

Sterically Hindered Phenols as Antioxidant

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Abstract

Hindered phenolics are the compounds which will act as an antioxidant compared to the general phenolic compounds. Especially BHT compounds are shown here and which modifications will be responsible for the enhancing and reducing the efficacy of the phenolic compounds. These moieties are easily available materials which found mostly in the foods, fruits and vegetables and also in several supplements. The free radical oxidation of organic substrates is inhibited by phenols and also involved in recovering from several pathophysiological conditions. In this review mentioned the several phenolic compounds which exhibit the effect of scavenging free radicals in the several pathophysiological conditions and daily life processes.

Keywords: *Hindered phenolics, Antioxidants, Free radicals, Oxidative stress*

1. INTRODUCTION

Phenolic compounds provide labile hydrogen for trapping the free radicals thus protecting the oxidation of organic substances. The kind of substituent's and the number of hydroxyl groups in a phenolic compound affects its antioxidant activity. The decrease in the redox potential of hydroxyl group due to ortho, para substitutions on the ring increases its antioxidant activity. Phenol Type antioxidants take 50 % of the market world as plastic stabilizers and 30 % for resins[1-5].

The free radical oxidation of organic substrates is inhibited by phenols that are substituted thus improving the characteristic property of various substances. The effectiveness of the phenol depends on the size and position of the substituent's [6]. The presence of a sterically demanding group like tertiary butyl beside a phenolic hydroxyl group in hindered phenols has been used as an antioxidant and acceptable food preservative. The steric effect of the tertiary butyl groups is the main reason for the important role of hindered phenols. They have been used for the stabilization of rubbers and can protect fat and products of nutrition value. They are highly efficient and non toxic because of which they have found wide application in medicine and biology.[7-9]

They are used in industries as rubber processing and fuels because of their less toxic and eco friendly nature[10]. A well known synthetic antioxidant used in industry is BHT or butylated hydroxytoluene, used as a food preservative, taste improver and stabilizer, by improving the metabolism of plasma lipid and also shows antioxidant responses[11, 12]. Thus sterically hindered phenols exhibit various biological activities like antitumor, antiviral, antibacterial and anti-inflammatory[13-15]. They have also been considered as promising drugs in treating Alzheimer's disease[16]. Thus due to the presence of biological activity in hindered phenolic compounds as potential antioxidants, new derivatives are being synthesized to enhance their biological activity.

2. LITERATURE REVIEW

The α -glucosidase inhibitory activity shown by the free phenolic groups in chalcone, flavones derivatives have been taken in much importance[17]. The design of hindered phenol-flavonoid hybrids to improve their biological activity and to improve antioxidant activity of hydrazones by incorporating a 2,6-di-*t*-butylphenolic unit have also been reported[18]. Few reports have been reported to show that aminothiazoles also show antioxidant activity[19, 20]. Thus a set of hybrid compounds of hindered phenols and 2-aminothiazole moieties in Figure 1 were synthesized known as 4-amino-2-(arylamino)-5-(3,5-di-*t*-butyl-4-hydroxybenzoyl)thiazoles.

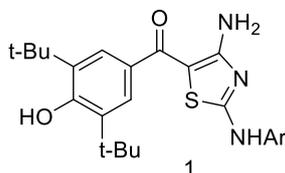


Figure1:[4-amino-2-(phenylamino)-5-thiazolyl](3,5-di-*t*-butyl-4-hydroxyphenyl)methanone where Ar for 1a is C₆H₅, 1b is 4-Me-C₆H₄ and 1c is 4-MeO-C₆H₄

α -glucosidase inhibition activity and α -amylase inhibition activity was exhibited by 1a and 1b. The best antioxidant activity was exhibited by 1c and it was enhanced as compared to Butylated hydroxytoluene (BHT) and vitamin C[21].

The hybrid phenols having isonorbonyl and tertiary butyl groups have been synthesized. The hybrid compounds exhibited higher antioxidant activity than the liposoluble antioxidant butylated hydroxyl anisole[22, 23]. Furthermore when alkylation of isonorbonylphenols was done in the presence of allyl benzene using hetero and homogeneous catalysts it was observed that the compounds formed interacted with peroxy radical actively. Among the studied compounds Figure 2 represents the compounds showing maximum rate constant when reacted with peroxy radical. The compounds 2,3,4 and 5 exhibited good activity against peroxide radical.[21]

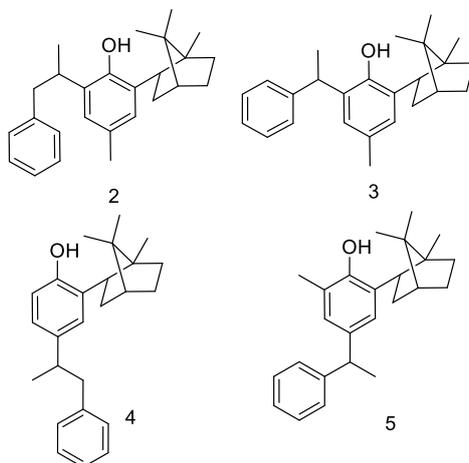


Figure 2: Hybrid compounds of Isonorbonyl phenols

The antioxidant activity of the compounds mainly depends on the types and the position of substituents with respect to the OH of the phenol. If a bulky group was introduced at both the ortho position the rate was seen to decrease due to much steric hindrance when phenol reacts with the peroxide radical. It was observed that as the number of alkyl and phenylpropyl substituent's increase the rate of the reaction with peroxy radical also increased. The maximum activity was shown by 2. The presence of a bulky group phenylpropyl at the para

position to the OH group as shown in 4 as compared to ortho position increased the rate two times. If a bulky group was introduced at both the ortho position the rate was seen to decrease due to much steric hindrance when phenol reacts with the peroxide radical[24].

A series of phosphoryl sterically hindered phenolic groups in 2,6-diaminopyridines were able to show enhanced antioxidant activity as compared to their structural analogues. A number of compounds synthesized among which figure 3 depicts the ones having highest antioxidant activity. The introduction of a heteroaryldiamine moiety in the structure leads to the enhanced antioxidant activity of the compounds[25].

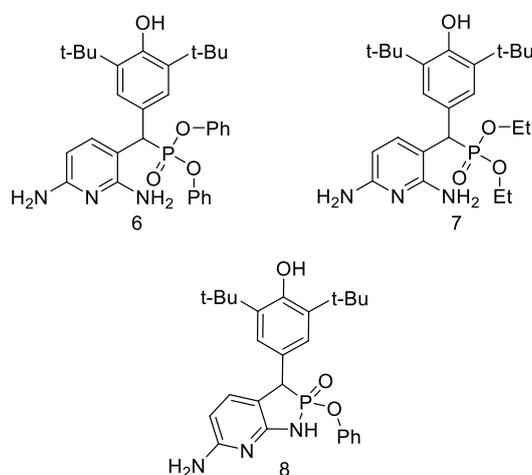


Figure 3: Structures of 2,6-diaminopyridines analogues containing a sterically hindered benzylphosphonate moiety

The introduction of a heteroaryldiamine moiety in the structure leads to the enhanced antioxidant activity of the compounds. The compound 6 was the most active compound towards MCF-7 cell line. It was revealed through the study that the activity towards M-Hela and MCF-7 cell line was due to the substituent at the phosphorus atom and the maximum activity was shown by the presence of phenoxy substituent in compound 6. The compounds 6, 7, 8 exhibited the best antioxidant activity[25].

The best antioxidant additives from the AO-I group are Irganox 1010® and Irganox 1076®. They are sterically hindered phenols which are derived from butylated hydroxytoluene moiety[26]. The non toxic nature, powerful antioxidant activity of the naturally occurring p-hydroxycinnamic acids (HCAs), like ferulic, caffeic, sinapic, and p-coumaric acids have also been taken in consideration by the additive industry[27–31].

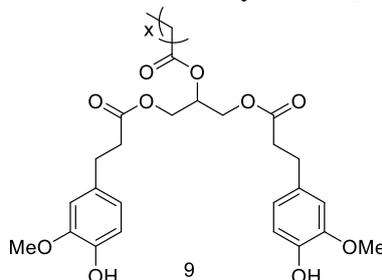


Figure 4: Structure of GDF_x where x = 10, 14 and 16

The compound 9 exhibited the highest antioxidant efficacy due to the blend of rapid kinetics and capability of H atom donation. The capability of H atom donation and rapid kinetics of the bisphenols when evaluated by DPPH free radical technique was seen to be improved against the earlier antioxidants available commercially. The bisphenol 9 was synthesized

using ferulic acid and vegetable oil demonstrated a effective antioxidant showing high radical scavenging activity[32].

In order to synthesize antioxidants having hindered phenols like polyalcohol, polyamine organic compounds having active groups and high molecular weight have been used[33]. The well defined molecular structure of dendrimers enhances their solubility and stability due to dendritic effect. The use of a dendrimer as a linker can provide good activity to a compound[34]. The dendritic hindered phenols synthesized have been represented in figure 5.

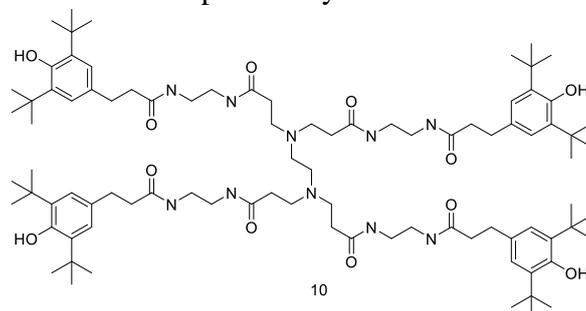


Figure 5: Structure of dendritic hindered phenol

The increase in the molecular weight of the hindered phenol leads to the decrease in its scavenging activity and increased when the concentration of phenol hydroxyl groups increased. The scavenging activity of 10 was more than the antioxidants having same number of phenol hydroxyl groups. The dendritic phenol 10 having low molecular weight had higher scavenging activity than the one having high molecular weight[35].

An aliphatic diamine having bridged hindered phenol, structure similar to Iragnox is represented in figure 6. It had outstanding processing property and resistance to oxidation in polyolefin. It was seen that the antioxidant activity increased with the increase in the length of the bridged group. The C8 phenol had the maximum oxidative induction temperature also the polyolefin stabilized by it exhibited better antioxidant activity than C8, C6 and C2, which was due to their less term effect on the stabilization of the polyolefin[36].

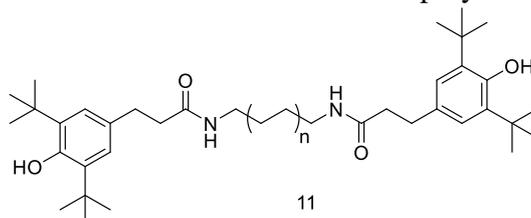


Figure 6: Structure of aliphatic diamine bridged hindered phenols where n = C2, C4, C6 and C8

The structurally hindered phenols show antioxidant activity towards quenching peroxy radical of substrate to form hydroperoxides by transferring hydroxylic hydrogen[37]. Hyper branched hindered phenols in Figure 7 have good scavenging ability for DPPH• and ROO•, this underline the significance of the alkyl chain length of the bridged groups. Results state that the antioxidant activity decreases with the increase in alkyl chain length of bridged groups. C14 phenol showed the best antioxidant activity for ROO• and antioxidant activity of C16 was better than that of C18 phenol. As the chain length increase the steric effect is enhanced because of which the reactivity of the hindered phenol and the free radical decreases. The hyper branched molecules in figure 7 have high molecular weight and a number of antioxidant groups that are responsible for the activity[38].

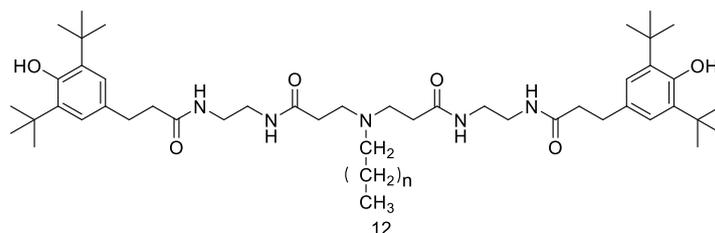


Figure 7: Structure of hyper branched macromolecule bridged hindered phenols where $n =$ C14, C16 and C18.

2,6-Dialkylphenols have low toxicity and show biological activity as inhibitors of radical chain oxidation of organic molecules[39]. Sterically hindered phenols also are effective antioxidants and inhibit oxidation of various substrates [40]. Nitrogen, sulphur and oxygen containing amide and amine derivatives having 2,6-di-*tert*-butylphenol moiety are inhibitors of cyclooxygenase and show anti-inflammatory activity [41]. The phenolic antioxidants with nitroaromatic and heterocyclic substituent's are shown in figure 8.

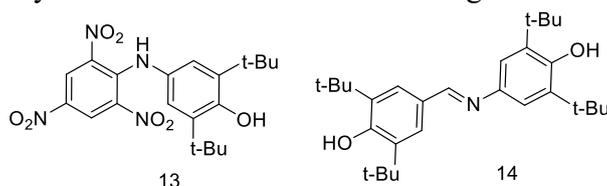


Figure 8: Phenolic antioxidants having nitroaromatic and heterocyclic substituent's.

Compounds 13 having a single atom NH spacer showed the most effective antioxidant activity and 14 having two phenol groups was more active than the standard antioxidant ionol. The picryl moiety in conjugation with phenol group acts as an acceptor providing increased stability of the phenoxy radical and inhibitory activity is due to the 2,6-di-*tert*-butylphenol moiety. Thus the presence of a 2,6-di-*tert*-butylphenol moiety along with NH spacer provided a significant increase in the antioxidant activity of the compound[42].

The treatment of complex neurodegenerative diseases and other diseases can be done using a multitarget pharmacological approach[43]. In order to increase the bioavailability, solubility, stability of antioxidants nanotechnology approach can be used[44]. It has also been seen that antioxidants encumbered with drugs into liposome protect the degradation of the system[45].

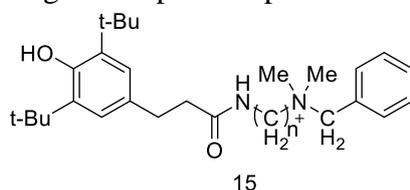


Figure 9: Structure of derivative of hindered phenol having a quaternary ammonium moiety where $n =$ 2 and 3

New derivatives of hindered phenols having quaternary ammonium moiety is depicted in figure 9. It was observed that the interaction of the compound 15 with free radicals was far exceeding than that of the standard compound ionol. The compound having $n =$ 2 exhibited more enhanced antioxidant activity than when $n =$ 3[46].

Ammonium salts are seen to be compounds that are physiologically active[47]. Their ability to be engrossed to the bacterial membrane that is negatively charged forms their biomedical applications as anesthetic, antifungal, anti inflammatory and analgesic[48,49]. They are also able to slow down human leukocyte elastase[50]. The sterically hindered phenolic groups having quaternary onium salt and a phosphoryl group are shown in figure 10.

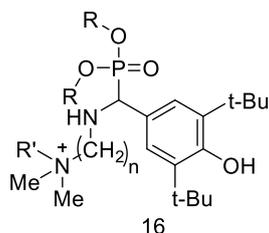


Figure 10: Structure of hindered phenol having onium salt where (16a: R= Et, R'= C₂H₅, n= 3), (16b: R= Et, R'= C₁₀H₂₁, n= 2), (16c: R= Et, R'= C₁₀H₂₁, n= 3)

The compound 16b exhibited the highest antimicrobial activity and all the three compounds 16a, b, c showed enhanced antioxidant activity as compared to the standard compound ionol. They were able to react with the free radicals present caused a steady reduction in the chemiluminescence intensity of the free radical generator[11].

The introduction of a polymer chain in a macromolecular antioxidant leads to the lowering in the antioxidant efficacy. The antioxidant efficacy can be improved by the preparation of a macromolecular hindered phenol antioxidant having antioxidant groups like phosphites and thioether[51–53]. The synthesized macromolecular hindered phenol antioxidant having phosphites and thioether is shown in figure 11.

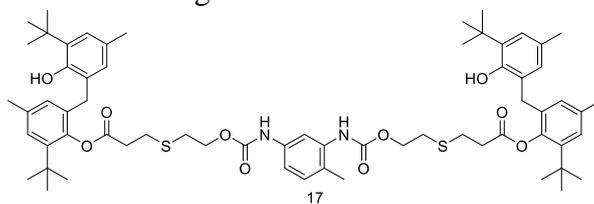


Figure 11: Structure of hindered phenol antioxidant having phosphate and thioether groups.

The compound 17 shows admirable antioxidative ability. The urethane group inhibits degradation and functions similarly like an aromatic amine antioxidant. The urethane group supplies proton and free radicals can be conjugated by the aromatic ring, thus imparting stability and increased ability of supplying proton for the termination of free radical. Hydroperoxide is decomposed by thioether group forming stable products[54]. The thioether shown in figure 12 showed stronger antioxidant activity than the standard compounds due to the formation of stable radicals by hydrogen atom abstraction and can neutralize a large number of radicals due to fragments of sterically hindered pyrocatechol. The presence of two thioether also increases the activity of compound towards hydroperoxides. Thus its reaction with DPPH radical showed high activity and was greater than the standard antioxidant tocopherol[55].

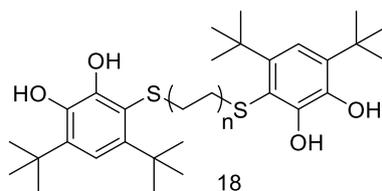


Figure 12: Structure of sterically hindered bispyrocatechol thioether where n=1 and 3.

The presence of two phenolic groups in a single molecule known as bisphenols have greater antioxidant performance and improved thermal stability because of which they have found wide application in academic world and industry[56–59]. The molecule having three phenolic groups in a single molecule is represented in figure 12.

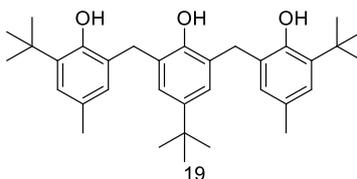


Figure 13: Structure of trisphenol

The high molecular weight compound 19 exhibited greater thermal stability than mono and bisphenols. The ortho trisphenol 19 exhibited the greatest antioxidant activity as compared to the para substituted which showed worst activity. It showed superior activity towards alkyl peroxy radical. The compound has improved performance due to the presence of intramolecular hydrogen bonds which stabilizes the phenolic radical and the activity increased on increasing the concentration [60-62].

3. CONCLUSION

The sterically hindered phenols exhibit various biological activities depending on the nature and the type of substituents on the aromatic ring. The presence of tertiary butyl groups on the phenol ring majorly imparts for the activity of the compounds. The antioxidant activity also depends on the hydrogen atom transfer capacity thereby stabilizing the reactive species. Depending on the modification of hindered phenol various new antioxidants show promising activity better than the standards used thus providing better antioxidant activity.

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