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A REVIEW ON EDARAVONE AS POTENTIAL ANTIOXIDANTS

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Abstract

Edaravone and their derivatives are the most dominating compounds that can be used as potential pharmaceutical and medicinal substance. More prominently, their behavior against Neuroprotective effects is considerable. In present days, Edaravone derivatives have often attracted the interest of medicinal chemist due to their exceptional antioxidant properties. The present study is a review based on Edaravone as antioxidants, carried out by medicinal and pharmaceutical researchers in the discovery of new antioxidants.
Keywords: Edaravone, Antioxidants, Neuroprotective effects, Inducible Nitric Oxide Synthase (iNOS), Alzheimer's disease.

Introduction

When there is variance between the fabrication of antioxidants and free radical in the body it leads to a condition termed as oxidative stress and further leads to the production of reactive oxygen species. These reactive oxygen species formed play a very detrimental part in the acute and late stages of cerebral ischemia. According to researchers oxidative stress shows a pivotal part in the emergence of acute ischemic stroke. Ischemic stroke is caused when there is reduced flow of blood to the brain due to the narrowing of arteries or the blockage by clots. It has been observed that 87% of the stroke is ischemic (Mudilla *et al*., 2018, 2019). The immoderate reactive oxygen species aggregation leads to cellular oxidative stress, mitochondrial dysfunction and initiation of cell death. The therapeutic properties of antioxidant involve the scavenging of these reactive oxygen species in order to prevent the injuries caused by ischemic stroke (Bonita *et al*., 2004; Cherubini *et al*., 2005; Sies *et al*., 1997; Walt *et al*., 2004; Sharma *et al*., 2016, 2017, 2018, 2019).

In 2001 the regulatory administration of Japan validated a novel antioxidant and free radical scavenger known as Edaravone. It was the first to be used in the administration of acute ischemic stroke. It was developed by Mitsubishi Tanabe Pharma Corporation and is also known as Radicut. It scavenges reactive oxygen species and inhibits the proinflammatory responses after brain ischemia in animals and humans. It can also improve the post ischemic inflammation which leads to brain edema and endothelial cell death. Edaravone shows neuroprotective effects by the inhibition of lipid per oxidation and damage due to oxidative stress in brain cells, cells in the nerves, scavenging the free radicals, thereby lessening cerebral ischemia decreasing the harm caused to the tissue. It also improves the neurological deficits due to acute cerebral infarction and its neuroprotective effects have also been confirmed in animal models. Edaravone is known to exist in three tautomeric forms: amide, keto and enol form. It has been seen that the rate of oxidation of edaravone commenced by an azo compound shows rise with rising pH which proposed the more reactive nature of Edaravone. Thus it is majorly present in its anionic form under physiological conditions and the free radicals are scavenged by the anion through donation of one electron to the radical. In 2015 it was approved by the Japanese manufacturing and in 2017 by for the United State Food and Drug Administration for the therapy of amyotrophic lateral sclerosis (Kumar *et al*., 2010, 2013, 2014,2015, 2016,2017, 2018, 2019). Thus Edaravone also used for the therapy of acute ischemic stroke and cerebral infarction (Singh *et al*., 2014, 2015, 2016, 2017, 2018, 2019; Kaur *et al*., 2015, 2017, 2018, 2019). New derivatives of Edaravone are thus being synthesized to enhance the property of the drug and synthesizing more potent antioxidant and free radical scavengers (Abe *et al*., 2004; Lapchak *et al*., 2010; Nishi *et al*., 1989; Otomo *et al*., 2003; Walker *et al*., 2011; Watanabe *et al*., 2008; Yamamoto *et al*., 1996; Yoshida *et al*., 2006).

Review of Literature

Due to the complex nature of in vivo systems it becomes difficult to determine the antioxidant properties of a compound, thus the usage of theoretical parameters was done to measure the antioxidant properties. The electron donating power is used as a parameter in order to measure the tendency of a molecule to accept or donate electrons (Cerezo *et al*., 2012; Martínez *et al*., 2008; Gázquez *et al*., 2007). The electron donating power and the spin densities have been taken as the main parameters in order to discover the antioxidant activity of substituted edaravone.

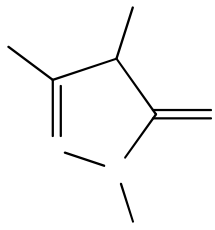

Fig. 1: Edaravone active positions

Through the reported data it was observed that the introduction of a cyclohexyl group at position R_1 or a NH_2- at R_2 position would increase the efficiency of the antioxidant as the structures represented in figure 2 and 3.

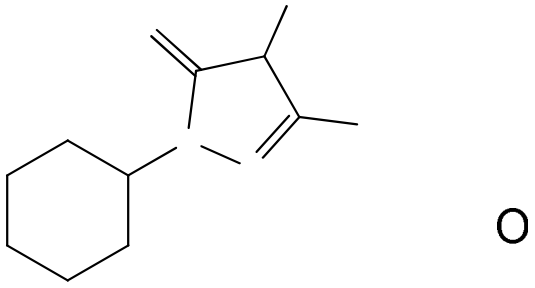

Fig. 2

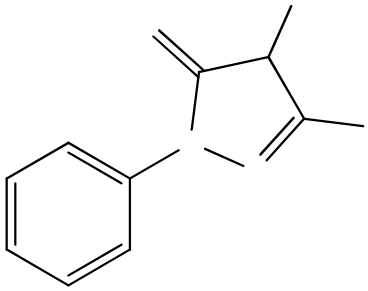

Fig. 3

The synergistic effect of the groups provides a more potent antioxidant than edaravone both in deprotonated and neutral form (Cerón-Carrasco *et al*., 2014).

The vasodilatatory action of NO is well known as it protects the ischemic tissue during the condition of ischemia. When NO reacts with the superoxide radicals during reoxygenation it impends the reaction chain for formation of reactive oxygen species, reducing the creation of inflammatory intermediaries and leukocyte activation [30]. The hybrid compound in Figure 4 has both antioxidant property due to the substructure of edaravone and vasodilator properties due to the presence of NO-donor (Chegaev *et al*., 2009).

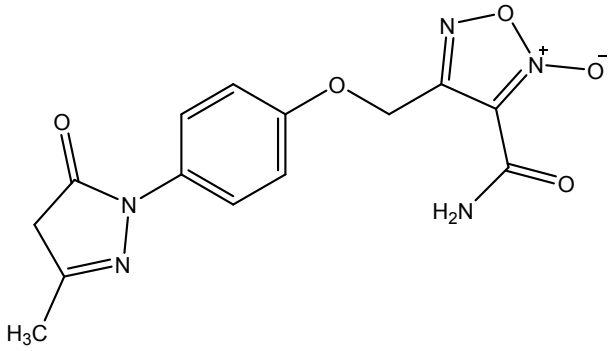

Fig. 4

The hybrid compound in Figure 4 could reduce the injury caused by Ischemia/Reperfusion induced renal dysfunction and decrease the damage in the necrotic cells in proximal tubes due to injury. It could partially prevent lipid peroxidation and could inhibit induced Inducible Nitric Oxide Synthase (iNOS) expression and cytokine production which resulted due to I/R injury. Hybrid compound in the dose range of 1.2-6 showed its protective effects whereas Edaravone in this range showed no effects as Edaravone could show its effects at a higher doze of 30 µmol/kg (Chiazza *et al*., 2015).

In order to form a new class of Edaravone derivatives palladium catalysed cross coupling was done between hetero aryl chlorides and hydrazine hydrate to form monoaryl hydrazine intermediates. These when treated with ethylacetoacetate in acidic medium gave the desired pyrazolone. The class of compounds formed was then subjected to check their antioligomer activity and inhibition towards Amyloid beta (Maclean *et al*., 2016).

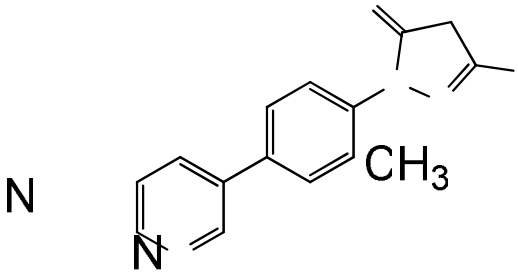

Fig. 5

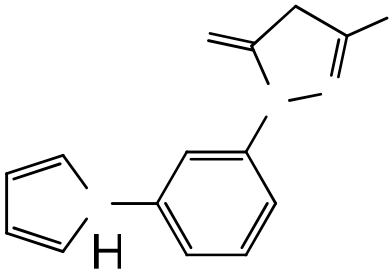

Fig. 6

The derivatives represented in Figure 5,6,7,8 represented high misfolding activity and inhibition towards Amyloid Beta aggregation.

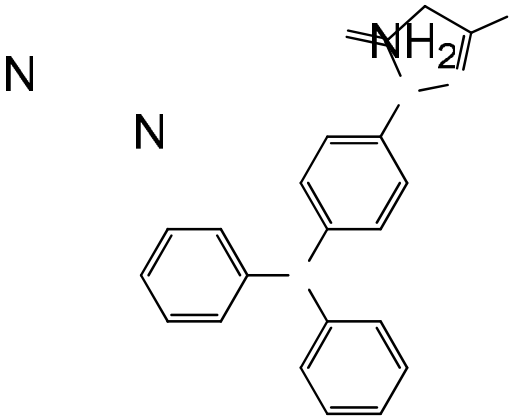

Fig. 7

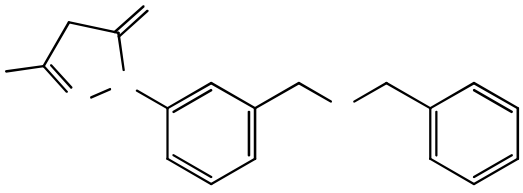

Fig. 8

When aromaticity was introduces at any position in the N-aryl pyrazolone the power of the compound to act as an antiaggregant increased as compared to Edaravone. The derivative in figure 7 and figure 8 having N-linked heterocycles involved to N-aryl pyrazolone exhibited high misfolding activity (Maclean *et al*., 2016). The N-aryl pyrazolone mortif provides biological activity including antimicrobial, antibacterial, anti-inflammatory, antitumor, antidepressant and neuroprotection thus providing therapeutic importance (Gupta *et al*., 2015).

The State Food and Drug regulatory body of China (2002) approved a natural drug for the dealing of ischemic stroke known as 3-n-butylpthalide It shows a various biological activities like anti-thrombosis, aggregation, and anti-platelet decreasing the infarct volume (Liu *et al*., 2007; Zhu *et al*., 2004). Figure 11 shows derivative of 3-n-butylpthalide known as HPBA formed by the ring opening mechanism. (Wang *et al*., 2011; Wang *et al*., 2012; Wang *et al*., 2013) the compound formed is shown in Figure 9 and it is made up of two moieties as shown in Figure 10, 11.

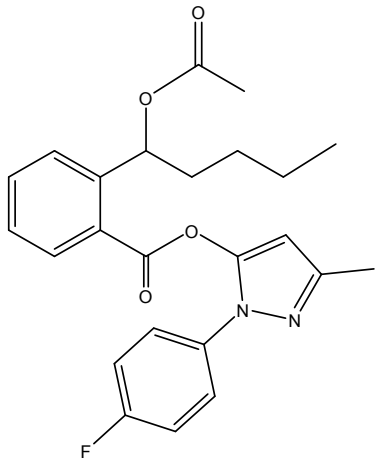

Fig. 9

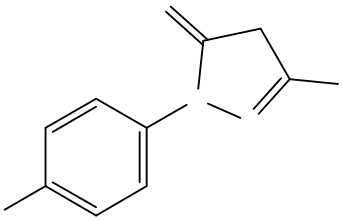

Fig. 10

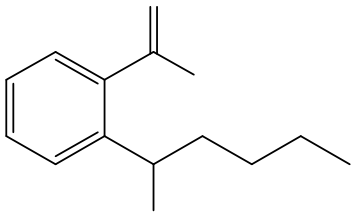

Fig. 11

The hybrid compound in Figure 9 showed better nerve cell protection, protective effects against hydrogen peroxide induced cell damage, better scavenging of hydroxyl and superoxide radical than Edaravone, 3-n-butylpthalide and Edaravone together with 3-n-butylpthalide.The presence of an ester bond between the two moieties in Figure 10 and 11 makes the hybrid compound more liposoluble for entering the cell. Thus claiming that the ester bond will take more time to break providing more time for the action .Moreover the hydrolysis of the hybrid by esterase's yields edaravone analogue fig 10 and NPB ring opening derivative fig 11 thus there is a synergistic effect of the two leading to better curing power of the hybrid (Sheng *et al*., 2015).

Researchers have found that the Suzuki coupling of aromatic, aromatic moieties having hetero atoms and an amide substituent at the C_3 position of Edaravone can increase the lipophillic factor of derivatives in order to reach the biological membrane (Jose, G. *et al*., 2015). Among the class of derivatives synthesized the following showed promising biological activity.

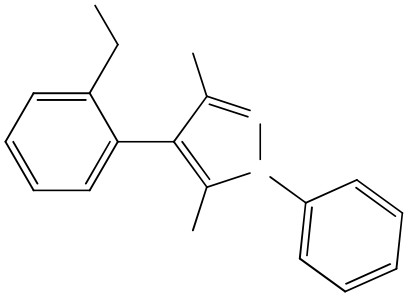

Fig. 12

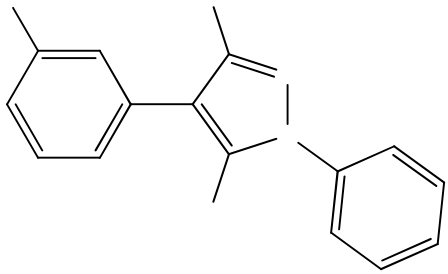

Fig. 13

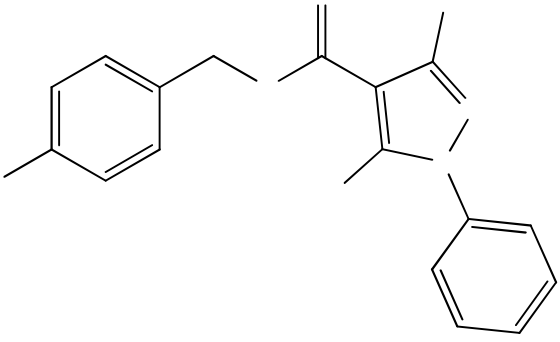

Fig. 14

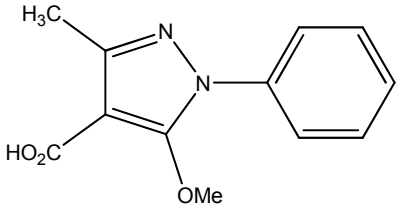

Fig. 15

The compound in figure 12 due to ethereal group at ortho position showed good activity towards inhibiting A549 cells due to the increase in lipophilicity and the reduced stearic effects. The compounds in Figure 13 and 14 demonstrated highest anticancer activity. The compound in figure 14 showed the highest activity among the carboxamides as a good electron withdrawing substituent is present, enhanced lipophilicity, good enduring power for metabolic destruction as a halogen bond is present and also the amide linkage is considered valuable for the action against lung cancer. The compounds Figure 14 and 15 showed the most free radical scavenging activity due to multiple sites where scavenging can take place and the transfer of hydrogen atom from OH and NH groups. Thus the compounds in Figure 12, 13, 14 exhibited superior anticancer activity and Figure 14, 15 exhibited best antioxidant activity (Polkam *et al*., 2015; Polkam *et al*., 2016; Rangaswamy *et al*., 2012).

Peroxynitrite is a powerful nitrating agent and oxidant. When nitric acid reacts with superoxide anion peroxynitrite is formed and it contributes towards the injury caused by ischemia (Guven *et al*., 2008; Love *et al*., 2006; Suofu *et al*., 2010; Szabó *et al*., 2012). The reaction of peroxynitrite reacts with residues of tyrosine present in proteins forms 3-nitrotyrosine, which has been found in patients suffering from diseases related to heart, blood and diabetes (Pacher *et al*., 2007). Peroxynitrite reacts with edaravone by electrophillic attack of peroxynitrite at the C-4 carbon of edaravone to give 4-NO-edaravone as the predominant product. Experimentally when equimolar concentration of uric acid and edaravone were examined through peroxynitrite, edaravone reaction was 30-foldmore than that of uric acid. The reaction proceeds through the following pathway leading to the formation of 4-NO-edaravone as shown in Figure 16 (Fujisawa *et al*., 2015).

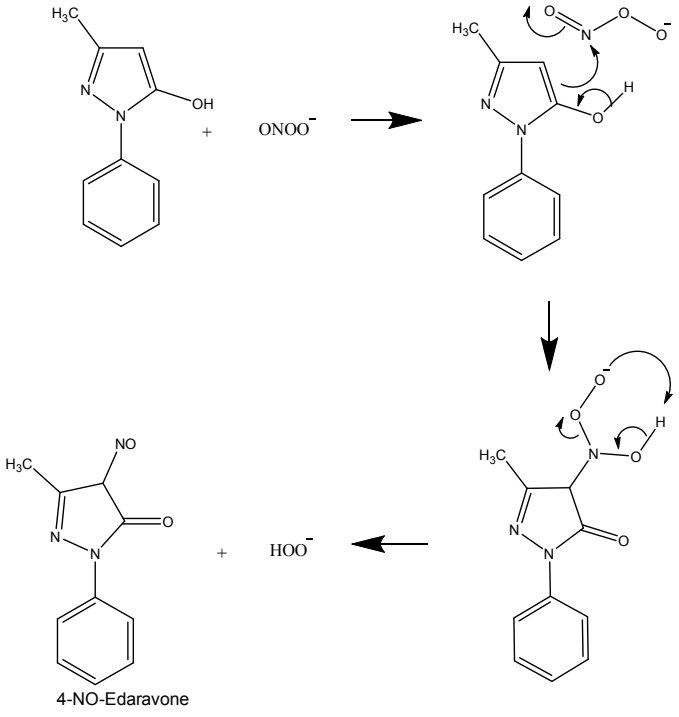

Fig. 16

Amyloid beta (Aβ) has important part in pathogenesis of Alzheimer's disease. The aggregation of amyloid beta induces oxidative stress and inflammation that further leads to neurodegeneration (Yang *et al*., 2015). It has also been seen that amyloid beta generation is itself high during the condition (Bolognesi *et al*., 2009). DL-NBP and edaravone have been proved as quite promising therapeutics for oxidative stress and amyloid beta aggregation (Peng *et al*., 2008; Peng *et al*., 2009). Thus hybrids of the compounds were made and their biological testing revealed significant results.

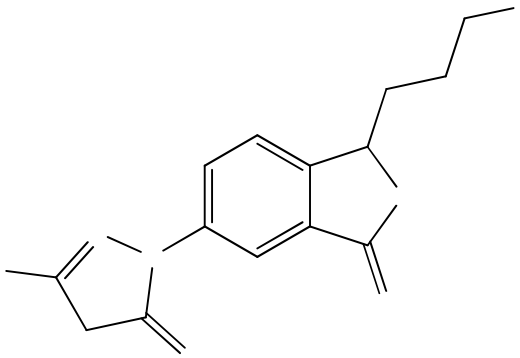

Fig. 17

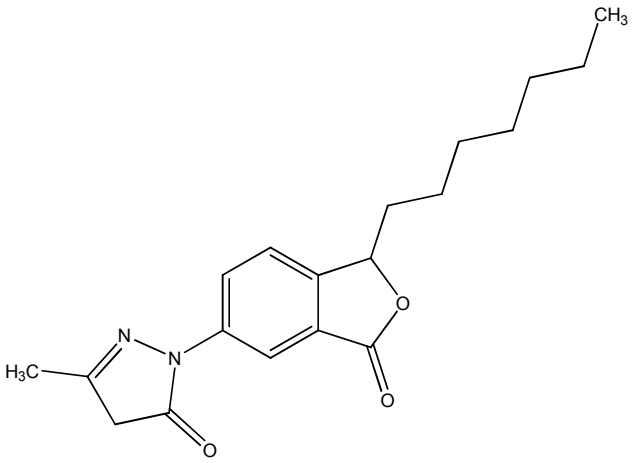

Fig. 18

Both the compounds in figure 17 and 18 exhibited good inhibitory activity towards self-induced ranging from 50.1%to 71.5% and they crossed the blood brain barrier and reached their goals in the CNS. Derivatives figure 18 exhibited better antioxidant activity as compared to edaravone(Qiang *et al*., 2017).

The presence of a methyl substituent in a molecule has a significant appearance of a biological activity in it. The methyl groups stereo electronic effects on molecules because of which they exhibit various biological effects (De Miranda *et al*., 2011). The N- methylated products were known to show some biological activity thus the products obtained are shown below:

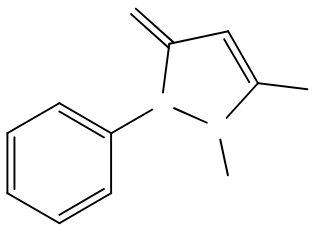

Fig. 19

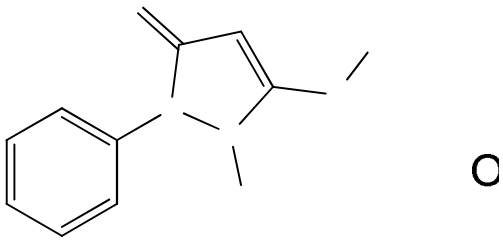

Fig. 20

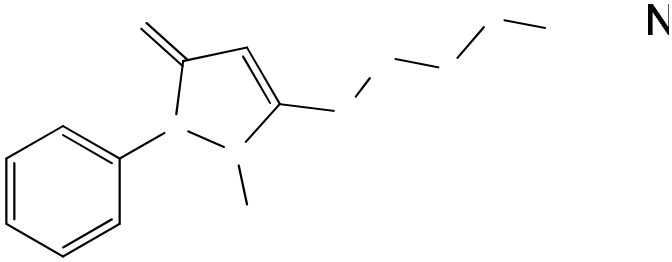

Fig. 21

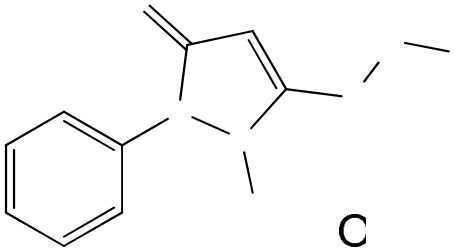

Fig. 22

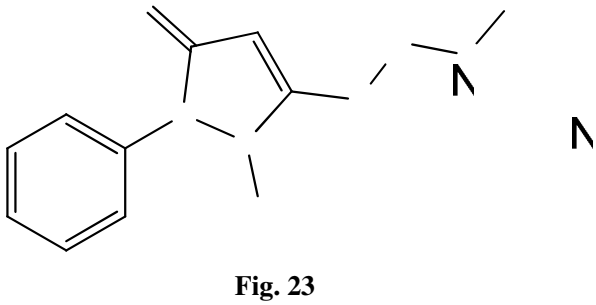

Fig. 23

Thus the N-methylated fluorinated analogs revealed significant analgesic activities in initial biological testing due to the presence of Antipyrineunit (Nemytova *et al*., 20).

Conclusion

From the above discussion, literature review and our ongoing interest we concluded that Edaravone and their derivatives have potential to use as antioxidants and discovery of new Edaravone antioxidants may produce a revolutionary step in the pharmaceutical as well as medicinal fields.

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