Organometallic Rhenium Tricarbonyl Ligands for Use as PET Imaging Agents for ER+ Breast Tumors

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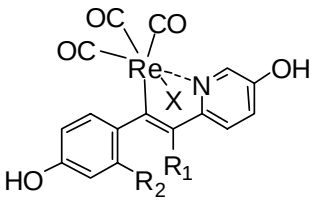
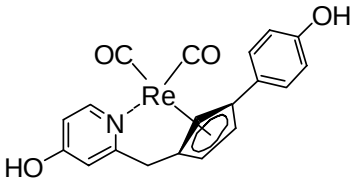
Of the three main types of cancer therapy—chemotherapy, radiation therapy, and hormone therapy—the first two are associated with a high incidence of side effects, such as nausea and hair-loss. By contrast, hormone therapy, when effective, is preferred because of the relatively low severity of side effects. It is known that 60-70% of breast tumors contain significant concentrations of estrogen receptor (ER). In these tumors, ER is thought to regulate cell growth, and as such, it is also able to mediate the anti-tumor effects of estrogen antagonists, such as tamoxifen. It has been shown that ER concentration in tumors correlates well with the effectiveness of anti-estrogen use in hormone therapy for breast cancer. Thus, an accurate determination of the ER content of a tumor allows identification of patients for whom hormone therapy will be effective, allowing certain patients to avoid radiation and chemotherapy. A non-invasive approach to determine ER concentration would be to use an ER ligand labeled with a radioactive element to image only those tumors with a high ER content.

Previous studies of technetium–99m labeled ER ligands for use as imaging agents have suffered from several problems. Inorganic chelates of ^{99m}Tc demonstrated molecular instability under biological conditions; also, the large size of many Tc complexes interferes with cellular uptake. Studies conducted in this laboratory suggest that an integrated organometallic design in which technetium bonded to carbon forms a part of the core structure will display the needed stability, as well the potential for high binding affinity to ER.

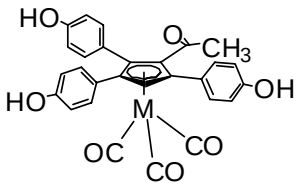
The goal of this project is to develop a novel design for ER ligands with an integrated organometallic core using ^{99m}Tc. A design modification in which the carbon skeleton of the ligand precursor folds around the technetium core will give the ligand a more modular structure, causing it to resemble estradiol, the natural ER ligand, more closely. This should increase the binding affinity of the ligand for ER, while maintaining the needed stability and small size. The combination of these three characteristics will allow for successful use in imaging of tumors with high concentrations of ER, thus enabling the identification of tumors that are susceptible to treatment with hormone therapy.



PIRB (VI) X = Br
PIRM (VII) X = OCH_3



PyCR (II)



ACR (IV) M = Re