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Original article

Known drug space as a metric in exploring the boundaries of drug-like chemical space

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ABSTRACT

In this work, marketed drug compounds (or known drug space) were used as a metric to test the principles of eliminating parent structures of the nitrenium ion (aryl-amine/nitro compounds) as well as sulphur and halogen containing molecules from screening compound collections. Molecules containing such moieties and/or atoms have biological and physiochemical properties, which possibly make them less attractive as leads in drug development. It was found that precursors to the nitrenium ion were relatively abundant in known drug space at 14%. Thus, their simple elimination from drug-like chemical space is *not* advisable. Interestingly, the mutagenic potential of the nitrenium ions is linked to their stability and quantum mechanical calculations can be used to estimate it. Furthermore, 24% of drugs investigated contained sulphur atoms and around 28% were halogenated. As some sulphur containing moieties were abundant whilst others were scarce, it was deduced that it would be more effective to eliminate specific molecular scaffolds rather than all sulphur containing molecules. In conclusion, it has been shown that by statistically analysing known drug space a better understanding of the boundaries of drug-like chemical space was established which can help medicinal chemists in finding rewarding regions of chemical space.

1. Introduction

The concept of drug-like chemical space is widely used in drug development for the selection of molecules for high-throughput screening compound collections and for assessing the quality of hit and lead compounds [1–4]. It has given medicinal chemists, who previously had little more than their intuition and experience to guide them, a cognitive tool to approach these tasks. Drug-like chemical space is defined by molecular descriptors such as lipophilicity (Log P), molecular weight, topological polar surface area (TPSA) and rotatable bonds [5–10]. Furthermore, certain 'undesirable' molecular moieties are used to exclude regions of chemical space. Many such moieties are reported in the literature and they are generally defined as those perturbing biochemical and/or cell-based assay formats [11–17].

Possible candidates for this class of 'undesirable' moieties are the parent compounds of the nitrenium ion, i.e., aromatic amines and aromatic nitro containing compounds. Many aromatic amines are linked to carcinogenesis due to their ability to react with DNA after enzymatic activation [18–20]. The first step in the bio-activation is the oxidation of the exocyclic amine nitrogen to form the corresponding hydroxylamine [19]. This can undergo heterolytic bond cleavage, in mildly acidic aqueous environment, forming a reactive arylnitrenium ion (see Scheme 1) [20]. This ion can also be formed via enzymatic reactions where the acetoxy- or sulphate-esters are formed as intermediates catalysed by *N*-acetyl-transferases or sulfotransferases [19,21,22]. Furthermore, aromatic nitro compounds can form hydroxylamine after enzymatic reduction [23] and then progress, like their aromatic amine counterparts, to form reactive arylnitrenium ions (see Scheme 1). Nitro-polycyclic aromatic hydrocarbons are widely distributed environmental pollutants [24] and the increased lung cancer risk, after exposure to these environmental sources, has led to considerable attention in assessing their genotoxic potential [25,26].

Thus, there is a clear case for elimination of these chemical moieties from drug-like chemical space. However, the question emerges whether valuable regions of chemical space would be excluded by not considering these moieties?

Excluding certain atoms is also an interesting strategy in determining the boundaries of drug-like chemical space. In this

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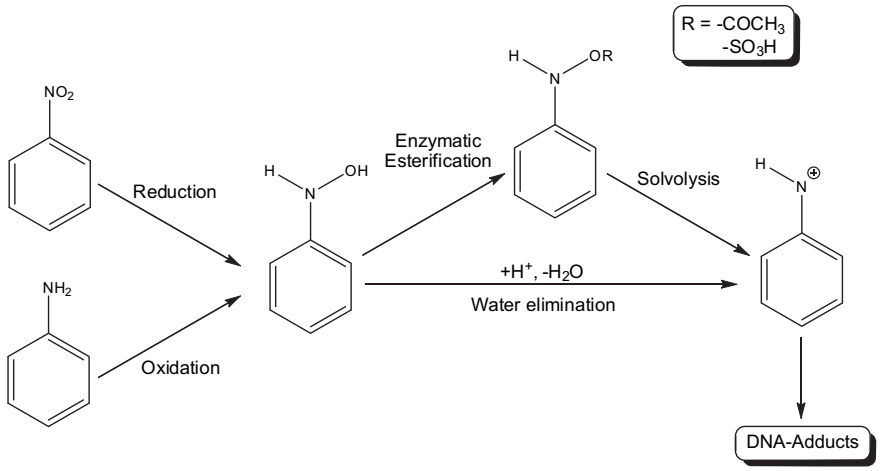
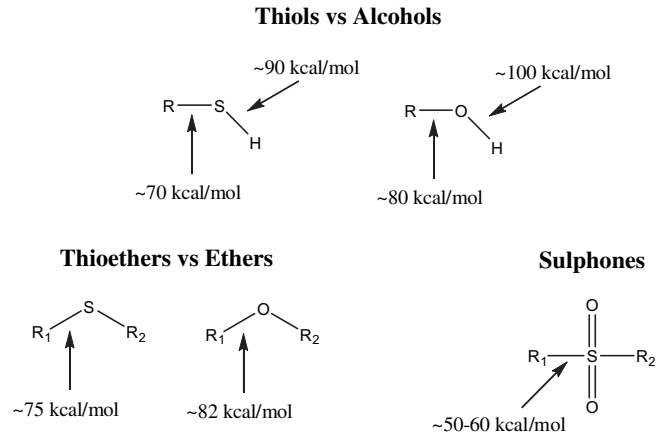


Scheme 1. Metabolic activation for aromatic amines and nitro compounds leading to the formation of nitrenium ions. The use of nitrobenzene and aniline in the scheme is only an example of the aryl-amine/nitro moieties.

study it was decided to investigate the effect of excluding compounds including sulphur atoms and molecules containing halogens.

The reason why sulphurous compounds were selected is because they are relatively unstable compared to their oxygen containing counterparts. As shown in Scheme 2, the C–S bonds have lower bond dissociation energies (BDEs) than their C–O counterparts by ~10 kcal/mol. Furthermore, sulphones have BDEs of only 50–60 kcal/mol. Another aspect of stability is oxidation. It is well known that thioethers can be oxidised by two electron successive steps to afford sulphoxides and sulphones in aqueous solutions [29,30]. Also, one-electron oxidation of sulphide salts ($R–S^-$) leads to formation of disulphides. These reactions could lead to unwanted products in biological systems that medicinal chemists may wish to avoid. When the ionisation potentials (IP) of aliphatic thioethers/thiols were compared to their ether/alcohol counterparts the former were ~1 eV (~23 kcal/mol) lower and, therefore, more easily oxidised and reactive [31,32].

In general, halogenated compounds are heavier and more lipophilic than organic molecules [33]. It is accepted that during the development of lead compounds molecular weight and lipophilicity (Log P) are considerably increased [36,37]. Therefore, it



Scheme 2. A comparison of the bond dissociation energies (BDEs) between sulphur and oxygen containing compounds with aliphatic groups (R). Averages are given based on experimental values [27,28]. Sulphones do not have an obvious oxygen containing counterpart.

is quite understandable why drug developers may wish to avoid halogenated compounds to work on at the beginning of a drug development project.

A plausible method for validating different ideas regarding the boundaries of drug-like chemical space is to quantify the occurrence of the atom, moiety or property in marketed drug compounds, i.e., using known drug space as a metric. This is based on the assumption that there is extensive overlap between known drug space and drug-like chemical space. Recently this approach was used to evaluate the predictive power of QSAR models [40] and for an investigation into the validity of using "undesirable" moieties in defining drug-like chemical space [41]. Also, in the field of bioinformatics analogous strategies based on published drug programmes are used, e.g., for evaluation or prioritisation of drug targets [42,43]. Fig. 1 presents graphically the questions asked, i.e., whether nitro/amine-aryl moieties and sulphur/halogen containing molecules should be included in drug-like chemical space?

2. Methodology

Spreadsheets of 1493 and 831 marketed drug compounds were compiled from the DrugBank database [44] using Microsoft Excel. The former for the aryl-amine/nitro drugs and the latter for the sulphur/halogen compounds. The following information was extracted: generic name, chemical formula, route of administration, and main therapeutic effect. Salts, solvents, and contrast media (e.g., calcium chloride, magnesium sulphate, Gadoversetamide) were omitted from the list as they were not considered relevant to this study. The aryl-amine/nitro collection was divided into the following categories: *primary aromatic amines, secondary aromatic amines, aliphatic amines, amines containing heterocyclic moieties, aromatic nitro rings, aliphatic nitro groups*, and finally, *drug compounds not containing any of these moieties*. The compiled drug compounds for the sulphur/halogen drugs were categorised into five groups according to atom content. The *CNOH group* comprised of compounds that only contained carbon, nitrogen, oxygen, and/or hydrogen. The *halogen group* consisted of drugs that contained fluorine, chlorine, bromine or iodine atoms, whilst the *sulphur group* included those drugs with one or more sulphur atoms. The *sulphur and halogen group* was a collection of drug compounds containing both sulphur as well as a halogen. Drugs that did not fulfil one of these criteria or that contained metal or phosphorus atoms were categorised as *miscellaneous*.

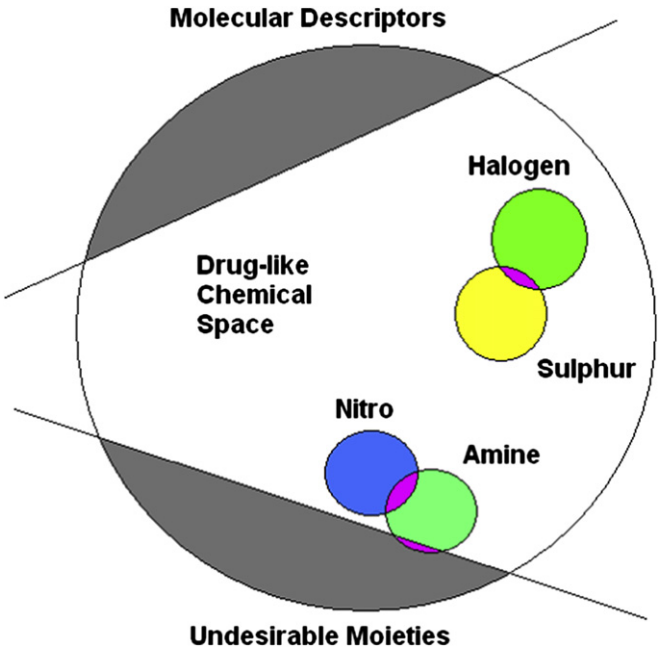


Fig. 1. A graphical representation of drug-like chemical space defined by molecular descriptors and "undesirable" moieties. This is only a simplified two-dimensional representation of drug-like chemical space, e.g., there can be overlap between the regions of undesirable moieties and molecular descriptors. The questions posed are whether nitro/amine-aryl moieties and sulphur/halogen containing molecules should be included in drug-like chemical space?

Seven categories for routes of administration were defined and these were: *oral, ophthalmic, topical, intravenous, multiple, miscellaneous,* and *not-known*. The therapeutic effects were divided into the following groups: *anaesthetic, anti-biotic, arthritis, anticancer, ophthalmic, cardiovascular, hypertension, nutrients, respiratory, antiviral, miscellaneous*, and *not-known*.

3. Results

3.1. The occurrence 1°, 2° amines and nitro compounds in known drug space

Fig. 2 depicts the general distribution of amine and nitro containing compounds in known drug space. Of the 1493 marketed drugs investigated, 215 (14.4%) contained either an aromatic amine or aromatic nitro moieties. 191 (12.8%) of these were aromatic amines and 24 (1.6%) were aryl-nitro compounds. 38% of the drugs had amine moieties as a part of a heterocyclic ring, aliphatic chain, amide or related chemical structure. Only 0.4% of the molecules investigated were aliphatic nitro compounds. Finally, 47% of the drug molecules did not include amine or nitro groups.

It was apparent that aryl-amine moieties were relatively prevalent in marketed drug compounds and by eliminating these from screening collections, and drug development in general, valuable regions of drug-like chemical space could be overlooked. However, aryl-nitro compounds were very scarce and indeed nitro containing compounds featured in only 2% of the drugs investigated.

1636 amine moieties were found in the drugs investigated. Aliphatic amines were the most prominent at 60% followed by heterocyclic amine compounds at 24%. Aromatic amines presented 16% (268 moieties) and of these 9% (150) were primary amines and 7% (118) were secondary amines. The most common second substituents were amides at 44% followed by a second aromatic moiety at 19%, i.e., a secondary amine flanked on both sides by an

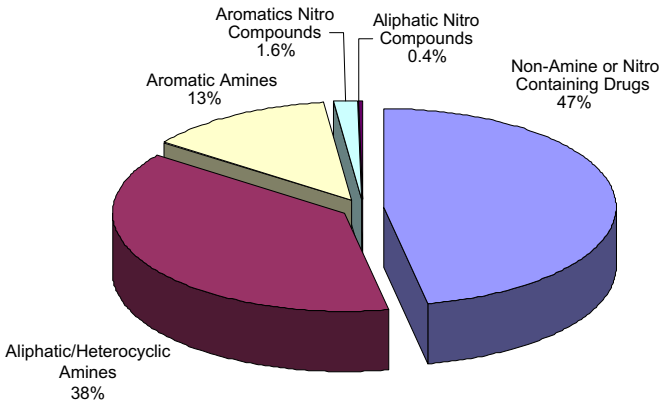


Fig. 2. The distribution of nitro and amine moieties based on a collection of 1493 marketed drug compounds. 100% = 1493 drug compounds.

aromatic system. Finally, 14% were aliphatic and unsaturated chains and the rest (23%) were termed miscellaneous.

The simplest explanation for the dearth of aliphatic nitro compounds was the relatively low bond dissociation energy (BDE) of the C–NO_2 bond, which was reported to be ~60 kcal/mol [28], and the consequent instability of the compounds. However, the BDE for the C_6H_5–NO_2 bond is higher at ~70 kcal/mol [28] and these compounds are, therefore, more stable. According to the information given in the DrugBank database, two of the 24 aryl-nitro compounds (azathioprine and metronidazole) were linked to carcinogenic effects, leading to the conclusion that these compounds should be excluded from drug-like chemical space unless there is a specific reason to keep this moiety. E.g., recently a very interesting mechanism was reported where aryl-nitro compounds were used to generate reactive nitrogen species via enzymatic reduction activation, killing tuberculosis bacteria [45]. A third of the aryl-nitro drugs were indicated as antibiotics and one can contemplate that this mechanism was responsible for their therapeutic effect. Furthermore, six of these drug compounds had five membered rings attached to the nitro group making them relatively difficult to reduce. This means that if the reductive enzyme in bacterium is more effective than its human counterpart these drugs are selectively activated.

The relatively large number of possible parent compounds to nitrenium ions in drug-like chemical space indicates that not all aryl-amine/nitro compounds should be eliminated from drug development. The stability of the nitrenium ions has been correlated to their mutagenic potential both using physical chemical methods [46,47] and quantum chemical calculations [48–51]. The rationale given was that more stable nitrenium ions had a relatively long lifetime enabling them to diffuse through the cytosol until they reached an electron rich target such as DNA [48,49]. The less stable ions reacted more readily with any bio-molecular compounds they encountered and were, therefore, not specific towards DNA [48,49]. Interestingly, the mutagenic property of the nitrenium ions has been correlated to the charge on the exocyclic nitrogen using density functional theory (DFT) [50,51]. Therefore, instead of eliminating this class of chemicals further calculations can be performed in order to establish inclusion or exclusion from drug-like chemical space, i.e., helping to define a more accurate boundary for drug-like chemical space.

3.2. Distribution of atom content

As depicted in Fig. 3, more than half of the 831 drug compounds studied fell into the CNOH group. This is not surprising since most

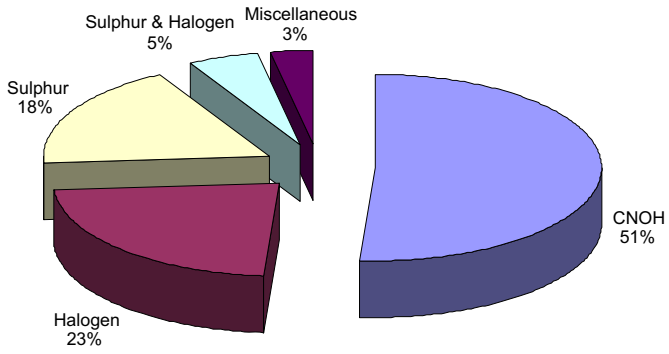


Fig. 3. The distribution of atom type groups defined based on a collection of 831 marketed drug compounds. 100% = 831 drug compounds.

drugs are either natural products, their derivatives, or are synthesized. The halogen group was the second most populated with a combined 28% of the total number of drug compounds. Around 24%, 200 of the drug compounds contained sulphur atoms. As a result of the 44 compounds containing both sulphur and a halogen, an overlap of around 5% was observed in the sulphur and halogen group regions in known drug space. Finally, the miscellaneous group comprised 27 drugs, 9 of which also contained a sulphur atom.

It was immediately clear that simply excluding sulphur and halogen containing compounds from screening collection was a counterproductive measure since these atoms were abundant in known drug space. However, more in depth investigation was required to establish the *value* in these ideas for reducing drug-like chemical space.

3.3. Sulphur compounds

Among the collection of 831 drug compounds, 275 sulphur atoms were found in 200 drugs. 154 of the drug compounds contained a single sulphur atom and the remaining 46 contained two or more. The 275 sulphur atoms were categorised according to the type of molecular moiety they formed a part of. The results of this analysis are depicted in Fig. 4. The majority of the sulphur atoms found, 41% or 112 sulphur atoms, were incorporated into heterocycles (e.g., thiophene). 80 of these sulphur heterocycle atoms formed part of a larger conjugated system increasing the stability of the sulphur bonds. 15 of the sulphur heterocycle atoms were close to a conjugated system but not in direct contact. The remaining 17 sulphur heterocycle atoms were not conjugated and most of them incorporated in penicillin derivatives. At 21%, the second most abundant sulphur-containing moiety was sulphonamides. There was some overlap between these categories. In five cases sulphonamide formed part of a ring structure and these were grouped with the sulphur heterocycles. Sulphates and thioether moieties made up more than 10% each of the total. Half of the thioethers had aliphatic side chains and the rest had at least one aryl ring system adjacent to the sulphur atom. The miscellaneous category was comprised of moieties that make up less than 5% of the total sulphur atoms. It included sulphonyls (3%), sulphinyls (2%), sulphonates (1%), and thiols (3%).

It is worth noting that the common amino acids cysteine and methionine contain a thiol and thioether moieties, respectively. Only 3% of the drugs investigated contain a thiol moiety, whereas 11% contain thioethers.

A number of 'undesirable' moieties used to define chemical space contain a sulphur atom [52]. Consequently, an overlap exists between regions of chemical space excluded by 'undesirable' moieties and that occupied by sulphur containing molecules. A more astute approach would be to eliminate specific sulphur moieties in defining drug-like chemical space, rather than excluding *all* compounds containing sulphur, thereby preventing valuable regions of drug-like chemical space from being overlooked. It can be concluded that moieties contained in the miscellaneous category, i.e., sulphonyls, sulphinyls, sulphonates, and thiols could be excluded from drug-like chemical space due to their scarcity in known drug space.

An interesting idea is to use molecular orbital calculations to estimate the stability of sulphur containing compounds. The DFT method has been shown to be successful in predicting ionisation energies and electron affinities for organic compounds [53–56],

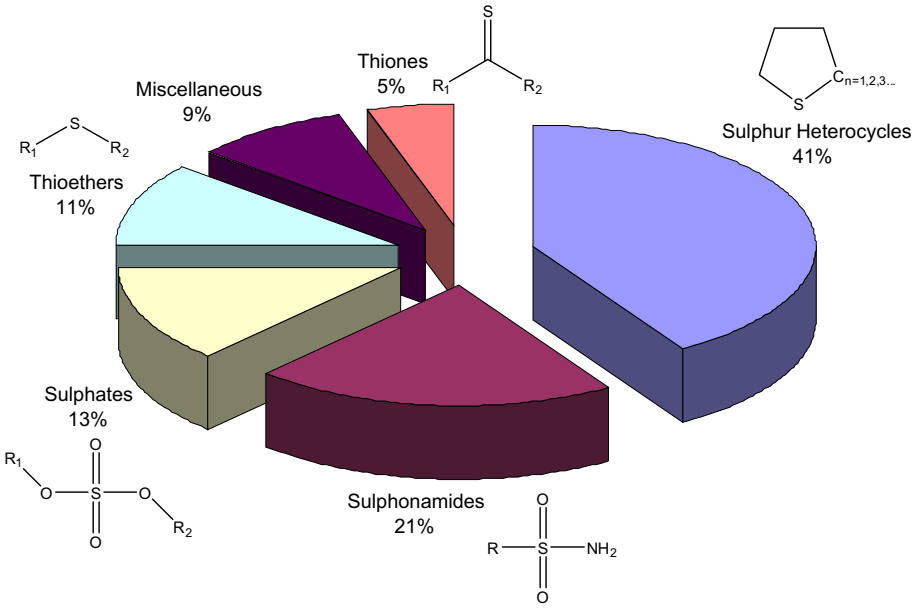


Fig. 4. The distribution of sulphur containing molecular moieties found in a collection of 831 marketed drug compounds. 275 sulphur atoms were found in 200 sulphur containing drugs. 100% = 275 sulphur atoms.

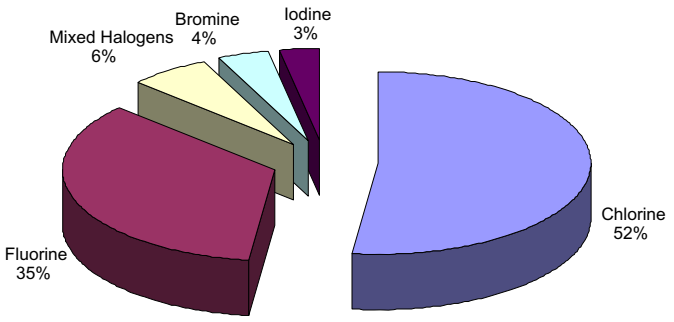


Fig. 5. The distribution of halogen type in a collection of 831 marketed drug compounds. 100% = 238 drugs.

which reflects their redox stability. Furthermore, bond dissociation energies (BDEs) derived from DFT calculations correlate well with their experimental counterparts [57]. With these theoretical tools the stability of sulphur containing molecules can be estimated. However, further work is needed to establish whether this approach can be applied in refining drug-like chemical space.

3.4. Halogens

In the collection of 831 marketed drugs, 238 compounds, around 28% contained halogen moieties. The distribution of halogen atoms according to type is shown in Fig. 5. Chlorine is the most widespread, found in 52% of the 238 compounds, followed by fluorine at 35%. Bromine and iodine were much less common at 4% and 3% respectively. The 'mixed halogens' category comprised of compounds that contained more than one halogen type and made up 6% of the total. Multiple halogen atoms were present in many of the drugs investigated. As a result, the total number of halogens encountered was 397. Chlorine atoms were still the most abundant with 187 atoms (47%) closely followed by fluorine with 181 atoms (46%). Finally, there were 17 instances of iodine (4%) and 12 of bromine (3%).

It is worth noting that bromine and iodine atoms were relatively scarce in drug compounds. They are the heaviest of the halogens investigated and cause the largest increase in lipophilicity [58]. This would suggest that there is sound justification for excluding these two atomic species from drug-like chemical space unless there is a specific reason not to do so. However, with the widespread use of quantifiable molecular descriptors such as MW and Log P, the occurrence of molecules with bromine and iodine is already diminished due to their high molecular weight and lipophilic nature. It could be argued that excluding chemicals purely based on the presence of these atomic species has relatively little effect as overlap already exists between the regions of chemical space excluded by MW and Log P and that occupied by bromine and iodine containing compounds.

3.5. Route of administration and therapeutic application

The route of administration was correlated in order to establish whether the drugs under investigation display trends distinguishing them from other drug molecules. The categories investigated displayed similar patterns, i.e., the oral administration form is the most predominant followed by intravascular formulation. This distribution is akin to a similar analysis of "undesirable" moieties in known drug space [41].

With regards to main therapeutic application, it was found that 18% of the sulphur containing drugs were anti-bacterial agents. This is not surprising since penicillin and its derivatives contain sulphur [59] as well as the sulfa drugs. Other than this, similar trends in therapeutic application were encountered between the different categories.

4. Discussion

By analysing the test cases with known drugs space we have demonstrated that 'mapping out' the boundaries of drug-like chemical space is possible. In the case of the aryl-amine/nitro compounds, they should not simply be excluded from drug-like chemical space but flagged and their carcinogenetic liability further investigated using, e.g., *ab initio* calculations. Again, for the sulphur compounds, just eliminating them is a very blunt approach and exclusion of certain sulphur containing moieties is more appropriate. Finally, excessively halogenated organic molecules are excluded from drug-like chemical space by the employment of the well-established molecular descriptors of molecular weight and Log P, which render the atom based filtering method redundant.

By working with marketed drug compounds, or known drug space, only molecular entities, which have passed clinical trials and consequently been successfully marketed, are examined. In this way only compounds that are known to be physiologically compatible for humans are used for the metric collection. Is there a better metric than the drugs that already improve the lives of millions of people every day?

The idea of excluding aryl-amine/nitro compounds and sulphur/halogen molecules was chosen to test this approach because physicochemical arguments for elimination from drug-like chemical space based on reactivity, stability and lipophilicity were present. These examples might be obvious to an experienced medicinal chemist, however, it is recognized that there may be diverse opinions on which molecular structures are suitable for drug development [60]. A systematic approach accessible to all scientists is needed. Finally, in carrying out this study, only information in the public domain was used in conjunction with widely available software.

5. Conclusion and suggestions

In this study, known drug space is used as a 'navigational tool' to evaluate ideas and strategies to define the boundaries of drug-like chemical space. This approach provided a simple means to validate the boundaries using data in the public domain. The ideas investigated were whether the parent molecular moieties of the nitrenium ion, a known carcinogen, and atom types such as the halogens and sulphur should be used to eliminate compounds *per se* from screening collections or from further consideration as hit compounds. In the case of the parent compounds of the nitrenium ion and for the sulphur containing compounds it was found that a simple elimination excludes valuable regions of chemical space and more *focused* methods are pertinent, i.e., charge density calculations for the nitrenium ions and elimination of certain sulphur containing moieties based on "undesirable" substructures. In the light of high rates of attrition for drug candidates in clinical trials [61,62] the concept of known drug space can be used to navigate drug designers to favourable regions of chemical space.

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Appendix. Supplementary material

Supplementary material can be found, in the online version, at doi:10.1016/j.ejmech.2009.08.014

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