Project Summary

Approximately 50% of the compounds in present high throughput drug screens are halogenated,[1] yet the role of the halogens in their bioactivity has not yet been elucidated. Halogen bonding has been proposed to have a potential to become a future tool for increased activity and selectivity of pharmaceutics. It is an electron density donation-based weak interaction that has so far almost exclusively been investigated in computational and crystallographic studies. It shows high similarities to hydrogen bonding; however, its applicability for molecular recognition processes long remained unappreciated and has not been thoroughly explored.

The main goals of this project are to develop halogenated reporter compounds and use them to achieve the first systematic description of halogen bonding in solution. These studies are expected to provide the basis of future applications of halogen bonding in solutions. Throughout the project halogenated, paramagnetic reporter compounds were prepared using solution-phase organic synthesis.

The synthesis of the first prototype of paramagnetic reporter compound was started with cyclen that is known as a strong metal ion complexing unit (**Figure 1**). For attachment of a halogen bond donor 2-methylquinoline was used as it provides an additional metal coordination site and was hence expected to strongly complex lanthanides.[2]

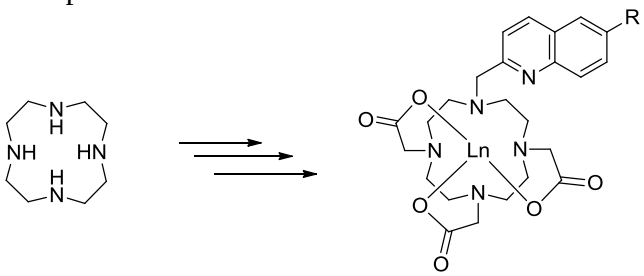

Figure 1: Synthesis of paramagnetic labelled reporter compound based on cyclene.

The synthesis of the first analogue having a linear biphenyl substituent attached to the quinolone moiety was optimized. The structure of the compound in complex with Yb^{3+} was evaluated by NMR spectroscopic and x-ray crystallographic techniques (**Figure 2**) and provided evidence for the ability of the chosen cage to strongly complex lanthanides.

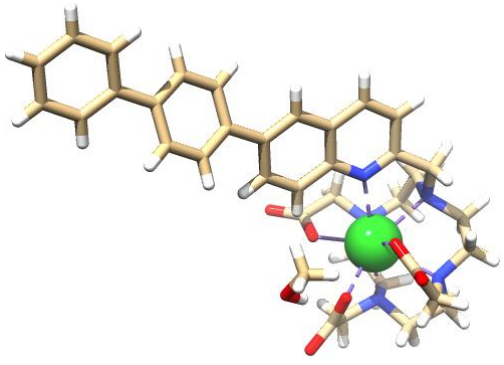

Figure 2: Crystal structure of ytterbium 2-methyl-6-biphenylquinole cyclen complex.

The compound allowed evaluation of its utility for induction of paramagnetic NMR parameters for evaluation of intermolecular interactions, i.e. RDCs and PCSs. The proton spectrum of the obtained

[1] P. Metrangolo, G. Resnati, *Science* **2008**, *321*, 918-919.
[2] P. H. Keizers *et al., J. Am Chem. Soc.* **2008**, *130*, 14802-14812.

ytterbium complex revealed that in agreement with previous studies the atoms closest to the lanthanide were broadened by paramagnetic relaxation mechanisms in an extent that did not allow their reliable detection. However, the four protons at furthest distance from the lanthanide complexing core provided NMR signals with reasonable line width allowing determination of pseudocontact shifts **(Figure 3**). Thus, this study demonstrated that the 2-methyl-6-phenylquinoline linker places a XB interaction site planned to be attached at the *para* position of the biphenyl linker (green, **Figure 3**) at an optimal distance from the paramagnetic centre.

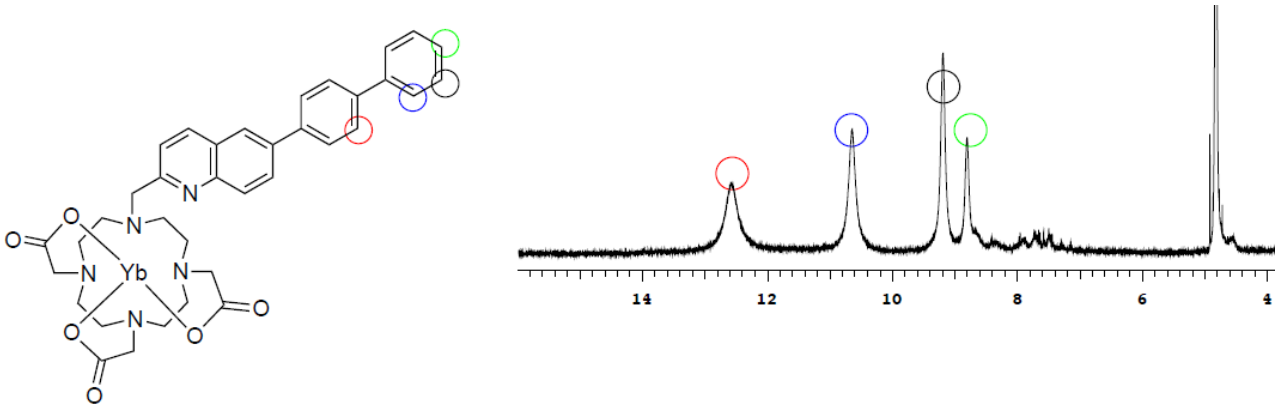

Figure 3: Proton spectrum, to the right, of ytterbium 2-methyl-6-biphenylquinole cylene complex, to the left, showing a large pseudocontact shift of the biphenyl signals.

Pseudocontact shifts (PCSs) and residual dipolar couplings (RDCs) were measured to validate the computational methods necessary for structure elucidation. Monte Carlo calculation was used to generate an ensemble of the synthesized complex and the program MSpin was used to elucidate the 3D-structure by fitting the experimental data with the computed conformers (**Figure 4**)

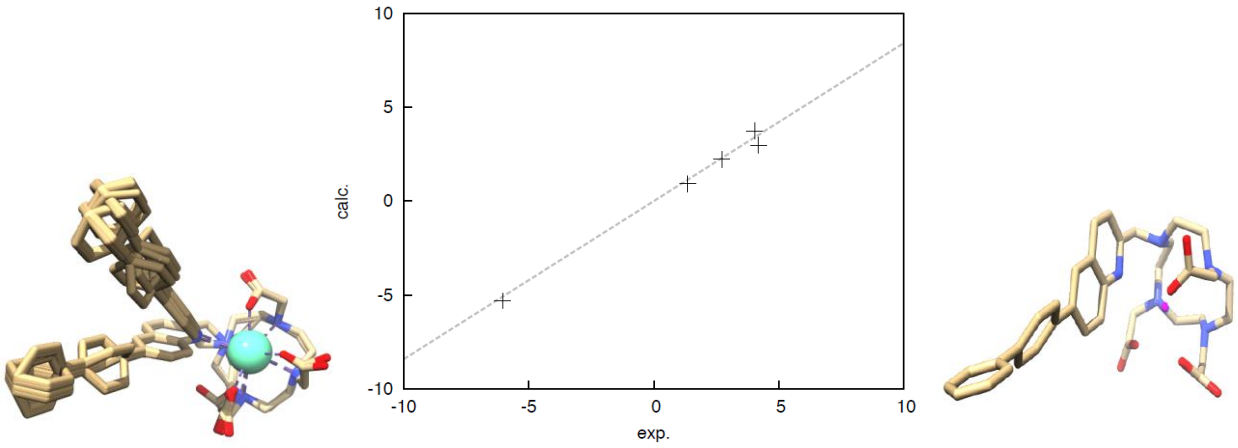

Figure 4: Ensemble of calculated structures (left), fit of experimental and calculated PCSs (middle) and a single structure best fitting to the data (right).

The achieved results pave the way for further systematic physicochemical study of halogen bonding in solutions. The method that is being developed will be applicable by the pharmaceutical industry for evaluating weak intermolecular interactions.