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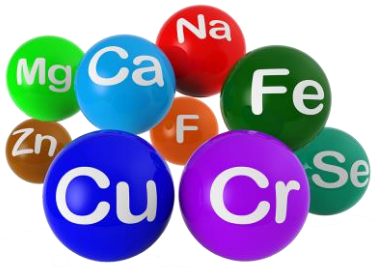

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Jean-Baptiste Langlois
Investigator II
Novartis Institutes for BioMedical Research

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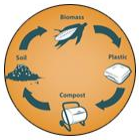
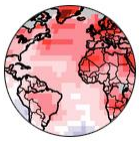


Thursday, March 5, 2015

"Making Plastic Greener Through Next Generation Polymers"

Dr. Marc Hillmyer, Director of the Center for Sustainable Polymers, University of Minnesota

Dr. Joseph Fortunak, Professor of Chemistry, Howard University



Thursday, March 12, 2015

"Bringing CO_2 Monitoring to You: Communicating Atmospheric Chemistry"

Alexis Shusterman, PhD candidate, UC Berkeley
Dr. Darcy Gentleman, Science Communicator, The American Chemical Society

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Division of Medicinal Chemistry

The MEDI Division is one of the largest ACS Divisions having ~9,600 members from 79 countries. The Division prepares and publishes Annual Reports in Medicinal Chemistry. This is a **600+ page volume containing timely reviews of progress in many therapeutic areas and on important new technologies, written by expert medicinal chemists**. This volume is provided free to members each year, and members have on-line access to previous volumes in the series.

Find out more about the ACS MEDI Division! www.acsmedchem.org

AAPS/DDDI Regional Meeting

Drug Discovery Paradigm Shift?
Strategies to Improve Science, Timelines and Clinical Candidate Quality

Friday, May 29th, 2015 (8:00am-4:30pm)
Merck & Co., Upper Gwynedd, Pennsylvania

Experts Speakers from the pharmaceutical field will share their views on drug design, discovery and early development, covering the most relevant pharmaceutical topics with a focus on multi-disciplinary collaboration and case studies

WHO SHOULD ATTEND

Pharmaceutical professionals with background, expertise and interest in different areas of drug discovery, particularly:

- ***Medicinal Chemistry***
- ***Discovery Biology***
- ***Pharmacology***
- ***Pharmacokinetics***
- ***Pharmacodynamics and Drug Metabolism***
- ***Pharmaceutical Sciences***
- ***Toxicology***

Visit Website (http://www.aaps.org/DDDIRM15/) for Featured Speakers and Registration ($100 for members and $150 for non-members)

aaps® American Association of Pharmaceutical Scientists

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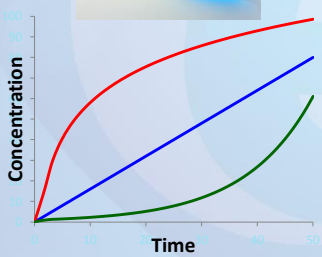
PPB AAPS PHYSICAL PHARMACY AND BIOPHARMACEUTICS SECTION



An ***interactive*** forum to discuss the ***impact*** of ***solubility***, physicochemical characteristics and delivery technologies on ***in-vivo*** drug exposures.

Find out more at: **http://www.aaps.org/PPB/**

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2015 Drug Design & Delivery Symposium

#ACSWebinars

Co-produced by
ACS Division of Medicinal Chemistry
American Association of Pharmaceutical Scientists (AAPS)

Module 1: Improving Drug Design Efficiency and Efficacy		
Jan 29	Designing Better Drug Candidates	*Dr. Paul Leeson*
Feb 26	Strategies to Improve Solubility of Drug Candidates	*Dr. Michael Walker*
Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization		
Mar 19	Fragment-Based Drug Design Strategies	*Dr. Dan Erlanson*
April 30	Screening Strategies	*Dr. David Swinney*
May 28	PAINS (Pan-Assay Interference Compounds)	*Dr. Jonathan Baell*
June 25	Positron Emission Tomography (PET) Labeling in Drug Discovery & Development	*Dr. Lei Zhang*
July 30	X-Ray Crystallography in Drug Discovery	*Dr. Jon Mason & Dr. Miles Congreve*
Module 3: Enabling Drug Discovery		
Aug 27	Choices and Trends in Solid Dosage Form Section	*Dr. Scott Trzaska & Dr. Ron Smith*
Sept 24	Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies	*Dr. Evan Thackaberry*
Module 4: Pharmacokinetics		
Oct 29	Pharmacokinetic Considerations in Drug Design and Development	*Dr. Punit Marathe*
Nov 19	Prodrugs in Drug Discovery	*Dr. John Higgins*

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ACS Chemistry for Life®

"2015 Drug Design and Delivery Symposium:
Strategies to Improve Solubility of Drug Candidates"

This Symposium is co-produced by ACS Webinars, the ACS Division of Medicinal Chemistry and AAPS

Strategies to Improve Solubility of Drug Candidates

Michael A. Walker
michael.a.walker@bms.com

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Today's Speaking Points

- Dose establishes the level of solubility which needs to be achieved
- Factors hampering the aqueous solubility of drugs
- Improving solubility by dissecting a molecule based on its interaction with its target
- Underappreciated and unexpected effects of certain structural modifications

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A Provisional Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan

Mol. Pharm. **2006**, *3*, 631

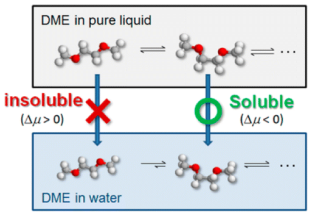
- Compounds defined as sparingly-to-practically insoluble made up 67% of the drugs in 2006
- The highest percent (37%) of drugs displayed solubility < 0.1 mg/mL

The demand for high potency and low dose means that poor solubility will remain an important issue in drug discovery.

THE JOURNAL OF PHYSICAL CHEMISTRY B

"Why Is Poly(oxyethylene) Soluble in Water? ….."

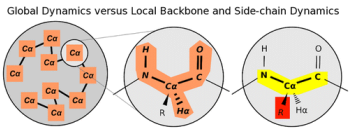
J. Phys. Chem. B **2014**, 118, 12223−12231



JCTC Journal of Chemical Theory and Computation

"Why is Benzene Soluble in Water? ……"

J. Chem. Theory Comput. **2015**, Ahead of Print

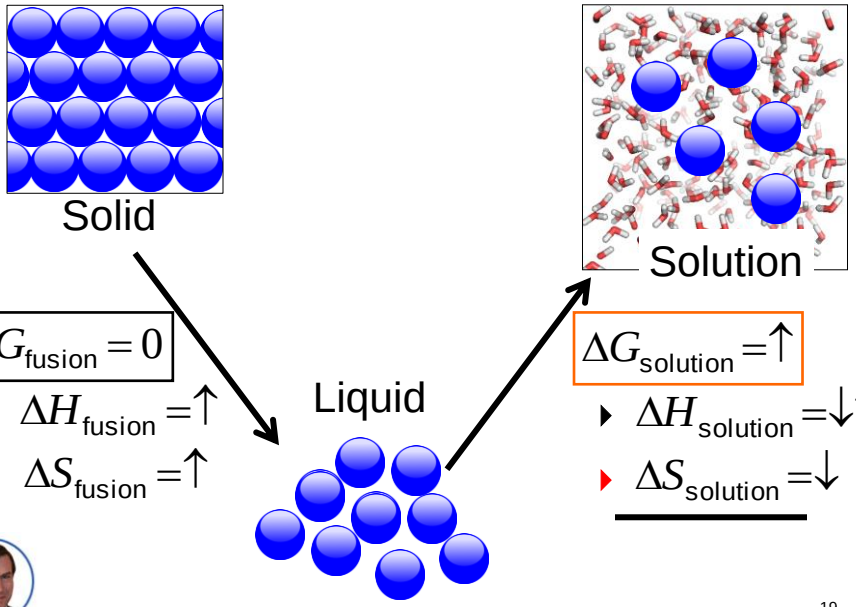


JOURNAL OF CHEMICAL EDUCATION

Erroneous Explanations for the Limited Water Solubility of Organic Liquids……"

J. Chem. Ed. **1994**, *71*, 281

Loss in Entropy Disfavors Dissolution



$\Delta G_{\text{fusion}} = 0$

- $\Delta H_{\text{fusion}} = \uparrow$
- $\Delta S_{\text{fusion}} = \uparrow$

$\Delta G_{\text{solution}} = \uparrow$

- $\Delta H_{\text{solution}} = \downarrow\uparrow$
- $\Delta S_{\text{solution}} = \downarrow$

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General Solubility Equation

$$\log S = \underbrace{0.5 - \log P}_{\text{Solution}} \underbrace{- 0.01(MP - 25)}_{\text{Crystal lattice}}$$

Assumptions

Small, rigid molecule

Compound is completely miscible with octanol, $\log X_o = 0.5$

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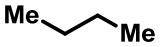
Audience Survey Question

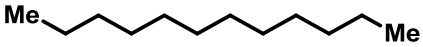
PLEASE SELECT THE ANSWER ON SCREEN

Which molecule, A or B, adopts a collapsed conformation in water?



A

(C_4H_{10})



B

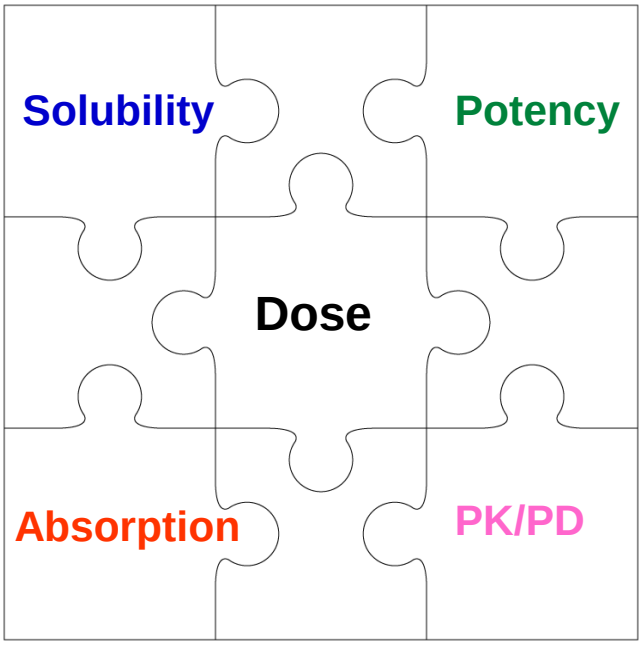
($C_{12}H_{26}$)

- A
- B
- Both A and B
- Neither A nor B

Answer: Neither A nor B

Numerous experiments have shown that n-alkanes up to at least C_{12} exist in a fully extended conformation in water. A recent study suggests that the trend continues up to at least C_{22}

J. Phys. Chem. B ***2009,*** *113,* *6405*



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Activity + *in vivo*-Exposure

↓

Dose

↓

Solubility

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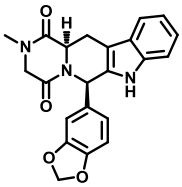
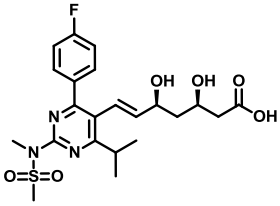
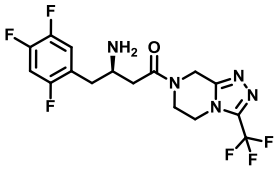
Dose ↔ Solubility

Top selling drugs of 2014







	Tadalafil	Rosuvastatin (Ca^{+2})	Sitagliptin (H_3PO_3)
*Sol, mg/mL	< 0.1	10 - 33	33 - 100
Dose, mg	2 - 20	5 – 40	25 - 100

http://www.medscape.com; Top 100 Most Prescribed, Top-Selling Drugs,
*USP solubility categories, practically insoluble, slightly soluble and soluble, resp.

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Dose → Target Solubility

$$S = 0.015 \times \left(\frac{D}{K_a} \right)$$

S = Target Solubility
D = Target dose
K_a = Intestinal absorption rate constant

Absorption Rate	S (mg/mL) relative to D (mg)
Low	≥ 0.01 D
High	≥ 0.001 D

Derived from the Maximum Absorbable Dose equation
Pharm. Res. **1996** *13, 1795*

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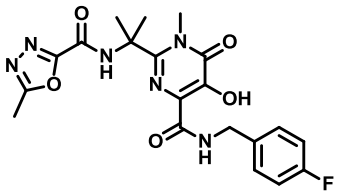
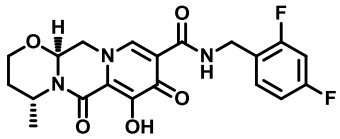
Activity + Exposure → Dose





Raltegravir (Merck)

Serum Adj EC_{95} = 31 nM

[a]C_{12} = 160, 350 nM

Dose = 400 mg BID

(Sol = 30 – 100 mg/mL)

Dolutegravir (ViiV)

Serum Adj EC_{90} = 152 nM

[b]C_{24} = 2,988(r), 701(d), 122(c) nM

Dose = 50 mg QD

(Sol = 1 – 10 mg/mL)

[a] Dog dosed at 2 and 10 mg/kg
[b]Rat, dog, cyno dosed at 5 mg/kg

J. Med. Chem., **2013**, *56*, 5901
J. Med. Chem., **2008**, *51*, 5843

Lessons Learned: Overcoming Poor Solubility

Reduce Dose

- Increase *in vitro* activity
  - Log P
  - Increase H-Bonding
  - Conformational control
  - Fill pockets (increase size)
- Optimize absorption
  - Log P
  - Reduce H-bonding
  - Reduce polarity
  - Reduce size

Etc….

Increase Solubility

- Lower Log P
  - H-Bonding to water
  - Reduce Size
  - Increase polarity
- Lower melting point
  - Reduce H-bonding
  - Increase flexibility

Etc….

Molecular Properties
Size and shape
Polarity
Hydrophibicity
Lipophilicity

Activity, Absorption

Solubility

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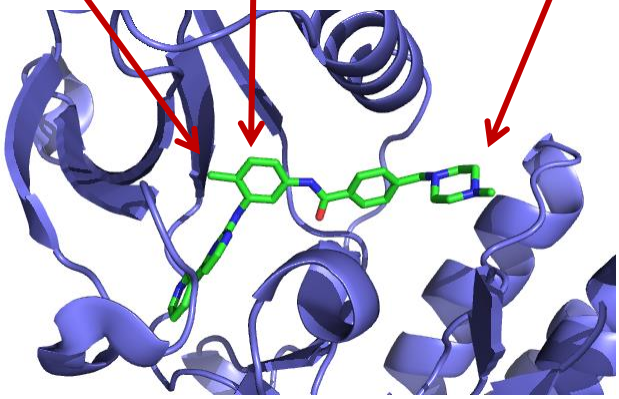
Dissection of Molecule

Ligand Scaffold Solubilizing Appendage



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Ligand Effects on Solubility

ΔLog S (% compounds with increased sol)			
	Leach *et al.*	Zhang *et al.*	Gleeson *et al.*
F	**-0.22 (34)**	**-0.45 (22)**	**-0.1 (9)[Ar]**
Cl	-0.67 (14)	-1.45 (4)	-0.35 (5)[Ar]
CF_3	-0.81 (17)	-0.77 (25)	-0.54 (3)
Me	**-0.21 (33)**	**-0.50 (26)**	**-0.11 (11)**
OMe	-0.11 (42)	-0.24 (43)	-0.03 (19)
CN	-0.26 (36)	-	-0.14 (9)
OH	0.07 (56)	0.97 (85)	0.31 (48)[Ali]
NH_2	-	0.76 (61)	0.37 (54)[Ali]
SO_2Me	0.26 (71)	-0.38 (0)	0.01 (27)
CO_2H	-	-0.05 (45)	0.57 (56)

J. Med. Chem. **2006**, *49*, 6672
Bioorg. Med. Chem. Lett. **2011**, *19*, 5763
Bioorg. Med. Chem. **2009**, *17*, 5906

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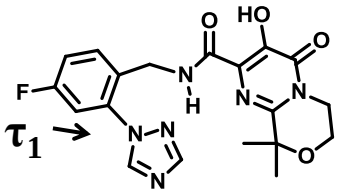
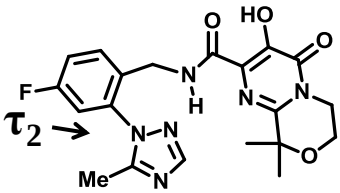
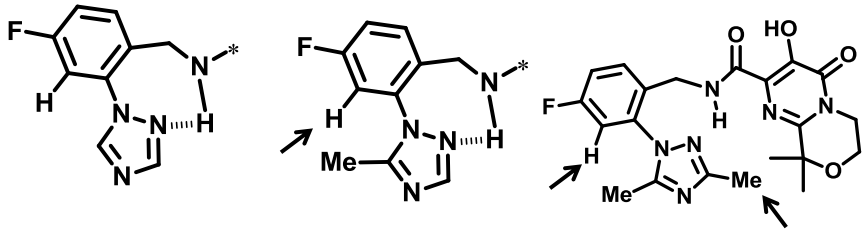
Addition of Methyl





	1	2
$Sol_{6.5}$ μg/mL	16	152
cLog *P*	0.42	0.56
log*P*	1.2	0.8
$*\tau_{1,2}$	65.8°	68.8°
Mp °C	243	237

*Determined by single crystal X-Ray crystallography



	1	2	3
$Sol_{6.5}$ µg/mL	16	152	660
δ NH ($CDCl_3$)	8.81	8.61	8.40

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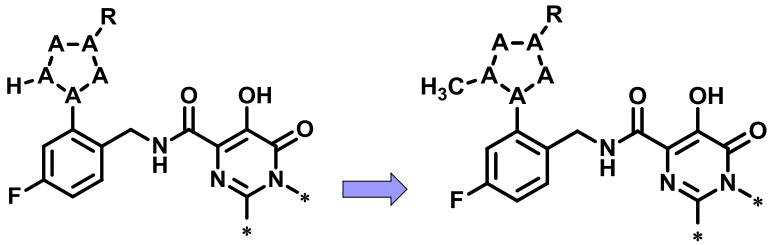
Matched Pair Analysis



N = 41
Avg. change in solubility = +0.2 mg/mL
# of compounds with increase = 34 (avg. change in sol = 0.265 mg/mL)
# of compounds with no change = 4
# of compounds with decrease = 3 (avg change in sol = -0.03 mg/mL)

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F Can Reduce Hydrophobicity

aryl versus akyl substitution

$CH_3CH_2CH_2CH_2CH_2X$

X	Δ log P	Δ log P
F	0.14	-0.17
Cl	0.71	0.39
Br	0.86	0.60

Fluorine addition to alkyl group reduces hydrophobicity

J Am Chem Soc (1964) 5175-5180
J Org Chem (1967) 2583-2586

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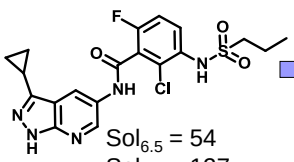
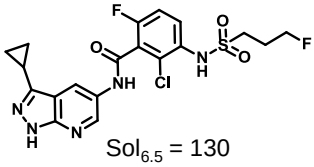
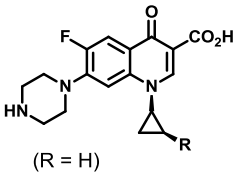
Use of **F** in Drug Design



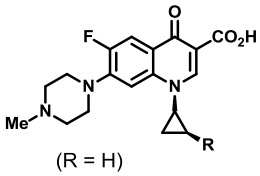
$Sol_{6.5}$ = 54
$Sol_{7.4}$ = 127
mp = 164 ºC
clog *P* = 2.19



$Sol_{6.5}$ = 130
$Sol_{7.4}$ = 265
mp = 154 ºC
clog *P* = 1.61



(R = H)
(R = F)
ΔK_{CHCl3} (H to F)= -0.75



(R = H)
(R = F)
ΔK_{CHCl3} (H to F)= -0.45

J. Med. Chem. **1993**, *36*, 3444
Bioorg Med Chem Lett **2012**, *22*, 912

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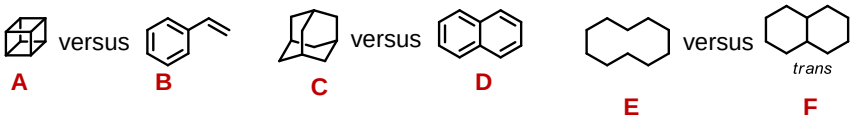
Audience Survey Question

PLEASE SELECT THE ANSWER ON SCREEN

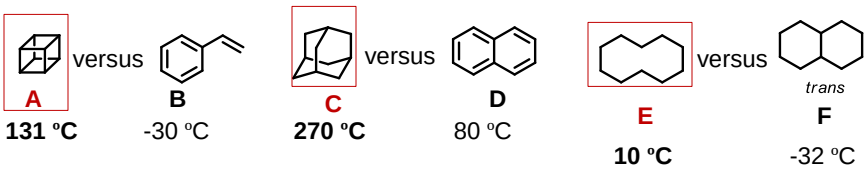
Which compound in each set has the higher melting point?



- A/C/E
- B/C/E
- A/D/E
- B/C/E
- B/C/F

Answer

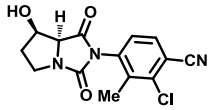
Which compound in each set has the higher melting point?



131 °C -30 °C **270 °C** 80 °C **10 °C** -32 °C

Disruption of H-Bonding

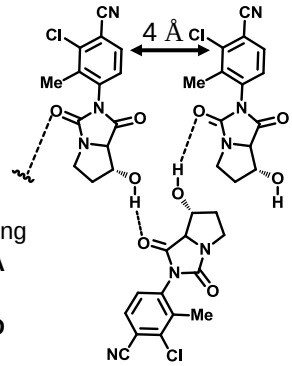
Selective Androgen Receptor Modulator



BMS-564929

Sol = 62 μM
log *P* = 1.3
Mp = 255 – 257 °C

Model of X-Ray Structure



H-bonding

D – A

A – D

- Crystal packing of BMS-564929 dominated by strong H-bonding
- Aryl rings are co-planar and close enough to π-stack

J Med Chem (2007) 3015-3025

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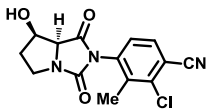
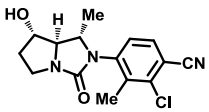
Remove H-Bond Acceptor

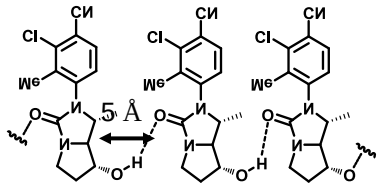


BMS-564929
Sol = 62 μM
log *P* = 1.3
Mp = 255 – 257 °C
C_k = 0.71



2
Sol = 2009 μM
log *P* = 2.2
Mp = 173-177 °C
C_k = 0.71

Model of X-Ray Structure



H-bonding

D – A ---- D – A ---- D – A

- Mp is reduced by ~80 °C leading to ~30 fold improvement in solubility
- Number of H-bonds is preserved
- Aryl rings are co-planar not close enough to π-stack

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Lessons Learned: Overcoming Poor Solubility

- Dose establishes the level of solubility which needs to be achieved
- Factors hampering the aqueous solubility of drugs
- Improving solubility by dissecting a molecule based on its interaction with its target
- Underappreciated and unexpected effects of certain structural modifications

Additional Resources

Internet Resources

Dr Bruno Villoutreix web site; http://www.vls3d.com/

Water in Biology; http://waterinbiology.blogspot.com

Drug database: http://www.drugbank.ca

PharmacoKinetics Knowledge Base (PKKB) http://cadd.ucsd.edu/adme

BCS database; http://tsrlinc.com

Solubility Reviews

Solubility: it's not just for physical chemists
DDT, **2006**, 11, 1012

Getting physical in drug discovery: a contemporary perspective on solubility and hydrophobicity
DDT 2010, 15, 648

Optimizing the Solubility of Research Compounds: How to Avoid Going Off Track
Am. Pharm. Rev. **2010**, May/June issue

Hydrophobic Effects. Opinions and Facts
Angew. Chem. Int. Ed. Engl. **1993**, *32*, 1545

Additional Resources

Analysis of approved compounds

Statistics on BCS Classification of Generic Drug Products Approved Between 2000 and 2011 in the USA
AAPS J. **2012,** *14*, 664

Molecular Characteristics for Solid-State Limited Solubility
J. Med. Chem. **2008**, *51*, 3035

Poorly Soluble Marketed Drugs Display Solvation Limited Solubility
J. Med. Chem. **2007**, *50*, 5858

BDDCS Applied to Over 900 Drugs
AAPS Journal, **2011**, *13*, 519

Experimental solubility profiling of marketed CNS drugs, exploring solubility limit of CNS discovery candidate
Bioorg. Med. Chem. Lett. **2010** *20*, 7312

Assessment of the Amorphous "Solubility" of a Group of Diverse Drugs Using New Experimental and Theoretical Approaches
Mol. Pharm., **2015**, *12*, 484

Molecular Characteristics for Solid-State Limited Solubility
J. Med. Chem. **2008**, *51*, 3035

A Provisional Biopharmaceutical Classification of the Top 200 Oral Drug Products in the United States, Great Britain, Spain, and Japan
Mol. Pharm. **2006,** *3*, 631

Additional Resources

Crystal Lattice

A medicinal chemistry perspective on melting point: matched molecular pair analysis of the effects of simple descriptors on the melting point of drug-like Compounds
Med. Chem. Commun., 2012, 3, 584

Strategies at the Interface of Drug Discovery and Development: Early Optimization of the Solid State Phase and Preclinical Toxicology Formulation for Potential Drug Candidates
J. Med. Chem. 2010, 53, 5897–5905

Predicting Intrinsic Aqueous Solubility by a Thermodynamic Cycle
Mol. Pharmaceutics, **2008**, *5* (2), pp 266–279

Improvement in Aqueous Solubility in Small Molecule Drug Discovery Programs by Disruption of Molecular Planarity and Symmetry
J. Med. Chem. 2011, 54, 1539–1554

Additional Resources

U.S. Pharmacopeia Solubility Definitions

USP Solubility	*Solublity Range mg/mL
Very Soluble	>1000
Freely Soluble	100-1000
Soluble	33-100
Sparingl Soluble	10-33
Slightly Soluble	1-10
Very Slightly Soluble	0.1-10
Practically Insoluble	<0.1

*Calculated. USP solubility is expressed as parts of solvent required to dissolve 1 part solute

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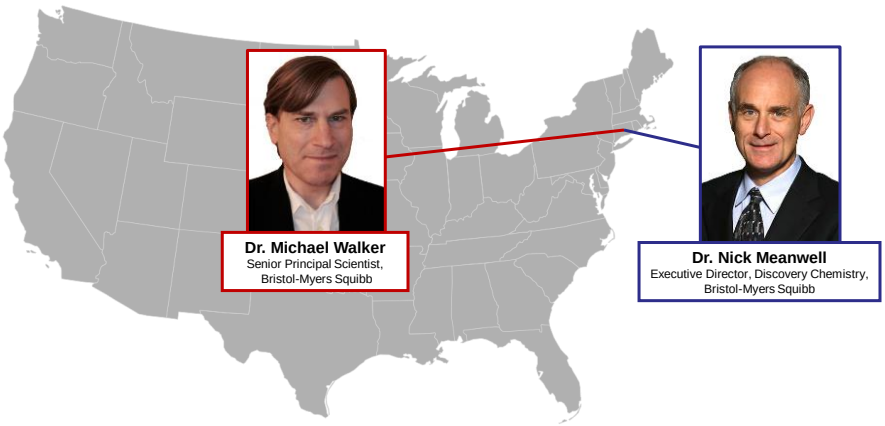

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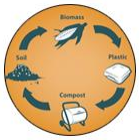
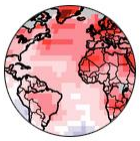


Thursday, March 5, 2015

"Making Plastic Greener Through Next Generation Polymers"

Dr. Marc Hillmyer, Director of the Center for Sustainable Polymers, University of Minnesota

Dr. Joseph Fortunak, Professor of Chemistry, Howard University



Thursday, March 12, 2015

"Bringing CO_2 Monitoring to You: Communicating Atmospheric Chemistry"

Alexis Shusterman, PhD candidate, UC Berkeley
Dr. Darcy Gentleman, Science Communicator, The American Chemical Society

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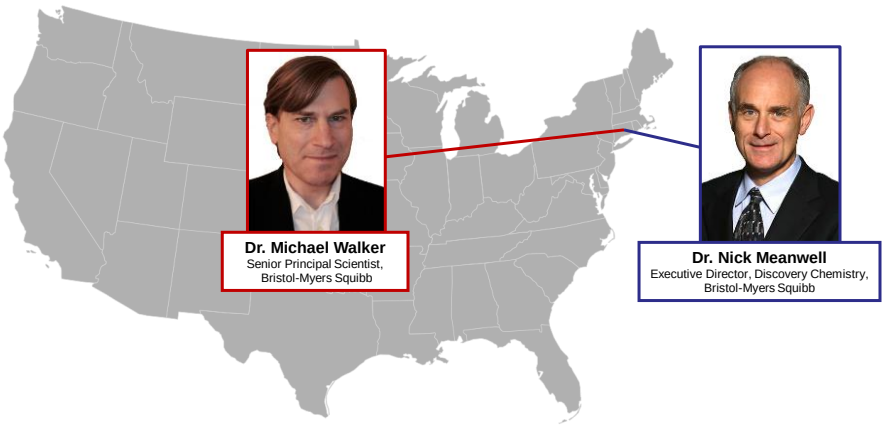

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AAPS/DDDI Regional Meeting

Drug Discovery Paradigm Shift?
Strategies to Improve Science, Timelines and Clinical Candidate Quality

Friday, May 29th, 2015 (8:00am-4:30pm)
Merck & Co., Upper Gwynedd, Pennsylvania

Experts Speakers from the pharmaceutical field will share their views on drug design, discovery and early development, covering the most relevant pharmaceutical topics with a focus on multi-disciplinary collaboration and case studies

WHO SHOULD ATTEND

Pharmaceutical professionals with background, expertise and interest in different areas of drug discovery, particularly:

- ***Medicinal Chemistry***
- ***Discovery Biology***
- ***Pharmacology***
- ***Pharmacokinetics***
- ***Pharmacodynamics and Drug Metabolism***
- ***Pharmaceutical Sciences***
- ***Toxicology***

Visit Website (http://www.aaps.org/DDDIRM15/) for Featured Speakers and Registration ($100 for members and $150 for non-members)

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2015 Drug Design & Delivery Symposium

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Jan 29	Designing Better Drug Candidates	*Dr. Paul Leeson*
Feb 26	Strategies to Improve Solubility of Drug Candidates	*Dr. Michael Walker*
Module 2: Activity/Potency Screening for Drug Lead & Candidate Optimization		
Mar 19	Fragment-Based Drug Design Strategies	*Dr. Dan Erlanson*
April 30	Screening Strategies	*Dr. David Swinney*
May 28	PAINS (Pan-Assay Interference Compounds)	*Dr. Jonathan Baell*
June 25	Positron Emission Tomography (PET) Labeling in Drug Discovery & Development	*Dr. Lei Zhang*
July 30	X-Ray Crystallography in Drug Discovery	*Dr. Jon Mason & Dr. Miles Congreve*
Module 3: Enabling Drug Discovery		
Aug 27	Choices and Trends in Solid Dosage Form Section	*Dr. Scott Trzaska & Dr. Ron Smith*
Sept 24	Delivery Options to Support Dose Escalation in Preclinical Toxicology and Pharmacodynamic Activity Studies	*Dr. Evan Thackaberry*
Module 4: Pharmacokinetics		
Oct 29	Pharmacokinetic Considerations in Drug Design and Development	*Dr. Punit Marathe*
Nov 19	Prodrugs in Drug Discovery	*Dr. John Higgins*