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## Assessing molecular scaffolds for CNS drug discovery

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Teaser sentence: A simple multi-parametric scoring system can help prioritise lead-like compounds and synthetic methodology that would serve as high-quality starting points for CNS drug discovery programmes.

## Assessing molecular scaffolds for CNS drug discovery

### Introduction

The molecular properties of hit compounds can profoundly influence the likelihood of development into high quality chemical tools or candidates worthy of clinical investigation [1, 2]. During lead-optimisation, molecular weight (MW), lipophilicity and complexity tend to increase and as such the properties required of screening library compounds differ significantly from those of drugs [3-5]. There is a need to continue the development of screening collections that would serve as high quality starting points. Analyses by scientists from GSK showed that the vast majority (>97%) of commercially-available compounds did not meet their criteria for lead-likeness [6]. Moreover, the problem of sourcing large numbers of lead-like molecules is heightened when the issue of chemical diversity is also considered. To address these challenges, lead-oriented synthesis has emerged as an approach in which molecular property and diversity analyses inform the development of new synthetic methodology [7-9].

Diseases of the Central Nervous System (CNS) represent an area of huge unmet medical need. Drug discovery within this therapeutic area faces some unique challenges, alongside issues of target selection and validation in often unrepresentative pre-clinical animal models, the challenge of controlling physicochemical properties is exacerbated [10, 11]. Following administration drugs must permeate the blood-brain barrier (BBB) and successfully modulate a target protein to achieve efficacy. As a consequence, CNS drugs tend to be less polar, smaller and more rigid than those marketed for non-CNS indications [12]. Furthermore, additional constraints on the number and/or type of functional groups incorporated (e.g. carboxylates or amides) are advisable to avoid poor permeability and active efflux [13]. Lead-like space for CNS drug discovery is therefore likely to be different than that defined for other therapeutic areas. Our aim was to establish and validate a framework for identifying scaffolds that may efficiently explore CNS-relevant, lead-like chemical space.

### Scoring metrics for CNS drugs

Approaches that can facilitate drug design within the confines of CNS-relevant physicochemical space have proved popular [14]. Scientists at Pfizer have recently shown that use of their CNS Multi-Parameter Optimisation (MPO) scoring tool has increased the percentage of clinical candidates discovered that possess desirable ADMET properties and cross the BBB [15]. This tool assigns a desirability score (0.05-1) for six physicochemical properties: MW; lipophilicity, calculated partition coefficient (cLogP); distribution coefficient at pH = 7.4 (cLogD); most basic centre (pK<sub>a</sub>); number of hydrogen bond donors (HBD) and topological polar surface area (TPSA) [16]. The sum of these scores provides an overall CNS MPO score on a 0.3-6 scale. For each individual property optimal ranges have been defined and, importantly, hard cut-offs were not used (Figure 1). In their original study, the authors

showed that a set of 119 marketed CNS drugs had generally higher CNS MPO scores than a set of 108 Pfizer CNS candidates [16]. Moreover, after routine application of the tool, nominated CNS candidates had been shifted towards more polar and less lipophilic property space [15]. Simplicity of application and a clear mechanistic link allow chemists to understand how modification of molecular structure changes the CNS MPO score. It can therefore significantly assist in the strategy of compound optimisation.

In an alternative approach, scientists from Merck recently describe a probabilistic MPO (pMPO) scoring function to describe CNS drug-likeness [17]. Statistical analysis of the properties in two training sets (299 brain penetrant and 366 non-brain penetrant marketed drugs) led to the identification of relevant molecular properties, their relative weighting and optimal values for each descriptor. Overall, compounds were then assigned a pMPO score on a 0-1 scale.

For most compounds, the CNS MPO and pMPO scores correlated reasonably well. However, larger and more lipophilic compounds, such as Pimozide (MW = 462, cLogD = 4.8; CNS MPO = 2.1, pMPO = 0.72), were penalised more heavily by their CNS MPO score. In contrast, smaller, more polar compounds such as Flucytosine (MW = 129, cLogD = -1.1; CNS MPO = 5.5, pMPO = 0.46) were penalised more heavily by their pMPO. Whilst neither system was intended solely as a prediction of BBB permeation, pMPO was able to better predict efflux liabilities for a set of 500 randomly chosen compounds from the Merck compound collection, particularly for compounds with low efflux ratios (<2). Both tools add value in the optimisation of CNS leads that must satisfy criteria including solubility, permeability, safety and the myriad of factors that may influence brain penetration [18, 19].

Alternative scoring systems have thus been developed to capture the drug-likeness of CNS drugs and drug candidates [15-17, 20, 21]. However, since the properties of drugs are substantially different to those of leads, none of these scores are appropriate for assessing the suitability of compounds in early-stage CNS drug discovery.

### **Identification of CNS lead-like scaffolds**

The identification of novel and diverse scaffolds that, on decoration, would yield lead-like compounds for CNS drug discovery is a significant challenge [22]. Whilst the scoring protocols described earlier have been constructed based on the properties of drugs and candidate drugs, no method currently exists that has been specifically designed for the purpose of assessing CNS lead-likeness. Our objective was to direct synthetic strategy and resource on the basis of the potential of a scaffold to produce CNS lead-like libraries. To assist the development of synthetic approaches to such scaffolds, we have utilised an MPO score that captures CNS lead-likeness. The CNS lead-likeness of potential scaffolds may be assessed by comparing the mean scores of virtual libraries obtained by decoration with a standard set of medicinal chemistry capping groups.

Our CNS Lead MPO score is a modification of Pfizer's CNS MPO score, and is the sum of desirability scores (0.05-1) for the same six molecular properties (MW, cLogP, cLogD, pK<sub>a</sub>, HBD and TPSA). We chose to modify this system as we believe this is a well understood and studied protocol within the CNS medicinal chemistry field. Rather than introduce a completely new protocol which may cause confusion, it is hoped that the CNS Lead MPO scoring protocol may complement use of the original system depending on the needs of a specific project or objective. The boundaries for optimal scores were reduced for MW, HBD and TPSA (Figure 1) to leave scope for subsequent lead optimisation. In addition to increasing molecular weight during optimisation, it can be helpful to be able to add more polar atoms (which will increase TPSA and HBD) to control other properties (such as cLogD) and to increase affinity for the target protein within the confines of CNS drug-like physicochemical space [23]. Whilst the changes made to the original protocol employed by Pfizer are subtle, the outcome when using the two systems to assess the CNS lead-likeness of a potential screening compound may be significant. This is illustrated by comparing four potential screening compounds derived from known literature scaffolds in figure 1, panel B. Assuming equal potency at a given target compounds **1** and **2** would represent highly attractive starting point for a drug discovery program. They are small enough and have sufficiently low TPSA such that chemists would be able to modify and grow the molecules in search of further potency and optimised properties during a lead optimisation process. This view is reflected in high scores using both the Pfizer and CNS Lead MPO protocols. Compounds **3** and **4** however are both higher in molecular weight and more polar. These compounds still maintain properties well within the accepted range for a CNS drug and as such score well using the Pfizer MPO system. However, they would represent less attractive starting points in comparison to compounds **1** and **2**. There is a much smaller window of molecular weight and polarity in which to grow and optimise during the lead optimisation process and this is reflected in their low (<4.0) CNS Lead MPO scores. Molecules **3** and **4** would not be suitable as synthetic targets for populating a CNS screening library compared to molecules **1** and **2**.

### [FIGURE 1]

In order to illustrate our approach and before undertaking any experimental work, we scored a range of related pyrrolidine-based scaffolds that would be potentially accessible using a unified synthetic approach [27]. We proposed 25 potential scaffolds that might be prepared by combining an allylic carbonate building block with variable amine and aryl bromide building blocks (Figure 2, Panel A). Each scaffold was virtually decorated using a set of 98 standard medicinal chemistry capping groups (see Appendix 1 in the supplementary information online). At this stage structural filters were applied, removing compounds where [no. of amides + no. of sulfonamides + no. of ureas + no. of carbamates] > 1. Properties were calculated using Chemaxon software (version 15.3.30.0. see <https://www.chemaxon.com>) for each virtual compound and compounds with more than

one basic centre with predicted  $pK_a > 8$  were removed. For each virtual compound a CNS Lead MPO score was then determined.

At the scaffold level, the mean CNS Lead MPO scores were generally good (ranging from 3.85 to 5.36), and it is likely that CNS lead-like molecules could be prepared from even the lowest-scoring scaffold (**16**) (Figure 2, Panels B and C). Compounds based on scaffold **16** are penalised by the presence of the highly lipophilic *p*-trifluoromethyl benzyl group, as well as the large bicyclic ring system. In contrast, compounds based on scaffold **12** have a mean score of 5.35, stemming from the lower molecular weight of the scaffold (247 c.f. 353 for **16**) and a lower mean cLogD. The high mean CNS Lead MPO score for scaffold **12** may offer greater flexibility for the design of screening compounds with good CNS lead-like properties. By considering the mean CNS Lead MPO scores for a diverse set of virtual scaffolds it is possible to productively direct synthetic efforts to where they are most likely to return high quality screening compounds.

## [FIGURE 2]

### Synthesis and assessment of selected scaffolds

Five exemplar scaffolds with high mean CNS Lead MPO scores were selected for preparation (Figure 3, Panels A and B). Initially, the allylic carbonate **30** was combined with five alternative amine building blocks using an Ir-catalysed amination reaction. The yields for this step were similar (58-63%) with alternative nucleophiles, and the enantioselectivity was generally good (>80% ee in three cases; 67% ee with pyrrolidine as nucleophile). Subsequent Pd-catalysed aminoarylation with either 3-bromopyridine or 5-bromopyrimidine gave the required Boc-protected scaffolds in 38-66% yield and with 83:17 to >95 :< 5 diastereoselectivity. Whilst the yields for the aminoarylation step were moderate, the variable groups were introduced late in the synthesis and, in some cases, scaffolds were produced on a multi-gram scale (see Appendix 2 in the supplementary information online). Crucially, it was demonstrated that the synthetic approach was tolerant of polar functionality that is typically found in diverse lead-like scaffolds.

With the five scaffolds in hand, a set of screening compounds was synthesised that had a range of predicted physicochemical properties. Experimental data was generated on a subset of these compounds (Figure 3, Panel C). A kinetic solubility assay demonstrated that the selected compounds have high solubility ranging from 79-108  $\mu\text{g/mL}$ . *In vitro* permeability and propensity for passive transport was assessed using a PAMPA assay. The data show that 14 out of the 16 tested compounds may be classed as being highly permeable ( $P_{app} > 10^{-5}$  cm/s) [14]. Pleasingly, a computational model of brain penetration predicts the majority of these compounds (14 out of 16) to be highly brain penetrant with  $\log([\text{brain}]:[\text{blood}]) > -0.5$  (StarDrop® 6.2, <http://www.optibrium.com>).

## [FIGURE 3]

## Concluding remarks

Access to structurally-diverse molecules that lie within CNS lead-like chemical space can increase the efficiency and success of CNS drug discovery. Crucially, in order to design high quality screening compounds, it is important to acknowledge the distinctive lead-like chemical space associated with CNS drug discovery. Scoring tools can facilitate the identification of synthetic methods that can yield high quality scaffolds (and screening compounds) for CNS drug discovery. This has been illustrated *via* the synthesis of a cluster of pyrrolidine based scaffolds that have yielded screening compounds with experimentally-determined properties that align with CNS lead generation needs. Whilst further exemplification is not within the remit of this manuscript, the authors intend to further demonstrate the utility of this approach across a wider array of scaffolds in further publications. Within Takeda, the CNS Lead MPO score has been used to guide the synthesis of >3000 diverse and novel molecules. This collection has provided numerous hits that have translated into high quality chemical tools for proof-of-concept studies and potential candidates. Indeed the vast majority of these compounds were shown to be permeable (94% had  $P_{app} > 5 \times 10^{-6}$  cm/s) and are predicted to be highly brain penetrant (96% have predicted ( $\log([brain]:[blood]) > -0.5$ ) as calculated using StarDrop® 6.2). Avoiding the need for deletion studies and the use of multiple design cycles to remove toxicophores or lipophilic/polar sub-groups can not only shorten the route to a candidate, but allow more rapid access to high quality compound series. As we strive to expand our exploration of CNS-relevant chemical space to improve the chances of identifying novel therapeutics, we must also identify enhanced synthetic methodologies that can enable this strategy.

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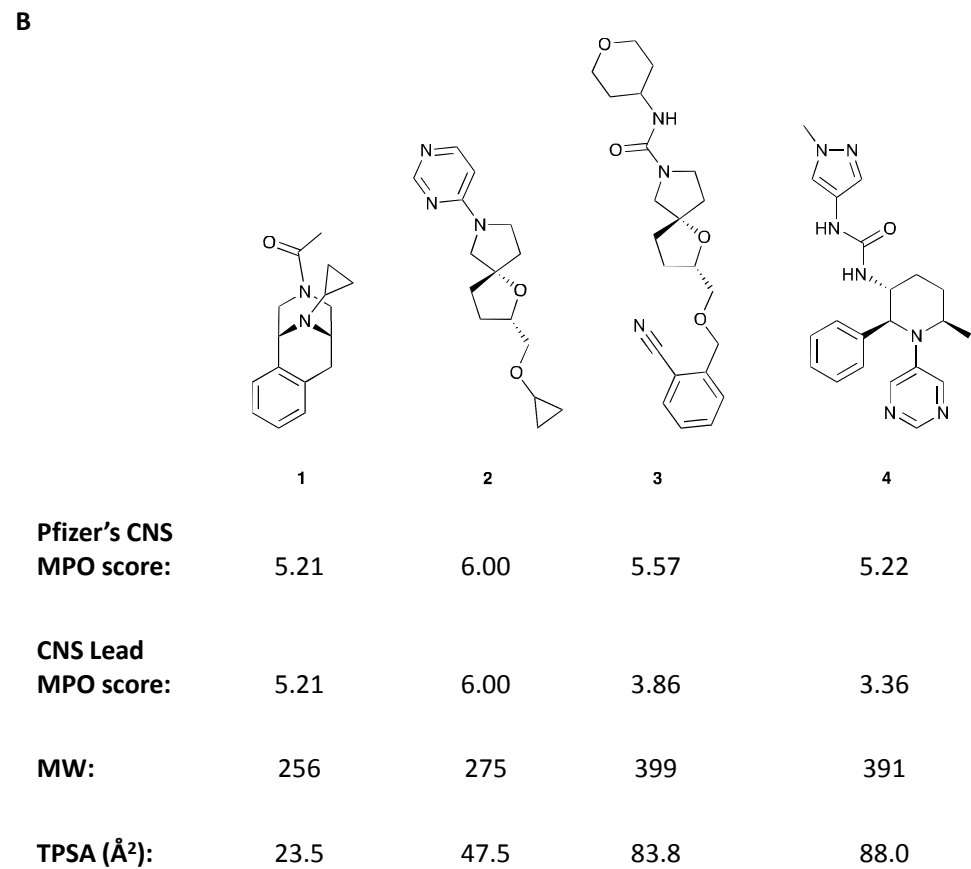
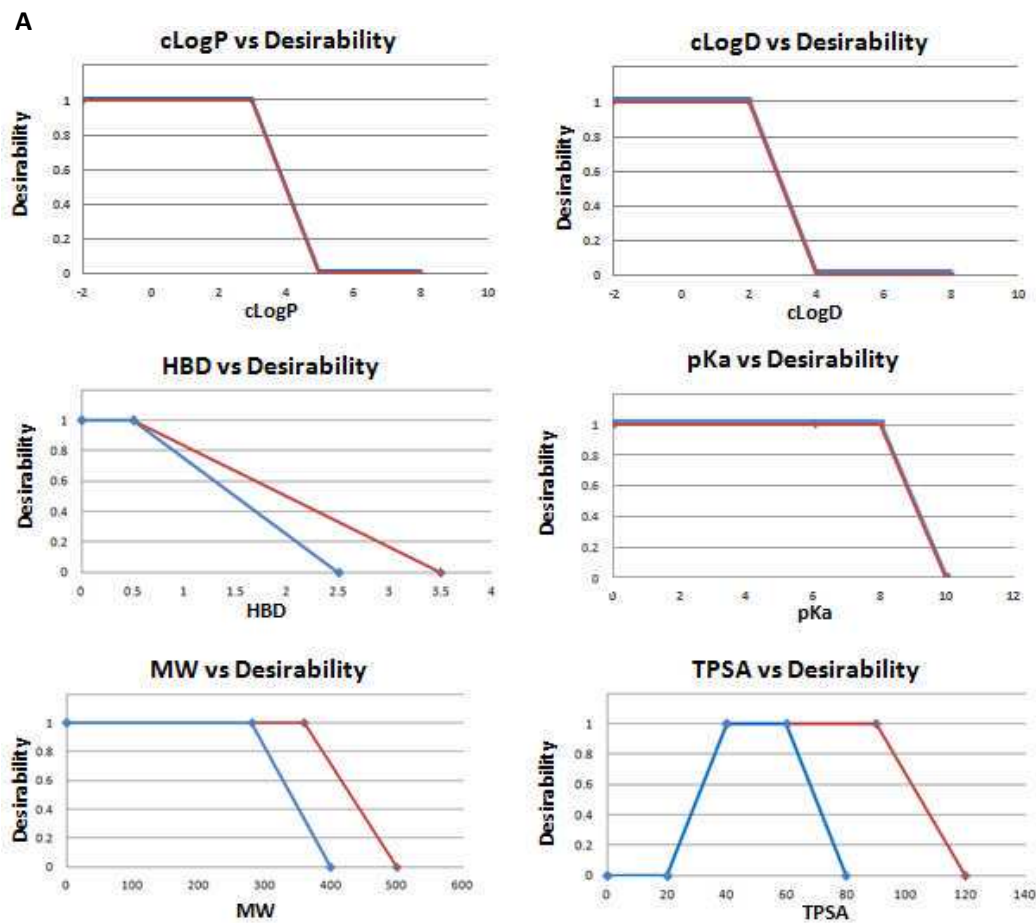
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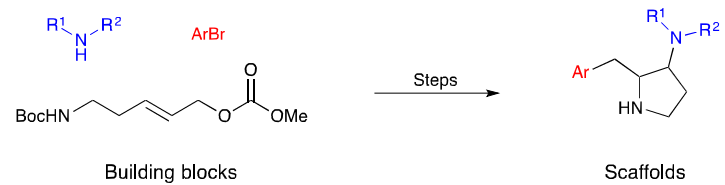
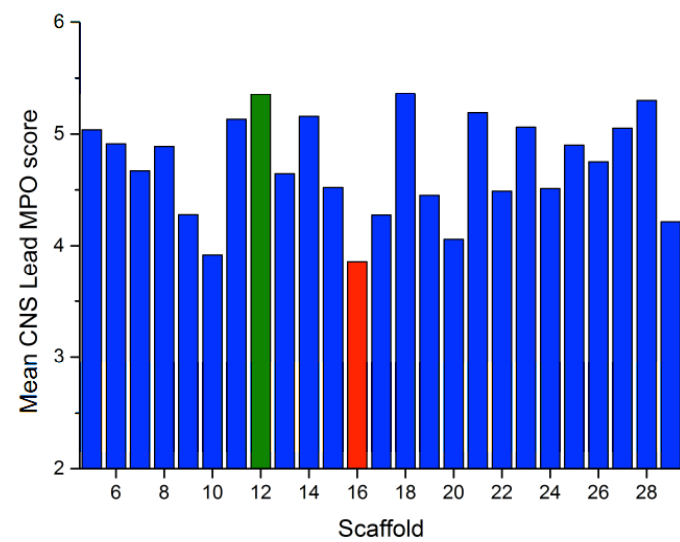
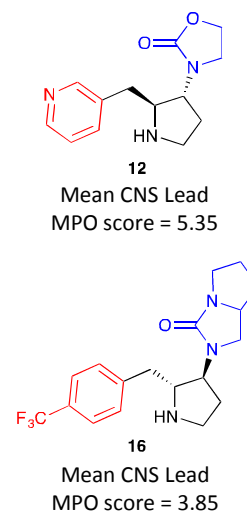
**Figure 1.** Comparison of the Pfizer's CNS MPO score and our CNS Lead MPO score. **Panel A:** Desirability scores that comprise Pfizer's CNS MPO score (red) and our CNS Lead MPO score (blue). A hump function is used for TPSA, whereas a monotonic decreasing function is used

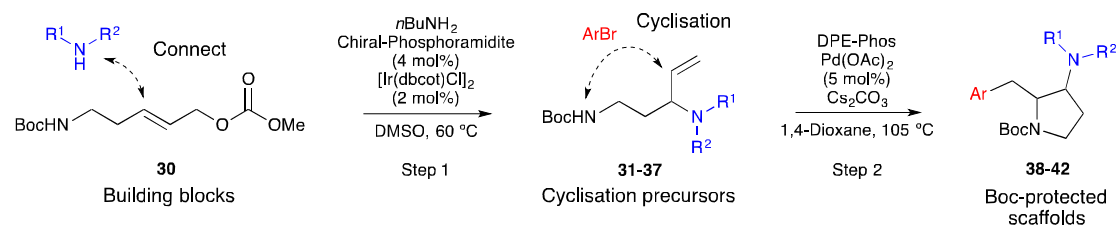
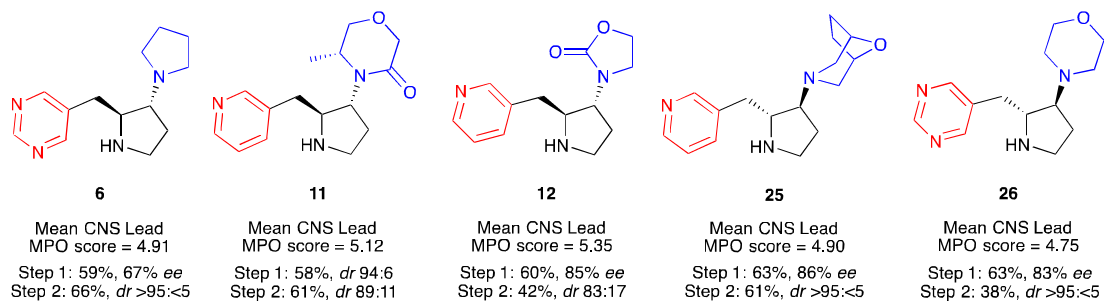
for the five other properties. **Panel B:** Pfizer's CNS MPO score, CNS Lead MPO score, MW and TPSA of some lead-like compounds derived from literature scaffolds (**1** [23], **2** and **3** [24] and **4** [25]).

**Figure 2.** Overview of our integrated synthetic and computational approach. **Panel A:** Strategy for the preparation of alternative pyrrolidine-based scaffolds. **Panel B:** Mean CNS Lead MPO scores for compounds based on 25 potential scaffolds including the highlighted scaffolds **12** (green) and **16** (red). **Panel C:** Structures and scores of the highlighted scaffolds **12** and **16**.

**Figure 3:** Synthesis and evaluation of five scaffolds. **Panel A:** Synthetic approach to the scaffolds. **Panel B:** Structure of the scaffolds synthesised and their mean CNS Lead MPO scores. **Panel C:** CNS Lead MPO scores and experimental data for a selection of synthesised screening compounds. dbcot (dibenzo[a,e]cyclooctatriene), DPE-Phos (bis-[2-(diphenylphosphino)phenyl]ether), MPO (Multi-Parameter Optimisation), ee (enantiomeric excess), dr (diastereomeric ratio), PAMPA (Parallel Artificial Membrane Permeability Assay).



**A****B****C**

**A****B****C**

Compound	CNS Lead MPO score	Exp. LogD <sub>7.4</sub>	PAMPA (10 <sup>-6</sup> cm/s)
<b>43</b>	4.82	1.92	132.4
<b>44</b>	5.13	1.27	70.8
<b>45</b>	4.81	1.79	138.3
<b>46</b>	4.60	1.05	34.4
<b>47</b>	5.34	1.13	17.1
<b>48</b>	5.37	1.89	116.8
<b>49</b>	4.48	1.35	38.6
<b>50</b>	5.49	1.41	55.5
<b>51</b>	4.86	0.90	10.6
<b>52</b>	5.00	1.03	6.0
<b>53</b>	4.60	0.57	7.4
<b>54</b>	5.24	1.90	71.3
<b>55</b>	5.26	0.85	40.2
<b>56</b>	4.73	2.17	186.3
<b>57</b>	5.05	1.37	118.6
<b>58</b>	5.00	2.02	125.5