Research Article

Synthesis, characterisation and biological evaluation of 1, 4 disubstituted 1, 2, 3 triazoles

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Abstract

Objective: The main objective of this research work was to synthesis the triazoles compounds by Click reaction and evaluated their antibacterial activities against gram positive and gram negative bacteria. **Material and Methods:** In this work 1,4-disubstituted 1,2,3-triazole compounds (3a-3i) were synthesized by Azide Alkyne Cycloaddition reaction and characterized by IR,^{1}H NMR and Mass spectroscopy. Further these compounds were evaluated for antibacterial activity against *Bacillus substilus*, *Staphylococcus aureus* and *Escherichia coli* by using Ciprofloxacin as standard compound with various concentrations. **Results:** Among all the compounds (3a-3i) which were screened for antibacterial activity, the compounds **3c, 3d, 3e** and **3i** were found to be excellent antibacterial agents. **Conclusion:**The presence of electron donating, electron withdrawing and halogen groups plays an important role of biological activity of compounds.

Keywords: Alkyne, antibacterial activity, azide, click reaction, triazole

Introduction

Triazoles are important five membered nitrogen heterocycles having three nitrogen atoms and two carbon atoms in ring. 1,2,4 triazole moiety containing drugs are now a days available in market due to their excellent biological activity, it includes Fluconazole, hexaconazole, rizatriptan as shown in figure 1.

Similarly 1,2,3 triazoles moiety containing drugs are excellent antimicrobial (Phillips et al., 2009), antitubercular (Patpi et al., 2012), antiallergic (Buckle et al., 1984), antrifungal (Ferreira et al., 2015), antiHIV (Mohammed et al., 2016), anti-inflammatory (Shafiet al., 2012), anticancer (Grana et al., 2006; Zhang et al., 2008) antiplatelet (Palhegan et al., 2001), anti-Alzheimer (Monceaux et al., 2011) and antiviral (Joan et al., 1998) agents. The biologically important drugs containing 1,2,3 triazole moieties are shown in figure 2.

In spite of biologically significant, the 1,2,3 triazoles are also found to have wide range of agricultural (Gisi et al., 2002) and industrial (Kim et al., 2010) applications. Due to simple structure and versatile applications of triazoles, several methods have been introduced for synthesis of 1,4 and 1,5 substituted triazoles compounds. The Husgen 1,3 dipolar cycloaddition reaction (Rostovtsev et al., 2002) is well known which produced 1,4 substituted triazole in presence of copper. The literature survey revealed (Holla et al., 2005) that 1,4 disubstituted 1,2,3 triazoles compounds with electron donating, withdrawing and halogens substituents plays an important role in bioactivity. Therefore the biological importance of 1,4 disubstituted 1,2,3 triazole with various substituents on ring inspired us to synthesis the substituted triazole and evaluate their biological activity. By taking the factors like presence of haloges, electron donating and withdrawing groups, position of substituent we have

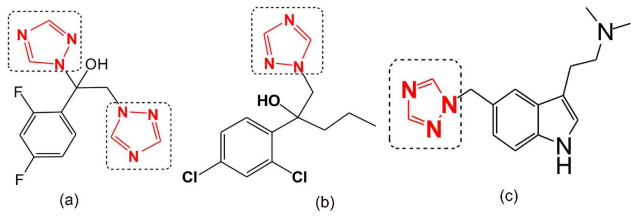

Figure1. Bioactive 1,2,4 Triazole Compounds: (a) Fluconazole as Antimycotics, (b) Hexaconazole as Antifungal, (c) Rizatriptan as Antimigrane

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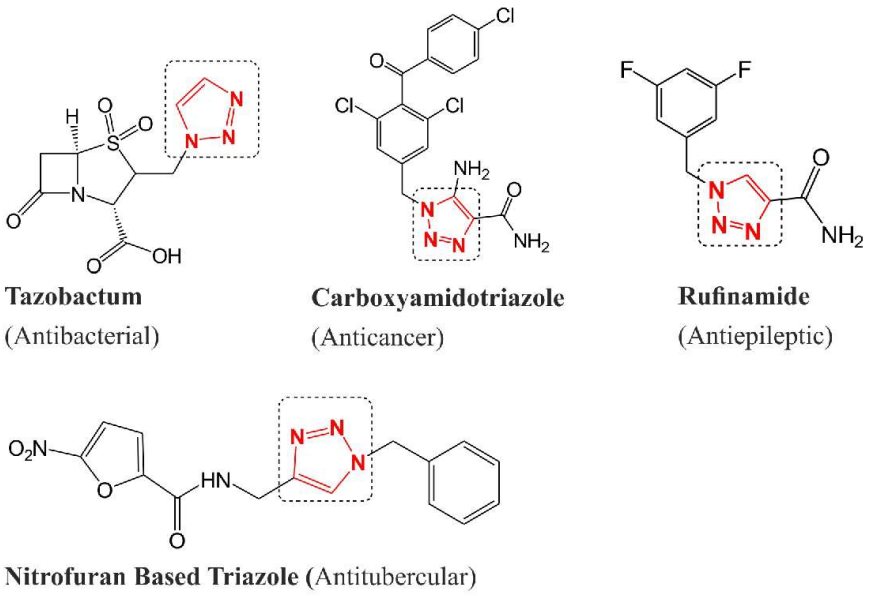
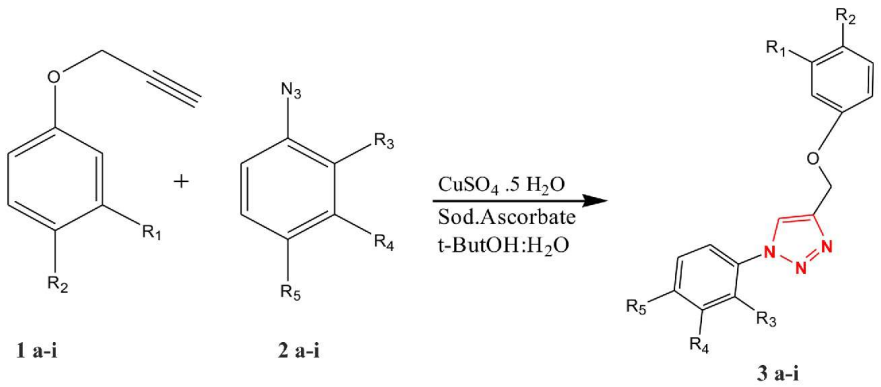


Figure 2. Examples of drugs containing 1,2,3 triazole moiety



Scheme 1. Synthesis of 1,4 disubstituted 1,2,3 Triazoles

1a : R_1=H, R_2=NO_2 **2a** : R_3=H,R_4=H,R_5=$COCH_3$ **3a** : R_1=H, R_2=NO_2, R_3=H,R_4=H,R_5=$COCH_3$

1b : R_1=H, R_2=OCH_3 **2b** : R_3=H,R_4=H,R_5=$COCH_3$ **3b** : R_1=H, R_2=OCH_3, R_3=H,R_4=H,R_5=$COCH_3$

1c : R_1=NO_2, R_2=H **2c** : R_3=H,R_4=H,R_5=$COCH_3$ **3c** : R_1=NO_2, R_2=H, R_3=H,R_4=H,R_5=$COCH_3$

1d : R_1=H, R_2=NO_2 **2d** : R_3=H,R_4=H,R_5=NO_2, **3d** : R_1=H, R_2=NO_2, R_3=H,R_4=H,R_5=NO_2,

1e : R_1=NO_2, R_2=H **2e** : R_3=H,R_4=H,R_5=NO_2, **3e** : R_1=NO_2, R_2=H, R_3=H,R_4=H,R_5=NO_2,

1f : R_1=H, R_2=NO_2 **2f** : R_3=$COCH_3$,R_4=H,R_5=H, **3f** : R_1=H, R_2=NO_2, R_3=$COCH_3$,R_4=H,R_5=H

1g : R_1=NO_2, R_2=H **2g** : R_3=$COCH_3$,R_4=H,R_5=H, **3g** : R_1=NO_2, R_2=H, R_3=$COCH_3$,R_4=H,R_5=H

1h : R_1=H, R_2=NO_2 **2h** : R_3=NO_2,R_4=NO_2,R_5=H **3h** : R_1=H, R_2=NO_2,R_3=NO_2,R_4=NO_2,R_5=H

1i : R_1=NO_2, R_2=H **2i** : R_3=NO_2,R_4=NO_2,R_5=H **3i** : R_1=NO_2, R_2=H, R_3=NO_2,R_4=NO_2,R_5=H

performed the reaction between alkyne **(1a-i)** with azides **(2a-i)** catalysed by copper to give the 1,4 disubstituted 1,2,3 triazoles **(3a-i)** as shown in scheme 1. The resulting triazoles **(3a-i)** were then screened for antibacterial activity against *Bacillus substilius*, *Staphylococcus aureus* and *Escherichia coli*.

Material and methods

The SD-Fine brand chemicals were used for this work. Melting points were determined in an open capillary by micro controller based melting point apparatus of Chemline company and are uncorrected. ^{1}H NMR spectra were

recorded on Bruker 400 MHz spectrometer by TMS as standard. Mass Spectra were recorded using Thermo Fischer mass spectrometer.IR Spectra were determined.

Synthesis of 1, 4 disubstituted 1,2,3-triazoles (3a-3i)

In a round bottom flask alkyne 1a-i (3 mmol) and azide 2a-i (3.5 mmol) were added in 1:1 mixture of ter-butyl alcohol and water (40 ml).Sodium Ascorbate (60 mg, 0.3 mmol, 1 ml of freshly prepared 3M solution in water) was added, followed by copper sulphate pentahydrate (7.5 mg, 0.03 mmol, 1 ml of 0.3 M solution in water). The resulting mixture was stirred at room temperature for 24 hrs the completion of reaction was confirmed by TLC. Then the reaction mixture was diluted with water, extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated in vacuum to give a crude product, which was purified by column chromatography on silica gel to obtain pure product. The structures of desired products were confirmed by ^{1}HNMR, Mass and IR Spectroscopy.

Antibacterial evaluation

The stock solution of all the synthesised compound (3a-i) were prepared by dissolving them in DMSO. The antibacterial activity of compounds 3a-i and Ciprofloxacin was performed by close disc method (Bhalodia et.al, 2011). All the cultures were placed for maintenance on nutrient agar and incubated at 40 ^{0} C overnight. After centrifugation and sterilisation 0.1 ml of bacterial culture solution was spread on nutrient agar plate. During the process Ciprofloxacin antibiotic disc was used as controller. The disc was then kept on nutrient agar plate and then incubated for 24 hours at 40^{0}C and zone of inhibition were measured in millimetre.

Results and discussion

1,4 disubstituted 1,2,3-triazoles **(3a-i)** were successfully synthesised by click reaction and their characterisation results showed the acceptable results. The synthesized compounds were evaluated for their antibacterial activity and found that all the compounds showed good to moderate antibacterial activity. The compounds **3c**, **3d**, **3e** and **3i** were found to be excellent antibacterial agents (Table 1).

Compound 3a (1-{4-[1-(4-Nitro-phenyl)-1H- 1,2,3-triazol-4-ylmethoxy]-phenyl}-ethanone):

Yield 73 %, m.f. $C_{17}H_{14}N_4O_4$, M.Pt.178-183 ^{0} C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.5 (s, 3H), 5.3 (s, 2H), 7.9 (s, 1H), 7.1 (d, 2H), 7.9 (d, 2H), 8.4 (d, 2H) 9.0 (d, 2H), LC–MS: *m/z*: 339.31 $(M+1)^+$, IR KBr cm^{-1} 2915(CH_3),1713(C=O),1597(NO_2)1257(OCH_2)

Compound 3b (1-{4-[1-(4-Methoxyphenyl)-1H- 1,2,3-triazol-4-ylmethoxy]-phenyl}-ethanone):

Yield 91 %, m.f. $C_{18}H_{17}N_3O_3$, M.Pt. 121 -127 ^{0} C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.5 (s, 3H), 3.8 (s, 2H),5.3 (s,2H), 7.0 (d, 2H), 7.1 (d, 2H), 7.6(s, 1H), 7.7 (d, 2H) 7.9 (d, 2H), LC–MS: *m/z*: 324.34 $(M+1)^+$, ,IR KBr cm^{-1} 2920(CH_3),1719(C=O),1250(OCH_2)

Compound 3c (1-{4-[1-(Nitro-phenyl)-1H- 1,2,3-triazol-4-ylmethoxy]-phenyl}-ethanone):

Yield 89 %, m.f. $C_{17}H_{14}N_4O_4$, M.Pt.155-161 ^{0} C ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.5 (s, 3H), 5.4 (s, 2H), 7.1 (d, 2H), 7.6 (d, 2H),7.7 (s,1H),8.1(d 1H), 8.2(d,2H),8.3 (m, 1H), 8.6 (s, 1H), LC–MS: *m/z*: 339.31 $(M+1)^+$, IR KBr cm^{-1} 2931(CH_3),1775(C=O),1696(CH=CH)

Compound 3d (1-(4-Nitro-phenoxymethyl)-1-(4-nitro-phenyl)-1H-1,2,3 triazole):

Yield 69 %, m.f. $C_{15}H_{11}N_5O_5$, M.Pt.210-216 ^{0} C ^{1}H NMR

Table 1. Antibacterial activity of 1, 4 disubstitiuted 1,2,3 triazoles (3a-3i) (Zone of inhibition in millimetre at 300 µg/ml concentration)

Compounds	Concentration (µg/ml)	*Bacillus subtillus*	*Staphylococcus aureus*	*Escherichia coli*
3a	300	17	19	18
3b	300	16	15	-
3c	300	11	12	14
3d	300	14	15	14
3e	300	10	11	13
3f	300	19	16	19
3g	300	14	16	-
3h	300	-	17	15
3i	300	11	10	11
Ciprofloxacin	30 (µg/disc)	23	21	22

($CDCl_3$, 400 MHz): δ 5.4 (s, 2H), 7.1 (d, 2H),7.5 (d,2H), 7.8 (s, 1H), 7.9 (d, 2H), 8.4(d, 2H), LC–MS: *m/z*: 342.18 $(M+1)^+$, IR KBr cm^{-1} 1720,(CH=CH),1590(NO_2),1255(OCH_2)

Compound 3e (1-(3-Nitro-phenoxymethyl)-1-(4-nitro-phenyl)-1H-1,2,3 triazole):

Yield 81 %, m.f. $C_{15}H_{11}N_5O_5$, M.Pt.163-167 ^{0}C ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.4 (s, 2H), 7.1-7.6 (m, 4H), 7.8 (d, 2H),7.7(s,1H), 8.3(d, 2H), LC–MS: *m/z*: 342.18 $(M+1)^+$, IR KBr cm^{-1} 1713(CH=CH),1574(NO_2)1260(OCH_2)

Compound 3f (1-{2-[1-(4-Nitro-phenyl)-1H- 1,2,3-triazol-4-ylmethoxy]-phenyl}-ethanone):

Yield 73 %, m.f. $C_{17}H_{14}N_4O_4$, M.Pt.127-131 ^{0}C ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.6 (s, 3H), 5.4 (s,2H),7.0-7.5 (m,4H), 7.4(d,2H),7.7(s,1H), 8.4(d, 2H), LC–MS: *m/z*: 339.31 $(M+1)^+$, IR KBr cm^{-1} 2913(CH_3),1725(C=O),1305(N-O)

Compound 3g (1-{2-[1-(3-Nitro-phenyl)-1H- 1,2,3-triazol-4-ylmethoxy]-phenyl}-ethanone):

Yield 82 %, m.f. $C_{17}H_{14}N_4O_4$, M.Pt.137-143 ^{0}C ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.6 (s, 3H), 5.4 (s,2H),7.0-7.7 (m,4H), 8.1-8.6(m,3H),7.7(s,1H), 8.6(s, 1H), LC–MS: *m/z*: 339.31 $(M+1)^+$, IR KBr cm^{-1} 2940(CH_3),1712(C=O),1561(NO_2)

Compound 3h (4-(2,3-Dinitro-phenoxymethyl)-1-(4-nitro-phenyl)-1H-1,2,3-trizole):

Yield 63 %, m.f. $C_{15}H_{10}N_6O_7$, M.Pt.171-175 ^{0}C ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.6 (s,2H),7.8 (d,2H), 8.1-8.4(m,3H),8.9(d,2H), LC–MS: *m/z*: 387.16 $(M+1)^+$, IR KBr cm^{-1} 1696(CH=CH),1539(NO_2),1261(OCH_2)

Compound 3i (4-(2,3-Dinitro-phenoxymethyl)-1-(3-nitro-phenyl)-1H-1,2,3-triazole):

Yield 63 %, m.f. $C_{15}H_{10}N_6O_7$,M.Pt.153-157 ^{0}C ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.6 (s,2H),7.2 (s,1H), 7.5-8.4(m,3H),8.7(s,1H),7.7-8.7(m,3H) LC–MS: *m/z*: 387.16 $(M+1)^+$, IR KBr cm^{-1} 1708(CH=CH),1570(NO_2),1211(OCH_2)

Conclusion

In conclusion we have synthesised the 1,4 disubstituted 1,2,3 triazoles by well known Click reaction and evaluate their antibacterial activities against *Bacillus subtilus*, *Staphylococcus aureus* and *Escherichia coli* and found that these are good antibacterial agents. Out of which, the compounds **3c, 3d, 3e** and **3i** showed excellent antibacterial activity, it is due to presence of nitro and carbonyl groups at different positions of ring which enhance the activity of these compounds as compared to other compounds.

Conflicts of interest

The author declares that there is no conflict of interest.

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