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Pelagia Research Library

Der Chemica Sinica, 2015, 6(3): 7-14

Der Chemica Sinica
Pelagia Research Library
ISSN: 0976-8505
CODEN (USA) CSHIA5

Synthesis and studying of antimicrobial and antioxidant activity of some novel furocoumarin and benzofuran derivatives containing thiazole moiety

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ABSTRACT

*Treatment of (4-methoxy-6-hydroxybenzofuran-5-yl)methyl ketone **(1)** with 2-aminothiazole or O-tolidin in presence of formaldehyde gave Mannich bases **(2a,b)**. Claisen condensation of [4-methoxy-5-acetyl-6-hydroxy-7-((thiazol-2-ylamino)methyl)] benzofuran **(2a)** and [4-methoxy-5-acetyl-6-hydroxy-7-((3,3'-dimethyl-4'-aminobiphenyl-4-ylamino)methyl)]benzofuran **(2b)** with diethyl carbonate in presence of sodium powder gave the corresponding -5-hydroxyfurocoumarins **(3a,b)** respectively. Treatment of **3a** with cinnamaldehyde under different conditions was discussed. Thus, when **3a** was refluxed with cinnamaldehyde for 20 minutes, 4-methoxy-5-hydroxy-6-[3'-hydroxy-1'-phenylprop-1'-en-3'-yl)-9-((thiazol-2-ylamino)methyl)]furo[3,2-g][1]benzopyran-7(H)-one **(4)** was formed. While, refluxing of **3a** with cinnamaldehyde for 3hrs.a dimer compound of 3,3-bis[4'-methoxy-5'-hydroxy-7'H-7'-oxo-9'-((thiazol-2-ylamino)methyl)furo[3,2-g][1] benzopyran-6'-]-1-phenyl prop-1-ene **(5)** was obtained. Chlorination of **3a** by phosphorusoxychloride gave 5-chlorofurocoumarin derivative **(6)** which reacted with sulphadiazine to yield **7**. On the other hand, bromination of **2a** in chloroform gave 5-bromoacetyl benzofuran derivative **(8)** which condensed with N-acetylthiosemicarbazide or thiourea to furnish the corresponding 2-(N-acetylhydrazino)thiazole and 2-aminothiazole derivatives **(9), (10)** respectively. Interaction of **10** with each one of cinnamaldehyde or 3-aminophenacylbromide gave Schiff base **(11)** and imidazolothiazole derivative **(12)**. Condensation of the latter compound **12** with triethyl orthformate gave **13**. Compounds **2a, 3a, 4, 5, 8, 9** and **11** demonstrate antimicrobial activity against the microorganisms E.coli, F.streptococcus and A.flavus. In addition compounds **2b**, **3b**, **8** and **10** illustrate antioxidant activity by using free radical scavenging activity test.*

Keywords: Benzofuran, furocoumarin, thiazole, antimicrobial antioxidant

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INTRODUCTION

Benzofuran derivatives have been reported to possess biological activities[1-7], hypotensive[8], antioxidant[9]and arrhythmic activity[10]. Also, furocoumarins show a broad spectrum anti-bacterial[11-13] and molluscicidal properties[14] ,they also possess photosensitizing activity[15-17]. Thiazoles are important scaffold in heterocyclic chemistry, they find applications as bacteriostatic, antibiotics[18-21], antitumor and anti-inflammatory[22]. Thus, the aim of the present work is to synthesis of some newly benzofuran derivatives and furocoumarins containing thiazole moiety in order to increase their antimicrobial and antioxidant activity.

MATERIALS AND METHODS

All melting points were determined in open capillaries and are uncorrected. IR spectra were measured using (KBr) discs and a pye Unicom SP-1000 spectro-photometer. ^{1}H NMR spectra were measured on a Varian EM-390-200 MHz instrument in DMSO-d_6) as solvent using TMS as internal started and chemical shifts are expressed as ppm. Mass spectra were measured and a shimadzu G CMSQP-100 Ex mass spectrometer at 70 eV.

Synthesis of [4-methoxy-5-acetyl-6-hydroxy-7-((3,3'-dimethyl-4'-aminobiphenyl-4-yl amino) methyl)] benzofuran (2b) .

To a solution of visnaginone **(1)** (0.01 mol) in ethanol (30 ml), o-tolidine (0.01 mol) and formaldehyde (0.01 mol) were added. The reaction mixture was refluxed for about 6hrs. The solid so formed was collected and recrystallized from ethanol as light brown crystals in 85% yield, m.p. > 360^{o}C, IR (KBr, cm^{-1}): 1698, (CO) , 3114 & 3192 [NH_2/NH], 3416 (OH). ^{1}H NMR (DMSO-d_6:δ, ppm.): 1.41, 2.11 (2s, 6H, 2CH_3), 2.55 (s, 3H, $COCH_3$), 3.95 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), 4.76 (s, 2H, NH_2, D_2O exchangeable), 6.12-7.97 (m, 8H,6H,Ar-H, 2H, furan protons), 8.89 (s, 1H, NH, D_2O exchangeable) and 11.01 (s, 1H, OH, D_2O exchangeable), MS: m/z(%) 430 (M^+, 23.2) with a base peak at 94. Anal. calcd. for $C_{26}H_{26}N_2O_4$ (430.50): C, 72.53: H, 6.87: N, 6.50%. Found: C, 72.54 : H, 6.88: N, 6.51.

Synthesis of [4-methoxy-5-hydroxy-9-((thiazol-2-yl amino) methyl)]furo[3,2-g][1] benzopyran-7(H)-one(3a) and [4-methoxy-5-hydroxy-9'-((3,3'-dimethyl-4'-aminobiphenyl-4-ylamino) methyl)]furo [3,2-g] [1]benzopyran-7(H)-one (3b) .

To a solution of **2a** or **2b** (0.01 mol) of each in diethyl carbonate (20 ml), powdered sodium (2gm) was added, the reaction mixture was refluxed for about 2hrs. then, the ethanol (20 ml) was added to destroy any unreacted sodium. The whole mixture was treated with water and extracted with ether. Acidification the aqueous layer gave the solid product which filtered and crystallized from the suitable solvent. The solid **3a** was recrystallized from ethanol as yellow crystals in 77% yield, m.p. 119-120^{o}C, IR (KBr, cm^{-1}): 1602 (C=N), 1711(CO) of α -pyrone, 3398(br, NH/OH). ^{1}H NMR (DMSO-d_6:δ , ppm.): 3.87 (s, 3H, OCH_3), 4.26 (s, 2H, CH_2), 6.36(d, 1H, *J* = 7.11Hz, CH_{-4} thiazole), 6.51-7.77 (m, 4H, 1H, CH_{-6} pyrone, 1H, CH_{-5} thiazole + 2H, furan protons), 8.97 (s, 1H, NH, D_2O exchangeable) and 10.78(br, 1H, OH, D_2O exchangeable). Anal. calcd. for $C_{16}H_{12}N_2O_5S$ (344.34): C, 55.80: H, 35.12: N, 8.13: S, 9.31%. Found : C, 55.81: H, 35.14: N, 8.14: S, 9.32.

The solid **3b** was recrystallized from acetone as brownish red crystals in 66% yield, m.p. 161-162^{o}C . IR (KBr, cm^{-1}): 1715 (CO) of α- pyrone, 3158 & 3246 (br,NH_2/NH), 3380 (OH),^{1}HNMR (DMSO-d_6:δ , ppm): 1.38, 1.92 (2s, 6H, 2CH_3), 3.89 (s, 3H, OCH_3), 4.18(s, 2H, CH_2), 5.12 (br, 2H, NH_2), 6.33-7.91 (m, 9H, 6H, Ar–H, 1H, CH_{-6} pyrone, 2H, C_{-3} & C_{-2} furan), 9.22 (s, 1H, NH, D_2O exchangeable) and 10.68 (s, 1H, OH, D_2O exchangeable). Anal. calcd. For $C_{27}H_{24}N_2O_5$ (465.49): C, 69.66: H, 5.19: N, 6.01%. Found : C, 69.67: H, 5.2 : N, 6.03.

Synthesis of 4-methoxy-5-hydroxy-6-[(3'-hydroxy-1'-phenyl-prop-1'-en-3'-yl)-9-((thiazol-2-yl amino)methyl)] furo[3,2-g][1] benzopyran-7(H)-one (4).

To a solution of **3a** (0.01 mol) in ethanol (30 ml), cinnamaldehyde (0.01 mol) was added. The reaction mixture was refluxed 20 minutes, the solid so obtained washed with petroleum ether (40-60^{o}C) and recrystallized from ethanol as brown crystals in 92% yield, m.p. 120-122^{o}C , IR (KBr, cm^{-1}): 1710, (CO),3111(NH), 3388 & 3401 (2OH), ^{1}H NMR (DMSO-d_6:δ , ppm.): 3.81-4.01 (m, 4H, 3H, OCH_3, 1H, CH), 4.32 (s, 2H, CH_2), 5.66 (d, 1H, *J* =6.11, CH=), 6.61-7.88 (m, 10H, 5H, Ar-H, 1H, =CH, 2H, 2CH thiazole + 2H, furan protons), 9.31 (s, 1H, NH, D_2O exchangeable), 10.85 & 11.22 (2s, 2H, 2OH, D_2O exchangeable). Anal. calcd. for $C_{25}H_{20}N_2O_6S$ (466.508): C, 64.36: H, 4.32: N, 6.00: S, 6.87%. Found: C, 64.37: H, 4.33: N, 6.01: S, 6.9.

Synthesis of 3,3-bis[4'-methoxy-5'-hydroxy-7'H-7'-oxo-9'- ((thiazol-2-yl amino) methyl) furo[3,2-g][1] benzopyran-6'-yl] 1-phenyl prop-1-ene(5).

To a solution of **3a** (0.02 mol) in ethanol (30ml), cinnamaldehyde (0.01 mol) was added. The reaction mixture was refluxed 3hrs. then cooled and the precipitate was filtered off, dried and recrystallized from ethanol as brown crystals in 72% yield, m.p. 76-78^{o}C, IR(KBr, cm^{-1}): 1717(br, 2CO), 3281 (br, 2NH) and 3919, 3421 (2OH), MS: m/z (%) 802 (M^+, 38.11) with a base peak at 94. Anal. calcd. for $C_{41}H_{30}N_4O_{10}S_2$ (802.83): C, 61.33: H, 3.76: N, 6.97: S, 7.98%. Found: C, 61.34: H, 3.77:N, 6.99: S, 7.99.

Synthesis of [4-methoxy-5-chloro-9-((thiazol-2-ylamino) methyl)]furo [3,2-g][1]benzopyran-7(H)-one (6).
A compound of **3a** (0.01 mol) was refluxed in phosphorus oxychloride (20 ml) for about 5hrs. The reaction mixture was poured into crushed ice, the solid product was filtered, dried and recrystallized from dimethylformamide as grey crystals in 52% yield, m.p.> 300^{o}C, IR(KBr, cm^{-1}): 1713 (CO), 3266 (NH), MS: m/z (%) 362(73.2) with a base peak at 97. Anal. calcd. for $C_{16}H_{11}N_2O_4SCl$ (362.71): C, 52.98: H, 3.03: N, 7.72: S, 8.84: Cl, 9.77%. Found: C, 52.97:H, 3.00: N, 7.7: S, 8.81: Cl, 9.75.

Synthesis of 5-[4-methoxy-7H-7-oxo-9-((thiazol-2-yl amino) methyl) furo[3,2-g][1]benzopyran-5-yl]4-amino (N-pyrimdino-2-yl)benzene- sulfonamide (7).
To a solution of **6** (0.01 mol) in dimethylformamide (20 ml), sulphadiazine (0.01 mol) was added and the reaction mixture was refluxed 12 hrs. The solvent was evaporated and the solid so formed was dried and recrystallized from chloroform as light brown crystals in 71% yield, m.p. 198-200^{o}C, IR (KBr, cm^{-1}): 1714(CO), 3132 & 3219 (br, 3NH), MS: m/z (%) 576 (M^+, 22.1), 462(13.4), 431(25.2), 113(34.11) with a base peak 95. Anal.calcd. for $C_{26}H_{20}N_6O_6S_2$ (576.61): C, 54.15 : H, 3.49: N, 14.57: S, 11.12% . Found: C, 54.2 : H, 3.51 : N, 14.53: S, 11.01.

Synthesis of [4-methoxy-5-bromoacetyl-6-hydroxy-7-((thiazol-2-yl amino) methyl)] benzofuran (8).
To a solution of **2a** (0.01 mol) in chloroform (20 ml) and bromine (0.5 mol) in chloroform (25ml) was added. The reaction mixture was stirred at room temperature for half an hour. The reaction mixture was heated for fifteen minutes on a water bath to expel most of the hydrogen bromide, cooled then, the solid so obtained filtered and recrystallized from chloroform as green crystals in 85% yield, m.p. > 360^{o}C ,IR (KBr , cm^{-1}):1718 (CO), 3401(br, NH/OH),^{1}H NMR(DMSO-d_6:δ , ppm.) 3.63 (s, 2H, CH_2Br), 3.92 (s, 3H, OCH_3), 4.14 (s, 2H, CH_2), 6.52-7.78 (m, 4H, 2H, 2CH thiazole + 2H, 2CH furan), 9.01 (s, 1H, NH, D_2O exchangeable) and 11.16 (s, 1H, OH, D_2O exchangeable). MS: m/z (%) 398 (M^+, 19.8) with a base peak at 145. Anal. calcd. for $C_{15}H_{13}N_2O_4SBr$ (398.73): C, 45.55: H, 3.28: N, 7.02: S, 8.04: Br, 20.03%. Found: C, 45.51: H, 3.25: N, 7: S, 8.02: Br, 20.01.

Synthesis of 2-(N-acetylhydrazino)-4-[4-methoxy-6-hydroxy-7- ((thiazol-2-yl-amino) methyl) benzofuran-5-yl] thiazole (9).
A mixture of **8** (0.01 mol) and 1-acetylthiosemicarbazide (0.01 mol) in dimethylformamide (20 ml) was refluxed for 3hrs. Concentrated hydrochloric acid (1 ml) was added then the reflux was continued for further 1hr. The solid was obtained , washed with boiling water and recrystallized from chloroform as brownish red crystals in 66% yield, m.p. 300-302^{o}C, IR(KBr, cm^{-1}): 1721(CO), 3321 & 3430[3NH/OH), ^{1}H NMR(DMSO-d_6:δ ,ppm): 2.52 (s, 3H, $COCH_3$), 3.88 (s, 3H, OCH_3), 4.21(s, 1H, CH_2), 6.41-7.98(m, 5H, 3H, 3CH of two thiazole moieties, 2H, furan protons), 8.89, 9.22, 10.01(3s, 3H, 3NH, D_2O exchangeable) and 11.33 (s, 1H, OH, D_2O exchangeable). Anal. calcd. for $C_{18}H_{17}N_5O_4S_2$(431.49): C, 50.13: H, 3.97: N, 16.23 : S, 14.86%. Found: C, 50.1: H, 3.93: N, 16.22: S, 14.82.

2-Amino-4-[4-methoxy-6-hydroxy-7-((thiazol-2-ylamino)methyl) benzofuran-5-yl] thiazole (10).
To a solution of **8** (0.008 mol) in hot ethanol (30 ml) and thiourea (0.02 mol) was added, then the reaction mixture was refluxed for 2hrs. The formed precipitate was filtered off and recrystallized from ethanol as yellow crystals in 57% yield, m.p. 126-128^{o}C, IR(KBr, cm^{-1}): 3112 & 3136 (br, NH_2/NH), 3414 (OH), ^{1}H NMR(DMSO–d_6: δ, ppm): 3.91 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2), 5.23 (br, 2H, NH_2) 6.61-7.87(m 5H, 3H, 3CH two thiazoles, 2H, 2CH furan protons), 9.21(s, 1H, NH, D_2O exchangeable) and 11.41 (s, 1H,OH, D_2O exchangeable). Anal. calcd. for $C_{16}H_{14}N_4O_3S_2$ (374.44): C, 51.32: H, 3.76 , N, 14.96: S, 17.12%. Found: C, 51.28: H, 3.72: N, 14.96: S, 17.07.

Synthesisof 2-(1-phenylprop-1,3-dienamino-4-[4-methoxy-6-hydroxy-7-((thiazol-2-yl amino) methyl) benzo furan-5-yl] thiazole (11).
A mixture of **10** (0.01 mol) and cinnamaldehde (0.01 mol) in ethanol (30 ml) was refluxed 4hrs. The solvent was removed and the solid recrystallized from ethanol as brown crystals in 82 % yield, m.p. 203-205^{o}C, IR(KBr, cm^{-1}): 1603 (N=CH), 3279 (NH) and 3389(OH) groups, ^{1}H NMR (DMSO–d_6: δ, ppm.): 3.96 (s, 3H, OCH_3), 4.17 (s, 2H, CH_2) 6.11 (d, 1H,*J*=6.22, =CH), 6.49-8.28(m, 12H, 5H, Ar–H, 1H, CH=, 3H, 3CH of two thiazole moieties, 2H, furan protons, 1H, N=CH), 9.19 (s, 1H, NH, D_2O exchangeable) and 11.10(s,1H,OH,D_2O exchangeable). Anal. calcd. for $C_{25}H_{20}N_4O_3S_2$ (488.59): C, 61.45: H, 4.12: N, 11.46: S, 13.12% . Found : C, 61.46: H, 4.13: N, 11.47: S, 13.13 .

Synthesis of 3-[4-methoxy-6-hyroxy-7-((thiazol-2-yl amino) methyl) benzofuran-5-yl)]-6-(3-aminophenyl) imidazolo[2,1-b] thiazole (12).

An ethanolic solution of **10** (10 mmol) was refluxed with 3-aminophenacylbromide (10 mmol) for about 6hrs. The resulting solid was filtered and recrystallized from ethanol as dark green crystals in 56% yield, m.p. 138-140^{o}C, IR(KBr, cm^{-1}): 3121 & 3149(NH_2), 3327(NH) and 3417 (OH) groups, MS: m/z(%) 489(M^+, 32%) with a base peak at 356. Anal. calcd. for $C_{29}H_{19}N_5O_3S_2$ (489.57): C, 58.88: H, 3.91: N, 14.3: S, 13.09%. Found: C, 58.89: H, 3.93: N, 14.33: S, 13.1 .

Synthesis of ethyl-N-{-3-[4-methoxy-6-acetoxy-7-((thiazol-2-N-acetylamino) methyl) benzofuran-5-yl] ((imidazolo [2,1-b]thiazol-6-yl)phenyl} methanimidate (13).

To a solution of **12** (0.01 mol) in ethanol (20 ml), acetic anhydride (5 ml) and triethyl orthoformate (0.01 mol) were added. The reaction mixture was refluxed 6hrs. The solid so obtained dried and recrystallized from dimethylformamide as dark red crystals in 45% yield, m.p.> 300^{o}C , IR(KBr, cm^{-1}): 1725 (CO) of $COCH_3$ and 1771(CO) of $OCOCH_3$ group, ^{1}HNMR (DMSO–d_6: δ ,ppm.): 2.18 (t, 3H, CH_3 of C_2H_5), 2.58 (s, 3H, $COCH_3$), 2.93 (s, 3H, $OCOCH_3$), 3.97 (s, 3H, OCH_3), 4.15(s, 2H, CH_2), 4.71(q, 2H, CH_2 of C_2H_5), 6.63-8.02(m, 10H, 4H, Ar–H, 1H, CH imidazole, 3H, 3CH, of two thiazole moieties, 2H, 2CH furan) and 8.41(s, 1H, N=CH), MS: m/z (%) 629 (M^+, 11.1). Anal. calcd. for $C_{31}H_{27}N_3O_6S_2$ (629.71): C, 59.12: H, 4.32: N, 11.12: S, 10.18 % . Found: C, 59.13: H, 4.29: N, 11.1: S, 10.77.

Biological evaluation :

a) Antimicrobial activity :

The antimicrobial activity of some newly synthesized compounds was assayed by the agar well diffusion method [28] against two bacterial strains [*Escherichia coli* (Gram negative) and faecal *Streptococcus* (Gram positive)]and one fungal strain (*Aspergillums flavus*). Tetracycline and Penicillin G sodium were used as standard anti bacterial drugs, while Nystatin was used as standard anti fungal drug . Dimethyl sulphoxide was used as solvent for tested compounds showed no inhibition zones.

b)Free Radical Scavenging Activity :

Free radical scavenging activity of the newly synthesized compounds were carried out according to the method recommended by Arnao *et al*.[29] with some modifications .2mM $ABTS^{\bullet+}$ (2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) and 2.45mM potassium per sulfate aqua solutions were prepared as stock solution .The working solution then prepared by mixing the two stock solutions in equal quantities and allowing them to react for 6h at room temperature in the dark . The solution was then diluted to obtain absorbance of 1.1 ± 0.02 units at 734 nm using the UV-Vis spectrophotometer. Fresh $ABTS^{\bullet+}$ solution was prepared for each assay. 1mL of different concentration of each compounds (10-30µg/mL) were added to 2.9 mL. of the $ABTS^{\bullet+}$ solution after vortexes allow to react for 2h in a dark. Then read absorbance at 734nm.Freeradical scavenging activity as percentage of the samples the standard and positive control ,were calculated using the following formula :

Radical Scavenging Activity(%) = [(A control–A sample) / control]x100 .

Where A control is the initial concentration of the $ABTS^{\bullet+}$ and A sample is the absorbance of the remaining concentration of $ABTS^{\bullet+}$ in the presence of the compounds or standards. Then IC50 values of the compounds and standards were evaluated. Initial $ABTS^{\bullet+}$ solution used as negative control.

Butylated hydroxyl anisol (BHA) Butylated hydroxyl tolune (BHT) and trolex were used as standard antioxidants

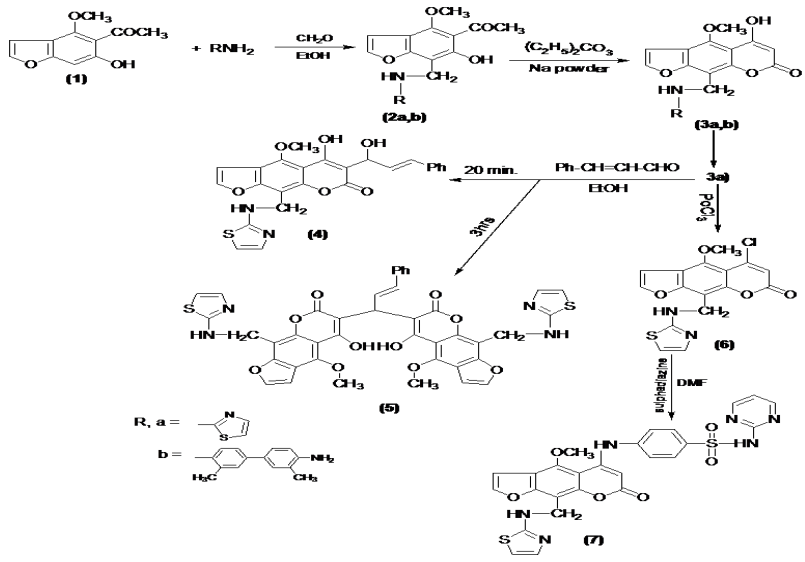
RESULTS AND DISCUSSION

Treatment of (4-methoxy-6-hydroxybenzofuran-5-yl)methyl ketone **(1)** with 2-aminothiazole or O-tolidin in presence of formaldehyde gave [4-methoxy-5-acetyl-6-hydroxy-7-((thiazol-2-ylamino)methyl)]benzofuran**(2a)** [23]and[4-methoxy-5-acetyl-6-hydroxy-7-((3,3'-dimethyl-4'-amino-biphenyl-4-ylamino)methyl)] benzofuran **(2b)** Scheme (1). Compound **2b** was confirmed through satisfactory elemental analysis and spectral data. The IR spectrum of **2b** showed strong absorption bands at 1698 cm^{-1} for (CO), 3114 & 3192 [NH_2/NH] and 3416(OH) groups, ^{1}H NMR spectrum of its compound exhibited signals at δ 1.41, 2.11 ppm. (2s, 6H, $2CH_3$), 2.55(s, 3H,

$COCH_3$), 4.16 (s, 2H, CH_2) and 4.76 (s, 2H, NH_2). Claisen condensation of **2a,b** with diethyl carbonate in presence of sodium powder gave 5-hydroxyfurocoumarins **(3a,b)** Scheme (1). The IR spectrum of **3a** showed bands at 1711 cm^{-1} for (CO) of α-pyrone, 3398(br, NH/OH) groups, ^{1}H NMR spectrum of **3a** showed singles at δ 6.36 ppm. (d, 1H, CH_{-4}, thiazole), 6.51-7.77 (m, 4H, 1H, CH_{-6} pyrone, 1H, CH_{-5} thiazole + 2H, furan protons). It was interesting to investigate the interaction of compound **3a** with cinnamaldehyde under different conditions. Thus, when compound **3a** was refluxed with cinnmaldehyde for 20 minutes, 4-methoxy-5-hydroxy-6-[(3'-hydroxy-1'-phenylprop-1'-en-3'-yl)-9-((thiazol-2-ylamino)methyl)]furo[3,2-g][1]benzopyran-7(H)-one**(4)** scheme (1) was obtained. While, refluxing 3a with cinnamaldhyde for 3hrs.gave3,3-bis[4'-methoxy-5'-hydroxy-7'H-7'-oxo-9'-((thiazol-2-ylamino)methyl)furo[3,2- g][1]benzopyran-6'-yl]-1-phenylprop-1-ene **(5)** scheme (1).

Compounds **4 and 5** were confirmed by correct elemental analysis and spectral data. ^{1}H NMR spectrum of compound **4** exhibited signals at δ 3.81-4.01 ppm. (m, 4H, 3H, OCH_3, 1H, CH), 5.66 (d, 1H, =CH), 9.31, 10.85 and 11.22 for NH and 2OH groups respectively. MS of compound **5** showed a molecular ion peak M^+ at m/z 802 (38.11%). All the previous compounds gave green color with aqueous ferric chloride solution and these were agreement with previous work [24] .

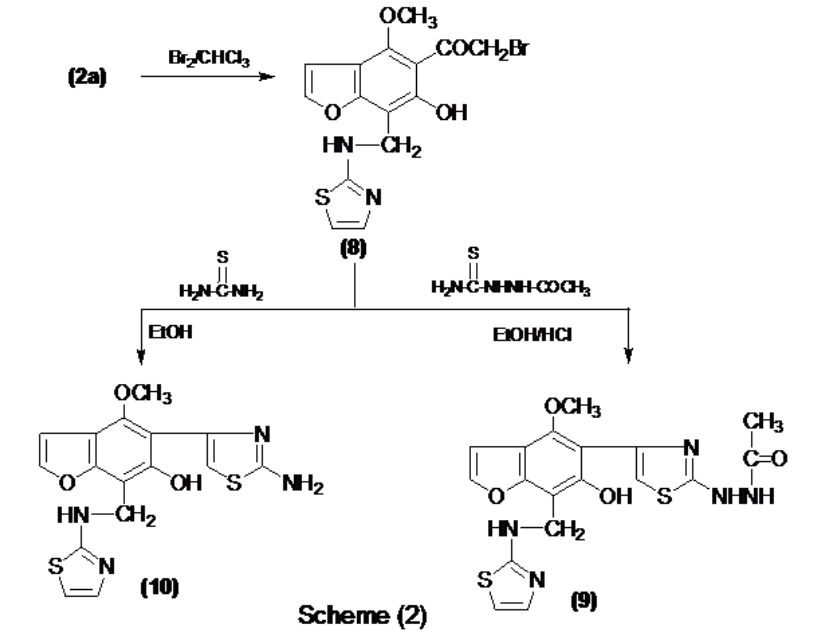
Moreover, Chlorination of **3a** with phosphorusoxychloride gave 5-chlorofurocoumarin derivative **(6)** scheme (1) which gave no green color with aqueous ferric chloride solution. Compound **6** was supported by analytical and spectral data, the IR spectrum of compound **6** showed the absence of hydroxyl group which found in the parent compound, MS of its compound afforded a molecular ion peak M^+ at m/z 362 (73.2%). Interaction of **6** with sulphadiazine in dimethylformamide gave sulfonamide derivative **(7)** scheme (1). The IR spectrum of **7** exhibited bands due to (CO), 3NH groups and MS of its compound revealed a molecular ion peak M^+ at m/z 576 (M^+, 22.1%) with a base peak at 95 ($C_4H_5N_3$).



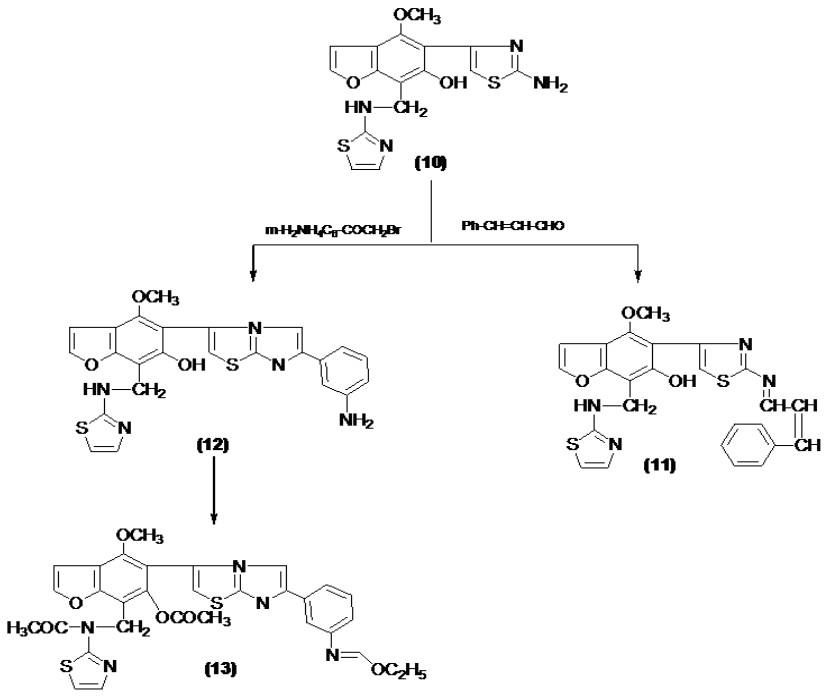
Scheme (1)

On the other hand, bromination of compound **2a** in chloroform gave 5-bromoacetylbenzofuran derivative **(8)** Scheme (2) which confirmed by elemental analysis and spectral data. The IR spectrum of **8** showed bands at 1718 cm^{-1} (CO) and 3401 (br, NH/OH) groups and MS of its compound afforded the molecular ion peak M^+ at m/z 398 (M^+, 19.8%) with a base peak at 145. The reactivity of compound **8** towards binucleophilic reagents was investigated. Thus, the interaction of **8** with N-acetylthiosemicarbazide gave 2-(N-acetylhydrazino)thiazole derivative **(9)** scheme (2). The IR spectrum of its compound showed strong absorption bands at 1721 cm^{-1}(CO) of acetyl group, 3321-3430 (br, 3NH/OH) groups. ^{1}H NMR spectrum of compound **9** showed signals at δ 2.52 ppm. (s, 3H, $COCH_3$), 6.41-7.98 (m, 5H, 3H, 3CH two thiazole moieties , 2H, furan protons), 8.89, 9.22, 10.01(3s, 3H, 3NH).

Similarly, condensation of **8** with thiourea caused cyclization to produce 2-amino-4-[4-methoxy-6-hydroxy-7-((thiazol-2-ylamino) methyl)benzofuran-5-yl]thiazole **(10)** scheme (2). The IR spectrum of **10** showed the disappearance of carbonyl group which found in the parent and exhibited bands at 3112 & 3136 cm^{-1} [NH_2/NH] and 3414 for (OH) groups, ^1H NMR spectrum of its compound showed signals at δ 5.23 ppm. (br, 2H, NH_2), 6.61-7.87(m, 5H, 3H, 3CH two thiazole moieties, 2H, furan protons). All of these compounds were in agreement with previous work [25].



Scheme (2)



Scheme (3)

Compound **10** was proved to be a versatile starting material for synthesis of some novel arylidene and thiazoloimidazole derivatives. Thus, condensation of **10** with cinnamaldehyde gave Schiff base **(11)** scheme (3)

which confirmed through satisfactory elemental analysis and spectral data. The IR spectrum of **11** showed the disappearance of NH_2 group found in the parent and appeared bands due to (N=CH), NH and OH groups. ^{1}H NMR spectrum of its compound revealed signals at δ 6.11 ppm. (d, 1H, =CH), 6.49-8.28 (m, 12H, 5H, Ar–H, 1H, CH=, 3H, 3CH two thiazole moieties, 2H, furan protons, 1H, N=CH). Also, interaction of compound **10** with 3-aminophenacylbromide yielded imidazolothiazole derivative **(12)** scheme (3). MS of **12** showed the molecular ion peak M^+ at m/z 489(M^+, 32%) and this was analogy with previous work [26].

Condensation of compound **12** with triethylorthoformate in presence of acetic anhydride produced ethyl methanimidate derivative **(13)** scheme (3) which gave no green color with aqueous solution of ferric chloride. The IR spectrum of **13** showed the absence of NH_2 group found in the parent and exhibited bands at 1725 & 1771 cm^{-1} (2CO) of acetyl and acetoxy groups respectively. ^{1}H NMR spectrum revealed signals at δ 2.18 ppm. (t, 3H, CH_3 of C_2H_5), 2.58 (s, 3H, $COCH_3$),2.93 (s, 3H, $OCOCH_3$), 4.71 (q, 2H, CH_2 of C_2H_5) and 8.41 (s, 1H, N= CH) and this was analogy with previous work [27].

Antimicrobial assay:

The antimicrobial activity data of some newly synthesized compounds were listed in table (1) which indicated that all tested compounds were effective against *E. coli* but not against *F. streptococcus* except compounds **3a , 9** and **11** were effective against both the gram positive and gram negative bacteria . Compounds **2a** , **3a and 9** were more potent than reference drug (Nystatin) in inhibition of sporulation growth of *A. flavus*. It is worth mention that compound **3a** was effective against all tested microorganisms.

Table (1) Antimicrobial activity of some new synthesized compounds

Compound No. .	Antibacterial		Antifungal	
			A. flavus	
	E. coli Inhibition zone	*F. streptococcus* of growth(mm)	Inhibition zone of sporulation (mm	Inhibition zone of growth (mm)
Tetracycline	21	20	0	0
Penicillin G–sodium	20	18	0	30
Nystatin	0	0	14	14
2a	15	0	23	45
3a	16	14	50	65
4	13	0	0	45
5	14	0	0	30
8	16	0	0	53
9	18	15	26	0
11	17	17	0	14

Table (2) : Antioxidant IC_{50} values of some new synthesized compounds by using free radical scavenging activity

Compounds	*IC50* µg/mL ±SD
2b	6.89 ± 0.23
3a	46.88 ± 0.35
3b	4.35 ± 0.14
4	25.02 ± 0.27
5	30.27 ± 0.35
6	32.40 ± 0.23
7	36.65 ± 0.75
8	3.05 ± 0.11
9	54.85 ±1.37
10	3.85 ± 0.12
11	55.04 ± 1.23
12	46.43 ± 0.57
13	58.86 ± 0.98
BHA	2.78 ± 0.01
BHT	4.34 ± 0.18
Trolox	5.27 ± 0.05

Free radical scavenging activity of synthesized compounds:

The IC_{50} radical scavenging activity data is presented in table (2) which indicated that the synthesized compounds **2b, 3b, 8** and **10**, show excellent free radical scavenging activity as compared to reference compounds. Compound **3b** has the highest scavenging activity while compound **13** has the lowest activity. Notably, compounds **4** an d **5** which have two hydroxyl groups possess IC_{50} scavenging activity higher than those compounds containing one hydroxyl group.

Moreover, phenolic compounds which have electron donating groups (CH_3 ,NH_2) increase the scavenging activity such as compounds **2b** , **3b and 10** .

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