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ORIGINAL ARTICLE

Synthesis and antimicrobial evaluation of 1,4-disubstituted 1,2,3-triazoles with aromatic ester functionality

C.P. Kaushik [a,*], Krishan Kumar [a], S.K. Singh [b], Dharmendra Singh [c], Sangita Saini [d]

[a] Department of Chemistry, Guru Jambheshwar University of Science & Technology, Hisar, Haryana 125001, India
[b] Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science & Technology, Hisar, Haryana 125001, India
[c] Centre for Research & Development, IPCA Lab Ltd., Kandivali, Mumbai, Maharashtra 400101, India
[d] Department of Pharmaceutical Sciences, PDM College of Pharmacy, Bahadurgarh, Haryana 124507, India

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Antibacterial activity;
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Abstract A series of 1,4-disubstituted 1,2,3-triazoles having p-substituted aromatic ester functionality were synthesized *via* Cu(I) catalysed click reaction between p-substituted benzoic acid prop-2-ynyl esters and aralkyl azides. The synthesized triazoles were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral techniques. These compounds were evaluated for their antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis*, *Candida albicans*, *Aspergillus niger* and *Aspergillus flavus* by two fold serial dilution method. Some of the synthesized 1,4-disubstituted 1,2,3-triazoles possess comparable or even better antibacterial, antitubercular and antifungal activities than reference drugs against tested bacterial, mycobacterial and fungal strains, respectively.

1. Introduction

The synthesis of substituted 1,2,3-triazoles is of key importance due to their large biological spectrum as antibiotic (Aufort et al., 2008), antimicrobial (Lal et al., 2012; Gaur et al., 2012; Demaray et al., 2008), antimalarial (D'hooghe et al., 2011), anticancer (Salmon et al., 2012), antihistaminic (Buckle et al., 1986), anti-HIV (Whiting et al., 2006) and antitubercular agents (Labadie et al., 2011). Good stability and high aqueous solubility of these compounds in biological system boost for appreciable biological activities. Further the 1,4-disubstituted 1,2,3-triazoles have also been used as ligation tool for the synthesis of neoglyco-conjugates (Perez-Balderas et al., 2003), multivalent dendrimeric peptides (Wu et al., 2004), ionic receptors (Kumar and Pandey, 2008), triazolophanes (Haridas et al., 2008), dendrimers (Haridas et al.,

* Corresponding author. Tel.: +91 1662 263152; fax: +91 1662 276240.
E-mail address: cpkaushik4@yahoo.co.in (C.P. Kaushik).

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2007), cyclic peptides (Turner et al., 2007), peptide nanotubes (Horne et al., 2003), peptidomimetics (Angell and Burgess, 2007) etc. Huisgen cycloaddition, the general method for the synthesis of 1,4-disubstituted 1,2,3-triazoles includes a 1,3-dipolar cycloaddition between azides and alkynes under thermal conditions to afford the equal mixture of 1,4- and 1,5-disubstituted isomers (Huisgen, 1963). A practical solution to avoid the formation of isomeric mixture in products, was given by Sharpless (Rostovtsev et al., 2002) and Meldal (Tornøe et al., 2002) through the catchy term ''click chemistry'' which refers to facile, efficient, selective and versatile chemical transformation of reactant to a single isomeric product. These reactions are simple to perform, modular, high yielding and lead to excellent selectivity in the product. Among various reactions, Cu(I) catalysed variant of Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes to give only 1,4-disubstituted 1,2,3-triazoles has been generally pointed as the primary standard of click chemistry. Herein, we report the synthesis of a series of 1,4-disubstituted 1,2,3-triazoles (**3a–3p**) from various azides and alkynes containing p-substituted aromatic ester functionalities. All the synthesized 1,4-disubstituted 1,2,3-triazoles were characterized by IR, ^{1}H NMR, ^{13}C NMR spectroscopy and mass spectrometry and also screened for their antibacterial, antitubercular and antifungal activities.

2. Experimental

2.1. Measurements

Melting points of synthesized compounds were recorded in °C by applying open capillary method and are uncorrected. The IR spectra were recorded on Shimazdu IR Affinity-I FT-IR spectrophotometer using potassium bromide (KBr) powder and values are given in cm^{-1}. The ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz/Bruker 300 MHz spectrophotometer and ^{13}C NMR on Bruker Avance II 400 at 100 MHz/Bruker 300 at 75 MHz, in deuterated chloroform using tetramethylsilane (TMS) as an internal standard (chemical shift in δ, ppm). Coupling constant (J) values are given in Hertz (Hz). Mass spectra were recorded on a Waters Micromass Q-Tof Micro (ESI) spectrophotometer. The completion of reactions and the purity of the compounds were analysed by thin layer chromatography (TLC) using readymade silica gel plates (SIL G/UV254, ALUGRAM) and visualized under ultraviolet lamp.

2.2. General procedure for the synthesis of 1,4-disubstituted 1,2,3-triazoles

The starting reactants p-substituted benzoic acid prop-2-ynyl esters (**2**) were prepared by reacting p-substituted benzoyl chlorides (**1**) and propargyl alcohol in the presence of N,N-dimethylaminopyridine (DMAP) in dry dichloromethane at 0–10 °C. The 1,4-disubstituted 1,2,3-triazoles (**3a–3p**) were synthesized by stirring p-substituted benzoic acid prop-2-ynyl esters (1 mmol) with different aralkyl bromides (1 mmol) in the presence of sodium azide (3 mmol), copper sulphate pentahydrate (0.10 mmol) and sodium ascorbate (0.20 mmol) using N,N-dimethylformamide:water (8:2) mixture as solvent at room temperature for 6–12 h (Scheme 1).

The reaction workup was carried out with aqueous ammonia-ammonium chloride solution and the compound was extracted three times with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to yield 1,4-disubstituted 1,2,3-triazoles.

2.3. Characterization of synthesized compounds

2.3.1. 4-Methylbenzoicacid-1-benzyl-1H-[1,2,3]triazol-4-ylmethylester (3a)

Appearance: white, crystalline solid; Yield: 82%; m.p. 118–120 °C; FT-IR (KBr): 3105 (C–H str., triazole ring), 3051, 2962, 1712, 1610, 1446, 1394 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 2.41 (s, 3H), 5.45 (s, 2H), 5.55 (s, 2H), 7.23 (d, 2H, J = 8 Hz), 7.28–7.31 (m, 3H), 7.38 (d, 2H, J = 12 Hz), 7.62 (s, 1H), 7.93 (d, 2H, J = 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.7, 54.3, 57.9, 123.8, 127, 128.2, 128.9, 129.2, 129.8, 134.4, 143.4, 144, 166.5; MS m/z: 308.0 [M$^+$], 309.0 [M$^+$ + 1].

2.3.2. 4-Methylbenzoicacid-1-(phenylpropyl)-1H-[1,2,3]triazol-4-ylmethylester (3b)

Appearance: off-white solid; Yield: 65%; m.p. 90–92 °C; FT-IR (KBr): 3116 (C–H str., triazole ring), 3068, 2943, 1712, 1610, 1448, 1400 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 2.17–2.24 (m, 2H), 2.39 (s, 3H), 2.64 (t, 2H), 4.32 (t, 2H), 5.43 (s, 2H), 7.12–7.30 (m, 7H), 7.64 (s, 1H), 7.92 (d, 2H, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCI_3$): 21.7, 36.8, 51.7, 57.9, 124.3, 127, 127.1, 128.7, 128.8, 129.1, 129.8, 136.9, 142.8, 143.9, 166.5; MS m/z: 336.0 [M$^+$], 337.0 [M$^+$ + 1].

2.3.3. 4-Methylbenzoicacid-1-(4-methylbenzyl)-1H-[1,2,3]triazol-4-ylmethylester (3c)

Appearance: creamy-white, crystalline solid; Yield: 68.5%. m.p. 104–106 °C; FT-IR (KBr): 3132 (C–H str., triazole ring), 3032, 2954, 2920, 1714, 1610, 1512, 1444 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 2.35 (s, 3H), 2.40 (s, 3H), 5.43 (s, 2H), 5.50 (s, 2H), 7.00–7.28 (m, 6H), 7.60 (s, 1H), 7.92 (d, 2H, J = 8 Hz); ^{13}C NMR (100 MHz, $CDCI_3$): 21.2, 21.7, 53.9, 54.1, 57.9, 123.7, 127, 127.2, 128.2, 129.1, 129.2, 129.8, 131.4, 138.8, 143.4, 143.9, 166.5; MS m/z: 322.0 [M$^+$], 323.0 [M$^+$ + 1].

2.3.4. 4-Methylbenzoicacid-1-(4-nitrobenzyl)-1H-[1,2,3]triazol–4-ylmethylester (3d)

Appearance: white, crystalline solid; Yield: 62.4%; m.p. 170–172 °C; FT-IR (KBr): 3130 (C–H str., triazole ring), 3082, 2962, 1699, 1606, 1525, 1435, 1348 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): 2.40 (s, 3H), 5.46 (s, 2H), 5.65 (s, 2H), 7.23 (d, 2H), 7.43 (d, 2H, J = 8.4 Hz), 7.73 (s, 1H), 7.91 (d, 2H, J = 8.0 Hz), 8.23 (d, 2H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCI_3$): 21.7, 53.2, 57.8, 124.1, 126.8, 129.2, 129.5,129.8, 141.4, 142.7, 144.1, 145.4, 148.1, 166.5; MS m/z: 353.0 [M$^+$], 354.0 [M$^+$ + 1].

2.3.5. 4-Methoxybenzoicacid-1-benzyl-1H-[1,2,3]triazol-4-ylmethylester (3e)

Appearance: off-white solid; Yield: 79%; m.p. 118–120 °C; FT-IR (KBr): 3136 (C–H str., triazole ring), 3064, 2951, 1712, 1604, 1508, 1452, 1323 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): 3.82 (s, 3H), 5.39 (s, 2H), 5.50 (s, 2H), 6.86 (d, 2H, J = 8 Hz), 7.28–7.33 (m, 5H), 7.60 (s, 1H), 7.95 (d, 2H,

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