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Jyoti Gupta; Puleng Thabana; Sabahat Samreen; Amir Azam; Robyn Van Zyl ...

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Synthesis and Biological Evaluation of 2-(3-((2-(2-(Quinoline-4-yloxy)acetyl)-hydrazineylidene)methyl)-1*H*-indol-1-yl)acetamide Derivatives as Antiprotozoal Agent: *In silico* Molecular Docking Study

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In an unremitting search for potential antiprotozoal agents, a series of 2-(3-((2-(2-(quinolin-4-yloxy)acetyl)hydrazineylidene)methyl)-1*H*-indol-1-yl)acetamide derivatives **(QC1-QC11)** was designed, synthesized, characterized and evaluated for its antiprotozoal activities. The anti-amoebic activity of these synthesized compounds was assessed against the HM1:IMSS strain of *Entamoeba histolytica*. All the compounds exhibited good to potent activity with IC_{50} values in the range of 0.36-30.94 µM and metronidazole (MTZ) was taken as standard (IC_{50} = 1.8 µM). Compound **QC4** was recorded with lowest IC_{50} value (0.36 µM). Antimalarial screening against *Plasmodium falciparum* strain (NF54) revealed the poor efficacy of these compounds. Derivatives **QC2** and **QC4** exhibited a slight inhibitory effect on the malaria parasite compared to quinine, while showing negligible impact on red blood cell integrity. Of all the derivatives, **QC4** displayed general toxicity to all the organisms and cells used in this study, with **QC2** showing minimal toxicity to these biological systems. The docking study of these derivatives indicated the promising binding affinity when interacted with enzyme *Eh*THRase (PDB id: 3D8X). **QC6** recorded with most negative binding free energy value (-8.9 kcal/mol) showing strongest interaction while **QC4** also had promising interaction with binding free energy -8.7 kcal/mol, hence, these derivatives are found to be promising anti-amoebic agents.

Keywords: Quinoline, Indole, *Entamoeba histolytica, Plasmodium falciparum,* Cytotoxicity.

INTRODUCTION

Amoebiasis and malaria, both are the parasitic protozoan diseases [1]. Amoebiasis is an infection caused by the protozoan *E. histolytica*, primarily affecting the intestines but potentially spreading to other organs such as the liver [2]. Recent data indicates that there are approximately 2.2 million clinical cases worldwide caused by amoebiasis, with about 55,000 deaths resulting from this disease [3]. Symptoms may range from mild diarrhea to severe dysentery (bloody diarrhea), abdominal cramps and colitis. When the parasite spreads through the bloodstream, it may infect the liver, leading to amoebic liver abscess. Symptoms include fever, pain in the upper abdomen and weight loss. It may also invade other organs like the lungs or brain, although these complications are rare [4]. Malaria is transmitted *via* injection of *Plasmodium* sporozoites into the bloodstream. Then, parasites travel to the liver, where they mature and reproduce, eventually invading red blood cells [5]. In 2022, about 249 million malaria infection were recorded globally, with about 608,000 deaths [6].

Heterocycles have always been the point of attraction for the medicinal chemists owing to their vast and versatile medicinal applications. Quinoline, an important pharmacophore, is present in a number of naturally occurring compounds [7]. Quinoline and its derivatives are a principal chemotherapeutic against several viruses, bacteria and protozoa [8]. Mefloquine (**1**) is an effective drug that treat and prevent malaria, particularly against *P. falciparum* and *P. vivax*. It is often used in areas

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where malaria is resistant to other drugs such as chloroquine [9]. Clioquinol (**2**) has been used as a topical antiseptic and antifungal agent [10,11], while ciprofloxacin (**3**) is widely used to treat various bacterial infections [12]. Further, indole, a naturally occurring heterocyclic organic compound, also holds significant medicinal importance due to its versatile biological activities as antimalarial, anticancer, antimicrobial, antiviral, antioxidant, anti-inflammatory, *etc*. Its derivatives are key components in many pharmaceutical drugs and have a broad range of therapeutic applications [13]. Indole-3-carbinol (**4**), a naturally occurring phytochemical, has considered a promising chemopreventive agent, as it has gained attention for its ability to modulate hormone related cancers, particularly breast, prostate and colon cancers [14,15]. Indomethacin (**5**) is primarily used to treat pain and inflammation associated with conditions like arthritis, gout and ankylosing spondylitis [16]. Sumatriptan (**6**) is widely used for the acute treatment of migraine attacks. It mimics serotonin and acts on specific receptors in the brain to relieve migraine symptoms [17] (Fig. 1).

Besides being the basic moiety in several currently used drugs, quinoline and indole derivatives are reported to show good activity as anti-amoebic. Saadeh *et al.* [18] explored new hybrid compounds having quinoline precursors and tested for their anti-parasitic potency. While, a new series of quinoline-hydrazone conjugates were tasted for their anti-amoebic and antimalarial activities [19]. Further, Husain *et al.* [20] reported the synthesis and anti-amoebic efficacy of indole-3-carboxaldehyde thiosemicarbazones and their Pd(II) complexes. While, Inam *et al.* [21] described the synthesis and pharmacological properties of nitroimidazole-indole conjugates as potential anti-amoebic agents. So, based on the literature survey (Fig. 2), the pioneering idea of combining two biologicals' cores in a single molecule can be an innovative tool in the treatment of antiprotozoal diseases. Hence, we designed and synthesized quinoline-indolylacetamide derivatives by linking the quinoline and indole moiety *via* hydrazone linkage and examined their antiprotozoal activity.

EXPERIMENTAL

All the chemicals, thin-layer chromatography (TLC) plates precoated aluminum sheets (silica gel 60 F_{254}, Merck, Germany), *etc*. were purchased from companies Aldrich Co. (USA), SRL *etc*. TLC spots were visualized under UV light. Elemental analyses were carried out using an Elementar Vario analyzer, with results under ± 0.4% of the theoretical values. Infrared peaks were recorded on a Bruker FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were acquired using a Bruker Spectrospin DPX 300 MHz and Bruker Spectrospin DPX 75 MHz spectrometer, respectively, with DMSO as solvent and tetramethylsilane (TMS) as internal standard. Electrospray ionization (ESI) mass spectra were recorded on a Microtof-Q II 10262 spectrometer. The melting points were determined using a Veego melting point apparatus (model REC-2203882) and are uncorrected.

Synthesis of *N*-substituted-2-(3-formyl-1*H*-indol-1-yl)-acetamide (C1-C11): The synthesis of derivatives (**C1-C11**) was carried out by a reported protocol in the literature [21].

Synthesis of 2-(quinolin-8-yloxy)acetohydrazide (5): The method of preparation was followed as reported [22].

General synthesis of 2-(3-((2-(2-(quinolin-4-yloxy)-acetyl)hydrazineylidene)methyl)-1*H*-indol-1-yl)acetamide derivatives (QC1-QC11): A mixture of compound **5** (10 mmol) and appropriate aromatic substituted indole 3-carboxaldehyde **(C1 -C11)** (10 mmol) in absolute ethanol (50 mL) and sulfuric acid in catalytic amount was continuously stirred for 4 h at room temperature. After cooling, the solid was filtered and dried to get crude solid product (**Scheme-I**).

***N′*-((1-(2-(*m*-Toluidino)-2-oxoethyl)-1*H*-indol-3-yl)-methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC1):**

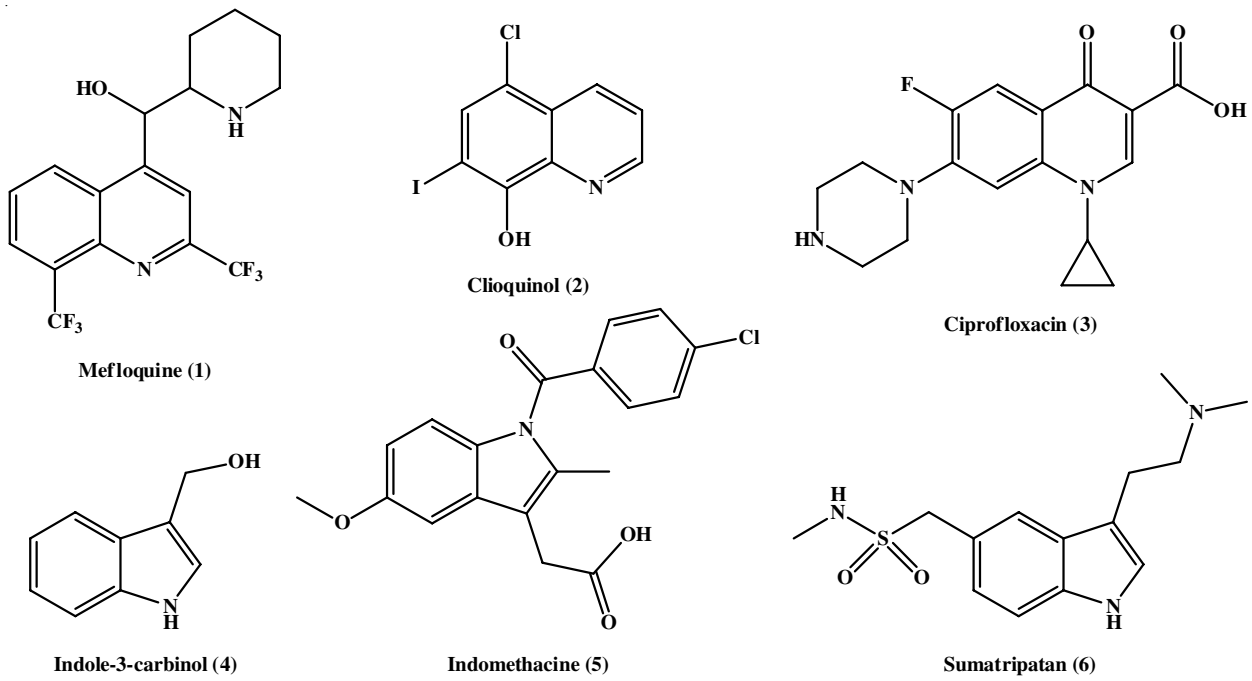


Fig. 1. Structure of some currently used clinical drugs bearing quinoline and indole nucleus

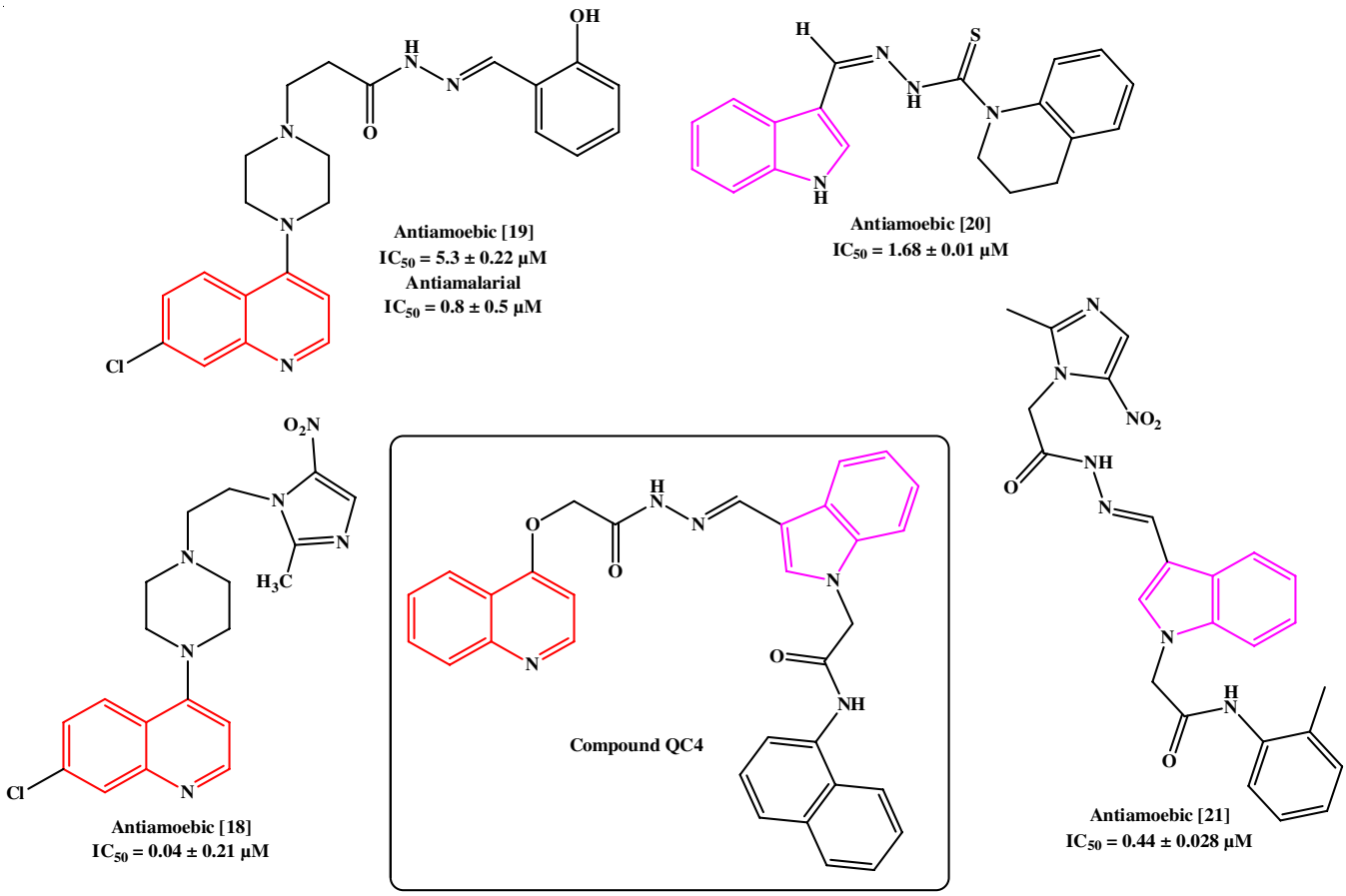


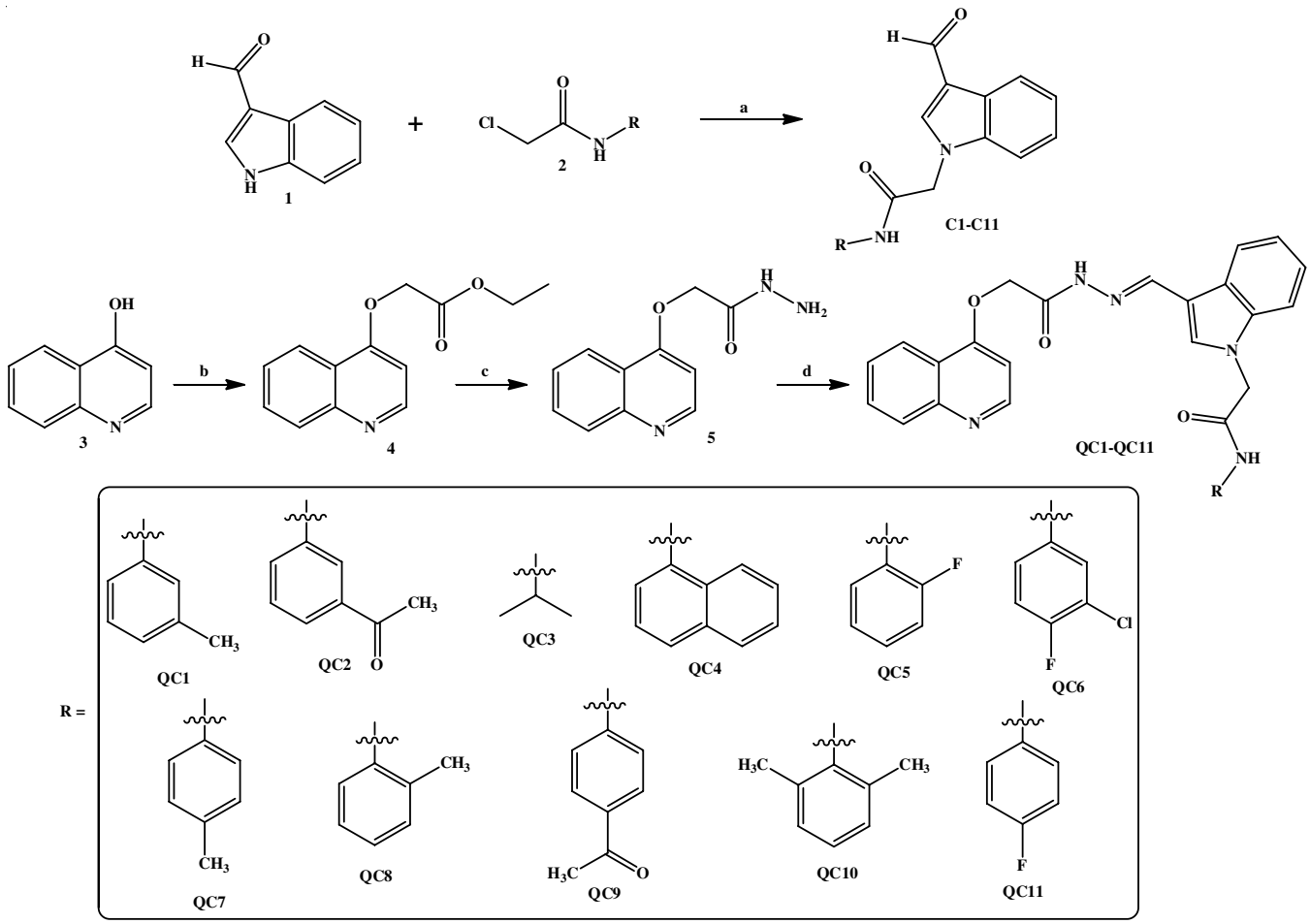
Fig. 2. Rationale designing of synthesized derivative

Yield: 61%; m.p.: 180-184 ºC; IR (KBr, ν_{max}, cm^{-1}): 3259 (-NH), 1670 (C=O), 1613 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.36 (s, 1H), 10.36 (s, 1H) 8.90-8.88 (m, 1H), 8.52 (s, 1H), 8.35-8.32 (m, 1H), 8.26 (s, 1H), 8.16 (d, 1H, *J* = 7.5 Hz), 7.89 (d 1H, *J* = 7.2 Hz) 7.65-7.43 (m 3H), 7.39 (d 2H *J* = 8.1 Hz), 7.34 (d, 1H, *J* = 6.6 Hz), 7.26-7.11 (m, 3H), 6.91 (d, 1H, *J* = 7.5 Hz), 5.45 (s, 2H), 5.11 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 168.63, 166.22, 164.05, 154.42, 153.91, 149.68, 149.42, 145.22, 141.49, 139.92, 138.61, 138.03, 137.10, 136.44, 135.04, 129.66, 129.19, 127.22, 125.02, 123.43, 122.38, 121.39, 120.44, 116.88, 111.49, 110.62, 69.02, 49.69, 21.56; ESI-MS: *m/z* 492.19 (M+1); Anal. calcd. (found) % for $C_{29}H_{25}N_5O_3$: C, 70.86 (70.83); H, 5.13 (5.35); N, 14.25 (14.39).

***N′*-((1-(2-(3-Acetylphenylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC2):** Yield: 81%; m.p.: 177-182 ºC; IR (KBr, ν_{max}, cm^{-1}): 3260 (-NH), 1675 (C=O), 1600 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.40 (bs, 1H), 10.67 (bs, 1H), 8.98 (s, 1H), 8.25-8.15 (m, 2H), 7.97 (s, 1H), 7.81-7.65 (m, 6H), 7.48-7.45 (m, 3H), 7.24-7.16 (m, 3H), 5.54 (s, 2H), 4.94 (s, 2H), 2.51 (ss, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 198.72, 168.42, 166.75, 163.81, 145.85, 143.32, 140.80, 139.14, 137.72, 135.26, 133.13, 129.91, 128.85, 127.22, 125.02, 124.38, 122.89, 122.53, 121.49, 120.91, 118.88, 113.62, 112.80, 111.41, 110.55, 69.12, 49.55, 27.07; ESI-MS: *m/z* 520.14 (M+1); Anal. calcd. (found) % for $C_{30}H_{25}N_5O_4$: C, 69.35 (69.05); H, 4.85 (4.82); N, 13.48 (13.49).

***N′*-((1-(2-(Isopropylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC3):** Yield 70%; m.p.182-186 ºC; IR (KBr, ν_{max}, cm^{-1}): 3262 (-NH), 1668 (C=O), 1642 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.96 (bs, 1H), 11.30 (bs, 1H), 8.95 (s, 1H), 8.40-8.11 (m, 4H), 7.99 (s, 1H), 7.78 (d, 1H, *J* = 8.4 Hz), 7.63-7.49 (m, 3H), 7.40-7.34 (m, 2H), 5.43 (s, 2H), 4.91 (s, 2H), 3.87 (m, 1H), 1.09 (d, 6H, *J* = 6.3 Hz); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 166.35, 134.05, 154.41, 149.67, 145.32, 141.58, 139.93, 137.82, 136.45, 135.04, 129.59, 127.22, 125.04, 123.32, 122.66, 122.24, 121.49, 120.47, 112.26, 111.28, 110.57, 69.02, 66.19, 49.30, 22.68; ESI-MS: *m/z* 444.01 (M+1); Anal. calcd. (found) % for $C_{25}H_{25}N_5O_3$: C, 67.71 (67.53); H, 5.68 (5.48); N, 15.79 (15.59).

***N′*-((1-(2-(Naphthalene-1-ylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC4):** Yield 83%; m.p.: 218-223 ºC; IR (KBr, ν_{max}, cm^{-1}): 3219 (-NH), 1668 (C=O), 1609 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.58 (bs, 1H), 11.39 (bs, 1H), 9.02 (s, 1H), 8.25-8.21 (m, 1H), 8.15 (d, 2H, *J* = 7.5 Hz), 7.92 (s, 1H), 7.87-7.74 (m, 3H), 7.71-7.63 (m, 4H), 7.50-7.39 (m, 4H), 7.22-7.13 (m, 3H), 5.55 (ss, 2H), 4.96 (ss, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 163.65, 152.27, 151.77, 148.32, 147.24, 146.07, 142.45, 141.82, 140.18, 137.53, 131.13, 129.80, 128.96, 128.47, 127.06, 126.54, 126.02, 124.71, 124.47, 123.19, 123.01, 122.86, 122.06, 121.57, 121.18, 120.78, 113.14, 112.36, 111.83, 111.31, 68.73, 66.69; ESI-MS: *m/z* 528.21 (M+1); Anal. calcd.



Scheme-I: Synthesis of substituted indole-3-carboxaldehyde **(C1-C11)** and 2-(3-((2-(2-(quinolin-4-yloxy)acetyl)hydrazineylidene)methyl)-1*H*-indol-1-yl)acetamide derivatives **(QC1-QC11)**; Reagents and conditions: (a) K_2CO_3, cat. KI, DMF, reflux, (b) ethylacetoacetate, EtOH, (c) $N_2H_4 \cdot xH_2O$, EtOH, reflux, (d) substituted indole-3-carboxaldehyde **(C1-C11)**, EtOH, 1-2 drops H_2SO_4

(found) % for $C_{32}H_{25}N_5O_3$: C, 72.85 (72.55); H, 4.78 (4.91); N, 13.27 (13.19).

***N′*-((1-(2-(2-Fluorophenylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC5):** Yield: 79%; m.p.: 175-179 ºC; IR (KBr, ν_{max}, cm^{-1}): 3214 (-NH), 1672 (C=O), 1608 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.40 (bs, 1H), 10.32 (bs, 1H), 8.95 (s, 1H), 8.86-8.79 (m, 1H), 8.43-8.40 (m, 1H), 8.37-8.30 (m, 1H), 7.99 (s, 1H), 7.93-7.86 (m, 1H), 7.61-7.45 (m, 4H), 7.33-7.23 (m, 3H), 7.16-7.02 (m, 3H), 5.48 (ss, 2H), 4.93 (ss, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.68, 166.90, 164.12, 155.70, 154.07, 153.68, 152.45, 149.35, 145.41, 141.69, 139.43, 138.17, 137.38, 136.87, 135.85, 129.60, 127.57, 126.24, 125.94, 124.89, 123.48, 122.78, 121.05, 120.88, 116.15, 112.16, 111.59, 110.62, 65.93, 49.57; ESI-MS: *m/z* 496.16 (M+1); Anal. calcd. (found) % for $C_{32}H_{25}N_5O_3$: C, 67.87 (67.85); H, 4.48 (4.32); N, 14.13 (14.02).

***N′*-((1-(2-(3-Chloro-4-fluorophenylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC6):** Yield: 77%; m.p.183-187 ºC; IR (KBr, ν_{max}, cm^{-1}): 3296 (-NH), 1667 (C=O), 1602 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.39 (bs, 1H), 10.25 (bs, 1H), 8.95 (s, 1H), 8.84 (d, 1H, *J* = 8.4 Hz), 8.73 (d, 1H, *J* = 8.1 Hz), 8.59 (s, 1H), 8.02 (s, 2H), 7.76-7.66 (m, 2H), 7.51-7.48 (m, 2H), 7.26-7.20 (m, 3H), 7.17-7.16 (m, 3H), 5.58 (ss, 2H), 5.00 (ss, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 168.17, 166.90, 163.57, 155.69, 152.43, 151.64, 147.78, 145.54, 142.75, 141.93, 138.20, 135.20, 129.83, 128.82, 126.12, 125.96, 125.23, 124.94, 123.44, 122.91, 121.58, 120.84, 116.17, 113.55, 111.51, 110.71, 68.69, 49.44; ESI-MS: *m/z* 530.16 (M+1); Anal. calcd. (found) % for $C_{28}H_{21}FClN_5O_3$: C, 63.460 (63.26); H, 3.99 (3.97); N, 13.21 (13.20).

***N′*-((1-(2-(*p*-Toluidino)-2-oxoethyl)-1*H*-indol-3-yl)-methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC7):** Yield: 65%; m.p.191-195 ºC; IR (KBr, ν_{max}, cm^{-1}): 3234 (-NH), 1658 (C=O), 1604 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.37 (bs, 1H), 10.34 (bs, 1H), 8.94 (s, 1H), 8.72-8.58 (m, 1H), 8.37-8.29 (m, 2H), 7.99 (s, 1H), 7.85-7.69 (m, 2H), 7.48 (bs, 4H), 7.28 (bs, 2H), 7.12 (d, 3H, *J* = 6.6 Hz), 5.55 (s, 2H), 4.97 (s, 2H), 2.23 (ss, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 166.03, 165.49, 152.45, 148.41, 147.44, 145.40, 142.74, 141.84, 139.99, 138.15, 136.48, 135.18, 133.18, 129.69, 128.79, 124.96, 123.04, 122.74, 121.47, 120.75, 119.76, 117.88, 113.25, 112.63, 11.29, 110.74, 68.90, 49.98, 20.86; ESI-MS: *m/z* 492.18 (M+1); Anal. calcd. (found) % for $C_{29}H_{25}N_5O_3$; C, 70.86 (70.62); H, 5.13 (5.10); N, 14.25 (14.19).

***N′*-((1-(2-(*o*-Toluidino)-2-oxoethyl)-1*H*-indol-3-yl)-methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC8):** Yield: 68%; m.p.166-170 ºC; IR (KBr, ν_{max}, cm^{-1}): 3298 (-NH), 1655 (C=O), 1595 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.77 (bs, 1H), 8.92 (bs, 1H), 8.71 (s, 1H), 8.52 (d, 1H, *J* = 8.1 Hz), 8.38 (d, 1H, *J* = 7.5 Hz), 7.98 (s, 1H), 7.67-7.65 (m, 2H), 7.61-7.53 (m, 3H), 7.40-7.38 (m, 1H), 7.30-7.22 (m, 4H), 7.15-7.08 (m, 2H), 5.19 (s, 2H), 4.95 (s, 2H), 2.22 (ss, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.51, 166.44, 155.26, 152.52, 148.55, 145.39, 138.95, 138.11, 137.40, 136.53, 136.04, 132.28, 130.90, 129.67, 127.95, 126.53, 125.71, 125.35, 123.51, 122.65, 121.64, 121.00, 111.89, 111.50, 110.77, 65.96, 49.60, 18.20; ESI-MS: *m/z* 492.18 (M+1); Anal. calcd. (found) % for $C_{29}H_{25}N_5O_3$: C, 70.86 (70.62); H, 5.13 (5.10); N, 14.25 (14.21).

***N′*-((1-(2-(4-Acetylphenylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC9):** Yield: 71%; m.p.191-195 ºC; IR (KBr, ν_{max}, cm^{-1}): 3253 (-NH), 1654 (C=O), 1590 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 10.83 (s, 1H), 8.97 (s, 1H), 8.96 (s, 1H), 8.64 (d, 2H, *J* = 6.6 Hz), 8.39 (d, 2H, *J* = 6.6 Hz), 8.033 (s, 1H), 7.965 (d, 2H, *J* = 8.1 Hz), 7.77-7.72 (m, 3H), 7.68-7.53 (m, 3H), 7.34-7.27 (m, 2H), 5.21 (s, 2H), 5.014 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 197.10, 170.37, 166.97, 155.27, 152.04, 148.13, 143.39, 140.10, 138.28, 136.73, 136.31, 132.47, 130.04, 129.73, 128.28, 127.90, 125.65, 123.53, 122.72, 121.62, 121.01, 119.25, 119.00, 112.03, 111.44, 65.98, 49.84, 26.89; ESI-MS: *m/z* 520.16 (M+1); Anal. calcd. (found) % for $C_{30}H_{25}N_5O_4$: C, 69.35 (69.30); H, 4.85 (4.81); N, 13.48 (13.21).

N′-((1-(2-(2,6-Dimethylphenylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC10): Yield: 58%; m.p.: 170-175 ºC; IR (KBr, ν_{max}, cm^{-1}): 3189 (-NH), 1655 (C=O), 1599 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 9.78 (bs, 1H), 9.67 (bs, 1H), 8.95 (s, 1H), 8.75-8.69 (m, 1H), 8.40-8.38 (m, H), 8.28-8.25 (m, 1H), 8.033 (s, 1H), 7.287-7.711 (m, 1H), 7.66-7.58 (m, 3H), 7.47-7.44 (m, 2H), 7.31-7.2 (m, 2H), 7.06-6.95 (m, 1H), 5.16 (ss, 2H), 4.99 (s, H), 2.17 (ss, 6H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 170.52, 168.6, 152.60, 148.64, 145.65, 143.21, 141.23, 138.7, 135.16, 132.50, 130.11, 129.66, 128.23, 127.0, 125.65, 123.33, 122.65, 121.72, 120.94, 119.75, 119.26, 112.55, 111.34, 110.85 65.65, 52.45, 18.49; ESI-MS: *m/z* 506.15 (M+1); Anal. calcd. (found) % for $C_{30}H_{27}N_5O_3$: C, 71.27 (71.10); H, 5.38 (5.23); N, 13.85 (13.31).

***N′*-((1-(2-(4-Fluorophenylamino)-2-oxoethyl)-1*H*-indol-3-yl)methylene)-2-(quinoline-4-yloxy)acetohydrazide (QC11):** Yield: 78%; m.p.: 215-220 ºC; IR (KBr, ν_{max}, cm^{-1}): 3206 (-NH), 1673 (C=O), 1605 (N=C); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 11.41 (bs, 1H), 10.52 (bs, 1H), 8.94 (s, 1H), 8.87 (d, 1H, *J* = 8.1 Hz), 8.74 (d, 1H, *J* = 8.4 Hz), 8.26 (d, 1H, *J* = 7.8 Hz), 8.00 (s, 1H), 7.92-7.84 (m, 2H), 7.75-7.69 (m, 2H), 7.62-7.57 (m, 2H), 7.48 (d, 2H, *J* = 7.2 Hz), 7.27-7.11 (m, 3H), 5.58 (s, 2H), 4.98 (s, 2H); ^{13}C NMR (300 MHz, DMSO-d_6) δ ppm: 168.22, 166.25, 163.64, 160.28, 157.09, 155.21, 151.66, 151.11, 147.85, 146.72, 145.59, 143.05, 142.03, 141.21, 138.08, 135.29, 129.84, 128.79, 124.98, 122.91, 121.65, 120.87, 116.05, 113.34, 111.27, 110.71, 68.55, 49.56; ESI-MS: *m/z* 496.17 (M+1); Anal. calcd. (found) % for $C_{30}H_{27}N_5O_3$: C, 67.87 (67.77); H, 4.48 (4.45); N, 14.13 (14.13).

Pharmacological evaluation

Anti-amoebic activity: By a microdilution method, the synthesized compounds **QC1-QC11** were evaluated for anti-amoebic activity against the HM1:IMSS strain of *E. histolytica* [23]. To culture trophozoites in Diamond TYIS-33 medium within a 96-well microtiter plate was used [24]. To test the anti-amoebic activity, 1 mg of each compound was dissolved in DMSO as stock solutions, ensuring the final concentration did not inhibit amoeba viability [25]. In each assay, metronidazole (MTZ) was as standard amoebicidal control and a negative control with combination of culture medium plus amoeba and a blank in which only culture medium was included. Parasite suspensions were adjusted to 10^5 cells/mL followed by addition to the wells and incubation at 37 ºC for 72 h under nitrogen. After incubation, amoeba growth was assessed microscopically. The culture medium was removed and the wells were cleaned with 0.9% NaCl at 37 ºC, dried, fixed by adding methanol and then stained with aqueous eosin (0.5%) for 15 min. The optical density (OD) was measured at 490 nm wavelength using a microplate reader to calculate the percentage inhibition of parasite growth. IC_{50} values were determined by non-linear regression method of the dose-response curves.

Antimalarial activity: The chloroquine-susceptible *P. falciparum* strain (NF54) was continuously maintained in the supplemented RPMI-1640 at 37 ºC in a controlled atmosphere (5% CO_2, 3% O_2, 92% N_2) [26]. Parasites were synchronized in the ring stage for which 5% D-sorbitol was used [27]. To assess the assay, synchronized parasites at 2% parasitaemia and haematocrit were titrated with serial dilutions of the test compounds and quinine. Following incubation for 48 h, samples were frozen at -70 ºC for 1 h and thawed for 2 h. Lysates were mixed with Malstat™ (reagent that reacts with pLDH to produce colour) and nitroblue tetrazolium/phenazine ethosulphate, followed by incubation at 37 ºC for 40 min [28] and then each well was treated with 5% acetic acid. The absorbance of formazan products was determined at 620 nm wavelength to evaluate the parasite viability. log sigmoid dose-response curves using GraphPad Prism® 5.0 software was used to calculate IC_{50} values.

Larvicidal activity: The larvicidal activity was evaluated by using *Anopheles arabiensis* (KGB) larvae that were sourced from a permanent colony housed at the Botha de Meillon Insectary and fed according to established WHO protocols [29]. Test compounds at 50 µM concentration were incubated with 25 fourth instar larvae, the last larval stage before pupation, dissolved in distilled water for 24 h at 25-28 ºC. Mortality of the treated larvae was compared to DDT (dichlorodiphenyltrichloroethane), the positive control and experiments were repeated in quadruplicate. Then, larvae were photographed at 3x magnification to assess morphological changes relative to untreated and DDT-treated controls [30].

Ovicidal assay: To evaluate the impact of the quinoline-indolylacetamide derivatives on mosquito development, *A. arabiensis* (KGB) eggs were treated with the derivatives, as well as controls such as DDT and 1% formaldehyde solution.

The aim of the study was to assess whether these compounds affect the hatching ability of the larvae and to observe any changes in the morphological appearance of the eggs and developing larvae [30]. The derivatives and controls were screened at 0.5 μM, a concentration 10 times the LC_{50} of DDT. Then, eggs were incubated for 48 and 72 h and the number of larvae hatched was recorded at these intervals. Hatched eggs were examined under 3x magnification and the number of hatched larvae was expressed as a percentage of the number observed in the untreated water control. The experiment was conducted in triplicate for the reliable results.

Cytotoxicity: Three different cell lines were used: human embryonic kidney epithelial (HEK-293) cells as the control (normal) cell line and two cancer cell lines, myelogenous leukemia (K562) cells and human neuroblastoma (SH-SY5Y) cells to evaluate the cytotoxicity and anticancer potential of the synthesized compounds. The selection of these cell lines was according to their relevance in testing both general cytotoxicity (HEK-293) and specific anticancer activity (K562 and SH-SY5Y). These cells were cultured in Dulbecco's modified Eagle's medium (DMEM), a standard medium for supporting the growth of a wide variety of cell types. The medium was enriched with 10% fetal bovine serum (FBS) to supply necessary growth factors and nutrients to the parasite, as well as addition of 100 IU/mL penicillin and 100 μg/mL streptomycin which prevent bacterial contamination. The cells were incubated at 37 ºC in a humidified atmosphere of 5% CO_2, a physiological condition essential that promote optimal cell growth. A cell suspension was prepared for all three cell lines and the appropriate number of cells was seeded into 96-well plates as 15000 K562 cells/well for leukemia studies, 20000 HEK-293 cells/well for cytotoxicity analysis and 20000 SH-SY5Y cells/well for neuroblastoma testing. After seeding, the cells were kept in a humidified incubator for 24 h at 37 ºC so that cells got adhere to the bottom of the wells and grow. Then, the cells were treated with serial dilutions of the synthesized compounds or the positive control, camptothecin, a well-known anticancer agent. DMSO was used as a solvent to dissolve the test compounds and ensured that its concentration in all wells was less than 1%, as DMSO concentrations above this level can affect cell viability. The cells were then incubated for an additional 48 h at 37 ºC to allow sufficient time for the compounds to exert their effects. After 48 h of treatment, addition of 40 μL of MTT solution that prepared by taking 5 mg/mL in phosphate-buffered saline (pH 7.3) to each well was performed and then incubated at 37 ºC for 2 h. During this time, viable cells reduced the yellow MTT reagent into purple formazan crystals. Following incubation, the supernatant was carefully removed to eliminate excess MTT reagent and DMSO was added to each well to dissolve the formazan crystals. The optical density (absorbance) was measured at 540 nm wavelength, with a 690 nm (a reference wavelength), using a Labsystems Multiskan RC plate reader [31]. The 690 nm wavelength was used to correct for background absorbance, thereby ensuring more accurate results. The percent cellular viability was determined by comparing the absorbance of the treated wells to the control wells (which contained cells without any test compounds). To ensure the accuracy and reliability of the data, the entire experiment was performed in triplicate.

Haemolysis assay: To evaluate the haemolytic activity of the test compounds, a suspension of fresh human red blood cells was prepared in RPMI-1640 culture media supplemented as required with a 1% haematocrit. The suspension was incubated for 48 h with 25 μL of each test compound or control, at a concentration of 50 μM [32]. After incubation, the absorbance of supernatant was measured at 412 nm using a spectrophotometer to assess the extent of haemolysis. The percentage haemolysis was calculated by comparing the absorbance of the test samples to that of a 0.2% Triton X-100 solution, which served as the 100% haemolytic control. Quinine was included as the reference agent for comparison.

Artemia lethality assay: *Artemia franciscana* eggs placed in sea salt (38 g/L) were hatched in an aerated environment at an optimal temperature for 18 h [33]. To each well, 40-60 live *Artemia* in 400 μL water were added with the derivatives/control compounds and the plates left overnight at room temperature. Dead *Artemia* nauplii were then counted at 0, 24 and 48 h. All *Artemia* were killed following the addition of 25% acetic acid and total number of *Artemia* per well counted. Percentage mortality was then calculated taking the controls into account, where potassium dichromate was used as the positive control. The experiment was repeated in triplicate.

Molecular docking: For molecular docking studies, the 3D structure of *Eh*THRase was obtained from the Protein Data Bank (PDB ID: 3D8X). The chemical structures of the selected compounds were drawn using ChemDraw Ultra 16.0 and converted into PDB format *via* the ChemDraw 3D. To assess the binding interaction between the compounds and *Eh*THRase, molecular docking was performed using InstaDock, a user-friendly and automated molecular docking software designed to streamline virtual screening. This software simplifies the typically complex process of docking by automating key steps, such as ligand preparation and search space setup, making it accessible to researchers for high-throughput screening of multiple compounds. The binding interaction of output files of protein and ligands was visualized through Discovery Studio.

RESULTS AND DISCUSSION

The synthetic route for 2-(3-((2-(2-(quinolin-4-yloxy)-acetyl)hydrazineylidene)methyl)-1*H*-indol-1-yl)acetamide derivatives (**QC1–QC11**) is outlined in **Scheme-I**. These final compounds were synthesized by multi-steps process. First, different indole-acetamides were synthesized (**C1-C11**) by the reaction of indole-3-carboxaldehyde with different substituted 2-chloroacetamides. Then ethyl 2-(quinolin-4-yloxy)acetate (**4**) was synthesized from 4-hydroxyquinoline (**3**) and it was followed by synthesis of 2-(quinolin-8-yloxy)acetohydrazide (**5**). In final step, the formation of 2-(3-((2-(2-(quinolin-4-yloxy)-acetyl)hydrazineylidene)methyl)-1*H*-indol-1-yl)acetamide derivatives (**QC1–QC11**) was achieved by the reaction of 2-(quinolin-8-yloxy)acetohydrazide (**5**) with different indole-acetamide (**C1-C11**) using ethanol as solvent and sulfuric acid in catalytic amount at room temperature. The compounds were obtained in good to moderate yield (61% to 88%). All the final

products were soluble in DMSO and stable in solid state at room temperature.

IR, ^{1}H NMR, ^{13}C NMR and mass spectra were used for the structural confirmation. IR spectra showed characteristic bands for the formation of these new derivatives **QC1-QC11** where the appearance of two bands at 3298-3189 cm^{-1} and 1675-1654 cm^{-1} were assigned to the N-H and C=O stretching, respectively and the band at 1642-1595 cm^{-1} due to (C=N) suggested the condensation of different aldehydes with 2-(quinolin-8-yloxy)acetohydrazide. The NMR spectra of all the compounds at 300 MHz and also favour the proposed structures. In all the compounds, the two (N-H) protons appeared as a singlet at δ 9.77-11.90 ppm (-NH-N) and δ 8.92-11.30 ppm (CONH), respectively. The aromatic substituted amide NH appeared at δ 10.13-10.70 ppm. The peak for aldehyde group in **C1-C15** was observed at δ 9.90-9.98 ppm but absent in final compounds (**QC1-QC11**) showed the formation of the desired products. The signals for the aromatic regions appeared in their respective region. Further the proton peaks for two -CH_2 groups in hydrazones appeared at δ 5.01-5.59 ppm and δ 4.90-5.11 ppm, respectively. ^{13}C NMR spectra also supported the structure of these compounds. The appearance of characteristic signals for carbonyl carbon atoms in the range of δ 170.68-168.8 ppm and δ 168.2-164.8 ppm clearly favoured the formation of the final compounds. The CHNS analysis data confirmed the purity of the compounds in accordance with 0.3%.

Biological evaluation

Anti-amoebic activity: The anti-amoebic results evaluated in comparison with MTZ (IC_{50} value = 1.80 μM) that IC_{50} values were determined to be in the range of 0.36 to 30.94 μM for 2-(3-((2-(2-(quinolin-4-yloxy)acetyl)hydrazineylidene)-methyl)-1*H*-indol-1-yl)acetamide derivatives (**QC1-QC11**). The hydrazone linkage was found to greatly enhance the anti-amoebic activity to a great extent (Table-1). Of the eleven compounds, eight compounds **QC2**, **QC3**, **QC4**, **QC5**, **QC6**, **QC7**, **QC8** and **QC11** were found to possess good activity *i.e.* better than MTZ. The bulkiest compound **QC4** showed the lowest IC_{50} value IC_{50} 0.36 ± 0.01 μM. The compounds with *p*-methyl **QC7** (IC_{50} = 0.87 ± 0.02 μM) and *o*-methyl **QC8** (IC_{50} = 0.58 ± 0.01 μM) substitution exhibited promising anti-amoebic activity, whereas the *meta* substituted methyl **QC1** (IC_{50} = 2.81 ± 0.02 μM) showed slightly higher IC_{50} value than MTZ. Incorporation of two methyl groups in **QC10** (IC_{50} = 30.94 ± 0.02 μM) highly reduced the activity by increasing the IC_{50} value to a great extent of making the compound inactive. The result concluded that these derivatives were potent against amoebic strain *E. histolytica.*

TABLE-1
In vitro ANTI-AMOEBIC ACTIVITY DATA OF QUINOLINE-INDOLYLACETAMIDE DERIVATIVES (**QC1-QC11**), AGAINST HM1:IMSS STRAIN OF *E. histolytica*

Compound	Anti-amoebic (72 h)	
	IC_{50} (μM)	± S.D
QC1	2.81	0.024
QC2	1.69	0.011
QC3	0.61	0.041
QC4	0.36	0.005
QC5	1.22	0.013
QC6	1.33	0.018
QC7	0.87	0.015
QC8	0.68	0.005
QC9	10.02	0.018
QC10	30.94	0.020
QC11	1.57	0.020
MTZ	1.80	0.000

Antimalarial activity and cytotoxicity profile: The antimalarial profile showed that compounds **QC1-QC11** were not active against the intra-erythrocytic malaria parasite with only ~23% inhibition observed for **QC2** and **QC4**; which was not comparable to that of standard antimalarial agent, quinine. The small inhibitory effect observed as the derivatives did not affect the permeability or viability of the host red blood cell as evident by the lack of haemolysis [haemolysis range: 0.11-2.94%] compared to 1.76% for quinine. When evaluated against a normalized human kidney epithelial (HEK293) cell line, the derivatives did not appear to be toxic to the cells with **QC5** the most toxic (38% inhibition of cell growth); where **QC2** and **QC4** only inhibited 12% and 23% cell viability, respectively. This greatly contrasted the inhibitory effect of these derivatives on the human SH-SY5Y neuroblastoma cell line with **QC2** and **QC4** inhibiting 52% and 64% cell viability, respectively. Overall, the human SH-SY5Y neuroblastoma cell line was the most sensitive to all the derivatives and warrants further investigation. The human erythroleukemia K562 cell line was not as sensitive to the effects of the derivatives as the SH-SY5Y cells, with only 32% and 40% of the cells being killed at 100 μM by **QC2** and **QC4**, respectively (Table-2). The latter results indicated that the inhibitory effects observed on these human cell lines and the malaria parasite could be against a common target or display general toxicity that does not support further investigation into these derivatives due to a low safety index.

The ovicidal activity of these derivatives on the hatching rate of the *Anopheles* eggs was compared to 1% formaldehyde and DDT over a time period of 72 h. DDT (8.80%), **QC2** (7.84%) and **QC7** (7.59%) produced similar minimal inhibition of hatching compared to 1% formaldehyde (100%), where the remainder of the derivatives lacked ovicidal activity. A similar trend was observed after 48 h of incubation of larvae with these derivatives. There was no indication of any alteration to the shape or morphology of the treated eggs or the hatching larvae. When the derivatives were incubated with older 4th instar larvae for 72 h, all the derivatives were observed to inhibit the viability of larvae (40-49%) in a time-dependent manner. The lethality assays indicated a maximum percentage inhibition of 49% by **QC1**, **QC6** and **QC7** compared to 100% by DDT. No gross morphological alterations to *Anopheles* larvae were observed compared to the untreated control, while larvae treated with DDT were greatly affected in size and morphology. Further, to ensure the inhibitory effects of these derivatives, they were directly targeted to the mosquito larvae, *Artemia franciscana* as a toxicity control. As for the larvicidal activity, **QC4** was the most toxic with 48.64% lethality of *Artemia* nauplii compared to 99.44% by potassium dichromate. Whilst the remaining derivatives were less toxic, indicating that the *Artemia* were

TABLE-2
ANTIMALARIAL AND CYTOTOXICITY ASSAY DATA OF QUINOLINE-INDOLYLACETAMIDE DERIVATIVES (**QC1-QC11**)

Compound	Antimalarial activity at 50 µM (% growth ± S.D.)	Cytotoxicity profile at 100 µM (% Growth ± S.D)		
		HEK-293	K562	SH-SY5Y
QC1	87.96 ± 2.44	70.43 ± 6.06	66.97 ± 2.91	49.99 ± 1.08
QC2	77.41 ± 26.4	86.77 ± 4.94	67.54 ± 3.23	47.97 ± 4.10
QC3	80.39 ± 9.9	88.12 ± 2.54	67.98 ± 1.74	50.27 ± 1.13
QC4	77.87 ± 9.41	76.55 ± 1.20	60.10 ± 2.46	33.59 ± 2.57
QC5	102.12 ± 10.05	62.03 ± 2.30	81.95 ± 2.26	75.6 0 ± 5.37
QC6	96.78 ± 8.47	78.60 ± 2.16	81.20 ± 3.96	54.45 ± 2.75
QC7	93.54 ± 16.08	74.70 ± 3.40	69.68 ± 3.95	49.33 ± 1.71
QC8	96.23 ± 17.13	74.43 ± 3.32	68.93 ± 3.64	50.30 ± 2.57
QC9	81.33 ± 26.54	92.47 ± 4.88	80.09 ± 2.34	47.46 ± 2.20
QC10	97.54 ± 9.55	88.26 ± 9.22	73.04 ± 1.13	53.15 ± 1.89
QC11	82.63 ± 28.13	79.93 ± 4.56	70.68 ± 0.96	49.15 ± 0.59
Quinine	20.51 ± 4.50	n.t	n.t	n.t
Camptothecin	n.t	0.13 ± 0.11	0.13 ± 0.04	0.53 ± 0.40

less sensitive to the derivatives than the larvae (lethality range: 0-9.03%), with **QC3** and **QC10** the more toxic (6.44% and 9.03%, respectively) (Table-3).

TABLE-3
% LARVICIDAL ACTIVITY, % OVICIDAL ACTIVITY AND % LETHALITY DATA OF *Artemia nauplii* OF QUINOLINE-INDOLYLACETAMIDE DERIVATIVES (**QC1-QC11**)

Compd.	Larvicidal activity at 50 µM (% Lethality)	% Ovicidal activity of *Anopheles* eggs at 50 µM	% Lethality of *Artemia nauplii* at 50 µM
QC1	49.00	100.20	0.00
QC2	45.00	92.16	0.86
QC3	40.00	97.72	6.44
QC4	45.00	100.88	48.54
QC5	48.00	104.04	0.00
QC6	49.00	104.20	0.00
QC7	49.00	92.41	0.00
QC8	40.00	94.86	0.00
QC9	48.00	96.49	5.33
QC10	46.00	99.12	9.03
QC11	41.00	98.49	0.00
DDT	100.00	98.49	n.t
$K_2Cr_2O_7$	n.t	n.t	99.44

Molecular docking studies: Interaction characteristics of 2-(3-((2-(2-(quinolin-4-yloxy)acetyl)hydrazineylidene)-methyl)-1*H*-indol-1-yl)acetamide derivatives (**QC1-QC11)** with enzyme *Eh*THRase revealed the good binding affinity for these compounds ranged -7.7 to -8.9 (kcal/mol). Compounds **QC4**, **QC5, QC6** and **QC7** were recorded with binding free energy of -8.7, -8.8, -8.9 and -8.6 (kcal/mol) showing strong binding interaction while **QC3** had the least negative value (-7.7 kcal/mol), implying weaker binding. Further, all compounds had *p*Ki in range between 5.65 to 6.53. The *p*Ki value was the highest 6.53 for **QC6**, showed stronger inhibition against biological targets and was lowest for **QC3**, with a *p*Ki of 5.65. Ligand efficiency values ranged from 0.216 kcal/mol/non-H atom (**QC1**) to 0.254 kcal/mol/non-H atom (**QC6**). The presence of multiple and stronger hydrogen bonds often correlates with better binding stability. Compound **QC4** showed short hydrogen bond distance 2.70 Å with amino acid GLY 39, **QC5** showed 2.28 Å with SER 88, **QC6** appeared with two short hydrogen bonds with 2.20 Å and 2.42 Å with amino acids ASP 264, GLY 274 while **QC7** distance was 2.23 Å with ASP 264. Based on the binding strength, efficiency and interactions with a target protein, these quinoline-indole hydrazone derivatives appeared to be promising candidates (Fig. 3, Table-4).

Conclusion

The synthesis and characterization of 2-(3-((2-(2-(quinolin-4-yloxy)acetyl)hydrazineylidene)methyl)-1*H*-indol-1-yl)-

TABLE-4
BINDING AFFINITY VALUES OF QUINOLINE-INDOLYLACETAMIDE DERIVATIVES (**QC1-QC11**)

Compound	Binding free energy (kcal/mol)	pKi	Ligand efficiency (kcal/mol/non-H atom)	Hydrogen bond	
				Amino acid residues	Distance (Å)
QC1	-8.0	5.87	0.216	GLN 274, SER 275	2.96, 3.42
QC2	-8.2	6.03	0.235	GLN 171, ASN 202	3.33, 3.31
QC3	-7.7	5.65	0.233	PRO 273, ASP 291	3.35, 3.21
QC4	-8.7	6.38	0.234	GLY 39, TRP 135, THR 49	2.70, 3.58, 3.69
QC5	-8.8	6.45	0.237	SER 88, ASN 38, ALA 253	2.28, 3.08, 3.58
QC6	-8.9	6.53	0.254	ASP 264, GLY 274	2.20, 2.42
QC7	-8.6	6.31	0.232	ASP 264, GLY 274	2.23, 3.02
QC8	-8.1	5.95	0.217	SER 275, GLN 290	3.38, 3.84
QC9	-8.3	6.11	0.220	THR 271, SER 274, GLN 303	3.35, 3.75, 3.58
QC10	-8.5	6.23	0.223	ALA 247	3.06
QC11	-8.4	6.17	0.235	GLN 290, SER 292, LYS 270	2.96, 3.36, 3.37

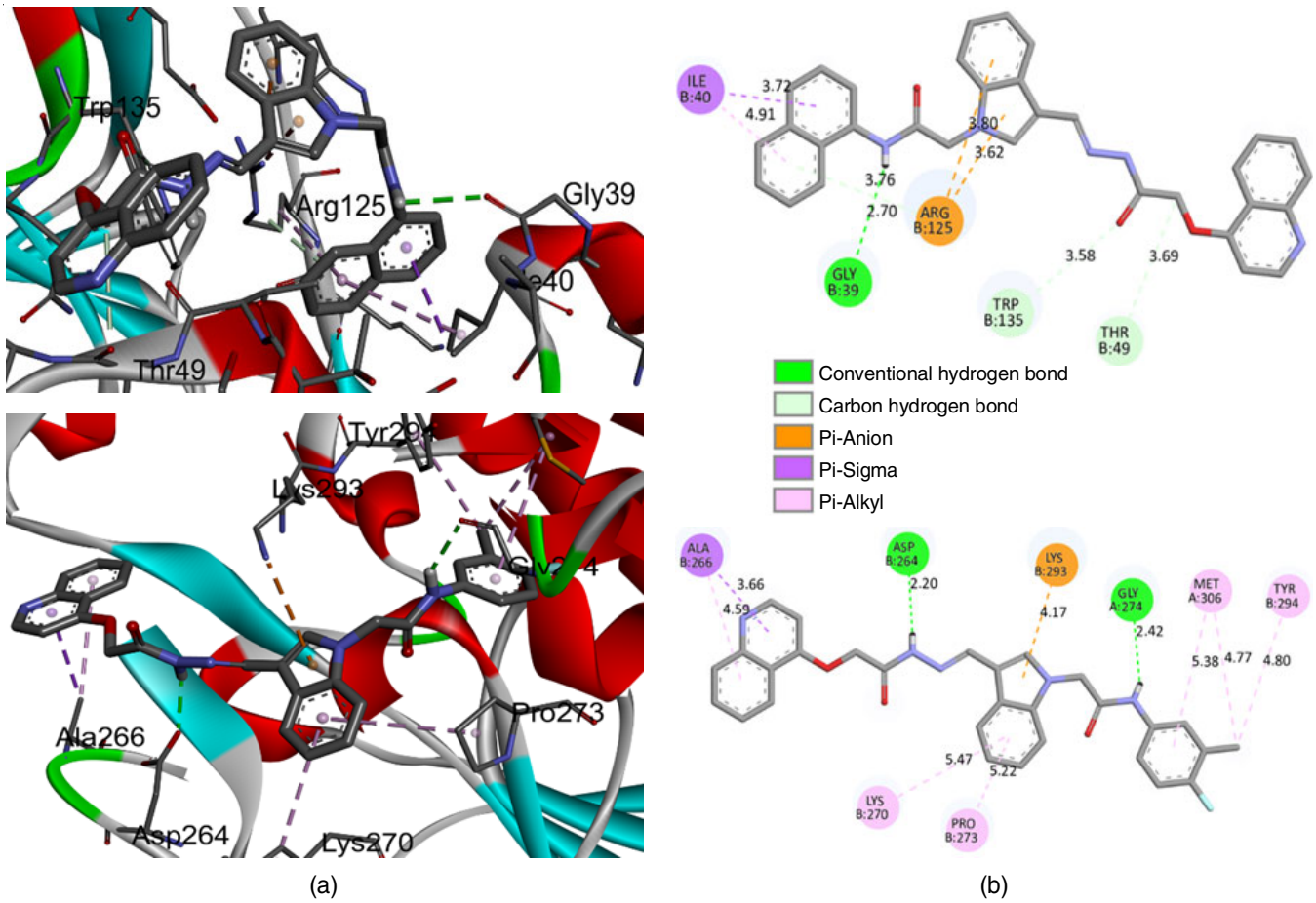


Fig. 3. Docking interaction between enzyme *Eh*THRase (PDB id: 3D8X) and derivatives **QC4** and **QC6**, (a) represent 3D interaction (b) represent 2D interaction

acetamide derivatives (**QC1-QC11**) was performed. The anti-amoebic activity of the synthesized derivatives was examined using HM1:IMSS strain of *E. histolytica* and the results showed that the derivatives **QC1-QC11** exhibited potent anti-amoebic activity. Eight compounds **QC2**, **QC3**, **QC4**, **QC5**, **QC6**, **QC7**, **QC8** and **QC11** were exhibited lower IC_{50} more effective than MTZ (IC_{50} = 1.8 µM). Among those, **QC4** was most potent with lowest IC_{50} value 0.36 ± 0.01 µM. But antimalarial activity of these compounds against NS54 strain of *P. falciparum* was negligible with small inhibitory effect of only two compounds **QC2** and **QC4** in comparison to quinine. Further, cytotoxicity profile showed that of all the derivatives, **QC4** displayed general toxicity to all the organisms and cells used in this study, with **QC2** showing minimal toxicity to these same biological systems. The molecular docking simulations with enzyme *Eh*THRase (PDB id: 3D8X) provided insights into the binding affinities showing these derivatives to be promising as drug candidates with binding free energy ranging -7.7 to -8.9 kcal/mol. Compound **QC6** had strongest binding interaction with binding energy -8.9 kcal/mol followed by **QC4** and **QC5** with -8.7 and -8.8 kcal/mol, respectively. **QC6** also had the highest *p*Ki of 6.53, correlating with its strong binding affinity. Overall, these derivatives **QC1-QC11** were potent against parasite *E. histolytica* and the data supported the further investigation of these type of compounds as anti-amoebic agent.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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