Ultrasound-Assisted Synthesis of 3-(Arylamino)-1-ferrocenylpropan-1-ones

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A successful aza-*Michael* addition of arylamines to a conjugated enone, acryloylferrocene, has been achieved by ultrasonic irradiation of the mixture of these reactants and the catalyst, *i.e.*, montmorillonite K-10. This solvent-free reaction, yielding ferrocene containing *Mannich* bases, 3-(arylamino)-1-ferrocenylpropan-1-ones, considered as valuable precursors in organic synthesis, has been performed by using a simple ultrasonic cleaner. Among 17 synthesized β-amino ketones, three were new ones, and these were fully characterized by spectroscopic means. X-Ray crystallographic analysis of three of these crystalline products enabled the insight into the conformational details of these compounds. All compounds were evaluated for their antibacterial activities against six *Gram*-positive and five *Gram*-negative strains in a microdilution assay. The observed promising antibacterial activity (with a *MIC* value of 25 μg/ml (*ca.* 0.07 μmol/ml) as the best result for almost all tested compounds against *Micrococcus flavus*) seems not only to be compound but also bacterial species-specific.

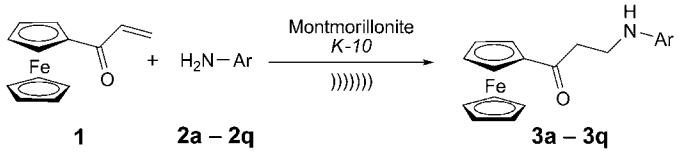
Introduction. – Ferrocene, an unusually stable metalorganic compound, has attracted the most widespread attention of chemists among all non-natural compounds. Since its discovery in 1951 [1][2], a plethora of studies dealing with ferrocene (which is now commercially available, and a relatively non-expensive compound), and/or its derivatives were carried out. This unprecedented interest is a consequence of several unique features of these compounds. By classical methods of organic chemistry, ferrocene could be easily functionalized to derivatives that possess an outstanding stability in both aqueous and non-aqueous media. Thus, ferrocenes have applications in numerous fields, particularly in those such as organic synthesis, catalysis, electronic absorption, and nonlinear optical materials [3][4]. Since the iron core of these compounds is able to exist in both Fe^{2+} and Fe^{3+}, they possess very interesting redox properties and, therefore, offer interesting possibilities for the formation of electrochemical actuators or switches [5]. Furthermore, bioconjugates containing ferrocene represent a new class of biomaterials, with the organometallic unit serving as a

molecular scaffold, a sensitive probe, a chromophore, a biological marker, a redox-active site, a catalytic site, *etc.* [6]. Biological properties of this class of compounds are particularly interesting. The earliest attempts to apply ferrocenes in medicine were unsuccessful [7][8], but it did not discourage chemists to search for new possibly biologically active derivatives of this metallocene. Several new compounds of this kind have been synthesized and biologically evaluated against certain diseases, and it turned out that many ferrocenyl compounds display interesting cytotoxic, antitumor, antimalarial, and antimicrobial activities [9–18]. All these investigations were prompted by the known fact that a formal substitution of an aromatic group from a compound possessing a certain property (*e.g.*, biological/pharmacological activity) might lead to a product with this feature being much more manifested. It was the main drawing force in many synthetic projects concerning ferrocenes: a plethora of new molecules were designed to be derivatives or analogs of known compounds (that already possess desired properties) in which a certain group was replaced with the ferrocene unit (expecting an improved property). The present study also follows this strategy. Namely, in the scope of a broader synthetic project, we needed recently some 3-(arylamino)-1-ferrocenylpropan-1-ones. In general, such compounds (β-amino ketones) have many applications, among which the most important ones are surely the synthesis of pharmaceuticals [19–22]. The introduction of a ferrocene nucleus into these molecules could be of a particular interest. The most frequently used general synthetic approach to these compounds is the *Mannich* reaction [19][23][24], but serious disadvantages of this approach exist and mostly encompass the drastic reaction conditions, long reaction times (causing many side reactions), and an inability of the use of primary amines in the synthesis of secondary ones (since the latter are also good substrates of the same reaction giving tertiary amines containing two 3-oxo groups). A very good alternative to this reaction is the aza-*Michael* addition, *i.e.*, the conjugate addition of amines to the olefinic bond of α,β-unsaturated CO groups [25]. The literature survey revealed that the addition of aliphatic amines to *Michael* acceptors proceeds readily (even without a catalyst [26][27]), whereas aromatic ones do not undergo this reaction easily because of their lower nucleophilicity, particularly when mild conditions and environmentally friendly catalysts were used [28–32]. Considering these literature findings, we developed recently a suitable method for the synthesis of 3-(arylamino)-1-ferrocenylpropan-1-ones by microwave irradiation of acryloyl ferrocene and the corresponding arylamines at the surface of montmorillonite K-10, without a solvent in good-to-excellent yields [33]. In continuation of our permanent interest in the synthesis of different ferrocene derivatives containing two or more heteroatoms (interesting from both synthetic and medicinal chemistry points of view) [18][34–36], herein we wish to report that this synthesis might be accomplished using a simple and cheap ultrasonic cleaner instead of the microwave oven. Since almost all products are crystal substances, suitable for X-ray analysis, in addition to the spectral data of newly synthesized compounds, we will compare here the structural features (molecular structure and ability to form intermolecular interactions) of some of the obtained *Mannich* bases with those of recently reported derivatives [33]. Our previous results on the antibacterial activity of these compounds encouraged us to screen the synthesized compounds against a broader panel of bacterial strains (in total eleven different bacteria) in order to provide a better understanding of the intrinsic features of these

compounds, responsible for their activity, and to possibly point out to the ones with higher or improved activity (in this context, the currently obtained minimal inhibitory concentrations (*MIC*) data together with those reported in [33] were subjected to an agglomerative hierarchical clustering analysis).

Results and Discussion. – *Synthesis.* The main advantages of the method described in our previous work for the synthesis of the title compounds over the classical ones are the simplicity, high efficiency, and the use of an environmentally friendly catalyst [33]. Even better results with respect to these parameters have been reported recently for the catalyst-free addition of aliphatic amines to conjugate systems of ferrocene analogs of chalcones supported by the ultrasonic irradiation [30]. However, as the authors reported, this reaction failed when aromatic amines were used as the nucleophiles. In our hands, on the other hand, the addition of aniline (**2a**) to acryloylferrocene (**1**) under conditions described in [33] gave the corresponding β-amino ketone (**3a**; *Scheme*), but in a relatively poor yield (< 40%). Since our microwave-assisted synthesis of the same compound starting from the same reactants was successful only in the presence of the catalyst (montmorillonite K-10) [33], we assumed that the addition of less nucleophilic aromatic amines to the conjugate system of enones might be facilitated also by the simultaneous action of this environmentally benign catalyst and ultrasonic irradiation. A very recent report, demonstrating once again that ultrasound has a positive effect on the conjugate addition of amines to *Michael* acceptors (appeared when the present manuscript has already been finished), confirms validity of this idea [37]. Thus, when a mixture of **1** (1 mmol), **2a** (2 mmol), and montmorillonite K-10 (100 mg) was irradiated in an ultrasonic cleaner for 1 h, β-amino ketone **3a** was obtained in high yield (80%). To check the generality of this reaction, additional 16 arylamines, **2b** – **2q** (*Scheme*), have been submitted to the same reaction conditions. The results are compiled in *Table 1*, and show that a simple and cheap ultrasonic cleaner can be used to accomplish the aza-*Michael* reaction as successfully as a microwave oven.

Scheme. *Ultrasound-Assisted Synthesis of 3-(Arylamino)-1-ferrocenylpropan-1-ones*



1 **2a – 2q** **3a – 3q**

An overview of the data collected in *Table 1* reveals that the yields of the corresponding β-amino ketones **3a** – **3q** depend on the structure of the starting amines **2a** – **2q** in an expected manner. Namely, when the starting amines contain an electron-withdrawing group, the yield of the corresponding *Mannich* base is lower. Thus, in the case of amines containing a C=O group (*i.e.*, **2l** – **2n**), the corresponding β-amino ketones were obtained in slightly lower yields (*Table 1*, *Entries 12 – 14*) than in the case of aniline, whereas the presence of a strong electron-withdrawing group, *i.e.*, the NO_2 group (amines **2o** – **2q**), causes a more considerable decrease of the yields (*Table 1*, *Entries 15 – 17*).

Table 1. *Structures of 3-(Arylamino)-1-ferrocenylpropan-1-ones,* **3a**–**3q**, *and the Corresponding Starting Amines* **2a**–**2q**, *Respectively, as Well as the Yields of the Reaction*

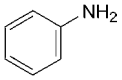
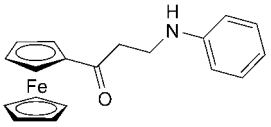
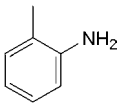
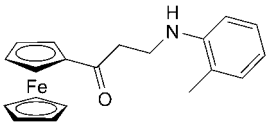
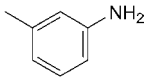
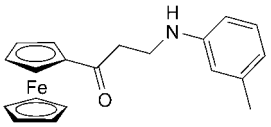
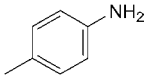
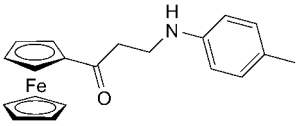
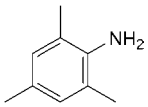
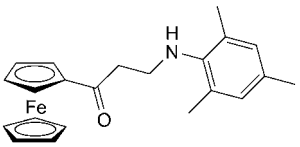
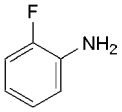
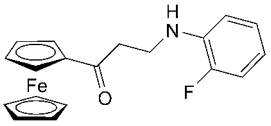
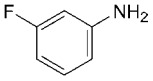
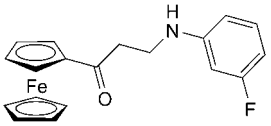
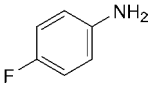
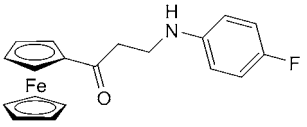
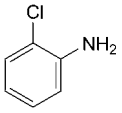
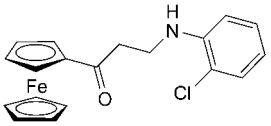
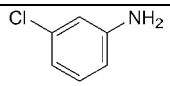
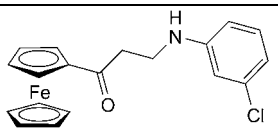
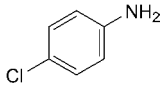
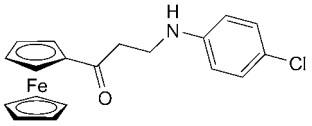
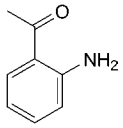
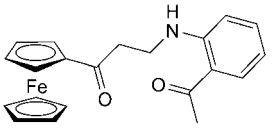
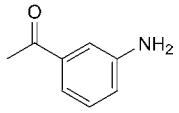
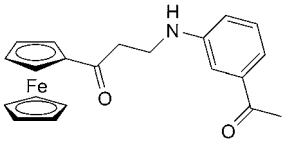
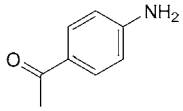
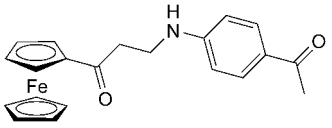
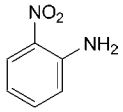
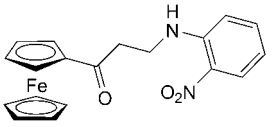
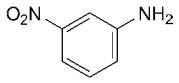
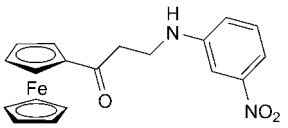
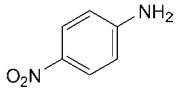
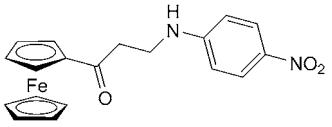
Entry	Amine		Product		Yield[a])
1		**2a**		**3a**	80
2		**2b**		**3b**	90
3		**2c**		**3c**	80
4		**2d**		**3d**	85
5		**2e**		**3e**	82
6		**2f**		**3f**	90
7		**2g**		**3g**	91
8		**2h**		**3h**	95
9		**2i**		**3i**	93

Table 1 (cont.)

Entry	Amine		Product		Yield[a])
10		**2j**		**3j**	90
11		**2k**		**3k**	89
12		**2l**		**3l**	77
13		**2m**		**3m**	75
14		**2n**		**3n**	70
15		**2o**		**3o**	35
16		**2p**		**3p**	61
17		**2q**		**3q**	59

[a]) Yields of isolated products based on the starting acryloylferrocene.

Spectral Characterization. The three newly synthesized compounds, **3l**–**3n**, described in this work (the rest of the compounds from *Table 1*, **3a**–**3k** and **3o**–**3q**, have been already reported in [33] including their spectral data) have been fully characterized by standard spectroscopic techniques (IR, and ^{1}H- and ^{13}C-NMR), as

well as elemental analyses. All spectral data were fully consistent with the proposed structures and with those reported in [33].

In the IR spectra of **3l**–**3n**, sharp, medium intensity absorptions of NH stretching vibrations are observed below 3400 cm^{-1}, indicating that all NH groups are involved in H-bonding interactions. The CO stretching vibration band of the 1′-ferrocene-carbonyl group appears in the range 1667–1677 cm^{-1}, suggesting the existence of inter- and/or intramolecular H-bonds to the CO functional group. The C=O absorptions of the Ac group show a similar trend and are all at higher frequencies when compared to the corresponding aminoacetophenones.

The ^{1}H- and ^{13}C-NMR spectra of compounds **3l**–**3n** display all signals expected for the proposed composition. With few exceptions (typically, the CH_2 C-atom signals having close values of their chemical shifts and overlapped signals), the H- and C-atom resonances could be assigned on the basis of chemical-shift theory, signal intensities and multiplicities, substituent effects, and by comparison with literature data [38] for the corresponding aminoacetophenones.

The ^{1}H-NMR data for the three newly synthesized compounds are typical of monosubstituted ferrocene (a characteristic intensity pattern of 2:2:5 for the cyclopentadienyl (Cp) H-atoms of ferrocene). Two slightly deshielded '*triplet*s' (or better *pseudotriplet*s) are observed for the Cp ring H-atoms at 4.51–4.53 and 4.77–4.80 ppm. The low-field *pseudotriplet* is assigned to the H-atoms at C(2) and C(5), whereas the high-field *pseudotriplet* is assigned to the ring H-atoms at C(3) and C(4). These are downfield of the *singlet*s assigned to the unsubstituted Cp ring at δ(H) 4.11–4.17, which is characteristic for ferrocenes with electron-withdrawing substituents (due to deshielding with the increased delocalization of electron density toward the C=O substituent [39]).

The involvement of the NH H-atom in **3l** in intramolecular H-bonding may be inferred from the chemical shift of this H-atom (9.01 ppm) in its ^{1}H-NMR spectrum, while, in the other two compounds, the NH is more probably involved in intermolecular H-bonding, and their signals are shifted upfield (δ(H) 4.43 and 4.81, for **3m** and **3n**, resp.). These slightly acidic H-atoms undergo a slow exchange reaction in $CDCl_3$ and the signal splits by coupling to the H-atoms of the adjacent CH_2 group (resulting in broad *triplet*s with a coupling constant of *ca.* 6 Hz). The slow exchange on the NMR time scale of these NH H-atoms seems to be a characteristic of these ferrocene containing compounds rather than of the Ph analogs (compounds obtained when the ferrocene nucleus is interchanged with a benzene ring), since the latter do not show this coupling and give broad *singlet*s for the NH H-atoms [33].

The off-resonance H-atom decoupled ^{13}C-NMR spectra of **3l**–**3n** exhibited the expected number of peaks in the aliphatic, aromatic, and CO regions. The CO C-atom signals appear at δ(C) 202.1–203.4 and 196.3–200.8 (for the Fc*C*O and Me*C*O group, resp.). The ^{13}C resonances of the $-CH_2CH_2-$ fragment in all three compounds were relatively non-sensitive to the position of the acyl substituent on neighboring phenylamino group and could be found in the following ranges: δ(C) 37.4–37.9 and 38.0–38.8. The same applies for the chemical shifts of the substituted Cp ring (δ(C) 69.2–69.3 (C(3′) and C(4′)) and 72.4–72.6 (C(2′) and C(5′))). The chemical equivalence of H–C(2′,5′) and H–C(3′,4′) atom pairs evidences a free and fast rotation around the C–C bond between the Cp rings and their substituents.

X-Ray Crystal Structure of **3c**, **3k**, *and* **3l**. The three 3-(arylamino)-1-ferrocenylpropan-1-ones, presented in *Fig. 1*, crystallize in different crystal systems: monoclinic (space group $C2/c$), triclinic ($P\bar{1}$), and orthorhombic ($P2_12_12_1$) for **3c**, **3k**, and **3l**, respectively. The Cp rings within their ferrocene units are nearly parallel (the maximum dihedral angle of 1.6(2)° is found in **3c**) and exhibit conformations which are close to the eclipsed ones. The torsion angle C1–Cg1–Cg2–C6, relating the eclipsed C-atoms through the corresponding Cp centroids, is equal to 13.1(5), 6.4(5), and 1.2(5)° for **3c**, **3k**, and **3l**, respectively. In each of the structures, the Fe ··· Cg1 distance (Cg1 is centroid

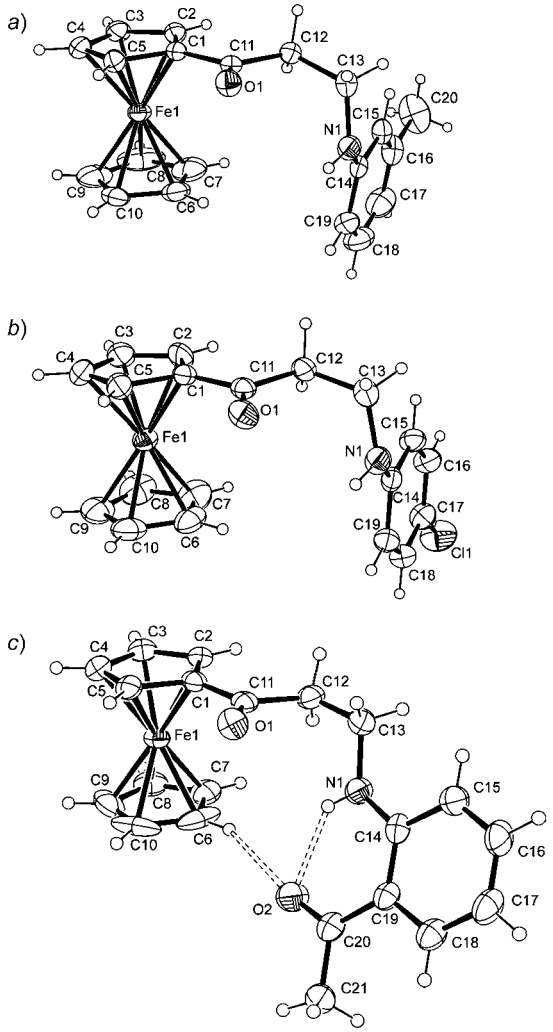


Fig. 1. *Molecular structures of* **3c** (*a*), **3k** (*b*), *and* **3l** (*c*) *with the atom numbering scheme.* Displacement ellipsoids are drawn at the 40% probability level. Dashed lines in **3l** indicate N1–H ··· O2 and C6–H ··· O2 intramolecular interactions

of the substituted Cp ring) is, in average, by 0.01 Å shorter than the distance toward the unsubstituted ring (Fe ··· Cg2). This is in accordance with the previously observed trend for similar ferrocene derivatives [33][40].

As defined by the O1–C11–C1–C5 torsion angle (– 5.8(4), 1.9(5), and – 5.3(4)° in **3c**, **3k**, and **3l**, resp.), the corresponding C1=O1 carbonyl fragment is almost co-planar with the substituted Cp ring. A similar co-planarity between the aromatic ring and the closely attached atoms can also be observed within the arylamino moiety. The torsion angle N1–C14–C15–C16 is equal to 176.2(3), 174.9(3), and 179.9(3)° in **3c**, **3k**, and **3l**, respectively. A number of selected structural parameters (*Table 2*) show values closely comparable with those recently reported for crystal structures of compounds **3j**, **3p**, and **3o** [33]. It is interesting to notice that, despite the allowed free rotation around the constituting single bonds, and the variation in type and position of the arylamino substituents, the C1–C11–C12–C13–N1 fragment within all six crystal structures displays a rather similar conformation. This is indicated by the similarity of the torsion angles C1–C11–C12–C13 and C11–C12–C13–N1, whose values of – 165.6(2)/76.2(3), – 172.5(3)/76.4(4), and – 178.6(2)/71.1(3)° in **3c**, **3k**, and **3l**, respectively, are consistent with those reported for **3j**, **3p**, and **3o** [33].

Table 2. *Selected Bond Lengths and Angles of* **3c**, **3k**, *and* **3l**

	3c	**3k**	**3l**
Bond lengths [Å]			
O1–C11	1.222(3)	1.218(4)	1.227(3)
N1–C14	1.389(4)	1.373(4)	1.355(4)
N1–C13	1.439(4)	1.445(5)	1.448(4)
C1–C11	1.477(3)	1.468(4)	1.469(4)
C11–C12	1.506(3)	1.509(4)	1.510(4)
C12–C13	1.524(3)	1.516(5)	1.505(4)
C16–C20	1.510(5)	–	–
C17–Cl1	–	1.738(4)	–
C15–C20	–	–	1.471(4)
C20–O2	–	–	1.223(3)
Bond angles [°]			
O1–C11–C1	120.9(2)	121.8(3)	120.4(3)
O1–C11–C12	121.1(2)	121.6(3)	121.4(3)
C1–C11–C12	117.9(2)	116.6(3)	118.2(3)
C11–C12–C13	112.9(2)	112.8(3)	113.5(3)
N1–C13–C12	113.6(2)	114.4(3)	111.3(2)
C14–N1–C13	122.2(2)	121.5(3)	124.7(3)

Among the presently discussed compounds, the most significant difference can be detected by a comparison of the C12–C13–N1–C14 torsion angle, which indicates a different orientation of the arylamino moiety in **3l** (– 176.4(3)°) with respect to its orientation in **3c** and **3k** (69.4(4) and 70.6 (4)°). The corresponding dihedral angle between the Fe1/C1/Cg1 plane (dividing the substituted Cp ring) and the best plane of the Ph ring has the values 85.1(5), 87.4(5), and 32.2(5)° in **3c**, **3k**, and **3l**, respectively. In comparison with the previously described structures, one can observe that the

structural features of **3c** and **3k** closely resemble those of **3j** and **3p**. Accordingly, it can be suggested that the conformation observed for these four compounds is favorable in the cases where the arylamino moiety has the substituent at C(3‴) or C(4‴). The conformation of **3l** is, on the other hand, similar to that of **3o** and quite different from those of **3c**, **3k**, **3j**, and **3p**. One possible explanation for the different orientations of the arylamino moieties in **3l** and **3o** structures (comparing to **3c**, **3k**, **3j**, and **3p**) could be found in their ability to form an intramolecular H-bond between the substituent at C(2‴) and the rest of the molecule (see *Fig. 1*, *c*).

Regardless of the type of substituents present in the arylamino moiety, conformationally similar derivatives possess a similar way of the intermolecular arrangement. As previously described for **3j** and **3p**, the crystal packing of **3c** and **3k** is also characterized by the formation of discrete H-bonding dimers where centrosymmetrically related molecules associate through pairs of strong N–H···O interactions (*Table 3*, *Fig. S1*[1])). This is not the case with **3l** where the corresponding C=O O-atom is engaged in two weak C–H···O interactions which lead to a more extended, chain-like molecular arrangement (*Table 3*). The crystal packing of **3l** is, however, comparable to that of **3o**, which, although containing additional acceptor sites (two O-atoms of the NO_2 substituent), involves exactly the same sets of atoms in intermolecular H-bonding (*Fig. S2*[1])). The arylamino N–H donor of **3l** (*Fig. 1*,*c*), as well as that of **3o**, is engaged only in the intramolecular H-bonding to the corresponding Ac and NO_2 substituents, respectively.

Table 3. *Geometrical Parameters of H-Bonds, and Selected C–H···O Interactions of* **3c**, **3k**, *and* **3l**. The C–H···O interactions are given, if H···O distance is shorter than 2.7 Å, and C–H···O angle is larger than 100°.

D–H···A	*d*(D–H) [Å]	*d*(D···A) [Å]	*d*(H···A) [Å]	∠(D–H···A) [°]
3c[a])				
N1–H1N···O1[i]	0.77(3)	3.036(3)	2.27(3)	172(3)
C4–H4···N1[ii]	0.93	3.483(4)	2.62	156
3k[b])				
N1–H1N···O1[i]	0.82(4)	3.054(4)	2.26(4)	162(3)
3l[c])				
N1–H1N···O2	0.75(3)	2.669(4)	2.07(3)	137(3)
C6–H6···O2	0.93	3.487 (5)	2.60	159
C2–H2···O1[i]	0.93	3.326 (3)	2.54	143
C12–H2b···O1[ii]	0.97	3.235(4)	2.57	126

[a]) Symmetry codes: [i] $-x+1/2, -y+1/2, -z$; [ii] $x+1/2, y+1/2, z$. [b]) Symmetry codes: [i] $-x+2, -y+1, -z+2$. [c]) Symmetry codes: [i] $x-1, y, z$; [ii] $x-1/2, -y+1/2, -z+2$.

Biology. Several ferrocenyl compounds display interesting cytotoxic, antitumor, antimalarial, antifungal, antibacterial, and DNA-cleaving activities [16]. In our previous work, we have demostrated that 3-(arylamino)-1-ferrocenylpropan-1-ones possess a certain degree of antibacterial potential, especially against an important human pathogen *S. aureus* [33]. This time we have retested compounds **3a**–**3k** and **3o**–

[1]) *Supplementary Material* may be obtained upon request from the authors.

3q against additional three *Gram*-positive (*Listeria monocytogenes*, *Micrococcus flavus*, and *Sarcina lutea*) and two *Gram*-negative (*Klebsiella pneumoniae* and *Shigella sonnei*) bacteria, while the remaining, newly synthesized compounds **3l**–**3n** were evaluated against the full panel of eleven bacterial strains. The results of the *MIC* determination as well as of the minimal bactericidal activity (*MBC*) are presented in *Tables 4* and *5* as the averages of five repetitions. The compounds have again been shown to possess inhibitory action on the growth of all bacteria with *MIC* values in the range of 0.025 and 25.00 mg/ml. Almost as a rule, *MBC* values were several folds higher than those of *MIC*, suggesting a better inhibitory than bactericidal activity. The only exception was the case of *P. aeruginosa* where the *MIC* against all tested strains was a cidal one. The most sensitive bacterium turned out to be a *Gram*-positive *M. flavus* with *MIC* value lower than 25 μg/ml and *MBC* being 25 μg/ml, but even this best result was one hundred times lower compared to the effect caused by tetracycline on the same bacterium. Once more, a *Gram*-positive strain, *Bacillus cereus*, was the most resistant one among the assayed, with the highest *MIC* values (66.5 μmol/ml) for **3l**–**3n**. Although having the least significant action on the growth of *B. cereus*, these three compounds were generally among the most active ones against all other bacteria, including the pathogenic *K. pneumoniae* (*MIC* 2.08–8.32 μmol/ml), *L. monocytogenes* (*MIC* 8.32–16.6 μmol/ml), and *S. soneii* (*MIC* 4.16–8.32 μmol/ml).

Table 4. *Minimal Inhibitory* (*MIC*) *and Minimal Bactericidal Concentrations* (*MBC*) *of the Synthesized Compounds* **3a**–**3k** *and* **3o**–**3q**

Compound	*MIC*/*MBC* [μmol/ml]				
	Gram (−) bacteria		*Gram* (+) bacteria		
	Klebsiella pneumoniae	*Shigella sonnei*	*Listeria monocytogenes*	*Micrococcus flavus*	*Sarcina lutea*
3a	9.36/75.0	18.8/37.5	9.36/37.5	< 0.0750/0.0750	0.150/0.150
3b	8.99/36.0	18.0/72.0	8.99/36.0	< 0.0720/0.0720	0.144/0.144
3c	2.25/18.0	18.0/72.0	2.25/4.50	< 0.0720/0.0720	0.144/0.144
3d	8.99/36.0	4.50/36.0	1.12/4.50	< 0.0720/0.0720	0.144/0.144
3e	4.16/66.6	16.6/66.6	4.16/66.6	< 0.0666/0.0666	0.133/0.133
3f	8.88/35.5	2.22/35.5	8.88/35.5	< 0.0712/0.0712	0.142/0.142
3g	17.8/35.5	17.8/35.5	17.8/35.5	< 0.0712/0.0712	0.142/0.142
3h	4.44/35.5	17.8/35.5	4.44/35.5	< 0.0712/0.0712	0.142/0.142
3i	2.12/33.9	17.0/33.9	2.12/17.0	< 0.0680/0.0680	0.136/0.136
3j	8.49/136	8.49/67.9	4.24/17.0	< 0.0680/0.0680	0.136/0.136
3k	8.49/33.9	2.12/33.9	2.12/33.9	< 0.0680/0.0680	0.136/0.136
3o	2.06/66.0	16.5/66.0	2.06/4.12	< 0.0661/0.0661	0.132/0.132
3p	4.12/33.0	8.25/33.0	4.12/33.0	< 0.0661/0.0661	0.0661/0.132
3q	0.529/16.5	16.5/66.0	0.529/8.25	< 0.0661/0.0661	0.132/0.132
Tetracycline[a])	2.25/2.25	2.25/2.25	36.0/36.0	0.563/0.563	55.4/55.4

[a]) *MIC*/*MBC* values are given in nmol/ml.

To better interpret the results obtained in antibacterial assays, we have statistically compared the obtained *MIC* values of compounds **3a**–**3q** against all eleven bacteria (results from the current work and those obtained in our previous study [33]). The

Table 5. *Minimal Inhibitory* (*MIC*) *and Minimal Bactericidal Concentrations* (*MBC*) *of the Synthesized Compounds* **3l**–**3n**

Bacterial strains	*MIC*/*MBC* [μmol/ml]			
	3l	**3m**	**3n**	Tetracycine[a])
Gram (−) bacteria				
Escherichia coli	0.533/0.533	0.533/0.533	0.267/0.533	3.51/3.51
Klebsiella pneumoniae	2.08/16.6	2.08/8.32	8.32/16.6	2.25/2.25
Pseudomonas aeruginosa	0.533/0.533	1.07/1.07	0.533/0.533	7.02/7.02
Salmonella enterica	1.07/1.07	2.08/2.08	0.267/0.533	7.02/7.02
Shigella sonnei	4.16/16.6	4.16/8.32	8.32/8.32	2.25/2.25
Gram (+) bacteria				
Bacillus cereus	66.5/66.5	66.5/66.5	66.5/66.5	3.51/3.51
Clostridium perfringens	16.6/33.3	16.6/33.3	66.5/66.5	3.51/3.51
Listeria monocytogenes	8.32/16.6	16.6/16.6	8.32/8.32	36.0/36.0
Micrococcus flavus	< 0.0666/0.0666	< 0.0666/0.0666	< 0.0666/0.0666	0.563/0.563
Sarcina lutea	0.267/0.533	0.267/0.533	0.0666/0.0666	55.4/55.4
Staphylococcus aureus	0.267/0.533	0.267/0.533	1.07/1.07	0.202/0.202

[a]) *MIC*/*MBC* values are given in nmol/ml.

results of agglomerative hierarchical clustering (*AHC*) analyses are presented in *Fig. 2*. The dendrogram indicates the existence of six groups of compounds. Compounds **3l**–**3n** were separated from the rest of the compounds, making the two highly related clades C5 and C6. The presence of an additional CO (AcO) group seems to have differentiated them from the other compounds, and resulted in the greatest decrease in activity against *B. cereus*, while retaining a significant degree of activity towards other bacteria as mentioned above (this is clearly observable from the centroid characteristics of these clades). The rest of the groups do not have such a clear-cut subdivision of the compounds. A number of subclades consist of compounds having substituents of similar electronic character, *e.g.*, electron-withdrawing ones in **3h**, **3q**, **3i**, and **3o** of class C3 second, and that are regiochemically the same (having substituents in the same position on the benzene ring), *e.g.*, **3i** and **3o**, C3 class; **3j** and **3p**, class C4; and **3d** and **3k**, the same class. This analysis also showed that clade C1 (a single compound, **3b**, making up this group) is the most related to, but still statistically different, from, clade C2 (again only one compound in this class, *i.e.* **3g**). The two compounds appear to be differentiated by the activity against *Salmonella enterica*, the latter being less active. These observations confirm the notion that, in general, compounds having an electron-acceptor functionality appeared not to be more or less effective in inhibiting the growth of all bacteria than compounds possessing an electron-donating substituent or no substituent at all. Although it is reasonable to expect that the *ortho*-regioisomers could have a steric impediment towards an interaction with the receptor of the test organisms, and this is substantiated by the corresponding mentioned grouping of these isomers, the extent of the activity does not seem to hold out on this hypothesis. The activity seems not only to be compound but also bacterial species-specific. It seems worthwhile to note that the activity of the compounds does not follow a trend of decreasing hydrophilic character (estimated [41] log $P_{o/w}$ values for the Ph analogs of compounds were used for

this purpose), hence, indicating that the well-known fact that the solubility of antimicrobials in the bilipid cell membranes may play a significant role in the activity, here has little if any importance. Thus, further work is necessary to establish the true mechanism of action of these ferrocenyl derivatives. Overall, these results are highly promising and suggest that a more detailed study of the antimicrobial (including the antifungal one) activity of this class of compounds could identify further derivatives with improved antibacterial properties.

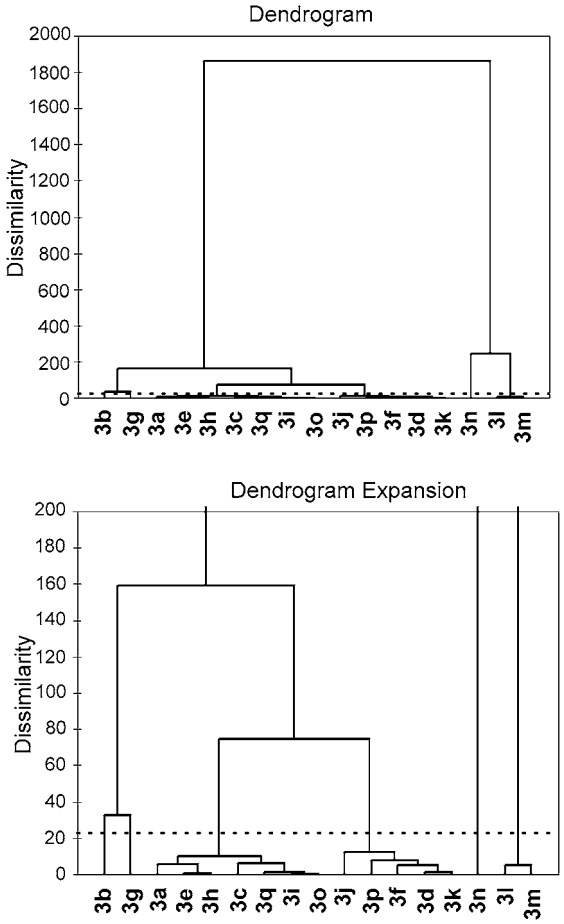


Fig. 2. *Dendrogram* (AHC analysis) *and its expansion* (left) *representing antibacterial activity* (the *MIC* values of compounds **3a**–**3q** against eleven bacterial strains) *dissimilarity relationships of the seventeen compounds* **3a**–**3q** *obtained by* Euclidean *distance dissimilarity, using aggregation criterion*-Ward*'s method.* Six groups of the compounds were found: C1–C6 (from left to right).

Conclusions. – We described, herein, a new, easily performable procedure for the conjugate addition of arylamines to acryloylferrocene to yield the corresponding *N*-aryl-3-amino-1-ferrocenylpropan-1-ones in good to excellent yields. This synthesis was

performed with montmorillonite K-10 as the catalyst, supported by ultrasonic irradiation. We unambiguously showed that both the catalyst and the irradiation play an important role in this synthesis. The procedure requires short reaction times, employs an environmentally friendly and non-expensive catalyst, as well as an ultrasonic cleaner, a cheap and simple apparatus, which almost every laboratory possesses. Among 17 compounds synthesized in this way, three were also characterized by single-crystal X-ray analysis. The investigation of their crystal structures and the comparison with recently reported ones suggest two favored conformations for 3-(arylamino)-1-ferrocenylpropan-1-ones. One of the factors influencing the conformation could be the position of the substituent in the arylamino moiety. The conformationally similar derivatives show considerable similarity in their manner of crystal packing. The results of antibacterial assays are highly promising and urge for a more mechanistic-oriented study of antimicrobial (both antibacterial and antifungal) activities of such compounds that could possibly identify further derivatives with improved activity. The observed antibacterial activity seems not only to be compound-(position of the substituent on the ring and its electron-donating/accepting properties) but also bacterial species-specific.

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Experimental Part

General Remarks. All chemicals were commercially available and used as received, except that the solvents were purified by distillation. Column chromatography (CC): silica gel *60* (230–400 mesh ASTM; *Merck*). TLC: silica gel *60* on Al plates, layer thickness 0.2 mm (*Merck*). M.p. (uncorrected): *Mel-Temp* cap. melting-point apparatus, model *1001*. IR Spectra: *Perkin-Elmer FTIR 31725-X* spectrophotometer. ^{1}H- and ^{13}C-NMR spectra: in $CDCl_3$, *Varian Gemini* (200 MHz) spectrometer; chemical shifts in δ(H) [ppm], rel. to the residual solvent H-atoms or $^{13}CDCl_3$ as the internal standards ($CDCl_3$: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C). Elemental analysis of C, H, and N: *Carlo Erba 1106* microanalyser; results in agreement with the calculated values. The reactions (ultrasonic-assisted syntheses) were performed by placing the probe with the reactants and the catalyst in an ultrasonic cleaner. An *Elmasonic S30* (*Elma*, Germany) ultrasound bath was used at a frequency of 37 kHz, with an effective ultrasonic power of 30 W and a peak of 240 W.

General Procedure for the Synthesis of the Mannich *Bases* **3a**–**3q**. A test tube containing a well-homogenized mixture of 240 mg (1 mmol) of acryloylferocene, 2 mmol of the corresponding arylamine, and 100 mg of montmorillonite *K-10* was placed in the ultrasonic cleaner and irradiated for 1 h. Then, CH_2Cl_2 (10 ml) was added to the mixture, and the contents were filtered off. The solid residue was washed with CH_2Cl_2, and the collected org. solns. were dried (Na_2SO_4) overnight. After the evaporation of the solvent, the crude mixture was fractioned by flash chromatography on a SiO_2 column. The amines eluted with toluene, whereas the *Mannich* bases **3a**–**3q** were washed from the column by a mixture of hexane and AcOEt 9:1 (*v*/*v*). In all cases, the complete excess of the amines was recovered. The spectral data of compounds **3a**–**3k** and **3o**–**3q** can be found in [33], whereas the data of the newly synthesized ones **3l**–**3n** are given below.

3-[(2-Acetylphenyl)amino]-1-ferrocenylpropan-1-one (**3l**). M.p. 119°. IR (KBr): 3322, 1667, 1630, 1567, 1515, 1503, 1458, 1250, 1228, 1205, 1168, 1146, 1107, 949, 752, 609. ^{1}H-NMR (200 MHz, $CDCl_3$): 9.01 (*t*, *J* = 5.8, NH); 7.75 (*dd*, *J* = 8.1, 1.6, H–C(3‴)); 7.40 (*ddd*, *J* = 8.6, 7.1, 1.6, H–C(5‴)); 6.83 (br. *d*, *J* = 8.6, H–C(6‴)); 6.61 (*ddd*, *J* = 8.1, 7.1, 1.1, H–C(4‴)); 4.80 (*pseudo-t*, H–C(2′), H–C(5′)); 4.51 (*pseudo-t*, H–C(3′), H–C(4′)); 4.17 (*s*, H–C(1″), H–C(2″), H–C(3″), H–C(4″), H–C(5″)); 3.68 (*dt*, *J* = 6.9, 5.8, CH_2(3)); 3.08 (br. *t*, *J* = 7.0, CH_2(2)); 2.57 (*s*, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 202.1 (C(1)); 200.8

(*C*OMe); 150.6 (C(1‴)); 135.1, 132.8 (C(3‴), C(5‴)); 117.8 (C(2‴)); 114.2, 111.5 (C(4‴), C(6‴)); 78.8 (C(1′)); 72.4 (C(2′), C(5′)); 69.8 (C(1″), C(2″), C(3″), C(4″), C(5″)); 69.3 (C(3′), C(4′)); 38.8, 37.4 (C(2), C(3)); 27.9 (Me). Anal. calc. for $C_{21}H_{21}FeNO_2$ (375.2419): C 67.22, H 5.64, N 3.73; found: C 67.30, H 5.67, N 3.71.

3-[(3-Acetylphenyl)amino]-1-ferrocenylpropan-1-one (**3m**). M.p. 106°. IR (KBr): 3363, 1677, 1652, 1600, 1519, 1473, 1453, 1283, 1263, 1106, 826, 782, 688. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.30–7.22 (*m*, overlapping peaks, H–C(2‴), H–C(4‴), H–C(5‴)); 6.84 (*ddd*, $J = 8.2, 2.6, 1.3$, H–C(6‴)); 4.77 (*pseudo-t*, $J = 2.0$, H–C(2′), H–C(5′)); 4.51 (*pseudo-t*, $J = 2.0$, H–C(3′), H–C(4′)); 4.43 (br. *t*, $J = 5.9$, NH); 4.11 (*s*, H–C(1″), H–C(2″), H–C(3″), H–C(4″), H–C(5″)); 3.62 (*pseudo-q*, $J = 5.9$, CH_2(3)); 3.04 (*t*, $J = 5.9$, CH_2(2)); 2.57 (*s*, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 203.4 (C(1)); 198.7 (*C*OMe); 147.9 (C(1‴)); 138.2 (C(3‴)); 129.4 (C(5‴)); 118.2, 118.0 (C(4‴),C(6‴)); 111.1 (C(2‴)); 78.7 (C(1′)); 72.5 (C(2′), C(5′)); 69.8 (C(1″), C(2″), C(3″), C(4″), C(5″)); 69.2 (C(3′), C(4′)); 38.6, 37.9 (C(2), C(3)); 26.7 (Me). Anal. calc. for $C_{21}H_{21}FeNO_2$ (375.2419): C 67.22, H 5.64, N 3.73; found: C 67.23, H 5.60, N 3.72.

3-[(4-Acetylphenyl)amino]-1-ferrocenylpropan-1-one (**3n**): M.p. 182°. IR (KBr): 3330, 1665, 1647, 1600, 1584, 1456, 1361, 1283, 1263, 1180, 1042, 959, 825, 584. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.84 (*AA′XX′*, $J_o = 8.9$, $J_m = 2.4$, H–C(3‴), H–C(5‴)); 6.61 (*AA′XX′*, $J_o = 8.9$, $J_m = 2.4$, H–C(2‴), H–C(6‴)); 4.81 (br. *t*, $J = 5.9$, NH); 4.78 (*pseudo-t*, $J = 2.0$, H–C(2′), H–C(5′)); 4.53 (*pseudo-t*, $J = 2.0$, H–C(3′), H–C(4′)); 4.11 (*s*, H–C(1″), H–C(2″), H–C(3″), H–C(4″), H–C(5″)); 3.66 (*pseudo-q*, $J = 5.9$, CH_2(3)); 3.04 (*t*, $J = 5.9$, CH_2(2)); 2.49 (*s*, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 203.0 (C(1)); 196.3 (*C*OMe); 151.6 (C(1‴)); 130.9 (C(3‴), C(5‴)); 126.8 (C(4‴)); 111.4 (C(2‴), C(6‴)); 78.6 (C(1′)); 72.6 (C(2′), C(5′)); 69.8 (C(1″), C(2″), C(3″), C(4″), C(5″)); 69.2 (C(3′), C(4′)); 38.0, 37.9 (C(2), C(3)); 26.0 (Me). Anal. calc. for $C_{21}H_{21}FeNO_2$ (375.2419): C 67.22, H 5.64, N 3.73; found: C 67.18, H 5.59, N 3.70.

X-Ray Crystallography. Single crystals suitable for X-ray-analysis of **3c**, **3k**, and **3l** were obtained by a slow evaporation from a mixture of CH_2Cl_2 and hexane. The diffraction data for **3k** and **3l** were collected on *Oxford Diffraction Xcalibur Sapphire3 Gemini*, while those for **3c** were collected on *Enraf Nonius CAD4* diffractometer, both equipped with MoK_α radiation ($\lambda = 0.71073$ Å). In the case of **3k** and **3l**, data were processed with CrysAlis software [42] with multi-scan absorption corrections applied using SCALE3 ABSPACK [42]. The data for **3c** were processed with *XCAD4-CAD4* data reduction program [43]. All three crystal structures were solved with SHELXS [44] and refined using SHELXL [44]. The refinement of the crystal structure **3k** revealed the presence of a disordered solvent molecule which could not be reliably modeled. The examination of the structure with SQUEEZE/SOLV procedures included in PLATON [45] indicated the presence of one solvent-accessible void per unit cell with the estimated volume of 205 Å^3. The volume of the cavity and the shape of the residual electron density suggest the incorporation of one toluene molecule. This solvent was used during the synthetic procedure for the chromatographic elution of the amine. The contribution of the solvent to the scattering factors was suppressed using the SQUEEZE procedure. A new data set, free of solvent contribution, was then used in the final refinement.

In all three structures, the H1-atom attached to N1 was located by difference *Fourier* synthesis and refined isotropically. All other H-atoms were placed at geometrically calculated positions with the C–H distances fixed to 0.93 from C(sp^2); 0.96 and 0.97 Å from Me and CH_2 C(sp^3), resp. The corresponding isotropic displacement parameters of the H-atoms were equal to 1.2 U_{eq} and 1.5 U_{eq} of the parent C(sp^2) and C(sp^3), resp.

The crystallographic data are compiled in *Table 6*. Figures were produced using ORTEP-3 [46] and MERCURY, Version 2.4 [47]. The software used for the preparation of the materials for publication: WinGX [48], PARST [49], PLATON [45].

Crystallographic data for **3c**, **3k**, and **3l** have been deposited at the *Cambridge Crystallographic Data Centre* (*CCDC*) with the deposition Nos. CCDC-846998, 846999, and 847000, resp. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Biology. Test Microorganisms. The synthesized 3-(arylamino)-1-ferrocenylpropan-1-ones, **3a**–**3q**, were assayed for antibacterial activity against a panel of strains belonging to the American Type Culture Collection (ATCC). Compounds **3a**–**3q** were tested against three *Gram*-positive (*Listeria monocyto-*

Table 6. *Crystallographic Data for* **3c**, **3k**, *and* **3l**

	3c	**3k**	**3l**
Empirical formula	$C_{20}H_{21}FeNO$	$C_{22.5}H_{22}ClFeNO$	$C_{21}H_{21}FeNO_2$
Formula weight	347.23	413.71	375.24
Color	Dark-orange	Dark-orange	Dark-orange
Crystal size [mm^3]	$0.30 \times 0.26 \times 0.22$	$0.22 \times 0.19 \times 0.12$	$0.23 \times 0.20 \times 0.18$
Temp. [K]	293(2)	293(2)	293(2)
Wavelength [Å]	0.7107	0.71073	0.71073
Crystal system	Monoclinic	Triclinic	Orthorhombic
Space group	*C*2/*c*	$P\bar{1}$	$P2_12_12_1$
Unit cell parameters			
a [Å]	18.365(4)	7.3916(4)	5.8045(2)
b [Å]	7.3680(10)	10.2424(5)	14.7344(5)
c [Å]	25.355(2)	13.8640(7)	20.2616(9)
α [°]	90	95.634(4)	90
β [°]	97.908(13)	102.539(4)	90
γ [°]	90	99.872(4)	90
V [Å^3]	3398.2(9)	999.4(3)	1732.9(1)
Z	8	2	4
D_{calc} [Mg/m^3]	1.357	1.375	1.438
μ [mm^{-1}]	0.891	0.899	0.884
θ Range for data collection [°]	1.62 to 25.97	3.04 to 29.08	3.32 to 29.03
Reflections collected	3320	7398	5655
Independent reflections, R_{int}	3320	4497, 0.0235	3447, 0.0284
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3320/0/212	4497/0/212	3447/0/231
Flack parameter [50]			−0.01(2)
Goodness-of-fit on F^2	0.995	1.028	1.030
R_1/wR_2 indices [$I > 2\sigma(I)$]	0.0421/0.1076	0.0613/0.1621	0.0429/0.0735
R_1/wR_2 indices (all data)	0.0736/0.1161	0.0829/0.1759	0.0563/0.0792
Largest diff. peak and hole [e A^{-3}]	0.358/−0.389	0.609/−0.254	0.265/−0.272

genes ATCC 7644, *Micrococcus flavus* ATCC 40240, and *Sarcina lutea* ATCC 9341) and two *Gram*-negative bacteria (*Klebsiella pneumoniae* ATCC 10031 and *Shigella sonnei* ATCC 25931). The three newly synthesized compounds, **3l**–**3n**, were additionally tested against three *Gram*-positive (*Bacillus cereus* ATCC 10876, *Clostridium perfringens* ATCC 19404, and *Staphylococcus aureus* ATCC 6538) and three *Gram*-negative bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Salmonella enterica* ATCC 13076). All of these bacterial strains were maintained on nutrient agar at 37°.

Screening of Antibacterial Activity. Antibacterial activity was evaluated using a broth microdilution method according to NCCLS [51]. Minimum inhibitory concentrations (*MIC*s) and minimal bactericidal concentrations (*MBC*s) were determined as described in [52]. Stock solns. of the compounds **3a**–**3q** were prepared in 10% (*v*/*v*) aq. DMSO in the concentration range of 0.025–50.00 mg/ml (the diluting factor 2). Tetracycline served as a positive control, while the solvent (10% DMSO(aq.)) was used as the negative one.

Statistical Analyses. Agglomerative hierarchical clustering (*AHC*) was performed using the *Excel* program plug-in XLSTAT (version 2011.4.04). The method was applied utilizing the *MIC* values of compounds **3a**–**3q** from this work and those reported in [33] against eleven bacterial strains as original variables without any recalculation. *AHC* was performed using *Pearson* dissimilarity (as aggregation

criteria simple linkage, unweighted pair-group average, and complete linkage were used) and *Euclidean* distance (aggregation criterion: weighted pair-group average, unweighted pair-group average and *Ward*'s method). The definition of the groups was based on *Pearson* correlation, using complete linkage and unweighted pair-group average method.

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