Synthesis, molecular docking, antioxidant and cholinesterase inhibitory activity of Coumarin based tri-hybridized molecules: An MTDL approach for the development of Anti-Alzheimer drugs.

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Introduction

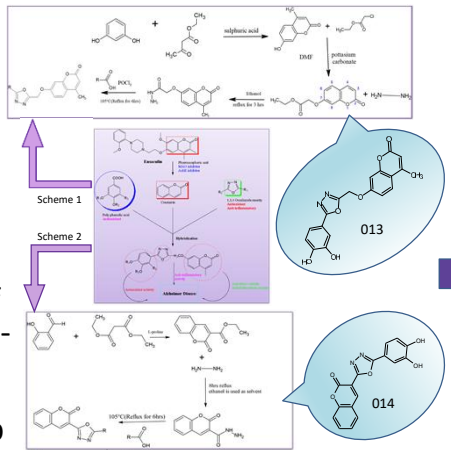
- Alzheimer's disease(AD) also known as "senile dementia" is a multi targeted neurodegenerative disease.
- WHO in 2012 reported approximately 40 million people suffered from AD worldwide.
- We have proposed the synthesis, characterization and *in-vitro assays* of trihybridized compounds in which Coumarin is tethered to 1, 3, 4-oxadiazole derivatives that can act on multiple targets such as Cycloxygenase (COX2), acetylcholinesterase (AChE) and butrylcholinesterase (BuChE). DPPH radical scavenging ability of the hybrid molecules is also assessed.

Aim and objectives

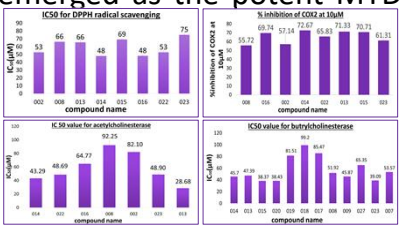
- To synthesize and evaluate inhibitory activity of designed trihybridized compounds on COX2, AChE and BUChE enzymes. Determination of DPPH radical scavenging activity of the designed ligands.

Methodology

- The key inter-mediates were synthesized by Pechman reaction and their purity was checked prior moving to the next step.



- The structures of all newly synthesized compounds were characterized with the help of IR, ^{1}H & ^{13}C NMR and Mass spectral studies. The spectral data was consistent with the chemical structure.
- All the synthesized hybrids exhibited good to moderate anti-cholinesterase, COX2 inhibition and antioxidant property.
- Compound 013 exhibited IC_{50} of 28.67µM ± 2.91, 34.71 µM ±2.87 for the enzymes AChE and BuChE respectively. It showed 71.34% inhibition of COX 2 enzyme at 10µM and IC_{50} of 65.57µM ±5.62 for DPPH radical scavenging. Standard galantamine used showed IC_{50} value of 74.74 µM± 0.54 for the enzyme AChE and standard gallic acid (for antioxidant) showed IC_{50} of 65.1µM ±5.50.
- Compound 014exhibited IC_{50} of 43.29µM ±3.44 and 45.70µM ±2.02 respectively. The compound showed 72.67% inhibition of the enzyme at 10µM concentration. It showed IC_{50} of 48.12µM ±1.67 for DPPH radical scavenging activity. Compound 015 showed the best BuChE inhibitory activity with IC_{50} value of 38.37µM±0.85.
- Compound 013 emerged as the potent MTDL acting at three targets. It also showed better inhibition of AChE than positive control.



Conclusion

- *In silico* prediction and biological assays conducted proved that the proposed compounds in particular compound 013 and 014 showed great potential to act against AD by inhibiting the most common targets observed in the disease.
- Further investigations and modification of these proposed compounds can lead to the development of highly potent therapeutics for the treatment of AD.

Reference

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