Screening for nutraceutical - drug interactions toward the non-covalent interactions of their solid binary systems (Case study on Piperine)

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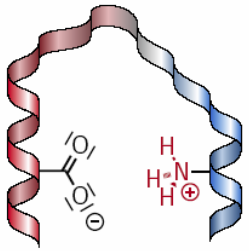
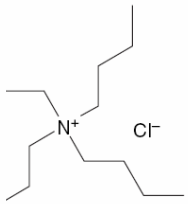
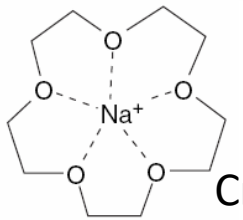
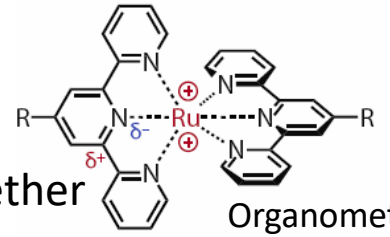
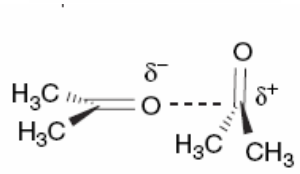
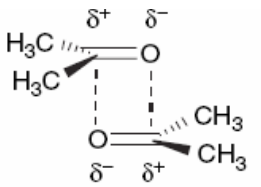
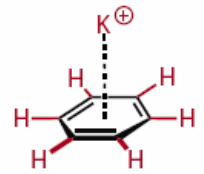
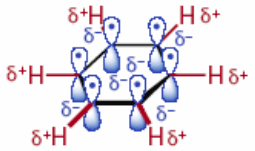
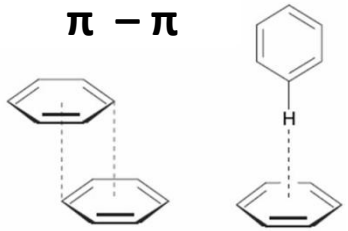
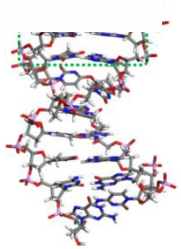
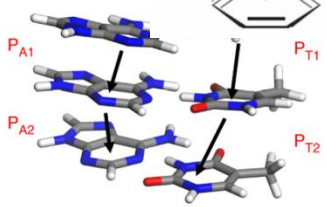
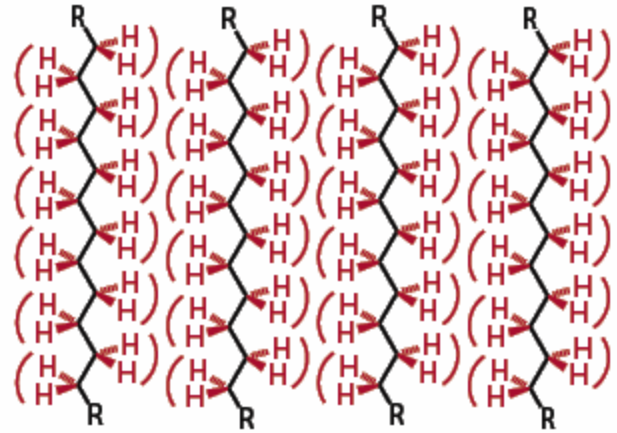
What is the nature of non-covalent interactions?

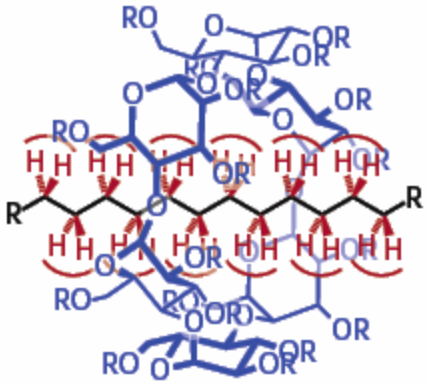
Interactions	Energy/Strength	Examples
Ion-Ion	Strong 200-300 KJ/mol	non-directional in nature, any orientation: Acid-base pairs in proteins Tetrabutyl ammonium salts
Ion - Dipole	Moderate 50 – 200 KJ/mol	Crown ether Organometal complex
Dipole – Dipole	Week 5 - 50 KJ/mol	Specific orientation of polar solvent/acetone
Cation – π	relatively weak 5 - 80 KJ/mol	80 kJ/mol in gas phase
π – π interactions	weak 5 - 50 KJ/mol	**π – π** In DNA

van der Waals interactions
week interactions



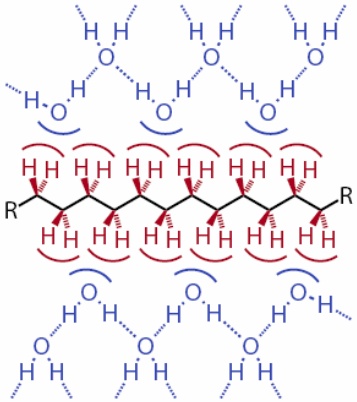
aliphatic chains
e.g., in lipid membranes



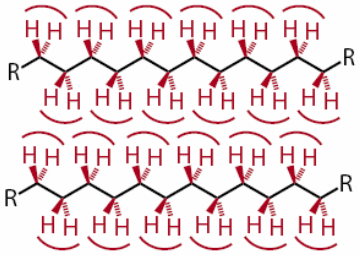
cyclodextrin
inclusion complexes

Hydrophobic effects-

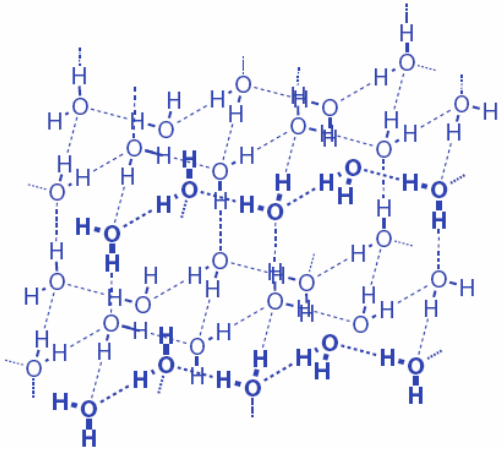
Enthalpy/ entropy driven

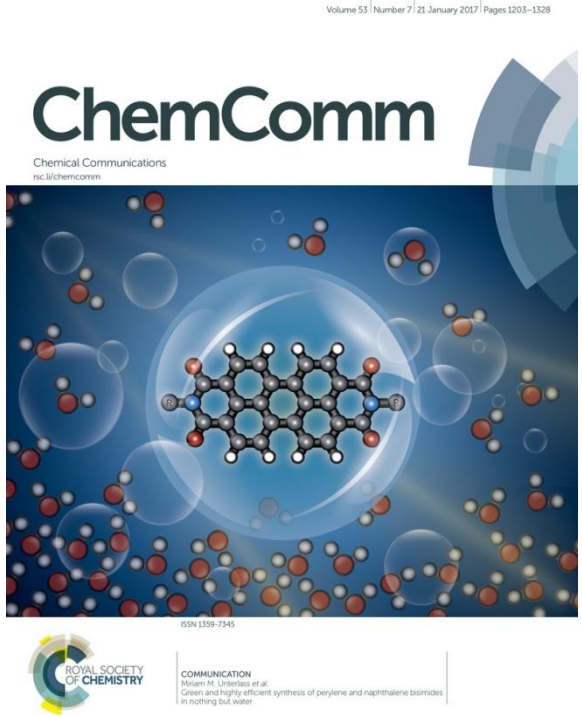


$\Delta G = \Delta H - T\Delta S$



phase segregation, interface minimization





What does make range and versatility of nature to the Hydrogen bonds?

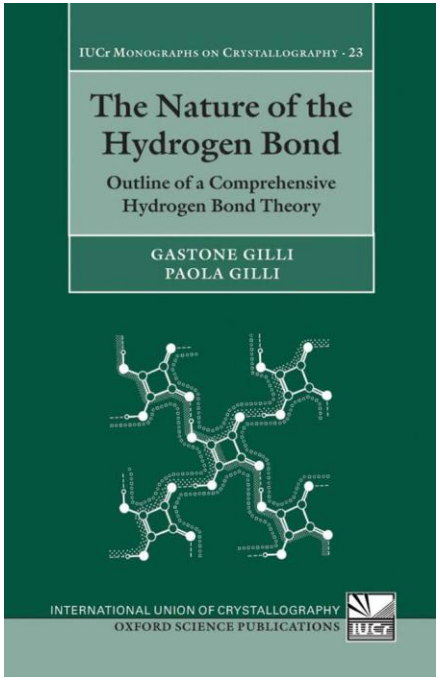
The Dual H-Bond Model

the H-bond is not really *a bond*

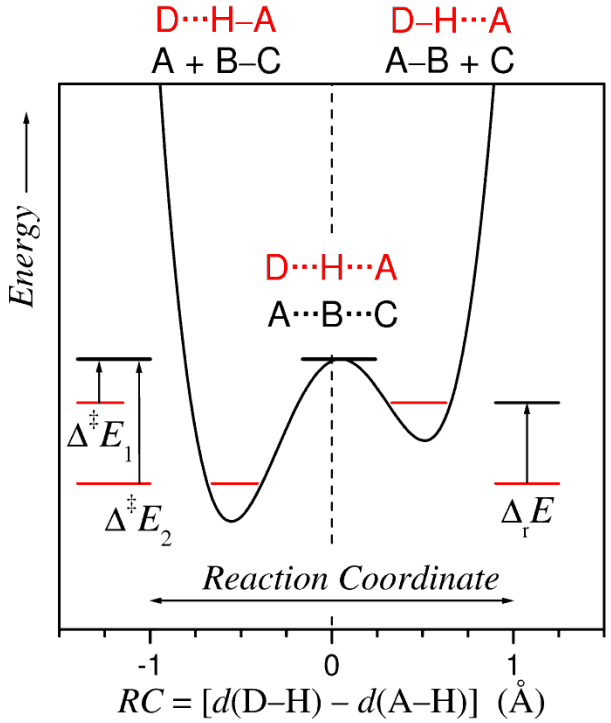
donated by the donor D–H to the acceptor :A but rather

consists of *two competing bonds*

formed by sharing a proton with two acceptors, each carrying an electron pair.



Gilli & Gilli, **2009**

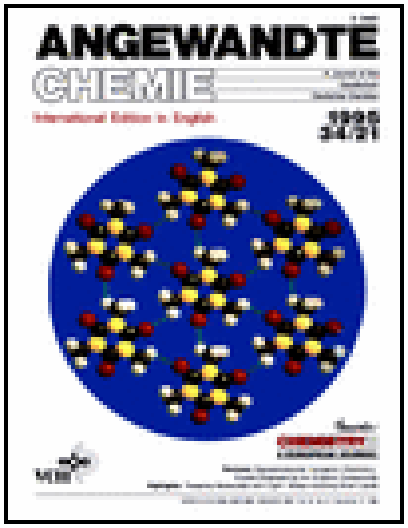


bimolecular proton-transfer (PT) reaction pathway

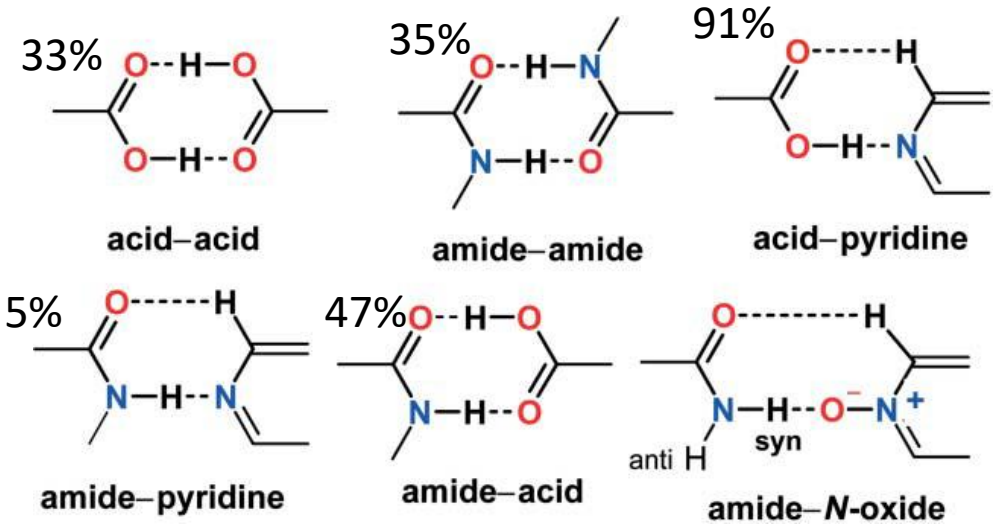
leading from D–H···A to D···H–A through the D···H···A transition state.

How do molecules interplay?

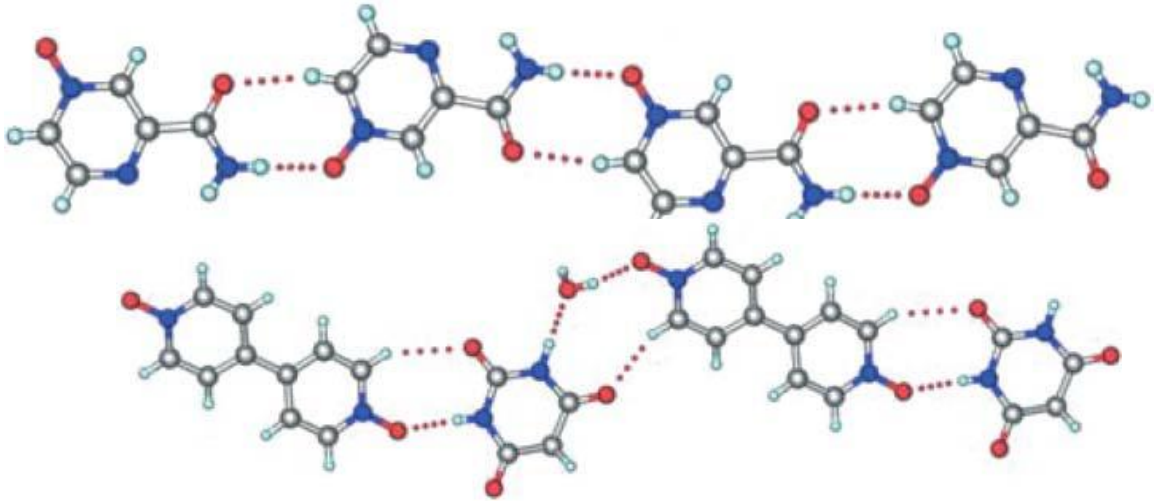
(Molecular dating)



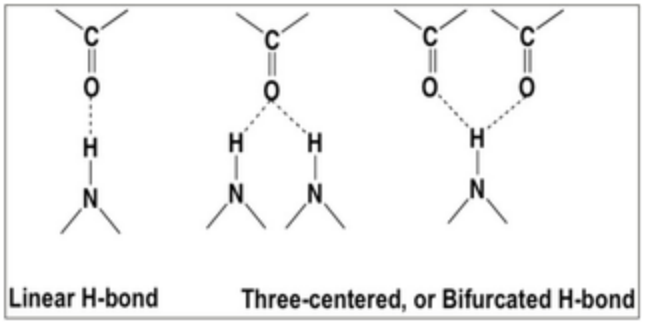
Angew. Chem. Int. Ed. **(1995)** Engl. 21, pp. 2328.

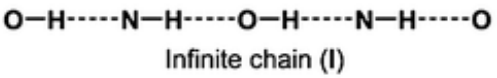


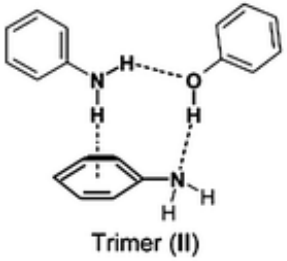
Prevalence of occurrence of structural unites: homo- & hetero synthons

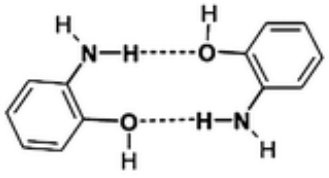


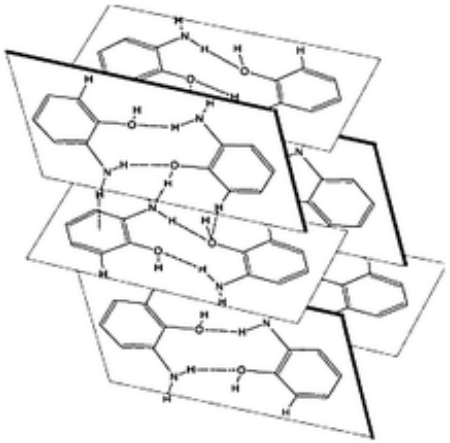
Chem. Commun., 2006, 1369–1371 |

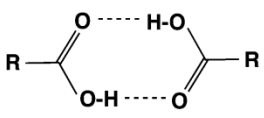


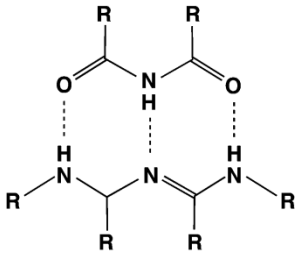


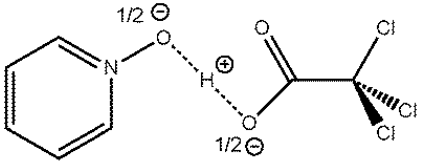


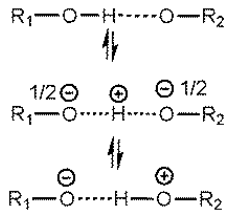


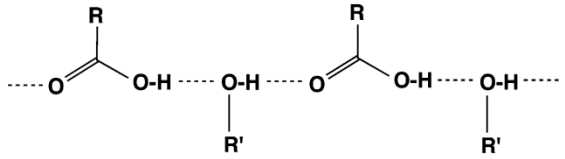


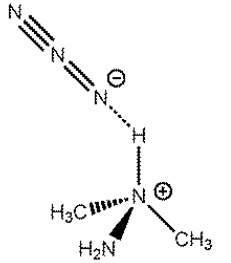


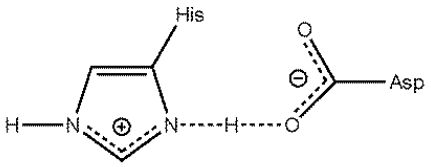


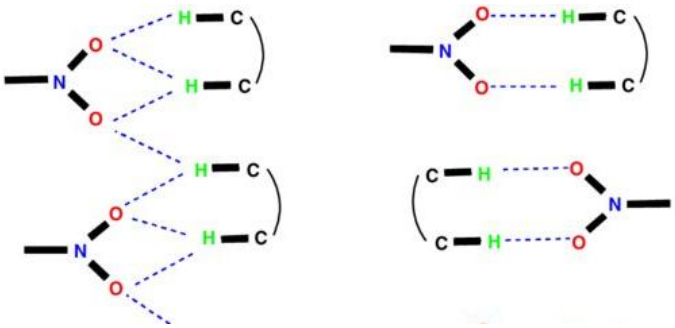


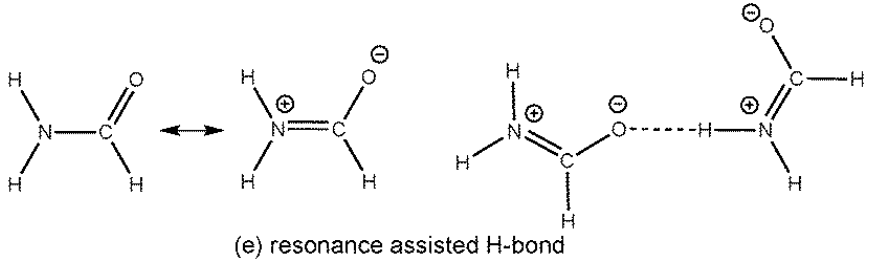








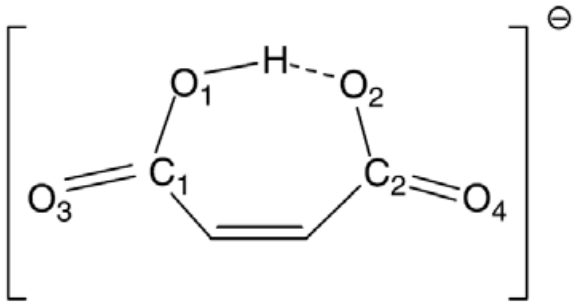




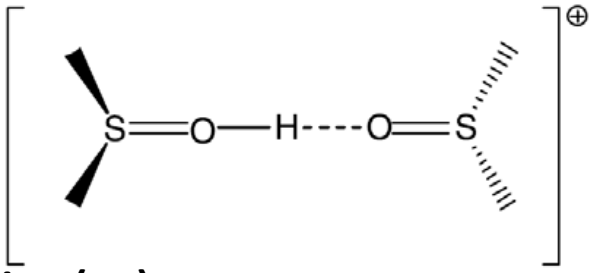
chelated C-H···O hydrogen bonding synthon-I forming catemer.

cyclic C-H···O hydrogen bonded dimer synthon-I

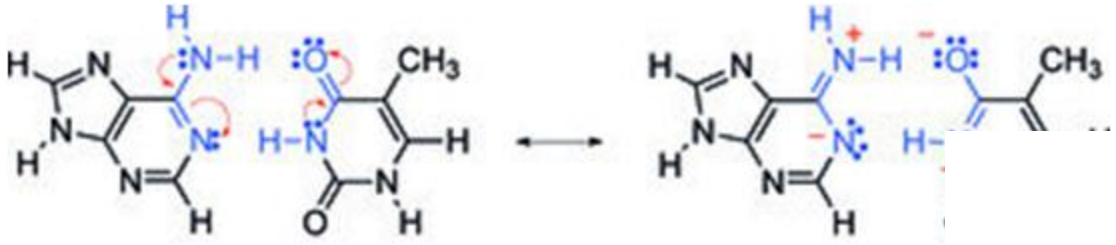
Negative charge assisted hydrogen bond [(–)CAHB]



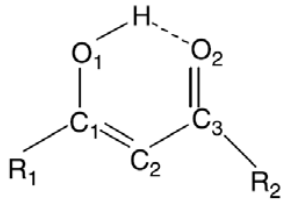
Positive charge assisted hydrogen bond [(+)CAHB]

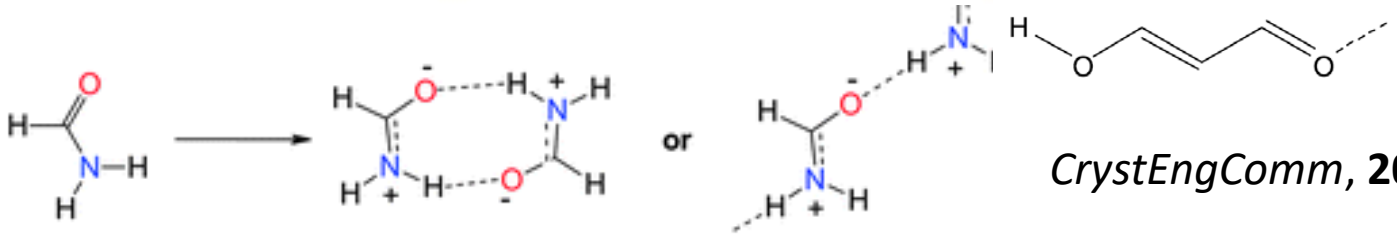


Resonance-assisted hydrogen bonding in adenine–thymine (AT)



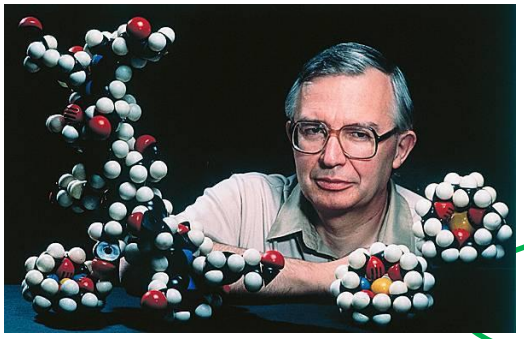
ChemistryOpen (2015) 4(3)



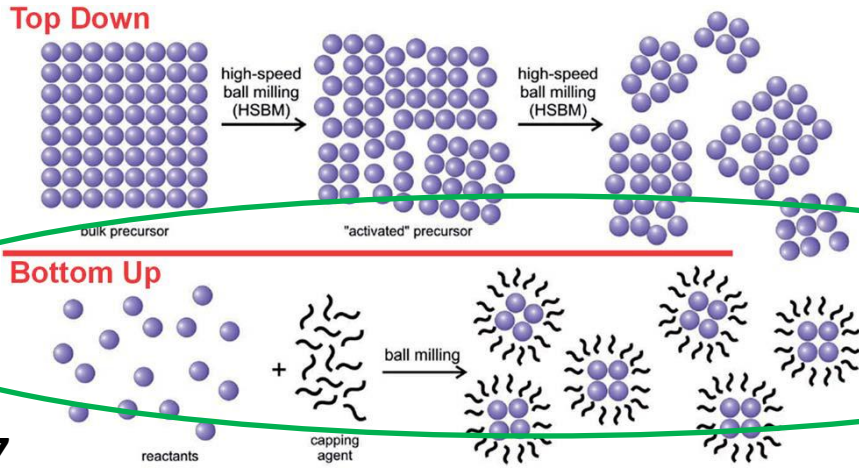


CrystEngComm, **2012,**14, 2571-2578

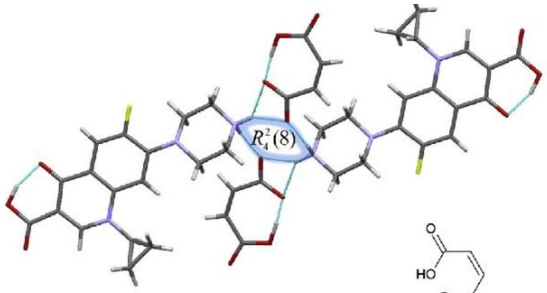
Chemistry beyond molecules (Supramolecular chemistry)

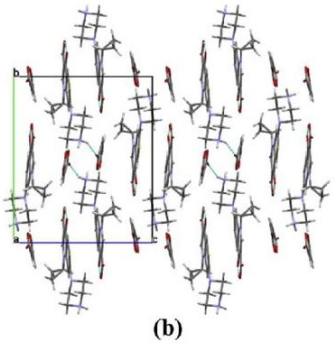


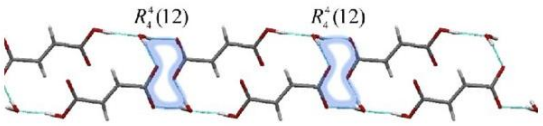
Jean-Marie Lehn,
Nobel Price in Chemistry 1987

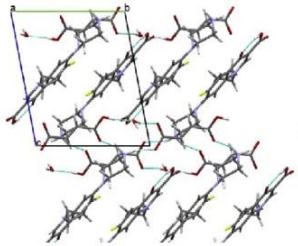


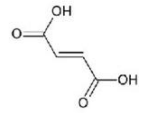
Faraday Discuss., 2014, 170, 411–422

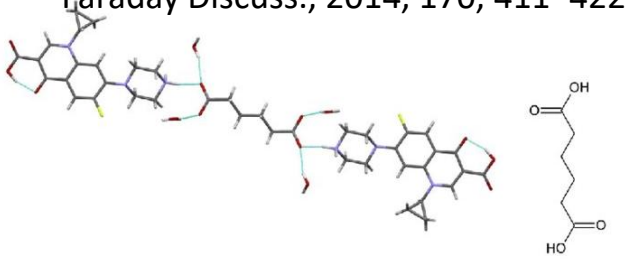


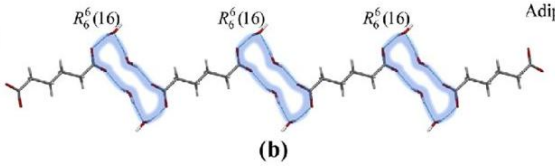


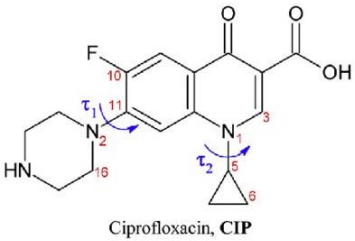


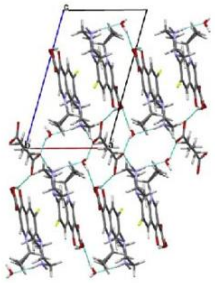












Eur. J. Pharm.Sci (2015) 77, 112–121

How does molecular recognition determine the bulk properties of supramolecular solids?

from properties to structure

Synthon – the structural unit for spatial repetition in retrosynthesis

Flexibility of Synthons depend on directionality of H-bonds and cooperativity

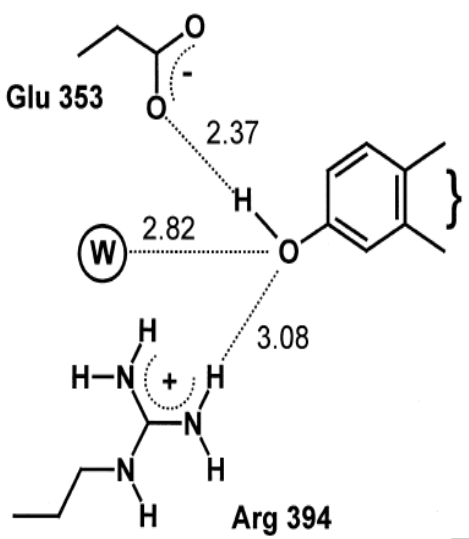
The prevalence of synthon occurrence and nature of non-covalent intermolecular interactions lead to formation of tow main classes of supramolecular structures:

1. Multicomponent structures based on Host - Guest interactions

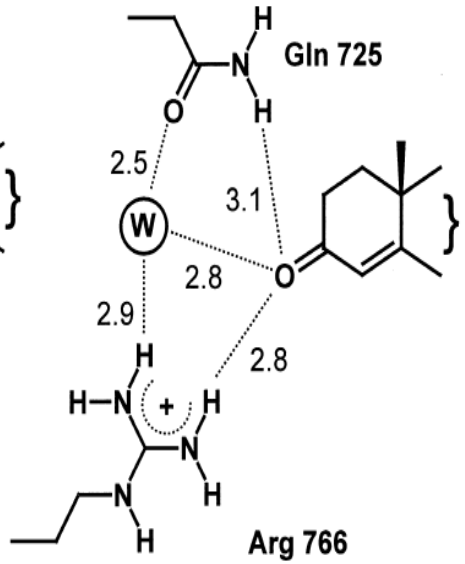
2. Self-assembled structures (mainly based on H-bonds)

What are the advantages of application of supramolecular chemistry for designing functional materials with life sci. relevance?

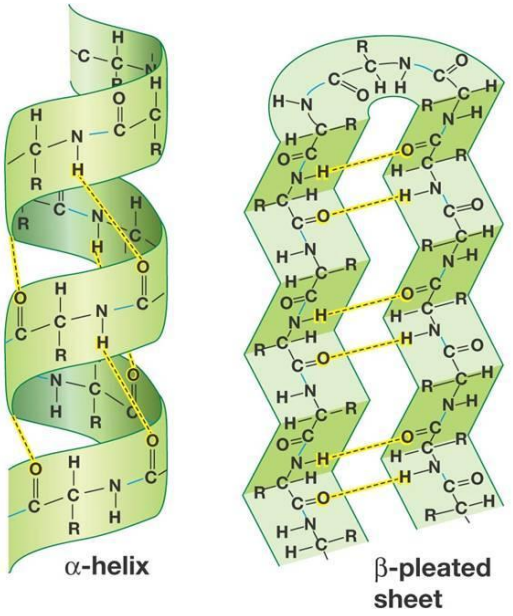
1. **Green Chemistry: Eco-friendly, free solvent processing using Mechanochemistry**
2. **Click-chemistry approach: atoms/ions/ molecules used as building blocks in bottom-up retrosynthesys**
3. **Design of structures of solid phases with desirable properties (e.g. enhanced water solubility of polymorphic form, salt or co-crystal of drug or nutrient that impact to its bioavailability, improved photostability of carotenoides by formation inclusion complexes with cyclodextrines , and etc.)**
4. **Design of artificial receptors**
5. **Design enzymes with mimic purposes**
6. **Study the mass transport across the biological membranes**
7. **Designed self-assembled structures (artificial membranes, particles, vesicles etc.)**
8. **Design of drug delivery systems (self-assembled structures for being loaded with drug models)**
9. **Designing the artificial viruses (self-assemble layer structures)**
10. **Study on mechanism of action in live organisms (metabolic paths, translation of gens, changes in protein folding that cause patophysiologycal conditions**



oestrogen receptor

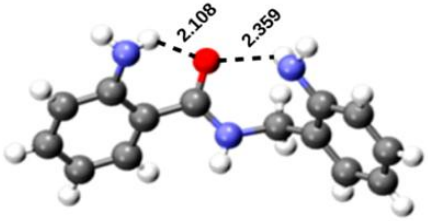


progesterone receptor



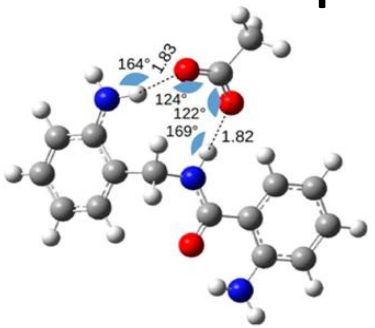
Acetate Binding to a New Diamine Receptor

*Nature (***1998)**, *393*, 392.



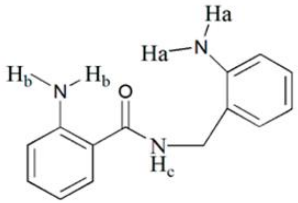
Crystal structure of free receptor R

$^{-}$OAc



Optimized geometry of receptor R bonded with acetate anion obtained from DFT calculation

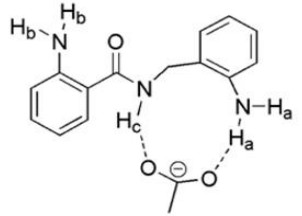
2-amino-*N*-(2-amino-benzyl)-benzamide (**R**)



Molecular model of receptor R

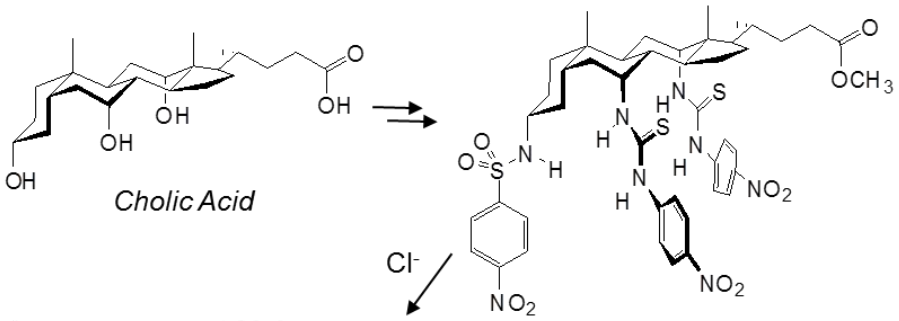
(a)

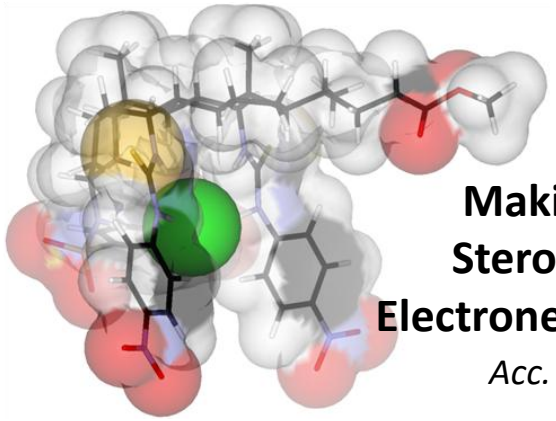
J. Phys. Chem. A 2016, 120, 2330−2341



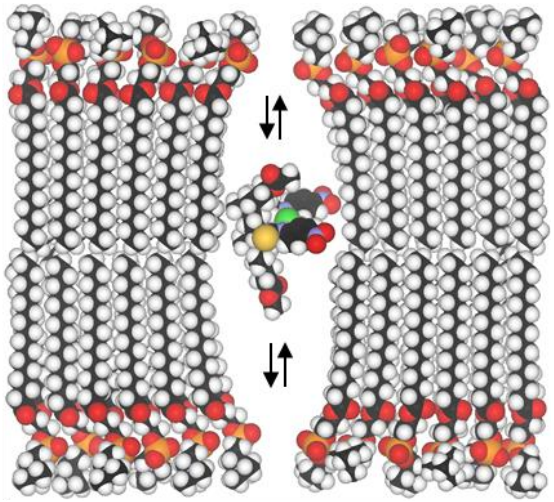
Molecular model of receptor R bonded with acetate anion (b)

Anion Recognition and Transport





Phospholipid membrane

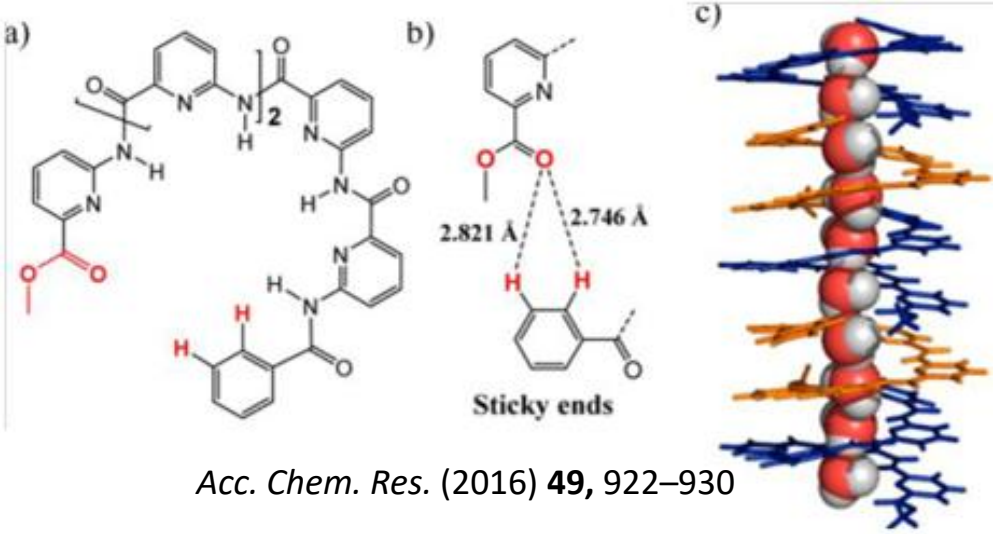


Cholapod binds anion and carries it through interior

Making a Match for Valinomycin: Steroidal Scaffolds in the Design of Electroneutral, Electrogenic Anion Carriers

Acc. Chem. Res. 2013, 46, 12, 2898-2909

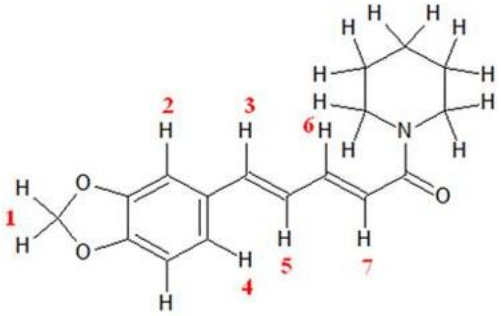
Aquaporines/ water channel



Acc. Chem. Res. (2016) **49,** 922–930

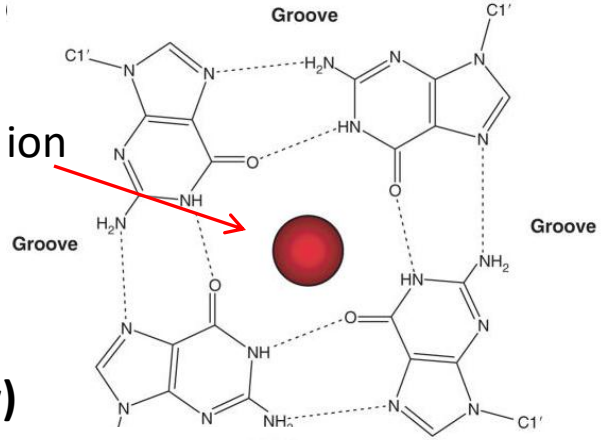
Case Study 1: Evidences for Piperine inhibiting cancer by targeting human G-quadruplex DNA sequences

Docking and Molecular Dynamics Simulation of *c-myc* G-quadruplex DNA – Piperine complex

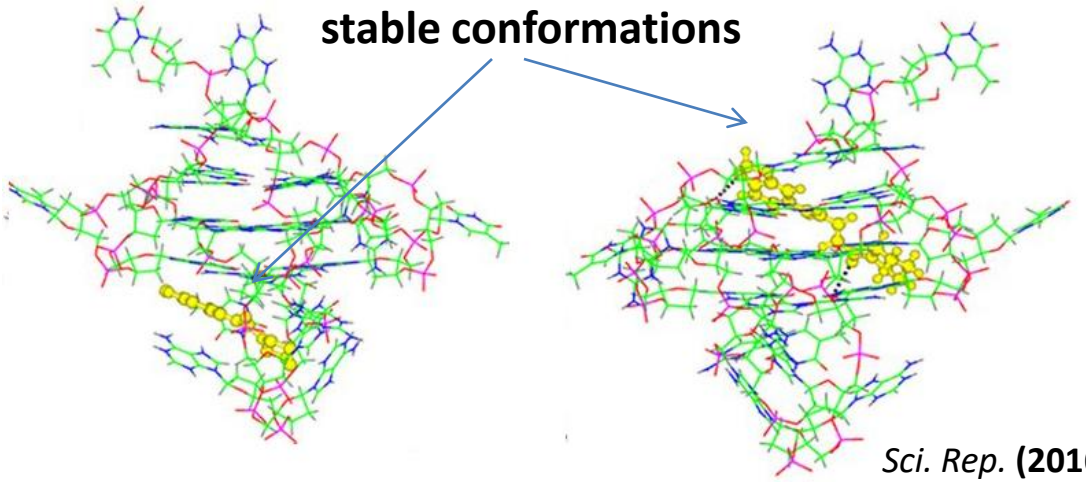


Piperine planar structure

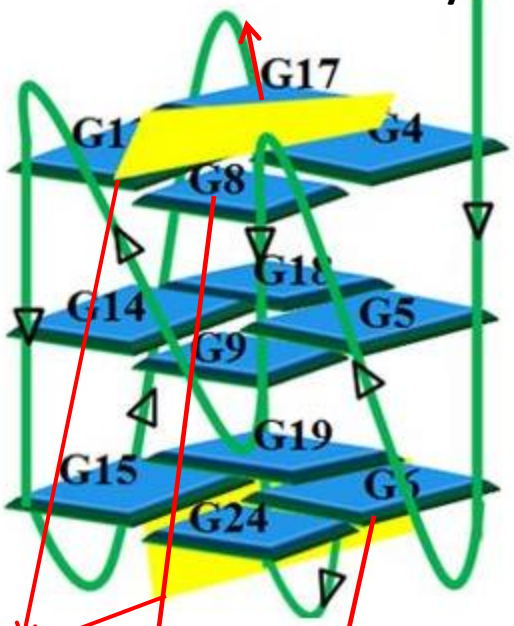
G- quadruplex DNA Pu24T complex (4 guanine bases, hydrogen bonded), targets for therapeutics



Piperine (yellow) stable conformations



(Site B) G17
π-π interaction
Eb –5.45 kcal/mol



G-quartet)

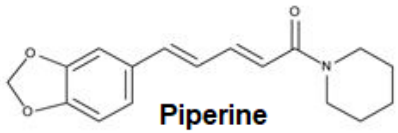
Piperine (yellow) in the lowest E

(Site A) G6
π-π interaction
Eb –7.18 kcal/mol

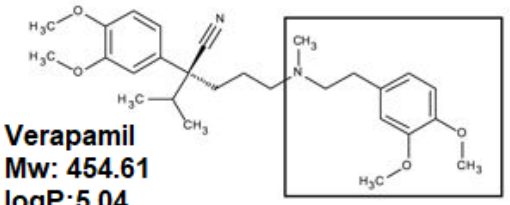
H-bond: C=O (piperine)…HN-(G8)

Sci. Rep. **(2016) 6**, 39239

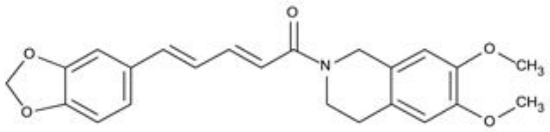
Case study 2: Targeting P-glycoprotein: Investigation of piperine analogs for overcoming drug resistance in cancer (*cont…*)



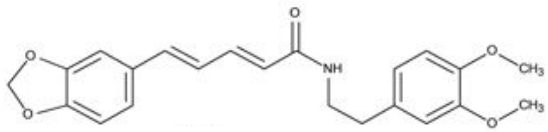
Piperine
Mw: 285.34
logP: 2.78



Verapamil
Mw: 454.61
logP:5.04



Pip 1
Mw: 393.43
logP: 3.38



Pip2
Mw: 381.428
logP: 3.30

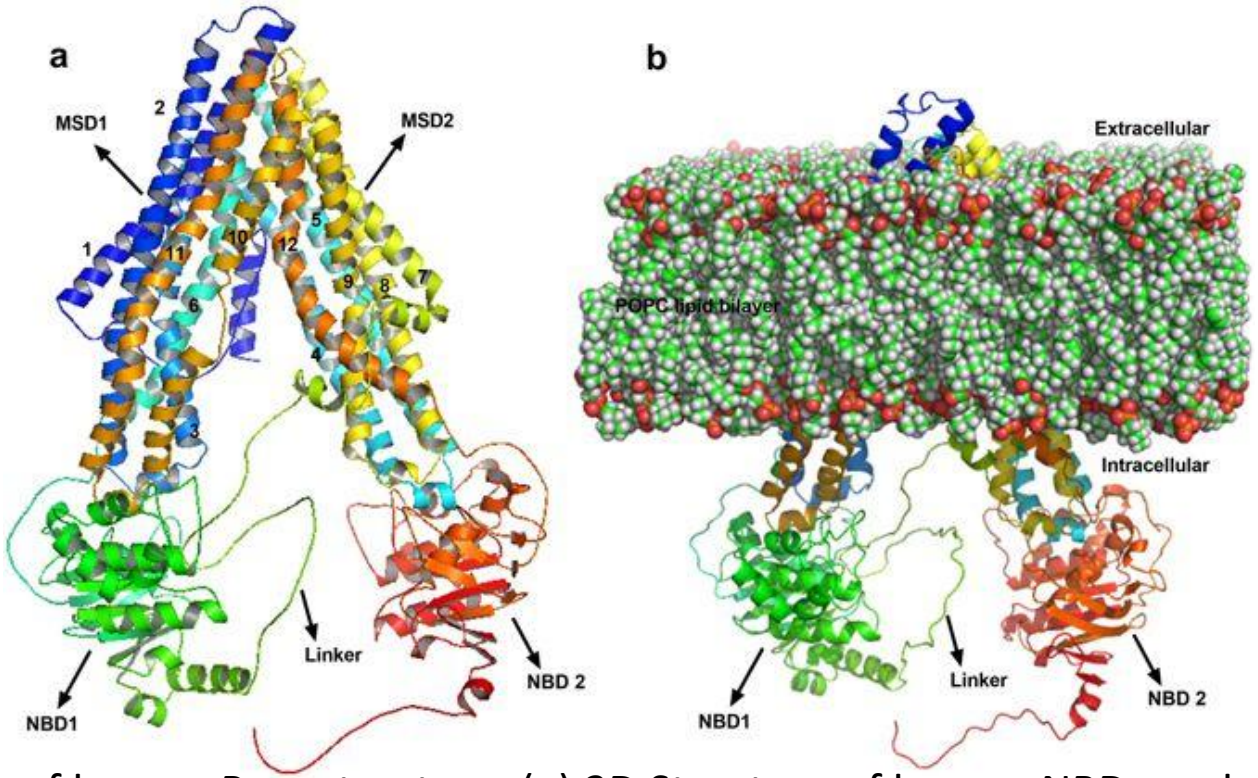
	Glide G-Score	Glide energy (kcal mol^{-1})	ΔG binding (kcal mol^{-1})	Interacting residues
Verapamil	−7.34	−39.50	−97.41	Phe336 (π-π interaction); Met69, Phe72, Phe336, Leu339, Ile340, Phe728, Ile868, Tyr953, Phe957, Phe978, Val981, Val982, Phe983, Ala985 and Met986 (hydrophobic interaction)
Piperine	−7.82	−26.85	−59.72	Tyr307 (Hydrogen bond); Met69, Phe72, Phe336, Leu339, Phe728, Tyr953, Val982, Phe983 and Met986 (hydrophobic interaction)
Pip1	−7.99	−26.06	−56.75	Phe72 and Phe983 (π-π interaction); Met69, Phe336, Leu339, Phe728, Tyr953, Phe978, Val982, Phe983 and Met986 (hydrophobic interaction)
Pip2	−8.16	−35.29	−74.95	Met69, Phe336, Leu339, Phe728, Ile868, Tyr953, Phe957, Phe978, Val981, Val982, Phe983, Ala985 and Met986 (hydrophobic interaction)

Sci. Reports **(2017)** 7, 7972

<u>Case study 2</u>: Targeting P-glycoprotein: Investigation of piperine analogs for overcoming drug resistance in cancer

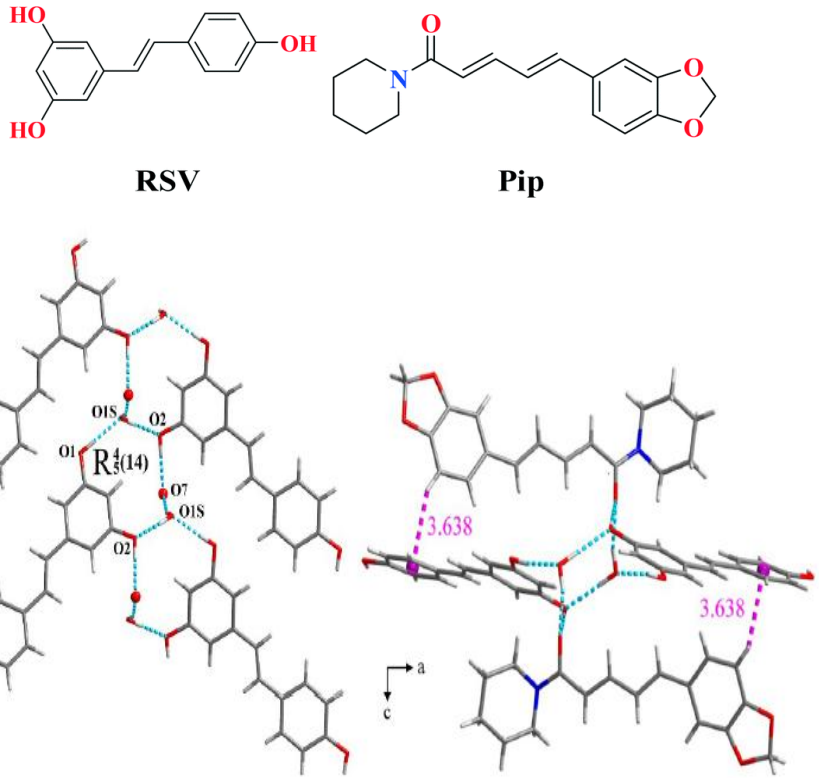
(Pip1 and Pip2) could interact with the drug binding site of the hP-gp protein in a manner very similar to that of the reference compounds, piperine and verapamil.

Ep (Pip1 -protein) < Ep (verapamil-protein) & Ep (Pip2 -protein) < Ep (verapamil-protein)

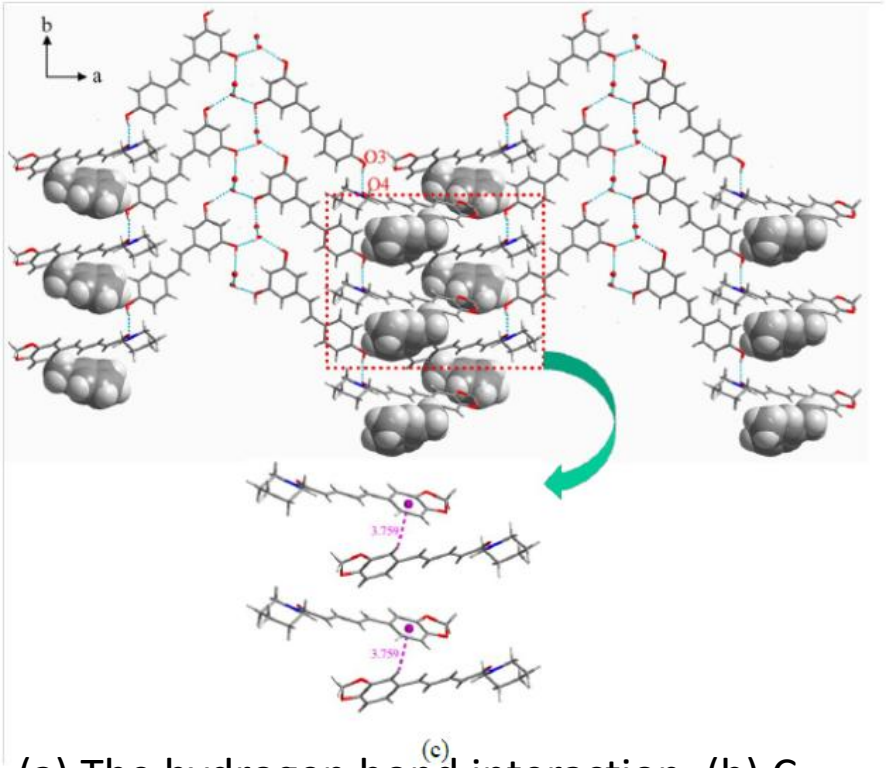


Molecular modeling of human P-gp structure. (**a**) 3D Structure of human NBD: nucleotide binding domain; Transmembrane (TM) helices are denoted by numbers from 1 to 12. (**b**) Human P-gp model embedded in the POPC lipid bilayer,

Case study 3. Structure, physicochemical properties and pharmacokinetics of resveratrol and piperine cocrystals



(a) the hydrogen bond interaction and (b) C-H**…π interaction between RSV** and Pip molecules in RSV-Pip co-4

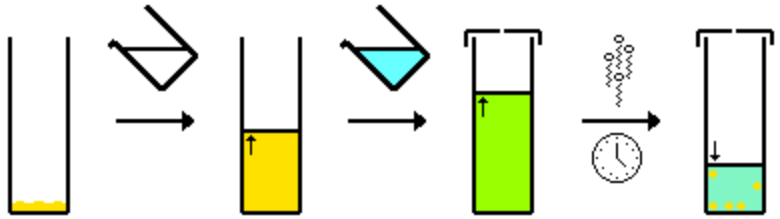


(a) The hydrogen bond interaction, (b) C-H**…π interaction between RSV and** Pip molecules, and (c) C-H**…π interaction between Pip molecules in the 2D packing** network of RSV-Pip co-3

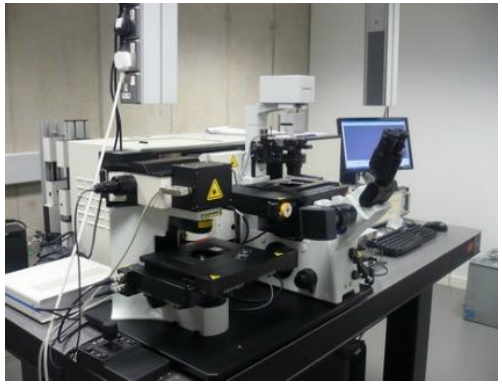
CrystEngComm, **(2017)** 41, 6154-6163

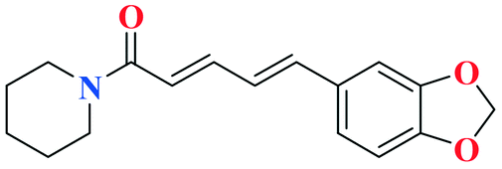
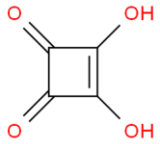
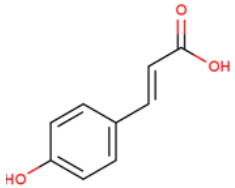
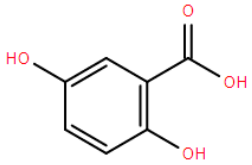
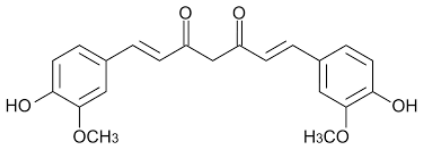
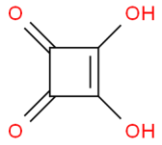
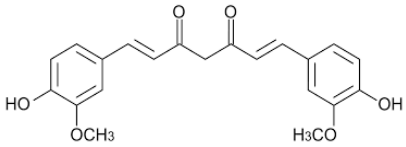
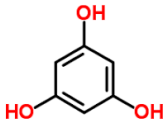
Case Study 4. Preliminary Screening for growing a single crystal of piperine in multicomponent systems: models for study H-bonding interactions

Growing single crystalline phases by solvent-evaporation method



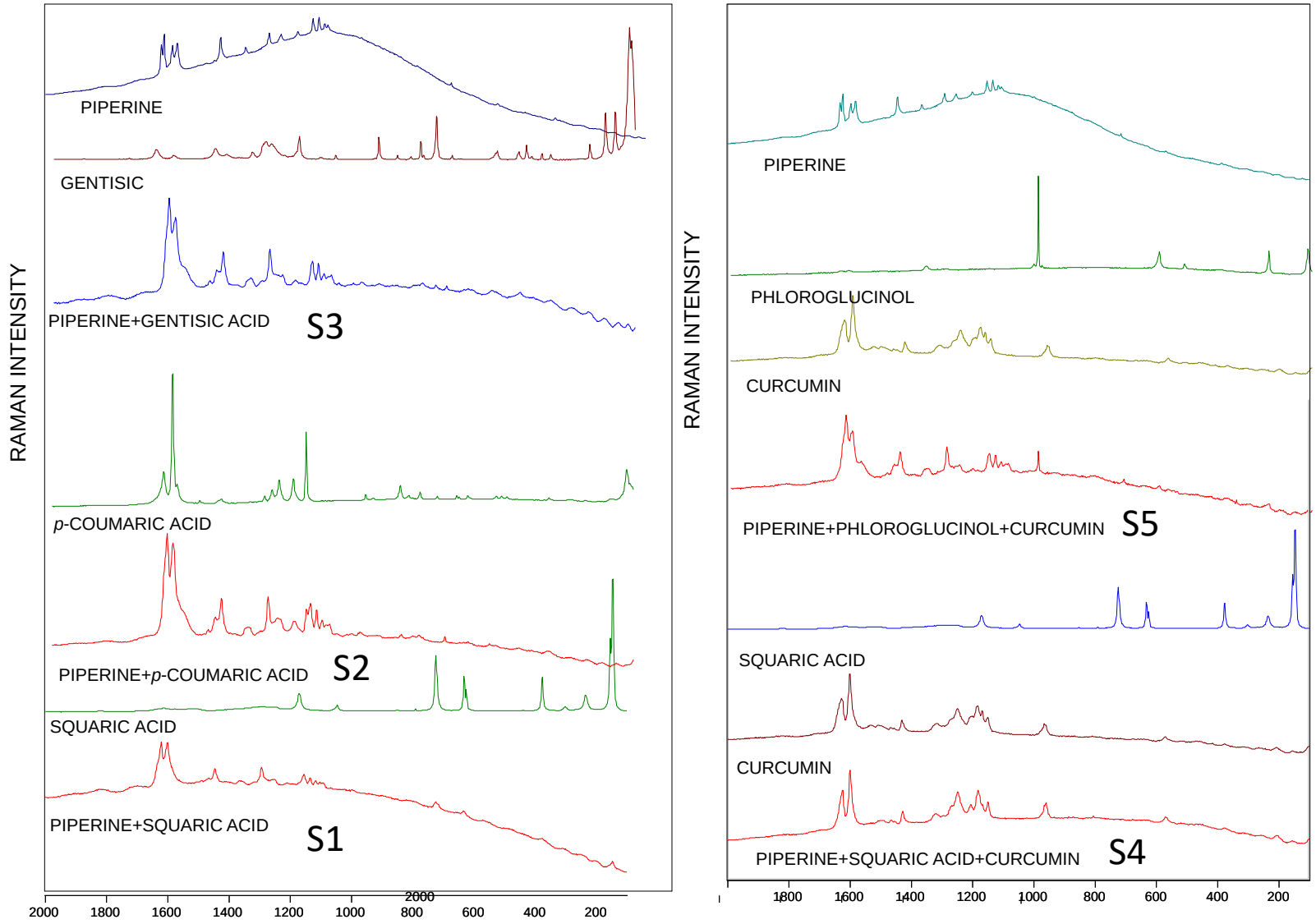
Method of analyses: Micro-*Raman spectrometer*
(Horiba Jobin-Yvon LabRam. 300)



Sample No	Model/ nutraceuticals	Coformer	Coformer	Mol ratio
S1	Piperine 	Squaric acid 		1/1
S2		*p*- Coumaric acid 		1/1
S3		Gentisic acid 		1/1
S4		Curcumine 	Squaric acid 	1/1
S5		Curcumin 	Phloroglucinol 	1/1

Case Study 4. Preliminary Screening for growing a single crystal of piperine in multicomponent systems:

In all 5 samples, there is no interactions between piperine and coformers



Thank you for your attention:

Acknowledgment to:

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