

NOVEL SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF N-(5BROMO-2-(5-PHENYL- 1,3,4-OXADIAZOL-2-YL)NAPHTHA[2,1-B]FURAN-1- YL)ACETAMIDE AND N-(5-NITRO-2-(5-PHENYL-1,3,4- OXADIAZOL-2-YL)NAPHTHA[2,1-B]FURAN-1-YL)ACETAMIDE AND THEIR DERIVATIVES

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ABSTRACT

The novel derivatives of naphtho-furan such N-(5bromo-2-(5-phenyl-1,3,4-oxadiazol-2-yl)naphtha[2,1-b]furan-1-yl)acetamide (8), N-(5-bromo-2-(hydrazinecarbonyl)naphtha[2,1-b]furan-1-yl)acetamide (7), ethyl-1-acetamido-5-bromonaphtho[2,1-b]furan-2-carboxylate (6), N-(5-nitro-2-(5-phenyl-1,3,4-oxadiazol-2-yl)naphtha[2,1-b]furan-1-yl)acetamide (5), N-(2-(hydrazinecarbonyl)-5-nitronaphtho[2,1-b]furan-1-yl)acetamide (4), ethyl-1-acetamido-5-nitronaphtho[2,1-b]furan-2-carboxylate (3), are prepared by ethyl-1-acetamidonaphtho[2,1-b]furan-2-carboxylate and ethyl 1-aminonaphtho[2,1-b]furan-2-carboxylate. All newly synthesized compounds were confirmed by Mass, NMR, and FTIR spectroscopic techniques. Those compounds were used for antimicrobial activity it exhibits good antibacterial and anti-fungal activity.

Keywords: Naphthofuran, Furan, Antibacterial Activity, Antimicrobial Activity, Oxidiazoles.

RASAYAN J. Chem., Vol. 16, No.1, 2023

INTRODUCTION

The Survey of the literature revealed that the attraction the researchers in the field of heterocyclic chemistry¹ is high, a wide range of heterocyclic molecules that have the greatest deal with their biological activeness and also they make good development of novel compounds with their unique properties. The new synthesis of a variety of heterocyclic moieties has to pay high attention to organic chemists over many years mainly due to their importance in pharmacological activity.² The existence of nitrogen and oxygen in a heterocyclic ring system has attracted the organic researcher because of their multiple effects on biological activities³ and pharmacological activities.⁴ Oxidiazoles⁵ are important five-membered heterocyclic compounds having nitrogen and oxygen as hetero atom. Oxadiazoles have shown a key role in the evolution of principles in heterocyclic chemistry and also are considered advantageous in the medicinal field. Oxadiazole forms four possible isomers. Now a day's most researchers are more attracted to the 1,3,4-oxadiazole⁶ isomer due to its high potential biological activeness.⁷ The synthesis of series 1,3,4-oxadiazole molecule with 2,5-disubstituted⁸ is known substantial pharmaceutical importance.⁸

Various biological potential derivatives of naphtho[2,1- *b*]furan⁹ fused with 1,3,4-oxadiazole ring were synthesized and evaluated for antibacterial¹⁰, anti-inflammatory¹¹, antifungal¹², analgesic¹³, diuretic¹⁴, anticonvulsant¹⁵ anthelmintic¹⁶, anticancer¹⁷, antitubercular¹⁸, antioxidant¹⁶, antitumor¹⁹, antidiabetic¹⁴, antiviral¹¹ and many more. From these view points, the main interest of this present work narrates the synthesis, characterization, and study of the antimicrobial activity of novel naphtho[2,1-*b*]furan moiety¹⁹ fused with 1,3,4-oxadiazole heterocycle. The novel naphthofuran derivatives such as compound (8), Compound (7), Compound (6), Compound (5), Compound (4), and compound (3), were prepared by ethyl-1-acetamidonaphtho[2,1-*b*]furan-2-carboxylate and ethyl-1-aminonaphtho[2,1-*b*]furan-2-carboxylate. All the prepared molecules were confirmed by Mass, FTIR, and NMR, analytic methods. Those molecules are used for biological activities, it exhibits good antibacterial and anti-functional activity.

EXPERIMENTAL

Reagents and Instruments

All the reagents and compounds were purchased from Sigma Aldrich. All the necessary chemicals were prepared with oxygen-free water. The functional groups of the prepared compounds were studied by FTIR spectra in the range of 4000-300 cm⁻¹ with FTIR Frontier Perkin Elmer Instrument. ¹H-NMR spectrum was noted on VNMR-400 Agilent-NMR instrument. The molecular weight of the compound was determined by using Water's SYNAPT G2 QTOF LCMS instrument.

Ethyl-1-aminonaphtho[2,1-*b*]furan-2-carboxylate (1) Synthesis:

The 2-hydroxy-1-naphthaldoxime (0.70 g, 0.035 M), ethyl chloroacetate (5.10 g, 0.035 M), and previously dried K₂CO₃ (4.12 g, 0.041 M) mixture were refluxed on water bath at 85-90 °C for about 18 hours in anhydrous dimethylformamide (60 mL) medium. The resulting crude product was cooled, the excess of K₂CO₃ which was remained after cooling, and the obtained product was poured into the beaker containing crushed ice to get a chocolate brown-colored solid (1). This colored compound was then filtered and it was purified by aqueous ethyl alcohol.²⁰

Ethyl-1-acetamidonaphtho[2,1-*b*]furan-2-carboxylate (2) Synthesis:

Compound 1 (3.10 g, 0.015 M) was mixed with aqueous sodium hydroxide (2.5N, 35 mL) and reacted with acetyl-chloride (6.0 mL) with continuous stirring for upto 45 minutes resulting in the compound was obtained, it was transferred into ice cold water. This resulting product was filtered and washed using water and it was re-crystallized from ethanol.²⁰

Ethyl-1-(acetylamido)-5-nitronaphtho[2,1-*b*]furan-2-carboxylate (3) Synthesis:

Compound (2) (1.80 g, 0.018 M) is dissolved in glacial acetic acid (25 mL) under 1- 5 °C. To this cooled mixture, conc. nitric acid and conc. sulphuric acid (1:1.8, 30mL) was added drop by drop for about 40 minutes with regular constant stirring on a magnetic stirrer for nearly 3.5 h. Then this reaction mixture was poured into ice-cold water, the lemon-yellow solid formed was collected by filtration and it was recrystallized from aqueous ethanol to obtain a pure compound (3).

N-[2-(hydrazinylcarbonyl)-5-nitronaphtho[2,1-*b*]furan-1-yl]acetamide(4) Synthesis:

The mixture of compound (3) (0.018 M) and hydrazine hydrate (0.018 M) in ethyl alcohol (38 mL) medium refluxed at 65-85°C in the water bath for about 16 h. The excess ethanol was distilled off and thus obtained crude solid product was filtered and was collected and recrystallized by ethanol to obtain a pure compound (4).

N-(5-nitro-2-(5-phenyl-1,3,4-oxadiazol-2-yl)naphtho[2,1-*b*]furan-1-yl)acetamide(5a-e):

Compound (4) (3.00 g, 0.02 M) in dioxane medium (20 mL), and benzoic acid (1.35 g, 0.02 M) were added to the RB flask. This mixture product was refluxed with phosphorous oxychloride in a water bath for 5 h. The obtained product was poured into a beaker containing crushed ice to obtain product (5a) and the resulting solid product was filtered and dried in the oven. The product separated was collected and it was recrystallized by using dioxane. Similarly compounds (5b-e) were synthesized by using appropriate substituted benzoic acids.

Ethyl 1-(acetamido)-5-bromonaphtho[2,1-*b*]furan-2-carboxylate (6)

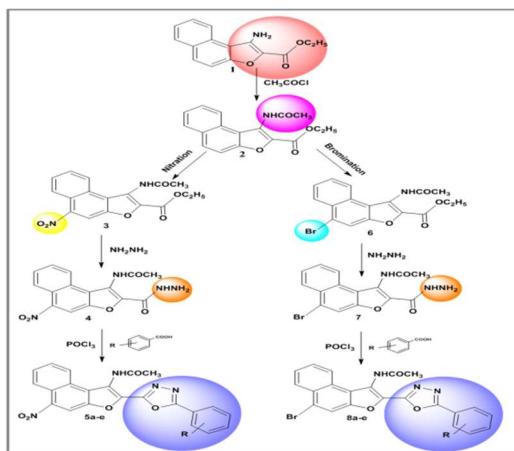
The compound (2) (2.5 g, 0.02 M), bromine solution (0.9 g, 0.02 M) in acetic acid (50 mL) was slowly added drop wise with constant stirring for 1 h at a temperature of 0-6 °C and this reaction mixture was stirred on stirrer continuously for 4 h. This product was transferred into crushed ice and the obtained solid was separated by filtration. It was dried and the resulting product was recrystallized by using ethanol.

***N*-(5-bromo-2-(hydrazinecarbonyl)naphtho[2,1-*b*]furan-1-yl)acetamide(7)**

Compound (6) (3.2g, 0.015 M) in ethanol hydrazine hydrate (25 mL) was added to a solution. The reaction mixture was refluxed in a water bath for 4h and it was allowed to cool. Then the obtained compound was separated, it was filtered, and purified using ethanol.

***N*-(5-bromo-2-(5-phenyl-1,3,4-oxadiazol-2-yl)naphtho[2,1-*b*]furan-1-yl)acetamide(8a-e)**

To a solution of *N*-(5-bromo-2-(hydrazinecarbonyl) naphtho[2,1-*b*]furan-1-yl)acetamide 7, (3.00 g, 0.015M) in dioxane (30mL), benzoic acid (1.36 g, 0.01 M) was added. The reaction mixture was heated under reflux with phosphorous oxychloride in the water bath for 4.5 h. Then it was allowed to cool and it was poured into crushed ice to get obtain product (8a) the resulting solid was separated by filtration and allowed to dry. The obtained product was collected and recrystallized by dioxane. Similarly compounds (8b-e) were synthesized by using appropriate substituted benzoic acids.



Scheme-1: Synthesis of Compound 3, 4, 5(a-e), 6, 7 and 8(a-e)

RESULTS AND DISCUSSION**NMR Spectra**

The ¹H-NMR spectra of the compound 5a, 6, 7, and 8b confirm the formation of compounds ¹H-NMR (DMSO) **5a**: δ 2.45 (3H, s). 7.45-7.55 (4H, tdd), 7.60 (dddd), 7.65 (ddd), 7.66-7.68 (1H, ddd), 7.78-8.05 (3H, dtd), 8.10-8.20 (d), 8.30-8.35 (2H, ddt), 8.40 (ddd), 10.0 (1H, s).

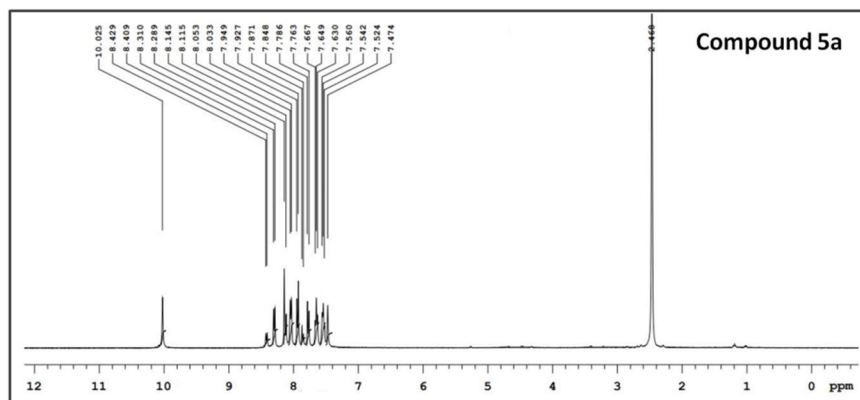


Fig-1: Compound (5a) NMR spectra

Compound **6**: δ 0.8 (3H, t, CH₃). 1.24 (3H, s), 2.45 (2H, q), 7.3-8.02 (3H, ddd, 7.95, ddd, 8.02, d), 8.16-.8.18 (2H, ddt), 8.40 (ddd, 2H), 8.89 (1H, dd), 10.01 (1H, s, NH). Compound **7**: δ 2.30 (3H, s, CH₃). 3.5 (2H, s, NH₂), 7.75 (1H, ddd), 7.75-7.80 (2H, ddd), 8.00-8.30 (2H, ddt), 8.41 (ddd, 1H), 8.80 (1H, dd), 10.05 (1H, s, NH). Compound **8b**: δ 2.35 (3H, s, CH₃). 3.25 (3H, s, CH₃), 7.50 (2H, ddd), 7.52-7.60 (6H, ddd), 7.65-7.68 (2H, td), 7.70-7.80 (ddt, 1H), 7.85-8.10 (1H, d), 8.25-8.30 (ddd), 8.51 (1H, ddd), 10.05 (1H, s, NH).

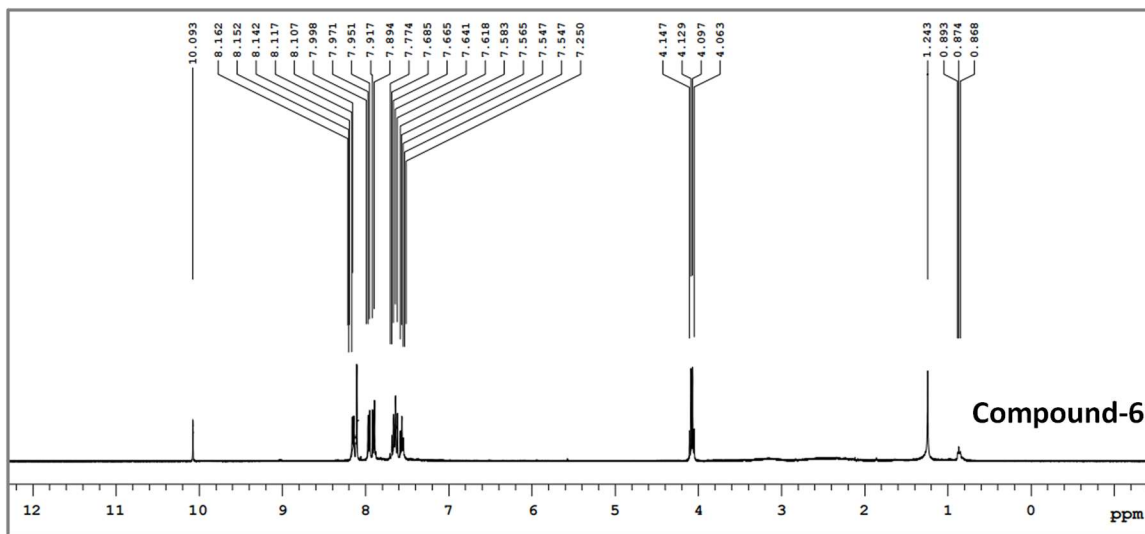


Fig.-2: Compound (6) NMR Spectra

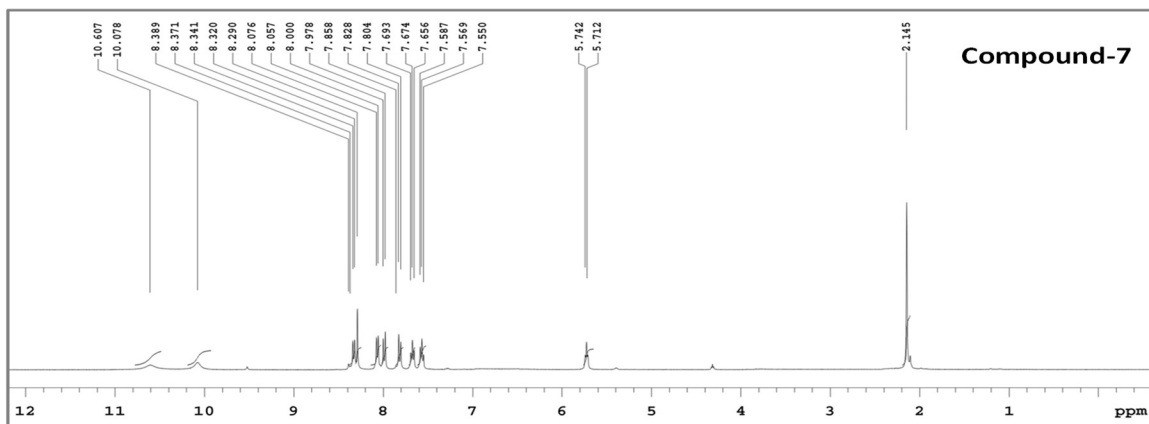


Fig.-3: Compound (7) NMR Spectra

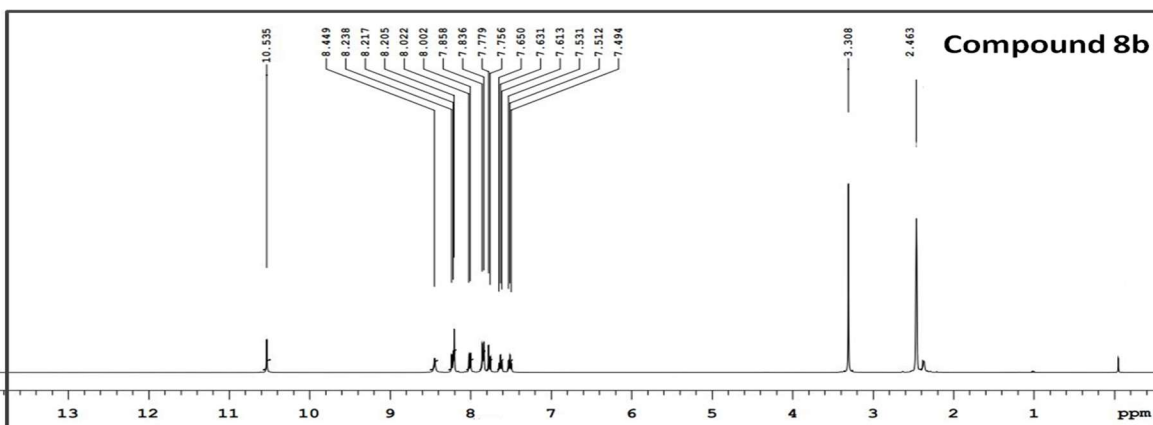


Fig.-4: Compound (8b) NMR Spectra

FTIR-Spectra

The FT-IR spectrum of compounds 5a, 6, 7, and 8b (Fig.-5)²⁰⁻²¹ IR (KBr) cm^{-1} . Compound (6): 3611-3260 (amide NH-str), 3150-2950 (aromatic C-H), 1651-1571 (C=O), 1806-1636 (C=C), 2005-1889 (C=N), 1585-1496 (C-NO₂), 668-595 (CH, aliphatic). Compound (7): 3645-3278 (amide NH-str), 3145-2903 (aromatic C-H), 1708-1649 (C=O), 1804-1706 (C=C), 1993-1889 (C=N), 1626-1583 (C-NO₂), 665-606 (CH, aliphatic). Compound 5a: 3473-3201 (amide N-H), 3011-2831 (Aromatic C-H), 1357-1285 (C-N), 1778-1485 (C=C), 1475-1409 (C-NO₂), 787-699 (aliphatic C-H), 1480-1424 (C=O). Compound 8b: 35653-3150 (amide N-H), 2970-2816 (Aromatic C-H), 1357-1280 (C-N), 1742-1598 (C=C), 787-715 (C-Br), 710-592 (aliphatic C-H), 1593-1495 (C=O). All the above data confirms the formation of given synthesized compounds.

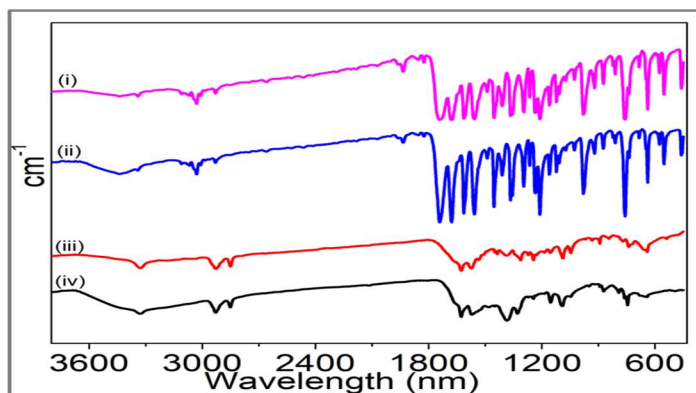


Fig.-5: The Compound(i) (6), (ii) 7, (iii) 5a, and (iv) (8b) FTIR Spectra

Mass Spectra

Figures-6,7, 8, and 9 show the mass spectra of the given prepared compounds. It gives information about the mass-to-charge ratio $[M+2]$ of ions. The actual molecular weight of compounds 5a, 6, 7, and 8b is 414.37, 376.20, 362.18, 448.27, and 478.30 and the practical molecular weight of the prepared compounds shows molecular ion peaks at 412.759, 375.70, 358.256, and 478.414.

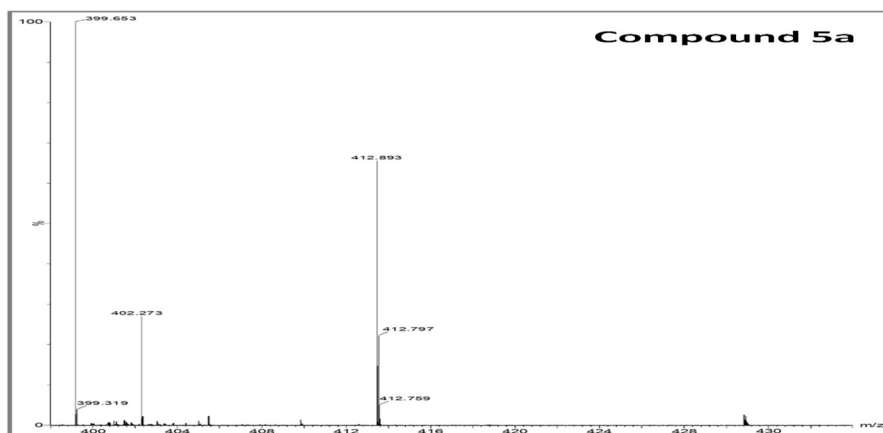


Fig.-6:Compound (5a) Mass Spectra

Biological Activities of Synthesized Compounds

The naphthofuran compounds were confined with oxadiazoles are shows a wide variety of biological activities. Hence, it was examined to appraise prepared compounds for their antimicrobial activities by using standard methods.

Antimicrobial Activity

All the prepared compounds were allowed to screen for their antibacterial activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, *Staphylococcus pyrogens*, and antifungal-activity against *Aspergillus niger*, *Candida albicans*, *Aspergillus flavus*, by using cup plate method versus all the organisms at a concentration of 0.006 μmL . Fluconazole and Chloramphenicol were used as standard

drugs for antifungal activity and antibacterial activity. The zone of inhibition was different from the standard drug after 48 h at 300 °C for antifungal activity and after 28 h of incubation at 250 °C for antibacterial activity. These results are given in Table-2.

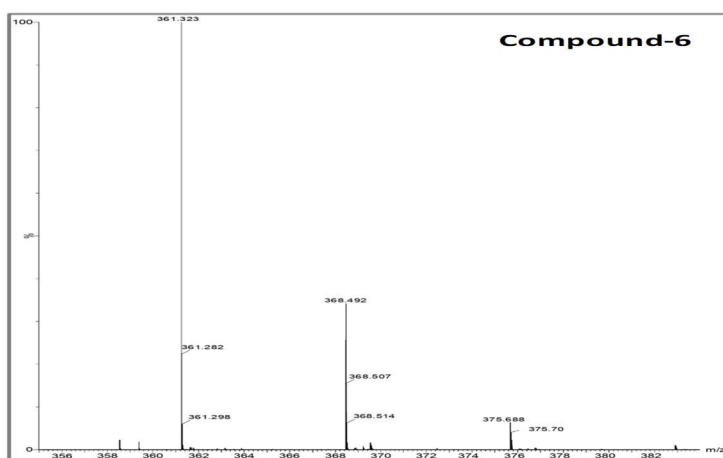


Fig.-7: Compound (6) Mass Spectra

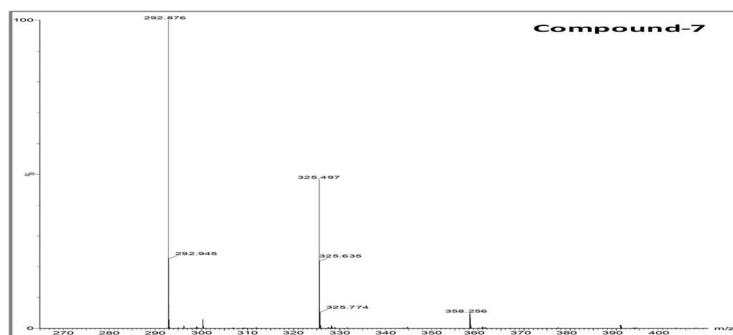


Fig.-8: Compound (7) Mass Spectra

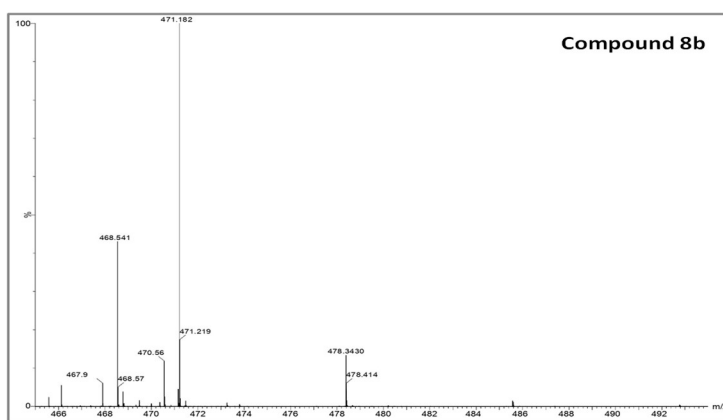


Fig.-9: Compound (8b) Mass Spectra

Elemental Analysis

Comp	R	Molecular Formula	Molecular Weight	Yield %	Elemental Analysis					
					C	H	N	O	Cl	Br
3	-	C ₁₇ H ₁₄ N ₂ O ₆	342.30	65	59.63	4.10	8.17	28.01	-	-
					(59.65)	(4.12)	(8.18)	(28.04)	-	-
4	-	C ₁₅ H ₁₂ N ₄ O ₅	328.08	60	54.82	3.64	17.05	24.34	-	-
					(54.88)	(3.68)	(17.07)	(24.37)	-	-
5a	H	C ₂₂ H ₁₄ N ₄ O ₅	414.37	68	63.76	3.39	13.50	19.27	-	-
					(63.77)	(3.41)	(13.52)	(19.30)	-	-
5b	OCH ₃	C ₂₃ H ₁₆ N ₄ O ₆	444.40	65	62.14	3.62	12.60	21.57	-	-

					(62.16)	(3.63)	(12.61)	(21.60)	-	-
5c	Cl	C ₂₂ H ₁₃ N ₄ O ₅ Cl	448.81	63	58.86	2.91	12.44	17.76	7.88	-
					(58.87)	(2.92)	(12.48)	(17.82)	(7.90)	-
5d	NO ₂	C ₂₂ H ₁₃ N ₅ O ₇	459.37	66	57.50	2.82	15.23	24.36	-	-
					(57.52)	(2.85)	(15.25)	(24.38)	-	-
5e	OH	C ₂₂ H ₁₄ N ₄ O ₆	430.37	70	61.36	3.25	13.00	22.28	-	-
					(61.40)	(3.28)	(13.02)	(22.30)	-	-
6	-	C ₁₇ H ₁₄ NO ₄ Br	376.20	68	54.20	3.72	3.68	17.00		21.20
					(54.28)	(3.75)	(3.72)	(17.01)	-	(21.24)
7	-	C ₁₅ H ₁₂ N ₃ O ₃ Br	362.18	69	49.72	3.31	11.58	13.22	-	22.01
					(49.74)	(3.34)	(11.60)	(13.25)	-	(22.06)
8a	H	C ₂₂ H ₁₄ N ₃ O ₃ Br	448.27	60	58.92	3.12	9.35	10.67	-	17.80
					(58.95)	(3.15)	(9.37)	(10.71)	-	(17.82)
8b	OCH ₃	C ₂₃ H ₁₆ N ₃ O ₄ Br	478.30	62	57.75	3.32	8.76	13.36	-	16.70
					(57.76)	(3.37)	(8.79)	(13.38)	-	(16.71)
8c	Cl	C ₂₂ H ₁₃ N ₃ O ₃ Br Cl	482.71	65	54.72	2.70	8.70	9.91	7.32	16.52
					(54.74)	(2.71)	(8.71)	(9.94)	(7.34)	(16.55)
8d	NO ₂	C ₂₂ H ₁₃ N ₄ O ₅ Br	493.00	72	53.55	2.62	11.32	9.92	-	16.52
					(53.57)	(2.66)	(11.36)	(9.94)	-	(16.55)
8e	OH	C ₂₂ H ₁₄ N ₃ O ₄ Br	464.27	70	56.90	3.01	9.02	13.75	-	17.19
					(56.91)	(3.04)	(9.05)	(13.78)	-	(17.21)

Table-2: Antimicrobial Activity Data of Desired Compounds:

Compd	R	Zone of inhibition in mm						
		Anti-bacterial activity				Anti-fungal activity		
		<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>S. pyogenes</i>	<i>S. aureus</i>	<i>A. niger</i>	<i>C. albicans</i>	<i>A. flavus</i>
3	-	19	20	19	20	12	14	12
4	-	18	19	19	16	14	15	13
5a	-	15	21	20	18	20	19	16
5b	4-OCH ₃	19	16	17	18	19	17	18
5c	4-Cl	22	22	21	21	20	19	20
5d	4-NO ₂	21	22	20	21	12	12	14
5e	4-OH	16	19	13	19	15	16	15
6	-	12	17	14	18	19	15	18
7	-	19	13	15	14	12	11	13
8a	-	14	15	15	14	11	12	15
8b	4-OCH ₃	19	15	16	17	13	12	15
8c	4-Cl	21	19	18	16	22	17	19
8d	4-NO ₂	22	22	20	22	21	19	21
8e	4-OH	20	16	21	15	19	20	20

The compounds of naphtho[2,1-*b*] furan with some oxadiazole heterocycle ring systems are known to show a number of biological activities. Hence, it was examined to study newly synthesized compounds for their antimicrobial activities by adopting standard literature procedures. The compounds 5c, 5d, 8c, and 8d possess the excellent activity and 3, 5b, 7, 8b, and 8e showed very good activity against *Bacillus subtilis*. The compound 5a, 5c, 8c, and 8d were found to be significantly active and 5b, 6, and 8e showed very good activity against *Aspergillus niger*. The compounds 5a, 5c, 5d, and 8d showed excellently and 4, 5e, and 8c exhibited very good antibacterial activity against *Pseudomonas aeruginosa*. The compounds 3, 4, 5a, 5c, 5d, 8d, 8e significantly active against *Staphylococcus pyogenes*. The compounds 5a, 5b, 8d, and 8e possess very good activity and 5b, 5e, and 8c showed moderate antifungal activity against *Candida albicans*. The compounds 3, 5c, 5d, and 8d exhibited excellent activity and 5a, 5b, 5, 6, and 8b showed very good antibacterial activity against *Staphylococcus aureus*. The compounds 5c, 8c, 8d, and 8e were showed very good activity and 5a, 5b, 5e, 8a, and 8b found to be moderate antifungal activity against *Aspergillus flavus*. The all-remaining compounds showed moderate or slight activity against some tested organisms.

CONCLUSION

The novel naphthofuran derivatives such N-(5-bromo-2-(5-phenyl-1,3,4-oxadiazol-2-yl)naphtha[2,1-b]furan-1-yl)acetamide (8), N-(5-bromo-2-(hydrazinecarbonyl)naphtha[2,1-b]furan-1-yl)acetamide (7), ethyl 1-acetamido-5-bromonaphtho[2,1-b]furan-2-carboxylate (6), N-(5-nitro-2-(5-phenyl-1,3,4-oxadiazol-2-yl)naphtha[2,1-b]furan-1-yl)acetamide (5), N-(2-(hydrazinecarbonyl)-5-nitronaphtho[2,1-b]furan-1-yl)acetamide (4), ethyl 1-acetamido-5-nitronaphtho[2,1-b]furan-2-carboxylate (3), are synthesized by ethyl 1-acetamidonaphtho[2,1-b]furan-2-carboxylate and ethyl 1-aminonaphtho[2,1-b]furan-2-carboxylate. All the desired molecules were characterized by FTIR, NMR, and Mass spectroscopic methods. These compounds were used for the antimicrobial activity it exhibits good antibacterial and anti-fungal activity.

ACKNOWLEDGMENTS

One of the authors K M Nagarsha thanks Sahyadri Science College, Kuvempu University, Shivamogga for providing facilities and encouragement.


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. The research profile of the authors can be verified from their ORCID ids, given below:


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[RJC-8088/2022]