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Cytotoxicity of New Selenoimine, Selenonitrone, and Nitrone Derivatives Against Human Breast Cancer MDA-MB231 Cells

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Abstract

A series of new nitrone, selenoimine and selenonitrone derivatives were synthesized. Nitrone and selenonitrone derivatives were synthesized through the condensation reaction between N-mono substitutedhydroxylamine and carbonyl compounds substituted with electron donating groups, such as di(4-methoxy)benzoyl diselenide, 4-(N, N-dimethylamino) benzoyl selenonitrile and 4, 4'-di(N, N- dimethylamino)benzil, afforded a variety of new nitrone and selenonitrone compounds. Selenoimine derivative was synthesized through the condensation reaction between tert-butyl amine and (4-methoxybenzoyl selenonitrile). The yield of synthesized compounds (N_1, N_2, N_3, N_4 and N_5 were (66, 60, 61, 62 and 45) %, respectively. The structures of the synthesized compounds were characterized by FT-IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra. Cytotoxicity of selenonitrone (N_1) and selenoimine (N_3) derivatives against breast cancer cells (MDA-MB231) were evaluated for 24 and 48 h via MTT assay. The IC_{50} value of compound N_1 was 1.714 and 1.897 µM for 24 h and 48 h, respectively. The IC_{50} value of compound N_3 was 1.438 and 2.469 µM for 24 h and 48 h, respectively. The results suggested selenonitrone (N_1) and selenoimine (N_3) as anti-breast cancer potential lead compound with future merit investigations.

Keywords: Benzil, MTT assay; Nitrone ; Selenocarbonyl; Selenoimine; Selenonitrones.

Introduction

The synthesis of nitrone with high biological activity has received considerable scientific interest [1]. Nitrone and Imine compounds extensive interest among scientists worldwide because of their versatility and they serves as a back bone for the synthesis of various heterocyclic compounds [2]. Organoselenium compounds can be used as building blocks in the synthesis of various natural and biologically active compounds [3,4]. There are many synthetic methods for the synthesis of nitrones and organoselenium compounds that have been reported by several reactions [5,6]. Nitrones are synthesized *via* the condensation method of carbonyl compounds with N- monosubstitutedhydroxylamines [7,8]. while the condensation of various substituted dibenzoyl diselenide and benzoyl selenonitrile with N- mono substituted hydroxylamines leads to form a series of selenonitrone compounds [9,10]. The preparation of benzoylselenonitrile is obtained by the reaction between benzoyl chloride and potassium selenonitrile) [11,12]. The alkaline hydrolysis of substiuted benzoylselenonitrile leads to the formation of dibenzoyl diselenide [13]. Hence, the chemotherapy used for treating many types of tumors with harmful side effects. Therefore, searching for the new chemotherapy agents with less side effects is still continuous [14].

Breast cancer is a common disease in women and caused via several factors like inherited and environmental factors [15]. According to world health organization statistics of breast cancer cases, in 2018, estimated about 627,000 women died and increased yearly in the worldwide [16]. In Iraq, breast cancer is the first in the list of top ten cancer types, in 2016, estimated about 897 women died and increased through the last three years because of poor knowledge and education of symptoms and risk factors between local women [17,18].

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The chemotherapy treatment of breast cancer is still continual to discover new agents as inhibitors for breast cancer proteins [19]. Hence, the continuous researches for looking a new chemotherapy agents as anti-breast cancer inhibitors or drugs with less toxic. In this research, synthesized one selenoimine derivative, three selenonitrone derivatives, and one nitrone compound. One derivative from each group of selenoimine (N_3) and selenonitrone (N_1) derivative were examined as anti-proliferation of breast cancer cells (MDA-MB231) with time exposure for 24 and 48 hours.

Experimental

Chemistry

All chemicals were obtained from standard commercial sources. The instrument Electro thermal IA 9200 used for melting points measures. Bruker spectrometer used for FT-IR spectra. Bruker NMR spectrometer used for ^{1}H and ^{13}C NMR spectra in DMSO and δ units downfield from internal reference Me4Si using a 300 MHz. Shimadzu QP GC-MS used for determining molecular weight of the synthesis compounds. Vario EL III instrument used for elemental analysis.

Synthesis of Carbonylselenonitrile [20]

In this procedure, solution contained KCN (0.8) and 50 ml of absolute ethanol was added to a solution of selenium metal (1 gm.; 1.25 moles) in 15 ml of absolute ethanol. 3 hours refluxed then a solution of substituted benzoyl chloride (2.06 ml 0.025 moles) was added and refluxed for 2 h. Finally, ethanol used to recrystallized.

Synthesis of Dibenzoyl diselenide [21]

Here, mixture of carbonylselenonytrile (0.28 gm; 1.02 moles) in 25 ml absolute ethanol were added to a solution of sodium hydroxide (0.16 gm; 2.47 moles) in 15 ml absolute ethanol. Stirred at 40 o C for 50 min and then refluxed for 1 h. A solution of substituted benzoyl chloride (2.06 ml 0.025 mole) was added and refluxed for 2 h. Next, cooled to room temperature and filtered with 10% HCL. The resultant was red solid compound, washed with a small amount of benzene and dried. Mixture of methanol and dichloro- methane (1:4) solvents used to recrystallization and obtained a red solid compounds.

Synthesis of Substituted Benzil [22]

Mixture of KCN (2.0 gm.; 0.036 mole) and 15 ml of H_2O was added to a mixture of benzaldehyde (3.7 gm.; 0.03 mole) and 30 ml of ethanol. 30 min refluxed for 0.5 h then cooled, the resultant was yellow solid compound of benzoin, washed with (1: 1- water: ethanol) and dried. Next, 14 ml of concentrated nitric acid added to a solution of benzoin (0.4 gm.; 0.018 moles) in ethanol (30 ml). Stirred and heated at 50 °C for 11 min and then 75 ml of H_2O was added. Then, cooled and obtained a yellow solid compound of benzil. Methanol used to recrystallized process.

Synthesis of Selenoimine [23]

A mixture of amine (0.028 mole) and 100 ml of absolute ethanol was stirred and then added to a mixture of anhydrous $CaCl_2$ (15 gm.) in 30 ml of absolute ethanol and placed in a 250 ml one-necked round bottomed flask. Next, stirred and then 3 drops of glacial acetic acid added to mixture of selenocarbonyl compound (0.028 mole) and 30 ml of absolute ethanol to work as a catalyst. Then, cooled, filtered and used absolute ethanol recrystallized process.

Synthesis of Nitrone and Selenonitrone [24]

Diphenyl diselenide used for synthesis (N_1), benzoylselenonitryl used for synthesis (N_3) and benzil used for synthesis (N_4). (0.02 mole) in 30 ml of absolute ethanol added to a mixture of anhydrous $CaCl_2$ (15 gm) in 30 ml of absolute ethanol and placed in 250 ml one-necked round bottomed flask. Next, stirred at 50 °C for 30 min and then [N-benzylhydroxylamine used for synthesis (N_1 and N_3), N-(2-hydroxylethylamine) used for synthesis (N_4)] in 30 ml of absolute ethanol. 3 drops of benzene sulfonic acid added to the mixture and refluxed in dark overnight. Then, cooled, filtered and recrystallized by absolute ethanol. The reaction steps of new compounds synthesis showed in **scheme** 1. FT-IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and Elemental analysis (CHN) were used to characterize the chemical structure of new compounds and approved it in agreement with the theoretical calculation. Physical properties of synthesized compounds are represented in **Table** (1).

MTT assay

MTT assay used according to Ali et al. method with some modification [24]. The anti-proliferative effects of compounds N_1 and N_3 on MDA-MB231 cells were examined. The cell lines were seeded in 96 plates/well for 24 h. The cells were exposure to various concentrations of compounds (0.7, 5, 25, 50, 250, 500) µM for 24 h, and 48 h respectively. Next, 50 µM of MTT was added to dissolve the purple formazan crystals, followed by 4 h incubation. The absorbance was measured at 570 nm in a thermo micro-plate reader. Equation (1) used to estimate the cell viability:

$$Cell\ viability\ \% = \left[\frac{Control - Treated}{Control}\right] X\ 1 \ldots (1)$$

Statically analysis:

GraphPad prism 8.1 software used to estimate IC_{50} values for compounds N_1 and N_3, and analyzed using three column analysis of XY variable slope equation.

Table (1) Physical properties of synthesized compounds

Compound symbol	M.p. °C	Time of reaction in minutes	Yield (%)
N_1	200-201	12	66
N_2	140-142	12	60
N_3	99-101	11	61
N_4	180-182	23	62
N_5	153-155	18	45

Results and discussion

Selenonitrone compounds, N_1, N_2, and N_4 were synthesized by treatment of N- benzylhydroxylamine with selenocarbonyl derivatives, **scheme**. 1 (A), while nitrone compound N5 was synthesized by the reaction of N-(2-hydroxylethyl) hydroxylamine with carbonyl derivative, benzil, as shown in **scheme**1 (B)). Selenoimine compound N_3 was synthesized by the reaction of tert-butyl amine with selenocarbonyl derivative. The synthesized compounds were in low yield this is mainly due to the easily decomposed of nitrone and organoselenium compounds in light and moisture. The synthesized nitrone compound (N_5) has been studied by using UV spectroscopy. Nitrone compound was measured at a concentration of 1*10-4 and the spectrum showed two bands for nitrone group (CH=N→O) and aromatic rings which due to the electronic transitions of n→π* and π→π*. All the FT-IR spectra of synthesized compounds (selenoimine, nitrone and selenonitrone) showed the disappearance peaks due to the stretching vibration of (C=O) of carbonyl band in the region **(1768-1665) cm^{-1}** and the appearance peaks due to the stretching vibration of (C=N) and the appearance peak due to the stretching vibration of (N-O) due to nitrone group, (C=N→O). The spectra showed peaks of stretching vibration of (C=C), (C-H) aliphatic and (C-H) aromatic ring. Nitrone compound (N_5) showed peak of the stretching vibration of (O-H) group. The compounds N_1, N_2, N_3 and N_4 were showed peaks of the stretching vibration of (C-Se). Selenonitrone (N_4) was showed a peak of the stretching vibration due to nitrile group, (C≡N). All the ^{1}H-NMR spectra of selenoimine, selenonitrones and nitrone were showed multiplet signals aromatic protons rings. The spectrum of nitrone (N_5) was showed two signals due to the protons of two CH_2 groups and showed a signal due to the proton of (OH) group, while the spectra of selenonitrone N_1, N_2, and N_4 were showed one signal due to the protons of CH_2 group. All the ^{13}C-NMR spectra of synthesized compounds were in agreement with the suggested structures. Mass spectra of selenoimine and selenonitrone compounds gave the molecular ion and other fragments which indicated the structure of synthesized selenonitrone compounds. Nitrone compounds N_5 have been diagnosed by elemental analysis, and all the results were in agreement with the calculated values. The synthesized compounds have been kept in dry and dark place because these compounds easily decomposed in moisture and light.

(N_1) Di(C-4-methoxy phenyl-*N*- benzyl nitrone) diselenide

Orange powder; yield: 66 %; m.p. 200-201 °C; FT-IR (ν cm^{-1}): 3111 (ν CH aromatic), 2890-2889 (ν CH aliphatic)1588 (ν C=N), 1453 (ν C=C), 1321 (C-N), 1299 (ν N-O), 589 (ν C-Se); ^{1}H-NMR (DMSO, 300 MHz; δ ppm) δ: 7.51 (m, 5H,Ph), 7. ٣٢(m, 4H, ph), 4. ٠٥(s, 2H, CH_2), 3.8 (s, OCH_3); ^{13}C-NMR (DMSO, 300 MHz; δ ppm): 57.04, ١٢١.00, 126.04, 128.21, 129.94, 130.75, 132.35, 141.20, 142.34, 145.24, 165.71; MS: m/z: 638.4753 (M^+).

(N_2) Di(C-4-methoxy phenyl-*N*-4-methoxybenzyl nitrone) diselenide

Yellow powder; Yields: 60%; m.p. 140-142 °C; FT-IR (ν cm^{-1}): 3209(CH aromatic), 2882-2870 (CH aliphatic), 1614 (ν C=N), 1554 (ν C=C), 1295(ν C-N), 1179 (ν N-O), 580 (C-Se),; ^{1}H-NMR (DMSO, 300 MHz; δ ppm) δ: 7.79 (m, 4H, ph), 7.70 (m, 4H,Ph), 4.20 (s, 2H, CH_2), 3.6 (s, 3H, OCH_3), 3.4 (s, 3H, OCH_3) ; ^{13}C-NMR (DMSO, 300 MHz; δ ppm): 60.00, 60.53, 113.74, 120.67, 123.75, 125.67, 129.67, 130.56, 140.67, 145.50, 160.81, 162.33; MS: m/z: (M+) 698.5250.

(N_3) *tert*-Butyl-*N*-(1, 1-(4-methoxyphenyl) selenonitrile methylidene) amine.

Yellow powder; yield: 61 %; m.p. 99-101 °C; FT-IR (ν cm^{-1}): 3120 (ν CH aromatic), 2898-2874 (ν CH aliphatic), 2194 (ν C≡N), 1601 (ν C=N), 1587 (ν C=C), 1360 (ν C-N), 588 (ν C-Se); ^{1}H-NMR (DMSO, 300 MHz; δ ppm): 7.0 (m, 4H, ph), 3.7 (s, 3H, OCH_3), 1.9 (s, ٩H, ٣CH_3(*t*-but)); ^{13}C-NMR (DMSO, 300 MHz; δ ppm): 56.74, 124.00, 125.81, 126.12, 131.75, 133.43, 134.32, 140.64, 162.96; MS: m/z: (M^+) 295.1198.

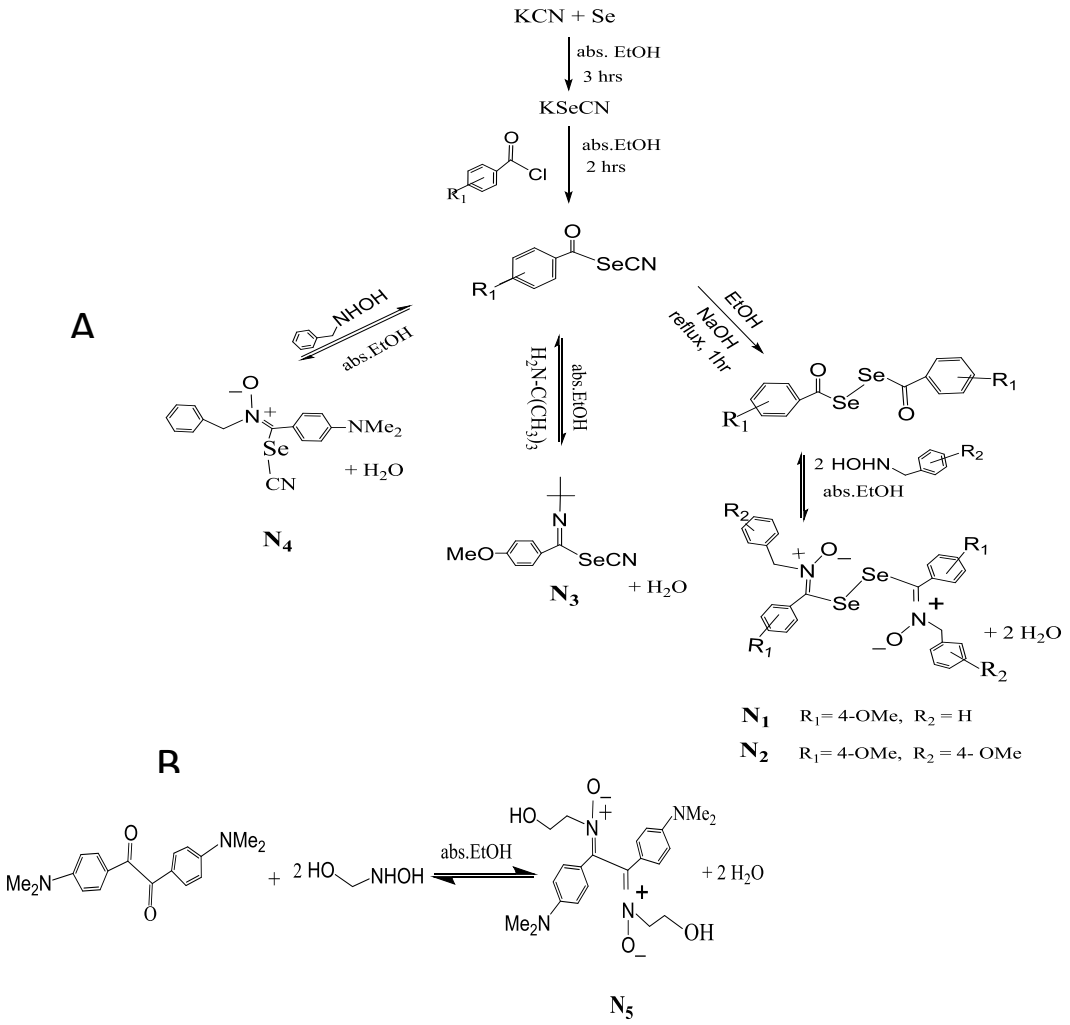
(N_4) C-(4- dimethylamino phenyl) seleno nitrile-*N*-benzyl nitrone

Orange powder; Yield: 62 %; m.p. 180-182 °C; FT-IR ν cm^{-1}: 3108 (ν CH arom.), 2917-2895 (ν CH aliph), 2101 (ν C≡N), 1589 (ν C=N), 1452 (ν C=C), 1375 (ν C-N), 1187 (ν N-O), 580 (ν C-Se); ^{1}H-NMR [300MHz, (DMSO), δ (ppm)]; 7.7 (m, 4H, ph) 7.3 (m, 5H, ph), 3.98 (s, 2H, CH_2), 1.7 (s, 2 CH_3); ^{13}C-NMR [300MHz, (DMSO), δ (ppm)]; 33.9, 35.1, 35.9,

35.9, 118.5, 120.O, 121.9, 122.6, 125.9, 123.9, 124.3, 140.9; MS: m/z: 358.2957 (M^+).

(N_5) C, C'-Bis(4-dimethylamino phenyl-*N*-benzyl nitrone)

Orange powder; yield: 45 %; m.p. 153-155 °C; UV (nm): 383-360 (n→π* nm) (C=N→O), 344-310 and 232-274 (π→π* nm) (C=N→O) and (aromatic); FT-IR (ν cm^{-1}): 3310 (ν OH), 3121 (ν CH aromatic), 2884-2868 (ν CH aliphatic), 1595 (ν C=N), 1563 (ν C=C), 1346 (ν C-N), 1172 (ν N-O); ^{1}H-NMR (DMSO, 300 MHz; δ ppm): 7.14 (m, 4H, ph), 4.10 (t, 2H, CH_2, J = 7.3 Hz), 3.95 (t, 2H, CH_2, J = 7.2 Hz), 3.50 (s, OH), 1.6 (s, CH_3); ^{13}C-NMR (DMSO, 300 MHz; δ ppm): 121.31, 123.10, 125.91, 127.32, 130.63, 13295, 141.76, 164.22; Anal. for C22H30N4O4: C 63.76, H 7.24, N 13.52. Found: C 63.66, H 7.20, N 13.36.



Scheme 1: The steps of chemical reactions: **A)** selenoimine and selenonitrone derivatives synthesis. **B)** Synthesis of nitrone compound.

To examine the anti-breast cancer activity of compounds N_1 and N_3, the MTT method was performed to estimate IC_{50} values for 24 h and 48 h.

Cell viability study of compounds (N_1 and N_3) on breast cancer cells

The previous studies showed that selenium element could prevent cancer risk in humans [25]. Therefore,

synthesis new organometallic derivatives contains selenium element in their structure may develop the new anticancer agents [26]. Recently, increased the interests of developing new selenium derivatives as chemopreventative agents against various tumor [27]. Although the relation between breast cancer risk and selenium element still unclear and requires extensive studies to understand the role of selenium element in develop of breast cancer risk [28]. Many organic selenium derivatives have been synthesized and examined against different types of cancers like breast cancer [29]. Liang et al. developed microwave-assisted method to synthesize benzimidazole-containing selenadiazole derivatives and examined their antiproliferative against human breast cancer and they found the compounds synthesized by microwave-assisted technique were exhibited a high level of antibreast or anticancer efficacy [30]. Inês et al. synthesized 6-selenocaffeine from caffeine by microwave-assisted method and examined it against breast cancer. They found it has low cytotoxic potential and may increase it by combined 6-selenocaffein with doxorubixin and oxalipaltin [31]. Wagner et al. synthesized selenium derivative from 3'-Azido-3'-deoxythymidine (AZT) examined against breast cancer cells and they suggested these compounds containing selenium in its formulation are playing a role in the potential therapeutic agents for breast cancer [32].

In this research, synthesized three selenitrone compounds (N_1, N_2, N_4), one selenimine compounds (N_3) and one free selenium nitrone compound (N_5). The cytotoxicity of N_1 and N_3 compounds against breast cancer cells MDA-MB231 were examined for 24h and 48h. IC_{50} values were estimated for compound N_1, 1.714 and 1.897 µM, respectively. The IC_{50} values of compound N_3 were 1.438 and 2.469 µM, respectively, **Fig**. 1 (A and B).

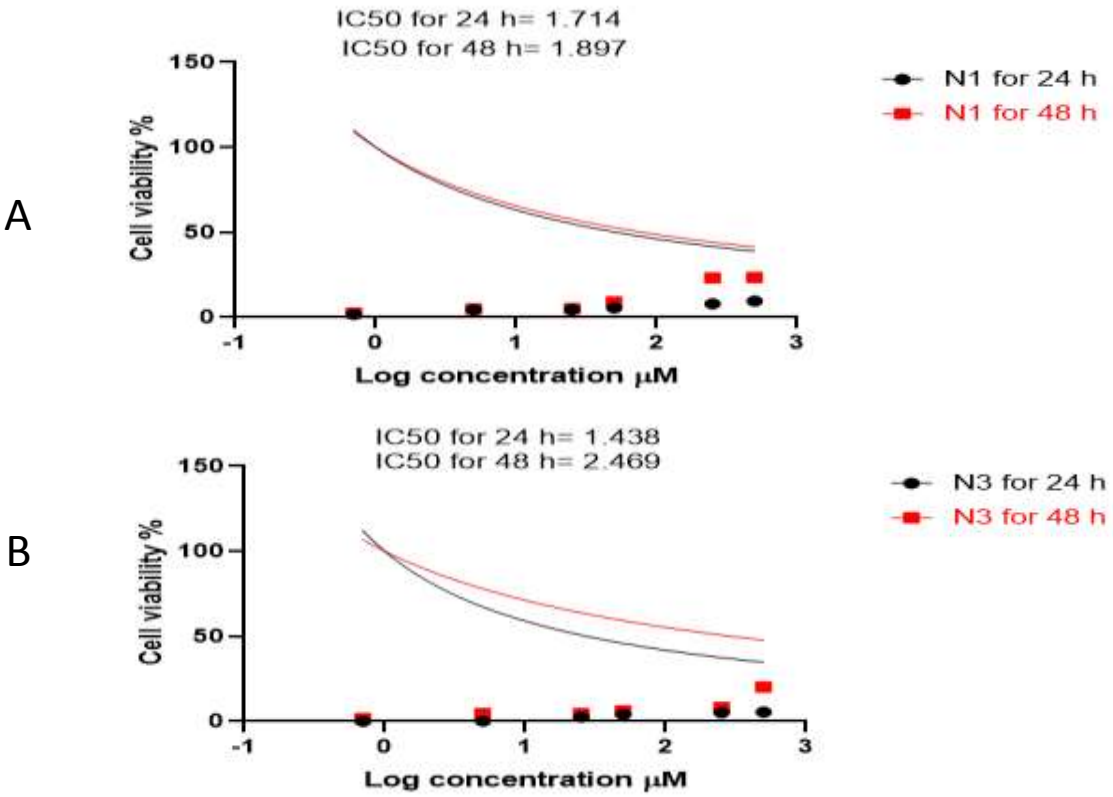


Fig 1: MTT assay analysis to estimate IC_{50} values at 570 nm for 24 h and 48 h for : **A)** Compound N_1. **B**) Compound N_3. GraphPad Prism 8.1 used to estimate IC_{50} values by three column XY variable slope method**.**

IC_{50} value of compound N_1 was slight increased with increased the time exposure, while compound N_3 significant increased with increased time exposure, these differences are minor and probably not biologically meaningful. The nature of chemical structure of compound N_1 enhanced it cytotoxicity function against breast cancer. N_1 compound has two methoxy groups (withdraw groups) in para position

of two molecules of selenonitrone, while compound N_3 has only one methoxy group in para position on one molecule of selenoimine. Increasing the number of function groups like methoxy group will enhance the cytotoxicity of selenium derivatives. We compared N_1 cytotoxicity with other withdraw groups like in Batool and Kawthar report [33] which synthesized a compound contained two fluoro groups in para position and this compound cytotoxicity was lower than compound N_1. Which means selenonitrone compounds involved methoxy groups showed higher toxicity than selenonitrone compounds involved flouro groups. Thus, an extensive study required to compare the function of increasing methoxy and fluoro groups numbers in selenonitrone derivatives.

Conclusions

This study carried out the synthesis of new organic selenium derivatives (three compounds of selenonitrone, one compound of nitrone and one compound of selenoimine). Selenonitrone and nitrone derivatives synthesized by the condensation reaction between carbonyl group and N-monosubstitutedhydroxylamines. Selenoimine derivative synthesized via the condensation reaction between selenocarbonyl group and tert-butyl amine. Among the five compounds, only two compounds selenonitrone (N_1) and selenoimine (N_3) used against breast cancer cells. Compounds N_1 and N_3 are potential anti-breast cancer agent and needed further investigations such as apoptosis, cell cycle, western blot experiments to identify their anticancer targets.

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Conflict of interests: There is no conflict of interest.

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