SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL ACTIVITY OF [1,2,4]TRIAZOLO[4,3-*B*][1,2,4,5]TETRAZINE DERIVATIVES

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Received 21.06.2024
Accepted 05.08.2024

Abstract: *A series of fused heterocyclic compound triazolotetrazine were prepared from the reaction of equimolar amount of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol via cyclization addition reaction with different aromatic aldehydes in presence of piperidine as catalyst to produce the target [1,2,4]triazolo[4,3-b][1,2,4,5] tetrazine derivatives. The synthesized compounds were characterized by spectral methods (FT-IR and ^{1}H-NMR, ^{13}C-NMR and mass). The newly synthesized compounds exhibited an anticancer effect when these compounds were docked inside the C-Met tyrosine kinase receptor. As shown by their docking scores, they range from -5.599 to -4.403 Kcal/mol, whereas Crizotinib binding affinity is -3.211 Kcal/mol. For antibacterial efficiency, 4e and 4f testing on a series of bacteria, Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, and Klebsiella, respectively, reveals that the compounds have exhibited moderate activity against negative and positive bacteria. Antifungal activity of (4g, 4i) was assessed against the representative typical fungi such as Candidiasis fungal and compared with Fluconazole as an antifungal drugs. The results indicated that tested compounds had good fungicide activity, which has good growth inhibition against Candidiasis.*

Keywords: *antibacterial, antifungal, characterization, pharmaceutical, synthesis, triazolotetrazine*
DOI: 10.32737/2221-8688-2025-1-78-94

1. Introduction

Fused heterocyclic chemistry is a branch of organic chemistry that focuses on the study and synthesis of compounds containing two or more fused heterocyclic rings that contain at least one nitrogen atom [1]. They are constructed by the combination of two or more cyclic structural units (components) when two or more heterocyclic rings are connected through a shared bond called a fused bond. For example, a quinolone (1), indole (2) and carbazole (3), as shown in Fig. 1 [2].

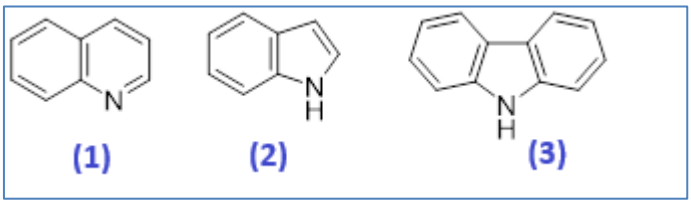


Fig. 1. Fused heterocyclic compounds

The researcher, in recent years, has paid attention to Triazolotetrazine as a fused heterocyclic compound because which have good physiochemical properties and highly pharmacological activity such as anticancer, antibacterial, antiviral and antifungal. Triazolotetrazine, recently used in computational chemistry, has higher prediction in target, thereby its capacity to target tumor cells specifically [3]. Triazolotetrazine (4) is synthesized by a fused combination of a five-member heterocyclic system 1,2,4-triazole (5) molecule with a member heterocyclic ring 1,2,4,5-Tetrazine (6) as shown in Fig. 2 [4].

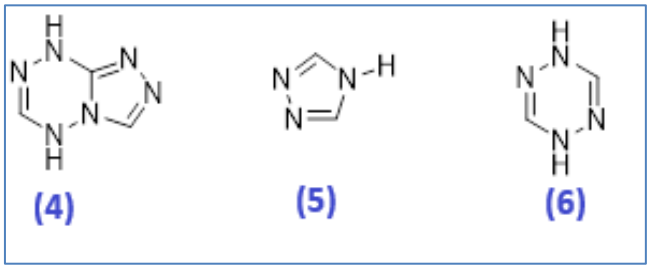


Fig. 2. Structure of triazolotetrazine

2. Experimental part

2.1. Synthesis of benzohydrazide (1)

Hydrazine hydrate (0.5 g, 0.01 mole) dissolved in absolute ethanol (70 ml), Methyl benzoate (1.36 g, 0.01 mole) was added dropwise and refluxed with stirring for 5 hrs. The reaction was monitored by T.L.C. using eluent (hexane: ethyl acetate/ 7:3). The solvent was evaporated gently under moderate temperature, and the precipitate was formed. The form solid crystals were filtered, dried and then purified by using the appropriate solvent. Table 1 illustrates the physical properties of prepared compounds [5].

2.2. Synthesis of 5-phenyl-1,3,4-oxadiazole-2-thiol (2)

To synthesize the titled Compound, the quantity of (0.68 g, 0.005 mole) benzohydrazide, (0.28 g, 0.005 mole) K.O.H. dissolved in 70 ml of absolute ethanol. CS_2 (0.4 g, 0.005 mole) was added slowly at 0 ^{0}C to the mixture. The mixture was heated under reflux for 72 hrs until stop H_2S evolved (H_2S tested by soaked lead acetate paper, which formed a black color due to the formation of blackish lead sulfide). The reaction was monitored by T.L.C. using eluent (hexan 7: ethyl acetate 3).

The solvent was removed and then acidified with 10% HCl. After the completion of the reaction, the mixture was poured into crushed ice. The formed and precipitated solid materials were filtered and washed with water and recrystallization from methanol solvent. The physical properties of synthesized compounds are shown in Table 1 [6, 7].

2.3. Synthesis of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiol (3)

A mixture of compounds 2 (1 g, 0.005 mole) and (0.28 g, 0.005 mole) K.O.H. in 100 ml of pyridine. Potassium hydroxide was reacted with thiol as a protecting group, and then hydrazine hydrate (0.25 g,0.005 mole) was added to the mixture. The resulting mixture was refluxed for (12) T.L.C. using eluent monitored hrs—the reaction (hexane 6: ethyl acetate 4). The solvent was concentrated and then acidified with 10% HCl. The formed precipitated materials were filtered, washed with water, and recrystallized. The physical properties of synthesized compounds are shown in Table 1 [8, 9, 10, and 11].

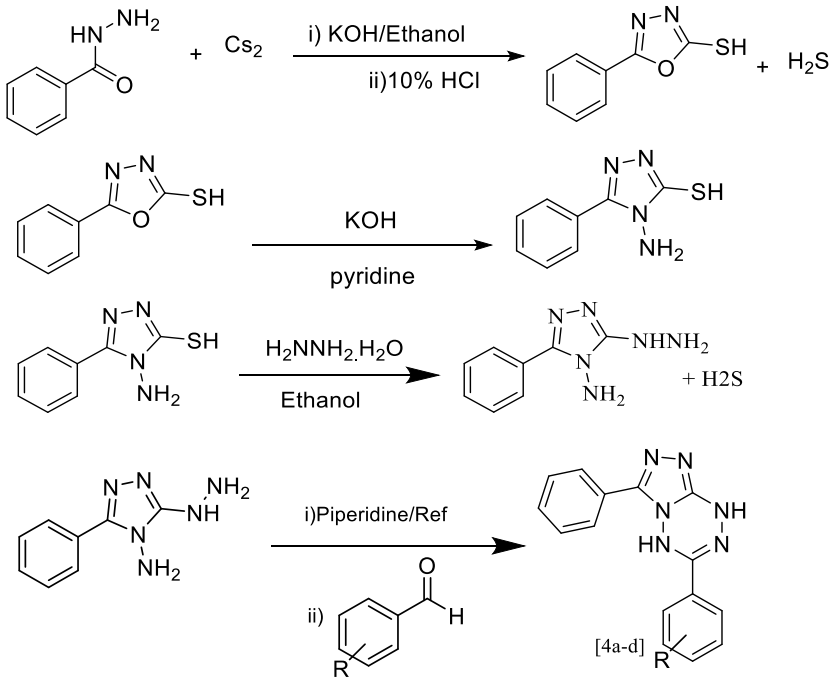
2.4. Synthesis of 3-hydrazineyl-5-phenyl-4*H*-1,2,4-triazole-4-amine (4)

A mixture (1g, 0.005 mole) of compounds 3 and (0.25g, 0.005 mole) of hydrazine hydrate in 100 ml of absolute ethanol. The resultant mixture was heated under reflux for 90 hrs till stop H_2S evolved (H_2S tested by soaked lead acetate paper, which formed a black color due to the formation of blackish lead sulfide). T.L.C., using eluent, monitored the reaction (hexan 6: ethyl acetate 4). The solvent was concentrated. The precipitated was formed are filtered, washed with water, and recrystallized from methanol. The physical properties of synthesized compounds are listed in Table 1 [12, 13].

2.5. Synthesis of [1,2,4]triazolo[4,3-*b*][1,2,4,5] tetrazine of derivatves (4e, 4f, 4h, 4i)

An equimolar mixture of (0.7g, 0.01 mole) piperidine and (2g, 0.01 mole) of compound 4 was heated under reflux, and then different aromatic aldehyde (0.01 mole) was added to the mixture. The resultant mixture was heated under reflux for six hrs. The reaction was monitored by T.L.C. using eluent (hexan 3: ethyl acetate 7). The solvent was concentrated; the mixture was allowed to cool and then poured onto crushed ice with scratching. The resulting solid was filtered off and recrystallized

from acetone. The physical properties of synthesized compounds are listed in Table 1 and shown in Fig. 3 [14, 15].



R: 4e = 3-OCH_3 , 4-OCH_3

R: 4f = 2-OH , 4-OH

R: 4h = 4-Cl

R: 4i= 4-Br

Fig. 3. Synthesis of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine derivatves (4e, 4f, 4h and 4i)

Table 1. Chemical materials and their supplier

Comp No	Molecular formula	Molecular weight	M.P, ^oC	Yield	R_f	Color
1	$C_7H_8N_2O$	136	138-140	92%	0.84	white needle
2	$C_8H_6N_2OS$	178	220-222	91%	0.92	white
3	$C_8H_8N_4S$	192	189-191	90%	0.66	pink
4	$C_8H_{10}N_6$	190	225-227	68 %	0.63	brown
5	$C_9H_6N_4S_2$	234	242-244	73%	0.92	beige
4e	$C_{17}H_{16}N_6O_2$	336	230-231	75%	0.52	brown
4f	$C_{15}H_{12}N_6O_2$	308	252-254	78%	0.55	deep brown
4h	$C_{15}H_{11}ClN_6$	311	249-251	73%	0.49	light yellow
4i	$C_{15}H_{11}BrN_6$	355	214-216	82%	0.51	light yellow

3. Results and discussion

Spectral Characterization of (1):

The FT-IR spectra of the benzohydrazide showed an appearance absorption band at I.R. (KBr), υ(cm-1): 3247, 3137, 3084 and 1648 due to stretching of NH_2, NH, ArC-H and carbonyl of benzo hydrazide [16].

Spectral Characterization of (2):

The FT-IR spectra of the 5-phenyl-1,3,4-oxadiazole-2-thiol showed an appearance absorption band at 2759, 3095, 1609, 1570, 1397, 1345 and 694 cm^{-1} due to (S.H.), ArC-H, C=N of oxadiazole ring, Asy(C-O-C), Sym(C-

O-C) and (C-S). The ^{1}H-NMR spectrum of compounds (2) showed singlet signals for (S.H.) at δ14.78 and 7.61 – 7.85 of (ArH), proving the formation of 5-phenyl-1,3,4-oxadiazole-2-thiol. The ^{1}C-NMR spectrum of compounds (2) showed signals at 177.42, 160.47 of (C=N-Ar), (C=N-S) respectively of oxadiazole ring and 132.26, 129.45, 126.06, 122.48 of aromatic carbon [17].

Spectral Characterization of (3):

The FT-IR spectra of 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiolate showed appearance absorption band at 3300, 3191, 3027, 1638, 1532, 1480 and 688 cm^{-1} due to (stretching of NH_2), N-H, ArC-H, C=N of triazole ring, Asy(C-O-C), Sym(C-O-C) and (C-S) respectively. The ^{1}H-NMR spectrum of compounds (3) showed singlet signals for (N.H.) at δ13.98 and 8.01–7.52 of (ArH), also showed new singlet signals at 5.81 for (NH_2) proved good information of synthesized 4-amino-5-phenyl-4H-1,2,4-triazole-3-thiolate.
The ^{1}C-NMR spectrum of compounds (3) showed signals at 166.84, 149.47, corresponding to (C=N-Ar), (C=N-SH) of triazole ring and 130.48, 128.53, 128.07, 125.77 of aromatic carbon [18-23].

Spectral Characterization of (4):

The FT-IR spectra of 3-hydrazineyl-5-phenyl-4H-1,2,4-triazol-4-amine (4) showed appearance absorption band at 3439-3351 cm^{-1} of (stretching of NH_2), 3184, 3078 cm^{-1} of N-H, ArC-H and 1611-1622 cm^{-1} of C=N of triazole ring, 1451 cm^{-1} of (C-N-C) and 695 cm^{-1} (C-N). The ^{1}H-NMR spectrum of compounds (4) showed doublet signals for (NH_2) at δ 12.75.98, and signal at δ 8.71, 8.17 – 7.80 of (ArH), also showed singlet signals at 5.81 for (NH_2) proved of good information of synthesized 3-hydrazineyl-5-phenyl-4H-1,2,4-triazol-4-amine. The ^{1}C-NMR spectrum of compounds (4) showed signals at 167.43, 149.95, corresponding to (C=N-Ar), (C=N-NH) of triazole ring and 130.90, 128.96, 128.50, 126.21 of aromatic carbon [24-29].

Spectral Characterization of (4e, 4f, 4h, and 4i)

The FT-IR spectra of [1,2,4]triazolo[4,3-b][1,2,4,5]tetrazine derivatives (4e, 4f, 4h, and 4i) showed appearance new band absorption at 3111-3184 cm^{-1} of NH, 3075-3084 cm^{-1} of ArC-H, 1592-1615 cm^{-1} of C=N of triazole ring, 1540-1692 cm^{-1} of C=N of tetrazine and 554-694 cm^{-1} (C-N). The ^{1}H-NMR spectrum of compounds (4a-4e) showed singlet signals for (N.H.) at δ 9.48 -10.43 and for (N.H.) signal at δ14.11-14.31 and 7.75–8.15 of (ArH).

The ^{1}C-NMR spectrum of compounds (4e-4i) showed a signal at 167.53-162.36, 149.95 corresponding to (C=N-Ar), (C=N-NH) of triazole ring and 130.90, 128.96, 128.50, 126.21 of aromatic carbon as shown in Fig. (4-17) [30-42].

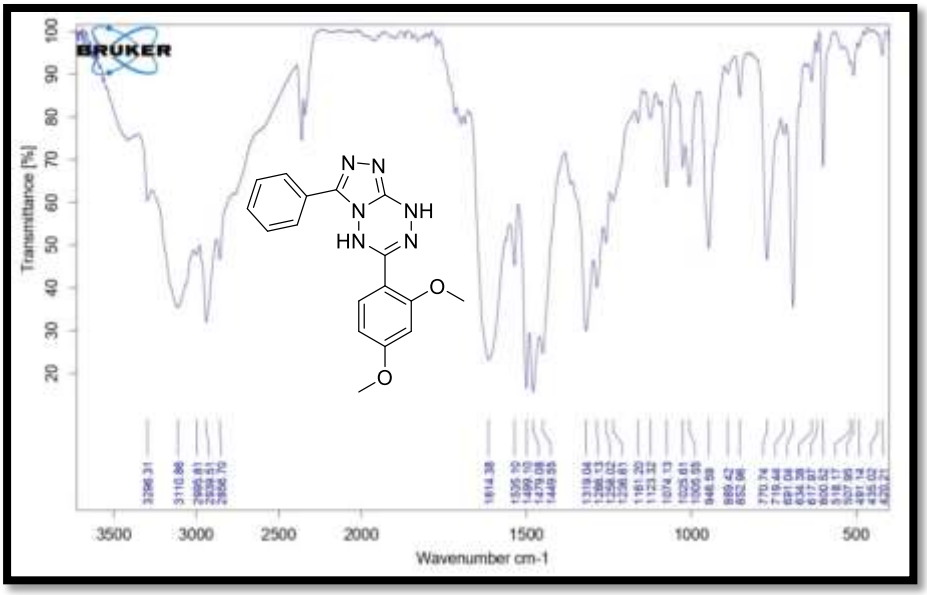


Fig. 4. FT-IR Spectrum of Compound (4a)

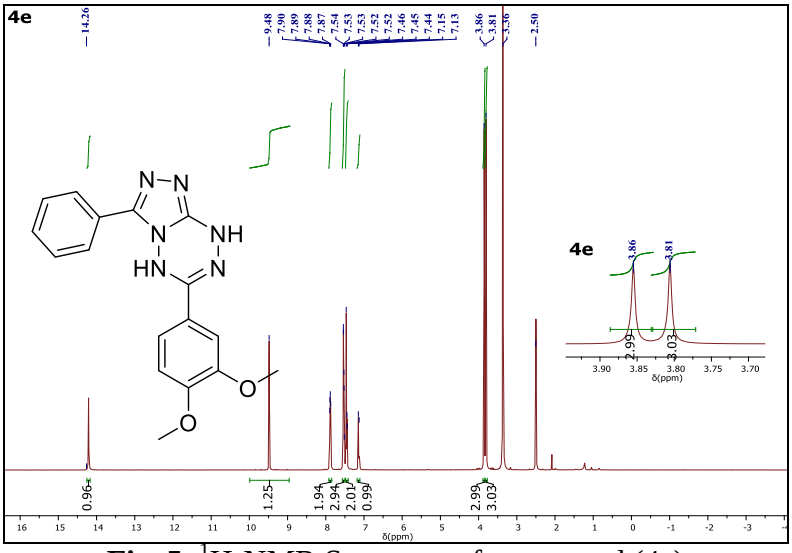


Fig. 5. ^{1}H-NMR Spectrum of compound (4e)

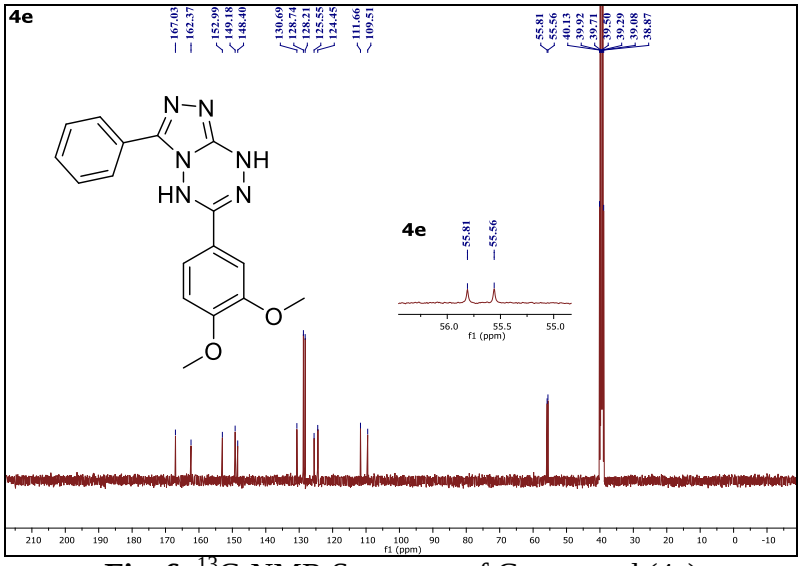


Fig. 6. ^{13}C-NMR Spectrum of Compound (4e)

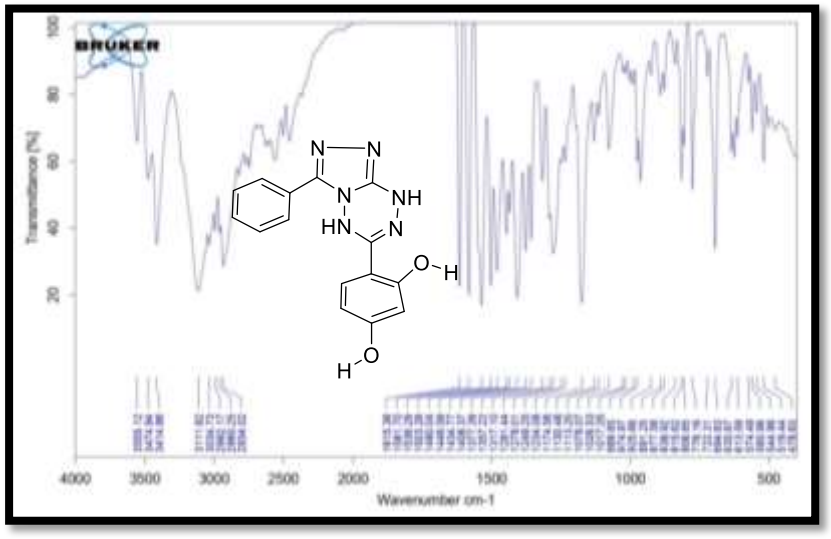


Fig. 7. FT-IR Spectrum of Compound (4f)

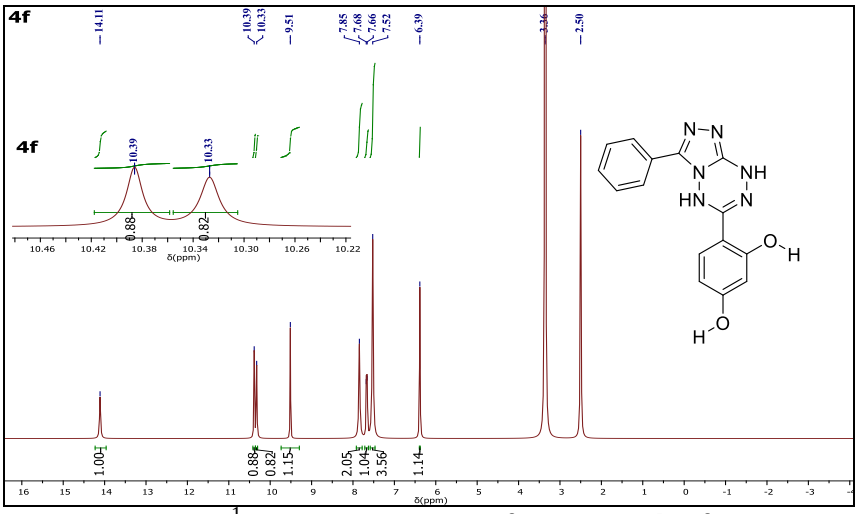


Fig. 8. ^{1}H-NMR Spectrum of Compound (4f)

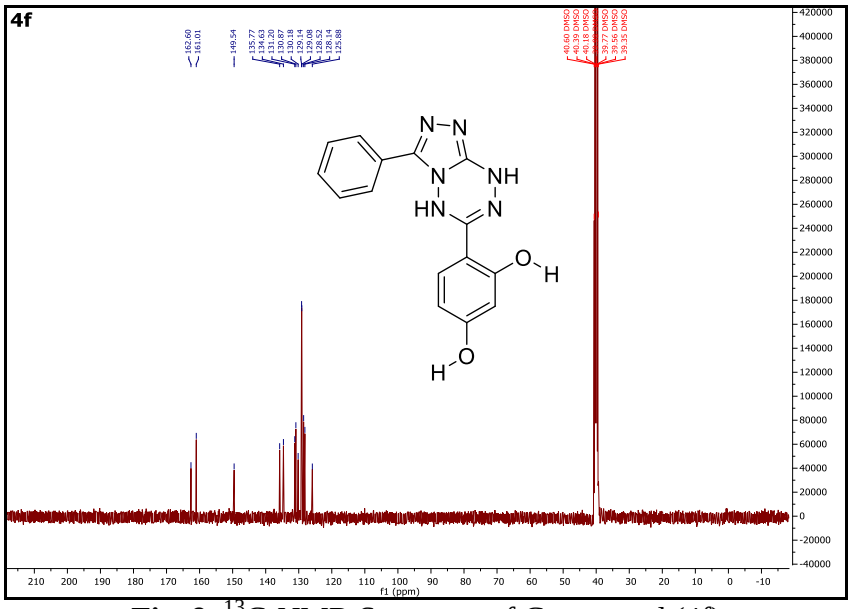


Fig. 9. ^{13}C-NMR Spectrum of Compound (4f)

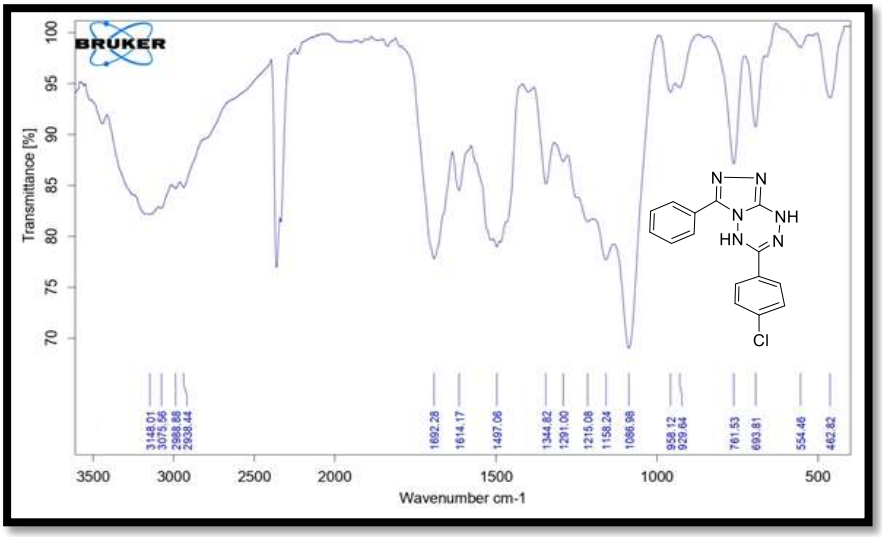


Fig. 10. FT-IR Spectrum of Compound (4h)

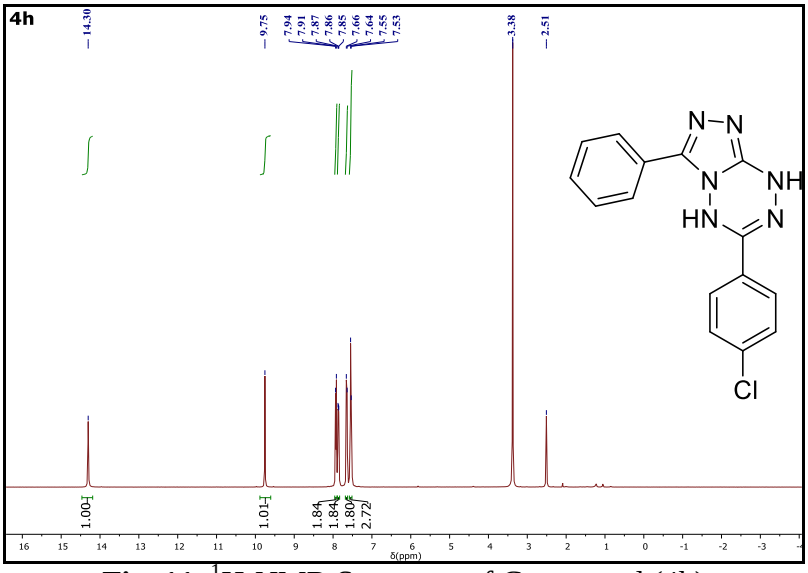


Fig. 11. ^{1}H-NMR Spectrum of Compound (4h)

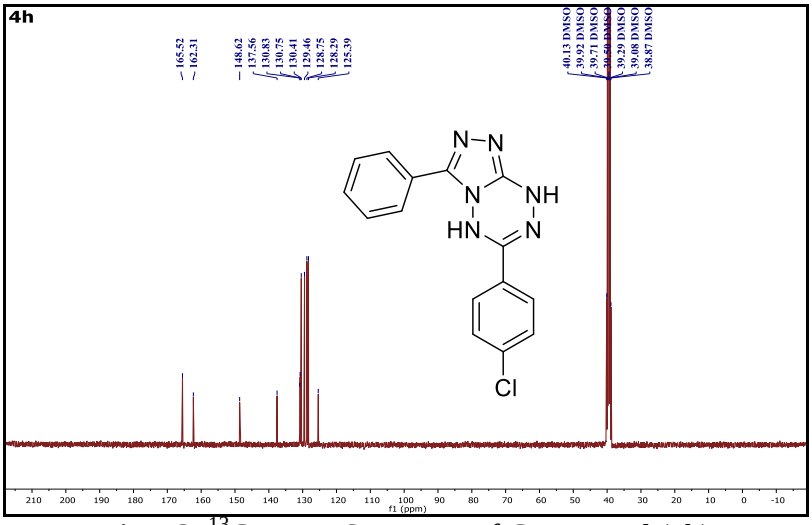


Fig. 12. ^{13}C-NMR Spectrum of Compound (4h)

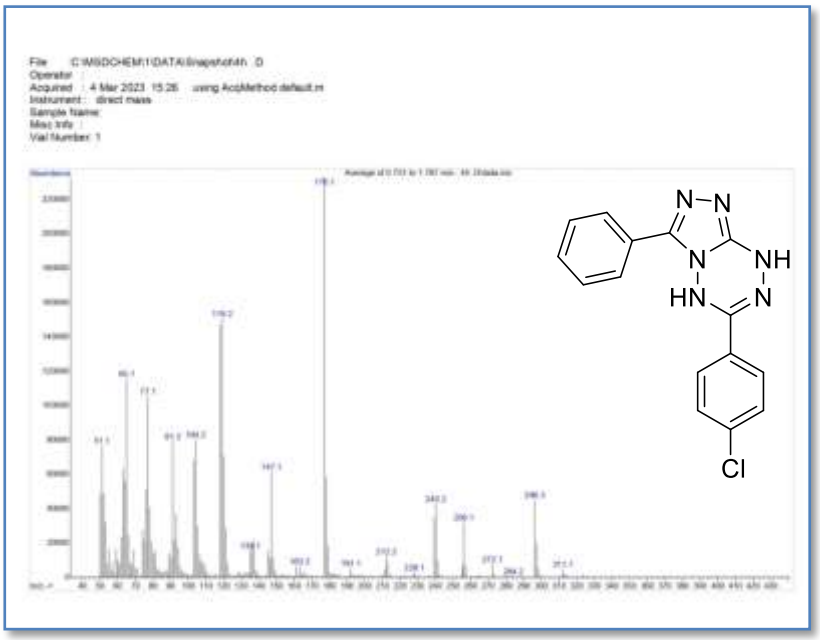


Fig. 13. MASS Spectrum of Compound (4h)

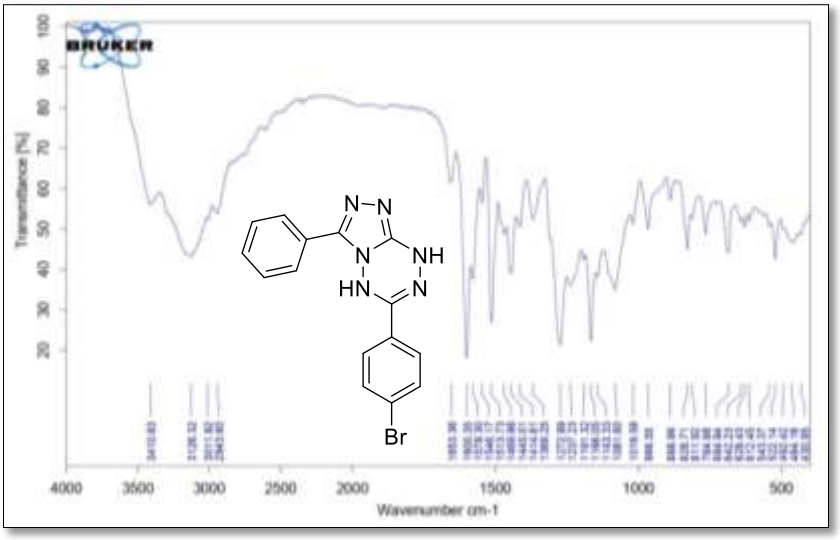


Fig. 14. FT-IR Spectrum of Compound (4i)

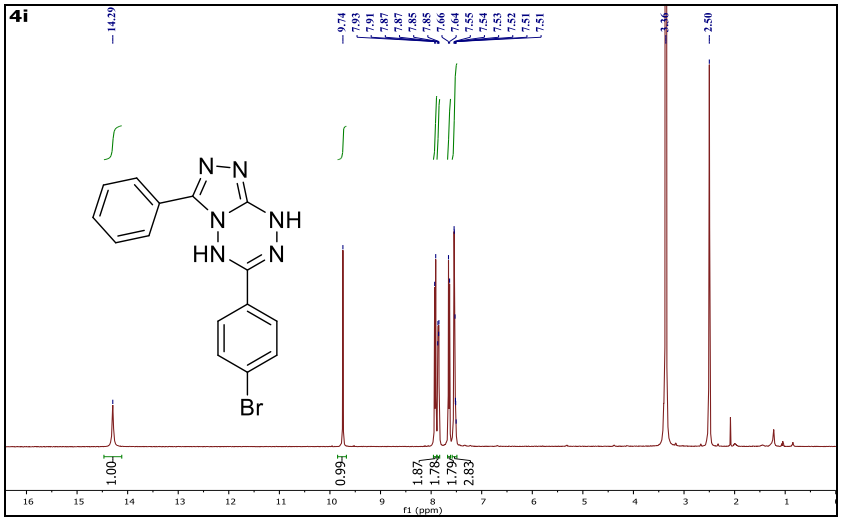


Fig. 15. ^{1}H-NMR Spectrum of Compound (4i)

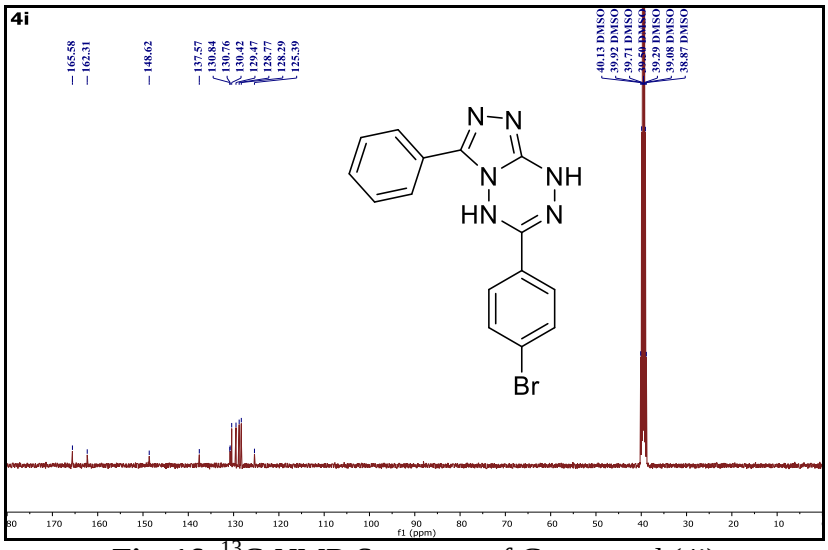


Fig. 16. ^{13}C-NMR Spectrum of Compound (4i)

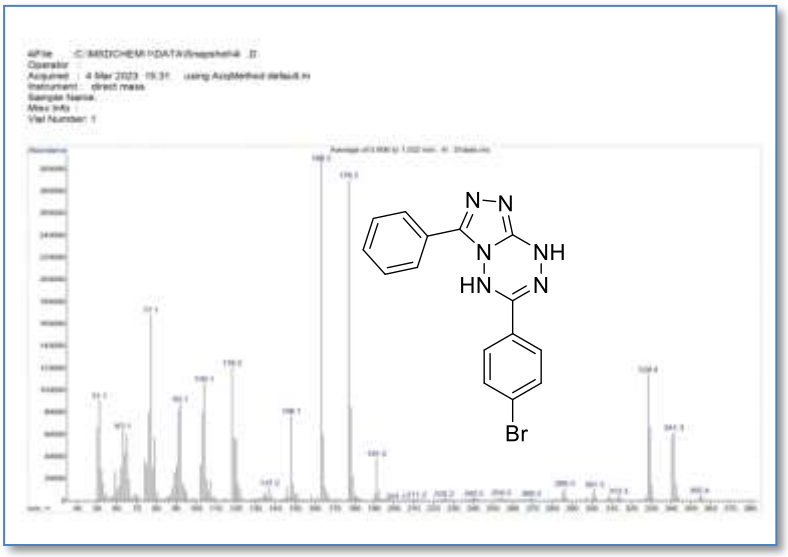


Fig. 17. MASS Spectrum of Compound (4i)

4. Molecular docking study

Molecular docking is becoming a more essential method for drug development. Its major goals are to estimate ligand-protein affinity and to achieve a ligand-receptor complex with an optimal conformation and lower binding free energy. The newly synthesized compounds exhibited an anticancer effect, as shown by the molecular docking study. The anticancer effects of these compounds are on the C-Met tyrosin kinase receptor, with varied scores [20]. Their docking scores range from -5.599 to -5.399 Kcal/mol, whereas Crizotinib binding affinity is -3.211 Kcal/mol. Moreover, Compound (4a) had the highest binding affinity -5.599 Kcal/mol). When these compounds are docked inside the C-Met tyrosin kinase receptor, they show anticancer effects with different binding affinity, as represented in the table [33].

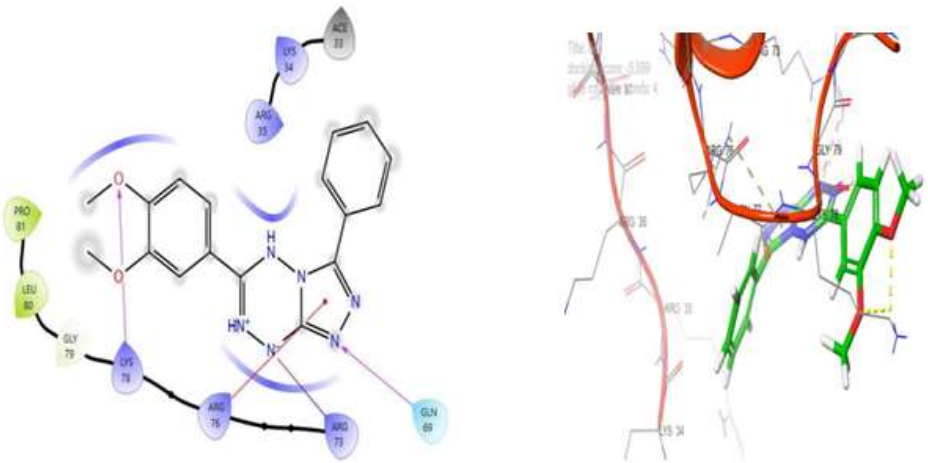


Fig. 18. D2 and D3 dimensional representations of molecular interactions between c-met tyrosine inhibitor and compounds (4e)

They form hydrogen bonds (H-bond) with amino acid residues at the protein receptor active site, as well as additional short contacts that enhance the interaction. Compound (4e) binds by two H-bond with L.Y.S. 78, G.L.N. 69, in addition, Salt bridge with A.R.G. 73 and pi-cation with A.R.G. 76 as shown in Fig. 18. Result of molecular docking showed the Compound (4f) bind by two H-bond between the hydroxyl group and G.L.N. 69 and other between (N-H) and A.S.N. 77 as shown in Fig. 19. Compound (4h) binds to the receptor by one pi-pi stacking between triazole ring and amino acid with T.R.P. 98, in addition form one Salt bridge with L.Y.S. 60, furthermore, it may form hydrophobic interaction with surrounding amino

acids as shown in Fig. 20. Compound (4i) bind by two H-bond with T.H.R. 75, SER 135, in addition two Salt bridges with ARG 134 & LYS 170. Furthermore, it forms several polar interactions with surrounding amino acids and pi-cation with LYS 137, as shown in Figures 21, 22 and 23 [43-47].

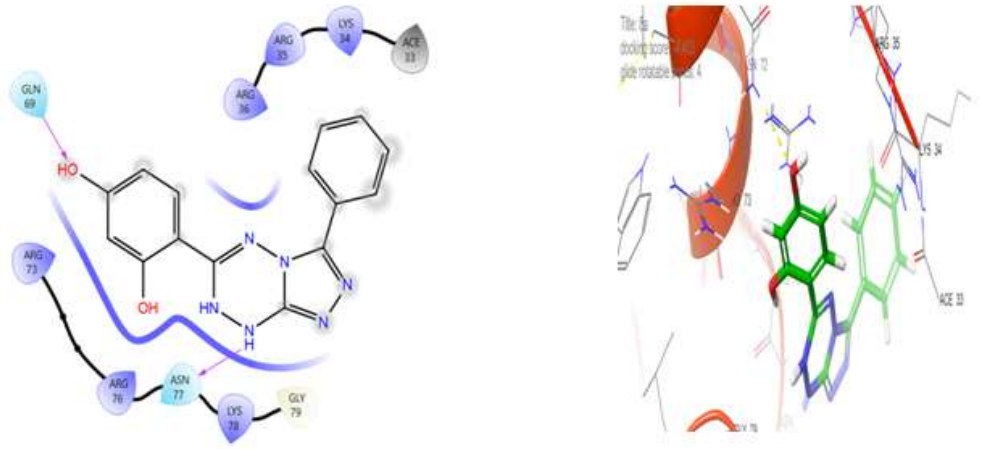


Fig. 19. D2 and D3 dimensional representations of molecular interactions between c-met tyrosine inhibitor and compounds (4f)

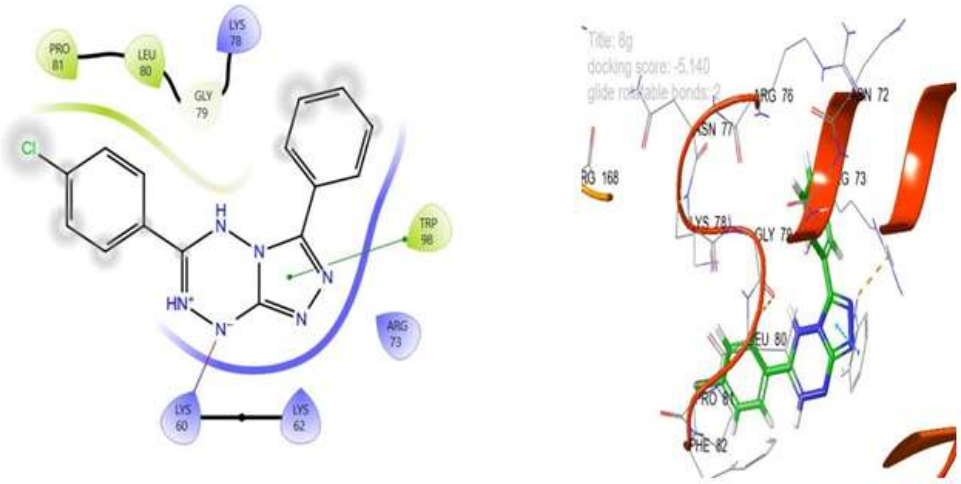


Fig. 20. D2 and D3 dimensional representations of molecular interactions between c-met tyrosine inhibitor and compounds (4h)

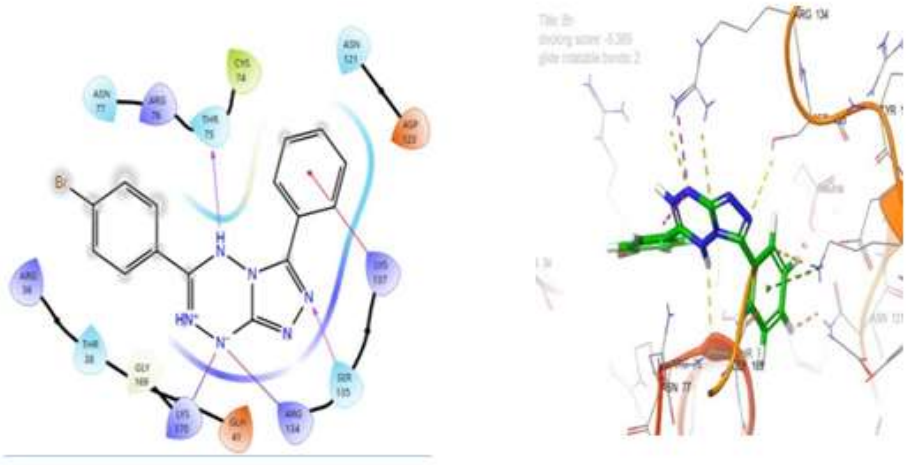


Fig. 21. D2 and D3 dimensional representations of molecular interactions between c-met tyrosine inhibitor and compounds (4i)

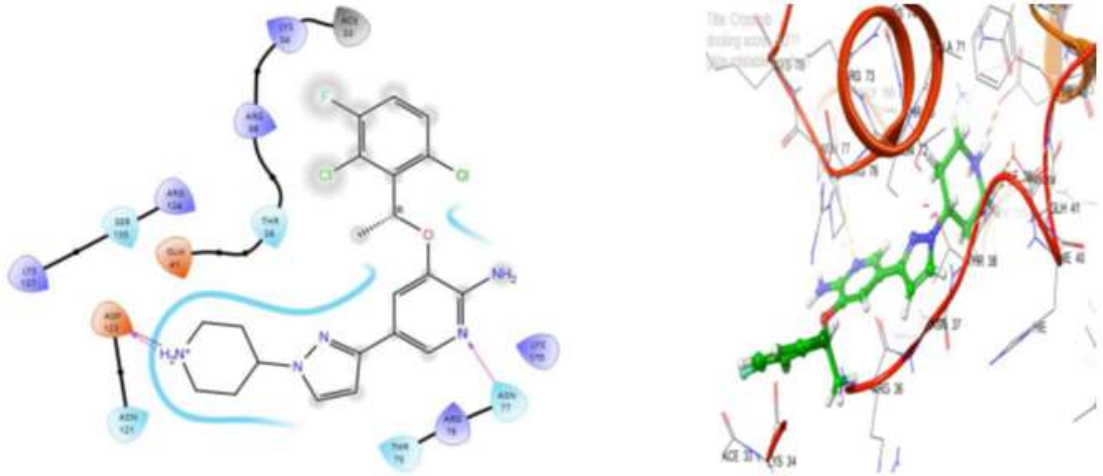


Fig. 22. D2 and D3 dimensional representations of molecular interactions between c-met tyrosine inhibitor and Crizotinib drug

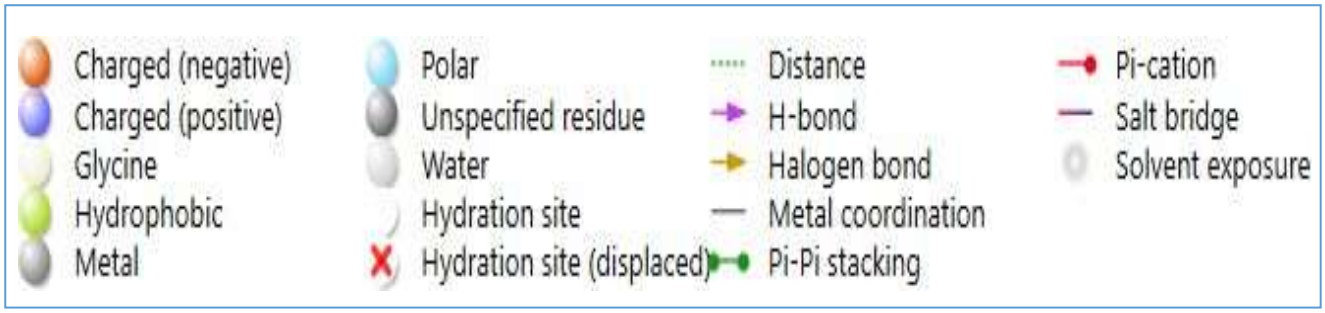


Fig. 23. H-bond and other bonds of molecular interactions between c-met tyrosine inhibitor and compounds (4e, 4f, 4h, 4i)

Table 2. Results of molecular interaction between c-met tyrosine inhibitor, compounds (4a-i) and reference Crizotinib drug

Title	Others bonds	H-bond	Docking score on ER–(Kcal/mol)
4e	Salt bridge A.R.G. 73,ARG76	L.Y.S. 78, G.L.N. 69	-5.599
4f	--	G.L.N. 69, A.S.N. 77	-4.403
4h	T.R.P. 98, salt bridge with L.Y.S. 60	--	-5.14
4i	LYS 137,salt bridge ARG 134, LYS 170	THR 75, SER 135	-5.369
Crizotinib drug	**Salt bridge with ASP 123**	**ASP 123, A.S.N. 77**	**-3.211**
Title	**Others bonds**	**H-bond**	**Docking score on ER–(Kcal/mol)**
4e	Salt bridge A.R.G. 73,ARG76	L.Y.S. 78, G.L.N. 69	-5.599
4f	--	G.L.N. 69, A.S.N. 77	-4.403
4h	T.R.P. 98, the salt bridge with L.Y.S. 60	--	-5.14
4i	LYS 137, salt bridge ARG 134, LYS 170	THR 75, SER 135	-5.369
Crizotinib drug	**Salt bridge with ASP 123**	**ASP 123, A.S.N. 77**	**-3.211**

5. Antibacterial activity of synthesized compounds:

Antibacterial activity of newly synthesized compounds (4e, 4f) was assessed In vitro by using the agar cup method Muller Hinton agar. The compounds were examined, the plates were incubated for 24 hrs at 37 °C, and the inhibitory zone was recorded in (mm). The chemical's biological effects on a series of bacteria [Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, and Klebsiella], respectively, which displayed intermediate inhibition, as shown in the following table. The synthesized compounds (4b, 4g) showed moderate activity against negative and positive bacteria, as shown in Fig 24 [48-50].

Table 3. Diameter of inhibition zone in mm of the antibacterial activity of compounds (4e and 4f)

Comp. Symbol	Conc. (µg/ml)	gram-positive		gram-negative	
		Enterococcus faecalis	Staphylococcus aureus	Escherichia coli	Klebsiella
4e	50	14	13	14	14
	100	15	16	17	15
4f	50	13	15	13	13
	100	15	14	15	15
Ciprolox acin	10	15	16	17	16

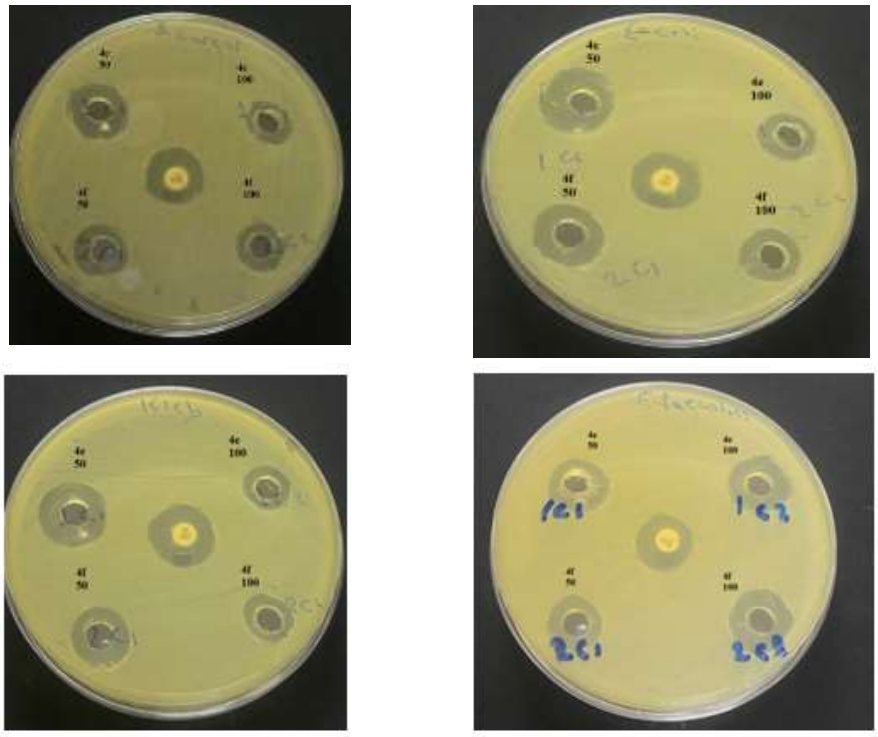


Fig. 24. Mean zone of inhibition (mm) of 4e and 4f compounds on E.faecalis, S. aureus, E.coli and Klebsiella on Muller Hinton agar.

6. Antifungal activity of synthesized compounds:

Antifungal activity of newly synthesized compounds (4g and 4h) was assessed against the representative typical fungi such as Candidiasis fungal were detected at 50 µg/mL and 100 µg/mL and compared with Fluconazole as antifungal drugs. The results indicated that

tested compounds had good fungicide activity, which has good growth inhibition against Candidiasis fungal, as shown in Table 4 and Fig. 25 [51, 52].

Table 4. Antifungal activity of compounds (4g and 4h)

Comp. Symbol	Conc. (µg/ml)	Diameter of inhibition zone in mm
		Candidiasis fungal
4g	50	14
	100	18
4h	50	12
	100	17
Fluconazole	100	15

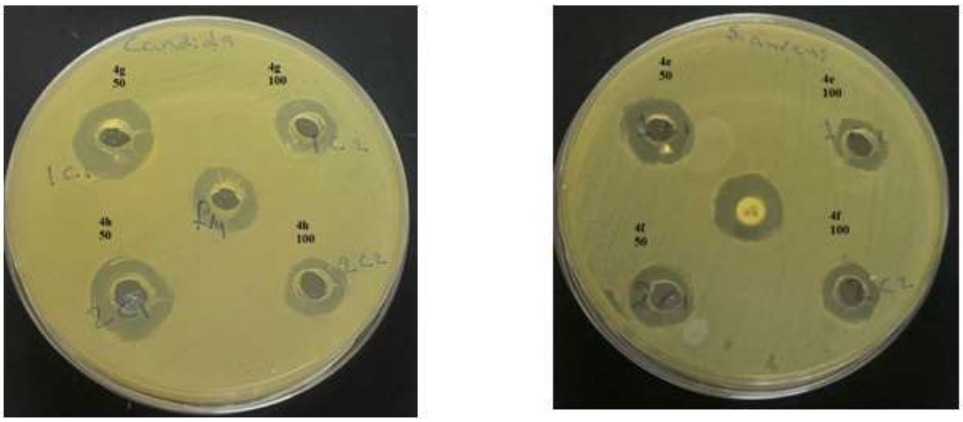


Fig. 25. Mean zone of inhibition (mm) of 4g and 4h compounds Candidiasis fungalon Muller Hinton agar.

4. Conclusion

In this study, [1,2,4]triazolo[4,3-*b*][1,2,4,5] tetrazine derivatives were synthesized via cyclization reaction. 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 these compounds were docked inside the C-Met tyrosin kinase receptor, as shown by their docking scores ranging from -5.599 to -4.404 Kcal/mol. In contrast, Crizotinib binding affinity is -3.211 Kcal/mol for antibacterial efficiency. The synthesized compounds have exhibited moderate activity against negative and positive bacteria. Antifungal activity: the results indicated that tested compounds had good fungicide activities that have good growth inhibition against Candidiasis.

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