Mn(II) chelates with potential interest for MRI

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Magnetic Resonance Imaging (MRI) has become one of the most successful diagnostic imaging modalities. A large number of MRI scans use paramagnetic contrast agents (CA), to enhance the image's contrast. Gd(III), with seven unpaired electrons and a long electronic relaxation time, is the most used metal ion for the preparation of CA. Mn(II) is also a good candidate for MRI contrast agents due to its five unpaired *d* electrons, a favorable electronic relaxation time, and the lability of the coordinated water molecule(s). Presently, there is one approved Mn(II)-based CA, Teslascan® ($[MnDPDP]^{4-}$, $DPDP^{6-}$ = *N,N'*-dipyridoxylethylenediamine-*N,N'*-diacetate-5,5'-bis-(phosphate), Figure 1).

Due to toxicity problems, the paramagnetic ions should be administrated as metal complexes of high thermodynamic and kinetic stabilities. Macrocyclic ligands are known to form such stable metal complexes. The presence of hydrophobic moieties in chelates allows them to bind to human serum albumin (HSA), the most abundant serum protein. The presence of binding sites with affinity for lipophilic groups [1] can be exploited as a strategy to increase the blood retention of the CA and also to enhance the relaxivity by increasing the tumbling time (τ_r) [2]. The formation of micelles can also be used with the goal of increasing the τ_r. Bifunctional ligands can be coupled to targeting molecules (i.e. peptides) with high affinity for biological receptors, preserving the coordination properties of the chalator. This consists in another strategy to target CA.

In this work, we developed three new triazapolycarboxylate ligands for Mn(II), NODAHep (1,4,7-triazacyclononane-*N,N'*-diacetate-*N''*-heptanil), NODABA (1,4,7-triazacyclononane-*N,N'*-diacetate-*N''*-bensoate), and NODAHA (1,4,7-triazacyclononane-*N,N'*-diacetate-*N''*-hexanoate) (Figure 1). These chelators are pentadentate, leaving one coordination site of the metal coordination sphere available for one water molecule. NODAHep has a lipophilic side chain, designed to endow the chelate with the capacity of forming micelles and of interacting non-covalently with HSA. This was expected to increase τ_r and consequently to increase the relaxivity. NODABA and NODAHA are bifunctional ligands that present a free carboxylic group in the pendant lateral chain, allowing their conjugation to targeting molecules.

^{1}H NMRD and ^{17}O NMR studies were performed for the three Mn(II) chelates, showing relaxivity values comparable to those of Gd(III) chelates with one water molecule in the inner coordination sphere of the metal ion. Potentiometric titrations allowed the determination of the pK_a's of the ligands and the thermodynamic stability constants of the Mn(II) and Zn(II)

chelates. The kinetic stability of [Mn(NODAHep)] in the presence of Zn(II) and at different pH values was also studied. The critical micellar concentration of the amphiphilic [Mn(NODAHep)] chelate was determined by fluorescence and ^{1}H NMRD.

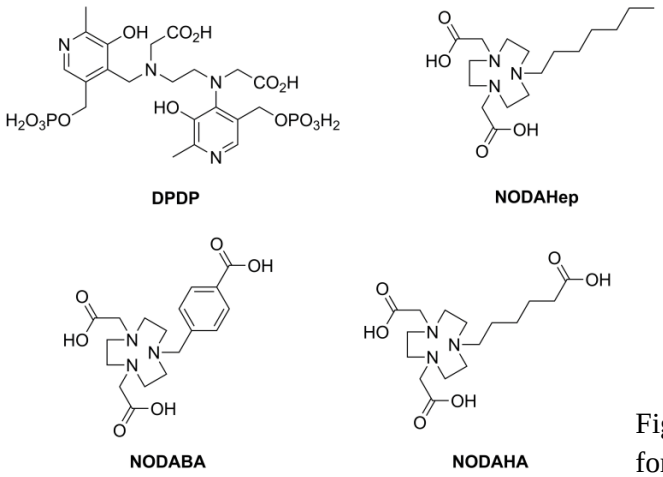

Figure 1 – Structure of the different chelators for Mn(II).

References:

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Topic: Metal-based drugs: therapy and diagnosis