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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF CHROMONE ANCHORED 1,2,3-TRIAZOLE DERIVATIVES

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ABSTRACT:
In present work, we have synthesized a series of novel (*E*)-1-(5-Chloro-2-hydroxyphenyl)-3-(5-fluoro-2-((1-(substitutedphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-ones (**3a-g**) from 6-chloro-2-(5-fluoro-2-(prop-2-yn-1-yloxy)phenyl)-4*H*-chromen-4-one **1** using Click chemistry. All developed compounds were analyzed using I.R., ^{1}H NMR, ^{13}C NMR, and mass spectrometry. Furthermore, all the synthesized compounds were evaluated for their in vitro antibacterial and antifungal activity.

KEYWORDS: Chromone, 1,2,3-Triazole, Click Chemistry, Antimicrobial

INTRODUCTION:

Chromones are promising structural scaffolds that can be employed as mimetics of short peptide. The relevance of having access to effective synthetic methods for chromone derivatives is implied by the broad range of applications noted for them and their prospective use in drug discovery.[i] The rigid bicyclic chromone fragment has been classified as a preferred structure in drug development since it is used in a wide spectrum of pharmacologically active molecules such as anticancer, anti-HIV, antibacterial, and anti-inflammatory medicines.[iix]

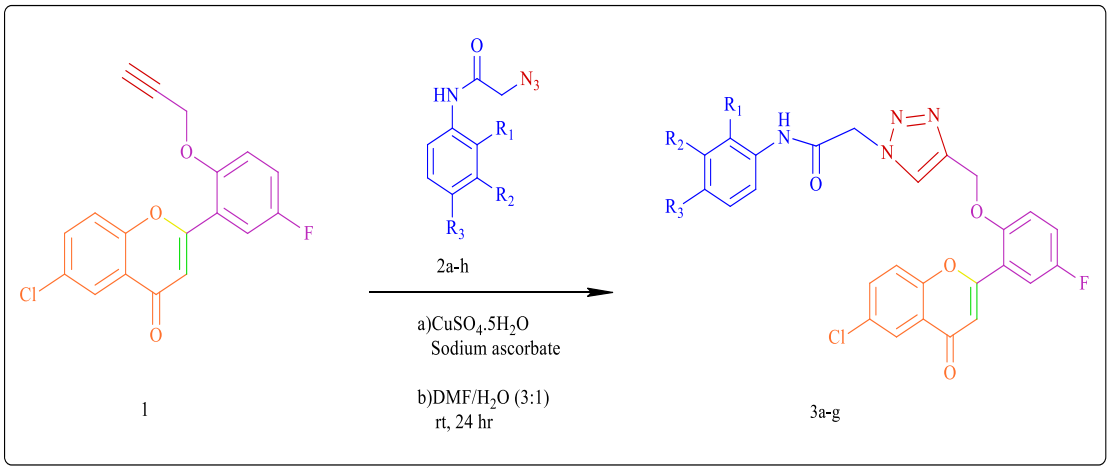
1,2,3-triazoles are five-membered heterocyclic compounds consisting of two carbon atoms and three neighbouring nitrogen atoms. The 1,2,3-triazole ring has received attention for its numerous applications in medical chemistry and drug discovery. 1,2,3-triazole moiety is a ubiquitous structural feature in the development of novel pharmaceuticals and can be generated by azide–alkyne cycloaddition processes, which is known as "click chemistry".[xi,xii]

Triazoles and their derivatives have attracted a lot of attention because of their potential uses in medicine and therapy, including anti-inflammatory,[xiii] anti-viral,[xiv] anti-cancer,[xv] anti-microbial,[xvi] anti-oxidant,[xvii] antifungal[xviii] and anticonvulsant properties.[xix] The 1,2,3-triazole scaffold has drawn particular interest in drug discovery recently due to the existence of many drug molecules with 1,2,3-triazole groups, such as rufinamide,[xx] cefatrizine[xxi] and tazobactum[xxii] that are used to treat bacterial infections and cancer. In recent years, molecular hybridization has been used in drug design and development to combine pharmacophoric moieties with diverse bioactivity to create a unique hybrid product with enhanced biological activity relative to the parent drug.[xxiii]

EXPERIMENTAL:

All chemicals and solvents were obtained from Chemsworth, Loba Chemie, and Molychem and utilized without additional purification. The reactions were monitored using thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh), and the spots were seen using UV light or an iodine chamber. The melting temperatures of the synthesized compounds were obtained using open-glass capillaries on the Stuart Scientific melting point instrument (SMP10) and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were obtained on a model FT-NMR spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C) and processed with Delta software. The λ_{max} of the synthesized compounds were measured using a Jasco V-630 UV-visible spectrophotometer. Mass spectra were obtained using electrospray ionization (ESI).

RESULTS AND DISCUSSION:



Scheme 1: Synthesis of 2-(4-((2-(4-oxo-4H-chromen-2-yl)phenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide derivatives **(3a-g)**

Compound	**R_1**	**R_2**	**R_3**
3a	H	H	H
3b	H	NO_2	H
3c	NO_2	H	H
3d	H	CN	H
3e	H	H	CN
3f	H	H	OCH_3
3g	OCH_3	H	NO_2

***General procedure for the synthesis of 6-chloro-2-(5-fluoro-2-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one* (1)**

In RBF, alkyne **(4)** was dissolved in a small amount of DMF. To this solution, add 8-10 balls of iodine and keep it under refluxing conditions at 160˚C for 3 hours. The development of the reaction was tracked using TLC. Following the completion of the reaction, the liquid was put into cooled water and neutralized with sodium thiosulphate. The chilled water temperature ranged from 2 to 5 °C. The product was filtered, dried at 60°C, and used without additional purification.

6-chloro-2-(5-fluoro-2-(prop-2-yn-1-yloxy)phenyl)-4H-chromen-4-one (1)

White solid, Yield: 98%; M.P: 178˚C λ_{max}: 371.5 nm, I.R.: 3309.85, 3140.11, 3086.11, 2970.38, 2931.80, 2854.65, 2129.41, 1635.64, 1566.20, 1504.48, 1465.90, 1442.75, 1350.17, 1288.45, 1249.87, 1180.44, 1026.13, 972.12, 856.39, 817.82, 794.67, 686.66, 624.94. ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 8.17 (d, *J* = 2.6 Hz, 1H), 7.61 (ddd, *J* = 11.0, 9.1, 2.8 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.16 – 7.13 (m, 2H), 4.81 (d, *J* = 2.4 Hz, 2H), 2.54 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ ppm δ 177.50, 159.40, 159.39, 158.14, 156.54, 154.73, 152.12, 152.10, 134.08, 131.21, 125.21, 125.19, 124.74, 119.85, 118.86, 118.71, 116.04, 115.87, 115.21, 115.15, 113.15, 56.99. HRMS (ESI): m/z calculated for $C_{18}H_{10}ClFO_3$: 329.0378 $[M+H]^+$ found: 329.0380

***General procedure for the synthesis of (E)-1-(5-Chloro-2-hydroxyphenyl)-3-(5-fluoro-2-((1-(substitutedphenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-one* (3a-g)**

In RBF, (E)-1-(5-chloro-2-hydroxyphenyl)-3-(5-fluoro-2-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one **(1)** (0.5 mmol) was dissolved in a DMF:H_2O (3:1, 12 ml) solvent mixture while stirring constantly. To this reaction mixture, copper sulphate (20 mol%) and a catalytic quantity of sodium ascorbate (5 mol%) were added and agitated for an additional 10-15 minutes. Following that, 0.5 mmol of aryl azide **(2a-g)** was added and mixed for the following 24 hours. The progress of the reaction was tracked using TLC. Following the end of the reaction, ice cold water was added to the reaction mixture and stirred for an additional 25-30 minutes. The solid was purified using column chromatography with an eluent of n-hexane:ethyl acetate (50:50) **(3a-g)**.

***2-(4-((2-(6-chloro-4-oxo-4H-chromen-2-yl)-4-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide* (3a)**

Buff solid, Yield: 70 %; M.P: 138˚C; λ_{max}: nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.34 (s, 1H), 8.33 (d, *J* = 23.0 Hz, 1H),), 8.32 (s, 1H), 7.88 (d, *J* = 31.9 Hz, 3H), 7.53 (d, *J* = 39.1 Hz, 4H), 7.04 (d, *J* = 112.0 Hz, 4H), 5.38 (d, *J* = 49.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 181.19, 168.75, 164.32, 160.76, 158.96, 158.46, 158.12, 146.88, 139.43, 136.71, 135.78, 129.21, 125.98, 121.39, 119.22, 117.07, 116.94, 94.42, 67.67, 60.38, 57.39, 34.16. Mass: MS (ESI-MS): m/z 503.89 $[M-H]^-$

***2-(4-((2-(6-chloro-4-oxo-4H-chromen-2-yl)-4-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-nitrophenyl)acetamide* (3b)**

Buff solid, Yield: 92 %; M.P: 95˚C; λ_{max}: 338.0 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.99 (s, 1H), 8.58 (s, 1H), 8.33 (d, *J* = 10.2 Hz, 1H), 8.02 – 7.87 (m, 3H), 7.84 (s, 1H), 7.69 – 7.37 (m, 3H), 7.11 (d, *J* = 55.7 Hz, 1H), 5.45 (d, *J* = 8.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 176.40, 165.45, 153.71, 148.47, 142.74, 139.94, 134.64, 131.03, 130.89, 130.37, 127.03, 125.70, 124.48, 124.11, 121.67, 118.80, 113.89, 112.19, 89.60, 62.94, 52.74. Mass: MS (ESI-MS): m/z 548.89 $[M-H]^-$

***2-(4-((2-(6-chloro-4-oxo-4H-chromen-2-yl)-4-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-nitrophenyl)acetamide* (3c)**

Dark yellow solid, Yield: 95%; M.P: 120˚C; λ_{max}: 331.5 nm;
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.74 (s, 1H), 8.38 (s, 1H), 8.35 – 8.18 (m, 2H), 8.07 – 7.70 (m, 4H), 7.59 – 7.38 (m, 2H), 7.06 – 6.98 (m, 3H), 5.40 (d, *J* = 4.6 Hz, 4H).
^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 176.48, 173.74, 165.34, 154.86, 153.35, 143.70, 142.74, 134.67, 133.35, 130.39, 128.56, 126.90, 126.35, 125.97, 125.55, 124.61, 124.12, 122.02, 121.64, 119.87, 117.82, 112.41, 63.00, 29.49. Mass: MS (ESI-MS): m/z 54789 $[M-2H]^-$

2-(4-((2-(6-chloro-4-oxo-4H-chromen-2-yl)-4-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-cyanophenyl)acetamide (**3d**)
Pale green solid, Yield: 60 %; M.P: 155˚C; λ_{max}: 333.0 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.60 (s, 1H), 8.12 (d, *J* = 2.3 Hz, 1H), 8.07 (s, 1H), 7.84 – 7.48 (m, 5H), 7.43 – 7.22 (m, 4H), 6.93 (s, 1H), 5.18 (d, *J* = 17.2 Hz, 4H).
^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 181.18, 172.50, 170.06, 164.35, 158.93, 144.38, 135.67, 132.62, 129.24, 129.09, 127.18, 125.70, 123.77, 116.98, 94.31, 67.71, 57.46.
Mass: MS (ESI-MS): m/z 530.90 $[M-H]^-$

2-(4-((2-(6-chloro-4-oxo-4H-chromen-2-yl)-4-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-cyanophenyl)acetamide (**3e**)
Pale yellow solid, Yield: 70%; M.P: 80˚C; λ_{max}: 336.5 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.92 (s, 1H), 8.32 (s, 2H), 7.85 (d, *J* = 45.1 Hz, 6H), 7.58 (s, 2H), 7.18 (s, 1H), 5.44 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 176.50, 165.51, 159.53, 154.21, 143.03, 142.80, 142.25, 133.93, 131.03, 127.05, 124.48, 119.78, 116.69, 115.86, 112.18, 106.05, 62.95, 52.79. Mass: MS (ESI-MS): m/z 530.90 $[M+H]^-$

2-(4-((2-(6-chloro-4-oxo-4H-chromen-2-yl)-4-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide (**3f**)
Pale green solid, Yield: 79 %; M.P: 240˚C; λ_{max}: 332.0 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.54 (s, 1H), 8.28 (s, 1H), 8.26 (s, 1H) 7.94 (d, *J* = 1.6 Hz, 1H), 7.84 (d, *J* = 2.2 Hz, 3H), 7.66 – 7.42 (m, 5H), 7.18 (d, *J* = 8.7 Hz, 3H), 7.04 (s, 1H), 5.38 (d, *J* = 22.7 Hz, 4H), 3.33 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 176.49, 164.50, 160.06, 157.52, 154.86, 153.38, 142.28, 135.26, 134.68, 130.37, 126.94, 124.62, 124.12, 121.70, 121.54, 121.46, 119.88, 116.54, 116.09, 115.87, 112.33, 62.92, 52.62. Mass: MS (ESI-MS): m/z 556.92 $[M+Na]^-$

2-(4-((2-(6-chloro-4-oxo-4H-chromen-2-yl)-4-fluorophenoxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxy-2-nitrophenyl)acetamide (**3g**)
Dark yellow solid, Yield: 73%; M.P: 95˚C; λ_{max}: 375.0 nm; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.33 (s, 1H), 10.55 (s, 1H), 8.33 – 8.17 (m, 2H), 8.03 (d, *J* = 9.6 Hz, 3H), 7.66 – 7.46 (m, 4H), 7.37 (d, *J* = 22.5 Hz, 4H), 7.02 (d, *J* = 8.7 Hz, 1H), 5.37 (d, *J* = 41.7 Hz, 6H), 3.84 (s, 5H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 192.89, 165.28, 160.73, 157.08, 154.17, 144.04, 138.71, 136.21, 130.16, 128.08, 126.96, 125.72, 124.79, 123.48, 123.39, 123.18, 122.52, 120.77, 120.21, 114.93, 109.74, 62.65, 56.52, 52.34. Mass: MS (ESI-MS): m/z 579.09 $[M]^+$

BIOLOGICAL SCREENING:

All the synthesized compounds were screened for antibacterial and antifungal activities. The bacterial strains *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96) and *Streptococcus pyogenes* (MTCC 442); fungal strains *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) were used. The minimum inhibitory concentration (MIC) was determined by the broth dilution method and ampicillin and griseofulvin were used as reference drugs. The results of antibacterial activity and antifungal activity are shown in **Table 1**.

The compounds **3f** (62.5 µg/mL) and **3a** and **3c-3d** (100 µg/mL) exhibited good antibacterial activity against *E. coli* compared with the standard drug ampicillin (100 µg/mL). Compound **3a** (62.5 µg/mL) and 3**e-3g** (100 µg/mL) exhibited good antibacterial activity against *P. aeruginosa* compared with the standard ampicillin (100 µg/mL). Compounds **3a, 3c**, **3e** and **3f** (100 µg/mL) exhibited good antibacterial activity against *s. aureus* compared with the standard ampicillin (100 µg/mL). Compounds 3**b** and **3f** (100 µg/mL) exhibited good antibacterial activity against *s. aureus* compared with the standard ampicillin (100 µg/mL).
The compounds **3a** and **3e** (250 µg/mL) against *C. albicans* exhibited good activity compared with the standard Griseofulvin (500 µg/mL). In comparison, none of the compounds showed good activity against *A. niger* and *A. clavatus*.

Table-1: *In Vitro* Antimicrobial activity of the compounds (**3a-g**) MIC (µg/mL)

Cpd	Antibacterial Activity				Antifungal Activity		
	EC	**PA**	**SA**	**SP**	**CA**	**AN**	**AC**
3a	100	62.5	100	125	250	1000	1000
3b	200	250	200	100	>1000	>1000	>1000
3c	100	125	100	200	1000	500	500
3d	100	125	250	250	500	500	500
3e	100	100	100	125	250	500	500
3f	62.5	100	100	100	500	1000	1000
3g	200	100	125	125	1000	500	500
AM	**100**	**100**	**100**	**100**	-	-	-
GF	-	-	-	-	**500**	**100**	**100**

Cpd: Compound; EC: *Escherichia coli* (MTCC 443); PA: *Pseudomonas aeruginosa* (MTCC 1688); SA: *Staphylococcus aureus* (MTCC 96); SP: *Streptococcus pyogenes* (MTCC 442) CA: *Candida albicans* (MTCC 227), AN: *Aspergillus niger* (MTCC 282); AC: *Aspergillus clavatus* (MTCC 1323); AM: Ampicillin; GF: Griseofulvin.

CONCLUSION:

In conclusion, we have reported a series of novel (*E*)-1-(5-Chloro-2-hydroxyphenyl)-3-(5-fluoro-2-((1-(substitutedphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy)phenyl)prop-2-en-1-ones (**3a-g**). All the synthesized compounds were screened for their antimicrobial activities. Some of the compounds showed good activities against the tested bacterial and fungal strains.

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