***Supplementary tables***

## Simplifying the Extended Clearance Concept Classification System to guide clearance prediction in drug discovery

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**Supplementary Table I:** Analytical methods employed to determine the concentration of test compounds in in-vitro samples.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Conditions** | **In-vitro studies** | | | | | | | | | |
| MDCK-LE permeability | | Microsomal incubation | | Hepatocyte incubation | | Liver S9 incubation | | Plasma protein and microsomal binding | |
| LC and autosampler | Shimadzu LC-30AD | | Shimadzu Nexera | | Shimadzu 30 | | Waters Acquity | | PAL | |
| Analytical column | Phenomenex Kintex Polar (C18, 30 x 2.1 mm, 2.6 µm) | | Phenomenex Kintex Polar (C18, 30 x 2.1 mm, 2.6 µm) | | ACE 3 (C18, 30 x 2.1 mm, 3 µm) | | Acquity UPLC® HSS T3 (50 x 2.1 mm, 1.8 µm) | | Phenomenex Synergi Polar-RP (50 x 2 mm, 4 µm) | |
| Column temp (°C) | 50 | | 50 | | 55 | | 50 | | 50 | |
| Mobile phase A | 0.1% formic acid in water | | 0.1% formic acid in water | | 0.1% formic acid in water | | 0.1% formic acid in water:methanol (19:1) | | 0.1% formic acid in water | |
| Mobile phase B | 0.1% formic acid and 4% water in acetonitrile | | 0.1% formic acid in acetonitrile | | 0.1% formic acid in acetonitrile | | 0.1% formic acid in water:methanol (1:19) | | 0.1% formic acid in acetonitrile | |
| Flow rate (mL/min) | 0.8 | | 0.8 | | 0.7 | | 0.7 | | 0.45 | |
| Gradient | 0.0 min | 2% B | 0.0 min | 2% B | 0.0 min | 5% B | 0.0 min | 10% B | 0.0 min | 5% B |
| 0.2 min | 2% B | 0.2 min | 2% B | 0.5 min | 5% B | 1.0 min | 95% B | 0.5 min | 5% B |
| 1.0 min | 60% B | 1.0 min | 60% B | 2.0 min | 95% B | 1.1 min | 95% B | 0.6 min | 95% B |
| 1.3 min | 100% B | 1.3 min | 100% B | 3.0 min | 95% B | 1.2 min | 10% B | 3.0 min | 95% B |
| 1.7 min | 100% B | 1.7 min | 100% B | 3.1 min | 5% B | 1.5 min | 10% B | 3.1 min | 5% B |
| 1.71 min | 2% B | 1.71 min | 2% B | 3.5 min | 5% B |  |  | 3.5 min | 5% B |
| 1.95 min | 2% B | 1.95 min | 2% B |  |  |  |  |  |  |
| Mass spectrometer | Sciex QTrap 5500 | | Sciex QTrap 5500 | | AB Sciex API 6500 | | Sciex QTrap 5500 | | TSQ Quantum  Discovery MAX | |

Note: The above methods were generally employed to quantitate compounds in the in-vitro samples; however, these methods were optimized for some compounds, wherever applicable, to enable optimal elution and peak area quantification. When using Sciex mass spectrometer, compound related parameters including parent mass (Q1), daughter mass (Q3), declustering potential (DP), collision energy (CE), collision cell exit potential (CXP), etc were obtained using auto-tuning application in Discovery Quant (Optimize mode).

**Supplementary Table II.** Evaluation of MDCK Papp and sinusoidal hepatocyte PSinf,pas to categorize test compounds into the EC3S classes.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Compound** | **PSinf,pas**  [mL/min/kg] | **EC3S Class**  (based on PSinf,pas) | **Papp**  [10-6 cm/sec] | **EC3S Class**  (based on Papp) |
| Aliskiren | 25 | 3/4 | 0.78 | 3/4 |
| Atazanavir | 21 | 3/4 | 11 | 1/2 |
| Atorvastatin | 58 | 3/4 | 4.5 | 3/4 |
| Bosentan | 62 | 3/4 | 8.5 | 1/2 |
| Alpelisib | 279 | 1/2 | 12 | 1/2 |
| Cerivastatin | 244 | 1/2 | 11 | 1/2 |
| Cimetidine | 3.6 | 3/4 | 1.5 | 3/4 |
| Ciprofloxacin | 23 | 3/4 | 1.2 | 3/4 |
| Cyclosporine A | 42 | 3/4 | 4.1 | 3/4 |
| Digoxin | 6.9 | 3/4 | 1.8 | 3/4 |
| Erythromycin | 20 | 3/4 | 0.44 | 3/4 |
| Fluvastatin | 326 | 1/2 | 13 | 1/2 |
| Furosemide | 24 | 3/4 | 0.75 | 3/4 |
| Imatinib | 299 | 1/2 | 6.5 | 1/2 |
| Ribociclib | 130 | 1/2 | 6.5 | 1/2 |
| Lovastatin acid | 146 | 1/2 | 10 | 1/2 |
| Pitavastatin | 259 | 1/2 | 7.6 | 1/2 |
| Pravastatin | 36 | 3/4 | 0.26 | 3/4 |
| Propranolol | 276 | 1/2 | 25 | 1/2 |
| Quinidine | 109 | 1/2 | 17 | 1/2 |
| Rosiglitazone | 47 | 3/4 | 16.6 | 1/2 |
| Rosuvastatin | 25 | 3/4 | 0.28 | 3/4 |
| Valsartan | 19 | 3/4 | 0.67 | 3/4 |
| Verapamil | 258 | 1/2 | 14 | 1/2 |

Note: Passive uptake (PSinf,pas, mL/min/kg) of the above test compounds was determined in suspended HHep and values were collected from Riede 2016, 2017 (1, 2). Apparent passive permeability (Papp, x 10-6 cm/sec) was determined using MDCK-LE cells as described in Materials & Methods section. Test compounds were assigned to EC3S Classes 1/2 if PSinf,pas >100 mL/min/kg or Papp >5 x 10-6 cm/sec, otherwise to Class 3/4. The above set of twenty four compounds was only used to establish a categorical alignment between in-vitro MDCK-LE Papp and sinusoidal hepatocyte PSinf,pas as shown in Fig.2. EC3S, Extended Clearance Concept Classification System.

**Supplementary Table III:** Scaled in-vitro intrinsic clearance values obtained from HLM, HHep (stability and media loss), liver S9 fractions and observed human systemic clearance of test compounds used for IVIVE analysis.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **Ion Class** | **logD7.4**  **or clogPa** | **scaled CLint**  [mL/min/kg] | | | | **fumic** | **fuhep** | **fup** | **CLobs** [mL/min/kg] | **Ref** |
|  |  |  | **HLM** | **HHep stability** | **HHep media loss** | **S9** |  |  |  |  |  |
| ***EC3S Class 12ab*** |  |  |  |  |  |  |  |  |  |  |  |
| Benzydamine | B | 4.05 | 60.6 | 22.4 | 55.0 | 11.0 | 0.22 | 0.18 | 0.10 | 2.7 | (3) |
| Bupivacaine | B | 3.69 | 97.3 | 30.3 | 31.3 | 9.65 | 0.86 | 0.83 | 0.24 | 4.3 | (4) |
| Diclofenac | A | 1.73 | 272 | 171 | 148 | 77.8 | 0.85 | 0.82 | 0.0069 | 3.8 | (5) |
| Imatinib | B | 4.53 | 62.2 | <10.2 | 27.0 | 4.15 | 0.13 | 0.11 | 0.050 | 3.3 | (6) |
| Luminespib | Z | 2.81 | 84.1 | 222 | 1116 | 32.3 | 0.28 | 0.24 | 0.053 | 14.7 | NP |
| Lumiracoxib | A | 1.66 | 199 | 205 | 169 | 63.2 | 0.86 | 0.83 | 0.0010 | 1.8 | (7) |
| Midazolam | N | 3.42 | 654 | 43.3 | 42.0 | 58.0 | 0.55 | 0.49 | 0.030 | 5.6 | (8) |
| Nicardipine | B | 5.23 | >1418 | 416 | 1698 | 231 | 0.13 | 0.11 | 0.0035 | 9.0 | (9, 10) |
| Nimodipine | N | 4.00 | >1418 | 446 | 977 | 219 | 0.18 | 0.15 | 0.018 | 16.7 | (11-13) |
| O6-Benzylguanine | N | 2.20 | 29.8 | <10.2 | <12.2 | 17.1 | 0.96 | 0.95 | 0.13 | 15.7 | (14) |
| Patupilone | N | 3.22 | 779 | 129 | 109 | 65.2 | 0.77 | 0.73 | 0.12 | 2.1 | (15) |
| Propranolol | B | 2.75 | 66.5 | 19.4 | 64.4 | 8.02 | 0.60 | 0.54 | 0.36 | 20.4 | (16, 17) |
| Quinidine | B | 2.79 | 29.3 | 23.9 | 14.0 | <3.11 | 0.58 | 0.53 | 0.26 | 4.3 | (18) |
| Nateglinide | A | 1.10 | 40.2 | 12.1 | 14.2 | <3.11 | 0.93 | 0.91 | 0.020 | 1.8 | (19) |
| Venlafaxine | B | 3.27 | 28.2 | <10.2 | 19.8 | 3.36 | 0.43 | 0.38 | 0.73 | 14.0 | (20) |
| Verapamil | B | 4.47 | 439 | 48.3 | 129 | 26.1 | 0.58 | 0.52 | 0.093 | 20.0 | (21) |
| ***EC3S Class 2cd*** |  |  |  |  |  |  |  |  |  |  |  |
| Acetaminophen | N | 0.49 | <25.6 | 25.6 | <12.2 | <3.11 | 0.96 | 0.96 | 0.88 | 7.0 | (22) |
| Antipyrine | N | 0.20 | <25.6 | <10.2 | <12.2 | - | 0.98 | 0.97 | 0.93 | 0.64 | (23) |
| Betamipron | A | -2.20 | <25.6 | <10.2 | <12.2 | <3.11 | 1.00 | 1.00 | 0.070 | 9.2 | (24) |
| Bisoprolol | B | 1.83 | <25.6 | <10.2 | <12.2 | - | 0.83 | 0.80 | 0.66 | 3.7 | (25, 26) |
| Carbazeran | N | 1.83 | <25.6 | 87.0 | 116 | 398 | 0.83 | 0.80 | 0.066 | 37.6 | (27) |
| Citalopram | B | 3.13 | <25.6 | 18.3 | 26.5 | - | 0.48 | 0.42 | 0.20 | 4.3 | (28) |
| Codeine | B | 0.98 | <25.6 | <10.2 | <12.2 | <3.11 | 0.94 | 0.92 | 0.96 | 10.7 | (29) |
| Fleroxacin | Z | -0.33 | <25.6 | <10.2 | <12.2 | - | 0.99 | 0.98 | 0.73 | 2.4 | (30) |
| Gatifloxacin | Z | -0.27 | <25.6 | <10.2 | <12.2 | - | 0.99 | 0.98 | 0.80 | 2.8 | (31) |
| Ketoprofen | A | -0.35 | <25.6 | 33.4 | 14.5 | <3.11 | 0.99 | 0.98 | 0.019 | 1.2 | (32) |
| Lorazepam | N | 2.37 | <25.6 | 19.6 | 24.9 | <3.11 | 0.76 | 0.72 | 0.088 | 1.0 | (33) |
| Metoprolol | B | 1.49 | <25.6 | <10.2 | 14.0 | - | 0.88 | 0.86 | 0.88 | 13.0 | (34-36) |
| Moxifloxacin | Z | -0.08 | <25.6 | 13.8 | <12.2 | 4.15 | 0.98 | 0.98 | 0.60 | 2.2 | (37) |
| Mycophenolic Acid | A | -0.46 | <25.6 | 27.6 | 46.6 | - | 0.99 | 0.99 | 0.015 | 3.3 | (38) |
| Oxazepam | N | 2.31 | <25.6 | <10.2 | - | - | 0.72 | 0.68 | 0.054 | 1.0 | (22) |
| Pitavastatin | A | 1.16 | <25.6 | 35.6 | 31.3 | <3.11 | 0.92 | 0.90 | 0.0042 | 5.9 | (39, 40) |
| Rsv604 | N | 3.02 | <25.6 | <10.2 | <12.2 | 14.7 | 0.43 | 0.38 | 0.040 | 0.70 | NP |
| Theophylline | N | -0.03 | <25.6 | <10.2 | <12.2 | - | 0.98 | 0.98 | 0.61 | 0.64 | (41) |
| Vadimezan | A | 0.11 | <25.6 | 25.6 | 60.0 | - | 0.98 | 0.97 | 0.0058 | 1.1 | (42) |
| Zaleplon | N | 1.43 | <25.6 | <10.2 | <12.2 | <3.11 | 0.89 | 0.87 | 0.40 | 16.0 | (43) |
| ***EC3S Class 34ab*** |  |  |  |  |  |  |  |  |  |  |  |
| Aliskiren | B | 3.51 | 51.2 | <10.2 | <12.2 | 5.52 | 0.36 | 0.31 | 0.31 | 2.1 | NP |
| Dacinostat | B | 2.14 | 49.1 | 34.1 | 108.6 | 15.5 | 0.77 | 0.72 | 0.23 | 11.6 | NP |
| Erythromycin | B | 1.61 | 58.3 | <10.2 | 21.6 | 9.26 | 0.87 | 0.84 | 0.36 | 5.6 | (44) |
| Etoposide | N | 0.03 | 32.9 | 17.2 | <12.2 | <3.11 | 0.98 | 0.98 | 0.030 | 0.53 | (45) |
| Indinavir | B | 3.68 | 562 | 41.7 | 48.9 | 37.7 | 0.68 | 0.63 | 0.39 | 18.0 | (46) |
| Panobinostat | B | 2.64 | 33.0 | 13.1 | 142 | - | 0.63 | 0.58 | 0.11 | 7.9 | (47) |
| ***EC3S Class 34cd*** |  |  |  |  |  |  |  |  |  |  |  |
| Almotriptan | B | 1.79 | <25.6 | - | - | - | 0.84 | 0.80 | 0.60 | 8.9 | (48) |
| Cefazolin | A | -4.39 | <25.6 | <10.2 | <12.2 | <3.11 | 1.00 | 1.00 | 0.34 | 0.89 | (49, 50) |
| Cefmetazole | A | -4.84 | <25.6 | <10.2 | <12.2 | - | 1.00 | 1.00 | 0.30 | 1.5 | (51, 52) |
| Cefodizime | A | -1.50 | 26.8 | <10.2 | <12.2 | - | 1.00 | 1.00 | 0.12 | 0.74 | (53, 54) |
| Cefoperazone | A | -3.69 | <25.6 | <10.2 | <12.2 | - | 1.00 | 1.00 | 0.072 | 1.3 | (55) |
| Cefpiramide | A | -3.16 | <25.6 | <10.2 | <12.2 | - | 1.00 | 1.00 | 0.0087 | 0.26 | (56) |
| Ceftizoxime | A | -0.66 | <25.6 | <10.2 | <12.2 | 9.98 | 0.99 | 0.99 | 0.72 | 2.8 | (57) |
| Ciprofloxacin | Z | -0.73 | <25.6 | <10.2 | <12.2 | <3.11 | 0.99 | 0.99 | 0.70 | 8.7 | (58) |
| Elinogrel | A | 1.66 | <25.6 | <10.2 | 12.5 | 7.09 | 0.86 | 0.83 | 0.0070 | 0.30 | NP |
| Famotidine | N | -0.60 | <25.6 | <10.2 | <12.2 | - | 0.99 | 0.99 | 0.91 | 6.6 | (59) |
| Furosemide | A | -1.40 | <25.6 | <10.2 | <12.2 | 19.1 | 1.00 | 1.00 | 0.043 | 1.6 | (60, 61) |
| Gavestinel | A | 2.19 | <25.6 | 341 | 91.6 | 16.4 | 0.10 | 0.08 | 0.000082 | 0.089 | (62) |
| Napsagatran | Z | 1.29 | <25.6 | - | <12.2 | - | 0.91 | 0.89 | 0.55 | 6.1 | (63) |
| Piperacillin | A | -1.80 | <25.6 | <10.2 | - | - | 1.00 | 1.00 | 0.50 | 4.0 | (64, 65) |
| Pravastatin | A | -0.77 | <25.6 | <10.2 | <12.2 | <3.11 | 0.99 | 0.99 | 0.55 | 13.5 | (66, 67) |
| Rosuvastatin | A | -0.80 | <25.6 | <10.2 | <12.2 | <3.11 | 0.99 | 0.99 | 0.13 | 11.5 | (39) |
| Sulfinpyrazone | A | -1.84 | <25.6 | <10.2 | <12.2 | 1028 | 1.00 | 1.00 | 0.011 | 0.34 | (68) |
| Susalimod | A | 1.06 | <25.6 | 10.7 | 44.8 | - | 0.93 | 0.91 | 0.0019 | 0.070 | (69) |
| Valsartan | A | -0.40 | <25.6 | <10.2 | <12.2 | - | 0.99 | 0.99 | 0.040 | 0.52 | (70) |
| Vildagliptin | B | 0.69 | <25.6 | <10.2 | <12.2 | <3.11 | 0.95 | 0.94 | 0.89 | 9.9 | (71) |
| Zidovudine | N | 0.04 | <25.6 | 22.7 | <12.2 | - | 0.98 | 0.98 | 0.69 | 20.0 | (22) |
| Zoniporide | B | 1.58 | <25.6 | 11.2 | 13.2 | 13.6 | 0.87 | 0.84 | 0.41 | 21.0 | (72) |

Note: Intrinsic clearance (CLint) values obtained from HLM, HHep and liver S9 fractions were scaled using the scalars described in the data analysis section and expressed as mL/min/kg. CLint < 25.6, <10.2, <12.2, and <3.1 mL/min/kg in HLM, HHep (stability assay), HHep (media loss assay), and liver S9, respectively indicates no turnover of compounds and data were not considered for statistical analysis on the human clearance predictions. Fraction unbound in microsomal incubation (fumic) and fraction unbound in hepatocyte incubation (fuhep) data were generally predicted according to the Austin *et al*., 2002 (73) and Kilford *et al*., 2008 (74), respectively. For compounds with logD7.4/clogP > 2, fumic was measured in-house. CLobs (mL/min/kg) for all test compounds were collected from references provided in the table and refers to systemic drug clearance from plasma assuming equal blood-to-plasma distribution (Rb = 1). In our data analysis, the value of Rb was used as unity since this parameter is typically not measured in early drug discovery. A, acid; B, base; N, neutral; Z, zwitterion; -, not determined; alogD7.4 and clogP are reported for acids and bases, respectively. NP, data not published (internal data). fup, fraction unbound in plasma; HLM, human liver microsomes; HHep, human hepatocytes.

**Supplementary Table IV:** The impact of Rb on the statistical analysis of the human clearance predictions using scaled in-vitro CLint from HLM, HHep and liver S9 fractions.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Method** | **n** | **success rate** | **AFE** | **AAFE** | **within**  **3-fold** |
| ***EC3S Class 12ab*** |  |  |  |  |  |
| Microsomes | 16 | 100% | 0.88 | 2.37 | 69% |
| Hepatocytes (stability) | 16 | 81% | 0.57 | 2.93 | 77% |
| Hepatocytes (media loss) | 16 | 94% | 0.70 | 2.80 | 80% |
| Liver S9 fractions | 16 | 88% | 0.39 | 2.94 | 57% |
| ***EC3S Class 2cd*** |  |  |  |  |  |
| Microsomes | 20 | 0% | NA | NA | NA |
| Hepatocytes (stability) | 20 | 45% | 0.48 | 3.46 | 56% |
| Hepatocytes (media loss) | 19 | 42% | 0.79 | 3.18 | 60% |
| Liver S9 fractions | 10 | 30% | 0.95 | 1.81 | 100% |
| ***EC3S Class 34ab*** |  |  |  |  |  |
| Microsomes | 6 | 100% | 1.60 | 2.33 | 83% |
| Hepatocytes (stability) | 6 | 67% | 0.60 | 2.11 | 75% |
| Hepatocytes (media loss) | 6 | 67% | 1.36 | 1.56 | 83% |
| Liver S9 fractions | 5 | 80% | 0.79 | 2.10 | 100% |
| ***EC3S Class 34cd*** |  |  |  |  |  |
| Microsomes | 22 | 5% | 4.96 | 4.96 | 0% |
| Hepatocytes (stability) | 20 | 20% | 0.83 | 3.31 | 50% |
| Hepatocytes (media loss) | 20 | 20% | 1.04 | 2.06 | 80% |
| Liver S9 fractions | 11 | 55% | 1.14 | 3.92 | 67% |

Note: Statistical parameters on the hepatic clearance prediction were determined using the well-stirred liver model corrected for both fub and fuinc. To obtained fub value, fup was divided with Rb value that is provided in the Supplementary Table V for each compound. “n” represents number of compounds incubated in HLM, HHep, and liver S9 fractions for each EC3S Class, respectively. Success rate represents % of compounds that showed CLint value above the assay limit in the HLM, HHep, and liver S9 fractions and whose predicted human clearance data was used in the statistical analysis for IVIVE. NA represents not applicable for statistical analysis. AFE, average fold-error; AAFE, absolute average fold-error.

**Supplementary Table V:** The blood to plasma ratio (Rb) of test compounds.

|  |  |  |
| --- | --- | --- |
| **Compound** | **Rb** | **Reference** |
| ***EC3S Class 12ab*** |  |  |
| Benzydamine | 0.76 | (75) |
| Bupivacaine | 0.57 | (76) |
| Diclofenac | 0.6 | (76) |
| Imatinib | 0.87 | (76) |
| Luminespib | 1 | Assumed |
| Lumiracoxib | 0.55 | Assumed |
| Midazolam | 0.68 | (76) |
| Nicardipine | 0.59 | (76) |
| Nimodipine | 0.77 | (76) |
| O6-Benzylguanine | 1 | Assumed |
| Patupilone | 1 | Assumed |
| Propranolol | 1.08 | (76) |
| Quinidine | 1.02 | (76) |
| Nateglinide | 0.6 | (77) |
| Venlafaxine | 1.19 | (76) |
| Verapamil | 0.83 | (76) |
| ***EC3S Class 2cd*** |  |  |
| Acetaminophen | 1.04 | (76) |
| Antipyrine | 0.92 | (76) |
| Betamipron | 0.59 | (76) |
| Bisoprolol | 0.95 | (76) |
| Carbazeran | 0.7 | (78) |
| Citalopram | 1.39 | (76) |
| Codeine | 1.0 | (79) |
| Fleroxacin | 0.88 | (76) |
| Gatifloxacin | 1.01 | (76) |
| Ketoprofen | 1.09 | (76) |
| Lorazepam | 1.1 | (76) |
| Metoprolol | 1.15 | (76) |
| Moxifloxacin | 0.92 | (76) |
| Mycophenolic Acid | 0.69 | (76) |
| Oxazepam | 1.11 | (76) |
| Pitavastatin | 0.65 | (80) |
| Rsv604 | 1 | Assumed |
| Theophylline | 0.92 | (76) |
| Vadimezan | 0.67 | (81) |
| Zaleplon | 0.99 | (76) |
| ***EC3S Class 34ab*** |  |  |
| Aliskiren | 0.68 | Assumed |
| Dacinostat | 1 | Assumed |
| Erythromycin | 0.82 | (76) |
| Etoposide | 0.6 | (76) |
| Indinavir | 1.05 | (76) |
| Panobinostat | 1.4 | (82) |
| ***EC3S Class 34cd*** |  |  |
| Almotriptan | 1.15 | (76) |
| Cefazolin | 0.6 | (76) |
| Cefmetazole | 0.55 | Assumed |
| Cefodizime | 0.72 | (76) |
| Cefoperazone | 0.55 | (76) |
| Cefpiramide | 0.53 | (76) |
| Ceftizoxime | 0.54 | (76) |
| Ciprofloxacin | 1.04 | (76) |
| Elinogrel | 0.55 | Assumed |
| Famotidine | 0.74 | (76) |
| Furosemide | 0.8 | (76) |
| Gavestinel | 0.49 | (76) |
| Napsagatran | 0.56 | (83) |
| Piperacillin | 0.65 | (76) |
| Pravastatin | 0.59 | (76) |
| Rosuvastatin | 0.57 | (80) |
| Sulfinpyrazone | 0.54 | (76) |
| Susalimod | 0.55 | Assumed |
| Valsartan | 0.7 | (77) |
| Vildagliptin | 1.0 | (76) |
| Zidovudine | 1.11 | (76) |
| Zoniporide | 0.75 | (78) |

Note: Rb values were collected from the literature whose references are provided in the table. For compounds whose Rb values were not available, if they were acid, the Rb value was assumed to be 0.55 and if they were basic or neutral, the Rb value was assumed to be 1, as previously used by Wood et al. 2017 (79).

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