

Cytotoxic Activity of New Thiol Derivatives

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ABSTRACT

This research included synthesized ten new compounds (1–10) based on alkyl halides, and estimated their anti-cancer effectiveness. All prepared products are proven by Proton nuclear magnetic resonance (¹H NMR) and infrared spectroscopy (IR). The anti-cancer effect of compounds 6, 9, and 10 were assessed on MCF-7 breast cancer in human cells, then WRL68 cancer cells. Compound 9 revealed to be most strong with IC₅₀ 119.2 µg/mL against MCF-7, while other compounds showed moderate anti-cancer activity. The discoveries of ponder can upgrade the understood of natural exercises of these thiols compounds.

Keywords: Anti-cancer activity, Chloromethylation, Thiols.

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INTRODUCTION

The authors would like to make it clear that thiols come from alkyl halides. It is an important source of sulfur, ordinarily, sodium hydrosulfide or thiourea subsidiaries,¹ sulfide are exceptionally profitable and critical compounds within the various areas, particularly within the amalgamation of natural and pharmaceutical active materials. The alkylation of thiols is the foremost common technique for the blend of thioethers.² Organosulfur chemistry is one of the foremost imperative and important branches of in natural union. Compounds containing C-S bond in specific sulfides have a wealthy date as amazing intermediates in natural chemistry.³ In natural synthesis, sulfides are for the most part utilized for the amalgamation of sulfoxides, sulfones, sulfonamides, sulfonyl chlorides, and olefins.⁴ Within the field of pharmaceutical, organosulfur compounds broadly utilized for treatment of different maladies such as cancer, disease, Alzheimer's, Parkinson, and tuberculosis.⁵ Besides, alkyl aryl sulfides play a critical part within the synthesis of natural products additionally are vital and supplement reagents within the synthesis of the foremost of anti-microbials and restorative dynamic compounds.⁶ Within the field of industry, sulfides play a noteworthy and vital part in most of industry forms particularly in nourishment supplement, natural solvents, scent, and restorative materials generation.⁷ Cancer is utilized as a common term depicting a bunch of roughly 120 diverse maladies, which can influence different parts of the body. It can be moreover characterized as the state characterized by uncontrolled cell expansion and typical tissue attack. Agreeing to the established for wellbeing measurements and assessment

[Institute for Health Metrics and Evaluation (IHME)] report, cancer is the moment driving cause of passing around the world.⁸ Aromatic particles are effectively utilized as crude materials within the petrochemical industry. The inclusion of chloromethyl (-CH₂Cl) bunch on the fragrant of a few compounds permits substitution of numerous capacities. Up to present, the chloromethylated bunches were presented by the Friedel-Crafts alkylation with mono chloromethyl ether (MCME). This compound has been found to be profoundly carcinogenic.⁹ The writing overview uncovered that 4-thiazolidinone and their subsidiaries had a wide run of pharmacological exercises such as anti-inflammatory, pain-relieving, anticonvulsant, and antimicrobial (antibacterial and antifungal).¹⁰ Breast cancer is one of the foremost visit dangerous neoplasms happening in ladies in around the world, and metastasis is the major reason of cancer-related passing in patients.¹¹ Apoptosis is a fundamental life handle for all cellular living beings. Controlled cell passing play about a key part in different organic forms in all creatures, which happen in the midst of commonplace embryogenesis, tissue homeostasis, cell turnover, acknowledgment, and back of safe resistance, the advancement of the worried system, in addition to endocrine subordinate tissue rot.¹²

EXPERIMENTAL

Materials and Methods

Solvents and chemicals were pure reagents. Infrared spectra on record utilize Bruker FTIR spectrophotometer. NMR spectra on record during Varian 500 spectrometer (500 MHz for ¹H NMR, individually utilizing DMSO-d₆. Chemical shifts

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were listed in ppm. Prepared outputs proven by thin-layer chromatography (TLC).

Synthesis of Chloromethylation Derivatives

The 0.02 moles from the aromatic compounds were dissolved in 20 mL ethanol, then 4.5 grams of paraformaldehyde solid and 32 mL for concentration HCl were added to aromatic solution and mixed at room temperature overnight with 3 grams $ZnCl_2$, then filtered the precipitate and washed with distilled water.¹³

Synthesis of Thiols Derivatives

A 0.2 mole of alkyl halides derivatives and 0.2 moles of thiourea in 60 mL of distilled water and add 140 mL of DMF solvent with reflux at 85°C. After 30 minutes, added 4% from NH_4OH for 20 minutes, boiled, and then acidity by 18% HCl. Then cooled the solution and filtered the precipitate and washed by distilled water.¹⁴

DISCUSSION AND RESULTS

This research included the aromatic compounds, which are accompanied by a reaction of aromatic compounds with HCl and paraformaldehyde. Compound to produce the chloromethylation derivatives (1, 2, 3, 4, 5) (Schemes 1 and 2), its beginning material to the preparation of thiols derivatives. This reaction goes ahead under moderate state in ethanol at room temperature to output thiol compound with product percentage (85%). The fashioning of compound (6, 7, 8, 9, 10) was the prepared product was demonstrated to thiol group by (S-H) at 2,584, 2,933 (C-H), 2,864 (C-H), 1,350, 1,293, 1,112 cm^{-1} . The 1H NMR band output 6 for one aromatic peak was obtained at δ 6.7 (s, H-2, H-4, H-5) identical to three aromatic protons; furthermore, the 1H NMR spectrum appeared resonances of CH_2Cl group at δ 4.3 with a single sign, the 1H NMR spectra expose resonances of SH groups at δ 1, 9 of 10 as single signal, the structure of combination were illustrated by 1H NMR and FTIR. We would like to show that laboratory and animal studies and most of the evidence indicate that ginger plant and its active components prevent the growth of cancer cells, such as, colon cancer, skin cancer, and brain cancer. Also, ginger plant has important properties, such as, anti-inflammatory, antioxidant, and anti-mutagenic properties, and other biological activities.¹⁵

Compound 1: 4-(chloromethyl)-2-isopropyl-5-methylphenol

Brown liquid compound in 75% yield, chemical formula $C_{11}H_{15}ClO$, IR ν_{max} cm^{-1} 3500 (OH), 850 (C-Cl). 1H NMR δ (ppm): 7.12 (1H, s, H-2), 7.02 (1H, s, H-5), 2.60 (3H, s, CH_3 -1), 3.18 (1H, m, CH-4), 1.32 (6H, s, $2CH_3$), 5.01 (2H, s, CH_2 -6).

Compound 2: 3-(chloromethyl)-4-hydroxy-5-methoxybenzaldehyde

Black solid compound in 70% yield, chemical formula $C_9H_9ClO_3$, IR ν_{max} cm^{-1} 3300 (OH), 1721 (C=O), 840 (C-Cl). 1H NMR δ (ppm): 8.01 (1H, s, H-2), 7.82 (1H, s, H-6), 3.98 (3H, s, OCH_3 -1), 10.12 (1H, s, CHO), 5.09 (2H, s, CH_2 -5).

Compound 3: 1-(chloromethyl)-2,4-dimethoxybenzene

Red solid compound in 85% yield, chemical formula $C_8H_{11}ClO_2$, IR ν_{max} cm^{-1} : 855 (C-Cl). 1H NMR δ (ppm): 7.73 (1H, s, H-2), 7.12 (1H, d, J = 8.0 Hz, H-4), 7.26 (1H, d, J = 8.0 Hz, H-5), 4.02 (3H, s, OCH_3 -1), 5.14 (2H, s, CH_2 -4).

Compound 4: 2-(chloromethyl)-1,4-dimethoxybenzene

White solid compound in 85% yield, chemical formula $C_9H_{11}ClO_2$, IR ν_{max} cm^{-1} : 860 (C-Cl). 1H NMR δ (ppm): 7.08 (1H, s, H-2), 7.20 (1H, d, J = 8.0 Hz, H-5), 7.30 (1H, d, J = 8.0 Hz, H-6), 3.96 (3H, s, OCH_3 -1), 4.08 (3H, s, OCH_3 -4), 5.06 (2H, s, CH_2 -5).

Compound 5: 5-(chloromethyl)-2-hydroxybenzoic acid

White solid compound in 80% yield, chemical formula $C_9H_{11}ClO_3$, IR ν_{max} cm^{-1} : 3300 (OH), 1700. (C=O), 850 (C-Cl). 1H NMR δ (ppm): 7.42 (1H, d, J = 7.75 Hz, H-3), 7.28 (1H, d, J = 7.75 Hz, H-4), 8.16 (1H, s, H-6), 5.18 (2H, s, CH_2 -5), 11.21 (1H, s, COOH).

Compound 6: (2, 5-dimethoxyphenyl)methanethiol

White solid compound in 85% yield, chemical formula $C_9H_{12}SO_2$, IR ν_{max} cm^{-1} : 770 (C-S), 2584 (S-H). 1H NMR δ (ppm): 7.01 (1H, s, H-2), 7.08 (1H, d, J = 8.0 Hz, H-5), 7.16 (1H, d, J = 8.0 Hz, H-6), 3.91 (3H, s, OCH_3 -1), 3.97 (3H, s, OCH_3 -4), 3.99 (2H, s, CH_2 -5), 1.9 (1H, m, SH) (Figure 1 and Table 1).

Compound 7: (2,4-dimethoxyphenyl)methanethiol

Yellow solid compound in 80% yield, chemical formula $C_8H_{12}SO_2$, IR ν_{max} cm^{-1} : 840 (C-S), 2450 (S-H). 1H NMR δ (ppm): 7.63 (1H, s, H-2), 6.93 (1H, d, J = 8.0 Hz, H-4), 7.21 (1H, d, J = 8.0 Hz, H-5), 4.09 (3H, s, OCH_3 -1), 3.98 (2H, s, CH_2 -4), 1.88 (1H, m, SH).

Compound 8: 4-hydroxy-3-(mercaptomethyl)-5-methoxybenzaldehyde

Black solid compound in 70% yield, chemical formula $C_9H_{10}SO_3$, IR ν_{max} cm^{-1} : 3400 (OH), 1715 (C=O), 750 (C-S), 2520 (SH). 1H NMR δ (ppm): 8.08 (1H, s, H-2), 7.71 (1H, s, H-6), 3.92 (3H, s, OCH_3 -1), 10.02 (1H, s, CHO), 4.01 (2H, s, CH_2 -5), 1.5 (1H, m, SH).

Compound 9: 2-hydroxy-5-(mercaptomethyl) benzoic acid

White solid compound in 88% yield, chemical formula $C_9H_{12}SO_3$, IR ν_{max} cm^{-1} : 3300 (OH), 1720 (C=O), 800 (C-S), 2515 (S-H). 1H NMR δ (ppm): 7.34 (1H, d, J = 8.0 Hz, H-3), 7.14 (1H, d, J = 8.0 Hz, H-4), 8.08 (1H, s, H-6), 4.11 (2H, s, CH_2 -5), 11.09 (1H, s, COOH), 1.7 (1H, m, SH) (Figure 2 and Table 2).

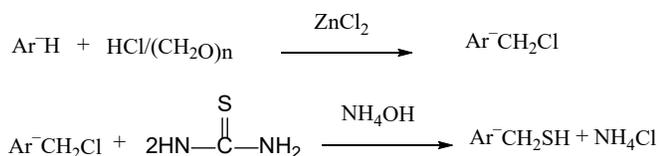
Compound 10: 2-isopropyl-4-(mercaptomethyl)-5-methylphenol

Brown liquid compound in 90% yield, chemical formula $C_{11}H_{16}SO$, IR ν_{max} cm^{-1} : 3500 (OH), 800. (C-S), 2500 (S-H). 1H NMR δ (ppm): 7.10 (1H, s, H-2), 7.00 (1H, s, H-5), 2.58 (3H, s, CH_3 -1), 3.18 (1H, m, CH-4), 1.24 (6H, s, $2CH_3$), 4.12 (2H, s, CH_2 -6), 1.92 (1H, m, SH) (Table 3).

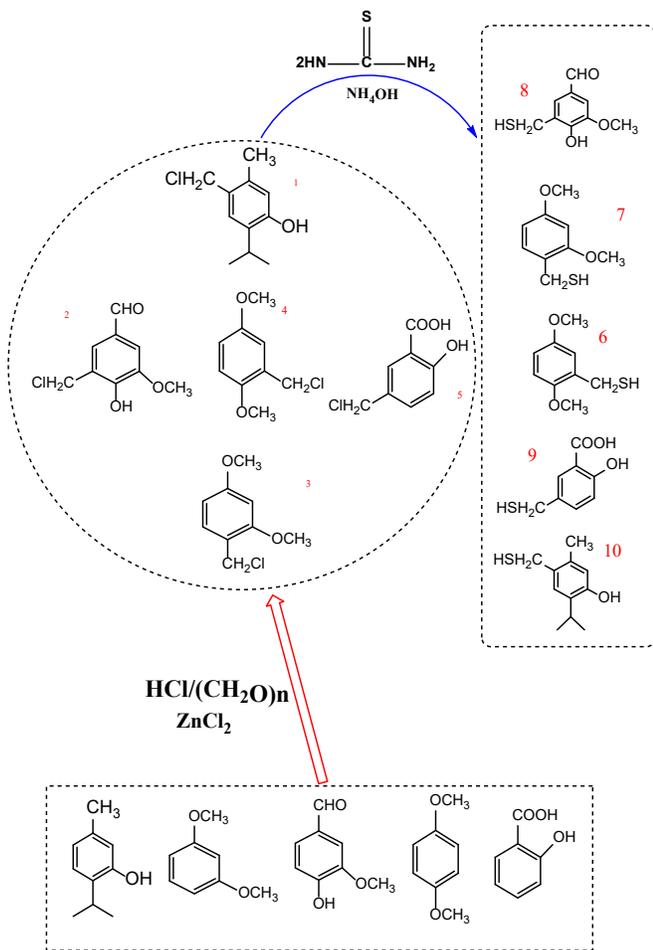
The cytotoxic impacts of three compounds (6, 9, and 10) were studied onto MCF-7 human breast cancer cells and

WRL68 cancer cells. The results revealed that there had been high cell viability inhibitory effects in the cancer cell lines after 48 hours of treatment. The values of IC₅₀ are presented in Figures 3 to 10, respectively.

Chemotherapy is broadly utilized to treat cancer, which is the moment driving cause of passing worldwide.¹⁶



Scheme 1: Chloromethylation and thiol synthesis equations



Scheme 2: Structure of compounds (1–10)

Table 1: Anti-cancer cultures of compound 6

Cell line	MCF-7		WRL68	
Concentration (µg/mL)	Viability%	SD	Viability%	SD
400	54.09	2.568	73.11	1.414
200	65.239	4.945	80.941	0.884
100	74.306	3.069	91.281	4.729
50	82.716	0.821	95.332	1.183
25	95.949	0.904	94.830	0.522
12.5	94.869	0.291	95.949	1.028
6.25	94.83	0.707	95.949	0.2

The breast cancer cells MCF-7 *in vitro* was refined. Once in a way, the cells arrive at their dynamic organize, the

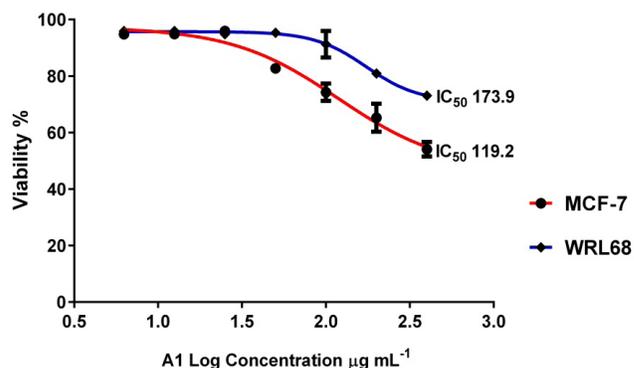


Figure 1: Anti-cancer activity of compound 6

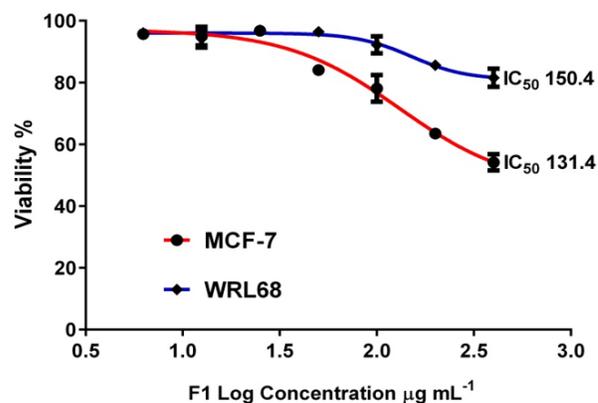


Figure 2: Anti-cancer activity of compound 9

Table 2: Anti-cancer cultures of compound 9

Cell line	MCF-7		WRL68	
Concentration (µg/mL)	Viability%	SD	Viability%	SD
400	54.197	2.655	81.559	2.952
200	63.534	1.27	85.609	1.853
100	78.083	4.323	92.207	2.778
50	84.059	1.381	96.489	1.291
25	96.798	0.936	96.952	1.142
12.5	95.023	3.042	94.29	2.979
6.25	95.679	0.571	96.065	0.116

Table 3: Anti-cancer cultures of compound 10

Cell line	MCF-7		WRL68	
Concentration (µg/mL)	Viability%	SD	Viability%	SD
400	50.949	2.504	69.105	3.908
200	65.864	5.351	84.105	1.772
100	73.241	9.322	94.29	1.831
50	87.639	5.91	95.833	0.306
25	94.56	2.806	95.37	0.904
12.5	96.103	1.706	96.644	0.704
6.25	96.875	0.989	95.679	0.406

concentration of 1×10^4 cells/well and 100 μ L of cell were exchanged into 96-well tissue culture plate, commentary into each well. The cells in the dampen CO_2 were brooded.¹⁷

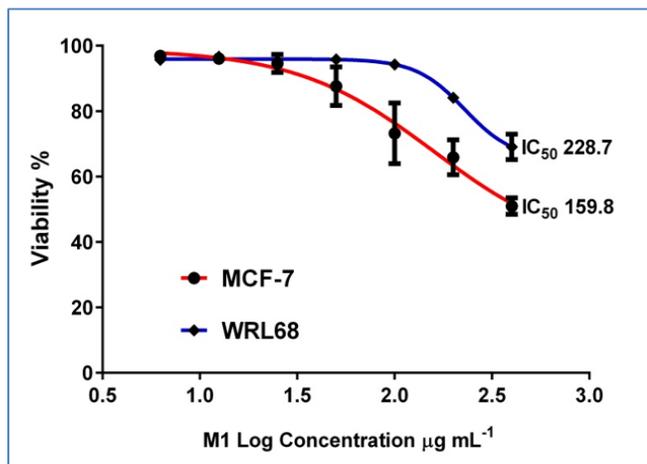


Figure 3: Anti-cancer activity of compound 10

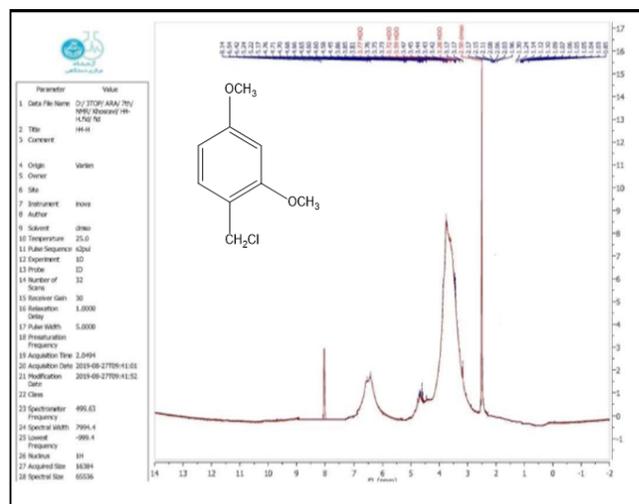


Figure 6: Compound 3 of ^1H NMR spectrum

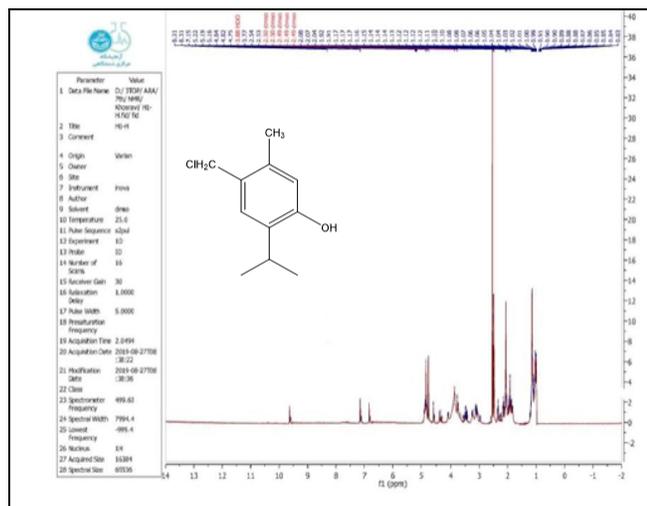


Figure 4: Compound 1 of ^1H NMR spectrum

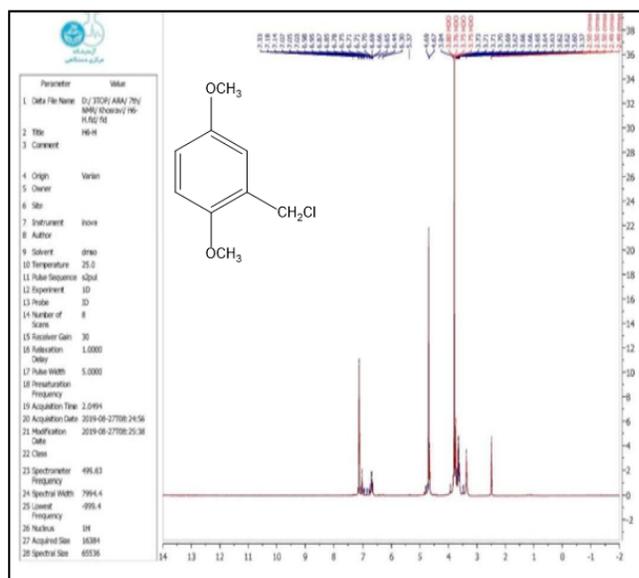


Figure 7: Compound 4 of ^1H NMR spectrum

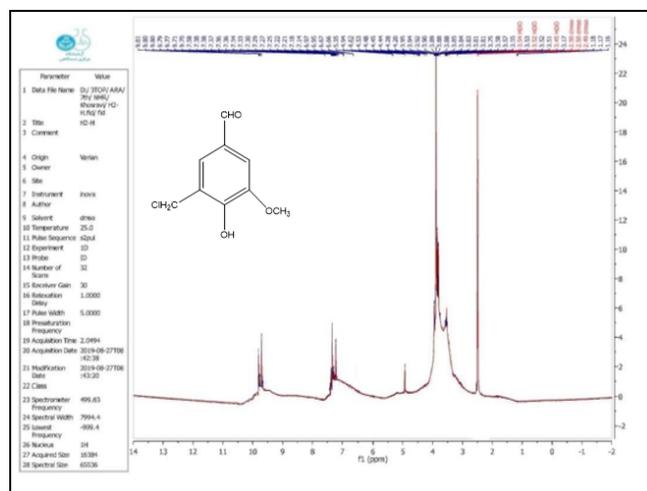


Figure 5: Compound 2 of ^1H NMR spectrum

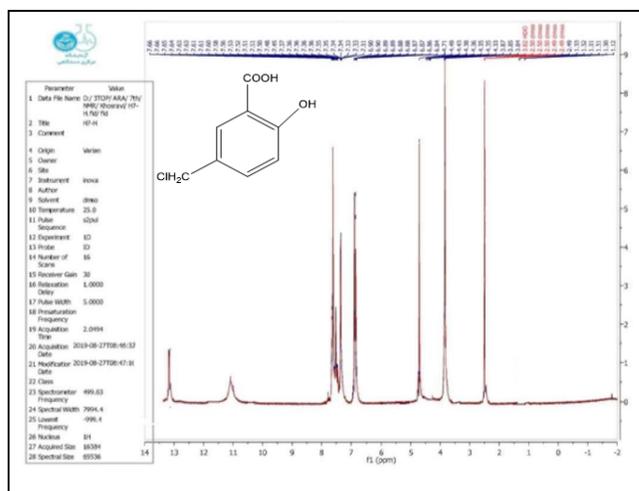


Figure 8: Compound 5 of ^1H NMR spectrum

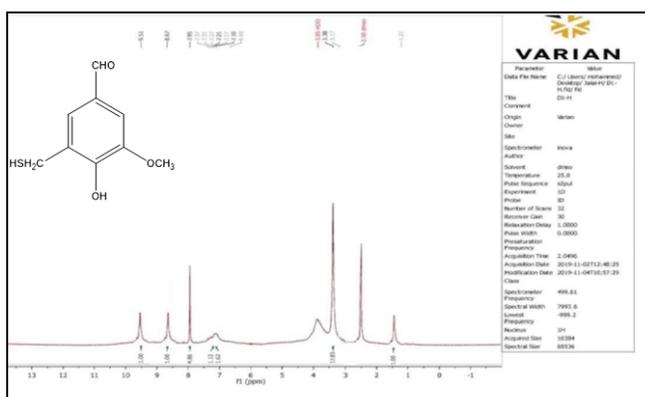
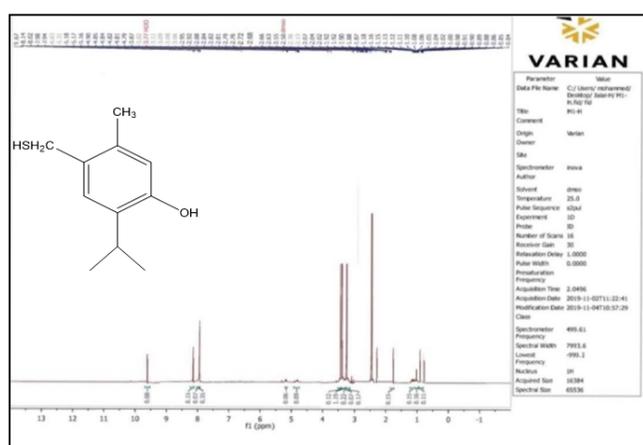
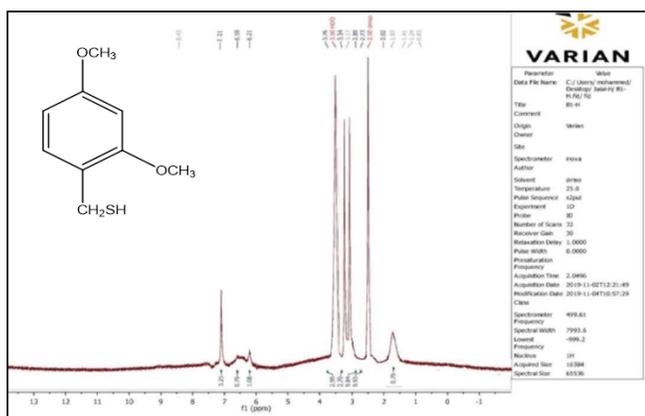
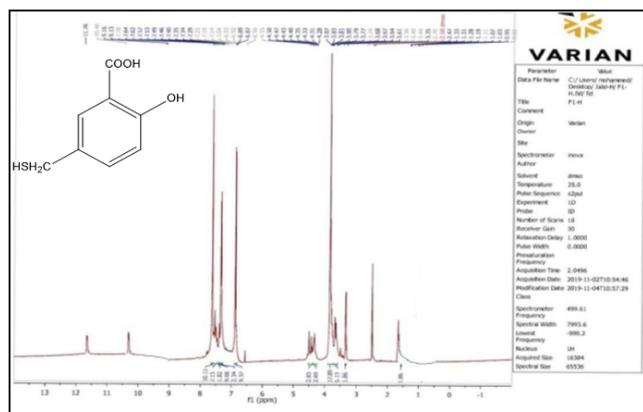
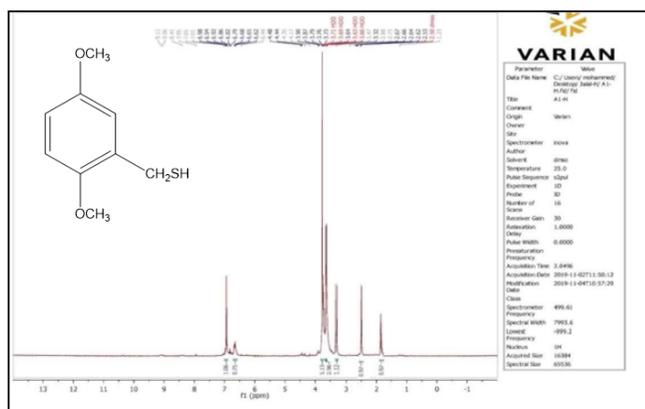


Figure 11: Compound 8 of ¹H NMR spectrum

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REFERENCES

1. CremLyn RJ. An Introduction to Organosulfur Chemistry; John Wiley and Sons: New York, 1996.
2. Clayden J, Greeves N, Warren S, Wothers P. Organic Chemistry; Oxford University Press, 2001.
3. Wu XM, Hu WY. Direct synthesis of diaryl sulfides by copper-

catalyzed coupling of aryl halides with aminothiourea. Chinese Chemical Letters. 2012 Apr 1;23(4):391-394.

4. Shaabani A, Rezayan AH. Catal. Commun. 8 (2007) 1112.
5. Omar SH, Al-Wabel NA. Organosulfur compounds and possible mechanism of garlic in cancer. Saudi Pharmaceutical Journal. 2010 Jan 1;18(1):51-58.
6. Rho SB, Kim BR, Kang S. A gene signature-based approach identifies thioridazine as an inhibitor of phosphatidylinositol-3'-kinase (PI3K)/AKT pathway in ovarian cancer cells. Gynecologic oncology. 2011 Jan 1;120(1):121-7.
7. Smiglak M, Kukawka R, Lewandowski P, Pospieszny H. Cationic derivatives of the plant resistance inducer benzo [1, 2, 3] thiadiazole-7-carbothioic acid S-methyl ester (BTH) as bifunctional ionic liquids. Tetrahedron Letters. 2014 Jun 18;55(25):3565-3568.
8. Brana MF, Cacho M, Gradillas A, de Pascual-Teresa B, Ramos A. Intercalators as anticancer drugs. Curr Pharm Des. 2001;7: 1745–1780. <http://dx.doi.org/10.2174/138161201397113>
9. March, Advanced organic chemistry, reactions mechanism and structure, J. March, Wiley Interscience, 1985, 495.
10. Hassan F, Hameed AA, Alshanon A, Abdullah BM, Huri HZ, Hairunisa N, Yousif E. Asian Journal of Biochemistry. 2015;10 (6):252-266.
11. Majeed GM, Hassan FA. Biochemical *In vitro* Study of Tamoxifen Effect on CYP2D6 Enzyme and Cytotoxicity in Iraqi Premenopausal Women with Breast Cancer, A Thesis

- Submitted to the college of science / Al-Nahrain University as partial fulfillment of the requirements for the Degree of Master of Science in chemistry, 2016.
12. Hamood IFA. Sanad Baqir Mohammed, Biochemical Study on a Group of Iraqi Patients with Thyroid Cancer in Relation to Osteopontin, To the Council of College of Science for Women –University of Baghdad in a Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Chemistry (Biochemistry), 2019.
 13. Eglinton M. New studies in aromatic chloromethylation, Durham theses, Durham University. Available at Durham E-Theses Online. 1992. <http://etheses.dur.ac.uk/5997/>.
 14. Snow AW, Foos EE. Conversion of alcohols to thiols via tosylate intermediates. *Synthesis*. 2003 Mar;2003(04):509-512. ISSN 0039-7881 © Thieme Stuttgart. New York.
 15. Ascar IF, Al-A'Arabi SB, Alshanon AF. Cytotoxicity and Antioxidant Effect of Ginger Gold Nanoparticles on Thyroid Carcinoma Cells. *Journal of Pharmaceutical Sciences and Research*. 2019 Mar 1;11(3):1044-1051.
 16. Meegan MJ, O'Boyle NM. Special Issue "Anticancer Drugs". *Pharmaceuticals* 2019, 12, 134; doi:10.3390/ph12030134.
 17. Obaid AK, Azziz SS, Bakri YM, Nafiah MA, Awang K, Aowda SA, *et al.* Antioxidative and cytotoxic activities of crude and isolated compounds of *P. Lateriflora* (bl.) King. *Journal of Pharmaceutical Sciences and Research*. 2018 Nov 1;10(11):2718-21.