A crystallographic route to understand drug solubility: the case of 4-aminoquinoline antimalarials

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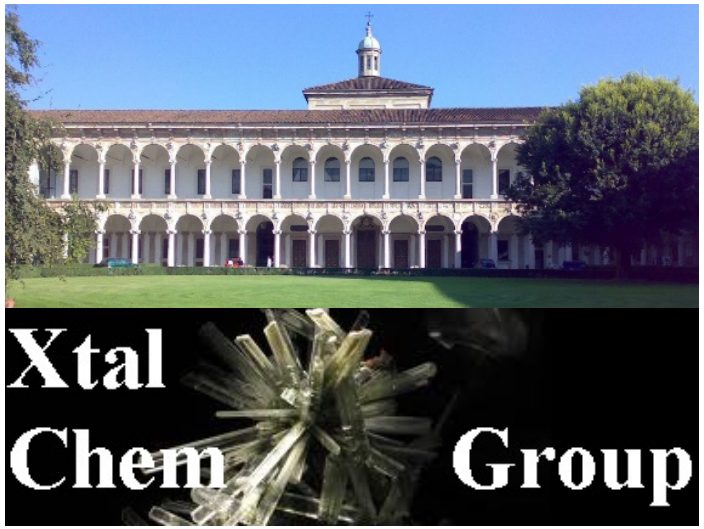


Università degli Studi di Milano

06.09.2019, MISCA V, Naples, Italy

Outline

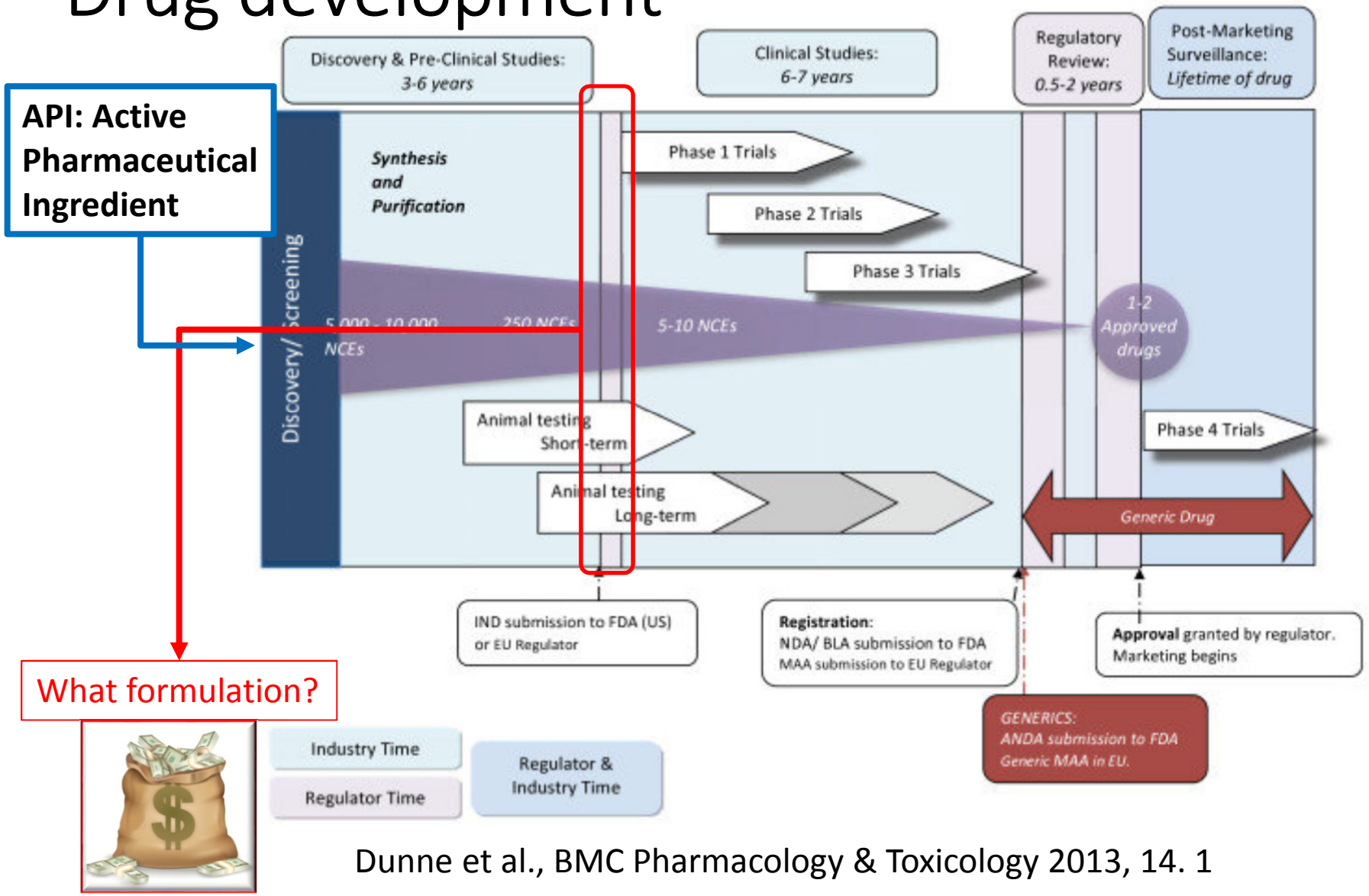
(i) Motivation

(ii) Malaria

(iii) The case of piperaquine

(iv) Conclusions

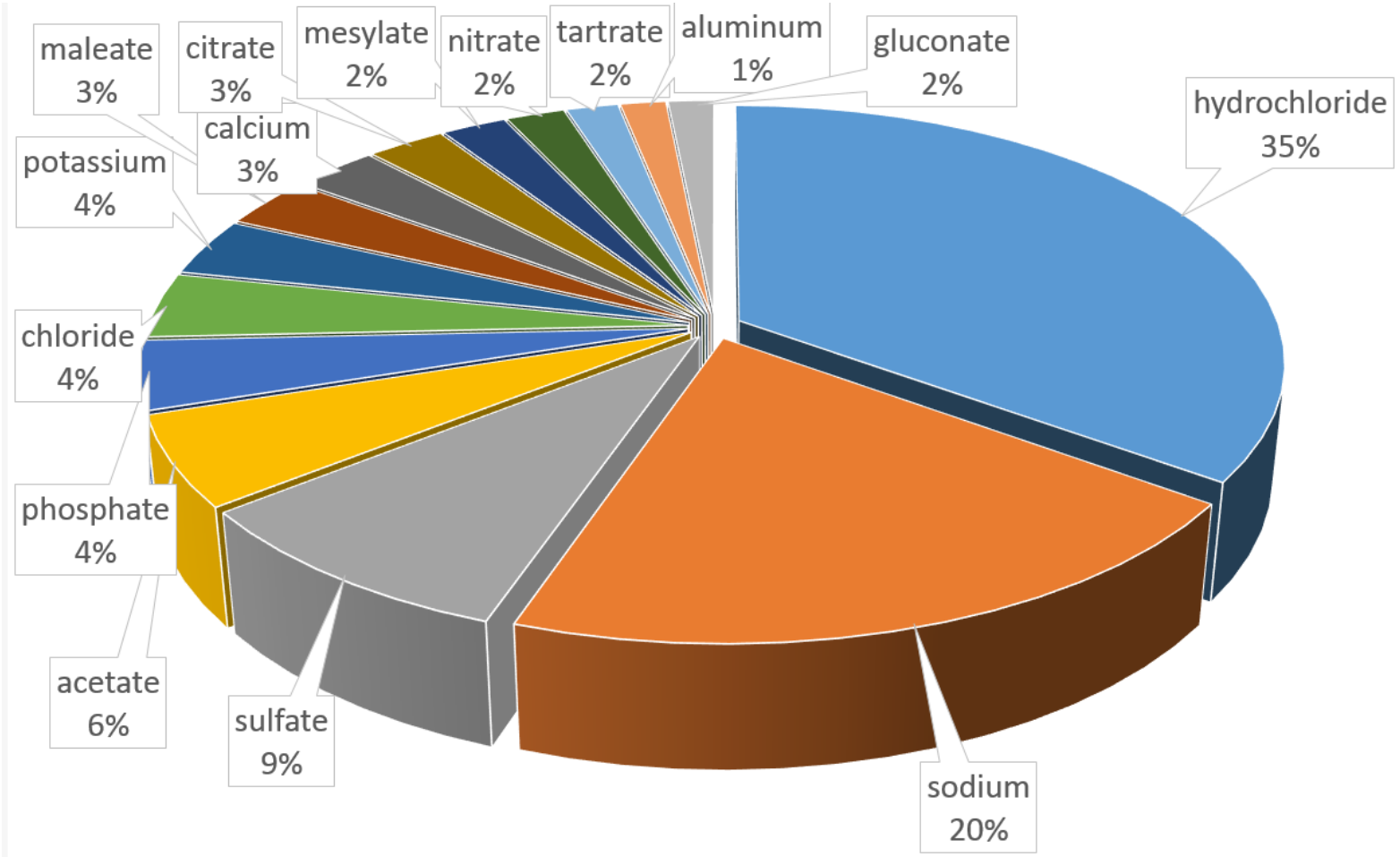
Drug development



Dunne et al., BMC Pharmacology & Toxicology 2013, 14. 1

Salts

~ 50 % of commercialized API are salts



Equivalent / alternative drugs

Pharmaceutically **equivalent** drugs	Pharmaceutically **alternative** drugs
Same active ingredient (API)	Same active ingredient (API)
Possibly different inactive ingredients (excipients, stabilizers, dyes, flavouring agents…)	Possibly different inactive ingredients (excipients, stabilizers, dyes, flavouring agents…)
Same **salt**, ester, complex	Different **salt**, ester, complex
Same dosage forms	Different dosage forms
Same release rate	Different release rate
Same solubility	Different solubility

Therapeutically equivalent (same clinical effect and safety profile)

Biologically equivalent (same metabolic target, but generally different pharmacokinetics)

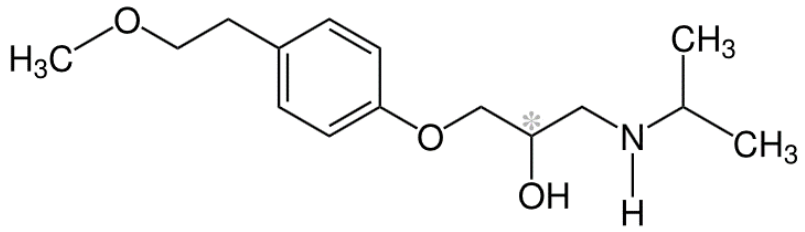
Advantages of salts

Liquids are more difficult to purify and maintain in pure form

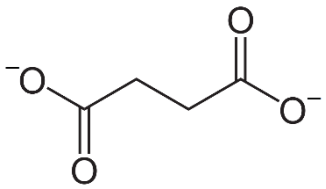
Solids are easier to stock and transport

Higher melting points often mean improved milling and compactability

Control of dissolution rates (and timing of API release)

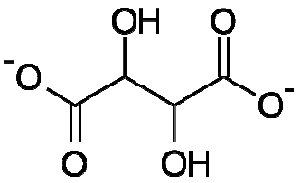


Metoprolol



Succinate

Slow release rate, more lipophilic



Tartrate

Fast release rate, more hydrophilic

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Disadvantages of salts

Gould, Int. J. Pharm. 1986, 33, 1-3, 2011-2017
Kumar et al., Pharm. Technol. 2008, 32, 128-146

Careful **salt selection study** needed

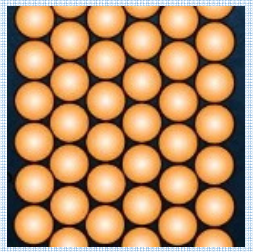
Table Ib: Disadvantages of salt formation for drug properties.

Disadvantage of salt formation
Decreased percentage of active content of drug candidate in the formulation: • Inactive counterions generally represent 20–50% of the weight of the drug substance • Increased powder volume causes problems for tableting and capsule filling (the tablet or capsule must be small enough to be easily swallowed) or patient compliance
Increased formation of hydrates and polymorphs, resulting in greater variability of the drug's pharmaceutical properties
Reduced dissolution rate or solubility for hydrochloride salts in gastric fluid resulting from precipitated free acid or base at the surface of the solid dosage form
Increased chance of poor solid-state stability at the microenvironment pH of the salt
Corrosiveness of salts, resulting in tableting problems (e.g., highly acidic hydrochloride salts damage punch tooling)
Possible disproportionation (dissociation) of hydrochloride or hydrobromide, resulting in the release of hydrohalide gas or reaction with excipients or process-related chemicals
Additional step in the synthesis of a medicinal compound

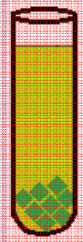
Salt selection study

Most critical

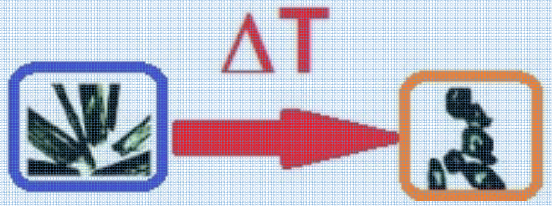
Crystallinity



Solubility (T, pH)



To Identify the salt form most suitable for further development and clinical trials



Stability (degradation and polymorphism)

Hygroscopicity

Salt selection study

Criteria for salt formers

Class	Criteria	Example	
		Acids	Bases
1	Salt formers that can be used without restriction because they contain physiologically ubiquitous ions and/or ions that occur as intermediate metabolites in biochemical pathways. Frequently used in the past and present	Acetic, citric, fumaric, maleic, hydrochloric, sulphuric, succinic	L-Arginine, calcium, lysine, magnesium, sodium, potassium
2	Salt formers that while not naturally occurring have through a number of applications shown low toxicity and good tolerability	Besylate, mesylate, napsylate nicotinate, tosylate,	Diethylamine, tromethamine,
3	Salt formers that are occasionally used, mainly for the purposes of achieving ion-pair formation. Sometimes suitable to solve particular problems	Nitric, formic, hydrobromide	Piperazine, ethylenediamine

Williams et al. Pharm. Rev. 2013, 65, 315-499

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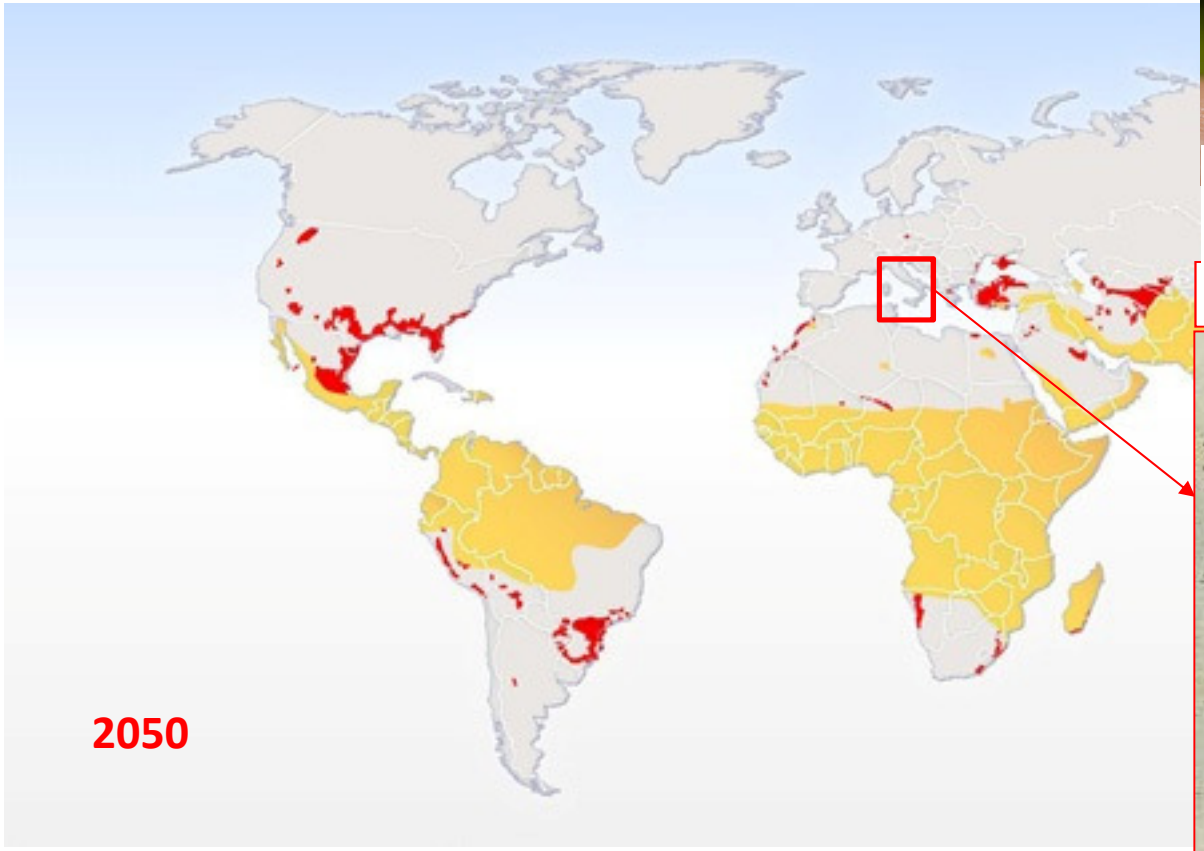
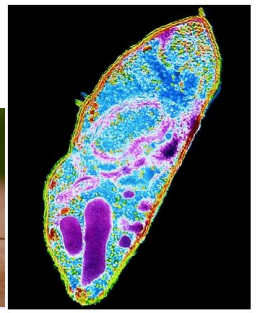
Malaria diffusion



Anopheles mosquito



P. Falciparum

Torelli, Map of malaria in Italy, 1882

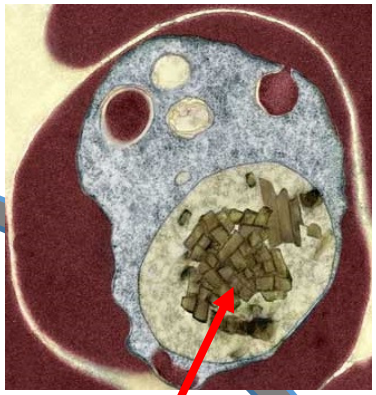
Siraj *et al*. *Science*, **2014**, *343*, 1154
Rogers, *Science*, **2000**, *289*,1763

Yellow: endemic

Red: next diffusion

Heme detoxification

'Malaria pigment'



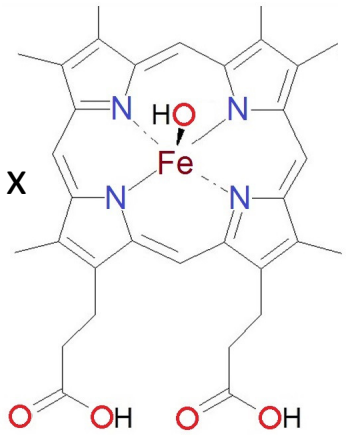
Parasite Digestive Vacuole (DV) pH ~ 4.5-5.5

Dimerization

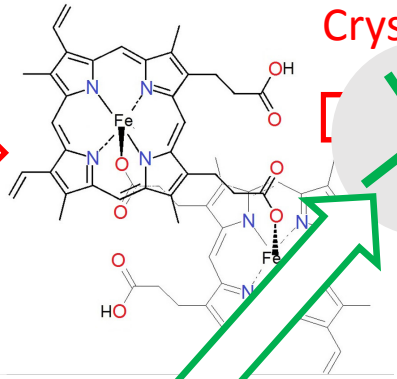
2 H_2O

Crystallization

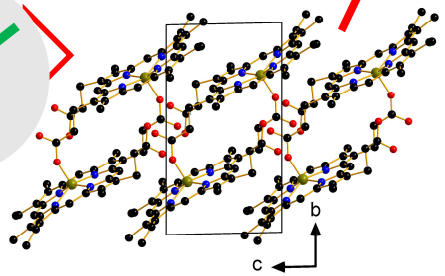
2 x



FePPIX(OH)H_2



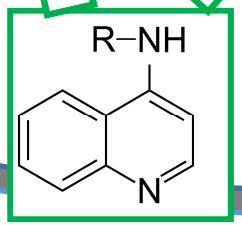
FePP ePPIXH)H



Hemozoin (natural)

β-Hematin (synthetic)

P $\bar{1}$

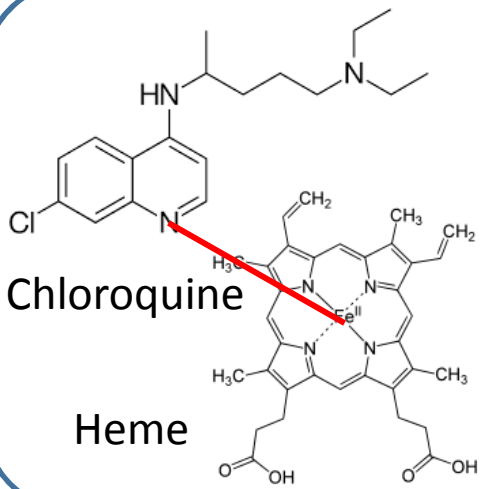


Aminoquinoline drugs

Pagola *et al. Nature*, **2000**, *404*, 307

Metabolic target

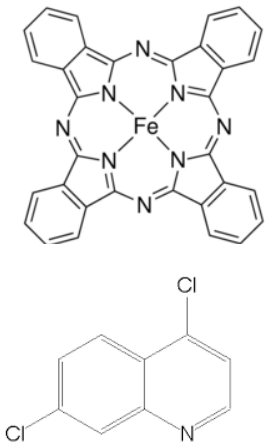
BM26A & ID26, ESRF, Grenoble (FR)



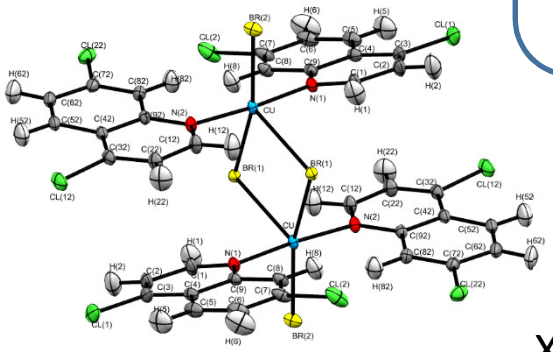
Chloroquine

Heme

Model systems

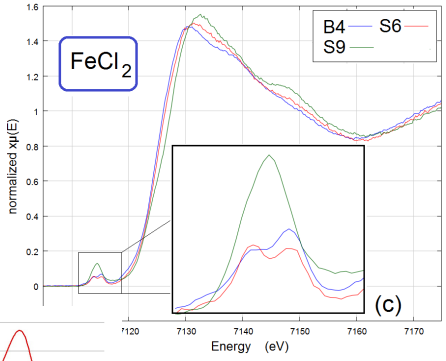


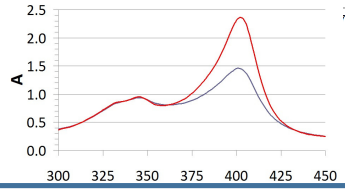
+ $CuBr_2$



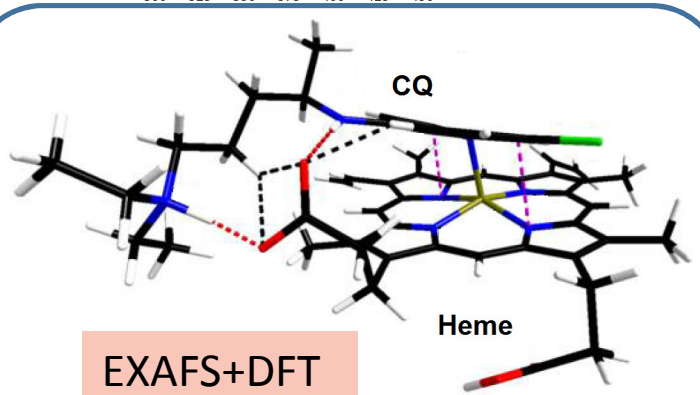
X-ray crystallography

XAS





UV-Vis



EXAFS+DFT

Macetti, Rizzato, Beghi, Silvestrini, Lo Presti, *Physica Scripta* **2016**, *91*, 023001

Macetti, Loconte, Rizzato, Gatti, Lo Presti, *Crystal Growth Des*. **2016**, *16*, 6043-6054

Finocchio, Rizzato, Lo Presti, *in preparation*

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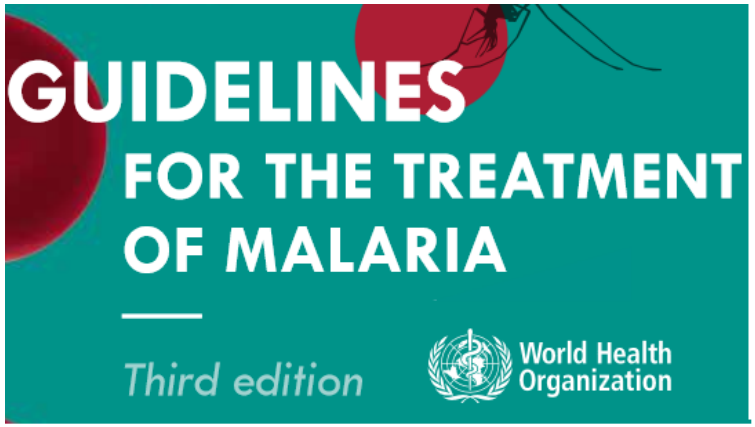
Piperaquine



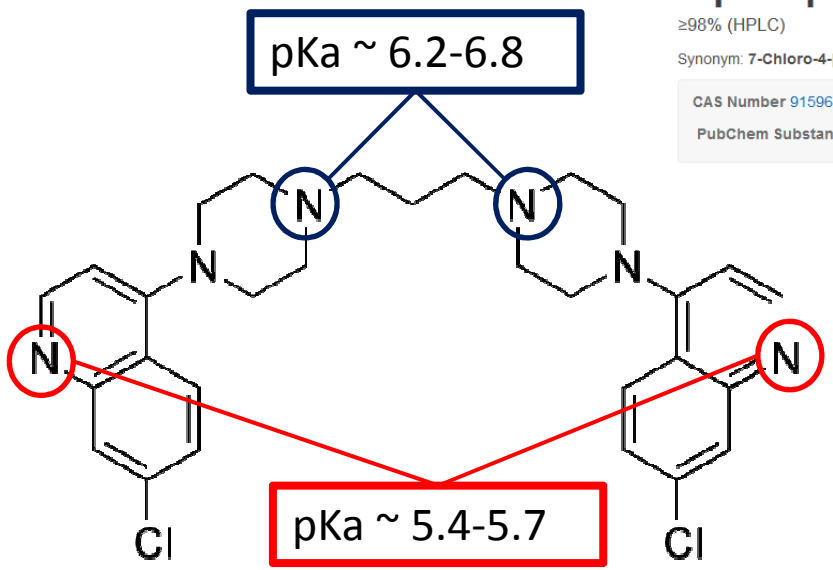
Treating uncomplicated *P. falciparum* malaria

Treatment of uncomplicated P. falciparum malaria

Treat children and adults with uncomplicated *P. falciparum* malaria (except pregnant women in their first trimester) with one of the following recommended artemisinin-based combination therapies (ACT):

- artemether + lumefantrine
- artesunate + amodiaquine
- artesunate + mefloquine
- dihydroartemisinin + piperaquine
- artesunate + sulfadoxine–pyrimethamine (SP)

Strong recommendation, high-quality evidence



Piperaquine, PQ

C7874 Sigma-Aldrich

Piperaquine tetraphosphate tetrahydrate

≥98% (HPLC)

Synonym: **7-Chloro-4-[4-[3-[4-(7-chloroquinolin-4-yl)piperazin-1-yl]propyl]piperazin-1-yl]quinoline**

CAS Number 915967-82-7 | **Empirical Formula (Hill Notation)** $C_{29}H_{32}Cl_2N_6 \cdot 4H_3PO_4 \cdot 4H_2O$ | **Molecular Weight** 999.55 | **MDL number** MFCD11870901

PubChem Substance ID 329775155

$PQH_4^{4+}(H_2PO_4^-)_4 \cdot 4H_2O$

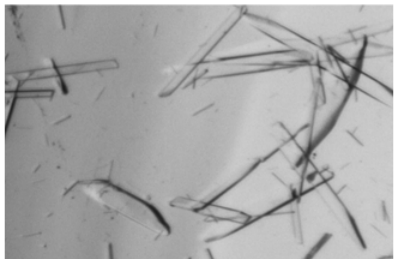
Poorly soluble in water → Reduced oral bioavailability

No other PQ salts are known

Possibility to improve formulation?

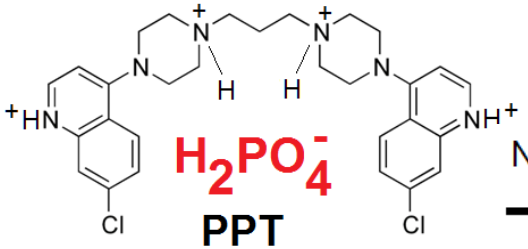
Synthesis

Sacchi, Loconte, Macetti, Rizzato, Lo Presti, *Crystal Growth Des.* **2019**,*19*, 1399-1410

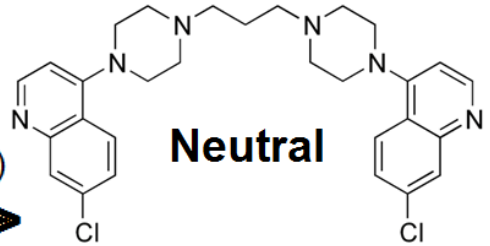


Class 1

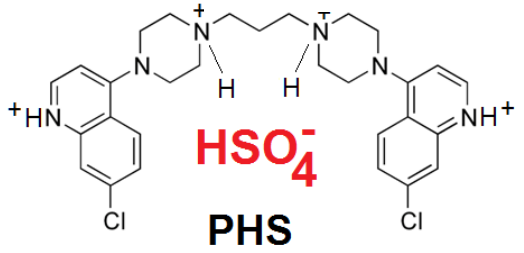
Hydrogen phosphate



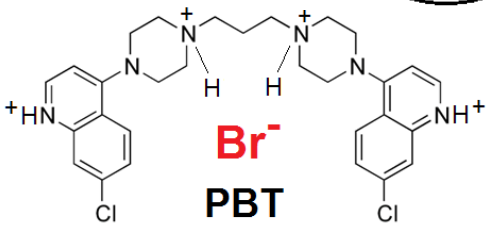
NH_3 (aq)



H_2SO_4 conc.
55 °C

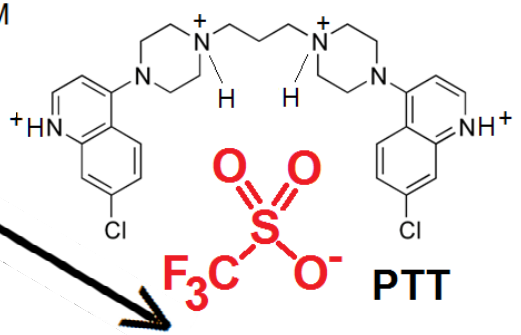


HBr conc.
AcOH 10 M

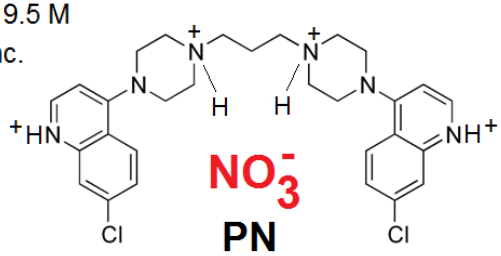


Recrystallization
$CHCl_3$

CF_3SO_3H 4.2 M
AcOH 10 M

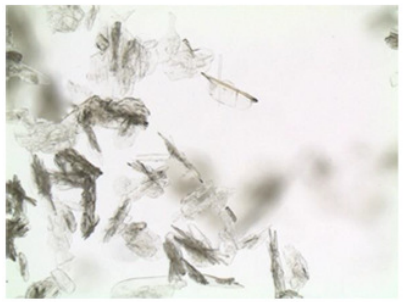


HNO_3 aq. 9.5 M
HNO_3 conc.



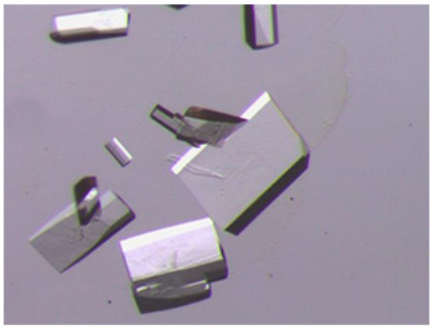
Unknown

Triflate



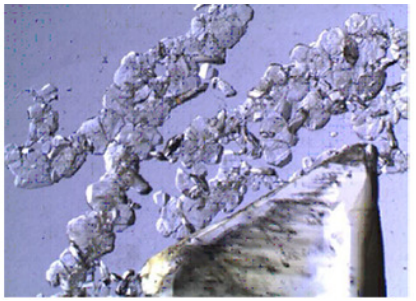
Class 1

Hydrogen sulphate



Class 3

Bromide



Class 3

Nitrate

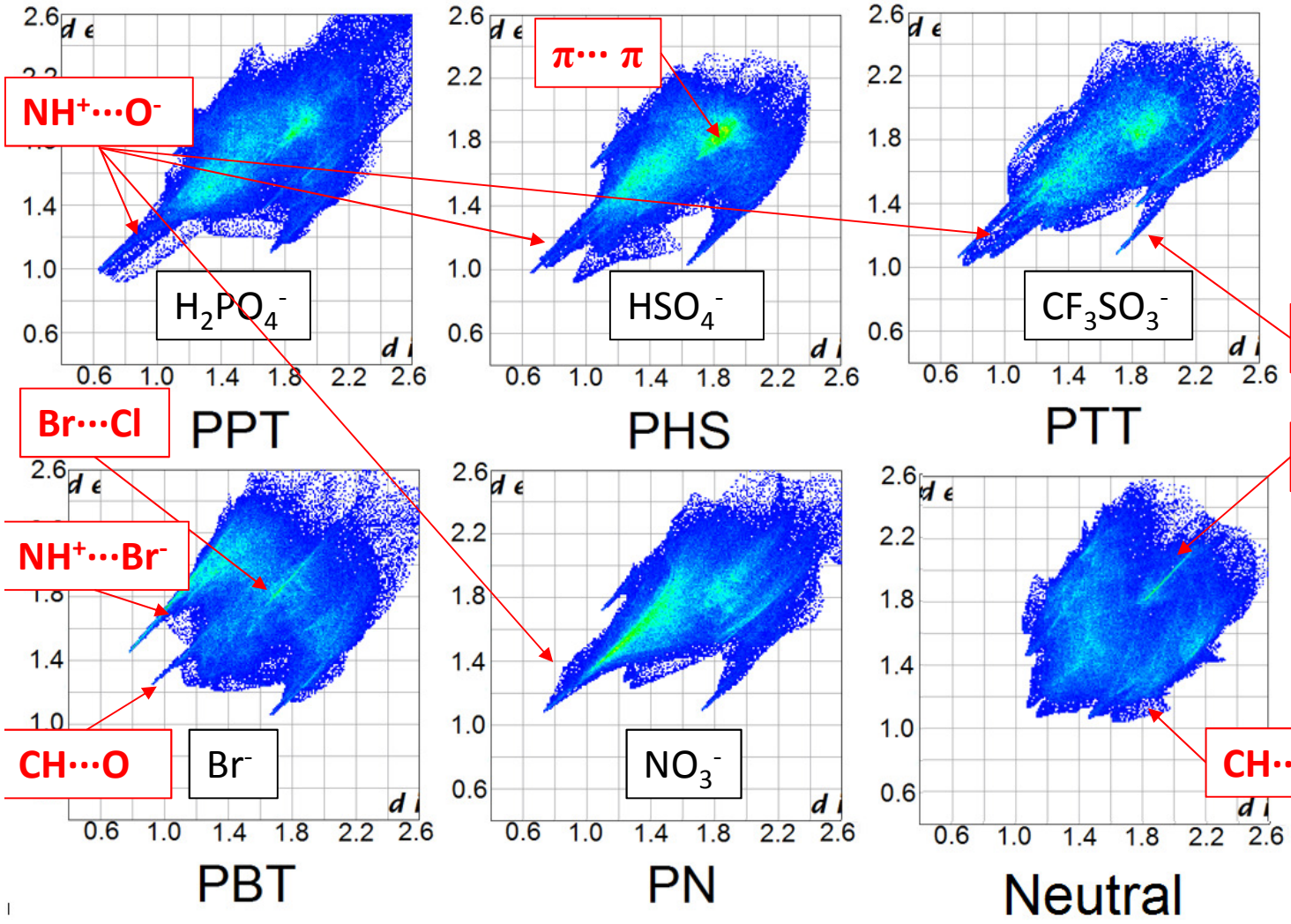
Salts

Counterion	Label	Habit	Disorder	Water content	Space group
None	Neutral	Prism	No	No	$P2_1/n$
$H_2PO_4^-$	PPT	Needles	Rotational (2 $H_2PO_4^-$) + water	>4	$P2_1/n$
HSO_4^-	PHS	Needles	Rotational (all HSO_4^-) + water	~6.6 + 1 H_3O^+	Cc
$CF_3SO_3^-$ (triflate)	PTT	Plates	Rotational (1 $CF_3SO_3^-$) + water	3	C2/c
Br^-	PBT	Prisms	No	3 + 1 H_3O^+	$P\bar{1}$
NO_3^-	PN	Prisms	No	No	$P\bar{1}$

Sacchi, Loconte, Macetti, Rizzato, Lo Presti, *Crystal Growth Des.* **2019**,*19*, 1399-1410

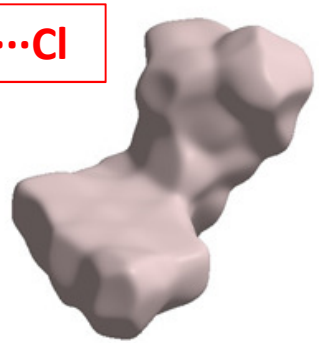
Single crystal X-ray diffraction
Max resolution: 0.77-0.71 Å
Completeness: 99.3-100 %
R_{int} = 0.019-0.033
120 K – RT

Crystal packing

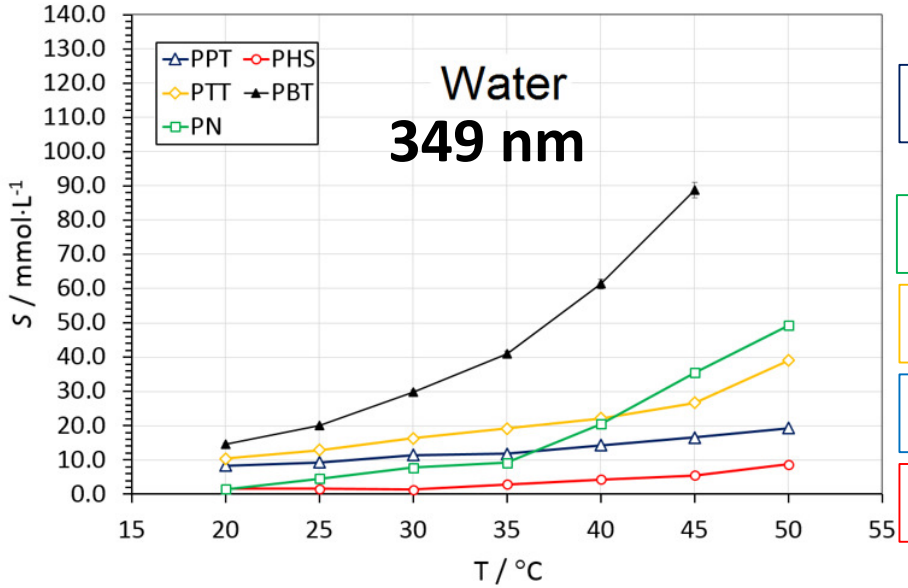


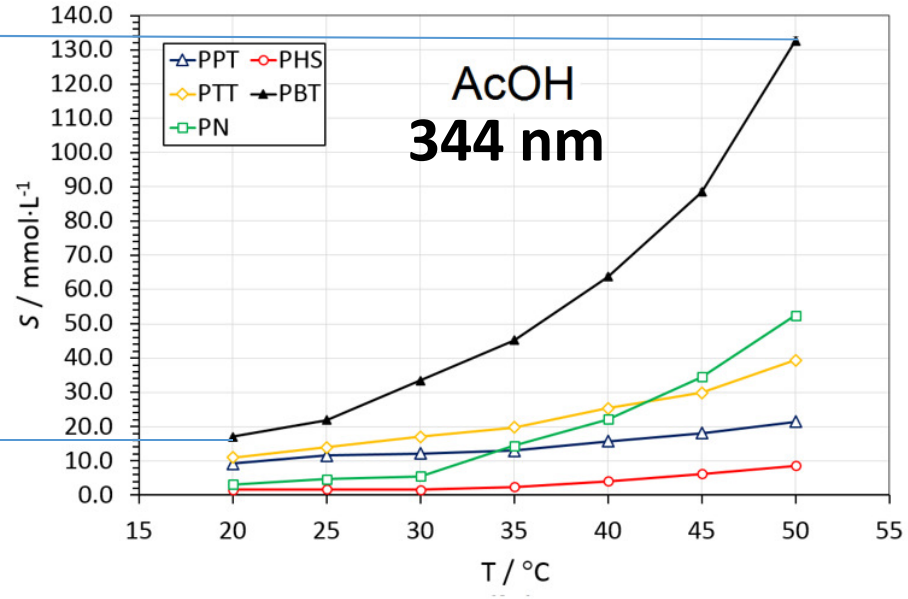
Hirshfeld surface fingerprint plots

$$w_j(\mathbf{r}) = \frac{\rho_j^{promol}(\mathbf{r})}{\rho^{procryst}(\mathbf{r})}$$



Solubility





+740%

Br^-

NO_3^-

$CF_3SO_3^-$

$H_2PO_4^-$

HSO_4^-

Br^-

NO_3^-

$CF_3SO_3^-$

$H_2PO_4^-$

HSO_4^-

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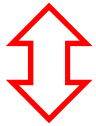
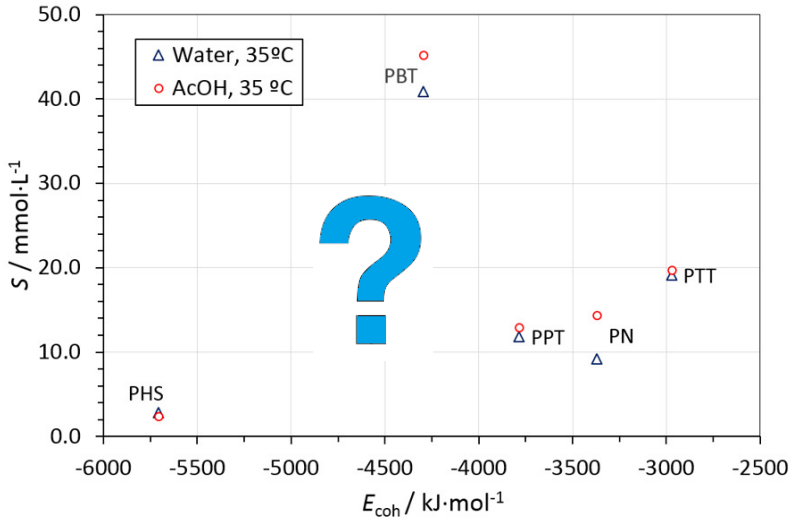
Understanding Solubility

Solubility



Cohesive Lattice energies

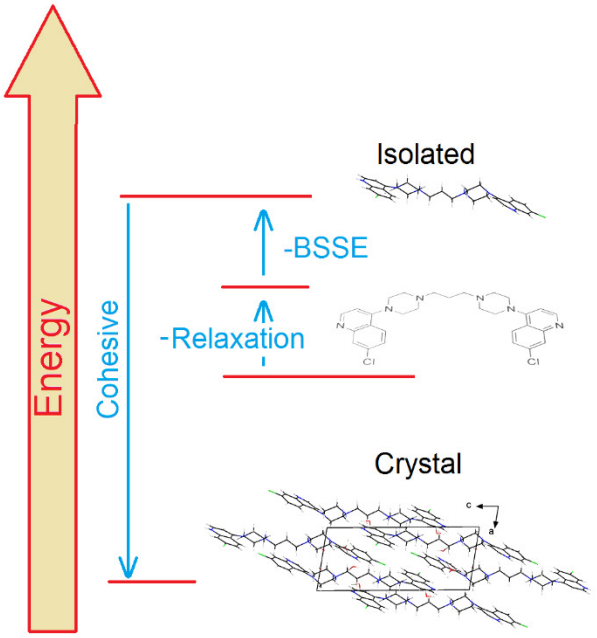


The model lacks of:

- Solute-solvent interactions
- Entropic effects

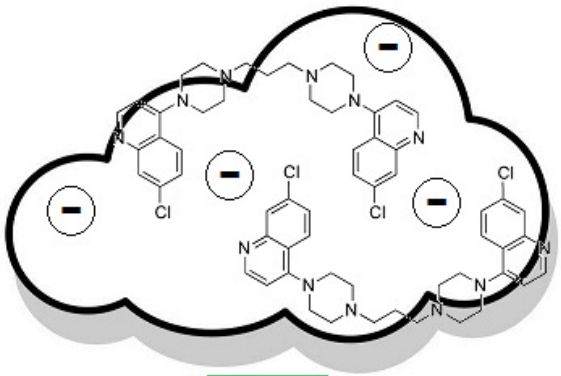
DFT M06

$$E_{\mathrm{coh}} = E_{\mathrm{bulk}} - \sum_{i=1}^{n}\left(E_{\mathrm{iso},i} + \Delta E_{\mathrm{rel},i} - \Delta E_{\mathrm{BSSE},i}\right)$$



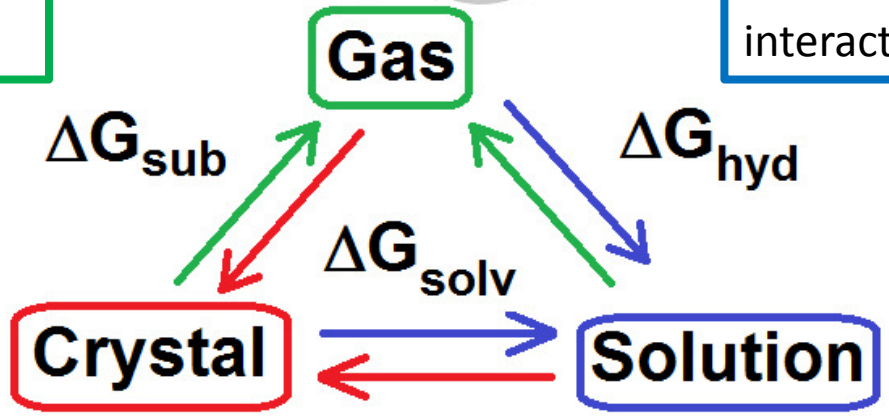
Estimating solvation energies

Sacchi, Loconte, Macetti, Rizzato, Lo Presti, *Crystal Growth Des.* **2019**,*19*, 1399-1410



Strength of crystal cohesion

Solute-solvent interactions



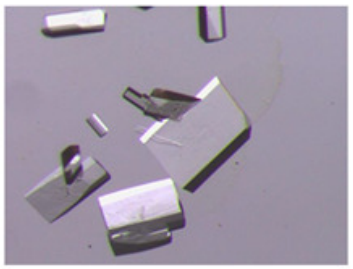
Skyner et al., PCCP 2015, 17, 6174

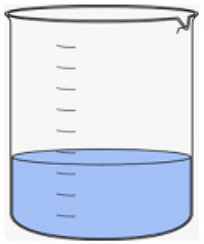
Crystalline molar volume

$V_m = N_A V_{cell}/(Z \cdot Z')$

$\Delta G_{solv} = -\mathrm{RTln}(S \cdot V_m)$

Experimental solubility





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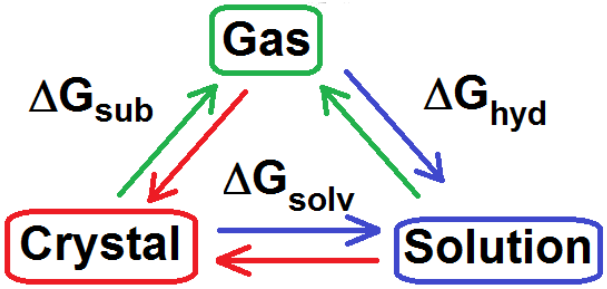
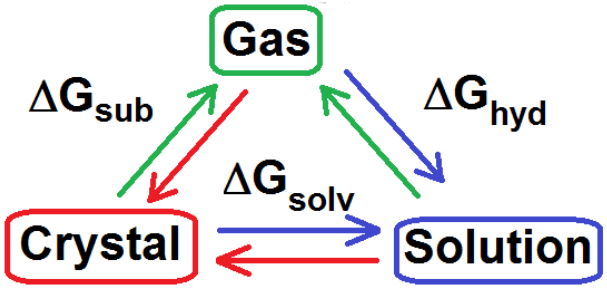
Crystal cohesion



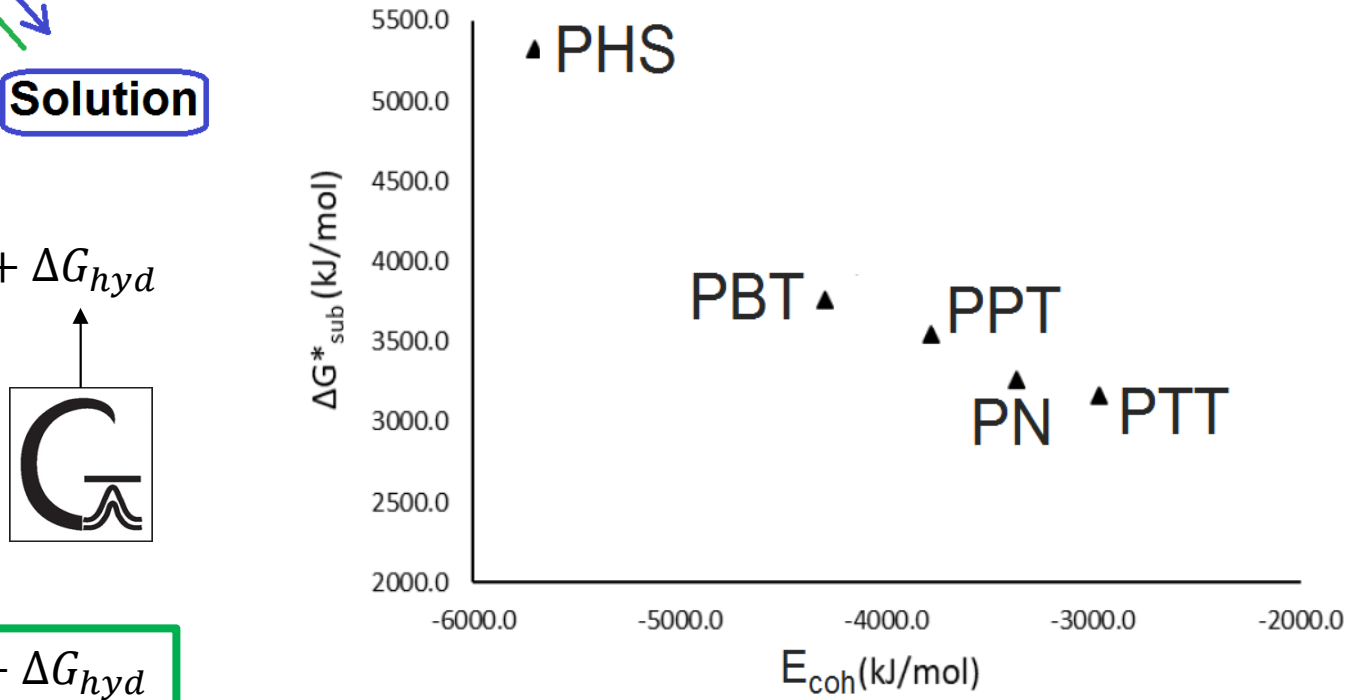
Sacchi, Loconte, Macetti, Rizzato, Lo Presti, *Crystal Growth Des.* **2019**,*19*, 1399-1410

Crystal cohesion



$$\Delta G_{solv} = \Delta G_{sub} + \Delta G_{hyd}$$

Experiment



$$\Delta G_{sub} = \Delta G_{solv} - \Delta G_{hyd}$$

Sacchi, Loconte, Macetti, Rizzato, Lo Presti, *Crystal Growth Des.* **2019**,*19*, 1399-1410

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Entropic term

$$\Delta S^0_{solv} \cong \Delta S^0_{sub}$$

$$\Delta S^0_{solv} \approx \Delta S^o_{sub} = 1/T\,(\Delta H^o_{sub} - \Delta G^o_{sub})$$

$$\Delta H^o_{\mathrm{sub}} = -E_{\mathrm{coh}} - 2 \cdot \mathrm{R}T$$

From quantum simulations in the solid state

$$\Delta G_{sub} = \Delta G^o_{sub} - RT ln \left[\frac{V_m p_0}{RT}\right]$$

Conversion to standard p, T state

Assumptions:

(1) ΔS crystal → gas ≈ ΔS crystal → solution

(2) Ensemble of non–interacting species

Sacchi, Loconte, Macetti, Rizzato, Lo Presti, *Crystal Growth Des.* **2019**,*19*, 1399-1410

Most soluble
Softest anion
High ΔS_{solv}

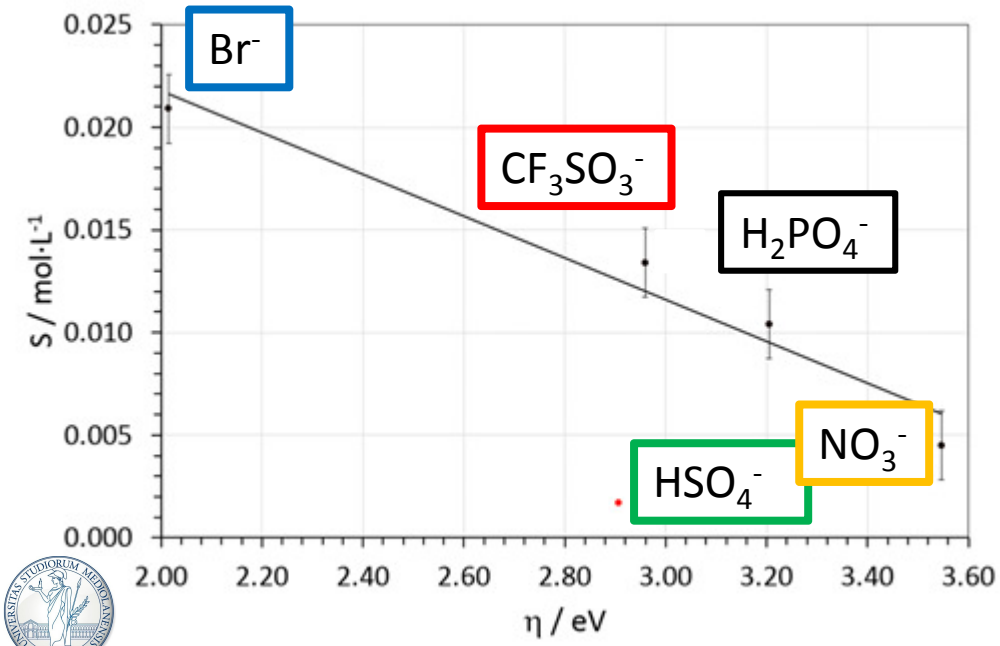
Results

$$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})/2$$

Quantities referred to 25 ºC

PQH_4^{4+}: hard acid

Substance	S / mol·L^{-1}	ΔS^o_{solv} / kJ·mol^{-1}·K^{-1}	ΔG^o_{sub} / kJ·mol^{-1}	η(anions) /eV
$H_2PO_4^-$	0.0104	2.02	3543.8	3.20
HSO_4^-	0.0017	2.09	5326.8	2.91
$CF_3SO_3^-$	0.0134	0.51	3162.3	2.96
Br^-	0.0209	2.04	3756.4	2.02
NO_3^-	0.0045	1.11	3263.4	3.55



Lowest cohesive energy
But: low ΔS_{solv} and ΔG_{hyd}

Hardest anion

Highest cohesive energy
(largest Coulomb interactions)

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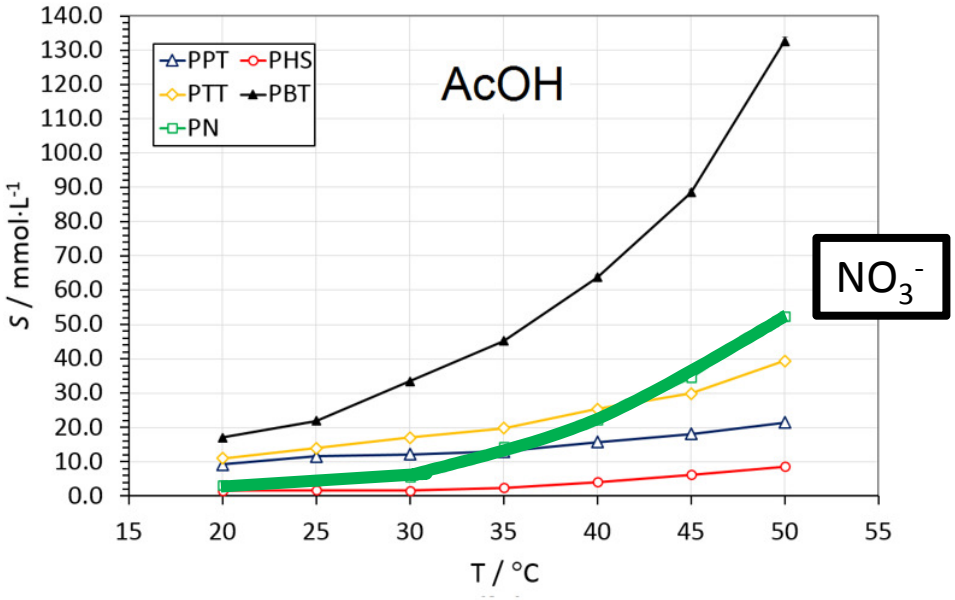
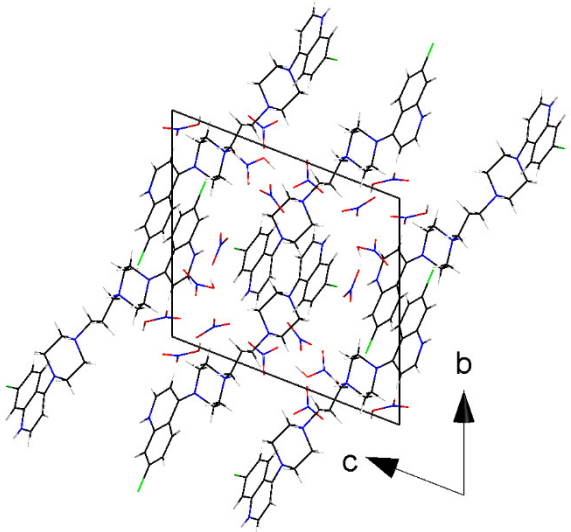
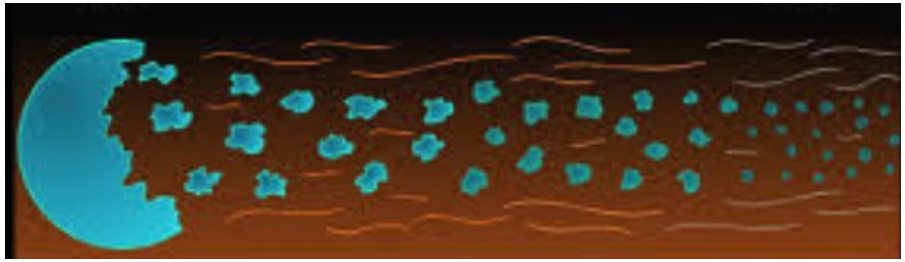
The behaviour of nitrate





No water and no disorder



Highest entropy gain upon dissolution than any other salt

The effect is more pronounced at higher T

Outline

(i) Motivation

(ii) Malaria

(iii) The case of piperaquine

(iv) Conclusions

Conclusions

Five salts of piperaquine (PQ) were synthesized and characterized

π···π stacking modes, or the number and type of hydrogen bonds, have no direct effect on the observed solubilities

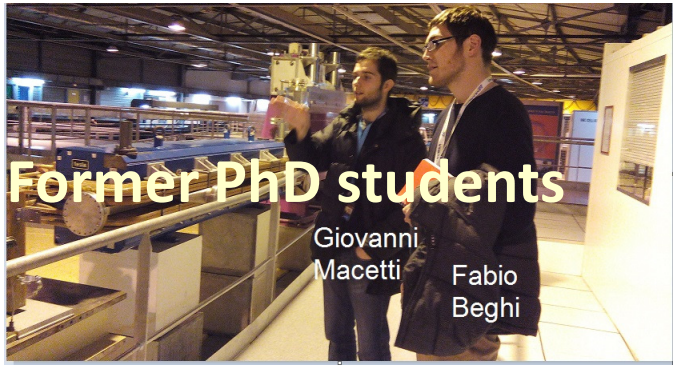
Solubility stems from cooperative effects. If the crystal cohesion is very large, it dominates; otherwise, the η of the anion plays a central role.

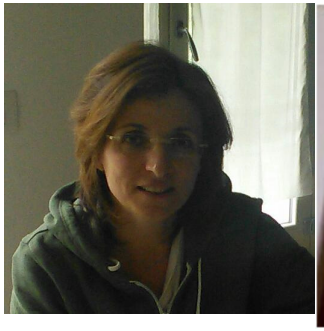
Fully ordered bromide and nitrate have solubilities that increase faster as *T* is raised

- Coupling of the drug with soft anions to increase solubility and improve bioavailability
- Low disorder to have salts more soluble at higher T

Acknowledgements

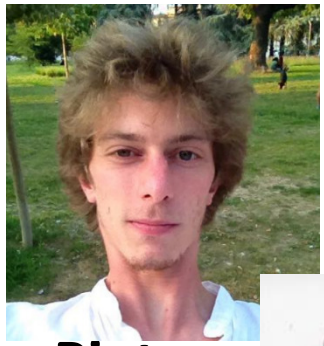
Prof. Silvia Rizzato





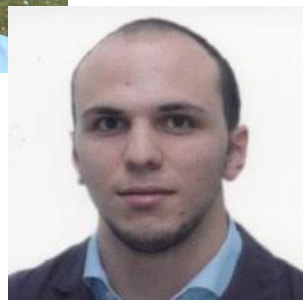
Dr. Laura Loconte

Dr. Lucia Silvestrini



Pietro Sacchi

Gers Tusha



Matteo Frigerio

Giada Finocchio

Funding:
Development Plan for 2016-2017 (project NOVAQ)

ISCRA C initiative
(Project MODELPIP)

Italian Crystal Growth 2020

Thank you for your kind attention

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