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Synthesis of 4-Amino-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)one-[1,2,3]triazole-benzenesulphonamide Bioactive Hybrids as Novel Therapeutic Agents

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A novel 1*H*-pyrazol[1,2,3]triazole-benzenesulphonamide hybrids (**7a-o**) were synthesized with benzenesulfonamide and substituted aromatic azides/benzyl azides by Click reaction conditions using Cu(II) and aqueous sodium ascorbate as an inexpensive catalyst in the solvent ratio 1:1 H_2O-^{t}Bu-OH around 12-14 h at room temperature with high yields (81-92%) under eco-friendly conditions. These newly designed hybrids were characterized by IR, ^{1}H NMR and mass spectroscopic studies. These hybrids were also screened for *in vitro* antimicrobial activities and correlated with molecular docking studies. Among the derivatives, compound **7c** was found to be a potent antibacterial and antifungal agents with minimum inhibition concentration (MIC) of *in vitro* values were compared with standard molecules. The docking studies of these derivatives revealed that compound **7c** having greater binding affinity against the drug target haemoglobin receptor IsdB (3RTL) and it was confirmed by the *in vitro* screening.

Keywords: 1,2,3-Triazole hybrids, Click reaction, Sodium ascorbate, Biological activities.

INTRODUCTION

In the current world, microbial infections mainly caused due to continuous exposure to pathogens for a long time has become a main health concern, which are usually associated with mortality, morbidity and higher costs for its treatment. In order to treat these lives menacing infections and also considering the development of resistance towards frequently used antimicrobials, the advance investigation on new antimicrobials that could competently fight contrary to resistant microbes, has extremely increased [1-4]. Probing for new modes to cure such infections, researchers started to target the widely used azole heterocycles, which exhibit diverse effects of biological activities [5]. In addition, the toxicity, high therapeutic index, costs and well-being along with other aspects represent the superiority of azole derivatives act as antimicrobial agents. It has also been entrenched that azole compounds are emerged as a key role in new structure entity for various medicinal applications [5,6]. Among them, pyrazole, which falls under this azole family and its products, are critical as their significant biological applications such as of biological activities such as analgesic [7], antidiabetic [8], anticonvulsant [9], antimicrobial [10], antidepressant [11], anti-inflammatory [12], antiviral [13] and anticancer activities [14-16]. Further, a pyrazole ring linked to other heterocyclic systems or favoured structures may acquire a part of hopeful pharmacological and other biological activities [17,18].

Triazoles also belong to azole family and their constituted derivatives have drawn great attention by their synthetic and biological assay [19-21]. Particularly, 1,2,3-triazoles have gained unique recognition as widespread biological activities [22-32]. This triazole core strongly associate with hydrogen bond formation, which improves their solubility and ability with biomolecular targets and dipole-dipole interactions because of their strong dipole moments.

Similarly, benzenesulphonamides exhibit a strong and typical property of action as bridging ligands with metal ions [33,34]. Sulphonamide is the base of various groups of drugs of which benzenesulphonamide is an important structural motif shared by a number of bioactive compounds, ranging a wide collection of biological effects [35-40]. These compounds obtained as better therapeutic properties by replacement of hydrogen atom of SO_2NH_2 by heterocyclic ring compounds. The protein binding as this nitrogen atom is lipophilic in nature

and due to this nature, they are incorporated into most of the bioactive agents [41,42].

These findings, along with the ongoing investigation of nitrogen containing compounds with the chemotherapeutic activities, have motivated us to synthesize a novel series of bioactive hybrid molecules containing pyrazole, [1,2,3]triazole and benzenzenesulphonamide moieties in the same scaffold. As part of our continuous research, the present study describes the synthesis of new pyrazole-triazole derivatives that are coupled with benzenesulfonamide moiety of the pyrazole ring at N1 in search of promising antimicrobial compounds. We have designed some newly substituted derivatives, synthesized and confirmed by IR, ^{1}H NMR and mass spectroscopic studies. The biological assays for *in vitro* screening of the synthesized compounds for the antifungal and antibacterial studies were used to measure the extent of their activities. Further, the docking of the synthesized molecules was carried out with the fungal-targeted protein hemoglobin receptor IsdB (3RTL), primarily responsible in the haemoglobin cell wall anchored protein.

EXPERIMENTAL

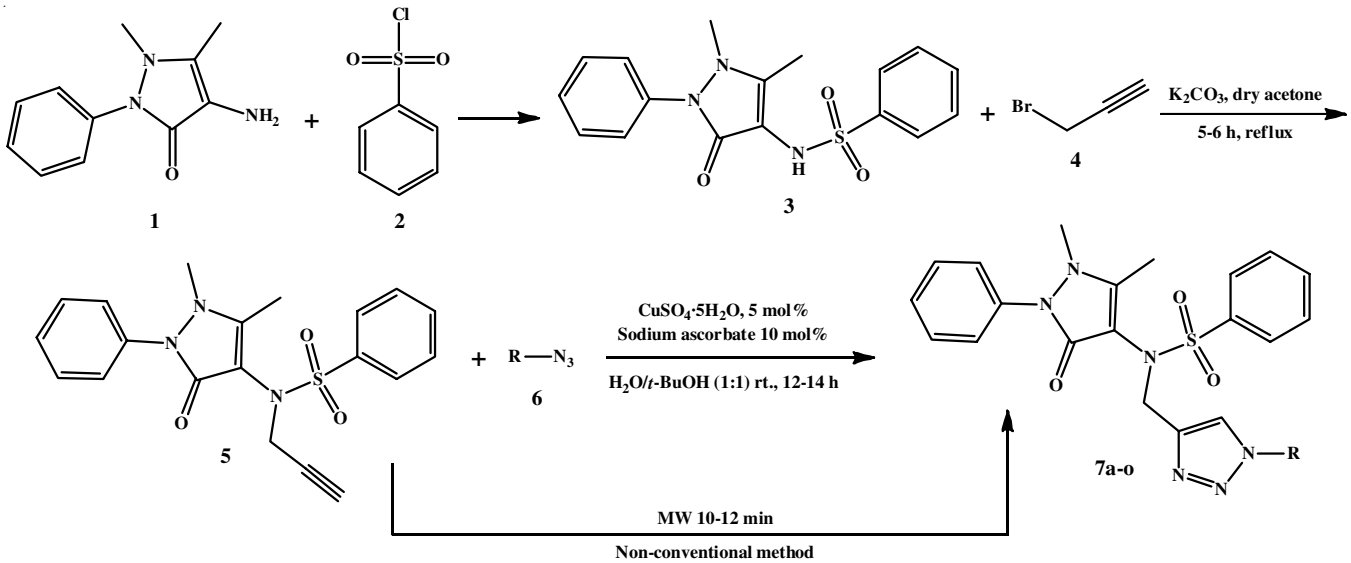
All the chemicals and solvents were of reagent grade as received from the commercial sources. The solvents were used without further purification. Purification of the products was carried out by column chromatography using 60-120 mesh silica gel. The functional groups were identified using a FTIR BRUKER optics TENSOR 27 spectrometer in the range of 4000-400 cm^{-1} as KBr pellets. The ^{1}H and ^{13}C NMR were recorded on a BRUKER Biospin Avenger III FTNMR digital spectrometer. High-resolution mass spectrometry (HRMS) was determined on Agilent 6520 (Q-TOF) mass spectrometer with Agilent 1200 HPLC system.

Synthesis of *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (5): 4-Amino-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (**1**) and benzenesulfonyl chloride (**2**) were dissolved in ethanol at room temperature with appropriate stirring for 2 h to obtain *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (**3**) to this propargyl bromide (**4**) was added in presence of anhydrous K_2CO_3 in dry acetone under reflux about 4 h to obtain *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-N-(prop-2-yn-1-yl)benzenesulfonamide (**5**).

Synthesis of 1*H*-pyrazol-3(2*H*)-one-1,2,3-triazole hybrids (7a-o): By the addition of 3 mmol of *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-(prop-2-yn-1-yl)-benzenesulfonamide (**5**) and 3 mmol of substituted aromatic azides/benzyl azides (**6**) under Click reaction conditions in the presence of $CuSO_4{\cdot}5H_2O$ and aqueous sodium ascorbate 0.3 mmol each as catalyst in 12 mL of H_2O-^{t}BuOH solvent (1:1) with under vigorous stirring around 12-14 h at room temperature and the complete reaction was monitored by TLC. After the completion of reaction, the cool reaction mixture was poured to 50 mL ice-cold water to obtain a white precipitate. This precipitate was washed with cold water, dried under vacuum and purified by column chromatography with ethyl acetate in hexane (**Scheme-I**).

Microwave irradiated technique (MW): The aforementioned reaction mixture was heated in a laboratory microwave oven at 300 W for 10-12 min. Upon completion of the reaction, the reaction was diluted into 50 mL of water and cooled in ice to precipitate out. This precipitate was purified by the column chromatography with ethyl acetate in *n*-hexane after being washed with cold water and dried in a vacuum.

***N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-((1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)benzenesulfonamide (7a):** White solid, m.p.: 176-178 ºC. IR (KBr, ν_{max}, cm^{-1}): 3160 (C-H *str.*), 3087 (C-H), 2122 (N=N), 1740 (C=O), 1665 (C=C), 1336 (S=O), 665 (C=C bend.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.98 (s, 1H, triazole C-H-5), 8.45 (s, Ar 4H′′), 8.21-7.92 (s, Ar 4H), 7.67 (t, *J* = 6.9 Hz, Ar 1H-4), 7.58 (s, Ar 4H), 7.35 (t, *J* = 6.8 Hz, Ar 1H-4), 4.84 (dd, *J* = 13.7, 14.7 Hz, aliphatic 2H-CH_2), 3.08 (3H,s, CH_3), 2.04



Scheme-I: Synthesis of 1*H*-pyrazol-3(2*H*)-one-1,2,3-triazole hybrids **(7a-o)**

(3H, s, CH_3). ^{13}C NMR (100 MHz, DMSO) δ ppm: 161.20 (C-3′), 156.09 (C-Ar 4″), 146.67(C-Ar 1″), 144.59 (C-Ar 1), 140.69 (C-Ar 1′), 139.03 (C-Ar 4), 134.57 (C-5′), 133.11 (C-Ar 1′), 129.10 (C-Ar-3,5), 127.36 (C-Ar 2,6), 126.97 (C-Ar3″,5″), 125.55 (C-Ar 4″), 124.60 (C-Ar 3″,5″), 122.53 (C-Ar 2′,6′), 120.48 (C-Ar 2″,6″), 120.07 (C-5), 106.62 (C-4′), 43.57 (aliphatic CH_2), 35.09 (N1″-CH_3), 10.54 (C5″-CH_3). MS (ESI) (*m/z*) 545 (M+1) observed for $C_{26}H_{23}N_7O_5S$.

***N*-((1-(4-Acetylphenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7b):** White solid, m.p.: 175-178 ºC. IR (KBr, ν_{max}, cm^{-1}): 3071 (C-H), 2971 (C-H *str.*), 2113 (N=N), 1740 (C=O), 1680 (C=C), 1343 (S=O), 693 (C=C bend). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.25 ((s, 1H, triazole C-H-5),8.05-7.92 (s, Ar-4H-2,6,3″,5″), 7.88-7.72 (m, Ar-2H-2″,6″), 7.60-7.35 (m, Ar-5H-3,4,5,3′,5′), 7.37-7.24 (m, Ar-3H-2′4′6′), 4.89 (s, 2H-CH_2), 3.13 (s, 3H, CH_3), 2.66 (s, 3H CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 196.61 (C_4-Ar-1 C″=O), 161.98 (C=O, C3′), 155.91 (C-Ar-1″), 139.91 (C4′ triazole), 139.17(C-Ar-4), 136.72 (C-Ar-1), 134.43 (C-Ar-3,5), 133.04 (C-Ar-3″,5″), 130.02 (C-Ar-2,6),129.31 (C-Ar-2′,6′), 128.93 (C-Ar-2′,6′)127.75 (C-Ar-4′),127.40 (C5-triazole), 127.39 (C4-pyrazole), 35.28 (N-CH_2), 26.69 (C4-ArC2-CH_3), 11.12 (C5″-CH_3). MS (ESI) (*m/z*) 542 (M+1) observed for $C_{28}H_{26}N_6O_4S$.

***N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-((1-(4-fluorophenyl)-1H-1,2,3-triazol-4-yl)-methyl)benzenesulfonamide (7c):** Yellow solid, m.p.: 165-166 ºC. IR (KBr, ν_{max}, cm^{-1}): 3089 (C-H), 2971 (C-H), 1740 (C=O), 1650 (C=C), 1367 (S=O), 691 (C=C bend). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.09 (s, 1H, H-5), 8.02 (d, *J* = 7.4 Hz, 2H, Ar-H 2,6), 7.62 (dd, *J* = 8.4, 4.4 Hz, 2H, Ar-H, 3′,5′), 7.55 (t, *J* = 7.1 Hz, Ar-1H, 4), 7.51-7.39 (m, 4H, Ar-H-3,5, 3″5″), 7.31(t, *J* = 7.5 Hz, 1H, Ar-H-4′), 7.18 (t, *J* = 8.3 Hz, 2H, Ar-H-2, 6), 7.02 (dd, *J* = 18.8, 6.3 Hz, 2H, Ar-H-2″, 6″), 4.86 (s, 2H, CH_2), 3.11 (s, 3H, N-CH_3), 2.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 163.60 (C-ArC4-F), 162.02 (C=O), 156.01 (C-Ar-1), 139.26 (C-Ar-1″), 134.55 (C-Ar-1′), 133.02 (C-triazole C4″), 129.33 (C5″), 128.95 (C-Ar-2, 6), 127.82 (C-Ar-2″, 6″), 127.34 (C-Ar-4), 124.84 (C-Ar-4″), 122.38 (C-Ar-2′, 6′), 120.38 (triazole-C5),120.30 (C4″), 116.71 (C-Ar-3′,5′), 44.83 (CH_2), 35.32 (CH_2), 11.14 (CH_3). MS (ESI) (*m/z*) 518 (M+1) observed for $C_{26}H_{23}FN_6O_3S$.

***N*-((1-(4-Chloro phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7d):** White solid, m.p.: 167-168 ºC. IR (KBr, ν_{max}, cm^{-1}): 3015 (C-H *str.*), 2971 (C-H), 1740 (C=O *str.*), 1642 (C=O conjuct.), 1331 (S=O), 697 (C=C bend.). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.12 (s, 1H, C-H5″), 8.02 (d, *J* = 7.4 Hz, Ar -2H,-2,6), 7.60 (d, *J* = 8.6 Hz, Ar-2H, 3,5), 7.54 (t, *J* = 7.1 Hz, Ar-1*H*-4), 7.50-7.40 (m, Ar-5H 3,4,5,3′,5′), 7.31 (t, *J* = 7.5 Hz, Ar-2H 2′,6′), 6.96 (t, *J* = 8.6 Hz, Ar-1H 4′), 4.86 (s, 2H, CH_2), 3.11 (s, 3H″ CH_3), 2.19 (s, 3H″ CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.05 (C=O), 156.05 (C-Ar-1), 139.24 (C-Ar-1″), 135.40 (C-Ar-4″), 134.52 (C-Ar-1′), 134.41 (C4 triazole), 133.04 (C5 pyrazole), 129.87 (C-Ar-3′,5′), 129.37 (C-Ar-3,5), 128.95 (C-Ar-2,6), 127.81 (C-Ar-2′,6′), 127.36 (C-Ar-4′), 124.84(C-Ar-2″, 6″), 121.79 (C5 triazole), 121.51 (C4 pyrazole), 44.84 (CH_2), 35.32 (CH_3), 11.15 (CH_3). MS (ESI) (*m/z*) 534 (M+1) observed for $C_{26}H_{23}ClN_6O_3S$.

***N*-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7e):** Yellow solid, m.p.: 162-165 ºC. IR (KBr, ν_{max}, cm^{-1}): 3064 (C-H *str.*), 2946 (C-H *str.*), 2129 (N=N), 1740 (C=O), 1642 (C=C), 1330 (S=O), 696 (C=C bend.). ^{1}H NMR (400 MHz, CDC^l_3) δ ppm: 8.12 (s, 1H triazole -H5), 8.02 (d, *J* = 6.6 Hz, Ar-2H 2,6)), 7.61 (d, *J* =7.6 Hz, Ar-2H-3′,5′), 7.58-7.37 (m, Ar-9H H3,4,5,3′,5,2″,3″,5″,′6″), 7.32 (t, *J* = 6.1 Hz, Ar-2H 2′,6′), 6.91 (t, *J* = 7.8 Hz, Ar-1H, -H4), 4.86 (s, 2H, CH_2), 3.12 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.06 (C=O), 156.06 (C-Ar-1), 139.24 (C-Ar-1″), 135.88 (C-Ar-1′), 134.52 (C4″), 132.84 (C-Ar-4), 132.78 (C5′), 131.03 (C-Ar-3′,5′), 129.34 (C-Ar-3, 5), 128.95 (C-Ar-2″,6″), 127.82 (C-Ar-2,6), 127.36 (C-Ar-2′,C6′), 124.84 (C-Ar-4′), 121.74 (C5″), 120.68 (C4′), 44.84 (CH_2), 35.32 (CH_3), 11.15 (CH_3). MS (ESI) (*m/z*) 578 (M+1) observed for $C_{26}H_{23}BrN_6O_3S$.

***N*-((1-(2,6-Dichloro-4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7f):** White solid, m.p.: 178-179 ºC. IR (KBr, ν_{max}, cm^{-1}): 3039 (C-H *str.*), 2948 (C-H *str.*), 2131 (N=N), 1740 (C=O), 1653 (C=C), 1343 (S=O), 695 (C=C bend.). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.35 (s, 2H (Ar-2H, 3″,5″), 8.05 (d, *J* = 4.6 Hz, Ar-2H 2,6), 7.98 (s, 1H 5″ triazole), 7.65-7.33 (m, Ar-5H 3, 4, 5, 3′, 5′), 7.31-7.28 (m, Ar-3H 2′, 6′), 4.92 (d, *J* = 12.9 Hz, 2H, CH_2), 3.12 (s, 3H CH_3), 2.18 (s, 3H CH_3).^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.85 (C=O), 161.20 (C-ArC4′), 156.09 (C-Ar2″, 6″), 144.59 (C-Ar 1), 140.69 (C-Ar 1″), 139.03 (C-Ar 1′), 134.57 (C4″), 133.11 (C5′), 129.10 (C-Ar4), 127.36 (C-Ar 3′,5′), 126.97 (C-Ar 3,5), 125.55 (C-Ar 2,6), 124.60 (C-Ar 2′,6′), 122.53 (C-Ar 4′), 120.48 (C-Ar 3″,5″), 120.07 (C4″), 43.57 (CH_2), 35.09 (CH_3), 10.55 (CH_3). MS (ESI) (*m/z*) 613 (M+1) observed for $C_{26}H_{21}Cl_2N_7O_5S$.

***N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-((1-(3-methoxy-4-nitro phenyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (7g):** Yellow solid, m.p.: 172-175 ºC. IR (KBr, ν_{max}, cm^{-1}): 3085 (C-H *str.*), 2970 (C-H *str.*), 2125 (N=N), 1740 (C=O), 1649 (C=C), 1314 (S=O), 694 (C=C). ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.49 (s, 1H 5′), 7.99-7.83 (m, Ar 1H 5′), 7.81-7.72 (m, Ar 1H 2, 6), 7.70-7.64 (m, Ar 1H 6′), 7.62-7.53 (m, Ar 3H 3,4,5), 7.52-7.38 (m, Ar 2H 3″,5″), 7.37– 7.31 (m, Ar 1H 4″), 7.30-7.15 (m, Ar 2H 2″,6″), 4.80 (dd, *J* = 12.4, 13.0 Hz, 2H, CH_2″), 3.94 (s, 3H CH_3), 3.08 (s, 3H CH_3), 2.00 (s, 3H CH_3). ^{13}C NMR: (100 MHz, DMSO) δ ppm: 162.00 (C=O), 158.09 (C-Ar3′), 151.05 (C-Ar4′), 141.27 (C-Ar 1), 139.20 (C-Ar1′), 138.11 (C-Ar1″), 134.44 (C4′), 133.11 (C-Ar4), 130.58 (C5″), 129.54 (C-Ar 3′,5′), 129.35 (C-Ar3,5), 129.01 (C-Ar 2,6), 127.86 (C-Ar 5′), 127.36 (C-Ar-2′,6′), 127.24 (C-Ar 4′), 125.72 (C-Ar C6′), 124.67 (C5′), 108.34 (C4″), 48.26 (O-CH_3′), 44.80 (CH_2′), 35.42 (CH_3″), 10.17 (CH_3″). MS (ESI) (*m/z*) 575 (M+1) observed for $C_{27}H_{25}N_7O_6S$.

***N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-((1-(2-methyl-3-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)methyl)benzenesulfonamide (7h):** Yellow solid, m.p.: 180-182 ºC. IR (KBr, ν_{max}, cm^{-1}): 3029 (C-H *str.*), 2946

(*str.*), 2127 (N=N), 1740 (C=O), 1655 (C=C), 1339 (S=O), 694 (C=C bend.). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.06 (d, *J* = 7.5 Hz, Ar 2H-2,6), 8.01 (d, *J* = 6.9 Hz, Ar 1H 4′), 7.93 (s, 1H 5″), 7.58 (t, *J* = 7.1Hz, Ar 1H4)), 7.55-7.41 (m, Ar 5H 3,4,5, 3″,5″), 7.35-7.29 (m, Ar 2H 2′,6′), 4.91 (d, *J* = 4.5 Hz, 2H, CH_2), 3.15 (s, 3H CH_3), 2.25 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.00 (C=O), 156.01 (C-Ar 3′), 151.05 (C-Ar1), 141.27 (C-Ar1″), 139.20 (C4′), 138.11 (C-Ar 2′), 134.44 (C5″), 133.11 (C-Ar 3″,5″), 130.58 (C-Ar 3, 5C-Ar 1′), 129.54 (C-Ar 2, 6), 129.35 (C-Ar 5′), 129.01 (C-Ar6′), 127.86 (C-Ar 2″,6″), 127.36 (C-Ar 4″), (C5′), 108.34 (C-4′), 44.80 (CH_2′), 35.42 (CH_3″), 14.40 (CH_3″), 11.17 (ArCH_3). MS (ESI) (*m/z*) 559 (M+1) observed for $C_{27}H_{25}N_7O_5S$.

***N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-((1-phenyl-1*H*-1,2,3-triazol-4-yl)methyl)-benzenesulfonamide (7i):** White solid, m.p.: 176-177 ºC. IR (KBr, ν_{max}, cm^{-1}): 3062 (C-H *str.*), 2930 (C-H *str.*), 2127 (N=N), 1740 (C=O), 1649 (C=C), 1346 (S=O), 687 (C=C bend). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.12 (s, 1H) (C5′-H), 8.04 (d, *J* = 7.3 Hz, Ar 2H 2,6), 7.66 (d, *J* = 7.6 Hz, Ar2H2′,6′), 7.61-7.46 (m, Ar 5H 2′,3′,4′,5′,6′), 7.45-7.38 (m, Ar3H 3,4,5), 7.32-7.27 (m, Ar 5H 2″,3″,4″,5″,6″), 4.86 (d, *J* = 12.7 Hz, 2H, CH_2″), 3.11 (s, 3H, CH_3), 2.18 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 162.03 (C=O), 156.19 (C-Ar 1,1′), 139.26 (C-Ar 1″), 136.94 (C4′), 134.56 (C-Ar 4), 133.13 (C5″), 133.01 (C-Ar 3,5), 129.73 (C-Ar 3″,C5″), 129.31 (C-Ar 3′,4,5′), 128.95 (C-Ar 2,6), 128.70 (C-Ar 2″,6″), 127.82 (C-Ar 4″), 127.30 (C-Ar 2′,6′), 124.84 (C5′), 121.81 (C4″), 108.27, 44.71 (CH_2), 35.32 (CH_3), 11.12 (CH_3). MS (ESI) (*m/z*) 500 (M+1) observed for $C_{26}H_{24}N_6O_3S$.

***N*-((1-(3,4-Dichlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7j):** White solid, m.p.: 160-162 ºC, IR (KBr, ν_{max}, cm^{-1}): 3072 (C-H *str.*), 2971 (C-H *str.*), 2112 (N=N), 1740 (C=O), 1657 (C=C), 1332 (S=O), 683 (C=C bend.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.89 (s, 1H 5′), 8.26 (s, Ar-1H 2′), 8.02-7.80 (m, Ar 4H), 7.67-7.44 (m, Ar 5H), 7.35-7.14 (m, Ar 3H), 4.81 (d, *J* = 18.3 Hz, 2H CH_2), 3.07 (s, 3H CH_3), 2.03 (s, 3H CH_3).^{13}C NMR (100 MHz, DMSO) δ ppm: 166.42 (C=O), 161.42 (C-Ar1), 149.48 (C-Ar1′), 145.18 (C-Ar1″), 144.28 (C-Ar 3″,4″), 144.23 (C4″), 139.83 (C-Ar4, C-Ar 5″), 138.14 (C5′), 137.60 (C-Ar 3′,5′), 137.01(C-Ar 3,5), 136.18 (C-Ar 2,6), 134.34 (C-Ar6), 132.60 (C-Ar 2′,6′), 132.18 (C-Ar 6″), 129.80 (C-Ar 2″), 126.86 (C4′), 126.41 (C-Ar5″), 125.14 (C-Ar 4′), 108.82, 48.76 (CH_2′), 40.36 (CH_3), 15.81 (CH_3). MS (ESI) (*m/z*) 568 (M+1) observed for $C_{26}H_{22}Cl_2N_6O_3S$.

***N*-((1-(2,3-Difluorophenyl)-1*H*-1,2,3-triazol-4-yl)-methyl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7k):** White solid, m.p.: 157-158 ºC, IR (KBr, ν_{max}, cm^{-1}): 3032 (C-H *str.*), 2942 (C-H *str.*), 2117 (N=N), 1740 (C=O), 1658 (C=C), 1348 (S=O), 692 (C-H bend.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.87 (s, C-H 1H 5′), 8.03-7.85 (m, Ar 2H, 2,6), 7.80-7.73 (m, Ar 2H, 3,5), 7.70-7.64 (m, Ar 1H 4), 7.62-7.53 (m, Ar 2H, 3′,5′), 7.51-7.38 (m, Ar 3H, 2′,4′,6′), 7.34-7.27 (m, Ar 1H 6″), 7.24-6.93 (m, Ar 2H, 5″,4″), 4.81 (d, *J* = 12.4 Hz, 2H, CH_2), 3.07 (s, 3H, CH_3), 2.03 (s, 3H, CH_3).^{13}C NMR (100 MHz, DMSO) δ ppm: 163.94 (C=O), 161.63 (C-Ar 2″), 161.15 (C-Ar 3″), 156.17 (C-Ar1), 144.28 (C-Ar1′), 139.00 (C4″), 138.21(C5′), 134.59 (C-Ar 3′,5′), 133.10 (C-Ar 3,5), 129.10 (C-Ar 2,6), 129.07 (C-Ar 6″), 127.30 (C-Ar 5″), 126.93 (C-Ar 2′,6′), 124.55 (C-Ar 4′), 122.40 (C5″), 105.52 (C-Ar4″), 103.89 (C4′), 43.44 (CH_2), 35.11 (CH_3), 10.55 (CH_3). MS (ESI) (*m/z*) 536 (M+1) observed for $C_{26}H_{22}F_2N_6O_3S$.

4-(4-((*N*-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)phenylsulfonamido)methyl)-1*H*-1,2,3-triazol-1-yl)benzoic acid (7l): White solid, m.p.: 184-185 ºC. IR (KBr, ν_{max}, cm^{-1}): 3069 (C-H *str.*), 2970 (C-H *str.*), 2490 (S-N), 1740 (C=O), 1698 (C=C), 1347 (S=O), 639 (C=C bend.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 13.29 (s, 1H, -COOH), 8.84 (s, 1H, 5′), 8.20-7.87 (m, Ar 5H, 2,3,4,5,6), 7.79-7.44 (m, Ar 5H 2″,3″,4″,5″,6″), 7.46-7.10 (m, Ar 4H, 2′,3′,5′,6′), 4.81 (dd, *J* = 12.9, 14.4 Hz, 2H, CH_2), 3.07 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO) δ ppm: 169.00 (Ar-C=O), 161.23 (C=O), 156.13 (C-Ar1′), 144.21 (C-Ar1), 143.12 (C-Ar1″), 139.26 (C4′), 139.15 (C-Ar4), 139.07 (C5″), 138.37 (C-Ar3′,5′), 134.59 (C-Ar4′), 133.09 (C-Ar3″,5″), 129.09 (C-Ar3,5), 127.36 (C-Ar2,6), 126.94 (C-Ar2″, 6″), 124.57 (C-Ar2′,6′), 122.20 (C-Ar4″), 119.83 (C5′), 105.65 (C4″), 43.62 (CH_2), 35.11 (CH_3), 10.53 (CH_3). MS (ESI) (*m/z*) 544 (M+1) observed for $C_{27}H_{24}N_6O_5S$.

***N*-((1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl)-*N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-benzenesulfonamide (7m):** Yellow solid, m.p.: 161-163 ºC. IR (KBr, ν_{max}, cm^{-1}): 3142 (C-H *str.*), 2970 (C-H *str.*), 2129 (N=N), 1740 (C=O), 1657 (C=C), 1333 (S=O), 691 (C=C bend.). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.99 (d, *J* = 7.5 Hz, Ar 2H, 2,6), 7.58 (s, 1H, 5″), 7.52 (t, *J* =12.2 Hz, Ar 1H, 4), 7.47-7.38 (m, Ar 4H, 2″,3″,5″,6″), 7.35-7.31 (m, Ar 3H, 2′,4′,6′), 7.28 (d, *J* =10.2 Hz, Ar 1H, 4″), 7.24-7.16 (m, -CH_2-Ph4H, 2,3,5,6), 5.45 (d, *J* = 2.9 Hz, 2H, CH_2), 4.74 (dd, *J* = 15.1, 14.7 Hz, 2H, CH_2), 3.03 (s, 3H, CH_3), 2.00 (s, 3H, CH_3). ^{13}C NMR 100 MHz, $CDCl_3$) δ 161.75 (C=O), 156.22 (C-Ar1), 144.34 (C-Ar1′), 139.23 (C-Ar1″), 134.82 (C5′), 134.51 (C-Ar 3′,5′), 132.95 (C-Ar 3″,5″), 129.26 (C-Ar3,5), 129.05 (C-Ar 2″,6″), 128.92 (C-Ar 2,6), 128.69 (C-Ar4″), 127.96 (C-Ar 2′,6′), 127.76 (C-Ar 4′), 127.17 (C5″), 124.69 (C4′), 54.07 (CH_2), 44.48 (CH_2), 35.33 (CH_3), 10.83 (CH_3). MS (ESI) (*m/z*) 514 (M+1) observed for $C_{27}H_{26}N_6O_3S$.

***N*-((1-(3,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7n):** White solid, m.p.: 160-163 ºC, IR (KBr, ν_{max}, cm^{-1}): 3039 (C-H *str.*), 2948 (C-H *str.*), 2131 (N=N), 1740 (C=O), 1653 (C=C), 1343 (S=O), 695 (C=C bend.). ^{1}H NMR (400 MHz, DMSO) δ ppm: 8.89 (s, 1H 5″), 8.26 (s, Ar 1H, 5″), 8.02-7.80 (m, Ar 4H, 2′,4′,6′,2″), 7.67-7.44 (m, Ar 5H 3,4,5, 3′, 5′), 7.35-7.14 (m, Ar 3H, 2,6,6″), 5.67 (s, 2H, CH_2), 4.81 (d, *J* = 18.3 Hz, 2H, CH_2), 3.07 (s, 3H, CH_3), 2.03 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO) δ ppm: 162.75 (C=O), 162.13 (C-Ar 1), 156.22 (C-Ar 1″), 144.34 (C-Ar 1′), 139.23 (C-Ar4), 134.82 (C-Ar3″), 134.51 (C5′), 132.95 (C4″), 129.26 (C-Ar 4″), 129.05 (C-Ar 2″), 128.92 (C-Ar 5″), 128.69 (C-Ar 3″,5″), 127.96 (C-Ar 3,5), 127.76 (C-Ar 6″), 127.17 (C-Ar 2′,6′), 124.69 (C-Ar 4″), 123.50 (C4′),

54.12 (CH_2), 44.68 (CH_2), 35.41 (CH_3), 10.75 (CH_3). MS (ESI) (*m/z*) 582 (M+ 1) observed for $C_{27}H_{24}Cl_2N_6O_3S$.

***N*-((1-(2,4-Dichlorobenzyl)-1*H*-1,2,3-triazol-4-yl)-methyl)-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)benzenesulfonamide (7o):** White solid, m.p.: 161-163 ºC. IR (KBr, ν_{max}, cm^{-1}): 3072 (C-H *str.*), 2971 (C-H *str.*), 2112 (N=N), 1740 (C=O (ArC3′-H)), 1657 (C=C), 1332 (S=O), 683 (C=C bend). ^{1}H NMR (400 MHz, DMSO) δ ppm: 7.97 (s, Ar 1H, 2′′), 7.90 (d, *J* = 7.5 Hz, Ar 2, 6), 7.72 (s, 1H, 5′′), 7.66 (t, *J* = 7.1 Hz, Ar 1H, 4), 7.59-7.53 (m, Ar 2H, 3,5), 7.56-7.43 (m, Ar 3H, 2′, 4′, 6′), 7.35 (t, *J* = 7.2 Hz, Ar 1H, 4′′), 7.24-7.13 (m, Ar 3H), 5.67 (s, 2H, $\underline{CH_2}$-Ar)), 4.69 (dd, *J* = 12.3, 14.4 Hz, 2H, CH_2), 3.04 (s, 3H, CH_2), 2.09 (s, 3H, CH_3).^{13}C NMR (100 MHz, DMSO) δ 163.65 (C=O), 162.95 (C-Ar1), 156.22 (C-Ar1′′), 144.34 (C-Ar2′′), 139.23 (C-Ar1′), 134.82 (C-Ar4′′), 134.51 (C-Ar4), 132.95 (C5′), 129.26 (C4′′), 129.05 (C-Ar3′′), 128.92 (C-Ar3′, 5′), 128.69 (C-Ar3, 5), 127.96 (C-Ar2, 6), 127.76 (C-Ar5′′), 127.17 (C-Ar2′, 6′), 124.69 (C-Ar4′), 123.50 (C4′), 54.18 (CH_2), 44.63 CH_2),35.39 (CH_3), 10.69 (CH_3). MS (ESI) (*m/z*) 582 (M+1) observed for $C_{27}H_{24}Cl_2N_6O_3S$.

Biological evaluation

***In vitro* antimicrobial activity:** The micro dilution method was used using Mueller-Hinton broth and Luria-Bertania (LB) to evaluate the synthesized compounds for antibacterial activity. The compounds were made up to 2 mg/mL in culture broth after being produced in 10% DMSO. Then, concentrations ranging from 2 to 0.0156 mg/mL were attained with the addition of culture broth in 1:2 serial dilution. Dispersions of 0.1 mL of each dilution, along with a sterility control and a growth control, were made in 96-well plates. A bacterial suspension (10^8 CFU/mL or 10^5 CFU/well) was used to inoculate 0.005 mL of medium into each test and growth control well. Three replicates of each test were performed, and the microdilution trays were incubated at 36 ºC for 18 h. An alcoholic solution (0.5 mg/mL) (Sigma) was added to 0.02 mL of bacterial growth that had been detected beforehand by optical density (ELISA reader). The trays with the bacterial growth were incubated at 36 ºC for another 30 min. The minimal inhibitory concentration (MIC) was established as the concentration of each product required to totally halt microbial growth. All the synthesized compounds were compared to standard ciprofloxacin.

Molecular docking studies: Docking experiments were carried out with Schrödinger Maestro LLC INC with the objective of looking at the binding pattern of synthesized compounds with regards to their binding affinity. The 3RTL complex structures were obtained from the Protein Data Bank. Schrödinger Maestro LLC's Protein Preparation Protocol takes imported protein sequences and modifies them to fix issues like hydrogen atom deficiency, improper atom order among amino acids, and incorrect protonation states among ionizable side-chains and terminal groups. Energy reduction was performed with the OPLS3e force field by employing several algorithms until the protein attained a convergence gradient of 0.001 kcal/mol. This involved the removal of all hetero atoms and water molecules. Molecular dynamics were then used to achieve protein equilibration following energy minimization. The receptor cavity approach was used to predict the receptor's binding pockets. After the receptor grid was created, the locations were identified. Target protein binding sites (Grid) were identified by measuring the volume of the active site that is occupied by known ligands.

RESULTS AND DISCUSSION

The optimization of synthesis of 1*H*-pyrazol-3(2*H*)-one-1,2,3-triazole hybrids **(7a-o)** (**Scheme-I**) was carried out with various amount of catalysts and solvent ratios and it was finally fixed by the simple and economical viable catalytical mixture of 5 mol% of $CuSO_4$ and 10 mol% of sodium ascorbate with green solvent mixture of 1:1 H_2O-^{t}BuOH under vigorous stirring about 12-14 h at room temperature. Initially, *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-N-(prop-2-yn-1-yl)benzenesulfonamide (**5**) was synthesized by 1*H*-pyrazol-4-yl)benzenesulfonamide (**3**) and propargyl bromide (**4**) in presence of anhydrous K_2CO_3 in dry acetone under reflux conditions and finally addition of substituted aromatic azides/benzyl azides (**6**) to compound **5** offered 1*H*-pyrazol-3(2*H*)-one-1,2,3-triazole hybrids **(7a-o)** under Click chemistry mechanism (**Scheme-I**) and the same reactions conditions were maintained under microwave technique. This reaction conditions provide high yields with electron donating groups compared with electron withdrawing groups. This protocol provides very good yields with 81-91% under conventional method and 88-95% under microwave dramatically reduce reaction time 10-12 min compared conventional method 12-14 h at room temperature (Table-1) with eco-friendly conditions by avoiding tedious process for the recovery of derivatives without further purification.

TABLE-1
SYNTHESIS OF THE 1*H*-PYRAZOL-3(2*H*)-ONE-1,2,3-TRIAZOLE HYBRIDS (**7a-o**)

Compd.	Substituted azides R	Yield (%)	
		Conventional	MW
7a	4-NO_2-C_6H_5	91	95
7b	4-Ac-C_6H_5	90	93
7c	4-F-C_6H_5	90	93
7d	4-Cl-C_6H_5	86	92
7e	4-Br-C_6H_5	86	92
7f	2,6-Dichloro-4-nitrophenyl	90	94
7g	4-Nitro-3-anisyl	87	92
7h	3-Nitro-2-toluenyl	87	92
7i	C_6H_5	90	94
7j	3,4-Dichlorophenyl	82	88
7k	2,3-Difluorophenyl	87	92
7l	4-Carboxyphenyl	90	94
7m	Benzyl	81	87
7n	3,4-Dichlorobenzyl	84	90
7o	2,4-Dichlorobenzyl	85	90

Biological activities: In this study, 1*H*-pyrazol-3(2*H*)-one-1,2,3-triazole hybrids **(7a-o)** were screened for *in vitro* antibacterial activity against *P. aeruginosa* and *S. aureus*, while antifungal studies with *A. niger* and *C. albicans* using microdilution method (Table-2). Among the synthesized compounds, compound **7c** was found to be a prominent MIC *in vitro* value

TABLE-2
In vitro ANTIMICROBIAL ACTIVITY OF THE 1*H*-PYRAZOL-3(2*H*)-ONE-1,2,3-TRIAZOLE HYBRIDS (**7a-o**)

Compound	Minimum inhibitory concentration (µg/mL)			
	Antibacterial		Antifungal	
	S. aureus	*P. aeruginosa*	*A. niger*	*C. albicans*
7a	48	42	53	56
7b	52	46	54	55
7c	19	16	25	26
7d	24	22	41	44
7e	64	58	68	66
7f	45	38	49	51
7g	75	73	81	86
7h	31	26	39	41
7i	34	31	38	44
7j	50	43	56	58
7k	61	53	65	68
7l	35	31	46	49
7m	46	40	48	49
7n	79	76	83	86
7o	28	23	36	39
Ciprofloxacin	15	11	–	–
Fluconazole	–	–	18	19

of 19 and 16 µg/mL against *S. aureus* and *P. aeruginosa* similarly antifungal activity with MICs of 25 and 26 µg/mL against *A. niger* and *C. albicans*, respectively compared with the standard drugs ciprofloxacin and fluconazole, respectively.

Docking studies: The docking studies of the synthesized compounds against the drug target haemoglobin receptor IsdB (3RTL) (Fig. 1) revealed that compound **7c** having greater binding affinity, which supports the *in vitro* activity results are correlated with docking studies.

Fig. 1. Compound **7c** with haemoglobin receptor (IsdB) 3RTL

Conclusion

An efficient protocol for the development of 1*H*-pyrazol-3(2*H*)-one-1,2,3-triazole hybrids **(7a-o)** with *N*-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-*N*-(prop-2-yn-1-yl)benzenesulfonamide (**5**) and substituted aromatic azides/benzyl azides (**6**) in the presence of economical viable catalytical mixture of 5 mol% of $CuSO_4$ and 10 mol% of sodium ascorbate with green solvent mixture of 1:1 H_2O-^{t}BuOH under vigorous stirring about 12-14 h at room temperature is reported. The dramatically reducing reaction time of 10-12 min under microwave conditions was achieved by eliminating toxic chlorinated solvents, using eco-friendly catalyst and greenery technique with simple workup procedure. *In vitro* activity of 1*H*-pyrazol-3(2*H*)-one-1,2,3-triazole hybrids exhibited potent antibacterial and antifungal activity, which is calculated using a docking technique applied to the drug target haemoglobin receptor IsdB (3RTL).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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