Supplementary Information S1

This supplementary information section presents three tables (Tables S2, S3, S4) that are provided as separate .xls files, and the literature citations associated with them are provided at the end of this .pdf file. The .xls files can serve as a reader resource that can be downloaded and modified for personal use, or additional support can be obtained at http://www.lkcpharmaservices.com .

Table S2. Database of protein kinase targets for CNS indications. This table provides the detailed background information for the protein kinase targets and small molecule inhibitors summarized in Tables 1 and 2 in the main text.

For inclusion in the Table S2 database, protein kinase targets were limited to those with CNS indications and those for which small molecule compounds are available either in disclosed clinical trials or published preclinical *in vivo* efficacy studies in an animal model. Table S2 delineates the protein kinase targets, type of kinase (S/T or Y), therapeutic indication, and compound status (listed either as preclinical or as the NCT number if in clinical trials). For each compound, the compound name, CAS registry number (where available), chemical structure (SMILES), computed molecular properties (LogP, MW, PSA) and CYP substrate status (where available) are given in distinct spreadsheet cells. Literature citations documenting brain uptake or CNS involvement are also listed for each compound when available. Molecular properties were computed using ACD Labs v.11 (Advanced Chemistry Development, Inc., Toronto).

Table S3. Database of disclosed CNS-penetrant small molecules. This table is a database of CNS-penetrant small molecules with information about brain uptake, *in vivo* activity, computed molecular properties and status as substrates or inhibitors of cytochrome P450 (CYP) and P-glycoprotein (Pgp) transport enzymes.

Table S3 includes CNS-penetrant small molecules, with public-disclosed *in vivo* brain uptake data mined from the literature. A series of structured literature searches in PubMed, SciFinder Scholar, and Google Scholar were done using the keyword terms “LogBB” or “pharmacokinetic and brain” or a successive keyword search using the terms “drug or therapeutic”, followed by the terms “brain”, then “blood” to further restrict each group. Analysis of the resultant literature hits was done by inspection to find small molecules for which published *in vivo* brain uptake data were available. To identify studies that addressed potential interactions with CYP or Pgp, keyword searching for each compound used the following phrases: "CYP", "disposition", "metabolism", "P-glycoprotein", "efflux". Articles obtained through these searches were inspected for relevant data. The corresponding literature citations indicating CYP or Pgp status are provided in the Supporting Information Literature Cited section below.

Drugs approved by the FDA for selected CNS indications (e.g., Alzheimer's disease, epilepsy, Parkinson's disease, migraine, and pain that required CNS penetrance as a mechanism of action) were also added to the collection. Although many of these FDA-approved drugs lack reported brain uptake data in the literature, incorporation of these compounds into the database is based upon the assumption that experimental uptake data exist in preclinical data not available to the public but exist as part of disclosures to the FDA or internal company requirements.

To assist with import of data into end-user computational programs or with user updates, each compound has a separate spreadsheet cell entry for the CAS registry number (when registered), chemical structure (SMILES), chemical formula, *in vivo* brain uptake information (logBB), computed molecular properties (LogP, MW, PSA), and *in vivo* administration information (animal, dosing, route). Citations to CNS literature are also included.

A distribution analysis of the computed molecular properties of the Table S3 compounds demonstrates that the collection of molecules explores a normal distribution across a diverse range of multiple molecular properties, including A) LogP, B) MW and C) PSA. The mean LogP, MW, and PSA values (2.65, 310.09, 58.66) are consistent with the respective median values (2.70, 301.47, 55.25). The normal distribution provides support for the analysis of multi-property features of CNS-penetrant small molecules using the mean values as discussed in the main text.

Analysis of the mean values for computed molecular properties of CNS-penetrant small molecules reveals trends that are discussed in the main text. For example, PSA is the lone property in Table S3 to demonstrate a correlation with *in vivo* logBB values (r^2=-0.58). CNS-penetrant molecules had a significantly lower mean PSA value (58.92Å^2) than kinase inhibitor drugs (Table S4) or marketed drugs in general (dataset compiled by Vieth et al., 2004). Many of the kinase inhibitors listed in Table 1 possess PSA values far beyond this range. For example, the three mTOR inhibitors in clinical trials (everolimus, sirolimus and temsirolimus) all possess PSA values nearly four times higher. Other compounds in Table S3 with elevated PSA values (>120Å^2) show lower experimental brain uptake, with a mean logBB of -1.05. In general, compounds in Table S3 possess lower MW compared to kinase inhibitors (Table S2) and marketed drugs. Contrary to some prevailing assumptions, Table S3 compounds did not show a significant correlation of lipophilicity (logP) with *in vivo* logBB values.

Pgp-positive compounds in Table S2 possess higher LogP values versus Pgp-negative compounds (3.30 vs 2.45), have a higher mean PSA value compared to non-substrates (71.67 vs 55.80), and a higher MW (413.37 vs 300.37). The latter is consistent with previous reports (Varma, 2005) showing trends between molecular weight and substrate status. CYP3A4 substrates in Table S3 possess a higher mean LogP (3.43) than other CYP substrates (2.71). The mean PSA for CYP substrates (54.28 Å^2) was similar to the mean PSA value for the full set of compounds in Table S3 (58.92 Å^2).

Table S4. Small molecule protein kinase inhibitor drugs (approved and in clinical trial). This table is a listing of small molecule protein kinase inhibitors in clinical trials for any disease indication, and thus expands the analysis to those kinase inhibitor drugs with non-CNS indications compared to those in Table S2 with CNS indications.

The compounds included in Table S4 were selected based on a systematic search of the clinicaltrials.gov website. Search methods included using the keyword terms "kinase inhibitor", then removing biologics and duplicate compounds. Compound structures were obtained from SciFinderScholar. For each compound, the kinase target, therapeutic indication, the compound name, chemical structure (SMILES), CAS registry number (when registered), and computed molecular properties (LogP, MW, PSA) are given.

Analysis of the molecular property profiles of these small molecule kinase inhibitor drugs in clinical development reveals interesting trends compared to the CNS-penetrant compounds in Table S3, as discussed in the main text. The kinase inhibitor drugs in Table S4 show a higher MW and PSA compared to the Table S3 CNS-penetrant compounds.

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