

J. Serb. Chem. Soc. 81 (3) 233–242 (2016)
JSCS–4842

Synthesis and antimicrobial evaluation of some novel thiomorpholine derived 1,4-disubstituted 1,2,3-triazoles

KUMARASWAMY BATTULA¹, SIRASSU NARSIMHA¹, VASUDEVAREDDY NAGAVELLI^{1*}, PRIYANKA BOLLEPELLI² and MUTHENENI SRINIVASA RAO²

¹Department of Chemistry, Kakatiya University, Warangal-506009, India and ²Chemical Biology Laboratory, Indian Institute of Chemical Technology, Hyderabad-500007, India

(Received 18 August, revised 13 October, accepted 21 October 2015)

Abstract: A convenient synthesis of novel 1,4-disubstituted 1,2,3-triazoles (**4a–j** and **5a–j**) is reported *via* copper(I)-catalyzed one pot [3+2] cycloaddition of various alkyl halides, sodium azide with 4-(prop-2-yn-1-yl)thiomorpholine and 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide. All the synthesized compounds were investigated for their antimicrobial activity. Compounds **4a**, **4b**, **4c**, **4g**, **5a** and **5j** against *Staphylococcus epidermidis*, **4a**, **5a** and **5d** against *Pseudomonas aeruginosa*, **4a**, **4b** and **4g** against *Klebsiella pneumoniae*, **4b**, **5a** and **5d** against *S. aureus* and **5b**, **5e** and **5j** against *Bacillus subtilis* showed excellent antibacterial activity compared to the standard drugs penicillin and streptomycin. Compounds **4c**, **4e**, **4f**, **4j**, **5c**, **5d**, **5g** and **5j** registered moderate antifungal activity as compared with the standard drug amphotericin B.

Keywords: one pot synthesis; copper-catalyzed; azide alkyne cycloaddition; alkyl azides; antimicrobial activity.

INTRODUCTION

Nowadays, bacterial infection remains a serious threat to human lives due to their increasing resistance towards current antibiotics. Thus, there is a big scope for the invention of new antimicrobial agents. 1,4-Disubstituted 1,2,3-triazoles are known to possess many activities, such as anti-HIV,^{1,2} antimicrobial,³ anticancer,^{4–6} anti-inflammatory⁷ and fluorescent,⁸ as well as inhibitors of kinase-3 β ^{9,10} and other enzyme inhibitors.^{11–13} The 1,2,3-triazole moiety-containing drug molecules, such as tazobactam,¹⁴ cefatrizine¹⁵ and carboxyamido-triazole (CAI),¹⁶ are available (Fig. 1).

There are various methods available for the one-pot synthesis of 1,4-disubstituted-1,2,3-triazoles.^{17–19} However, the copper(I)-catalyzed one-pot three-component cycloaddition of alkyl halides with sodium azide and terminal

* Corresponding author. E-mail: vasujac3@gmail.com
doi: 10.2298/JSC150818088B

alkynes is one of the best methods for the multicomponent regioselective synthesis of 1,4-disubstituted-1,2,3-triazoles.²⁰ This method was independently pioneered by Fokin *et al.*²¹ in 2004 through dramatic modification of the Huisgen 1,3-dipolar cycloaddition reaction.²²

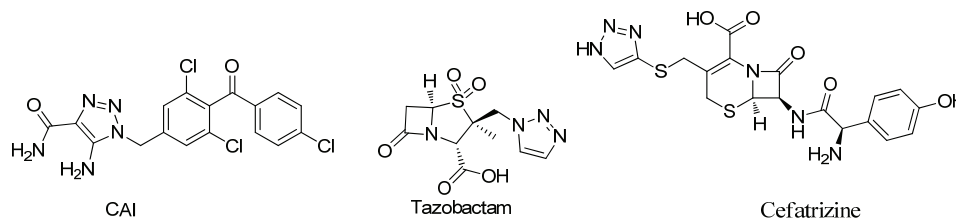


Fig. 1. Some 1,2,3-triazole ring-containing drugs on the market.

Previously, the synthesis and antibacterial activity of 1,2,3-triazole derivatives of morpholine-3-carboxylic acid ester were reported.²³ The morpholine moiety has played a significant role in medicinal chemistry.²⁴ Some of the morpholine ring-containing drugs are shown in Fig. 2. Thiomorpholine derivatives are known to exhibit biological activities including antimycobacterial,²⁵ anti-cancer,²⁶ anti-inflammatory and antioxidant agents²⁷ and dipeptidyl peptidase IV (DPP-IV) inhibitors.²⁸ In view of the above considerations and in continuation of ongoing research on the synthesis of 1,4-disubstituted-1,2,3-triazole derivatives, the synthesis of thiomorpholine derived 1,4-disubstituted-1,2,3-triazoles and their antimicrobial activity are reported herein.

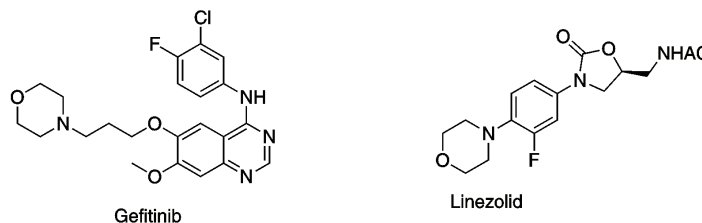


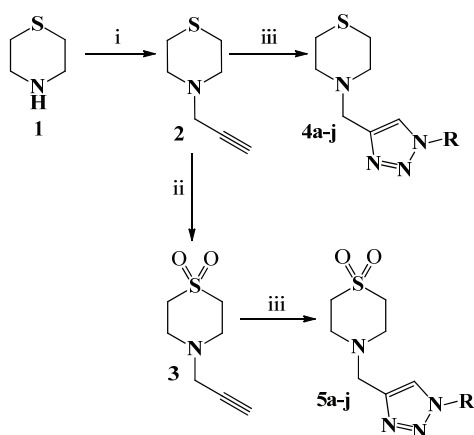
Fig. 2. Some of morpholine ring-containing drugs on the market.

RESULTS AND DISCUSSION

Chemistry

In the present work, a series of novel thiomorpholine derived 1,4-disubstituted-1,2,3-triazoles was synthesized employing the copper-catalyzed azide alkyne cycloaddition (CuAAC) reaction, Scheme 1. The 1,4-disubstituted-1,2,3-triazole derivatives were synthesized in a one-pot reaction, starting from alkyne, alkyl halide and sodium azide in the presence of Cu(I) catalyst. 4-(Prop-2-yn-1-yl)thiomorpholine (2) was synthesized by reacting thiomorpholine with propargyl bromide in the presence of Cs_2CO_3 in acetone at room temperature.

4-(Prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (**3**) was obtained by oxidation of the sulfur group in 4-(prop-2-yn-1-yl)thiomorpholine with 3-chloroperbenzoic acid (MCPBA) in dichloromethane at room temperature.²⁹ Cycloaddition of compounds **2** and **3** with *in situ* prepared alkyl azides in the presence of Cu(I) catalyst yielded 1,4-disubstituted-1,2,3-triazole derivatives **4a–j** and **5a–j** in good yields (Table I). The structures of the newly synthesized compounds were confirmed by spectral techniques, such as IR, ¹H-NMR, ¹³C-NMR and ESI-MS.

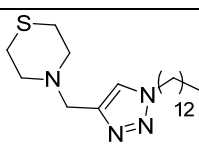
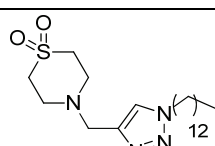
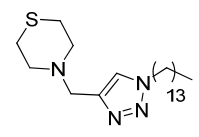
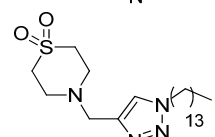
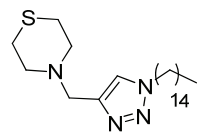
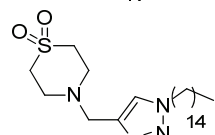
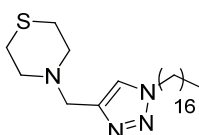
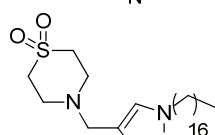
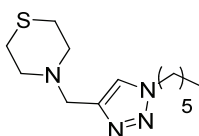
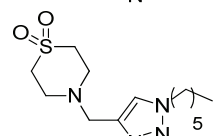
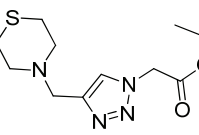
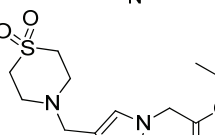
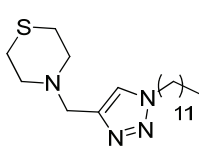
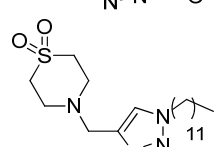


Scheme 1. Synthetic route to the 1,4-disubstituted-1,2,3-triazoles **4a–j** and **5a–j**. Reagents and conditions: i) propargyl bromide / Cs₂CO₃, acetone, r.t., 6 h; ii) MCPBA/DCM, r.t., 12 h; iii) R-Br / NaN₃, CuI, THF–H₂O (1:1), r.t.–50 °C, 8–12 h.

TABLE I. The 1,4-disubstituted-1,2,3-triazoles **4a–j** and **5a–j** synthesized from different alkyl bromides

| Entry | R ₁ -Br | Product | Entry | Product |
|-----------|------------------------------------|---------|-----------|---------|
| 4a | C ₇ H ₁₅ Br | | 5a | |
| 4b | C ₈ H ₁₇ Br | | 5b | |
| 4c | C ₁₀ H ₂₁ Br | | 5c | |

TABLE I. Continued

| Entry | R ₁ -Br | Product | Entry | Product |
|-----------|---|---|-----------|---|
| 4d | C ₁₃ H ₂₇ Br |  | 5d |  |
| 4e | C ₁₄ H ₂₉ Br |  | 5e |  |
| 4f | C ₁₅ H ₃₁ Br |  | 5f |  |
| 4g | C ₁₇ H ₃₅ Br |  | 5g |  |
| 4h | C ₆ H ₁₃ Br |  | 5h |  |
| 4i | C ₄ H ₇ O ₂ Br |  | 5i |  |
| 4j | C ₁₂ H ₂₅ Br |  | 5j |  |

Spectral analysis

The analytical and spectral data of the synthesized compounds are given in the Supplementary material to this paper. In general, compounds containing the 1,2,3-triazole ring show absorption in the region 3000–3100 cm⁻¹ in IR spectra. The newly synthesized compounds **4a–j** and **5a–j** exhibited a strong absorption band in the region 3018–3037 cm⁻¹, which confirmed the formation of the 1,2,3-triazole ring. For convenience, compound **4a** was selected for the NMR spectral

discussion. The presence of a singlet peak that appeared in the downfield region at 7.76 ppm (1H, *s*) confirmed the formation of the 1,2,3-triazole ring. The triplet that appeared at 4.35 ppm (2H *t*, $J = 7.32$ Hz) corresponded to an $-N-N-CH_2-$ group attached to a triazole ring. The singlet peak that appeared at 4.03 ppm (2H, *s*) corresponded to a $-CH_2-$ triazole group attached to thiomorpholine nitrogen. Two sets of multiplet signals that appeared in the upfield region 3.20–2.78 ppm (8H, *m*) corresponded to the thiomorpholine $-N-CH_2$ and $-S-CH_2$ groups. The multiplet peak present in the upfield region at 1.90–1.80 ppm (2H, *m*) corresponded to the $-N-N-CH_2-CH_2-$ group. The presence of one multiplet in the region 1.40–1.20 (8H, *m*) ppm confirmed the four methylene ($-CH_2-$) groups in the *n*-heptyl chain. The triplet peak that appeared in the upfield region at 0.87 ppm (3H, *t*, $J = 6.71$ Hz) corresponded to the methyl ($-CH_3$) group.

In the ^{13}C -NMR spectrum of compound **4a**, two carbon signals that appeared at 139.4 and 124.4 ppm confirmed the formation of the triazole ring. In the upfield region, the methyl group, thiomorpholine $-S-CH_2-$ and $-N-CH_2-$ carbons were observed at 13.7, 25.8 and 53.2 ppm, respectively. Five methylene ($-(CH_2)_5-$) group carbons were observed in the region 31.2–22.2 ppm. Thiomorpholine-N attached ($-N-CH_2-$) and triazole attached ($-N-N-CH_2-$) carbons were observed at 51.9 and 50.3 ppm, respectively. The ESI-mass spectra showed a 283 (M+H) peak, which confirmed the molecular weight of compound **4a**.

Antibacterial activity

All the synthesized compounds **4a–j** and **5a–j** were investigated for their *in vitro* antibacterial activity against various gram-positive microorganisms, *i.e.*, *Bacillus subtilis*, *Staphylococcus aureus* and *S. epidermidis*, and gram-negative microorganisms, *i.e.*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Penicillin and streptomycin were used as standard drugs for comparison. The results of the antibacterial activity screening (Table S-I of the Supplementary material to this paper) revealed that compound **4a**, possessing an 1-heptyl group on the triazole ring, showed excellent inhibition against *S. epidermidis*, *P. aeruginosa* and *K. pneumoniae* microorganisms with minimal inhibitory concentration (MIC) values of 2.34, 2.34 and 9.37 $\mu\text{g mL}^{-1}$, respectively. Compound **4b** having a 1-octyl group exhibited excellent inhibition against *S. epidermidis*, *S. aureus* and *K. pneumoniae* with MIC values of 1.17, 2.34 and 2.34 $\mu\text{g mL}^{-1}$, respectively. Compound **4c**, bearing 1-decyl substitution, showed very good inhibition against *S. epidermidis* as compared with the standard drugs. Compounds **4d**, **4e** and **4f**, possessing longer alkyl carbon chains on the triazole ring, showed no inhibition of any of the bacterial strains even at the highest concentration of 150 $\mu\text{g mL}^{-1}$. Whereas, compound **4g**, derived from the 1-heptadecyl group, exhibited excellent inhibition against *S. epidermidis* and *K. pneumoniae* strains with MIC values of 1.17 and 4.68 $\mu\text{g mL}^{-1}$, respectively. Surpris-

ingly, compound **4h**, derived from the 1-hexyl group, exhibited no inhibition against any of the bacterial strains even at the highest concentration of 150 $\mu\text{g mL}^{-1}$.

Compound **5a**, possessing 1-heptyl substitution on the triazole ring, showed equipotent inhibition against *S. aureus*, *S. epidermidis* and *P. aeruginosa* strains with MIC values of 2.34, 2.34 and 9.37 $\mu\text{g mL}^{-1}$, respectively, in comparison with the standard drugs. Compound **5b**, derived from the 1-octyl group, exhibited excellent inhibition of *B. subtilis* and *S. aureus* strains at lower concentrations (2.34 and 4.68 $\mu\text{g mL}^{-1}$). Moreover, compound **5d** against *P. aeruginosa* and **5e** against *B. subtilis* exhibited very good inhibition with MIC values of 4.68 and 9.37 $\mu\text{g mL}^{-1}$, respectively. Compounds **5f–i** exhibited no inhibition of any of the tested strains even at the highest concentration of 150 $\mu\text{g mL}^{-1}$. However, compound **5j**, carrying an *n*-dodecyl group, showed very good inhibition against *B. subtilis* and *S. epidermidis* strains with MIC values of 2.34 and 9.37 $\mu\text{g mL}^{-1}$, respectively.

Among all the synthesized compounds, **4a**, **4b** and **5a** showed equipotent to better antibacterial activity when compared with the activities of the thiomorpholine derivatives reported by several authors.^{30,31} The better activity of compounds **4a**, **4b**, **5a** and **5b** might be attributed to the presence of the 1-heptyl and 1-octyl groups on the 1,2,3-triazole ring.

Antifungal activity

All the synthesized compounds **4a–j** and **5a–j** were investigated for their *in vitro* antifungal activity against the fungal strains *Candida albicans*, *Saccharomyces cerevisiae*, *Aspergillus niger* and *A. flavus*. Amphotericin B was used as the standard drug for comparison. The results of the *in vitro* antifungal activity screening (Table S-II of the Supplementary material) revealed that compounds **4c**, **4e** and **5j** exhibited moderate antifungal activity against *C. albicans*, *A. niger* and *A. flavus* strains with zones of inhibition ranging from 9 to 16 mm. Compounds **4f**, **4j**, **5c** and **5d** exhibited moderate inhibition of *C. albicans* and *A. niger* strains with zones of inhibition ranging from 8 to 14 mm. Furthermore, compound **5g** registered moderate inhibition against *C. albicans* and *A. flavus* organisms. Compounds **4a**, **4b**, **4d**, **4g**, **4h**, **4i**, **5a**, **5b**, **5e**, **5f**, **5h** and **5i** exhibited no inhibition against all fungal strains, even at the highest concentration of 150 $\mu\text{g mL}^{-1}$. From the above observations, it is obvious that replacement of the 1-octyl group with 1-decyl, 1-dodecyl, 1-tetradecyl and 1-pentadecyl groups on the triazole ring resulted in better activity against all the tested organisms (except *S. cerevisiae*) as compared with the other synthesized thiomorpholine derivatives.

MATERIALS AND METHODS

All the reagents and solvents were purchased from Sigma–Aldrich/Merck Chemicals, India and used without further purifications. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F₂₅₄ precoated plates (0.25 mm) and silica gel (100–200 mesh) was used for column chromatography. The progress of the reactions as well as the

purity of the compounds was monitored by thin layer chromatography using ethyl acetate/hexane (7/3) as eluent. Phosphomolybdic acid (PMA) stain was used for detection. Melting points were determined using a Cintex apparatus and are uncorrected. 300 MHz and 500 Mz spectrometers were used for ^1H -NMR spectroscopy and the latter for ^{13}C -NMR spectroscopy of **4a–j**. Coupling constant (J) are presented in Hertz and spin multiples are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Mass spectra were recorded by using the ESI-MS method.

Synthesis of 4-(prop-2-yn-1-yl)thiomorpholine (2)

The title compound was prepared according to a known literature procedure.³²

Synthesis of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (3)

To a stirred solution of 4-(prop-2-yn-1-yl)thiomorpholine (3 g, 0.021 mol) in dichloromethane (100 mL) was added MCPBA (10.9 g, 0.0638 mol) at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, the solvent was removed under reduced pressure to afford the crude compound. The crude product was partitioned between ethyl acetate and aqueous NaHCO_3 solution. Then, the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford 2.8 g (77 %) of 4-(prop-2-yn-1-yl)thiomorpholine 1,1-dioxide (3).

General procedure for the synthesis of 1,4-disubstituted-1,2,3-triazoles (4a–j and 5a–j)

To a stirred solution of alkyl bromide (1.67 mmol, 1 eq.) in aqueous THF solution (H_2O :THF, 1:1), was added sodium azide (2.01 mmol, 1.2 eq.) and the resulting mixture was stirred at room temperature for 2 h. Then, alkyne (1.67 mmol, 1 eq.) and 10 mol % Cu(I) were added to the reaction mixture and stirred at ambient temperature for 8–12 h. After completion of the reaction, the mixture was diluted with water, extracted with ethyl acetate, dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude compounds. The crude compounds were purified by column chromatography using silica gel (100–200 mesh) and (20–30 %) ethyl acetate in n -hexane as eluent. Evaporation of the solvent afforded compounds **4a–j** and **5a–j** in good yields.

Antibacterial activity

The minimum inhibitory concentrations (MIC) of the synthesized compounds were tested against the gram-positive organisms *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96) and *S. epidermidis* (MTCC 2639) and the gram-negative organisms *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 741), and *Klebsiella pneumoniae* (MTCC 618) using the broth dilution method.^{33–37} Penicillin and streptomycin were also screened under identical conditions for comparison.

Antifungal activity

The *in vitro* antifungal activities of the synthesized compounds were determined against the fungal strains *Candida albicans* (MTCC 227), *Saccharomyces cerevisiae* (MTCC 36), *Aspergillus niger* (MTCC 282) and *Aspergillus flavus* (MTCC 8654) by the Agar Well Diffusion method.³⁸ Ready-made potato dextrose agar (PDA) medium (Hi-media, 39 g) was suspended in distilled water (1000 mL) and heated to boiling until it dissolved completely, the medium and Petri dishes were autoclaved at a pressure of 4.4 g m⁻² for 20 min. The medium was poured into sterile Petri dishes under aseptic conditions in a laminar air flow chamber. When the medium in the plates had solidified, 0.5 mL of week-old culture of the test organism was inoculated and uniformly spread over the agar surface with a sterile L-shaped rod. Solutions were prepared by dissolving the compound in dimethyl sulfoxide (DMSO) and

different concentrations (100 and 150 $\mu\text{g mL}^{-1}$) were made. After inoculation, the wells were scooped out with a 6 mm sterile cork borer and the lids of the dishes were replaced. Different concentrations of the test solutions were added to each well and controls were maintained. The treated samples and the controls were kept at 27 °C for 48 h. Inhibition zones were measured and the diameters were calculated in mm. Three to four replicates were maintained for each treatment. Amphotericin B was used as the standard drug for comparison.

CONCLUSIONS

In summary, some novel thiomorpholine derived 1,4-disubstituted-1,2,3-triazoles were synthesized and their antimicrobial activities investigated. The majority of the compounds were found to possess interesting antibacterial activities against the tested bacterial strains when compared to the standard drugs penicillin and streptomycin. Some of the synthesized compounds also registered moderate antifungal activity. The antimicrobial activities of the compounds were modulated by structural modifications in the alkyl group attached to the triazole ring. Thus, these active compounds could be very good candidates for further antimicrobial investigations.

SUPPLEMENTARY MATERIAL

Analytical and spectral data of the synthesized compounds and the results of the antimicrobial screening (Tables S-I and S-II) are available electronically from <http://www.shd.org.rs/JSCS/>, or from the corresponding author on request.

Acknowledgments. Financial assistance from University Grants Commission, New Delhi, for major research project to V. R. Nagavelli is highly acknowledged. Narsimha is thankful to the Council of Scientific and Industrial Research New Delhi, for the award of senior research fellowship.

ИЗВОД

СИНТЕЗА И ИСПИТИВАЊЕ АНТИМИКРОБНЕ АКТИВНОСТИ НОВИХ ДЕРИВАТА 1,4-ДИСУПСТИТУИСАНИХ 1,2,3-ТРИАЗОЛА И ТИОМОРФОЛИНА

KUMARASWAMY BATTULA¹, SIRASSU NARSIMHA¹, VASUDEVAREDDY NAGAVELLI¹, PRIYANKA BOLLEPELLI² и MUTHENENI SRINIVASA RAO²

¹Department of Chemistry, Kakatiya University, Warangal-506009, India и ²Chemical Biology Laboratory, Indian Institute of Chemical Technology, Hyderabad-500007, India

Приказана је погодна синтеза нових 1,4-дисупституисаних 1,2,3-триазола **4a–j** и **5a–j**, бакар (I)-катализованом [3+2] циклоадицијом различитих халогеналкана и натријум-азида са 4-(проп-2-ин-1-ил)тиоморфолином и 4-(проп-2-ин-1-ил)тиоморфолин-1,1-диоксидом. Испитана је антимикробна активност свих синтетисаних једињења. Најбољу активност показују једињења **4a**, **4b**, **4c**, **4g**, **5a** и **5j** према *Staphylococcus epidermidis*, **4a**, **5a** и **5d** према *Pseudomonas aeruginosa*, **4a**, **4b** и **4g** према *Klebsiella pneumoniae*, **4b**, **5a** и **5d** према *S. aureus* и **5b**, **5e** и **5j** према *Bacillus subtilis*, када се упореде са стандардним лековима пеницилином и стрептомицином. Једињења **4c**, **4e**, **4f**, **4j**, **5c**, **5d**, **5g** и **5j** имају умерену антифунгалну активност када се упореде са стандардним леком амфотерицином Б.

(Примљено 18. августа, ревидирано 13. октобра, прихваћено 21. октобра 2015)

REFERENCES

1. R. Alvarez, S. Velazquez, A. S. Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **37** (1994) 4185
2. S. Velazquez, R. Alvarez, C. Perez, F. Gago, E. De Clercq, J. Balzarini, M. J. Camarasa, *Antiviral Chem. Chemother.* **9** (1998) 481
3. B. S. Holla, M. Mahalinga, M. S. Karthikeyan, B. Poojary, P. M. Akberali, N. S. Kumari, *Eur. J. Med. Chem.* **40** (2005) 1173
4. Y. Chen, M. L. Sanchez, D. N. Savoy, D. D. Billadeau, G. S. Dow, A. P. Kozikowski, *J. Med. Chem.* **51** (2008) 3437
5. C. J. Carroux, G. M. Rankin, J. Moeker, L. F. Bornaghi, K. Katneni, J. Morizzi, S. A. Charman, D. Vullo, C. T. Supuran, S. A. Poulsen, *J. Med. Chem.* **56** (2013) 9623
6. J. A. Stefely, R. Palchaudhuri, P. A. Miller, R. J. Peterson, G. C. Moraski, P. J. Hergenrother, M. J. Miller, *J. Med. Chem.* **53** (2010) 3389
7. S. Shafi, M. M. Alam, M. Naveen, M. Chaitanya, G. Vanaja, A. M. Kalle, R. Pallu, M. S. Alam, *Eur. J. Med. Chem.* **49** (2012) 324
8. C. Dyrager, K. Borjesson, P. Diner, A. Elf, B. Albinsson, L. M. Wilhelmsson, M. Grotli, *Eur. J. Org. Chem.* (2009) 1515
9. V. Pande, M. J. Ramos, *Bioorg. Med. Chem. Lett.* **15** (2005) 5129
10. P. H. Olesen, A. R. Sorensen, B. Urso, P. Kurtzhals, A. N. Bowler, U. Ehrbar, B. F. Hansen, *J. Med. Chem.* **46** (2003) 3333
11. A. Krasinski, Z. Radic, R. Manetsch, J. Raushel, P. Taylor, K. B. Sharpless, H. C. Kolb, *J. Am. Chem. Soc.* **127** (2005) 6686
12. V. P. Mocharla, B. Colasson, L. V. Lee, S. Roper, K. B. Sharpless, C. H. Wong, H. C. Kolb, *Angew. Chem. Int. Ed.* **44** (2005) 116
13. P. Diner, T. Andersson, J. Kjellen, K. Elbing, S. Hohmann, M. Grotli, *New J. Chem.* **33** (2009) 1010
14. I. S. Bennet, G. Brooks, N. J. P. Broom, S. H. Calvert, K. Coleman, I. Francois, *J. Antibiot.* **44** (1991) 969
15. G. A. Stilwell, H. G. Adams, M. Turck, *Antimicrob. Agents Chemother.* **8** (1975) 751
16. M. J. Soltis, H. J. Yeh, K. A. Cole, N. Whittaker, R. P. Wersto, E. C. Kohn, *Drug Metab. Dispos.* **24** (1996) 799
17. Y. M. A. Yamada, S. M. Sarkar, Y. Uozumi, *J. Am. Chem. Soc.* **134** (2012) 9285
18. M. Liu, O. Reiser, *Org. Lett.* **13** (2011) 1102
19. K. Odlo, E. A. Hoydahl, T. V. Hansen, *Tetrahedron Lett.* **48** (2007) 2097
20. P. Li, L. Wang, *Lett. Org. Chem.* **4** (2007) 23
21. A. K. Feldman, B. Colasson, V. V. Fokin, *Org. Lett.* **6** (2004) 3897
22. H. Rolf, *Angew. Chem. Int. Ed.* **75** (1963) 604
23. S. Narsimha, T. R. Kumar, N. S. Kumar, S. Yakoob, N. V. Reddy, *Med. Chem. Res.* **23** (2014) 5321
24. A. V. Shcherbatiuk, O. S. Shyshlyk, D. V. Yarmoliuk, O. V. Shishkin, S. V. Shishkina, V. S. Starova, O. A. Zaporozhets, S. Zozulya, R. Moriev, O. Kravchuk, O. Manoilenko, A. A. Tolmachev, P. K. Mykhailiuk, *Tetrahedron* **69** (2013) 3796
25. M. Biava, G. C. Porretta, D. Deidda, R. Pompei, A. Tafi, F. Manetti, *Bioorg. Med. Chem.* **11** (2003) 515
26. S. K. Srivastava, A. Abraham, B. Bhat, M. Jaggi, A. T. Singh, V. K. Sanna, G. Singh, S. K. Agarwal, R. Mukherjee, A. C. Burman, *Bioorg. Med. Chem. Lett.* **16** (2006) 4195
27. G. N. Ziakas, E. A. Rekka, A. M. Gavalas, P. T. Eleftheriou, P. N. Kourounakis, *Bioorg. Med. Chem.* **14** (2006) 5616

28. B. Han, J. L. Liu, Y. Huan, P. Li, Q. Wu, Z. Y. Lin, Z. F. Shen, D. L. Yin, H. H. Huang, *Chin. Chem. Lett.* **23** (2012) 297
29. H. Kai, H. Hinou, S. I. Nishimura, *Bioorg. Med. Chem.* **20** (2012) 2739
30. U. Singh, B. Raju, S. Lam, J. Zhou, R. C. Gadwood, C. W. Ford, G. E. Zurenko, R. D. Schaadt, S. E. Morin, M. F. Gordeev, *Bioorg. Med. Chem. Lett.* **13** (2003) 4209
31. S. Yan, M. J. Miller, T. A. Wencewicz, U. Mollmann, *Bioorg. Med. Chem. Lett.* **20** (2010) 1302
32. H.-R. Tsou, N. Mamuya, B. D. Johnson, M. F. Reich, B. C. Gruber, F. Ye, R. Nilakantan, R. Shen, C. Discafani, R. D. Blanc, R. Davis, F. E. Koehn, L. M. Greenberger, Y.-F. Wang, A. Wissner, *J. Med. Chem.* **44** (2001) 2719
33. National Committee for Clinical Laboratory (NCCL), *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 5th Ed, Approved Standard M7-A5, National Committee for Clinical Laboratory Standards, Villanova, PA, 2000
34. R. Trivedi, E. R. Reddy, C. K. Kumar, B. Sridhar, K. P. Kumar, M. S. Rao, *Bioorg. Med. Chem. Lett.* **21** (2011) 3890
35. B. V. S. Reddy, M. R. Reddy, C. Madan, K. P. Kumar, M. S. Rao, *Bioorg. Med. Chem. Lett.* **20** (2010) 7507
36. B. V. S. Reddy, N. Rajeswari, M. Sarangapani, G. R. Reddy, C. Madan, K. P. Kumar, M. S. Rao, *Bioorg. Med. Chem. Lett.* **21** (2011) 6510
37. E. Rajanarendar, M. N. Reddy, K. R. Murthy, K. G. Reddy, S. Raju, M. Srinivas, B. Praveen, M. S. Rao, *Bioorg. Med. Chem. Lett.* **20** (2010) 6052
38. E. M. Lindsay, *Practical Introduction to Microbiology*, E & F. N. Spon Ltd., London, 1962, p. 177.