FULL PAPER

Synthesis and Antimicrobial Activity of Racemic 1,5-Diols: 2-(1,3-Diaryl-3-hydroxypropyl)cyclohexan-1-ol Derivatives

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A series of novel racemic 2-(1,3-diaryl-3-hydroxypropyl)cyclohexan-1-ol derivatives were synthesized from 1,5-diketones. All the synthesized compounds were characterized by spectroscopic methods. The antibacterial activities of obtained chiral 1,5-diols were investigated against four *Gram*-positive and three *Gram*-negative bacteria by determining of minimum inhibitory concentrations (*MICs*) *in vitro*. Compounds **3b**, **3c**, and **3d** were found to be active against *Enterococcus faecalis* and *Escherichia coli.* In addition, compound **3j** were found to be moderately active against all tested bacterial strains.

Keywords: Chalcones, 1,5-Diketone compounds, 1,5-Diols, *Michael* addition, Antimicrobial activity.

Introduction

Chalcones are an important class of compounds that can be prepared synthetically or isolated from natural sources. The chalcones have attracted a great deal of attention due to their synthetic applications and wide range of biological activity [1 – 7]. The presence of α,β-unsaturated C=O system on chalcone skeleton makes them polyfunctional synthetic building block. Thus, they are used as starting material in synthesis of natural heterocyclic compounds [2][8][9] and synthetically valuable intermediates [5][6]. For instance, 1,5-diketones are a valuable intermediates and they can be used in different type reactions including synthesis of pharmacologically active heterocyclic compounds [10], fused-ring systems [11][12], cyclohexenones [7][13], bicyclic compounds [14], and oxathianes [15]. 1,5-Diketones can be obtained from 1,4-*Michael* addition of ketones to chalcones. Various synthetic methods for conjugated addition of cyclic ketones to chalcones have been presented in the literature, including the following: tandem *retro*-Aldol [16], di-enamine mechanism [17] and barium isopropoxide [18], chiral benzoylthiourea–pyrrolidine [19], hydroxyphthalimide [20], pyrrolidine-based imides [21], pyrrolidine-pyridine [22], amino acid ionic liquid [23], pyrrolidine-sulfonamide-catalyzed [24] 1,5-diketone syntheses. In many of these methods [18 – 24], a chiral catalyst was used, and (*S*)-2-((*R*)-1,3-diaryl-3-oxopropyl)cyclohexanone derivatives were synthesized in high enantioselectivities. However, synthesis and application areas of 1,5-diols are importance in the organic chemistry. 1,5-Diols are useful intermediates in synthesis of heterocycle located in natural and bioactive products, such as dihydropyrans [25], tetrahydropyrans [26], δ-lactones [27][28], morpholine [29], and anabasine [30]. Also, chiral 1,5-diols are used in the synthesis of enantiomerically pure 2,6-disubstituted and 3,5-disubstituted six-membered heterocycles [31].

In our previous studies, we have reported the syntheses of 1,5-diketones from the *Michael* addition of cyclohexanone to chalcone derivatives [2][32]. We thought that 1,5-diketone derivatives could be transformed to the 1,5-diols. Therefore, in present study, we have synthesized racemic 2-(1,3-diaryl-3-hydroxypropyl)cyclohexan-1-ol derivatives **3a** – **3j** of racemic 1,5-diketones **2a** – **2j**.

Results and Discussion

Herein, we report the synthesis of racemic 2-(1,3-diaryl-3-hydroxypropyl)cyclohexan-1-ol derivatives **3a** – **3j** that have four stereogenic centers. The chalcone derivatives **1a** – **1j** were prepared by treatment of related aromatic ketones and aromatic aldehydes with NaOH in EtOH at room temperature [33][34]. 1,5-Diketones **2a** – **2j** were synthesized by modifying our reference method [2][32] *via Michael* addition in yields ranging from 80 to 90% (*Table 1*). In the syntheses of 1,5-diketones, no chiral catalyst was used, therefore the products are racemic mixture. The obtained racemic 1,5-diketones **2a** – **2j** were characterized by spectroscopic studies and literature data [2][32].

1,5-Diols **3a** – **3j** were obtained by reaction of **2a** – **2j** with $NaBH_4$ in THF/MeOH (5:1) solvent mixture at room temperature (*Scheme*). TLC studies and ^{1}H- and ^{13}C-NMR analyses indicated that at least four

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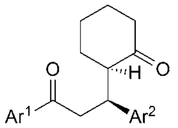
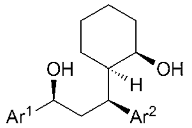
Table 1. Synthesized 1,5-diketones **2a** – **2j**



Entry	Ar^1	Ar^2	Product	Yield [%]
1	4-MeOC$_6$H$_4$	4-ClC$_6$H$_4$	**2a**	90
2	4-ClC$_6$H$_4$	4-MeOC$_6$H$_4$	**2b**	84
3	4-MeOC$_6$H$_4$	4-BrC$_6$H$_4$	**2c**	86
4	4-BrC$_6$H$_4$	4-MeOC$_6$H$_4$	**2d**	82
5	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	**2e**	80
6	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	**2f**	81
7	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	**2g**	82
8	4-MeOC$_6$H$_4$	4-MeC$_6$H$_4$	**2h**	87
9	4-MeC$_6$H$_4$	Thiophen-2-yl	**2i**	84
10	Thiophen-2-yl	Thiophen-2-yl	**2j**	81

Table 2. Synthesized 1,5-diols **3a** – **3j**



Entry	Ar^1	Ar^2	Product	Yield [%]
1	4-MeOC$_6$H$_4$	4-ClC$_6$H$_4$	**3a**	71
2	4-ClC$_6$H$_4$	4-MeOC$_6$H$_4$	**3b**	73
3	4-MeOC$_6$H$_4$	4-BrC$_6$H$_4$	**3c**	75
4	4-BrC$_6$H$_4$	4-MeOC$_6$H$_4$	**3d**	75
5	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	**3e**	70
6	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	**3f**	76
7	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	**3g**	76
8	4-MeOC$_6$H$_4$	4-MeC$_6$H$_4$	**3h**	78
9	4-MeC$_6$H$_4$	Thiophen-2-yl	**3i**	70
10	Thiophen-2-yl	Thiophen-2-yl	**3j**	65

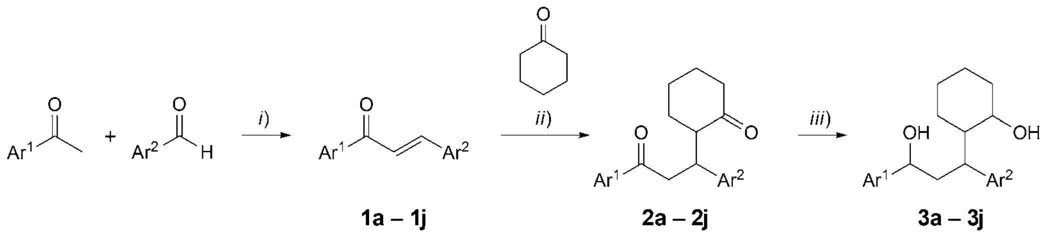
diastereoisomeric products were occurred during the reaction. But diastereoisomeric composition of the reaction mixture could not be determined because the ^{1}H- and ^{13}C-NMR spectra were very complex. The mixture was subjected to crystallization in Et$_2$O/hexane (3:1) [35]. Only one pure diastereoisomer was obtained by crystallization of **3a** – **3j** in high yields (65 – 78%) (*Table 2*). Viscous oily product that remaining after the crystallization was subjected to column chromatography on silica gel eluting with AcOEt/hexane (2:8) and different eluent systems (AcOEt/toluene, CHCl$_3$/hexane, *etc.*), but other diastereoisomers cannot be isolated.

The structures of synthesized 1,5-diols **3a** – **3j** were determined by spectroscopic studies (^{1}H-, ^{13}C-, 2D-NMR, IR, GC/MS, and elemental analysis). The full analysis of HSQC and HMBC spectra of **3a** confirmed the presence of 1,5-diol structure (*Table 3*). In the HMBC spectrum of **3a**, the location of benzylic OH group was confirmed with correlations of between OH–C(3) to C(3), C(2), and C(1″). Also the location of aliphatic OH group was confirmed by HMBCs of between OH–C(1′) to C(1′), C(2′), and C(6′) (*Table 3*, *Fig. 1*). In the ^{1}H-NMR spectrum of **3a**, the OH H-atoms of benzyl alcohol and cyclohexanol gave a *doublet* at δ(H) 4.79 (*d*, *J* = 4.7 Hz) and 4.18 (*d*, *J* = 4.2 Hz), respectively. The benzylic H-atom H–C(3) adjacent to the OH group gave a *multiplet* at δ(H) 3.89 – 3.86 and CH H-atom H–C(1′) adjacent to the OH group of cyclohexanol gave a broad *singlet* at δ(H) 4.01. Other benzylic H-atom H–C(1) on structure gave a *triplet* of *doublet* at δ(H) 2.90 (*J* = 11.1, 3.2 Hz) and CH H-atom H–C(2′) on cyclohexanol ring gave a *triplet* δ(H) 1.35 (*J* = 11.2 Hz). While one of the CH$_2$(2) H-atoms on propane chain gave a *multiplet* at δ(H) 2.17 – 2.09, the other gave a *triplet* at δ(H) 1.56 (*J* = 12.5 Hz). All the aliphatic and aromatic signals in the spectrum were consistent with the structure of **3a** (*Table 3*).

The relative configuration of the compound **3c** was established by an X-ray diffraction analysis [35]. The X-ray diffraction analysis confirmed that the proposed structure is *rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-1-(4-bromophenyl)-3-hydroxy-3-(4-methoxyphenyl)propyl]cyclohexanol (**3c**; *Fig. 2*).

All the newly synthesized 1,5-diols **3a** – **3j** were investigated for their *in vitro* antibacterial activity against four *Gram*-positive bacteria (*Bacillus cereus* ATCC 10987, *Bacillus subtilis* ATCC 6633, *Enterococcus faecalis* ATCC 29212, and *Staphylococcus aureus* ATCC 25923) and three *Gram*-negative bacteria (*Escherichia coli* ATCC 11229, *Pseudomonas aeruginosa* ATCC 27853, and *Shigella boydii* ATCC 9905). The antibacterial activity

Scheme. Syntheses of 1,5-diols **3a** – **3j** starting from chalcones **1a** – **1j**.



i) NaOH, EtOH, r.t., 3 h. *ii*) KOH, Benzyltriethylammonium chloride (TEBAC), CH$_2$Cl$_2$, r.t., 3 h. *iii*) NaBH$_4$, THF/MeOH, r.t., 16 h.

Table 3. ^{1}H- (600 MHz) and ^{13}C-NMR (150 MHz) data of **3a** in (D$_6$)DMSO. δ in ppm, J in Hz.

Position	HSQC (H → C)		HMBC (H → C)	
	δ(H)	δ(C)	^2J	^3J
1	2.90 (*td*, J = 11.1, 3.2)	43.9	C(2), C(2′), C(1‴)	C(3), C(1′), C(3′), C(2‴), C(6‴)
2	2.17 – 2.09 (*m*),	43.0	C(1), C(3)	C(1″), C(1‴)
	1.56 (*t*, J = 12.5)		C(1), C(3)	C(1″), C(1‴), C(2′)
3	3.89 – 3.86 (*m*)	69.9	C(2), C(1″)	C(2″), C(6″)
1′	4.01 (br. *s*)	64.5		C(3′), C(5′)
2′	1.35 (*t*, J = 11.2)	47.1	C(1), C(3′)	C(1‴)
3′	1.15 (*ddd*, J = 25.2, 12.8, 3.0),	25.6	C(2′), C(4′)	C(1′), C(5′)
	0.76 (*d*, J = 11.0)		C(2′), C(4′)	C(1′), C(5′)
4′	1.47 – 1.42 (*m*),	26.3		C(2′), C(6′)
	0.98 – 0.88 (*m*)		C(3′)	
5′	1.52 – 1.49 (*m*),	20.0		C(3′)
	1.30 – 1.23 (*m*)		C(4′)	C(1′)
6′	1.71 (*d*, J = 12.3),	34.2	C(1′), C(5′)	C(2′), C(4′)
	1.30 – 1.23 (*m*)		C(1′), C(5′)	C(4′)
1″	–	139.7		
2″	7.05 (*d*, J = 8.5)	126.9		C(4″), C(6″)
3″	6.78 (*d*, J = 8.6)	113.7		C(1″), C(5″)
4″	–	158.3		
5″	6.78 (*d*, J = 8.6)	113.7		C(1″), C(3″)
6″	7.05 (*d*, J = 8.5)	126.9		C(4″), C(2″)
1‴	–	144.6		
2‴	7.18 (*d*, J = 8.3)	130.4	C(3‴)	C(6‴)
3‴	7.31 (*d*, J = 8.3)	128.4	C(4‴)	C(1‴), C(5‴)
4‴	–	130.7		
5‴	7.31 (*d*, J = 8.3)	128.4	C(4‴)	C(1‴), C(3‴)
6‴	7.18 (*d*, J = 8.3)	130.4	C(3‴)	C(3‴)
HO–C(3)	4.79 (*d*, J = 4.7)	–	C(3)	C(2), C(1″)
HO–C(1′)	4.18 (*d*, J = 4.2)	–	C(1′)	C(2′), C(6′)
MeO	3.68 (*s*)	55.4		C(4″)

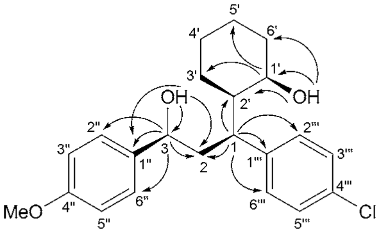


Fig. 1. Selected HMBCs of **3a**.

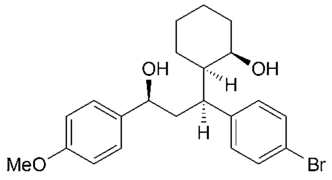


Fig. 2. Structure of **3c**.

tests were carried out by the microdilution method using 96-well microplates. Minimal inhibitory concentrations (*MICs*) of the synthesized 1,5-diols were determined and the results are given in *Table 4*. Piperacillin/tazobactam (8:1) was employed as a reference antibacterial agent.

As seen in *Table 4*, the most active compound was **3c** against *E. faecalis* and *E. coli* with an *MIC* value of 15.6 μg/ml. Compound **3d** (*MIC* 15.6 μg/ml) had the same effect as **3c** against *E. coli*, and also **3b** and **3j** have exhibited lower activity from them with the *MIC* values of 31.3 and 250 μg/ml, respectively. While compounds **3d** and **3j** showed moderate activity (*MIC* 125 μg/ml) against *E. faecalis*, **3b** showed about one-quarter of the activity of them (*MIC* 500 μg/ml). Besides, compound **3j** exhibited moderate activity against other tested bacterial strains with the *MIC* values of 125 μg/ml (*P. aeruginosa*) and 250 μg/ml (*B. cereus*, *B. subtilis*, and *S. aureus*), respectively. The rest of the tested compounds were found to be inactive against the selected bacteria at the tested concentrations.

In conclusion, a series of novel racemic (1*RS*,2*RS*)-2-((1*SR*,3*SR*)-1,3-diaryl-3-hydroxypropyl)cyclohexan-1-ol derivatives **3a** – **3j** have been synthesized by reduction of **2a** – **2j** with $NaBH_4$ in good yields. The structures of new compounds were established on the basis of spectroscopic methods. The antimicrobial activities of synthesized 1,5-diols **3a** – **3j** were screened against four *Gram*-positive and three *Gram*-negative bacteria. While compounds **3b**,

Table 4. Minimum inhibitory concentrations of 1,5-diols **3a** – **j**

Microorganism	Compound and *MIC* [μg/ml]										
	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**	P/T[a])
Gram-positive											
B. cereus	–[b])	–	–	–	–	–	–	–	–	250	125
B. subtilis	–	–	–	–	–	–	–	–	–	250	62.5
S. aureus	–	–	–	–	–	–	–	–	–	250	62.5
E. faecalis	–	500	15.6	125	–	–	–	–	–	125	62.5
Gram-negative											
E. coli	–	31.3	15.6	15.6	–	–	–	–	–	250	7.8
P. aeruginosa	–	–	–	–	–	–	–	–	–	125	62.5
S. boydii	–	–	–	–	–	–	–	–	–	250	62.5

[a]) P/T, piperacillin/tazobactam (8:1). [b]) Inactive (*MIC* > 500 μg/ml).

3c, and **3d** were found to be active against *E. faecalis* and *E. coli*, compound **3j** were found to be moderately active against all tested bacterial strains. These obtained 1,5-diols **3a** – **3j** have potential applications in the synthesis of biologically and naturally valuable compounds.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
http://dx.doi.org/10.1002/hlca.201600048

Experimental Part

General

Na_2SO_4 was used as a drying agent for the org. phase. Column chromatography (CC): silica gel (60 – 230 mesh; *Merck,* Darmstadt, Germany). M.p.: Electrothermal *9100* apparatus (*Bibby Scientific*, Staffordshire, UK). IR Spectra: *JASCO FT/IR-430* spectrometer (*JASCO*, Tokyo, Japan) in KBr disc; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance DPX-400* NMR instrument (*Bruker*, Billerica, MA, USA) in $CDCl_3$ (for **2b** – **2j**) and (D_6)DMSO (for **3a** – **3j**); δ in ppm rel. to Me_4Si (δ 0.00) for ^{1}H-NMR, $CDCl_3$ (δ 77.0) and (D_6)DMSO (δ 39.5) for ^{13}C-NMR spectra as internal standards, *J* in Hz. 2D-NMR spectra of **2a** and **3a**: *Agilent 600 MHz Premium COMPACT* NMR instrument (*Agilent*, Santa Clara, CA, USA) in (D_6)DMSO. GC/MS: *PerkinElmer Clarus 500* (*PerkinElmer*, Waltham, MS, USA). Elemental analyses: *LECO CHNS 932* elemental analyzer (*LECO*, Saint Joseph, MI, USA); in percent.

General Procedure for the Synthesis of 1,5-Diketones **2a** – **2j**

To a soln. of chalcone **1a** – **1j** (3 mmol), cyclohexanone (6 mmol), and benzyltriethylammonium chloride (TEBAC; 10 mol-%) in CH_2Cl_2 (5 ml) was added 5M KOH (0.2 ml). The mixture was stirred at r.t. for 3 h. Then, the mixture was neutralized with diluted HCl and extracted with CH_2Cl_2 (3 × 10 ml). Extract was dried (Na_2SO_4), and the solvent was removed in vacuum. The crude product was crystallized from EtOH/Et_2O 3:1.

2-[1-(4-Chlorophenyl)-3-(4-methoxyphenyl)-3-oxopropyl]-cyclohexanone (**2a**) [2]. ^{1}H-NMR: 7.87 (*d*, *J* = 8.9, H–C(2″,6″)); 7.25 (*d*, *J* = 8.7, H–C(3‴,5‴)); 7.23 (*d*, *J* = 8.6, H–C(2‴,6‴)); 6.97 (*d*, *J* = 8.8, H–C(3″,5″)); 3.80 (*s*, MeO); 3.60 (*td*, *J* = 8.3, 6.4, H–C(1)); 3.31 (*m*, CH_2(2)); 2.81 – 2.74 (*m*, H–C(2′)); 2.38 (*td*, *J* = 12.2, 5.8, 1 H of CH_2(6′)); 2.31 – 2.25 (*m*, 1 H of CH_2(6′)); 1.90 (*m*, 1 H of CH_2(5′)); 1.65 (*dd*, *J* = 10.2, 4.5, 1 H of CH_2(4′)); 1.51 (*m*, 1 H of CH_2(4′), 1 H of CH_2(3′), 1 H of CH_2(5′)); 1.10 – 0.97 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 212.62 (C(1′)); 197.09 (C(3)); 163.45 (C(4″)); 141.93 (C(1‴)); 131.09 (C(4‴)); 130.82 (C(2‴,6‴)); 130.58 (C(2″,6″)); 130.09 (C(1″)); 128.37 (C(3‴,5‴)); 114.22 (C(3″,5″)); 55.91 (MeO); 54.82 (C(2′)); 43.23 (C(2)); 42.48 (C(6′)); 40.16 (C(1)); 32.35 (C(3′)); 28.37 (C(5′)); 24.54 (C(4′)).

2-[3-(4-Chlorophenyl)-1-(4-methoxyphenyl)-3-oxopropyl]-cyclohexanone (**2b**). Yield 84%. White solid. M.p. 128 – 131 °C. IR: 3027*m*, 2935*s*, 1702*s* (C=O), 1685*s* (C=O), 1590*s*, 817*s*. ^{1}H-NMR: 7.84 (*d*, *J* = 8.4, H–C(2″,6″)); 7.31 (*d*, *J* = 8.4, H–C(3″,5″)); 7.03 (*d*, *J* = 8.6, H–C(2‴,6‴)); 6.75 (*d*, *J* = 8.6, H–C(3‴,5‴)); 3.67 (*s*, MeO); 3.63 – 3.56 (*m*, H–C(1)); 3.45 (*dd*, *J* = 15.8, 3.8, 1 H of CH_2(2)); 3.08 (*dd*, *J* = 15.8, 9.6, 1 H of CH_2(2)); 2.66 (*td*, *J* = 10.0, 4.8, H–C(2′)); 2.46 – 2.43 (*m*, 1 H of CH_2(6′)); 2.38 – 2.30 (*m*, 1 H of CH_2(6′)); 1.93 (br. *s*, 1 H of CH_2(5′)); 1.72 – 1.62 (*m*, 1 H of CH_2(4′), 1 H of CH_2(4′), 1 H of CH_2(3′)); 1.54 – 1.48 (*m*, 1 H of CH_2(5′)); 1.22 – 1.15 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 213.6 (C(1′)); 197.7 (C(3)); 158.1 (C(4‴)); 139.0 (C(4″)); 135.3 (C(1″)); 133.5 (C(1‴)); 129.6 (C(2″,6″)); 129.1 (C(3″,5″)); 128.7 (C(2″,6″)); 113.8 (C(3‴,5‴)); 55.8 (MeO); 55.0 (C(2′)); 44.5 (C(2)); 42.4 (C(6′)); 40.5 (C(1)); 32.6 (C(3′)); 28.6 (C(5′)); 24.3 (C(4′)). Anal. calc. for $C_{22}H_{23}ClO_3$ (370.13): C 71.25, H 6.25; found: C 71.16, H 6.32.

2-[1-(4-Bromophenyl)-3-(4-methoxyphenyl)-3-oxopropyl]-cyclohexanone (**2c**). Yield 86%. White solid. M.p. 102 – 105 °C. IR: 3021*m*, 2931*s*, 1704*s* (C=O), 1668*s*

(C=O), 1600*s*, 815*s*. ^{1}H-NMR: 7.92 (*d*, *J* = 9.0, H–C(2″,6″)); 7.38 (*d*, *J* = 8.4, H–C(3‴,5‴)); 7.08 (*d*, *J* = 8.4, H–C(2‴,6‴)); 6.90 (*d*, *J* = 9.0, H–C(3″,5″)); 3.84 (*s*, MeO); 3.69 (*td*, *J* = 9.8, 5.6, H–C(1)); 3.45 (*dd*, *J* = 16.1, 3.6, 1 H of CH_2(2)); 3.14 (*dd*, *J* = 16.1, 9.8, 1 H of CH_2(2)); 2.70 (*td*, *J* = 10.0, 4.8, H–C(2′)); 2.52 – 2.47 (*m*, 1 H of CH_2(6′)); 2.43 – 2.38 (*m*, 1 H of CH_2(6′)); 2.02 – 1.99 (*m*, 1 H of CH_2(5′)); 1.80 – 1.65 (*m*, 1 H of CH_2(4′), 1 H of CH_2(4′), 1 H of CH_2(3′)); 1.58 – 1.54 (*m*, 1 H of CH_2(5′)); 1.29 – 1.11 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 213.1 (C(1′)); 196.9 (C(3)); 163.3 (C(4″)); 141.1 (C(1‴)); 131.5 (C(3‴,5‴)); 130.4 (C(2″,6″)); 130.1 (C(2‴,6‴)); 129.9 (C(1″)); 120.3 (C(4‴)); 113.6 (C(3″,5″)); 55.5 (MeO); 55.4 (C(2′)); 43.5 (C(2)); 42.4 (C(6′)); 40.7 (C(1)); 32.5 (C(3′)); 28.5 (C(5′)); 24.3 (C(4′)). Anal. calc. for $C_{22}H_{23}BrO_3$ (414.08): C 63.62, H 5.58; found: C 63.49, H 5.65.

2-[3-(4-Bromophenyl)-1-(4-methoxyphenyl)-3-oxopropyl]cyclohexanone (**2d**). Yield 82%. White solid. M.p. 130 – 133 °C. IR: 3058*m*, 2933*s*, 1704*s* (C=O), 1683*s* (C=O), 1585*s*, 825*s*. ^{1}H-NMR: 7.80 (*d*, *J* = 8.6, H–C(2″,6″)); 7.55 (*d*, *J* = 8.6, H–C(3″,5″)); 7.05 (*d*, *J* = 8.8, H–C(2‴,6‴)); 6.79 (*d*, *J* = 8.8, H–C(3‴,5‴)); 3.74 (*s*, MeO); 3.61 (*td*, *J* = 10.0, 4.0, H–C(1)); 3.48 (*dd*, *J* = 15.8, 3.8, 1 H of CH_2(2)); 3.09 (*dd*, *J* = 15.8, 9.8, 1 H of CH_2(2)); 2.68 (*td*, *J* = 10.0, 5.0, H–C(2′)); 2.51 – 2.46 (*m*, 1 H of CH_2(6′)); 2.43 – 2.38 (*m*, 1 H of CH_2(6′)); 2.01 – 1.97 (*m*, 1 H of CH_2(5′)); 1.78 – 1.64 (*m*, 1 H of CH_2(4′), 1 H of CH_2(4′), 1 H of CH_2(3′)); 1.57 – 1.53 (*m*, 1 H of CH_2(5′)); 1.24 – 1.20 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 213.7 (C(1′)); 198.0 (C(3)); 158.1 (C(4‴)); 135.7 (C(1″)); 133.5 (C(1‴)); 131.7 (C(3″,5″)); 129.8 (C(2″,6″)); 129.1 (C(2‴,6‴)); 127.9 (C(4″)); 113.8 (C(3‴,5‴)); 55.9 (MeO); 55.1 (C(2′)); 44.5 (C(2)); 42.5 (C(6′)); 40.6 (C(1)); 32.6 (C(3′)); 28.6 (C(5′)); 24.3 (C(4′)). Anal. calc. for $C_{22}H_{23}BrO_3$ (414.08): C 63.62, H 5.58; found: C 63.53, H 5.67.

2-[1,3-Bis(4-methoxyphenyl)-3-oxopropyl]cyclohexanone (**2e**). Yield 80%. White solid. M.p. 104 – 106 °C. IR: 3014*m*, 2933*s*, 1702*s* (C=O), 1600*s* (C=O), 1573*s*, 823*s*. ^{1}H-NMR: 7.92 (*d*, *J* = 8.4, H–C(2″,6″))); 7.08 (*d*, *J* = 8.8, H–C(2‴,6‴)); 6.88 (*d*, *J* = 8.8, H–C(3‴,5‴)); 6.78 (*d*, *J* = 8.4, H–C(3″,5″)); 3.81 (*s*, MeO); 3.73 (*s*, MeO); 3.67 (*td*, *J* = 10.2, 3.8, H–C(1)); 3.41 (*dd*, *J* = 15.6, 4.0, 1 H of CH_2(2)); 3.11 (*dd*, *J* = 15.6, 9.6, 1 H of CH_2(2)); 2.68 (*td*, *J* = 9.8, 5.2, H–C(2′)); 2.52 – 2.47 (*m*, 1 H of CH_2(6′)); 2.40 – 2.37 (*m*, 1 H of CH_2(6′)); 1.97 (br. *s*, 1 H of CH_2(5′)); 1.79 – 1.65 (*m*, 1 H of CH_2(4′), 1 H of CH_2(4′), 1 H of CH_2(3′)); 1.56 – 1.52 (*m*, 1 H of CH_2(5′)); 1.27 – 1.22 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 213.9 (C(1′)); 197.5 (C(3)); 163.2 (C(4″)); 158.0 (C(4‴)); 133.8 (C(1‴)); 130.5 (C(2″,6″)); 130.0 (C(1″)); 129.2 (C(2‴,6‴)); 113.7 (C(3‴,5‴)); 113.5 (C(3″,5″)); 56.0 (MeO); 55.3 (MeO); 55.0 (C(2′)); 44.0 (C(2)); 42.3 (C(6′)); 40.5 (C(1)); 32.4 (C(3′)); 28.5 (C(5′)); 24.0 (C(4′)). Anal. calc. for $C_{23}H_{26}O_4$ (366.18): C 75.38, H 7.15; found: C 75.26, H 7.23.

2-[1,3-Bis(4-methylphenyl)-3-oxopropyl]cyclohexanone (**2f**). Yield 81%. White solid. M.p. 108 – 110 °C. IR: 3025*m*, 2938*s*, 1702*s* (C=O), 1677*s* (C=O), 1606*s*, 817*s*. ^{1}H-NMR: 7.85 (*d*, *J* = 8.2, H–C(2″,6″))); 7.23 (*d*, *J* = 8.2, H–C(3″,5″))); 7.08 (*s*, H–C(2‴,6‴), H–C(3‴,5‴)); 3.72 (*td*, *J* = 10.2, 3.8, H–C(1)); 3.46 (*dd*, *J* = 16.0, 5.2, 1 H of CH_2(2)); 3.20 (*dd*, *J* = 16.0, 9.6, 1 H of CH_2(2)); 2.72 (*td*, *J* = 9.8, 5.2, H–C(2′)); 2.55 – 2.52 (*m*, 1 H of CH_2(6′)); 2.44 – 2.40 (*m*, 1 H of CH_2(6′)); 2.40 (*s*, Me); 2.30 (*s*, Me); 2.00 – 1.97 (*m*, 1 H of CH_2(5′)); 1.83 – 1.67 (*m*, 1 H of CH_2(4′), 1 H of CH_2(4′), 1 H of CH_2(3′)); 1.59 – 1.55 (*m*, 1 H of CH_2(5′)); 1.31 – 1.26 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 213.8 (C(1′)); 198.5 (C(3)); 143.5 (C(4″)); 138.9 (C(1‴)); 136.0 (C(4‴)); 134.5 (C(1″)); 129.2 (C(3″,5″)); 129.1 (C(2‴,6‴)); 128.3 (C(3‴,5‴)); 128.2 (C(2″,6″)); 55.9 (C(2′)); 44.1 (C(2)); 42.2 (C(6′)); 40.7 (C(1)); 32.3 (C(3′)); 28.5 (C(5′)); 24.0 (C(4′)); 21.6 (Me); 21.0 (Me). Anal. calc. for $C_{23}H_{26}O_2$ (334.19): C 82.60, H 7.84; found: C 82.52, H 7.89.

2-[1-(4-Methoxyphenyl)-3-(4-methylphenyl)-3-oxopropyl]cyclohexanone (**2g**). Yield 82%. White solid. M.p. 117 – 120 °C. IR: 3058*m*, 2927*s*, 1704*s* (C=O), 1679*s* (C=O), 1608*s*, 825*s*. ^{1}H-NMR: 7.84 (*d*, *J* = 8.0, H–C(2″,6″)); 7.22 (*d*, *J* = 8.0, H–C(3″,5″)); 7.10 (*d*, *J* = 8.6, H–C(2‴,6‴)); 6.80 (*d*, *J* = 8.6, H–C(3‴,5‴)); 3.76 (*s*, MeO); 3.69 (*td*, *J* = 9.8, 4.4, H–C(1)); 3.44 (*dd*, *J* = 16.0, 4.0, 1 H of CH_2(2)); 3.17 (*dd*, *J* = 16.0, 9.6, 1 H of CH_2(2)); 2.69 (*td*, *J* = 9.8, 5.0, H–C(2′)); 2.54 – 2.49 (*m*, 1 H of CH_2(6′)); 2.42 – 2.40 (*m*, 1 H of CH_2(6′)); 2.39 (*s*, Me); 2.00 – 1.97 (*m*, 1 H of CH_2(5′)); 1.82 – 1.75 (*m*, 1 H of CH_2(4′), 1 H of CH_2(4′)); 1.72 – 1.54 (*m*, 1 H of CH_2(3′), 1 H of CH_2(5′)); 1.29 – 1.25 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 213.8 (C(1′)); 198.6 (C(3)); 158.0 (C(4‴)); 143.5 (C(4″)); 134.5 (C(1″)); 133.9 (C(1‴)); 129.2 (C(3″,5″)); 129.1 (C(2″,6″)); 128.3 (C(2‴,6‴)); 113.8 (C(3‴,5‴)); 56.0 (MeO); 55.1 (C(2′)); 44.2 (C(2)); 42.2 (C(6′)); 40.3 (C(1)); 32.3 (C(3′)); 28.5 (C(5′)); 24.0 (C(4′)); 21.6 (Me). Anal. calc. for $C_{23}H_{26}O_3$ (350.19): C 78.83, H 7.48; found: C 78.72, H 7.55.

2-[3-(4-Methoxyphenyl)-1-(4-methylphenyl)-3-oxopropyl]cyclohexanone (**2h**). Yield 87%. White solid. M.p. 131 – 134 °C. IR: 3027*m*, 2933*s*, 1698*s* (C=O), 1662*s* (C=O), 1602*s*, 819*s*. ^{1}H-NMR: 7.94 (*d*, *J* = 8.8, H–C(2″,6″)); 7.07 (*s*, H–C(2‴,6‴), H–C(3‴,5‴)); 6.89 (*d*, *J* = 8.8, H–C(3″,5″)); 3.83 (*s*, MeO); 3.70 (*td*, *J* = 9.6, 4.0, H–C(1)); 3.44 (*dd*, *J* = 15.6, 4.0, 1 H of CH_2(2)); 3.15 (*dd*, *J* = 15.6, 9.6, 1 H of CH_2(2)); 2.72 (*td*, *J* = 9.8, 5.2, H–C(2′)); 2.54 – 2.49 (*m*, 1 H of CH_2(6′)); 2.43 – 2.37 (*m*, 1 H of CH_2(6′)); 2.28 (*s*, Me); 2.00 – 1.96 (*m*, 1 H of CH_2(5′)); 1.81 – 1.75 (*m*, 1 H of CH_2(4′), 1 H of CH_2(4′)); 1.71 – 1.66 (*m*, 1 H of CH_2(3′)); 1.57 – 1.53 (*m*, 1 H of CH_2(5′)); 1.29 – 1.27 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 213.8 (C(1′)); 197.6 (C(3)); 163.2 (C(4″)); 138.9 (C(1‴)); 135.9 (C(4‴)); 130.5 C(2″,6″)); 130.1 (C(1″)); 129.1 (C(2‴,6‴)); 128.2 (C(3‴,5‴)); 113.5 (C(3″,5″)); 55.9 (MeO); 55.4 (C(2′)); 43.9 (C(2)); 42.3 (C(6′)); 40.9 (C(1)); 32.4 (C(3′)); 28.6 (C(5′)); 24.0 (C(4′)); 21.0 (Me). Anal. calc. for $C_{23}H_{26}O_3$ (350.19): C 78.83, H 7.48; found: C 78.70, H 7.57.

2-[3-(4-Methylphenyl)-3-oxo-1-(thiophen-2-yl)propyl]cyclohexanone (**2i**). Yield 84%. White solid. M.p. 103 – 106 °C. IR: 3068*m*, 2935*s*, 1700*s* (C=O), 1677*s* (C=O), 1606*s*, 809*s*, 688*s*. ^{1}H-NMR: 7.86 (*d*, *J* = 8.0, H–C(2″,6″)); 7.24 (*d*, *J* = 8.0, H–C(3″,5″)); 7.12 (*d*, *J* = 4.8, H–C(4‴)); 6.90 – 6.87 (*m*, H–C(3‴)); 6.84 (*d*, *J* = 2.8, H–C(2‴)); 4.18 – 4.13 (*m*, H–C(1)); 3.38 (*dd*, *J* = 16.3, 4.8, 1 H of CH_2(2)); 3.33 (*dd*, *J* = 16.3, 8.7, 1 H of CH_2(2)); 2.76 – 2.69 (*m*, H–C(2′)); 2.51 – 2.46 (*m*, 1 H of CH_2(6′)); 2.42 – 2.37 (*m*, 1 H of CH_2(6′)); 2.40 (*s*, Me); 2.03 – 2.00 (*m*, 1 H of CH_2(5′)); 1.89 – 1.82 (*m*, CH_2(4′)); 1.75 – 1.59 (*m*, 1 H of CH_2(3′), 1 H of CH_2(5′)); 1.39 – 1.33 (*m*, 1 H of CH_2(3′)). ^{13}C-NMR: 212.6 (C(1′)); 197.9 (C(3)); 145.7 (C(1‴)); 143.7 (C(4″)); 134.4 (C(1″)); 129.2 (C(3″,5″)); 128.3 (C(2″,6″)); 126.4 (C(4‴)); 125.5 (C(3‴)); 123.6 (C(2‴)); 56.2 (C(2′)); 44.4 (C(2)); 42.3 (C(6′)); 36.2 (C(1)); 31.9 (C(3′)); 28.2 (C(5′)); 24.4 (C(4′)); 21.6 (Me). Anal. calc. for $C_{20}H_{22}O_2S$ (326.13): C 73.58, H 6.79, S 9.82; found: C 73.45, H 6.84, S 9.87.

2-[3-Oxo-1,3-di(thiophen-2-yl)propyl]cyclohexanone (**2j**). Yield 81% (95% [19], 67% [21], 65% [24]). White solid. M.p. 121 – 124 °C. IR: 3068 *m*, 2940*s*, 1695*s* (C=O), 1660*s* (C=O), 1517*m*, 1415*s*, 742*s*, 688*s*. ^{1}H-NMR: 7.80 (*dd*, *J* = 4.0, 0.8, H–C(4″)); 7.59 (*dd*, *J* = 4.0, 0.8, H–C(2″)); 7.13 – 7.09 (*m*, H–C(3″), H–C(4‴)); 6.89 – 6.84 (*m*, H–C(2‴), H–C(3‴)); 4.12 (*td*, *J* = 8.8, 4.4, H–C(1)); 3.38 (*dd*, *J* = 15.9, 4.8, 1 H of CH_2(2)); 3.27 (*dd*, *J* = 15.9, 9.0, 1 H of CH_2(2)); 2.77 – 2.72 (*m*, H–C(2′)); 2.50 – 2.45 (*m*, 1 H of CH_2(6′)); 2.41 – 2.37 (*m*, 1 H of CH_2(6′)); 2.04 – 2.00 (*m*, 1 H of CH_2(5′)); 1.89 – 1.81 (*m*, CH_2(4′)); 1.72 – 1.59 (*m*, CH_2(3′), 1 H of CH_2(5′)). ^{13}C-NMR: 212.6 (C(1′)); 191.1 (C(3)); 145.2 (C(1‴)); 144.2 (C(1″)); 133.6 (C(2″)); 132.2 (C(4″)); 128.1 (C(3″)); 126.5 (C(4‴)); 125.6 (C(3‴)); 123.7 (C(2‴)); 56.0 (C(2′)); 45.1 (C(2)); 42.4 (C(6′)); 36.6 (C(1)); 32.0 (C(3′)); 28.3 (C(5′)); 24.5 (C(4′)). Anal. calc. for $C_{17}H_{18}O_2S_2$ (318.07): C 64.12, H 5.70, S 20.14; found: C 64.09, H 5.76, S 20.19.

General Procedure for the Synthesis of Chiral 1,5-Diols **3a** – **3j**

The synthesis of **3a** – **3j** were carried out according to our previous paper [20]. To a soln. of **2a** – **2j** (1 mmol) in THF/MeOH 5:1 (12 ml) was added $NaBH_4$ (3 mmol) and stirred for 16 h at r.t. 10% HCl (10 ml) was added to the mixture, and the mixture was dried extracted with Et_2O (3 × 20 ml). The org. layer was dried (Na_2SO_4) and evaporated. The crude product was crystallized from Et_2O/hexane 3:1.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-1-(4-Chlorophenyl)-3-hydroxy-3-(4-methoxyphenyl)propyl]cyclohexanol** (**3a**). Yield 71%. Colorless crystals. M.p. 198 – 200 °C. IR: 3357*s* (br., OH), 3289*s* (br., OH), 3064*m*, 2938*s*, 1612*m*, 1513*s*, 1249*s*, 819*s*. ^{1}H-NMR: 7.31 (*d*, *J* = 8.3, H–C(3‴,5‴)); 7.18 (*d*, *J* = 8.3, H–C(2‴,6‴)); 7.05 (*d*, *J* = 8.5, H–C(2″,6″)); 6.78 (*d*, *J* = 8.6, H–C(3″,5″)); 4.79 (*d*, *J* = 4.7, HO–C(3)); 4.18 (*d*, *J* = 4.2, HO–C(1′)); 4.01 (*s*, H–C(1′)); 3.89 – 3.86 (*m*, H–C(3)); 3.68 (*s*, MeO); 2.90 (*td*, *J* = 11.1, 3.2, H–C(1)); 2.17 – 2.09 (*m*, 1 H of CH_2(2)); 1.71 (*d*, *J* = 12.3, 1 H of CH_2(6′)); 1.56 (*t*, *J* = 12.5, 1 H of CH_2(2)); 1.52 – 1.49 (*m*, 1 H of CH_2(5′)); 1.47 – 1.42 (*m*, 1 H of CH_2(4′)); 1.35 (*t*, *J* = 11.2, H–C(2′)); 1.30 – 1.23 (*m*, 1 H of CH_2(5′), 1 H of CH_2(6′)); 1.15 (*ddd*, *J* = 25.2, 12.8, 3.0, 1 H of CH_2(3′)); 0.98 – 0.88 (*m*, 1 H of CH_2(4′)); 0.76 (*d*, *J* = 11.0, 1 H of CH_2(3′)). ^{13}C-NMR: 158.3 (C(4″)); 144.6 (C(1‴)); 139.7 (C(1″)); 130.7 (C(4‴)); 130.4 (C(2‴,6‴)); 128.4 (C(3‴,5‴)); 126.9 (C(2″,6″)); 113.7 (C(3″,5″)); 69.9 (C(3)); 64.5 (C(1′)); 55.4 (MeO); 47.1 (C(2′)); 43.9 (C(1)); 43.0 (C(2)); 34.2 (C(6′)); 26.3 (C(4′)); 25.6 (C(3′)); 20.0 (C(5′)). GC/MS: 358 ([M – H_2O]$^+$, 0.6), 273 (2.0), 222 (2.4), 191 (0.6), 137 (100.0), 109 (15.2), 77 (13.6). Anal. calc. for $C_{22}H_{27}ClO_3$ (374.16): C 70.48, H 7.26; found: C 70.36, H 7.32.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-(4-Chlorophenyl)-3-hydroxy-1-(4-methoxyphenyl)propyl]cyclohexanol** (**3b**). Yield 73%. Colorless crystals. M.p. 142 – 144 °C. IR: 3336*s* (br., OH), 3035*m*, 2927*s*, 1608*m*, 1509*s*, 1245*s*, 836*s*. ^{1}H-NMR: 7.34 (*d*, *J* = 8.2, H–C(3″,5″)); 7.17 (*d*, *J* = 8.2, H–C(2″,6″)); 6.94 (*d*, *J* = 8.6, H–C(2‴,6‴)); 6.86 (*d*, *J* = 8.6, H–C(3‴,5‴)); 5.03 (*d*, *J* = 4.4, HO–C(3)); 4.06 (*s*, HO–C(1′), H–C(1′)); 4.04 – 4.01 (*m*, H–C(3)); 3.74 (*s*, MeO); 2.31 (*t*, *J* = 10.0, H–C(1)); 2.09 (*t*, *J* = 10.8, 1 H of CH_2(2)); 1.97 (*td*, *J* = 12.0, 4.0, 1 H of CH_2(2)); 1.73 (br. *d*, *J* = 12.2, 1 H of CH_2(6′)); 1.48 – 1.40 (*m*, 1 H of CH_2(5′), 1 H of CH_2(4′)); 1.35 – 1.23 (*m*, H–C(2′), 1 H of CH_2(5′), 1 H of CH_2(6′)); 1.00 – 0.88 (*m*, 1 H of CH_2(3′), 1 H of CH_2(4′)); 0.74 (br. *d*, *J* = 12.2, 1 H of CH_2(3′)). ^{13}C-NMR: 157.7 (C(4‴)); 144.5 (C(1″)); 137.0 (C(1‴)); 131.7 (C(4″)); 129.5 (C(3″,5″)); 129.1 (C(2‴,6‴)); 128.2 (C(2″,6″)); 113.9 (C(3‴,5‴)); 71.4 (C(3)); 64.7 (C(1′)); 55.3 (MeO); 47.5 (C(2′)); 43.3 (C(1)); 41.4 (C(2)); 34.3 (C(6′)); 26.3 (C(4′)); 25.3 (C(3′)); 20.0 (C(5′)). GC/MS: 376 (M^+, 0.9), 356 (1.0), 338 (1.8), 257 (12.1), 202 (11.8), 141 (69.6), 135 (100.0), 77 (44.0). Anal. calc. for $C_{22}H_{27}ClO_3$ (374.16): C 70.48, H 7.26; found: C 70.41, H 7.33.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-1-(4-Bromophenyl)-3-hydroxy-3-(4-methoxyphenyl)propyl]cyclohexanol** (**3c**). Yield 75%. Colorless crystals. M.p. 197 – 199 °C [20]. IR: 3361*s* (br., OH), 3311*s* (br., OH), 3064*m*, 2940*s*, 1614*m*, 1513*s*, 1247*s*, 819*m*. ^{1}H-NMR: 7.48 (*d*, *J* = 8.4, H–C(3‴,5‴)); 7.16 (*d*, *J* = 8.4, H–C(2‴,6‴)); 7.07 (*d*, *J* = 8.8, H–C(2″,6″)); 6.81 (*d*, *J* = 8.4, H–C(3″,5″)); 4.83 (*d*, *J* = 4.4, HO–C(3)); 4.24 (*d*, *J* = 4.0, HO–C(1′)); 4.02 (br. *s*, H–C(1′)); 3.89 – 3.86 (*m*, H–C(3)); 3.70 (*s*, MeO); 2.91 (*td*, *J* = 10.7, 3.4, H–C(1)); 2.14 (*td*, *J* = 12.1, 3.4, 1 H of CH_2(2)); 1.73 (br. *d*, *J* = 11.6, 1 H of CH_2(6′)); 1.61 – 1.45 (*m*, 1 H of CH_2(2), 1 H of CH_2(5′), 1 H of CH_2(4′)); 1.40 – 1.20 (*m*, H–C(2′), 1 H of CH_2(5′), 1 H of CH_2(6′)); 1.19 – 1.12 (*m*, 1 H of CH_2(3′)); 1.00 – 0.91 (*m*, 1 H of CH_2(4′)); 0.78 (br. *d*, *J* = 11.6, 1 H of CH_2(3′)). ^{13}C-NMR: 158.3 (C(4″)); 145.1 (C(1‴)); 139.7 (C(1″)); 131.3 (C(3‴,5‴)); 131.2 (C(2‴,6‴)); 126.8 (C(2″,6″)); 118.9 (C(4‴)); 113.7 (C(3″,5″)); 69.9 (C(3)); 64.5 (C(1′)); 55.4 (MeO); 47.0 (C(2′)); 43.9 (C(1)); 42.8 (C(2)); 34.1 (C(6′)); 26.3 (C(4′)); 25.6 (C(3′)); 20.0 (C(5′)). GC/MS: 400 ([M – H_2O]$^+$, 10.3), 302 (3.9), 244 (17.9), 182 (40.2), 134 (100.0), 108 (51.0), 91 (30.8), 77 (33.8). Anal. calc. for $C_{22}H_{27}BrO_3$ (418.11): C 63.01, H 6.49; found: C 62.96, H 6.53.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-(4-Bromophenyl)-3-hydroxy-1-(4-methoxyphenyl)propyl]cyclohexanol** (**3d**). Yield 75%. Colorless crystals. M.p. 162 – 164 °C. IR: 3334 (br. *s*, OH), 3033*m*, 2925*s*, 1608*m*, 1508*s*, 1245*s*, 835*s*. ^{1}H-NMR: 7.48 (*d*, *J* = 8.4, H–C(3″,5″)); 7.08 (*d*, *J* = 8.4, H–C(2″,6″)); 6.92 (*d*, *J* = 8.4, H–C(2‴,6‴)); 6.86 (*d*, *J* = 8.4, H–C(3‴,5‴)); 5.03 (*d*, *J* = 4.4, HO–C(3)); 4.07 – 4.05 (*m*, HO–C(1′), H–C(1′)); 4.00 – 3.94 (*m*, H–C(3)); 3.74 (*s*, MeO); 2.27 (*t*, *J* = 10.0, H–C(1)); 2.07 – 2.01 (*m*, 1 H of CH$_2$(2)); 1.93 (*td*, *J* = 12.2, 4.0, 1 H of CH$_2$(2)); 1.71 (br. *d*, *J* = 12.4, 1 H of CH$_2$(6′)); 1.46 – 1.39 (*m*, 1 H of CH$_2$(5′); 1 H of CH$_2$(4′)); 1.34 – 1.22 (*m*, H–C(2′), 1 H of CH$_2$(5′), 1 H of CH$_2$(6′)); 0.98 – 0.87 (*m*, 1 H of CH$_2$(3′), 1 H of CH$_2$(4′)); 0.71 (br. *d*, *J* = 12.4, 1 H of CH$_2$(3′)). ^{13}C-NMR: 157.6 (C(4‴)); 144.9 (C(1″)); 136.9 (C(1‴)); 131.1 (C(3″,5″)); 129.5 (C(2″,6″), C(2‴,6‴)), 120.2 (C(4″)); 113.9 (C(3‴,5‴)); 71.4 (C(3)); 64.6 (C(1′)); 55.3 (MeO); 47.4 (C(2′)); 43.3 (C(1)); 41.3 (C(2)); 34.3 (C(6′)); 26.2 (C(4′)); 25.3 (C(3′)); 20.0 (C(5′)). GC/MS: 420 (M^+, 1.0), 384 (0.8), 303 (5.00), 185 (29.6), 135 (100.0), 121 (34.8), 77 (28.3). Anal. calc. for $C_{22}H_{27}BrO_3$ (418.11): C 63.01, H 6.49; found: C 62.93, H 6.55.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-Hydroxy-1,3-bis(4-methoxyphenyl)propyl]cyclohexanol** (**3e**). Yield 70%. Colorless crystals. M.p. 160 – 163 °C. IR: 3451 (br. *s*, OH), 3066*m*, 2923*s*, 1610*m*, 1509*s*, 1247*s*, 831*s*. ^{1}H-NMR: 7.06 (*d*, *J* = 8.8, H–C(2‴,6‴)); 6.91 (*d*, *J* = 8.4, H–C(2″,6″)); 6.87 – 6.83 (*m*, H–C(3″,5″), H–C(3‴,5‴)); 4.76 (*d*, *J* = 4.4, HO–C(3)); 4.07 (br. *s*, H–C(1′)); 4.03 (*d*, *J* = 4.0, HO–C(1′)); 3.96 – 3.90 (*m*, H–C(3)); 3.74 (*s*, 2 MeO); 2.31 (*t*, *J* = 9.6, H–C(1)); 2.11 – 2.04 (*m*, H–C(2)) 1.92 (*td*, *J* = 12.2, 4.0, 1 H of CH$_2$(2)); 1.72 (br. *d*, *J* = 12.4, 1 H of CH$_2$(6′)); 1.48 – 1.22 (*m*, 1 H of CH$_2$(4′), H–C(2′), CH$_2$(5′), 1 H of CH$_2$(6′)); 0.98 – 0.88 (*m*, 1 H of CH$_2$(3′), 1 H of CH$_2$(4′)); 0.73 (br. *d*, *J* = 12.4, 1 H of CH$_2$(3′)). ^{13}C-NMR: 158.6 (C(4″)); 157.6 (C(4‴)); 137.4 (C(1‴)); 137.2 (C(1″)); 129.5 (C(2″,6″)); 128.4 (C(2‴,6‴)); 113.9 (C(3‴,5‴)); 113.6 (C(3″,5″)); 71.6 (C(3)); 64.7 (C(1′)); 55.4 (MeO); 55.3 (MeO); 47.5 (C(2′)); 43.5 (C(1)); 41.3 (C(2)); 34.4 (C(6′)); 26.3 (C(4′)); 25.3 (C(3′)); 20.0 (C(5′)). GC/MS: 371 (M^+, 0.6), 334 (0.7), 253 (21.0), 202 (12.6), 137 (100.0), 135 (74.4), 121 (67.3), 77 (22.2). Anal. calc. for $C_{23}H_{30}O_4$ (370.21): C 74.56, H 8.16; found: C 74.44, H 8.19.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-Hydroxy-1,3-bis(4-methylphenyl)-propyl]cyclohexanol** (**3f**). Yield 76%. Colorless crystals. M.p. 134 – 136 °C. IR: 3399*s* (br., OH), 3332*s* (br., OH), 3019*m*, 2933*s*, 1511*s*, 1249*s*, 971*s*, 819*s*. ^{1}H-NMR: 7.12 – 7.04 (*m*, C(2″,6″), C(3″,5″), C(2‴,6‴)); 6.91 (*d*, *J* = 7.2, C(3‴,5‴)); 4.83 (*d*, *J* = 3.2, HO–C(3)); 4.11 (*s*, H–C(1′)); 4.05 (*s*, HO–C(3)); 4.00 (br. *s*, H–C(3)); 2.30 (*s*, 2 Me); 2.14 (*t*, *J* = 9.6, H–C(1)); 1.98 (*m*, 1 H of CH$_2$(2)); 1.75 (br. *d*, *J* = 12.0, 1 H of CH$_2$(6′)); 1.50 – 1.27 (*m*, 1 H of CH$_2$(2), 1 H of CH$_2$(4′), H–C(2′), CH$_2$(5′), 1 H of CH$_2$(6′)); 1.03 – 0.89 (*m*, 1 H of CH$_2$(3′), 1 H of CH$_2$(4′)); 0.78 (br. *d*, *J* = 12.4, 1 H of CH$_2$(3′)). ^{13}C-NMR: 142.5 (C(1″)); 142.4 (C(1‴)); 136.1 (C(4″)); 134.8 (C(4‴)); 129.1 (C(3″,5″)); 128.8 (C(3‴,5‴)); 128.6 (C(2‴,6‴)); 127.3 (C(2″,6″)); 71.9 (C(3)); 64.7 (C(1′)); 47.5 (C(2′)); 43.9 (C(1)); 41.4 (C(2)); 34.4 (C(6′)); 26.4 (C(4′)); 25.4 (C(3′)); 21.2 (Me); 21.1 (Me); 20.1 (C(5′)). GC/MS: 339 (M^+, 0.6), 320 (1.8), 302 (3.7), 246 (1.4), 221 (24.6), 186 (43.0), 121 (100.0), 105 (71.5), 91 (58.1), 77 (32.5). Anal. calc. for $C_{23}H_{30}O_2$ (338.22): C 81.61, H 8.93; found: C 81.52, H 8.97.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-Hydroxy-1-(4-methoxyphenyl)-3-(4-methylphenyl)propyl]cyclohexanol** (**3g**). Yield 76%. Colorless crystals. M.p. 166 – 168 °C. IR: 3442*s* (br., OH), 3031*m*, 2919*s*, 1608*m*, 1509*s*, 1236*s*, 829*s*. ^{1}H-NMR: 7.10 (*d*, *J* = 8.0, H–C(2″,6″)); 7.04 (*d*, *J* = 8.0, H–C(3″,5″)); 6.92 (*d*, *J* = 8.4, H–C(2‴,6‴)); 6.86 (*d*, *J* = 8.4, H–C(3‴,5‴)); 4.83 (*d*, *J* = 4.0, HO–C(3)); 4.08 (br. *s*, H–C(1′)); 4.04 (*d*, *J* = 4.0, HO–C(1′)); 4.00 – 3.95 (*m*, H–C(3)); 3.75 (*s*, MeO); 2.36 – 2.30 (*m*, H–C(1)); 2.29 (*s*, Me); 2.12 – 2.06 (*m*, 1 H of CH$_2$(2)); 1.93 (*td*, *J* = 12.2, 4.2, 1 H of CH$_2$(2)); 1.73 (br. *d*, *J* = 12.4, 1 H of CH$_2$(6′)); 1.48 – 1.42 (*m*, 1 H of CH$_2$(5′), 1 H of CH$_2$(4′)); 1.34 – 1.23 (*m*, H–C(2′), 1 H of CH$_2$(5′), 1 H of CH$_2$(6′)); 1.00 – 0.88 (*m*, 1 H of CH$_2$(3′), 1 H of CH$_2$(4′)); 0.73 (br. *d*, *J* = 11.6, 1 H of CH$_2$(3′)).^{13}C-NMR: 157.7 (C(4‴)); 142.5 (C(1″)); 137.2 (C(4″)); 136.1 (C(1‴)); 129.5 (C(3″,5″)); 128.8 (C(2‴,6‴)); 127.3 (C(2″,6″)); 113.9 (C(3‴,5‴)); 71.9 (C(3)); 64.7 (C(1′)); 55.3 (MeO); 47.6 (C(2′)); 43.5 (C(1)); 34.4 (C(6′)); 26.3 (C(4′)); 25.4 (C(3′)); 21.2 (Me); 20.0 (C(5′)). GC/MS: 354 (M^+, 1.6), 318 (1.1), 237 (14.8), 202 (9.0), 135 (60.8), 121 (100.0), 91 (27.5), 77 (16.1). Anal. calc. for $C_{23}H_{30}O_3$ (354.22): C 77.93, H 8.53; found: C 77.87, H 8.55.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-Hydroxy-3-(4-methoxyphenyl)-1-(4-methylphenyl)propyl]cyclohexanol** (**3h**). Yield 78%. Colorless crystals. M.p. 172 – 174 °C. IR: 3353*s* (br., OH), 3288*s* (br., OH), 3052*m*, 2927*s*, 1614*m*, 1511*s*, 1247*s*, 819*s*. ^{1}H-NMR: 7.11 – 7.05 (*m*, H–C(2″,6″), H–C(2‴,6‴), H–C(3‴,5‴)); 6.81 (*d*, *J* = 8.8, H–C(3″,5″)); 4.77 (*d*, *J* = 4.8, HO–C(3)); 4.18 (*d*, *J* = 4.0, HO–C(1′)); 4.04 (br. *s*, H–C(1′)); 3.95 – 3.92 (*m*, H–C(3)); 3.70 (*s*, MeO); 2.89 – 2.84 (*m*, H–C(1)); 2.28 (*s*, Me); 2.14 (*t*, *J* = 10.2, 1 H of CH$_2$(2)); 1.73 (br. *d*, *J* = 11.6, 1 H of CH$_2$(6′)); 1.60 – 1.44 (*m*, 1 H of CH$_2$(2), 1 H of CH$_2$(5′), 1 H of CH$_2$(4′)); 1.37 – 1.29 (*m*, H–C(2′), 1 H of CH$_2$(5′), 1 H of CH$_2$(6′)); 1.21 – 1.09 (*m*, 1 H of CH$_2$(3′)); 1.00 – 0.90 (*m*, 1 H of CH$_2$(4′)); 0.83 (br. *d*, *J* = 11.6, 1 H of CH$_2$(3′)). ^{13}C-NMR: 158.3 (C(4″)); 142.5 (C(1‴)); 140.0 (C(4‴)); 134.7 (C(1″)); 129.1 (C(3‴,5‴)); 128.7 (C(2‴,6‴)); 126.8 (C(2″,6″)); 113.7 (C(3″,5″)); 69.9 (C(3)); 64.6 (C(1′)); 55.4 (MeO); 47.3 (C(2′)); 43.9 (C(1)); 43.2 (C(2)); 34.2 (C(6′)); 26.4 (C(4′)); 25.7 (C(3′)); 21.1 (Me); 20.1 (C(5′)). GC/MS: 354 (M^+, 0.9), 318 (0.9), 237 (18.3), 186 (17.8), 137 (100.0), 118 (56.2), 105 (34.4), 77 (20.6). Anal. calc. for $C_{23}H_{30}O_3$ (354.22): C 77.93, H 8.53; found: C 77.89, H 8.57.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-Hydroxy-3-(4-methylphenyl)-1-(thiophen-2-yl)propyl]cyclohexanol** (**3i**). Yield 70%. Colorless crystals. M.p. 152 – 155 °C. IR: 3399*s* (br., OH), 3033*m*, 2927*s*, 1444*s*, 1000*s*, 823*s*, 700*s*. ^{1}H-NMR: 7.34 (*d*, *J* = 4.8, H–C(4‴)); 7.16 – 7.12 (*m*, H–C(2″,6″), H–C(3″,5″)); 6.97 – 6.94 (*m*, H–C(3‴)); 6.65 (*d*, *J* = 3.2, H–C(2‴)); 4.98 (*d*, *J* = 4.0, HO–C(3)); 4.19 – 4.12 (*m*, H–C(3)); 4.12 (*s*, HO–C(1′), H–C(1′)); 2.57 – 2.51 (*m*, H–C(1)); 2.48 – 2.41 (*m*, 1 H of CH$_2$(2)); 2.32 (*s*, Me); 1.97 – 1.90 (*m*, 1 H of CH$_2$(2)); 1.77 (br. *d*, *J* = 12.4, 1 H of CH$_2$(6′)); 1.49 (br. *s*, 1 H of CH$_2$(5′), 1 H of CH$_2$(4′)); 1.38 – 1.28 (*m*, H–C(2′), 1 H of CH$_2$(5′), 1 H of CH$_2$(6′)); 1.13 – 0.94 (*m*, CH$_2$(3′), 1 H of CH$_2$(4′)). ^{13}C-NMR: 149.7 (C(1‴)); 142.2 (C(1″)); 136.2 (C(4″)); 128.9 (C(3″,5″)); 127.4 (C(2″,6″)); 126.8 (C(4‴)); 124.9 (C(3‴)); 123.6 (C(2‴)); 71.8 (C(3)); 64.6 (C(1′)); 48.8 (C(2′)); 42.8 (C(1); C(2)); 34.3 (C(6′)); 26.4 (C(4′)); 25.4 (C(3′)); 21.3 (Me); 20.0 (C(5′)). GC/MS: 313 (M^+, 0.6), 294 (7.5), 213 (31.2), 196 (46.6), 178 (59.3), 121 (100), 110 (77.2), 97 (55.5), 77 (43.2). Anal. calc. for $C_{20}H_{26}O_2S$ (330.17): C 72.69, H 7.93, S 9.70; found: C 72.61, H 7.95, S 9.72.

***rel*-(1*R*,2*R*)-2-[(1*S*,3*S*)-3-Hydroxy-1,3-di(thiophen-2-yl)-propyl]cyclohexanol** (**3j**). Yield 65%. Colorless crystals. M.p. 122 – 125 °C. IR: 3378*s* (br., OH), 3106*m*, 2927*s*, 1442*m*, 968*m*, 696*s*. ^{1}H-NMR: 7.41 (*dd*, *J* = 5.0, 1.4, H–C(4″)); 7.35 (*d*, *J* = 5.2, H–C(4‴)); 6.96 – 6.93 (*m*, H–C(2″), H–C(3″)); 6.87 (br. *d*, *J* = 3.2, H–C(2‴)); 6.69 – 6.67 (*m*, H–C(3‴)); 5.38 (*d*, *J* = 4.4, HO–C(3)); 4.39 – 4.34 (*m*, H–C(3)); 4.17 (*d*, *J* = 4.0, HO–C(1′)); 4.03 (br. *s*, H–C(1′)); 2.69 – 2.63 (*m*, H–C(1)); 2.41 – 2.34 (*m*, 1 H of CH$_2$(2)); 1.90 (*dd*, *J* = 12.2, 4.0, 1 H of CH$_2$(2)); 1.73 (br. *d*, *J* = 12.4, 1 H of CH$_2$(6′)); 1.50 – 1.42 (*m*, 1 H of CH$_2$(5′), 1 H of CH$_2$(4′)); 1.36 – 1.25 (*m*, H–C(2′), 1 H of CH$_2$(5′), 1 H of CH$_2$(6′)); 1.09 – 0.95 (*m*, 1 H of CH$_2$(3′), 1 H of CH$_2$(4′)); 0.90 (br. *d*, *J* = 12.4, 1 H of CH$_2$(3′)). ^{13}C-NMR: 149.7 (C(1‴)); 149.3 (C(1″)); 126.9 (C(4″)); 126.6 (C(4‴)); 125.1 (C(2″)); 124.9 (C(2‴)); 124.0 (C(3″)); 123.8 (C(3‴)); 67.5 (C(3)); 64.6 (C(1′)); 48.6 (C(2′)); 43.6 (C(1), C(2)); 34.1 (C(6′)); 26.2 (C(4′)); 25.4 (C(3′)); 19.9 (C(5′)). GC/MS: 322 (M^+, 0.9), 286 (3.3), 220 (9.2), 196 (31.3), 178 (47.7), 113 (100), 110 (69.8), 97 (67.2), 85 (44.3). Anal. calc. for $C_{17}H_{22}O_2S_2$ (322.11): C 63.32, H 6.88, S 19.88; found: C 63.27, H 6.94, S 19.91.

Antimicrobial Activity, Determination of MICs

The broth microdilution method was employed for the determination of antimicrobial activities of the compounds according to the recommendations of the CLSI [36]. The minimal inhibitory concentration (*MIC*) values of the compounds were studied using the microwell dilution method for the bacterial strains. Overnight broth cultures were used to prepare the inocula of the microorganisms and suspensions were adjusted to 0.5 *McFarland* standard turbidity. After the dissolution of the **3a** – **3j** for testing in *Mueller–Hinton* broth (MHB) which has 10% (*v*/*v*) DMSO, serial twofold dilutions were prepared in 96-well plates with MHB at a concentration varying between 7.8 and 500 μg/ml. A *Bio Tek* microplate reader (*Bio Tek Instruments, Inc.*, Winooski, VT, USA) was used to measure the optical density (*OD*) at 620 nm and it was measured again following the incubation for 24 h at 37 °C. *MIC* was determined as the lowest concentration of **3a** – **3j** that inhibits the growth of test bacteria.

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