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Facile synthesis, antimicrobial activity and docking simulation of N-((1-substituted aryl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde analogues

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Abstract: N-((1-substituted aryl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde analogues were synthesized in good yield from the reaction of 1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde with various organic azides in the presence of Cu(I) catalyst. The structure elucidation of methylene linked imidazole-triazole compounds was achieved by various spectral methods i.e. FT-IR, 1D-NMR, 2D-NMR and MS. The newly constructed molecules were screened *in-vitro* against bacterial strains *Bacillus subtilis*, *Staphylococcus epidermidis*, *Escherichia coli* and *Pseudomonas aeruginosa* and fungal strains *Candida albicans* and *Aspergillus niger*. Compound **3e** was most potent against *E. coli* and *S. epidermidis* and **3j** was potent against all tested strains. The docking study showed that compound **3e** inhibited the enzyme DNA gyrase in fruitful manner.

Keywords: Imidazole, 1,2,3-triazole, antimicrobial activity, docking simulation.

Introduction

In the past two decades, imidazole containing drugs have found extensive use in the field of pharmaceutical chemistry e.g. antiprotozoal[1], antitumor[2], anti-inflammatory[3], inhibitors of urease[4] and antifungal[5-7]. Similarly, the 1,2,3-triazole moiety is a recognized nitrogen pharmacophore[8] in the family of nitrogen heterocycle that finds prominent place among approved pharmaceuticals[9]. The 1,2,3-triazoles have biological potential against proliferation[10], cancer[11,12], malaria[13,14], tuberculosis[15,16], trypanosomiasis[17], leishmaniasis[18], HIV[19,20], influenza[21], dengue[22], pain[23], epilepsy[24,25], obesity[26], inflammation[27] and bacterial infection[28,29]. The conventional method for synthesizing 1,2,3-triazole moieties consists of

Cu(I)-catalyzed alkyne-azide cycloaddition[30-34]. However, recently azide-enolate 1,3-dipolar cycloaddition has appeared as novel method for synthesizing these valuable heterocycles.

Many commercial drugs contain imidazole and 1,2,3-triazole moieties, which encourages the synthetic chemist to construct imidazole and triazole hybrids. In the present work, we report the synthesis, characterization, antimicrobial activity and docking study of some newly synthesized methylene linked imidazole-triazole hybrids.

Materials and Methods

The melting points were measured in open capillaries and are uncorrected. FT-IR spectra were recorded on SHIMADZU affinity spectrophotometer in KBr. 1D & 2D-NMR spectra were scanned on a Bruker Avance-III 400 MHz FT-NMR. Chemical shift values are expressed in δ (ppm) and spin-spin coupling constant (J) value is given in Hertz. MS were recorded on VG 70 EB and PE-Biosystems Mariner ESI-TOF mass spectrometer. Azide precursors were prepared as per literature[35].

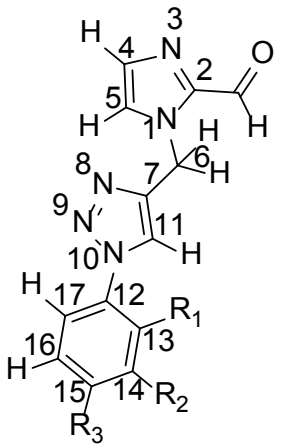
General procedure applied for the synthesis of N-((1-substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde (3a-3m)

1-(Prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde (**2**) was prepared by stirring of imidazole-2-carbaldehyde (**1,** 1.0 mmol), K_2CO_3 and propargyl bromide (1.0 mmol) in 20 mL N,N-dimethylformamide at 0-5 ºC for 6h. The workup of reaction was carried out with ice cold water and extracted three times (3 x 20 mL) with ethyl acetate and concentrated under vacuum to get alkyne.

N-((1-substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde (**3a-3m**) were synthesized by stirring 1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde (**2**, 1.0 mmol) with different organic azides (1.0 mmol), $CuSO_4.5H_2O$ (0.10 mmol) and sodium ascorbate (0.20 mmol) using DMF : H_2O (7 : 3) as solvent at 45 ºC for 6-8h[36]. The reaction progress was checked by TLC and workup was carried out with aq. NH_3 solution. The residue thus obtained was filtered, washed with water and dried under vacuum.

General procedure for synthesis of N-((1-substituted aryl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-imidazole-2-carbaldehyde (4a-4c) To a solution of substituted benzyl bromide (1.0 mmol), NaN_3 (3.0 mmol), and 1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde (**2**, 1.0 mmol) in DMF : H_2O (7:3), $CuSO_4.5H_2O$ (0.10 mmol) and sodium ascorbate (0.20 mmol) was added with stirring at 45 ºC for 6-8h[36] and the reaction progress was observed by TLC. Ice-cold water was added to cooled reaction mixture followed by aq. NH_3 solution. The precipitates so formed were filtered, washed with water and dried to produce desired product.

Spectral analysis



1) **N-((1-(3-chloro-2-methylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3a**) yield 69%, Off-white

solid, mp 94-96 ºC. IR (KBr, v_{max}, cm^{-1}): 3130 (C-H str), 3119, 2967, 2862 (C-H str, CHO), 1683 (C=O str), 1599, 1577, 1477, 1452 (C=C str, aromatic ring), 1413, 1229 (C-O asym. str), 1149 (C-O sym. str), 1041, 987. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H, CHO), 7.88 (s, 1H, C-H triazole), 7.56 (d, J = 8Hz, H_{15}), 7.53 (s, H_5), 7.34 (s, H_4), 7.29 (t, J = 8Hz, H_{16}), 7.23 (d, J = 8Hz, H_{17}), 5.79 (s, 2H, N-CH_2), 2.17 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.49 (CHO), 142.62 (C_7), 137.25, 136.16, 132.77, 132.12, 131.09, 127.20, 126.96, 124.98, 124.80, 42.29 (NCH_2), 15.36 (Ar-CH_3). MS: *m/z* [M^+] Calcd for $C_{14}H_{12}ClN_5O$: 301.1, Found 302.1 $[M+H]^+$.

2) **N-((1-(3-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3b**) yield 67%, Off-white solid, mp 96-98 ºC IR (KBr, v_{max}, cm^{-1}): 3116 (C-H str), 2912, 2854 (C-H str, CHO), 1678 (C=O str), 1593, 1539, 1489, 1458 (C=C str, aromatic ring), 1411, 1236 (C-O asym. str), 1159 (C-O sym. str), 1045, 927. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 8.11 (s, 1H, C-H triazole), 7.77 (t, H_{13}), 7.63 (m, H_{15}), 7.50 (s, H_5), 7.48 (dd, J = 4Hz, H_{17}), 7.44 (d, J = 4Hz, H_{16}), 7.34 (s, H_4), 5.78 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.59 (CHO), 143.54 (C_7), 137.57, 135.70, 132.15, 130.89, 129.10, 126.86, 121.35, 120.91, 118.56, 42.24 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_{10}ClN_5O$: 287.1, Found 288.0 $[M+H]^+$.

3) **N-((1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3c**) yield 63%, Off-white solid, mp 156-158 ºC. IR (KBr, v_{max}, cm^{-1}): 3134 (C-H str), 3086, 2959, 2932 (C-H str, CHO), 1681 (C=O str), 1612, 1516, 1440 (C=C str, aromatic ring), 1423, 1253 (C-O asym. str), 1149 (C-O sym. str), 1045, 991. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 8.01 (s, 1H, C-H triazole), 7.60 (d, J = 4Hz, H_{13}, H_{17}), 7.50 (s, H_5), 7.32 (s, H_4), 7.03 (d, J = 4Hz, H_{14}, H_{16}), 5.77 (s, 2H, N-CH_2), 3.88 (s, 3H, OCH_3). MS: *m/z* [M^+] Calcd for $C_{14}H_{13}N_5O_2$: 283.1, Found 284.1 $[M+H]^+$.

4) **N-((1-(p-tolyl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-imidazole-2-carbaldehyde** (**3d**) yield 64%, White solid, mp 124-126 ºC. IR (KBr, v_{max}, cm^{-1}): 3132 (C-H str), 2922, 2852, (C-H str, CHO), 1680 (C=O str), 1618, 1543, 1454, 1429 (C=C str, aromatic ring), 1417, 1224 (C-O asym. str), 1130 (C-O sym. str), 1051, 926. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 8.06 (s, 1H, C-H triazole), 7.58 (d, J = 4Hz, H_{13}, H_{17}), 7.51 (s, H_5), 7.33 (d, J = 4Hz, H_{14}, H_{16}), 7.32 (s, H_4), 5.78 (s, 2H, N-CH_2), 2.44 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.58 (CHO), 143.11 (C_7), 139.26, 132.11, 130.30, 126.83, 121.34 (C_{11}), 120.55, 42.31 (NCH_2), 21.09 (Ar-CH_3). MS *m/z* [M^+] Calcd for $C_{14}H_{13}N_5O$: 267.1, Found 268.1 $[M+H]^+$.

5) **N-((1-(4-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3e**) yield 76%, White solid, mp 152-154 ºC. IR (KBr, v_{max}, cm^{-1}): 3116 (C-H str), 3094, 3076, 2856 (C-H str, CHO), 1666 (C=O str), 1636, 1539, 1497, 1437 (C=C str, aromatic ring), 1410, 1230 (C-O asym. str), 1186 (C-O sym. str), 1072, 948. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 8.10 (s, 1H, C-H triazole), 7.66 (d, J = 8Hz, H_{13}, H_{17}), 7.61 (d, J = 8Hz, H_{14}, H_{16}), 7.50 (s, H_5), 7.33 (s, H_4), 5.78 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.62 (CHO), 143.55 (C_7), 142.75, 135.71, 132.99, 132.17, 126.86, 122.82 (C_{11}), 122.00, 121.22, 42.25 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_{10}BrN_5O$: 331.0 (^{79}Br) and 333.0 (^{81}Br), Found 332.1 (^{79}Br) and 334.1 (^{81}Br) $[M+H]^+$.

6) **N-((1-(2-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3f**) yield 63%, Off-white solid, mp 122-124 ºC. IR (KBr, v_{max}, cm^{-}

[1]): 3130 (C-H str), 2922, 2847, (C-H str, CHO), 1684 (C=O str), 1603, 1512, 1462, 1410 (C=C str, aromatic ring), 1254 (C-O asym. str), 1121 (C-O sym. str), 1047, 956. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 8.22 (s, 1H, C-H triazole), 7.74 (dd, J = 8Hz, H_{17}), 7.52 (s, H_5), 7.45 (t, J = 8Hz, H_{14}), 7.32 (s, H_4), 7.10 (dd, J = 8Hz, H_{15}, H_{16}), 5.80 (s, 2H, N-CH_2), 3.90 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.44 (CHO), 151.09, 141.83 (C_7), 131.98, 130.38, 126.83, 125.99, 125.45, 125.37, 121.23(C_{11}), 112.25, 55.99 (NCH_2), 42.32 (Ar-OCH_3). MS: *m/z* [M^+] Calcd for $C_{14}H_{13}N_5O_2$: 283.1, Found 284.1 [M+H]$^+$.

7) **N-((1-(3-bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3g**) yield 74%, Off-white solid, mp 112-114 ºC. IR (KBr, ν_{max}, cm^{-1}): 3118 (C-H str), 3097, 2857, (C-H str, CHO), 1684 (C=O str), 1589, 1489, 1468, 1412 (C=C str, aromatic ring), 1273 (C-O asym. str), 1160 (C-O sym. str), 1047, 935. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 8.11 (s, 1H, C-H triazole), 7.92 (s, H_{13}), 7.67 (d, J = 8Hz, H_{15}), 7.60 (d, J = 8Hz, H_{17}), 7.50 (s, H_5), 7.41 (t, J = 8Hz, H_{16}), 7.33 (s, H_4), 5.78 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.61 (CHO), 143.55 (C_7), 142.70, 137.63, 132.17, 132.11, 131.12, 126.86, 123.74 (C_{11}), 121.35, 119.08, 42.25 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_{10}BrN_5O$: 331.0 (^{79}Br) and 333.0 (^{81}Br), Found 332.0 (^{79}Br) and 334.0 (^{81}Br) [M+H]$^+$.

8) **N-((1-(4-chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3h**) yield 58%, Off-white solid, mp 126-128 ºC. IR (KBr, ν_{max}, cm^{-1}): 3116 (C-H str), 3091, 2856 (C-H str, CHO), 1666 (C=O str), 1624, 1539, 1502, 1475 (C=C str, aromatic ring), 1412, 1232 (C-O asym. str), 1157 (C-O sym. str), 1047, 945. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H, CHO), 8.09 (s, 1H, C-H triazole), 7.67 (d, J = 8Hz, H_{13}, H_{17}), 7.53 (s, H_5), 7.51 (d, J = 8Hz, H_{14}, H_{16}), 7.34 (s, H_4), 5.78 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.61 (CHO), 143.52 (C_7), 135.20, 134.95, 132.14, 130.02, 127.03, 121.79, 121.32, 42.28 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_{10}ClN_5O$: 287.1, Found 288.0 [M+H]$^+$.

9) **N-((1-(4-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3i**) yield 46%, Off-white solid, mp 156-158 ºC. IR (KBr, ν_{max}, cm^{-1}): 3128 (C-H str), 3089, 2845 (C-H str, CHO), 1668 (C=O str), 1643, 1543, 1516, 1477 (C=C str, aromatic ring), 1417, 1234 (C-O asym. str), 1159 (C-O sym. str), 1047, 952. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H, CHO), 8.07 (s, 1H, C-H triazole), 7.69 (dd, J = 8Hz, H_{13}, H_{17}), 7.51 (s, H_5), 7.34 (s, H_4), 7.24 (t, J = 8Hz, H_{14}, H_{16}), 5.78 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.58 (CHO), 143.42 (C_7), 133.03, 132.07, 126.97, 122.70, 122.63(C_{11}), 121.59, 116.92, 116.69, 42.29 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_{10}FN_5O$: 271.1, Found 272.1 [M+H]$^+$.

10) **N-((1-(4-chloro-2-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3j**) yield 64%, Yellow solid, mp 114-116 ºC. IR (KBr, ν_{max}, cm^{-1}): 3149 (C-H str), 3107, 2856 (C-H str, CHO), 1680 (C=O str), 1548, 1500 (C=C str, aromatic ring), 1409, 1240 (C-O asym. str), 1159 (C-O sym. str), 1045, 946. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.85 (s, 1H, CHO), 8.12 (s, 1H, H_{14}), 8.01 (s, 1H, C-H triazole), 7.79 (d, H_{16}), 7.55(d, H_{17}), 7.52 (s, H_5), 7.35 (s, H_4), 5.79 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.48 (CHO), 143.20 (C_7), 137.21, 133.90, 132.10, 130.67, 129.04, 128.5, 128.36, 126.84, 125.95, 125.00, 42.15 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_9ClN_6O_3$: 332.0, Found 333.0 [M+H]$^+$.

11) **N-((1-(2,3-dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3k**) yield 64%, Off-white

solid, mp 190-192 ºC. IR (KBr, v_{max}, cm^{-1}): 3134 (C-H str), 3089, 2915 (C-H str, CHO), 1680 (C=O str), 1649, 1568, 1497 (C=C str, aromatic ring), 1440, 1298 (C-O asym. str), 1198 (C-O sym. str), 1045, 947. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 7.89 (s, 1H, C-H triazole), 7.54-7.35 (m, H_{14}, H_{16}, H_{17}, H_5, H_4), 5.83 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.48 (CHO), 143.24 (C_7), 137.21, 133.98, 132.10, 130.67, 129.04, 128.45, 128.36, 126.34, 125.95, 125.00, 42.15 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_9Cl_2N_5O$: 321.0, Found 322.0 [M+H]$^+$.

12) **N-((1-(2,4-dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3l**) yield 61%, Off-white solid, mp 185-187 ºC. IR (KBr, v_{max}, cm^{-1}): 3138 (C-H str), 3082, 2917 (C-H str, CHO), 1682 (C=O str), 1653, 1577, 1483 (C=C str, aromatic ring), 1433, 1286 (C-O asym. str), 1238 (C-O sym. str), 1045, 931. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H, CHO), 8.12 (s, 1H, C-H triazole), 7.68-7.35 (m, H_{14}, H_{16}, H_{17}, H_5, H_4), 5.81 (s, 2H, N-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.47 (CHO), 142.46 (C_7), 136.12, 134.79, 132.09, 131.87, 128.47, 127.93, 127.69, 126.37, 126.12, 125.34, 42.25 (NCH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_9Cl_2N_5O$: 321.0, Found 322.0 [M+H]$^+$.

13) **N-((1-(2-fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**3m**) yield 48%, Off-white solid, mp 152-154 ºC. IR (KBr, v_{max}, cm^{-1}): 3132 (C-H str), 2918, 2850 (C-H str, CHO), 1682 (C=O str), 1651, 1539, 1516, 1489 (C=C str, aromatic ring), 1413, 1278 (C-O asym. str), 1166 (C-O sym. str), 1070, 943. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H, CHO), 8.21 (s, 1H, C-H triazole), 7.92-8.20 (m, H_{13}), 7.51 (d, J = 8Hz, H_{15}), 7.47 (d, J = 8Hz, H_{17}), 7.34-7.32 (m, H_{16}, H_5, H_4), 5.82 (s, 2H, N-CH_2). MS: *m/z* [M^+] Calcd for $C_{13}H_{10}FN_5O$: 271.1, Found 272.1 [M+H]$^+$.

14) **N-((1-(4-nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**4a**) yield 63%, Off-white solid, mp 142-144 ºC. IR (KBr, v_{max}, cm^{-1}): 3132 (C-H str), 3080, 3016, 2949 (C-H str, CHO), 1672 (C=O str), 1633, 1606, 1519, 1494 (C=C str, aromatic ring), 1456, 1346, 1286 (C-O asym. str), 1174 (C-O sym. str), 1051, 952. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (s, 1H, CHO), 8.25 (s, 1H, C-H triazole), 7.69-7.31 (m, 6H, H_5, H_4, H_{13}, H_{14}, H_{16}, H_{17}), 5.70 (s, 2H, N-CH_2), 5.62 (s, 2H, benzyl-CH_2). MS: *m/z* [M^+] Calcd for $C_{14}H_{12}N_6O_3$: 312.3, Found 313.3 [M+H]$^+$.

15) **N-((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde** (**4b**) yield 62%, Off-white solid, mp 184-186 ºC, IR (KBr, v_{max}, cm^{-1}): 3126 (C-H str), 2922, 2852 (C-H str, CHO), 1682 (C=O str), 1635, 1620, 1539 (C=C str, aromatic ring), 1456, 1273, 1228 (C-O asym. str), 1126 (C-O sym. str), 1051, 963. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (s, 1H, CHO), 7.54 (s, 1H, C-H triazole), 7.43 (s, H_5), 7.22 (s, H_4), 7.18-7.02 (m, J = 4Hz, H_{13}, H_{14}, H_{16}, H_{17}), 5.76 (s, 2H, N-CH_2), 5.45 (s, 2H, benzyl-CH_2), 2.37 (3H, s, CH_3). MS: *m/z* [M^+] Calcd for $C_{15}H_{15}N_5O$: 281.1, Found 282.1 [M+H]$^+$.

16) **N-((1-benzyl-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-imidazole-2-carbaldehyde** (**4c**) yield 64%, Off-white solid, mp 134-136 ºC. IR (KBr, v_{max}, cm^{-1}): 3109 (C-H str), 2922, 2854 (C-H str, CHO), 1676 (C=O str), 1637, 1629, 1618, 1583, (C=C str, aromatic ring), 1533, 1490, 1346, 1290 (C-O asym. str), 1168 (C-O sym. str), 1044, 962. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H, CHO), 7.58 (s, 1H, C-H triazole), 7.44 (s, H_5), 7.38-7.28 (m, J = 4Hz, H_4, H_{13}, H_{14}, H_{15}, H_{16}, H_{17}), 5.67 (s, 2H, N-CH_2), 5.50 (s, 2H, benzyl-CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.70 (CHO), 138.18 (C_7), 137.86, 129.41, 127.26, 124.46, 124.20, 123.37, 122.05 (C_{11}), 118.23, 49.59 (NCH_2),

37.50 (benzyl-CH_2). MS *m/z* [M^+] Calcd for $C_{14}H_{13}N_5O$: 267.1, Found 268.1 [M+H]$^+$.
Due to very low solubility of the products, ^{13}C NMR of compounds **3c, 3m, 4a, 4b** could not be reported.

General procedure for biological evaluation

The synthesized N-((1-substituted aryl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde were screened for their *in-vitro* antibacterial activity against two gram(+) bacteria i.e *Bacillus subtilis* and *Staphylococcus epidermidis* and two gram(-) bacteria i.e. *Escherichia coli* and *Pseudomonas aeruginosa*. The synthesized compounds were screened for antifungal activity against *Candida albicans* and *Aspergillus niger*. Double strength nutrient broth-I.P. and Sabouraud dextrose broth-I.P. were employed for bacterial and fungal growth, respectively. MIC value was determined by means of standard serial dilution method using a stock solution of 100 µg/mL. All the newly constructed molecules displayed appreciable *in-vitro* activity against the used strains. Ciprofloxacin and fluconazole are the most effective antibacterial and antifungal agents respectively, and were used as a reference drugs. The stock solution of control drug and newly constructed molecules were diluted to different concentration of 50, 25, 12.5, 6.25 and 3.12 µg/mL. All the samples were prepared in DMSO and the tubes containing bacterial strain were incubated at 37 ± 0.5 °C and the tubes containing fungal strain *C. albicans* were incubated at 30 ± 0.5 °C for 48h except in case of *A. niger* which was incubated for 7 days and then compared with control drug.

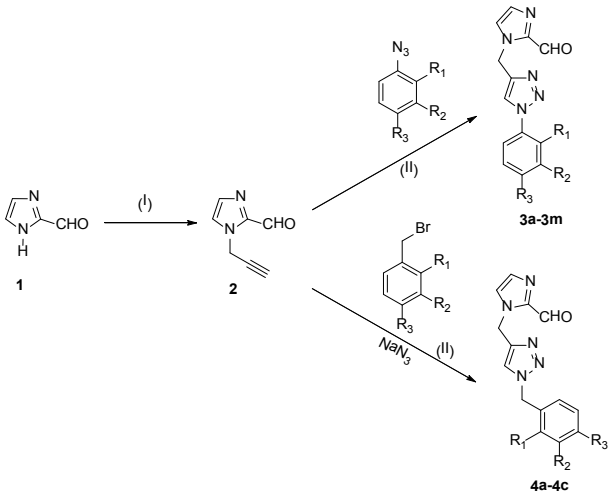
Computational details

Docking studies were carried out as per literature procedure[37] using Auto dock Vina program.

Results and discussion

1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde (**2**) was prepared by reaction of imidazole-2-carbaldehyde (**1**) and propargyl bromide at 0-5 ºC. Organic azides were obtained from aryl amines by diazotization-azidation process. N-((1-substituted phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde (**3a-3m**) were synthesized by stirring 1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde with different organic azides in presence of $CuSO_4.5H_2O$ and sodium ascorbate (**Scheme 1**).

N-((1-substituted aryl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-imidazole-2-carbaldehyde (**4a-4c**) were synthesized from 1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde and substituted benzyl bromide in presence of sodium azide (**Scheme 1**). The synthesized compounds were characterized by different spectroscopic techniques.



Scheme 1 (I) Reagent and conditions: K_2CO_3; propargyl bromide; DMF; 0-5 ºC.
(II) Reagent and conditions: copper sulphate; sodium ascorbate;
DMF: H_2O (7:3); 45 ºC, 6-8h.

Compounds	R_1	R_2	R_3	Yield %
3a	CH_3	Cl	H	69
3b	H	Cl	H	67
3c	H	H	CH_3O	63
3d	H	H	CH_3	64
3e	H	H	Br	76
3f	CH_3O	H	H	63
3g	H	Br	H	74
3h	H	H	Cl	58
3i	H	H	F	46
3j	NO_2	H	Cl	64
3k	Cl	Cl	H	64
3l	Cl	H	Cl	61
3m	F	H	H	58
4a	H	H	NO_2	63
4b	H	H	CH_3	62
4c	H	H	H	64

In IR, the band at 3116 cm^{-1} was C-H str. of aromatic ring and 1666 cm^{-1} was due to C=O str. of imidazole aldehyde. ^{1}H-NMR of **3e** showed the presence of the six signals in the aromatic region and one signal in aliphatic region; singlets at δ 5.78 ppm for NCH_2, at δ 8.10 ppm for C-H of triazole ring and at δ 9.86 ppm of imidazole aldehyde.

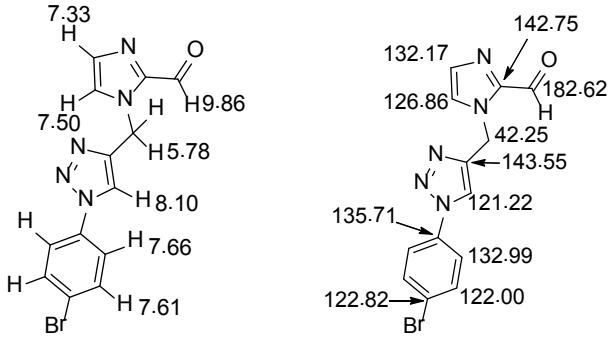


Figure 1 ^{1}H NMR and ^{13}C NMR of compound **3e**

The above assignment was supported by 2D-NMR eg. COSY, TOCSY and ROESY. The ^{1}H-^{1}H correlation between CHO and C_5-H, C_5-H and C_4-H, C_5-H and C_6-H, C_6-H and C_{11}-H was ascertained through COSY spectrum. The TOCSY experiment suggested the correlation of C_6-H with C_4-H, C_5-H, C_{11}-H, C_{13}-H/C_{17}-H and C_{14}-H/C_{16}-H; H of CHO with C_5-H, C_6-H and C_{11}-H. However the interaction in space between H of CHO with C_{11}-H, C_{13}-H/C_{17}-H and C_{14}-H/C_{16}-H; C_6-H with C_4-H, C_{11}-H, C_{13}-H/C_{17}-H and C_{14}-H/C_{16}-H was established by ROESY spectrum (**Figure 1**).

In DEPT-135 ^{13}C signals confirmed the presence of five peaks of 3º carbon, one peak of 2º carbon and the remaining for 4º carbons. In order to completely establish, the assignment of each carbon HSQC and HMBC spectra were scanned. HSQC confirm the assignment of carbon signals at δ 182.62 (CHO), 132.99 (C_{13} & C_{17}), 132.15 (C_4), 126.86 (C_5), 122.00 (C_{14} & C_{16}), 121.24 (C_{11}) and 42.25 ppm (C_6) because the key correlation was δ 9.86 → 182.62, 7.67 → 132.99, 7.33 → 132.17, 7.50 → 126.86, 7.61 → 122.00, 8.10 → 121.22 and 5.78 → 42.25 ppm (**Figure 1**). The assignment of 4º carbon signals was established through two bond correlation experiment HMBC at δ 143.55 (C_7), 142.75 (C_2), 135.71 (C_{12}), 122.82 ppm (C_{15}). This assignment was confirmed through the correlation of signals at δ 8.10 to 143.55 & 135.71; 7.67 to 135.71 & 122.82; 7.61 to 135.71 & 122.82; 7.50 & 7.30 to 142.75 and 5.78 to 143.55 ppm. The overall 2D-NMR analysis of **3e** established the structure of the desired compound.

Antimicrobial activity

N-((1-substituted aryl)-1*H*-1,2,3-triazol-4-yl) methyl)-1*H*-imidazole-2-carbaldehydes were screened for their *in-vitro* antimicrobial activity. In general, the synthesized compounds showed antibacterial activity ranging from 0.0936 to 0.0188 μmol/mL as depicted in **Table 1**. Compounds **3g** & **3j** (0.0188 μmol/mL) were

found to be more effective against *P. aeruginosa* and **3e** (0.0189 µmol/mL) exhibited promising activity against *E. coli*. Similarly, compounds **3e** & **3j** (0.0189 µmol/mL) were found to be more active against *S. epidermidis* and **3c** & **3f** (0.0221 µmol/mL) were found to be more active against *B. subtilis*.

Table 1 *In-vitro* antibacterial screening of compounds **3a-3m** and **4a-4c** (MIC in µmol/mL)

Entry	Compounds	*B. subtilis*	*S. epidermidis*	*E. coli*	*P. aeruginosa*
1	3a	0.0415	0.0208	0.0415	0.0415
2	3b	0.0871	0.0435	0.0435	0.0435
3	3c	0.0221	0.0442	0.0442	0.0442
4	3d	0.0468	0.0234	0.0936	0.0468
5	3e	0.0378	0.0189	0.0189	0.0378
6	3f	0.0221	0.0221	0.0442	0.0442
7	3g	0.0378	0.0378	0.0378	0.0189
8	3h	0.0871	0.0218	0.0435	0.0218
9	3i	0.0461	0.0231	0.0461	0.0231
10	3j	0.0377	0.0188	0.0377	0.0188
11	3k	0.0779	0.0389	0.0389	0.0389
12	3l	0.0389	0.0195	0.0389	0.0389
13	3m	0.0922	0.0461	0.0461	0.0461
14	4a	0.0801	0.0400	0.0400	0.0400
15	4b	0.0445	0.0445	0.0445	0.0445
16	4c	0.0936	0.0468	0.0468	0.0468
17	Ciprofloxacin	0.0047	0.0047	0.0047	0.0047

In the study against fungal strains, it was observed that the compounds synthesized in the present investigation were moderately active against the fungal strain as shown in **Table 2**. Compounds **3e** and **3g** (0.0094 µmol/mL) showed good potency against *C. albicans*. In case of *C. albicans*, maximum number of synthesized compounds with (Cl, Br, NO_2) substituents exhibited better activity than other methylene linked imidazole-triazole compounds with MIC value in the range of 0.0094-0.0110 µmol/mL.

Table 2 *In-vitro* antifungal screening of compounds **3a-3m** and **4a-4c** (MIC in µmol/mL)

Entry	Compounds	*A. niger*	*C. albicans*
1	3a	0.0415	0.0104
2	3b	0.0435	0.0109
3	3c	0.0442	0.0110
4	3d	0.0468	0.0117
5	3e	0.0755	0.0094
6	3f	0.0442	0.0110
7	3g	0.0755	0.0094
8	3h	0.0435	0.0109
9	3i	0.0461	0.0231
10	3j	0.0377	0.0188
11	3k	0.0779	0.0195
12	3l	0.0389	0.0097
13	3m	0.0922	0.0231
14	4a	0.0400	0.0200
15	4b	0.0889	0.0111
16	4c	0.0468	0.0117
17	Fluconazole	0.0102	0.0050

Docking Studies

The docking simulation of compounds **3e** was performed in the active site of DNA gyrase of *E. coli* utilizing Autodock vina program[37] for finding the plausible mechanism of action of the compounds for antimicrobial activity. All the protocols and the procedure for this study were followed as given in the work reported[36]. The most favorable conformation of compound **3e** in the binding site is shown in **Figure 2**. Analysis of **Figure 2** indicates that the compound **3e** is anchored in the binding site by means of various types of interactions. Nitrogen atom of triazole ring formed hydrogen bond (green dashed line) with Thr165. Pi orbitals of substituted phenyl

ring exhibited electrostatic interactions (yellow dashed line) with Glu50, Arg76 and imidazole ring showed pi-sigma interactions (magenta dashed line) with Thr165. The remaining parts of the molecule were involved in hydrophobic interactions (light pink dashed line) with the active site residues that were also involved in binding of clorobiocin ligand in the active site. Therefore, it can be explained that compound **3e** inhibits the enzyme DNA gyrase in fruitful manner. The cartoon diagram of the protein along with docked and co-crystallized molecule is shown in **Figure 3**.

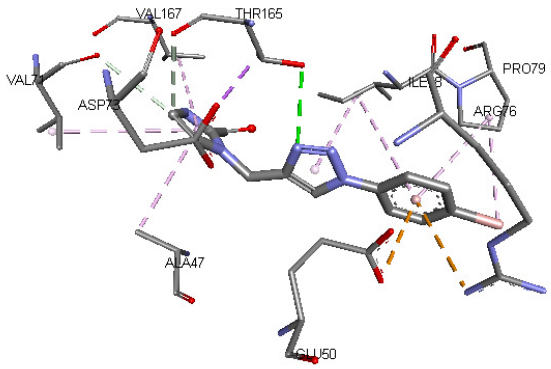


Figure 2 Binding interactions of compound **3e** in the active site of DNA gyrase

Figure 3 Docked compound **3e** (yellow) along with clorobiocin (grey) in DNA gyrase

Conclusions

In conclusion, we have synthesized N-((1-substituted aryl)-1*H*-1,2,3-triazol-4-yl)methyl)-1*H*-imidazole-2-carbaldehyde analogues in good yields by stirring 1-(prop-2-yn-1-yl)-1*H*-imidazole-2-carbaldehyde and different aryl azides using copper(I) catalyzed cycloaddition reaction. The compounds were examined for *in-vitro* antimicrobial activity and have substantial antibacterial and antifungal activity with MIC values ranging from 0.0936 to 0.0188 and 0.0889 to 0.0094 µmol/mL respectively. Compound **3e** was substantially more potent against *S. epidermidis* and *E. coli* (0.0189 µmol/mL) as well as *C. albicans* (0.0094 µmol/mL). Similarly, compound **3j** was potent against *P. aeruginosa* and *S. epidermidis* (0.0188 µmol/mL), *A. niger* (0.0377 µmol/mL) and *C. albican* (0.0188 µmol/mL). Docking study found that the residues showing interactions of compound **3e** were also involved in binding of clorobiocin ligand in the active site.

Supplementary Information

1D & 2D-NMR and MS spectra are available as Supplementary Information.

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References

1. E Garcia, J C Coa, E Otero, M Carda, I D Velez, S M Robledo, W I Cardona, Med. Chem. Res. 27, **2018**, 497.
2. V Verma, K Singh, D Kumar, T M Klapatke, J Stierstorfer, B Narasimhan, A K Quzi, A Hamid, S Jaglan, Eur. J. Med. Chem. 56, **2012**, 195.
3. D V Sowmya, S S Basha, P U M Devi, Y Lavanyalatha, A Padmaja, V Padmavathi, Med. Chem. Res. 26, **2017**, 1010.
4. J A Khan, A Wahab, S Javaid, M A Ghamdi, E Huwait, M Shaikh, A Shafqat, M I Choudhary, Med. Chem. Res. 26, **2017**, 2452.

5. M Grudzien, A Krol, G Paterek, K Stepien, F Plucinski, A P Mazurek, Eur. J. M. Chem. 44, **2009**, 1978.
6. S Chauhan, V Verma, D Kumar, A Kumar, Synth. Comm. 49, **2019,** 1427.
7. S Chauhan, V Verma, D Kumar, A Kumar, J. Het. Chem. **2019,** doi.org/10.1002/jhet.3655.
8. C H Zhou, Y Wang, Curr. Med. Chem. 19, **2012**, 239.
9. H X Ding, C A Leverett, R E Kyne, K K C Liu, S J Fink, A C Flick, C J O'Donnell, Bioorg. Med. Chem. 23, **2015**, 1895.
10. D J Fu, Y H Hou, S Y Zhang, Y B Zhang, J. Chem. Sci. 130(6), **2018**, 1.
11. L Y Ma, L P Pang, B Wang, M Zhang, B Hu, D Q Xue, K P Shao, B L Zhang, Y Liu, E Zhang, H M Liu, Eur. J. Med. Chem. 86, **2014**, 368.
12. B E Gryder, M J Akbashev, M K Rood, E D Raftery, W M Meyers, P Dillard, S Khan, A K Oyelere, ACS Chem. Biol. 8, **2013**, 2550.
13. K Kumar, B Pradines, M Madamet, R Amalvict, N Benoit, V Kumar, Eur. J. Med. Chem. 87, **2014**, 801.
14. R Raj, J Gut, P J Rosenthal, V Kumar, Bioorg. Med. Chem. Lett. 24, **2014**, 756.
15. T Yempala, J P Sridevi, P Yogeeswari, D Sriram, S Kantevari, Eur. J. Med. Chem. 71, **2014**, 160.
16. M H Shaikh, D D Subhedar, L Nawale, D Sarkar, F A K Khan, J N Sangshetti, B B Shingate, Med. Chem. Commun. 6, **2015**, 1104.
17. P de Andrade, O A Galo, M R Carvalho, C D Lopes, Z A Carneiro, R SestieCosta, E B de Melo, J S Silva, I Carvalho, Bioorg. Med. Chem. 23, **2015**, 6815.
18. T T Guimaraes, M C F R Pinto, J S Lanza, M N Melo, R L do Monte-Neto, I M M de Melo, E B T Diogo, V F Ferreira, CA Camara, W O Valença, R N de Oliveira, F Frezard, E N da Silva Jr, Eur. J. Med. Chem. 63, **2013**, 523.
19. S K V Vernekar, L Qiu, J Zacharias, R J Geraghty, Z Wang, Med. Chem. Commun. 5, **2014**, 603.
20. R Aneja, A A Rashad, H Li, R V K Sundaram, C Duffy, L D Bailey, I Chaiken, J. Med. Chem. 58, **2015**, 3843.
21. B H Fraser, S Hamilton, A M Krause-Heuer, P J Wright, I Greguric, S P Tucker, A G Draffan, V V Fokin, K B Sharpless, Med. Chem. Commun. 4, **2013**, 383.
22. S K V Vernekar, L Qiu, J Zhang, J Kankanala, H Li, R J Geraghty, Z Wang, J. Med. Chem. 58, **2015**, 4016.
23. J L Díaz, U Christmann, A Fern_andez, A Torrens, A Port, R Pascual, I_Alvarez, J Burgue, X Monroy, A Montero, A Balada, J M Vela, C Almansa, J. Med. Chem. 58, **2015**, 2441.
24. S K Kessler, A McCarthy, A Cnaan, D J Dlugos, Epilepsy Res. 112, **2015**, 18.
25. J Gilchrist, S Dutton, M Diaz-Bustamante, A McPherson, N Olivares, J Kalia, A Escayg, F Bosmans, ACS Chem. Biol. 9, **2014**, 1204.
26. H H Kinfe, Y H Belay, J S Joseph, E Mukwevho, Bioorg. Med. Chem. Lett. 23, **2013**, 5275.
27. S Shafi, M M Alam, N Mulakayala, C Mulakayala, G Vanaja, A M Kalle, R Pallu, M S Alam, Eur. J. Med. Chem. 49, **2012**, 324.
28. M R El SayedAly, H A Saad, M A M Mohamed, Bioorg. Med. Chem. Lett. 25, **2015**, 2824.
29. H Kuhn, D Gutelius, E Black, C Nadolny, A Basu, C Reid, Med. Chem. Commun. 5, **2014**, 1213.
30. S Hassan, T J J Müller, Adv. Synth. Catal. 357, **2015**, 617.
31. J Totobenazara, A J Burke, Tetrahedron Lett. 56, **2015**, 2853.
32. B Dervaux, F E Du Prez, Chem. Sci. 3, **2012**, 959.
33. M Meldal, C W Tornøe, Chem.Rev. 108, **2008**, 2952.
34. V D Bock, H Hiemstra, J H van Maarseveen, Eur. J. Org. Chem. **2006**, 51.
35. S Xu, X Zhuang, X Pan, Z Zhang, L Duan, Y Liu, L Zhang, X Ren, K Ding, J. Med. Chem. 56, **2013**, 4631.
36. K Lal, C P Kaushik, A Kumar, Med. Chem. Res. 24, **2015**, 3258.
37. O trott, A J Olson, J. Comput. Chem. 31, **2010**, 455.