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## Discovery of novel aryl hydrocarbon receptor (AhR) antagonists using homology modelling and ligand-based drug design

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Aryl hydrocarbon receptor (AhR) is a transcription factor activated by ligand. However, AhR also modulates many physiological and pathological processes that affect inflammatory and immunological responses. There is a growing interest in discovery of selective competitive antagonists for AhR, where the most potent ones exhibit acceptable antagonist properties but they also show partial agonist activity or exhibit agonist activity on estrogen receptors (ER). Also, limited availability of selective and pure competitive AhR antagonists and scarce structural information regarding AhR binding domain (located in the PAS-B domain) are reported. In this work, a preliminary search in the Protein Data Bank (PDB) for AhR structures revealed only one – a PAS-A domain, but not PAS-B. A homology model of the PAS-B domain of the AhR receptor was then carried out, using PAS-B structures of ARNT as templates. A flexible docking approach was then used with the most potent AhR antagonists reported, allowing us to derive (and to validate) a pharmacophoric pattern common to the compounds thus aligned. Two subsequent virtual screening experiments were then performed in databases of commercially available compounds, using: (1) the pharmacophore model; (2) the shape and electrostatic potential of the most potent AhR antagonist reported. In sequence, 29 compounds were filtered regarding to both atoxicity and good pharmacotherapeutic profile, thus predicted *in silico*. Finally, at least 5 novel atoxic AhR antagonists have been discovered, which experimentally showed atheroprotective efficacy correlated to the AhR antagonism, since they inhibited, almost completely, AhR-mediated oxLDL uptake by murine macrophages, induced by TCDD.

### Biography

Carlos Henrique Tomich de Paula da Silva has completed his PhD from University of Sao Paulo and Postdoctoral studies from University of Sao Paulo and PRBB, at Barcelona-Spain. He is the Associate Professor of Pharmaceutical Chemistry at University of Sao Paulo, with a drug design research position. He has published more than 120 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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