Supplementary material

A simple model to solve complex drug toxicity problem

Vaibhav Anil Dixit

Department of Pharmacy, Birla Institute of Technology and Sciences Pilani (BITS Pilani),

VidyaVihar Campus, street number 41, Pilani, 333031, Rajasthan. India.

Phone No. +91 1596 255652, Mob. No. +91-7709129400,

Email: vaibhav.dixit@pilani.bits-pilani.ac.in, vaibhavadixit@gmail.com

Table of Contents

List of tables

DTI values for different WHO ATC drug classes

Single parameter one-way ANOVA test was run on the data for 13 WHO ATC drug categories to understand the variations in the physicochemical, PD, PK parameters, their contributions to DTI or DTI between different drug groups. As seen in Table S1, except the OBA, IC50 at the target, and contributions of log D and IC50 at CYP450 to DTI, all the parameters considered were significantly (P = 0.05) different among these groups. These results thus can be used to identify properties which differentiate withdrawn drugs from other drug categories.

Table S1. One-way (single factor) ANOVA for different physicochemical, PD, PK parameters, their contributions to DTI or DTI used to differentiate between the groups. F (critical) = 1.77

Parameter	**F value**	**P (0.05) value**
Dose	10.28	8.01E-19
Molecular weight	15.21	1.14E-28
Molar dose	6.00	4.99E-10
Oral bioavailability	1.22	0.264139
IC50 at the target	0.47	0.932922
Free Cmax	3.75	1.56E-05
PPB (fraction unbound)	4.95	6.78E-08
ACD log D (pH = 7.4)	7.29	1.09E-12
ACD log P	3.25	0.000141
LEI	5.13	2.94E-08
PTI (Pharmacodynamic-IC50, contribution to DTI)	3.98	5.58E-06
CTI (Pharmacokinetic-Cmax contribution to DTI)	3.01	0.000395
Log D-TI (log D contribution to DTI)	0.92	0.528790
DTI (using log D)	11.76	8.20E-22

The IC50 values at the target are not statistically different among different groups and as recommended by others should not be used alone to evaluate the relative potency of different drug candidates.(*1-3*) Thus using a functional form of IC50 to predict toxicity potential (Equation 1 and Equation 4, in main manuscript) is more effective than IC50 itself. To gain further insight into the origin of these differences pairwise T-test analysis was performed among these 13 WHO ATC drug groups. These results can be used to understand the variation of individual parameters among various pairs of WHO ATC classes of drugs. The average values of classical physicochemical parameters like log D, log P, and dose (mg) are similar among many drug group (only 49, 35, and 55 % of the 78 pairs are statistically different, see SI Table S13-27). Molar dose is different among 49.4 % of pairs. Using molecular weight one can differentiate 63.5 % of pairs. Average DTI (using log D) values for 63.5 % of the WHO ATC drug category pairs are different and additionally give the chance for understanding the PK, PD and physicochemical factors responsible for the differences among different drug groups. Kim

et al. have reviewed methods for comparing the efficacy of various drugs used for the same indication.(*4*) Studies comparing the efficacy and safety of drugs across different therapeutic areas are rare.

Failure to distinguish withdrawn drugs from the antiparasitic and blood categories may reflect the inherent toxicities of these drugs. But considering the small number of drugs (11 and 15 respectively) a larger dataset is required for further validation. Similarly for the systemic and hormonal category, the results should be interpreted with caution (n = 11). Many drugs from the musculoskeletal category are NSAIDs, have GIT and cardiovascular side effects. DTI captures similar toxicity profile since values for withdrawn and musculoskeletal category are not statistically different (P = 0.0886). Only four other drug classes (CNS, antiviral, cardiovascular and antineoplastic) have statistically different LEI values from the withdrawn drugs, while CNS drugs have avg LEI values statistically different from nine other categories (see SI, Table S13-27). Although, molecular weight gives statistically significant differences among withdrawn and ten other drug classes, it cannot be directly used to gain further insights into the cause of toxicity. Whereas DTI is a logarithmic sum of toxicity contributions and can be used to get mechanistic insights into the toxicity profiles (discussed below).

Interestingly, antibiotics tend to have lower PPB (avg = 0.56), ACD log D (avg = -0.06) which are statistically different from 12 and 11 other WHO ATC categories respectively. GentioUrinary and Sex category drugs have high avg PPB (0.93), and are different from nine other categories (see SI, Table S13-27). Since WHO ATC classification puts Cobicistat in the "various" category, it was not considered in this analysis.

Identifying potentially toxic and relatively safer drugs

The antibiotic class of drugs show a wider range of DTI values (max = 3.20, avg. = 1.24, min = -1.12). Hypersensitivity and hepatotoxicity with the use of Ampicillin (DTI = 3.20) although rare is well established in the literature giving it a likelihood score C.(*5*) Voriconazole (DTI = 3.04), although an effective antifungal agent in immunocompromised patients, is an established cause of liver injury, serum enzyme elevations, neurological, and visual toxicity.(*6*) Moxifloxacin (DTI = 1.28) has shown comparatively lower rates of enzyme elevations and toxicity, but is black-boxed for tendinitis and neuropathy.(reference (*5*) and FDA approval package) Erythromycin (DTI = 1.16) has low incidence of hepatotoxicity, but cases are well established with all formulations giving it a likelihood score of A. Azithromycin (DTI = -0.08), has very low incidence of liver injury, but is given a score of A mostly due to a long history of usage leading to > 50 reported case series. Since antibiotics are administered at larger doses (avg MD = 2.35 for drugs considered in this study) compared to other classes of approved drugs (avg MD = 0.92), they are expected to have a higher likelihood or incidence of toxicities.

Alimentary Tract and Metabolism category of drugs have DTI values max = 2.48, avg = 0.33 and min = -1.01). Aprepitant (DTI = 2.48), although initially not detected(*7*) has now been found to cause drug-drug interactions leading to toxicity during anticancer therapy.(*8*) Lansoprazole (DTI = 0.39) has consistently shown lower rates of liver toxicity.(*5*) Eluxadoline with lowest DTI in this class is rarely associated with serum enzyme elevations and only in patients without gallbladder.(*5, 9*) For this category a DTI cut off of 1.0 gave sensitivity = 0.77, specificity 0.44, accuracy = 0.72 and MCC = 0.18, thus suggesting respectable prediction of clinical toxicity and efficacy data.

Drugs from the Nervous System (CNS) category have DTI max = 3.43, avg = 0.39, and min = -1.78, values. Ethosuximide with largest DTI value has low off target toxicity, but has potential to cause common and some rare adverse drug reactions related to primary mechanism of action i.e. PD on target toxicities.(*10*) This is captured by its PK and PD contributions to DTI. Amantadine (DTI = 0.40), has not been found liver toxic and is associated with nervous system side effects only in patients with kidney failure who have low clearance, high Cmax values and off target effects.(*11, 12*) Nicotine (lowest DTI value) when used therapeutically has not been associated with liver injury or nervous system side effects and is toxic only in cases of accidental or deliberate overdoses.(*13*)

Gentio-Urinary and Sex category of drugs have DTI max = 3.42, avg = 0.19, and min = -1.29 values. Mifepristone has not been found hepatotoxic(*5*) and is only contraindicated in specific circumstances.(*14*) DTI value of this drug is maximum in this category mostly due to its high potency (IC50 = 0.045 nM) for the target receptor and high lipophilicity. Thus the current formulation of DTI is unable to capture this typical profile of Mifepristone, but unknown off target effects can't be completely ruled out. Danazol (DIT = 1.28), is known to cause serum enzyme elevations and liver injury in many cases.(*5*) DTI correctly predicts (via log D contribution to DTI) that this toxicity is mostly attributed to the lipophilic nature of the drug. Solifenacin (DTI = 0.24), is not generally hepatotoxic, but one case has been reported recently.(*15*) Ritodrine (min DTI value) has not been associated with liver injury.(*16*)

Antiviral drugs have DTI max = 3.89, avg = 1.71 and min = -1.55 values. Velpatasvir, with max DTI value, in combination with Sofosbuvir (a prodrug) is suspected to cause liver injury and it has also been reported to cause bradycardia in some patients.(reference (*5*) and EPCLUSA® US-FDA label). Efavirenz (DTI = 1.91) has been associated with serum enzyme elevations in 1-8 % of patients and many cases of liver injury have been recorded.(*5*) It also has weak association with neuronal toxicity.(*17*) Entecavir with the lowest DTI value has not been associated with liver toxicity and the serum enzyme elevations or lactic acidosis seen during treatment are mostly due to the underlying hepatitis B.(*5*)

DTI values max = 2.09, avg = 0.23, and min = -1.33, were observed for drugs from the Respiratory system category. Dyphylline has high DTI value and is predicted to have high toxicity, but limited information is available on this drug. Rupatadine's (DTI = 1.59) potential to cause liver, renal, cardio and genotoxicities at high doses in rodent models hasn't been realized in human since approval in 2012. It has been discontinued in the UK.(*18*) Montelukast (DTI = 0.23) leads to serum enzyme elevations in only 1-2 % of patients and is very rarely associated with liver injury.(*5*) Salbutamol (lowest DTI) is generally safe with no reports of liver injury(*5*) and only rare cases of lactic acidosis with escalated dosage in children.(*19*)

Drugs used for cardiovascular diseases have DTI max = 3.67, avg = 0.39, and min = -2.94. Amiodarone with highest DTI value in this category causes consistent serum enzyme elevations and is a well-known to have liver (categorized A) and pulmonary toxicity.(*5, 20*) Timolol with a DTI value of 0.39, causes only mild serum enzyme elevations in up to 1 % of patients and clinical apparent liver injury is not yet known.(*5*) Atorvastatin (DTI = 0.07) also has very low incidence of liver injury, but due to extensive use and > 50 reported cases of rare hepatotoxicity, it is categorized A by LiverTox database.(*5*) Moxonidine has the lowest DTI value in this category and appears to be safe for the recommended indications mostly due to limited metabolism,(*21*) but limited data exists to thoroughly verify these claims. Withdrawn drugs from this category have higher avg DTI value (1.19) than approved drugs. With a DTI cut off of 1, cardiovascular drugs are correctly predicted safe with a sensitivity = 0.74, specificity = 0.63, accuracy = 0.72 and MCC = 0.26.

Drugs from the antineoplastic category have DTI values max = 2.94, avg = 1.09, min = -1.24. Lapatinib with max DTI value has been associated with serum enzyme elevations in up to 15 % of patients and clinically apparent liver injury has been documented in many cases. From the PD (on/off target), PK and physicochemical contributions to DTI, it appears that toxicity is a combination of all these factors. Acalabrutinib (DTI = 1.10), a newly introduced kinase inhibitor, has FDA-label warning for haemorrhage and secondary infections. DTI prediction suggests a chance for toxicity and drug interactions. Topotecan with lowest DTI value has been associated with mild serum enzyme elevations, but rarely to liver injury. Its use may have bone marrow toxicity at recommended doses which can be controlled with dosage adjustments.(*22*)

Horizontal view of DTI applications in drug discovery process.

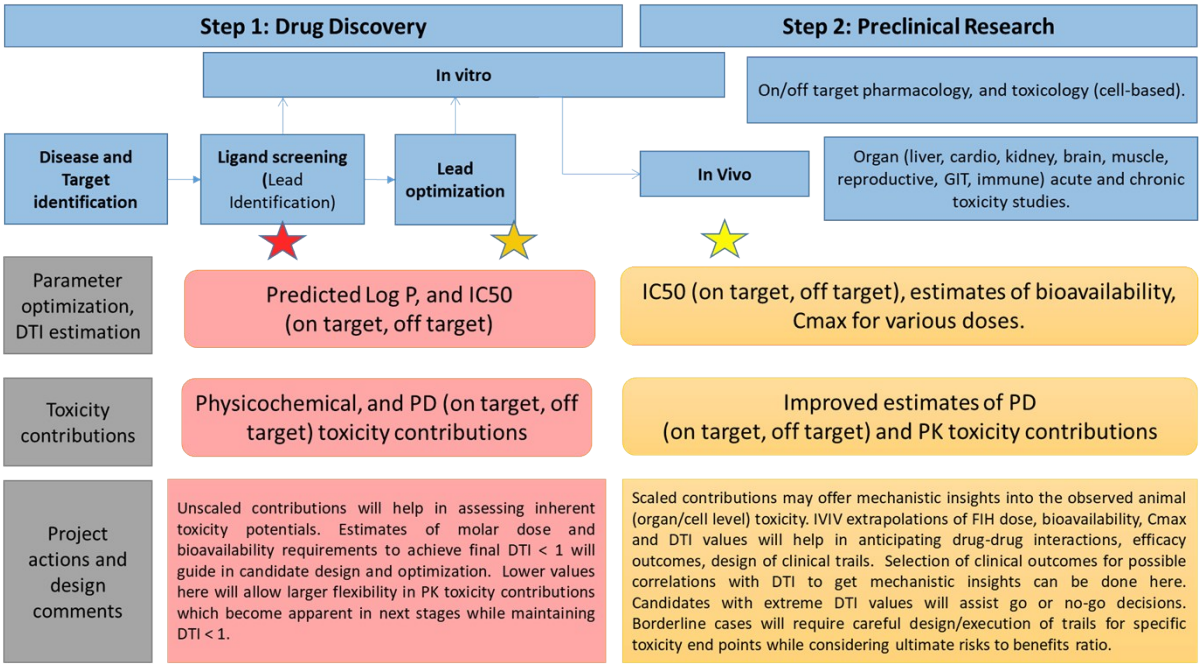

Figure S1. Application of different toxicity contributions and DTI during early drug discovery phases and preclinical research.

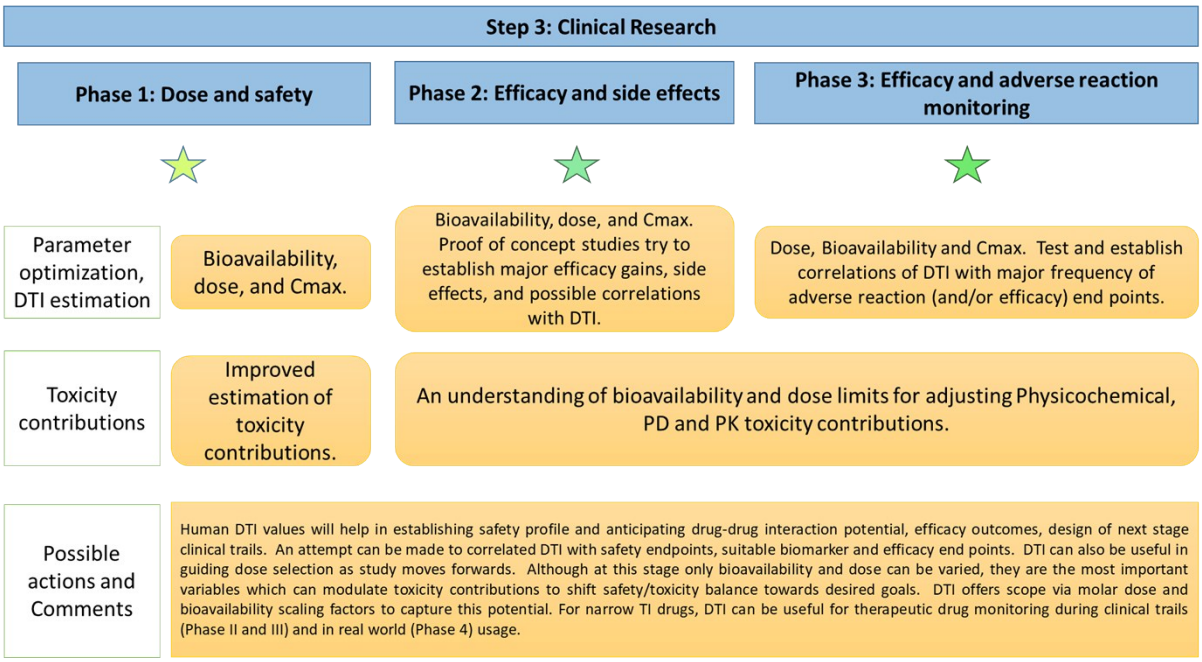

Figure S2. Application of toxicity contributions and DTI during clinical research.

Methods

Data collection

Names of the small molecule approved drugs were identified from the Drug Bank (version 5.0.11).(*23*) The names of the withdrawn small molecule drugs were collected from Onakpoya et al.(*24*) Different salts and esters were considered as one molecular entity or drug. Ester prodrugs and other prodrugs were excluded from the analysis unless a clear information on the pharmacological activity of prodrug and reliable prodrug plasma concentration values could be identified in the literature. When available the data on IC50 for on and off-targets, MIC (for antibiotic class of drugs), Ki (converted into IC50, assuming an reversible binding and IC50 = 2 * Ki)(*25*) molecular weight, ACD logD (pH = 7.4), ACD logP, absolute oral bioavailability, fraction bound to plasma proteins, mechanism of action for orally administered drugs (approved, and withdrawn) was collected from three main databases namely ChEMBL(*26*), PUBCHEM(*27*), and Drug Bank.(*23, 28*) The drug list on Drug Bank website was search using WHO ATC drug categories and drug name, smiles pattern, absolute oral bioavailability, percentage protein binding (converted into fraction) were extracted, while mechanism of action and approval status were noted. Based on this information the molecular weight, heavy atom count, IC50 values for on target and off target (CYP450s: 3A4, 2C9/2C19, 2C8, 2E, 1A2/1A1 and 2D6; hERG, BSEP) proteins, ACD log D (pH = 7.4) and ACD log P values were extracted from ChEMBL database. A selection criterion based on the confidence-score was applied to IC50 values reported in ChEMBL database. Thus the lowest reported IC50 values were selected only when their confidence score was 9, 8 or 7. This was done to ensure that the IC50 value corresponds to either a direct single protein, homologous single protein or direct protein complex subunit assignment respectively. The lowest IC50 value with the highest available confidence score (9, 8 or 7) were selected for analysis i.e. when IC50 value with confidence score 9 was available (in ChEMBL), it was selected even if the values with confidence score 8 or 7 were lower. Since the MIC values are associated with a confidence score of 1, the lowest values against the most susceptible microorganism was selected for analysis. Absolute oral bioavailability, IC50/MIC, and percentage protein binding when not available in the Drug Bank, ChEMBL, PubChem databases, were searched in the US-FDA drug approval packages (available on the FDA's access data website https://www.accessdata.fda.gov/scripts/cder/daf/), other scientific literature including the textbook "Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th edition.(*29*) Since these sources are already peer-reviewed and considered reliable, lowest values IC50/MIC, and average values for other parameters were used for analysis. Dose values (mg) were selected for which corresponding Cmax values were available from either Drug Bank, scientific literature, US-FDA drug approval packages or Goodman and Gilman's textbook.(*29*) In rare cases when absolute oral bioavailability data was not available, relative bioavailability or absolute oral bioavailability values for

appropriate animal species were taken from US-FDA drug approval packages or estimated from renal excretion data. ChEMBL, DRUGBANK IDs, and links to all the references used in data collection for all the drugs considered in this work are given in the supporting information (excel files) along with additional comments about data points when appropriate. Information (as comments) about the toxicity (liver and others) of these drugs, when available on the LiverTox website,(*5*) scientific literature and US-FDA approval packages, has been included.

Absolute oral bioavailability (OBA) estimation is not always possible. Thus use of predictions from physicochemical, animal or in vitro data is required. These methods are known introduce an unpredictable error.(30) OBA for Probenecid, Rifaximin, Gliclazide, Osimertinib, Brigatinib, Ibrutinib, Vandetanib, and Alitretinoin, was estimated from the renal excretion, OBA for Nitazoxanide, Sulfadoxine, Rifapentine, Etravirine, Tipiracil, Regorafenib, was relative to another formulation, for Cinnarizine, Pimozide, Promazine, Bupropion, Cyclofenil, Celecoxib, Bithionol, Progesterone, Lopinavir, Telaprevir, Dolutegravir, Lumacaftor, Dyphylline, Cilostazol, Ambrisentan, Neratinib, and Lapatinib, OBA data was unconfirmed estimates, for Trimipramine, and Clioquinol, OBA data was based on small number of subjects, while for Artemether, Posaconazole, Bedaquiline, Ethosuximide, Cytisine, Levamisole, Alpidem, Rimantadine, Voxilaprevir, Ledipasvir, Rilpivirine, Glecaprevir, Pleconaril, Dextromethorphan, Ibudilast, Desloratadine, Fenofibric acid, Ribociclib, Ceritinib, Ponatinib, Olaparib, Idelalisib, Afatinib, Vemurafenib, Enzalutamide, and Venetoclax, animal OBA was used.

Using this methodology 2,656 drugs were searched in the Drug Bank and considered for inclusion in the analysis. Out of these only 711 drugs were finally selected for data collection and analysis. The reasons for dropping other drugs were any one of the following; unavailability of IC50, pharmacokinetic (oral bioavailability, Cmax or PPB) data, non-oral route of administration, drug being a prodrug, protein, polymer, polynucleotide, vitamin, nutrient, vaccine, a cell-based therapy or not included in the drug list by both US-FDA and WHO ATC. Thus the total number of drugs not considered for analysis was 1945 (withdrawn: 107, approved: 1499, non US-FDA and WHO ATC 339).

Data analysis

The PK, PD and physicochemical data collected was used to estimate “Drug Toxicity Index” (DTI) values. The data was collected for different drugs was categorized based on their approval status and WHO ATC therapeutic area classification system. WHO website (https://www.whocc.no/atc_ddd_methodology/purpose_of_the_atc_ddd_system/) gives a disclaimer mentioning that the ATC/DDD system is not intended to imply relative efficacy of these drugs. Nevertheless, study of trends or relationships between different therapeutic areas and drug

toxicity may prove useful in gaining a deeper understanding into drug safety and in respective drug discovery programs.

Thus the data was collected for a total of 711 drugs belonging to the following WHO ATC drug categories, Alimentary Tract And Metabolism (A, 48), Blood and Blood Forming Organs (B, 15, referred as Blood), Cardiovascular System (C, 111), Genito Urinary System and Sex Hormones (G, 40), Systemic Hormonal Preparations: Excluding Sex Hormones and Insulins (H, 11), Antiinfectives for Systemic Use (J, 50, referred as antibiotics), Antivirals for Systemic Use (J05, 41, referred as antivirals), Antineoplastic and Immunomodulating Agents (L, 68, referred as anticancer), Musculo-Skeletal System (M, 38), Nervous System (N, 154, referred as CNS), Antiparasitic Products, Insecticides And Repellents (P, 11), and Respiratory System (R, 36). The antiviral class of drugs were considered as a separate class since IC50 value for the biological target were mostly available from the sources cited above, while for the antibiotic class of drugs IC50 values at the target were rarely available in the literature. Drugs withdrawn due to hepatotoxicity/ADR, or withdrawn due to other organ or pharmacological toxicities were included in the "Withdrawn" category and their WHO ATC classification was also noted. Only 88 drugs from the 462 withdrawn medicinal products discussed by Onakpoya et al.(*24*) were considered for analysis as data for the remaining molecules was not available in the public domain.

Free Cmax concentrations were calculated from the fraction of the drug unbound (fu) to plasma proteins (fu = 1-fb, where fb is the fraction bound to plasma proteins) using the formula, Free Cmax = Cmax * fu. The inhibitory potential of a small molecule drug towards different CYP450 isoforms is considered an important factor in the efficacy and safety profiles.(31) Although candidates with low (< 0.1 μM) IC50 value at a given CYP450 isoform are generally avoided in drug development, a low IC50 value need not necessarily translate into a high potential for drug-drug interaction and toxicity. This is mainly because, that particular CYP450 isoform may not play a major role in the metabolism and disposition of other drugs under consideration, the concentration of the CYP450 protein or the activity of the CYP450 isoform may compensate for the partial inhibition, the dose of the inhibiting drug may not be high enough to reach IC50 values in plasma/liver.(32) Thus the IC50 values and their contributions to toxicity should be scaled by a factor which can account for these effects. Many experimental studies have established the utility of using the relative protein content, or relative activity factor in estimating the relative contribution of various CYP450 isoforms towards to overall metabolic profile observed in Human Liver Microsomal (HLM) and in vivo studies.(33-35) Most of these studies have found the RAF and relative abundance methods nearly equivalent. The RAF values are known for a smaller set of CYP450 isoforms, whereas relative abundances for the major drug metabolizing CYP450 isoforms are known in the literature. Thus a consensus CYP450 IC50 value

calculated by scaling the individual IC50 values for major CYP450 isoforms by their corresponding relative abundances and then taking the average of non-zero values. Therefore, if IC50 values for only two CYP450 isoforms are non-zero, then these values are scaled by the corresponding relative abundances and the sum is divided by two to get the consensus IC50 value. The relative abundances used in this work are; CYP450 3A4 (0.39), 2C9/19 (0.25), 2C8 (0.07), 2E (0.18), 1A1 (0.019). In the case of CYP450 2C family, when values for both isoforms (2C9 and 2C19) were available the average of the minimum reported values was considered and then scaled by 0.25. The individual IC50 values for other CYP450 isoforms were collected for each drug according the same protocol discussed above for on target IC50 values.

Drug toxicity index (DTI) was calculated using the empirically derived Equation 4 which accounts for the non-linear relationship of drug toxicity with IC50 (on/off-target), Cmax and log D values. The individual toxicity contributions were scaled by dose and absolute oral bioavailability since these factors are known to affect the efficacy and toxicity potential of majority of the orally administered drugs.(36, 37) The use of molar dose unit in clinical practice has been discussed earlier and has some advantages over the mass dose units.(38) Thus the molar dose was considered instead of mass dose to scale the DTI contributions.

Equation 4. Drug Toxicity Index (DTI) as the logarithmic sum of physicochemical, pharmacokinetic and pharmacodynamic contributions to toxicity scaled by absolute oral bioavailability (OBA), and molar dose (MD). Here, X_t is potency (IC50 or MIC) at the target protein, Cmax is the maximum unbound (free Cmax) plasma drug concentration, X_{ot} is binding affinity at the off-target receptors/proteins (CYP450 isoforms, hERG channel and BSEP transporter), and log D is the ACD log D at pH = 7.4. PD, PK contributions to DTI are defined only when Xt, Cmax and Xot are greater than zero. When these terms are zero or cannot be measured due to experimental limitations, their contributions to DTI are undefined and considered zero.

$$DTI = \log\left(OBA * MD\left[\left(\frac{{x_t}^2 + 1}{10 * x_t}\right) + \left(\frac{{C_{max}}^2 + 1}{10 * C_{max}}\right) + \left(\frac{e^{-x_{ot}} * \sqrt{x_{ot}} + 10}{\sqrt{x_{ot}}}\right)\right] + [OBA * MI \right)$$

Table S2. Comparison of Drug Toxicity Index (DTI) values with the clinical risk of gastrointestinal complications from using NSAIDs (relative to Ibuprofen). Only drugs for which DTI values could be calculated are considered here.

Drug	Case-control studies(39)	DTI values
Ibuprofen	1.0	0.24
Fenoprofen	1.6	0.37
Diclofenac	1.8	-0.04*
Sulindac	2.1	0.32
Naproxen	2.2	0.72
Indomethacin	2.4	0.46
Tolmetin	3.0	0.71

Piroxicam	3.8	-0.31
Ketoprofen	4.2	0.83
*Inclusion of IC50 value for COX-1 and corresponding PD contribution to DTI gives a DTI value of 0.84.		

Table S3. Comparison of Drug Toxicity Index (DTI) values with the adverse effects (relative to Ciprofloxacin). Only drugs for which DTI values could be calculated and included in the network meta-analysis given in reference(40) are considered here.

Drug/Drug Combination	Adverse effects	DTI
Ciprofloxacin	1.00	0.97
Norfloxacin	1.53	1.68
Amoxicillin–Clavulanate	1.55	1.14
Gatifloxacin	1.16	0.53
Trimethoprim/Sulfamethoxazole	1.42	1.85[a]
[a]DTI for the combination is calculated using the modified formula g12 = g1*MD1*g2*MD2, where g12 is the response to combination, g1 response to drug 1, g2 response to drug 2, MD1 is molar dose for drug 1 and MD2 is the molar dose for drug 2.		

Table S4. Odds ratio (all cause discontinuation) for antipsychotic drugs and their corresponding DTI values. Thirteen drugs for which DTI values could be calculated are included here.

Antipsychotic drugs	All Cause Discontinuation	DTI
Amisulpride	0.43	-0.17
Olanzapine	0.46	0.42
Paliperidone	0.48	-1.31
Risperidone	0.53	-0.44
Aripiprazole	0.61	0.25
Quetiapine	0.61	-0.19
Chlorpromazine	0.65	1.13
Iloperidone	0.69	0.46
Ziprasidone	0.72	1.40
Lurasidone	0.77	1.07
Sertindole	0.78	2.14
Haloperidol	0.80	0.78
Clozapine	0.46	1.69

Additionally, the meta-analysis by Leucht et al., did not estimate QTc prolongation and prolactin increase associated odds ratio of Clozapine. This might have contributed to its relatively low OR for the all-cause discontinuation.(41)

Table S5. Odds ratio (OR) for response, tolerability, and DTI values for different antidepressants. Fluoxetine was considered as reference treatment because of its long history of use and efficacy.

Antidepressant	Response OR	Tolerability OR	DTI
Agomelatine	1.46	0.48	0.85

Duloxetine	1.14	2.23	1.47
Escitalopram	1.33	0.92	-0.03
Fluoxetine	1.00	1.00	1.51
Fluvoxamine	1.23	1.50	0.73
Paroxetine	1.15	1.38	1.84
Sertraline	1.11	0.75	1.26
Trazodone	1.06	1.24	1.12
Venlafaxine	1.45	1.41	0.19

Table S5 shows the OR for the response rate, tolerability and DTI values for 9 (out of 10) antidepressant drugs considered.(42) Tolerability has poor correlation (r = 0.22) with DTI values. Since most of the results for tolerability did not reach statistical significance, as mentioned by the authors in Figure 4 of reference, the poor correlation is not surprising. Duloxetine and Trazodone had lower OR for response rates and correspondingly had larger DTI values. Thus DTI values may be useful in estimating the relative efficacy and response rates of different class of antidepressant drugs.

Table S6. Variation in different biochemical parameters from the use of different type 2 diabetes treatment options and relative risk of side-effects estimated by Mearns et al.(43) using network meta-analysis (NMA), corresponding DTI values and their correlations of DTI values. UTI (urinary tract infections), GTI (genital tract infection), BW (body weight).

Drug vs. Placebo	**NMA Hypoglycemia**	**NMA UTI**	**NMA GTI**	**NMA HbA1c**	**NMA BW**	**NMA Systolic BP**	**DTI**
Alogliptin	0.16	1.06	-	-0.57	0.05	-	0.25
Canagliflozin	0.91	1.25	8.03	-0.72	-2.15	-4.14	1.20
Dapagliflozin	0.97	1.28	2.16	-0.48	-2.17	-4.50	0.60
Empagliflozin	0.51	0.86	6.84	-0.69	-2.08	-5.14	0.55
Glimepiride	4.00	0.89	1.28	-0.73	2.19	0.26	-0.71
Glipizide	11.67	0.55	0.47	-0.55	2.44	0.50	-0.85
Linagliptin	0.46	0.95	0.77	-0.64	-0.04	-1.58	0.53
Pioglitazone	1.28	1.40	-	-0.69	2.06	-2.74	0.45
Saxagliptin	0.88	1.19	-	-0.51	0.06	0.64	1.26
Sitagliptin	1.30	0.96	2.33	-0.64	0.21	0.64	0.29
Vildagliptin	0.75	0.90	-	-0.63	0.04	-3.88	1.72
Gliclazide	10.02	-	-	-0.70	1.19	-	-0.32
Nateglinide	7.19	-	-	-0.48	0.60	-	0.07
Repaglinide	18.92	-	-	-1.08	3.27	-	-0.71
Rosiglitazone	1.01	-	-	-0.75	2.15	-	-0.17
Correlation of DTI with partial data	-0.71	0.51	0.70	0.07	-0.60	-0.51	-
Correlation of DTI with all small molecule drugs considered in reference (43)	-0.68	-	-	0.36	-0.70	-	-

Excluding drugs in Table S5 for which relative risk for UTI, Systolic BP values were not available leads to a minor improvement in the correlation (r = -0.71). Since DTI values are expected to model toxicity effects, it's none and weak correlations with efficacy parameters (HbA1c and Systolic BP respectively) are understandable.

Table S7. Relative efficacy, frequency of adverse effects against placebo and DTI values for PDE5 inhibitors used for treatment of erectile dysfunction.

PDE5 inhibitor	RE	Frequency of Adverse effects	DTI
Sildenafil	0.47	18.42	0.50
Avanafil	0.29	16.44	0.47
Tadalafil	0.38	10.23	-0.09
Udenafil	0.33	11.42	0.23
Vardenafil	0.39	25.11	0.55

As expected relative efficacy data did not correlate with DTI values for PDE5 inhibitors in Table S6 (r = 0.13).

Table S8. DTI values and molar dose (MD) for selected antiretroviral drugs considered in the network meta-analysis by Patel et al.(44)

Antiretroviral drug	DTI	MD
Atazanavir (ATV)	2.89	0.43
Ritonavir (r)	2.10	0.83
Dolutegravir (DTG)	0.64	0.12
Darunavir (DRV)	3.00	0.73
Efavirenz (EFV)	1.90	1.90
Elvitegravir (EVG)	1.21	0.22
Cobicistat (c)	0.05	0.19
Lopinavir (LPV)	2.27	0.64
Raltegravir (RAL)	1.13	0.90
Rilpivirine (RPV)	1.54	0.41

Table S9. Efficacy and safety parameters for various antiretroviral drugs and their combinations compared with Dolutegravir. Combined DTI values are the product of DTI values and MD for the combined drugs. Correlation coefficient between different parameters and DTI values are also given.

Antiretroviral drug (combination)	Viral suppression	CD4+ cell increase	TC	HDL-C increase	LDL-C increase	Triglycerides increase	AE	Discontinuation due to AE	Combined DTI	Drug DTI
ATV/r	0.45	-36.20	11.50	1.73	5.44	12.04	1.72	4.17	2.15	2.89
DRV/r	0.51	-27.19	19.17	1.01	10.67	50.07	0.94	2.22	3.83	3.00
EFV	0.54	-37.94	24.29	5.64	13.50	12.54	1.75	3.85	1.90	1.90
EVG/c	0.65	-21.41	14.24	2.72	6.20	-2.84	1.30	2.63	0.00	1.21
LPV/r	0.38	-26.70	28.69	3.23	10.98	47.86	1.85	4.76	2.53	2.27
RAL	0.77	-3.44	1.78	0.07	1.66	-12.78	0.90	1.15	1.13	1.13
RPV	0.66	-23.33	0.96	0.75	-2.12	8.17	1.27	1.35	1.54	1.54
DTG	1.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00	0.64	0.64
Correlation with combined DTI	-0.66	-0.52	0.52	0.11	0.54	0.86	0.16	0.38		
Correlation with Drug DTI	-0.86	-0.77	0.60	0.26	0.59	0.75	0.42	0.63		

AE = adverse events; ATV/r = atazanavir with ritonavir; DTG = dolutegravir; DRV/r = darunavir with ritonavir; EFV = efavirenz; EVG/c = elvitegravir with cobicistat; FPV/r = fosamprenavir with ritonavir; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LPV/r = lopinavir and ritonavir; NFV = nelfinavir; RAL = raltegravir; RPV = rilpivirine; TC = total cholesterol.

Adverse events (AE) OR did not correlate well with either the combined or individual DTI values. The effect of combination on DTI values is uncertain and good correlation of individual DTI values with toxicity/safety parameters suggests that contribution of Ritonavir and Cobicistat in relative toxicity and efficacy may cancel out.

Table S10. Odds ratio (OR) for different toxicity end points for antithrombotic drugs, their DTI values and correlation coefficient between DTI and different end points. Odds ratios were taken from either the base-case mixed treatment or pairwise meta-analysis of direct evidence reported by Tawfik et al.(45)

Base-case mixed treatment analysis							
Antithrombotic drugs	**All strokes**	**Ischemic stroke**	**Myocardial infraction**	**Overall mortality**	**Major bleeding**	**Intracranial haemorrhage**	**DTI**
Warfarin	1.00	1.00	1.00	1.00	1.00	1.00	-0.17
ASA+C*	1.44	1.87	1.05	1.02	1.16	1.32	2.06
Placebo	2.39	3.75	1.96	1.22	0.57	0.22	0.00
Apixaban	0.82	0.97	0.87	0.89	0.71	0.42	0.34
Rivaroxaban	0.85	0.95	0.82	0.94	1.03	0.65	0.37
Edoxaban	0.89	1.01	0.94	0.92	0.80	0.46	0.76
Correlation with DTI	-0.03	-0.05	-0.24	-0.16	0.56	0.61	
Pairwise meta-analysis of direct evidence							
Antithrombotic drugs	**All strokes**	**Ischemic stroke**	**MI**	**Overall mortality**	**Major bleeding**	**Intracranial haemorrhage**	**DTI**
Warfarin	1.00	1.00	1.00	1.00	1.00	1.00	-0.17
ASA+C*	1.70	2.15	1.57	1.01	1.09	1.92	2.06
Placebo	1.26	1.47	--	0.78	0.39	0.33	0.00[#]
Apixaban	0.79	0.96	0.88	0.90	0.69	0.42	0.34
Rivaroxaban	0.85	0.94	0.82	0.94	1.03	0.67	0.37
Edoxaban	0.88	1.00	0.94	0.92	0.80	0.47	0.76
Correlation with DTI	0.69	0.76	0.86	0.46	0.47	0.77	

*C is Clopidogrel. Since ASA is a prodrug its DTI value was not calculated and thus the DTI value for Clopidogrel is considered for the ASA+C combination without any modification.
[#]DTI value for placebo is not defined by Equation 4 and thus was considered zero.

Dabigatran, a prodrug, was not considered for estimation of DTI. These results are suggestive only since one set of data points was for placebo and another ignored the contribution of the prodrug aspirin (ASA) to the DTI values of the ASA and Clopidogrel combinations

Table S11. Percentage of drugs satisfying different efficiency (LEI, LLE), therapeutic index (TI), dose and physicochemical parameter criteria recently recommended. Comparison of average DTI values against these widely used parameters for lead optimization suggest that DTI criteria of < 1 is better in many cases and equal in others (except antineoplastic and antiviral drugs).

% Drugs satisfying criteria	LEI >0.3	LLE >5	PD on target	PK	Physicochemical LogD	PD off target			DTI <1 or avg	Exposure based TI	TI CYP450	TI hERG	TI BSEP	Dose < 100 mg	log D < 3	log P< 3	RO2	
						CYP450 PD off target contr.	hERG PD off target contr.	BSEP PD off target contr.									log D	log P
Musculoskeletal	58	24	71	89	84	84	95	89	**84**	13	5	5	13	34	97	55	32	26
Antiparasitic	45	18	73	82	91	100	91	82	**55**[a]	0	27	9	27	27	82	73	27	27
Antibiotic	36	54	94	86	80	84	86	76	**54**[b]	0	0	10	40	0	90	80	0	0
Metabolic and GIT	46	63	83	96	83	83	83	90	**77**	17	31	27	25	69	90	79	63	52
CNS	69	44	94	86	84	90	85	90	**73**	21	29	32	21	68	84	62	55	36
Sys. and Hormonal	45	55	82	91	91	82	100	82	**91**	9	27	0	27	82	82	64	73	55
Withdrawn[e]	53	67	18	14	1	11	18	9	**50**	0	32	16	3	43	24	43	13	20
Gentio-Urinary-Sex	40	38	98	98	90	90	88	90	**85**	20	33	30	25	80	48	38	40	30
Antiviral	24	61	80	73	93	76	85	76	**51**[c]	7	39	34	29	17	56	39	10	10
Respiratory	61	31	89	78	83	89	83	92	**83**	17	22	25	19	75	75	47	53	33
Blood	33	27	93	87	87	87	80	87	**73**	13	27	13	20	53	73	40	40	13
Cardiovascular	37	31	86	98	89	86	89	88	**74**	11	22	21	21	63	70	48	41	24
Antineoplastic	35	56	82	85	90	85	81	87	**43**[d]	10	44	41	26	35	62	50	26	22
Average across therapeutic area	45	44	80	82	80	81	82	80	**69**	11	26	20	23	50	72	55	36	27

Following average DTI values for the respective therapeutic areas were used as cut off; [a]1.12, [b]1.4, [c]1.72, [d]1.09. [e]For withdrawn category criteria of LEI < 0.3, LLE < 5, DTI > 0.67 (avg for withdrawn), ACD log D >3 and log P > 3 was used. For exposure based TI the criteria was IC50/Cmax value between 0.5-2. For classical TI (CYP450, hERG, BSEP) the criteria was ≥ 30. None of the antibiotic class of drugs considered here had a dose < 100 mg. Average values used as cut off for PD on/off target, PK and physicochemical parameters are given in Table 3.

Table S12. Number of drugs considered from different WHO ATC drug categories, % drugs with negative DTI values, and average values for various PD, PK, and physicochemical (ACD log D) contributions to DTI.

WHO ATC category/Average	No. of drugs	% Drugs with negative DTI	PD on target	PK	ACD log D	PD of target		
						CYP450 PD off target	hERG PD off target	BSEP PD off target
Musculoskeletal	38	34.21	1.27	4.24	2.36	0.96	0.05	0.12
Antiparasitic	11	9.09	37.34	2.03	51.58	0.00	2.54	0.57
Antibiotic	50	8.00	64.79	21.37	20.94	3.50	0.61	0.61
Metabolic and GIT	48	7.41	8.27	2.80	2.40	0.67	0.14	0.07
CNS	154	37.01	20.87	5.49	1.49	2.34	0.66	0.09
Sys. and Hormonal	11	63.64	0.81	2.49	4.77	0.15	0.00	0.01
Withdrawn	88	29.55	6.93	16.28	40.76	4.64	0.67	0.05
Gentio-Urinary-Sex	40	52.50	54.49	27.45	13.77	0.57	0.11	0.30
Antiviral	41	4.88	370.74	1.79	78.26	2.74	1.48	11.29
Respiratory	36	33.33	4.50	2.69	1.10	0.35	0.07	0.04
Blood	15	26.67	11.46	370.09	21.09	0.57	0.14	0.16
Cardiovascular	111	34.23	4.33	43.86	4.22	1.47	0.69	0.08
Antineoplastic	68	16.18	41.10	3.07	20.15	1.86	1.34	0.39

Table S13. Average values for DTI, exposure based TI, dose, Mol. Wt., molar dose, OBA, target IC50, off target IC50 (CYP450, hERG, BSEP), Free Cmax, ACD log D, log P, LLE (log D, and log P), LEI, and PBB (fraction bound to plasma proteins).

WHO ATC category	Avg. DTI	Avg. Exposure TI	Avg. dose	Avg. Mol. Wt.	Avg. Molar Dose	Avg. OBA	Avg. target IC50 (uM)	Avg. CYP450 IC50 (uM)	Avg. hERG IC50 (uM)	Avg. Free Cmax	Avg. ACD logD 7.4	Avg. ACD logP	Avg. LLE (LogD)	Avg. LLE (logP)	Avg. LEI	Avg. BSEP IC50 (uM)	PPB (fraction bound)
Musculoskeletal	0.41	8.09	287.50	283.95	1.14	0.81	5.09	1.51	3.83	2.44	0.14	2.80	6.21	4.09	0.34	62.17	0.87
Antiparasitic	1.12	7908.61	401.82	314.71	1.22	0.68	32.95	2.71	3.82	0.57	2.21	3.43	4.48	3.26	0.31	23.86	0.76
Antibiotic	1.24	9.10	706.02	434.68	2.35	0.73	4.41	1.42	32.80	32.40	-0.06	1.88	7.23	5.29	0.29	245.34	0.57
Metabolic and GIT	0.33	9.49	144.97	365.67	0.58	0.62	2.56	5.17	45.96	2.26	0.84	1.99	6.85	5.71	0.32	71.24	0.70
CNS	0.38	37.76	111.55	305.55	0.49	0.71	47.92	2.70	36.79	5.52	1.54	2.60	5.80	4.74	0.35	64.18	0.69
Sys. and Hormonal	-0.19	667.26	59.82	394.23	0.23	0.81	1.50	7.04	0.00	0.77	1.97	2.65	5.45	4.77	0.36	104.02	0.84
Withdrawn	0.68	100.86	271.72	330.91	0.89	0.65	19.48	1.37	11.34	6.83	1.73	2.96	4.99	3.76	0.31	29.33	0.74
Gentio-Urinary-Sex	0.21	3.60	81.21	383.12	0.21	0.54	0.78	1.82	19.05	0.03	2.98	3.64	5.05	4.40	0.30	5.47	0.93
Antiviral	1.72	2.60	472.95	533.80	1.06	0.62	2.50	4.30	136.81	1.61	2.19	3.07	6.40	5.52	0.26	28.53	0.76
Respiratory	0.23	200.02	121.64	339.55	0.42	0.59	9.03	1.47	4.79	1.72	1.42	2.85	5.87	4.44	0.32	33.39	0.79
Blood	0.89	2427.52	566.34	386.93	3.68	0.56	4.07	1.77	0.75	77.07	1.54	2.80	5.32	4.06	0.28	11.69	0.80
Cardiovascular	0.39	96.07	138.71	385.03	0.44	0.59	28.66	2.84	50.21	1.01	1.62	3.16	5.39	3.85	0.28	52.93	0.73
Antineoplastic	1.09	257.96	279.69	449.69	0.63	0.53	0.97	4.52	12.84	0.53	2.32	3.03	6.04	5.33	0.28	36.05	0.85
Avg parameter values	0.66	902.23	280.30	377.52	1.03	0.65	12.30	2.97	27.61	10.21	1.57	2.83	5.77	4.55	0.31	59.09	0.77

Table S14. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using DTI.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.0056	0.0000	0.3176	0.4270	0.0130	0.1323	0.0000	0.1613	0.0440	0.4490	0.0000	0.0886
Antiparasitic	0.0056	0.5000	0.3483	0.0044	0.0061	0.0028	0.0088	0.0505	0.0101	0.3079	0.0099	0.4662	0.1004
Antibiotic	0.0000	0.3483	0.5000	0.0000	0.0000	0.0000	0.0000	0.0124	0.0000	0.1156	0.0000	0.1893	0.0008
Metabolic and GIT	0.3176	0.0044	0.0000	0.5000	0.3671	0.0368	0.2510	0.0000	0.2952	0.0639	0.3589	0.0000	0.0305
CNS	0.4270	0.0061	0.0000	0.3671	0.5000	0.0250	0.1398	0.0000	0.1736	0.0272	0.4745	0.0000	0.0143
Sys. and Hormonal	0.0130	0.0028	0.0000	0.0368	0.0250	0.5000	0.1195	0.0000	0.1038	0.0131	0.0310	0.0005	0.0071
Gentio-Urinary-Sex	0.1323	0.0088	0.0000	0.2510	0.1398	0.1195	0.5000	0.0000	0.4471	0.0353	0.1422	0.0000	0.0067
Antiviral	0.0000	0.0505	0.0124	0.0000	0.0000	0.0000	0.0000	0.5000	0.0000	0.0082	0.0000	0.0012	0.0000
Respiratory	0.1613	0.0101	0.0000	0.2952	0.1736	0.1038	0.4471	0.0000	0.5000	0.0402	0.1749	0.0000	0.0088
Blood	0.0440	0.3079	0.1156	0.0639	0.0272	0.0131	0.0353	0.0082	0.0402	0.5000	0.0388	0.2768	0.2510
Cardiovascular	0.4490	0.0099	0.0000	0.3589	0.4745	0.0310	0.1422	0.0000	0.0388	0.0388	0.5000	0.0000	0.0290
Antineoplastic	0.0000	0.4662	0.1893	0.0000	0.0000	0.0005	0.0000	0.0012	0.2768	0.2768	0.0000	0.5000	0.0051
Withdrawn	0.0886	0.1004	0.0008	0.0305	0.0143	0.0071	0.0067	0.0000	0.2510	0.2510	0.0290	0.0051	0.5000
Significantly different pairs	6	7	9	6	7	10	6	11	5	7	7	9	9

Table S15. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using PD on target contribution to DTI.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.0010	0.0722	0.0533	0.2659	0.2419	0.1630	0.0317	0.1295	0.0550	0.0968	0.0020	0.0248
Antiparasitic	0.0010	0.5000	0.3682	0.0125	0.3892	0.0490	0.3834	0.1842	0.0759	0.1197	0.0000	0.4408	0.0901
Antibiotic	0.0722	0.3682	0.5000	0.0727	0.1027	0.2152	0.4376	0.0425	0.0578	0.2217	0.0088	0.2772	0.0651
Metabolic and GIT	0.0533	0.0125	0.0727	0.5000	0.3261	0.1776	0.1971	0.0203	0.2133	0.3854	0.1130	0.0103	0.3613
CNS	0.2659	0.3892	0.1027	0.3261	0.5000	0.3654	0.2746	0.0003	0.1503	0.4254	0.1837	0.1620	0.2495
Sys. and Hormonal	0.2419	0.0490	0.2152	0.1776	0.3654	0.5000	0.1610	0.1592	0.0997	0.1888	0.2098	0.0018	0.1256
Gentio-Urinary-Sex	0.1630	0.3834	0.4376	0.1971	0.2746	0.1610	0.5000	0.0569	0.1896	0.2169	0.1772	0.3819	0.1899
Antiviral	0.0317	0.1842	0.0425	0.0203	0.0003	0.1592	0.0569	0.5000	0.0297	0.1288	0.0008	0.0446	0.0027
Respiratory	0.1295	0.0759	0.0578	0.2133	0.1503	0.0997	0.1896	0.0297	0.5000	0.2577	0.4784	0.0253	0.2361
Blood	0.0550	0.1197	0.2217	0.3854	0.4254	0.1888	0.2169	0.1288	0.2577	0.5000	0.0858	0.0407	0.2294
Cardiovascular	0.0968	0.0000	0.0088	0.1130	0.1837	0.2098	0.1772	0.0008	0.0858	0.0858	0.5000	0.0039	0.1311
Antineoplastic	0.0020	0.4408	0.2772	0.0103	0.1620	0.0018	0.3819	0.0446	0.0407	0.0407	0.0039	0.5000	0.0068
Withdrawn	0.0248	0.0901	0.0651	0.3613	0.2495	0.1256	0.1899	0.0027	0.2294	0.2294	0.1311	0.0068	0.5000
Significantly different pairs	4	4	2	3	1	2	0	8	2	1	4	8	3

Table S16. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using PK contribution to DTI.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.2948	0.0703	0.3197	0.3904	0.3395	0.1905	0.1264	0.2620	0.0190	0.2888	0.3126	0.1026
Antiparasitic	0.2948	0.5000	0.1830	0.4321	0.3348	0.4249	0.1682	0.4026	0.3216	0.1348	0.3760	0.2248	0.0118
Antibiotic	0.0703	0.1830	0.5000	0.0374	0.0100	0.1889	0.4143	0.0384	0.0331	0.0117	0.3590	0.0358	0.3312
Metabolic and GIT	0.3197	0.4321	0.0374	0.5000	0.2535	0.4730	0.1762	0.3327	0.4814	0.1033	0.2582	0.4553	0.0566
CNS	0.3904	0.3348	0.0100	0.2535	0.5000	0.3559	0.2035	0.1892	0.1241	0.0000	0.1386	0.1557	0.0242
Sys. and Hormonal	0.3395	0.4249	0.1889	0.4730	0.3559	0.5000	0.1733	0.3114	0.4683	0.1351	0.3773	0.4081	0.2152
Gentio-Urinary-Sex	0.1905	0.1682	0.4143	0.1762	0.2035	0.1733	0.5000	0.1659	0.1859	0.1193	0.3690	0.1128	0.3395
Antiviral	0.1264	0.4026	0.0384	0.3327	0.1892	0.3114	0.1659	0.5000	0.2246	0.0149	0.2694	0.1279	0.0549
Respiratory	0.2620	0.3216	0.0331	0.4814	0.1241	0.4683	0.1859	0.2246	0.5000	0.1033	0.1613	0.4080	0.0158
Blood	0.0190	0.1348	0.0117	0.1033	0.0000	0.1351	0.1193	0.0149	0.1033	0.5000	0.0160	0.1035	0.0011
Cardiovascular	0.2888	0.3760	0.3590	0.2582	0.1386	0.3773	0.3690	0.2694	0.0160	0.0160	0.5000	0.1635	0.2557
Antineoplastic	0.3126	0.2248	0.0358	0.4553	0.1557	0.4081	0.1128	0.1279	0.1035	0.1035	0.1635	0.5000	0.0180
Withdrawn	0.1026	0.0118	0.3312	0.0566	0.0242	0.2152	0.3395	0.0549	0.0011	0.0011	0.2557	0.0180	0.5000
Significantly different pairs	1	1	6	1	3	0	0	2	3	6	1	2	5

Table S17. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using ACD log D contribution to DTI.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.0216	0.0501	0.4879	0.2272	0.2051	0.1609	0.1363	0.0989	0.0428	0.2757	0.0681	0.2503
Antiparasitic	0.0216	0.5000	0.1496	0.0115	0.0000	0.1574	0.2167	0.4194	0.1449	0.2442	0.0009	0.2570	0.4274
Antibiotic	0.0501	0.1496	0.5000	0.0328	0.0003	0.2217	0.3161	0.1739	0.0234	0.4971	0.0093	0.4795	0.3040
Metabolic and GIT	0.4879	0.0115	0.0328	0.5000	0.2046	0.2116	0.1619	0.1086	0.1152	0.1472	0.2586	0.0687	0.2246
CNS	0.2272	0.0000	0.0003	0.2046	0.5000	0.0833	0.1431	0.0123	0.3048	0.0002	0.0500	0.0590	0.0821
Sys. and Hormonal	0.2051	0.1574	0.2217	0.2116	0.0833	0.5000	0.2337	0.2850	0.2292	0.2171	0.4633	0.1144	0.3673
Gentio-Urinary-Sex	0.1609	0.2167	0.3161	0.1619	0.1431	0.2337	0.5000	0.1708	0.1468	0.3622	0.2053	0.3591	0.2450
Antiviral	0.1363	0.4194	0.1739	0.1086	0.0123	0.2850	0.1708	0.5000	0.1250	0.3033	0.0332	0.1958	0.2986
Respiratory	0.0989	0.1449	0.0234	0.1152	0.3048	0.2292	0.1468	0.1250	0.5000	0.1316	0.0496	0.1215	0.1452
Blood	0.0428	0.2442	0.4971	0.1472	0.0002	0.2171	0.3622	0.3033	0.1316	0.5000	0.0169	0.4823	0.4145
Cardiovascular	0.2757	0.0009	0.0093	0.2586	0.0500	0.4633	0.2053	0.0332	0.0169	0.0169	0.5000	0.0926	0.1651
Antineoplastic	0.0681	0.2570	0.4795	0.0687	0.0590	0.1144	0.3591	0.1958	0.4823	0.4823	0.0926	0.5000	0.2996
Withdrawn	0.2503	0.4274	0.3040	0.2246	0.0821	0.3673	0.2450	0.2986	0.4145	0.4145	0.1651	0.2996	0.5000
Significantly different pairs	2	4	4	2	4	0	0	2	2	3	5	0	0

Table S18. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using ACD log P.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.1596	0.0112	0.0330	0.2620	0.4114	0.0097	0.2757	0.4486	0.4949	0.1542	0.2634	0.3222
Antiparasitic	0.1596	0.5000	0.0109	0.0275	0.0643	0.2112	0.3908	0.3250	0.2227	0.1981	0.3271	0.2915	0.2581
Antibiotic	0.0112	0.0109	0.5000	0.3965	0.0065	0.1201	0.0000	0.0043	0.0088	0.0452	0.0001	0.0009	0.0008
Metabolic and GIT	0.0330	0.0275	0.3965	0.5000	0.0230	0.1833	0.0000	0.0131	0.0249	0.0532	0.0005	0.0048	0.0034
CNS	0.2620	0.0643	0.0065	0.0230	0.5000	0.4582	0.0001	0.0734	0.2220	0.3277	0.0068	0.0573	0.0634
Sys. and Hormonal	0.4114	0.2112	0.1201	0.1833	0.4582	0.5000	0.0910	0.2975	0.3963	0.4190	0.2085	0.3023	0.3070
Gentio-Urinary-Sex	0.0097	0.3908	0.0000	0.0000	0.0001	0.0910	0.5000	0.0937	0.0156	0.0331	0.0451	0.0395	0.0104
Antiviral	0.2757	0.3250	0.0043	0.0131	0.0734	0.2975	0.0937	0.5000	0.3161	0.3381	0.4129	0.4565	0.3793
Respiratory	0.4486	0.2227	0.0088	0.0249	0.2220	0.3963	0.0156	0.3161	0.5000	0.4619	0.1890	0.3220	0.3796
Blood	0.4949	0.1981	0.0452	0.0532	0.3277	0.4190	0.0331	0.3381	0.4619	0.5000	0.2473	0.3084	0.3782
Cardiovascular	0.1542	0.3271	0.0001	0.0005	0.0068	0.2085	0.0451	0.4129	0.2473	0.2473	0.5000	0.3306	0.2287
Antineoplastic	0.2634	0.2915	0.0009	0.0048	0.0573	0.3023	0.0395	0.4565	0.3084	0.3084	0.3306	0.5000	0.4098
Withdrawn	0.3222	0.2581	0.0008	0.0034	0.0634	0.3070	0.0104	0.3793	0.3782	0.3782	0.2287	0.4098	0.5000
Significantly different pairs	3	2	10	9	4	0	9	2	3	2	4	3	3

Table S19. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using ACD log D (at pH = 7.4).

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.0024	0.3417	0.0653	0.0000	0.0050	0.0000	0.0002	0.0024	0.0140	0.0002	0.0000	0.0000
Antiparasitic	0.0024	0.5000	0.0032	0.0310	0.1333	0.3841	0.1249	0.4934	0.1273	0.1993	0.1970	0.4357	0.2303
Antibiotic	0.3417	0.0032	0.5000	0.0293	0.0000	0.0065	0.0000	0.0001	0.0008	0.0131	0.0000	0.0000	0.0000
Metabolic and GIT	0.0653	0.0310	0.0293	0.5000	0.0167	0.0577	0.0000	0.0061	0.0902	0.1276	0.0220	0.0002	0.0080
CNS	0.0000	0.1333	0.0000	0.0167	0.5000	0.2359	0.0000	0.0413	0.3556	0.4952	0.3872	0.0053	0.2364
Sys. and Hormonal	0.0050	0.3841	0.0065	0.0577	0.2359	0.5000	0.0506	0.4013	0.1872	0.2827	0.3036	0.2819	0.3453
Gentio-Urinary-Sex	0.0000	0.1249	0.0000	0.0000	0.0000	0.0506	0.5000	0.0585	0.0000	0.0087	0.0000	0.0405	0.0001
Antiviral	0.0002	0.4934	0.0001	0.0061	0.0413	0.4013	0.0585	0.5000	0.0722	0.2032	0.0930	0.4047	0.1357
Respiratory	0.0024	0.1273	0.0008	0.0902	0.3556	0.1872	0.0000	0.0722	0.5000	0.4222	0.2937	0.0154	0.1957
Blood	0.0140	0.1993	0.0131	0.1276	0.4952	0.2827	0.0087	0.2032	0.4222	0.5000	0.4477	0.0913	0.3625
Cardiovascular	0.0002	0.1970	0.0000	0.0220	0.3872	0.3036	0.0000	0.0930	0.4477	0.4477	0.5000	0.0177	0.3528
Antineoplastic	0.0000	0.4357	0.0000	0.0002	0.0053	0.2819	0.0405	0.4047	0.0913	0.0913	0.0177	0.5000	0.0369
Withdrawn	0.0000	0.2303	0.0000	0.0080	0.2364	0.3453	0.0001	0.1357	0.3625	0.3625	0.3528	0.0369	0.5000
Significantly different pairs	10	3	11	8	6	2	9	4	3	3	5	8	5

Table S20. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using PPB (fraction bound to plasma proteins).

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.1213	0.0000	0.0055	0.0007	0.3786	0.1003	0.0601	0.0890	0.2047	0.0076	0.3544	0.0131
Antiparasitic	0.1213	0.5000	0.0306	0.2740	0.2220	0.2230	0.0463	0.4949	0.4080	0.3843	0.3661	0.1776	0.4118
Antibiotic	0.0000	0.0306	0.5000	0.0233	0.0094	0.0037	0.0000	0.0025	0.0003	0.0074	0.0011	0.0000	0.0008
Metabolic and GIT	0.0055	0.2740	0.0233	0.5000	0.4254	0.0869	0.0000	0.1840	0.0893	0.1466	0.2784	0.0038	0.2097
CNS	0.0007	0.2220	0.0094	0.4254	0.5000	0.0578	0.0000	0.0952	0.0285	0.0990	0.1407	0.0000	0.0928
Sys. and Hormonal	0.3786	0.2230	0.0037	0.0869	0.0578	0.5000	0.0901	0.2263	0.2165	0.3448	0.1221	0.4547	0.1426
Gentio-Urinary-Sex	0.1003	0.0463	0.0000	0.0000	0.0000	0.0901	0.5000	0.0025	0.0015	0.0774	0.0000	0.0225	0.0000
Antiviral	0.0601	0.4949	0.0025	0.1840	0.0952	0.2263	0.0025	0.5000	0.3630	0.3559	0.2908	0.0719	0.3719
Respiratory	0.0890	0.4080	0.0003	0.0893	0.0285	0.2165	0.0015	0.3630	0.5000	0.4447	0.1460	0.0980	0.2135
Blood	0.2047	0.3843	0.0074	0.1466	0.0990	0.3448	0.0774	0.3559	0.4447	0.5000	0.2110	0.2833	0.2523
Cardiovascular	0.0076	0.3661	0.0011	0.2784	0.1407	0.1221	0.0000	0.2908	0.2110	0.2110	0.5000	0.0015	0.3836
Antineoplastic	0.3544	0.1776	0.0000	0.0038	0.0000	0.4547	0.0225	0.0719	0.2833	0.2833	0.0015	0.5000	0.0056
Withdrawn	0.0131	0.4118	0.0008	0.2097	0.0928	0.1426	0.0000	0.3719	0.2523	0.2523	0.3836	0.0056	0.5000
Significantly different pairs	5	2	12	4	5	1	9	2	3	1	4	6	4

Table S21. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using Free Cmax.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.2334	0.0202	0.4679	0.3454	0.2595	0.0424	0.2778	0.3498	0.0472	0.0594	0.0882	0.1774
Antiparasitic	0.2334	0.5000	0.1199	0.3157	0.3650	0.3816	0.0265	0.1353	0.1842	0.1828	0.2994	0.4574	0.0216
Antibiotic	0.0202	0.1199	0.5000	0.0105	0.0032	0.1214	0.0063	0.0142	0.0090	0.1589	0.0001	0.0069	0.0258
Metabolic and GIT	0.4679	0.3157	0.0105	0.5000	0.3188	0.3369	0.0937	0.3640	0.3990	0.1539	0.1424	0.1553	0.1453
CNS	0.3454	0.3650	0.0032	0.3188	0.5000	0.3703	0.0762	0.2994	0.1730	0.0021	0.1589	0.0971	0.4073
Sys. and Hormonal	0.2595	0.3816	0.1214	0.3369	0.3703	0.5000	0.1286	0.1974	0.2482	0.1835	0.3898	0.3626	0.2426
Gentio-Urinary-Sex	0.0424	0.0265	0.0063	0.0937	0.0762	0.1286	0.5000	0.0010	0.0778	0.1470	0.0001	0.0892	0.0140
Antiviral	0.2778	0.1353	0.0142	0.3640	0.2994	0.1974	0.0010	0.5000	0.4662	0.0392	0.1257	0.0274	0.1231
Respiratory	0.3498	0.1842	0.0090	0.3990	0.1730	0.2482	0.0778	0.4662	0.5000	0.1522	0.2895	0.1130	0.0617
Blood	0.0472	0.1828	0.1589	0.1539	0.0021	0.1835	0.1470	0.0392	0.1522	0.5000	0.0016	0.1485	0.0094
Cardiovascular	0.0594	0.2994	0.0001	0.1424	0.1589	0.3898	0.0001	0.1257	0.0016	0.0016	0.5000	0.1054	0.0300
Antineoplastic	0.0882	0.4574	0.0069	0.1553	0.0971	0.3626	0.0892	0.0274	0.1485	0.1485	0.1054	0.5000	0.0210
Withdrawn	0.1774	0.0216	0.0258	0.1453	0.4073	0.2426	0.0140	0.1231	0.0094	0.0094	0.0300	0.0210	0.5000
Significantly different pairs	3	2	9	1	2	0	6	4	3	5	4	3	6

Table S22. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using target IC50.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.0182	0.4195	0.2246	0.2615	0.2379	0.0591	0.2019	0.2756	0.4116	0.1422	0.0693	0.0811
Antiparasitic	0.0182	0.5000	0.0071	0.0052	0.4523	0.0918	0.0944	0.0069	0.1657	0.0771	0.4587	0.0956	0.2906
Antibiotic	0.4195	0.0071	0.5000	0.2649	0.2283	0.2581	0.0467	0.2432	0.2357	0.4660	0.1033	0.0586	0.0160
Metabolic and GIT	0.2246	0.0052	0.2649	0.5000	0.2235	0.4052	0.2050	0.4910	0.1573	0.3293	0.0915	0.2344	0.0326
CNS	0.2615	0.4523	0.2283	0.2235	0.5000	0.3549	0.0787	0.2409	0.1252	0.3407	0.3178	0.0796	0.2604
Sys. and Hormonal	0.2379	0.0918	0.2581	0.4052	0.3549	0.5000	0.2777	0.3810	0.1123	0.2184	0.2531	0.3395	0.1706
Gentio-Urinary-Sex	0.0591	0.0944	0.0467	0.2050	0.0787	0.2777	0.5000	0.1645	0.0766	0.1214	0.0157	0.4192	0.0030
Antiviral	0.2019	0.0069	0.2432	0.4910	0.2409	0.3810	0.1645	0.5000	0.1505	0.3128	0.1084	0.1982	0.0424
Respiratory	0.2756	0.1657	0.2357	0.1573	0.1252	0.1123	0.0766	0.1505	0.5000	0.2269	0.0832	0.0362	0.1222
Blood	0.4116	0.0771	0.4660	0.3293	0.3407	0.2184	0.1214	0.3128	0.2269	0.5000	0.2411	0.1370	0.1707
Cardiovascular	0.1422	0.4587	0.1033	0.0915	0.3178	0.2531	0.0157	0.1084	0.2411	0.2411	0.5000	0.0163	0.2622
Antineoplastic	0.0693	0.0956	0.0586	0.2344	0.0796	0.3395	0.4192	0.1982	0.1370	0.1370	0.0163	0.5000	0.0033
Withdrawn	0.0811	0.2906	0.0160	0.0326	0.2604	0.1706	0.0030	0.0424	0.1707	0.1707	0.2622	0.0033	0.5000
Significantly different pairs	1	4	3	2	0	0	3	2	0	0	2	3	5

Table S23. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using absolute oral bioavailability (OBA).

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.0683	0.0961	0.0012	0.2732	0.4992	0.0000	0.0009	0.0004	0.0009	0.0001	0.0000	0.0030
Antiparasitic	0.0683	0.5000	0.2696	0.2783	0.4615	0.1016	0.0717	0.2543	0.1517	0.1134	0.1882	0.0451	0.3470
Antibiotic	0.0961	0.2696	0.5000	0.0266	0.4302	0.1991	0.0016	0.0234	0.0091	0.0150	0.0032	0.0001	0.0446
Metabolic and GIT	0.0012	0.2783	0.0266	0.5000	0.2824	0.0249	0.1084	0.4717	0.2754	0.2025	0.2817	0.0440	0.3405
CNS	0.2732	0.4615	0.4302	0.2824	0.5000	0.3719	0.0417	0.2877	0.0968	0.2882	0.1220	0.0224	0.2866
Sys. and Hormonal	0.4992	0.1016	0.1991	0.0249	0.3719	0.5000	0.0017	0.0180	0.0055	0.0053	0.0135	0.0008	0.0518
Gentio-Urinary-Sex	0.0000	0.0717	0.0016	0.1084	0.0417	0.0017	0.5000	0.1219	0.2705	0.4020	0.1941	0.4168	0.0450
Antiviral	0.0009	0.2543	0.0234	0.4717	0.2877	0.0180	0.1219	0.5000	0.2988	0.2343	0.3169	0.0529	0.3195
Respiratory	0.0004	0.1517	0.0091	0.2754	0.0968	0.0055	0.2705	0.2988	0.5000	0.3812	0.4466	0.1764	0.1523
Blood	0.0009	0.1134	0.0150	0.2025	0.2882	0.0053	0.4020	0.2343	0.3812	0.5000	0.3558	0.3239	0.1648
Cardiovascular	0.0001	0.1882	0.0032	0.2817	0.1220	0.0135	0.1941	0.3169	0.3558	0.3558	0.5000	0.0852	0.1192
Antineoplastic	0.0000	0.0451	0.0001	0.0440	0.0224	0.0008	0.4168	0.0529	0.3239	0.3239	0.0852	0.5000	0.0090
Withdrawn	0.0030	0.3470	0.0446	0.3405	0.2866	0.0518	0.0450	0.3195	0.1648	0.1648	0.1192	0.0090	0.5000
Significantly different pairs	8	1	8	4	2	7	5	3	3	3	3	7	4

Table S24. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using molecular weight.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.0891	0.0000	0.0000	0.0841	0.0013	0.0000	0.0000	0.0039	0.0001	0.0000	0.0000	0.0038
Antiparasitic	0.0891	0.5000	0.0349	0.0551	0.3734	0.1045	0.0115	0.0015	0.2097	0.0570	0.0372	0.0001	0.2767
Antibiotic	0.0000	0.0349	0.5000	0.0206	0.0000	0.2797	0.0550	0.0169	0.0037	0.2050	0.0331	0.3297	0.0009
Metabolic and GIT	0.0000	0.0551	0.0206	0.5000	0.0001	0.2346	0.1642	0.0000	0.1239	0.2800	0.1729	0.0001	0.0250
CNS	0.0841	0.3734	0.0000	0.0001	0.5000	0.0025	0.0000	0.0000	0.0403	0.0009	0.0000	0.0000	0.0223
Sys. and Hormonal	0.0013	0.1045	0.2797	0.2346	0.0025	0.5000	0.4248	0.0335	0.1855	0.4533	0.4134	0.1808	0.0387
Gentio-Urinary-Sex	0.0000	0.0115	0.0550	0.1642	0.0000	0.4248	0.5000	0.0001	0.0176	0.4570	0.4535	0.0021	0.0004
Antiviral	0.0000	0.0015	0.0169	0.0000	0.0000	0.0335	0.0001	0.5000	0.0000	0.0109	0.0000	0.0176	0.0000
Respiratory	0.0039	0.2097	0.0037	0.1239	0.0403	0.1855	0.0176	0.0000	0.5000	0.1093	0.0181	0.0000	0.3372
Blood	0.0001	0.0570	0.2050	0.2800	0.0009	0.4533	0.4570	0.0109	0.1093	0.5000	0.4783	0.0513	0.0274
Cardiovascular	0.0000	0.0372	0.0331	0.1729	0.0000	0.4134	0.4535	0.0000	0.4783	0.4783	0.5000	0.0008	0.0004
Antineoplastic	0.0000	0.0001	0.3297	0.0001	0.0000	0.1808	0.0021	0.0176	0.0513	0.0513	0.0008	0.5000	0.0000
Withdrawn	0.0038	0.2767	0.0009	0.0250	0.0223	0.0387	0.0004	0.0000	0.0274	0.0274	0.0004	0.0000	0.5000
Significantly different pairs	10	5	8	6	10	4	7	12	6	4	8	9	10

Table S25. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using dose (mg).

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.2077	0.0005	0.0359	0.0001	0.0276	0.0015	0.0215	0.0169	0.1188	0.0021	0.4593	0.4364
Antiparasitic	0.2077	0.5000	0.0838	0.0234	0.0001	0.0196	0.0307	0.3172	0.0508	0.3500	0.0009	0.2270	0.2182
Antibiotic	0.0005	0.0838	0.5000	0.0000	0.0000	0.0014	0.0000	0.0296	0.0000	0.2930	0.0000	0.0001	0.0001
Metabolic and GIT	0.0359	0.0234	0.0000	0.5000	0.2088	0.2133	0.1305	0.0001	0.3662	0.1213	0.4463	0.0246	0.0761
CNS	0.0001	0.0001	0.0000	0.2088	0.5000	0.2104	0.1644	0.0000	0.4190	0.0001	0.1577	0.0004	0.0007
Sys. and Hormonal	0.0276	0.0196	0.0014	0.2133	0.2104	0.5000	0.3120	0.0012	0.1444	0.1105	0.1283	0.0002	0.1049
Gentio-Urinary-Sex	0.0015	0.0307	0.0000	0.1305	0.1644	0.3120	0.5000	0.0000	0.2173	0.0896	0.0450	0.0010	0.0019
Antiviral	0.0215	0.3172	0.0296	0.0001	0.0000	0.0012	0.0000	0.5000	0.0000	0.3439	0.0000	0.0090	0.0204
Respiratory	0.0169	0.0508	0.0000	0.3662	0.4190	0.1444	0.2173	0.0000	0.5000	0.1090	0.3692	0.0143	0.0236
Blood	0.1188	0.3500	0.2930	0.1213	0.0001	0.1105	0.0896	0.3439	0.1090	0.5000	0.0010	0.2100	0.0708
Cardiovascular	0.0021	0.0009	0.0000	0.4463	0.1577	0.1283	0.0450	0.0000	0.0010	0.0010	0.5000	0.0031	0.0181
Antineoplastic	0.4593	0.2270	0.0001	0.0246	0.0004	0.0002	0.0010	0.0090	0.2100	0.2100	0.0031	0.5000	0.4575
Withdrawn	0.4364	0.2182	0.0001	0.0761	0.0007	0.1049	0.0019	0.0204	0.0708	0.0708	0.0181	0.4575	0.5000
Significantly different pairs	8	5	10	5	7	5	7	10	4	2	8	8	6

Table S26. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using molar dose (mmol).

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.4343	0.0273	0.0694	0.0022	0.0237	0.0002	0.3862	0.0086	0.0645	0.0001	0.0274	0.2256
Antiparasitic	0.4343	0.5000	0.1587	0.1510	0.0275	0.0286	0.0298	0.3339	0.0693	0.2156	0.0028	0.1260	0.2636
Antibiotic	0.0273	0.1587	0.5000	0.0017	0.0000	0.0293	0.0001	0.0145	0.0004	0.2151	0.0000	0.0009	0.0048
Metabolic and GIT	0.0694	0.1510	0.0017	0.5000	0.3437	0.2697	0.0930	0.0752	0.3107	0.1272	0.2448	0.4292	0.1743
CNS	0.0022	0.0275	0.0000	0.3437	0.5000	0.2326	0.0080	0.0027	0.3662	0.0001	0.3368	0.1480	0.0189
Sys. and Hormonal	0.0237	0.0286	0.0293	0.2697	0.2326	0.5000	0.4453	0.0044	0.1855	0.1343	0.1945	0.0098	0.1119
Gentio-Urinary-Sex	0.0002	0.0298	0.0001	0.0930	0.0080	0.4453	0.5000	0.0000	0.1155	0.1011	0.0121	0.0013	0.0005
Antiviral	0.3862	0.3339	0.0145	0.0752	0.0027	0.0044	0.0000	0.5000	0.0038	0.0496	0.0000	0.0116	0.2871
Respiratory	0.0086	0.0693	0.0004	0.3107	0.3662	0.1855	0.1155	0.0038	0.5000	0.1153	0.4717	0.1274	0.0359
Blood	0.0645	0.2156	0.2151	0.1272	0.0001	0.1343	0.1011	0.0496	0.1153	0.5000	0.0004	0.1301	0.0081
Cardiovascular	0.0001	0.0028	0.0000	0.2448	0.3368	0.1945	0.0121	0.0000	0.0004	0.0004	0.5000	0.0557	0.0141
Antineoplastic	0.0274	0.1260	0.0009	0.4292	0.1480	0.0098	0.0013	0.0116	0.1301	0.1301	0.0557	0.5000	0.1177
Withdrawn	0.2256	0.2636	0.0048	0.1743	0.0189	0.1119	0.0005	0.2871	0.0081	0.0081	0.0141	0.1177	0.5000
Significantly different pairs	7	4	10	1	7	5	8	8	5	4	7	5	6

Table S27. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using LEI.

WHO ATC drug categories	Musculoskeletal	Antiparasitic	antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawan
Musculoskeletal	0.5000	0.1753	0.0178	0.1997	0.2630	0.3361	0.0086	0.0006	0.1380	0.0243	0.0016	0.0011	0.0764
Antiparasitic	0.1753	0.5000	0.3033	0.3649	0.0823	0.1793	0.3384	0.1022	0.3987	0.2356	0.2196	0.2001	0.4537
Antibiotic	0.0178	0.3033	0.5000	0.0818	0.0001	0.0564	0.3534	0.1595	0.0958	0.4139	0.4191	0.3756	0.1184
Metabolic and GIT	0.1997	0.3649	0.0818	0.5000	0.0348	0.1829	0.0810	0.0064	0.4270	0.0903	0.0195	0.0169	0.3205
CNS	0.2630	0.0823	0.0001	0.0348	0.5000	0.4474	0.0000	0.0000	0.0172	0.0040	0.0000	0.0000	0.0017
Sys. and Hormonal	0.3361	0.1793	0.0564	0.1829	0.4474	0.5000	0.0855	0.0091	0.1912	0.0540	0.0155	0.0495	0.0989
Gentio-Urinary-Sex	0.0086	0.3384	0.3534	0.0810	0.0000	0.0855	0.5000	0.0469	0.0910	0.2894	0.1982	0.1674	0.1150
Antiviral	0.0006	0.1022	0.1595	0.0064	0.0000	0.0091	0.0469	0.5000	0.0069	0.2951	0.1326	0.1712	0.0059
Respiratory	0.1380	0.3987	0.0958	0.4270	0.0172	0.1912	0.0910	0.0069	0.5000	0.1049	0.0251	0.0162	0.3911
Blood	0.0243	0.2356	0.4139	0.0903	0.0040	0.0540	0.2894	0.2951	0.1049	0.5000	0.4439	0.4812	0.1249
Cardiovascular	0.0016	0.2196	0.4191	0.0195	0.0000	0.0155	0.1982	0.1326	0.4439	0.4439	0.5000	0.4236	0.0245
Antineoplastic	0.0011	0.2001	0.3756	0.0169	0.0000	0.0495	0.1674	0.1712	0.4812	0.4812	0.4236	0.5000	0.0162
Withdrawn	0.0764	0.4537	0.1184	0.3205	0.0017	0.0989	0.1150	0.0059	0.1249	0.1249	0.0245	0.0162	0.5000
Significantly different pairs	6	0	2	4	9	3	3	7	2	2	6	6	4

Table S28. Pairwise T-test (P = 0.05) for different WHO ATC drug categories using LLE (log P).

WHO ATC drug categories	Musculoskeletal	Antiparasitic	Antibiotic	Metabolic and GIT	CNS	Sys. and Hormonal	Gentio-Urinary-Sex	Antiviral	Respiratory	Blood	Cardiovascular	Antineoplastic	Withdrawn
Musculoskeletal	0.5000	0.0906	0.0026	0.0002	0.0224	0.1281	0.2179	0.0006	0.1830	0.4772	0.2663	0.0008	0.2268
Antiparasitic	0.0906	0.5000	0.0025	0.0008	0.0048	0.0380	0.0562	0.0009	0.0496	0.1619	0.1963	0.0040	0.2338
Antibiotic	0.0026	0.0025	0.5000	0.1681	0.0378	0.2237	0.0147	0.2995	0.0191	0.0241	0.0001	0.4613	0.0001
Metabolic and GIT	0.0002	0.0008	0.1681	0.5000	0.0012	0.0993	0.0013	0.3341	0.0018	0.0056	0.0000	0.1762	0.0000
CNS	0.0224	0.0048	0.0378	0.0012	0.5000	0.4819	0.1331	0.0090	0.1663	0.0827	0.0002	0.0248	0.0002
Sys. and Hormonal	0.1281	0.0380	0.2237	0.0993	0.4819	0.5000	0.2685	0.1325	0.2944	0.1758	0.0887	0.1765	0.0970
Gentio-Urinary-Sex	0.2179	0.0562	0.0147	0.0013	0.1331	0.2685	0.5000	0.0043	0.4512	0.2832	0.0561	0.0100	0.0479
Antiviral	0.0006	0.0009	0.2995	0.3341	0.0090	0.1325	0.0043	0.5000	0.0057	0.0096	0.0000	0.3194	0.0001
Respiratory	0.1830	0.0496	0.0191	0.0018	0.1663	0.2944	0.4512	0.0057	0.5000	0.2563	0.0416	0.0154	0.0363
Blood	0.4772	0.1619	0.0241	0.0056	0.0827	0.1758	0.2832	0.0096	0.2563	0.5000	0.3606	0.0187	0.3282
Cardiovascular	0.2663	0.1963	0.0001	0.0000	0.0002	0.0887	0.0561	0.0000	0.3606	0.3606	0.5000	0.0000	0.3957
Antineoplastic	0.0008	0.0040	0.4613	0.1762	0.0248	0.1765	0.0100	0.3194	0.0187	0.0187	0.0000	0.5000	0.0000
Withdrawn	0.2268	0.2338	0.0001	0.0000	0.0002	0.0970	0.0479	0.0001	0.3282	0.3282	0.3957	0.0000	0.5000
Significant pairs	5	7	8	8	8	1	5	8	5	4	6	8	7
Total unique pair													78
Total unique significant pairs													40

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