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Combining Rapid Isomer Separations and Physicochemical Property Predictions for Drug Molecules with Differential Mobility Spectrometry

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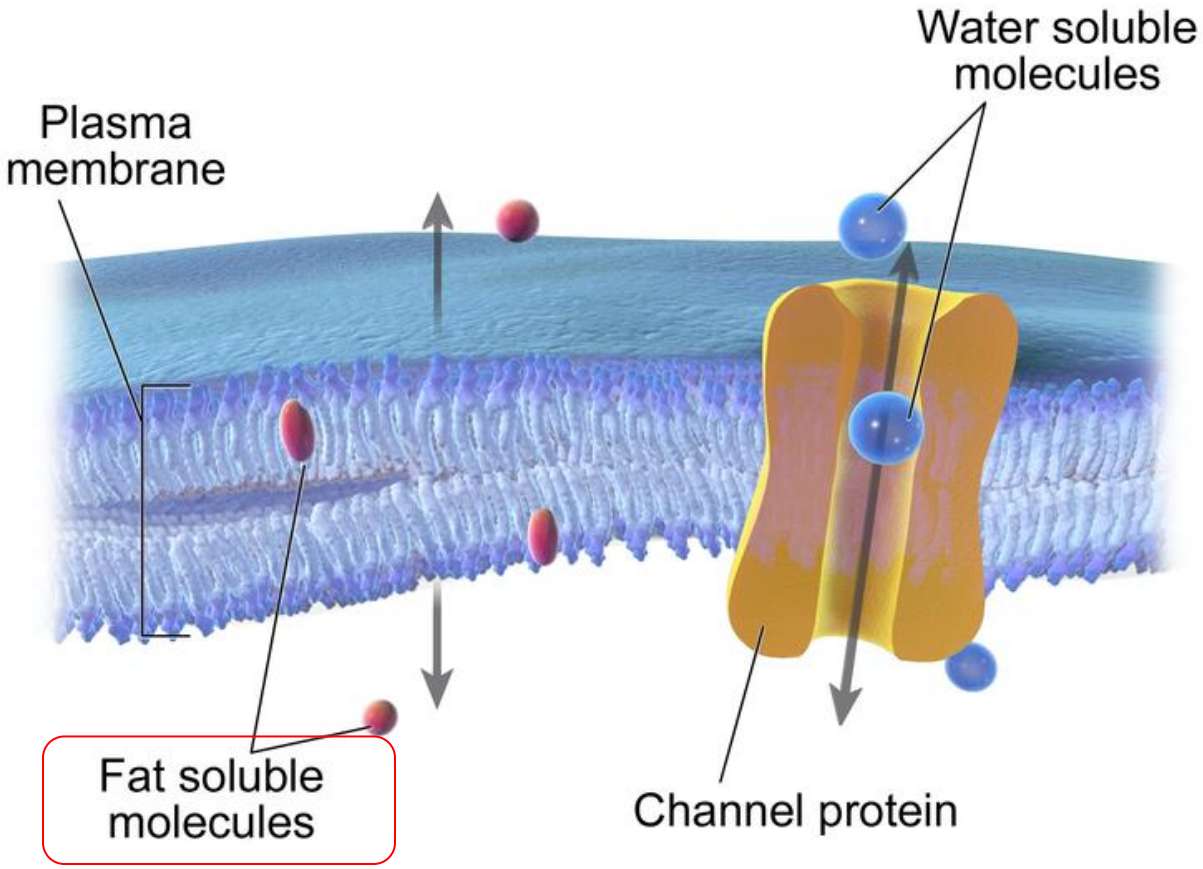
ASMS 2016, San Antonio, June 6th, 2016

Drug designers are keen to speed up drug development



Good cell permeability

↓

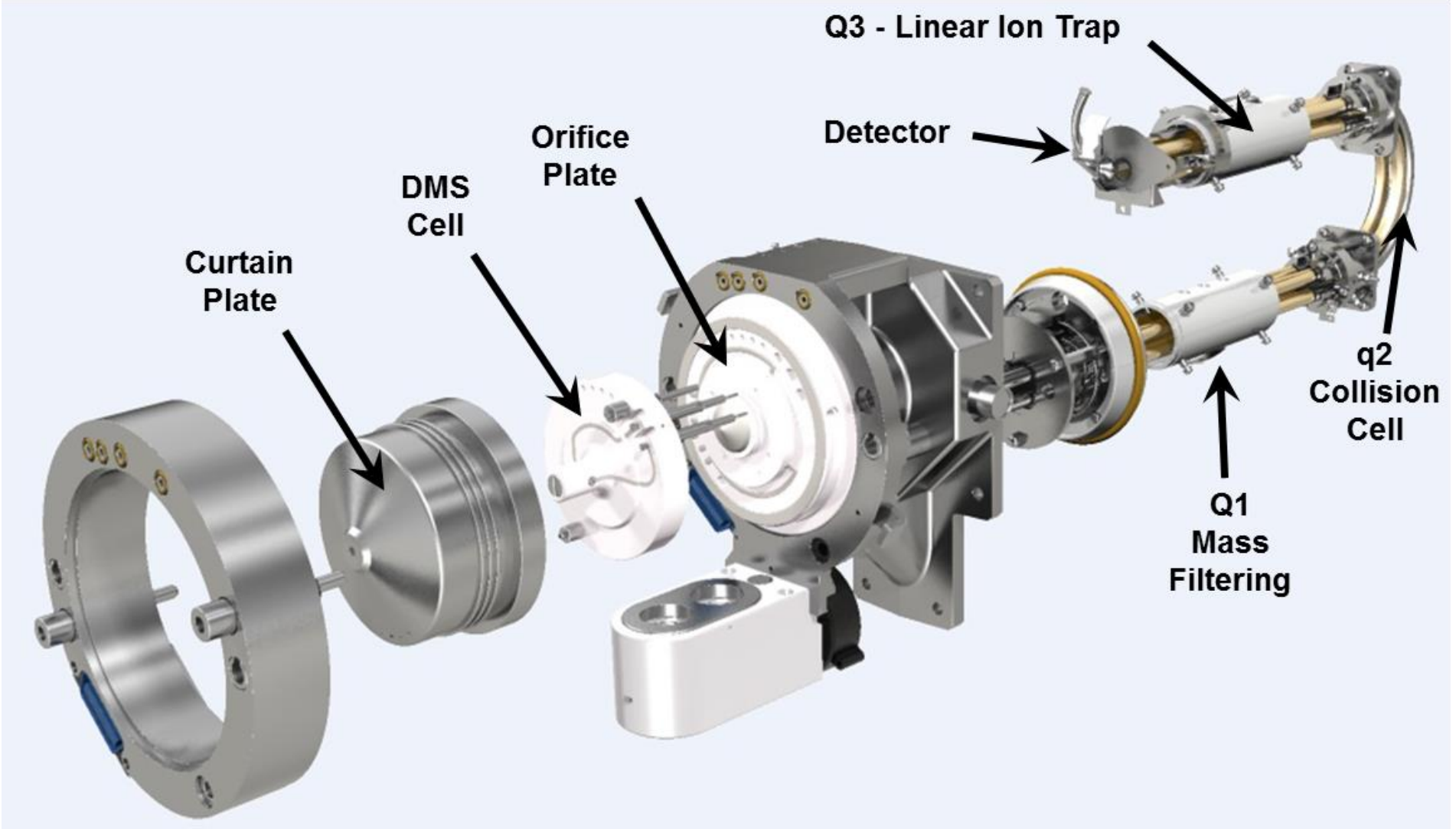
Good drug transport

↓

Good drug candidate

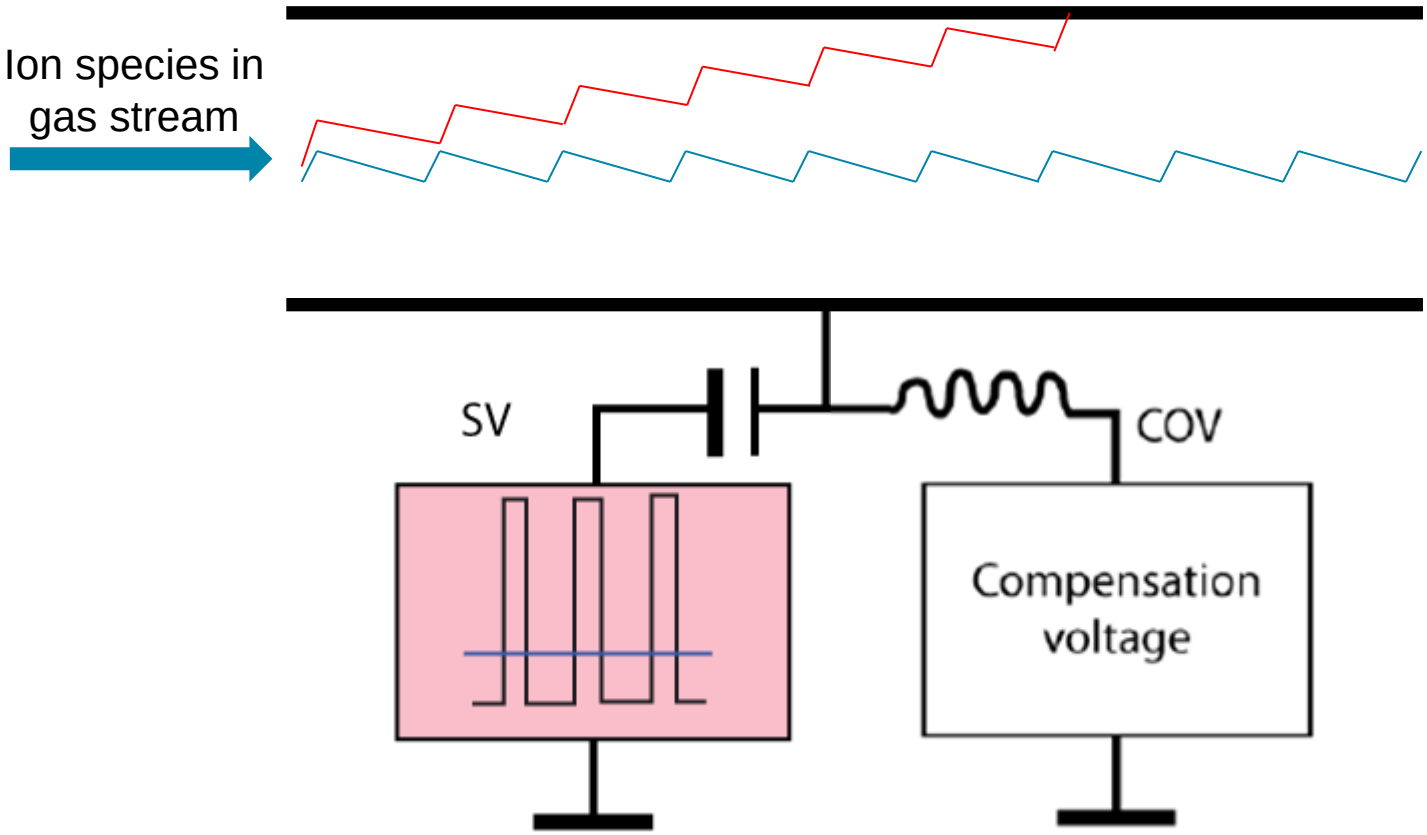
Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine.

Differential mobility spectrometry (DMS)



SCIEX SelexION® Differential Mobility Spectrometer with QTRAP® 5500 Mass Spectrometer System

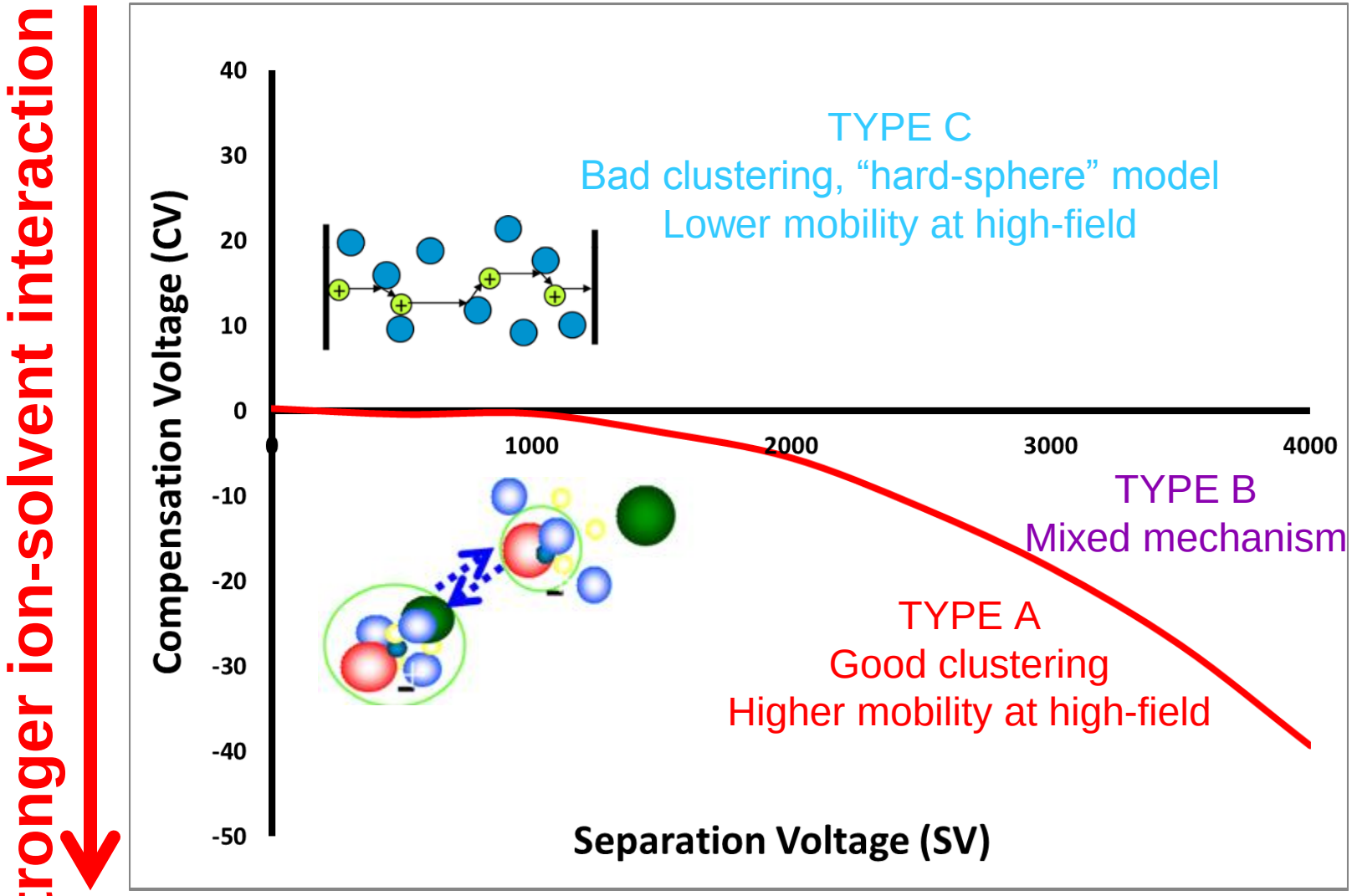
Differential mobility spectrometry (DMS)



The magnitude of the compensation voltage is a measure of the ion-solvent interaction.

Krylov and Nazarov, *Int. J. Mass Spectrom.* **2009**, *285*, 149.

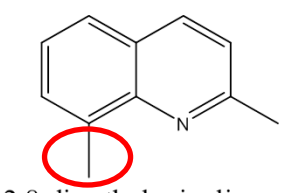
Three types of DMS behaviors



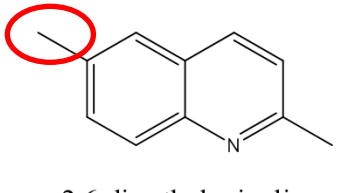
Purves and Guevremont, *Anal. Chem.* **1999**, *71*, 2346

Isomer separation with DMS

Steric effects can be a dominating factor in isomer separation

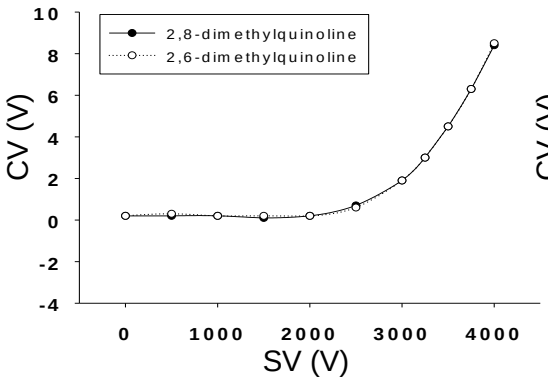


2,8-dimethylquinoline



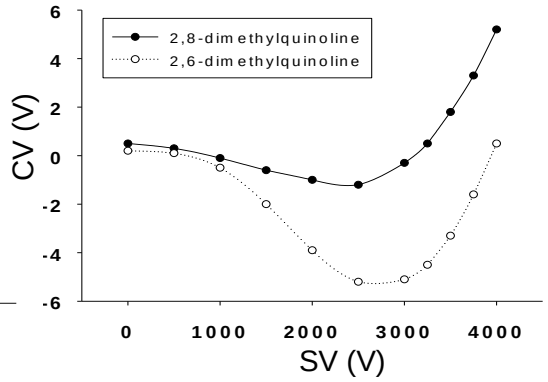
2,6-dimethylquinoline

No modifier (N_2 Only)



Type C

Water

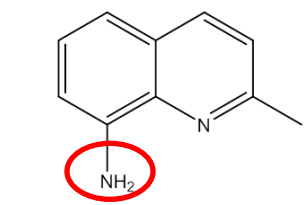


Type B

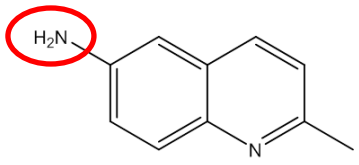
Liu et al., *Analyst*, **2015**, *140*, 6897-6903.

Isomer separation with DMS

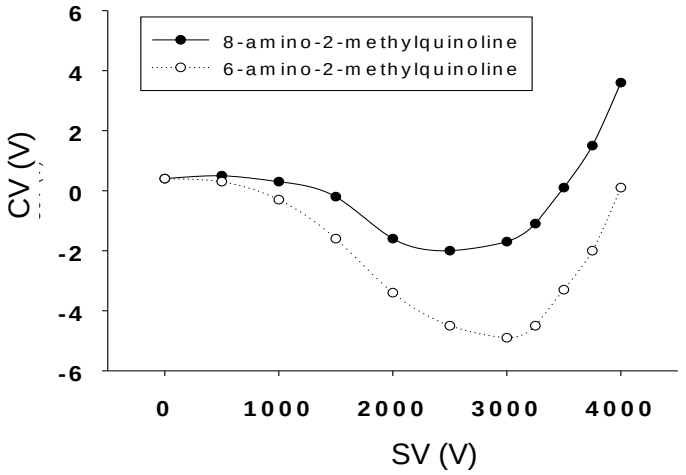
Steric effects can be a dominating factor in isomer separation in the presence of solvent (e.g., water, methanol)



8-amino-2-methylquinoline

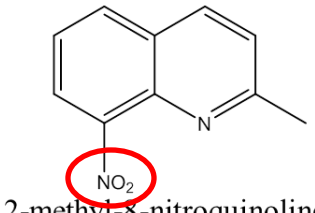


6-amino-2-methylquinoline

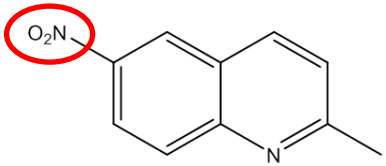


Water

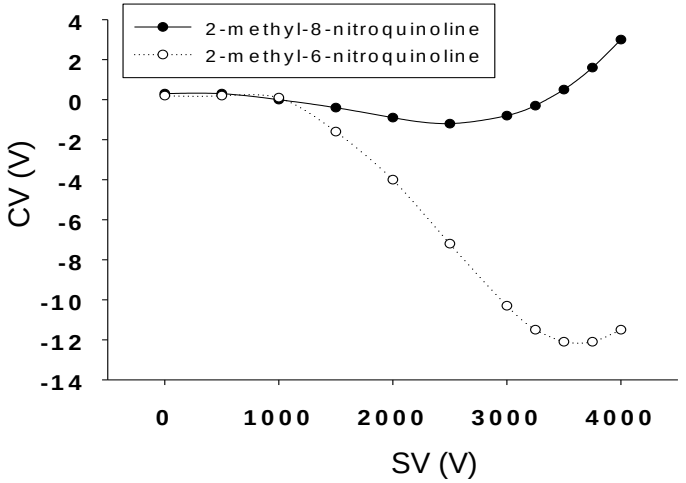
Type B



2-methyl-8-nitroquinoline



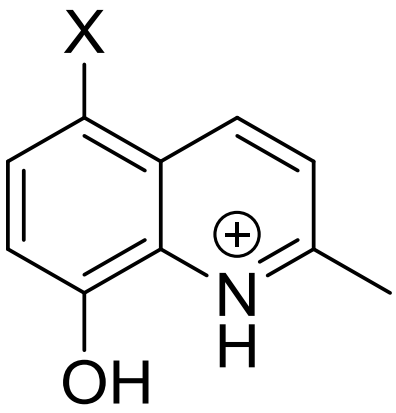
2-methyl-6-nitroquinoline



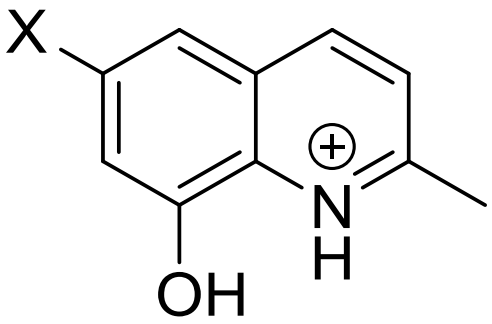
Liu et al., *Analyst*, **2015**, *140*, 6897-6903.

Isomer separation with DMS:
Next level drug molecules – Quinolin-8-ols

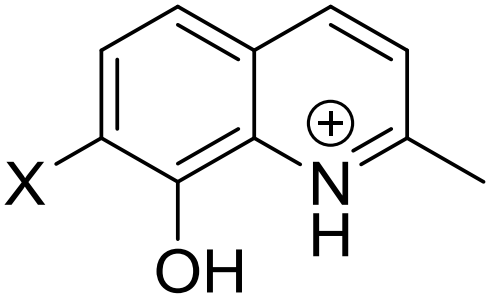
5-substituted
2-methyl-quinolin-8-ol



6-substituted
2-methyl-quinolin-8-ol

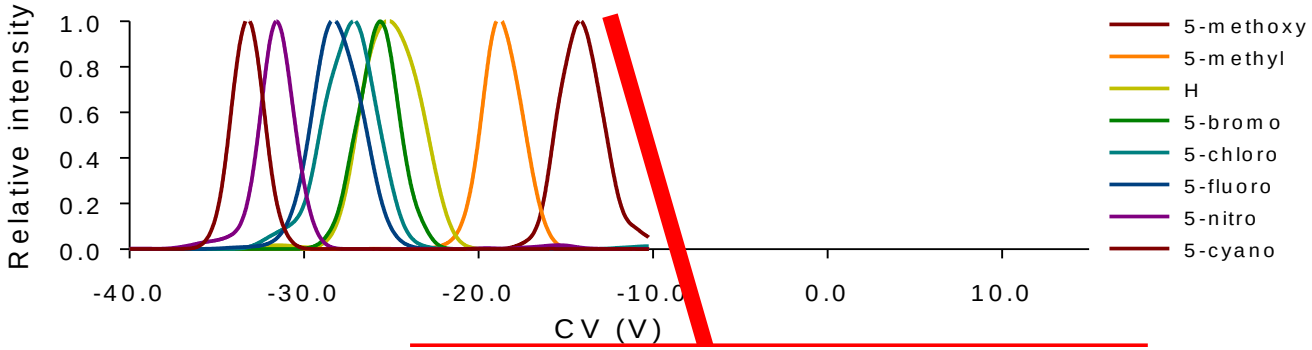


7-substituted
2-methyl-quinolin-8-ol

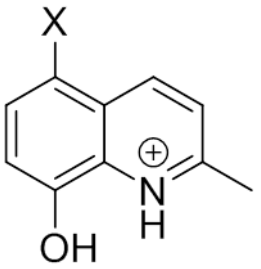


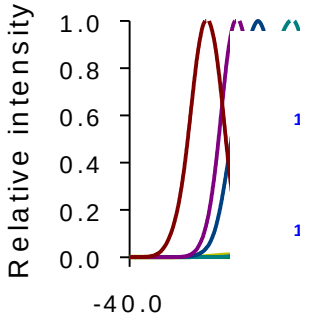
X = -OCH_3, -CH_3, -H, -Br, -Cl, -F, -NO_2, or -CN

DMS ionograms reveal ion/solvent interaction strength:
5-, 6-, and 7-substituted 2-methyl-8-hydroxyquinolines and MeOH

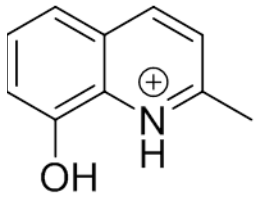


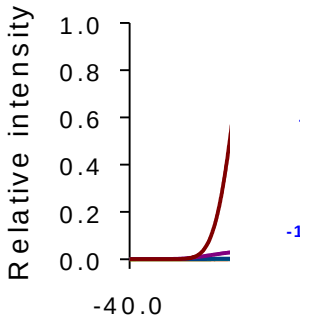
5-substituted
2-methyl-quinolin-8-ol



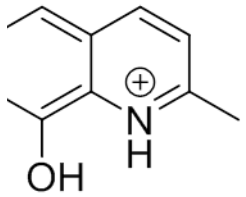


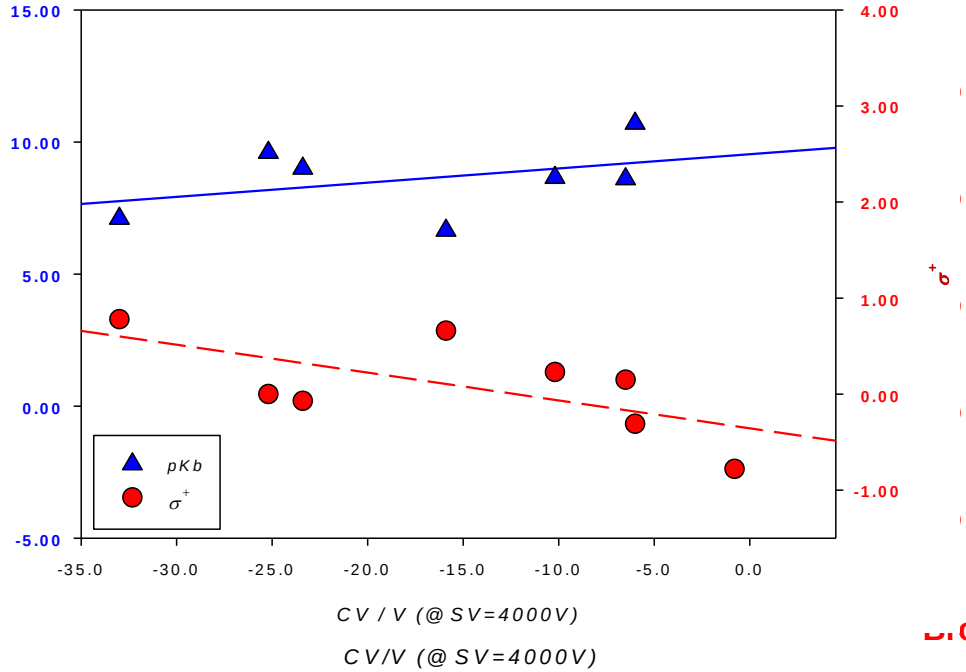
-substituted
hyl-quinolin-8-ol





-substituted
thyl-quinolin-8-ol



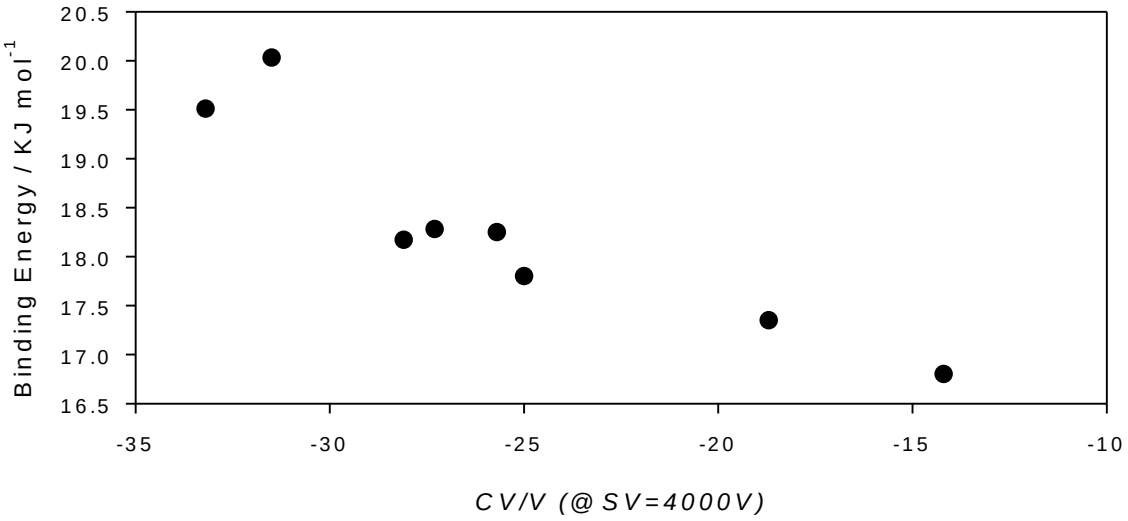


Brown and Okamoto

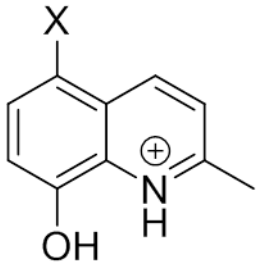
J. Am. Chem. Soc. 1958, *80*, 4979

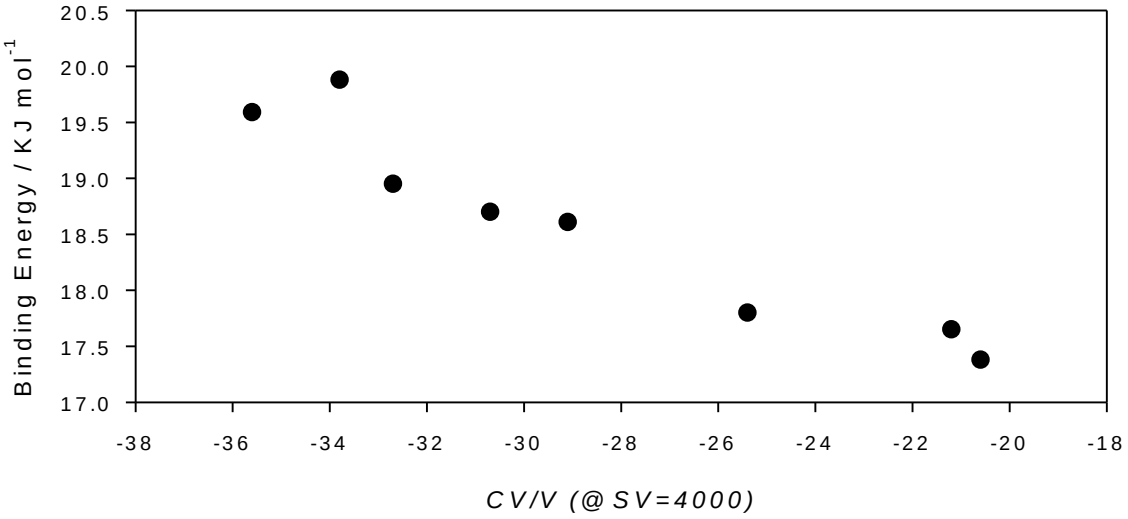
Cyano	.56	.562	.660	.659
Nitro	.710[b]	.674	.778[b]	.790

DMS correlation with calculated binding energy

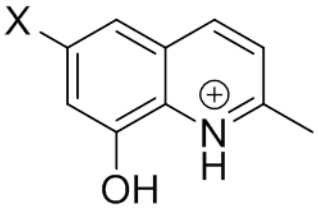


5-substituted
2-methyl-quinolin-8-ol



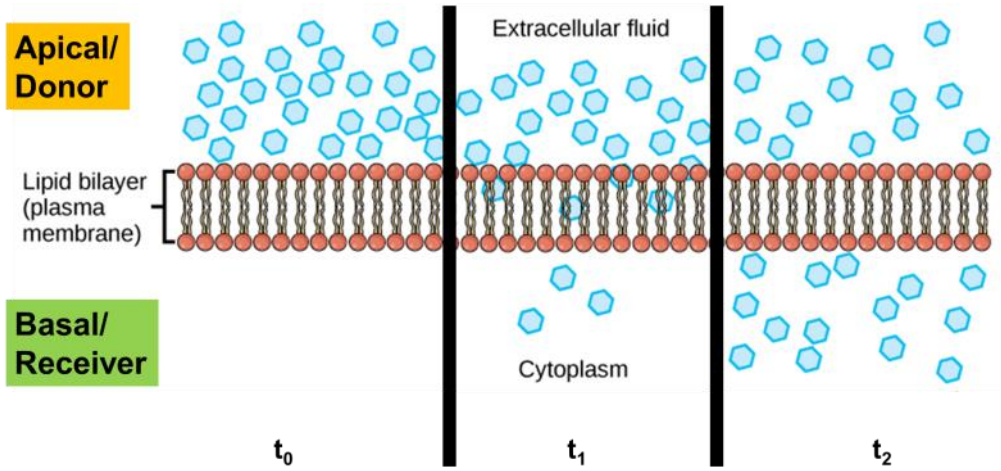


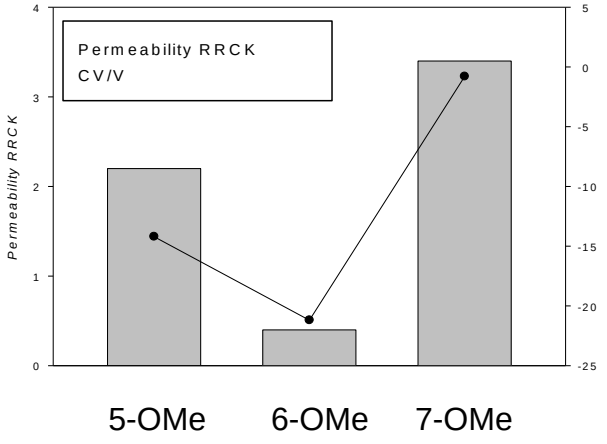
6-substituted
2-methyl-quinolin-8-ol

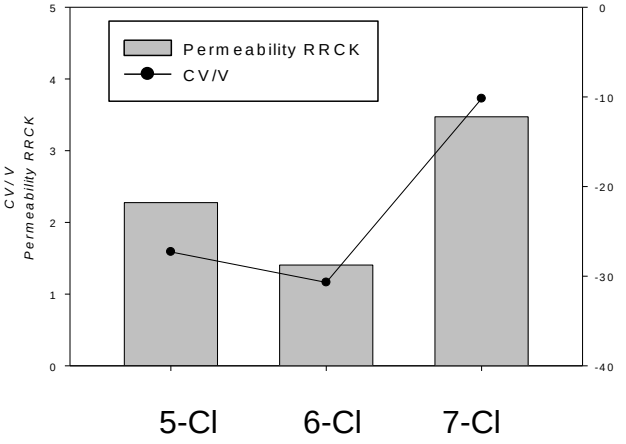


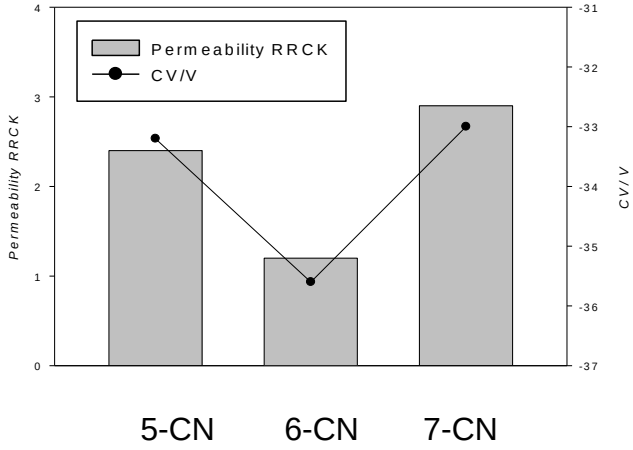
Wales and Doye, *J. Phys. Chem. A* 1997, *101*, 5111; Hopkins et al., *J. Phys. Chem. A* 2013, *117*, 10714

Cell permeability (RRCK) data among isomeric drug molecules also agrees with DMS









Li, D. et. al, *J. Pharm. Sci.* **2011**, *100*, 4974

Conclusions

- DMS is a powerful platform for isomer separations, for studying the ion-solvent interaction strength, and ...
- DMS shows promise as a fast approach to predict the cell permeability (RRCK) of drug candidates.
- Data strongly correlates to
  - calculated binding energies with solvent molecules
  - physical organic constants from the 1950s
  - RRCK data among isomeric drug molecules
  - pKa
- Both steric effect and electronic effect influence the ion-solvent interaction.
  - Steric effect: weak ion-solvent interaction when a bulk substituent is close to the charge site
  - Electronic effect: resonance structures disperse charge density and reduce ion-solvent interactions

Acknowledgements

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