Copper-Catalyzed Asymmetric Hydroboration Reaction of Novel Methylene Isoindolinone Compounds through Microwave Irradiation and Their Antileishmanial and Antitoxoplasma Activities

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Copper-Catalyzed Asymmetric Hydroboration Reaction of Novel Methylene Isoindolinone Compounds through Microwave Irradiation and Their Antileishmanial and Antitoxoplasma Activities

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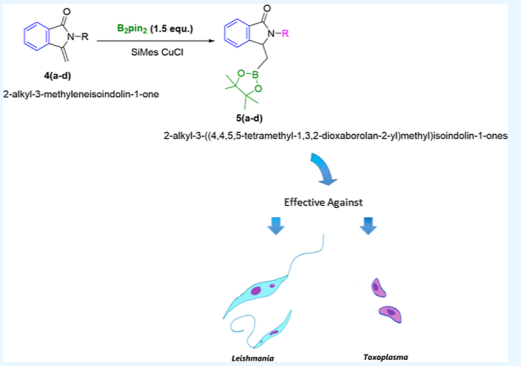
ABSTRACT: The aim of this study was devoted into molecular docking calculations to discover the potential antileishmania and antitoxoplasma activities of newly synthesized compounds obtained by applying a practical and simple method under microwave irradiation. All these compounds were tested in vitro for their biological activity against *Leishmania major* promastigotes, amastigotes, and *Toxoplasma gondii* tachyzoites. Compounds **2a**, **5a**, and **5e** were the most active against both *L. major* promastigotes and amastigotes, with IC_{50} values of less than 0.4 μM mL^{-1}. Compounds **2c**, **2e**, **2h**, and **5d** had a strong antitoxoplasma activity of less than 2.1 μM mL^{-1} against *T. gondii*. We can conclude that aromatic methyleneisoindolinones are potently active against both *L. major* and *T. gondii*. Further studies for mode of action evaluation are recommended. Compounds **5c** and **5b** are the best drug candidates for antileishmania and antitoxoplasma due to their SI values being over 13. The docking studies of compounds **2a-h** and **5a-e** against pteridine reductase 1 and *T. gondii* enoyl acyl carrier protein reductase reveal that compound **5e** may be an effective antileishmanial and antitoxoplasma drug discovery initiative.



1. INTRODUCTION

Over the years, the isoindolinone structure has intrigued scientists due to its diverse pharmaceutical and biological properties, such as antiretroviral, antibacterial, anticancer, and anxiolytic effects.[1−4] As a result, there has been ongoing investigation into developing and enhancing this unique scaffold.[5−7] In contrast, it is worth noting that the structure of isoindolinone has seized the attention of researchers for an extended period. With a myriad of substitutions and functionalizations, a diverse range of naturally occurring chemicals exhibit an extensive array of biological potentials.[8−18]

The production of isoindolinone derivatives requires various procedures, with expensive catalysts, prolonged reaction periods, and hazardous organic solvents needed for some.[19−23] Meanwhile, microwave (MW) irradiation has been commonly utilized for organic synthesis.[24−31] In fact, over the past decade, MW radiation has become a popular energy source in organic synthesis. Different approaches[32−37] have been utilized for isoindolinone derivative synthesis, although they often entail higher costs, longer wait times, and the use of toxic solvents. The green novel method for organic synthesis, the MW heating strategy, boasts high yields and quick reaction times, minimizing the formation of byproducts and increasing product purities. Heterocycles are important targets in organic synthesis, especially nitrogen-containing ones because of their prominent presence in natural products and significant use in the pharmaceutical industry.[38−42]

Herein, we report our recent research findings on the construction of isoindolinone derivatives through microwave irradiation and their antileishmanial and antitoxoplasma activities. Furthermore, molecular docking simulations showed that compounds **5e**, **5a**, and **2e** had the best docking values for the target enzymes (Scheme 1).

2. RESULTS AND DISCUSSION

Treatment of compound **1** with p-toluenesulfonic acid (PTSA) in refluxing toluene in the presence of primary amines afforded compound **2** in good yield (Scheme 2 and Table 1). Compounds **3a−h** were obtained in good yields as a racemic mixture by adding methylmagnesium bromide to phthalimide[43] in Et_2O for 2 or 1 h. Products **3b** and **3c** were obtained in good yields (70% and 84%, respectively) after complete

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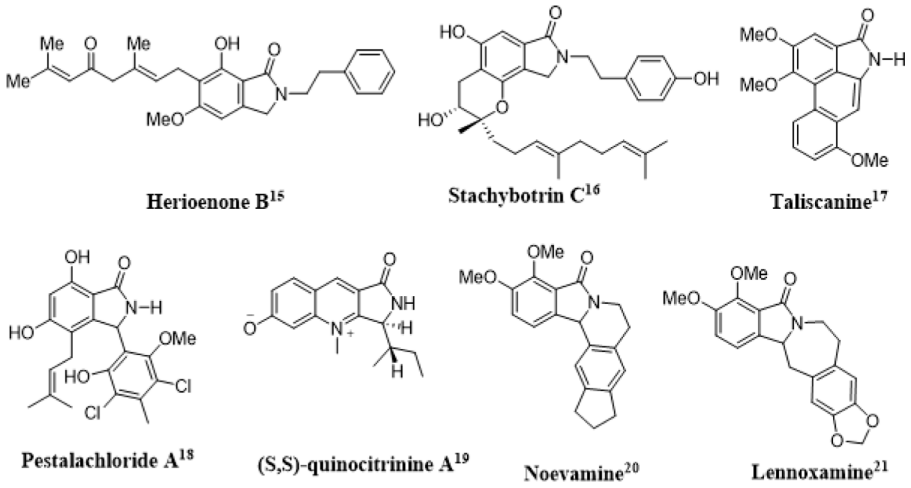
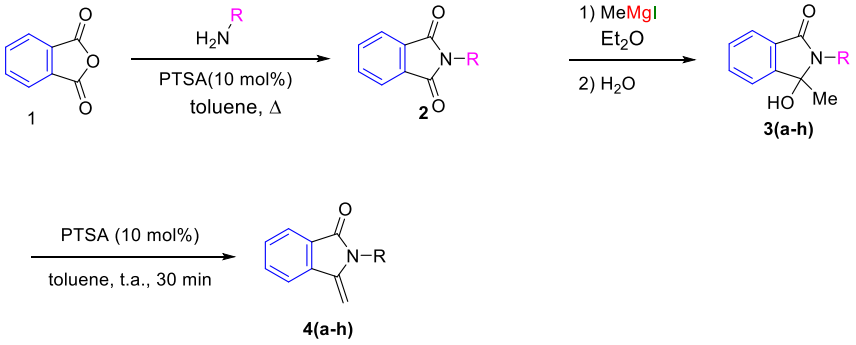
Scheme 1. Natural Compounds Containing Isoindolinone Nuclei



Scheme 2. Protocol Synthesis of Compound 4



conversion to the Grignard reagent within 1 h. The treatment of compounds **3** with PTSA in toluene at reflux for 30 min gave compounds **4**.[43] All synthesized compounds were characterized by various spectroscopy methods.

The scope of the copper-catalyzed hydroboration of compound **4** was explored. First, the evaluation of the model reaction of compound **4a** and B_2pin_2 under microwave irradiation (55 °C/180 W, 10 min) in the presence of SiMes CuCl at reflux of dimethyl carbonate (DMC) provided the corresponding compound **5a** in 65% yield. Scheme 3.

In order to determine the optimal reaction conditions, DMC was used as the solvent, and the reaction was carried out at different times and SiMesCuCl concentrations.

The present optimization studies revealed that the yield smoothly increased with the catalyst load and the use of larger amounts of the catalyst did not improve the yields, while its decreasing amount decreased the yields, which were the best conditions, obtaining compound **5a** in 65% yield (Table 1, entry 1). Thus, MW conditions had a beneficial effect on this reaction. Afterward, concentration was within the scope of this reaction with the variety of amines (Scheme 4) in order to check the viability of this protocol in obtaining a library of compounds **5** (Scheme 4).

All the reactions were completed within 10−15 min, respectively. In these reactions, there was no need for the column purification of the products. The obtained solid products were just filtered off from the reaction mixture, dissolved in hot ethanol, refiltered to separate any contaminated catalyst with the product, and finally recrystallized from the filtrate to obtain pure compounds **5.**

^{1}H NMR spectra of compound **5a** displayed a signal at 3.58 ppm which corresponds to the methoxy group. Additionally, the two doublets of vinylidene protons of compound **5a** appeared at 4.52 and 5.74 ppm, respectively. Aromatic protons resonated between 6.67 and 7.34 ppm. Furthermore, in the ^{13}C NMR spectra, carbon (a,b,c,d) and methoxylic carbon exhibit signals at 81.08 and 54.8 ppm, respectively. The signals at 167.6 and 55.6 ppm correspond to CO and C−N carbons. The aromatic carbons appeared between 113.7 and 130.9 ppm. However, methylic carbons resonated at 24.3 ppm.

2.1. Biological Activities. *2.1.1. Antileishmanial Activity.* From Table 3, it can be seen that the compounds **2** possess antileishmanial activity against *Leishmania major* amastigotes with IC_{50} values of less than 4 μM mL^{-1}, except **2g**. The most potent compounds, namely, **2a** and **2e**, had IC_{50} values of 1.3 and 1.7 μM mL^{-1}, respectively. However, the compounds **5** are more active against *L. major* amastigotes, and three of them had IC_{50} values of less than 0.4 μM mL^{-1}, namely, **5a, 5d**, and **5e**. Four compounds **2** were highly active against *L. major* promastigotes with IC_{50} values less than 0.4 μM mL^{-1}: **2c, 2d, 2f**, and **3h**. Three compounds **5** showed the same activity against *L. major* promastigotes: **5a, 5d**, and **5e**. Isoindolinone compounds exhibited very strong activity against different *Leishmania* species.[45] However, all the aromatic groups of methylene isoindolinones compounds were found to have strong antileishmanial activity against both amastigotes and promastigotes. This finding agrees with previous studies in compounds with related structures against *Leishmania* parasites due to their high affinity in inhibiting the tryparedoxin peroxidase enzyme, which is necessary for the parasite life

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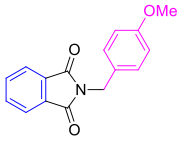
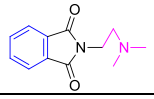
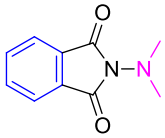
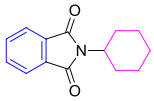
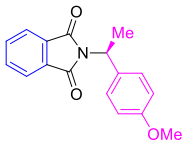
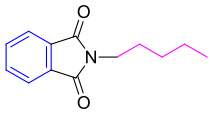
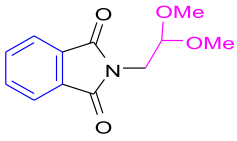
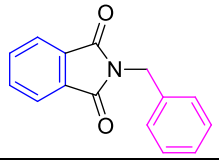
Table 1. Structure of Compounds 2

Entry		Compound
1		2a
2		2b
3		2c
4		2d
5		2 e
6		2f
		2 g
7		2h

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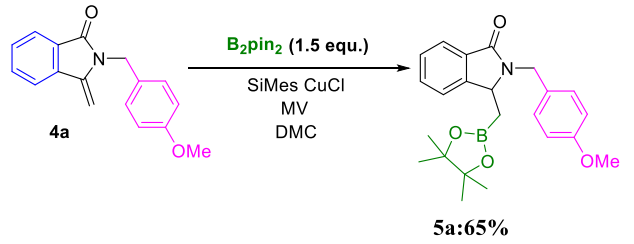
Scheme 3. Scope of the Copper-Catalyzed Hydroboration Reaction of Compounds 4a



Scheme 4. Hydroboration of compounds 4 with B_{2pin2}

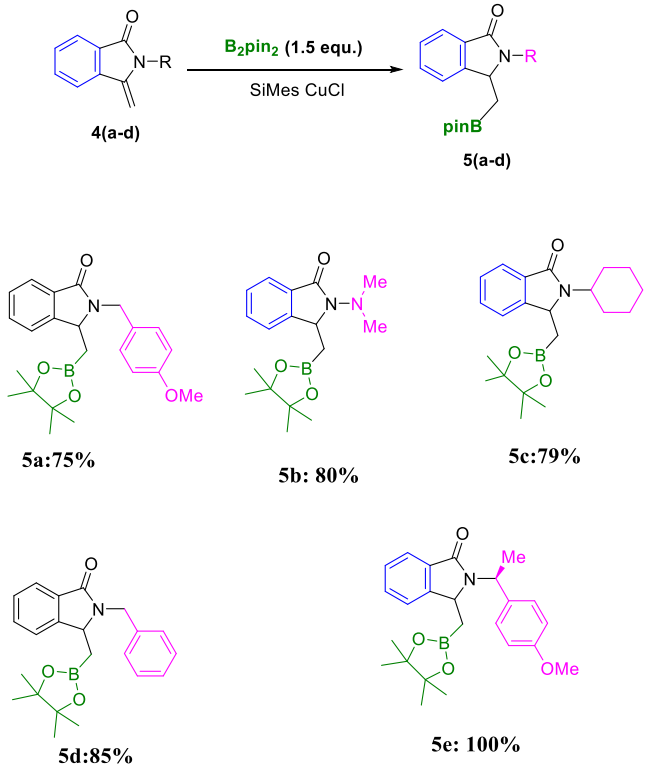


Table 2. Synthesis of Compound 5a

entry	R	conditions	yield (%)
1	*p*-$OCH_3C_6H_4$	55 °C, 10 min[a] SiMesCuCl (15 mmol)	65
2	*p*-$OCH_3C_6H_4$	55 °C, 10 min[a] SiMesCuCl (20 mmol)	55
3	*p*-$OCH_3C_6H_4$	55 °C, 10 min[a] SiMesCuCl (25 mmol)	50
4	*p*-$OCH_3C_6H_4$	60 °C, 15 min.[a] SiMesCuCl (30 mmol)	45
5	*p*-$OCH_3C_6H_4$	60 °C, 30 min[a] SiMesCuCl (20 mmol)	43

[a]The reaction was carried out at 180 watts.

cycle.[44] Consequently, an in silico evaluation for molecular docking of these active compounds against tryparedoxin peroxidase enzyme is recommended. Moreover, compound **5c** can be considered the best drug candidate for antileishmanial due to its SI values for both amastigotes and promastigotes of 13.21 and 15.15, respectively.

2.1.2. Antitoxoplasma Activity. Table 4 shows that all the compounds **3** possessed antitoxoplasma activity against *Toxoplasma gondii* in vitro with IC_{50} values of less than 8 μM mL^{-1}, except **2g**; however, four of them had IC_{50} values of less than 0.4 μM mL^{-1}, i.e., **2a, 2c, 2e**, and **2h**. Only one compound **5** had an IC_{50} less than 0.4 μM mL^{-1} and that was **5d**. Although our previous investigations of isoindoline against *T. gondii* produced fewer promising results,[45] we found five compounds with potent antitoxoplasma activity against *T. gondii* tachyzoites. These results agree with the previous finding regarding thiazolidinone derivatives,[46] especially for those compounds with bicyclic aromatic rings substituting the amine group, which could be due to the same reason as our results. Further studies are recommended to determine their mode of action evaluation. Compound **5b** is the best antitoxoplasma drug candidate, with an SI of 16.52.

2.2. Molecular Docking. To gain more insights into the biological antileishmanial and antitoxoplasma activities of the synthetized compounds **2a-h** and **5a-e**, molecular docking simulations were performed. Molecular docking is a reliable computational technique for drug discovery and design of new therapies for diseases. It is used to predict and inspect the conformations and binding interactions of a ligand in the active site of the target enzyme. Leishmaniasis is a major public health problem throughout the tropical and subtropical world. Pteridine reductase 1 (PDB ID: 2XOX) of *Leishmania donovani* is used as an antileishmanial drug target. It is an essential enzyme for pterin salvage in the *Leishmania* parasite and can potentially be used as a target in the development of improved therapies. The docking study responsible for the salvage of pteridines claims that it is a potential target for chemotherapeutic intervention.[47] Herein, the crystal structure of PDB ID: 2XOX[48,49] was an antileishmanial target. The *T. gondii* enoyl acyl carrier protein reductase (PDB ID: 2O2S) was chosen to explore the antitoxoplasma activity of the studied compound. The accuracy of the docking results may be checked by redocking self-docking of the cocrystallized ligand into the receptor. The binding affinity scoring, the root-mean-square deviation (RMSD) and the binding interactions were used to evaluate the biological activities. The scoring and RMSD values are given in Table 5. The best pose of the top-ranked score compound **5e** in the protein targets along with their binding interactions is depicted in Figures 1 and 2. The best pose through self-docking and the possible interactions between the reference ligand (TCL) and *T. gondii* PDB ID: 2O2S protein are plotted in Figure 3. It has been clearly shown that the redocked pose of the reference TCL ligand fits its original conformation well. These findings prove the accuracy of our molecular docking simulations. The inspection of the docking results summarized in Table 5 clearly shows that compounds **5e**, **5a**, and **2e** have the best affinity against the target enzyme. Moreover, one may conclude that compound **5e** has the highest biological activities (2XOX: $S = -6.80$ kcal/mol, RMSD = 1.66; 2O2S: $S = -7.80$ kcal/mol, RMSD = 1.84) compared to other synthetized compounds. Furthermore, the **6e** ligand shows more antitoxoplasma activity than the cocrystallized ligand.

Figure 1 illustrates how the leucine Leu66 residue contributes to the interactions between ligand **5e** and the target protein through H-interactions. Figure 2 demonstrates how the ligand's carbonyl group and the lysine residue Lys197 engage through hydrogen bonding to stable the best position ligand **6e** in the target protein for antitoxoplasma activity.

2.3. Theoretical Details. Molecular docking of synthesized compounds **2a−h** and **5a−e** to antileishmania and antitoxoplasma protein targets was performed using the software package Molecular Operating Environment (MOE 2015.10). The crystal structures of PDB ID: 2XOX as an antitoxoplasma drug target protein and *T. gondii* PDB ID:

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ACS Omega 2023, 8, 23067−23077

Table 3. Antileishmanial Activity of Selected Compounds[a]

compound	CC_{50} toxicity against Vero cells	amastigote IC_{50}	promastigotes IC_{50}	amastigote SI	promastigote SI
2a	2.55 ± 0.31	4.9 ± 0.61	31.5 ± 5.2	0.52	0.08
2b	15.6 ± 2.7	18.8 ± 2.4	37.2 ± 4.9	0.83	0.42
2c	<2.1		<2.1		
2d	<1.7	17.0 ± 2.2	<1.7		
2e	37.8 ± 5.4	7.8 ± 1.2	12.4 ± 2.9	0.48	0.30
2f	<1.8	16.6 ± 3.1	<1.8		
2g	300.5 ± 52.7	158.6 ± 21.6	290.1 ± 39.8	1.89	1.04
2h	<1.7	11.9 ± 1.8	<1.7		
5a	2.3 ± 0.37	<1.0	<1.0		
5b	203.8 ± 31.4	94.6 ± 14.5	238.3 ± 33.6	2.15	0.86
5c	174.9 ± 20.3	13.2 ± 2.7	11.5 ± 1.8	13.21	15.15
5d	<1.1	<1.1	<1.1		
5e	1.3 ± 0.21	<1.0	<1.0		
AmB	7.7 ± 1.3	0.47 ± 0.06	0.83 ± 0.15	16.4	9.2

[a]Values are the means of three independent experiments in μM mL^{-1} ± S.D. Selectivity index (CC_{50}/IC_{50}) calculated from the corresponding CC_{50} values for Vero cells and the IC_{50} values against *L. major*, either amastigotes or promastigotes. Amphotericin B (AmB) was used as control positive.

Table 4. Antitoxoplasmal Activity of Selected Compounds[a]

compounds	CC_{50} toxicity of Vero cells	Toxoplasma IC_{50}	SI Toxoplasma
2a	2.55 ± 0.31	<1.5	
2b	15.6 ± 2.7	33.0 ± 5.3	0.47
2c	<2.1	<2.1	
2d	<1.7	10.5 ± 1.9	
2e	37.8 ± 5.4	<1.8	
2f	<1.8	2.3 ± 3.8	
2g	300.5 ± 52.7	311.3 ± 42.5	0.97
2h	<1.7	<1.7	
5a	2.3 ± 0.37	6.6 ± 0.80	0.35
5b	203.8 ± 31.4	12.3 ± 2.1	16.51
5c	174.9 ± 20.3	183.5 ± 24.6	0.96
5d	<1.1	<1.1	
5e	1.3 ± 0.21	2.1 ± 0.33	0.61
ATO	9.5 ± 1.7	0.07 ± 0.01	136

[a]Values are the means of three independent experiments in μM mL^{-1} ± S.D. Selectivity index (CC_{50}/IC_{50}) calculated from the corresponding CC_{50} values for Vero cells and the IC_{50} values against *T. gondii*. Atovaquone (ATO) was used as control positive.

2O2S as an antitoxoplasma drug target protein were retrieved from protein databases. The studied ligand was drawn and minimized with the MOE package using the same force field. The London dG scoring function was chosen to score the top 1000 poses obtained from the triangle matcher placement method. The top 30 poses are evaluated by London dG and minimized within the rigid receptor using the MMFF94x force field. The docking score represents the binding free energy calculated by his GBVI/WSA scoring function for S-field, the final stage score. Table 5.

3. CONCLUSIONS

In conclusion, we describe a simple method for the preparation and characterization of several different 3-methylene-isoindolinones under microwave conditions. It turns out that microwave-enabled devices are cleaner and more responsive. ^{1}H NMR, ^{13}C NMR, IR, and elemental analysis were used to characterize the isolated molecules. Molecular docking, SAR, and in vitro studies are required to approve their use before clinical trials can begin; however, based on the results of this work, we can conclude that all aromatic methyleneisoindolinones target *L. major* and *T. gondii* are strong candidates for drug development. Molecular docking simulations show that compounds **5e**, **5a**, and **2e** have the best docking values for the target enzymes.

Table 5. Results of Molecular Docking for Ligands 2a-h and 5a-e in Selected Enzymes

receptor	ligand	*S* (kcal/mol)	RMSD
pteridine reductase 1 (PDB ID: 2XOX)	**2a**	−5.18	1.79
	2b	−5.32	0.63
	2c	−4.48	1.64
	2d	−4.42	1.38
	2e	**−6.00**	**1.34**
	2f	−4.78	1.92
	2g	−5.26	1.88
	2h	−4.98	1.23
	5a	**−6.51**	**1.14**
	5b	−5.61	1.85
	5c	−5.69	1.24
	5d	−6.06	1.25
	5e	**−6.80**	**1.66**
T. gondii enoyl-ACP reductase (PDB ID: 2O2S)	**2a**	−6.01	1.75
	2b	−4.98	1.55
	2c	−4.96	1.07
	2d	−5.55	1.54
	2e	**−6.23**	**1.58**
	2f	−5.87	1.52
	2g	−5.63	0.96
	2h	−5.59	0.87
	5a	**−7.58**	**1.85**
	5b	−6.37	0.99
	5c	−6.66	0.86
	5d	−7.16	1.84
	5e	**−7.80**	**1.84**
	TCL	−5.90	1.78

4. EXPERIMENTAL SECTION

All starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Reactions were performed on a CEM Co., Discovery

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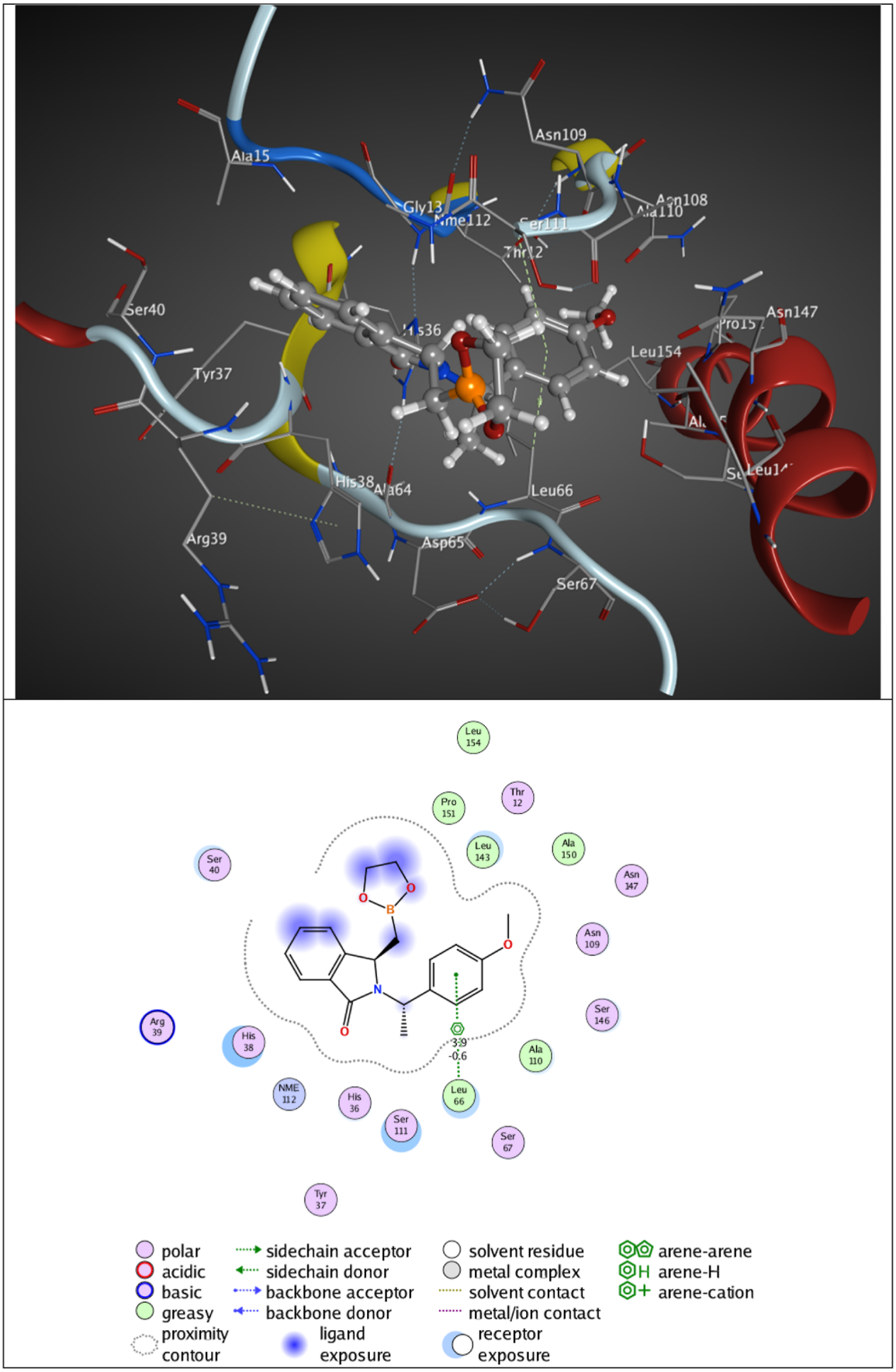

Figure 1. 3D best poses of the **5e** ligand in the 2XOX target enzyme (top) along with 2D ligand−protein interactions (bottom).

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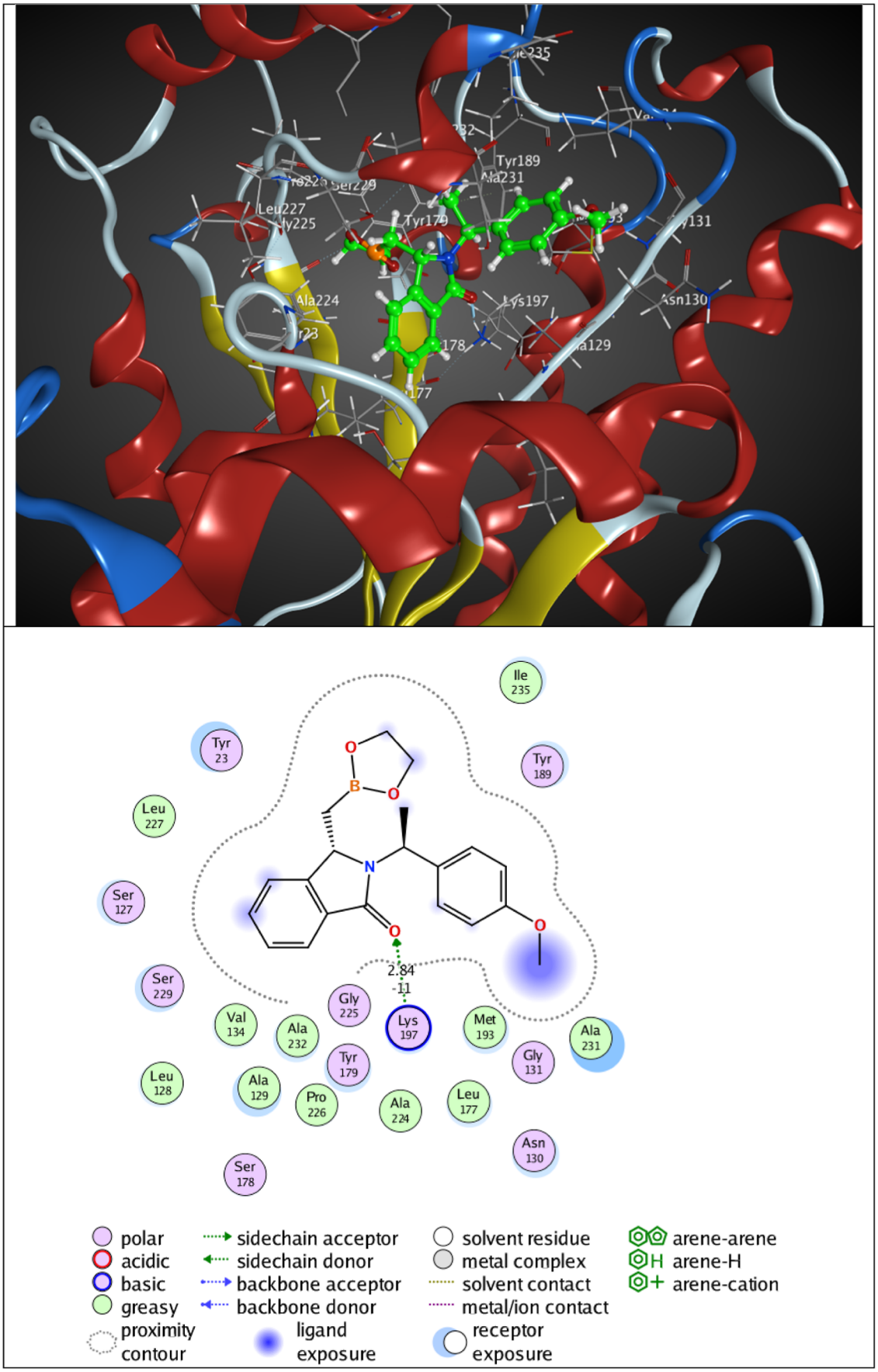

Figure 2. 3D best poses of the **5e** ligand in the 2O2S target enzyme (top) along with 2D ligand−protein interactions (bottom).

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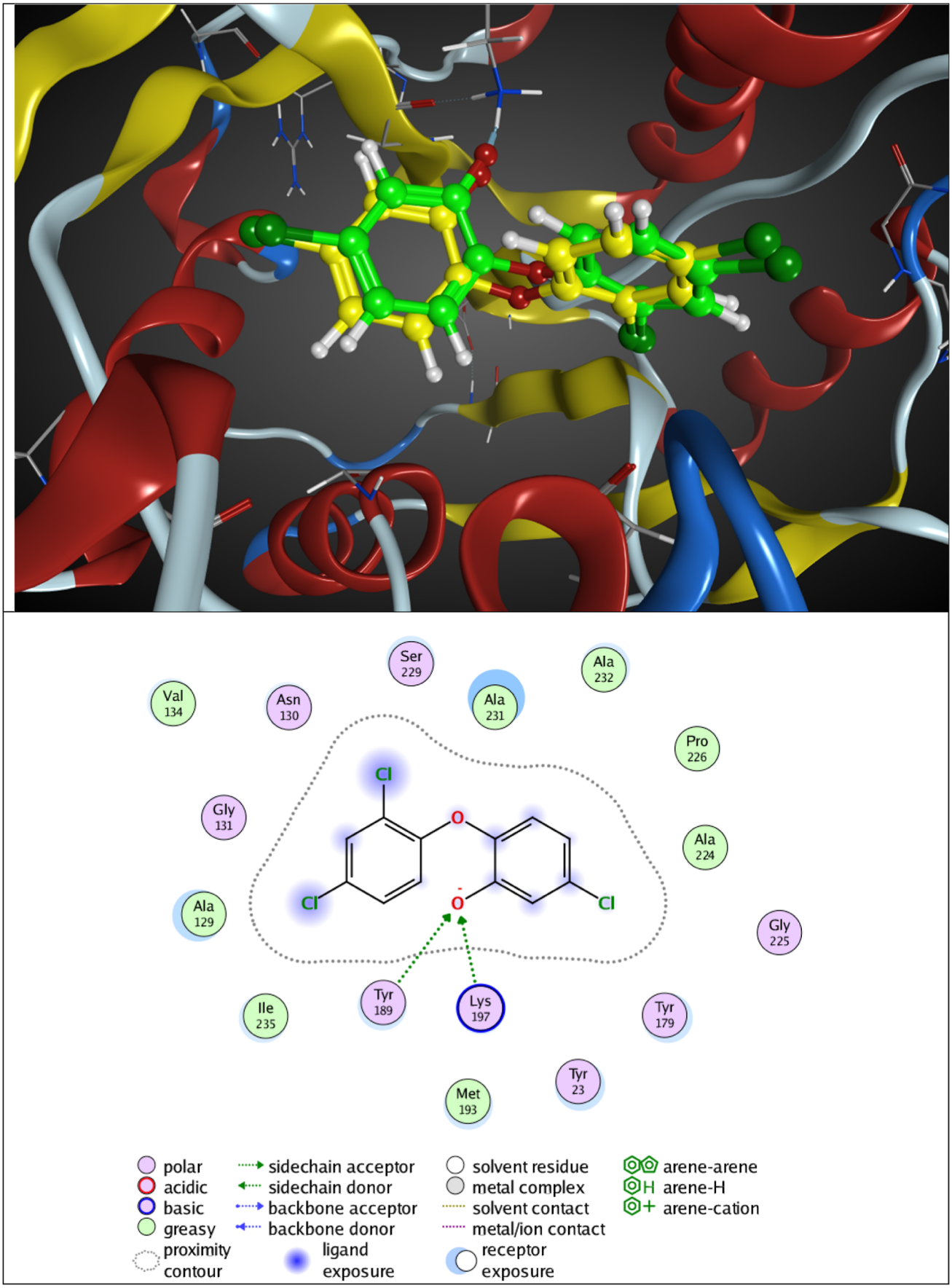

Figure 3. Superimposition of the original pose and self-docking pose of the TCL cocrystallized ligand in the 2O2S target enzyme (top) along with possible interactions (bottom).

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ACS Omega 2023, 8, 23067−23077

microwave reactor with sealed vessels. Unless otherwise specified ^{1}H- and ^{13}C NMR spectra were recorded on a Bruker AC-300 FT-NMR spectrometer at 300 and 76 MHz, respectively. 11B-NMR spectra were recorded on a Bruker Avance 600 FT-NMR spectrometer at 193 MHz. All 11B chemical shifts were referenced to external $BF_3{\cdot}OEt_2$ (0.0 ppm). Data is represented as follows: chemical shifts (ppm), multiplicity: (s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad), and coupling constant J (Hz). Melting points were determined by using a Fargo MP-2D melting point apparatus and were uncorrected. High resolution ESI mass spectra were obtained on a Finnigan MAT 95S instrument.

4.1. Synthesis of Compounds 5. Enamide (0.2 mmol) and bis(pinacolato)diboron (1.5 equiv) were added into a mixture of Cesium carbonate (0.1 equiv) and [(SiMes)]CuCl (10 mol %), and then EtOH (5 mL) was added. The resultant mixture was then inserted into a microwave oven (Samsung, model KE300R) at 450W for varying intervals (refer to Table 2). Once the solvent was removed under vacuum conditions, we obtained pure **5(a-d)**.

*4.1.1. 2-(4-Methoxybenzyl)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl)isoindolin-1-one(**5a**).* Yield (%) = 75; IR(cm^{-1}): 2933 (CH_2), 1726 (C═O), 1507 (C═C_{arom}), 1200 (C−O). ^{1}H NMR (300 MHz, $CdCl_3$) δ(ppm): 1.25 (m, 2H, CH_2), 4.25 (s, 2H, CH_2),1.94−1.96 (s, 12H, CH_3), 3.58 (s, 3H, OCH_3), 4.05−4.10 (d, 1H, CH), 6.67−7.34 (m, 8H, H_{arom}).^{13}C NMR (75 MHz, $CdCl_3$) δ(ppm): 24.33($4CH_3$), 42.53(CH_2), 50.4(CH_2), 54.81(OCH_3), 55.62(CH−N),81.08(2Cq), 113.73−130.94(Carom), 167.62(CO). Anal. Calcd for $C_{22}H_{26}BNO_4$: C, 69.67%; H, 6.91%; N, 3.69%. Found: C, 69.7; H, 7.1; N, 3.7%. ^{11}B-NMR ($CDCl_3$): δ ppm 34.82.

*4.1.2. 2-(Dimethylamino)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoindolin-1-one (**5b**).* Yield (%) = 80; IR(cm^{-1}): 2935 (CH_2), 1729 (C═O), 1510 (C═C_{arom}), 1207 (C−O).

^{1}H NMR (300 MHz, $CdCl_3$) δ(ppm):4.73 (m, 1H), 2.92 (s, 6H), 4.61 (m, 2H, CH_2), 7.29−7.45(m, H_{arom}). ^{13}C NMR (75 MHz, $CdCl_3$) δ(ppm): 24.81($4CH_3$), 25.03($2CH_3$), 44.18-(CH_2), 98.82 (CH), 127.8−131.5(Carom), 166.22(C). Anal. Calcd for $C_{17}H_{25}BN_2O_3$: C, 64.57%; H, 7.97%; N, 8.86%. Found: C, 64.6; H, 7.8; N, 8.9%.

*4.1.3. 2-Cyclohexyl-3-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-ylmethyl)-2,3-dihydro-isoindol-1-one (**5c**).* Yield (%) = 79, IR(cm^{-1}): 2937 (CH_2), 1728 (C═O), 1510 (C═C_{arom}), 1210 (C−O). ^{1}H NMR (300 MHz,$CdCl_3$) δ(ppm): 1.07−1.11 (d, 12H), 1.52 (m, 2H), 1.84−1.91 (m, 10H, CH_2), 4.68 (m, 1H, CH); 7.39−7.48 (m, 4H, H_{arom}). ^{13}C NMR (75 MHz, $CdCl_3$) δ(ppm) 24.90($4CH_3$), 30.81 (CH_2), 31.22($2CH_2$), 34.05 ($2CH_2$), 53.72(CH_2), 44.20(CH_2), 64.36(CH), 83.64 (2C);,122,12−130.99(4CHarom), 168.25(CO). Anal. Calcd for $C_{21}H_{30}BNO_3$: C, 70.99%; H, 8.51%; N, 3.94%. Found: C, 71.1; H, 8.6; N, 4.0%.

*4.1.4. 2-Benzyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxazolidin-2-yl)methyl)isoindolin-1-one (**5d**).* Yield (%) = 85; IR (cm^{-1}): 2938 (CH_2), 1730 (C═O), 1510 (C═C_{arom}), 1209 (C−O).

^{1}H NMR (300 MHz, $CdCl_3$) δ(ppm): 0.88 (m, 2H, CH_2), 4.26 (s, 2H, CH_2), 1.01−1.04 (s, 12H, CH_3), 4.46−4.50 (m, 1H), 7.15−7.81 (m, 9H, H_{arom}).^{13}C NMR (75 MHz, $CdCl_3$) δ(ppm): 24.85($4CH_3$), 43.63(CH_2), 56.23(CH_2), 83.64 (2C), 122.56−131.44(Carom), 168.33(CO). Anal. Calcd for $C_{22}H_{26}BNO_3$: C, 72.74%; H, 7.21%; N, 3.86%. Found: C, 72.8; H, 7.3; N, 3.9%.

*4.1.5. 2-((S)-1-(4-Methoxyphenyl)ethyl)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoindolin-1-one-(**5e**).* Yield (%) = 100; IR(cm^{-1}): 2935 (CH_2), 1727 (C═O), 1511 (C═C_{arom}), 1208 (C−O).

^{1}H NMR (300 MHz, $CdCl_3$) δ(ppm):1.69 (m, 2H, CH_2), 4.27 (s, 1H, CH), 1.69−1.76 (s, 12H, CH_3), 1.47 (s, 3H, CH_3), 4.71−4.75 (d, 1H, CH), 6.73−7.76 (m, 8H, H_{arom}). ^{13}C NMR (75 MHz, $CdCl_3$) δ(ppm): 24.25($4CH_3$), 42.62(CH_2), 17.45 (CH), 56,28 (OCH_3), 54.72 (CH−N), 83.05(2Cq), 114.63−133.75(Carom), 168.47(CO). Anal. Calcd for $C_{23}H_{28}BNO_4$: C, 70.24%; H, 7.18%; N, 3.56%. Found: C, 70.3; H, 7.2; N, 3.6%.

L. major cell isolation, *T. gondii* cell line, culture conditions, and assays.

T. gondii cell line, culture conditions, and assay were done according to our previous work refs 45−47..

■ ASSOCIATED CONTENT

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this paper.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c02362.

^{1}H NMR spectrum of compound **5a** (in $CDCl_3$, 300 MHz, 25 °C, TMS); ^{13}C NMR spectrum of compound **5a** (in $CDCl_3$, 75 MHz, 25 °C, TMS); ^{1}H NMR spectrum of compound **5b** (in $CDCl_3$, 300 MHz, 25 °C, TMS); ^{13}C NMR spectrum of compound **5b** ($CDCl_3$, 75 MHz, 25 °C, TMS); ^{1}H NMR spectrum of compound **5c** ($CDCl_3$, 300 MHz, 25 °C, TMS); ^{13}C NMR spectrum of compound **5c** (in $CDCl_3$, 75 MHz, 25 °C, TMS); ^{1}H NMR spectrum of compound **5d** ($CDCl_3$, 300 MHz, 25 °C, TMS); ^{13}C NMR spectrum of compound **5d** ($CDCl_3$, 75 MHz, 25 °C, TMS); ^{1}H NMR spectrum of compound **5e** ($CDCl_3$, 300 MHz, 25 °C, TMS); and ^{13}C NMR spectrum of compound **5e** ($CDCl_3$, 75 MHz, 25 °C, TMS) (PDF)

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Ibrahim S. Al Nasr, Waleed S. Koko, and Tariq A. contributed to biological activities. Hamida Jelali, Nasser Amri, and Yousef E. Mukhrish contributed to the synthesis and characterization of the compounds. Houcine Ghalla contributed to the software and docking party, Eric Deniau and Mathieu Sauthier contributed to resources. Naceur Hamdi writing—original draft preparation, N·H.; writing—review, and editing. All authors have read and agreed to the published version of the manuscript.

Notes

The authors declare no competing financial interest.

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ACS Omega 2023, 8, 23067−23077