Asian Journal of Chemistry; Vol. 38, No. 6 (2026), 1393-1402
ASIAN JOURNAL OF CHEMISTRY
https://doi.org/10.14233/ajchem.2026.35534

Synthesis, Characterisation of Substituted 2-[4-Methyl-6-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-3-yl]benzothiazole: Evaluation of their Cytotoxic, Antimicrobial and Molecular Docking Studies

LAKAVATH RAMDAS, JADHAV RAMCHANDER*, and RAVI GUGULOTH

Department of Chemistry, University College of Science, Osmania University, Hyderabad-500007, India

*Corresponding author: E-mail: ramorgchemou@gmail.com

Received: 29 December 2025 *Accepted*: 26 March 2026 *Published online*: 31 May 2026 AJC-22365

A series of newly synthesised substituted 2-[4-methyl-6-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-3-yl]benzothiazole derivatives (**7a-l**) were synthesised *via* click chemistry and characterised using ^{1}H and ^{13}C NMR, mass and IR spectral techniques. The cytotoxic activity of compounds **7a-l** was evaluated against MCF-7, PC-3 and HeLa cancer cell lines at concentrations of 5 and 10 μM. Several compounds, notably **7b**, **7g**, **7j** and **7k**, exhibited significant cytotoxic effects compared to other compounds. The synthesised benzothiazole-1,2,3-triazoles hybrid derivatives (**7a-l**) were also evaluated for *in vitro* antibacterial activity against six different bacterial species. Compounds **7b**, **7c**, **7e**, **7h** and **7i** exhibited more bacterial potent compared to other compounds. The antifungal activity of compounds **7a-l** was assessed at 100 μg/mL against four fungal strains. Compounds **7b**, **7c**, **7e**, **7h** and **7i** demonstrated significant activity compared to other compounds, indicating potential as effective antifungal agents. Docking investigations were conducted sequentially to analyse binding interactions targeting ERK2 (PDB ID: 4ZXT) and MAPK1. Among the tested compounds **7e**, **7f**, **7k** and **7l** exhibited favourable binding energies -8.9 to -9.0 kcal/mol, indicating potential strong interactions with the target proteins.

Keywords: Anticancer activity, Antimicrobial activity, Molecular docking studies, 1,2,3-Triazole, Benzothiazole derivatives.

INTRODUCTION

Cancer is one of the most prevalent and life-threatening diseases, characterized by the uncontrolled proliferation of abnormal cells that can arise in virtually any tissue or organ of the human body [1-4]. The global incidence of cancer continues to increase significantly, with approximately 18.1 million new cases and nearly one in six deaths reported worldwide in 2018 [5-8]. Although substantial progress has been achieved in cancer diagnosis and chemotherapy, severe adverse effects and drug resistance associated with existing anticancer agents continue to limit therapeutic success. Consequently, the development of safer and more effective anticancer compounds remains an important area of medicinal research [9-12].

Nitrogen-containing heterocyclic compounds occupy a prominent position in drug discovery, among which 1,2,3-triazoles have attracted considerable attention due to their remarkable pharmacological versatility [17]. Derivatives of 1,2,3-triazole exhibit a broad spectrum of biological activities including antimicrobial, antifungal, antiviral, antitubercular, antioxidant, anti-inflammatory, anticholinesterase, antidiabetic, antihistaminic and anticancer properties [18-25]. These diverse biological effects are primarily attributed to the ability of the triazole ring system to establish various non-covalent interactions with biological targets such as enzymes, receptors and nucleic acids. Several clinically important molecules, including cefatrizine and carboxyamidotriazole, contain the 1,2,3-triazole scaffold and demonstrate significant therapeutic potential, particularly in anticancer applications [26].

Substituted benzaldehyde derivatives have also been reported to possess promising anticancer properties. Based on literature reports describing the biological significance of both substituted benzaldehydes and 1,2,3-triazoles, the design of hybrid molecules integrating these two pharmacophores has emerged as an attractive strategy for enhancing antineoplastic activity. The combination of benzazole and 1,2,3-triazole moieties within a single molecular framework may improve biological potency through synergistic structural and electronic effects. Therefore, several hybrid derivatives have been syn-

thesised and evaluated for their *in vitro* anticancer and antimicrobial activities using different human cell lines [27-36].

EXPERIMENTAL

Analytical grade chemicals, solvents and reagents used were sourced from commercial suppliers such as Avra, Sigma-Aldrich, BLD, Qualikems and/or Merck and used as such. Every reaction was carried out on equipment that had been oven-dried. Thin layer chromatography (TLC) was performed on silica gel plates (60 F_{254}) to monitor the reactions and UV light and iodine vapours were utilised to visualize the reactions. Column chromatography was carried out on silica gel (60-120 mesh) using distilled hexane and ethyl acetate solvents. The ^{1}H and ^{13}C NMR spectra were obtained using 500 and 125 MHz spectrometers, respectively, specifically the Bruker Avance II 400 MHz instrument in $CDCl_3$ and some DMSO. Mass spectra were recorded using the QSTAR XL GCMS mass spectrometer. Infrared spectra were recorded using the Shimadzu FT-IR-8400s instrument. Melting points were determined using an DbkProg. melting point apparatus in an open glass capillary tube and are uncorrected.

Synthesis of compound 3: The synthetic route for 4-methyl-6-prop-2-ynyloxy-pyridine-3-carbaldehyde (**3**) was carried out by reaction with 6-hydroxy-4-methyl-pyridine-3-carbaldehyde (0.02 mol) (**1**) and 3-bromo-propyne (0.024 mol) in the presence of K_2CO_3 (0.04 mol) and DMF (3 vol) at RT for 4-5 h to afford compound (**3**).

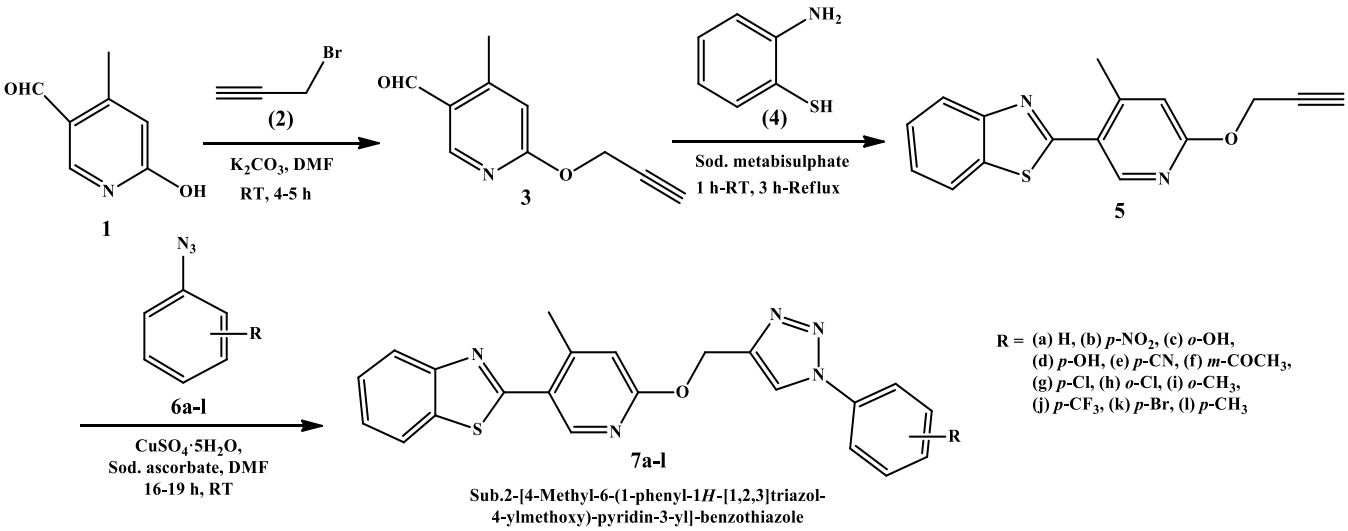
Synthesis of compound 5: The synthetic route for 2-(4-methyl-6-prop-2-ynyloxy-pyridin-3-yl)-benzothiazole (**5**) was carried out in between compound **3** (0.02 mol) and 2-amino-benzenethiol (0.02 mol) (**4**) in the presence of sodium metabisulphite (0.06 mol), at 1-2 h RT and 3-4 h reflux condition to obtain compound **5**.

General procedure for the synthesis of 7a-l compounds: Click chemistry was used to synthesise substituted 2-[4-methyl-6-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy) pyridin-3-yl]benzothiazole (**7a-l**) by reacting with 2-(4-methyl-6-prop-2-ynyloxy-pyridin-3-yl)-benzothiazole (**5**) (0.01 mmol) with various aryl azides (**6a-l**) (0.012 mmol) in $CuSO_4 \cdot 5H_2O$ with DMF (3 vol.) and sodium ascorbate at room temperature for 6-7 h. The progress of the reaction was monitored by TLC. After finishing, the contents were transferred into a 100 mL beaker filled with crushed ice. Substituted 2-[4-methyl-6-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-3-yl]benzothiazoles (**7a-l**) were isolated by filtration using a Büchner funnel and dried under reduced pressure in vacuum (**Scheme-I**). These crude compounds were then purified by column chromatography using hexane/ethyl acetate (1:3 v/v), which produced excellent yields of 72-85%.

4-Methyl-6-(prop-2-ynyloxy)nicotinaldehyde (3): Yield: 76%, m.p.: 159-161 ºC; colour: off white solid. IR (KBr, ν_{max}, cm^{-1}): 3329, 3086, 2933, 2212, 1711, 1658, 1512, 1251. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.89 (CHO, s, 1H), 7.91 (Ar, s, 1H), 6.83 (Ar, s, 1H), 4.89 (CH_2, s, 2H), 2.82 (≡C–H, s, 1H), 2.63 (CH_3, s, 3H). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 183.45, 166.28, 152.81, 148.86, 119.82, 117.68, 79.89, 77.57, 18.48. ESI-MS *m/z*: 176 $[M+1]^+$. Elemental analysis of $C_{10}H_9NO_2$, calcd. (found) %: C, 68.56 (68.53); H, 5.18 (5.16); N, 8.00 (8.03); O, 18.27 (18.23).

2-(4-Methyl-6-(prop-2-ynyloxy)pyridin-3-yl)benzo[*d*]-thiazole (5): Yield: 78%, m.p.: 162-164 ºC; colour: yellow solid. IR (KBr, ν_{max}, cm^{-1}): 3311, 3056, 2924, 2216, 1682, 1501, 1249; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.32 (d, 1H, *J* = 8 Hz) 8.18 (d, 1H, *J* = 7.6 Hz), 8.011 (s, 1H), 7.76 (m, 2H), 6.68 (Ar, s, 1H), 4.90 (CH_2, s, 2H), 2.83 (≡C–H, s, 1H), 2.68 (CH_3, s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 164.46, 155.69, 152.43, 148.10, 142.36, 134.89, 127.01, 126.79, 124.36, 123.43, 122.24, 116.77, 80.01, 77.64, 56.78, 18.10. ESI-MS *m/z*: 281 $[M+1]^+$. Elemental analysis of $C_{16}H_{12}N_2OS$, calcd. (found) %: C, 68.55 (68.51); H, 4.31 (4.34); N, 9.99 (9.97); O, 5.71 (5.68); S, 11.44 (11.47).

2-[4-Methyl-6-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-3-yl]benzothiazole (7a): Yield: 82%, m.p.: 168-178 ºC; colour: pale yellow solid. R_f = 0.40 (EtOAc:*n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3060.50, 2923.12, 1497.99, 739.76, 696.81; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): δ 8.88 (s, 1H), 8.34 (s, 1H, CH), 8.11 (t, 1H, *J* = 7.6 Hz, Ar),



Scheme-I: Synthetic route of different substituted 2-[4-methyl-6-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-pyridin-3-yl]-benzothiazole

8.00 (t, 1H, *J* = 8.2 Hz, Ar), 7.47 (m, 5H, Ar), 7.16 (d, 1H, *J* = 5.6 Hz, Ar), 6.85 (d, 1H, *J* = 5.2 Hz, Ar), 6.76 (s, 1H, Ar), 6.54 (s, 1H, Ar), 5.39 (s, 2H, CH_2), 1.33 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 165.98, 164.87, 162.09, 159.88, 156.06, 151.57, 145.74, 142.33, 141.40, 136.09, 131.66, 130.85, 125.92, 125.76, 125.46, 120.87, 119.00, 113.01, 109.87, 43.65, 20.67. ESI-MS: *m/z* 399.5 $[M+1]^+$. Elemental analysis of $C_{22}H_{17}N_5OS$: calcd. (found) %: C, 66.15 (66.12); H, 4.29 (4.32); N, 17.53 (17.50); O, 4.01 (4.32); S, 8.03 (8.66).

2-{4-Methyl-6-[1-(4-nitro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]pyridin-3-yl}benzothiazole (7b): Yield: 76%, m.p.: 178-180 ºC; colour: pale yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3031.85, 2922.32, 1582.16, 1562.10, 754.21, 672.45; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 9.28 (s, 1H), 8.80 (s, 1H, CH), 7.89 (d, 2H, *J* = 6.99 Hz, Ar), 7.61 (d, 2H, *J* = 6.81 Hz, Ar), 7.57 (d, 1H, *J* = 8.23 Hz, Ar), 7.51 (d, 1H, *J* = 5.6 Hz, Ar), 7.49 (s, 1H, Ar), 6.84 (s, 1H, Ar), 6.63 (s, 1H, Ar), 5.39 (s, 2H, CH_2), 2.45 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): δ 162.76, 159.91, 157.87, 154.93, 152.09, 145.80, 142.95, 142.42, 136.46, 131.76, 129.93, 128.93, 122.72, 120.10, 119.07, 116.54, 113.64, 110.98, 43.96, 20.72. ESI-MS: *m/z* 444.5 $[M+1]^+$; Elemental analysis of $C_{22}H_{16}N_6O_3S$: calcd. (found) %: C, 59.45 (59.43); H, 3.63 (3.60); N, 18.91 (18.94); O, 10.80 (10.78); S, 7.21 (7.17).

2-[4-(5-Benzothiazol-2-yl-4-methyl-pyridin-2-yloxymethyl)[1,2,3]triazol-1-yl]-phenol (7c): Yield: 84%, m.p.: 170-172 ºC; colour: white solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3357.21, 3066.75, 2979.45, 1508.60, 807.14, 628.44; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): δ 10.38 (s, 1H), 8.84 (s, 1H, CH), 8.04 (s, 1H, Ar), 7.94 (t, 1H, *J* = 6.42 Hz, Ar), 7.88 (t, 1H, *J* = 8.21 Hz, Ar), 7.85 (t, 1H, *J* = 6.45 Hz, Ar), 7.80 (d, 1H, *J* = 5.65 Hz, Ar), 7.78 (d, 1H, *J* = 6.55 Hz, Ar), 7.14 (t, 1H, *J* = 6.21 Hz, Ar), 6.85 (d, 1H, *J* = 6.82 Hz, Ar), 6.63 (d, 1H, *J* = 6.21 Hz, Ar), 6.43 (s, 1H, Ar), 5.39 (s, 2H, CH_2), 2.50 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 168.09, 166.35, 163.12, 159.85, 157.09, 155.52, 151.09, 145.75, 143.15, 142.41, 135.63, 132.78, 131.99, 122.11, 121.99, 121.44, 119.05, 116.84, 114.04, 111.45, 43.91, 20.68. ESI-MS: *m/z* 415.5 $[M+1]^+$; Elemental analysis of $C_{22}H_{17}N_5O_2S$: calcd. (found) %: C, 63.60 (63.57); H, 4.12 (4.16); N, 16.86 (16.84); O, 7.70 (7.67); S, 7.72 (7.70).

4-[4-(5-Benzothiazol-2-yl-4-methyl-pyridin-2-yloxymethyl)-[1,2,3]triazol-1-yl]phenol (7d): Yield: 83%, m.p.: 176-178 ºC; colour: yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3395.24, 2949.77, 1508.10, 1241.59, 755.93. ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): δ 10.23 (s, 1H, OH), 9.30 (s, 1H, Ar), 9.02 (s, 1H, CH), 8.45 (s, 1H, Ar), 8.23 (d, 2H, *J* = 6.44 Hz, Ar), 7.84 (d, 2H, *J* = 6.67 Hz, Ar), 7.60 (d, 1H, *J* = 6.10 Hz, Ar), 7.23 (d, 1H, *J* = 5.87 Hz, Ar), 6.63 (d, 1H, *J* = 6.02 Hz, Ar), 6.45(d, 1H, *J* = 5.26 Hz, Ar), 5.42 (s, 2H, CH_2), 2.50 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 165.98, 163.93, 159.85, 156.03,153.92, 146.78, 145.80, 143.66, 142.45, 140.66, 131.78, 125.58, 122.53, 120.65, 119.07, 116.43, 114.86, 43.95, 20.69. ESI-MS: *m/z* 415.5 $[M+1]^+$. Elemental analysis of $C_{22}H_{17}N_5O_2S$: calcd. (found) %: C, 63.60 (63.56); H, 4.12 (4.10); N, 16.86 (16.83); O, 7.70 (7.73); S, 7.72 (7.70).

4-[4-(5-Benzothiazol-2-yl-4-methyl-pyridin-2-yloxymethyl)-[1,2,3]triazol-1-yl]benzonitrile (7e): Yield: 85%, m.p.: 166-168 ºC; colour: yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3032.85, 2923.32, 1583.16, 1561.10, 753.21, 673.45; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 9.27 (s, 1H, Ar), 8.50 (s, 1H, CH), 7.58 (d, 1H, *J* = 7.16 Hz, Ar), 7.56 (t, 1H, *J* = 6.73 Hz, Ar), 7.34 (t, 1H, *J* = 9.27 Hz, Ar), 7.11 (t, 2H, *J* = 6.46 Hz, Ar), 6.99 (t, 2H, *J* = 5.26 Hz, Ar), 6.41 (s, 1H, Ar), 5.38 (s, 2H, CH_2), 2.45 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 168.93, 166.63, 164.00, 161.66, 159.82, 157.95, 152.00, 149.47, 145.68, 142.25, 136.98, 131.59, 130.18, 125.01, 124.29, 119.47, 118.93, 116.97, 112.00, 43.68, 20.61. ESI-MS: *m/z* 424.5 $[M+1]^+$. Elemental analysis of $C_{23}H_{16}N_6OS$: calcd. (found) %: C, 65.08 (65.05); H, 3.80 (3.83); N, 19.80 (19.78); O, 3.77 (3.74); S, 7.55 (7.58).

1-{3-[4-(5-Benzothiazol-2-yl-4-methyl-pyridin-2-yloxymethyl)-[1,2,3]triazol-1-yl]phenyl}ethanone (7f): Yield: 84%, m.p.: 162-164 ºC; colour: pale yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3). IR (KBr, ν_{max}, cm^{-1}): 3036.85, 2926.32, 1578.16, 1557.10, 755.24, 671.42. ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): δ 9.18 (s, 1H, Ar), 8.63 (s, 1H, CH), 8.43 (s, 1H, Ar)), 8.42 (d, 1H, *J* = 6.75 Hz, Ar), 8.21 (d, 1H, *J* = 7.93 Hz, Ar), 8.09 (t, 1H, *J* = 6.42 Hz, Ar), 7.80 (t, 1H, *J* = 6.23 Hz, Ar), 7.76 (t. 1H, *J* = 7.03 Hz), 7.71 (t, 1H, *J* = 7.32 Hz, Ar), 6.87 (d, 1H, *J* = 6.88 Hz, Ar), 6.65 (s, 1H, Ar), 5.50 (s, 2H, CH_2), 2.67 (s, 3H, $COCH_3$), 2.33 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): δ 189.04, 169.04, 166.09, 161.44, 160.76, 159.86, 157.81, 155.94, 153.02, 151.06, 145.71, 142.36, 139.03, 136.99, 133.44, 131.69, 128.57, 121.93, 119.02, 116.01, 114.77, 58.0, 43.89, 20.68. ESI-MS: *m/z* 441.5 $[M+1]^+$. Elemental analysis of $C_{24}H_{19}N_5O_2S$: calcd. (found) %: C, 65.29 (65.27); H, 4.34 (4.30); N, 15.86 (17.86); O, 7.25 (7.23); S, 7.26 (7.28).

2-{6-[1-(4-Chloro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-4-methyl-pyridin-3-yl}benzothiazole (7g): Yield: 82%, m.p.: 178-180 ºC; colour: pale yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3017.46, 2993.49, 1563.27, 1543.23, 748.65, 673.52; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): δ 8.65 (s, 1H, Ar), 8.32 (s, 1H, CH), 7.72 (s, 1H, Ar), 7.49 (d, 2H, *J* = 8.65 Hz, Ar), 7.44 (d, 2H, *J* = 8.35 Hz, Ar), 7.20 (t, 1H, *J* = 5.69 Hz, Ar), 7.01 (d, 1H, *J* = 5.39 Hz, Ar), 6.80 (d, 1H, *J* = 7.21 Hz, Ar), 6.52 (t, 1H, *J* = 6.63 Hz, Ar), 5.33 (s, 2H, CH_2), 2.14 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 169.99, 167.01, 165.09, 163.09, 161.03, 159.85, 153.00, 145.75, 143.12, 142.40, 135.23, 133.04, 131.72, 129.86, 122.17, 121.76, 119.05, 112.94, 43.91, 20.68. ESI-MS: *m/z* 433.9 $[M+1]^+$; Elemental analysis of $C_{22}H_{16}ClN_5OS$: calcd. (found) %: C, 60.90 (60.87); H, 3.72 (3.70); Cl, 8.17 (8.20); N, 16.14 (16.11); O, 3.69 (3.71); S, 7.39 (7.42).

2-{6-[1-(2-Chloro-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-4-methyl-pyridin-3-yl}benzothiazole (7h): Yield: 78%, m.p.: 166-168 ºC; colour: white solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3021.56, 2998.52, 1559.85, 1538.45, 752.65, 677.27; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.65 (s, 1H, Ar), 8.35 (s, 1H, CH), 8.11 (t, 1H, *J* = 7.76 Hz, Ar), 8.09(d, 1H, *J* = 6.26 Hz, Ar), 8.08 (t, 1H, *J* = 6.16 Hz, Ar), 7.71 (d, 1H, *J* = 6.73 Hz, Ar), 7.69 (t, 1H, *J* = 5.97 Hz, Ar), 7.51 (d, 1H, *J* = 7.23 Hz, Ar), 7.45 (t, 1H, *J* = 6.12 Hz, Ar),

7.12 (d, 1H, *J* = 6.97 Hz, Ar), 6.82 (s, 1H), 5.53 (s, 2H, CH_2), 2.14 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 168.01, 165.04, 163.22, 161.23, 159.86, 155.20, 148.02, 145.73, 142.37, 141.72, 136.07, 132.99 131.68, 131.36, 129.88, 127.00, 125.97, 119.03, 116.04, 112.32, 43.75, 20.68 (CH_3); ESI-MS: *m/z* 433.9 $[M+1]^+$, Elemental analysis of $C_{22}H_{16}ClN_5OS$: calcd. (found) %: C, 60.90 (60.87); H, 3.72 (3.75); Cl, 8.17 (8.13); N, 16.14 (16.17); O, 3.69 (3.67); S, 7.39 (7.36).

2-[4-Methyl-6-(1-*o*-tolyl-1*H*-[1,2,3]triazol-4-ylmethoxy)-pyridin-3-yl]-benzothiazole (7i): Yield: 82%, m.p.: 178-180 ºC; colour: yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3013.78, 2994.45, 1512.43, 1508.72, 756.71, 671.27; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 9.27 (s, 1H, Ar), 8.75 (s, 1H, CH), 8.54 (t, 1H, *J* = 8.21 Hz, Ar), 8.12 (d, 1H, *J* = 8.51 Hz, Ar), 7.76 (d, 1H, *J* = 7.76 Hz, Ar), 7.74 (t, 1H, *J* = 5.68 Hz, Ar), 7.39 (t, 1H, *J* = 6.65 Hz, Ar), 7.37 (d, 1H, *J* = 6.91 Hz, Ar), 7.01 (t, 1H, *J* = 7.76 Hz), 6.73 (d, 1H, *J* = 6.67 Hz, Ar), 6.43 (s, 1H), 5.38 (s, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.32 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 169.00, 167.05, 165.32, 162.92, 159.84(Ar-C), 156.84, 153.66, 148.02, 145.71 142.79, 142.38, 138.40, 134.19, 131.69, 130.21, 121.91, 119.91, 119.02, 114.03, 112.05, 43.91, 20.66, 20.54. ESI-MS: *m/z* 413.5 $[M+1]^+$. Elemental analysis of $C_{23}H_{19}N_5OS$: calcd. (found) %: C, 66.81 (66.78); H, 4.63 (4.65); N, 16.94 (16.92); O, 3.87 (3.89); S, 7.75 (7.73).

2-{4-Methyl-6-[1-(4-trifluoromethyl-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]pyridin-3-yl}benzothiazole (7j): Yield: 79%, m.p.: 168-170 ºC; colour: pale yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3028.61, 2993.91, 1511.43, 1505.62, 751.65, 678.27; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): δ 9.27 (s, 1H, Ar), 8.70 (s, 1H, CH), 8.54 (d, 1H, *J* = 7.76 Hz, Ar), 7.79 (d, 2H, *J* = 6.19 Hz, Ar), 7.77 (d, 1H, *J* = 6.56 Hz, Ar), 7.45 (t, 2H, *J* = 6.15 Hz, Ar), 7.13 (d, 1H, *J* = 6.07 Hz, Ar), 6.93 (t, 1H, *J* = 6.78 Hz, Ar), 6.43 (s, 1H, Ar), 5.37 (s, 2H, CH_2), 2.50 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 164.84, 159.84, 159.31, 155.02, 150.22, 147.39, 145.73, 142.65, 142.38, 137.00, 133.03, 131.69, 129.85, 122.03, 121.73, 119.03, 114.85, 111.02, 55.55, 43.89, 20.68. ESI-MS: *m/z* 467.5 $[M+1]^+$. Elemental analysis of $C_{23}H_{16}F_3N_5OS$: calcd. (found) %: C, 59.10 (59.07); H, 3.45 (3.48); F, 12.19 (12.21); N, 14.98 (14.95); O, 3.42 (3.40); S, 6.86 (6.83).

2-{6-[1-(4-Bromo-phenyl)-1*H*-[1,2,3]triazol-4-ylmethoxy]-4-methyl-pyridin-3-yl}benzothiazole (7k): Yield: 82%, m.p.: 178-180 ºC; colour: pale yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3016.73, 2991.41, 1510.38, 1507.12, 749.61, 671.65. ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 9.29 (s, 1H, Ar), 8.96 (s, 1H, CH), 8.15 (d, 2H, *J* = 7.74 Hz, Ar), 8.13 (t, 2H, *J* = 6.37 Hz, Ar), 8.08 (d, 1H, *J* = 6.95 Hz, Ar), 7.62 (d, 1H, *J* = 6.35 Hz, Ar), 7.42(t, 1H, *J* = 6.56 Hz, Ar), 6.78 (t, 1H, *J* = 6.91 Hz, Ar), 6.44 (s, 1H, Ar), 5.41 (s, 2H, CH_2), 2.50 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 164.33, 162.90, 159.85, 156.83, 153.09, 147.55, 145.78, 143.48, 142.42, 139.35, 134.29, 131.75, 122.34, 120.49, 119.06, 118.07, 116.34, 111.15, 43.92, 20.68. ESI-MS: *m/z* 478.4 $[M+1]^+$; Elemental analysis of $C_{22}H_{16}BrN_5OS$: calcd. (found): C, 55.24 (55.22); H, 3.37 (3.40); Br, 16.70 (16.68); N, 14.64 (14.61); O, 3.34 (3.32); S, 6.70 (6.73).

2-[4-Methyl-6-(1-*p*-methyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-3-yl]benzothiazole (7l): Yield: 79%, m.p.: 168-170 ºC; colour: pale yellow solid: R_f = 0.40 (EtOAc: *n*-hexane 2:3); IR (KBr, ν_{max}, cm^{-1}): 3011.52, 2989.39, 1508.41, 1501.49, 731.32, 668.42; ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 9.30 (s, 1H, Ar), 8.96 (s, 1H, CH), 8.56 (t, 1H, *J* = 7.69 Hz, Ar), 8.16 (d, 2H, *J* = 6.72 Hz, Ar), 8.14 (d, 2H, *J* = 6.98 Hz, Ar), 7.99 (t, 1H, *J* = 6.41 Hz, Ar), 7.97 (d, 1H, *J* = 6.72 Hz, Ar), 7.53 (d, 1H, *J* = 6.87 Hz, Ar), 6.99 (d, 1H, *J* = 6.61 Hz, Ar), 6.44 (s, 1H, Ar), 5.41 (s, 2H, CH_2), 2.50 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6, δ ppm): 165.02, 163.46, 159.86, 156.97, 154.98, 149.03, 145.78, 143.38, 142.43, 139.22, 134.56, 131.75, 127.20, 122.36, 120.55, 119.06, 114.02, 112.45, 43.93, 20.68; ESI-MS: *m/z* 413.5 $[M+1]^+$, Elemental analysis of $C_{23}H_{19}N_5OS$: calcd. (found) %: C, 66.81 (66.78); H, 4.63 (4.62); N, 16.94 (16.97); O, 3.87 (3.85); S, 7.75 (7.72).

Biological studies

Anticancer study: Cell viability was evaluated using the MTT cell viability assay kit, a sensitive and quantitative colorimetric method for determining viable cell populations in culture. Cells were seeded in appropriate culture plates and treated with the synthesized compounds at different concentrations. After the incubation period, MTT reagent was added to each well and the plates were further incubated to allow formation of formazan crystals by metabolically active cells. Subsequently, the formed crystals were dissolved using solubilization buffer and the absorbance was measured at 570 nm using a microplate reader. The percentage of cell viability was calculated relative to untreated control cells. A decrease in absorbance indicated reduced cell viability and cytotoxic activity of the tested compounds.

Antibacterial studies: Six bacterial strains *viz*. three Gram-positive (*B. subtilis*, *B. sphaericus* and *S. aureus*) and three Gram-negative (*P. aeruginosa*, *K. aerogenes* and *C. violaceum*) were used to test the antibacterial activity of a novel series of **7a-l** compounds. For this assessment, the disc diffusion approach was used. Using a glass spreader, standard inoculums containing 1-2 × 10^7 cfu/mL were equally distributed onto sterile agar plates. These inoculums were made using 0.5 McFarland standards. After being sterilised for 1 h at 140 ºC, sterile 6.26 mm diameter discs produced from Whatman No. 1 filter paper were submerged in known concentrations of the test chemicals.

Antifungal activity: The synthesised novel compounds **7a-l** were tested for antifungal activity against *C. albicans*, *A. fumigatus*, *T. rubrum* and *T. mentagrophytes* using the disc diffusion method. DMSO was employed to dissolve the compounds, while amphotericin B served as the reference standard. The efficacy of the compounds was evaluated by determining their minimum inhibitory concentration (MIC) and zone of inhibition values.

Molecular docking studies: Molecular docking studies were performed for the synthesized compounds **7a-l** and the standard drug doxorubicin against ERK2 (extracellular signal-regulated kinase 2; PDB ID: 4ZXT), also known as MAPK1. ERK2 plays a vital role in cellular signalling pathways associated with cell proliferation, differentiation and survival. Dysregulation of ERK2 is strongly associated with cancer prog-

ression, making it an important therapeutic target for anticancer drug development.

RESULTS AND DISCUSSION

The newly synthesised substituted **7a-l** derivatives were obtained successfully. Initially, compound 4-methyl-6-prop-2-ynyloxy-pyridine-3-carbaldehyde (**3**) was synthesised in good yield by reaction in between propargylation of 6-hydroxy-4-methyl-pyridine-3-carbaldehyde (**1**), 3-bromopropyne (**2**) and K_2CO_3 basic conditions with DMF at RT 4-5 h. The synthesised 4-methyl-6-prop-2-ynyloxy-pyridine-3-carbaldehyde (**3**) reacted with 2-amino-benzenethiol (**4**) in the presence of $Na_2S_2O_5$ at room temperature for 1 h and 2 h for reflux and 2-(4-methyl-6-prop-2-ynyloxy-pyridin-3-yl)-benzothiazole (**5**). Finally substituted 2-[4-methyl-6-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethoxy)pyridin-3-yl]-benzothiazole (**7a-l**) was synthesised in a reaction between 2-(4-methyl-6-prop-2-ynyloxy-pyridin-3-yl)-benzothiazole (**5**) and different substituted aryl azides (**6a-l**) in the click chemistry. The newly developed compounds **5** and **7a-l** underwent confirmation using proton and carbon NMR, mass and IR spectroscopic techniques.

The proton signals triazole protons are given signals that appear as singlets at in between δ 8.45 and 9.30 ppm; the methylene (O-CH_2) protons give singlet signals in between δ 5.40-5.80 ppm. The remaining protons signals appear at their corresponding integral values. The carbon signals for triazole ring carbon appeared at 121-130 ppm and the O-CH_2 signals were at 45-60 ppm. In the FTIR spectra, all derivatives **7a-l** exhibited characteristic absorption bands within the range of 4000-400 cm^{-1} corresponding to their respective functional groups (**Scheme-I**).

Cytotoxicity activity: The cytotoxic activity of the synthesized compounds (**7a-l**) was evaluated against MCF-7, PC-3 and HeLa cancer cell lines at concentrations of 5 and 10 μM. Doxorubicin was used as the standard anticancer drug, while untreated cells served as the control. The results, expressed as percentage cell viability, are presented in Table-1. Preliminary screening revealed that compounds **7b**, **7j** and **7k** exhibited significant anticancer activity, exhibiting 73-95% inhibition of cancer cell growth compared with the other synthesised derivatives. Compounds **7c**, **7d** and **7g** demonstrated moderate cytotoxic activity, whereas compounds **7a**, **7e**, **7f**, **7i**, **7h** and **7i** displayed comparatively weak anticancer effects with higher cell viability values.

Among the tested compounds, **7b**, **7j** and **7k** showed the most potent cytotoxic activity with IC_{50} values comparable to or lower than that of doxorubicin. In contrast, compounds **7c**, **7d** and **7g** exhibited moderate activity, while derivatives **7a**, **7e**, **7h**, **7i** and **7l** demonstrated weak cytotoxic potential with relatively higher IC_{50} values (Table-2).

TABLE-1
CYTOTOXICITY ACTIVITY DATA OF SYNTHESISED BENZOTHIAZOLE-FUSED ANALOGUES (7a-l)

Compound	MCF-7		PC-3		HeLa	
	5 μM	10 μM	5 μM	10 μM	5 μM	10 μM
7a	71	76	59	68	67	74
7b	87	95	74	81	80	85
7c	77	83	63	70	72	74
7d	74	86	68	71	72	74
7e	67	71	57	65	64	71
7f	72	78	62	65	68	70
7g	78	81	68	69	72	75
7h	66	72	55	63	61	68
7i	68	74	58	61	64	72
7j	92	98	73	81	89	95
7k	90	95	83	88	86	92
7l	71	76	56	66	69	68
Doxorubicin	94	99	85	94	88	98
Control	10	10	10	10	10	10

TABLE-2
IC_{50} VALUES OF SYNTHESISED BENZOTHIAZOLE-FUSED ANALOGUES (**7a-l**)

Compound	IC_{50} (μM ± SEM)		
	MCF-7	PC-3	HeLa
7a	8.48 ± 0.03	10.79 ± 0.12	9.23 ± 0.09
7b	4.62 ± 0.03	6.53 ± 0.09	6.63 ± 0.06
7c	6.34 ± 0.04	10.27 ± 0.07	9.24 ± 0.08
7d	6.78 ± 0.04	8.57 ± 0.06	7.34 ± 0.09
7e	8.73 ± 0.06	11.91 ± 0.10	8.82 ± 0.14
7f	8.41 ± 0.05	10.62 ± 0.14	9.07 ± 0.11
7g	4.71 ± 0.08	6.51 ± 0.12	6.53 ± 0.14
7h	8.82 ± 0.09	11.98 ± 0.10	8.95 ± 0.16
7i	8.61 ± 0.05	11.87 ± 0.10	8.75 ± 0.16
7j	3.71 ± 0.03	3.13 ± 0.06	3.71 ± 0.05
7k	3.18 ± 0.05	3.21 ± 0.03	3.08 ± 0.02
7l	8.48 ± 0.03	11.79 ± 0.11	8.60 ± 0.12
Doxorubicin	2.70 ± 0.04	3.81 ± 0.03	3.13 ± 0.08

Antimicrobial activity

Antibacterial assay: The antibacterial activity of the newly synthesized analogues (**7a-l**) was evaluated against six bacterial strains using the disc diffusion method. The results demonstrated that compounds **7b**, **7c**, **7e**, **7h** and **7i** exhibited comparatively superior antibacterial activity relative to the other synthesized derivatives, indicating their potential as promising broad-spectrum antibacterial agents (Table-3). Compounds **7d**, **7j** and **7l** showed moderate antibacterial activity, suggesting that further structural modification may enhance their biological efficacy. In contrast, compounds **7a**, **7f**, **7g** and **7k** displayed comparatively lower antibacterial potency against the tested bacterial strains. Structural optimization through functional group modification, improved solubility and alteration of molecular size may further enhance their interactions with bacterial targets and improve antibacterial performance.

Antifungal activity: The antifungal effects of the novel 1,2,3-triazole analogues (**7a-l**) was evaluated against four fungus isolates. Compounds **7b**, **7c**, **7e**, **7h** and **7i** displayed appreciable good antifungal potent compared to the reference drug, exhibited significant inhibitory zones showing their potential to be potent therapeutics against these infections. Analogues **7d, 7j** and **7k** revealed moderate antifungal potentials. Furthermore, derivatives **7a**, **7f**, **7g** and **7l** showed weaker antifungal effects, signalling those further modifications are required for enhancing their efficacy (Table-4).

Molecular docking studies: Molecular docking studies were performed to evaluate the binding interactions of the

TABLE-3
ANTIBACTERIAL ACTIVITY DATA OF SYNTHESISED BENZOTHIAZOLE-FUSED ANALOGUES (7a-l)

Compound	MIC values in 100 µg/mL (Minimum inhibitory concentration)					
	B. subtilis	*B. sphaericus*	*S. aureus*	*P. aeruginosa*	*K. aerogenes*	*C. violaceum*
7a	49.5	52.6	47.9	59.8	62.7	54.8
7b	10.8	12.3	10.1	15.5	16.7	13.2
7c	12.6	13.9	11.9	16.8	18.1	15.1
7d	16.5	17.7	15.6	19.7	20.5	19.1
7e	9.4	10.7	8.5	13.9	15.4	11.3
7f	43.8	45.2	42.7	52.5	54.8	47.4
7g	37.5	39.1	36.6	44.9	46.6	42.8
7h	8.1	9.5	6.9	13.4	14.2	10.4
7i	7.5	8.8	6.3	12.7	13.5	9.7
7j	19.4	20.8	18.3	22.9	23.8	22.3
7k	29.7	30.8	28.8	32.7	33.9	34.7
7l	23.6	24.7	22.7	26.8	27.7	26.8
Streptomycin	5.7	6.3	5.2	10.9	11.1	7.9

TABLE-4
ANTIFUNGAL ACTIVITY DATA OF SYNTHESISED BENZOTHIAZOLE-FUSED ANALOGUES (**7a-l**)

Compound	MIC values in 100 µg/mL (Minimum inhibitory concentration)			
	C. albicans	*A. fumigatus*	*T. rubrum*	*T. mentagrophytes*
7a	72.6	65.7	67.6	70.7
7b	17.4	12.3	13.6	16.7
7c	25.7	19.8	23.6	24.1
7d	40.2	33.6	37.1	39.1
7e	28.1	22.6	24.5	25.3
7f	66.5	53.5	61.5	63.6
7g	52.4	41.8	46.2	48.7
7h	14.9	10.1	12.7	14.1
7i	13.5	8.9	11.7	12.6
7j	32.3	26.5	28.6	29.2
7k	37.4	30.8	33.4	35.5
7l	58.7	46.3	55.3	56.1
Amphotericin B	11.8	7.1	9.5	10.6

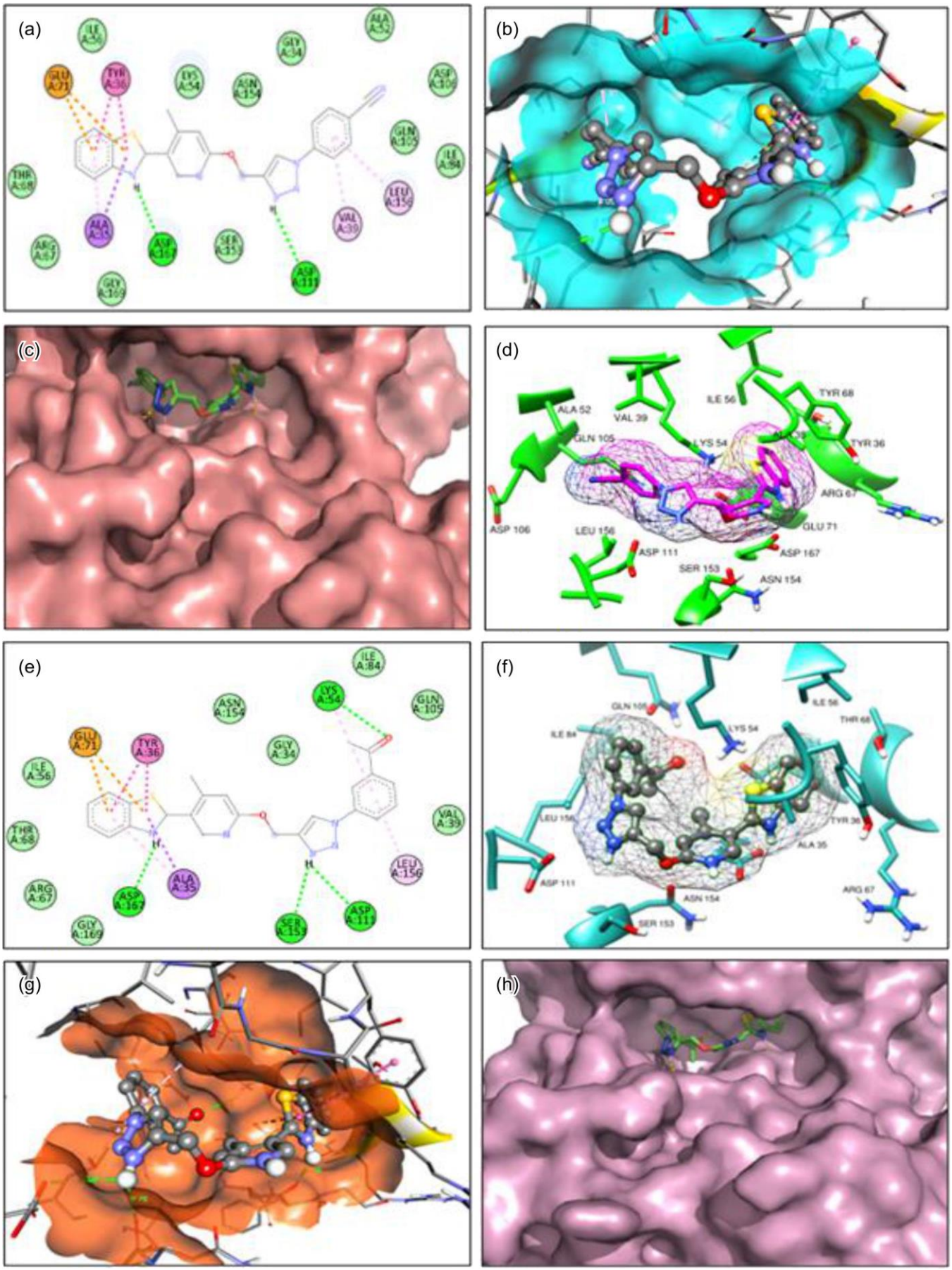
newly synthesized benzothiazole-fused derivatives (**7a-l**) and the standard drug doxorubicin against ERK2 (extracellular signal-regulated kinase 2; PDB ID: 4ZXT). ERK2 plays a crucial role in regulating signal transduction pathways associated with cell proliferation, differentiation and survival through modulation of nuclear gene expression [37]. Moreover, dysregulation of ERK2 is strongly associated with cancer progression, making it an important molecular target for anticancer drug development [38].

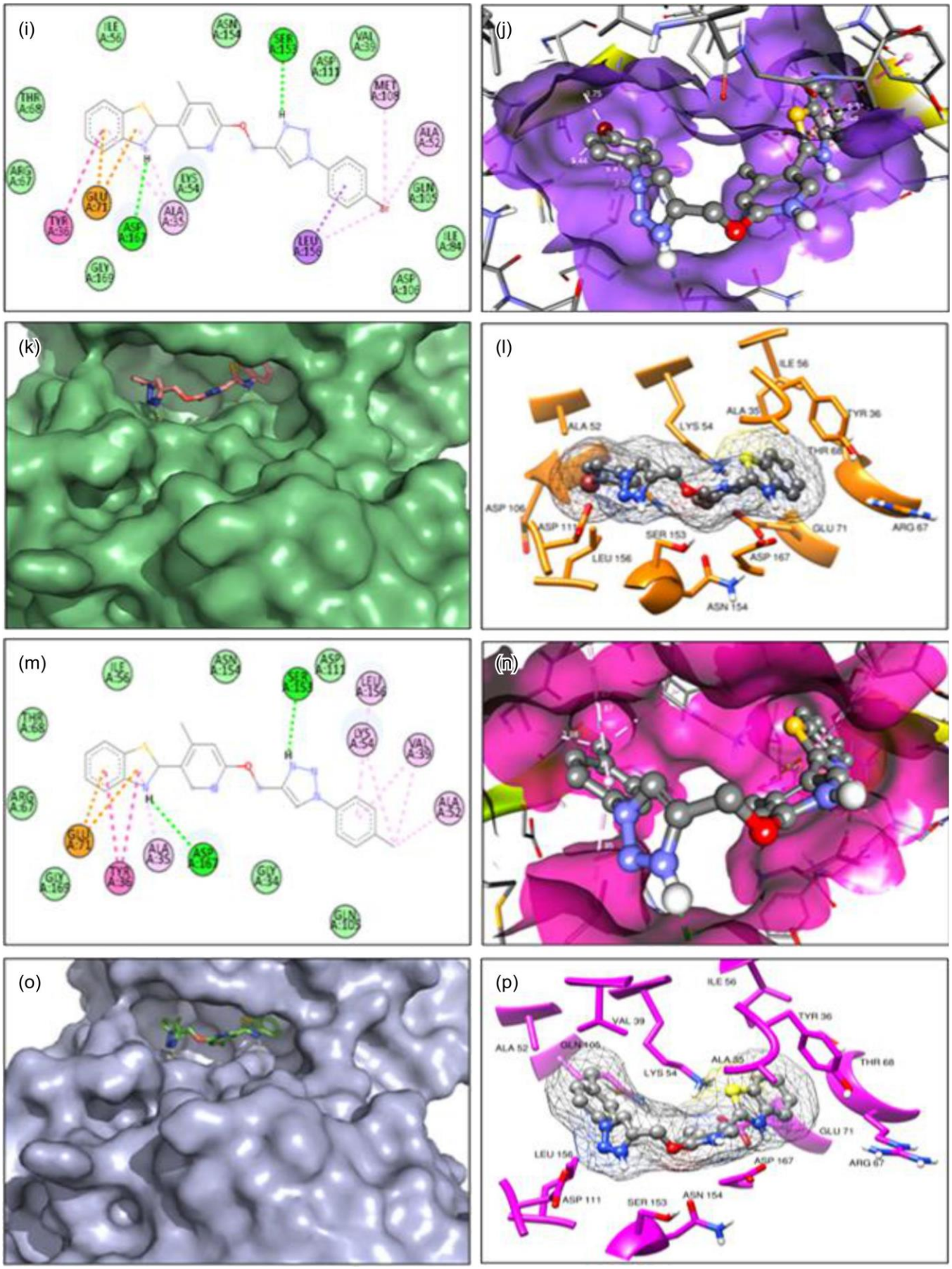
The calculated binding energies of compounds **7a-l** ranged from -8.3 to -9.0 kcal/mol, which were comparable to or higher than that of doxorubicin (-8.6 kcal/mol). Among the synthesised derivatives, compounds **7e**, **7f**, **7k** and **7l** demonstrated the highest binding affinities with docking scores of -8.9, -9.0, -8.9 and -8.9 kcal/mol, respectively. The enhanced binding affinity of these compounds may be attributed to favourable interactions within the active site of ERK2 including conventional hydrogen bonding, C–H bonding, π-σ, π- anion, π-cation, π-alkyl and van der Waals interactions (Fig. 1).

The docking results suggest that the synthesized benzothiazole-triazole hybrids possess promising binding potential toward the ERK2 receptor. However, the molecular docking primarily provides a theoretical prediction of ligand–protein interactions and binding affinity and therefore cannot independently confirm biological efficacy. The observed cytotoxic activity is influenced by multiple pharmacokinetic and biochemical factors, including cellular permeability, metabolic stability, bioavailability and possible off-target interactions.

Conclusion

A new series of benzothiazole-fused analogues (**7a-l**) was successfully synthesised utilising Cu(I)-catalysed click chemistry and the structures of intermediates and final compounds were validated using a variety of spectroscopic methods. The MTT assay was used to assess the *in vitro* anticancer activity against the MCF-7, PC-3 and HeLa cells. Compounds **7b**, **7j** and **7k** showed cytotoxic effects similar to the conventional medication. Benzothiazole-1,2,3-triazole hybrids exhibited good antibacterial action. Compounds **7i**, **7h**, **7e**, **7b** and **7c** shown outstanding antibacterial and considerable antifungal properties, making them intriguing applicants for additional studies. Molecular docking experiments against ERK2 indicated favourable binding energies, particularly for compounds **7e**, **7f**, **7k** and **7l**, which are supported by important intermolecular interactions.


(a)
(b)
(c)
(d)
ILE 56
TYR 68
ALA 52
VAL 39
GLN 105
LYS 54
TYR 36
ARG 67
ASP 106
LEU 156
GLU 71
ASP 111
ASP 167
SER 153
ASN 154
(e)
(f)
ILE 84
LYS 54
GLN 105
ASN 154
GLU 71
TYR 36
GLY 34
ILE 56
THR 68
VAL 39
LEU 156
ARG 67
ALA 35
ASP 167
ASP 111
SER 153
GLY 169
(g)
(h)


(i)
(j)
(k)
(l)
ILE 56
ALA 52
LYS 54
ALA 35
TYR 36
THR 68
ASP 106
ASP 111
SER 153
GLU 71
ARG 67
LEU 156
ASP 167
ASN 154
(m)
(n)
(o)
(p)
ILE 56
VAL 39
TYR 36
ALA 52
GLN 105
ALA 85
LYS 54
THR 68
GLU 71
LEU 156
ASP 167
ARG 67
ASP 111
SER 153
ASN 154

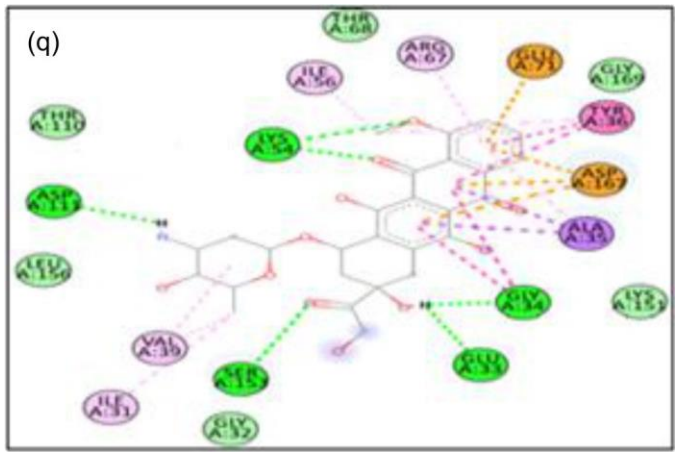


Fig. 1. Molecular docking interactions of doxorubicin and compounds **7e**, **7f**, **7k** and **7l** with ERK2 (PDB ID: 4ZXT): (a-d) 2D, 3D, binding pocket and residue interactions of **7e**; (e-h) corresponding interactions of **7f**; (i-l) corresponding interactions of **7k**; (m-p) corresponding interactions of **7l** with ERK2 and (q) doxorubicin 2D interaction

ACKNOWLEDGEMENTS

The authors are thankful to the University Grants Commission (UGC), for providing funding facility as UGC-JRF and SRF. The authors also express their gratitude to Head, Department of chemistry, Osmania University, Hyderabad for providing research facilities. Thanks are also due to CFRD analytical team for providing spectral analytical facilities.

CONFLICT OF INTEREST

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

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

REFERENCES

1. D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.*, **71**, 30 (2017); https://doi.org/10.1016/j.bioorg.2017.01.010
2. B. Schulze and U.S. Schubert, *Chem. Soc. Rev.*, **43**, 2522 (2014); https://doi.org/10.1039/c3cs60386e
3. L. Liang and D. Astruc, *Coord. Chem. Rev.*, **255**, 2933 (2011); https://doi.org/10.1016/j.ccr.2011.06.028
4. X. Wang, B. Huang, X. Liu and P. Zhan, *Drug Discov. Today*, **21**, 118 (2016); https://doi.org/10.1016/j.drudis.2015.08.004
5. M. Meldal and C.W. Tornøe, *Chem. Rev.*, **108**, 2952 (2008); https://doi.org/10.1021/cr0783479
6. S.G. Agalave, S.R. Maujan and V.S. Pore, *Chem. Asian J.*, **6**, 2696 (2011); https://doi.org/10.1002/asia.201100432
7. M.C. Van Zandt, M.L. Jones, D.E. Gunn, L.S. Geraci, J.H. Jones, D.R. Sawicki, J. Sredy, J.L. Jacot, A.T. DiCioccio, T. Petrova, A. Mitschler and A.D. Podjarny, *J. Med. Chem.*, **48**, 3141 (2005); https://doi.org/10.1021/jm0492094
8. M.M. Butler, J.D. Williams, N.P. Peet, D.T. Moir, R.G. Panchal, S. Bavari, D.L. Shinabarger and T.L. Bowlin, *Antimicrob. Agents Chemother.*, **54**, 3974 (2010); https://doi.org/10.1128/AAC.00484-10
9. M. Giampieri, A. Balbi, M. Mazzei, L.P. Colla, C. Ibba and R. Loddo, *Antiviral Res.*, **83**, 179 (2009); https://doi.org/10.1016/j.antiviral.2009.05.001
10. P.A. Grieco and M.D. Kaufman, *J. Org. Chem.*, **64**, 7586 (1999); https://doi.org/10.1021/jo9909960
11. H. Hagiwara, T. Choshi, H. Fujimoto, E. Sugino and S. Hibino, *Tetrahedron*, **56**, 5807 (2000); https://doi.org/10.1016/S0040-4020(00)00543-3
12. B. Tan, G.H. Torres and C.F. Barbas, *J. Am. Chem. Soc.*, **133**, 12354 (2011); https://doi.org/10.1021/ja203812h
13. A.J. Kochanowska-Karamyan and M.T. Hamann, *Chem. Rev.*, **110**, 4489 (2010); https://doi.org/10.1021/cr900211p
14. Y. Xu, R. Chen, Y. Liu, Y. Wang and W. Zheng, *J. Anal. Appl. Pyrol.*, **195**, 107701 (2026); https://doi.org/10.1016/j.jaap.2026.107701
15. A.A. Al-Karmalawy, M.E. Eissa, N.A. Ashour, T.A. Yousef, A.O. Al Khatib and S.S. Hawase, *RSC Adv.*, **15**, 36441 (2025); https://doi.org/10.1039/D5RA05472A
16. H.-Y. Min and H.-Y. Lee, *Exp. Mol. Med.*, **54**, 1670 (2022); https://doi.org/10.1038/s12276-022-00864-3
17. D. Dheer, V. Singh and R. Shankar, *Bioorg. Chem.*, **71**, 30 (2017); https://doi.org/10.1016/j.bioorg.2017.01.010
18. D.F. Taber and P.K. Tirunahari, *Tetrahedron*, **67**, 7195 (2011); https://doi.org/10.1016/j.tet.2011.06.040
19. H. Wu, J. Ge and S.Q. Yao, *Angew. Chem. Int. Ed.*, **49**, 6528 (2010); https://doi.org/10.1002/anie.201003257
20. R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968); https://doi.org/10.1021/jo01270a024
21. V. Rostovtsev, L.G. Green, V.V. Fokin and K.B. Sharpless, *Angew. Chem.*, **114**, 2708 (2002); https://doi.org/10.1002/1521-3757(20020715)114:14<2708::AID-ANGE2708>3.0.CO; 2-0
22. A.R. Katritzky, X.F. Lan, J.Z. Yang and O.V. Denisko, *Chem. Rev.*, **98**, 409 (1998); https://doi.org/10.1021/cr941170v
23. S. Chuprakov, S.W. Kwok, L. Zhang, L. Lercher and V.V. Fokin, *J. Am. Chem. Soc.*, **131**, 18034 (2009); https://doi.org/10.1021/ja908075u
24. N. Grimster, L. Zhang and V.V. Fokin, *J. Am. Chem. Soc.*, **132**, 2510 (2010); https://doi.org/10.1021/ja910187s
25. A.R. Katritzky and S. Rachwal, *Chem. Rev.*, **110**, 1564 (2010); https://doi.org/10.1021/cr900204u
26. Z. Xu, S.-J. Zhao, and Y. Liu, *Eur. J. Med. Chem.*, **183**, 111700 (2019); https://doi.org/10.1016/j.ejmech.2019.111700
27. M. Kurum, K. Sasaki, H. Takata and T. Nakayama, *Heterocycles*, **12**, 2809 (2000).

28. G. Mitchell and C.W. Rees, *J. Chem. Soc., Perkin Trans. 1*, **1**, 413 (1987); https://doi.org/10.1039/p19870000413
29. B. Prasad, M. Phanindrudu, D.K. Tiwari and A. Kamal, *J. Org. Chem.*, **84**, 12334 (2019); https://doi.org/10.1021/acs.joc.9b01534
30. H.G. Bonacorso, F.M. Libero, G.M. Dal Forno, E.P. Pittaluga, L.M. Porte, M.A. Martins and N. Zanatta, *Tetrahedron Lett.*, **56**, 5190 (2015); https://doi.org/10.1016/j.tetlet.2015.07.035
31. A. Ali, A.G. Correa, D. Alves, J. Zukerma-Schpector, B. Westermann, M.A.B. Ferreira and M.W. Paixao, *Chem. Commun.*, **50**, 11926 (2014); https://doi.org/10.1039/C4CC04678A
32. S.S. Van Berkel, S. Brauch, L. Gabriel, M. Henze, S. Stark, D. Vasilev and L.A. Westermann, *Angew. Chem. Int. Ed.*, **51**, 5343 (2012); https://doi.org/10.1002/anie.201108850
33. A. Kolarovic, M. Schniurch and M.D. Mihovilovic, *J. Org. Chem.*, **76**, 2613 (2011); https://doi.org/10.1021/jo1024927
34. P.R. Clark, G.D. Williams, J.F. Hayes and N.C.O. Tankinson, *Angew. Chem. Int. Ed.*, **58**, 6391 (2019); https://doi.org/10.1002/anie.201900095
35. S. Mirshafiee, A. Salamatmanesh and A. Heydari, *Appl. Organomet. Chem.*, **35**, e6255 (2021); https://doi.org/10.1002/aoc.6255
36. M. Wan, L. Zhang, Y. Chen, Q. Li, W. Fan, Q. Xue, F. Yan and W. Song, *Front. Oncol.*, **9**, 274 (2019); https://doi.org/10.3389/fonc.2019.00274
37. C. Frémin and S. Meloche, *J. Hematol. Oncol.*, **3**, 8 (2010); https://doi.org/10.1186/1756-8722-3-8
38. E. Lavoie, H. Gagnons and M. Therrien, *Nature Rev. Mol. Cell Biol.*, **21**, 607 (2020); https://doi.org/10.1038/s41580-020-0255-7