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Design and synthesis of 1,2-dithiolane derivatives and evaluation of their neuroprotective activity

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Abstract—We designed and synthesized new analogues containing 1,2-dithiolane-3-alkyl and protected or free catechol moieties connected through heteroaromatic rings such as triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, tetrazole or thiazole in order to explore the influence of the bioisosteric replacement of the amide group on the neuroprotective activity of the lipoic acid/dopamine conjugate. Evaluation of the activity of the new compounds, using glutamate-challenged hippocampal HT22 cells, showed that incorporation of heteroaromatic rings in the alkyl-1,2-dithiolane moieties in conjunction with another antioxidant, in this case catechol, may result in strong neuroprotective activity.

Oxidative stress is a ubiquitously observed hallmark of neurodegenerative disorders.[1] Neuronal cell dysfunction and cell death due to oxidative stress may causally contribute to the pathogenesis of progressive neurodegenerative disorders, as well as of acute syndromes of neurodegeneration.[2–5] The pathways to nerve cell death induced by a diverse array of neurotoxins, including peptides, excitatory amino acids, and cytokines, commonly share oxidative downstream processes which can cause oxidative destruction of key regulators of cell survival and/or activation of secondary events leading to apoptosis.[6–8]

Elevated levels of the excitatory amino acid glutamate are thought to be responsible for CNS disorders through various mechanisms causing oxidative stress *via* depletion of intracellular glutathione (GSH). Maintenance of normal GSH levels within the brain may hold an important key to the prevention and therapy for neurodegenerative diseases. In this respect, neuroprotective antioxidants are considered a promising approach to slowing the progression and limiting the extent of neuronal cell loss in these disorders. However, clinical evidence demonstrating that antioxidant compounds can act as a means to prevent and/or treat neurodegenerative disease is still relatively scarce.[9]

α-Lipoic acid (LA)[10–12] was first isolated in 1951 and is known by a diversity of names including 1,2-dithiolane-3 pentanoic acid, 1,2-dithiolane-3 valeric acid, and thioctic acid. The naturally occurring *R*-enantiomer of LA is an essential cofactor in α-ketoacid dehydrogenase complexes and is known to be covalently attached to the amino group of a lysine residue. Exogenously supplied LA is transported to tissues and reduced to dihydrolipoic acid (DHLA). LA and DHLA were found to be highly reactive against a variety of ROS in vitro. The antioxidant activity of LA is also attributed to its capacity to regenerate intracellular GSH, vitamin C, and vitamin E.[13–15] Numerous studies have reported that LA is beneficial in a number of oxidative stress models of cell death pertinent to ischemia–reperfusion injury, neurodegeneration, diabetes, inflammation, and radiation injury. Thus, LA possesses the potential to intervene in various therapeutically interesting pathways.[16–20] However, it should be noted that LA reportedly exerts most of its effects at high micromolar concentrations; that amides of LA exhibit higher biological activity than the parent compound;[21,22] and that molecular combinations obtained by coupling LA with an amino-substituted bioactive moiety possess multifunctional activity.[23–31]

Keywords: Lipoic acid; Heteroaromatic; Oxidative stress; Neurodegeneration.
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The present work involves replacement of the amide functionality by heterocyclic five-membered rings. Organic compounds containing five-membered aromatic heterocyclic rings are widely distributed in nature and often play an important role in various biochemical processes. Moreover, heteroaromatic rings serve as bioisosteres of several substituents such as amides, esters, phenyl rings and can contribute substantially higher pharmacological activity to the resulting compounds.[32–34] In the light of this, they are often incorporated into new chemical entities by medicinal chemists.

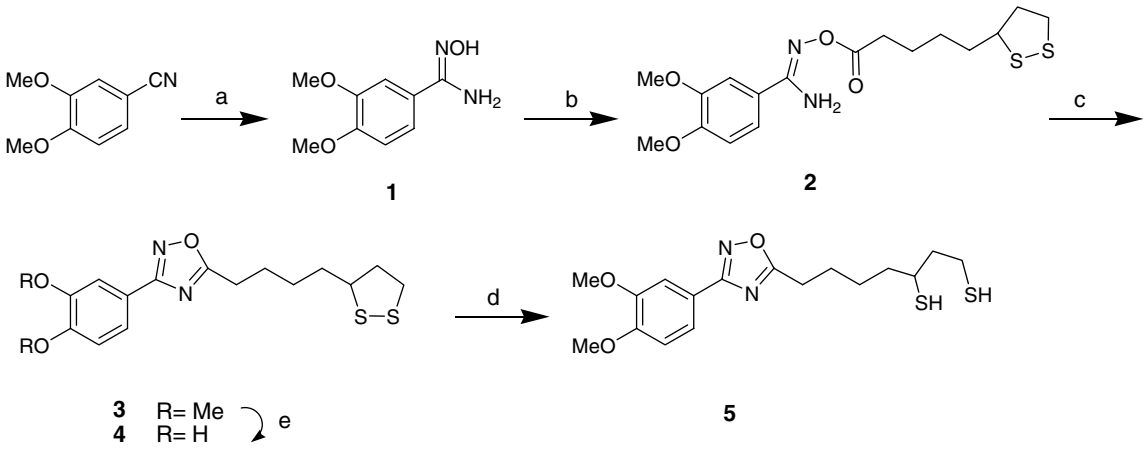
We designed and synthesized new LA analogues containing 1,2-dithiolane-3-alkyl and protected or free catechol moieties connected through heteroaromatic rings such as triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole, tetrazole or thiazole. The aim of this work is to compare the neuroprotective activity of the new compounds with that of LA as well as its amide with dopamine. The neuroprotective activity of the new derivatives was evaluated using glutamate-challenged HT22 mouse hippocampal cells.[35,36]

The synthesis of 1,2,4-oxadiazole containing derivatives is illustrated in Scheme 1. 3,4-Dimethoxybenzonitrile was converted to *N*-hydroxy-amidine **1** by treatment with hydroxylamine hydrochloride. Reaction of **1** with LA in the presence of DCC afforded the acyl amidoxime **2.** Intramolecular cyclization in the presence of tetrabutylammonium fluoride[37] gave the oxadiazole analogue **3** which was deprotected using $BF_3(SMe)_2$. Reduction of the 1,2-dithiolane ring of **3** using $NaBH_4$ afforded dithiol **5**.

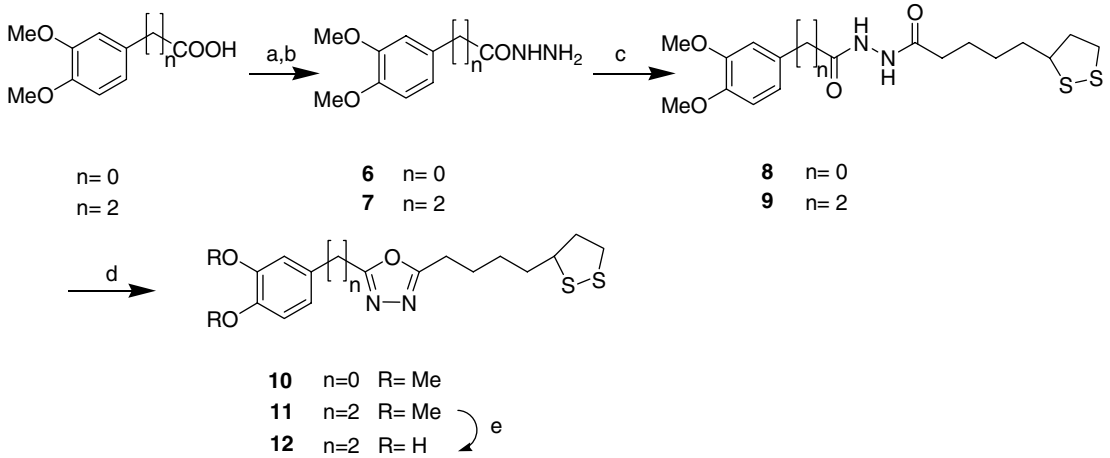
1,3,4-Oxadiazole containing analogues were synthesized as shown in Scheme 2. Hydrazides **6** and **7** were prepared from the corresponding esters and then reacted with *N*-hydroxysuccinimide-activated LA to give **8** and **9**. Cyclodehydration in boiling $POCl_3$[38] afforded **10** and **11**.

Triazoles (Scheme 3) were synthesized by cycloaddition[39] of lipoylazide and 3,4-dimethoxyphenylacetylene. Azide **14** was prepared by reduction of LA with catechol borane, conversion of the resulting alcohol to mesylester **13** and then to azide **14** by treatment with sodium azide.

The synthesis of tetrazole derivatives is depicted in Scheme 4. *N*-Hydroxysuccinimide-activated LA reacted



Scheme 1. Reagents: (a) $NH_2OH{\cdot}HCl$, Et_3N; (b) lipoic acid, DCC, THF; (c) TBAF, THF; (d) $NaBH_4$, EtOH; (e) $BF_3{\cdot}S(Me)_2$, CH_2Cl_2.



Scheme 2. Reagents and condition: (a) dimethyl sulfate, K_2CO_3, TBAI, acetone; (b) $NH_2NH_2{\cdot}H_2O$, MeOH; (c) *N*-hydroxysuccinimide-activated LA, THF; (d) $POCl_3$, reflux; (e) $BF_3{\cdot}S(Me)_2$, CH_2Cl_2.