stage (sleep architecture) can have a significant impact on memory consolidation and the restorative function of sleep.[53] In the absence of more sophisticated biomarkers, however, it would not be possible to distinguish between a candidate compound that induced normal sleep and one that globally suppresses CNS activity, such as the γ-aminobutyric acid (GABAa) system modulators Halcion® (Triazolam, Figure 10.8(a))[54] and Restoril®

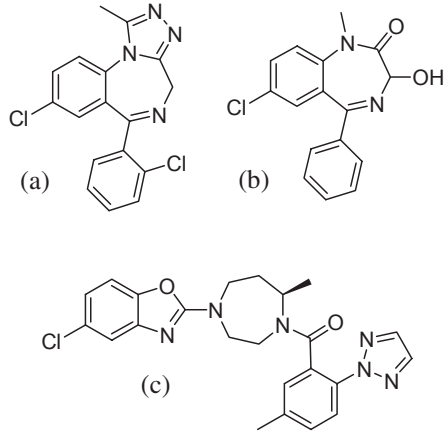

FIGURE 10.8 (a) Halcion® (Triazolam) (b) Restoril® (Temazepam) (c) Belsomra® (Suvorexant, MK-4305).

(Temazepam).[55] Determining the impact of candidate compounds on sleep architecture would also be impossible, as there would be no means of distinguishing between the different stages of sleep. These issues were addressed by Merck in a program designed to identify novel orexin receptor antagonists that culminated in the identification of Belsomra® (Suvorexant, Figure 10.8(c)), a potential treatment of insomnia.

The orexin receptor system is a critical regulatory component of the sleep/wake cycle. It is composed of two GPCRs, orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R), and two associated ligands, orexin A and orexin B, and there is a high degree of structural conservation across multiple species.[56] In a normal sleep/wake cycle, orexin levels and activation of the corresponding receptor are maintained during wakeful periods, but the system is essentially inactive during sleep periods.[57] Genetically engineered mice that are unable to produce the orexin peptides display symptoms associated with narcolepsy (e.g., excessive daytime sleepiness, sleep fragmentation),[58] while knockout mice that are missing both OX1R and OX2R are acutely narcoleptic.[59] In human narcoleptics, there are substantially fewer orexin-producing neurons and low levels of orexin A during wakeful periods. These features are believed to be causative in symptomology.[60]