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BIOLOGICAL IMPORTANCE OF SCHIFF AND MANNICH BASES IN ALZHEIMER- A REVIEW

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ABSTRACT

Alzheimer is a neurological disease that causes memory loss and a steady decline in cognitive function. According to WHO Alzheimer's disease is estimated from 74.4 million in 2023 to 152.8 million cases in 2050. There are many hypotheses about the neurodegeneration process. Currently the availability of approved drugs for treating the Alzheimer's disease, produced no effective pharmacological therapy for slowing, or reversing neurodegeneration. Due to the limitations of existing drugs, because of efficacy problems, adverse effects and toxicity there is an urgent need to develop new drug molecules to address these issues. The chemistry of Schiff base and Mannich base-containing compounds has been an interesting field of study in drug design and Development. As a result, these derivatives are a crucial class of molecules for developing a new chemical entity. Schiff and Mannich bases are an essential organic class of compounds with diverse biological activities. They exhibit a wide range of biological activities, including anti-microbial, anti-bacterial, anti-fungal, anti-viral,anti-convulsant, anti-Alzheimer activity etc. This review examines the extensive literature reports that have revealed the chemistry of different derivatives of substituted Schiff and Mannich bases as promising lead molecules for targeting various Alzheimer'disease pathologies over

the past two decades. Hence it is a worthy review study to explore the biological importance of Schiff and Mannich base against Alzheimer's disease.

Keywords: Alzheimer's disease, Schiff base, Mannich base, anti-microbial, anti-convulsant, anti-fungal

INTRODUCTION:

Alzheimer's disease is a chronic, irreversible neurological condition that causes speech impairment, memory loss, and a loss of cognitive function over time **[1]**. It is predicted that 74.7 million individuals will have Alzheimer's disease worldwide by 2023 as the population ages and the number of cases rises **[2]**. With various conflicting ideas, including the cholinergic, amyloid, oxidative stress, and metal chelation hypotheses, the pathophysiology of Alzheimer's disease is still unknown as of this writing **[3, 4]**. The most widely recognized theory contends that insufficient levels of neurotransmitters, like acetylcholine (ACh), in the neuronal and neuromuscular regions are the root cause of Alzheimer's disease. Acetylcholine transferase activity was shown to be lower in the brain tissue of Alzheimer's disease patients, and there was less Ach produced, taken up, and released. ACh deficiency in the brain is caused by either decreased production or active acetylcholinesterase (AChE) enzymes. Acetylcholinesterase inhibitors (Donepezil, Rivastigmine, and Galantamine) and NMDA receptor antagonists (Memantine) are two groups of medications that are currently clinically available to lessen the symptoms of Alzheimer's disease **[5, 6]**.

Aβ-plaques are caused by extracellular deposits of fibrils and amorphous aggregates of the Aβ peptide. The amyloid hypothesis, which holds that Aβ plaque deposition or partially aggregated soluble A cause a neurotoxic cascade causing Alzheimer's disease pathology **[7-9]**, has long been the most effective theory to explain the cause of Alzheimer's disease. The soluble forms of Aβ are more closely linked to memory loss and Alzheimer's disease progression than Aβ plaques, but all aggregated forms are hazardous **[10]**.

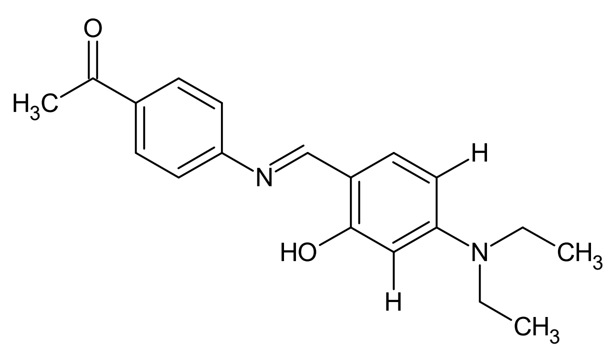
Another intracellular hallmark of Alzheimer's disease is Neurofibrillary tangles, which are composed of tau proteins. Tau is a microtubule-associated protein that plays a crucial role as a scaffolding protein, and is particularly enriched in axons. However, under pathological conditions, the aggregation of tau can negatively affect the axons of neurons, ultimately leading to neurodegeneration. Following numerous failures of Aβ-targeting drugs for Alzheimer's disease, there has been an increased interest in exploring the therapeutic potential of targeting tau, especially as studies of biomarkers have indicated that tau pathology is more closely linked to the progression of Alzheimer's disease **[11]**.

Biological applications for schiff bases include use as antibacterial, antifungal, anti-inflammatory and anticancer agents, as well as in the production of cosmetics and as effective enzyme inhibitors **[12-15]**. One of the most crucial characteristics of Schiff bases is that they are vulnerable to nucleophilic attack, particularly in acidic. This causes the imine bond to break down, releasing the original reagents **[16-18]**.

Mannich bases also exhibit a wide range of biological activities, including the inhibition of carbonic anhydrase **[19-21]**, cytotoxicity **[22-25]**, analgesia **[26]**, anticonvulsant **[27]**, and acetyl cholinesterase inhibitory **[28]**. Thiol alkylation, interaction with enzymes crucial to antioxidant mechanisms **[29, 30]**, inhibition of mitochondrial respiration **[31-32]** and inhibition of topoisomerase enzyme **[33-34]** are the mechanisms that have been reported for Mannich bases' bioactivities.

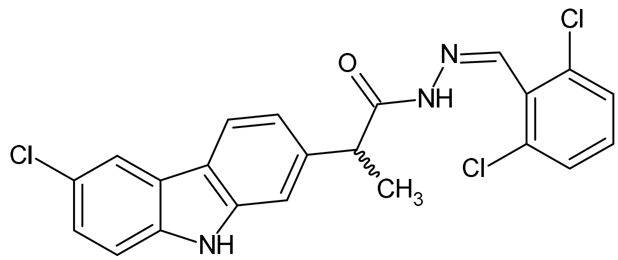
BIOLOGICAL ACTIVITY OF SCHIFF BASE AND MANNICH BASE:

Basma M. Abd Razik *et al .,*2016, reported a variety of Schiff base derivatives were created and their inhibitory ability against the cholinesterase enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) was assessed using Ellman's method. Compound **1** among them has higher AChE and BuChE inhibitory activity than Galantamine, the reference drug **[35]**.



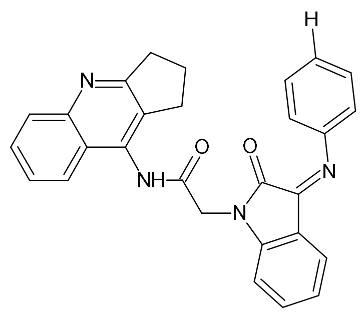
(1)

Speranta Avram *et al .,* 2021, reported that, Schiff bases derivatives was synthesized by (2RS)-2-(6-chloro-9H-carbazol-2-yl) propane hydrazide condensing with aromatic aldehyde using microwave irradiation method and evaluated using bioinformatic tools. Among this compound **2** have excellent potential to use for neurodegenerative disorder **[36]**.



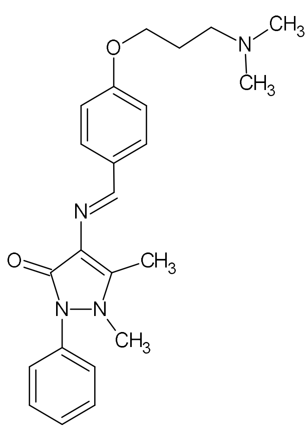
(2)

New Cycloalkyl Fused Quinolines Tethered to Isatin Schiff Bases were synthesized and assessed for their Acetylcholinesterase and Butyrylcholinesterase activity as well as in vivo behavioral tests, according to Baswaraju Macha *et al .,* 2020. Strong inhibitory activity has been demonstrated for compounds having propionyl and butyroyl linker between amine and isatin Schiff base scaffold. A powerful acetylcholinesterase and butyrylcholinesterase inhibitor, compound **3** is one of these **[37]**.



(3)

According to Fatih Tok *et al .,* 2018, Antipyrine's Schiff base derivative's inhibitory activity was investigated for its effects on the enzymes AChE, BuChE, MAO-A, and MAO-B. IR, 1H-NMR, 13C-NMR, and mass spectroscopies were used to characterize the produced compounds. The most potent derivatives were discovered to be compounds **4 and 5** based on the AChE enzyme inhibition experiment **[38]**.



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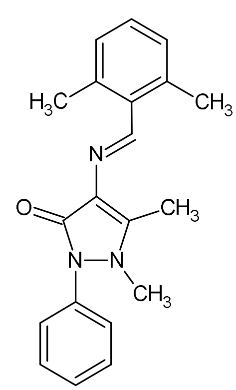
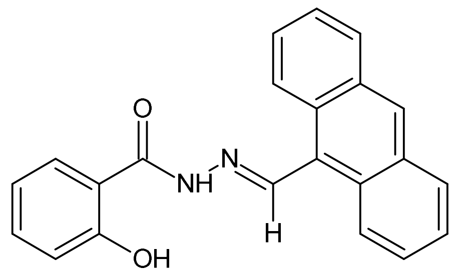


(5)

According to Fazal Rahim *et al .,* 2016, a number of Hydrazide Schiff base derivatives were created using a multitargeted method and tested against Acetylcholinesterase and Butyrylcholinesterase. When compared to the standard drug Eserine, compound **6 and 7** have strong inhibitory efficacy against AChE and BuChE, respectively **[39]**.



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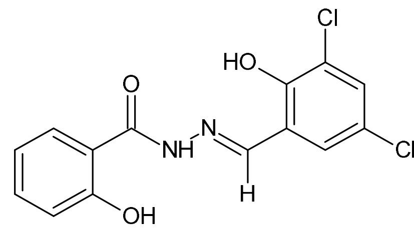
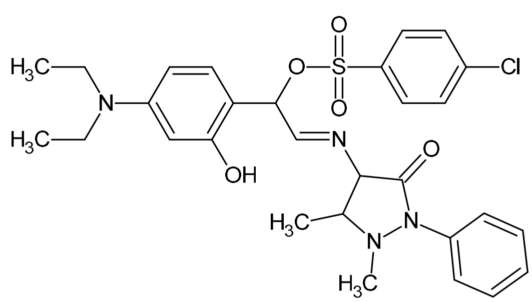


(7)

A number of Schiff base derivatives were synthesized and their activity was tested using the DPPH and ABTS tests against the enzymes AChE and BuChE, according to Ercan Cinar *et al* ., 2022. Compound **8** (2E)-1-[4-(diethylamino)-2-hydroxyphenyl] is present in these derivatives. AChE assay results reveal that compound **9** ((2*E*)-2-[(1,5-dimethyl-3-oxo-2-phenylpyrazolidin-4-yl)imino]ethyl 4-chlorobenzene-1-sulfonate) exhibits strong inhibitory action.In comparison to galantamine, 1-(2-hydroxynaphthalen-1-yl)ethyl4-chlorobenzene-1-sulfonate) has more inhibitory activity in the BuChE assay **[40]**.



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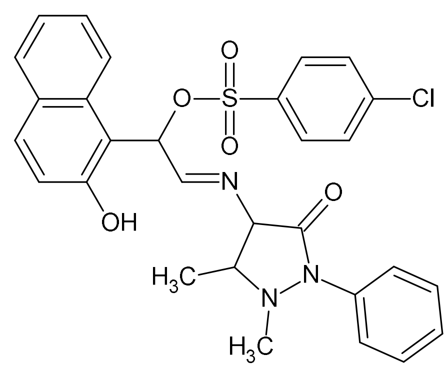
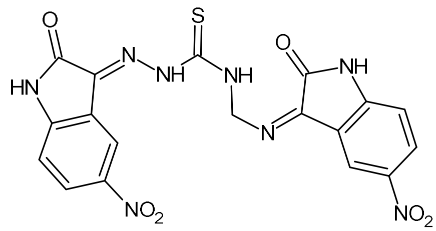


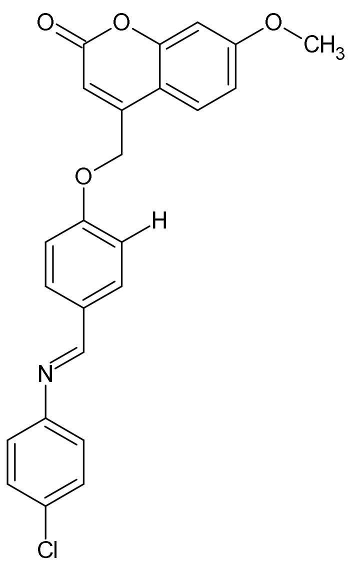
(9)

Isatin bis-Schiff bases based on thiocarbohydrazone were created, characterized by NMR and HR-ESI-MS, and tested for inhibitory activity against acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), according to Shoaib Khan *et al* ., in 2023. Due to the presence of oxygen and the nitro motif forms hydrogen bonding with the active sites of AChE and BuChE enzymes, compound **10** exhibits potent inhibitory activity toward the AChE and BuChE than the standard Donepezil **[41]**.



(10)

A number of novel coumarin-schiffs base hybrids were designed, synthesized and evaluated for their anti-acetylcholinesterase action, according to Aso Hameed Hasan *et al* ., in 2023. Fourier transform infrared (FTIR), nuclear magnetic resonance (NMR), and high-resolution mass spectrometry (HRMS) analyses were used to carry out the characterization. Among these, compounds **11 and 12** demonstrated strong acetylcholinesterase inhibitory action **[42]**.



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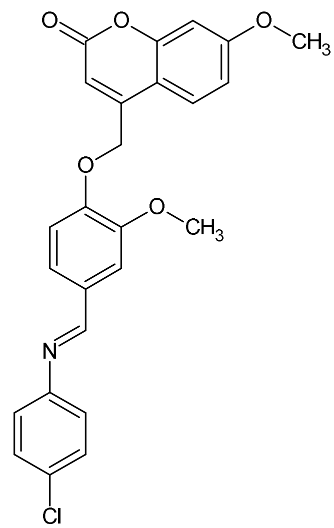
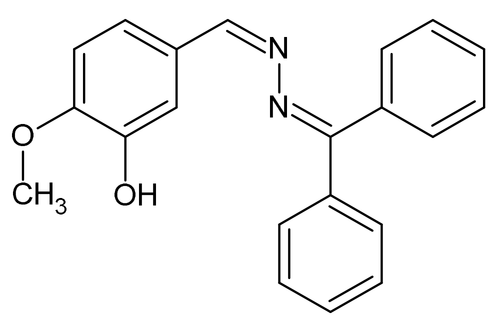


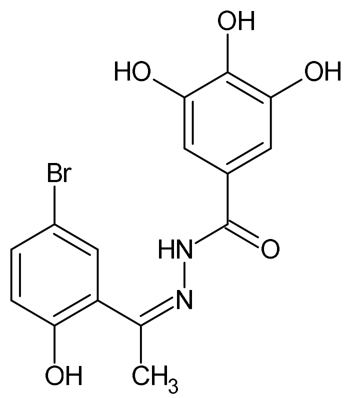
(12)

According to Sertan Aytac *et al .,* 2023, a number of Schiff bases and hydrazinylidene derivatives with phenol moieties were produced using a microwave technique, and their antioxidant and cholinesterase inhibitory activity was then assessed. It was discovered that compound **13** is a powerful cholinesterase inhibitor **[43]**.



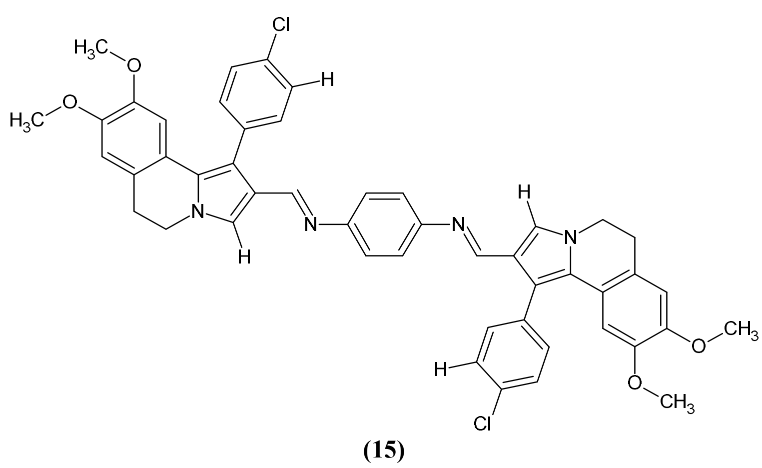
(13)

According to Nura Suleiman Gwaram*et al .,* 2012 report, many new ketone derivatives of Schiff bases produced from gallic hydrazides were created and tested for their antioxidant and acetyl cholinesterase-inhibiting properties. With the use of spectroscopy and X-ray crystallography, the chemicals were identified. The 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ferric reducing antioxidant power (FRAP) experiments demonstrated that all the compounds exhibit potent antioxidant properties. The compound**14** has a greater inhibitory effect on human acetylcholinesterase **[44]**.



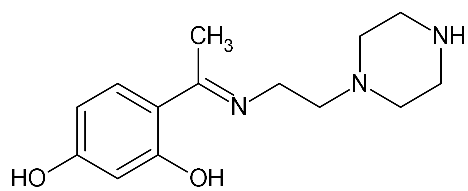
(14)

According to Alisa A. Nevskaya*et al .,* 2021, unique aliphatic and aromatic Schiff bases were used to synthesize a number of imino adducts of DHPPIQ 2-carbaldehyde. A phenylene bridge connecting Bis-DHPPIQ Schiff bases was tested for its effectiveness against Alzheimer's disease. Human acetylcholinesterase, monoamine oxidase-A, and self-induced -amyloid aggregation are all effectively inhibited by compound **15** **[45]**.



(15)

According to Saleh M. Salga *et al* ., 2011 report, new 1-(2-ketoiminoethyl) piperazine derivatives of the Schiff base were synthesized. The structure of the synthesized derivatives were characterized by mass spectroscopy, FT-IR, UV-Visible, ^{1}H and ^{13}C-NMR, and tested for their antioxidant and human acetylcholinesterase activity. In the DPPH experiment, compound **16** (4-[(1*E*)-1-[2-(piperazin-1-yl) ethyl]imino-ethyl]benzene-1,3-diol) and compound **17** (*E*)-[2-(piperazin-1-yl)ethyl] both exhibit stronger AChE inhibitory activity. In the FRAP experiment, [1-(pyridin-2-yl)ethylidene]amine] exhibits stronger inhibitory action **[46]**.



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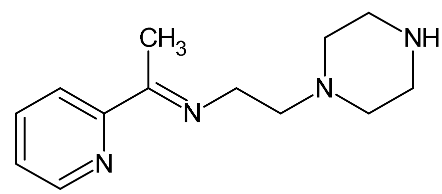
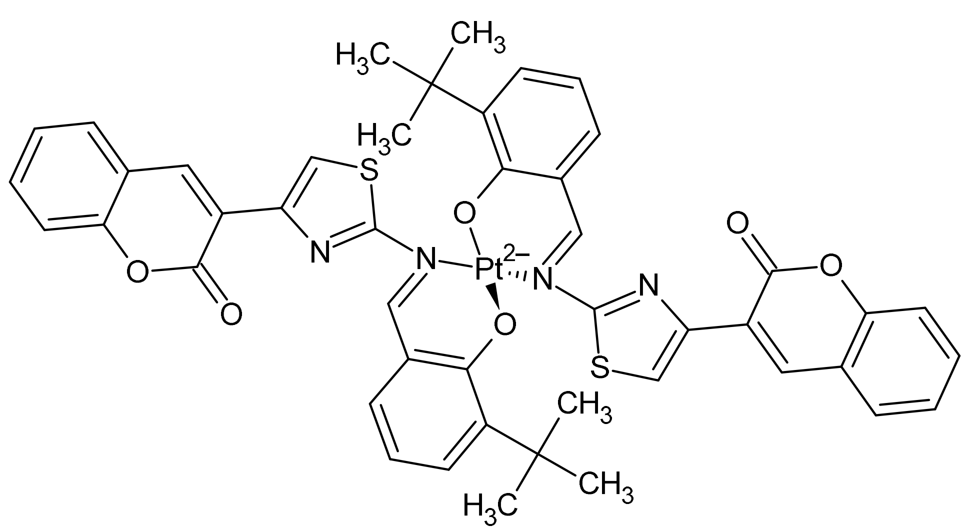


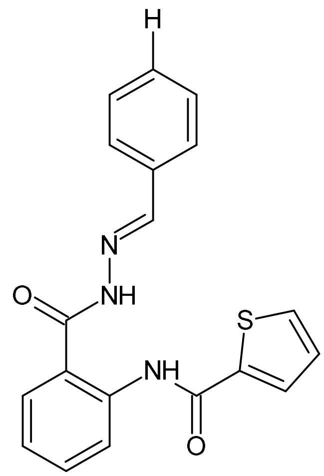
(17)

Omer Sahin *et al* . 2021 reported that novel Schiff bases and their palladium and platinum metal complexes were synthesized and studied by ^{1}H-NMR, ^{13}C-NMR, FT-IR, and LC-MS. This was done by linking coumarin and thiazole with 3-tertiary butyl salicylaldehyde into a single molecule. According to research on the photophysical characteristics of CTS, Schiff base is sensitive to CN, F, and AcO anions. The acetylcholinesterase and butyrylcholinesterase inhibitory activity of the compounds is assessed. Compound **18** in this Pt (II) complex has strong inhibitory action against AChE and BChE **[47]**.



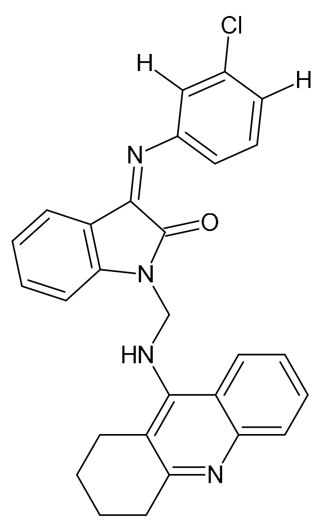
(18)

A number of new hydrazone derivatives of benzo hydrazide based on thiophene-2-carboxamide were created and tested for their antioxidant and cholinesterase inhibitory properties by Naghmana Kausar *et al* . 2021. The majority of the substances have good inhibitory action. Compound **19** was concluded to be the most effective cholinesterase inhibitor compared to the standard drug Donepezil. SAR demonstrates that compounds' actions against enzymes were increased when the benzene ring was substituted with more electronegative groups **[48]**.



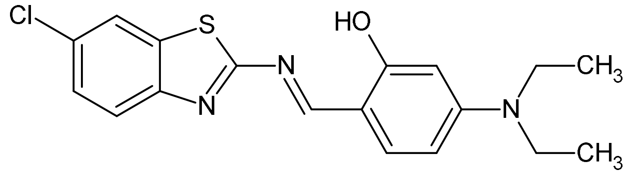
(19)

A number of novel tacrine-isatin Schiff base hybrid compounds were created and tested for their AChE and BChE inhibitory action in Alzheimer's disease by E. Riazimontazer*et al.* 2019. These substances are also great metal chelators. The majority of the drugs exhibited strong inhibitory activity, with **20** of them exhibiting both strong and mixed inhibition **[49]**.



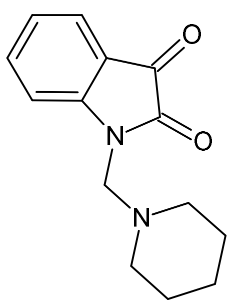
(20)

According to Manojkumar Jadhao *et al* ., 2016 **[50]** spectroscopic methods were used to assess the multifunctional activities of a synthesized benzothiazole Schiff base (E)-2-((6-chlorobenzo[d]thiazol-2-ylimino)methyl)-5-diethylamino)phenol. Amyloid peptide showed copper-induced aggregation in compound **21**.



(21)

Mannich bases of Isatincontaining 1-[piperidin-1-yl (P1)/morpholin-4-yl (P2)/N-methylpiperazin-1-yl (P3)]methyl)-1*H*-indole-2,3-dione) moieties were tested against human carbonic anhydrase, AChE, BuChE, and isoenzymes hCA I and hCA II, according to Dilan Ozmen Ozgun *et al* ., 2016. When compared to the reference drug Tacrine, the compound **22-24** has a greater inhibitory impact on the enzymes AChE, BChe, and carbonic anhydrase **[51]**.



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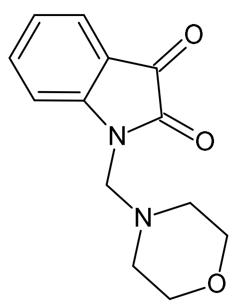

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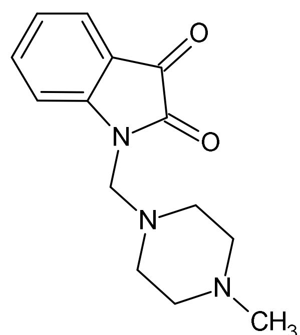
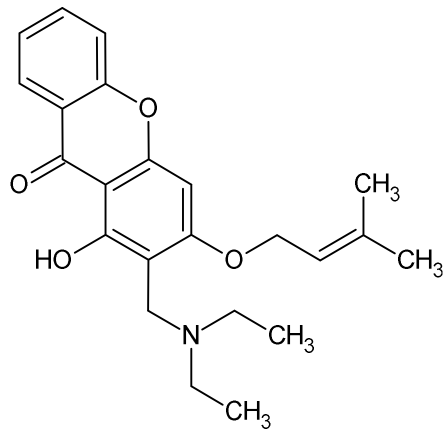


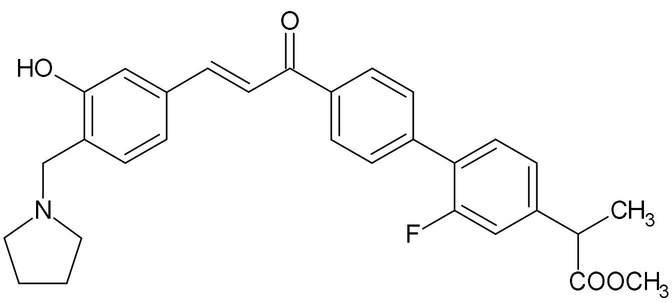
(24)

A series of novel 1, 3-dihydroxyxanthone Mannich base derivatives were created and tested for cholinesterase inhibitory action, according to a study by Jiangke Qin *et al* ., 2013 values against butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) at micromole level concentration. The early structure-activity analysis revealed that the kinds of dialkylamine methyl in position 2 of xanthones affected cholinesterase activities and AChE/BuChE selectivity, while the alkoxy or alkenoxy substituents in position 3 of xanthones had a favorable effect on the inhibitory potency. AChE and BChE are effectively inhibited by compound **25** (2-((diethylamino)methyl)-1-hydroxy-3-(3-methylbut-2-enyloxy)-9*H*-xanthen-9-one) **[52]**.



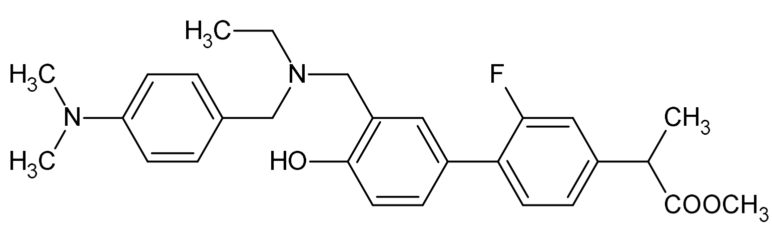
(25)

According to Chaoquan Titan *et al .,* 2019, a number of flurbiprofen-chalcone hybrid Mannich base derivatives were created and tested against AChE and Monoamine oxidase B. The compound **26** with a pyrrolidine group among these shown effective inhibition of AChE and Monoamine oxidase-B. display appropriate in vitro blood brain barrier permeability as well as anti-neuroinflammatory activities **[53]**.



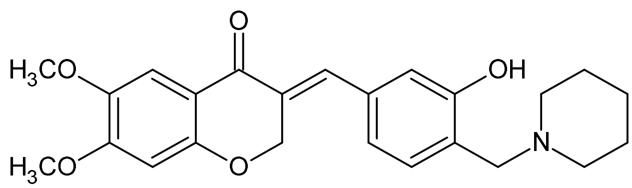
(26)

According to Hongyan Liu *et al .,* 2019 a number of mannich base derivatives of 4'OH flurbiprofen were synthesized. For the most part, these compounds exhibit good multifunctionality. The compound **27** listed below has a good inhibitory impact on self-induced A-aggregation. Additionally showed good blood-brain barrier permeability, biometal chelating, anti-neuroinflammatory action *in vitro*, and antioxidant activity **[54]**.



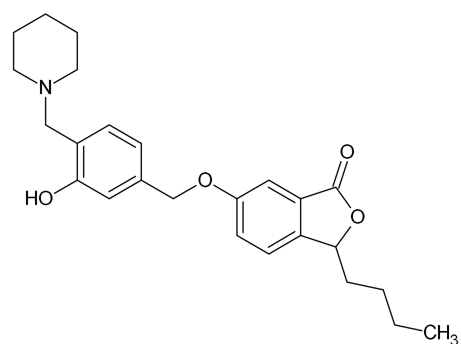
(27)

A series of mannich base substituted homoisoflavonoids' derivatives were created and tested as multifunctional agents against Alzheimer's disease, according to Yan Li *et al* . in 2016. It shown that the most of the compounds were effective dual inhibitors of AChE and Monamineoxidase-B. Compound **28** has significant self- and Cu^{2+}-induced Ab1-42 aggregation inhibitory efficacy, antioxidant activity, bio metal chelating capacity, and high BBB permeability in addition to high Ache and Monoamine Oxidase B inhibitory action **[55]**.



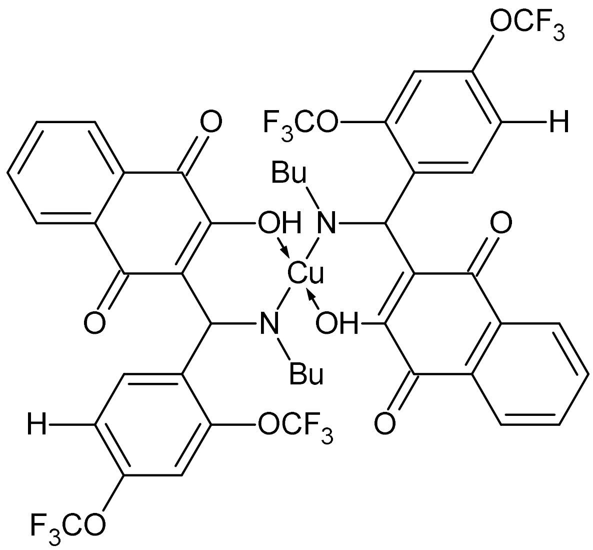
(28)

A number of 3-butyl-6-benzyloxy phthalide Mannich base derivatives were created and synthesized, according to Zhuolin Liu *et al* ., 2022. These substances all exhibit multitarget inhibitory efficacy against Alzheimer's disease. Among these, compound **29** exhibits strong inhibitory efficacy against EeAChE, HuAChE, and MAO-B, as well as favorable blood brain barrier permeability, Cu2+ chelation, anti-neuroinflammation, and amelioration of oxidative stress **[56]**.



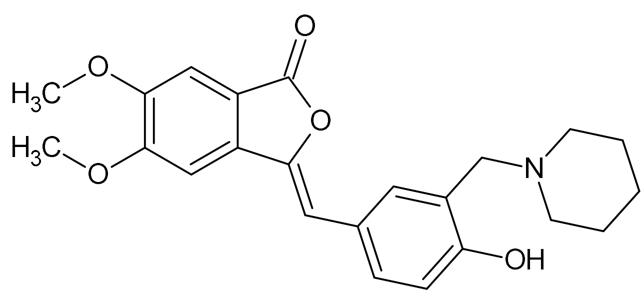
(29)

A number of Mannich bases produced from 2-hydroxy-1,4-naphthoquinone (lawsone), substituted benzaldehydes, and two primary amines, as well as their Cu^{2+} complexes, were synthesized and evaluated for their selective cholinesterase inhibitory action, according to Adriana F. L. Vilela *et al*., 2016. To calculate the inhibitory potency, butyryl cholinesterase (BuChE) and acetylcholinesterase (AChE)-containing immobilized capillary enzyme reactors were utilized. Compound **30** displays a solid inhibitory profile, but not one that outperforms Galantamine, a common medication **[57]**.



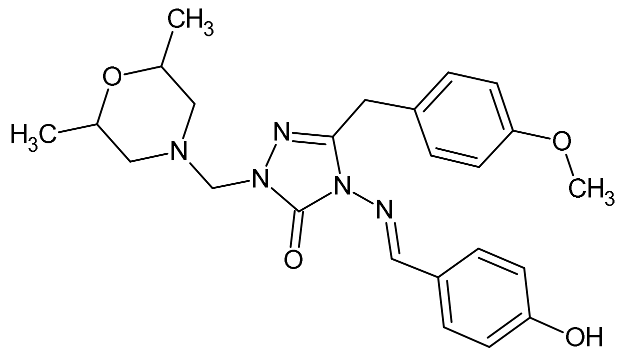
(30)

A variety of 3-benzylidene/benzyl phthalide Mannich base compounds were created and their potential for several functions were assessed, according to Zhong Cheng Cao *et al* ,. in 2021. Among them, compound **31** demonstrated strong MAO-B inhibitory activity, EeAChE and HuAChE inhibition, and excellent antioxidant activity. In addition, it demonstrated effective antiplatelet aggregation activity, biometal chelating capacity, Cu^{2+}-induced Ab1-42 aggregation inhibitory potency, disaggregation ability on A1-42 fibrils, and desirable BBB permeability **[58]**.



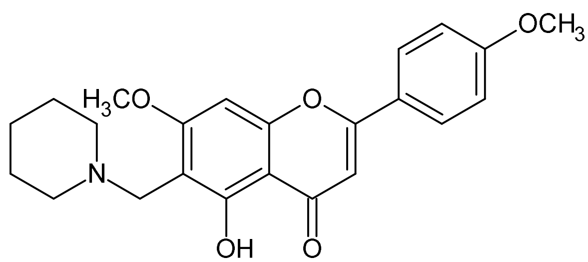
(31)

A series of 1-(2,6-dimethylmorpholino-4-yl-methyl)-3-substituted-4-(4-hydroxybenzylidenamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones were created and tested against the AChE, BuChE, and glutathione S-transferase (GST) enzymes, according to Songül Boy *et al*. in 2020. By using spectroscopic methods such as IR, ^{1}H-NMR, ^{13}C-NMR, and HR-MS, the produced compounds were evaluated. Among this compound **32** was found to be the most potent inhibitor **[59]**.



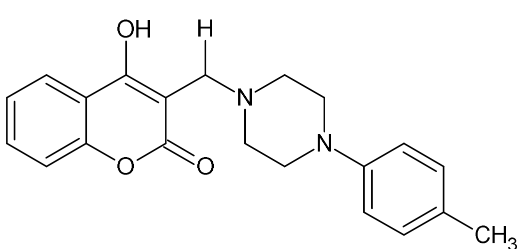
(32)

According to Hao-ran Liu *et al .,* (2016), a variety of acacetin 7-O-methyl ether Mannich base derivatives were produced from Naringin. Acetylcholinesterase (AChE) inhibitory activity of all synthesized compounds has been assessed. Compound **33** among them demonstrated more AChE selectivity and inhibitory action than the gold standard (Rivastigmine) **[60]**.

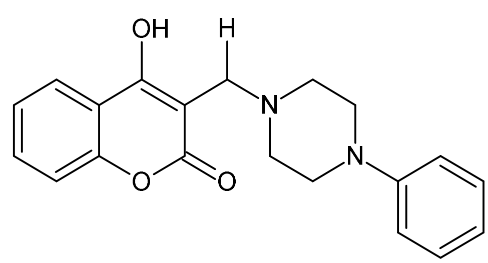


(33)

A series of coumarin Mannich bases were produced using a one-pot, three-component process, according to A. Kiani *et al.* (2018), who also used Ellman's technique to test the inhibitory activity of the compounds against the enzymes AChE and BuChE. Among them, compound **35** with the phenylpiperazine moiety had good BuChE activity and compound **34** with the p-tolyl piperazine group shown good AChE inhibitory activity. According to "Lipinski Rule of 5" analysis, the produced chemical crosses the BBB **[61]**.

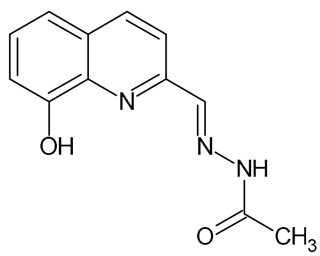


(34)

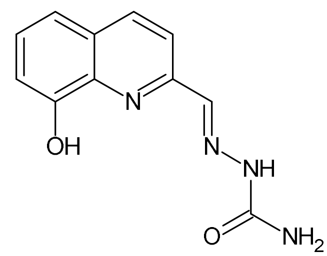


(35)

Luiza M.F. Gomes *et al* .,2014, reported that, synthesis of acetohydrazone, thiosemicarbazon, and semicarbazone derived from 8-hydroxyquinoline were complexes with Cu (II) and evaluated for their disaggregation of Aβ plaques in Alzheimer's disease. In this Acetohydrazone (compound **36**) and Semicarbazone (compound **37**) showed good disaggregation activity **[62]**.

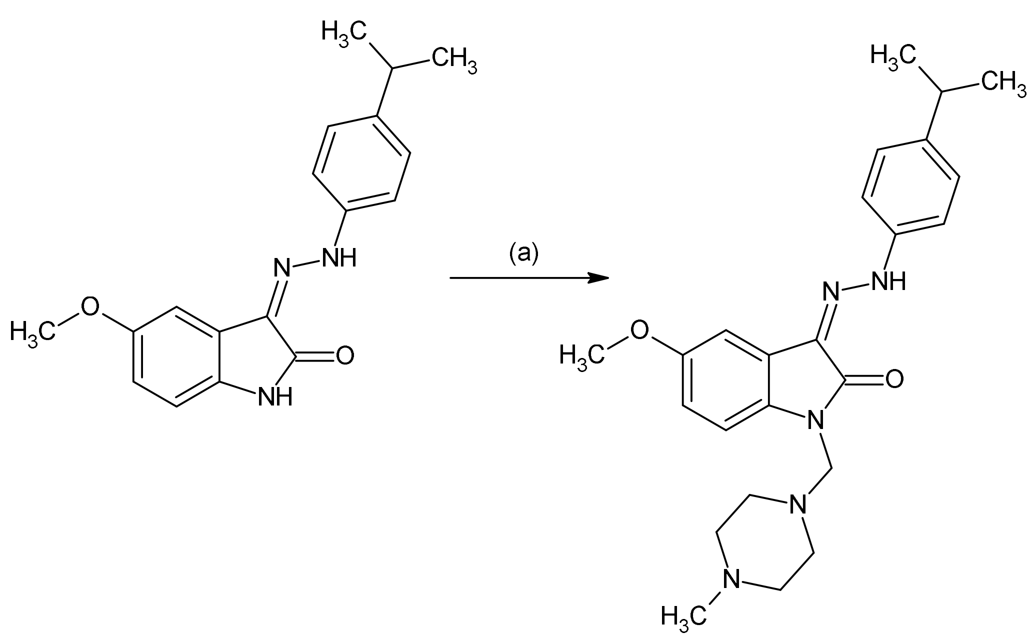


(36)



(37)

According to Leonardo Pisani *et al* ., 2017 study, 5-methoxyisatin 3-(4-isopropylphenyl) hydrazone was discovered to be a multitarget inhibitor of Aβ aggregation and cholinesterase. It has been shown to have antiaggregating activity of a family of indolin-2-ones that inhibits Aβ fibrillization. A Mannich-base that resulted in the synthesis of the N-methyl piperazine derivative (Compound **38**) to boost the water solubility was proven by turbidimetric technique **[63]**.



(38)

(a) - ethyl alcohol, formaldehyde 37% in wt. in water, N-methylpiperazine, 12 h, room temperature

CONCLUSION:

` The review article demonstrates that Schiff and Mannich bases, as well as their derivatives, have strong anti-Alzheimer actions. It might be said that the biological potential of the Schiff and Mannich bases is extraordinary and untapped. Therefore, Schiff and Mannich bases should be employed as a promising precursor for the creation of new Alzheimer's disease medications.

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