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RESEARCH ARTICLE

Inclusion Studies of 8-OH Quinoline with β-Cyclodextrin

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Abstract

Cyclodexterins are well known for their ability to form inclusion complexes with molecules that can fit (completely or partially) into their central cavity. 8-Hydroxy Quinoline is a bifunctional hydrogen-bonding molecule, which in an alcoholic solution simultaneously acts as a H-donor at the OH site and an acceptor at the N-atom. Combination of these two entities was found to exhibit interesting photophysical properties. Host- Guest complexion studies between 8-OH Quinoline and β-Cyclodextrin were carried out with the steady state absorption, fluorescence excitation and emission spectral analysis. A fascinating observation was made regarding the concentration dependence of the host-guest complex. Appreciable association constant was arrived numerically from the spectral values.

INTRODUCTION

Cyclodextrins- CDs (sometimes called cycloamyloses) are a family of compounds made up of sugar molecules bound together in a ring. The α-, β- and γ-cyclodextrins (CDs) are cyclic oligosaccharides consisting of 6, 7 and 8 D-glucose units, respectively. They are well known for their ability to form inclusion complexes with molecules that can fit (completely or partially) into their central cavity [1]. There is a vast amount of literature concerning applications of cyclodextrins and their derivatives in pharmacy, chromatography, food and cosmetics industry.
The peculiar structure of β-CD is as shown in Scheme 1.

Since CDs are hydrophobic inside and hydrophilic outside, they can form complexes with hydrophobic compounds. Thus they can enhance the solubility and bioavailability of such compounds. Host-guest interactions [2] through these cavities lead to the formation of inclusion complexes within the cavities with guest molecules smaller than the cavity size. The driving forces for the formation of inclusion complexes arise from apolar-apolar interactions between guest molecules and host cavities, the CD ring strain release on complexation and van der Waals interactions [3]. In the binding process, besides several weak intermolecular non covalent forces, such as dipole-dipole (ion), hydrophobic, electrostatic, van der Waals and hydrogen bonding interactions, the solvent, environment and conformations of hosts and guests will also affect the stability of host-guest complexes. The strong binding affinity of CD's to hydrophobic molecules in aqueous media enables them to be effective receptors for organic, inorganic and biological substrates [4]. This is of high interest for pharmaceutical as well as dietary supplement applications in which hydrophobic compounds shall be delivered. As a result, these molecules have found a number of applications in a wide range of fields. Cyclodextrins can also solubilize hydrophobic drugs in pharmaceutical applications, and crosslink to form polymers used for drug delivery.

The natural cyclodextrins, in particular β-cyclodextrins, are of limited aqueous solubility meaning that complexes resulting from interaction of lipophiles with these cyclodextrin can be of limited solubility resulting in precipitation of solid cyclodextrin complexes from water and other aqueous systems. In fact, the aqueous solubility of the natural cyclodextrins is much lower than that of comparable acyclic saccharides. This is thought to be due to relatively strong intermolecular hydrogen bonding in the crystal state. In addition, cyclodextrins can be used to

reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions, or to convert oils and liquid drugs into microcrystalline or amorphous powders. The versatility of applications of CDs in pharmaceutical field is pictorially represented in Scheme 2.

Cyclodextrin derivatives of pharmaceutical interest include the hydroxypropyl derivatives of β- and γ-cyclodextrin, the randomly methylated β-cyclodextrin, sulfobutylether β-cyclodextrin, and the so-called branched cyclodextrins such as glucosyl-β- cyclodextrin. Here in our present investigation, we carry out a basic host –guest complextion study between native β-cyclodextrin and 8-OH quinoline (8-HQ).

Quinoline is a heterocyclic scaffold of paramount importance to human race. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Indeed quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases [5]. Compounds containing quinoline motif are most widely used as antimalarials, [6] antibacterials, [7] antifungals [8] and anticancer agents. [9] Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents. [10]

8-Hydroxyquinoline (8-HQ), a derivative of quinoline, in specific, is a monoprotic bidentate chelating agent. The complexes as well as the heterocycle itself exhibit antiseptic, disinfectant, and pesticide properties [10], functioning as a transcription inhibitor. Its solution in alcohol is used in liquid bandages. It once was of interest as an anti-cancer drug. The reaction of 8-hydroxyquinoline with aluminium(III) [12] results in Alq3, a common component of organic light-emitting diodes (OLED's). Variations in the substituents on the quinoline rings affect its luminescence properties [13]. 8-HQ and its derivatives also hold medicinal properties such as antineurodegenerative, anticancer, antioxidant, antimicrobial, anti-inflammatory, and antidiabetic activities [14].

The double binding site of the 8-HQ molecule opens up exciting research when studied for its photoluminescence properties. Upon photoexcitation, then acid/base properties of this molecule change significantly at both the sites, rendering OH- group more acidic and the N-atom more basic. In 8-HQ, the acidic (H-bond donating) and basic (H-bond accepting) groups of the molecule are relatively close to each other and hence a single solvent can bind to both the sites simultaneously and monomer molecules can arrange to form dimers via H-bonding. Also 8-HQ is expected to show Excited State Proton Transfer (ESPT) and Non-Linear properties [15].

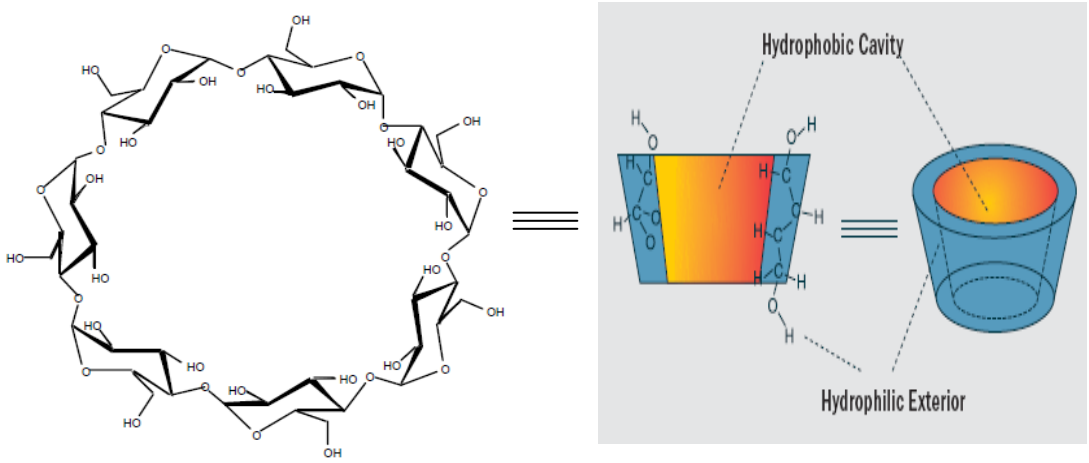
The reason for the choice of 8-HQ as the host and β-CD as the guest to form a mutual complex is the appealing properties of the two molecules. β-CD possess a truncated cone like structure with a cavity size of around 0.6 nm which is ready to bind with molecules of matching size. And 8-HQ is a small planar molecule with a metal chelating ability. In the present investigation, we have explored the ability of 8-HQ to bind with β-CD, and hence to analyse the stability of the complex. In future we would also like to study the diverse applications, their mechnaisms of actions and the structure-activity relationships.

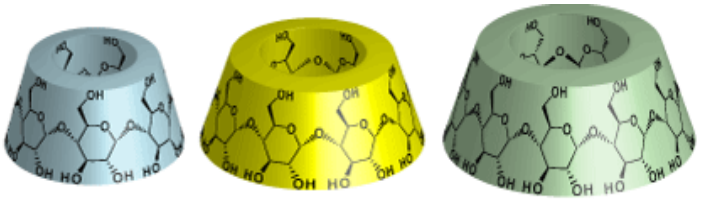
1. Experimental details

8- hydroxyl quinolone used for the studies were obtained from S.D. Fine Chemicals Pvt. Ltd. Methanol used was of HPLC grade and was obtained from Qualigens India Ltd. β-CD received from Cyclolab was recrystallized from water before use. Triple distilled water was used for the spectral analyses. Absorption spectra were recorded in an Agilent 8453 diode array spectrophotometer. Fluorescence spectra were recorded using a Horiba Jobin Yvon Fluoromax 4P Spectrofluorimeter.

2. Results and Discussion

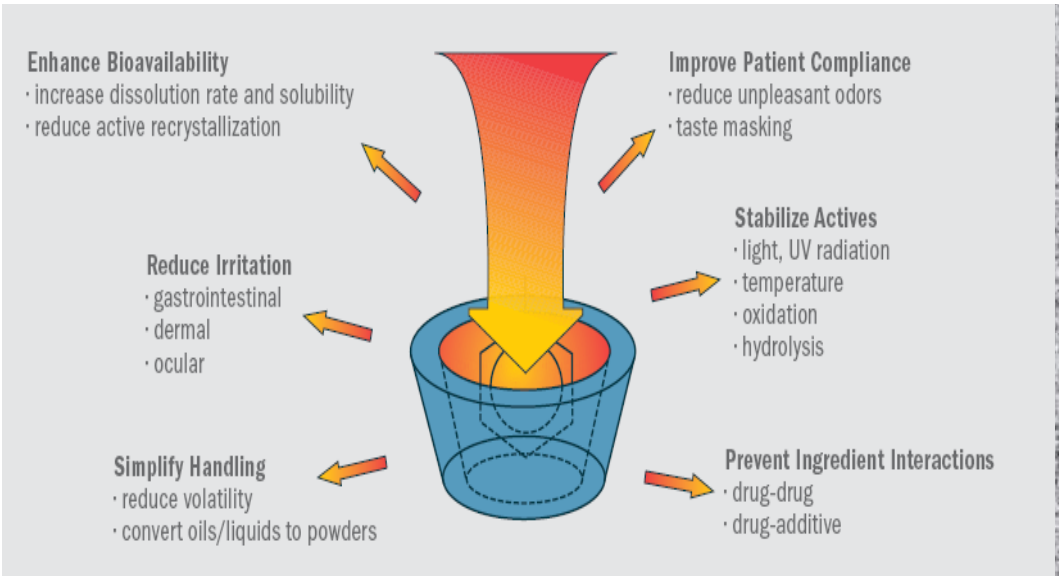
Binding studies of suitable molecules into the cavities of natural or synthetic receptors have received great interest over last few years in endeavours to establish new host-guest systems that will have potential application, especially in the pharmaceutical field. In particular, β- CDs have generated considerable interest among the synthetic chemists as it is witnessed in recent articles dealing with targeted drug delivery. Restrictions in the usage of quinoline for its versatile medical applications was primarily due to the lipophilic nature of the molecule. In recent years, numerous publications have been made on the functionalization of quinoline which results in a decorative skeleton. One such functionalization was 8-OH quinoline which turned out to be an effective medicinal drug. Being a lipohilic drug, it possesses some practical constraints in being delivered at specific sites. Binding with a well-known molecular receptor like β-CD can solve this issue to a greater extent. Possibility of formation of a binding complex between 8-HQ (host) and β-CD (guest) is widely studied in this paper. Spectral analyses were carried out by recording the absorption, excitation and steady state emission of the host-guest complex and the binding constants were calculated.





	α-CD	β-CD	γ-CD
No. of Glucose Units	6	7	8
Cavity Diameter (nm)	0.47	0.60	0.75
Height of Torus (nm)	0.79	0.79	0.79

Scheme 1 : Structure and cavity sizes of Cyclodextins



Scheme 2 : Multiple applications and benefits of CD in pharmaceutical Formulations

2.1. Absorption studies

An exhaustive excitation spectrum recorded for 8-OH quinoline in methanol solution is as shown in Fig 1. The peaks at 218 nm & 250 nm are due to the $\pi \rightarrow \pi^*$ transitions of the molecule and the peak at 314 nm is attributed to the $n \rightarrow \pi^*$ transition [16]. The sharp peak at 367 nm is due to the mechanism of charge transfer between the benzanoid ring and positively charged pyridinium ring [17].

In presence of 0 M to 8 x 10^{-4} M concentrations of β-CD, the absorption behavior was markedly different (Fig 2). The peak at 367 nm had vanished and only the native peaks of 8-HQ could be observed in the spectrum. This implies that, in the presence of β-CD, the hydroxyl group of the benzanoid ring is more involved in the formation of hydrogen bonds with the hydroxyl groups of β-CD. This also comes as an evidence for the formation of a host-guest complex between β-CD and 8-HQ. It was also noticed that there occurred no appreciable change in the absorbance at 314 nm which is indicative of the fact that the native structure of 8-HQ is also not lost in the process of complex formation.

3.2 Emission studies

As far as emission behavior is concerned, the records of 8-HQ is very peculiar. It shows a notable dependence on concentration with respect to emission. It has been already established that in an alcoholic medium it shows two distinct bands; one around 330 to 365 nm (band-I), and another from 400 to 450 nm (band-II). The concentration dependence study on the emission spectrum reveals that band II continuously increases with an increase in concentration of 8-HQ and ultimately only the II band exists at a concentration of 1 x 10^{-3} M. Hence the II band is established as the one due to the formation of dimers or associates in the excited state [15].

The host –guest complex upon excitation at 314 nm, shows an emission profile as shown in Fig 3. As the concentration of 8-HQ was well maintained in the micromolar region (1 x 10^{-6}M), the formation of dimers is not expected in this concentration range. However, the concentration of β-CD was increased from 0 M to 8 x 10^{-4}M. The steady state emission spectrum of β-CD/8-HQ system (Fig 3) clearly shows the emission pattern of 8-HQ namely two bands at 393 nm and 419 nm. The observed red shift in the two bands is attributed to the solvent effects. The decrease in fluorescence intensity with an increase in concentration of β-CD observed in the spectrum is due to the stabilization of the system. The cavity of β-CD provides more number of hydroxyl groups which get involved in the formation of hydrogen bonding with the hydroxyl groups of 8-HQ . Interestingly, an iso-emissive point was observed at 483 nm which is a clear cut indication of the formation of host-guest complex in the system of β-CD/8-HQ. This was further supported by the calculation of binding constant for the complex.

However, when the study was carried out with a concentration of 8-HQ as 1 x 10^{-4}M, no such iso - emissive point was observed, and there was only a decrease in the fluorescence intensity of the system when the concentration of β-CD was increased from 0 M to 8 x 10^{-4}M (Fig 5). This entails that, at higher concentration range of 8-HQ, where dimers are formed, there occurs no host- guest complex formation with β-CD.

3.3 Binding studies

In order to understand the binding capacity of the 8-HQ within the cavities of β-CD, binding studies were carried out by mixing a fixed concentration of 8-HQ (1 x 10^{-6} M) with several aliquots of β-CD ranging from 0 M, 5 x 10^{-5} M, 1 x 10^{-4} M, 2 x 10^{-4} M, 4 x 10^{-4} M and 8 x 10^{-4} M. The corresponding absorption and emission spectra of 8-HQ/ β-CD host-guest system is as shown in Figures 2 and 3 respectively. Since the change in emission intensity is anticipated due to the formation of a complex between β-CD and 8-HQ, it is possible to use a Benesi—Hildebrand plot to find out the association constants of the complexes. The derivation of this method as it is applied to CD-complexes is already reported elsewhere [18]. Accordingly, from the emission spectrum, a Benesi-Hildebrand plot was constructed and the binding constant was determined for the host-guest complex as 1.2 x 10^{6} M^{-1}.The stoichiometry of complexation is assigned as a 1:1 complex from the nature of the plot as inferred from Fig 4. The high factor of association constant obtained is in good correlation with the stability of the host-guest of β-CD-8-HQ proposed [19].

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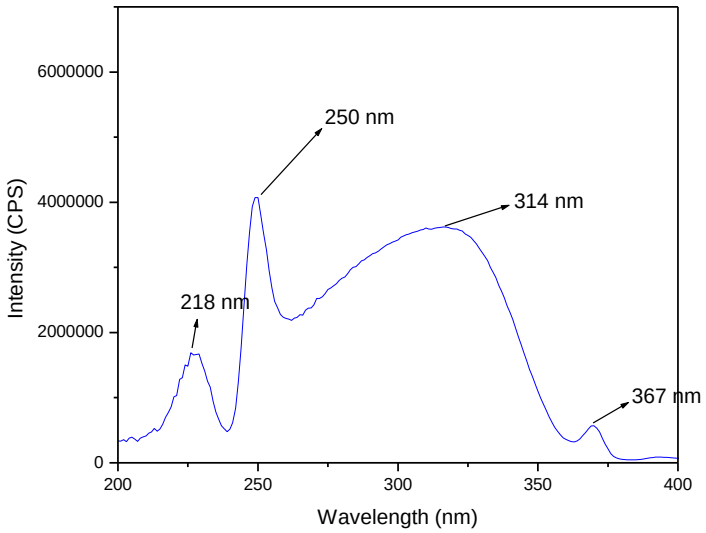

Fig 1: Excitation spectrum of 8-Hydroxy Quinoline. λ_{exc} = 400 nm.

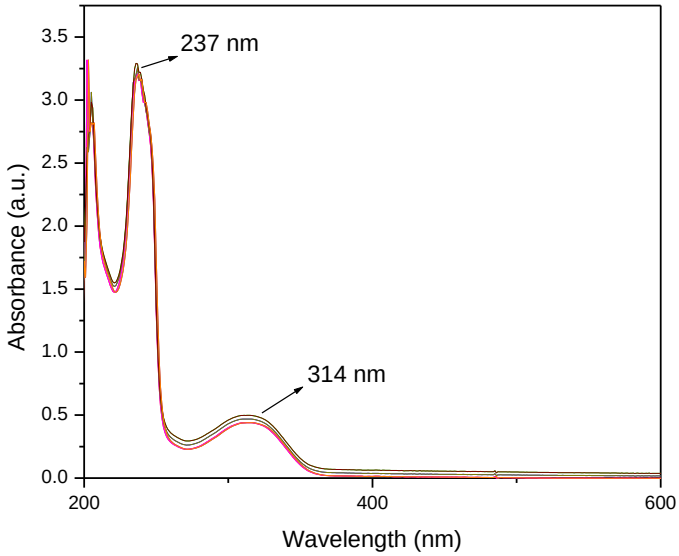

Fig 2: Absorption spectrum of 8-Hydroxy Quinoline/β-CD system. [8-Hydroxy Quinoline] = 1 x 10-^{6} M. [β-CD] = 0 M → 8 x 10^{-4}M.

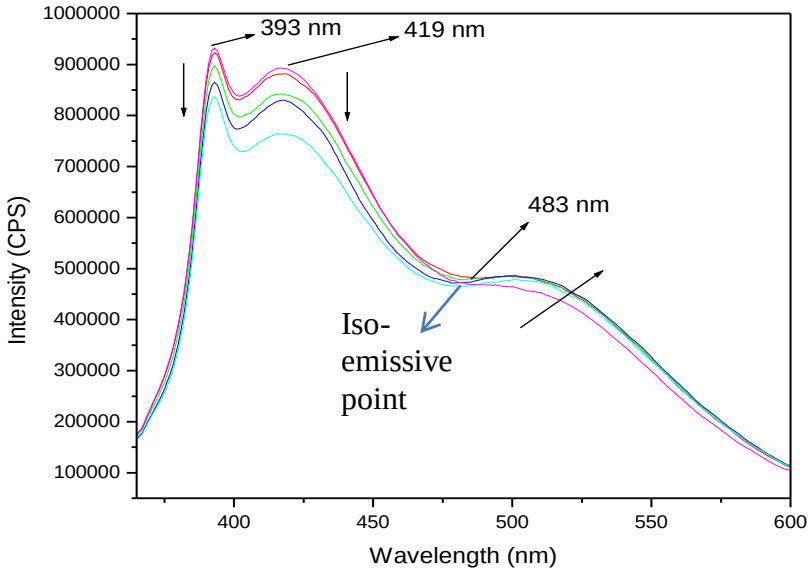

Fig 3: Emission spectrum of 8-Hydroxy Quinoline/β-CD system. [8-Hydroxy Quinoline] = 1 x 10^{-6} M. [β-CD] = 0 M → 8 x 10^{-4}M. λ_{exc} = 310 nm.

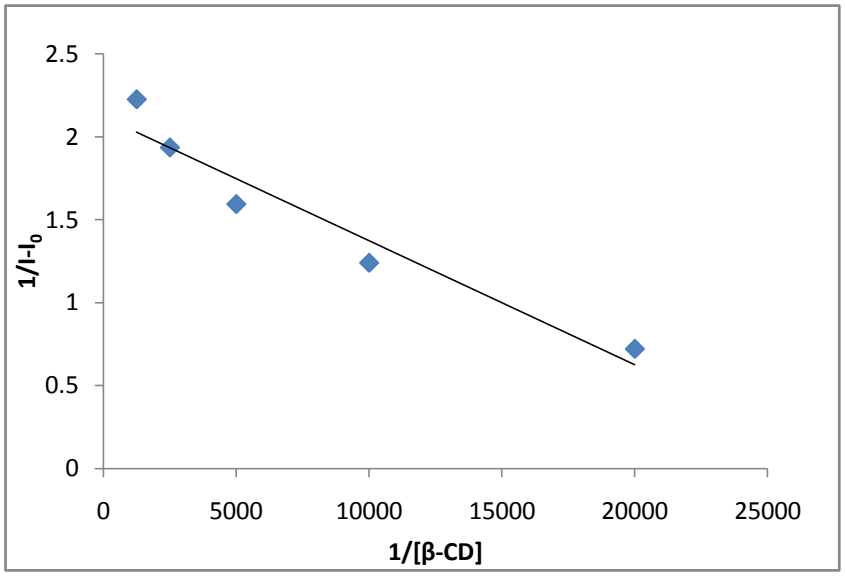

Fig 4: Benesi-Hildebrand plot of 8-Hydroxy Quinoline/β-CD system. [8-Hydroxy Quinoline] = 1 x 10^{-6} M. [β-CD] = 0 M → 8 x 10^{-4}M.

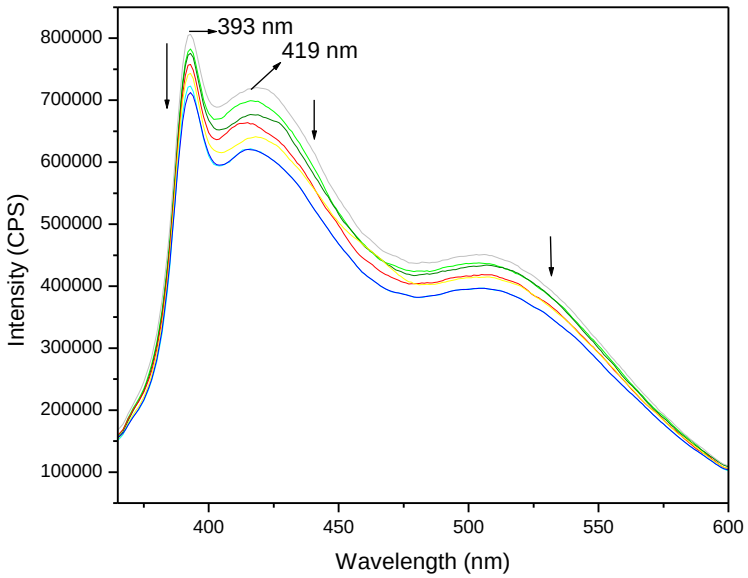

Fig 5: Emission spectrum of 8-Hydroxy Quinoline/β-CD system. [8-Hydroxy Quinoline] = 1 x10^{-4} M. [β-CD] = 0 M → 8 x 10^{-4}M. λ_{exc} = 310 nm.

3. Conclusion

Photophysical behavior of 8-Hydrpxy quinoline was recorded in an alcoholic medium. Characteristic absorption and emission spectrum were observed for the molecule. The binding behavior of the molecule was analysed with a well-known host viz., β-CD. As expected, the host-guest complex was eventually formed and was also found to be highly stable when compared to the free entity of 8-Hydorxy Quinoline as evidenced from the red shifts observed in absorption studies of the complex. The formation of a host-guest complex is revealed by the observance of an iso-emissive point in the emission spectrum. This was further supported by the high association constant obtained from Benesi-Hildebrand plot. Hence a brand new host-guest complex of β-CD-8-Hydroxy Quinoline is hereby proposed and studied effectively.

4. Acknowledgement

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5. References

1. Barreto, Lívia; Cunha Filho and Marcílio (2008) Cyclodextrin: important pharmaceutical functional excipient, Latin American Journal of Pharmacy, 27 (4): 629–636.
2. Isnin. R, Salam. C and Kaifer A.E., (1991) Bimodal cyclodextrin complexation of ferrocene derivatives containing n-alkyl chains of varying length, J. Org. Chem., 56, 35-41.
3. Lee J and Park S., (1998) Electrochemistry of Guest Molecules in Thiolated Cyclodextrin Self-Assembled Monolayers: An Implication for Size-Selective Sensors, J. Phys. Chem. B, , 102, 9940-9945.
4. Liu Y et al., (2004) Spectrophotometric Study of Inclusion Complexation of Aliphatic Alcohols by β-Cyclodextrins with Azobenzene Tether, J. Phys. Chem. B ,108, 8836-8843.
5. Bilker, O. et. al., (1998) Identification of xanthurenic acid as the putative inducer of malaria development in the mosquito, Nature, 392, 289-292.

6. Fang, K. -C. et al., (2004) Synthesis and Antibacterial Activity of a Novel Class of 4‘-Substituted 16-Membered Ring Macrolides Derived from Tylosin, Med. Chem., 47, 2965-2968.
7. Luis Miguel Bedoya et al., (2010) Quinoline-based compounds as modulators of HIV transcription through NF-κB and Sp1 inhibition, Antiviral Research, 87, 338-344.
8. Dassonneville, L. et al., (2000) Cytotoxicity and cell cycle effects of the plant alkaloids cryptolepine and neocryptolepine: relation to drug-induced apoptosis, Eur. J. Pharmacol., 409, 9-18.
9. Holla, B. S. et al., (2006) Synthesis of some novel pyrazolo [3,4-d]pyrimidine derivatives as potential antimicrobial agents, Bioorg. Med. Chem., 14, 2040–2047.
10. Smirnov, R. F. , (1973) Polymerization of quinoline catalysed by alkyl halides, Polymer Science U.S.S.R., 15, 832-841.
11. Phillips, J. P. (1956) The Reactions of 8-Quinolinol, Chemical Reviews 56 (2): 271–297.
12. Katakura, R. and Koide, Y. (2006). Configuration-Specific Synthesis of the Facial and Meridional Isomers of Tris (8-hydroxyquinolinate)aluminum (Alq3), Inorganic Chemistry 45 (15): 5730–5732.
13. Montes, V. A. et al., (2006). Effective Manipulation of the Electronic Effects and Its Influence on the Emission of 5-Substituted Tris (8-quinolinolate) Aluminum (III) Complexes, Chemistry - A European Journal 12 (17): 4523–4535.
14. Veda Prachayasittikul et al., (2013) 8-Hydroxyquinolines: a review of their metal chelating properties and medicinal applications, Drug Des Devel Ther, 7: 1157–1178
15. L. R. Naik and N. N. Math, (2005) Photophysical properties of 8-hydroxy quinoline, Indian Journal of Pure & Applied Physics , Vol. 43, 743-749.
16. Denise A. Phillips et al., (1986) Enhancement and quenching of fluorescence of metal chelates of 8-hydroxyquinoline-5-sulfonic acid, Microchim. Acta, 88, 201-220.
17. Elisabeth. B. et al., (1994) Photoinduced Coupled Proton and Electron Transfers. 1. 6-Hydroxyquinoline, J. Phys. Chem., 98, 2357.
18. Nigam, S and Durocher, G, (1996) Spectral and Photophysical Studies of Inclusion Complexes of Some Neutral 3H-Indoles and Their Cations and Anions with β-Cyclodextrin, J. Phys. Chem.,100,7135–7142
19. Kim D, Scranton AB and Stansbury JW, (2009) Analysis of Association Constant For Ground State Dye-Electron Acceptor Complex of Photoinitiator Systems And The Association Constant Effect on The Kinetics of Visible-Light-Induced Polymerizations, J PolymSci A Polym Chem., , 47(5), 1429-1439.