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Original Article

Synthesis, Anti-Cancer, and Molecular Docking Studies of Alkyne Derivatives Bearing Imidazo Pyridine Moiety

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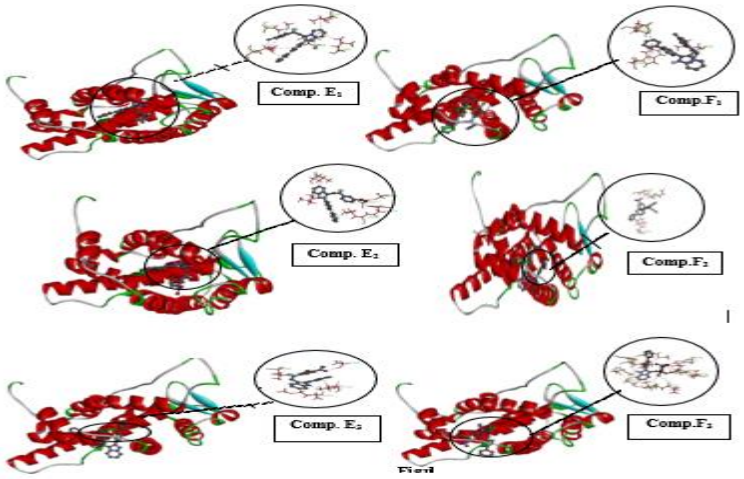
ABSTRACT

A series of alkynes Mannich bases containing Imidazo [1,2-a] pyridine ring was synthesized from reacting Mannich bases with propargyl bromide in the presence of potassium carbonate as well as two compounds were evaluated as anti-breast cancer agents using 3-(dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT assay and other compounds were examined their binding affinities by molecular docking studies. The best molecular docked complex between the Breast cancer gene1 (BRCA1) structure and the 11 derivatives were analyzed based on the Glide docked score and binding orientation for both the standard precision (SP) and the extra precision (XP) mode. The 2D-QSAR analysis reflected a significant correlation between the experimental and the predicted biological activities. The above mentioned compounds were also assessed by various spectroscopic techniques such as FT-IR ,1H-NMR and 13C-NMR spectroscopy.

GRAPHICAL ABSTRACT



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Introduction

Heterocyclic compounds containing a bridge of nitrogen atom are of high importance in medical chemistry and industrial applications Imidazo [1,2-a] pyridines are a common and significant class of fused heterocyclic systems with two nitrogen atoms that resemble purines structurally [1]. The structural imidazo (1,2-a) pyridine is present in many physiologically and pharmaceutically active molecules [2]. The other uses for them include anti-cancer [3], anti-bacterial [4], anti-fungal [5], and anti-proliferative [6].

Imidazo [1,2-a] pyrimidines have been also found in a number of investigational drugs, such as zolpidem Hypnotic, Miroprofen (NSAID), DS-I GABAA PAM, Zolimidine Antiulcer, Olprinone cardio stimulant, and Mindronic acid osteoporotic [1]. The focus of the search is on adding chemical diversity to the molecular framework to create therapeutic active molecules with various compositions.

Mannich bases also serve as significant pharmacophores or bioactive leads that are employed to synthesize various possible high-value drugs with amino alkyl chains [2]. Cocaine, fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, procyclidine, ranitidine, and biperiden are some examples of clinically effective Mannich bases that contain an amino alkyl chain and so on [3]. It is well recognized that Mannich bases are essential for the advancement of synthetic medicinal chemistry. In this search, a novel series of Mannich bases derivatives containing imidazo (1,2a) pyridine will be synthesis.

Studies in the literature showed that Mannich bases are highly reactive and easily transform into other compounds [4], according to the published studies in the literature reduced to produce amino alcohols having physiological action, for instance. It is well-known that Mannich bases have potent effects, such as anti-inflammatory, anticancer properties [5], antimicrobial, anti-filarial [6], and anticonvulsant [7].

On the other hand, propargyl amines were synthesized by the reaction of Mannich bases derivatives with propargyl bromide [8]. Propargyl amines are widely used in organic synthesis to form diverse heterocyclic compounds, natural products, and bioactive compounds [9]. These compounds have a significant role in many pharmaceutical and biological applications, such as anti-cancer [10], anti-bacterial [11], and anti-fungal [12]. The creation of new compounds with effective anti-cancer properties is urgently needed. Our study focuses on creating therapeutic active molecules with diverse chemical compositions by introducing chemical diversity into the molecular framework.

Materials and Methods

The electro thermal melting point device was utilized to record the melting point. Chemical shift values are listed in the δ scale. The IR spectra were recorded on Shimadzu FT-IR spectrophotometer using potassium bromide discs. Isfahan University of Technology (IUT), Iran, used a Bruker model Ultra shield 500 MHz. The (^{1}H and ^{13}C-NMR) spectra were recorded on Bruker ultra-shield 500 MHz spectrometer using DMSO-d_6 as solvent as an internal standard. Cytotoxic effect of some compounds on MCF-7 cell line (breast cancer cell line) *in vitro* using MTT Assay in AL-Nahrain university/college of Biotechnology.

Procedure

General synthesis of 2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridine and 2-(4-bromophenyl) imidazo [1,2-a] pyridine (A, A1) [13]

A combination of 2-amino pyridine (0.1 mmol) (0.01 g) with 4-bromo phencyl bromide 4-phenyl phencyl bromide (0.1 mmol) was dissolved in 25 mL of ethanol. The mixture was refluxed for 8 hours. The solution was then cooled and basified with NaOH (1 M) until pH 9 was achieved.

Spectral data of compounds (A, A1): $C_{19}H_{14}N_2$

IR (KBr/Cm^{-1}): 3074, 3047, 3002, (Aryl-H), 1633 (C=N) imidazole, pyridine 1541(C=C). ^{1}H-NMR

(DMSO, 300 MHZ): δ 6.89-8.51 (m Aryl-H), ^{13}C-NMR (DMSO, 300 MHz): δ 145, 130, 113 (C=N), 127, 128, 129 (C=C).

Synthesis of Mannich bases (general procedure) [14] (E1-E7)

A 0.001 of formaldehyde and (0.1 N) HCl stirred for 15 minutes using ethanol as solvent then added primary amine and 2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridine compound (E) (Figure 1). The mixture was refluxed for 10-48 hours at 125 °C. The Thin Layer Chromatography uses track the reaction evolution. The finished product obtined with monitoring by TLC and the product was poured over crushed ice to obtain an analytically pure product, the product was isolated, and a suitable solvent was used to purify it. All the HNMR spectra are shown in Supplementary materials (S1-S7). All the synthesized compounds are listed in Table 1.

N-((2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridines -2-yl) methyl)-4-methylaniline compound E_1

Spectral data of compounds: $C_{27}H_{23}N_3$

IR (KBr /cm^{-1}): 3375 (N-H), 3076 (Ar-H), 1620 (C=N) imidazo, 1573 (C=C), 1348 (C-NO_2). ^{1}H-NMR (DMSO, 500 MHZ): δ 6.85-8.30 (m, Ar-H), 6.81 (s, 1H, NH). ^{13}C-NMR (DMSO, 500 MHZ): δ 144.8 (C=N), and 114 -128 (C=C).

N-((2-([1,1-biphenyl]-4-ylimidazo[1,2-a] pyridines -2-yl) methyl)-3-methoxy-4-nitroaniline E_3

Spectral data of compounds: $C_{27}H_{23}N_4O_3$

IR (KBr /cm^{-1}): 3411 (N-H), 3097 (Aryl-H), 2977 (C-H), 1518 (C=N) imidazo, 1535 (C=C), ^{1}H-NMR (DMSO, 500 MHZ): δ 7.21-8.47 (m, Aryl-H), 6.88 (s, 1H, NH), 4.02 (s, 3H, CH_3). ^{13}C-NMR (DMSO, 500 MHZ): 144.8 (C=N), 117.3 -129.1 (C=C), and 54.8 (C-O).

4-(((2-([1,1-biphenyl]-4-yl) imidazole[1,2-a] pyridines -2-yl) methyl) amino) phenol E_4

Spectral data of compounds $C_{26}H_{21}N_{30}$

IR (KBr/cm^{-1}): 3515 (O-H), 3407 (N-H), 3028 (Ar-H), 1577 (C=N) imidazo, and 1514 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 9.44 (s, 1H, OH) 7.21-8.30 (m, Ar-H) 6.28 (s, 1H, NH), 4.33 (s, 2H, CH_2). ^{13}C-NMR (DMSO, 500 MHZ): δ 146.9 (C-OH), 144.8 (C=N), 117.3 -129.2 (C=C), 124.8 (C-N).

N-(4-((2-([1,1-biphenyl]-4-ylimidazo[1,2-a] pyridines -2-yl) methyl) amino) phenyl) acetamide (E_5)

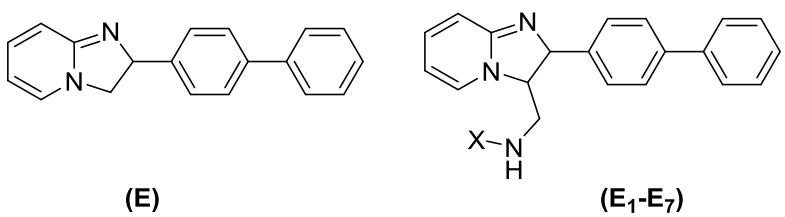
Spectral data of compounds: $C_{27}H_{19}N_4$

IR (KBr /cm^{-1}): 3253 (N-H), 3047 (Aryl-H), 1633 (C=N) imidazo, 1598 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 6.75-8.30 (m, Aryl-H), δ 5.08 (s, 1H, NH) 4.33 (s, 2H, CH_2). ^{13}C-NMR (DMSO, 500 MHZ): δ 144.8 (C=N), and 117.3 -129.1 (C=C).

N-((2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridin-2-yl) methyl) benzo[b]thiophen-2-amine (E_7)

Spectral data of compounds: $C_{27}H_{19}N_4$

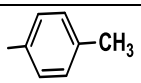
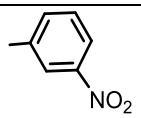
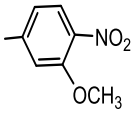
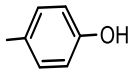
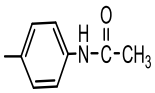
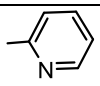
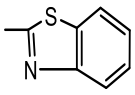
IR (KBr /cm^{-1}): 3409 (N-H), 3047 (Aryl-H), 1631 (C=N) imidazo, 1575 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 6.85-8.30 (m, Aryl-H), 6.28 (s, 1H, NH), 4.33 (s, 2H, CH_2). ^{13}C-NMR (DMSO, 500 MHZ): δ 144.8 (C=N), 144.8-129.2 (C=C), and 126 (C-S).



(E) **(E_1-E_7)**

Figure 1: The chemical structure of compound E and the general structures of compounds E1-E7

Table 1: Physical characteristics of substances (E_1-E_7)

Compound symbol	X	Molecular formula	Melting Point (°C)	Color	Yield (%)
E	-	$C_{19}H_{13}N_2$	213-216	yellow	90
E_1		$C_{27}H_{23}N_3$	220-222	Brown	70
E_2		$C_{26}H_{19}N_4O_2$	193-195	yellow	75
E_3		$C_{27}H_{23}N_4O_3$	152-154	yellow	64
E_4		$C_{26}H_{21}N_3O$	163-165	brown	69
E_5		$C_{28}H_{24}N_4O$	oily	Off white	73
E_6		$C_{24}H_20N_4$	155-157	Off white	70
E_7		$C_{26}H_{21}N_4S$	oily	brown	60

Synthesis of propargyl amines compounds [15] (General procedure) (F_1-F_7)

A mixture of compounds (E1-E7) (0.001 mol) and K_2CO_3 (0.001 mol) in DMF (25 mL) was stirred for 15-30 min. After that, propargyl bromide (2-3 mL) and toluene 3 drops were added to previous mixture and heated under reflux for 24-48 hours at 40-50 °C with monitoring by TLC (EtoAc: petroleum ether), the product was isolated, and ethanol solvent was used to purify it. The general chemical strutures of these proposed copounds are depicted in Figure 2. All the ^{1}H-NMR spectra are shown in Supplementary materials (F1-F7).

N-((2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridin-2-yl) methyl)-4-methoyl-N-(prop-2-yn-1-yl) aniline (F_1)

Spectral data of compounds: $C_{18}H_{17}N_3$

IR (KBr/cm^{-1}): 3236 (C≡C-H), 2125 (C≡C), 1629 (C=N) imidazo, 1589 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 7.1-8.2 (m, Aryl-H), 4.09 (s, 2H, CH_2), 3.08 (s, 1H, C≡C-H). ^{13}C-NMR (DMSO, 500 MHZ): δ 144.8 (C=N), 124.8-129.2 (C=C), 78.2 (C≡C), 46.3 (CH_2), and 130.7 (C-CH_3).

N-((2-([1,1-biphenyl]-4-yl) imidazo [1,2-a] pyridin-3-yl) methyl) meta-nitro-N-(prop-2-yn-1-yl) aniline (F_2)

Spectral data of compounds: $C_{18}H_{17}N_4O_2$

IR (KBr/cm^{-1}): 3292 (C≡C-H), 2125 (C≡C), 1639 (C=N) imidazo, 1622 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 7.1-8.2 (m. Aryl-H), 4.09 (s.2H, CH_2), 3.08 (s, 1H, C≡C-H), ^{13}C-NMR (DMSO, 500 MHZ): δ 144.8 (C=N), 124.8-129.2 (C=C), 78.2 (C≡C), 46.3 (CH_2), and 130.7 (C-CH_3).

N-((2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridin-2-yl) methyl)-3-methoxy-4-nitro-N-(prop-2-yn-1-yl) aniline (F_3)

Spectral data of compounds: $C_{18}H_{17}N_4O_3$

IR (KBr/cm^{-1}): 3284 (C≡C-H), 2125 (C≡C), 1620 (C=N) imidazo, 1591 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 6.85-8.30 (m, Aryl-H), 4.09 (s, 2H, CH_2), 3.08 (s, 1H, C≡C-H). ^{13}C-NMR (DMSO, 500 MHZ): δ 144.8 (C=N), 114.2-129.2 (C=C), 78.2 (C≡C), and 155.0 (C-CH_2).

4-(((2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridines -2-yl) methyl) (prop-2-yn-1-yl) amino) phenol (F_4)

Spectral data of compounds: $C_{17}H_{15}N_3O$

IR (KBr/cm^{-1}): 3284 (C≡C-H), 2125 (C≡C), 1620 (C=N) imidazo, 1591 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 6.85-8.30 (m, Aryl-H), 4.09 (s, 2H, CH_2), 3.08 (s, 1H, C≡C-H). ^{13}C-NMR (DMSO, 500 MHZ): δ 144.8 (C=N), 114.2-129.2 (C=C), 78.2 (C≡C), and 155.0 (C-CH_2).

N-(4-(((2-([1,1-biphenyl]-4-yl) imidazo[1,2-a] pyridines -2-yl) methyl) (prop-2-yn-1-yl) amino) phenyl) acetamide (F_5)

Spectral data of compounds: $C_{19}H_{18}N_4O$

IR (KBr/cm^{-1}): 3288 (C≡C-H), 2125 (C≡C), 1639 (C=N) imidazo, 1593 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): 9.78 (s, 1H, NH), 6.85-8.30 (m, Aryl-H), 2.06 (s, 3H, CH_3), and 3.08 (s, 1H).

N-((2-([1,1-biphenyl]-4-yl imidazo[1,2-a] pyridin-3-yl) methyl)-N-(prop-2-yn-1-yl)-4-(pyridin-2-yl) aniline (F_6)

Spectral data of compounds: $C_{17}H_{17}N$

IR (KBr/cm^{-1}): 3259 (C≡C-H), 2125 (C≡C), 1631 (C=N) imidazo, 1583 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 6.85-8.30 (m, Aryl-H), 4.09 (s, 2H, CH_2), and 3.08 (s, 1H, C≡C-H).

N-((2-([1,1-biphenyl]-4-ylimidazo[1,2-a] pyridines -2-yl) methyl)-4-(benzo[b]thiophen-2-yl)-N-(prop-2-yn-1-yl) aniline (F_7)

Spectral data of compounds: $C_{17}H_{17}N$

IR (KBr/cm^{-1}): 3288 (C≡C-H), 2123 (C≡C), 1629 (C=N) imidazo, 1575 (C=C). ^{1}H-NMR (DMSO, 500 MHZ): δ 6.85-8.30 (m, Aryl-H), 4.09 (s, 2H, CH_2), and 3.08 (s, 1H, C≡C-H).

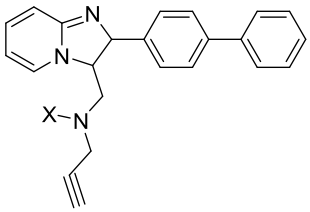


Figure 2: The general chemical structures of synthesized compounds (F_1-F_7)

Estrogen Receptor Alpha

Binding Site

The binding site resembles a jar with a narrow neck and a volume of 4,105 Å3. The majority of the binding pocket is made of Leu391, Leu428, Phe404, Meth421, Leu346, Leu346, Met343, Leu391, Arg394, Leu525, Leu391, Leu387, Met388, Glu353, Leu387, Ala350, Thr347, Leu384, and Trp383.

Methodology

The crystal structure of the Human Estrogen Receptor (-ER) with the co-crystallized ligand 4-HYDROXYTAMOXIFEN was obtained from the protein data bank (pdb code 3ERT). Prior to docking, all ions and water molecules were removed; box grid-based docking was performed using Auto dock vina; visualization was performed using chimera; the charge of the protein molecules was modeled using the AMBERff14SB force field, whereas small molecules (Ligands) were modeled using AM1-BCC. The box grid dimensions are demonstrated in Table 3.

Results and Discussion

Chemistry

In Figure 3, step one show compound 2-([1,1-biphenyl],-4-yl) imidazo,[1,2-a] pyridine compound (E) was formation. The evidence of the formation of this compound is the disappearance of the group NH_2 and, appearance new band of (C=N) cyclic imidazo with new absorption band that had emerged at 1633 cm^{-1} in FT-IR spectra. The physical characteristics of synthesized compounds are shown in Table 2.

Table 2: Physical characteristics of substances (F_1-F_7)

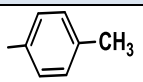
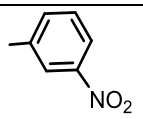
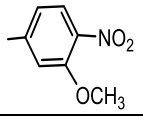
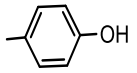
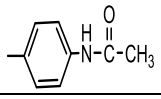
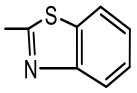
Compound symbol	X	Molecular formula	Melting Point (°C)	Color	Yield (%)
F_1		$C_{27}H_{23}N_3$	220-222	Brown	70
F_2		$C_{26}H_{19}N_4O_2$	193-195	Yellow	75
F_3		$C_{27}H_{23}N_4O_3$	152-154	Yellow	64
F_4		$C_{26}H_{21}N_3O$	163-165	Brown	69
F_5		$C_{28}H_{24}N_4O$	oily	Off white	73
F_6		$C_{24}H_{20}N_4$	155-157	Off white	70
F_7		$C_{26}H_{21}N_4S$	oily	Brown	60

Table 3: The box grid dimensions of the prepared molecules

Center	28.466	-1.734	26.847
Size	29.526	24.26	34.017

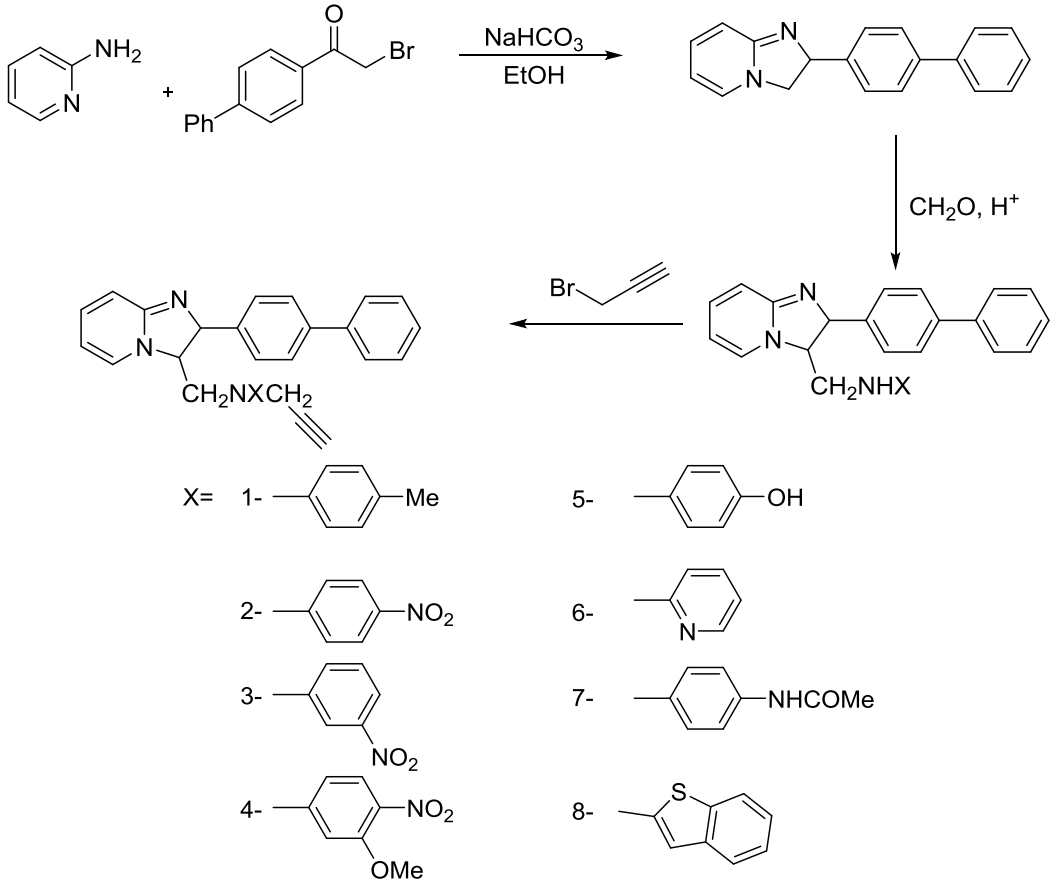


Figure 3: The reaction of synthesized compounds (E1-E7)) with propargyl bromide as SN_2 reaction

In the second step, a series of Mannich bases (E1-E7) were synthesized by nucleophilic addition of a substituted primary amine with carbonyl group followed by dehydration to the Schiff base. The Schiff base is an electrophile which reacts in the second step in an electrophilic addition with a compound containing an acidic proton (compound A). The structures of the compounds were confirmed, FT-IR and NMR spectra. The evidence for the formation of these basses appeared in band NH at 3375-313 cm^{-1}.

The third step was the synthesis of acetylenic mannich by the reaction of E1-E7 compounds with propargyl bromide as SN_2 reaction (Figure 3). The absorption at 2125-2123 cm^{-1} was the best proof formation band of C≡C.

Biological activity

The cytotoxic impact of (E_2 and F_2) chemical on breast cancer cell line was evaluated using 3-(dimethylthiazol,-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) (MCF-7) [16]. Using varied concentrations of (E_2 and F_2) chemical, the MTT test was used to calculate the cell viability and inhibition rate on the tumor cell line. Compared with the normal cell line Hdfn the percentage viability of treated cells was calculated. On MCF-7 cells, the chemical (E2, F2) had cytotoxic effects at concentrations between 15.6 and 500 g/mL, which led to a dose-dependent decline in cell viability (Table 4). By raising the concentration of the (E_2, F_2) molecule, cell viability was lowered. The lowest MCF-7 cell viability (%) was observed at 500g/ml (54.30±4.68) and 62.91±2.14) 82%, respectively, while the maximum MCF-7 cell viability was observed at 15.60 g/ml (94.97±0.6) and (96.30±1.10), respectively. A (E_2 and F_2) molecule was shown to have cytotoxic action, with IC50 values of 215.1 and 303.3 g/ml, respectively. The effect of (E_2 and F_2) chemical on HdFn normal cell line as shown in Tables 4 and 5 and Figures 4 and 5 yielded an IC50 of 854.6,407.9 g/mL, respectively.

Table 4: Cytotoxicity effect of (E_2) compound on MCF-7 and WRI-68 cells after 24 hours incubation at 37 °C

MCF-7	HdFn	
Conc. g/mL	Mean ± SD	Mean ± SD
500.00	54.30±4.86	78.22±4.09
250.00	63.19±3.75	86.07±3.08
125.00	71.64±0.42	90.08±1.05
62.00	83.84±6.21	93.87±1.10
31.20	86.00±2.14	94.64±0.48
15.60	94.79±0.61	95.10±0.24

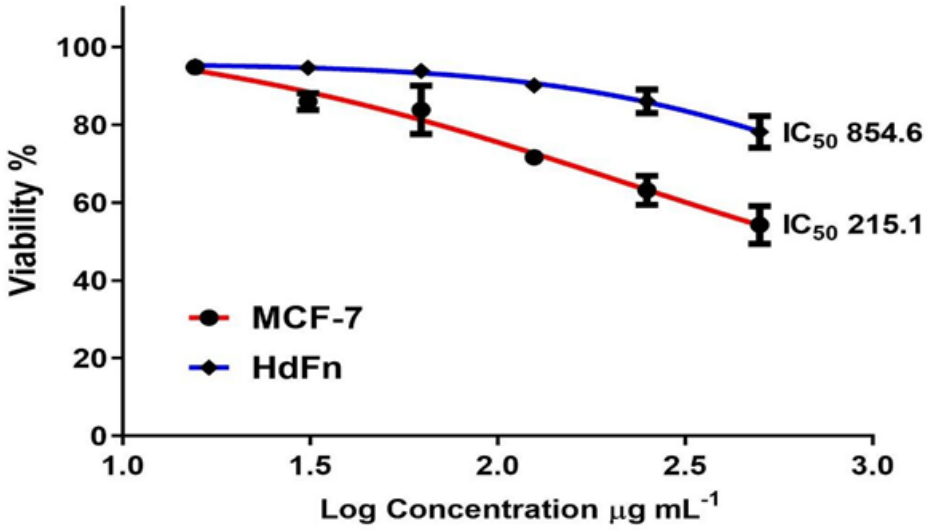


Figure 4: The effect of compound (E_2) concentrations on the cell viability %

Table 5: Cytotoxicity effect of (F_2) compound on MCF-7 and WRI-68 cells after 24 hours incubation at 37 ºC

MCF-7	HdFn	
Conc. g/ml	Mean ± SD	Mean ± SD
500.00	62.19±0.93	69.81±5.58
250.00	76.93±2.34	84.03±1.25
125.00	89.16±3.60	92.28±1.00
62.50	94.06±2.15	96.33±0.41
31.20	97.84±0.70	96.30±0.87
15.60	96.30±1.10	97.11±1.04

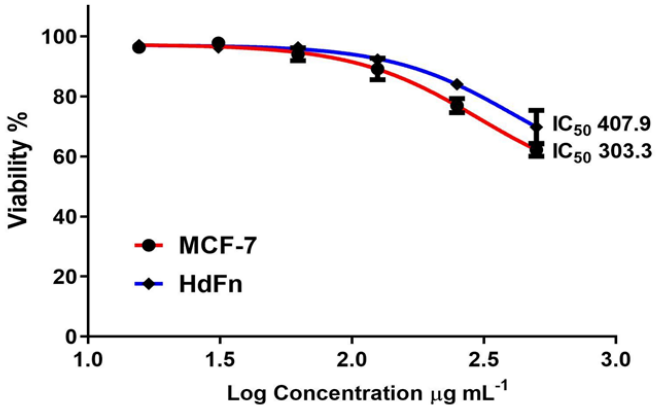


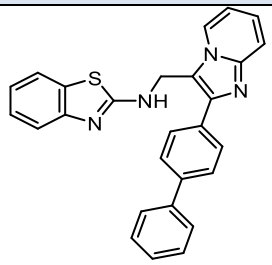
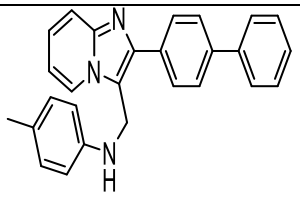
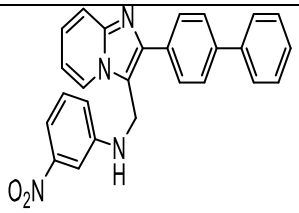
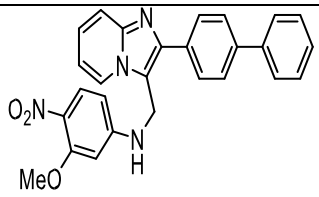
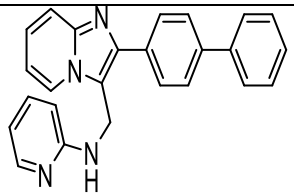
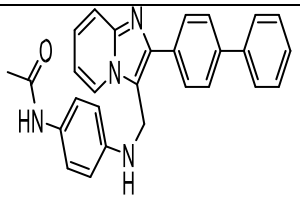
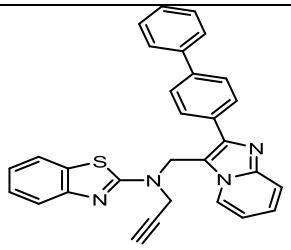
Figure 5: The effect of compound (F_2) concentrations on the cell viability %

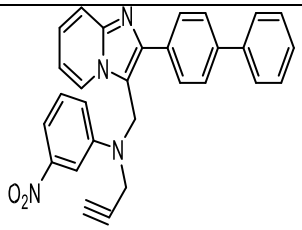
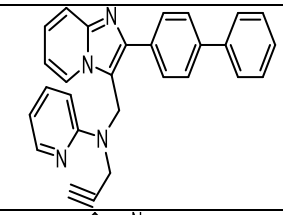
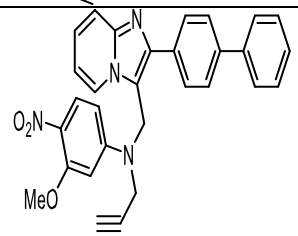
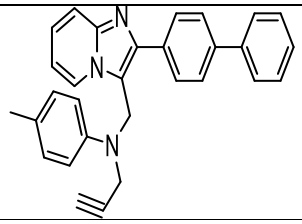
Molecular docking

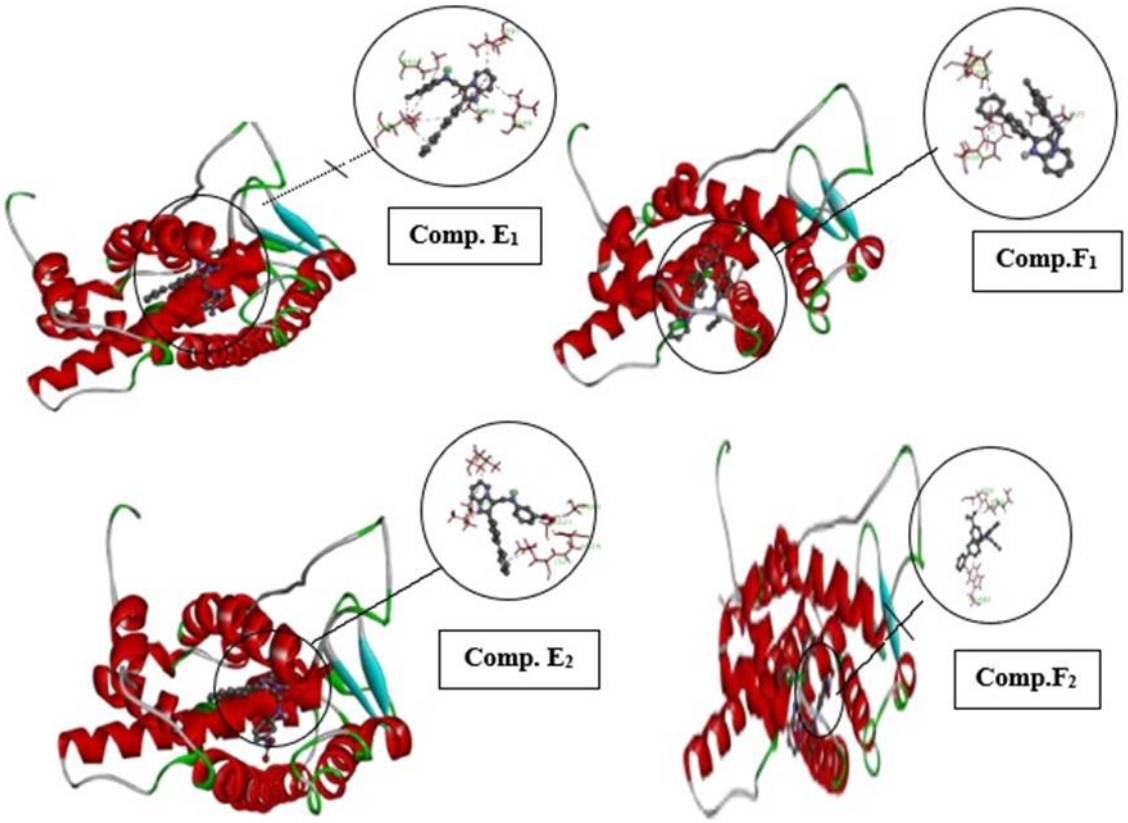
Inhibitors of breast cancer alpha estrogen receptor by Molecular Docking [17]

Comp E7 has a large Pi system, which has helped to increase its affinity for the receptor. In contrast, its propargyl analogue (Comp F7), has a different conformation (due to the sp carbon of propargyl, which has made a Pi-alkyl bond with Tyr526) and less binding energy due to the benzimidazole orientation, which has a negative interaction with Leu536 (donor-donor interaction). Compared with Comp E7, Comp E1 has demonstrated a marginal reduction in the amount of binding energy, which can be attributed to a smaller contact Pi system. The binding energy, on the other hand, was reduced by one kilocalorie when Comp E1was converted into its propargyl analogue, Comp F1. This was because the interaction of the propargyl with Tyr526 resulted in a conformation that was less favorable. The formation of an H-bond with His524 was achieved by introducing a nitro group to the meta position (Comp E2) rather than a para-methyl group, which resulted in a greater decrease in HIthe binding energy. However, the propargyl addition resulted in an unfavorable conformation that clashed with Leu536, so further addition of propargyl was not successful. Comp 5 is unique and comparable to comp 1 despite having fewer pi-system contacts due to the fact that there are more pi-alkyl interactions, a pi-pi stacking interaction between the pyridine moiety and Trp383, a pi-sulfur interaction with Cys530, and the absence of any clashes. The addition of phenyl acetamide to the pharmacophore (Comp E6) was completely useless and resulted in a decrease in binding energy as a result of a reduced interaction with the Pi system and an interaction with acetamide that was essentially nonexistent. In addition, switching out the phenyl ring for a bromide one was not a smart move. Overall, it is beneficial to maintain the benzimidazole in conjunction with the biphenyl system as an inhibitor pharmacophore for the alpha estrogen receptor. This should be done while avoiding propargyl and introducing more moieties that keep the pharmacophore (especially the benzimidazole ring) at a considerable distance from Leu536 [17] (Table 6 and Figure 7).

Table *6*: Lustrations of the docking score, H-bond length that established with the particular residue, and the non-hydrogen bond interactions

ID	Structure	Docking Score (kcal/mol)	H-bond (Angstrom)	Non-H-bonds interactions
E_7		-10.8		Leu387 (Pi-Alkyl), Glu353 (pi-anion), and Met421 (Pi-sulfur)
E_1		-10.4	Leu346 (3.09)	Met421 (Pi-sulfur), Leu525 (Pi-alkyl)
E_2		-10.1	His524 (2.38)	Gly420 (C-H bond), Leu525 (Pi-Alkyl), Leu387 (Pi-Alkyl), and Ala350 (Pi-Alkyl)
E_3		-8.8	Cys530 (2.09), Met522 (3.34)	LEU525 (Pi-Alkyl)
E_6		-10.7		Cys530 (Pi-Sulfur), Trp383 (Pi-Pi stacking), Leu525 (Pi-Alkyl), Thr347, Asp351, Leu384, and Met528 (all of them are involved in Van der Waals interaction)
E_5		-8.8		Trp383 (Pi-Pi stacking), Leu525 (Pi-Alkyl), and plenty of weak bonds (Van der Waals) with nearby residues such as Thr347, Asp351, and Leu384
F_7		-9.7		Asp351 (Pi-Anion), Trp383 (Pi-Pi stacking), and Leu525 (Pi-Alkyl)

F_2		-9.6	Cys530 (2.25)	Trp383 (Pi-Pi stacking), Leu525, Leu354, and Ala350 (Pi-Alkyl)
F_6		-9.2		Trp383 (Pi-Pi stacking), Leu354, and Ala350 (Pi-Alkyl), Asp351 (Pi-Anion)
F_3		-9.3	Leu536 (2 bonds;2.86 and 2.30), Leu525 (2.81)	Cys530, Met528 (Pi-Alkyl), Tyr256 (Amide-Pi stacked), and Met522 (Pi-Sulfur).
F_1		-9.4		Asp351 (Pi-Anion), Trp383 (Pi-Pi stacked), Ala350 , and Leu525 (Pi-Alkyl)



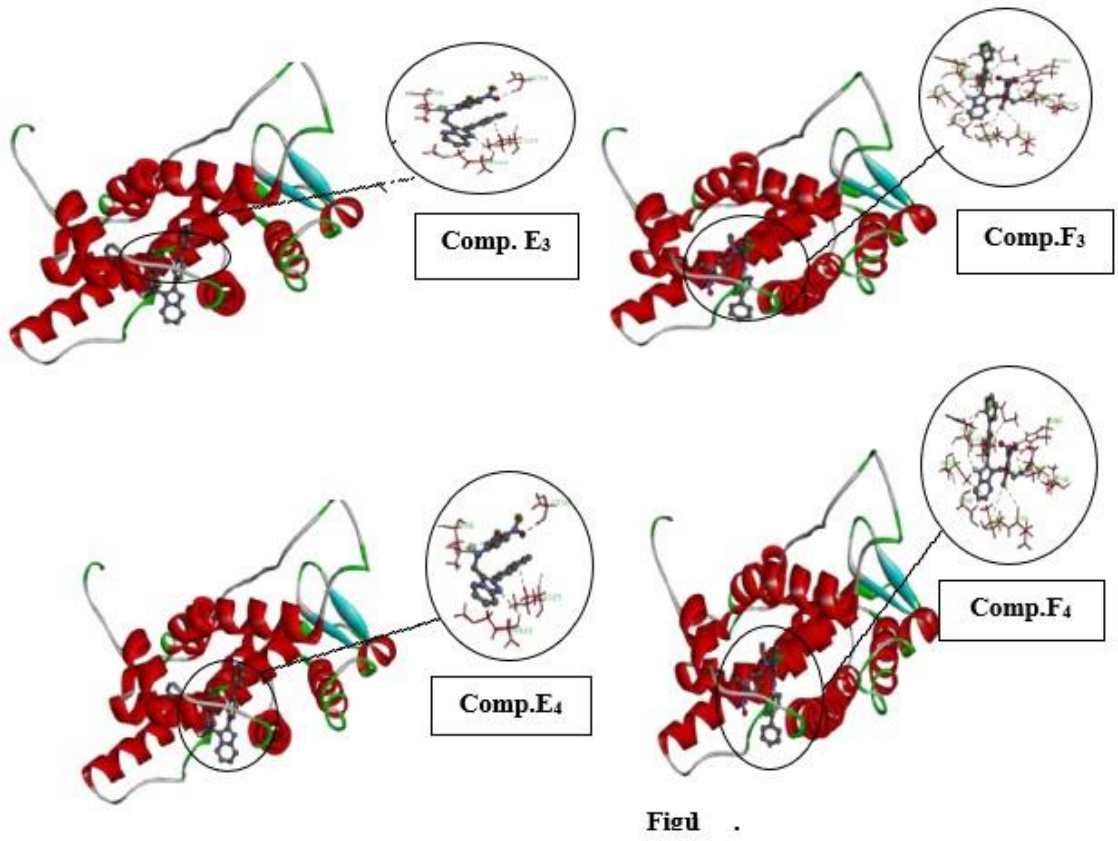


Figure 7: Molecular docking of compound (E_1-E_4) and (F_1-F_4)

Conclusion

The authors have synthesized fourteen new products of mannich bases (E1-E10) and alkyne mannich bases (F1-F7) derivative from imidazo [1,2-a] pyridine utilizing starting materials by reaction of 2-aminopyridine with 4-biphenyl phencyl bromide (Figure 1). Spectroscopic data were introduced as reactivity indices. Two compounds (E_2) and (F_2) showed a good inhibitory activity mainly against breast cancer cell lines a molecule was shown to have cytotoxic action, with IC50 values of 215.1 and 303.3 g/ml, respectively. The effect of (E_2 and F_2) chemical on HdFn normal cell line (Tables 4 and 5) yielded an IC50 of 854.6,407.9 g/mL, respectively. All of the imidazo (1,2a) pyridine derivatives (E1-F7) were able to interact strongly with the estrogen receptor; the biphenyl derivatives comp E7, E1, E2, and E6 are the strong candidates for further optimization and should be the focus of efforts to develop a promising chemotherapeutic agent to combat breast cancer. The toxicological and *in vivo* studies are also encouraged.

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Authors contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The author declared that they have no conflict of interest.

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Supporting Information

Copies of ^{1}H-NMR (500 MHz, DMSO) and ^{13}C-NMR (125 MHz, DMSO) spectra of synthesized compounds (pdf).

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