Malaria is an immense global public health issue. Nearly half of the world’s inhabitants live at menace of malaria, which causes a probable 10 lac deaths and 45 crore *Plasmodium falciparum* and 39 crore *P. vivax* cases each year\(^{244,246}\). Efforts to diminish malaria disease and death include control of the mosquito vector (using insecticide treated nets and indoor residual drenching) and quick treatment with active antimalarial drugs. Extraordinary levels of political, methodological and fiscal support have assisted the scaling-up of antimalarial interventions, mostly changes in malarial treatment procedure from low-cost yet failing monotherapies, chloroquine and sulfadoxine–pyrimethamine, to suggested artemisinin combination therapies (ACTs). ACTs are commonly deliberated as best present treatment of unsophisticated *falciparum malaria*\(^{247}\), as they have great medication rates, has quicker parasite clearance times and have potency to diminish both antimalarial resistance and communication. All type of malaria is communicated by female mosquitoes Anopheles. Humans are mostly infected by 4 species of *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale* and *P. malariae*, although human taints with the monkey malaria parasite, *P. knowlesi* have also been reported in the forested regions of Southeast Asia\(^{248,249}\). Almost all severe malaria is initiated by *P. falciparum*. Severe disease and deaths due to *P. vivax* and *P. knowlesi* have also been reported.

The sporozoite form of parasite is injected into humans when bitten by an infected female Anopheles. Sporozoites penetrates into liver cells, here they multiply
and develops thousands of merozoites. These merozoites enter in bloodstream, here they attack RBC’s and again multiply to develop new merozoites. Infected RBC’s ruptured, and release merozoites that infect new RBC’s. This is called as asexual blood phase, the phase of plasmodial life cycle which causes the medical signs and indications of malaria. Some merozoites that attack the RBC’s develop into gametocytes, termed as sexual phase of parasite. Gametocytes are swallowed by mosquito when it receipts blood meal. In the mosquito gut, gametocytes mature into gametes those fuse to develop zygote. Upon fertilisation, this zygote changes into a motile ookinete, this infiltrates the mosquito’s stomach wall and develops an oocyst\textsuperscript{250-251}. The oocyst division produces sporozoites, which travel into salivary glands, from where other human can be infected when mosquito sucks blood (Fig. 1).

\textbf{Fig. 1}  Lifecycle of malaria parasite in human and female Anopholes carrier.
7.1 Classification of Antimalarial Drugs\\\(^{252,253}\):\\

7.1.1 Classification based on Chemical Structure:

a) 4- Aminoquinolines: Amodiaquine, Chloroquine

b) Chinona alkaloids: Quinine

c) Quinoline-methanol: Mefloquine

d) Acridine: Mepacrine, Quinacrine

e) 8-Aminoquinolines: primaquine

f) Biguanides: proguanine

g) Diaminopyrimidines: pyrimethamine

h) Phenantherine-methanol: Halofanterine, Lumifanterine

i) Antibiotics: Doxycycline, Tetracycline, Clindamycin

j) Sulfonamides & Sulfones: Sulfadoxine & Dapsone

7.1.2 Classification based on Action:

Some drugs can be used prophylactically to prevent malaria, while others are directed towards treating acute attacks. In general, antimalarial drugs are categorized on the basis of their mode of action against the different stages of life cycle of malarial Parasite.

7.1.2.1 Blood schizonticidal agents: are used to treat the acute attack. They have activity against erythrocytic stage of plasmodium.

a) Atremisinin

b) Chloroquine

c) Quinine
7.1.2.2 Tissue schizonticidal agents: Have a radical cure effect by acting on the parasites in the liver, these drugs also destroy gametocytes and thus reduce the spread of infection. E.g. Primaquine

7.2 In vitro antimalarial screening

All the synthesized compounds were screened for antimalarial activity in the Microcare laboratory & TRC, Surat, Gujarat.

The in vitro antimalarial test was carried out in 96 well microtitre plates according to microassay procedure of Rieckmann and co-workers with insignificant adjustments. Cultures of *P. falciparum* strain were preserved in RPMI 1640 medium improved with 25 mM HEPES, 1% D-glucose, 0.23% NaHCO\(_3\) and 10% heat deactivated human serum. The asynchronous parasites of *P. falciparum* were harmonised after treated with 5% D-sorbitol to get ring phase parasitized cells. For carrying out test, a total volume of 200 µl of medium RPMI-1640 with 0.8 to 1.5% at 3% haematocrit in a preliminary ring phase parasitaemia was firm by Jaswant Singh Bhattacharya staining to evaluate the percent parasitaemia and uniformly maintained with 50% RBCs (O⁺). A standard solution of 5mg/ ml was prepared in DMSO for each test sample and consequent dilutions were ready with culture medium. Diluted samples in 20 µl capacity were added to test mines to get ultimate concentrations (at fivefold dilutions) between 0.4 µg/ ml to 100 µg/ ml in identical well having parasitized cell preparation. Culture plates were nurtured at 37°C. After 36 to 40 hrs gestation, thin blood marks were prepared from each well and stained with JSB stain. The slides were microscopically observed to record development of ring stage into trophozoites and schizonts in occurrence of diverse concentrations of test agents. Test concentration which stops comprehensive
maturation into schizonts was termed as minimum inhibitory concentrations (MIC). Chloroquine was used as the reference drug\textsuperscript{254, 255}.

7.3. \textit{In vitro} observations of antimalarial screening

The mean of rings, trophozoites and schizonts noted per 100 parasites from identical wells after gestation for 38 hrs, and per hundred development inhibition with respect to control. The $IC_{50}$ values of synthesized compounds in comparison with standard drugs are represented in the Table-1 and Table-2.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Sr. No. & Sample ID & \textit{P.falciparum} IC\textsubscript{50} (\textmu g/ml) & Sr. No. & Sample ID & \textit{P.falciparum} IC\textsubscript{50} (\textmu g/ml) \\
\hline
1 & IA-CH01-A1 & 0.95 & 16 & IA-CH01-B8 & 0.7 \\
2 & IA-CH01-A2 & 1.25 & 17 & IA-CH01-C1 & 1.26 \\
3 & IA-CH01-A3 & 1 & 18 & IA-CH01-C2 & 1.32 \\
4 & IA-CH01-A4 & 1.1 & 19 & IA-CH01-C3 & 0.95 \\
5 & IA-CH01-A5 & 0.8 & 20 & IA-CH01-C4 & 0.8 \\
6 & IA-CH01-A6 & 1.5 & 21 & IA-CH01-C5 & 1.52 \\
7 & IA-CH01-A7 & 1.15 & 22 & IA-CH01-C6 & 1.8 \\
8 & IA-CH01-A8 & 1.38 & 23 & IA-CH01-C7 & 1.22 \\
9 & IA-CH01-B1 & 1.2 & 24 & IA-CH01-C8 & 1.05 \\
10 & IA-CH01-B2 & 1.62 & 25 & IA-CH01-D1 & 0.95 \\
11 & IA-CH01-B3 & 0.65 & 26 & IA-CH01-D2 & 1.42 \\
12 & IA-CH01-B4 & 1.45 & 27 & IA-CH01-D3 & 1.7 \\
13 & IA-CH01-B5 & 1.38 & 28 & IA-CH01-D4 & 0.82 \\
14 & IA-CH01-B6 & 1.1 & 29 & IA-CH01-D5 & 1.32 \\
15 & IA-CH01-B7 & 0.95 & 30 & IA-CH01-D6 & 1.53 \\
\hline
\end{tabular}
\caption{\textit{In vitro} antimalarial activity of novel pyrazole derivatives in comparison with standard drugs:}
\end{table}

Reference Drugs:
\begin{itemize}
\item Chloroquine 0.02
\item Quinine 0.27
\end{itemize}
7.3.1. Graphical representation of some pyrazole compounds with standard drugs:

![Graphical representation of some pyrazole compounds with standard drugs](image)

Table-2: Invitro antimalarial activity of novel indole derivatives in comparison with standard drugs:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Sample ID</th>
<th>P. falciparum IC50 (µg/ml)</th>
<th>Sr. No.</th>
<th>Sample ID</th>
<th>P. falciparum IC50 (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IA-CH02-A1</td>
<td>0.7</td>
<td>14</td>
<td>IA-CH02-B4</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>IA-CH02-A2</td>
<td>1.16</td>
<td>15</td>
<td>IA-CH02-B5</td>
<td>1.26</td>
</tr>
<tr>
<td>3</td>
<td>IA-CH02-A3</td>
<td>0.9</td>
<td>16</td>
<td>IA-CH02-B6</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>IA-CH02-A4</td>
<td>0.5</td>
<td>17</td>
<td>IA-CH02-B7</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>IA-CH02-A5</td>
<td>1.58</td>
<td>18</td>
<td>IA-CH02-B8</td>
<td>0.92</td>
</tr>
<tr>
<td>6</td>
<td>IA-CH02-A6</td>
<td>0.6</td>
<td>19</td>
<td>IA-CH02-B9</td>
<td>1.37</td>
</tr>
<tr>
<td>7</td>
<td>IA-CH02-A7</td>
<td>0.95</td>
<td>20</td>
<td>IA-CH02-B10</td>
<td>1.45</td>
</tr>
<tr>
<td>8</td>
<td>IA-CH02-A8</td>
<td>1.16</td>
<td>21</td>
<td>IA-CH02-C1</td>
<td>0.95</td>
</tr>
<tr>
<td>9</td>
<td>IA-CH02-A9</td>
<td>1</td>
<td>22</td>
<td>IA-CH02-C2</td>
<td>1.12</td>
</tr>
<tr>
<td>10</td>
<td>IA-CH02-A10</td>
<td>1.62</td>
<td>23</td>
<td>IA-CH02-C3</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>IA-CH02-B1</td>
<td>0.9</td>
<td>24</td>
<td>IA-CH02-C4</td>
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<tr>
<td>12</td>
<td>IA-CH02-B2</td>
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<td>25</td>
<td>IA-CH02-C5</td>
<td>1.45</td>
</tr>
<tr>
<td>13</td>
<td>IA-CH02-B3</td>
<td>0.95</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference Drugs:
- Chloroquine 0.02
- Quinine 0.27
7.3.2. Graphical representation of some indole compounds with standard drugs:

![Graphical representation of P.falciparum IC50(µg/ml) for various compounds and standard drugs.](image-url)