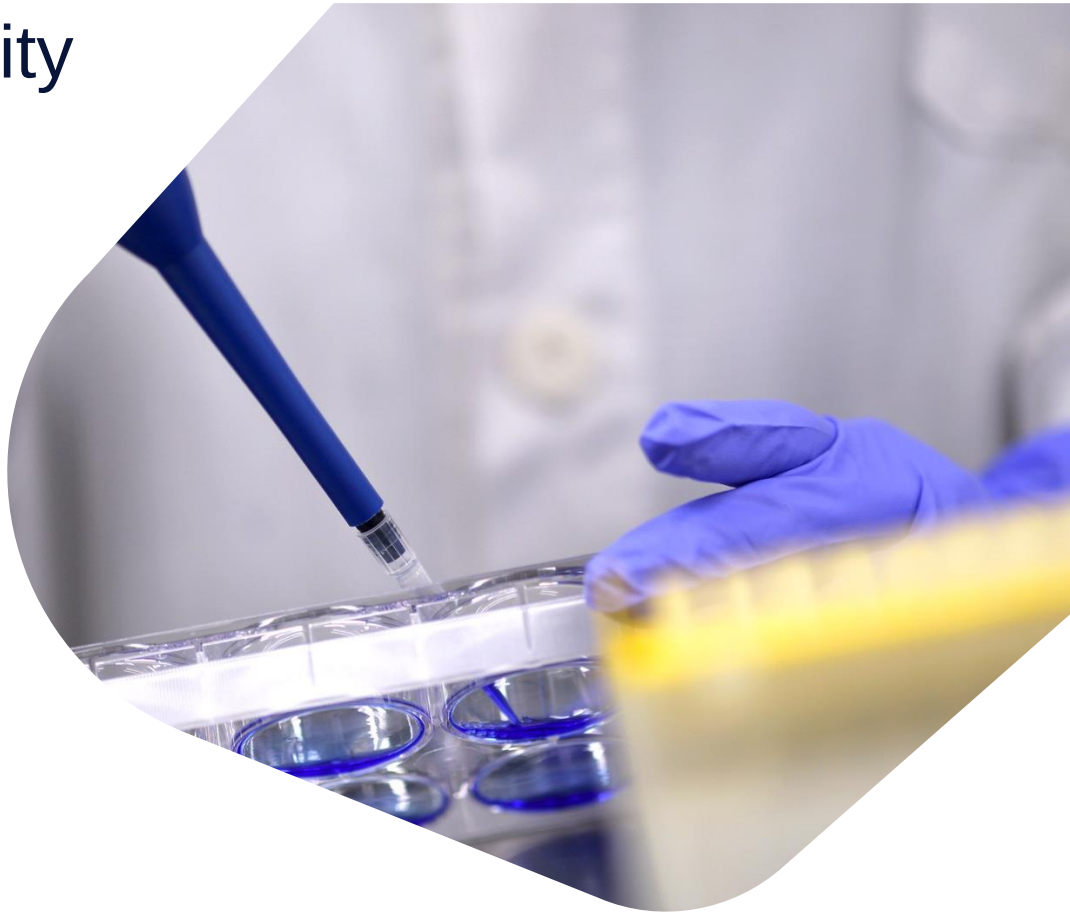
Emerging Modalities and Compound Developability Assessment in Small Molecule Early Development



MCERSI Co-Processed API and Regulatory Requirements

Ahmad Sheikh

July 13, 2022

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Last two decades

Journal of Medicinal Chemistry

Perspective

Cite This: J. Med. Chem. 2019, 62, 1701−1714

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Two Decades under the Influence of the Rule of Five and the Changing Properties of Approved Oral Drugs

Miniperspective

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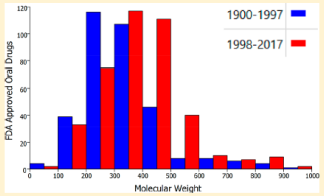
Supporting Information

ABSTRACT: Two decades have passed since the rule of five ushered in the concept of "drug-like" properties. Attempts to quantify, correlate, and categorize molecules based on Ro5 parameters evolved into the introduction of efficiency metrics with far reaching consequences in decision making by industry leaders and scientists seeking to discover new medicines. Examination of oral drug parameters approved before and after the original Ro5 analysis demonstrates that some parameters such as clogP and HBD remained constant while the cutoffs for parameters such as molecular weight and HBA have increased substantially over the past 20 years. The time dependent increase in the molecular weight of oral drugs during the past 20 years provides compelling evidence to disprove the hypothesis that molecular weight is a "drug-like" property. This analysis does not validate parameters that have not changed as being "drug-like" but instead calls into question the entire hypothesis that "drug-like" properties exist.



J. Med. Chem. 2019, 62, 4, 1701−1714

Table 2. Analysis of FDA Approved Oral NCEs from 1998 to 2007[a]

	clogP	MW	HBD	HBA	TPSA	RotB	Fsp^3	#ArRNG
1997 90th percentile	4.7	470.3	4.0	10	139.8	10.0	0.83	3
90th percentile	4.7 (0)	525.5 (+ 55.2)	4.0 (0)	9.6 (-0.4)	142.3 (+2.5)	11 (+1)	0.78 (-0.05)	3.0 (0)
p value*	0.3	**0.0026**	>0.99	0.69	0.97	**0.039**	0.082	>0.99
Median	2.6 (+0.3)	348.4 (+40.1)	1 (0)	6 (+2)	74.7 (+7.2)	6 (+2)	0.43 (+0.03)	2 (+1)
Mean	2.4 (+0.3)	360.1 (+28.1)	1.8 (-0.1)	6.0 (+0.5)	82.0 (+3.2)	5.9 (+0.9)	0.46 (+0.03)	1.7 (+0.3)
p value†	0.35	0.28	0.94	0.55	0.94	**0.066**	0.56	**0.025**
p value‡	0.46	**0.014**	>0.99	**0.044**	0.43	**0.0085**	0.73	0.73
10th percentile	-0.4 (+0.2)	201.3 (+30.1)	0.0 (0)	2.0 (0)	30.5 (+9.2)	1.0 (0)	0.08 (+0.1)	0 (0)
p value*	0.6	**<0.0001**	>0.99	>0.99	0.37	>0.99	**<0.0001**	>0.99

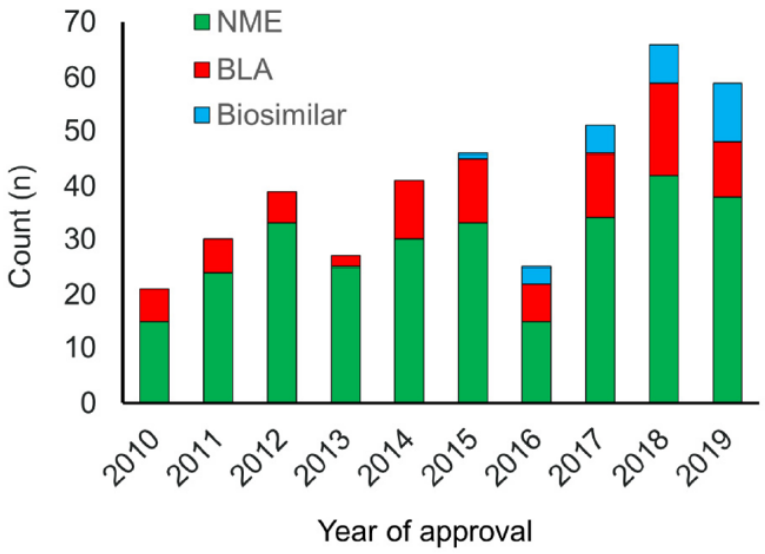
[a] n = 195, or 26% of all FDA approved oral NCEs. The 90th percentile values determined for FDA approved oral drugs from 1900 to 1997 are included for reference. The change in values from FDA approved oral drugs from 1900 to 1997 values are in parentheses. *p value of the 10th and 90th percentile cutoffs based on one-way ANOVA analyses. †p values from one-way ANOVA (normal distribution). ‡p values from Kurskal–Wallace (non-normal distribution). Differences that achieve statistical significance ($p < 0.05$) are in bold. Categories that have a statistically significant increase are shaded in red.

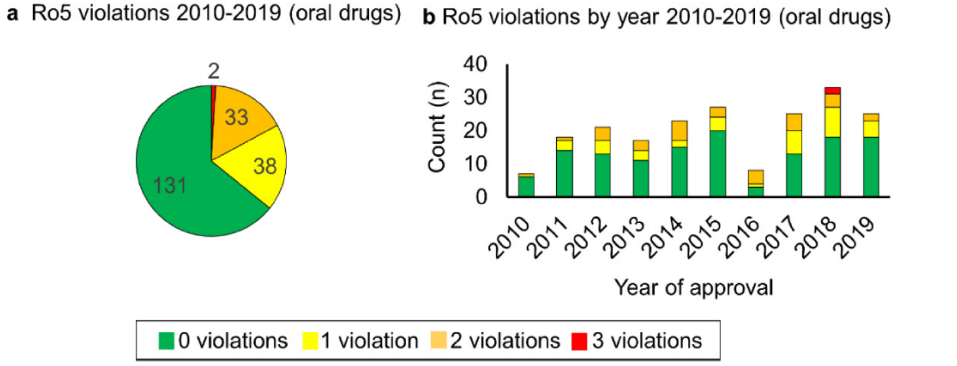
Table 3. Analysis of FDA Approved Oral NCEs from 2008 to 2017[a]

	clogP	MW	HBD	HBA	TPSA	RotB	Fsp^3	#ArRNG
1997 90th percentile	4.7	470.3	4.0	10	139.8	10.0	0.83	3
90th percentile	5.0 (+0.3)	607.3 (+137.0)	4.0 (0)	11.7 (+2.0)	150.7 (+10.9)	13.7 (+3.7)	0.69 (-0.14)	4.0 (+1.0)
p value*	0.27	**<0.0001**	>0.99	**<0.0001**	0.20	**<0.0001**	**<0.0001**	**<0.0001**
Median	3.3 (+1.0)	420.0 (+111.7)	2 (+1)	6 (+2)	80.8 (+13.3)	6 (+2)	0.38 (-0.02)	2 (+1)
Mean	2.9 (+0.8)	436.5 (+104.5)	2.1 (+0.2)	6.8 (+1.4)	93.6 (+14.8)	7.0 (+2.0)	0.40 (-0.03)	2.2 (+0.8)
p value†	**<0.0001**	**<0.0001**	0.57	**0.0008**	**0.037**	**<0.0001**	0.65	**<0.0001**
p value‡	**<0.0001**	**<0.0001**	0.35	**<0.0001**	**0.005**	**<0.0001**	0.99	**>0.99**
10th percentile	0.3 (+0.9)	235.5 (+64.3)	0.0 (0)	3.0 (+1)	39.7 (+14.8)	3 (+2)	0.16 (+0.07)	0 (0)
p value*	**<0.0001**	**<0.0001**	>0.99	**0.024**	**0.0049**	**<0.0001**	**0.0005**	>0.99

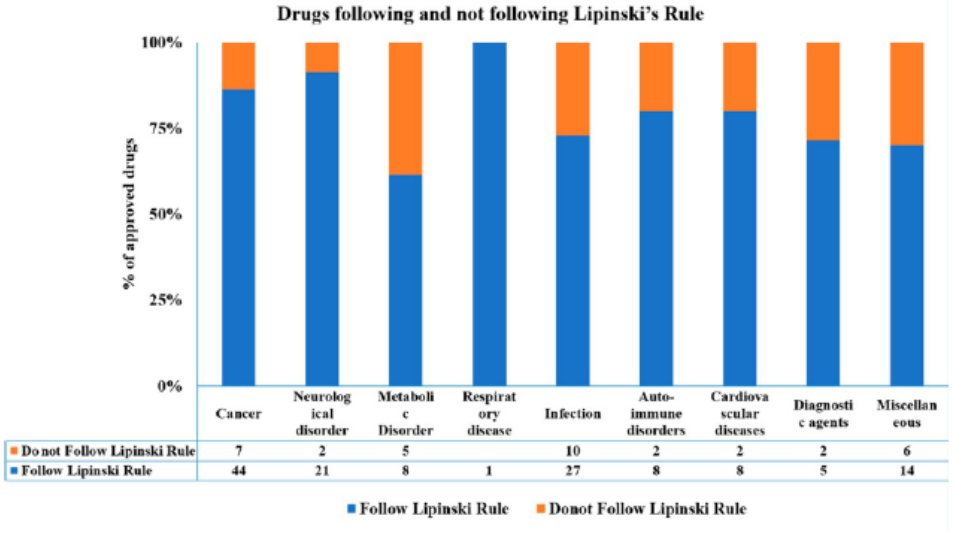
[a] n = 214, or 29% of all FDA approved oral NCEs. The 90th percentile values determined for FDA approved oral drugs from 1900 to 1997 are included for reference. The change in values from FDA approved oral drugs from 1900 to 1997 values are in parentheses. *p value of the 10th and 90th percentile cutoffs based on one-way ANOVA analyses. †p values from one-way ANOVA (normal distribution). ‡p values from Kurskal–Wallace (non-normal distribution). Differences that achieve statistical significance ($p < 0.05$) are in bold. Categories that have a statistically significant increase are shaded in red, and those that have a statistically significant decrease are shaded in green.

Last decade





(a) Total analysis of Ro5 violations for 204 approved oral drugs and (b) Ro5 violations per year on 204 approved oral drugs.



	Cancer	Neurological disorder	Metabolic Disorder	Respiratory disease	Infection	Auto-immune disorders	Cardiovascular diseases	Diagnostic agents	Miscellaneous
Donot Follow Lipinski Rule	7	2	5		10	2	2	2	6
Follow Lipinski Rule	44	21	8	1	27	8	8	5	14

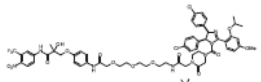
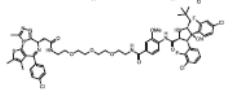
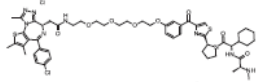
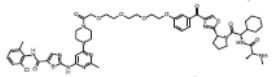
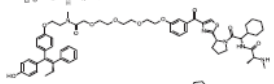
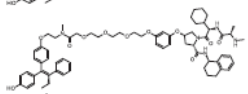
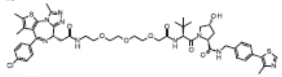
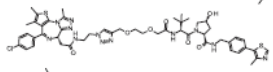
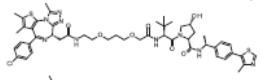
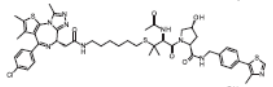
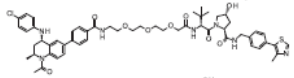
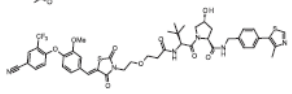
Bar graph represents percent of approved FDA drugs from the year 2015 until June 2020, following and not following Lipinski's Rule.

J. Med. Chem. 2021, 64, 5, 2312−2338

J. Med. Chem. 2021, 64, 5, 2339−2381

PROTAC's
way beyond rule of 5

Table 1
Representative recent PROTACs organized by E3 warhead: MDM2, IAP, VHL, and CRBN binders.

PROTAC	Structure	Name	Target (POI)	E3 Ligase	DC_{50}/D_{max}	Cellular/in vivo	Ref
1		Compound 14	AR	MDM2	10 μM/–	*In vitro*	18
2		A1874	BRD4	MDM2	32 nM/98% at 100 nM	*In vitro*	19
3		SNIPER(BRD4)-1	BRD4	IAP	> 3 nM & < 10 nM/70% at 10 nM	*In vitro* probe	20
4		SNIPER(ABL)-39	ABL	IAP	> 3 nM & < 10 nM/ > 90% at 100 nM	*In vitro* probe	21
5		SNIPER(ER)-87	ERα	IAP	> 1nM & < 3 nM/70% at 10 nM	*In vivo* efficacy (IP injection)	22
6		SNIPER(ER)-110	ERα	IAP	< 3 nM/80% at 100 nM	*In vivo* probe	23
7		MZ1	BRD4	VHL	< 100 nM (BRD4)/ > 96% at 50 nM	*In vitro* cellular probe	26
8		12b	BRD4	VHL	0.083 μM/–	*In vitro*	27
9		ARV-771	BRD4	VHL	< 5 nM for BRD2/3/4/ > 99%	*In vivo* (SC) efficacy	28
10		AT1	BET	VHL	> 10 nM & < 100 nM for BRD4 short/ > 90%	*In vitro* prob	29
11		MZP54	BET	VHL	10 nM- < 100 nM/87% at 50 nM	*In vitro* cellular prob	30
12		PROTAC,ERRα (1)	ERRα	VHL	100 nM/86% at 1 μM	*In vivo* probe (IP injection)	31

(continued on next page)

Will these be orally bioavailable
Would we crystallize them
What would the formulations be

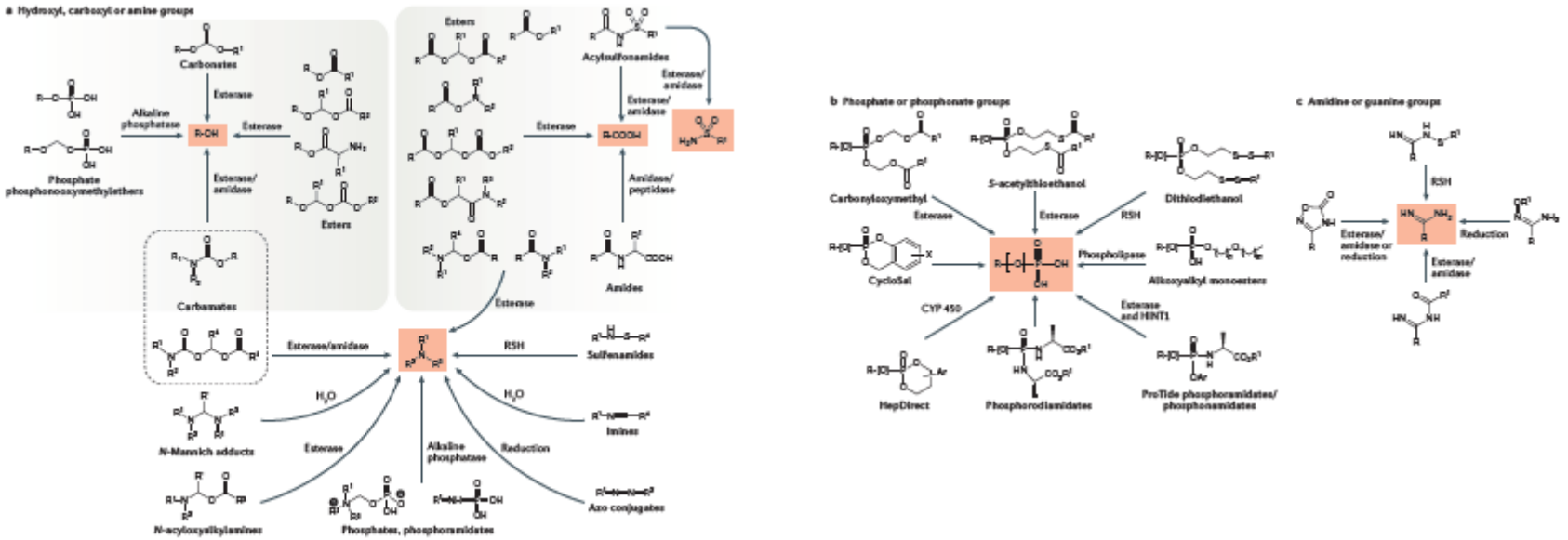
Table 2
In silico metrics for selected PROTACs.

Compound	E3 Ligase	MW	cLogP	HBD	HBA	PSA	nRotB	$N_{rule\text{-}of\text{-}5}$	Ar Rings	cLogD	AB-MPS
1	MDM2	1210	11	4	22	268	31	3	5	7.3	40.3
2	MDM2	1174	9.1	4	16	200	27	3	6	7.9	37.9
Average	MDM2	1192	10.1	4.0	19	234	29	3.0	5.5	7.6	39.1
3	IAP	1057	6.1	3	17	197	27	3	5	4.7	33.7
4	IAP	1115	5.7	4	20	228	29	3	5	5.9	36.9
5	IAP	1044	8.9	3	15	182	31	3	6	6.5	40.5
6	IAP	1122	11.4	4	16	196	33	3	5	7.5	42.5
Average	IAP	1085	8.0	3.5	17	201	30	3.0	5.3	6.2	38.4
7	VHL	1003	4.9	4	17	210	25	2	5	3.5	30.5
8	VHL	1040	4.2	4	19	229	24	2	6	3.4	30.4
9	VHL	987	5.9	4	16	202	23	3	5	3.2	28.2
10	VHL	973	6.1	4	14	184	22	3	5	4.4	28.4
11	VHL	1037	6.3	5	16	211	27	3	5	4.6	33.6
12	VHL	949	6.9	3	15	202	21	3	4	4.5	26.5

Bioorganic & Medicinal Chemistry Letters 29 (2019) 1555–1564

Prodrugs- chemically labile by design

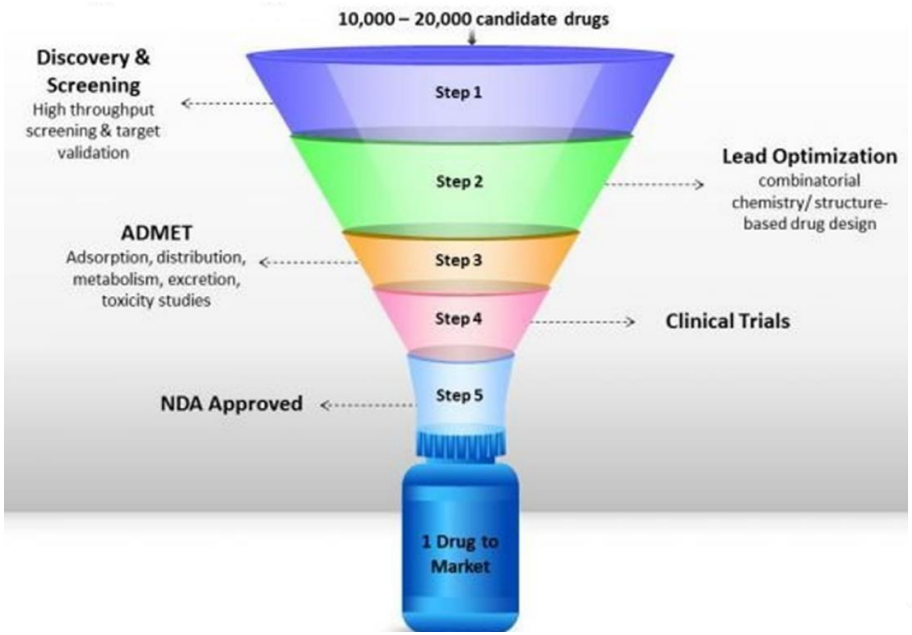
- Over 30 approved in the last decade (‘08-17), representing ~ 12% of all approved small molecules

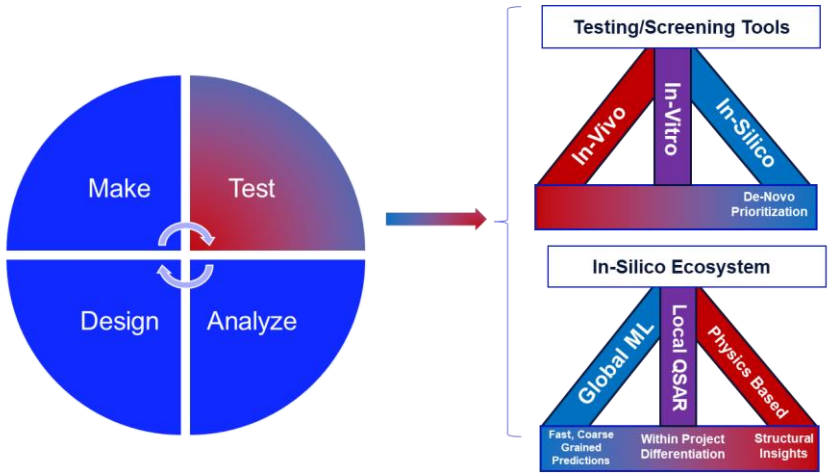


- Limited stability across physiologically relevant pH range, limited understanding of bio-conversion and metabolism
- Complex synthesis, complex solid state, analytical (CMC and bio-analytical)
- Regulatory challenges in setting specs for impurities such as “parent” and other pro-drug type impurities

Nature Reviews Drug Discovery, (2018) 559-587

Positioning of Developability earlier in the LO Funnel





Absorption	Distribution	Metabolism	Excretion	Toxicity	PhysChem
Caco-2 permeability	Human serum albumin binding	Microsomal stability	CL_{int}	Ames mutagenicity	Aq. solubility
Caco-2 efflux ratio	Plasma-protein binding	Hepatocyte stability	Terminal half-life	CYP inhibition	LogD
PAMPA permeability	Fraction unbound (fu)	Site of metabolism		Phaspholipidosis	Membrane affinity
Blood-brain barrier penetration	Volume of distribution (vdss)			hERG inhibition	pKa
	Brain/plasma ratio (Kp)			Drug-induced liver injury (DILI)	

Drug Disc Today, Volume 27, Issue 4, 2022, 967-984

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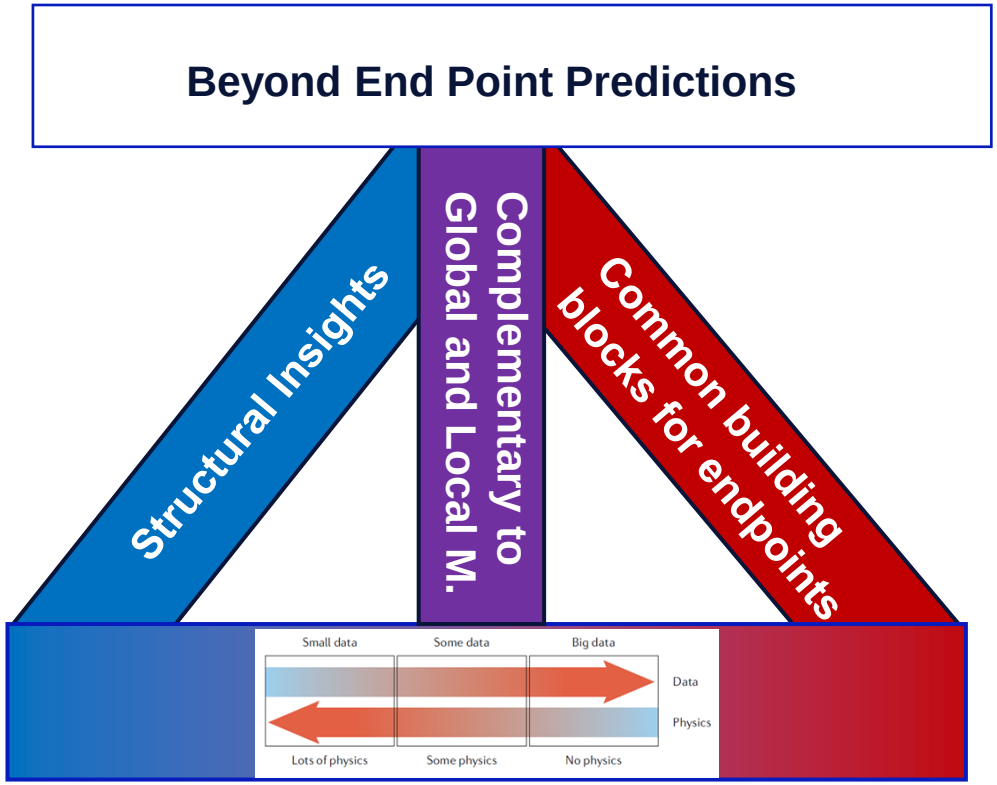
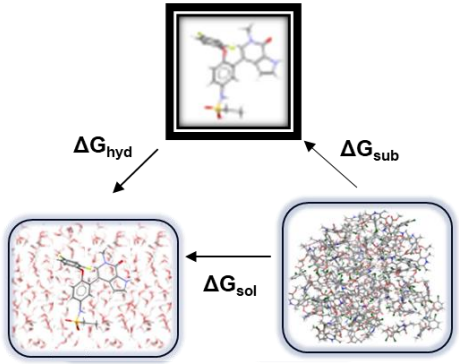
Physics Based Models

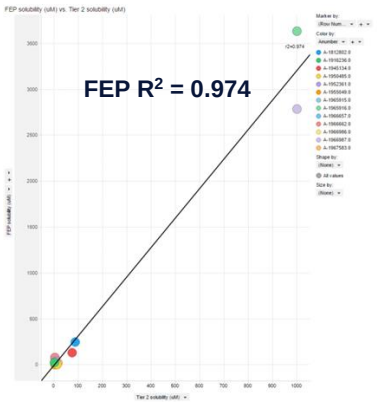


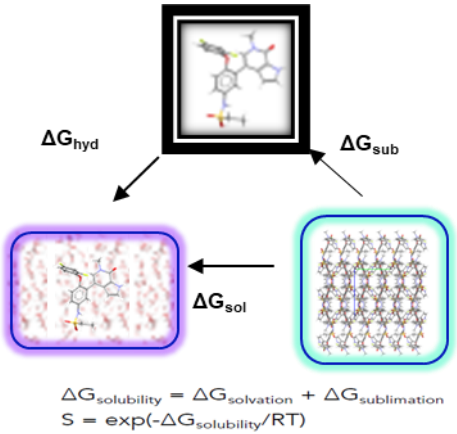
Nat Rev Phys **3,** 422–440 (2021)

Solubility Prediction: Trending and Quantitatively differentiating Structurally Related Molecules



Utilizing a thermodynamic cycle, solvation & sublimation energies are calculated





- Ability to qualitatively predict solubility within a series
- Help remove low soluble compounds with ~30 % false negative

- Crystal structure prediction (CSP) to identify energetically favorable 3-D crystal packing using 2-D molecular structure
- Global minimum from CSP as input for thermodynamic cycle

Quick version of CSP to bring efficiency for LO stage

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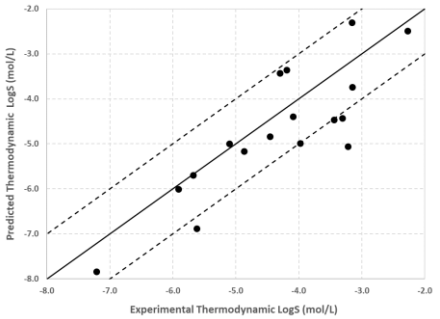
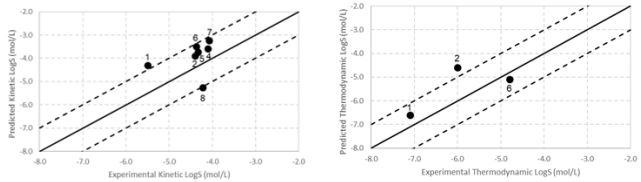
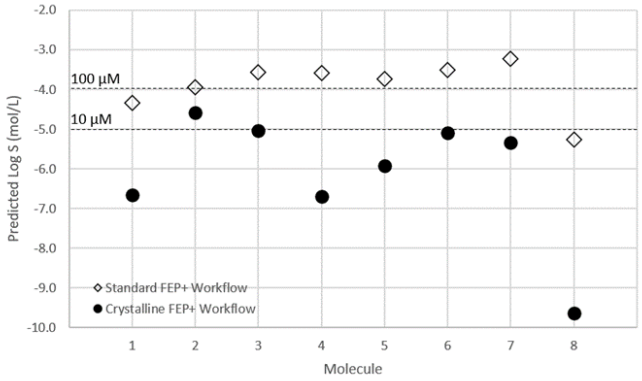
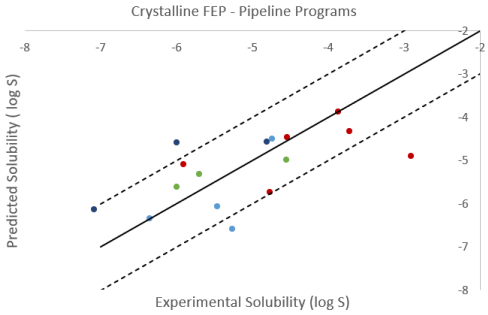
Thermodynamic Solubility Prediction before Synthesis and Crystallization



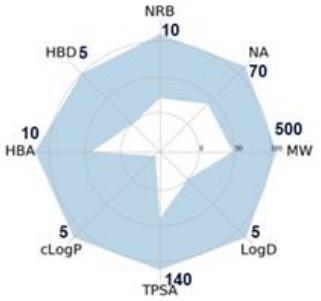
Structurally distinct AbbVie Dataset (17)







Structurally related AbbVie Dataset (4 series)



JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

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Novel Physics-Based Ensemble Modeling Approach That Utilizes 3D Molecular Conformation and Packing to Access Aqueous Thermodynamic Solubility: A Case Study of Orally Available Bromodomain and Extraterminal Domain Inhibitor Lead Optimization Series

Richard S. Hong, Alessandra Mattei, Ahmad Y. Sheikh,* Rajni Miglani Bhardwaj, Michael A. Bellucci, Keith F. McDaniel, M. Olivia Pierce, Guangxu Sun, Sizhu Li, Lingle Wang, Sayan Mondal, Jianguo Ji, and Thomas B. Borchardt

Cite This: *J. Chem. Inf. Model.* 2021, 61, 1412−1426 | Read Online

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ABSTRACT: Drug design with patient centricity for ease of administration and pill burden requires robust understanding of the impact of chemical modifications on relevant physicochemical properties early in lead optimization. To this end, we have developed a physics-based ensemble approach to predict aqueous thermodynamic crystalline solubility, with a 2D chemical structure as the input. Predictions for the bromodomain and extraterminal domain (BET) inhibitor series show very close match (0.5 log unit) with measured thermodynamic solubility for cases with low crystal anisotropy and good match (1 log unit) for high anisotropy structures. The importance of thermodynamic solubility is clearly demonstrated by up to a 4 log unit drop in solubility compared to kinetic (amorphous) solubility in some cases and implications thereof, for instance on human dose. We have also demonstrated that incorporating predicted crystal structures in thermodynamic solubility prediction is necessary to differentiate (up to 4 log unit) between solubility of molecules within the series. Finally, our physics-based ensemble approach provides valuable structural insights into the origins of 3-D conformational landscapes, crystal polymorphism, and anisotropy that can be leveraged for both drug design and development.

J. Chem. Inf. Model. 2021, 61, 3, 1412−1426

Incorporation of Physical Properties considerations in the design cycle

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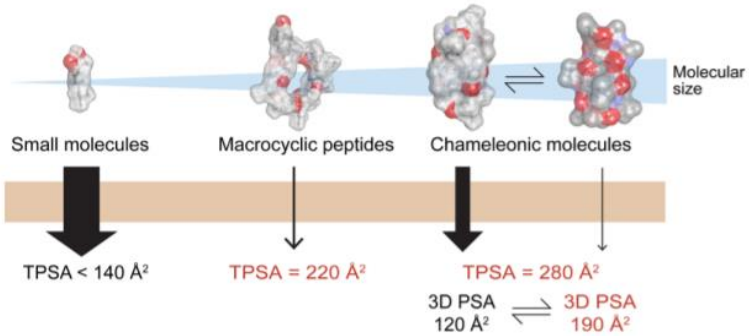
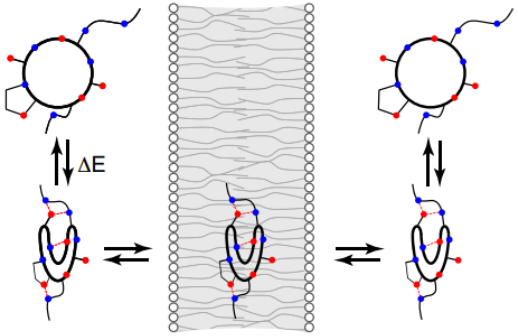
bR05 Chameleonicity: Towards Improved Passive Permeability

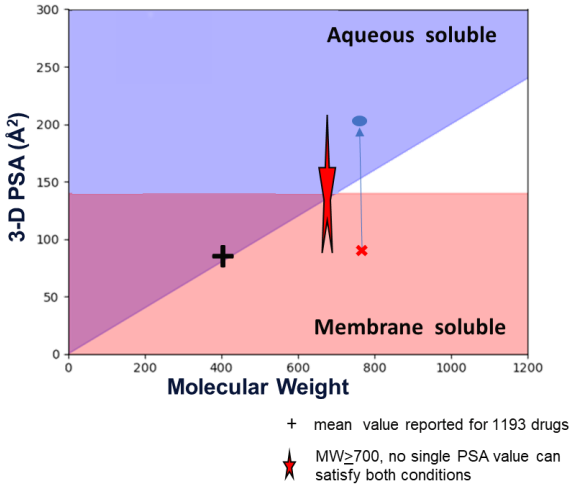


Size boundaries for membrane-permeable molecules

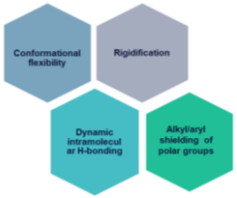


Conformational changes due to intramolecular hydrogen bonding (IMHB) + alkyl/ aryl shielding of polar groups facilitate permeation

A Framework to Quantify Chameleonic Behavior



Generation of conformations in polar (aqueous) and non-polar (membrane) media and calculation of their BW SA 3D-PSA
Provide information on IMHB, shielding of polarity in non-polar media which help improving the permeability



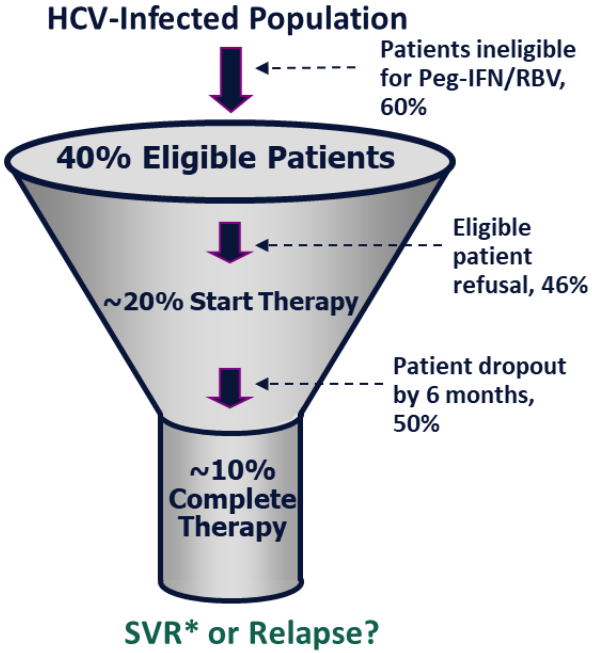
J Med Chem, 2017, 60, 1662−1664
Drug Disc Today, 21, 2016, 713-717

Hepatitis C Infection- where were we a decade ago

170 million people infected worldwide

- USA: 4 million
- Western Europe: >5 million
- Latin America: 3.5 million
- Japan: >1.6 million
- China: 30 – 40 million
- India: 10 – 12 million

3 to 4 million new cases diagnosed annually



First treatment: PEG-IFN/Ribarvirin

- PEG-IFN: fatigue, flu-like symptoms, headache, dizziness, anorexia, depression, abdominal pain, irritability, insomnia, injection-site reaction, partial hair loss
- Ribavirin: hemolytic anemia, insomnia, teratogenic effects

Sustained viral response (SVR)

- Genotype 1 (48 wks, ≤50% SVR)
- Genotype 2 (24 wks, 80% SVR)

Poor response in special populations

- Cirrhosis patients (SVR 30%)
- HIV co-infected patients (SVR < 30%)
- African American patients (SVR < 20%)

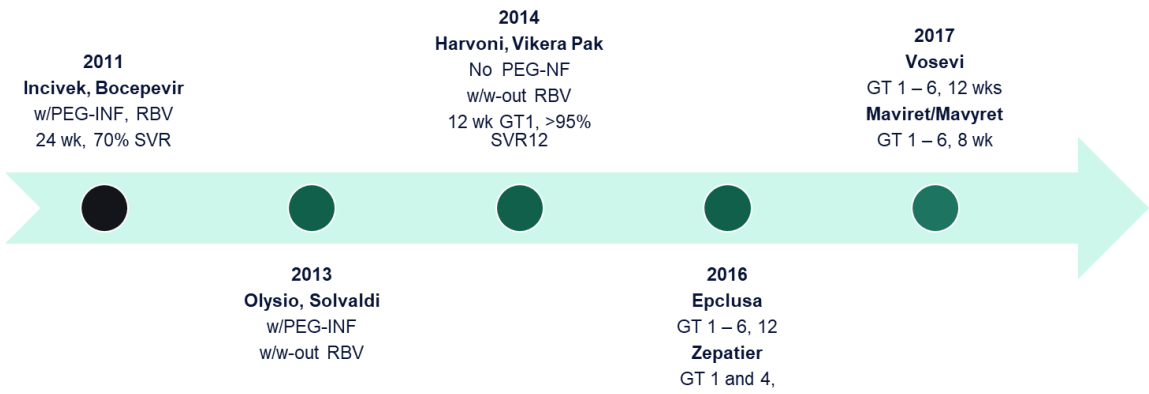
and Since..

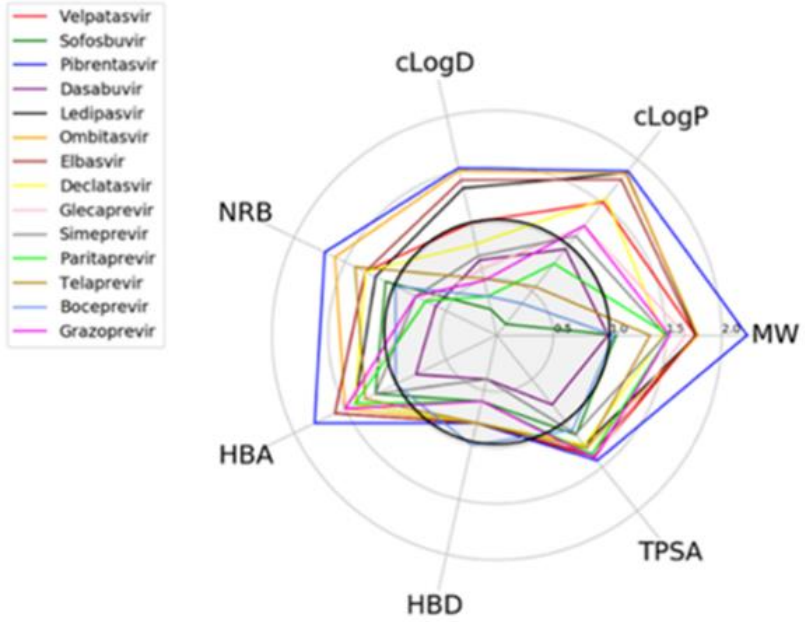
7 approved all-oral interferon free direct-acting antiviral (DAA) combination regimens.

Target nonstructural proteins responsible for replication and infection of HCV

Reach SVR12 > 95% across all prevalent genotypes

SVR12 also reduces adverse liver outcomes, such as cirrhosis, hepatic decompensation, and mortality





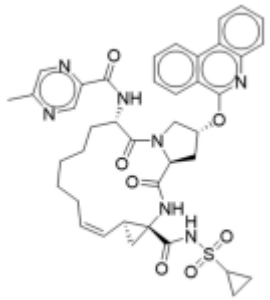
Paritaprevir- the molecule

First generation NS3/4A protease inhibitor- discovered by AbbVie and Enanta Pharmaceuticals

Approved in 2014 as part of 1st gen DAA treatment regimen

Among 25 highest molecular weight approved oral drugs

Large triaryl phenanthridine group required for high potency in flat and featureless active binding site



Paritaprevir

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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS Article

Implications of the Conformationally Flexible, Macrocyclic Structure of the First-Generation, Direct-Acting Anti-Viral Paritaprevir on Its Solid Form Complexity and Chameleonic Behavior

Ahmad Y. Sheikh,* Alessandra Mattei, Rajni Miglani Bhardwaj, Richard S. Hong, Nathan S. Abraham, Gabriela Schneider-Rauber, Kenneth M. Engstrom, Moiz Diwan, Rodger F. Henry, Yi Gao, Vivian Juarez, Erin Jordan, David A. DeGoey, and Charles W. Hutchins

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CRYSTAL GROWTH & DESIGN
pubs.acs.org/crystal Article

Distinct Hybrid Hydrates of Paritaprevir: Combined Experimental and Computational Assessment of their Hydration−Dehydration Behavior and Implications for Regulatory Controls

Published as part of a Crystal Growth and Design virtual special issue in Celebration of the Career of Roger Davey

Richard S. Hong, Rajni Miglani Bhardwaj, Rodger Henry, Alessandra Mattei, Moiz Diwan, Albert Thomas, Gerald D. Danzer, and Ahmad Y. Sheikh*

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CRYSTAL GROWTH & DESIGN
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Origins and Implications of Extraordinarily Soft Crystals in a Fixed-Dose Combination Hepatitis C Regimen

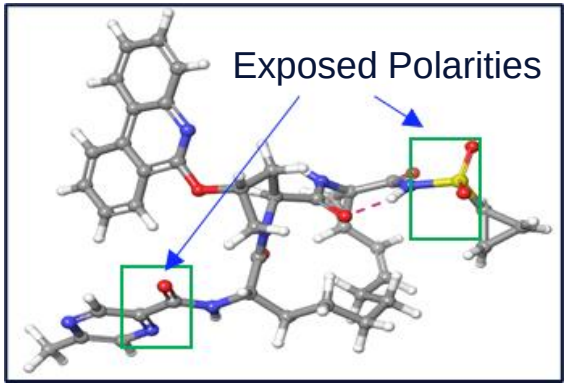
Published as part of a Crystal Growth and Design joint virtual special issue on Crystallizing the Role of Solid-State Form in Drug Delivery

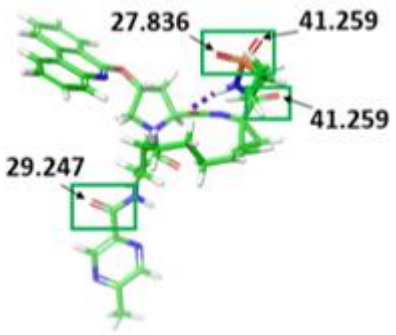
Rajni Miglani Bhardwaj, Raimundo Ho, Yue Gui, Paul Brackemeyer, Gabriela Schneider-Rauber, Fredrik L. Nordstrom, and Ahmad Y. Sheikh*

Cite This: https://doi.org/10.1021/acs.cgd.2c00264 Read Online

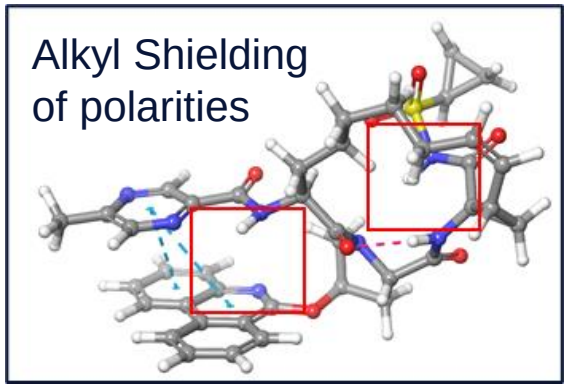
Computational Assessment of Chameleonicity

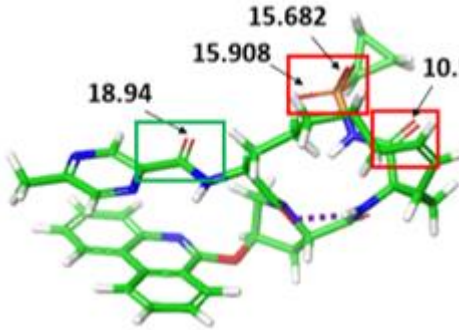
Water Conformation*
3D PSA: 201.2 A^2



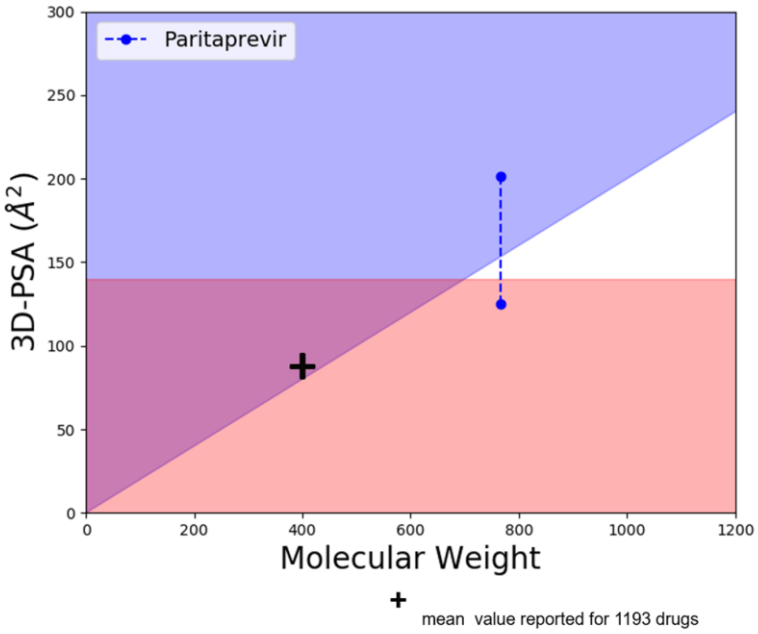


Chloroform Conformation
3D PSA: 125.1 A^2





Measured logD $^{1\text{-octano/pH }6.8}$ 3.1
Caco-2 permeability of > 60×10^{-6} cm/second
EPSA 132 A^2



Whitty, et.al, DDT, 21, 2016

*open conformations ensemble account for 52% compared to 10% in gas phase

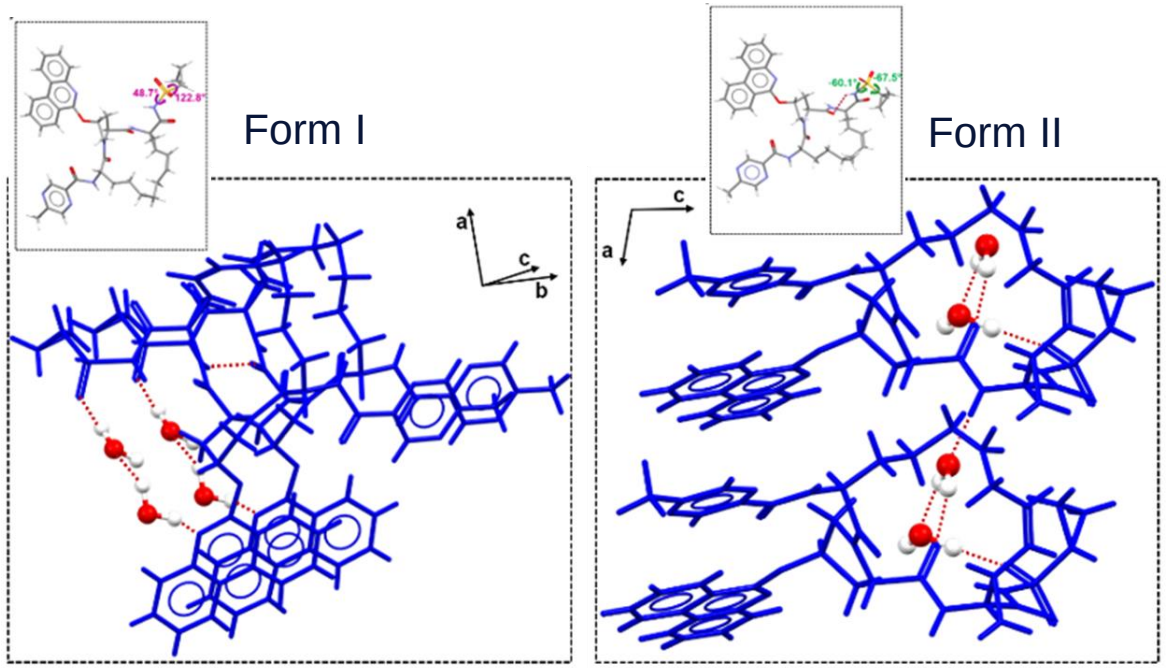
J. Am. Chem. Soc. 2021, 143, 42, 17479−17491

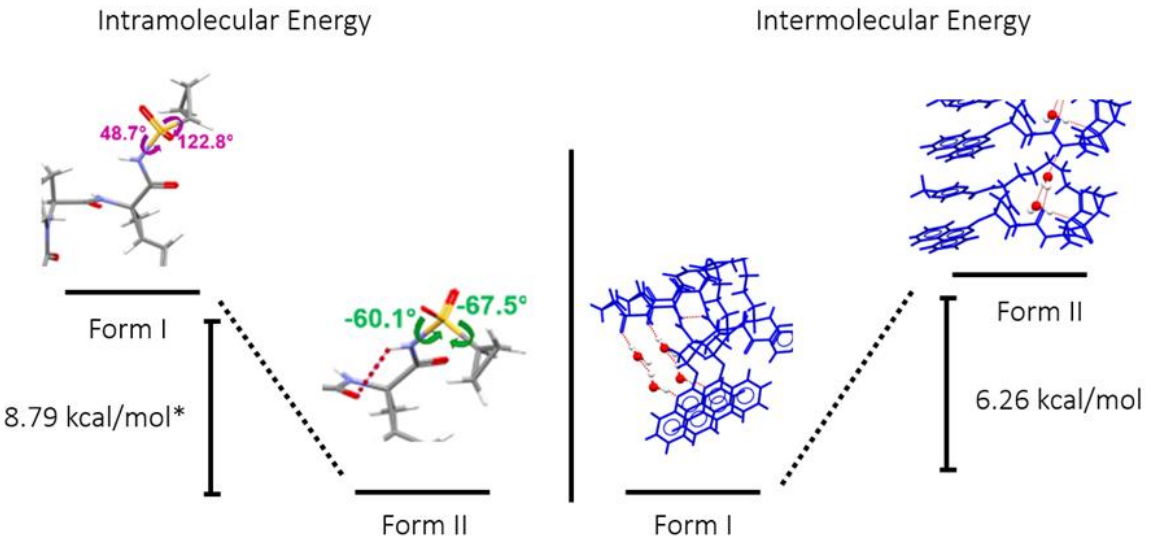
Form I and II- Conformations and interactions

Form I- No IMHB. Two intermolecular Hydrogen bonded chain motifs, leading to H-bonded planes parallel to *bc* plane. Weak π-π interactions along *c* axis between Interdigitated phenanthridine rings

Form II- IMHB between the carbonyl oxygen and the sulfonamide N-H. Stacking related layers parallel to the *bc* plane related, stabilized by weak O···H-C intermolecular interactions*

* May result in offset between layers, higher void volume and lower long-range periodicity



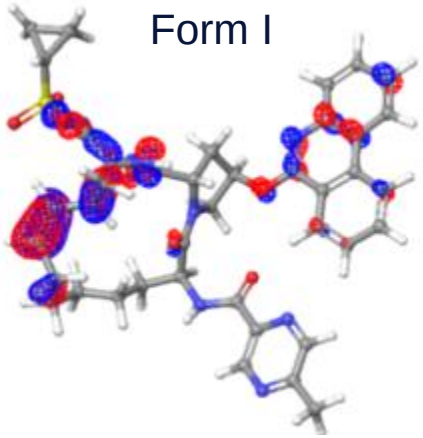


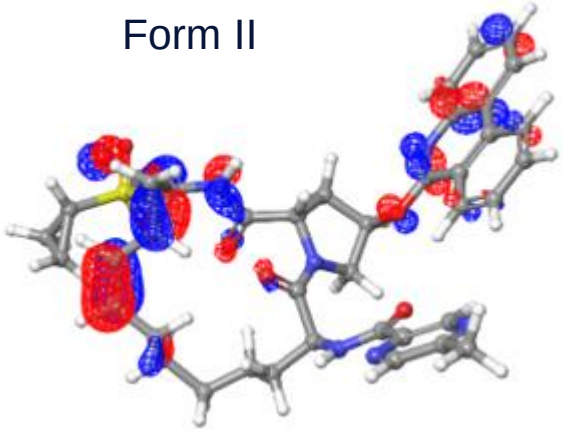
J. Am. Chem. Soc. 2021, 143, 42, 17479−17491

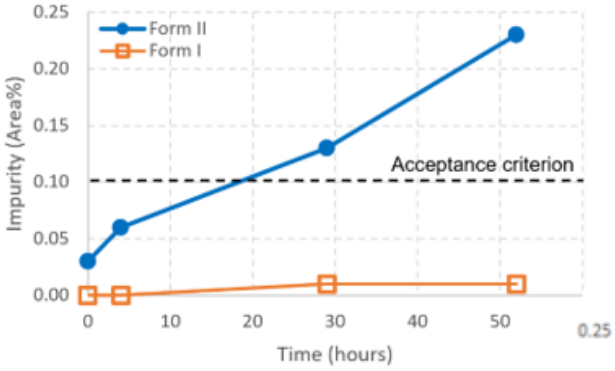
Form I and II- Differing solid state chemical reactivity

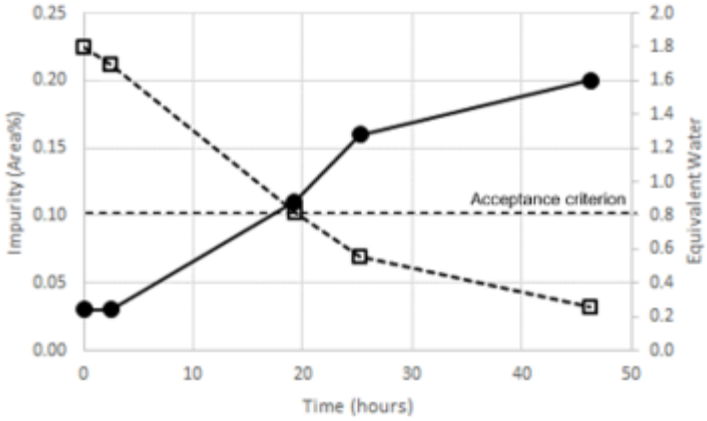
In Form I conformation, HOMO distribution spreads over double bond of macrocycle ring and not delocalized on the sulfonamide group. Distance between the centers of mass of the cyclopropyl-sulfonamide moiety and the olefin group is 1.3 Å larger than for Form II

In Form II conformation, HOMO distribution mainly delocalized on double bond of macrocycle ring and sulfonamide group. Electron density map indicates cyclopropyl-sulfonamide moiety and olefin groups can react to form the observed oxidative impurity. Removal of water adversely affects the reaction









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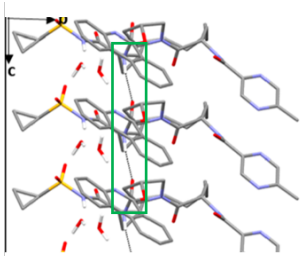
Dehydration

Form I exhibits strong host-host intermolecular interactions due to its lack of IMHB while Form II exhibits weak host-host interactions but strong host-water interactions

Due to weaker host-host interactions, Form II more amenable for hot melt extrusion processing

Form II exhibits hybrid stoichiometric and non-stoichiometric behavior with an enthalpically favored “stoichiometric regime and entropically favored non-stoichiometric regime consisting of ensembles of water bonding networks

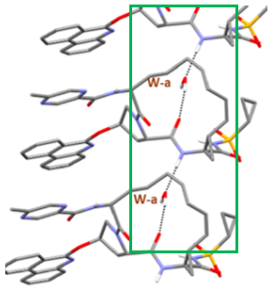
Form I



Molecules Hydrogen Bonded to Each Other

Host-Host Interaction: -78.91 kcal/mol
Host-Water Interaction: -31.98 kcal/mol

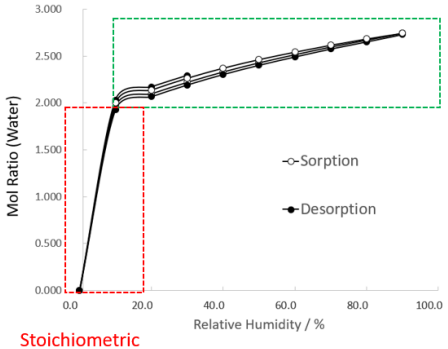
Form II



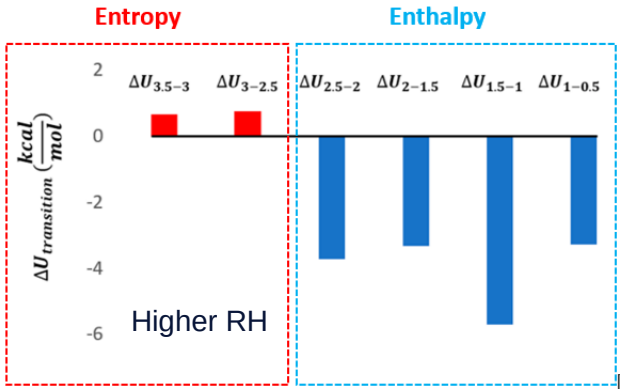
Molecule “Bridged” Together by Water H-Bonding

Host-Host Interaction: -63.83 kcal/mol
Host-Water Interaction: -39.49 kcal/mol

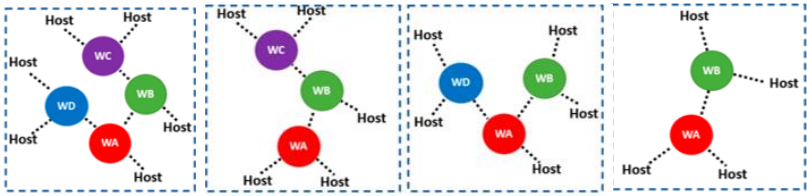
Non-stoichiometric behavior – loosely bound wate



Stoichiometric behavior – tightly bound water Di-Hydrate



Lower RH



Cryst. Growth Des. 2022, 22, 1, 726−737

Concluding Summary

Reducing or Managing complexity

- Screen out developability challenges to the extent possible
- Some targets can only be engaged with complex matter
- Early identification of the liabilities
- Broader toolkit
  - Co-processed API


abbvie