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Synthesis of Some Multi-cyclic Sulfhydryl Donor Compounds Containing 1,2-dithiol-3-thione moiety

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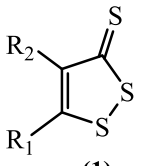
Abstract

1,2-Dithiol-3-thiones are a sulfur containing five membered heterocyclic compounds, which constitute an important class of biologically active compounds owing to their ability to release sulfhydryl (SH) group. In this research a new series of multi-cyclic compounds, containing 1,2-dithiol-3-thione moiety, was synthesized. To pursue this goal, five chalcones (1a-e) were synthesized via the condensation of 1-tetralone with aromatic aldehydes under the influence of 5% ethanolic sodium hydroxide solution. These chalcones were converted to β-ketoesters (2a-e) via its reaction with ethyl acetoacetate in presence of 5% ethanolic sodium hydroxide solution. The thionation of these β-ketoesters with phosphorous penta sulfide in xylene afforded the titled compounds (3a-d). The chemical structures of the synthesized compounds were elucidated by the physical and spectral (IR and NMR) data.

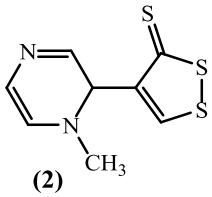
Keywords: Sulfhydryl donor, dithiol-3-thione, oltipraz, thionation, chalcones, β-ketoesters.

1. Introduction

l,2-Dithiole-3-thione compounds (1) are one of pseudo-aromatic dithiol-ethione poly-sulfur heterocyclic compounds [1]. This class of organo-sulfur compounds is one of the most hopeful classes and attracted wide interest as potential cancer chemo-preventive agents [2,3] .



(1)



(2)

1,2-Dithiole-3-thione moiety characterized as hydrogen sulfide donor. Hydrogen sulfide is known to be a gaseous transmitter owing to its ability to influence the main physiological functions[4]. On the other hand, H_2S can also protect cells from the oxidative stress via increment of glutathione production[5,6].1,2-Dithiole-3-thiones was considered to be strong antioxidant, free radical scavenger and lipid peroxidation inhibitor[7].

Indeed, the most important compound among this type of compounds is oltipraz (4-methyl-5-pyrazinyl-3H-1,2-dithiole-3-thione (2), which is originally used as an anti-schistosomal agent owing to its noticeable activity against *Schistosoma mansoni* [8]. It is also demonstrated that this compound inhibits HIV-1 (AIDS) virus reproduction via irreversible binding to the viral reverse transcriptase enzyme [9,10]. On the other hand, other studies illustrated that oltipraz protects against carcinogenesis of many organs, in addition to its chemoprotective activity against variety of carcinogens. [11,12,13,14]. It was also consideration that a pharmacophore containing 1,2-dithiole-3-thione moiety capable of improving insulin sensitivity under the hyperosmotic stress condition[15]. Moreover, the 1,2-dithiole-3-thione derivatives were used in treatment of intestinal allergies and jaundice[16], and it may be useful to inhibit human neoplasia[17]. Moreover, other derivatives such as 4-aryl-5-chloro-3*H*-1,2-dithiole-3-thiones were investigated to possess a fungi-toxic action[18,19] and they were also used as insecticides[20]. Furthermore, some l,2-dithiol-3-

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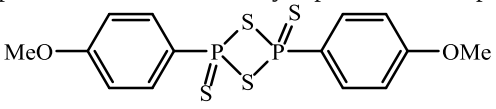
thiones have industrial applications as antioxidant additives in rubber, metals, and commercial oils and greases[21]. The synthesis of 1,2-dithiole-3-thione compounds was performed via different methods, such as the reaction of eugenol or isoeugenol with sulfur[22], reaction of β-keto esters with phosphorous pentasulfide (P_2S_5)[23,24,25]. Later, the P_2S_5 was replaced by Lawesson's reagent (3) and used in combination with elemental sulphur for thionation of β-ketoesters to give an excellent yields of 1,2-dithiole-3-thione compounds[24] but this method gives by products that are not easily separated and disposed.



(3)

On the other hand, the addition of hexamethyldisiloxane ($Me_3SiOSiMe_3$, HMDO) to the thionating agent P_2S_5 and elemental sulfur will increase their usefulness as a thionating agent and give an excellent percentage yield of the 1,2-dithiol-3-thiones[26]. The 1,2-dithiole-3-thione compounds can also be prepared from thionation of allylic system (-CH=CH-CH_3) with sulfur or P_2S_5[27,28]. Moreover, the terminal acetylenic compounds can be easily sulfurized via a sequential treatment of lithium acetylide[29,30] and magnesium acetylide[31] with carbon disulfide and elemental sulfur. The goal of this research was focused on the synthesis of several newer 1,2-dithiol-3-thione compounds containing four fused rings using 1-tetralone as a precursor. It was found through the theoretical study using the Docking program that some heterocyclic compounds have an effect on the emerging corona virus[32].

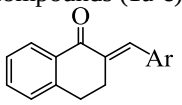
2. MATERIALS and METHODS

The melting points were measured on SMP 10 melting point apparatus using open capillary tubes and uncorrected. Infrared spectra were recorded as neat on Alfa Bruker ATR-FT-IR Co. Germany, 2003. ^{1}HNMR spectra were recorded on a Bruker-Avance II 400 (400 MHz), spectrometer, using TMS as internal standard and (DMSO-d6) as solvent.

2.1. Synthesis of 2-arylidine-3,4-dihydronaphthalen-1(2H)-one compounds (1a-e)[33,34]:

An ethanolic sodium hydroxide solution (5 %) (10 ml) was dropwise added with stirring at ambient temperature to a solution of 1-tetralone (0.01 mole, 1.46 g) and an aromatic aldehyde (0.01 mole) in ethanol (20 ml). The stirring was continued for 5 h at room temperature. The precipitate was formed after the addition of an ice-water mixture to the resulted mixture. The precipitate was filtered off, washed thoroughly with cold water, dried, then recrystallized using ethanol. The physical data for synthesized 2-arylidine-3,4-dihydronaphthalen-1(2H)-one compounds (1a-e) were illustrated in Table-1.

Table-1: The physical data for 2-arylidine-3,4-dihydronaphthalen-1(2H)-one compounds (1a-e):

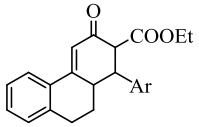


Comp. No.	Ar	m.p. °C	Yield %	color
1a		88-89(B.P.: 435)	94	Yellow
1b		111-112	89	Yellow
1c		68-69(B.P.: 415)	92	Red
1d		131-133	85	Yellow
1e		75-76	95	Yellow

2.2. Synthesis of the ethyl 1-aryl-3-oxo-1,2,3,9,10,10a-hexahydro phenanthrene-2-carboxylate (2a-e):

To a mixture of equimolar of compounds (1a-e) and ethyl acetoacetate (5 mmole), an ethanolic sodium hydroxide solution (5 %, 10 ml) was dropwise added with stirring at room temperature. After the addition was completed, the reaction mixture was refluxed for 8h then cooled. An ice-water (50 ml) was gradually added to the reaction mixture. The resulted precipitate (for compounds 2b,c,e) was filtered off, washed thoroughly with cold water, dried and finally recrystallized using ethanol. The gummy products (resulted from compounds 2a and 2d) were treated with cyclohexane :ethanol (1:1) with stirring to yield solid products. The physical data for the titled β-keto esters (2a-e) were illustrated in Table-2.

Table-2: The physical data for the ethyl 1-aryl-3-oxo-1,2,3,9,10,10a-hexahydro phenanthrene-2-carboxylate (2a-e):

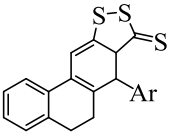


Comp. No.	Ar	m.p. °C	Yield %	Color
2a		158-160	72	Orange
2b		122-124	65	Yellow
2c		92-94	77	Orange
2d		139-140	61	Yellow
2e		119-120	82	Brown

2.3. Synthesis of 1,2-dithiol-3-thione compounds (3a-e):

A solution of ethyl 1-aryl-3-oxo-1,2,3,9,10,10a-hexahydro phenanthrene-2-carboxylate (2a-e**)** (0.001 mole) and phosphorous penta-sulfide (0.003 mole, 1.33 g) in 30 ml of xylene was refluxed at its boiling point for 10h. The reaction mixture was accompanied by a change of color from yellow to orange during the proceeding of the reaction. The reaction mixture was cooled and the solid material was removed by filtration. The filtrate was washed with 10 ml of water containing few drops of concentrated ammonium hydroxide. The organic layer was separated, washed with water, dried with magnesium sulfate then condensed under reduced pressure to its half volume. A few drops of ethanol were added to the remaining material. The compounds (3a,c,e) were precipitated as fine powder, while compounds (3b and 3d) separated from the mixture as gummy material, which then treated with cyclohexane:absolute ethanol (1:1) mixture to yield fine powder. The physical data of compounds (3a-e) were listed in Table-3.

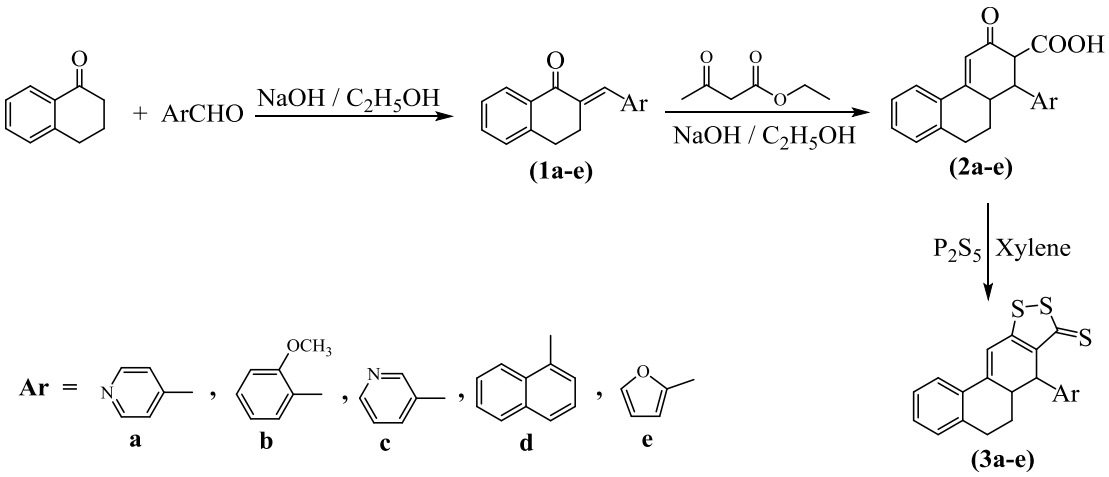
Table-3: The physical data of the 1,2-dithiol-3-thione compounds (3a-e).



Comp. No.	Ar	m.p. °C	Yield %	Color
3a		260-262	58	Brown
3b		215(dec.)	55	Red
3c		250-251	47	Yellow
3d		195-197	52	Brown
3e		294-296	46	Brown

3. RESULTS AND DISCUSSION

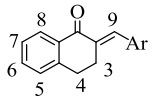
The synthetic routes for this research to obtain the targeted compounds (3a-e) are depicted in the following Scheme(1):

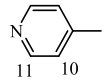
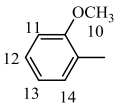
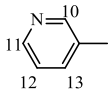
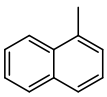
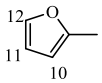


Scheme -1-

The first route in this research involves the synthesis of α,β-unsaturated ketones (1a-e) via the condensation of 1-tetralone as a synthon with five aromatic aldehydes under the influence of 5 % ethanolic sodium hydroxide solution at room temperature. The structure of the synthesized compounds confirmed on the base of the spectral data[35,36].The IR spectra of compounds (1a-e) showed the following absorption bands (Table-4) at 1656-1672 Cm^{-1} assigned to the C=O bond stretching, 1579-1592 Cm^{-1} related to the conjugated C=C bond stretching, 1440-1446 Cm^{-1} attributed to the aromatic C=C bond stretching in addition to the absorption bands of the C-O bond stretching for compound (1b) at 1225 Cm^{-1} and at 1220 Cm^{-1} for compound (1e), respectively. The assignment of the ^{1}HNMR spectra of compounds (1a-e) was illustrated in Table-4.

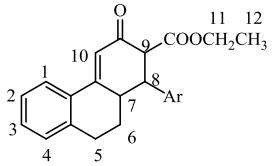
Table-4: The spectral data of compounds (1a-e).

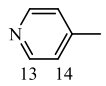
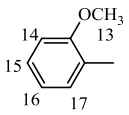
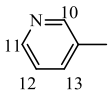
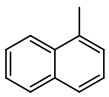
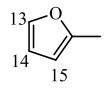


Compd. No.	Ar	IR (ν, Cm^{-1})	^{1}HNMR (δ, ppm)
1a		1672 C=O 1592,1565,1430 C=C, C=N	2.79-3.06 (m,4H,C3,C4); 7.59 (s,1H,C9); 7.3-8.51 (m,6H,Ar-H); 8.55-8.65 (d,2H,C11).
1b		1668 C=O 1591,1555, 1515 C=C 1077,1225 C-O-C	2.57-2.95 (m,4H,C3,C4); 3.8 (s,3H,C10); 7.91 (s,1H,C9); 6.94-7.57 (m,8H,Ar-H).
1c		1661 C=O 1588,1565,1530 C=C, C=N	2.95 (t,2H,C4); 3.08(t,2H,C3); 7.96 (s,1H,C9); 7.37-7.96 (m,6H,Ar-H); 8.57-8.73 (m,2H,C10, C11).
1d		1660 C=O 1589,1554,1515 C=C	2.71-2.8 (m,4H,C3,C4); 7.58 (s,1H,C9); 7.32-8.3 (m,11H,Ar-H).
1e		1657 C=O 1600,1580,1537 C=C 1071,1220 C-O-C	2.98 (t,2H,C4); 3.25 (t,2H,C3); 6.68 (t,1H,C11); 7.02-7.4 (m,4H,Ar-H); 7.46 (s,1H,C9); 7.93 (d, 2H,C12);

The second route involves the synthesis of the β-keto esters (2a-e) via the reaction of the synthesized chalcones (1a-e) with ethyl acetoacetate in presence of 5% alcoholic sodium hydroxide solution. The IR spectra of compounds (2a-e) showed the following absorption bands (Table 5) at 1730-1733 $Cm^{-1}$for the esteric C=O bond stretching, at 1654-1668 Cm^{-1} for the ketonic C=O bond stretching, at 1587-1592 for the C=C bond stretching, in addition to the absorption bands at 1206-1228 for the C-O bond stretching. The assignment of the ^{1}HNMR spectra of compounds (2a-e) was illustrated in Table-5.

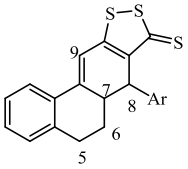
Table-5: The spectral data of compounds (2a-e).

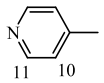
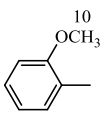
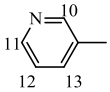
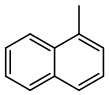
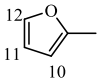


Compd. No.	Ar	IR (ν, Cm^{-1})	^{1}HNMR (δ, ppm)
2a		1733, C=O ester 1658, C=O ketone 1590,1560,1480 C=C, C=N 1076,1206, C-O-C	1.07 (t,3H,C12); 1.99 (m,2H,C6); 2.73 (t,2H,C5); 3.23 (m,1H,C7); 3.32 (d,1H,C8); 3.95 (d,1H,C7); 4.09 (q,2H,C11); 6.84 (s,1H,C10); 7.11-7.32 (m,4H,Ar-H); 7.96 (d,2H,C13); 8.55 (d,2H,C14).
2b		1730 C=O ester 1668 C=O ketone 1592,1537,1498 C=C 1056,1228 C-O-C	0.88 (t,3H,C12); 1.99 (m,2H,C6); 2.73 (m,1H,C7); 2.93 (m,2H,C5); 3.23 (m,1H,C8); 3.32 (m,1H,C9); 3.98 (s,3H,C13); 4.09 (q,2H,C11); 6.84 (s,1H,C10); 7.11-8.35 (m,8H,Ar-H).
2c		1733 C=O ester 1660 C=O ketone 1590,1556,1418 C=C, C=N 1067,1209 C-O-C	0.87 (t,3H,C12); 1.04 (m,2H,C6); 2.18 (m,1H,C7); 2.65 (m,1H,C8); 2.75 (m,2H,C5); 3.15 (d,1H,C9); 3.85 (q,2H,C11); 6.76-7.4 (m,6H,Ar-H,C15,C16); 8.49 (d,1H,C13); 8.57 (s,1H,C14).
2d		1731 C=O ester 1657 C=O ketone 1587,1537,1490 C=C 1056,1216 C-O-C	1.08 (t,3H,C12); 1.66 (m,2H,C6); 2.49 (m,1H,C7), 2.79 (m,2H,C5); 2.86 (m,1H,C8); 2.92 (m,1H,C9); 3.9 (q,2H,C11); 7.28-8.19 (m,11H,Ar-H).
2e		1730 C=O ester 1654 C=O ketone 1610,1589,1495 C=C 1066,1220 C-O-C	1.01 (t,3H,C12); 1.72 (m,2H,C6); 2.82 (m,1H,C7); 2.98 (m,2H,C5); 3.29 (m,1H,C8); 3.34 (m,1H,C9); 3.94 (q,2H,C11); 6.69 (s,1H,C10); 7.02-7.96 (m,7H,Ar-H, fur-H).

The third route involves the synthesis of 1,2-dithiol-3-thione compounds (3a-e) via refluxing the β-keto esters (2a-e) with phosphorous penta-sulfide (P_2S_5) in xylene as solvent. The IR spectra of the synthesized compounds (3a-2e) indicated the absence of the absorption bands of the ketonic and esteric C=O bond stretching and appearance of absorption bands at 1147-1159 $Cm^{-1}$for the C=S bond stretching, in addition to absorption bands at 451-456 Cm^{-1} for the S-S bond stretching, at 610-625 Cm^{-1} for the C-S bond stretching and at 1586-1606 Cm^{-1} for the C=C bond stretching. The assignment of the ^{1}HNMR spectra of compounds (1a-e) was illustrated in Table-6.

Table-6: The spectral data of compounds (3a-e).



Compd. No.	Ar	IR (ν, Cm^{-1})	^{1}HNMR (δ, ppm)
3a		1154 C=S 452 S-S 1588,1565,1485 C=C, C=N 625 C-S	1.09 (m,2H,C6); 2.4 (m,1H,C7); 2.73 (m,2H,C5); 3.32 (d,1H,C8); 3.32 (d,1H,C8); 7.42 (s,1H,C9); 6.5-7.22 (m,6H,Ar-H , C10); 8.51 (d,2H,C11).
3b		1147 C=S 456 S-S 1600,1585,1537 C=C 610 C-S 1056,1241 C-O-C	1.38 (m,2H,C6); 2.19 (m,1H,C7); 2.59 (m,2H,C5); 3.72 (d,1H,C8); 3.9 (s,3H,C10); 6.97-7.97 (m,8H,Ar-H); 7.29 (s,1H,C9).
3c		1150 C=S 454 S-S 1588,1542,1478 C=C, C=N 614 C-S	1.21 (m,2H,C6); 2.24 (m,1H,C7); 2.93 (m,2H,C5); 3.63 (d,1H,C8); 7.34 (s,1H,C9); 6.92-7.94 (m,6H,Ar-H,C12,C13); 8.4 (m,2H,C10,C11).
3d		1158 C=S 451 S-S 1587,1556,1490 C=C 615 C-S	2.14 (m,2H,C6); 2.24 (m,1H,C7), 2.86 (m,2H,C5); 3.56 (d,1H,C8); 7.42 (s,1H,C9); 7.11-7.99 (m,11H,Ar-H).
3e		1159 C=S 452 S-S 1606,1586,1542 C=C 618 C-S 1070,1242 C-O-C	1.21 (m,2H,C6); 2.24 (m,1H,C7), 2.87 (m,2H,C5); 3.29 (d,1H,C8); 7.25 (s,1H,C9); 7.09-7.88 (m,7H,Ar-Hand Fur-H).

4. CONCLUSIONS

In this work new 2-arylidine-3,4-dihydronaphthalen-1(2H)-one compounds was synthesized via Claisen – Schmidt condensation of 1-tetralone and different aldehydes under alkaline conditions in with excellent percentage yields. The Robinson annulation reaction was used to construct β-ketoesters containing three fused rings. The construction of compounds containing four fused rings was performed by thionation of β-ketoesters by phosphorous penta-sulfide. This thionation process gives moderate percentage yields in comparison with the other methods of thionation.

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REFERENCES

1) Pedersen, C. T. (1995). Adv. Heterocyclic Chem. 1982, 31, 63. *Sulfur Rep*, *16*, 173.
2) Maxuitenko, Y. Y., Libby, A. H., Joyner, H. H., Curphey, T. J., MacMillan, D. L., Kensler, T. W., & Roebuck, B. D. (1998). Identification of dithiolethiones with better chemopreventive properties than oltipraz. *Carcinogenesis*, *19*(9), 1609-1615.
3) Munday, R., Zhang, Y., Paonessa, J. D., Munday, C. M., Wilkins, A. L., & Babu, J. (2010). Synthesis, biological evaluation, and structure− activity relationships of dithiolethiones as inducers of cytoprotective phase 2 enzymes. *Journal of medicinal chemistry*, *53*(12), 4761-4767.
4) Wang, D. W., Zhang, F., & Qian, J. Q. (2002, March). Contribution of cytochrome P450 4a1 to the long term control of arterial pressure: Evidence from somatic CYP 4a1 gene modifications. In *FASEB JOURNAL* (Vol. 16, No. 4, pp. A486-A486).

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5) Yan, S. K., Chang, T., Wang, H., Wu, L., Wang, R., & Meng, Q. H. (2006). Effects of hydrogen sulfide on homocysteine-induced oxidative stress in vascular smooth muscle cells. *Biochemical and biophysical research communications*, *351*(2), 485-491.
6) Khanna, S., Sen, C. K., Roy, S., Christen, M. O., & Packer, L. (1998). Protective effects of anethole dithiolethione against oxidative stress-induced cytotoxicity in human Jurkat T cells. *Biochemical pharmacology*, *56*(1), 61-69.
7) Sen, C. K., Traber, K. E., & Packer, L. (1996). Inhibition of NF-κB activation in human T-cell lines by anetholdithiolthione. *Biochemical and biophysical research communications*, *218*(1), 148-153.
8) Barreau, M., Cotrel, C., & Jeanmart, C. (1977). German Patent 2705641. *Chem. Abst*, *87*, 152171.
9) Prochaska, H. J., Rubinson, L., Yeh, Y., Baron, P., & Polsky, B. (1994). Elevation of glutathione levels by phase II enzyme inducers: lack of inhibition of human immunodeficiency virus type 1 replication in chronically infected monocytoid cells. *Molecular pharmacology*, *45*(5), 916-921.
10) Prochaska, H. J., Fernandes, C. L., Pantoja, R. M., & Chavan, S. J. (1996). Inhibition of Human Immunodeficiency Virus Type 1 Long Terminal Repeat-Driven Transcription by anin VivoMetabolite of Oltipraz: Implications for Antiretroviral Therapy. *Biochemical and biophysical research communications*, *221*(3), 548-553.
11) Saeed, B. B., Al-Iraqi, M. A., & Abachi, F. T. (2012). Synthesis of new 1, 2 dithiol 3-thione fluoroquinolone esters possessing anticancer activity in-vitro. *Iraqi J. Vet. Sci*, *26*, 115-121.
12) Sadeek, G., Mauf, R., Saleh, M. (2021). Synthesis and Identification of some new Derivatives Oxazole, Thiazole and Imidazol from Acetyl Cysteine. Egyptian Journal of Chemistry, (), -. doi: 10.21608/ejchem.2021.88755.4267
13) Doherty, G. P., Leith, M. K., Wang, X., Curphey, T. J., & Begleiter, A. (1998). Induction of DT-diaphorase by 1, 2-dithiole-3-thiones in human tumour and normal cells and effect on anti-tumour activity of bioreductive agents. *British journal of cancer*, *77*(8), 1241-1252.
14) Munday, R., & Munday, C. M. (2004). Induction of phase II enzymes by 3 H-1, 2-dithiole-3-thione: dose–response study in rats. *Carcinogenesis*, *25*(9), 1721-1725.
15) Bae, E. J., Yang, Y. M., & Kim, S. G. (2008). Abrogation of hyperosmotic impairment of insulin signaling by a novel class of 1, 2-dithiole-3-thiones through the inhibition of S6K1 activation. *Molecular pharmacology*, *73*(5), 1502-1512.
16) Fields, E. K. (1957). *U.S. Patent No. 2,816,116*. Washington, DC: U.S. Patent and Trademark Office.
17) Davidson, N. E., Egner, P. A., & Kensler, T. W. (1990). Transcriptional control of glutathione S-transferase gene expression by the chemoprotective agent 5-(2-pyrazinyl)-4-methyl-1, 2-dithiole-3-thione (oltipraz) in rat liver. *Cancer research*, *50*(8), 2251-2255.
18) Hagen, H.; Fleig, H. Ger. Offen. Patent 2,460,783; Chem. Abst. 1976, 85, 123899.
19) Bader, J.; Gaetzi, K. Ger. Offen. Patent 1,27 8,701; Chem. Abst. 1969, 70, 115147
20) Misra, P. K., & AS, M. (1979). Heterocyclic fungicides and insecticides.
21) Lozac'h, N., & Stavaux, M. (1981). The 1, 2- and 1, 3-Dithiolium Ions. In *Advances in Heterocyclic Chemistry* (Vol. 27, pp. 151-239). Academic Press.
22) Mathur, P., Avasare, V. D., Ghosh, A. K., & Mobin, S. M. (2004). Formation of 5-phenyl-1, 2-dithiole-3-thione from molybdenum dithiopropiolato complexes. *Journal of organometallic chemistry*, *689*(7), 1325-1327.
23) Lee, Y. H., Lee, J. M., Kim, S. G., & Lee, Y. S. (2016). Synthesis and biological evaluation of 1, 2-dithiol-3-thiones and pyrrolo [1, 2-a] pyrazines as novel hypoxia inducible factor-1 (HIF-1) inhibitor. *Bioorganic & medicinal chemistry*, *24*(12), 2843-2851.
24) Pedersen, B. S., & Lawesson, S. O. (1979). Studies on organophosphorus compounds—XXVIII: Syntheses of 3H-1, 2-dithiole-3-thiones and 4H-1, 3, 2,-oxazaphosphorine derivatives from the dimer of p-methoxyphenyl-thionophosphine sulfide and der. *Tetrahedron*, *35*(20), 2433-2437.
25) Curphey, T. J. (2002). Thionation with the reagent combination of phosphorus pentasulfide and hexamethyldisiloxane. *The Journal of organic chemistry*, *67*(18), 6461-6473.

26) Curphey, T. J. (2002). Thionation with the reagent combination of phosphorus pentasulfide and hexamethyldisiloxane. *The Journal of organic chemistry*, *67*(18), 6461-6473.
27) Bottcher, B., & Bauer, F. (1951). Some new trithiones. *Chem. Ber*, *84*(458463), 17.
28) Thuilbier and J. Vlalla, Bull. Soc. Chim. Fr. (1959) 1398.
29) Adams, H., Chung, L. M., Morris, M. J., & Wright, P. J. (2004). A convenient route to 4-mercapto-1, 2-dithiole-3-thiones from terminal alkynes. *Tetrahedron letters*, *45*(41), 7671-7674.
30) Takimiya, K., Morikami, A., & Otsubo, T. (1997). A convenient preparation of 1, 3-dithiole-2-thione and 1, 3-diselenole-2-selone derivatives. *Synlett*, *1997*(3), 319-321.
31) AL-IRAQI, M. A., & SAAD-ALDEEN, R. A. (2019). Synthesis of New 3-Substiuted Quinazolin-4 (3H)-one Compounds. *The Eurasia Proceedings of Science Technology Engineering and Mathematics*, *7*, 93-98.
32) Aldahham, B. J., Al-Khafaji, K., Saleh, M. Y., Abdelhakem, A. M., Alanazi, A. M., & Islam, M. A. (2020). Identification of naphthyridine and quinoline derivatives as potential Nsp16-Nsp10 inhibitors: a pharmacoinformatics study. *Journal of Biomolecular Structure and Dynamics*, 1-8.
33) Saleh, M., Ayoub, A. I., & Hammady, A. O. (2020). Synthesis biological studies of some new heterocyclic compound derived from 2-chloro-3-formyl quinoline and 4-(benzyl sulfonyl) acetophenone. *Egyptian Journal of Chemistry*, *63*(12), 4-6.
34) Abdullah, L., Saied, S., Saleh, M. (2021). Deep eutectic solvents (Reline) and Gold Nanoparticles Supported on Titanium Oxide (Au–TiO2) as New Catalysts for synthesis some substituted phenyl(substituted-3-phenyloxiran)methanone Enantioselective Peroxidation. *Egyptian Journal of Chemistry*, 64(8), 4381-4389. doi: 10.21608/ejchem.2021.68511.3498
35) Crews, P., Rodríguez, J., & Jaspars, M. (2010). *Organic structure analysis* (Vol. 636). New York: Oxford University Press.
36) Kalsi, P. S. (2007). *Spectroscopy of organic compounds*. New age international.