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DESIGN, SYNTHESIS, MOLECULAR DOCKING, AND ANTIMICROBIAL STUDY ON NAPHTHOFURAN DERIVATIVES

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ABSTRACT

The ethyl-naphtho[2,1-b]furon-2-carboxylate 2, hydrazine hydrate in the presence of a catalytic quantity of conc. HCl in ethanol was refluxed at 30 ^{0}C to get the naphtho[2,1-*b*]furan-2-carbohydrazide 3. The reaction of aromatic acids with methanol in the presence of an acid catalyst gives esters, these esters on treatment with hydrazine hydrazide produce acid hydrazides 4a-f. These acid hydrazides 4a-f, in reaction with carbon disulphide produces 2-(substituted)phenylhydrazine-potassiumcarbodithioate 5a-f. The reaction of 5a-f with compound 3 in ethanol produces *N*-[3-phenyl-5-sulphanyl-4H-1,2,4-triazole-4-yl)-naphtho[2,1-*b*]furan-2-carboxamide 6a-f. Elemental analysis, FTIR, NMR, and mass spectral analyses have been used to characterize the synthesized compounds. They have also been applied to research on antimicrobial studies and have also done the docking investigation of the synthesized compounds with the various biological molecules to get excellent results.

Keywords: Naphthofuran, Triazole, Molecular Docking, Antibacterial Activity, Antifungal Activity, Hydrazine Hydrazide.

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INTRODUCTION

Synthetic chemistry plays an important role in the blooming of drug discoveries. Large numbers of the consolidated heterocycles and bi-heterocycles including naphthofuran have accounted for a wide range of pharmacological activities.[1-4] Naphthofuran cores are key primary moieties found in countless organically significant normal products.[5-6] Naphthofuran subsidiaries have been isolated from different natural sources, such as Fusarium, Oxysporum, Gossipium barbendanse, and so on, and are notable for different natural exercises like antitumor, antifertility, mutagenic, development inhibitory, and osterogenic.[7-9] The literature review revealed that the prepared subsidiaries of naphtho[2,1-b]furans show an extensive variety of pharmacological and biological action.[10-14] Recently, reviews on derivatives of arene ring-fused furans exhibit very potent and diverse pharmacological activities.[15-16] The literature survey reveals the importance of triazoles, which shows magnificent biological medicinal properties. Due to their numerous biological functions, the substituted triazoles are a very significant class of chemicals that have attracted the interest of numerous chemists and biologists in the domains of organic synthesis, medicine, and pharmaceuticals. like antitubercular, antimicrobial, anticonvulsant, antibacterial antifungal, and anticancer.[17-21] The effectiveness of substituted triazoles as antibacterial and antitubercular medicines has been supported by a substantial body of research in recent years. Biheterocyclic compounds involving 1,2,4,-triazole derivatives designed with a new approach have efficient antitubercular and Antimicrobial qualities.[22] Substituted alkyl and aryl derivatives encompassing 1,2,4-triazole moiety are used as very effective antifungal drugs.[23] In these years, 1,2,4-Triazole hybrids have been found as potential

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antibacterial agents against both drug-sensitive and drug-resistant pathogens.[24] Thus, naphthofuran derivatives show diverse pharmacological activities.[25-27] In view of the several biological activities of heterocyclic compounds comprising the naphthofuran entity, our present investigation describes to formulation and synthesis of different derivatives of naphthofurans and to study their antimicrobial activities as per the scheme given below. The derivatives of title compounds were confirmed by elemental analysis, UV-Visible, FT-IR, NMR, and Mass Spectral studies.

EXPERIMENTAL

Chemicals and Instruments

All of the chemicals and reagents were purchased from Sigma Aldrich. Double distilled water is used to prepare all the required compounds. The synthesized compounds' functional groups were investigated using FTIR spectra in the 4000-300 cm^{-1} range with an FTIR Frontier Perkin Elmer instrument. With the Agilent VNMRS-400 NMR instrument, the 1H-NMR spectrum was detected. The molecular weight of the molecule was calculated by using Water's SYNAPT G2 QTOF LCMS equipment.

Synthesis of 2-hydroxy-1-naphthaldehyde (1)

The 2-Naphthol (0.05 M) was dissolved in 20 mL of ethanol, then add sodium hydroxide (0.26 M) was in 25 mL water the solution was stirred in the reaction vessel and simultaneously add dropwise 4.3 mL of chloroform, then the reaction mixture was stirred for 2 h to get the required product. The product was poured into ice-cold water and neutralized with dilute HCl, the solid product separates and it is filtered and dried[25] Scheme-1.

Synthesis of ethyl naphtho[2,1-*b*]furan-2-carboxylate (2)

The compound **1** (0.04 M), N,N-dimethyl formamide (30 mL), ethyl-chloroacetate (0.04 M), and anhydrous K_2CO_3 (0.95 M) were added in the reaction vessel and refluxed In water bath for 26 h. The reaction mixture was filtered and the filtrate was concentrated by distillation and then transferred into ice-cold water, the solid product separates and was filtered and dried Scheme-1.

Synthesis of naphtho[2,1-*b*]furan-2-carbohydrazide (3)

The compound **2** (0.02 M), catalytic quantity of conc. HCl and hydrazine hydrate (0.04 M), and absolute ethanol (30 mL) were refluxed for 2 h in a water bath. Then the product was cooled at 28 ^{0}C, the solid product was obtained and it is filtered and dried Scheme-1.

Synthesis of substituted acid hydrazides (4a-f)

A solution of aromatic acid (0.03 M) in methanol (60 mL), for this solution add a few drops of conc. sulphuric acid and reflux the reaction mixture for 18 h at 40 ^{0}C. Then add hydrazine hydrate (3 mL 0.06 M) and the reaction mixture was refluxed for 12 h. The excess methanol was eliminated under reduced pressure and the reaction mixture was transferred into ice-cold water. The separated solid product is obtained and it is filtered and dried [25-26] Scheme-1.

Synthesis of 2-(substituted)phenylhydrazine-potassiumcarbodithioate (5a-f)

To a solution of 4a (0.02 M) in ethanol (30 mL), carbon disulphide (1.5 mL, 0.026 M), and KOH (0.025 M) were added and stirred for 20 h at 28 ^{0}C. The solid product was obtained and it is filtered, and washed with diethyl ether to get the required 5a compound. The same methodology was used for the synthesis of 5b-f from 4b-f[27] Scheme-1.

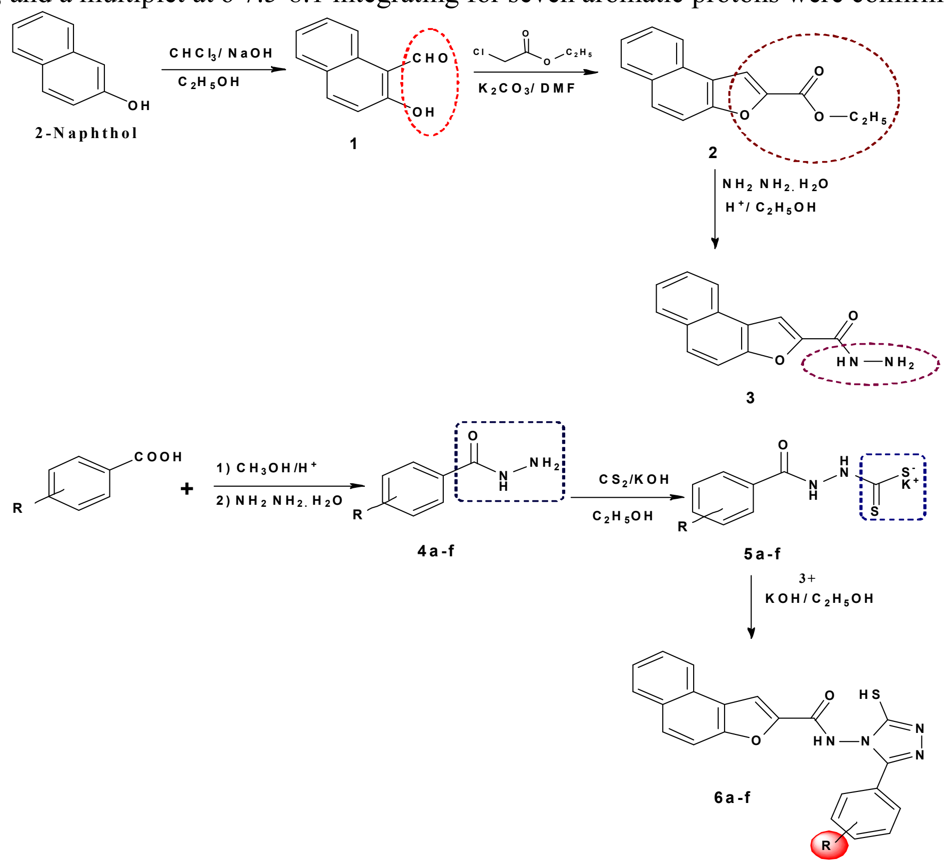
Synthesis of *N*-[3-phenyl-5-sulphanyl-4H-1,2,4-triazol-4-yl)-naphtho[2,1-*b*]furan-2-carboxamide (6a-f)

The compound **3** (0.02 M) and phenyl hydrazine-potassium carbodithioate aromatic acid hydrazide **5a** (0.02 M) were refluxed at 60 ^{0}C in a water bath for 6 h. The obtained product was transferred into ice-cold water and neutralized with conc. HCl. The precipitated triazole was filtered and purified from ethanol, the same methodology was used for the synthesis of 6b-f Scheme-1.

RESULTS AND DISCUSSION

Spectral Characterization

All the synthesized compounds were characterized using FTIR, Mass, and NMR Spectroscopy techniques. The FTIR spectra of 2 show an absorption band at 1733 cm^{-1} due to the carbonyl group of ester Fig.-1. In ^{1}H-NMR spectra ($CDCl_3$), a triplet at δ 1.6 due to $-CH_3$ protons, a quartet at δ 4.6 due to $-CH_2$ protons, and a multiplet at δ 7.5-8.1 integrating for seven aromatic protons were confirmed Fig.-4.



Scheme-1: Synthetic Route of Naphthofuran Derivatives (6a-f)

The FTIR spectra of 3 show an absorption band at 3303-2968 cm^{-1} due to amino and an absorption band at 1656 cm^{-1} due to carbonyl group Fig.-2. ^{1}H-NMR spectra of 3 show a broad singlet at δ 4.6, 1H, NH, (D_2O exchangeable), multiplet δ 7.4-8.6, for seven aromatic protons, and a singlet at δ 9.8 for two amino group protons. The FTIR spectra of 4d show an absorption band at 3300-2970 cm^{-1} due to the amino group and an absorption band at 1652 cm^{-1} due to the carbonyl group. ^{1}H-NMR spectra of 4d show a broad singlet at δ 3.8, 3H, for methoxy, singlet at δ 4.1, 1H, NH, (D_2O exchangeable), multiplet δ 6.5-6.9 for four aromatic protons and a singlet at δ 9.1 for two amino protons. The FTIR (KBr) spectrum of 6a absorption band at 1667 cm^{-1} due to carbonyl group. ^{1}H-NMR spectra (DMSO-d_6) of 6a shows a singlet at δ 6.95, 1H, SH, singlet at δ 12.12, 1H, NH, multiplet δ 7.2-8.5, for twelve aromatic protons. The Mass spectral analysis indicates the m/z 386. The FTIR (KBr) spectrum of 6b absorption band at 1668 cm^{-1} due to carbonyl group. ^{1}H-NMR spectra (DMSO-d_6) of 6b shows a broad singlet δ 5.8, 1H, OH, singlet at δ 6.95, 1H, SH, singlet at δ 12.10, 1H, NH, multiplet δ 7.3-8.4, for eleven aromatic protons. The Mass spectral analysis indicates the m/z 402. The FTIR (KBr) spectrum of the 6c absorption band at 1666 cm^{-1} is due to the C=O group. ^{1}H-the NMR spectra (DMSO-d_6) of 6c shows a singlet at δ 6.97, 1H, SH, singlet at δ 12.21, 1H, NH, multiplet δ 7.4-8.6, for eleven aromatic protons. The Mass spectral analysis indicates the m/z 431. The FTIR (KBr) spectrum of the 6d absorption band at 1667 cm^{-1} due to the carbonyl group and 3284.61 cm^{-1} due to the –NH group Fig.-3. ^{1}H-NMR spectra (DMSO-d_6) of 6d shows a singlet at δ 3.8, 3H, OCH_3, singlet at δ 7.05, 1H, SH, singlet at δ 12.2, 1H, NH, multiplet δ 7.6-8.6, for eleven aromatic protons Fig.-5. The Mass spectral analysis indicates the m/z 416 Fig.-6. The FTIR (KBr) spectrum of 6e absorption band at 1669 cm^{-1} due to carbonyl group. ^{1}H-NMR spectra (DMSO-d_6) of 6e show a singlet at δ 6.98, 1H, SH, singlet at δ 12.23, 1H, NH, multiplet δ 7.6-8.7, for eleven aromatic protons. The Mass spectral analysis indicates the m/z 421. The FTIR (KBr) spectrum of 6f absorption band at 1669 cm^{-1} due to carbonyl group. ^{1}H-NMR spectra (DMSO-d_6) of 6f show a singlet at δ 1.7, 3H, CH_3 singlet at δ 7.05, 1H, SH, singlet at δ 12.01, 1H, NH, multiplet δ 7.5-8.6, for eleven aromatic protons. The Mass spectral analysis indicates the m/z 400.

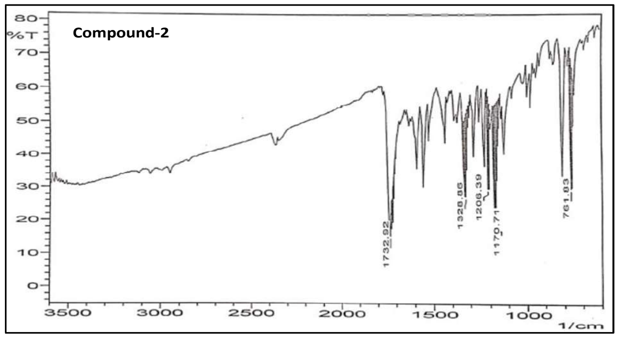


Fig.-1: FTIR Spectra of Compound 2

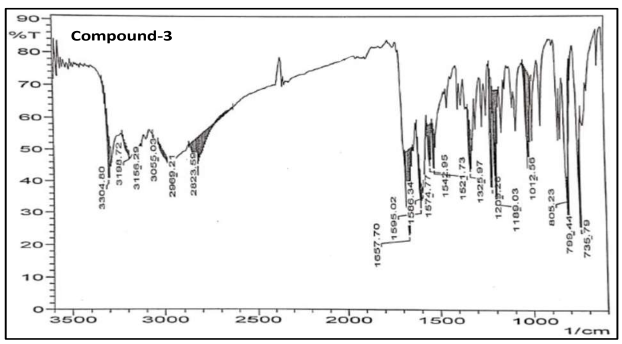


Fig.-2: FTIR Spectra of Compound 3

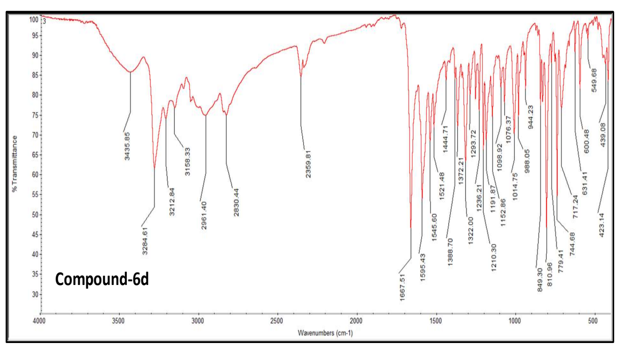


Fig.-3: FTIR Spectra of Compound 6d

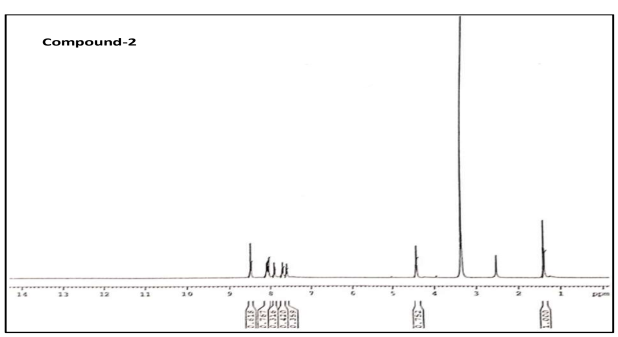


Fig.-4: NMR Spectra of Compound 2

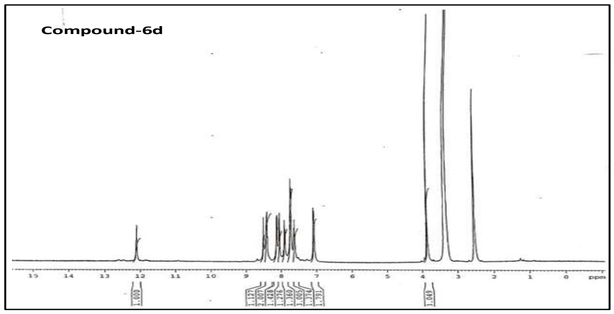


Fig.-5: NMR Spectra of Compound 6d

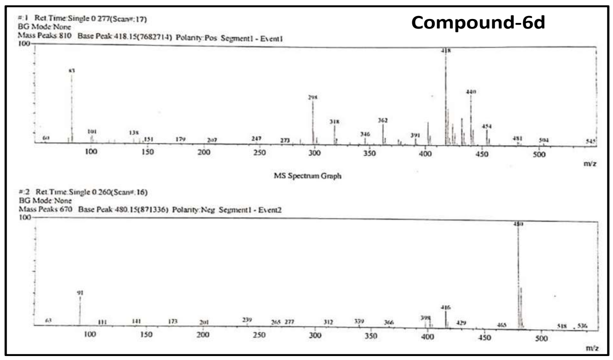


Fig.-6: Mass Spectra of Compound 6d

Elemental Analysis

Table-1: Elemental Data of Newly Synthesized Compounds

Comp.	R	M.p. ^{0}C	Yield (%)	Mol. formula	Clad (Found) %		
					C	H	N
1	-----	81	64	$C_{12}H_{10}O_2$	------	------	------
2	----	102	65	$C_{15}H_{12}O_3$	------	------	------
3	----	268	66	$C_{13}H_{10}N_2O_2$	------	------	------
4a	H	114	73	$C_7H_8 N_2O$	------	------	------
4b	2-OH	139	67	$C_7H_8 N_2O_2$	------	------	------
4c	3-NO_2	146	65	$C_7H_7 N_3O_3$	------	------	------
4d	4-OCH_3	198	69	$C_8H_{10} N_2O_2$	------	------	------
4e	4-Cl	159	70	$C_7H_7 ClN_2O_2$	------	------	------
4f	4-CH_3	119	69	$C_8H_{10} N_2O$	------	------	------
6a	H	260	68	$C_{21}H_{14} N_4O_2S$	65.27 64.34	3.65 3.41	14.50 13.89
6b	2-OH	279	63	$C_{21}H_{14} N_4O_3S$	62.68 61.83	3.51 3.21	13.92 12.97
6c	3-NO_2	294	65	$C_{21}H_{13} N_5O_4S$	58.46 57.55	3.04 2.74	16.23 15.16
6d	4-OCH_3	273	68	$C_{22}H_{16} N_4O_3S$	63.45 62.53	3.87 3.57	13.45 13.27
6e	4-Cl	268	67	$C_{21}H_{13} ClN_4O_2S$	59.93 58.87	3.11 2.66	13.31 12.19
6f	4-CH_3	286	64	$C_{22}H_{16} N_4O_2S$	65.98 64.81	4.03 3.59	13.99 12.89

Biological Activity of Synthesized Compounds

Antimicrobial Activity

The cup-plate technique was used to test the in vitro antibacterial activity against cultures of six bacteria and two fungi that had been grown for 24h.[28] The compounds 6a-f have been determined for their antibacterial activity against *S. aureus, S. epidermidis, B. cereus, P. aeruginosa V. cholerae, and E. coli* and antifungal activity against *A. aureus* and *A. fumigatus.* Standards for antibacterial and antifungal activity were *chloramphenicol* and *fluconazole*, respectively. The substances were tested against all species in DMF at a different concentration of 25, 50,100 *µg/ml*. After incubation for 48 hours at 30 ^{0}C for antifungal activity and 24 hours at 25 ^{0}C for antibacterial activity, the zone of inhibition was compared to the reference medication. The outcomes are shown in Table-2 and Table-3.

Table–2: Antibacterial Activity of Compounds 6a-f

Compound	Concentration in *µg/ml*	Growth inhibition against *bacteria in mm*					
		S.aureus	*S.epidermidis*	*B. cereus*	*P.aeruginosa*	*V.cholerae*	*E.coli*
6a	25	15.26±0.23	15.28±0.26	13.48±0.21	14.26±0.14	16.48±0.27	14.88±0.46
	50	18.21±0.01	17.29±0.27	16.57±0.06	18.26±0.13	19.24±0.31	17.25±0.04
	100	23.23±0.12	19.26±0.21	21.26±0.01	21.24±0.13	22.57±0.32	19.52±0.26
6b	25	13.44±0.25	13.18±0.26	14.48±0.20	14.12±0.13	14.42±0.27	13.79±0.46
	50	15.92±0.08	16.26±0.27	15.88±0.05	16.23±0.13	17.42±0.38	14.88±0.04
	100	18.59±0.13	20.13±0.23	19.56±0.00	20.22±0.13	19.25±0.32	19.45±0.23
6c	25	15.43±0.05	16.83±0.16	17.49±0.16	16.58±0.22	17.02±0.21	15.68±0.19
	50	19.46±0.08	18.35±0.30	21.48±0.05	19.26±0.22	18.23±0.04	15.25±0.19
	100	25.46±0.32	23.98±0.35	27.45±0.02	23.15±0.22	26.25±0.25	24.55±0.09
6d	25	10.26±0.13	10.87±0.35	11.86±0.25	11.26±0.26	13.22±0.05	12.36±0.15
	50	15.25±0.16	13.48±0.15	14.84±0.18	14.27±0.15	14.89±0.12	13.47±0.23
	100	20.15±0.58	20.77±0.26	23.43±0.14	18.45±0.11	21.58±0.13	21.85±0.15
6e	25	15.85±0.14	15.85±0.03	14.78±0.02	14.32±0.15	16.23±0.07	16.43±0.12
	50	19.55±0.55	19.24±0.01	18.54±0.07	18.21±0.16	18.45±0.05	18.34±0.23
	100	26.25±0.13	23.12±0.06	28.21±0.14	22.22±0.07	26.88±0.24	24.83±0.02
6f	25	16.78±0.26	14.90±0.12	13.25±0.02	13.23±0.22	15475±0.07	12.90±0.23
	50	19.45±0.23	18.51±0.09	16.24±0.20	16.22±0.13	17.58±0.03	18.21±0.24
	100	21.53±0.19	20.52±0.05	22.82±0.03	19.25±0.15	22.17±0.05	20.62±0.13
Control	100	-	-	-	-	-	-
Std	100	27.13±0.02	25.04±0.32	30.06±0.44	24.01±0.02	28.28±0.15	26.12±0.21

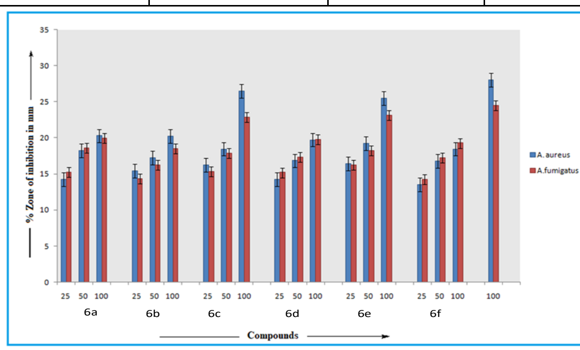


Fig.-7: Graphical Representation Chart of Antibacterial Activity of Compounds 6a-f

Table–3: Antifungal Activity of Compounds 6a-f

Compound	Concentration in *µg/ml*	Growth inhibition against *fungicides in mm*	
		A.aureus	*A.fumigatus*
6a	25	14.35±0.26	15.25±0.23
	50	18.25±0.32	18.58±0.23
	100	20.28±0.25	29.99±0.22
6b	25	15.42±0.18	14.30±0.18
	50	17.23±0.22	16.29±0.18
	100	20.25±0.35	18.55±0.19
6c	25	16.23±0.18	15.30±0.15
	50	18.45±0.18	17.90±0.08
	100	26.45±0.05	22.85±0.05

6d	25	14.25±0.18	15.20±0.15
	50	16.85±0.25	17.35±0.28
	100	19.73±0.25	19.78±0.18
6e	25	16.45±0.15	16.26±0.08
	50	19.25±0.26	18.27±0.07
	100	25.45±0.15	23.13±0.03
6f	25	13.55±0.03	14.24±0.15
	50	16.74±0.23	17.29±0.14
	100	18.48±0.14	19.25±0.02
Control	100	-	-
Std	100	28.06±0. 13	24.51± 0.16

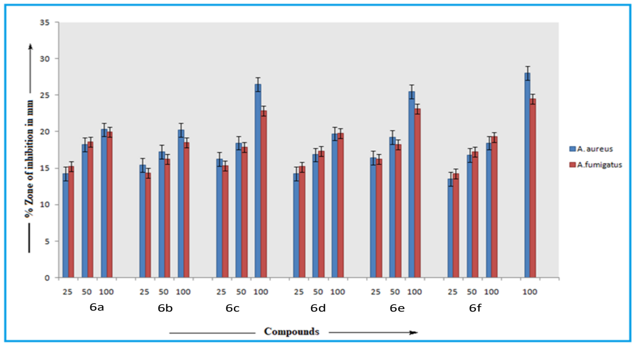


Fig.-8: Graphical Representation of Antifungal Activity of Compounds 6a-f

The zone of inhibition against the test organisms is measured and comparing it to a standard reference, the antibacterial activity and antifungal activities were assessed. The inhibitory zones that were found are shown in Table-2 and Table-3. This led to the excellent zone of inhibition in the main screening against the bacterial and fungal strains and also, as shown in Fig-7 and Fig-8. It was shown that the existence of electron-withdrawing groups bound to the Naphthofuran ring had a significant impact on the antibacterial activity. For instance, the compounds 6c and 6e had increased activity as a result of having nitro and chloro substituents in their structures, which showed that all of the examined compounds in this series had outstanding antibacterial activity.

Molecular Docking Studies

The docking of molecules examinations was ultimately completed using the described methodology.[29,30] The antitubercular receptor (PDB code: 2MBR), whose crystal structure was got from the Protein Data Bank (PDB: http://www.rcsb.org/pdb), had been subjected to In-silico molecular docking. The water molecules and heteroatoms were removed before screening. The protein preparations module of the HEX modeling package 8.0 was used for constructing the receptor structure before it was used in the docking investigation. Except for the water molecules that were 5 Å away from the ligand, During the production of the protein, all hetero and water molecules from the crystal structure were taken out. Utilizing discovery studio 3.2, the three-dimensional configurations of each ligand and the receptor binding interactions were visualized to optimize the quality. All molecules were docked at the receptor's active binding sites. The outcomes of the in silico molecular docking process offer crucial insight into the potential affinity of the newly developed drugs for the active regions of the receptor. We used the docking values that were acquired to guide our wet study of antimicrobial activity. All derivatives demonstrated improved binding interaction with receptors nearby through hydrogen bonds, alkyl, pi-alkyl, Vander walls, and other interactions with a range of amino acids of the receptor, potentially limiting the receptor's ability to cause bacterial infections. The binding energy of all the complexes showed prominent binding interactions, with E. Coli murbenzyme receptor by the key of amino acid residues ARG327, TRP89, PHE328, VAL52, VAL326, ILE110, ASN51, GLN120, GLU325, GLU334, LEU107, LEU104, ILE122, VAL132, LEU178, LEU53, and VAL326. To identify the interaction positions, which will be the potential ligand binding sites in each scenario, the hydrophobic and hydrophilic spheres are used. Finally, when compared to antimicrobial murbenzyme receptor binding receptors, the synthesized compounds are antimicrobial competitive inhibitors, according to molecular docking investigations for the chosen compounds. The bonding interactions are shown in following Fig.-9 to Fig.-14.

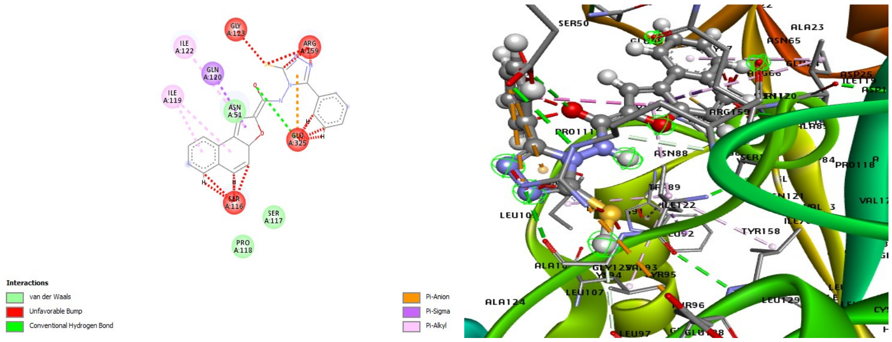


Fig.-9: 2D and 3D Bonding Interactions of 2MBR Receptor with Compound 6a

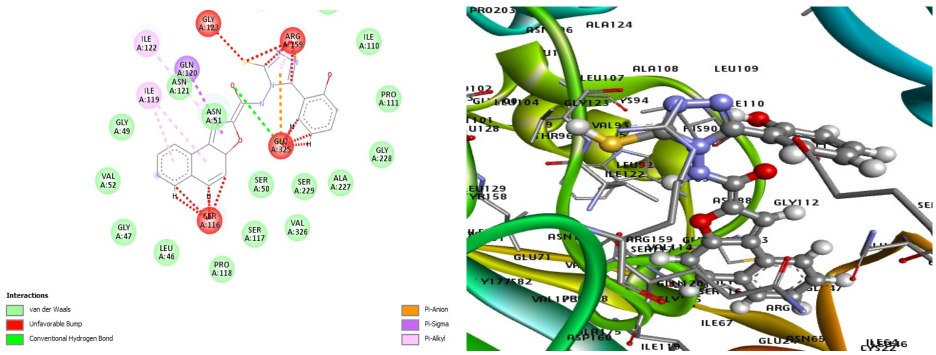


Fig.-10: 2D and 3D Bonding Interactions of 2MBR Receptor with Compound 6b

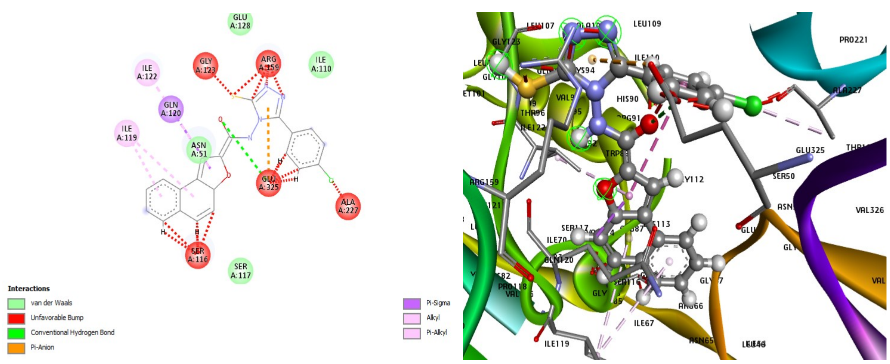


Fig.-11: 2D and 3D Bonding Interactions of 2MBR Receptor with Compound 6c

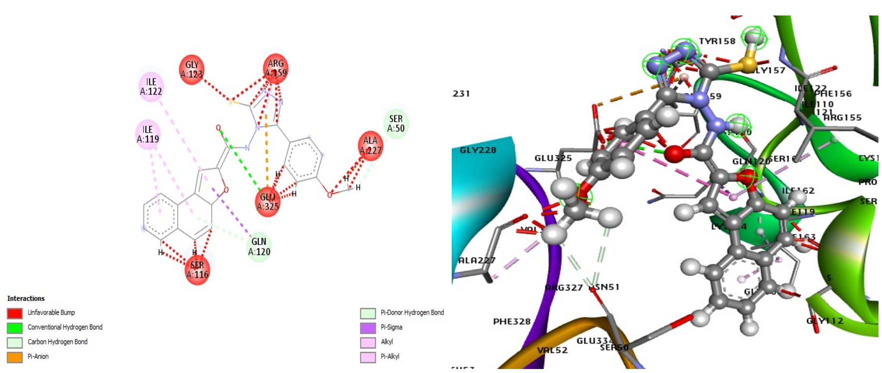


Fig.-12: 2D and 3D Bonding Interactions of 2MBR Receptor with Compound 6d

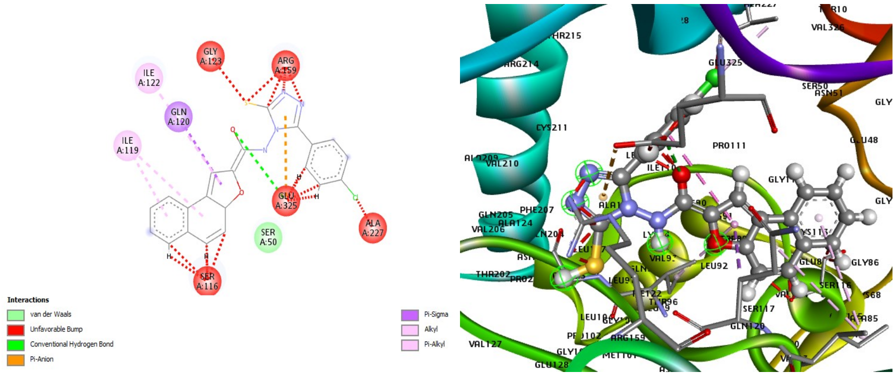


Fig.-13: 2D and 3D Bonding Interactions of 2MBR Receptor with Compound 6e

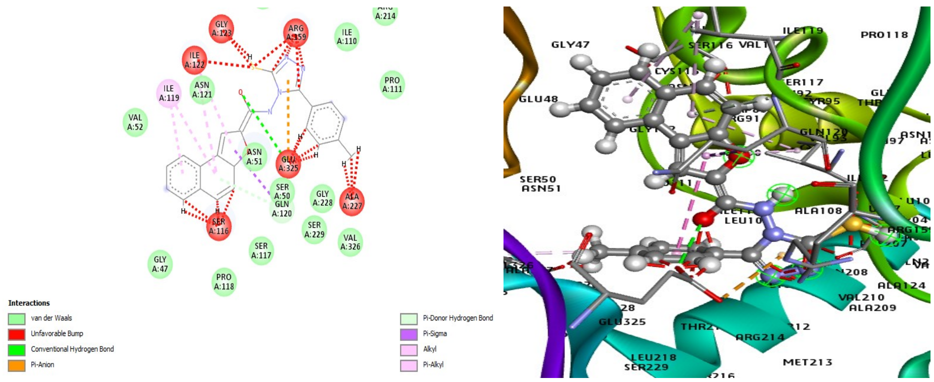


Fig.-14: 2D and 3D Bonding Interactions of 2MBR Receptor with Compound 6f

The synthetic molecules 6(a-f) were molecularly docked with potential biological target molecules for the antibacterial receptor. (PDB ID: 2MBR). Using computational docking investigations with the HEX 8.0 engine, the binding energies of the synthesized compounds 6(a-e) with their receptors were determined. Table-3 provided a list of these docking energy values and potential binding interaction types. Results from antibacterial docking suggested that 6a, 6b, and 6d may interact. The 6f has a greater affinity of -322.71 kcal mol-1 for the 2MBR receptor than the other compounds. In the protein surrounding the receptor molecule, the amino acids 6c, 6d, and 6e interact with amino acids in a hydrophobic (Pi-alkyl), alkyl-alkyl, and hydrogen bonding manner. The optimal docking positions of receptors 6(a–e) and 2MBR are depicted in Fig.-9 to Fig.-14, as reported in Table-4.

Table–4: Binding Energies of Compound 6(a–f) with 2MBR Receptor

Entry	Receptor PDB code	ΔG (Kcal/mol) With MurB
6a	2MBR	-287.02
6b	2MBR	-288.44
6c	2MBR	-283.17
6d	2MBR	-311.18
6e	2MBR	-283.37
6f	2MBR	-322.71
Ciprofloxacin (STD)	2MBR	-237.66

CONCLUSION

In our work, we have successfully confirmed the Synthesized compounds of 2-hydroxy-1-naphthaldehyde (1), Synthesis of naphtho[2,1-*b]*furan-2-carboxylate (2), Synthesis of naphtho[2,1-*b*]furan-2-carbohydrazide (3), Synthesis of various acid hydrazides. (4a-f), Synthesis of 2-(substituted)phenylhydrazine-potassiumcarbodithioate (5a-f), Synthesis of [5-(4-substituted-phenyl-3-sulphanyl-4H-1,2,4-triazol-4-yl)-(naptho[2,1-b]furan-2-yl) carboxamide (6a-f) by UV-Visible, Fourier transform infrared radiations (FT-IR), Nuclear Magnetic Resonance (NMR) and Mass Spectral studies.

On the basis of their antibacterial activity and antifungal activity, the newly synthesized compounds were assessed. Each substance demonstrated a considerable level of antibacterial action by studying their molecular docking studies.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication.

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[RJC-8459/2023]