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Perspective

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Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals

Miniperspective

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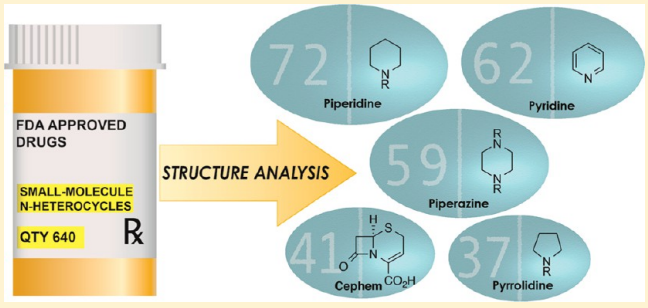
ABSTRACT: Nitrogen heterocycles are among the most significant structural components of pharmaceuticals. Analysis of our database of U.S. FDA approved drugs reveals that 59% of unique small-molecule drugs contain a nitrogen heterocycle. In this review we report on the top 25 most commonly utilized nitrogen heterocycles found in pharmaceuticals. The main part of our analysis is divided into seven sections: (1) three- and four-membered heterocycles, (2) five-, (3) six-, and (4) seven- and eight-membered heterocycles, as well as (5) fused, (6) bridged bicyclic, and (7) macrocyclic nitrogen heterocycles. Each section reveals the top nitrogen heterocyclic structures and their relative impact for that ring type. For the most commonly used nitrogen heterocycles, we report detailed substitution patterns, highlight common architectural cores, and discuss unusual or rare structures.



We recently compiled a database of all U.S. FDA approved pharmaceuticals and used that information to create new types of pharmaceutical posters corresponding to 12 disease categories.[1] Our goal was to create new research and teaching tools that exploit the beautiful graphical language of organic chemistry while celebrating the amazing and centrally significant accomplishments of organic chemists around the world to public health. Our minimalist design format presents opportunities for pharmaceutical laymen, like us, to gain insight on topics such as structural patterns and frequency of atoms and substructures while also observing and learning about what type of chemical structures are absent from approved pharmaceuticals. Furthermore, the format of these new posters allows such analyses to be presented as a function of time (date of U.S. FDA approval) and disease condition for which the drugs were approved. Our first such study focused on learning about the exact frequency, distribution, and diversity of sulfur- and fluorine-containing pharmaceuticals.[2] In this review it is our aim to comprehensively analyze the nitrogen heterocycle composition, frequency, and structural diversity among U.S. FDA approved small-molecule drug architectures.[3] Following a short global overview, our analysis is broken into several sections based on nitrogen heterocyclic ring size.

A cursory glance at any of our pharmaceutical posters reveals that nitrogen heterocycles are common drug fragments. This initial quick survey convinced us that it would be of broad interest to gather further information and obtain exact details about this important data set. Given our laboratory's interest in developing new useful methods for making nitrogen heterocycles,[4] we were confident that such an in-depth analysis could also aid academic research programs like our own by highlighting which nitrogen heterocycles have been incorporated into approved pharmaceuticals and their relative prevalence.

Our database contains 1994 pharmaceuticals (Figure 1).[5] We decided that the best measure of the frequency of nitrogen heterocycles would be to focus exclusively on structurally unique[6] small-molecule drugs. Subtracting biologics (146, 7%), combination drugs (253, 13%), and peptides (23, 1%) and removing any drug duplications[7] (537, 27%), we were left with 1035 unique small-molecule drugs to analyze. This number is slightly larger (1086) because among combination drugs there are 51 unique small-molecule drugs that were never approved on their own but only as part of a combination. Of these 51 drugs, 36 contain a nitrogen atom and 27 contain a nitrogen heterocycle. Thus, the total number of unique drugs containing at least one nitrogen atom rises from 874 to 910 (84%), while of those containing at least one nitrogen heterocycle rises from 613 to 640 (59%). These are incredibly high percentages, far surpassing the impact numbers for sulfur and fluorine (26% and 13%, respectively), which we disclosed recently. Interestingly, the average number of nitrogen atoms per drug is 2.3 N/drug for all the small-molecule drugs, while it is 35% higher in those containing a nitrogen heterocycle (3.1 N/drug).

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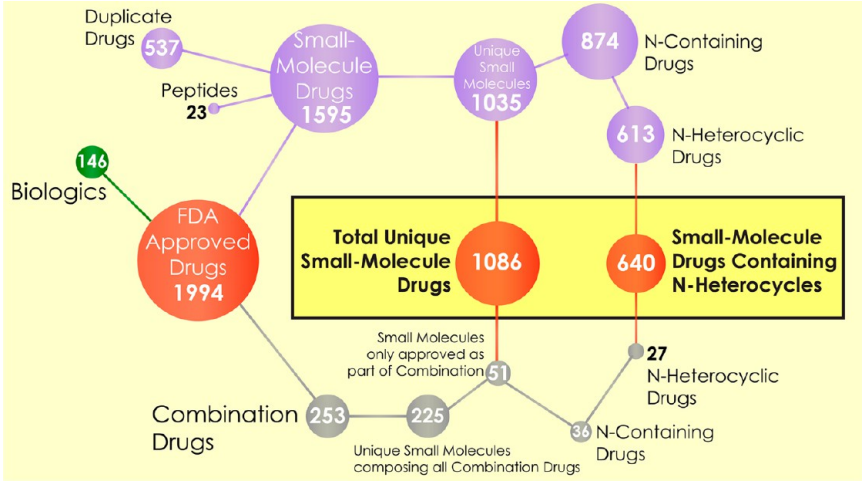

Figure 1. Breakdown of U.S. FDA approved drugs.

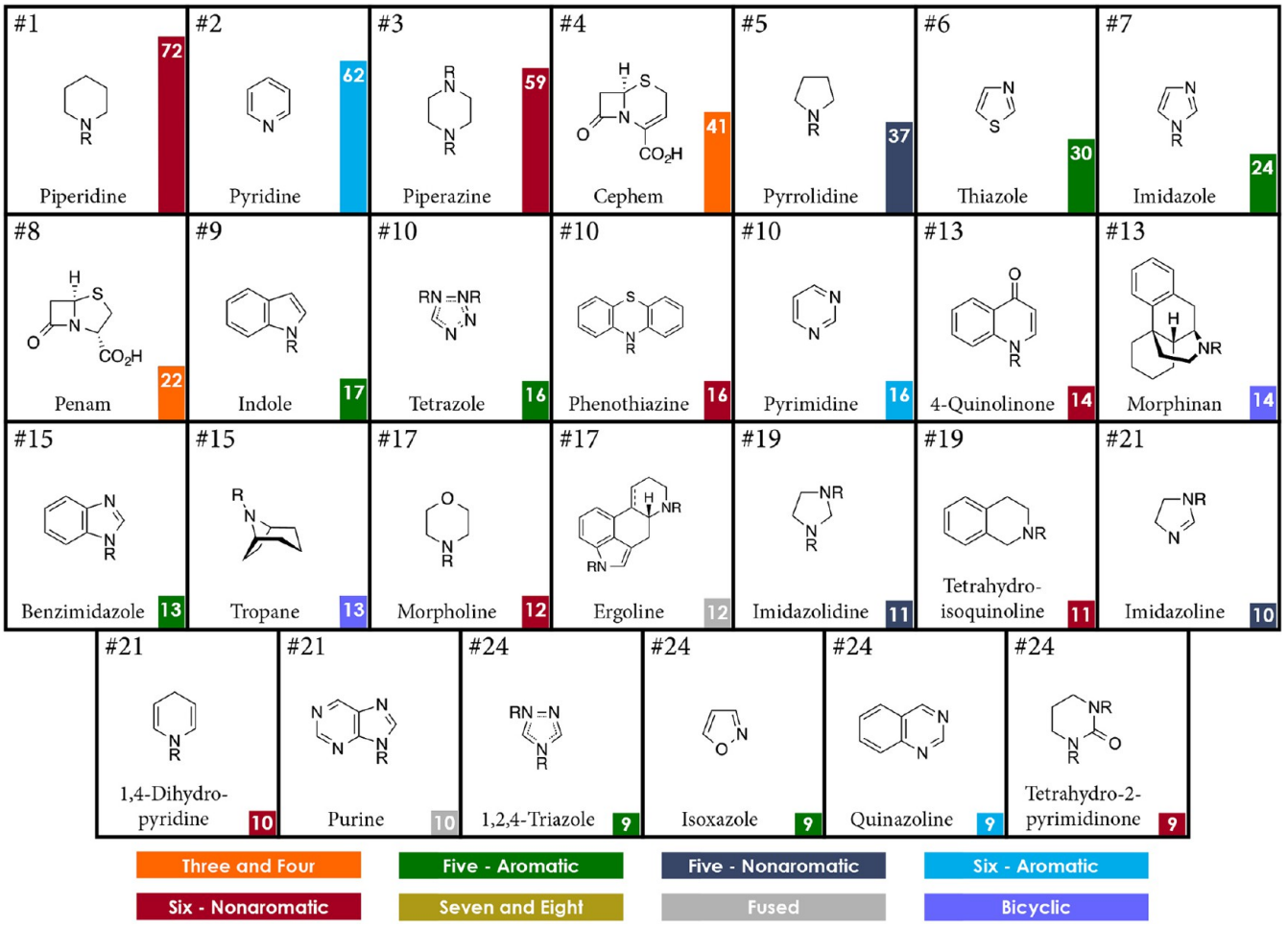

Figure 2. Top 25 most frequent nitrogen heterocycles in U.S. FDA approved drugs.

Having compiled and categorized all of the 640 pharmaceuticals containing a nitrogen heterocycle, we chose to first determine which are most common. Shown in Figure 2 are the results of our analysis. Figure 2 displays the top 25 nitrogen heterocycles in order of decreasing frequency represented by a drawn-to-scale solid colored bar, which highlights the various ring system classes. The most prevalent nitrogen ring system, found in a total of 72 unique small-molecule drugs, is piperidine. Pyridine and piperazine are the second and third most common nitrogen heterocycles, appearing in 62 and 59 drugs, respectively. Significantly behind the top three is cephem, a β-lactam core found in 41 approved drugs followed by pyrrolidine accounting for 37 drugs. Two more five-membered nitrogen heterocycles, thiazole and imidazole, are sixth and seventh most prevalent, respectively. Rounding off the top 10, with approximately equal representation, are penam,

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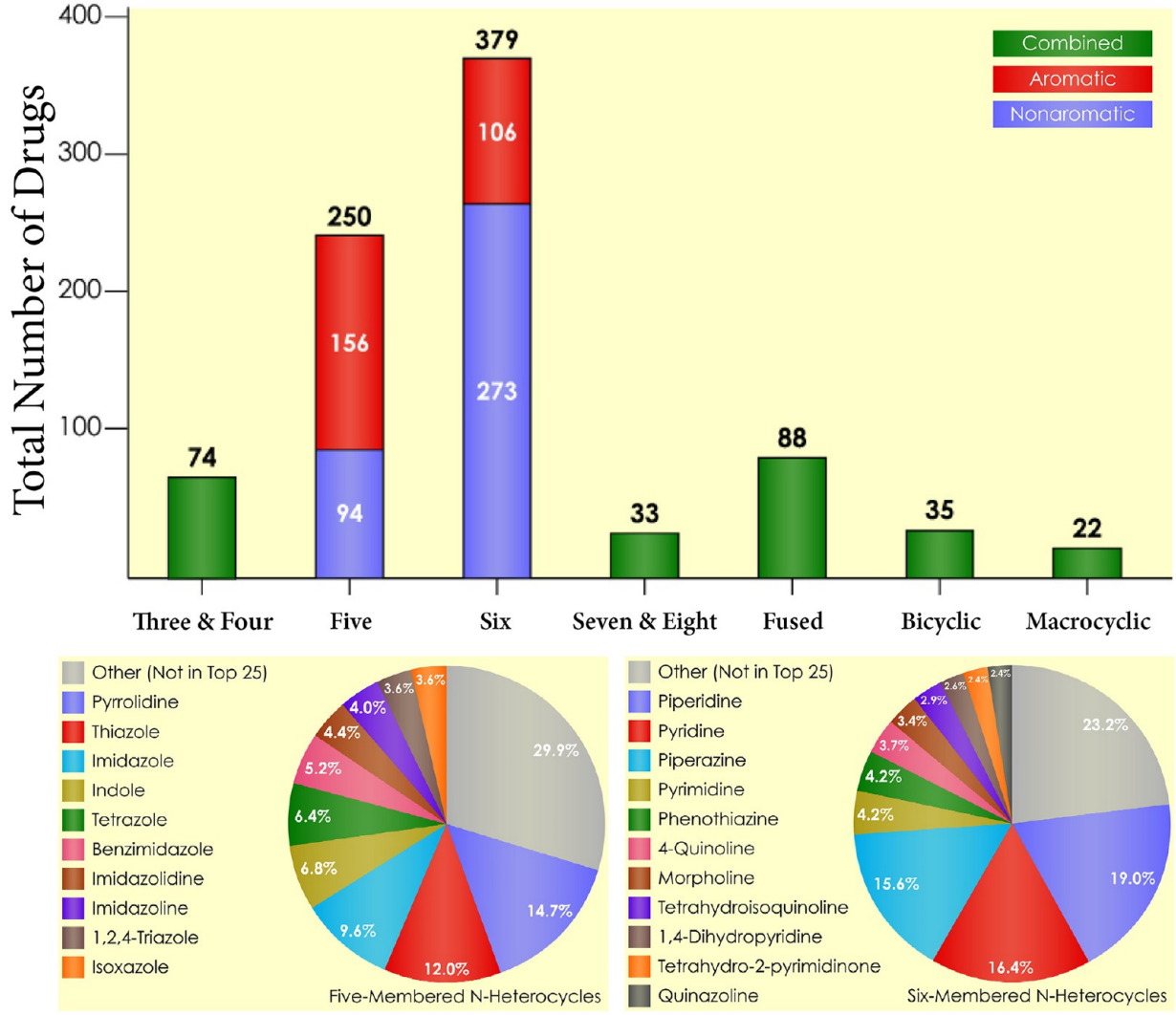

Figure 3. (Top) Nitrogen heterocyclic structural classes and their relative distribution. (Bottom) Distribution of five- and six-membered nitrogen heterocycles.

indole, tetrazole, phenothiazine, and pyrimidine. It is interesting to note that 4 of the 10 most commonly used nitrogen heterocycles also contain a sulfur atom (cephem, thiazole, penam, and phenothiazine). The remaining nitrogen heterocycles in the top 25 are similarly represented in terms of their frequency but remarkable for their amazing diversity with structures ranging from simple five-membered rings to complex natural motifs (morphinan, ergoline, and tropane). Only two of the nitrogen heterocycles ranked 13−25 contain a heteroatom other than nitrogen (morpholine and isoxazole).

The breakdown with respect to number of nitrogen atoms within these 25 heterocycles is such that 15 (56%) contain a single nitrogen atom, nine (33%) contain two, 1,2,4-triazole alone (4%) contains three nitrogens, and two, namely, tetrazole and purine (7%), contain four nitrogen atoms. Fifteen (56%) of the top 25 consist of a single ring, with even representation by six- (7/15) and five-membered (8/15) rings. Aromatic rings are common structural components of many approved pharmaceuticals, and aromatic nitrogen heterocycles, which compose 41% of the top 25 motifs, are no exception. There are only four nitrogen heterocycles from this top 25 list that contain a carbonyl group as part of their primary ring systems: cephem, penam, quinolinone, and tetrahydropyrimidinone.

In our quest to provide a more in-depth insight into the diversity, distribution, and significance of the various nitrogen heterocycles, we have divided our discussions and analyses into seven sections: (1) three- and four-membered rings, (2) five-membered rings,[8] (3) six-membered rings,[9] (4) fused rings, (5) seven- and eight-membered rings, (6) bicyclic rings, and (7) macro- and metallocycles. As is evident from Figure 3,[10] the relative prevalence of the various nitrogen heterocyclic classes varies significantly. Six-membered rings (59%) are the most frequently utilized, followed by five-membered (39%) and fused rings (14%). Given the importance of five- and six-membered rings, we decided to further split our analysis and coverage for these two sections into aromatic and nonaromatic nitrogen heterocyclic subsections. The bar graph in Figure 3 reveals remarkable differences between the two ring sizes, with 62% of five-membered nitrogen heterocycles being aromatic compared to only 28% of six-membered rings. The two accompanying pie charts showcase the relative impact of heterocycles from these two key categories and highlight their composition among the top 25 of all nitrogen heterocycles and those ranked further down (gray). The fused ring section focuses on ring systems that contain more than one nitrogen heterocycle fused together. The final section, macro- and metallocycles, captures

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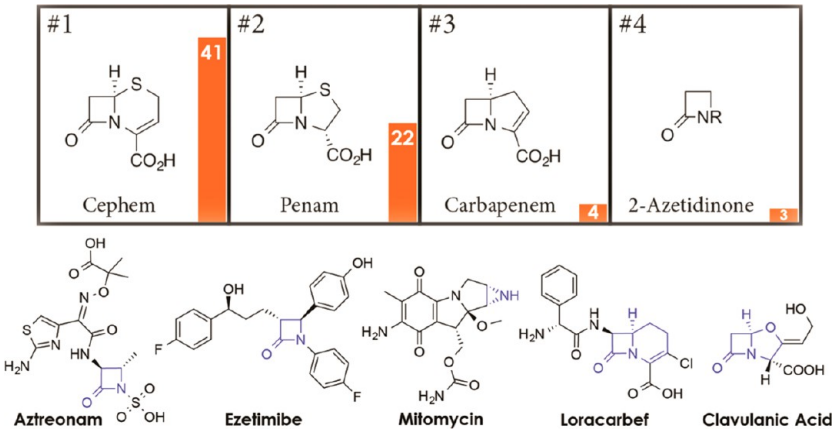

Figure 4. Top four most common four-membered nitrogen heterocycles.

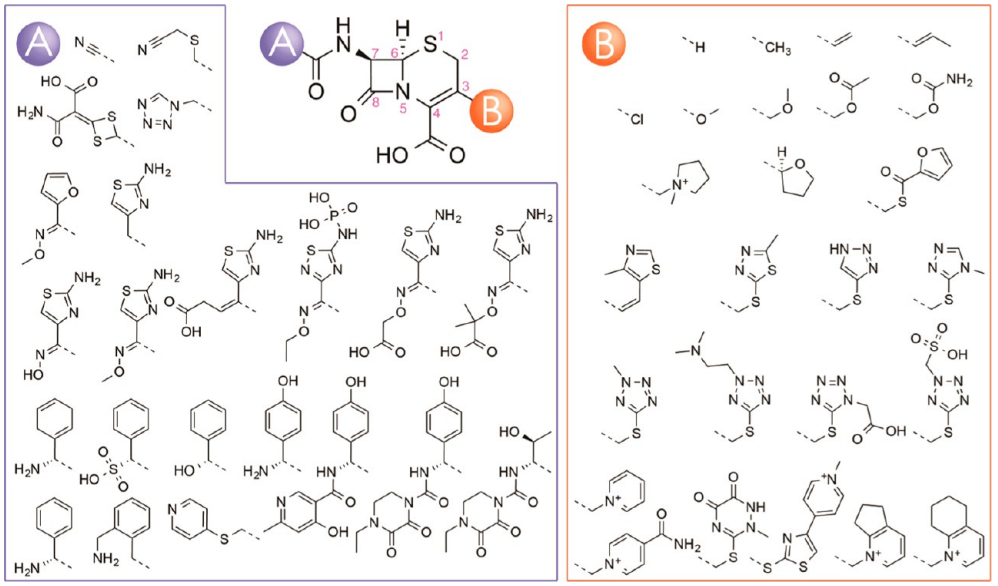

Figure 5. Structural variations of approved cephem pharmaceuticals.

the rest of the nitrogen heterocyclic motifs while also serving as a reminder of the fascinating organic architectures that have been approved as drugs.

THREE- AND FOUR-MEMBERED NITROGEN HETEROCYCLES

The top four ring systems in this subclass are shown in Figure 4. With the exception of a single aziridine-containing drug (mitomycin), the nitrogen heterocycles in this section are all β-lactams, of which 95% are fused to another ring with the nitrogen atom shared. The pharmaceutical architectures featured in this section are least diverse in terms of diseases they are used to treat. Case in point, all but the cholesterol lowering agent ezetimibe[11] of the β-lactam drugs[12] are antibiotics or used in combination with antibiotics. Aztreonam is an intriguing azetidinone structure containing free carboxylic acid, sulfonic acid, and amine functionalities in addition to the unusual architecture they belong to. The β-lactams belong to four structural families, whose central cores primarily differ in terms of the ring fused to the β-lactam (cephems, penams, or carbapenems), or in the case of monobactams, the absence of a fused ring. The cephems of the cephalosporin family and the penams of the penicillin family are the most common central cores, representing 55% and 30% of the approved β-lactam antibiotics, respectively. In a distant third place, with much less representation (5%) are the carbapenems, wherein the sulfur atom of the penam core has been replaced with a methylene group and the unsaturation that is part of the cephem core has been added. Three single atom permutations of these successful cores (penams and cephems) have been approved as drugs, with the sulfur atom replaced by either an oxygen or carbon atom as exemplified in Figure 4 by clavulanic acid and loracarbef.

Cephems. With the cephalosporins (cephems) being the β-lactam subfamily with the most approved members (41) we decided to take a closer look at their structural diversity. Our goal was to learn what positions on the cephem core were most commonly altered and what types of groups were added to these positions (Figure 5).[13] Our analysis reveals that two main positions are altered on the cephem core: the nitrogen amide acyl group (labeled A) and the β-olefin position of the carboxylate group (labeled B). The acyl amide group occurs in 26 different structural permutations among the 41 U.S. FDA approved cephalosporin drugs, while the β-position of the carboxylate is represented by 21 different substitution variations. Both positions commonly contain a heterocycle,

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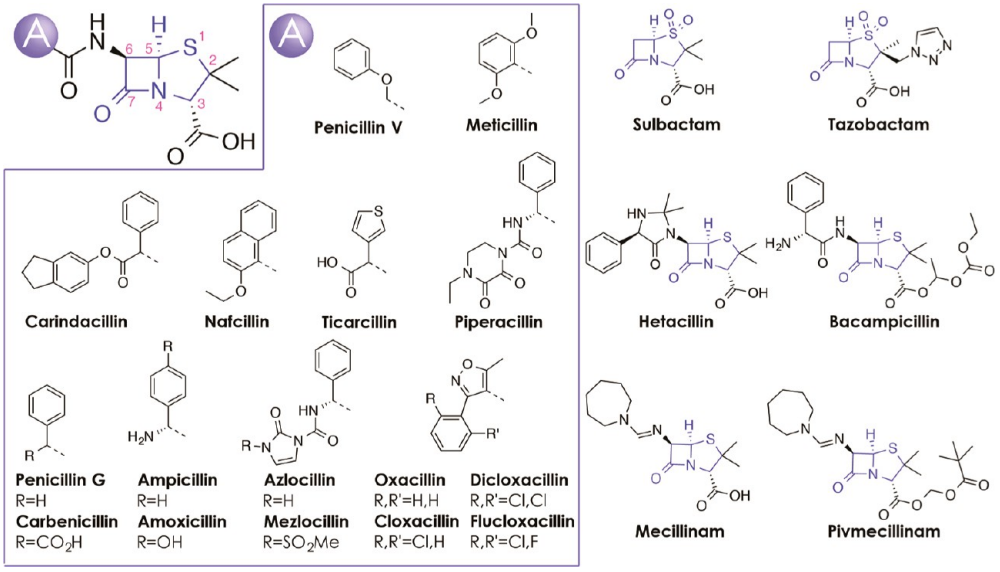

Figure 6. Structural variations of approved penam pharmaceuticals.

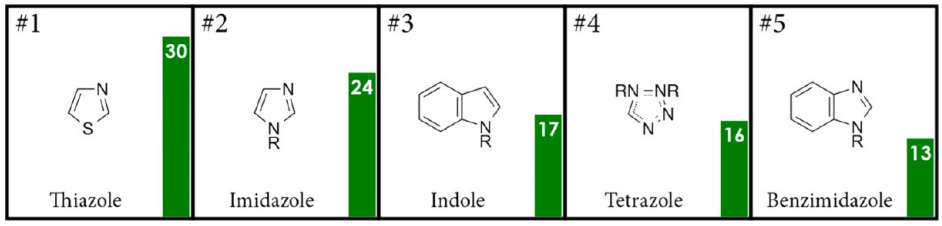

Figure 7. Top five most common five-membered aromatic nitrogen heterocycles.

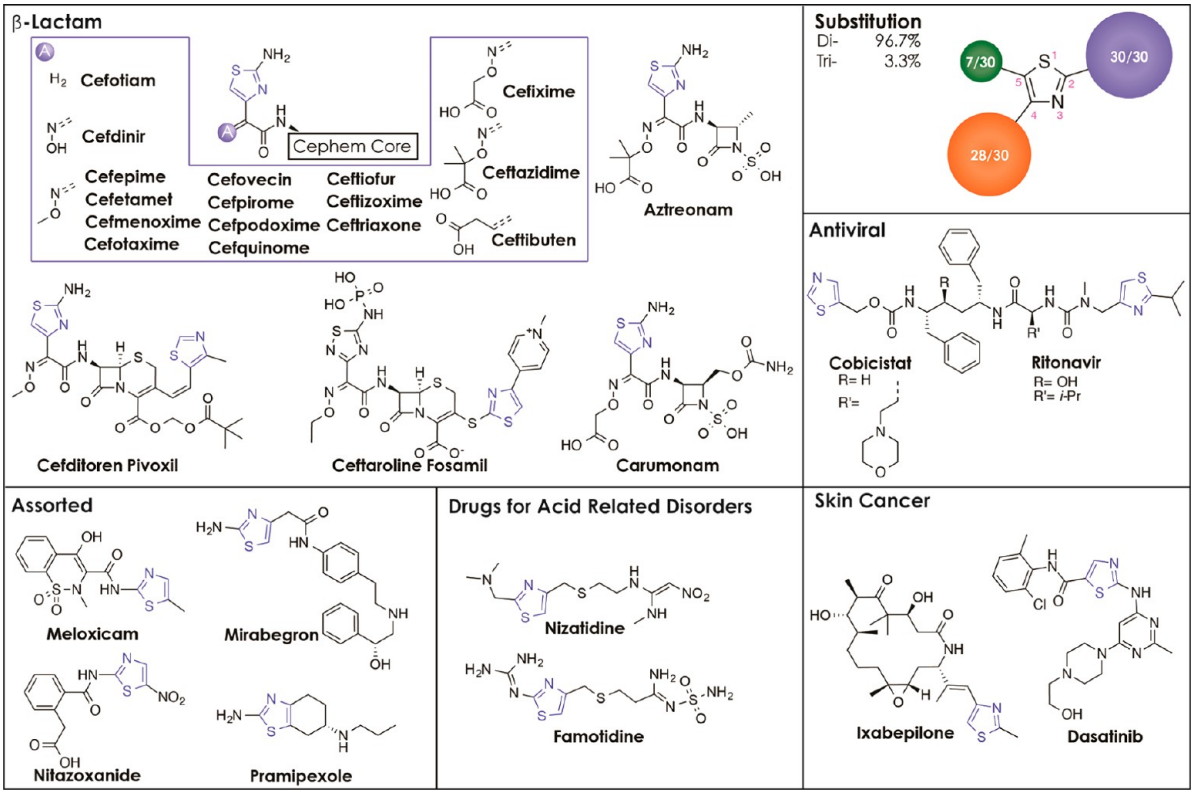

Figure 8. Pharmaceuticals containing thiazoles.

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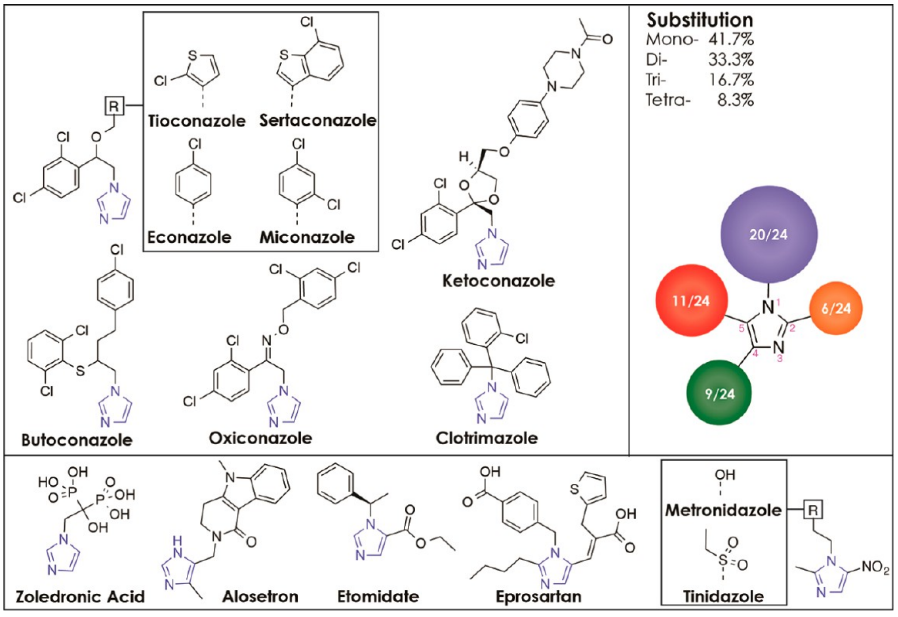

Figure 9. Pharmaceuticals containing imidazoles.

with a substitution frequency of 65% and 62% at the acyl amide and β-olefin positions, respectively. Notably, each of the side chains contain a total of 11 permutations having at least one sulfur atom. For the acyl amide chain, the sulfur atom is usually part of a thiazole (64%) while for the β-olefin positions the sulfur atom is most likely to be an arylated sulfide (73%). A significant number of the β-olefin substitution permutations contain short acyclic chains (35%), which is far less common (10%) for the acyl amide group. With respect to polar groups, the two cephem positions are substituted very differently. 81% of the acyl amide side chains contain a free polar group (hydroxyl, acid, amide, phosphonic acid, or an amine), which is not the case for the β-olefin side chain (19%) wherein cyclic ammonium groups (19%) are more common. Of the many interesting substituents found in these side chains, the densely decorated four-membered dithietane heterocycle found in cefotetan is truly remarkable. Cefotetan is also unique for the fact that it is one of only a handful of cephem drugs containing an additional substituent at C7, which are commonly referred to as cephamycins. The cephalosporin family of β-lactam drugs is even more diverse than shown in Figure 5, with close to 20 other structurally unique cephalosporin drugs approved internationally by agencies other than the U.S. FDA.

Penams. The penams are the second largest family of β-lactam antibiotics,[14] with 22 unique U.S. FDA approved structures depicted in Figure 6. The majority of penams (73%) only contain structural variations at the 6-aminoacyl group, with 38% directly connected to an aryl group and 50% attached to a benzylic amino or carboxylate functionality. Sulbactam and tazobactam are notable for the fact that they are both β-lactamase inhibitors, making them the only penams solely approved as part of a combination drug. Furthermore, they are unique among this family, as they both lack the 6-amino group in addition to having the common cyclic sulfide group in a higher oxidation state (sulfone). Mecillinam and ampicillin both have approved carboxylate prodrug variants (pivmecillinam and bacampicillin), wherein the carboxylate group in the 3-position has been derivatized with labile acetal tethers. Additionally, ampicillin also has an approved amido prodrug variant (hetacillin), which contains a labile cyclic diamino ketal (imidazolidinone) functionality.[15] Among the already highlighted drugs, mecillinam (and therefore its prodrug pivmecillinam) is structurally unique for the 6-amino group being part of an imine instead of an amide.

FIVE-MEMBERED AROMATIC NITROGEN HETEROCYCLES

The top five[16] most commonly used heterocycles in this class are presented in Figure 7, along with numbers showing how many different unique pharmaceutical structures each is a part of. These top five aromatic heterocycles appear in a total of 101 drugs, which is 9% of the total number of unique U.S. FDA approved small molecules (1086). Only indole contains a single heteroatom with the other four having additional nitrogen (imidazole, tetrazole, and benzimidazole) or sulfur (thiazole) atoms. In the following sections we take a closer look at all of the top five five-membered aromatic nitrogen heterocycles.

Thiazoles. In the analysis of the structures of unique U.S. FDA approved drugs containing a thiazole group[17] (Figure 8), it becomes evident that one of the reasons for its high frequency among five-membered aromatic nitrogen heterocycles is that it has emerged as a widely used functional group for the large class of β-lactam antibiotics. Remarkably, 67% of all thiazole-containing pharmaceuticals belong to this important class of drugs. Every thiazole drug contains a substituent in the C2-position (indigo), with most also being decorated with an additional substituent at the C4-position (orange). While there is not a single approved monosubstituted thiazole drug, pramipexole is the only approved trisubstituted thiazole drug. The anti-HIV drugs ritonavir and cobicistat[18] are noteworthy not only for their structural similarity but also for having two different thiazole groups along with cefditoren pivoxil. The peptic ulcer disease drugs nizatidine and famotidine are structurally intriguing for also containing thioethers and interesting nitro and sulfonamide groups. Figure 8 also utilizes a diagram highlighting the relative substitution frequency among approved thiazole-containing drugs, represented by a drawn-to-scale colored bubble.

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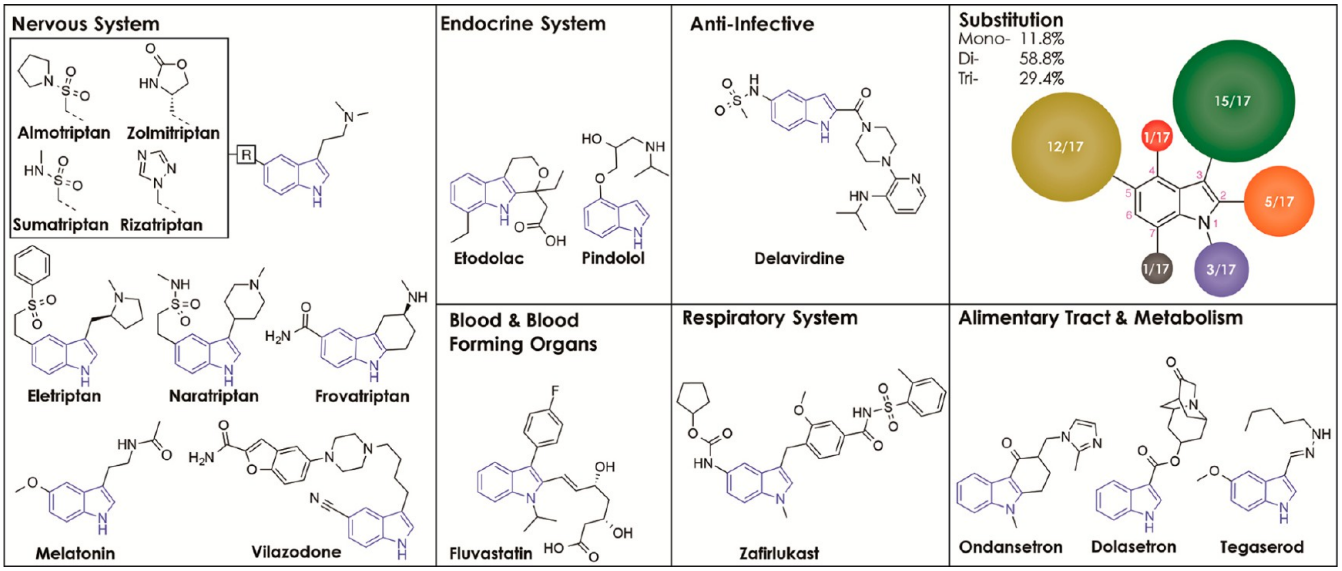

Figure 10. Pharmaceuticals containing indoles.

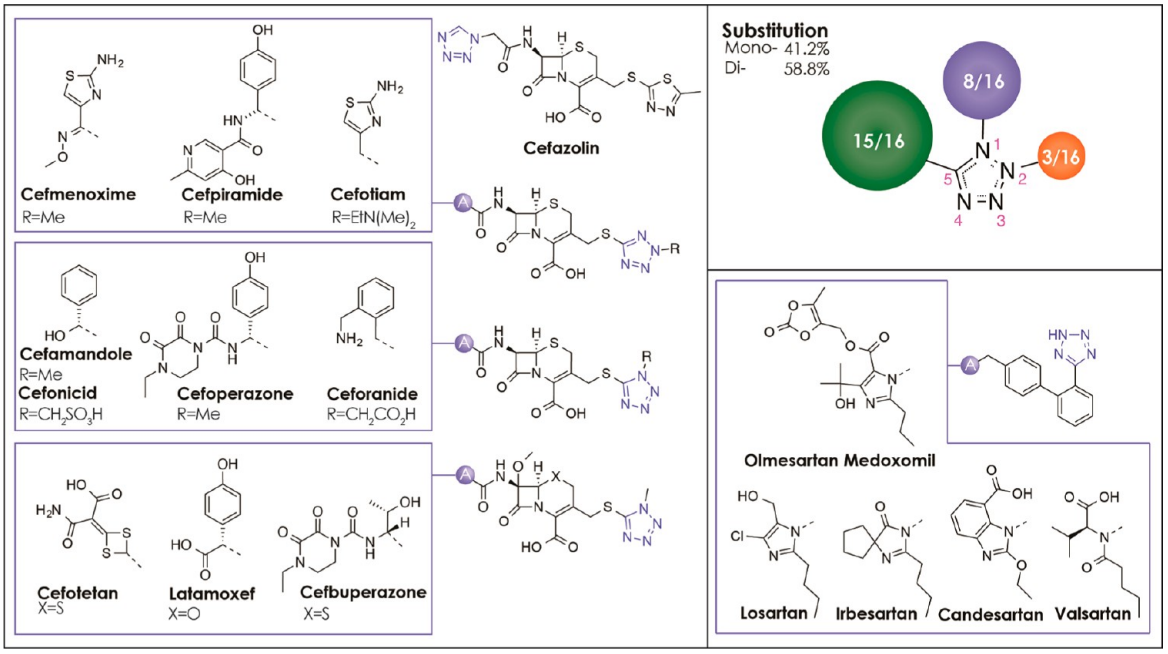

Figure 11. Pharmaceuticals containing tetrazoles.

Imidazoles. Imidazoles, a selection of which are displayed in Figure 9, are the second most common five-membered aromatic nitrogen heterocycles among our database.[19] Of these 24 imidazole-containing structures, eight (33%) belong to a class of antifungal agents. These eight drugs share similar substitution patterns, such as the presence of chlorinated aromatic rings and a monosubstituted imidazole group. All chiral structures of this antifungal class are sold in racemic form except ketoconazole. The antibacterial drugs metronidazole and tinidazole are notable for their small size and the presence of a nitro substituent on the imidazole ring. Substitution pattern analysis reveals that 42% of imidazoles are monosubstituted, of which all but one are substituted at the N1-position (indigo). The remaining imidazole drugs are di- (33%), tri- (17%), or tetrasubstituted (8%), with no clear substitution preference among them.

Indoles. Indole is an important nitrogen heterocycle found in countless natural products, part of an essential amino acid (tryptophan), and a key structural component of many value added chemicals including pharmaceuticals. In our database we found 17 indole-containing drugs, all of which are shown in Figure 10, along with their disease indications.[20] The indole core has seven positions that can be substituted. A survey of these 17 structures reveals that 2 (12%) are monosubstituted, 10 (59%) are disubstituted, and the remaining 5 (29%) are trisubstituted. A closer looks reveals that there are preferred substitution patterns with a vast majority of these drugs containing a substituent at C3 (88%, green) and/or C5 (71%, mustard). These strongly favored positions are followed by C2 (29%, orange), N1 (18%, indigo), C4, and C7 (6%, red and gray, respectively) with no indole drug being substituted at C6. Three (frovatriptan, ondansetron, and etodolac) indole drugs

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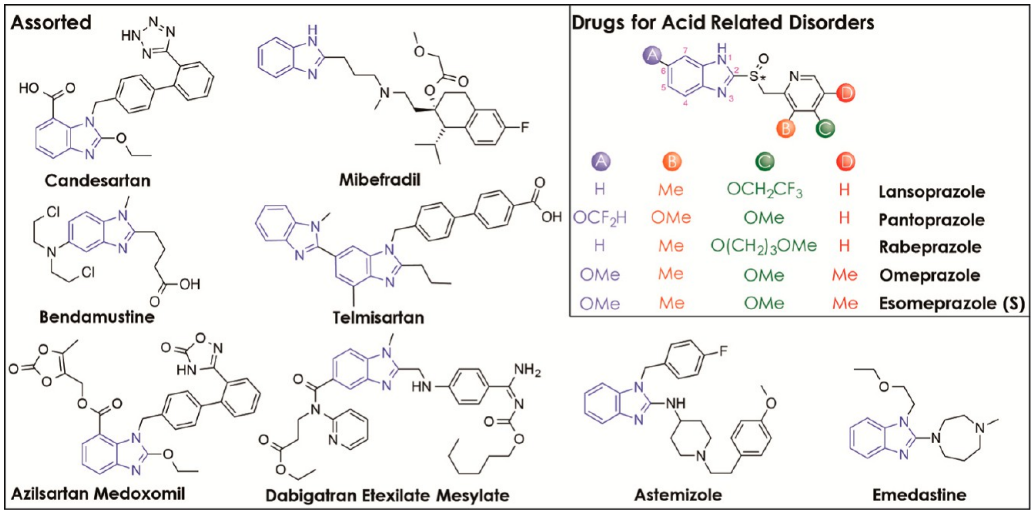

Figure 12. Pharmaceuticals containing benzimidazoles.

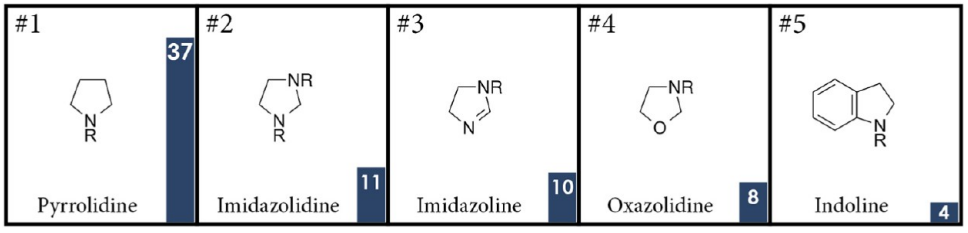

Figure 13. Top five most common five-membered nonaromatic nitrogen heterocycles.

are decorated with a fused ring, which in all cases is a six-membered ring connected to the indole at C2 and C3. The blood pressure medicine pindolol is particularly interesting, as it is one of the only two approved indole drugs that are monosubstituted but more importantly the only one that contains a substituent at C4 (red). The largest drug class containing indoles in the form of a tryptamine core is analgesics (41%).

Tetrazoles. Tetrazole is a unique nitrogen heterocycle that is present in a total of 16 U.S. FDA approved pharmaceuticals (Figure 11). The tetrazole core has three positions that can be substituted, with a maximum of two substitutions at a time because it can either be a 1*H*- or a 2*H*-tetrazole (therefore, only 1,5- or 2,5-disubstitution). Substitution pattern analysis reveals that the vast majority of tetrazoles (15/16) are substituted at the C5-position (green) and half (8/16) at the N1-position (indigo). Tetrazoles are resistant to biological degradation, which makes them useful bioisosteres for various functional groups, such as carboxylate and *cis*-amide groups.[21] Because of this, it is not surprising that all but one of the tetrazole-containing pharmaceuticals contain an additional nitrogen heterocycle, which in the majority of cases (63%) is a cephem. Tetrazoles not only are structurally very similar, they also share a high degree of homology in terms of the pharmaceutical areas in which they are utilized, with 69% of them being used as a part of antibacterial agents (those containing an additional cephem or oxocephem cores) and the remaining 31% found in antihypertensive agents (those containing an additional imidazole or derivative of imidazole cores). Interestingly, all of the antibacterial tetrazoles were approved between the 1970s and 1980s, while all of the antihypertensive tetrazoles have been approved from the late 1990s on. Among the antihypertensive tetrazoles, losartan is the first approved (1995) and olmesartan medoxomil, which is a prodrug that hydrolyzes in vivo to form the active olmesartan, was the last approved (2002). Losartan and olmesartan medoxomil are noteworthy not only for being blockbuster drugs but also for being structurally similar, both featuring an additional biphenyl and tetrasubstituted imidazole.

Benzimidazoles. Benzimidazoles (Figure 12) are found in 13 U.S. FDA approved pharmaceuticals. Five of those drugs are structurally similar proton-pump inhibitors[22] containing a sulfoxide group with a pyridine side chain in the C2-position. Of these, esomeprazole is a single enantiomer sulfoxide variant of the best known member of this family, omeprazole. Three of the benzimidazole drugs are used to treat hypertension: candesartan, telmisartan, and azilsartan medoxomil.[23] Of the drugs highlighted, candesartan and the prodrug azilsartan medoxomil are noteworthy for being nearly identical structures differing only in the nitrogen heterocycle attached to the biphenyl group while telmisartan is the only drug with two benzimidazole groups. Surprisingly, all benzimidazoles are substituted at the C2-position, which in the majority of cases (77%) is a heteroatom (O, S, or N), and 46% of them are substituted at the N1-position.

FIVE-MEMBERED NONAROMATIC NITROGEN HETEROCYCLES

The distribution among the top five most commonly employed five-membered nonaromatic nitrogen heterocycles in pharmaceuticals is less even than among the aromatic ones (Figure 13). Pyrrolidine is the most prevalent by far, appearing in 37 drugs. The next three heterocycles (imidazolidine, imidazoline, and oxazolidine) in the top five are not only about equally represented but also all contain two heteroatoms separated by a

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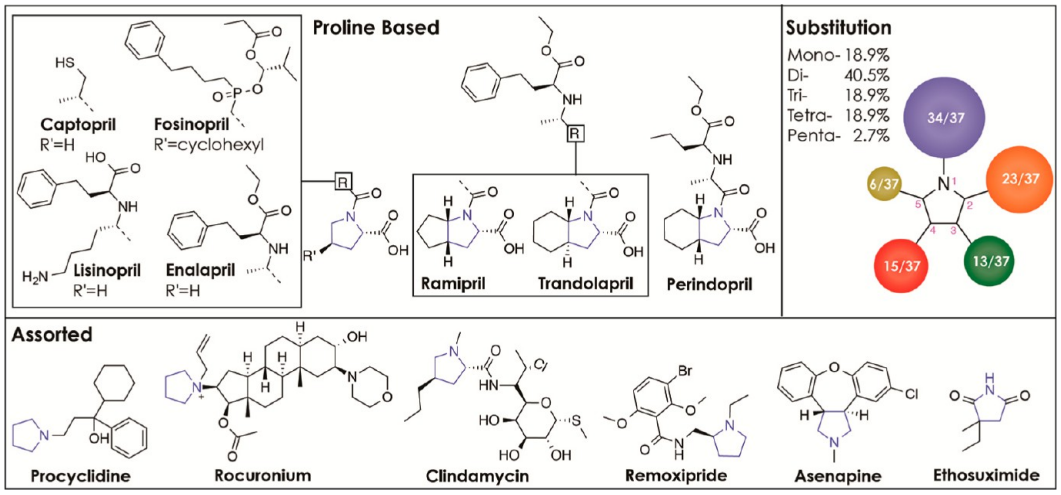

Figure 14. Pharmaceuticals containing pyrrolidines.

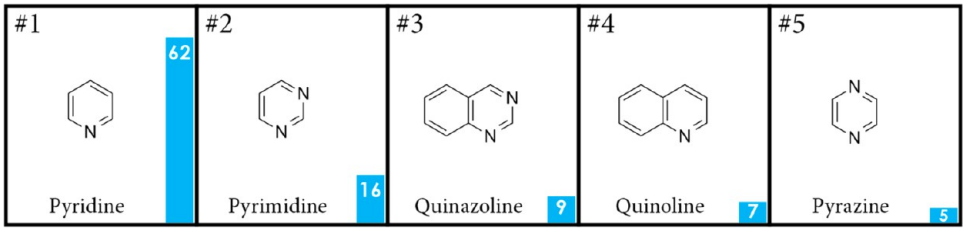

Figure 15. Top five most common six-membered aromatic nitrogen heterocycles.

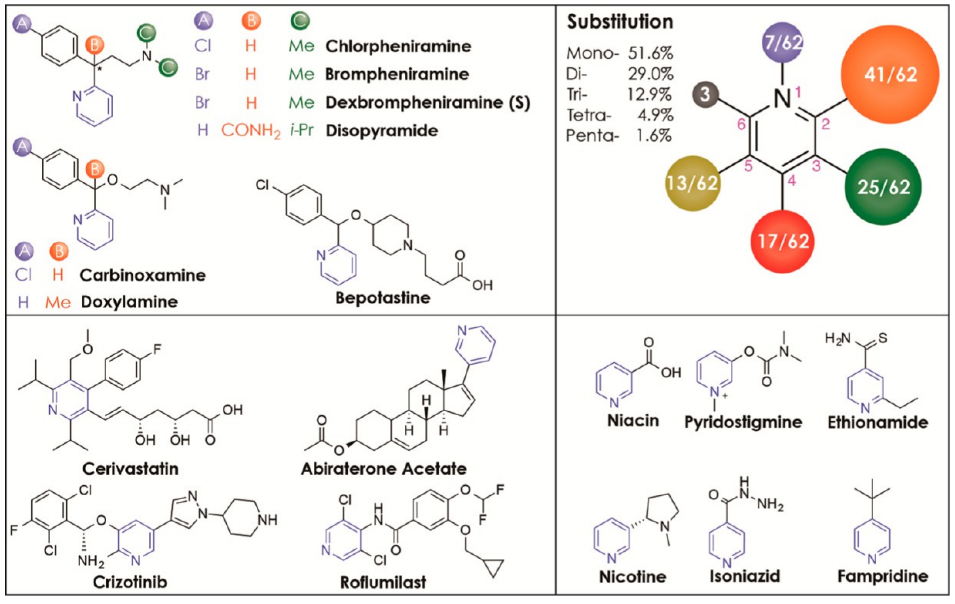

Figure 16. Pharmaceuticals containing pyridines.

carbon atom. Rounding off the top five is indoline. Given the success of pyrrolidine, we take a closer look in the following section at the structures of pharmaceuticals containing this important heterocycle.

Pyrrolidines. In the category of U.S. FDA approved drugs containing five-membered nonaromatic nitrogen heterocycles, pyrrolidine is the most frequently used core, being present in more drugs than the rest of the top five combined. Representative members of this heterocyclic family and analysis of their structural patterns are presented in Figure 14. Substitution pattern analysis reveals that a vast majority (92%) of pyrrolidine drugs are substituted at the N1-position (indigo) and more than half (62%) are substituted at the C2-position (orange). For pyrrolidines, disubstitution is the most dominant pattern (41%), which is followed by an equal distribution of mono-, tri-, and tetrasubstitution (19%). The natural proline core is a commonly employed pyrrolidine structural fragment as evident from the highlighted examples shown in Figure 14.[24] This chiral fragment is the core of most of the angiotensin converting enzyme (ACE) inhibitors. All of

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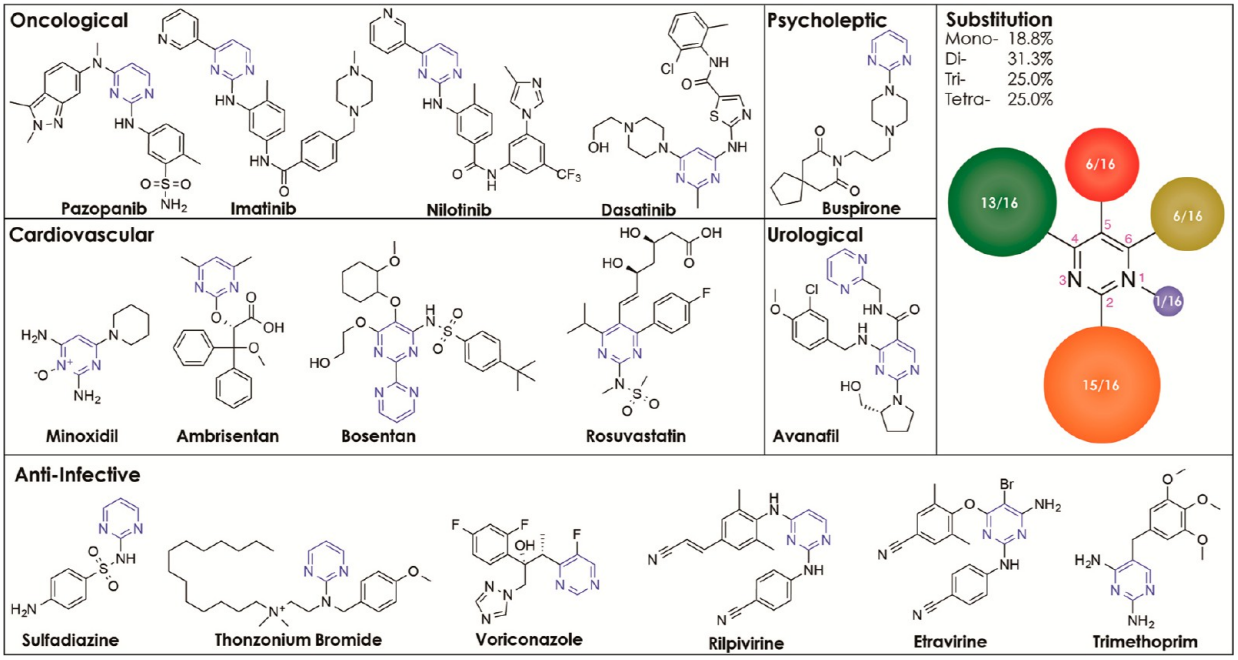

Figure 17. Pharmaceuticals containing pyrimidines.

these inhibitors contain an additional chiral amide chain, half of which have a chiral phenethyl substituted α-amino ester. Lincomycin, clindamycin,[25] and remoxipride all contain a proline derived core, of which clindamycin and lincomycin also have a thiosugar group and a chiral secondary chloride atom. Rocuronium is an interesting steroidal drug[26] with two nitrogen heterocycles attached to the A and D rings, with the pyrrolidine group in the form of an allylammonium salt. Of the other drugs highlighted in Figure 14, procyclidine is an example of a simple monosubstituted pyrrolidine drug, and the antipsychotic medicine, asenapine,[27] is an intriguing instance of a 3,4-fused pyrrolidine ring system that at first glance looks C2-symmetrical were it not for the presence of single chlorine atom. Structurally, the least complicated pyrrolidine drug is the antiseizure drug ethosuximide, which is a dialkylated *N*-succinimide derivative.

SIX-MEMBERED AROMATIC NITROGEN HETEROCYCLES

The top five of the most commonly used six-membered aromatic nitrogen heterocycles are shown in Figure 15. These five appear in 99 drugs, accounting for 9% of the total number of unique structures among U.S. FDA approved pharmaceuticals. More than 60% of the structures represented by these top five contain a pyridine, and 16% contain a pyrimidine. Three of the five heterocycles in this category contain an additional heteroatom, which in all cases is a nitrogen atom (pyrimidine, quinazoline, and pyrazine). Given these different structure distributions, in the following two sections we will focus our in-depth analysis and discussion only on pyridine and pyrimidine.

Pyridines. Pyridine is the second most commonly used nitrogen heterocycle among all U.S. FDA approved pharmaceuticals and number 1 among aromatics.[28] Analysis of the substitution patterns for these 62 pyridine drugs is presented in Figure 16. Our study reveals that the pyridine C2-position (orange) is the preferred position, followed by the C3-position (green), with a frequency of 66% and 40%, respectively. A closer look at these substitution patterns reveals that monosubstituted pyridines are found in more than 50% of these drugs, followed by di- and trisubstitution accounting for 29% and 13% representation, respectively. We have chosen to highlight a family of antihistamine drugs with a remarkably similar structural core, wherein all contain a benzylic group decorated with a trialkylamine chain substituted at the C2-position. The oldest of these drugs are chlorpheniramine, brompheniramine, and its enantiomer dexbromopheniramine, which were all approved by the U.S. FDA in the 1950s. Carbinoxamine and doxylamine are strikingly similar structures differing from the other three antihistamine drugs by the addition of an oxygen atom in the trialkylamine tether and in the case of doxylamine also by a quaternary benzylic center. The most recently approved member of this family, bepotastine, contains a longer and more rigid side chain, as well as a carboxylic acid tail. Although disopyramide does not belong to the antihistamine class, it is highlighted because of its remarkable structural homology with antihistamines. Unique among pharmaceuticals containing a nitrogen heterocycle is the number of pyridines containing one small substituent, six of which (niacin, pyridostigmine, ethionamide, nicotine, isoniazid, and fampridine) are shown in Figure 16. Additionally, we have chosen to present and discuss another four interesting pyridine drugs, three of which are fluorinated, three were approved in 2011 (roflumilast, abiraterone acetate, and crizotinib), and two originate from natural product cores. Withdrawn in 2001, cerivastatin is one of only three drugs that have a pentasubstituted pyridine cores. Roflumilast, in addition to a dichlorinated pyridine core, has intriguing difluoroether and cyclopropylmethanol substitutents attached to a catechol group. The prostate cancer drug, abiraterone acetate, is a prodrug that loses an acetate group in vivo to form abiraterone, which is easily synthesized by converting the ketone of readily available steroid dehydroepiandrosterone (DHEA) to a vinylpyridine group. Another anticancer drug, crizotinib,[29] is structurally notable for the presence of three nitrogen heterocycles (pyridine, piperidine, and pyrazole) and an electron rich trisubstituted pyridine core.

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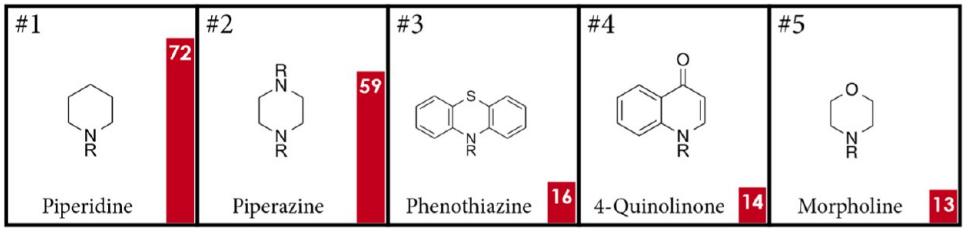

Figure 18. Top five most common six-membered nonaromatic nitrogen heterocycles.

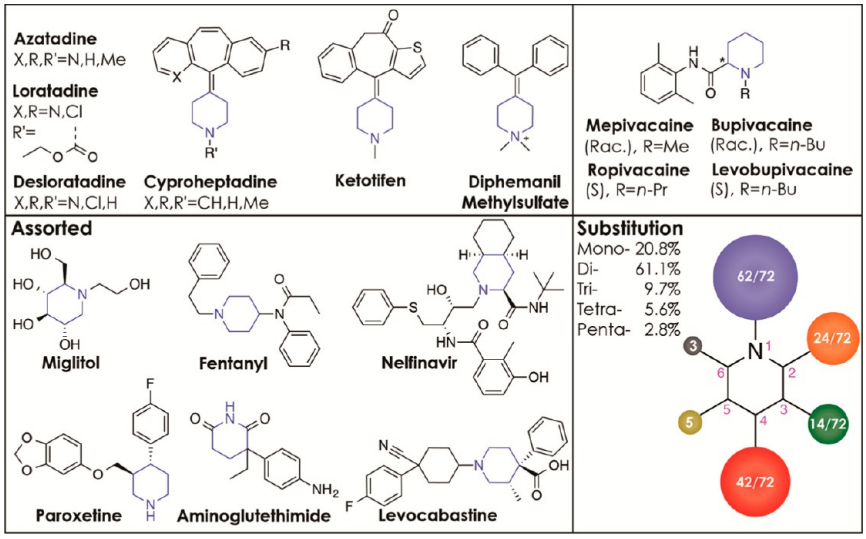

Figure 19. Pharmaceuticals containing piperidines.

Pyrimidines. Shown in Figure 17 are the 16 approved pyrimidine-containing drugs arranged according to disease indication.[30] The oldest pyrimidine drugs are the anti-infectives sulfadiazine and thonzonium bromide, which were approved by the FDA in 1941 and 1962, respectively. With the exception of the recently approved erectile dysfunction medicine avanafil (2012)[31] and the general anxiety disorder drug buspirone, the other pyrimidine drugs are used for the treatment of three main disease classes: anti-infective, cardiovascular, and oncological. The oncological drug imatinib, which was approved in 2001, is particularly noteworthy as a breakthrough rationally designed drug.[32] Many other tyrosine kinase inhibitors like imatinib have since been approved as oncological drugs, including three containing a pyrimidine group (dasatinib, pazopanib, and nilotinib). Rosuvastatin, a top-selling pyrimidine drug with multibillion-dollar sales per year, is a member of the statin family.[33] Our pyrimidine substitution pattern analysis reveals that the C2- (orange) and C4-positions (green) are strongly favored, with 94% and 81% substitution frequency, respectively. There is close to an even distribution of mono-, di-, tri- and tetrasubstituted pyrimidines. Almost all pyrimidine drugs contain a nitrogen substituent (88%) of which 38% are a 2-amino group and another 38% are 2,4-diamino groups. Particularly noteworthy for containing two nitrile groups are the anti-HIV drugs rilpivirine and etravirine.[34] Of the drugs highlighted in Figure 17, many of the pyrimidine drugs contain multiple rings connected linearly. Minoxidine and etravirine are structurally remarkable for the fact that not only is the pyrimidine core tetrasubstituted but all of the substitutents are heteroatoms.

SIX-MEMBERED NONAROMATIC NITROGEN HETEROCYCLES

The family of nonaromatic six-membered nitrogen heterocycles is remarkably represented by three rings in the top 10, which include the number 1 (piperidine) and 3 (piperazine) positions. Even more impressively, the top five in this category (Figure 18) appear cumulatively in a little over a quarter (27%) of all drugs containing a nitrogen heterocycle. Three of the five contain two heteroatoms in the ring, which in all cases is in the 4-position (O, S, or N) with respect to the common nitrogen atom. In the following sections, we take a closer look at the three most frequent of those five, namely, piperidine-, piperazine-, and phenothiazine-containing drugs.

Piperidines. Piperidine is the most commonly used nitrogen heterocycle among U.S. FDA approved pharmaceuticals. Shown in Figure 19 are two important piperidine drug classes: a selection of interesting piperidine drugs and an analysis of the positions of preferred piperidine substituents. It is evident from this diagram that the N1- (indigo) and C4-positions (red) are strongly favored with drugs in this class having 86% or 58% likelihood, respectively, of containing a substituent in those positions. The C2- (orange) and C3-positions (green) follow with 33% and 19% representation, respectively, and only a handful of drugs have a substituent in the C5- (mustard) and C6-positions (gray). Scrutinizing these substitution patterns reveals that unlike piperidine's aromatic counterpart, for which monosubstituted drugs are most common, piperidine drugs are much more likely to be disubstituted (61%) vs monosubstituted (21%). Within this disubstituted group of piperidine drugs there is a strong bias toward 1,4-disubstituted (39%) architectures. Piperidines are

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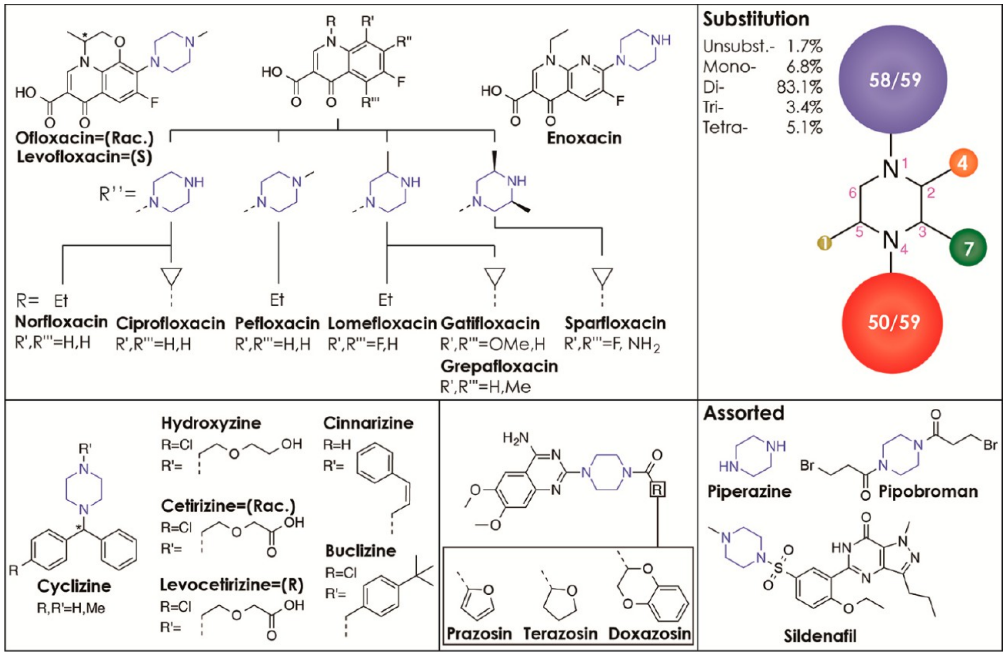

Figure 20. Pharmaceuticals containing piperazines.

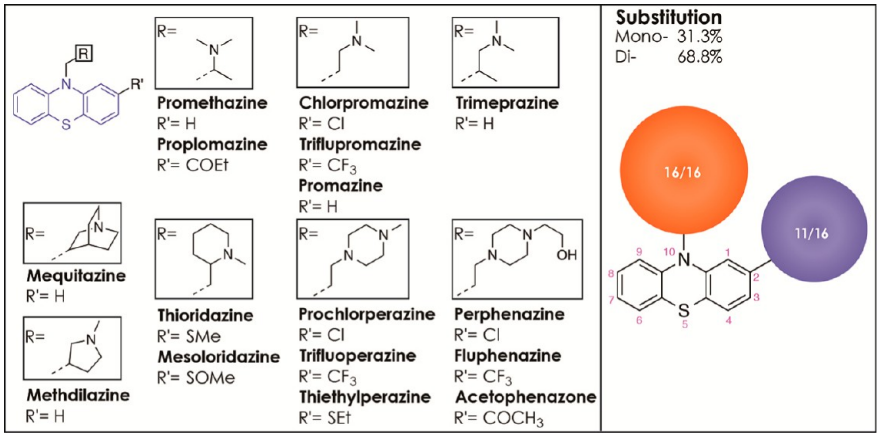

Figure 21. Pharmaceuticals containing phenothiazines.

prominent among the antihistamine class of drugs (azatadine, loratadine, desloratadine, cyproheptadine, and ketotifen), all of which contain an exo-tetrasubstituted olefin at the 4-position connected to a fused tricyclic system with a central seven-membered ring. Strikingly similar to the antihistamine drugs, while lacking the central fused ring, is the antimuscarinic agent diphemanil methylsulfate. Mepivacaine, bupivacaine, ropivacaine, and levobupivacaine are all local anesthetic drugs[35] that share a common piperidine core with an *o*-xylene amide in the C2-position (orange) with a varying *N*-alkyl group chain length. Levobupivacaine is simply a single enantiomer of racemic bupivacaine, yet is considered a unique drug. In addition, six structurally and medicinally intriguing piperidine-containing drugs are shown, of which miglitol is an interesting desoxy aminosugar, while fentanyl, a powerful analgesic, serves as nice representative example of a 1,4-disubstituted piperidine drug, which is the most commonly employed substitution pattern. Nelfinavir is an antiviral agent containing a tetrasubstituted piperidine that is part of a fused core and connected to a side chain containing two chiral centers, a thioether, and a phenol group. The billion-dollar antidepressant, paroxetine, contains two stereocenters on the piperidine ring, while the anti-hormone drug aminoglutethimide is a glutarimide with ethyl and aniline groups in the α-position. Of the drugs highlighted, the antiallergic drug, levocabastine, is structurally interesting because it is made of four rings connected linearly, of which two of the junctions are quaternary and one of them is chiral. Furthermore, the piperidine core of levocabastine is decorated with four substituents including a carboxylic acid and a distant fluorophenyl group connected to a tertiary nitrile.

Piperazines. Piperazine (Figure 20) is an important nitrogen heterocycle that has been shown to be an essential structural component for three families of pharmaceuticals, of which 32% of them belong to.[36] The largest of these, with 10 approved structures, is the fluoroquinolone family of antibiotics, followed by a group of antihistamine drugs containing cyclizine cores and the homologous blood pressure medications, prazosin, terazosin, and doxazosin. Analysis of the piperazine substitution pattern reveals a lack of structural diversity, with almost every single drug in this category (83%) containing a

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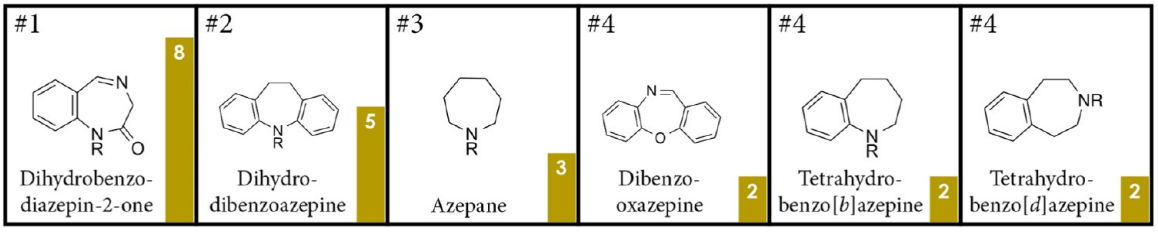

Figure 22. Top five most common seven-membered nitrogen heterocycles.

substituent at both the N1- (indigo) and N4-positions (red) compared to only a handful having a substituent (methyl or C=O) at any other position (C2, C3, C5, and C6). Also shown in Figure 20 are two of the smallest piperazine-containing drugs (piperazine and pipobroman) as well as the more recently approved blockbuster drug sildenafil.[37]

Phenothiazines. The third most commonly used six-membered nonaromatic nitrogen heterocycle is phenothiazine (Figure 21), which accounts for 16 unique small-molecule drugs.[38] Phenothiazine is a linearly fused tricyclic architecture that could also be described as a thiomorpholine core with two fused benzo groups. What is striking about phenothiazine drugs is their high degree of structural and disease function homology, placing it in its own class among significant nitrogen heterocycles. As is apparent from Figure 21, these drugs are all substituted at only two positions, namely, the N10- (orange), and the C2-position (indigo). The C2-position, when substituted, contains a small polar group (R′ = Cl, CF_3, SEt, SMe, SCOMe, COEt, or COMe), while the N10-position in all cases is substituted with a short alkyl tether containing a trialkylamine group either three or four atoms away. The alkyl tether is generally (75%) linearly connected to the trialkylamine that in most cases is part of a heterocycle (63%), which is typically a piperazine. Not only are these 16 phenothiazines structurally similar, but they all belong to the same psycholeptic drug class (the "azines") first introduced in the 1950s, where over a 4-year period (1956–1959), 7 (44%) of the 16 members of this class were approved. The last member to be approved in this class of pharmaceuticals was trifluprom azine in 1983.

SEVEN- AND EIGHT-MEMBERED NITROGEN HETEROCYCLES

Although certainly less common than their five- and six-membered ring counterparts, seven- and eight-membered nitrogen heterocycles are important pharmaceutical core fragments. Shown in Figure 22 are the top five most commonly employed heterocycles in this category representing 26 different pharmaceuticals. Not surprisingly the famous benzodiazepine core is at the top, followed by several reduced and fused azepine variants.

Benzodiazepines and Dibenzoazepines. Shown in Figure 23 are the two most significant seven-membered nitrogen heterocyclic cores (benzodiazepine and dibenzoazepine). The eight benzodiazepine drugs[39] are remarkably similar, differing in the nature of the substituent at only four positions (A–D), where position D is substituted with a chlorine atom in all but one member. Most of the other substitution variations are minor, representing simple atom (halogens) or small group (methyl, OH, NO_2) variations. The dibenzoazepine core pharmaceuticals are even more homologous, with remarkably similar substitution patterns consisting of the presence or absence of a methyl group, or in a single case aryl C–H or aryl C–Cl (clomipramine).

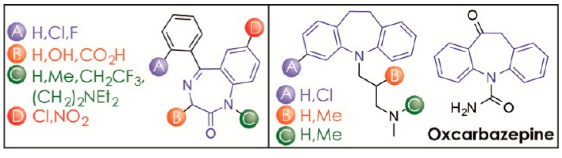

Figure 23. Structural diversity of top two seven-membered nitrogen heterocycles.

FUSED NITROGEN HETEROCYCLES

We now turn our focus on fused ring systems (Figure 24), which we define as those nitrogen heterocycles that contain more than one nitrogen heterocycle, although not necessarily fused directly adjacent to each other. We included this category so we would not count structures like the ergoline core as belonging both to the indole and piperidine families of heterocycles. The top two members in this category are the natural product architectures purine and ergoline, the latter being slightly more prevalent.

Ergoline Alkaloids. The most common fused nitrogen heterocycle is the natural product core belonging to the ergot family of alkaloids, of which most members are derivatives of ergotamine. Shown in Figure 25 are the positions on the ergotamine core and peptidic side chain that have been permutated to access other members of this class. Drugs in this class are used to treat conditions such as dementia, Parkinson's disease, and migraines.[40] The antiparkinson agent lisuride[41] is structurally unique among all these approved ergot alkaloids for having the opposite stereochemistry at the critical C8-stereocenter. Furthermore, lisuride is structurally very similar to lysergic acid diethylamide (LSD), differing only in an additional nitrogen atom (urea instead of an amide) and the opposite C8-stereochemistry. Interestingly, the pharmaceutical agent ergoloid is a combination of dihydroergocornine, dihydroergocristine, dihydroergocryptine, and epicriptine, which differ structurally only in substitution at a single position and are all approved only as part of a combination.

Purines. All of the purine drugs are either approved as anticancer or antiretroviral agents.[42] The majority (70%) of the purine-containing drugs (Figure 26) are nucleosides of which all except abacavir are remarkably similar. The antiretrovirals tenofovir and adefovir are also structurally nearly identical, with their purine cores attached at the same position to a short chain terminated by a phosphonic acid group.

Bridged Bicyclic Nitrogen Heterocycles. The top four most commonly occurring bridged bicylic drug cores are shown in Figure 27. All are derived from or inspired by natural products, with the top position belonging to the morphine architecture, followed closely by the tropane family of alkaloids and quinuclidine representing the third most frequently used

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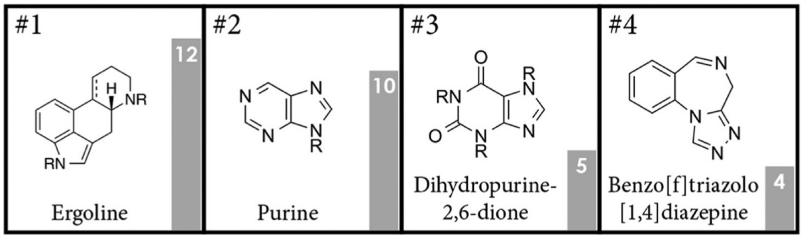

Figure 24. Top four most common fused nitrogen heterocycles.

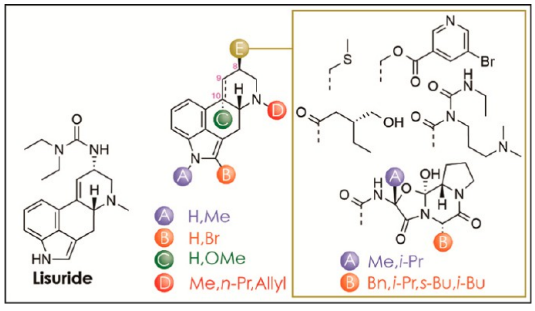

Figure 25. Pharmaceuticals containing ergoline cores.

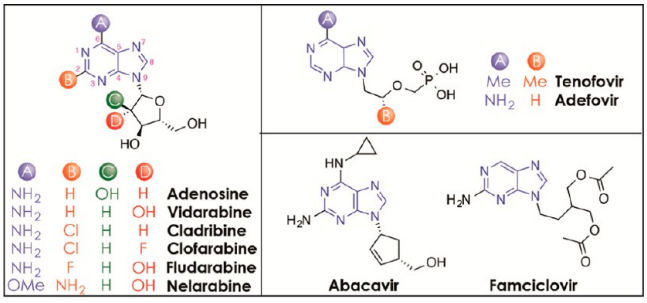

Figure 26. Pharmaceuticals containing purines.

core. Cocaine is the most infamous of the tropane alkaloids, but almost all of the U.S. FDA approved drugs containing the tropane core are symmetrical and lack the carboxylate group found in cocaine. The family of pharmaceuticals represented by the morphinan core has a rich history,[43] with morphine, oxycodone, hydromorphone, and codeine as its most utilized members.

Morphinans. A closer look at the morphinan core substitution pattern variations is displayed in Figure 28. Morphine and codeine,[44] which only differ in methylation at the C3-phenol group, are the only drugs in this group that contain a C7−C8 double bond. Most of the other morphinans, represented by dihydrocodeine and oxycodone, only deviate in their subtle substitution differences at C6, C14, N17, and the C3 phenol. The changes at the C3-phenol or C14 involve only the absence or presence of a methyl or hydroxyl group, respectively, while the N17 modifications involve permutations of short alkyl chains. Dextromethorphan and butorphanol are the most reduced members of this class in that they both lack the furan heterocycle as well as any C6 oxygenation. Buprenorphine is the most complex morphinan, with an additional side chain at C7 and an intriguing bridging carbon chain between C14 and C6, while dextromorphan is the only morphinan with the opposite stereocenters at C9 and C13. A common feature of morphinan drugs is their high prevalence in combination drug therapies.

Tropanes. The [3.2.1]-bridged bicyclic tropane core is the second most frequently utilized bicyclic nitrogen heterocycle among U.S. FDA approved drugs (Figure 29).[45] Natural products are the reason for the existence of this important class of drugs, as atropine, hyoscyamine, scopolamine, and cocaine are all natural products with other members being derivatives. For example, homatropine has one less methylene group than atropine, while methylscopolamine and ipratropium are alkylammonium salts of scopolamine and atropine, respectively.

Quinuclidines. Quinuclidine is an interesting [2.2.2]-bridged bicyclic nitrogen heterocycle with a nitrogen atom located at the bridgehead. All of the U.S. FDA pharmaceuticals containing a quinuclidine are displayed in Figure 30. The natural products quinine[46] and quinidine are without a doubt the most well-known members of the quinuclidine family, with a long history in folk medicine, as pharmaceuticals, and in recent decades as privileged chiral organic ligands in catalysis. Dolasetron and palonosetron, despite being drastically dissimilar with respect to their quinuclidine substituents, both are prescribed for the treatment of vomiting and nausea associated with chemotherapy. Interestingly, all of the approved quinuclidine drugs contain at least one additional heterocycle, which with the exception of aclidinium are all nitrogen heterocycles (quinolones, phenothiazine, indole, and isoquinolones). Aclidinium, used for the treatment of chronic obstructive pulmonary disease (COPD), is the most recently approved (2012) of these pharmaceuticals.

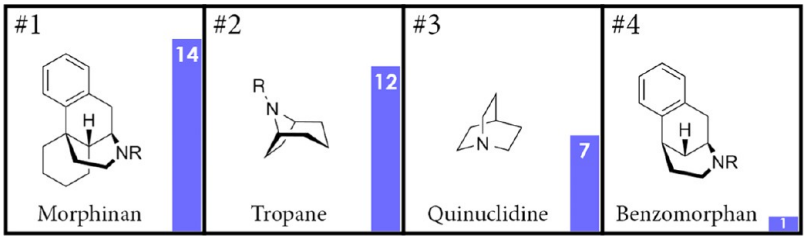

Figure 27. Top four most common bridged bicyclic nitrogen heterocycles.

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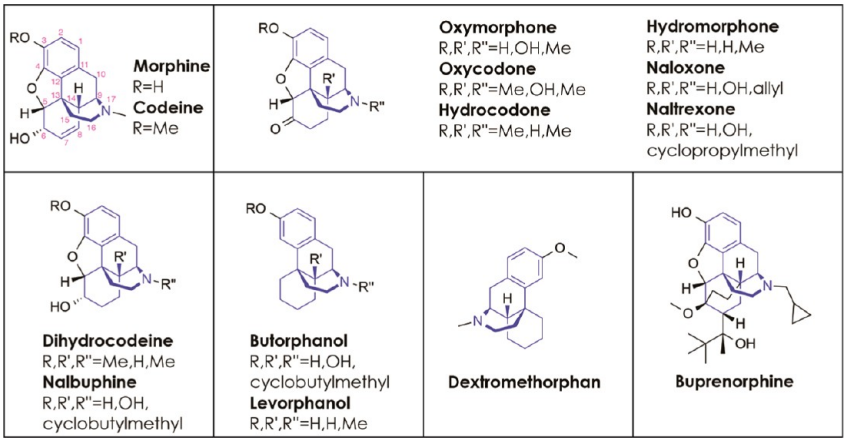

Figure 28. Pharmaceuticals containing morphinans.

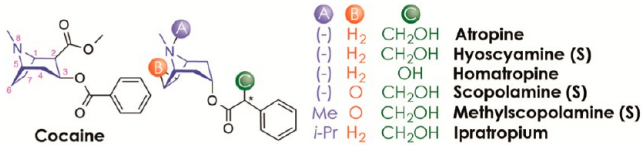

Figure 29. Pharmaceuticals containing tropanes.

MACROCYCLIC AND METALLOCYCLIC NITROGEN HETEROCYCLES

Macrocyclic nitrogen heterocycles are critical parts of important pharmaceuticals (Figure 31), of which the family of immunosuppressive agents derived from the natural products rapamycin (sirolimus) and FK-506 (tacrolimus) is most significant. Not surprisingly, almost all of the approved nitrogen macrocycles are natural products or derivatives of natural products. In addition to rapamycin and FK-506, these include the antibiotics azithromycin, which is a simple derivative of erythromycin, and rifaximin, which is derived from rifamycin. Plerixafor is a fascinating symmetrical structure with two 16-membered tetraaza-crown groups connected to a central *p*-xylyl group. The epothilone derivative ixabepilone is a macrolactam whose only structural deviation from the natural product it originated from (epothilone B) is the lactam nitrogen.[47]

Finally, there is one structurally intriguing nitrogen heterocycle that also contains a metal atom.[48] This nitrogeneous metallocycle is oxaliplatin, which was approved in 2002, and belongs to a small but successful family of platinum-containing oncological drugs of which cisplatin was first approved (1978). In all cases, the platinum atom is connected to four ligands of which two are always amines, with the other two being chloride atoms or a carboxylate group.

SUMMARY

In conclusion, this review presents the first detailed analysis of the nitrogen heterocyclic composition of U.S. FDA approved unique small-molecule pharmaceuticals. The fact that 59% of small-molecule drugs contain a nitrogen heterocycle firmly ranks them as the most privileged and significant structures among pharmaceuticals. This analysis was made possible for pharmaceutical nonexperts by the recent creation and publication of our disease focused pharmaceutical posters. Our analysis revealed the relative frequency by which the various nitrogen heterocycles have been incorporated into approved drug architectures, wherein the top three spots were ruled by piperidine, pyridine, and piperazine. Rounding off the top five were cephem and pyrrolidine rings. The analyses and relative distributions presented in Figure 3 reveal just how impactful only a handful of nitrogen heterocycles have been. Within each heterocyclic subcategory we chose to reveal interesting common structural patterns that these nitrogen heterocycles were part of and highlight any apparent substitution pattern biases or lack thereof.

It is quite informative to look over the schemes in this review and be intrigued by the many successful but structurally near identical frameworks that have been used for countless drugs. Most notable of the structurally similar drugs, in our opinion, are the ones containing cephem (Figure 5), penam (Figure 6), piperazine (Figure 20), phenothiazine (Figure 21), or morphinan (Figure 28) cores. With respect to nitrogen heterocyclic substitution diversity among U.S. FDA pharmaceuticals, it is quite eye opening to review the drawn-to-scale substitution pattern color bubbles presented in Figures 8−11, 14, 16, 17, and 19−21 for the most commonly used nitrogen heterocycles. It is our hope that this structure focused analysis will stimulate incorporation and synthesis of new nitrogen heterocycles as well as the development of new, robust, flexible, and scalable methods to access both the most significant

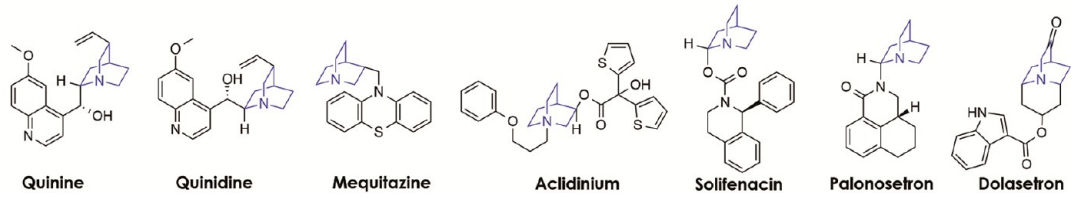

Figure 30. Pharmaceuticals containing quinuclidines.

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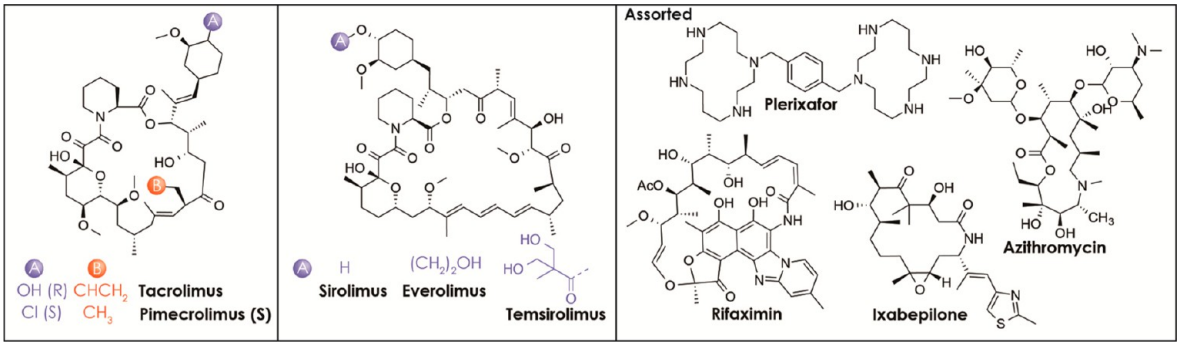

Figure 31. Examples of U.S. FDA approved nitrogen macrocycles.

nitrogen heterocycles featured in this study and those currently underrepresented.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

FDA, Food and Drug Administration; HIV, human immunodeficiency virus; ACE, angiotensin converting enzyme; DHEA, dehydroepiandrosterone; COPD, chronic obstructive pulmonary disease

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(1) These new types of pharmaceutical posters are freely accessible to anyone as PDF files at http://cbc.arizona.edu/njardarson/group/content/disease-focused-pharmaceutical-posters. Information about the posters' origin and designs and the posters as new tools for research and teaching can be found at the following: Ilardi, E. A.; Vitaku, E.; Njardarson, J. T. An In-*Pharm*-ative Educational Poster Anthology Highlighting the Therapeutic Agents That Chronicle Our Medicinal History. *J. Chem. Educ.* **2013**, *90*, 1403−1405. These new posters are a logical extension of our top 200 pharmaceutical posters, which we have updated continuously since 2006: http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster. McGrath, N. A.; Brichacek, M.; Njardarson, J. T. A Graphical Journey of Innovative Organic Architectures That Have Improved Our Lives. *J. Chem. Educ.* **2010**, *87*, 1348−1349.

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