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ARTICLE

An Efficient Synthesis of Novel Triazolo-pyrimidine Derivatives using Copper Catalyzed Click Chemistry (CuAAC) Approach

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ABSTRACT

To synthesize new chemical entities, we have a focus on the aryl or heteroaryl compounds. The current work also relates to the synthesis of pharmaceutical and medicinally active compositions containing these types of compounds and their vast application of treating a wide class of diseases *i.e.* anticancer, antibacterial, antifungal, antimalarial *via* administering substituted aryl or heteroaryl compounds. In this work, an efficient synthetic route is developed to explore a wide variety of 1*H*-1,2,3-triazol-1-yl-N-(4-phenylpyrimidin-2-yl)acetamide derivatives and convergent access a diverse array of triazolo-pyrimidine analogs *via* click chemistry approach. The structures elucidation was completed by using ^{1}H & ^{13}C NMR, FT-IR, mass spectroscopy, elemental analysis. The developed morpholino-pyrimidine derivatives were further utilized of a diverse range of their chemotherapeutic value.

KEYWORDS

Heteroaryl compounds, Pyrimidine, Aminopyrimidine, 1,2,3-Triazole, Biological activity.

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INTRODUCTION

The term "click chemistry" was introduced by K. Barry Sharpless *et al.* [1], which is also called linkage chemistry and it is a versatile approach that uses only the most practical and reliable chemical transformations [2]. The click approach shows the modern development of a set of powerful, highly reliable and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through hetero-atom links [3,4].

In recent decades, click chemistry become most popular towards the assembly of new medium-sized novel molecular entities in numerous bioactive, medicinal pharmaceutical and nanoparticle areas, which shows the representative example having a promising potential [5-8]. Click chemistry includes copper-catalyzed cycloaddition, strain-promoted azide-alkyne cycloaddition and inverse-demand Diels-Alder reaction [9]. Herein, we provide an update on recent application of the click chemistry with the development of morpholino-pyrimidine derivatives and its modification with 1,2,3-triazole formation and its targeted delivery.

Currently, the Cu(I)-catalyzed "click" reaction between an azide and terminal alkyne to form a 1,2,3-triazole (CuAAC)

is a versatile and bio-orthogonal approach that is being adopted for the efficient synthesis of organic and bioorganic compounds [10,11]. Present references that outlined the special nature of triazole chemistry with an emphasis on the potential use of the reaction in biochemical studies that range from discovery and optimization to tagging of biological systems, such as proteins, nucleotides and whole organisms and literature including excellent articles are available with remarkably biological significance *i.e.* anticancer [12], HIV protease inhibitors [13], antituberculosis [14], antiviral [15], antipsychotic [16], antifungal [17], antibacterials [18], *etc*.

Presented work on a heteroaryl azoles compound incorporation with morpholino-pyrimidine motifs containing triazole was synthesized and well-characterized by various analytical techniques and undergoes lead discovery and optimization to the tag of biological activities.

EXPERIMENTAL

All the chemicals used for synthesis were purchased from Loba Chemie, Spectrochem, Merck and Sigma-Aldrich and used as it is received. Reaction monitoring was done by thin layer chromatography (TLC) on pre-coated silica gel GF_{254} plates. Melting points were determined in open capillaries and which are uncorrected. The IR spectra of compounds were recorded on Shimadzu-FTIR-8400 using KBr pellet, Mass Spectra were obtained by Shimadzu GCMS-QP-2010 using Direct Injection Probe technique and ^{1}H NMR & ^{13}C NMR spectra recorded with Bruker Avance-III 400 MHz spectrometer using TMS as an internal standard.

Synthesis of 2-chloro-N-(4-phenylpyrimidin-2-yl)-acetamide (Int-a): Round bottom flask charged substituted amine (5 mmol, 1 equiv.) using acetone as a solvent and chloroacetyl chloride (5 mmol, 1 equiv.) was added dropwise to the flask and the resulting mixture was stirred for 30-40 min at room temperature. The reaction mixture was then poured into crushed ice and the solid mass was obtained. The solid product was separated (**Int-a**), filtered and washed with water 3-4 times, dried and use in the next step without further purification.

Synthesis of 2-azido-N-(4-phenylpyrimidin-2-yl)-acetamide (Int-b): To a solution of **Int-a** (0.1 mmol, 1 equiv.) in DMF, sodium azide (NaN_3) (0.3 mmol, 3 equiv.) was added in the round bottom flask. The resulting reaction mixture was stirred at room temperature for 24 h progress of the reaction was checked by TLC and after completion of the reaction, the reaction mass was poured into crushed ice. The product (**Int-b**) was separated and isolated with washes of water and hexane.

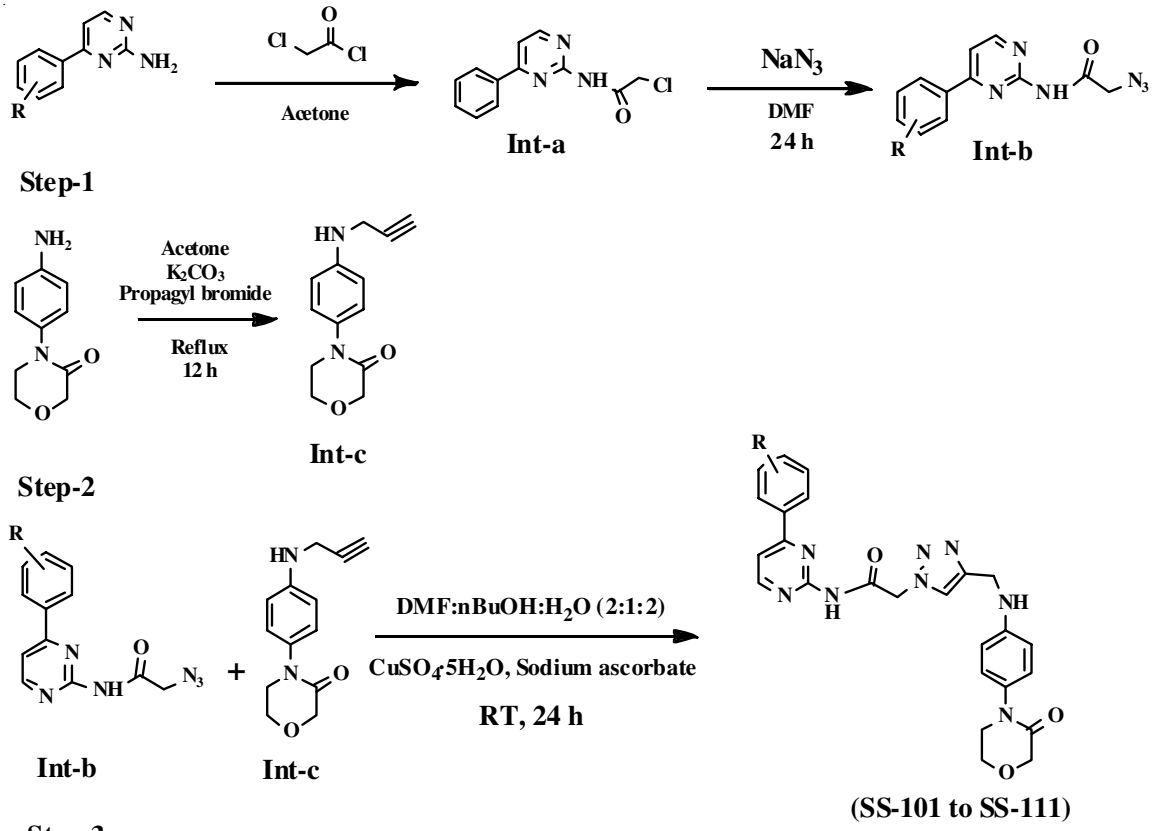
Synthesis of 4-(4-(prop-2-yn-1-ylamino)phenyl)morpholin-3-one (Int-c): In 250 mL round bottom flask, take substituted amine (**Int-a**) (50 mmol, 1equiv.) in acetone (150 mL) and added anhydrous K_2CO_3 (100 mmol, 2 equiv.) with constant stirring in cooling condition (0-5 ºC), after 5-10 min propagyl bromide (55 mmol, 1.05 equiv.) was added slowly, as the addition was completed then reflux the reaction mass for 12 h, with continuous stirring. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into the crushed ice. Filtered the separated product and washed with water to afford the final compound.

Synthesis of substituted 2-(4-(((4-(3-oxomorpholino)-phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-phenyl pyrimidin-2-yl)acetamide derivatives (SS-101 to SS-111): In a round bottom flask containing DMF:*n*-butanol:H_2O (2:1:2), **Int-c** (1 equiv.) and **Int-b** (1 equiv.) were added at room temperature and followed by the addition of the catalytic amount of sodium ascorbate and copper sulfate pentahydrate. Stirred the resulting reaction mixture at room temperature for 24 h. After the completion of reaction, the mixture was poured into the crushed ice and filtered the separated product and washed with dil. NH_3 and filtered the product again (**Scheme-I**).

2-(4-(((4-(3-Oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-phenylpyrimidin-2-yl)acetamide (SS-101): Off white solid, yield: 93%, m.p.: 186-188 ºC; *m.w.*: 484.52; R_f value: 0.22 (9:1, DCM, MeOH), , FT-IR: (KBr, ν_{max}, cm^{-1}): 3571 (-NH, *str.* amide), 3052 (-NH-, *str.*, cy amine), 1976-1840 (-N=N=N-, *str.*) 1656 (C=O), 1502 (-NH-, bend, *sec.* amine), 1383-1334 (C=C, *str.*, aromatic), 1044 (C-H, bend, aromatic), 840 (*p*-disubs. aromatic ring). MS: (*m/z*): 485(M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.13 (s, 1H, NH-amide), 8.75-8.73 (d, *J* = 8.0 Hz, 1H), 8.22-8.20 (m, 2H), 7.99 (s, 1H), 7.80-7.79 (d, *J* = 4.0 Hz, 1H), 7.56-7.54 (m, 3H), 7.04-7.02 (d, *J* = 8.0 Hz, 2H), 6.66-6.64 (d, *J* = 8.0 Hz, 2H), 6.28-6.25 (t, 1H, NH), 5.66 (s, 2H) 4.34-4.33 (d, *J* = 4 Hz, 2H), 4.12 (s, 2H), 3.92-3.90 (t, 2H), 3.60-3.58 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 164.03, 162.61, 159.60, 154.65, 138.21, 135.40, 133.30, 130.15, 128.00, 127.08, 119.91, 118.50, 117.06, 114.41, 77.60, 69.21, 58.05, 57.18. Elemental analysis of m.f. $C_{25}H_{24}N_8O_3$ calcd. (found) %: C, 61.97 (60.18); H, 4.99 (5.08); N, 23.13 (24.28).

***N*-(4-(4-Bromophenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (SS-102):** Off white solid, yield: 78%, *m.w.*: 563.42; m.p.: 182-184 ºC, R_f value 0.24 (9:1, DCM, MeOH), FT-IR: (KBr, ν_{max}, cm^{-1}): 3541 (-NH, *str.* amide), 3054 (-NH-, *str.*, cyamine), 1950-1839 (-N=N=N-, *str.*) 1662 (C=O), 1506 (-NH-, bend, *sec.* amine), 1363-1236 (C=C, *str.*, aromatic), 1006 (C-H, bend, aromatic),827 (*p*-disubs. aromatic ring), MS: (*m/z*): 565(M^{+2}), ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.19 (s, 1H, NH-amide), 8.76-8.75 (d, *J* = 4.0 Hz, 1H), 8.17-8.15 (d, *J* = 8.0 Hz, 2H), 7.99 (s, 1H), 7.83-7.81 (d, *J* = 8.0 Hz, 1H), 7.77-7.75 (d, *J* = 8.0 Hz, 2H), 7.03-7.01 (d, *J* = 8.0 Hz, 2H), 6.65-6.64 (d, *J* = 4.0 Hz, 2H), 6.30-6.27 (t, 1H, NH), 5.63 (s, 2H) 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.12 (s, 2H), 3.92-3.90 (t, 2H), 3.60-3.58 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 162.03, 159.61, 158.90, 155.95, 134.20, 133.45, 129.30, 127.20, 125.90, 125.03, 119.91, 118.10, 117.05, 114.41, 76.60, 68.21, 59.05, 57.20, 56.15, 48.10. Elemental analysis of m.f. $C_{25}H_{23}N_8O_3Br$ calcd. (found) %: C, 53.30 (52.32); H, 4.11 (4.55); Br, 14.18 (15.36); N, 19.89 (18.69).

***N*-(4-(4-Chlorophenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (SS-103):** Off white solid, yield: 69%, *m.w.*: 518.96; m.p.: 188-190 ºC, R_f value 0.25(9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3537 (-NH, *str.* amide), 3058 (-NH-, *str.*, cy amine), 1944-1842 (-N=N=N-, *str.*) 1668 (C=O), 1509 (-NH-, bend, sec. amine), 1358-1244 (C=C, *str.*, aromatic), 1027 (C-H, bend, aromatic),830 (*p*-disubs. aromatic ring), MS: (*m/z*): 520 (M^+), ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.15



where R= H, 4-F, 4-Br, 4-Cl, 4-OCH_3, 4-CH_3, 4-OH, 2-OCH_3, 3-OH, 3-Cl, 3-CH_3

Reaction condition

Step-1: Acetone, K_2CO_3, RT & DMF, NaN_3, RT, 24 h

Step-2: Acetone, K_2CO_3, Propagyl bromide Reflux, 12 h

Step-1: DMF:nBuOH: H_2O (2:1:2), $CuSO_4 \cdot 5H_2O$, Sodium ascorbate, RT, 24 h

Scheme-I

(s, 1H, NH-amide), 8.74-8.73 (d, *J* = 4.0 Hz, 1H), 8.15-8.13 (d, *J* = 8.0 Hz, 2H), 7.98 (s, 1H), 7.81-7.79 (d, *J* = 8.0 Hz, 1H), 7.76-7.74 (d, *J* = 8.0 Hz, 2H), 7.04-7.02 (d, *J* = 8.0 Hz, 2H), 6.64-6.63 (d, *J* = 4.0 Hz, 2H), 6.29-6.28 (t, 1H, NH), 5.61 (s, 2H) 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.11 (s, 2H), 3.92-3.90 (t, 2H), 3.60-3.58 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 163.03, 158.61, 156.90, 153.98, 133.20, 130.47, 128.30, 127.20, 126.90, 124.03, 120.91, 118.10, 116.05, 115.41, 77.60, 65.20, 58.09, 56.20, 55.18, 49.20. Elemental analysis of m.f.: $C_{25}H_{23}N_8O_3Cl$ calcd. (found) %: C, 57.86 (58.19); H, 4.47 (3.65); Cl, 6.83 (7.34); N, 21.59 (20.95).

***N*-(4-(4-Methoxyphenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (SS-104):** Off white solid, yield: 82%, *m.w.*: 514.55, m.p.: 186-188 ºC, R_f value 0.27(9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3534 (-NH, *str.* amide), 3048 (NH-, *str.*, cy amine), 2923-2863(CH, *str.*). 1905-1806 (-N=N=N-, *str.*) 1652 (C=O), 1524 (-NH-, bend, *sec.* amine), 1356-1248 (C=C, *str.*, aromatic), 1025 (C-H, bend, aromatic), 824 (*p*-disubs. aromatic ring), MS: (*m/z*): 514, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.17 (s, 1H, NH-amide), 8.76-8.74 (d, *J* = 4.0 Hz, 1H), 8.18-8.16 (d, *J* = 8.0 Hz, 2H), 7.96 (s, 1H), 7.80-7.78 (d, *J* = 8.0 Hz, 1H), 7.64-7.62 (d, *J* = 8.0 Hz, 2H), 7.20-7.18 (d, *J* = 8.0 Hz, 2H), 6.65-6.64 (d, *J* = 4.0 Hz, 2H), 6.30-6.29 (t, 1H, NH), 5.65 (s, 2H) 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.94-3.93 (t, 2H), 3.72 (s, 3H), 3.59-3.57 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 162.03, 158.61, 145.95, 133.21, 131.75, 128.30, 126.80, 124.90, 120.53, 119.91, 118.10, 112.41, 73.60, 67.20, 58.33, 55.20, 54.15, 45.10. Elemental analysis of m.f. $C_{26}H_{26}N_8O_4$ calcd. (found) %: C, 60.69 (61.14); H, 5.09 (4.72); N, 21.78 (20.90).

2-(4-(((4-(3-Oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-(*p*-tolyl)pyrimidin-2-yl)acetamide (SS-105): Off white solid, yield: 80%, *m.w.*: 498.55, m.p.: 190-192 ºC; R_f value 0.23 (9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3532 (-NH, *str.* amide), 3056 (NH-, *str.*, cy amine), 2927-2872(CH, *str.*). 1930-1815 (-N=N=N-, *str.*) 1682 (C=O), 1520 (-NH-, bend, *sec.* amine), 1340-1278 (C=C, *str.*, aromatic), 1021 (C-H, bend, aromatic), 820 (*p*-disubs. aromatic ring), MS: (*m/z*): 499 (M^+), ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.16 (s, 1H, NH-amide), 8.75-8.73 (d, *J* = 4.0 Hz, 1H), 8.17-8.15 (d, *J* = 8.0 Hz, 2H), 7.92 (s, 1H), 7.81-7.79 (d, *J* =

8.0 Hz, 1H), 7.66-7.64 (d, *J* = 8.0 Hz, 2H), 7.18-7.16 (d, *J* = 8.0 Hz, 2H), 6.64-6.63 (d, *J* = 4.0 Hz, 2H), 6.27-6.26 (t, 1H, NH), 5.63 (s, 2H) 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.94-3.93 (t, 2H), 3.59-3.57 (t, 2H), 2.29(s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm:163.02, 162.30, 161.00, 159.60, 144.80, 133.20, 133.10, 129.70, 127.80, 123.90, 120.50, 118.90, 112.20, 74.50, 68.10, 59.32, 57.10, 55.03, 44.00, 22.30., Elemental analysis of *m.f.* $C_{26}H_{26}N_8O_3$ calcd. (found) %: C, 62.64 (61.74); H, 5.26 (4.98); N, 22.48 (23.90).

***N*-(4-(4-Hydroxyphenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (SS-106):** Off white solid, yield: 78%, *m.w.*: 500.52, m.p.: 184-186 ºC, R_f value 0.25 (9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3522 (-NH, *str.* amide), 3358 (OH, *str.*), 3065 (NH-, *str.*, cy amine), 2932-2884(CH, *str.*). 1940-1827 (-N=N=N-, *str.*) 1657 (C=O), 1524 (-NH-, bend, *sec*. amine), 1323-1284 (C=C, *str.*, aromatic), 1031 (C-H, bend, aromatic), 829 (*p*-disubs. aromatic ring), MS: (*m/z*): 501(M). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.01(s, 1H, OH), 11.06 (s, 1H, NH-amide), 8.74-8.73 (d, *J* = 4.0 Hz, 1H), 8.23-8.21 (d, *J* = 8.0 Hz, 2H), 7.91 (s, 1H), 7.83-7.82 (d, *J* = 8.0 Hz, 1H), 7.65-7.63 (d, *J* = 8.0 Hz, 2H), 7.20-7.18 (d, *J* = 8.0 Hz, 2H), 6.64-6.63 (d, *J* = 4.0 Hz, 2H), 6.27-6.26 (t, 1H, NH), 5.63 (s, 2H) 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.94-3.93 (t, 2H), 3.59-3.57 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 164.20, 158.23, 144.95, 134.21, 132.73, 129.32, 127.10, 123.90, 121.45, 119.92, 118.00, 113.42, 73.42, 68.21, 59.30, 56.21, 55.12, 46.13, Elemental analysis of m.f. $C_{25}H_{24}N_8O_4$ calcd. (found) %: C, 59.99 (58.81); H, 4.83 (5.35); N, 22.39 (22.89).

***N*-(4-(4-Fluorophenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (SS-107):** Off white solid, yield: 68%, *m.w.* 502.51, m.p.: 192-194 ºC, R_f value 0.27(9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3520 (-NH, *str.* amide), 3044 (-NH-, *str.*, cy amine), 1938-1813 (-N=N=N-, *str.*) 1652 (C=O), 1501 (-NH-, bend, *sec*. amine), 1357-1226 (C=C, *str.*, aromatic), 1009 (C-H, bend, aromatic), 832 (*p*-disubs. aromatic ring), MS: (*m/z*): 505(M^{+2}). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.20 (s, 1H, NH-amide), 8.74-8.73 (d, *J* = 4.0 Hz, 1H), 8.14-8.12 (d, *J* = 8.0 Hz, 2H), 7.97 (s, 1H), 7.81-7.79 (d, *J* = 8.0 Hz, 1H), 7.75-7.73 (d, *J* = 8.0 Hz, 2H), 7.05-7.03 (d, *J* = 8.0 Hz, 2H), 6.63-6.62 (d, *J* = 4.0 Hz, 2H), 6.29-6.28 (t, 1H, NH), 5.61 (s, 2H) 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.12 (s, 2H), 3.92-3.90 (t, 2H), 3.60-3.58 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 164.30, 163.03, 160.61, 158.01, 155.50, 148.95, 144.30, 134.28, 132.75, 130.30, 128.80, 127.10, 120.08, 117.10, 114.43, 73.65, 66.20, 57.33, 55.20, 54.25, 44.90. Elemental analysis of m.f. $C_{25}H_{23}N_8O_3F$ calcd. (found) %: C, 59.75 (59.99); H, 4.61 (3.94); F, 3.78 (3.05); N, 22.30 (22.78).

***N*-(4-(2-Methoxyphenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (SS-108):** Off white solid, yield: 69%, *m.w.* 514.55, m.p.: 190-192 ºC, R_f value 0.29 (9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3521 (-NH, *str.* amide), 3045 (NH-, *str.*, cy amine), 2920-2854 (CH, *str.*). 1923-1827 (-N=N=N-, *str.*) 1672 (C=O), 1522 (-NH-, bend, *sec*. amine), 1336-1284 (C=C, *str.*, aromatic), 1015 (C-H, bend, aromatic), 823-752 (*p*, *o*, aromatic ring), MS: (*m/z*): 514 (M). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.21 (s, 1H, NH-amide), 8.52 (d, *J* = 4.8 Hz, 1H,), 7.84 (s, 1H,), 7.79 (dd, *J* = 8.6, 1.2 Hz, 1H,), 7.45 (d, *J* = 4.8 Hz, 1H), 7.38 (m, 1H), 7.19-7.09 (m, 3H), 6.90 (m, 1H), 6.65-6.64 (d, *J* = 4.0 Hz, 2H), 6.30-6.29 (t, 1H, NH), 5.65 (s, 2H), 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.94-3.93 (t, 2H), 3.79(s, 3H), 3.59-3.57 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 161.00, 156.60, 144.90, 132.20, 130.70, 129.70, 128.50, 127.80, 122.90, 121.50, 118.90, 117.90, 111.40, 73.50, 66.10, 59.30, 56.10, 55.00, 43.00. Elemental analysis of m.f.: $C_{26}H_{26}N_8O_4$ calcd. (found) %: C, 60.69 (59.99); H, 5.09 (3.94); N, 21.78 (22.38).

***N*-(4-(3-Hydroxyphenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (SS-109):** Creamish white solid, yield: 81%, *m.w.*: 500.52, m.p.: 192-194 ºC, R_f value 0.29 (9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3496 (-NH, *str.* amide), 3301 (OH, *str.*), 3025 (NH-, *str.*, cy amine), 2915-2896 (CH, *str.*). 1910-1827 (-N=N=N-, *str.*), 1668 (C=O), 1564 (-NH-, bend, sec. amine), 1319-1206 (C=C, *str.*, aromatic), 1039 (C-H, bend, aromatic), 810-751 (*p*, *m*-disubs. aromatic ring), MS: (*m/z*): 501(M$^+$), ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.01(s, 1H, OH), 11.18 (s, 1H, NH-amide), 8.44 (d, *J* = 4.8 Hz, 1H,), 7.84 (s, 1H,), 7.60 - 7.48 (m, 2H,), 7.38 (t, 1H, 2), 7.28 (t, 1H), 7.19 -7.10 (m, 2H,), 6.82 (m, 1H), 6.69-6.60 (m, 2H,), 6.06 (t, 1H), 5.24 (s, 2H,), 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.94-3.93 (t, 2H), 3.59-3.57 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.20, 159.23, 143.95, 139.21, 134.72, 139.31, 127.12, 123.97, 121.05, 119.52, 117.90, 114.32, 74.40, 68.25, 58.35, 56.21, 55.13, 46.12, Elemental analysis of m.f. $C_{25}H_{24}N_8O_4$ calcd. (found) %: C, 59.99 (58.11); H, 4.83 (3.91); N, 22.39 (21.05).

***N*-(4-(3-Chlorophenyl)pyrimidin-2-yl)-2-(4-(((4-(3-oxomorpholino)phenyl)amino) methyl)-1*H*-1,2,3-triazol-1-yl)acetamide(SS-110):** Creamish white solid, yield: 70%, m.p.: 188-190 ºC, R_f value 0.29 (9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3550 (-NH, *str.* amide), 3072 (NH-, *str.*, cy amine), 1950-1849 (-N=N=N-, *str.*) 1676 (C=O), 1589 (-NH, bend, *sec*. amine), 1328-1232 (C=C, *str.*, aromatic), 1032 (C-H, bend, aromatic), 817-720 (*p, m*-disubs. aromatic ring), MS: (*m/z*): 521(M^{+2}), ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.12 (s, 1H, NH-amide), 8.42 (d, *J* = 4.8 Hz, 1H,), 7.85 (s, 1H,), 7.58-7.50 (m, 2H,), 7.34 (t, 1H,), 7.26 (t, 1H), 7.17 -7.09 (m, 2H,), 6.58 (m, 1H), 6.67-6.57 (m, 2H,), 6.04 (t, 1H), 5.22 (s, 2H,), 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.94-3.93 (t, 2H), 3.59-3.57 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.28, 164.20, 159.61, 158.28, 155.96, 138.08, 133.47, 130.33, 129.30, 128.20, 125.04, 124.20, 117.10, 112.01, 74.04, 58.09, 43.20. Elemental analysis of m.f. $C_{25}H_{23}N_8O_3Cl$ calcd. (found) %: C, 57.86 (56.99); H, 4.47 (3.05); Cl, 6.83 (6.79); N, 21.59 (20.78).

2-(4-(((4-(3-Oxomorpholino)phenyl)amino)methyl)-1*H*-1,2,3-triazol-1-yl)-N-(4-(*m*-tolyl)pyrimidin-2-yl)acetamide (SS-111): Off white solid, yield: 88%, *m.w.* 498.55, m.p.: 186-188 ºC, R_f value 0.25 (9:1, DCM, MeOH). FT-IR: (KBr, ν_{max}, cm^{-1}): 3548 (-NH, *str.* amide), 3072 (NH-, *str.*, cy amine), 2910-2862 (CH, *str.*). 1925-1827 (-N=N=N-, *str.*) 1673 (C=O), 1501 (-NH-, bend, *sec*. amine), 1319-1289 (C=C, *str.*, aromatic), 1017 (C-H, bend, aromatic), 833-703 (*p*, *m*, -disubs. aromatic ring), MS: (*m/z*): 499, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm:

11.14 (s, 1H, NH-amide), 8.39 (d, *J* = 4.8 Hz, 1H,), 7.82 (s, 1H,), 7.56-7.51 (m, 2H,), 7.37 (t, 1H,), 7.28 (t, 1H), 7.15-7.07 (m, 2H), 6.57 (m, 1H), 6.66-6.57 (m, 2H,), 6.08 (t, 1H), 5.27 (s, 2H), 4.34-4.32 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 3.94-3.93 (t, 2H), 3.59-3.57 (t, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 164.02, 164.30, 162.00, 158.60, 148.80, 132.20, 131.10, 129.70, 128.80, 126.80, 122.40, 117.60, 111.40, 75.50, 69.10, 57.32, 56.03, 42.10, 21.06. Elemental analysis of m.f. $C_{26}H_{26}N_8O_3$ calcd. (found) %: C, 62.64 (61.99); H, 5.26 (4.05); N, 22.48 (21.03).

Antimicrobial activity: All of the synthesized compounds (**SS-101** to **SS-111**) were assessed *in vitro* for antibacterial and antifungal activity (MIC) with two Gram-positive bacteria using the broth dilution method [19,20]. *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 442, *Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 424 and three fungal species. Ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin have been used as standard drugs *versus Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323. The standard strains were acquired from the Institute of Microbial Technology's Microbial Type Culture Collection (MTCC) and Gene Bank in Chandigarh, India.

The MIC values for all the newly synthesized compounds were determined using the microdilution broth method according to NCCLS standards [21], which would be defined as the lowest concentration of the component that prevents observable growth. In Mueller-Hinton agar, serial dilutions of the test compounds and reference drugs were established. DMSO was used to dissolve the drugs (10 mg) (1 mL).

To acquire the needed concentrations, further progressive dilutions with melting Mueller-Hinton agar were performed. All the synthesized compounds were evaluated at the concentrations of 1000, 500 and 250 μg mL^{-1} in primary screening. The active synthesized drugs revealed in the primary screening were tested against all microorganisms in the second set of dilutions at 125, 100, 62.5, 50, 25, 12.5 and 6.25 μg mL^{-1} concentrations. The tubes were implanted with 10^8 cfu mL^{-1} and cultured for 24 h at 37 ºC.

RESULTS AND DISCUSSION

A simple and economical route is described for the synthesis of triazole derivatives in excellent yield. In an round bottom flask containing DMF:*n*-butanol:H_2O (2:1:2), **Int-c** and **Int-b** were added at room temperature. Then the addition of a catalytic amount of sodium ascorbate and copper sulfate pentahydrate. Then starring the resulting solution for room temperature for 24 h. After the completion of reaction, the reaction mass was poured into the crushed ice. Then filtered the separated product and diluted with ammonia and again filtered the product. The reaction optimization study was carried out using $CuSO_4$ along with sodium ascorbate. Sodium ascorbate plays a dual role, it acts as a ligand and reducing agent. It was observed that without the use of a reducing agent reaction was not progressed (Table-1, entry 1). The reaction optimization studies also describe the solvent ratio of DMF: *n*-BuOH:H_2O with (2:1:2) ratio gets the highest yield (Table-1, entry 2). All the compounds were synthesized in good to high yield. The structure of the synthesized compounds was confirmated based on the spectroscopic techniques.

All synthesized homologous undergo their biological evaluation with Gram-positive and Gram-negative bacterial satins as well as a fungal species stain with their activities (Table-2).

Conclusion

In summary, the advantages of this currently developed method over other prevailing methods are reduced milder conditions, higher yields, low costs, fewer hazards and environmental safety. A series of substituted 1*H*-1,2,3-triazol-1-yl)-*N*-(4-phenylpyrimidin-2-yl)acetamide have been designed and synthesized in good to an excellent yield. Suitable reaction condition for the synthesis of targeted triazole motifs by using copper(I) catalyzed azide-alkyne cycloaddition (CuAAC) click chemistry approach to synthesize various analogous of morpholino-pyrimidine clubbed 1,2,3-triazole containing core skeletons (**SS-101 to 111**). All the compounds were well characterized by the various methods of analysis techniques and evaluated their potency against various microbial strains. The significant results would be useful to develop a new strategy for the next target with better quality effectiveness and influence of molecules for an additional therapeutic position.

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TABLE-1
REACTION OPTIMIZATION OF COPPER-CATALYZED CLICK CHEMISTRY

Entry	Solvent	Catalyst	Reducing agent	Yield (%)
1	DMF:*n*-BuOH:Water (2:1:2)	$CuSO_4·5H_2O$	–	Traces
2	DMF:*n*-BuOH:Water (2:1:2)	$CuSO_4·5H_2O$	Sodium ascorbate	93
3	DMF:*n*-BuOH:Water (2:1:2)	CuI-DIPEA	–	87
4	DMF:*n*-BuOH:Water (2:1:2)	CuBr-DIPEA	–	85
5	DMF:*n*-BuOH:Water (2:1:2)	$Cu(OAc)_2$	Sodium ascorbate	86
6	DMF:*n*-BuOH:Water (2:1:2)	$Cu(OAc)_2$	–	Traces
7	DMF:*n*-BuOH:Water (1:1:1)	$CuSO_4·5H_2O$	Sodium ascorbate	82
8	*n*-BuOH	$CuSO_4·5H_2O$	Sodium ascorbate	42
9	MeOH	$CuSO_4·5H_2O$	Sodium ascorbate	83
10	THF	$CuSO_4·5H_2O$	Sodium ascorbate	52

Reaction condition: Starting materials, 2-azido-*N*-(4-phenylpyrimidin-2-yl)acetamide (**Int-b**) (1 mmol), 4-(4-(prop-2-yn-1-ylamino)phenyl)-morpholin-3-one (**Int-c**) (1 mmol), 0.2 equiv. of Cu-sources, reducing agent and solvent.

TABLE-2
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF THE SYNTHESIZED COMPOUND

Compounds	Minimum inhibition concentration (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	Staphylococcus aureus	*Streptococcus pyogenes*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*	*Aspergillus niger*	*Aspergillus clavatus*
SS-101	100	100	250	250	100	100	250
SS-102	62.5	100	62.5	62.5	100	100	100
SS-103	100	100	62.5	62.5	100	100	100
SS-104	100	100	250	250	125	125	100
SS-105	100	100	250	250	100	100	250
SS-106	62.5	62.5	100	100	100	125	125
SS-107	62.5	100	100	62.5	100	100	125
SS-108	250	250	125	125	250	250	125
SS-109	62.5	100	100	100	100	100	100
SS-110	62.5	62.5	100	100	125	100	100
SS-111	250	250	125	125	125	125	100
Ampicillin	250	100	100	100	–	–	–
Chloramphenicol	50	50	50	50	–	–	–
Ciprofloxacin	50	50	25	25	–	–	–
Norfloxacin	10	10	10	10	–	–	–
Nystatin	–	–	–	–	100	100	100
Griseofulvin	–	–	–	–	500	100	100

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