# A Click-Chemistry Approach to New, Potentially Substituted Chemical Structure, Synthesis, And In Vitro Antimicrobial, Cytotoxic, And Antifungal Activity of Novel Chromene Derivatives

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**Abstract:** A group of chromene derivatives, labeled as 4a-c, were produced by a three-step process using sodium carbonate as a catalyst. The experiment used a solvent mixture consisting of 96% ethanol and water, with a volume ratio of 1:5. A successful reaction between the corresponding hydroxyl chromenes derivatives and propargyl bromide resulted in the propargyl ether compounds **5a-c**, which are derived from chromene-3-carbonitriles. 4H-chromene-chlorophenyl conjugates **7a-c** were produced by 1H-1,2,3-triazole-tethered click chemistry with propargyl ethers **5a-c** and 1-azido-2-chlorobenzene. Copper ions were the most effective catalysts for these chemical reactions. The yields of 1H-1,2,3-triazole varied between 75% and 80%. The antimicrobial activity of all three triazoles (**a-c**) was studied in vitro. In the study conducted by MCC in 2010, four compounds were found to be effective against B. subtilis, four against S. aureus, four against P. aeruginosa, and five against E. coli.

**Keywords:** Propargyl ether, Click chemistry, Antibacterial, Antifungal, Cytotoxicity.

## INTRODUCTION:

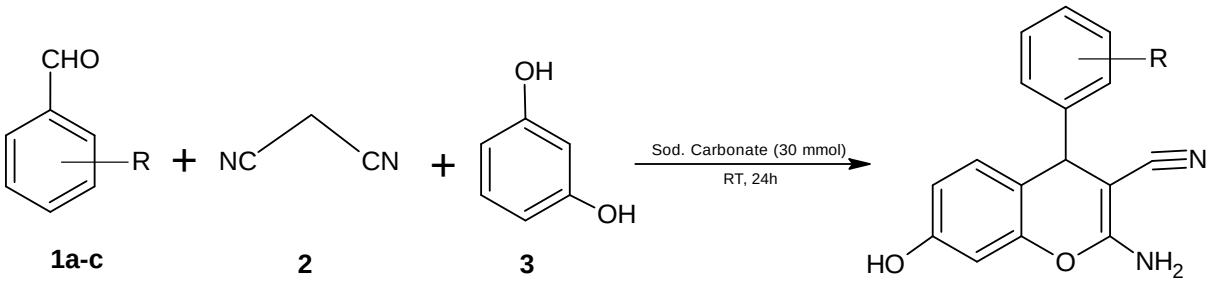
The inherent conveniences and multiple benefits of multi-component coupling reactions (MCRs) make them highly attractive in the field of organic synthesis. In these reactions, three or more initial substances undergo a chemical transformation, resulting in the formation of a product that clearly shows a significant or complete contribution of atoms from the starting materials. In a multicomponent reaction (MCR), a product is synthesized by assembling components or members through a series of sequential chemical reactions.
The remarkable biological activity of 4H-chromene derivatives and compounds containing a chromene moiety make their use interesting in chemical synthesis. These chemicals act as important pharmacophores, linked to a wide range of pharmacological activities. The substances have been identified to possess antibacterial properties [1,2], as well as hypolipidemic [3], anti-inflammatory [4,5], anti-proliferative [6], antioxidant [7,8], anticoagulant [9,10], antileishmanial [11,12], antitumor [6,13], cytotoxic [2,14], and anticancer activities.
Several heterocyclic, such as 1H-1,2,3-triazole, 4H-chromene, and 4H-pyran, have recently demonstrated the ability to elicit interesting biological effects when combined [15,16]. Using appropriate 1-alkynes, click chemistry allows for the synthesis of the aromatic ring that is heterocyclic known as the ring of 1H-1,2,3-triazole. For the implementation of click chemistry via CuAAC (Copper(I)-catalyzed Alkyne-Azide Cycloaddition), the synthesis of 1-alkynes and organic azides is necessary.
These 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles can be converted to 2-amino 4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles with methoxy as the substituent, according to this study's synthetic approach. We also looked at the antimicrobial screening results of one of the products in this series.

## EXPERIMENTAL:

The provided melting points are unprocessed results obtained from an open capillary method experiment conducted on the Myra melting point apparatus. Infrared spectra of the KBr disc were captured using the Brucker FT-IR Spectrometer. The Bruker Avance II HD NMR 500MHz, employing TMS as the internal standard, was utilized for acquiring $^1$H NMR spectra in DMSO-d6. ESI mass spectra in methanol were acquired using the LC-MS Agilent (ThermoScientific). Ultra-pure chemical reagents were supplied by the S. d. Fine Chemical Company in India. All ingredients for organic synthesis were of reagent quality. aluminum sheets of Silica gel 60 WF254S from Merck, India were used for analytical thin-layer chromatography (TLC), with UV light used for visualization.

## THE CHROMENE DERIVATIVES (4A-C): A SYNTHETIC PROCEDURE:

An appropriate mixture of 25 mL of water, 10 mmol of substituted methoxy benzaldehyde **1a-c**, 10 mmol of malononitrile **2**, and 10 mmol of resorcinol **3** was combined with 30 mmol of sodium carbonate in 25 mL of water, and 1 mL of 96% ethanol. Maintaining the reaction mixture at 25 °C (monitored by TLC), it was stirred for 24 hours. The resulting compounds **4a-c** were obtained after filtration with suction and washing with water to pH 7.




**1a-c** **2** **3** **4a-c**

Where **a** = 2-methoxy, **b** = 3-methoxy, **c** = 4-methoxy

**Figure 1:** 2-Amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitrile synthesis **(4a-c)**

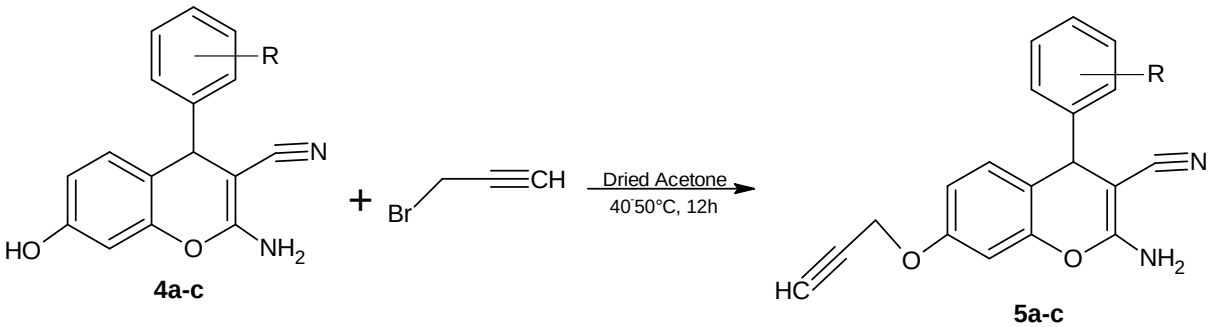
**2-amino-7-hydroxy-4-(2-methoxyphenyl)-4H-1-benzopyran-3-carbonitrile (4a):**
White crystals. From 2-methoxybenzaldehyde **1a** (20 mmol), malononitrile (MN) **2** (20 mmol), and resorcinol (RS) **3** (20 mmol). M. p. 197 °C; FT-IR ($cm^{-1}$): 3322, 2953, 202, 1595/1441, 1347/1312; $^1H$ NMR (δ) (*s*, 1H, -OH), 7.205 (*ddd*, *J* = 8.20, 7.41, 1.27 Hz, 1H, Ar-H), 6.971 (*s*, 2H, $-NH_2$), 6.827-6.904 (*m*, 4H, Ar-H), 6.445 (*dd*, *J* = 7.93, 2.68 Hz, 1H, Ar-H), 6.376 (*dd*, *J* = 2.70, 0.43 Hz, 1H, Ar-H), 4.983 (*s*, 1H), 3.791 (*s*, 3H, $-OCH_3$). ESI/HRMS: $C_{17}H_{14}N_2O_3$, m/z 293.1446 $[M + H]^+$; C, 69.33; H, 4.78; N, 9.53%; Found: C, 69.28; H, 4.73; N, 9.35%.

**2-amino-7-hydroxy-4-(3-methoxyphenyl)-4H-1-benzopyran-3-carbonitrile (4b):**
White crystals. From 3-methoxybenzaldehyde **1b** (20 mmol), MN **2** (20 mmol), and RS **3** (20 mmol). M. p. 192 °C; IR ($cm^{-1}$): 3300, 2979, 2185, 1598/1435, 1392/1303; $^1H$ NMR (δ): 10.072 (*s*, 1H, -OH), 7.203-7.243 (*dt*, *J* = 7.88, 2.58 Hz, 1H, Ar-H), 6.384-6.481 (*s*, 2H, $-NH_2$), 6.716-6.868 (*m*, 5H, Ar-H), 4.580 (*s*, 1H, Ar-H), 3.722 (*s*, 3H, $-OCH_3$). ESI/HRMS: $C_{17}H_{14}N_2O_3$, m/z 295.2546 $[M + H]^+$; C, 69.33; H, 4.78; N, 9.53%; found: C, 69.22; H, 4.75; N, 9.50%.

**2-amino-7-hydroxy-4-(3-methoxyphenyl)-4H-1-benzopyran-3-carbonitrile (4c):**
White crystals. From 3-methoxybenzaldehyde **1b** (20 mmol), MN **2** (20 mmol), and RS **3** (20 mmol). M. p. 195 °C; IR ($cm^{-1}$): 3305, 2980, 2180, 1599/1435, 1392/1303; $^1H$ NMR (δ): 10.070 (*s*, 1H, -OH), 7.206-7.242 (*dt*, *J* = 7.88, 2.58 Hz, 1H, Ar-H), 6.384-6.481 (*s*, 2H, $-NH_2$), 6.716-6.868 (*m*, 5H, Ar-H), 4.580 (*s*, 1H, Ar-H), 3.722 (*s*, 3H, $-OCH_3$). ESI/HRMS: $C_{17}H_{14}N_2O_3$, M = 294.36 Da, Found: m/z 295.2546 $[M + H]^+$; C, 69.33; H, 4.78; N, 9.53%; found: C, 69.22; H, 4.75; N, 9.50%.

**METHOD FOR THE PREPARATION OF PROPARGYLOXY-CHROMENE DERIVATIVES THAT HAVE BEEN REPLACED WITH METHOXY (5A-C):**

A solution of the suitable **4a-c** was mixed with 15 mmol of dry $K_2CO_3$. in 25 mL of dried acetone, 10 mmol of each of **4a-c**. Following that, the suspension mixture was gradually supplemented with a propargyl bromide solution (5 mmol, 80 wt.% in toluene). After 12 hours of stirring, the reaction mixture was brought to a temperature of 50 □C. Finally, the solvent was allowed to evaporate under a vacuum until it reached ambient temperature. The inorganic salts ($K_2CO_3$) were dissolved by adding water to the residue. The propargyl ethers **5a-c** of **4a-c** were obtained by filtering the solid product, washing it with water, and then recrystallizing it from a combination of 1:2 (96% ethanol and toluene).




**4a-c** **5a-c**

Where **a** = 2-methoxy, **b** = methoxy, **c** = 4-methoxy

**PROCEDURE 2: METHOXY SUBSTITUTED 3-CARBONITRILES OF 2-AMINO-7-PROPARGYLOXY-4H-CHROMENE (5A-C)**

**2-amino-4-(2'-methoxyphenyl)-7-propargyloxy-4H-chromene-3-carbonitrile (5a):**
Brown crystals. From **4a** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 196 °C; IR ($cm^{-1}$): 3199, 3072, 2965, 2225, 1607/1452, 1348/1303; $^1H$ NMR (δ): 7.812-7.831 (*s*,

2H, -$NH_2$), 7.666-7.780 (*ddd*, *J* = 7.81, 0.29 Hz, 1H, Ar-H), 7.598 (*ddd*, *J* = 7.33, 7.16, 1.50 Hz, 1H, Ar-H), 7.102-7.119 (*m*, 6H, Ar-H), 7.049-7.068 (*dd*, *J* = 2.43, 0.44 Hz, 2H, Ar-H), 5.290 (*s*, 2H, Ar-H), 4.819 (*s*, 1H), 3.183 (*s*, 3H, -$OCH_3$), 1.193 (*s,* 1H, CH). ESI/HRMS: $C_{20}H_{16}N_2O_3$, m/z 330.7789 $[M + H]^+$; C, 72.28; H, 4.85; N, 8.43%; found: C, 71.96; H, 4.77; N, 8.40%.

**2-amino-4-(3'-methoxyphenyl)-7-propargyloxy-4H-chromene-3-carbonitrile (5b):**

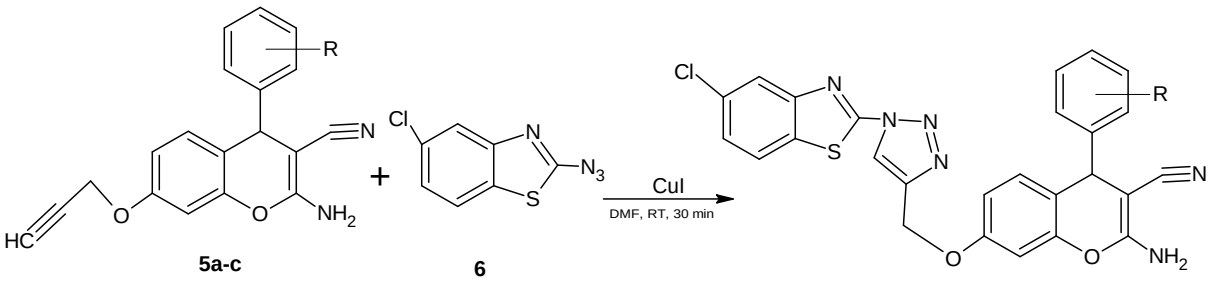
Brown crystals. From **4b** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 192 °C; IR ($cm^{-1}$): 3112, 2774, 2225, 1601/1480, 1340, 1282, 1073, 740; $^1$H NMR (δ): 7.819-7.833 (*s*, 2H, -$NH_2$), 7.615-7.776 (*dd*, *J* = 7.77, 0.32 Hz, 1H, Ar-H), 7.602 (*ddd*, *J* = 7.31, 7.10, 1.45 Hz, 1H, Ar-H), 7.146-7.226 (*m*, 6H, Ar-H), 7.106-7.123 (*dd*, *J* = 2.39, 0.43 Hz, 2H, Ar-H), 5.302 (*s*, 2H, Ar-H), 4.888 (*s*, 1H), 3.266 (*s*, 3H, -$OCH_3$), 1.133 (*s,* 1H, CH). ESI/HRMS: $C_{20}H_{16}N_2O_3$, m/z 331.2357 $[M + H]^+$; C, 72.28; H, 4.85; N, 8.43%; found: C, 72.03; H, 4.81; N, 8.42%.

**2-amino-4-(2'-fluorophenyl)-7-propargyloxy-4H-chromene-3-carbonitrile (5c):**

Brown crystals. From **4c** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 189 °C; IR ($cm^{-1}$): 3178, 3110, 2963, 2227, 1582/1451, 1301, 1223, 1070, 741; $^1$H NMR, δ (ppm): 7.802-7.822 (*s*, 2H, -$NH_2$), 7.680-7.730 (*dd*, *J* = 7.88, 0.32 Hz, 2H, Ar-H), 7.620 (*ddd*, *J* = 7.99, 7.33, 1.51 Hz, 1H, Ar-H), 7.091-7.113 (*m*, 6H, Ar-H), 7.049-7.088 (*dd*, *J* = 2.39, 0.43 Hz, 2H, Ar-H), 5.291 (*s*, 2H, -$CH_2$-), 4.808 (*s*, 1H), 1.206 (*s,* 1H, CH). ESI/HRMS: $C_{19}H_{13}N_2O_2F$, m/z 324.1477 $[M + H]^+$; C, 71.24; H, 4.09; N, 8.75%; found: C, 70.88; H, 4.01; N, 8.69%.

**Method for the click chemistry of organically substituted the 2-amino7a–c) 1-azido-3-chlorobenzene with -4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles:**

To prepare the reaction mixture, 25 mL of N, N-dimethylformamide (DMF) was added to 10-mmol of **5a-c**, 5-mmol of CuI, and 10-mmol of 1-azido-3-chlorobenzene **6**. To help the reactants dissolve, gentle stirring was used. After that, the stirred reaction mixture received 50 mL of distilled water. A uniform shade of greenish-yellow was achieved. Subsequently, the substance was purified using filtration, washed with water, and finally crystallized with a solvent mixture of toluene and 96% ethanol in a mix of 2:1 by volume. The processes described above resulted in the solid, greenish-yellow compounds **7a–c**.




Where **a** = 2-methoxy, **b** = methoxy, **c** = 4-methoxy

**Schemes 3:** Methoxy Substituted the carbonitriles of 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-with 1-azido-2-chlorobenzene **(7a-c)**

**2-Amino-4-(2'-methoxyphenyl)-7-((5-chloro-1,3-benzothiazole)-1H-1,2,3-triazole-4-yl)methoxy)-4H-chromene-3-carbonitrile (7a):**

Greenish yellow. From **5a** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 203 °C; IR ($cm^{-1}$): 3340, 3056, 2196, 1598/1440, 1456, 1397/1329, 1253, 1023, 752, 688; $^1$H NMR (δ): 7.758 (*s*, 2H, -$NH_2$), 7.557-7.559 (*dd*, *J* = 2.43, 0.40 Hz, 3H, Ar-H), 7.179 (*dt*, *J* = 7.93, 2.59 Hz, 1H, Ar-H), 6.868-6.906 (*ddd*, *J* = 7.92, 2.59, 0.41 Hz, 3H, Ar-H), 6.741 (*ddd*, *J* = 8.19, 2.66, 2.53 Hz, 1H, Ar-H), 6.759-6.764 (*ddt*, *J* = 8.00, 4.32, 3.20 Hz, 1H, Ar-H), 5.200 (*s*, 2H, -$CH_2$-), 5.000 (*s*, 1H), 3.775 (*s,* 3H, -$OCH_3$). ESI/HRMS: $C_{27}H_{19}N_6O_3ClS$, m/z 542.1546 $[M + H]^+$; C, 59.72; H, 5.53; N, 15.48%; found: C, 59.06; H, 5.11; N, 15.38%.

**2-Amino-4-(3'-methoxyphenyl)-7-((5-chloro-1,3-benzothiazole)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (7b):**

Greenish yellow. From **5b** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 209 °C; IR ($cm^{-1}$): 3380, 3056, 2117, 1573/1423, 1490, 1378/1312, 1262, 1195, 1021, 762, 688; $^1$H NMR, δ (ppm): 7.757 (*s*, 2H, -$NH_2$), 7.574-7.665 (*ddd*, *J* = 8.15, 7.73, 1.52 Hz, 3H, Ar-H), 7.230-7.250 (*dt*, *J* = 7.93, 2.59 Hz, 1H, Ar-H), 6.970-6.993 (*dd*, *J* = 2.44, 0.41 Hz, 1H, Ar-H), 6.774-6.780 (*ddd*, *J* = 8.22, 2.69, 2.54 Hz, 3H, Ar-H), 6.716-6.726 (*ddt*, *J* = 8.03, 4.33, 3.19 Hz, 2H, Ar-H), 5.218 (*s*, 2H, -$CH_2$-), 4.640 (*s*, 1H), 3.699 (*s,* 3H, -$OCH_3$). ESI/HRMS: $C_{27}H_{19}N_6O_3ClS$, m/z 542.1546 $[M + H]^+$; C, 59.72; H, 5.53; N, 15.48%; found: C, 59.12; H, 5.49; N, 15.33%.

**2-Amino-4-(2'-fluorophenyl)-7-((5-chloro-1,3-benzothiazole)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (7c):**

Greenish yellow. From **5c** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 209 °C; IR ($cm^{-1}$): 3311, 3053, 2201, 1595/1439, 1348, 1250, 1071, 738, 689; $^1$H NMR (δ): 7.340 (*s*, 2H, -$NH_2$), 7.549-7.620 (*ddd*, *J* = 8.10, 7.70, 1.50 Hz, 3H, Ar-H), 7.265-7.289 (*dd*, *J* = 2.52, 0.47 Hz, 1H, Ar-H), 7.182-7.552

(*ddd*, *J* = 8.29, 1.52, 0.50 Hz, 3H, Ar-H), 6.934 (*ddt*, *J* = 8.00, 4.31, 3.22 Hz, 1H, Ar-H), 6.779-6.924 (*dd*, *J* = 16.20, 8.05 Hz, 2H, -$CH_2$-), 4.920 (*d*, *J* = 7.78, 2.49 Hz, 1H, Ar-H). ESI/HRMS: $C_{27}H_{19}N_6O_3ClS$, m/z 530.1546 $[M + H]^+$; C, 58.81; H, 3.04; N, 15.83%; found: C, 57.92; H, 3.02; N, 15.73%.

**BIOLOGICAL ASSAYS:**

***In vitro* antimicrobial activity:**

In vitro, evaluation was performed on the synthesized **7a-c** to determine their antibacterial and antifungal efficacy against a variety of bacterial species, including Gram-positive and negative. The study used *B. subtilis* and *S. aureus* as Gram-positive bacteria and *E. coli* and *P. aeruginosa* as Gram-negative bacteria. As described in an earlier paper [18], the MIC approach was used to conduct the evaluations. Using Mueller-Hinton broth, micro broth dilutions were conducted [19]. A 1 mg/mL solution of the test chemicals was dissolved in dimethyl sulfoxide (DMSO). The reference medications that were used were streptomycin and vancomycin (**Table 1**). Through the process of diluting the test chemicals and standard medicines, concentrations ranging from 400 to 0.78 millimolar (mM) were produced. The ideal concentration of the inoculum in the test tray was 5 x $10^5$ CFU/mL, which was achieved by diluting it with broth media. A turbidity level comparable to a 0.5 McFarland standard was used for adjustment. All plates were left to incubate at 35°C for a full day. The concentration that inhibited growth was defined as the minimum inhibitory concentration (MIC). Experiments were conducted in triplicate, and MIC values are presented in **Table 1**.

Two fungal strains, including *S. cerevisiae* (MCC 1033) and *Candida albicans* (MCC 1439), were used to evaluate the antifungal activity of compounds **7a-b** in vitro. To prepare Sabouraud's dextrose agar (Hi-Media), the agar dilution method was used [17]. *Fluconazole* served as a reference drug. Solutions were produced at concentrations of 0.78-200 mM for each chemical and standard drug. Suspensions of each microbe were made to achieve a concentration of 10 colony-forming units per milliliter (CFU/mL), applied onto agar plates previously diluted with the substances under investigation. MICs were determined after 72 hours of incubation at 35°C [18]. Minimal inhibitory doses were determined for each drug against standard fungal strains, with experiments conducted on three separate occasions. **Table 2** presents the MIC values for the investigated substances and reference drugs.

**RESULTS AND DISCUSSION:**

The synthesis of **4a-c** was accomplished through a three-component process involving substituted methoxy benzaldehydes **1a-c**, MN **2**, and RS **3** (**Scheme 1**). Sodium carbonate was utilized as a catalyst at a concentration of 30 mmol, and the reaction proceeded at RT for 24 hours [19–21]. A co-solvent comprising 96% ethanol was employed at a volumetric ratio of 1:10, resulting in isolated yields ranging from 75 to 80%. Subsequently, the **4a-c** were subjected to a conversion process, yielding distinct substituted 7-propargyl ethers **5a-c**.

Another precursor used in click chemistry was 1-azido-3-chlorobenzene **6**, synthesized by reacting 3-chlorobenzene with sodium azide in dried DMF or acetone water [22-24]. Dried acetone served as a solvent to prevent azide group degradation by water, facilitating efficient acetone removal from the reaction mixture. This 1-azido-3-chlorobenzene **6** was successfully synthesized on a multi-gram scale.

Various catalysts have been identified for click chemistry catalysis [25]. To determine optimal conditions for the click chemistry reaction between **5a-c** and 1-azido-3-chlorobenzene **6**, a comprehensive study was conducted on the CuI catalytic conditions using compound **7a-c** and the mentioned 1-azido-3-chlorobenzene (**Scheme 3**).

For 4H-chromenes **4a-c**, the hydroxyl group was identified by an absorption band in the IR spectrum between 2928 and 2979 $cm^{-1}$, and the amino group was verified by additional absorption bands between 3300 and 3330 $cm^{-1}$. The nitrile functional group exhibited absorption at 2202-2230 $cm^{-1}$. The proton at position 4 displayed a distinctive signal at □ = 4.580-4.983 ppm in the $^1$H NMR spectra of chromenes **4a-c**. The hydroxyl group at position 7 was confirmed by a chemical shift at □ = 9.631-10.072 ppm, and the amino group at position 2 was indicated by a resonance signal at □ = 6.384-7.205 ppm.

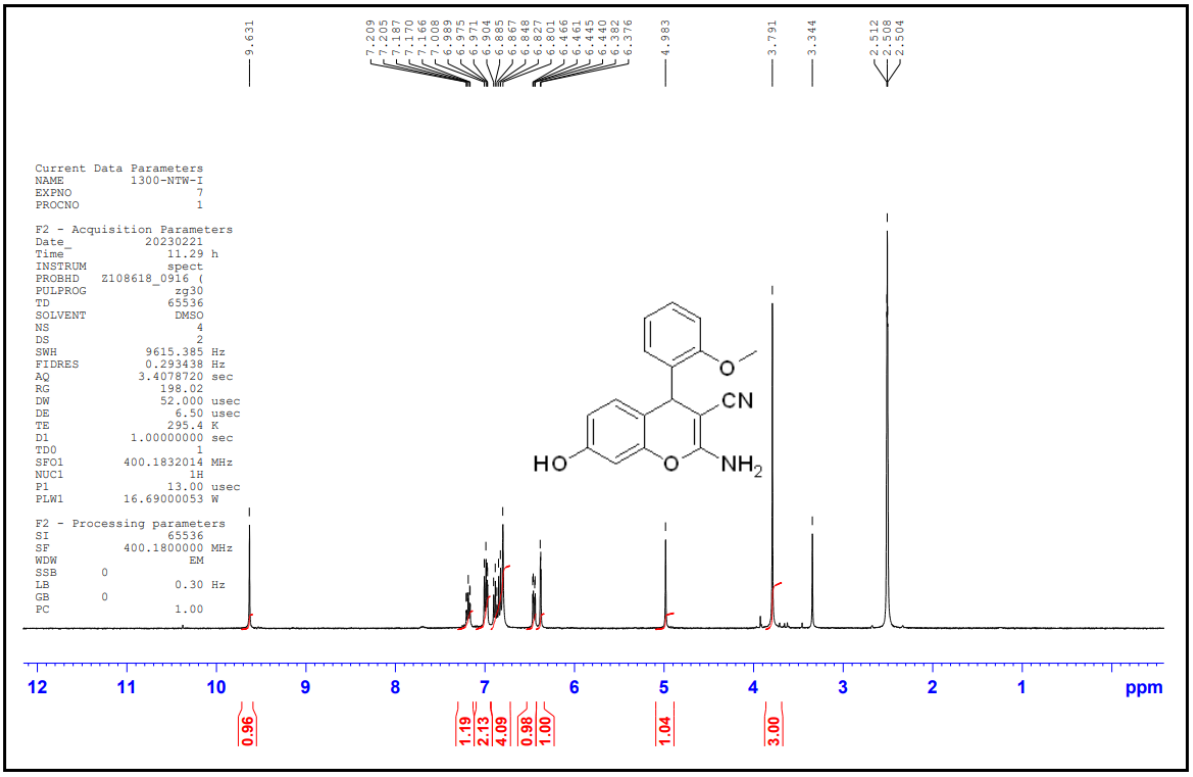



**Figure 1:** NMR spectrum of compound **4a**

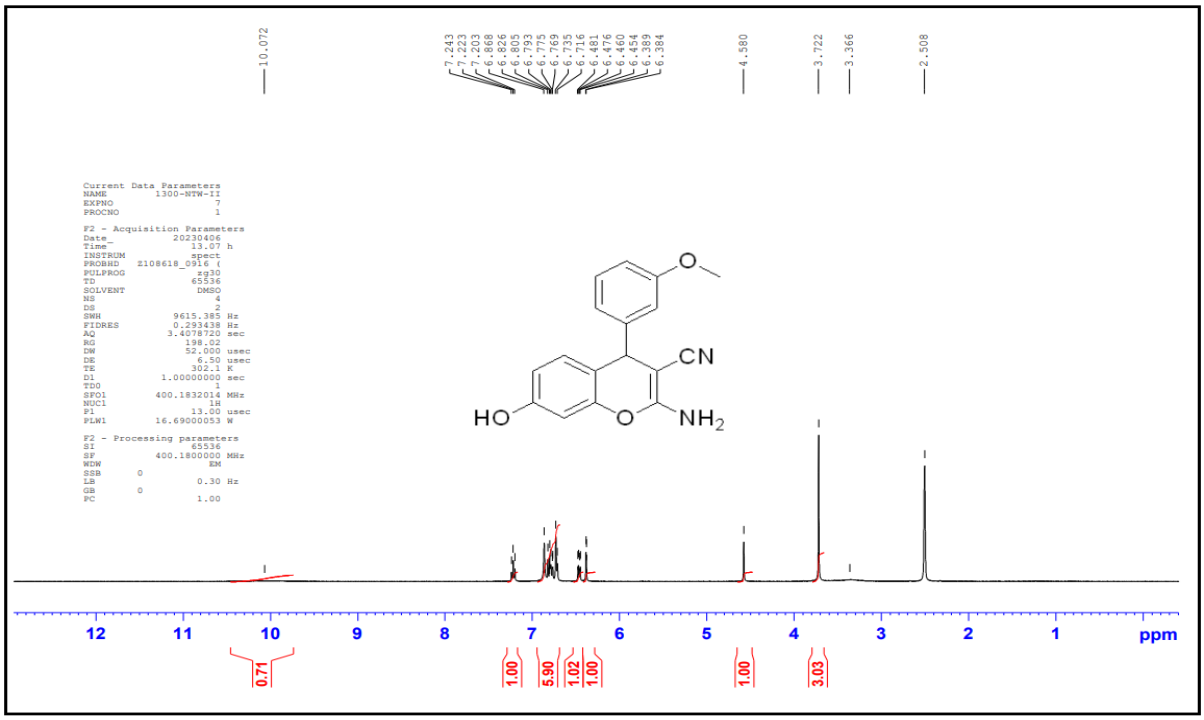



**Figure 2:** NMR spectrum of compound **4b**

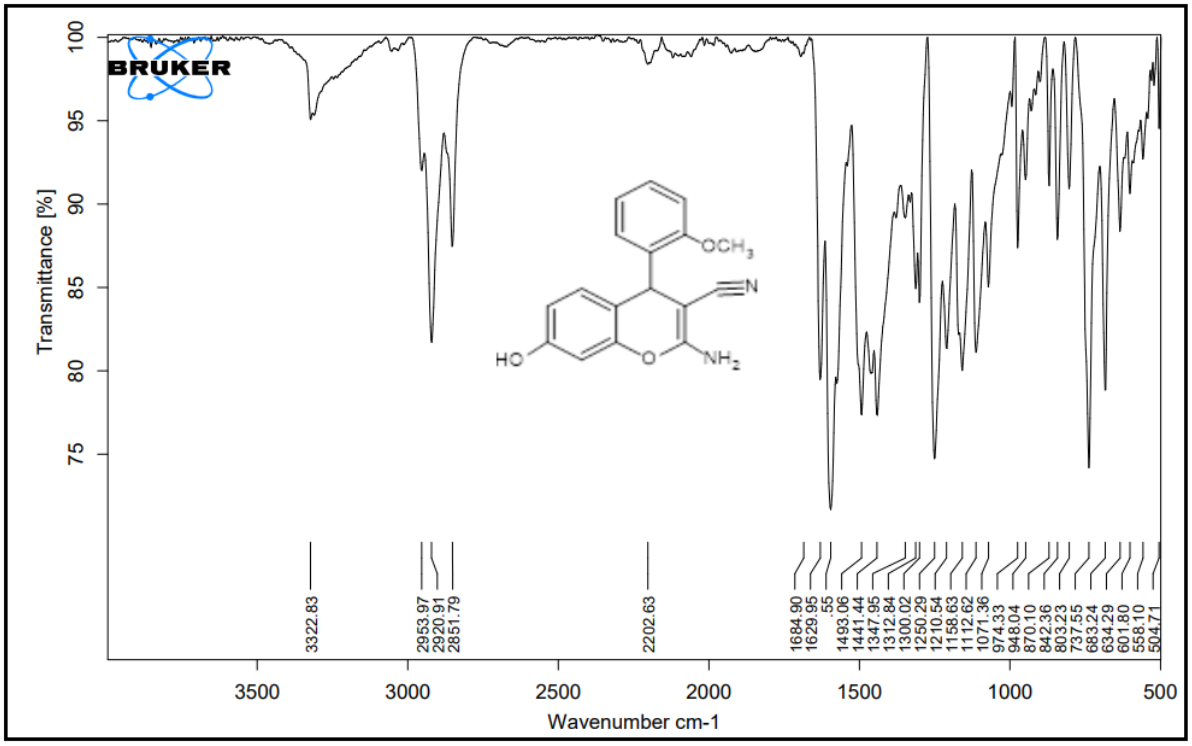



**Figure 3:** FT(IR) spectrum of compound **4a**

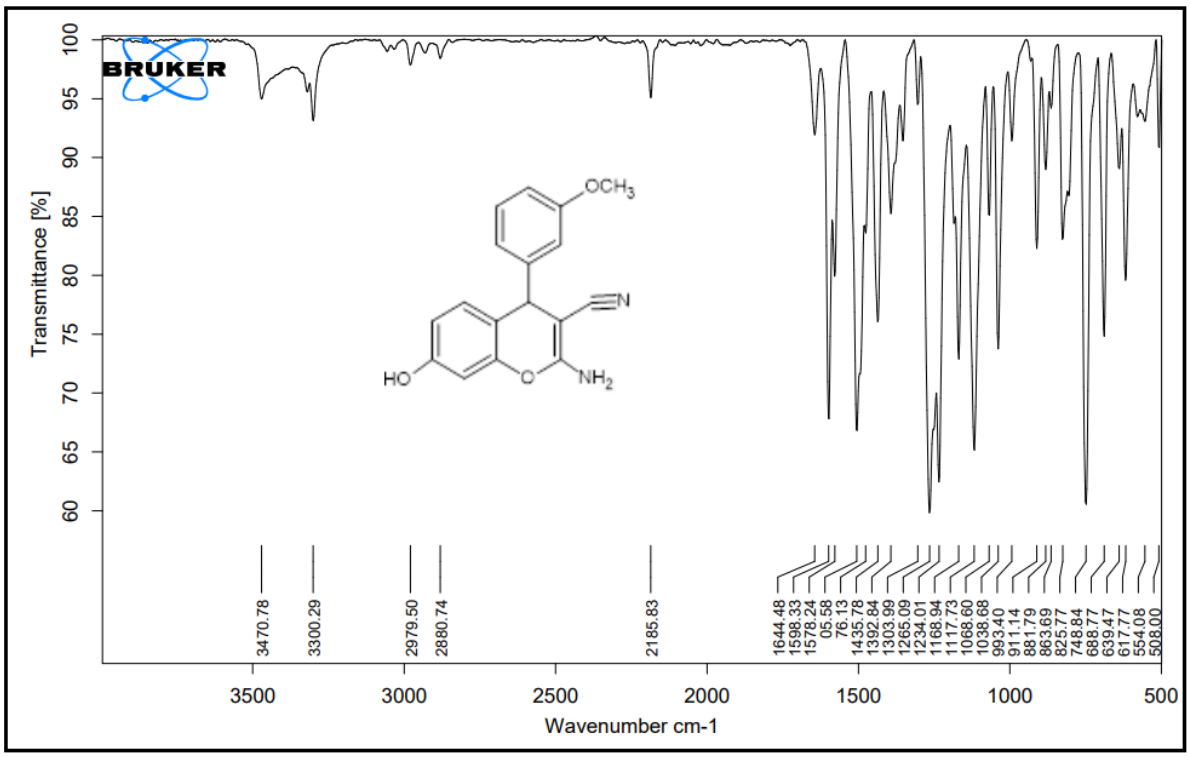



**Figure 4:** FT(IR) spectrum of compound **4b**

It was determined that **5a-c** was structurally synthesized from **4a-c** by analyzing spectral data (IR, NMR, and MS). Using infrared and nuclear magnetic resonance spectra, the acetylenic unit in the propargyl ethers' terminal triple bond was identified. In the IR spectra, the absence of absorption bands associated with the acetylene group (between 2900 and 2950 $cm^{-1}$) and the appearance of bands related to CH and CC bonds (3380-3390 $cm^{-1}$ and 2120–2100 $cm^{-1}$) indicated the presence of the acetylenic unit. The nitrile group's absorption band at 2200-2180 $cm^{-1}$ was strong. In **5a-c**, the amino group's presence was indicated by absorption bands at 3450-3440 and 3280-3200 $cm^{-1}$. Resonance signals for the amino group at position 2 and no shift in the hydroxyl group at position 7 were observed in the $^{1}H$ NMR spectra.

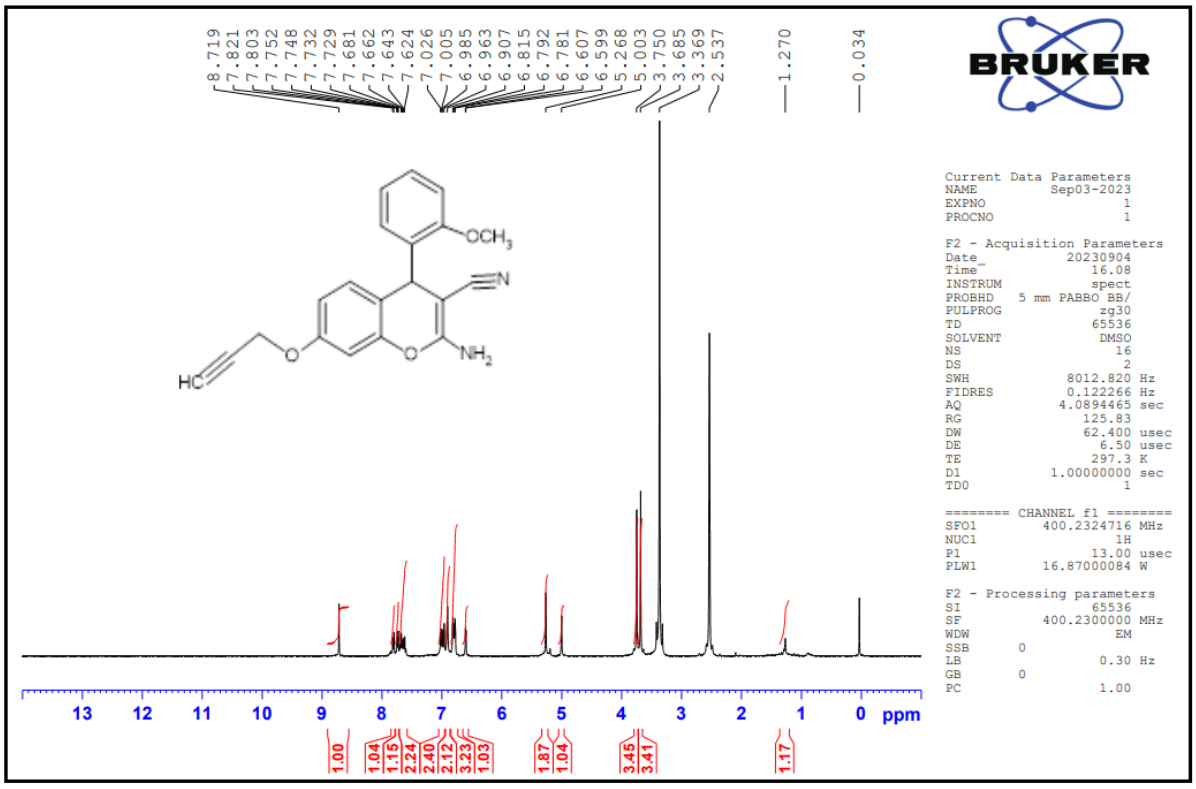



**Figure 5:** NMR spectrum of compound **5a**

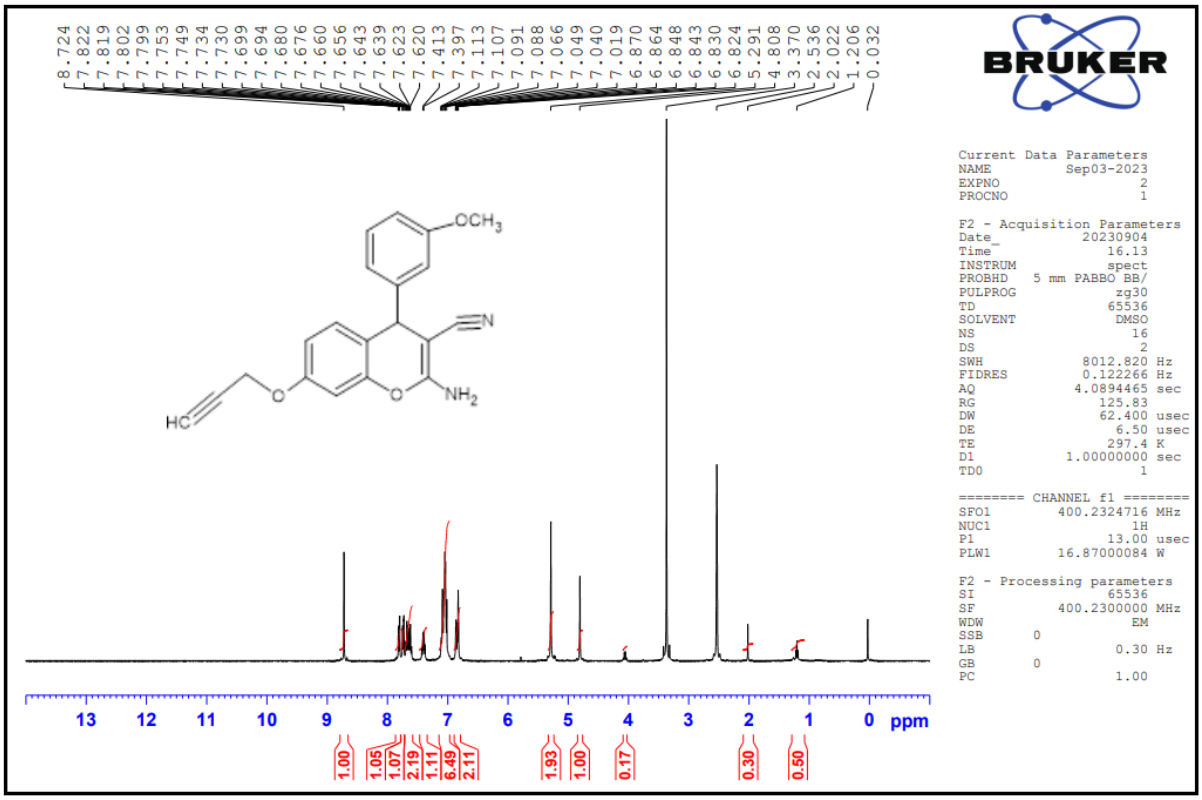



**Figure 6:** NMR spectrum of compound **5b**

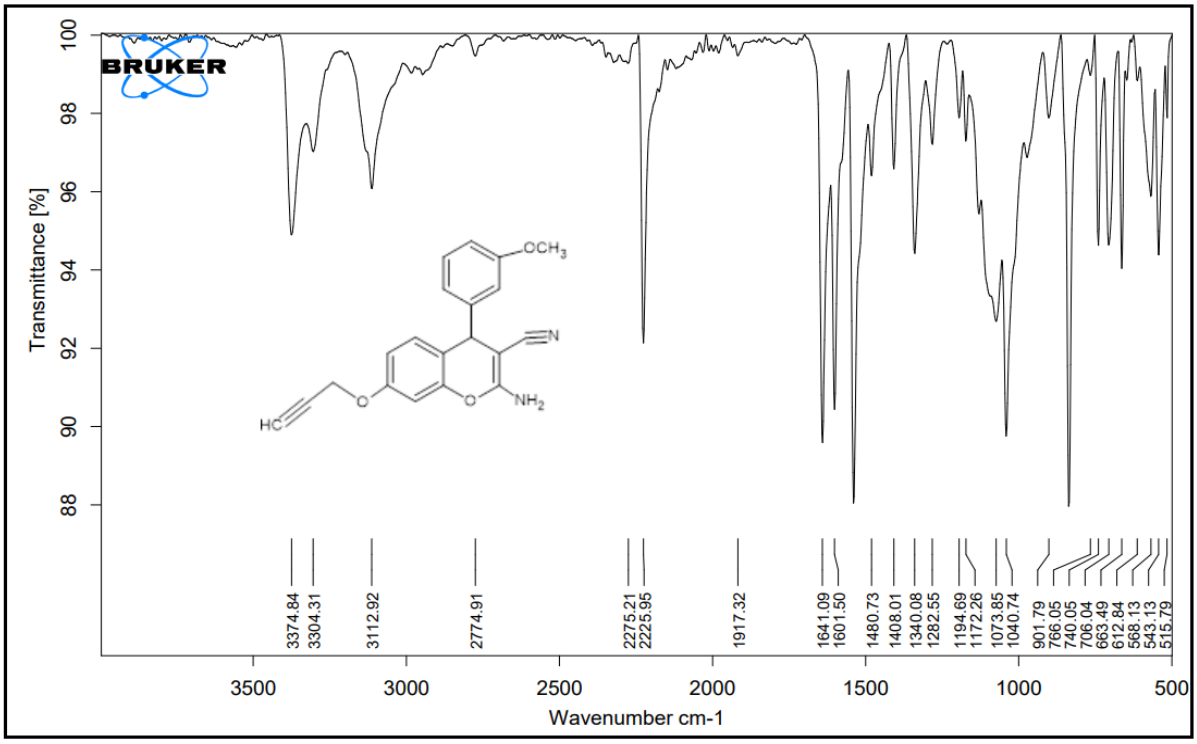



**Figure 7:** FT(IR) spectrum of compound **5a**

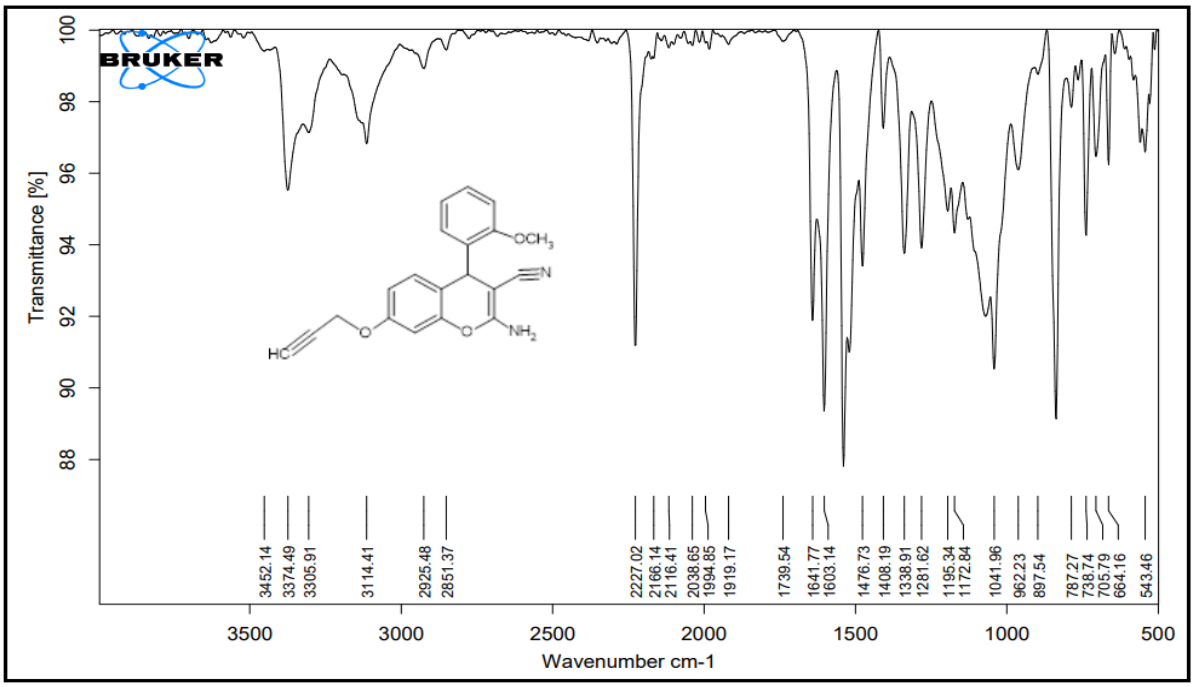



**Figure 8:** FT(IR) spectrum of compound **5b**

The presence of propargyl group signals in the $^1$H NMR spectra and an absorption band at 2225-2288 cm$^{-1}$ from the nitrile functional group confirmed a change in the original 7-hydroxy chromene derivatives. The acetylenic proton's characteristic region in the o-propargyl group was observed between  1.113 and 1.193 ppm, with a triplet signal due to interactions with two methylene protons in the propargyl chain ($J$ = 2.18–2.56 Hz). The methylene group's signal was in the range of  = 3.266-3.309 ppm (triplet, $J$ = 2.62-2.77 Hz).
Resonance signals for the chromene ring proton at position 4 were observed at  5.290-5.302 ppm (singlet), with a magnetic interaction between three protons in the benzene ring resulting in the AMX spin pattern. Proton H-5 had  7.102-7.123 ppm (doublet, $J$ = 8.00-8.12 Hz), proton H-6 had  7.220-7.598 ppm (doublet of doublets, $J$ = 0.39-0.43 and 7.8-7.9 Hz), and proton-8 had  6.60-6.76 ppm (doublet, $J$ = 1.90-2.33 Hz). Signals and absorption bands confirmed the presence of aromatic rings.
The confirmation of the structural synthesis of methoxy-substituted 5a-c with 1-azido-3-chlorobenzene **7a-c** is supported by the analysis of spectrum data, including FTIR, PMR, and MS. The investigation focused on the

identification of the acetylenic unit, the propargyl ethers of chromenes include a terminal triple bond. Infrared and nuclear magnetic resonance spectra were used to achieve this. In the infrared spectra of these ethers, a notable absence of absorption bands was seen, specifically in the area between 2900 and 2950 $cm^{-1}$, which is typically associated with the stretching vibration of the acetylene group. Concurrently, two absorption bands were seen within the spectral range of 2150–2175 $cm^{-1}$, it is caused by the N=N bond's stretching vibration. In contrast, the infrared spectra of **7a-c** exhibited two additional absorption bands within the spectral range of 3311-3380 $cm^{-1}$, indicating the existence of the amino group within these compounds. These absorption bands were also visible in the early **5a-c** infrared spectra. The presented evidence demonstrates that, in the context of 1-azido-3-chlorobenzene reactions, The absence of a chemical shift in the δ1.113-1.193 ppm (singlet, 1H) areas, which correspond to the acetylene group, was used to prove its presence.

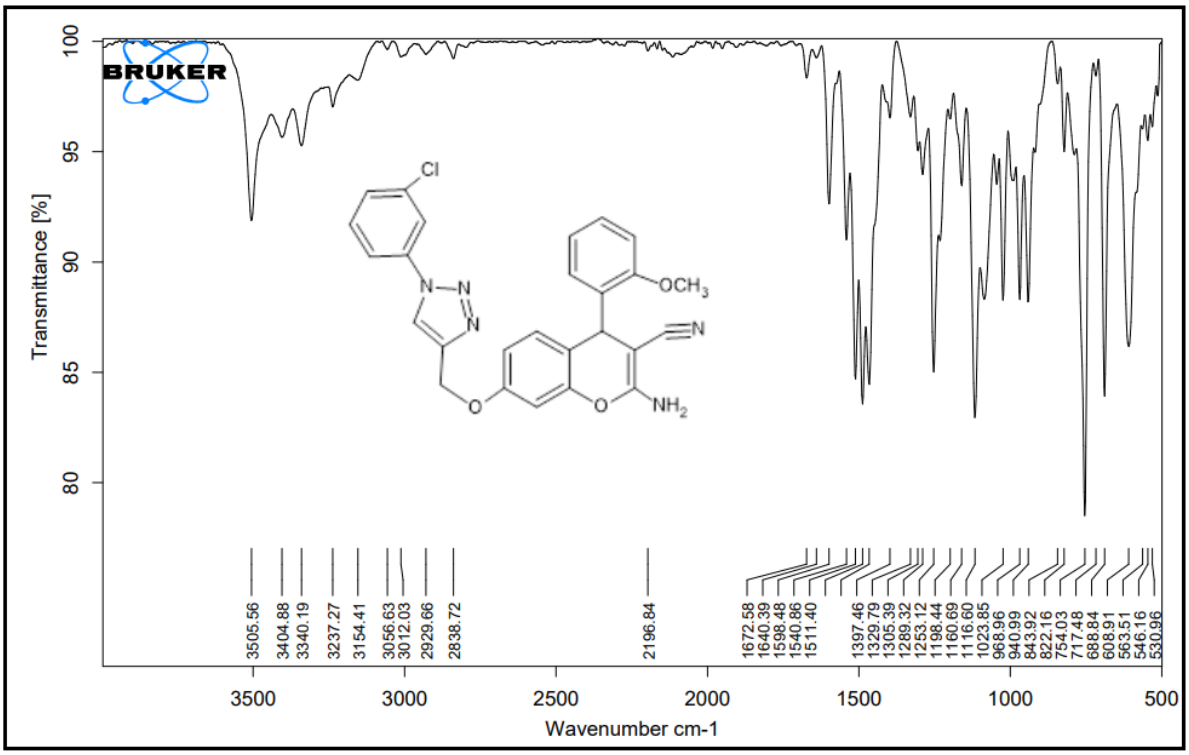



**Figure 9:** FT(IR) spectrum of compound **7a**

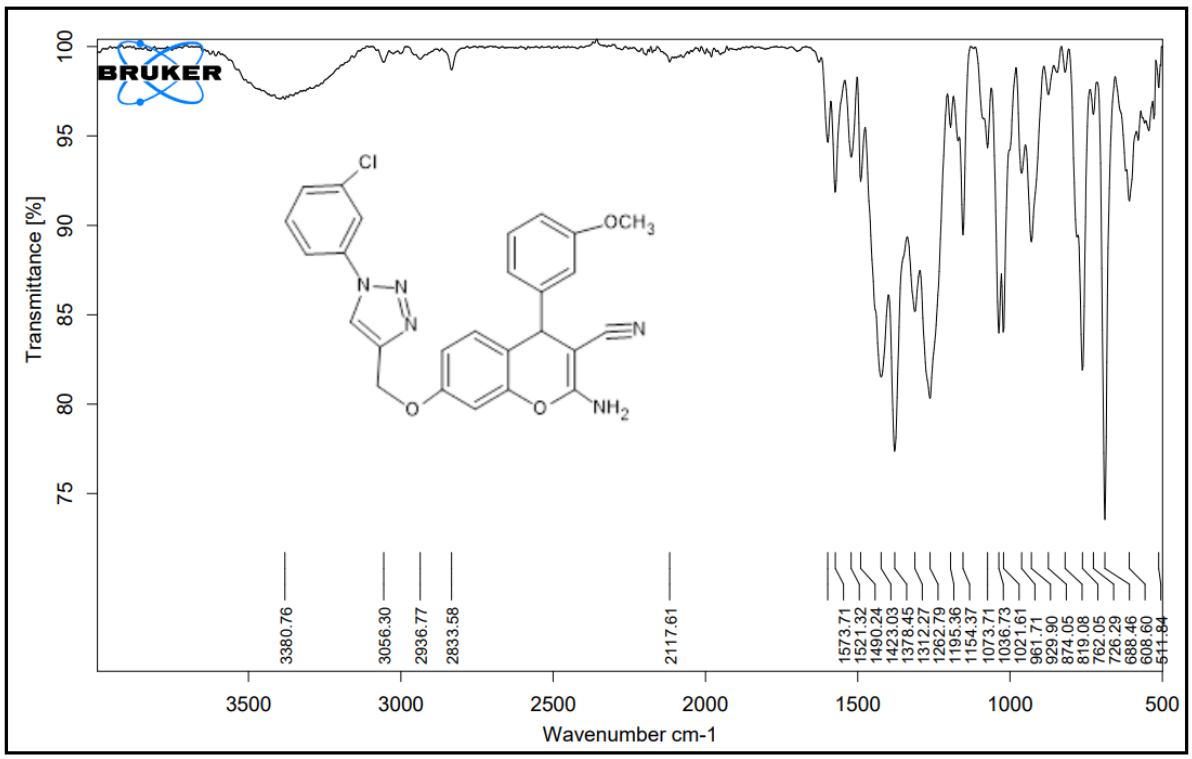


**Figure 10:** FT(IR) spectrum of compound **7b**

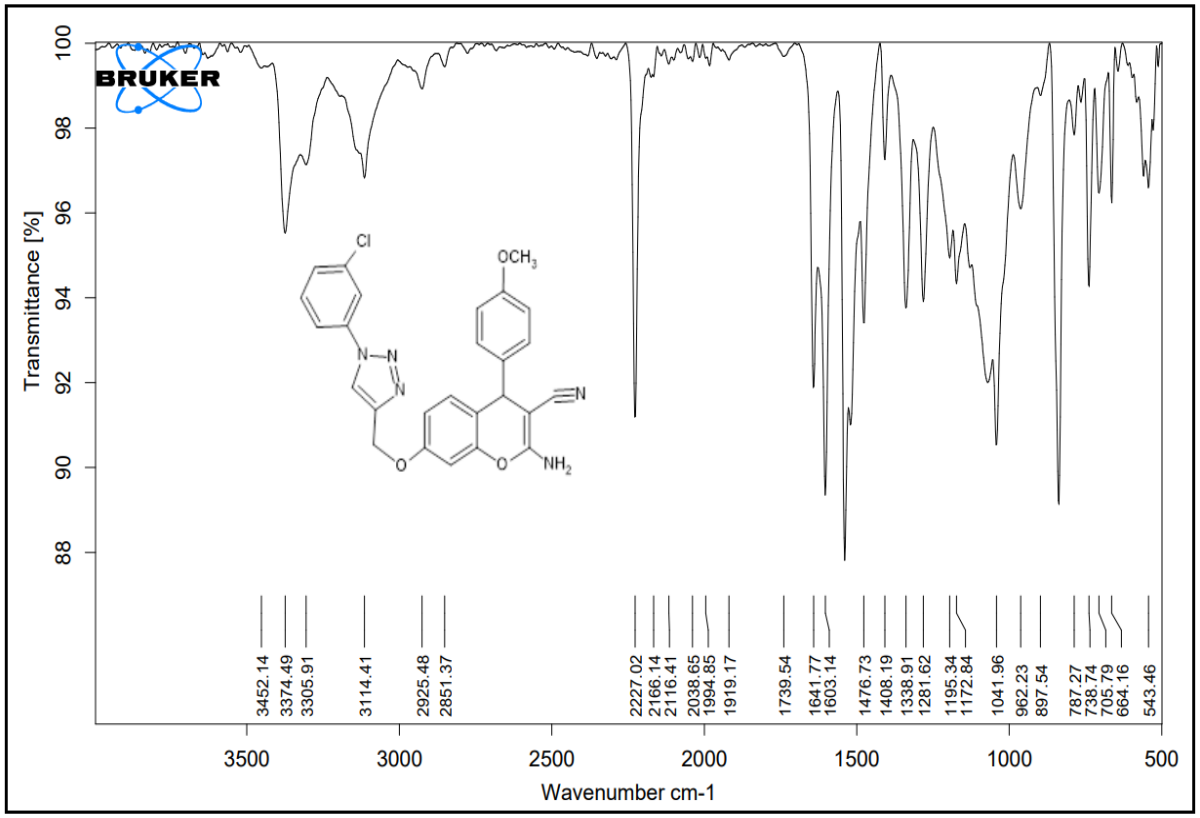



**Figure 11:** FT(IR) spectrum of compound **7c**

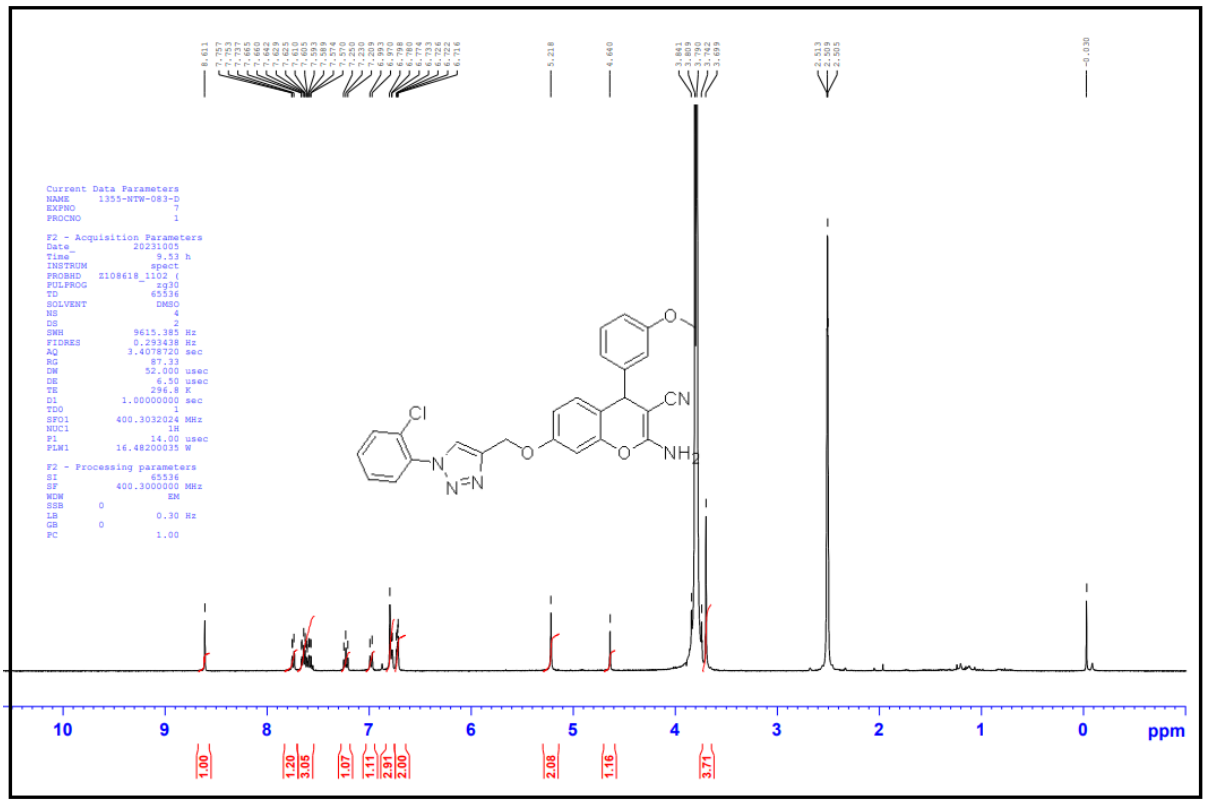



**Figure 12:** NMR spectrum of compound **7a**

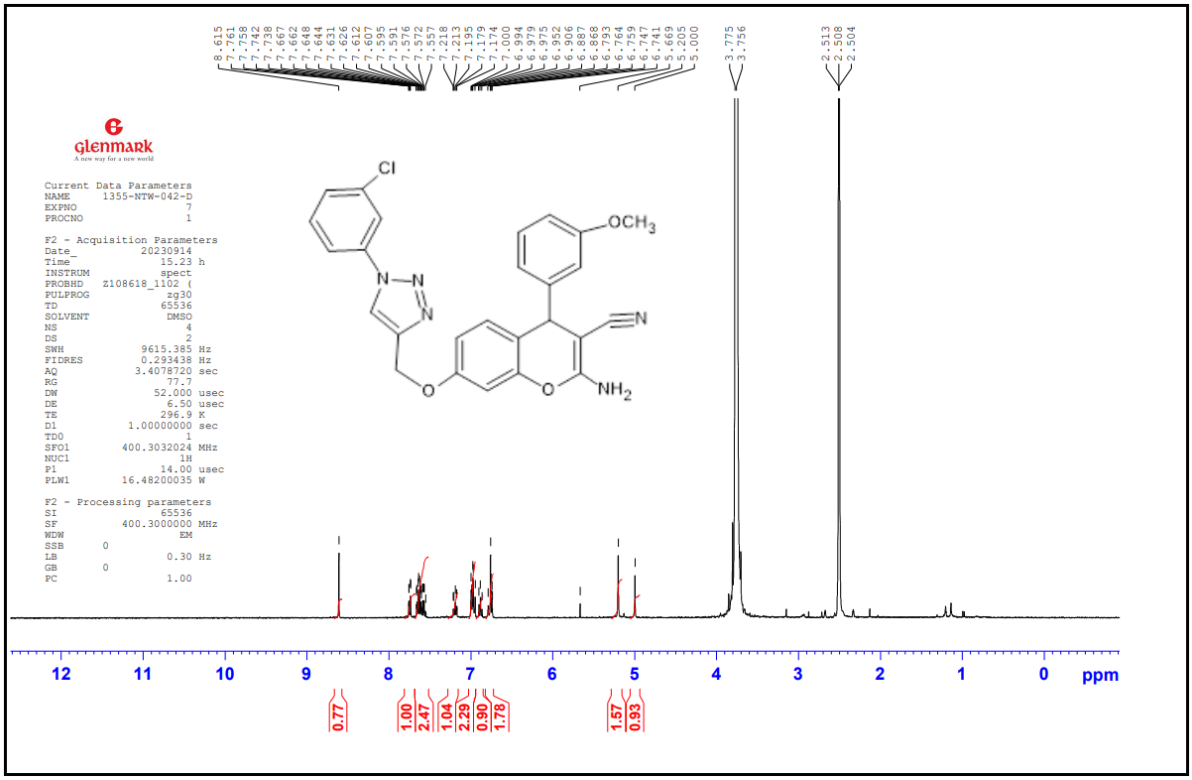
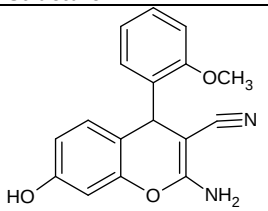
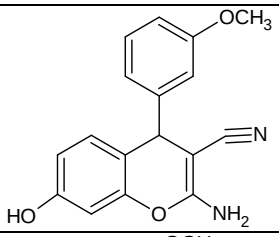
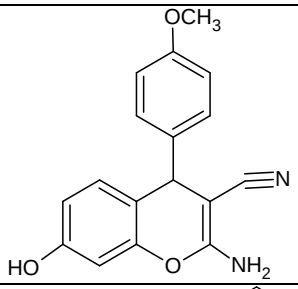
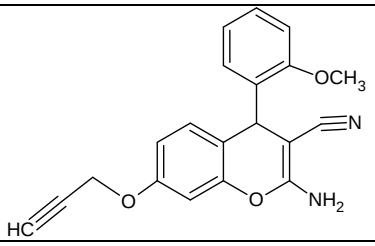
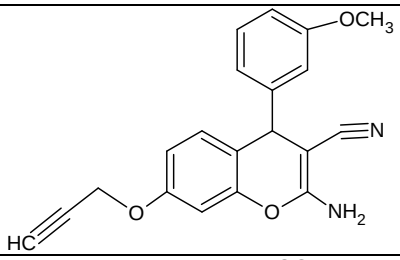
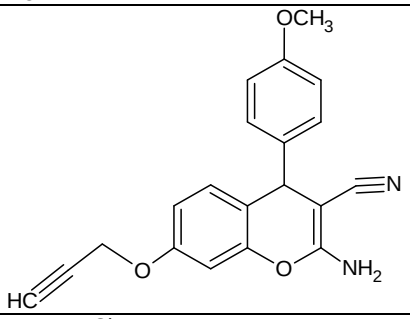
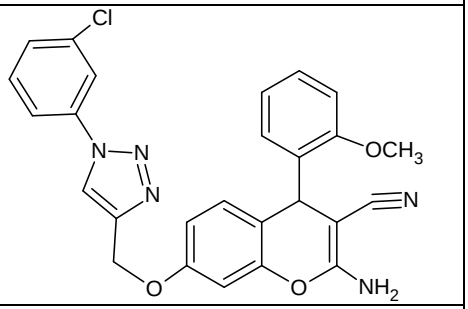
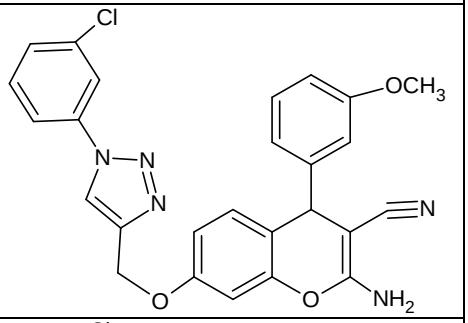
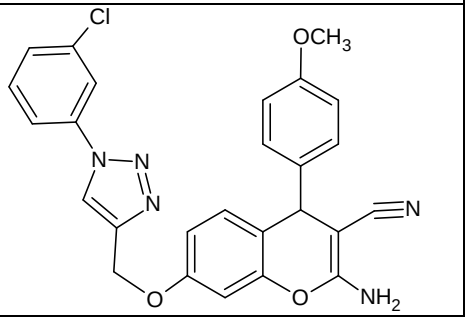



**Figure 13:** NMR spectrum of compound **7b**

**Table 1:** Based on spectral studies, the structures of complexes are assigned as follows;

| Comp Code | MW | Formula | MP | Structure |
|---|---|---|---|---|
| 4a | 294 | $C_{17}H_{14}N_2O_3$ | 197 |  |
| 4b | 294 | $C_{17}H_{14}N_2O_3$ | 192 |  |
| 4c | 294 | $C_{17}H_{14}N_2O_3$ | 193 |  |
| 5a | 332 | $C_{20}H_{16}N_2O_3$ | 196 |  |

| | | | | |
|---|---|---|---|---|
| 5b | 332 | $C_{20}H_{16}N_2O_3$ | 192 |  |
| 5c | 332 | $C_{20}H_{16}N_2O_3$ | 189 |  |
| 7a | 542 | $C_{27}H_{19}N_6O_3Cl$ | 203 |  |
| 7b | 542 | $C_{27}H_{19}N_6O_3Cl$ | 209 |  |
| 7c | 530 | $C_{26}H_{16}N_6O_2F$ | 208 |  |

**BIOLOGICAL SCREENING:**

**Antibacterial assays:**

In vitro antibacterial screening was performed on all synthesised 1H-1,2,3-triazoles against two gram-positive and two gram-negative bacteria, and the results showed that they were more efficient than streptomycin and vancomycin. **Table 2** presents evaluations for items **7a-c**, indicating both low and high concentrations of the tested molecules displayed antibacterial action against the microorganisms. Almost every molecule that was examined showed only weak to moderate action against the organisms when compared to the MIC values of reference substances. Gram-positive bacteria needed 6.25 mM of ciprofloxacin and Gram-negative bacteria needed 3.12 mM of vancomycin, according to the given MIC values. Certain final compounds, such as **7c** (MIC = 3.12 mM), **7b** (MIC = 6.25 mM), and **7a** (MIC = 3.12 mM), demonstrated notable inhibitory activity against *B. subtilis*. Similarly, the MICs of **7a**, **7b**, and **7c** against *S. aureus* were 3.12, 6.25, and 3.12 mM, respectively.

Triazoles had MIC values ranging from 12.5 to 25 mM, with some showing less activity than others. Their inhibitory activity was higher than that of ciprofloxacin but lower than that of vancomycin.
For antifungal efficacy, the **7a-c** were tested against *Candida albicans* and *Saccharomyces cerevisiae*, with *fluconazole* as a reference. The MICs for **7b**, and **7c** were less than 3.12-12.5 mM, making them effective against S. cerevisiae. Inhibitory concentrations (MIC) of **7a** against these fungi were as low as 1.56 mM.

## CONCLUSION:

In conclusion, Williamson's ether synthesis was employed to produce **5a-c** from the corresponding **4a-c** using the $K_2CO_3$/acetone method. Spectral studies confirmed the structure of 5a-c. Click chemistry was applied to these propargyl ethers by reacting with 1-azido-3-chlorobenzene using the CuI method, with CuI identified as the optimal catalyst. The resulting **7a-7c** displayed inhibitory actions against selected bacteria and yeasts, with certain compounds showing considerable inhibitory activity against investigated bacteria, including clinical MRSA isolates with MIC values ranging from 1.56 to 6.25 mM.

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