ABSTRACT

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Title of diploma thesis:

Synthetic routes to 2-phenylbenzothiazoles with potential application in cancer therapy and PET imaging

There are three main tasks reported in this thesis. The first is the report of an improved procedure for synthesis of biologically relevant 2-phenylbenzothiazoles with various substituents on phenyl ring. Reported 2-phenylbenzothiazoles were synthesised by heating equimolar amounts of 2-aminothiophenol disulfides with appropriate benzaldehydes with *p*-toluenesulfonic acid in the presence of polymer-bound triphenylphosphine using mixture of toluene and DMF as a solvent. Main features of reported method include simple product isolation (removal polymer-bound by-product by filtration through Celite® layer), avoidance of column chromatography, rapid synthesis and good yields of correspondent benzothiazole.

The second goal of this thesis is the solution phase synthesis of 2-phenylbenzothiazoles bearing different substituents on both the benzothiazole and phenyl ring. Attempts were made to synthesise different 2-phenylbenzothiazoles by heating equimolar amount of substituted 2-aminobenzothiazoles with relevant benzaldehydes in high-boiling solvents using sodium metabisulfite as mild oxidant. The results of this method were unconvincing. We got several traces of desired compound with 6-methyl or 6-methoxy substituted 2-aminobenzothiazoles but in other cases we could not isolate our desired compounds.

The third task was the synthesis of precursors of [^{18}F]-radiolabelled 6-fluoro-2-(2,3-dimethoxyphenyl)benzothiazole and 5-fluoro-2-(2,3-dimethoxyphenyl)benzothiazole (GW 610) as potential PET agents for Alzheimer´s disease diagnosis and developing potential methods for their radiolabelling. Particularly of interest was the synthesis of [^{18}F] fluorinated GW 610 because of its extraordinary anticancer activity *in vitro* and *in vivo*, reported in recent years. Successful synthesis of 2-(2,3-dimethoxyphenyl)-6-nitrobenzothiazole via Jacobson cyclisation and the direct aromatic nucleophilic substitution of the nitro precursor using F^- in presence of Kryptofix 2.2.2® using both DMSO and DMF as a solvent to establish condition for future radiolabelling was subsequently performed. Furthermore two candidates for [^{18}F]-F labelling, namely 2-(2,3-dimethoxyphenyl)-6-tributylstannylbenzothiazole and 2-(2,3-dimethoxyphenyl)-5-tributylstannylbenzothiazole (GW610) were synthesised via Jacobson cyclisation followed by palladium-catalyzed stannylation. Both organotin compounds can be used for both direct [^{18}F] fluorination using [^{18}F]-F, and for more favourable preparation even more reactive diaryliodonium salt, suitable precursors for [^{18}F]$^-$ / Kryptofix 2.2.2® labelling.