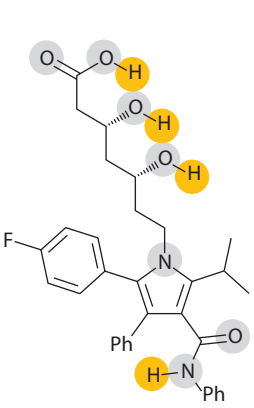
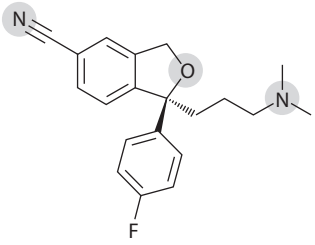
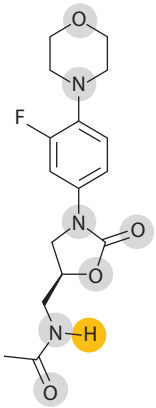
TABLE 5.2
Calculation of the CNS MPO-Score for Atorvastatin, Escitalopram, and Linezolid



Lipitor (Atorvastatin)



Lexapro (Escitalopram)



Zyvox (Linezolid)

Property	Value	Score	Value	Score	Value	Score
MW	559	0.00	324	1.00	337	1.00
TPSA	112	0.27	36	0.80	71	1.00
pK_a	—	1.00	8.91	0.55	2.45	1.00
Log P	4.46	0.27	3.13	0.94	0.17	1.00
Log $D_{7.4}$	1.70	1.00	1.60	1.00	0.17	1.00
HBD count	4	0.00	0	1.00	1	0.83
CNS MPO score	Σ	2.54	Σ	5.28	Σ	5.83

Note: The H-bond donors are indicated in orange and the polar atoms contributing to TPSA in gray.

compared 591 peripheral drugs with 273 CNS drugs in terms of Ro5 compliance, location inside/outside the Golden Triangle, and the MPO-score. The data are summarized in Figure 5.5. It is evident that the oral small-molecule drugs, in particular the CNS drugs, are indeed highly compliant with the Lipinski Ro5. Although it was developed for CNS drug discovery, the MPO algorithm is equally applicable to peripheral drugs with 70% of both drug classes having a score above 4. Almost 80% of the CNS drugs are found within the Golden Triangle, whereas nearly half of the peripheral drugs fall outside. This analysis illustrates that CNS drugs are found in a more constrained physicochemical space than their peripheral counterparts. This difference is most likely a consequence of the requirement for passage across the blood–brain barrier (BBB), including the possibility for a CNS drug to escape the many protective protein efflux pumps which are integrated in the BBB.

5.3 DECISION MAKING IN MEDICINAL CHEMISTRY

A number of metrics have appeared in the medicinal chemistry literature over the last two decades that relate the target affinity to a fundamental descriptor of molecular size (for example, MW or TPSA) or lipophilicity (typically log P). Herein, we discuss two of them: ligand efficiency (LE) and ligand lipophilic efficiency (LLE). These key metrics allow informed optimization of the potency averaged for molecular size and normalized for lipophilicity, respectively. Increasing the size of the molecular footprint and especially the lipophilicity is known to be associated with increased attrition in clinical development of drug candidates. The ADME properties of compounds typically