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discover together

nanoform
small is powerful

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Not Your Grandparents' Drugs: How Approved Drugs Have Evolved Since the 70's

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.

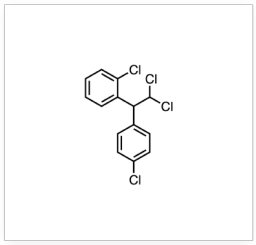
We recently explored how the lipophilicity (logP) of drugs has changed over time and found that, on average, drugs have become more lipophilic through the decades, primarily attributable to the industry's move away from natural products. Despite this shift, it is clear from a broad qualitative comparison of structures from past decades to today that fully synthetic drugs continue to grow in diversity and complexity (Figure 1).

Read this article online to see all of the resources and download the PDF reference poster
https://drughunters.com/NF-NYGPD

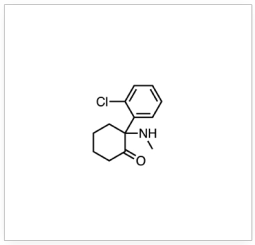
Figure 1. Select Examples of Fully Synthetic Approved Drugs and Drug Hunter's Molecules of the Month/Year Candidates

Select Examples of Fully Synthetic, Approved Drugs and Drug Hunter's Molecules of the Month/Year Candidates

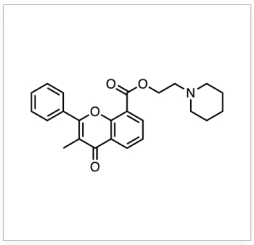
1970



mitotane
HRA Pharma (Bristol-Myers)

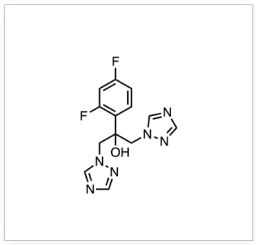


ketamine
Par Sterile Products (Parke-Davis)

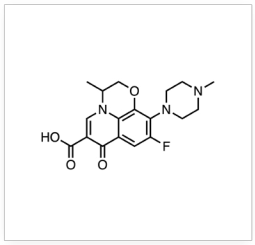


flavoxate
Ortho-McNeil-Janssen

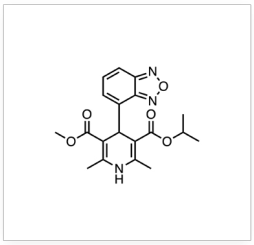
1990



fluconazole
Pfizer

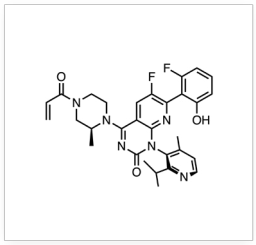


ofloxacin
Janssen (Daiichi Sankyo)

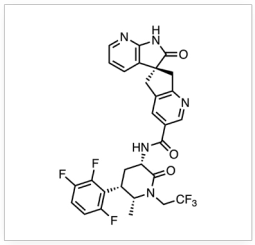


isradipine
SmithKline Beecham (Sandoz)

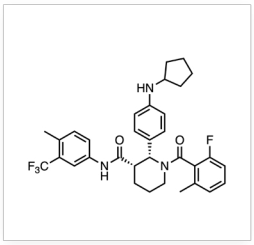
2021



sotorasib
Amgen

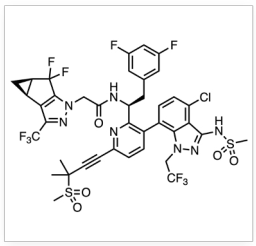


atogepant
AbbVie (Merck Sharp and Dohme)

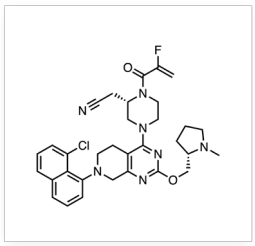


avacopan
Amgen (ChemoCentryx)

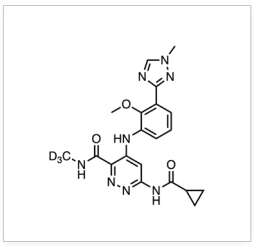
2022



lenacapavir
Gilead

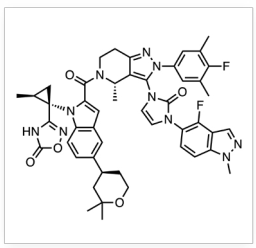


adagrasib
Mirati (Array BioPharma & Mirati)

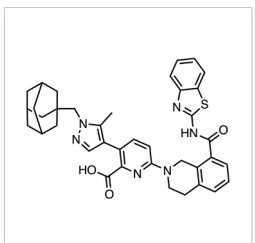


deucravacitinib
BMS (Syngene & BMS)

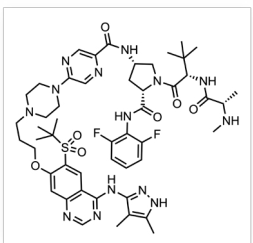
Molecules of the Month/Year



LY3502970
Eli Lilly



A-1331852
AbbVie/Genentech



compound 20
GSK

In the 1970's and 1990's, it would have been rare to see a molecule with a single resolved chiral center. Many of these older, fully synthetic drugs were small, relatively flat, and non-polar (low TPSA). In terms of size, the synthetic molecules of this era did not get much larger than flavoxate or isradipine. Of the six highlighted in Figure 1, five of these molecules were manufactured in their racemic forms, although the FDA recently approved chirally pure (S)-ketamine for treatment-resistant depression in 2019.

In contrast, it is now common to see molecules among contemporary approved drugs (2021-2022) with multiple stereocenters or more than five rings. Synthetically challenging motifs including gem-difluoroalkanes, cyclopropanes, or spirocycles are regularly found in these therapeutics, and previously rare features such as axial chirality or deuterium incorporation are even making their way into drugs. Quantitatively, many modern molecules have property values that would have raised eyebrows several decades ago, such as lenacapavir with a MW of 968, avacopan with a LogP of 7.2, several orally available molecules with >10 HBA and/or a TPSA >130. Lenacapavir even set a new record for the number of fluorines present in an approved drug – 10!

Table 1. Physicochemical properties of selected approved drugs and drug candidates.

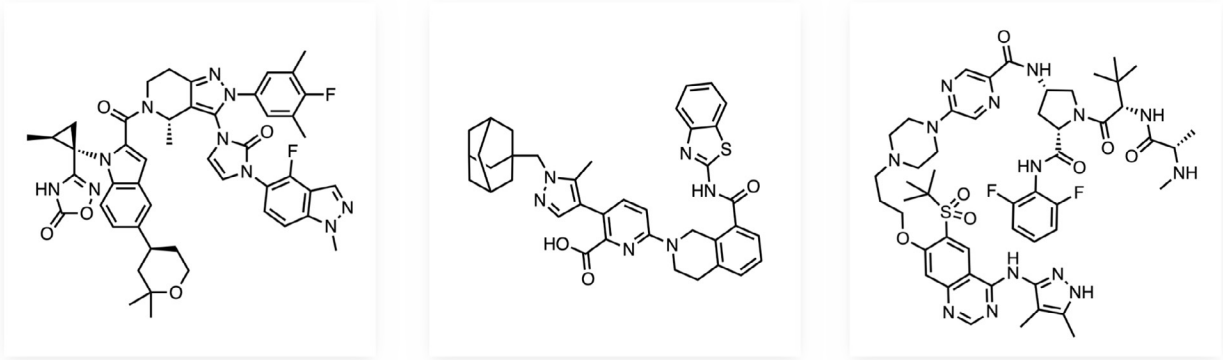
Drug Name	Approval Year	MW	LOGP	HBA	HBD	FSP^3	TPSA ($Å^2$)
mitotane	1970	320	6.2	0	0	0.14	0
ketamine	1970	238	2.2	2	1	0.46	29.1
flavoxate	1970	392	4.3	5	0	0.33	55.8
fluconazole	1990	306	0.4	7	1	0.23	81.6
ofloxacin	1990	361	-0.4	8	1	0.44	73.3
isradipine	1990	371	4.3	8	1	0.37	104.0
sotorasib	2021	561	4.0	7	1	0.30	102.0
atogepant	2021	604	3.4	11	2	0.34	104.0
avacopan	2021	582	7.2	7	2	0.39	61.4
lenacapavir	2022	968	6.4	19	2	0.36	175.0
adagrasib	2022	604	5.0	9	0	0.44	88.8
deucravacitinib	2022	426	1.2	8	3	0.30	136.0
LY3502970	N/A	883	6.8	10	1	0.38	144.0
A-1331852	N/A	659	7.5	8	2	0.39	142.0
compound 20	N/A	1045	4.7	18	6	0.50	270.0

The originator of the drug shown in parentheses in Fig. 1 was identified using the earliest patent listed in the FDA Orange Book or from the NCATs Inxight database for drug approvals before 1990, and sponsor information was acquired from the FDA's approval database (Drugs@FDA). Physicochemical properties from PubChem were used. The cLogP data were calculated using XLogP3 3.0, molecular weights were calculated using PubChem 2.1, and HBD, HBA, and TPSA were calculated using Cactvs 3.4.8.18. Fsp^3 was calculated manually.

WHAT WILL THE NEXT GENERATION'S DRUGS LOOK LIKE?

Despite pharmaceutical companies shying away from natural products and the inherent discovery and development challenges that came with them in the 20th century, new synthetic drug candidates have nevertheless evolved to a comparable level of complexity. This has been enabled by tremendous advances in synthesis, isolation, and compound characterization, allowing scientists to access chemical matter that was previously unattainable, on larger scales and at the pace required for drug development. A look through recent molecules in Drug Hunter's Molecules of the Month series provides a glimpse at the complexity of the molecules that are on their way to becoming the drugs of the future.

Figure 2. Selected Examples from Drug Hunter's "Molecules of the Month" Series



LY3502970
Eli Lilly
featured Nov 2020

A-1331852
AbbVie/Genentech
featured Jul 2020

compound 20
GSK
featured Aug 2021

Selected examples from the Drug Hunter "Molecules of the Month" series, including LY3502970, a GLP-1R partial agonist, A-1331852, an oral BCL-XL inhibitor, and "compound 20," a RIPK2 heterobifunctional degrader.

With further innovations in synthetic technologies such as catalysis, machine learning, automation, and evolving lead generation and screening approaches, even more complex but druggable molecules are likely to be developed, paving the way for advanced therapeutics in time for us as retirees, and for the next generations of patients to come.

MODERN DRUG FORMULATION TECHNOLOGY FOR MODERN DRUGS

Even though we've drifted away from natural products as the primary source of inspiration for complex structures, drug candidates of today have evolved to another level of intricacy with the corresponding unique physicochemical properties. Increased lipophilicity, aromatic ring counts, heavy atoms and related properties will require innovative 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 molecules we'll soon see approved in the future.

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

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FURTHER READING

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DNA-encoded libraries
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Machine learning in drug discovery
Advances in covalent drug discovery

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