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Efficient synthesis via azide–alkyne Huisgen [3+2] cycloaddition reaction and antifungal activity studies of novel triazoloquinolines

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Abstract New functionalized 1,2,3-triazoloquinolines were achieved by intramolecular azide–alkyne Huisgen [3+2] cycloaddition. These derivatives were synthesized via the key Baylis–Hillman adduct under mild, neutral conditions in short duration and consistently good yield. The structures of final compounds were characterized by spectral analysis. Antifungal activities of these analogues against *Trichophyton mentagrophytes*, *Candida albicans*, and *Aspergillus niger* were also assayed.

Keywords Huisgen cycloaddition · Baylis–Hillman reaction · Triazoles · Quinolines

Introduction

Triazoles are important five-membered heterocyclic compounds containing three nitrogen atoms in the five-membered ring, showing various medicinal properties such as antimalarial [1], antimicrobial [2], antiinflammatory [3], anticonvulsant [4], and antineoplastic activity [5]. Substituted 1,2,4-triazoles find many useful applications. Some of them are used as analytical reagents for determination of boron [6], antimony [7], and cobalt [8]. Other triazoles find many synthetic uses as halogenating agents or as activating polymeric reagents [9]. In recent years, 1,2,3-triazole derivatives have been widely used as antiproliferative [10] and anticancer agents [11]. In medicinal chemistry, great attention has been paid to synthesis of 1,2,3-triazoles fused with other heterocycles and investigation of their biological activity [12–14].

The basic core formed from a quinoline ring results in greater antifungal strength compared with aromatic systems. The additional presence of the triazole motif

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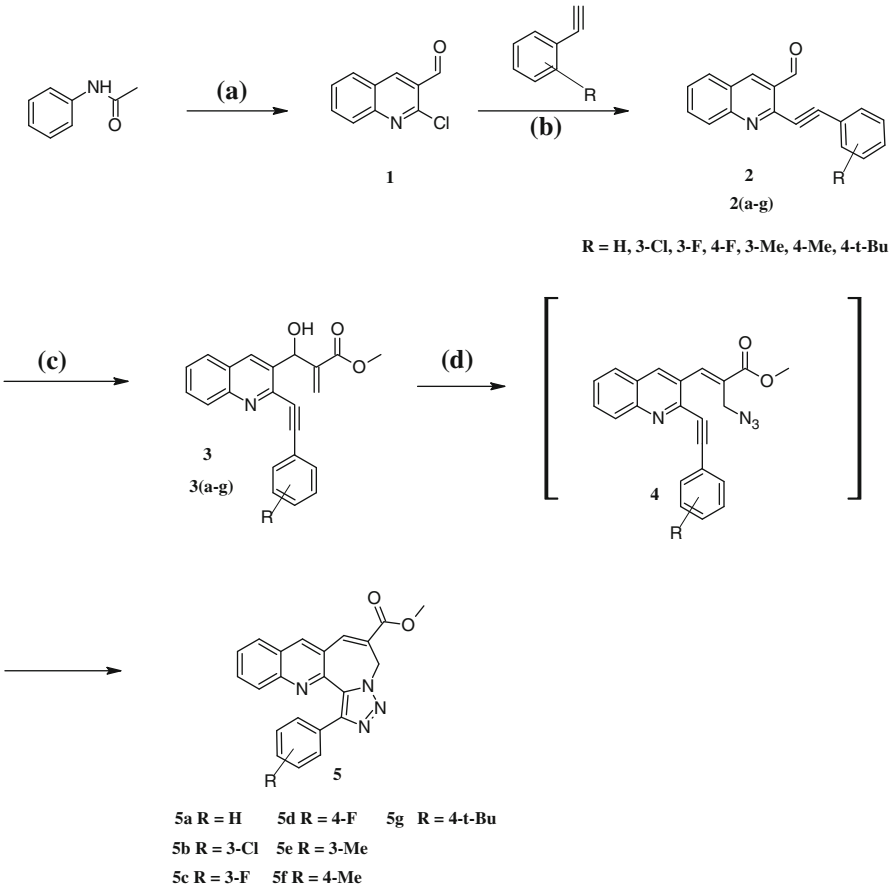
further increases the potency to a higher level. Introduction of halogens such as fluorine or chlorine atom into these compounds could alter their pharmacological activity [1]. The azole class of drugs are β-lactamase inhibitors [15] and exhibit a wide range of therapeutic activities. In recent years, study of their synthesis and pharmacology has gained in importance among scholars. Some 1,2,3-triazoles are used as DNA cleaving agents [10] and potassium channel activators [16].

Cycloaddition reactions are one of the most important classes of reactions in synthetic chemistry. Within this class, the 1,3-dipolar cycloaddition reaction has found extensive use as a high-yielding, efficient, regio- and stereocontrolled method for synthesis of many different heterocyclic compounds. 1,3-Dipolar cycloaddition [17] is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring. Mechanistic investigation and synthetic application were established through the work of Rolf Huisgen. Hence, this reaction is sometimes referred to as Huisgen cycloaddition (a term used to describe specifically 1,3-dipolar cycloaddition between an organic azide and an alkyne to generate a 1,2,3-triazole). The intramolecular alkyne–azide Huisgen [3+2] cycloaddition reaction has been studied as a "click chemistry" reaction without a metal catalyst under aerobic conditions. Our method can provide extension of the preparation of triazoles and their uses in synthetic organic chemistry. Azide–alkyne cycloaddition (AAC) to produce 1,2,3-triazoles has been extensively developed since the Cu catalyst conditions (CuAAC) were reported [18, 19]. Due to their numerous applications, especially in chemical biology [20, 21], ligand/material design [22], and pharmaceuticals [23], many groups have reported mild, rapid, and Cu-free triazolations [24]. Recently, triazoles have found extensive use in the developing field of material and agrochemical research.

Chemistry

As part of our ongoing research, synthesis of triazoloquinolines [25] was achieved through intramolecular 1,3-dipolar cycloaddition with Baylis–Hillman adducts. α-Methylene-β-hydroxy esters are easily prepared by the Baylis–Hillman reaction [26–29], being used as vital building blocks for construction of triazoloquinolines. 2-Chloro-3-formylquinolines were obtained by subjecting the suitable acetanilide to Vilsmeier reagent [$POCl_3$/dimethylformamide (DMF)] [30]. Compound **1** undergoes Sonogashira coupling reaction with terminal acetylenes in the presence of $Pd(PPh_3)_2Cl_2$, CuI/Et_3N to yield compound **2** [31]. Further, the quinoline skeleton was achieved through Baylis–Hillman reaction by treating **2** with ethyl acrylate in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO). Having in hand the internal activated alkynes **3**, we turned our attention to synthesis of azide–alkyne Huisgen [3+2] cycloadducts **5**. First, we tried the reaction of **3** with sodium azide at room temperature to obtain the intermediate **4**, but found no reaction. The same reaction was heated to 80 °C, achieving cycloadducts through elimination followed by in situ azide–alkyne Huisgen [3+2] cycloaddition [32]. These reactions were carried out in anhydrous DMF and afforded new triazoloquinolines in good yields.



Scheme 1 *a* $POCl_3$, DMF, 90 °C; *b* $Pd(PPh_3)_2Cl_2$, CuI, triethylamine, THF; *c* Ethyl acrylate, DABCO; *d* NaN_3, DMF, 80 °C

The formation of cycloadducts was confirmed by ^1H nuclear magnetic resonance (NMR) and mass spectroscopy (Scheme 1; Table 1).

Experimental

Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone, DMF from CaO and distilled $POCl_3$. All reactions were performed under nitrogen atmosphere. All products were confirmed by their spectral data. ^1H and ^{13}C NMR spectra were recorded on a Bruker Biospin spectrometer at 400 MHz. Mass spectra were recorded on an Agilent mass spectrometer. Flash column chromatography was performed on Merck silica gel (230–400 mesh).

Synthesis of 2-chloroquinoline-3-carbaldehyde (**1**)

At 0 °C to a stirred solution of $POCl_3$ (39.6 g, 259 mmol) and anhydrous DMF (8 g, 111 mmol) was added acetanilide (5 g, 37 mmol). The mixture was then heated to 65 °C, and the progress of the reaction was monitored by thin-layer chromatography (TLC) analysis. After 8 h the reaction mixture was cooled to room temperature and added cautiously into ice-cold water. The precipitated solid was collected by filtration to isolate compound **1a** as yellow solid. Yield 6.2 g (87 %), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.58 (s, 1H), 8.78 (s, 1H), 8.10 (m, 1H), 8.01 (m, 1H), 7.91 (m, 1H), 7.67 (m, 1H); LCMS: *m*/*z* 192.0 (M^+).

General procedure for synthesis of substituted quinoline carbaldehydes **2a–g**

At 0 °C to a solution of 2-chloroquinoline-3-carbaldehyde (0.2 g, 0.1 mmol) in anhydrous THF (5 mL) were added tetrakis(triphenylphosphine)palladium (0.012 g, 0.01 mmol), CuI (0.02 g, 0.01 mmol), phenylacetylene (0.1 g, 0.1 mmol), and triethylamine (0.42 g, 0.4 mmol). The reaction mixture was allowed to stir at room temperature for 1 h. After completion of the reaction, the reaction mixture was diluted with water, and extracted with ethyl acetate (2 × 15 mL). The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash column chromatography to yield compound **2** as pale-brown solid. Yield 0.21 g (77 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.84 (s, 1H), 8.79 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.92 (m, 1H), 7.74 (m, 2H), 7.72 (m, 1H), 7.45 (m, 3H). LCMS: *m*/*z* 258.2 (M^+).

General procedure for synthesis of substituted α-methylene-β-hydroxy esters **3a–g**

To a mixture of compound **2** (0.2 g, 0.7 mmol) in ethyl acrylate (0.3 g, 3.1 mmol) was added 1,4-diazabicyclo[2.2.2]octane (0.34 g, 3.1 mmol), followed by standing at room temperature for 48 h. The crude product was purified by silica-gel column chromatography to afford compound **3** (0.22 g, 82 %) as colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 8.17 (m, 1H), 7.84 (m, 1H), 7.75 (m, 1H), 7.58 (m, 3H), 7.37 (m, 3H), 6.40 (s, 1H), 6.30 (s, 1H), 5.70 (s, 1H), 3.76 (s, 3H). LCMS: *m*/*z* 344.2 (M^+).

General procedure for synthesis of triazoloquinoline derivatives **5a–g**

To a solution of compound **3** (0.05 g, 0.14 mmol) in anhydrous DMF (5 mL) was added sodium azide (0.019 g, 0.29 mmol), and the reaction mixture was heated to 80 °C for 1 h. After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with water (10 mL), and the contents were extracted with ethyl acetate. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure. The crude material thus obtained was purified by flash column chromatography to yield the title compound **5**.

Table 1 Yields of triazoloquinoline derivatives

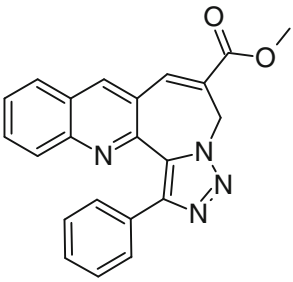
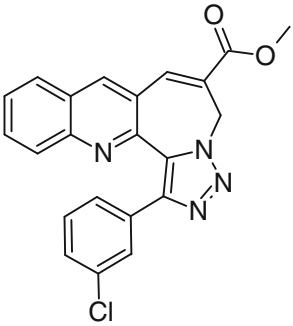
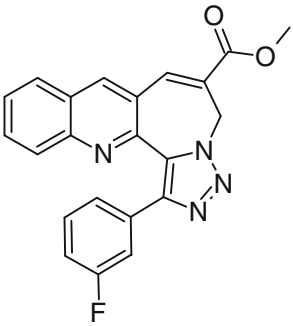
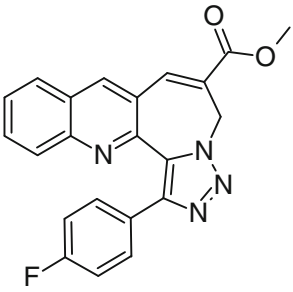
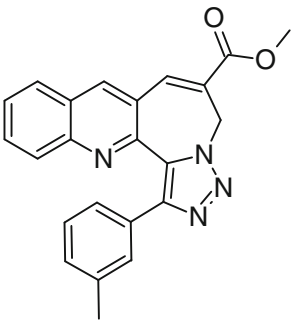
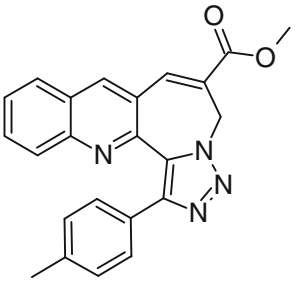
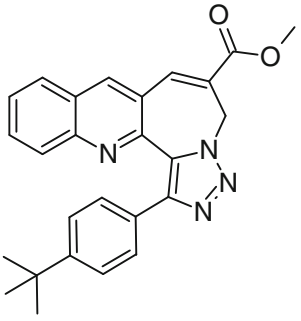
Compound	Product	Time (h)	Yield (%)
5a		1	75
5b		1	77
5c		1	82
5d		1	75

Table 1 continued

Compound	Product	Time (h)	Yield (%)
5e		1	84
5f		1	78
5g		1	80

Methyl 1-phenyl-5*H*-[1,2,3]triazolo[1′,5′:1,2]azepino[3,4-*b*]quinoline-6-carboxylate (**5a**)

Yield: 0.04 g (75 %) as brown solid. HRMS: 368.8 (M). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.14 (s, 1H), 7.97 (m, 2H), 7.85 (m, 3H), 7.69 (m, 1H), 7.34 (m, 3H), 5.47 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): 164.8, 147.8, 144.7, 140.4, 131.9, 129.5, 128.7, 126.7, 52.9, 45.1.

Methyl 1-(3-chlorophenyl)-5*H*-[1,2,3]triazolo[1′,5′:1,2]azepino[3,4-*b*]quinoline-6-carboxylate (**5b**)

Yield: 0.045 g (77 %) as white solid. HRMS: 402.6 (M). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.20 (s, 1H), 8.12 (m, 2H), 7.96 (m, 1H), 7.80 (m, 1H), 7.65 (m, 3H), 7.22 (m, 1H), 5.47 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.5, 159.6, 152.3, 142.6, 141.2, 135.7, 132.2, 128.9, 125.5, 124.5, 122.2, 119.6, 116.6, 44.6.

Methyl 1-(3-fluorophenyl)-5*H*-[1,2,3]triazolo[1′,5′:1,2]azepino[3,4-*b*]quinoline-6-carboxylate (**5c**)

Yield: 0.046 g (82 %) as viscous liquid. HRMS: 386.8 (M). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.14 (s, 1H), 8.05 (m, 2H), 7.96 (m, 1H), 7.87 (m, 1H), 7.71 (m, 3H), 7.30 (m, 1H), 5.47 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.4, 160.4, 154.3, 146.2, 141.2, 137.6, 133.4, 129.4, 125.3, 122.2, 121.2, 116.6, 45.8.

Methyl 1-(4-fluorophenyl)-5*H*-[1,2,3]triazolo[1′,5′:1,2]azepino[3,4-*b*]quinoline-6-carboxylate (**5d**)

Yield: 0.042 g (75 %) as viscous liquid. HRMS: 386.8 (M). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.20 (s, 1H), 7.96 (m, 1H), 7.84 (m, 2H), 7.73 (m, 2H), 7.30 (m, 3H), 5.46 (s, 2H), 3.96 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.4, 162.3, 155.4, 145.3, 143.6, 142.2, 139.9, 135.6, 129.8, 127.5, 124.3, 121.2, 117.6, 45.3.

Methyl 1-(*m*-tolyl)-5*H*-[1,2,3]triazolo[1′,5′:1,2]azepino[3,4-*b*]quinoline-6-carboxylate (**5e**)

Yield: 0.046 g (84 %) as off-white solid. HRMS: 382.5 (M). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.34 (m, 1H), 7.95 (m, 1H), 7.84 (m, 2H), 7.75 (m, 2H), 7.52 (m, 1H), 7.32 (m, 2H), 5.47 (s, 2H), 3.95 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.6, 154.3, 145.4, 144.3, 138.3, 135.4, 128.4, 125.3, 129.6, 123.2, 120.1, 45.6, 22.2.

Methyl 1-(*p*-tolyl)-5*H*-[1,2,3]triazolo[1′,5′:1,2]azepino[3,4-*b*]quinoline-6-carboxylate (**5f**)

Yield: 0.044 g (78 %) as white solid. HRMS: 382.5 (M). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.32 (m, 1H), 7.93 (m, 1H), 7.73 (m, 2H), 7.56 (m, 3H), 7.19 (m, 2H), 5.43 (s, 2H), 3.95 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 168.6, 156.6, 143.3, 141.2, 138.6, 135.4, 130.2, 125.3, 121.2, 119.9, 45.3, 22.2.

Methyl 1-(4-(*tert*-butyl)phenyl)-5*H*-[1,2,3]triazolo[1′,5′:1,2]azepino[3,4-*b*]quinoline-6-carboxylate (**5g**)

Yield: 0.049 g (80 %) as viscous oil. HRMS: 424.9 (M). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.25 (s, 1H), 8.09 (m, 1H), 7.94 (m, 1H), 7.85 (m, 1H), 7.71 (m, 1H), 7.64 (m, 2H), 7.38 (m, 2H), 5.51 (s, 2H), 3.95 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.3, 163.2, 153.2 145.3, 143.6, 140.2, 139.9, 135.6, 128.8, 126.5, 123.2, 121.2, 117.6, 45.2, 25.4.

Antifungal assay

The agar well diffusion method was used to evaluate the antifungal potency of the final analogues. Each fungal isolate was suspended in brain–heart infusion (BHI) broth and diluted to approximately 10^5 colony-forming units (CFU) per mL. They were flood-inoculated onto the surface of BHI agar and then dried. Dimethyl sulfoxide (DMSO) was used as solvent control. Compound (5 μg) in 500 μL DMSO was used as stock solution. Five-millimeter-diameter wells were cut from the agar using a sterile cork-borer, and 30 μL of sample solution was poured into the wells. The plates were incubated for 18 h at room temperature for fungi. Antifungal activity was evaluated by measuring the zone of inhibition in millimeters against the test microorganisms. Ketoconazole was used as reference antifungal agent. The tests were carried out in triplicate.

Antifungal activity

All synthesized triazoloquinoline compounds were assayed for antifungal (*Trichophyton mentagrophytes*, *Candida albicans*, and *Aspergillus niger*) activities using the disc diffusion method [33]. The results for the antifungal effect of all the tested compounds are reported as the zone of inhibition in millimeters in Table 2. The results revealed that most of the newly synthesized derivatives exhibit moderate

Table 2 Antifungal activity of triazoloquinoline derivatives

Compound	*Candida albicans*	*Aspergillus niger*	*Trichophyton mentagrophytes*
5a	NZ	NZ	8
5b	NZ	NZ	5
5c	NZ	NZ	5
5d	NZ	NZ	7
5e	NZ	NZ	5
5f	NZ	NZ	5
5g	NZ	NZ	5
Ketoconazole (reference)	23	10	9

Experiments used 5 μg compound in 500 μL DMSO

NZ no zone of activity

antifungal activity against *Trichophyton mentagrophytes* except two compounds (**5a** and **5g**) with zone of inhibition nearly matching that of the standard ketoconazole.

In vitro evaluation of antifungal activity was carried out for the analogues, and the results are summarized in the table. The zone of inhibition of triazoles **5a–g** against the mentioned fungal strains was investigated. The derivatives revealed inhibitory efficiency against *Trichophyton mentagrophytes* in the range of 5–8 mm, being moderate to equipotent compared with the standard drug ketoconazole. The activity of the final analogues towards the fungal strains remained unchanged irrespective of the presence of either electron-withdrawing or electron-donating groups.

Conclusions

We synthesized triazoloquinoline derivatives via azide–alkyne Huisgen [3+2] cycloaddition reaction in good yields. The advantages of the present procedure are experimental simplicity, easy workup procedure, mild reaction conditions, and no requirement for any catalyst. All synthesized compounds showed moderate antifungal activity invariably.

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References

1. M. Jilino, M.F.G. Stevens, J. Chem. Soc. Perkin Trans. **1**, 1677–1684 (1998)
2. M.D. Chen, S.J. Lu, G.P. Yuag, S.Y. Yang, X.L. Du, Hetrocycl. Commun. **6**, 421–426 (2000)
3. R.J. Singh, Rasayan J. Chem. **2**, 706–708 (2009)
4. M.I. Husain, M. Amir, J. Indian Chem. Soc. **63**, 317–319 (1986)
5. A. Passannanti, P. Diana, P. Barraja, F. Mingoia, A. Lauria, G. Cirrincione, Heterocycles **48**, 1229–1235 (1998)
6. C. Temle Jr, Chem. Hetyrocycl. Compd. **37**, 1 (1981)
7. J.B. Polya, M. Woodruff, Aust. J. Chem. **26**, 1585 (1973)
8. C. Calzolari, L. Favretto, Analyst **93**, 494 (1968)
9. M. Mokotoff, M. Jhao, S.M. Roth, J.A. Shelley, J.N. Slavoskiand, N.M. Kouttab, J. Med. Chem. **33**, 354 (1990)
10. S. Manfredini, C.B. Vicentini, M. Manfrini, N. Bianchi, C. Rutigliano, C. Mischiati, R. Gambari, Bioorg. Med. Chem. **8**, 2343–2346 (2000)
11. S. Danoun, G. Baziard-Mouysset, J. Stigliani, M. Payard, M. Selkti, B. Viossat, A. Thomas, Hetrocycl. Commun. **4**, 45–51 (1998)
12. S. Pautus, S. Yee, M. Jayne, M.P. Coogan, C. Simons, Bioorg. Med. Chem. **14**, 3653–4643 (2006)
13. D. Kim, J. Kim, H. Park, Bioorg. Med. Chem. **12**, 2014–2020 (2004)
14. P. Zoumpoulakis, C. Camoutsis, G. Pairas, M. Sokovic, J. Glamoclija, C. Potamitis, A. Pitsas, Bioorg. Med. Chem. **20**, 1569–1583 (2012)
15. T. Weide, S.A. Saldanha, D. Minod, T.P. Spicer, J.R. Fotsing, M. Spaargaren, J.-M. Frere, C. Bebrone, K.B. Sharpless, P.S. Hodder, V.V. Fokin, ACS Med. Chem. Lett. **1**(4), 150–154 (2010)
16. G. Biagi, V. Calderone, I. Giorgi, O. Livi, E. Martinotti, A. Martelli, A. Nrdi, Farmaco **59**, 397–404 (2004)
17. N. Saravanan, M. Arthanareeswari, P. Kamaraj, Int. J. Chem. **34**, 1143–1147 (2013) ISSN: 2051-3240

18. L. Ackermann, H.K. Potukuchi, Org. Biomol. Chem. **8**, 4503–4513 (2010)
19. C.W. Tornoe, C. Christensen, M. Meldal, Chem. Rev. **108**, 2952–3015 (2008)
20. P. Thirumuruga, D. Matosiuk, K. Jozwaik, Chem. Rev. **113**, 4905-4979 (2013)
21. C.H. Wong, S.C. Zimmerman, Chem. Commun. **49**, 1679–1695 (2013)
22. L. Casarrubios, M.C. de la Torre, M.A. Sierra, Chem. Eur. J. **19**, 3534–3541 (2013)
23. H.Y. Hsieh, W.C. Lee, G.C. Senadi, W.P. Hu, J.J. Liang, T.R. Tsai, Y.W. Chou, K.K. Kuo, C.Y. Chen, J.J. Wang, J. Med. Chem. **56**, 5422–5435 (2013)
24. M.E. Meza Avina, M.K. Patel, C.B. Lee, T.J. Dietz, M.P. Croatt, Org. Lett. **13**, 2984–2987 (2011)
25. R.V. Patel, S.W. Park, Eur. J. Med. Chem. **71**, 24–30 (2014)
26. D. Basavaiah, P. Darma Rao, R.S. Hyma, Tetrahedron **52**, 8001–8062 (1996)
27. S.E. Drewes, G.H.P. Roos, Tetrahedron **44**, 4653–4670 (1988)
28. G.P. Black, F. Dinon, S. Fratucello, P.J. Murphy, M. Nielsen, H.L. Williams, Tetrahedron Lett. **38**, 8561–8564 (1997)
29. L.J. Brzezinski, S. Rafel, J.W. Leahy, Tetrahedron **53**, 16423–16434 (1997)
30. O. Meth-Cohn, B. Narine, B. Tarnowski, J. Chem. Soc. Perkin Trans. **1**, 1520–1530 (1981)
31. M. Zahid, V.O. Iaroshenko, A. Saghyan, C. Fischer, Tetrahedron **69**, 3451–3458 (2013)
32. V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angew. Chem. Int. Ed. **41**, 2596–2599 (2002)
33. B.A.A. Skaggs et al., J. Clin. Microbiol. **38**, 2254–2260 (2000)