Since the discovery of the first AchE inhibitor, physostigmine (30), a large number of studies have been performed to identify more effective inhibitors.According to structure–activity relationship studies, the design of novel potent multi–target inhibitors should have the following characteristics: i) The presence of a nitrogen atom with a positive charge (91); ii) the size of the alkyl chain attached to the nitrogen atom should be small, such as a methyl group (92); iii) the presence of an oxygen atom able to form hydrogen bonds, such as an ester (93); iv) the presence of electron–donating groups such as hydroxyl and methoxy groups (83); and v) the presence of a two–carbon unit between nitrogen and oxygen atoms (91).These inhibitors cause milder side effects than traditional drugs and may have improved properties, such as better BBB permeability and increased effectiveness (11,67).Other inhibitors include analogues of the traditional inhibitors, derivatives of natural compounds and hybrids of synthetic inhibitors.protein, metal dyshomeostasis and oxidative stress.