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Synthesis of egonol derivatives and their antimicrobial activities

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ABSTRACT

Eighteen derivatives of egonol (**A**–**R**) were synthesized and evaluated for their antimicrobial activities against *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC 10231 and *Escherichia coli* ATCC 8739 microorganisms comparing with egonol. The obtained data reported that compound **B** exhibited improved activities against all tested bacteria than egonol, others have shown different range of activities.

1. Introduction

Lignans and neolignans are important targets for organic synthesis due to the wide variety of biologically active products, which are members of these classes.[1,2] Benzofuran neolignans and norneolignans, which are contained in most plants, especially in the *Styracaceae* family, such as *Styrax japonicum, Styrax formosanus, Styrax obassia, Styrax macranthus* and *Styrax officinalis* show a variety of biological activities including insecticidal, fungicidal, antimicrobial, anti sweet, antiproliferative, cytotoxic and antioxidant properties.[3] The phytochemical investigation on this genus increased in 1915, when Okada isolated egonol for the first time, as an unsaponifiable constituent of the seed oil of *S. Japonica*.[4]

Egonol, a natural 2-aryl benzofuran, is known to be an effective pyrethrum synergist.[5] Egonol and its derivatives attracted the attention of synthetic chemists due to their antibacterial and antifungal,[6] anti-complement[7] activities besides their considerable cytotoxic activities against human leukaemic HL-60 cells.[8] It was also reported that significant activities were observed for egonol against C6 (rat glioma) and Hep-2 (larynx epidermoid carcinoma) cell lines.[9]

As part of our ongoing studies, a series of new benzofuran derivatives (**A**–**R**) derived from egonol scaffold were prepared and their antimicrobial activities were evaluated hereby.

2. Results and discussion

2.1. Synthesis of egonol derivatives

The synthesis of egonol derivatives was figured out in Figures 1 and 2. The starting material was isolated from the seeds of *S. officinalis* and its isolation procedure was explained in our previous work.[10]

The reaction of egonol with triethylamine and chloroacetyl chloride in dry diethyl ether at room temperature gave compound **A**, whose molecular formula is $C_{21}H_{19}ClO_6$ and the molecular ion peaks were at *m/z* 403.0 and 405.0 $[M]^+$. Most of the ^1H and ^{13}C NMR signals of compound **A** were similar to those of egonol, which is isolated in our previous work,[10] besides the extra ^1H NMR signal at δ_H 4.05 (2H, s) and ^{13}C NMR signal at δ_C 41.10 which correspond to two hydrogen and methylene carbon signals of chloroacetyl group, respectively. Moreover, the signal for carbonyl carbon at δ_C 167.56 in the ^{13}C NMR spectrum indicated that hydroxyl group was converted to an ester group. Apart from these, shifting of C-3″ signal from δ_C 62.70 to δ_C 65.74 in the ^{13}C NMR spectrum and also the chemical shifts of H-3″ from δ_H 3.73 to 4.25 in the ^1H NMR spectrum showed that the primary alcohol group was converted to chloroester group. In the IR spectrum of **A** absorption band at 1750 cm^{-1} and the disappearance of hydroxyl absorption band at 3741 cm^{-1} also confirmed completion of the substitution reaction. On the basis of these spectroscopic data compound **A** was elucidated as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate*.

In order to synthesise compound **B**, egonol was reacted with sulfuric acid in a mixture of acetonitrile and CH_2Cl_2. The positive ion mode LCMS/APCI analysis of compound **7** gave the molecular ion peaks at *m/z* 406.0 $[M]^+$ and 327.0 for the $[M-(HSO_3)+2H]^+$. The shifting of both H-3″ and C-3″ signals from δ_H 3.73 to 4.06 and δ_C 62.70 to 67.30 in ^1H and ^{13}C NMR spectra, respectively, proved the conversion of primary alcohol to hydrogen sulfate. Furthermore, the IR spectrum exhibited strong absorption bands at 1214 cm^{-1}, consistent with the presence of sulfate groups. According to the above mentioned results, compound **B** was deduced as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl hydrogen sulfate* whose molecular formula is $C_{19}H_{18}O_8S$.

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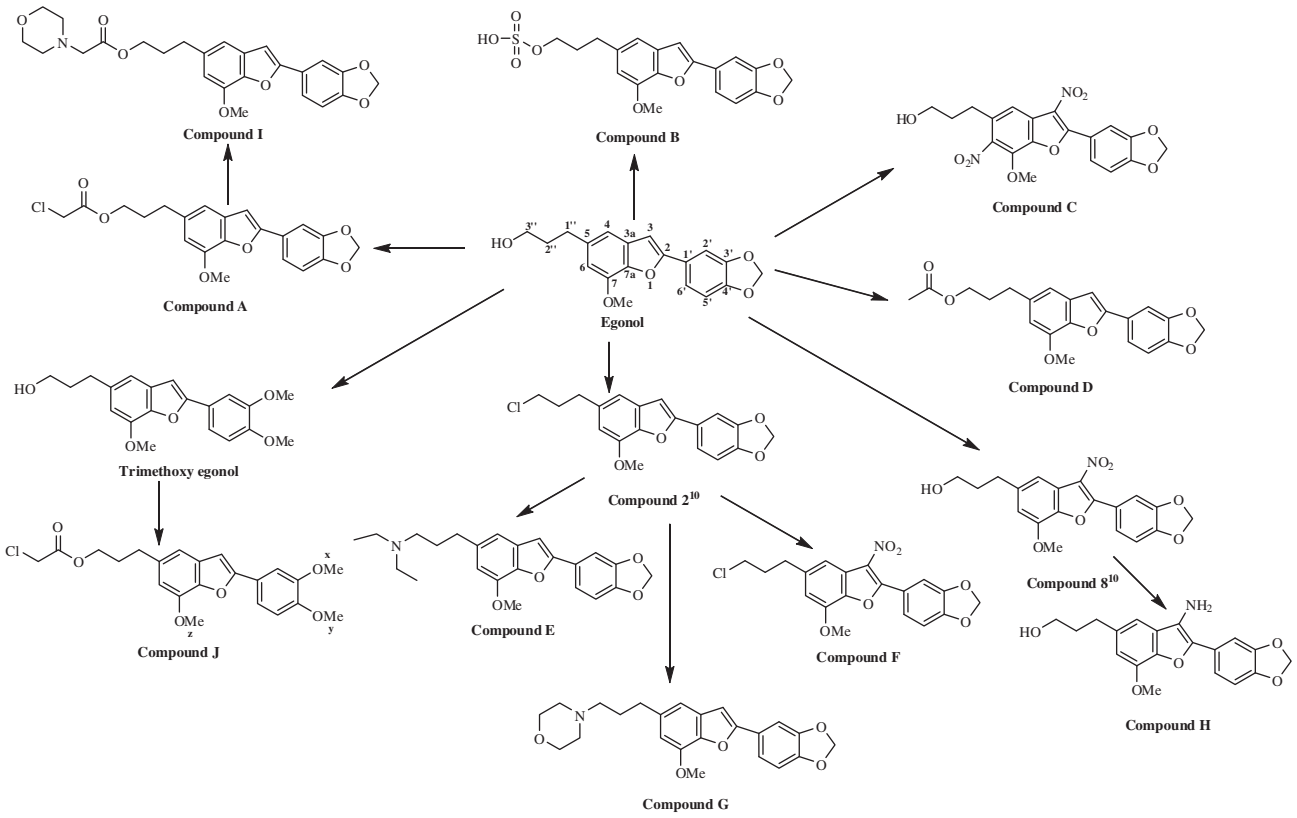

Figure 1. Synthetic pathway of compounds **A**–**J**.

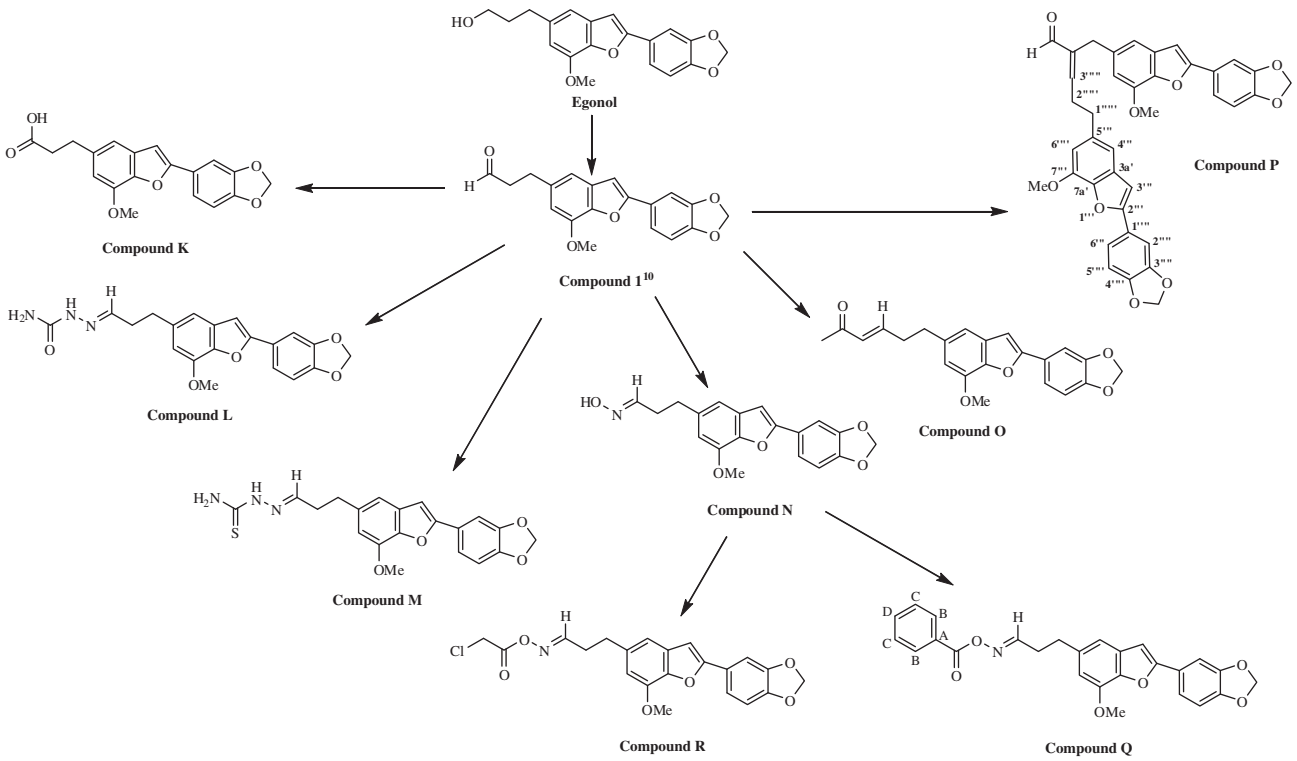

Figure 2. Synthetic pathway of compounds **K**–**R**.

Adding egonol into potassium nitrate in sulfuric acid media in CH_2Cl_2 resulted in compound **C**. The molecular formula of compound **C** was established as $C_{19}H_{16}N_2O_9$ by positive ion mode LCMS/APCI analysis, the peaks were at *m*/*z* 416.10 $[M]^+$, 403.0 $[M-(OH)+3H]^+$, 327.05 $[M-2\times(NO_2)+H]^+$. The disappearance of ^1H NMR signals at δ_H 6.81 and 6.66 for H-3 and H-6, respectively,

consistent with electrophilic aromatic nitration of egonol that was placed at C-3 and C-6 positions. The chemical shifts of C-3 and C-6, from δ_C 100.76 to 125.51 for the former and from δ_C 107.86 to 140.38 for the latter in ^{13}C NMR spectra also supported nitration of C-3 and C-6 positions of egonol. The presence of typical absorption bands at 1543 cm^{-1} (N–O asymmetric stretch) and 1354 cm^{-1} (N–O symmetric stretch) in the IR spectrum in the final product confirmed the successful nitration of egonol. Thus, the structure of new compound **C** was established as *5-[3″-hydroxypropyl]-7-methoxy-3,6-dinitro-2-(3′,4′methylene dioxyphenyl) benzofuran*.

Compound **D,** which was previously isolated from *Styrax* species,[11] was obtained from the reaction of egonol with acetic anhydride. The reaction of egonol with acetic anhydride gave *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propylacetate* (**D**). LCMS/APCI spectrum gave the peaks at *m*/*z* 368 $[M]^+$, 279.0 $[M-(CH_3–COO–CH_2–CH_2)-2H]^+$ and is appropriate for a molecular formula of $C_{21}H_{20}O_6$. Analysis of ^1H and ^{13}C NMR data of **D** in comparison with those of egonol, clearly indicated that the difference between the two compounds should be confined to the occurrence of acetoxy group instead of a primary alcoholic function. In the ^1H NMR spectrum of compound **D**, a new additional signal belonging to methyl protons of acetoxy group at δ_H 2.13 (s, 3H) and shifting of H-3″ signal from δ_H 3.73 (t, 2H, *J* = 6.4, 6.4) to 4.13 (t, 2H, *J* = 6.4, 6.8) indicated that hydroxyl group was acetylated. This conversion was also supported by an absorption band at 1736 cm^{-1} (C=O stretching) in the IR spectrum. These results allowed us to deduce the structure *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl acetate* for **D**.

Compounds **E**, **F**, and **G** were synthesized from *5-[3″-chloropropyl]-7-methoxy-2-(3′,4′-methylenedioxyphenyl) benzofuran* (compound **2**), which was isolated in our previous study.[10] The reaction of compound **2** and diethylamine in chloroform afforded compound **E**. LCMS/APCI spectrum gave *m*/*z* 382.10 $[M+H]^+$ (100), 383.10 $[M+2H]^+$ (24.3), 354.10 $[M-(2\times CH_3)+3H]^+$ (4.8), 307 $[M-(N(CH_3CH_2)_2)+2H]^+$ (3.5) and is appropriate for a molecular formula of $C_{23}H_{27}NO_4$. In the ^1H NMR spectrum, the three methylene groups of the alkyl chain were observed at δ_H 2.87 (H-1″), 2.14 (H-2″), and 2.77 (H-3″) instead of at δ_H 2.86, 2.16 and 3.57 for compound **2**. New additional signals belonging to methylenic and methylic protons of $–(N–CH_2CH_3)_2$ group were recorded at δ_H 2.98 (4H, m) and at δ_H 1.27 (6H, q), respectively. ^{13}C NMR data of the compound also confirmed the proposed structure. Characteristic signals were observed at δ_C 46.75 and 9.34 for methylene and methyl carbons of $–(N–CH_2CH_3)_2$ group, respectively. Moreover, the ^{13}C NMR spectrum showed that the C-3″ signals resonated at δ_C 51.12 instead of at δ_C 44.46 for compound **2** (Table 4). Thus, the structure of **E** was established as *{3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl}diethylamine*.

The product of the reaction of compound **2** with KNO_3 and H_2SO_4 gave compound **F**, whose molecular formula is $C_{19}H_{16}ClNO_6$ and the molecular ion peaks were at *m*/*z* 391.2 $[M+H]^+$ and 392.2 $[M]^+$. Full assignments of the proton and carbon signals of **F** in comparison with those of **2** showed their considerable structural similarity. (Tables 2 and 4). The difference consisted only absence of the signals at δ_H 6.77/δ_C 100.56 (H-3/C-3 in compound **2**) and the presence of a signal at δ_C 140.48 instead of δ_C 100.56 in compound **F,** which indicated that the nitration reaction took place at C-3 position. On the basis of these evidence, the structure of compound **F** was established as *5-(3″-chloropropyl)-7-methoxy-3-nitro-2-(3′,4′methylene dioxyphenyl)benzofuran*.

The reaction of compound **2** with morpholine gave compound **G**, which was identified as a morpholine derivative of compound **2**. LCMS/APCI of **G** gave a pseudomolecular ion peak at *m*/*z* 396.10 $[M+H]^+$, appropriate for a molecular formula of $C_{23}H_{25}NO_5$. A multiplet in the ^1H NMR spectrum at δ_H 3.66 with an integral area of four protons is assigned to the H-6‴ and H-2‴ methylenes, adjacent to the ether oxygen of the morpholine ring and this signal correlates to a single $–CH_2–$ peak at δ_C 67.15 in ^{13}C NMR spectrum. Similarly, a ^1H NMR multiplet at δ_H 2.38 corresponding to four protons is assigned to the H-5‴ and H-3‴ methylene protons adjacent to the nitrogen atom and correlates to a single $–CH_2–$ peak at δ_C 53.93 in ^{13}C NMR spectrum. Therefore, compound **G** was determined as *4-{3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl}morpholine*.

Compound **H** was prepared from *5-[3″-hydroxypropyl]-7-methoxy-3-nitro-2-(3′,4′-methylenedioxyphenyl)benzofuran* (compound **8**),[10] and hydrazine monohydrate in EtOH. The LCMS/APCI mass spectrum of **H** showed a major ion peak at *m*/*z* 345.10 $[M+4H]^+$ ascribable to the molecular formula $C_{19}H_{19}O_5N$ and also a peak at *m*/*z* 327.0 $[M-(NH_2)+2H]^+$ corresponding to the loss of $–NH_2$ group. The NMR data of **H** were in good agreement with those of compound **8**,[10] except for the downfield shift of C-3 at δ_C 168.32, C-2 at δ 122.68, and C-4 at δ 163.12, suggesting that **H** was a *{5-[3″-hydroxypropyl]-7-methoxy-3-amino-2-(3′,4′methylene dioxyphenyl) benzofuran}*.

In order to synthesize compound **I**, compound **A** was reacted with morpholine. LCMS/APCI mass spectrum of **I** showed major ion peaks at *m*/*z* 454.10 $[M+H]^+$ and 455.10 $[M+2H]^+$ ascribable to the molecular formula $C_{25}H_{27}NO_7$ and also a peak at *m*/*z* 327.10 $[M-(O-(CH_2CH_2)2N–CH_2–CO)+H]^+$. The signals due to methine protons at δ_H 3.76 on oxygen-bearing carbon atoms and at 2.60 on nitrogen-bearing carbon atoms appeared in the ^1H NMR spectrum. The resonances for the oxygenated carbons also indicated the presence of two oxymethine carbons at δ_C 67.01 and two nitrogenated carbons at δ_C 53.53. Besides, the proton signal of $–CH_2COO–$ group was shifted to upfield region δ_H 3.20 (Table 2). Thus, the structure of **I** was determined as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl morpholin-4-ylacetate*.

Compound **J** was obtained from the reaction of trimethoxy egonol with chloroacetyl chloride in dried diethyl ether. LCMS/APCI of **J** gave a molecular ion peak at *m*/*z* 419.10 $[M]^+$, appropriate for a molecular formula of $C_{22}H_{23}ClO_6$. The chloroacetylation of trimethoxy egonol supported by the presence of methylene signal at δ_H 4.26 in the $^{1H\ NMR}$ spectrum and also the carbonyl peak at 1731 cm^{-1} in the IR spectrum. Shifting of H-3″ signal from δ_H 3.57 to 4.26 in the ^1H NMR spectrum also showed that the primary alcohol group converted to chloroester group. Therefore, the structure of compound **J** was assigned as *3-[2-(3,4-dimethoxyphenyl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate*.

3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propanal (compound **1**)[10] was used as a starting material for the synthesis of compounds **K**–**P**. The reaction of compound **1** with H_2O_2 in acetone gave the oxidation product (compound **K**). The positive ion mode LCMS/APCI analysis of compound **K** gave the pseudomolecular ion peaks at *m*/*z* 341.0 $[M+H]^+$ and 323.0 for the $[M-OH]^+$. The disappearing of the aldehyde proton signal at δ_H 9.85 and shifting of C-3 signal to δ_C 174.63 indicated that compound **K** was *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanoic acid*.

The reaction of compound **1** and semicarbazide in MeOH afforded compound **L**. The molecular formula of compound **L** was established as $C_{20}H_{19}N_3O_5$ by positive ion mode LCMS/APCI mass spectrum peaks at *m*/*z* 380.0 $[M+H]^+$, 307 $[M-(NH_2CONHN)+H]^+$. The semicarbazone derivative exhibited characteristic amide bonds at 3466–3196 cm^{-1} and 1698 cm^{-1} in the IR spectrum. A sharp band at 1582 cm^{-1} in the semicarbazone derivative was attributed to the characteristic –C=N group. Moreover, extra ^1H NMR signals at δ_H 6.07 ($NH_2C=O$) and 9.75 (NH_2CONH) and shifting H-3″ signal from δ_H 9.85 to 7.20 also confirmed completion of the reaction. Thus, compound **L** was identified as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal semicarbazone*.

When compound **1** was reacted with thiosemicarbazide in MeOH, the product was compound **M**. The molecular formula of compound **M** was established as $C_{20}H_{19}O_4N_3S$ by LCMS/APCI mass spectrum (398.05 $[M+H]^+$, 307.0 $[M-(H_2N-CS-NH-N)-H]^+$, 308.0 $[M-(H_2N-CS-NH-N)]^+$). The IR spectrum of compound **M** showed a stretching band of C=S at 1262 cm^{-1} and the absorption bands of $-NH_2$ group at 3417 and 3263 cm^{-1}, its ^1H NMR spectrum showed the signal of H-3″ at δ_H 7.45 (1H, t) instead of δ_H 9.85 in compound **1**[10] and –C=SNH signal was displayed at δ_H 11.03. In the ^{13}C NMR spectra, the signals belonging to –N=CH and $NH_2C=S$ appeared at δ_C 147.43 and 178.3, respectively. Therefore, compound **M** established as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal thiosemicarbazone*.

A hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) and sodium acetate in acetonitrile undergo a reaction with compound **1** to give **N** as a product. In the IR spectrum of compound **N** a broad OH absorption peak was observed between 3428 and 3419 cm^{-1}. In the ^1H NMR spectra, the signals belonging to HC=N– and =N–OH appeared at δ_H 6.69 and 10.78, respectively. In the ^{13}C NMR spectra of compound **N**, C=N signal was displayed at δ_C 150.42 while C=O signal disappeared. Thus, the structure of compound **N** was determined as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal oxime*.

In order to obtain the Wittig product, compound **1** reacted with the Wittig reagent [1-(triphenylphosphoranylidene) acetone; $PPh_3=CHCOCH_3$] in THF and afforded compound **O**. The molecular formula $C_{22}H_{20}O_5$ was deduced from LCMS/APCI 365.0 $[M+H]^+$, 307.0 $[M-(CH_3-CO-C)-2H]^+$, 279.0 $[M-(CH_3-CO-C=CH-C)-H]^+$, ^1H and ^{13}C NMR spectroscopic data. The signals belonging to carbonyl carbon and methyl carbon of acetyl group were seen at δ_C 197.46 and 33.59, respectively, in the ^{13}C NMR spectrum of compound **O**. In the ^1H NMR spectrum, the singlet at δ_H 2.15, which corresponds carbonyl bonded methyl group, and two olefinic protons at δ_H 6.75 and 6.06 proved the formation of Wittig product and led to compound *6-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] hex-3-en-2-one*.

The reaction of compound **1** and KOH in THF gave the aldol product (compound **P**). The olefinic proton signal at δ_H 6.45 in the ^1H NMR spectrum and olefinic carbon signals at δ_C 143.31 and 155.35 in the ^{13}C NMR spectrum were exhibited the formation of condensation product. Thus, the structure of compound **P** was determined as *5-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]-2-{[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]methyl}pent-2-enal* with molecular formula $C_{38}H_{30}O_9$.

The reaction of compound **N** with benzoyl chloride in dried THF gave compound **Q**, whose molecular formula is $C_{26}H_{21}NO_6$ and the molecular ion peak was at *m/z* 442 $[M-H]^+$. The characteristic monosubstituted aromatic ring signals in the ^1H NMR (δ_H 7.35, 7.45 and 8.02) and ^{13}C NMR spectra (δ_C 130.37, 132.82 and 123.59) showed the oxime hydroxyl group was converted to aromatic ester. Furthermore, this conversion was also supported by carbonyl peak at 1719 cm^{-1} in the IR spectrum. Therefore, compound **Q** was established as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal O-benzoyloxime*.

Compound **R** was obtained from the reaction of compound **N** with chloroacetyl chloride. The LCMS/APCI spectrum of **R** (*m/z* 416 $[M]^+$) supported a molecular formula of $C_{21}H_{18}ClNO_6$. The major ion peak at *m/z* 307.0 was assigned to $[M-(Cl-CH_2-COON)+H]^+$. The formation of chloroacetyl ester was proved by the absorption peak at 1651 cm^{-1} (C=O) and signals displayed at δ_C 166.31 (C=O), 43.96 ($-CH_2Cl$) in the ^{13}C NMR spectra besides the extra ^1H NMR signal at δ_H 4.17 ($-CH_2Cl$). Thus, the structure of compound **R** was established as *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal O-(2-chloroacetyl)oxime*.

2.2. Biological evaluation

Egonol and its derivatives were evaluated for their antimicrobial activities against *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC 10231 and *Escherichia coli* ATCC 8739 microorganisms using a standard Muller Hilton Broth (MHB) method. Stock solution of all compounds was prepared in DMSO. The minimum inhibitory concentration (MIC in μg/mL) was determined for each compound. All results are presented in Table 1.

The obtained data reported that compound **B** exhibited improved activities against all tested bacteria than egonol. While the compounds **F**, **G**, **L**, **P** and **R** were found to be the most active against *C. albicans*, aldol condensation product of egonol (compound **P**) was found to the most active derivative against *S. aureus* with values of 25 μg/mL. Compounds **A**, **B**, **D**, **E**, **J**, **K**, **M**, **O** and **Q** also showed noticeable activity against *C. albicans* showing MIC values between 200 and 50 μg/mL.

Among compounds **A**, **D**, **E**, **N**, and **O** were inactive against all tested microorganisms except *C. albicans*, indicating that the introduction at C-3′ groups different from the hydroxyl substituent was in general detrimental for the antibacterial activity, but positive for antifungal activity except compound **C**. Regarding compound **C**, the results showed that substitution of C-3′ hydroxyl group with sulfonic acid moiety increased activity against all tested bacteria other than *S. aureus*, which remained the same. In case of compound **B**, keeping the hydroxyl group at C-3′ fixed and bearing $-NO_2$ groups at 3-, 6-positions led to an improvement of the MIC values. On the other hand reduction of $-NO_2$ group at C-3, as in compound **H**, caused loss of activity except against *C. albicans*.

3. Experimental

3.1. General

The 1D and 2D NMR spectra were measured in $CDCl_3$ at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR on a Varian AS-400 spectrometer. LC–MS was recorded on an AGILENT 1100MSD spectrometer and FAB-MS was obtained using a zapSpec FAB (+) spectrometer. CC and PTLC were carried out on Si Gel 60 Merck 7734 and 5554. TLC was carried out on Si Gel 60 F254 aluminium plates (Merck 5554).

Table 1
Antimicrobial activity of egonol and synthesised compounds (in DMSO)

Compound	*S. aureus*[a]	*B. subtilis*[a]	*C. albicans*[a]	*E. coli*[a]
Egonol	800	800	25	800
A	*	*	100	*
B	400	400	50	400
C	800	400	400	400
D	*	*	200	*
E	*	*	200	*
F	*	*	25	800
G	200	*	25	*
H	*	*	800	*
I	*	*	*	800
J	400	400	200	*
K	200	800	50	*
L	*	400	25	*
M	*	400	200	*
N	*	*	800	*
O	*	*	200	*
P	25	*	25	*
Q	*	400	100	*
R	*	*	25	800

[a] MIC (μg/mL), minimum inhibition concentration.
* Not active.

Table 2
^{1}H NMR data (J in Hz) of egonol and compounds **A–I** (400 MHz, δ ppm, in $CDCl_3$)

Position	Egonol	Compound								
		A	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
3	6.81, s, 1H	6.78, s, 1H	6.89, s, 1H	–	6.78, s, 1H	6.77, s, 1H	–	6.86, s, 1H	–	6.77, s, 1H
4	6.99, s, 1H	6.94, s, 1H	6.94, s, 1H	7.78, s, 1H	6.95, s, 1H	6.94, d, 1H, J = 1.6	7.57, s, 1H	7.24, s, 1H	7.43, s, 1H	6.94, s, 1H
6	6.66, s, 1H	6.59, s, 1H, J = 0.8	6.73, s, 1H	–	6.60, s, 1H	6.62, d, 1H, J = 1.2	6.77, s, 1H	6.53, s, 1H	6.51, s, 1H	6.59, d, 1H
2′	7.34, d, 1H, J = 1.5	7.31, d, 1H, J = 1.6	7.30, d, 1H, J = 1.6	7.47, d, 1H, J = 1.6	7.31, d, 1H, J = 1.6	7.31, d, 1H, J = 1.6	7.50, d, 1H, J = 2.0	6.70, 1H, J = 1.6	6.55, d, 1H, J = 1.6	7.31, d, 1H, J = 1.6
5′	6.90, d, 1H, J = 8.1	6.87, d, 1H, J = 8.4	6.88, d, 1H, J = 8.4	7.00, d, 1H, J = 8.4	6.87, d, 1H, J = 8.4	6.87, d, 1H, J = 8.4	6.95, d, 1H, J = 8.4	6.79, d, 1H, J = 8.4	6.84, d, 1H, J = 8.8	6.87, d, 1H, J = 8.4
6′	7.43, dd, 1H, J = 1.6, 8.1	7.40, dd, 1H, J = 1.2, 1.6	7.39, dd, 1H, J = 1.6, 1.6	7.64, dd, 1H, J = 1.6, 8.0	7.40, dd, 1H, J = 1.6, 1.6	7.40, dd, 1H, J = 1.6, 8.0	7.64, dd, 1H, J = 1.6, 2.0	7.32, dd, 1H, J = 0.8, 7.2	7.45, dd, 1H, J = 2.0, 7.6	7.40, dd, 1H, J = 1.6, 1.6
–OCH_2O–	6.02, s, 2H	5.99, s, 2H	5.99, s, 2H	6.11, s, 2H	5.99, s, 2H	5.99, s, 2H	6.07, s, 2H	5.91, s, 2H	5.97, s, 2H	6.00, s, 2H
1″	2.81, t, 2H, J = 7.5, 7.8	2.78, t, 2H, J = 7.6, 7.6	2.79, t, 2H, J = 7.2, 8.0	2.82, t, 2H, J = 7.6, 8.0	2.76, t, 2H, J = 7.2, 8.0	2.87, m, 2H, J = 8.0, 8.0	2.93, t, 2H, J = 7.6, 7.6	2.33, t, 2H, J = 7.6, 7.6	2.55, t, 2H, J = 7.2, 8.0	2.75, t, 2H, J = 7.2, 8.0
2″	1.97, p, 2H	2.08, p, 2H	2.02, p, 2H	1.96, p, 2H	2.03, p, 2H	2.14, p, 2H	2.19, p, 2H	1.81, p, 2H	1.78, p, 2H	2.03, p, 2H
3″	3.73, t, 2H, J = 6.4, 6.4	4.25, t, 2H, J = 6.4, 6.4	4.06, t, 2H, J = 6.4, 6.4	3.71, t, 2H, J = 6.4, 6.0	4.13, t, 2H, J = 6.4, 6.8	2.77, t, 2H, J = 7.2, 7.2	3.58, t, 2H, J = 6.0, 6.8	2.64, t, 2H, J = 6.8, 6.4	3.57, t, 2H, J = 6.0, 6.8	4.20, t, 2H, J = 6.8, 6.8
–OMe	4.05, s, 3H	4.03, s, 3H	4.00, s, 3H	4.30, s, 3H	4.03, s, 3H	4.03, s, 3H	4.02, s, 3H	3.94, s, 3H	3.83, s, 3H	4.03, s, 3H
Cl–CH_2–		4.05, s, 2H								
CH_3–C=O					2.13, s, 3H					
CH_3CH_2N–						1.27, t, 6H, J = 7.2, 2.8				
CH_3CH_2N–						2.98, q, 4H				
–NCH_2CH_2O–								2.38, t, 4H		2.60, t, 4H, J = 4.8, 4.4
–NCH_2CH_2O–								3.66, t, 4H		3.76, t, 4H, J = 4.8, 4.8
–NH_2									1.58, s, 2H	
–CH_2COO–										3.20, s, 2H

3.2. Plant material

Fruits of *S. officinalis* L. were collected from Aydın, Turkey in September 2005. A voucher specimen was deposited in the Herbarium of Ege University (EGE 4759).

3.3. Extraction

Air-dried and powdered plant material of 241 g. *S. officinalis* was extracted with *n*-hexane at room temperature. After filtration, the solvent was removed by rotary evaporation to give a crude extract (113.72 g). An aliquot of the crude was hydrolysed with 33% KOH at 100 °C for 3 h. The reaction mixture was collected and extracted with CH_2Cl_2, then the organic phase was subjected into Si-gel CC to afford egonol. The identification of the achieved 6 g egonol was done by ^1H and ^{13}C NMR.

3.4. Synthesis

3.4.1. Compound A

3.4.1.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate ($C_{21}H_{19}ClO_6$). To a solution of egonol (100 mg, 3.06×10^{-4} mol) in dry Et_2O (5 mL) in a round bottomed two-necked flask was added Et_3N (10.5 mg, 1.04×10^{-4} mol). The reaction mixture was stirred at room temperature under Ar for 30 min. After cooling to 0 °C, the mixture was stirred for a further 1 h while purging with Ar. A solution of chloroacetyl chloride (13.19 mg, 1.16×10^{-4} mol) in dry Et_2O (5 mL) was added to the reaction flask and stirred for 15 min at 0 °C. After leaving 96 h, a solution of $NaHCO_3$ (10%) was added into reaction flask. The aqueous solution was extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was purified via column chromatography on silica gel using hexane/EtOAc (10:1) as an eluent to yield **A** (74.2 mg, 60.1%); mp: 111.4 °C; UV λ_{max} CH_2Cl_2: 230.0, 318.0 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3741, 3648, 2934, 2668, 1750, 1643, 1585, 1500, 1412, 1325, 1229, 1122, 1033, 1009, 825, 696; LCMS/APCI *m/z* (rel. int.): 405.0 $[M]^+$ (17.0), 403.0 $[M]^+$ (48.5), 327 $[M-(Cl-CH_2-C{=}O)+H]^+$ (11.7); ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.2. Compound B

3.4.2.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl hydrogen sulfate ($C_{19}H_{18}O_8S$). Concentrated H_2SO_4 (3 mL) was added slowly to a solution of egonol (150 mg, 4.60×10^{-4} mol) in a acetonitrile/CH_2Cl_2 (10 mL:2 mL). The solution was stirred for 2 h at 0 °C and for an additional 16 h at room temperature. Organic solvents were then removed and water (10 mL) was added to the mixture and then extracted with *n*-BuOH (3x10 mL). *n*-BuOH phase was neutralized with $NaHCO_3$ (10%, 10 mL) and the water layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were evaporated to dryness. The residue was purified by column chromatography on silica gel using CH_2Cl_2 to afford **B** (75.7 mg, 40.5%); mp: 180 °C (dec); UV λ_{max} MeOH: 217.0, 316.0; IR spectrum ν_{max} MeOH cm^{-1}: 3666, 2966, 2923, 1599, 1473, 1448, 1231, 1214, 1054, 1013, 927; LCMS/APCI *m/z* (rel. int.): 406.0 $[M]^+$ (0.8), 327 $[M-(HO-SO_2)+2H]^+$ (9.1), 403 $[M-3H]^+$ (50.3); ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.3. Compound C

3.4.3.1. 5-[3″-Hydroxypropyl]-7-methoxy-3,6-dinitro-2-(3′,4′methylene dioxyphenyl) benzofuran ($C_{19}H_{16}N_2O_9$). Powdered KNO_3 (50.5 mg, 5.00×10^{-4} mol) was treated with the appropriate amount of H_2SO_4 (96%, 1 mL) and the mixture was stirred for 15 min at room temperature. CH_2Cl_2 (25 mL) was added to the homogeneous slurry and the mixture was cooled at 0 °C with vigorous stirring. A solution of egonol (163 mg, 5.00×10^{-4} mol) in CH_2Cl_2 was added drop wise to the solution, and then, stirred at room temperature for the required time. The reaction mixture was washed twice with 10% aqueous Na_2HCO_3 and then organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The residue was purified by PTLC using hexane/EtOAc/H_2O (6:4:0.5) to afford **C** (24 mg, 11,5%); mp: 188.7–189.0 °C; UV λ_{max} CH_2Cl_2: 229.0, 269.0, 384.0 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3664, 3642, 3354, 3109, 2924, 2853, 2335, 1882, 1736, 1698, 1605, 1543, 1507, 1467, 1439, 1354, 1320, 1277, 1230, 1144, 1099, 1056, 1032, 960, 910, 876, 821, 765, 688, 674; LCMS/APCI *m/z* (rel. int.): 416.10 $[M]^+$ (0.2), 403.0 $[M-(OH)+3H]^+$ (100), 327.05 $[M-2\times(NO_2)+H]^+$ (15.4); ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.4. Compound D

3.4.4.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl acetate ($C_{21}H_{20}O_6$). To a mixture of egonol (50 mg, 1.53×10^{-4} mol) and THF (5 mL) were added acetic anhydride (14.5 mL) and $AlCl_3$ (20 mg, 1.50×10^{-4} mol). After stirring at 0 °C for 1 h, the mixture was allowed to stir for an additional 48 h at room temperature. After addition of a solution of HCl (1%, 10 mL), the mixture was extracted with CH_2Cl_2 (3×10 mL). And then the CH_2Cl_2 phase was extracted with $NaHCO_3$ solution (10%; 3×10 mL). The organic layer was dried (Na_2SO_4) and concentrated to yield **D** (48.5 mg, 85.9%): (mp 85.9–87.0 °C; LCMS/APCI *m/z* (rel. int.): 368 $[M]^+$, 279.0 $[M-(CH_3-COO-CH_2-CH_2)-2H]^+$ (1.1); UV λ_{max} CH_2Cl_2: 230.0, 318.0 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3453, 2923, 2852, 2043, 1736, 1620, 1600, 1503, 1477, 1449, 1386, 1366, 1334, 1233, 1145, 1116, 1039, 995, 962, 930, 871, 819, 742, 722, 696, 649, 605, 512, 459; ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.5. Compound E

3.4.5.1. {3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl}diethylamine ($C_{23}H_{27}NO_4$). *5-[3″-Chloropropyl]-7-methoxy-2-(3′,4′-methylenedioxyphenyl) benzofuran* (compound **2**)[10] (40 mg, 1.16×10^{-4} mol) was added to a mixture of diethylamine (20 mL) in chloroform (3 mL) and stirred for 96 h at room temperature. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3×7 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC using hexane/EtOAc (9:2) to gave **E** (22.0 mg, 49.7%); mp 127.0–128.0 °C; LCMS/APCI *m/z* (rel. int.): 382.10 $[M+H]^+$ (100), 383.10 $[M+2H]^+$ (24.3), 354.10 $[M-(2\times CH_3)+3H]^+$ (4.8), 307 $[M-(N(CH_3CH_2)_2)+2H]^+$ (3.5); UV λ_{max} CH_2Cl_2: 230.0, 319.0 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3736, 3642, 2928, 2851, 2642, 2318, 2000, 1736, 1662, 1621, 1500, 1470, 1443, 1363, 1273, 1259, 1234, 1209, 1523, 1105, 1034, 927, 814, 762, 749, 691; ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.6. Compound F

3.4.6.1. 5-(3″-Chloropropyl)-7-methoxy-3-nitro-2-(3′,4′methylene dioxyphenyl)benzofuran ($C_{19}H_{16}ClNO_6$). KNO_3 (112 mg, 1.10×10^{-3} mol) and 96% H_2SO_4 (0.3 mL) was stirred for 15 min at 0 °C. After addition of CH_2Cl_2 (7 mL), a solution of compound **2** (40 mg, 1.16×10^{-4} mol) in CH_2Cl_2 (3 mL) was slowly added to the mixture and stirred for 48 h at room temperature. Water (10 mL) was added to the mixture and then extracted with CH_2Cl_2 (3×10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The obtained residue was purified via column chromatography on silica gel using hexane/EtOAc (9:1) to afford **F** (23.0 mg, 50.9%); mp: 137.3–138.3 °C; LCMS/APCI *m/z* (rel. int.): 391.2 $[M+H]^+$ (15.3), 392.2 $[M]^+$ (5.3), 341.0

$[M-(Cl-CH_2)]^+$ (4.5), 327.05 $[M-(Cl-CH_2-CH_2)]^+$ (5.6); UV λ_{max} CH_2Cl_2: 228.0, 268.0, 381.0 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3680, 2972, 2512, 2844, 1738, 1473, 1346, 1259, 1215, 1054, 1013, 765, 750; ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.7. Compound G

3.4.7.1. 4-{3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl}morpholine ($C_{23}H_{25}NO_5$). To a solution of compound **2** (40 mg, 1.16×10^{-4} mol) in toluene (7 mL) was added morpholine (5.11×10^{-3} mg, 5.87×10^{-5} mol) and the mixture was heated under reflux for 40 h. Water (10 mL) was added to the resulting mixture and extracted with CH_2Cl_2 (3×7 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. 38.5 mg compound was obtained (83.9%); LCMS/APCI *m/z* (rel. int.): 396.10 $[M+H]^+$ (100), 397.1 $[M+2H]^+$ (23.4), 307.05 $[M-(O-(CH_2CH_2)_2N)-2H]^+$ (2.7); UV λ_{max} CH_2Cl_2: 233, 318 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 2924, 2854, 1620, 1600, 1550, 1503, 1476, 1449, 1365, 1332, 1263, 1232, 1214, 1144, 1116, 1070, 1038, 929, 861, 819, 741, 602, 512, 479, 459; ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.8. Compound H

3.4.8.1. 5-[3″-Hydroxypropyl]-7-methoxy-3-amino-2-(3′,4′methylene dioxyphenyl) benzofuran ($C_{19}H_{19}NO_5$). Two milligrams of 10% Pd–C catalyst was added to a solution of *5-[3″-hydroxypropyl]-7-methoxy-3-nitro-2-(3′,4′-methylenedioxyphenyl)benzofuran* (compound **8**)[10] (29 mg, 7.81×10^{-5} mol) in EtOH (3 mL) while stirring under Ar atmosphere and heated to 65 °C. A solution of hydrazine monohydrate (1 mL) in EtOH (3 mL) was slowly added into a flask and stirred for 24 h at room temperature while purging with Ar. Pd–C was filtered off, then the solvent was evaporated under vacuum. The crude product was eluted through an alumina column with CH_2Cl_2/MeOH (10:1) to afford compound **H** as an amorphous powder (11.7 mg, 43.9% yield); LCMS/APCI *m/z* (rel. int.): 345.10 $[M+4H]^+$ (37.7), 327.0 $[M-(NH_2)+2H]^+$ (40.2); UV λ_{max} CH_2Cl_2: 230.0, 279.0, 311.0 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3478, 3329, 2924, 2857, 2346, 1731, 1676, 1593, 1501, 1443, 1355, 1273, 1259, 1229, 1146, 1075, 1037, 930, 809, 765, 750; ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.9. Compound I

3.4.9.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propyl morpholin-4-ylacetate ($C_{25}H_{27}NO_7$). A mixture of compound **A** (40 mg, 9.93×10^{-5} mol) and morpholine (3.72×10^{-3} mg, 4.28×10^{-5} mol) in THF (5 mL) was refluxed with stirring for 10 h. The reaction mixture was diluted with water (10 mL) and then extracted with CH_2Cl_2 (3×7 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. Compound **I** was obtained as an amorphous powder (37.3 mg, 82.8% yield); LCMS/APCI *m/z* (rel. int.): 454.10 $[M+H]^+$ (100), 455.10 $[M+2H]^+$ (27.0), 327.10 $[M-(O-(CH_2CH_2)2N-CH_2-CO)+H]^+$ (19.6); UV λ_{max} CH_2Cl_2: 231, 318 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 2919, 1744, 1599, 1476, 1365, 1232, 1146, 1115, 1036, 929, 868, 820; ^1H and ^{13}C NMR data are presented in Tables 2 and 4.

3.4.10. Compound J

3.4.10.1. 3-[2-(3,4-Dimethoxyphenyl)-7-methoxy-1-benzofuran-5-yl]propyl chloroacetate ($C_{22}H_{23}ClO_6$). A solution of trimethoxy egonol (100 mg, 3.06×10^{-4} mol) and triethylamine (10.5 mg, 1.04×10^{-4} mol) in dry diethyl ether (5 mL) was stirred for 30 min at room temperature under Ar atmosphere. The solution was cooled at 0 °C and stirred for a further 2 h while purging with Ar. Chloroacetyl chloride (13.19 mg, 1.16×10^{-4} mol) in dry

Table 3
^1H NMR data (*J* in Hz) of compounds **J–O**, **Q** and **R** (400 MHz, δ ppm, in $CDCl_3$)

Position	Compound								
	J	**K**	**L**	**M**	**N**	**O**	**Q**	**R**
3	6.60, s, 1H	7.17, s, 1H	7.00, s, 1H	7.00, s, 1H	7.17, s, 1H	6.71.s, 1H	6.69, s, 1H	6.73, s, 1H
4	6.96, s, 1H	6.98, d, 1H	7.18, s, 1H	7.18, s, 1H	6.99, s, 1H	6.87, s, 1H	7.21, s, 1H	6.93, s, 1H
6	6.83, s, 1H	6.78, d, 1H, *J* = 1.2	6.76, d, 1H, *J* = 1.2	6.78, s, 1H	6.76, s, 1H	6.52, d, 1H, *J* = 1.2	6.55, s, 1H	6.60, s, 1H
2′	7.36, d, 1H, *J* = 1.6	7.37, d, 1H, *J* = 1.6	7.40, d, 1H, *J* = 1.6	7.40, d, 1H, *J* = 1.6	7.39, d, 1H, *J* = 1.6	7.24, d, 1H, *J* = 1.6	6.89, d, 1H, *J* = 1.6	7.24, d, 1H, *J* = 1.6
5′	6.93, d, 1H, *J* = 8.0	7.01, d, 1H, *J* = 7.6	7.07, d, 1H, *J* = 8.0	7.10, d, 1H, *J* = 8.0	7.01, d, 1H, *J* = 8.0	6.78, d, *J* = 8.0	6.78, d, 1H, *J* = 8.0	6.80, d, 1H, *J* = 8.0
6′	7.46, dd, 1H, *J* = 1.6, 1.6	7.40, dd, 1H, *J* = 1.2, 2.0	7.38, dd, 1H, *J* = 2.0, 2.0	7.38, dd, 1H, *J* = 8.0, 1.6	7.34, dd, 1H, *J* = 1.6, 8.0	7.32, dd, *J* = 8.0, 1.6	7.31, dd, 1H, *J* = 8.4, 9.6	7.33, dd, 1H, *J* = 1.6, 8.0
–OCH_2O–	–	6.06, s, 2H	6.03, s, 2H	6.07, s, 2H	6.06, s, 2H	5.91, s, 2H	5.95, s, 2H	5.93, s, 2H
1″	2.79, t, 2H, *J* = 7.2, 8.0	2.88, t, 2H, *J* = 7.6, 7.6	2.84, t, 2H, *J* = 7.6, 7.6	2.81, t, 2H, *J* = 7.2, 8.0	2.80, t, 2H, *J* = 7.2, 8.0	2.77, t, 2H, *J* = 8.0	2.94, t, 2H	2.95, t, 2H
2″	2.07, p, 2H	2.57, t, 2H, *J* = 7.2, 8.4	2.53, m, 2H	2.57, p, 2H	2.59, p, 2H	2.51, q, 2H, *J* = 8.0	3.91, q, 2H	3.51, q, 2H
3″	4.26, t, 2H, *J* = 6.8, 6.4	–	7.20, t, 1H, *J* = 0.8, 1.6	7.45, t, 1H	6.69, t, 1H, *J* = 5.2, 5.2	6.75, t, 1H	7.35, t, 1H	6.73, t, 2H
–OMe	–	3.93, s, 3H	3.94, s, 3H	3.95, s, 3H	3.93, s, 3H	3.95, s, 3H	3.95, s, 3H	3.98, s, 3H
Cl–CH_2–	4.05, s, 2H							4.17, s, 2H
–OMe (*x*, *y*, *z*)	3.92/3.98/4.04, s, 3H							
–N*H*–C=O			9.75, 1H	–		6.06, d, 1H, *J* = 16		
NH_2–C=O			6.07, 2H			2.15, s, 3H		
–N*H*–C=S							8.02, d, 2H, *J* = 8.0	
HO–N–				11.03			7.35, t, 2H, *J* = 7.6, 7.2	
–*CH*–C=O					10.78		7.45, d, 1H	
–CH_3							–	
B								
C								
D								

diethyl ether (5 mL) was added to the mixture. After stirring for 15 min at 0 °C, the mixture was warmed to room temperature and stirred for a further 96 h. The reaction was quenched by addition of aqueous $NaHCO_3$ solution and the mixture was extracted with diethyl ether (3 × 10 mL). The ether phase was dried over anhydrous sodium sulfate, evaporated to dryness and the solid was purified via column chromatography on silica gel by using hexane/EtOAc (10:1) to give **J** (10.6 mg; 8.7%). Mp: 63 °C; UV λ_{max} CH_2Cl_2: 230.0, 315.0 nm.; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3424, 2922, 2851, 1731, 1708, 1598, 1510, 1463, 1250, 1140, 1023, 932, 853, 741; LCMS/APCI *m/z* (rel. int.): 419.10 $[M]^+$ (11.5), 421.10 $[M]^+$ (4.1), 369.0 $[M-(Cl-CH_2)]^+$ (1.3); ^1H and ^{13}C NMR data are presented in Tables 3 and 5.

3.4.11. Compound K

3.4.11.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanoic acid ($C_{19}H_{16}O_6$). To a mixture of *3-[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]propanal* (compound **1**)[10] (61.5 mg, 1.90×10^{-4} mol) in acetone (9 mL), a solution of H_2O_2 (30%, 24 mL) was added and the mixture was stirred for 120 h at room temperature. Acetone was distilled off, 10 mL water was added and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness to give **K** (43.5 mg, 67.4%); mp: 148.2–149.0 °C; UV λ_{max} MeOH: 216.0, 316.0 nm.; IR spectrum ν_{max} MeOH cm^{-1}: 3738, 2978, 2862, 1733, 1681, 1454, 1363, 1209, 1054, 1033, 1009; LCMS/APCI *m/z* (rel. int.): 341.0 $[M+H]^+$ (100), 342.0 $[M+2H]^+$ (19.0), 323 $[M-OH]^+$ (3.5); ^1H and ^{13}C NMR data are presented in Tables 3 and 5.

3.4.12. Compound L

3.4.12.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal semicarbazone ($C_{20}H_{19}N_3O_5$). A solution of semicarbazide (32 mg, 4.00×10^{-4} mol) in water (7 mL) was added to a solution of compound **1** (100 mg, 3.08×10^{-4} mol) in MeOH (7 mL) under stirring. The mixture was kept a reflux for 1.5 h and then cooled to room temperature. After stirring overnight, water (10 mL) was added to the mixture and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated. Column chromatography on silica gel (CH_2Cl_2) afforded **L** (29.4 mg; 25.0%); mp: 200.2 °C; UV λ_{max} MeOH: 220.0, 316.0 nm.; IR spectrum ν_{max} MeOH cm^{-1}: 3466, 3196, 2923, 2853, 1698, 1582, 1475, 1439, 1372, 1271, 1232, 1218, 1127, 1040, 929, 766, 743, 633; LCMS/APCI *m/z* (rel. int.): 380.0 $[M+H]^+$, 354.0 $[M-(NH_2C)+H]^+$ (8.3), 307 $[M-(NH_2CONHN)+H]^+$ (100); ^1H and ^{13}C NMR data are presented in Tables 3 and 5.

3.4.13. Compound M

3.4.13.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal thiosemicarbazone ($C_{20}H_{19}N_3O_4S$). A solution of thiosemicarbazide (30 mg, 3.29×10^{-4} mol) in water (7 mL) was added to a solution of compound **1** (77 mg, 2.37×10^{-4} mol) in MeOH (7 mL). The mixture was refluxed for 1 h and then stirred at room temperature for 48 h. Water (10 mL) was added to the reaction mixture and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed on silica gel using CH_2Cl_2/MeOH (20:1) to give **M** (27 mg; 28.6%); mp: 181.7–182.5 °C; UV λ_{max} CH_2Cl_2: 216.0, 274.0, 316.0 nm.; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3417, 3263, 3159, 3000, 2923, 2846, 2675, 2318, 2032, 1733, 1593, 1525, 1497, 1478, 1445, 1360, 1262, 1229, 1209, 1144, 1111, 1034, 993, 927, 861, 812, 768, 749, 581; LCMS/APCI *m/z* (rel. int.): 398.05 $[M+H]^+$ (10.3), 307.0 $[M-(H_2N-CS-NH-N)-H]^+$ (57.5), 308.0 $[M-(H_2N-CS-NH-N)]^+$ (11.6); ^1H and ^{13}C NMR data are presented in Tables 3 and 5.

3.4.14. Compound N

3.4.14.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal oxime ($C_{19}H_{17}NO_5$). A mixture of the compound **1** (100 mg, 3.08×10^{-4} mol), hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$) (5.5 mg, 7.94×10^{-5} mol) and sodium acetate (9.6 mg, 1.17×10^{-4} mol) were dissolved in acetonitrile (6 mL) and water (2 mL). The solution was stirred at room temperature for 24 h. Acetonitrile was evaporated. After addition of 10 mL water, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous sodium sulfate and concen-

Table 4
^{13}C NMR data of egonol and compounds **A–C**, and **E–I** (100 MHz, δ ppm, in $CDCl_3$)

Position	Egonol	Compound							
		A	**B**	**C**	**E**	**F**	**G**	**H**	**I**
2	156.51	156.45	155.81	156.94	156.58	156.91	156.31	163.12	156.43
3	100.76	100.55	102.11	125.51	100.51	140.48	100.58	168.32	100.54
3a	131.46	131.38	131.14	132.80	131.45	139.85	131.24	131.58	131.36
4	112.72	112.60	112.79	115.58	112.57	112.92	112.51	122.43/122.68/122.92	112.56
5	137.92	136.74	138.45	132.80	135.92	123.84	137.94	132.30	136.95
6	107.86	107.69	108.56	140.38	107.48	109.74	107.78	107.97/108.23/110.68	107.68
7	145.20	145.11	145.01	142.10	145.28	147.96	144.97	148.13/148.75/149.59	145.09
7a	142.88	142.82	142.32	137.20	142.93	145.09	142.71	143.64	142.80
$-OCH_2O-$	101.71	101.54	101.76	102.39	101.55	102.11	101.51	101.59	101.53
1′	125.12	124.90	124.75	120.20	124.80	121.21	124.98	122.43/122.68/122.92	124.90
2′	105.95	105.79	105.65	109.91	105.79	110.12	105.77	107.97/108.23/110.68	105.78
3′	148.46	148.31	148.64	151.62	148.33	150.83	148.29	148.13/148.75/149.59	148.31
4′	148.39	148.27	148.47	148.28	148.33	150.83	148.21	148.13/148.75/149.59	148.26
5′	109.02	108.84	109.50	108.92	108.86	108.62	108.83	107.97/108.23/110.68	108.84
6′	119.62	119.47	119.42	126.09	119.51	125.79	119.43	122.43/122.68/122.92	119.46
1″	32.83	30.66	31.56	28.13	33.52	33.54	29.91	34.46	30.86
2″	35.08	32.51	32.02	33.87	26.05	34.57	34.14	31.80	32.14
3″	62.70	65.74	67.30	62.04	51.12	44.31	56.39	62.31	64.31
–OMe	56.57	56.45	55.48	61.95	56.58	56.45	58.55	56.09	59.87
–*C*OO		167.56							
Cl–*C*H$_2$–		41.10							
*C*H$_3$CH$_2$N–					9.34				
CH$_3$*C*H$_2$N–					46.75				
–N*C*H$_2$CH$_2$O–							53.93		53.53
–NCH$_2$*C*H$_2$O–							67.15		67.01
–*C*H$_2$COO–									56.45
–*C*=O									170.36

Table 5
^{13}C NMR data of compounds **K–O**, **Q**, and **R** (100 MHz, δ ppm, in $CDCl_3$)

Position	Compound						
	K	**L**	**M**	**N**	**O**	**Q**	**R**
2	155.89	155.86	155.93	155.922	155.25	155.51	155.50
3	102.12	101.69	101.74	101.74	99.33	100.34	99.34
3a	131.14	131.15	131.19	131.20	132.10	131.73	130.37
4	112.73	112.91	112.87	112.73	111.29	111.45	111.48
5	137.72	137.90	137.77	137.90	135.38	141.61	132.90
6	108.43	108.48	108.60	108.34	106.43	107.63	107.64/106.41
7	145.01	144.94	145.03	145.08	143.87	144.10	144.12
7a	142.41	142.31	142.38	142.42	141.63	143.91	142.03
–OCH_2O–	101.74	102.09	102.13	102.12	100.30	104.54	100.37
1′	124.69	124.61	124.69	124.68	123.64	127.41	123.46
2′	105.66	105.56	105.68	105.66	104.54	106.12	106.41
3′	148.64	148.59	148.65	148.64	146.07/147.08	147.15	147.17
4′	148.51	148.47	148.52	148.51	146.07/147.08	147.09	147.13
5′	109.50	109.56	109.51	109.50	107.62	111.23	107.64/106.41
6′	119.43	119.49	119.45	119.44	118.25	118.31	118.32
1″	31.50	32.87	32.67	32.40	25.92	28.67	30.95
2″	36.67	34.38	34.48	27.29	33.59/33.79	30.93	39.89
3″	–	–	–	150.42	130.18/130.91	204.02	166.26
–OMe	56.49	56.46	56.51	56.49	55.23	55.24	55.27
–*C*=O					197.46	212.47	166.31
Cl–*C*H_2–							43.96
–*C*OOH	174.63						
–NH–*C*=O		144.39/144.94	147.43				
NH_2–*C*=O		144.39/144.94	178.33				
NH_2–*C*=S			25				
–*C*H–*C*=O					130.18/130.91		
–*C*H_3					33.59/33.79		
A						200.73	
B						123.59	
C						130.37	
D						132.82	

trated. Compound (100 mg) was obtained (95.7%). Mp: 150.0–153.0 °C; UV λ_{max} MeOH: 230.0, 319.0 nm.; IR spectrum ν_{max} MeOH cm^{-1}: 3428 (OH stretching), 2082, 1640, 663; LCMS/APCI *m/z* (rel. int.): 307.05 $[M-(OH-N)-H]^+$ (3.5), 279.0 $[M-(OH-N{=}CH-C)]^+$ (23.0); ^1H and ^{13}C NMR data are presented in Tables 3 and 5.

3.4.15. Compound O

3.4.15.1. 6-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] hex-3-en-2-one ($C_{22}H_{20}O_5$). To a solution of compound **1** (22 mg, 6.78×10^{-5} mol) in THF (7 mL) was added $PPh_3{=}CHCOCH_3$ (25.5 mg, 8.0×10^{-5} mol) and the mixture was refluxed for 10 h then allowed to cool. The mixture was hydrolysed with 10% HCl solution and then neutralized with a 5% solution of NaOH. The residue was extracted with CH_2Cl_2 (3×7 mL) and CH_2Cl_2 phase dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give **O** as an amorphous powder (21.3 mg, 86.2%); UV λ_{max} CH_2Cl_2: 230.0, 319.0 nm.; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 2960, 1668, 1478, 1433, 1260, 1184, 1118, 1021, 799, 749, 716, 540; LCMS/APCI *m/z* (rel. int.): 365.0 $[M+H]^+$ (1.8), 307.0 $[M-(CH_3-CO-C)-2H]^+$ (11.0), 279.0 $[M-(CH_3-CO-C{=}CH-C)-H]^+$ (100.0); ^1H and ^{13}C NMR data are presented in Tables 3 and 5.

3.4.16. Compound P

3.4.16.1. 5-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]-2-{[2-(1,3-benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl]methyl}pent-2-enal ($C_{38}H_{30}O_9$). To a solution of compound **1** (50 mg, 1.54×10^{-4} mol) in THF (5 mL), a solution of KOH (20 mg, 3.57×10^{-4} mol) in water was added portion wise. The reaction mixture was stirred at 0 °C for 6 h and then allowed to stand at 4 °C overnight. After dilution with water (10 mL), the solution was extracted with CH_2Cl_2 (3×7 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by PTLC using hexane/EtOAc/H_2O (6:4:0.5) to give **P** (16 mg, 16.5%). Mp: 85.0–87.0 °C; UV λ_{max} CH_2Cl_2: 230.0, 319.0 nm.; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3010, 2923, 2846, 2719, 1731, 1681, 1621, 1599, 1502, 1476, 1448, 1364, 1330, 1260, 1232, 1143, 1114, 1038, 987, 929, 871, 815, 751; ^1H and ^{13}C NMR data are presented in Table 6.

3.4.17. Compound Q

3.4.17.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal *O*-benzoyloxime ($C_{26}H_{21}NO_6$). A solution of compound **N** (60 mg, 1.77×10^{-4} mol) in dry THF (7 mL) was placed in a 50 mL two-necked flask with a reflux condenser. Benzoyl chloride (15.2 mg, 1.09×10^{-4} mol) was added to the reaction mixture and refluxed at 50 °C for 15 h under Ar atmosphere. Reaction mixture was cooled and then 10% $NaHCO_3$ solution (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×10 mL) and CH_2Cl_2 phase was dried over anhydrous sodium sulfate, concentrated to dryness to afford the product (77 mg, 98.2%). Mp: 126.0–128.0 °C; UV λ_{max} CH_2Cl_2: 230.0, 318.0 nm.; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3444, 2962, 2245, 1719 (C=O stretching), 1621, 1601, 1475, 1366, 1261, 1233, 1146, 1115, 1038, 929, 870, 802 (N–O stretching), 742, 601, 517; LCMS/APCI *m/z* (rel. int.): 442 $[M-H]^+$ (5.7), 307 $[M-(C_6H_5-CO-ON)-H]^+$ (37.1), 279.0 $[M-(C_6H_5-COON{=}CH-CH_2)-2H]^+$ (23.4); ^1H and ^{13}C NMR data are presented in Tables 3 and 5.

3.4.18. Compound R

3.4.18.1. 3-[2-(1,3-Benzodioxol-5-yl)-7-methoxy-1-benzofuran-5-yl] propanal O-(2-chloroacetyl)oxime ($C_{21}H_{18}ClNO_6$). Compound **N** (30 mg, 8.82×10^{-5} mol) and dry THF (7 mL) were placed in a 50 mL two-necked flask with a reflux condenser. Chloroacetyl chloride (4.95 mg, 4.38×10^{-5} mol) was added to the mixture and refluxed at 50 °C for 13 h under Argon. Reaction mixture was

Table 6
^{1}H (J in Hz) and ^{13}C NMR data of compound **P**

Position	Compound **P**	
	δ ^{1}H	δ ^{13}C
2	–	156.30
3	6.57, s, 1H	100.52
3a	–	131.20
4	6.66, s, 1H	112.43
5	–	134.95
6	6.43, d, 1H, J = 1.2	107.62
7	–	145.00
7a	–	142.76
–OCH$_2$O–	5.92, s, 2H	101.52
1′	–	124.80
2′	7.18, d, 1H, J = 2.0	105.73
3′	–	148.26
4′	–	148.20
5′	6.76, d, 1H, J = 8.0	108.81
6′	7.27, dd, 1H, J = 1.6, 4.8	119.42
1″	3.58, s, 2H	35.00
2″	–	143.31
3″	9.41, s, 1H	194.92
–OMe	3.88, s, 3H	56.39
2‴	–	156.48
3‴	6.63, s, 1H	100.59
3a′	–	131.42
4‴	6.73, s, 1H	112.55
5‴	–	136.30
6‴	6.52, d, 1H, J = 1.6	107.86
7‴	–	145.10
7a‴	–	142.86
–OC′H$_2$O–	5.93, s, 2H	101.54
1⁗	–	124.89
2⁗	7.20, d, 1 H, J = 1.2	105.75
3⁗	–	148.29
4⁗	–	148.20
5⁗	6.78, d, 1H, J = 4.0	108.84
6⁗	7.29, dd, 1H, J = 2.0, 2.0	119.47
1⁗′	2.74, t, 2H	31.68
2⁗′	2.74, q, 2H	30.08
3⁗′	6.45, t, 1H	155.35
–OMe′	3.89, s, 3H	56.42

cooled and neutralized with NH_3 solution. After addition of water (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic phase was dried over anhydrous sodium sulfate and evaporated to dryness to afford **R** as an amorphous powder (31.1 mg, 84.6%). UV λ_{max} CH_2Cl_2: 230.0, 318.0 nm; IR spectrum ν_{max} CH_2Cl_2 cm^{-1}: 3626, 3444, 2098, 1651–1633 (C=O stretching), 1504, 1476, 1365, 1260, 1233, 1146, 1115, 1037, 928, 744 (N–O stretching), 766; LCMS/APCI m/z (rel. int.): 416 $[M]^+$ (7.3), 355 $[M-(Cl-CH_2-C)+H]^+$ (6.8), 322.0 $[M-(Cl-CH_2-CO-O)+H]^+$ (55.9), 307 $[M-(Cl-CH_2-COON)+H]^+$ (100); ^{1}H and ^{13}C NMR data are presented in Tables 3 and 5.

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