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New Bifunctional Chelators for 225Ac and 227Th Radioimmunotherapy

The short particle range of alpha particles offers advantages for localized cancer treatment, sparing neighboring healthy tissue. Particularly interesting alpha-emitting radioisotopes include long-lived 225Ac (t1/2=9.92d) and 227Th (t1/2=18.7d), while the former also generates four net alpha particles through the short-lived progeny, rendering it highly potent. The key is to securely deliver the radioactive isotope to the cancerous tissue through stable complexation with a bifunctional chelator. For radioimmunotherapy, an acyclic chelator that allows quantitative radiolabeling in high stability at room temperature is strongly preferred. Therefore, the foci in this work is to compare the chelation chemistry of 225Ac and 227Th with three recently developed chelators from our group–H4octapa(N4O4), H4pypa(N5O4) and H4py4pa(N7O4), which cover potential coordination numbers from 8 to 11 with combinations of hard donor atoms, N and O, that possess strong affinity for actinides. While at least one bifunctional analog has been developed for each chelator, herein conjugates of monoclonal antibody, trastuzumab along with the non-bifunctional chelators are the foci. Synthesis and characterization of the ligands will be discussed, together with the radiolabeling and serum stability studies.
All synthesized chelators were characterized by NMR spectrometry, high-resolution mass spectrometry and elemental analysis. For the studies with 225Ac, despite the difference in chemical properties and covalency, non-radioactive Lanthanum(La) was chosen as an adequate analog due to the absence of stable actinides, and the complexation with H4pypa and H4py4pa was investigated by NMR spectrometry, showing a vast difference in complex geometry, where [La(pypa)]- appeared as an asymmetric complex while [La(py4pa)]- was highly symmetric. pM values of [La(octapa)]- and [La(pypa)]- were determined to be 19.7 and 19.9, respectively, by potentiometric titration and UV-vis spectrophotometry, while that of [La(py4pa)]- is in progress. Radiolabeling of [225Ac][Ac(L)]- (L=octapa, pypa, py4pa) was performed at room temperature in 30 minutes and the radiochemical yield percentages(RCY %) were analyzed by iTLC-salicylic acid impregnated, showing H4py4pa and H4octapa being the most promising (98%, 10-6M) while H4pypa required 10-fold higher concentration for 93% RCY, which was still significantly better than DOTA. The stabilities in human serum are being determined, in parallel with the experiments for the trastuzumab-conjugates. Besides 225Ac, H4py4pa also exhibited encouraging RCY in 2 hours at room temperature with 227Th and the complex was stable over at least 2 days. More studies with the bifunctional analog are in progress.
To summarize, three reported chelators have demonstrated promising radiolabeling results with 225Ac, while H4py4pa also has potential for 227Th. More studies are in progress.

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