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Are Drugs Becoming More Lipophilic Over Time?

By Jamie Unwin and Christian Jones.

Nanoform is a nanoparticle medicine enabling company that works with pharma and biotech partners globally to provide hope for patients. We are focused on reducing clinical attrition and on enhancing drug molecules' performance through our nanoforming technologies and formulation services. Our capabilities include GMP manufacturing, and our services span the small to large molecule development space with a focus on solving solubility and bioavailability challenges and on enabling novel drug delivery applications.

Drug lipophilicity is a core property that contributes to drug solubility, permeability, metabolic disposition, and other key properties. Increasing lipophilicity can often lead to increased affinity in relevant biological assays due to the hydrophobic nature of many protein binding pockets, but this may also increase promiscuity to off-targets. High drug lipophilicity can lead to challenges including but hardly limited to poor solubility in water, which limits bioavailability and the maximum absorbable dose.

There's a feeling throughout the industry that the drugs of today are different from the drugs of decades past. Did the chemists of the 1970s use the phrase "brick dust" to describe their molecules as frequently as modern chemists on kinase programs do? Given the importance of drug lipophilicity, we decided to dig into feeling this a bit further and investigate how drug lipophilicity has changed over the last few decades with some data.

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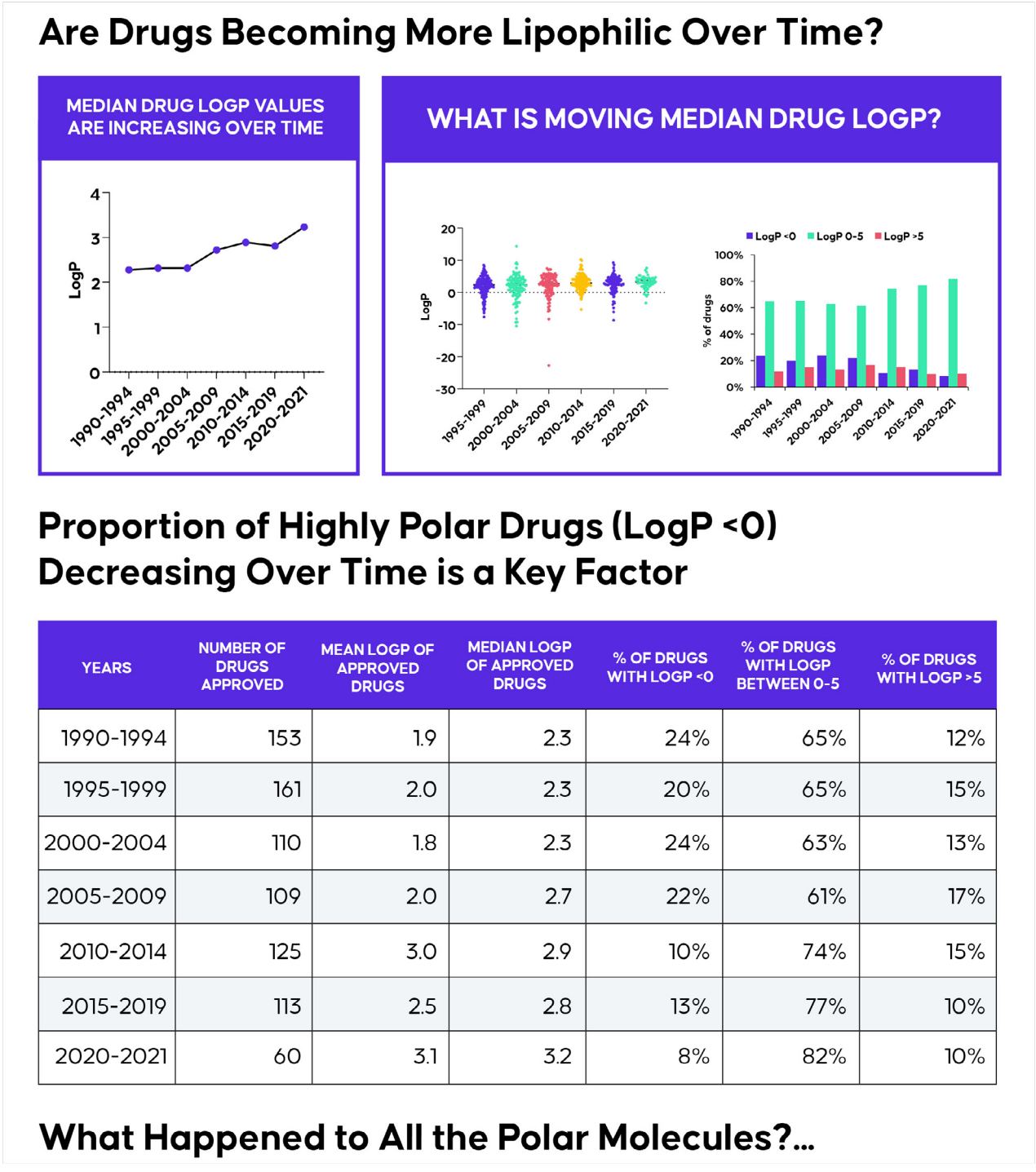
DRUGS ARE GETTING MORE LIPOPHILIC OVER TIME

LogP is a well-established barometer for drug lipophilicity. Analyzing the LogP values of approved drugs from 1990-2021 (in 5 year bins) revealed that both the mean and median drug LogP values appear to be increasing over time.[1]



YEARS	NUMBER OF DRUGS APPROVED	MEAN LOGP OF APPROVED DRUGS	MEDIAN LOGP OF APPROVED DRUGS	% OF DRUGS WITH LOGP <0	% OF DRUGS WITH LOGP BETWEEN 0-5	% OF DRUGS WITH LOGP >5
1990-1994	153	1.9	2.3	24%	65%	12%
1995-1999	161	2.0	2.3	20%	65%	15%
2000-2004	110	1.8	2.3	24%	63%	13%
2005-2009	109	2.0	2.7	22%	61%	17%
2010-2014	125	3.0	2.9	10%	74%	15%
2015-2019	113	2.5	2.8	13%	77%	10%
2020-2021	60	3.1	3.2	8%	82%	10%

Figure 1. Drugs are becoming more lipophilic over time, but what is moving median drug LogP? The proportion of highly polar drugs (LogP <0) decreasing over time appears to be a key factor.

The mean and median values over time show a surprisingly large 1 unit increase in LogP over the last two decades. This change appears especially significant given the logarithmic nature of LogP – every additional unit of LogP translates to an order of magnitude' increase in lipophilicity.

WHY DO DRUGS APPEAR TO BE GETTING MORE LIPOPHILIC?

What is moving median drug LogP? Our first suspicion was that the number of highly lipophilic molecules was increasing. However, the proportion of highly lipophilic drugs (LogP >5) remained relatively constant or decreased over this timeframe (see Table above). So, the increase in median LogP was not explained by growth in the number of highly lipophilic molecules.

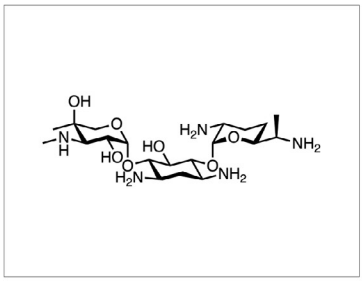
On the other hand, a decrease in the number and proportion of highly polar molecules (LogP < 0) appeared to occur, most noticeably by 2010. This suggests that a primary driver of the apparent increase in the overall lipophilicity of drugs is actually the decrease in the proportion of highly polar molecules.

WHAT HAPPENED TO ALL THE POLAR MOLECULES?

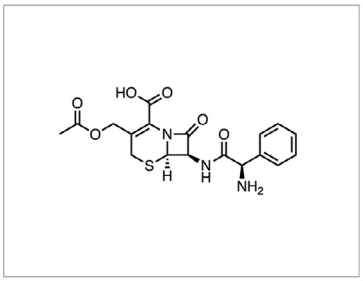
As chemistry aficionados, seeing the numbers alone wasn't satisfying. To better understand what was happening at the molecular level, we looked at the structures of highly polar drugs approved from 1970 and 2021. A closer look at the structures of these hydrophilic molecules revealed that they were largely natural products or natural product-derived molecules, which likely brings immediate clarity to industry practitioners.

Examples of Polar Drugs from 1970 and 2021

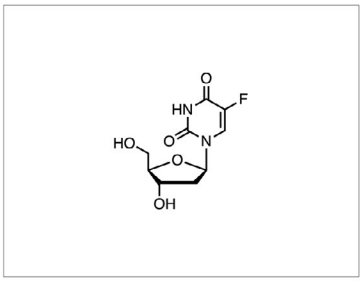
1970



gentamicin
cLogP = -4.1

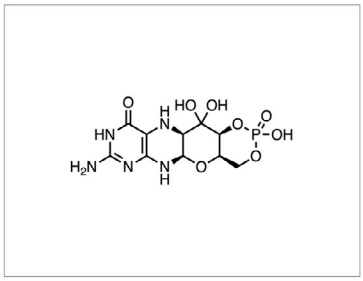


cephaloglycin
cLogP = -3.0

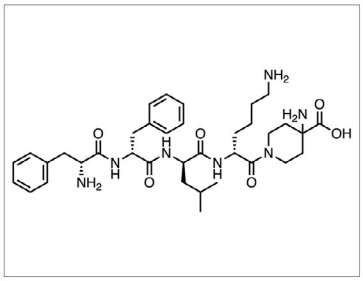


floxuridine
cLogP = -1.2

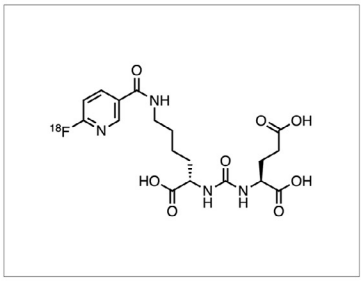
2021



fosdenopterin
cLogP = -4.0



difelikefalin
cLogP = -0.6



piflufolastat F-18
cLogP = -0.1

Figure 2. Examples of polar drugs from 1970 and 2021. Most polar drugs that are approved each year are predominantly natural products or natural product-derived molecules. cLogP = calculated LogP from PubChem (XlogP3 3.0).

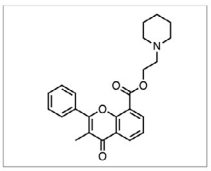
From 1981-2010, approximately 50% of the new FDA-approved drugs were related to natural products (e.g., semi-synthetic analogs). However, issues relating to synthetic tractability, purification, and off-target toxicity led to the reduction or discontinuation of natural product drug discovery programs by many pharmaceutical companies in the 1990s and early 2000s in favor of modern target-oriented drug discovery. This corresponds to the data seen in Figure 1, resulting in a decline in lead compounds in the 2000s, translating to a decrease in FDA approvals by 2010, which precipitated the increase in median LogP.

DESPITE MOVING AWAY FROM NATURAL PRODUCTS FULLY SYNTHETIC DRUGS CONTINUE TO GROW IN DIVERSITY AND COMPLEXITY

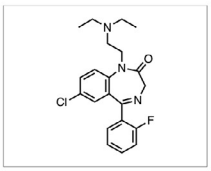
We were also curious about how fully synthetic molecules have changed since 1970. Representative structures of fully-synthetic molecules from 1970 and 2021 are shown in Figure 3, along with key properties.

Examples of fully-synthetic molecules from 1970 and 2021

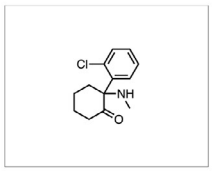
1970



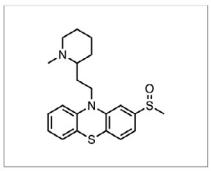
flavoxate
MW = 392
LogP = 4.3
HBA = 5
HBD = 0
Fsp^3 = 0.33



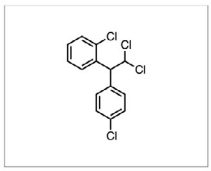
flurazepam
MW = 388
LogP = 3.0
HBA = 4
HBD = 0
Fsp^3 = 0.33



ketamine
MW = 238
LogP = 2.2
HBA = 2
HBD = 1
Fsp^3 = 0.46

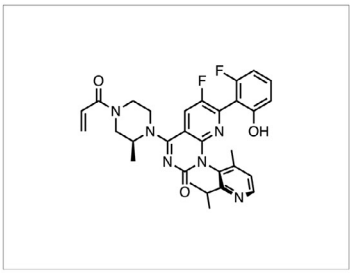


mesoridazine
MW = 387
LogP = 4.5
HBA = 5
HBD = 0
Fsp^3 = 0.43

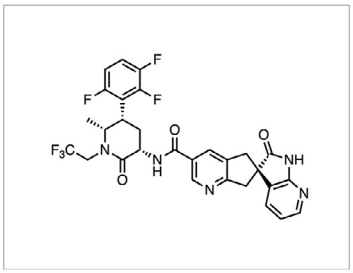


mitotane
MW = 320
LogP = 6.2
HBA = 0
HBD = 0
Fsp^3 = 0.14

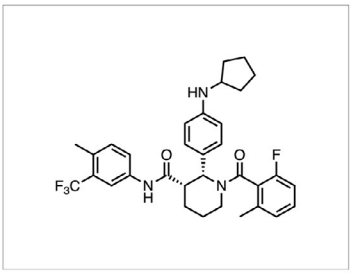
2021



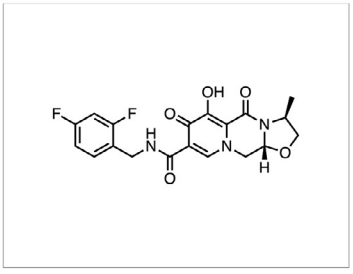
sotorasib
MW = 561
LogP = 4.0
HBA = 7
HBD = 1
Fsp^3 = 0.30



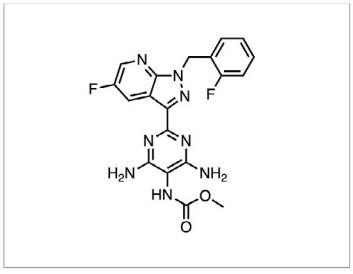
atogepant
MW = 604
LogP = 3.4
HBA = 11
HBD =2
Fsp^3 = 0.34



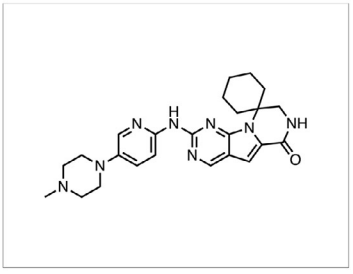
avacopan
MW = 582
LogP = 7.2
HBA = 7
HBD = 2
Fsp^3 = 0.39



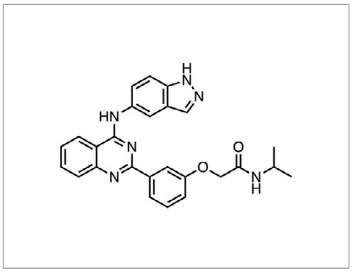
cabotegravir
MW = 405
LogP = 2.1
HBA = 8
HBD = 2
Fsp^3 = 0.32



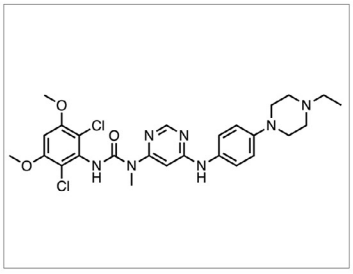
vericiguat
MW = 426
LogP = 1.5
HBA = 10
HBD = 3
Fsp3 = 0.10



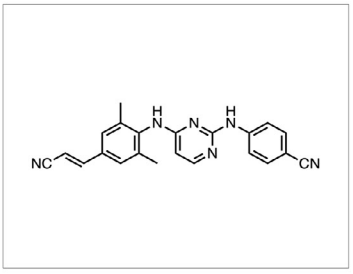
trilaciclib
MW = 447
LogP = 2.6
HBA = 7
HBD = 2
Fsp^3 = 0.50



belumosudil
MW = 453
LogP = 4.8
HBA = 6
HBD = 3
Fsp^3 = 0.15



infigratinib
MW = 561
LogP = 4.7
HBA = 8
HBD = 2
Fsp^3 = 0.35



rilpivirine
MW = 366
LogP = 4.5
HBA = 6
HBD = 2
Fsp^3 = 0.09

Figure 3. Examples of fully-synthetic molecules from 1970 and 2021, with calculated properties. For consistency, data were acquired from PubChem, where MW stands for molecular weight, HBA stands for hydrogen bond acceptor, HBD stands for hydrogen bond donor, Fsp3 is the fraction of sp3 carbons to the total number of carbons. The calculated LogP values ("cLogP") were calculated using XLogP3 3.0. HBA counts include fluorine atoms and heterocyclic nitrogen atoms; although many chemists would not consider these to be strong hydrogen-bond acceptors, they are unadjusted for consistency.

On visual inspection, the fully-synthetic molecules of today tend to be more complex than their 1970s counterparts. This is not surprising given the modern advances in synthetic chemistry. Sotorasib, one of the molecules approved in 2021, for example, is manufactured as a configurationally stable atropisomer.

MODERN TECHNOLOGY FOR MODERN DRUGS

Even though we've drifted away from natural products as the primary source of inspiration for complex structures, today's drug candidates have evolved to another level of intricacy with unique physicochemical properties. Increased lipophilicity, greater aromatic ring counts, and related properties are likely to increase the need for strategies to improve bioavailability beyond compound optimization alone. Enabling technologies like nanoformulation can be leveraged to facilitate oral bioavailability of these new drugs and further expand the diversity and complexity of the drug molecules we'll soon see in the future.

Reach out to our team at Nanoform to learn more about how we can help you solve bioavailability and drug delivery challenges with modern technology.

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FURTHER READING

- For an excellent previous review of how oral drug properties changed from the period before 1983 to 2002, see: Leeson, P. D. and Davis, A. M., "Time-Related Differences in the Physical Property Profiles of Oral Drugs." J. Med. Chem. 2004, 47, 6338-6348.
- For a recent analysis of the percentage of FDA-approved drugs that are natural products, see: Partridge, E. et al. "An analysis of FDA-approved drugs: natural products and their derivatives." Drug Discov. Today, 2016, 21, 204-207

Footnotes

[1]Data on small molecule FDA-approved drugs between 1990 to 2021 from the Pharmaprojects database (Citeline), including their LogP values (measured where available or calculated when not). Drugs were binned in 5-year increments according to the year of their respective approval and further subdivided by their LogP values.

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