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FULL PAPER

Acid-catalyzed intramolecular imination / nucleophilic trapping of 4-aminobutanal derivatives: one-pot access to 2-(pyrazolyl)pyrrolidines.

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Abstract: A first successful synthesis of 2-(pyrazolyl)pyrrolidines is reported starting from readily available reagents. A wide variety of *N*-substituted 2-(pyrazolyl)pyrrolidines are obtained with up to 96% yield. The influence of obtained compounds on the biofilm formation by *V. aquamarinus* DSM 26054 and *A. calcoaceticus* VKPM B-10353 have been studied. Some of the tested compounds were found to suppress the bacterial biofilms growth at nanomolar concentrations and thus are promising candidates for further studies.

Introduction

Pyrrolidine ring is an important structural part of many natural alkaloids[1–4] and one of the most frequently occurring heterocyclic scaffolds in approved drugs.[5] In recent years, the number of 2-diazole substituted pyrrolidine derivatives patented as drugs increased sharply, indicating growing interest in the practical application of such compounds. Examples are antiviral drugs Velpatasvir[6] and Daclatasvir[7] used in the treatment of hepatitis C infection, anti-cancer drugs Acalabrutinib[8] (approved by FDA in 2017) (Figure 1).

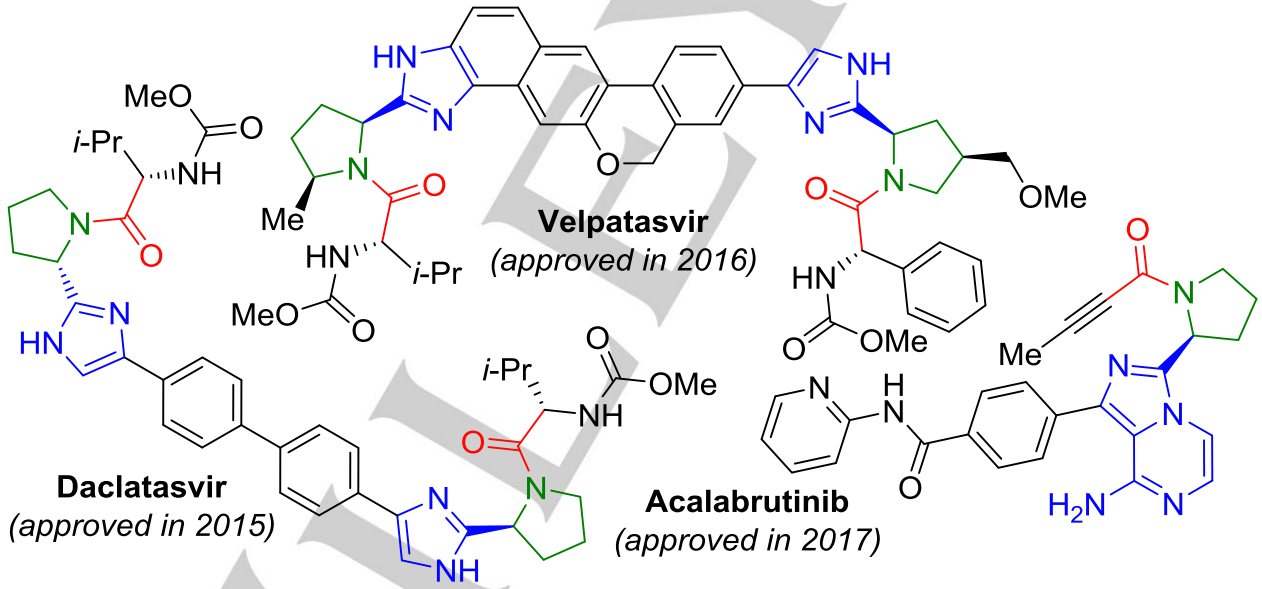

Figure 1. Approved drugs containing 2-(diazolyl)pyrrolidine moiety.

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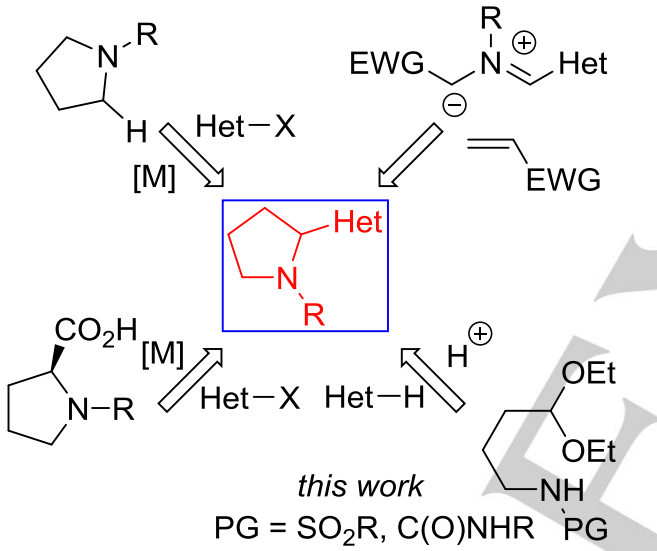
However, despite the increasing number of research aimed at obtaining and study of 2-(hetaryl)pyrrolidines, synthesis of these compounds meets certain difficulties. Approaches to these compounds can be divided into two main groups (Scheme 1). The first one includes the modification of an existing pyrrolidine fragment. Various cross-coupling reactions of heteroaromatics with appropriately substituted pyrrolidine derivatives,[9–14] including oxidative[15–17] and photooxidative ones,[18–21] are the most often

used within this pathway. Synthesis of enantiomerically pure 2-(hetaryl)pyrrolidines in several cases has been also accomplished by decarboxylative heteroarylation of proline derivatives.[22–28]

The second approach to the 2-(hetaryl)pyrrolidines is based on the formation of pyrrolidine ring from acyclic precursors. Within this approach, the intermolecular [3+2] dipolar cycloaddition of activated alkenes to azomethine ylides plays a significant role.[29–33] The activation of alkene double bond is achieved by introducing an electron-withdrawing substituent – a carboxyl, carbonyl, or nitro group, in fewer cases – a cyano or trifluoromethyl group.[34] As a rule, these reactions proceed with a high degree of stereoselectivity, which is achieved by employing complex chiral metal catalysts. As a typical example, the 1,3-dipolar cycloaddition of glycine imines to (*E*)-3-phenyl-1-(1H-pyrazol-1-yl)prop-2-en-1-one in the presence of a chiral Ag(I) complex[35] can be mentioned.



Scheme 1. Synthesis strategies to 2-(hetaryl)pyrrolidines.

Essential drawbacks of above mentioned approaches are the need in expensive metal catalysts and/or harsh reaction conditions, as well as the need of preliminary synthesis of starting compounds with appropriate functional groups and desired hetaryl fragment. Hence, methods employing non-expensive, readily available reagents and catalysts and allowing simultaneous pyrrolidine ring closure and C-$C_{hetaryl}$ bond formation are of a special interest.

Earlier, we have developed the metal-free approach to the 2-arylsubstitued pyrrolidine derivatives based on the acid-catalyzed intramolecular imination of 4,4-diethoxybutyl-1-amine derivatives leading to the formation of pyrrolinium cation. Further Mannich-type reaction of this cyclic iminium ion with various electron-rich aromatic nucleophiles allowed us to obtain a range of 2-arylpyrrolidine derivatives.[36–43]

We anticipated that the usage of heterocyclic nucleophiles instead of aromatics in these reactions should lead to the pyrrolidine derivatives bearing heterocyclic moiety at the 2nd position of pyrrolidine ring.

Pyrazolones were chosen as substrates for this reaction due to their significant pharmacological activities[44,45] as well as many possibilities of modification and manipulation for obtaining new valuable compounds.[46,47] Notably, although many 2-(hetaryl) substituted pyrrolidines have been described, no pyrrolidine derivatives possessing pyrazolone moiety are known until now.

Thus, herein we report the first succcessful one-pot synthesis of 2-pyrazolyl substituted pyrrolidines via acid-catalyzed intramolecular imination / nucleophilic trapping of 4,4-diethoxybutyl-1-amine derivatives with various pyrazolones. Either *C*- or *N*-alkylation of the pyrazolone derivative may occur depending on its nature. The proposed approach benefits from mild reaction conditions, simple work-up procedure and usage of readily available starting materials and catalysts.

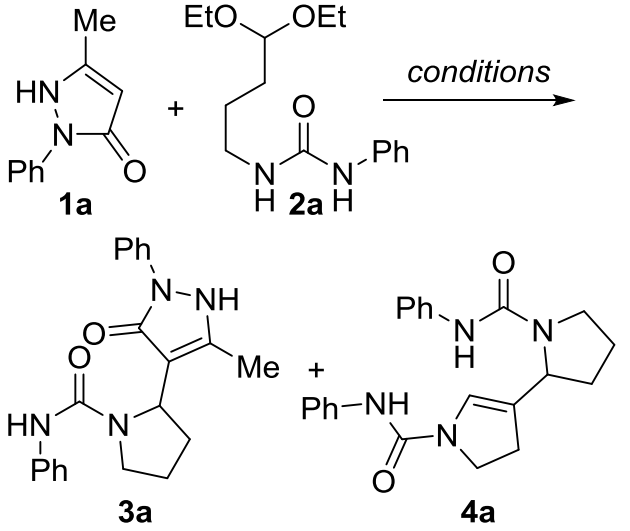
Results and Discussion

We initiated our studies with the screening of the reaction conditions for the interaction of 3-methyl-1-phenyl-pyrazol-5-one **1a** with 1-(4,4-diethoxybutyl)-3-phenylurea **2a**. The results are summarized in Table 1. First, we have tried conditions previously found[36] to be optimal for the reaction of urea **2a** with phenols. However, the reaction of pyrazol-5-one **1a** with urea **2a** in chloroform in the presence of 1 equivalent of trifluoroacetic acid led to the bispyrrole derivative **4** as the only product (Table 1, entry 1). The formation of this compound may be explained by the intramolecular imination of the urea **2a** and subsequent dimerization of dihydropyrrole derivative thus formed, as described by us previously.[48] The same result was obtained when the trifluororacetic acid was used as the solvent (Table 1, entry 5). Carrying out the reaction in ethanol and water in the presence of excess of hydrochloric acid or one equivalent of trifluoroacetic acid allowed us to obtain the desired 2-pyrazolylprrolidine **3a**, albeit in low yield (Table 1, entries 2-4). The yield of target compound **3a** increased up to 60% when acetic acid was employed as the solvent and catalyst (Table 1, entry 6). The similar yield was achieved in benzene in the presence of trifluoroacetic acid (Table 1, entry 7). In all cases, the formation of bispyrrole **4a** was the competing reaction. However, it could be suppressed by diluting the reaction mixture, thus allowing us to obtain the 2-pyrazolylprrolidine **3a** with up to 95% yield (Table 1, entries 8, 9). The substitution occurs at the fourth position of pyrazolone ring, which is confirmed by the absence of C4-H proton in ^{1}H NMR spectra of the compound **3a** as well as 2D NMR data.

With the optimized conditions in hand, we next explored the scope of ureas **2** with different substituents in the phenyl moiety using the pyrazol-5-one **1a** as the model compound (Table 2, **3a-h**). Electron-donating methoxy group produced the corresponding product **3b** with fairly high yield, whereas electron-withdrawing carboxyl substituent in aromatic ring decreases the yield of target compound **3c** significantly. This behavior is consistent with our previous observations[36] and can be explained by the decrease of electron density on the nitrogen atoms, which hinders the

intramolecular imination leading to the formation of pyrrolidine ring.

Table 1. Optimization of reaction conditions of the pyrazol-5-one **1a** and (4,4-diethoxybutyl)urea **2a**[a]

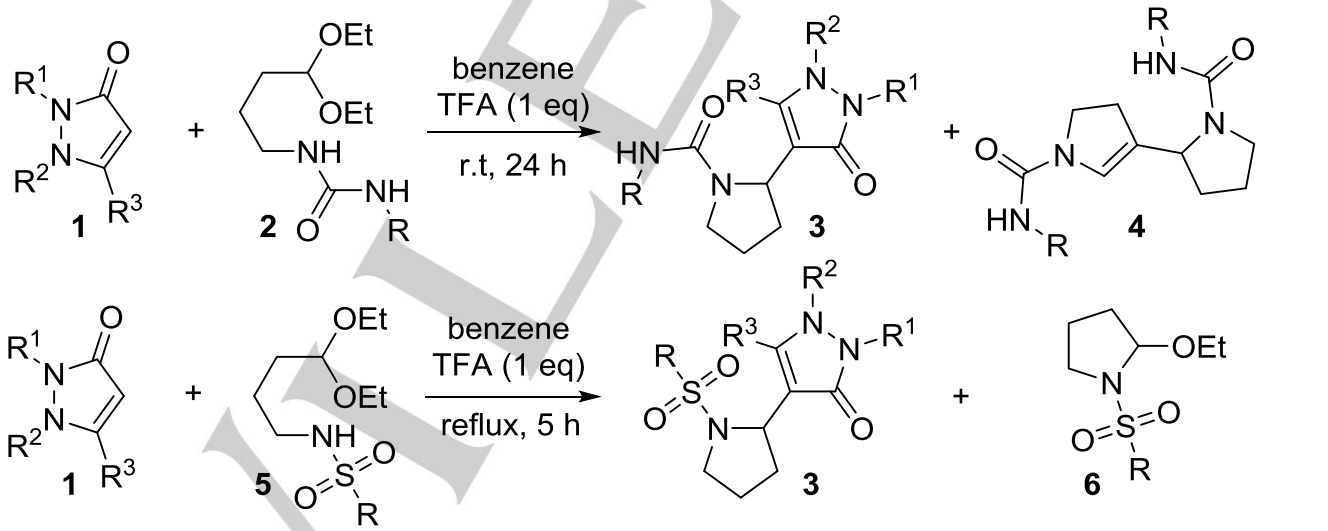


Entry	Solvent (volume, mL)	Catalyst	Yield of **3a**, %[b]
1	$CHCl_3$ (5)	TFA, 1 eqiuv	–[c]
2	H_2O (5)	HCl, excess	10
3	EtOH (5)	HCl, excess	25
4	EtOH (5)	TFA, 1 eqiuv	15
5	TFA (5)	–	–[c]
6	AcOH (5)	–	60
7	C_6H_6 (5)	TFA, 1 eqiuv	67
8	C_6H_6 (20)	TFA, 1 eqiuv	80
9	C_6H_6 (30)	TFA, 1 eqiuv	95

[a] Reaction conditions: urea **3a** (1.79 mmol), pyrazol-5-one **1a** (1.79 mmol), r.t., 24 h. [b] According to ^{1}H NMR data. [c] Bispyrrole **4a** was isolated as the only product.

The substrate scope was further tested by utilizing different substituted pyrazol-5-ones. The pyrazol-5-one possesing methyl group in aromatic fragment reacted smoothly to give target compound **3e** with 57% isolated yield. In contrast, pyrazol-5-ones containing nitro- and carboxy- groups in the aryl fragment did not react at all and were recovered from the reaction mixture unchanged. The only product isolated in this case was the bispyrrole derivative **4**. Thus, the presence of strong electron-withdrawing substituents in aromatic ring of the pyrazol-5-one prevents the reaction. The chloro-substituted pyrazolone reacted with urea **2a** to give product **3f** with moderate yield. Similarly, reaction of ureas **2** with antipyrine resulted in the formation of 2-(pyrazolyl)pyrrolidines **3g,h**.

Table 2. Trifluoroacetic acid-catalyzed one-pot synthesis of 2-(pyrazolyl)pyrrolidines **3**.[a]



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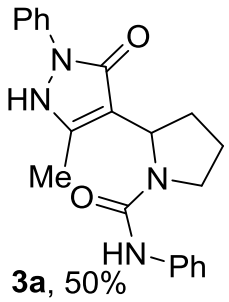
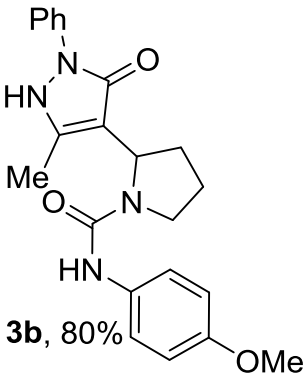
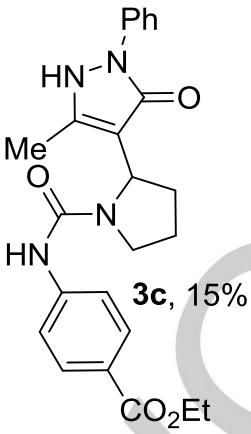
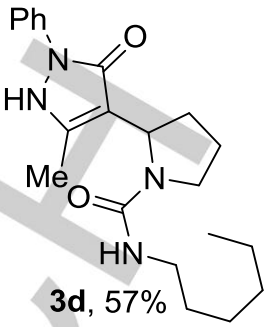
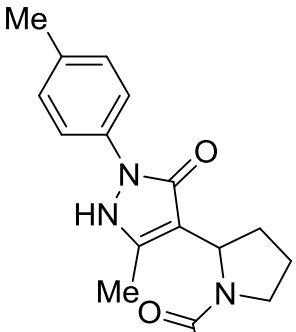
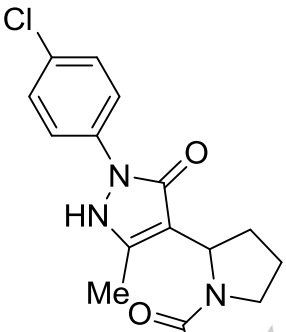

3a, 50%

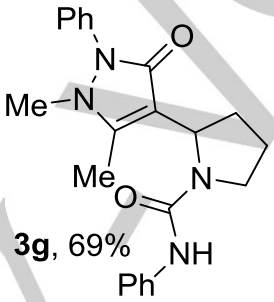

3b, 80%

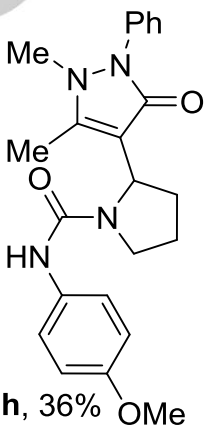

3c, 15%

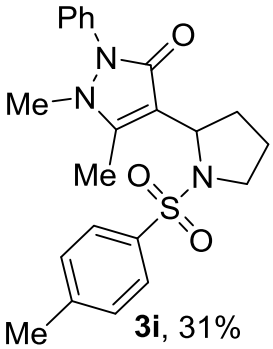

3d, 57%

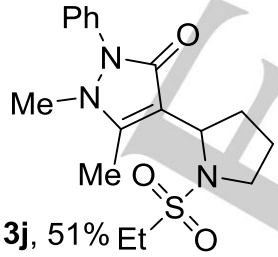

3e, 57%

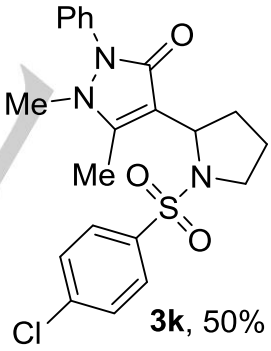

3f, 35%

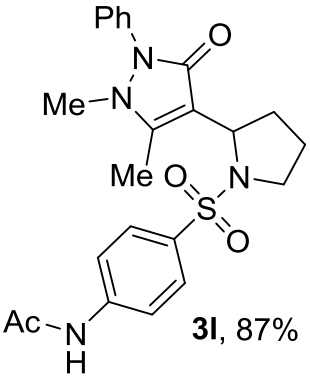

3g, 69%

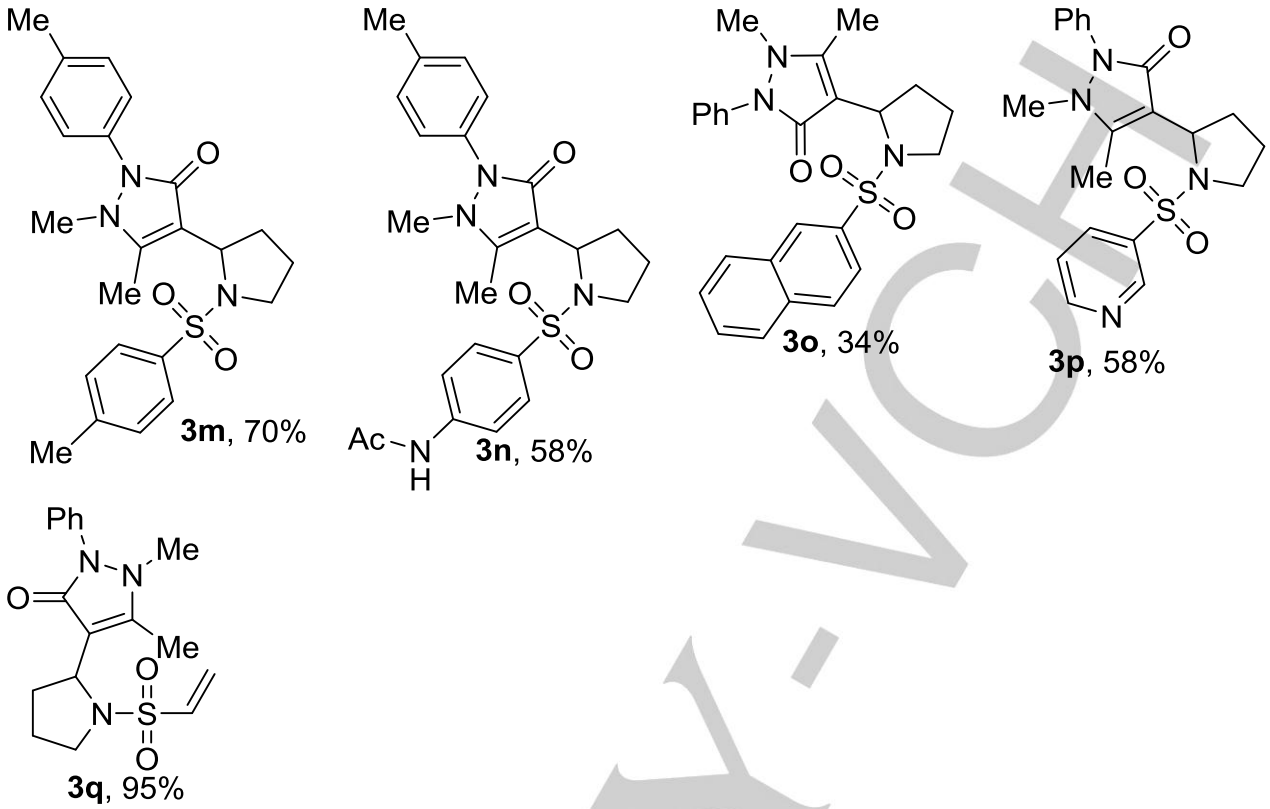

3h, 36%


3i, 31%


3j, 51%


3k, 50%

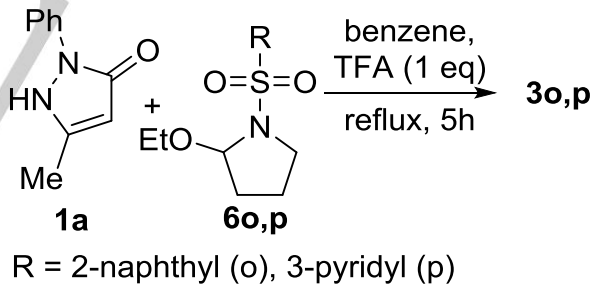

3l, 87%



[a] Isolated yield

Next, we extended the scope of this reaction to *N*-(4,4-diethoxybutyl)sulfonylamides **5**. Sulfonylamides possessing alkyl, aryl and heteroaryl substituents at sulfur atom reacted smoothly giving 1-sulfonyl-2-(pyrazolyl)pyrrolidines **3i-q**. Yields vary somewhat, and no straightforward influence of the substituent on the yield of the target compounds was detected. According to ^{1}H NMR data, 2-ethoxypyrrolidines **6** were formed as byproducts. Again, reaction of pyrazol-5-ones containing electron-withdrawing groups in the aryl fragment didn't result in target compounds formation and 2-ethoxypyrrolidines **6** were the only products. Notably, no such compounds were observed in case of N-(4,4-diethoxybutyl)ureas **2**.

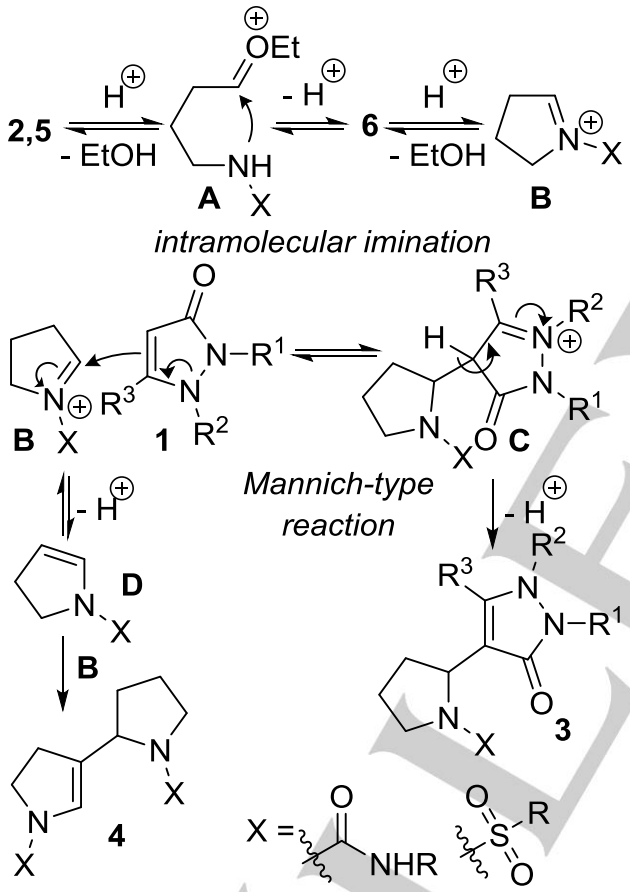
We supposed that 2-ethoxypyrrolidines **6** could be intermediates in the 2-(pyrazolyl)pyrrolidines formation as is the case with 2-arylpyrrolidines previously described by us.[42,49] To check this hypothesis, we carried out the reaction of pyrazol-5-one **1a** with 2-ethoxypyrrolidines **6o,p**. The reaction proceeded in the refluxing benzene in the presence of 1 equivalent of trifluoroacetic acid to give the pyrrolidines **3o,p** with 50-63% isolated yield (Scheme 2).



Scheme 2. Reaction of 2-ethoxypyrrolidines **6o,p** with pyrazolone **1a**.

On the basis of the above investigations and previous reports,[42,49] we propose a plausible mechanism of 2-(pyrazolyl)pyrrolidines **3** formation as shown in Scheme 3. The first stage of the reaction is the carboxonium ion **A** formation via protonation of oxygen atom and elimination of ethanol molecule. Subsequent intramolecular imination of this cation leads to the iminium ion **B** through the intermediate 2-ethoxypyrrolidine **6**. 1-Pyrrolinium ion **B** thus formed is a highly reactive species and undergoes rapidly two concurrent reactions. The first one is the interaction with pyrazol-5-one **1** molecule to give the cation **C**. Further elimination of proton results in 2-(pyrazolyl)pyrrolidines **3** formation. These stages may be considered as intermolecular Mannich-type

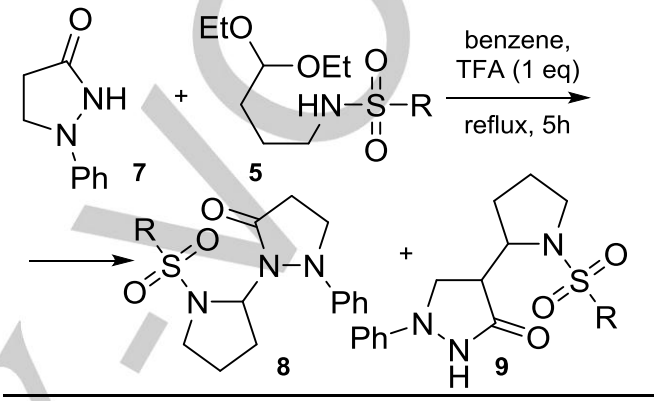
reaction. The other reaction is the deprotonation of the cation **B** resulting in enamide **D**. Subsequent reaction of this intermediate compound with another iminium cation **B** leads to the formation of bispyrrole derivative **4**. Obviously, the less a nucleophilicity of the pyrazol-5-one **1**, the more bispyrrole **4** is formed, and vice versa. Thus, in case of the reaction of *N*-(4,4-diethoxybutyl)ureas **2** with pyrazol-5-ones **1** containing electron-withdrawing substituents second pathway becomes dominant and only bispyrrole **4** formation is observed. However, in case of *N*-(4,4-diethoxybutyl)sulfonylamides **5** the reaction stops at the 2-ethoxypyrrolidines **6** formation. This may be attributed to the higher electron density on the nitrogen atom in sulfonylamides compared to ureas,[50,51] which stabilizes the iminium cation **B** and decreases its deprotonation rate.

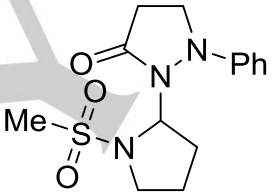


Scheme 3. Plausible mechanism of 2-(pyrazolyl)pyrrolidines **3** formation and side reaction leading to bispyrrole derivatives **4**.

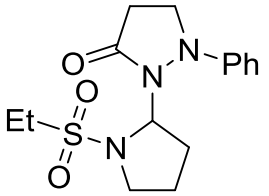
Next, we tested in these reactions the saturated analog of pyrazolones, 1-phenylpyrazolidin-3-one **7**. *N*-(4,4-diethoxybutyl)ureas **2** produced complex mixture of products, which could not be separated. In contrast, sulfonylamides **5** reacted smoothly to give 2-(pyrazolidin-1-yl)pyrrolidines **8** (Table 3). Surprisingly, the *C*-alkylated products **9** was also observed in ^{1}H NMR spectra of reaction mixture, although could not be isolated in pure form. The formation of compounds **9** is likely to proceed via Mannich-type reaction of enolized pyrazolidin-3-one **7**. Notably, carboxylic acid derivatives, both cyclic and acyclic, usually require usage of either strong bases[52,53] or Lewis acid/base combination[54,55] to undergo the reaction with iminium ion. To the best of our knowledge, no such reactions in the presence of Bronsted acid were reported until now.

Table 3. Synthesis of 2-(pyrazolidin-1-yl)pyrrolidines **8**.[a]

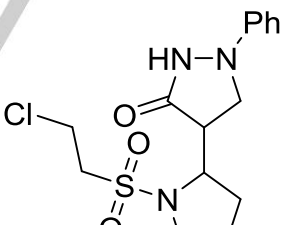




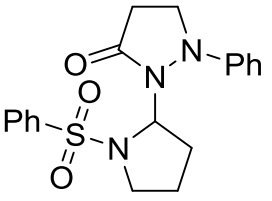
8a, 85%
8a:**9a** (>99:1)[b]



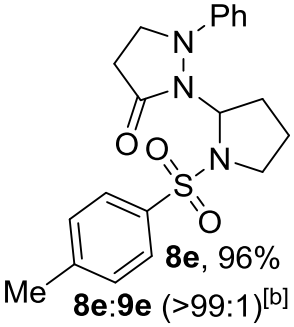
8b, 63%
8b:**9b** (>99:1)[b]



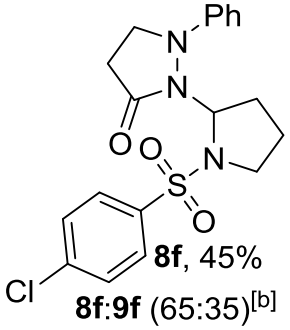
8c, 62%
8c:**9c** (87:13)[b]



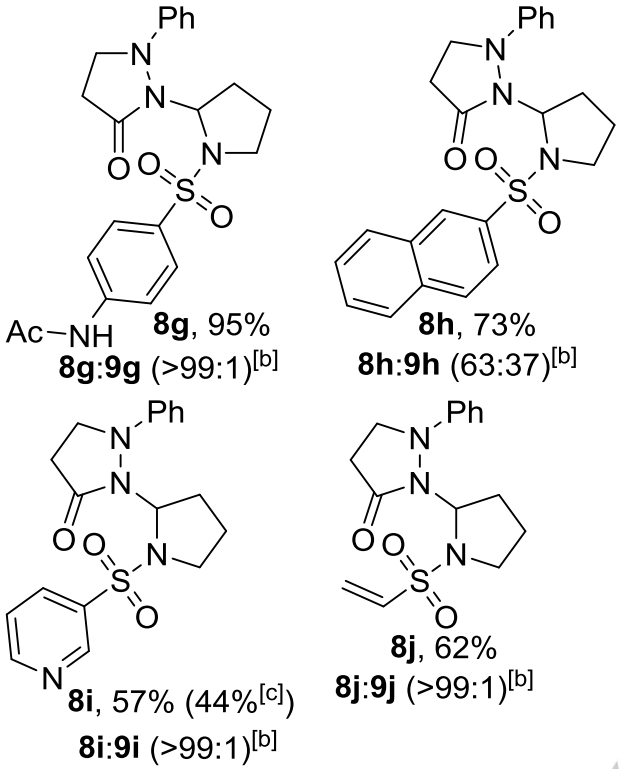
8d, 74%
8d:**9d** (85:15)[b]



8e, 96%
8e:**9e** (>99:1)[b]



8f, 45%
8f:**9f** (65:35)[b]



[a] Isolated yield; [b] According to ^{1}H NMR data; [c] Isolated as trifluoroacetate salt.

The structures of the compounds **3h,m,o** and **8e** were additionally proved by x-ray analysis. The molecular structure of compound **3h** is given as an example in Figure 2 (See Supporting Information for details).

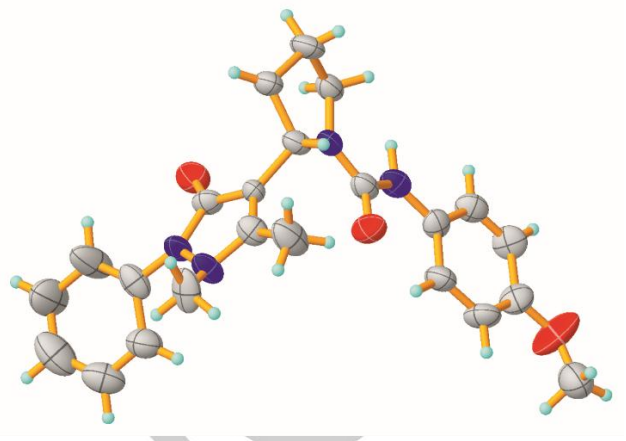


Figure 2. The molecular structure of compound **3h** in crystal. Ellipsoids are shown with 50% probability.

Next, we studied the influence of some synthesized (pyrazolyl)pyrrolidines on bacterial biofilms formation. The natural strain *V. aquamarinus* DSM 26054 and *A. calcoaceticus* VKPM B-10353 were chosen as models due to their ability to actively form biofilms. Microbial biofilms are responsible for the etiology and pathogenesis of many acute and, especially, chronic bacterial infections in humans.[56] It has been estimated that more than 80% of diseases of humans and animals are associated with the presence of stable bacterial communities enclosed in biofilms.[57,58] At the same time, the drug resistance of bacteria living in biofilms is much higher than that of planktonic bacteria.[59,60] Thus, one of the strategies for controlling pathogenic bacteria is to either inhibit biofilm formation or to degrade biofilms.[61] The obtained biological activity results are summarized in Table 4.

Table 4. Biofilm formation (%) by A. *calcoaceticus* VKPM B-10353 and *V. aquamarinus* DSM 26054 in the presence of 2-(pyrazolyl)pyrrolidines **3,8** in reference to control (control=100%)[a]

Entry	Cmpd	Strain	Concentration, M				
			1×10^{-9}	1×10^{-8}	1×10^{-7}	1×10^{-6}	1×10^{-5}
1	**3a**	*A. calcoaceticus* VKPM B-10353	106,70	72,88*	72,13*	77,45*	80,97*
		V. aquamarinus DSM 26054	5,07*	64,31*	27,04*	98,56	82,29
2	**3b**	*A. calcoaceticus* VKPM B-10353	97,21	54,90*	71,57*	83,91	90,09*
		V. aquamarinus DSM 26054	25,18*	13,97*	37,73*	96,99	96,16
3	**3f**	*A. calcoaceticus* VKPM B-10353	111.73*	40,00*	46,39*	85,95	114.66*
		V. aquamarinus DSM 26054	6,08*	34,94*	106,23	195.10*	143.56*
4	**3g**	*A. calcoaceticus* VKPM B-10353	121,79	98,04	64,32*	74,94*	80,92*
		V. aquamarinus DSM 26054	153,16	82,83*	61,58*	98,13	77,43
5	**3o**	*A. calcoaceticus* VKPM B-10353	90,50*	61,44*	59,53*	81,50	98,58
		V. aquamarinus DSM 26054	4,12*	25,31*	42,07*	97,05	52,68*

6	**3q**	*A. calcoaceticus* VKPM B-10353	98,88	42,61*	51,51*	72,43*	74,35*
		V. aquamarinus DSM 26054	5,01*	59,53	110,84	137,33	87,25
7	**8b**	*A. calcoaceticus* VKPM B-10353	105,59	47,73*	44,50*	73,21*	90,71
		V. aquamarinus DSM 26054	14,27*	76,63*	85,14	83,92	87,20
8	**8e**	*A. calcoaceticus* VKPM B-10353	101,12	79,08*	63,02*	73,98*	123,72
		V. aquamarinus DSM 26054	29,04*	27,72*	40,97*	101,57	81,95
9	**8f**	*A. calcoaceticus* VKPM B-10353	91,06*	60,13*	69,68*	79,36*	90,94
		V. aquamarinus DSM 26054	5,17*	22,85*	45,30*	101,31	151.69*
10	**8g**	*A. calcoaceticus* VKPM B-10353	102,79	59,80*	63,96*	84,80	96,32
		V. aquamarinus DSM 26054	20,71*	7,83*	46,80*	97,33	110.97*
11	**8h**	*A. calcoaceticus* VKPM B-10353	108,38	60,46*	63,96*	74,85*	80,15
		V. aquamarinus DSM 26054	4,08*	38,70*	36,90*	98,97	81,31
12	**8i*TFA**	*A. calcoaceticus* VKPM B-10353	125.16*	41,39*	48,59*	63,39*	81,85
		V. aquamarinus DSM 26054	4,23*	50,63*	51,98*	108.33*	117.37*
13	**8j**	*A. calcoaceticus* VKPM B-10353	102,08	49,53*	54,83*	82,08*	82,58*
		V. aquamarinus DSM 26054	87,70	74,36	77,48	107.90*	92,97

[a] The solutions of appropriate solvent in ethanol with the same concentration were used as control; eight replicates were done for each treatment and control; [*] differences compared to the control samples are statistically significant, t-criterion, $p<0.05$.

According to the data obtained, the most promising candidates for further studies are pyrrolidines **3a,b,o** and **8e,h**. The substantial inhibition of biofilm formation was observed for these substances in the range of rather low concentrations – $1x10^{-7}$-$1x10^{-9}$M. At 10^{-7} and 10^{-8}M the formation of biofilms of both the *V. aquamarinus* DSM 26054 and the *A. calcoaceticus* VKPM B-10353 strains is inhibited. Besides this, the formation of *V. aquamarinus* DSM 26054 biofilm is inhibited at nanomolar concentration of these compounds (Table 4, entries 1,2,5,8,11).

The activity of pyrrolidines **3f** and **8f,g,i,j** appeared to be concentration-dependent. Lower concentrations of compound **8i** stimulated the *A. calcoaceticus* VKPM B-10353 biofilm formation, whereas at higher concentrations it was suppressed (Table 4, entry 12). Compounds **3f** and **8f,g,i,j** promoted the *V. aquamarinus* DSM 26054 biofilm formation at high concentrations, and inhibited it at lower concentrations (Table 4, entries 3,9,10,12,13). Interestingly, pyrrolidine **3f** stimulated *A. calcoaceticus* VKPM B-10353 biofilm formation at lowest (1×10^{-9}M) and highest (1×10^{-5}M) concentrations, and suppressed it in other cases. Although these results seem to be interesting from theoretical point of view, the multidirectional dose-dependent effects render these compounds unsuitable for pharmacological application.

Conclusions

In conclusion, an efficient method for the synthesis of various *N*-substituted 2(pyrazolyl)pyrrolidines was developed for the first time using easily accessible 4-aminobutanal acetals and pyrazolones as starting materials and an inexpensive trifluoroacetic acid as catalyst. A mechanism involving intramolecular imination – Mannich-type reaction sequence was proposed. Some of the some of the synthesized compounds were found to inhibit a bacterial biofilm formation at nanomolar concentrations and thus are promising for further studies as antibacterial substances.

Experimental Section

General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 (working frequency 400.1 MHz for ^{1}H, 100.6 for ^{13}C), Avance 500 (working frequency 500.1 MHz for ^{1}H, 125.8 for ^{13}C) and Avance 600 (working frequency 600.1 MHz for ^{1}H, 150.9 for ^{13}C) spectrometers in $(CD_3)_2SO$, $CDCl_3$ and CD_3OD relative to the residual solvent protons. ESI-TOF mass spectra were recorded on a AmazonX (Bruker Daltonik GmbH) instrument. MALDI-TOF mass spectra were recorded on a Bruker ULTRAFLEX III TOF/TOF instrument (with 2,5-dihydroxybenzoic acid matrix) instrument. IR spectra were obtained with a Bruker Vector 22 spectrometer. Elemental analysis was performed on Carlo Erba EA 1108 instrument. Melting points were determined in glass capillaries with a Stuart SMP 10 apparatus. All solvents were purified and dried according to standard procedures. *N*-(4,4-

diethoxybutyl)ureas **2**[36] and *N*-(4,4-diethoxybutyl)sulfonylamides **5**[42,62] were obtained according to known procedures.

X-ray studies

The X-Ray diffraction data for crystals of compounds **3h,o** and **8e** were collected at 296K on a Bruker AXS Smart Apex II CCD diffractometer in the ω and φ-scan modes using graphite monochromated MoKα (λ 0.71073Å) radiation. The structure was solved by direct method and refined by the full matrix least-squares using SHELXTL[63] program. All non-hydrogen atoms were refined anisotropically. The positions of hydrogen atoms were located from the Fourier electron density synthesis and were included in the refinement in the isotropic riding model approximation. All figures were made using OLEX2.[64]

Crystal data for **3h**: $C_{23}H_{26}N_4O_3$, M = 406.48, colorless crystal 0.12 x 0.15 x 0.15 mm, monoclinic, space group $P2_1/c$, Z = 4, a = 11.169(3), b = 20.958(5), c = 9.562(3)Å, β = 113.059(3)° , V = 2059.5(9)Å^3, ρ_{calc} = 1.311 g/cm^3, μ =0.089 mm^{-1}, 18627 reflections collected (±h, ±k, ±l), 4963 independent (Rint 0.0425) and 3058 observed reflections [I ≥ 2\s (I)], 331 refined parameters, R =0.0474, wR2 = 0.1353, max. residual electron density is 0.198 (-0.166) eÅ^{-3}.

Crystal data for **3m**: $C_{23}H_{27}N_3O_3S$, M = 425.54, colorless crystal 0.2 x 0.15 x 0.15 mm, monoclinic, space group $P2_1/n$, Z = 4, a = 14.6487(18), b = 8.0198(9), c = 18.938(2)Å, β = 100.040(4)° , V = 2190.8(4)Å^3, ρ_{calc} = 1.290 g/cm^3, μ = 0.177 mm^{-1}, 28394 reflections collected (±h, ±k, ±l), 4777 independent (Rint 0.087) and 2281 observed reflections [I ≥ 2\s (I)], 275 refined parameters, R = 0.0687, wR2 = 0.2031, max. residual electron density is 0.31 (-0.32) eÅ^{-3}.

Crystal data for **3o**: $C_{25}H_{25}N_3O_3S$, M = 447.54, colorless crystal 0.16 x 0.14 x 0.11 mm, triclinic, space group P-1, Z = 3, a = 7.2073(6), b = 15.8405(14), c = 113.048(5)Å, α = 113.048(5), β = 97.125(5), γ = 95.401(5) ° , V = 1649.1(3)Å3, ρ_{calc} = 1.352 g/cm^3, μ =0.180 mm^{-1}, 26524 reflections collected (±h, ±k, ±l), 14553 independent (Rint 0.0425) and 9838 observed reflections [I ≥ 2\s (I)], 871 refined parameters, R =0.0589, wR2 = 0.1484, max. residual electron density is 0.466 (-0.395) eÅ^{-3}.

Crystal data for **8e**: $C_{20}H_{22}N_3O_3S$, M = 384.46, colorless crystal 0.12 x 0.15 x 0.15 mm, triclinic, space group P-1, Z = 2, a = 7.3141(16), b = 11.488(3), c = 12.196(3), α = 78.020(17), β = 74.948(14), γ = 82.012(13)° , V = 964.2(4)Å^3, ρ_{calc} = 1.324 g/cm^3, μ =0.193 mm^{-1}, 8017 reflections collected (±h, ±k, ±l), 3767 independent (R_{int} 0.1039) and 1692 observed reflections [I ≥ 2\s (I)], 252 refined parameters, R =0.0935, wR2 = 0.2972, max. residual electron density is 0.566 (-0.447) eÅ^{-3}

Crystallographic data for **3h**, **3m, 3o** and **8e** have been deposited in the Cambridge Crystallographic Data Centre, CCDC numbers are 1909796, 1918389, 1909797 and 1909798 respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK).

Chemistry

General procedure for the synthesis of 2-pyrazolylpyrrolidines 3a-h. To the solution of urea **2** (1.79 mmol) in dry benzene (30 ml) pyrazole-5-one **1** (1.79 mmol) and trifluoroacetic acid (0.204 g, 1.79 mmol) were added. The reaction mixture was stirred at room temperature for 24 hours and the solvent was evaporated under reduced pressure. The residue was washed with acetonitrile (3x20 ml), filtered and dried in vacuum (10 torr, 10 h, r.t.) to give the target compounds **3**.

General procedure for the synthesis of 2-pyrazolylpyrrolidines 3i-q. To the solution of sulfonylamide **5** (1.79 mmol) in dry benzene (30 ml) pyrazole-5-one **1** (1.79 mmol) and trifluoroacetic acid (0.204 g, 1.79 mmol) were added. The reaction mixture refluxed for 5 hours and the solvent was evaporated under reduced pressure. The residue was washed with diethyl ether (3x30 ml), filtered and dried in vacuum (10 torr, 10 h, r.t.) to give the target compounds.

General procedure for the synthesis of 2-(pyrazolidin-1-yl)pyrrolidines 8a-j. To the solution of sulfonylamide **5** (1.79 mmol) in dry benzene (30 ml) 5-methyl-1-phenylpyrazolidin-3-one (0.315 g, 1.79 mmol) and trifluoroacetic acid (0.204 g, 1.79 mmol) were added. The reaction mixture refluxed for 5 hours and the solvent was evaporated under reduced pressure. The residue was washed with diethyl ether (3x30 ml), filtered and dried in vacuum (10 torr, 10 h, r.t.) to give the target compounds.

2-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-N-phenylpyrrolidine-1-carboxamide (3a). Beige solid (0.32 g, 50%), mp 153-154°C. Found: C 69.8; H 6.25; N 15.2. Calc. for $C_{21}H_{22}N_4O_2$: C 69.8; H 6.1; N 15.4%. IR (KBr): ν_{max}/cm^{-1} 1595, 1638, 2872, 2917, 2971, 3099, 3302. ^{1}H NMR (400MHz, CD_3OD/DMSO-d_6 90/10): δ 1.93-2.04 (1H, m, CH_2), 2.12-2.24 (2H, m, CH_2), 2.24-2.35 (1H, m, CH_2), 2.29 (3H, s, CH_3), 3.63-3.74 (2H, m, CH_2), 4.90-4.98 (1H, m, CH), 6.99 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.24 (2H, t, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 7.30 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.38 (2H, d, $^3J_{HH}$ 8.3 Hz, CH_{Ar}), 7.47 (2H, t, $^3J_{HH}$ 7.9 Hz, CH_{Ar}), 7.64 (2H, d, $^3J_{HH}$ 7.6 Hz, CH_{Ar}). ^{13}C NMR (150MHz, CD_3OD/DMSO-d_6 90/10): δ 10.1; 24.5; 31.7; 47.; 51.8; 106.2; 118.8; 120.34; 120.9; 122.6; 126.0; 128.3; 128.8; 136.3; 139.5; 146.6; 155.4. ESI-TOF, *m/z*: 363 [M+H]$^+$, 385 [M+Na]$^+$.

2-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-N-(4-methoxyphenyl)pyrrolidine-1-carboxamide (3b). Beige solid (0.56 g, 80%), mp 162-163°C. Found: C 67.55; H 5.9; N 14.5%. Calc. for $C_{22}H_{24}N_4O_3$: C 67.3; H 6.1; N 14.3%. IR (KBr): ν_{max}/cm^{-1} 11597, 1635, 2836, 2949, 3067, 3304. ^{1}H NMR (400MHz, CD_3OD/DMSO-d_6 60/40): δ 1.81-1.94 (1H, m, CH_2), 2.00-2.10 (2H, m, CH_2), 2.10-2.20 (1H, m, CH_2), 2.17 (3H, s, CH_3), 3.50-3.57 (2H, m, CH_2), 3.64 (3H, s, OCH_3), 4.79-4.83 (1H, m, CH), 6.73 (2H, d, $^3J_{HH}$ 9.0 Hz, CH_{Ar}), 7.16 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.20 (2H, d, $^3J_{HH}$ 8.9 Hz, CH_{Ar}), 7.37 (2H, t, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 7.59 (2H, d, $^3J_{HH}$ 7.6 Hz, CH_{Ar}). ^{13}C NMR (150 MHz, CD_3OD/DMSO-d_6 60/40): δ 10.2, 23.9, 30.9, 46.3, 51.2, 54.1, 105.8, 112.9, 119.6, 121.6, 124.9, 127.5, 128.3, 132.1, 136.2, 146.2, 154.6, 154.8. ESI-TOF, *m/z*: 415 [M+Na]$^+$.

Ethyl 4-(2-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)pyrrolidine-1-carboxamido)benzoate (3c). White solid (0.12 g, 15%), mp 190-192°C. Found: C 66.50; H 5.9; N 13.0%. Calc. for $C_{24}H_{26}N_4O_4$: C 66.4; H 6.0; N 12.9%. IR (KBr): ν_{max}/cm^{-1} 1596, 1630, 2933, 2979, 3366. ^{1}H NMR (400MHz, CD_3OD): δ 1.36 (3H, t, $^3J_{HH}$ 6.9 Hz, CH_3), 1.94-2.04 (1H, m, CH_2), 2.14-2.25 (2H, m, CH_2), 2.26-2.38 (1H, m, CH_2), 2.30 (3H, s, CH_3), 3.62-3.78 (2H, m, CH_2), 4.31-4.37 (2H, m, CH_2), 4.91-4.99 (1H, m, CH), 7.29 (1H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.46 (2H, t, $^3J_{HH}$ 6.5 Hz, CH_{Ar}), 7.53 (2H, d, $^3J_{HH}$ 8.3 Hz, CH_{Ar}), 7.62 (2H, d, $^3J_{HH}$ 8.1 Hz, CH_{Ar}), 7.89 (2H, d, $^3J_{HH}$ 8.3 Hz, CH_{Ar}). ^{13}C NMR (150MHz, CD_3OD): δ 10.1, 13.3, 24.5, 31.5, 48.5, 52.1, 60.4, 105.9, 117.2, 118.5, 121.0, 123.7, 126.1, 128.8, 129.9, 130.2, 144.5, 146.6, 154.7, 166.7. ESI-TOF, *m/z*: 435 [M+H]$^+$, 457 [M+Na]$^+$.

N-hexyl-2-(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)pyrrolidine-1-carboxamide (3d). Beige solid (0.38 g, 57%), mp 144-145°C. Found: C 68.3; H 8.4; N 15.3%. Calc. for $C_{21}H_{30}N_4O_2$: C 68.1; H 8.2; N 15.1%. IR (KBr): ν_{max}/cm^{-1} 1596, 1633, 2924, 2989, 3260, 3326. ^{1}H NMR (400MHz, CD_3OD): δ 0.88 (3H, t, $^3J_{HH}$ 6.3 Hz, CH_3), 1.22-1.36 (6H, m, CH_2), 1.40-1.51 (2H, m, CH_2), 1.86-1.99 (1H, m, CH_2), 2.03-2.15 (2H, m, CH_2), 2.19-2.35 (1H, m, CH_2), 2.24 (3H, s, CH_3), 2.99-3.12 (1H, m, CH_2), 3.15-3.26 (1H, m, CH_2), 3.47-3.59 (2H, m, CH_2), 4.74-4.81 (1H, m, CH), 7.30 (1H, t,

$^3J_{HH}$ 7.2 Hz, CH_{Ar}), 7.47 (2H, t, $^3J_{HH}$ 7.8 Hz, CH_{Ar}), 7.64 (2H, d, $^3J_{HH}$ 7.9 Hz, CH_{Ar}). ^{13}C NMR (150MHz, CD_3OD): δ 10.1, 13.0, 22.3, 24.1, 26.2, 29.9, 31.3, 32.3, 40.1, 46.6, 51.7, 106.3, 120.7, 126.0 128.8, 136.3, 146.2 157.8. ESI-TOF, *m/z*: 371 $[M+H]^+$, 393 $[M+Na]^+$.

2-(5-hydroxy-3-methyl-1-(p-tolyl)-1H-pyrazol-4-yl)-N-phenylpyrrolidine-1-carboxamide (3e). White solid (0.38 g, 57%), mp 166-167°C. Found: C 70.0; H 6.8; N 14.9%. Calc. for $C_{22}H_{24}N_4O_2$: C 70.2; H 6.6; N 14.9%. IR (KBr): ν_{max}/cm^{-1} 1597, 1635, 2957, 2982, 3249, 3362. ^{1}H NMR (400MHz, $(CD_3)_2SO$): δ 1.80-1.93 (1H, m, CH_2), 2.01-2.09 (2H, m, CH_2), 2.10-2.20 (1H, m, CH_2), 2.17 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.55-3.64 (2H, m, CH_2), 4.80-4.88 (1H, m, CH), 6.83 (1H, s, NH), 7.15-7.25 (4H, m, CH_{Ar}), 7.33 (1H, m, CH_{Ar}), 7.44 (2H, d, $^3J_{HH}$ 8.5 Hz, CH_{Ar}), 7.58 (2H, d, $^3J_{HH}$ 8.6 Hz, CH_{Ar}). ^{13}C NMR (150MHz, $(CD_3)_2SO$): δ 20.9, 25.0, 31.7, 34.7, 47.43 51.9, 106.7, 118.1, 119.8, 122.1, 128.7, 129.1, 129.8, 134.4, 140.9, 146.1, 154.4, 155.7. ESI-TOF, *m/z*: 377 $[M+H]^+$, 399 $[M+Na]^+$.

2-(1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)-N-phenylpyrrolidine-1-carboxamide (3f). Beige solid (0.25 g, 35%), mp 193-194°C. Found: C 63.7; H 5.1; Cl 9.0; N 14.3%. Calc. for $C_{21}H_{21}ClN_4O_2$: C 63.55; H 5.3; Cl 8.9; N 14.1%. IR (KBr): ν_{max}/cm^{-1} 1598, 1637, 2922, 3426. ^{1}H NMR (400MHz, $(CD_3)_2SO$): δ 1.84-1.96 (1H, m, CH_2), 2.05-2.23 (4H, m, CH_2), 2.20 (3H, s, CH_3), 3.55-3.63 (2H, m, CH_2), 4.78-4.90 (1H, m, CH), 6.86 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.14 (2H, t, $^3J_{HH}$ 7.8 Hz, CH_{Ar}), 7.36 (2H, d, $^3J_{HH}$ 8.6 Hz, CH_{Ar}), 7.41 (2H, d, $^3J_{HH}$ 8.1 Hz, CH_{Ar}), 7.74 (2H, d, $^3J_{HH}$ 8.6 Hz, CH_{Ar}). ^{13}C NMR (150MHz, $(CD_3)_2SO$): δ 12.4, 25.1, 31.5, 47.5, 51.9, 118.1, 119.8, 120.7, 121.4, 122.0, 128.7, 129.0, 129.3, 140.9, 141.0, 154.3, 155.7. ESI-TOF, *m/z*: 397 $[M+H]^+$, 419 $[M+Na]^+$, 335 $[M+K]^+$.

2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-N-phenylpyrrolidine-1-carboxamide (3g). Beige solid (0.46 g, 69%), mp 157-158°C. Found: C 71.0; H 6.2; N 15.0%. Calc. for $C_{22}H_{24}N_4O_2$: C 70.9; H 6.4; N 14.9%. IR (KBr): ν_{max}/cm^{-1} 1595, 1634, 1662, 2964, 3052. ^{1}H NMR (400MHz, CD_3OD): δ 1.93-2.06 (1H, m, CH_2), 2.15-2.32 (3H, m, CH_2), 2.35 (3H, s, CH_3), 3.14 (3H, s, CH_3), 4.89-4.96 (1H, m, CH), 7.00 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.22-7.27 (2H, m, CH_{Ar}), 7.33-7.39 (4H, m, CH_{Ar}), 7.42 (1H, t, $^3J_{HH}$ 7.5 Hz, CH_{Ar}), 7.52 (2H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}). ^{13}C NMR (150MHz, CD_3OD): δ 9.5, 24.7, 31.3, 33.7, 47.2, 52.1, 107.7, 120.4, 122.6, 125.7, 127.7, 128.2, 129.1, 134.2, 139.4, 152.3, 155.4, 164.3. ESI-TOF, *m/z*: 377 $[M+H]^+$, 399 $[M+Na]^+$.

2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-N-(4-methoxyphenyl)pyrrolidine-1-carboxamide (3h). White solid (0.26 g, 36%), mp 113-114°C. Found: C 68.1; H 6.6; N 14.85. Calc. for $C_{23}H_{26}N_4O_3$: C 68.0; H 6.45; N 14.8. IR (KBr): ν_{max}/cm^{-1} 1608, 1652, 2835, 2949, 3063. ^{1}H NMR (400 MHz, CD_3OD): δ 1.89-2.06 (1H, m, CH_2), 2.15-2.30 (3H, m, CH_2), 2.34 (3H, s, CH_3), 3.14 (3H, s, CH_3), 3.61-3.75 (2H, m, CH_2), 3.76 (3H, s, CH_3), 4.88-4.96 (1H, m, CH), 6.82 (2H, d, $^3J_{HH}$ 9.0 Hz, CH_{Ar}), 7.25 (2H, d, $^3J_{HH}$ 8.7 Hz, CH_{Ar}), 7.35 (2H, d, $^3J_{HH}$ 7.5 Hz, CH_{Ar}), 7.40 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.51 (2H, t, $^3J_{HH}$ 7.8 Hz, CH_{Ar}). ^{13}C NMR (150MHz, CD_3OD): δ 9.6, 24.7, 31.3, 33.8, 39.5, 52.2, 54.5, 108.0, 113.4, 121.3, 122.8, 125.5, 127.6, 129.0, 134.3, 152.4, 155.8, 156.0, 164.4. ESI-TOF, *m/z*: 407 $[M+H]^+$, 429 $[M+Na]^+$, 445 $[M+K]^+$.

1,5-Dimethyl-2-phenyl-4-(1-tosylpyrrolidin-2-yl)-1,2-dihydro-3H-pyrazol-3-one (3i). White solid (0.23 g, 31%), mp 142-143°C. Found: C 64.3; H 6.2; N 10.3; S 7.9%. Calc. for $C_{22}H_{25}N_3O_3S$: C 64.4; H 6.1; N 10.2; S 7.8%. IR (KBr): ν_{max}/cm^{-1} 1156, 1594, 1658. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.37-1.48 (1H, m, CH_2), 1.87-1.98 (2H, m, CH_2), 1.99-2.11 (1H, m, CH_2), 2.28 (3H, s, CH_3), 2.31 (3H, s, CH_3), 2.99 (3H, s, CH_3), 4.44-4.53 (1H, m, CH), 7.23 (2H, d, $^3J_{HH}$ 7.8 Hz, CH_{Ar}), 7.28 (1H, t, $^3J_{HH}$ 7.5 Hz, CH_{Ar}), 7.31 (2H, d, $^3J_{HH}$ 8.1 Hz, CH_{Ar}), 7.46 (2H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.60 (2H, d, $^3J_{HH}$ 8.0 Hz, CH_{Ar}). ^{13}C NMR (100MHz, $(CD_3)_2SO$): δ 11.2, 21.38, 25.4, 31.4, 35.8, 49.7, 54.4, 108.5, 123.7, 126.3, 127.4, 129.3, 130.0, 135.4, 136.0, 143.3, 154.6, 164.0. ESI-TOF, *m/z*: 412 $[M+H]^+$, 434 $[M+Na]^+$.

4-(1-(Ethylsulfonyl)pyrrolidin-2-yl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3j). White solid (0.32 g, 51%), mp 160-161°C. Found: C 58.6; H 6.7, N 12.2; S 9.3%. Calc. for $C_{17}H_{23}N_3O_3S$: C 58.4; H 6.6; N 12.0; S 9.2%. IR (KBr): ν_{max}/cm^{-1}1154, 1593, 1653. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.12 (3H, t, $^3J_{HH}$ 7.3 Hz, CH_3), 1.73-1.85 (1H, m, CH_2), 2.02-2.11 (1H, m, CH_2), 2.11-2.22 (2H, m, CH_2), 2.25 (3H, s, CH_3), 2.91 (2H, q, $^3J_{HH}$ 7.1 Hz, CH_2), 3.02 (3H, s, CH_3), 3.34-3.41 (1H, m, CH_2), 3.47-3.55 (1H, m, CH_2), 4.61-4.69 (1H, m, CH), 7.28-7.34 (3H, m, CH_{Ar}), 7.44-7.53 (2H, m, CH_{Ar}). ^{13}C NMR (100MHz, $(CD_3)_2SO$): 8.0, 11.0, 26.0, 31.5, 36.0, 44.6, 49.4, 54.0, 108.7, 123.9, 126.5. 129.4, 135.7, 155.0, 164.5. MALDI-TOF, *m/z*: 350 $[M+H]^+$, 372 $[M+Na]^+$, 388 $[M+K]^+$.

4-(1-((4-Chlorophenyl)sulfonyl)pyrrolidin-2-yl)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3k). White solid (0.39 g, 50%), mp 155-156°C. Found: C 58.5; H 5.2, Cl 8.3; N 9.9; S 7.5%. Calc. for $C_{21}H_{22}ClN_3O_3S$: C 58.4; H 5.1; Cl 8.2; N 9.7; S 7.4%. IR (KBr): ν_{max}/cm^{-1} 1158, 1593, 1656. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.49-1.60 (1H, m, CH_2), 1.95-2.05 (2H, m, CH_2), 2.07-2.17 (1H, m, CH_2), 2.27 (3H, s, CH_3), 3.00 (3H, s, CH_3), 3.52-3.64 (2H, m, CH_2), 4.51-4.59 (1H, m, CH), 7.19 (2H, d, $^3J_{HH}$ = 7.9 Hz, CH_{Ar}), 7.28 (1H, t, $^3J_{HH}$ = 7.6 Hz, CH_{Ar}), 7.45 (2H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.54 (2H, d, $^3J_{HH}$ 8.5 Hz, CH_{Ar}), 7.68 (2H, d, $^3J_{HH}$ 8.4 Hz, CH_{Ar}). ^{13}C NMR (150MHz, $(CD_3)_2SO$): δ 11.0, 25.5, 31.3, 35.7, 49.7, 54.4, 107.7, 123.9, 126.5, 129.2, 129.4, 129.6, 135.3, 137.9, 138.3, 154.6, 163.8. ESI-TOF, *m/z*: 455 $[M+Na]^+$.

N-(4-((2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)pyrrolidin-1-yl)sulfonyl)phenyl)acetamide (3l). Yellow oil (0.68 g, 87%). Found: C 60.83.17; H 5.82, N 12.37; S 7.09. Calc. for $C_{23}H_{26}N_4O_4S$: C 60.78; H 5.77; N 12.33; S 7.05. IR (KBr): ν_{max}/cm^{-1} 1149, 1598, 1638, 3254. ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 1.35-1.47 (1H, m, CH_2), 1.85-2.00 (2H, m, CH_2), 2.00-2.09 (1H, m, CH_2), 2.07 (3H, s, CH_3), 2.26 (3H, s, CH_3), 2.96 (3H, s, CH_3), 3.40-3.52 (2H, m, CH_2), 4.43-4.51 (1H, m, CH), 7.20 (2H, d, $^3J_{HH}$ 7.8 Hz, CH_{Ar}), 7.26 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.42 (2H, t, $^3J_{HH}$ 7.8 Hz, CH_{Ar}), 7.65 (2H, d, $^3J_{HH}$ 8.3 Hz, CH_{Ar}), 7.74 (2H, d, $^3J_{HH}$ 8.5 Hz, CH_{Ar}), 10.42 (1H, s, NH). ^{13}C NMR (150MHz, $(CD_3)_2SO$): 11.1, 24.4, 25.3, 31.5, 35.6, 49.7, 54.4, 108.2, 119.0, 124.2, 128.5, 129.3, 132.6, 135.2, 143.5, 154.2, 164.0, 169.8. ESI-TOF, *m/z*: 455 $[M+H]^+$, 477 $[M+Na]^+$.

1,5-Dimethyl-2-(p-tolyl)-4-(1-tosylpyrrolidin-2-yl)-1,2-dihydro-3H-pyrazol-3-one (3m). White solid (0.53g, 70%), mp 127-128°C. Found: C 60.5.17; H 6.5, N 10.0; S 7.6%. Calc. for $C_{23}H_{27}N_3O_3S$: C 64.9; H 6.4; N 9.9; S 7.5%. IR (KBr): ν_{max}/cm^{-1} 1151, 1598, 1637. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 1.37-1.49 (1H, m, CH_2), 1.87-2.00 (2H, m, CH_2), 2.01-2.14 (1H, m, CH_2), 2.27 (3H, s, CH_3), 2.33 (6H, s, CH_3), 2.97 (3H, s, CH_3), 3.43-3.50 (2H, m, CH_2), 4.47-4.52 (1H, m, CH), 7.11 (2H, d, $^3J_{HH}$ 8.3 Hz, CH_{Ar}), 7.26 (2H, d, $^3J_{HH}$ 8.2 Hz, CH_{Ar}), 7.32 (2H, d, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 7.61 (2H, d, $^3J_{HH}$ 8.3 Hz, CH_{Ar}). ^{13}C NMR (150MHz, $(CD_3)_2SO$): 11.2, 21.0, 21.4, 25.4, 31.4, 35.7, 49.7, 54.5, 108.4, 124.0, 127.5, 129.8, 130.0, 133.0, 135.8, 136.2, 143.2, 154.1, 163.9. MALDI-TOF, *m/z*: 426 $[M+H]^+$, 448 $[M+Na]^+$, 464 $[M+K]^+$.

N-(4-((2-(1,5-dimethyl-3-oxo-2-(p-tolyl)-2,3-dihydro-1H-pyrazol-4-yl)pyrrolidin-1-yl)sulfonyl)phenyl)acetamide (3n). White solid (0.49g, 58%), mp 256-257°C. Found: C 61.7.17; H 6.3, N 12.2; S 7.0%. Calc. for $C_{24}H_{28}N_4O_4S$: C 61.5; H 6.0; N 12.0; S 6.9%. IR (KBr): ν_{max}/cm^{-1} 1510, 1592, 1636, 1693, 2928, 3047. ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 1.36-1.47 (1H, m, CH_2), 1.87-2.00 (2H, m, CH_2), 2.03-2.07 (1H, m, CH_2), 2.08 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.98 (3H, s, CH_3), 3.42-3.50 (2H, m, CH_2), 4.45-4.52 (1H, m, CH), 7.10 (2H, d, $^3J_{HH}$ 8.3 Hz, CH_{Ar}), 7.24 (2H, d, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 7.66 (2H, d, $^3J_{HH}$ 8.8 Hz, CH_{Ar}), 7.72 (2H, d, $^3J_{HH}$ 8.9 Hz, CH_{Ar}), 10.26 (1H, s, NH). ^{13}C NMR (150MHz, $(CD_3)_2SO$): 11.2,

21.1, 24.6, 25.4, 31.4, 35.6, 49.7, 54.5, 108.3, 118.9, 124.4, 128.6, 129.8, 132.6, 132.9, 136.0, 143.5, 153.9, 163.9, 169.4. MALDI-TOF, *m/z*: 469 $[M+H]^+$, 491 $[M+Na]^+$, 507 $[M+K]^+$.

1,5-Dimethyl-4-(1-(naphthalen-2-ylsulfonyl)pyrrolidin-2-yl)-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (3o). White solid (0.27 g, 34%), mp 126-127°C. Found: C 67.3; H 5.7, N 9.5; S 7.3%. Calc. for $C_{25}H_{25}N_3O_3S$: C 67.1; H 5.6; N 9.4; S 7.2%. IR (KBr): ν_{max}/cm^{-1} 1154, 1593, 1653. ^1H NMR (400 MHz, $(CD_3)_2SO$): δ 1.45-1.55 (1H, m, CH_2), 1.92-2.03 (2H, m, CH_2), 2.03-2.14 (1H, m, CH_2), 2.30 (3H, s, CH_3), 2.88 (3H, s, CH_3), 4.57-4.64 (1H, m, CH), 6.97 (2H, d, $^3J_{HH}$ 7.9 Hz, CH_{Ar}), 7.23 (1H, t, $^3J_{HH}$ 7.5 Hz, CH_{Ar}), 7.35 (2H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.62 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.67 (2H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.74 (1H, d, $^3J_{HH}$ 6.9 Hz, CH_{Ar}), 7.99 (1H, d, $^3J_{HH}$ 8.2 Hz, CH_{Ar}), 8.02 (1H, d, $^3J_{HH}$ 8.6 Hz, CH_{Ar}), 8.11 (1H, d, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 8.35 (1H, s, CH_{Ar}). ^{13}C NMR (150MHz, $(CD_3)_2SO$): 11.2, 25.5, 31.4, 35.6, 49.8, 54.5, 108.0, 123.1, 123.9, 126.4, 127.9, 128.2, 129.1, 129.2, 129.4, 128.6, 129.7, 132.1, 134.7, 135.2, 136.6, 154.4, 163.8. ESI-TOF, *m/z*: 448 $[M+H]^+$, 470 $[M+Na]^+$.

3-((2-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)pyrrolidin-1-yl)sulfonyl)pyridin-1-ium 2,2,2-trifluoroacetate (3p). Yellow oil (0.41 g, 58%). Found: C 51.7; H 4.7; N 11.1; S 6.4%. Calc. for $C_{22}H_{23}F_3N_4O_5S$: C 51.5; H 4.5; N 10.9; S 6.3%. IR (KBr): ν_{max}/cm^{-1} 1165, 1593, 1659. ^1H NMR (400 MHz, CD_3Cl): δ 1.82-1.94 (1H, m, CH_2), 2.13-2.25 (2H, m, CH_2), 2.29-2.36 (1H, m, CH_2), 2.38 (3H, s, CH_3), 3.10 (3H, s, CH_3), 3.64-3.74 (1H, m, CH_2), 3.74-3.84 (1H, m, CH_2), 4.72-4.79 (1H, m, CH), 7.16 (2H, d, $^3J_{HH}$ 7.3 Hz, CH_{Ar}), 7.33 (1H, t, $^3J_{HH}$ 7.5 Hz, CH_{Ar}), 7.41-7.48 (2H, m, CH_{Ar}), 8.17-8.25 (1H, m, CH_{Ar}), 8.58 (1H, d, $^3J_{HH}$ 5.1, $^4J_{HH}$ 1.5 Hz, CH_{Ar}), 8.84 (1H, d, $^3J_{HH}$ 1.5 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, CD_3Cl): 10.8, 25.7, 31.7, 34.8, 49.8, 54.2, 106.6, 124.8, 124.7, 126.4 (q, $^1J_{CF}$ 211.6 Hz), 127.8, 129.3, 133.3, 137.4, 138.1, 145.0, 149.6, 152.2, 159.9 (q, $^2J_{CF}$ 39.3 Hz), 162.8. ESI-TOF, *m/z*: 399 $[M-CF_3CO_2]^+$.

1,5-Dimethyl-2-phenyl-4-(1-(vinylsulfonyl)pyrrolidin-2-yl)-1,2-dihydro-3H-pyrazol-3-one (3q). Yellow oil (0.62g, 99%). Found: C 59.0; H 6.3, N 12.2; S 9.3%. Calc. for $C_{17}H_{21}N_3O_3S$: C 58.8; H 6.1; N 12.1; S 9.2%. IR (KBr): ν_{max}/cm^{-1} 1149, 1594, 1659. ^1H NMR (400 MHz, CD_3Cl): δ 1.79-1.94 (1H, m, CH_2), 2.01-2.25 (2H, m, CH_2), 2.28-2.38 (1H, m, CH_2), 2.32 (3H, s, CH_3), 3.10 (3H, s, CH_3), 3.46-3.60 (2H, m, CH_2), 4.60-4.69 (1H, m, CH), 5.78 (1H, d, $^3J_{HH}$ 10 Hz, CH), 6.08 (1H, d, $^3J_{HH}$ 16.5 Hz, CH), 6.41 (1H, dd, $^2J_{HH}$ 16.5, $^3J_{HH}$ 9.9 Hz, CH), 7.31-7.34 (3H, m, CH_{Ar}), 7.45 (2H, t, $^3J_{HH}$ 7.8 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, CD_3Cl): 11.0, 25.5, 31.7, 35.7, 49.1, 54.2, 108.1, 125.0, 126.4, 127.6, 128.3, 129.3, 134.0, 152.6, 163.7. ESI-TOF, *m/z*: 348 $[M+H]^+$, 370 $[M+Na]^+$.

2-(1-(Methylsulfonyl)pyrrolidin-2-yl)-1-phenylpyrazolidin-3-one (8a). White solid (0.47g, 85%), mp 143-144°C. Found (%): C 54.5; H 6.4; N 13.8; S 10.5%. Calc. for $C_{14}H_{19}N_3O_3S$ (%): C 54.4; H 6.2; N 13.6; S 10.4%. IR (KBr): ν_{max}/cm^{-1} 1150, 1593, 1724. ^1H NMR (600 MHz, $(CD_3)_2SO$) δ: 1.69-1.82 (2H, m, CH_2), 1.86-1.94 (1H, m, CH_2), 2.02-2.12 (1H, m, CH_2), 2.30-2.37 (2H, m, CH_2), 2.97 (3H, s, CH_3), 3.05-3.12 (1H, m, CH_2), 3.17-3.14 (1H, m, CH_2), 3.73-3.81 (2H, m, CH_2), 5.89-5.94 (1H, m, CH), 7.04 (1H, t, $^3J_{HH}$ 7.3 Hz, CH_{Ar}), 7.19 (2H, d, $^3J_{HH}$ 7.6 Hz, CH_{Ar}), 7.31 (2H, t, $^3J_{HH}$ 7.6 Hz, CH_{Ar}). ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ: 23.9, 29.5, 31.3, 36.0, 48.6, 58.0, 69.9, 119.3, 123.7, 129.3, 152.6, 176.2. ESI -TOF, *m/z*: 332 $[M+Na]^+$.

2-(1-(Ethylsulfonyl)pyrrolidin-2-yl)-1-phenylpyrazolidin-3-one (8b). White solid (0.36g, 63%), mp 120-121°C. Found (%): C 55.8; H 6.5; N 13.1; S 9.8%. Calc. for $C_{15}H_{21}N_3O_3S$ (%): C 55.7; H 6.6; N 13.0; S 9.9%. IR (KBr): ν_{max}/cm^{-1} 1143, 1593, 1719. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, $^3J_{HH}$ 7.4 Hz), 1.69-1.76 (1H, m, CH_2), 1.82-1.91 (1H, m, CH_2), 1.96-2.07 (2H, m, CH_2), 2.36-2.46 (1H, m, CH_2), 2.51-2.61 (1H, m, CH_2), 3.11 (3H, q, CH_3, $^3J_{HH}$ 7.4 Hz), 3.29-3.38 (1H, m, CH_2), 3.43-3.50 (1H, m, CH_2), 3.63-3.70 (1H, m, CH_2), 3.95-4.04 (1H, m, CH_2), 5.99-6.07 (1H, m, CH), 7.09 (1H, t, $^3J_{HH}$ 7.3 Hz, CH_{Ar}), 7.16 (d, 2H, $^3J_{HH}$ 7.6 Hz, CH_{Ar}), 7.16 (2H, t, $^3J_{HH}$ 7.6 Hz, CH_{Ar}). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 7.9, 23.5, 29.4, 31.1, 45.0, 48.7, 58.0, 69.3, 119.4, 124.2, 129.2, 152.2, 177.3. ESI-TOF, *m/z*: 324 $[M+H]^+$, 346 $[M+Na]^+$.

2-(1-((2-Chloroethyl)sulfonyl)pyrrolidin-2-yl)-1-phenylpyrazolidin-3-one (8c). White solid (0,41g, 62%), mp 108°C. Found (%): C 50.5; H 5.7; Cl 9.8; N 11.8; S 9.0%. Calc. for $C_{15}H_{20}ClN_3O_3S$ (%): C 50.4; H 5.6; Cl 9.9; N 11.7; S 8.96%. IR (KBr): ν_{max}/cm^{-1} 1146, 1595, 1721. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.68-1.80 (2H, m, CH_2), 1.81-1.94 (1H, m, CH_2), 2.03-2.10 (1H, m, CH_2), 2.11-2.17 (2H, m, CH_2), 2.29-2.40 (2H, m, CH_2), 3.22-3.36 (4H, m, CH_2), 3.69-3.86 (4H, m, CH_2), 5.91-5.99 (1H, m, CH), 7.06 (1H, t, $^3J_{HH}$ 7.3 Hz, CH_{Ar}), 7.18 (2H, d, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 7.31 (2H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}). ^{13}C NMR (150 MHz, $(CD_3)_2SO$)δ: 23.8, 26.8, 29.4, 31.2, 43.8, 46.9, 48.7, 58.0, 69.7, 119.4, 123.9, 129.4, 152.6, 176.3. MALDI-TOF, *m/z*: 394 $[M+Na]^+$.

1-Phenyl-2-(1-(phenylsulfonyl)pyrrolidin-2-yl)pyrazolidin-3-one (8d). White solid (0.49g, 74%), mp 126-127°C. Found (%): C 64.5; H 5.8; N 11.5; S 8.8%. Calc. for $C_{19}H_{21}N_3O_3S$ (%): C 61.4; H 5.7; N 11.3; S 8.6%. IR (KBr): ν_{max}/cm^{-1} 1164, 1597, 1709. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.31-1.47 (1H, m, CH_2), 1.58-1.71 (2H, m, CH_2), 1.71-1.87 (1H, m, CH_2), 2.28-2.44 (2H, m, CH_2), 3.06-3.15 (1H, m, CH_2), 3.19-3.28 (1H, m, CH_2), 3.68-3.80 (2H, m, CH_2), 5.67-5.77 (1H, m, CH), 7.05 (1H, t, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.18 (2H, d, $^3J_{HH}$ 7.4 Hz, CH_{Ar}), 7.30 (2H, t, $^3J_{HH}$ 7.9 Hz, CH_{Ar}), 7.67 (2H, t, $^3J_{HH}$ 7.6 Hz, CH_{Ar}), 7.74 (1H, t, $^3J_{HH}$ 7.5 Hz, CH_{Ar}), 7.89 (2H, d, $^3J_{HH}$ 7.2 Hz, CH_{Ar}). ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ: 23.4, 29.4, 30.8, 49.2, 58.1, 69.6, 119.4, 123.9, 127.6, 129.4, 130.0, 133.76, 137.7, 152.6, 176.6. MALDI-TOF, *m/z*: 394 $[M+Na]^+$, 410 $[M+K]^+$.

1-Phenyl-2-(1-tosylpyrrolidin-2-yl)pyrazolidin-3-one (8e). White solid (0.66g, 96%), mp 144-145°C. Found (%): C 62.4; H 6.1; N 10.8; S 8.4%. Calc. for $C_{20}H_{23}N_3O_3S$ (%):C 62.3; H 6.0; N 10.9; S 8.3%. IR (KBr): ν_{max}/cm^{-1} 1162, 1596, 1725. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.31-1.41 (1H, m, CH_2), 1.58-1.67 (2H, m, CH_2), 1.71-180 (1H, m, CH_2), 2.28-2.38 (1H, m, CH_2), 2.40 (3H, s, CH_3), 3.01-3.10 (1H, m, CH_2), 3.16-3.26 (1H, m, CH_2), 3.70-3.78 (2H, m, CH_2), 5.65-5.71 (1H, m, CH), 7.04 (1H, t, $^3J_{HH}$ 7.3 Hz, CH_{Ar}), 7.16 (2H, d, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.30 (2H, t, $^3J_{HH}$ 7.5 Hz, CH_{Ar}), 7.46 (2H, d, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 7.75 (2H, d, $^3J_{HH}$ 8.2 Hz, CH_{Ar}). ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ: 21.5, 21.5, 23.4, 29.4, 30.7, 49.2, 58.1, 69.5, 119.3, 123.9, 127.7, 129.4, 130.4, 134.7, 144.3, 152.5, 176.7. ESI-TOF, *m/z*: 408 $[M+Na]^+$.

2-(1-((4-Chlorophenyl)sulfonyl)pyrrolidin-2-yl)-1-phenylpyrazolidin-3-one (8f). White solid (0.33g, 45%), mp 168°C. Found (%): C 56.3; H 5.1; Cl 8.9; N 10.5; S 7.8%. Calc. for $C_{19}H_{20}ClN_3O_3S$ (%): C 56.2; H 5.0; Cl 8.7; N 10.4; S 7.9%. IR (KBr): ν_{max}/cm^{-1} 1162, 1595, 1731. ^1H NMR (600 MHz, $(CD_3)_2SO$) δ: 1.34-1.48 (1H, m, CH_2), 1.60-1.83 (3H, m, CH_2), 2.28-2.44 (2H, m, CH_2), 3.03-3.12 (1H, m, CH_2), 3.19-3.28 (1H, m, CH_2), 3.71-3.77 (2H, m, CH_2), 5.63-5.70 (1H, m, CH), 7.05 (1H, t, $^3J_{HH}$ 7.0 Hz, CH_{Ar}), 7.15 (2H, d, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.29 (2H, t, $^3J_{HH}$ 7.6 Hz, CH_{Ar}), 7.73 (2H, d, $^3J_{HH}$ 8.2 Hz, CH_{Ar}), 7.87 (2H, d, $^3J_{HH}$ 8.4 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 23.3, 29.3, 30.6, 49.2, 58.0, 69.5, 119.3, 124.0, 129.4, 129.5, 130.1, 136.4, 138.8, 152.4, 176.7. ESI-TOF, *m/z*: 428 $[M+Na]^+$.

N-(4-((2-(5-oxo-2-phenylpyrazolidin-1-yl)pyrrolidin-1-yl)sulfonyl)phenyl)acetamide (8g). White solid (0.73g, 95%), mp 86-87°C. Found (%): C 58.8; H 5.8; N 13.2; S, 7.9%. Calc. for $C_{21}H_{24}N_4O_4S$ (%): C, 58.9; H, 5.7; N, 13.1; S, 7.8%. IR (KBr): ν_{max}/cm^{-1} 1159, 1592, 1695, 2988, 3058. ^1H NMR (600 MHz, $(CD_3)_2SO$) δ: 1.30-1.41 (1H, m, CH_2), 1.56-1.70 (2H, m, CH_2), 1.72-1.82 (1H, m, CH_2), 2.10 (3H, s, CH_3), 2.30-2.43 (2H, m, CH_2), 3.04-3.10 (1H, m, CH_2), 3.18-3.24 (1H, m, CH_2), 3.69-3.79 (2H, m, CH_2), 5.65-5.73 (1H, m, CH), 7.04 (1H, t, $^3J_{HH}$ 6.8 Hz, CH_{Ar}), 7.17 (2H, d, $^3J_{HH}$ 7.6 Hz, CH_{Ar}), 7.29 (2H, t, $^3J_{HH}$ 7.3 Hz, CH_{Ar}), 7.80 (2H,

d, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 7.85 (2H, d, $^3J_{HH}$ 8.4 Hz, CH_{Ar}), 10.51 (1H, s, NH). ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ: 23.4, 24.5, 24.6, 29.4, 30.8, 49.2, 58.1, 69.6, 117.2, 119.3, 123.8, 128.8, 129.3, 131.1, 144.1, 152.6, 169.7, 176.6. ESI-TOF, *m/z*: 451 $[M+Na]^+$.

2-(1-(Naphthalen-2-ylsulfonyl)pyrrolidin-2-yl)-1-phenylpyrazolidin-3-one (8h). White solid (0.55g, 73%), mp 153°C. Found (%): C 65.6; H 5.6; N 10,1; S 7.7%. Calc. for $C_{23}H_{23}N_3O_3S$ (%): C, 65.5; H, 5.5; N, 10.0; S, 7.6%. IR (KBr): ν_{max}/cm^{-1} 1157, 1531, 1718. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 1.28-1.40 (1H, m, CH_2), 1.56-1.67 (2H, m, CH_2), 1.70-1.80 (1H, m, CH_2), 2.25-2.43 (2H, m, CH_2), 3.07-3.18 (1H, m, CH_2), 3.21-3.31 (1H, m, CH_2), 3.70-3.77 (2H, m, CH_2), 5.75-5.80 (m, 1H, CH), 7.04 (1H, t, $^3J_{HH}$ 7.2 Hz, CH_{Ar}), 7.15 (2H, d, $^3J_{HH}$ 7.8 Hz, CH_{Ar}), 7.28 (2H, t, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.66-7.75 (2H, m, CH_{Ar}), 7.89 (1H, d, $^3J_{HH}$ 8.4 Hz, CH_{Ar}), 8.06 (1H, d, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 8.17 (2H, t, $^3J_{HH}$ 8.0 Hz, CH_{Ar}), 8.49 (1H, s, CH_{Ar}). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 23.4, 29.4, 30.7, 49.3, 58.0, 69.6, 119.3, 122.9, 123.9, 128.3, 128.3, 128.9, 129.3, 129.6, 129.8, 130.1, 132.2, 134.8, 135.0, 152.4, 176.7. ESI-TOF, *m/z*: 444 $[M+Na]^+$.

1-Phenyl-2-(1-(pyridin-3-ylsulfonyl)pyrrolidin-2-yl)pyrazolidin-3-one (8i). White solid (0.38g, 57%), mp 153-154°C. Found (%): C 58.3; H 5.5; N 15.1; S 8.7%. Calc. for $C_{18}H_{20}N_4O_3S$ (%): C 58.1; H 5.4; N 15.0; S 8.6%. IR (KBr): ν_{max}/cm^{-1} 1170, 1597, 1718, 2992. ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ: 1.34-1.49 (1H, m, CH_2), 1.58-1.69 (1H, m, CH_2), 1.72-1.82 (2H, m, CH_2), 2.24-2.48 (m, 2H, CH_2), 3.15-3.23 (m, 1H, CH_2), 3.26-3.34 (m, 1H, CH_2), 3.69-3.82 (m, 2H, CH_2), 3.66-3.73 (1H, m, CH), 7.06 (1H, t, $^3J_{HH}$ 7.3 Hz, CH_{Ar}), 7.17 (2H, d, $^3J_{HH}$ 7.6 Hz, CH_{Ar}), 7.30 (2H, t, $^3J_{HH}$ 7.9 Hz, CH_{Ar}), 7.22 (1H, dd, $^3J_{HH}$ 8.7 Hz, $^4J_{HH}$ 4.9 Hz, CH_{Ar}), 8.28 (1H, dt, $^3J_{HH}$ 8.1 Hz, $^5J_{HH}$ 1.6 Hz, CH_{Ar}), 8.91 (1H, dd, $^3J_{HH}$ 4.8 Hz, $^5J_{HH}$ 1.5 Hz, CH_{Ar}), 9.04 (1H, d, $^3J_{HH}$ 2.2 Hz, CH_{Ar}). ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 23.3, 29.4, 30.6, 49.3, 58.0, 69.5, 119.4, 124.0, 125.1, 129.4, 134.2, 135.7, 148.0, 152.5, 154.3, 176.7. ESI-TOF, *m/z*: 488 $[M+H]^+$.

1-Phenyl-2-(1-(vinylsulfonyl)pyrrolidin-2-yl)pyrazolidin-3-one (8j). White solid (0.35g, 62%), mp 104-105°C. Found (%): C 56.2; H, 6.1; N 13.2; S 10.1%. Calc. for $C_{15}H_{19}N_3O_3S$ (%): C 56.1; H 6.0; N 13.1; S 10.0%. IR (KBr): ν_{max}/cm^{-1} 1150, 1595, 1734. ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ: 1.62-1.69 (1H, m, CH_2), 1.72-1.79 (1H, m, CH_2), 1.84-1.91 (1H, m, CH_2), 1.94-2.03 (1H, m, CH_2), 2.34 (2H, t, CH_2, $^3J_{HH}$ 7.1 Hz), 3.09 (2H, t, CH_2, $^3J_{HH}$ 7.0 Hz), 3.78 (2H, t, CH_2, $^3J_{HH}$ 7.1 Hz), 5.76-5.83 (1H, m, CH), 6.12-6.20 (2H, m, CH_2), 6.90 (1H, dd, CH, $^2J_{HH}$ 16.4 Hz, $^3J_{HH}$ 10.1 Hz), 7.05 (1H, d, $^3J_{HH}$ 7.2 Hz, CH_{Ar}), 7.20 (2H, d, $^3J_{HH}$ 7.7 Hz, CH_{Ar}), 7.31 (2H, t, $^3J_{HH}$ 7.9 Hz, CH_{Ar}). ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ: 23.9, 29.4, 31.2, 48.7, 58.1, 69.9, 119.3, 123.8, 129.2, 129.3, 133.2, 152.6, 176.2. MALDI-TOF, *m/z*: 344 $[M+Na]^+$.

Biological studies

Bacterial strains and cultivation conditions. The strain of *Vibrio aquamarinus* DSM 26054 and *Acinetobacter calcoaceticus* VKPM B-10353 were used to study the biofilms formation. *A. calcoaceticus* VKPM B-10353 strain was grown in Luria-Bertani (LB) medium.[65] *V. aquamarinus* DSM 26054 strain was grown in LB medium supplemented with 3% NaCl.

Chemicals. All of the chemicals used were of analytical grade. Crystal violet was obtained from «Sigma-Aldrich» (USA). DMSO was obtained from «Serva» (Russia). Test solutions were prepared immediately before the tests.

Compounds preparation. The test compounds were dissolved in DMSO to the concentration of 1x10^{-2} M. Further dilutions were prepared by adding ethanol. The control solutions were analogous dilutions of DMSO in ethanol.

Test system for biofilm formation evaluation. To quantify the formation of biofilms, the crystal violet assay with some modifications was used.[66] The necessary concentrations of the test compounds were prepared as described above.

V. aquamarinus DSM 26054 was cultivated for 24 hours in LB medium supplemented with 3% NaCl in the Innova 40R shaker incubator («New Brunswick Scientific», USA) at 25°C and 200 rpm. *A. calcoaceticus* VKPM B-10353 was cultivated for 24 hours in LB medium in the Innova 40R shaker incubator («New Brunswick Scientific», USA) at 30°C and 200 rpm. Then, a suspension of the daily culture was diluted with culture medium to the density of 3×10^8 cells/ml (1 MacFarland standart). Turbidity was measured with DEN-1 («BioSan») instrument.

The resulting suspension (190 µl) was added to the wells of a polystyrene microplate ("Nuova Aptaca", Italy). To some of the wells, 10 µl of the test substances at various concentrations were added. Since solvents used could also influence the biofilm formation, 10 µl of the appropriate solvent was added to the other part of the wells at same dilutions. Sterile nutrient broth was used as negative control. To a part of the 10 µl of deionized water was added, which was used as a positive control. Eight replicates were done for each treatment and control. The microplate was covered with a lid and wrapped with a Parafilm ("Bemis Company, Inc.", USA). Evaluation of the effect of the studied substances on the biofilm formation was carried out by comparing the results of the experiment with the corresponding controls to the solvent.

After incubation at 25°C for 72 hours (*V. aquamarinus* DSM 26054) or at 30°C for 24 hours (*A. calcoaceticus* VKPM B-10353), biofilms were stained. The contents in the wells were removed by means of a dispenser. The wells were then carefully washed three times with 250 µl of sterile saline. The microplates were shaken to remove all non-adherent bacteria. Biofilms were fixed with 200 µl of 96 % ethanol for 15 minutes.

After the microplates had dried in air, 200 µl of 0.5 % crystall violet prepared according to Hooker[67] was introduced into the wells. After 10 minutes, the dye was removed. The excess dye was removed by washing with 250µl of water three times. After the microplates were air-dried, the dye in the wells bound to biofilms was dissolved with 200 µl of 96 % ethanol. The extraction level (absorption) of crystal violet by ethanol was measured after 60 minutes at a wavelength of 570 nm using a FLUOstar Omega microplate reader ("BMG Labtech", Germany) in optical density units (OD_{570}). The intensity of biofilm formation directly corresponds to the intensity of staining of the contents of the wells with the dye. Biofilm formation was determined by the difference between the mean OD readings obtained in the presence of compounds and the control.

Each experiment was performed in triplicate. The values were expressed as mean ± SD. Student's T-test was used to compare these values. Differences were considered statistically significant at $p< 0.05$.

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