Chemistry Europe
European Chemical Societies Publishing

Synthesis and Antimicrobial Evaluation of Bis-morpholine Triazine Quaternary Ammonium Salts

Andrea Morandini,[a] Benedetta Leonetti,[b] Pietro Riello,[a, c] Roberto Sole,[a, d] Vanessa Gatto,[a, e] Isabella Caligiuri,[f] Flavio Rizzolio,[a, f] and Valentina Beghetto*[a, e]

Efficient, environmentally and economically sustainable, and nontoxic antibacterial products are of global relevance in the fight against microorganism contamination. In this work, an easy and straightforward method for the synthesis of bis-morpholino triazine quaternary ammonium salts (bis-mTQAS) is reported, starting from 2,4,6-trichloro-1,3,5-triazine or 2,4-dichloro-6-methoxy-1,3,5-triazine and various *N*-alkylmorpholines. Bis-mTQAS were tested as antimicrobials against Gram-negative and Gram-positive bacterial strains. The best-performing bis-mTQAS were found to achieve total disinfection against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 at 50 and 400 μg/mL, respectively. Distinctively, bis-mTQAS with the highest antimicrobial efficiency had lowest cytotoxicity.

Today, the fight against infectious diseases still poses a serious challenge for healthcare worldwide.[1] According to statistical data reported in the literature, bacteria are becoming quickly resistant to commercially available antibiotics and antiseptics.[2]

Since their first introduction by Domagk in 1935,[3] quaternary ammonium salts (QAS) have become among the most widespread and used disinfectants worldwide.[4]

Generally, QAS contain four alkyl, aryl or heterocyclic groups bonded to a nitrogen atom (see Figure 1) and are subdivided into mono-, bis- and multi-QAS according to the overall charge present on the compound. The number of charges and the nature of the functional groups bonded to the nitrogen atom define both the physicochemical properties of QAS and their antimicrobial activity and toxicity.[5] Commercially available mono-QAS such as benzalkonium chloride, cetylpyridinium chloride, cetyltrimethylammonium chloride, have been widely used for different applications (Figure 1).[6]

As far as their mechanism is concerned, it is generally accepted that positively charged QAS electrostatically interact with the surface of the bacterial membrane (negatively charged) and penetrate the cell wall; this phenomenon is promoted by the affinity of the long lipophilic chain within the cell membrane (Figure 2) gradually causing the cell death.[7]

Thus, antimicrobial efficiency of QAS depends on the presence of a hydrophobic chain (tail), which is similar in structure to the bilayer of the membrane, and one or more polar "heads" interacting with the phospholipid acids. One of the disadvantages of QAS is their high toxicity together with

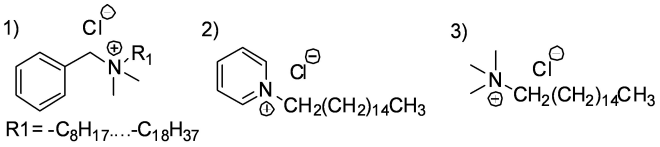


Figure 1. Examples of commercially available mono-QAS. 1) benzalkonium chloride, 2) cetylpyridinium chloride, 3) cetyltrimethylammonium chloride.

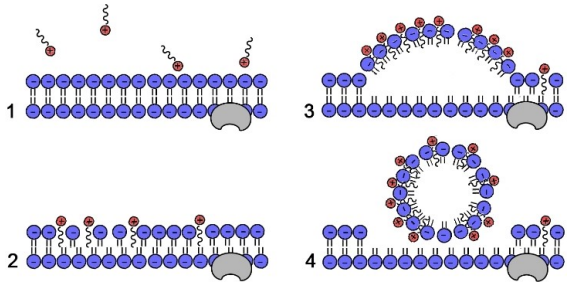


Figure 2. General mechanism of action of QAS where the phospholipid membranes are indicated in blue and quaternary ammonium salts in red.

[a] Dr. A. Morandini, Prof. P. Riello, Dr. R. Sole, V. Gatto, Prof. F. Rizzolio, Prof. V. Beghetto
Dipartimento di Scienze Molecolari e Nanosistemi
Università Ca' Foscari di Venezia
Via Torino 155, 30172, Venezia Mestre, (Italy)
E-mail: beghetto@unive.it
[b] B. Leonetti
Brenta S.r.l. – Nine trees group
Viale Milano, 26, 36075 Montecchio Maggiore Vicenza (Italy)
[c] Prof. P. Riello
European Centre for Living Technology (ECLT)
Ca' Bottacin, Dorsoduro 3911, 30123 Venice (Italy)
[d] Dr. R. Sole
CIRCC,
via C. Ulpiani 27, 70126 Bari, Italy
[e] V. Gatto, Prof. V. Beghetto
Crossing S.r.l.
Viale della Repubblica 193/b, 31100 Treviso (Italy)
[f] I. Caligiuri, Prof. F. Rizzolio
Pathology Unit,
Centro di Riferimento Oncologico (CRO) IRCCS
Via F. Gallini 2, 33081, Aviano (Italy)

Supporting information for this article is available on the WWW under https://doi.org/10.1002/cmdc.202100409

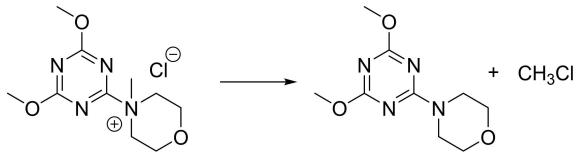
the development of bacterial resistance.[8,9] On the contrary, bis-QAS are more efficient as antimicrobials, less toxic and induce lower bacterial resistance compared to mono-QAS.[10]

Additionally, QAS are mostly prepared by direct alkylation of a tertiary amine in the presence of haloalkanes[11] requiring high temperatures, long reaction times and often, toxic reagents.[11b]

Our research group has long been interested in sustainability issues related to reduced consumption of toxic chemicals, process simplification and implementation of industrial sustainability.[12]

In this concern, extensive studies have been carried out on the synthesis and use of 1,3,5-triazine derived quaternary ammonium salts, such as 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chloride (**4**, Scheme 2) as dehydro-condensation agents for the synthesis of fine chemicals and polymers.[13] Although **4** is a quaternary ammonium salt, the possibility to use **4** or similar triazine based QAS as antimicrobial agents has never been taken into consideration and therefore, we deemed it interesting to verify this possibility.

Few features have been taken into consideration to achieve the proposed objective: **4** and other triazine derived quaternary ammonium salts prepared according to the literature are very efficient and reactive dehydro-condensation agents with reduced stability in solution.[14] It is generally accepted that the presence of a methyl substituent on the tertiary amine improves the reactivity of the condensation agent and consequently reduces its stability in time. According to the literature **4** and in general 4-(4,6-dialkoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chlorides are subject to demethylation of the methyl-morpholine moiety leading to the formation of a neutral unreactive species (see Scheme 1).



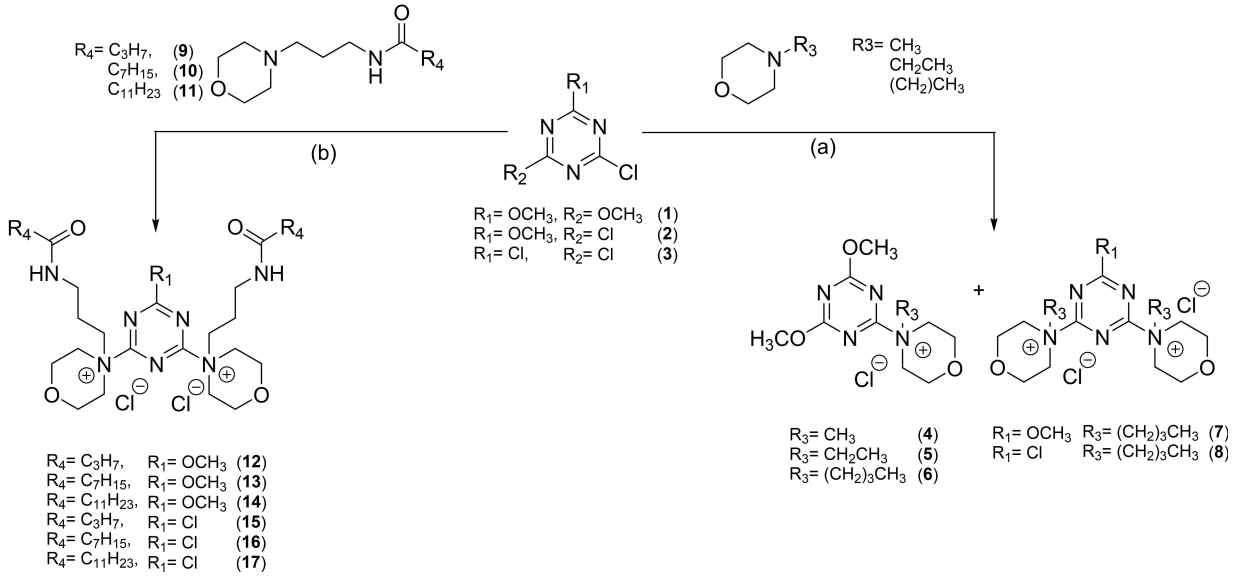
Scheme 1. Demethylation reaction of 4-(4,6-dialkoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium chlorides.

Since antimicrobial agents require to be stable in solution for long times, the stability of the triazine quaternary ammonium salts had to be improved. According to the literature substitution of the *N*-methyl group with an *N*-ethyl substituent should improve the stability of the triazine salt.

Further, efficient antimicrobial QAS require a hydrophobic chain and a hydrophilic head, *i.e.* one or more nitrogen atoms bearing a positive charge.[7a–b,10] Thus, we investigated the possibility to synthesize multi-charged TQAS similar to **4**, starting from 2-chloro-4,6-disubstituted-1,3,5-triazine and morpholino amines bearing hydrocarbon chains of different length (see Scheme 2a).

First experiments were carried out to study the stability of different triazine quaternary ammonium salts prepared by reaction of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and different tertiary amines, respectively *N*-methyl, *N*-ethyl and *N*-butyl morpholine (Scheme 2, compounds **4**–**6**), the synthesis of the first two compounds was already reported by Kunishima et al.[15] While water solutions of **4** totally decomposed within 48 h, 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-ethyl-morpholynium chloride (**5**) was stable in solution for over 60 days. These data clearly highlight that TQAS stability is strongly dependent on the nature of the amine, and careful choice of the tertiary amines allowed preparing very stable TQAS. Nevertheless, probably due to the absence of a long alkyl chain within the structure of **5**, this TQAS had no antimicrobial activity against bacterial strains tested.

Therefore, the possibility to prepare *N*-alkylmorpholine derived TQAS, bearing a long alkyl chain was tested starting



Scheme 2. Synthetic strategy and chemical structure of morpholine TQAS tested.

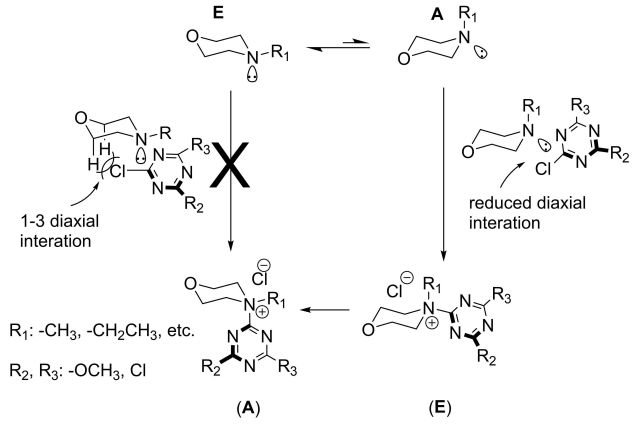
from commercially available *N*-butylmorpholine (**6**). Unfortunately, in all reaction conditions tested, *N*-butylmorpholine was totally unreactive towards CDMT and **6** could not be synthesized. This is probably to be ascribed to steric hindrance phenomena.

In fact, Kunishima et al. reported that **4** and similar triazine compounds obtained by reaction of CDMT and a cyclic aliphatic tertiary amine are formed by interchange of the less abundant equatorial conformer (**E**) of the amine which then rearranges to the most stable axial conformer (**A**).[15]

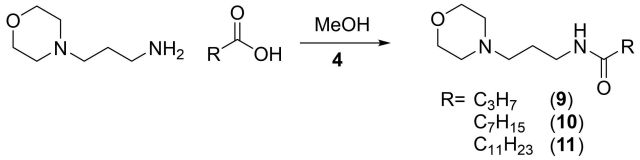
A similar behaviour may occur also for the formation of quaternary ammonium salts by reaction of 2,4-dichloro-1,3,5-triazine and 2,4,6-trichloro-1,3,5-triazine as reported in Scheme 3.[15]

In the case of **5**, steric hindrance is supposed to derive not only from the substituents present on the triazine but also from the butyl-chain of the tertiary amine inhibiting the formation of the desired product.

To reduce steric hindrance and promote the formation of *N*-alkylmorpholine TQAS, an alternative synthetic strategy was adopted starting from 2,4-dichloro-6-methoxy-1,3,5-triazine or 2,4,6-trichloro-1,3,5-triazine (Scheme 2b), since the covalent radius of the Cl^- atom is smaller than the one of the $-OCH_3$ group, decreasing steric hindrance around the triazine core.[16] In this way, 4,4′-(6-methoxy-1,3,5-triazine-2,4-diyl)bis(4-butylmorpholin-4-ium)chloride (**7**) and 4,4′-(6-chloro-1,3,5-triazine-2,4-diyl)bis(4-butylmorpholin-4-ium)chloride (**8**) could be synthesized in very mild reaction conditions (see experimental). Nevertheless, as for **4** and **5**, also these two TQAS showed no antimicrobial activity.



Scheme 3. Possible mechanism of equatorial, axial interchange of conformer (**E**) and conformer (**A**).



Scheme 4. Synthesis of amidoamines **9**–**11**.

An adequate strategy to introduce longer alkyl chains on the structure of the triazine was evidently required. Commercially no morpholine with longer *N*-alkyl chains were available, so an alternative way to easily prepare a set of tertiary amines of variable carbon length was devised starting from 4-(3-aminopropyl)morpholine and different aliphatic carboxylic acids in the presence of **4** as dehydro-condensation agent (Scheme 4).

In fact, with this strategy tertiary amines with up to twelve carbon atoms were synthesized in good yield, from easily available, cost effective and nontoxic chemicals. According to the synthetic strategy reported in Scheme 1, 4,4′-(6-methoxy-1,3,5-triazine-2,4-diyl)bis(4-(3-alkylamidopropyl)morpholin-4-ium) chlorides (**12**–**14**), were prepared by reaction of **2** and amidoamines **9**–**11**, and analogously 4,4′-(6-chloro-1,3,5-triazine-2,4-diyl)bis(4-(3-alkylamidopropyl)morpholin-4-ium) chlorides (**15**–**17**), by reaction of **3** and amidoamines **9**–**11**, at room temperature in 1 h. All compounds were fully characterized, and data are reported in the supporting information section.

Interestingly, according to the ESI-MS analysis only disubstituted compounds were isolated even if 2,4-dichloro-6-methoxy-1,3,5-triazine or 2,4,6-trichloro-1,3,5-triazine and amidoamines **9**–**11** were used in a molar ratio 1/1. According to the literature this behaviour may be explained because of the strong electron-withdrawing character of the NR_3^+ substituent[13b,17] promoting nucleophilic substitution in meta position, despite the presence of very bulky amidoamines **9**–**11**. In fact, according to the Hammett substituent constants,[18] different NR_3^+ have σ_m between $+0.86$ and $+1.76$, thus highly more electron-withdrawing than $-Cl$ (σ_m $+0.37$) or $-OMe$ (σ_m $+0.12$), justifying the high reactivity of the $-Cl$ atoms of intermediate mono-TQAS species, promoting the formation of bis-mTQAS.

Also, for TQAS **15**–**17**, double substitution products prevailed while no trisubstituted products were formed with any of the amidoamines tested, probably due to the high steric hindrance of the two substituents and to the low solubility of **15**–**17** in the reaction solvent, preventing further substitution.

Antimicrobial activity of these morpholinium bis-mTQAS was evaluated against Gram-positive (*Staphylococcus aureus* ATCC 25923) and Gram-negative (*Escherichia coli* ATCC 25922) bacterial strains. The lipophilicity of the synthesized bis-mTQAS was expressed in terms of their partition coefficient values (Log*P*) calculated using online platform Chemicalize (ChemAxon).[21] TQAS **12** and **15** still showed no inhibition against *S. aureus* and *E. coli*, even at concentrations above 400 μg/mL (Table 1). As the length of the alkyl chain present on the quaternary ammonium salts increased, a gradual improvement of the efficacy of bis-mTQAS was observed. In particular, best inhibition was achieved with compound **16**, giving total inhibition towards *S. aureus* at concentrations of 50 μg/mL and for *E. coli* at 400 μg/mL. These data are comparable to the activity of other bis-QAS reported in the literature, giving MIC values between 8 and 83 mgμg/mL[RS1] for Gram-positive bacterial strains, while higher concentrations are required for more resistant Gram-negative bacterial strains.[8,22] Generally,

Table 1. MIC, IC_{50} and Log*P* values of TQAS.[a]

Entry	TQAS	Chain length	*S. aureus* [μg/mL]	*E. coli* [μg/mL]	IC_{50} [μg/mL][b]	Log*P*[c]
1	**12**	8	>400	>400	36	−5.13
2	**13**	12	300	>400	34	−2.07
3	**14**	16	>400	300	62	+1.98
4	**15**	8	>400	>400	25	−4.91
5	**16**	12	50	400	59	−1.44
6	**17**	16	300	200	67	+2.60

[a] Minimal inhibitory concentration (MIC) was calculated taking as reference the negative control as the lowest concentration which inhibits bacterial growth. All the experiments were carried out both in biological and technical triplicate. [b] IC_{50} values were determined on eukaryotic fibroblasts MRC-5 cells. [c] Log*P* calculated using online platform Chemicalize.

data achieved confirm what Gilbert and Moore reported about the selective effect of the length of the alkyl chain on Gram-positive and Gram-negative bacteria.[7c] Very recently Sapozhnikov[8a] reported the synthesis of mono-QAS containing aminoamides, prepared from different carboxylic acids and a dimethyl alkylamine, and highest MIC were observed with lauric acid residues in the amide fragment, in agreement with data reported in Table 1 for compound **16**.

To gain deeper insight into the behaviour of morpholine bis-mTQAS, Log*P* were calculated and are reported in Table 1. In the case of *S. aureus* for which morpholine bis-mTQAS are more efficient, a minimum between MIC values and Log*P* was observed, confirming that, as for QAS, lipophilicity and hydrophobicity of the compound influence the efficiency of bis-mTQAS, so that too long or too short alkyl chains adversely affect the antimicrobial activity of morpholine bis-mTQAS (See Figure 3).[23]

Interestingly, all IC_{50} of morpholino bis-mTQAS are rather high compared to other commercially available QAS indicating a low cytotoxicity profile of the compounds.[8,23] Distinctively, bis-mTQAS **16**, which gave best MIC, had one of the highest IC_{50}, consequently the most efficient antimicrobial bis-mTQAS corresponds also to one of the least cytotoxic. In general, the toxicity of QAS depends on the length of the alkyl chain and is correlated to the efficacy as antimicrobial, so that QAS bearing C12–C14 alkyl chains normally have highest MIC and lowest

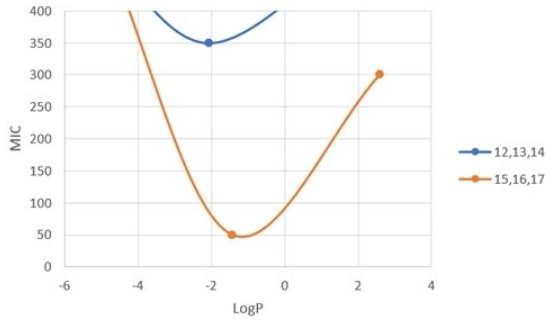


Figure 3. Graphical representation of Log*P* versus MIC values of compounds **12**–**17** against *S. aureus* bacterial strain.

IC_{50}. In the case of morpholinium bis-mTQAS there seems to be an opposite correlation between the chain length and the toxicity of the product (compare entries 1, 3 or 4, 6, Table 1). Studies are in progress to further investigate this phenomenon.

In conclusion, in this work the synthesis of a promising new class of triazine derived antimicrobial agents has been reported. Distinctively, best MIC values were obtained with less toxic bis-mTQAS. Moreover, triazine moiety has been verified as an interesting core structure, highly reactive and versatile which will allow to prepare a plethora of new antimicrobial agents. Studies are in progress for the synthesis of different libraries of mono- and bis-TQAS and their use as antimicrobial agents.

Conflict of Interest

The authors declare no conflict of interest.

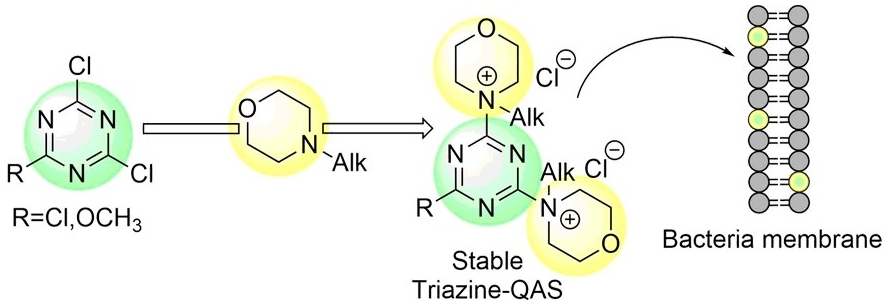
Keywords: triazine quaternary ammonium salts · antimicrobial agents · low toxicity antimicrobials · QAS

[1] a) Y. Zhao, Y. Jia, J. Xu, L. Han, F. He, X. Jiang, *Chem. Commun.* **2021**, *57*, 2998–3001; b) Z. Song, H. Wang, Y. Wu, J. Gu, S. Li, H. Han, *ACS Omega* **2018**, *3*, 14517–14525; c) P. I. Hora, S. G. Pati, P. J. McNamara, W. A. Arnold, *Environ. Sci. Technol. Lett.* **2020**, *7*, 622–631.
[2] a) N. A. Turner, B. K. Sharma-Kuinkel, S. A. Maskarinec, E. M. Eichenberger, P. P. Shah, M. Carugati, T. L. Holland, V. G. Fowler Jr, *Nat. Rev. Microbiol.* **2019**, *17*, 203–218; b) P. Collignon, *Intern. Med. J.* **2015**, *45*, 1109–1115.
[3] G. Domagk, *Dtsch. Med. Wochenschr.* **1935**, *61*, 829–832.
[4] a) S. E. Al-Khalifa, M. C. Jennings, W. M. Wuest, K. P. C. Minbiole, *ChemMedChem* **2017**, *12*, 280–283; b) N. W. Gunther, A. Abdul-Wakeel, E. R. Reichenberger, S. Al-Khalifa, K. P. C. Minbiole, *Food Control* **2018**, *94*, 187–194; c) O. Soukup, M. Benkova, R. Dolezal, R. Sleha, D. Malinak, S. Salajkova, A. Markova, M. Hympanova, L. Prchal, L. Ryskova, L. Hobzova, K. Sepčić, N. Gunde-Cimerman, J. Korabecny, D. Jun, V. Bostikova, P. Bostik, J. Marek, *Eur. J. Med. Chem.* **2020**, *206*, 1–23; d) B. M. P. Pereira, I. Tagkopoulos, *Appl. Environ. Microbiol.* **2019**, *85*, 1–13.
[5] a) Y. Jiao, L. Niu, S. Ma, J. Li, F. R. Tay, J. Chen, *Prog. Polym. Sci.* **2017**, *71*, 53–90; b) X. Xie, W. Cong, F. Zhao, H. Li, W. Xin, G. Hou, C. Wang, *J. Enzyme Inhib. Med. Chem.* **2017**, *33*, 98–105; c) U. Daood, J. P. Matinlinna, M. R. Pichika, K. Mak, V. Nagendrababu, A. S. Fawzy, *Sci. Rep.* **2020**, *10*, 10970.
[6] a) U. Tezel, S. G. Pavlostathis in *Antimicrobial Resistance in the Environment*, (Eds.: P. L. Keen, M. H. M. M. Montforts), Wiley-Blackwell, **2012**, pp. 349–387; b) C. P. Gerba, *Appl. Environ. Microbiol.* **2015**, *81*, 464–469.
[7] a) M. Tischer, G. Pradel, K. Ohlsen, U. Holzgrabe, *ChemMedChem* **2012**, *7*, 22–31; b) S. Zhang, S. Ding, J. Yu, X. Chen, Q. Lei, W. Fang, *Langmuir* **2015**, *31*, 12161–12169; c) P. Gilbert, L. E. Moore, *J. Appl. Microbiol.* **2005**, *99*, 703–715; d) D. Kwaśniewska, Y. Chen, D. Wieczorek, *Pathogenesis* **2020**, *9*, 459.
[8] a) S. V. Sapozhnikov, A. E. Sabirova, N. V. Shtyrlin, A. Y. Druk, M. N. Agafonova, M. N. Chirkova, R. R. Kazakova, D. Y. Grishaev, T. V. Nikishova, E. S. Krylova, E. V. Nikitina, A. R. Kayumov, Y. G. Shtyrlin, *Eur. J. Med. Chem.* **2021**, *211*, 113100; b) O. Soukup, M. Benkova, R. Dolezal, R. Sleha, D. Malinak, S. Salajkova, A. Markova, M. Hympanova, L. Prchal, L. Ryskova, L. Hobzova, K. Sepcic, N. Gunde-Cimerman, J. Korabecny, D. Jun, V. Bostikova, P. Bostik, J. Marek, *Eur. J. Med. Chem.* **2020**, *206*, 112584.
[9] a) U. Tezel, S. G. Pavlostathis, *Curr. Opin. Biotechnol.* **2015**, *33*, 296–304; b) G. Baysal, H. Aydın, S. Uzan, H. Hoşgören, *Russ. J. Phys. Chem. B* **2018**, *12*, 695.
[10] M. C. Jennings, K. P. C. Minbiole, W. M. Wuest, *ACS Infect. Dis.* **2015**, *1*, 288–303.
[11] a) W. R. Brasen, C. R. Hauser, *Org. Synth.* **1954**, *34*, 58; b) K. H. Kosswig, in *Ullmann's Encyclopedia of Industrial Chemistry, Vol. 35*, Wiley-VCH,

Weinheim, **2012**, pp. 431–506; c) F. Xi, C. P. Lilly, W. Bassett, O. Vogl, *Monatsh. Chem.* **1985**, *116*, 401–412.
[12] a) R. Sole, L. Taddei, C. Franceschi, V. Beghetto, *Molecules* **2019**, *24*, 2979; b) A. Scrivanti, M. Bortoluzzi, R. Sole, V. Beghetto, *Chem. Pap.* **2018**, *72*, 799–808; c) S. Paganelli, M. M. Alam, V. Beghetto, A. Scrivanti, E. Amadio, M. Bertoldini, U. Matteoli, *Appl. Catal. A* **2015**, *503*, 20–25; d) V. Beghetto, A. Scrivanti, M. Bertoldini, M. Aversa, A. Zancanaro, U. Matteoli, *Synthesis* **2015**, *47*, 272–278.
[13] a) R. Sole, V. Gatto, S. Conca, N. Bardella, A. Morandini, V. Beghetto, *Molecules* **2021**, *26*, 191–205; b) R. Sole, L. Agostinis, S. Conca, V. Gatto, N. Bardella, A. Morandini, C. Buranello, V. Beghetto, *Synthesis* **2021**, *53*, 1672–1682; c) V. Beghetto, V. Gatto, S. Conca, N. Bardella, C. Buranello, G. Gasparetto, R. Sole, *Carbohydr. Polym.* **2020**, *249*, 116810.
[14] a) T. I. Al-Warhi, H. M. A. Al-Hazimi, A. El-Faham, *J. Saudi Chem. Soc.* **2012**, *16*, 97–116; b) M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki, S. Tani, *Tetrahedron* **1999**, *55*, 13159–13170; c) Z. J. Kaminski, P. Paneth, J. Rudzinski, *J. Org. Chem.* **1998**, *63*, 4248–4255.
[15] M. Kunishima, T. Ujigawa, Y. Nagaoka, C. Kawachi, K. Hioki, M. Shiro, *Chem. Eur. J.* **2012**, *18*, 15856–15867.
[16] a) E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., **1994**, p. 696; b) E. L. Eliel, S. H. Wilen, M. P. Doyle, *Basic Organic Stereochemistry*, John Wiley & Sons, Inc., **2001**, p. 443; c) J. A. Hirsch in *Topics in Stereochemisty, Vol. 1* (Eds.: N. L. Allinger, E. L. Eliel), John Wiley & Sons, Inc., **1967**, pp. 199–222.
[17] M. Kunishima, D. Kato, N. Kimura, M. Kitamura, K. Yamada, K. Hioki, *Beilstein J. Org. Chem.* **2016**, *12*, 1897–1903.
[18] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165–195.
[19] H. Taycher, M. Botoshansky, V. Shteiman, M. Kaftory, *Supramol. Chem.* **2001**, *13*, 181–192.
[20] K. W. Woods, C. Lai, J. M. Miyashiro, Y. Tong, A. S. Florjancic, E. K. Han, N. Soni, Y. Shi, L. Lasko, J. D. Leverson, E. F. Johnson, A. R. Shoemaker, T. D. Penning, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1940–1943.
[21] https://chemaxon.com/products/chemicalize.
[22] a) M. Soltani, T. J. Ravine, J. H. Davis, *Bioorg. Med. Chem. Lett.* **2021**, *36*, 127808–127813; b) A. Tăbăcaru, A. V. D. Botezatu, G. Horincar, B. Furdui, R. M. Dinică, *Molecules* **2019**, *24*, 2424.
[23] a) Z. H. Asadov, G. A. Ahmadova, R. A. Rahimov, S. Z. F. Hashimzade, S. M. Nasibova, E. H. Ismailov, S. A. Suleymanova, S. A. Muradova, N. Z. Asadova, F. I. Zubkov, *Colloids Surf. A* **2019**, *575*, 212–221; b) J. Ma, N. Liu, M. Huang, L. Wang, J. Han, H. Qian, F. Che, *J. Mol. Liq.* **2019**, *294*, 111669; c) R. Mancuso, R. Amuso, B. Armentano, G. Grasso, V. Rago, A. R. Cappello, F. Galiano, A. Figoli, G. De Luca, J. Hoinkis, B. Gabriele, *ChemPlusChem* **2017**, *82*, 1235.

Manuscript received: June 7, 2021
Revised manuscript received: July 18, 2021
Accepted manuscript online: July 20, 2021
Version of record online: ■■, ■■■

COMMUNICATIONS



*Dr. A. Morandini, B. Leonetti, Prof. P. Riello, Dr. R. Sole, V. Gatto, I. Caligiuri, Prof. F. Rizzolio, Prof. V. Beghetto**

An easy and straightforward methodology for the synthesis of bis-morpholino triazine quaternary ammonium salts (bis-mTQAS) is reported, starting from 2,4,6-trichloro-1,3,5-triazine or 2,4-dichloro-6-methoxy-1,3,5-triazine and various *N*-alkylmorpholines. These bis-mTQAS show significant promise as antimicrobial agents against Gram-negative and Gram-positive bacterial strains.