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Efficient Click Chemistry Towards Novel Some Substituted 2-Amino-4-Aryl-7-Propargyloxy-4H-Chromene-3-Carbonitriles: Design, Synthesis, And Evaluation of in Vitro Antibacterial, Cytotoxic and Antifungal Activities

Nayan Taterao Waghmare[1], Amardeep Sahadev Jagtap[2], Rajendra Arun Ughade[3,] and Dr. Sushilkumar A. Dhanmane[4]*

[1*,2,3,4]Dept of Chemistry, Fergusson College, Fergusson College Rd, Shivajinagar, Pune, Maharashtra 411004.

***Corresponding author**: Dr. Sushilkumar A. Dhanmane
*Dept of Chemistry, Fergusson College, Fergusson College Rd, Shivajinagar, Pune, Maharashtra 411004.

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Keywords: -

1H-1,2,3-Triazoles, 2-Amino-4H-chromene-3-carbonitriles, Propargyl ether, Click chemistry, Antibacterial, Antifungal, Cytotoxicity.

Abstract:

A group of 2-amino-7-hydroxy-4H-chromene-3-carbonitriles **4a-e** was prepared *via* a three-component process employing sodium carbonate as a catalyst. The experiment was conducted using a solvent mixture consisting of 96% ethanol and water, with a volume ratio of 1:20. The propargyl ether compounds **5a-e**, which are derivatives of chromene-3-carbonitriles, were effectively produced by reacting the respective hydroxyl chromenes derivatives with propargyl bromide. 1H-1,2,3-Triazole-tethered click chemistry between propargyl ethers **5a-e** and 1-azido-2-chlorobenzene yielded 4H-chromene-chlorophenyl conjugates **7a-e**. For this chemical reaction, CuI was the best catalyst. The 1H-1,2,3-triazole yields ranged from 78.77% to 85.47 %. All triazoles **7a-e** were investigated *in vitro* for anti-microorganism activity. Four compounds were effective against *B. subtilis* (MCC 2010), four compounds were effective against *S. aureus* (MCC 2408), four compounds were effective against *P. aeruginosa* and five compounds were effective against *E. coli* (MCC 2412).

Introduction:

Multi-component coupling reactions (MCRs) are of significant interest in the field of organic synthesis owing to their inherent conveniences and numerous benefits. In the aforementioned reactions, it is observed that three or more initial substances undergo a chemical transformation, resulting in the formation of a product in which a significant or complete contribution of atoms from the starting materials is evident. In a multicomponent reaction (MCR), a product is synthesized by assembling components or members through a series of sequential chemical reactions. The utilization of 4H-chromene derivatives and compounds containing a chromene moiety is noteworthy in the field of organic synthesis owing to their significant biological activities. These chemicals serve as significant pharmacophores, which are linked to a wide array of pharmacological activity. The substances in question have been found 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. In recent times, the association of some heterocycles, including 4H-pyran, 4H-chromene, and 1H-1,2,3-triazole, [15,16] has shown potential in eliciting intriguing biological effects. The formation of the 1H-1,2,3-triazole ring, a heterocyclic aromatic ring, occurs via click chemistry by employing suitable 1-alkynes. The user's text is already in an academic format, as it includes a citation range. The synthesis of 1-alkynes and organic azides is imperative for the implementation of click chemistry via CuAAC (Copper(I)-catalyzed Alkyne-Azide Cycloaddition). This paper presents a synthetic method for producing fluoro and methoxy-substituted 2-amino 4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles from the corresponding 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles. Additionally, the antimicrobial screening of a typical product within this series is investigated.

Journal of Chemical Health Risks

www.jchr.org

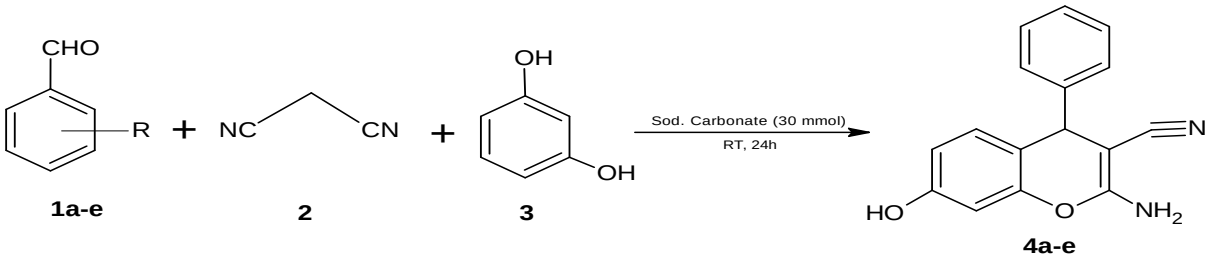
JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

Experimental:

The melting points presented here are raw data from an open capillary method experiment performed on the Myra melting point apparatus. The Brucker FT-IR Spectrometer was used to capture the infrared spectra of the KBr disc. The Bruker Avance II HD NMR 500MHz was used to acquire ^{1}H NMR spectra in DMSO-d_6 using TMS as the internal standard. The LC-MS Agilent (ThermoScientific) was used to acquire ESI mass spectra in methanol. The S. d. Fine Chemical Company (in India) supplied us with ultra-pure chemical reagents. For organic synthesis, all ingredients were of reagent quality. The silica gel 60 WF254S aluminum sheets (Merck, India) were used for the analytical thin-layer chromatography (TLC) and UV light was used for visualization.

General procedure for the synthesis of 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles (4a-e):

A solution of sodium carbonate (30 mmol) in 25 mL of water was added to a mixture of suitable fluoro- and methoxy-substituted benzaldehyde **1a-e** (10 mmol), malononitrile **2** (10 mmol), and resorcinol **3** (10 mmol) in water (25 mL) and 96% ethanol (1 mL). At 25 degrees Celsius (under TLC supervision), the reaction mixture was stirred for 24 hours. Recrystallization from a combination of 96% ethanol and toluene (1:1 or 2:1 by volume) afforded the named compounds 4a-l following filtration with suction, and washing with water to pH 7.



1a-e **2** **3** **4a-e**

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

Scheme 1: Synthesis of 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles (**4a-e**)

2-amino-7-hydroxy-4-(2-methoxyphenyl)-4H-1-benzopyran-3-carbonitrile (4a):

White crystals. From 2-methoxybenzaldehyde **1a** (20 mmol), malononitrile **2** (20 mmol), and resorcinol **3** (20 mmol). M. p. 197 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3322, 2953, 202, 1595/1441, 1347/1312; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 9.631 (*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: calcd. for $C_{17}H_{14}N_2O_3$, M = 294.36 Da, found: m/z 293.1446 $[M + H]^+$; Elemental anal., calcd: C, 69.38; H, 4.79; N, 9.52%; found: C, 69.30; H, 4.74; N, 9.36%.

2-amino-7-hydroxy-4-(3-methoxyphenyl)-4H-1-benzopyran-3-carbonitrile (4a):

White crystals. From 3-methoxybenzaldehyde **1b** (20 mmol), malononitrile **2** (20 mmol), and resorcinol **3** (20 mmol). M. p. 192 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3300, 2979, 2185, 1598/1435, 1392/1303; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 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: calcd. for $C_{17}H_{14}N_2O_3$, M = 294.36 Da, found: m/z 295.2546 $[M + H]^+$; Elemental anal., calcd: C, 69.38; H, 4.79; N, 9.52%; found: C, 69.22; H, 4.75; N, 9.50%.

2-amino-7-hydroxy-4-(2-fluorophenyl)-4H-1-benzopyran-3-carbonitrile (4c):

White crystals. From 2-fluorobenzaldehyde **1c** (20 mmol), malononitrile **2** (20 mmol), and resorcinol **3** (20 mmol). M. p. 187 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3330, 2962, 2230, 1604/1455, 1365, 1278; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 9.578 (*s*, 1H, -OH), 7.215 (*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). ESI/HRMS: calcd. for $C_{17}H_{14}N_2O_3$, M = 294.36 Da, found: m/z 293.1446 $[M + H]^+$; Elemental anal., calcd: C, 69.38; H, 4.79; N, 9.52%; found: C, 69.30; H, 4.74; N, 9.36%.

2-amino-7-hydroxy-4-(3-fluorophenyl)-4H-1-benzopyran-3-carbonitrile (4d):

White crystals. From 3-fluorobenzaldehyde **1d** (20 mmol), malononitrile **2** (20 mmol), and resorcinol **3** (20 mmol). M. p. 189 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3305, 2925, 2227, 1603/1476, 1338, 1281; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 10.024 (*s*, 1H, -OH), 7.615 (*ddd*, *J* = 8.19, 7.42, 1.25 Hz, 1H, Ar-H), 6.988 (*s*, 2H, -NH_2), 6.745-6.897 (*m*, 4H, Ar-H), 6.537 (*dd*, *J* = 7.95, 2.67 Hz, 1H, Ar-H), 6.379 (*dd*, *J* = 2.66, 0.41 Hz, 1H, Ar-H), 3.145 (*s*, 1H). ESI/HRMS:

Journal of Chemical Health Risks

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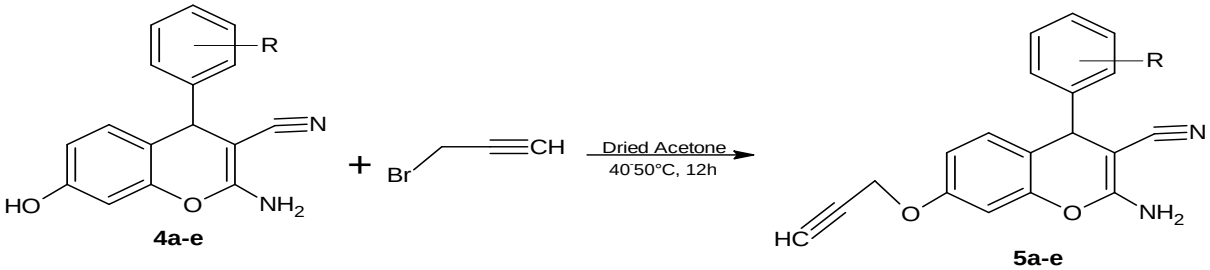
calcd. for $C_{17}H_{14}N_2O_3$, M = 294.36 Da, found: m/z 293.1446 $[M + H]^+$; Elemental anal., calcd: C, 69.38; H, 4.79; N, 9.52%; found: C, 69.30; H, 4.74; N, 9.36%.

2-amino-7-hydroxy-4-(4-fluorophenyl)-4H-1-benzopyran-3-carbonitrile (4e):

White crystals. From 4-fluorobenzaldehyde **1e** (20 mmol), malononitrile **2** (20 mmol), and resorcinol **3** (20 mmol). M. p. 195 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3303, 2928, 2226, 1601/1481, 1339, 1282; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 10.356 (*s*, 1H, -OH), 7.578 (*ddd*, *J* = 8.22, 7.39, 1.19 Hz, 1H, Ar-H), 6.887 (*s*, 2H, -NH_2), 6.739-6.893 (*m*, 4H, Ar-H), 6.535 (*dd*, *J* = 7.95, 2.67 Hz, 1H, Ar-H), 6.376 (*dd*, *J* = 2.65, 0.40 Hz, 1H, Ar-H), 3.146 (*s*, 1H). ESI/HRMS: calcd. for $C_{17}H_{14}N_2O_3$, M = 294.36 Da, found: m/z 295.2345 $[M + H]^+$; Elemental anal., calcd: C, 69.38; H, 4.79; N, 9.52%; found: C, 69.22; H, 4.71; N, 9.35%.

General procedure for the synthesis of fluoro and methoxy substituted 2-amino-7-propargyloxy-4H-chromene-3-carbonitriles (5a-e):

Anhydrous potassium carbonate (15 mmol) was added to a solution of appropriately fluoro and methoxy substituted 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles **4a-e** (10 mmol) in dried acetone (25 mL). Propargyl bromide **5** (10 mmol of solution 80 wt.% in toluene) was then added dropwise into this suspension mixture. The reaction mixture was heated by stirring at 40 °C or 50 °C in a water bath for 12 h. After that, the solvent was completely evaporated in a vacuum at ambient temperature. Water was added to the residue to dissolve inorganic salts (K_2CO_3 and KBr). The separated solid product was filtered, washed with water, and recrystallized from a mixture of 96% ethanol and toluene (1:1 to 1:2, by volumes) to afford the title propargyl ethers **5a-e** of fluoro and methoxy substituted 4H-chromene-3-carbonitriles.



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

Scheme 2: Synthesis of fluoro and methoxy substituted 2-amino-7-propargyloxy-4H-chromene-3-carbonitriles **(5a-e)**

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

Brown crystals. From 2-amino-7-hydroxy-4-(2-methoxyphenyl)-4H-1-benzopyran-3-carbonitrile **4a** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 196 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3199, 3072, 2965, 2225, 1607/1452, 1348/1303; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 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: calcd. for $C_{20}H_{16}N_2O_3$, M = 332.35 Da, fund: m/z 330.7789 $[M + H]^+$; Elemental anal., calcd: 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 2-amino-7-hydroxy-4-(3-methoxyphenyl)-4H-1-benzopyran-3-carbonitrile **4b** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 192 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3112, 2774, 2225, 1601/1480, 1340, 1282, 1073, 740; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 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: calcd. for $C_{20}H_{16}N_2O_3$, M = 332.35 Da, fund: m/z 331.2357 $[M + H]^+$; Elemental anal., calcd: 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 2-amino-7-hydroxy-4-(2-fluorophenyl)-4H-1-benzopyran-3-carbonitrile **4c** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 189 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3178, 3110, 2963, 2227, 1582/1451, 1301, 1223, 1070, 741; ^{1}H NMR (500 MHz, DMSO-d_6), 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,

Journal of Chemical Health Risks

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JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

0.43 Hz, 2H, Ar-H), 5.291 (*s*, 2H, -CH_2-), 4.808 (*s*, 1H), 1.206 (*s*, 1H, CH). ESI/HRMS: calcd. for $C_{19}H_{13}N_2O_2F$, M = 320.32 Da, found: m/z 324.1477 $[M + H]^+$; Elemental anal., calcd: C, 71.24; H, 4.09; N, 8.75%; found: C, 70.88; H, 4.01; N, 8.69%.

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

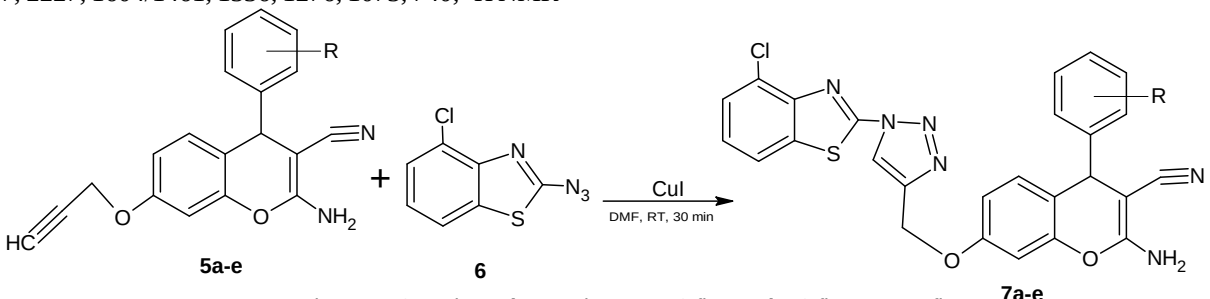
Brown crystals. From 2-amino-7-hydroxy-4-(3-fluorophenyl)-4H-1-benzopyran-3-carbonitrile **4d** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 193 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3113, 2979, 2932, 2288, 1603/1438, 1335, 1268, 1040, 740; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 7.811-7.866 (*s*, 2H, -NH_2), 7.688-7.766 (*dd*, *J* = 7.11, 7.29 Hz, 2H, Ar-H), 7.666 (*ddd*, *J* = 7.66, 7.28, 1.49 Hz, 1H, Ar-H), 7.099-7.119 (*m*, 6H, Ar-H), 7.046-7.066 (*dd*, *J* = 2.33, 0.42 Hz, 2H, Ar-H), 5.288 (*s*, 2H, -CH_2-), 4.816 (*s*, 1H), 1.193 (*s*, 1H, CH). ESI/HRMS: calcd. for $C_{19}H_{13}N_2O_2F$, M = 320.32 Da, found: m/z 321.0546 $[M + H]^+$; Elemental anal., calcd: C, 71.24; H, 4.09; N, 8.75%; found: C, 70.96; H, 4.08; N, 8.71%.

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

Brown crystals. From 2-amino-7-hydroxy-4-(4-fluorophenyl)-4H-1-benzopyran-3-carbonitrile **4e** (10 mmol), propargyl bromide (10 mmol), and anhydrous potassium carbonate (30 mmol). M. p. 196 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3115, 2937, 2227, 1604/1461, 1336, 1276, 1073, 740; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 7.816-7.903 (*s*, 2H, -NH_2), 7.619-7.708 (*dd*, *J* = 7.11, 7.29 Hz, 2H, Ar-H), 7.718 (*ddd*, *J* = 7.61, 7.21, 1.45 Hz, 1H, Ar-H), 7.093-7.203 (*m*, 6H, Ar-H), 7.055-7.088 (*dd*, *J* = 2.29, 0.39 Hz, 2H, Ar-H), 5.267 (*s*, 2H, -CH_2-), 4.867 (*s*, 1H), 1.218 (*s*, 1H, CH). ESI/HRMS: calcd. for $C_{19}H_{13}N_2O_2F$, M = 320.32 Da, found: m/z 320.1456 $[M + H]^+$; Elemental anal., calcd: C, 71.24; H, 4.09; N, 8.75%; found: C, 71.03; H, 4.06; N, 8.62%.

General procedures for click chemistry of fluoro and methoxy substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles with 1-azido-2-chlorobenzene (7a-e):

The reaction mixture was prepared by combining 2-amino-4-phenyl-7-propargyloxy-4H-chromene-3-carbonitrile **5a-e** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol) in N, N-dimethylformamide (DMF) with a volume of 25 mL. The solution was subjected to gentle stirring to facilitate the dissolution of the reactants. Distilled water (50 mL) was subsequently introduced into the agitated reaction mixture. A solid of greenish yellow color was successfully isolated. The solid substances that were separated underwent filtration, followed by washing with water and subsequent crystallization from a solvent mixture consisting of 96% ethanol and toluene in a ratio of 2:1 by volume. This process resulted in the formation of the compounds **7a-e**, which were obtained as greenish-yellow solids.



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

Scheme 3: Synthesis of fluoro and methoxy substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles with 1-azido-2-chlorobenzene **(7a-e)**

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

Greenish yellow. From 2-amino-4-(2'-methoxyphenyl)-7-propargyloxy-4H-chromene-3-carbonitrile **5a** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 203 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3340, 3056, 2196, 1598/1440, 1456, 1397/1329, 1253, 1023, 752, 688; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 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: calcd. for $C_{27}H_{19}N_6O_3ClS$, M = 542.96 Da, found: m/z 542.1546 $[M + H]^+$; Elemental anal., calcd: C, 59.72; H, 5.53; N, 15.48%; found: C, 59.06; H, 5.11; N, 15.38%.

Journal of Chemical Health Risks

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JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

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

Greenish yellow. From 2-amino-4-(3'-methoxyphenyl)-7-propargyloxy-4H-chromene-3-carbonitrile **5b** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 209 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3380, 3056, 2117, 1573/1423, 1490, 1378/1312, 1262, 1195, 1021, 762, 688; ^{1}H NMR (500 MHz, DMSO-d_6), 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: calcd. for $C_{27}H_{19}N_6O_3ClS$, M = 542.96 Da, found: m/z 542.1546 $[M + H]^+$; Elemental anal., calcd: 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-((4-chloro-1,3-benzothiazole)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (7c):

Greenish yellow. From 2-amino-4-(2'-fluorophenyl)-7-propargyloxy-4H-chromene-3-carbonitrile **5c** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 209 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3311, 3053, 2201, 1595/1439, 1348, 1250, 1071, 738, 689; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 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: calcd. for $C_{26}H_{16}N_6O_2ClSF$, M = 530.96 Da, found: m/z 530.1546 $[M + H]^+$; Elemental anal., calcd: C, 58.81; H, 3.04; N, 15.83%; found: C, 57.92; H, 3.02; N, 15.73%.

2-Amino-4-(3′-fluorophenyl)-7-((4-chloro-1,3-benzothiazole)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (7d):

Greenish yellow. From 2-amino-4-(3'-fluorophenyl)-7-propargyloxy-4H-chromene-3-carbonitrile **5d** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 205 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3305, 3114, 2226, 1602/1462, 1408, 1338, 1268, 1072, 740, 680; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 7.746 (*s*, 2H, -NH_2), 7.547 (*dd*, *J* = 7.83, 0.40 Hz, 3H, Ar-H), 7.203 (*ddd*, *J* = 8.43, 1.20, 0.53 Hz, 2H, Ar-H), 7.134 (*ddd*, *J* = 7.90, 7.69, 1.24 Hz, 2H, Ar-H), 6.773 (*dd*, *J* = 7.77, 0.41 Hz, 2H, Ar-H), 6.767 (*ddd*, *J* = 8.42, 1.20, 0.53 Hz, 2H, Ar-H), 5.210 (*dd*, *J* = 2.44, 0.39 Hz, 2H, Ar-H), 4.699 (*s*, 1H, Ali CH), 3.150 (*s*, 1H, Ali CH). ESI/HRMS: calcd. for $C_{26}H_{16}N_6O_2ClSF$, M = 530.96 Da, found: m/z 530.1546 $[M + H]^+$; Elemental anal., calcd: C, 58.81; H, 3.04; N, 15.83%; found: C, 58.37; H, 3.00; N, 15.76%.

2-Amino-4-(4′-fluorophenyl)-7-((4-chloro-1,3-benzothiazole)-1H-1,2,3-triazol-4-yl)methoxy)-4H-chromene-3-carbonitrile (7e):

Greenish yellow. From 2-amino-4-(4'-fluorophenyl)-7-propargyloxy-4H-chromene-3-carbonitrile **5e** (10 mmol), CuI (5 mmol), and 1-azido-2-chlorobenzene **6** (10 mmol). M. p. 211 °C (from 96% ethanol/toluene 2:1); IR (KBr), υ(cm^{-1}): 3339, 3295, 3080, 2193, 1592/1448, 1408, 1352, 1309, 1286, 1073, 732; ^{1}H NMR (500 MHz, DMSO-d_6), δ (ppm): 7.770 (*s*, 2H, -NH_2), 7.688 (*ddd*, *J* = 8.44, 1.20, 0.53 Hz, 2H, Ar-H), 7.575 (*ddd*, *J* = 7.99, 7.69, 1.24 Hz, 2H, Ar-H), 6.961 (*dd*, *J* = 7.80, 0.42 Hz, 3H, Ar-H), 6.646 (*ddd*, *J* = 8.43, 1.27, 0.56 Hz, 2H, Ar-H), 5.525 (*dd*, *J* = 2.48, 0.45 Hz, 2H, Ar-H), 4.754 (*s*, 1H, Ali CH), 3.168 (*s*, 1H, Ali CH). ESI/HRMS: calcd. for $C_{26}H_{16}N_6O_2ClSF$, M = 530.96 Da, found: m/z 530.1546 $[M + H]^+$; Elemental anal., calcd: C, 58.81; H, 3.04; N, 15.83%; found: C, 58.55; H, 3.03; N, 15.80%.

Biological assays:

***In vitro* antimicrobial activity:**

The synthesized 1H-1,2,3-triazoles **7a-e** were subjected to *in vitro* screening to evaluate their antibacterial and antifungal activity against both Gram-positive and Gram-negative bacterial species. The Gram-positive bacteria used for this study were *B. subtilis* (MCC 2010), and S. aureus (MCC 2408). The Gram-negative bacteria included *E. coli* (MCC 2412), and *P. aeruginosa* (MCC 2408). The evaluations were conducted using the minimum inhibitory concentration (MIC) method, as outlined in our earlier publication [18]. The technique of micro broth dilutions was employed, using Mueller-Hinton broth [19]. The compounds under investigation were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mg/mL. The drug references included in **Table 1** were *streptomycin* and *vancomycin*. The solutions with concentrations of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 millimolar (mM) were generated by diluting the test compounds and standard drugs mentioned earlier. The inoculum was generated by adjusting a 4-6 h broth to a turbidity level comparable to a 0.5 McFarland standard. This was then diluted in broth media to achieve a final concentration of 5 x 10^5 CFU/mL in the test tray. The plates were incubated at a temperature of 35°C for a duration of 24 hours. The minimum inhibitory concentration (MIC) was determined as the concentration of the substance that resulted in complete suppression of observable growth. The experiments were conducted in triplicate. The minimum inhibitory concentration (MIC) values for all

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JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

substances tested, as well as the reference medication, are presented in **Table 1**.

***In vitro* antifungal activity:**

antifungal activity of compounds **7a-e** was assessed in vitro against three fungal strains, namely *S. cerevisiae* (MCC 1033), and *C. albicans* (MCC 1439). The agar dilution method was employed using Saburoud's dextrose agar (Hi-Media), as detailed earlier reported [17]. *Fluconazole* was employed as a pharmacological agents to assess its efficacy in combating fungal infections. The solutions were produced at concentrations of 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, and 0.78 mM for each examined chemical and standard drug. Suspensions of each microbe were made to achieve a concentration of 10 colony-forming units per milliliter (CFU/mL). These suspensions were then put onto agar plates that had been previously diluted with the substances under investigation. The plates were subjected to incubation at a temperature of 35 °C. The minimum inhibitory concentrations (MICs) were established after 72 hours [18].

The investigation involved determining the minimal inhibitory doses of each drug against standard fungal strains. The experiments were conducted on three separate occasions. **Table 2** displays the minimum inhibitory concentration (MIC) values for the investigated substances as well as the reference drugs.

Results and Discussion:

The synthesis of 2-amino-4-aryl-7-hydroxyl-4H-chromene-3-carbonitriles **4a-e** was achieved using a three-component process involving substituted fluoro and methoxy benzaldehydes **1a-e**, malononitrile **2**, and resorcinol **3** (**Scheme 1**). The experimental parameters for this three-component procedure involved the use of sodium carbonate as a catalyst, with a concentration of 30 mmol. The reaction was conducted at room temperature for 24 hours, as depicted in **Scheme 1** [19–21]. A co-solvent consisting of 96% ethanol was employed at a volumetric ratio of 1:20. The isolated yields ranged from 74.11 to 84.54%. Subsequently, the aforementioned 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles **4a-e** was subjected to a conversion process, resulting in the formation of distinct substituted 7-propargyl ethers **5a-e**.

Another precursor used in click chemistry was 1-azido-2-chlorobenzene **6**. This compound was synthesized by reacting 2-chlorobenzene with sodium azide in either dried DMF or acetone water [22-24]. Dried acetone was employed as a solvent in order to prevent the degradation of the azide group by water. Additionally, the use of acetone facilitated the efficient removal of acetone from the reaction mixture. The crystalline solid of this 1-azido-2-chlorobenzene **6** was successfully synthesized on a multi-gram scale.

According to the current research, various catalysts have been identified for the catalysis of click chemistry [25]. To determine the most favorable conditions for the click chemistry reaction involving propargyl ether of 4H-chromene-3-carbonitriles **5a-e** and 1-azido-2-chlorobenzene **6**, a comprehensive study was conducted on the catalytic conditions of the CuI reaction using compound **7a-e** and the 1-azido-2-chlorobenzene mentioned above (**Scheme 3**).

For 4H-chromenes **4a-e**, the hydroxyl group was identified by an absorption band in the IR spectrum between 2928 and 2979 cm^{-1}, and the presence of an amino group was verified by two additional absorption bands between 3300 and 3330 cm^{-1}. Absorption peaking at 2202-2230 cm^{-1} was associated with the nitrile functional group. One proton's integral height at δ = 4.580-4.983 ppm was characteristic of all ^1H NMR spectra of chromenes **4a-e**, indicating that this signal belonged to the proton at position 4. This signal might be used to distinguish between 4H-pyrans and 4H-chromenes. In addition, the hydroxyl group at position 7 of the chromene ring was confirmed by the chemical shift observed at δ = 9.631-10.072 ppm. Resonance signal at δ = 6.384-7.205 ppm was found for the amino group at position 2 in chromenes **4a-e**.

Spectral data (IR, NMR, and MS) confirm the structural synthesis of 7-propargyl ether **5a-e** from 7-hydroxy-4H-chromes **4a-e**. IR and NMR spectra were used to look for the acetylenic unit found in the terminal triple bond of propargyl ethers of chromenes. The absorption bands in the IR spectra of these ethers that are characteristic of the stretching vibration of the hydroxyl group have faded away, disappearing between 3300 and 3350 cm^{-1}. Absorption bands were observed simultaneously at 3380-3390 cm^{-1} and 2120–2100 cm^{-1}, elucidating the stretching vibrations of CH and CC bonds. The nitrile group's absorption band was exceptionally strong in the region of 2200-2180 cm^{-1}, which was in close proximity to the rather modest CC absorption band. However, in the IR spectra of 7-propargyloxy-4H-chromenes **5a-e**, the presence of the amino group was indicated by the appearance of two additional absorption bands in the areas 3450-3440 and 3280-3200 cm^{-1}. Initial 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles **4a-e** exhibited similar absorption bands in their IR spectra. This data demonstrated that the main amino group at position 2 of the pyran moiety of the chromene ring was O-alkylated rather than N-alkylated during the reaction with propargyl bromides. This was verified by the ^1H NMR spectra of chromenes **5a-e**, which showed no chemical shift in the regions at δ 9.63-10.72 ppm (singlet, 1H) of the hydroxyl group at position 7 and resonance signals at δ 7.624-7.902 ppm (singlet, 2H) of the amino group at position 2.

Journal of Chemical Health Risks

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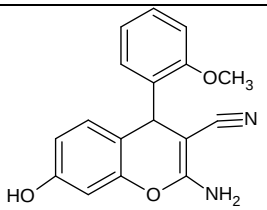
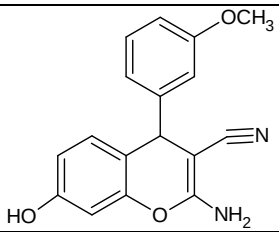
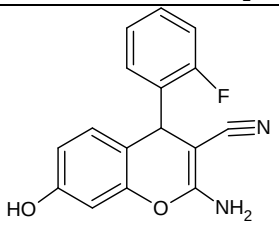
JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

The absorption band for the nitrile functional group was located at 2225-2288 cm^{-1}. The change was confirmed by the appearance of propargyl group signals in the ^1H NMR spectra of the original 7-hydroxy chromene derivatives. It was determined that the characteristic spectral region for the acetylenic proton in the *o*-propargyl group lies between δ 1.113 and 1.193 ppm, with an integral intensity of one proton. This signal had a multiplicity of three because of its interactions with the two methylene protons in the propargyl chain, whose coupling constant was J = 2.18–2.56 Hz. The methylene group resonance signal was found to be in the range of δ = 3.266-3.309 ppm (in triplet) and J = 2.62-2.77 Hz. The diamagnetic effect of the electronegative oxygen atom caused this signal to move downfield.

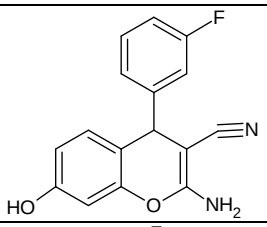
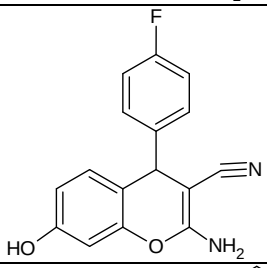
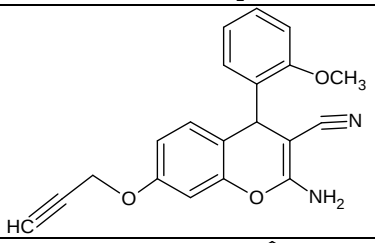
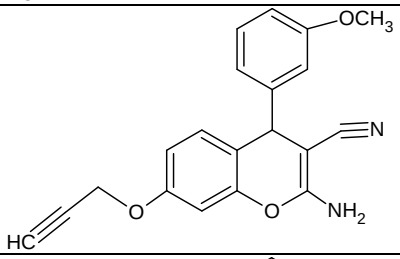
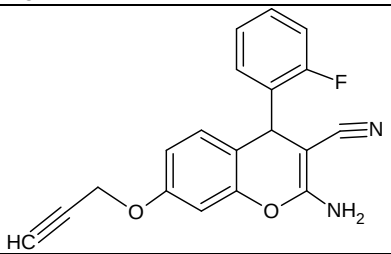
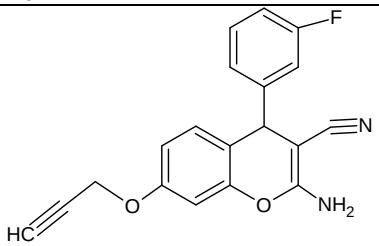
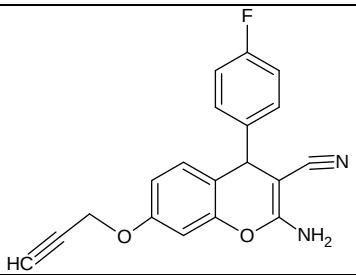
Shape resonance singlet signals were seen for the chromene ring proton at position 4 (allylic-type proton) in the range of δ 5.290-5.302 ppm (in singlet). There was a magnetic interaction between three protons in the benzene ring of chromene, and their chemical changes matched the AMX spin pattern. Proton H-5 had δ 7.102-7.123 ppm (in doublet with J = 8.00-8.12 Hz), proton H-6 had δ 7.220-7.598 ppm (in doublet of doublets with J = 0.39-0.43 and 7.8-7.9 Hz), and proton-8 had δ 6.60-6.76 ppm (in doublet with J = 1.90-2.33 Hz). The signals of the proton and carbon resonances, as well as the absorption bands in the range of 1590-1607 cm^{-1}, all corroborated the presence of the aromatic rings.

The confirmation of the structural synthesis of fluoro and methoxy-substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles with 1-azido-2-chlorobenzene **7a-e** is supported by the analysis of spectrum data, including infrared spectroscopy (IR), nuclear magnetic resonance (NMR), and mass spectrometry (MS). The investigation focused on the identification of the acetylenic unit, which consists of a terminal triple bond, present in propargyl ethers of chromenes. This was accomplished by the analysis of IR and NMR spectra. 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}. These bands can be attributed to the stretching vibration of the N=N bond. In contrast, the infrared spectra of **7a-e** exhibited two additional absorption bands within the spectral range of 3311-3380 cm^{-1}, indicating the existence of the amino group within these compounds. The IR spectra of the early **5a–e** exhibited the presence of these absorption bands as well. The presented evidence demonstrates that, in the context of 1-azido-2-chlorobenzene reactions, the acetylene group. The absence of a chemical shift in the regions at δ1.113–1.193 ppm (singlet, 1H) corresponds to the acetylene group.

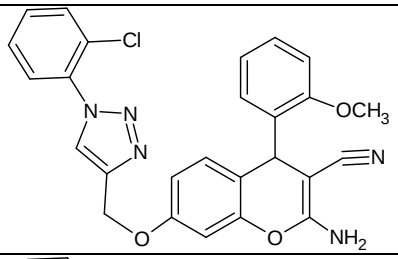
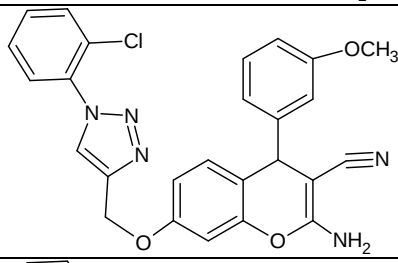
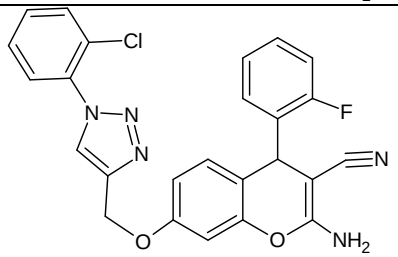
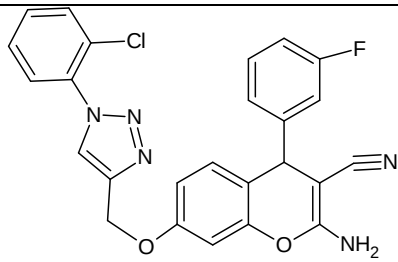
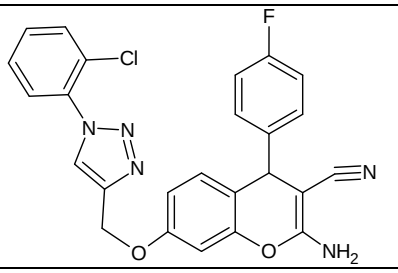
Table 1: Based on spectral studies, the structures of complexes are assigned as follows;

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	282	$C_{16}H_{11}N_2O_2$	187	

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

4d	282	$C_{16}H_{11}N_2O_2$	189	
4e	282	$C_{16}H_{11}N_2O_2$	195	
5a	332	$C_{20}H_{16}N_2O_3$	196	
5b	332	$C_{20}H_{16}N_2O_3$	192	
5c	320	$C_{19}H_{19}N_2O_2F$	189	
5d	320	$C_{19}H_{19}N_2O_2F$	193	
5e	320	$C_{19}H_{19}N_2O_2F$	196	

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

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	
7d	530	$C_{26}H_{16}N_6O_2F$	205	
7e	530	$C_{26}H_{16}N_6O_2F$	211	

Biological screening:

Antibacterial assays:

All the synthesized 1H-1,2,3-triazoles were screened for their in vitro antibacterial activity against two representative gram-positive bacteria, *B. subtilis* (MCC 2010), *S. aureus* (MCC 2408), and two representative Gram-negative bacteria, which were *E. coli* (MCC 2412), *P. aeruginosa* (MCC 2080). Antibacterial effectiveness was measured against *streptomycin* and *vancomycin*. *Streptomycin* and *vancomycin* are still used to treat a range of bacterial illnesses, with the former used to treat severe, life-threatening infections by Gram-positive bacteria that (are) refractory to other antibiotics. These latter drugs were used to treat life-threatening conditions brought on by Gram-negative bacteria like *P. aeruginosa*. Tabulated evaluations for items **7a-e** are provided there. **Table 2** shows that both low and high concentrations of the new molecules tested showed antibacterial action against the tested microorganisms. When compared to the MIC values of the reference chemical, practically all of the compounds tested exhibited low to moderate activity against the organisms used in the tests. Here are the MICs for these commonly used drugs: The MICs for *ciprofloxacin* (6.25 mM for Gram-positive bacteria) and for vancomycin (3.12 mM for Gram-negative bacteria)

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JCHR (2023) 13(6), 2936-2946 | ISSN:2251-6727

are, respectively. MIC values of 3.12-12.5 mM were found for certain 1H-1,2,3-triazoles against Gram-positive bacteria (*B. subtilis*, and *S. aureus*). Compounds **7d** (MIC = 3.12 mM), **7e** (MIC = 6.25 mM), and **7a** (MIC = 3.12 mM) were the most effective triazoles against *B. subtilis*. The minimum inhibitory concentrations (MICs) of **7a, 7c**, and **7d** against S. aureus were 3.12, 6.25, and 3.12 mM, respectively. With the exception of **7a, 7b, 7d**, and **7e** (MICs = 3.12 mM), the aforementioned triazoles exhibited more significant inhibitory activity than *ciprofloxacin* but less than *vancomycin*. Some others were less active against these bacteria with MIC values of 12.5-25 mM.

Antifungal assay:

The aforementioned 1H-1,2,3-triazoles **7a-e** were tested for their antifungal efficacy against a variety of fungal strains. These included *Candida albicans* (MCC 1439), and *Saccharomyces cerevisiae* (MCC 1039), reference included *fluconazole*. *Fluconazole* is an antifungal drug that belongs to the first generation of triazoles. *Fluconazole* had MIC values of 1.56, and 3.12 against the same two.

Table 3 displays the acquired results. Notably, the triazoles **7a-e** examined were more resistant to *Candida albicans* (MCC 1439) than fluconazole, but they were more active against *S. cerevisiae*. The MICs for **7b, 7c**, and **7d** were all less than 3.12-12.5 mM, making them all effective against *S. cerevisiae*. Inhibitory concentrations (MIC) of **7a** and **7e** against these fungi were as low as 1.56-3.12 mM.

Conclusion:

Williamson's ether synthesis was used to produce a sequence of 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles (**5a-t**) from the equivalent 2-amino-7-hydroxy-4H-chromene-3-carbonitriles (**4a-e**). The K_2CO_3/acetone method was employed in these synthesis reactions involving propargyl bromide. This technique gave the ethers **5a-e** in excellent yields. The spectral studies help to confirm the structure of 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles.

By reacting with 1-azido-2-chlorobenzene using the CuI method, click chemistry was applied to these propargyl ethers. Research was done on the catalysts used in this chemical. Based on the data, it was clear that CuI was the best catalyst for the aforementioned chemical reaction. From 74.11 to 84.54%, 1H-1,2,3-triazoles **7a-7e** were produced. Inhibitory actions against selected Gram-positive and Gram-negative bacteria as well as yeasts were tested for in all synthesized fluoro and methoxy-substituted 2-amino-4-aryl-7-propargyloxy-4H-chromene-3-carbonitriles with 1-azido-2-chlorobenzene conjugates. With MIC values between 3.12 and 12.5 mM, certain compounds showed considerable inhibitory action against the investigated bacteria. The MIC values of the triazoles **7c, 7d**, and **7e** against three clinical MRSA isolates ranged from 1.56 to 6.25 mM, respectively.

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