Small Diverse Antioxidant Functionalities for Oxidative Stress Disease Drug Discovery

D. Sikazwe*[1], A. Grillo[1], S. Ramsinghani[1], J. Davis[2], K. McQuiston[2] and S.Y. Ablordeppey[3]

[1]*Department of Pharmaceutical Sciences, Feik School of Pharmacy, University of the Incarnate Word, San Antonio, TX 78209;* [2]*Chemistry Department, School of Mathematics, Science and Engineering , University of the Incarnate Word, San Antonio, TX 78209;* [3]*Division of Pharmaceutical Sciences, College of Pharmacy, Florida A & M University, Tallahassee, FL 32307-3104, USA*

Abstract: There is an up-surge of interest in antioxidants because of their potential use in mitigating a wide array of oxidative stress mediated diseases. In the course of our literature search for diverse functional groups, with utility in the design of potential drugs for preventing oxidative stress related cell injury, we have collected a small literature library of core structures or moieties possessing antioxidant activities. These functional groups can be re-configured into robust antioxidants drug molecules, in their own right, or incorporated into drug structures where the antioxidant capability is required. The lack of single papers presenting a collection of diverse small molecule antioxidant moieties as potential design leads prompted us to write this short review of twenty five such functionalities.

Keywords: Catalase, cytoprotective, neuroprotective, oxidative stress, phenolic, radicals, scavengers, superoxide dismutase.

INTRODUCTION:

Failure of the antioxidant defense capacity provided by enzymes like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), or exposure to ionizing radiation lead to beyond threshold accumulations of reactive molecules in the form of free radicals, reactive oxygen (RO) and reactive nitrogen (RN) species. Although structurally distinct, these molecules are collectively referred to as reactive oxygen species (ROS), and induce oxidative stress reactions which culminate in cellular damage/death. Detailed descriptions of ROS and their reaction mechanisms have been provided elsewhere [1,2], however, the commonly encountered reactive species include: *hydroxyl* ($OH^{\bullet}$)**,** *hydroperoxyl* ($HOO^{\bullet}$)**,** *alkoxy* ($RO^{\bullet}$)*, peroxy* ($ROO^{\bullet}$)*, superoxide anion* ($O_2^{\bullet-}$)*, lipid peroxy* ($LOO^{\bullet}$)*, hydrogen peroxide* (H_2O_2)**,** *hypochlorous acid (HOCl), nitrous acid* (HNO_2)*, peroxynitrite* ($ONOO^-$)*, nitrogen dioxide* ($NOO^{\bullet}$)*, and nitric oxide* ($NO^{\bullet}$). From a biological standpoint, ROS have been implicated in direct/indirect, early/late stage disruptions in DNA, proteins, lipids, and often underlie a variety of neurological (Alzheimer's, Parkinson's, Huntington's, Amyotrophic Lateral Sclerosis or ALS, *etc*.) and non-neurological (Atherosclerosis, Cancer, Diabetes, Inflammation, Cardiovascular, *etc*.) chronic diseases [3]. Therefore, the general view is that pharmacologically effective exogenous antioxidants can prevent or minimize oxidative stress related cell injury by complementing the endogenous antioxidant defense system. Since most antioxidants are diet based, their effectiveness depends on several factors including amounts consumed, undesirable metabolic outcomes, and sometimes membrane permeability difficulties. Thus, to improve effectiveness, potent agents with desirable pharmacological profiles can be designed by incorporating known core moieties possessing antioxidant activities.

The aim of this review is to provide a summary of a select number of small but diverse functional groups which canserve as leads in drug design endeavors. We point out some key attributes of the moieties but do not present global antioxidant activity data nor do we provide synthetic procedures of the groups covered. The emphasis of this review is therefore to organize and provide brief descriptions of structurally different *small molecule organic* antioxidant functional groups, especially in light of the paucity of articles conveying this type of collective information.

FUNCTIONAL GROUPS

Our literature search for antioxidant functional groups yielded a variety of moieties. Herein, we present twenty five such small organic moieties. For simplicity, we have categorized these moieties as: *phenolic* (Table **1**), *sulfur containing non-phenolic* (Table **2**), and *non-sulfur containing non-phenolic* (Table **3**) functional groups. These molecules are amenable to structural modifications in order to improve their ADMET (absorption, distribution, metabolism, elimination and toxicity) profiles, enhance antioxidant activities, or broaden their pharmacological ranges of activities (*i.e.*, conversion into multi-functional agents), and therefore can be utilized in drug design for oxidative stress associated pathologies. Please note that in order to maintain consistency and lessen nomenclature confusion, the common and chemical names indicated herein (Tables **1**, **2**, and **3**) for structure identity are as they appear in the referenced articles.

Table **1** lists a few of the phenolic moieties with antioxidant properties. Sesamol or 3,4-methylenedioxy-

*Address correspondence to this author at the Univ. of The Incarnate Word, 4301 Broadway, CPO 99, San Antonio, TX 78209, USA; Tel: 210-883-1174; Fax: 210-822-1516; E-mail: Sikazwe@uiwtx.edu

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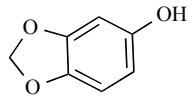
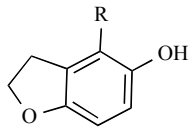
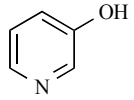
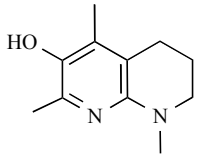
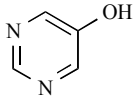
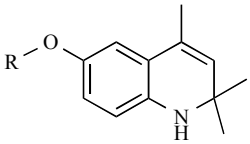
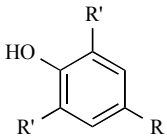
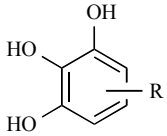
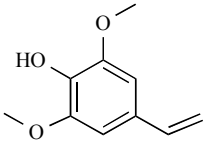
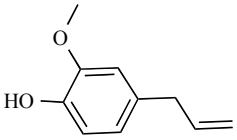
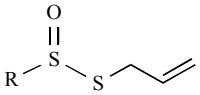
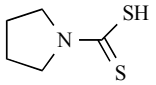
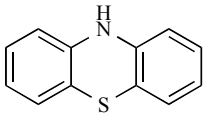
Table 1. Antioxidant Phenolic Functional Groups

Entry	Structure	Identity	References
1		Sesamol or 3,4-Methylenedioxyphenol	[4,5]
2		2,3-Dihydro-5-benzofuranol	[6,7]
3		3-Pyridinol	[8]
4		2,4-Dimethyl pyridinol	[8, 9]
5		5-Pyrimidinol	[8]
6		Dihydroquinolinol	[8]
7		Bulky phenols (R' =*iPr*or *t-Bu*)	[10, 11]
8		Pyrrogalol	[12, 13]
9		Canolol or 4-vinyl-2,6-dimethoxyphenol	[14, 15]
10		Eugenol or 1,4-Allyl-2-methoxyphenol	[16, 17]

phenol (**1**) is an antioxidant constituent of dietary sesame oil. This moiety's capacity to scavenge diverse free radicals including biologically generated ones [*i.e.*, hydroxyl (- $OH^{\bullet}$), superoxide anion (- $O_2^{\bullet-}$), nitric oxide ($NO^{\bullet}$)], its potential antioxidant mechanism of action, and other pharmacological activities have been documented [4, 5]. For instance, in whole body irradiation experiments of albino mice, sesamol exhibited protective effects against ionizing radiation induced DNA damage in lymphocytic cells [4]. On the other hand, Hammond *et al* [6] prepared isomeric and isosteric analogs containing the 2,3-dihydro-5-benzofuranol (**2**) skeleton as potential anti-inflammatory agents acting *via*

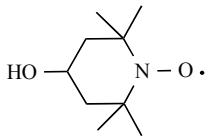
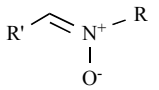
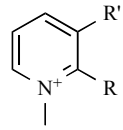
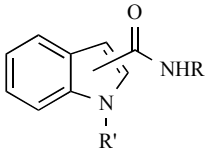
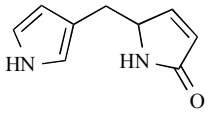
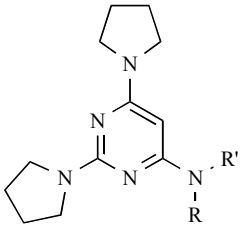
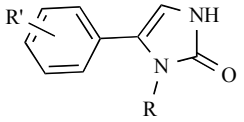
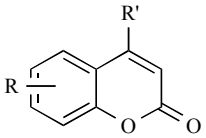
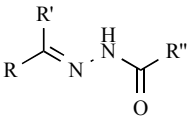
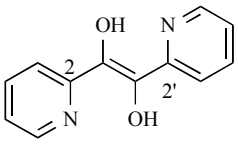
Table 2. Sulfur Containing Non-phenolic Antioxidant Functional Groups

Entry	Structure	Identity	References
11		1,2-Dithiolane	[21-24]
12		Allyl-thiosulfinate	[22]
13		2,3-Dihydrothiazole	[23]
14		Pyrrolidinedithiocabamate	[24, 25]
15		Phenothiazine	[26]

antioxidant inhibition of leukotriene production. Tamura *et al.* [7] have also synthesized and evaluated sterically hindered and lipophilic 2,3-dihydro-5-benzofuranol derivatives as antioxidant-based antiatherogenic agents, that is, inhibitors of low density lipoprotein (LDL) oxidation. Entries **3** and **4** are different versions of pyridinols whereas **5** is a pyrimidinol [8]. All these groups are chain-breaking antioxidants. Structure **4**, also known as 2,4-dimethyl pyridinol, is conformationally constrained and a structural analog of α-tocopherol's heterocyclic rings [9]. Unlike other phenols these moieties are stable to air oxidation. It is also reported that *ortho or para*-methyl, methoxy and amino electron donating (ED) substituents on the aromatic rings promote OH hydrogen abstraction by the free radical because they lower the O-H bond dissociation enthalpy (BDE) through aryloxy radical stabilization. Another mode of antioxidant activity is suggested to be related to their ability to catalyze the otherwise slow N-acetylcysteine's reaction with peroxy free radicals [8]. Dihydroquinolinol (**6**) is also described as an antioxidant aromatic amine with low bond dissociation energies for N-H bonds and therefore can donate hydrogen to free radicals to form resonance stabilized aminyl radicals [8]. Ethoxyquin, exemplifies dihydroquinolinol antioxidants and is commercially used to stabilize pet foods against peroxy radicals [8]. Bulky phenolic cores (**7**), represented by *di-iso*-propyl and *di-tert*-butyl phenols, are among the most potent phenolic antioxidants [10, 11]. These functional groups have been incorporated in the design of a variety of potential antioxidant drug molecules. Auvin *et al* [11] utilized the two phenols in their design of single molecules with dual antioxidant/nitric oxide synthase inhibitor activities. According to Furuno *et al* [12] the pyrrogalol moiety (**8**), another phenolic functional group, has superb superoxide anion scavenging capability and when present in other structures, such as flavinoids, enhances the overall antioxidant properties. Mechanistic and structure activity studies related to pyrogallol's antioxidant activity have also been reported [13]. Canolol or 4-vinyl-2,6-dimethoxyphenol (**9**) and eugenol or allyl-2-methyoxyphenol (**10**) are antioxidant compounds found in canola and clove extracts, respectively. Canolol's reactive species neutralizing capacity has received attention in several articles. Evidently, canolol exhibits antioxidant activity against peroxynitrite ($ONOO^-$) and peroxy ($ROO^{\bullet}$) species [14, 15]. On the other hand, eugenol is known to be cell protective against radicals like $OH^{\bullet}$ and $O_2^{\bullet-}$ perhaps by trapping the radicals as opposed to breaking radical chain reactions [16, 17]. In addition, dimeric forms of eugenol have proven to be even stronger antioxidants and inhibitors of lipid peroxidation [17].

Structures **11**, **12**, **13**, **14** and **15**, in Table **2,** represent sulfur bearing non-phenolic small molecule functionalities. Antioxidant properties of α-lipoic acid (LA, 1,2-dithiolane-3-pentanoic acid) are due to the presence of 1,2-dithiolane (**11**) group in the molecule. The intact 1,2-dithiolane moiety seems to scavenge hydroxyl radicals, whereas peroxy radicals are deactivated by the reduced dithiol form [18]. Dithiol structures possess enhanced antioxidant potencies and may be accessed *in vivo via* metabolic reductive opening of the 1,2-dithiolane ring. This metabolic process, for instance, converts LA into dihydrolipoic acid (DHLA) [19]. Lipophilic and hybrid compounds characterize some of the derivatives of 1,2-dithiolane [20, 21]. The allyl-thiosulfinate (**12**) structural feature, present in garlic clove extract constituents like allicin, endows garlic with antioxidant properties. A further understanding of this moiety's radical scavenging activity can be elicited from allicin's kinetic and mechanistic studies by Okada *et al* [22]. Another class of sulfur-bearing antioxidants contains the 2,3-dihydrothiazole (**13**) structure. This functional group displays a rapid 1,1-diphenyl-2-picrylhydrazyl ($DPPH^{\bullet}$) radical abstraction capacity and reportedly plays a significant role in the antioxidant properties of sydonyl thiazolidinone and thiazoline compounds [23]. A dual mechanistic molecule pyrrolidine dithiocarbamate (**14**) or PTDC inhibits nuclear

Table 3. Non-Sulfur Containing Non-phenolic Antioxidant Functional Groups

Entry	Structure	Identity	References
16		Tempol or 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl	[27-30]
17		Nitrone	[31-34]
18		*N*-methyl pyridinium	[35, 36]
19		Indolecarboxamide	[37, 38]
20		Dipyrrinone	[39, 40]
21		Pyrrolopyrimidine	[41, 42]
22		Aryl-imidazoline	[43]
23		Coumarin	[44-49]
24		Hydrazone	[50-53]
25		A-Pyridion	[54, 55]

factor- kappa B or NF-kB transcription protein and also acts as an antioxidant. PTDC has therefore been a molecule of interest in both inflammatory and oxidative stress related diseases [24]. Among other antioxidant activities, PTDC has displayed the capacity to neutralize hypochlorous acid (HOCl) and prevent chemically (*e.g.*, paraquat,

thioacetamide or TAA) induced oxidative stress injury in rat lung and liver cells [24, 25]. The phenothiazine group (**15**), is a common moiety in a variety of drugs including antipsychotics (*e.g.*, chlorpromazine, fluphenazine), antihistamines (*e.g.*, promethazine) and anticholinergics (*eg.*, ethopropazine). This group is now being investigated for its antioxidant-based cell protective effects. For example, González-Muñoz *et al* [26] have demonstrated that phenothiazines can protect human neuroblastoma cells from H_2O_2-induced oxidative stress.

A sampling of the non-sulfur containing non-phenolic antioxidant moieties is illustrated in Table **3**. Here we find molecules like Tempol or 4-hydroxy-2,2,6,6-tetramethyl-piperidine-*N*-oxyl (**16**). Tempol is a stable piperidine nitroxyl antioxidant which reportedly mimics superoxide dismutase (SOD), deactivates the peroxyradical (*ROO•)*, inhibits the formation of hydroxyl radicals from hydrogen peroxide, and is membrane-permeable [27, 28]. This moiety has been extensively experimented on and shown to diminish oxidative stress related injury. For example, Tempol was neuropro-tective in animal models of Parkinson's disease (animals treated with 6-hydroxydopamine or 6-OHDA, an inducer of apoptosis *via* ROS) [27]. In separate experiments, Tempol was shown to decrease $O_2^{\bullet-}$ mediated lipid peroxidation in lungs of mice and elevated glutathione (GSH) levels [28]. Soule *et al.* [29] and Wilcox [30] have provided more detailed descriptions of Tempol, including: alimited SAR (i.e., piperidine, pyrrolidine, pyrroline, and oxazoline analogs), other indirect antioxidant reaction mechanisms, and clinical applications. The nitrone (**17**) functionality is a free radical trap. This structural feature is taken advantage of in the design of potential neuroprotective molecules like 2-[[(1,1-dimethylethyl)oxidoimino]-methyl]-3,5,6-trimethyl-pyrazineor TBN and derivatives, stilbazulenyl nitrone or STAZN, and nitrone bearing *N*-arylpyridinium salts which are mitochondria selective antioxidants [31-34]. The protective effect of this functional group lies in its ability to react with free radicals and produce stable and long lived nitroxides [31]. Like Tempol, nitroxides quench superoxide anions *via* a mechanism that closely resembles superoxide dismutase. Small molecule heteroaryl nitrones and their free radical inhibitory activities have been reported by Porcal *et al.* [34]. The *N*-methylpyridinium (**18**) or NMP group is one of the many antioxidants, present in roasted coffee, with potential DNA and cellular protective activities [35]. NMP is a low molecular weight *N*-arylpyridiniumcationic salt. It is alipophilic, free radical scavenging moiety capable of penetrating and accumulating in the mitochondrial matrix. Robertson and Hartley [36] have incorporated this moiety in their design of *N*-arylpyridinium/nitrone compounds as mitochondria selective antioxidants. The rationale for targeting the mitochondria is that malfunctioning mitochondria generates excessive ROS (more oxidative stress) and less adenosine triphosphate (ATP) for cellular energy.

N-substituted indole 2- and 3-carboxamides (**19**) are strong scavengers of the superoxide anion and inhibit lipid peroxidation reactions [37]. Structural evaluations indicate that the benzyl group is the preferred substituent at nitrogen and that N-substitued indole 2-carboxamides are the more active antioxidants [38]. The dipyrrinone (**20**) functional groupis found in bilirubin and other bile pigments. Dipyrrinone endows bilirubin with antioxidant capacity in human plasma [39, 40]. Structure activity relationship studies suggest that dipyrrinones must have two free N-H bonds to possess antioxidant activity [31]. Groups like the pyrrolopyrimidines (**21**) represent potent blood brain barrier penetrating antioxidants capable of inhibiting peroxynitrite mediated cell damage (*via* initiation of lipid peroxidation) and with potential utility as neuroprotective agents [41]. Bundy *et al.* [42], through their limited analysis of pyrrolopyrimidine prototypes, have demonstrated that this moiety is stable under non-biological mildly oxidative environments such as O_2 in ethyl acetate, aqueous H_2O_2 in methanol, iodine in methylene chloride, *etc.*, and that the electron donating substituents on pyrrolidinyl contribute to its overall antioxidant properties. Structure **22** is a member of 5-aryl-imidazolin-2-ones.Watanabe *et al.* [43] synthesized and evaluated a number of analogs containing this moiety and concluded that the 5-aryl-imidazolin-2-one feature possessed radical scavenging capability and inhibited lipid peroxidation. They also rationalized that 5-aryl-imidazolin-2-ones undergo a form of keto-enol tautomerism to generate aromatic hydroxyl groups with comparable antioxidant activity to phenolic OHs and diminished acute toxicity.

Natural and synthetic molecules containing the coumarin (**23**) or 1,2-benzopyrone functional group possess a wide range of pharmacological activities including anti-inflammatory, antioxidant, anti-cancer, and antiviral. The coumarin moiety imparts antioxidant properties and has therefore been incorporated in the design of a number of potential drug molecules. A review by Kostova [44] has provided ample examples of structurally diverse coumarins with antioxidant activities. Since free radicals play significant roles in inflammatory cascades, it is reasoned that the anti-inflammatory activity of coumarins is related to their ability to scavenge ROS [45]. Differently substituted *3-aryl-, 4-hydroxy-,* and *5,7-dihydroxy*coumarin derivatives are examples of how to design coumarins with different *in vitro* antioxidant potencies [46-49]. Independent to the above, Rollas and Kucukguzel [50] have suggested that drug molecules containing the hydrazone moiety (**24**) possess a wide range of biological activities –from anticonvulsant to schistosomiasis. The antioxidant capability of this moiety has, for example, been illustrated using syringic and pyridoxal isonicotinoyl hydrazones. Syringic hydrazones were determined to be cytoprotective against $O_2^{\bullet-}$and low-density lipoprotein (LDL) oxidation [51]. Mauricio *et al* [52]have demonstrated that the inhibition of $OH^{\bullet}$ radical formation stems from hydrozone's ability to diminish Fe^{2+} availability presumably by chelation, thereby preventing the Fenton type reactions ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^{\bullet} + OH^-$; $Fe^{2+}/Fe^{3+} + O_2^{\bullet-} + H_2O_2 \rightarrow OH^{\bullet} + OH^- + O_2$) from occurring. In addition to showing that aroylhydrazones were cytoprotective antioxidants, Hruskova *et al* [53] further determined that conditions like pH, substituent position and electronic nature which affect imine (C═N) nitrogen protonation, have influence on hydrazone ability to undergo hydrolysis. Structure **25** is an enediol antioxidant called α-pyridoin or 2,2'-pyridoin or 1,2-di(2-pyridyl)-1,2-

ethenediol). This molecule and its derivatives can scavenge free radicals and have demonstrated cytoprotective capacity against H_2O_2-induced cell death and lipid peroxidation [54]. The lipophilic aspect of α-pyridoin is due to intra-molecular hydrogen bonding between nitrogens and hydroxyl groups, and enables the molecule to enter cells rapidly and exert its antioxidant activities before being oxidized to the less active 1,2-diketo form called 2,2'-pyridil [55]. Additionally, pyridine ring substituents with both electron withdrawing and donating groups have been shown to influence the reducing properties of enediol and the ultimate antioxidant activity of α-pyridoin.

SUMMARY

Although endogenously generated reactive oxygen species($OH^{\bullet}$, $HOO^{\bullet}$, $RO^{\bullet}$, $ROO^{\bullet}$, $O_2^{\bullet-}$, $LOO^{\bullet}$, H_2O_2, HOCl, HNO_2, $ONOO^-$, $NOO^{\bullet}$, $NO^{\bullet}$, *etc*.) may play essential roles in intracellular signaling and homeostasis, their over production, under normal physiological conditions or as a consequence of disease, is problematic because it promotes cellular damage or death. The discovery and development of cytoprotective agents in the form of efficient and appropriately active ROS scavengers/neutralizers, commonly referred to as antioxidants, has therefore become an urgent task. The structures reviewed herein are representative of diverse, small molecule (< 250 MW) functionalities with built in antioxidant capacities. These structures can serve as design leads for compounds with enhanced antioxidant activities. Although brief, our descriptions of the said functional groups highlight some of the salient points related to theirpotential utility as antioxidants. For the most part, phenolic fragments dominate the realm of antioxidant functional groups, and we have presented some of them, but we also made a concerted effort to seek out the non-phenolic groups. Furthermore, the inherent metal complexation capacity of some of the reviewed functional groups is noteworthy. The ability to complex or chelate Fe, Cu, and other elements involved in free radical generating Fenton type reactions perhaps accounts for their indirect antioxidant properties.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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