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(REVIEW ARTICLE)

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Anti-Alzheimer potential of coumarin derivatives: A review

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Abstract

Alzheimer's is a type of neurodegenerative diseases (NDs) found in old age people which main causes the dementia and various brain disorders. FDA approved drugs used commonly in treatment of moderate to severe Alzheimer's disease are Donepezil, Rivastigmine, Galantamine and Memantine. However, these approved drugs provide only palliative support not complete cure. So, urgency of new molecules has been becoming so important to cure this complex Disease.

Coumarin or 2-H-Chromen-2-one is an oxygenated heterocyclic compound, which is isolated from plants named Dipteryx odorata Willd, (Fabaceae). Synthetic coumarin derivatives has been well presence in literature due to existence of their potential pharmacological activities in literature. This review covers the anti-Alzheimer activities of chemically synthesized coumarin derivatives from 2016-2023. Coumarin derivatives profound found exhibits potential anti-Alzheimer activities in literature. Coumarin derivatives showed their anti-Alzheimer potential through various pharmacological pathways such as monoamine oxidase (MAO) inhibitor, acetylcholinesterase (AChE) & Butyl cholinesterase (BuChE) inhibitory activity, Aβ amyloid inhibition, Beta secretase 1 (BACE1 inhibitors). Multi-target directed ligands (MTDLs) approach also extensively reported to design and synthesis of novel coumarin scaffold as potential multifunctional Anti-Alzheimer activities in last one decade. We also covered literature of some coumarin hybrids derivatives as potential Anti-Alzheimer activities. Some common synthetic methods of coumarin structure also covered in this review article. This review supported that coumarin derivatives found excellent anti-Alzheimer activities and it can be play major role to solve the problem of complex AD disease.

Keywords: Coumarin derivatives; Acetylcholinesterase enzyme (AChE); Multi-target directed ligands (MTDLs); Perkin reaction; Cryptolepine

1. Introduction

Alzheimer's disease (AD) has characteristic of predominant impairment of anterograde episodic memory, which is a typically accompanied by a multitude of cognitive impairments in this domain, which is language, visuospatial, and executive function [1]. There are several range and impact of symptoms that are diverse in disease spectrum. AD is a typically neurodegenerative disorder which main causes the dementia and various brain disorders [2-3]. Main drugs used in treatment of moderate to severe Alzheimer's disease are Donepezil, Rivastigmine, Galantamine and Memantine [4-5]. Donepezil, Rivastigmine, Galantamine are acetylcholinesterase inhibitors whereas Memantine acts on regulating the activity of glutamate, a messenger chemical widely involved in brain functions — including learning and memory[4-6]. However, another drug Tacrine used in treatment of Alzheimer's disease are discontinued due to side effects associated with.

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Coumarin also known as 2-H-Chromen-2-one. The polyphenolic compounds that belong a group which is colour less and crystalline oxygenated heterocyclic that are Coumarins, which is isolated from plants named *Dipteryx odorata* Willd, (Fabaceae) which is a Tonka bean plant. With their class name of 'Coumarou' from which it is derived as coumarin. There are various sub types of coumarin basically four types that is normal coumarin**1**, furanocoumarins **3**, pyranocoumarins **2** and the pyrone-substituted Coumarins (**Fig. 1**). Normal coumarin have some examples of coumarin, 7-hydroxycoumarin and 6,7-dihydroxycoumarin. Whereas, Furanocoumarins has the five membered ring in its compounds which is attached with nucleus of coumarin. Pyranocoumarin which has analogous members to the furanocoumarins but it has six membered ring. Coumarin substituted in the pyrone ring which include 4-hydroxycoumarin [7]. Coumarins are found in large amount in plant kingdom particularly in cinnamon bark oil, lavender oil. There are some important members of coumarin members that is isolated from microbial sources such as novobiocin and coumermycin that is from Streptomyces, and aflatoxins from the species of Aspergillus.

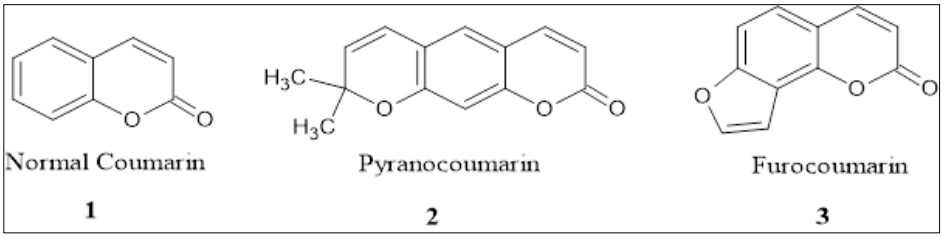

Figure 1 Chemical structures of Normal coumarin (1), Pyranocoumarin (2), Furocoumarin (3)

As it has been seen that acetylcholinesterase (AChE) which involves in the extraneous non cholinergic functions of the early phase of Alzheimer Disease (AD) which binds to the Aβ, therefore it accelerates the polymerization into oligomers and fibrils which increases the neurotoxicity of Aβ [6-8]. Many of the derivatives of coumarin have also been protecting the neurons against Aβ which induced free radicles and oxidative stress [7-8]. As coumarin interact primarily with PAS of AChE, there are several coumarin based dual inhibitor of AChE were designed which incorporates a catalytic site interact with moiety through an appropriate spacer. Whereas the result shows that the 3rd and 4th position of coumarin moiety is considered as the most favourable linking moiety for CAS but not 6th and 7thposition to obtain the dual potent site for AChE inhibitors [8]. Coumarin is family of G-protein-coupled receptors (GPCRs) which is specially most important in treatment of neurological and psychiatric disorders like Parkinson's [9] and Alzheimer's disease [10], epilepsy [11], and schizophrenia [12]. Inflammatory[13], antithrombotic[14], anticancer[15], anticoagulant[16] activities, and cyclooxygenase[17], lipoxygenase[18], cholinesterase (ChE) and monoamine oxidase (MAO) inhibitor activity, CNS stimulant[19], vasodilator, and cytotoxic[20] effects. There are various derivatives of coumarins and chromenes, which were evaluated for their biological activities. Structural diversity of coumarin which makes it potential active against fungal agents like various fungi *A. niger, H. oryzae*. [21].

2. Chemical profile of coumarin

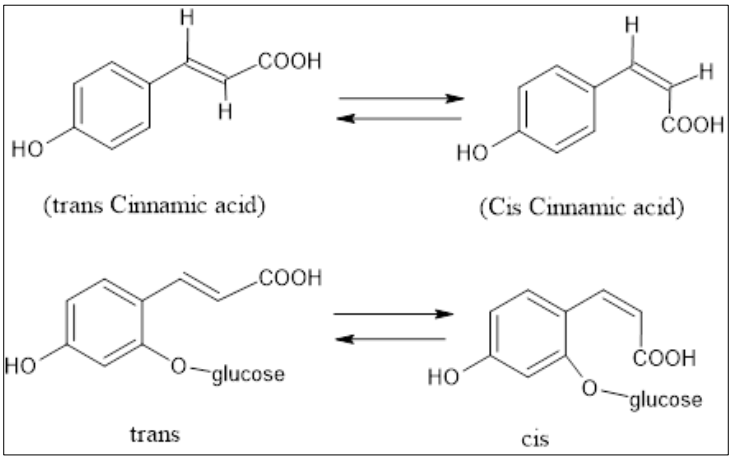

Figure 2 Chemical properties of Coumarin

Coumarin and derivatives of coumarin are the principal oral anticoagulants. Coumarins are water insoluble, whereas 4-hydroxy substitution of coumarin confers the weakly acidic properties of the molecule which make it water soluble under slightly alkaline conditions (**Fig.2**)

The structure of coumarin is derived from a cinnamic acid through ortho-hydroxylation, isomerisation of trans-cis side chain**3,4**, double bond and lactonization. Its Trans form is much more stable and could not cyclise, thus there should be the enzyme isomerase is implicated and isomerisation of some sort (**Fig. 3**)[7,22].

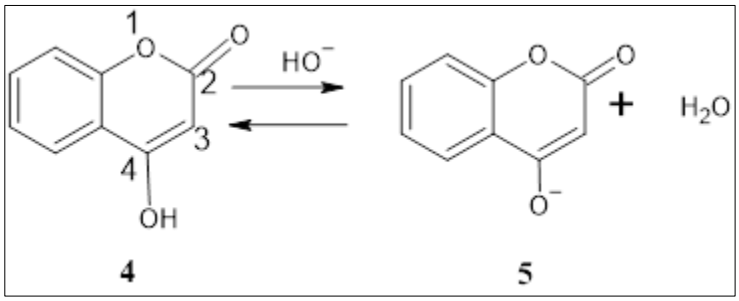

Figure 3 Coumarin structure derived from Cinnamic acid pathway

2.1. Review literature of Anti-Alzheimer Potential of Coumarin Derivatives

Extracts of plants and their isolated compounds which is used as inhibitors of enzymes involved in neurodegenerative disease. Coumarin glycyrol, isolated from *Glycyrrhiza uralensis*, used to inhibit the butyrylcholinesterase (BuChE), acetylcholinesterase (AChE) and MAO-B in micro-molar range[22].

Coumarin-chalcone hybrids found as a potent and selective monoamine oxidase B (MAO-B) inhibitor[8,22]. Coumarin-chalcone hybrids is also attracted the attention by being an modulator of adenosine receptor[7-9]. In 2018, Lu Kang et al. reported 36 new coumarin–chalcone hybrids with diverse side-chains as acetylcholinesterase and butyrylcholinesterase inhibitors. Structure activity relationship study also investigated of these coumarin–chalcone hybrids(**Fig. 4**). One coumarin chalcone hybrid **6 b** displayed potent in vitro activity anti-AChE activity (IC_{50} = 0.15 ± 0.01μmol/L). Further, two coumarin–chalcone hybrids (**6 a, 6c**) also displayed in vitro activity anti-AChE activity 0.37 and 0.69 μmol/L respectively. This coumarin chalcone hybrid 6 b also showed good binding affinity interaction to Trp 279, Tyr334 and Trp 84 in AChE pocket. (**Fig. 4**).

Another interesting research work, Curcumin-Coumarin hybrids as multitargeted agents which found against the neurodegenerative disorders (**Fig. 4**) [23]. Two Curcumin-Coumarin hybrids (**7 and 9**) at 100 μM concentration inhibit the activity of both AChE and butyrylcholinesterase (BuChE) by approximately 50%.Other Curcumin-Coumarin hybrid 8also showed IC50 (hMAO-B) = 26.18 ± 1.76 μM, which also exhibited greater selectivity over MAO-B. (**Fig. 4**) [12,24].

Many of the coumarins {3-(7-phenyl-3,5-dioxohepta-1,6-dien-1-yl)} has proved to be moderate inhibitor of hMAO, AChE, and BuChE, which also display antioxidant activity. Two compounds have shown the neuroprotective activity against the hydrogen peroxide (H_2O_2) in the SH-SY5Y cell line which improves the property of nanoparticles from their derivatives [8,22]. These SH-SY5Y cells has the integrity which indicates a potential neuroprotective effect. Some coumarin scaffolds have shown that it has highest activity against BChE and more protective effect than reference compound donepezil [25,26,27].

Novel fused tricyclic coumarin derivatives as multifunctional anti-Alzheimer agents reported by S. J. Basha (**10,Fig. 4**). All final compounds found different amounts of inhibitory activity to AChE with IC50 values ranging from the sub micromolar to micromolar range (IC50 0.003 ± 0.0003–2.6 ± 0.249 μM). One fused tricyclic coumarin derivative containing N-(3-bromobenzyl) amide moiety **19** displayed potent acetylcholinesterase (AChE) inhibitory activity (IC50-value of 0.003 ± 0.0007 μM) compare to galantamine (IC50value of 0.665 ± 0.02 μM)[28,29,30].

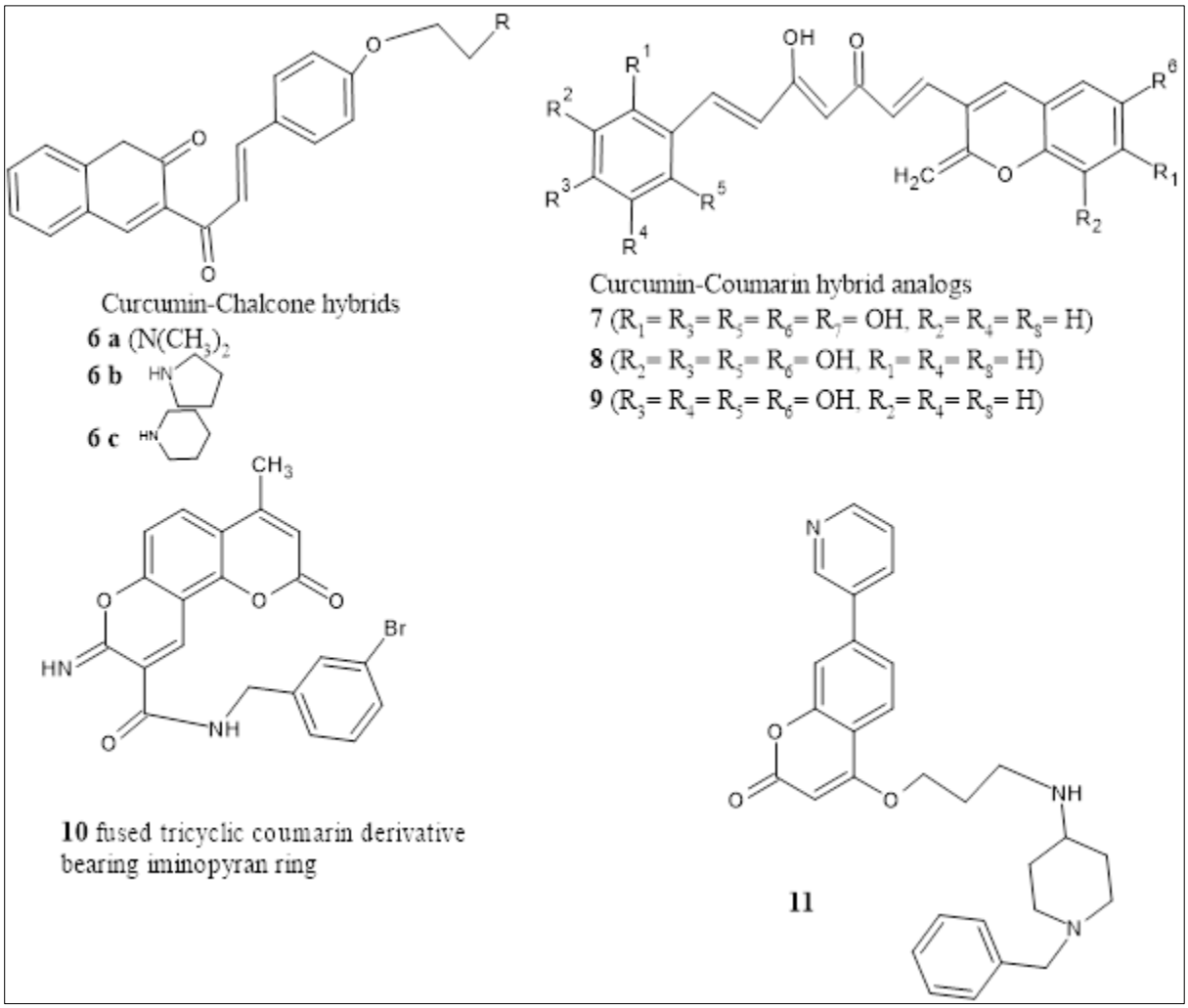

Figure 4 Structure of some potent multifunctional anti-Alzheimer Agents (6-11)

Another research work, W. Liu et al. reported synthesis and anti-Alzheimer activities of novel coumarin hybrids (**Fig. 4**) and assessed their inhibitory activities on cholinesterase(AChE, BuChE), GSK-3β, and BACE 1. One coumarin hybrid11 showed displayed potential AChE inhibitor activitywithIC50 = 1.313 ± 0.099 μM. BACE1 (IC50 = 1.227 ± 0.112 μM). Compound **11** found moderate HepG2 cytotoxicity, SH-SY5Y cytotoxicity, low HL-7702 cytotoxicity, as well as good blood-brain barrier (BBB) permeability [30-31]. A detail review on topic coumarin linked heterocyclic hybrids also displayed a promising approach to develop multifunctional agents against AD [32,33,34].

LU53439 (**Fig. 5**)**13**. There are two isoenzyme forms of MAOs, which are MAO-A and MAO-B they both shows highly inhibitor sensitivity and substrate selective like Esuprone,3-Aceyl coumarin, 7-benzyloxy coumarin derivatives**12,14, 15**. Oxidation of rat brain, dopamine, tryptamine, serotonin, noradrenaline and adrenaline is done by MAO-A whereas, studies on human brain revealed that same amines are deaminated and phenylethylamine and benzylamine are oxidizes by MAO-B which are *bis*-coumarin MAO-A and MAO-B inhibitors as potential anti-Alzheimer activities(**Fig. 5**)**16 a, b, c, d, e, f, g**[35]. Drugs like Cryptolepine and Donepezil are used as the positive controls for ChEs. 4-hydroxycoumarin is not a good inhibitor of AChE, BChE and BACE-1, when placing some electron withdrawing groups on benzyl ring which increase the activity of the group. This helps in boosting the inhibition of ChE which was notice by substitution of –Cl group on benzyl ring. Substation of –F also boost ChE inhibition but only at the ortho-position. The substation of the powerful electron withdrawing group at ortho-position, like trifluoromethyl, which yields a compound that inhibits the AChE, BChE and BACE-1 which have IC50 values of 4.83, 7.04, and 10.17μM, respectively [36-37].

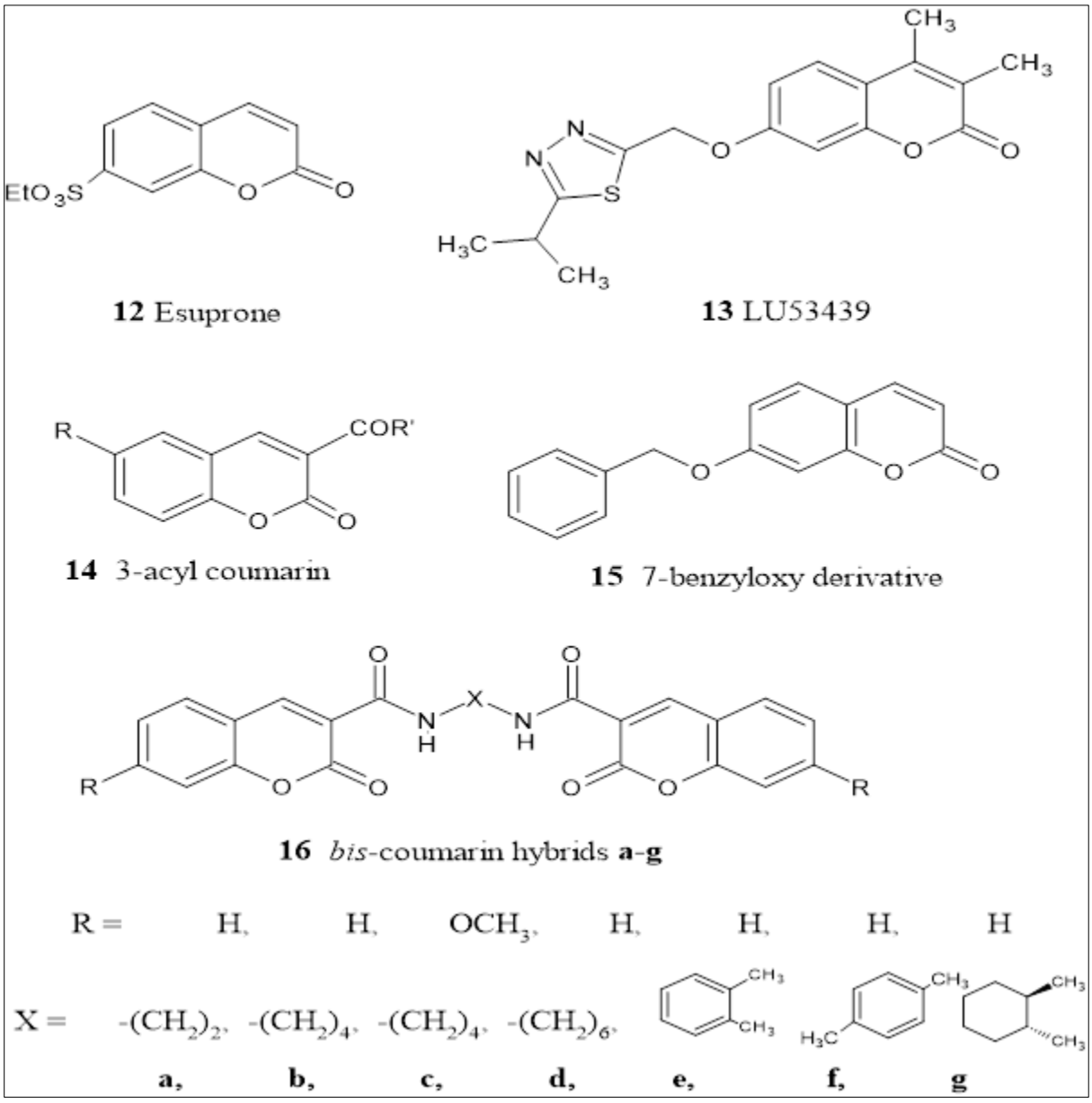

Figure 5 Chemical structures of Esuprone, LU53439, 3-Aceyl coumarin, 7-benzyloxy coumarin derivatives, *bis*-coumarin MAO-A and MAO-B inhibitors as potential anti-Alzheimer activities

Many coumarin derivative has the antioxidant properties which was expressed on the basis of electron transfer in DPPH, FRAP, phosphomolybdate assay. Some of the natural coumarins possess the anti-oxidant activity like umbelliferone. Neurotransmission and development of normal brain depends on the activity of these enzymes which can influence the aspects of personality or addictive behavior [21,35].

Newly reported carbazole-coumarin hybrids (**Fig. 6**) evaluated their acetylcholinesterase inhibitor activity[15-16]. One carbazole-coumarin hybrid **17 a** (R_1=CH_3, n=5) showed good acetylcholinesterase (AChE) inhibitory activity (IC_{50}value of 6.72 μM) and another compound **17 b** (n=4) that exhibits highly selective (over butyrylcholinesterase (BuChE) inhibitory activity (IC_{50}= 0.50μM).These carbazole-coumarin hybrids found very promising Anti-Alzheimer activities as a selective and they have dual binding site inhibitor of AChE [38-39].

Another interesting research work, S.S. Xie et al. reported design, synthesis and pharmacological evaluation of novel Donepezil-Coumarin Hybrids as Multi-Target Agents for the treatment of complex AD[40-41]. They combined N-benzylpiperidine moiety of donepezil structure to coumarin into in a single molecule to improve their anticholinesterase and MAO-B inhibitory activity. One Donepezil-Coumarin Hybrid (**18**) was the most potent inhibitor for eeAChE and eqBuChE (0.87 μM and 0.93 μM, respectively) with reference to standard drug Donepezil. This coumarin

hybrid **18** also showed good inhibitor to hChEs and hMAO-B (1.37 μM for hAChE; 1.98 μM for hBuChE; 2.62 μM for hMAO-B) hybrids (**Fig. 6**)[40].

E. Babaei et al. reported coumarin pyridine hybrids via a flexible aliphatic linkage were synthesized and assessed their anti-Alzheimer activities[42]. All coumarin pyridine hybrids found potential acetylcholinesterase (AChE) inhibition activity in the nanomolar range (IC50 = 2–144 nM) and remarkable butyrylcholinesterase (BuChE) inhibition property (IC50 = 9–123 nM) compared to donepezil as the standard drug (IC50 = 14 and 275 nM, respectively). One Compound **19** showed best showed best acetylcholinesterase (AChE) inhibitory activity (IC_{50}value of 2nM) and BuChE inhibition activity (IC50 = 24 nM) respectively [42](**Fig. 6**).

N. George et al. reported design, synthesis and ant-Alzheimer activities of coumarin linked 1,3,4-oxadiazole hybrids[43]. Two compounds (**20 b** and **20 c**) showed potential *in vitro* anticholinesterase activity, with IC50 values = 29.56 and 28.68 μM respectively. These coumarin linked 1,3,4-oxadiazole hybrids molecules also exhibited good to excellent in vitro antioxidant and anti-inflammatory activities (**Fig. 6**) [44].

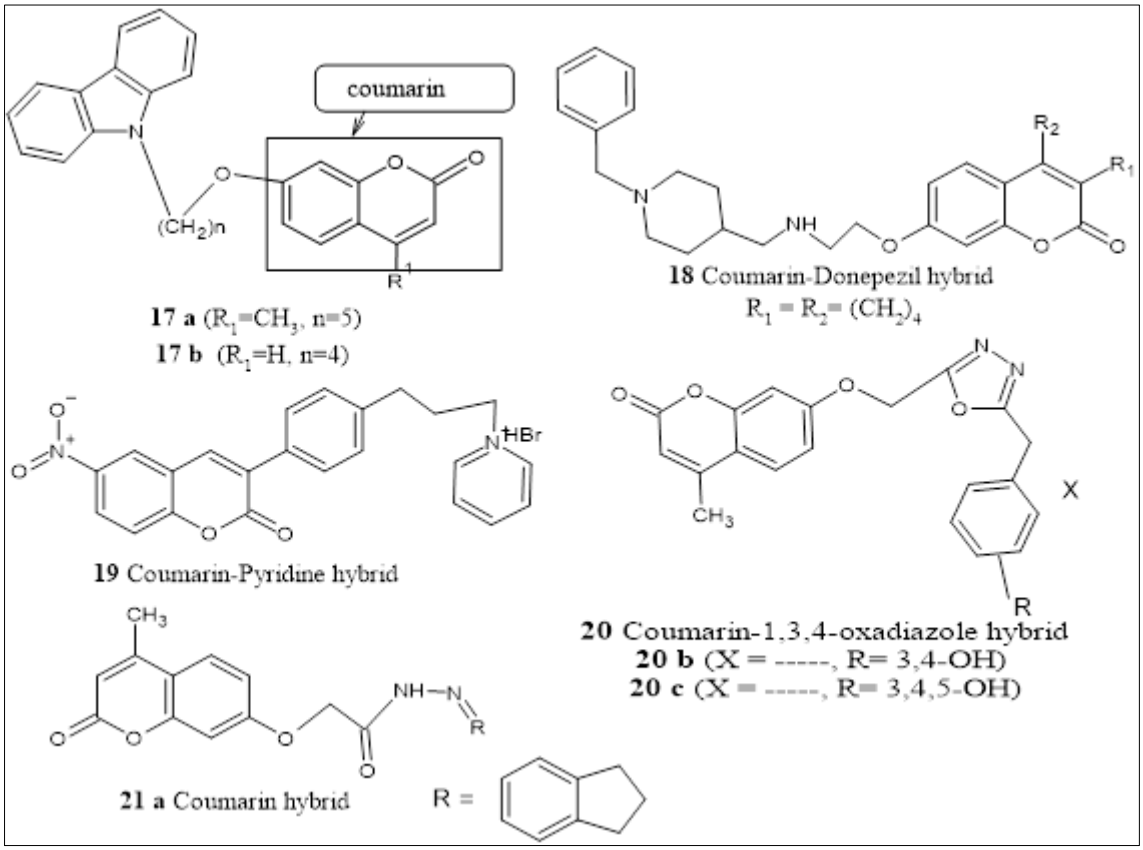

Figure 6 Structure of some compounds coumarin hybrids showed potential anti-Alzheimer agents (17-21)

Nahla N. Kamel reported novel coumarin as potential anti-Alzheimer activities[45]. These compounds were evaluated for acetylcholinesterase inhibition activity (**Fig. 6**). They also novel coumarin derivatives based on MTDLs approach. One coumarin derivative **21 a** found potent in vitro acetylcholinesterase inhibition activity with an IC50 value of 0.802 μM compare to Donepezil (0.802 μM). In vivo study investigated the amelioration in the cognitive function of AD-rats treated with **21 a** through the T-maze and beam balance behavioral tests. The study of coumarin derivative (**21 a**) exhibited a promising anti-Alzheimer's disease efficiency.

When isoxazole-type hetrocycles is incorporated with coumarin-carboxamide hybrids also showed inhibitory action against AChE/BuChE and beta secretase 1 (BACE1) [38]. The various pharmacological activity of coumarin is basically depend upon its chemical structure and physio-chemical properties of its oxahetrocyclic ring which allows the many protein target for easily binding. Moreover, a lactone group which is present in the coumarin molecule that has the ability of making stronger polar bonds and some of the enzymes which have esterase activity they can also open the lactone ring, and resulting the hydrolysis. Here coumarin act as pro drug. This mechanism of action of coumarin is proposed for the inhibition of carbonic anhydrase, which also has the esterase activity from natural coumarin [46].

Coumarin compound can be metabolise by two larger effective metabolic routes which are: a) 7-hydroxylation b) 3,4-epoxidation in humans and rats, mouse respectively. Cytochrome P450 enzyme responsible for biotransformation of coumarin, family of enzymes CYP1, CYP2, CYP3 in which CYP2A6 is responsible for 7-hydroxylation [47].

3. Synthesis methods for the preparation of coumarin scaffold

Coumarins can be synthesized by various reactions such as Pechmann condensation reaction [45], Knoevenagel condensation reaction [48], Perkin reaction [49], Wittig reaction [50], Claisen condensation reaction [51]. Among all these reactions Pechmann reaction are the mostly used reaction which involves the simple starting materials like phenols and β–ketoesters in the presence of acidic condensing agents to produce coumarins.

Perkin reaction: In this chemical reaction coumarin-based derivatives**25** was formed from heat dependent reaction of acetic anhydride**23** with salicylaldehyde**22** by using basic dry salts like sodium acetate. Intermediate of this reaction is orth- hydroxycinnamic acid**24** and spontaneously lactonized which forms the desired product (**Fig. 7**)[51].

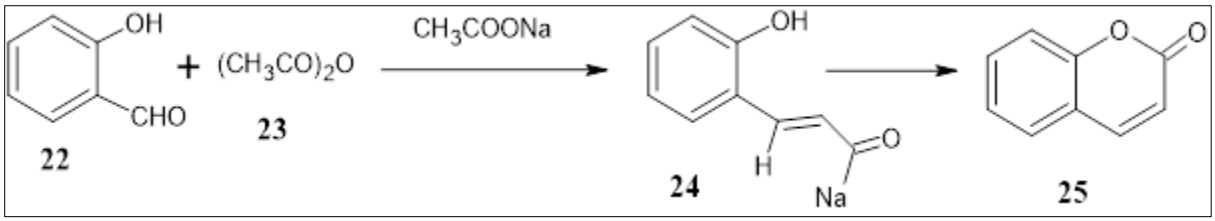

Figure 7 Perkin reaction

Pechmann reaction: In this chemical reaction, it implies the synthesis of coumarin-based derivatives**28** through the utilization of the conc. inorganic acid to catalysed the condensation reaction of dicarboxylic acid**27**-containing compounds with phenolic derivative**26** (**Fig. 8**)[52].

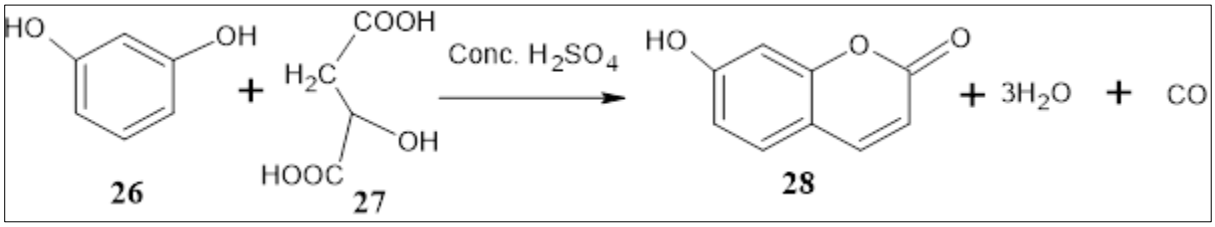

Figure 8 Pechmann reaction

Wittig reaction: Wittig reaction of aldehyde or ketone**29** is mixed with a Wittig phosphine reagent which is a triphenyl phosphonium**30** yield that produces expected olefin**31** in good yields along with phosphine oxide**32** as a by-product (**Fig. 9**) [53].

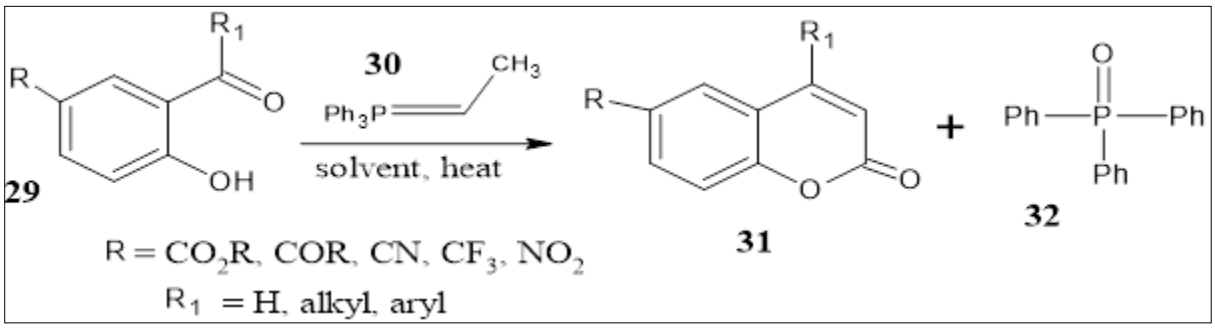

Figure 9 Wittig reaction

Claisen Rearrangement: In this reaction of phenol reacts with protected allyl alcohol in the presence of basic conditions and moderate temperature followed by tautomerism of intermediates **33 a, b, c** which produces 3,4 substituted coumarin**34** (**Fig. 10**) [54].

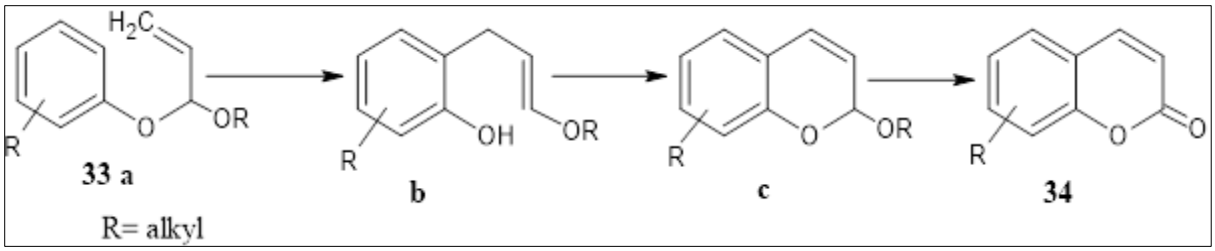

Figure 10 Claisen Rearrangement

4. Conclusion

In this review article, synthetic coumarin derivatives extensively found potential activity against neurodegenerative diseases. We studied about the coumarins which have different biological and physical properties. It shows greater effect in the treatment of Alzheimer disease. Coumarins and its derivatives have potential in inhibitor of AChE, BChE enzymes. Coumarin derivatives also found very well Aβ amyloid inhibition, Beta secretase 1 inhibitor and monoamine oxidase (MAO) inhibitor in literature. MTDLs approach found crucial for design, synthesis and anti-Alzheimer activities of novel coumarin hybrids well reported by researchers in literature. Coumarin can be prepared by synthetic routes such as Perkin, Pechmann reactions etc. Since there are many commercial drugs that are available for the treatment but coumarins can play major role as building blocks for treatment of this neurodegenerative type disease such as AD.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors declare no conflict of interest for this this review article.

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