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Synthesis of Novel Series of 1,2,3-Triazoles Tethered to Pyrazolo[3,4-*d*]pyrimidine Scaffold with Methoxyphenoxy Linker

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A novel series of hybrid heterocycles having pyrazolopyrimidine based 1,2,3-triazole scaffold with two ether linkages were synthesized by 1,3-dipolar cycloaddition reaction of pyrazolopyrimidines tethered to phenoxy alkynes and differently substituted aromatic azides using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate mixture as catalyst in DMSO-H_2O solvent mixture. The synthesized triazole hybrids were characterized by using various spectroscopic techniques.

Keywords: Pyrazolopyrimidines tethered to phenoxy alkynes, Hybrid triazoles, Click reaction, Dihydroxy acetophenone.

INTRODUCTION

Pyrazolopyrimidine is a prominent bioheterocycle, structurally analogous to the biogenic purine base, synthesized through the heterocyclic fusion of the pyrimidine and pyrazole rings. As a result, they are extremely adaptable drug-like templates that have been extensively exploited in the development of many biologically active medications [1]. Several publications and reviews have been published on discussing the chemistry and its pharmacological activities of this class of molecules [2-5]. Compounds containing this scaffold have been shown to have diverse pharmacological effects, including analgesic [6], antihypertensive [7], antitubercular [8,9], osteoporosis therapy [10] and anti-obesity medicines [11]. They have been important in the evaluation of a disease and final clinical diagnosis through tumour imaging [12].

1,2,3-Triazoles are the significant five-membered heterocyclic compounds with molecular formula $C_2H_3N_3$, due to their widespread applications in the synthetic organic chemistry and pharmacological fields and also act as key intermediates in many industrial applications. The diverse applications of triazoles include antibacterial [13,14], anti-tubercular [15], fungicidal [16], insecticidal [17], antiviral [18], anti-HIV [19,20], anti-proliferative [21], anticancer [22,23], antimicrobial [24-27], antiepileptic [28] and anti-HSV activities [29].

Few reports are available on the hybrid heterocycles having pyrazolo[3,4-*d*]pyrimidin-4-one based triazole skeleton and their cytotoxic activity [1,30]. However to our best of the knowledge, only one report is available on pyrazolo[3,4-*d*]-pyrimidine based triazole hybrids [31]. In view of these observations, we were inspired to explore a new series of hybrids having pyrazolopyrimidine as well as triazole scaffolds with linker to increase their potentiality as drug leads or drug intermediates in the pharmaceutical industry. Herein, a novel series of pyrazolopyrimidine based triazoles with methoxy phenoxy linker using click chemistry from pyrazolopyrimidine based alkyne as a suitable precursor has been reported.

EXPERIMENTAL

All the reagents and solvents purchased from Sigma-Aldrich, USA of laboratory grade were used directly without further purification. Melting points (ºC) were recorded by Labtronics digital melting point apparatus (Panchkula, India). IR spectra were recorded on Bruker-27 in ATR method. The ^{1}H NMR & ^{13}C NMR spectra of the synthesized compounds using TMS

as an internal reference in $CDCl_3$ solvent were captured on JEOL JNM-ECZ500R/S1 instrument at 500 MHz and 100 MHz, respectively. Mass spectrometry analyses were carried out on a Jeol SX-102 spectrometer (Tokyo, Japan). TLC plates, aluminium sheets pre-coated with silica gel G (Merck) were used to predict the progress of the reaction.

Synthesis of 1-(2-hydroxy-5-((1-phenyl-1*H*-pyrazolo-[3,4-*d*]pyrimidin-4-yl)oxy)phenyl)ethan-1-ones (3a,b): Dehydrochlorination reaction of 1-(2,4-dihydroxyphenyl)-ethan-1-one (**2**) (3 mmol) was carried out independently with 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1a**) (3 mmol) and 4-chloro-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**1b**) (3 mmol) in presence of K_2CO_3 (2 mmol) in 6 mL DMF solvent at room temperature for 2.5 h. After completion of the reaction, the mixture was poured into the crushed ice and the obtained solid was filtered. Using petroleum ether-ethyl acetate as eluent, column chromatography was used to purify the crude product and produce the corresponding pure products **3a** and **3b**. Compounds **3a** and **3b** are new compounds and their structural elucidation were determined based on their spectral data.

Synthesis of pyrazolopyrimidine tethered to phenoxy based alkynes (5a,b): The reaction of compounds **3a** and **3b** (2 mmol) was carried out independently with propargyl bromide (**4**) (2 mmol) in presence of K_2CO_3 (1 mmol) in 4 mL of DMF solvent at room temperature for 3 h. The progress of reaction was monitored using TLC. After complete formation of products, the mixture was poured into ice-chilled water and the resulting solid was filtered. The column chromatography was used to purify the crude product and produce the respective pure products **5a** and **5b**. Ethyl acetate-petroleum ether solvent mixture was used as the eluent. The structures of novel compounds of **5a** and **5b** were established based on their spectral data.

General procedure for the synthesis of pyrazolopyrimidine based triazoles with methoxyphenoxy linker (7a-j): To a stirred solution of terminal alkyne compound **5a,b** (2 mmol) in 5 mL of DMSO:H_2O (4:1), sodium ascorbate solution (10 mol%), aqueous cupric sulphate solution (15 mol%) and appropriate phenyl azide (**6a-e**, 2 mmol) were added successively. The resulting reaction mixture was stirred at room temperature for 4 h. The reaction progress was observed using TLC. Upon completion of the reaction, crushed ice (10 g) was added to the reaction mixture, the obtained solid product was filtered off and which was purified by silica gel chromatography eluting with petroleum ether, ethyl acetate (8:2) to obtain the corresponding pure products **7a-j**.

1-(2-Hydroxy-4-((1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)phenyl)ethan-1-one (3a): Yield: 90%; m.p.: 142-143 ºC. IR (ATR, ν_{max}, cm^{-1}): 1739, 3601; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.54 (s, 1H), 8.66 (s, 1H), 8.29 (s, 1H), 8.24-8.18 (m,2H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.59-7.52 (m, 2H), 7.42-7.36 (m, 1H), 6.94 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.3 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.56, 164.25, 162.67, 157.90, 155.62, 155.14, 138.58, 132.52, 132.35, 129.32, 127.17, 121.60, 118.02, 112.93, 111.34, 104.29, 26.79; mass analysis of $C_{19}H_{14}N_4O_3$: *m/z* 347.2 $[M+H]^+$.

1-(2-Hydroxy-4-((6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-yl)oxy)phenyl)ethan-1-one (3b): Yield: 90%; m.p.: 143-144 ºC. IR (ATR, ν_{max}, cm^{-1}): 1749, 3603; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.54 (s, 1H), 8.23 (dd, *J* = 8.6, 3.2 Hz, 2H), 8.07 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.33 (t, *J* =7.4 Hz, 1H), 6.94 (d, *J* = 3.3 Hz, 1H), 6.84 (dd, *J* = 8.7, 3.4 Hz, 1H), 2.66 (d, *J* = 10.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.52, 166.45, 164.20, 161.94, 158.31, 156.21, 138.85,132.39, 132.18, 129.21, 126.80, 121.43, 117.72, 112.84, 111.05, 102.21, 26.75, 26.28; mass analysis of $C_{19}H_{14}N_4O_3$: *m/z* 361.15 $[M+H]^+$.

1-(4-((1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-oxy)-2-(prop-2-yn-1-yloxy)- phenyl)ethan-1-one (5a): Yield: 86%; m.p.: 167-168 ºC. IR (ATR, ν_{max}, cm^{-1}): 1737, 2126; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (s, 1H), 8.26 (s, 1H), 8.22-8.19 (m, 2H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.58-7.54 (m, 2H), 7.41-7.37 (m, 1H), 7.04 (d, *J* = 3.1 Hz, 1H), 7.00 (dd, *J* = 8.5, 3.2 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 2H), 2.68 (s, 3H), 2.57 (t, *J* = 3.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.01, 162.93, 158.09, 155.91, 155.66, 155.14, 138.57, 132.57, 132.31, 129.34, 127.21, 126.64, 121.62, 114.93, 107.06, 104.23, 80.47, 78.16, 56.55, 32.03; mass analysis of $C_{22}H_{16}N_4O_3$: *m/z* 385.20 $[M+H]^+$.

1-(4-((6-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)-2-(prop-2-yn-1-yloxy)phenyl)ethan-1-one (5b): Yield: 85%; m.p.: 166-167 ºC. IR (ATR, ν_{max}, cm^{-1}): 1736, 2115; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.23 (dd, *J* = 8.7, 1.1 Hz, 2H), 8.02 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.56-7.52 (m, 2H), 7.38-7.34 (m, 1H), 7.07 (d, *J* =2.1 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.1 Hz, 1H), 4.82 (d, *J* = 2.4 Hz, 2H), 2.69 (s, 6H), 2.56 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.11, 166.46, 162.24, 158.02, 156.32, 156.23, 138.83, 132.45, 132.10, 129.22, 126.83, 126.36, 121.46, 114.85, 106.97, 102.08, 80.38, 78.14, 56.53, 32.03, 26.30; mass analysis of $C_{23}H_{18}N_4O_3$: *m/z* 399.4 $[M+H]^+$.

1-(2-((1-Phenyl-1*H*-1,2,3-triazol-4-yl)methoxy)-4-((1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)phenyl)-ethan-1-one (7a): Yield: 80%; m.p.: 195-196 ºC. IR (ATR, ν_{max}, cm^{-1}): 1686, 1736; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.27 (s, 1H), 8.20 (dd, *J* = 8.6, 3.1 Hz, 2H), 8.12 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.76-7.73 (m, 2H), 7.58-7.52 (m, 4H), 7.49-7.44 (m, 1H), 7.41-7.36 (m, 1H), 7.18 (d, *J* = 3.2 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.42 (s, 2H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.13, 163.33, 162.91, 161.91, 158.58, 156.03, 155.61,155.11, 143.74, 138.54, 133.08, 132.56, 132.30, 129.34, 127.22, 126.53, 122.69, 121.65, 116.96, 114.70, 107.13, 104.25, 62.63, 31.93; mass analysis of $C_{28}H_{21}N_7O_3$: *m/z* 504.10 $[M+H]^+$.

1-(2-((1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-4-((1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-oxy)phenyl)ethan-1-one (7b): Yield: 81%; m.p.: 196-197 ºC. IR (ATR, ν_{max}, cm^{-1}): 1685, 1737; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.26 (s, 1H), 8.20 (dd, *J* = 8.6, 1.0 Hz, 2H), 8.08 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.74-7.71 (m, 2H), 7.58-7.54 (m, 2H), 7.41-7.37 (m, 1H), 7.26-7.22 (m, 2H), 7.17 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.42 (s, 2H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.05, 162.91, 158.52, 156.02, 155.59, 155.14, 143.91, 138.56, 135.76, 133.05, 132.53, 132.31, 129.33, 127.21, 126.58, 122.85, 122.01, 121.65, 121.02, 114.72, 107.13,104.25, 62.63, 31.90; mass analysis of $C_{28}H_{20}N_7O_3F$: *m/z* 522.50 $[M+H]^+$.

1-(2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-4-((1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-oxy)phenyl)ethan-1-one (7c): Yield: 79%; m.p. 193-194 ºC. IR (ATR, ν_{max}, cm^{-1}): 1689,1739; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.26 (s, 1H), 8.22-8.19 (m, 2H), 8.10 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.72-7.68 (m, 2H), 7.58-7.54 (m, 2H), 7.54-7.50 (m, 2H), 7.42-7.37 (m, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.42 (s, 2H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.04, 162.89, 158.52, 156.00, 155.58, 155.12, 143.86,138.54, 135.26, 134.96, 132.53, 132.30, 130.07, 129.32, 127.20, 126.55, 121.78, 121.63, 121.06, 114.71, 107.10,104.24, 62.61, 31.90; mass analysis of $C_{28}H_{20}N_7O_3Cl$: *m/z* 538.40 $[M+H]^+$.

1-(2-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)-methoxy)-4-((1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-oxy)phenyl)ethan-1-one (7d): Yield: 82%; m.p.: 196-197 ºC. IR (ATR, ν_{max}, cm^{-1}): 1690, 1738; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.26 (s, 1H), 8.22-8.18 (m, 2H), 8.10 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.69-7.62 (m, 4H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.5, 3.0 Hz, 1H), 5.41 (s, 2H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.05, 162.91, 158.52, 156.02, 155.59, 155.14, 143.91, 138.56, 135.76, 133.05, 132.53, 132.31, 129.33, 127.21, 126.58, 122.85, 122.01, 121.65, 121.02, 114.72, 107.13, 104.25, 62.63, 31.90; mass analysis of $C_{28}H_{20}N_7O_3Br$: *m/z* 582.40 $[M+H]^+$.

1-(4-((1-Phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)-2-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)-ethan-1-one (7e): Yield: 81%; m.p.: 192-193 ºC. IR (ATR, ν_{max}, cm^{-1}): 1699, 1734; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.63 (s, 1H), 8.27 (s, 1H), 8.20 (dd, *J* = 8.6, 1.0 Hz, 2H), 8.07 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.59-7.54 (m, 2H), 7.39 (dd, *J* = 14.0, 0.9 Hz, 1H), 7.33 (d, *J* = 8.2Hz,2H), 7.17 (d, *J* = 2.1 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.1 Hz,1H), 5.41 (s, 2H), 2.64 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.10, 162.92, 158.68, 156.03, 155.62, 155.14, 143.41, 139.32, 138.59, 134.53, 132.56, 132.28, 130.37, 129.32, 127.18, 126.55, 121.66, 121.18, 120.55, 114.63, 107.13, 104.26, 62.73, 31.98, 21.16; mass analysis of $C_{29}H_{23}N_7O_3$: *m/z* 518.40 $[M+H]^+$.

1-(4-((6-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)-2-((1-phenyl-1*H*-1,2,3-triazol-4-yl)-methoxy)-phenyl)ethan-1-one (7f): Yield: 80%; m.p.: 191-192 ºC. IR (ATR, ν_{max}, cm^{-1}): 1695, 1736; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 7.8 Hz, 2H), 8.10 (s, 1H), 8.03 (s, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.8 Hz, 4H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.9 Hz, 1H), 5.41 (s, 2H), 2.66 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.19, 166.45, 162.24, 158.65, 156.45, 156.20, 143.66, 138.84, 136.82, 132.40, 132.10, 129.88, 129.21, 129.13, 126.81, 126.20, 121.47, 121.14, 120.65, 114.65, 106.95, 102.10, 62.73, 31.99, 26.29; mass analysis of $C_{29}H_{23}N_7O_3$: *m/z* 518.50 $[M+H]^+$.

1-(2-((1-(4-Fluorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4-((6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)phenyl)ethan-1-one (7g): Yield: 80%; m.p.: 195-196 ºC. IR (ATR, ν_{max}, cm^{-1}): 1695, 1736; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23-8.21 (m, 2H), 8.06 (s, 1H), 8.00 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.73-7.70 (m, 2H), 7.56-7.52 (m, 2H), 7.38-7.34 (m, 1H), 7.25-7.21 (m, 2H), 7.17 (d, *J* = 2.1 Hz, 1H), 7.01 (dd, *J* = 8.5, 3.1 Hz, 1H), 5.40 (s, 2H), 2.67 (s, 3H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.16, 166.43, 163.85, 162.23, 161.37, 158.57, 156.45, 156.19, 143.81, 138.82, 133.07, 132.37, 132.10, 129.21, 126.82, 126.22, 121.45, 116.98, 116.75, 114.68, 106.97, 102.08, 62.68, 31.94, 26.29; mass analysis of $C_{29}H_{22}N_7O_3F$: *m/z* 536.20 $[M+H]^+$.

1-(2-((1-(4-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4-((6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)phenyl)ethan-1-one (7h): Yield: 79%; m.p.: 193-194 ºC. IR (ATR, ν_{max}, cm^{-1}): 1694, 1734; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 7.7 Hz, 2H), 8.09 (s, 1H), 7.99 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.56-7.49 (m, 4H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 1.9 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.0 Hz, 1H), 5.40 (s, 2H), 2.66 (s, 3H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.16, 166.43, 162.23, 158.54, 156.45, 156.19, 143.77, 138.81, 135.27, 134.94, 132.36, 132.11, 130.05, 129.21, 126.82, 126.22, 121.78, 121.45, 121.04, 114.69, 106.97, 102.07, 62.66, 31.93, 26.29; mass analysis of $C_{29}H_{22}N_7O_3Cl$: *m/z* 552.20 $[M+H]^+$.

1-(2-((1-(4-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-4-((6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)phenyl)ethan-1-one (7i): Yield: 80%; m.p.: 193-194 °C. IR (ATR, ν_{max}, cm^{-1}): 1694, 1732; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (dd, *J* = 8.6, 2.1 Hz, 2H), 8.09 (s, 1H), 7.99 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.67-7.61 (m, 4H), 7.56-7.52 (m, 2H), 7.39-7.33 (m, 1H), 7.16 (d, *J* = 3.1 Hz, 1H), 7.01 (dd, *J* = 8.5, 3.2 Hz, 1H), 5.40 (s, 2H), 2.66 (s, 3H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.16, 166.44, 162.24, 158.53, 156.45, 156.20, 143.96,138.82, 135.75, 133.03, 132.36, 132.12, 129.21, 126.83, 126.23, 122.82, 122.00, 121.46, 120.95, 114.70, 106.97, 102.07, 62.65, 31.93, 26.29; mass analysis of $C_{29}H_{22}N_7O_3Br$: *m/z* 596.60 $[M+H]^+$.

1-(4-((6-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)oxy)-2-((1-(*p*-tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy)-phenyl)ethan-1-one (7j): Yield: 78%; m.p.: 198-199 ºC. IR (ATR, ν_{max}, cm^{-1}): 1692, 1739; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (dd, *J* = 8.6, 1.0 Hz, 2H), 8.06 (s, 1H), 8.01 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.56-7.51 (m, 2H), 7.37-7.30 (m, 3H), 7.17 (d, *J* = 2.0 Hz, 1H), 7.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 5.40 (s, 2H), 2.66 (s, 3H), 2.65 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.20, 166.45, 162.24, 158.68, 156.45, 156.20, 143.47, 139.29, 138.84, 134.53, 132.39, 132.08, 130.35, 129.20, 126.79, 126.19, 121.46, 121.12, 120.54, 114.61, 106.95,102.09, 62.75, 32.01, 26.29, 21.15; mass analysis of $C_{30}H_{25}N_7O_3$: *m/z* 532.60 $[M+H]^+$.

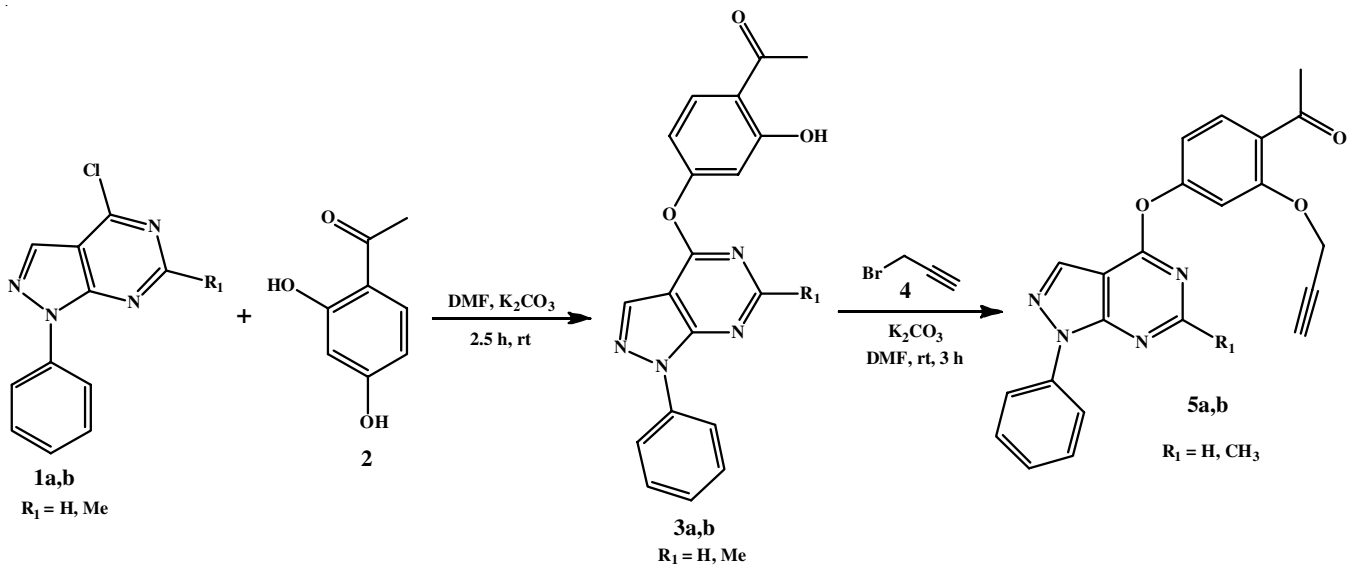
RESULTS AND DISCUSSION

4-Chloropyrazolo[3,4-*d*]pyrimidine **1a** and its methyl analogue **1b** were chosen as suitable starting precursors for the synthesis of target hybrid heterocycles and were prepared using literature procedure [32]. Dehydrochlorination reaction of 4-chloro1-pyrazolo[3,4-*d*]pyrimidines (**1a,b**) was independently carried out with (2,4-dihydroxyphenyl)ethan-1-one (**2**) utilizing K_2CO_3 base in DMF at room temperature for 2.5 h.

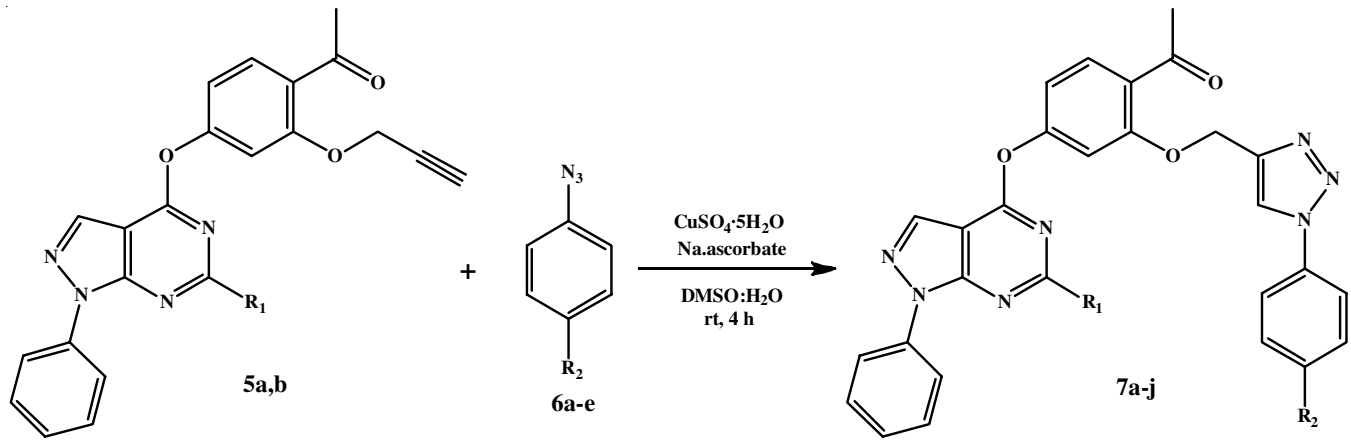
The corresponding new pyrazolopyrimidine based aryl ethers **3a,b** were isolated in 80% yield (**Scheme-I**) and are confirmed based on their spectral analysis. The hydroxy and methyl keto groups in the product **3a** are confirmed by showing the peaks at 3600 cm^{-1} (broad) and 1739 cm^{-1} respectively in IR spectrum, singlet peaks at δ 12.54 and 2.67 ppm ^{1}H NMR spectrum. Further, its ^{13}C NMR spectrum showed prominent peaks at δ 203.56 and 26.79 ppm for keto carbonyl and methyl carbons.

The pyrazolopyrimidine based terminal alkyne having two ether linkages **5a,b** was prepared from the base catalyzed substitution reaction of **3a/3b** with propargyl bromide. These alkynes **5a,b** are confirmed from their analytical data. The presence of propargyl group in product **5a** is evidenced from IR, ^{1}H NMR, ^{13}C NMR spectra by showing the prominent peaks at 2133 cm^{-1} (C≡C); a doublet peak at δ 4.83 ppm due to O-C<u>H</u>$_2$ and a triplet at δ 2.57 ppm due to alkyne proton; acetylene carbon signals at δ 80.47, 78.16 ppm and O-C<u>H</u>$_2$ carbon signal at δ 56.55 ppm respectively. The protonated molecular ion peak is observed at *m/z* 385.1 in LC-MS spectrum.

A new series of hybrid heterocycles with two ether linkages having pyrazolopyrimidine and 1,2,3-triazole scaffolds was planned using the terminal alkynes **5a,b** and the aryl azides **6a-e** in copper catalyzed 1,3-dipolar cycloaddition reaction under click conditions. The reaction of **5a** with phenyl azide **6a** in DMSO-H_2O solvent mixture was carried out using $CuSO_4 \cdot 5H_2O$ in the presence of sodium ascorbate as a copper catalyst source at room temperature. The reaction was completed in 4 h, after the usual workup, the isolated product was purified by column chromatography to afford product **7a** in 80% yield (**Scheme-II**). The product **7a** showed a band due to keto carbonyl group at 1736 cm^{-1} in IR spectrum; the characteristic singlet signal at δ 8.12 ppm for triazole ring proton and two more singlet signals at δ 5.42 ppm for two protons and at δ 2.64 ppm integrating for three protons due to O-CH_2 and keto-methyl protons, respectively in the ^{1}H NMR spectrum. Its ^{13}C NMR spectrum showed a keto carbon peak at δ198.13 ppm, substituted triazole carbon peaks at δ 143.74, 121.65 ppm, O-CH_2 carbon signal at δ 62.6 and keto-methyl carbon signal at δ 31.93 ppm. The LC-MS



Scheme-I: Synthesis of pyrazolo[3,4-*d*]pyrimidine based alkyne with methoxyphenoxy linker (**5a-b**)



7a: R_1=H, R_2= H; **7b:** R_1=H, R_2= F; **7c:** R_1=H, R_2= Cl; **7d:** R_1=H, R_2= Br; 7**e:** R_1=H, R_2= Me; **7f:** R_1= Me, R_2= H; **7g:** R_1= Me, R_2= F; **7h:** R_1= Me, R_2= Cl; **7i:** R_1= Me, R_2= Br; **7j:** R_1= Me, R_2=Me

Scheme-II: Synthesis of pyrazolo[3,4-*d*]pyrimidine based triazoles with two ether linkages (**7a-j**)

spectrum showed the protonated molecular ion peak at *m/z* 504.2, which confirmed the structure for product **7a** along with other spectral data.

A cluster of new pyrazolopyrimidine based triazoles with two ether linkages **7b-j** were obtained using diversely substituted aryl azides **6b-e** as sorrogates in copper catalyzed dipolar reaction of **5a/5b** under click conditions (**Scheme-II**).

Conclusion

A novel series of hybrid heterocycles having pyrazolopyrimidine based triazole scaffold with two ether linkages **7a-j** was synthesized from 1,3-dipolar cycloaddition reaction of pyrazolopyrimidines tethered to phenoxy alkynes **5a**, **5b** and differently substituted aromatic azides **6a-e** using $CuSO_4 \cdot 5H_2O$ and sodium ascorbate mixture as catalyst in click reaction manner in DMSO-H_2O solvent mixture. The alkynes **5a**, **5b** in turn were obtained from dehydrobromination of corresponding hydroxy compounds **3a**, **3b** with propargyl bromide. The compounds **3a** and **3b** were prepared using the starting precursor **1a**,**1b** and dihydoxyacetophenone (**2**).

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CONFLICT OF INTEREST

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

REFERENCES

1. A. Rahmouni, S. Souiei, M.A. Belkacem, A. Romdhane, J. Bouajila and H.B. Jannet, *Bioorg. Chem.*, **66**, 160 (2016); https://doi.org/10.1016/j.bioorg.2016.05.001
2. M. Chauhan and R. Kumar, *Bioorg. Med. Chem.*, **21**, 5657 (2013); https://doi.org/10.1016/j.bmc.2013.07.027
3. M.C. Bagley, M. Baashen, V.L. Paddock, D. Kipling and T. Davis, *Tetrahedron*, **69**, 8429 (2013); https://doi.org/10.1016/j.tet.2013.07.055
4. V. Masevicius, R. Juskenas and S. Tumkevicius, *J. Heterocycl. Chem.*, **49**, 315 (2012); https://doi.org/10.1002/jhet.724
5. M.H. Elnagdi, M.R.H. Elmoghayar and G.E.H. Elgemeie, *Adv. Heterocycl. Chem.*, **41**, 319 (1987); https://doi.org/10.1016/S0065-2725(08)60164-6
6. M.R. Shaaban, T.S. Saleh, A.S. Mayhoub, A. Mansour and A.M.S. Farag, *Bioorg. Med. Chem.*, **16**, 6344 (2008); https://doi.org/10.1016/j.bmc.2008.05.011
7. T. Shiota, T. Yamamori, K. Sakai, M. Kiyokawa, T. Honma, M. Ogawa, K. Hayashi, N. Ishizuka, K. Matsumura, M. Hara, M. Fujimoto, T. Kawabata and S. Nakajima, *Chem. Pharm. Bull.*, **47**, 928 (1999); https://doi.org/10.1248/cpb.47.928
8. P. Modi, S. Patel and M. Chhabria, *Bioorg. Chem.*, **87**, 240 (2019); https://doi.org/10.1016/j.bioorg.2019.02.044
9. C.S. de Melo, T.-S. Feng, R. van der Westhuyzen, R.K. Gessner, L.J. Street, G.L. Morgans, D.F. Warner, A. Moosa, K. Naran, N. Lawrence, H.I.M. Boshoff, C.E. Barry III, C.J. Harris, R. Gordon and K. Chibale, *Bioorg. Med. Chem.*, **23**, 7240 (2015); https://doi.org/10.1016/j.bmc.2015.10.021
10. N. Petek, B. Štefane, M. Novinec and J. Svete, *Bioorg. Chem.*, **84**, 226 (2019); https://doi.org/10.1016/j.bioorg.2018.11.029
11. D.A. Griffith, D.M. Hargrove, T.S. Maurer, C.A. Blum, S. De Lombaert, J.K. Inthavongsay, L.E. Klade, C.M. Mack, C.R. Rose, M.J. Sanders and P.A. Carpino, *Bioorg. Med. Chem. Lett.*, **21**, 2641 (2011); https://doi.org/10.1016/j.bmcl.2010.12.116
12. J. Xu, H. Liu, G. Li, Y. He, R. Ding, X. Wang, M. Feng, S. Zhang, Y. Chen, S. Li, M. Zhao, Y. Li, C. Qi and Y. Dang, *Molecules*, **17**, 3774 (2012); https://doi.org/10.3390/molecules17043774
13. D. Kumar, Beena, G. Khare, S. Kidwai, A.K. Tyagi, R. Singh and D.S. Rawat, *Eur. J. Med. Chem.*, **81**, 301 (2014); https://doi.org/10.1016/j.ejmech.2014.05.005
14. M.J. Genin, D.A. Allwine, D.J. Anderson, M.R. Barbachyn, D.E. Emmert, S.A. Garmon, D.R. Graber, K.C. Grega, J.B. Hester, D.K. Hutchinson, J. Morris, R.J. Reischer, C.W. Ford, G.E. Zurenko, J.C. Hamel, R.D. Schaadt, D. Stapert and B.H. Yagi, *J. Med. Chem.*, **43**, 953 (2000); https://doi.org/10.1021/jm990373e
15. R.S. Keri, S.A. Patil, S. Budagumpi and B.M. Nagaraja, *Chem. Biol. Drug Des.*, **86**, 410 (2015); https://doi.org/10.1111/cbdd.12527
16. T.M.A. Thabit, E.M. Abdelkareem, N.A. Bouqellah and S.A. Shokr, *Molecules*, **26**, 1784 (2021); https://doi.org/10.3390/molecules26061784
17. I.K. Boddy, G.G. Briggs, R.P. Harrison, T.H. Jones, M.J. O'Mahony, I.D. Marlow, B.G. Roberts, R.J. Willis, R. Bardsley and J. Reid, *Pestic. Sci.*, **48**, 189 (1996); https://doi.org/10.1002/(SICI)1096-9063(199610)48:2<189::AID-PS461>3.0.CO;2-#
18. M. de Lourdes G. Ferreira, L.C.S. Pinheiro, O.A. Santos-Filho, M.D.S. Peçanha, C.Q. Sacramento, V. Machado, V.F. Ferreira, T.M.L. Souza and N. Boechat, *Med. Chem. Res.*, **23**, 1501 (2014); https://doi.org/10.1007/s00044-013-0762-6
19. L.-S. Feng, M.-J. Zheng, F. Zhao and D. Liu, *Arch. Pharm. (Weinheim)*, **354**, 2000163 (2021); https://doi.org/10.1002/ardp.202000163
20. H.B. Lazrek, M. Taourirte, T. Oulih, J. Barascut, J. Imbach, C. Pannecouque, M. Witrouw and E. De Clercq, *Nucleosides Nucleotides Nucleic Acids*, **20**, 1949 (2001); https://doi.org/10.1081/NCN-100108325
21. S.G. Agalave, S.R. Maujan and V.S. Pore, *Chem. Asian J.*, **6**, 2696 (2011); https://doi.org/10.1002/asia.201100432
22. A. Kamal, N. Shankaraiah, V. Devaiah, K.L. Reddy, A. Juvekar, S. Sen, N. Kurian and S. Zingde, *Bioorg. Med. Chem. Lett.*, **18**, 1468 (2008); https://doi.org/10.1016/j.bmcl.2007.12.063
23. Y. Laamari, A. Oubella, A. Bimoussa, A.-E. El Mansouri, E.M. Ketatni, O. Mentre, M.Y. Ait Itto, H. Morjani, M. Khouili and A. Auhmani, *Bioorg. Chem.*, **115**, 105165 (2021); https://doi.org/10.1016/j.bioorg.2021.105165
24. A.K. Jordão, P.C. Sathler, V.F. Ferreira, V.R. Campos, M.C.B.V. de Souza, H.C. Castro, A. Lannes, A. Lourenco, C.R. Rodrigues, M.L. Bello, M.C.S. Lourenço, G.S.L. Carvalho, M.C.B. Almeida, A.C. Cunha and V.F. Ferreira, *Bioorg. Med. Chem.*, **19**, 5605 (2011); https://doi.org/10.1016/j.bmc.2011.07.035
25. M.L. Ferreira, M.V.N. Souza, S.M.S.V. Wardell, J.L. Wardell, T.R.A. Vasconcelos, V.F. Ferreira and M.C.S. Lourenço, *J. Carbohydr. Chem.*, **29**, 265 (2010); https://doi.org/10.1080/07328303.2010.511749
26. X.-L. Wang, K. Wan and C.-H. Zhou, *Eur. J. Med. Chem.*, **45**, 4631 (2010); https://doi.org/10.1016/j.ejmech.2010.07.031

27. L.V.R. Reddy, P. Venkat Reddy, N.N. Mishra, P.K. Shukla, G. Yadav, R. Srivastava and A.K. Shaw, *Carbohydr. Res.*, **345**, 1515 (2010); https://doi.org/10.1016/j.carres.2010.03.031
28. S. Palhagen, R. Canger, O. Henriksen, J.A. van Parys, M.E. Riviere and M.A. Karolchyk, *Epilepsy Res.*, **43**, 115 (2001); https://doi.org/10.1016/S0920-1211(00)00185-6
29. A.K. Jordão, V.F. Ferreira, T.M.L. Souza, G.G. de Souza Faria, V. Machado, J.L. Abrantes, M.C.B.V. de Souza and A.C. Cunha, *Bioorg. Med. Chem.*, **19**, 1860 (2011); https://doi.org/10.1016/j.bmc.2011.02.007
30. M. Allam, A.K.D. Bhavani, A. Mudiraj, N. Ranjan, M. Thippana and P.P. Babu, *Eur. J. Med. Chem.*, **156**, 43 (2018); https://doi.org/10.1016/j.ejmech.2018.06.055
31. V.H. Kapupara, D.G. Gojiya, T.D. Bhatt, S.D. Hadiyal, D.H.S. Joshi, *Russ. J. Bioorgan. Chem.*, **46**, 803 (2020); https://doi.org/10.1134/S1068162020050106
32. K. Somakala, S. Tariq and M. Amir, *Bioorg. Chem.*, **87**, 550 (2019); https://doi.org/10.1016/j.bioorg.2019.03.037