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Design, synthesis, antimicrobial evaluation and in silico studies of symmetrical bis (urea-1,2,3-triazole) hybrids

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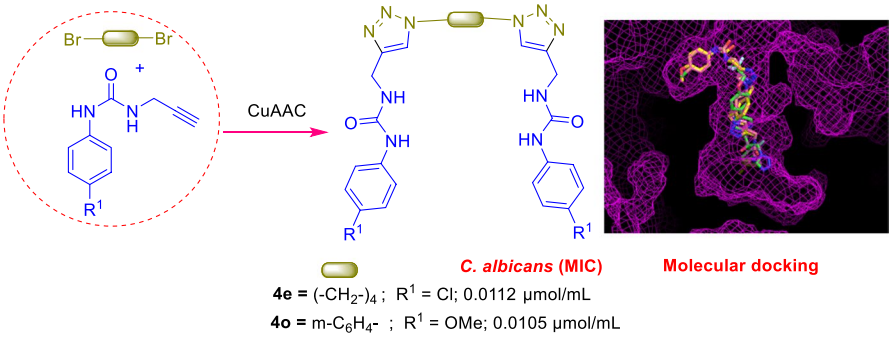
Abstract

In search of 1,2,3-triazole-based antimicrobials, some symmetrical bis(urea-1,2,3-triazole) hybrids were synthesized via clicked Huisgen cycloaddition. The structural characterization was done by different physical and spectral techniques like NMR, FTIR and HRMS. In vitro antimicrobial evaluation of all the synthesized compounds was performed against three bacterial strains (*Staphylococcus epidermidis, Escherichia coli* and *Bacillus subtilis*) and two fungal strains (*Aspergillus niger* and *Candida albicans*). All the synthesized urea-linked bis(1,2,3-triazole) hybrids (**4a–4o**) were found to exhibit higher potency than their alkyne precursors (**3a–3c**). Also, all the synthesized hybrids elicited better antifungal activity than the reference drug Fluconazole against both the fungal strains. Compound **4e** and **4o** were found to be more potent toward *C. albicans* with lowest MIC values 0.0112 µmol/mL and 0.0105 µmol/mL, respectively. The docking studies of compounds **4e** and **4o** and their respective alkynes **3b** and **3c** were carried out in the active site of sterol 14-α-demethylase of *C. albicans*.

Graphic abstract



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Extended author information available on the last page of the article

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Keywords Urea · Bis-triazoles · Antimicrobial activity · In silico studies

Introduction

The day-by-day increase in antimicrobial resistance has hampered the effective treatment of different human diseases caused by various microbes. There is a need for integral efforts to develop methodologies to provide new classes of drugs with better efficacy and low toxicity because the cases of multidrug resistance among various microorganisms toward currently available drugs continue to spread inevitably [1–4]. In this regard, clicked Huisgen cycloaddition chemistry has evolved as an important strategy for rapid and selective synthesis of 1,4-disubstituted 1,2,3-triazoles [5–7]. This cycloaddition has been proved to be a very useful technique in the functional modification of biomolecules mainly because of its high selectivity, yield and biocompatibility as well as its stability toward metabolic degradation [8–11]. This reaction has been studied extensively because of its number of applications counting drug discovery [12, 13], bioconjugation [14], ion recognition [15], polymer chemistry [16], radiochemistry, etc. 1,4-Disubstituted 1,2,3-triazoles possess high dipole moment, and exhibit various interactions like Van der Waals forces, hydrogen bonding, dipole–dipole, hydrophobic and other non-covalent interactions with a diversified range of biomolecular targets [17]. Organic molecules containing 1,2,3-triazole framework are reported to possess a diverse range of pharmacological activities including anticancer [18, 19], antimicrobial [20–22], antidiabetic [23–25], anti-inflammatory [26, 27], anti-oxidant [28], antiviral [29], antituberculosis [30, 31], etc.

Urea linkage has also been recognized as an important pharmacophore present in a number of naturally occurring and synthetic bioactive molecules [32]. Some symmetrical and unsymmetrical mono- and bis-amides linked with thiophene are reported with antiproliferative activity [33]. There are various reports on urea derivatives exhibiting a plethora of pharmacological activities such as antitubercular [34], antimicrobial [35], antidiabetic [36] and anti-HIV [37]. It has been observed that with slight structural modifications in the molecular framework around the urea skeleton, significant changes in the pharmacological properties of the hybrid molecules are reported. Further, a synergistic improvement of the biological potential has been achieved by the covalent attachment of combination of urea linkage with one or more pharmacophores including aziridine, trifluoromethyl coumarinyl, 1,2,4-triazole, 1,2,3-triazole, 4-piperazinyl quinoline [38, 39], etc.

1,2,3-Bistriazole derivatives are of significant importance due to the presence of two triazole scaffolds which will further enhance their practical utility in the field of supramolecular chemistry [40, 41], medicinal chemistry [42, 43], polymer chemistry [44], etc. The synthesis of 1,2,3-bistriazoles with different spacers can be achieved either by reacting diacetylenes with azides or by diazides with acetylenes. 1,2,3-Bistriazoles have been synthesized from dialkyne spacers linked with

ester, amide, amino acids, carbohydrates, benzothiazoles, chalcones, phenanthroline, pyridine, etc. with good-to-moderate antimicrobial and anticancer activities [45–51]. Also, some articles are available on the synthesis of biologically active 1,2,3-bistriazoles through diazide spacers linked with ferrocene, anthracene, pyridine [52–54], etc. The structures of some pharmacologically active 1,2,3-bistriazoles (**I**–**VI**) are shown in (Fig. 1).

Therefore, in view of the aforementioned and our interest in the development of bioactive 1,2,3-triazole hybrids [18, 21, 25, 38, 61], we planned to synthesize some symmetrical bis(urea-1,2,3-triazole) hybrids with different aliphatic and aromatic spacers. Herein, we depict the synthesis of some new symmetrical bis(urea-1,2,3-triazole) hybrids as antimicrobial agents from different aliphatic and aromatic diazides.

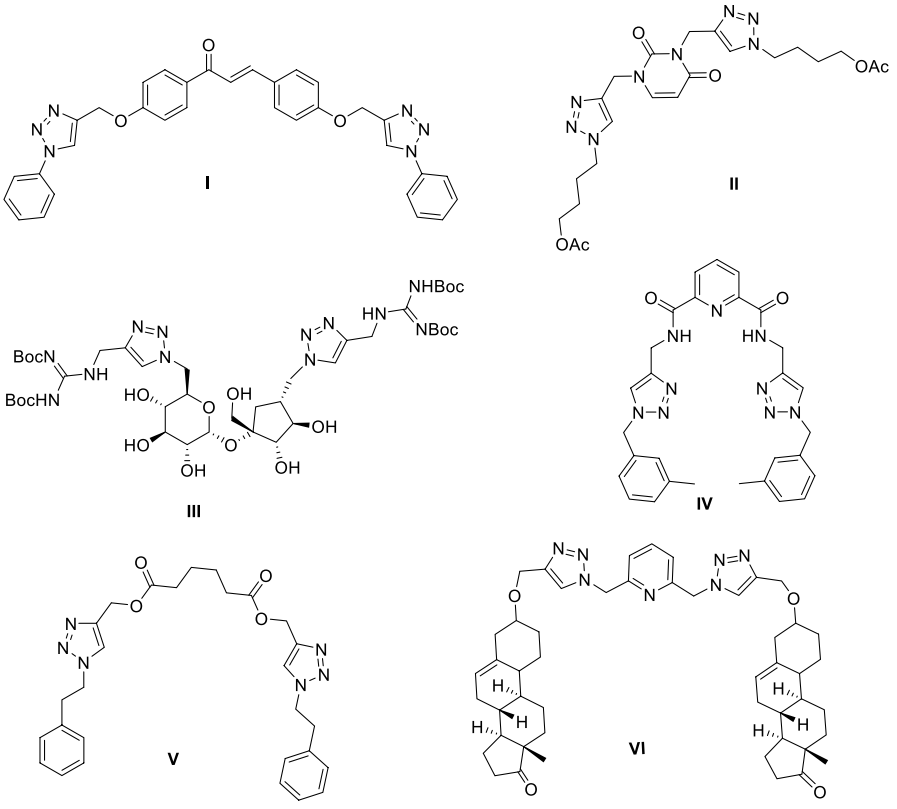


Fig.1 Structures of some pharmacologically important 1,2,3-bistriazoles

Materials and methods

General

Commercially available chemicals were used for the preparation of reactants (**2a**–**2e**) and (**3a**–**3c**). Then, the products were synthesized and open capillaries were used for examining their melting points, which were reported as such. After monitoring the reaction by TLC on silica plated aluminum sheets (SIL G/UV254, ALUGRAM), successful visualization was done under the UV chamber. Then, SHIMADZU IR AFFINITY-I FTIR spectrophotometer was used for recording the IR spectra of the synthesized compounds in the range of 400–4000 cm^{-1}. Bruker 400 MHz spectrophotometer was used for determining the NMR spectra of the compounds with TMS as the internal standard. The chemical shift values and the coupling constant values were reported in δ and Hz, respectively.

General method for synthesizing bis-urea-triazoles (4a–4o) Dibromides of n-alkanes and m-xylylene (**1a**–**1e**; 1.042 mmol) were used for the synthesis of diazides (**2a**–**2e**) by reacting with sodium azide (6.252 mmol) in dimethylformamide (4 mL). The reaction mixture was allowed to stir for 8 h at 70 °C. Then, urea-alkynes (**3a**–**3c**; 2.084 mmol) dissolved in dimethylformamide (2 mL) were transferred to the ongoing reaction. After the addition of copper sulfate (0.2084 mmol) dissolved in water (2 mL) and sodium ascorbate, the mixture was heated at 45 °C for 4–5 h. The mixture was filtered after the successful completion of the reaction, providing the white colored solid. Then, the obtained solid was washed with ice-cold aqueous ammonia, water and a small amount of ethyl acetate to yield pure symmetrical bis(urea-1,2,3-triazole) hybrids (**4a**–**4o**).

1,1′-((1,1′-(Propane-1,3-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-fluorophenyl)urea) (4a) Yield 71%; White solid; mp: 286–289 °C; IR (KBr, ν_{max}/cm^{-1}): 3312 (NH str), 3128 (C–*H* str, triazole), 1630 (C=O str), 1515 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.58 (s, 2H, 2NH), 7.99 (s, 2H, triazolyl-2H), 7.40 (dd, J = 7.7, 4.8 Hz, 4H, Ar–H), 7.06 (t, J = 8.6 Hz, 4H, Ar–H), 6.57 (broad triplet, 2H, 2NH), 4.35 (dd, J = 16.4, 6.0 Hz, 8H), 2.42–2.33 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.57, 156.22, 155.58, 146.08, 137.18, 123.21, 119.81, 119.74, 115.66, 115.44, 47.06, 35.34, 30.81. HRMS: m/z $(M+H)^+$ cacld. for $C_{23}H_{25}F_2N_{10}O_2$: 511.2130 found: 511.2121.

1,1′-((1,1′-(Propane-1,3-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-chlorophenyl)urea) (4b) Yield 75%; White solid; mp: 262–264 °C; IR (KBr, ν_{max}/cm^{-1}): 3319 (NH str), 3134 (NH str), 3091 (C–H str, triazole), 1633 (C=O str), 1598 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72 (s, 2H, 2NH), 8.00 (s, 2H, triazolyl-2H), 7.44–7.41 (m, 4H, Ar–H), 7.28–7.24 (m, 4H, Ar–H), 6.64 (t, J = 5.6 Hz, 2H, 2NH), 4.35 (dd, J = 15.4, 6.3 Hz, 8H), 2.37 (dt, J = 14.0, 7.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.37, 145.94, 139.83, 128.93,

125.06, 123.23, 119.63, 47.06, 35.32, 30.80. HRMS: m/z $(M+Na)^+$ cacld. For $C_{23}H_{24}Cl_2N_{10}NaO_2$: 565.1358 found: 565.3611.

1,1′-((1,1′-(Propane-1,3-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-methoxyphenyl)urea) (4c) Yield 74%; White solid; mp: 272–274 °C; IR (KBr, ν_{max}/cm^{-1}): 3313 (NH str), 3133 (C–H str, triazole), 1634 (C=O str), 1578 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 2H, 2NH), 7.98 (s, 1H, triazolyl-2H), 7.31–7.26 (m, 4H, Ar–H), 6.84–6.79 (m, 4H, Ar–H), 6.46 (t, $J=5.6$ Hz, 2H), 4.39–4.31 (m, 8H), 3.69 (s, 6H, $2OCH_3$), 2.38 (*p*, $J=7.1$ Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.77, 154.50, 146.22, 133.94, 123.19, 119.96, 114.36, 55.62, 47.07, 35.35, 30.81. HRMS: m/z $(M+H)^+$ cacld. for $C_{25}H_{31}N_{10}O_4$: 535.2530 found: 535.2111.

1,1′-((1,1′-(Butane-1,4-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-fluorophenyl)urea) (4d) Yield 77%; White solid; mp: 274–278 °C; IR (KBr, ν_{max}/cm^{-1}): 3308 (NH str), 3128 (C–H str, triazole), 1633 (C=O str), 1465 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 2H, 2NH), 7.94 (s, 2H, triazolyl-2H), 7.40 (dd, $J=8.6$, 4.9 Hz, 4H, Ar–H), 7.06 (t, $J=8.8$ Hz, 4H, Ar–H), 6.59 (t, $J=5.1$ Hz, 2H, 2NH), 4.38–4.30 (m, 8H), 1.77 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.56, 156.20, 155.59, 145.94, 137.21, 123.04, 119.78, 119.70, 115.65, 115.44, 49.02, 35.33, 27.35. HRMS: m/z $(M+H)^+$ cacld. for $C_{24}H_{27}F_2N_{10}O_2$: 525.2287 found: 525.2884.

1,1′-((1,1′-(Butane-1,4-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-chlorophenyl)urea) (4e) Yield 72%; White solid; mp: 265–268 °C; IR (KBr, ν_{max}/cm^{-1}): 3305 (NH str), 3134 (C–H str, triazole), 1635 (C=O str), 1595 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 2H, 2NH), 7.95 (s, 2H, triazolyl-2H), 7.42 (d, $J=8.4$ Hz, 4H, Ar–H), 7.26 (d, $J=8.4$ Hz, 4H, Ar–H), 6.63 (broad triplet, 2H, 2NH), 4.40–4.30 (m, 8H), 1.76 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.36, 145.84, 139.84, 128.93, 125.12, 123.06, 119.62, 49.03, 35.32, 27.35. HRMS: m/z $(M+H)^+$ cacld. for $C_{24}H_{27}Cl_2N_{10}O_2$: 557.1695 found: 557.2104.

1,1′-((1,1′-(Butane-1,4-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-methoxyphenyl)urea) (4f) Yield 78%; White solid; mp: 266–270 °C; IR (KBr, ν_{max}/cm^{-1}): 3311 (NH str), 3128 (C–H str, triazole), 1635 (C=O str), 1563 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (s, 2H. 2NH), 7.93 (s, 2H, triazolyl-2H), 7.29 (d, $J=8.6$ Hz, 4H, Ar–H), 6.81 (d, $J=8.4$ Hz, 4H, Ar–H), 6.48–6.42 (m, 2H, 2NH), 4.40–4.28 (m, 8H), 3.69 (s, 6H, OCH_3), 1.77 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.82, 154.48, 141.71, 133.93, 123.01, 119.90, 114.29, 55.60, 49.02, 35.34, 27.35. HRMS: m/z $(M+H)^+$ cacld. for $C_{26}H_{33}N_{10}O_4$: 549.2686 found: 549.2913.

1,1′-((1,1′-(Pentane-1,5-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-fluorophenyl)urea) (4g) Yield 71%; White solid; mp: 270–273 °C; IR (KBr, ν_{max}/cm^{-1}): 3314 (NH str), 3128 (C–H str, triazole), 1631 (C=O str), 1509 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (s, 2H, 2NH), 7.94 (s, 2H, triazolyl-2H), 7.40 (dd, $J=7.7$, 4.9 Hz, 4H, Ar–H), 7.06 (*t*, $J=8.6$ Hz, 4H, Ar–H),

6.56 (s, 2H, 2NH), 4.32 (d, $J = 5.6$ Hz, 8H), 1.87–1.78 (m, 4H), 1.25–1.15 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.61, 156.21, 155.57, 145.86, 137.18, 122.93, 119.79, 119.71, 115.66, 115.44, 49.44, 35.34, 29.57, 23.29. HRMS: m/z $(M+H)^+$ cacld. for $C_{25}H_{29}F_2N_{10}O_2$: 539.2443 found: 539.2440.

1,1′-((1,1′-(Pentane-1,5-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-chlorophenyl)urea) (4h) Yield 77%; White solid; mp: 265–270 °C; IR (KBr, ν_{max}/cm^{-1}): 3318 (NH str), 3126 (C–H str, triazole), 1634 (C=O str), 1504 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 2H, 2NH), 7.94 (s, 2H, triazolyl-2H), 7.42 (d, $J = 8.9$ Hz, 4H, Ar–H), 7.26 (d, $J = 8.9$ Hz, 4H, Ar–H), 6.62 (t, $J = 5.6$ Hz, 2H, 2NH), 4.31 (dd, $J = 7.6$, 6.7 Hz, 8H), 1.87–1.77 (m, 4H), 1.25–1.15 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.36, 145.81, 139.84, 128.93, 125.06, 122.96, 119.62, 49.45, 35.33, 29.56, 23.28. HRMS: m/z $(M+H)^+$ cacld. for $C_{25}H_{29}Cl_2N_{10}O_2$: 571.1852 found: 571.1857.

1,1′-((1,1′-(Pentane-1,5-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-methoxyphenyl)urea) (4i) Yield 79%; White solid; mp: 260–262 °C; IR (KBr, ν_{max}/cm^{-1}): 3311 (NH str), 3128 (C–H str, triazole), 1635 (C=O str), 1563 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 2H, 2NH), 7.93 (s, 2H, triazolyl-2H), 7.29 (d, $J = 8.9$ Hz, 4H, Ar–H), 6.81 (d, $J = 9.0$ Hz, 4H, Ar–H), 6.46 (t, $J = 5.6$ Hz, 2H, 2NH), 4.31 (dd, $J = 9.2$, 4.8 Hz, 8H), 3.69 (s, 6H, 2OCH$_3$), 1.86–1.78 (m, 4H), 1.20 (dt, $J = 15.3$, 7.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.73, 154.45, 146.00, 133.94, 122.91, 119.90, 114.34, 55.60, 49.44, 35.34, 29.57, 23.29. HRMS: m/z $(M+H)^+$ cacld. for $C_{27}H_{35}N_{10}O_4$: 563.2843 found: 563.2815.

1,1′-((1,1′-(Hexane-1,6-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-fluorophenyl)urea) (4j) Yield 76%; White solid; mp: 260–264 °C; IR (KBr, ν_{max}/cm^{-1}): 3305 (NH str), 3131 (C–H str, triazole), 1630 (C=O str), 1561 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.59 (s, 2H, 2NH), 7.94 (s, 2H, triazolyl-2H), 7.39 (s, 4H, Ar–H), 7.06 (t, $J = 8.4$ Hz, 4H, Ar–H), 6.56 (s, 2H, 2NH), 4.31 (s, 8H), 1.77 (s, 4H), 1.24 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 158.57, 156.21, 155.57, 145.85, 137.19, 122.91, 119.78, 119.70, 115.66, 115.44, 49.58, 35.34, 29.99, 25.68. HRMS: m/z $(M+H)^+$ cacld. for $C_{26}H_{31}F_2N_{10}O_2$: 553.2600 found: 553.2591.

1,1′-((1,1′-(Hexane-1,6-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene))bis(3-(4-chlorophenyl)urea) (4k) Yield 74%; White solid; mp: 268–272 °C; IR (KBr, ν_{max}/cm^{-1}): 3309 (NH str), 3102 (C–H str, triazole), 1636 (C=O str), 1596 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 2H, 2NH), 7.94 (s, 2H, triazolyl-2H), 7.42 (d, $J = 8.8$ Hz, 4H, Ar–H), 7.26 (d, $J = 8.8$ Hz, 4H, Ar–H), 6.62 (t, $J = 5.3$ Hz, 2H, 2NH), 4.30 (dd, $J = 12.7$, 6.1 Hz, 8H), 1.76 (s, 4H), 1.23 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.36, 145.73, 139.82, 128.93, 125.06, 122.93, 119.61, 49.58, 35.33, 29.98, 25.68. HRMS: m/z $(M+H)^+$ cacld. for $C_{26}H_{31}Cl_2N_{10}O_2$: 585.2008 found: 585.2013.

1,1′-((1,1′-(Hexane-1,6-diyl)bis(1H-1,2,3-triazole-4,1-diyl))bis(methylene)) bis(3-(4-methoxyphenyl)urea) (4l) Yield 76%; White solid; mp: 267–270 °C; IR (KBr,

ν_{max}/cm^{-1}): 3310 (NH str), 3134 (C–H str, triazole), 1628 (C=O str), 1516 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.34 (s, 2H, 2NH), 7.94 (d, J = 5.5 Hz, 2H, triazolyl-2H), 7.29 (d, J = 8.6 Hz, 4H, Ar–H), 6.81 (d, J = 8.6 Hz, 4H, Ar–H), 6.45 (t, J = 5.1 Hz, 2H, 2NH), 4.30 (d, J = 5.4 Hz, 8H), 3.69 (s, 6H, 2OCH_3), 1.79 (dd, J = 12.3, 5.2 Hz, 4H), 1.24 (s, 4H). ^{13}C NMR (101 MHz, DMSO): δ 155.76, 154.45, 145.95, 133.91, 122.90, 119.89, 114.34, 55.60, 50.97, 49.58, 35.34, 29.99, 28.53, 25.96, 25.87, 25.69. HRMS: m/z $(M+H)^+$ cacld. for $C_{28}H_{37}N_{10}O_4$: 577.2999 found: 577.2960.

1,1′-((1,1′-(1,3-Phenylenebis(methylene))bis(1H-1,2,3-triazole-4,1-diyl)) bis(methylene))bis(3-(4-fluorophenyl)urea) (4m) Yield 79%; White solid; mp: 264–268 °C; IR (KBr, ν_{max}/cm^{-1}): 3317 (NH str), 3128 (C–H str, triazole), 1633 (C=O str), 1509 (C=C str). ^{1}H NMR (400 MHz, DMSO): δ 8.57 (s, 2H, 2NH), 8.00 (s, 2H, triazolyl-2H), 7.39 (dd, J = 9.0, 5.1 Hz, 5H, Ar–H), 7.35 (d, J = 2.8 Hz, 1H, Ar–H), 7.25 (d, J = 7.7 Hz, 2H, Ar–H), 7.05 (t, J = 8.9 Hz, 4H, Ar–H), 6.56 (t, J = 5.5 Hz, 2H, 2NH), 5.56 (s, 4H), 4.32 (d, J = 5.5 Hz, 4H). ^{13}C NMR (101 MHz, DMSO): δ 158.58, 156.22, 155.57, 146.33, 137.18, 129.69, 128.19, 128.09, 123.24, 119.81, 119.74, 115.65, 115.43, 52.94, 35.35. HRMS: m/z $(M+H)^+$ cacld. for $C_{28}H_{27}F_2N_{10}O_2$: 573.2287 found: 573.2290.

1,1′-((1,1′-(1,3-Phenylenebis(methylene))bis(1H-1,2,3-triazole-4,1-diyl)) bis(methylene))bis(3-(4-chlorophenyl)urea) (4n) Yield 72%; White solid; mp: 280–282 °C; IR (KBr, ν_{max}/cm^{-1}): 3316 (NH str), 3134 (C–H str, triazole), 1635 (C=O str), 1511 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 2H, 2NH), 8.01 (s, 2H, triazolyl-2H), 7.42 (d, J = 8.9 Hz, 4H, Ar–H), 7.38 (d, J = 7.7 Hz, 1H, Ar–H), 7.34 (d, J = 2.4 Hz, 1H, Ar–H), 7.26 (d, J = 8.8 Hz, 5H, Ar–H), 7.24 (s, 1H, Ar–H), 6.63 (t, J = 5.5 Hz, 2H, 2NH), 5.56 (s, 4H), 4.32 (d, J = 5.5 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.38, 146.23, 139.83, 137.14, 129.70, 128.93, 128.21, 128.11, 125.08, 123.28, 119.64, 52.95, 35.33. HRMS: m/z $(M+H)^+$ cacld. for $C_{28}H_{27}Cl_2N_{10}O_2$: 605.1695 found: 605.1700.

1,1′-((1,1′-(1,3-Phenylenebis(methylene))bis(1H-1,2,3-triazole-4,1-diyl)) bis(methylene))bis(3-(4-methoxyphenyl)urea) (4o) Yield 76%; White solid; mp: 262–268 °C; IR (KBr, ν_{max}/cm^{-1}): 3322 (NH str), 3128 (C–H str, triazole), 1630 (C=O str), 1534 (C=C str). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.33 (s, 2H, 2NH), 7.99 (s, 2H, triazolyl-2H), 7.38 (d, J = 7.8 Hz, 1H, Ar–H), 7.35 (d, J = 3.8 Hz, 1H, Ar–H), 7.30–7.27 (m, 4H, Ar–H), 7.25 (dd, J = 7.5, 1.3 Hz, 2H, Ar–H), 6.83–6.79 (m, 4H, Ar–H), 6.47 (t, J = 5.6 Hz, 2H, 2NH), 5.56 (s, 4H), 4.31 (d, J = 5.6 Hz, 4H), 3.69 (s, 6H, 2OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.74, 154.46, 146.47, 137.15, 133.92, 129.69, 128.19, 128.08, 123.22, 119.93, 114.34, 55.60, 52.93, 35.35. HRMS: m/z $(M+H)^+$ cacld. for $C_{30}H_{33}N_{10}O_4$: 597.2686 found: 597.2653.

Pharmacology

Already reported procedure by Kaushik et al. was used to study the antimicrobial activities [55].

Docking details

The crystal structure of protein *C. albicans* sterol 14-α-demethylase was retrieved from the protein data bank with PDB ID: 5TZ1. The preparation of protein and compounds was carried out according to the procedure reported by us in previous studies [55–57]. The docking simulations were accomplished with Autodock Vina software [58] using search box with dimensions center_x = 72.0224738378, center_y = 63.8191053546, center_z = 5.24372711084, size_x = 25.0, size_y = 28.2139473943 and size_z = 25.0 and visualization work was performed with discovery studio visualizer [59] and PyMOL [60].

Results and discussion

Chemistry

Symmetrical bis(urea-1,2,3-triazole) hybrids have been synthesized in two steps starting from the commercially available dibromides (**1a**–**1e**) which on reaction with sodium azide in dimethylformamide at 70 °C generated diazides (**2a**–**2e**). Then, without isolating, these diazides were subjected to CuACC reaction with other precursors, i.e., urea-linked terminal alkynes (**3a**–**3c**) using sodium ascorbate and catalytic amount of copper sulfate pentahydrate to yield the hybrid compounds (**4a**–**4o**; Scheme 1). The urea-linked alkynes (**3a**–**3c**) were synthesized via reacting phenyl isocyanate derivatives with propargyl amine in the presence of triethylamine in dichloromethane by a well-known method reported previously [61]. A possible mechanism for the click synthesis of symmetrical bis(urea-1,2,3-triazole) hybrids is depicted in Scheme 2.

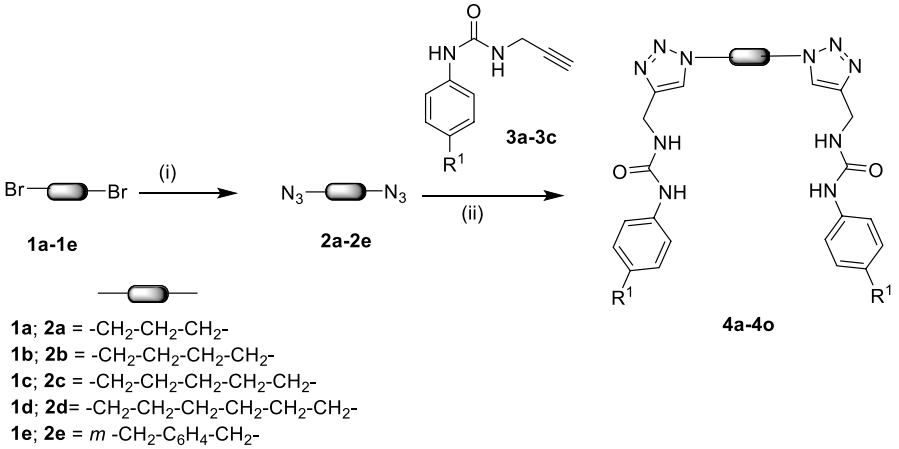
Spectroscopic techniques like FTIR, ^{1}H NMR, ^{13}C NMR and HRMS were used for analyzing the structures of all the products.

IR analysis

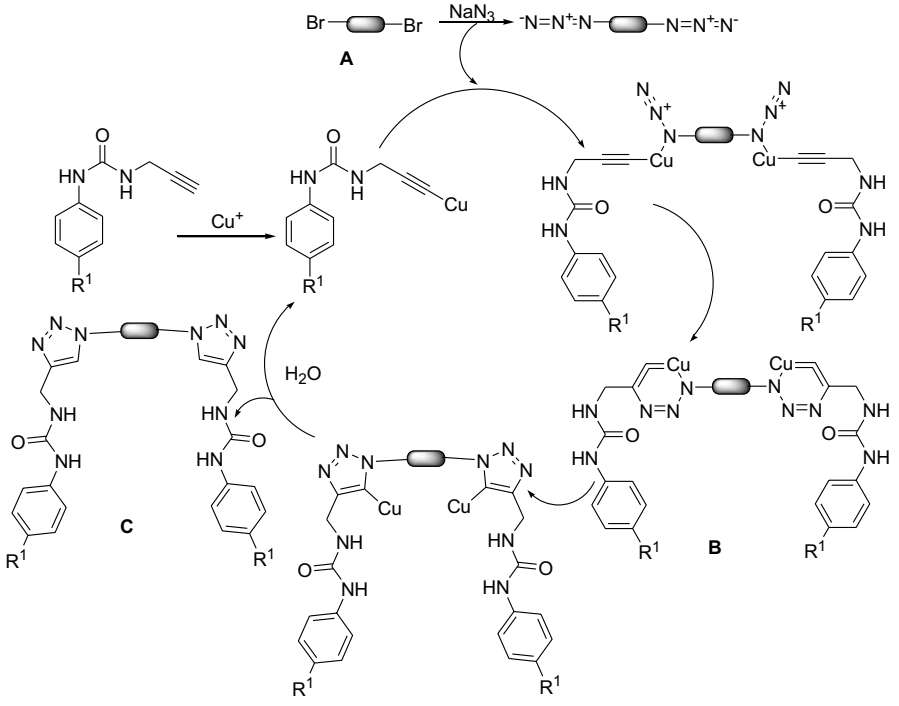
For instance, in the IR spectrum of **4 h**, the presence of a band at 3129 cm^{-1} due to C–H stretching of triazole confirmed the formation of a triazole ring. A band at 3318 cm^{-1} was due to the N–H stretching of the urea group, and a strong band at 1634 cm^{-1} was observed due to the C=O stretching vibrations of urea functionality.

^{1}H NMR analysis

A sharp singlet confirming the triazole ring formation was observed at δ 7.94 in the ^{1}H NMR spectrum of the synthesized compound **4 h**. The signal due to two protons (NH) of bis-urea-triazole appeared as a singlet at δ 8.71. The other–NH–protons of urea moiety observed as a triplet signal at δ 6.62 with a coupling constant of 5.6 Hz. The eight–NCH_2–protons observed as a doublet of doublet signal at δ 4.31 (J = 7.6, 6.7 Hz). Methylene protons adjacent to nitrogen of triazole ring appeared as



Scheme 1 **i** Sodium azide, DMF, 70 °C; 8 h; **ii** $CuSO_4.5H_2O$, sodium ascorbate, Water:DMF (1:3); 45 °C; 4–5 h

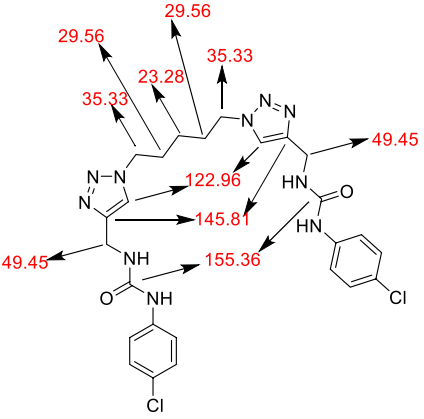


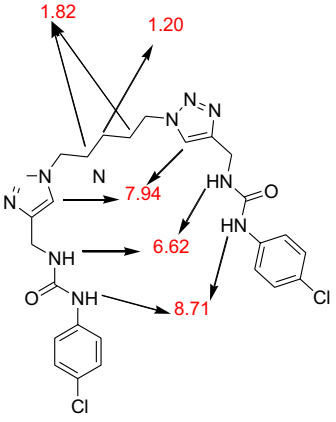
Scheme 2 Plausible mechanism for synthesis of symmetrical bis(urea-1,2,3-triazole) hybrids

a multiplet of eight protons at δ 1.82. The other methylene protons attached present at the central carbon atom of the pentyl group appeared as a multiplet at δ 1.20.

^{13}C NMR analysis

On analyzing the ^{13}C NMR spectra of compound **4 h**, different peaks were allocated to the carbon atoms of the compound by means of techniques like DEPT-135, ^{13}C NMR and the previous literature. The carbonyl carbon atom observed at δ 155.36 and those of the triazole ring appeared at δ values 122.96 (C–5) and 145.81 (C–4), respectively. The chemical shift values to the carbon atoms of the n-pentyl group can be assigned on the basis of the deshielding of protons in the ^{1}H NMR spectra of compound **4 h**.





Important chemical shift values (δ ppm) in ^{13}C NMR and ^{1}H NMR spectrum of compound **4 h.**

HRMS analysis

The structures of synthesized hybrids were further confirmed on the basis of their HRMS spectra, e.g., compound **4 h** demonstrated a signal at m/z 571.1857 analogous to $[M+H]^+$ which closely resembles the calculated value (m/z = 571.1852).

Antimicrobial activity

In vitro screening for antimicrobial activity of the synthesized compounds against gram-positive bacteria (*Staphylococcus epidermidis* and *Bacillus subtilis* MTCC 441), gram-negative bacterium (*Escherichia coli* MTCC 16,521) and fungal strains (*Aspergillus niger* MTCC 8189 and *Candida albicans* MTCC 227) was done using the standard serial dilution method. The reference drugs Ciprofloxacin and Fluconazole were taken for comparing the values of antibacterial and antifungal activity of bis(urea-1,2,3-triazole) hybrids. Minimum inhibitory concentrations (MIC in μmol/mL) evaluated for all the synthesized hybrids along with the reference drugs are listed in Table 1. Only a few of the synthesized hybrids, in antibacterial screening,

Table 1 Biological activity results of the synthesized bis(urea-1,2,3-triazole) hybrids

S. No	Compounds		R^1	*E. coli*	*B. subtilis*	*S. epidermidis*	*C. albicans*	*A. niger*
1	**3a**	–	F	0.1301	0.1301	0.1301	0.1301	0.1301
2	**3b**	–	Cl	0.1198	0.1198	0.1198	0.1198	0.1198
3	**3c**	–	OMe	0.1224	0.1224	0.1224	0.1224	0.1224
4	**4a**	$(–CH_2–)_3$	F	0.0245	0.0245	0.0245	0.0245	0.0122
5	**4b**	$(–CH_2–)_3$	Cl	0.0231	0.0231	0.0470	0.0115	0.0231
6	**4c**	$(–CH_2–)_3$	OMe	0.0234	0.0234	0.0117	0.0234	0.0234
7	**4d**	$(–CH_2–)_4$	F	0.0238	0.0238	0.0238	0.0238	0.0238
8	**4e**	$(–CH_2–)_4$	Cl	0.0225	0.0225	0.0458	0.0112	0.0225
9	**4f**	$(–CH_2–)_4$	OMe	0.0228	0.0228	0.0465	0.0228	0.0057
10	**4 g**	$(–CH_2–)_5$	F	0.0232	0.0232	0.0232	0.0232	0.0116
11	**4 h**	$(–CH_2–)_5$	Cl	0.0110	0.0447	0.0219	0.0219	0.0110
12	**4i**	$(–CH_2–)_5$	OMe	0.0222	0.0454	0.0222	0.0222	0.0111
13	**4j**	$(–CH_2–)_6$	F	0.0226	0.0226	0.0462	0.0227	0.0227
14	**4 k**	$(–CH_2–)_6$	Cl	0.0214	0.0214	0.0437	0.0214	0.0214
15	**4 l**	$(–CH_2–)_6$	OMe	0.0217	0.0217	0.0442	0.0217	0.0217
16	**4 m**	m–CH_2–C_6H_4–CH_2–	F	0.0218	0.0218	0.0218	0.0218	0.0218
17	**4n**	m–CH_2–C_6H_4–CH_2–	Cl	0.0207	0.0422	0.0207	0.0207	0.0207
18	**4o**	m–CH_2–C_6H_4–CH_2–	OMe	0.0428	0.0207	0.0207	0.0105	0.0207
19	Ciprofloxacin	–	–	0.0094	0.0094	0.0094	–	–
20	Fluconazole	–	–	–	–	–	0.0408	0.0408

were found to have comparable activity to that of the standard drug Ciprofloxacin. Activity results showed that compound **4c** owing an MIC value of 0.0117 µmol/mL was significantly potent against *S. epidermidis.* Compound **4 h** with an MIC value of 0.0110 µmol/mL also displayed good biological activity against *E. coli*. The antifungal screening results revealed that all the synthesized compounds showed better activity than that of the standard drug Fluconazole. Compound **4b**, **4e** and **4o** with MIC values of 0.0115 µmol/mL, 0.0112 µmol/mL and 0.0105 µmol/mL, respectively were more potent than other compounds against *C. albicans*. Also, compounds **4a**, **4 g**, **4 h** and **4i** were observed to be more active against *A. niger* with MIC values ranging in between 0.0110 µmol/mL to 0.0122 µmol/mL. Among all the synthesized bis(1,2,3-triazole)urea hybrids, **4f** was the most potent compound against *A. niger* with MIC value of 0.0057 µmol/mL.

Structure–activity relationship

On analyzing the data for antimicrobial evaluation of the synthesized hybrids, the following structure–activity relationship was established:

1. All the synthesized symmetrical bis(urea-1,2,3-triazole) hybrids (**4a**–**4o**) showed better activity than their alkyne precursors (**3a**–**3c**) [60]. The synergistic effect of enhanced pharmacophoric activity was clearly shown by the hybrid bis-urea-triazoles.
2. Substitution by methoxy group in some of the compounds like **4c** led to an increase in the results of antibacterial activity of the synthesized symmetrical bis(urea-1,2,3-triazole) hybrids against *S. epidermidis* bacterial strain.
3. Compounds bearing the Cl substituent were found to be significantly active against all the tested microorganisms except *S. epidermidis.*
4. Compound **4f** with para methoxy group showed the highest potency against all the tested strains, and it was also found to be even more potent against *A. niger* than the reference drug Fluconazole.
5. Compound **4o** bearing the methoxy group at the para position and benzene ring as the spacer linker showed high activity than the standard drug Fluconazole against *C. albicans*.

Docking Studies

The antimicrobial evaluation data of target compounds shows that the bistriazoles exhibited excellent antifungal activity even higher than the standard drug fluconazole. Azole drugs act on sterol 14-α-demethylase (CYP51) and block the synthesis of ergosterol in fungi [62]. Therefore, to study the binding profile of the most active compounds and to find out the reason for enhancement in antifungal activity after conversion of alkynes to triazole, target molecules **4e** and **4o** along with alkynes **3b** and **3c** were docked into the active site of sterol 14-α-demethylase of *C. albicans*.

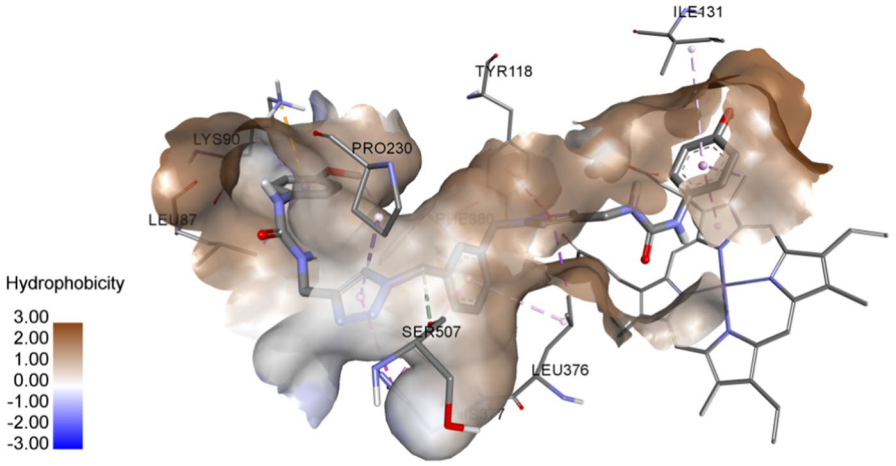


Fig. 2 Interactions of compound **4o** with active site of fungal sterol 14-α-demethylase

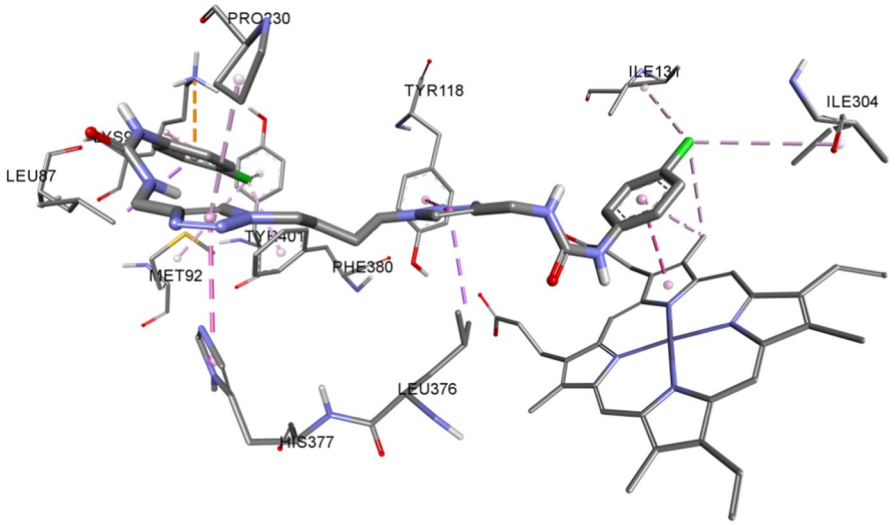


Fig. 3 Interactions of compound **4e** with active site of fungal sterol 14-α-demethylase

As shown in Figs. 2 and 3, one of the terminal p-substituted phenyl rings of both the compounds **4e** and **4o** entered deep into the binding site and created pi–pi stacked interactions with pi electrons of one ring of the heme molecule as well as hydrophobic interactions with Ile131 and Ile304. One nitrogen atom of the urea moiety attached to this deeply residing phenyl ring lie close to the heme iron. The distance between the heme iron and nitrogen of compound 4e was 3.83 Å while that of compound 4o was 3.86 Å although these nitrogen atoms did not form coordination

bond with heme due to less basicity. The other part of the molecules extends through the substrate entrance channel and stretches up to the channel gate.

The compound protein complex was mainly stabilized by the hydrophobic interactions as the environment of the substrate channel is also hydrophobic as exhibited in Fig. 1. The surface on the compound **4o** clearly indicates the more hydrophobic nature of the channel. The different types of binding interactions of docked compounds along with the residues involved and interaction distance are grouped in Table 2.

The docked conformations of both molecules **4e** and **4o** are presented in the mesh diagram of protein in Fig. 4.

The binding affinity values for compounds **4e**, **4o**, **3b** and **3c** were − 12.1, − 12.2, − 7.6 and − 7.5 kcal/mol, respectively. Observed activity trend among these compounds was also in the same order, i.e., **4o** > **4e** > **3b** > **3c**. Therefore, as hypothesized by us, the antimicrobial activity got enhanced after conversion into triazole. The in silico trends also confirm the observed activity trend. The binding score of the co-crystallized ligand VT-1161 was − 12.0, which was less than that of our compounds. This ligand showed 98% inhibition of *C. albicans* sterol 14-α-demethylase as compared to 54% by fluconazole as reported by Hargrove et al. [62]. The experimental outcomes of our study are also in the same direction. All the above facts have proved the compounds synthesized in the present study to be very influential antifungal agents.

Table 2 Details of interactions of compounds 4e and 4o

Compound **4o**				Compound **4e**		
Sr. No	Residue	Type of interaction	Distance	Residue	Type of interaction	Distance
1	SER507	Carbon Hydrogen Bond	3.34599	LYS90	Pi-Cation	4.10628
2	LYS90	Pi-Cation	4.04607	LEU87	Pi-Sigma	3.98529
3	LEU87	Pi-Sigma	3.93789	LEU376	Pi-Sigma	3.99243
4	LEU376	Pi-Sigma	3.72739	HEM601	Pi-Pi Stacked	3.69331
5	HEM601	Pi-Sigma	3.78227	HIS377	Pi-Pi T-shaped	4.29618
6	PHE380	Pi-Sigma	3.83015	TYR118	Pi-Pi T-shaped	4.88989
7	HEM601	Pi-Pi Stacked	3.83183	HEM601	Alkyl	3.89546
8	HIS377	Pi-Pi T-shaped	5.24277	LYS90	Alkyl	4.89884
9	HIS377	Pi-Pi T-shaped	4.30204	MET92	Alkyl	4.80931
10	TYR118	Pi-Pi T-shaped	4.83527	ILE131	Alkyl	3.74549
11	LEU376	Pi-Alkyl	4.63474	ILE304	Alkyl	4.7695
12	ILE131	Pi-Alkyl	5.48695	PHE380	Pi-Alkyl	4.10363
13	PRO230	Pi-Alkyl	4.32584	TYR401	Pi-Alkyl	4.188
14	LYS90	Pi-Alkyl	5.38273	PRO230	Pi-Alkyl	4.35868
15				LYS90	Pi-Alkyl	5.43881
16				HEM601	Pi-Alkyl	4.05739

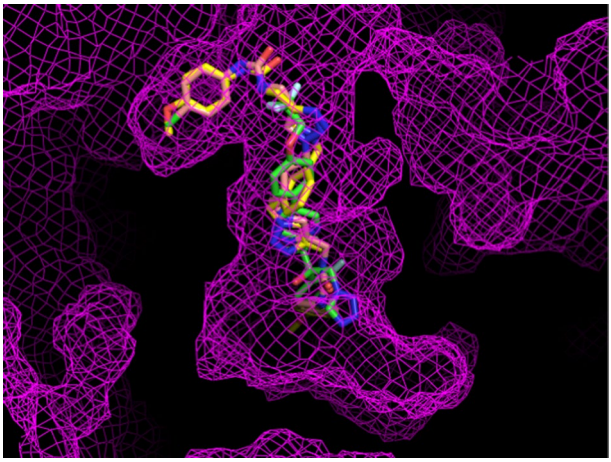


Fig. 4 Docked conformation of compounds **4e** (light pink) and **4o** (yellow) along with co-crystallized ligand (green) in the substrate channel of *C. albicans* sterol 14-α-demethylase. (Color figure online)

Conclusion

In summary, various bis-urea-triazoles have been synthesized by click chemistry and their antimicrobial evaluation is reported. The bioactivity studies of the synthesized compounds revealed that some of the tested compounds exhibited comparable activity to the standard drug Ciprofloxacin against all the tested bacteria. Also, all the compounds (**4a-4o**) showed superior antifungal potency than Fluconazole. Compound **4f** was the most potent compound of the series toward *A. niger* with an MIC value of 0.0057 µmol/mL. Also, the compounds **4e** and **4o** showed better activity against *C. albicans* than reference drug taken, which have been supported by docking simulation into active sites of sterol 14-α-demethylase. So, the synthesized compound **4e, 4o** and **4f** may be used for further studies in the field of drug discovery.

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Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interest.

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