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Novel curcumin derivatives for Alzheimer's disease therapeutics

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Alzheimer's disease (AD) is a progressive deteriorating disease of insidious onset that affects higher mental functions, usually appearing in late life. The present therapeutics of AD is only symptomatic. Further research is focused on disease modifying treatments based on its pathophysiology, mostly involving specific proteins (Aβ and tau), enzymes (secretases and kinases) and other targets like nicotinic ACh, N-methyl-D-Aspartate, serotonin, histamine and adrenergic receptors. Acetyl cholinesterase enzyme and Aβ protein are the main targets involved in neurodegeneration. Development of acetyl cholinesterase inhibitors and Aβ aggregation inhibitors is the current approach for AD therapeutics by several investigators.

Curcumin, a natural herb, commonly called as diferuloyl methane is a hydrophobic polyphenol with multipotency to combat AD with the activities of scavenging radicals, blocking Aβ aggregation, acetyl cholinesterase inhibition and chelation of metal ions. In the present study, we have synthesized several curcumin analogues (1-7) using microwave assisted synthesis on solid support. Series of novel derivatives (8-34) with modification at active methylene link between both keto groups were prepared by subjecting compounds 1-7 to mannich reaction with various primary or secondary amines or tacrine (a potent acetyl cholinesterase inhibitor) and formaldehyde to get the final products. The molecules were evaluated for acetyl cholinesterase inhibition, antioxidant activity, Aβ aggregation inhibition and compared with curcumin as well as tacrine and data was statistically analyzed to verify the significance of the results.

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