Drug-likeness, herbicide-likeness and toxicity of herbicidal compounds – *in silico* analysis

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Summary

Instead of conventional process of discovery of novel drugs which is complex, time-consuming and expensive, revealing novel targets and therapeutic applications of existing drugs is an alternative and efficient approach used for increasing productivity in the pharmaceutical industry. We explored the data set of 509 approved herbicides for their use as a chemical library for finding novel lead molecules. Herbicides were analysed in terms of drug-likeness by applying common *in silico* filters for nondrug-like molecules. Descriptors were calculated by the program DataWarrior and analysis was performed by using *R* packages and Excel. The herbicides were compared with 2106 drugs. Most of herbicides are drug-like compounds and the set of structurally diverse herbicides is recommended as a screening library for medicinal chemistry projects. Herbicides are neutral or negatively charged molecules. Their *clogP* and *TPSA* values are mainly in the ranges 0.5-3.5 and (20-100) $Å^2$, respectively, which are possessed by around 1/3 of drugs. However, the successful application of herbicides in medicine may depend upon their toxicity for humans. More than 2/5 of the herbicides are estimated to be mutagenic, carcinogenic, toxic for reproduction and irritant. In comparison, around 1/5 of drugs are estimated to be toxic.

Keywords: drug-likeness, herbicide, herbicide-likeness, screening, toxicology

Introduction

Herbicides are chemical compounds used for selective eradication of weeds. More than five hundred herbicides have been approved for application so far (Gandy et al., 2015; Gong et al., 2013; Kim et al., 2016) In the last two decades, the two global issues have appeared in connection with the wide use of herbicides: 1) increase in weed resistance and 2) health issues (Forouzesh et al., 2015). Accordingly, there is a search for novel herbicides which have a known and possibly new mechanism of action and no toxic and detrimental effects for humans, animals and environment (Westwood et al., 2018). Many methods and approaches, such as high-throughput screening and various *in vitro* and *ex vivo* mechanistic secondary assays as well as selectivity and liability assays which have been developed as a part of process of rational design of novel drugs (Hughes et al., 2011), are also applied in the design of novel and safe herbicides (Rao et al., 2015). Such approaches are commonly performed by using rationally built chemical libraries. Physicochemical properties of the chemical compounds are commonly used for guiding the design and selection of chemical libraries (Hughes et al., 2011). These properties are primarily associated with absorption, distribution, metabolism and excretion (ADME) features of chemical compounds which largely influence their pharmacokinetic profiles. In the Biopharmaceutics Classification System (BCS), drugs are differentiated on the basis of their physicochemical properties solubility and permeability in order to characterize their oral bioavailability (Benet, 2013). The physicochemical properties are generally associated with the concept of drug-likeness.

Drug-likeness is a qualitative concept used in drug design for estimation how much drug-like a substance is with respect to pharmacokinetics properties like oral bioavailability (Lipinski et al., 2001; Veber et al., 2002; Muegge et al., 2001). It is based on comparison of properties like lipophilicity, solubility and permeability and simple structural features such as numbers of hydrogen bond acceptor (*HBA*) or donor (*HBD*) atoms with those of drugs. Drug-likeness concept is successfully used by medicinal chemists in the early stages of lead and drug discovery as a way to reduce attrition rate in late clinical phases (Waring et al., 2015).

The distributions of physicochemical properties and simple structural parameters have been analysed for various pesticides including various subsets of herbicides (Tice, 2001; Tice, 2002; Clarke et al., 2003; Rao et al., 2015; Zhang et al., 2018). Such analyses have been carried out mainly in order to find herbicide-likeness rules (in analogy with drug-likeness rules) and thus facilitate design and development of novel herbicide molecules.

The main objective of this work is to provide qualitative characterizations of known herbicides in terms of drug-like properties (Delaney et al., 2006). Drug repurposing allows prediction of novel applications of medications or even new therapeutic classes of drugs using gene expression data before and after drug treatment (Aliper et al., 2016). Drug discovery is a complex, time-consuming and expensive process aimed to discovering novel medicines whose potency and selectivity are well balanced against their pharmacokinetic profile (dose and dosing interval) which is mostly determined by their ADME properties (Hughes et al., 2011; Daina et al., 2017). The link between the ADME properties of small compounds with their bulk physicochemical properties and simple molecular structure features are quite well established. Due to this understanding, during early phase of drug discovery simple *in silico* filters and various *in vitro* assays are commonly performed to efficiently eliminate compounds with properties commensurate with high attrition risks. Our study has provided results of analysis of data set of approved herbicides by using well-known *in silico* filters commonly used for sorting out nondrug-like molecules. The aim of the study was to investigate drug-likeness of herbicides in order to estimate their potential to be used for design of screening library for identification of novel lead molecules for medicinal chemistry projects (Delaney et al., 2006; Mignani et al., 2018). Some of organophosphate herbicides, like non-selective paraquat and round-up (glyphosate), cause the reduction of certain groups of biota in soil medium, like heterotrophic aerobic bacterial count and fungal population, and also suppress the biodiversity of soil microbes (Usman et al., 2017). In addition to potential anti-infective activity, herbicides also modify activity and/or expression of macromolecules within humans (Delaney et al., 2006). Some herbicide compounds have been found to act as endocrine disruptors modulating activity or expression of estrogen, progesterone, pregnane X or androgenic receptors as well as aromatase activity (Mnif et al., 2011).

We present the results of analysis of the comprehensive data set of herbicides from the aspect of drug-likeness. For this purpose, herbicides were compared with the set of approved drugs collected in the database DrugBank (Wishart et al., 2017). The analysis revealed that herbicides are drug-like molecules, but with characteristic, herbicide-like ranges of some properties. The analysis supports the use of the set of structurally diverse herbicides as a valuable screening library for finding novel lead molecules.

Materials and Methods

The data set of 509 herbicides has been collected from the literature (Gandy et al., 2015.) and internet database resources (Gong et al., 2013; Kim et al.,

2016; http://www.alanwood.net/pesticides/). The dataset of 2106 approved small molecule drugs was downloaded from the database DrugBank (version 5.1.1, released 2018-07-03) (Wishart et al., 2017). The compounds were represented in the SMILES format. Counter-ions and solvent molecules were removed from the structures. A set of 1D and 2D descriptors was calculated by the freely available program DataWarrior (Sander et al., 2015). The calculated descriptors used for the analysis were molecular weight (*MW*), numbers of *HBA* and *HBD* atoms, n-octanol/water partition coefficient (*clogP*), aqueous solubility *clogS*, topological polar surface area (*TPSA*), fragment-based druglikeness (for traded drugs mainly within the range -1 to 4), molecular flexibility (low < 0.5 < high), shape index (spherical < 0.5 <linear), molecular complexity, and numbers of non-H atoms, C-atoms, heteroatoms, stereo centers, sp^3-atoms, aromatic atoms, rotatable bonds (*RB*), rings and aromatic rings. In addition, numbers of fragments - amide, alkyl- and aromatic amine, aromatic nitrogen, basic nitrogen and acidic oxygen were calculated. Formal charge was calculated as a difference between the numbers of basic nitrogens and acidic oxygens. DataWarrior was also used for predictions of toxicity. DataWarrior outputs risk alerts regarding mutagenic, tumorigenic, reproductive and irritating toxicity with high sensitivity and specificity. The models within DataWarrior are classification ones based on the presence of fragments associated with the corresponding toxicity type (von Korff et al., 2006). The program R (https://www.r-project.org/) was used for statistical analysis and plotting. The histograms were made by Excel.

Results and Discussion

Drug-likeness

The set of 509 organic herbicides belong to different chemical classes. However, drug-likeness rules are commonly defined in terms of molecular properties which are independent upon the chemical class. This is because the passage of a compound through intestine and entrance into the blood as well as its further distribution through the body is mainly determined by bulk physicochemical properties, aqueous solubility and permeability. It is well described within BCS that compounds which are highly water soluble and membrane permeable will be highly bioavailable in the blood (Benet, 2013). In opposite, compounds of low solubility and permeability generally have low bioavailability. Both water solubility and membrane permeability depend upon the third physiochemical property – lipophilicity which is usually represented by n-octanol/water partition coefficient log*P*. In general, the aqueous solubility of a compound decreases and its permeability increases with increasing log*P* value.

In the last two decades, numerous rules in terms of physicochemical properties and/or simple structural properties have been set up in order to estimate potential of novel compounds to have adequate, drug-like ADME profile. The corresponding molecular properties are simple conceptually and also computationally. Thus, they have been widely accepted with medicinal chemistry community for filtering out compounds which are likely to be non-bioavailable and nondrug-like. Herein, we have applied the three sets of rules for estimation of drug-likeness of herbicides: four Lipinski's rules of five, two Veber's rules and a set of Muegge's pharmacophore rules (Lipinski et al., 2001; Veber et al., 2002; Muegge et al., 2001).

So far, analyses of physicochemical properties and simple structural features have been performed several times for herbicides. Their aim was mainly to reveal rules for herbicide-likeness in analogy with the drug-likeness concept. Property profiles for herbicides found in this study are consistent with those reported previously. In difference to previous study focused on the examination of potential usage of herbicides in development of new medicines (Delaney et al., 2006), we compared commercial herbicides with approved small drug molecules downloaded from DrugBank.

The Lipinski rule of 5 (*LR5*) has been widely used in the early phase of virtual screening for filtering out compounds which are likely to be poorly permeable through membrane of the gastrointestinal (GI) tract (Lipinski et al., 2001). The *LR5* was set up by exploration of the Pfizer experimental data collected for drugs. According to the *LR5*, small molecular weight compound which is orally bioavailable, that is present in the blood when it is orally administrated, may violate at most one of the following rules: i) number of *HBD* atoms (OH, NH) is less than or equal to (≤) 5; (ii) number of *HBA* atoms (O,N) is ≤ 10; (iii) *MW* ≤ 500 and (iv) the calculated log*P* value *clogP* ≤ 5. The 99% of all herbicides satisfy *LR5*. Only one of the rules is not met by 41 compounds. The most broken rule is the *HBA* one which is not satisfied by 36 herbicides (Fig. 1). At most two *HBD* atoms, the *clogP* value at most 5 and *MW* as highest as 500 have 94.9%, 99.2% and 98.6% of herbicides, respectively (Table 1). For comparison, 89.6% of drugs satisfy at least three *LR5* rules. Around 14% drugs which do not fit with *LR5*, are generally large molecules with *MW* greater than 500 and more than ten *HBA* O or N atoms. Most of these outliers are natural or semisynhetic derivatives such as macrolactones, macrolactames or steroids.

Table 1 Proportions (%) of herbicides and drugs having specific structural and physicochemical properties defining *LR5* (L), Veber's (V) and Muegge's (M) sets of rules for drug-likeness.

Rule	Herbicides	Drugs
***HBA* (O, N) ≤ 10** [L,M]	92.9	90.3
***HBD* (OH, NH) ≤ 5** [L,M]	100	95.3
***MW* ≤ 500** [L] **(200 ≤ *MW* ≤ 600)**[,M]	98.6 (90.4)	88.3 (79.5)
***clogP* ≤ 5**[L]	99.2	97.2
***TPSA* ≤ 140 Å^2** [V] **(150 Å^2)**[M]	90.6 (93.5)	85.0 (87.0)
***RB* ≤ 10** [V] **(≤ 15)** [M]	98.2 (100)	89.6 (97.2)
C-atoms > 4 [M]	97.2	97.7
Heteroatoms > 1 [M]	99.4	96.9
Rings ≤ 7 [M]	100	98.7

The Veber's rules have been discovered by using *in vivo* data collected within GlaxoSmithKline (Veber et al., 2002). Reduced molecular flexibility as measured by the number of rotatable bonds (*RB*) and low polarity as described by total polar surface area (*TPSA*), are found to be important criteria of good oral bioavailability. Reduced *TPSA* correlates better with increased permeation rate, while increased *RB* count has a negative effect on the permeation rate. According to Veber's rules, a compound with $RB \leq 10$ and $TPSA \leq 140$ Å^2 or equivalently 12 or fewer *HBD* and *HBA*, may be expected to be well absorbed or permeable from the GI tract when it is administrated *per os* (Veber et al., 2002). These rules are not met by 10.8% of herbicides of which many (87.3%) have $TPSA > 140$ Å^2 (Fig. 2). The 3/4 of all herbicides has $TPSA \leq 100$ Å^2 (Fig. 2). For comparison, 21.5% of drugs do not satisfy the two criteria (Table 1). The calculated *TPSA* (Ertl et al., 2000) is correlated closely with the total hydrogen bond (HB) count, the sum of *HBD* and *HBA*. For the herbicide data set, the correlation coefficient *r* is 0.911 and for the drug set *r* is 0.945. For herbicides 6.7% /10.6% compounds have total HB count greater than 12/11, while for drugs the corresponding values are considerably higher 13.5%/20.0%.

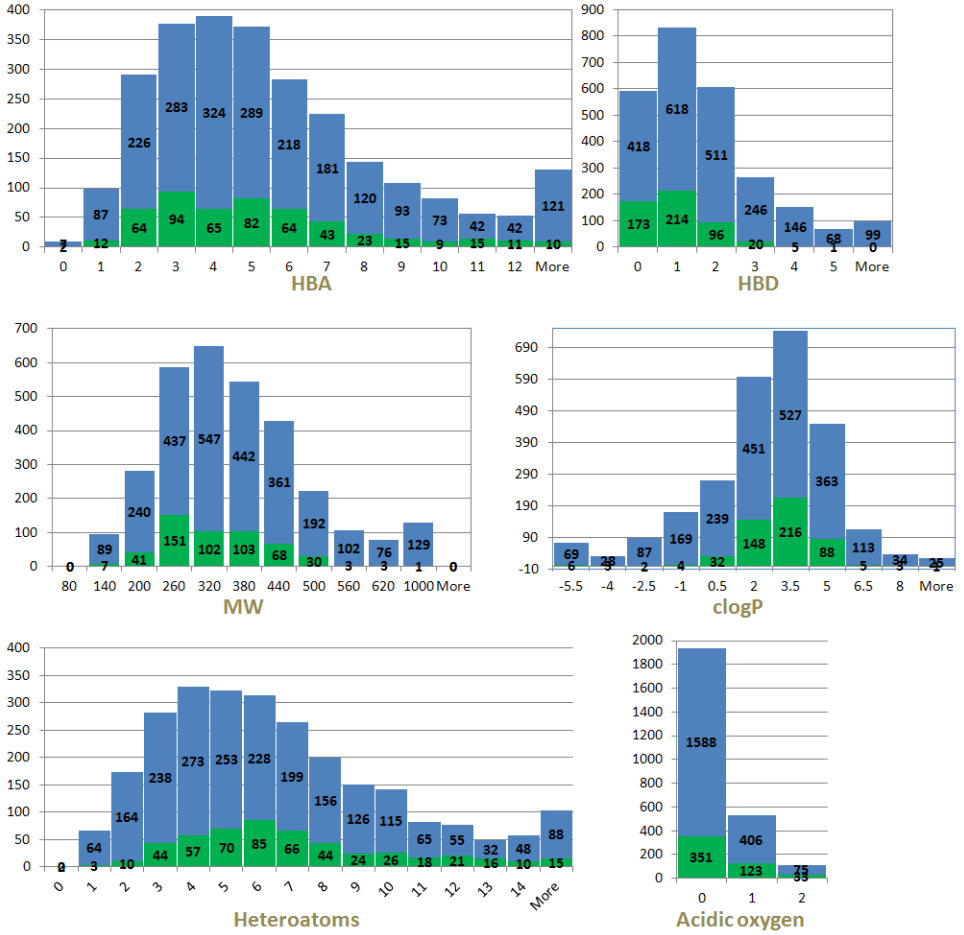

Fig. 1 Distribution of structural parameters (numbers of hydrogen bond acceptors (HBA) and donors (HBD), heteroatoms as well as acidic oxygen atoms, and of molecular weight (MW)) in data sets of herbicides (green) and drugs (blue). Numbers of compounds within each bin are denoted.

Hence, most of herbicides pass through the *LR5* and Veber's filters which are regularly applied in the drug discovery for eliminating non-bioavailable compounds. From this aspect, most of these phytotoxic molecules are probable to pass human GI tract and enter the blood which may distributes them throughout the body to the place where they may exert either beneficial or adverse action.

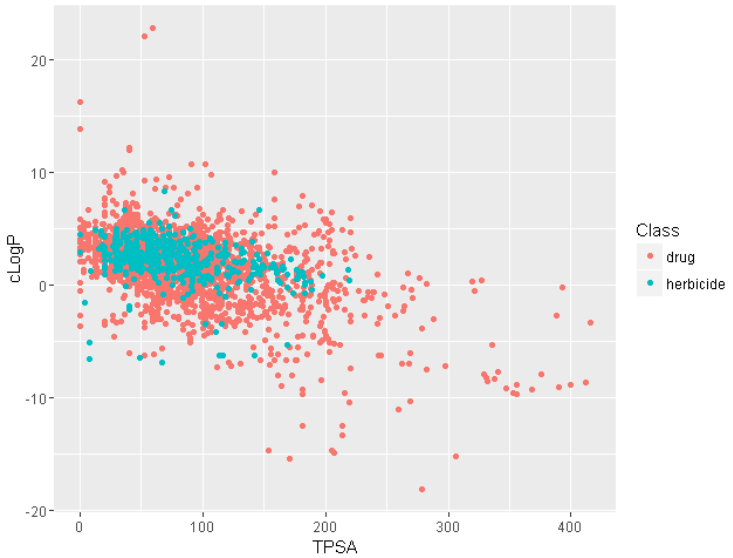

Fig. 2 Distribution of herbicides (cyan) and drugs (red) within physicochemical space defined by calculated parameters *clogP* and *TPSA*.

Muegge's filter is developed by Bayer's scientists by comparing simple structural and physicochemical properties of non-drugs from the database ACD (Available Chemicals Directory) with drugs represented by the CMC (Comprehensive Medicinal Chemistry) and the MDDR (MACCS-II Drug Data Report) databases (Muegge et al., 2001). It is a pharmacophore-like filter developed for the classification of small *MW* molecules as drug-like or nondrug-like. To be classified as a drug-like, a compound should possess a minimum count of drug-like pharmacophore points defined through simple structural rules (Table 1). By applying this filter (Daina et al., 2017), around 93% of herbicides and "only" 80% of the drugs are classified as drug-like molecules (Table 1).

According to the three filters commonly used for elimination of non-drug-like molecules from pipeline, herbicides are drug-like compounds. They are highly probable to exert activity on humans. However, there are some differences in the optimal properties for herbicides and drugs. The most significant difference identified between drugs and herbicides is the lower numbers of *HBD* atom allowed in the latter cases (Fig. 1) (Tice, 2001; Delaney et al., 2006). More than 3/4 of these agrochemicals have no or at most one *HBD* atom OH or NH while the allowed number of *HBA* atoms O or N are considerably higher (Fig. 1). In herbicides, there is a clear bias towards heteroatoms (Clarke et al., 2003). Almost all herbicides contain at

least one N or O atoms as well as other heteroatoms mostly sulphur and/or halogen atoms. There are different classes of herbicides which contain specific heteroatomic groups and/or heterocycles like phenoxy acids, carbamates, dinitroanilines, triazines, triazoles, ureas, sulfonylureas and organophosphorous herbicides. A lower carbon to heteroatom balance in the case of herbicides may be required to achieve acceptable aqueous solubility and lipophilicity for uptake and movement in plants.

Herbicide-likeness

Herbicides differentiate from drugs also in lipophilicity and polarity profiles. Almost 3/4 of herbicides have *TPSA* and *clogP* values within the relatively narrow ranges 20 $Å^2$ < *TPSA* ≤ 100 $Å^2$ and 0.5 < *clogP* ≤ 3.5, respectively (Fig. 2) (Tice , 2002). In comparison, 1/3 of these properties are met by the drugs. Furthermore, 95.0% of herbicides have *clogP* values ranging from 0.5 to 5 (Fig. 1) in difference to drugs whose lipophilicity coefficient *clogP* spans wider range from very hydrophilic compounds with *clogP* < -5 to highly lipophilic molecules with *clogP* > 5 (Fig. 2).

Furthermore, while drugs are mainly neutral or basic molecules, herbicides are primarily neutral or acidic molecules (Fig. 3). Around 30% of herbicides are negatively charged (Fig. 3) (Clarke et al., 2003). Poor bioavailability is likely only for anions with the polar surface area exceeding 75 $Å^2$ (Martin, 2005). For almost half of anionic herbicides *TPSA* is < 75 $Å^2$, and thus these herbicidal acids may be reasonable starting points for drugs (Delaney et al., 2006).

A charge of a compound considerably influences its distribution properties, either in the case of herbicides or drugs (Trapp, 2009). Anionic character is a desirable herbicidal property for phloem mobility. Phloem transportation is increased by ion trapping when dissociable acid groups are introduced into the molecule. The herbicides are distributed throughout plants from their leaves or roots by plant vascular tissues phloem and xylem (Trapp, 2009). Phloem serves for bidirectional translocation of food and nutrients from leaves to storage organs and growing parts of plant. Xylem has a cell wall built of water resistant lignins and transports water and mineral in one direction from roots up the plant's stem to aerial parts of the plant.

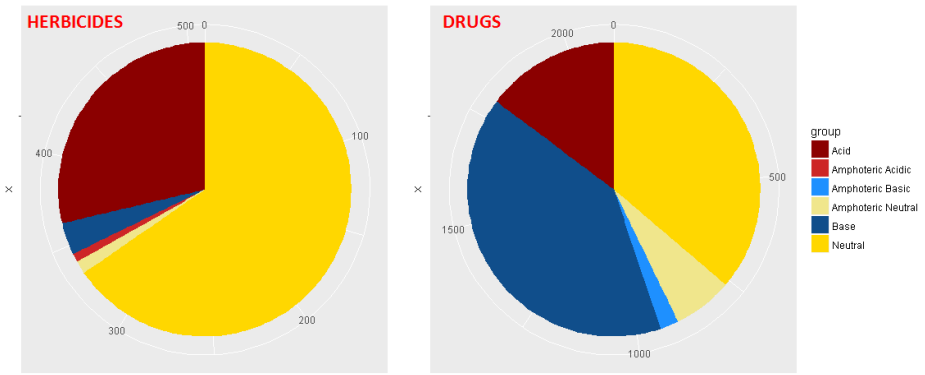

Fig. 3 Distributions of herbicides and drugs with regard to their net molecular charge. Acids and amphoteric acidic compounds have negative net charge, while bases and amphoteric basic molecules have positive net charge. The net charge of neutral molecules and zwitter ions is zero.

Toxicity

Herbicides are toxic agrochemicals, which are used to fight against the existence of weeds in farms and gardens. Hence, we also evaluated their toxicity for humans. The toxicity of herbicides and drugs are evaluated by using classification models for mutagenic, tumorigenic and irritating effects as well as reproductive toxicity. The models are based on presence of specific structural motifs within a molecule (von Korff et al., 2006). As expected, drugs are predicted to be much less hazardous as compared with herbicides (Fig. 4). Almost half of herbicides are estimated to have mutagenic activity and reproductive toxicity. The toxic effects are significantly associated with decreasing of *TPSA*.

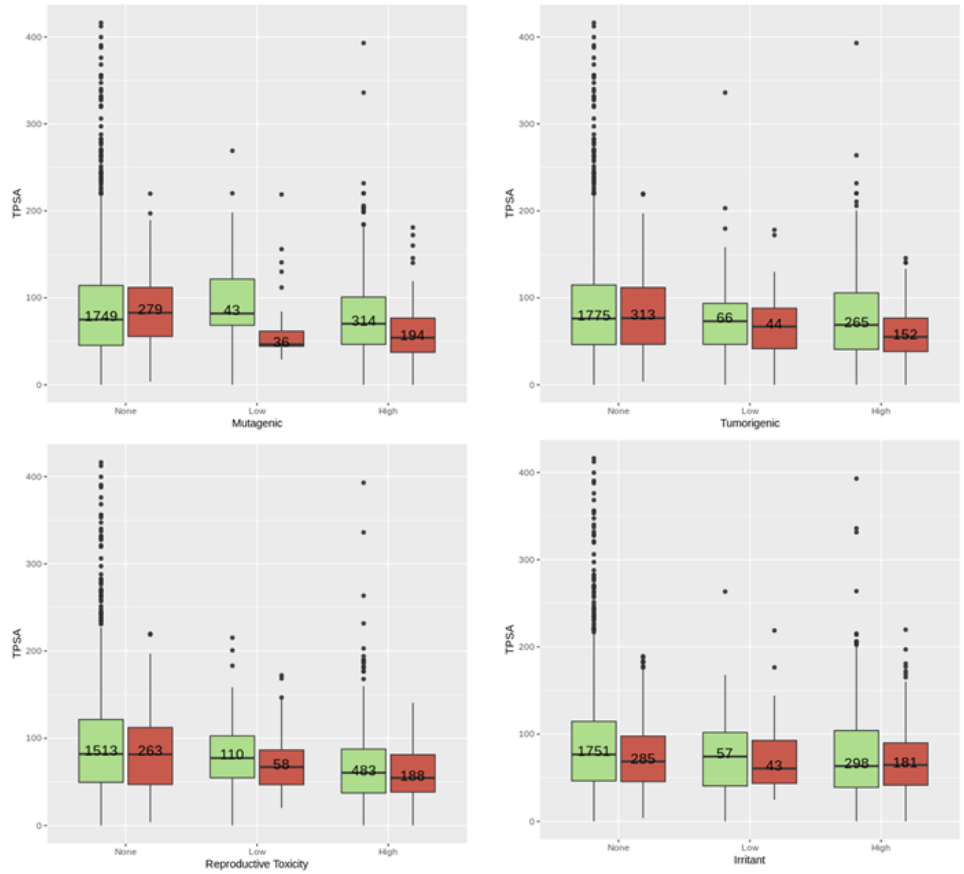

Fig. 4 Dependence of four types of toxicity - mutagenic, tumorigenic and irritating effects as well as reproductive toxicity, upon *TPSA* for herbicides (red) and drugs (green).

Conclusions

The data set of herbicides has been compared *in silico* with the data set of approved drugs downloaded from DrugBank, from the aspects of drug-likeness, herbicide-likeness and toxicity. The three sets of rules which have been developed for the purpose of discriminating between drug-like and nondrug-like molecules within the high-throughput screening (HTS) approach, were applied. According to Lipinski rule of 5, Veber's rules and Muegge's filter, 99%, 89% and 93% of herbicides, respectively, are classified as drug-like molecules what is significantly higher than the corresponding proportions of already approved drugs, 89.6%, 78.5% and 80%, respectively. Although herbicides are drug-like, their properties span specific herbicide-

like ranges. Most herbicides are neutral or negatively charged species. They have no or one *HBD* atom, low C-atom to heteroatom ratio and *clogP* and *TPSA* within the lead-like ranges 0.5-3.5 and 20-100 $Å^2$, respectively. Hence, a set of synthetic accessible herbicides correspond to a reasonable chemical library for either *in vitro* or *in silico* HTS. A chance that some of herbicides will be identified as lead molecules is quite high. However, the serious issue that may raised is toxicity.

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