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A Computational Approach For The Supramolecular Assembly Of Amodiaquine And Chloroquine With Native Cyclodextrins

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Abstract
The inclusion complexes of AQ and CQ with the different native cyclodextrins (α, β and γ-CD) have been analyzed by using molecular docking with the help of Patch-Dock server. The guest molecules such as AQ and CQ along with different native CDs as the host has been organized by AM1 method. An interaction has been proposed in virtual state based on the data obtained through docking outcome. According to geometric shape complementarity score, approximate interface area size of the complex and atomic contact energy for the obtained supramolecular complexes of the chosen guest with three different native CDs, the structure has been provided and compared with each other for the applications such as anti-bacterial activity and so on.
Keywords: AQ; CQ; Native cyclodextrins; Molecular docking; AM1

INTRODUCTION

Supramolecular chemistry is still a young field; meaning that it can be rather difficult to define exactly what it encompasses-indeed it is a field that has developed rapidly due to contributions from a variety of related fields. The supramolecular chemistry gives a broad idea of intermolecular interactions has been performed by host-guest system. The cyclodextrin is mostly hopeful to form inclusion complexes, especially with different kind of guest molecules with proper and suitable structure **[1]**.In supramolecular chemistry; host-guest chemistry describes complexes that are composed of two or more molecules or ions that are held together in unique structural relationships by forces other than those of full covalent bonds. Host-guest chemistry encompasses the idea of molecular recognition and interactions through non covalent bonding. There are commonly mentioned types of non-covalent interactions: hydrogen bonding, dipole-dipole, charge transfer, van der Waals, and π-π stacking interactions. The non-covalent interactions possess many number of advantages than the covalent interactions. All supramolecular chemistry is based on how to recognize molecules, how to affect molecules, and how to express specific functions due to molecular interactions via non covalent interactions.

The understanding of non-covalent all intermolecular interactions are of supreme importance in supramolecular chemistry and in biological chemistry **[2]**. Supramolecular chemistry which is also defined as ‘‘chemistry beyond the molecule’’ is based on the molecular recognition to greater extent and a hot topic in current chemical research. Therefore, in order to get across the basic concepts of “supermolecules” and “supramolecular chemistry”, it is worth using an analogy from daily life. The construction of supramolecular system involves selective and specific molecular assembly between host

and guest **[3-4]**. Towards this goal, the molecular recognition of many simple host molecules, such as crown ethers, cyclodextrins and calixarenes, have been extensively studied **[5]**. The synthetic host-guest inclusion complexes have better then natural system defined conformations and therefore can be investigated experimentally and theoretically in more detail.
Supramolecular systems are becoming progressively important and extensively useful in various areas of chemistry, such as control and catalysis of chemical reactions **[6-7]**, organic synthesis **[8]**, molecular recognition **[9]**, design of materials for molecular-scale electronics **[10]**, chemical separations **[11]**, bio-organic chemistry **[12]** and so on. The macrocyclic molecule like CDs has attracted an increasing popularity, especially for their applications in biomedical field. One major reason is that the CDs are basically friendly to the biological environment and exhibit good biocompatibilities **[13-17]**. Another reason is that the host-guest inclusion complexation based on the macrocyclic molecule is a facile and reversible process, which provides the possibility of feasible to design stimuli-responsive supramolecular systems **[18]**. The various biomedical applications of the host-guest systems discussed contain several leading directions, that is, drug delivery, gene delivery, drug/gene co delivery, bio imaging and photodynamic therapy (PDT). Therefore, a lot of research has demonstrated the significant roles of CDs in supramolecular chemistry, especially for the preparation of CD-based supramolecular assemblies for biological applications **[19-22].**

Computational approaches that 'dock' small molecules into the structures of macromolecular targets and 'score' their expected complementarity to binding sites are generally utilized in hit identification and lead optimization. To be sure, there are presently a various drugs whose development was intensively influenced by or dependent on structure- based design and screening techniques, for example, HIV protease inhibitors. All things considered, there stay huge difficulties in the application of these approaches, specifically according to current scoring schemes. On a fundamental level, docking process involves the prediction of ligand conformation and orientation (or posing) inside a focused on a targeted binding site. In general, there are two aims of docking studies: accurate structural modeling and correct prediction of activity. However, the identification of molecular features that is responsible for specific biological recognition, or the prediction of compound modifications that improve potency, are complex issues that are frequently hard to understand **[23]**.

To assess different docking methods, it is important to consider how the protein and ligand are spoken or represented. There are three fundamental representations of the receptor: atomic, surface and grid **[24].** Among these, atomic representation is commonly just utilized in conjunction with a potential energy function **[25]** and regularly just during final ranking procedures (due to the computational complexity of evaluating pair-wise atomic interactions). Surface-based docking programs are typically, but not exclusively, used in protein-protein docking **[26].**The molecular surface representations is essentially answerable for generating a great part of the examination here **[27].** These methods endeavor to adjust points on surfaces by minimizing the angle between the surfaces of opposing molecules. Subsequently, a rigid body approximation is still the standard for many protein-protein docking techniques. The utilization of potential energy grids was pioneered by Goodford in 1985 and various docking programs use such grid representations for energy calculations. The essential thought is to store information about the receptor's energetic contributions on grid points with the goal that is just should be perused during ligand scoring. In the most basic form, grid points store two kinds of possibilities: electrostatic and van der Waals.

Since 1995, a great number of researches were focused on the study of inclusion complex of cyclodextrins by semi-empirical methods AM1 and PM3 to obtain electronics properties and to have more information about geometry of the complex. The results suggested that PM3 should be more advantageous than AM1 and give results which coincide with the experimental observations. In 2000 some studies were carried out about the performances of AM1 and PM3 methods on CD systems. On the basis of AM1 and PM3 calculation results for some model compounds including hydroxyethyl ether and α (1–4)-glucobiose, it suggested that PM3 should be advantageous to AM1 in CD chemistry because PM3 can predict the O–H…O hydrogen bonds better than AM1. This proposal was supported by direct structure optimization of α and β-CD with AM1 and PM3, in which AM1 gave badly distorted geometries due to unreasonable hydrogen bonding, whereas PM3 reproduced the crystalline structures rather well.

Computational approach have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed and its formulations. Rational Drug

Design (RDD) helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds **[28, 29]**. One such method is the docking of the drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor.9 Docking is the process by which two molecules fit together in 3D space.

[12] Christensen JG, Zou HY, Arango ME,et al. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther 2007;6:3314-22.
[13] Leite TB, Gomes D, Miteva MA, Chomilier J, Villoutreix BO, et al. Frog:a Free Online drug 3D conformation generator. Nucleic Acids Res (2007) ,35

Therefore, docking is useful for predicting both the strength and type of signal produced. Molecular docking is one of the most frequently used methods in structure-based drug design, due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site.

2. Molecular docking study

The most probable structure of the guests like AQ and CQ with three different types of CDs was determined also by molecular docking studies using the Patch-Dock server **[30].** The 3D structural data of host and guests was obtained from crystallographic databases. The guest molecules was docked in to the host molecules cavity using Patch-Dock server by submitting the 3D coordinate data of guest and host molecules. Docking was performed with complex type configuration settings. Patch-Dock server follows a geometry-based molecular docking algorithm to find the docking transformations with good molecular shape complementarity. Patch-Dock algorithm separates the Connolly dot surface representation **[31-32]** of the molecules into concave, convex and flat patches. These divided complementary patches are matched in order to generate candidate transformations and evaluated by geometric fit and atomic desolvation energy scoring **[33]** function. RMSD (root mean square deviation) clustering is applied to the docked solutions to select the non-redundant results and to discard redundant docking structures.

Semi-empirical quantum mechanical calculations

The ground state of guest molecules were optimized using Argus Lab program by AM1 method. MolSoft, MolBrowser tool was used to visualize the 3D structural data.

3. RESULTS AND DISCUSSION

3.1. Complexation Of Aq In Different Native Cds

3.1.1. Complexation Of Aq In A-Cds

The crystallographic databases are provided 3D structures of α-CD and AQ and shown in **Figures 1a and 1b**. With the help of Patch-Dock server, the AQ (guest molecule) molecule was docked into the inner cavity of α-CD. Further the server has given the several possible docked molecule for the most probable and suitable structure according to the energy parameter, geometric shape complementarity score, approximate interface areas size and atomic contact energy of the assumed complex [**Table 1**]. According to **Table 1**, highest geometric shape complementarity score in 4028, approximate interface area size is 470.00 $Å^2$ and atomic contact energy -318.96 kcal/mol for the docked AQ: α-CD with 1:1 stoichiometric structure and taken as the highest probable and energetically favorable model.

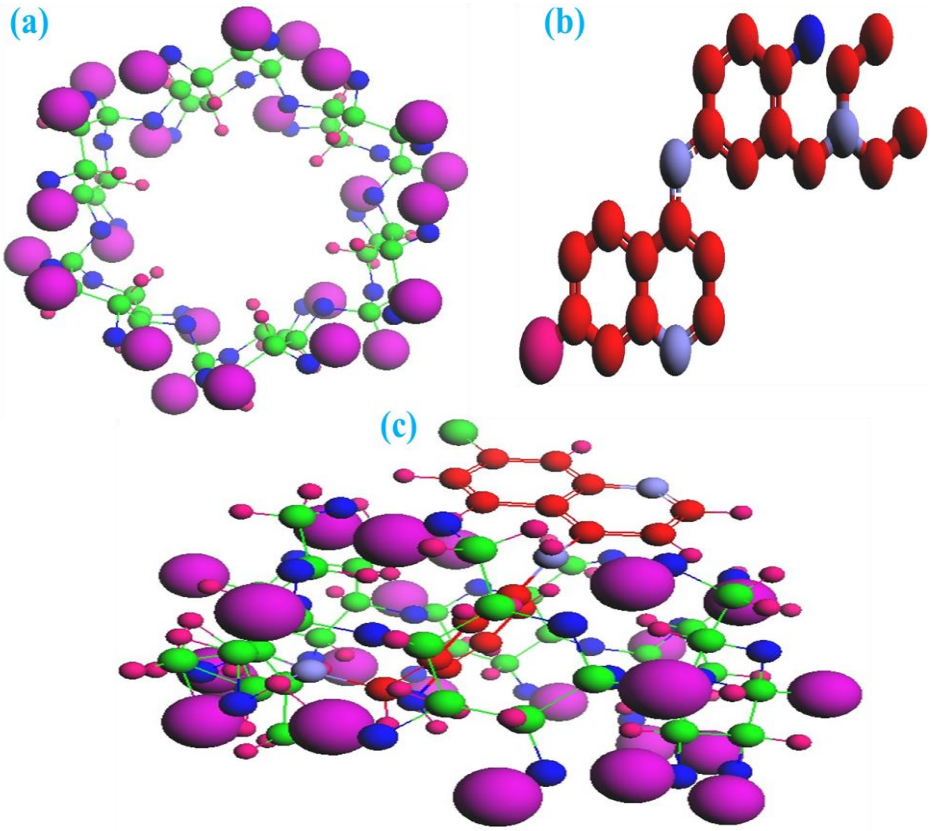

Fig.1. Ball and stick representation of (a) α-CD (b) AQ and (c) 1:1 inclusion complex; the oxygen atoms are shown as blue, carbon atoms are shown as green, hydrogen atoms are shown as rose, nitrogen atoms are shown as light blue and chlorine atoms are shown as light rose.

Table 1. Scores of the top 10 docked models of AQ:α-CD inclusion complex computed using Patch-Dock server.

Model	Geometric shape complementarity score	pproximate interface area size of the comple Å^2	tomic contact energ kcal/mol
1	4028	470.00	-318.96
2	3922	464.50	-325.37
3	3780	472.30	-373.82
4	3716	437.50	-344.10
5	3682	461.10	-369.60
6	3600	419.50	-384.85
7	3516	406.00	-378.83

8	3482	423.80	-376.59
9	3414	420.90	-310.57
10	3414	419.70	-294.82

Semi-empirical quantum mechanical calculations

The internal diameter and the height of the α-CD are approximately 5.7 Å and 7.8 Å (**Figure 2**) respectively. According to the shape and dimensions of α-CD molecule, it is clear that the guest AQ molecule cannot be included the whole part into the α-CD cavity, because of the overall height is around double about 11.10 Å (i.e., the vertical distance between $C_1 - C_{118}$). Hence, it is possible to locate the half of AQ molecule inside the α-CD cavity.

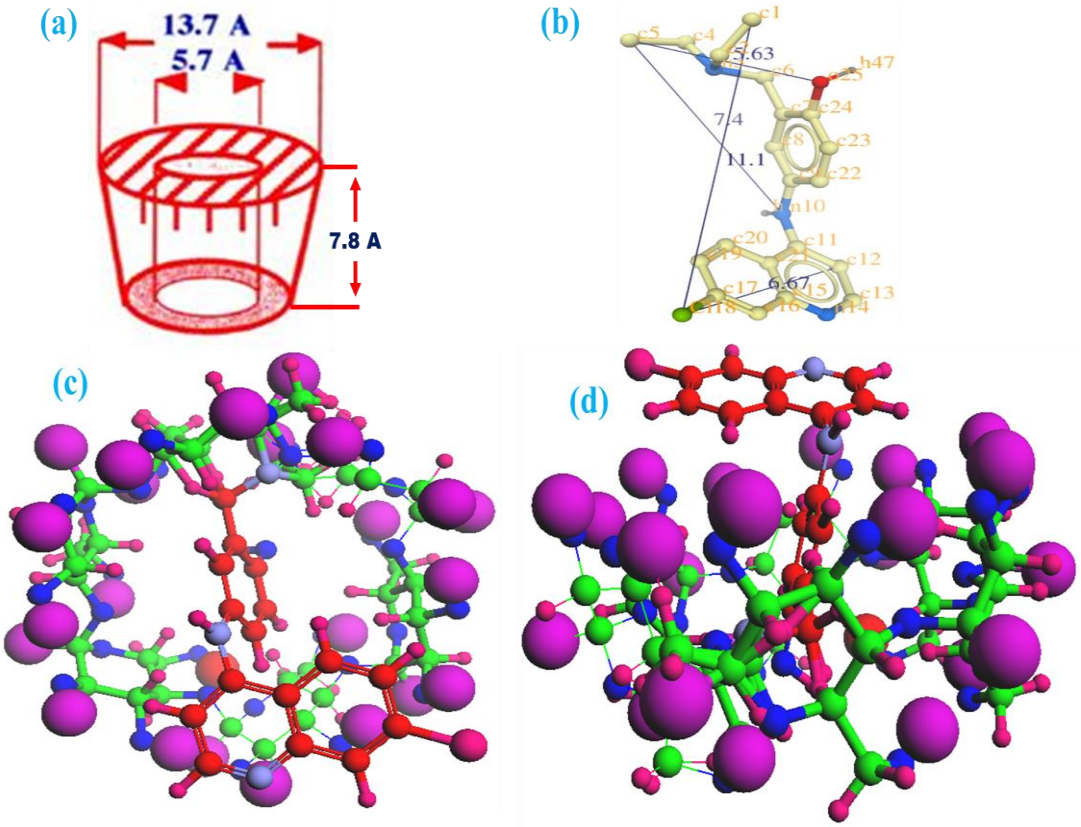

Fig 2 (a) Structure of α-CD, (b) structure of AQ, (c) Front pose and (d) Back pose structure of 1:1 host-guest inclusion complex of AQ: α-CD.

Table 2. Bond distances and orientations is AQ.

AQ bond distance in Å		Orientation
$C_1 - C_{118}$	11.10	Vertical
$C_5 - N_{10}$	7.40	Vertical
$C_5 - O_{25}$	5.63	Horizontal
$C_{118} - C_{12}$	6.67	Horizontal

3.1.2. COMPLEXATION OF AQ IN β-CDs

The crystallographic databases are provided 3D structures of β-CD and AQ and shown in **Figures 3 and 3b**. With the help of Patch-Dock server, the AQ (guest molecule) molecule was docked into the inner cavity of β-CD. Further the server has given the several possible docked molecule for the most probable and suitable structure according to the energy parameter, geometric shape complementarity score, approximate interface areas size and atomic contact energy of the assumed complex [**Table 3**]. According to Table 3, highest geometric shape complementarity score in 4028, approximate interface area size is 473.00 Å2 and atomic contact energy -341.71 kcal/mol for the docked AQ:β-CD with 1:1 stoichiometric structure and taken as the highest probable and energetically favorable model.

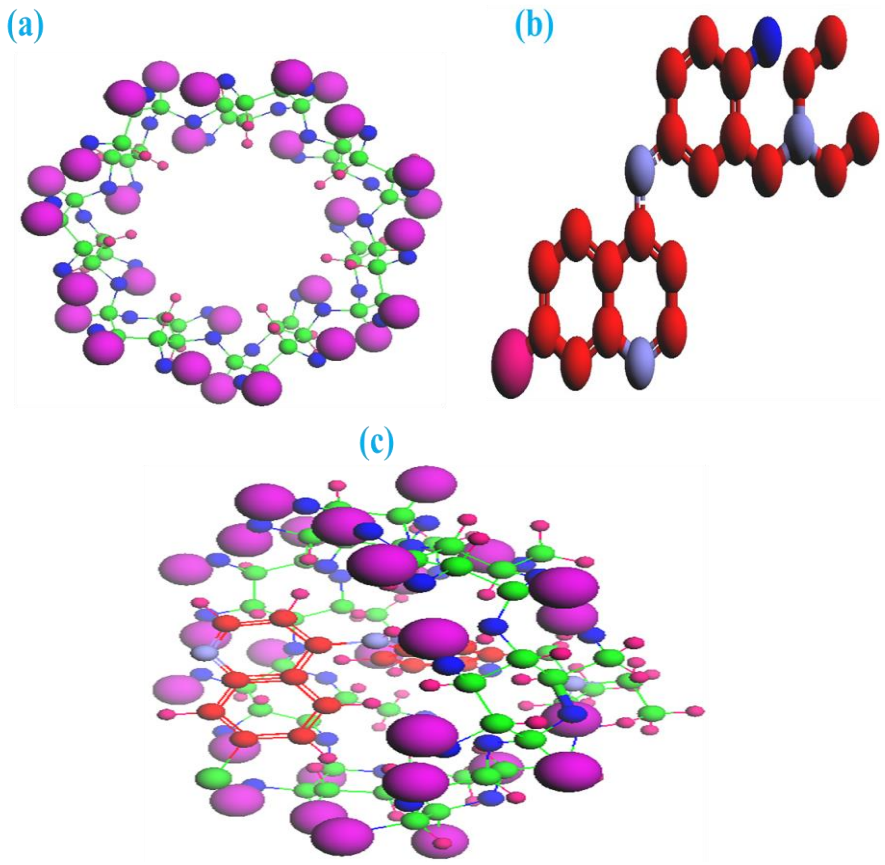

Fig.3. Ball and stick representation of (a) β-CD (b) AQ and (c) 1:1 inclusion complex; the oxygen atoms are shown as blue, carbon atoms are shown as green, hydrogen atoms are shown as rose, nitrogen atoms are shown as light blue and chlorine atoms are shown as light rose.

Table 3. Scores of the top 10 docked models of AQ: β-CD inclusion complex computed using Patch-Dock server.

Model	Geometric shape complementarity score	pproximate interface area size of the compl Å^2	tomic contact energ kcal/mol
1	3982	473.70	-341.71
2	3962	478.70	-320.49

3	3892	468.00	-344.86
4	3870	504.00	-340.05
5	3852	467.70	-334.21
6	3830	399.10	-290.95
7	3790	491.00	-371.36
8	3744	465.60	-356.89
9	3744	477.20	-353.45
10	3720	520.80	-388.54

Semi-empirical quantum mechanical calculations

The internal diameter and the height of the β-CD are approximately 7.8 Å and 7.8 Å (**Fig 4**) respectively. According to the shape and dimensions of β-CD molecule, it is clear that the guest AQ molecule cannot be included the whole part into the β-CD cavity, because of the overall height is around double about 11.10 Å (i.e., the vertical distance between $C_1 - C_{118}$),). Hence, it is possible to locate the half of AQ molecule inside the β-CD cavity.

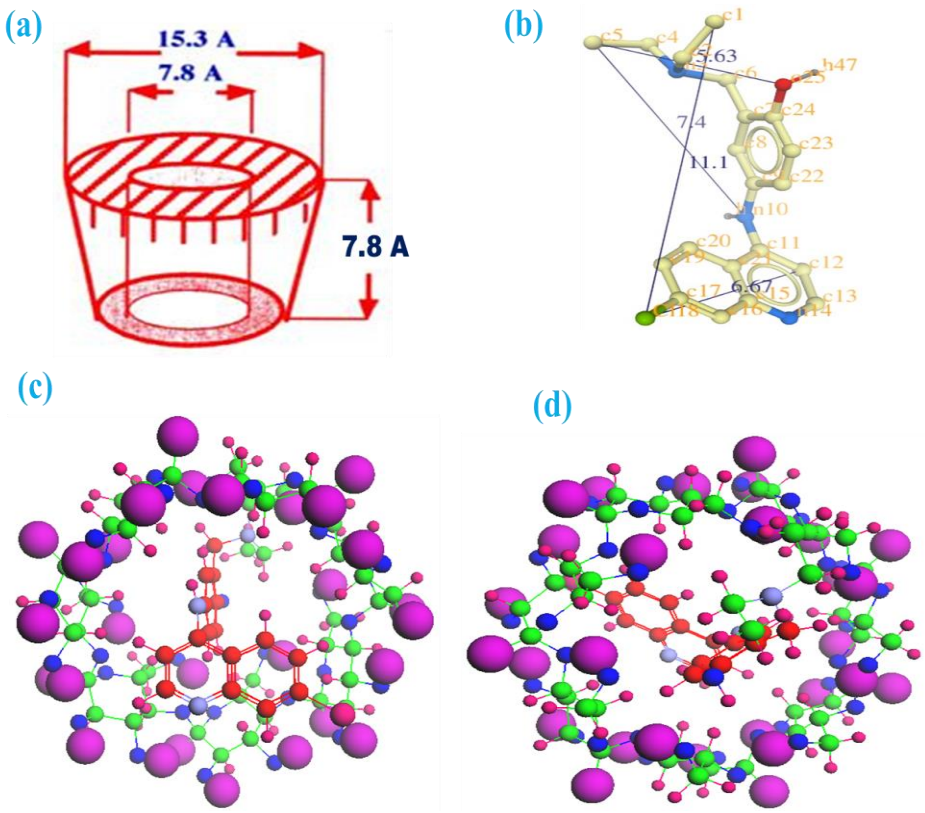

Fig 4 (a) Structure of β-CD, (b) structure of AQ, (c) Front pose and (d) Back pose structure of 1:1 host-guest inclusion complex of AQ: β-CD.

3.1.3. COMPLEXATION OF AQ IN γ-CD

The crystallographic databases are provided 3D structures of γ-CD and AQ and shown in **Figures 5a and 5b**. With the help of Patch-Dock server, the AQ (guest molecules) molecule was docked into the inner cavity of γ-CD. Further the server has given the several possible docked molecule for the most probable and suitable structure according to the energy parameter. Geometric shape complementarity score, approximate interface areas size and atomic contact energy of the assumed complex [**Table 4**]. According to table 4, highest geometric shape complementarity score in 4150, approximate interface area size is 491.00 $Å^2$ and atomic contact energy -347.49 kcal/mol for the docked AQ: γ-CD with 1:1 stoichiometric structure and taken as the highest probable and energetically favorable model.

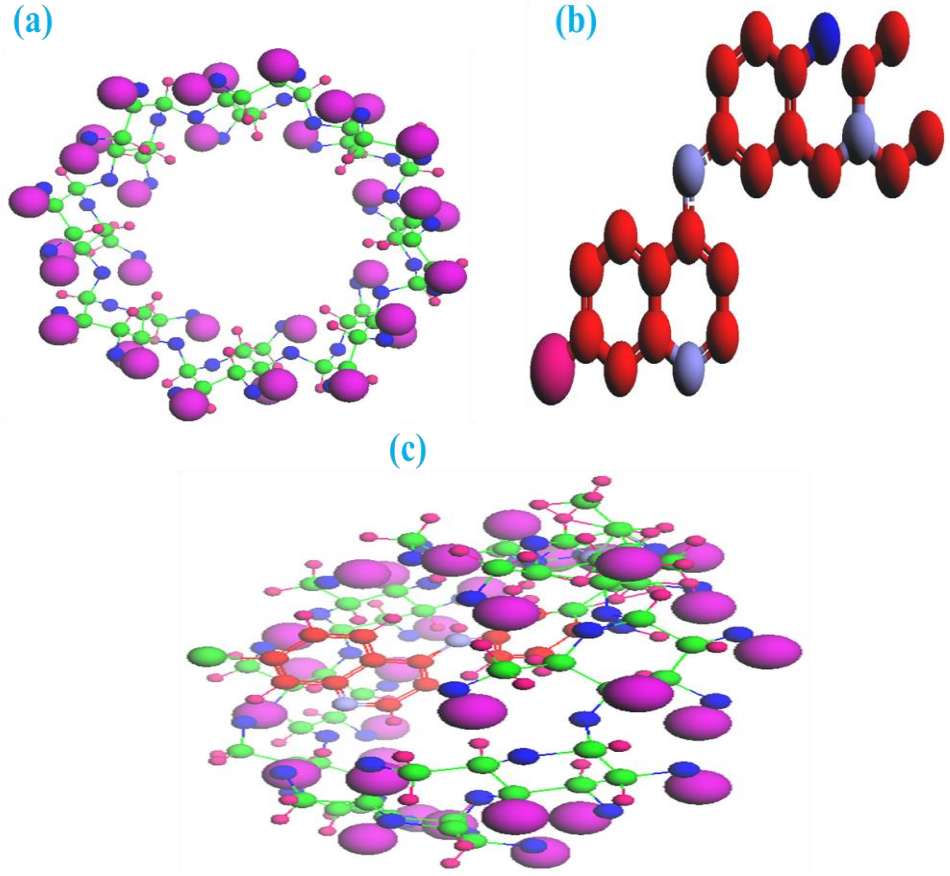

Fig.5 Ball and stick representation of (a) γ-CD (b) AQ and (c) 1:1 inclusion complex; the oxygen atoms are shown as blue, carbon atoms are shown as green, hydrogen atoms are shown as rose, nitrogen atoms are shown as light blue and chlorine atoms are shown as light rose.

Table 4. Scores of the top 10 docked models of AQ: γ-CD inclusion complex computed using Patch-Dock server.

Model	Geometric shape complementarity score	pproximate interface area size of the compl $Å^2$	tomic contact energ kcal/mol
1	4150	491.60	-347.49
2	4072	494.00	-350.81

3	4052	486.80	-342.99
4	3842	467.60	-330.16
5	3828	456.40	-332.08
6	3770	502.10	-334.64
7	3734	436.80	-334.03
8	3718	447.90	-331.11
9	3706	451.10	-340.39
10	3680	452.10	-338.69

Semi-empirical quantum mechanical calculations

The internal diameter and the height of the γ-CD are approximately 9.5 Å and 7.8 Å (**Fig. 6**) respectively. According to the shape and dimensions of γ-CD molecule, it is clear that the guest AQ molecule cannot be included the whole part into the γ-CD cavity, because of the overall height is around double about 11.10 Å (i.e., the vertical distance between $C_1 - C_{118}$). Hence, it is possible to locate the half of AQ molecule inside the γ-CD cavity.

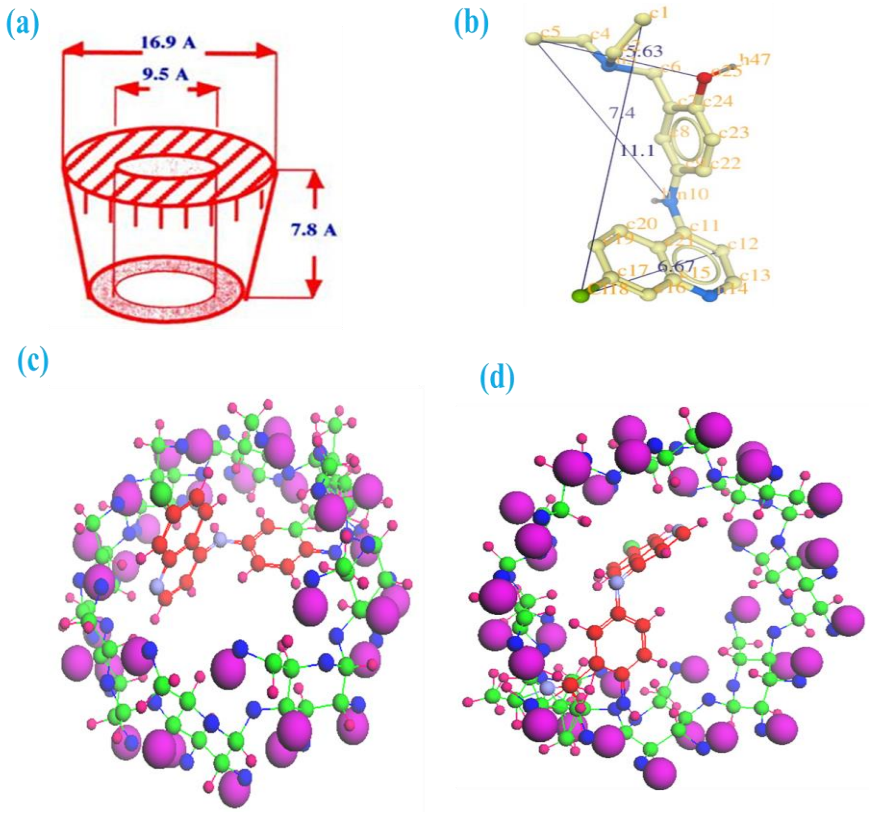

Fig 6. (a) Structure of γ-CD, (b) structure of AQ, (c) Front pose and (d) Back pose structure of 1:1 host-guest inclusion complex of AQ: γ-CD.

3.2. COMPLEXATION OF CQ IN DIFFERENT NATIVE CDs

3.2.1. Complexation Of Cq In A-Cd

The crystallographic databases are provided 3D structures of α-CD and CQ and shown in **Figures 7a and 7b**. With the help of Patch-Dock server, the CQ (guest molecule) molecule was docked into the inner cavity of α-CD. Further the server has given the several possible docked molecule for the most probable and suitable structure according to the energy parameter. Geometric shape complementarity score, approximate interface areas size and atomic contact energy of the assumed complex [**Table 5**]. According to **Table 5**, highest geometric shape complementarity score in 3982, approximate interface area size is 472.90 $Å^2$ and atomic contact energy -336.81 kcal/mol for the docked CQ: α-CD with 1:1 stoichiometric structure and taken as the highest probable and energetically favorable model.

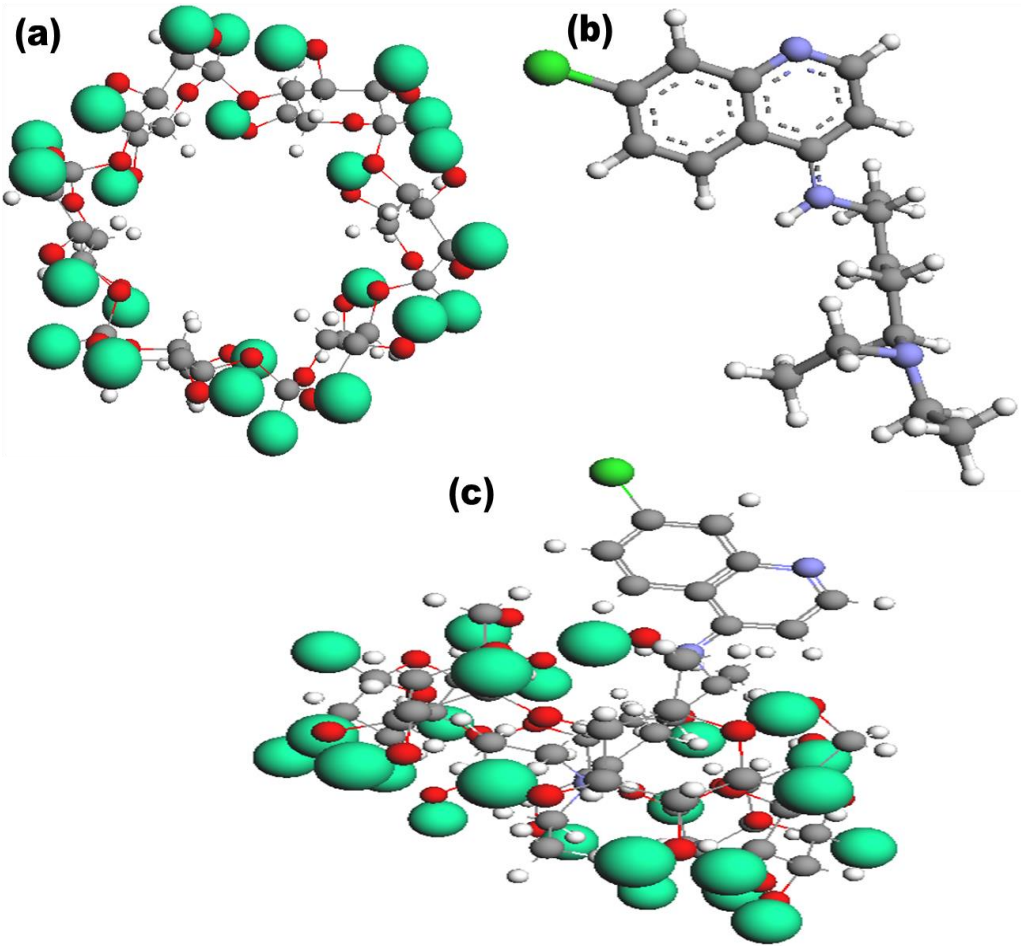

Fig.7. Ball and stick representation of (a) α-CD (b) CQ and (c) 1:1 inclusion complex; the oxygen atoms are shown as blue, carbon atoms are shown as brown, hydrogen atoms are shown as white, nitrogen atoms are shown as light blue and chlorine atoms are shown as green.

Table 5. Scores of the top 10 docked models of CQ: α-CD inclusion complex computed using Patch-Dock server.

Model	Geometric shape complementarity score	pproximate interface area size of the comple $Å^2$	tomic contact energ kcal/mol
1	3982	472.90	-336.81

2	3606	462.20	-370.43
3	3594	440.10	-345.47
4	3580	443.20	-274.95
5	3546	461.30	-368.11
6	3468	422.20	-337.52
7	3430	411.10	-324.57
8	3344	426.00	-332.36
9	3292	414.50	-321.27
10	3288	437.40	-359.54

Semi-empirical quantum mechanical calculations

The internal diameter and the height of the α-CD are approximately 5.7 Å and 7.8 Å (**Fig 8**) respectively. According to the shape and dimensions of α-CD molecule, it is clear that the guest CQ molecule cannot be included the whole part into the α-CD cavity, because of the overall height is around double about 12.0 Å (i.e., the vertical distance between $Cl_{19} - C_5$). Hence, it is possible to locate the half of CQ molecule inside the α-CD cavity.

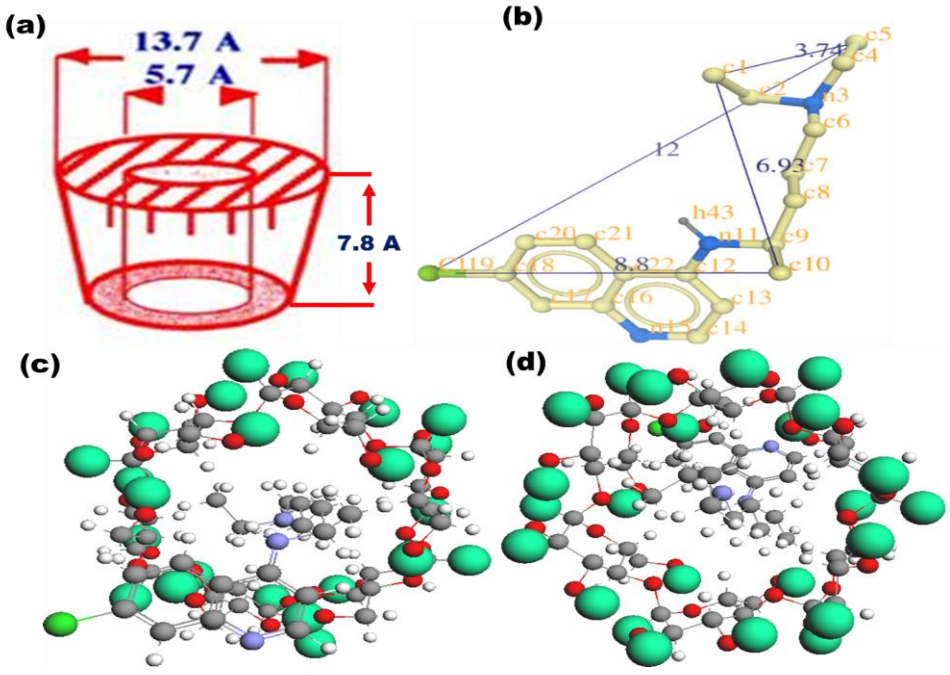

Figure 8. (a) Structure of α-CD, (b) structure of CQ, (c) Front pose and (d) Back pose structure of 1:1 host-guest inclusion complex of CQ:α-CD.

3.2.2. COMPLEXATION OF CQ IN β-CD

The crystallographic databases are provided 3D structures of β-CD and CQ and shown in **Figures 9a and 9b**. With the help of Patch-Dock server, the CQ (guest molecules) molecule was docked into the inner cavity of β-CD. Further the server has given the several possible docked molecule for the most probable and suitable structure according to the energy parameter. Geometric shape complementarity score, approximate interface areas size and atomic contact energy of the assumed complex [**Table 6**]. According to **Table 6**, highest geometric shape complementarity score in 4036, approximate interface area size is 486.70 $Å^2$ and atomic contact energy -326.73 kcal/mol for the docked CQ: β-CD with 1:1 stoichiometric structure and taken as the highest probable and energetically favorable model.

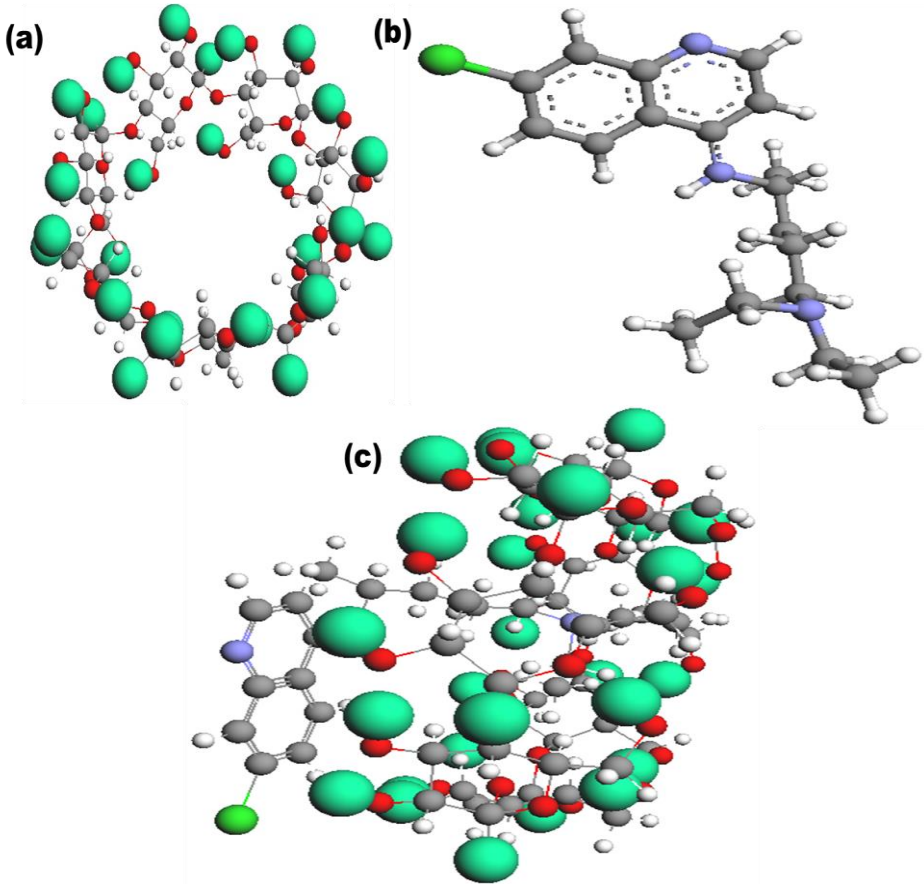

Fig. 9. Ball and stick representation of (a) β-CD (b) CQ and (c) 1:1 inclusion complex; the oxygen atoms are shown as red, carbon atoms are shown as brown, hydrogen atoms are shown as white, nitrogen atoms are shown as light blue and chlorine atoms are shown as green.

Table 6. Scores of the top 10 docked models of CQ: β-CD inclusion complex computed using Patch-Dock server.

Model	Geometric shape complementarity score	pproximate interface area size of the comple $Å^2$	tomic contact energ kcal/mol
1	4036	486.70	-326.73
2	4036	518.30	-294.70

3	3990	478.70	-313.21
4	3856	496.50	-290.67
5	3822	455.00	-321.70
6	3770	520.70	-353.82
7	3722	390.60	-257.34
8	3682	400.30	-297.55
9	3632	476.99	-324.58
10	3590	446.90	-296.79

Semi-empirical quantum mechanical calculations

The internal diameter and the height of the β-CD are approximately 7.8 Å and 7.8 Å (**Fig 10**) respectively. According to the shape and dimensions of β-CD molecule, it is clear that the guest CQ molecule cannot be included the whole part into the β-CD cavity, because of the overall height is around double about 12.00 Å (i.e., the vertical distance between $C_1 - C_{118}$). Hence, it is possible to locate the half of CQ molecule inside the β-CD cavity.

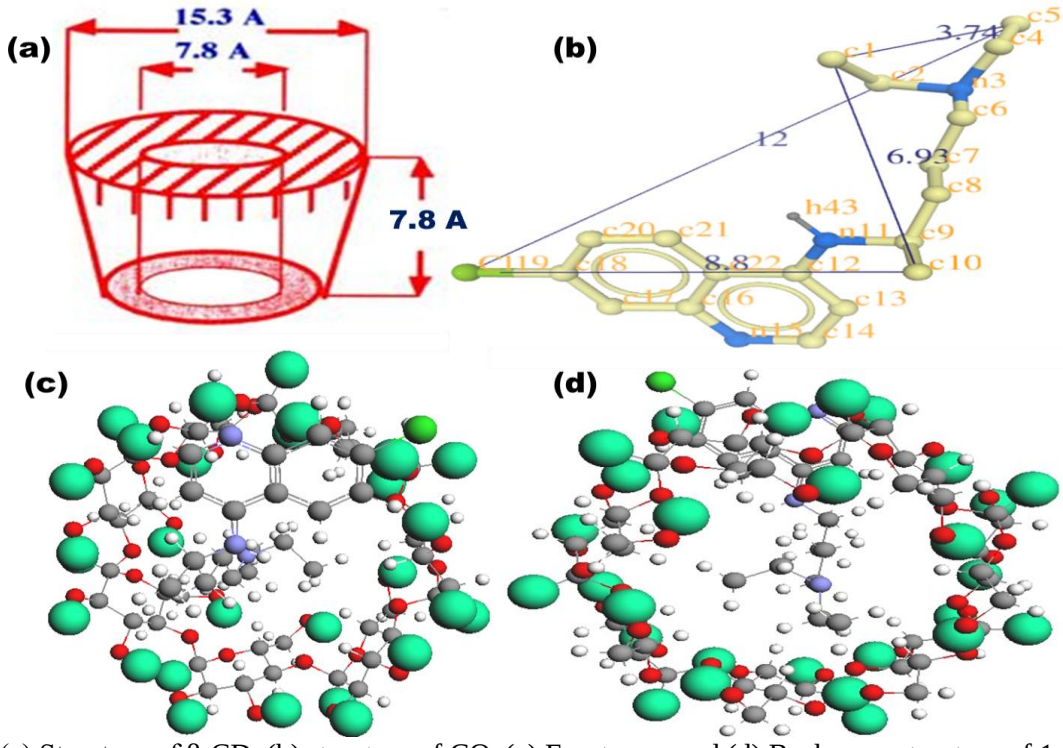

Fig.10. (a) Structure of β-CD, (b) structure of CQ, (c) Front pose and (d) Back pose structure of 1:1 host-guest inclusion complex of CQ: β-CD.

3.2.3. COMPLEXATION OF CQ IN γ-CD

The crystallographic databases are provided 3D structures of γ-CD and CQ and shown in **Figures 11a and 11b**. With the help of Patch-Dock server, the CQ (guest molecules) molecule was docked into the inner cavity of γ-CD. Further the server has given the several possible docked molecule for the most probable and suitable structure according to the energy parameter. Geometric shape complementarity score, approximate interface areas size and atomic contact energy of the assumed complex [**Table 7**]. According to **Table 7**, highest geometric shape complementarity score in 3886, approximate interface area size is 466.60 Å^2 and atomic contact energy -273.99 kcal/mol for the docked CQ: γ-CD with 1:1 stoichiometric structure and taken as the highest probable and energetically favorable model.

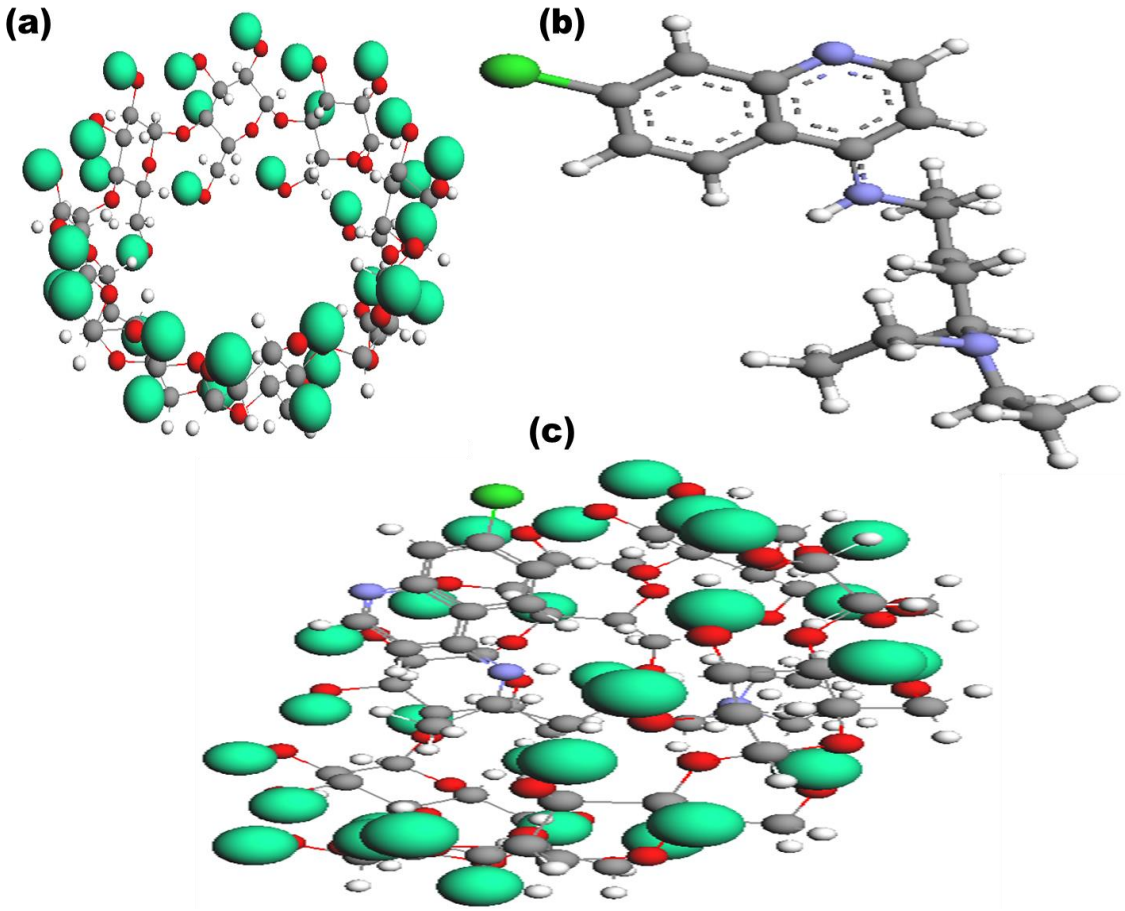

Fig. 11. Ball and stick representation of (a) γ-CD (b) CQ and (c) 1:1 inclusion complex; the oxygen atoms are shown as Red, carbon atoms are shown as brown, hydrogen atoms are shown as white, nitrogen atoms are shown as light blue and chlorine atoms are shown as green.

Table 7. Scores of the top 10 docked models of CQ: γ-CD inclusion complex computed using Patch-Dock server.

Model	eometric shape complementarit score	pproximate interface area size of the comple Å^2	tomic contact energ kcal/mol
1	3886	466.60	-273.99
2	3672	448.40	-283.29

3	3646	473.60	-301.86
4	3616	409.70	-265.05
5	3510	420.60	-271.65
6	3496	474.50	-292.60
7	3480	426.20	-269.27
8	3376	397.30	-252.92
9	3332	434.20	-269.27
10	3288	334.30	-252.92

Semi-empirical quantum mechanical calculations

The internal diameter and the height of the γ-CD are approximately 9.5 Å and 7.8 Å (**Fig 12**), respectively. According to the shape and dimensions of γ-CD molecule, it is clear that the guest CQ molecule cannot be included the whole part into the γ-CD cavity, because of the overall height is around double about 12.00 Å (i.e., the vertical distance between $C_1 - C_{118}$). Hence, it is possible to locate the half of CQ molecule inside the γ-CD cavity.

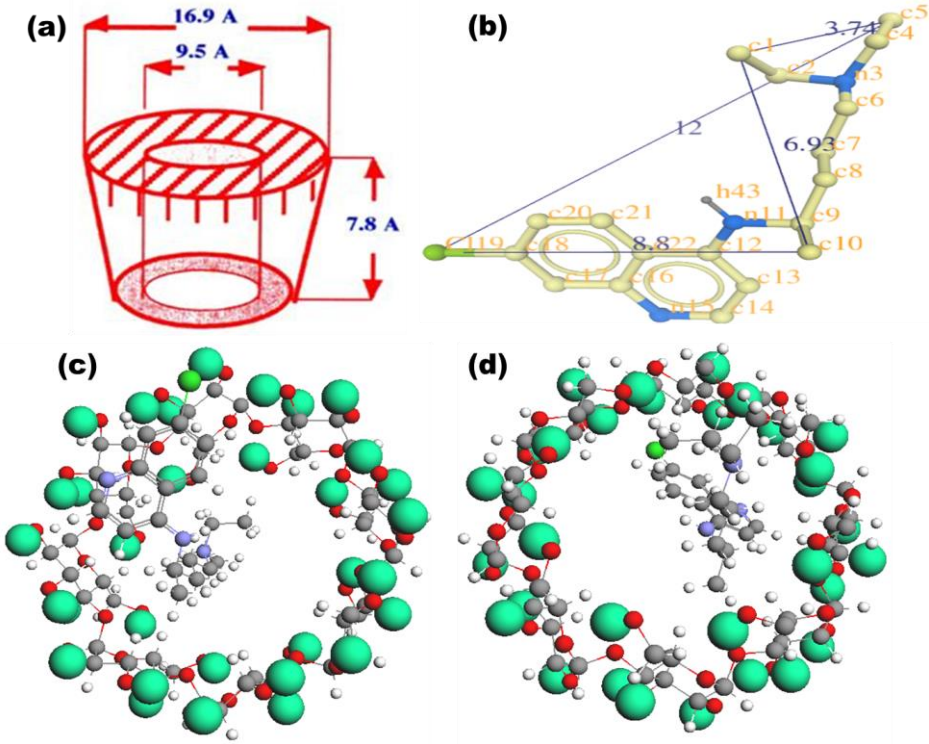

Fig.12. (a) Structure of γ-CD, (b) structure of CQ, (c) Front pose (d) Back pose structure of 1:1 host-guest inclusion complex of CQ: γ-CD.

Table 8. Scores of the docked models of AQ and CQ with three different CDs using Patch-Dock server.

Sample	Type of CDs	Model	Geometric shape complementarity score	Approximate interface area size of the complex ($Å^2$)	Atomic contact energy (kcal/mol)
AQ	α	1	4028	470.00	-318.96
		2	3922	464.50	-325.37
	β	1	3982	473.70	-341.71
		2	3962	478.70	-320.49
	γ	1	4150	491.60	-347.49
		2	4072	494.00	-350.81
CQ	α	1	3982	472.90	-336.81
		2	3606	462.20	-370.43
	β	1	4036	486.70	-326.73
		2	4036	518.30	-294.70
	γ	1	3886	466.60	-273.99
		2	3672	448.40	-283.29

Here, the docking score for both the guest molecules with the different native CDs are consolidated. Among the ten most preferred and probable structural poses based on the parameters that are discussed in the previous section, the top two only selected for comparison. From the docking results, it is quite clear that both the drug molecules (AQ and CQ) can accommodate only half of the part to the cavity of all the chosen CDs, even its bond distances are increased while enhancing.

While taking into account, the complexes of AQ:α-CD, AQ:β-CD, AQ:γ-CD, CQ:α-CD, CQ:β-CD and CQ:γ-CD are compared here on the basis of Patch-Dock output and its data. Among the above complexes, AQ:γ-CD is the most probable complex than the others based on the parameter value geometric shape complementarity score. The results represented that the supramolecular complex formation for the guest AQ with γ-CD and CQ with β-CD are the preferable one than the others. This information will helps to identify the nature of drug molecules for any biological applications such as anti-bacterial activity and so on. However the results are preliminary and certainly need experimental confirmation, which will be conducted in near future via molecular biology studies but considering all these structural aspects and its score, AQ and CQ may possibly be a primary choice as a biologically active molecule which could be exploited to design anticancer agents of future.

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