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Synthesis, Characterization and Biological Evaluation of Novel Triazole Linked Chromone Biheterocycle Analogs

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The current work focused on the synthesis of novel chromone biheterocycle analogs followed by its characterization through physico-chemical and spectral techniques like FTIR, mass and NMR spectroscopy. The basic triazole heterocycle and its analogs have different biological properties. At the point when one biological active molecule is connected to another, the resultant shows improved potency (biheterocycles). Chromone and triazole are selected in this study to develop new efficient, simple, economically viable and biologically active synthetic compounds. All the novel derivatives of triazole linked chromone biheterocycles were synthesized *via* a click chemistry procedure and screened for *in vitro* antimicrobial, antifungal and antioxidant studies. Among them, the compounds CRN-F (IC_{50} = 35.97), CRN-H (IC_{50} = 28.76) and CRN-J (IC_{50} = 29.72) have significant free radical scavenging activity in comparison with the ascorbic acid as control standard (IC_{50} = 23.07). Some of these novel derivatives exhibited moderate antimicrobial and antifungal activity compared to that of the reference standards. Hence, the novel chromone biheterocycle analogs played a protective role against oxidative damage.

Keywords: Chromones, Triazoles, Biheterocycle analogs, Antimicrobial activity, Antioxidant activity.

INTRODUCTION

Chromone is one of the lead pharmacophores in drug discovery belongs to the category of naturally occurring flavones. Khellin was the first chromone, which has been isolated from the seeds of the plant *Ammi visnaga* [1]. Several naturally occurring chromones such as genistein [2], quercetin [3], diosmin [4], isoquercetin [5] are being investigated for many types of therapeutic applications. A large range of synthetic chromones and its derivatives have been shown antimicrobial, anti-inflammatory, antioxidant and anticancer activities [6-8]. An enormous study on *in vitro*, *in vivo* and clinical examinations has set up the role of chromones in alleviating allergies, reducing oxidative damage, inhibiting cancer, infections and inflammation and for the treatment of neurological and psychiatric disorders [9]. Chromones are also reported to inhibit HIV-1 reverse transcriptase, interleukin-1 production, protein kinases and have mimicking bradycardia.

The most significant and recent investigations revealed that triazole derivatives have a wide range of therapeutic applications such as antimicrobial activity [10], analgesic [11], antineoplastic activity [12,13], antidiabetic [14], anti-inflammatory and antimalarial, activity, antileishmanial and neuro-protective agents [15-17]. A wide verity of drugs containing triazole moiety available in market (Fig. 1) such as tebuconazole, posaconazole, tazobactam, rufinamide, itraconazole, fluconazole, paclobutrazol, letrozole, vorozole and antiviral ribavirin [18-20].

Considering expected therapeutic applications of chromones and triazoles, both the heterocyclic moieties are chosen in the current study with a view to develop new efficient, simple, economically viable and biologically active triazole linked chromone biheterocycles. Click chemistry which involves 1,3-dipolar cycloaddition between an azide and alkyne have been broadly utilized as a proficient, flexible tool for the synthesis of 1,2,3-triazoles with 1,4-disubstitution using copper as a catalyst [21-23].

EXPERIMENTAL

Reagents and solvents utilized in the present work were of synthetic grade from Finar synthetics Ltd., (Mumbai, India),

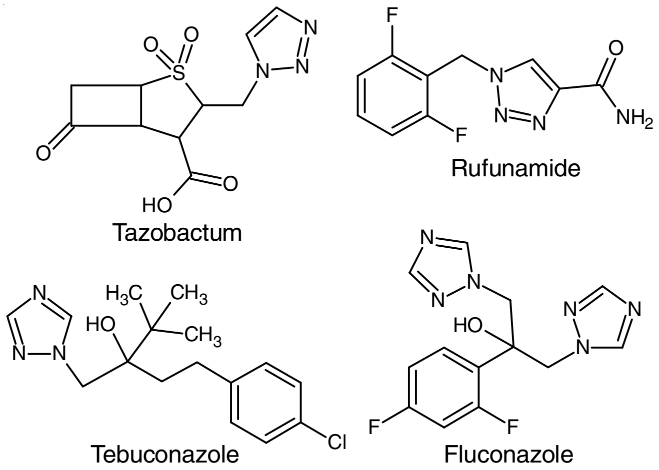


Fig. 1. Triazole related medicines available in the market

Merck, SD Fine-Chemicals. All the chemicals and solvents used were of synthetic grade from Finar chemicals Ltd., India, E. Merck, S.D. Fine-Chemicals. Melting points were estimated with a Fischer-Johns melting point apparatus. Nuclear magnetic resonance (NMR) spectral studies were conducted on Bruker with 300 MHz using suitable solvents with TMS as the internal standard and the chemical shifts are addressed with δ scale. ^{13}C NMR spectral studies were conducted using 125 MHz spectrometer. ESI-MS data were collected using an ion trap mass analyzer of Thermo Finnigan LCQ make and of the electron spray ionizer. Every one of the reactions was observed by analytical Thin-layer chromatography (TLC) using silica gel GF$_{254}$ coated TLC plates. Visualization of the TLC plates using short-wavelength UV light (254 nm) and other visualization techniques like exposure to iodine vapours and/or with the use of dipping solvents like PMA solution (phosphomolybdic acid-ceric sulfate-sulfuric acid solution), followed by heating around 100 ºC. Rota evaporator was used to remove the solvents. Column chromatography was performed for the purification of the synthesized compounds using a suitable solvent.

Synthetic methodology

Step 1: Synthesis of 4-(3-bromopropoxy)benzaldehyde (3): Taken 4-hydroxy benzaldehyde (**1**) (1 equiv.) into the reaction vessel and dissolved in 5 mL of dry DMF. To the solution added 3 equivalents of anhydrous potassium carbonate and 42.5 mmol of 1,3-dibromopropane (8.58) (**2**). The reaction mixture was refluxed for about 12 h. The reaction was monitored with TLC and after completing the reaction, the carbonate was removed using suction filtration. After that solvent was evaporated to offer the crude product which was then purified using column chromatography technique with ethyl acetate and hexane as a mobile phase to furnish a black colour semi-solid product. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.36 (2H, m, CH_2), 3.61 (2H, t, J = 6.48 Hz, O-CH_2), 4.20 (2H, t, J = 5.87 Hz, Br-CH_2), 7.00 (2H, d, J = 8.80 Hz, Ar- H), 7.83 (2H, d, J = 8.80 Hz, Ar- H, 9.89 (1H, s, O- CH).

Step 2: Synthesis of 4-(3-azidopropoxy)benzaldehyde (4): Taken compound **3** (1 equiv.) in reaction vessel and dissolved in 20 mL of dry DMF. Added 7.12 mmol of sodium azide and stirred the reaction mixture for about 12 h at 80 ºC. After completing the reaction, it was then cool down to ambient temperature and then added 20 mL of water, which was then extracted with ethyl acetate and washed with 20 mL of brine and dried using Na_2SO_4 and concentrated under reduced pressure. The resultant was then purified using column chromatography (5% ethyl acetate/hexane) to give yellow coloured azido compound **4**. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.04-2.11 (2H, m, CH_2), 3.54 (2H, t, J = 6.60, O-CH_2), 4.14 (2H, t, J = 5.99 Hz, CH_2), 7.00 (2H, d, J = 8.68 Hz, Ar-H), 7.83 (2H, d, J = 8.80 Hz, Ar-H), 9.89 (1H, s, O-CH). The ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.5, 31.9, 65.5, 114.7, 130.0, 131.9, 163.6, 190.7.

Step-3: Synthesis of (*E*)-3-(4-(3-azidopropoxy)phenyl)-1-(2hydroxyphenyl)prop-2-en-1-one (6): Taken 1 equivalent each of 4-(3-azidopropoxy)benzaldehyde (**4**) and 1-(2-hydroxyphenyl)ethan-1-one (**5**) into the reaction vessel and dissolved in 20 mL of ethanol followed by the addition of 10 mL 40% NaOH solution. The reaction mixture was stirred at room temperature for 0.5 h. The resulting product was then poured into the crushed ice and allowed for acidification with diluted hydrochloric acid. It was then filtered, dried over Na_2SO_4 and recrystallized using ethanol to offer the yellow coloured solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.09 (2 H, m, CH_2), 3.54 (2 H, t, J = 6.60, O-CH_2), 4.22 (2H, t, J = 5.99 Hz, CH_2), 6.94-6.97 (3 H, m, Ar-CH), 7.02 (2H, d, J = 8.19 Hz, Ar-H), 7.47-7.57 (2 H, m, Ar-CH), 7.62 (2H, d, J = 8.68 Hz, Ar-H), 7.89-7.94 (2H, m, HC=CH), 12.92 (1H, s, OH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 28.6, 48.1, 64.6, 114.9, 117.7, 118.4, 118.7, 120.0, 127.57, 129.5, 130.5, 136.1, 145.2, 161.0, 163.5, 193.6.

Step 4: Synthesis of 2-(4-(3-azidopropoxy)phenyl)-4*H*-chromen-4-one (7): One equivalent of compound **6** dissolved in DMSO and added 10.0 mL/mmol of (((*E*)-3-(4-(3-azidopropoxy)phenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one and 0.01 equivalent of iodine was added. The reaction mixture was then refluxed for about 2 h. The reaction was monitored with TLC and after completing the reaction, the mixture was then poured into a crushed ice and allowed for quenching with sodium thiosulphate (hypo) solution. The resultant was then filtered and purified using column chromatography to get 2-(4-(3-azidopropoxy)phenyl)-4*H*-chromen-4-one as pale yellow coloured compound with 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.05-2.01 (2H, m, CH_2), 3.55 (2 H, t, J = 6.60, O-CH_2), 4.12 (2H, t, J = 5.99 Hz, CH_2), 6.74-6.75 (1H, m, Ar-CH), 6.92-7.01 (2H, m, Ar-CH), 7.40 (1H, t, J = 7.70 Hz, Ar-H), 7.51-7.55 (1H, m, Ar-CH), 7.66-7.70 (1H, m, -H), 7.86-7.88 (2H, m, Ar-H), 8.21-8.23 (1H, dd, J = 7.825, CH-C=O).

Step 5: Synthetic procedure for triazolyl chromone biheterocycles (CRN-A to CRN-N): To a 1 equivalent of azido compound **7**, 1.1 equivalents of various substituted alkynes were added, dissolved in THF and water with equal ratio. To that added 20 mol% each of copper sulfate pentahydrate and sodium ascorbate. The reaction mixture was then kept for stirring at room temperature for about 6 h. The reaction was monitored by TLC and the resultant is extracted with 2 × 10 mL portions of ethyl acetate and 5 mL of water. The combined organic layers were then collected and dried over anhydrous sodium sulfate, concentrated and allowed for purification using column chromatography to furnish the novel triazole linked chromone biheterocycles (**Scheme-I**).

2-(4-(3-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)propoxy)-phenyl)-4*H*-chromen-4-one (CRN-A): Yield: 84%, light yellow coloured solid, m.p.: 162-164 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.47-2.55 (2H, m, CH_2), 4.08-4.12 (2H, m, N-CH_2), 4.66 (2H, t, *J* = 6.725 Hz, O-CH_2), 6.74-6.76 (1H, m, Ar-H), 6.99-7.04 (2H, m, Ar-H), 7.31-7.34 (1H, m, Ar-H), 7.39-7.45 (3H, m, Ar-H), 7.54 (1H, d, *J* = 8.314 Hz, CH), 7.67-7.71 (1H, m, Ar-H), 7.78-7.88 (5H, m, Ar-H), 8.21-8.23 (1H, m, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.8, 47.0, 64.3, 106.2, 114.8, 117.9, 120.0, 123.8, 124.4, 125.1, 125.6, 128.0, 128.2, 128.8, 130.3, 133.6, 147.8, 156.1, 161.1, 163.2, 178.3. Mass spectra of compound CRN-A shows abundant molecular ion peaks at *m/z* 424 (M+1), m.f.: of $C_{26}H_{21}N_3O_3$ exact mass: 423.16 m.w.: 423.46 *m/e*: C, 73.74; H, 5.00; N, 9.92; O, 11.33.

2-(4-(3-(4-(*p*-Tolyl)-1*H*-1,2,3-triazol-1-yl)propoxy)-phenyl)-4*H*-chromen-4-one (CRN-B): Yield: 86%, Off white solid, m.p.: 168-170 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.37-2.39 (3H, m, CH_3), 2.47-2.55 (2H, m, CH_2), 4.08-4.12 (2H, m,N-CH_2), 4.66 (2H, t, *J* = 6.725 Hz, O-CH_2), 6.74-6.76 (1H, m, Ar-H), 6.99-7.04 (2H, m, Ar-H), 7.21-7.35 (2H, m, Ar-H), 7.39-7.45 (1H, m, Ar-H), 7.67-7.71 (1H, m, Ar-H), 7.71-7.78 (4H, m, Ar-H), 7.82-7.88 (2H, m, Ar-H), 8.21-8.23 (1H, m, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 21.2, 29.8, 46.9, 64.3, 106.2, 114.8, 117.9, 119.6, 123.8, 124.4, 125.1, 125.6, 127.5, 128.0, 129.5, 133.6, 138.0 147.8, 156.1, 161.1, 163.2, 178.3. Mass spectra of compound CRN-B shows abundant molecular ion peaks at *m/z* 438.30 (M+1), m.f.: $C_{27}H_{23}N_3O_3$, exact mass: 437.17, m.w.: 437.49, *m/e*: 437.17 (100.0%), 438.18 (29.6%), 439.18 (4.8%), 438.17 (1.1%), C, 74.12; H, 5.30; N, 9.60; O, 10.97.

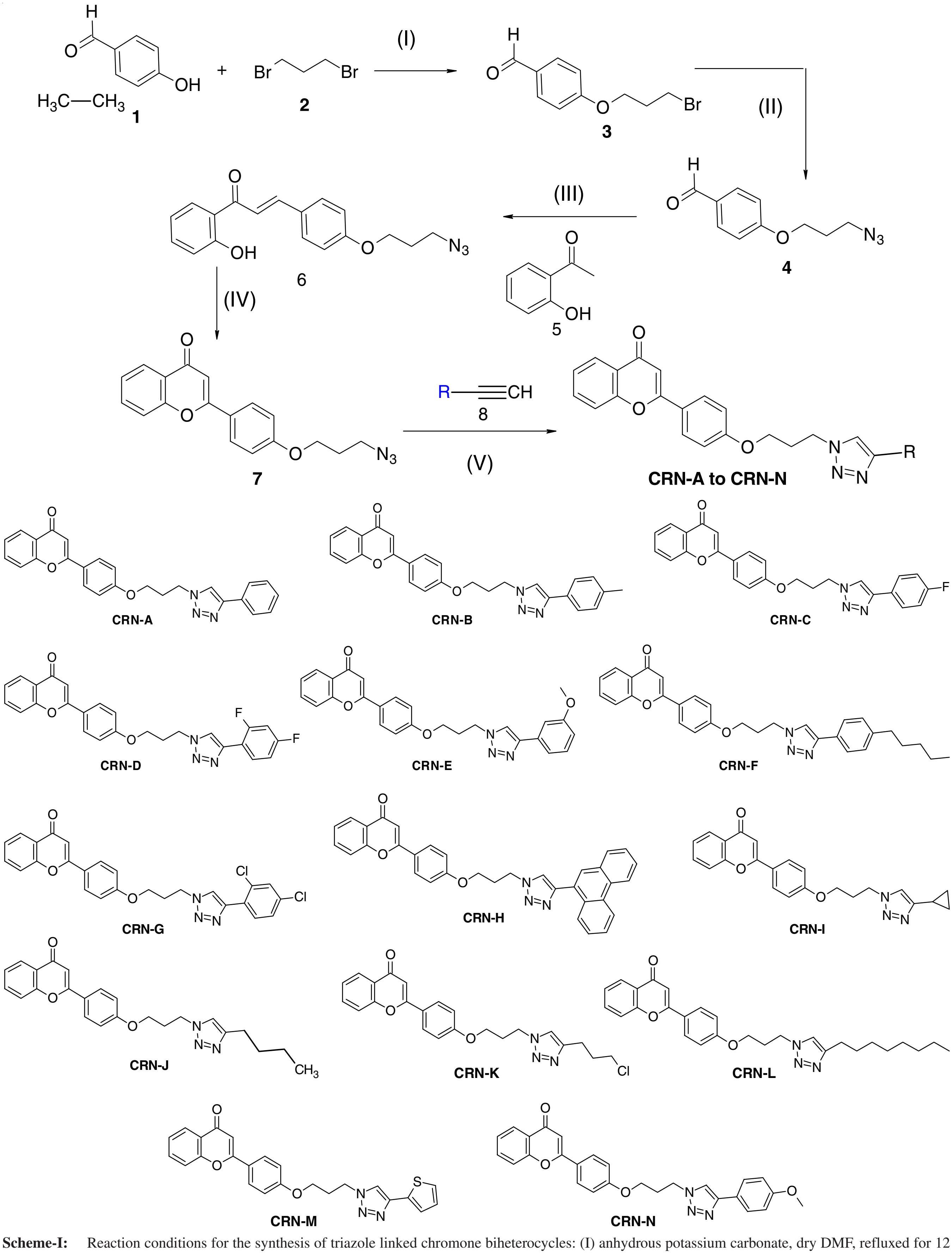
2-(4-(3-(4-(4-Fluorophenyl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-C): Yield: 89%, pale brown solid, m.p.: 156-158 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.47-2.53 (2H, m, CH_2), 4.09-4.12 (2H, m,N-CH_2), 4.66 (2H, t, *J* = 6.86 Hz, O-CH_2), 6.74-6.77 (1H, m, Ar-H), 6.99-7.04 (2H, m, Ar-H), 7.09-7.12 (2H, m, Ar-H), 7.39-7.43 (1H, m, Ar-H), 7.54 (1H, d, *J* = 8.39 Hz, Ar-H), 7.68-7.72 (1H, m, Ar-H), 7.74 (1 H, s, Ar-H), 7.77-7.79 (2 H, m, Ar-H), 7.87-7.89 (2H, m, Ar-H), 8.22-8.24 (1 H, m, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.7, 47.0, 64.3, 106.2, 114.8, 114.9, 115.9, 117.9, 119.7, 123.8, 124.4, 125.1, 125.6, 126.6, 127.3, 127.4, 128.0, 128.5, 133.6, 146.9, 156.1, 161.1, 161.3, 163.1, 163.8, 178.3. Mass spectra of compound CRN-C shows abundant molecular ion peaks at *m/z* 442.30 (M+1), m.f.: $C_{26}H_{20}FN_3O_3$ exact mass: 441.15, m.w.: 441.45, *m/e*: 441.15 (100.0%), 442.15 (29.3%), 443.16 (3.9%), C, 70.74; H, 4.57; F, 4.30; N, 9.52; O, 10.87.

2-(4-(3-(4-(2,4-Difluorophenyl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-D): Yield: 86%, Off-white solid, m.p.: 156-158 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.46-2.53 (2H, m, CH_2), 4.06-4.12 (2H, m, N-CH_2), 4.65-4.67 (2H, m, O-CH_2), 6.75 (1H, s, Ar-H), 6.99-7.02 (2H, m, Ar-H), 7.26 (2H, s, Ar-H), 7.39-7.43 (1H, m, Ar-H), 7.67-7.72 (1H, m, Ar-H), 7.65-7.75 (3H, m, Ar-H), 7.78-7.90 (2 H, m, Ar-H), 8.22-8.24 (1H, m, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.7, 47.1, 64.3, 106.3, 114.6, 114.8, 117.6, 117.8, 117.9, 120.1, 121.6, 124.6, 125.1, 125.6, 128.1, 133.6, 156.1, 161.1, 161.3, 163.1, 178.3. Mass spectra of compound CRN-D shows abundant molecular ion peaks at *m/z* 460.30 (M+1), m.f.: $C_{26}H_{19}F_2N_3O_3$, exact mass: 459.14, m.w.: 459.44, *m/e*: 459.14 (100.0%), 460.14 (29.3%), 461.15 (3.9%), C, 67.97; H, 4.17; F, 8.27; N, 9.15; O, 10.45.

2-(4-(3-(4-(3-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-E): Yield: 85%, Off-white solid, m.p.: 160-162 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.47-2.54 (2H, m, CH_2), 3.85 (3H, s, OCH_3), 4.08-4.12 (2H, m,N-CH_2), 4.66 (2H, t, *J* = 6.73 Hz, O-CH_2), 6.77-6.76 (1H, m, Ar-H), 6.87-6.90 (1H, m, Ar-H), 7.00-7.04 (2H, m, Ar-H), 7.29-7.34 (2H, m, Ar-H), 7.40-7.44 (2H, m, Ar-H), 7.54-7.56 (1H, m, Ar-H), 7.67-7.71 (1H, m, Ar-H), 7.77-7.78 (1H, m, Ar-H), 7.87-7.89 (2H, m, Ar-H), 8.21-8.24 (1H, dd, *J* = 1.589 Hz, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.8, 47.0, 55.3, 64.3, 106.2, 110.7, 114.2, 114.8, 115.0, 117.9, 118.0, 120.2, 123.8, 124.5, 125.1, 125.6, 126.0, 126.5, 128.0, 128.5, 129.8, 131.6, 133.6, 143.2, 147.6, 156.1, 160.0, 161.1, 163.2, 178.3. Mass spectra of compound CRN-E shows abundant molecular ion peaks at *m/z* 454.25 (M+1), m.f.: $C_{27}H_{23}N_3O_4$, exact mass: 453.17, C, 71.51; H, 5.11; N, 9.27; O, 14.11.

2-(4-(3-(4-(4-Pentylphenyl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-F): Yield: 83%, light brown solid, m.p.: 148-150 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.37-2.39 (3H, m, CH_3), 2.47-2.55 (2H, m, CH_2), 4.08-4.12 (2H, m, N-CH_2), 4.66 (2H, t, *J* = 6.725 Hz, O-CH_2), 6.74-6.76 (1H, m, Ar-H), 6.99-7.04 (2H, m, Ar-H), 7.21-7.35 (2H, m, Ar-H), 7.39-7.45 (1H, m, Ar-H), 7.67-7.71 (1H, m, Ar-H), 7.71-7.78 (4H, m, Ar-H), 7.82-7.88 (2H, m, Ar-H), 8.21-8.23 (1H, m, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 13.9, 22.4, 27.7, 29.7, 31.0, 35.6, 46.9, 64.3, 68.4, 106.2, 114.8, 115.0, 117.9, 119.6, 123.8, 124.4, 125.1, 125.5, 125.6, 127.7, 128.0, 128.5, 128.8, 133.6, 143.1, 147.9, 156.1, 161.1, 163.2, 178.4. Mass spectra of compound CRN-F shows abundant molecular ion peaks at *m/z* 494.35 (M+1), m.f.: $C_{31}H_{31}N_3O_3$, exact mass: 493.23, m.w.: 493.59, *m/e*, C, 75.43; H, 6.33; N, 8.51; O, 9.73.

2-(4-(3-(4-(2,4-Dichlorophenyl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-G): Yield: 84%, off-white solid, m.p.: 156-158 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.47-2.54 (2H, m, CH_2), 4.06-4.13 (2H, m, N-CH_2), 4.66-4.69 (2H, m, O-CH_2), 6.76 (1H, s, Ar-H), 7.00-7.02 (2H, m, Ar-H), 7.40 (1H, t, *J* = 8.07, Ar-H), 7.49 (1H, d, *J* = 8.43 Hz, Ar-H), 7.54 (1H, d, *J* = 7.95, Ar-H), 7.63-7.71 (2H, m, Ar-H), 7.79 (1 H, s, Ar-H), 7.90 (3H, m, Ar-H), 8.22-8.24 (1H, dd, *J* = 1.589 Hz, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.7, 47.2, 64.2, 106.3, 114.8, 117.9, 120.4, 123.9, 124.8, 125.1, 125.6, 127.4, 128.1, 130.4, 130.8, 132.0, 133.0, 133.6, 145.7, 156.1, 161.0, 163.1, 178.3. Mass spectra of compound CRN-G shows abundant molecular ion peaks at *m/z* 492.40 (M+1), m.f.: $C_{26}H_{19}Cl_2N_3O_3$, exact mass: 491.08, m.w.: 492.35, *m/e*: C, 63.43; H, 3.89; Cl, 14.40; N, 8.53; O, 9.75.



Scheme-I: Reaction conditions for the synthesis of triazole linked chromone biheterocycles: (I) anhydrous potassium carbonate, dry DMF, refluxed for 12 h; (II) dry DMF, sodium azide, 80 °C for 12 h; (III) ethanol, 40% NaOH, 0.5 h, RT; (IV) DMSO, reflux for 2 h; (V) THF and water in 1:1 ratio, 20 mol % of $CuSO_4·5H_2O$ and 20 mol % of sodium ascorbate for 5-6 h at RT

2-(4-(3-(4-(Phenanthren-9-yl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-H): Yield: 81%, light brown solid, m.p.: 161-163 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.57-2.63 (2 H, m, CH_2), 4.15-4.18 (2 H, m, N-CH_2), 4.78 (2H, t, *J* = 6.84 Hz, O-CH_2), 6.76 (1 H, s, Ar-H), 7.03-7.08 (2H, m, Ar-H), 7.40-7.44 (1H, m, Ar-H), 7.54-7.61 (3H, m, Ar-H), 7.65-7.71 (3H, m, Ar-H), 7.87-7.91 (4H, m, Ar-H), 7.96 (1H, s, Ar-H), 8.22-8.25 (1 H, dd, *J* = 1.589 Hz, N-CH), 8.33-8.35 (1 H, m, Ar-H). 8.69-8.71 (1 H, d, *J* = 8.314 Hz, Ar-H), 8.75-8.78 (1 H, d, *J* = 8.314 Hz, Ar-H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.8, 47.0, 55.3, 64.3, 106.3, 110.7, 114.2, 114.8, 115.0, 117.9, 118.0, 120.2, 123.3, 124.5, 125.1, 125.6, 126.0, 126.5, 128.0, 128.5, 129.8, 131.6, 133.6, 143.2, 147.6, 156.1, 160.0, 161.1, 163.2, 178.3. Mass spectra of compound CRN-H shows abundant molecular ion peaks at *m/z* 524.30 (M+1), m.f.: $C_{34}H_{25}N_3O_3$, exact mass: 523.189, m.w.: 523.58, *m/e*: C, 77.99; H, 4.81; N, 8.03; O, 9.17.

2-(4-(3-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)propoxy)-phenyl)-4*H*-chromen-4-one (CRN-I): Yield: 83%, Off-white solid, m.p.: 152-154 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.79-0.88 (2H, m, cyclopropyl CH_2), 0.91-0.98 (2H, m, cyclopropyl CH_2), 1.92-0.98 (1H, m, cyclopropyl CH_2), 2.42-2.49 (2H, m, CH_2), 4.06-4.13 (2H, m,N-CH_2), 4.66-4.69 (2H, m, O-CH_2), 6.76 (1H, s, Ar-H), 6.99-7.08 (2H, m, Ar-H), 7.21-7.28 (1H, m, Ar-H), 7.42-7.48 (1H, m, Ar-H), 7.54 (1H, d, *J* = 7.95, Ar-H), 7.67-7.71 (1H, m, Ar-H), 7.88-7.91 (2H, m, Ar-H), 8.21-8.24 (1 H, dd, *J* = 1.589 Hz, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 6.6, 7.7, 29.6, 29.7, 46.7, 64.4, 106.2, 114.8, 115.0, 117.9, 120.4, 123.8, 124.4, 125.1, 125.6, 128.0, 133.5, 143.2, 150.2, 156.1, 161.1, 163.1, 178.3. Mass spectra of compound CRN-I shows abundant molecular ion peaks at *m/z* (M+2) 391.35, 454.30, 354.20 respectively, m.f.: $C_{23}H_{21}N_3O_3$, exact mass: 387.16, m.w.: 387.43, C, 71.30; H, 5.46; N, 10.85; O, 12.39.

2-(4-(3-(4-Butyl-1*H*-1,2,3-triazol-1-yl)propoxy)phenyl)-4*H*-chromen-4-one (CRN-J): Yield: 78%, light brown coloured solid, m.p.: 145-147 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.94-0.97 (3H, m, CH_3), 1.39-1.42 (4H, m, aliphatic CH_2), 1.63-1.72 (2H, m, aliphatic CH_2), 2.40-2.47 (2H, m, aliphatic CH_2), 2.67-2.700 (2H, m, propyl CH_2), 4.05 (2H, t, *J* = 5.79, N-CH_2), 4.57 (2H, t, *J* = 6.85, O-CH_2), 6.76 (1H, s, Ar-H), 6.91-6.93 (2H, m, Ar-H), 7.23-7.28 (1H, m, Ar-H), 7.42-7.44 (1H, m, Ar-H), 7.55-7.57 (1H, m, Ar-H), 7.68-7.72 (1H, m, Ar-H), 7.88-7.90 (2H, m, Ar-H), 8.22-8.24 (1H, dd, *J* = 1.589 Hz, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 13.9, 22.3, 22.5, 29.1, 29.8, 31.4, 44.1, 46.7, 64.4, 106.3, 114.8, 117.9, 121.0, 123.9, 124.4, 125.1, 125.6, 128.0, 133.6, 146.3, 156.1, 161.2, 163.1, 178.4. Mass spectra of compound CRN-J shows abundant molecular ion peaks at *m/z* (M+1) 418.35, m.f.: $C_{25}H_{27}N_3O_3$, exact mass: 417.20, m.w.: 417.50 *m/e*: C, 71.92; H, 6.52; N, 10.06; O, 11.50.

2-(4-(3-(4-(3-Chloropropyl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-K): Yield: 84%, Off-white solid, m.p.: 150-152 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.14-2.18 (2H, m, propyl CH_2), 2.45 (2H, t, *J* = 5.99, propyl CH_2), 2.89 (2H, t, *J* = 7.34, propyl CH_2), 3.56 (2H, t, *J* = 6.36, propyl CH_2), 4.05 (2 H, t, *J* = 5.75, N-CH_2), 4.59 (2H, t, *J* = 6.85, O-CH_2), 6.76 (1 H, s, Ar-H), 6.99-7.01 (2H, m, Ar-H), 7.36-7.38 (1H, m, Ar-H), 7.40-7.44 (1H, m, Ar-H), 7.55-7.57 (1H, m, Ar-H), 7.68-7.72 (1H, m, Ar-H), 7.88-7.91 (2H, m, Ar-H), 8.22-8.24 (1 H, dd, *J* = 1.589 Hz, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 22.5, 29.7, 31.7, 44.1, 46.7, 64.3, 106.2, 114.8, 117.9, 121.5, 120.4, 123.8, 124.4, 125.1, 125.6, 128.0, 133.6, 146.3, 156.1, 161.1, 163.1, 178.4. Mass spectra of compound CRN-K shows abundant molecular ion peaks at *m/z* (M+3) 426.22, m.f.: $C_{23}H_{22}ClN_3O_3$, exact mass: 423.13, m.w.: 423.8 *m/e*: C, 65.7; H, 5.23; Cl, 8.36; N, 9.91; O, 11.32.

2-(4-(3-(4-Octyl-1*H*-1,2,3-triazol-1-yl)propoxy)-phenyl)-4*H*-chromen-4-one (CRN-L): Yield: 82%, Light green solid, m.p.: 150-152 ºC, ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 0.86 (3H, t, *J* = 7.172, CH_3), 1.26-1.36 (6H, m, aliphatic CH_2), 1.60-1.67 (2H, m, aliphatic CH_2), 1.90-1.95 (2H, m, CH_2), 2.23-2.29 (1H, m, aliphatic CH_2), 2.42-2.54 (3H, m, aliphatic CH_2), 2.70 (2H, t, *J* = 7.78, propyl CH_2), 4.05 (2 H, t, *J* = 5.79, N-CH_2), 4.57 (2H, t, *J* = 6.85, O-CH_2), 6.76 (1 H, s, Ar-H), 6.99-7.04 (2H, m, Ar-H), 7.26-7.28 (2H, m, Ar-H), 7.40-7.44 (1H, m, Ar-H), 7.55-7.57 (1H, m, Ar-H), 7.68-7.72 (1H, m, Ar-H), 7.88-7.90 (2H, m, Ar-H), 8.22-8.24 (1 H, dd, *J* = 1.589 Hz, N-CH). Mass spectra of compound CRN-L shows abundant molecular ion peaks at *m/z* (M+1) 460.35, m.f.: $C_{28}H_{33}N_3O_3$, exact mass: 459.25,m.w.: 459.57 *m/e*: C, 73.18; H, 7.24; N, 9.14; O, 10.44.

2-(4-(3-(4-(Thiophen-2-yl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-M): Yield: 81%, light brown coloured solid, m.p.: 158-160 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.49 (2H, t, *J* = 5.49, CH_2), 4.09 (2 H, t, *J* = 4.73 Hz, N-CH_2), 4.65 (2H, t, *J* = 6.41, O-CH_2), 6.77 (1H, d, *J* = 9.92, Ar-H), 6.99-7.01 (2H, m, Ar-H), 7.32-7.43 (3H, m, Ar-H), 7.545-7.56 (1H, d, *J* = 8.24 Hz, Ar-H), 7.67-7.69 (3H, m, Ar-H), 7.87 (2H, d, *J* = 8.39 Hz, Ar-H), 8.22 (1H, d, *J* = 7.48 Hz, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.7, 46.9, 64.3, 106.2, 114.8, 115.0, 117.9, 119.8, 121.1, 123.8, 124.4, 125.1, 125.6, 125.7, 126.3, 128.0, 128.5, 131.6, 133.6, 143.9, 156.1, 161.1, 163.1, 178.3. Mass spectra of compound CRN-M shows abundant molecular ion peaks at *m/z* 430.25 (M+1), m.f.: $C_{24}H_{19}N_3O_3S$, exact mass: 429.11, m.w.: 429.49, *m/e*: 429.11 (100.0%), 430.12 (26.3%), 431.11 (4.5%), 431.12 (4.4%), 430.11 (1.9%), 432.11 (1.2%), C, 67.12; H, 4.46; N, 9.78; O, 11.18; S, 7.47.

2-(4-(3-(4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-propoxy)phenyl)-4*H*-chromen-4-one (CRN-N): Yield: 82%, Off-white solid, m.p.: 160-162 ºC, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 2.48-2.51 (2 H, m, CH_2), 3.83 (3H, s, OCH_3), 4.08-4.11 (2 H, m,N-CH_2), 4.65 (2H, t, *J* = 6.73 Hz, O-CH_2), 6.75 (1H, s, Ar-H), 6.94-6.96 (2H, m, Ar-H), 6.99-7.02 (2H, m, Ar-H), 7.39-7.43 (1H, m, Ar-H), 7.54 (1H, d, *J* = 7.95, Ar-H), 7.69-7.74 (4H, m, Ar-H), 7.87-7.89 (2H, m, Ar-H), 8.22-8.24 (1 H, dd, *J* = 1.59 Hz, N-CH). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 29.8, 46.9, 55.2, 64.3, 106.2, 114.2, 114.8, 115.0, 117.9, 119.2, 123.1, 123.8, 124.4, 125.0, 125.6, 126.9, 128.0, 128.5, 133.5, 143.2, 147.6, 156.1, 159.6, 161.1, 163.1, 178.3. Mass spectra of compound CRN-N shows abundant molecular ion peaks at *m/z* 454.25 (M+1), m.f.: $C_{27}H_{23}N_3O_4$, exact mass: 453.17, C, 71.51; H, 5.11; N, 9.27; O, 14.11.

RESULTS AND DISCUSSION

In present work, derivatives of triazole linked chromone biheterocycles were synthesized in five stages using simple procedure. The targeted compounds **CRN-A** to **CRN-N** were accomplished in excellent yields (71-86%) by the reaction of 2-(4-(3-azidopropoxy)phenyl)-4*H*-chromen-4-one (**7**) with various substituted alkynes (**8A-N**) utilizing click chemistry principle (**Scheme-I**).

All the derivatives were characterized by ^{1}H NMR, ^{13}C NMR and mass spectra. The compound CRN-A formation was affirmed from the ESI-MS spectrum with (M+H) peak at *m/z* 424, triazole-CH was authenticated by the multiplet at δ 8.22-8.24 ppm from ^{1}H NMR spectrum, also confirmed by the signals in the ^{13}C NMR spectrum at δ 178.3 ppm.

in vitro antioxidant activity

Free radical scavenging activity (DPPH): Antioxidant activity of methanolic extract of 1,2,3-triazole derivatives was estimated by utilizing 2,2-diphenyl-1-picrylhydrazyl (DPPH) method of Blois [24]. Prepared the solution of DPPH using methanol as the solvent in the concentration 0.2 mM. From this, taken 100 µL of DPPH solution and added to methanolic extracts of 1,2,3-triazole derivatives at the concentrations of 50, 100, 150, 200 and 250 µg/mL. Absorbance was recorded after 0.5 h at 517 nm. All the experiments were conducted in triplicates and the percentage of inhibition of the test solutions was determined by comparing the absorbance values with that of the control. Most of the novel derivatives of triazolyl chromone biheterocycles have shown good to excellent activities in comparison with control standard ascorbic acid (Table-1).

TABLE-1
ANTIOXIDANT ACTIVITY OF TRIAZOLE LINKED CHROMONE BIHETEROCYCLES BY DPPH FREE RADICAL SCAVENGING ACTIVITY METHOD

Compound code	IC_{50} of antioxidant potential	Compound code	IC_{50} of antioxidant potential
CRN-A	108.58	**CRN-I**	111.46
CRN-B	107.85	**CRN-J**	29.72
CRN-C	72.24	**CRN-K**	40.95
CRN-D	81.64	**CRN-L**	66.14
CRN-E	82.55	**CRN-M**	92.17
CRN-F	35.97	**CRN-N**	98.99
CRN-G	71.47	Ascorbic acid	23.07
CRN-H	28.76		

***in vitro* antimicrobial activity studies:** Antimicrobiological assay studies were conducted based on the agar disc diffusion method. Zone of inhibition produced by the test compounds were compared with that of the standard ciprofloxacin. The title compounds were evaluated for antibacterial and antifungal activities as per the reported methods. From the biological evaluation of novel triazole linked chromone biheterocycles, it was observed that the synthesized compounds (**CRN-F, CRN-H, CRN-J**) possessing 4-pentylphenyl, phenanthren-9-yl and butyl substituents exhibited significant antioxidant activity. Also, compounds (**CRN-E, CRN-G, CRN-L**) possessing 3-methoxy, 3,5-dichloro phenyl and octyl substituents exhibited moderate antimicrobial and antifungal activity (Table-2).

Conclusion

Total of fourteen derivatives have been synthesized by eco-friendly procedures. The chemical structures of the novel synthetic compounds were confirmed on the basis of physical and spectral data. These have been evaluated for *in vitro* antimicrobial, antifungal and antioxidant screening tests. Some of these novel derivatives exhibited moderate antimicrobial and antifungal activity compared to that of the reference standard. Most of these novel triazole linked chromone biheterocycle derivatives have shown good to excellent free radical scavenging activity. Further, appropriate modifications of the compounds may show significant biological activities.

CONFLICT OF INTEREST

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

TABLE-2
ANTIMICROBIAL ACTIVITY DATA OF TRIAZOLE LINKED CHROMONE BIHETEROCYCLES

Compound name	Antibacterial activity				Antifungal activity	
	Escherichia coli (µg/mL)	*Salmonella typhi* (µg/mL)	*Bacillus subtilis* (µg/mL)	*Staphylococcus aureus* (µg/mL)	*Aspergillus niger* (µg/mL)	*Candida albicans* (µg/mL)
CRN-A	165.78	136.07	81.60	81.33	154.45	115.22
CRN-B	189.80	178.98	264.40	287.75	98.43	88.34
CRN-C	171.27	153.25	170.89	163.00	58.37	88.06
CRN-D	124.65	131.25	98.42	73.35	83.84	61.60
CRN-E	62.59	62.35	68.06	68.61	46.26	41.17
CRN-F	148.53	143.63	86.56	81.28	66.42	56.13
CRN-G	68.06	66.39	74.31	79.54	35.75	65.69
CRN-H	79.81	88.91	98.62	85.36	54.92	43.30
CRN-I	153.12	139.89	208.82	153.25	256.0	101.69
CRN-J	111.41	98.81	103.66	77.47	55.76	49.62
CRN-K	75.06	76.68	92.02	76.46	52.14	40.26
CRN-L	70.75	72.84	79.91	75.95	44.26	41.91
CRN-M	104.50	122.33	97.77	71.47	116.22	62.31
CRN-N	149.04	172.36	106.58	132.11	179.91	135.18
Ciprofloxacin	13.87	11.31	12.54	14.90	–	–
Ampho-B	–	–	–	–	1.94	1.90

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