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A total of 669 molecular decriptors, representing mainly the molecular size, flexibility, connectivity, polarity, charge, and hydrogen bonding potential of the molecules, were calculated from the 3D structures using DragonX version 3.0 (Talete, Milano, Italy), ADMETPredictor version 1.2.4 (SimulationsPlus, Lancaster, CA), and
HYBOT
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MOLPRO-2001
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TimTec
, Newark, DE).

Abstract
The chemical space of registered oral drugs was explored for inhibitors of the human multidrug-resistance associated protein 2 (MRP2; ABCC2), using a data set of 191 structurally diverse drugs and drug-like compounds. The data set included a new reference set of 75 compounds, for studies of hepatic drug interactions with transport proteins, CYP enzymes, and compounds associated with liver toxicity. The inhibition of MRP2-mediated transport of estradiol-17β-
d
-glucuronide was studied in inverted membrane vesicles from Sf9 cells overexpressing human MRP2. A total of 27 previously unknown MRP2 inhibitors were identified, and the results indicate an overlapping but narrower inhibitor space for MRP2 compared with the two other major ABC efflux transporters P-gp (ABCB1) and BCRP (ABCG2). In addition, 13 compounds were shown to stimulate the transport of estradiol-17β-
d
-glucuronide. The experimental results were used to develop a computational model able to discriminate inhibitors from noninhibitors according to their molecular structure, resulting in a predictive power of 86% for the training set and 72% for the test set. The inhibitors were in general larger and more lipophilic and presented a higher aromaticity than the noninhibitors. The developed computational model is applicable in an early stage of the drug discovery process and is proposed as a tool for prediction of MRP2-mediated hepatic drug interactions and toxicity.