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Rational design, synthesis and biological evaluation of ubiquinone derivatives as IDO1 inhibitors

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ABSTRACT

Indoleamine 2,3-dioxygenase 1 (IDO1) is an attractive therapeutic target for the treatment of cancer, chronic viral infections and neurological disorders characterized by pathological immune stimulation. Herein, a series of known metal-chelating ubiquinone derivatives were designed, synthesized and evaluated for the IDO1 inhibiting activities. The docking studies showed that the compounds **11**, **16**, **18** and coenzyme-Q1 exhibited different binding modes to IDO1 protein. Among these compounds, the most active compound is **16d** with an IC_{50} of 0.13 μM in enzymatic assay. The results reveal that a possible halogen bonding interaction between the bromine atom (3-Br) and Cys129 significantly enhances the inhibition activity against IDO1. This study provides structural insights of the interactions between ubiquinone analogues and IDO1 protein for the further modification and optimization.

1. Introduction

Indoleamine 2,3-dioxygenase 1 (IDO1) is a heme-containing non-secretory blood enzyme, which degrades essential amino acid tryptophan in the kynurenine pathway [1,2]. It catalyzes the first and also the rate limiting step of kynurenine formation. Depletion of tryptophan and the accumulation of the kynurenine pathway metabolites can inhibit the immune response and induce T cell inactivation and apoptosis. In addition, up-regulation of IDO1 can promote T cell differentiation into immunosuppressive regulatory T cells [3–5]. The expression of IDO1 has been identified as an important immune effector for tumor cells to escape effective innate and adaptive immune responses. In addition, IDO1 up-regulation is associated with poor prognosis of serous ovarian cancer, endometrial cancer, colorectal cancer and acute myeloid leukemia [6–8]. Earlier studies have suggested that neurological disorders, including Huntington's disease, Alzheimer's disease and Parkinson's disease are also associated with pathological tryptophan metabolism [9–11]. Therefore, IDO1 has emerged as a valid drug target for treatment of various disease conditions.

In the past decade, several IDO1 inhibitors with different structural scaffolds have been identified from rational structure design, high throughput screening, and natural product screenings [12–17] (Fig. 1). Currently, there are at least seven small molecule IDO1 inhibitors under clinical development, being evaluated alone or in combinations with other agents [18–24]. Unfortunately, Incyte's new immunotherapy drug Epacadostat [25–28] failed to demonstrate desired efficacy in conjunction with Merck's melanoma drug Keytruda in a recent trial. This Epacadostat-Keytruda trial failure had cast a shadow over other programs [29,30]. As IDO1 inhibitors offer promising potential in immunotherapy and other fields, new chemical entities with structural diversity and improved efficacy are greatly needed.

A number of natural product-derived IDO1 inhibitors containing quinone moiety have been identified, which display moderate inhibition activities in enzymatic assays [31,32]. Mechanistically, the quinone moiety was known to be able to coordinate with heme iron metal. Some earlier studies have highlighted concerns on whether the quinone moiety blocks the catalytic activity of IDO1 by a specific mechanism of action or by an unspecific redox-cycling mechanism [14,31,33]. More recent studies however have proved a direct binding interaction between quinone bearing compounds and IDO1, sustaining argument in favor of a specific mechanism of action for this class of inhibitors [31,34,35].

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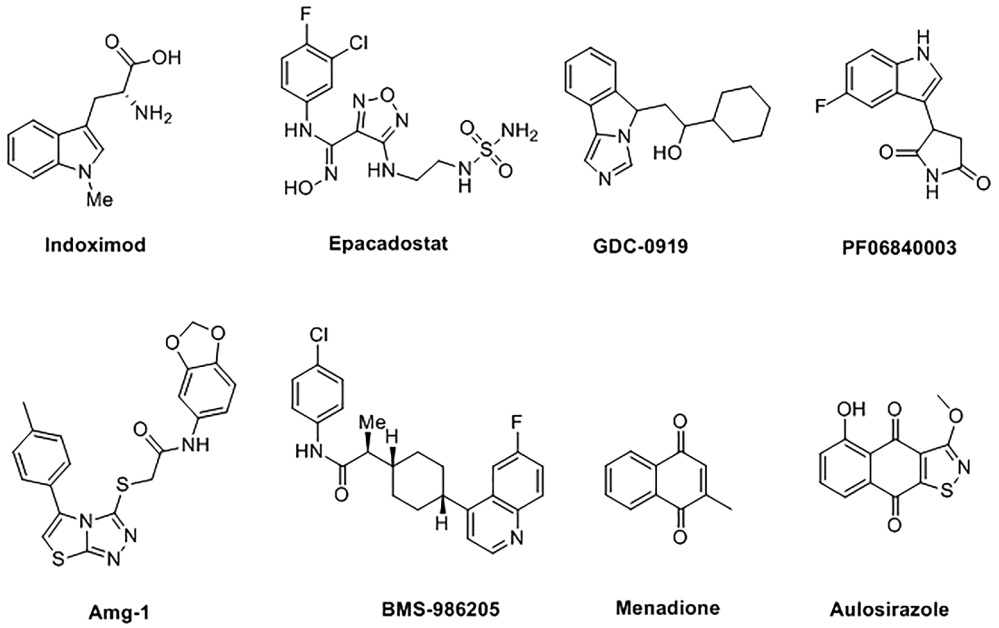


Fig. 1. The representative IDO1 inhibitors.

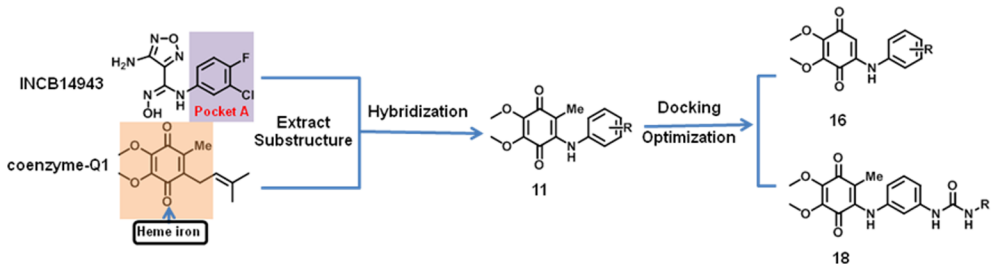


Fig. 2. Structure modification strategy.

There are many approved drugs or diet supplement containing the quinone scaffold, such as Idebenone and coenzyme Q10 (CoQ10). Idebenone and CoQ10 share the same *p*-quinone headgroup (CoQ0) and both of them are treated as a drug or dietary supplement in many countries [36–43]. CoQ10 is a main homologue of CoQ existing in humans, and Idebenone, a synthetic quinone with similarities to coenzyme-Q1, had been introduced to the market in 1986 under the name Avan in Japan [36–43]. Normally, if the quinone moiety has strong electron donating groups such as OR, NR_2, the quinone becomes less active toward reduction and nucleophilic additions. Based on this fact, we wanted to examine if the CoQ0 scaffold can be an effective heme Fe ion chelator for IDO1 enzyme. We first designed a series of new analogs and found that coenzyme-Q1 demonstrated a moderately potent IDO1 inhibitor activity with an IC_{50} value of 1.3 μM in enzyme assay. Using this as a lead molecule, we then designed and synthesized a series of novel ubiquinone derivatives for IDO1 inhibitory biological evaluation. Since several crystal structures of IDO1 in complex with different inhibitors have been reported to date, we also conducted structure-guided optimization of our designed inhibitors through a docking-based strategy (Fig. 2).

2. Chemistry

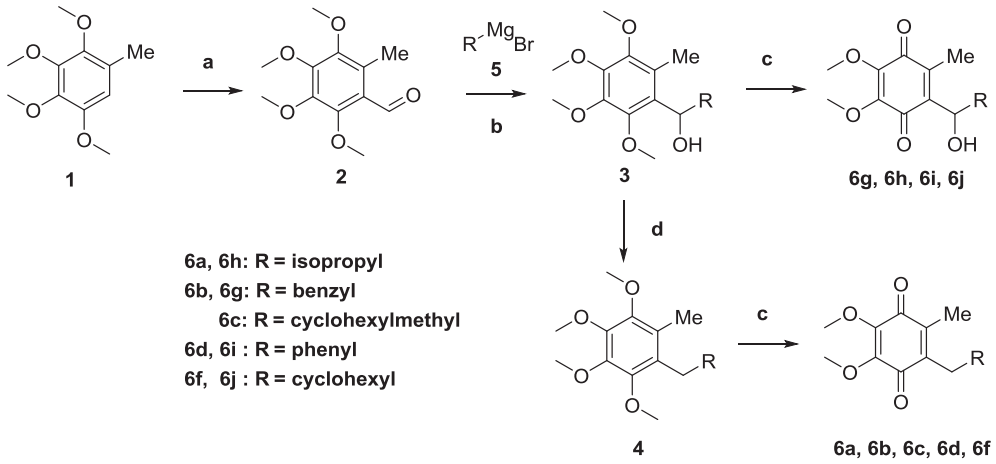
The general synthetic route for the target compounds **6a-d** and **6f-j** is shown in Scheme 1. Initially, 2,3,4,5-tetramethoxytoluene **1** was reacted with 1,1-dichlordimethyl ether and titanium tetrachloride to afford an intermediatory product 2,3,4,5-tetramethoxyl 6-methylbenzaldhyde **2** [44]. The product **2** was then reacted with various Grignard reagents **5** through Grignard reaction to form corresponding compounds **3**, which were then oxidized with CAN to get the desired compounds **6g-j** [45]. Similarly, the dehydroxylation of compounds **3** in the presence of catalytic Pd/C gave the corresponding compounds **4**, which were further oxidized with CAN to yield target compounds **6a-d** and **6f**.

Scheme 2 illustrates the synthesis of compound **8** which was obtained by treatment of commercially available 2,3-dimethoxy-5-methylbenzoquinone **7** with bromine in presence of carbon tetrachloride [46], and then coupled with phenylboronic acid through a Suzuki-Miyaura coupling to afford compound **6e** [47]. Similarly, compounds **11a-r** were obtained by treatment of **7** with various amines in presence of alcohol [48,49].

As shown in Scheme 3, oxidation of commercially available 2,3,4-tetramethoxybenzaldehyde **12** through Baeyer-Villiger oxidation with *m*-CPBA produced **13**. Compound **13** was then hydrolyzed into 2,3,4-trimethoxyphenol **14** with sodium hydroxide, which was then oxidized with CAN to provide 2,3-dimethoxycyclohexa-2,5-diene-1,4-dione **15** [50]. Finally, the compound **15** was reacted with various amines to yield target compounds **16a-j**. In scheme 4, compounds **18a-j** were obtained with treatment of **11j** with various isocyanates in ethanol.

3. Results and discussion

All the synthesized compounds were evaluated by *in vitro* IDO1 enzymatic inhibition assay (Supplementary information), and the results are summarized in Tables 1-4. Overall, the compounds **11a** (0.7 μM), **16d** (0.13 μM), and **18a** (0.4 μM) were found to be the most active ones among the synthesized series.



Scheme 1. Reagents and conditions: (a) CH_3OCHCl_2, $TiCl_4$, 0 °C to rt, 4 h; (b) RMgBr, THF, 0 °C to rt, 1 h; (c) CAN, CH_3CN/H_2O, rt, 0.5 h; (d) Pd/H_2, EtOH, 90 °C, 24 h.

Design of target compounds and modeling studies

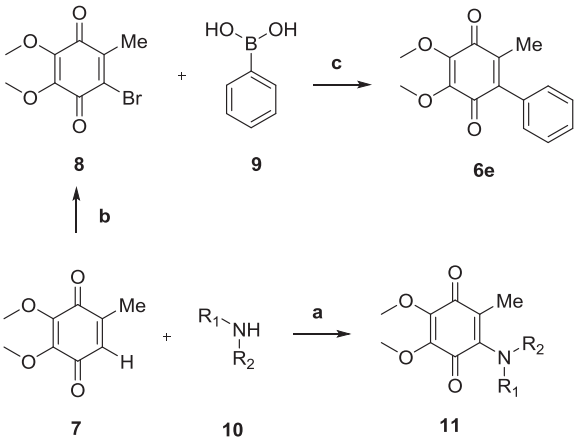
First, the chemical modification started with coenzyme-Q1 as the lead compound and most of the modifications were carried out based on the published crystal structure of IDO1 [23,24,51–53] in complex with INCB14943 (PDB ID: 5XE1). According to our docking analysis, coenzyme-Q1 is situated ~3.5 Å above the plane of the heme, coordinates with the heme iron and forms an edge-to-face π-π interaction with Phe163, which was predicted to contribute to the inhibitory activity against IDO1. However, the isoallyl of coenzyme-Q1 could not bind to the hydrophobic pocket A [53], which is surrounded by residues Leu234, Val130 and Phe164 (Fig. 3B).

Recent studies [23,26,52,53] have shown that the halogenated aromatic moieties can efficiently bind into the pocket A of IDO1 binding site. Therefore, we used the hybridization strategy to conjugate ubiquinone with aniline (aromatic moiety) to afford compound **11a**, which demonstrated an improved potency with an IC_{50} value of 0.70 μM. Through analysis of structure-activity relationship (SAR) and docking results of **11a** (Fig. 4A and Table 2), we concluded that the aniline moiety was not able to stretch itself into the pocket A. Most probably, the steric restriction of methyl and the aniline moiety prevented its placement into the narrow entrance of pocket A. Therefore, we decided to take advantage of ubiquinone skeleton and further modify it by removing the methyl group, thereby obtaining demethylated derivatives **16**. Finally, this strategy worked for us and we obtained compound **16d** with an IC_{50} value of 0.13 μM equivalent to Epacadostat.

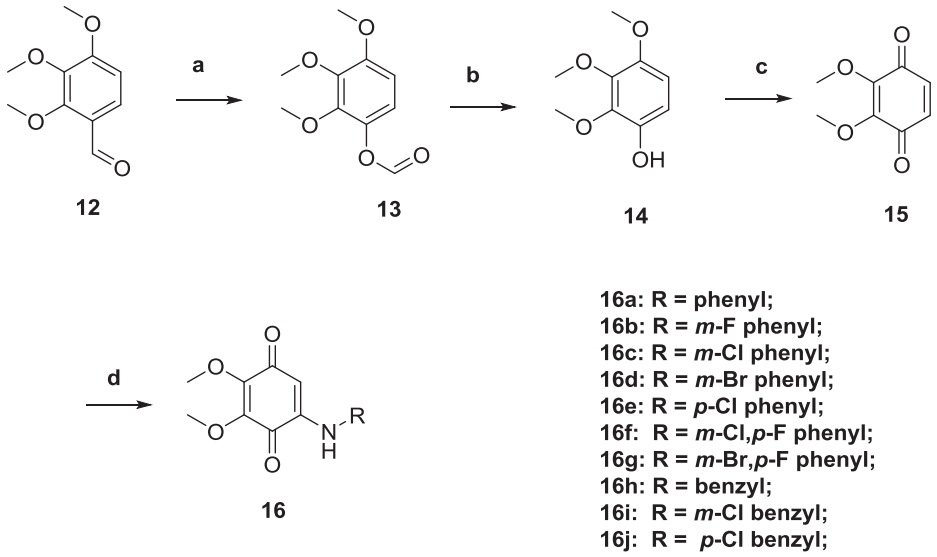
The docking analysis of **16d** (shown in Fig. 4B) revealed that the interaction between the bromine atom and the sulphur atom of Cys129 could be essential for potent IDO1 inhibitory activity. Whereas, the binding mode of **18a** suggested that the hydrogen bonding interaction between the urea moiety and heme carboxylic acid may contribute significantly to the inhibitory activity against IDO1. Interestingly, these ubiquinone derivatives were predicted to have different binding modes to the IDO1 protein (Figs. 3 and 4). Finally, the results of the SAR analysis and optimization strategies were summarized in Fig. 5.

3.1. SAR of ubiquinone derivatives

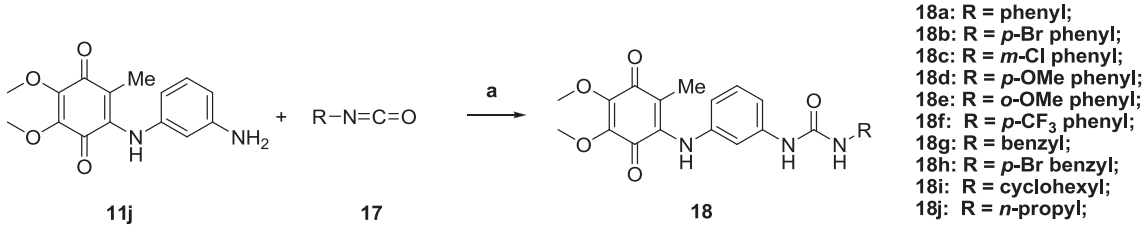
As shown in Table 1, 17 compounds were evaluated in IDO1 inhibition enzyme assay. As we expected, some compounds displayed moderately potent IDO1 inhibitory activities. To begin with the SAR, we first investigated the effect of linker region on the potency of inhibitory activity. We found that the compounds **6b** and **6d** with a linker of one or two carbon atoms displayed moderate inhibition of IDO1 with IC_{50} values 3.54 μM and 5.11 μM, respectively. However, a significant loss of inhibitory potency was observed for compound **6e** (IC_{50} > 10 μM), which possesses no linker region. Further comparison of **6d** with **11a** (IC_{50} = 0.70 μM) and **6b** with **11n** (IC_{50} = 1.12 μM) revealed that NH group of the linker was essential to enhance the



Scheme 2. Reagents and conditions: (a) EtOH, rt, 2 h; (b) Br_2, CCl_4, rt, 12 h; (c) K_2CO_3, 9.2 mol% Pd-Tetrakis (triphenylphosphine), $CHCl_3/H_2O$/MeOH, 60 °C, 12 h.

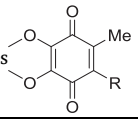


Scheme 3. Reagents and conditions: (a) *m*-CPBA, DCM, 0 °C to rt, 3 h; (b) NaOH, MeOH/H_2O, 0 °C to rt, 16 h; (c) CAN, CH_3CN/H_2O, rt, 1.5 h; (d) EtOH, RNH_2, rt, 2 h.



Scheme 4. Reagents and conditions: (a) EtOH, rt, 1 h.

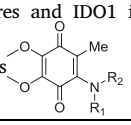
Table 1

Structures and IDO1 inhibitory activities of the coenzyme-Q1 ubiquinone derivatives 

Compd.	R	IDO1 inhibition IC_{50} (μM)[a]	Compd.	R	IDO1 inhibition IC_{50} (μM) [a]
coenzyme-Q0	H	> 10	**6 h**		> 10
coenzyme-Q1		1.30 ± 0.05	**6i**		> 10
6a		2.80 ± 0.21	**6j**		> 10
6b		3.54 ± 0.17	**11a**		0.70 ± 0.09
6c		4.52 ± 0.31	**11n**		1.12 ± 0.21
6d		5.11 ± 0.38	**11o**		3.92 ± 0.47
6e		> 10	**11p**		1.91 ± 0.25
6f		> 10	**Epacadostat**		0.12 ± 0.03
6 g		> 10			

[a] IC_{50} values are the means of more than two independent assays, presented as mean ± SD.

inhibitory activity. Moreover, the compounds **6g-i** with hydroxyl group at linker lost inhibitory potency (IC_{50} > 10 μM) in comparison to their parent molecules **6a** (IC_{50} > 2.8 μM), **6b** (IC_{50} > 3.54 μM), and **6d** (IC_{50} > 5.11 μM), respectively. On the other hand, the compounds **11a**, **11n** and **11p** possessing the same NH group on linker demonstrated approximately five-fold increased inhibitory potency compared to their corresponding parent compounds **6b**, **6d** and **6f**, respectively. Through a series of further comparisons (**6b** vs **6c**, **6d** vs **6f**, **11a** vs **11p**, and **11a** vs **11o**), we concluded that the substitution with aromatic group could improve inhibitory potency in comparison to

Table 2
Structures and IDO1 inhibitory activities of the NH-linker ubiquinone derivatives 

Compd.	R_1	R_2	IDO1 inhibition IC_{50} (μM) [a]
11a	H		0.70 ± 0.09
11b	H		0.60 ± 0.08
11c	H		0.72 ± 0.04
11d	H		0.51 ± 0.04
11e	H		0.63 ± 0.13
11f	H		0.58 ± 0.08
11g	H		0.60 ± 0.05
11h	H		0.67 ± 0.03
11i	H		0.61 ± 0.04
11j	H		0.63 ± 0.11
11k	H		0.78 ± 0.13
11l	H		0.82 ± 0.09
11m	H		1.08 ± 0.07
11n	H		1.12 ± 0.21
11o	H		3.92 ± 0.47
11p	H		1.91 ± 0.25
11q	Me		> 10
11r			> 10

[a] IC_{50} values are the means of more than two independent assays, presented as mean ± SD.

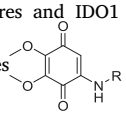
lipophilic substitutions. Overall, compound **11a** emerged as the most potent compound in this series, with an IC_{50} value of 0.70 μM in the *in vitro* enzymatic assay.

The results from first SAR encouraged us to further study the effect of the substitution groups on the aniline moiety, and compounds **11a-r** were synthesized and evaluated as shown in Table 2.

Surprisingly, mono-substituted compounds **11b-m** (IC_{50} = 0.51–1.08 μM) did not show much improvement of inhibitory activity versus their parent compound **11a** (IC_{50} = 0.70 μM). Similarly, compounds with aliphatic amine group (**11n-p)** were also substantially less potent than compounds with anilines. The influence of NH linker was also investigated and the SAR results revealed that the tertiary amine moiety gave inactive compounds (**11q** and **11r)**.

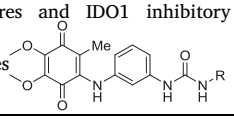
To further optimize compound **11a**, modifications were performed to place the aniline moiety into pocket A. For this purpose, we took advantage of structure-guided optimization strategy while analyzing the binding mode of **11a** after docking. Our binding mode analysis revealed that methyl group of **11a** was so big that the aniline moiety could not stretch to the pocket A (Fig. 4A).

Based on the insights from our modeling studies (discussed above), 10 compounds, **16a-j**, were synthesized and evaluated (Table 3). The SAR of compounds **16b-g** accompanied by docking analysis of **16d** (the most potent one) suggested that the halogen bonding interaction between halogen atoms and the sulphur atom of Cys129 was beneficial to the IDO1 inhibition potency (Fig. 4B). The analyses further revealed

Table 3
Structures and IDO1 inhibitory activities of the de-methyl ubiquinone derivatives 

Compd.	R	IDO1 inhibition IC_{50} (μM) [a]
16a		0.60 ± 0.21
16b		0.32 ± 0.11
16c		0.23 ± 0.05
16d		0.13 ± 0.02
16e		0.27 ± 0.01
16f		0.25 ± 0.03
16g		0.16 ± 0.02
16h		0.67 ± 0.04
16i		0.56 ± 0.07
16j		0.69 ± 0.13

[a] IC_{50} values are the means of more than two independent assays, presented as mean ± SD.

Table 4
Structures and IDO1 inhibitory activities of the urea ubiquinone derivatives 

Compd.	R	IDO1 inhibition IC_{50} (μM) [a]
18a		0.40 ± 0.08
18b		0.71 ± 0.15
18c		0.86 ± 0.11
18d		1.36 ± 0.37
18e		0.92 ± 0.09
18f		3.22 ± 0.26
18g		1.26 ± 0.15
18h		1.30 ± 0.87
18i		0.86 ± 0.14
18j		0.39 ± 0.05

[a] IC_{50} values are the means of more than two independent assays, presented as mean ± SD.

that the weaker activity of fluorine and chlorine substitutions (**16b** and **16c**) versus that of bromine (**16d**) would be consistent with principles of halogen bonding events, since fluorine and chlorine are electronegative and small, being unfavorable for effective halogen binding compared to bromine. Further, disubstitued derivatives **16f** and **16 g** were tolerated and showed no improvement in inhibitory activity compared to monosubstituted derivatives (**16c** and **16d**). Finally, replacement of the aniline with benzylamine **16h-j** resulted in a dramatic decrease in inhibitor potency (Table 3).

According to our docking analysis, the **18a** and **11a** showed similar binding mode to the IDO1 protein. (Fig. 4C and Fig. 4A). For compound **18a**, there was an additional interaction between the two nitrogen

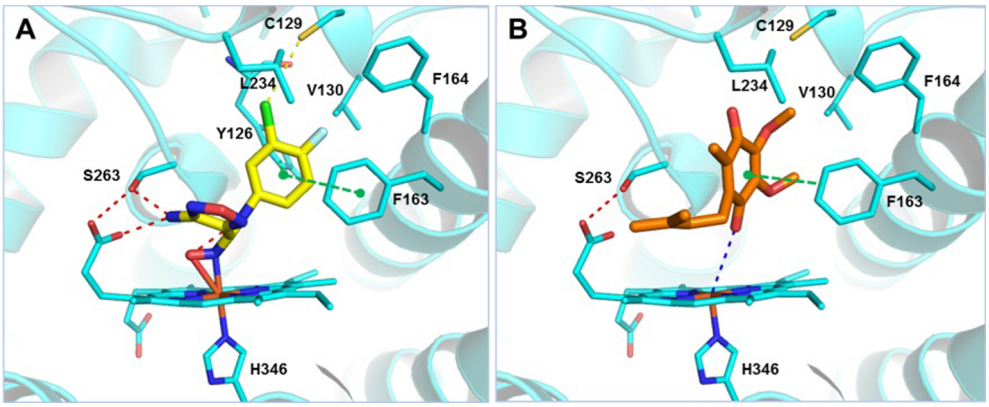


Fig. 3. (A) Binding details of IDO1 (cyan) with INCB14943 (yellow) (Glide SP: −7.599). (B) Proposed binding mode of coenzyme-Q1 (orange) with IDO1 (Glide SP: −4.661). Residues involved in interactions are shown as stick. The green dash line indicates π-π interaction, the yellow dash line indicates halogen interaction, and the red dash line indicates hydrogen bond interaction, respectively. (PDB: 5XE1) [46].

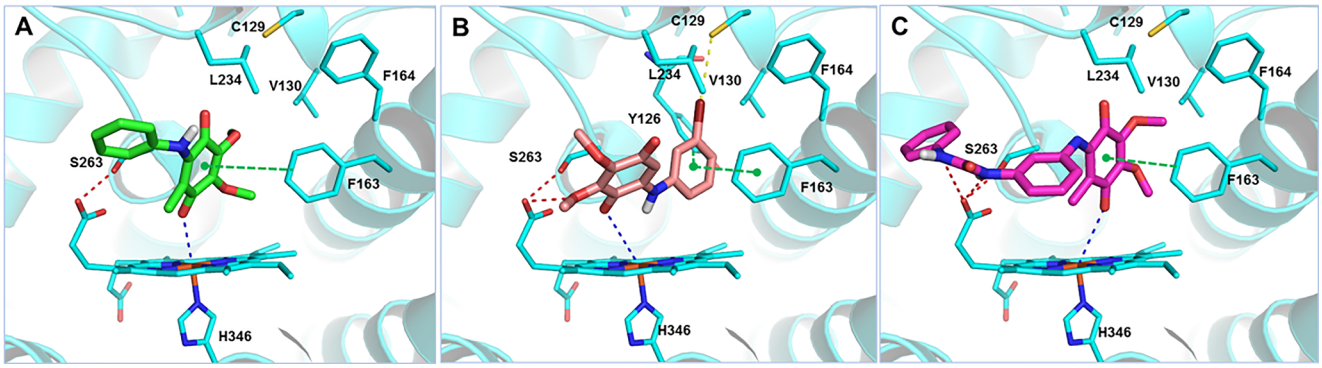


Fig. 4. (A) Proposed binding mode of **11a** (green) (Glide SP: −5.404). (B) Proposed binding mode of **16d** (salmon) (Glide SP: −5.702). (C) Proposed binding mode of **18a** (magenta) (Glide SP: −5.676). The green dash lines indicate π-π interactions, the yellow dash line indicates halogen interaction, the red dash lines indicate hydrogen bond interactions, and the blue dash lines indicate interactions between heme iron and carbonyl, respectively.

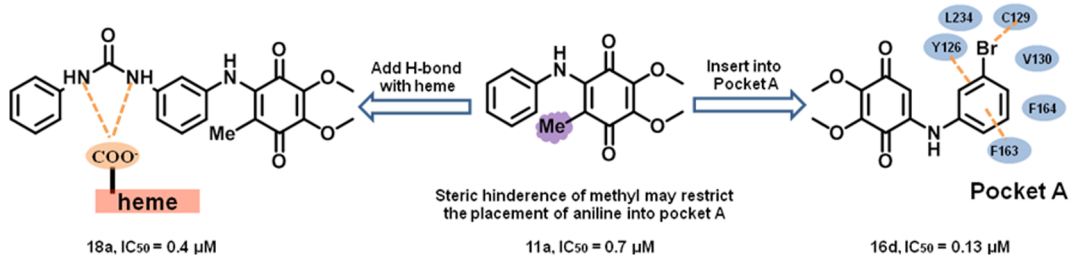


Fig. 5. The docking-guided optimization and SAR of ubiquinone derivatives.

Table 5
Cell-based Assay of ubiquinone derivatives.

Compd.	Cytotoxic activities HEK293T, IC_{50} (μM)	Inhibitory activities HeLa, IC_{50} (μM)
11a	18.9	19.9
16d	28.0	11.2
18a	72.1	11.1
Doxorubicin	3.1	

atoms of urea and carboxylic acid of heme, which possibly contribute to inhibitory potency for this series of compounds. Among these compounds (Table 4), **18a** and **18j** exhibited higher inhibitory potency with values of 0.40 μM and 0.39 μM, respectively. The SAR analyses of these urea derivatives demonstrated that the substitution of aniline ring always led to decreased IDO1 inhibitory activity. The benzylamine derivatives (**18g** and **18h**) and cyclohexylurea derivative (**18i**) exhibited slightly less inhibitory potency.

In this study, ubiquinone was discovered to be a novel key pharmacophore with potent IDO1 inhibitory activity. At the beginning, the lead compound coenzyme-Q1, a commercially available compound, exhibited moderate inhibition potency. Our hybridization strategy to replace isoallyl with aniline (**11a**), improved the inhibitory potency (IC_{50} = 0.70 μM) and prompted us to further investigate this series of compounds. Based on the modeling predictions for **11a** (discussed above), we synthesized the demethylated series (**16a-j**) among which compound **16d** was found to be a most potent IDO1 inhibitor with IC_{50} of 0.13 μM. Further optimizations also confirmed the critical interaction of the halogen atom and Cys129 in pocket A. Similarly, in case of **18a**, the interactions between urea moiety and hydroxyl of Ser263 and carboxylic acid of heme were predicted essential to improve the inhibitory activity. Overall, our computational and SAR analyses revealed that there are two important factors affecting ubiquinone derivatives IDO1 inhibitory activity: the formation of halogen bonding in pocket A and the interaction with carboxylic acid of heme, which could provide further insights for future optimization.

3.2. Cellular IDO1 inhibitory activity assay

For the cell-based IDO1 inhibitory evaluation, we selected the

compounds **11a**, **16d**, and **18a** which were the most potent ones among the synthesized series. The results showed that **11a**, **16d**, and **18a**, though having potent *in vitro* enzymatic inhibition, did not demonstrate similar inhibition in cellular assay (Table 5), which might be because of their weak membrane permeability or complexity of kynurenine pathway. Our future studies will endeavor to improve the cell-activity of ubiquinone derivatives.

3.3. Cell viability assay

In cell viability assay, **11a**, **16d** and **18a** displayed significantly higher IC_{50} values as compared to the standard drug doxorubicin (Table 5). The results showed ubiquinone derivatives had weak cytotoxicity against the HEK293T cells, indicating possible their high selectivity towards IDO1.

3.4. Determination of the inhibition type

The inhibition type was determined by dilution experiment. The results showed that **16d** was a reversible inhibitor. (Supplementary material Fig. S1).

4. Conclusion

In summary, a new structural class of IDO1 inhibitors, ubiquinone derivatives, has been discovered. Among these, 27 compounds exhibited sub-micromolar potency in the *in vitro* enzyme inhibition assay and the most active compound is **16d** with an IC_{50} of 0.13 μM. Docking studies have shown that coenzyme-Q1, **11**, **16** and **18** adopted different binding modes to the IDO1. Halogenation of the aniline ring was found particularly important in improving potency. SAR and modeling studies were performed to understand the interactions of ubiquinone analogues to IDO1 protein, which give us a direction for further lead optimization. We believe that the ubiquinone derivatives may serve as novel and useful chemical probes for the design of more effective IDO1 inhibitors.

Acknowledgements

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Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.03.044.

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