AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 08, October 2022

SYNTHESIS, CHARACTERIZATION OF SOME NEW ACYLSELENOUREA AND ACYLTHIOUREA DERIVATIVES

Huda S. Farhan[a], Suzan A. AL-azizz[b] and Shaker A.N. AL-jadaan[c]

a-Department of Clinical Laboratory, College of Pharmacy, University of Basrah, Basrah, Iraq.
b-Department of Veterinary Microbiology and Parasitology, College of Veterinary Medicine, University of Basrah, Basrah, Iraq.
c-Department of Pharmaceutical Chemistry, College of Pharmacy, University of Basrah, Basrah, Iraq.

Corresponding Author's E-Mail: huda.alkhaledy78@gmail.com

Abstract:
A new series of acylselenourea, i.e., 4-Nitro-N-((4-(N-(pyrimidin-2-yl) sulfamoyl) phenyl) carbamoselenoyl) Benz amide**(1)**, 4-Methyl-N-((4-(N-(pyrimidin-2-yl) sulfamoyl) phenyl) carbamoselenoyl) Benz amide**(2)**, 4-Nitro-N-((4-nitrophenyl) carbamo selenoyl) Benz amide**(4)**, N-(2,6-dioxo-1,2,3,6-tetrahydropyrimidine-1-carbonoselenoyl)-4-nitrobenzamide**(5)**, these compounds were prepared from reaction of KSeCN with 4-Nitrobenzoyl chloride in dry THF followed by adding appropriate anime compound in situ, i.e. sulfadiazine, 4-Nitroaniline and Uracil. One acylthiourea derivative, i.e., 4-Methyl-N-((4-(N-(pyrimidin-2-yl) sulfamoyl phenyl) carbamothioyl) Benz amide**(3)**was prepared from reaction of 4-Methylbenzoyl chloride with KSCN in dry THF followed by addition of sulfadiazine in situ. All prepared compounds were characterized by FT-IR, CHNS, ^{1}H-NMR and ^{13}C-NMR spectroscopic data which confirm the proposed structures for the prepared compounds.
Key words: Sulfadiazine, Selenourea, Thiourea, Potassium selenocyanate.

1-Introduction

J.J. Berzelius was discovered elemental selenium in 1817 [1].Ethylselenol was the first organoselenium compound reported in 1847 by F. Wöhler and C. Siemens [2].The chemistry of organoselenium compounds were progress and developed through more than 100 years later, many organic selenium compounds are high toxic and unstable many synthesized method were developed to prepare more stable, less toxic, easy to prepare and safe to handle organic selenium derivatives which used as antioxidant and anticancer[3-5], antiviral [6], antihypertensive [7], antibacterial [8], and other medicinal applications [9-11]. Organic compounds of the type RC(O)NHC(Se)NR'R" are called Acylselenourea derivatives. These compounds were prepared since 1937 from the reaction of KSeCN with acyl halides to give organoselenonitrile followed by subsequent addition of appropriate amine in suitable organic solvents [12]. Organoselenonitrile and organoisoselenonitrile were used as precursor in organoselenium chemistry [13-18]. In this

study some of acylselenourea derivatives and acylthiourea derivative were synthesized from reaction of acyl chlorides with KSeCN or KSCN followed by addition of appropriate amine compounds, characterized by spectroscopic data which confirm the proposed structures.

2- Experimental

Materials and Reagents

The chemicals and solvents (HPLC grade) uses in this study obtained from commercial sources and used as received, Solvents were dried according to literature methods [19]. All reactions were carried out under dry conditions and were monetarized using thin-layer chromatography (TLC) and the spots were visualized under UV light. KSeCN was prepared from the reaction of elemental Se with KCN according to literature [20]. The reaction products were purified by column chromatography using silica gel 60 A°, with benzene/ethanol (9:1) as the elusion solvent.

Physical measurements

Melting points of all prepared compounds were determined using electro thermal melting point apparatus which is heated electrically and are uncorrected. The prepared compounds specimens were mixed as KBr pellets and measured using Shimadzu FT-IR spectrophotometer of range 4000-500 Cm^{-1}. Micro analysis for carbon, hydrogen, nitrogen and sulfur for the prepared compounds were performed by Elemental Analyzer Instrument-Eager 300. ^{1}H and ^{13}C-NMR were recorded on Bruker Varian 500 MHz and some of them on Bruker AVANCE NEO 400 MHz spectrophotometer with TMS as an internal reference and using DMSO–d_6 as a solvent. Chemical shifts were reported in δ values (ppm) units downfield from internal reference Me_4Si.

Synthesis

1-Synthesis of 4-nitro-N-((4-(N-(pyrimidin-2-yl) sulfamoyl) phenyl) carbamoselenoyl) Benz amide **(1)**

All synthesized compounds were prepared according to a literature method [14] with some modificationas following:

A solution of freshly prepared potassium selenocyanate (15 mmol) from reaction of potassium cyanide (0.98 gm, 15 mmol) with elemental selenium powder (1.19 gm, 15 mmol) in dry THF 20mL, the mixture was stirred at room temperature until all selenium was disappeared (ca~ 30 minutes). To this solution (2.78 gm, 15 mmol) of 4-nitrobenzoyl chloride dissolved in 20 mL of dry THF was added. The mixture was stirred for 1hr, then a solution of sulfadiazine (3.74gm, 15mmol) dissolved in dry THF (50mL) was added and the reaction mixture was stirred for a further 1hr at room temperature. The reaction was monitored with TLC. then poured into 0.1 M HCl (ca~200mL) and left overnight. Orange precipitate was filtered washed wit distilled water and dried. Crude product was purified by column chromatography using benzene/ethanol, 9:1 as eluent. The combined eluate was dried (Na_2SO_4) and the solvent was removed by rotary evaporator. The resulting precipitate was recrystallized by absolute ethanol to give orange powder (3.46 gm, Yield = 46%), MP. 165-166C°. R_f value= 0.0 using benzene/ethanol; 9:1.IR (KBr) cm^{-1}: 3379 (N-H), 3039($CH\text{-}_{arom}$), 1720(C=O), 1589($C{=}N_{Sulfa}$), 1527($NO_{2asym.}$), 1342 ($NO_{2sym.}$), 1327(SO_2), 1280 (C=Se),1157(SO_2), 945(S-N), 717 (C=Se).^{1}H NMR (500 MHz, DMSO-d6); *δ*/ppm: (s, $2H_{24,23}$)10.89, (s,$1H_{22}$)10.85, (d $2H_{18,20}$)8.51, (d,$2H_{2,6}$)8.00, (d,$2H_{3,5}$)7.63,

(d,2$H_{12,14}$)7.34, (d,2$H_{11,15}$)6.56, (t,1H_{19})7.05.^{13}C-NMR [500 MHz, (DMSO), δ (ppm)]: C=O, 164.7, C=Se, 158.7, C_{16} 157.6, C $_{8,20}$, 153, C_1, 150, C_{10}, 135, C_4, 131, C $_{13}$, 130, $C_{3,5}$, 129, C $_{12,14}$, 125, $C_{2,6}$, 124, $C_{11,15}$, 123, C_{19}, 112. Anal. Calcd. For $C_{18}H_{14}N_6O_5SSe$: C ,42.78, H, 2.79, N,16.63, S,6.34. Found: C,42.98, H,2.55, N,16.50, S, 6.43.

2- Synthesis of 4-Methyl-N-((4-(N-(pyrimidin-2-yl) sulfamoyl) phenyl) carbamoselenoyl) Benz amide **(2)**

A yellow precipitate of compound **(2)** was formed (4.1gm, Yield 58%)/ MP. 221-222C°. R_f value= 0.0 using benzene/ethanol; 9:1. IR (KBr) cm^{-1}: 3363 (N-H), 3032 (CH-$_{arom}$), 2939 (CH-$_{Aliph.}$)1658 (C=O), 1589(C=N_{sulfa}), 1327(SO_2), 1265 (C=Se) ,1157(SO_2), 948(S-N), 678 (C=Se). ^{1}H NMR (500 MHz, DMSO-d6); *δ*/ppm:(s, 1H_{24})10.73, (s,1H_{22})10.94, (s,1H_{23})9.63, (,2$H_{18,20}$)8.51, (d,2$H_{3,5}$)80, (d,2$H_{2,6}$)7.60, (d,2$H_{12,14}$)7.34, (t,1H_{19})7.05, (d,2$H_{11,15}$)6.58, (s,3H_7)2.37.^{13}C-NMR [500 MHz, (DMSO), δ (ppm)]: C=O, 174, C=Se, 158.72, C_{16}, 157.66, C $_{18,20}$, 153.54, C_{10}, 145.20,C_{13}, 139.60, C_4, 130.28, $C_{12,14}$, 129.48, C $_{11,15}$, 128.65, C $_{3,5}$, 125.20, C $_{2,6}$, 117.10, $C_{1,19}$,112.56, C_7, 21.63. Anal. Calcd. For $C_{19}H_{17}N_5O_3SSe$: C,48.18, H, 3.61, N,14.76, S,6.76. Found: C, 48.63, H, 3.80, N,14.53, S, 6.62.

3- Synthesis of 4-Methyl-N-((4-(N-(pyrimidin-2-yl) sulfamoyl phenyl) carbamothioyl) Benz amide **(3)**

A white precipitate of compound **(3)** was formed (4.8gm, Yield 75%)/ MP. 233-235C°. R_f value= 0.0 using benzene/ethanol; 9:1. IR (KBr) cm^{-1}: 3387 (N-H), 3032 (CH-$_{arom}$), 2939 (CH-$_{Aliph.}$) 1674 (C=O), 1589(C=N_{Sulfa}), 1327(SO_2), 1265 (C=Se) ,1157(SO_2), 1103 (C=S), 941(S-N). ^{1}H NMR (500 MHz, DMSO-d6); *δ*/ppm:(s,2$H_{22,24}$)10.33, (s,1H_{23})10.58, (d,2$H_{18,20}$)8.51, (d,2$H_{3,5}$)7.99, (d,2$H_{12,14}$)7.96, (d, 2$H_{2,6}$)7.87, (d,2$H_{11,15}$)7.33, (t,1H_{19})7.04, (s,3H_7)2.38. ^{13}C-NMR [500 MHz, (DMSO), δ (ppm)]: C=S, 178.73, C_{16}, 168.10, C=O, 159.52, C $_{18,20}$, 151.27, C_{10}, 144.23, C_4, 139.44, C $_{2,6}$, 129.52, $C_{3,5}$, 129.31, C $_{12,14}$, 128.78, $C_{11,15}$, 124.24. C_{19}, 111.60, C_7, 21.62. Anal. Calcd. For $C_{19}H_{17}N_5O_3S_2$: C, 53.38, H,4.01, N,16.41, S, 14.99. Found: C, 53.83, H, 3,93, N,16.84, S, 14.69.

4- Synthesis of 4-Nitro-N-((4-nitrophenyl) carbamoselenoyl) Benz amide**(4)**

A red crystals of compound **(4)** was formed (4.1gm, Yield 71%)/ MP. 167-168C°. R_f value= 0.0 using benzene/ethanol; 9.5:0.5. IR (KBr) cm^{-1}:3371 (N-H), 3116(CH-$_{arom}$), 1689(C=O),1527($NO_{2asym.}$), 1350 ($NO_{2sym.}$), 1111 (C=Se), 725 (C=Se).^{1}H NMR (400 MHz, DMSO-d6); *δ*/ppm: (s,1H_{15})7.95, (s,1H_{16})7.62, (d,2$H_{2,6}$)8.38, (d,2$H_{3,5}$)8.36, (d,2$H_{11,13}$)8.09, (d,2$H_{10,14}$)6.6. ^{13}C-NMR [400 MHz, (DMSO), δ (ppm)]: C=O, 166.25, C=Se, 156.14, C_1, 150.45, C_{12},136, C_9, 131.15, C_4, 131.02, C $_{3,5}$, 126.84, C $_{11,13}$, 124.31, C $_{2,6}$, 124.18, C $_{10,14}$, 112.81. Anal. Calcd. For $C_{14}H_{10}N_4O_5Se$: C, 42.76, H, 2.56, N, 14.25. Found: C,42.89, H, 2.19, N, 14.86**.**

5-Synthesis of N-(2,6-dioxo-1,2,3,6-tetrahydropyrimidine-1-carbonoselenoyl)-4-nitrobenzamide **(5)**

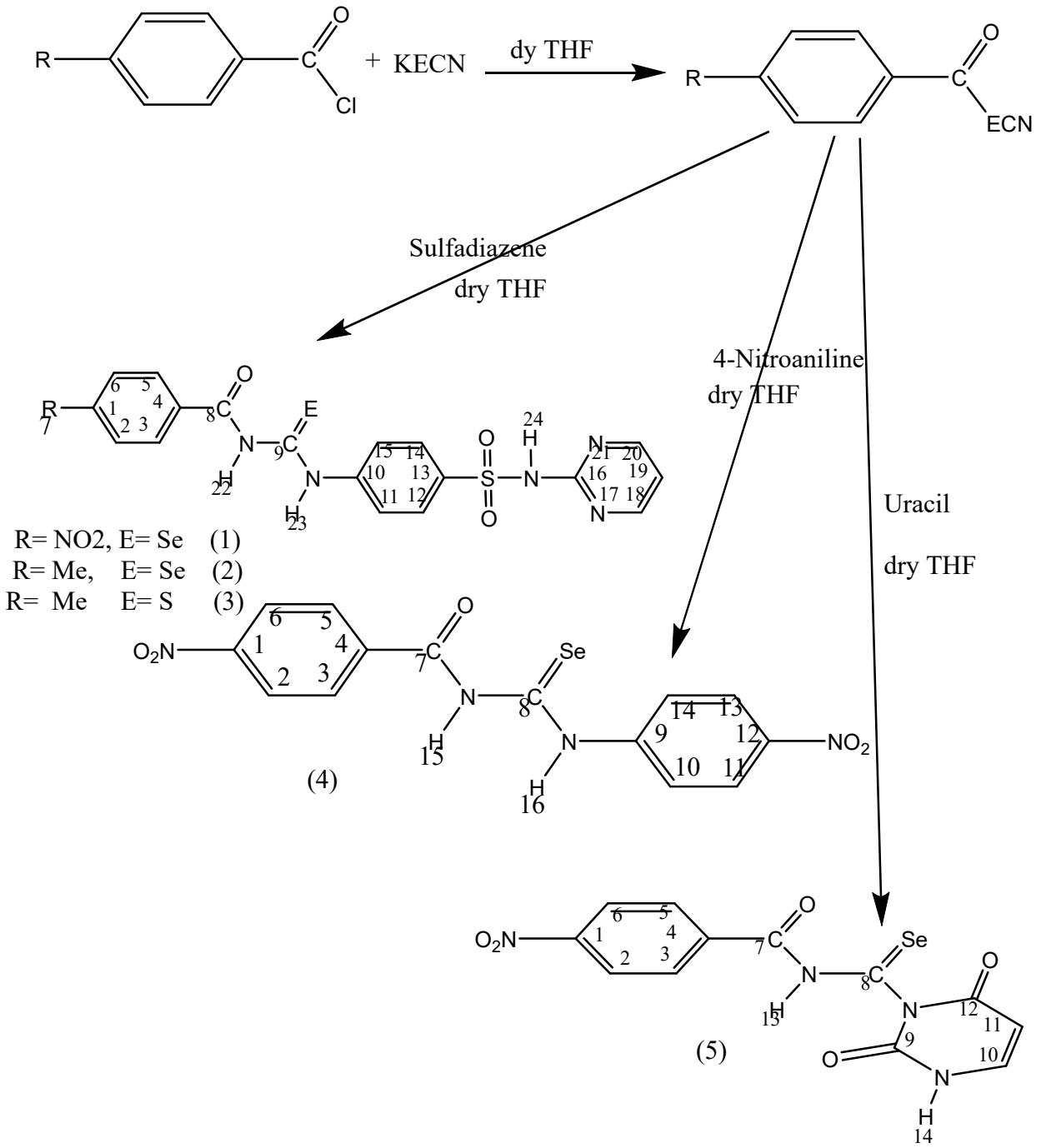
A deep red bright crystals of compound **(5)** was formed (4.1gm, Yield 75%)/ MP. 58-60C°. R_f value= 0.0 using benzene/ethanol; 9.5:0.5. IR (KBr) cm^{-1}: 3471 (N-H), 3078(CH-$_{arom}$), 1697(C=O),1535 ($NO_{2asym.}$), 1324 ($NO_{2sym.}$), 1111 (C=Se), 709 (C=Se).^{1}H NMR (400 MHz, DMSO-d6); *δ*/ppm: (s,1H_{13})10.045, (s,1H_{14}) 11,145, (d,2$H_{2,6}$) 8.49, (d,2$H_{3,5}$)8.15, (d,1H_{10})8.13,

(d,1H_{11})7.72. ^{13}C-NMR [500 MHz, (DMSO), δ (ppm)]: C_7, 166.68, C_{12}, 165.25, C=Se, 150.45, C_9, 149.50, C_1, 140.43, C_{10}, 136.87, C_4, 131.38, $C_{3,5}$,129.35, $C_{2,6}$, 124.44, C_{11}, 123.86. Anal. Calcd. For $C_{12}H_8N_4O_5Se$: C, 39.37, H, 2.24, N, 15.58. Found: C, 39.25, H, 2.20, N,15.28**.**

Results and discussion

Four of the acylselenourea compounds were prepared in a one pot method from the reaction of KSeCN with appropriate substituted acyl chloride followed by addition of appropriate ammine in dry THF. while one acylthiourea compound was prepared from reaction of KSCN with 4-Methylbenzoyl chloride in one pot procedure in dry THF to afford compounds **1, 2, 3, 4** and **5**as shown in (Scheme 1). All prepared compounds (1-5) are solids, stablenon-hygroscopic and dissolved in common organic solvents. The prepared compounds were characterized by elemental analysis which gave satisfactory results. *(see experimental section)*.All compounds were confirmed by FT-IR spectroscopy. All IR spectra of prepared compounds were shows strong stretching vibrational frequencies in the range of (3363-3387) cm^{-1} attributed to NH stretching vibration. Weak band between (3116-3032) cm^{-1} due to symmetrical vibrations of C-H aromatic. Weak bands at 2939 cm^{-1} due to symmetrical vibrations of C-H aliphatic (compounds 2 and 3). All prepared compounds show strong bands between (1658-1720) cm^{-1} assignable to the stretching of carbonyl groups (υC=O). Compounds 1,2 and 3 show strong bands at 1589 cm^{-1} attributed to the stretching vibration of C=N bond in sulfadiazine moiety and tow strong bands at 1327 cm^{-1} and 1157 cm^{-1} due to asymmetrical and symmetrical stretching vibration of SO_2 group respectively. Strong bands between (941-948) cm^{-1} due to stretching vibration of S-N bond in sulfadiazine moiety. Compounds (1, 4 and 5) displayed tow bands one strong between (1527-1535) cm^{-1} and medium between (1324-1350) cm^{-1} attributed to asymmetrical and symmetrical stretching vibration of NO_2 group respectively [21-23]. Compounds (1,2,4 and 5) show tow medium bands one between (1111-1280) cm^{-1} and second band between (678-725) cm^{-1} attributed to the stretching contribution of C=Se [23,24]. Compound (3) show strong band at (1103) assigned to stretching vibration of C=S bond [24]. These assignments were agreeing well with previously reported values and confirm the formation of the studying compounds. Structures of all synthesized compounds (1-5) were confirmed by ^{1}H NMR spectra. The NH protons of all compounds(1-5) showed signals at (7.62-11.45) ppm attributed to $NH_{Sulf.}$ (comp.1,2 and 3), $NH_{acylseleno\ and\ acylthiourea}$. (1-5)and NH $_{uracil}$(5). [14,23,25] (see experimental section). Compounds (1,2 and 3) showed a doublet signal of 2H protons at (8.51) ppm attributed to $H_{18,20}$ of diazene ring, triplet signals at (7.04-7.05) ppm attributed to proton of diazene ring i.e. H_{19}[23].The singlet signal at (2,37-2,38) ppm assigned to methyl group in compounds (2 and 3), i.e. (s,3H_7). The ^{1}H-NMR spectra of all synthesized compounds (1-5) showed a signals at expected range of aromatic protons. Generally, all ^{1}H-NMR spectra of synthesized compounds gave all the expected peaks with the proper intensity ratio, see Experimental section and Scheme (1).Structures of all synthesized compounds (1-5) were confirmed also by ^{13}C-NMR spectra. The spectra show signals at (164-174) ppm attributed to C=O of acyl moiety of all compounds (1-5) furthermore tow carbonyl groups of uracil moiety, i.e. C_{12} at 165.25 ppm and C_9 at 149.50 ppm. See experimental section. The spectra of compound (1,2,4 and 5) show signals at (150.45-158.72)ppm due to C=Se, while compound (3) show a signal at

(178.73) ppm due to C=S [24,26]. The spectra of compounds (1-3) show a signal at (157.6-168.10) ppm, (151.27-153.53) ppm and (111.60-112.57) ppm assigned to carbons of sulfadiazine ring, i.e. C_{16}, $C_{18,20}$ and C_{19}, respectively [17,26]. All the ^{13}C-NMR spectra of synthesized compounds (1-5) were in agreement with the suggested structures. See experimental section and Scheme (1).



Scheme 1. Synthesis of acylselenourea 1, 2, 4, 5 and acylthiourea

4. Conclusion

A new series of acylselenourea were prepared from reaction of KSeCN with 4-Nitrobenzoyl chloride.

References

1. Berzelius, J. J. Afhandl. Fys. Kemi Mineral. 1818, 6, 42.
2. Wöhler, F.; Siemens, C. Ueber das Selenmercaptan. Ann. Chem. 1847, 61, 360-362.
3. Block, E.; Bird, S.; Tyson, J. F.; Uden, P. C.; Zhang, X.; Denoyer, E. The search for anticarcinogenic organoselenium compounds from natural sources. Phosphorus Sulfur Silicon Relat. Elem. 1998, 136, 1-10.
4. Nadheerah F. Neamah, Abdul-Razzak Naaeem Khudair and Shaker.A.N.Al-Jadaan. Antioxidant activity of novel selena-diazole derivative against oxidative stress induced by dipyrone in female rats, Physiol Pharmacol 24 (2020) 202-210.
5. Wu, W.; Murakami, K.; Koketsu, M.; Yamada, Y.; Saiki, I. Induction of apoptosis in human gastric adenocarcinoma cells by two novel organoselenium compounds and TS-2 and TS-6. Anticancer Res. 1999, 19, 5375-5382.
6. Parnham, M. J.; Graf, E. Pharmacology of synthetic organic selenium compounds. Prog. Drug. Res. 1991, 36, 9-47.
7. May, S. W.; Wang, L.; Gill-Woznichak, M. M.; Browner, R. F.; Ogonowski, A. A.; Smith, J. B.; Pollock, S. H. An orally active selenium-based antihypertensive agent with restricted CNS permeability. J. Pharm. Exp. Ther. 1997, 283, 470-477.
8. Nadheerah F. Neamah, Abdul-Razzak Naaeem Khudair and Shaker.A.N.Al-Jadaa, Synthesis, Characterization, Antimicrobial Activity And Acute Toxicity Test of Anovel 4,4 - (4, 5, 6, 7-Tetrahydro- [1, 2, 3 -] Selenad Iazolo [4, 5 e] Pyridine-4, 6-Diyl) BIS(Benzene-1, 3-Diol), Egypt.J.Chem. Vol. 63, No.2. pp. 669-681 (2020).
9. May, S. W. Selenium-based pharmacological agents: an update. Exp. Opin. Invest. Drugs 2002, 11, 1261-1269.
10. Nadheerah F. Neamah Abdul-Razzak .Naaeem Khudair and Shaker.A.N.Al-Jadaan, The Effects Of 4,4-(4,5,6,7-Tetrahydro- [1,2,3-] Selenadiazolo [4,5e] Pyridine-4,6-Diyl) Bis(Benzene-1,3- Diol) On Fertility, Reproductive Hormones And Ovarian Histological Changes In Female Rats Treated With Dipyrone, Bas.J.Vet.Res.Vol.18, No.1, 2019.
11. Nadheerah F. Neamah And Shaker.A.N.Al-Jadaan, Activity of a novel Selena-diazole derivative compound on primary neuron cells isolation from cortex and hippocampus of 18th day aged fetus of pregnant Wister rat. | International Journal of Pharmaceutical Research | Oct - Dec 2020 | Vol 12 | Issue 4
12. Douglass, I. B. I, AM, Chem. Soc. 1937, 59, 740.
13. Batool S Haddad, Der Pharma Chemica, 2017, 9(20): 25-28.
14. Anja Molter, Jörg Rust, Christian W. Lehmann, and Fabian Mohr. ARKIVOC 2011 (vi) 10-1.
15. Petrov, M. L.; Zmitrovich, N. I. Russ. J. Gen. Chem. 1999, 69, 245.
16. Garud, D. R.; Koketsu, M.; Ishihara, H. Molecules 2007, 12, 504.

17. Ana Carolina Ruberte, Sandra Ramos-Inza, Carlos Aydillo, Irene Talavera, Ignacio Encío, Daniel Plano and Carmen Sanmartín, Novel N, N' -Disubstituted Acylselenoureas as Potential Antioxidant and Cytotoxic Agents. Antioxidants 2020, 9, 55; doi:10.3390/antiox9010055.
18. Dinesh Ramesh Garud, Mamoru Koketsu and Hideharu Ishihara, Review Isoselenocyanates: A Powerful Tool for the Synthesis of Selenium-Containing Heterocycles. Molecules 2007, 12, 504-535.
19. A. I. Vogel Text book of practical organic chemistry, 3rd ed. Longman, London, (1974).
20. Swank, Duane D.; Willett, Roger D. (1965). "The Crystal Structure of Potassium Selenocyanate". Inorganic Chemistry. 4: 499– 50. doi:10.1021/ic50026a013.
21. J. B. Lambert, H.F. Shurvell, D. Lighter, R. G. Cooks, Introduction to Organic Spectroscopy, Collier Macmillan publishers, London (1987).
22. R. Silverstein, G. Brasster and T. C. Morril, Spectrometric Identification of Organic Compounds, 4thed. J. Wiley and Sons, NY (1981).
23. Bushra K. Al-Salamia , Ali J. Hameeda and Ali Z. Al-Rubaie, Egypt. J. Chem. Vol. 64, No. 2 pp. 751 - 759 (2021).
24. B. A. Gingras, T. Suprunchuk, and C. H. Bayley, Canadian Journal of Chemistry. Vol.43, pp 1650-1655 (1965).
25. European Patent Application, EP 3 351 535 A1. Bulletin 2018. /30.
26. Marta Díaz, Héctor de Lucio,E sther Moreno, Socorro Espuelas, Carlos Aydillo, Antonio Jiménez-Ruiz, Miguel Ángel Toro, Killian Jesús Gutiérrez, Victor Martínez-Merino, Alfonso Cornejo, Juan Antonio Palop, Carmen Sanmartín, Daniel Plano. American Society for Microbiology, Antimicrobial Agents and Chemotherapy, Volume 63, Issue 5, May 2019. doi:10.1128/AAC.02200-18.