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Tandem synthesis, antibacterial evaluation and SwissADME prediction study of new bis(1,3,4-oxadiazoles) linked to arene units

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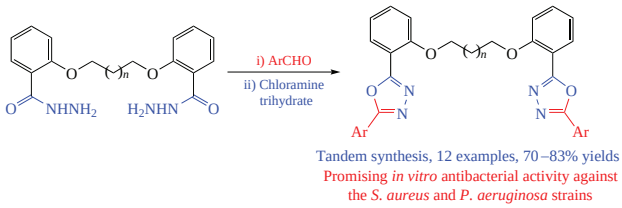
A three-component tandem protocol involving the reactions of bis(benzohydrazides), aromatic aldehydes and chloramine trihydrate yielded a new series of bis(1,3,4-oxadiazoles). The target hybrids were formed by an initial bis(*N*-benzoylhydrazones) formation, followed by chloramine trihydrate-mediated oxidative cyclization. The 4-methoxyphenyl-containing compounds demonstrated promising antibacterial activity against the *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains with MIC value of 1.6 μM.



Keywords: *N*-acylhydrazones, benzohydrazide, chloramine trihydrate, intramolecular cyclization, *in vitro* antibacterial screening, multicomponent reactions, 1,3,4-oxadiazoles, oxidative cyclization, SwissADME prediction study, tandem reactions.

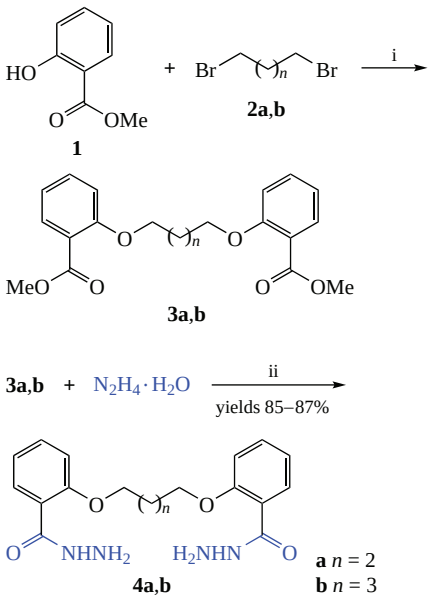
One of the most serious problems confronting modern medicine is antimicrobial resistance.[1] Prior resistance complicates treatment and is estimated to kill over 700,000 people annually worldwide.[2,3] Unless this trend is altered, the previous figure could rise to 10 million by 2050, with Africa and Asia accounting for more than 4 million deaths every year.[4] Research efforts are working to create new antibacterial agents that will prevent the development of resistance.[5,6]

1,3,4-Oxadiazoles are excellent bio-isosteres of amides and esters with increased bioactivity *via* hydrogen-bonding interactions,[7] including anticonvulsant,[8] antitumor,[9] antiviral,[10] and anti-inflammatory[11] properties. They belong to a large class of potential antimicrobial scaffolds among which Furamizole[12] is used against a wide variety of strains, particularly *Staphylococcus aureus* strains.[13] This is due in part to the presence of a toxophoric –N=C–O– linkage unit which may react with the microbial cells nucleophilic centers.[14] According to Zheng *et al*.,[15] 1,3,4-oxadiazoles may affect the transcription of biofilm-related genes like sarA and fnbB, which are required for biofilm formation.

Oxidative cyclization of *N*-acylhydrazones[16,17] and dehydrative cyclization of 1,2-diacylhydrazines[18,19] are the general procedures for producing 2,5-diaryl-1,3,4-oxadiazoles. Condensation of aldehydes or carboxylic acids with hydrazides yields *N*-acylhydrazones[20] and 1,2-diacylhydrazines.[21]

In this study, we aimed to prepare a new series of bis(1,3,4-oxadiazoles) containing different arene units utilizing new bis(benzohydrazides)prepared by a tandem protocol (Scheme 1). Potassium carbonate-mediated bis-*O*-alkylation[22] of methyl salicylate **1** with α,ω-dibromoalkanes **2a**,**b** afforded bis(salicylates) **3**, which were then reacted with hydrazine hydrate to give bis(benzohydrazides) **4a**,**b**.[23]

Next, a tandem protocol was investigated to prepare the target bis(1,3,4-oxadiazoles) (Scheme 2). The typical synthesis of target **7a** comprised the reaction of bis(benzohydrazide) **4a** with benzaldehyde **5a** in pyridine at 110 °C for 60 min. After the condensation step[24] was completed, crude intermediate bis(*N*-benzoylhydrazone) **6** was then subjected to oxidative cyclization. Different reagents, mediums, reaction time and temperature were examined to select the optimal reaction conditions (see Online Supplementary Materials).[25–28] The best conditions involved the use of three equivalents of chloramine trihydrate in ethanol at 80 °C for 150 min (for the detailed mechanism of the heterocyclization, see Online Supplementary Materials).[29] With this protocol, bis(benzohydrazides) **4a**,**b** were reacted first with different aromatic aldehydes **5a**–**f** and then with chloramine trihydrate to afford the target bis(1,3,4-oxadiazoles) **7a**–**f** and **8a**–**f** in 70–83% yields (see Scheme 2).



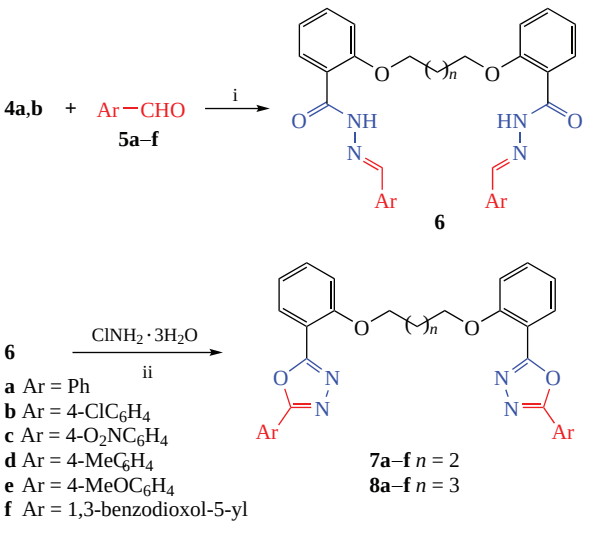
Scheme 1 *Reagents and conditions*: i, K_2CO_3, DMF, room temperature, 6 h; ii, EtOH, 80 °C, 3 h.

Table 1 MIC values in μM of new bis(1,3,4-oxadiazoles) **7a–f** and **8a–f**.

Compound	MIC / μM					
	S. aureus	*S. mutans*	*E. faecalis*	*E. coli*	*P. aeruginosa*	*K. pneumoniae*
7a	7.3	> 250	235.6	29.4	14.7	235.6
7b	26.0	> 250	> 250	52.1	13.0	> 250
7c	25.1	> 250	> 250	50.3	25.1	> 250
7d	3.4	> 250	111.8	27.9	3.4	223.7
7e	1.6	> 250	105.8	26.4	1.6	105.8
7f	3.1	> 250	202.0	25.2	3.1	101.0
8a	7.2	> 250	229.5	28.6	14.3	229.5
8b	12.7	> 250	> 250	50.9	25.4	> 250
8c	24.6	> 250	> 250	49.2	24.6	> 250
8d	3.4	> 250	218.3	54.5	3.4	109.1
8e	1.6	> 250	103.3	25.8	1.6	103.3
8f	3.0	> 250	98.7	24.6	3.0	197.5
Ciprofloxacin	2.9	2.9	2.9	2.9	2.9	2.9

New bis(1,3,4-oxadiazoles) **7** and **8** were screened *in vitro* against each of *Staphylococcus aureus* (ATCC:6538), *Streptococcus mutans* (ATCC:25175), *Enterococcus faecalis* (ATCC:29212), *Escherichia coli* (ATCC:9637), *Pseudomonas aeruginosa* (ATCC:27953), and *Klebsiella pneumoniae* (ATCC:10031) bacterial strains. The MIC values against the selected strains were assessed using the microbroth serial dilution method using ciprofloxacin as a standard drug (MIC values of 2.9 μM) (see Table 1).[30,31] Compounds **7e** and **8e** displayed more effective antibacterial activity than ciprofloxacin against the *S. aureus* and *P. aeruginosa* strains with MIC values of 1.6 μM. Moreover, hybrids **7d**,**f** and **8d**,**f** showed comparable efficacy to ciprofloxacin with MIC values ranging from 3.0 to 3.4 μM against these strains. The remaining hybrids had lower activity, with MIC values ranging from 7.2 to 26.0 μM against the *S. aureus* strain and 13.0 to 25.4 μM against the *P. aeruginosa* strain. With regards to the *E. coli* strain, all tested hybrids displayed comparable efficacy with MIC values ranging from 25.2 to 54.5 μM. Additionally, all tested bis(1,3,4-oxadiazoles) showed weak antibacterial activity against the *S. mutans*, *E. faecalis*, and *K. pneumoniae* bacterial strains. They had MIC values in the range of 98.7 to more than 250 μM.

The selectivity of bis(1,3,4-oxadiazoles) **7** and **8** against *S. aureus* and *P. aeruginosa* strains is consistent with studies on similar hybrids by Navin[32] and Rezki.[33] Several papers have been published in an attempt to explain the mechanism of action of 1,3,4-oxadiazoles on above bacterial strains. As a result, Hofny[34] and Omar[35] reported the ability of 1,3,4-oxadiazoles to inhibit bacterial topoisomerases II (DNA gyrase) and IV, which are required for bacterial DNA replication. Furthermore, Shingare[36] demonstrated that 1,3,4-oxadiazoles have the ability to inhibit MurD ligase, an enzyme involved in the biosynthesis of cytoplasmic peptidoglycan precursor.



Scheme 2 *Reagents and conditions*: i, pyridine, 110 °C, 45–75 min; ii, $ClNH_2 \cdot 3H_2O$ (3 equiv.), EtOH, 80 °C, 120–180 min.

SwissADME (http://www.swissadme.ch) was used to estimate physicochemical properties, lipophilicity, and drug likeness of new compounds (see Online Supplementary Materials).[37] Lipinski's rule of five states that orally active drugs must not violate more than one of the following physicochemical properties: molecular weights (MW) ⩽ 500, hydrogen bond donors (HD) ⩽ 5, hydrogen bond acceptors (HA) ⩽ 10 and the partition coefficient between octanol and water (log $P_{o/w}$) ⩽ 5.[38] According to this rule, the hybrids **7a**,**d**,**e** and **8a**,**d**,**e** violate only one parameter (MW > 500) and are thus classified as drug-like. Other hybrids are not classified as drug-like scaffolds because they violate two parameters: hybrids **7b** and **8b** had MW > 500 and log $P_{o/w}$ > 5, whereas hybrids **7c**,**f**, and **8c**,**f** had MW > 500 and HA > 10.

To summarize, a tandem protocol was used to produce new bis(1,3,4-oxadiazoles) *via* initial formation of the intermediate bis(*N*-benzoylhydrazones) followed by their oxidative cyclization using chloramine trihydrate. Some of the new hybrids demonstrated promising antibacterial activity against *S. aureus* and *P. aeruginosa* strains and could be classified as drug-like, as predicted by SwissADME.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.014.

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