Synthesis, reactions, of naphtho[2,1-b]furan derivatives and antimicrobial activity

Abstract
Condenstation of 2-acetylnaphtho[2,1-b]furan (3) with malononitrile afforded 2-(2,2-dicyano-1-methylvinyl)naphtho[2,1-b]furan (4) and reaction of compound 3 with phenyl hydrazine gave 2-(1-phenylhydrazonoethylnaphtho[2,1-b]furan (6) Interaction of 4 with sulfur via Gewald reaction produced 2-(5-amino-4-cyano-3-thienyl)naphtho[2,1-b]furan (7) while with benzene diazonium chloride afforded the 2-(1-Naphtho[2,1-b]furan-2-yl-2-phenylazo-vinyl)-malononitrile (8b). Treatment of 7 with triethyl orthoforamte in acetic anhydride at reflux afforded the N-acetylamino derivative 9, while with formic acid gave the N-formylamino derivative 11 and reaction of compound 4 with various substituted α-cyanocinnaminitriles (13a-f) in boiling ethanol containing a few drops of piperidine, afforded 2-(3-amino-2,4-dicyano-5-arylphenyl)naphtho[2,1-b]furan (16a-c). The structure of these novel compounds were confirmed using IR, 1H- and 13C-NMR as well as MS spectroscopy. The structure activity relationship (SAR) studies of the target compounds agreed with the in vitro essays and confirmed higher potent antimicrobial activity as well as some of the tested microorganisms.

Keywords: naphtho[2,1-b]furan, phenyl hydrazine, α-cyanocinnaminitriles and antimicrobial activity

Introduction
Many compounds involving a naphthofuran ring have attracted much attention in view of their diverse pharmacological properties, such as antibacterial, antitumor, antihermimic, antifertility, mutagenetic, growth inhibitory and oestrogenicactivities.1,4 Spectrum of biological activities that are constituents of important natural product.9-16 The wide pharmacological potential of these bioactive moieties has attracted many organic and medicinal chemists to develop efficient routes for their syntheses. The promising results of previous studies17-24 prompted us to further extend our research towards the synthesis of annulation of heterocyclic systems of potential biological application. In continuation of our previous work we are reporting here the synthesis of some more analogues of naphthofuran moiety as a base unit and antimicrobial activities. The structure activity relationships (SAR) are discussed in this work to correlate between the substituent effects and the activities that aid in drug design.

Experimental
General
Melting points were determined with a Stuart Scientific Co., Ltd. apparatus. IR spectra were determined as KBr pellets on a Jasco FT/IR 460 plus spectrophotometer. 1H NMR and 13C NMR spectra were recorded using a Bruker AV 400MHz spectrometer. Mass spectra were measured on a Shimadzu GC/MS-QP5050A spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 microanalyzer in the Faculty of Science, Cairo University, Egypt.

Synthesis
Synthesis of 2-Acetyl naphtho[2,1-b]furan (3):25 A mixture of 2-hydroxy-1-naphthaldehyde (1) (1.72g, 0.01mol), chloroacette (2) (0.92g, 0.01mol) and anhydrous potassium carbonate (0.20mol) in anhydrous acetone (50mL) was refluxed for 8h. The mixture allowed to cool and poured on to crushed ice (50g) and water (100mL) then acidified with conc. HCl. The solid product was formed filtered off and washed with water and recrystallized from ethanol

Synthesis of 2-(2,2-dicyano-1-methylvinyl)naphtho[2,1-b]furan (4)
A solution of 2-acetyl naphtho[2,1-b]furan (3) (2.10g, 0.01mol) and benzene diazonium chloride (0.32g) in dry benzene (100mL) was added malononitrile (0.66g, 0.01mol), ammonium acetate (2g) and acetic acid (2mL). The reaction mixture was refluxed using a Dean and Stark water separated until water ceased to be collected. The product obtained was crystallized from the benzene.

Synthesis of 2-(1-phenylhydrazonoethylnaphtho[2,1-b]furan (6)
Method A: A mixture of compound 4 (2.58g, 0.01mol) and phenylhydrazine (1.08g, 0.01mol) in ethanol (50mL) was refluxed for 2h, the separated solid on heating was filtered off and recrystallized from ethanol.
Method B: A solution of compound 3 (2.10g, 0.01mol) and phenylhydrazine (1.08g, 0.01mol) in ethanol (50mL) was refluxed for 2h, the separated solid on heating was filtered off and recrystallized from ethanol.

Synthesis of 2-(5-amino-4-cyano-3-thienyl)naphtho[2,1-b]furan (7)
A mixture of 4 (2.58g, 0.01mol) and elemental sulfur (0.32g) in ethanol (50mL) were treated with a few drops of triethylamine. was refluxed for 3h. The obtained product was filtered off and recrystallized from the dioxane.
Synthesis of 2-(1-Naphtho[2,1-b]furan-2-yl-2-phenylazo-vinyl)-malononitrile (8b)
To a cold solution of 4 (2.58g, 0.01mol ) in pyridine (20mL) was added benzenediazonium chloride (0.01mol) [prepared by diazotization of aniline (0.01mol) in HCl (6M, 6mL)] with sodium
nitrite (0.7g) at 0-5ºC) portion wise over 30 min with constant stirring. After complete addition, the reaction mixture was stirred for a further 2h at 0-5ºC. The solid product was filtered off, washed with water, dried and finally recrystallized from ethanol.

**Synthesis of 2-(5-Acetylamino/formylamino-4-cyano-3-thienyl)-naphtho[2,1-b]furan (9,11) A mixture of compound 7 (2.90g, 0.01mol), with triethyl orthoformate (0.01mol) in acetic anhydride (20mL) and/or formic acid was heated under reflux for 3h. The obtained product was filtered off and recrystallized from ethanol/benzene.

**Synthesis of 2-(3-amino-2,4-dicyano-5-arylphenyl)-naphtho[2,1-b]furan (16a-c) A mixture of compound 4 (2.58g, 0.01mol), with various α-cyanocinnamionitriles (13a-f) (0.01 mol) in ethanol (30 mL) and few drops of piperidine was refluxed for 3h, the solid product was collected by filtration and recrystallized from ethanol/benzene.

**Antibacterial Activity: All the newly synthesized compounds 3-6a-c were screened for their in vitro antimicrobial activity at 30µg/mL to determine the zone of inhibition against four Gram-positive bacteria: Staphylococcus aureus (NCTC 7447)(SA) and Bacillus subtilis (ATCC 7972)(BS) and two Gram-negative pathogenic bacteria: Pseudomonas aeruginosa (ATCC 10415)(PA) and Escherichia coli (NCTC 10416)(EC) using standard antibiotics (Neomycin) as reference drugs, and two fungi: Aspergillus fumigatus (ATCC 6275)(AN) and Candida albicans ((IMRU 3669)CA) using standard antibiotics (Mycostatine) as reference drugs. The activities of these compounds were tested by agar diffusion method using Mueller-Hinton agar medium for bacteria and Sabouraud’s agar medium for fungi.25,27 The tested compounds were dissolved in N,N-dimethylformamide (DMF) to give a solution of 1mg/mL. The inhibition zones (diameter of the hole) were measured in millimeters (6mm) at the end of an incubation period of 48h at 28°C; N,N-dimethylformamide showed no inhibition zone. The inhibitory effects of the synthetic compounds against these organisms are given in Figure 1 & Table 3.

**Results and discussion

**Chemistry**

Thus, treatment of 2-hydroxy-1-naphthaldehyde (1) with chloroacetone (2) in refluxing acetone in the presence of anhydrous potassium carbonate gave the 2-acetynaphtho[2,1-b]furan (3). Condensation of 2-acetyl naphtho[2,1-b]furan (3) with malononitrile in boiling benzene containing ammonium acetate and acetic acid afforded 2-(2,2-dicyano-1-methyl vinyl) naphtho[2,1-b]furan (4) (Scheme 1).

In contrast to the anticipated formation of 5-imino-4-(naphtho[2,1-b]furan-2-ylmethylen)-1-phenyl-4,5-dihydro-1H-pyrazol-3-amine (5). The reaction of compound 4 with phenyl hydrazine in boiling ethanol gave 2-(1-phenylhydrazonoethyl) naphtho [2,1-b]furan (6) and is assumed to proceed via elimination of malononitrile. The proposed structure for 6 was supported by its independent synthesis from 3 by refluxing with phenylhydrazine in boiling ethanol (m.p. and mixed m.p.) (Scheme 1).

The structure of compounds 3-6 were established by spectral data. The IR spectrum of compound 3 showed absorptions at 1666 cm⁻¹ (CO), while compound 4 showed absorption at 2225, 2228cm⁻¹ (2CN), 1567cm⁻¹ (C=C) and compound 6 showed absorptions at 3459, 3346cm⁻¹ (NH), 1601cm⁻¹ (C=N). The 1H NMR of compounds 3 – 6 showed chemical shifts at δ 7.89-7.60 (s, 1H, H-3), 2.62- 2.35 (s, 3H, CH₃) and compound 6 showed absorptions at 3459, 3346cm⁻¹ (NH), 1601cm⁻¹ (C=N). The 13C NMR of compound 3 showed δ 187.19 (CO), 26.31 (CH₃), while compound 4 showed δ 118.01 (CN), 26.21 (CH₃), while compound 6 showed δ 151.72 (C=N), 27.30 (CH₃). The mass spectra of compounds 3-6 displayed [M+] ion peaks m/z 210 (M+, 32), 258 (M+, 100), 300 (M+, 100), respectively Table 2.

Interaction of 4 with sulfur via Gewald reaction29 produced 2-(5-amino-4-cyano-3-thienyl) naphtho[2,1-b]furan (7) while with benzene diazonium chloride afforded the open chain product 8a-8c instead of the closed product 2,3-dihydro-3-imino-5-(naphtho[2,1-b]furan-2-yl)-2-phenylhydrazine-4-carbonitrile (8d). The proposed open chain structures 8a-8c was ruled out on the bases of spectroscopic data (no C=C(CN), & NH bands) (Scheme 2). Treatment of 7 with triethyl orthoformate in acetic anhydride at reflux afforded the N-acetylamino derivative 9 instead of the 2-(5-ethoxymethyleneamino-4-cyano-3-thiényl)naphtho[2,1-b]furan (10), while with formic acid gave the N-formylamino derivative 11 instead of the pyrimidine derivative 12 (Scheme 2).

**Figure 1** Antimicrobial activity of the tested compounds compared to neomycin and mycostatine.

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The structure of compounds 7-11 were established by spectral data. The IR spectrum of compound 7 showed absorptions at 3420, 3198 cm\(^{-1}\) (NH\(_2\)), 2205 cm\(^{-1}\) (CN) while compound 8b showed absorption at 2226 cm\(^{-1}\) (CN), compound 9 showed absorptions at 3262, 3210 cm\(^{-1}\) (NH\(_2\)), 1704 cm\(^{-1}\) (CO). The \(^1\)H NMR of compound 7 showed chemical shifts at δ 7.50 (s, 1H, H-3), 6.87 (brs, 2H, NH\(_2\)), while compound 8b showed chemical shifts at δ 8.69 (s, 1H, CH=C), 4.41 (s, 1H, CH-CN), compound 9 showed chemical shifts at δ 8.83 (brs, 1H, NH), 2.36 (s, 3H, CH\(_3\)), and compound 11 showed chemical shifts at δ 8.83 (brs, 1H, NH), 2.36 (s, 3H, CH\(_3\)), while compound 11 showed chemical shifts at δ 8.83, 2.36 (s, 3H, CH\(_3\)). The mass spectra of compounds 7-11 displayed [M+] ion peaks m/z 290 (M+, 100), 362 (M+, 62), 332 (M+, 48), 362 (M+, 62), 318 (M+, 100), respectively.

**Table 1** Elemental analyses of new compounds

| Compd. | Yield (%) | M.P (°C) | Crystal colour | Molecular formula (Mr) | Analysis (%) | Found/calculate
|--------|-----------|----------|----------------|------------------------|-------------|-----------------------|
| 3      | 90        | 108-110 Lit. 17 | Yellow | C\(_7\)H\(_8\)O\(_2\) (210.23) | 79.95 79.98 | 4.78 4.79
| 4      | 80        | 224-226 | Yellow | C\(_8\)H\(_9\)N\(_2\)O (58.27) | 70.4 79.06 | 3.90 3.90
| 6      | 78        | 172-174 | Yellow | C\(_8\)H\(_9\)N\(_2\)O (300.35) | 79.96 79.98 | 5.35 5.37
| 7      | 80        | 220-222 | Yellow | C\(_8\)H\(_9\)N\(_2\)O (320.34) | 70.30 3.45 | 3.47 3.47
| 8b     | 75        | 173-175 | Yellow | C\(_8\)H\(_9\)N\(_2\)O (362.38) | 76.20 76.23 | 3.87 3.89

**Chart 1** The fragmentation pattern of compounds 8b,c, 9, and 11 are illustrated in (Chart 1).

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Interaction of 4 with various substituted \( \alpha \)-cyanocinnamionitrides (13a-f) in boiling ethanol containing a few drops of piperidine, afforded 2-(3-amino-2,4-dicyano-5-arylphenyl)naphtho[2,1-b]furan (16a-c) (Scheme 3). The formation of 16 from the reaction of 4 and 13a-c is assumed to proceed via a Michael type addition of the methyl function in 4 to the activated double bond to yield the acyclic Michael adduct 14a which then cyclizes into (15a). The latter readily loses HCN to yield the final isolable thermodynamically stable compounds (16a-c) (Scheme 3). In contrast to the anticipated formation of the esters 17, the reaction of 4 with various substituted ethyl \( \alpha \)-cyanocinnamates (13d-f) afforded 16a-c and are assumed to proceed via elimination of ethyl formate from the intermediate(15b) (Scheme 3).

![Scheme 3](image-url)
The structure of compounds 16a-c were established by spectral data. The IR spectrum of compounds 16a-c showed absorptions at 3470-3236 cm\(^{-1}\) (NH\(_2\)), 2216 (CN) cm\(^{-1}\). The \(^1\)H NMR of compounds 16a-c showed chemical shifts at \(\delta\) 7.32-7.25 (s, 1H, H-3), 6.85-6.77 (brs, 2H, NH\(_2\)). The \(^13\)C NMR of compound 16a-c showed \(\delta\) 116.10-14.86 (CN). The mass spectra of compounds 16a-c displayed [M+] ion peaks m/z 385 (M+, 100), 399 (M+, 100), 415 (M+, 100), respectively Table 2 & Chart 2.

Chart 2 The fragmentation pattern of compounds 16a-c are illustrated in (Chart 2).

Table 2 Spectral data of prepared compounds

| Comp. No | IR (\(\nu\),cm\(^{-1}\)) | \(^1\)HNMR/\(^{13}\)CNMR | Ms; m/z |
|----------|----------------------|----------------------|--------|
| 3        | 1666 (CO)            | 187.19 (CO), 151.36 (C-9a), 151.90 (C-2), 130.11 (C-3a), 129.90 (C-8), 128.98 (C-7), 127.85 (C-7a), 127.52 (C-6), 125.60 (C-5), 123.64 (C-4), 122.61 (C-3b), 113.69 (C-3), 112.74 (C-9), 26.33 (CH\(_3\)). | 210 (M\(^+\), 32), 168 (3), 139 (100), 113 (11), 89 (15), 63 (38). |
| 4        | 2225, 2228 (2CN), 1567 (C=C) | 154.45 (C-9a), 152.74 (C-2), 130.54 (C-3a), 129.83 (C-8), 128.57 (C-7), 127.62 (C-7a), 127.10 (C-6), 124.72 (C-5), 124.54 (C-4), 123.24 (C-3b), 118.01 (CN), 117.22 (CN), 113.79 (C-3), 112.45 (C-9), 26.21 (CH\(_3\)). | 258 (M\(^+\), 100), 168 (16), 139 (33), 88 (23). |
| 6        | 345.3346 (NH\(_2\)), 1601 (C=N) | 154.81 (C-9a), 151.72 (C=N), 145.45 (C-2), 132.94 (C-1'), 130.01 (C-3a), 129.94 (C-8), 128.66 (C-3'), 127.06 (C-7a), 126.44 (C-7'), 125.28 (C-6), 124.75 (C-5), 106.6 (C-3'), 27.30 (CH\(_3\)). | 300 (M\(^+\), 100), 286 (45), 168 (13), 88 (16), 51 (62). |
| 7        | 3420, 3312, 3198 (NH\(_2\)), 2205 (CN) | 154.72 (C-2), 151.10 (C-9a), 149.68 (C-4'), 130.08 (C-2'), 128.75 (C-7), 127.35 (C-7a), 127.03 (C-3a), 120.69 (C-4'), 125.85 (C-5), 124.89 (C-6), 123.47 (C-3b), 116.37 (CN), 111.97 (C-9), 105.87 (C-3'), 100.97 (C-9), 80.58 (C-3') | 290 (M\(^+\), 100), 168 (13), 139 (51), 138 (24), 129 (61), 88 (8), 51 (43). |

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The structure activity relationship (SAR)

The structure activity relationship (SAR) studies of compounds 3-16a-c revealed, compound 7 good activity inhibitory effect range 19.9±0.1, 20.3±0.4, 18.6±0.1 and 17.2±0.1µg/mL. Good or more activity was observed, as compared to the standard antibiotics (Mycostatine). Compound 216 which show weak activity inhibitory effect against Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli as compared to the standard antibiotics (neomycin). Nucleus with a lipophilic hydrophobic group (CH=C=NNHPh, benzene ring), while compound 16a-c which show weak inhibition zone diameter against Bacillis subtilis, Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli as compared to the standard antibiotics (neomycin). Compound 6 which show weak inhibition zone diameter 11.6±0.3, 13.2±0.3µg/mL against Aspergillus fumigatus and Candida albicans as compared to the standard antibiotics (Mycostatine), while compound 16a-c which show weak activity inhibitory effect range 12.1±0.2 and 11.1±0.3µg/mL against Candida albicans as compared to the standard antibiotics (Mycostatine), while compound 16b which show weak activity inhibitory effect range 13.1±0.1µg/mL against Aspergillus fumigatus as compared to the standard antibiotics (Mycostatine).

This may suggest that the substituent at 2-position plays a key role in antimicrobial activity, compounds containing a thiophene ring (Mycostatine) as reference drugs Table 3.

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This may suggest that the substituent at 2-position plays a key role in antimicrobial activity, compounds containing a thiophene ring (Mycostatine) as reference drugs Table 3.
Table 3 Antimicrobial activity of the new compounds

| Compound | Minimum inhibitory concentration (MIC) (μg/mL) |
|----------|-----------------------------------------------|
|          | Bacterial strains | Fungal strains |
|          | Gram-positive bacteria | Gram-negative bacteria |
|          | Bacillus | Staphylococcus | Escherichia | Pseudomonas | Candida | Asperillus |
|          | Subtilis | Aureus | | Coli | Aeruginosa | Albican | Niger | (ATCC-7972) | (NCTC-7447) | (NCTC-10416) | (ATCC-10415) | (IMRU- 3669) | (ATCC- 6275) |
| 3        | NA | NA | NA | NA | NA | NA | NA |
| 4        | NA | NA | NA | NA | NA | NA | NA |
| 6        | 18.2±0.2 | 16.7±0.1 | 19.1±0.3 | 17.5±0.4 | 11.6±0.3 | 13.2±0.3 | 17.2±0.1 |
| 7        | 14.6±0.1 | 19.9±0.3 | 15.1±0.1 | 20.3±0.4 | 18.6±0.1 | NA |
| 8b       | NA | NA | NA | NA | NA | NA | NA |
| 9        | NA | NA | NA | NA | NA | NA | NA |
| 11       | NA | NA | NA | NA | NA | NA | NA |
| 16a      | 14.2±0.1 | 16.3±0.3 | 12.1±0.2 | 17.2±0.2 | 12.1±0.2 | NA |
| 16b      | 17.1±0.3 | 13.2±0.1 | 10.3±0.2 | 19.1±0.1 | NA | NA |
| 16c      | 12.1±0.2 | 18.2±0.1 | 16.1±0.2 | 15.2±0.1 | 11.1±0.3 | NA |
| Neomycine| 20.1±0.2 | 24.2±0.1 | 26.1±0.2 | 20.2±0.1 | - | 23.2±0.4 | 20±0.1 |

ac=1mg/mL of new compounds in DMF
NA=not active
Diameter of the hole=6mm
Data are expressed in the form of mean±SD.

Conclusion

Briefly, we have reported the synthetic strategies for the synthesis of new naphtho[2,1-b]furan derivatives starting from1-naphthaldehyde (1). The newly prepared compounds were studied for their antimicrobial activities four bacteria using standard Neomycin as reference drugs and two fungi standard using standard mycostatine as reference drugs. The data showed that the compound 2-(5-amino-4-cyano-3-thienyl) naphtho[2,1-b]furan (7) was most active against all the tested bacteria and fungi. Compound 3,4, 8 and 9 which show inactive inhibition zone diameter as compared to the standard antibiotics, neomycin and mycostatine as reference drugs.

Acknowledgements

None.

Conflict of interest

The author declares that there is no conflict of interest.

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