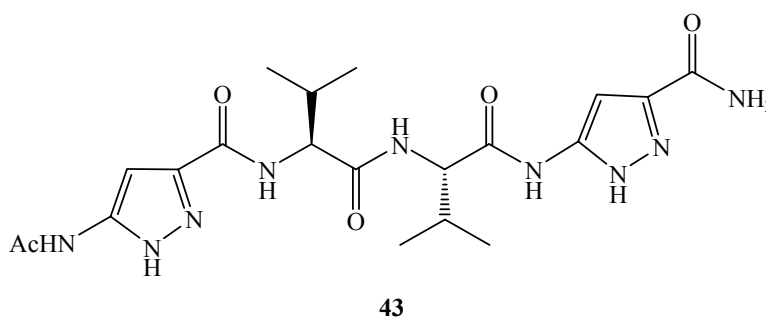


## 2.2 Unnatural oligomers and macrolactam analogues

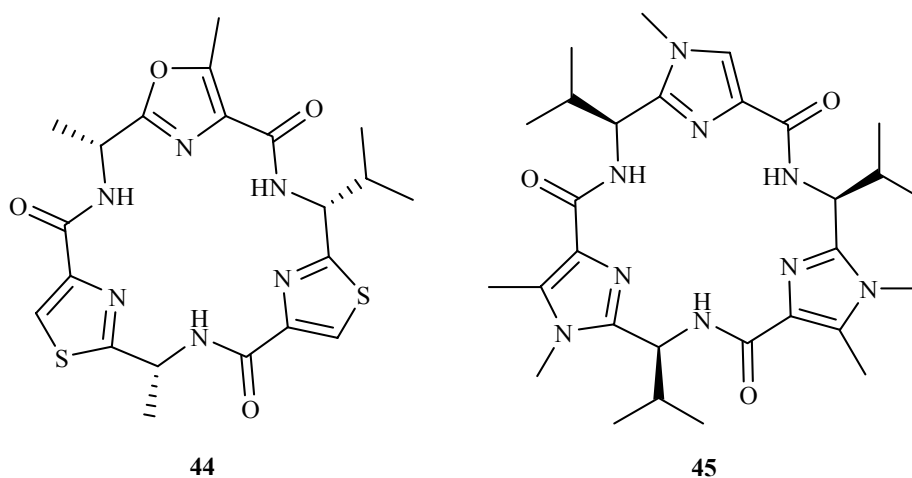
Oligomers composed of unnatural monomers form characteristic secondary structures and may act as useful molecules for studies of peptidomimetics and peptide recognition, as well as bioactive peptidomimetics. Starting with the pioneering studies of Gellman and Seebach on  $\beta$ -peptides ( $\beta$ -amino acid oligomers),<sup>[46, 47]</sup> this concept was extended and has led to other peptidomimetic structures such as  $\gamma$ -peptides,<sup>[48, 49]</sup>  $\delta$ -peptides<sup>[50-53]</sup> and oxa-peptides.<sup>[54, 55]</sup> Furthermore, complex structures based on rigid heterocycles with multiple H-bonding donor and acceptor sites have been synthesized and investigated as recognition molecules<sup>[56]</sup> – molecules of this type can form hydrogen bonds that are complementary to peptide  $\beta$ -sheets structures. Unnatural units can be also combined with naturally occurring amino acids and hybrid peptides in an extended conformation complementary with  $\beta$ -sheets can be synthesized.<sup>[57]</sup> Design of specific  $\beta$ -sheet ligands represent one of the most promising approaches for the prevention of amyloid aggregation, which is the pathological process discussed as the primary cause of Alzheimer's disease; the conversion of  $\alpha$ -helices to larger  $\beta$ -sheet aggregates is also found with Creutzfeldt-Jakob disease, BSE and other protein folding diseases.<sup>[58, 59]</sup> Compound **43** represents one known example of a  $\beta$ -sheet ligand which has shown extremely promising preliminary results on screening carried out for efficiency and selectivity toward A $\beta$  aggregation as well as toxicity for the cells (Scheme 19).<sup>[57]</sup>



**Scheme 19.** Aminopyrazole Peptide Hybrid Ligand

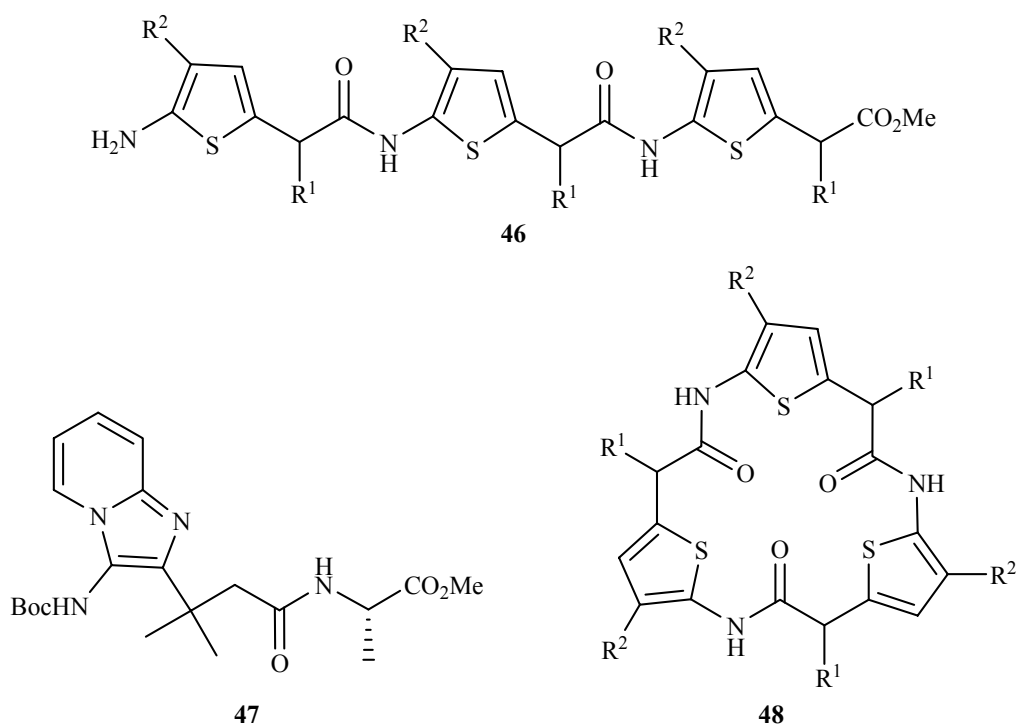
Rigid macrolactam molecular platforms, found in marine sources, very often possess interesting biological activity, for example Dendroamide A (**44**, Scheme 20)<sup>[60]</sup> could be useful against cancers.<sup>[61-64]</sup> Such molecules attract the attention of chemists not only as possible drugs, but also as useful recognition molecules and synthetic receptors. Besides macrolactam natural products, analogues containing heterocyclic building blocks are also

synthesized (**45**, Scheme 20).<sup>[65]</sup> The distance and the relative orientation of functional groups are of major importance in molecules of this type.



**Scheme 20.** Natural macrolactam Dendroamide A **44** and macrolactam analogue **45**

Novel  $\delta$ -amino acids described in this work (Scheme 18) should be used as building blocks for unnatural or hybrid peptides like **46** and **47** respectively, and macrocycles like **48** (Scheme 21). The structure (including hydrogen bond pattern) of the compounds should be highly interesting.



**Scheme 21.** Examples of unnatural oligomers and macrocycle composed of novel  $\delta$ -amino acids