SYNTHESIS OF DIPHENOLIC BIS-2-AMINOTHIAZOLES AS NOVEL ANTIOXIDANTS

FINAL TECHNICAL REPORT

BACK TO LAB PROGRAMME
(Sanction No: 446/2013/KSCSTE dated 27/03/2013)
(Period from 16/4/2013 FN to 14/10/16 AN)

WOMEN SCIENTISTS DIVISION
KERALA STATE COUNCIL FOR SCIENCE TECHNOLOGY AND ENVIRONMENT GOVT. OF KERALA

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AUTHORIZATION

The work entitled “Synthesis of diphenolic bis-2-aminothiazoles as novel antioxidants” by Dr. Sandhya V. Satheesh, was carried out under the “Back to Lab Programme” of Women Scientists Division, Kerala State Council for Science Technology and Environment, Govt. of Kerala. The work was carried out at Department of Chemistry, University of Kerala Karyavattom, Kerala - 695581. The project was initiated wide sanction No: 446/2013/KSCSTE dated 27/03/2013 with scheduled completion by a period of three years starting from 16/04/2013 to 16/04/2016. As the principal investigator Dr Sandhya V. Satheesh, had joined Devaswom Board college as Assistant professor in chemistry on 7/07/2015 had requested for an extension of the project and as per the request Kerala State Council for Science Technology and Environment has extended the tenure of the project from 15/04/16 to 14/10/16 without any additional financial assistance. The laboratory works were completed by 14/10/16, however an additional period of six more months were permitted (without additional financial commitments) to the principal investigator for compilation of results and preparation of final report as requested by the principal investigator. The project was completed on 08/04/2017 with a financial expenditure of Rs. 13,855.47.00 lakhs
ACKNOWLEDGEMENTS

I am deeply indebted to Kerala State Council for Science, Technology and Environment for the financial aid through “Back to Lab Programme for Women” which helped me to get an independent project and a persistent exposure to research leading to my career development. I am grateful to Dr. K. R. Lekha, Head, Women Scientists Division for the encouragement, motivation, suggestions and support throughout the tenure of the project work.

I am thankful to Dr. T. S. Anirudhan, Department of Chemistry for giving consent to become the mentor of the project. His excellent guidance, encouragement and the delightful patience are inimitable. I wish to express my sincere thanks to Dr. S. M. A. Shibli, Head of the Department of Chemistry for all the infrastructural facilities provided. I take this opportunity to thank Emeritus Professors of the Department, Dr. K. N. Rajasekharan, Dr. K. Mohanan for their suggestions and help rendered to me. I am thankful to my lab members Dr. Priya Rani M., Ms. Krishanpriya K. G. and Akhila V. R. for their whole hearted support.

I would like to express my gratitude to Dr M. Padmanabha Pillai, Principal D. B. College, Thalayolaparambu for extending the support during the work.

I am grateful to the authorities of STIC, CUSAT, Kochi, and NIIST, Thiruvananthapuram for the NMR and IR spectral facilities provided.

Dr. Sandhya V. Satheesh
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Abstract

Generation of free radicals within biological systems cannot be avoided as long as the metabolic processes are maintaining the living condition of the cells in various life forms. Free radical damage in humans can result in various diseases such as cancer, respiratory tract disorders, rheumatic arthritis, cataract, asthma, heart diseases, stroke, atherosclerosis and diabetes. Even though body can be defensive using the endogenous antioxidants, these are sometimes not sufficient at the time of excessive oxidative stress. If the discrepancy between the production of deleterious radicals and the neutralization by body’s defense mechanism persists, synthetic antioxidants are to be supplemented. Thus a demand for new antioxidant scaffold is high at all times. Therefore, the design of newer antioxidant molecule is always a point of interest among the synthetic chemists.

Synergetic strategies are always an effective approach in drug design since often the effect of the combined action of a hybrid molecule is greater than sum of each acting separately. We felt that the combination of two or more antioxidant units would have an improved activity profile than that of the components acting individually. Aminothiazoles are isosteric with phenols in their antioxidant activity. Hindered phenols such as butylated hydroxy anisole and butylated hydroxy toluene are permitted, synthetic food additives which act as antioxidants. Accordingly, in this project, it was proposed to design, synthesize and evaluate the antioxidant properties of a molecular system that incorporates a hindered phenolic unit appended to a 2-aminothiazole unit. The reaction of bisacylthioureas of the type R₁R₂N-CS-NH-[1,4-C₆H₄]-CO-NH-CS-NR₁R₂, with α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone was expected to produce 4,4’-phenylene-bis[5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-2-][(disubstituted amino]thiazoles. Thus, several bisacetylthioureas were prepared and reacted with α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone to yield the targeted bisthiazoles. However, the extreme insolubility of these compounds was a hindrance for their characterization and evaluation. Therefore the molecular target was redesigned as monophenolic 4-phenylaminothiazoles. The starting monoacetylthioureas of the type
$\text{C}_6\text{H}_5\text{-CO-NH-CS-NR}^1\text{R}^2$ were prepared. Their reaction with $\alpha$-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone afforded hitherto unreported 2-amino-5-(2,6-di-t-butyl-4-hydroxyphenyl)-4-phenylthiazoles. Their antioxidant properties were evaluated and compared with a reference antioxidant.
Introduction and review of literature

Antioxidants - Introduction

To maintain the living state of cells and organisms, oxidative metabolism is necessary which in turn is divided into two: catabolism which refers to the breakdown of molecules to obtain energy and anabolism in which the synthesis of all compounds needed by the cells occurs. Nutrition is the input for a healthy metabolism which in turn produces energy which sequentially required by the body to synthesize new proteins, nucleic acids for the synthesis of DNA and RNA. Although oxygen is essential for the survival of cells, it is a potent source of harmful free radicals (Burits and Bucar, 2000). Antioxidants are substances that can inhibit the oxidation. Humans have their own intrinsic antioxidant defenses that involve molecules such as ascorbic acid (vitamin C), alpha-tocopherol (vitamin E), beta-carotene, coenzyme Q10 and endogenous as well as enzymes such as catalase and superoxide dismutase. Trace elements like selenium and zinc also have a crucial role in antioxidant defenses. A wide variety of diet components such as blueberries, dark chocolates, nuts like pecans and all leafy vegetables and fruits contain antioxidant molecules in plenty. Yet, at the time of oxidative stress, body’s defense mechanism may become inadequate and thus necessitating external supplementation of antioxidants.

Polyphenol antioxidant contains phenol groups or bulky alkyl group substituted phenolic groups. As the main source of antioxidant is dietary polyphenols, synthetic designs parallel to polyphenols have grabbed attraction recently. By donating a hydrogen atom to the ROS, mainly to peroxyl radicals (ROO•), a phenolic antioxidant would deactivate the ROS species. The phenoxide radicals thus formed are later stabilized by resonance or by quenching the effect by combining with another phenoxide thus a chain termination might happen.

Commonly known synthetic food additives which acts as antioxidants are BHT (1) and BHA (2).
Although the 2-aminothiazole moiety, strictly speaking, cannot be considered as a bioisosteric replacement of the acidic phenol group, it has been assigned such a status by medicinal chemists (Zhang et al., 2003). This is because the 2-amino group may effectively substitute for the phenolic hydroxyl group by forming hydrogen bonds in receptor binding site. This has been known to result in improved pharmacological properties (Zhiqing et al., 2004).

The present project attempts to unite two active antioxidant molecular species leading to a proposed hybrid system comprising of two t-butyl group shielded phenolic unit and a 2-aminothiazole unit. Further, the design and synthesis of molecules that incorporate two such units, leading to bisphenolic-2-aminothiazoles, have not been attempted hitherto. It is expected that such a hybrid species would result in enhanced antioxidant ability. In summary, the focus of the project has been the design, synthesis and evaluation of antioxidant properties of bisphenolic-2-aminothiazoles. However during the course of the work, the physical properties of the targeted bisphenolic-2-aminothiazoles led us to consider the synthesis of mono phenolic counterparts leading to novel mono phenolic-2-aminothiazoles.

**Review of literature**

The reported bioactivities of 2-aminothiazoles (3) include plasminogen activator inhibition, antibacterial (Narendra et al., 2010), anesthetic (Geronokaki et al., 2003; Bhargava et al., 1982), anti-inflammatory (Franklin et al., 2009), antifilarial (Varman et al., 2004)), antitumor, anti-schizophrenia (Juan et al., 1990), immunoregulatory (Zhou et al., 2006), antihelmintic, blood cholesterol lowering, diuretic, antitubercular (Khadse et al., 2003), antiarthritic (Pathak et al., 1981), antithrombotic (Badorc et al., 1997), antidiabetic, anticonvulsant (Azam et al., 2008) antifungal, antitubercular, anti-HIV, anti-inflammatory, anticancer, antidiabetic, antihypertensive, antiprotozoal,
dopaminergic, neuroprotective, antiallergic, analgesic and antioxidant activities (Shih et al., 2004).

There are numerous aminothiazole derivatives that exhibit a wide array of pharmacological activities. Some of these examples are outlined below. It has been reported (Dighe, et al., 2011) that 2-amino-4-aryltiazoles (4&5) exhibits antibacterial properties.

The anti-inflammatory activity of thiazolylformazanylindoles (6) has been reported. (Singh et al., 2008)
The antioxidant activity of the free base meso-tetrakis (3,5-di-tert-butyl-4-hydroxyphenyl)porphyrin, R4PH2 (7) has been reported (Natalya et al., 2010).

The 2-aminothiazole derivatives synthesized by the reaction of tetrahydropyrimidinylthiourea with ω-hydroxy-3-substituted methylacetophenones have been disclosed in a US patent (8).

There are reports (Venkatachalam et al., 2001) that aromatic and heterocyclic thiazolylthioureas (9) can act as anti-HIV agents.
The neuroprotective ability of 2-aminomethyl-4-(3,5-di-t-butyl-4-hydroxyphenyl)thiazoles (10) has been reported (Harnett et al., 2004). This also is one of the few reports on the antioxidant properties of amino substituted thiazole derivatives.

Arylaminothiazoles (11 and 12) have been screened for anti-inflammatory activity (Holla, et al., 2003).

The antihelmintic activity of thiazole (13) has been reported (Himaja, et al., 2008)
Certain anticonvulsant 2-aminothiazoles (14) have been synthesized (Amin, et al., 2008).

There are reports (Gauda et al., 2010) that the thiazole derivatives (15-17) show promising antioxidant activity.
N-Bis(trifluoromethyl)alkyl-N'-thiazoylureas (18) have been reported (Luzina, et al., 2009) which possess anticancer activity against human cancer cell line.
Objectives

The objectives of the present project have been summarized as follows.

The primary objective had been to design a synthetic path to bisphenolic-2-aminothiazoles such as 4,4'-phenylene-bis[5-(3,5-di-t-butyl-4-hydroxybenzoyl)-2-(disubstituted)aminothiazole] (19) with variations on the NR$_2$ substituent.

After the successful synthesis of the compounds, these compounds were purified and characterized spectroscopically by FTIR, $^1$H and $^{13}$C NMR and high resolution ESI-MS methods and were screened for antioxidant potentials. Based upon the experimental results and also on the computational work further exploration of the changes and modification to adopt in molecular design.
Materials and methods

General Procedures

A retro synthetic analysis for the synthesis of 4,4’-phenylene-bis[5-(3,5-di-t-butyl-4-hydroxybenzoyl)-2-(disubstituted)aminothiazole] (19) was done based on the Scheme I.

From the retro synthetic analysis, the precursors for the synthesis are identified as terephthaloyl-bis[1-(3-N,N-disubstituted)thiourea and the α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone.
Synthesis of 3,5-di-tert-butyl-4-hydroxyacetophenone

The required 3,5-di-tert-butyl-4-hydroxyacetophenone was prepared by acetylating 2,6-di-tert-butylphenol by Friedel-Crafts acylation in the presence of AlCl₃ (Portnykh, et al., 1966). Anhydrous aluminium chloride (0.037 mol, 5 g) was stirred well with acetyl chloride (10 mL, 0.140 mol), while the reaction vessel was being kept under ice-sodium chloride (3:1) freezing mixture at -20°C. To this mixture, 2,6-di-tert-butylphenol (6.1 g, 0.029 mol) was added. After five minutes, cold water was added to the system, to get a reddish brown precipitate. The 3,5-di-tert-butyl-4-hydroxyacetophenone (or 4-acetyl-2,6-di-tert-butylphenol) was then repeatedly crystallized from carbon tetrachloride to obtain a pure white solid. Yield: 93%, m.p. 146-147°C; lit. m.p. 146-147°C (Portnykh, et al., 1966; Suda, et al., 1982); 150°C (Matsuura et al., 1962).

Synthesis of α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20)

The methyl ketone thus obtained was then converted to a bromomethyl ketone by a bromination reaction using molecular bromine, The recrystallized, 3,5-di-tert-butyl-4-hydroxyacetophenone (1 mmol, 0.248 g.) was dissolved in diethyl ether (10 mL). To the reaction mixture, molecular bromine (1 mmol, 4.05 mL) was added within a period of 5-10 minutes. The reaction mixture was then exposed to sunlight till the reddish brown color vanished. The reaction mixture was kept in sunlight for about 30 minutes before pouring into crushed ice. Creamy white crystals of (20) formed was filtered, washed with water and dried under room temperature. This was used as such and stored for a short while, if needed, at -3°C in a desiccator away from light. Yield, 93%, m.p. 93-95°C; lit. m.p. 96-98°C (Volod'kin et al., 1967).
Synthesis of terephthaloylbis[1-(3-N,N-disubstituted)thioureas (21)]

A bond disconnection analysis was done to identify the synthons for the synthesis of terephthaloylbis[1-(3-N,N-disubstituted)thioureas which is shown in Scheme II.

Several variations of -NRR have been selected and a set of secondary amines including cyclic dialkyl and alkylaryl amines, were proposed to be used as starting materials as given in Table 1.

<table>
<thead>
<tr>
<th>No</th>
<th>21a</th>
<th>21b</th>
<th>21c</th>
<th>21d</th>
<th>21e</th>
<th>21f</th>
<th>21g</th>
<th>21f</th>
</tr>
</thead>
<tbody>
<tr>
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<td>-N</td>
<td>-N</td>
<td>-N</td>
<td>-N</td>
<td>MePhN-</td>
<td>EtPhN-</td>
<td>Me₂N-</td>
<td></td>
</tr>
</tbody>
</table>

Table 1

Terephthaloyl chloride was converted to terphthalolyl bisisothiocyanate which was then treated with amines to produce terephthaloyl bis[1-(3-N,N-disubstituted)thioureas. Terephthalolyl bisisothiocyanate was synthesized by dissolving terephthalolyl chloride in benzene and was stirred with aqueous potassium thiocyanate in the presence of tetra butyl ammonium bromide to form terephthaloyl...
bisisothiocynate. This in unisolated state was then treated with secondary amines for the preparation of terephthalolylbis[1-(3-N,N-disubstituted)thioureas.]  

Synthesis of N,N-terephthalolyl-bis[1-(thiocarbamoylpyrrolidine)] (21a)  

Yield: 80%, m.p: 189-190°C,  
IR(KBr) cm⁻¹: 2932, 2965, 2857 2366, 1631, 1296, 1240, 1114  

Fig. 1. IR spectrum of N,N terephthalolylbis(1-(thiocarbamoylpyrrolidine) (21a)
Synthesis of \( N,N\)-terephthaloyl-bis[1-(thiocarbamoyl piperidine)] (21b)

Yield: 80% m.p: 171-178°C,  
IR(KBr) cm\(^{-1}\): 3389, 2948, 1248, 1170, 860

Synthesis of \( N,N\)-terephthaloyl-bis[1-(thiocarbamoyl morpholine)](21c)

Yield: 82% m.p: 180-182°C  
IR(KBr) cm\(^{-1}\): 3589, 2895, 2850,1803,1505,1516,1233

Fig. 2. IR spectrum of \( N,N\) terephthaloylbis(1-(thiocarbamoyl morpholine) (21c)
Synthesis of N,N-terephthaloyl-bis[1-(thiocarbamoyl N-methylpiperazine)] (21d)

\[
\text{H}_3\text{C} \quad \text{N} \quad \text{S} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{S} \quad \text{N} \quad \text{N} \quad \text{CH}_3 \\
\text{21d}
\]

Yield: 78% m.p: 150-151°C
IR(KBr) cm\(^{-1}\): 3444, 2970, 2895, 1684, 1445, 1186

Synthesis of N,N-terephthaloyl-bis[1-(thiocarbamoyl tetrahydroquinoline)] (21e)

\[
\text{O} \quad \text{N} \quad \text{S} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{S} \\
\text{21e}
\]

Yield: 80%; m.p: 178-180°C
IR(KBr) cm\(^{-1}\): 3610, 2946, 2805, 1158, 1114

Fig.3. IR spectrum of N,N-terephthaloylbis(1-(thiocarbamoyl-1,2,3,4-tetrahydroquinolone)

\] (21e)
Synthesis of \( \text{N,N-terephthaloyl-bis[N-(thiocarbamoyl-N-methylaniline)](21f)} \)
Yield: 65\%, m.p: 152-154°C
IR(KBr) cm\(^{-1}\): 3355, 2442, 1587, 1430, 1368, 1263, 1176

![Fig.4. IR spectrum of N,N terephthaloylbis(1-(thiocarbamoyl N-methylaniline)(21f)](image)

Synthesis of \( \text{N,N-terephthaloyl-bis[N-(thiocarbamoyl-N-ethylaniline)] (21g)} \)
Yield: 68\%, m.p: 138-140°C
IR(KBr) cm\(^{-1}\): 3386, 2970, 1265, 1480, 1127,
Synthesis of N,N-terephthaloyl-bis[N-thiocarbamoyl-N,N-dimethylamine] (21h)

Yield: 77% , m.p: 123-127°C  
IR(KBr) cm\(^{-1}\): 3386,3278,2970,2932,2369,2105,1531,1265,1480, 1127,1054

Fig.5. IR spectrum of N,N terephthalolyrbis(1-(thiocarbamoyl N,N-dimethylamine) (21h)

Attempted synthesis of 4,4’-phenylene-bis[5-(3,5-di-t-butyl-4-hydroxybenzoyl)-2-(disubstituted) thiazoles (19a-h)

The synthesis of the targeted 4,4’-phenylene-bis[5-(3,5-di-t-butyl-4-hydroxybenzoyl)-2-(disubstituted) thiazoles (19a-h) was next explored. Thus, 0.05 mmol of terephthaloyl-bis[1-(3-N,N-disubstituted)thioureas (21a-h) in DMF was reacted with 0.1 mmol α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20) at 80-95°C. The reaction was worked up after the disappearance of the starting thioureas as indicated by TLC analysis. The reaction mixture was added with stirring to ice cold water and the solid product obtained was washed with water, and collected by
filtration. Attempts to purify these crude products or the analysis of their homogeneity and purity by TLC were frustrating as by the complete insolubility of these products in common organic solvents. For this reason we planned to elaborate our synthetic target to include the corresponding monophenolic aminothiazoles (23)

As part of this attempt, a bond disconnection analysis for the targeted thiazole (23) was first attempted as shown in scheme III. This analysis indicated that the synthetic target monophenolic aminothiazoles (23) could be accessed by the reaction of 0.1 mmol α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20) with acylthioureas of the type Ph-CO-NH-CS-NR\(^1\)R\(^2\) (22).
Synthesis of 1-Benzoyl-3-(N,N-disubstituted)thioureas (22a-h)

The required 1-benzoyl-3-(N,N-disubstituted)thioureas (22a-h) were obtained by following a procedure that was described above for preparing the bisacylthioureas (21) except that benzoyl chloride was used in place of terephthaloyl chloride. The benzoyl isothiocyanate so obtained was reacted without isolation with acyclic and cyclic secondary dialkyl and alkylaryl amines to obtain 1-Benzoyl-3-(N,N-disubstituted)thioureas (22a-h).

Synthesis of 1-Benzoyl-3-(N,N-pyrrolidinyl)thiourea (22a)

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocyanate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added and stirred for another 30 minutes. The aqueous layer was separated from the organic layer by using a 100 mL separating funnel and to the dried organic layer pyrrolidine (0.015 mol, 0.76 mL) was added. And stirring continued for another 30 more minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed, dried and recrystallized from ethanol/water (m.p: 135°C).

Yield: 72%, m.p: 135-148°C

IR(KBr) cm\(^{-1}\): 3517, 3052, 3133, 2957, 2945, 2909, 2865, 2350, 2116, 1825, 1639, 1133

Fig. 6. IR spectrum of 1-Benzoyl-3-(N,N-pyrrolidinyl)thiourea (22a)
Synthesis of 1-Benzoyl-3-(N,N-piperidinyl)thiourea (22b)

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocyanate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added and stirred for another 30 minutes The aqueous layer was separated from the organic layer by using a 100 mL separating funnel and to the dried organic layer piperidine (0.015 mol, 1.56 mL) was added. And the stirring continued for another 30 minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed, dried and recrystallized from ethanol/water (m.p 125°C).

Yield: 69%, m.p: 125-128°C

IR(KBr) cm\(^{-1}\): 3155, 3058, 2850, 2824, 2112, 1989, 1903, 1545, 1540, 1520, 1240, 1132

Fig.7. IR spectrum of 1-Benzoyl-3-(N,N-piperidinyl)thiourea (22b)

Synthesis of 1-Benzoyl-3-(N,N-morpholinyl)thiourea (22c)

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocyanate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added and stirred for another 30 minutes The aqueous layer was separated from the organic layer by using a 100 mL separating funnel and to the dried organic layer morpholine (0.015
mol, 1.297 mL) was added. The stirring was continued for another 30 minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed, dried and recrystallized from ethanol/water (m.p 143°C).

Yield: 64% m.p: 143-145°C
IR(KBr) cm⁻¹: 3503, 3230, 2950, 2909, 2842, 2105, 1803, 1538, 1516, 1263, 1110

Fig.8. IR spectrum of 1-Benzoy-3-(N,N-morpholinyl)thiourea (22c)

**Synthesis of 1-Benzoyl-3-(N,N-methylpiperazinyl)thiourea (22d)**

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocyanate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added and stirred for another 30 minutes. The aqueous layer was separated from the organic layer by using a 100 mL separating funnel dried and to the dried organic layer N-Methylpiperazine (0.015 mol, 1.650 mL) was added. And the stirring continued for another 30 minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed, dried and recrystallized from ethanol/water (m.p 171°C)

Yield: 76 % m.p: 171-175°C
IR(KBr) cm⁻¹: 3058, 3155, 2824, 2567, 1989, 1506, 1345, 1132, 858
Synthesis of 1-Benzoyl-3(N,N-1,2,3,4-tetrahydroquinolinyl)thiourea (22e)

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocyanate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added, stirring continued for another 30 minutes. The aqueous layer was separated from the organic layer by using a 100mL separating funnel and to the dried organic layer, 1,2,3,4-tetrahydroquinoline (0.015 mol, 1.88 mL) was added. And the stirring continued for another 30 more minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed, dried and recrystallized from ethanol/water (m.p 143.0°C)

Yield: 67%, m.p: 143-145°C

IR(KBr) cm⁻¹: 3707,3177, 2958, 2338,1989,1598,1508,1482,1382,1173,1051

Fig.9. The IR spectrum of 1-Benzoyl-3(N,N-1,2,3,4-tetrahydroquinolinyl)thiourea (22e)

Synthesis of 1-Benzoyl-3-(N-methyl-N-phenyl)thiourea (22f)

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocyanate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added and stirred for another 30 minutes. The aqueous layer was separated from the organic layer by using a 100 mL separating funnel and to the dried organic layer, N-methylaniline (0.015 mol, 1.62 mL) was added. And the stirring continued for another 30 more
minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed dried and recrystallized from ethanol/water (m.p 134°C)

Yield: 70% m.p: 134-135°C
IR(KBr) cm⁻¹: 3547,3058,3189,3155,2338,2054,1550,1485,1367,1105

Fig.10. IR spectrum of 1-Benzoyl-3-( N,N-N-methyl-N-phenyl)thiourea (22f)

**Synthesis of 1-Benzoyl-3-(N-ethyl-N-phenyl)thiourea (22g)**

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocyanate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added and stirred for another 30 minutes. The aqueous layer was separated from the organic layer by using a 100 mL separating funnel and to the dried organic layer N-ethylaniline (0.015 mol, 1.893 mL) was added. And the stirring continued for another 30 more minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed, dried and recrystallized from ethanol/water (m.p 140°C)

Yield: 79% m.p: 140-143°C
IR(KBr) cm⁻¹: 3498, 3181, 3052,2945,2865,1865,1650, 1508,1300,1233,
Fig.11. IR spectrum of 1-Benzoyl-3-(N-ethyl-N-phenyl)thiourea (22g)

**Synthesis of 1-Benzoyl-3-(N,N-dimethylanilinethiourea (22h)**

To 10 mL of benzene in a round bottom flask, 5 mL of saturated solution of potassium thiocynate was added and to this tetrabutylammonium bromide (0.2 g) was added and stirred for 30 minutes. To this 0.015 mol of benzoyl chloride was added and stirred for another 30 minutes. The aqueous layer was separated from the organic layer by using a 100 mL separating funnel and to the dried organic layer dimethylamine (0.015 mol, 0.89 mL) was added. And the stirring continued for another 30 more minutes. The reaction mixture was then transferred to a beaker and petroleum ether was added to separate the precipitated thiourea. The product filtered, washed, dried and recrystallized from ethanol/water (m.p 154°C)

Yield: 61% m.p: 154-158°C

IR(KBr) cm⁻¹: 3397,2898,2854,2447,1702,1516,1510,1471,1419,1300,1236,1114
Synthesis of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles (23a-h)

The synthesis of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles (23a-h) was next attempted. Thus, an equimolar (0.005 mol each) amount of 1-benzoyl-3-(N,N-disubstituted)thiourea and α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20) in DMF was reacted at 80-95°C for about 2 to 3 hours generally. The reaction mixture was worked up by stirring into ice cold water and the solid product obtained was collected by filtration and washed with water. In these cases, the solubility was better and the product could be crystallized from organic solvents.

Synthesis of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a)

1-Benzoyl-3-(N,N-pyrrolidinyl)thiourea (22a, 0.005 mol, 0.195 g) was dissolved in 3 mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.5mmole, 0.1636 gm) dissolved in 3 mL DMF is warmed separately and added to the warmed solution of 1-benzoyl-3-(N,N-pyrrolidinyl)thiourea (22a) in portions and allowed to react for 2.5 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water. The crude product was recrystallized from ethanol/water (m.p 154°C)
Synthesis of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(piperidin-1-yl)thiazole (23b)

1-Benzoyl-3-(N,N-piperidinyl)thiourea (22b, 0.005 mol, 0.117 g) was dissolved in 3 mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.005 mol, 0.16 g) dissolved in 3mL DMF is warmed separately and added to the warmed solution of 1-benzoyl-3-(N,N-piperidinyl)thiourea (22b) in portions and allowed to react for 3 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water. The crude product was recrystallized from ethanol/water (m.p.121°C)

Synthesis of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(morpholin-4-yl)thiazole (23c)

1-Benzoyl-3-(N,N-morpholinyl)thiourea (22c, 0.005 mol, 0.211 g) was dissolved in 3 mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.005 mol, 0.16 g) dissolved in 3 mL DMF is warmed separately and added to the warmed solution of 1-benzoyl-3-(N,N-morpholinyl)thiourea (22c) in portions and allowed to react for 2.5 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water. The crude product was recrystallized from ethanol/water (m.p.130°C)

Synthesis of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(N-methylpiperazine-4-yl)thiazole (23d)

1-Benzoyl-3-(N,N-methylpiperazinyl)thiourea (22d, 0.005 mole, 0.234gm) was dissolved in 3mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.005 mole,0.1636gm ) dissolved in 3mL DMF is warmed separately and added to the warmed solution of 1-benzoyl-3-(N,N-methylpiperazinyl)thiourea (22d) in portions and allowed to react for 2.5 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water. The crude product was recrystallized from ethanol/water (m.p.122°C)

Synthesis of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(1,2,3,4-tetrahydroquinolin-1-yl)thiazole (23e)

1-Benzoyl-3(N,N-1,2,3,4-tetrahydroquinolinyl)thiourea (22e, 0.005 mol, 0.25 g) was dissolved in 3 mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.005 mol,0.16 g ) in 3 mL DMF is warmed separately and
added to the warmed solution of 1-benzoyl-3(N,N-1,2,3,4-tetrahydroquinolinyl)thiourea (22e) in portions and allowed to react for 2.5 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water.

Synthesis of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-N-methylaniline-1-yl)thiazole (23f)

1-Benzoyl-3-(N-methyl-N-phenyl)thiourea (22f, 0.005 mol, 0.134 g) was dissolved in 3 mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.005 mol, 0.16 g) dissolved in 3 mL DMF is warmed separately and added to the warmed solution of 1-Benzoyl-3-(N-methyl-N-phenyl)thiourea (22f) in portions and allowed to react for 2.5 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water. The crude product was recrystallized from ethanol/water (m.p. 133°C)

Synthesis of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-N-ethylaniline-1-yl)thiazole (23g)

1-Benzoyl-3-(N-ethyl-N-phenyl)thiourea (22g, 0.005 mole, 0.142 g) was dissolved in 3 mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.005 mole, 0.1636 g) dissolved in 3 mL DMF is warmed separately and added to the warmed solution of 1-Benzoyl-3-(N-ethyl-N-phenyl)thiourea (22g) in portions and allowed to react for 2.5 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water. The crude product was recrystallized from ethanol/water (m.p. 134°C)

Synthesis of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-N,N-dimethylaniline-1-yl)thiazole (23h)

1-Benzoyl-3-(N,N-dimethylanilinethiourea (22h, 0.005mol, 0.104 g) was dissolved in 3 mL DMF and warmed in hot water. α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20, 0.005 mol, 0.16 g) dissolved in 3 mL DMF is warmed separately and added to the warmed solution of 1-Benzoyl-3-(N,N-dimethylanilinethiourea (22h) in portions and allowed to react for 2.5 hours under base free conditions. The product was isolated by pouring the reactant to ice-cold water. The crude product was recrystallized from ethanol/water (m.p. 132°C).
Antioxidant capacity assay for 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles (23a-h)

2,2-Diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity

The DPPH radical scavenging efficacy of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles was evaluated based on a reported procedure (Brand-Williams et al., 1995). Briefly, aliquots of the test samples leading to a concentration range of 100-500 µM were mixed with a methanolic solution of DPPH (1.5 mL, 25 mg/L), kept in the dark for 30 min and the absorbance was measured at 517 nm against control. BHT served as the standard. The percentage radical scavenging activity, calculated as Scavenging Effect (SE %) = (1-A_{sample}/A_{control}) x 100, where A is the absorbance, was plotted against concentration to obtain 50% inhibition (IC_{50}) values.
Section V

Results and discussion

The reaction of terephthalolylbis[1-(3-N,N-disubstituted)thioureas (21-h) with α-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20) yielded a solid product in all cases attempted. However, the product was found to be insoluble in all common organic solvents including DMF and DMSO. The check for homogeneity and purity could not be done by TLC and crystallization was also not possible. This unexpected insolubility was thus found to be a problem. The FTIR spectrum of the crude product showed that no significant amount of starting material was present, by comparison with the IR spectrum of the starting bisthioureas. It also seemed to indicate the expected product formation, but not conclusively. Sonication, microwave heating etc also did not improve the solubility. Attempts to purify the compound using solvent extraction also were unsuccessful as homogeneity could not be established afterwards. Lack of solubility in methanol and acetonitrile precluded ESI or APCI mass spectral analysis. Moreover the insolubility in methanol posed a problem with antioxidant assays, the usual solvent for these assays being methanol. The IR spectra of the crude products and the expected structure of the product are given below.

![IR spectrum of 4,4'-phenylene-bis[5-(3,5-di-t-butyl-4-hydroxybenzoyl)-2-(morpholin-4-yl)thiazole]](image)

Fig.13. IR spectrum of 4,4'-phenylene-bis[5-(3,5-di-t-butyl-4-hydroxybenzoyl)-2-(morpholin-4-yl)thiazole]
Based on these circumstances we further planned to make a structural modification. By keeping aspects like larger the molecules of the solute the larger is their molecular weight and their size. So if the molecule is bigger it is very difficult for the solvent molecules to surround them and thus the solubility reduces. A general rule can be found that larger particles are generally less soluble or the factors like pressure
and temperature are the same than out of two solutes of the same polarity, the one with smaller particles is usually more soluble. Also one of the criterions for an orally active drug by Lipinski's rule of five is that the molecular mass of a drug compound should be less than 500 daltons. Keeping all these factors, we planned to modify our synthetic target to monophenolic aminothiazoles (23).

The reaction of 1-benzoyl-3-(N,N-disubstituted)thioureas (22a-h) with \( \alpha \)-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20) yielded a solid products in all cases. Thus, the reaction between 1-Benzoyl-3-(pyrrolidinyl) thiourea (22a) and \( \alpha \)-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone (20) under base free conditions, as detailed in the experimental, yielded an light yellow orange colored compound as the sole product. The elucidation of the structure was done by IR, \(^1\)H NMR and \(^{13}\)C NMR.

As shown in fig. 15 the IR spectrum of the product showed a sharp band at 3617 cm\(^{-1}\) indicating the presence of the O-H group. Bands due to \( \nu_c-H \) stretch were seen at 2946 and 2865 cm\(^{-1}\). The O-H group is indicated by the band at 3613 cm\(^{-1}\) and the \( \nu_C=O \) stretch is assigned to the strong band shown at 1553 cm\(^{-1}\). The conjugation of the 2-amino group nitrogen lone pairs over to the 5-CO group could be the reason for this low value for carbonyl stretch.

![Fig.15. IR spectrum of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a)](image-url)
The $^1$H NMR spectra (Fig. 16 & Fig. 18) showed a singlet at δ 1.40 which was assigned to di-tert-butyl group. A multiplet at δ 7.04-7.34 established the presence of five aromatic hydrogens. A singlet present at δ 2.04 is assigned to hydrogen attached to thiazole nitrogen. Expansion of the region δ 6.6-8.2. is shown in fig. 17. The $^{13}$C NMR spectrum (fig.18) of the compound showed twenty two signals. The peaks at 30 ppm and 35 ppm were indicative of the tert-butyl group. The presence of C=O carbon is assigned to the peak of 187 shown in the spectrum. On the basis of the above spectral data evidences, we assigned the structure of the product obtained from (22a) and (20) as 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a)

Fig.16. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a)
Fig. 17. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a). Expansion of the region δ 6.6-8.2.

Fig. 18. $^{13}$C NMR spectrum (400 MHz, CDCl$_3$) of 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a)
All these evidences establishes the structure to be

Fig 19. 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a)

After the successful completion of the synthesis 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a) we checked the solubility of the compound and find that it is soluble in all major organic solvents. Then we planned to check the generality of the synthesis and solubility of monophenolic aminothiazoles (23). For generating more examples of monophenolic aminothiazoles (23) we introduced several variations by introducing cyclic secondary dialkyl and alkylaryl amines. This investigation led us to produce seven more thiazoles namely 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(piperidin-1-yl)thiazole (23b), 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(morpholin-4-yl)thiazole (23c), 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(N-Methylpiperazine-4-yl)thiazole (23d), 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(1,2,3,4-tetrahydroquinolinol-1-yl)thiazole (23e), 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-N-methylaniline-1-yl)thiazole (23f), 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-N-ethylaniline-1-yl)thiazole (23g) and 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-N,N-dimethylamine-1-yl)thiazole (23h). The details of their structures are given in Table 2.
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure</th>
<th>No.</th>
<th>Structure</th>
</tr>
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<td>23h</td>
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Table2. Structure of 5-(3,5-diter-Butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles (23a-h)

A few representative spectra are presented of the compounds is shown in Fig 20 to 24
Fig. 20. $^{13}$C NMR spectrum (100MHz, CDCl$_3$) 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(piperidin-1-yl)thiazole (23b)

Fig. 21. $^{13}$C NMR spectrum (100MHz, CDCl$_3$) (3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl- N-methylaniline -1-yl)thiazole (23f)
Fig. 22. $^1$H NMR spectrum (400 MHz, CDCl$_3$) 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(piperidin-1-yl)thiazole (23b) (expansion from 7 to 10 ppm)

Fig. 23. $^{13}$C NMR spectrum (100MHz, CDCl$_3$) 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(piperidin-1-yl)thiazole (23b)
Fig. 24. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(1,2,3,4-tetrahydroquinolin-1-yl)thiazole (23e)
Computational Studies

The antioxidant properties of molecules have recently been extensively investigated by computational methods. The results of such studies provide information about the electronic orbitals and their energy levels. Among the several parameters calculated, the computation of the electronic distribution of the highest occupied molecular orbital HOMO and the lowest unoccupied molecular orbital LUMO, their shape, energy and the energy gap have been studied in relation to antioxidant properties. It is reported that the HOMO energy level, expressed in eV, is a good indicator of antioxidant activity (Al-Amiery et al., 2017). It is further observed that a higher HOMO energy level indicates a better electron-donating ability of the molecule under study. This electron donating ability can be taken as an indicator for AO activity. Thus, the HOMO energy value as an electronic orbital energy level based parameter for assessing the antioxidant ability has been reported (Borgers et al., 2013). Such an observation has also been made in the case of phenolic antioxidants recently (Muhamed et al., 2013).

In the present study, computations were performed using Gaussian software and the molecular geometry states were optimized in vacuum typically by taking 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a) as an example.

The electronic density distribution of the HOMO of the bisphenolic thiazole 19a was computed after optimizing its geometry in vacuum. The optimized structure (Fig.25.) and the HOMO (Fig.26.) is shown below. It can be seen that the electronic density is not at the phenolic part, but is on the thiazole-benzene-thiazole part. The energy of the HOMO has been computed to be (-) 5.577 eV. A similar calculation on BHT indicated that its HOMO energy to be (-) 5.879 eV. Therefore, between these two molecules, computation shows that the bisphenolic thiazole (19a) has a higher HOMO energy value and hence would be a better AO molecule.
Fig. 25. Optimized geometry of the bisphenolic thiazole (19 a) obtained by computation

Fig. 26. The HOMO of bisphenolic thiazole 19 a obtained by computation

Later, when it became evident that the physical properties of these bisphenolic thiazole hybrids are not favorable, we turned our attention to the monophenolic thiazole. The computational results of the optimized geometry (Fig. 27) HOMO energy and electronic distribution pattern (Fig. 28) are shown below.
The HOMO energy of 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(pyrrolidin-1-yl)thiazole (23a) was calculated to be (-) 5.268 eV and thus is found to be higher than that of the bisphenolic thiazole system. The electronic density appears thiazole part of the molecule. This study seemed to suggest that between the bis and monophenolic thiazole molecular systems, the monophenolic thiazole has a higher HOMO energy. Hence it could be a better AO system.
DPPH radical scavenging activity

The antioxidant activity of monophenolic 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles (23a-f) were assessed based on DPPH radical scavenging assay. The 1,2,3,4-tetrahydroquinolin-1-yl derivative (23 e) (EC50 500 μM) showed better radical scavenging activity than the N-methyl-N-phenyl derivative (23f) (EC50 520 μM), N-ethyl-N-phenyl derivative (23g) (EC50 731 μM) and the piperidin-1-yl derivative (23b) (EC50 1066 μM), in comparison with the standard BHT (EC50 157 μM) (Table 3). Morpholin-1-yl (23c) and pyrrolidin-1-yl (23a) derivatives failed to show any significant activity. On comparison with the antioxidant activity of BHT as a reference, the 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles (23) are not very active.

<table>
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<td>&gt;&gt;1000</td>
</tr>
<tr>
<td>23b</td>
<td>1066</td>
</tr>
<tr>
<td>23c</td>
<td>&gt;&gt;1000</td>
</tr>
<tr>
<td>23 e</td>
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<tr>
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<td>BHT</td>
<td>157</td>
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</table>

Table 3. DPPH radical scavenging activity of X1-6
Section VI

Summary

Heterocyclic is the major structural moiety in natural products like alkaloids (morphine, reserpine), antibiotics (penicillin) and also had wide applications in pharmaceutical and drug chemistry. Thiazole based HIV-protease inhibitor ritonavir was used for the combination therapy of highly active antiretroviral therapy (HAART). Among the thiazoles, 2-aminothiazoles hold a special place due to its activity against allergies, hypertension, inflammation, tumor, cancer, bacterial and HIV infections. Our laboratory has reported the biological activities of many 2-aminothiazole derivatives. And as part of our long standing interest in 2-aminothiazoles synthesis had led us to plan a hybrid molecular system that incorporates a hindered phenolic unit appended to a 2-aminothazole unit.

The specific objectives of the project were:

1. To synthesize a group of:
   (i) 4,4’-phenylene-bis[5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-2-[(disubstituted amino]thiazoles

   (ii) To evaluate the antioxidant properties of the newly synthesized 2-aminothiazoles using standard assay protocol like DPPH assay

   (iii) Computational studies on the proposed synthetic targets

2. Based upon these results, further molecular design changes will be effected.

Due to the insolubility problem of the thiazoles we modified our structural motif to 5-(3,5-di-tert-Butyl-4-hydroxybenzoyl)-4-phenyl-2-[(disubstituted amino]thiazoles

Organization of the project report and results

The report is structured in nine sections. The section I present the abstract of the work. The section II has two parts in which the first part is an introduction for antioxidants and the second part be a review literature of antioxidants which gives a brief introduction to the biological activities of aminothiazoles and a detailed review on the synthesis of 2-amino thiazoles and bisthiazoles.
The objectives of the project work are summarized in section III. The materials and method for the synthesizes of thiazoles of the type (19) and (23) is explained in section IV.

The results and discussion of the project is explained in section V. This section details why we opted a structural modification and why we adopted the change in structural motif. Section VI is devoted mainly for the computation studies and HOMO- LUMO energy calculations. A review of DPPH radical scavenging activity is detailed in Section VII. The summary of the report is given in section VI. The outcomes of the project are explained in Section VII. The salient achievements are given in the section VII.i. The publication for the work is given in Section VII.ii. The Papers/Posters presented in conferences is given in VII.iii. Section VIII is completely devoted for explaining scope for the future work. The complete references are given in section IX.
Section VII

Outcome of the project

- Synthesis of 8 bisacylthioureas of the type $R_1^1R_2^2N\text{-CS\text{-CO-[1,4-C}_6\text{H}_4\text{-CO\text{-CS\text{-NR}_1^1R_2^2]}}$.
- The bisacyl thioureas were reacted with $\alpha$-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone to synthesis 4,4’-phenylene-bis[5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-2-[(disubstituted amino]thiazoles] 
- Synthesis of 8 monoacylthioureas of the type $C_6\text{H}_5\text{-CO\text{-CS\text{-NR}_1^1R_2^2}$.
- Monoacylthioureas were reacted with $\alpha$-bromo-3,5-di-tert-butyl-4-hydroxyacetophenone to access 2-amino-5-(2,6-di-t-butyl-4-hydroxyphenyl)-4-phenylthiazoles. Their structure was elucidated using the spectral studies.
- The antioxidant activity of the compounds are elucidated using DPPH assay.
- These compounds showed only one third the antioxidant activity of the standard reference compound BHT ($EC_{50}$ 157µM).
- 5-(3,5-di-tert-butyl-4-hydroxybenzoyl)-4-phenyl-2-(1,2,3,4-tetrahydroquinolin-1-yl)thiazole (23e) showed antioxidant activity of 500 µM which is expressed as $EC_{50}$ values.
- Thus the monophenolic 2 aminothiazole derivatives presently synthesized shows only moderate antioxidant activity based on the DPPH assay.
- The computational studies show that between bis and monophenolic thiazole molecular systems, the monophenolic thiazole has a higher HOMO energy.
Salient achievements

- Synthesized eight hitherto unreported mono phenolic aminothiazoles of the type 2-amino-5-(2,6-di-t-butyl-4-hydroxybenzoyl)-4-phenylthiazoles
- Antioxidant properties of the thiazoles were evaluated using DPPH assay
- Based on computational work, the potential antioxidant activity of the bis and mono phenolic thiazoles were estimated by calculating the HOMO energy values
Research publications

Papers/Posters presented in Conferences

1. Sandhya, V. S , Priyi, R M., Synthesis of hindered phenol-aminothiazole hybrids, Ctric-2017, Department of chemistry, Cusat, Cochin, February 4 and 5, 2017

2. Sandhya, V. S , Akhila, V. R. Krishnapriya, K.G Rajasekharan, K.N., Priyi, R M., One pot access to antioxidant, aminothiazole-hindered phenol hybrids, Sitca-2016, Department of chemistry, Chrstitian College, Kattakada July 19 and 20, 2017
Scope for future work

The present study has initially targeted the synthesis of bisphenolic amino thiazoles. These were expected to show good antioxidant activity due to presence of two hindered phenolic units in the compound. However the insolubility made further studies on these compounds difficult. As a result the structure was modified and the synthetic target was altered to mono phenolic amino thiazoles. These on antioxidant evaluation showed only moderate antioxidant activity. Based on these results, it appears that the presence of a keto group para to the phenolic group could be a reason reducing the electron density of the phenolic unit. On the basis of this, future structural design should focus on either the reduction of the C=O unit to an alcohol or designing molecular hybrids bearing no C=O in the 5th position of the thiazole ring.
References


