Acta Poloniae Pharmaceutica – Drug Research, Vol. 70 No. 4 pp. 667–679, 2013 ISSN 0001-6837
Polish Pharmaceutical Society

A CONCISE SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF A NOVEL SERIES OF NAPHTHYLPYRIDINE-3-CARBONITRILE COMPOUNDS

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Abstract: A novel series of acyclic nucleosides **2**-**5** and **13a**-**c** were synthesized by utilizing 4-phenyl-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropridine-3-carbonitrile (**1**) as a key starting material. Chlorination of **1** yielded the chloro analogue **6** that was allowed to react with urea, thiourea, thiosemicarbazide and alicyclic secondary amines to produce the corresponding derivatives **7a**-**c** and **11a**-**c**. Further condensation of **6** with various amino acids provided the compounds **8**-**10**, whereas hydrazinolysis of **6** yielded the hydrazinyl analogue **12** which was condensed with different isothiocyanates and acid anhydrides to afford derivatives **18**-**20**, respectively. Upon treatment of **12** with sodium nitrite, the azide derivative **14** was obtained which was subjected to reaction with various active methylene compounds to obtain the corresponding triazolo derivatives **15**-**17**. The structure assignment of the new compounds is based on chemical and spectroscopic evidence. Antimicrobial evaluation of the newly synthesized derivatives was performed using ciprofloxacin and fluconazole as reference antibacterial and antifungal drugs. The most effective compounds against the tested bacterial and fungal isolates were the benzothiohydrazide compound **18b** followed by the hydrazone and the phthalic anhydride derivatives **13c** and **20**, respectively.

Keywords: Naphthyl-2-pyridines, acyclic nucleosides, hydrazones, triazoles, antimicrobial evaluation

Antibiotics are among the most prescribed drugs in the world today since their development and commercialization have saved countless millions of lives. Antimicrobials are very important therapeutic agents and have been found to be clinically effective in many protozoan bacterial and fungal infections (1, 2). Over the past decade, fungal infection became an important complication and a major cause of morbidity and mortality in immunocompromised individuals such as those suffering from tuberculosis, cancer or AIDS and in organ transplant cases (3).

The search of novel antimicrobial agents still continues as the clinical use of the existing antimicrobials has been limited by their relatively high risk of toxicity, pharmacokinetic problems and development of bacterial and fungal resistance resulting from the widespread use and misuse of classical antimicrobial agents (4). Such serious global health problem demands a renewed effort seeking the development of new antimicrobial agents effective against pathogenic microorganisms resistant to currently available treatments. Antibacterial resistance to a drug, pharmacokinetic properties and cellular permeability of a drug can be modulated by designing new derivatives of the existing drugs (5).

Pyridine nucleus is one of the most popular N-heteroaromatic ring system incorporated into the structure of many antimicrobial pharmaceuticals. Among these, are cyanopyridines and aminocyanopyridines substituted with different alkyl and aryl groups (6-10).

Furthermore, according to literature survey, several naphthalene containing drugs are available, such as nafacillin, naftifine, tolnaftate, terbinafine, etc., which play vital role in the control of microbial infection (11, 12). Various naphthalene analogues have been identified as a new range of potent antimicrobials that are effective against wide range of human pathogens. They occupy a central place

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among medicinally important compounds due to their diverse and interesting antibiotic properties with minimum toxicity (13, 14).

Since the search for new antimicrobial agents will always remain an important challenging task for medicinal chemists, and as a continuation of our efforts to identify new naphthalene candidates (15-17) that may be of value in designing new potent, selective, less toxic and less resistant antimicrobial agents, we report in the present work the synthesis and antimicrobial screening of some new derivatives bearing naphthalene-pyridine ring system as a parent core.

MATERIALS AND METHODS

Chemistry

All melting points are uncorrected and were recorded on an open glass capillary tubes using an Electrothermal IA 9100 digital melting point apparatus. Elemental micro-analyses were carried out at Microanalytical Unit, Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt, using Vario Elementar apparatus and were found within ± 0.4% of the theoretical values. Infrared spectra were recorded on a Jasco FT/IR-6100, Fourier transform, infrared spectrometer (Japan) at cm^{-1} scale using KBr disc technique at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. ^{1}H- and ^{13}C-NMR spectra were determined using a JEOl EX-270 & 500 NMR spectrometer at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. All chemical shifts were reported as δ (ppm) scale using TMS as the internal standard and coupling constant values are given in Hz. The mass spectra were measured with a Finnigan MAT SSQ-7000 mass spectrometer at Central Services Laboratory, National Research Centre, Dokki, Cairo, Egypt. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminium sheets (Type 60, F 254, Merck, Darmstadt, Germany) and the spots were detected by exposure to UV lamp at λ 254/366 nm for few seconds.

6-(2-Naphthyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (1)

It was synthesized according to the reported method (17).

General procedure for synthesis of compounds 2-5

To a solution of compound **1** (3.22 g, 10 mmol) in dry DMF (50 mL), sodium hydride (0.24 g, 10 mmol) was added. Thereafter, the reaction mixture was stirred at room temperature for 1 h. Then, the appropriate alkyl halides namely: ethyl iodide, 2-chloroethanol, 2-chloro-1,1-dimethoxyethane and 2-(2-chloroethoxy)ethanol (15 mmol) was added and the reaction mixture was stirred at 70°C for 10-24 h. The solvent was evaporated under reduced pressure and the residue was washed with water, filtered, dried and recrystallized from ethanol to give the corresponding compounds **2-5**.

1-Ethyl-6-(2-naphthyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (2)

Yield: 63%; m.p. 151-153°C. IR (KBr, cm^{-1}): 2216 (CN), 1665 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.12 (t, J = 7.1 Hz, 3H, CH_2CH_3), 4.21 (q, J = 7.1 Hz, 2H, CH_2CH_3), 7.16 (s, 1H, pyridine-H5), 7.26-8.29 (m, 12H, Ar-H). MS m/z (%): 350 (M^+ 20). Analysis: calcd. for $C_{24}H_{18}N_2O$ (350.41): C, 82.26; H, 5.18; N, 7.99%; found: C, 82.36; H, 5.29; N, 7.72%.

1-(2-Hydroxyethyl)-6-(2-naphthyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (3)

Yield: 71%; m.p. 248-249°C. IR (KBr, cm^{-1}): 3400 (OH), 2220 (CN), 1668 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.75 (t, J = 4.5 Hz, 2H, N-CH_2), 4.61 (t, J = 4.55 Hz, 2H, CH_2-O), 5.34 (bs, 1H, OH, D_2O exchangeable), 7.20 (s, 1H, pyridine-H5), 7.50-8.10 (m, 12H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ, ppm): 44.3, 59.3 ($2CH_2$-OH), 104.9, 115.2, 123.2, 125.1, 126.4, 127.5, 128.4, 128.7, 133.1, 133.6, 134.4, 135.1, 158.9 (aromatic-C), 168.8 (C=O). MS m/z (%): 366 (M^+ 25). Analysis: calcd. for $C_{24}H_{18}N_2O_2$ (366.41): C, 78.67; H, 4.95; N, 7.65%; found: C, 78.59; H, 4.79; N, 7.82%.

1-(2,2-Dimethoxyethyl)-6-(2-naphthyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (4)

Yield: 62%; m.p. 217-219°C. IR (KBr, cm^{-1}): 2210 (CN), 1665 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.75 (s, 6H, $2OCH_3$), 4.06 (d, J = 4.55 Hz, 2H, N-CH_2), 4.62 (t, J = 7.3 Hz, 1H, CH), 7.10 (s, 1H, pyridine-H5), 7.23-8.24 (m, 12H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ, ppm): 45.3, 53.3, 101.2 (CH_2-CH-(OCH_3)$_2$), 105.9, 115.2, 123.8, 125.5, 126.4, 127.5, 128.0, 128.7, 133.3, 133.8, 134.4, 135.1, 157.9 (aromatic-C), 168.8 (C=O). MS m/z (%): 410 (M^+ 19). Analysis: calcd. for $C_{26}H_{22}N_2O_3$ (410.46): C, 76.08; H, 5.40; N, 6.82%; found: C, 75.95; H, 5.52; N, 7.01%.

1-[2-(2-Hydroxyethoxy)ethyl]-6-(2-naphthyl)-2-oxo-4-phenyl-1,2-dihydropyridine-3-carbonitrile (5)

Yield: 59%; m.p. 254-256°C. IR (KBr, cm^{-1}): 3330 (OH), 2223 (CN), 1655 (C=O); ^{1}H-NMR

(DMSO-d_6, δ, ppm): 2.19 (t, *J* = 4.6 Hz, 2H, N-CH_2), 3.01 (t, *J* = 4.5 Hz, 2H, CH_2-O), 3.68 (m, 4H, OCH_2CH_2OH), 4.88 (bs, 1H, OH, D_2O exchangeable), 7.20 (s, 1H, pyridine-H5), 7.30-8.20 (m, 12H, Ar-H). MS *m/z* (%): 410 (M^+ 30). Analysis: calcd. for $C_{26}H_{22}N_2O_3$ (410.46): C, 76.08; H, 5.40; N, 6.82%; found: C, 76.22; H, 5.53; N, 6.64%.

2-Chloro-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (6)

A solution mixture of compound **1** (3.22 g, 10 mmol), phosphorous oxychloride (10 mL) and phosphorous pentachloride (0.5 g) was heated on boiling water bath for 8 h. After the reaction was completed, the solution mixture was cooled and poured gradually onto crushed ice. The obtained precipitate was filtered off and dried to obtain the chloro analogue **6**.

Yield: 64%; m.p. 181-182°C. IR (KBr, cm^{-1}): 2217 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.20 (s, 1H, pyridine H-5), 7.36-7.98 (m, 12H, Ar-H). MS *m/z* (%): 340 (M^+ 30), 342 (M^+ + 2; 10). Analysis: calcd. for $C_{22}H_{13}ClN_2$ (340.81): C, 77.53; H, 3.84; N, 8.22%; found: C, 77.41; H, 3.96; N, 8.09%.

General procedure for synthesis of compounds 7a-c

A solution mixture of the chloro compound **6** (3.50 g, 10 mmol) and either urea, thiourea or thiosemicarbazide (10 mmol) in absolute ethanol (30 mL) containing few drops of triethylamine was heated under reflux for 12 h. Upon reaction completion, the mixture was concentrated and the obtained precipitate was filtered off and recrystallized from ethanol to get the desired derivatives **7a-c**, respectively.

1-(3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl)urea (7a)

Yield: 68%; m.p. 201-203°C. IR (KBr, cm^{-1}): 3420-3250 (NH, NH_2), 2210 (CN), 1665 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.43 (bs, 2H, NH_2, D_2O exchangeable), 7.11 (s, 1H, pyridine-H5), 7.32-8.21 (m, 12H, Ar-H), 9.21 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 117.4, 111.3, 124.3, 126.1, 127.4, 128.2, 128.9, 129.3, 132.3, 134.4, 135.6, 138.2, 158.2, 165.6, 174.6 (aromatic-C). MS *m/z* (%): 364 (M^+ 15). Analysis: calcd. for $C_{23}H_{16}N_4O$ (364.40): C, 75.81; H, 4.43; N, 15.38%: found: C, 76.00; H, 4.32; N, 15.49%.

1-(3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl)thiourea (7b)

Yield: 80%; m.p. 272-274°C . IR (KBr, cm^{-1}): 3400-3245 (NH, NH_2), 2213 (CN), 1140 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.49 (bs, 2H, NH_2, D_2O exchangeable), 7.21 (s, 1H, pyridine-H5), 7.27-8.08 (m, 12H, Ar-H), 9.26 (s, 1H, NH, D_2O exchangeable). MS *m/z* (%): 380 (M^+ 42). Analysis: calcd. for $C_{23}H_{16}N_4S$ (380.46): C, 72.61; H, 4.24; N, 14.73; S, 8.43%. Found: C, 72.85; H, 4.08; N, 14.59; S, 8.27%.

N-(3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl)thiosemicarbazide (7c)

Yield: 64%; m.p. 254-256°C. IR (KBr, cm^{-1}): 3440-3245 (2NH, NH_2), 2226 (CN), 1160 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.10 (bs, 2H, NH_2, D_2O exchangeable), 7.21 (s, 1H, pyridine-H5), 7.25-8.31 (m, 12H, Ar-H), 9.21, 10.00 (2s, 2H, 2NH, D_2O exchangeable). MS *m/z* (%): 396 (M^+ + 1; 40). Analysis: calcd. for $C_{23}H_{17}N_5S$ (395.48): C, 69.85; H, 4.33; N, 17.71; S, 8.11%; found: C, 70.01; H, 4.46; N, 17.59; S, 7.98%.

General procedure for synthesis of compounds 8-10

The suitable amino acid namely: glycine, D-isoleucine and D-phenylalanine (20 mmol) and Na_2CO_3 (15 mmol) were dissolved in water (15 mL), and the pH was adjusted to 9-9.5. Then, the chloro derivative **6** (3.50 g, 10 mmol) dissolved in ethanol (10 mL) was added to the previous solution and the reaction mixture was stirred at 100°C for 8 h at the controlled pH. The reaction mixture was left overnight at room temperature then was treated with cold formic acid. The solid obtained was filtered off, washed with H_2O and crystallized from methanol to yield the corresponding derivatives **8-10**.

2-(3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-ylamino)acetic acid (8)

Yield: 80%; m.p. 283-285°C. IR (KBr, cm^{-1}): 3440-3234 (OH, NH), 2218 (CN), 1680 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.81 (d, 2H, *J* = 7.6 Hz, CH_2), 7.01 (s, 1H, pyridine-H5), 7.56-8.37 (m, 12H, Ar-H), 8.91 (t, 1H, *J* = 3.4 Hz, NH), 11.12 (s, 1H, OH, D_2O exchangeable). MS *m/z* (%): 379 (M^+ 40). ^{13}C-NMR (DMSO-d_6, δ, ppm): 45.5 (*C*H_2NH), 110.1, 117.2, 124.4, 125.9, 126.2, 127.4, 129.1, 128.4, 132.4, 134.3, 135.6, 138.5, 159.3, 166.5 (aromatic-C), 173.4 (C=O). Analysis: calcd. for $C_{24}H_{17}N_3O_2$ (379.41): C, 75.97; H, 4.52; N, 11.08%; found: C, 75.83; H, 4.41; N, 10.95%.

2-[3-Cyano-6-2-(naphthyl)-4-phenylpyridin-2-ylamino]-3-methylpentanoic acid (9)

Yield: 53%; m.p. 291-292°C. IR (KBr, cm^{-1}): 3448-3245 (OH, NH), 2220 (CN), 1701 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.11 (s, 6H, 2CH_3), 1.30

(m, 2H, CH_2), 2.31 (m, 1H, β-C*H*), 3.71 (d, 1H, *J* = 7.6 Hz, α-C*H*), 7.22 (s, 1H, pyridine-H5), 7.12-8.08 (m, 12H), 9.23 (t, 1H, *J* = 3.4 Hz, NH, D_2O exchangeable), 11.54 (s, 1H, OH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 12.5, 16.0, 11.1, 25.0, 36.2, 69.2 (isoleucine side chain-C), 117.1, 124.5, 125.9, 126.2, 127.4, 128.5, 129.5, 132,2, 134.4, 135.6, 138.1, 145.2, 158.1, 165.4 (aromatic-C), 174.1 (C=O). MS *m*/*z* (%): 435 (M^+ 10). Analysis: calcd. for $C_{28}H_{25}N_3O_2$ (435.52): C, 77.22; H, 5.79; N, 9.65%; found: C, 77.02; H, 5.54; N, 9.85%.

2-[3-Cyano-6-(2-naphthyl)-4-phenylpyridin-2-ylamino]-3-phenylpropanoic acid (10)

Yield: 43%; m.p. > 300°C. IR (KBr, cm^{-1}): 3450-3239 (OH, NH), 2220 (CN), 1701 (C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.60 (d, 2H, *J* = 7.2 Hz, β -CH_2), 3.80 (m, 1H, α-C*H*), 7.11 (s, 1H, pyridine-H5), 7.37-8.36 (m, 17H, Ar-H), 9.10 (t, 1H, *J* = 3.4 Hz, NH, D_2O exchangeable), 11.00 (s, 1H, OH, D_2O exchangeable). MS *m*/*z* (%): 469 (M^+ 20). Analysis: calcd. for $C_{31}H_{23}N_3O_2$ (469.53): C, 79.30; H, 4.94; N, 8.95%; found: C, 79.12; H, 5.17; N, 8.79%.

General procedure for synthesis of compounds 11a-c

A mixture of compound **6** (3.50 g, 10 mmol) and the appropriate secondary amine: morpholine, 4-methylpiperazine and 4-methylpiperidine (10 mmol) in absolute ethanol (30 mL) was heated under reflux for 12 h. Upon the reaction completion, the solution was concentrated and the obtained precipitate was filtered off and recrystallized from ethanol to get the desired derivatives **11a-c**, respectively.

2-Morpholino-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (11a)

Yield: 75%; m.p. 266-267°C. IR (KBr, cm^{-1}): 2225 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.75 (m, 4H, N-(CH_2)$_2$), 3.81 (m, 4H, O-(CH_2)$_2$), 7.03 (s, 1H, pyridine-H5), 7.23-8.11 (m, 12 H, Ar-H). MS *m*/*z* (%): 391(M^+ 17). Analysis: calcd. for $C_{26}H_{21}N_3O$ (391.46): C, 79.77; H, 5.41; N, 10.73%; found: C, 79.60; H, 5.32; N, 10.97%.

2-(4-Methylpiperazin-1-yl)-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (11b)

Yield: 61%; m.p. 272-274°C. IR (KBr, cm^{-1}): 2222 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 2.35 (s, 3H, CH_3), 2.71-3.31 (m, 8H, piperazine ring), 7.11 (s, 1H, pyridine-H5), 7.20-8.25 (m, 12 H, Ar-H). MS *m*/*z* (%): 404 (M^+ 30). Analysis: calcd. for $C_{27}H_{24}N_4$ (404.51): C, 80.17; H, 5.98; N, 13.85%; found: C, 80.06; H, 6.09; N, 13.71%.

2-(4-Methylpiperidin-1-yl)-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (11c)

Yield: 65%; m.p. 276-278°C. IR (KBr, cm^{-1}): 2220 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.21 (s, 3H, CH_3), 1.71 (m, 5H, β-2CH_2, δ-CH of piperidine ring), 2.74 (m, 4H, α-2CH_2 of piperidine ring), 7.00 (s, 1H, pyridine-H5), 7.13-7.95 (m, 12H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ, ppm): 20.4, 32.1 (*C*H_3, 2*C*H_2), 50.2 (N-(*C*H_2)$_2$), 111.5, 117.1, 126.3, 127.5, 128.1, 129.2, 132,2, 134.4, 124.1, 125.3, 135.8, 157.5, 167.1, 138.4, 145.2 (aromatic-C). MS *m*/*z* (%): 403 (M^+ 35). Analysis: calcd. for $C_{28}H_{25}N_3$ (403.52): C, 83.34; H, 6.24; N, 10.41%; found: C, 83.49; H, 6.49; N, 10.26%.

2-Hydrazinyl-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (12)

A mixture of the chloropyridine derivative **6** (3.50 g, 10 mmol) and hydrazine hydrate 99% (1.6 mL, 50 mmol) in dioxane (10 mL) was stirred under reflux for 8 h. The formed precipitate was filtered off, dried and recrystallized from methanol to give the hydrazinyl derivative **12**.

Yield: 63%; m.p. 246-247°C. IR (KBr, cm^{-1}): 3430-3240 (NH, NH_2), 2218 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.34 (s, 2H, NH_2, D_2O exchangeable), 7.21 (s, 1H, pyridine-H5), 7.37-8.15 (m, 12H, Ar-H), 9.43 (s, 1H, NH, D_2O exchangeable). MS *m*/*z* (%): 338 (M^+ + 2; 13). Analysis: calcd. for $C_{22}H_{16}N_4$ (336.39): C, 78.55; H, 4.79; N, 16.66%; found: C, 78.72; H, 4.85; N, 16.53%.

General procedure for synthesis of compounds 13a-c

A solution of the hydrazinyl derivative **12** (3.5 g, 10 mmol) and the appropriate monosaccharides namely: D-arabinose, D-xylose or D-galactose (10 mmol) in ethanol (30 mL) containing a catalytic amount of glacial acetic acid (3 drops) was heated with continuous stirring at 80°C for 2 h. The formed precipitate was filtered off, dried and recrystallized from ethanol to give compounds **13a-c**.

2-D-Arabinose-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (13a)

Yield: 63%; m.p. 222-224°C, IR (KBr, cm^{-1}): 3439–3220 (broad, OH + NH), 2216 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.32–3.48 (m, 3H, protons of the alditol congregated with the solvent absorption), 3.71–3.79 (m, 2H, *C*H_2OH), 4.26–5.00 (m, 4H, 4OH, D_2O exchangeable), 7.00 (s, 1H, pyridine-

H5), 7.09–7.96 (m, 13H, Ar-H + NH), 8.35 (s, 1H, N=CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 64.5, 66.1, 70.1, 71.6, 72.5 (monosaccharide-C), 111.2 , 117.3, 124.4, 125.3, 126.2, 127.2, 129.1, 128.6, 132.1, 134.4, 135.7, 146.1, 153.2, 157.1, 165.2 (aromatic-C). MS *m*/*z* (%): 468 (M^+ 34). Analysis: calcd. for $C_{27}H_{24}N_4O_4$ (468.50): C, 69.22; H, 5.16; N, 11.96%; found: C, 69.30; H, 5.31; N, 12.09%.

2-D-Xylose-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (13b)

Yield: 52%; m.p. 294-296°C, IR (KBr, cm^{-1}): 3445–3219 (broad, OH + NH), 2219 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 3.27–3.52 (m, 3H, protons of the alditol congregated with the solvent absorption), 3.68–3.83 (m, 2H, CH_2OH), 4.37–5.05 (m, 4H, 4OH, D_2O exchangeable) 7.00 (s, 1H, pyridine-H5), 7.01–7.90 (m, 13H, Ar-H + NH), 8.30 (s, 1H, N=C*H*). MS *m*/*z* (%): 468 (M^+ 25). Analysis: calcd. for $C_{27}H_{24}N_4O_4$ (468.50): C, 69.22; H, 5.16; N, 11.96%; found: C, 69.41; H, 5.00; N, 11.87%.

2-D- Galactose -6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (13c)

Yield: 54%; m.p. 276-278°C., IR (KBr, cm^{-1}): 3451–3229 (broad, OH + NH), 2220 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): δ 3.24–3.41 (m, 4H, protons of the alditol congregated with the solvent absorption), 3.63–3.74 (m, 2H, CH_2OH), 4.19–5.12 (m, 5H, 5OH, D_2O exchangeable), 7.10 (s, 1H, pyridine-H5), 7.22–8.12 (m, 13H, Ar-H+ NH), 8.39 (s, 1H, N=C*H*). MS *m*/*z* (%): 498 (M^+ 37). Analysis: calcd. for $C_{28}H_{26}N_4O_5$ (498.53): C, 67.46; H, 5.26; N, 11.24%: found: C, 67.30; H, 5.09; N, 11.03%.

2-Azido-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (14)

A solution of compound **12** (3.5 g, 10 mmol) in acetic acid (30 mL) was treated with 10% sodium nitrite solution (2.76 g, 40 mmol) which was added dropwisely at -5°C with continuous stirring for 1 h. The solid product was filtered off and recrystallized from ethanol to obtain the azido analogue **14**.

Yield 65%; m.p. 156-158°C. IR (KBr, cm^{-1}): 2240 (azido gruop), 2210 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.21 (s, 1H, pyridine-H5), 7.59-8.06 (m, 12H, Ar-H). MS *m*/*z* (%): 347 (M^+ 10). Analysis: calcd. for $C_{22}H_{13}N_5$ (347.37): C, 76.07; H, 3.77; N, 20.16%; found: C, 76.21; H, 3.68; N, 20.01%.

General procedure for synthesis of compounds 15-17

An ethanolic solution of sodium ethoxide (prepared by dissolving 0.56 g of Na in 100 mL of dry ethanol) was added in one portion to an ice-cold solution of compound **14** (3.47 g, 10 mmol) and an active methylene compound (malononitrile, thioglycolic acid or ethyl acetoacetate) (10 mmol). The mixture was stirred at room temperature for two days, the solvent was evaporated *in vacuo*, and the concentrated ethanol solution was then poured into cold water. The corresponding products were collected by filtration and recrystallized from ethanol to give the corresponding derivatives **15**-**17**.

2-(5-Amino-4-cyano-1H-1,2,3-triazol-1-yl)-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (15)

Yield: 70%; m.p. 163-165°C. IR (KBr, cm^{-1}): 3420, 3325 (NH_2), 2212 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.67 (s, 2H, NH_2, D_2O exchangeable), 7.04 (s, 1H, pyridine-H5), 7.11-8.12 (m, 12 H, Ar-H). MS *m*/*z* (%): 413 (M^+ 13). Analysis: calcd. for $C_{25}H_{15}N_7$ (413.43): C, 72.63; H, 3.66; N, 23.72%; found: C, 72.96; H, 3.42; N, 23.61%.

2-(5-Hydroxy-4-mercapto-1H-1,2,3-triazol-1-yl)-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (16)

Yield: 62%; m.p. 176-178°C. IR (KBr, cm^{-1}): 3450 (OH), 2220 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 5.67 (s, 1H, SH, D_2O exchangeable), 7.23-7.99 (m, 13H, Ar-H + pyridine H-5), 10.01 (s, 1H, OH, D_2O exchangeable). MS *m*/*z* (%): 421 (M^+ 30). Analysis: calcd. for $C_{24}H_{15}N_5OS$ (421.47): C, 68.39; H, 3.59; N, 16.62; S, 7.61%; found: C, 68.55; H, 3.74; N, 16.43; S, 7.39%.

Ethyl 1-[3-cyano-6-(2-naphthyl)-4-phenylpyridin-2-yl]-5-hydroxy-1H-1,2,3-triazole-4-carboxylate (17)

Yield: 67%; m.p. 168-170°C. IR (KBr, cm^{-1}): 3453 (OH), 1690 (C=O), 2226 (CN); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.01 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 4.21 (q, *J* = 7.6 Hz, 2H, CH_2 CH_3), 7.13 (s, 1H, pyridine-H5), 7.21-8.11 (m, 12 H, Ar-H), 10.11 (s, 1H, OH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 14.1, 60.2 (CH_2CH_3), 111.1, 117.1, 121.1, 124.3, 125.2, 126.3, 127.1, 128.3, 129.5, 132.1, 133.1, 134.2, 135.3, 138.3, 138.9, 146.2, 154.2, 159.2 (aromatic-C), 167.3 (C=O). MS *m*/*z* (%): 461 (M^+ 25). Analysis: calcd. for $C_{27}H_{19}N_5O_3$ (461.47): C, 70.27; H, 4.15; N, 15.18%; found: C, 70.48; H, 3.95; N, 15.25%.

General procedure for synthesis of compounds 18a,b

A mixture of the hydrazinyl derivative **12** (3.5 g, 10 mmol)**,** the appropriate isothiocyanate namely: ethyl isothiocyanate and phenyl isothiocyanate (10 mmol) in DMF (15 mL) containing few drops of tri-

ethylamine was refluxed for 12 h. The solvent was evaporated under reduced pressure and the obtained solid was filtered off and recrystallized from isopropanol to give the desired compounds **18a**,**b**, respectively.

N'-[3-cyano-6-(2-naphthyl)-4-phenylpyridin-2-ylamino] propanethiohydrazide (18a)

Yield: 65%; m.p. 266-267°C. IR (KBr, cm^{-1}): 3445-3345 (3NH), 2210 (CN); 1180 (C=S). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.11 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 4.11 (q, *J* = 7.1 Hz, 2H, CH_2 CH_3), 7.15 (s, 1H, pyridine-H5), 7.23-7.98 (m, 12H, Ar-H), 9.43, 9.51, 10.00 (3s, 3H, 3NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 15.00, 36.7 (CH_2CH_3), 116.1, 117.1, 120.1, 124.3, 125.8, 126.3, 127.0, 128.3, 129.3, 132.2, 134.4, 135.6, 156.1 (aromatic-C), 158.5 (C=S). MS *m*/*z* (%): 423 (M^+ 25). Analysis: calcd. for $C_{25}H_{21}N_5S$ (423.53): C, 70.90; H, 5.00; N, 16.54; S, 7.57%; found: C, 70.76; H, 5.22; N, 16.41; S, 7.69%.

N'-[3-cyano-6-(naphthalen-2-yl)-4-phenylpyridin-2-ylamino]benzothiohydrazide (18b)

Yield: 34%; m.p. 271-273°C. IR (KBr, cm^{-1}): 3440-3335 (3NH), 2210 (CN), 1665 (C=S); ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.02 (s, 1H, pyridine-H5), 7.11-8.00 (m, 17H, Ar-H), 9.43, 9.51, 10.00 (3s, 3H, 3NH, D_2O exchangeable). MS *m*/*z* (%): 471 (M^+ 30). Analysis: calcd. for $C_{29}H_{21}N_5S$ (471.58): C, 73.86; H, 4.49; N, 14.85, S, 6.80%; found: C, 73.69; H, 4.81; N; 15.06, S, 7.00%.

General procedure for synthesis of compounds 19, 20

To a solution of compound **12** (3.5 g, 10 mmol) in acetic acid, maleic anhydride or phthalic anhydride (10 mmol) was added. The mixture was refluxed for 8 h, then poured onto ice/H_2O. The formed precipitate was filtered off, washed with water and recrystallized from dioxane to give the corresponding derivatives **19**, **20**.

2-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-ylamino)-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (19)

Yield: 69%; m.p. 292-294°C. IR (KBr, cm^{-1}): 3410 (NH), 2217 (CN), 1701 (2C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.99 (s, 1H, pyridine-H5), 7.16-8.01 (m, 14 H, Ar-H), 9.11 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 116.2, 117.1, 124.1, 125.6, 126.2, 127.1, 129.3, 128.1, 132.4, 134.5, 135.2, 136.0, 138.2, 145.2, 156.1 (aromatic-C), 158.9, 164.0 (2C=O). MS *m*/*z* (%): 416 (M^+ 61). Analysis: calcd. for $C_{26}H_{16}N_4O_2$ (416.43): C, 74.99; H, 3.87; N, 13.45%; found: C, 75.12; H, 3.96; N, 13.61%.

2-(1,3-Dioxoisoindolin-2-ylamino)-6-(2-naphthyl)-4-phenylpyridine-3-carbonitrile (20)

Yield: 65%; m.p. > 300°C. IR (KBr, cm^{-1}): 3410 (NH), 1698 (2C=O); ^{1}H-NMR (DMSO-d_6, δ, ppm): 7.02 (s, 1H, pyridine-H5), 7.29-8.22 (m, 16 H, Ar-H), 9.11 (s, 1H, NH, D_2O exchangeable). MS *m*/*z* (%): 466 (M^+ 27). Analysis: calcd. for $C_{30}H_{18}N_4O_2$ (466.49): C, 77.24; H, 3.89; N, 12.01%; found: C, 77.02; H, 4.00; N, 12.21%.

Antimicrobial assay

Preparation of microbial suspensions

Antimicrobial activities were carried out against highly pathogenic strains; two Gram positive bacteria *(Staphylococcus aureus, Bacillus cereus*), two Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) and two mycotic strains (*Candida albicans*, *Asprigillus niger*) isolated from minced meat. Agar disk diffusion (qualitative method) and minimum inhibitory concentration (MIC) (quantitative method) were used in this study. Suspensions of bacterial and mycotic isolates were freshly prepared by inoculating fresh stock culture from each strain into separate broth tubes, each containing 7 mL of Mueller Hinton broth for bacterial strains and Sabouraud dextrose broth for mycotic strains. The inoculated tubes were incubated at 37°C and 28°C for 24 h, respectively. Serial dilutions were carried out for each strain, dilution matching with 0.5 Mc-Farland standard (about 1×10^8 cells/mL), was selected for screening of antimicrobial activities. Ciprofloxacin 100 µg/mL and fluconazole 100 µg/mL were used as reference drugs (Oxoid). DMSO was used as a negative control.

Determination of antimicrobial activity by disk-diffusion method

Mueller Hinton and Sabouraud dextrose agar plates were prepared. Bacterial and fungal strains matching with 0.5 Mc-Farland standard were spread onto the surface of the agar plates using sterile cotton swabs. For evaluation of antibacterial activities, Whatman no. 1 filter paper disks were saturated with 50 µL of the compound dissolved in DMSO (100 µg of the tested compound dissolved in 1 mL DMSO), others were saturated with 50 µL ciprofloxacin (100 µg/mL) and others with 50 µL DMSO as a negative control. The same method was used for evaluation of the antimycotic activities using fluconazole (100 µg/mL)**.** Disks were dried and then placed onto inoculated agar plates and left for 1 h at 25°C to allow a

period of pre-incubation diffusion in order to minimize the effects of variation in time between the applications of different solutions. The plates were reincubated at 37°C and 28°C for 24 h for bacterial and mycotic isolates, respectively. After incubation, plates were observed for antimicrobial activities by determining the diameters of the zones of inhibition for each of the samples. For an accurate analysis, tests were run in triplicate for each strain to avoid any error.

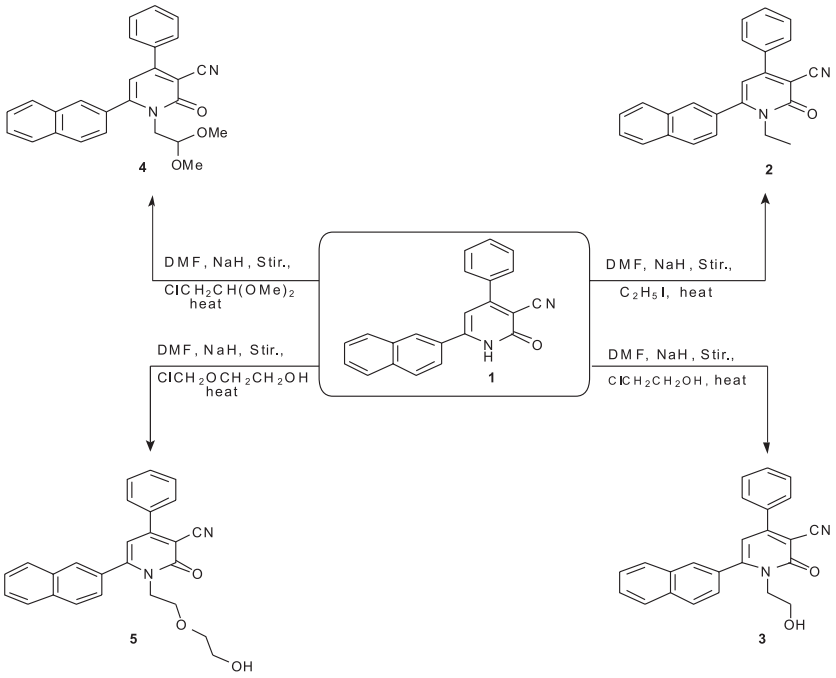
Determination of minimum inhibitory concentration (MIC)

Microtiter dilution plate quantitative method i.e., the minimum inhibitory concentration (MIC) was used for evaluation of the antimicrobial activity of tested compounds. Determination of MIC of extract against tested strains was achieved using 96-well sterile micro plates. The first well contains the concentrated form of the tested compound used in the agar disk diffusion method (100 µg of the tested compound dissolved in 1 mL DMSO), then, twofold serial dilutions was carried out for the tested compounds, reference drugs (ciprofloxacin and fluconazole) and DMSO. Then, wells were inoculated with 100 µL of tested isolates (0.5 Mc-Farland standard, about 1×10^8 cells/mL) and incubated at 37°C and 28°C for 24 h for bacterial and fungal strains, respectively. After incubation, plates were examined visually for bacterial or fungal growth precipitation. The experiment was repeated three times. The lowest concentration that showed complete inhibition of growth was taken as MIC.

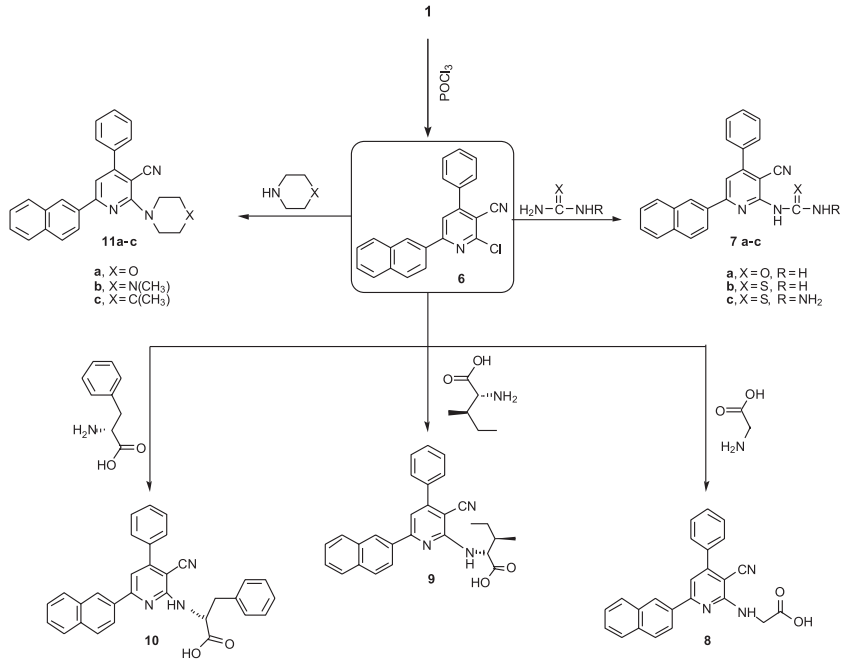
RESULTS AND DISCUSSION

Chemistry

In this investigation, 4-phenyl-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile **1** (17) was utilized as a key starting material in the synthesis of different novel heterocyclic compounds. A series of respective *N*-acyclic nucleosides **2-5** were synthesized by condensing the sodium salt of compound **1** (generated in situ) with either ethyl iodide, 2-chloroethanol, 2-chloro-1,1-dimethoxyethane or 2-(2-chloroethoxy)ethanol in hot DMF (Scheme 1). Nucleophilic attack was carried out on the nitrogen atom of the parent derivative **1**, not on the oxygen atom. The structures of the aforementioned series were confirmed on the basis of microanalytical and spectral data. As an example, IR spectra exhibited absorption bands at 2223-2210 and 1668-1655 cm^{-1} due to the presence of CN and C=O groups, respectively. Regarding the ^{1}H-NMR spec-



Scheme 1. Synthesis of compounds **2-5**

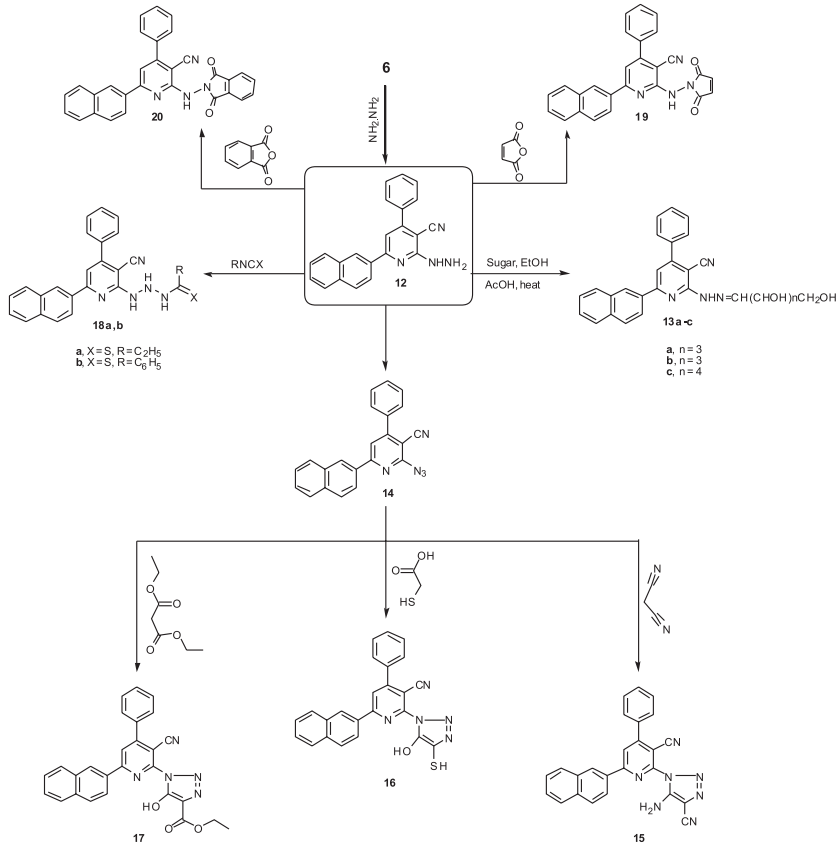


Scheme 2. Synthesis of compounds **6**-**11**

tra of the analogues, that of **3**, exhibited two triplet signals at δ 3.75 and 4.61 ppm due to 2 CH_2 protons of the alkyl side chain, in addition to a singlet signal at δ 5.39 ppm exchangeable with D_2O representing OH proton. Also, ^{1}H-NMR spectrum of the analogue **4** revealed the presence of a singlet signal at δ 3.75 ppm due to 6H of 2OCH_3 groups, while N-CH_2-CH protons of the acyclic sugar part appeared as a doublet-triplet pattern at δ 4.06 and 4.62 ppm. With respect to ^{1}H-NMR spectrum, the analogue **5** showed two triplets at δ 2.19, 3.01 ppm and multiplet signals at δ 3.68 ppm due to 8H of 2 –CH_2-CH_2- groups of the acyclic sugar side chain. The other expected protons of the molecules appeared at their suitable regions.

As the chloro derivatives are good precursors for the synthesis of different new heterocyclic analogues due to their reactivity towards many types of nucleophiles, especially the nitrogen and oxygen nucleophiles (18, 19), the starting pyridone compound **1** was converted to the chloro analogue **6** by its refluxing with a mixture of phosphorus oxychloride/phosphorus pentachloride for 3 h. IR spectrum of **6** showed the disappearance of absorption band of C=O group and the presence of the characteristic absorption band of CN group at 2217 cm^{-1}. Nucleophilic replacement of chlorine atom of **6** was performed by its reaction with urea, thiourea and thiosemicarbazide in boiling ethanol containing a catalytic amount of triethylamine to get the substituted urea, thiourea and thiosemicarbazide derivatives **7a**-**c**, respectively. The IR spectra of the resultant compounds exhibited absorption bands at 3440-3245 cm^{-1} representing NH, NH_2 groups, at 1665 cm^{-1} due to C=O group of compound **7a** and at 1160-1140 cm^{-1} due to C=S groups of **7b**,**c**. Mass spectra showed the molecular ion peaks of the derivatives **7a**-**c** at m/e 364, 380 and 396, respectively. Further nucleophilic displacement was carried out by heating the chloro derivative **6** with different secondary alicyclic amines such as: morpholine, 4-methylpiperazine and 4-methylpiperidine in boiling ethanol for 12 h to afford the corresponding amino analogues **11a**-**c**. Microanalyses and spectral data of **11a**-**c** were in agreement with their structures.

Since the α-carboxyl and α-amino groups of all amino acids exhibit characteristic chemical reactivity, this investigation represented the interaction of the chloro derivative **6** with different amino acids: glycine, isoleucine and phenylalanine in the presence of Na_2CO_3 as a catalytic base at pH 9-9.5 (20) to get the naphthyl-pyridine amino acid derivatives



Scheme 3. Synthesis of compounds **12**-**20**

8-**10**, respectively. Regarding the IR spectra of the newly synthesized derivatives, they showed broad absorption bands at the region 3448-3234 cm^{-1} due to OH and NH groups and at 1701-1680 cm^{-1} assigned for C=O groups of the amino acid side chain. Mass spectra represented the molecular ion peaks at m/e 379, 435 and 469, respectively.

Hydrazinolysis of the intermediate chloro derivative **6** was carried out by its reaction with excess hydrazine hydrate in refluxing dioxane to get the hydrazine analogue **12**. The IR spectrum of the latter derivative exhibited the characteristic absorption bands of NH_2 and NH at 3440 and 3240 cm^{-1}. Compound **12** was considered as the parent derivative for the synthesis of novel hydrazones and heterocyclic ring systems. Thus, compound **12** was allowed to react with some mono saccharides namely: D-arabinose, D-xylose and D-galactose in ethanol containing a catalytic amount of glacial acetic acid, to yield the corresponding hydrazone derivatives **13a**-**c**. IR spectra of these derivatives were characterized by the appearance of broad absorption bands of OH and NH groups at the range 3451-3219 cm^{-1}, while HC=N group appeared at 1590 cm^{-1}. ^{1}H-NMR spectra revealed the alditol protons of the sugar part as multiplet signals at δ 3.24–3.41 ppm, OH protons as multiplet signals at δ 4.19–5.00 ppm, while the aromatic and NH protons were represented as multiplet signals at δ 7.09-8.12 ppm. Azomethine protons CH=N- were detected as singlet signals at δ 8.35 ppm.

Furthermore, the treatment of **12** with the sodium nitrite in acetic acid yielded the corresponding azide derivative **14.** Its IR and ^{1}H-NMR spectra were free from the bands and signals of NH and NH_2 groups. The reaction of compound **14** with active methylene derivatives namely: malononitrile, thioglycolic acid and diethylmalonate in sodium ethoxide solution afforded the corresponding triazolo derivatives **15**-**17** (Scheme 3). The structures of the latter derivatives were confirmed depending upon their elemental analyses and spectral data. For example, the IR spectra of compounds **15** and **16** indicated the presence of absorption bands at 3450,

3420 and 3325 cm^{-1} of OH and NH_2 groups, respectively. ^{1}H-NMR spectrum of **17** revealed the triplet-quartet pattern of the ethyl group at δ 1.01 and 4.21 ppm, in addition to the other protons of the molecule that appeared at their expected regions. Also, considering mass spectra of **15**, **16** and **17**, they exhibited their molecular ions peaks at m/e 413, 421 and 461, respectively.

On the other hand, condensation of the parent hydrazinyl derivative **12** with ethyl (phenyl) isothiocyanate in dry DMF in the presence of a catalytic amount of triethylamine afforded the corresponding substituted thiosemicarbazide derivatives **18a**,**b**. The IR spectra of the resultant compounds indicated the appearance of three bands in the range 3445-3335 cm^{-1} due to 3 NH groups. The molecular ion

Table 1. Agar well diffusion method showing antimicrobial activities of the tested compounds compared with the reference drugs, results given in millimeters.

Strains → **Samples ↓**	*S. aureus*	*B. cereus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
2	-ve	-ve	12	-ve	-ve	-ve
3	9s	18	18	18s	19	-ve
4	-ve	12	17	-ve	-ve	-ve
5	-ve	-ve	15	-ve	-ve	-ve
6	13	-ve	-ve	-ve	12	16
7a	11	12	11	10	-ve	10
7b	-ve	13	-ve	12	12	12
7c	11	12	-ve	-ve	-ve	10
8	18	-ve	21	-ve	15	12
9	12	-ve	-ve	-ve	-ve	-ve
10	-ve	-ve	-ve	-ve	-ve	-ve
11a	-ve	12	11	12	12	-ve
11b	13	16	19	14	15	12
11c	-ve	-ve	12	-ve	9	12
12	13	-ve	-ve	-ve	-ve	-ve
13a	-ve	-ve	12	-ve	-ve	-ve
13b	12	12	10	-ve	10	-ve
13c	17	20	21	11	20	19
14	19	14	17	15	16	18
15	17	15	17	17	15	11
16	19	15	17	12	16	15
17	14	14	13	17	14	14
18a	11	12	13	15	12	13
18b	26	23	20	29	10	22
19	15	-ve	12	-ve	-ve	12
20	20	16	20	13	16	-ve
Ciproflo-xacin 100 µg/mL	39	38	42	37	ND	ND
Fluconazole 100 µg/mL	ND	ND	ND	ND	32	31
Control negative (DMSO)	-ve	-ve	-ve	-ve	-ve	-ve

ND = not defined, -ve = indicates that the tested compound did not show any inhibition against the tested isolate.

Table 2. Minimum inhibitory concentration showing antimicrobial activities of the tested compounds compared with reference drugs, results given in µg/mL.

Strains → **Samples ↓**	*S. aureus*	*B. cereus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
2	ND	ND	100	ND	ND	ND
3	-ve	12.5	12.5	-ve	12.5	ND
4	ND	100	12.5	ND	ND	ND
5	ND	ND	50	ND	ND	ND
6	100	ND	ND	ND	100	50
7a	-ve	100	-ve	100	100	100
7b	-ve	100	-ve	100	100	100
7c	-ve	100	ND	ND	ND	-ve
8	12.5	ND	6.125	ND	50	100
9	100	ND	ND	ND	ND	ND
10	ND	ND	ND	ND	ND	ND
11a	ND	100	100	100	100	ND
11b	100	50	12.5	50	50	100
11c	ND	ND	100	ND	-ve	100
12	100	ND	ND	ND	ND	ND
13a	ND	ND	100	ND	ND	ND
13b	100	100	-ve	ND	-ve	ND
13c	25	6.25	3.125	100	6.25	12.5
14	12.5	50	25	50	25	12.5
15	25	50	25	25	50	100
16	12.5	50	25	100	25	50
17	50	50	100	25	50	50
18a	100	100	100	50	100	100
18b	3.125	3.125	6.25	1.56	-ve	3.125
19	50	ND	100	ND	ND	100
20	6.25	50	6.25	100	25	ND
Ciproflo-xacin 100 µg/mL	1.56	1.56	0.78	1.56	ND	ND
Fluconazole 100 µg/mL	ND	ND	ND	ND	1.56	1.56
Control negative (DMSO)	-ve	-ve	-ve	-ve	-ve	-ve

ND = not defined, -ve = indicates that the tested compound did not show any inhibition against the tested isolate.

peaks of the derivatives in their mass spectra appeared at m/e 423 and 471, respectively.

Further condensation reaction was carried out by the reaction of the hydrazinyl derivative **12** with different acid anhydrides, namely: maleic and phthalic anhydrides in glacial acetic acid to achieve the corresponding derivatives **19** and **20**. The IR spectra of both derivatives showed the carbonyl stretching bands at 1702-1698 cm^{-1}, in addition to NH and CN stretching bands at 3440-3410 and 2217-2210 cm^{-1}, respectively. The ^{1}H-NMR spectrum of **19** revealed the presence of two doublets at δ 6.12 and 6.32 ppm attributed for the vinylic protons, in addition to a singlet signal at δ 9.11 ppm attributed to NH proton.

Biological evaluation

All the newly synthesized compounds were screened for their *in vitro* antibacterial activity against two strains of Gram positive bacteria *(Staphylococcus aureus, Bacillus cereus*), and two strains of Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) using ciprofloxacin as a standard drug (100 µg/mL). They were also evaluated for their *in vitro* antifungal activity against the mycotic strains (*Candida albicans* and *Aspergillus niger*) using fluconazole as a standard antifungal drug (100 µg/mL). Agar-diffusion method (21) was used in this investigation for determination of the preliminary antibacterial and antifungal activity and the results were recorded for each tested compound as the average diameter of inhibition zones (IZ) of bacterial or fungal growth around the discs in mm (Table 1).

The minimum inhibitory concentrations (MIC) were determined for compounds showing promising growth inhibition, using the twofold serial dilution method (22). The MIC (µg/mL) values against the tested bacterial and fungal isolates are presented in Table 2.

According to the data obtained in Tables 1 and 2, it is clear that the best antimicrobial activity against both tested bacterial and fungal strains was gained by compound **18b** which bears the parent naphthyl-pyridine nucleus attached to benzothiohydrazide side chain, giving zones of inhibition and MIC values very close to those obtained by the reference drugs ciprofloxacin and fluconazole. The antibacterial potency against *P. aeruginosa* of the same derivative was equipotent to ciprofloxacin (MIC; 1.56 µg/mL), while the values of the zones of inhibition and MIC of the other ethyl thiosemicarbazide analogue **18a** were much higher than those of the standard drugs indicating lower antibacterial and antimycotic activity. At the same time, promising activity was shown by derivative **20** that carries naphthyl-pyridine nucleus attached to phthalic anhydride moiety, but the antimicrobial activity was reduced to a large extent by the other derivative bearing maleic anhydride moiety. Furthermore, the resultant data exhibited that the intermediate hydrazinyl derivative **12** was inactive as antibacterial and antifungal agent against the tested strains, while its conversion to the azido derivative **14** and the cyclized triazolo derivatives **15**, **16** and **17** increased both antibacterial and antifungal potency but still less than the standard drugs. The formation of hydrazone derivatives bearing the aldoses: D-arabinose and D-xylose gave the inactive or slightly active compounds **13a**,**b**, respectively. However, the hydrazone analogue carrying D-galactose (**13c**) exhibited good antimicrobial potency comparing to the reference drugs. In addition, the zone of inhibition and MIC values of the intermediate chloro derivative **6** and its thiosemicarbazide analogues **7a**-**c** represented weak antimicrobial activity. Also, approximate weak or complete loss of activity was obtained by the amino acid derivatives **8**-**10**. The *N*-acyclic nucleosides **2**, **4**, **5** were inactive analogues, while the derivative **3** that bears 2-ethanol side chain exhibited good antimicrobial activity.

According to these results, more modifications are required for designing and synthesis of new lipophilic derivatives (23) of more potency as antibacterial and antifungal compounds.

CONCLUSION

In this study, 4-phenyl-6-(naphthalen-2-yl)-2-oxo-1,2-dihydropridine-3-carbonitrile **1** was used to synthesize novel series of *N*-acyclic nucleosides **2**-**5**, urea, thiourea and thiosemicarbazide derivatives **7a**-**c**, various amino acid analogues **8**-**10**, hydrazones **13a**-**c** and other different heterocyclic derivatives **14**-**20** to examine their antimicrobial potency against a number of bacterial and mycotic strains. The obtained data indicated that most of these derivatives showed moderate activity, while the benzothiohydrazide compound **18b** followed by the hydrazone and the phthalic anhydride derivatives **13c** and **20** exhibited promising antibacterial and antifungal potency in comparison to the standard drugs ciprofloxacin and fluconazole.

Acknowledgment

The authors are grateful for National Research Centre for its support of this work

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Received: 30. 08. 2012