DESIGN, SYNTHESIS, CHARACTERIZATION, AND ANTIBACTERIAL ACTIVITY OF SOME NEW MANNICH BASES FROM ACETYLENE ETHER

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Abstract. *Some new Mannich bases* ***3a-3f*** *were produced by the treatment of 4,4'-(phenylmethylene)bis((prop-2-yn-1-yloxy)benzene)* ***2a-2f*** *with acetylene ether in the presence of formaldehyde in ethanol. The 4,4'-(((phenylmethylene)bis(4,1-phenylene))bis(oxy))bis(N,N-diethylbut-2-yn-1-amine) (Mannich bases) demonstrated anticancer efficacy through docking with the C-met tyrosine kinase receptor protein, evidenced by docking scores ranging from -3.58 to -5.0 kcal/mol, in comparison to the control Crizotinib value of -6.86 kcal/mol. The new compounds were assessed for their in vitro antibacterial activity by using the agar cup method of Muller Hinton agar and tested against a series of bacteria (Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa). The synthesized compounds exhibited significantly high activity against negative and positive bacteria. The study showed a good theoretical molecular docking result towards the C-met tyrosine kinase receptor protein close to crizotinib and displayed high inhibition as antibacterial activity.*

Keywords: *Antibacterial, Acetylene Ether, Design, Mannich Bases.*
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Introduction

Since the discovery of acetylene, new areas of acetylene chemistry have been continuously developed. Coupling and addition reactions can exemplify the rich scope of chemical transformations available for a C≡C triple bond [1]. Removing trace acetylene from ethylene has led to another important process, selective hydrogenation of acetylene. Recently, several opportunities for controlled acetylene accommodation in microporous materials have appeared. New functional materials separate, sense, and store acetylene and other small molecules [2].

The acetylene group has good biological activity and is an important source of intermediate pharmaceuticals for taking action for novel antibacterials [3]. The compound contains the acetylene group used for Parkinson's disease [4], such as inhibiting drugs. Acetylcholine gives an ether acetylene group in nucleosides, and the acetylene group, as shown in Fig. 1, creates medicines and dyes [5].

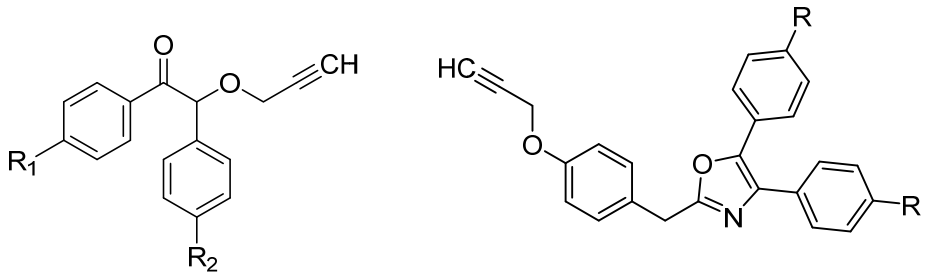


Fig. 1. Structure of acetylene compounds

The Mannich reaction is an organic reaction that consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group by formaldehyde and a primary

or secondary amine or ammonia. The final product is a β-amino-carbonyl compound [6], a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered Mannich reactions because these imines form between amines and aldehydes [7]. The reaction is named after chemist Carl Mannich. The Mannich reaction is an example of nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base [8]. The Schiff base is an electrophile that reacts in the second step in an electrophilic addition with a compound containing an acidic proton (which is, or had become, an enol) [9]. The Mannich reaction is also considered a condensation reaction. Mannich base compounds are important for medicinal chemistry [10]. The most important and widely used aminoalkylation of CH-acidic compound is the Mannich reaction or alkaloids Mannich. The most active uses are anticholinergic agents [11-14], hypertensive agents, CNS stimulant agents, antispasmodic agents, local anesthetics, and anticancer agents. Mannich-type reactions are among organic preparation's most important carbon-carbon bond-forming reactions [15]. They provide amino carbonyl compounds, important synthetic intermediates for various pharmaceuticals and natural products. They can be readily converted to derivatives with useful applications in paint and polymer chemistry, plant protection, medicine, and the pharmaceutical industry [16, 17]. A series of acetylenes containing bis(2-chloroethyl)amine' functionalities synthesized by the Mannich reaction in good yields showed antitumor properties. The representative examples are biological applications, activities, antimicrobial, and anticancer therapeutic potential, with the highest antitumor activity [18]. *Antimicrobial activity of Mannich bases*. Antimicrobials are considered one of the most successful forms of therapy in medicine. However, their efficacy is adversely affected by antibiotic-resistant pathogens [19]. The compounds were examined using the BHI (brain heart infusion) broth dilution method for antifungal activity against Candida albicans and Aspergillus niger, as shown in Fig. 2.

Crizotinib, sold under the brand name Xalkori, is an anti-cancer medication used to treat non-small cell lung carcinoma (NSCLC). Crizotinib inhibits the c-Met/Hepatocyte growth factor receptor (HGFR) tyrosine kinase, which is involved in the oncogenesis of several other histological malignant neoplasms. It also acts as an ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1) inhibitor structure, as shown in Fig. 3.

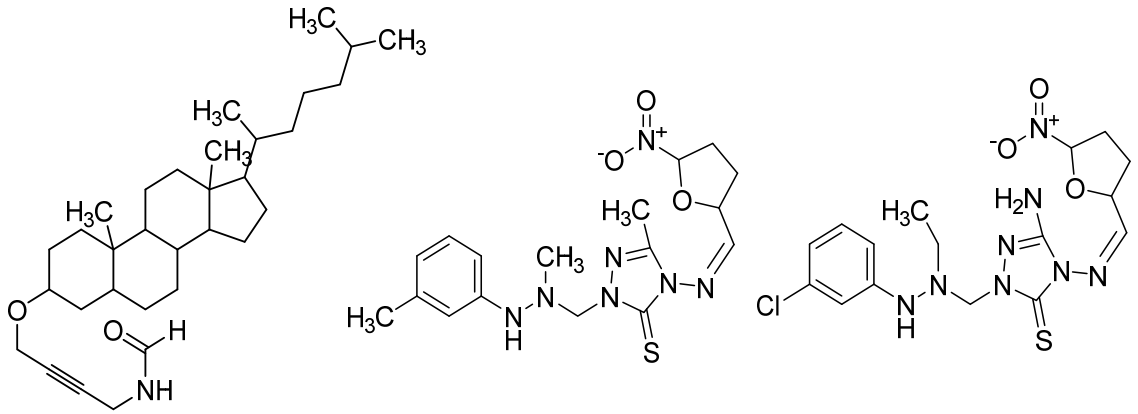


Fig. 2. Structure of Mannich base compounds

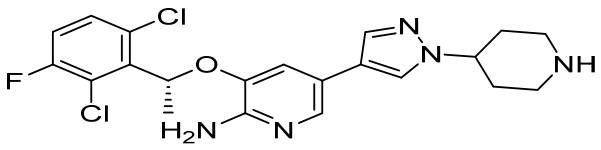


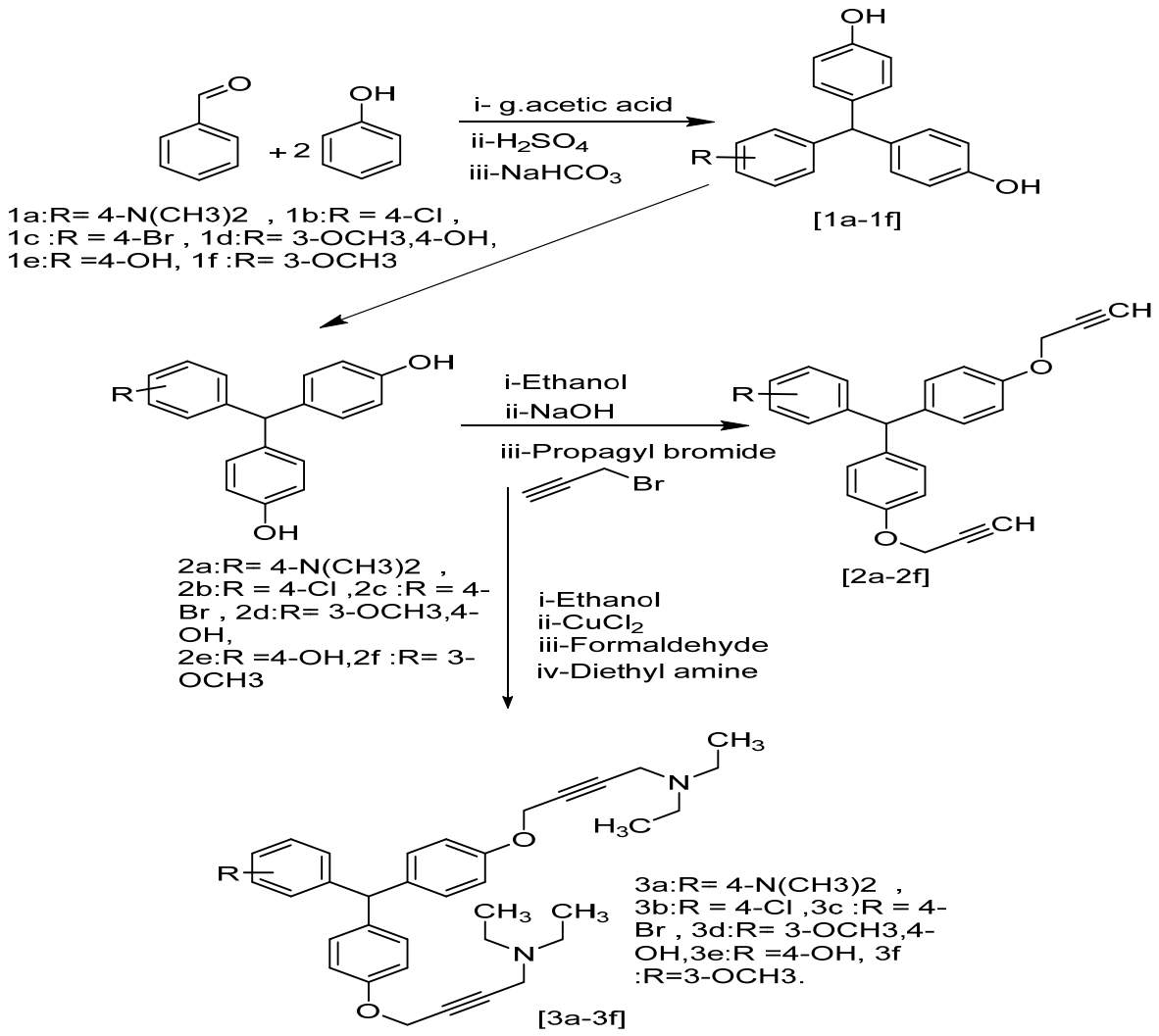
Fig 3. Chemical structure of Crizotinib

Experimental part

The chemicals and reagents were purchased from Merck and Aldrich. The spectra were obtained using various instruments, namely, Fourier-transform infrared spectroscopy (FT-IR), Perkin Elmer toner 27 (Bruker, Germany), nuclear magnetic resonance spectrometer (^{1}H-NMR, ^{13}C-NMR) BioSpin GmbH 400,100 MHz (Bruker, Germany), and mass spectrometer U3500, mass selective detector (5973) (Agilent Technologies, USA).

Synthesis of Synthesis of 4,4'-(phenylmethylene)diphenol derivatives [1a-1f]. In the round-bottom flask, phenols (1.88 gm, 0.02 moles) were dissolved in 20 ml of glacial acetic acid. Then, a different aromatic aldehyde (0.01 mole) 40% was added to the mixture at 0 to 5 ℃, (2:1) ratio. The mixture was heated under reflux for 1 hrs. The reaction mixture was stirred cold for an additional three hours and was then stirred at room temperature 24 hr after the beginning of the reaction. It was poured into cold water; the precipitate was filtered off and neutralized with sodium bicarbonate solution and purified using the ethanol solvent 81-85.

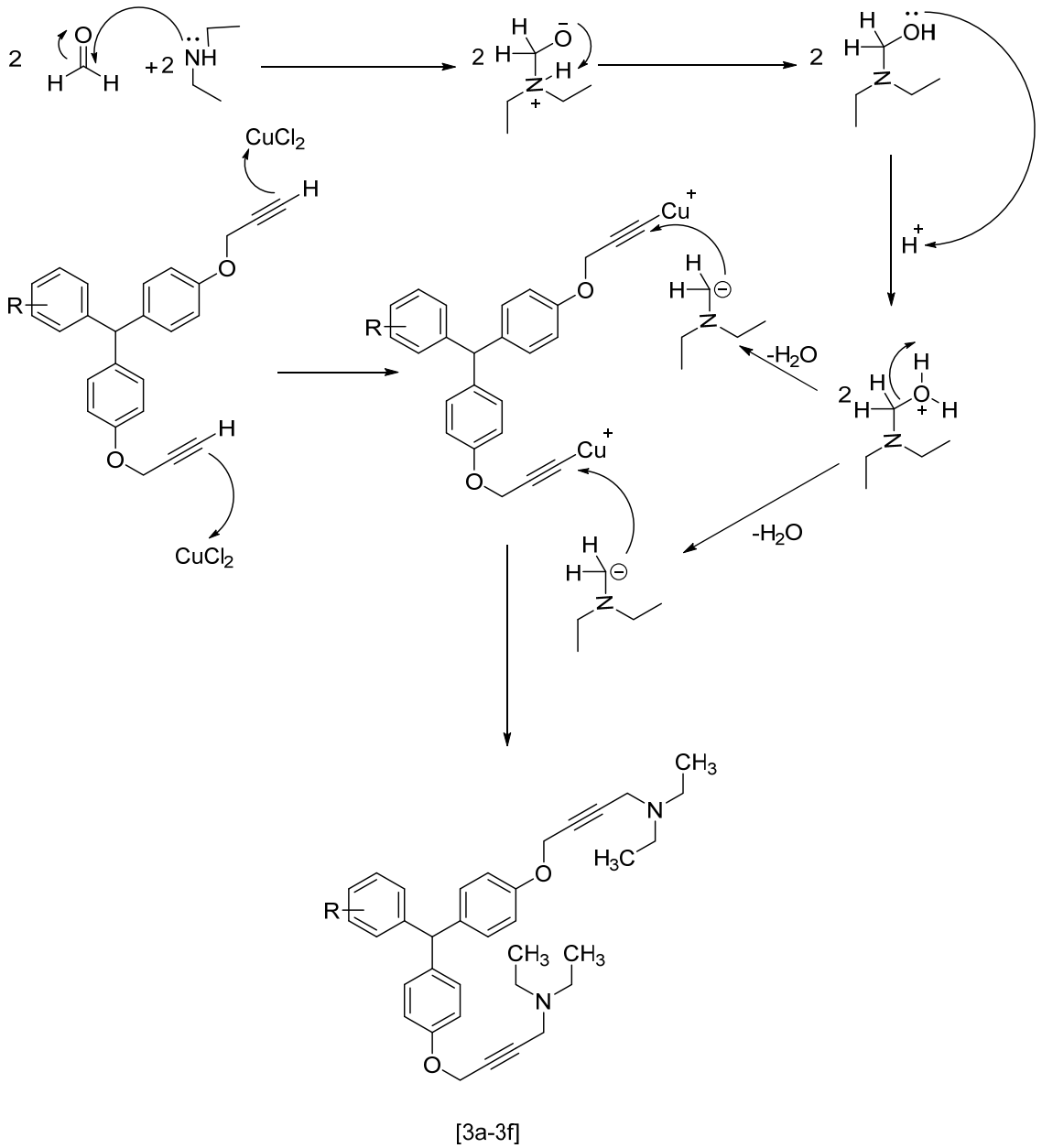
1a; m.p. 88-90 ºC, yield 79 %, Rf=0.84, dark violet color. **1b**; m.p. 80-83 ºC, yield 78 %, Rf=0.92, dark brown color. **1c**; m.p. 84-89 ºC, yield 82 %, Rf=0.66, medium walnut color. **1d**; m.p. 92-95 ºC, yield 68 %, Rf=0.63, medium violet color. **1e**; m.p. 85-88 ºC, yield 82%, Rf=0.62, dark pink color. **1f**; m.p. 86-90 ºC, yield 73 %, Rf=0.67, brown color [20-22].



Scheme 1. Synthesis of Mannich bases compounds [3a-3f]

Synthesis of 4,4'-(phenylmethylene)bis((prop-2-yn-1-yloxy)benzene) [2a-2f]. The mixture of compounds [1a-1f] methylene derivatives

(0.01mole) in 25 ml of ethanol in a round-bottom flask and 10 gm of sodium hydroxide dissolved in 50 ml of D.W. The mixture was heated under reflux for 15 min. Then, propargyl bromide (2.4 ml and 0.02 mole) was added. The mixture was sublimated using a reflective condenser for 3 hours at temperatures of 60-70, then cooled at room temperature and poured into 10 ml of cold water. The organic layer was extracted twice using benzene then the material was left to dry in an oven for two hours at a temperature of 50 ℃ to get rid of the solvent [23-24]. The solvent was evaporated gently under a moderate temperature till forming the precipitate. **2a**; m.p. 80-83 ºC, yield 67 %, Rf=0.63, pink color. **2b**; m.p. 80-83 ºC, yield 78 %, Rf= 0.92, color dark brown. **2c**; m.p. 72-76 ºC, yield 80 %, Rf=0.62, light violet color. **2d;** m.p. 76-79 ºC, yield 82 %, Rf=0.65, beige. **2e;** m.p. 60-62 ºC, yield 80%, Rf=0.61, pastel pink color. **2f;** m.p. 66-70 ºC, yield 72 %, Rf=0.83, color light beige.



[3a-3f]

Scheme 2. The reaction mechanism of the synthesized compounds [3a-3f]

Synthesis of 4,4'-(((phenylmethylene)bis (4,1-phenylene))bis (oxy))bis(N,N-diethy lbut-2-yn-1-amine) (Mannich bases) [3a-3f]. In a round bottom flask, a mixture of (1.2 g, 0.002 mole) of compound [2a-2f] and (0.002 ml, 0.02 mole) of acetylene ether derivatives was dissolved with (0.01) formaldehyde in (50) ethanol, Then (0.02mole) of the secondary amine

diethyl amine was added. The resultant mixture was heated under reflux for 3 hrs at (70 ℃), in the presence of (0.098 g, 0.001 mole) cuprous chloride as catalyst. The reaction was monitored by TLC using eluent (3:7) hexan:ethyl acetate. The solvent was concentrated. The mixture was allowed to cool and then poured onto crushed ice with a scratching 90-94. The resulting solid was filtered off and recrystallized from ethanol to remove the cuprous chloride [26-29]. **3a;** m.p. 78-82 ºC, yield 73 %, Rf=0.85, color pink. **3b**; m.p 80-86 ºC, yield 72 %, Rf=0.82, color light green. **3c**; m.p. 74-79 ºC, yield 74 %, Rf=0.84, color light pink. **3d**; m.p. 86-88 ºC, yield 73 %, Rf=0.84, light beige. **3e**; m.p. 82-86 ºC, yield 73%, Rf=0.92, color light pink. **3f**; m.p 82-88 ºC, yield 81 %, Rf=0.88, color light brown (Schemes 1 and 2).

Results and discussion

The FT-IR spectrum of [**3a**] showed an appearance absorption band at 3057, 2948 cm^{-1} due to stretching vibration of C-H aromatic, Ali C-H respectively (Fig. 3).

The ^{1}H-NMR spectrum of compounds [**3a**] showed at δ 7.65 (m, 2H), 7.16 (m, ArH, 4H), 6.74 (m, ArH,4H), 5.00 (s, CH, 1H), 4.49 (s, J = 13.8 Hz, CH_2, 4H), 3.83 (s, CH_2, 4H), 3.12 (s, CH_2, 4H), 2.17 – 1.84 (q, CH_2,8H),1.36 – 0.51 (t, CH_3, 12H) (Fig. 4).

The ^{13}C-NMR spectrum of compounds [**3a**] showed at δ 154.07, 140.31, 133.44, 131.08, 130.52, 124.73, 123.40, 121.51 carbon of aromatic ring, 79.34, 62.07 carbon of acetylene,58.47 carbon of CH_2-O, 55.58 carbon of CH, 51.75 carbon of CH_2-CH_3, 40.44 carbon of (CH_3-N-CH_3), 35.22 carbon of CH_2-N, 14.34 carbon of CH_3 (Fig. 5).

The FT-IR spectrum of [**3b**] showed an appearance absorption band at 3113, 2978 cm^{-1} due to stretching vibration of C-H aromatic, Ali C-H respectively [30-33].

The ^{1}H-NMR spectrum of compounds [**3b**] showed at δ 7.34 (m, ArH, 2H), 7.17 (m, ArH, 2H), 6.93 (J = 9.6 Hz, m, ArH, 4H), 6.46 (m, ArH, 4H), 5.01 (s, CH, 1H), 3.90 (CH_2, 4H), 3.45 (s, CH_2, 4H), 2.18 (q, CH_2, 8H), 1.09 – 0.88 (t, CH_3, 12H).

The ^{13}C-NMR spectrum of compounds [**3b**] showed at δ 176.74, 162.23, 152.25, 151.97, 128.86, 124.65, 116.14, 115.57 carbon of aromatic ring, 73.21, 71.96 carbon of acetylene, 55.98 carbon of CH_2-O, 63.74 carbon of CH, 58.26 carbon of CH_2-CH_3, 44.29 carbon of CH_2-N, 22.18 carbon of CH_3.

The FT-IR spectrum of [**3c**] showed an appearance absorption band at 3057 2968 cm^{-1} due to stretching vibration of C-H aromatic Ali C-H respectively.

The ^{1}H-NMR spectrum of compounds [**3c**] showed at δ 7.70 (m, J = 77.2 Hz ArH, 2H), 7.42 (m, ArH, 2H), 7.28 (m, J = 25.4 Hz, m, ArH, 2H), 6.80 (m, J = 50.8 Hz, m, ArH, 4H), 6.63 – 6.37 (m, ArH, 2H), 5.24 (s, CH, 1H), 4.94 (s, CH_2, 4H), 3.55 (s, 4H), 2.29 (d, J = 17.3 Hz, 8H), 1.62 – 0.69 (m, CH_3, 12H) [33-37].

The FT-IR spectrum of [**3d**] showed an appearance absorption band at 3034, 2964 cm^{-1} due to stretching vibration of C-H aromatic Ali C-H respectively.

The ^{1}H-NMR spectrum of compounds [3d] showed at δ 9.49 (s, OH, 1H), 7.91 (m, ArH, 1H), 7.40 (m, J = 29.2 Hz, ArH, 2H), 7.28 (m, ArH, 2H), 6.86 (m, ArH, 2H), 6.67 (m, J = 19.3 Hz, ArH, 4H), 5.32 (s, CH, 1H), 4.65 (s, CH_2, 4H), 3.90 (s, CH_3, 3H), 3.70 (s, CH_2, 4H), 2.44 – 1.43 (q, CH_2, 8H), 1.56 –0.37 (t, CH_3, 12H).

The^{13}C-NMR spectrum of compounds [**3d**] showed at δ 152.04, 149.43, 139.74, 136.96, 127.14, 123.97, 111.92, 109.47 carbon of aromatic ring, 84.05, 77.12 carbon of acetylene, 55.66 carbon of CH, 55.58 carbon of CH_2-O, 50.66 carbon of CH_2- CH_3, 46.37 carbon of CH3-O, 35. 47 carbon of CH_2-N, 17.04 carbon of CH_3.

The FT-IR spectrum of [**3e**] showed an appearance absorption band at 3030, 2993 cm^{-1} due to stretching vibration of C-H aromatic Ali C-H respectively.

The ^{1}H-NMR spectrum of compounds [**3e**] showed at δ 9.34 (s, OH, 1H), 8.11 (m, ArH, 2H), 7.07 (m, ArH, 3H), 7.05 (m, ArH, 3H), 6.88 (m, ArH, 2H), 6.78 (m, ArH, 2H), (s, 12H), 5.27 (s, CH, 1H), 4.71 (s, CH_2, 4H), 3.51(s, CH_2, 4H), 2.6 (q, CH2, 8H), 0.95 (t, CH_3, 12H).

The ^{13}C-NMR spectrum of compounds [**3e**] showed at δ 164.96, 158.36, 142.63, 142.61, 137.32, 131.30, 130.90, 124.73, 123.40, 121.51 carbon of aromatic ring, 78.93, 70.63 carbon of acetylene, 61.58 carbon of H, 58.62 carbon of

CH_2-O, 44.26 carbon of CH_2-CH_3, 39.65 carbon of CH_2-N, 14.43 carbon of CH_3.

The FT-IR spectrum of [**3f**] showed an appearance absorption band at 3050 2981cm^{-1} due to stretching vibration of C-H aromatic Ali C-H respectively.

The ^{1}H-NMR spectrum of compounds [**3f**] showed at δ 8.51 (m, ArH, 2H), 8.46 (m, ArH, 3H), 7.50-7.57 (m, ArH, 3H), 7.28 (m, ArH, 2H), 7.20 (m, ArH, 2H), (s,12H), 5.44 (s, CH, 1H), 4.88 (s, CH_2, 4H), 3.69(s, CH_2, 4H), 2.96 (q, CH_2, 8H), 2.41 (s, CH_3, 3H). 1.35 (t, CH_3, 12H).

The ^{13}C-NMR spectrum of compounds [**3f**] showed at δ 161.26, 152.04, 150.73, 128.50, 123.50, 111.76, 108.77 carbon of aromatic ring, 86.08, 81.14 carbon of acetylene, 56.09 carbon of CH, 55.86 carbon of CH_2-O, 53.90 carbon of CH_2-CH_3, 50.76 carbon of CH_3-O, 45. 83 carbon of CH_2-N 14.26 carbon of CH_3.

The ^{1}H-NMR spectrum of compounds [**3g**] δ 8.51 (m, ArH, 2H), 8.46 (m, ArH, 3H), 7.50-7.57 (m, ArH, 3H),7.28 (m, ArH, 2H), 7.20 (m, ArH, 2H), (s,12H), 5.44 (s, CH,1H), 4.88 (s, CH_2, 4H), 3.69(s, CH_2, 4H), 2.96 (q, CH_2, 8H), 2.41 (s, CH_3, 3H), 1.35 (t, CH_3, 12H).

The ^{1}H-NMR spectrum of compounds [**3h**] δ 7.42 (m, ArH, 4H), 7.31 (m, ArH, 1H), 7.25-7.16 (m, ArH, 2H), 6.64 (m, ArH, 4H), 5.29 (s, CH, 1H), 4.21 (s, CH_2, 4H), 3.23 (s, CH_2, 3H), 3.22 (s, CH_2, 3H), 3.13 (s, CH_2, 4H), 2.07 (q, CH_2, 8H), 0.81 (t, CH_3, 12H) [38-41].

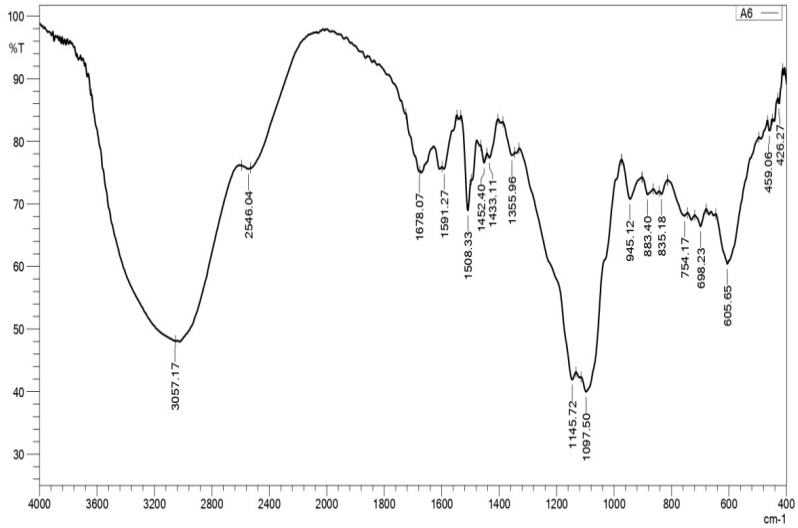


Fig. 3. FT-IR Spectrum of [3a]

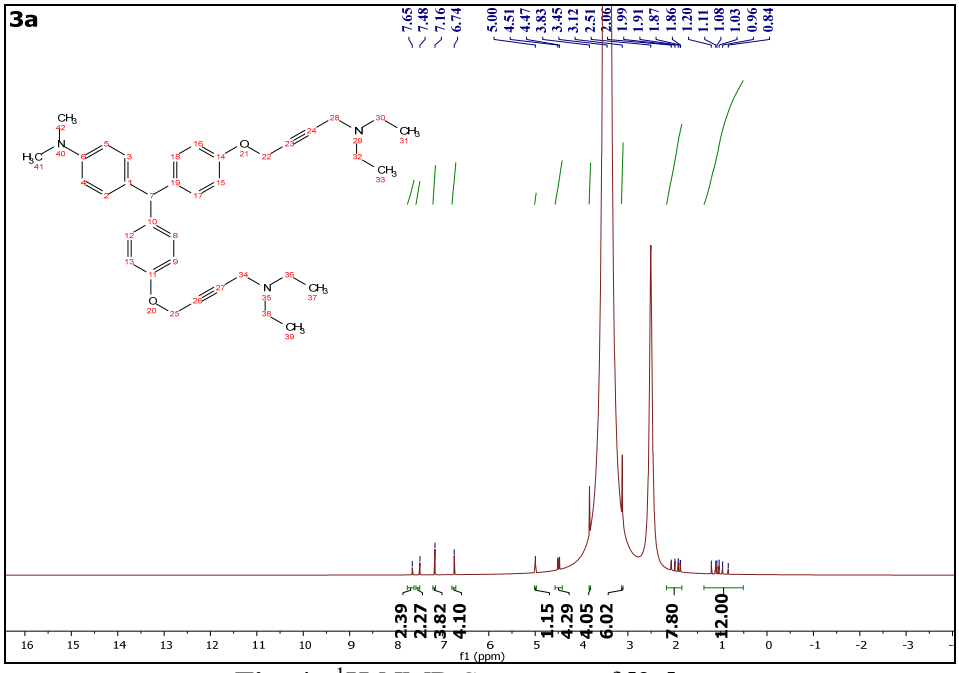


Fig. 4. ^{1}H-NMR Spectrum of [3a]

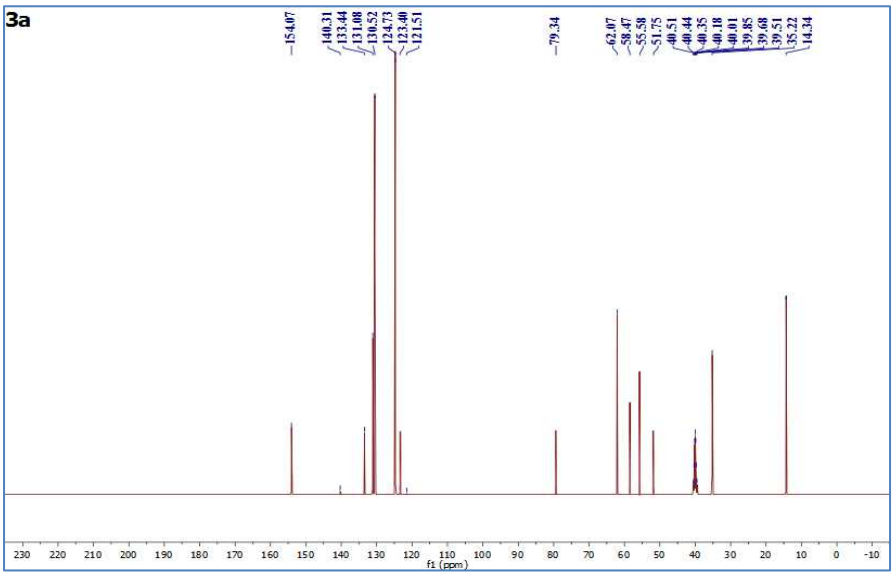


Fig. 5. ^{13}C-NMR Spectrum of [3a]

Molecular docking study. Traditional chemotherapy uses anticancer drugs to destroy rapidly dividing cancer cells throughout the body. Since cytotoxic anticancer drugs cannot distinguish between cancer cells and naturally rapidly dividing normal cells in the body, they may cause one or more of the following side effects. Targeted anticancer drugs bind specifically to cancer cells, resulting in fewer adverse effects than cytotoxic drugs that aim to selectively target molecules or proteins implicated in the proliferation and metastasis of cancer cells. Molecular docking plays an increasingly important part in the targeted drug discovery and development process since it saves time, cost, and research effort and reduces side effects of anticancer drugs. Molecular docking is becoming a more essential method for drug development. Its primary goals are to estimate ligand-protein affinity and to achieve a ligand-receptor complex with an optimal conformation and lower binding free energy. As the molecular docking study shows, the newly synthesized compounds exhibited an anti-cancer effect.

The anticancer effects of these compounds are on the C-Met tyrosine kinase receptor [42-44], with varied scores. Their docking scores range from -3.95 to -5.00 kcal/mol, whereas Crizotinib binding affinity is -6.86 kcal/mol.

Table 1. Results of molecular interaction between C-met tyrosine inhibitor compounds (3a-3f)

NO.	Docking score on ER-(Kcal/mol)
3a	-4.42
3b	-5.00
3c	-4.66
3d	-3.95
3e	-4.46
3f	-4.29
3g	-4.27
Crizotinib	-6.86

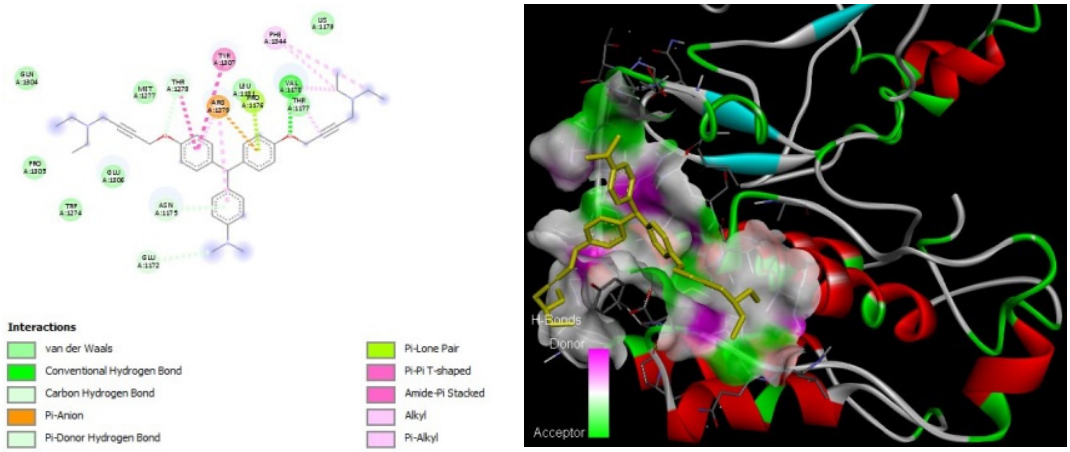


Fig. 6. 2D and 3D dimensional representations of molecular interactions between C-met tyrosine inhibitor and (3a) compound

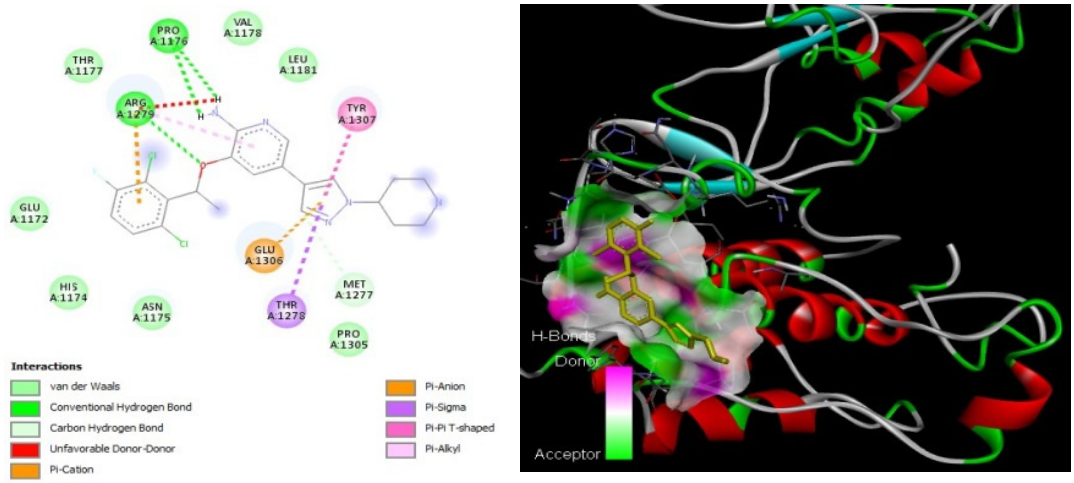


Fig.7. D2 and D3 dimensional representations of molecular interactions between C-met tyrosine inhibitor and (Crizotinib) compound

Table 2. Diameter of the inhibition zone in *mm* of the antibacterial activity of compounds (3a-3g and Amoxicillin)

Comp. Symbol	Conc. (µg/ml)	Gram-positive		Gram-negative	
		Enterococcus faecalis	***Staphylococcus aureus***	***Escherichia coli***	***Pseudomonas aeruginosa***
3a	100	20	15	12	14
3b	100	25	18	17	21
3c	100	24	14	13	24
3g	100	21	17	24	81
Amoxicillin	100	19	20	16	18

Antibacterial activity of synthesized compounds. The antibacterial activity of newly synthesized compounds (3a, 3b, 3c, 3g, and Amoxicillin) was assessed *in vitro* using the Muller-Hinton agar cup method. The compounds were examined, the plates were incubated for 24 hrs at 37 °C, and the inhibitory zone was recorded in *mm*. The chemicals' biological effects on a series of bacteria [*Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, and*

Pseudomonas aeruginosa], respectively, displayed high inhibition as shown in the following Table 2 and Fig. 8. The synthesized compounds (3a, 3b, 3c, 3g, and Amoxicillin) showed high activity against negative and positive bacteria [45-47].

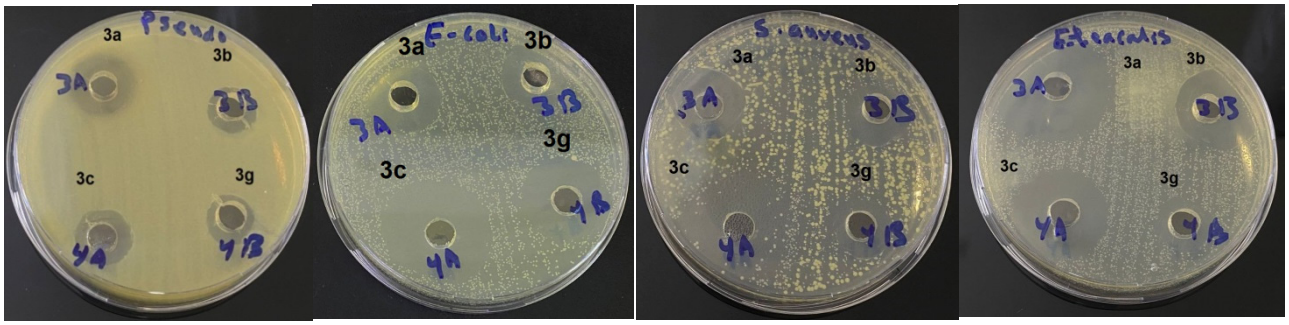


Fig. 8. Mean zone of inhibition (*mm*) of 3a, 3b, 3c, and 3g compounds against *Enterococcus faecalis, Staphylococcus aureus, E. coli and Pseudomonas aeruginosa* on Muller-Hinton agar.

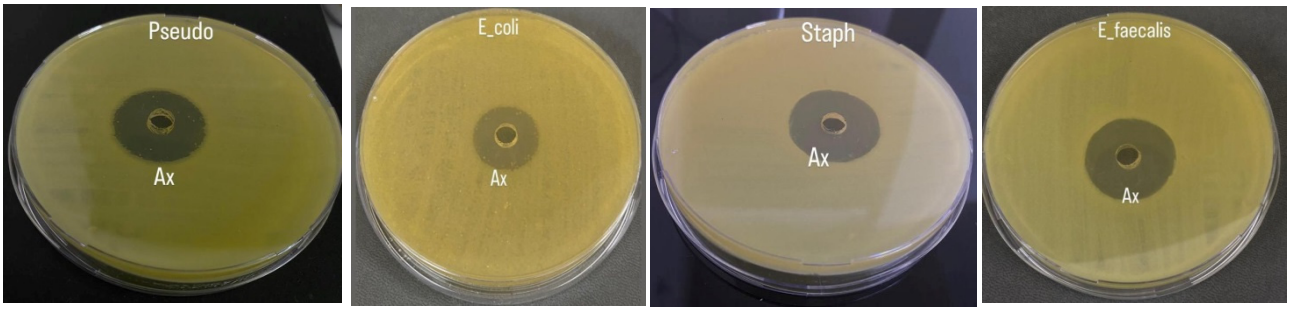


Fig. 9. Mean zone of inhibition (*mm*) of Amoxicillin against Enterococcus faecalis, Staphylococcus aureus, E. coli, and Pseudomonas aeruginosa on Muller-Hinton agar

Conclusion

This study involved the synthesis of seven new Mannich-base derivatives. The synthesized compounds were confirmed by some spectral methods such as FTIR, ^{1}H-NMR, and ^{13}C-NMR. The newly synthesized compounds exhibited an anticancer effect when docked with the C-Met tyrosine kinase receptor, as shown by their docking scores ranging from -3.95 to -5.0 kcal/mol. In contrast, Crizotinib binding affinity is -6.86 kcal/mol for antibacterial efficiency. The synthesized compounds have exhibited high activity against negative and positive bacteria [Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa], respectively, better than Amoxicillin.

Acknowledgments

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