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Original research article

Theoretical Investigation of Cyclodextrin Encapsulation to Enhance the Solubility of Ethionamide and Its Synergistic Boosters

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) remains a global health challenge, necessitating novel strategies to improve the effectiveness of existing second-line treatments. Ethionamide, a key antitubercular agent, suffers from poor solubility, low oral bioavailability, and formulation challenges due to its crystalline nature. Synergistic booster compounds such as BDM43266 have been developed to enhance ethionamide bioactivation, but they face similar pharmacokinetic limitations. This study investigates the potential of native cyclodextrins (α-CyD, and β-CyD) to form inclusion complexes with ethionamide and its synergistic boosters using molecular modelling approaches. Molecular docking and complexation energy calculations were conducted to assess binding stability and host–guest interactions. The results reveal that β-CyD forms the most stable complexes with ethionamide and selected boosters, particularly BDM41907 and BDM41906, due to optimal steric fit and favourable interaction energies. These findings support the use of cyclodextrin-based drug delivery systems to improve the solubility and therapeutic performance of ethionamide and its synergistic boosters in MDR-TB treatment.

Keywords: Host-guest interaction; Inclusion complex; Molecular docking; Multidrug-resistant tuberculosis; Semi-empirical method

1. Introduction

Drug-resistant Mycobacterium tuberculosis continues to pose a significant threat to global health, underscoring the need for improved therapeutic strategies alongside existing tuberculosis treatments. Ethionamide (ETH), a key second-line anti-TB agent, plays a critical role in the man-

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agement of multidrug-resistant tuberculosis (MDR-TB). To enhance its efficacy, pharmacological boosters such as BDM43266 have been developed to promote ETH's intracellular bioactivation [1]. However, these agents suffer from pharmacokinetic limitations, including poor aqueous solubility, low oral bioavailability, and dose-dependent gastrointestinal toxicity, all of which hinder their clinical effectiveness [2]. Moreover, ETH tends to crystallize readily, complicating drug formulation and resulting in inconsistent therapeutic responses [3].

To address these limitations, several booster molecules—including BCD41907, BDM41906, BDM31381, and BDM31343—have been investigated for their ability to enhance ETH activation in mycobacterial cells [4–6]. Among formulation strategies aimed at improving solubility and bioavailability, the use of cyclodextrins (CyDs) has shown promise. CyDs are cyclic oligosaccharides composed of D-glucose units connected by α-1,4-glycosidic bonds. The three naturally occurring CyD types—α-, β-, and γ-CyD—consist of six, seven, and eight glucose units, respectively [7].

Their unique toroidal structure features a hydrophobic inner cavity and a hydrophilic outer surface, enabling the formation of water-soluble inclusion complexes with hydrophobic guest molecules. The primary and secondary hydroxyl groups located on the narrower and wider rims of the CyD molecule, respectively, play key roles in host–guest binding [8]. In this study, we explore the potential of α-CyD and β-CyD to form stable inclusion complexes with ETH and its synergistic boosters using molecular modeling techniques. We employ molecular docking simulations and complexation energy calculations to evaluate the binding affinities and interaction geometries between the drugs and the three CyD types. This theoretical approach offers a rapid and cost-effective screening tool for the rational design of CyD-based drug delivery systems to enhance ETH's bioavailability and therapeutic efficacy.

2. Materials and Methods

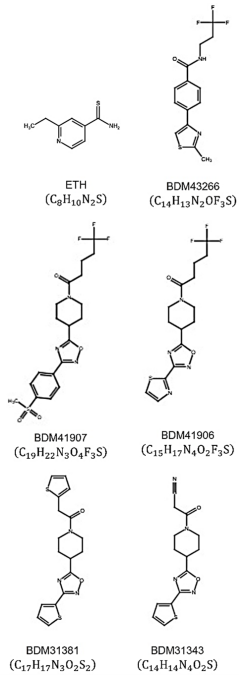


Fig. 1. Ligands used in this study [4-6].

2.1 Molecular structure preparation

The molecular structures of α-CyD and β-CyD and two key ligands (ETH and BDM41907) were retrieved from the Cambridge Crystallographic Data Centre (CCDC) using the following identifiers: α-CyD (CCDC No. 1106001) [9], β-CyD (1107192) [10], ETH (1150421) [11], and BDM41907 (966227) [12]. Additional booster molecules listed in Fig. 1 were modeled based on the BDM41907 scaffold, with structural modifications performed us-

ing Discovery Studio 2020 [13]. All ligand structures were optimized in the gas phase using the semi-empirical PM7 method as implemented in Gaussian 16 [14].

2.2 Complexation energy calculations

The inclusion complexes were optimized were optimized using the PM7 method to study their molecular interactions. The complexation energy (ΔE) was calculated using Eq. (2.1):

$$\Delta E = E_{complex}^{opt} - \left(E_{host}^{opt} + E_{guest}^{opt}\right), \tag{2.1}$$

where $E_{complex}^{opt}$, E_{host}^{opt} and E_{guest}^{opt} are the optimized heat of formation energy of the complex, host, and guest molecules, respectively. More negative ΔE values indicate more favorable and stable host–guest interactions.

2.3 Binding constant calculations

In this study, the binding constant ($K_{1:1}$)was estimated based on the complexation energy (ΔE), which is assumed to approximate the standard Gibbs free energy change (ΔG) of the host–guest interaction. Under this assumption, the following thermodynamic, Eq. (2.2), relationship was used:

$$\Delta G \approx \Delta E = -RT \ln K_{1:1}, \tag{2.2}$$

where R is the gas constant (1.987×10^{-3} kcal·mol^{-1}·K^{-1}), T is the temperature (298.15 K), and $K_{1:1}$is the binding constant. Rearranging this expression gives Eq. (2.3):

$$K_{1:1} = \exp\left(-\frac{\Delta R}{RT}\right). \tag{2.3}$$

This approach provides a useful approximation for comparing relative binding affinities of the systems being evaluated.

3. Result and Discussion

3.1 Validation of molecular modeling protocol

To evaluate the reliability of our molecular modeling protocol, we investigated the 1:1 inclusion complex formed between ethionamide (ETH) or the booster molecule BDM43266 and two native cyclodextrins (α-CyD, and β-CyD). These model systems were selected for comparison with available experimental data [1]. Molecular docking simulations were employed to explore possible binding conformations, with the cyclodextrin (host) structures held rigid and the guest molecules (ETH and BDM43266) allowed full conformational flexibility within the cyclodextrin cavity. The docking results revealed two dominant binding modes (Conformations I and II) for each guest molecule within cyclodextrin hosts, supporting the formation of stable 1:1 inclusion complex. These predicted binding geometries are illustrated on Fig. 2.

PM7 geometry optimization results (Table 1) indicated that all inclusion complexes had large HOMO–LUMO energy gaps (7.40 to 8.76 eV), suggesting that the complexes are stable and chemically inert. The calculated complexation energies (ΔE) were all negative, indicating energetically favorable host-guest interactions. ETH showed the stronger binding with β-CyD (ΔE = –50.82 kcal/mol) than α-CyD (ΔE = -40.79 to –42.04 kcal/mol), which was consistent with the experimental binding constants [1]. These results suggest that β-CyD provides the most optimal steric fit and electrostatic interactions for ETH. For the booster molecule BDM43266, β-CyD again formed the most stable complexes, with ΔE values ranging from –60.86 to –64.63 kcal/mol.

These findings highlight the impor-

Table 1. PM7 calculated HOMO–LUMO energy gaps (Δ|HOMO-LUMO|, in eV), heats of formation (ΔH_f, in kcal/mol), and complexation energies (ΔE, in kcal/mol) for the 1:1 inclusion complex. The calculation of binding constant ($K_{1:1}$, in M^{-1}) at 298.15 K.

Compound	Conf.[a]	Δ|HOMO-LUMO|	ΔH_f	ΔE	$K_{1:1}$
α-CyD		10.8	-1372.99		
β-CyD		10.97	-1608.31		
γ-CyD		8.3	-1807.23		
ETH		7.89	39.53		
BDM43266		8.03	-159.39		
BDM41907		8.54	-130.52		
BDM41906		8.16	-160.01		
BDM31381		8.14	25.73		
BDM31343		8.11	32.63		
Complex with α-CyD					
ETH	I	7.92	-1374.25	-40.79	7.99×10^{29}
	II	7.56	-1375.5	-42.04	6.59×10^{30}
BDM43266	II	8.33	-1587.6	-55.22	3.02×10^{40}
Complex with β-CyD					
ETH	I	7.73	-1619.6	-50.82	1.80×10^{37}
BDM43266	I	8.6	-1832.33	-64.63	2.39×10^{47}
	II	8.05	-1828.56	-60.86	4.12×10^{44}
BDM41907	I	8.76	-1934.61	-195.78	3.33×10^{143}
	II	8.41	-1939.63	-200.8	1.59×10^{147}
BDM41906	I	7.86	-1824.17	-55.85	8.76×10^{40}
	II	8.14	-1831.7	-63.38	2.90×10^{46}
BDM31381	I	7.95	-1634.03	-51.45	5.21×10^{37}
	II	7.4	-1639.68	-57.1	7.23×10^{41}
BDM31343	I	8.08	-1628.39	-52.71	4.37×10^{38}
	II	8.14	-1631.52	-55.84	8.61×10^{40}

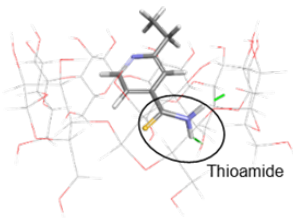
[a] the conformations in each complexed system are not identical

tance of steric compatibility and cavity size in determining the stability of inclusion complexes. The comparative analysis indicates that the stability of host–guest inclusion complexes is primarily governed by steric compatibility and cavity size of the cyclodextrins. β-CyD consistently emerged as the most suitable host for both ETH and BDM43266, owing to its optimal cavity dimensions and favorable interaction energies. The strong agreement between computationally predicted stability and experimental binding data underscores the reliability of our molecular modeling protocol. These results validate the use of our in-silico approach for screening potential inclusion complexes of ETH and its boosters before proceeding to experimental investigations.

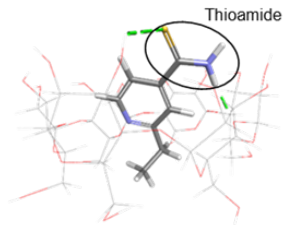
3.2 β-CyD Complexes with additional boosters

Further studies focused on β-CyD as a carrier for enhancing the solubility and bioavailability of ETH and its boosters. The PM7 energies of the 1:1 inclusion complex formed between β-CyD and various boosters (BDM41907, BDM41906, BDM31381, and BDM31343) are also presented in Table 1. The calculated complexation energies indicated that all boosters favor the formation of inclusion complexes with β-CyD. The binding constants calculated from these energies were consistent with experimental values. The orientations of the inclusion complexes investigated are shown in Fig. 3.

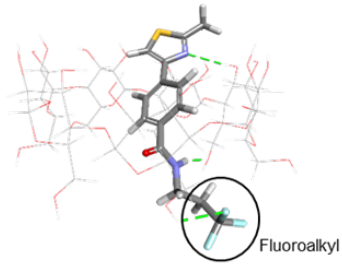
For the BDM41907 booster, although it showed strong binding with β-CyD (ΔE = –195.78 to –200.80 kcal/mol),



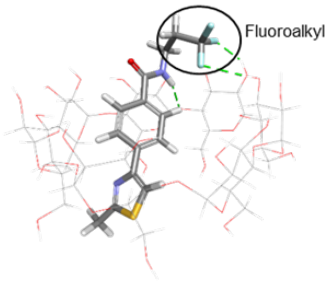
(a) ETH/CyD conformation I



(b) ETH/CyD conformation II



(c) BDM43266/CyD conformation I



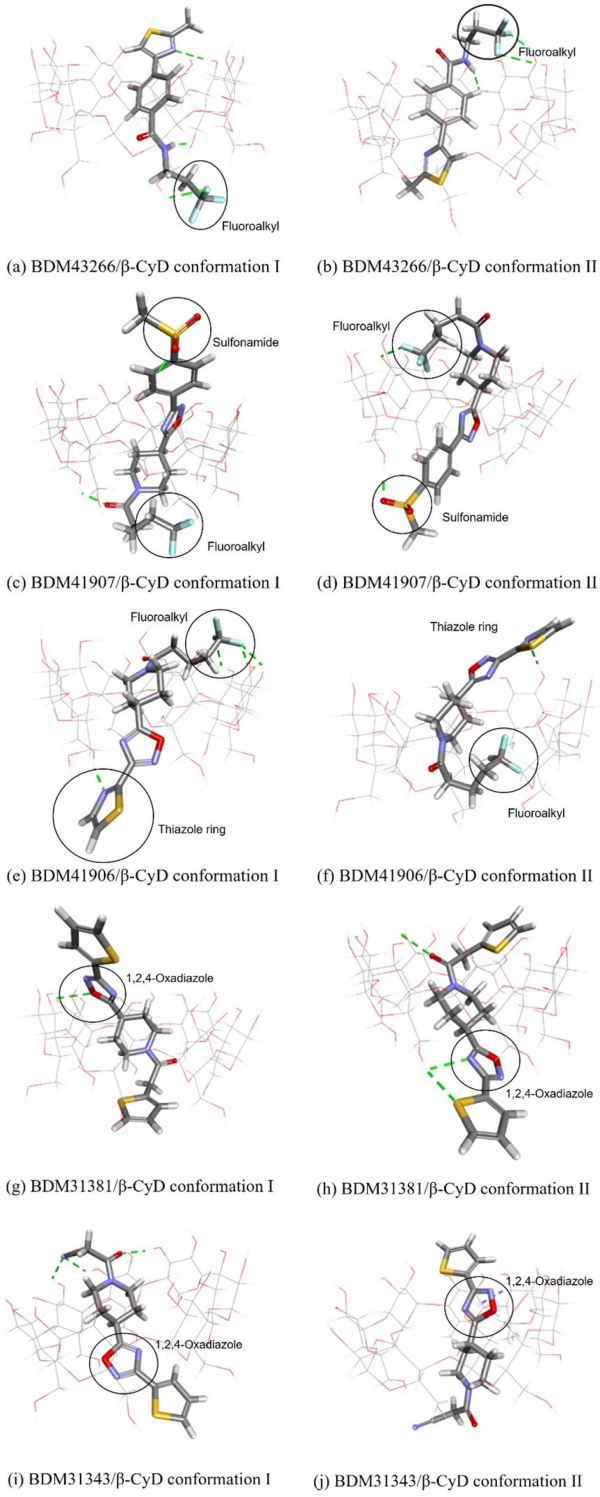
(d) BDM43266/CyD conformation II

Fig. 2. Two possible orientations of the cyclodextrins (CyDs) inclusion complex with ETH and BDM43266 from molecular docking calculations.

the complexation might not be ideal for dual-action with ETH due to slow guest release from the β-CyD cavity. The strong binding of BDM41907 was attributed to its functional groups, sulfonamide, which formed strong hydrogen bonds with the hydroxyl groups of β-CyD at either the primary or secondary rim depending on the orientation, and the trifluoromethyl group, which engages in hydrophobic and van der Waals interactions within the β-CyD cavity. Further experimental or kinetic modeling studies are needed to confirm this behavior.

BDM41906 also exhibited strong binding affinity with β-CyD (ΔE = -55.85 to -63.38 kcal/mol), comparable to BDM43266, indicating a well steric fit with the β-CyD cavity. Docking analysis showed favorable steric complementarity, with the trifluoromethyl group directed toward the hydrophobic core, thereby contributing to van der Waals stabilization (Fig. 3).

BDM31381 and BDM31343 exhibited weaker complexation with β-CyD, with ΔE values of –57.10 and –55.84 kcal/mol, respectively, in their most stable conformations. BDM31381 displayed slightly more negative ΔE and demonstrated a marginally more favorable interaction profile, as evidenced by a higher calculated binding constant. The reduced complex stability in both systems may be attributed to limited hydrogen bonding capacity and suboptimal steric compatibility within the β-CyD cavity. Both compounds also lack strongly polar or bulky hydrophobic groups at the termini, which may further weaken host–guest interactions. These findings suggest that while BDM31381 and BDM31343 can form inclusion complexes with β-CyD, their lower binding affinities and less favorable structural characteristics may limit their suitability for formulation. In contrast, BDM43266, BDM41907, and BDM41906 demonstrated more favorable interaction profiles. Over-



(a) BDM43266/β-CyD conformation I (b) BDM43266/β-CyD conformation II

(c) BDM41907/β-CyD conformation I (d) BDM41907/β-CyD conformation II

(e) BDM41906/β-CyD conformation I (f) BDM41906/β-CyD conformation II

(g) BDM31381/β-CyD conformation I (h) BDM31381/β-CyD conformation II

(i) BDM31343/β-CyD conformation I (j) BDM31343/β-CyD conformation II

Fig. 3. The PM7 o ptimized conformations of β-CyD inclusion complex with various boosters.

all, BDM41907 and BDM41906 were identified as the most promising candidates for β-CyD-based ETH delivery due to their strong, well-balanced host–guest interactions.

4. Conclusion

This theoretical investigation demonstrates that β-cyclodextrin (β-CyD) is a highly suitable host for improving the solubility and potential bioavailability of ethionamide (ETH) and its synergistic boosters. Molecular docking and complexation energy analyses indicate that β-CyD forms the most stable inclusion complexes, particularly with BDM41906 and BDM41907, due to optimal steric compatibility and favorable host–guest interactions. These findings validate the use of molecular modeling as a predictive tool for screening drug–cyclodextrin complexes and support the development of cyclodextrin-based delivery systems to enhance the pharmacological performance of ETH in MDR-TB treatment. Future studies should focus on experimental validation and release kinetics to optimize these complexes for clinical application.

Acknowledgements

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