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Perspective

An Update on the Nitrogen Heterocycle Compositions and Properties of U.S. FDA-Approved Pharmaceuticals (2013−2023)

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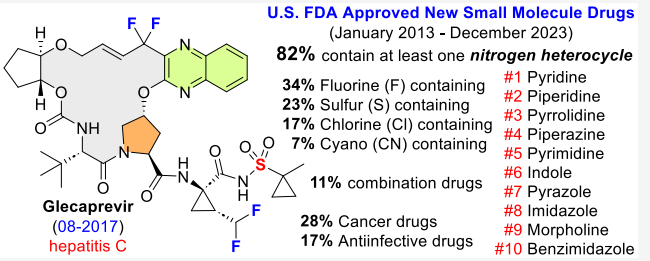
ABSTRACT: This Perspective is a continuation of our analysis of U.S. FDA-approved small-molecule drugs (1938−2012) containing nitrogen heterocycles. In this study we report drug structure and property analyses of 321 unique new small-molecule drugs approved from January 2013 to December 2023 as well as information about frequency of important heteroatoms such as sulfur and fluorine and key small nitrogen substituents (CN and NO_2). The most notable change is an incredible increase in drugs containing at least one nitrogen heterocycle—82%, compared to 59% from preceding decades—as well as a significant increase in the number of nitrogen heterocycles per drug. Pyridine has claimed the #1 high-frequency nitrogen heterocycle occurrence spot from piperidine (#2), with pyrimidine (#5), pyrazole (#6), and morpholine (#9) being the big top 10 climbers. Also notable is high number of fused nitrogen heterocycles, apparently driven largely by newly approved cancer drugs.



■ SIGNIFICANCE

This Perspective reinforces the significant role nitrogen heterocycles play as diverse tunable structural components of U.S. FDA-approved drugs (2013−2023). This follow-up study reveals major increases in 1) the percentage of drugs containing a nitrogen heterocycle, 2) the number of nitrogen heterocycles per drug, and 3) the diversity of nitrogen heterocycles as well as the important roles fluorine and sulfur substituents continue to play. New atoms (B, D, and Si) are also introduced into this arena.

■ INTRODUCTION

This Perspective is a continuation and an update to our 2014 Perspective[1] focused on the frequency, substitutions, structures, and disease-focused applications of unique small-molecule U.S. FDA-approved drugs containing nitrogen heterocycles. Our earlier study covered small-molecule drugs approved by the FDA since its founding until December 2012. This update covers drugs approved from January 2013 to December 2023 (11 years), which are represented by 321 unique small-molecule drugs (Figure 1), of which 36 (11%) are new structural components of combination drugs.[2] This dataset also includes several new small-molecule diagnostic agents, most notably represented by metal-chelated cyclen structures. In drawing the line for what constitute small molecules, we decided to include all structures wherein every single atom, bond, and functional group could be presented clearly in a reasonable size image without any abbreviations; thus, a handful of medium-sized peptide drugs are also presented. This study reveals an incredible increase in drugs containing nitrogen heterocycles, with previous study revealing a 59% representation of drugs containing at least one nitrogen heterocycle, whereas the present study reveals that **82%** of new small-molecule drugs approved during this period contain a nitrogen heterocycle. Furthermore, the number of nitrogen heterocycles per drug is also significantly on the rise (Figure 1a), with large numbers of drugs containing two (33%), three (23%), or four (8%) nitrogen heterocycles and with two approved structures containing six nitrogen heterocycles. A key new significant growth trend is the use of diverse types of fused nitrogen heterocycles, the majority of which were absent in the earlier study. Six-membered non-aromatic nitrogen heterocycles appear most frequently, followed by fused and six-membered aromatic ones (Figure 1b). Not surprisingly, the majority of these nitrogen heterocycles are composed of six- or five-membered aromatic or non-aromatic rings, with nitrogen macrocycles being the largest category beyond those. Classic natural-product-derived nitrogen heterocycles such as cephems, penams, morphinans, tropanes, and ergolines are barely present in this dataset.[3] To add more dimensions to this study, and in the spirit of the other two Perspectives we reported the same year[4,5] as our seminal nitrogen heterocycle study, we have also analyzed the frequency and specific structural details of this dataset with respect to

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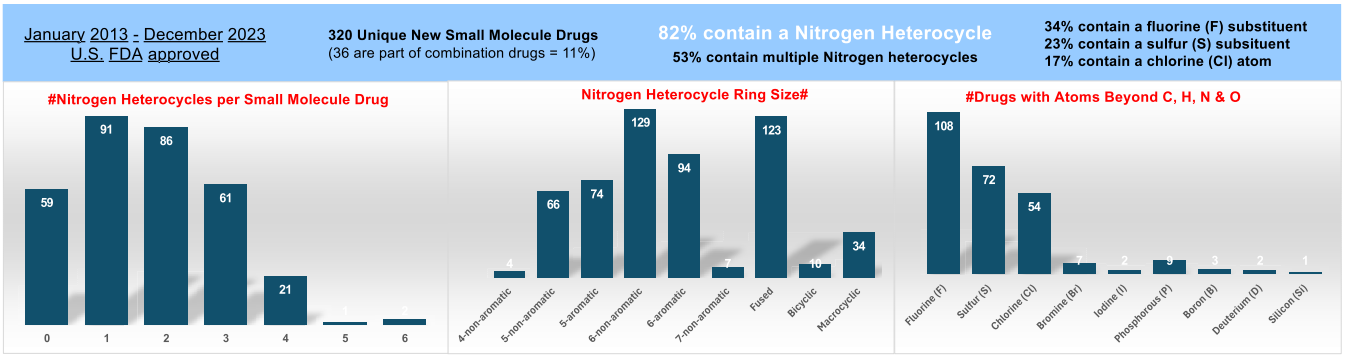

Figure 1. Breakdown of the nitrogen heterocycle composition of U.S. FDA-approved small-molecule drugs (January 2013−December 2023).

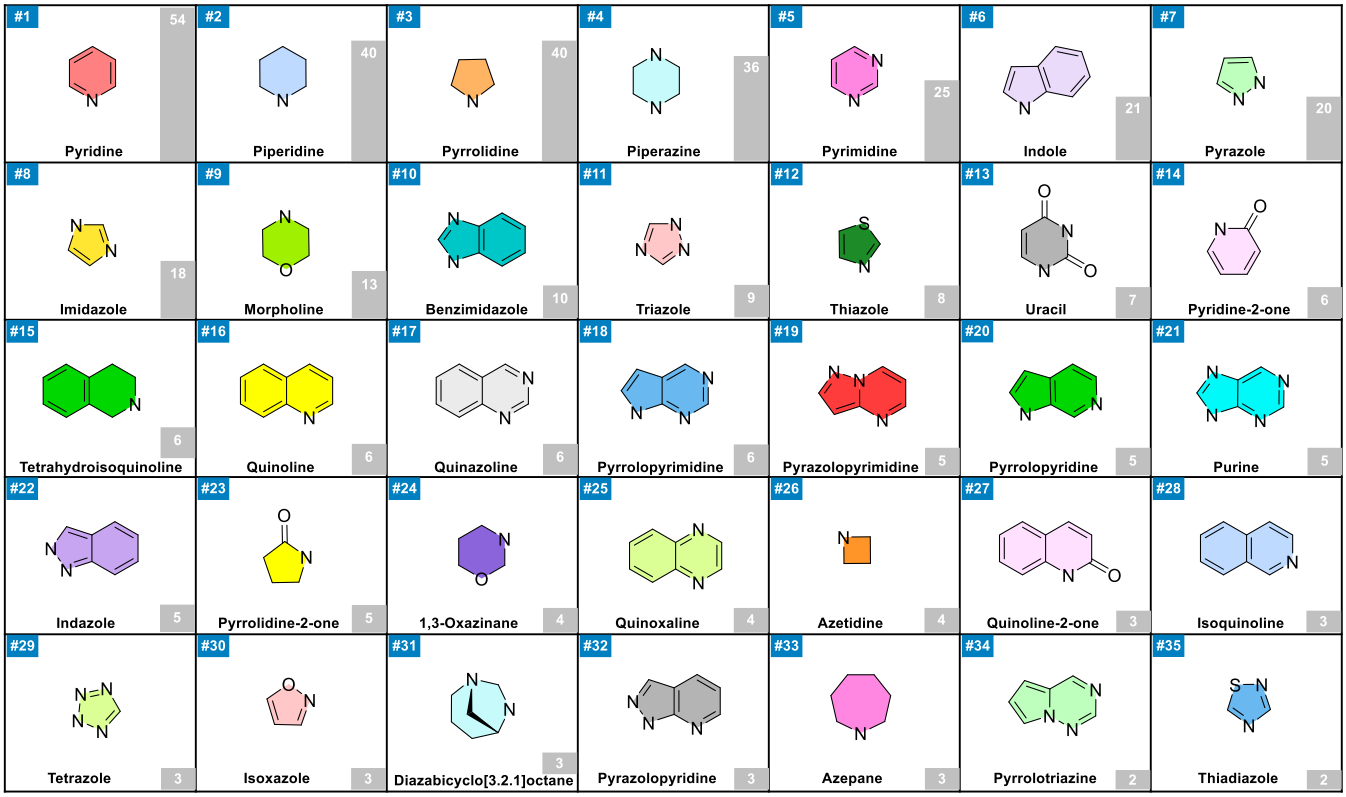

Figure 2. Top 35 most frequently appearing nitrogen heterocycles in U.S. FDA-approved drugs (January 2013−December 2023).

occurrences of elements beyond carbon, hydrogen, oxygen, and nitrogen, as summarized in Figure 1c, with fluorine,[6−8] sulfur,[9] and chlorine representing the most significant of these atom substitutions. This dataset reveals that 34% of these drugs contain at least one fluorine substituent, 23% contain a sulfur substituent, and 17% contain at least one chlorine atom.

The largest group (89, 28%) of these new small-molecule drugs are approved for cancer treatments, of which 55 are kinase inhibitors.[10,11] Anti-infective drugs constitute the second most frequent disease category, represented by 56 (17%) new drugs, of which 10 are approved for hepatitis C—an incredible success story on the frontier of antiviral drug discovery. These new hepatitis C drugs are further notable for their complexity, stereochemical richness, use of symmetry, diversity of substituents, and use of the uncommon quinoxaline nitrogen heterocycle along with a pyrrolidine and in many cases a nitrogen-containing macrocycle.[12] This dataset also includes five new migraine[13] and six new diabetes[14] small-molecule drugs as well as new Parkinson's disease,[15] MS,[16] and ALS[17] medications. Multiple new small-molecule treatments for eye-,[18] skin-, and bowel-related conditions have emerged during the past decade. In the following figures, the structures of nearly all of these small-molecule drugs are shown, along with their disease indications.

Displayed in Figure 2 are the top 35 nitrogen heterocycles that appear in this dataset of unique new small-molecule U.S. FDA-approved drugs, organized according to their frequency of appearance. Each box displays a color-coded nitrogen heterocycle along with its (a) frequency of appearance rank (#), (b) international nonproprietary name (INN) drug name, and (c) drawn-to-scale bar (gray) displaying how many drugs this nitrogen heterocycle appears in. In deciding when to include or separate oxidized version of certain ring types, we chose to include oxidized versions of non-aromatic rings (such as lactams), the only exception being 2-pyrrolidinone, while separating into different sections oxidized versions of aromatic

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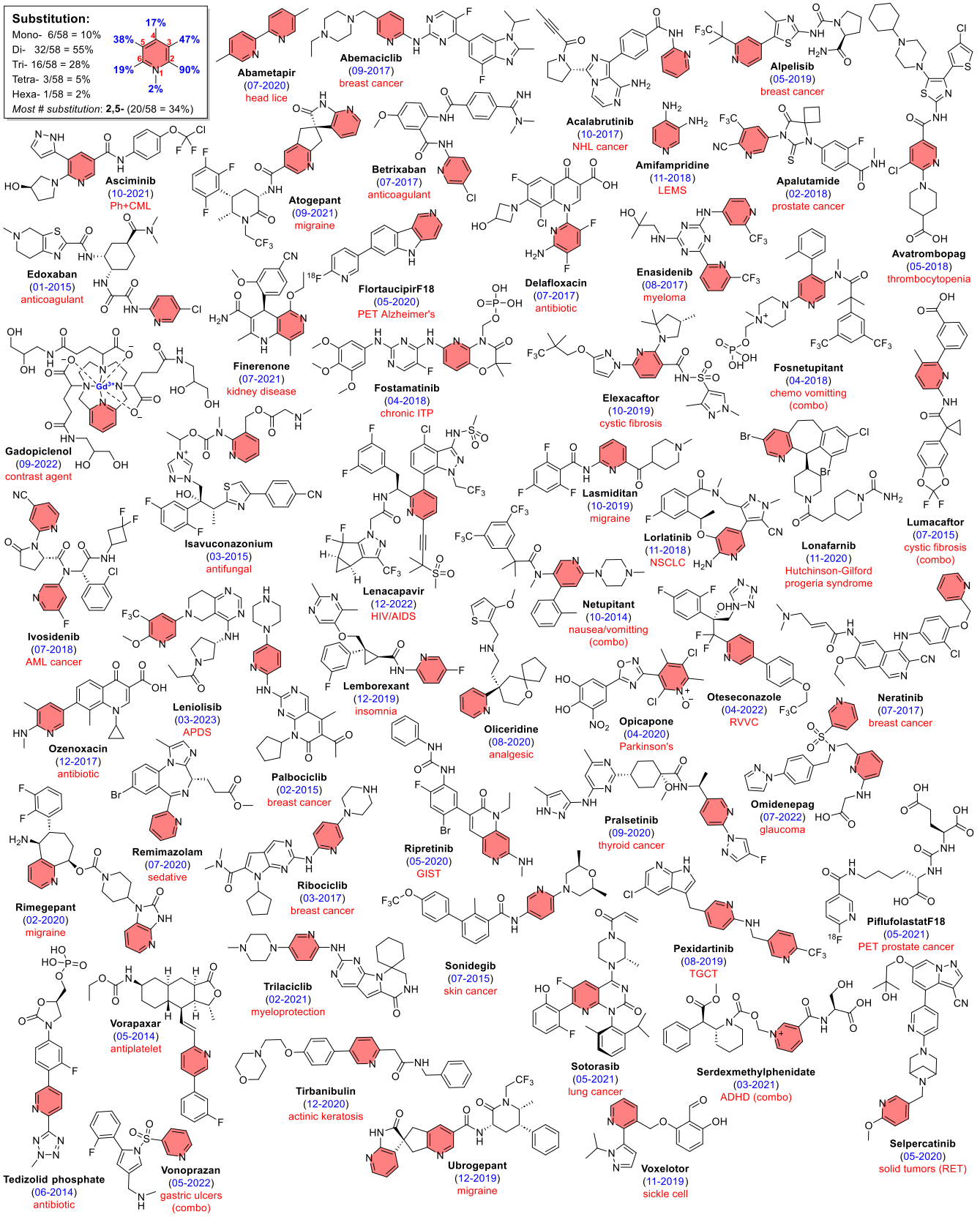

Figure 3. New U.S. FDA-approved small-molecule pyridine (#1)-containing drugs.

rings (pyridine vs pyridine-2-one and quinoline vs quinoline-2-one). Comparing this top 35 list of nitrogen heterocycles appearing in the 321 drugs from January 2013 to December 2023 (11 years) to the top 25 list from the founding of the U.S. FDA to December of 2012 from our earlier study 10 years ago reveals some significant changes. With respect to the top five most frequent nitrogen heterocycles, pyridine has claimed the #1 spot from piperidine (#2), pyrrolidine has jumped to a tie

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with piperidine from #5, piperazine has dropped to #4 from #3, and pyrimidine is the big newcomer, landing the #5 spot, representing a big climb from #10 earlier. When fused and oxidized derivatives of pyridines are also factored in, its rank as #1 becomes even more dominating. Cephem-containing drugs represented the #4 spot in our earlier studies, and their drop is certainly not surprising, given less focus on synthesis and approval of β-lactam antibiotics, although it is noteworthy that during these past 11 years two new cephem drugs (ceftolozane and cefiderocol) were approved. For the rest of the top 10, penams (another classic β-lactam antibiotic core) and phenothiazines are not found anymore, and tetrazoles have dropped from #10 to #29. The most notable new entry and biggest climber is pyrazole (#6), which was absent in the earlier dataset, with indoles and imidazoles maintaining similar positions (#7 and #8 respectively, compared to #9 and #7 earlier) and major climbs for morpholine (#9 from #17 before) and benzimidazole (#10 from #15). In terms of changes in the top 11−20, triazoles (from #24 to now #11) are the biggest climber, with a significant fall for thiazoles (from #6 to now #12) and a number of new quinoline derivatives and fused nitrogen heterocycles, such as pyrrolopyrimidine and pyrazolopyrimidine. The remainder of the top 35 is represented by multiple fused nitrogen heterocycles, of which many contain more than one nitrogen atom, as well as one strained (azetidine, #26) and one bridged bicyclic (#31) nitrogen heterocycle. It is interesting to note that oxazole does not appear in the top ranks in this study (two benzoxazole drugs were approved) or in our earlier study, despite its significant representation in natural products,[19] although its far less naturally occurring isomeric counterpart isoxazole continues its top-ranking appearance (dropped from #24 to #30).

U.S. FDA-APPROVED NITROGEN-CONTAINING DRUGS (JANUARY 2013−DECEMBER 2023)

The following sections and accompanying figures provide detailed insights about each of the top 35 nitrogen heterocycles: the exact chemical structures of all relevant members, each highlighted with the color code presented in Figure 2, along with their international nonproprietary name (INN), date of approval, and disease indication. It is our hope and intention that this approach will, in the spirit of our Top 200 pharmaceutical poster series,[20,21] allow non-experts and experts alike to quickly absorb structural themes, patterns, new architectures, disease application areas, date of approval landscape, and many more insights far more effectively than text, tables, or other non-chemical-structure formats are able to realize. The powerful graphical language of organic chemistry, which all scientists interested in making molecules and structures broadly rely on for communicating and learning, is an incredible vehicle for concisely communicating a wealth of knowledge, and our emphasis in this Perspective is to display within the following sections close to every single chemical structure that appears in this exciting drug dataset.

Pyridine (#1). Pyridine is the most frequently occurring nitrogen heterocycle in this dataset of small-molecule drugs approved January 2013−December 2023, dethroning piperidine which held the number one spot in our earlier analysis. The 54 pyridine-containing drugs are presented in Figure 3 (note: structures are presented alphabetically in Figure 3 and the following figures) along with a graphical summary of pyridine substitution statistics. When fused rings such as quinolines, isoquinolines, and pyrrolopyridines and oxidized pyridine variants (pyridine-2-one and pyridine-4-one) are also factored in, this number jumps significantly, and pyridine's number one spot is further cemented. The vast majority (90%) of pyridine drugs contain a substituent in the 2-position, with disubstituted pyridines being most common (55%), of which the 2,5-substitution is most frequent. Interestingly, more than 50% of these pyridine drugs are achiral.[22] These new pyridine-containing drugs are structurally diverse and are approved for treatment of a wide range of diseases and conditions. The vast majority of pyridine-containing drugs are used to treat cancers and cancer-related side effects and conditions. Among those are sotorasib (approved 5/2021), which is a first-in-class drug approved for treatment of non-small-cell lung cancers (NSCLC) that is also notable for being a stable atropisomer of which pyridine is a key fragment, which has received additional high visibility for its innovative synthetic assembly.[23] Leniolisib (approved 3/2023) is also a first-in-class medication approved for treatment of activated PI3K delta syndrome (APDS).[24] Leniolisib's compact core contains no less than four nitrogen heterocycles (pyridine, piperidine, pyrrolidine, and pyrimidine). Particularly notable in this pyridine dataset are four drugs approved for the treatment of migraine, of which all three members of the migraine "gepant" [25] drug family were approved recently during this period, namely utrogepant (approved 12/2019), rimegepant (approved 2/2020), and atogepant (approved 9/2021). Structurally, these are most intriguing drugs, with multiple nitrogen heterocycles, including two pyridines. Atogepant is a derivative of ubrogepant, wherein one of the aryl groups in atogepant has three aryl fluoride substituents whereas ubrogepant has none. These two drugs are also notable for intriguing spiro-ring systems, multiple chiral centers, and an intriguing trifluoroethyl lactam group. Lasmiditan (approved 10/2019) was also approved for migraine treatment during this period. This class of pyridine drugs also includes three new antibiotics, namely the prodrug tedizolid phosphate (approved 6/2014), delafloxacin (approved 7/2017), and ozenoxacin (approved 12/2017), the latter two being quinolone antibiotics.[26] Opicapone (approved 4/2020) is a new Parkinson's disease medication and the only hexa-substituted pyridine drug, as the pyridine nitrogen atom is oxidized. Abametapir (approved 7/2020) and amifampridine (approved 11/2018), approved for treating head lice and Lambert−Eaton myasthenic syndrome (LEMS), respectively, are the structurally smallest of the pyridine drugs, with one being a simple bipyridine and the other a 3,4-diamino-substituted pyridine, suggesting that both could also be potential metal chelators. Lenacapavir (approved 12/2022),[27] which is a first-in-class drug, is the only new pyridine drug approved for treating HIV/AIDS and is structurally most intriguing for its complexity and for containing multiple sulfur (sulfone and sulfonamide) and fluorine (aryl C−F and CF_3 and alkyl CF_2 and CF_3 groups) substituents as well as an alkyne and a fused cyclopropane group. Lonafarnib (approved 11/2020)[28] is also a first-in-class medication, approved for treatment of Hutchinson−Gilford progeria syndrome. Voxelotor (approved 11/2019) is a new pyridine-containing drug approved for treatment of sickle cell disease,[29] which is notable for a resorcinol aldehyde substituent.[30] Serdexmethylphenidate (approved 3/2021) is a prodrug of dexmethylphenidate used for the treatment of attention deficit hyperactivity disorder (ADHD). Finally, this dataset also contains one gadolinium contrast agent, gadopiclenol (approved 9/2022), and a fluorinated radioactive diagnostic agent,

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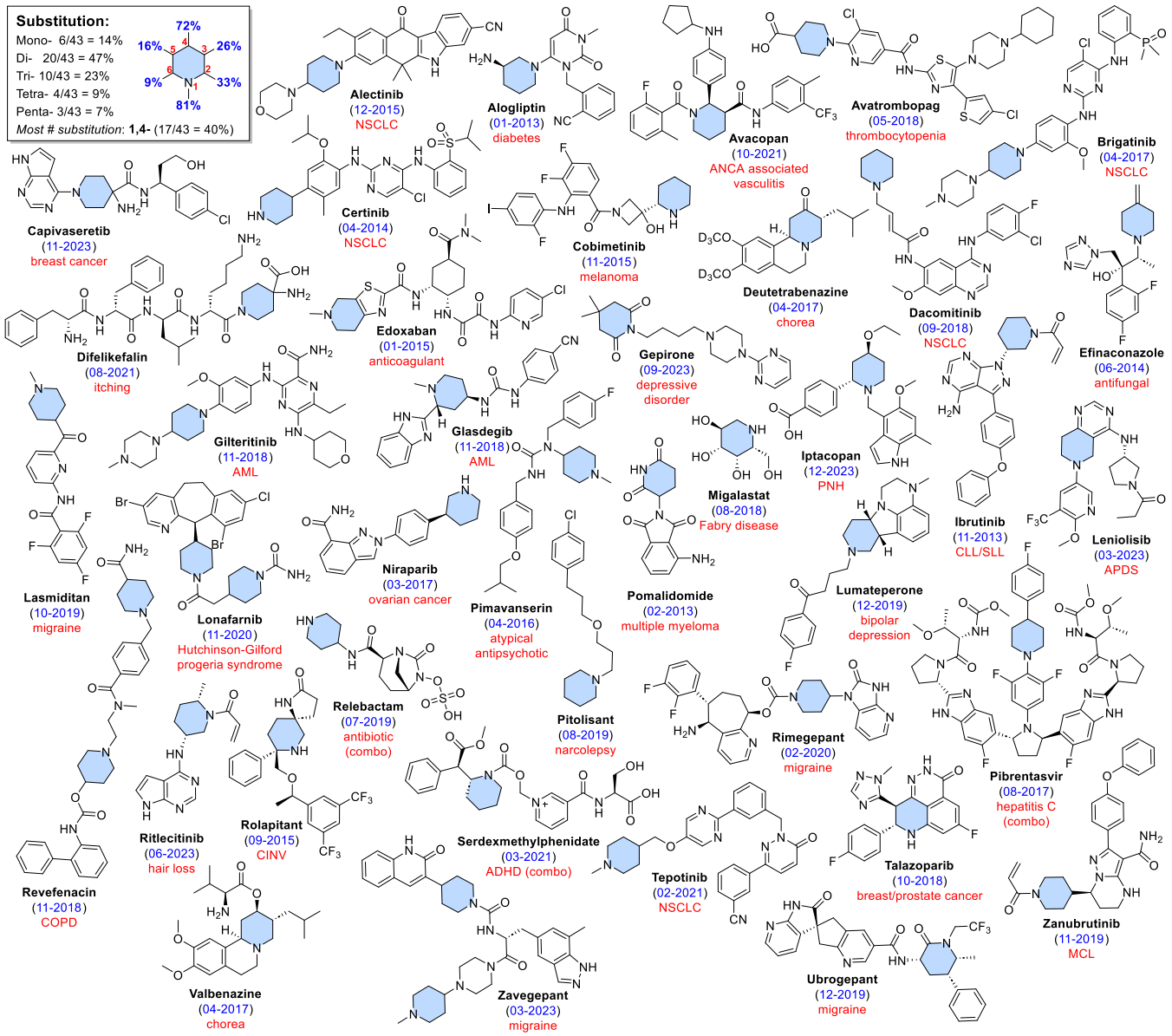

Figure 4. New U.S. FDA-approved small-molecule piperidine (#2−3)-containing drugs.

flortaucipir F18 (approved 5/2020), for use in Alzheimer's disease.

Piperidine (#2−3). A total of 40 piperidine-containing drugs were approved in the past 11 years (Figure 4). Included in this piperidine group are one lactam (ubrogepant) and two glutarimides (gepirone and pomalidomide). The majority of these piperidine drugs contain a substituent in the 1- (81%) or 4-position (72%) or both (40%). Half of the piperidines are disubstituted, followed by tri- (23%) and monosubstitutions (14%). Thirteen (33%) of these piperidine drugs are achiral, and a total of 16 (40%) of the piperidine cores contain at least one chiral carbon atom. The majority of these piperidine drugs are approved for treatment of cancer, with most being kinase inhibitors.[31] These include five new drugs for treatment of NSCLC: alectinib (approved 12/2015), brigatinib (approved 4/2017), certinib (approved 4/2014), dacomitinib (approved 9/2018), and tepotinib (approved 2/2021). Gilteritinib and glasdegib (both approved 11/2018) are new drugs for acute myeloid leukemia (AML). Valbenazine and deutetrabenazine (both approved 4/2017) are new medications for decreasing involuntary movements. Deutetrabenazine[32,33] is a deuterated version—two phenolic methyl ethers fully deuterated—of the drug tetrabenazine. For several of these drugs the piperidine is the only nitrogen heterocycle. These include difelikefalin (approved 8/2021) for itching, pimavanserin (approved 4/2016) as a new atypical antipsychotic, pitolisant (approved 8/2019) for treating narcolepsy,[34] revefenacin (approved 11/2018) as a new bronchodilator, and migalastat (approved 8/2018) as a first-in-class medication approved for treatment of Fabry disease.[35] Migalastat is structurally the smallest of the piperidine-containing drug and is a deoxy-iminosugar. The latest piperidine drug to be approved is ritlecitinib (approved 6/2023)[36] for treating hair loss. Ritlecitinib is a kinase inhibitor with a reactive acrylamide warhead, just like the piperidine-containing drug ibrutinib (approved 11/2013), which is an anticancer agent on the World Health Organization (WHO)'s List of Essential Medicines. Four piperidine-containing drugs are approved for migraine, of which three appeared in the preceding pyridine section (lasmiditan, rimegepant, and

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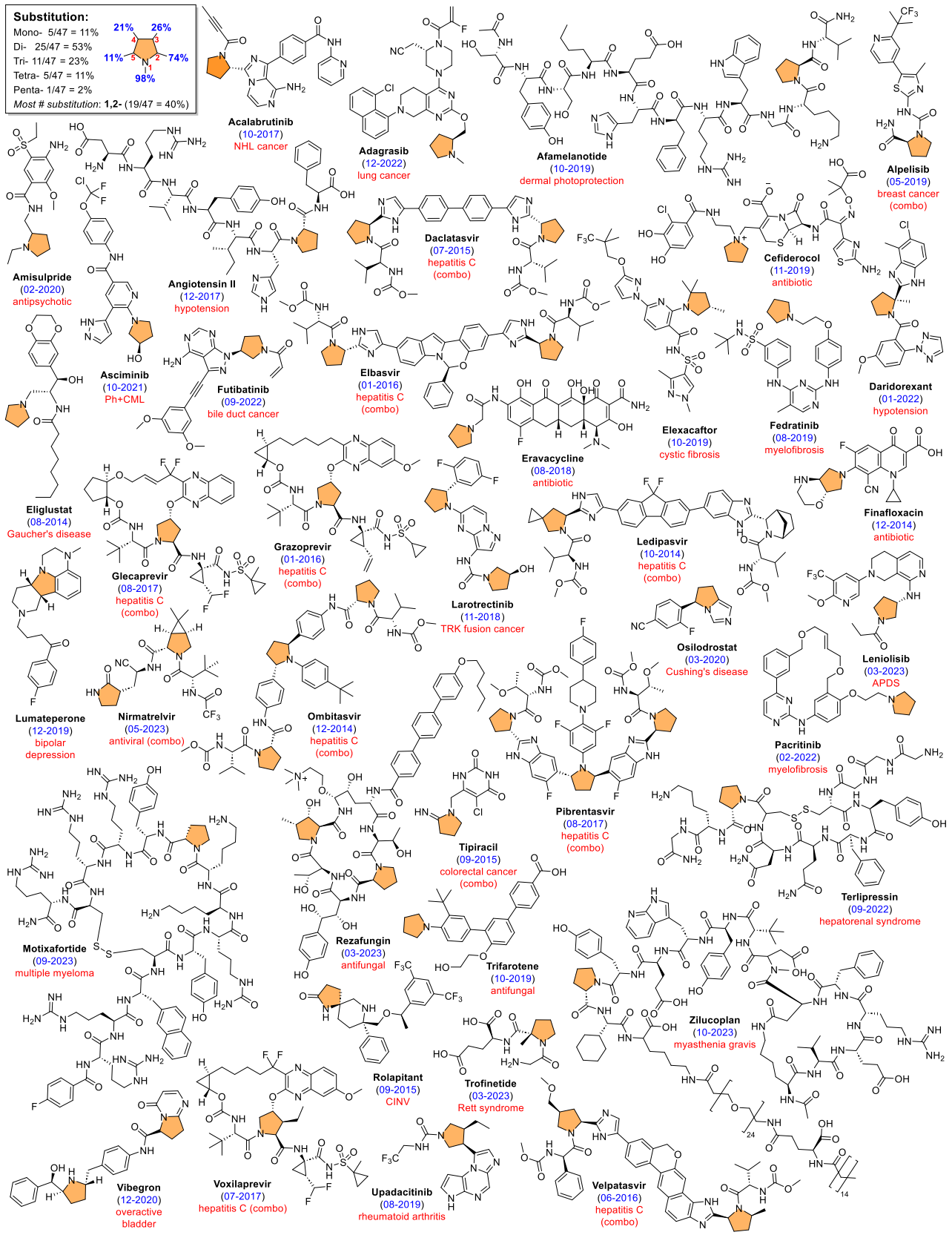

Figure 5. New U.S. FDA-approved small-molecule pyrrolidine (#2−3)-containing drugs.

ubrogepant), with the addition of zavegepant (approved 3/2023).

Pyrrolidine (#2−3). A total of 40 pyrrolidine-containing drugs appear in this dataset (Figure 5). All but one of these drugs are substituted at the pyrrolidine nitrogen (1-position), the only exception being the antiviral combination component nirmatrelvir (approved 5/2023). The majority (53%) of these pyrrolidine drugs are disubstituted, with the most common

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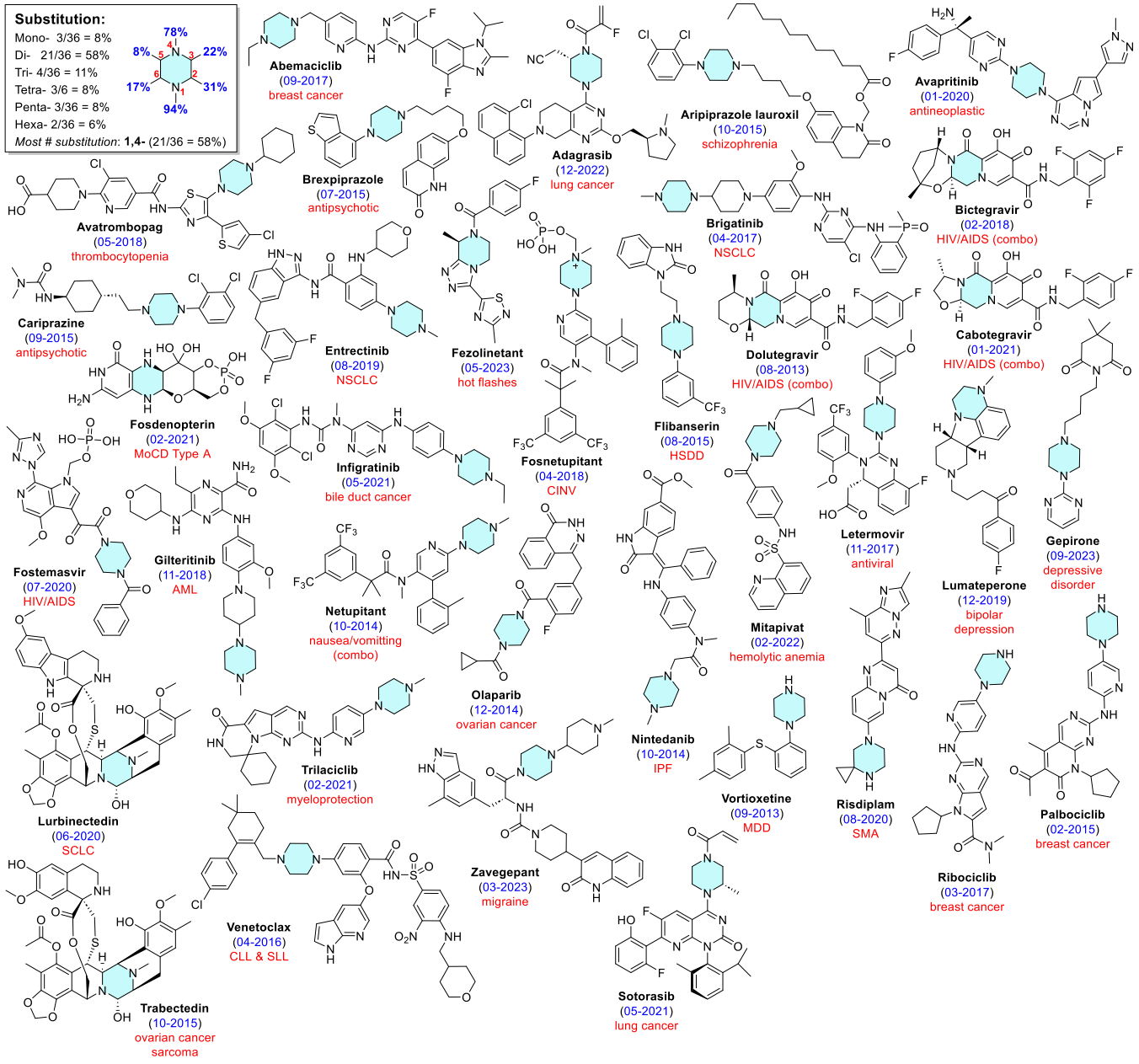

Figure 6. New U.S. FDA-approved small-molecule piperazine (#4)-containing drugs.

being 1,2-disubstitution, followed by 23% being trisubstituted. A total of 35 of these drugs (88%) are chiral, with only five achiral drugs, namely amisulpride (approved 2/2020), fedratinib (approved 8/2019), pacritinib (approved 2/2022), tipiracil (approved 9/2015), and trifarotene (approved 10/2019). Most notable are incredible new hepatitis C (combination) drugs containing two or three pyrrolidines, namely daclatasvir (approved 7/2015), elbasvir (approved 1/2016), ombitasvir (approved 12/2014), pibrentasvir (approved 8/2017), and velpatasvir (approved 6/2016), as well as pyrrolidine-containing macrocycles glecaprevir (approved 9/2017), grazoprevir (approved 1/2016), and voxilaprevir (approved 7/2017). These drugs represent not only incredible achievements in treating hepatitis C, with these eight drugs approved within only 4 years, but also drug discovery and design at its best.[37] About the same number (seven) of pyrrolidine-containing drugs are approved for cancer treatments. Also included are pyrrolidine-containing peptide drugs such as afamelanotide (approved 10/2019) for dermal protection, angiotensin II (approved 12/2017) for hypotension, motixafortide (approved 9/2023) for multiple myeloma, rezafungin (approved 3/2023) as an antifungal,[38] the first-in-class medication terlipressin (approved 9/2022)[39] for hepatorenal syndrome, and zilucoplan (approved 10/2023) for myasthenia gravis. Osilodrostat (approved 3/2020)[40] for Cushing's disease is the smallest of the pyrrolidine drugs. For a handful of pyrrolidine drugs, the pyrrolidine is the only nitrogen heterocycle. These include the antipsychotic amisulpride[41] (approved 2/2020), the Gaucher's disease drug eliglustat (approved 8/2014),[42] the antifungal trifarotene (approved 10/2019), and Rett syndrome drug trofinetide (approved 3/2023). Vibegron (approved 10/2020)[43] contains two chiral pyrrolidine fragments and is used to treat overactive bladder. Lumateperone (approved 12/2019),[44] which contains a penta-substituted

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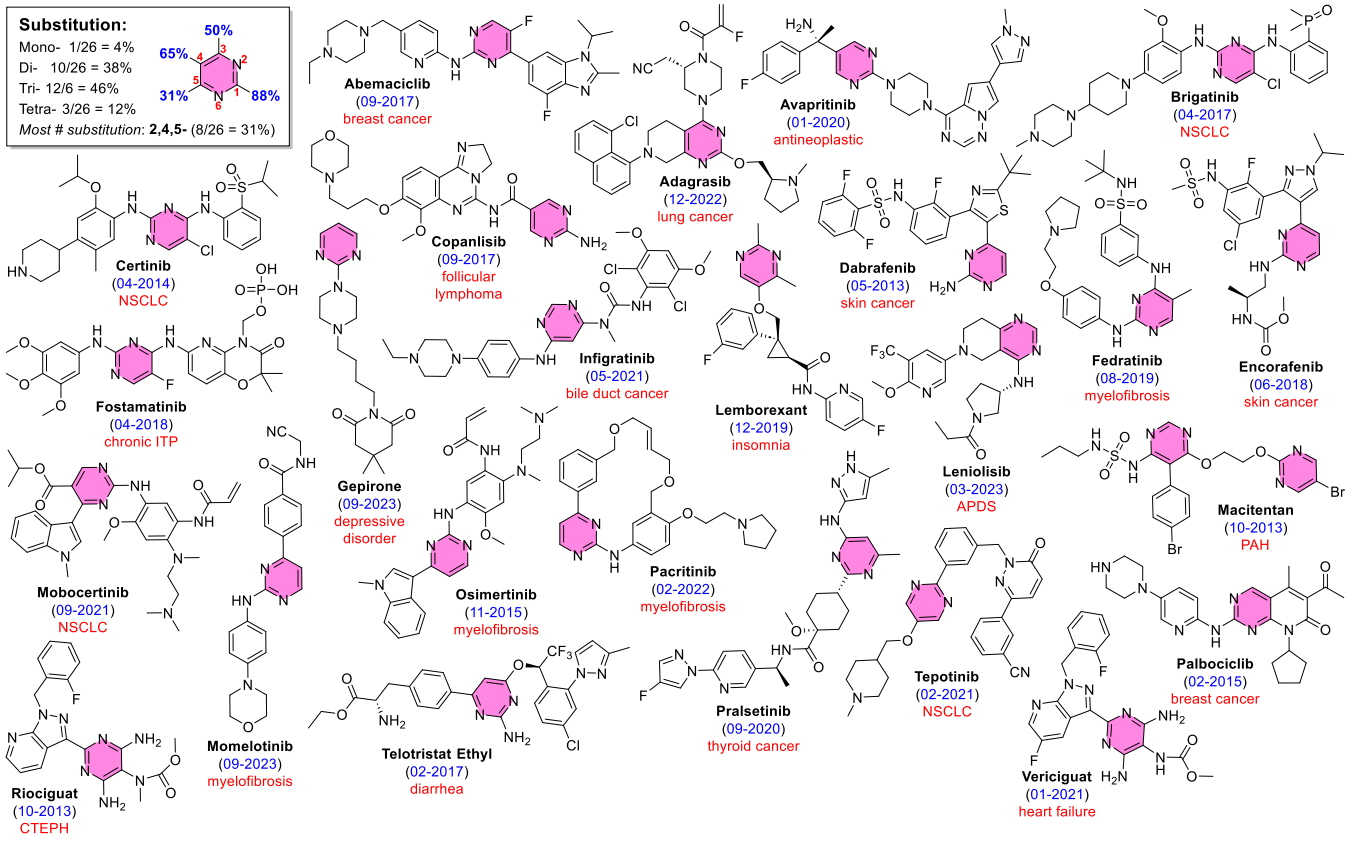

Figure 7. New U.S. FDA-approved small-molecule pyrimidine (#5)-containing drugs.

central core pyrrolidine group, is approved for treating bipolar depression and schizophrenia.

Piperazine (#4). Piperazine-containing drugs are the fourth most common nitrogen heterocycles within this dataset, represented by 36 unique new small-molecule drugs (Figure 6). Not surprisingly, most piperazine substitutions involve two nitrogen atoms, with 1,4-substituted piperazines representing 21 drugs (58%). Two natural product cancer drugs, trabectedin (approved 10/2015) and lurbinectedin (approved 6/2020),[45] are the only piperazines substituted at all six positions. Following the isolation and discovery of the antitumor agent ecteinascidin 743 (travebectedin), intense synthetic campaigns followed around the world, resulting in the first synthesis being completed by the Corey group.[46,47] Interestingly, the majority (23, 64%) of these piperazine-containing drugs are achiral. Only nine (25%) of these 36 piperazines have a chiral substituent on the piperazine carbon atoms. Important members of this category are the antiretroviral combination drug components bictegravir (approved 2/2018), cabotegravir (approved 1/2021), and dolutegravir (approved 8/2013).[48] Also, most notable among these chiral piperazines are the tetracyclic cyclic phosphate-containing drug fosdenopterin (approved 2/21),[49] which is used to treat patients with molybdenum cofactor deficiency (MoCD),[50] and the fluoroacrylamide-decorated lung cancer drug adagrasib (approved 12/2022). A significant number of these piperazine drugs are anticancer agents. Interestingly, this category of drugs is represented by several antipsychotics and drugs aimed at treating depression, such as brexpiprazole (approved 7/2015), aripiprazole lauroxil (approved 10/2015), cariprazine[51,52] (approved 9/2015), lumateperone (approved 12/2019), gepirone (approved 9/2023), and vortioxetine[53] (approved 9/2013), with vortioxetine also being the smallest of the drug architectures in this category. Cariprazine and vortioxetine are the only drugs in this group with piperazine as their only nitrogen heterocycle. Risdiplam (approved 8/2020) is an unusual cyclopropane-substituted piperazine prescribed for the treatment of spinal muscular atrophy (SMA).[54] Fezolinetant[55] (approved 5/2023) is an intriguing new nitrogen-heterocycle-rich chiral piperazine drug structure for treatment of hot flashes due to menopause.

Pyrimidine (#5). Pyrimidine-containing drugs are ranked fifth, with a total of 25 new small-molecule drug members (Figure 7). Interestingly, most pyrimidine drugs are trisubstituted (46%), followed closely by disubstituted (38%) ones, with 2,4,5-substituted pyrimidines being the most common (31%) substitution pattern. Interestingly, only seven (28%) pyrimidine drugs are chiral. These include, for example, the diarrhea drug teoltristat ethyl (approved 2/2017), the cyclopropane-containing insomnia[56] drug lemborexant (approved 12/2019),[57] and the skin cancer drug encorafenib (approved 6/2018).[58] Three pyrimidine drugs are substituted at all four positions, namely the antineoplastic drug adagrasib (approved 1/2020), the guanylate cyclase stimulant riociguat (approved 10/2013), and its structural derivative vericiguat (approved 1/2021).[59] Within this pyrimidine category of drugs there are is a high number (15, 60%) of kinase inhibitors: abemaciclib (approved 9/2017), avapritinib (approved 1/2020), brigatinib (approved 4/2017), certinib (approved 4/2014), dabrafenib (approved 5/2013), encorafenib (approved 6/2018), fedratinib (approved 8/2019), fostamatinib (approved 4/2018), mobocertinib (approved 9/2021), momoletinib (approved 8/2023), osimertinib (approved 11/2015), pacritinib[60] (approved 2/2022), palbociclib (approved 2/2015), pralsetinib (approved 9/2020), and tepotinib (approved 2/2021). These kinase

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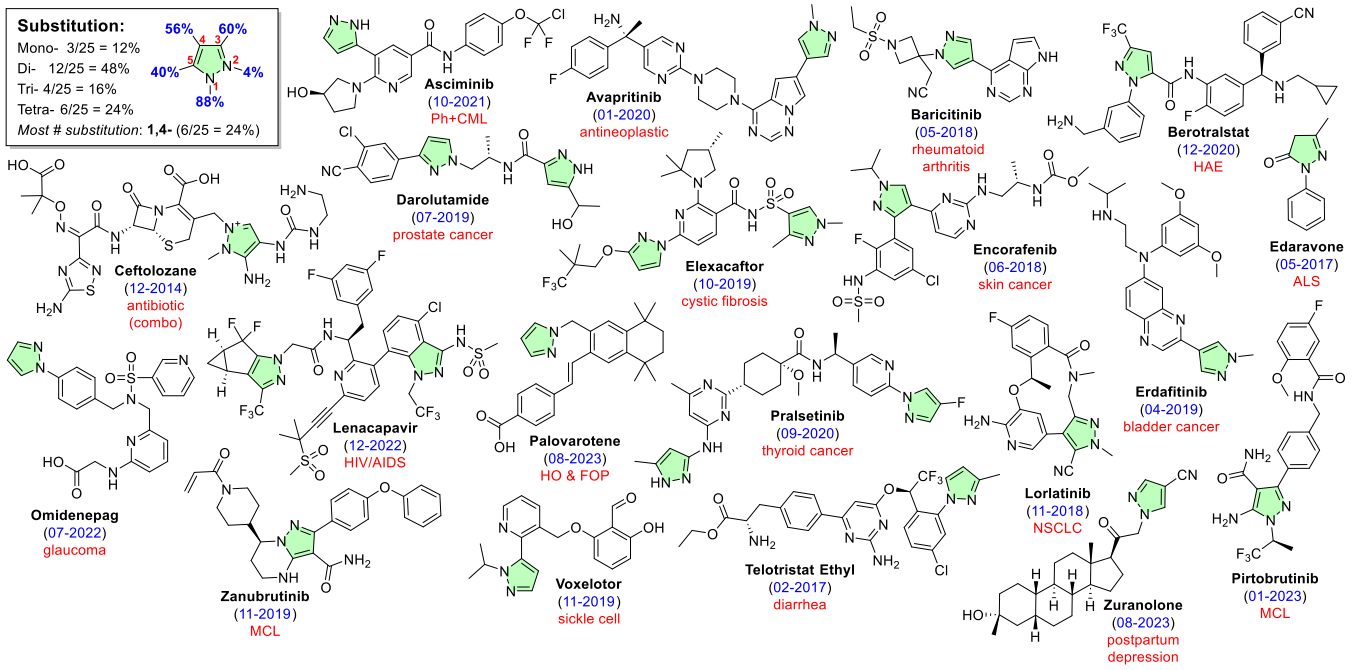

Figure 8. New U.S. FDA-approved small-molecule pyrazole (#6)-containing drugs.

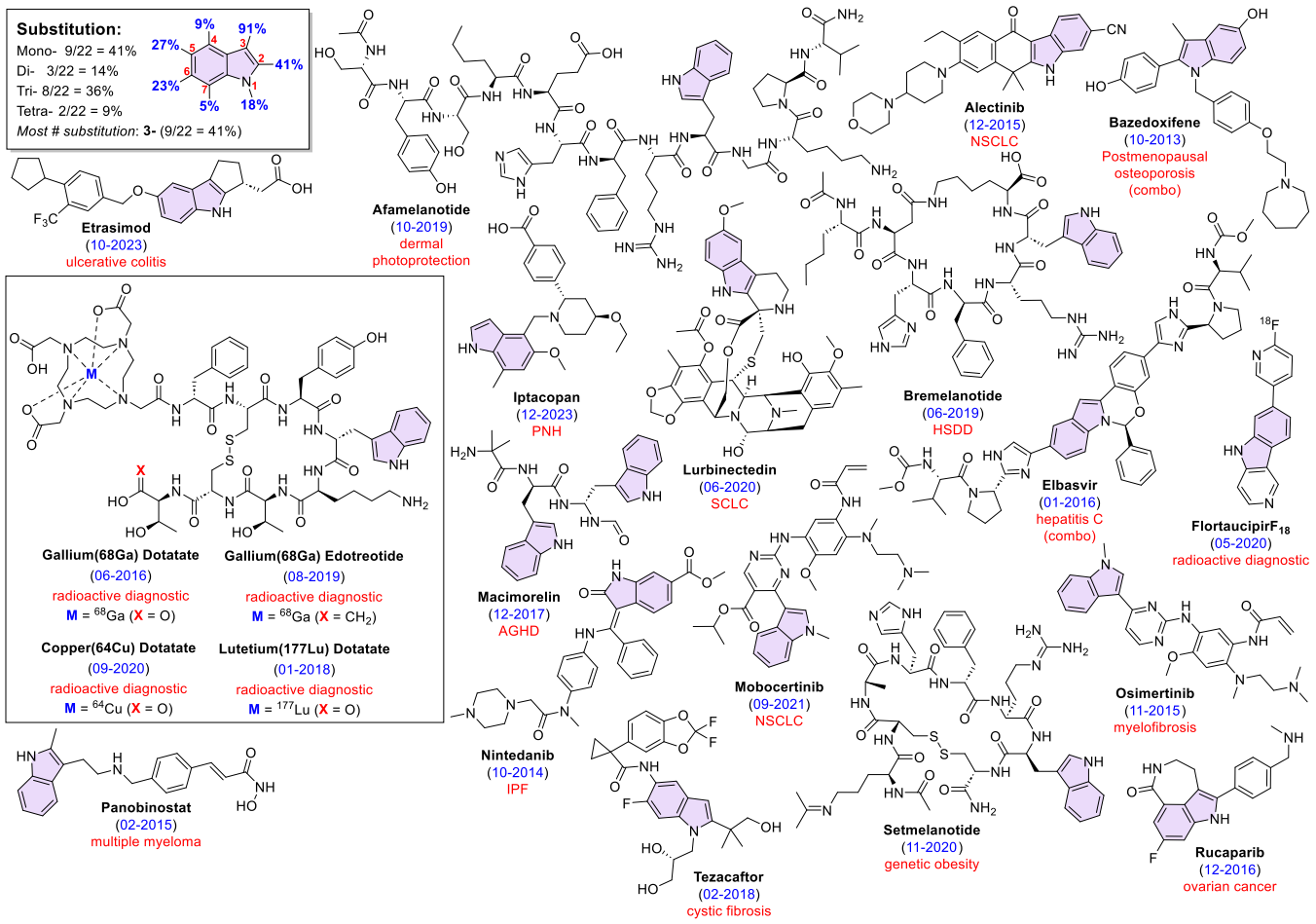

Figure 9. New U.S. FDA-approved small-molecule indole (#7)-containing drugs.

inhibitors usually contain multiple other nitrogen heterocycles and are commonly elongated multiring structures, except for pacritinib, which has a pyrimidine embedded within its macrocycle.

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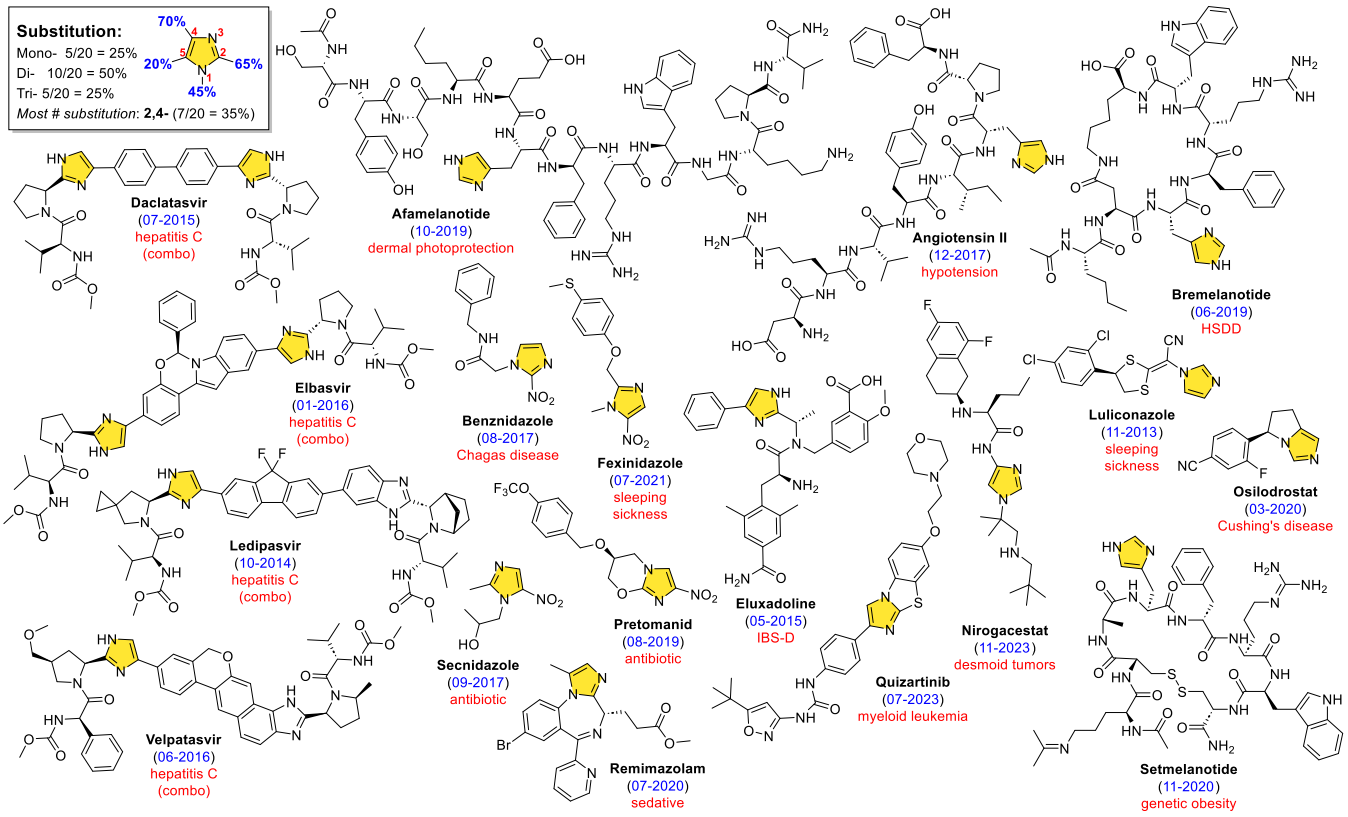

Figure 10. New U.S. FDA-approved small-molecule imidazole (#8)-containing drugs.

Pyrazole (#6). Pyrazoles are the biggest climbers of the nitrogen heterocycles in this dataset, being not represented in the top 25 in our original U.S. FDA drug analysis and now in the past 11 years appearing in no less than 20 unique small-molecule drugs (Figure 8).[61] Half of the pyrazole drugs (12/25) are disubstituted, of which 1,4-substitution (24%) is most prevalent. The structurally simplest drug in this category is the amyotrophic lateral sclerosis (ALS) drug edaravone (approved 5/2017).[62,63] Interestingly, in addition to edaravone there are five other pyrazole drugs wherein pyrazole is the sole nitrogen heterocycle. Those are the steroid zuranolone[64] (approved 8/2023), which is used for treating postpartum depression, the retinoid palovarotene[65] (approved 8/2023), the prostate cancer drug darolutamide[66] (approved 7/2019), the mantle cell lymphoma (MCL) drug pirtobrutinib[67] (approved 1/2023), and berotralstat (approved 12/2020), which is used to prevent attacks of hereditary angioedema (HAE).[68] Given that pyrazole is a rising new nitrogen heterocycle, it is noteworthy that darolutamide (approved 7/2019), elexacaftor (approved 10/2019), lenacapavir (approved 12/2022), and pralsetinib (approved 9/2020) contain two pyrazole groups. Two of the pyrazole drugs contain a free N−H nitrogen (asciminib and pralsetinib), and the antibiotic combination component ceftolazane (approved 12/2014) has a pyrazolium group.

Indole (#7). Twenty-one small-molecule indole drugs and diagnostics have been approved during this period (Figure 9), which include four cyclen metal-chelated radioactive diagnostics. Most of these indole drugs are either mono- (41%) or trisubstituted (36%), with substitutions at the indole 3-position being most common (41%). Almost half (9, 43%) of the indole drugs are achiral. Interestingly, when indole substitution patterns are compared to other nitrogen heterocycles it is noteworthy that vast majority (76%) of indole drugs contain no substituent at the indole N−H, which is quite uncommon for other nitrogen heterocycles appearing in this dataset. Indole is the only nitrogen heterocycle for several of these indole drugs. These include the ulcerative colitis drug etrasimod[69] (approved 10/2023), the radioactive diagnostic flortaucipir F18 (approved 5/2020), the hydroxamic acid-containing multiple myeloma drug panobinostat[70] (approved 2/2015), and the cystic fibrosis drug tezacaftor[71] (approved 2/2018). Notable structures in this category are the macrocycle peptide drug bremelanotide (approved 6/2019), which is prescribed for hypoactive sexual desire disorder (HSDD), and the genetic obesity drug setmelanotide[72] (approved 11/2020). The largest of the indole drugs is the first-in-class dermal photoprotection peptide afamelanotide (approved 10/2019). Iptacopan,[73] which is a first-in-class drug for the treatment of paroxysmal nocturnal hemoglubinuria (PNH), is the most recently approved indole drug (10/2023).

Imidazole (#8). Eighteen imidazole-containing drugs appear in this dataset (Figure 10). Half of the imidazole drugs are disubstituted, with 2,4-substitution being most common (35%). All but three imidazole drugs are chiral. This dataset contains several disease themes, such as the four hepatitis C combination components daclatastvir (approved 7/2015), elbasvir (approved 1/2016), ledipasvir (approved 10/2014), and velpatasvir (approved 6/2016), of which daclatasvir and elbasvir contain two imidazoles. Second most notable among the imidazole-containing groups are the four nitro-substituted imidazole drugs benznidazole (approved 8/2017) and fexnidazole (approved 7/2021), for treatment of Chagas disease and sleeping sickness, respectively, and the antibiotics pretomanid (approved 8/2019) and secnidazole (approved 9/2017).[74] A third category is represented by the peptide drugs afamelanotide, angiotensin II, bremelanotide, and setmelanotide, which also contain an indole

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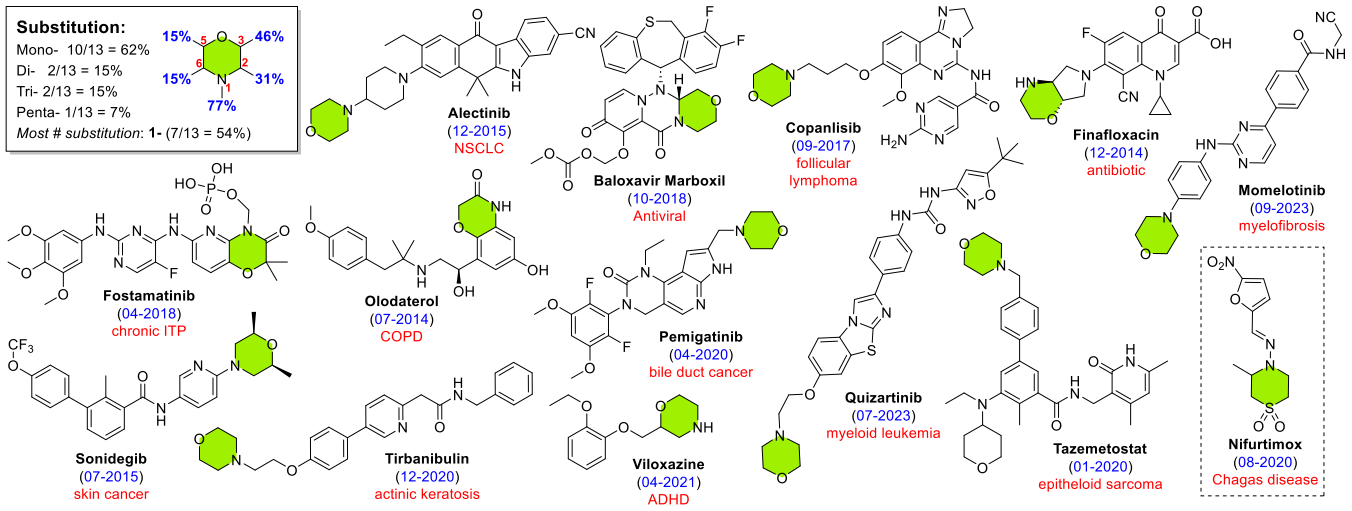

Figure 11. New U.S. FDA-approved small-molecule Morpholine (#9)-containing drugs.

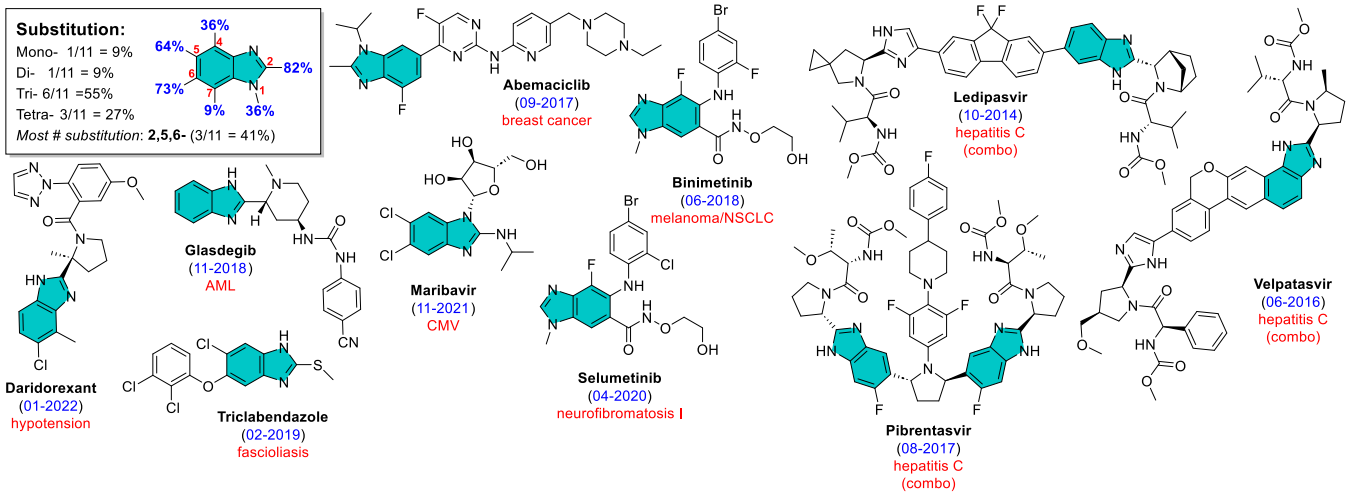

Figure 12. New U.S. FDA-approved small-molecule benzimidazole (#10)-containing drugs.

and were discussed in an earlier section. Luliconazole (approved 11/2013), which is used to treat sleeping sickness, is a most intriguing drug structure, containing a dithiolane, a cyano group, and two chlorines in addition to imidazole.[75] Eluxadoline (approved 5/2015), which is used for the treatment of irritable bowel syndrome with diarrhea (IBS-D),[76] is another drug in this category wherein imidazole is the sole nitrogen heterocycle.

Morpholine (#9). Thirteen new morpholine-containing drugs have been approved in the past 11 years (Figure 11), which is one more than were approved in the previous decades, thus doubling the total number of morpholine drugs, resulting in an increase in morpholine drug ranks' from #17 in our earlier study to #9 in this dataset. The majority of these morpholine drugs are monosubstituted at nitrogen (54%), with the tyrosine kinase inhibitor fostamatinib (approved 4/2018) being the most substituted of the morpholine drugs. Only three of the morpholine drugs are chiral, and interestingly all of them contain their chiral substituents on the morpholine. These drugs are the antiviral baloxavir marboxil[77] (approved 10/2018), the antibiotic finafloxacin (approved 12/2014), and the skin cancer drug sonidegib[78] (approved 7/2015). Most of the morpholine drugs are approved for cancer-related treatments, including multiple kinase inhibitors. The structurally simplest morpholine drug is viloxazine[79] (approved 4/2021), which is an old drug that was used for decades as an antidepressant but was approved in 2021 for treatment of ADHD. Olodaterol[80] (approved 7/2014) is prescribed for relieving airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The myeloid leukemia drug quizartinib[81] (approved 7/2023), which is notable for a long linear multiring system structure, is the most recently approved morpholine-containing drug. Also displayed is the thiomorpholine-containing Chagas disease drug nifurtimox (approved 8/2020).

Benzimidazole (#10). The final nitrogen heterocycle in the top 10 is benzimidazole, which is represented by 10 new small-molecule drugs (Figure 12). Benzimidazole substitution patterns are unusual compared to other nitrogen heterocycles in the top 10, with the majority of drugs being tri- (55%) or tetra-substituted (27%) and only a single drug each containing mono- or disubstituted benzimidazoles. The 2-, 5-, and 6-positions of benzimidazoles are substituted 82%, 64%, and 73%, respectively. The anticancer benzimidazole drugs binimetinib (approved 6/2018) and selumetinib[82] (approved 4/2020) contain an interesting hydroxamic fragment and differ by a single atom substitution (fluorine vs chlorine). The hepatitis C combination drugs ledipasvir, pibrentasvir, and velpatasvir, which were discussed in the pyrrolidine section, feature prominently in this dataset. Maribavir[83] (approved 11/2021) is a new antiviral

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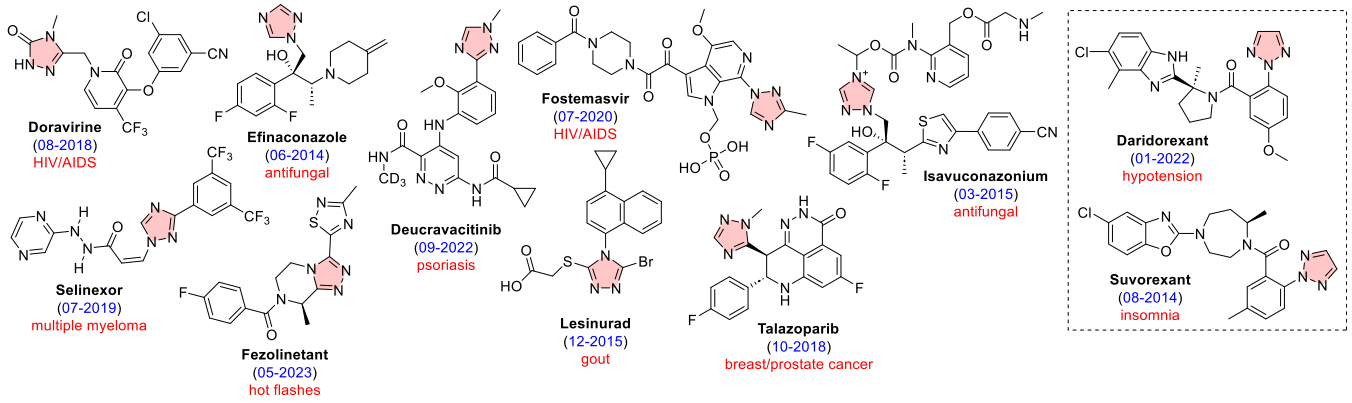

Figure 13. New U.S. FDA-approved small-molecule 1,2,3/4-triazole (#11)-containing drugs.

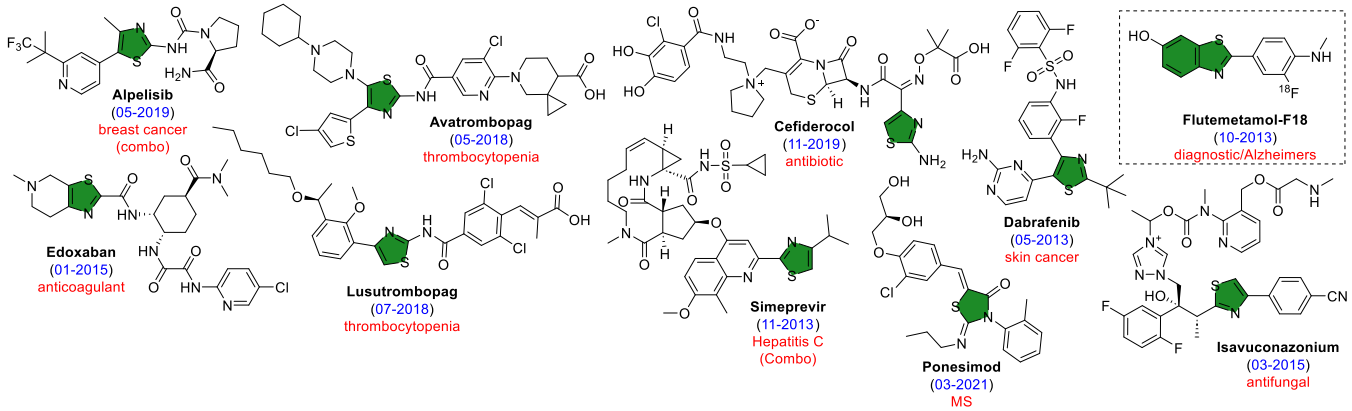

Figure 14. New U.S. FDA-approved small-molecule thiazole (#12)-containing drugs.

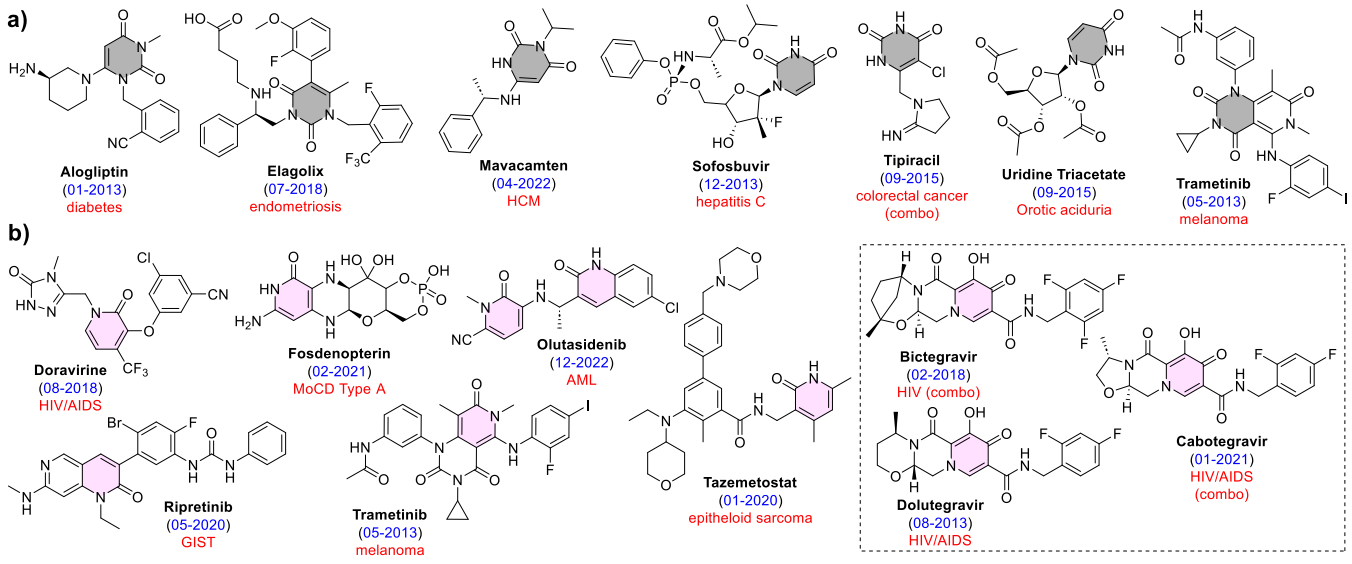

Figure 15. New U.S. FDA-approved small-molecule a) uracil (#13)- and b) pyridine-2/4-one (#14)-containing drugs.

kinase inhibitor approved for the treatment of cytomegalovirus (CMV). Triclabendazole[84] (approved 2/2019), which is approved for treatment of chronic fascioliasis, is an intriguing small benzimidazole drug with three chlorine atoms and a 2-thiomethyl substituent.

1,2,3/4-Triazole (#11). The 11th ranked nitrogen heterocycle is 1,2,4-triazole, with nine new small-molecule drugs (Figure 13) along with the 1,2,3-triazole drugs daridorexant (approved 1/2022) and suvorexant (approved 8/2014), which are approved for hypotension and insomnia, respectively.[85] This dataset includes the antifungal triazolium drug isavuconazonium (approved 3/2015) and the oxidized triazole HIV/AIDS drug doravirine (approved 8/2018). The triazole in the gout[86] drug lesinurad (approved 12/2015) is its only nitrogen heterocycle. Lesinurad is also notable for a thio and bromine substitution on the triazole ring along with an aryl cyclopropyl substituent.

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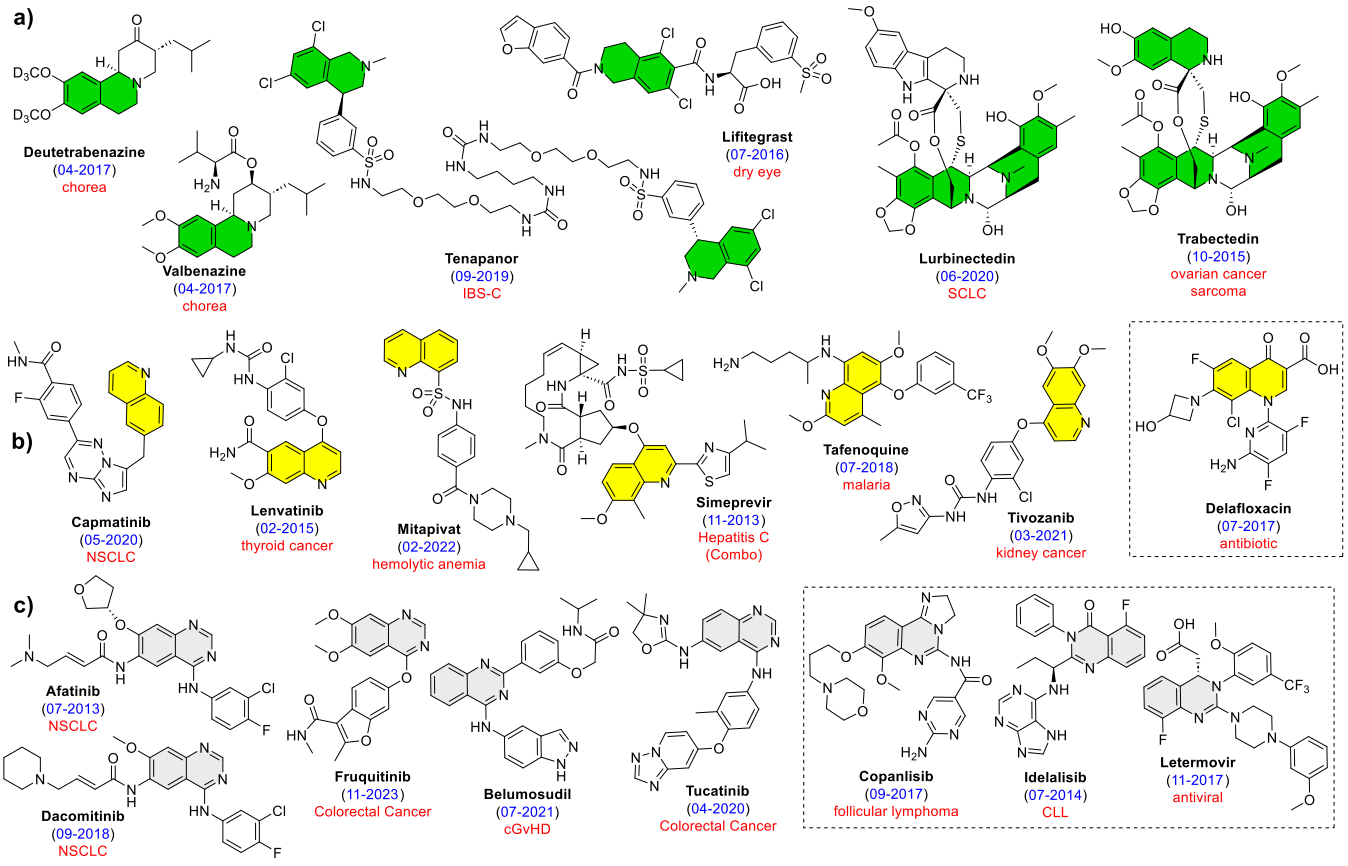

Figure 16. New U.S. FDA-approved small-molecule a) tetrahydroisoquinoline (#15)-, b) quinoline (#16)-, and c) quinazoline (#17)-containing drugs.

Deucravacitinib[87] (approved 9/2022) is a new tyrosine kinase inhibitor for the treatment of psoriasis and significant for containing the first approved deuterated methyl group on an amide. Selinexor[88] (approved 7/2019), which is a first-in-class drug for treating multiple myeloma, contains a rare *Z*-vinylogous triazole amide substituent. Fezolinetant (approved 5/2023) is a new drug for treating hot flashes and is also the only fused triazole drug, which also contains a thiadiazole as well as a piperidine within its compact structure.

Thiazole (#12). Thiazoles[89] are the 12th most frequently appearing nitrogen heterocycles in this dataset, with eight unique new small-molecule drugs (Figure 14) along with the oxidized thiazole multiple sclerosis (MS) drug ponesimod (approved 3/21) and benzothiazole diagnostic agent flutemetamol F18 (approved 10/2013). Half of the thiazoles are 2,4,5-substituted, with the other half being 2,4-substituted. Six of the thiazole drugs are chiral. Avatrombopag (approved 5/2018) and lusutrombopag (approved 7/2018) are both used for the treatment of thrombocytopenia.[90] Alpelisib[91] (approved 5/2019) and dabrafenib (approved 5/2013) are anticancer drugs used for treating breast and skin cancers, respectively. Edoxaban (approved 1/2015),[92] which is the only ring-fused thiazole, is used to prevent blood clots and is on the WHO's List of Essential Medicines. The hepatitits C combination component simeprevir (approved 11/2013) is the most complex of the thiazole drugs, containing multiple chiral centers, a nitrogen macrocycle, two cyclopropyl fragments, and a sulfonamide in addition to the thiazole.

Uracil (#13). A total of seven uracil-containing drugs[93] appear in this dataset, which include the first-in-class myosin inhibitor mavacamten[94] (approved 4/2022) and the hepatitis C drug sofosbuvir (approved 12/2013), which is on the WHO's List of Essential Medicines and is a structurally intriguing nucleoside with a tertiary alkyl fluoride and a phosphoramidate group (Figure 15a). With respect to uracil substitution, two are monosubstituted, two are disubstituted, two are trisubstituted, and the melanoma drug trametinib (approved 5/2013) is a fused uracil. The colorectal cancer combination component tipiracil (approved 9/2015) is the structurally simplest and smallest[95] uracil drug and notable for a chlorine substituent on the uracil ring and an unusual pyrrolidine-2-imine substituent.

Pyridine-2/4-one (#14). The 14th ranked nitrogen heterocycle is pyridine-2-one, with six new small-molecule drug members, along with three pyridine-4-one drugs (Figure 15b). Half of the pyridine-2-one drugs are ring fused, and four are approved for cancer treatment. These are the kinase inhibitors olutasidenib[96] (approved 12/2022), ripretinib (approved 5/2020), and trametinib (approved 5/2013) as well as tazemetostat (approved 1/2020). Doravirine (approved 8/2018) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used for the treatment of HIV/AIDS. All the pyridine-4-one approved drugs are also used in the treatment of AIDS, with integrase inhibitor dolutegravir (approved 8/2013) being on the WHO's List of Essential Medicines. Bictegravir (approved 2/2018) and cabotegravir (approved 1/2021) are derivatives of dolutegravir wherein the original fused dolutegravir oxazinane ring has been converted into a bicyclic derivative or ring contracted.

Tetrahydroisoquinoline (#15). Six tetrahydroisoquinoline-containing drugs were approved in the past 11

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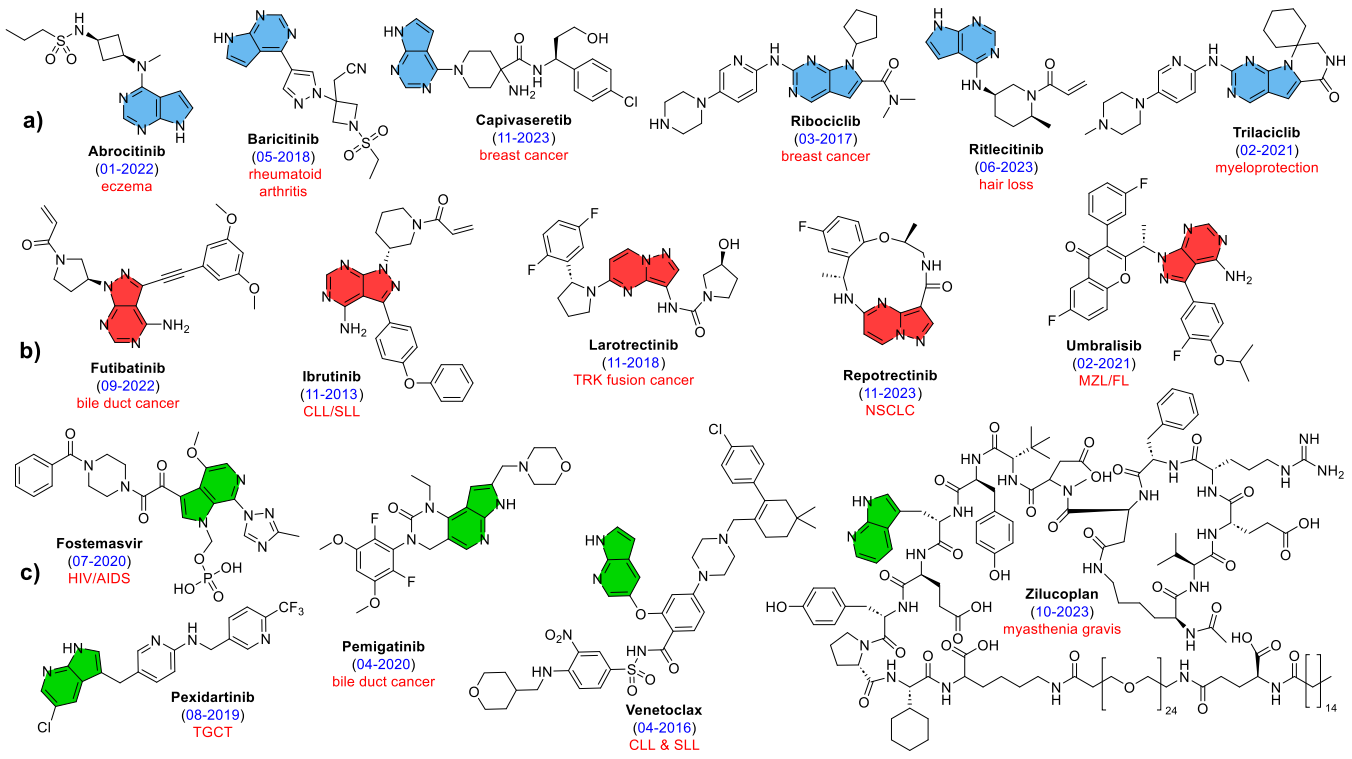

Figure 17. New U.S. FDA-approved small-molecule a) pyrrolopyrimidine (#18)-, b) pyrazolopyrimidine (#19)-, and c) pyrrolopyridine (#20)-containing drugs.

years (Figure 16a),[97] which include the chorea tetrahydroisoquinoline fused drugs valbenazine and deutetrabenazine as well as the highly complex natural-product-derived anticancer agents trabectedin and lurbinectedin, which are notable for containing three and two tetrahydroisoquinolines respectively within their structures, all of which have been discussed in earlier sections. Interestingly, for the other two drugs in this category the tetrahydroisoquinoline is the only nitrogen heterocycle, which in both cases is dichlorinated. These drugs are lifitegrast[98] (approved 7/2016), which is used to treat dry eyes, and the first-in-class tetrahydroisoquinoline dimer IBS-C drug tenapanor[99] (approved 9/2019).

Quinoline (#16). Six quinoline drugs and the oxidized quinoline delafloxacin are contained within this dataset (Figure 16b), which includes the anticancer kinase inhibitors capmatinib (approved 5/2020), lenvatinib (approved 5/2015), and tivozanib (approved 3/2021) as well as the hepatitis C drug component simeprevir discussed previously. Mitapivat (approved 2/2022),[100] which contains a single quinoline sulfonamide substituent in the 8-position, is a first-in-class medication for the treatment of hemolytic anemia. Tafenoquine (approved 7/2018),[101] which is a new antimalaria medication, contains a highly oxidized penta-substituted quinoline core.

Quinazoline (#17). Newly approved quinazoline-containing drugs are also displayed in Figure 16c, which include the oxidized quinazoline idealalisib (approved 7/2014) and the reduced quinazoline antiviral drug letermovir (approved 11/2017). The majority of drugs in this structural category are anticancer kinase inhibitors, including the γ-amino acrylamide-containing afatinib (approved 7/2013) and its derivative dacomitinib (approved 9/2018), used for the treatment of NSCLC. The colorectal cancer drugs tucatinib (approved 4/2020) and the more recently approved fruquintinib[102] (approved 11/2023) share many structural similarities to each other. Belumosudil (approved 7/2021) is a serine/threonine kinase inhibitor for the treatment of chronic graft-versus host disease (cGVHD).[103]

Pyrrolopyrimidine (#18). A total of six new pyrrolopyrimidines drugs[104] have been approved, all of which are kinase inhibitors, of which three are used for the treatment of cancer (Figure 17a). Abrocitinib[105] (approved 1/2022) and barcitinib (approved 5/2018) contain strained cyclobutane and azetidine rings respectively as part of their architecture and are prescribed for eczema in the case of abrocitinib and rheumatoid arthritis in the case of barcitinib. Ritlecitinib (approved 6/2023), which contains a reactive acrylamide substituent and a 4-substituted pyrrolopyrimidine, like abrocitinib and barcitinib, is used for the treatment of alopecia areate (hair loss). Finally, the structures of ribociclib (approved 3/2017) and trilaciclib[106] (approved 2/2021) are nearly identical, differing only in the amide part of the former being changed to a lactam and a cyclopentane replaced by a cyclohexane moiety.

Pyrazolopyrimidine (#19). Five new pyrazolopyrimidine-containing drugs have been approved, all of which are kinase inhibitors for the treatment of cancer,[107] with three containing a free 4-amino substituent (Figure 17b). It is important to note that three of these pyrazolopyrimidines are pyrazolo[3,4-*d*]pyrimidines, with the other two being isomeric pyrazolo-[1,5-*a*]pyrimidines. Futibatinib (approved 9/2022) and ibrutinib (approved 11/2013), both of which contain an acrylamide warhead, as well as umbralisib (approved 2/2021), belong to the former, with larotrectinib (approved 11/2018) and repotrectinib (approved 11/2023) belonging to the latter isomeric pyrazolopyrimidine family. Larotrectinib,[108] which is a first-in-class drug for the treatment of solid tumors, is decorated with two chiral pyrrolidine substituents, while the fast-tracked NSCLC drug repotrectinib[109] is most notable for the pyrazolopyrimidine being part of a chiral macrocyclic amide.

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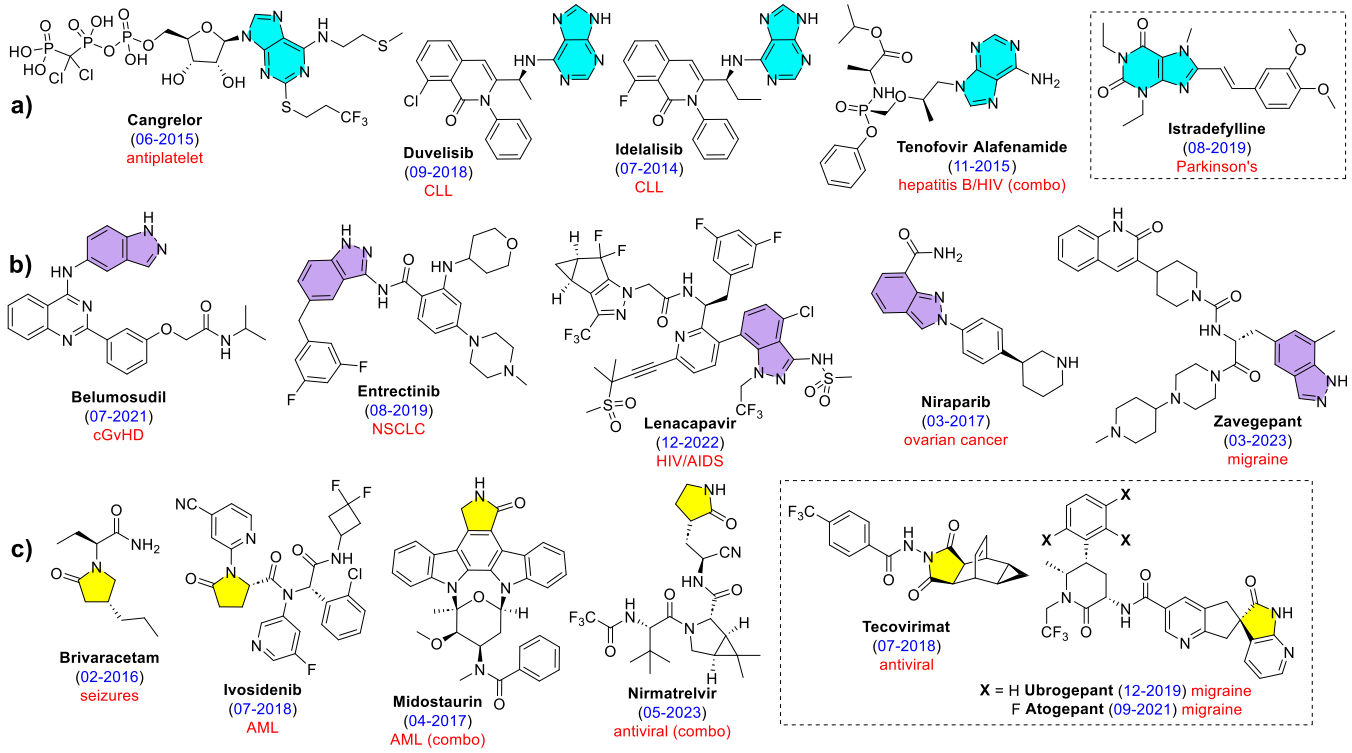

Figure 18. New U.S. FDA-approved small-molecule a) purine (#21)-, b) indazole (#22)-, and c) pyrrolidine-2-one (#23)-containing drugs.

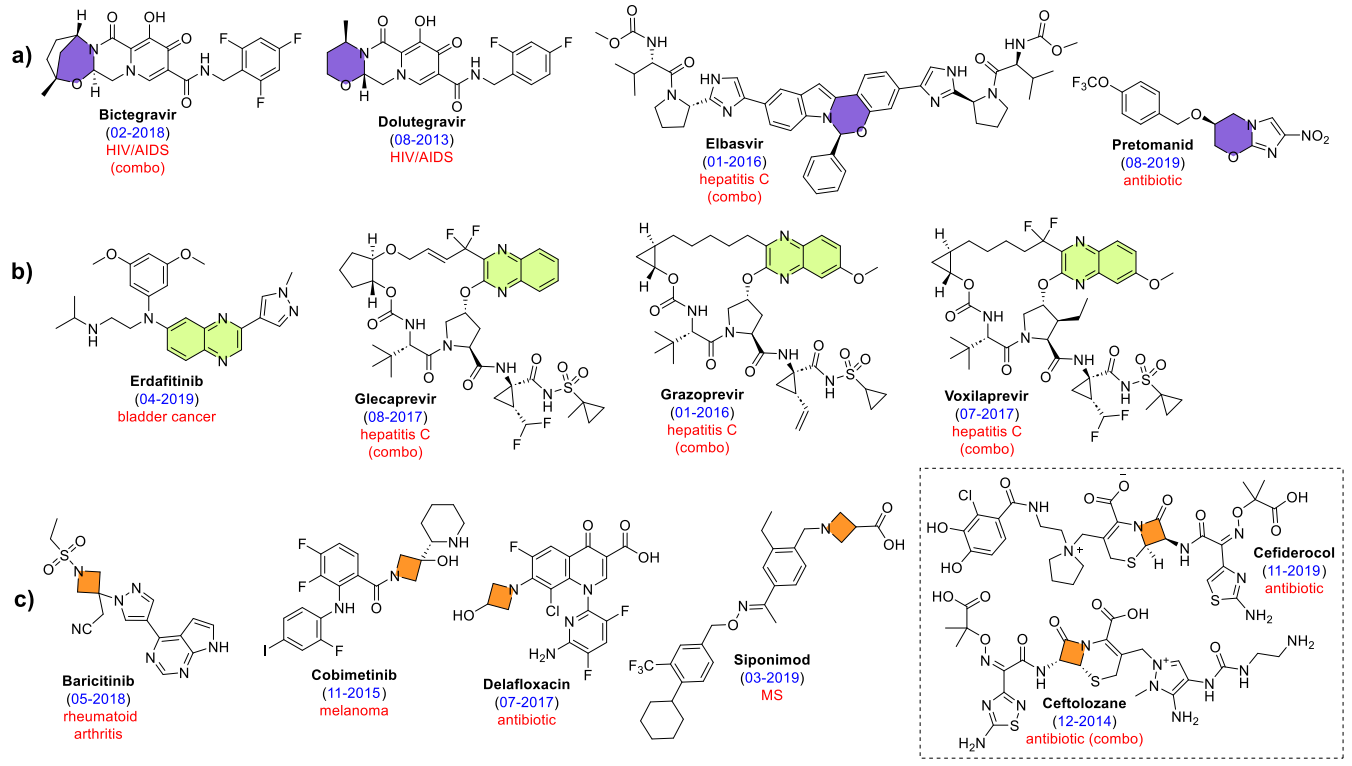

Figure 19. New U.S. FDA-approved small-molecule a) 1,3-oxazinane (#24)-, b) quinoxaline (#25)-, and c) azetidine (#26)-containing drugs.

Pyrrolopyridine (#20). Pyrrolopyridine is another emerging fused nitrogen heterocycle, with five new members of its family approved (Figure 17c), of which four belong to the pyrrolo[2,3-*b*]pyridine family and one, the HIV/AIDS drug fostemsavir (approved 7/2020), is a pyrrolo[2,3-*c*]pyridine. This small dataset contains two large drugs, namely the anticancer agent venetoclax (approved 4/2016 for CLL, SLL, and AML)[110] and the peptide drug zilucoplan (approved 10/2023),[111] which is used for treatment of myasthenia gravis. Finally, the kinase inhibitors pexidartinib (approved 8/2019) and pemigatinib[112] (approved 4/2020) are prescribed for

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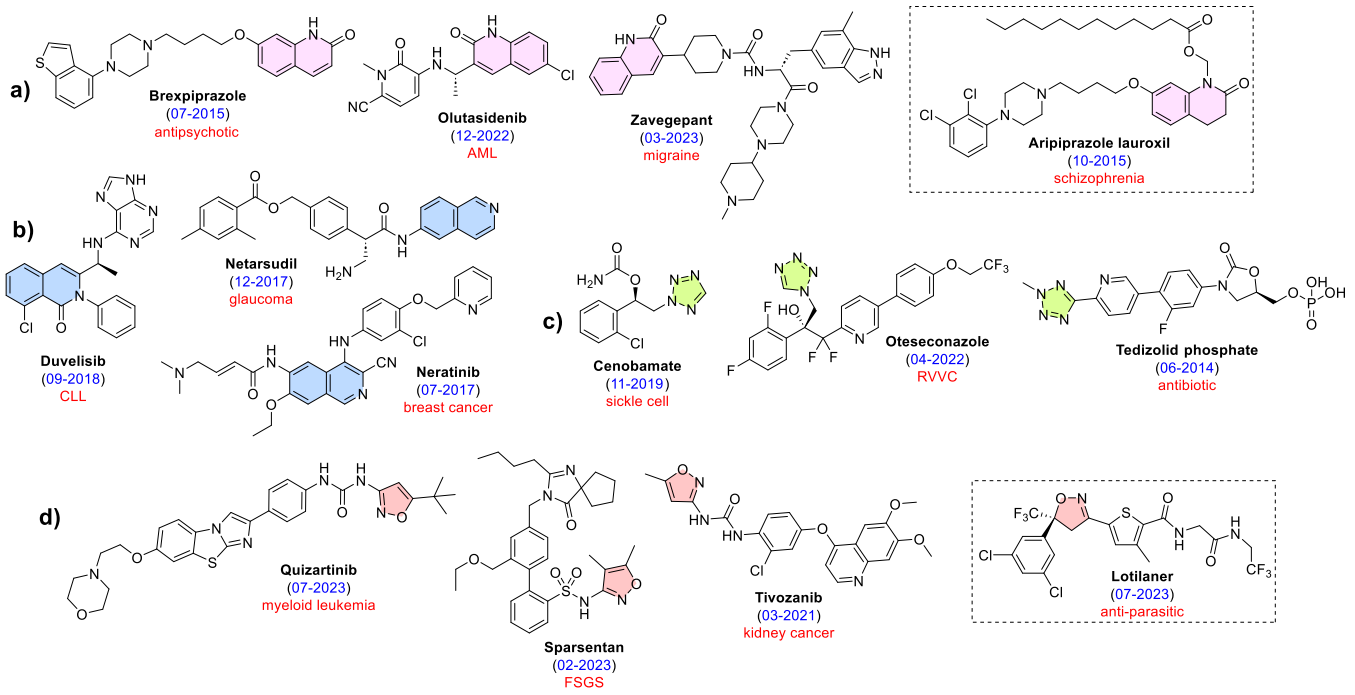

Figure 20. New U.S. FDA-approved small-molecule a) quinoline-2-one (#27)-, b) isoquinoline (#28)-, c) tetrazole (#29)-, and d) isoxazole (#30)-containing drugs.

patients with tenosynovial giant cell tumor (TGCT) and bile duct cancer, respectively.

Purine (#21). Four purine-containing dugs are represented in this dataset along with istradefylline[113] (approved 8/2019), which is an oxidized purine derivative used for treating conditions associated with Parkinson's disease (Figure 18a). Idealisib (approved 7/2014) and its fluoro derivative duvelisib (approved 9/2018) are kinase inhibitors prescribed for patients suffering from chronic lymphocytic leukemia (CLL).[114] Cangrelor (approved 6/2015) is a nucleoside antiplatelet drug containing an intriguing phosphate group with two chlorine atoms as well as two thioether side chains.[115] Tenofovir alafenamide (approved 11/2015 as a combination component) is also a nucleoside, albeit lacking the typical dihydrofuran core and containing a chiral phosphoramidate side chain.

Indazole (#22). Indazole is another rising fused nitrogen heterocycle, with five members approved, which include belumosudil, lenacapavir, and zavegepant discussed in earlier sections (Figure 18b). Entrectinib[116] (approved 8/2019) is a pyrazole-containing tyrosine kinase inhibitor used for the treatment of NSCLC, while niraparib (approved 3/2017) targets poly(ADP-ribose) polymerase (PARP)[117] enzymes and is prescribed for treating ovarian cancer.

Pyrrolidine-2-one (#23). Four new pyrrolidine-2-one drugs have been approved recently along with the antiviral drug tecovirimat (approved 7/2018), which is a pyrrolidine-2,5-dione, as well as pyridine-fused migraine drugs ubrogepant and atogepant (Figure 18c). Nirmatrelvir is an antiviral drug presented in the pyrrolidine section. Brivaracetam (approved 2/2016),[118] which is a propyl derivative of the epilepsy drug levetiracetam, is the smallest of these four and is used to treat seizures. Midostaurin[119] (approved 4/2017) is an N-benzoylated derivative of the natural product staurosporine and is approved for AML patients. Ivosidenib (approved 7/2018), which is also prescribed for AML, is a peptide-like structure with two pyridines, multiple cyclobutyl group halogens, and a cyano group.[120]

1,3-Oxazinane (#24). Four 1,3-oxazinane-containing drugs appear in this dataset (Figure 19a), of which three are antiviral along with the antibiotic pretomanid (approved 8/2019). In all cases the 1,3-oxazinane nitrogen heterocycle is either fused or bridged bicyclic with no free-standing examples, and each one of them contains at least one chiral substituent, with three in the case of bictegravir. The prescribed applications of these drugs have been covered in preceding sections.

Quinoxaline (#25). Four quinoxaline drugs have been approved in the past 11 years, of which three are part of the incredibly successful drug discovery efforts aimed at treating hepatitis C (Figure 19b). Glecaprevir, grazoprevir, and voxilaprevir, which were discussed in the pyrrolidine section, are stereochemically rich macrocycles with the quinoxaline nitrogen heterocycle embedded within the macrocycle. These combination drug components are structurally remarkably similar, differing primarily in their fluorine and cyclopropane substitutions and in the absence or presence of a methoxy group on the quinoxaline. Erdafitinib[121] (approved 4/2019) is a first-in-class quinoxaline-containing drug prescribed for treating patients suffering from bladder cancer.

Azetidine (#26). Four new azetidine-containing drugs have been approved during the analysis period (Figure 19c) along with the two new cephem antibiotics, ceftolozane and cefiderocol (approved 11/2019). All four azetidine substituents are 1,4-substituted, thus none are chiral. Barcitinib and delafloxacin have been covered in earlier sections. Cobimetinib (approved 11/2015) is a kinase inhibitor used for treating melanoma.[122] Azetidine is the only nitrogen heterocycle in siponimod (approved 3/2019),[123] which is prescribed for MS.

Quinoline-2-one (#27). Three quinoline-2-one drugs are part of this dataset along with the reduced quinoline-2-one member aripiprazole lauroxil[124] (approved 10/2015), which is a prodrug derivative of the 2002-approved schizophrenia drug

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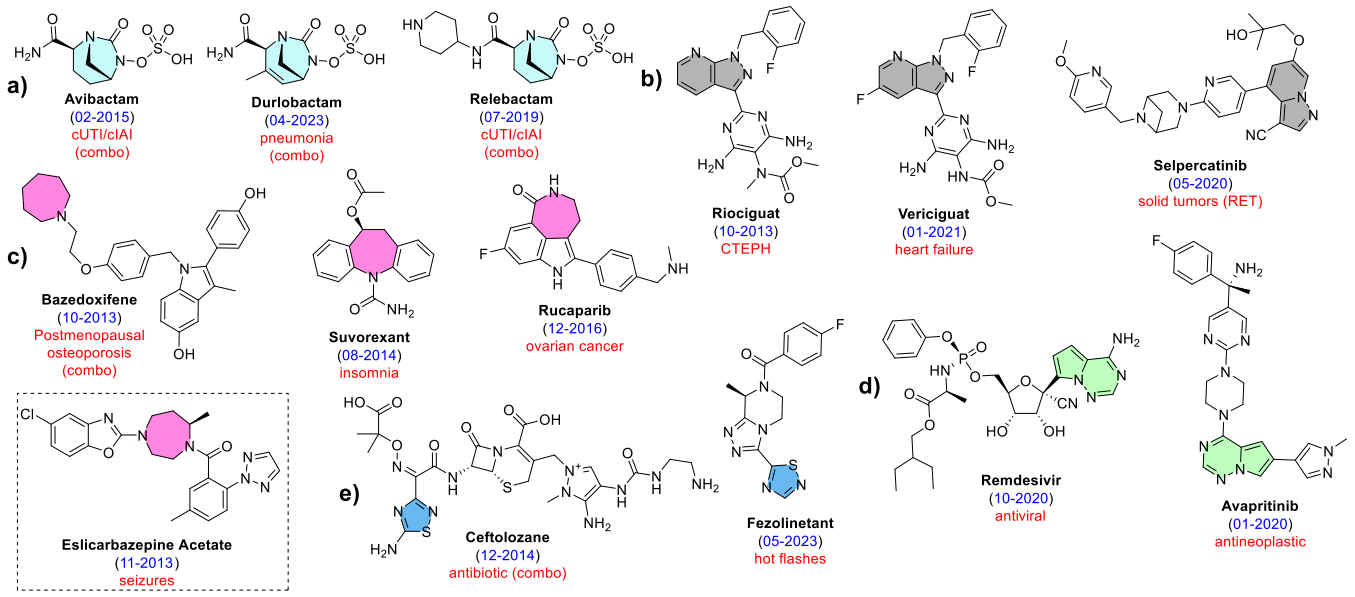

Figure 21. New U.S. FDA-approved small-molecule a) diazabicyclo[3.2.1]octane (#31)-, b) pyrazolopyridine (#32)-, c) azepane (#23)-, d) pyrrolotriazine (#34)-, and e) thiadiazole (#35)-containing drugs.

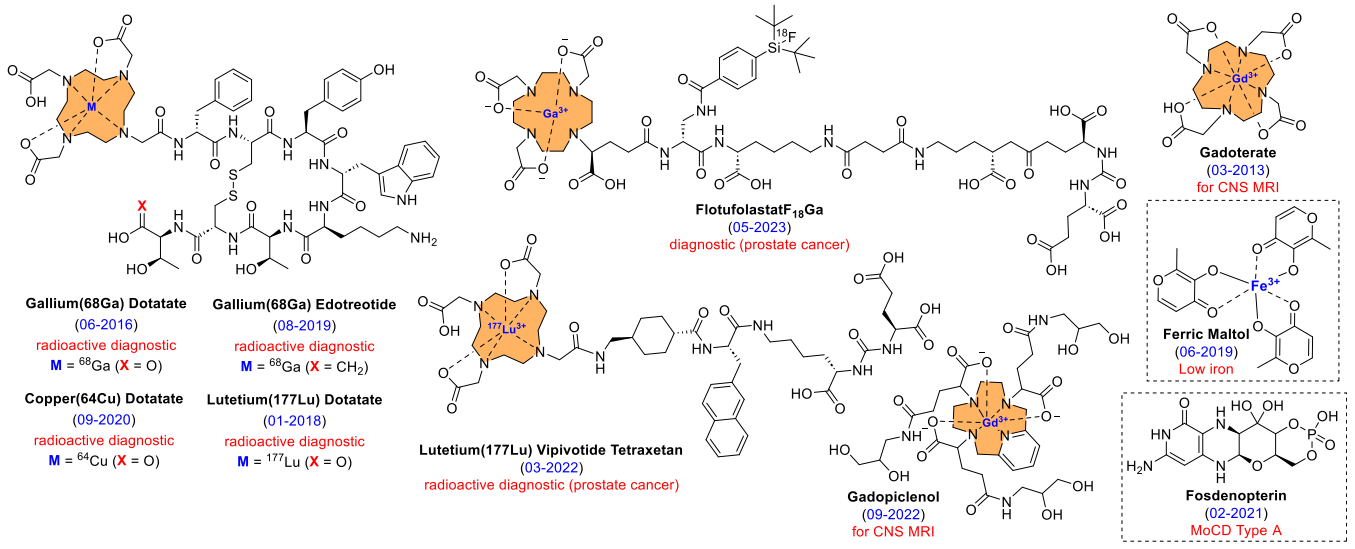

Figure 22. New U.S. FDA-approved small cyclen-based small-molecule diagnostic agents.

aripiprazole (Figure 20a). Brexpiprazole, presented in the piperazine section, is another member of this family of antipsychotics. Zavegepant is one of the most recently approved migraine drugs, and olutasidenib is a new AML drug, both of which were covered in earlier sections.

Isoquinoline (#28). Three isoquinoline drugs appear in this drug collection (Figure 20b), including the oxidized variant duvelisib. Netarsudil[125] (approved 12/2017) is a first-in-class medication for treating glaucoma, with isoquinoline being the sole nitrogen heterocycle component of its structure. Neratinib (approved 12/2017) is a tyrosine kinase inhibitor for treatment of metastatic breast cancer.[126] The isoquinoline core of neratinib is tetra-substituted with acrylamide, aniline, ethoxy, and cyano substituents.

Tetrazole (#29). Three new tetrazole drugs are part of this dataset, including cenobamate[127] (approved 11/2019), a new drug to treat partial-onset seizures (Figure 20c). Oteseconazole[128] (approved 4/2022) is a new azole antifungal for the treatment of recurrent vulvovaginal candidiasis (RVVC). Tedizolid phosphate, an antibiotic, was presented in the pyridine section.

Isoxazole (#30). Three isoxazole drugs have been approved recently (Figure 20d), along with the reduced isoxazole antiparasitic lotilaner (approved 7/2023), which is notable for having two alkyl CF_3 substituents, two chlorine atoms, and a thiophene ring. The anticancer drug kinase inhibitors quizartinib and tivozanib have been covered in earlier sections. Sparsentan[129] (approved 2/2023) is a first-in-class medication for patients suffering from focal segmental glomerulosclerosis (FSGS). In addition to the isoxazole, sparsentan is also decorated with an unusual oxidized spiro-imidazole nitrogen heterocycle.

Diazabicyclo[3.2.1]octane (#31). The three newly approved diazabicyclo[3.2.1]octane-containing drugs are all non-β-lactam β-lactamase inhibitors,[130] with avibactam (approved 2/2015) being the first to be approved, used as combination

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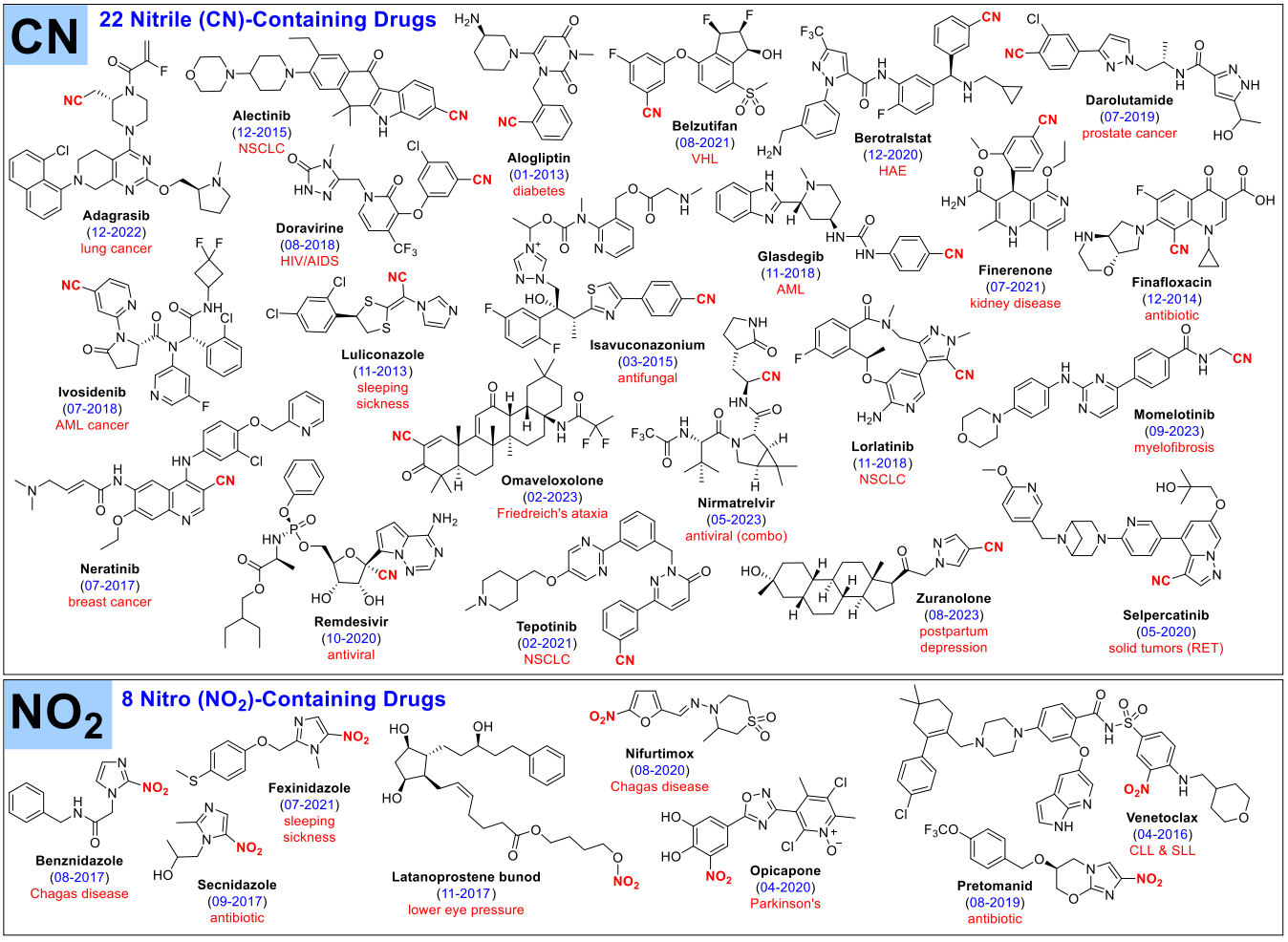

Figure 23. New U.S. FDA-approved small-molecule nitrile- and nitro-containing drugs.

component to treat infections (Figure 21a). Relebactam (approved 7/2019) was the second in this category to be approved, followed by durlobactam (approved 4/2023).[131] Relebactam is an amide piperidine derivative of avibactam, while durlobactam has a double bond and a methyl group embedded within the bicyclic framework of avibactam. These drugs are also notable for containing amino sulfonic acid substituents.

Pyrazolopyridine (#32). Three pyrazolopyridine-containing drugs have been approved during this period (Figure 21b), including riociguat and its desmethyl fluoro derivative vericiguat, which were both presented in the pyrimidine section. Selpercatinib (approved 5/2020) is a new nitrogen-heterocycle-rich kinase inhibitor used for treatment of patients with cancers and rearranged during transfection (RET)[132] gene alterations.

Azepane (#33). Three new azepane drugs appear in this dataset, along with the diazepane drug suvorexant (approved 8/2014),[133] which is used to treat insomnia (Figure 21c). Eslicarbazepine acetate (approved 11/2013) is an acetate prodrug of licarbazepine prescribed for treatment of partial-onset seizures of epilepsy[134] patients. Bazedoxifene[135] (approved 10/2013) is used in combination with conjugated estrogens to treat menopause symptoms.

Pyrrolotriazine (#34). Two pyrrolotriazine drugs are included in this update (Figure 21d), which are the antibiotic combination component ceftolozane and the menopause drug fezolinetant, both of which have been discussed in earlier sections.

Thiadiazole (#35). The final nitrogen heterocycle making it into the top 35 is thiadiazole, represented by two members, both approved in 2020 (Figure 21e). These are the first-in-class antiviral drug remdesivir[136] (approved 10/2020), which received accelerated approval during the COVID-19 pandemic, and the anticancer kinase inhibitor avapritinib[137] (approved 1/2020).

Cyclens. During these past 11 years, eight members of a unique metal-chelating class of macrocycles[138] called cyclens have been approved as small-molecule, disease-focused diagnostic agents (Figure 22). The structurally simplest of these cyclen agents is gadoterate, which is a DOTA (tetraxetan) gadolinium (Gd)-based MRI contrast agent,[139] wherein the metal coordinates to the four amines of the cyclen macrocycle as well as the appended carboxylates. Other members of this cyclen family all maintain the four chelating interactions with the most engaging three carboxylate ligands, with the fourth carboxylates in many cases converted into an amine and connected to complex peptides. Chelating metals represented in this cyclen category are copper, gadolinium, gallium, and lutetium.[140] Also displayed is the newly approved iron chelate ferric maltol (approved 6/2019) for treating patients with low iron as well as fosdenopterin, which is prescribed for molybdenum cofactor deficiency type A.

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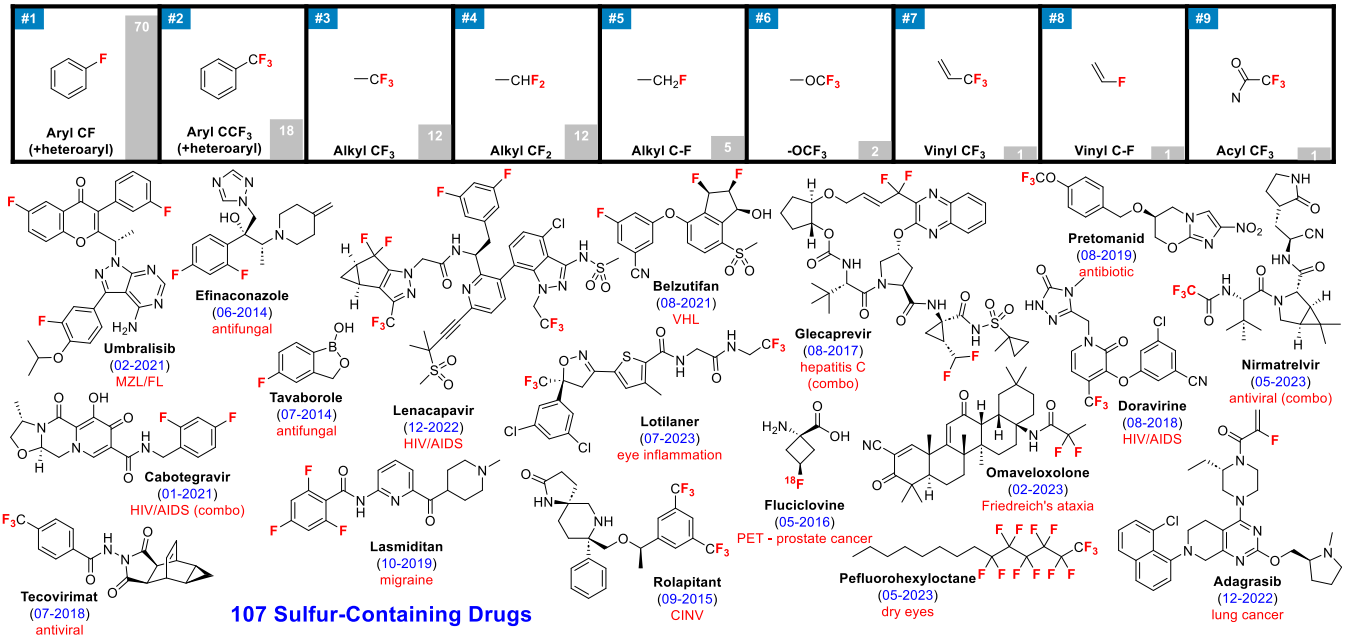

Figure 24. New U.S. FDA-approved small-molecule fluorine-containing drugs.

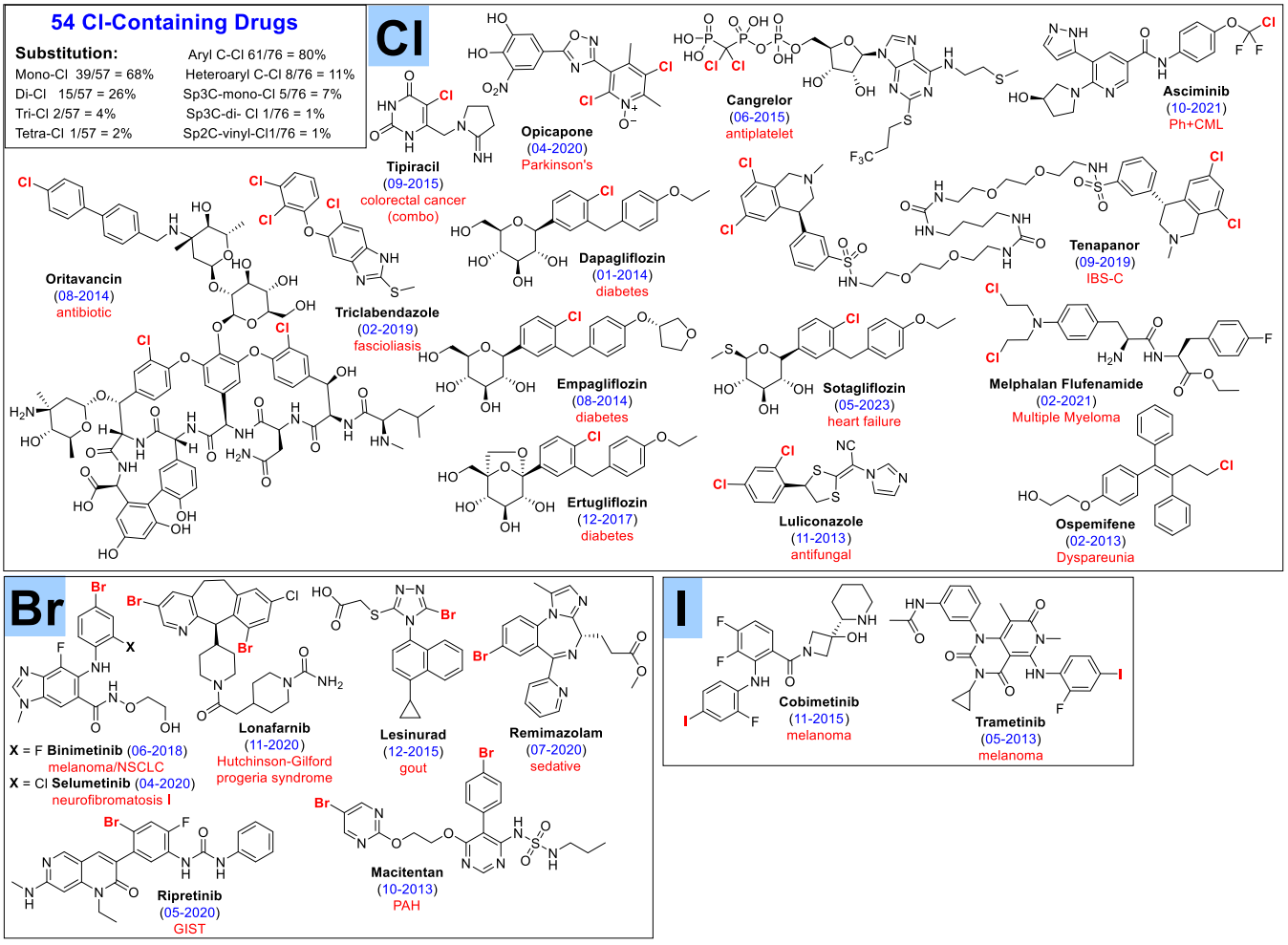

Figure 25. New U.S. FDA-approved small-molecule chlorine-, bromine-, and iodine-containing drugs.

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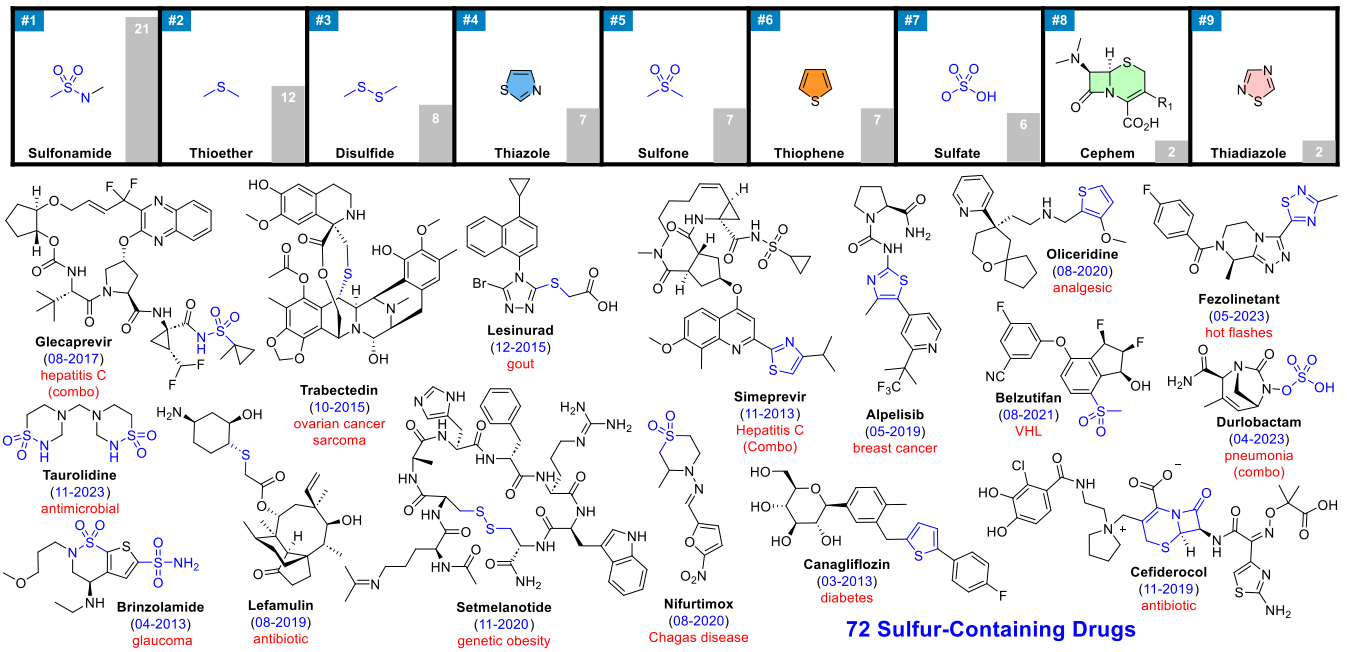

Figure 26. New U.S. FDA-approved small-molecule sulfur-containing drugs.

ANALYSIS OF FREQUENT AND EMERGING FUNCTIONAL GROUPS AND ATOMS

With this Perspective being focused primarily on nitrogen heterocycles, we decided to also include a summary of drugs approved during this period which contain the smallest and most significant of nitrogen substituents found in drug architectures, namely nitrile (CN)[141] and nitro (NO_2)[142] groups (Figure 23). Impressively, 22 new nitrile-containing drugs have been approved in the past 11 years, of which half (11) are approved for treating cancer and five for treating viral and fungal infections. The structurally most intriguing and reactive or labile of nitrile groups within this dataset are likely to be those found in luliconazole (conjugated nitrile) and remdesivir (nucleoside nitrile). Eight new nitro-group-containing drugs appear in this dataset, of which half (4) are substituents on an imidazole ring and members of the nitroimidazole antibiotics. Two of these nitro drugs (benznidazole and nifurtimox) are approved for treatment of Chagas disease. The most intriguing and reactive of these nitro-containing drugs, and interestingly lacking a nitrogen heterocycle, is the prostaglandin analog latanoprostene bunod[143] (approved 11/2017), which is used to reduce intraocular pressure in patients.

In celebration of our earlier "heteroatom-focused" Perspectives (beyond nitrogen and oxygen atoms), which appeared the same year as our nitrogen-heterocycle-focused Perspective, which is the focus of this update, we decided to include in the following paragraphs and figures short updates on new drugs with halogen, sulfur, phosphorus, and newly emerging heteroatoms approved in the past 11 years. Not surprisingly, fluorine reigns supreme within this dataset of newly approved heteroatom-substituted small-molecule drugs, with 107 new members (34%). A summary of rank and frequency of occurrence of the various fluorine substitutions appearing along with a selected sample of new fluorine-containing drugs is presented in Figure 24. A clear winner in terms of the number one rank are aryl/heteroaryl C-F substituents (a total of 70), followed by a distant second rank of aryl trifluoromethyl groups ($Ar\text{-}CF_3$, a total of 18). Tied for third and fourth place are alkyl trifluoromethyl ($alkyl\text{-}CF_3$) and difluoroalkyl substituents, with appearances in 12 drugs each. Fifth place is represented by monofluoro alkyl substituents, with remaining fluorine substituents being trifluoromethoxy (pretomanid), vinyl-trifluoromethyl (doravirine), vinyl-fluoride (adagrasib), and trifluoroacylamide (nirmatrelvir). Several of the fluorinated drugs displayed in Figure 24 do not contain a nitrogen heterocycle, such as the antifungal tavaborole (approved 7/2014), the anticancer drug belzutifan[144] (approved 8/2021), the positron emission tomography (PET) prostate cancer diagnostic agent fluciclovine (approved 5/2016), Friedreich's ataxia drug omaveloxolone[145] (approved 2/23), and most intriguingly the newly approved drug for dry eyes, perfluorohexyloctane (approved 5/2023).

Other newly approved halogen-containing small-molecule drugs are presented in Figure 25, with chlorine-containing drugs being represented by 54 new members. The majority of these new chlorinated drugs contain a single chlorine atom (39, 68%), with 15 drugs being substituted with two chlorine atoms (26%), two drugs (triclabendazole and oritavancin) having three chlorine atoms, and one drug (tenapanor) having four chlorine atoms. With respect to types of substitutions in which these chlorine atoms participate, a total of 61 (80%) are aryl carbon chlorine bonds, followed by a distant 11% represented by heteroaryl chlorine bonds. Only six of these drugs have chlorine attached to an sp^3-carbon atom (examples include asciminib, cangrelor, melphalan flufenamide, and ospemifene), with a single drug being represented by a vinyl C-Cl substituent (tipiracil). Dapagliflozin (approved 1/2014), empagliflozin (approved 8/2014), ertugliflozin (approved 12/2017), and sotagliflozin (approved 5/2023) belong to a family of sodium-dependent glucose cotransporters (SGLTs)[146] and are notable for having similar structures and the absence of nitrogen heterocycles. The seven new bromine-containing small-molecule drugs are also presented in Figure 25, of which all are aryl bromides, with two drugs (lonafarnib and macitentan) containing two bromine atom substituents. Four of the bromine-containing drugs are kinase inhibitors. Finally, two new iodine-

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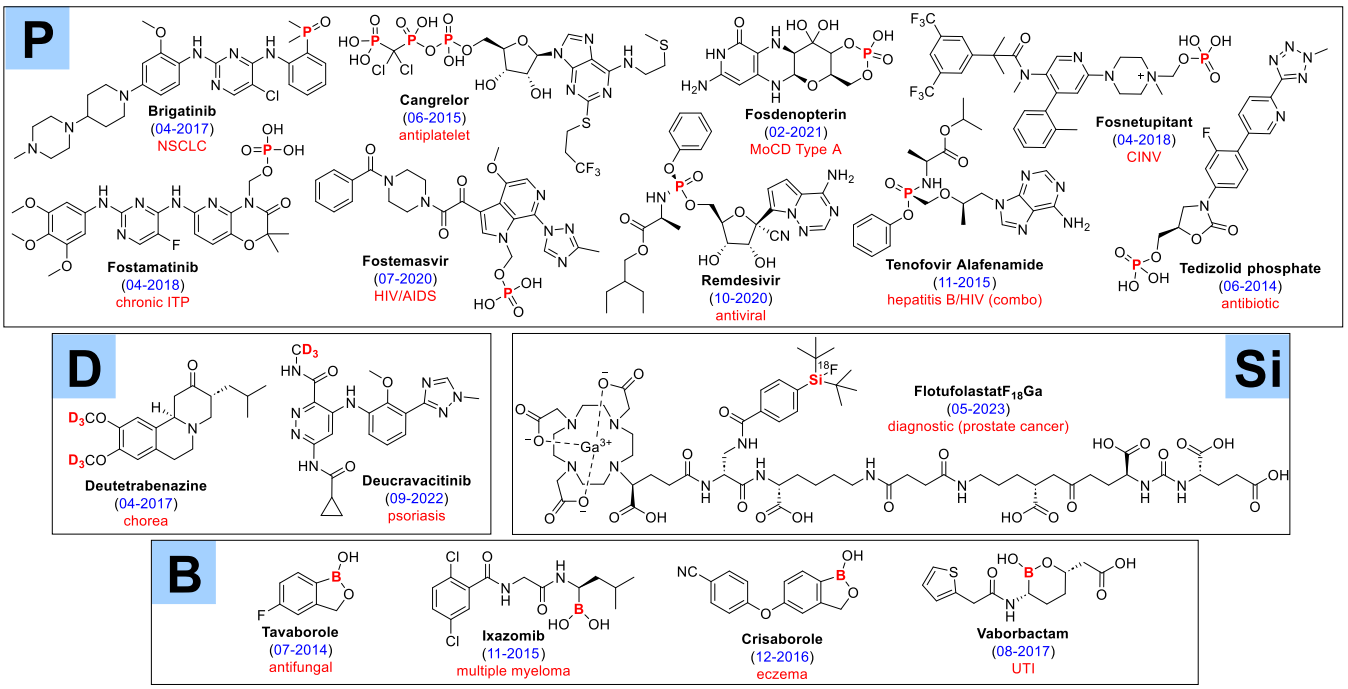

Figure 27. New U.S. FDA-approved small-molecule phosphorus-, deuterium-, boron-, and silicon-containing drugs.

containing kinase inhibitor melanoma drugs (cobimetinib and trametinib) have been approved during this period.

Drugs containing sulfur substituents continue to be approved in high numbers, with 72 (23%) new small-molecule sulfur-containing drugs being part of this dataset (Figure 26). A graphical summary of the most frequently occurring sulfur substituents and heterocycles, their relative rank, along with selected examples are presented. With sulfur being the structurally most versatile of the atoms found in drug architectures and beyond, this diversity is reflected in this collection of new sulfur-containing drugs, with sulfonamide maintaining the top rank (21 new drugs), followed by thioethers in second place (12 new drugs), disulfide securing third place (8 new drugs), and a tie for fourth−sixth places among thiazoles, sulfones, and thiophenes (at 7 new drugs each). Closely following in seventh place are sulfates (6 new drugs), with cephems and thiadiazoles rounding off the remaining sulfur-containing substitutions. Many of these drugs have been discussed in previous sections, but notable members containing two sulfonamide groups are the antimicrobial drug taurolidine (approved 11/2023) and brinzolamide (approved 4/2013), which is used for treatment of glaucoma. The thiophene-containing drug canagliflozin (approved 3/2013), prescribed for diabetes, and the natural product antibiotic lefamulin[147] (approved 8/2019) are examples of sulfur-containing drugs lacking a nitrogen heterocycle.

Presented in Figure 27 are all the new small-molecule drugs containing phosphorus, deuterium, boron, and silicon atom substituents. A total of nine new phosphorus-containing drugs are in this dataset, with cangrelor being particularly notable for containing three phosphorus atoms. Fosdenopterin is the only one with a cyclic phosphate, and brigatinib is substituted with a highly unusual dialkyl-aryl phosphine oxide. Remdesivir and tenofovir alafenamide both contain phosphoramidate groups. Since the approval of bortezomib in 2006, boron substituents have become a serious functional group to consider in drugs. In the past 11 years, four new boron-containing drugs have been approved, all of which are relatively small molecules and none of which contains a nitrogen heterocycle. These drugs are represented by three cyclic acids and one acyclic acid. Tavaborole (approved 7/2014) is a new antifungal, ixazomib (approved 11/2015) is used to treat multiple myeloma, crisaborole (approved 12/2016) is used for eczema, and vaborbactam (approved 8/2017) is prescribed for urinary tract infections (UTIs). Two new deuterium drugs (deutetrabenazine and deucravacitinib), another newer and growing atom-substitution approach in drug discovery,[148,149] have been approved in recent years. Finally, the diagnostic prostate cancer agent flotufolastat F18Ga is the first U.S. FDA-approved silicon-containing drug.

TEMPORAL ANALYSIS OF THE IN SILICO PHYSICOCHEMICAL PROPERTIES OF DRUG COHORTS FROM 2013 TO 2023 AND PRIOR TO 2013

In the quest to understand the differences in the physicochemical properties of FDA-approved drugs over time, we introduced a benchmarked set of drugs, for comparison, from a recent comprehensive analysis by Leeson.[150] This set comprised of 642 drugs approved over several decades extracted from the chEMBL database.[151] Given that this set contained drugs up to 2021, we selected and extracted drugs up to 2013 to provide a set of 536 drugs approved prior to the 2013−2023 drug set from this analysis. To standardize the analysis, and for a more accurate comparison of properties, we combined both sets of drugs and, using AbbVie's proprietary in silico design platform, calculated multiple physicochemical properties which we used in the following analysis. We also analyzed the overall compliance of drugs with Lipinski's Rule of Five (Ro5) as a widely accepted guideline for discerning the likelihood of compound progression, with compounds failing Ro5 more likely to have issues in drug optimization compared to compounds that pass Ro5. Of course, there are many other factors to consider during optimization; however, Ro5 compliance is still an important

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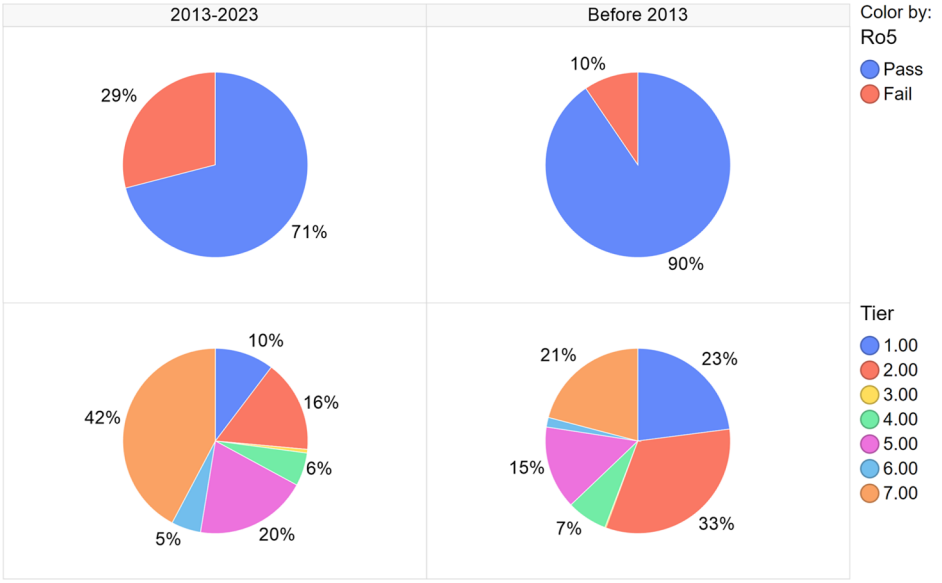

Figure 28. Percentage of drugs passing Ro5 before 2013, taken from the recent analysis by Leeson ($n = 536$),[150] and between 2013 and 2023 ($n = 310$), taken from this current analysis. Bottom pie plot shows the AbbVie Physicochemical Tier (APT) distribution of the two cohorts of drugs.

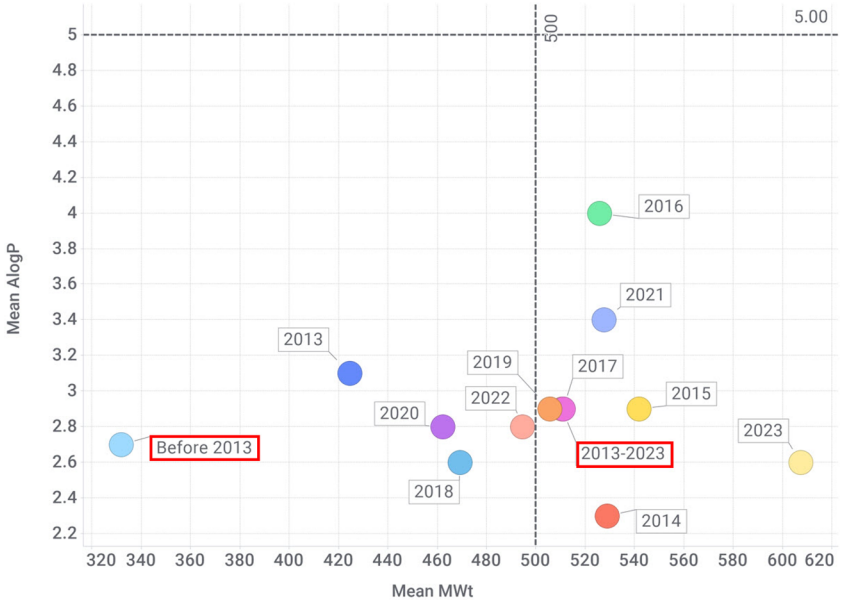

Figure 29. Plot of Mean AlogP vs Mean MWt for drugs over the past few decades. The lines show the Lipinski thresholds of MWt (500) and AlogP (5). Red boxes show the combined averages for both cohorts of drugs.

guideline to be cognizant of and something we discuss in this analysis.

The first clear and obvious trend is that there has been a significant shift in the physicochemical property trajectory of drugs toward less favorable profiles, leading to a potentially more challenging optimization path necessary to produce chemical matter equipped to functionally modulate and drug desired protein targets. Leeson's study[150] clearly shows a trend toward the more recent approval of significantly larger and more lipophilic drugs, and therefore to a greater preponderance of so-called beyond Rule of Five (bRo5) drugs. This can be attributed to a shift in the focus of the pharmaceutical industry to more challenging protein targets such as protein−protein interaction (PPI) targets (exemplified by drugs such as venetoclax and lumakras) and a recent paradigm shift directed at developing drugs focused on new promising drug modalities, such as targeted protein degradation. Due to this, the emergence of larger, more complex, less tractable, and more challenging to drug molecules such as bifunctional PROTACs[152] will no doubt lead to an even greater upshift in the percentage of bRo5 drugs. Although bifunctional PROTACs have yet to be approved by the FDA, this upshifted trend is nevertheless evident, particularly in the past 11 years, with drugs now more commonly failing Lipinski's rules,[153] leading to a significant increase in the number of bRo5 drugs. Indeed, the percentage of bRo5 drugs has almost tripled in the past decade versus the previous three. This is illustrated in the pie charts in Figure 28, with only 10% of drugs failing Ro5 prior to 2013 compared to 29% between 2013 and 2023.

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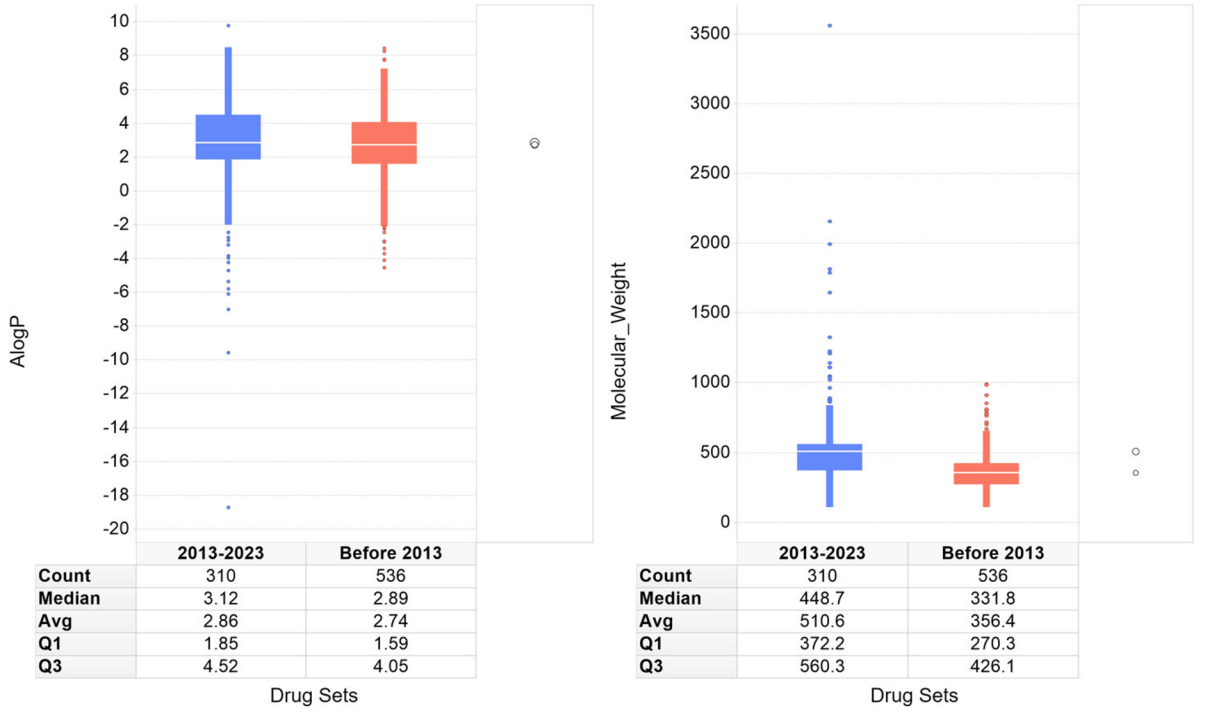

Figure 30. Box-plot comparison of the property distributions of the two drug sets, showing a statistically significant difference in molecular weight but not lipophilicity (AlogP) and showing a temporal shift in drug property space to a large, not greasy paradigm.

Additionally, we calculated the Abbott (AbbVie) Physicochemical Tiering (APT)[154] profile of each set of drugs, the distributions of which are shown in Figure 28. Note that Abbott (AbbVie) Physicochemical Tiering is a simple method of binning compounds based on their overall in silico physicochemical property profiles. There are seven tiers in total, with Tier 1 having the most favorable and Tier 7 the least favorable properties. We have shown that the tiers correlate with the odds of favorable ADME properties and are therefore an effective way of categorizing the overall quality of compounds from an in silico physicochemical property perspective. The drug set prior to 2013 has a significantly more favorable APT distribution profile, with over 50% in the first three more favorable tiers, compared to just over 25% for the 2013−2023 drug set, plus half as many compounds in the least favorable Tier 7 property space. In addition to a greater Ro5 failure rate, the APT profiles show that drugs in the past decade possess other less favorable properties, such as greater numbers of aromatic rings and lower saturation (Fsp^3).[155]

The reason for these observations, as mentioned above, is the significant shift of drug discovery and development portfolios, with targets such as kinase inhibitors now the dominating class compared to aminergic GPCRs prior to the 1990s. Indeed, there has been a total of 80 kinase drugs approved in the past 20 or so years, 58 of which were approved in the past decade.[156] In terms of physicochemical properties, kinase drugs are typically on the cusp of Ro5 property space, with 66% having at least one and 21% having more than one Ro5 violation (Mean MWt = 489, AlogP = 3.74). In contrast, all aminergic GPCR drugs pass Ro5 and in many cases pass Ro4, possessing properties more synonymous with fragments (Ro3) and/or leads (Ro4) (Mean MWt = 324.8, AlogP = 2.33); note that values for GPCR drugs were calculated after extraction from the Leeson study.[150] In order to further contrast the differences in properties, we calculated the mean AlogP and MWt of each set of drugs by year (2013−2023), added the mean values from the Leeson analysis, and visualized the results as a scatter plot (Figure 29).

Clearly, there has been a significant shift in the molecular weight of drugs in the past decade compared to the previous decades; however, there has been little to no significant shift in the lipophilicity of drugs. This is evident from the distributions of the properties of the two cohorts of drugs, with statistical significance seen for the differences (α value = 0.05) in MWt but not AlogP (Figure 30). Note that Leeson noticed a significance in lipophilicity over time by binning by decade.[150] Here we have combined all the drugs prior to 2013 from his study, and we observe no significance in AlogP between this cohort of drugs and the drugs in this study between 2013 and 2023.

Another indication of the shift of drugs toward more challenging, less tractable chemical matter is manifest in the drop in overall compound quality. Compound quality can be quantified using proxies of drug-likeness such as QED,[157] PFI,[158] and AB-MPS.[159] In all cases the averages for these have moved in a direction indicative of poorer quality (Table 1).

Indeed, there are significant differences in the distributions of these properties between the two drug sets, showing that drug

Table 1. Comparison of the Average Composite Scoring Functions/Proxies of Drug-likeness (QED, PFI, and AB-MPS) Plus Size (MWt) and Lipophilicity (AlogP) of the Two Drug Sets, 2013−2023 and Before 2013

Drug Set	2013−2023	Before 2013
# Drugs	310	536
Mean QED	0.44	0.63
Mean PFI	4.71	3.72
Mean AB-MPS	12.6	8.9
Mean AlogP	2.86	2.74
Mean MWt	510.6	356.4

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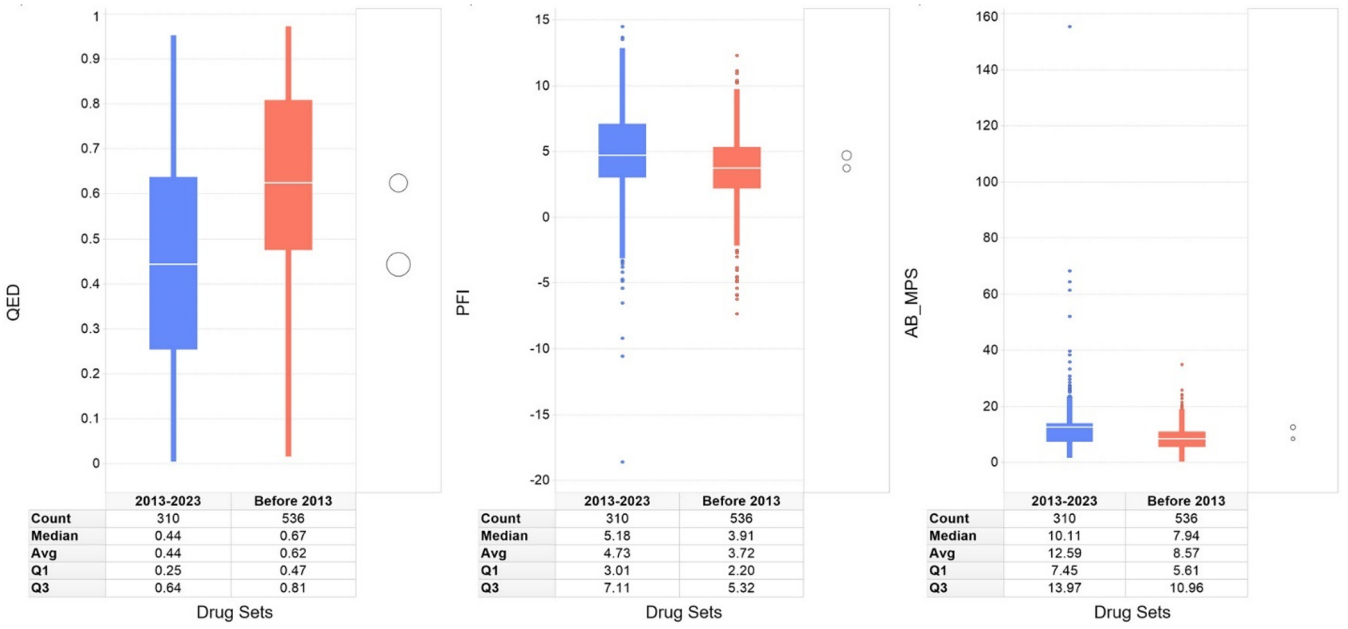

	2013-2023	Before 2013
Count	310	536
Median	0.44	0.67
Avg	0.44	0.62
Q1	0.25	0.47
Q3	0.64	0.81

	2013-2023	Before 2013
Count	310	536
Median	5.18	3.91
Avg	4.73	3.72
Q1	3.01	2.20
Q3	7.11	5.32

	2013-2023	Before 2013
Count	310	536
Median	10.11	7.94
Avg	12.59	8.57
Q1	7.45	5.61
Q3	13.97	10.96

Figure 31. Box-plot comparison of the property distributions of the two drug sets, showing a statistically significant difference for all proxies of drug quality (QED, PFI, and AB-MPS).

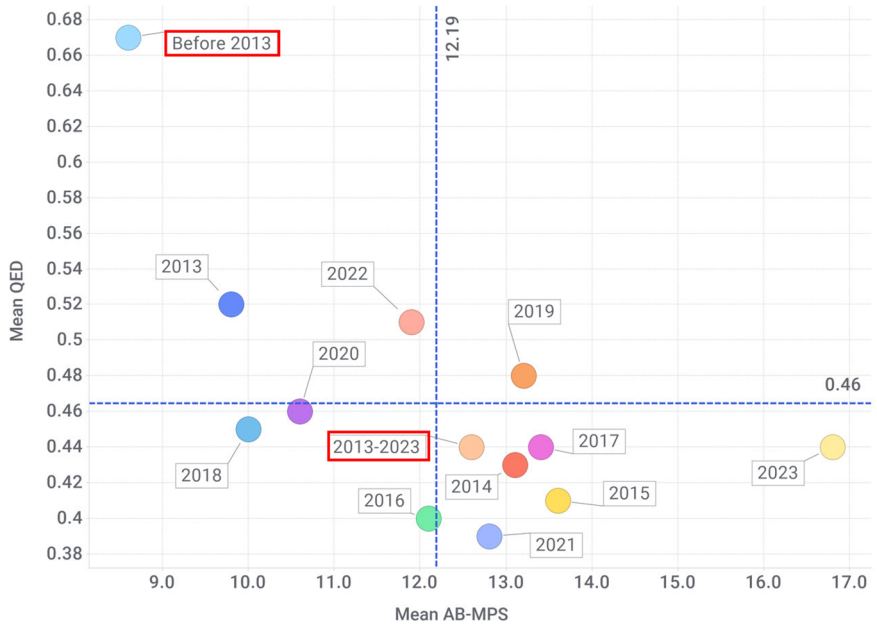

Figure 32. Plot of Mean QED versus Mean AB-MPS for the drug sets over the past few decades. The blue dotted lines are the overall averages for the complete set of drugs. Red boxes show the combined averages for both cohorts of drugs.

quality, in relative terms, has decreased in the past decade versus previous decades (Figure 31).

This trend is also evident in the APT distributions, with drugs prior to 2013 having compounds in much more favorable physicochemical tiers. To further illustrate the differences in the quality metrics of the cohorts of drugs, we plotted the mean QED versus mean AB-MPS and highlighted the overall average values as blue dotted lines (Figure 32). Clearly, prior to 2013, drugs on average had more favorable drug-like properties, as evidenced by superior composite scores. This plot also shows that the drugs approved before 2013 have, on average, the most favorable composite property scores.

One other significant change in the properties of drugs over time is the marked upshift in overall topological polar surface area (TPSA), indicating that drugs are becoming more polar with increasing size. This increase in TPSA is not wholly a function of increased molecular weight, as the TPSA per heavy atom is also significantly different in the past decade compared to before 2013 (Figure 33). This increase is likely due to the upshift in the percentage of nitrogen and oxygen atoms in drugs, with an increase of approximately 17% in the past decade evident versus the previous decades.

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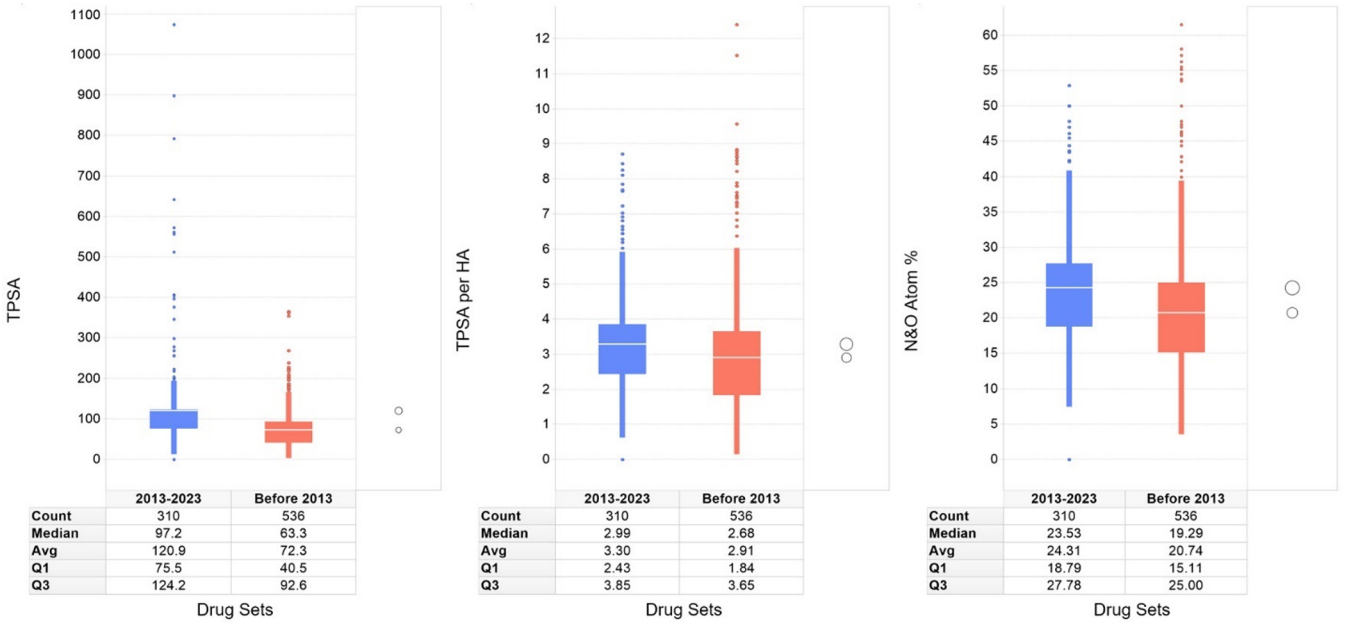

Figure 33. Comparison of property distributions of the two cohorts of drugs for TPSA, TPSA per heavy atom, and percentage of N and O atoms in a drug (= N+O count/Num Heavy Atoms).

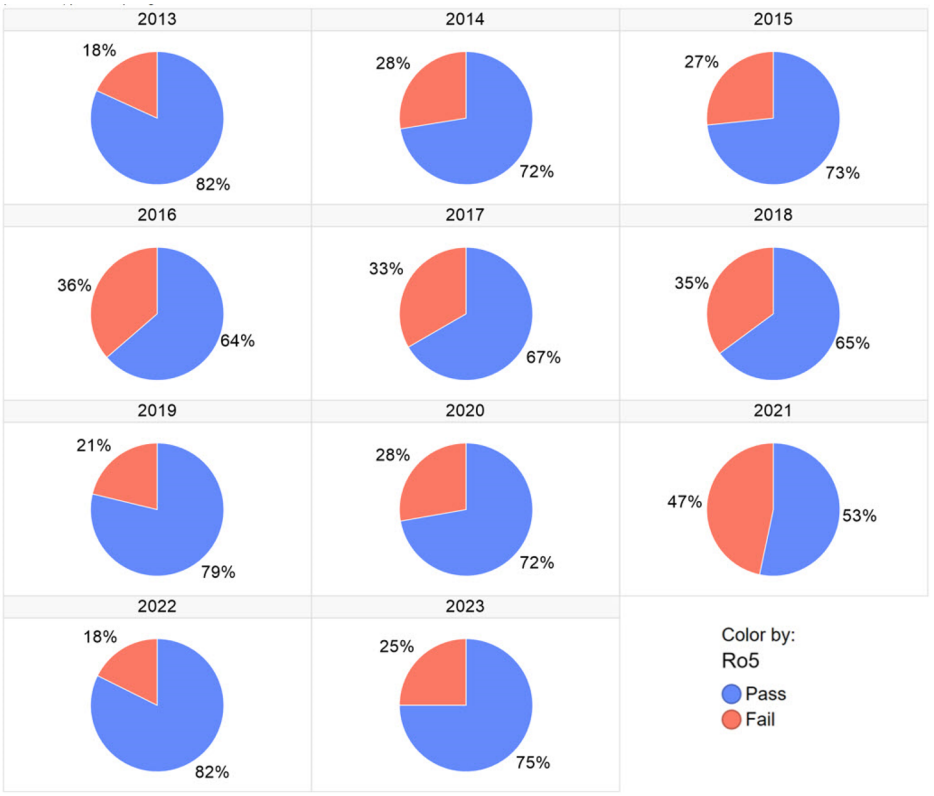

Figure 34. Percentage of drugs passing Ro5 each year from 2013 to 2023.

PHYSICOCHEMICAL PROPERTY ANALYSIS OF DRUGS BY YEAR FROM 2013 TO 2023

As mentioned earlier, we calculated a comprehensive set of in silico physicochemical properties of the drug set 2013−2023, the statistics of which are tabulated in Table 2. In the past 11 years from 2013 to 2023, there has been a clear shift toward less favorable physicochemical properties and a consequential drop in Ro5 compliance. Indeed, this is evident in the pie charts in Figure 34, which show the percentage of Ro5 compliance by year from 2013 to 2023.

The percentage of Ro5 compliance drops significantly after 2013. All years including 2013 have much higher percentage failures compared to the drug set prior to 2013, with 2021 having the greatest Ro5 failure rate at 47%.

We analyzed the property violations that contributed to the Ro5 failures, with 94% violating MWt > 500, by far the greatest

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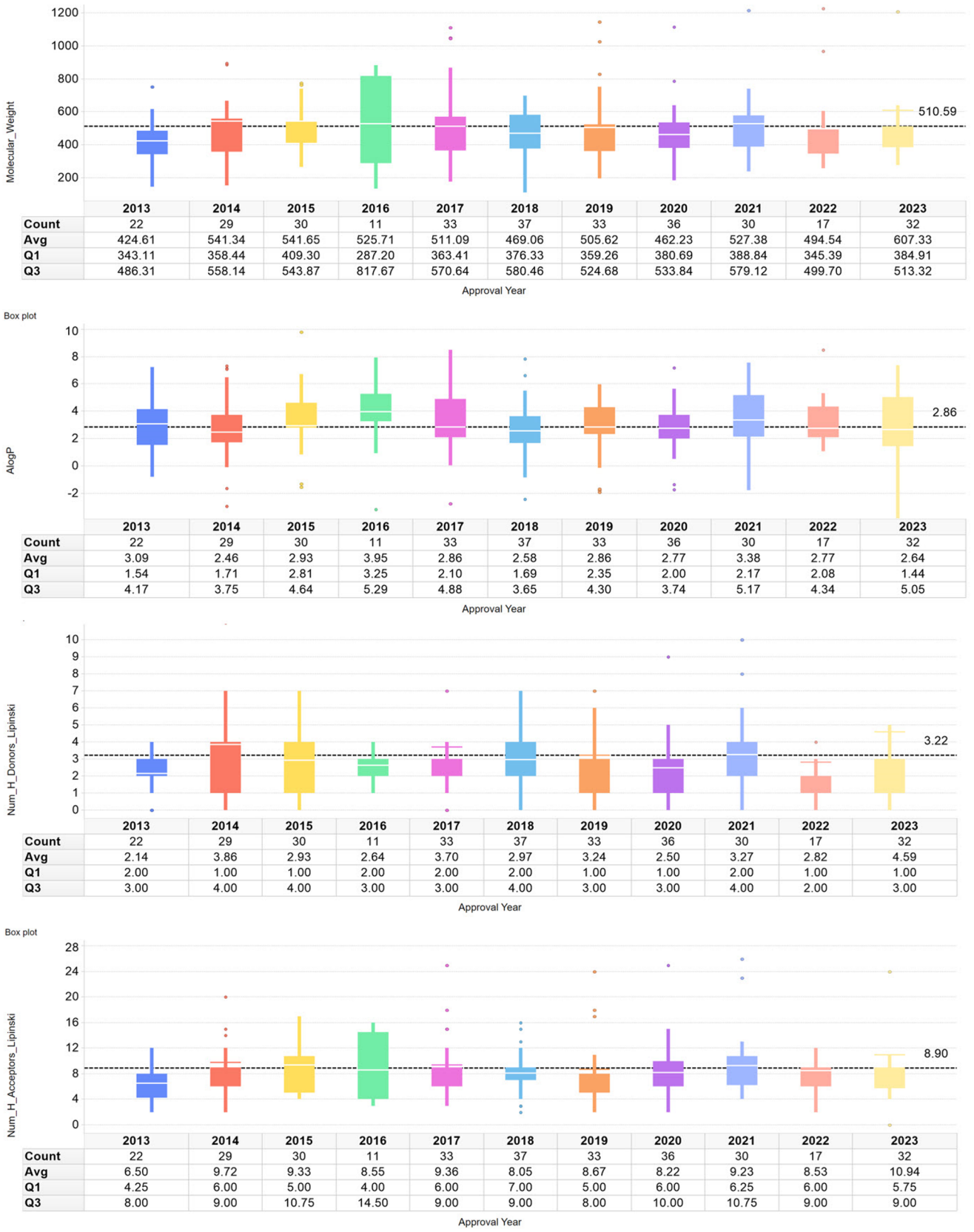

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Count	22	29	30	11	33	37	33	36	30	17	32
Avg	424.61	541.34	541.65	525.71	511.09	469.06	505.62	462.23	527.38	494.54	607.33
Q1	343.11	358.44	409.30	287.20	363.41	376.33	359.26	380.69	388.84	345.39	384.91
Q3	486.31	558.14	543.87	817.67	570.64	580.46	524.68	533.84	579.12	499.70	513.32

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Count	22	29	30	11	33	37	33	36	30	17	32
Avg	3.09	2.46	2.93	3.95	2.86	2.58	2.86	2.77	3.38	2.77	2.64
Q1	1.54	1.71	2.81	3.25	2.10	1.69	2.35	2.00	2.17	2.08	1.44
Q3	4.17	3.75	4.64	5.29	4.88	3.65	4.30	3.74	5.17	4.34	5.05

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Count	22	29	30	11	33	37	33	36	30	17	32
Avg	2.14	3.86	2.93	2.64	3.70	2.97	3.24	2.50	3.27	2.82	4.59
Q1	2.00	1.00	1.00	2.00	2.00	2.00	1.00	1.00	2.00	1.00	1.00
Q3	3.00	4.00	4.00	3.00	3.00	4.00	3.00	3.00	4.00	2.00	3.00

	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
Count	22	29	30	11	33	37	33	36	30	17	32
Avg	6.50	9.72	9.33	8.55	9.36	8.05	8.67	8.22	9.23	8.53	10.94
Q1	4.25	6.00	5.00	4.00	6.00	7.00	5.00	6.00	6.25	6.00	5.75
Q3	8.00	9.00	10.75	14.50	9.00	9.00	8.00	10.00	10.75	9.00	9.00

Figure 35. Molecular property distributions of the drugs by year from 2013 to 2023. Black dotted horizontal lines denote global property averages.

property violation for this drug set. In addition to this, 47% violated AlogP > 5, 73% H-bond acceptors > 10, and 34% H-bond donors > 5. [Note that we used the original Lipinski criteria for counting H-bond donors and acceptors.]

We also analyzed the properties of drugs by year from 2013 to 2023. On average, 2013 produced drugs with the lowest (424.6) and 2023 the highest (607.3) molecular weight. In terms of lipophilicity, 2014 had the lowest (2.46) and 2016 (3.95) had

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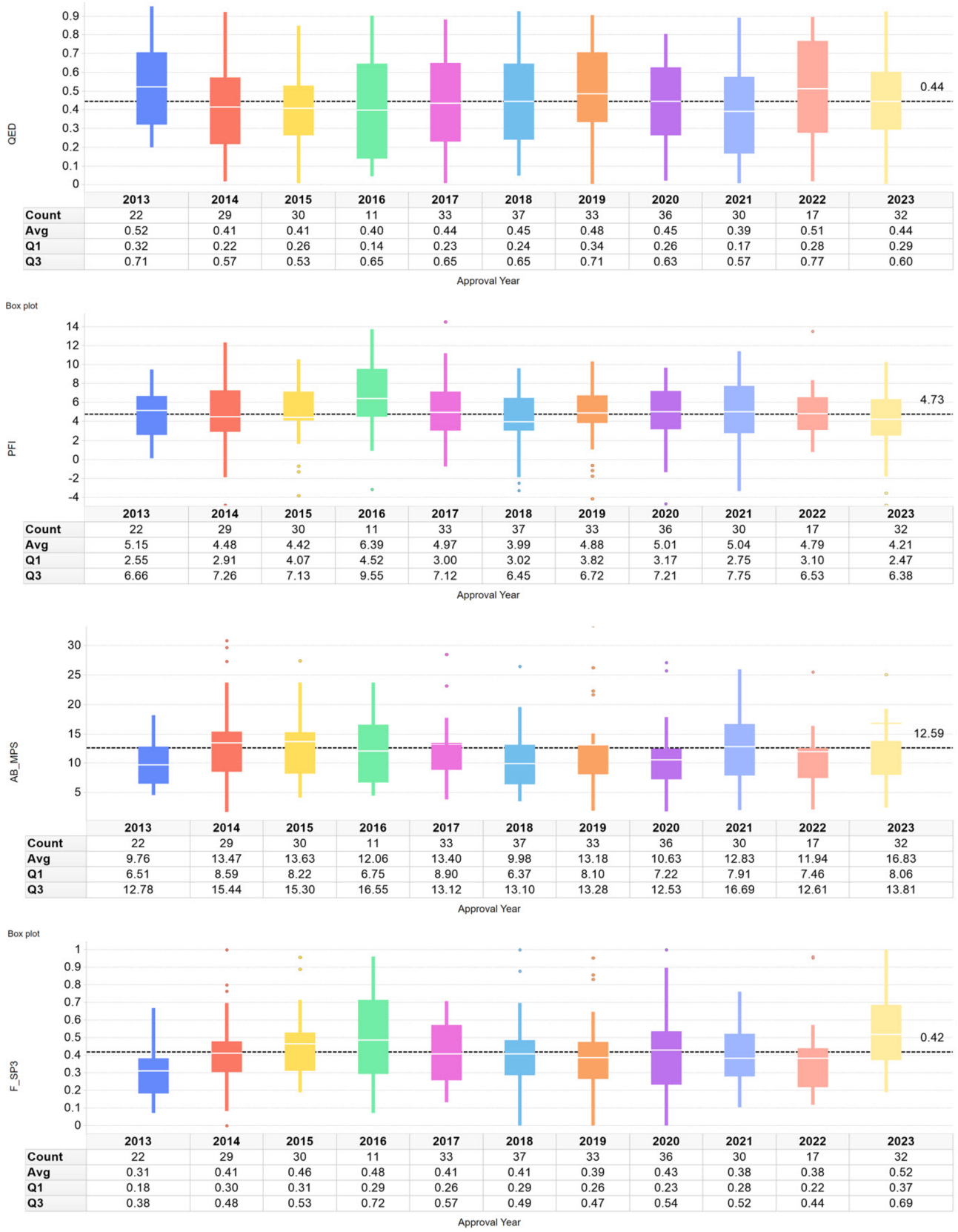

Figure 36. Composite property and Fsp^3 distributions of drugs from 2013 to 2023. Black dotted horizontal lines denote global property averages.

the highest average lipophilicity (AlogP). Again, 2013 stands out as the year in the past decade with drugs that have the most reasonable properties, and this is evident for both the average numbers of hydrogen bond donors and acceptors, which are significantly lower than the global average for all the years in this analysis. The reasonable properties for drugs in 2013 translate into more favorable composite scores of drug likeness, such as QED and AB-MPS, and these drugs again are significantly

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Table 2. Statistics of the Physicochemical Property Profiles of the Drugs in This Study (2013−2023)[a]

Property	Median	Mean	Q1	Q3	IQR
MWt	448.7	510.6	372.2	560.3	188.1
AlogP	3.1	2.9	1.9	4.5	2.6
cLogD	2.2	1.6	0.7	3.6	2.9
TPSA	97	121	75	124	49
NHBD	2	3	1	3	2
NHBA	8	8.9	6	9	3
NAR	2	2.4	1	3	2
NR	4	4	3	5	2
NRB	6	8	4	9	5
Fsp^3	0.38	0.42	0.26	0.51	0.25
PFI	5.2	4.7	3.0	7.1	4.1
QED	0.43	0.44	0.25	0.64	0.39
AB-MPS	10	12.6	7.5	14.0	6.5

[a]**MWt** = molecular weight, **AlogP** = atom-based LogP, **LogD** = calculated ChemAxon LogD, **TPSA** = topological polar surface area (NO only), **NHBD** = number hydrogen bond donors, **NHBA** = number hydrogen bond acceptors, **NAR** = number of aromatic rings, **NR** = number of rings, **NRB** = number of rotatable bonds, **Fsp^3** = fraction of sp^3 carbons, **PFI** = property forecast index, **QED** = quantitative estimate of drug-likeness, and **AB-MPS** = AbbVie multiparametric score. **Q1** = lower quartile, **Q3** = upper quartile, **IQR** = interquartile range.

superior to the global average values, as shown in Figures 35 and 36.

The past decade, compared to previous decades, has seen a significant shift in the property profiles of drugs, leading to chemical matter that is more challenging to drug and more frequently violates Lipinski's rules. Ultimately, the dominance of less tractable and challenging targets in pharma portfolios has necessitated this paradigm shift and led to an increase in the preponderance of bRo5 drugs approved by the FDA. This trend is only set to increase if one considers the impact that both bifunctional PROTAC drugs and less tractable targets such as PPIs will have on the property profiles of drugs in the coming years. It is also clear that the pharmaceutical industry is adapting to the challenges associated with developing drugs in less favorable property space, with the dogma of the Ro5, for many, an artifact of the past.

CONCLUSION

This analysis of small-molecule drugs approved by the U.S. FDA in the past 11 years is a continuation of our earlier nitrogen heterocycle analysis with additional summarized updated insights into newly approved fluorine, sulfur, chlorine, bromine, iodine, phosphorus, deuterium boron, and silicon as well as nitro- and cyano-containing drugs to add a layer of richness to the presentation and analysis. An important design part of this Perspective is the focus on displaying as many of these newly approved drug structures as possible within the figures to enable expert and non-expert readers to navigate this fantastically rich dataset in a plethora of ways that can only be realized by displaying the structures. With respect to nitrogen heterocycle representation, the changes are most significant, with an increase from 59% in the earlier dataset to 82% of newly approved drugs containing a nitrogen heterocycle, as well as a major shift toward drugs with multiple nitrogen heterocycles. Many of the top-ranked nitrogen heterocycles are the same, but the rank has changed with many new members such as pyrazole and numerous fused nitrogen heterocycles, at the expense, in many cases, of classic natural-product-type nitrogen heterocycles. The diversity of drug architectures within this dataset, their complexity, and the inclusion of new atoms and functional groups are truly impressive and inspiring. This increase in chemical complexity has led to a concomitant increase in the size (MWt) of drugs in the past 11 years, compared to previous decades, and to an upshift in the number of drugs approved that are beyond the Ro5. Clearly, the pursuit of high-value drug targets for the benefit of patients far outweighs the potentially more challenging, and expensive, path associated with the development of larger, less tractable chemical entities. This is a testament to the brilliance and bravery of our community of drug discovery scientists who stop at nothing to cure human disease and suffering.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.4c01122.

List of all of the drugs in this dataset along with their data of approval (XLSX)

SMILES strings for the drugs in this dataset (CSV)

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Notes

The authors declare no competing financial interest.

Biographies

Christopher M. Marshall graduated in May of 2018 with a B.S. in chemistry from the University of Arizona, at which point he joined Accelerate Diagnostics in Tucson, AZ, and worked as a formulation chemist. In August 2021, Christopher started his chemistry doctoral studies at the University of Arizona and later that fall joined the research group of Professor Njardarson.

John G. Federice obtained his B.S. in chemistry from Canisius University in Buffalo, NY. John started his studies as a graduate student in the Department of Chemistry and Biochemistry in the Fall of 2023 and became a member of the Njardarson group in January of 2024.

Chloe N. Bell is an undergraduate student at the University of Arizona in the Honors College and has been training in the Njardarson group since August 2023.

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Jon T. Njardarson received his Ph.D. at Yale University in 2001 with Professor John L. Wood. Following postdoctoral training with Professor Samuel J. Danishefsky at The Memorial Sloan-Kettering Cancer Center he started his independent career in 2004 at Cornell University. In 2010, Professor Njardarson moved his research group to the University of Arizona.

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■ ABBREVIATIONS USED

AB-MPs, AbbVie multiparametric score; ADHD, attention deficit hyperactivity disorder; AGHD, adult growth hormone deficiency; AIDS, acquired immunodeficiency syndrome; AlogP, atom-based LogP; ALS, amyotrophic lateral sclerosis; AML, acute myeloid leukemia; ANCA, antineutrophil cytoplasmic antibody; APDS, activated phosphoinositide 3-kinase delta syndrome; APT, AbbVie Physicochemical Tier; bRo5, beyond Rule of Five; cIAI, complicated intra-abdominal infections; CINV, chemotherapy-induced nausea and vomiting; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease of 2019; CTEPH, chronic thromboembolic pulmonary hypertension; cUTI, complicated urinary tract infection; DOTA, dodecanetetraacetic acid; FDA, U.S. Food & Drug Administration; FL, follicular lymphoma; FOP, fibrodysplasia ossificans progressive; FSGS, focal segmental glomerulosclerosis; Fsp^3, fraction of sp^3-hybridized carbons; GIST, gastrointestinal stromal tumor; GPCR, G protein-coupled receptor; GVHD, graft-versus host disease; HAE, hereditary angioedema; HCM, hypertrophic cardiomyopathy; HIV, human immunodeficiency virus; HO, heterotopic ossification; HSDD, hypoactive sexual desire disorder; IBS-D, irritable bowel syndrome with diarrhea; INN, international nonproprietary name; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; ITP, immune thrombocytopenia; LEMS, Lambert−Eaton myasthenic syndrome; MCL, mantel cell lymphoma; MDD, major depressive disorder; MoCD, molybdenum cofactor deficiency; MRI, magnetic resonance imaging; MS, multiple sclerosis; MWt, molecular weight; MZL, marginal zone lymphoma; NAR, number of aromatic rings; NHBA, number of hydrogen bond acceptors; NHBD, number of hydrogen bond donors; NHL, non-Hodgkin lymphoma; NNRTI, non-nucleoside reverse transcriptase inhibitor; NR, number of rings; NRB, number of rotatable bonds; NSCLS, non-small-cell lung cancer; PAH, pulmonary arterial hypertension; PARP, poly(ADP-ribose) polylmerase; PET, positron emission tomography; PFI, property forecast index; Ph+CML, Philadelphia chromosome-positive chronic myeloid leukemia; PNH, paroxysmal nocturnal hemoglobinuria; PROTAC, proteolysis targeting chimera; Q1, lower quartile; Q3, upper quartile; QED, quantitative estimate of drug-likeness; RET, rearranged during transfection; Ro5, Rule of five; RVVC, recurrent vulvovaginal candidiasis; SCLC, small-cell lung cancer; SGLT, sodium-dependent glucose cotransporter; SLL, small lymphocytic lymphoma; SMA, spinal muscular atrophy; TGCT, tenosynovial giant cell tumor; TPSA, topological polar surface area; TRK, tropomyosin receptor kinase; UTI, urinary tract infection; VHL, von Hippel−Lindau disease; WHO, World Health Organization

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