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Synthesis, Characterization and Molecular docking Analysis of Triazole, Schiff bases and Tetrazole Derivatives Derived from Nitrilotriacetic acid Against Breast Cancer Targets

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ABSTRACT

This study reports the synthesis of novel heterocyclic compounds via a three-step approach: formation of tris(4-aminotriazole-3-thione) (N1) from nitrilotriacetic acid and thiocarbohydrazide, derivatization to Schiff bases (N2–N11) using various aromatic aldehydes, and subsequent conversion to tetrazoles (N12–N19) via reaction with sodium azide. The synthesized compounds were characterized by FT-IR, ^{1}H-NMR, and ^{13}C-NMR. Molecular docking studies against PI3K and HER2 receptors showed strong binding affinities (ΔG values up to -9.8 kcal/mol), indicating promising anticancer potential.

Keywords: Heterocyclic compounds, thiocarbohydrazide, nitrilotriacetic acid, 4-aminotriazole-3-thione, Schiff bases, Tetrazole, Molecular docking, Breast cancer.

INTRODUCTION

Cancer is a highly dangerous disease that poses a high risk to human lives. It is considered the most common reason for loss of lives in the world[1]. Nowadays, chemotherapy, radiotherapy, and surgery are the commonly used techniques for the treatment of cancer. Although resistance to chemotherapeutic drugs is a real problem in chemotherapy,[2] there is a continuous need for new drug development, like heterocyclic compounds that have a wide and significant field within medicinal chemistry because of their large-scale applications in drug design and discovery.[3] However, triazole derivatives attracted considerable attention during the past few decades due to their biological properties, such as anticancer,[4] anti-diabetic,[5] antifungal,[6] antioxidant,[7] antimicrobial,[8] and anti-Alzheimer[9].

The presence of electrons in an sp^2 hybridized orbital of the nitrogen atom of the azomethine group in Schiff's bases is very important in both the chemistry and biology fields; therefore, these compounds have a broad spectrum of biological applications, like analgesic, antioxidant, anticancer, antimicrobial, antiviral, and anti-inflammatory activities, and numerous applications in many fields, including analytical chemistry, dyes, corrosion inhibitors, and ligands for metal complexes.[10] Moreover, tetrazole derivatives can be prepared from the reaction of Schiff bases

with sodium azide by the cyclic addition process. Moreover, tetrazole derivatives can be prepared from the reaction of Schiff bases with sodium azide by the cyclic addition process. These derivatives have shown significant promise in medicinal chemistry, particularly in the design of new pharmaceuticals. As scientists continue to explore their diverse applications, the potential for groundbreaking discoveries in drug development and materials science becomes increasingly apparent. This reaction not only expands the utility of Schiff bases but also opens new avenues for the synthesis of novel compounds with enhanced biological activities.[11] The versatility of these derivatives makes them valuable in developing pharmaceuticals and materials with specific functions. Tetrazole is frequently used as a precursor to create more stable medications for the body, such as viral infection,[12] antifungal,[13] and anticancer,[14] treatments.

As a result of the significant biological activity of the mentioned compounds, we present newly synthesized compounds that show potential as breast cancer treatments, as demonstrated by our molecular docking studies and their biological activities. This research represents an extension of our dedicated efforts in designing and developing a flexible protocol for the synthesis of these crucial compounds, including novel triazole, Schiff bases, and tetrazole derivatives.

EXPERIMENTAL

MATERIALS AND METHODS

Melting points (uncorrected) were measured by electro-thermal SMP30- Stuart melting point apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded using Bruker Bio Spin GmbH Spectrophotometer (400 MHz using TMS as internal standard and using DMSO-d_6 as a solvent) [(s) singlet, (d) doublet, (m) multiply]. FT-IR spectra were recorded using a Japanese-made device (Bruker FT-IR-ATR) in a region confined between 400 and 4000 cm^{-1}. TLC aluminum sheets silica gel 60 F254 were used to monitor the progress of all reactions and the homogeneity of the produced compound. As for the used mobile phase, it consisted of a mixture of ethyl acetate and n-hexane in a ratio of (3:7).

Preparation of thiocarbohydrazide by two different methods

First methods

Carbon disulphide (0.22 mole, 13 mL) was added drop wise to vigorously stirred solution of $NH_2NH_2.H_2O$ (80%) (0.44 mole, 24 mL) in (15 mL) dis. water during (30 minutes). Then the temperature of the reaction was raised to 100-110°C and the reaction mixture was refluxed until the emission of H_2S gas was stopped [(identified by using paper saturated with lead acetate (~3 h)], then the mixture cooled at room temperature. The precipitated thiocarbohydrazide was filtered off, washed with dis. water and then air dried. m.p.: 168- 170°C, yield 35%, color: Pale Yellow Powder. FT-IR ν (cm^{-1}): 3304 and 3267 (primary NH_2), 3165 (N-H), 1279 (C=S).

Second methods

Carbon disulphide (0.20 mole, 12 mL) was added drop wise to vigorously stirred solution of $NH_2NH_2.H_2O$ (80%) (0.22 mole, 12 mL) during 30 minutes. Then the temperature of the reaction was raised to 100-110°C and the reaction mixture was refluxed for (6 hours), then the mixture cooled at room temperature. The precipitated thiocarbohydrazide was filtered off, washed with dis. water and then air dried. m.p: 168-170°C, yield 65%, color pale yellow powder. FT-IR ν (cm^{-1}): 3304 and 3267 (primary NH_2), 3165 (N-H), 1279 (C=S).

Preparation of 5,5',5''-(nitrilotris(methylene)) tris(4-amino-2,4-dihydro-3H-1,2,4-triazole-3-thione) N1[15]

A mixture of Nitrilotriacetic acid (0.0052 mole, 1.0 g) with (0.0157 mole, 1.66 g) of thiocarbo-hydrazide in (30 mL) of absolute EtOH was refluxed for 7 hours. After that, the mixture was cooled at room temperature, the formed precipitate was filtered, washed with ethanol and dried. Table 1, 2, Scheme 1.

Preparation of Schiff Bases (N2-N11)[15,16]

A mixture of N1 (0.00125 mole, 0.5 g) with (0.00375 mole) of different substituted aromatic aldehydes in (30 mL) of absolute ethanol and 7 drops of glacial acetic acid as catalyst was refluxed for 9 hours. After that, the mixture was cooled at room temperature, the formed precipitate was filtered, washed with ethanol and dried. Table 1, 2, Scheme 1.

Table 1: Physical Properties and FT-IR data of triazole (N1), Schiff Bases (N2-N11) and Tetrazole Compounds (N12-N19)

Compounds No	m.p., °C	Yield%	Color	FT-IR, ν(cm^{-1})						
			NH	=CH	CH	C=NC=C(aromatic)			C=S	Others
N1	166-168	95	Milky	3268	3040	2958	1698	…….	1138	3341, 3304 (NH_2)
N2	239-241	81	Yellow	3269	3109	2971	1613	…….	1247	1519 (NO_2)
N3	233-235	50	Yellow	3279	…….	2988	1603	1507	1204	3534 (OH)
N4	244-246	51	Brawn	2989	…….	2957	…….	…….	1201	3039 (OH)
N5	172-175	81	Orange	3131	3040	2983	1647	1593	1167	…….
N6	212-214	84	Yellow	3287	3132	2991	1643	1598	1237	…….
N7	199-200	82	Pale yellow	3250	3136	2962	1606	1504	1242	…….
N8	182-184	80	Milky	3282	3150	2982	1601	1531	1242	…….
N9	194-195	72	Milky	3171	3038	3005	1622	1552	1277	3208 (OH)
N10	213-215	75	Yellow	3289	3120	2968	1644	1506	1266	…….
N11	228-230	72	Yellow	3182	3029	2989	1598	1580	1200	3282 (OH)
N12	Decomposed	45	Yellow	3377, 3268	3105	2973	1615	1517	1244	…….
N13	218-222	86	Yellow	3234	3122	2950	1666	1593	1228	…….
N14	Decomposed	35	Milky	3391	3085	2951	1666	1626	1240	…….
N15	Decomposed	31	White	3390	3085	2951	1665	1626	1240	…….
N16	Decomposed	36	Yellow	3391	3040	2950	1666	1627	1204	…….
N17	Decomposed	30	Yellow	3085	3009	2950	1665	1626	1239	3393 (OH)
N18	Decomposed	56	White	3287	3147	2818	1669	1513	1243	
N19	Decomposed	36	Milky	3009		2951	1663	1624	1240	3085 (OH)

Table 2: The ^{1}H-NMR and ^{13}C-NMR spectral data of Compounds (N1, N5, N6, N8-N10, N13, N17, N18)

Compounds No	^{1}H-NMR (DMSO-d_6,400 MHz), δ (ppm)	^{13}C-NMR (DMSO-d_6,100 MHz), δ (ppm)
N1	3.48 (s, 6H, 3*CH_2), 6.80 (br,9H, 3*NH & 3*NH_2)	(CH_2 = 55.52), (C=N = 173.14), (C=S = 181.92)
N5	2.99 (s, 18H, 3*-N(CH_3)$_2$), 3.50 (s, 6H, 3*CH_2) 6.69-8.51 (m, 15H, 3* Ar-H & 3*=CH), 11.19-11.49 (d, 3H, 3* NH)	
N6	3.50 (s, 6H, 3*CH_2), 3.87 (s, 9H, 3*OCH_3), 6.94-8.54 (m, 15H, 3*Ar-H & 3*=CH), 11.43-11.87 (t, 3H, 3*NH)	
N8	3.51 (s, 6H, 3*CH_2), 7.36-8.01 (m, 18H, 3*Ar-H & 3*=CH), 11.43-11.92 (t, 3H, 3*NH)	
N9	3.51 (s, 6H, 3*CH_2), 6.80-8.77 (m, 15H, 3*Ar-H & 3*=CH), 11.38-11.64 (d , 3H, 3*NH), 11.90-12.09 (d, 3H, 3*OH)	
N10	3.51 (s, 6H, 3*CH_2), 3.74-3.83 (m, 18H, 6*OCH_3), 6.94-7.93 (m, 12H, 3*Ar-H & 3*=CH), 11.34 (s, 3H, 3* NH)	(3* CH2= 55.21), (6*OCH3= 55.97-56.21), (carbon aromatic ring =108.90-149.50), (3* N=C = 149.61), (3* C=N for triazole ring = 150.96), (3* C=S = 172.94)
N13	2.96-2.99 (s, 24H, 3*CH2, 6*CH_3), 6.69-7.99 (m, 18H, 3*Ar-H & 3*NH of tetrazole ring), 11.19-11.49 (d, 3H, 3*NH of triazole ring)	
N17	3.17 (s, 6H, 3*CH_2), 6.81-7.42 (m, 18H, 3*Ar-H, 3*(CH & NH of tetrazole ring)), 7.72 (s, 3H, 3*OH), 9.00 (s, 3H, 3*NH)	
N18	3.79 (s, 9H, 3*OCH_3), 3.83 (s, 9H, 3*OCH_3), 4.82 (s, 6H,3*CH_2), 6.94-7.14 (m, 12H, Ar-H & CH of tetrazole ring), 9.80 (s, 3H, 3*NH of tetrazole ring), 11.31 (s, 3H, 3*NH of triazole ring)	

Preparation of Tetrazole Compounds (N12-N19)[17]

A mixture of different Schiff bases (0.0006 mole) with (0.117 g, 0.0018 mole) of sodium azide in (30 mL) of dry-THF was refluxed for 8 hours. After that, the mixture was cooled at room temperature, the formed precipitate was filtered, washed with ethanol and dried. Table 1, 2, Scheme 1.

Molecular docking

The binding orientation and interaction of the potent antitumor derivatives (N2, N4, N11, N16, N17 and N19) as shown in Fig. (1-12) into anticancer regulating protein namely PI3K (Phosphoinositide 3-Kinase) and HER2 Tyrosine Kinases (e.g., HER2 receptor kinase).were simulated using MCULE Docking and BIOVIA discovery studio 2024 software. And the selected protein three dimensional 3D was downloaded from the PDB (protein data bank) website as 6zad which mutated in breast cancer, and the attribute active side of enzyme was took from

swiss target prediction, protein and Ligands were added to molecular docking, Molecular docking is to estimate best position, orientation and confirmation of miniature molecule (drug candidate) when bind to protein make it much easier to optimize the drugs later[18]. MCULE assesses the binding strength between the chemical compound and enzyme by calculating the interaction's ΔG value (free energy) as shown in tables (3-6). ΔG value give information about the strength of interaction and its potential impact on the enzyme as it show in higher negative value mean the binding is spontaneous its more prefer[19]. Molecule docking (discovery studio) give the 2d and 3D image of the interaction between the enzyme and prepared chemical compounds as shown in Figures (1-12).

Molecular docking showed highest negative value of Schiff bases N4 (-9.6), and tetrazole compounds N17 (-9.8) with enzyme PI3K, while with enzyme HER2 Schiff bases and tetrazole compounds showed highest negative scores as following data N4 (-9.1) and tetrazole compounds N12 and N16 were (-9.3); this because of some reasons hydrogen bonds: the more hydrogen bonds the compound forms with the protein, the stronger the binding. Hydrophobic interactions: some compounds fit into water-repellent (hydrophobic) pockets inside the protein, enhancing binding. Electrostatic Attraction: opposite charges between the compound and the protein increase binding strength. Shape compatibility: how well the compound's shape fits the binding site in the protein, molecular flexibility: some compounds are flexible and can adjust their shape to bind more effectively. Chemical Structure: the presence of active chemical groups like amines or carboxyl groups helps form stronger interactions.

Table 3: Binding energies of the potent anticancer derivatives (Schiff bases) with examined protein PI3K

Ligands	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11
PI3K ΔG Kcal/mol	-6.6	-9.3	-7.9	-9.6	-5.3	-7.9	-7.8	-8.0	-8.3	-6.5	-8.8

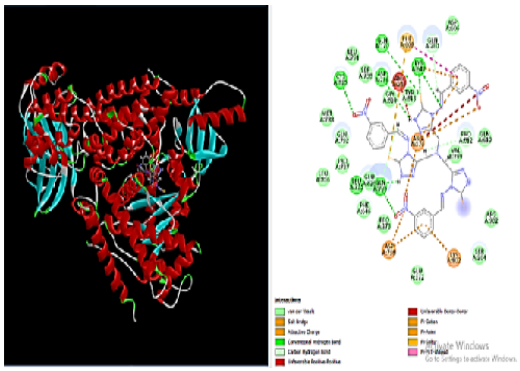


Fig. 1. 3D & 2D Illustrated of possible interaction of compound N2 with the PI3K protein

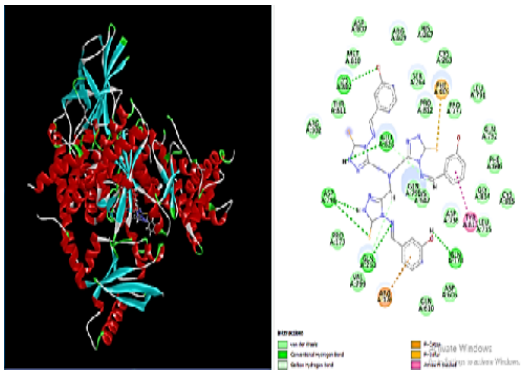


Fig. 2. 3D & 2D Illustrated of possible interaction of compound N4 with the PI3K protein

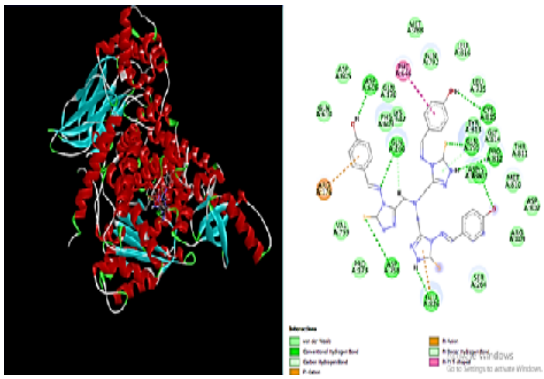


Fig. 3. 3D & 2D Illustrated of possible interaction of compound N11 with the PI3K protein

Table 4: Binding energies of the potent anticancer derivatives (Schiff bases) with examined protein HER2

Ligands	N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11
HER2 ΔG Kcal/mol	-7.5	-7.9	-7.4	-9.1	-7.6	-7.8	-6.7	-8.1	-8.0	-6.8	-7.5

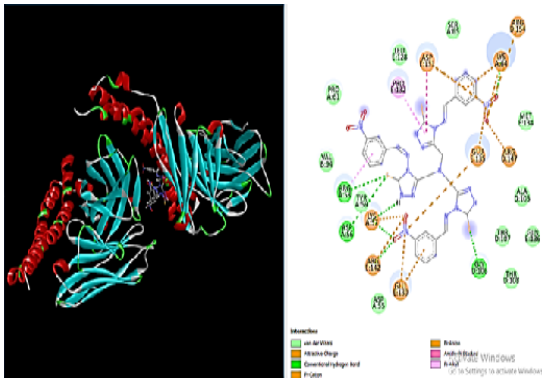


Fig. 4. 3D & 2D Illustrated of possible interaction of compound N2 with the HER2 protein

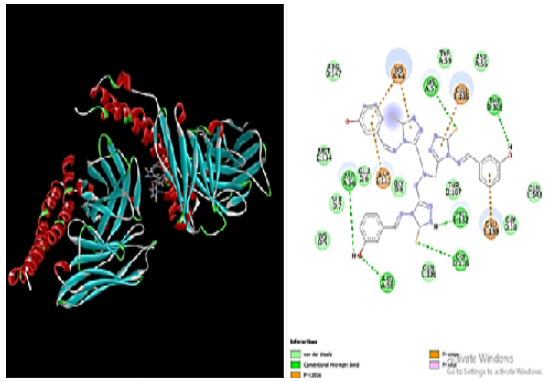


Fig. 5. 3D & 2D Illustrated of possible interaction of compound N4 with the HER2 protein

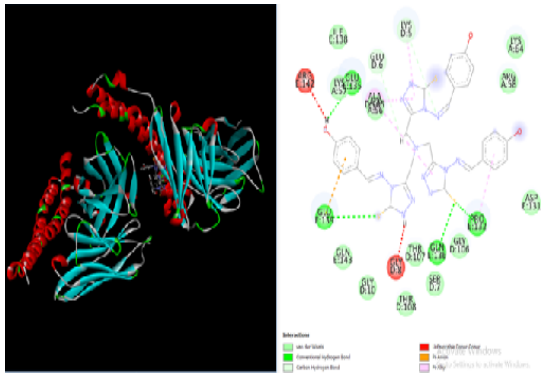


Fig. 6. 3D&2D Illustrated of possible interaction of compound N11 with the HER2 protein

Table 5: Binding energies of the potent anticancer derivatives (tetrazole compounds) with examined protein PI3K

Ligands	N12	N13	N14	N15	N16	N17	N18	N19
PI3K ΔG Kcal/mol	-7.7	-7.4	-6.8	-8.0	-9.4	-9.8	-6.0	-9.6

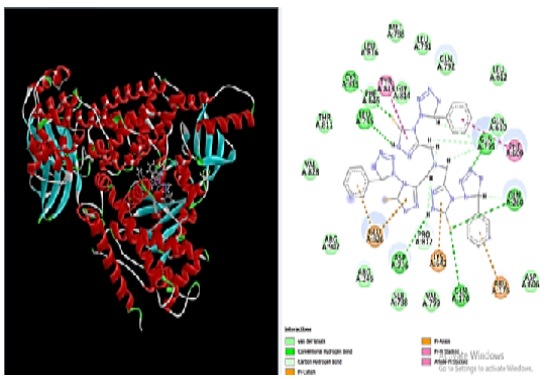


Fig. 7. 3D & 2D Illustrated of possible interaction of compound N16 with the PI3K protein

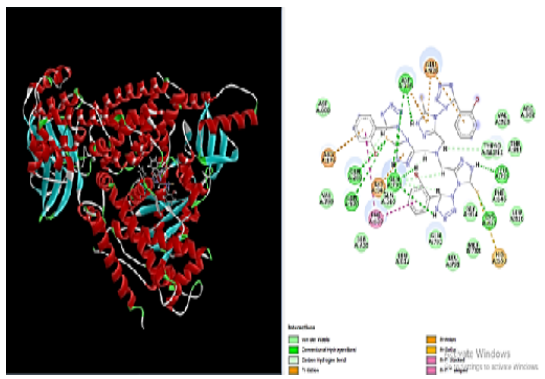


Fig. 8. 3D & 2D Illustrated of possible interaction of compound N17 with the PI3K protein

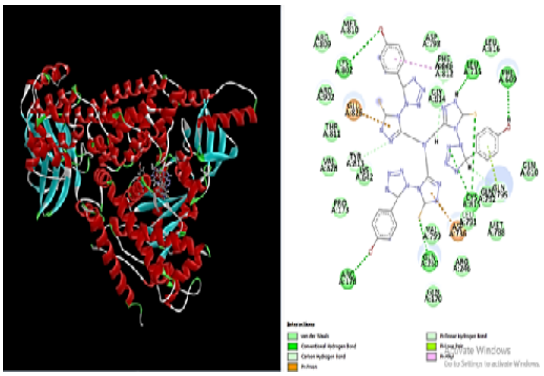


Fig. 9. 3D & 2D Illustrated of possible interaction of compound N19 with the PI3K protein

Table 6: Binding energies of the potent anticancer derivatives (tetrazole compounds) with examined protein HER2

Ligands	N12	N13	N14	N15	N16	N17	N18	N19
HER2 ΔG Kcal/mol	-9.3	-8.1	-9.2	-8.9	-9.3	-8.5	-6.9	-8.7

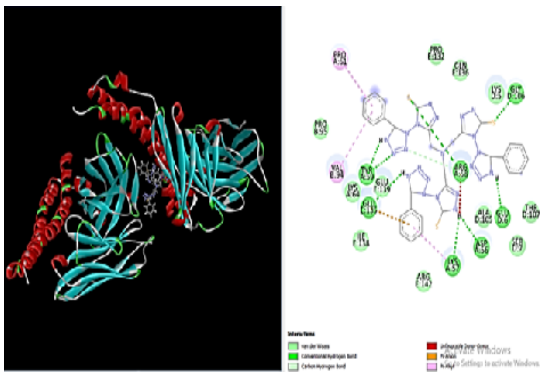


Fig. 10. 3D & 2D Illustrated of possible interaction of compound N16 with the HER2 protein

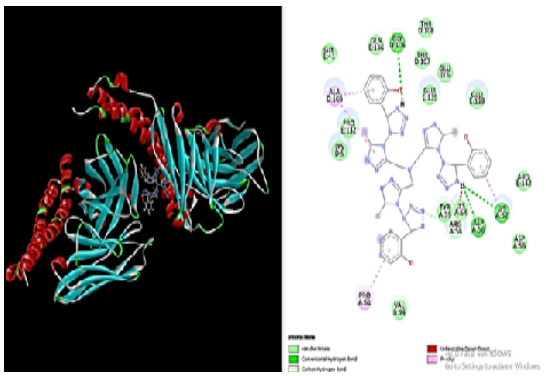


Fig. 11. 3D & 2D Illustrated of possible interaction of compound N17 with the HER2 protein

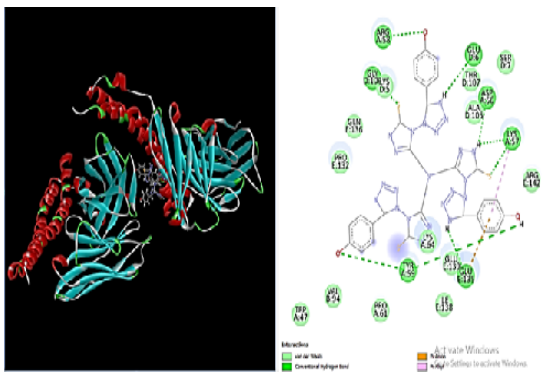


Fig. 12. 3D & 2D Illustrated of possible interaction of compound N19 with the HER2 protein

RESULTS AND DISCUSSION

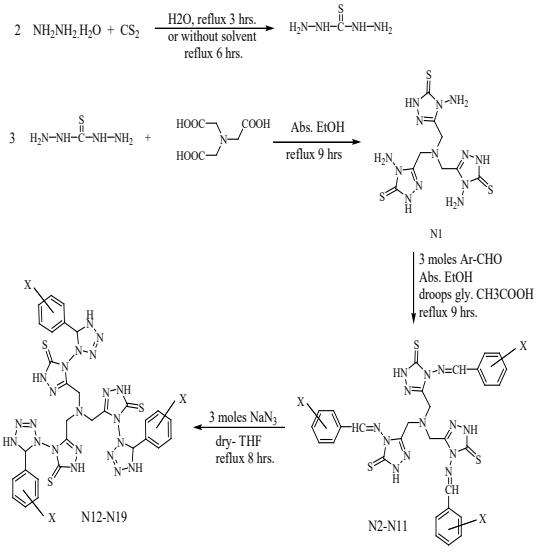
In this study, the nitrilotriacetic acid was reacted in three different paths to obtain many compounds that are expected to be biologically effective as the similar compounds prepared before[20-32]. Where the first path includes the preparation of Tris-4-aminotriazole-3-thione compound (N1), the second path includes the preparation of Schiff bases compounds (N2-N11), while the third path

includes the preparation of heterocyclic compounds represented by tetrazoles derivatives.

The Tris-4-aminotriazole-3-thione compound (N1) was prepared from the reaction of nitrilotriacetic acid with thiocarbohydrazide by refluxing in absolute ethanol, as shown in Scheme 1, and the compound was diagnosed using spectrophotometry (FT-IR, ^{1}H-NMR & ^{13}C-NMR). The FT-IR spectrum gave two absorption bands for the (NH_2) group at the frequency 3341-3304 cm^{-1}, also absorption bands for the (NH) group at 3268 cm^{-1}, in addition absorption bands for the (=CH) group at 3040 cm^{-1} as well as an absorption band at 2958 cm^{-1} belonging to the (C-H aliphatic), and also (C=N) group that gave an absorption band at 1698 cm^{-1}, in addition, the frequency 1138 cm^{-1} belonging to the (C=S) group, where the results were functional groups give an excellent evidence about the compound N1 formation. The (^{1}H-NMR) spectrum also gave a signal at δ 3.48 ppm for the (N-CH_2-) group and a broad signal at δ 6.80 ppm for the (NH & NH_2). The (^{13}C-NMR) spectrum also gave a signal at δ 55.52 ppm for the (-CH_2-) group and a signal at δ 173.14 ppm for the (C=N) and finally, a signal at δ 181.92 ppm for the (C=S). Where the results were identical to the proposed compound N1.

The new Schiff bases compounds (N2-N11) were prepared from the reaction of compound N1 with aromatic aldehyde substitutes, using ethanol as a solvent and glacial acetic acid as a catalyst, Scheme 1. The structure of the Schiff base compound N10 was confirmed according to (IR, ^{1}H-NMR &^{13}C-NMR) spectral data. The appearance of a characteristic stretching absorption band, in the IR spectrum, at 3289 cm^{-1} for (N-H) functional group gives an excellent evidence about the compound N10 formation, in addition to appearance of stretching absorption at 3120 cm^{-1} for (aromatic C-H), at 2968 cm^{-1} for (aliphatic C-H), at 1644 cm^{-1} for (C=N), at 1506 cm^{-1} for (aromatic C=C), at 1266 cm^{-1} for (C=S). The ^{1}H-NMR spectrum of compound N10 showed the following chemical shifts (δ, ppm): 3.51 (s, 6H, 3*CH_2), 3.74-3.83 (m, 18H, 6*OCH_3), 6.94-7.93 (m, 12H, 3*Ar-H & 3*=CH), 11.34 (s, 3H, 3* NH). Also, the ^{13}C-NMR spectrum of the compound N10 gave signals at δ 55.21 ppm (3* CH_2), 55.97, 56.21 ppm (6*OCH_3), 108.90-149.50 ppm (carbon aromatic ring), 149.61 ppm (3* C=N), 150.96 ppm (3* C=N for triazole ring), 172.94 ppm (3* C=S), and this is a good evidence of the formation of the required product N10, where The results were identical to the proposed compound N10.

The last path is the preparation of tetrazole derivatives N12-N19 were prepared from the reaction of compound N2-N11 with sodium azide, using ethanol as a solvent, Scheme 1. The IR spectrum of compound N18 showed the following stretching absorption bands (ν, cm^{-1}): 3287 for (NH), 3147-3001 for (aromatic C-H), 2818 for (aliphatic C-H), 1669 for (C=N), 1513 for (aromatic C=C), 1243 for (C=S), what distinguishes the spectrum of this compound is the disappearance of the absorption band (C=N) at the frequency 1644 cm^{-1}, that was present in Schiff base (N10), and this is a good evidence of the formation of the tetrazole compound N18, On the other hand, the ^{1}H-NMR spectrum of the compound N18 showed clear evidence of the formation of this compound through the appearance of a distinctive signal belonging to the proton (NH of tetrazole ring) at 9.80 ppm with the disappearance of the signal (CH=N) that was present in Schiff base (N10). In addition to other indications that confirm the formation of the tetrazole compound and its ^{1}H-NMR spectrum showed the following chemical shifts (δ, ppm): 3.79 (s, 9H, 3*OCH_3), 3.83 (s, 9H, 3* OCH_3), 4.82 (s, 6H, 3* CH_2), 6.94-7.14 (m, 12H, Ar-H & CH of tetrazole ring), 9.80 (s, 3H, 3*NH of tetrazole ring), 11.31 (s, 3H, 3*NH of triazole ring).



X = 3-NO_2, 3-OCH_3 4-OH, 3-OH, 4-$N(CH_3)_2$, 2-OCH_3, 4-OCH_3, H, 2-OH, 3,4-Di-OCH_3, 4-OH

Scheme 1. Thiocarbohydrazide, Triazole, Schiff bases and Tetrazole Compounds

CONCLUSION

In this study, using straightforward and simple working strategies, reaction conditions, and available and cheap chemicals, we were able to prepare important compounds such as triazole, Schiff base, and tetrazole derivatives, which are believed to have medical applications such as breast cancer, based on our study of molecular docking; therefore, our research concentrated on these derivatives. Compounds N4, N12, N16, and N17 exhibited the most favorable docking scores against PI3K and HER2, respectively, indicating strong potential as anticancer agents.

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Conflicts of interest

There are no conflicts to declare.

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