Multi target –directed imidazole derivatives for neurodegenerative diseases

A G Eliewi*, Z S Al-Garawi, F F Al-Kazzaz and A J K Atia

1Mustansiriyah University, College of Science, Department of Chemistry, Baghdad-Iraq
* Corresponding Author: amjadgali11@gmail.com

Abstract. Neurodegenerative diseases NDDs, such as Alzheimer’s and Parkinson’s diseases influence the brain tissues and cells that led to perpetual damage, reduce the quality of life and life-threatening, although considerable advances in conception the mechanisms of these diseases and their pathogenesis. Thus, developing effective treatments against neurodegenerative disorders still challenging. In this regard, imidazole derivatives have showed a potential to be multi target-directed agent that has multifunctional biological activities to restrict NDDs. Imidazole is a heterocyclic compound with structural features enable different biological activities based on the substituted. This review discusses the roles of different imidazole derivatives to be candidate as a treatment of NDDs. Modification of imidazole moiety has been recognized so as favorable multi target to treat NDDs. Herein, we suggest that imidazole can be modified properly to increase its potential to be applied for pre-clinical and clinical studying of NDDs treatment.

Key words: Neurodegenerative diseases, imidazole derivatives, biological activity, Alzheimer disease

1. Introduction

Neurodegeneration is a progressive disease that rises lack of specific neuron sorts, allocation central nervous system (CNS) dysfunction and dysregulation of neurons. Alzheimer’s and Parkinson’s disease are the most important neurodegenerative diseases. Alzheimer disease AD includes a progressive degeneration of the brain tissues that is caused absence or decrease in acetylcholine (Ach), which has a polyclinic pathology [1-4]. Aggregation of extracellular amyloid –beta (Aβ) in senile plaques, lack of cholinergic activity in particular parts of the brain and intracellular neurofibre synaptic, including the plethoraphosphorylated tau protein (as a long neuro inflammation), are all observed in Alzheimer disease [5-7]. Although there are high interest for treating Alzheimer disease, only several drugs have been approved by the FDA, such as donepezil, tacrine and rivastigmin [8]. However, the multi-differential factors of these NDDs is one of the main hurdles to drug development [9]. Over the years, a variety of novel molecules or compounds and molecular targets have been intended, considering the development of new NDDs treatments.

One of the most concerted pathways in this context is imidazole derivatives which are for the most pivotal and ecumenical heterocycles compounds. These molecules display a wide spectrum of biological activities and significant pharmacological characters for drug discovery [10,11]. Due to their special structural
features, several important types of imidazole have been existed depending on the target, such as mitotic spindle microtubules and DNA receptor tyrosine, etc [12-14]. This review focuses on exploring new trends of imidazole derivatives and their applications that contribute to reduce neurodegenerative pathway, such as that of Alzheimer and Parkinson’s disease.

2. Imidazole

Imidazole nucleus is an important five-membered aromatic pharmacophore widely presented in natural products and synthetic compounds. it is also forms the main structure of some components of human organs, as structural base of DNA purines, a component in the amino acid histidine residue and vit –B12 and biotin [15]. The structural characteristic of imidazole ring with its active electron-rich feature is profitable for imidazole derivatives to be easily associated with enzymes and receptors in the biological environment, and therefore a wide range of medical applications [16].

In recent decades, many classical ways for synthesizing these derivatives have been used debus-radziszewski imidazole synthesis [17], Wallach imidazole synthesis [18], van leusen imidazole synthesis [19] and etc. Among these, the prominent is the van leusen imidazole synthesis using TosMICs due to its important advantages, such as available raw materials, easy manipulation and a widely range of substrates [20].

3. Pharmacological use of imidazole derivatives:

Many well-known and marketed drugs used to treat various illnesses, for instance miconazole, clotrimazole, misonidazole, alpidem ketoconazole, flumazenil, metronidazole, luliconazole dacarbazine, cimetidine and clonidine contain imidazole moiety [21]. New derivatives are actively developing for therapy purposes [22-24]. Imidazole –based compounds possessed biological activity, such as anticancer [25], antifungal, antibacterial, anti-inflammatory, anti-parasitic, antiviral and anti-neuropathic [10], Table 1. Synthesis of imidazole and its derivatives has been of a high interest by organic chemists and pharmaceutical chemists, however there is still a need for an efficient and simple method to raise the imidazole heterocyclic skeleton.
Table 1. Various biological activities and chemical structures of molecules containing imidazole [20]

| Biological activities | chemical structure |
|-----------------------|--------------------|
| Antibacterial         | ![Chemical structure](Image1) |
| Antifungal            | ![Chemical structure](Image2) |
| Anti-inflammatory     | ![Chemical structure](Image3) |
| Antiviral             | ![Chemical structure](Image4) |
| Antiparasitic         | ![Chemical structure](Image5) |
| Anticancer            | ![Chemical structure](Image6) |
| Antihistaminic        | ![Chemical structure](Image7) |
| Enzyme inhibitor      | ![Chemical structure](Image8) |
Neurodegeneration, described as a progressive is not treatable mental illness, where specific neuron species lost, dysfunction in the distribution of the central nervous system (NCS), and dysregulation of neurons [26]. Neurdegenerative diseases (NDDs) such as Alzheimer, Parkinson’s, huntingtons, amyotropic lateral sclerosis disease and the spino cerebellar ataxias [27] are varied in their pathophysiology and symptoms. Cognitive impairment and memory loss and reduce the person’s ability to speak, move and breath [28]. Effective treatments are therefore urgently needed but will only applied when understanding their mechanisms of actions. Most of neurodegenerative diseases are recognized by the intracellular and extracellular aggregation of the misfolded proteins [29].

4.1 Alzheimer disease AD

Alzheimer disease (AD), a form of dementia, affect aged people worldwide. This disease associated with aggregation of amyloid-β (Aβ) around tissues and form neurofibrillary tangles NFTs through hyper phosphorylation of the tau proteins connected with cellular microtubules [30]. Aβ is a membrane glycoprotein precursor protein of the plaques that accumulate around neurons and cause senile cells. Aβ can be species cleavage of different lengths, depending on the exist number of amino acids, between 37-42 residues. Its cleavage stimulated by α- or β-secretase aproyeolysis process in the presence of Υ-secretase enzyme, lead to the accumulation of neurotoxic fragments of Aβ [31]. The segment of 42 residues Aβ 42 presents pro-accumulating properties. A pathological increase in the formation of Aβ 42 associates with presence of Alzheimer disease [32]. Thus it is of high concern to prevent production and accumulation of Aβ 42 or at least, remove the accumulated Aβ 42 along with the barring of tau–related toxicity [33]. The protein tau is important in the sense of stabilizing microtubules [34], which depends on the inhibition of tau phosphorylation, with microtubule stabilization and banning of tau oligomerization [35].

4.2 Parkinson’s disease:

Another common type of NDDs attaining around 4% of the people above 85 years old and about 1% above 60 years old is Parkinson’s disease (PD) [36]. Parkinson’s people suffer from characteristic symptoms, such as cognitive impairment, gradual loss of memory due to reduction of dopamine-containing neuron in substantia nigra neurons lead to low levels of dopamine in the striatum [37]. Loss of these neurons and inclusion of an insoluble protein “Lewy bodies (LBS)” are the significant pathology of the final stage of the disease [38], where accumulation of α-synuclein protein. Aggregation of amyloid, cholinergic dysfunction, together with the accumulation of α-synuclein cause cognitive impairment in PD patients [39]. Some studies have shown that occupational exposure to some chemicals, such as heavy metals and pesticides is associated with an increased risk of developing PD [40].

4.3 Other known NDDs:

Other types of NNDs have been associated with protein misfolding and accumulation in the fibrils that are completely unattainable their neuronal function. Amyotrophic lateral sclerosis ALS is described by progressive loss of the lower and upper motor neurons at the bulbar level or spinal [41] and leads to swallowing or speaking difficulties. Huntington’s disease is a NDDs with chorea, psychiatric symptoms and behavioral and ultimately dementia. It is resulted from a CAG triplet expansion in the huntingtonin gene. Clinically, it depended on the development of chorea together with abnormalities of movement such as dystonia, motor incoordination and bradykinesia. Frontotemporal dementia is related with language and
cognition difficulties that influence older population, characterized by frontal executive deficits and progressive behavioral changes and/or selective language difficulties. Transmissible spongiform encephalopathies (TSE) or prion diseases are progressive neurodegenerative troubles occurs due to misfolding of the normal cellular prion protein (prpc), which influences the nervous system of many mammals [42].

The friedreich’s ataxia is a tardily progressive, described by decreased production of the mitochondrial protein frataxin. It leads to increased free-radical formation and intra mitochondrial iron aggregation in the liver, heart, dentate nucleus of the fibroblasts and cerebellum. The trouble has as characteristics limbataxia and progressive, cardiomyopathy, dysarthria abnormal proprioception and vibratory sense and loss of reflexes. The pathological characteristic of this disease is the production of abnormal protein LBS in the cerebral cortex.

5. Synthesis and development of multi target-directed imidazole derivatives

In 2001, Matosiuk et al [43] synthesized carbonyl derivatives of 1-aryl-2-iminoimidazolidine, figure 1. The authors tested compounds C and found a considerable depressive effect on the central nervous system CNS, with very low toxicity and anti-nociceptive activity in behavioral models. Carbonyl derivatives of 1-aryl-2-iminoimidazolidine can be then suggested as opioid-like mechanism of anti-nociception, besides an impact on the serotonin neurotransmission pathway.

In 2015 Elzbieta et al, [44] investigated a novel series of heterocyclic compounds containing imidazole moieties estimated for their central nervous system activity, figure 2.
During 2017, Anne’s group [45] developed the mechanisms of elementary multi targeted therapeutics against many diseases started from a series of 1,5-diarylimidazoles with structural similarities and known NSAIDs and microtubule (MT)-stabilizing activity. The authors conducted structure–activity linkage studies that led to involve multi targeted prototypes as inhibitors of the MT-stabilizing agent pathways of cyclooxygenase (COX), 5-lipoxygenase (5-LOX) as in figure 3. As MT-stabilizing agents showed activity against tau-mediated neurodegeneration in animal models, and/or COX- and 5-LOX-derived eicosanoids, those stabilizing agents are thought to participate to Aβ plaque segregation.

Among the methods used to reduce NDDs Alzheimer’s and Parkinson’s disease, selective COX-2 inhibitors [46,47] and that is synthesis of novel imidazole derivatives as atypical selective cyclooxygenase-2 inhibitors [48] figure 4.
Figure 4. Synthesis of compounds 5a-e

Reagents and conditions [48]:
(a) Potassium thiocyanate, dihydroxyacetone, acetic acid/H$_2$O (93/7), 55 °C, 18 h; 
(b) Sodium iodide, NaOH 10%, ethanol, rt, 1 h; 
(c) Oxone, THF/H$_2$O, room temperature, 24 h; 
(d) SOCl$_2$, 70 °C, 4 h; 
(e) Proper amine, KI, K$_2$CO$_3$, ACN, 80 °C, 24 h.

Imidazole derivatives brought attention to scientists in the field as enzymes inhibitors. In 2017, García, Salado, Perez et al. [49] described the synthesis of imidazole-like PDE10A inhibitors and showed their neuroprotective effects. PDE10A is a dual substrate phosphodiesterase that can hydrolyze the second messengers cGMP, and cAMP. This enzyme is highly abundant in brain in comparison with other tissues. PDE 10A enzyme is able to regulate the levels of cAMP, which is partially mediated of neuro inflammation being highly expressed in striatum, (compound 34 in figure 5). The inhibition effects of PDE10A have been used in the treatment of PD.

Figure 5. Compound 34 [49]
In 201, a novel series of benzimidazole derivatives designed multiple ligands (DMLs) was applied at the neuronal nitric oxide synthase (nNOS) enzyme and the μ-opioid receptor [50]. The functional activity was assayed in the cyclic adenosine monophosphate cAMP secondary messenger. The results indicated a full agonist activity, which represented this series of benzimidazole as a novel approach for the treatment of pain. Compound 53 in figure 6 is a dual-acting inhibitor of nNOS (IC50 of 0.44 μM) and agonist of the μ-opioid receptor.

![Figure 6. Compound 53 [50]](image)

Theses developed derivatives provide alternatives for the treatment of NDDs, and are able to combine with other heterocyclic molecules and possessed pharmacological activities, as well as the conditions related to NDDs.

6. Impact of imidazole derivatives on AD

We first talked about Alzheimer’s disease and its causes. As for this topic, we will address the effect of the synthesized imidazole derivatives in reducing the risk of the disease and ways to reduce it. The treatment for AD has been depended on the in a cholinergic point of view, treatment of AD is connected with an impairment in cholinergic transmission [51]. This lead to suggest that inhibitors of cholinesterase (ChE) would likely stop a shortage in the substrate “acetylcholine”. In 2013 the Yeong group reported a novel synthesis of some inhibitors of the enzyme acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) containing benzimidazole moiety [52]. Benzimidazole derivatives have been used in bioactive molecular design using click chemistry for designing and modulating the AD agents depending on their π–π and hydrophobic interactions with the targets [53]. The excellent inhibitory activity (for BChE, IC50 = 8.63 μM and for AChE, IC50 = 5.12 μM) coincides to the compound 5IIc (ethyl 1-(3-(1H-imidazol-1-yl)propyl)-2-(4-nitrophenyl)-1H-benzo[d]imidazole-5-carboxylate), figure 7.
For compound 5IIC, R1=N-propylimidazole, R2=4-Nitrophenyl.

**Figure 7.** Synthesis of benzimidazole derivatives [52]

In 2014, they also synthesized of 1H-phenanthro [9,10d] imidazole derivatives [54]. Figure 8 shows the organic synthesis of the target compounds 7a–9f. These have been showed a potent multi-target-directed agent for Alzheimer's disease, such as inhibition of self-mediated and metal-induced Aβ1–42 aggregation, anti-oxidation activity, inhibition of acetylcholinesterase and butyrylcholinesterase.

**Figure 8.** Synthesis of of 1H-phenanthro [9,10-d] imidazole derivatives [54] Reagents and conditions: (a) 1,2-dibromoethane or 1,3-dibromopropane, or 1,4-dibromobutane, K₂CO₃, acetone, reflux 6 h; (b) phenanthrene-9,10-dione, NH₄OAc, AcOH, 120 °C, 3 h; (c) RNH, K₂CO₃, acetonitrile, reflux, 5–6 h.
Figure 9. Binding mode for 9g–AChE complex. (A) 3D ligand-interaction diagram. (B) 2D ligand-interaction diagram. (C) The polar and hydrophobic surface profile of human AChE with compound 9g. (D) Superposition of 9g with F11 in ligand-binding pocket. Blue carbon represents compound 9g [54].

In 2017, Yi-xiang and Huan [55] developed a brief, novel propargylamine-modified pyrimidinylthiourea derivatives containing imidazole core structure as multiple functional agents for AD therapy such as AChE and monoamine oxidase-B (MAO-B) inhibitors (figure 10). MAO plays a very important role in the pathogenesis of AD, since high level of MAO in the brain may result in a cascade of biochemical events, which lead to neuronal dysfunction [56].
compound 1b which represents the same composition above with a universe (R=CH₃) displayed good selective inhibitory activities against AChE and MAO-B and showed mild antioxidant ability at the same year, Manman Li et al, reported novel process for synthesis of imidazole derivatives conjugated diphenyl (figure 11), which acting as Glutaminyl Cyclase GC Inhibitors [57] high concentration of GC participates to the initiation of AD by catalyzing the formation of neurototoxic pyroglutamate (pE)-modified (Aβ) peptides. QC inhibitors prevent formation of pE-Aβs. Treatment with compound 28 in figure 11 significantly decreased the formation of pE-Aβ₃–₄₂ in living cells and inhibit the activation of hQC without meddlesome with its expression.
In 2019, they formerly reported a procedure to synthesis of novel benzimidazole derivatives for inhibiting acetyl cholinesterase activity [58]. Several benzimidazole derivatives have been express to be useful as amyloid imaging probes because of their high binding affinity to Aβ accumulates and high uptake into the brain [59]. As well, benzimidazole scaffold is the ring isoster of indanone pharmacophore of donepezil which is one of the most important AChEI [60]. Synthesis of the target derivatives summarized in figure 12.

![Figure 12. Synthesis of benzimidazole derivatives [58]](image)

From all the mentioned, the possibility of synthesis imidazole derivatives to its unique composition where it was possible to enter interactions easily with other heterogeneous cyclic compounds that have a high biological efficacy and we will have developed new molecules can act as agents for neurodegenerative disorders such as Alzheimer’s diseases.

7. Conclusion

The over critical diverse of imidazole derivatives is considerably depends on the types of heterocyclic molecules. It has been recognized so far that modification of the imidazole moiety offered favorable multi targeted to treat NDDs and it is fascinating to look that numerous imidazole ring stimulating medicinal qualities. Moreover, it is still to be revealed the best a way of action of imidazoles. It will be interesting to manage this new pharmacological part for future development of such effective molecules; thus we mightly suggest that imidazole can be used in pre-clinical and clinical studies of the neurodegenerative diseases.

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8. Abbreviations:

Aß (amyloid-ß), AD (Alzheimer’s disease), ALS (amyotrophic lateral sclerosis), APP (amyloid precursor protein), Ach (acetylcholinesterase), BchE (butyrylcholinesterase), ChEs (cholinesterases) CNS (central nervous system), COX (cyclooxygenase), cAMP (cyclic adenosine monophosphate), cGMP (cyclic guanosine monophosphate), LOX (5-lipoxygenase), ML (microtubule (MT)-stabilizing), MAOs (monoamine oxidases), NDDs (neurodegenerative diseases), NFTs (neurofibrillary tangles), nNOS (nitric oxide synthase), PD (Parkinson’s disease), PrPc (prion protein), TSE (transmissible spongiform encephalopathies), TosMics (tosylmethylisocyanides).

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