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Synthesis of 2-(*N*-cyclicamino)quinoline combined with methyl (*E*)-3-(2/3/4-aminophenyl)acrylates as potential antiparasitic agents

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Abstract

A rationally designed series of 2-(*N*-cyclicamino)quinolines coupled with methyl (*E*)-3-(2/3/4-aminophenyl)acrylates was synthesized and subjected to in vitro screening bioassays for potential antiplasmodial and antitrypanosomal activities against a chloroquine-sensitive (3D7) strain of *Plasmodium falciparum* and nagana *Trypanosoma brucei brucei* 427, respectively. Substituent effects on activity were evaluated; *meta*-acrylate **24** and the *ortho*-acrylate **29** exhibited the highest antiplasmodial (IC_{50} = 1.4 μM) and antitrypanosomal (IC_{50} = 10.4 μM) activities, respectively. The activity against HeLa cells showed that the synthesized analogs are not cytotoxic at the maximum tested concentration. The ADME (absorption, distribution, metabolism, and excretion) drug-like properties of the synthesized compounds were predicted through the SwissADME software.

KEYWORDS
2-(*N*-cyclicamino)quinolines, ADME, aminophenylacrylates, antiplasmodial, antitrypanosomal

1 | INTRODUCTION

Malaria and human African trypanosomiasis (HAT) remain serious health risks and are caused by infection with *Plasmodium* spp. and *Trypanosoma brucei* spp., respectively. These protozoan parasitic diseases are responsible for significant morbidity and mortality and are predominantly rife in low-income countries.[1–4] Despite progress regarding the development of vaccines and new compounds with sought-after activity, the rising incidence of drug resistance and excessive peril of systemic toxicity have limited the efficacy of the frontline therapeutic agents.[5–9] Therefore, there is a pressing need to develop new and safe therapeutics with desirable therapeutic window and low propensity for drug resistance.

Quinoline-containing compounds display a broad range of biological activities including antimalarial,[10] antitrypanosomal,[11] antitubercular,[12] antifungal,[13] antibacterial,[14] anticancer,[15] and anti-human immunodeficiency virus (HIV)[16] activities. Quinoline derivatives diversely functionalized with 2-*N*-cyclicamino moieties have been demonstrated to exhibit a variety of pharmacological activities. For example, the research group of Raval prepared quinoline-containing morpholine derivative **1** (Figure 1) that showed

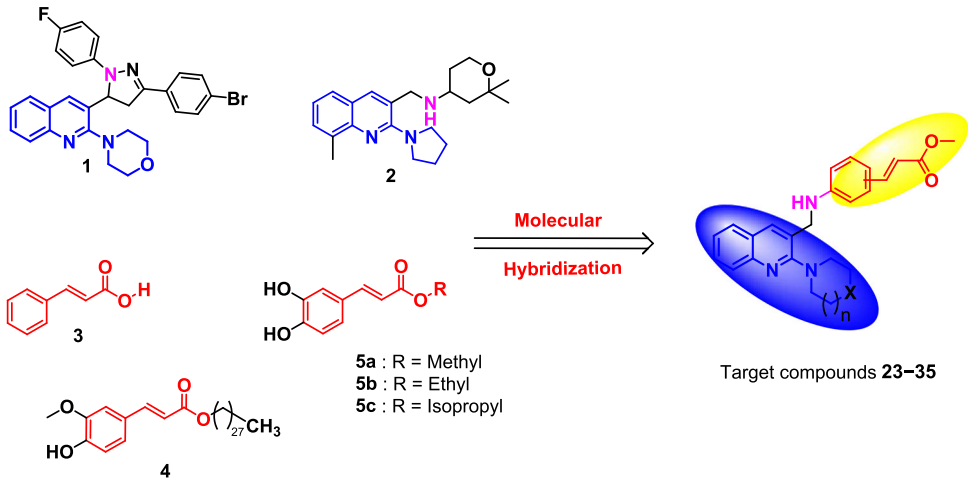


FIGURE 1 Representative biologically active 2-(*N*-cyclicamino)quinolines (**1**, **2**), cinnamic compounds (**3**–**5**), and the target hybrid compounds **23**–**35**

effects as an antimalarial agent.[17] In a separate study, Dias and coworkers reported compound **2** containing the pyrrolidine ring that displayed a superior (IC_{50} = 22 nM) antimalarial potency.[18] However, cinnamic acid **3** and its derivatives are widely distributed in nature and have attracted the attention of many medicinal chemists due to the common occurrence in plants and the low toxicity for humans, animals, and environment.[19,20] The potential of cinnamic acid derivatives as therapeutics for the treatment of malaria,[21] HAT,[22] tuberculosis,[23] fungal infections,[24] HIV,[25] and cancer[26] is well documented in the literature. For instance, cinnamic acid ester derivative **4** isolated from the bark of *Erythrina caffra* exhibited moderate antiplasmodial activity against a chloroquine-sensitive (NF54) strain of the *Plasmodium falciparum* parasite. More recently, the groups of Alson[27] and Schmidt[28] reported readily accessible cinnamic acid derivatives **5a–c** that displayed good antiplasmodial and antitrypanosomal activities against *P. falciparum* and *Trypanosoma brucei rhodesiense*, respectively.

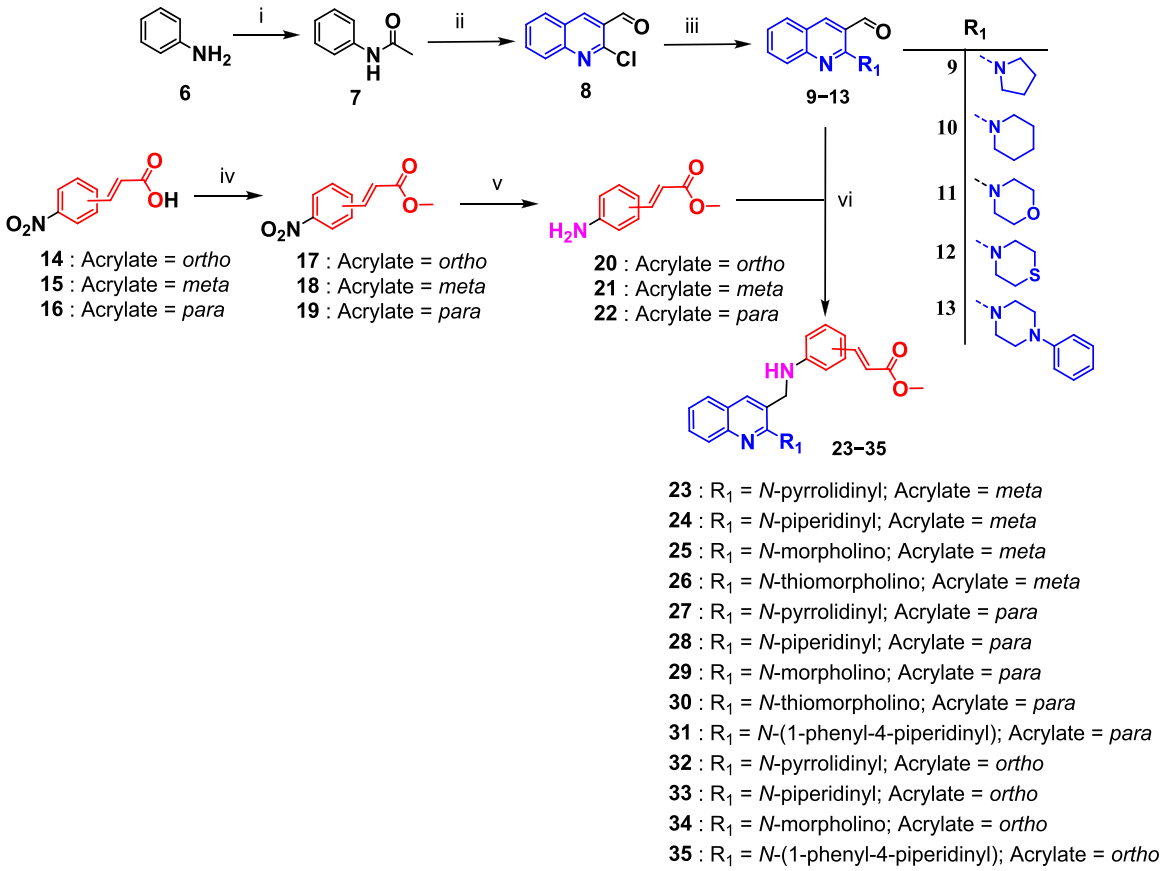
The hybridization of two or more bioactive structural units into a single molecule is an appealing approach that has been extensively utilized to design bioactive compounds in the field of medicinal chemistry.[29] This recent rational approach of drug design characterized as covalent biotherapy involves linking two known biologically active molecules by virtue of the presence of critical structural features essential for desired pharmacologic effect into a single agent, thus imprinting dual activities into a single hybrid molecule.[30] In this study, we employed a molecular hybridization approach to design a target series of functionalized quinoline 2-(*N*-cyclicamino) scaffold and cinnamic acid esters. From the above observations, we hoped that the synthesis of novel quinolines incorporating the cinnamic acid ester structural motif could lead to potent anti-infective compounds against protozoan infectious parasitic diseases caused by *P. falciparum* and *T. b. brucei*. Consequently, we wish to report the synthesis and characterization of a representative series of novel and nontoxic cinnamate-based quinoline derivatives, alongside their in vitro antiplasmodial and antitrypanosomal activities.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

Synthesis of our target compounds **23**–**35** followed the general pathway illustrated in Scheme 1. Treatment of aniline **6** with acetic anhydride in glacial acetic acid afforded the corresponding *N*-phenylacetamide **7** in an excellent yield (98%). Cyclization of compound **7** through the Vilsmeier–Haack reaction conditions afforded quinoline scaffold **8**, which contains –Cl and –CHO moieties on C-2 and C-3, respectively. Both moieties serve as handles to expand the series by exploring the chemical space around the quinoline ring. Thus, treatment of quinoline **8** with various cyclic amines under refluxing conditions led to the nucleophilic substitution of the –Cl atom on C-2 to obtain critical precursors **9**–**13** in yields ranging from 61% to 80%. Esterification of the *trans*-nitro cinnamic acids **14**–**16** was carried out using acidified methanol solution to afford methyl *trans*-nitro cinnamate esters **17**–**19** in 88–98% yields. Selective reduction of the NO_2 moiety in the obtained esters using activated Zn powder and NH_4Cl as a hydrogen source furnished methyl *trans* amino cinnamate esters **20**–**22** in good yields. Finally, Schiff base condensation reaction between precursors **9**–**13** and *trans* amino cinnamate esters **20**–**22**, followed by in situ reduction of the imine intermediates with sodium cyanoborohydride, afforded target compounds **23**–**35** in 31–75% yields.

All the target compounds were fully characterized by routine spectroscopic techniques. Infrared (IR) spectra of **23**–**35** showed a single spike weak band at ca. 3450–3300 cm^{-1}, which is indicative of the secondary amino (N–H) group. The ^1H NMR spectra confirmed all the aromatic and aliphatic protons, thus supporting key structural



SCHEME 1 Synthesis of the target compounds **23–35**. Reagents and conditions: (i) Ac_2O, AcOH, reflux, 30 min; (ii) DMF-$POCl_3$, 80°C, 5-18 h; (iii) DMF, K_2CO_3, cyclic amines, reflux, 2.5–10 h; (iv) MeOH, H_2SO_4 (cat), reflux, 3 h; (v) Zn, NH_4Cl, MeOH, r.t, 3 h; (vi) (a) MeOH, AcOH (cat), reflux, 12 h, (b) $NaCNBH_3$, 0°C to r.t, 12 h

features of each compound. More importantly, the disappearance of aldehydic signal at ca. 10.5 ppm observed in intermediates **9–13** and the appearance of a singlet methylene group at chemical shift ca. 4.48 ppm in the target compounds served as an indication of successful reductive amination between compounds **9–13** and **20–22** to form the desired compounds. The ^{1}H NMR of the target compounds showed a broad singlet at ca. 5.05–4.40 ppm on their respective spectrum, suggesting the successful formation of –HN–CH_2– moiety. Furthermore, the two doublets (J = 15.7–16.0 Hz) at δ ca. 6.13–6.39 and 7.62–7.86 ppm are attributed to the two –CH groups of methyl acrylate. These coupling constants are consistent with a *trans* geometry (J_{trans}) at the double bond found in our cinnamate ester bond. ^{13}C NMR spectra of precursors **9–13** showed a peak at ca. 190 ppm that was assigned to the –CHO unit of the aldehyde, and the appearance of a new peak at ca. 51.5 ppm in compounds **23–35** further corroborates the coupling of an aldehyde unit and the primary amine to yield the secondary –HN–CH_2– amine functionality.

2.2 | Pharmacology

The synthesized compounds were subjected to in vitro screening bioassays, as described in the experimental section. Compounds **23–25** were initially tested at a single concentration (20 μM) to determine cell viability, and the results are summarized in Figure 2. Cytotoxicity against HeLa cells, antiplasmodial activity against the chloroquine-sensitive strain (3D7) of *P. falciparum*, and antitrypanosomal activity against *T. b. brucei* 427 were evaluated using solutions of the synthesized compounds. Emetine, chloroquine, and pentamidine were used as positive controls for cytotoxicity, antiplasmodial, and antitrypanosomal activity, respectively.

From Figure 2, none of the compounds reported herein reduced HeLa cell viability to below 50% during a 24 h incubation, suggesting

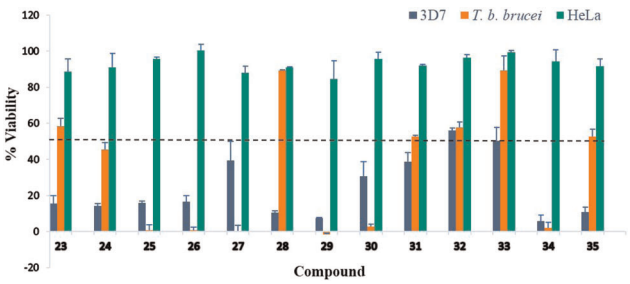


FIGURE 2 Percentage viability assessments of the 3D7 chloroquine-sensitive strain of *Plasmodium falciparum*, *Trypanosoma brucei brucei* 427 strain, and HeLa cells at 20 μM concentration of test compounds **23–35**

TABLE 1 IC_{50} values for inhibition of 3D7, *T. b. brucei*, and ADME values of compounds **23–35**

Compound	IC_{50} (μM)		XlogP3	Mw	ROF	PA
	P. falciparum 3D7[a]	*T. b. brucei*[a]				
23	9.1 ± 0.25	>50	4.9	397.47	None	None
24	**1.4 ± 0.05**	21.1 ± 2.35	**5.3**	401.50	None	None
25	**3.1 ± 0.13**	41.8 ± 2.67	4.0	403.47	None	None
26	**3.1 ± 0.17**	27.3 ± 1.79	4.8	419.54	None	None
27	26.3 ± 2.43	33.7 ± 3.23	4.8	387.47	None	None
28	7.0 ± 1.23	>50	5.3	401.50	None	None
29	16.6 ± 1.78	10.4 ± 0.58	4.0	403.47	None	None
30	16.7 ± 2.55	13.3 ± 1.82	4.8	419.54	None	None
31	**1.8 ± 0.08**	>50	**6.0**	478.58	None	None
32	>50	>50	4.8	387.47	None	None
33	>50	>50	5.3	401.50	None	None
34	7.5 ± 0.98	10.7 ± 1.61	4.0	403.47	None	None
35	8.3 ± 1.24	>50	6.0	478.58	None	None
CQ	0.023	–	–	–	–	–
PMD	–	0.017	–	–	–	–

Note: All the parameters were calculated or predicted using the free online SwissADME tool.

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; CQ, chloroquine; Mw, molecular weight; PA, pain alert; PMD, pentamidine; ROF, Lipinski's rule of five; XlogP3, calculated lipophilicity.

[a]The values are the mean ± *SD* of experiments performed in triplicate.

that they possess little overt cytotoxicity risk at the concentrations used for antiplasmodial and antitrypanosomal evaluation. With regard to antiplasmodial activity, eleven quinoline–cinnamate derivatives (excluding **32** and **33**) exhibited required activities with a *P. falciparum* cell viability of less than 50%, whereas six analogs from the series (**25**, **26**, **27**, **29**, **30**, and **34**) showed an antitrypanosomal activity with a *T. b. brucei* cell viability as low as less than 3% at 20 μM.

Subsequently, dose–response analyses were conducted for compounds exhibiting a reduced parasite viability of less than 50% to generate the corresponding IC_{50} values (Table 1). It is observed that structural variation around the quinoline ring (R) and/or position of acrylate scaffold influenced the antiparasitic activity. Compound inhibition levels, as evidenced by the IC_{50} data, vary significantly from ligand to ligand, and observed structure–activity trends suggested that the target compounds were more selective toward *P. falciparum* as compared with the *T. b. brucei*. Majority of compounds showed a moderate antiplasmodial activity with IC_{50} values in the low micromolar range, and compound **24** emerged as the most active compound with an IC_{50} value of 1.4 μM. Compounds **23**, **27**, and **32** exhibiting the pyrrolidine moiety at position 2 of the quinoline scaffold showed poor activity in the respective *meta*, *para*, and *ortho* acrylates, and this suggests that the size of the cycloamine influences biological activity. Regarding the *trans*-cinnamic acid ester, the inhibitory activities of the ligands against *P. falciparum* appear in the following order: *meta* position as shown by **23** (9.11 μM), **24** (1.4 μM), **25** (3.10 μM), **26** (3.09 μM) > *para* position **27** (26.3 μM), **28** (7.0 μM), **29** (16.6 μM), **30** (16.7 μM), **31** (1.8 μM) > *ortho* position **32** (>50 μM), **33** (>50 μM), **34** (7.5 μM), **35** (8.3 μM). The ADME (absorption, distribution, metabolism, and excretion) drug-like properties of the synthesized compounds were predicted through the SwissADME software.[31] The calculated lipophilicity (XlogP3) value for these compounds was four or above, but not more than six, and their water solubility profiles were predicted to be moderately or poorly soluble. These compounds were also predicted to have a low risk of acting as pan-assay interference (PAIN) compounds and they all satisfied Lipinski's rule of five.

In silico docking studies were undertaken to assess the binding affinity of compounds **23–35** on an X-ray structure of falcipain-2 (a well-studied *P. falciparum* drug target) co-crystallized with E-64 (PDB ID 3BPF). Studied using Glide Ligand Docking as implemented in Maestro in the Schrödinger package, the detailed results are summarized (Table 1S) in the Supporting Information file. The crystal structure ligand has a binding affinity of −5.985 kcal/mol, whereas the structures presented in this study have a binding affinity between −4.711 and −5.775 kcal/mol. These values indicate that the compounds presented in this study have a relatively good binding affinity, comparable to the crystal ligand. The crystal ligand has an intramolecular interaction with CYS42 residue of 3BPF; the same interaction is observed for compound **30** that has the best binding affinity of −5.775 kcal/mol, as shown in Figures 3a and 3b, respectively. Compound **26** that has the least binding affinity of −4.711 kcal/mol has no similar interactions with 3BPF, as shown in

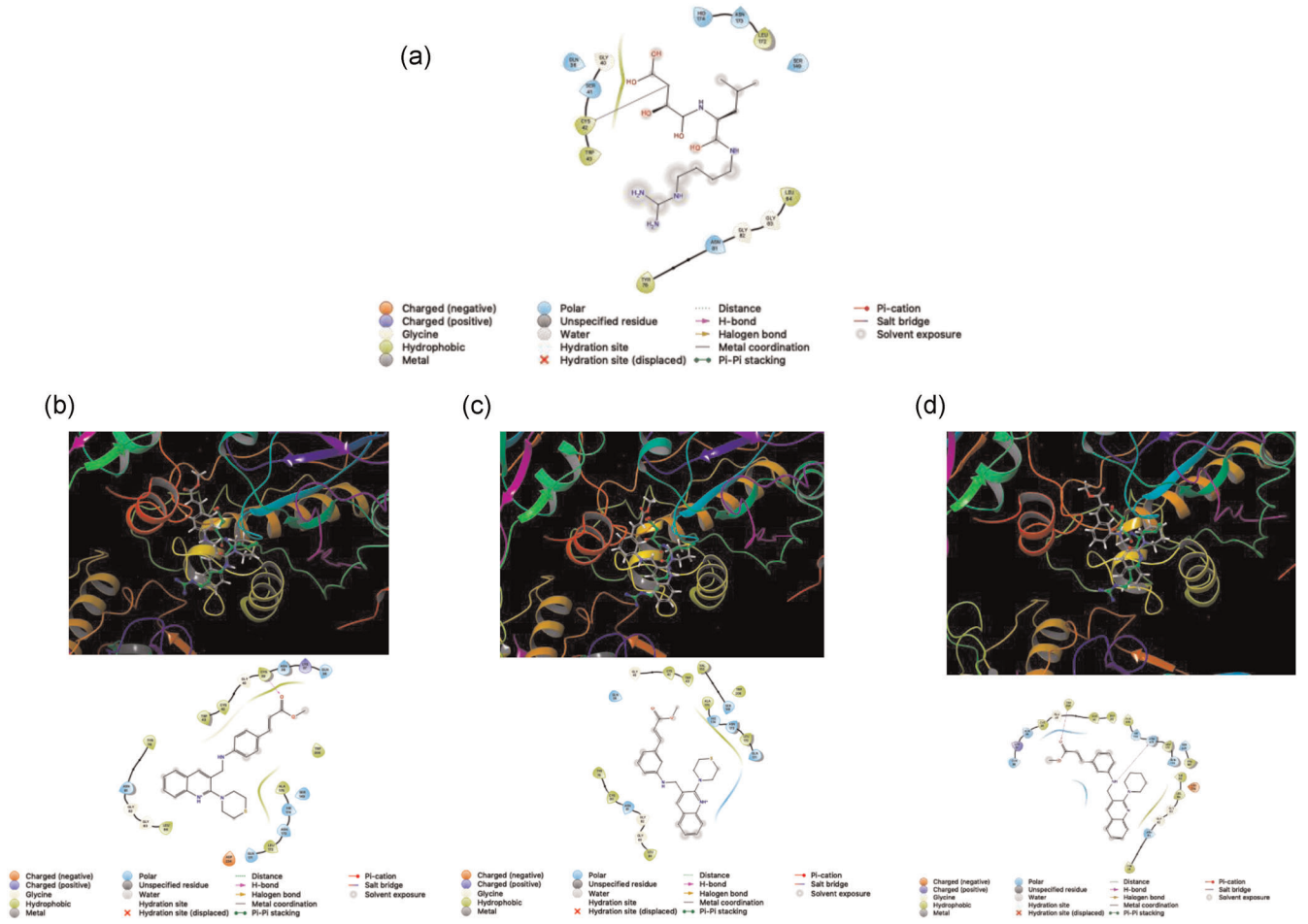


FIGURE 3 (a) Protein–ligand interaction of 3BPF and its crystal ligand reference E-64. (b) Docking pose of crystal ligand and compound **30** and protein–ligand interaction of compound **30**. (c) Docking pose of crystal ligand and compound **26** and protein–ligand interaction of compound **26**. (d) Docking pose of crystal ligand and compound **24** and protein–ligand interaction of compound **24**

Figure 3c. Compound **24** that showed the best antiplasmodial activity experimentally has the binding affinity of −5.405 kcal/mol. The protein–ligand interactions of compound **24** in Figure 3d show the presence of two intramolecular hydrogen bonds, one with TRP206 residue where oxygen of compound **24** acts as an acceptor in the hydrogen bonding and the other with ASN173 residue where hydrogen of the amine of compound **24** serves as a donor.

3 | CONCLUSION

Herein, we presented a focused series of 2-(*N*-cyclicamino)quinolines incorporating a cinnamic acid ester unit. Target compounds were realized through a simple hybridization strategy and tested against HeLa cells, 3D7 strain of *P. falciparum*, and *T. b. brucei* to evaluate the cytotoxicity, antiplasmodial, and antitrypanosomal potentials, respectively. Although none of the compounds showed a potential cytotoxic risk, 11 exhibited antiplasmodial and seven exhibited antitrypanosomal activities. The preliminary structure–activity relationship suggested that the presence of the *meta* acrylate in the quinoline–cinnamate derivatives displayed high inhibition potency against 3D7 of the *P. falciparum* parasite. Molecular docking insights of these derivatives have shown comparable binding affinities as falcipain-2 inhibitors. Even in the event that additional assays related to toxicity on other human cells, genotoxicity, in vivo experiments, and mechanism of action will be required to estimate their real potential, more important, biological data generated in this report revealed that this structurally new class of bioactive compounds has potential medicinal applications in the search for improved therapy, warranting further investigations.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All chemicals and solvents used were purchased from Merck®. Where necessary, solvents were purified according to procedures described by Vogel et al.[32] Thin-layer chromatography was performed using Merck

silica gel 60 PF_{254} plates and viewed under the UV light, and the silica gel column chromatography was carried out using Merck Kieselgel 60 Å: 70–230 (0.068–0.2 mm). Melting points were determined using a Stuart melting point apparatus SMP30 and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker Biospin 300, 400, or 600 MHz spectrometers, and the chemical shifts were reported in parts per million (ppm). The high-resolution mass spectra (HRMS) were recorded on a Waters API Q-TOF Ultima spectrometer (Stellenbosch University) and the IR spectra were recorded on a PerkinElmer 100 FT-IR spectrometer in the mid-IR range (640–4000 cm^{-1}). Compounds **7–13** and **17–22** were synthesized as per reported procedures; physical and spectral properties were in accordance with literature values.[33–36] The original spectra of the investigated compounds are provided as electronic supporting information (electrospray ionization [ESI]).

The InChI codes of the investigated compounds, together with some biological activity data, are also provided as ESI.

4.1.2 | General procedure for the synthesis of compounds **23–35**

To a solution of 2-(*N*-cyclicaminoquinoline-3-carbaldehydes **9–13** (0.50 mmol) in methanol (10 ml) and methyl amino cinnamate esters **20–22** (0.50 mmol), a few drops of glacial acetic acid were added, and the resultant reaction mixture was heated under reflux for 12 h. Thereafter, the reaction mixture was cooled to 0°C in an ice bath and sodium cyanoborohydride (1.0 mmol) was added portion-wise over a period of 10 min. The reaction mixture was allowed to stir at room temperature overnight. The solvent was evaporated in vacuo and the residue was dissolved in water (10 ml) and extracted with EtOAc (2 × 20 ml). The organic layers were combined and washed with brine (25 ml) and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (EtOAc–hexane 1:1) to give the desired products.

*Methyl-(E)-3-[3-({[2-(pyrrolidin-1-yl)quinolin-3-yl]methyl}amino)-phenyl] acrylate (**23**)*

Yellow solid; yield: 35%; m.p.: 99–101°C; ν_{max}/cm 3337 (N–H) and 1712 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.85 (1H, s, H-4), 7.75 (1H, d, *J* = 8.3 Hz, H-8), 7.62 (1H, d, *J* = 16.0 Hz, H-1‴), 7.54–7.52 (2H, m, H-6, H-5), 7.22–7.17 (2H, m, H-5‴, H-7), 6.92 (1H, d, *J* = 7.5 Hz, H-6‴), 6.77 (1H, s, H-2‴), 6.65 (1H, dd, *J* = 8.0, 1.9 Hz, H-4‴), 6.39 (1H, d, *J* = 16.0 Hz, H-2‴), 4.42 (2H, s, H-3′), 3.79 (3H, s, OCH_3), 3.73–3.70 (4H, m, H-2″), and 1.99–1.93 (4H, m, H-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.5, 155.9, 147.0, 144.3, 136.7, 134.4, 128.8, 128.3, 126.0, 125.2, 122.6, 121.5, 121.1, 116.7, 116.5, 113.9, 112.8, 110.9, 50.6, 48.7, 45.7, and 24.6; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2025, found 388.2023.

*Methyl-(E)-3-[3-({[2-(piperidin-1-yl)quinolin-3-yl]methyl}amino)-phenyl] acrylate (**24**)*

Yellow solid; yield: 57%; m.p.: 104–106°C; ν_{max}/cm 3426 (N–H) and 1724 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.03 (1H, s, H-4), 7.90 (1H, d, *J* = 8.4 Hz, H-8), 7.64–7.55 (3H, m, H-5, H-6, H-1‴), 7.35–7.31 (1H, m, H-7), 7.17 (1H, t, *J* = 7.8 Hz, H-5‴), 6.89 (1H, d, *J* = 7.6 Hz, H-6‴), 6.76 (1H, s, H-2‴), 6.65 (1H, dd, *J* = 8.0, 1.9 Hz, H-4‴), 6.37 (1H, d, *J* = 16.0 Hz, H-2‴), 4.73 (1H, s, NH), 4.44 (2H, s, H-3′), 3.79 (3H, s, OCH_3), 3.30–3.25 (4H, m, H-2″), 1.81–1.76 (4H, m, H-3″), and 1.70–1.65 (2H, m, H-4″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 161.2, 148.4, 146.5, 145.5, 136.6, 135.4, 129.8, 129.0, 127.5, 127.1, 126.7, 125.5, 124.4, 117.8, 117.5, 115.1, 112.0, 51.7 (2C), 44.7, 26.4, and 24.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182, found 402.2180.

*Methyl-(E)-3-(3-{[(2-morpholinoquinolin-3-yl)methyl]amino}phenyl)-acrylate (**25**)*

Brown solid; yield: 70%; m.p.: 131–133°C; ν_{max}/cm 3395 (N–H) and 1696 (CO); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.09 (1H, s, H-4), 7.90 (1H, d, *J* = 8.4 Hz, H-8), 7.66 (1H, d, *J* = 8.0 Hz, H-5), 7.63–7.58 (2H, m, H-6, H-1‴), 7.39–7.35 (1H, m, H-7), 7.18 (1H, t, *J* = 7.9 Hz, H-5‴), 6.91 (1H, d, *J* = 7.5 Hz, H-6‴), 6.76 (1H, s, H-2‴), 6.65 (1H, dd, *J* = 8.0, 1.9 Hz, H-4‴), 6.36 (1H, d, *J* = 16.0 Hz, H-2‴), 4.58 (1H, s, NH), 4.45 (2H, s, H-3′), 3.93–3.90 (4H, m, H-3″), 3.79 (3H, s, OCH_3), and 3.38–3.34 (4H, m, H-2″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.5, 159.9, 148.1, 146.5, 145.3, 137.2, 135.4, 129.9, 129.3, 127.7, 127.2, 126.0, 125.7, 124.8, 118.0, 117.6, 115.1, 111.9, 67.2, 51.7, 50.9, and 44.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_3$ $[M+H]^+$: 404.1974, found 404.1974.

*Methyl-(E)-3-(3-{[(2-thiomorpholinoquinolin-3-yl)methyl]amino}-phenyl) acrylate (**26**)*

Brown solid; yield: 45%; m.p.: 73–75°C; ν_{max}/cm 3418 (N–H) and 1704 (C=O); ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.08 (1H, s, H-4), 7.90 (1H, d, *J* = 8.4 Hz, H-8), 7.65 (1H, d, *J* = 8.3 Hz, H-5), 7.63–7.56 (2H, m, H-6, H-1‴), 7.37 (1H, t, *J* = 7.5 Hz, H-7), 7.18 (1H, t, *J* = 7.8 Hz, H-5‴), 6.90 (1H, d, *J* = 7.4 Hz, H-6‴), 6.74 (1H, s, H-2‴), 6.64 (1H, dd, *J* = 8.1, 2.0 Hz, H-4‴), 6.35 (1H, d, *J* = 16.0 Hz, H-2‴), 4.52 (1H, s, NH), 4.42 (2H, s, H-3′), 3.78 (3H, s, OCH_3), 3.63–3.60 (4H, m, H-2″), and 2.88–2.85 (4H, m, H-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.5, 160.7, 148.1, 146.4, 145.3, 137.0, 135.4, 129.9, 129.3, 127.7, 127.2, 126.3, 125.7, 124.8, 118.0, 117.6, 115.1, 111.9, 52.9, 51.7, 44.5, and 28.0; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2S$ $[M+H]^+$: 420.1746, found 420.1745.

*Methyl-(E)-3-[4-({[2-(pyrrolidin-1-yl)quinolin-3-yl]methyl}amino)-phenyl] acrylate (**27**)*

Yellow solid; yield: 31%; m.p.: 96–98°C; ν_{max}/cm 3423 (N–H) and 1707 (C=O); ^1H NMR (600 MHz, $CDCl_3$): δ_H 7.88 (1H, s, H-4), 7.61 (1H, d, *J* = 15.9 Hz, H-1‴), 7.57–7.51 (3H, m, H-8, H-5, H-7), 7.38 (2H, d, *J* = 8.5 Hz, H-2‴), 7.22 (1H, t, *J* = 7.4 Hz, H-6), 6.60 (2H, d, *J* = 8.6 Hz, H-3‴), 6.22 (1H, d, *J* = 15.9 Hz, H-2‴), 4.48 (2H, s, H-3′), 3.78 (3H, s, OCH_3), 3.73–3.71 (4H, m, H-2″), and 1.98–196 (4H, m, H-3″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 168.2, 161.2, 149.4, 145.1, 144.4, 134.0, 132.8, 130.0, 129.6, 127.0, 124.1, 122.7, 121.8, 112.9, 112.7, 111.9, 51.5, 49.8, 46.4, and 25.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2025; found 388.2031.

*Methyl-(E)-3-[4-({[2-(piperidin-1-yl)quinolin-3-yl]methyl}amino)-phenyl] acrylate (**28**)*

Yellow solid; yield: 35%; m.p.: 146–148°C; ν_{max}/cm 3422 (N–H) and 1704 (C═O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 8.00 (1H, s, H-4), 7.89 (1H, d, *J* = 8.2 Hz, H-8), 7.63 (1H, d, *J* = 8.0 Hz, H-5), 7.61–7.56 (2H, m, H-7, H-1‴), 7.37–7.32 (3H, m, H-6, H-2‴), 6.60 (2H, d, *J* = 8.6 Hz, H-3‴), 6.21 (1H, d, *J* = 15.9 Hz, H-2‴), 4.96 (1H, s, NH), 4.48 (2H, s, H-3′), 3.77 (3H, s, OCH_3), 3.29–3.23 (4H, m, H-2″), 1.78–1.76 (4H, m, H-3″), and 1.69–1.63 (2H, m, H-4″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 168.2, 161.1, 149.8, 146.5, 145.2, 136.6, 132.9, 130.0, 129.2, 127.5, 127.1, 126.2, 125.4, 124.5, 123.9, 112.8, 51.6, 51.4, 44.6, 26.4, and 24.5; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182; found 402.2181.

*Methyl-(E)-3-(4-{[(2-morpholinoquinolin-3-yl)methyl]amino}phenyl)-acrylate (**29**)*

Yellow solid; yield: 40%; m.p.: 147–149°C; ν_{max}/cm 3422 (N–H) and 1708 (C═O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 8.05 (1H, s, H-4), 7.91 (1H, d, *J* = 8.0 Hz, H-8), 7.66 (1H, d, *J* = 8.0 Hz, H-5), 7.63–7.57 (2H, m, H-7, H-1‴), 7.39–7.35 (3H, m, H-6, H-2″), 6.59 (2H, d, *J* = 8.5 Hz, H-3‴), 6.22 (1H, d, *J* = 15.9 Hz, H-2‴), 4.83 (1H, s, NH), 4.48 (2H, s, H-3′), 3.92–3.89 (4H, m, H-3″), 3.77 (3H, s, OCH_3), and 3.36–3.33 (4H, m, H-2″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 168.1, 159.7, 149.5, 146.1, 145.0, 137.2, 132.9, 130.0, 129.5, 127.6, 127.2, 125.6, 124.9, 124.2, 113.0, 112.8, 67.1, 51.5, 50.8, and 44.5; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_3$ $[M+H]^+$: 404.1974; found 404.1975.

*Methyl-(E)-3-(4-{[(2-thiomorpholinoquinolin-3-yl)methyl]amino}-phenyl) acrylate (**30**)*

Yellow solid; yield: 32%; m.p.: 94–98°C; ν_{max}/cm 3379 (N–H) and 1685 (C═O); ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 7.96 (1H, s, H-4), 7.83 (1H, d, *J* = 8.3 Hz, H-8), 7.57 (1H, d, *J* = 8.2 Hz, H-5), 7.54–7.49 (2H, m, H-7, H-1‴), 7.29–7.27 (3H, m, H-6, H-2″), 6.50 (2H, d, *J* = 8.5 Hz, H-3‴), 6.13 (1H, d, *J* = 15.9 Hz, H-2‴), 4.70 (1H, s, NH), 4.37 (2H, s, H-3′), 3.68 (3H, s, OCH_3), 3.54–3.50 (4H, m, H-2″), and 2.79–2.77 (4H, m, H-3″); ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 168.1, 160.4, 149.6, 145.0, 144.4, 136.1, 132.6, 130.0, 129.9, 127.6, 127.2, 126.0, 125.6, 125.0, 124.2, 112.8, 52.9, 51.5, 44.3, and 28.0; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2S$ $[M+H]^+$: 420.1746; found 420.1742.

*Methyl-(E)-3-[4-({[2-(4-phenylpiperazin-1-yl)quinolin-3-yl]methyl}-amino)phenyl] acrylate (**31**)*

Yellow solid; yield: 35%; m.p.: 160–162°C; ν_{max}/cm 3426 (N–H) and 1704 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.06 (1H, s, H-4), 7.93 (1H, d, *J* = 8.0 Hz, H-8), 7.67 (1H, d, *J* = 8.0 Hz, H-5), 7.64–7.59 (2H, m, H-1‴, H-7), 7.40–7.36 (3H, m, H-5, H-2″), 7.31 (2H, t, *J* = 7.9 Hz, H-6″), 7.01 (2H, d, *J* = 8.2 Hz, H-5″), 6.90 (1H, t, *J* = 7.3 Hz, H-7″), 6.61 (2H, d, *J* = 8.5 Hz, H-3‴), 6.23 (1H, d, *J* = 15.9 Hz, H-2‴), 4.87–4.84 (1H, m, NH), 4.52 (2H, d, *J* = 3.9 Hz, H-3′), 3.78 (3H, s, OCH_3), 3.55–3.51 (4H, m, H-3″), and 3.42–3.39 (4H, m, H-2″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.2, 159.8, 151.2, 149.6, 146.5, 145.1, 137.0, 130.0, 129.4, 129.2, 127.7, 127.2, 125.7, 125.6, 124.9, 124.1, 120.0, 116.2, 112.9, 112.8, 51.5, 50.3, 49.4, and 44.5; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_4O_2$ $[M+H]^+$: 479.2447, found 479.2439.

*Methyl-(E)-3-[2-({[2-(pyrrolidin-1-yl)quinolin-3-yl]methyl}amino)-phenyl] acrylate (**32**)*

Yellow solid; yield: 52%; m.p.: 98–100°C; ν_{max}/cm 3341 (N–H) and 1704 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.89 (1H, s, H-4), 7.86 (1H, d, *J* = 15.9 Hz, H-1‴), 7.77 (1H, d, *J* = 8.4 Hz, H-8), 7.57 (1H, d, *J* = 8.1 Hz, H-5), 7.56–7.51 (1H, m, H-6), 7.40 (1H, dd, *J* = 8.0, 0.96 Hz, H-6‴), 7.25–7.20 (2H, m, H-7, H-4‴), 6.76 (1H, t, *J* = 7.5 Hz, H-5‴), 6.60 (1H, d, *J* = 8.2 Hz, H-3‴), 6.38 (1H, d, *J* = 15.7 Hz, H-2‴), 4.66 (1H, s, NH), 4.48 (2H, d, *J* = 4.5 Hz, H-3′), 3.79 (3H, s, OCH_3), 3.71–3.68 (4H, m, H-2″), and 1.99–1.95 (4H, m, H-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 157.2, 147.0, 146.1, 140.2, 137.5, 131.7, 129.4, 128.4, 127.1, 126.5, 123.8, 122.7, 122.1, 120.2, 118.3, 117.9, 111.7, 51.7, 49.7, 46.8, and 25.7; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2$ $[M+H]^+$: 388.2025, found 388.2025.

*Methyl-(E)-3-[2-({[2-(piperidin-1-yl)quinolin-3-yl]methyl}amino)-phenyl] acrylate (**33**)*

Yellow solid; yield: 65%; m.p.: 111–113°C; ν_{max}/cm 3368 (N–H) and 1708 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.93 (1H, s, H-4), 7.84 (1H, d, *J* = 15.8 Hz, H-1‴), 7.80 (1H, d, *J* = 8.5 Hz, H-8), 7.56 (1H, d, *J* = 7.9 Hz, H-5), 7.51–7.47 (1H, m, H-6), 7.31 (1H, dd, *J* = 7.7, 1.1 Hz, H-6‴), 7.28–7.23 (1H, m, H-7), 7.14–7.09 (1H, m, H-4‴), 6.64 (1H, t, *J* = 7.5 Hz, H-5‴), 6.51 (1H, d, *J* = 8.2 Hz, H-3‴), 6.31 (1H, d, *J* = 15.7 Hz, H-2‴), 5.08 (1H, s, NH), 4.42 (2H, s, H-3′), 3.71 (3H, s, OCH_3), 3.20–3.16 (4H, m, H-2″), 1.70–1.66 (4H, m, H-3″), and 1.59–1.54 (2H, m, H-4″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.7, 161.1, 146.6, 146.4, 140.3, 136.6, 131.7, 129.1, 128.3, 127.5, 127.2, 126.3, 125.5, 124.5, 120.2, 118.1, 117.8, 111.8, 51.7, 51.6, 45.2, 26.3, and 24.6; HRMS (ESI): *m/z* calcd for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182, found 402.2178.

*Methyl-(E)-3-(2-{[(2-thiomorpholinoquinolin-3-yl)methyl]amino}-phenyl) acrylate (**34**)*

Yellow solid; yield: 38%; m.p.: 117–119°C; ν_{max}/cm 3399 (N–H) and 1696 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.96 (1H, s, H-4), 7.85–7.80 (2H, m, H-8, H-1‴), 7.57 (1H, d, *J* = 7.7 Hz, H-5), 7.52 (1H, t, *J* = 7.7 Hz, H-6), 7.32 (1H, d, *J* = 7.7 Hz, H-6‴), 7.29 (1H, t, *J* = 7.5 Hz, H-7), 7.12 (1H, t, *J* = 7.7 Hz, H-4‴), 6.66 (1H, t, *J* = 7.5 Hz, H-5‴), 6.47 (1H, d, *J* = 8.3 Hz, H-3‴), 6.32 (1H, d, *J* = 15.7 Hz, H-2‴), 4.88 (1H, s, NH), 4.39 (2H, s, H-3′), 3.71 (3H, s, OCH_3), 3.54–3.50 (4H, m, H-2″), and 2.78–2.75 (4H, m, H-3″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.7, 160.6, 146.4, 146.2, 140.1, 137.0, 131.7, 129.3, 128.3, 127.7, 127.2, 126.0, 125.7, 124.9, 120.2, 118.3, 118.0, 111.7, 52.8, 51.7, 44.9, and 27.9; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_2S$ $[M+H]^+$: 420.1746, found 420.1745.

*Methyl-(E)-3-[2-({[2-(4-phenylpiperazin-1-yl)quinolin-3-yl]methyl}-amino)phenyl] acrylate (**35**)*

Pale yellow solid; yield: 75%; m.p.:122–124°C; ν_{max}/cm 3445 (N–H) and 1904 (C═O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.09 (1H, s, H-4), 7.97–7.90 (2H, m, H-8, H-1‴), 7.69 (1H, d, *J* = 7.9 Hz, H-5), 7.63 (1H, t, *J* = 7.6 Hz, H-6), 7.42–7.38 (2H, m, H-7, H-6‴), 7.30 (2H, t, *J* = 7.8 Hz, H-6″), 7.23 (1H, t, *J* = 7.7 Hz, H-4‴), 7.00 (2H, d, *J* = 8.1 Hz,

H-5″), 6.90 (1H, t, *J* = 7.2 Hz, H-7″), 6.76 (1H, t, *J* = 7.4 Hz, H-5‴), 6.61 (1H, d, *J* = 8.2 Hz, H-3‴), 6.39 (1H, d, *J* = 15.7 Hz, H-2‴), 5.07 (1H, s, NH), 4.55 (2H, s, H-3′), 3.77 (3H, s, OCH_3), 3.56–3.53 (4H, m, H-3″), and 3.43–3.38 (4H, m, H-2″); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.6, 159.7, 151.3, 146.3, 146.2, 140.2, 137.4, 131.7, 129.5, 129.2, 128.3, 127.5, 127.3, 125.7, 125.6, 124.9, 120.3, 120.0, 118.4, 118.1, 116.2, 111.7, 51.7, 50.3, 49.4, and 45.2; HRMS (ESI): *m/z* calcd for $C_{30}H_{31}N_4O_2$ $[M+H]^+$: 479.2447, found 479.2449.

4.2 | Biological assays

4.2.1 | In vitro cytotoxicity assay

Cultures of HeLa cells (Cellonex) seeded in 96-well plates were incubated with test compounds, and cell viability was assessed by adding 20 μl of resazurin as described previously.[37] Fluorescence readings (excitation 560 nm, emission 590 nm) obtained for the individual wells were converted to % cell viability, relative to the average readings obtained from untreated control wells.

4.2.2 | In vitro antiplasmodial assay

The 3D7 strain of *P. falciparum* was routinely cultured in a medium consisting of RPMI1640 containing 25 mM Hepes (Lonza), supplemented with 0.5% (w/v) Albumax II (Thermo Fisher Scientific), 22 mM glucose, 0.65 mM hypoxanthine, 0.05 mg/ml gentamicin, and 2–4% (v/v) human erythrocytes. Cultures were maintained at 37°C under an atmosphere of 5% CO_2, 5% O_2, and 90% N_2. To assess antiplasmodial activity, threefold serial dilutions of test compounds in culture medium were added to parasite cultures (adjusted to 2% parasitaemia, 1% hematocrit) in 96-well plates and incubated for 48 h. Three wells per compound concentration were used. Parasite lactate dehydrogenase (pLDH) enzyme activity in the individual wells was determined as previously described.[37] Absorbance values were converted to % parasite viability, relative to untreated control cultures, and plotted against log[compound] to derive IC_{50} values by nonlinear regression using GraphPad Prism (v. 5.02) software.

4.2.3 | In vitro antitrypanosomal assay

T. b. brucei 427 trypomastigotes were cultured in Iscove's modified Dulbecco's medium (Lonza) and supplemented with 10% fetal calf serum, HMI-9 supplement,[38] hypoxanthine, and penicillin/streptomycin at 37°C in a 5% CO_2 incubator. Serial dilutions of test compounds were incubated with the parasites in 96-well plates for 24 h. Residual parasite viability in the wells was determined by adding 20 μl resazurin toxicology reagent (Sigma-Aldrich) and incubating for an additional 24 h. Reduction of resazurin to resorufin by viable parasites was assessed by fluorescence readings (excitation 560 nm, emission 590 nm) in a Spectramax M3 plate reader (Molecular Device). Fluorescence readings were converted to % parasite viability, relative to the average readings obtained from untreated control wells. IC_{50} values were determined by plotting % viability versus log [compound] and performing nonlinear regression using GraphPad Prism (v. 5.02) software.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest.

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