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ACS Chemical Neuroscience

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Central Nervous System Multiparameter Optimization Desirability: Application in Drug Discovery

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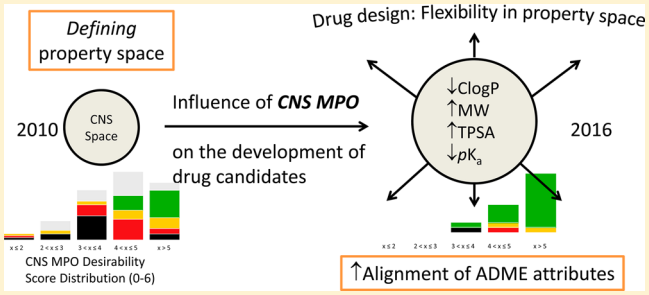
ABSTRACT: Significant progress has been made in prospectively designing molecules using the central nervous system multiparameter optimization (CNS MPO) desirability tool, as evidenced by the analysis reported herein of a second wave of drug candidates that originated after the development and implementation of this tool. This simple-to-use design algorithm has expanded design space for CNS candidates and has further demonstrated the advantages of utilizing a flexible, multiparameter approach in drug discovery rather than individual parameters and hard cutoffs of physicochemical properties. The CNS MPO tool has helped to increase the percentage of compounds nominated for clinical development that exhibit alignment of ADME attributes, cross the blood−brain barrier, and reside in lower-risk safety space (low ClogP and high TPSA). The use of this tool has played a role in reducing the number of compounds submitted to exploratory toxicity studies and increasing the survival of our drug candidates through regulatory toxicology into First in Human studies. Overall, the CNS MPO algorithm has helped to improve the prioritization of design ideas and the quality of the compounds nominated for clinical development.



KEYWORDS: *Attrition, central nervous system (CNS), CNS candidates, CNS drugs, CNS drug design, CNS MPO, desirability score, efficacious drug concentration (C_{eff}), Harrington optimization, human liver microsome stability, hydrogen-bond donor, lipophilicity, Madin−Darby canine kidney, molecular weight, most basic pK_a, multiparameter optimization (MPO), multivariant optimization, passive permeability, P-glycoprotein (P-gp), polarity, topological polar surface area, unbound intrinsic clearance*

In an effort to reduce attrition of our clinical candidates and prospectively increase our odds of success, we began to consider alternative ways to assess the quality of our design ideas. In 2010, we reported our initial analysis of central nervous system (CNS) drug property space, which included examination of physicochemical, *in vitro* absorption, distribution, metabolism, and elimination (ADME) attributes, and *in vitro* potency property space for a set of CNS drugs and candidates.[1] In that work, the two compound sets could be differentiated by their physicochemical properties and their ADME and safety attributes; we utilized the drug set to define a historical optimal chemical space possessing alignment of key drug properties for CNS therapeutic agents. In an effort to use this knowledge prospectively in design, *before compounds are synthesized*, we searched for a way to incorporate this information into an easy-to-use design tool. We began experimenting with the concept of multiparameter optimization (MPO). Multiparameter optimization methods provide a means to assess and balance several variables based on their importance to the overall objective.[2] Using this approach, we developed the CNS MPO desirability tool, which consisted of six fundamental physicochemical properties [(a) lipophilicity, calculated partition coefficient (ClogP); (b) calculated distribution coefficient at pH 7.4 (ClogD); (c) molecular weight (MW); (d) topological polar surface area (TPSA); (e) number of hydrogen-bond donors (HBDs); and (f) most basic center (pK_a)] that we determined were important factors in the alignment of ADME and safety drug attributes.[1,3] In contrast to a quantitative structure−activity relationship or machine learning model,[4,5] the CNS MPO desirability tool is built upon medicinal chemistry experience on ranges of desirable property space and simple piecewise linear transformational functions with values between 0 and 1 (defined as T0 for each property).[3] A monotonic decreasing function was used for ClogP, ClogD, MW, pK_a, and HBD, whereas a hump function was used to define TPSA (Figure 1).[3] Each parameter was weighted equally, and the collective score ranged from 0 to 6, with higher CNS MPO scores being more desirable. Most of the compounds in the drug set had CNS MPO desirability scores greater than 4, which differentiated them from the historical candidate set. The advantages of the CNS MPO desirability method lie in (a) its simplicity, with parameters derived from best medicinal chemistry practices, (b) its ability to balance multiple variables while avoiding hard cutoffs, and

Received: February 2, 2016
Accepted: March 18, 2016
Published: March 18, 2016

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DOI: 10.1021/acschemneuro.6b00029
ACS Chem. Neurosci. 2016, 7, 767−775

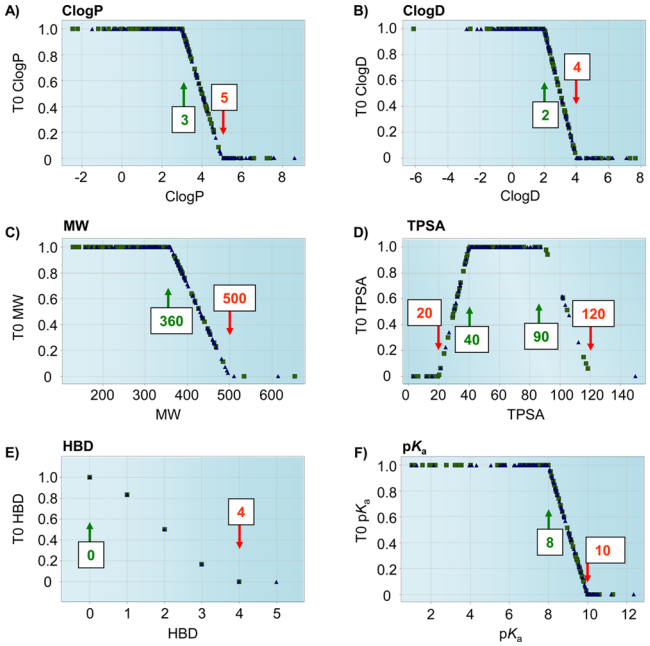

Figure 1. Each plot represents one of the six physicochemical property desirability functions used to generate the CNS MPO. Each point on a plot represents a drug or candidate. (A) ClogP, (B) ClogD, (C) MW, (D) TPSA, (E) HBD, and (F) pK_a. The most desirable (T0 = 1.0) and least desirable (T0 = 0.0) inflection points are marked with green and red arrows, respectively. A linear function was used to determine the desirability scores between the inflection points. Reprinted from ref 3. Copyright 2010 American Chemical Society.

(c) its demonstrated alignment with desirable *in vitro* ADME attributes. Importantly, CNS MPO can be used prospectively in molecular design.

Prior to the publication of our work in 2010, we began to routinely use the CNS MPO desirability method to help prioritize design ideas for advancement to synthesis. After nearly 8 years of use, we have reassessed the robustness of this tool and report herein the analysis and comparison of our second wave of candidates, post-CNS MPO implementation, with the original candidate set.

■ RESULTS AND DISCUSSION

Twenty-one clinical candidates identified post-CNS MPO implementation ("CNS MPO candidate set" henceforth) and the original candidate (108) and drug (119) sets from our 2010 publication[1] were evaluated using the original set of six physicochemical properties used to define the CNS MPO algorithm: ClogP, ClogD, MW, TPSA, HBD, and pK_a (Figure 2). The ClogP median value (2.2) for the CNS MPO candidate set is a log unit lower than that of the previous candidates (3.3) and one-half log unit lower than that of the drug set (2.8). The ClogP values for the majority of the CNS MPO candidates varied from 1.7 (25th percentile) to 3.0 (75th percentile). The median value for ClogD (3.0) of the CNS MPO candidate set was higher than the corresponding ClogD median values for the drug and candidate sets (1.6 and 2.3, respectively). Comparison of the most basic pK_a median value for the three sets of compounds showed that the CNS MPO candidate set had a lower median basic pK_a (4.1) than the drug (8.0) and candidate (8.3) sets; this difference of 4 log units was statistically significant. Given that the CNS MPO candidate set is more neutral in nature, the higher median value for ClogD (3.0) vs ClogP (2.2) for this compound set suggests that the ClogD calculator may be overestimating ClogD values (*vide infra*). The CNS MPO candidate set MW (397.9) median value was higher than the drug set MW (305.3) and the candidate set MW (360.4) by 94.6 and 37.5 Da, respectively. Polarity, as described by TPSA, ranged from 73.4 Å^2 (25th percentile) to 88.4 Å^2 (75th percentile), with a median value of 80.8 Å^2 for the CNS MPO candidate set, nearly double that of the drug set (44.8 Å^2). The shift to more polar property space was intentional and designed to improve safety outcomes; this is discussed later in the article. All three sets of compounds had a minimal number of HBDs, with the median value being one HBD, suggesting that optimization of HBD to ≤1 may increase the odds of identifying CNS-penetrant compounds. From this analysis, it is clear that the CNS MPO candidate set occupies a different property space from that of either the original candidate or drug set. By focusing on the multiparameter approach, rather than being limited by single parameters and hard cutoffs in design, we have expanded "traditional CNS space" to include molecules that are less lipophilic, less basic, more polar, and larger while retaining good CNS exposure. This approach has enabled access to new CNS target classes such as kinases and proteases, which may require different physical chemical property ranges in order to achieve higher potency.

We calculated the CNS MPO desirability scores for the three compound sets and compared the compound distribution across the desirability continuum (0−6) (Figure 3).[3] The CNS MPO candidate set had a higher overall desirability score than the candidate and drug sets despite the fact that median ClogD and MW values were in the less desirable range. The improvement in CNS MPO desirability is achieved because the median ClogP and TPSA values were in a more desirable range, reinforcing the value of a flexible multiparameter approach. The CNS MPO candidate set had the highest numerical percentage of compounds with CNS MPO desirability score >5 (48%) compared to that of both the drug (40%) and candidate (30%) sets. The original candidate set had a large percentage (31%) of compounds in the 3−4 range, whereas the CNS MPO candidate set had only 19% in this range, which is comparable to that of the drug set (16%). The overall distribution of the CNS MPO candidate set resembles that of the drug set, with the number of compounds in each bin increasing with the desirability score. Furthermore, no compound in the CNS MPO candidate set exhibited a desirability score less than 2. Collectively, this suggests that our compound designs are effectively using CNS MPO to explore and balance compound properties.

In our original analysis of drugs and candidates, the probability of a compound possessing desirable *in vitro* ADME attributes (high P_{app}, low P-gp efflux liability, low unbound human liver microsome clearance) increased as its CNS MPO desirability score increased. In the current analysis, the CNS MPO candidate set had a higher CNS MPO median value (5.0) than the original candidate set, and indeed, across all three ADME assessments, the CNS MPO candidate set provided a higher percentage of optimal values (Figure 4). All 21 compounds in the CNS MPO set were tested in each of the *in vitro* assays: 86% of the compounds had high passive permeability, 90% exhibited low P-pg efflux liability, and 90% displayed low metabolic clearance. It is interesting to note that the CNS MPO candidate set also outperformed the drug set in

DOI: 10.1021/acschemneuro.6b00029
ACS Chem. Neurosci. 2016, 7, 767−775

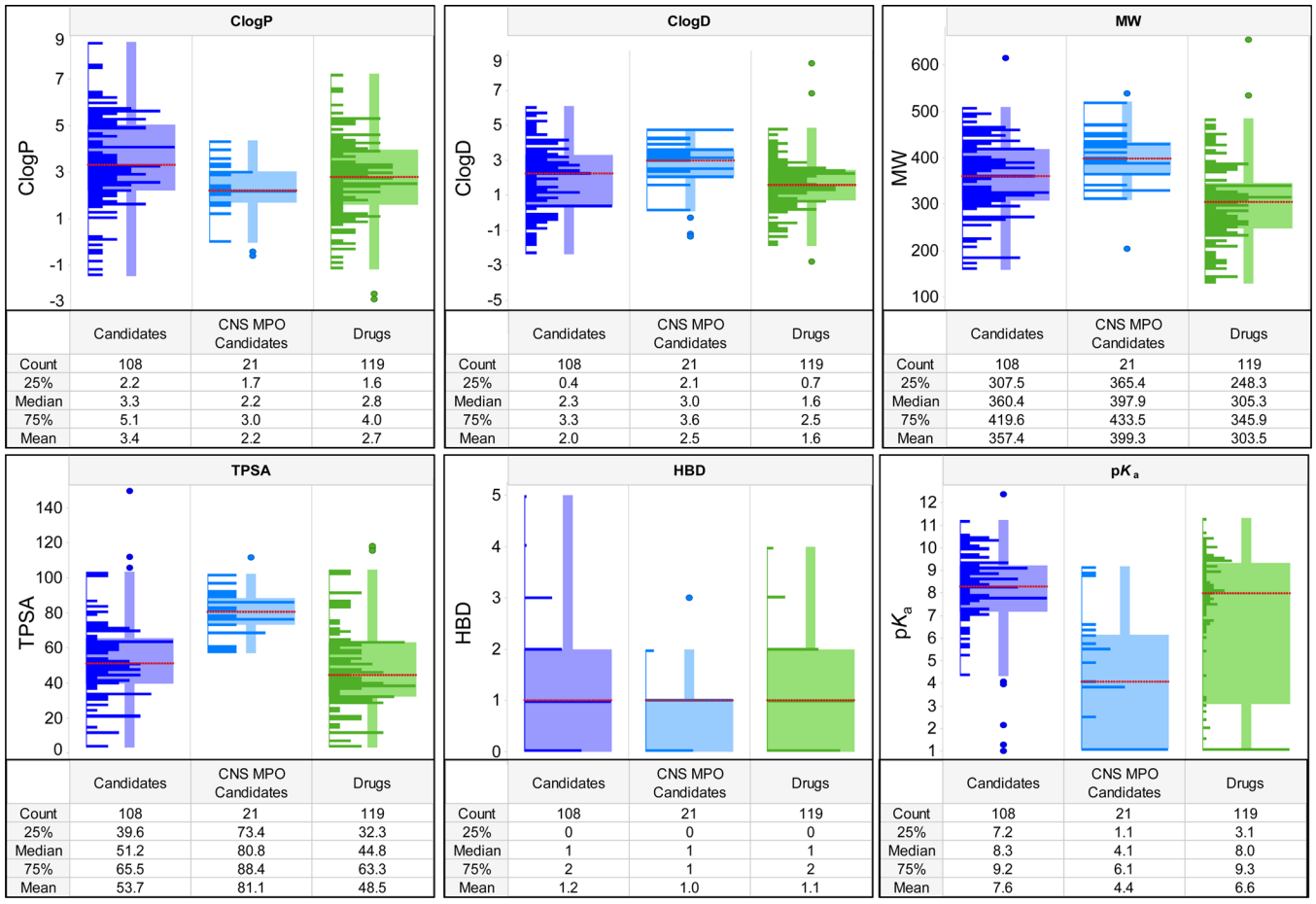

Figure 2. Physicochemical property distribution of drugs, candidates, and candidates post-CNS MPO implementation (CNS MPO candidates) for ClogP, ClogD, MW, TPSA, HBD, and most basic pK_a. BioByte (version 4.3) was used to calculate ClogP, and ACD software (version 12.1) was used to calculate ClogD and pK_a. Count represents the number of compounds included in each analysis. Red dotted line represents the median value.

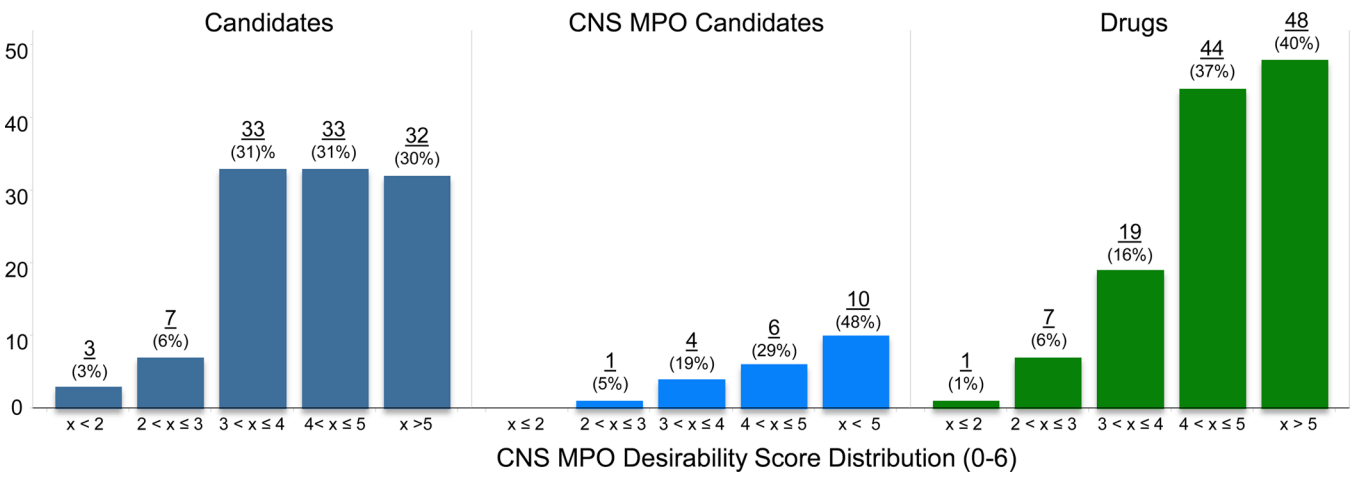

Figure 3. CNS MPO desirability scores for candidates, CNS MPO candidates, and drugs were plotted from low to high CNS MPO desirability score along the *x* axis. The compound count and percentage for each bin appear above the corresponding bar.

having a higher percentage of compounds with optimal ADME values.

Previously, we reported that an increase in the CNS MPO desirability score led to an increase in the number of individual compounds with alignment of *in vitro* ADME attributes defined as a compound satisfying one or more criteria of high P_{app}, low P-gp ER, and low $CL_{int,u}$. We compared the three sets to determine if the ADME alignment trend would hold true for the new compound set (Figure 5). A clear distribution of compounds exhibiting varying degrees of alignment was observed across the CNS MPO desirability continuum. Compounds having full alignment of ADME attributes heavily populated the higher end of the CNS MPO score spectrum; for the CNS MPO candidate set, the preponderance (94%) of

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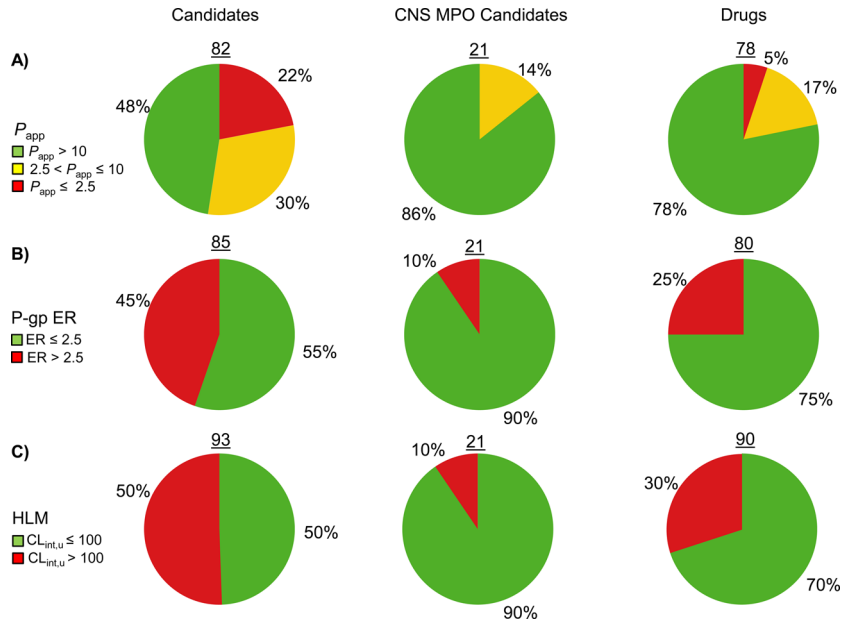

Figure 4. Distribution of *in vitro* permeability P_{app}, P-gp efflux ratio, and unbound human liver microsome (HLM) intrinsic clearance ($CL_{int,u}$) for candidates, CNS MPO candidates, and drugs. (A) Binned values for P_{app} obtained from the RRCK assay, which are color-coded by high permeability (P_{app} > 10, green), moderate permeability (2.5 < P_{app} ≤ 10, yellow), and low permeability (P_{app} ≤ 2.5, red) in units of 10^{-6} cm/s. (B) Binned values for P-gp efflux liability obtained from the MDCK-MDR1 assay, which are color-coded by low P-gp liability (ER ≤ 2.5, green) or high P-gp liability (ER > 2.5, red). (C) Binned values for clearance ($CL_{int,u}$) assessed in a HLM stability assay, which are color-coded by low clearance ($CL_{int,u}$ ≤ 100 mL/min/kg, green) and high clearance ($CL_{int,u}$ > 100 mL/min/kg, red). Pie charts are color-coded based on the value of the bin, from desirable values (green) to undesirable values (red), and the number of compounds in each pie is shown above each pie graph.

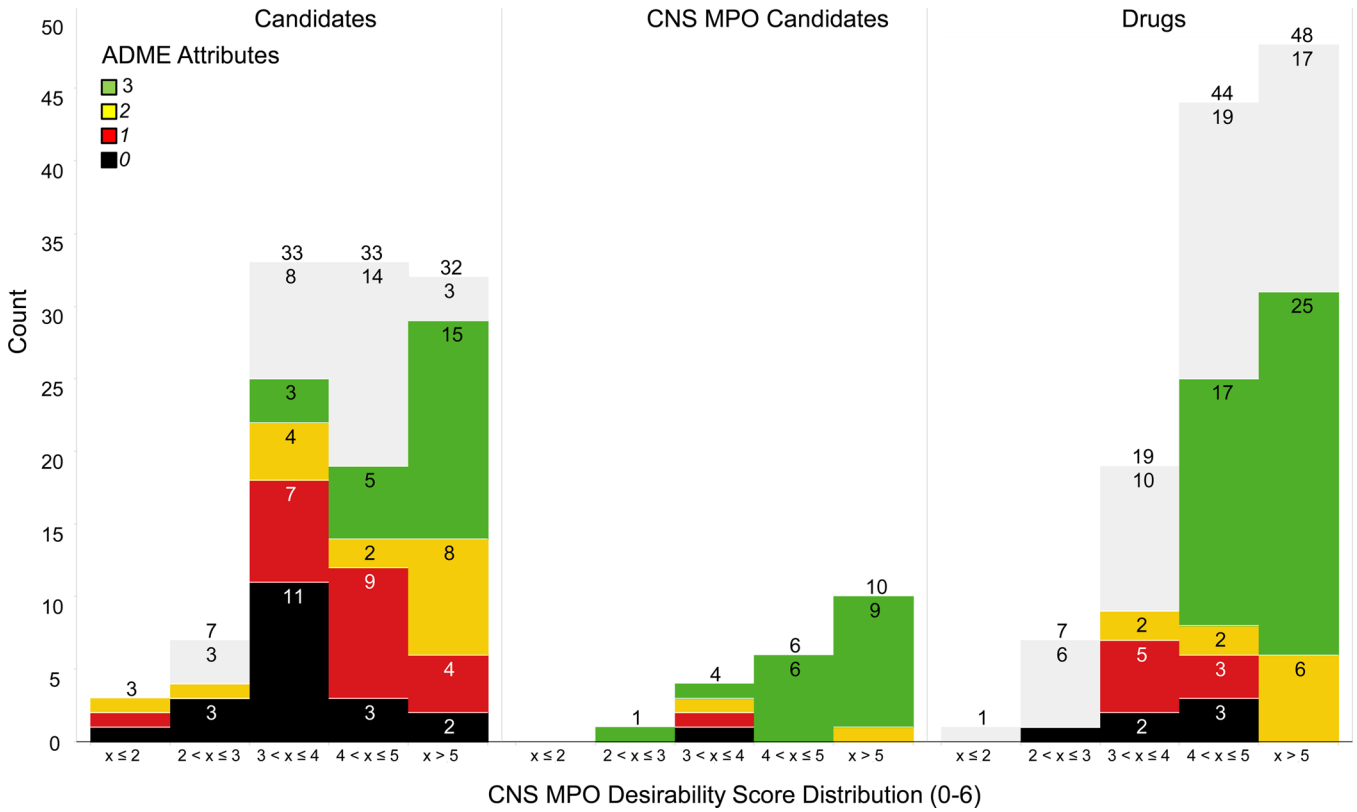

Figure 5. Bar chart of binned values for alignment of desired ADME attributes in one molecule: high P_{app}, low P-gp ER, and low $CL_{int,u}$. Color-coding for number of desired ADME attributes being satisfied: 3/3 (green), 2/3 (yellow), 1/3 (red), 0/3 (black), and not available (gray). Binned CNS MPO scores are plotted along the *x* axis, and compound count is plotted along the *y* axis. The number of compounds in each bar is given above the bar graph, and the number of compounds with the defined alignment is within the bar.

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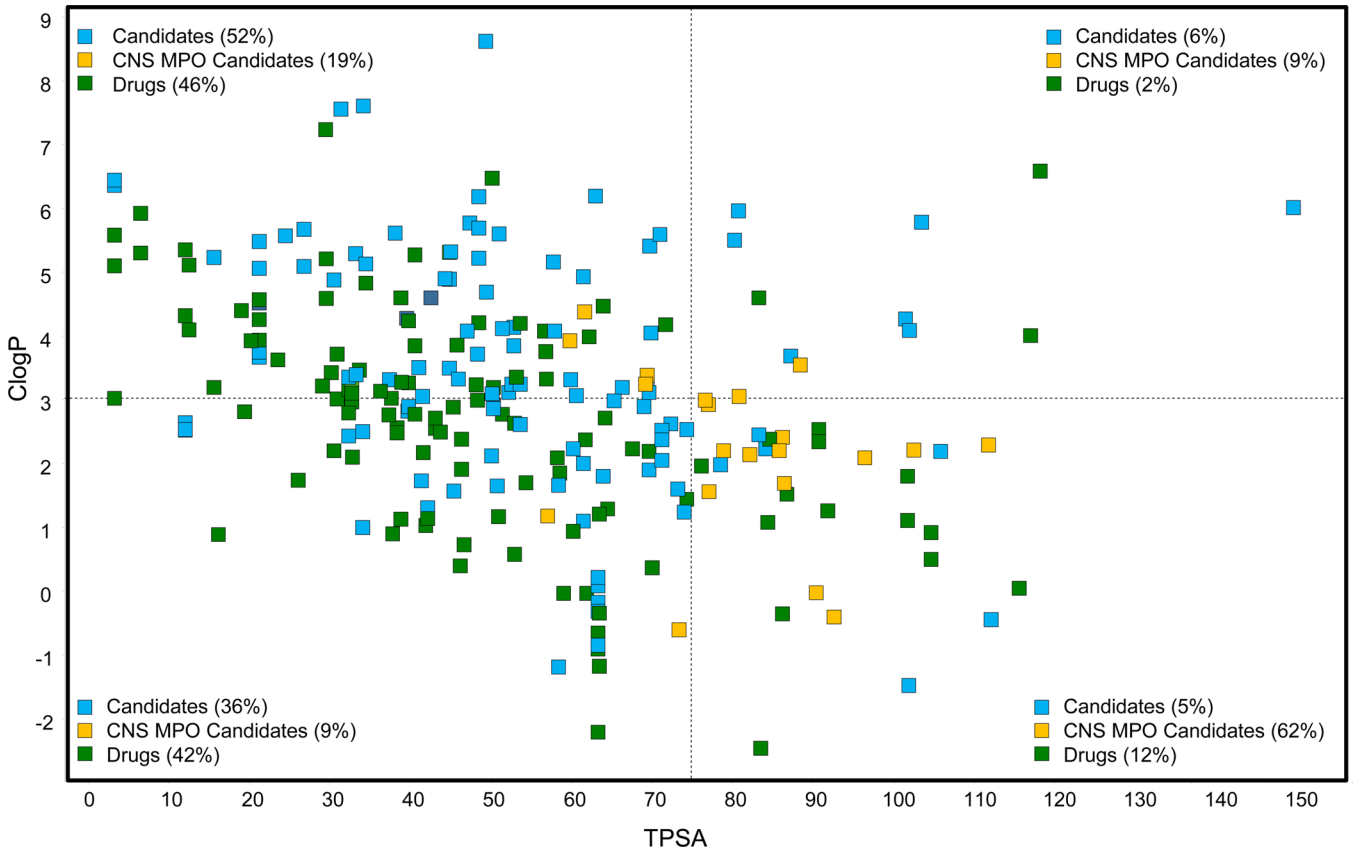

Figure 6. Distribution of candidate (n = 108), CNS MPO candidate (n = 21), and drug (n = 119) sets across the ClogP and TPSA property spaces. Dotted black lines represent the cutoffs for preferred ClogP (≤3) and TPSA (>75 Å) values, as proposed by Hughes et al.[6] Compounds are colored by compound set: candidates (light blue), CNS MPO candidates (yellow), and drugs (green). The percentage of each compound set occupying a given quadrant is provided in the corresponding quadrant.

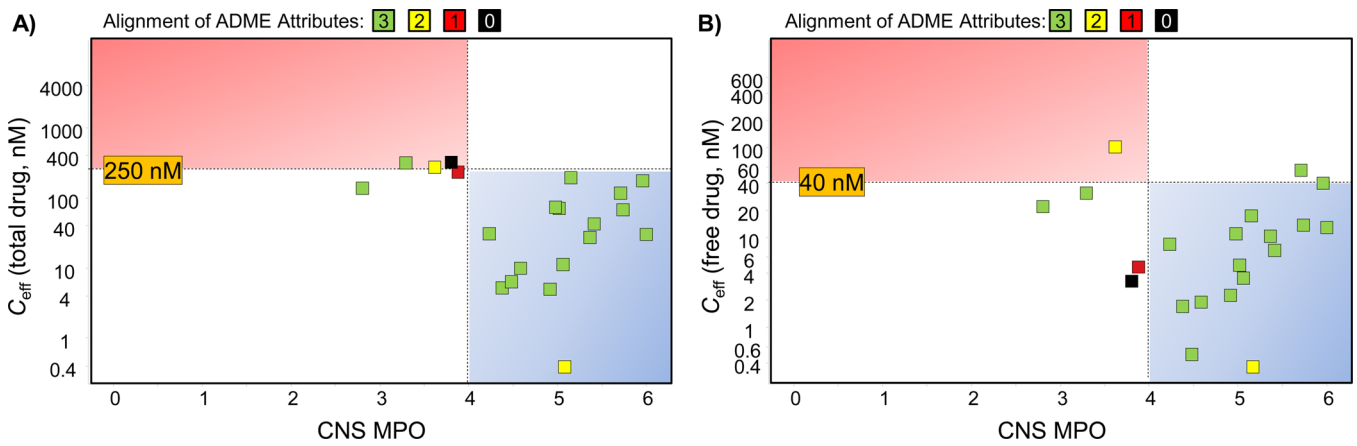

Figure 7. Distribution of the CNS MPO candidate set, plotted across CNS MPO desirability and (A) C_{eff} (total drug, nM) and (B) C_{eff} (free drug, nM). Compounds are colored by ADME attribute alignment: high P_{app}, low P-gp, and low $CL_{int,u}$. Color-coding for satisfying desired ADME attributes: 3/3 (green), 2/3 (yellow), 1/3 (red), and 0/3 (black).

compounds with CNS MPO scores above 4 displayed full alignment of ADME attributes.

In our original analysis of the drugs and candidates, we examined the distribution of the compounds from these two sets across the physicochemical properties ClogP and TPSA, which have been linked to safety risk (TPSA ≤ 75 Å^2, ClogP > 3).[6] One of the key objectives in our original work was to prospectively and successfully move CNS design into the more favorable safety risk property space (TPSA > 75 Å^2, ClogP ≤ 3) while maintaining good CNS penetration. Examination of the three sets suggested that the CNS MPO candidate set achieved this objective: 62% of the compounds in the CNS MPO candidate set reside in the lower safety risk quadrant in comparison to 12 and 5% for the drug and candidate sets, respectively (Figure 6). This shift in property space to higher polarity and lower lipophilicity suggests that the CNS MPO desirability tool can help to expand CNS property space while maintaining brain penetration, aligning ADME attributes, and

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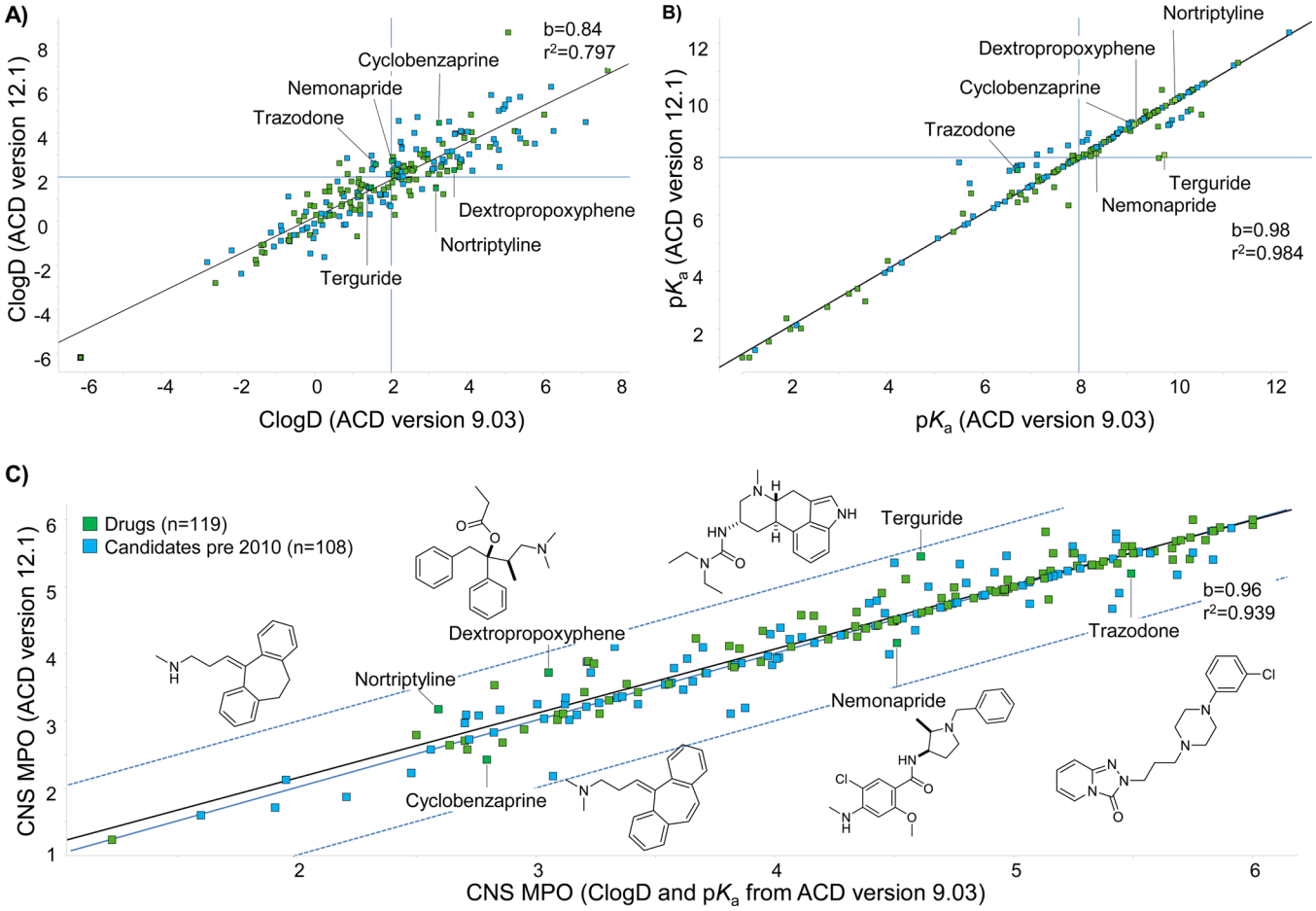

Figure 8. Each plot compares an end point from our original publication in 2010 to the current calculated values.[3] (A) ClogD, (B) Basic pK_a, and (C) CNS MPO. Compounds are colored by compound type: drugs are shown in light green and candidates are in light blue. A straight-line fit through the data is shown by the black line. For (C), the solid blue line represents a 1:1 correlation, and the dotted blue lines enclose a range of ±1 unit around the MPO desirability score.

Table 1. Representative Compounds for Which CNS MPO Changed with Updated Software

drug name	CNS MPO 2015	CNS MPO 2010	ClogD 2015	ClogD 2010	T0 ClogD 2015	T0 ClogD 2010	Delta T0 ClogD	Basic pK_a 2015	Basic pK_a 2010	T0 Basic pK_a 2015	T0 Basic pK_a 2010	Delta T0 Basic pK_a
trazodone	5.2	5.5	2.6	1.6	0.7	1.0	0.3	7.5	6.7	1.0	1.0	0.0
terguride	5.5	4.6	1.6	1.4	1.0	1.0	0.0	8.1	9.8	1.0	0.1	−0.8
dextropropoxyphene	3.7	3.1	2.3	3.7	0.8	0.2	−0.7	9.2	9.2	0.4	0.4	0.0
nemonapride	4.2	4.5	2.7	2.0	0.6	1.0	0.3	8.4	8.4	0.8	0.8	0.0
cyclobenzaprine	2.4	2.8	4.5	3.3	0.0	0.4	0.4	9.2	9.2	0.4	0.4	0.0
nortriptyline	3.2	2.6	1.5	3.2	1.0	0.4	−0.6	10.0	10.0	0.0	0.0	0.0

reducing safety risk. The ability to move design to more polar, less lipophilic property space is remarkable given the dogma in the literature indicating that CNS drugs require enhanced lipophilicity and low polarity to facilitate passage through the blood−brain barrier.[7]

Recently, we reported that the projected human efficacious concentration (C_{eff}) was a critical end point for predicting whether a CNS compound would survive two-species exploratory toxicology studies.[8] Compounds that had a C_{eff} (total drug) of less than 250 nM and a C_{eff} (free drug) of less than 40 nM had a greater chance of surviving animal safety studies and progressing into regulatory toxicology studies. We examined the relationship between C_{eff} and CNS MPO desirability score to understand where the CNS MPO candidate set resided (Figure 7). Although not all of the compounds achieved the C_{eff} total (≤250) and free (≤40) drug level objectives, most compounds did, and a majority of these compounds also had full alignment of ADME attributes and high CNS MPO scores. It is worth noting that the five compounds that did not achieve the C_{eff} objective were on the border of achieving this goal. This fact should remind us that the optimal values for CNS MPO and C_{eff} end points are guiding principles to drive toward compound quality, low projected daily dose, and improved compound survival; they should not be used as hard cutoffs or rules.

In designing the CNS MPO desirability tool, we chose six fundamental physicochemical properties that had been extensively used by the medicinal chemistry community to optimize *in vitro* ADME attributes and to address safety risks. While some properties are either invariant (MW) or well-

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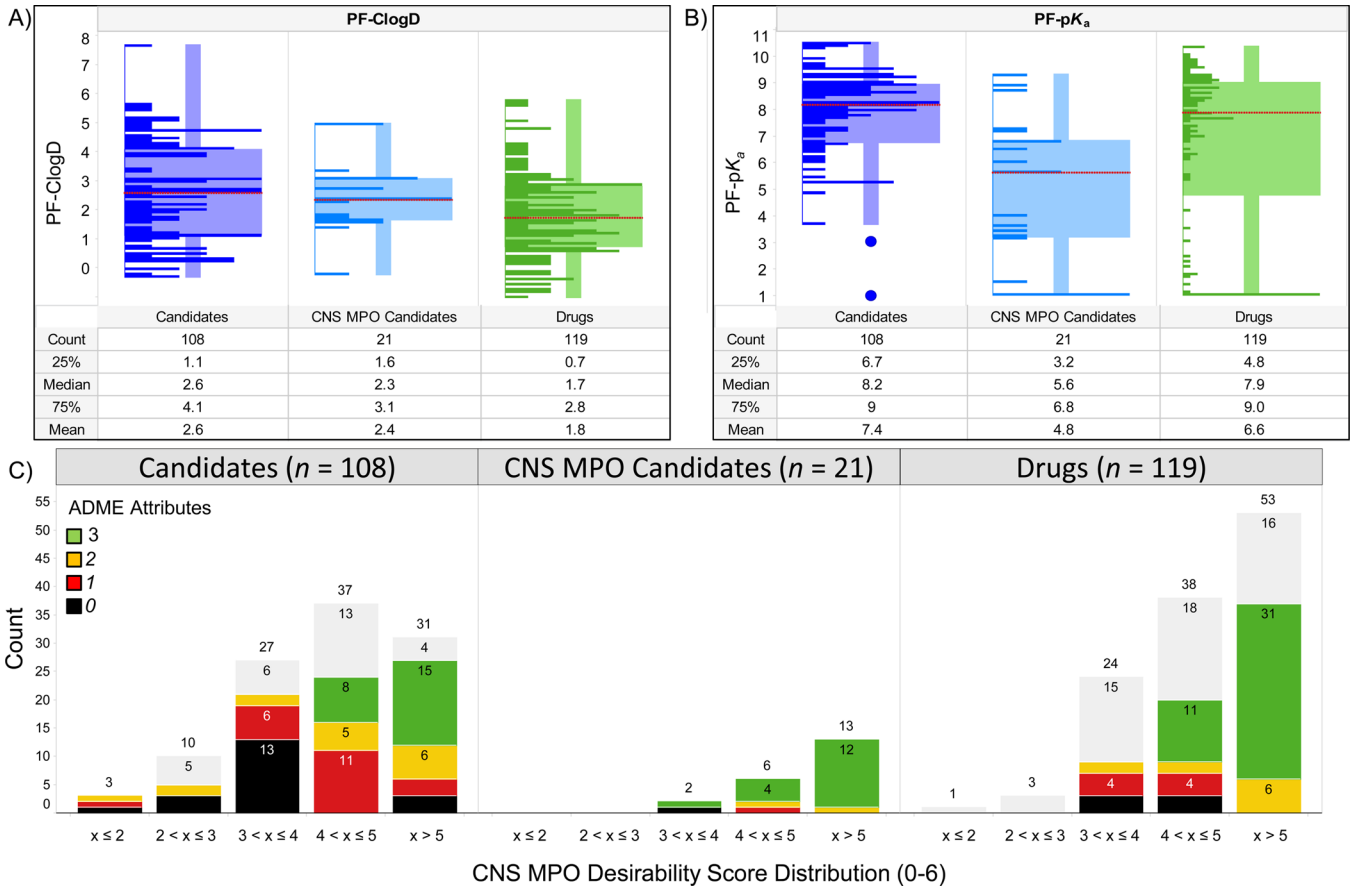

Figure 9. Physicochemical property distribution of drugs, candidates, and candidates post-CNS MPO implementation for Pfizer-parametrized (A) ClogD and (B) pK_a. Count represents the number of compounds included in each analysis. The dotted red line indicates the median value for the given property. (C) Bar chart of binned values for alignment of desired ADME attributes in one molecule: high P_{app}, low P-gp, and low $CL_{int,u}$. Color-coding for desired number of ADME attributes being satisfied versus CNS MPO desirability score: 3/3 (green), 2/3 (yellow), 1/3 (red), and 0/3 (black); compounds with data not available are captured in the total compound count. Binned CNS MPO scores are plotted along the *x* axis, and compound count is plotted along the *y* axis and scaled to 100%. The number of compounds in each bar is given above the bar, and the number of compounds with the defined alignment is within the bar.

defined (TPSA[9] and HBD), others are modeled based on experimental values (ClogP, ClogD, and pK_a). Because of the utilization of piecewise linear transformation functions, we expected the CNS MPO score to be relatively insensitive to small variability in these modeled properties. Of these three modeled properties, we have observed that the predicted ClogD and pK_a values generated by ACD/Laboratories software are most subject to change. For some compounds, predictions from the recent version of ACD software (version 12.1) vary more than one unit in ClogD or pK_a from those with the previous release (version 9.03) (Figure 8A,B). As anticipated, when using the newer model calculations of ClogD and pK_a to compute the CNS MPO desirability score, we observed very good correlation and small variances in the CNS MPO score (R^2 = 0.94, slope = 0.96), consistent with our original objective of a robust algorithm (Figure 8C). The changes in CNS MPO desirability score resulting from the modified values of ClogD and pK_a are all less than one unit. Some of the largest changes in the drug set are detailed in Table 1. For example, dextropropoxyphene originally had a CNS MPO desirability score of 3.1. When recalculated using the updated ACD/Laboratories software, this value shifted to 3.7; the change in score is driven solely by a change in ClogD (Δ = 1.4). The fact that most compounds' CNS MPO desirability scores change very little highlights an additional advantage of multiparameter optimization and serves as another caveat about relying on a single parameter to drive the decision to invest resources in compound synthesis.

The commercial BioByte and ACD/Laboratories software packages for calculating ClogP, ClogD, and pK_a represent two sources for these calculated end points. Many pharmaceutical companies have their own computational tools for generating these values. Highlighted in the property section analysis above was the fact that ACD/Laboratories predicted the median ClogD at pH 7.4 for the CNS MPO candidates to be higher than ClogP, which suggested to us that this calculator was overestimating ClogD. Therefore, we examined the distribution of the three compound sets using our internally parametrized ClogD calculator (PF-ClogD; Figure 9A). The median ClogD values for the candidate (2.6) and drug (1.7) sets were in line with the values obtained from ACD ClogD (version 12.1); however, the median ClogD value (2.3) for the CNS MPO compound set decreased nearly a log unit (0.7) from the ACD ClogD value. The ClogD values from the internally parametrized calculator are likely closer to measured values for the CNS MPO candidate set as it is trained with a large set of Pfizer internal experimental data. We also examined the distribution of compounds using an internally parametrized pK_a calculator (Figure 9B). For the CNS MPO compound set, pK_a increased from the ACD pK_a of 4.1 to 5.6. Using the internally

DOI: 10.1021/acschemneuro.6b00029
ACS Chem. Neurosci. 2016, 7, 767−775

parametrized calculated values for ClogD and pK_a in the CNS MPO algorithm, we re-evaluated the alignment of drug properties across the CNS MPO continuum. Overall, a better relationship emerged between higher desirability scores and alignment of drug properties (PF-pK_a; Figure 9C). The analysis suggests that, once validated, other ClogP, ClogD, and pK_a calculators can be used to further enhance prospective use of the CNS MPO score in aligning ADME and safety attributes in a single molecule.

CONCLUSIONS

Significant progress has been made in prospectively designing molecules using the CNS MPO desirability tool. This tool, based on an algorithm using a set of six fundamental physicochemical properties, has expanded the design space for CNS candidates and demonstrated the advantage of utilizing a flexible, multiparameter approach rather than individual cutoffs for physicochemical properties. The desirability tool has helped to increase the percentage of compounds being nominated with robust alignment of ADME attributes and suitable brain penetration and has moved design into a lower-risk safety space.[6] One additional advantage of using the CNS MPO approach in drug discovery is that it is not biased toward individual historical physicochemical end points. This is exemplified by the CNS MPO candidate set, which is less lipophilic, less basic, more polar, and larger than the marketed CNS drug set. Despite changes in calculated values for ClogD and pK_a since 2010, the analysis provided by the CNS MPO tool remains valid, with only small changes in overall desirability scores for the drug and candidates sets. The CNS MPO design tool has played a role in reducing the number of compounds submitted to exploratory toxicity studies and increasing the survival of the CNS MPO candidates through regulatory toxicology into First in Human studies. Furthermore, all compounds for which we have measured human CSF drug levels exhibited good CSF/$C_{p,u}$ ratios and sufficient free drug levels to adequately engage the target mechanism in the CNS compartment. While there will always be the possibility of idiosyncratic findings and on/off-target pharmacological side effects, utilization of the CNS MPO tool in our design phase has reduced attrition and improved compound quality. Furthermore, it has been used as a design tool elsewhere, both within and outside Pfizer. A Google Scholar search on the original CNS MPO manuscript yielded over 200 citations. These reports evaluating the CNS MPO tool are from authors with over 100 unique affiliations, ranging from universities to large and small pharmaceutical companies. In one example, Rankovic has shown that an increasing CNS MPO score correlates with increasing in vivo brain exposure in preclinical species.[10] Rankovic analyzed a diverse set of 616 compounds from Lilly's database for which experimental unbound brain concentration ($C_{b,u}$) data was available and demonstrated that 81% of compounds with a high CNS MPO score (>5) had $C_{b,u}$ values classified as high; conversely, 100% of compounds with low CNS MPO scores (≤2) had low $C_{b,u}$ values.[10]

The CNS MPO tool is only one of several approaches that medicinal chemists can use for decision making in the design of novel drug candidates. One of its advantages is its simplicity. The CNS MPO tool is easy to implement using common software such as Excel; it can also be formatted into a mobile app. Table 2 provides an active table that allows rapid calculation of CNS MPO scores: to activate, follow this link or the one in the table, double-click the table that opens, and enter values for each property.

Table 2. Active CNS MPO Calculator[a]

CNS MPO calculator		
property	value	T0
ClogP	3.7	0.65
ClogD	2.7	0.65
TPSA	90	1.00
MW	375	0.89
HBD	1	0.83
pK_a	9	0.50
CNS MPO		**4.5**

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METHODS

Data Collection. *Pfizer CNS MPO Candidates.* The CNS MPO candidates included in our analysis consisted of 21 compounds that met the appropriate preclinical profile to advance into regulatory safety studies and, if appropriate, clinical studies. The drug and candidate sets used in this analysis were the same as those in our 2010 publication.[3]

Desirability Functions and MPO Score Calculation. For the work herein, calculated physicochemical properties were obtained using standard commercial packages: BioByte, version 4.3, for ClogP calculations, ACD/Laboratories, version 9.03 or version 12.1, for ClogD at pH 7.4, and ACD/Laboratories, version 9.03 or version 12.1, for pK_a. For calculation of TPSA, the Ertl methodology was employed.[9] The CNS MPO scores were calculated using the previously published method.[3]

Data Analyses. The data was visualized with JMP or TIBCO Spotfire.[10−12] In the histogram and box plots (Figures 2 and 9), the interquartile range (25th to 75th percentiles) is represented by the larger box with median values in a red dash line, and upper and lower adjacent values are represented by the thin bar. Points outside upper and lower adjacent values are defined as outliers (dots).

Statistical analyses were carried out using SAS JMP 10 statistical software.[11] Student's *t* tests of pairs were carried out to compare the sets (Table 3). The small sample size of the CNS MPO candidate set degrades the power of statistics in some comparisons.

Table 3. Statistical Analysis

	candidates vs CNS MPO candidates *p*-value	drugs vs CNS MPO candidates *p*-value
MW	0.0428*	<0.0001*
ClogP	0.0050*	0.2288
ClogD	0.2973	0.0444*
TPSA	0.1075	<0.0001*
HBD	0.4601	0.7251
pK_a	<0.0001*	0.0020*

ADME Data. Data on the following *in vitro* ADME properties was generated in-house utilizing the following high-throughput assays: (a) passive apparent permeability (P_{app}), assayed utilizing the RRCK cell line;[13] (b) P-glycoprotein (P-gp) efflux liability, assessed via an assay utilizing the MDCK-MDR1 cell line, an MDCK line stably transfected with the MDR1 gene, which expresses a functionally active human P-gp;[14] (c) metabolic stability, expressed as unbound intrinsic clearance ($CL_{int,u}$), calculated according to eq 1[15] using the measured intrinsic clearance (CL_{int}), obtained via an *in vitro* high-throughput human liver microsome assay, and an *in silico* model for free microsome fraction ($cF_{u,mic}$):[16]

$$CL_{int,u} = \frac{CL_{int}}{cF_{u,mic}} \quad (1)$$

DOI: 10.1021/acschemneuro.6b00029
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Compounds included in these studies were handled as 30 mM stock solutions generated, dispensed, and checked for purity by Pfizer's internal sample bank and subsequently assayed in the ADME and safety assays. The data generated from these assays for the drugs and candidates are included in the previous publication.[1]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acschemneuro.6b00029.

Drug and candidate set data in tabulated form: PubName, Set, MW, ClogP, TPSA, ClogD, HBD, pK_a, P_{app} Op, P_{app} Mean, P_{app} SD, P_{app} CV, P_{app} SEM, P_{app} Upp95, P_{app} Low95, P_{app} N, P-gp OP, P-gp Mean, P-gp SD, P-gp CV, P-gp SEM, P-gp Upp95, P-gp Low95, P-gp N, $cF_{u,mic}$, CLIA OP, CLIA Mean, CLIA SD, CLIA CV, CLIA SEM, CLIA Upp95, CLIA Low95, CLIA N, and CLIu. CNS MPO component and desirability scores for drugs (119), candidates (108), and the CNS MPO candidate set (21). CNS MPO desirability distribution plot for drugs with target class labeled (PDF)

Web-Enhanced Feature

A table that allows rapid calculation of CNS MPO scores is available in the online version of the article.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the entire Worldwide Medicinal Chemistry group at Pfizer for support in implementing and applying the CNS MPO desirability approach in the design of drug molecules. The authors thank Katherine Brighty for her insightful comments on this manuscript.

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DOI: 10.1021/acschemneuro.6b00029
ACS Chem. Neurosci. 2016, 7, 767−775