Synthesis and Some Reactions of Some New Benzofuran Derivatives with Possible Biological Activity

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Abstract: 3-[4-Methoxy-6-hydroxy-5-benzofuranyl] and 3-[4,6-dimethoxy-5-benzofuranyl] 1,3-diketo byrate **(1a,b)**[1] were obtained from the reaction of [4-hydroxy (or methoxy) benzofuran-5-yl] methyl ketone **($A_{a,b}$)** with ethyl acetate in presence of sodium metal. **(1a,b)** were reacted with α-cyanothioacetamide in the presence of ammonium acetate[2] to give mercapto-3-carbonitrile-4-methyl-6-[4-methoxy-6-hydroxy-5-benzofuranyl] pyridine **(2a)** and 2-mercapto-3-carbonitrile-4-methyl-6-[5,6-dimethoxy-5-benzofuranyl] pyridine **(2b)** (or possible isomers **(3a,b)** respectively for the preparation of some novel benzofuran derivatives **(4a,b), ($5_{a,b}$), ($6_{a,b}$), ($7_{a,b}$), (8_{a-d}), ($9_{a,b}$)** and **($10_{a,b}$)**. On the other hand sterylketone **(11_{a-c})** were obtained by condensation of **($A_{a,b}$)** with aromatic aldehyde. Compounds **($11_{b,c}$)** gave new benzofuran derivatives **($12_{a,b}$), (13), (15), (16)** and **(17)**. Selected members of the prepared compounds were screened for antimicrobial and antifungal activities.

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Keywords: New benzofuran derivatives are starting material for the preparation of heterocyclic compounds containing benzofuran moieties.

1. Introduction

The benzofuran ring system itself is a common structure element that appears in a large number of medicinally important compounds[3]. The benzofuran nucleus is widely distributed in nature products particularly among plant kingdom. In the chemistry of benzofuran in a large number of natural as pharmacological agents[4]. Benzofuran derivatives are known to possess hypotensive, vasodilating and spasmolytic activities[5]. Moreover, some derivatives are used as anti-inflammatory, anlagen[6,7] and antihistaminic drugs[8-11]. In addition of that some benzofuran derivatives show antibacterial activity as well as antiparasitic properties[12,13], anti-HIV activities[14], antitubercular activity[15], antidiabetic activity[16], antidepressant activity[17], anti-oxidant activity[18], anticonvulsant activity[19], analgesin activity[20], antimicrobial activity[21-24], antitumor[25,26], antifungal[27,28] and anticonvulsant[29]. Furthermore, recent studies showed that benzofuran ring system fused with heterocyclic moieties exhibit a wide spectra of pharmacological activities and especially antitumor activity[30-31].

The aim of the present investigation is to synthesize some new benzofuran derivatives with expected biological activity.

2- Experimental:

Melting point were recorded on a Stuart melting point apparatus. Infrared spectra were recorded on a Shimadyu 440, infrared spectrophotometer (Shimadzu) Japan, using KBr-technique, ^{1}HNMR spectra were recorded on a BRUKER proton NMR Advance 300 (300M Hz) in DMSO-d_6 or $CDCl_3$ as solvent using (TMS) as internal standard. Mass spectra were run on HP model MS-5988. Elemental analysis is determined on a Perkin Elmer, 240 (microanalysis). Microanalytical laboratory, Cairo, University, Giza, Egypt.

Synthesis of Ethyl-3-Carbonitrile-4,6-disubstituted pyridine-2-ylthioacetic ester ($4_{a,b}$):

A mixture of (2a,b) or its isomer (3a,b) (0.01 mol), ethyl chloroacetate (0.01 mol) and fused sodium acetate (0.03 mol in dry acetone (30 ml) was refluxed on a water-bath for 8hrs. The reaction mixture was cooled and poured into water. The resultant solid was filtered, washed with water, dried and recrystallized to give **($4_{a,b}$)**

Compound **4_a** m.p. 168°-169°C yield 62%, crystallized from ethanol. The IR (KBr) spectrum of **4_a** showed strong absorption bands at 3189 (OH),1747(>C=O)of ester), 2213 (C≡N) and 1614cm^{-1} (>C=N)cm^{-1}. Mass spectrum (m/z, relative intensity), 398 (M^+, 86), 399 (M^++1,48) 325 (M^+–$COOC_2H_5$, 83), 310 (M^+–$C_4H_8O_2$, 18). Anal. calcd. for **4a** $C_{20}H_{18}N_2O_5S$ (398.26); C, 60.26; H, 4.52; N, 7.03; S, 8.03. Found, C, 60.32; H, 4.70; N. 7.10; S, 8.30.

Compound **4_b** m.p. 240-242°C yield 55% crystallized from ethanol. ^{1}H-NMR of **4_b** (DMSO): showed signals at δ 1.95 (s, 3H, CH_3), 2.35 (t, 3H, $CH_2.CH_3$), 3.37 (s, 6H, $2OCH_3$), 3.6-3.8 (m, 4H, SCH_2 and CH_2–CH_3), 6.6 (d, J=2.1 Hz, 1H, CH_{-1} of furan moiety), 7.2 (s, 2H, 1H of pyridine and 1H of benzofuran moieties and 7.6 (d, J = 2.1 Hz, 1H, H_{-2} of furan moiety). Anal. calcd for **4_b** ($C_{21}H_{20}N_2O_5S$)

(412.27) C, 61.18; H, 4.82; N, 6.79; S, 7.76. Found C, 61.17; H, 5.02; N, 7.0; S, 7.78.

Synthesis of 3- Carbonitrile-4,6-disubstituted -2-pyridine thioacetyl hydrazine (5_{a-b}) and (7_{a-b}):

A solution of (0.01 mol) of **($4_{a,b}$)** and hydrazine hydrate (0.01 mol) in ethanol (30 ml) was heated under reflux for 6hr. The product obtained after cooling was filtered, dried and recrystalized to give **(5_{a-b})** and **(7_{a-b})** respectively.

Compound **5_a**m.p. 240-241°C, yield 55% crystallized from benzene. IR (KBr) spectra of **5_a** showed strong absorption bands at 3348 (OH), 3433-3284 (NH_2/NH) 2203, (C≡N) and, 1663 (>C=O amide) cm^{-1}. Anal. calcd for **5a** $C_{18}H_{16}N_4O_4S$ (384.26); C, 56.21; H, 4.16; N, 14.57; S, 8.33. Found C, 56.28; H, 4.01; N, 14.62; S, 8.23.

Compound **5_b** m.p. 210°-212°C, yield 50% crystallized from ethanol. IR (KBr) spectra of **5_b**showed 3433-3284 (NH_2/NH) 2203, (C≡N) and 1663 (>C=O) amide cm^{-1}**.** Anal**.** calcd for **5_b** $C_{19}H_{18}N_4O_4S$ (398.27); C, 57.25; H; 4.52; N, 14.06, S, 8.03. Found C, 57.40; H, 4.60; N, 14.08; S, 8.05.

Compound **7_a**m.p. 80°-81°C yield 50% crystallized from P.E. 60-80.

Mass spectrum of **7_a** (m/z, relative intensity): 460 (M^+ , 65%), 461 (M^+ H, 42%), 383 (M^+–C_6H_5, 18%), 352 (M^+–$C_6H_8N_2$, 10%), 279(M^+–$C_8H_9N_2SO$, 27%), 264 (M^+–$C_9H_{12}N_2SO$, 35%), 162 (M^+–$C_{15}H_{13}NOS$, 10%).**7_a** Anal., calcd. for **7_a**$C_{24}H_{20}N_4O_4S$ (460.32; C, 62.57; H, 4.3; N, 12.17; S, 6.95. Found , C, 62.71; H, 4.51; N, 12.00; S, 7.02.

Compound **7_b**m.p. 200 210°C yield 60% crystallized from ethanol.The IR (KBr) spectrum of **7_b** showed strong absorption at 3147 (NH), 2207 (C≡N), 1630 (>C=O) and 1597 (>C=N) cm^{-1}. Anal., calcd. for **7_b** $C_{25}H_{22}N_4O_4S$ (474.33), C, 63.25; H, 4.64; N, 11.81; S, 6.75. Found, C, 63.41; H, 4.70; N, 12.00; S, 6.80.

Synthesis of 3-Carbonitrile-4,6-disubstituted -2-pyridinyl thioacetyl thiosemcarbazide (6a-b):

Equimolar quantities of **(5_{a-b})** (0.01 mol) and phenyl isothiocyanate (0.01 mol) were refluxed in absolute ethanol (50 ml) for 3hrs. The excess of solvent was removed. The solid mass obtained was washed with ice cold ethanol, dried and recrystalized to give (6_{a-b}).

Compound **6_a**m.p. 250-252°C, yield55% crystallized from ethanol. IR (KBr) spectrum of **6_a** appeared broad band at 3330 (OH/NH), strong band at 3194 (NH), 2210 (C≡N), 1660 (C=O), 1598 (>C=N) and 1376 (C=S). ^{1}H-NMR (DMSO): δ 1.36 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 4.3(s, 2H, SCH_2), 6.87 (d, J=2.2Hz, 1H, H_{-3} of furan moiety), 7.0-7.45 (m, 7H, 5H aromatic,1H, of pyridine and 1H of benzofuran moieties), 7.59 (d, J=2.2Hz. 1H, H_{-2} of furan moiety), 9.8 (br, s, 2H, NH CSNH), 9.97 (s, 1H, CONH) and 11.0 (s, 1H, OH, exchangeable with D_2O). Mass spectrum m/z 2358. ($M^+C_7H_8N_3S$ fragment) Anal. Calcd. for **6_a** $C_{25}H_{21}N_5O_4S_2$ (519.39), C, 57.8; H, 4.04; N, 13.48; S, 12.32. Found C, 58.01; H, 4.02; N, 13.5; S, 12.34.

Compound **6_b**m.p. 225-227°C yield 50% and crystallized from ethanol. IR (HBr) of **6_b**band 3300 for (NH) strong bands at 3194 (NH), 2210 (C≡N), 1660 (>C=O) 1590 (>C=N) and 1375(C=S). Anal.calcd**.** for **6_b** $C_{26}H_{23}N_5O_4S_2$ (533.34) C, 58.55; H, 4.31; N 13.13; S 12.00 , Found C, 58.61; H, 4.01; N, 13.3; S, 12.02.

Synthesis of *N*-Substiuted-2-amino-4,6-disubstituted pyridine-3-carbonitrile derivatives (8a-d).

A solution of **(2_{a-b})** or its isomer **($3_{a,b}$)** (0.01 mol) and a primary amine (aniline, p-toluidine) (0.01 mol) in ethanol (30 ml) was heated under reflux for 6hrs. The product obtained after cooling was filtered and air dried to give **(8_{a-d})**

Compound **8_a**crystallized from ethanol m.p. 160-161°C yield 75%. IR (KBr) for **8_a** showed strong adsorption bands at 3348 (OH), 3198 (NH), 2180 (C≡N) and 1620 (>C=N) cm^{-1}.Anal. Calcd. for **8_a** $C_{22}H_{17}N_3O_3$ (371.23) calcd. C, 71.14; H, 4.58; N, 11.32 Found C, 71.09; H, 4.70; N, 11.20.

Compound **8_b** m.p. 130-132°C, yield 70% crystallized from P.E. 80-100. ^{1}H-NMR spectrum of **8_b** in DMSO showed signals of δ 2.34 (s, 3H, CH_3), 3.34 (s,6H, $2OCH_3$), 6.6(d, J = 2H, 1H, H_{-3} of furan moiety), 6.8-7.7 (m, 8H, 5H aromatic, 1H pyridine, 1H benzofuran and 1H, H_{-2} furan moieties) and 10.6 (s, 1H, NH). Anal calcd. for **8_b** $C_{23}H_{19}N_3O_3$ (385.24) C, 71.64, H, 4.93; N, 10.91. Found C, 71.50; H, 5.20; N, 11.00

Compound **8_c**yield 50% m.p. 170-171°C crystallized from ethanol**.** IR (KBr) for compound **8_c** showed strong adsorption bands at 3360(OH), 3130(NH), 2183 (C≡N) and for (>C=N) at 1620cm^{-1}.Anal. calcd. for **8_c**$C_{23}H_{19}N_3O_3$ (385.24) H, 71.64; H, 4.93; N, 10.91 Found C, 71.40; H, 4.90; N, 11.00.

Compound **8_d**m.p.200-202°C, yield 50% crystallized from ethanol. The structure of **8_d** was established by IR (KBr) spectrum showed strong absorption bands at 3190 (NH), 2183 (C≡N) and 1618 (>C=N) Anal. calcd. for **8_d** $C_{24}H_{21}N_3O_3$ (399.24) C,

72.14; H, 5.26; N, 10.52 Found C, 72.01; H, 5.02; N, 10.50.

Synthesis of 2-Hydrazino-2-Phenyl hydrazine-4,6-disubstituted pyridine-3-carbonitrile derivatives (9a-b) and (10a-b)

A solution of **(2a-b)** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.01 mol) in ethanol (30 ml) was heated under reflux for 6hrs. The precipitate was filtered and recrystallized to give **($9_{a,b}$)** and **($10_{a,b}$)** respectively.

Compound **9_a**crystallized from ethanol m.p. 180-2°C yield 70%. IR of the compound **9_a**showed stretching frequency at 3300 (OH), 3121, 3188 (NH_2/NH), 2207 (C≡N) and 1627(>C=N) cm^{-1}.

The ^{1}H-NMR spectrum of **9_a** in (DMSO) showed signals at δ 2.3 (s, 3H, CH_3) 3.34 (s, 3H, OCH_3) 6.6 (broad s, 3H, NH, NH_2), 6.8 (d, J=Hz, 1H, H_{-3} furan moiety), 7.11 (s, 2H, 1 pyridine and 1H, benzofuran moieties), 7.7(d, J=2Hz, 1H, H_{-2} furan moiety) and 12 (broad s, 1H, OH, exchangeable with D_2O). Anal. calcd. for **9_a**$C_{16}H_{14}N_4O_3$(310.18),. C, 61.90; H, 4.50 N; 18.06. Found C, 62.00; H, 4.34; N, 18.0.

Compound **9_b** crystallized from methanol, m.p. 189-190°C, yield 65% IR of the compound **9_b** showed frequency at 3189, 3148 (NH_2, NH) 21.82 (C≡N) and 1600 (>C=N)Anal. calcd. for **9_b**$C_{17}H_{16}N_4O_3$ (324.19) C, 62.93; H, 4.93; N, 17.28 Found, C, 63.00; H, 5.00; N, 17.27.

Compound **10_a**crystallized from ethanol m.p. 150-152°C yield 55%. IR (KBr) showed 3325 (OH), 3121 (NH) 2180 (C≡N) and 1660 (>C=N) cm^{-1} Anal.calcd. for **10_a**$C_{22}H_{17}N_4O_3$ (385.24), C, 68.53; H, 4.41; N, 14.54 Found C, 68.70; H, 4.51; N, 14.21

Compound **10_b** crystallized from benzene m.p. 180-182°C yield 60%. Compound **10_b** IR showed bands at 3150 (NH), 2185 C≡N 1670 (C=N) cm^{-1} Anal**.** calcd. for **10_b**$C_{23}H_{19}N_4O_3$ (399.25) C, 69.11; H, 4.76; 14.03 Found C, 69.09; H, 4.90; N, 14.01.

Synthesis of 5-Cinnamoyl-4-methoxy-6-hydroxy (or methoxy) benzofuran (11a-c)

A mixture of compound **($A_{a,b}$)** (0.01 mole), aromatic aldehyde (0.0l mole) and triethylamine (5 ml) in ethanol (30 ml) was refluxed for one hour, then allowed to cool. The solid product was collected and recrystallized from suitable solvent to give **11_{a-c}.**

Compound **11_a**crystallized from methanol m.p. 119-121°C yield 75%, IR (KBr) spectrum of the compound **11_a** exhibited OH at 3402 (broad),C–H aliphatic at 2950 cm^{-1} and C=O at 1650cm^{-1}. Anal. calcd. for **11_a** $C_{22}H_{16}O_4$ (344.366) C, 76.66; H, 4.65. Found C, 76.71; H, 4.70.

Compound **11_b**crystallized from ethanol m.p. 230-231°C yield 70% IR spectrum of the compound **11_b**displayed bands C–H aromt. at 3000 C–H aliph. at 2930cm^{-1} (>C=O) at 1648 cm^{-1}. and (OH) at 3346 cm^{-1}, Anal. calcd. for **11_b** $C_{22}H_{16}O_4$ (344.366), C, 76.66; H, 4.65 Found C, 76.72; H, 4.69.

Compound **11_c**crystallized from ethanol m.p. 161-162°C yield 89%. IR of the compound **11_c** showed C–H aliphatic at 2924, 2850 and (>C=O) at 1640 cm^{-1} . ^{1}HNMR spectrum of **12_c** (DMSO-d_6)displayed singles δ 3.80, 4.01 (2s, 6H, $2OCH_3$). δ 77.10-8.2 (m, 12H, ArH + Olefinic and furan –H).

The mass spectrum of compound (**11_c** $C_{23}H_{18}O_4$) exhibited a molecular ion peak (M^+) at m/z 358 (8.92%) and the base peak was found in the spectrum at m/z 205. Anal. calcd. for **11_c**$C_{23}H_{18}O_4$ (358.393) C, 77.01; H, 5.02 Found C, 7,10; H, 5.10.

Synthesis of 2-Amino-3-cyano-4 aryl-6-(4-methoxy-6-substitued-benzofuran-5-yl)-pyrdine ($12_{a,b}$):

A mixture of compound **($11_{b,c}$)** (0.01 mole), malonitrile (0.01 mole) and ammonium acetate[32] (0.02 mol) was fused at 100°C for 1 hour, then allowed to cool and poured into ethanol. The solid product was collected and recrystallized from suitable solvent to give compound **$12_{a,b}$**.Compound **12_a**recrystallized from methanol, m.p. 136-137°C yield 62%.IR (KBr) spectrum of the compound **12_a**showed bands at 3346: (broad OH/NH_2), C–Haliph at 2921, 2856 and C≡N at 2207 cm^{-1}. Anal. calcd. for **12_a**$C_{25}H_{17}N_3O_3$ (407.429) C, 73.63; H, 4.17; N, 10.31 Found C, 73.70; H, 4.20; N, 10.30.

Compound **12_b**recrystallized from ethanol, m.p. 120-122°C yield 81%. IR spectrum of the compound **12_b** exhibited bands at 3330, 3213 for NH_2 group C–H aliph. at 2922, 2852 and C≡N2212cm^{-1}. ^{1}H-NMR spectrum of compound **12_b** ($CDCl_3$) revealed signals δ at 3.76, 4.10 (2s, 6H, 2 OCH_3), 4.97 (s, 2H, NH_2), 6.78-8.12 (m, 11H, Ar–H + pyridine –H and furan protons). The mass spectrum of compound (**12_b**$C_{26}H_{19}N_3O_3$) exhibited a molecular ion peak at m/z 423 (M+2, 11.1%) and base peak was found in the spectrum at m/z 205. Anal. Calcd. for **12_b**$C_{26}H_{19}N_3O_3$ (421.436) C, 74.03; H, 4.51; N, 9.97. Found C, 74.10; H, 4.60; N, 10.00.

Synthesis of 2-(Naphthalidene) amino-3-cyano-4-(1 naphthyl)-6-(4,6-dimethoxy-benzofuran-5-yl) pyridine (13):

A mixture of compound **12_b** (0.01 mole), α-naphthaldehyde (0.01 mole) and piperidin (0.3 ml), in ethanol (40 ml) was refluxed for 4 hours, then allowed to cool. The solid product **13** was collected and crystallized fromethanol 251-2 yield 50%.

Schiff base **(13)** was obtained from the reaction of **(12_b)** with α-naphthaldehyde in the presence of piperidine as a catalyst. The compound **(13)** was supported by IR and mass spectrum. IR (KBr) spectrum of the compound **(13)** revealed the disappearance of NH_2 group and presence of bands. $CH_{aliph.}$ at 2937 C≡N 2222cm^{-1}. The mass spectrum of compound (**13**; $C_{37}H_{25}N_3O_3$) showed a molecular ion peak M^+ at m/z 559 (10.6%) and the base peak was found in the spectrum at m/z 412. Anal. calcd. for **13** $C_{37}H_{25}N_3O_3$ (559.625); C, 79.42; H, 4.48; N, 7.51. Found C, 79.45; H, 4.50; N, 7.55.

Synthesis of 3-Phenyl-4-imino-5-(1-naphthyl)-7-(4,6-dimethoxy-benzofuran-5-yl)-1,2,3,4-tetrahydro-2-thioxopyrido[2,3-d] pyrimidine (15):

A mixture of compound **(12_b)** (0.01 mole) and phenylisothocyanate (0.01 mole) in pyridine (10 ml) was heated under reflux for 24 hours. Then allowed to cool and poured into cold water. The solid product was collected and recrystallized from suitable solvent to give compound **(15)**. Compound **15** recrystallized from ethanol m.p. 300-302°C yield 60%.

The structure of compound **15** was supported by IR and mass spectrum IR spectrum of compound **(15)** exhibited the disappearance of cyano group and the presence of NH band at 3322 C–$H_{aliph.}$ at 2930, 2851 and C=N at 1619cm^{-1}. The mass spectrum of compound **15** ($C_{33}H_{24}N_4O_3S$) displayed a molecular ion peak at m/z 555 (M–1, 25.8%) and base peak was found in the spectrum at m/z 181. Anal. calcd for **15** $C_{33}H_{24}N_4O_3S$ (556.646) C, 71.22; H, 4.31; N, 10.07; S, 5.76. Found C, 71.28; H, 4.30 ; N, 10.10; S, 5.80.

Synthesis of 2-amino-3-ethoxy carbonyl-4-(1-naphthyl)-6-(4,6-dimethoxy benzofuran-5-yl) pyridine (16):

A mixture of compound **11c** (0.01 mole), ethylcyanoacetate (0.01 mole) and piperidine (3 drops) in ethanol (40 ml) was refluxed for 2 hours, then allowed to cool, the solid product was collected and recrystallyzed from methanol to give compound **(16)** m.p. 120-121°C yield 53%.

The structure of compound (**16)** was supported by IR, ^{1}H-NMR and mass spectrum. IR spectrum of compound **(16)** exhibited bands at 3422, 3380 for NH_2 group and 1684 for $\rangle C{=}O$ cm^{-1} group. ^{1}H-NMR spectrum of compound **(16** ; $CDCl_3$) showed signals. δ 1.32 (t, 3H, CH_3), δ 2.67 (br 2H, NH_2), δ 3.72, 4.14 (2s, 6H, $2OCH_3$), δ 2.40 (q, 2H, CH_2), δ 6.87 (s, 1H, pyridine), δ 7.05 (d, 1H, H_{-3} furan), 7.51-7.90(m, 8H, ArH) and δ 8.26 (d, 1H, H_{-2} furan). The mass spectrum of compound (**16**; $C_{28}H_{24}N_2O_5$) revealed a molecular ion peak M^+ at m/z 468 (5.2%) with a base peak at m/z 205. Anal. calcd. for **16** $C_{28}H_{24}N_2O_5$ (468.509) C, 71.79; H, 5.13; N, 5.98. Found C, 71.81; H, 5.20; N, 6.00.

Synthesis of 2-Amino-4-(1-naphthayl)-6-(4,6-dimethoxybenzofuran) pyrimidine (17):

A mixture of compound **11_c** (0.01 mole) and guanidine (0.01 mole) and potassium hydroxide (1gm) in ethanol (30 ml) was refluxed for 4 hours then allowed to cool. The solid product was collected and recrystallyzed from benzene to give **17** m.p. 189-191 yield 60%.

The structure of compound **17** was supported with spectral data. IR spectrum of compound **(17)** revealed the disappearance of carbonyl group and presence of two bands at 3153, 3124cm^{-1} for NH_2 group. ^{1}HNMR spectrum of compound (**17**; DMSO-d_6) afforded signals δ at 3.89, 4.12 (2s, 6H, $2OCH_3$), 6.08 (s, 1H, pyrimidine-H), 6.99-8.10 (m, 10H, Ar–H and Furan) and 9.22, 9.99 (2s, 2H, 2NH). Anal. calcd. for **17** $C_{24}H_{19}O_3N_3$ (397.410) C, 72.53; H, 4.82; N, 10.75. Found C, 72.60, H, 4.79; N, 10.60.

3- Results and Discussion

In the present study 3-[4-Methoxy-6-hydroxy-5-benzofuranyl] **(1_a)** and 3-[4,6-dimethoxy-5-benzofuranyl] 1,3 diketobtyrate **(1_b)** reacted with α-cyanothioacetamide in presence of ammonium acetate to give 2-mercapto-3-carbonitrile-4-methyl-6-[4-methoxy-6-hydroxy-5-benzo-furanyl] pyridine **(2_a)** and 2-mercapto-3-carbonitrile-4-methyl-6-[4,6-dimethoxy-5-benzofuranyl] pyridine **(2_b)** (or possible isomers **($3_{a,b}$)**[(1)] respectively. Alkylation of **2_{a-b}** (or its isomers **$3_{a,b}$**) with ethyl chloroacetate in the presence of sodium acetate in acetone yielded the ethyl 3-carbonitrile 4,6-disubstituted pyridine-2-ylthioacetic ester **($4_{a,b}$)**[(2)]

Condensation of this ester **(4_{a-b})** with hydrazine hydrate (99%) in absolute ethanol resulted in the formation of 3-carbonitrile-4,6-disubstituted-2-pyridinylthioacetyl hydrazine **(5_{a-b}).**

Condensation of this hydrazine **(5_{a-b})** with phenylisothiocyanate resulted in the formation of 3-carbonitrile-4,6-disubstituted-2-pyridinyl thioacetyl thiosemicarbazide **(6_{a-b}).**

Condensation of the ester **(4_{a-b})** with phenyl hydrazine in absolute ethanol resulted in the formation of 3-carbonitrile 4,6-disusbtituted-2-pyridinyl thioacetyl phenyl hydrazine **(7_{a-b})**.

The ethanolic solution of **(2_{a-b})** with primary amines such as aniline and p-toulidine gave the corresponding *N*-substituted-2-amino-3-carbonitrile-4,6-disubstituted pyridine **(8_{a-d})**.

A similar reaction of **(2_{a-b})** with hydrazinehydrate and phenylhydrazine afforded the corresponding 2-hydrazino and 2-phenylhydrazino-3-carbonitrile-4,6-disubstituted pyridine **(9_{a-b})** and **(10_{a-b})** respectively (Scheme 1).

On other hand sterylketones **11_{a-c}** were obtained by the condensation of [4 methoxy-6-hydroxy or methoxy benzofuran-5-yl] methylketone **$A_{a,b}$** with

aromatic aldehydes in ethanol in the presence of triethylamine under reflux.

The α-β, unsaturated ketone **$11_{b,c}$** were allowed to cyclo condensation reaction with malononitrile in the presence of ammonium acetate[32] to give the corresponding pyridine derivatives **$12_{a,b}$**.

Schiff base **(13)** was obtained from the reaction of **(12_b)** with α-naphthaldehyde in presence of piperidine as catalyst compound **(13)** revealed the disappearance of NH_2 group.

Reaction of compound **12_b** with phenyl isothiocynate in pyridine under reflux gave pyrido[2,3d] pyrimidine derivatives **(15)**.

Also compound **(11_c)** was cyclized with ethyl cyano acetate in refluxing ethanol containing a catalytic amount of piperidine to afford the pyridine derivatives **(16)**.

Reaction of **11_c** towards binucleophilic reagent was investigated. Thus interaction of **11_c** with guanidine in the presence of sodium methoxide to produce the pyrimidine derivative **(17)**. The reaction was proceeded via Michael addition followed by intermolecular cyclization and H_2O elimination. (Scheme 2).

Antimicrobial activity

The antimicrobial screening of some synthesized compounds was undertaken using the diffusion agar technique[33]. Tables (1,2) lists the screening results of the tested compounds against the Gram-positive bacteria *Staphylococcus aureus & Bacillus subtilis* and the Gram-negative bacteria: *Peudomonas aeruginosa & Escherichia coli.* In addition to the pathogenic fungi: *Aspergillusfumgiatus& Aspergillus flavus, Penicillium* species and *Candida albicans*. The reference antibiotic Chloramphenicol and fungicide Terbinafin were used as positive controls for comparison. The fungi cultures were maintained on Czapek Dox agar medium. The tested compounds were dissolved in *N,N*-dimethylformamide (DMF) which showed no inhibition zones. Some of the tested compounds were found to be in higher activity against the organism and fungi.

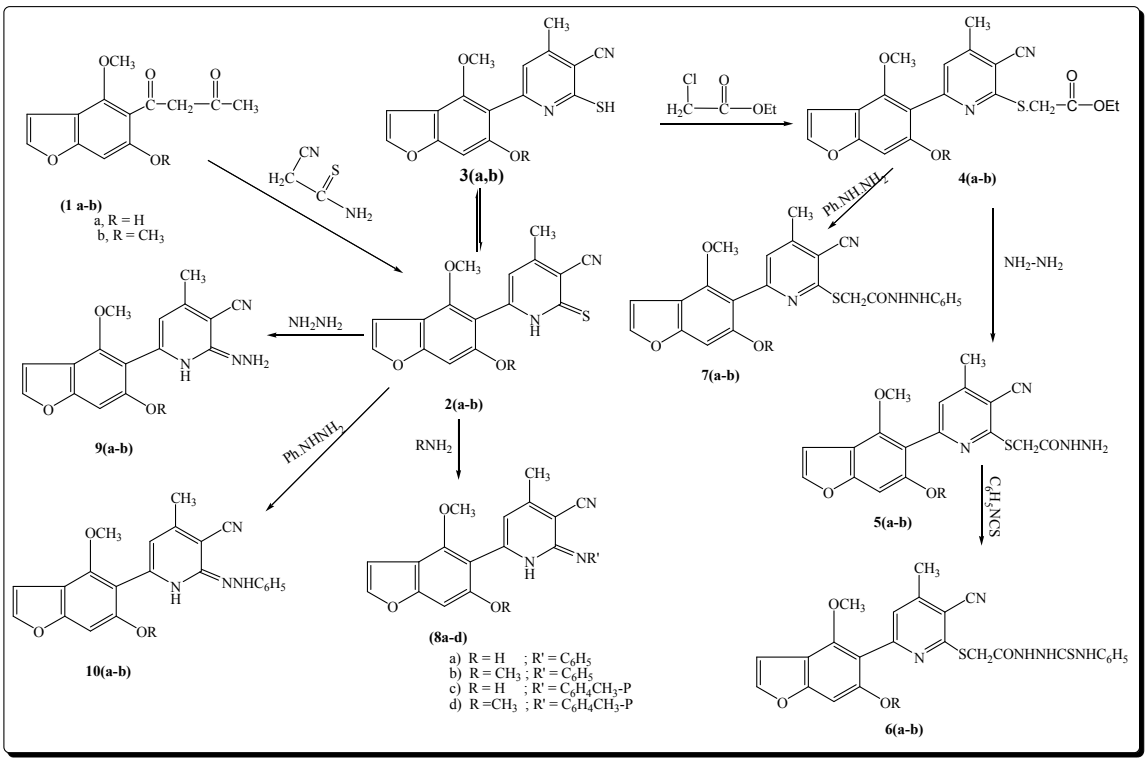
Table (1): The antimicrobial activity of the tested compounds

Comp. No.	Gram-positive		Gram-negative	
	Staphylococcus aureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*
4b	+	++	+	+
5a	++	R	++	++
6b	R	++	+++	+
7a	+	+++	++	++
8a	+++	++	+++	+
8c	+++	R	+	+++
9a	++	+	R	+
12c	++	++	R	+
14	R	+++	++	++
15	+	R	++++	+++
17	+	R		+
References	++++	++++	++++	++++

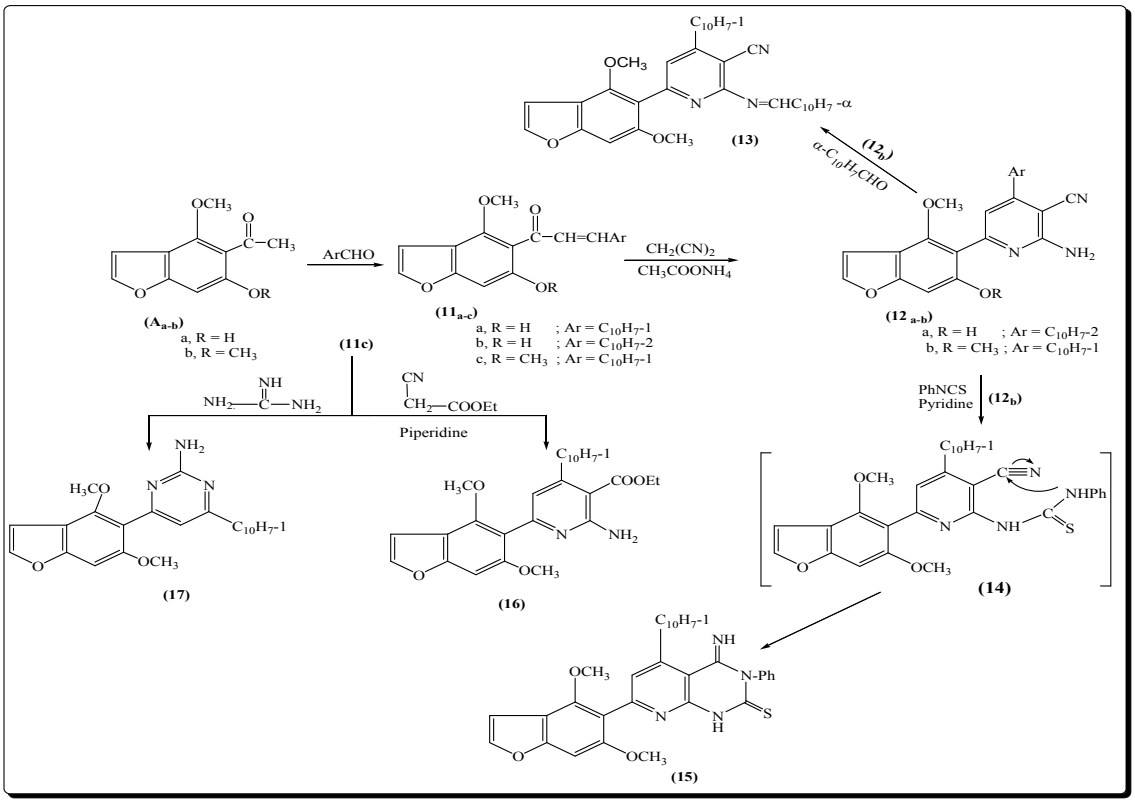
Table (2): The antifungal activity of the tested compound

Comp. No.	*Aspergillus fumigatas*	*Aspergillus flavus*	*Pencillium species*	*Candida albicans*
4a	(+++)	R	R	(+)
5b	R	R	+	R
6b	+	+++	R	+
7a	++	+	R	R
14	+	(+++)	(+)	(+++)
15	(+++)	(+++)	(++)	(+++)
17	(+++)	R	++	(+++)
References	++++	++++	++++	++++

R : Resistance +: less active (0.2-0.5mm) ++: Moderately active (0.6-1.0 mm)
+++ : Highly active (1.1-1.5 mm) ++++ : Very highly active (over 2 mm)



Scheme (1)



Scheme (2)

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