Synthesis of 3-Aryl-3-(Furan-2-yl)Propanoic Acid Derivatives, and Study of Their Antimicrobial Activity

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Abstract: Reactions of 3-(furan-2-yl)propenoic acids and their esters with arenes in Brønsted superacid TfOH affords products of hydroarylation of the carbon–carbon double bond, 3-aryl-3-(furan-2-yl)propanoic acid derivatives. According to NMR and DFT studies, the corresponding O,C-diprotonated forms of the starting furan acids and esters should be reactive electrophilic species in these transformations. Starting compounds and their hydroarylation products, at a concentration of 64 µg/mL, demonstrate good antimicrobial activity against yeast-like fungi Candida albicans. Apart from that, these compounds suppress Escherichia coli and Staphylococcus aureus.

Keywords: furans; Friedel–Crafts reaction; carbocations; superelectrophilic activation; antibacterial activity

1. Introduction

Nowadays, biomass-derived furans such as furfural and 5-hydroxymethylfurfural (5-HMF) are paid great attention to, and they are considered platform chemicals [1–4]. These compounds and their derivatives are widely used for the synthesis of many fine chemicals, pharmaceuticals, polymers, resins, solvents, adhesives, fungicides, paints, antifreeze, fuels, and others [5–10]. It should be especially emphasized that furans and tetrahydrofurans are well-known drugs that are actively used for medicine and veterinary practices, for instance, Nitrofural, Nitrofurantoin, and Lasalocid (antibacterial agents); Monensin and Nigericin (polyether antibiotics); Nifurtimox (antiparasitic drug); Naftidrofuryl (peripheral vasodilator drug); Ranitidine (histamine H2 antagonist); Darunavir (HIV protease inhibitor); and Ribavirin, Taribavirin, Remdesivir, and Molnupiravir (drugs to treat virus infections, including COVID-19) [11,12]. Thus, the further development of synthesis of novel compounds from furfural and 5-HMF is an actual goal not only for organic chemistry but also for medicine, material science, and for other fields.

Based on our research on superelectrophilic activation in organic synthesis [13,14] and our investigation in furan chemistry [15,16], we undertook this study on the synthesis of
novel compounds from furfural and 5-HMF. The main goals of this work were the synthesis of 3-(furan-2-yl)propenoic acids and their esters, investigation of their reactions with arenes under the activation by strong Brønsted (triflic acid TfOH (CF$_3$SO$_2$H)) and Lewis (AlCl$_3$ and AlBr$_3$) acids, study on the reaction cationic intermediates by NMR and DFT calculations, and study on the biological activity of the reaction products.

2. Results and Discussion

Starting 3-(furan-2-yl)propenoic acids 1a–f were synthesized by condensation of the corresponding furan-2-carbaldehydes (furfural (for 1a), 5-HMF, and its derivatives (for 1b–d), 2,5-DFF (for 1e), and benzofurfural (for 1f)) with malonic acid, methyl esters 1g, 1h, and 1i were obtained by esterification of acids 1a, 1e, and 1f, respectively (Figure 1). Acid 1b was obtained as a mixture of E-,Z-isomers. Other compounds of 1 were isolated as E-isomers. See the preparation and characterization of compounds 1a–i in the Experimental part and SI.

![Figure 1. Starting 3-(furan-2-yl)propenoic acid derivatives 1a–i used in this study.](image)

First, reactions of acid 1a with benzene under the actions of various Brønsted or Lewis acids have been investigated. It was found that compound 2a as product of hydrophenylation of the carbon–carbon double bond has been formed (Table 1). The highest yield of 2a (65%) has been achieved under the use of AlCl$_3$ at room temperature for 1 h (entry 4). Prolongation of the reaction time until 4 h leads to a decrease of the yield of 2a to 47% (entry 5). Reaction with AlBr$_3$ gives a comparable yield of the target compound (entry 7). Acidity of trifluoroacetic acid has been found to be not enough for electrophilic activation of starting substrate 1a (entry 1). On the other hand, H$_2$SO$_4$ and FeBr$_3$ lead to the formation of mixtures of oligomeric materials (entries 2 and 3). Yields of 2a for reactions in TfOH under different conditions are moderate, 22–33%, at the complete conversion of starting acid 1a (entries 7–10).

Then, reactions of acid 1a with other arenes have been studied. Reactions with methylated arenes (o-, m-, p-xylenes, mesitylene, and durene) in TfOH at 0 °C for 2 h afford the corresponding products of hydroarylation 2b–f in good yields of 55–98% (Scheme 1). Contrary to the reaction with benzene (Table 1, entry 4), AlCl$_3$-promoted transformations of 1a with these methylated arenes lead mainly to oligomeric compounds with the formation of small amounts of target compounds 2b–h. It should be noted that the reaction of 1a with electron-donating arenes, anisole (methoxybenzene), veratrole (1,2-dimethoxybenzene), or electron-poor 1,2-dichlorobenzene under the action of both TfOH and AlCl$_3$ give oligomeric materials.
Table 1. Reaction of acid 1a with benzene under the action of Bronsted or Lewis acids leading to compound 2a.

| Entry | Reaction Conditions | Yield of 2a, % |
|-------|---------------------|---------------|
|       | Acid (Equiv.)       | Temperature, °C | Time, h |               |
| 1     | CF₃CO₂H (19)        | r.t.           | 1       | no reaction   |
| 2     | H₂SO₄ (52)          | r.t.           | 1       | oligomerization |
| 3     | FeBr₃ (5.5)         | r.t.           | 1       | oligomerization |
| 4     | AlCl₃ (5.5)         | r.t.           | 1       | 65             |
| 5     | AlCl₃ (5.5)         | r.t.           | 4       | 47             |
| 6     | AlBr₃ (5.5)         | r.t.           | 1       | 52             |
| 7     | TfOH (16)           | r.t.           | 1       | 22             |
| 8     | TfOH (16)           | 0              | 0.25    | 28             |
| 9     | TfOH (16)           | 0              | 1       | 32             |
| 10    | TfOH (16)           | 0              | 2       | 33             |

Scheme 1. Reactions of acid 1a with methylated arenes in TfOH leading to compounds 2b–f.

Reaction of acids 1b–d, obtained from 5-HMF, with benzene under the action of TfOH or AlCl₃ furnishes compound 2g (Table 2). Apart from hydrophenylation of the carbon–carbon double bond, the additional alkylation of benzene by the CH₂OH or CH₂oMe groups takes place for acids 1b,c. Yields of target compound 2g are comparable for a reaction with TfOH or AlCl₃ (compare pairs of entries: 2 and 6, 7 and 9, and 10 and 12).
Table 2. Reaction of acids 1b–d with benzene under the action of Bronsted or Lewis acids leading to compound 2i.

| Entry | Starting Compound 1b–d | Reaction Conditions | Yield of 2g, % |
|-------|------------------------|---------------------|----------------|
| 1     | 1b                     | H₂SO₄ (55) r.t. 1 | oligomerization |
| 2     | 1b                     | AlCl₃ (5.5) r.t. 1 | 44             |
| 3     | 1b                     | AlCl₃ (5.5) r.t. 4 | 17             |
| 4     | 1b                     | TiOH (19) r.t. 1   | 37             |
| 5     | 1b                     | TiOH (19) 0 0.25   | 43             |
| 6     | 1b                     | TiOH (19) 0 1     | 37             |
| 7     | 1c                     | AlCl₃ (5.5) r.t. 1 | 36             |
| 8     | 1c                     | TiOH (19) 0 0.25   | 39             |
| 9     | 1c                     | TiOH (19) 0 1     | 46             |
| 10    | 1d                     | AlCl₃ (5.5) r.t. 1 | 75             |
| 11    | 1d                     | TiOH (19) 0 0.25   | 60             |
| 12    | 1d                     | TiOH (19) 0 1     | 63             |

Hydroarylation of ester 1g by different arenes in TiOH at 0 °C for 2 h is shown in Scheme 2. These reactions lead to the formation of compounds 2h–q in good yields. In general, yield of esters 2 are higher with the use of TiOH rather than AlCl₃ (see yields for 2j in Scheme 2). Reactions with anisole and durene give mixtures of isomers 2n and 2o and 2p and 2q, respectively.

In the same transformation, diester 1h with benzene under the action of TiOH or AlCl₃ gives a product of double hydrophenylation 2r as an equimolar mixture of diastereomers in a moderate yield (Scheme 3).

Diacid 1e, and benzo furan derivatives 1f and 1i in reactions with benzene and other arenes under the action of both TiOH and AlCl₃ afford complex mixtures of oligomeric materials.

As it has been mentioned above, acids 1a (Table 1, entry 2) and 1b (Table 2, entry 1) in reactions with benzene in H₂SO₄ at room temperature for 1 h gave oligomeric compounds. According to the HPLC-HRMS analysis (Figure S51), the latter were represented by a number (about 20–25 chromatographic peaks for each parent compound) of dimers–hexamers with molecular weights in the range of 200–700 Da, while the most intense signals belonged to trimeric and tetrameric compounds (Table 3).

Table 3. The main products detected in reaction mixtures of 1a and 1b with benzene in H₂SO₄ by HPLC-ESI-HRMS.

| Starting Compound | Retention Time, min | Peak Area, Arb. Units | Elemental Composition | RDB ∆ | [M+H]+ m/z (Found) | [M+H]+ m/z (Calcul.) | Δ, ppm |
|-------------------|---------------------|-----------------------|----------------------|-------|--------------------|-----------------------|-------|
| 1a                | 10.0                | 472                   | C₁₃H₁₄O₅             | 7     | 251.0914           | 251.0914              | 0     |
|                   | 10.9                | 1400                  | C₁₉H₁₅O₇             | 11    | 359.1124           | 359.1125              | −0.4  |
|                   | 11.6                | 1550                  | C₂₀H₂₂O₉             | 10    | 407.1335           | 407.1337              | −0.4  |
|                   | 12.4                | 900                   | C₂₃H₂₆O₁₀            | 11    | 463.1591           | 463.1599              | −1.7  |
Table 3. Cont.

| Starting Compound | Retention Time, min | Peak Area, Arb. Units | Elemental Composition | RDB a | [M+H]⁺ m/z (Found) | [M+H]⁺ m/z (Calcul.) | ∆, ppm |
|-------------------|---------------------|-----------------------|-----------------------|-------|---------------------|----------------------|-------|
| 1b                | 17.7                | 907                   | C₂₉H₂₈O₇              | 16    | 475.1744            | 475.1751             | −1.5  |
|                   | 18.3                | 410                   | C₂₀H₂₉O₄              | 11    | 325.1436            | 325.1434             | 0.5   |
|                   | 19.8                | 712                   | C₂₁H₃₀O₆              | 10    | 415.2117            | 415.2115             | 0.4   |
|                   | 23.4                | 1220                  | C₂₈H₂₃O₅              | 15    | 445.2008            | 445.2010             | −0.3  |

Note. a RDB is a ring and double bond equivalent or unsaturation degree.

Scheme 2. Reactions of ester 1g with arenes in TfOH leading to compounds 2h–q.

Scheme 3. Reactions of ester 1h with benzene under the action of TfOH or AlCl₃ leading to compound 2r.
A specific feature of these products is a surprisingly large number of oxygen atoms in their elemental compositions and RDB (ring and double bond equivalent or unsaturation degree) values lower than expected. Tandem mass spectra of the corresponding precursor ions presented in the Supplementary Materials demonstrate the loss of 1–4 (depending on compound) water molecules (−18.0106 Da), which is evidence of the presence of aliphatic hydroxyl groups in their structures. This makes it possible to assume that, under applied reaction conditions, the hydration of carbon–carbon double bonds in the side chain and furane ring occurs in addition to the hydrophenylation described above for other reaction systems and confirmed by the presence of the tropylium ion [C\textsubscript{7}H\textsubscript{7}]\textsuperscript{+} signal at \( m/z \) 91.0565. Moreover, in most cases, the same double bond simultaneously undergoes phenylation and hydroxylation. The further oligomerization proceeds through the addition of 1a or its hydrated derivatives and, thus, the formation of ether or ester bonds, in some cases along with the side processes of decarboxylation (the latter also can proceed during ESI in the ion source). In the case of starting compound 1b, the same patterns were observed; however, the structures of the oligomers typically included two phenyl moieties. The plausible structural formulas and tandem mass spectra for all products listed in Table 3 are presented in the Supplementary Materials (Figures S52–S59). These oligomers are humin-like compounds similar to those obtained from furan derivatives in acidic media [17,18].

To investigate the reaction mechanism, we carried out a NMR study on the protonation of compounds 1 in TfOH. NMR monitoring of the solutions of compounds 1a–d,f,g,i, having only one conjugated enone system, has shown that these compounds are rapidly transformed into oligomeric materials in TfOH. That reveals a high electrophilic reactivity of intermediate cations. Contrary to that, diacid 1e and diester 1h, having two conjugated enone systems, give stable solutions of O,O-diprotonated species Ae and Ah, respectively (see \(^{13}\text{C} \) NMR data in Table 4). Comparison of the chemical shifts of carbon atoms in starting compounds 1e and 1h and their protonated forms Ae and Ah show large down field shifts of the corresponding signals in cations. A positive charge is substantially delocalized from the carbonyl group into the carbon–carbon double bond and furan ring. Thus, differences in chemical shifts \( \Delta\delta \) for carbons C\textsubscript{3} and C\textsubscript{5} are around 7 and 27 ppm, correspondingly (Table 4).

**Table 4.** \(^{13}\text{C} \) NMR data of starting compounds 1e and 1h and their protonated forms Ae and Ah generated in TfOH.

| Compound/Cation | \(^{13}\text{C} \) NMR, \( \delta \), ppm |
|-----------------|-----------------|
| Acid 1e in CDCl\textsubscript{3} | \begin{align*}
C^1 & = 166.9 \\
C^2 & = 129.7 \\
C^3 & = 117.3 \\
C^4 & = 151.8 \\
C^5 & = 118.1
\end{align*} |
| Cation Ae in TfOH | \begin{align*}
C^1 & = 182.2 \\
C^2 & = 128.5 \\
C^3 & = 110.1 \\
C^4 & = 155.8 \\
C^5 & = 145.0
\end{align*} |
| \( \Delta\delta = \delta_{\text{Ae}} - \delta_{1\text{e}} \) | \begin{align*}
\Delta\delta & = 15.3 \\
\delta & = 1.2 \\
\delta & = 7.2 \\
\delta & = 4.0 \\
\delta & = 26.9
\end{align*} |

| Compound/Cation | \(^{13}\text{C} \) NMR, \( \delta \), ppm |
|-----------------|-----------------|
| Ester 1h in CDCl\textsubscript{3} | \begin{align*}
C^1 & = 166.2 \\
C^2 & = 129.4 \\
C^3 & = 116.7 \\
C^4 & = 151.8 \\
C^5 & = 115.9 \\
C^6 & = 51.0
\end{align*} |
| Cation Ah in TfOH | \begin{align*}
C^1 & = 181.5 \\
C^2 & = 128.0 \\
C^3 & = 110.3 \\
C^4 & = 155.6 \\
C^5 & = 143.6 \\
C^6 & = 62.7
\end{align*} |
| \( \Delta\delta = \delta_{\text{Ah}} - \delta_{1\text{h}} \) | \begin{align*}
\Delta\delta & = 15.3 \\
\delta & = 1.4 \\
\delta & = 6.4 \\
\delta & = 3.8 \\
\delta & = 27.7 \\
\delta & = 11.7
\end{align*} |
Then, we did DFT calculations of intermediate cations \( \text{AA-Ch} \) derived under the protonation of 3-(furan-2-yl)propenoic acid derivatives \( 1\alpha.g \), diacid \( 1e \), and diester \( 1h \) to estimate the electrophilic properties and reactivity of these species (Table 5). Gibbs energies \( \Delta G_{298} \) of protonation reactions \( 1 \rightarrow A \rightarrow B \rightarrow C \); electronic and orbital characteristics (charge distribution, HOMO/LUMO energies, contribution of atomic orbitals into LUMO, and global electrophilicity index \( \omega \) [19]) of cations \( \text{AA-Ch} \) have been calculated.

Big negative values of Gibbs energies of the protonation of acid \( 1\alpha \) and diester \( 1g \), leading to the corresponding O-protonated forms \( \text{AA} \) and \( \text{Ag} \), reveal that these reactions are thermodynamically favorable (entries 1 and 3). Despite positive values of Gibbs energies for the second protonation of cations, \( \text{AA} \) and \( \text{Ag} \) with the formation of O,C-diprotonated species \( \text{Ba} \) and \( \text{Bg} \) (entries 2 and 4), for two-step processes \( 1\alpha \rightarrow \text{AA} \rightarrow \text{Ba} \) and \( 1g \rightarrow \text{Ag} \rightarrow \text{Bg} \), the \( \Delta G \) values are negative. That indicates the possibility of the formation of dications \( \text{Ba} \) and \( \text{Bg} \) in Brønsted superacids. Thus, one may propose that dications \( \text{B} \), generated from 3-(furan-2-yl)propenoic acid derivatives \( 1\alpha-d,f,g \), are key reactive electrophilic intermediates. Calculations of electrophilic properties of species \( \text{Ba} \) and \( \text{Bg} \) show that they have values of the electrophilicity index \( \omega \) 5.2 and 5.3 eV, correspondingly. These species bear small positive charges \((0.02 \text{ e})\) on the reactive center \( C^3 \). However, this carbon gives a big contribution to LUMO \((-27\%–30\%)\) (entries 2 and 4). This points out that the reactivity of carbon \( C^3 \) in dications \( \text{B} \) is explained by orbital factors rather than electronic ones.

Diprotonation of carbonyl oxygens in diacid \( 1e \) and diester \( 1h \), leading to O,O-diprotonated species \( \text{Ae} \) and \( \text{Ah} \), is thermodynamically favorable, and the corresponding \( \Delta G \) values are \(-117.3 \text{ and } -54.6 \text{ kJ/mol} \) (entries 5 and 8). The next protonation steps \( \text{Ae} \rightarrow \text{Be} \rightarrow \text{Ce} \) and \( \text{Ah} \rightarrow \text{Bh} \rightarrow \text{Ch} \) are much less thermodynamically favorable. It should be emphasized that dications \( \text{Ae} \) and \( \text{Ah} \) have electrophilicity indexes \( \omega \) 5.2 and 5.4 eV, and these values are very close to indexes for dications \( \text{Ba} \), \( \text{Bg} \) derived from compounds \( 1\alpha \) and \( 1g \) (vide supra). Taking into account NMR data on the formation of solutions of dications, \( \text{Ae} \) and \( \text{Ah} \) in TIOH (Table 4), one may propose that these species may be reactive intermediates in reactions with aromatic nucleophiles. Electronic properties of dications \( \text{Ae} \) and \( \text{Ah} \) show that these reactions are more thermodynamically favorable, and the corresponding \( \Delta G \) values are \(-54.6 \text{ kJ/mol} \) (entries 5 and 8).

Based on the data obtained on the reactions of compounds \( 1 \) with arenes (Tables 1 and 2 and Schemes 1–3), NMR (Table 3) and DFT (Table 4) studies of intermediate cations, one may propose a plausible reaction mechanism of the reaction of compounds \( 1 \), except diester \( 1h \) (vide infra), with arenes leading to products of hydroarylation \( 2 \) (Scheme 4). The first protonation of substrates \( 1 \) in Brønsted superacid TIOH occurs onto carboxyl oxygen forming O-protonated species \( \text{A} \). Then, the protonation of the carbon–carbon double bond may give O,C-diprotonated species \( \text{B} \). In principle, both species \( \text{A} \) and \( \text{B} \) may take part in electrophilic aromatic substitution with arenes. However, taking into account a strong electron-donating character of furan substituent, the second protonation of the conjugated C=C bond may proceed, leading to dications \( \text{B} \). Moreover, the formation of such O,C-diprotonated species from various conjugated enones, such as butenones [20], indenones [21], cinnamic acids, and their esters and amides [22–25], was proven by NMR in Brønsted superacids. These dications are key reactive intermediates in various processes of electrophilic aromatic substitution [20–28]. Thus, it is the most probable that dications \( \text{B} \) lie in the reaction pathway from compounds \( 1 \) to \( 2 \). Reactions under the action of AlCl\(_3 \) proceed in the same manner when the electrophilic activation of substrate \( 1 \) is achieved by coordination of this strong Lewis acid onto carboyl oxygen of the carbon–carbon double bond, leading to reactive intermediate species.
Table 5. Selected calculated (DFT) electronic characteristics of the protonated forms of furans, and values of Cribbs energies of protonation reactions (∆G, kJ/mol).

| Entry | Species | E\text{HOMO}, eV | E\text{LUMO}, eV | ω, a eV | q(C\text{1}), b e | q(C\text{3}), b e | k(C\text{1})\text{LUMO}, c % | k(C\text{3})\text{LUMO}, c % | ∆G, d kJ/mol |
|-------|---------|----------------|----------------|---------|----------------|----------------|----------------------------|----------------------------|--------------|
| 1     | Aa      | −6.85          | −3.28          | 3.6     | 0.83           | −0.08          | 22.0                      | 27.1                      | 1a → Aa −69.1 |
| 2     | Ba      | −9.17          | −4.63          | 5.2     | 0.94           | 0.02           | 6.9                       | 30.6                      | Aa → Ba 26.0  |
| 3     | Ag      | −6.86          | −3.34          | 3.7     | 0.83           | −0.08          | 23.2                      | 26.0                      | Ig → Ag −39.9 |
| 4     | Bg      | −9.18          | −4.63          | 5.3     | 0.95           | 0.02           | 13.2                      | 27.0                      | Ag → Bg 30.8  |
| 5     | Ae      | −7.02          | −4.06          | 5.2     | 0.86           | −0.19          | 11.8                      | 11.6                      | 1e → Ae −117.3 |
| 6     | Be      | −8.82          | −5.25          | 6.9     | C\text{1} 0.89 | C\text{1}′ 0.94 | C\text{3} −0.17          | C\text{3}′ 0.01          | C\text{4} 4.3 | C\text{4}′ 6.2 | C\text{3} 4.0 | C\text{3}′ 19.1 | Be → Ce 222 |
| 7     | Ce      | −10.61         | −7.28          | 12.0    | 0.94           | 0.24           | 2.2                       | 21.0                      | 1h → Ah −54.6 |
| 8     | Ah      | −7.03          | −4.13          | 5.4     | C\text{1} 0.91 | C\text{1}′ 0.95 | C\text{3} −0.18          | C\text{3}′ 0.03          | C\text{4} 5.2 | C\text{4}′ 6.5 | C\text{3} 4.6 | C\text{3}′ 19.5 | Ah → Bh 60.7 |
| 9     | Bh      | −10.62         | −7.28          | 12.0    | 0.95           | 0.24           | 11.0                      | 10.8                      | Bh → Ch 208  |

*a* Global electrophilicity index $ω = (E\text{HOMO} + E\text{LUMO}) / 2(E\text{LUMO} − E\text{HOMO})$.

*b* Natural charges.

*c* Contribution of atomic orbital into the molecular orbital.

*d* Gibbs energy of protonation reactions.
Scheme 4. Plausible reaction mechanism of the reaction of 3-(furan-2-yl)propenoic acid derivatives 1 (except diester 1h) with arene in Brønsted superacid TfOH, leading to compounds 2.

In the case of diester 1h, the reaction in TfOH proceeds through the intermediate formation of O,O-diprotonated species Ah, which reacts with benzene, affording bis-hydrophenylation product 2r (Scheme 5).

Scheme 5. Plausible reaction mechanism of the reaction of diester 1h with benzene in TfOH, leading to compounds 2t.

At the final stage of this study, the antimicrobial activity of the starting furan derivatives 1 and products of their hydroarylation 2 were investigated relative to the bacteria *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213 and to yeast-like fungi *Candida albicans* (ATCC 10231) (see details in SI). It was found that all the compounds 1 and 2 inhibited the growth of yeast-like fungi *Candida albicans* at a concentration of 64 µg/mL. Concerning to the *S. aureus* strain, a minimum inhibitory concentration (MIC) was 128 µg/mL for most of the tested objects. The best result demonstrated acid 2d, which suppressed the growth of microorganisms at a concentration of 64 µg/mL. However, the tested compounds 2i, 2m, and 2r did not show antimicrobial activity at the specified concentrations. For most of the tested compounds, the MIC against *E. coli* ranged between 64 and 128 µg/mL.

Disinfectants, such as benzalkonium chloride and cetylpyridinium chloride, have similar MIC values for *E. coli* and *S. aureus* bacterial strains. Wu et al. investigated the antimicrobial activity of quaternary ammonium compounds (QAC). According to their results, for *E. coli*, the MIC values ranged from ≤8 to 128 µg/mL benzalkonium chloride (MIC<sub>90</sub> = 128 µg/mL) and ≤32 and 256 µg/mL cetylpyridinium chloride (MIC<sub>90</sub> = 128 µg/mL). For *S. aureus*, isolates MIC of QAC varied from ≤2 to 128 µg/mL of benzalkonium chloride (MIC<sub>90</sub> = 128 µg/mL) and from ≤4 to 256 µg/mL of cetylpyridinium chloride (MIC<sub>90</sub> = 256 µg/mL) [29]. Zhang et al. established the susceptibility to cetylperidinium chloride and benzalkonium chloride of 255 *E. coli* retail meat isolates. The MIC for cetylperidinium chloride against *E. coli* ranged from 8 to 512 µg/mL and from 16 to 1024 µg/mL to benzalkonium chloride [30]. Guskova et al. established, that hydroxymethylquinoloxaline dioxide (dioxidine) has antibacterial and antifungal activity ranging between 64 and 512 µg/mL against *S. aureus* strains, MIC = 16 µg/mL against the *E.coli* reference strain and MIC = 1024 µg/mL for yeast-like fungi *C. albicans* [31].

3. Conclusions

A novel method of synthesis of 3-aryl-3-(furan-2-yl)propenoic acid derivatives has been developed on the basis of hydroarylation of the carbon–carbon double bond of 3-(furan-2-yl)propenoic acids and their esters by arenes under superelectrophilic activation conditions in neat triflic acid TfOH. The obtained furans have demonstrated a high level of
antimicrobial activity against yeast-like fungi *Candida albicans*, and they also can inhibit *Escherichia coli* and *Staphylococcus aureus*.

4. Experimental Part

4.1. General Information

The NMR spectra of solutions of compounds in CDCl$_3$ were recorded on Bruker AM-500 spectrometer (Bruker Company, Germany) at 25 °C at 500 and 125 MHz for $^1$H and $^{13}$C NMR spectra, respectively. The residual proton-solvent peaks CDCl$_3$ ($\delta$ 7.26 ppm), DMSO-$d_6$ ($\delta$ 2.50 ppm), CD$_3$OD ($\delta$ 3.31 ppm), (CD$_3$)$_2$CO ($\delta$ 2.05 ppm) for $^1$H NMR spectra, and the carbon signals of CDCl$_3$ ($\delta$ 77.0 ppm), DMSO-$d_6$ ($\delta$ 39.52 ppm), CD$_3$OD ($\delta$ 49.00 ppm), (CD$_3$)$_2$CO ($\delta$ 29.84 ppm) for $^{13}$C NMR spectra were used as references. NMR spectra in the superacids TfOH at room temperature were recorded on Bruker 400 spectrometer at 400 and 100 MHz for $^1$H and $^{13}$C NMR spectra, respectively. NMR spectra in TfOH were referenced to the signal of CH$_2$Cl$_2$ added as the internal standard: $\delta$ 5.30 ppm for $^1$H NMR spectra and $\delta$ 53.52 ppm for $^{13}$C NMR spectra. HRMS was carried out with instruments Bruker maXis HRMS-ESI-QTOF and Varian 902-MS MALDI Mass Spectrometer. IR spectra of the compounds in KBr were taken with a FSM-1201 spectrometer. GC-MS spectra were taken with the Shimadzu GCMS QP-2010 SE machine. The preparative reactions were monitored by thin-layer chromatography carried out on silica gel plates (Alugram SIL G/UV-254), using UV light for detection.

The study of oligomeric products was carried out using a TripleTOF 5600+ high-resolution quadrupole time-of-flight (QTOF) mass spectrometer (AB Sciex, Concord, ON, Canada) equipped with a Duospray ion source with ESI probe. A mass spectrometer was combined with an LC-30 Nexera HPLC system (Shimadzu, Kyoto, Japan) consisting of a DGU-5A vacuum degasser, two LC-30AD chromatographic pumps, an SIL-30AC autosampler, and an STO-20A column thermostat.

Chromatographic separation was achieved at 40 °C on a Nucleodur PFP column (Macherey-Nagel, Duren, Germany) with a pentafluorophenyl-propyl stationary phase, 150×2 mm, particle size 1.8 µm. A mixture of water (A) and acetonitrile (B) containing 0.1% formic acid was used as a mobile phase. The gradient elution was programmed as follows: 0–3 min: 10% B, 3–40 min: ramp to 100% B, and 40–45 min: 100% B. The mobile phase flow rate was 0.3 mL/min, and the injection volume was 5 µL. Nontargeted screening of reaction products was performed in a data-dependent acquisition mode using positive electrospray ionization (ESI+). The following ion source parameters were used: nebulizing, drying, and gas curtain pressure—40, 40, and 30 psi, respectively, capillary voltage—5500 V, and source temperature—400 °C. The parameters used for recording the mass spectra in a TOF MS mode were as follows: declusterization potential—80 V, $m/z$ range—150–1200, and acquisition time—150 ms. Tandem (CID) mass spectra were recorded for precursor ions with signal intensities above a threshold of 100 cps. Nitrogen was used as the collision gas and collision energy—50 eV with a spread of 30 eV. The maximum number of simultaneously fragmented precursor ions—15, $m/z$ range—20–1200. Data processing was performed using MasterView and Formula Finder (AB Sciex, Concord, ON, Canada) software packages. Elemental compositions of the detected compounds were determined based on the accurate masses of ions, their isotopic distributions, and product ions $m/z$. The following constraints were applied: maximal number of atoms: C—100, H—300, O—20, mass error < 5 ppm (MS) and <10 ppm (MS/MS), and signal-to-noise ratio (S/N) > 10.

4.2. DFT Calculations

All computations were carried out at the DFT/HF hybrid level of theory using hybrid exchange functional B3LYP by using GAUSSIAN 2009 program packages [32]. The geometries optimization was performed using the 6-311+G(2d,2p) basis set (standard 6-311G basis set added with polarization (d,p) and diffuse functions). Optimizations were performed on all degrees of freedom, and solvent phase optimized structures were verified as true
minima with no imaginary frequencies. The Hessian matrix was calculated analytically for the optimized structures in order to prove the location of correct minima and to estimate the thermodynamic parameters. Solvent-phase calculations used the Polarizable Continuum Model (PCM, solvent = water).

4.3. Study of Biological Activity

MICs of furan compounds against *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, and *Candida albicans* ATCC 10231 were determined using broth microdilution as described in ISO 20776-1:2019 and ISO 16256:2021. Stock solutions of furan compounds in neat (pure) DMSO were prepared in sterile tubes and used on the same day. Two-fold dilutions of the furan compounds in the appropriate culture medium were added to the wells of a 96-well plate. The final concentrations of the test substances (after inoculation) were 256, 128, 64, 32, 16, 8, 4, 2, and 1 µg/mL. Solutions of furan compounds were added to the wells of the plates, 50 µL per well for *S. aureus* and *E. coli* and 100 µL for *C. albicans*.

RPMI-1640 medium, buffered with MOPS (3-(N-morpholino)propanesulfonic acid) containing l-glutamine and lacking sodium bicarbonate was used for *C. albicans*. The medium for *E. coli* and *S. aureus* was Mueller–Hinton broth. The fungus inoculum was prepared in the test medium and adjusted to match the turbidity of a 0.5 McFarland standard. A 1:100 dilution followed by a 1:20 dilution was performed for the yeast strain to obtain a final inoculum ranging from 0.5 to $2.5 \times 10^3$ CFU/mL. Then, 100 µL of the fungal inoculum was added to each well containing furan compounds.

Bacterial inoculums were prepared in sterile sodium chloride solution and adjusted to the 0.5 McFarland standard. A volume of 50 µL of this suspension was diluted in 10 mL of Mueller–Hinton broth until a concentration of approximately $5 \times 10^5$ CFU/mL was reached. Of this suspension, 50 µL was inoculated into each furan compounds-containing wells.

To ensure that the inoculum contained the required number of cells, the viability of the inoculum suspensions was counted. One hundred microliters of the inoculum was taken from the growth control tube immediately after inoculation and diluted in 9.9 mL of sodium chloride solution. One hundred microliters of this dilution were applied to the surface of a suitable agar plate (Sabouraud dextrose agar plate for *C. albicans* and Trypticase soy agar plate for *S. aureus* and *E. coli*), which were then incubated overnight.

After inoculation, the plates were incubated at 37 °C for 18 h for bacterial strains, 22 h for *C. albicans*. The susceptibility to furans was assessed on the basis of visual observation of growth the strains in the culture media. The minimal inhibitory concentration (MIC) is the lowest concentration of an antimicrobial that inhibits visible growth of a bacterial culture under a defined set of experimental conditions.

4.4. Preparation and Characterization of Compounds

4.4.1. General Procedure for Synthesis of 3-(furan-2-yl)propenoic Acids 1a–f from furan-2-carbaldehydes and Malonic Acid

Malonic acid (0.91 g, 8.9 mmol) and substituted furan-2-carbaldehyde (8.9 mmol) were added to pyridine (10 mL). Then, piperidine (0.23 g, 2.7 mmol) was added dropwise for 5 min, and the mixture was stirred 4 h at 115 °C. The mixture was poured into water (50 mL), and aqueous HCl was added to a slightly acidic medium (pH 5–6), while orange precipitate was observed. A precipitate was filtered off and washed with water.

4.4.2. General Procedure for Synthesis of 3-(furan-2-yl)-3-phenylpropanoic Esters 1g-i from 3-(furan-2-yl)propenoic Acids 1a,e,f

The solution of NaOH (0.29 g, 7.2 mmol) in MeOH (3 mL) was added to a stirring mixture of acids 1 (7.2 mmol) in MeOH (5 mL). Dimethyl sulfate (1.21 g, 8.6 mmol) was added dropwise for 5 min, and the mixture was stirred for 1 h at 60 °C. The mixture was poured into water (50 mL) and extracted with diethyl ether (3 × 50 mL). The extracts were combined, washed with water, and dried with Na$_2$SO$_4$; the solvent was distilled under reduced pressure.
4.4.3. General Procedure for Synthesis of 3-(furan-2-yl)-3-phenylpropanoic Acids and Esters 2a-r from Compounds 1 and Arenes under the Action of TiOH

To the mixture of compound 1 (0.36 mmol), arene (0.1 mL), and CH₂Cl₂ (1 mL) was added TiOH (0.5 mL, 6.45 mmol). The reaction mixture was stirred at 0 °C for 2 h and poured into water (50 mL) and extracted with chloroform (3 × 50 mL). The combined extract was washed with water (3 × 50 mL) and dried over Na₂SO₄; the solvent was distilled under a reduced pressure.

4.4.4. General Procedure for Synthesis of 3-(furan-2-yl)-3-phenylpropanoic Acids and Esters 2 from Compounds 1 and Benzene under the Action of AlX₃ (X = Cl, Br)

Compound 1 (0.36 mmol) was added to a suspension of AlX₃ (1.8 mmol) in benzene (2 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h and poured into 50 mL of water. Extracted with ethyl acetate (3 × 30 mL), the combined organic extracts with washed with water (3 × 50 mL) and dried with Na₂SO₄. The solvent was distilled under a reduced pressure.

3-(Furan-2-yl)propenoic acid (1a) [32] was obtained as light orange solid from furan-2-carbaldehyde in a yield of 53%. M.p. 145–145.4 °C (lit. 140 °C [33]). ¹H NMR (500 MHz, CDCl₃): δ = 6.62 d (1H, =CH, J = 15.7 Hz), 6.49–6.50 m (1H₂hetarom.), 6.67 d (1H₂hetarom., J = 3.4 Hz), 7.51–7.54 m (2H). ¹³C NMR (125 MHz, CDCl₃): δ = 112.6, 115.0, 115.9, 133.2, 145.4, 150.8, 172.6. IR (KBr), cm⁻¹: ~3000 (O–H), 1696 (C=O). GC-MS, m/z, (I₁rel, %): 138 (100) [M⁺], 121 (38), 110 (30), 92 (27), 81 (20), 65 (46), 53 (11).

3-(Hydroxymethyl)furan-2-carbaldehyde as mixture of E-/Z-isomers was obtained from furan-2-carbaldehyde in a yield of 48%. M.p. 143–145 °C. ¹H NMR (500 MHz, CDCl₃): δ = 4.55 s (2H, CH₂), 6.24 d (1H, =CH, J = 15.7 Hz), 6.42 d (1H, H₂hetarom., =CH, J = 3.3 Hz), 6.69 d (1H, H₂hetarom., =CH, J = 3.3 Hz), 7.40 d (1H, =CH, J = 15.7 Hz). ¹³C NMR (125 MHz, CDCl₃), from the spectrum of the mixture of isomers: δ = 57.5, 111.0, 116.2, 117.2, 132.8, 151.8, 159.0, 170.4. IR (KBr), cm⁻¹: ~3000 (O–H), 1699 (C=O). GC-MS, m/z, (I₁rel, %): 138 (100) [M⁺], 121 (38), 110 (30), 92 (27), 81 (20), 65 (46), 53 (11).

Z-3-(Hydroxymethyl)furan-2-carbaldehyde was obtained as a light orange solid from 5-hydroxymethylfuran-2-carbaldehyde in a yield of 49%. M.p. 118–120 °C. ¹H NMR (500 MHz, CDCl₃): δ = 4.55 s (2H, CH₂), 6.17 d (1H, =CH, J = 15.7 Hz), 6.31 d (1H₀hetarom., =CH, J = 3.3 Hz), 6.69 d (1H₁hetarom., =CH, J = 3.3 Hz), 7.38 d (1H₁hetarom., =CH, J = 15.7 Hz). ¹³C NMR (125 MHz, CDCl₃), from the spectrum of the mixture of isomers: δ = 28.3, 111.0, 115.8, 117.6, 132.7, 151.5, 155.4, 170.4. HRMS, for the mixture of isomers, m/z calculated for C₇H₁₀O₄ [M⁺]: 169.0495. Found: 169.0497.

3-(5-Hydroxymethyl)furan-2-carbaldehyde in a yield of 83%. M.p. 143–145 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.41 s (3H, Me), 4.43 s (2H, CH₂), 6.33 d (1H, =CH, J = 15.7 Hz), 6.42 d (1H₀hetarom., =CH, J = 3.3 Hz), 6.62 d (1H₁hetarom., =CH, J = 3.3 Hz), 7.48 d (1H, =CH, J = 15.7 Hz). ¹³C NMR (125 MHz, CDCl₃), from the spectrum of the mixture of isomers: δ = 28.3, 111.0, 115.8, 117.6, 132.7, 151.5, 155.4, 170.4. HRMS, for the mixture of isomers, m/z calculated for C₇H₁₀O₄ [M⁺]: 169.0495. Found: 169.0497.
7.37 d (2H, =CH, J = 15.5 Hz). 13C NMR (125 MHz, CDCl3): δ = 117.3, 118.1, 129.7, 151.8, 166.9. IR (KBr), cm⁻¹: ~3000 (O–H), 1680 (C=O). HRMS, m/z calculated for C10H8O5 [M+H]: 209.0445. Found: 209.0447.

3-(Benzofuran-2-yl)propanoic acid (1f) [35] was obtained as a light orange solid from benzofuran-2-carboxaldehyde in a yield of 65%. M.p. 225–227 °C. 1H NMR (500 MHz, CDCl3): δ = 6.49–6.53 m (1H), 7.27–7.20 m (2H), 7.41–7.44 m (1H), 7.56–7.58 m (1H), 7.60–7.64 m (1H), 7.69–7.70 m (1H). 13C NMR (125 MHz, CDCl3): δ = 112.1, 112.2, 119.9, 122.9, 124.4, 127.5, 129.5, 132.3, 153.4, 154.0, 156.5, 167.3. IR (KBr), cm⁻¹: ~3000 (O–H), 1700 (C=O).

Methyl 3-(furan-2-yl)propanoate (1g) [36] was obtained as a dark orange oil from acid 1a in a yield of 60%. 1H NMR (500 MHz, CDCl3): δ = 3.78 s (3H, Me), 6.31 d (1H, =CH, J = 15.8 Hz), 6.45–6.46 m (1H, Hhetatrom., J = 8.0 Hz), 7.41–7.48 m (2H). 13C NMR (125 MHz, CDCl3): δ = 51.7, 112.4, 114.9, 115.6, 131.3, 144.9, 151.0, 167.6. IR (KBr), cm⁻¹: ~3000 (O–H), 1696 (C=O). GC-MS, m/z, (Irel., %): 152 (58) [M⁺], 121 (100), 65 (58), 53 (4).

Methyl 3-[5-(2-methylcarbonylethenyl)]furan-2-yl)propanoate (1h) [34] was obtained as a yellow solid from acid 1a in a yield of 92%. M.p. 115–118 °C. 1H NMR (500 MHz, CDCl3): δ = 3.80 s (3H, Me), 6.42 d (1H, =CH, J = 15.8 Hz), 6.65 s (1H, Hhetatrom.), 7.39 d (1H, =CH, J = 15.8 Hz). 13C NMR (125 MHz, CDCl3): δ = 51.0, 115.9, 116.7, 129.4, 151.6, 166.2. IR (KBr), cm⁻¹: 1694 (C=O).

Methyl 3-(benzofuran-2-yl)propanoate (1i) [37] was obtained as a light orange solid from acid 1e in a yield of 53%. M.p. 224–226 °C. 1H NMR (500 MHz, CDCl3): δ = 3.81 s (3H, Me), 6.58 d (1H, =CH, J = 15.7 Hz), 6.91 s (1H, Hhetatrom.), 7.23 t (1H, Hhetatrom., J = 7.6 Hz), 7.35 t (1H, Hhetatrom., J = 8.0 Hz), 4.74 d (1H, Hhetatrom., J = 16.5 Hz), 7.58–7.53 m (2H). 13C NMR (125 MHz, CDCl3): δ = 51.9, 111.3, 111.5, 118.5, 121.8, 123.4, 126.5, 128.4, 131.5, 152.4, 155.6, 167.2. IR (KBr), cm⁻¹: 1698 (C=O).

3-(Furan-2-yl)-3-phenylpropanoic acid (2a) was obtained as a light orange oil from acid 1a and benzene in TfOH in yields of 33% (in TfOH), 52% (under the action of AlBr₃) and 65% (under the action of AlCl₃) (see Table 1). NMR 1H NMR (500 MHz, CDCl3): δ = 2.98 dd (1H, CH₂, J = 16.2, 7.7 Hz), 3.15 dd (1H, CH₂, J = 16.2, 7.7 Hz), 4.54 t (1H, CH, J = 7.7 Hz), 6.06 (1H, Hhetatrom., J = 3.0 Hz), 6.29 dd (1H, Hhetatrom., J = 3.0, 1.9 Hz), 7.15–7.32 m (6Hhetatrom.). 13C NMR (125 MHz, CDCl3): δ = 39.5, 41.1, 106.0, 110.3, 127.3, 127.8, 128.8, 141.0, 141.9, 156.0, 177.4. IR (KBr), cm⁻¹: ~3000 (O–H), 1701 (C=O). GC-MS, m/z, (Irel., %): 216 (16) [M⁺], 157 (100), 141 (11), 128 (30), 115 (12), 77 (8), 65 (4). HRMS, m/z calculated for C13H12O3[M+H]: 217.0859. Found: 217.0859.

3-(Furan-2-yl)-3-(4-methylphenyl)propanoic acid (2b) was obtained as a light orange oil from acid 1a and toluene in TfOH in a yield of 92%. 1H NMR (500 MHz, CDCl3): δ = 2.32 s (3H, Me), 2.92 dd (1H, CH₂, J = 16.1, 7.7 Hz), 3.13 dd (1H, CH₂, J = 16.1, 7.7 Hz), 4.50 t (1H, CH, J = 7.7 Hz), 6.04 d (1H, Hhetatrom., J = 3.1 Hz), 6.28 m (1H, Hhetatrom.), 7.11–7.20 m (4Hhetatrom.), 7.31 brs (1H, Hhetatrom.). 13C NMR (125 MHz, CDCl3): δ = 21.1, 39.5, 40.8, 105.8, 110.2, 127.7, 129.5, 136.9, 138.0, 141.9, 156.3, 177.2. IR (KBr), cm⁻¹: ~3000 (O–H), 1698 (C=O). HRMS, m/z calculated for C14H14O3[M+H]: 231.1016. Found: 231.1018.

3-(Furan-2-yl)-3-(3,4-dimethylphenyl)propanoic acid (2c) was obtained as a light orange oil from acid 1a and ortho-xylene in TfOH in a yield of 86%. 1H NMR (500 MHz, CDCl3): δ = 2.22 s (6H, 2Me), 2.91 dd (1H, CH₂, J = 16.1, 7.6 Hz), 3.11 dd (1H, CH₂, J = 16.1, 8.0 Hz), 4.46 t (1H, CH, J = 7.7 Hz), 6.04 d (1H, Hhetatrom., J = 3.1 Hz), 6.26–6.27 m (1H, Hhetatrom.), 6.97–7.00 m (2Hhetatrom.), 7.05–7.07 m (1H, Hhetatrom.), 7.30 brs (1H, Hhetatrom.). 13C NMR (125 MHz, CDCl3): δ = 19.5, 20.0, 39.5, 40.8, 105.8, 110.2, 125.1, 129.1, 130.0, 135.5, 136.9, 138.5, 141.8, 156.4, 177.1. IR (KBr), cm⁻¹: ~3000 (O–H), 1701 (C=O). HRMS, m/z calculated for C15H16O3[M+H]: 245.1172. Found: 245.1173.

3-(Furan-2-yl)-3-(2,4-dimethylphenyl)propanoic acid (2d) was obtained as a light orange oil from acid 1a and meta-xylene in TfOH in a yield of 84%. 1H NMR (500 MHz, CDCl3): δ = 2.28 s (3H, Me), 2.36 s (3H, Me), 2.91 dd (1H, CH₂, J = 16.3, 7.3 Hz), 3.11 dd (1H, CH₂, J = 16.3, 8.1 Hz), 4.75 t (1H, CH, J = 7.7 Hz), 5.98 d (1H, Hhetatrom., J = 3.2 Hz), 6.25–6.26 m...
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(1H_{hetarom.}), 6.96–6.99 m (2H_{hetarom.}), 7.03–7.04 m (1H_{hetarom.}), 7.29–7.30 m (1H_{hetarom.}). 13C NMR (125 MHz, CDCl3): δ = 19.5, 21.1, 36.6, 38.8, 105.9, 110.2, 126.8, 127.2, 131.6, 135.9, 136.1, 136.6, 141.8, 156.3, 177.0. IR (KBr), cm⁻¹: ~3000 (O–H), 1699 (C=O). HRMS, m/z calculated for C_{15}H_{16}O_3 [M+H]^+: 245.1172. Found: 245.1172.

3-(Furan-2-yl)-3-(2,5-dimethylphenyl)propanoic acid (2e) was obtained as a light orange oil from acid 1a and para-xylene in TiOH in a yield of 98%. 1H NMR (500 MHz, CDCl3): δ = 2.91 dd (1H, CH₂, J = 16.1, 7.8 Hz), 3.11 dd (1H, CH₂, J = 16.1, 7.8 Hz), 3.90 s (2H, CH₂-2Ar), 4.49 t (1H, CH, J = 7.8 Hz), 5.84 d (1H_{hetarom.}, J = 2.6 Hz), 5.91 d (1H_{hetarom.}, J = 1.9 Hz). 13C NMR (125 MHz, CDCl3): δ = 39.7, 41.5, 52.0, 105.9, 110.3, 127.2, 127.9, 128.8, 130.4, 131.9, 141.8, 156.7, 172.0. IR (KBr), cm⁻¹: ~3000 (O–H), 1700 cm⁻¹. HRMS, m/z calculated for C_{15}H_{16}O_3[M+H]^+: 259.1329. Found: 259.1330.

3-(5-Benzylfuran-2-yl)-3-phenylpropanoic acid (2g) was obtained as a dark orange oil from benzene under the action of TfOH in yields of 98%. NMR (500 MHz, CDCl3): δ = 2.28 s (3H, Me), 2.37 s (3H, Me), 2.88 dd (1H, CH₂, J = 15.8, 7.3 Hz), 3.08 dd (1H, CH₂, J = 16.3, 8.3 Hz), 5.07 t (1H, CH, J = 7.6 Hz), 5.97 brs (1H_{hetarom.}), 6.30 m (1H_{hetarom.}), 6.82–6.84 m (2H_{hetarom.}), 7.30 brs (1H_{hetarom.}). 13C NMR (125 MHz, CDCl3): δ = 19.1, 21.3, 36.8, 38.7, 106.0, 110.2, 127.6, 129.7, 130.7, 132.9, 135.8, 138.99, 141.8, 156.1, 177.0. IR (KBr), cm⁻¹: ~3000 (O–H), 1702 cm⁻¹. HRMS, m/z calculated for C_{15}H_{16}O_3 [M+H]^+: 259.1172. Found: 259.1172.

3-(5-Benzylfuran-2-yl)-3-(4-methylphenyl)propanoic acid (2i) was obtained as a light orange oil from ester 1g and toluene in TiOH in a yield of 84%. 1H NMR (500 MHz, CDCl3): δ = 2.31 s (3H, Me), 2.89 dd (1H, CH₂, J = 15.3, 7.9 Hz), 3.09 dd (1H, CH₂, J = 14.5, 7.9 Hz), 3.62 s (3H, Me), 4.52 t (1H, CH, J = 7.9 Hz), 6.04 d (1H_{hetarom.}, J = 3.0 Hz), 6.28 dd (1H_{hetarom.}, J = 1.9, 3.0 Hz). 13C NMR (125 MHz, CDCl3): δ = 21.1, 39.7, 41.1, 51.8, 105.7, 110.2, 127.7, 129.4, 136.7, 138.3, 141.8, 156.6, 172.0. IR (KBr), cm⁻¹: 1699 (C=O). HRMS, m/z calculated for C_{15}H_{16}O_3 [M+H]^+: 231.1016. Found: 231.1016.

Methyl 3-(furan-2-yl)-3-(4-methylphenyl)propanoate (2j) was obtained as a light orange oil from ester 1g and toluene in TiOH in a yield of 84%. 1H NMR (500 MHz, CDCl3): δ = 2.31 s (3H, Me), 2.89 dd (1H, CH₂, J = 15.3, 7.9 Hz), 3.09 dd (1H, CH₂, J = 14.5, 7.9 Hz), 3.62 s (3H, Me), 4.52 t (1H, CH, J = 7.9 Hz), 6.04 d (1H_{hetarom.}, J = 3.0 Hz), 6.28 dd (1H_{hetarom.}, J = 1.9, 3.0 Hz). 13C NMR (125 MHz, CDCl3): δ = 21.1, 39.7, 41.1, 51.8, 105.7, 110.2, 127.7, 129.4, 136.7, 138.3, 141.8, 156.6, 172.0. IR (KBr), cm⁻¹: 1699 (C=O). HRMS, m/z calculated for C_{15}H_{16}O_3 [M+H]^+: 245.1172. Found: 245.1174.

Methyl 3-(furan-2-yl)-3-(3,4-dimethylphenyl)propanoate (2k) was obtained as a light orange oil from ester 1g and ortho-xylene in TiOH in a yield of 89%. 1H NMR (500 MHz, CDCl3): δ = 2.22 s (3H, Me), 2.23 s (3H, Me), 2.88 dd (1H, CH₂, J = 16.1, 7.8 Hz), 3.08 dd (1H, CH₂, J = 16.1, 8.0 Hz), 3.62 s (3H, Me), 4.49 t (1H, CH, J = 7.8 Hz), 6.05 d (1H_{hetarom.}, J = 3.0 Hz). 13C NMR (125 MHz, CDCl3): δ = 19.5, 20.0, 39.7, 41.1, 51.8, 105.6, 110.2, 125.1, 129.1, 130.0, 135.4, 136.9, 138.7, 141.8, 156.7, 172.1. IR (KBr), cm⁻¹: 1700 (C=O). HRMS, m/z calculated for C_{15}H_{16}O_3 [M+H]^+: 259.1329. Found: 259.1331.
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(1H, CH₂, J = 15.8, 8.2 Hz), 3.62 s (3H, Me), 4.76 t (1H, CH, J = 7.7 Hz), 5.97 d (1H₂etarom., J = 2.7 Hz), 6.2–6.25 m (1H₂etarom.), 6.95–6.98 m (2H₃rom.), 7.02–7.04 m (1H₃rom.), 7.29 br.s (1H₂etarom.). ¹³C NMR (125 MHz, CDCl₃): δ = 19.5, 21.1, 36.9, 39.0, 51.9, 105.8, 110.2, 126.9, 127.1, 131.6, 135.9, 136.3, 136.5, 141.7, 156.5, 172.2. IR (KBr), cm⁻¹: 1701 (C=O). HRMS, m/z calculated for C₁₆H₁₈O₃[M+H]: 259.1329. Found: 259.1330.

Methyl 3-(furan-2-yl)-3-(2,5-dimethylphenyl)propanoate (2l) was obtained as a light orange oil from ester 1g in TIOH in a yield of 74%. ¹H NMR (500 MHz, CDCl₃): δ = 2.27 s (3H, Me), 2.37 s (3H, Me), 2.90 dd (1H, CH₂, J = 15.8, 7.1 Hz), 3.09 dd (1H, CH₂, J = 17.0, 8.4 Hz), 3.63 s (3H, OMe), 4.78 t (1H, CH, J = 7.8 Hz), 6.00 d (1H₂etarom., J = 3.1 Hz), 6.26 dd (1H, H₂etarom., J = 1.9, 3.1 Hz), 6.94–6.95 (2H₃rom.), 7.04–7.06 m (1H₃rom.), 7.30 d (1H₂etarom., J = 1.9 Hz). ¹³C NMR (125 MHz, CDCl₃): δ = 20.6, 31.0, 36.5, 36.9, 37.4, 39.1, 51.9, 56.0, 105.1, 105.7, 110.1, 110.4, 111.6, 121.0, 128.2, 129.1, 131.2, 132.1, 133.2, 133.7, 137.8, 141.0, 141.7, 156.9, 172.9. IR (KBr), cm⁻¹: 1700 (C=O). HRMS, m/z calculated for C₁₆H₂₂O₃[M+H]: 273.1485. Found: 273.1487.

Methyl 3-(furan-2-yl)-3-(2,3,5,6-tetramethylphenyl)propanoate (2n) was obtained in a yield of 14%. ¹H NMR (500 MHz, CDCl₃): δ = 2.18–2.25 m (12H, Me), 2.83 dd (1H, CH₂, J = 15.1, 5.7 Hz), 3.34 dd (1H, CH₂, J = 14.6, 8.2 Hz), 5.24 t (1H, CH, J = 6.8 Hz), 5.91–5.94 m (1H₂etarom.), 6.85–6.94 m (1H₃rom.), 7.29 br.s (1H₂etarom.). ¹³C NMR (125 MHz, CDCl₃): δ = 20.9, 36.0, 36.7, 51.9, 105.3, 110.3, 127.0, 128.5, 134.6, 136.5, 137.0, 141.2, 156.3, 172.7. IR (KBr), cm⁻¹: 1699 (C=O). HRMS, m/z calculated for C₁₆H₂₀O₃[M+H]: 287.1642. Found: 287.1641.

Methyl 3-(furan-2-yl)-3-(2,3,4,5-tetramethylphenyl)propanoate (2o) was obtained as an oily mixture of regioisomers in a ratio of 1:0.2 from ester 1g and durene in TIOH in a general yield of 84%. ¹H NMR (500 MHz, CDCl₃), from the spectrum of a mixture of isomers: δ = 2.18–2.25 m (11H, Me), 2.88–2.96 m (1H, CH₂), J = 15.3, 8.2 Hz), 6.00 br.s (1H₂etarom.), 6.26 br.s (1H₂etarom.), 6.85–6.94 m (1H₃rom.), 7.29 br.s (1H₂etarom.). ¹³C NMR (125 MHz, CDCl₃), from the spectrum of a mixture of isomers: δ = 16.0, 16.4, 19.2, 19.3, 19.5, 20.6, 31.0, 36.5, 36.9, 37.4, 39.1, 51.9, 56.0, 105.1, 105.7, 110.1, 110.4, 111.6, 121.0, 128.2, 129.1, 131.2, 132.1, 133.2, 133.7, 137.8, 141.0, 141.7, 156.9, 172.9. IR (KBr), cm⁻¹: 1701 (C=O). HRMS, m/z calculated for C₁₆H₂₂O₃[M+H]: 287.1642. Found: 287.1641.

Methyl 3-(furan-2-yl)-3-(4-methoxyphenyl)propanoate (2p) and methyl 3-(furan-2-yl)-3-(2,3,4,5-tetramethylphenyl)propanoate (2o) were obtained as an oily mixture of regioisomers in a ratio of 1:0.2 from ester 1g and anisole in TIOH in a general yield of 71%.

Methyl 3-(furan-2-yl)-3-(2-methoxyphenyl)propanoate (2q) was obtained as a light orange oil from ester 1g in TIOH in a yield of 55%. ¹H NMR (500 MHz, CDCl₃), from the spectrum of a mixture of isomers: δ = 2.84–3.10 (m, AB system, CH₂, 2H), 3.61 (s, MeO, 3H), 3.78 (s, MeO, 3H), 4.50 (t, J = 7.8 Hz, CH, 1H), 6.02 (d, J = 3.2 Hz, 1H), 6.26–6.27 (m, 1H), 6.84 (d, J = 8.7 Hz, 2H₃rom.), 7.17 (d, J = 8.7 Hz, 2H₃rom.), 7.31 (br. s, 1H) ¹³C NMR (125 MHz, CDCl₃), from the spectrum of a mixture of isomers: δ = 39.7, 40.6, 51.7, 55.2, 105.5, 110.0, 114.0, 128.7, 133.2, 141.6, 156.5, 158.5, 171.9. IR (KBr), for a mixture of isomers, cm⁻¹: 1702 (C=O). HRMS, for a mixture of isomers, m/z calculated for C₁₅H₁₇O₄ [M+H]: 261.1121. Found: 261.1123.
Methyl 3-(furan-2-yl)-3-(2-methoxyphenyl)propanoate (2q) was obtained as a light orange oil from ester 1g in TfOH in a yield of 16%.\textsuperscript{1}H HMR (500 MHz, CDCl\textsubscript{3}), from the spectrum of a mixture of isomers: \(\delta = 2.90–3.02\) m (2H, CH\textsubscript{2}), 3.62 s (3H, Me), 3.84 s (3H, Me), 5.00–5.02 m (1H, CH), 6.07 d (1H, \(J = 3.0\) Hz), 6.27–6.28 m (1H), 6.83–7.31 m (5H arom.).\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}), from the spectrum of a mixture of isomers: \(\delta = 34.6, 38.2, 51.6, 55.5, 105.8, 110.8, 119.0, 120.6, 128.0, 128.2, 128.7, 141.4, 156.0, 158.5, 171.9\). IR (KBr), for a mixture of isomers, cm\textsuperscript{-1}: 1702 (C=O). HRMS, for a mixture of isomers, \(m/z\) calculated for C\textsubscript{15}H\textsubscript{17}O\textsubscript{4}[M+H]: 261.1121. Found: 261.1123.

Methyl 3-[5-(2-methylcarbonyl-1-phenylethyl)furan-2-yl]-3-phenylpropenoate(2r) was obtained as a light orange oil from ester 1h and benzene as an equimolar mixture of diastereomers in yields of 29% (in TfOH) and 38% (under the action of AlCl\textsubscript{3}). NMR \(\textsuperscript{1}H\) (500 MHz, CDCl\textsubscript{3}): \(\delta = 2.82–2.87\) m (4H), 3.01–3.06 m (4H), 3.56 s (12H, Me), 4.48 t (2H, CH, \(J = 7.8\) Hz), 5.58 s (2H), 5.59 s (2H), 7.19–7.37 m (40H arom.).\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta = 39.8, 41.5, 51.8, 106.6, 127.1, 127.8, 141.3, 155.4, 172.0\). GC-MS, \(m/z\), (I\textsubscript{rel.}, %): 392 (10) [M]+, 319 (25), 259 (53), 229 (100), 187 (9). IR (KBr), cm\textsuperscript{-1}: 1703 (C=O). HRMS, \(m/z\) calculated for C\textsubscript{24}H\textsubscript{25}O\textsubscript{5}[M+H]: 393.1697. Found: 393.1691.

Cation Aa generated at the protonation of compound 1e in TfOH. \(\textsuperscript{1}H\) NMR (400 MHz, TfOH): \(\delta = 6.94\) s (2H, CH), 7.52 s (2H, CH), 8.31 s (2H hetarom.).\textsuperscript{13}C NMR (100 MHz, TfOH): \(\delta = 110.1, 128.5, 145.0, 155.8, 182.2\).

Cation Ah generated at the protonation of compound 1h in TfOH. \(\textsuperscript{1}H\) NMR (400 MHz, TfOH): \(\delta = 6.08\) s (3H, Me), 7.71 s (2H, CH), 8.21 s (2H, CH), 8.96 s (2H hetarom.).\textsuperscript{13}C NMR (100 MHz, TfOH): \(\delta = 62.7, 110.3, 128.0, 143.6, 155.6, 181.5\).

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/molecules27144612/s1, NMR spectra of compounds and cations, study of oligomeric compounds by liquid chromatography-high-resolution mass-spectrometry, study of biological activity of compounds, Data of DFT calculations.

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