# Improving bioavailability of poorly soluble oral drugs

**Taslima Binte Kamal**
PhD Research Student
Supervisor: Dr. Anthony Day
University of New South Wales, Australia

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NEXT-GENERATION DELIVERY INNOVATIONS

# Background

Therapeutic agents

Solubility

Efficacy

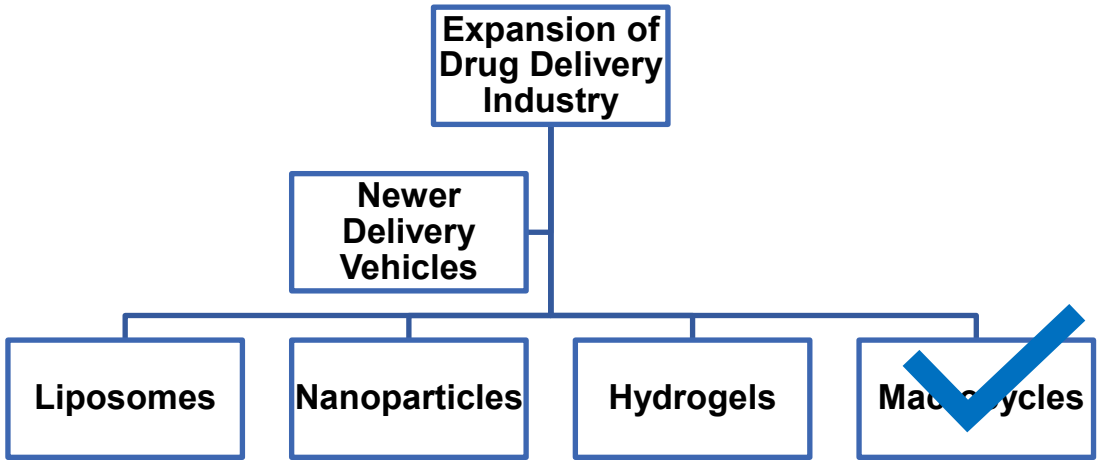
Low solubility of oral drugs

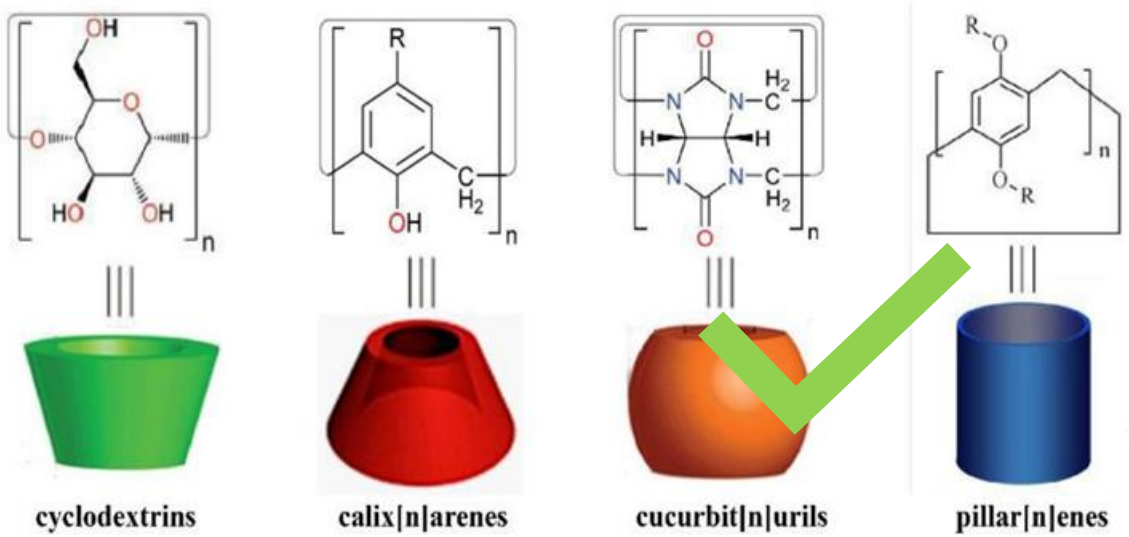
Incomplete dissolution in GI fluid

Poor oral bioavailability

Poor drug efficacy

Drug Delivery Strategies → Improve Drug Solubility

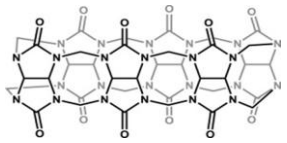



(Jiang et al., 2020)

# Why Cucurbiturils?

**Cucurbituril**



**Superiority over similar macrocycles**

- Stronger Binding Affinity
- Relative Non-toxicity
- High Stability to GIT

**Chemical modifications**

- Functionally modified Q[*n*] derivatives

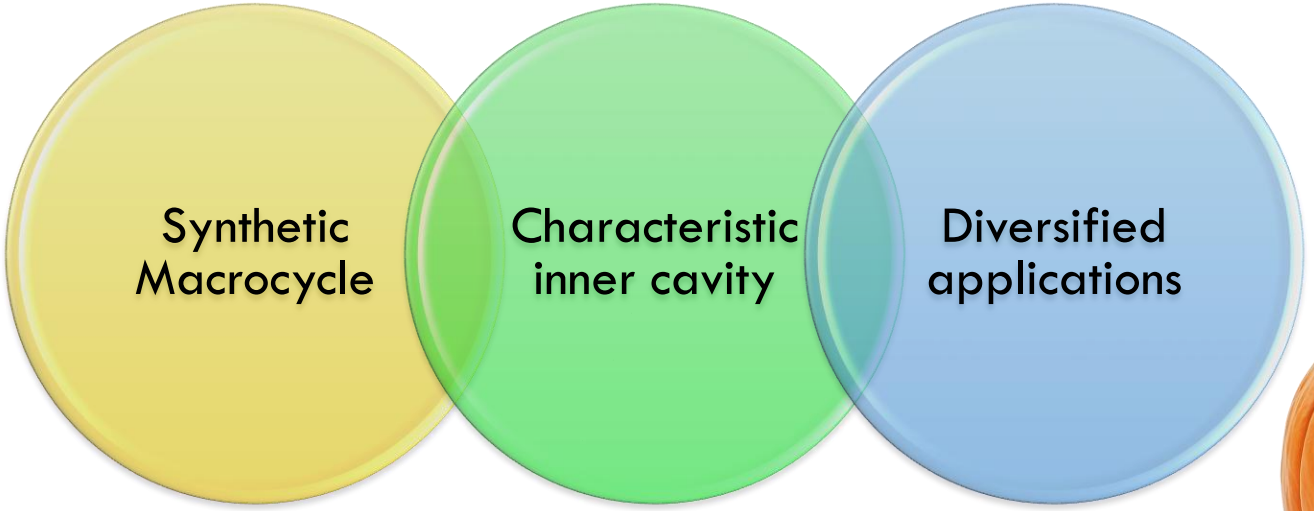
**Improvement of drug pharmacokinetic profile**

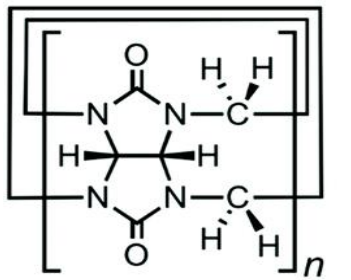
- Solubility
- Bioavailability
- Stability etc.

**Synthetic modifications**

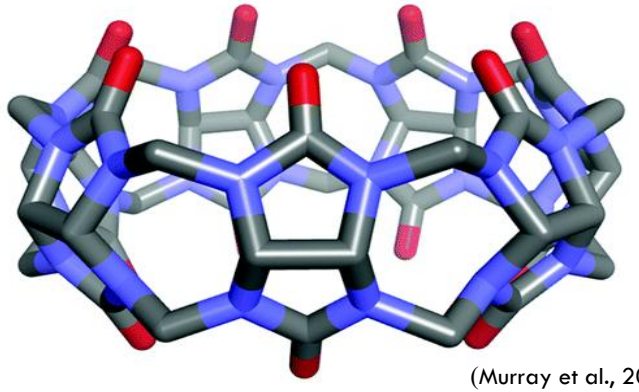
- Inverted Q[*n*]s
- Acyclic Q[*n*]s
- HemiQ[*n*]s
- Tiara[*n*]urils etc.

# What is Cucurbit[n]uril(Q[n]s)?

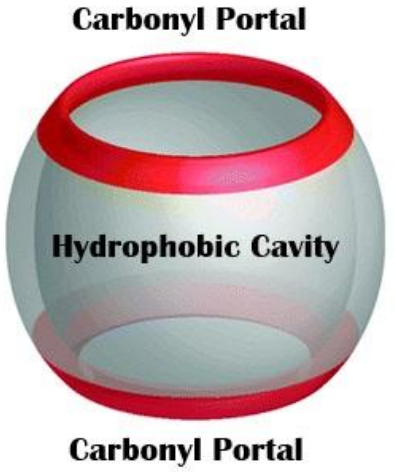



***n* = 5-8, 10, 13-15**



(Murray et al., 2017)

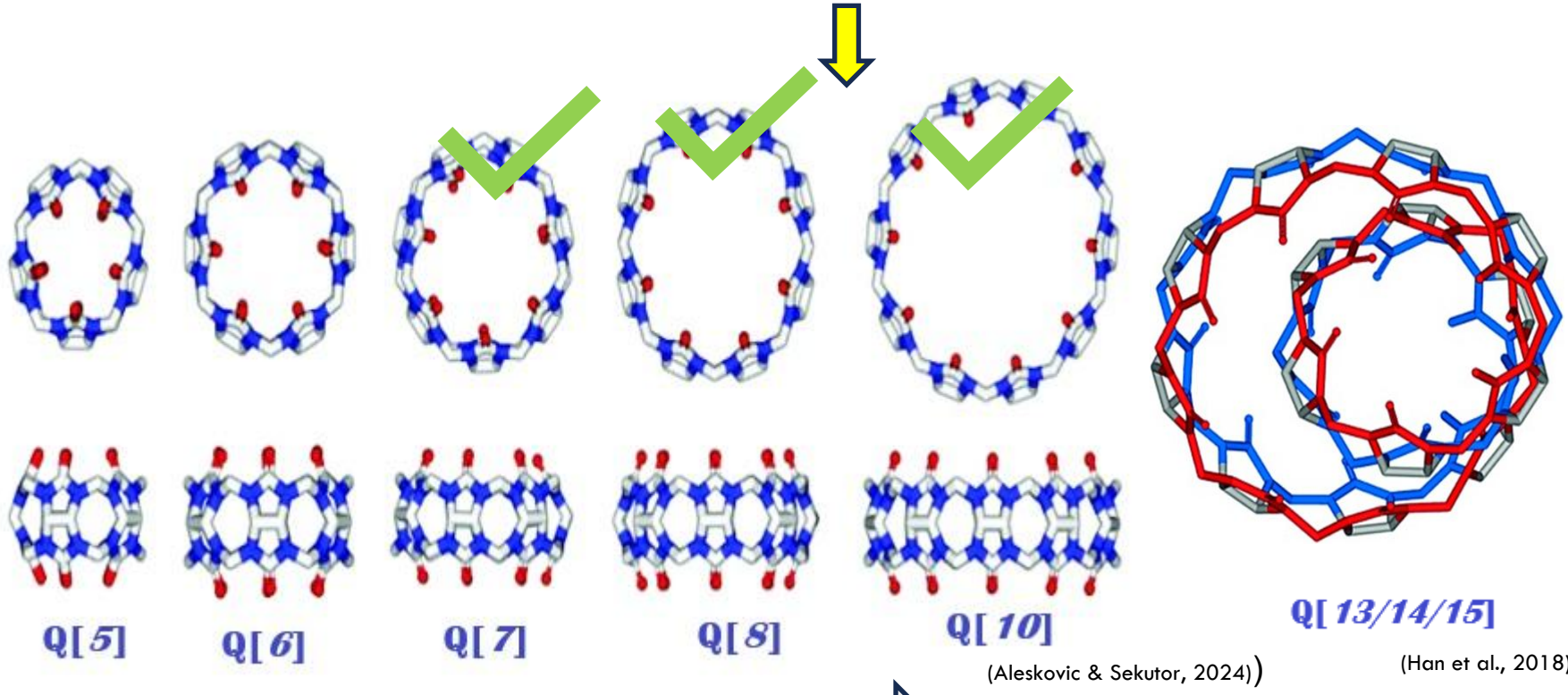


# Cucurbituril Homologues

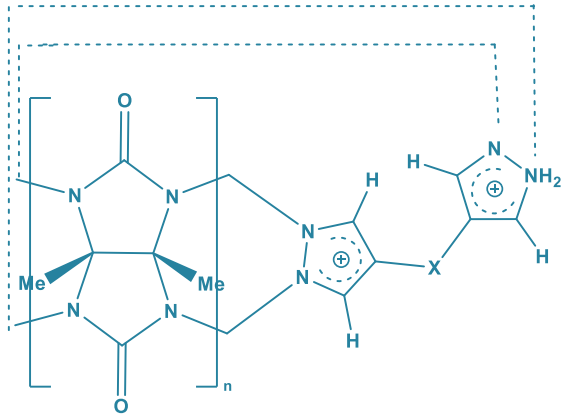
**Drug Delivery Applications**

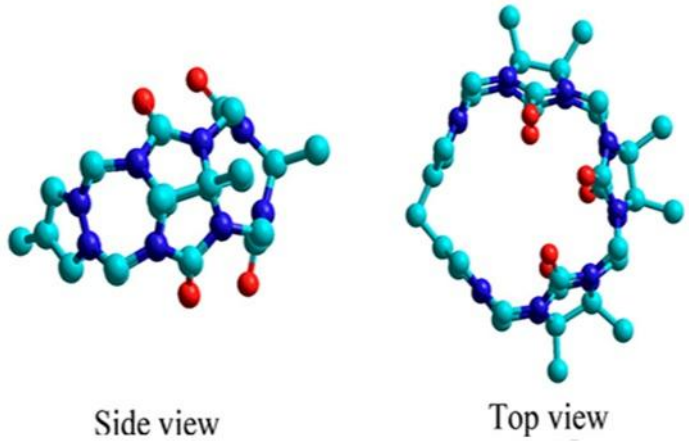
Number of Glycoluril unit

Different sizes of Q[n]s



# Newest Cucurbituril Analogue and its derivatives



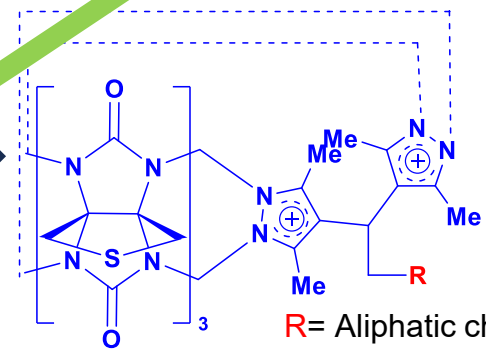



Tiara[*n*]uril (Tu[*n*])

(Chandrakumar et al., 2019)

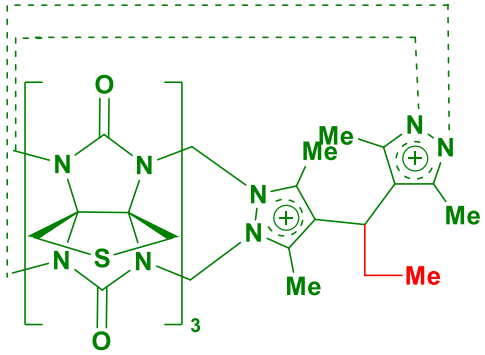
Amphiphilic Derivatives

Potential for Drug Delivery

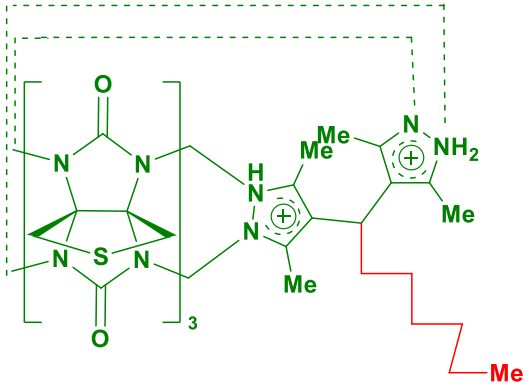



THTTu[3] with aliphatic chains

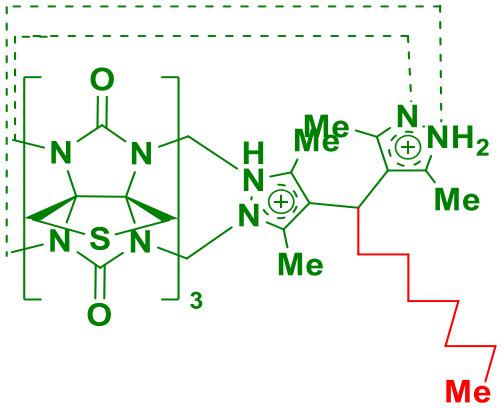
Examples



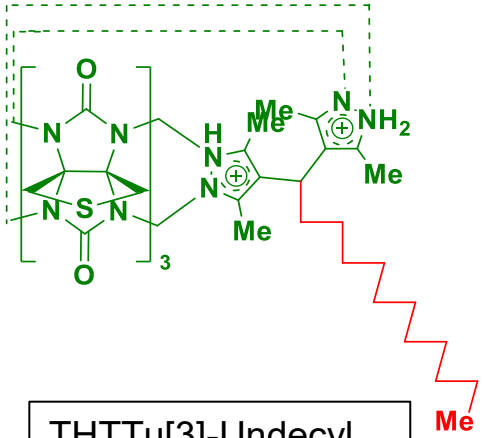
THTTu[3]-Ethyl



THTTu[3]-Hexyl



THTTu[3]-Heptyl



THTTu[3]-Undecyl

# Exceptional Features of Q[n]s

| | |
|---|---|
| **Stability** | Excellent **thermal & chemical** stability<br>(Stability at temperature as high as **420$^0$C)** (Lee et al., 2003) |
| **Affinity and Selectivity** | **Superior** affinity and selectivity compared to other macrocyclic host carriers like **cyclodextrins & crown ethers** (Lagona et al., 2005; Wang & Kaifer*, 2009) |
| **Non-Toxicity** | Relative **non-toxicity** as drug-delivery vehicle (Zhang et al., 2018) |
| **Solubility** | Good aqueous solubility of **functionally modified** Q[*n*] derivatives and **newer** Q[*n*] analogues like **Tiara[n]urils** (Tu[*n*]s) (Chandrakumar et al., 2019; Liu & Guo, 2022) |

# Recognition properties of Q[n]s

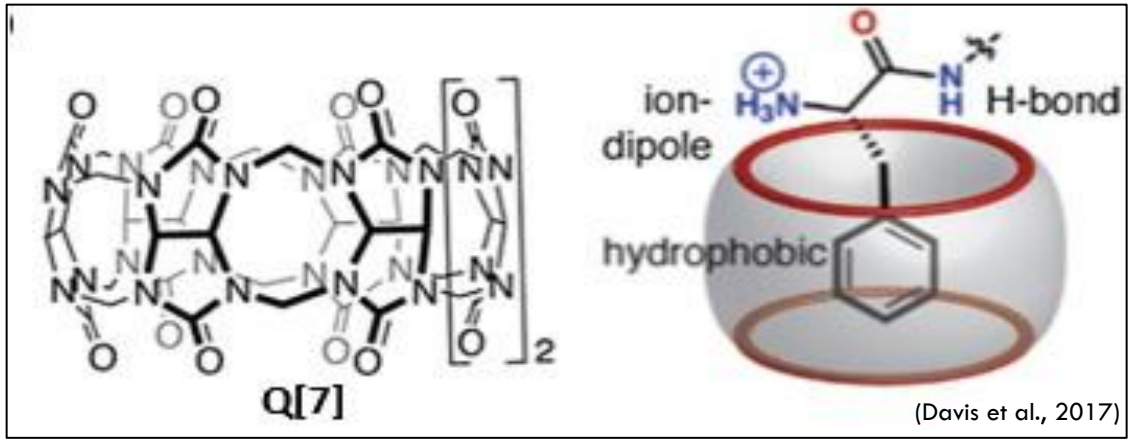
❑**Conventional Q[*n*]s** with high affinity and selectivity for many cationic and neutral guests-

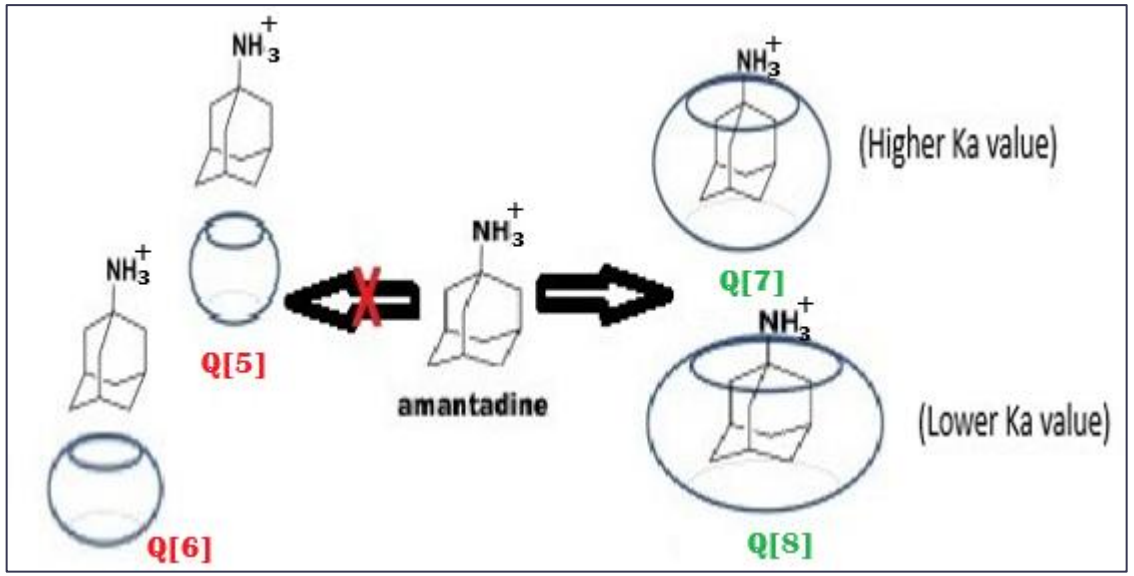
➢Hydrophobic van der Waals interactions at the cavity

➢Ion-dipole and H-bonding interactions at the carbonyl portals

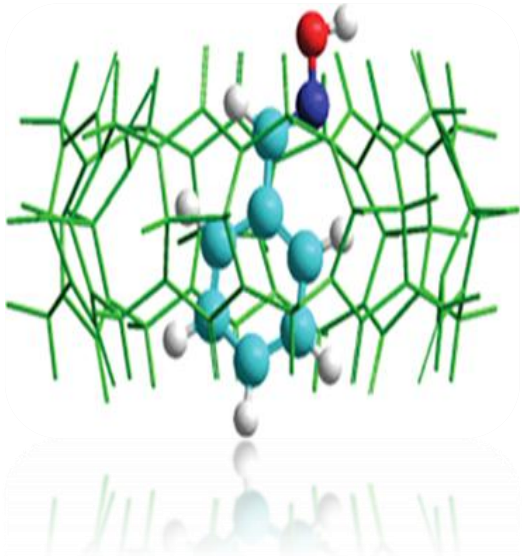
➢Symmetrical portal diameters leads to stronger binding

➢Diversified cavity sizes of different Q[n]s allow size selective guest encapsulation



# Aims of the Research



**Purpose of this research is to explore**

Drug Delivery with different Q[*n*]s, its analogues and/or their different derivatives-

To improve solubility

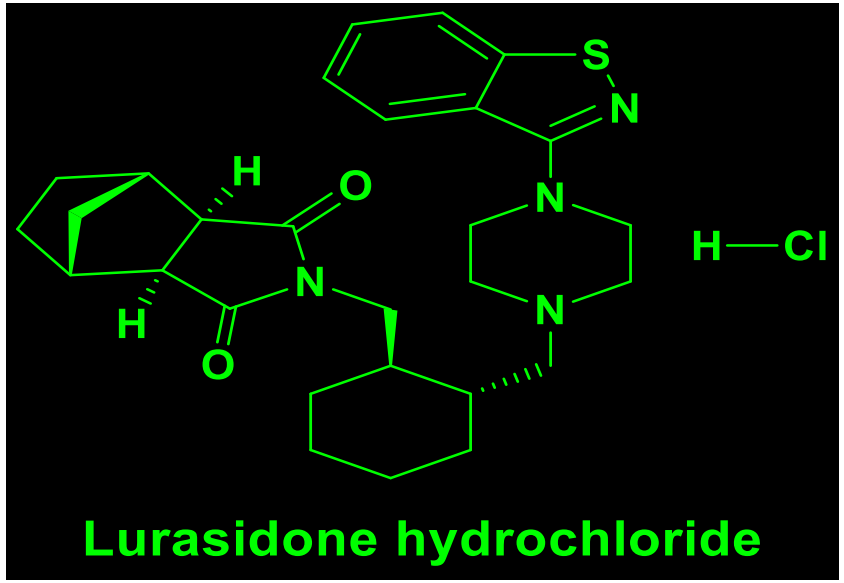
To enhance bioavailability

# Therapeutic agent used…

Poorly soluble drug

**Antipsychotic drug**

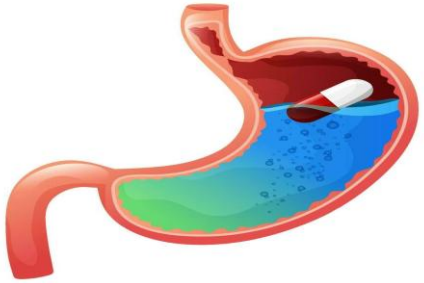
- Lurasidone Hydrochloride



# Reasons for choosing Lurasidone Hydrochloride (LH)

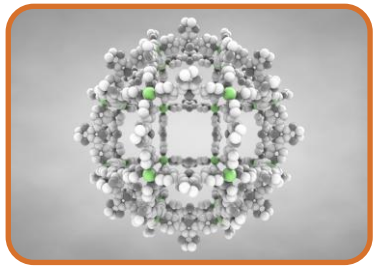
**Lurasidone Hydrochloride (LH)** formulations have-

- Poor aqueous solubility **(0.42mM or 0.224 mg/ml)**
- Extremely low bioavailability **(9 to 19%)** (Wang et al., 2022, Londhe et al., 2018)



Available solubility enhancing oral formulations-

- **Require fed state to improve** bioavailability
- Have negative impact on **gut microbiota** (Meola et al., 2024)



Other macrocyclic drug delivery vehicles-

- Will be required in e**xcessive concentration** compared to Cucurbiturils (Das et al., 2019)
- **Lower stability** and negative impact on **intestinal** microbiome

# pH dependent solubility impact of LH

**Lurasidone Hydrochloride**

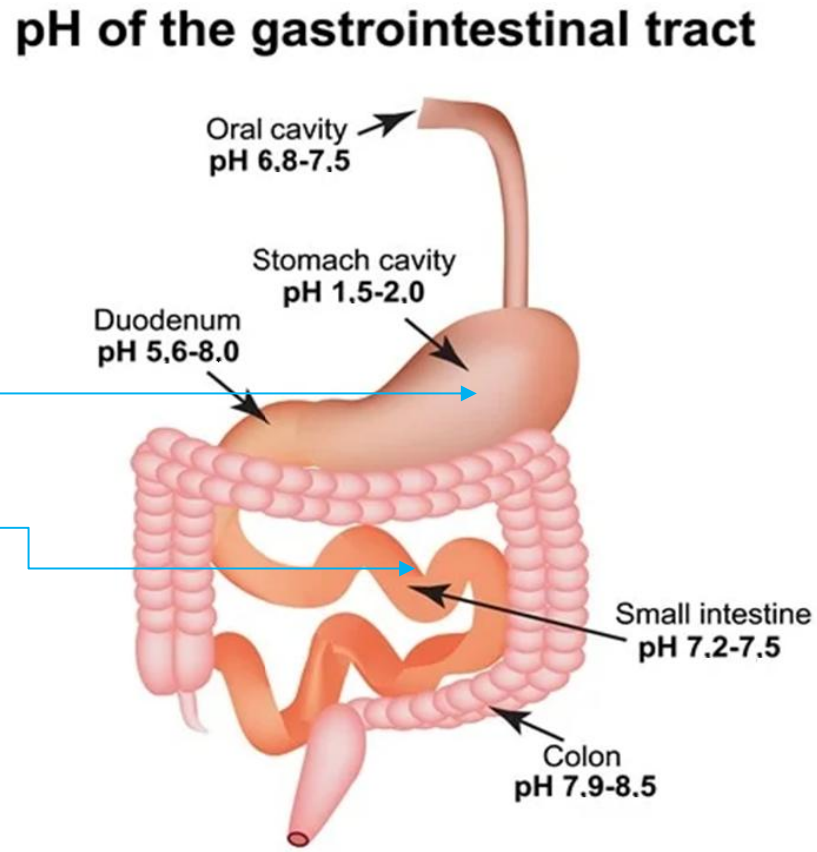
- **pH dependent solubility variation causes drug precipitation in intestine**

Maximum solubility at pH 3.8

- Soluble at Stomach pH

Sharp fall in solubility above pH 4.5

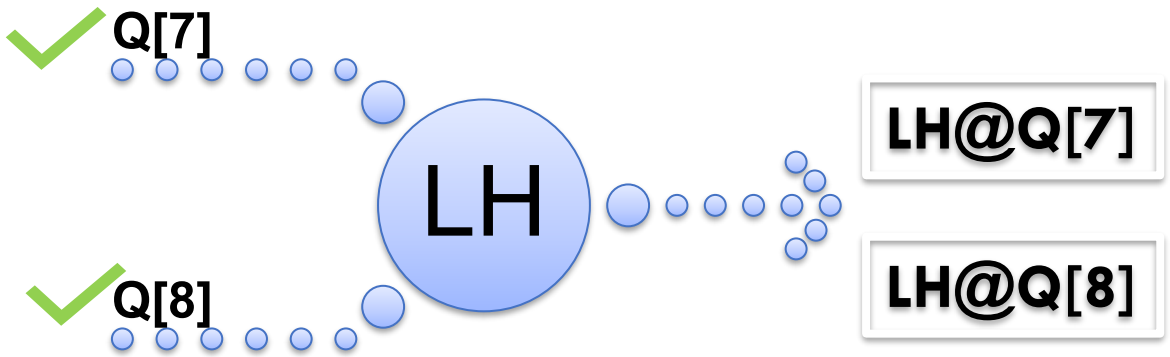
- Precipitates at Intestinal pH

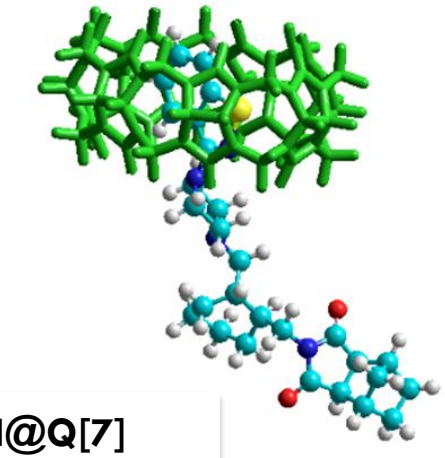



Salt of a weak base → Drug pKa impacts solubility

# Experimental approaches with Q[*n*]s & LH

- **Attempts toward encapsulation of LH inside Q[*n*]s:**

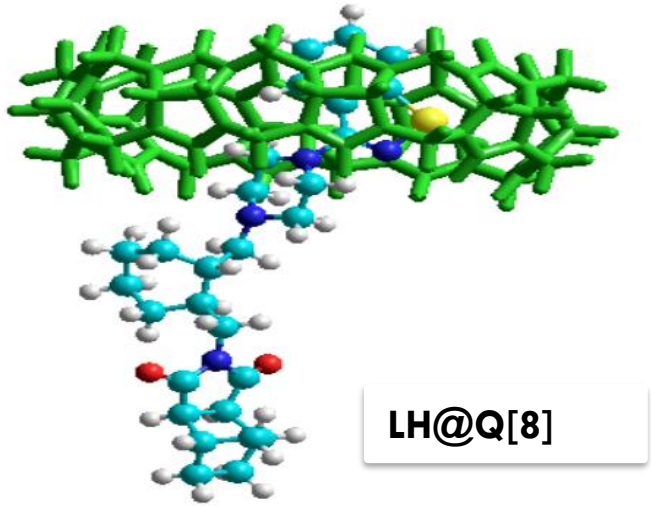


LH@Q[7]

- **Solubility Profile Investigation of the LH@Q[*n*] complexes**

| | |
|---|---|
| LH@Q[7] | • Improved solubility |
| LH@Q[8] | • Improved solubility |

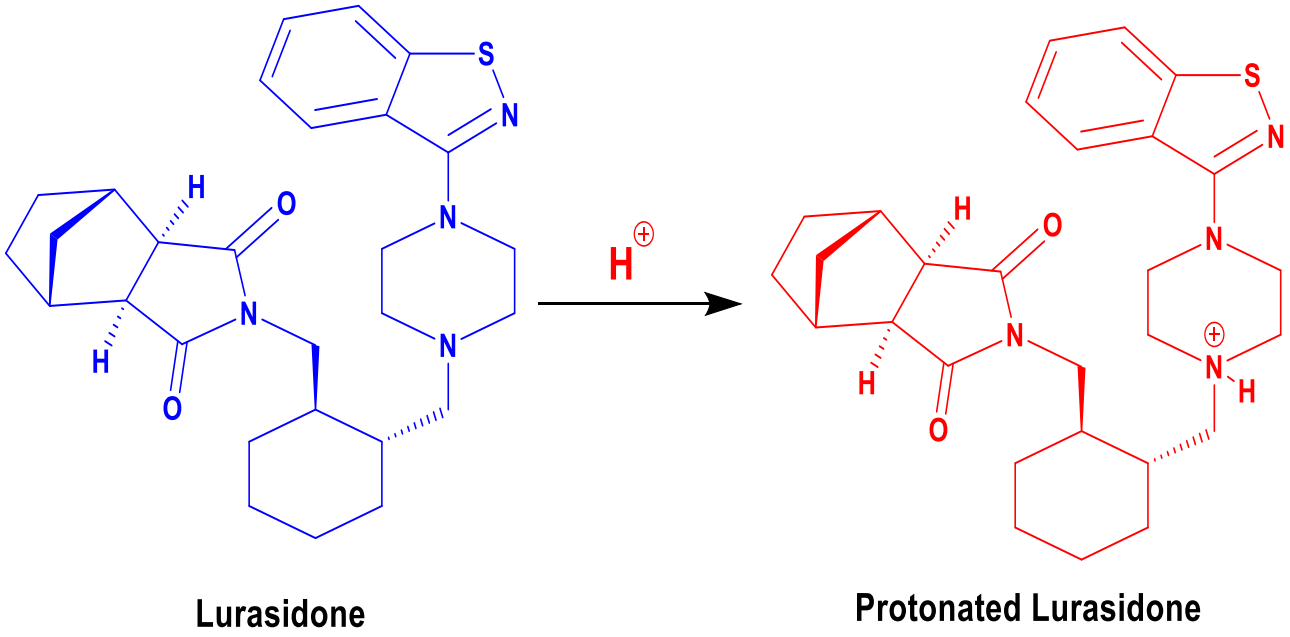


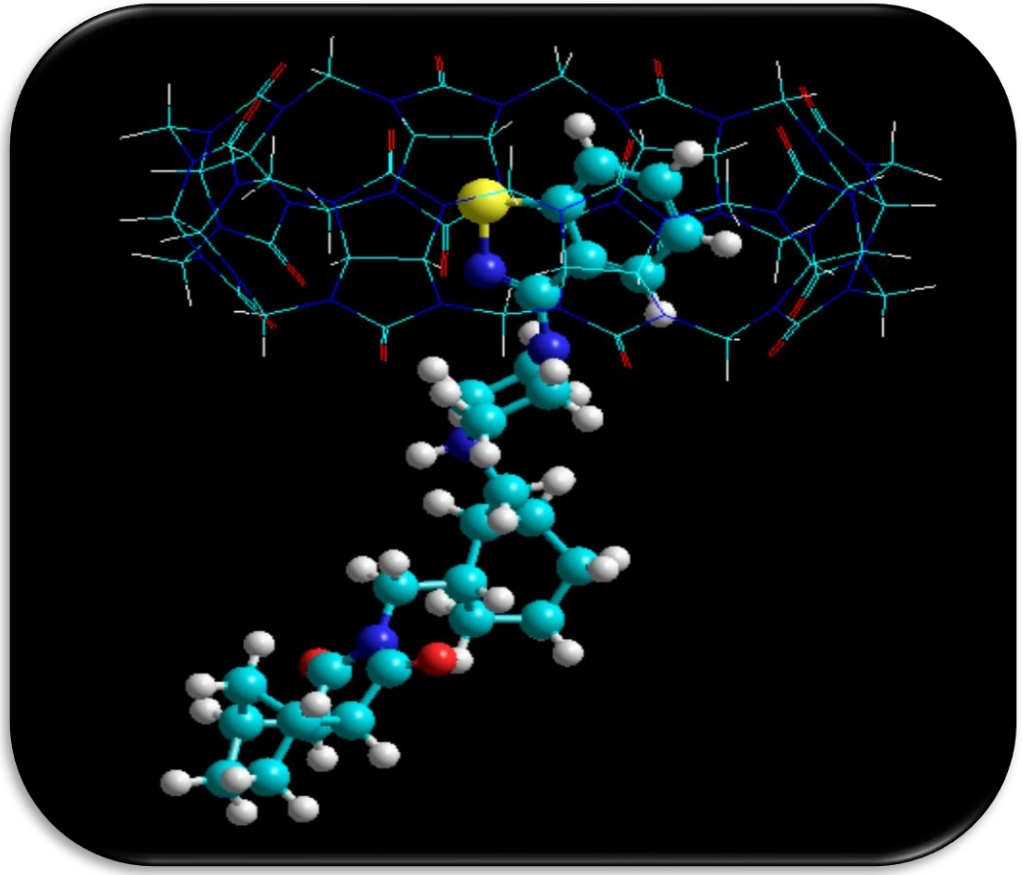
LH@Q[8]

- **pKa determination of the LH@Q[*n*] complexes**

| | |
|---|---|
| LH@Q[7] | • Higher pKa |
| LH@Q[8] | • Higher pKa |

# Lurasidone encapsulation inside Q[*n*]s

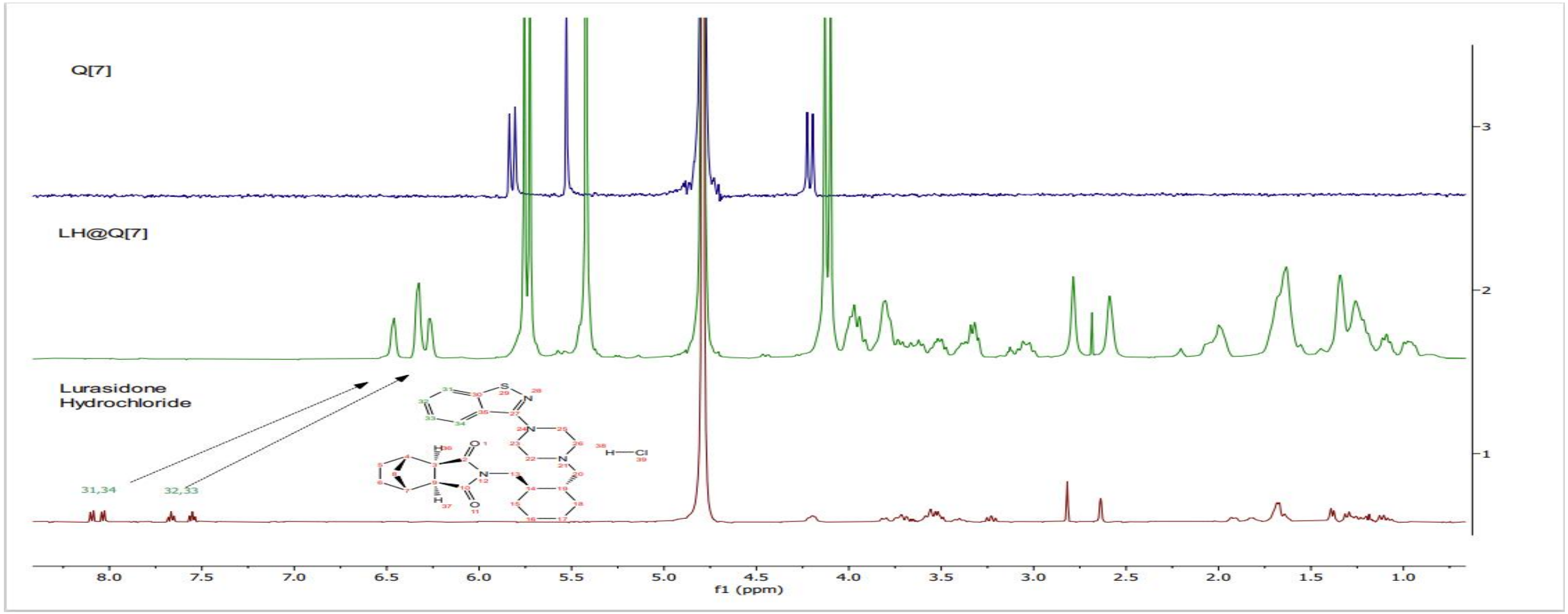


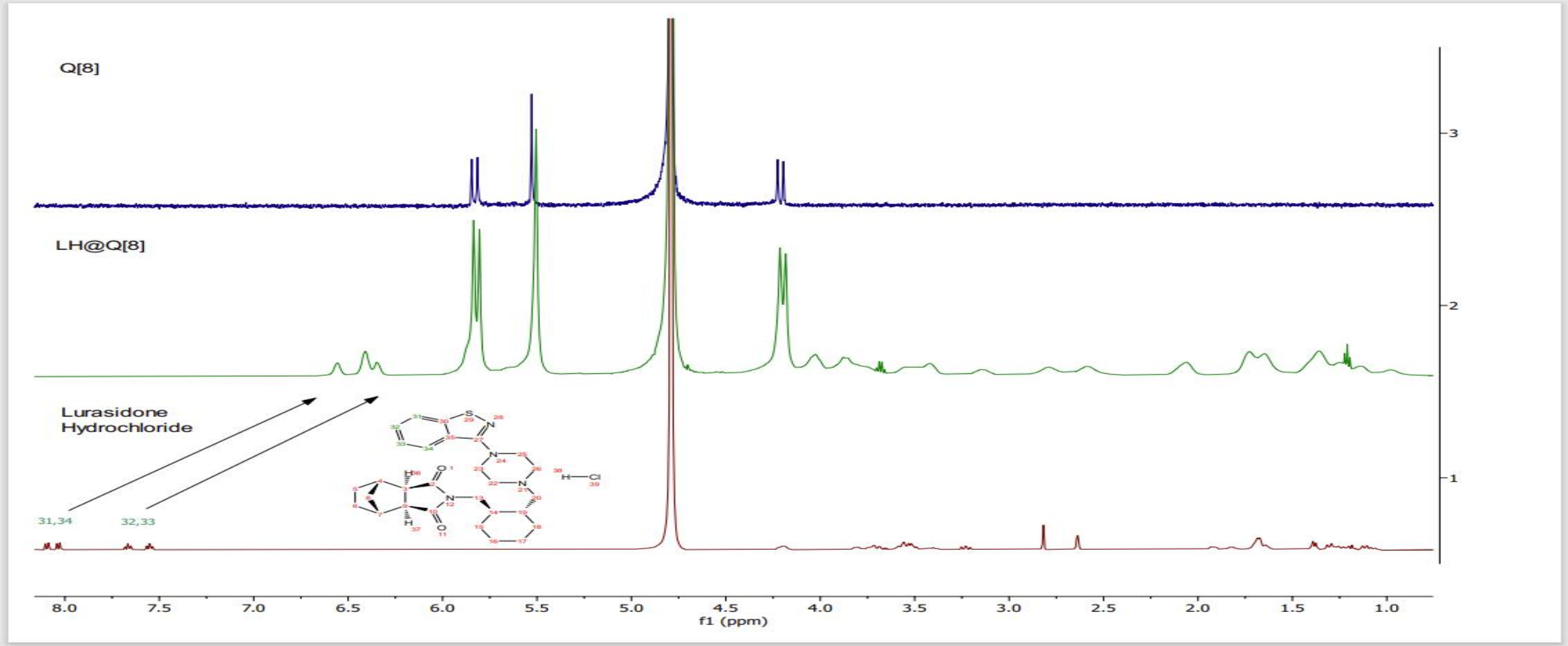
pKa of free Lurasidone: 7.6

Protonated Lurasidone@Q[8]

# Proton NMR spectra for LH@Q[7] complexation



# Proton NMR spectra for LH@Q[8] complexation



# Findings so far…

❑ **Lurasidone Hydrochloride (LH) with Q[*n*]s**

10 folds

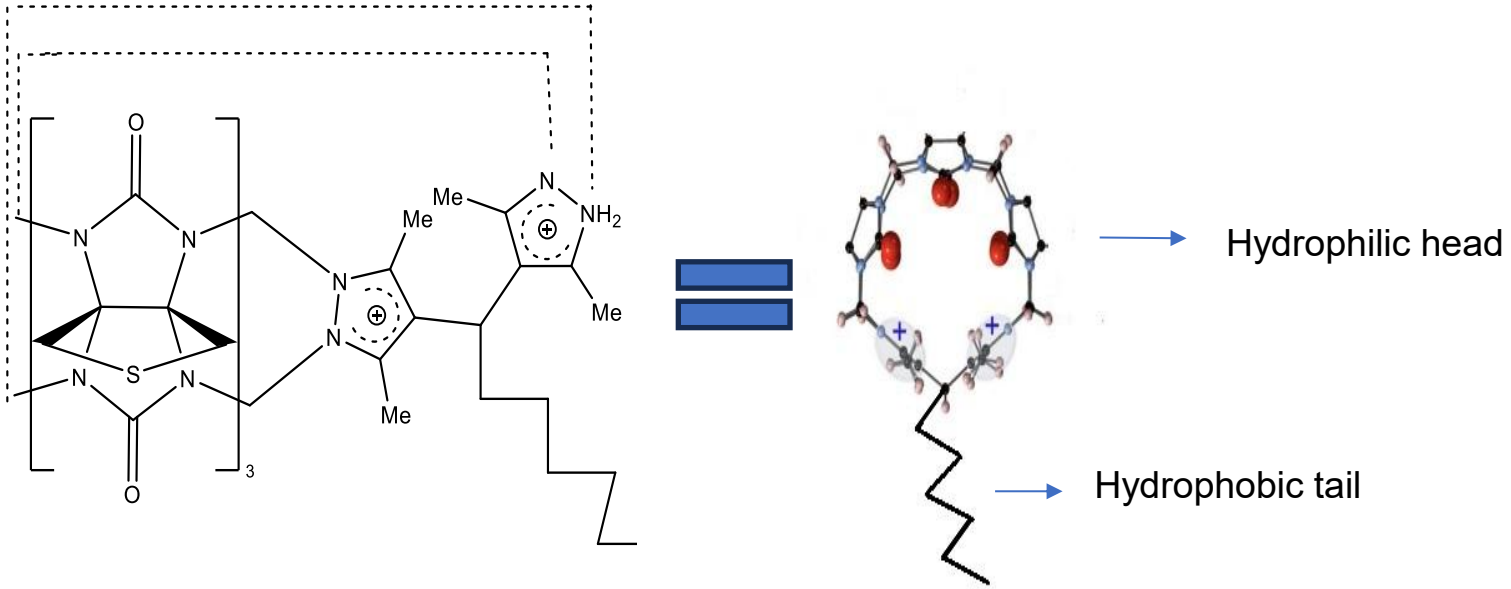
13 folds

| Parameters | LH@Q[7] | LH@Q[8] | Free LH |
|---|---|---|---|
| **Solubility** | 4.26mM or 2.25 mg/ml | 5.6mM or 2.96 mg/ml | 0.42mM or 0.22 mg/ml |
| **Saturated Solution pH** | 6.57 | 4.43 | 3.6 |
| **pKa** | 8 | 8.3 | 7.6 |

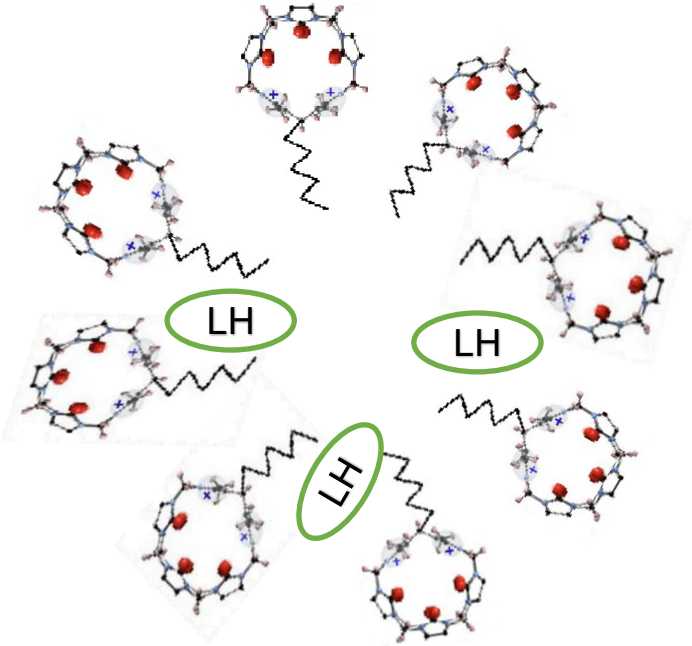
Positive pKa shift

# Current investigations…

## Experimental approaches with THTTu[3]hexyl & LH:



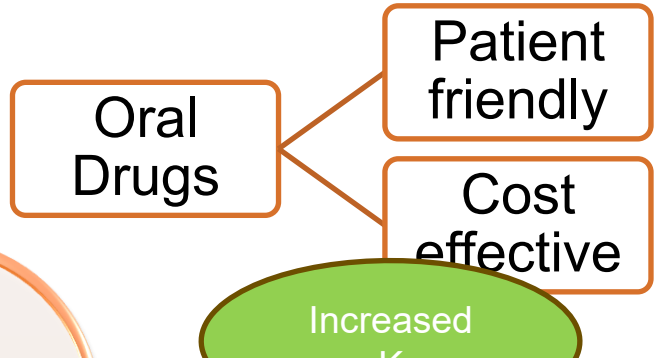

Tetrahydrothiphene Tiara[3]uril-hexyl
(THTTu[3]-Hexyl)

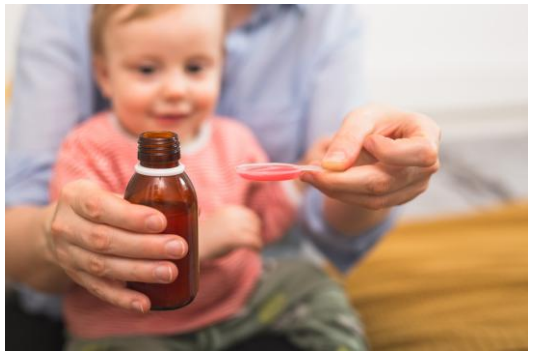


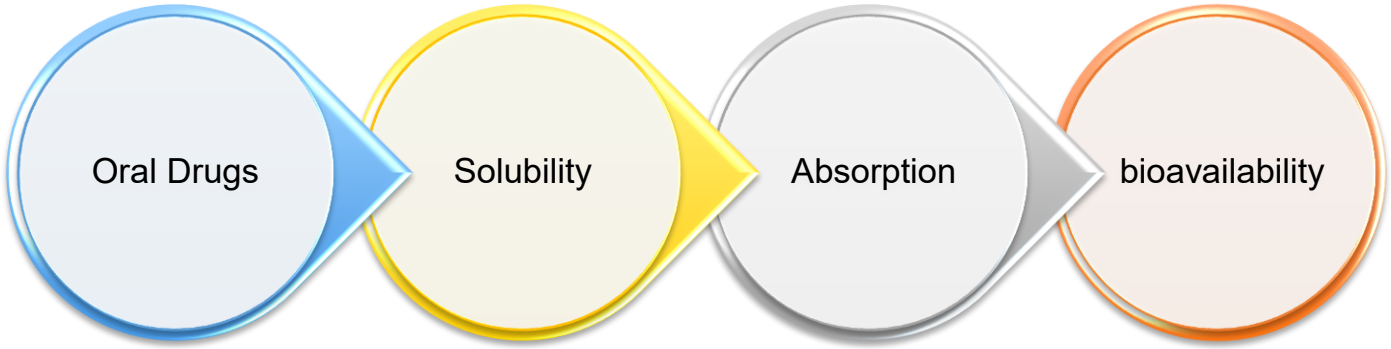

Micelle Formation by amphiphilic Tu derivatives

THTTu [3]-Hexyl + LH = Improved LH solubility ← 31.9 folds

# Overview and Takeaways

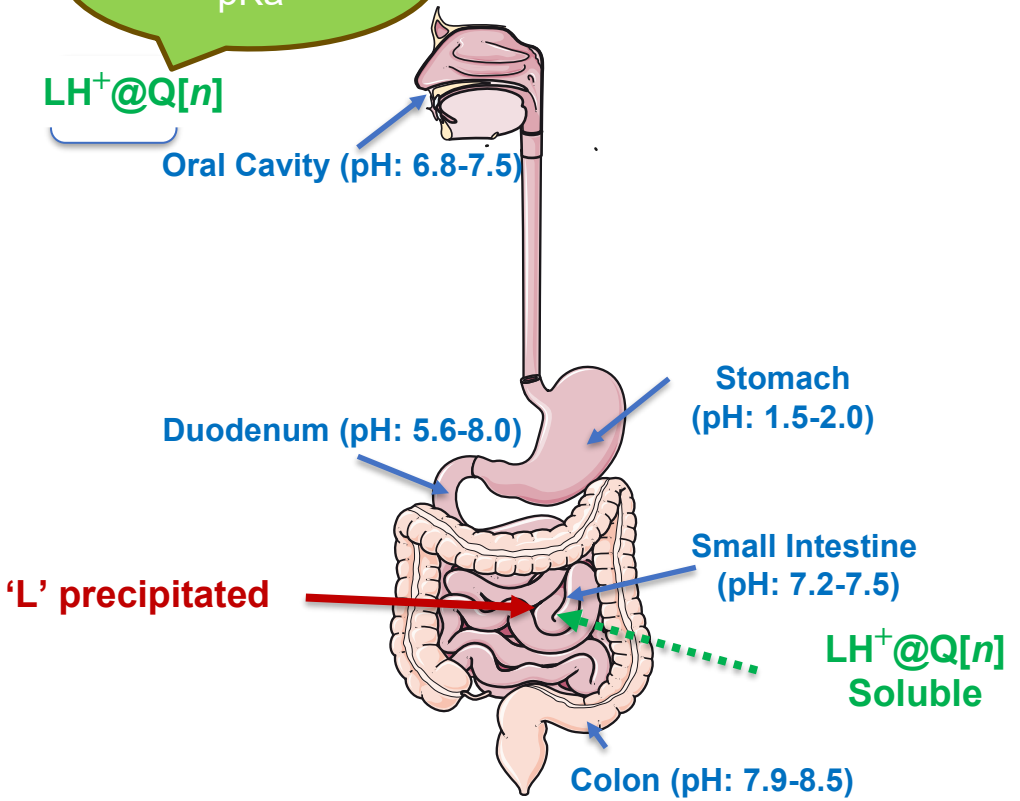





Increased pKa

$LH^+@Q[n]$




Complexation of LH with Q[*n*]s & Tu[3] derivative

Improved Solubility of LH

Potential for improved bioavailability

# Future Works…

Investigation of LH with different amphiphilic Tiara[*n*]uril derivatives.

Complexation and analysis of the LH with some functionally modified Q[*n*] derivative.

# References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# Thank You