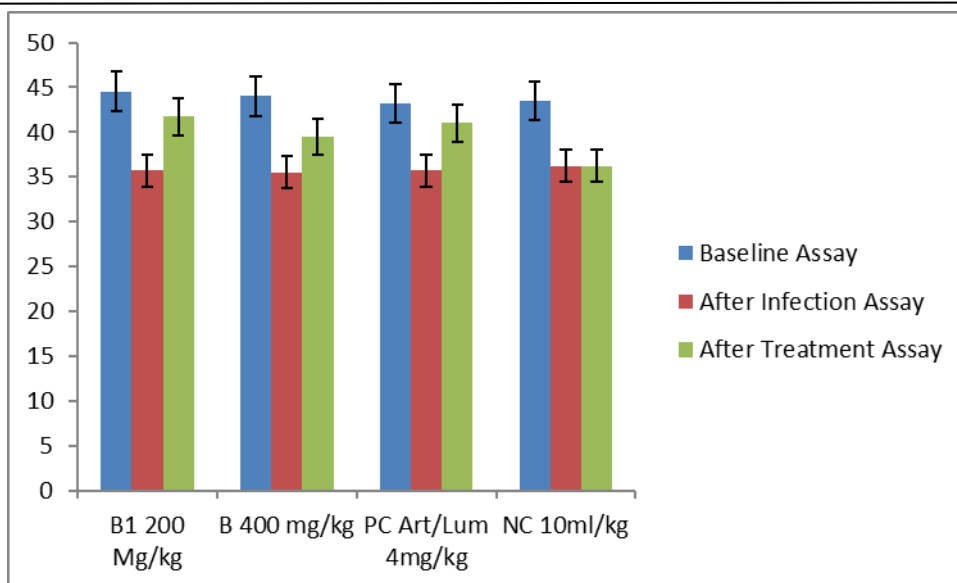
**Summary of the effect of Compound (3a-b) on Packed Cell Volume**

**Table 6:** Effect of Compound (3a-b) on the Packed Cell Volume of the mice induced with *Plasmodium berghei*

Compound/dosage	PCV 1 (Baseline)	PCV 2 (After induction)	PCV 3 (After treatment)	D	%D
A1 (200 mg/kg )	44.45	36.25	41	4.75	11.59
B1 (200 Mg/kg )	44.5	35.75	41.75	6	14.37
A (400 mg/kg)	43.75	36	34.25	-1.75	-5.11
B (400 mg/kg)	44	35.5	39.5	4	10.12
Art/Lum (4 mg/kg)	43.25	35.75	41	5.25	12.8
NC (10 ml/kg)	14.47	12.45	12.48	0.03	0.24



**Figure 3:** Graph representing the effect of 2-(3-hydroxy,4-methoxyphenyl) benzothiazole(3a) on the Packed Cell Volume

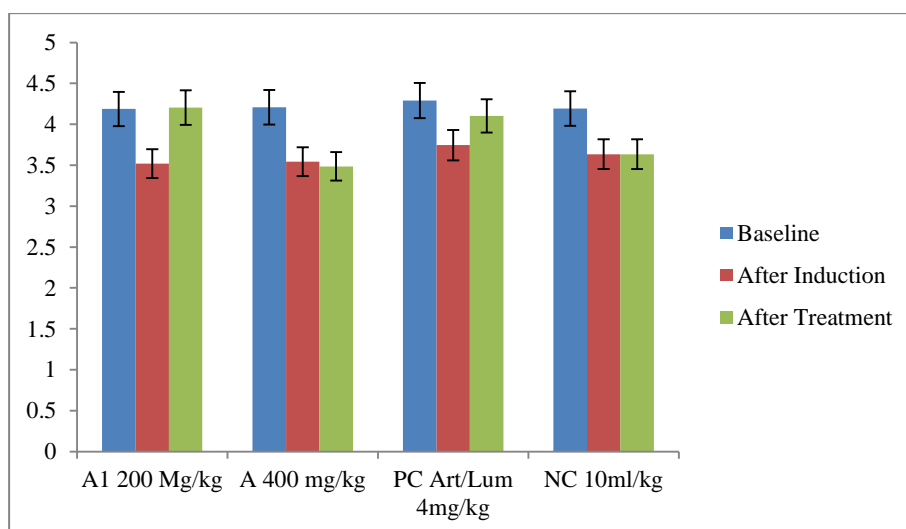


**Figure 4:** Graph representing the effect of 2-(2,4-dimethoxyphenyl)benzothiazole (3b) on the packed cell volume of the mice induced with *Plasmodium berghei*

**Summary of the effect of 2-(3-hydroxy,4-methoxyphenyl)benzothiazole on Red Blood Count**

**Table 7:** Effect of Compound (3a-b) on the Red Blood Count of the mice induced with *Plasmodium berghei*

Compound/dosage	RBC 1 (Baseline)	RBC 2 (After induction)	RBC 3(After treatment)	D	%D
A1 (200 mg/kg )	4.18	3.52	4.2	0.68	16.19
B1 (200 Mg/kg )	4.16	3.52	4.18	0.66	15.78
A (400 mg/kg)	4.2	3.54	3.48	-0.06	-1.72
B (400 mg/kg)	4.1	3.51	4.05	0.54	13.33
Art/Lum (4 mg/kg)	4.29	3.74	4.1	0.36	8.78
NC (10 ml/kg)	4.19	3.63	3.63	0	0



**Figure 5:** Graph representing the effect 2-(3-hydroxy, 4-methoxyphenyl) benzothiazole (3a) on the Red Blood Count

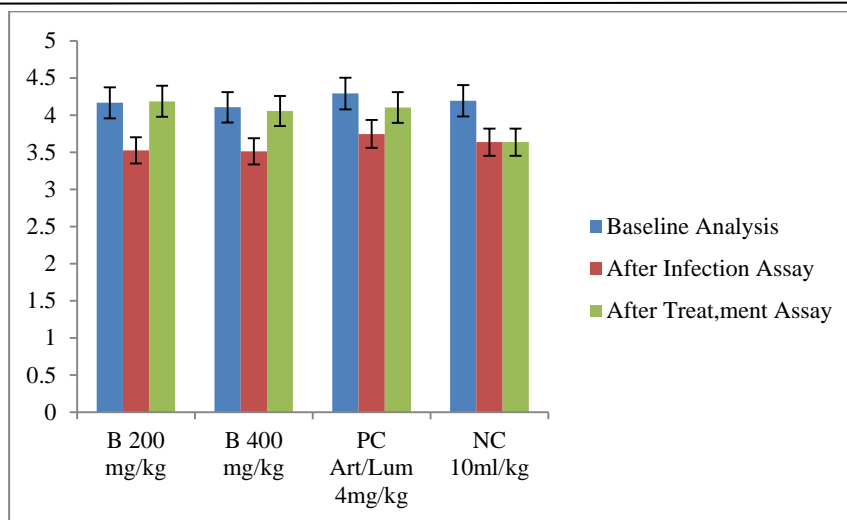


Figure 6: Graph representing the effect of 2-(2, 4-dimethoxyphenyl) benzothiazole (3b) on the Red Blood Count of the mice induced with *Plasmodium berghei*

Summary of the effect of Compound (3a-b) on parasthemia count

Table 8: Effect of Compound (3a-b) on the parasthemia count of mice induced with *Plasmodium berghei*

Compound/dosage	Parasthemia count 1 (After induction)	Parasthemia count 2 (After treatment)	D	%D
A1 200 Mg/kg	36	3.5	32.5	90.28
B1 200 mg/kg	35	3	32	91.42
A 400 mg/kg	34.5	3.25	31.25	90.58
B 400 mg/kg	34	1.75	32.25	94.85
Art/Lum 4mg/kg	33.8	1.25	32.55	96.3
NC 10ml/kg	35	35	0	0

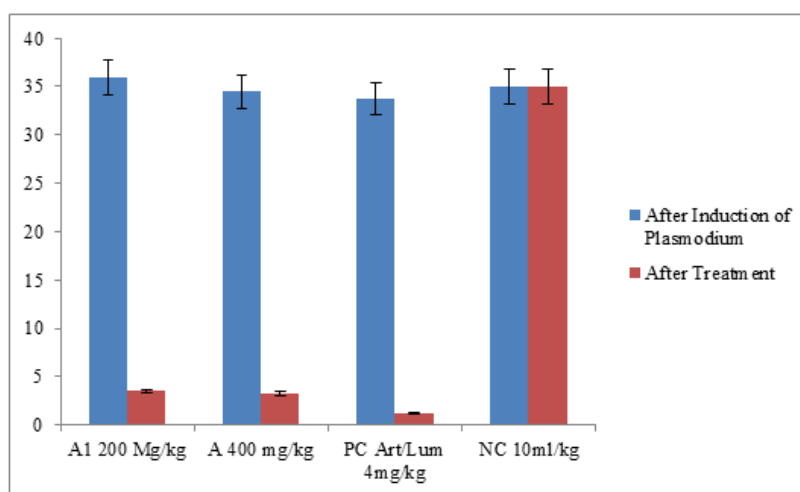
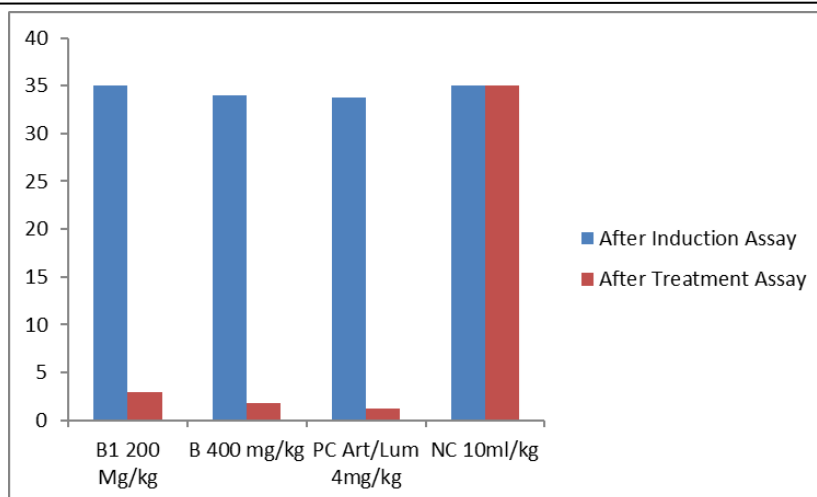


Figure 7: Graph representing the effect of 2-(3-hydroxy,4-methoxyphenyl)benzothiazole (3a) on the parasthemia count





**Figure 8:** Graph representing the effect of 2-(2,4-dimethoxyphenyl)benzothiazole(3b) on the parasthemia count of mice induced with *Plasmodium berghei*

## DISCUSSION

### Antimalarial activity of benzothiazole derivatives on mice infected with *Plasmodium berghei*

This work presents the anti-malarial activity of benzothiazole derivatives (3a-b). Benzothiazole derivatives have been reported to have diverse Chemical reactivity and a broad spectrum of biological activity such as antitumor [36-37], antimicrobial [38], analgesic [39], anti-inflammatory[40], Antimalarial [8] However, its antimalarial activity has been poorly investigated [1].

The results obtained in Tables [2-8] shows the analysis of the parasthemia count and haematological indices. The baseline values obtained from Table 2 show that before the mice were passaged with the plasmodium berghei, their haematological indices (HB, RBC, PCV) were all normal hence there were no differences from the negative control.

Four days after inoculation, their blood samples were collected and analyzed and it was seen that their parasthemia count increased significantly (30-40%) implying that the animals were now infected with malarial parasite hence manifested every sign and symptom including the reduction of the haematological indices just as with other kinds of disease condition Table 3. This result confirms documented reports about the effect of malaria Parasite on hematological parameter (HB, RBC, PCV) as reported by [41-42], who stated that changes in haematological parameter are likely to be Influenced by any disease condition including diseases such as malaria that can affect the health of mankind with various clinical presentation.

After three days of treatment, their blood samples were collected and analyzed. Compound 3b shows a better antimalarial activity than compound 3a in terms of their effectiveness in their haematological indices when compare with standard drug (Artemether & Lumefantrine). However, compound 3a showed a better activity than 3b in terms of reduction in the parasthemia count.

## CONCLUSION AND RECOMMENDATION

This study shows the synthesis of benzothiazole derivatives using a simple one-pot synthesis, characterization, and its physical properties. The *in-Vitro* antimalarial activity of the compound was also studied using albino mice induced with *Plasmodium berghei*. The haematological indices of the mice were monitored during the experiment as well as the parasitemia count. The results obtained showed that the synthesized compound Possesses Antimalarial activity and it is less toxic. This research is self-funded and is limited to two derivatives due to lack of funding. Therefore there is a need to explore other heterocycles containing benzothiazole moieties and investigate their activity against some biological targets.

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