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SYNTHESIS OF N-SUBSTITUTED NAPTHOFURAN CARBOXAMIDES DERIVATIVES AS POTENTIAL ANTIMICROBIAL AGENTS

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ABSTRACT

Prompted by the varied biological activities of carboxamides and napthofurans, a series of N-substituted napthofuran carboxamides (NFC_{1-5}) derivatives were prepared. The starting material naphthol was treated with paraformaldehyde, triethyl amine, magnesium chloride and methyl cyanide to form 1-hydroxy-2-naphthaldehyde. Further reaction of corresponding naphthaldehyde with ethyl bromo acetate form Ethyl Naphtho[1,2-b]furan-2-carboxylate which undergo hydrolysis to prepare naphofuroic acids Which on treated with aromatic primary amines to convert into N-substituted napthofuran carboxamides. The structures of these compounds were confirmed by IR, NMR, Mass and elemental analysis. The newly synthesized compounds were evaluated for antibacterial and antifungal activity. The results show that compound NFC_{1-5} exhibited moderate to good antibacterial and antifungal activity.

KEYWORDS: The starting material naphthol was treated with paraformaldehyde, triethyl amine, magnesium chloride and methyl cyanide to form 1-hydroxy-2-naphthaldehyde.

INTRODUCTION

Naphthofuran is a bicyclic organic compound that results from the fusion of a naphthalene ring to a heterocyclic furan ring.[1] Naphthofuran nuclei are key structural moieties found in a large number of biologically important natural products.[2,3] Many of the natural naphthofurans, such as (±)- Laevigatin[4,5] (1), (+)-Heritol[6-8] and Balsaminone A,[9] possess interesting pharmacological and cytotoxic properties. Several synthetic compounds containing this ring skeleton are associated with diverse biological activities such as antifungal, antibacterial[10,11], antiviral[12], antitumor[13], anthelmintic[14], anti-trypanosomal and cytotoxicity.[15]

Naphthofurans possess a broad range of biological activities that are constituents of important natural products. These plant extracts are being used for traditional medicines, and some of them for example mansonone D,[16] Dunnione,[17] etc are also vital biologically active agents. Hence, with these observations we examine the feasibility and efficiency of an approach to synthesis naphthofuran coupled with aromatic amines to naphthofuran carboxamide derivatives, which turns to exhibit significant antimicrobial activities.

MATERIALS AND METHODS

Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and 1H NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz. LC-MS of selected samples taken on LC-MSD-Trap-SL-01046. The purity of compounds was checked by thin layer chromatography on silica gel plate of 0.25 mm thickness using different solvent system. All the chemicals were laboratory grade and purchased from local market and naphtho[1,2-b]furan carboxamide derivatives was prepared by reported method.

The Experimental Work Comprises in Four Steps.

Step-I: Preparation of 1-Hydroxy-2-naphthaldehyde[18]

To a solution of naphthalene-1-ol (2.0 g, 13.89 mmol) and paraformaldehyde (2.4 g, 83.34 mmol) in acetonitrile (50 mL) were added magnesium chloride (1.98 g, 20.8 mmol) and triethylamine (7.2 mL, 51.4 mmol). After being stirred at reflux for 15 h, the mixture was diluted with water (50 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water and 5% aqueous hydrogen chloride solution, dried over anhydrous sodium sulfate, and concentrated in vacuo, to obtain of the title compound.

Step-II: Preparation of Ethyl Naphtho[1,2-*b*]furan-2-carboxylate

To a solution of 1-hydroxy-2-naphthaldehyde (1, 100 mg, 0.58 mmol) and ethyl bromoacetate (98 mg, 0.69 mmol) in acetonitrile (3 mL) was added potassium carbonate (161 mg, 1.16 mmol). After being stirred at reflux for 1.5 h, the mixture was diluted with water (20 mL), and extracted with ethyl acetate (50 mL). The organic layer was dried over anhydrous sodium sulphate and concentrated in vacuo, to obtain of the title compound.

Step-III: Naphtho[1,2- *b*]furan-2-carboxylic acids[19]

Ethyl naphtho[2,1-b]furan 2-carboxylate was dissolved in methanol and mixed with 10% NaOH solution. The mixture was refluxed for 2h. After the completion of the hydrolysis, the reaction mixture was poured into ice cold water and acidified with hydrochloric acid. Solid separated is filtered and recystallised from ethanol.

Step-IV: Naphtho[1,2-b]furoyl-N-substituted benzene carboxamide[19] (NFC_{1-5})

To an equimolecular mixture of suitable substituted aromatic amine (10 mmol) and naphtho-furoic acid (10 mmol), phosphorus oxychloride (2ml, 20 mmol) was added. The resulting mixture was refluxed for 1h on water bath. The reaction mixture was poured into crushed ice with stirring. The resultant solid was collected, washed with water and filtered off to obtain the solid product **(NFC_{1-5}).** These compounds were purified by recrystallisation from ethanol. The sequence of the reaction is depicted in the Scheme.

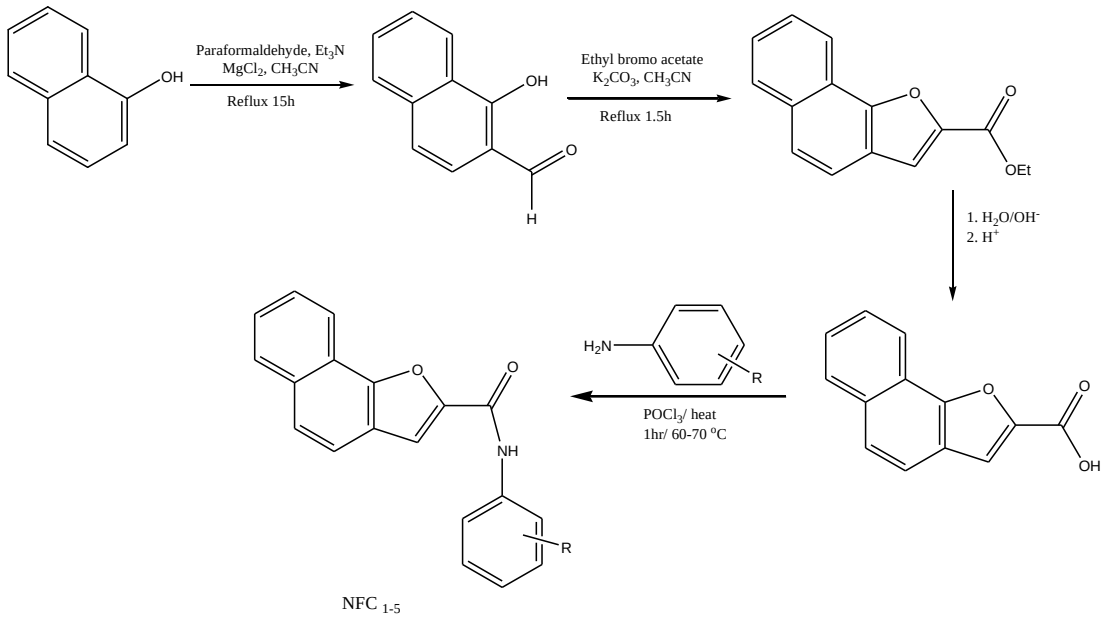
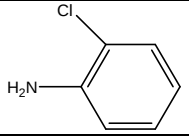
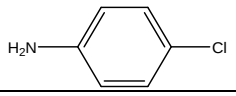
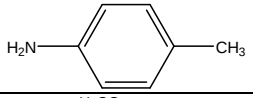
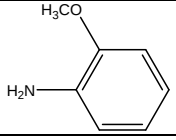
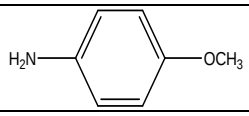


Figure 1: Scheme: Synthetic route of targeted compounds.

Table 1: List of Various Aromatic Amines.

S. No.	Compounds Code	Substituted Aromatic Amine (R)	Structure of Aromatic Amine (R)
1	NFC 1	o-chloro Aniline	
2	NFC 2	p-chloro Aniline	
3	NFC 3	p-anisidine	
4	NFC 4	o-methoxy Aniline	

5	NFC 5	p-methoxy Aniline	

Biological Activity

The synthesized compounds were screened for the antibacterial activity and antifungal by using the agar diffusion technique (Cup-plate method)[20] in nutrients agar and potato dextrose agar media, respectively. Chloramphenicol and Fluconazole were used as standard drug for the antibacterial and antifungal activity respectively and zone of inhibition of all newly synthesized compounds (NFC1-5) at three different concentrations (25, 50 and 100 µg/ml) was measured against these standard drugs (Table 2). We used microbial strains- *Staphylococcus aureus* as gram positive and *Staphylococcus pyrogens* as gram negative bacterial strains, *E coli* and *Aspergillus niger* as fungal strains for biological test.

RESULTS AND DISCUSSION

Chemistry: All the novel naphthofuran carboxamide derivatives were synthesized, purified and separated by using column chromatography or recrystallization method. Synthesized compounds were characterized by using Elemental analysis, FT-IR, ^{1}HNMR and Mass Spectrometric studies. The integration curves fully support the orientation of protons in the analyzed compounds. Furthermore, all the compounds demonstrated the characteristic chemical shifts for the naphthofuran nucleus. Additionally, synthesized compounds were analyzed by mass spectra and indicated no difference in the fragmentation pattern among the set of synthesized series.

NFC1: N-(2-chlorophenyl)naphtho[1,2-b]furan-2-carboxamide

Yellowish brown colored solid, Molecular Formula: $C_{19}H_{12}ClNO_2$, Molecular weight: 321.76, Yield: 67.38%, M.P.: 232-234^{o}C, R_f value: 0.86, **FT-IR (KBr, cm^{-1}):** 3436. 67 (=N-H Str.), 3117. 92 (=C-H Str.), 1295.73 (C-O Str.),1577.45 (C=C Str.), 1686.50 (C=O Str.), 1254.35 (C-N Bend.), 717.45 (Ar C-H Bend.), 729.12 (C-Cl Bend.), **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 6.94-7.67 (m, 11H, Ar-H), 8.00 (s, 1H, NH), **Elemental Analysis, % found (% required):** C 70. 33 (70. 93); H 3.76 (3.92); N 4.58 (4.35); O 9.71 (9. 94).Cl, 11.07 (11.02)

NFC2: N-(4-chlorophenyl)naphtho[1,2-b]furan-2-carboxamide

Creamish yellow colored solid, Molecular Formula: $C_{19}H_{12}ClNO_2$, Molecular weight: 321.76 Yield: 70.18%, M.P.: 236-238^{o}C, R_f value: 0.82, **FT-IR (KBr, cm^{-1}):** 3677.03 (=N-H Str.), 3107.22 (=C-H Str.), 1277.17 (C-O Str.),1674.15 (C=C Str.), 1695.40 (C=O Str.), 1257.53 (C-N Bend.), 717.45 (Ar C-H Bend.), 739.52 (C-Cl Bend.), **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 7.13-7.67 (m, 11H, Ar-H), 8.00 (s, 1H, NH), **Elemental Analysis, % found (% required):** C 70.42 (70. 93); H 3.77 (3.92); N 4.28 (4.35); O 9.73 (9. 94), Cl, 11.07 (11.02)

NFC3: N-p-tolylnaphtho[1,2-b]furan-2-carboxamide

Pale red colored solid, **Molecular formula:** $C_{20}H_{15}NO_2$, **Molecular weight:** 301.34, **Yield:** 74.24%, **M.P.:** 255-257^{o}C, **R_f value:** 0.76, **FT-IR (KBr, cm^{-1}):** 3555.23 (=N-H Str.), 3177.52 (=C-H Str.), 1247.07 (C-O Str.),1623.42 (C=C Str.), 1715.30 (C=O Str.), 1277.42 (C-N Bend.), 754.15 (Ar C-H Bend.), **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 2.35 (s, 3H, CH_3), 7.04-7.67 (m, 11H, Ar-H), 8.00 (s, 1H, NH), **Elemental Analysis, % found (% required):** C 78.22 (79.72); H 5.57 (5.02); N 4.28 (4.65); O 9.99 (10.62).

NFC4: N-(2-methoxyphenyl)naphtho[1,2-b]furan-2-carboxamide

Pale Brown colored solid, **Molecular Formula:** $C_{20}H_{15}NO_3$, **Molecular weight:** 317.34 **Yield:** 71.84%, **M.P.:** 282-284^{o}C, **R_f value:** 0.78, **FT-IR (KBr, cm-1):** 3454.23 (=N-H Str.), 3143.02 (=C-H Str.), 1244.17 (C-O Str.),1654.11 (C=C Str.), 1705.02 (C=O Str.), 1255.42 (C-N Bend.), 723.55 (Ar C-H Bend.), **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 3.73 (s, 3H, OCH_3), 6.75-7.67 (m, 11H, Ar-H), 8.00 (s, 1H, NH), **Elemental Analysis, % found (% required):** C 75.20 (75.70); H 4.37 (4.76); N 4.08 (4.41); O 15.73 (15.12).

NFC5: N-(4-methoxyphenyl)naphtho[1,2-b]furan-2-carboxamide

Creamish Brown colored solid, **Molecular Formula:** $C_{20}H_{15}NO_3$, **Molecular weight:** 317.34 **Yield:** 64.96 %, **M.P.:** 263-265^{o}C, **R_f value:** 0.87, **FT-IR (KBr, cm-1):** 3423.54 (=N-H Str.), 3134.02 (=C-H Str.), 1233.14 (C-O Str.),1614.17 (C=C Str.), 1713.52 (C=O Str.), 1275.32 (C-N Bend.), 722.01 (Ar C-H Bend.), **^{1}H-NMR (400 MHz, DMSO, δ ppm):** 3.73 (s, 3H, OCH_3), 6.75-7.67 (m, 11H, Ar-H), 8.00 (s, 1H, NH), **Elemental Analysis, % found (% required):** C 75.20 (75.70); H 4.37 (4.76); N 4.08 (4.41); O 15.73 (15.12).

Biological Activity

The novel synthesized compounds have shown moderate to strong activity against bacterial and fungal strain compared to standard drug. The compound having 2-chloro substituent on phenyl ring NFC 1 was found to be most active against all the bacterial and fungal strain exhibiting zone of inhibition of 22, 22, 27, and 30 mm at concentration of 100 µg/ml against S. *aureus*, *S. pyrogens*, *E. coli* and *A. niger*, respectively. The chloro substituent at meta positions of phenyl ring decreased the antibacterial potency of molecules against both gram-positive, gram-negative bacteria and fungal starins in dose-dependent manner. Electron withdrawing substituents have better activity.

Table 2: Antibacterial evaluation of naphthofuran carboxamide derivatives.

Bacterial strain	***S.aureus***				***S. pyrogens***				***E. coli***				***A. niger***		
Conc. (µg/ml)	**25**	**50**	**100**		**25**	**50**	**100**		**25**	**50**	**100**		**25**	**50**	**100**
Compound number	**Zone of Inhibition in mm**														
NFC 1	17	19	22		19	21	22		20	25	27		23	27	30
NFC 2	11	13	17		15	17	19		9	14	17		11	17	19
NFC 3	8	8	12		9	10	14		7	10	11		7	9	13
NFC 4	10	12	17		10	15	17		13	17	20		9	15	24
NFC 5	9	13	16		11	15	18		10	21	24		13	17	23
Control (DMSO)	-	-	-		-	-	-		-	-	-		-	-	-
Chloramphenicol	20	23	25		22	24	25		NA	NA	NA		NA	NA	NA
Fluconazole	NA	NA	NA		NA	NA	NA		24	27	29		26	30	31

S.aureus:Staphylococcus aureus,S.pyrogens:Staphylococcus pyrogens, E.coli: Escherichia coli, A.niger:Aspergillus niger

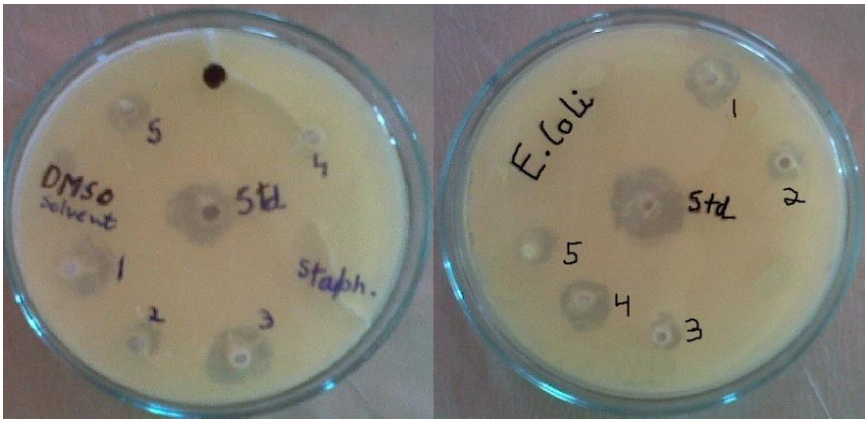


Figure 2: Antimicrobial activity of synthesized compounds.

CONCLUSION

A series of N-substituted napthofuran carboxamides derivatives NFC_{1-5} had been synthesized and characterized by IR, NMR, mass and elemental analysis. The final compounds were screened for in vitro antibacterial and antifungal activity against gram-positive, gram-negative and fungal strains by cup-plate method. Among the various derivative, the compounds NFC 1show excellent inhibition of bacterial and fungal growth as compared to standard drug chloramphenicol and fluconazole.

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REFERENCES

1. Vagdevi, H. M., Latha, K. P., Vaidya, V. P., Kumar, M. V., & Pai, K. S. R. (2001). Synthesis and pharmacological screening of some novel naphtho [2, 1-b] furo-pyrazolines, isoxazoles and isoxazolines. *Indian journal of pharmaceutical sciences*, *63*(4): 286-291.
2. Ravindra, K. C., Vagdevi, H. M., Vaidya, V. P., & Padmashali, B. (2006). Synthesis, antimicrobial and antiinflammatory activities of 1, 3, 4-oxadiazoles linked to naphtho [2, 1-b] furan.
3. Abdelwahab, A. H. F., & Fekry, S. A. H. (2021). Synthesis, reactions and applications of naphthofurans: A review. *European Journal of Chemistry*, *12*(3): 340-359.
4. Bohlmann, F., & Zdero, C. (1977). Natürlich vorkommende Terpen-Derivate, 80. Einige Inhaltsstoffe der Gattung Chromolaena. *Chemische Berichte*, *110*(2): 487-490.
5. de Oleveira, A. B., de Oleveira, G. G., & Carazza, F. (1978). Filho, RB; Bacha, CTM; Bauer, L.; de AB Silva, GA and Siqueira, NCS. *Tetrahedron Lett*, *2653*.
6. Miles, D. H., Lho, D. S., De la Cruz, A. A., Gomez, E. D., Weeks, J. A., & Atwood, J. L. (1987). Toxicants from mangrove plant. 3. Heritol, a novel ichthyotoxin from the mangrove plant Heritiera littoralis. *The Journal of Organic Chemistry*, *52*(13): 2930-2932.
7. Zubaidha, P. K., Chavan, S. P., Racherla, U. S., & Ayyangar, N. R. (1991). Synthesis of (±) heritol. *Tetrahedron*, *47*(30): 5759-5768.
8. IRIE, H., MATSUMOTO, R., NISHIMURA, M., & ZHANG, Y. (1990). Synthesis of (±)-heritol, a sesquiterpene lactone belonging to the aromatic cadinane group. *Chemical and pharmaceutical bulletin*, *38*(7): 1852-1856.

9. Ishiguro, K., Ohira, Y., & Oku, H. (1998). Antipruritic dinaphthofuran-7, 12-dione derivatives from the pericarp of Impatiens balsamina. *Journal of natural products*, *61*(9): 1126-1129.
10. Ajana, A., Bideau, J. P., Cotrait, M., Buisson, J. P., Demerseman, P., Einhorn, J., & Royer, R. (1988). Molecular and electronic structures of some mutagenic nitronaphthofurans: structure—activity relationships. *European journal of medicinal chemistry*, *23*(4): 341-346.
11. Ramesh, D., Kumaraswamy, M. N., & Nagarsha, K. M. (2021). Synthesis and Antimicrobial activity of Novel5-(8-Bromonaphtho [2, 1-B] Furan-2-Yl)-N-Alkyl/Aryl-1, 3, 4-Thiadiazole-2-amines and 5-(8-Bromonaphtho [2, 1-B] Furan-2-Yl-4-Sustituted-4h-1, 2, 4-Triazole-3-Thiols. *International Journal of Pharmaceutical, Chemical & Biological Sciences*, *11*(1).
12. Swallow, D. L. (1984). Antiviral agents 1978–1983. *Progress in Drug Research/Fortschritte der Arzneimittelforschung/Progrès des recherches pharmaceutiques*, 127-195.
13. Gach, K., Modranka, J., Szymański, J., Pomorska, D., Krajewska, U., Mirowski, M., ... & Janecka, A. (2016). Anticancer properties of new synthetic hybrid molecules combining naphtho [2, 3-b] furan-4, 9-dione or benzo [f] indole-4, 9-dione motif with phosphonate subunit. *European Journal of Medicinal Chemistry*, *120*: 51-63.
14. Mahadevan, K. M., Padmashali, B., & Vaidya, V. P. (2001). Studies in naphthofurans: Part V-synthesis of 2-aryl-1, 2, 3, 4-tetrahydropyrido (naphtho [2, 1-b] furan)-4-ones and their biological activity. *Indian Journal of Heterocyclic Chemistry*, *11*(1): 15-20.
15. Budiyanto, F., Alhomaidi, E. A., Mohammed, A. E., Ghandourah, M. A., Alorfi, H. S., Bawakid, N. O., & Alarif, W. M. (2022). Exploring the Mangrove Fruit: From the Phytochemicals to Functional Food Development and the Current Progress in the Middle East. *Marine Drugs*, *20*(5): 303.
16. Nagaraja, G. K., Kumaraswamy, M. N., Vaidya, V. P., & Mahadevan, K. M. (2006). Microwave assisted synthesis of naphtho [2, l-6] furan-l, 3, 4-benzotriazepines: a potent antimicrobial agent. *Arkivoc*, *10*: 211-219.
17. Belina, S. P., Qing, S. Y., Dudziński, P., Matsnev, A. V., Mück-Lichtenfeld, C., Haufe, G., & Thrasher, J. S. (2021). Preparation and Characterization of Pentafluoro-λ6-sulfanyldifluoromethane and Pentafluoro-λ6-sulfanyl-1, 1, 2, 2-tetrafluoroethane. *Helvetica Chimica Acta*, *104*(10): e2100138.
18. Ramesh, D., Chandrashekhar, C., & Vaidya, V. P. (2008). Synthesis of novel naphtho [2, 1-b] furo [3, 2-b] pyridine derivatives as potential antimicrobial agents, 47B: 753-758.
19. Shet Prakash, M., & Vaidya, V. P. (2011). Synthesis, characterization and antimicrobial studies of novel N-substituted napthofuran carboxamides. *J Pharm SciTec*, *3*(10): 996-1002.
20. Veena, K., Ramaiah, M., Vanita, G. K., Avinash, T. S., & Vaidya, V. P. (2011). Synthesis of symmetrical and asymmetrical azines encompassing naphtho [2, 1-b] furan by a novel approach. *E-Journal of chemistry*, *8*(1): 354-360.