Ibn Al-Haitham Journal for Pure and Applied Sciences
Journal homepage: jih.uobaghdad.edu.iq
PISSN: 1609-4042, EISSN: 2521-3407
IHJPAS. 2024, 37(4)

A Brief Review of Phenolic Antioxidant and their Biological Activity

Raied Mustafa Shakir[1,*], Husam Salman Jasim[2] and Shaimaa Abed Saoud[3]

[1,2,3]Department of Chemistry, College of Education for Pure Science (Ibn Al-Haitham), University of Baghdad, Baghdad, Iraq.

*Corresponding Author.

Received: 14 February 2023 Accepted: 28 August 2023 Published: 20 October 2024

doi.org/10.30526/37.4.3287

Abstract

Antioxidant compounds are considered essential materials because they prevent or reduce free radical side chain reactions, which cause much damage. It is widely acknowledged that these damages are a major contributing factor to numerous diseases. Phenolic antioxidants are considered one of the most important antioxidant species. There is ample evidence that the antioxidant substances found in fruits and vegetables can prevent various diseases such as cancer, heart disease, diabetes, and cataracts. The food and pharmaceutical industries also make extensive use of it. Additionally, quite several phenolic medicinal compounds for anticancer, anti-inflammatory, anti-necrotic, hepato-protective, and neuroprotective purposes possess antioxidant abilities. The synthetic phenolic compounds exhibited remarkable antioxidant capacity in addition to various biological activities. These facts prompted the researchers to focus on newly synthesized phenolic compound derivatives and explore their biological activities, particularly those containing heterocyclics in their molecular structures. The biological activities of heterocyclic compounds are widely recognized.

Keywords: Antioxidant, biological activity, heterocyclic, phenolic compounds, reactive oxygen species, synthetic compounds.

1. Introduction

Free radicals, as well as the ROS (reactive oxygen species), are well known as extremely harmful molecules; moreover, they are believed to be the main source of much impairment in proteins, lipids, DNA, and carbohydrates [1]. A large number of illnesses were caused by the existence of free radicals, such as cancer [2], inflammation [3], degenerative diseases, and chronic diseases [4]. Antioxidant compounds are significant because they can prevent any damage that free radicals may cause. Furthermore, many researchers have emphasized that anti-inflammatory medicines and anticancer drugs possess antioxidant abilities [5]. There are two major types of antioxidants. The first one is the natural antioxidant, and the second type is the synthetic antioxidant, as demonstrated in **Figures 1** and **2**. The antioxidant compounds usually share common structure features that account for their antioxidant properties, such as the existence of a multi-phenol group as in polyphenols and flavonoids, long-range conjugation as in α-tocotrienol (vit E) [6], and the existence of a steric hindrance phenolic group [7, 8].

Two mechanisms can be used by the antioxidant substrates to delay or prevent the propagation reaction of the free radical. The first mechanism is known as hydrogen-atom transfer (HAT) [9], as demonstrated in lipid peroxidation, as shown in **Scheme 1**.

The next mechanism recognized is single electron transfer (SET) [10], as presented in **Scheme 2**. Phenolic compounds are considered one of the most important antioxidant materials. This work will present the most significant phenolic antioxidant compounds. The compound coded as AO-60, as in **Figure 3** is commonly used to protect rubber from oxidation in commercial settings [11].

Numerous phenolic compounds have demonstrated therapeutic and diverse biological activity. For instance, researchers proved compound R-830 to be a potent inhibitor of guinea pig lung lipoxygenases and an efficient anti-inflammatory drug [12]. The compound coded E-5110 is recognized for its medicinal uses as a non-steroidal anti-inflammatory agent [13], while KME-4 in **Figure 4** is recognized for its analgesic capability besides its anti-inflammatory properties [14]. **Table 1** illustrates the significant antioxidant and various biological activities of several *di-tert-butyl* phenols attached to heterocyclics.

2. Materials and Methods

2.1 Synthesized phenolic derivative

The 5-Aryl Oxadiazole derivatives containing di-*tert*-butyl phenol were synthesized, and their antioxidant capability was screened utilizing DPPH and FRAP assays. This study found the type and position of the substituted group at the aryl group play a significant role in enhancing or minimizing the antioxidant ability [23], as depicted in **Figure 5**.

3. Results and Discussion

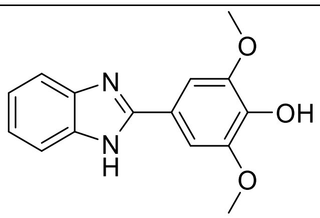
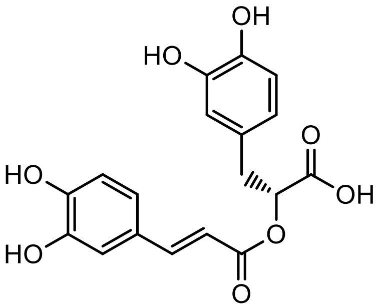
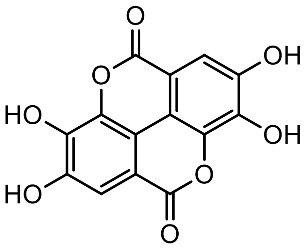
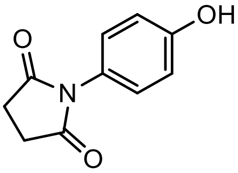
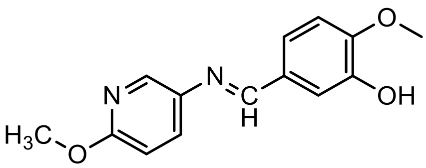
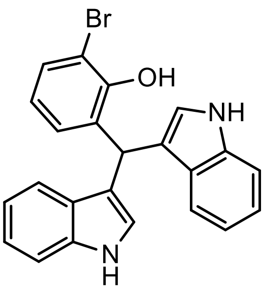
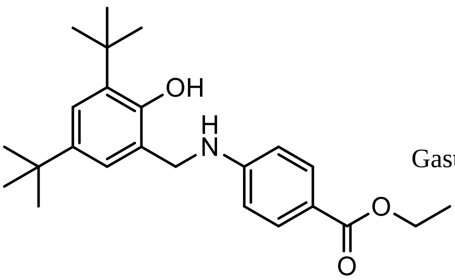
The synthesized 1,3,4-oxadiazole ring derivatives at position six of the 2-methyl phenol are illustrated in **Figure 6**. This work tested the antioxidant and antibacterial activity of these compounds. This study concluded an inverse relationship between increasing the antioxidant ability and the antibacterial capacity [24].

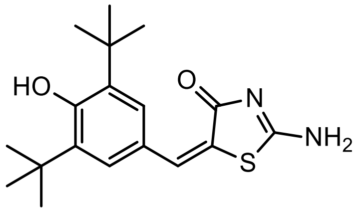
Figure 7 shows the synthesis of hydro-pyrimidine, a compound with a multi-phenol group. These compounds presented antibacterial activity in addition to their significant antioxidant ability. Furthermore, the simulation study of these compounds exhibited potential inhibitors of the gyrase enzyme [25]. The fused triazole of 2-methyl phenol derivatives, shown in **Figure 8** exhibits significant antioxidant activity. In addition to exhibiting considerable antioxidant activity, these compounds demonstrated potent tubulin inhibitors when compared to colchicine as a reference [26].

Bromo Phenolic derivatives were synthesisied as new sagnificant antioixdant capacity [27] as depicted in **Figure 9**. Phenolic thiazolidine-2,4-dione derivatives were synthesized and investigated for their antioxidant ability using a fragment assay, a phosphomolybdate assay for total antioxidant capacity (TAC), a reducing power assay (RP), and the bond dissociation energy [28]. This study found that the number of hydroxyl groups and O-alkyls play an important role in enhancing antioxidant ability in **Figure 10**.

New phenolic derivatives containing imidazole rings in **Figure 11** were synthesized. These compounds exhibited remarkable antioxidant activity [29]. The 2,6-bis-(1,1-dimethylethyl) phenol derivatives in **Figure 12** were synthesized. These compounds exhibited a noteworthy anti-inflammatory capacity [30].

Table 1. Some phenolic antioxidant and biological activities.

No	Structure	Biological activity	Reference
1		NFkB inhibitor for treating cancers	[15]
2		anticancer	[16]
3		antidiabetic activity	[17]
4		anti-inflammatory	[18]
5		antibacterial	[19]
6		antifungal	[20]
7		Gastroprotective Activity	[21]

8		anti-inflammatory drugs (**Darbufelone)**	[22]

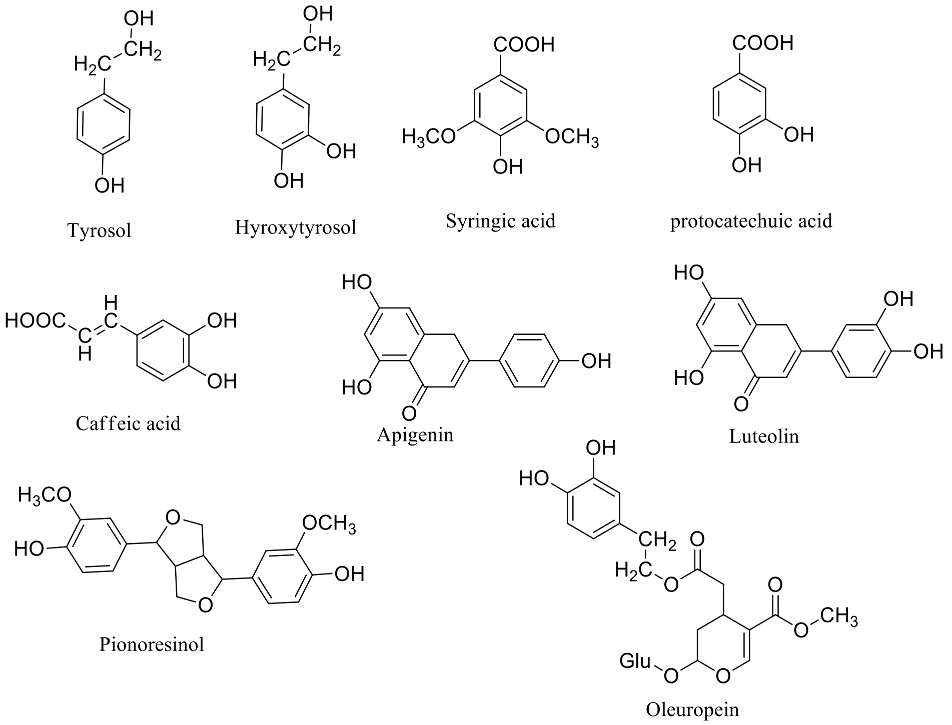


Figure 1. Some natural phenolic compounds in plants and fruits.

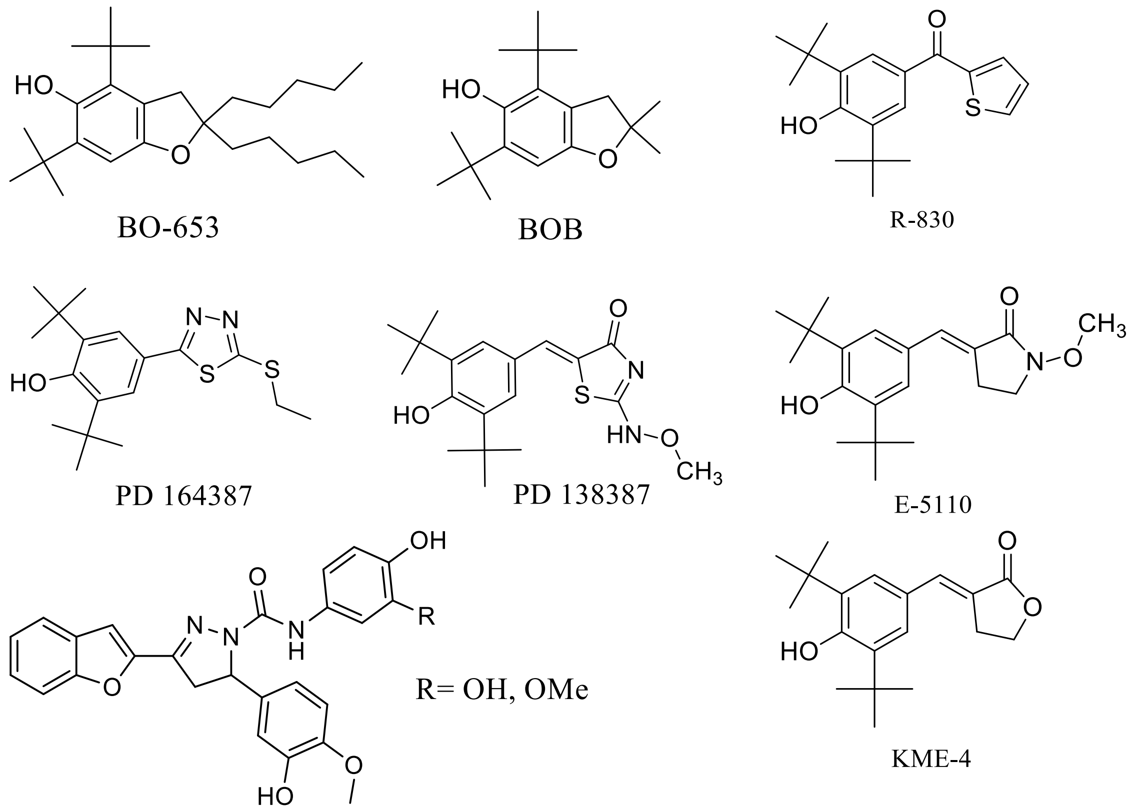
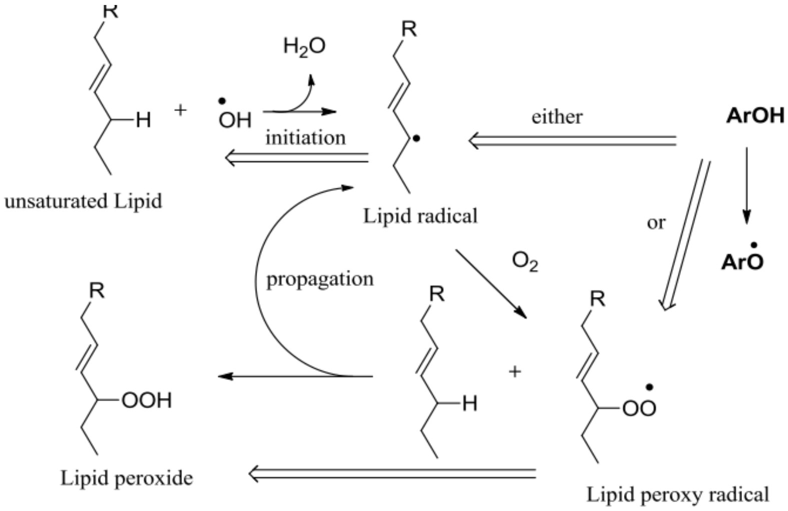


Figure 2. Some synthetic phenolic compounds.



Scheme 1. Rote of HAT mechanism.

$$R\dot{O}_2 + ArOH \longrightarrow R\bar{O}_2 + Ar\overset{\bullet +}{O}H \quad \text{electron transfer}$$

$$Ar\overset{+\bullet}{O}H + H_2O \rightleftharpoons Ar\dot{O} + H_3\overset{+}{O} \quad \text{deprotonation equilibirum}$$

$$R\bar{O}_2 + H_3\overset{+}{O} \rightleftharpoons ROOH \quad H_2O \quad \text{hydroperoxide formation}$$

Scheme 2. Rote of SET mechanism.

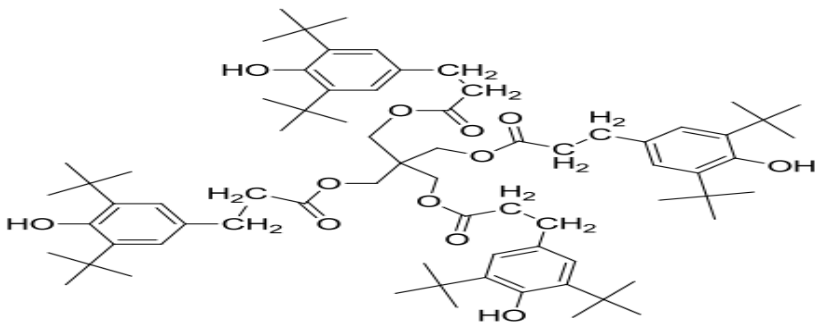
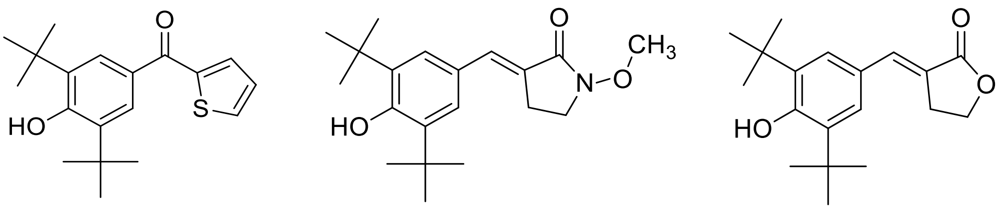


Figure 3. The AO-60 compound.



R-830 E-5110 KME-4

Figure 4. Structure of R-830, E-5110, KME-4.

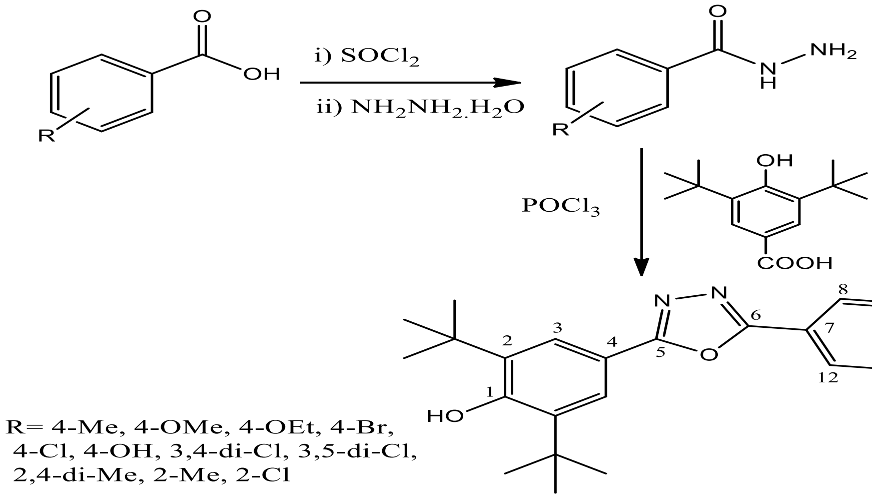


Figure 5. Synthesized rote of 5-Aryl Oxadiazole derivative as antioxidant.

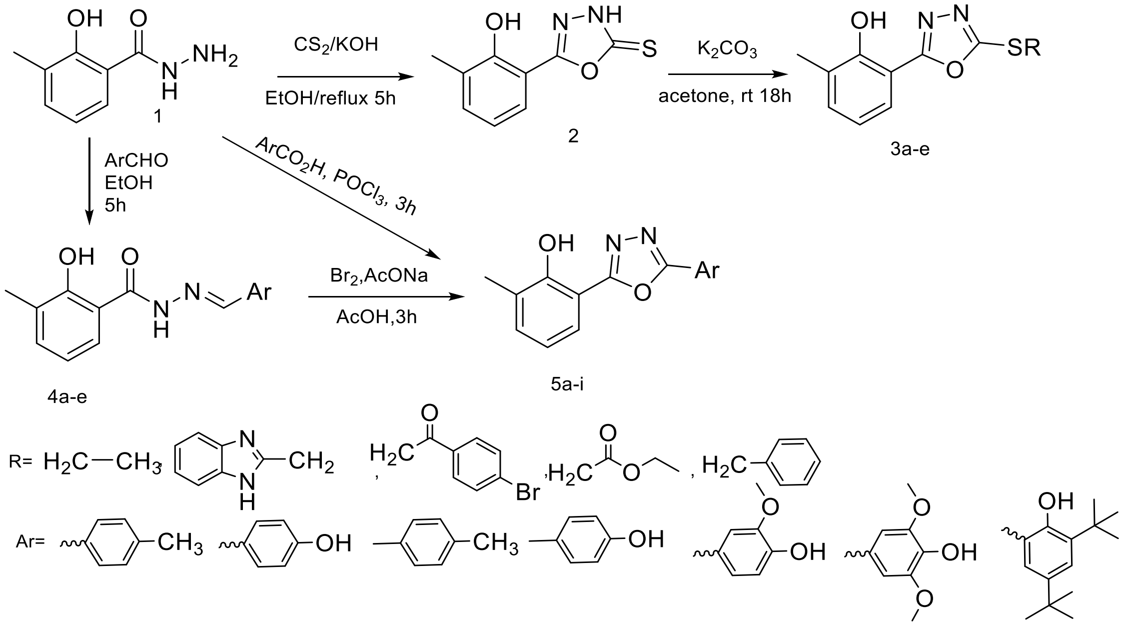
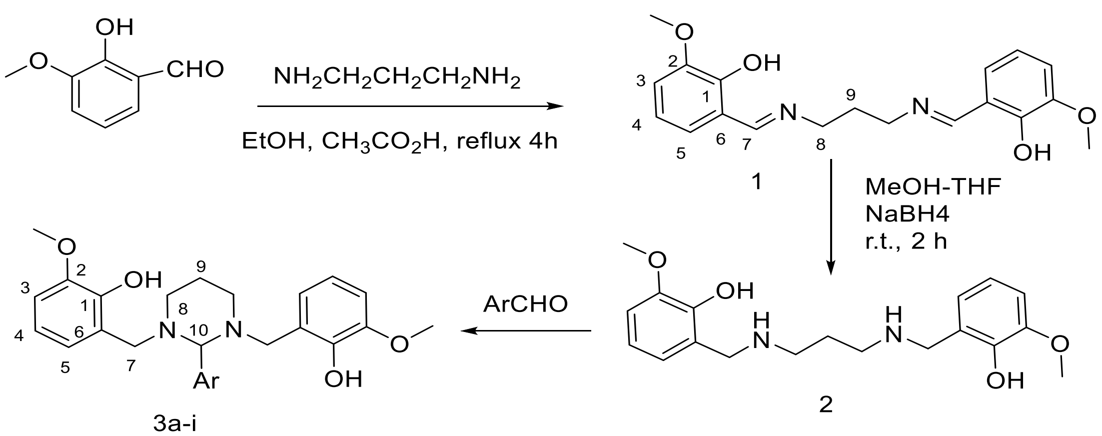


Figure 6. Synthesis rote of 2-methylphenol derivative as promising antioxidant and antibacterial.



Ar = 4-Clph,4-Brph, 4-NO_2-ph,4-Meph, 4-OHph, 3-OMe-4-OHph,
3-OMe-2-OHph,3,5-diOMe-4-OHph,3.5-di-tert-Bu-2-OH-ph

Figure 7. Hydro-pyrimidine moiety of multi phenol.

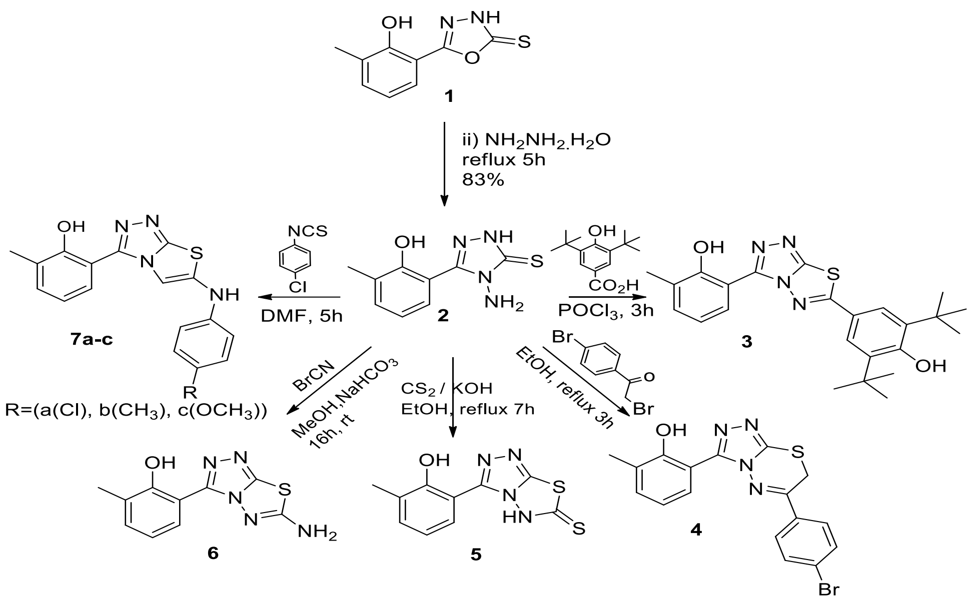
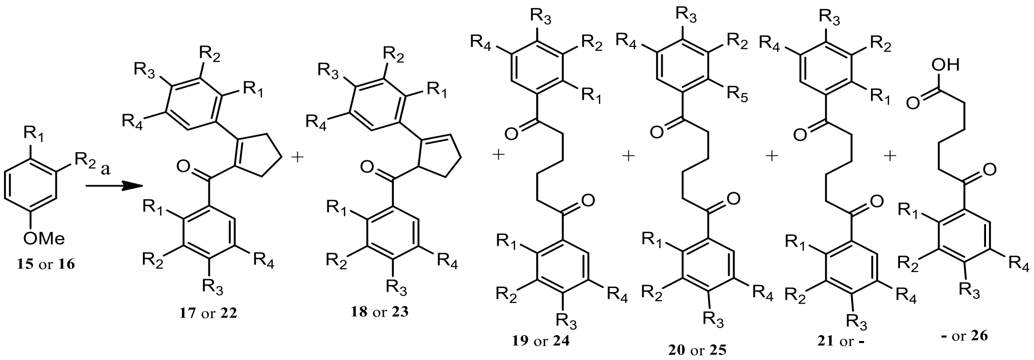
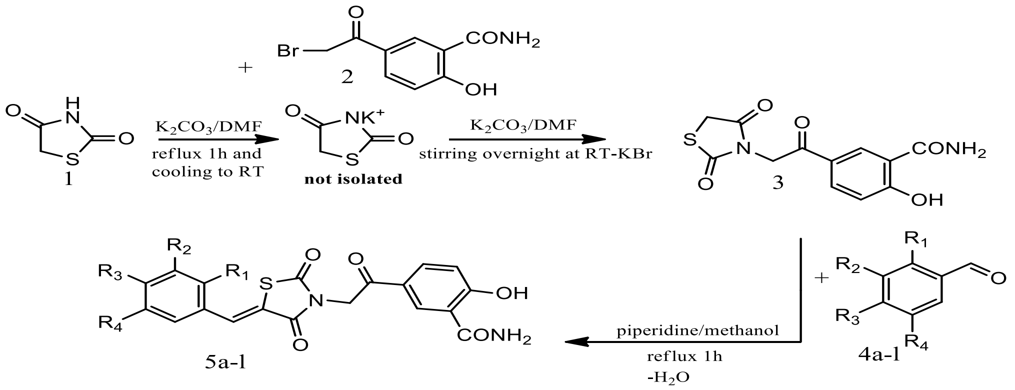


Figure 8. Rote of synthesis fused triazole containing phenol as tubulin inhibitor.



R= H, R_2= OMe for **15**, R_2= H, R_1= OMe for **16**, R_1=R_3=OMe, R_2=R_4=H for **18** and **19**, R_1=R_3=OMe, R_2=R_4=H, R_5=OH for **20**, R_1=OH, R_3=OMe, R_2=R_4=H for **21**, R_2=R_3=H, R_1=R_4=OMe for **22,23,24** and **26**, R_1=R_4=OMe, R_2=R_3=H, R_5=OH for **25**.

Figure 9. Bromophenol derivative as significant antioxidant.



Compound		R_1	R_2	R_3	R_4
4a	5a	H	H	OH	H
4b	5b	H	OH	H	H
4c	5c	H	OCH_3	OH	H
4d	5d	OH	H	H	H
4e	5e	H	OH	OCH_3	H
4f	5f	OH	OH	H	H
4g	5g	OH	H	H	Br
4h	5h	H	OCH_2CH_3	OH	H
4i	5i	OH	OCH_2CH_3	H	H
4j	5j	H	OCH_3	OH	OCH_3
4k	5k	OH	H	OH	H
4l	5l	H	OH	OH	H

Figure 10. Synthetic phenolic thiazolidine-2,4-dione derivatives.

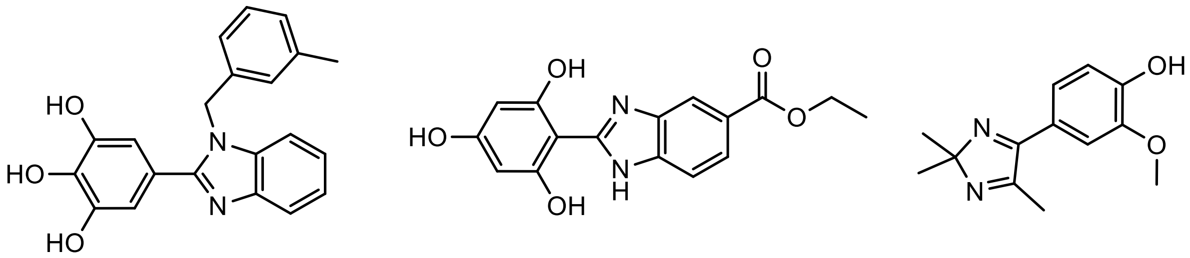
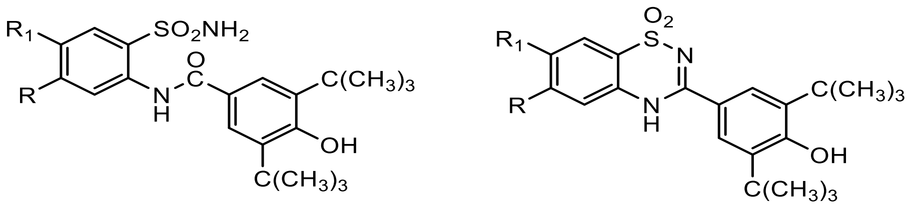


Figure 11. Imidazole derivative consist phenol.



No.	R	R1	M.P °C	Formula
1	H	H	184-185	$C_{21}H_{28}N_2O_4S$
2	Cl	Cl	222-224	$C_{21}H_{26}Cl_2N_2O_4S$
3	H	H	319-322	$C_{21}H_{26}N_2O_3S$
4	Cl	Cl	>360	$C_{21}H_{24}Cl_2N_2O_3S$

Figure 12. Phenolic derivatives exhibited anti-inflammatory capacity.

4. Conclusion

Natural phenolic compounds gain important attention due to their widespread existence in plants. especially those that exhibit pharmaceutical effects. The synthetic phenolic compound also received serious attention from researchers due to its significant antioxidant ability and various biological activities. Phenolic derivatives containing heterocyclics gain most attention due to their significant biological activity besides their antioxidant abilities.

Acknowledgment

The authors thank the University of Baghdad/ College of Education for Pure Science (Ibn Al-Haitham) for approving this work.

Conflict of Interest

The authors declare there are no conflicts of interest. All authors alone are accountable for the content and writing of the paper.

Funding

There is no financial support.

Ethical Clearance

This work has been approved by the Scientific Committee at the University of Baghdad/ College of Education for Pure Science (Ibn Al-Haitham).

References

1. Shacter, E. Quantification and Significance of Protein Oxidation in Biological Samples. *Drug Metabolism Reviews* **2000**, *32(3-4)*, 307-326. https://doi.org/10.1081/DMR-100102336.
2. Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M. T.; Mazur, M.; Telser, J. Free Radicals and Antioxidants in Normal Physiological Functions and Human Disease. *The International Journal of Biochemistry & Cell Biology* **2007**, *39(1)*, 44-84. https://doi.org/10.1016/j.biocel.2006.07.001.
3. Silpak, B.; Rintu, D.; Ena Ray, B. Role of Free Radicals in Human Inflammatory Diseases. *AIMS Biophysics* **2017**, *4(4)*, 596-614. https://doi.org/10.3934/biophy.2017.4.596.
4. Khan, F.; Garg, V. K.; Singh, A. K.; Kumar, T. Role of Free Radicals and Certain Antioxidants in the Management of Huntington's Disease: A Review. *Journal of Analytical and Pharmaceutical Research* **2018**, *7(4)*, 386-392. https://doi.org/10.15406/japlr.2018.07.00256.
5. Grigalius, I.; Petrikaite, V. Relationship between Antioxidant and Anticancer Activity of Trihydroxyflavones. *Molecules (Basel, Switzerland)* **2017**, *22(12)*, 2169. https://doi.org/10.3390/molecules22122169.
6. Flora, S.J. Structural, Chemical and Biological Aspects of Antioxidants for Strategies Against Metal and Metalloid Exposure. *Oxidative Medicine and Cellular Longevity* **2009**, *2(4)*, 191-206. https://doi.org/10.4161/oxim.2.4.9112.
7. Shakir, R.M. Synthesis and Antioxidant Ability of Some 4-(((4-(5-(Aryl)-1,3,4-Oxadiazol-2-Yl) Benzyl)Oxy)Methyl)-2,6-Dimethoxyphenol. *Oriental Journal of Chemistry* **2016**, *32(5)*, 2611-2619. http://dx.doi.org/10.13005/ojc/320533.
8. Mustapha, A. Influence of Steric Hindrance on the Antioxidant Activity of Some Schiff Base Ligands And Their Copper(II) Complexes. *Oriental Journal of Chemistry* **2014**, *30*, 1529-1534. http://dx.doi.org/10.13005/ojc/300410.
9. Ostrea, J.E.M.; Cepeda, E.E.; Fleury, C.A.; Balun, J.E. Red Cell Membrane Lipid Peroxidation and Hemolysis Secondary to Phototherapy. *Acta Paediatrica Scandinavica* **1985**, *74(3)*, 378-381. https://doi.org/10.1111/j.1651-2227.1985.tb10987.x
10. Wright, J.S.; Johnson, E.R.; DiLabio, G.A. Predicting the Activity of Phenolic Antioxidants: Theoretical Method, Analysis of Substituent Effects, and Application to Major Families of Antioxidants. *Journal of the American Chemical Society* **2001**, *123(6)*, 1173-1183. https://doi.org/10.1021/ja002455u.
11. Chifei Wu, T-A.Y.; Nakamoto, Y.; Ishida, Sh-I.; Kubota, S.; Nitta, K.H. Organic Hybrid of Chlorinated Polyethylene and Hindered Phenol. II. Influence of the Chemical Structure of Small Molecules on Viscoelastic Properties. *Journal of Polymer Science Part B: Polymer Physics* **2000**, *38(11)*, 1496–1503. https://doi.org/10.1002/(SICI)1099-0488(20000601)38:11.
12. Moore, G.G.S.K. 2,6-Di-Tert-Butyl-4-(2'-Thenoyl)Phenol(R-830): A Novel Nonsteroidal Anti-Inflammatory Agent with Antioxidant Properties. *Agents Actions* **1982**, *12(5-6)*, 674-683. https://doi.org/10.1007/BF01965078.
13. Shirota, H.C.K.; Ono, H.; Yamamoto, H.; Kobayashi, S.; Terato, K.; Ikuta, H.; Yamatsu, I.; Katayama, K. Pharmacological Properties of the Novel Non-Steroidal Antiinflammatory Agent N-Methoxy-3-(3,5-Di-Tert-Butyl-4-Hydroxybenzylidene)Pyrrolidin-2 -One. *Arzneimittelforschung* **1987**, *37(8)*, 930-936. PMID: 3499909.
14. Hidaka, T.H.K.; Yamashita, T.; Watanabe, K.; Hiramatsu, Y.; Fujimura, H. Analgesic and Anti-Inflammatory Activities in Rats of Alpha-(3,5-Di-T-Butyl-4-Hydroxybenzylidene)-Gamma-Butyrolactone (KME-4), and its Intestinal Damage. *The Journal of Pharmacy and Pharmacology* **1986**, *38(10)*, 748-753. https://doi.org/10.1111/j.2042-7158.1986.tb04483.x.
15. Cheemanapalli, S.; Palaniappan, C.; Mahesh, Y.; Iyyappan, Y.; Yarrappagaari, S.; Kanagaraj, S. In Vitro and in Silico Perspectives to Explain Anticancer Activity of a Novel Syringic Acid Analog ((4-(1H-1, 3-Benzodiazol-2-Yl)-2, 6-Dimethoxy Phenol)) Through Apoptosis Activation and Nfkb

Inhibition In K562 Leukemia Cells. *Computers in Biology and Medicine* **2023**, *152*, 106349. https://doi.org/10.1016/j.compbiomed.2022.106349.
16. Tatipamula, V.B.; Kukavica, B. Phenolic Compounds As Antidiabetic, Anti-Inflammatory, and Anticancer Agents and Improvement of their Bioavailability by Liposomes. *Cell Biochemistry and Function* **2021**, *39(8)*, 926-944. https://doi.org/10.1002/cbf.3667.
17. Grewal, A.S.; Sharma, N.; Singh, S.; Arora, S. Molecular Docking Studies of Phenolic Compounds from Syzygium cumini with Multiple Targets of Type 2 Diabetes. Journal of Pharmaceutical Technology. *Research and Management* **2018**, *6(2)*, 125-133.https://doi.org/10.15415/jptrm.2018.62009.
18. Zulfiqar, S.; Haroon, M.; Baig, M.W.; Tariq, M.; Ahmad, Z.; Tahir, M.N.; Akhtar, T. Synthesis, Crystal Structure, Anti-Cancer, Anti-Inflammatory Anti-Oxidant and Quantum Chemical Studies of 4-(Pyrrolidine-2,5-Dione-1-Yl)Phenol. *King Fahd University of Petroleum and Minerals* **2021**, *1224*, 129267. https://doi.org/10.1016/j.molstruc.2020.129267.
19. Mariswamy, V.H.; Bindya, S.; Costa, R.A.; Prasad, S.K.; Shivamallu, C.; Begum, S.M.; Veerapur, R.; Syed, A.; Kollur, S.P. 2-Methoxy-5-(6-Methoxypyridin-3-Yl-Imino-Methyl)Phenol and its Transition Metal Complexes as Potent Antibacterial Agents: Synthesis, Characterization, Theoretical Investigations and Biological Evaluation. *Results in Chemistry* **2021**, *3*, 100120. https://doi.org/10.1016/j.rechem.2021.100120.
20. Jiang, Y.; Su, L.; Liao, Y.; Shen, Y.; Gao, H.; Zhang, Y.; Wang, R.; Mao, Z. Synthesis And Antifungal Evaluation of Phenol-Derived Bis(Indolyl)Methanes Combined with FLC Against Candida Albicans. *Bioorganic and Medicinal Chemistry Letters* **2022**, *58*, 128525. https://doi.org/10.1016/j.bmcl.2022.128525.
21. Halabi, M.F.; Shakir, R.M.; Bardi, D.A.; Al-Wajeeh, N.S.; Ablat, A.; Hassandarvish, P.; Hajrezaie, M.; Norazit, A.; Abdulla, M.A. Gastroprotective Activity of Ethyl-4-[(3,5-Di-Tert-Butyl-2-Hydroxybenzylidene) Amino]Benzoate Against Ethanol-Induced Gastric Mucosal Ulcer in Rats. *PLOS One* **2014**, *9(5)*, e95908. https://doi.org/10.1371/journal.pone.0095908.
22. Ye, X,Z.W.; Li, Y.; Sun, Y.; Zhang, Y.; Ji, H.; Lai, Y. Darbufelone, a Novel Anti-Inflammatory Drug, Induces Growth Inhibition of Lung Cancer Cells Both in Vitro and in Vivo. *Cancer Chemotherapy and Pharmacology* **2010**, *66(2)*, 277-285. https://doi.org/10.1007/s00280-009-1161-z.
23. Shakir, R.M.; Ariffin, A.; Abdulla, M.A. Synthesis of New 2,5-Di-Substituted 1,3,4-Oxadiazoles Bearing 2,6-Di-Tert-Butylphenol Moieties and Evaluation of their Antioxidant Activity. *Molecules (Basel, Switzerland)* **2014**, *19(3)*, 3436-3449. https://doi.org/10.3390/molecules19033436.
24. Saoud, S.A.; Ali, K.F.; Shakir, R.M. Relationship between the Structure of Newly Synthesized Derivatives of 1,3,4-Oxadiazole Containing 2-Methylphenol and their Antioxidant and Antibacterial Activities. *Oriental Journal of Chemistry* **2017**, *33(4)*, 1781-1798.http://dx.doi.org/10.13005/ojc/330423.
25. Skakir, R.M.; Jasim, H.S.; Saoud, S.A.; Hussain, D.F.; Ali, K.F. Synthesis, Antioxidant, Antibacterial and Docking Structure of New Dihydro-Pyrimidine Derivatives Containing Multi Phenol. *Journal of Pharmaceutical Negative Results* **2022**, *13(2)*, 57-68. https://doi.org/10.47750/pnr.2022.13.02.009.
26. Shakir, R.M.; Jasim, H.S.; Hussain, D.F. Synthesis, Antioxidant Activity and Molecular Docking Study of 1,2,4-Triazole and their Corresponding Fused Rings Containing 2-Methylphenol. *International Journal of Drug Delivery Technology* **2021**, *11(2)*, 501-5011. https://doi.org/10.25258/ijddt.11.2.47.
27. Artunc, T.; Menzek, A.; Taslimi, P.; Gulcin, I.; Kazaz, C.; Sahin, E. Synthesis and Antioxidant Activities of Phenol Derivatives from 1,6-Bis(Dimethoxyphenyl)Hexane-1,6-Dione. *Bioorganic Chemistry* **2020**, *100*, 103884. https://doi.org/10.1016/j.bioorg.2020.103884.
28. Marc, G.; Stana, A.; Oniga, S. D.; Pîrnău, A.; Vlase, L.; Oniga, O. New Phenolic Derivatives of Thiazolidine-2,4-dione with Antioxidant and Antiradical Properties: Synthesis, Characterization, In

Vitro Evaluation, and Quantum Studies. *Molecules (Basel, Switzerland)* **2019**, *24(11)*, 2060. https://doi.org/10.3390/molecules24112060.

29. Gerasimova, E.L.; Gazizullina, E. R.; Borisova, M.V.; Igdisanova, D.I.; Nikiforov, E.A.; Moseev, T. D.; Varaksin, M.V.; Chupakhin, O.N.; Charushin, V.N.; Ivanova, A.V. Design and Antioxidant Properties of Bifunctional 2H-Imidazole-Derived Phenolic Compounds-A New Family of Effective Inhibitors for Oxidative Stress-Associated Destructive Processes. *Molecules (Basel, Switzerland)* **2021**, *26(21)*, 6534. https://doi.org/10.3390/molecules26216534.
30. Costantino, L.; Parenti, C.; Di Bella, M.; Zanoli, P.; Baraldi, M. Anti-Inflammatory Activity of Newly Synthesized 2,6-Bis-(1,1-Dimethylethyl)Phenol Derivatives. *Pharmacological Research* **1993**, *27(4)*, 349-358. https://doi.org/10.1006/phrs.1993.1034.