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SYNTHESIS, ANTIPLASMODIAL, ANTIOXIDANT, AND MOLECULAR DOCKING INVESTIGATION OF NOVEL 4-AMINOQUINOLINE-ISOINDOLIN-1-ONES HYBRIDS

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ABSTRACT

Four novel 4-aminoquinoline-isoindolin-1-one hybrids 5a-d have been designed as antiplasmodial and antioxidant agents by combining the 4-aminoquinoline unit and isoindolin-1-one moiety using the flexible alkyl linker. The hybrids were synthesized in two steps *via* aromatic nucleophilic substitution and nucleophilic addition reactions and were obtained with yields up to 83%. The evaluation of their anti-plasmodial activity was conducted against *Plasmodium falciparum* 3D7, whereas the antioxidant activity was assessed using the DPPH method. Among the four hybrids, the hybrid of 3-benzyl-2-(6-((7-chloroquinolin-4-yl)amino)hexyl)-3-hydroxyisoindolin-1-one 5c demonstrated excellent antiplasmodial (IC_{50} of 0.01 µg/mL) and antioxidant (IC_{50} of 46.58 µg/mL) activities. The molecular docking study was conducted using *Pf*OAT as the protein target. The docking results were in line with the *in vitro* antiplasmodial assay, where hybrid 5c displayed the lowest binding energy of -8.43 kcal/mol.

Keywords: Isoindolin-1-one, 4-Aminoquinoline, Hybrid Drugs, Alkyl Linker, Anti plasmodial, Antioxidant, Molecular Docking.

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INTRODUCTION

Malaria is a severe infectious disease caused by *Plasmodium falciparum* leading to a high number of death worldwide.[1] Previous studies reported that malaria parasites may induce the immune system and certain cells to generate reactive oxygen species (ROS). This condition may lead to the degradation of hemoglobin. The production of ROS is also associated with systematic complications in hosts due to malaria infection.[2] The control of malaria is mainly constrained by the rapid resistance of malaria parasites toward standard drugs such as chloroquine and artemisinin.[3] One of the strategies to develop effective antimalarial drugs is through the hybridization approach,[4] where two or more pharmacophore units with different biological activities are combined in a single hybrid molecule. Compared to combination therapy, this strategy offers several advantages such as delayed resistance, reduced toxicity as well as lower cost for the preclinical evaluation. The potential candidates for antimalarial drugs are 4-aminoquinoline hybrids.[5] Literature studies showed that 4-aminoquinoline hybrids can be designed by linking 4-aminoquinoline scaffolds with various moieties such as pyrimidines,[6] triazoles,[7] sulfonamides,[8] pyranopyrazoles[9] and peptides.[10]

Among the biologically active nitrogen heterocycles, isoindolin-1-ones are interesting compounds which can be found in numbers of natural products.[11] Several isoindolin-1-ones are shown to have an antiplasmodial activity such as aristo lactam, cepharanone B, taliscanine, sauristolactam, and Entonalactam A. Other isoindolin-1-one derivatives of (*S*)-pazinaclone and pestalachloride A display antiretroviral and antimicrobial activities, respectively.

This study aimed to develop new candidates of 4-aminoquinoline hybrids namely 4-aminoquinoline-isoindolin-1-one hybrids as the candidates for antiplasmodial and antioxidant. We presented herein the synthesis, *in vitro* anti-plasmodial as well as antioxidant assays, and molecular docking study of novel 4-aminoquinoline-isoindolin-1-one hybrids.

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EXPERIMENTAL

Material and Methods

The FTIR analysis was conducted using Shimadzu Prestige-21. The NMR analyses were carried out using the NMR spectrometer Bruker AC400. The HRMS spectra (ESI-MS) were recorded using SYNAPT G2 HDMS or QSTAR Elite mass spectrometer (Applied Biosystems SCIEX) mass spectrometer. The UV-Vis spectra were obtained from Spectrophotometer UV-Vis (UV-1800 Shimadzu). For the molecular docking study, *Plasmodium falciparum* ornithine aminotransferase (*Pf*OAT) was used as the protein target and the 3D structure was obtained from www.rcsb.org. The preparation of both protein and ligand utilized Autodocktools1.5.6, whereas the docking simulation used Autodock Vina and Autodock4.2 (www.scrips.edu) for virtual screening and individual docking, respectively. Marvin Sketch was used to sketch the 2D structure of ligands. The 3D structure and the docking pose were visualized using Biovia Discovery Studio 2016.

Synthesis of Primary Amines 3a-d

The mixture containing 4,7-dichloroquinoline 1 (0.98 g, 4.9 mmol, 1 equiv.) and diamines 2a-d (24.7 mmol, 5 equiv.) was heated at 135 °C overnight. The cooled reaction mixture was then extracted with ethyl acetate (3 x 50 mL). The organic phase was washed with brine (3 x 50 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure.

Synthesis of 4-Aminoquinoline-isoindolin-1-one Hybrids 5a-d

3-Benzylidenephtalide 4 (111 mg, 0.5 mmol, 1 equiv.), primary amines 3a-d (1 mmol, 2 equiv.) *iso*-propanol (4 mL) were introduced to a flask. After heating the reaction mixture at 50 °C overnight, the mixture was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with brine (3 x 10 mL) and dried over Na_2SO_4. The crude products were purified using column chromatography using the mixture of *n*-hexane: EtOAc. The products 5a-d were elucidated using ^{1}H-NMR, ^{13}C-NMR, FTIR, and HRMS spectrometers.

3-Benzyl-2-(3-((7-chloroquinolin-4-yl)amino)propyl)-3-hydroxyisoindolin-1-one 5a

White solid; m.p.: 189-192 °C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ (ppm) 8.28 (d, *J* = 5.6 Hz, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 2 Hz, 1H), 7.47 (t, *J* = 6 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.37-7.27 (m, 4H), 6.95-6.89 (m, 3H), 6.67-6.65 (m, 3H), 6.40 (d, *J* = 5.6 Hz, 1H), 3.65-3.58 (m, 1H), 3.48-3.42 (m, 1H), 3.42-3.17 (m, 4H), 2.03-1.99 (m, 2H); ^{13}C-NMR (DMSO-d6, 100 MHz): δ (ppm) 166.3, 151.9, 150.1, 149.1, 147.1, 135.2, 133.4, 131.5, 131.4, 129.8 (2C), 129.0, 127.6 (2C), 127.5, 126.4, 124.1, 124.0, 122.9, 121.9, 117.5, 98.8, 91.1, 42.4, 40.5, 36.8, 27.6; FTIR (KBr): 3395, 3063, 2932, 1682, 1582, 1450, 1412, 1080, 702 cm^{-1}; HRMS (ESI-MS) calcd for $C_{27}H_{25}ClN_3O_2^+$ ($M+H^+$) 458.1630, found 458.1627.

3-Benzyl-2-(4-((7-chloroquinolin-4-yl)amino)butyl)-3-hydroxyisoindolin-1-one 5b

Yellow solid; m.p.: 201-204 °C; ^{1}H-NMR (DMSO-d6, 300 MHz): δ (ppm) 8.33 (d, *J* = 5.4 Hz, 1H), 8.22 (d, *J* = 9 Hz, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.52-7.46 (m, 1H), 7.41-7.34 (m, 4H), 7.24 (br t, *J* = 5.1 Hz, 1H), 6.99-6.93 (m, 3H), 6.74-6.71 (m, 2H), 6.56 (br s, 1H), 6.45 (d, *J* = 5.4 Hz, 1H), 3.62-3.52 (m, 1H), 3.44-3.20 (m, 5H), 1.82-1.68 (m, 4H); ^{13}C-NMR (DMSO-d6, 75 MHz): δ (ppm) 166.0, 151.9, 150.2, 149.1, 147.0, 135.2, 133.4, 131.5, 131.4, 129.8 (2C), 129.0, 127.5 (2C), 127.4, 126.4, 124.1, 124.0, 122.9, 121.8, 117.5, 98.7, 91.0, 42.5, 42.3, 38.6, 26.7, 25.6; FTIR (KBr): 3372, 3032, 2924, 1674, 1582, 1335, 1080, 764 cm^{-1}; HRMS (ESI-MS) calcd for $C_{28}H_{27}ClN_3O_2^+$ ($M+H^+$) 472.1786, found 472.1786.

3-Benzyl-2-(6-((7-chloroquinolin-4-yl)amino)hexyl)-3-hydroxyisoindolin-1-one 5c

Yellow solid; m.p.: 99-102 °C; ^{1}H-NMR (MeOD, 400 MHz): δ (ppm) 8.29 (d, *J* = 5.2 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.37-7.32 (m, 1H), 7.04-6.98 (m, 3H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.45 (d, *J* = 5.2 Hz, 1H), 3.71-3.64 (m, 1H), 3.48-3.42 (m, 2H), 3.34-3.25 (m, 3H), 1.87-1.70 (m, 4H), 1.57-1.49 (m, 1H); ^{13}C-NMR (MeOD, 100 MHz): δ (ppm) 169.2, 152.8, 152.3, 149.6, 148.3, 136.3, 136.2, 133.0, 132.8, 131.1 (2C), 130.3, 128.7 (2C), 127.7, 127.5, 125.9, 124.3, 124.0, 123.3, 118.7, 99.3, 93.2, 44.0, 43.9, 40.7, 30.1, 29.2, 28.1, 27.8; FTIR (KBr): 3441, 3032, 2925, 1674, 1466, 1072, 702 cm^{-1}; HRMS: calcd for $C_{30}H_{31}ClN_3O_2^+$ ($M+H^+$) 500.2099, found 500.2099.

3-Benzyl-2-(8-((7-chloroquinolin-4-yl)amino)octyl)-3-hydroxyisoindolin-1-one 5d
White solid; m.p.: 214-223 °C; ^{1}H-NMR (DMSO-d6, 400 MHz): δ (ppm) 8.30 (d, *J* = 5.2 Hz, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.47-7.44 (m, 1H), 7.38-7.330 (m, 4H), 7.22 (br t, *J* = 5.2 Hz, 1H), 6.95-6.94 (m, 3H), 6.70-6.68 (m, 2H), 6.49 (br s, 1H), 6.37 (d, *J* = 5.2 Hz, 1H), 3.47-3.22 (m, 3H), 3.20-3.16 (m, 3H), 1.60-1.50 (m, 4H), 1.32-1.15 (m, 8H); ^{13}C-NMR (DMSO-d6, 100 MHz): δ (ppm) 165.8, 151.9, 150.2, 149.0, 147.0, 135.3, 133.4, 131.6, 131.3, 129.8 (2C), 128.9, 127.5 (2C), 127.4, 126.4, 124.1, 124.0, 122.8, 121.8, 117.5, 98.6, 90.9, 42.5, 42.4, 39.0, 28.8 (2C), 28.7, 27.8, 26.8, 26.6; FTIR (KBr): 3426, 3032, 2924, 1674, 1412, 1080, 702 cm^{-1}; HRMS: calcd for $C_{32}H_{35}ClN_3O_2^+$ ($M+H^+$) 528.2412, found 528.2411.

Anti plasmodial Assay of 4-Aminoquinoline-isoindolin-1-one Hybrids
The *in vitro* anti-plasmodial assay of 4-aminoquinoline-isoindolin-1-one hybrids was performed against *Plasmodium falciparum* 3D7 using the previously developed method.[12] Chloroquine and artemisinin were employed as the positive controls.

Antioxidant Assay of 4-Aminoquinoline-isoindolin-1-one Hybrids
The antioxidant assay of 4-aminoquinoline-isoindolin-1-one hybrids was carried out using the DPPH method. The positive control utilized in this study was vitamin C.[13]

Molecular Docking Studies of 4-Aminoquinoline-isoindolin-1-one Hybrids
The *Pf*OAT protein was separated from its native ligand and the water molecules. The proteins were then protonated and given Kollman charges, whereas the ligands were given gasteiger charges. The binding site was auto-located by the default Pyrx system and then the docking using the Autodock Vina algorithm was run with an exhaustiveness of 64 covering and 9 conformations for each ligand. The results were obtained in free energy of binding (ΔG_{bind}) data (kcal/ mol) and the best binding affinity was selected from 9 conformations for each ligand. The binding pocket location was mapped according to the information reported by the previous study.[14] The center of mass was set to x = -13.612; y = 22.614; z = -52.87 with the grid box size 118 x 118 x 118 and 0.375 spacing grid. The docking parameter was set as followed: run 100; rmstol 2 Å; energy evaluation number of 2,500,000; population size 150; and lamarckian genetic algorithm. The docking simulation was run using Autodock4.2. The results were analyzed based on the free binding energy of the most populated cluster and the H-bond interactions.

RESULTS AND DISCUSSION

Synthesis of 4-Aminoquinoline-isoindolin-1-one Hybrids
The design of novel anti-plasmodial hybrids was carried out by connecting 4-aminoquinoline moiety and isoindolin-1-one scaffold using a linker. In this context, the selection of the linkers should be considered since they might control the pharmacokinetic behavior of the drugs.[15] Based on the previous studies, the flexible linkers displayed better antiplasmodial activities than the rigid ones.[16] Therefore, we decided to employ flexible alkyl groups (containing 3, 4, 6, and 8 carbon atoms) as the linkers for 4-aminoquinoline-isoindolin-1-one hybrids. Four novel 4-aminoquinoline-isoindolin-1-one hybrids were synthesized in only two steps (Fig.-1). Initially, 4-aminoquinoline moiety was incorporated into the primary amines by reacting 4,7-dichloroquinoline 1 and various diaminoalkanes 2 under the solvent-free conditions at 135°C overnight through aromatic nucleophilic substitution reaction. The ^{1}H-NMR, ^{13}C-NMR, and FTIR spectra of the generated primary amines bearing 4-amino quinoline skeleton 3a-d were similar to the previous report.[17]

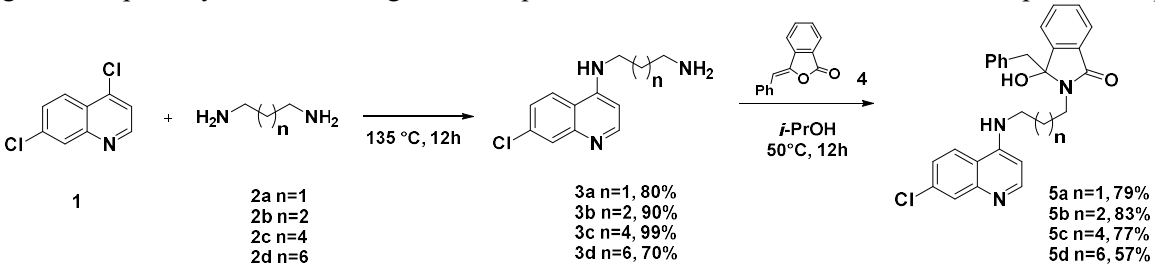

Fig.-1: Synthesis of 4-Aminoquinoline-isoindolin-1-one Hybrids

The synthesized amines 3a-d and readily available 3-benzylidenephtalide 4 were then subjected to the nucleophilic addition reaction (Fig.-1). Having performed the reaction under the mild condition in the biobased solvent of *iso*-propanol, we were pleased to obtain the desired 4-aminoquinoline-isoindolin-1-one hybrids 5a-d in good yields. Based on the ^{1}H-NMR analysis, the presence of a broad singlet peak around 6.5 ppm representing hydroxyl proton along with the aromatic protons of quinoline and isoindolin-1-one moieties at the region of 6.3-8.3 ppm confirmed the formation of the isoindolin-1-one moiety. In addition, the peak of hemiaminal and lactam carbons was detected around 91 and 166 ppm, respectively. The peaks observed in FTIR spectra were also in good agreement with the functional groups in the structure of the hybrids 5a-d. The HRMS analysis demonstrated that the experimental exact mass of the hybrids 5a-d was in full accordance with the structure of 4-Aminoquinoline-isoindolin-1-one hybrids 5a-d.

Anti plasmodial Assay of 4-Aminoquinoline-isoindolin-1-one Hybrids

With 4-aminoquinoline-isoindolin-1-one hybrids 5a-d in our hand, we turned our attention to the anti-plasmodial assay against *Plasmodium falciparum* 3D7 (Table-1). The positive controls used for the assay were artemisinin and chloroquine diphosphate. The results showed that the length of the linker had no linear effect on the activities, presumably because the higher number of carbon atoms might be associated with the increase of conformation number and flexibility of the hybrids.[5]

Table-1: Anti-plasmodial and Antioxidant Activities of 4-Aminoquinoline-isoindolin-1-one Hybrids

Compound	Antiplasmodial IC_{50} (μM)	Antiplasmodial IC_{50} (μg/mL)	Classification	Antioxidant IC_{50} (μg/mL)	Classification
5a	1.74	0.799	Active	17.53	Very strong
5b	510.63	241.02	Inactive	86.62	Strong
5c	0.02	0.01	Very active	46.58	Very strong
5d	18.93	9.99	Moderate	839.98	Weak
Chloroquine	0.03	0.015	Very active	-	-
Artemisinine	0.002	0.0006	Very active	-	-
Vitamin C	-	-	-	1.73	Very strong

According to the IC_{50} value, the anti-plasmodial activities can be classified into very active, active, moderate, and inactive performance.[18] Among the synthesized hybrids, hybrid 5c and 5a displayed excellent activity against 3D7 strains. It should be noted that the activity of hybrid 5c was even better than that of standard antimalaria of chloroquine diphosphate (CQ). Compared to CQ, the longer alkyl chain might improve the lipophilic character of the hybrid 5c. Moreover, the longer alkyl linker might facilitate the interaction between the secondary nitrogen of the 4-aminoquinoline unit and the iron of heme, resulting in a decrease of the rate of hemozoin formation.[19] The presence of an isoindolin-1-one unit might add the number of hydrogen bond donors and acceptors to the 4-aminoquinoline unit. In this context, the carbonyl and hydroxyl groups of the hybrids might generate the interaction with heme through the formation of hydrogen bonds.[20]

Antioxidant Assay of 4-Aminoquinoline-isoindolin-1-one Hybrids

The antioxidant activities of 4-aminoquinoline-isoindolin-1-one hybrids were determined using the DPPH method (Table-1). Despite the ascorbic acid displaying better activity than the hybrids, hybrids 5a-c were still considered as strong antioxidants.[21,22] It should be noted that the hybrid 5c which possessed very active antiplasmodial activity also exhibited very strong antioxidant activity. The results indicated that hybrid 5c could be considered a potential candidate for antiplasmodial and antioxidant agents.

Molecular Docking of 4-Aminoquinoline-isoindoline-1-one Hybrids

The evaluation of the binding mode among 4-aminoquinoline-isoindolin-1-one hybrids 5a-d and the proteins of the malaria parasite was carried out through the molecular docking study. In this report, *Plasmodium falciparum* ornithine aminotransferase (*Pf*OAT) was used as the target protein. Since the OAT of *P. falciparum* has homology with the OAT of humans (HOAT),[23] the location in which the ligands are being docked was near loop 147-172 as well as loop 287-293. The results of molecular docking were depicted in Table-2. The docking of the four hybrids was carried out into the *Pf*OAT binding pocket with the ΔG_{bind} order of 5b < 5d < 5a < 5c, which was consistent with the experimental IC_{50} (Table-1). The

binding pose of each ligand was visualized in Fig.-2. Hybrid 5a showed three H-bond interactions with GLY287 and two times interactions with HIS289, contributing to the ΔG_{bind} of -7.84 kcal/mol (Table-2 and Fig.-2a). The presence of hydrogen bonding interactions with GLY287 and HIS289 might be the important point of the antiplasmodial activity of the hybrid. The four carbon-linker on 5b made the ligand lose the interaction with any amino acid residues (Table-2 and Fig.-2b). The lowest ΔG_{bind} of -7.31 seemed due to the sole weak hydrophobic interaction, which could be the strong reason why 5b was the least active.

Table-2: Docking Score and Type of Interaction of 4-aminoquinoline-isoindolin-1-one hybrids to Amino Acid Residues of *Pf*OAT

Hybrid	ΔG_{bind} (kcal/mol)	Interacting Amino Acids
5a	-7.84	GLY287, HIS 289, HIS289
5b	-7.31	-
5c	-8.43	GLY287, LYS285, HIS289
5d	-7.76	MET281

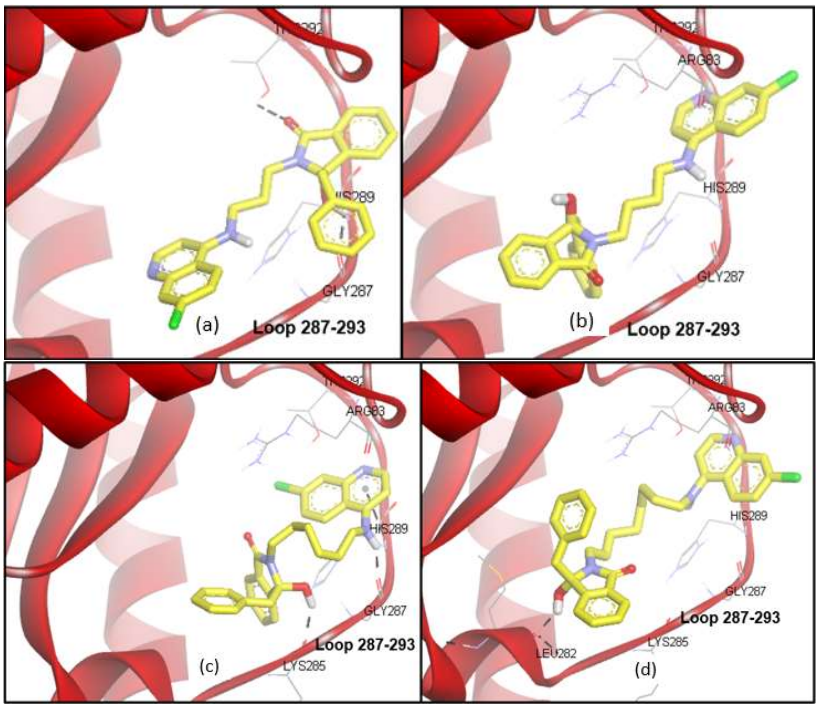

Fig-2: Binding Interaction of 4-aminoquinoline-isoindolin-1-one Hybrids (a) 5a; (b) 5b; (c) 5c; (d) 5d to *Pf*OAT

Hybrid 5c exhibited a ΔG_{bind} of -8.43 kcal/mol resulting from the interaction with LYS285, GLY287, and HIS289 (Table-2 and Fig.-2c). Similar interactions with GLY287 and HIS289 were also observed in 5a and were absence in 5b and 5d, indicating that these interactions were essential for the anti-plasmodial activity. The ΔG_{bind} of 5c might be decreased due to the interaction of LYS285 which was absent in 5a. This could make an understanding that LYS285 might be also another key point of interaction. Hybrid 5d might be too flexible, therefore, it lost all important amino acid residue interaction which contributed to the higher ΔG_{bind} of -7.76 kcal/ mol (Table-2 and Fig.-2d). The only H-bond interaction was with MET281 which might give impacted to its moderate activity. From the structure-activity relationship, the longer alkyl chain bridge seemed like performing hydrophobic interaction with *Pf*OAT thus increasing the binding affinity to the *Pf*OAT. However, the certain alkyl linker (such as linker containing four and eight carbon), the binding affinity tended to decrease along with the experimental IC_{50}. It indicated that the hydrophobicity along with the flexibility was not the only point affecting the binding affinity but rather the correct binding conformation.

CONCLUSION

Four novel 4-aminoquinoline-isoindolin-1-one hybrids with various length of the alkyl linker 5a-d were successfully synthesized in good yields. Among the hybrids, hybrid 5c exhibited excellent anti-plasmodial

and antioxidant activities with the IC_{50} of 0.01 and 46.58 µg/mL, respectively. Having performed molecular docking against the *Pf*OAT protein, we found that the most important amino acid residue for the *Pf*OAT activity was GLY287 and HIS289. In addition, the hybrid 5c displayed the lowest binding energy of -8.43 kcal/mol. Based on the biological evaluation and molecular docking study, hybrid 5c could be a promising antioxidant and anti-plasmodial candidate.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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