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EDARAVONE BASED ANTIOXIDANTS FOR CARDIOPROTECTION AND NEUROPROTECTION

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Abstract

Coronary Heart Disease (CHD) which also known as Coronary Artery Disease is a group of diseases that includes stable and unstable anginal event, Myocardium infarction (MI) and sudden death due to cardiac arrest. CHD is the most common cause of death globally accounting for over 7 million deaths of people per year (approx 45 % deaths from total numbers are because of cardiac diseases). In Japan, edaravone (EDV) is already been used as a highly efficient ROS scavenger, and is also used for treatment of patients with acute brain infarction. EDV has protective effects on myocardium injury followed by ischemia/reperfusion injury in patients with chronic myocardial infarction in cardiovascular diseases. This drug is already a known efficient free radical scavenging agent for the cardioprotection and combining the nitronyl nitroxide with edaravone which will be efficient as anticancer agent. These chemical entities have potential effect on cardiovascular ischemia and also on cerebral ischemia.

Keywords: Ederavone, Nitronyl nitroxide, Free radicals, Oxidative stress.

Introduction

Ischaemia is a sign in both stroke and myocardial infarction which can results in less supply of blood oxygen to body cells and tissues. This can leads to dysfunction of body especially brain. Therefore, in patients with cerebral or myocardial infraction it is necessary to short the ischemic period which can improve their sudden and long term effects**.** The potential therapy to reduce infarct size involves early encounter of thrombolytic treatments along with antiplatelet agents. However, only these therapies are not enough to avoid neuronal dysfunction or myocardium injury as oxygen free radicals are found in both during ischaemia and reperfusion injury (Mankar *et al.,* 2018).

In neurodegenerative, cerebrovascular and cardiovascular diseases oxidative stress plays a very important role. In brain and heart injuries body's own energy generation mechanism reduces the formation of reactive free radicals including H_2O_2, hydroxyl radicals and superoxide radicals. These radicals can induce further damage to the cell membrane, leads to development of cerebral edema, infarction along with left ventricular dysfunction. During crucial phases of heart attack and stroke, protections of cells from oxygen free radicals are a very important target for research.

Edaravone or 3-methyl-1-phenyl-2-pyrazolin-5-one is a neuro-protective agent that is approved in the treatment of ischemic stroke, and it has high potential to protect against radical induced toxicity. Edaravone neuro-protective effects have been studied in cerebral ischemia models and also this compound decreases the excessive levels of radicals generated after ischemia. The protective effect of EDV comes from free radical scavenging activity mainly from 2-pyrazolin-5-one and its derivatives. The modifications of basic moiety of EDV will be give new clues for further research on edaravone as a better antioxidant.

Cardioprotective Effect

The development of drugs in order to suppress lipid per oxidation has recently been given due attention. The functional destruction caused in the biological membranes is also an outcome of lipid per oxidation. The derivative of Edaravone shown in figure 1 has a C18 hydrocarbon chain at the C-4 position. This could significantly improve the protection of lipid peroxidation as the C-18 chain being lipophillic increase the bilayer protection when radical initiation is generated in lipid phase. The well-built interaction happening between the hydrophobic carbon chain of the lipid tails leads to a better affinity towards the membranes of cell producing an improved ability to protect retinal cells. This new derivative formed may thus act as a good antioxidant in cellular and cell free systems and can be used in the diseases that are associated with oxidative stress. (Minnelli C *et al.,* 2019)

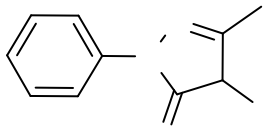

Fig. 1: Edaravone derivative having C-18 chain at carbon four

All the four compounds in figure 2 exhibited fine anti-inflammatory and antimicrobial activity. They are predicted to be free from any toxicity risks. Biological evaluation and screening using computers clearly show that the compounds synthesized have the potential to be developed as an anti-inflammatory agent. 2, 5 also showed good anti-pyretic and analgesic activity, thus can be used for developing Nonsteroidal anti-inflammatory drugs (NSAIDS). (Alam *et al.* 2015; Mankar *et al.,* 2016).

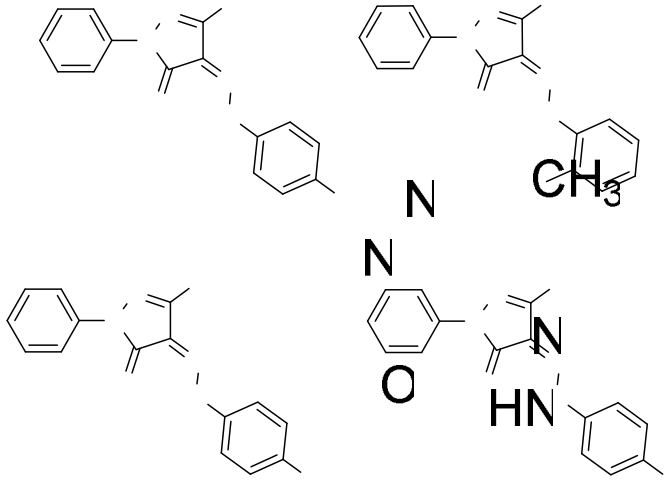

Fig. 2: Substituted Pyrazolone Based Hydrazone Derivatives

Three new compounds were found to inhibit the phagocytosis of sensitized RBCs shown in figure 3. The study revealed that the presence of 2 atom spacer arm and N having alkyl substitution was significant for the inhibition of antibody mediated phagocytosis of opsonized RBCs.The compounds carried different linkers that connected the two pyrazole moieties. Macrophages induced Phagocytosis of antibody-opsonized in human RBCs was inhibited by potent hydroxy-pyrazole derivative 8 (Purohit *et al.*, 2014).

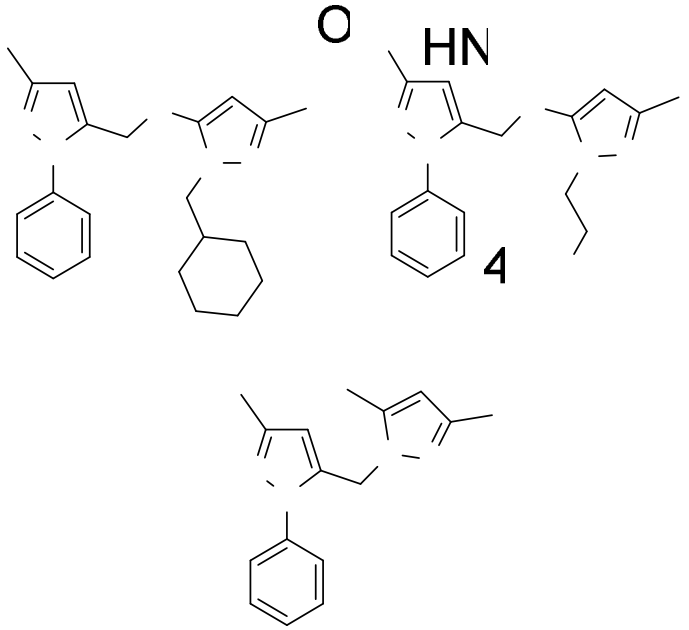

Fig. 3: Hydroxy-pyrazolone derivative

Hybrids of Edaravone and DL-NPB were also evaluated for their inhibition against beta amyloid aggregation and enzyme monoamine oxidases in order to treat Alzheimer's disease. All hybrids shown in figure 4 exhibited better inhibition of $A\beta_{1-42}$ aggregation with the 57.7–71.5% inhibition ratio. Reported data showed results that the hybrids in compound 9 and 12 can cross the blood brain barrier which property will be useful to reach site of action in the CNS (Qiang *et al.,* 2017).

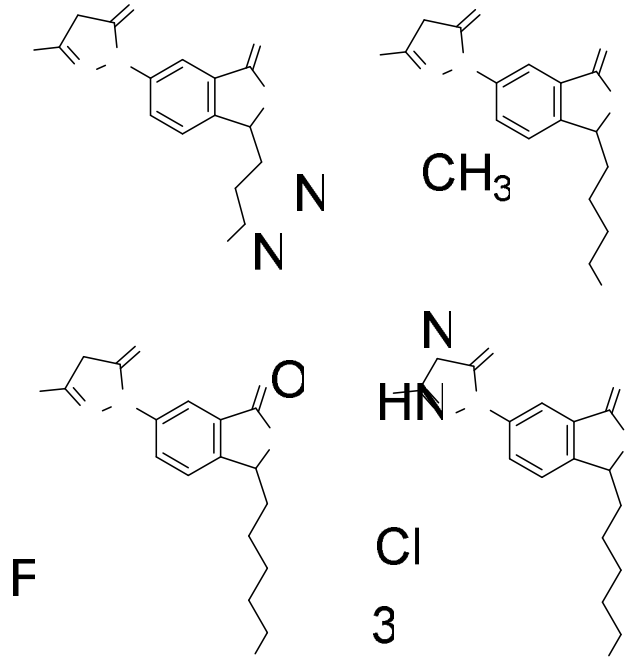

Fig. 4: Hybrids compounds of Edaravone and DL-NPBNO is well known for its vasodilator properties as it protects the ischemic tissue during ischemia. It reacts with the superoxide radicals thereby hindering the chain of reaction that produces more reactive oxygen species. By doing so it decreases leukocyte activation and inflammatory mediators (Rhoden *et al.* 2002). A new compound 13 represented in figure 5 was synthesized to study the antioxidant properties of NO donor (Chegaeve *et al.,* 2007; Cena *et al.,* 2008).

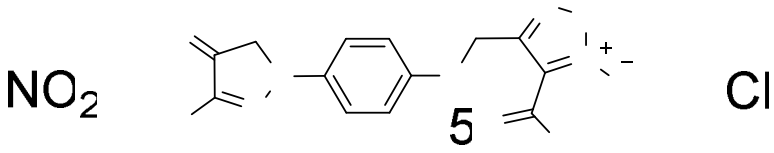

Fig. 5: Structure of NO donor Edaravone

It reduced Ischemic/Reperfusion induced injury as well as the damage caused in the cells caused due to the injury. It prevented lipid peroxidation and inhibited inducible nitric oxide synthase expression. These protective effects were showed at a less dose than edaravone of about 1.2-6 µmol/kg whereas edaravone showed its protective effects at 30 µmol/kg (Chiazza *et al*., 2015; Sharma *et al.,* 2015, 2016, 2017, 2018; Kumar *et al*., 2010, 2013, 2014, 2015, 2019). The compound 13 has the substructure of edaravone and a NO donor group which provides a good balance between antioxidant and vasodilator properties (Chegaev K *et al.,* 2009).

It has been observed that the increase in lipophillic factor of a compound results in better permeation in lipid phase to reach the biological membrane. Thus a new class of Edaravone derivatives was formed by Suzuki coupling in order to increase the lipophillic factor (Jose *et al.,* 2015). Figure 6 shows the compounds which exhibited promising biological activities.

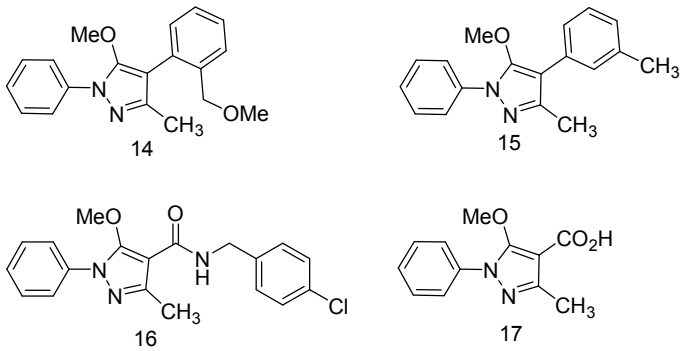

Fig. 6 : New Edaravone derivatives with increased lipophillic factor

The compound 14 showed good inhibition towards A 549 cells as it has better lipophilicity. The compound 16 and 15 exhibited highest anti cancer activity against human cancer cell lines. The compound 16 has higher electron withdrawing substituent and enhanced lipophilicity as there is a halogen bond and amide linkage that is considered useful for activity against lungs cancer. The most free radical scavenging activity was shown by compound 16 and 17 because of more scavenging sites and hydrogen atom transfer between hydroxyl and amino group. The compounds 14, 15, 16 exhibited superior anti cancer activity and 16, 17 exhibited best anti oxidant activity (Polkam *et al.,* 2016; 2015; Rangaswamy *et al.,* 2012).

Neuroprotective effect:

3-n-butylpthalide also shows biological activity like anti-platelet aggregation, anti-thrombosis and improves cerebral microcirculation. It was extracted from celery seeds and was approved in 2002 for the treatment of ischemic stroke (Liu CL *et. al.* 2007; Zhu XZ *et al.* 2004). Its ring opening derivative is known as HPBA. It has been established that HPBA in grouping with active molecules gave more curative participation in ischemic stroke (Wang X *et. al.* 2011; 2012; 2013). The figure 7 shows the compound 18 made up of two moieties 19 and 20.

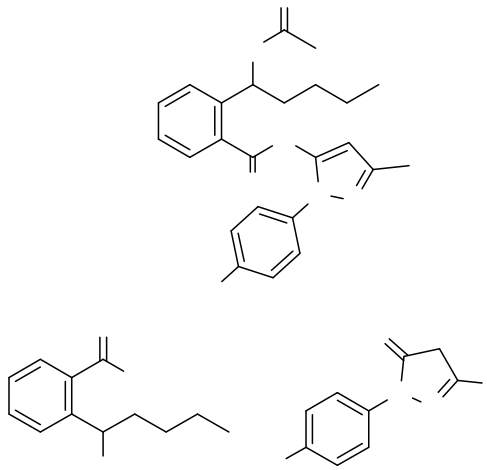

Fig. 7 : Derivative of Edaravone and 3-n-butylpthalide

The compound 18 showed better hydroxyl and superoxide anion radical scavenging activity. Nerve cell protection and reducing hydrogen peroxide induced cell damage was also better than Edaravone, 3-n-butylpthalide and the combination of both. The two moieties 19 and 20 have an ester bond between them that makes the compound 18 more liposoluble, also the ester bond will take more time to break providing increased time for action. The hydrolysis of the bond will give edaravone and 3-n-butylpthalide analogues 19, 20 providing a synergistic effect that enables more curing ability of the compound 18 (Sheng *et al*., 2015; Mudila *et al.*, 2018, 2019, 2016, 2018; Kumar *et al.*, 2018).

A pigment isolated from Curcuma longa known as Curcumin also shows pharmacological properties. It shows anti-inflammation activity and also inhibits the synthesis of oxygen centered free radicals. A derivative of pyrazole and curcumin 21 is shown in figure 8.

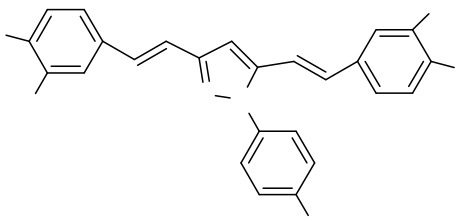

Fig. 8 : Curcumin and Pyrazole derivative

It enhanced cell strength and the release rate of Lactic acid dehydrogenase of cells at 5μM whereas edaravone showed the effect at a 100μM. It could decrease the oxidative damage and restore the potential of mitochondrial membrane. The Nrf2 pathway was involved the least in the neuroprotective effects shown by 21 on PC12 cells. This was due to the presence of a cyanide group that is electron withdrawing in nature (Liao *et al.,* 2019). The classical methods used for the preparation of Nitronyl Nitroxide Radicals have a number of drawbacks. The controlled oxidation of a dihydroxyimidazolidine leads to the formation of Nitronyl Nitroxide Radicals. Excess of oxidizing agent is required when $NaIO_4$ is used and the reaction needs to be carried out in a two phase system which makes it quite difficult for organic compounds that are water sensitive (Osiecki *et al.,* 1968; Ullman *et al.* 1970; 1972; Mankar *et al.,* 2009; Kumar *et al.,* 2017). The involvement of destructive pollutants like PbO_2, AgO_2 as oxidizing agents and lethal species like SeO_2 for preparation of NNRs is also a major drawback. The cost of these agents and the byproducts formed in the reactions create problems for the synthesis of NNRs (Tretyakov *et al.* 2003; Ziessel *et al.,* 2000; Harada *et al*., 2003; Ionita *et al.,* 2001; Wautelet *et al.,* 2003; Mankar *et al.,* 2010; Kumar *et al.,* 2016).

Conclusion

To increase the number of patients with Coronary heart diseases (CHD), able to benefit from the CHD treatment in the future, the inhibition of free radicals formed and reducing oxidative stress is extremely important**.** At present, edaravone is the only efficient neurodegenerative and cardio-protective agent available to scavenge these effects. However, the current treatment for the CHD and neurological diseases available is inadequate and furthermore , there is a chance on increasing the efficacy of edaravone by combining certain biologically active agents with edaravone will be beneficial against mentioned pathological conditions.

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