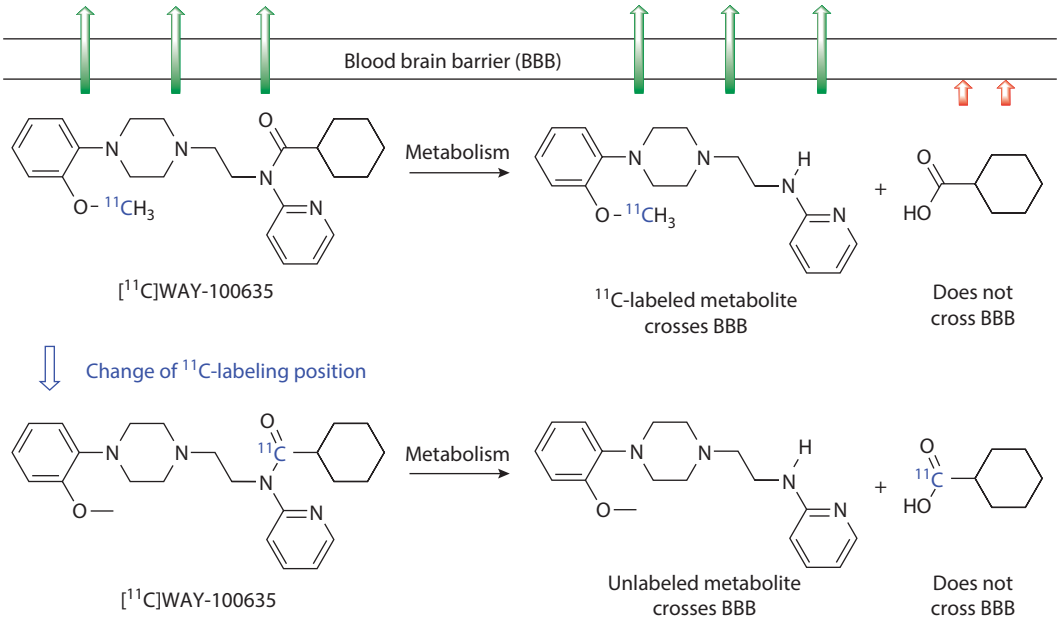

FIGURE 8.7 Metabolism of a PET ligand may lead to a metabolite that compromises the PET images as shown for [^{11}C]WAY-100635—used to image the 5-HT$_{1A}$ receptor. Judicious choice of labeling position can circumvent the problem.

[^{11}C]WAY-100635, a PET ligand used to image 5-HT$_{1A}$ receptors in the CNS, may most conveniently be labeled at the methoxy group as shown at the top of Figure 8.7. However, the primary pathway for its degradation in vivo is via hydrolysis of the amide bond in plasma to give the shown amine and cyclohexyl carboxylic acid. The formed ^{11}C-labeled metabolite is able to cross the BBB and enter the CNS, thereby adding to the combined PET image. Simply moving the site of labeling to the amide carbonyl leads to the formations of [^{11}C]cyclohexyl carboxylic acid as the radiolabeled metabolite that does not cross the BBB, avoiding the contamination of the final images. Even though the unlabeled metabolite is able to cross the BBB, the amount of compound present is so low that it does not impact the binding of the PET ligand to the target.

8.8 IMAGING IN DRUG DISCOVERY AND DEVELOPMENT

Molecular imaging methods such as PET are increasingly involved in the development of novel drugs since they are able to identify a biological target associated with a specific disease, to determine the drug mechanism of action, to examine the drug's biological characteristics such as target engagement, nonspecific binding or metabolism, to determine the optimal drug dosage, and thereby to improve the efficiency of selecting the appropriate drug candidate for clinical trials.

8.8.1 Application of Molecular Imaging Probes

There are many different phases of the drug discovery and development process where molecular imaging can be utilized (Figure 8.8). Table 8.2 lists some examples of PET ligands that have been used to study different parameters.

In the following, some examples of how PET can be used in the different phases of the drug discovery and development are discussed.