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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Efficient synthesis and antimicrobial evaluation of 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehydes and their oxime derivatives

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Abstract A series of 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehydes was prepared by the propargylation of 2-hydroxynaphthaldehyde followed by Copper(I)-catalyzed azide-alkyne cycloaddition with various organic azides. 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehyde analogues were transformed to corresponding oxime derivatives upon grinding with hydroxylamine hydrochloride under solvent free conditions. All the synthesized compounds were characterized by various analytical and spectral techniques and screened in vitro for antimicrobial activity. The activity data revealed that most of the compounds exhibited good to significant activities. Compounds **4c** and **5c** exhibited very good and broad spectrum activity towards all the tested bacterial strains. Further, to understand the binding interactions, **4c** and **5c** were docked into the active sites of *E. coli* topoisomerase II DNA gyrase.

Keywords 1,2,3-Triazoles · Click Chemistry · Green chemistry · Homogenous catalysis · Molecular modeling

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Introduction

Five-membered heterocyclic compounds occupy a significant place among several classes of organic compounds owing to their diverse biological activities (Joule and Mills 2000; Saracoglu 2007). Among a wide variety of pharmaceutically important heterocyclic compounds, 1,2,3-triazole moiety has been extensively studied as an promising drug candidate with antimicrobial (Abdel-Wahab et al. 2012; Banday et al. 2012), anticancer (Ying et al. 2015; Xu et al. 2016), antiprotozoal (Bakunov et al. 2010), antitubercular (Keri et al. 2015), anti-HIV potential (Rai et al. 2014) etc. Ever since the development of a Copper(I)-catalyzed variant of Huisgen thermal azide-alkyne cycloaddition yielding 1,4-disubstituted 1,2,3-triazoles (Huisgen 1984; Tornoe et al. 2002; Rostovtsev et al. 2002), this moiety has attracted increased attention not only from organic chemists but also of medicinal chemists for the development of novel libraries of biologically active molecules. This so called "click" reaction has numerous advantages over Huisgen thermal cycloaddition such as high selectivity, better yield, and accelerated rate of the reaction.

Oximes are the important class of organic compounds, which are highly crystalline, stable and are used for the purification, protection, and characterization of carbonyl compounds (Greene et al. 1999). These are broadly used as intermediates for the preparation of amides (Kleeman et al. 1999), nitriles (Chakravarti et al. 2014), nitrones (Kirilmis et al. 2009) nitrile oxides (Xu et al. 2010; Donaruma and Helst 1960), hydroximinoyl chlorides, amines (Dewan et al. 2006), chiral α-sulfinyloximes (Smith and Gloyer 1975) and nitro compounds (Liu et al. 1980). Further, compounds containing oxime moiety are known to possess wide range of bioactivities (Chiang 1971) such as anticancer (Negi et al. 1996), antiallergic (Kataoka et al. 2002), antimicrobial

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(Hajipour and Mahboubghah 1998), antidotal (Jokanovic and Stojiljkovic 2006), antifungal (Dave and Forshar 1996), herbicidal activity (Song et al. 2005), antiepileptic (Hainzl et al. 2002), anti-inflammatory (Chen et al. 2006), etc. Oximes are easily accessed via reaction of carbonyl compounds with hydroxylamine hydrochloride in refluxing alcohol using pyridine (Kizil and Murphy 1997; Hwu et al. 1999). However, this method is associated with many drawbacks like long reaction time, tedious work up, toxicity of pyridine, low product yields, and environmental pollution by the use of organic solvents, etc. The synthesis of oximes has also been reported under solvent free conditions by simply grinding aldehydes with hydroxylamine hydrochloride at room temperature without using any solvent (Saikia et al. 2011; Damljanovic et al. 2006). This method can circumvent above-mentioned problems and has attracted attention of the researchers interested in green chemistry (Tanaka and Toda 2000).

Therefore, keeping in view of the pharmacological importance of 1,2,3-triazoles and oximes and in continuation of our interest in the synthesis of biologically active 1,2,3-triazoles (Lal et al. 2014, 2015; Kaushik et al. 2014), it was thought worthwhile to synthesize some 1,2,3-triazole-oximes hybrids via molecular hybridization approach which allows the combination of two or more pharmacophores with possible enhanced biological potential (Tietze et al. 2003). Herein, we report the efficient synthesis and antimicrobial evaluation of 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehydes (**4a–4h**) and their oxime derivatives (**5a–5h**).

Materials and methods

Chemistry

Melting points (°C) of all the synthesized compounds were determined by using electrothermal melting apparatus and are uncorrected. The infrared (IR) spectra were recorded in KBr on SHIMAZDU IR AFFINITY-I FTIR spectrophotometer. The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on BrukerAvance III 400 nano bay in $CDCl_3$ using tetramethysilane as an internal standard at 400 and 100 MHz, respectively. Chemical shift are reported in δ (ppm) and coupling constants are given in Hz. Mass spectra (MS) of all the synthesized compounds were recorded on waters 2618 EQD, ESI instrument. Elemental analysis of the synthesized compounds were performed on Thermo Scientific FLASH-2000 CHN analyzer. The results for C, H, and N were found to be within $\pm$0.4% of the theoretical values. Monitoring of reaction progress and the purity of reported compounds was checked by thin-layer chromatography (TLC) on readymade silica gel plates (SIL G/UV254, ALUGRAM) and visualized under Ultraviolet lamp. Starting materials were used without further purification.

*Procedure for the synthesis of 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**2**)*

To a mixture of 2-hydroxy-1-naphthaldhyde (1.0 mmol) and anhydrous potassium carbonate (1.5 mmol) in dimethyformamide (DMF) (10 mL), propargyl bromide (80% in toluene, 1.5 mmol) was added slowly at 0 °C and stirred for 8 h. After the completion of the reaction as monitored by TLC, ice cold water was added to it. The solid residue thus obtained was filtered and crystallized from chloroform-hexane to yield the desired alkyne (**2**).

*2-(Prop-2-yn-1-yloxy)-1-naphthaldehyde (**2**)*

Light-yellow solid, 79% yield, mp: 94–96 °C. IR (KBr, ν_{max}/cm^{-1}): 3255 (C–H, alkyne), 2978, 2871, 2806 (C–H str, CHO), 2118 (alkyne), 1654 (C=O str), 1623, 1458, 1437, 1365, 1268, 1211 (C–O str), 1149 (C–O str), 1072, 1054, 1025, 806. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60 (t, 1H, J = 2.4 Hz, CH), 4.95 (d, 2H, J = 2.4 Hz, OCH_2), 7.39 (d, J = 9.2 Hz, 1H, CH_{Ar}), 7.46–7.49 (m, 1H, CH_{Ar}), 7.63–7.65 (m, 1H, CH_{Ar}), 7.80 (d, J = 8.0 Hz, 1H, CH_{Ar}), 8.08 (d, J = 9.2 Hz, 1H, CH_{Ar}), 9.30 (d, J = 8.0 Hz, 1H, CH_{Ar}), 10.92 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.94 (CHO), 161.88 (C_{Ar}), 137.26 (C_{Ar}), 131.45 (C_{Ar}), 129.89 (C_{Ar}), 129.15 (C_{Ar}), 128.25 (C_{Ar}), 125.22 (C_{Ar}), 125.13 (C_{Ar}), 118.09 (C_{Ar}), 114.04 (C_{Ar}), 77.69, 76.80, 57.43 (OCH_2).

*General procedure for synthesis of 1,4-disubtituted 1,2,3-triazoles (**4a–4e**)*

A mixture of substituted benzyl bromide (**3**, 1.0 mmol), sodium azide (3.0 mmol), alkyne (**2**, 1.0 mmol), copper sulfate pentahydrate (10 mol %), and sodium ascorbate (20 mol%) in DMF :water (1:1) was stirred with the aid of a magnetic stirrer for 6–10 h at room temperature. Then the reaction mixture was poured in to ice cold water while stirring. The solid product thus formed was filtered, washed with aqueous ammonium chloride: ammonia (9:1) solution followed by water and recrystallized from ethyl acetate-hexane to give the 1,4-disubstituted 1,2,3-triazoles (**4a–4e**).

*2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4a**)*

White solid, 87% yield, mp: 96–98 °C. IR (KBr, ν_{max}/cm^{-1}): 3143 (C–H str, triazole), 3106, 2942, 2882, 2803 (C–H str, CHO), 1655 (C=O str), 1517, 1242 (C–O

str), 1189, 1154 (C–O str), 1084, 1048, 864, 819, 714. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.48 (s, 2H, NCH_2), 5.57 (s, 2H, OCH_2), 7.28–7.30 (m, 2H, CH_{Ar}), 7.38–7.49 (m, 5H, CH_{Ar}), 7.59 (s, 1H, triazolyl–H), 7.62–766 (m, 1H, CH_{Ar}), 7.80 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 8.08 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 9.26 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 10.86 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.81 (CHO), 162.12 (C_{Ar}), 137.57 (C–4), 129.92 (C_{Ar}), 129.24 (C_{Ar}), 128.97 (C_{Ar}), 128.27 (C_{Ar}), 128.11 (C_{Ar}), 125.09 (C_{Ar}), 124.96 (C–5), 113.99 (C_{Ar}), 63.57 (OCH_2), 54.43 (NCH_2). MS (*m/z*) 366.12 $(M + Na)^+$. Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.53; H, 4.82; N, 12.39.

*2-((1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4b**)*

Light-yellow solid, 85% yield, mp: 116–118 °C. IR (KBr, ν_{max}/cm^{-1}): 3145 (C–H str, triazole), 3109, 2930, 2874, 2809 (C–H str, CHO), 1656 (C=O str), 1515, 1464, 1438, 1349, 1271, 1252 (C–O str), 1156, 1122 (C–O str), 1086, 807, 752, 714. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.51 (s, 2H, NCH_2), 5.67 (s, 2H, OCH_2), 7.40 (d, $J = 8.8$ Hz, 2H, CH_{Ar}), 7.45–7.48 (m, 2H, CH_{Ar}), 7.62–7.66 (m, 1H, CH_{Ar}), 7.68 (s, 1H, triazolyl–H), 7.80 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.08 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 8.19–8.23 (m, 2H, CH_{Ar}), 9.22 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 10.86 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.72 (CHO), 162.34 (C_{Ar}), 148.17 (C_{Ar}), 144.24 (C_{Ar}), 141.24 (C_{Ar}), 137.61 (C–4), 131.42 (C_{Ar}), 130.02 (C_{Ar}), 128.98 (C_{Ar}), 128.60 (C_{Ar}), 128.31 (C_{Ar}), 125.24 (C_{Ar}), 124.90 (C_{Ar}), 124.39 (C_{Ar}), 123.11 (C–5), 117.62 (C_{Ar}), 114.00 (C_{Ar}), 63.56 (OCH_2), 53.28 (NCH_2). MS (*m/z*) 411.12 $(M + Na)^+$. Anal. Calcd for $C_{21}H_{16}N_4O_4$: C, 64.94; H, 4.15; N, 14.43. Found: C, 64.79; H, 4.02; N, 14.55.

*2-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4c**)*

White solid, 79% yield, mp: 94–96 °C. IR (KBr, ν_{max}/cm^{-1}): 3147 (C–H str, triazole), 3081, 2942, 2880, 2818 (C–H str, CHO), 1671 (C=O str), 1610, 1513, 1430, 1244 (C–O str), 1220, 1151, 1109 (C–O str), 1043, 1021, 812, 755. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.48 (s, 2H, NCH_2), 5.53 (s, 2H, OCH_2), 7.05–7.10 (m, 2H, CH_{Ar}), 7.26–7.30 (m, 2H, CH_{Ar}), 7.44–7.48 (m, 2H, CH_{Ar}), 7.59 (s, 1H, triazolyl–H), 7.62–7.66 (m, 1H, CH_{Ar}), 7.80 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.07 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 9.23 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 10.86 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.80 (CHO), 162.53 (C_{Ar}), 137.59 (C–4), 131.45 (C_{Ar}), 130.04 (C_{Ar}), 129.95 (C_{Ar}), 128.92 (C_{Ar}), 128.29 (C_{Ar}), 125.12 (C_{Ar}), 124.94 (C–5), 116.36 (C_{Ar}), 116.15 (C_{Ar}), 113.99 (C_{Ar}), 63.56 (OCH_2), 53.28 (NCH_2). MS (*m/z*) 384.11 $(M + Na)^+$. Anal. Calcd for $C_{21}H_{16}FN_3O_2$: C, 69.80; H, 4.46; N, 11.63. Found: C, 69.93; H, 4.32; N, 11.73.

*2-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4d**)*

Light-yellow solid, 85% yield, mp: 110–112 °C. IR (KBr, ν_{max}/cm^{-1}): 3145 (C–H str, triazole), 3109, 2947, 2882, 2801 (C–H str, CHO), 1657 (C=O str), 1590, 1511, 1436, 1345, 1270, 1246 (C–O str), 1152, 1120 (C–O str), 1057, 821, 756. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.48 (s, 2H, NCH_2), 5.51 (s, 2H, OCH_2), 7.15 (d, $J = 8.4$ Hz, 2H, CH_{Ar}), 7.44–7.52 (m, 3H, CH_{Ar+}triazolyl-H), 7.61–7.66 (m, 3H, CH_{Ar}), 7.80 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.07 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 9.25 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 10.87 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.78 (CHO), 162.49 (C_{Ar}), 137.58 (C–4), 133.27 (C_{Ar}), 132.42 (C_{Ar}), 131.46 (C_{Ar}), 129.96 (C_{Ar}), 129.68 (C_{Ar}), 128.94 (C_{Ar}), 128.29 (C_{Ar}), 125.14 (C_{Ar}), 124.96 (C–5), 123.17 (C_{Ar}), 114.00 (C_{Ar}), 63.59 (OCH_2), 53.68 (NCH_2). MS (*m/z*) 444.04 [(M+Na) (^{79}Br)]$^+$,446.98 [(M+Na) (^{81}Br)]$^+$. Anal. Calcd for $C_{21}H_{17}BrN_3O_2$: C, 59.73; H, 3.82; N, 9.95. Found: C, 59.67; H, 3.99; N, 9.81.

*2-((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4e**)*

White solid, 89% yield, mp: 98–100 °C. IR (KBr, ν_{max}/cm^{-1}): 3151 (C–H str, triazole), 3098, 2944, 2883, 2806 (C–H str, CHO), 1665 (C=O str), 1513, 1266, 1248 (C–O str), 1152, 1123 (C–O str), 1062, 1024, 816, 751. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.37 (s, 3H), 5.47 (s, 2H, NCH_2), 5.52 (s, 2H, OCH_2), 7.19–7.24 (m, 4H, CH_{Ar}), 7.44–7.49 (m, 2H, CH_{Ar}), 7.57 (s, 1H, triazolyl–H), 7.62–7.66 (m, 1H, CH_{Ar}), 7.80 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.07 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 9.26 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 10.86 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.85 (CHO), 162.61 (C_{Ar}), 138.93 (C_{Ar}), 137.56 (C–4), 131.48 (C_{Ar}), 131.20 (C_{Ar}), 129.90 (C_{Ar}), 128.91 (C_{Ar}), 128.27 (C_{Ar}), 128.18 (C_{Ar}), 125.07 (C_{Ar}), 124.98 (C–5), 117.43(C_{Ar}), 114.01 (C_{Ar}), 63.63 (OCH_2), 53.22 (NCH_2), 21.16 (CH_3). MS (*m/z*) 380.12 $(M+Na)^+$. Anal. Calcd for $C_{22}H_{19}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.62; H, 4.81; N, 12.39.

*General procedure for the synthesis of 1,4-disubtituted 1,2,3-triazoles (**4f–4h**)*

A mixture of substituted phenyl azide **3f–3h** (1.0 mmol), alkyne **2** (1.0 mmol) in DMF/water (1:1), copper sulfate pentahydrate (10 mol%) and sodium ascorbate (20 mol %) was stirred for 6 h to 10 h at room temperature. The progress

of the reaction was monitored by TLC and after completion of the reaction; the reaction mixture was diluted with ice cold water (30 mL). The solid residues were filtered, washed with aqueous ammonium chloride:ammonia solution (9:1) followed by water and recrystallized with ethyl acetate:hexane to get the desired 1,2,3-triazoles derivatives (**4f–4h**).

*2-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4f**)*

Yellow solid, 82% yield, mp: 110–112 °C. IR (KBr, ν_{max}/cm^{-1}): 3123 (C–H str, triazole), 3048, 2978, 2878, 2814 (C–H str, CHO), 1660 (C=O str), 1596, 1342, 1244 (C–O str), 1170, 1136 (C–O str), 1046, 854, 728. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (s, 2H, OCH_2), 7.47–7.53 (m, 3H, CH_{Ar}), 7.65–7.69 (m, 1H, CH_{Ar}), 7.83 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.03 (d, $J = 9.2$ Hz, 2H, CH_{Ar}), 8.13 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 8.25 (s, 1H, triazolyl–H), 8.46 (d, $J = 8.8$ Hz, 2H, CH_{Ar}), 9.26 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 10.98 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.86 (CHO), 162.68 (C_{Ar}), 137.64 (C–4), 135.88 (C_{Ar}), 134.98 (C_{Ar}), 132.56 (C_{Ar}), 130.65 (C_{Ar}), 130.45 (C_{Ar}), 129.09 (C_{Ar}), 128.62 (C_{Ar}), 125.79 (C_{Ar}), 124.97 (C–5), 122.42 (C_{Ar}), 114.28 (C_{Ar}), 63.87 (OCH_2). MS (*m*/*z*) 397.10 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{14}N_4O_4$: C, 64.17; H, 3.77; N, 14.97. Found: C, 64.29; H, 3.91; N, 14.85.

*2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4g**)*

Light-pink solid, 92% yield, mp: 178–180 °C. IR (KBr, ν_{max}/cm^{-1}): 3124 (C–H str, triazole), 3043, 2978, 2878, 2804 (C–H str, CHO), 1667 (C=O str), 1502, 1414, 1244 (C–O str), 1180, 1157 (C–O str), 1054, 817, 643. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.59 (s, 2H, OCH_2), 7.45–7.55 (m, 3H, CH_{Ar}), 7.51 (s, 1H, triazolyl–H), 7.63–7.73 (m, 3H, CH_{Ar}), 7.72 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.11 (d, $J = 9.2$ Hz, 2H, CH_{Ar}), 9.26 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 10.96 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.70 (CHO), 162.39 (C_{Ar}), 137.67 (C–4), 135.31 (C_{Ar}), 134.96 (C_{Ar}), 131.51 (C_{Ar}), 130.05 (C_{Ar}), 130.02 (C_{Ar}), 128.99 (C_{Ar}), 128.32 (C_{Ar}), 125.19 (C_{Ar}), 124.96 (C–5), 121.82 (C_{Ar}), 113.78 (C_{Ar}), 63.43 (OCH_2). MS (*m*/*z*) 386.07 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{14}ClN_3O_2$: C, 66.03; H, 3.88; N, 11.55. Found: C, 66.19; H, 3.79; N, 11.38.

*2-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde (**4h**)*

Light-pink solid, 93% yield, mp: 184–186 °C. IR (KBr, ν_{max}/cm^{-1}): 3124 (C–H str, triazole), 3048, 2986, 2878, 28803 (C–H str, CHO), 1669 (C=O str), 1514, 1268, 1244 (C–O str), 1180, 1156 (C–O str), 1042, 816, 644. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.59 (s, 2H, OCH_2), 7.45–7.53 (m, 1H, CH_{Ar}), 7.53 (s, 1H, triazolyl–H), 7.64–7.71 (m, 5H, CH_{Ar}), 7.82 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.11 (d, $J = 8.8$ Hz, 2H, CH_{Ar}), 9.26 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 10.96 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.68 (CHO), 162.38 (C_{Ar}), 137.65 (C–4), 133.03 (C_{Ar}), 130.02 (C_{Ar}), 129.00 (C_{Ar}), 128.31 (C_{Ar}), 125.19 (C_{Ar}), 124.97 (C–5), 122.04 (C_{Ar}), 117.52 (C_{Ar}), 113.79 (C_{Ar}), 63.44 (OCH_2). MS (*m*/*z*) 430.04 $[(M+Na)\ (^{79}Br)]^+$,432.04 $[(M+Na)\ (^{81}Br)]^+$. Anal. Calcd for $C_{20}H_{14}ClN_3O_2$: C, 58.84; H, 3.46; N, 10.29. Found: C, 58.99; H, 3.59; N, 10.46.

*General procedure for the synthesis of oximes (**5a–5h**)*

Triazole derivatives (**4a–4h**) (1.0 mmol), hydroxylamine hydrochloride (1.2 mmol) and sodium hydroxide (1.2 mmol) were grinded for 1–2 h using mortar and pestle under solvent free conditions. Thereafter, the reaction mixture was left overnight, washed with water to remove inorganic salt and recrystallized with ethyl acetate-hexane to yield the corresponding oxime derivatives (**5a–5h**).

*2-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5a**)*

White solid, 86% yield, mp: 138–140 °C. IR (KBr, ν_{max}/cm^{-1}): 3169, 3147 (C–H str, triazole), 3065, 2997, 1624 (C=N), 1508, 1458, 1436, 1315, 1249 (C–O str), 1180, 1146, 1126 (C–O str), 1060, 965, 923, 804, 732, 629. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.39 (s, 2H, OCH_2), 5.52 (s, 2H, NCH_2), 7.25–7.27 (m, 2H, CH_{Ar}), 7.34–7.41 (m, 5H, CH_{Ar}+CH), 7.49–7.53 (m, 1H, CH_{Ar}), 7.61 (s, 1H, triazolyl–H), 7.77 (d, $J = 7.6$ Hz, 1H, CH_{Ar}), 7.82 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 8.67 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 8.82 (bs, NOH, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.53 (C_{Ar}), 147.70(C=N), 144.29 (C–4), 134.40 (C_{Ar}), 132.13 (C_{Ar}), 129.52 (C_{Ar}), 129.16 (C_{Ar}), 128.82 (C_{Ar}), 128.38 (C_{Ar}), 128.08 (C_{Ar}), 127.87 (C_{Ar}), 125.66 (C_{Ar}), 124.43 (C–5), 122.90 (C_{Ar}), 114.54 (C_{Ar}), 63.76 (OCH_2), 54.28 (NCH_2). MS (*m*/*z*) 381.13 $(M+Na)^+$. Anal. Calcd for $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63. Found: C, 70.51; H, 5.29; N, 15.47.

*2-((1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5b**)*

White solid, 78% yield, mp: 162–164 °C. IR (KBr, ν_{max}/cm^{-1}): 3185, 3146 (C–H str, triazole), 3074, 2986, 1624 (C=N), 1522, 1345, 1250 (C–O str), 1160, 1136, 1111 (C–O str), 1060, 959, 814, 636. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.42 (s, 2H, OCH_2), 5.81 (s, 2H, NCH_2), 7.41–7.48 (m, 3H, CH_{Ar}), 7.54–7.56 (m, 1H, CH_{Ar}), 7.67

(d, $J = 9.2$ Hz, 1H, CH_{Ar}), 7.90 (d, $J = 8.0$ Hz, 1H, CH_{Ar}), 8.00 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 8.18 (d, $J = 8.8$ Hz, 2H, CH_{Ar}), 8.37 (s, 1H, triazolyl–H), 8.62 (s, 1H, CH), 8.85 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 11.33 (bs, NOH, 1H). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 155.09 (C_{Ar}), 147.17 (C=N), 145.31 (C_{Ar}), 143.39 (C–4), 142.98 (C_{Ar}), 131.40 (C_{Ar}), 130.73 (C_{Ar}), 129.04 (C_{Ar}), 128.82 (C_{Ar}), 128.35 (C_{Ar}), 127.51 (C_{Ar}), 125.63 (C_{Ar}), 125.23 (C_{Ar}), 124.15 (C–5), 123.83 (C_{Ar}), 114.63 (C_{Ar}), 62.76 (OCH_2), 51.89 (NCH_2). MS (*m/z*) 426.15 $(M+Na)^+$. Anal. Calcd for $C_{21}H_{17}N_5O_4$: C, 62.53; H, 4.25; N, 17.36. Found: C, 62.71; H, 4.39; N, 17.25.

*2-((1-(4-Fluorobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5c**)*

White solid, 82% yield, mp: 148–150 °C. IR (KBr, ν_{max}/cm^{-1}): 3167, 3143 (C–H str, triazole), 3072, 1608 (C=N), 1513, 1311, 1250 (C–O str), 1166, 1134 (C–O str), 1057, 1022, 967, 808, 711, 748, 538. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41 (s, 2H, OCH_2), 5.52 (s, 2H, NCH_2), 7.04–7.08 (m, 2H, CH_{Ar}), 7.25–7.28 (m, 3H, CH_{Ar}), 7.39–7.44 (m, 2H, CH_{Ar}), 7.54–7.57 (m, 2H, CH_{Ar}, triazolyl–H), 7.80 (d, $J = 7.6$ Hz, 1H, CH_{Ar}), 7.87 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 8.81 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 8.83 (bs, NOH, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.44 (C_{Ar}), 148.67 (C=N), 144.68 (C–4), 142.54 (C_{Ar}), 132.36 (C_{Ar}), 130.06 (C_{Ar}), 129.97 (C_{Ar}), 129.54 (C_{Ar}), 128.41 (C_{Ar}), 127.99 (C_{Ar}), 125.47 (C_{Ar}), 124.90 (C_{Ar}), 124.58 (C–5), 123.11 (C_{Ar}), 116.25 (C_{Ar}), 116.03 (C_{Ar}), 63.58 (OCH_2), 53.48 (NCH_2). MS (*m/z*) 399.11 $(M+Na)^+$. Anal. Calcd for $C_{21}H_{17}FN_4O_2$: C, 67.01; H, 4.55; N, 14.89. Found: C, 67.24; H, 4.71; N, 14.71.

*2-((1-(4-Bromobenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5d**)*

Offwhite solid, 81% yield, mp: 164–166 °C. IR (KBr, ν_{max}/cm^{-1}): 3176, 3168 (C–H str, triazole), 3074, 2986, 1624 (C=N), 1590, 1508, 1250 (C–O str), 1164, 1138 (C–O str), 1054, 1010, 928, 809, 632. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41 (s, 2H, OCH_2), 5.51 (s, 2H, NCH_2), 7.14 (d, $J = 8.4$ Hz, 2H, CH_{Ar}), 7.39–7.51 (m, 6H, CH_{Ar}+CH), 7.56 (s, 1H, triazolyl–H), 7.81 (d, $J = 7.6$ Hz, 1H, CH_{Ar}), 7.88 (d, $J = 8.8$ Hz, 1H, CH_{Ar}), 8.82 (d, $J = 8.4$ Hz,1H, CH_{Ar}), 8.86 (bs, 1H, NOH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.05 (C_{Ar}), 147.67 (C=N), 145.48 (C_{Ar}), 144.37 (C–4), 142.56 (C_{Ar}), 131.23 (C_{Ar}), 130.12 (C_{Ar}), 129.01 (C_{Ar}), 128.26 (C_{Ar}), 128.25 (C_{Ar}), 127.15 (C_{Ar}), 125.33 (C_{Ar}), 125.12 (C_{Ar}), 124.22 (C–5), 123.43 (C_{Ar}), 114.45 (C_{Ar}), 62.66 (OCH_2), 51.39 (NCH_2). MS (*m/z*) 459.09 [(M+Na) (^{79}Br)]$^+$, 461.98 [(M+Na) (^{81}Br)]$^+$. Anal. Calcd for $C_{21}H_{17}ClN_4O_2$: C, 57.68; H, 3.92; N, 12.81. Found: C, 57.51; H, 3.76; N, 12.92.

*2-((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5e**)*

White solid, 84% yield, mp: 108–110 °C. IR (KBr, ν_{max}/cm^{-1}): 3170, 3108 (C–H str, triazole), 3056, 2920, 1622 (C=N), 1591, 1514, 1458, 1436, 1337, 1249 (C–O str), 1183, 1125 (C–O str), 1049, 1021, 968, 812, 746, 627. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (s, 3H, CH_3), 5.43 (s, 2H, OCH_2), 5.51 (s, 2H, NCH_2), 7.13–7.28 (m, 5H, CH_{Ar}+CH), 7.39–7.48 (m, 2H, CH_{Ar}), 7.55–7.56 (m, 1H, CH_{Ar}), 7.69 (s, 1H, triazolyl–H), 7.78 (d, $J = 7.6$ Hz, 1H, CH_{Ar}), 7.84 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 8.75 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 8.81 (bs, NOH, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.46 (C=N), 145.78 (C=N), 143.88 (C–4), 132.03 (C_{Ar}), 131.36 (C_{Ar}), 129.84 (C_{Ar}), 129.80 (C_{Ar}), 129.19 (C_{Ar}), 128.37 (C_{Ar}), 128.14 (C_{Ar}), 127.81 (C_{Ar}), 125.63 (C_{Ar}), 124.39 (C–5), 114.57 (C_{Ar}), 113.75 (C_{Ar}), 63.76 (OCH_2), 54.14 (NCH_2), 21.14 (CH_3). MS (*m/z*) 395.14 $(M+Na)^+$. Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.71; H, 5.28; N, 15.26.

*2-((1-(4-Nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5f**)*

Light-yellow solid, 76% yield, mp: 106–108°C. IR (KBr, ν_{max}/cm^{-1}): 3149, 3142 (C–H str, triazole), 3075, 2979, 1618 (C=N), 1516, 1404, 1333, 1248 (C–O str), 1112 (C–O str), 1072, 1018, 972, 822, 725, 643. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 5.49 (s, 2H, OCH_2), 7.44–7.46 (m, 1H, CH_{Ar}), 7.54–7.57 (m, 1H, CH_{Ar}), 7.69–7.78 (m, 3H, CH_{Ar}), 7.82 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 7.98 (d, $J = 8.8$ Hz, 2H, CH_{Ar}), 8.13 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 8.69 (s, 1H, triazolyl–H), 8.86 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 9.23 (s, 1H, CH), 11.35 (bs, 1H, NOH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 155.19(C_{Ar}), 145.51 (C=N), 143.76 (C–4), 135.70 (C_{Ar}), 134.65 (C_{Ar}), 132.45 (C_{Ar}), 131.88 (C_{Ar}), 129.89 (C_{Ar}), 129.22 (C_{Ar}), 128.87 (C_{Ar}), 127.65 (C_{Ar}), 125.98 (C_{Ar}), 124.43 (C–5), 123.67 (C_{Ar}), 121.78 (C_{Ar}), 115.34 (C_{Ar}), 114.56 (C_{Ar}), 63.51 (OCH_2). MS (*m/z*) 412.13 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{15}N_5O_4$: C, 61.69; H, 3.88; N, 17.99. Found: C, 61.84; H, 3.65; N, 17.71.

*2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5g**)*

Offwhite solid, 86% yield, mp: 156–158 °C. IR (KBr, ν_{max}/cm^{-1}): 3150, 3142 (C–H str, triazole), 3074, 2986, 1618 (C=N), 1516, 1408, 1333, 1250 (C–O str), 1145 (C–O str), 1091, 1016, 819, 732, 643. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.48 (s, 2H, OCH_2), 7.41–7.44 (m, 1H, CH_{Ar}),

7.52–7.56 (m, 1H, CH_{Ar}), 7.67–7.72 (m, 3H, CH_{Ar}), 7.91 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 7.97 (d, $J = 8.8$ Hz, 2H, CH_{Ar}), 8.03 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 8.68 (s, 1H, triazolyl–H), 8.85 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 9.03 (s, 1H, CH), 11.34 (bs, 1H, NOH). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 155.09 (C_{Ar}), 145.31 (C=N), 143.86 (C–4), 135.30 (C_{Ar}), 133.05 (C_{Ar}), 131.47 (C_{Ar}), 130.78 (C_{Ar}), 129.84 (C_{Ar}), 129.02 (C_{Ar}), 128.37 (C_{Ar}), 127.54 (C_{Ar}), 125.64 (C_{Ar}), 124.14 (C–5), 123.03 (C_{Ar}), 121.85 (C_{Ar}), 115.06 (C_{Ar}), 114.43 (C_{Ar}), 62.50 (OCH_2). MS (*m/z*) 401.08 $(M+Na)^+$. Anal. Calcd for $C_{20}H_{15}ClN_4O_2$: C, 63.41; H, 3.99; N, 14.79. Found: C, 63.63; H, 3.75; N, 14.63.

*2-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-1-naphthaldehyde oxime (**5h**)*

Offwhite solid, 88% yield, mp: 160–162 °C. IR (KBr, ν_{max}/cm^{-1}): 3150, 3124 (C–H str, triazole), 3074, 2986, 1618 (C=N), 1508, 1426, 1325, 1243 (C–O str), 1191, 1155 (C–O str), 1072, 1047, 826, 734, 643. ^{1}H NMR (DMSO–d_6, 400 MHz): δ 5.48 (s, 1H, OCH_2), 7.41–7.44 (m, 1H, CH_{Ar}), 7.52–7.56 (m, 1H, CH_{Ar}), 7.64–7.72 (m, 4H, CH_{Ar}), 7.81 (d, $J = 8.4$ Hz, 2H, CH_{Ar}), 8.03 (d, $J = 9.2$ Hz, 1H, CH_{Ar}), 8.68 (s, 1H, triazolyl–H), 8.85 (d, $J = 8.4$ Hz, 1H, CH_{Ar}), 9.03 (s, 1H, CH), 11.33 (bs, 1H, NOH). ^{13}C NMR (DMSO–d_6, 100 MHz): δ 155.09 (C_{Ar}), 145.30 (C=N), 143.88 (C–4), 137.82 (C_{Ar}), 135.71 (C_{Ar}), 132.76 (C_{Ar}), 131.47 (C_{Ar}), 129.76 (C_{Ar}), 129.03 (C_{Ar}), 128.59 (C_{Ar}), 128.37 (C_{Ar}), 127.54 (C_{Ar}), 125.64 (C_{Ar}), 124.88 (C_{Ar}), 124.13 (C–5), 123.93 (C_{Ar}), 122.98 (C_{Ar}), 122.08 (C_{Ar}), 121.42 (C_{Ar}), 115.06 (C_{Ar}), 62.51 (OCH_2). MS (*m/z*) 445.04[(M+Na) (^{79}Br)]$^+$, 447.04 [(M+Na) (^{81}Br)]$^+$. Anal. Calcd for $C_{20}H_{15}BrN_4O_2$: C, 56.75; H, 3.57; N, 13.24. Found: C, 56.46; H, 3.73; N, 13.38.

Pharmacology

All the synthesized 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehydes along with their oxime derivatives (**4a–4h**, **5a–5h**) were evaluated in vitro for their antimicrobial activity against two Gram-positive bacteria (*Staphylococcus epidermidis* MTCC 6880 and *Bacillus subtilis* MTCC 441) and two Gram-negative bacteria (*Escherichia coli* MTCC 16521 and *Pseudomonas aeruginosa* MTCC 424) and two fungal strains viz. *Aspergillus niger* (MTCC 8189) and *Candida albicans* (MTCC 227) following standard serial dilution method. Double strength nutrient broth and Sabouraud dextrose broth were used as culture media for bacteria and fungi, respectively. Dimethyl sulphoxide (DMSO) was used as solvent control. The stock solutions of the test compounds were serially diluted in test tubes containing 1 mL of sterile medium to get the concentration of 50–3.12 µg/mL and then inoculated with 100 µL of suspension of respective microorganism in sterile saline. The inoculated test tubes were incubated at 37 ± 1°C for 24 h for bacterial strains and at 37 ± 1°C for 48 h in case of *C. albicans* and at 25 ± 1 °C for 120 h in case of *A. niger*. Ciprofloxacin and Fluconazole were used as standard drugs for bacteria and fungi, respectively, and were also evaluated under similar conditions for comparison with the synthesized compounds.

Computational studies

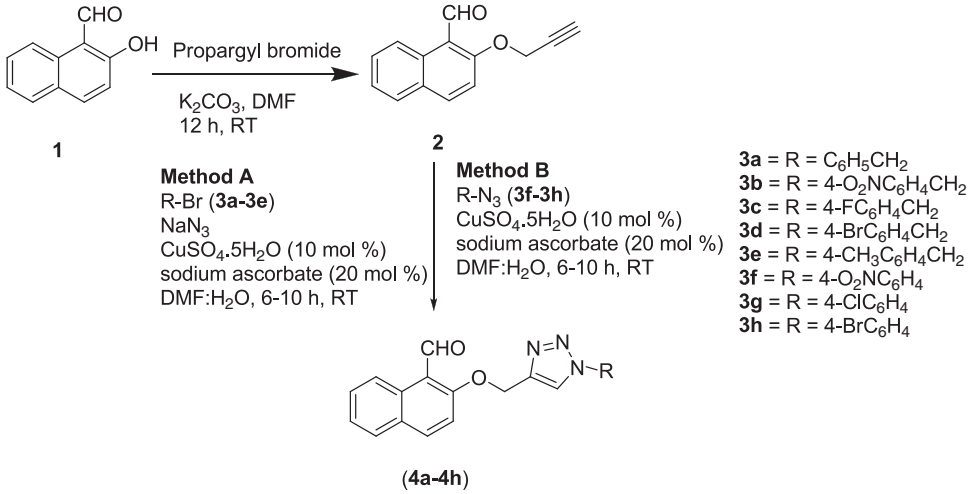
The docking studies were performed as per the procedure reported in the literature (Kumar et al. 2013). The crystal structure of *E. Coli* topoisomerase II DNA gyrase B was taken from the Brookhaven Protein Data Bank http://www.rcsb.org/pdb (PDB entry: 1kzn). The two-dimensional structures of various ligands drawn were changed into three-dimensional before minimizing their energy (Marvin Sketch 5.0.3 copyright ©1998–2008 Chem Axon Ltd A). Co-crystallized ligand was removed from pdb files and protein molecule was prepared by removing solvent molecules and non-complex ions using UCSF Chimera (Pettersen et al. 2004). Incomplete side chains were completed using Dunbrack Rotamer library (Dunbrack 2002). Gasteiger charges were determined using Antechamber (Wang et al. 2006) and the prepared file was saved as pdb format and used for further studies. All the files were converted into pdbqt format. Docking studies were performed on Auto Dock Vina 1.1.2 using the center and size of grid box as center_$x = 19.0577118729$, center_$y = 29.6584661732$, center_$z = 36.0719212982$ and size_$x = 25.0$, size_$y = 25.0$, size_$z = 25.0$. Exhaustiveness of the global search algorithm was set to be 8. The docked poses were visualized using Discovery studio 4 (Discovery Studio 2012) and Pymol (PyMol 2008). The protocols used for docking were validated by redocking co-crystalized ligand CBN into the active site of DNA gyrase B (1KZN). These parameters resulted in conformation of CBN similar to X-ray structure conformation. The root-mean square deviation between the conformations of the CBN from AutoDockVina and that from X-ray crystal structure was <2 Å (0.5275 Å). Hence, the used protocols were applied for docking studies of our compounds into the active site of DNA Gyrase B. Binding affinity of the docked compounds was calculated in kcal/mol using scoring function of AutoDockVina.

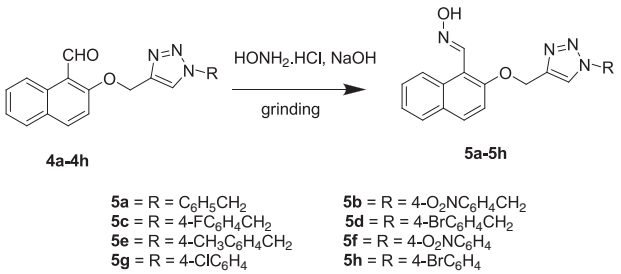
Results and discussion

Chemistry

The outlines for the synthesis of 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehydes and their oxime derivatives

Scheme 1 Synthesis of triazoles (**4a–4h**)





Scheme 2 Solvent free synthesis of triazole-oximes (**5a–5h**)

is presented in Scheme 1 and Scheme 2. Initially the O-alkylation of commercially available 2-hydroxy-1-naphthaldehyde (**1**) was performed with propargyl bromide in presence of anhydrous K_2CO_3 using DMF by reported procedure (Singh et al. 2016). The 2-O-propargylated naphthaldehyde (**2**) was reacted in one-pot multicomponent click reaction with variedly substituted benzyl bromides (**3a–3e**), sodium azide in presence of catalytic amount of copper sulfate pentahydrate and sodium ascorbate in aqueous DMF to furnish 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehydes (**4a–4e**) in very high yield. On the other hand, the compounds (**4f–4h**) were prepared in good yield by reacting substituted phenyl azides (**3f–3h**) with alkyne (**2**) by copper (I)-catalyzed azide-alkyne cyclo addition reaction. The substituted phenyl azides were in turn prepared from corresponding substituted aniline derivatives utilizing reported procedure (Xu et al. 2013).

Finally, all the triazole derivatives (**4a–4h**) with free aldehyde group were transformed into their corresponding oximes. The simple grinding of triazoles (**4a–4h**) with hydroxylamine hydrochloride in the presence of sodium hydroxide at room temperature yielded the expected 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehyde oximes (**5a–5h**) as per literature procedure (Damljanovic et al. 2006). The process employed enabled us to prepare the oxime derivatives in good to high yield under solvent free conditions, which has drawn large attention in green chemistry methodologies.

The structures of all the newly synthesized products were established on the basis of their elemental analysis and spectral (FTIR, ^{1}H NMR, ^{13}C NMR, LCMS) data. For example, the IR spectrum of compound **4b** exhibited a characteristic peak at 3145 cm^{-1} due to =C–H stretching of triazole ring. The signals due to C=O stretching and for C–H stretching of aldehyde group were observed at 1656 cm^{-1}, 2874 cm^{-1}, and 2809 cm^{-1}, respectively. The presence of two peaks at 1515 cm^{-1} and 1349 cm^{-1} indicated the presence of nitro functional group. The ^{1}H NMR spectrum of compound **4b** exhibited characteristic singlets at δ 7.68 and δ 10.86 due to triazolyl and aldehydic protons, respectively. The two singlets each integrating for protons of two methylene groups were observed at δ 5.51 and δ 5.67 and all the aromatic protons resonated in the region δ 7.38–9.23. In the ^{13}C NMR spectrum of compound **4b**, the peaks at δ 137.61 and δ 123.11 were assigned to the C-4 and C-5 carbon atoms of the triazole ring, respectively. A peak at δ 191.72 confirmed the presence of aldehydic carbon atom and the signals due to methylene carbons appeared at δ 63.56 and δ 53.28. The mass spectrum of compound **4b** displayed a peak at *m/z* 389.12 $(M+H)^+$, which is consistent with the molecular formula.

In the IR spectrum of compound **5b**, the disappearance of peak corresponding to aldehyde and the appearance of abroad peak due to =N-OH stretching in the region 3185 cm^{-1} showed formation of oxime. The presence of triazole ring was confirmed by a peak at 3146 cm^{-1} due to =C–H stretching of triazole ring. The ^{1}H NMR spectrum of compound **5b** in DMSO-d_6 exhibited a broad singlet exchange able with D_2O at δ 11.33, corresponding to the

Table 1 In vitro antibacterial screening of compounds **4a–4h**, **5a–5h** (MIC in μM/mL)

Entry	Compounds	*R*	*S. epidermidis*	*B. subtilis*	*E. coli*	*P. aeruginosa*
1	**4a**	$C_6H_5CH_2$	0.0728	0.0364	0.0364	0.0364
2	**4b**	$4\text{-}O_2NC_6H_4CH_2$	0.0322	0.0644	0.0322	0.0322
3	**4c**	$4\text{-}FC_6H_4CH_2$	0.0346	0.0346	0.0346	0.0346
4	**4d**	$4\text{-}BrC_6H_4CH_2$	0.0592	0.0592	0.0296	0.0296
5	**4e**	$4\text{-}CH_3C_6H_4CH_2$	0.1399	0.0699	0.0699	0.0699
6	**4f**	$4\text{-}O_2NC_6H_4$	0.1336	0.0668	0.0334	0.0334
7	**4g**	$4\text{-}ClC_6H_4$	0.0344	0.0687	0.0687	0.0344
8	**4h**	$4\text{-Br-}C_6H_4$	0.0306	0.0612	0.0612	0.0306
9	**5a**	$C_6H_5CH_2$	0.0349	0.0572	0.0349	0.0349
10	**5b**	$4\text{-}O_2NC_6H_4CH_2$	0.0620	0.0620	0.0310	0.0310
11	**5c**	$4\text{-}FC_6H_4CH_2$	0.0286	0.0286	0.0286	0.0286
12	**5d**	$4\text{-}BrC_6H_4CH_2$	0.0332	0.0664	0.0664	0.0664
13	**5e**	$4\text{-}CH_3C_6H_4CH_2$	0.0671	0.0671	0.0671	0.0336
14	**5f**	$4\text{-}O_2NC_6H_4$	0.0642	0.0321	0.0642	0.0642
15	**5g**	$4\text{-}ClC_6H_4$	0.0661	0.0330	0.0661	0.0330
16	**5h**	$4\text{-}BrC_6H_4$	0.0295	0.0295	0.0591	0.0148
17	Ciprofloxacin	–	0.0047	0.0047	0.0047	0.0047

proton of hydroxyl group of oxime. Two characteristic singlets observed at δ 8.62 and δ 8.37 were assigned to –CH of oxime and triazole functionalities, respectively. The ^{13}C NMR spectrum of compound **5b** displayed a peak at δ 147.17, which was assigned to –C=N of oxime moiety. The peaks at δ 143.39 and δ 124.15 were assigned to the C-4 and C-5 carbon atoms of the triazole ring, respectively. The mass spectrum of compound **5b** showed a peak at *m/z* 404.14 $(M+H)^+$, which is in good agreement with the molecular formula of the compound. Likewise, the remaining compounds showed the expected pattern as reported in case of **4b** and **5b**.

Pharmacology

Antibacterial activity

The synthesized 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehydes along with their oxime derivatives (**4a–4h**, **5a–5h**) were screened in vitro for antibacterial activity against two Gram-positive bacteria (*Staphylococcus epidermidis* MTCC 6880 and *Bacillus subtilis* MTCC 441) and two Gram-negative bacteria (*Escherichia coli* MTCC 16521 and *Pseudomonas aeruginosa* MTCC 424) following standard serial dilution method (Cappucino and Sherman 1999). Ciprofloxacin was used as standard drug and the minimum inhibitory concentrations (MIC) in μM/mL are listed in Table 1.

As evident from the antibacterial evaluation data most of the synthesized compounds exhibited good to significant activity with MIC value ranging from 0.0148 to 0.1399 μM/mL. In case of *S. epidermidis*, the insertion of election withdrawing group on benzyl enhances the activity to some extent while electron releasing group decreases the same. Compound **4h** containing bromine atom on benzene exhibited highest activity with MIC value 0.0306 μM/mL among compounds (**4a–4h**). Among the oxime derivatives, compound (**5c**) containing fluorine exhibited most potent activity with MIC value 0.0206 μM/mL. Compounds **5c** and **5h** exhibited promising activity against *B. subtilis* with MIC value 0.0286 and 0.0295 μM/mL, respectively. Bromo derivative of triazole (**4d**) and fluoro derivative of oxime (**5c**) showed good activity against *E. coli* with the MIC value 0.0296 and 0.0286 μM/mL, respectively. Among all the tested compounds (**4a–4h**, **5a–5h**), compound **5h** was found most potent with MIC value 0.0148 μM/mL against *P. aeruginosa*. On the basis of structure activity relationship analysis, it was observed that in most of the cases compounds containing electron-withdrawing substituent exhibited better activity than those with electron-releasing substituent. It was also observed that compounds **4c** and **5c** containing fluorine substituent displayed good and broad spectrum activity toward all the bacterial strains under study.

Antifungal activity

All the synthesized triazoles and oximes (**4a–4h**, **5a–5h**) were also tested in vitro for antifungal activity against two fungal strains viz. *Aspergillus niger* (MTCC 8189) and *Candida albicans* (MTCC 227) following standard serial dilution method (Cappucino and Sherman 1999).

Table 2 In vitro antifungal screening of compounds **4a–4h**, **5a–5h** (MIC in μM/mL)

Entry	Compounds	*R*	*A. niger*	*C. albicans*
1	**4a**	$C_6H_5CH_2$	0.0364	0.0728
2	**4b**	4-$O_2NC_6H_4CH_2$	0.0322	0.1287
3	**4c**	4-$FC_6H_4CH_2$	0.0346	0.0692
4	**4d**	4-$BrC_6H_4CH_2$	0.0592	0.0592
5	**4e**	4-$CH_3C_6H_4CH_2$	0.0350	0.0699
6	**4f**	4-$O_2NC_6H_4$	0.0167	0.0668
7	**4g**	4-ClC_6H_4	0.0344	0.0687
8	**4h**	4-Br-C_6H_4	0.0153	0.1225
9	**5a**	$C_6H_5CH_2$	0.0349	0.0698
10	**5b**	4-$O_2NC_6H_4CH_2$	0.0620	0.0310
11	**5c**	4-$FC_6H_4CH_2$	0.0332	0.0332
12	**5d**	4-$BrC_6H_4CH_2$	0.0143	0.0572
13	**5e**	4-$CH_3C_6H_4CH_2$	0.0336	0.0336
14	**5f**	4-$O_2NC_6H_4$	0.0161	0.0321
15	**5g**	4-ClC_6H_4	0.0165	0.0661
16	**5h**	4-BrC_6H_4	0.0148	0.0295
17	Fluconazole	–	0.0102	0.0051

Fluconazole was used as reference and MICs (MIC in μM/mL) are presented in Table 2. The activity data revealed that most of the compounds exhibited good to high antifungal activity. Furthermore, most of the tested compounds displayed better potency against *A. niger* than *C. albicans*. Compounds **4f**, **4h**, **5d**, **5f**, **5g**, and **5h** exhibited good potency with MIC value ranging 0.0148–0.0167 μM/mL compared to fluconazole (MIC=0.0102 μM/mL) against *A. niger*. The oxime derivative with bromine group (**5h**) was found to be most active and exhibited better activity among all the synthesized compounds with MIC values in the range 0.0148 μM/mL to 0.0295 μM/mL.

Computational studies

Molecular docking study

The *E. coli* DNA gyrase B enzyme has been a validated target for the antibacterial drugs (Pokrovskaya et al. 2009; Plech et al. 2015). Therefore, in an attempt to find out the binding conformation of most active compound in DNA gyrase B and to study its interactions with the active site residues, docking simulations of compound **5c** was performed in the active site of DNA gyrase B. Further, to unearth the reason behind more activity of this compound than its aldehyde counterpart **4c**, docking studies of the later were also carried out in the same active site. Fluorine containing compounds are known to exhibit better biological activities than their non-fluorinated counterparts

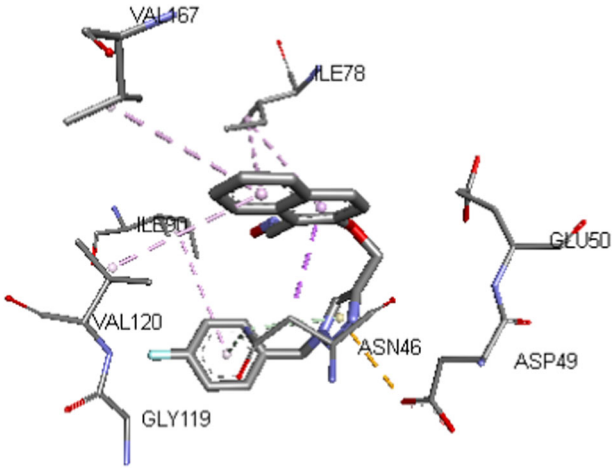


Fig. 1 Interactions (*dotted lines*) of compound **5c** docked in active site of DNA gyrase B showing hydrogen bonding (*green*), pi-donor hydrogen bond (*light green*), hydrophobic (*light pink*) and electrostatic (*yellow*) interactions

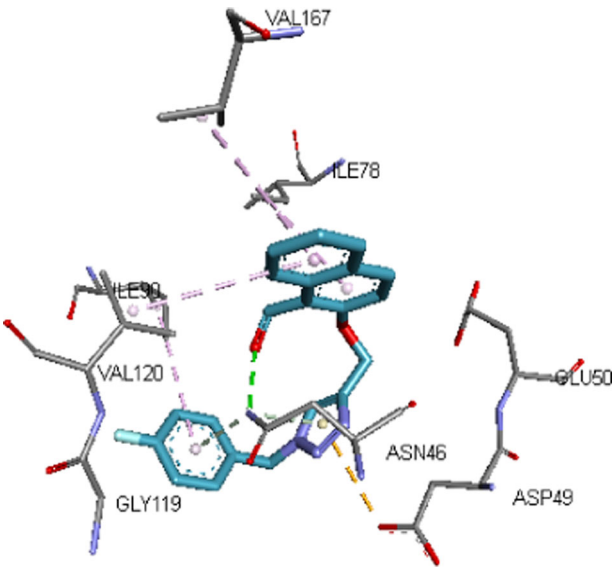


Fig. 2 Interactions (*dotted lines*) of compound **4c** docked in active site of DNA gyrase B showing hydrogen bonding (*green*), pi-donor hydrogen bond (*light green*), hydrophobic (*light pink*) and electrostatic (*yellow*) interactions

because of good lipophilicity, bioavailability, and metabolic stability (Purser et al. 2008). The binding interactions of docked compounds with the *E. coli* DNA gyrase enzyme are shown in Fig. 1 and Fig. 2. Compound **5c** was found to be most promising molecule among all the tested compounds. Phenyl and triazole rings of the compound **5c** interacted with Asn46 by pi-donor type hydrogen bonds while naphthyl ring showed pi-anion type electrostatic interactions with Asp49. Further, these three rings also exhibited pi-alkyl type hydrophobic interactions with Ile78,

Ile90, Val120, and Val167 residues. This compound also showed pi-sigma interactions with Asn46. The binding affinity of compound **5c** was −8.4 kcal/mol.

On the other hand compound **4c** presented hydrogen bond interactions with Asn46. All other interactions of this compound were similar and with same residues as that were of compound **5c** except hydrogen bonding with Val120, a pi-sigma interaction with Asn46 and one pi-alkyl type interaction Ile78 in case of the latter. The binding affinity of compound **4c** (−8.1 kcal/mol) was less than that of compound **5c**. Therefore, it can be said that introduction of oxime group in the molecule resulted in better anchoring of the compound in the active site of the enzyme, which caused more activity of compound **5c** as compared to compound **4c** as proved in our wet experimentation. This may be due to the greater molecular volume of compound **5c**, which is the result of oxime incorporation. Therefore, it can be assumed that the compounds under study inhibits the DNA gyrase B successfully, which may be the reason behind their antibacterial action. Surface diagram of the enzyme along with docked conformations of both compounds is depicted in Fig. 3.

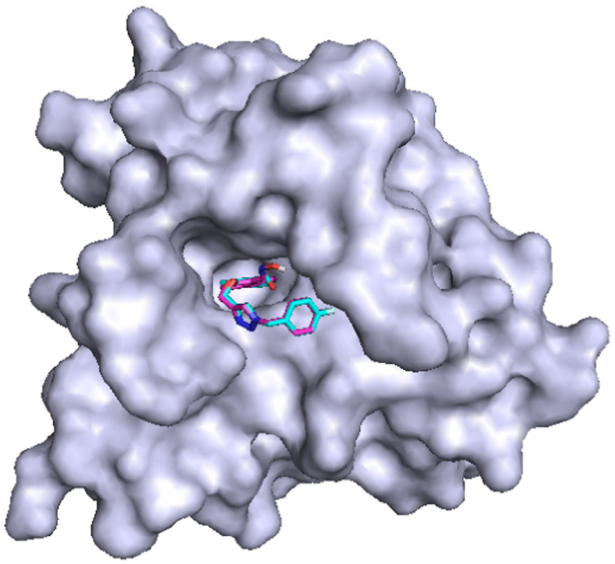


Fig. 3 Surface diagram topoisomerase II DNA gyrase B along with docked inhibitor compounds **4c** and **5c**

In silico absorption, distribution, metabolism, and elimination (ADME) properties of the synthesized compounds

To explore the drug-likeness of all the synthesized compounds (**4a**−**4h**, **5a**−**5h**), in silico study for ADME prediction was performed and depicted in Table 3. In the present study, we have calculated molecular weight (MW), logarithm of partition coefficient (milog P), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) molecular volume, and Lipinski's rule of five using the Molinspiration online property calculation toolkit (Molinspiration Cheminformatics Brastislava 2014).

All the synthesized compounds display good conformational flexibility because these are having sufficient number of rotatable bonds (5–7). It was also observed that all the compounds exhibits good absorption (% ABS = 68.16 –89.33). Absorption (% ABS) was calculated by % ABS = 109−(0.345 × TPSA) (Zhao et al. 2002).

Table 3 Molinspiration score of compounds **4a–4h**, **5a–5h**

Entry	Compounds	% Absorption	MW	ClogP	TPSA	n-ON	n-OHNH	n-ROTB	Volume
1	**4a**	89.33	343.39	4.24	57.02	5	0	6	309.48
2	**4b**	89.33	357.41	4.69	57.02	5	0	6	326.04
3	**4c**	73.52	388.38	4.20	102.85	8	0	7	332.81
4	**4d**	89.33	422.28	5.05	57.02	5	0	6	327.36
5	**4e**	89.33	361.38	4.40	57.02	5	0	6	314.41
6	**4f**	73.52	374.36	3.88	102.85	8	0	6	316.01
7	**4g**	89.33	363.80	4.60	57.02	5	0	5	306.21
8	**4h**	89.33	408.25	4.73	57.02	5	0	5	310.56
9	**5a**	83.97	358.40	4.87	72.54	6	0	6	321.77
10	**5b**	83.97	372.43	5.32	72.54	6	1	6	338.33
11	**5c**	68.16	403.40	4.83	118.37	9	1	7	345.11
12	**5d**	83.97	437.30	5.68	72.54	6	1	6	339.66
13	**5e**	83.97	376.39	5.03	72.54	6	1	6	326.70
14	**5f**	68.16	389.37	4.51	118.37	9	1	6	328.31
15	**5g**	83.97	378.82	5.23	72.54	6	1	5	318.51
16	**5h**	83.97	423.27	5.36	72.54	6	1	5	322.86

A molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following Lipinski's rule: milog P (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5. Furthermore, most of the compounds followed Lipinski's rule of five, except **4d**, **5d**, **5e**, **5g**, **5h**, which violated only one rule of five as represented by the log *P* value. Thus, the results showed the most possible utility of the series for developing compounds with good drug-like properties. The ADME predictions showed that most of the synthesized compounds followed the Lipinski's rule and are predicted to have good bioavailability.

Conclusion

In conclusion, a series of 2-((1-substituted-1*H*-1,2,3-triazol-4-yl)-1-naphthaldehyde was prepared by Copper (I)-catalyzed azide-alkyne cycloaddition and were transformed to their corresponding oximes under solvent free conditions. All the synthesized compounds were tested in vitro for their antimicrobial activity and most of the derivatives exhibited good to high activity. Two fluorinated compounds **4c** and **5c** exhibiting broad spectrum antibacterial activity were docked into the active sites of *E. Coli* topoisomerase II DNA gyrase. The various interactions of these compounds with target enzymes indicate the good antibacterial properties of the compounds. Further, the ADME prediction of all the synthesized compounds displayed good absorption and predicted to have good bioavailability. The results of present study can be utilized for the further development of potential antimicrobial leads.

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Conflict of interest The authors declare that they have no competing interests.

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