Synthesis, characterization and Anticancer Evaluation of thiophene based Triazole linked Hydrazones

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Abstract: Triazole derivatives exhibit a wide range of biological activities, such as antimicrobial, antifungal, antileishmanial, antiviral, antitubercular, anticancer, antioxidant, anticholinesterase, anti-inflammatory, antidepressant, antianxiety, and anticonvulsant properties. The recent study developed the synthesis of triazole-linked hydrazones, a stepwise reaction was employed. Initially, clopidogrel was treated with hydrazine monohydrate under reflux for 24 hours, producing acetohydrazide. This intermediate was then reacted with carbon disulfide (CS_2) in dimethylformamide (DMF) at 75°C for 4 hours, yielding oxadiazole derivatives. These oxadiazoles were further reacted with hydrazine monohydrate in ethanol under reflux for 10 hours to form the desired triazole compounds. Subsequently, these oxadiazole and triazole compounds were treated with various nitro benzaldehyde derivatives to produce triazole and oxadiazole analogues' NMR spectroscopy and Cytotoxic study also revealed that notably, derivative 4b demonstrated superior anti-cancer activity relative to the reference compound. Future research aims to enhance the synthesis of novel triazole derivatives with improved anti-cancer properties, striving to develop broad-spectrum efficacy, low-toxicity, and pharmacokinetically favorable drugs.

Keywords: CNS, DMF, FT-IR, NMR, Pharmacokinetic.

1.Introduction

The chemistry of nitrogen-containing heterocyclic compounds is currently attracting significant interest for their applications in the construction of polynuclear metal complexes, materials science, bioinorganic chemistry, the transport and activation of small molecules, and the discovery of new catalyst precursors. Triazoles, in particular, are a notable class of nitrogen-containing rings used both as benzo-fused materials and as core scaffolds in various applications (Şahin, Özgeriş, Kose, Bakan, & Tümer, 2021).

Tumors can arise in many sections of the body due to aberrant cell growth and proliferation, which is the hallmark of cancer, a systemic disease. It remains a significant health issue and ranks as the second leading cause of death worldwide (Khan et al.).

Cancer develops and progresses due to a combination of genetic and internal metabolic abnormalities, as well as the effectiveness of immune system defenses. The heterogeneity of cancer is caused by a variety of endogenous and exogenous causes, including altered glucose metabolism, metabolic dysfunctions, redox imbalances, and chronic inflammation. Precision medicine, immune response modulation, and the use of particular small compounds that disrupt altered metabolic pathways are some of the measures needed to prevent and treat cancer (Holota et al., 2021).

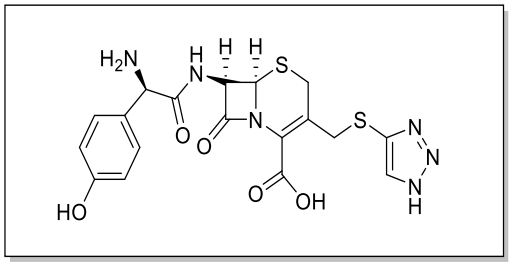


Figure 1: Structure of cefetrizole

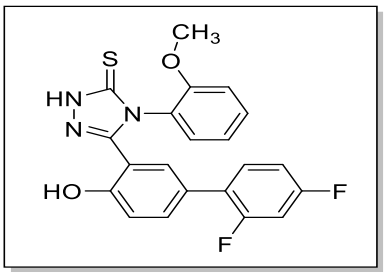


Figure 2: Diflunisal 1,2,4-Triazole

Triazole hybrids with chalcone, quinazoline, pyrazole and many other offer potentials for overcoming drug resistance and improving affinity and efficacy beyond that of their parent compounds. In this study triazole are linked with hydrazones because these versatile compounds demonstrate a broad spectrum of Biochemical and medicinal effects include antiseptic, anti-inflammatory, pain reliever, antimicrobial, antitubercular, antiviral properties, cancer prevention, anticoagulant, antimalarial medication, and anticonvulsant qualities (Korcz, Sączewski, Bednarski, & Kornicka, 2018).

Hydrazones, in particular, are a class of Schiff bases that are gaining popularity in pharmaceutical chemistry due to their distinct biological features Hydrazones have a twisted C=N bond with the active nitrogen atom's singular pair of electrons, hydrazones possess both electrophilic and nucleophilic carbon atoms, as well as nucleophilic nitrogen atoms (Han et al., 2019).

Notably, hydrazones exhibit more potent α-hydrogen compared to acidic ketones. Their ability to combine with other functional groups allows the creation of novel compounds with unique chemical and physical properties. This strategy seeks to leverage the combined biological assessment of both triazole and hydrazone scaffolds, aiming to create potent antitubercular/antimicrobial medications (Yadav, Kaushik, & Kumar, 2023).

In this research paper we focus on synthesis and anticancer evaluation of triazole linked hydrazones. Cytotoxic potential of synthesized compound was checked against lung carcinoma (A-549).

2. Materials and Methods

All reagents were purchased from commercial suppliers and were used without further purification. Melting points were determined on an Electrothermal 9100 melting point apparatus (Weiss-Gallen Kamp, Loughborough, UK) and are uncorrected. 1 H NMR and 13C NMR spectra were recorded on a Bruker 500 MHz and 125 MHz spectrometer (Bruker, Billerica, USA), respectively. While for FT-IR, Bruker Fourier-transform spectrometer was used.

2.1 Synthesis of compounds

2.1.1Preparation of 2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetohydrazide.

0.1g of methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) acetate was subjected to treatment with 0.07ml of hydrazine monohydrate at 0°C in a methanol solvent refluxed for a full day at room temperature in order to create hydrazide. To monitor the status of the reaction TLC was used and product was dried at room temperature. Resulting in 2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetohydrazide in a range of 82–85% (Aher et al., 2009).

2.1.2Preparation of 5-((2-chlorophenyl) (6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) methyl)-1,3,4-oxadiazole-2-thiol

0.05g of Compound 2-(2-chlorophenyl)-2-(6,7-dihydrothieno [3,2-c] pyridin-5(4H)-yl) acetohydrazide was treated with 0.3ml DMF stir for 15 minutes. After cooling the mixture to 0°C, 0.034 ml of carbon disulphide was added, and it was refluxed for four hours at 75°C in an oil bath. Completion of the reaction was checked by TLC yielding oxadiazole about 75% (Kant et al., 2016).

2.1.3 Preparation of 4-amino-5-((2-chlorocyclohexa-1,3-dien-1-yl) (6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) methyl)-4H-1,2,4-triazole-3-thiol

For ten minutes, the 0.1 g of 5-((2-chlorophenyl) (6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) methyl)-1,3,4-oxadiazole-2-thiol was swirled in 5ml of ethanol. 0.074 hydrazine monohydrate was then added, and it was refluxed for 10 hours at a temperature of roughly 50°C. To monitor the reaction's development, TLC was performed. Placed the reaction flask in an ice bowl when the reaction was finished, acidified it with two to three drops of 2N HCL. Precipitates start forming which was filtered and dried (Soleiman-Beigi, Alikarami, & Hosseinzadeh, 2013).

2.1.4 Preparation of of (E)-5-((2-chlorophenyl) (6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) methyl)-4-((2-nitrobenzylidene) amino)-4,5-dihydro-1,3,4-oxadiazole-2-thiol

0.05g of 5-((2-chlorophenyl) (6,7-dihydrothieno[3,2-c] pyridin-5(4H)-yl) methyl)-1,3,4-oxadiazole-2-thiol in 5 ml methanol then 0.022g of 2-nitrobenzaldehyde was added. Stir for 15 minutes, then add two to three drops of lemon extract. Stir for another 12-24 hours. Following the product's drying, TLC was used to monitor the reaction's progress (Bhusnure, Vibhute, Giram, Vibhute, & Bhusnure, 2015).

2.1.5 Preparation of of (E)-5-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-((3-nitrobenzylidene)amino)-4,5-dihydro-1,3,4-oxadiazole-2-thiol

can be obtained by mixing 0.5g of oxadiazole derivative **3** with 5 ml of methanol. After that, add 0.022g of 3-nitro benzaldehyde to the mixture and whisk for a further eight hours. Using TLC,the reaction's completion can be verified. Place it in an ice bath and allow it to cool after cooling precipitates start forming when the process completed filter it and dried it(Akbari Dilmaghani, Nasuhi Pur, & Hatami Nezhad, 2015).

2.1.6 Preparation of (E)-5-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-((2,4-dinitrobenzylidene)amino)-4,5-dihydro-1,3,4-oxadiazole-2-thiol

0.05g of oxadiazole derivatives dissolved in 5 ml methanol. After 15 minutes of stirring added 0.029 g of 2,4-di-nitrobenzaldehyde in it. Continue to stirr for 8 hours. Reaction progress monitored by TLC. Place the flask in ice bath when solution become cool precipitate start forming which is filtered and dried when the reaction is completed.the yield of the product is about 42% (Chittaboina, Xie, & Wang, 2005).

2.1.7 Preparation of (E)-5-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-((2-nitrobenzylidene)amino)-4H-1,2,4-triazole-3-thiol

0.015 g of triazole is added to 5 mL of methanol and .059 grams of 2-nitrobenzaldehyde. After 15 minutes of continuous stirring, add 2-3 drops of lemon extract and keep stirring for 24 hours. Following the drying of the product, TLC is used to monitor the progress of the reaction (Khan et al.).

2.1.8 Preparation of (E)-5-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-((3-nitrobenzylidene)amino)-4H-1,2,4-triazole-3-thiol

0.5g of Triazole derivative **4** was mixed with 5 ml of methanol, then 0.0198g of 3-nitro benzaldehyde was added. Stir continuously for eight hours. TLC verifies the completion of the reaction. After cooling the mixture by submerging the flask in an ice bath, precipitates begin to develop. These are subsequently filtered through filter paper, and the finished product is dried. Yield of product was about 42% (Bitla et al., 2021).

2.1.9 Preparation of (E)-5-((2-chlorophenyl)(6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-((2,4-dinitrobenzylidene)amino)-4H-1,2,4-triazole-3-thiol

By mixing 0.05g of triazole with 5 ml of methanol and continue stirring. After 15 minutes of continuous stirring added 0.025g of 2,4-di-nitro benzaldehyde and stirred for 8 hours. TLC verifies the completion of the reaction. After cooling the mixture by submerging the flask in an ice bath, precipitates begin to develop. These are subsequently filtered through filter paper, and the finished product is dried (Gil, Arévalo, & Lopez, 2007).

2.2 Cytotoxic Assay

The synthesized derivatives 3a-c and 4a-c were investigated against lung carcinoma A-549. Cancer cells were cultured at 37°C in DMEM (Dulbecco's Modified Eagles medium) supplemented with penicillin (100 units/mL) and streptomycin (100µg/mL), 10% FBS (Fetal Bovine Serum), and 5% CO2 in moistened air. Cell viability of these compounds was calculated

using the standard MTT assay (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide). The synthesized compounds were diluted in DMSO (dimethyl-sulfoxide). For cancer cells, a final dose of 0.05% DMSO was applied for 48 hours. several DMSO-treated cells were used as a control in several experimental techniques. MTT reagent (500µg/mL) was applied to the cells and incubated at 37°C for 4 hours. To determine absorbance, a solution of formazan crystals in DMSO was used. The absorbance was measured at 570 nm using a thermos scientific microplate reader. The cell viability was calculated in percentage % (Hafeez, Zahoor, Rasul, Ahmad, & Mansha, 2021).

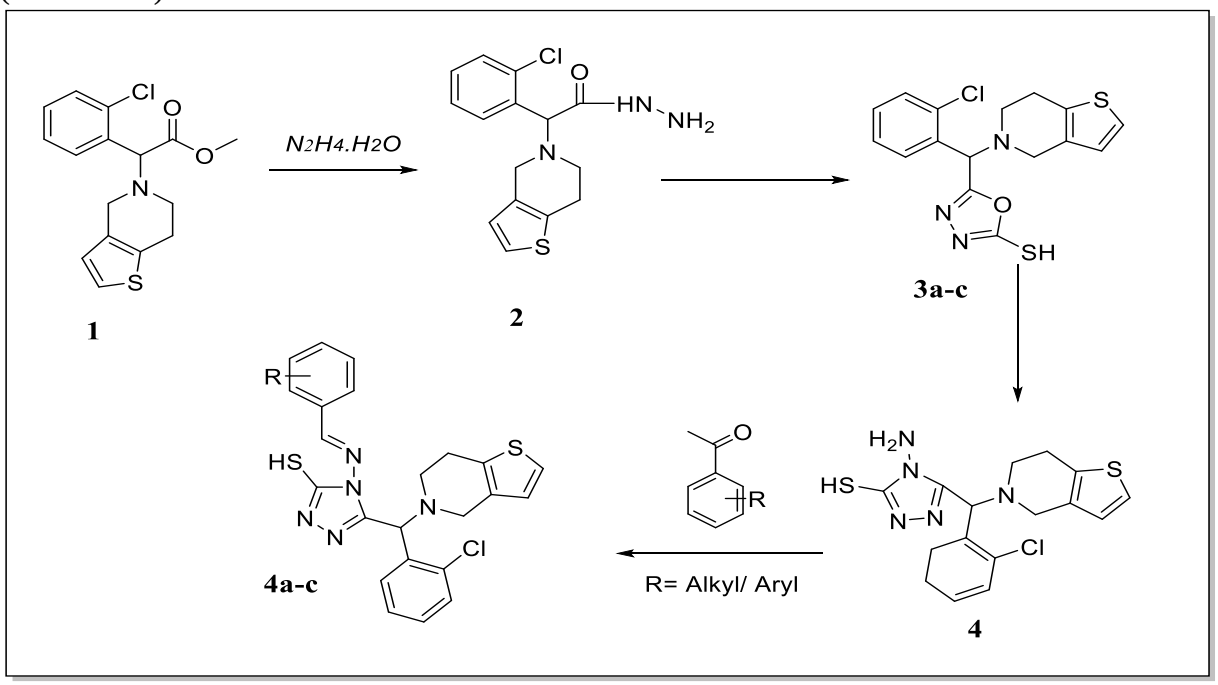
Statistical analysis:

All experiments were performed in triplicate, and the statistical analysis was carried out using Microsoft Excel 2010. Results for cell viability are shown as mean ± SD.

3.Results and Discussion

3.1 Chemistry

Triazoles and oxadiazole derivatives can be synthesized by using the given below (scheme 2.1).



Scheme 3.1: Synthesis of triazole and oxadiazole derivatives

Starting from a drug clopidogrel **1** treated with hydrazine monohydrate for 24 hours with continuous stirring resulting in corresponding hydrazide **2** yielding about 85%**.** Then the hydrazides were treated with CS_2 using DMF as a solvent forming oxadiazole **3.** Then the corresponding oxadiazole are treated with hydrazine monohydrate under reflux condition for 10 hours forming triazoles. These triazole and oxadiazole derivatives are treated with different aldehydes to form oxadiazole hydrazones **3a-c** and triazole hydrazones **4a-c** shown in Figure 3.

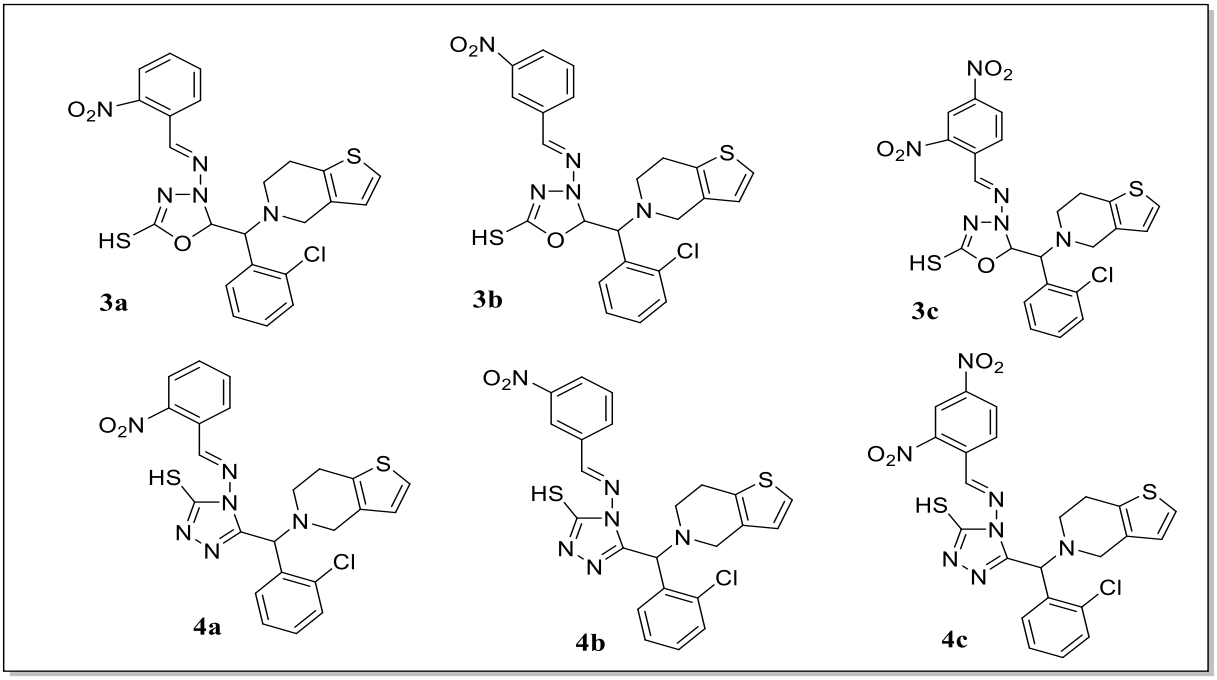


Figure 3: *Derivatives of oxadiazole and triazole.*

NMR values of synthesized compounds

Table 3.1: *NMR spectral values of compounds*

Compounds	NMR Values
2	Yellowish amorphous: 2.60 (CH2, t, 2H), 2.92 (CH2, t, 2H), 3.67(aryl, s, 2H), 4.22 (NH_2, d, 2H), 4.85(CH, s, 1H), 6.98 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d, 1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.68 (aryl, d, 1H), 9.08 (NH, t, 1H).
3	Brownish Yellowish amorphous:2.60 (CH2, t, 2H), 2.92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 5.19 (CH, s, 1H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d, 1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H) 7.68 (aryl, d, 1H), 13.28 (SH, s, 1H).
4	White amorphous: 2.60 (CH2, t, 2H), 2.92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 5.19 (CH, s, 1H), 5.66 (NH_2, s, 2H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d, 1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.68 (aryl, d, 1H), 13.79 (SH, s, 1H).
3a	Off white amorphous: 1.5 (SH, s, 1H), 2.60 (CH2, t, 2H), 2.92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 3.86 (CH, d, 1H), 5.06 (aryl, d, 1H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d, 1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.68 (aryl, d, 1H), 7.59 (aryl, dd, 1H), 7.69 (aryl, dd, 1H), 7.95 (aryl, d, 1H), 8.04 (aryl, d, 1H), 8.35 (CH, s, 1H).
3b	Off white amorphous: 1.5 (SH, s, 1H), 2.60 (CH2, t, 2H), 2.92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 3.86 (CH, d, 1H), 5.06 (aryl, d, 1H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d, 1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.59 (aryl, dd, 1H), 7.68 (aryl, d, 1H), 7.72 (aryl, dd, 1H), 8.09 (aryl, d, 1H), 8.12 (aryl, d, 1H), 8.35 (CH, s, 1H).
3c	Off white amorphous: 1.5 (SH, s, 1H), 2.60 (CH2, t, 2H), 2.92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 3.86 (CH, d, 1H), 5.06 (aryl, d, 1H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d, 1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.68 (aryl, d, 1H), 8.33 (aryl, d, 1H), 8.35 (CH, s, 1H), 8.73 (aryl, d, 1H), 9.15 (aryl, s, 1H).
4a	Off white amorphous: 2.60 (CH2, t, 2H), 2,92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 5.19 (CH, s, 1H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl,

	d,1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.59 (aryl, dd, 1H), 7.68 (aryl, d, 1H), 7.72 (aryl, dd, 1H), 7.98 (aryl, d, 1H), 8.08 (aryl, d, 1H), 9.97 (SH, s, 1H).
4b	Off white amorphous: 2.60 (CH2, t. 2H), 2.92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 5.19 (CH, s, 1H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d,1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.68 (aryl, d, 1H), 7.70 (aryl, dd, 1H), 8.09 (aryl, d, 1H), 8.15 (aryl, d, 1H), 8.48 (aryl, s, 1H), 9.97 (SH, s, 1H).
4c	Off white Amorphous: 2.60 (CH2, t. 2H), 2.92 (CH2, t, 2H), 3.67 (aryl, s, 2H), 5.19 (CH, s, 1H), 6.96 (aryl, d, 1H), 7.21 (aryl, dd, 1H), 7.22 (aryl, d,1H), 7.25 (aryl, dd, 1H), 7.44 (aryl, d, 1H), 7.68 (aryl, d, 1H), 8.33 (aryl, d, 1H), 8.73 (aryl, d, 1H), 9.33 (aryl, d, 1H), 9.97 (SH, s, 1H).

Cytotoxic Evaluation

The MTT assay was used to examine the anticancer potential of newly synthesized compounds 3a-c and 4a-c against the human lung cancer cell line (A-549). The position and no of substituent affect the cell viability of synthesized compounds which was recorded in percentage. First took cancer cells and incubated it for 24 hours. After 24 hours of incubation add MTT reagent dissolved in 10% FBS and incubated it for further 4 hours. After fours hours of incubation added .05% DMSO solution into it and incubated again for 2 hours then record the absorbance at 590nm. Several cells are used as control and other used as treatment in treatment we added the drug synthesized and checked the cell viability of those cells. The cell viability result of those cells indicates that the compound 4b have lowest cell viability as compare to other derivative synthesized that is why it is more potent anticancer drug than the other analogues.

Table 3.2: *Cytotoxic Impact of the synthetic variety Derivatives **3** (a-c), **4** (a-c) Towards A-549 Cancerous Lung Cells*

Compounds	A-549(% Cell viability ± SD)
3a	61.14±2.98
3b	47.31±1.75
3c	75.83±3.29
4a	69.4±4.17
4b	38.87±10.24
4c	81.32±0.69

The impact of nitro group position on the phenyl ring was investigated to provide a full understanding of the cytotoxic activities of produced analogues. This demonstrates that in general, the nitro group is an electron withdrawing group, which improves the anti-cancer activity of the compounds. Among the produced derivatives, 4b and 3b have exhibited stronger cytotoxic activity than other derivatives. Cells treated with 100 µg/mL compound 4b had a viability of 38.87%, while compound 3b had a viability of 47.31%, both lower than the other derivatives. This is owing to the fact that the nitro group in both compounds 4b and 3b is located at the meta position, which increases their anticancer potency.

Conclusion

A Series of novel triaole linked hydrazone derivatives and oxadiazole linked hydrazone derivatives have been synthesized and evaluated fort their cytotoxic study.The cytotoxic study of the derivatives revealed that the compound 4b have potent anti-cancer acticity as cpmpared to other derivatives synthesiszed. These results displayed that the derivatives are potent drug for future study.

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