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ORIGINAL ARTICLE

# Synthesis and anti-microbial activity of new (1-alkyl-1H-1,2,3-triazol-4-yl)methyl-2H-chromene-3-carboxylates: A click chemistry approach

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Chromene-3-carboxylates;
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Click reaction;
Anti- microbial activity

**Abstract** A series of new 1,4 disubstituted (1-alkyl-1H-1,2,3-triazol-4-yl)methyl-2H-chromene-3-carboxylates (**4ai**–**4eiii**) have been efficiently synthesized in moderate to excellent yields by the 1,3 dipolar cycloaddition between 2-propynyl-2H-chromene-3-carboxylates **3a–e** and various alkyl azides under Cu(I) catalyzed conditions. The structures of the synthesized compounds are established based on IR, NMR, MASS Spectrometric methods and elemental analyses. The antibacterial and antifungal activities of synthesized compounds were evaluated. Compounds **4biii**, **4ei, 4dii, 4ai, 4aii, 4bii** showed good activity against bacterial strains and the compounds **4bi, 4eii** against fungal strains.



## 1. Introduction

Chromenes, 2H-1-benzopyran derivatives, widely used as important intermediates in the synthesis of many natural products and medicinal agents (Passkeiter et al., 1992; Narkhede et al., 1990; Engler et al., 1993). There has been interest in the use of these structural elements for a new family of potassium channel activity drugs (Elomri et al., 1996; Atwal et al., 1995; Van Lommen et al., 1990). 1,2,3-Triazoles have been widely used in synthetic intermediates and industrial applications, such as dyes, anti calmative agents, photostabilisers, photographic elements and agrochemicals (Pinhua and Lei, 2007). 1,2,3-Triazoles also display biological activities as anti HIV (Alrarez et al., 1994), β-lactamase inhibitory (Micetich et al., 1987), selective $\beta_3$ adrenergic receptor agonists (Brockunier et al., 2000). As structural elements in drugs, 1,2,3-triazole moiety is aromatic with high chemical and metabolic stability, has a D.M of 5.2–5.6 D and the hydrogen bond accepting ability, capacity to participate in dipole–dipole interactions as well as π staking interactions, hence a good candidate for bioisosteric replacement in existing drugs or in the development of lead structures (Tron et al., 2007). Numerous synthetic methods for the preparation of 1,2,3-triazole derivatives have been developed (Jiang et al., 2009, 2011). Among them Huisgen 1,3-dipolar cycloaddition between an alkyne and azide is the classical and extensively used method (Finley and Montgomery, 1980). However, the

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regioselectivity of this cycloaddition reaction is low and the reaction leads to the mixture of 1,4 and 1,5-regioisomers (Huisgen and Padwa, 1984; Howell et al., 2001). The regioselectivity of the reaction improved by Cu(I) catalyzed ligation (click chemistry) of organic azides and terminal alkynes (Rostovtsex et al., 2002; Tornee et al., 2002; Bock et al., 2006). Exclusive regioselectivity, mild reaction conditions, effective catalytic system, wide substrate scope and high yields are the main advantages of this reaction.

In view of wide range of applications of triazoles and chromenes, we synthesized novel mixed heterocyclic compounds having 1,2,3-triazole and chromene, using 2-propynyl-2H-chromene-3-carboxylates as scaffolds by adopting Cu(I) catalyzed click chemistry. The products are exclusively 1,4-disubstituted regioisomers. A series of (1-alkyl-1H-1, 2,3-triazol-4-yl) methyl 2H-chromene-3-carboxylate analogues modified in the 6th and 8th position were prepared. All the synthesized compounds evaluated for anti microbial activity.

## 2. Experimental

### 2.1. General

Compounds 2*H*-3-chromenecarbonitriles **1a–e**, and 2*H*-3-chromenecarboxylic acids (Subramanian, 2001) **2a–e** and azides (Escaicu et al., 2008) are prepared by reported procedure. All melting points were obtained on a Polmon instrument, India (model MP 96) and are uncorrected. IR spectra were recorded on a Fourier transform (FT)-IR, USA (Perkin-Elmer model 337) instrument. $^1$H and $^{13}$C NMR spectra were recorded on Bruker 400 MHz and 300 MHz, Switzerland using TMS as an internal standard. *J*-Values are given in Hz. Mass spectral data were obtained with Agilent 6310 ion trap mass spectrometer, USA.

### 2.2. General procedure for synthesis of 2-propynyl 2H-3-chromenecarboxylates (*3a–e*)

A mixture of 2*H*-3-chromenecarboxylic acids **2a–e** (17.04 mmol) and excess of $SOCl_2$ (5 mL) in 50 ml of dry benzene was heated under reflux for 2 h with stirring. The excess of $SOCl_2$ was removed under reduced pressure. The reaction mixture was cooled under $N_2$ atmosphere and dissolved in dry $CH_2Cl_2$, added propargyl alcohol (25.50 mmol) and basified the reaction mixture with triethylamine (5 mL) and stirring maintained at ambient temperature for 6 h. After completion of the reaction another 100 ml of $CH_2Cl_2$ was added and washed with dil HCl to remove triethylamine and finally washed with water and dried over anhydrous $Na_2SO_4$. The crude product was purified by column chromatography to afford pure compounds **3a–e**.

#### 2.2.1. 2′-Propynyl 2H-3-chromenecarboxylate (*3a*)

Yield: 62%; white solid; Mp: 48–50 °C; IR (KBr): 1685 cm$^{-1}$ (C═O), 2150 cm$^{-1}$ (C≡C); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.53 (1H, s, H-4), 7.21 (1H, ddd, $J$ = 8.1 Hz, $J$ = 7.3 Hz, $J$ = 1.3 Hz, H-7), 7.12 (1H, d, $J$ = 7.5 Hz, H-5), 6.97(1H, ddd, $J$ = 1.3 Hz, $J$ = 7.5 Hz, $J$ = 7.3 Hz, H-6), 6.82 (1H, d, $J$ = 8.1 Hz, H-8), 4.99 (2H, s, $OCH_2$), 4.79 (2H, d, $J$ = 2.4 Hz, $COOCH_2$), 2.77 (1H, t, $J$ = 2.4 Hz, C≡CH); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 163.4 (C═O), 155.1 (C-8(a), 134.5 (C-7), 132.1 (C-4), 128.9 (C-5), 121.6 (C-6), 121.3 (C-3), 120.5 (C-4(a), 116.0 (C-8), 77.4 (C-4′), 75.1 (C-5′), 64.1 (C-2), 52.0 (C-3′); MS: $m/z$ 215$[M+H]^+$; *Anal.* Calc. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71. Found: C, 72.78; H, 4.85%.

#### 2.2.2. 2′-Propynyl 6-methyl 2H-3-chromenecarboxylate (*3b*)

Yield: 68%; white solid; Mp: 70–72 °C; IR (KBr): 1680 cm$^{-1}$ (C═O), 2160 cm$^{-1}$ (C≡C); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.48 (1H, s, H-4), 7.04 (1H, dd, $J$ = 8.4 Hz, $J$ = 2.0 Hz, H-7), 6.59 (1H, d, $J$ = 2.0 Hz, H-5), 6.75 (1H, d, $J$ = 8.4 Hz, H-8), 4.97 (2H, s, $OCH_2$), 4.82 (2H, d, $J$ = 2.4 Hz, $COOCH_2$), 2.52 (1H, d, $J$ = 2.4 Hz, C≡CH), 2.27 (3H, s, 6-$CH_3$); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 163.6 (C═O), 153.0 (C-8(a), 134.8 (C-7), 132.7 (C-5), 131.0 (C-3), 129.2 (C-4), 121.4 (C-4), 121.4 (C-6), 120.5 (C-4(a), 115.8 (C-8), 77.5 (C-4′), 75.0 (C-5′), 64.1 (C-2), 52.1 (C-3′), 20.3 (6-$CH_3$); ESIMS: $m/z$ 229$[M+H]^+$; *Anal.* Calc. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.78; H, 5.44%.

#### 2.2.3. 2′-Propynyl 6-chloro 2H-3-chromencarboxylate (*3c*)

Yield: 64%; white solid; Mp: 92–94 °C; IR (KBr): 1685 cm$^{-1}$ (C═O), 2150 cm$^{-1}$ (C≡C); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.39 (1H, s, H-4), 7.16 (1H, dd, $J$ = 8.4 Hz, 2.4 Hz, H-7), 7.11 (1H, d, $J$ = 2.4 Hz, H-6), 6.76 (1H, d, $J$ = 8.4 Hz, H-8), 4.98 (2H, s, $OCH_2$), 4.79 (d, $J$ = 2.4 Hz, $COOCH_2$), 2.46 (t, $J$ = 2.4 Hz, C≡CH); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 163.1 (C═O), 153.5 (C-8(a), 133.1 (C-7), 131.6 (C-5), 128.1 (C-4), 126.4 (C-3), 122.6 (C-4(a), 121.7 (C-6), 117.4 (C-8), 77.4 (C-4′), 75.2 (C-5′), 64.3 (C-2), 52.2 (C-3′); ESIMS: $m/z$ 249$[M+H]^+$; *Anal.* Calc. for $C_{13}H_9ClO_3$: C, 62.79; H, 6.65. Found: C, 62.87; H, 6.74%.

#### 2.2.4. 2′-Propynyl 6-methoxy 2H-3-chromenecarboxylate (*3d*)

Yield: 70%; yellow solid; Mp: 108–110 °C; IR (KBr): 1685 cm$^{-1}$ (C═O), 2150 cm$^{-1}$ (C≡C); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.48 (1H, s, H-4), 6.81 (2H, m, H-8, H-7), 6.70 (1H, d, $J$ = 2.4 Hz, H-5), 4.95 (2H, s, $OCH_2$), 4.82 (2H, d, $J$ = 2.4 Hz, $COOCH_2$), 3.77 (3H, s, 6-$OCH_3$), 2.52 (1H, d, $J$ = 2.4 Hz, C≡CH); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 163.5 (C═O), 154.2 (C-8(a), 149.1 (C-6), 134.6 (C-4), 122.3 (C-3), 121.2 (C-4(a), 118.0 (C-7), 116.8 (C-5), 113.0 (C-8), 77.4 (C-4), 75.1 (C-5′), 64.1 (C-2), 55.6 (6-$CH_3$), 52.1 (C-3′); ESIMS: $m/z$ 245$[M+H]^+$; *Anal.* Calc. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.96; H, 4.87%.

#### 2.2.5. 2′-propynyl 8-methoxy 2H-3-chromenecarboxylate (*3e*)

Yield: 65%; yellow solid; Mp: 82–84 °C; IR (KBr): 1685 cm$^{-1}$ (C═O), 2150 cm$^{-1}$ (C≡C); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 7.54 (1H, s, H-4), 6.94 (2H, m, H-7, H-5), 6.77 (1H, m, H-6), 4.86(2H, s, $OCH_2$), 4.79 (2H, d, $J$ = 2.4 Hz, $COOCH_2$), 3.78(3H, s, 8-$OCH_3$), 2.50 (1H, d, $J$ = 2.4 Hz, C≡CH); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta$ 163.3 (C═O),147.7 (C-8), (C-8(a), 144.0 (C-3),134.4 (C-6), 121.3 (C-4), 121.2 (C-4(a), 120.8 (C-5), 114.6 (C-7), 77.3 (C-4′), 75.0 (C-5′), 64.3 (C-2), 55.9 (8-$OCH_3$), 52.0 (C-3′); ESIMS: $m/z$ 245$[M+H]^+$; *Anal.* Calc. for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.91; H, 4.91%.

*2.3. General procedure for the synthesis of (1-alkyl-1H-1,2,3-triazol-4-yl)methyl 2H-3-chromenecarboxylates (**4ai–4eiii**)*

2-Propynyl 2H-3-chromenecarboxylates **3a–e** (10 mmol) and alkyl azide (**i–iii**) 10 mmol) were suspended in a 1:1 mixture of water and tert-butyl alcohol (20 mL). Sodium ascorbate (300 μL of freshly prepared 1 M solution in water) was added, followed by copper (II) sulfate pentahydrate (0.03 mmol, in 100 μL of water). The heterogeneous mixture was stirred vigorously overnightand TLC analysis indicated complete consumption of the reactants. The reaction mixture was diluted with water (100 mL), cooled in ice and the white precipitate was collected by filtration. After washing the precipitate with cold water (2 × 25 mL), it was dried under vacuum to afford (1-alkyl-1H-1,2,3-triazol-4-yl)methyl-2H-chromene-3-carboxylates **4ai**–**4eiii**.

*2.3.1. (1-Benzyl-1H-1,2,3-triazol-5-yl)methyl 2H-3-chromenecarboxylate (**4ai**)*

Yield: 91%; white solid; Mp: 127 °C; IR (KBr): 1725 $cm^{-1}$ (C═O); $^1$H NMR: (DMSO-$d_6$, 400 MHz): δ 8.30 (1H, s, H-5′), 7.52 (1H, s, H-4), 7.38–7.33 (6H, m, H-2″, H-6″,H-3″, H-4″, H-5″,H-5), δ 7.28 (1H, ddd, $J$ = 7.6 Hz, $J$ = 8.0 Hz, $J$ = 1.6 Hz, H-7), δ 6.96(1H, ddd, $J$ = 7.6 Hz, $J$ = 7.2 Hz, $J$ = 1.6 Hz, H-6), δ 6.86 (1H, d, $J$ = 8.0 Hz, H-8), δ 5.61 (2H, s, N─$CH_2$), δ 5.28 (2H, $COOCH_2$), δ 4.93 (2H, s, $OCH_2$); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 164.1 (C═O), 154.9 (C-8(a), 142.8 (C-4′), (C-1″), 134.2 (C-7), 131.9 (C-4), 128.9 (C-5), 128.8 (C-3″), (C-5″), 128.6 (C-2″), (C-6″), 127.9 (C-4′), 123.7 (C-5′), 121.6 (C-6),120.5 (C-3),(C-4(a),115.9 (C-8), 64.1 (C-2), 57.6 (C$H_2$─O─C═O), 54.0 (N─C$H_2$─Ph); ESIMS: $m/z$ 348$[M+H]^+$; *Anal.* Calc. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.09; H, 4.78; N, 12.17%.

*2.3.2. [1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl]methyl 2H-3-chromenecarboxylate (**4aii**)*

Yield: 86%; white solid; Mp: 185–186 °C; IR (KBr): 1690 $cm^{-1}$ (CON), 1730 $cm^{-1}$ (COO); $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 8.12 (1H, s, H-5′), 7.53 (1H, s, H-4),7.37 (1H, dd, $J$ = 7.4 Hz, $J$ = 1.3 Hz, H-5), 7.29 (1H, ddd, $J$ = 8.3 Hz, $J$ = 7.5 Hz, $J$ = 1.3 Hz, H-7), 6.96 (1H, dd, $J$ = 7.5 Hz, $J$ = 7.4 Hz, H-6), 6.85 (1H, d, $J$ = 8.3 Hz, H-8), 5.50 (2H, s, N─$CH_2$), 5.32 (2H, s, $COOCH_2$), 4.94 (2H, s, $OCH_2$), 3.56–3.68 (4H, 2t, $J$ = 4.3 Hz, $O(CH_2)_2$), 3.42–3.54 (4H, 2t, $J$ = 4.3 Hz, $N(CH_2)_2$); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 164.1 (N─C═O), 163.3 (O─C═O), 155.1 (C-8(a), 142.8 (C-4′), 134.3 (C-7), 132.0 (C-4), 128.9 (C-5), 125.6 (C-6), 121.7 (C-5′), 120.6 (C-4(a), (C-3), 116.0 (C-8), 66.4 (C-3″), 66.1 (C-5″), 64.2 (C-2), 57.6 (C$H_2$─O─C═O), 50.6 (N─C$H_2$─Ph), 45.5 (C-2″), 42.2 (C-6″); ESIMS: $m/z$ 385$[M+H]^+$; *Anal.* Calc. for $C_{19}H_{20}N_4O_5$: C, 59.37; H, 5.24; N, 14.58. Found: C, 59.49; H, 5.13; N, 12.17%.

*2.3.3. [1-(3-Morpholino-3-oxopropyl)-1H-1,2,3-triazol-4-yl]methyl 2H-3-chromenecarboxylate (**4aiii**)*

Yield: 92%; white solid; Mp: 96–98 °C; IR (KBr): 1685 $cm^{-1}$ (CON), 1720 $cm^{-1}$ (COO); $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 8.19 (1H, s, H-5′), 7.52 (1H, s, H-4), 7.36 (1H, dd, $J$ = 7.4 Hz, $J$ = 1.4 Hz, H-5), 7.29 (1H, ddd, $J$ = 8.4 Hz, $J$ = 7.5 Hz, $J$ = 1.3 Hz, H-7), 6.96 (1H, dd, $J$ = 7.5 Hz, $J$ = 7.4 Hz, H-6), 6.86 (1H, d, $J$ = 8.4 Hz, H-8), 5.28 (2H, s, $COOCH_2$), 4.93 (2H, s, $OCH_2$), 4.58 (2H, t, $J$ = 5.4 Hz, N─$CH_2$), 3.52 (4H, m, 3″,5″-$(CH_2)_2$), 3.42 (m, 2″,6″- $(CH_2)_2$), 2.99 (2H, t, $J$ = 5.4 Hz, $CH_2CO$); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 167.7 (N─C═O), 164.0 (O─C═O), 154.9 (C-8(a), 142.1 (C-3), (C-4′), 134.1 (C-7), 131.9 (C-4), 128.8 (C-5), 125.2 (C-6), 121.6 (C-5′), 120.6 (C-4(a), 115.9 (C-8(a), 66.4 (C-3″), 66.1 (C-5″), 64.1 (C-2), 45.7 (C-2″), 45.4 (C-6″), 41.8 (N─C$H_2$), 32.9 (O═C─C$H_2$); ESIMS: $m/z$ 399$[M+H]^+$. *Anal.* Calc. for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.18; H, 5.65; N, 14.15%.

*2.3.4. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl-6-methyl-2H-3-chromenecarboxylate (**4bi**)*

Yield: 92%; white solid; Mp: 137–139 °C; IR (KBr): 1680 $cm^{-1}$ (C═O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.28 (1H, s, H-5′), 7.46 (1H, s, H-4), 7.39–7.33 (5H, m, H-2″,3″,4″,5″,6″), 7.16 (1H, d, $J$ = 2.1 Hz, H-5), 7.09 (1H, dd, $J$ = 8.4 Hz, $J$ = 2.1 Hz, H-7), 6.76 (1H, d, $J$ = 8.4 Hz, H-8), 5.61 (2H, s, N─$CH_2$), 5.24 (2H, s, $COOCH_2$), 4.83 (2H, s, $OCH_2$), 2.21 (3H, s, 6-$CH_3$); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 164.2 (C═O), 152.9 (C-8(a),143.0 (C-4′), 134.4 (C-7),134.2 (C-1″), 132.6 (C-5), 130.9 (C-3″), 129.1 (C-4), 129.0 (C-2″),128.7 (C-4″), 128.0 (C-5′), 123.7 (C-3), 121.7 (C-6), 120.5 (C-4(a), 115.7 (C-8), 64.1 (C-2), 57.6 (C$H_2$─O─C═O), 54.1 (N─C$H_2$─Ph), 20.2 (6-$CH_3$); ESIMS: $m/z$ 362$[M+H]^+$; *Anal.* Calc. for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.86; H, 5.19; N, 11.72%.

*2.3.5. [1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl]methyl 6-methyl-2H-3-chromenecarboxylate (**4bii**)*

Yield: 88%; white solid; Mp: 172–174 °C; IR (KBr): 1685 $cm^{-1}$ (CON), 1725 $cm^{-1}$ (COO); $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 8.10 (1H, s, H-5′), 7.48 (1H, s, H-4),7.16 (1H, d, $J$ = 1.2 Hz, H-5), 7.09 (1H, dd, $J$ = 8.1 Hz, $J$ = 1.2 Hz, H-7), 6.76 (1H, d, $J$ = 8.1 Hz, H-8), 5.49 (2H, s, N─$CH_2$), 5.31 (2H, s, $COOCH_2$), 4.88 (2H, s, $OCH_2$), 3.66–3.57 (4H, 2t, $J$ = 4.2 Hz, $O(CH_2)_2$), 3.45–3.53 (4H, 2t, $J$ = 4.2 Hz, $N(CH_2)_2$); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 164.2 (N─C═0), 163.3 (O─C═O), 152.9 (C-8(a), 142.9 (C-4′), 134.5 (C-7), 132.6 (C-4), 131.0 (C-3), 129.1 (C-5), 125.6 (C-5′), 121.7 (C-6), 120.5 (C-4(a), 115.7 (C-8), 66.4 (C-3″), 66.1 (C-5″), 64.1 (C-2), 57.6 (C$H_2$─O─C═O), 50.6 (N─C$H_2$─Ph), 45.5 (C-2″), 42.4 (C-6″), 20.3 (6-$CH_3$); ESIMS: $m/z$ 399$[M+H]^+$; *Anal.* Calc. for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.18; H, 5.63; N, 14.15%.

*2.3.6. [1-(3-Morpholino-3-oxopropyl)-1H-1,2,3-triazol-4-yl]methyl 6-methyl-2H-3-chromenecarboxylate (**4biii**)*

Yield: 91%; white solid; Mp: 125–127 °C; IR (KBr): 1680 $cm^{-1}$ (CON), 1730 $cm^{-1}$ (COO); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 8.19 (1H, s, H-5′),7.46 (1H, s, H-4),7.15 (1H, d, $J$ = 1.3 Hz, H-5), 7.09 (1H, dd, $J$ = 7.6 Hz, $J$ = 1.3 Hz, H-7), 6.76 (1H, d, $J$ = 8.2 Hz, H-8), 5.28 (2H, s, $COOCH_2$), 4.88 (2H, s, $OCH_2$), 4.58 (2H, t, $J$ = 5.1 Hz, N─$CH_2$), 3.52 (4H, m, 3″,5″-$(CH_2)_2$), 3.40 (4H, m, 2″,6″─$(CH_2)_2$), 3.0 (2H, t, $J$ = 5.1 Hz, $CH_2CO$); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): δ 167.7 (N─C═O), 164.2 (O─C═O), 152.9 (C-8(a), 142.3 (C-4(a), 134.4 (C-7),132.6 (C-5),131.0 (C-3), 129.1 (C-4), 125.2 (C-5′), 121.7 (C-6), 120.5 (C-4(a), 115.7 (C-8), 66.5 (C-3″), 66.2

(C-5″), 64.1 (C-2), 57.6 (CH$_2$—O—C═O), 45.8 (C-2″), 45.5 (C-6″), 41.9 (N—CH$_2$—Ph), 33.0 (CH$_2$—C═O), 20.3 (6-CH$_3$); ESI MS: $m/z$ 413[M + H]$^+$; *Anal.* Calc. for $C_{21}H_{24}N_4O_5$: C, 61.16; H, 5.87; N, 13.58. Found: C, 61.07; H, 5.94; N, 13.71%.

### *2.3.7. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 6-chloro-2H-3-chromenecarboxylate (**4ci**)*

Yield: 90%; white solid; Mp: 141–143 °C; IR (KBr): 1685 cm$^{-1}$ (C═O); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 8.24 (1H, s, H-5′), 7.50 (1H, s, H-4), 7.48 (1H, d, $J$ = 1.6 Hz, H-5), 7.39–7.28 (6H, m, H-2″,3″,4″,5″,6″,7), 6.98 (1H, d, $J$ = 8.2 Hz, H-8), 5.61 (2H, s, N—CH$_2$), 5.31 (2H, s, COOCH$_2$), 4.99 (2H, s, OCH$_2$); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): $\delta$ 163.8 (C═O), 153.5 (C-8(a), 142.7 (C-4′), 134.2 (C-1″), 132.9 (C-7),131.5 (C-3″),129.0 (C-2″),128.7 (C-4″),128.0 (C-5),(C-5′),126.3 (C-3), 123.7 (C-4), 123.0 (C-4(a), 121.8 (C-6), 117.3 (C-8), 64.3 (C-2), 57.8 (CH$_2$—O—C═O), 54.1 (N—CH$_2$—Ph); ESIMS: $m/z$ 382[M + H]$^+$; *Anal.* Calc. for $C_{20}H_{16}ClN_3O_3$: C, 62.91; H, 4.22; N, 11.01. Found: 62.86; H, 4.29; N, 11.12%.

### *2.3.8. [1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl]methyl 6-chloro-2H-3-chromenecarboxylate (**4cii**)*

Yield: 91%; white solid; Mp: 184–186 °C; IR (KBr): 1680 cm$^{-1}$ (CON), 1730 cm$^{-1}$ (COO); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.11 (1H, s, H-5′), 7.52 (1H, s, H-4), 7.50 (1H, d, $J$ = 2.7 Hz, H-5), 7.30 (1H, dd, $J$ = 8.4 Hz, $J$ = 2.7 Hz, H-7), 6.88 (1H, d, $J$ = 8.4 Hz, H-8), 5.50 (2H, s, N—CH$_2$), 5.32 (2H, s, COOCH$_2$), 4.96 (2H, s, OCH$_2$), 3.65–3.57 (4H, 2t, $J$ = 4.2 Hz, O(CH$_2$)$_2$), 3.53–3.32 (4H, 2t, $J$ = 4.2 Hz, N(CH$_2$)$_2$); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): $\delta$ 163.9 (N—C═0), 163.3 (O—C═O), 153.6 (C-8(a), 142.7 (C-4′), 133.0 (C-7), 131.5 (C-5), 128.1 (C-5′), 126.4 (C-3), 125.7 (C-4), 123.1 (C-6), 121.9 (C-4(a), 117.4 (C-8), 66.5 (C-3″), 66.2 (C-5″), 64.4 (C-2), 57.8 (CH$_2$—O—C═O), 50.6 (N—CH$_2$—Ph), 45.7 (C-2″), 42.5 (C-6″); ESIMS: $m/z$ 419[M + H]$^+$; *Anal.* Calc. for $C_{19}H_{19}Cl\ N_4O_5$: C, 54.49; H, 4.57; N, 13.58. Found: C, 54.38; H, 4.66; N, 13.29%.

### *2.3.9. [1-(3-Morpholino-3-oxopropyl)-1H-1,2,3-triazol-4-yl]methyl 6-chloro-2H-3- chromenecarboxylate (**4ciii**)*

Yield: 88%; Yellow solid; Mp: 147–150 °C; IR (KBr): 1680 cm$^{-1}$ (CON), 1715 cm$^{-1}$ (COO); $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 8.19 (1H, s, H-5′), 7.51 (1H, s, H-4), 7.49 (1H, d, $J$ = 1.7 Hz, H-5),7.31 (1H, dd, $J$ = 8.4 Hz, H-7), 6.89 (1H, d, $J$ = 8.4 Hz, H-8), 5.28 (2H, s, COOCH$_2$), 4.97 (2H, s, OCH$_2$), 4.58 (2H, t, $J$ = 4.6 Hz, N—CH$_2$), 3.51 (4H, m, 3″,5″-(CH$_2$)$_2$), 3.42 (4H, m, 2″,6″-(CH$_2$)$_2$), 2.99 (2H, t, $J$ = 4.6 Hz, CH$_2$CO); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): $\delta$ 167.7 (N—C═O), 163.7 (O—C═O), 153.4 (C-8(a), 141.9 (C-4′), 132.8 (C-7), 131.4 (C-5), 128.0 (C-5′), 126.3 (C-3), 125.3 (C-4), 123.0 (C-6), 121.8 (C-4(a), 117.3 (C-8), 66.5 (C-3″), 66.1 (C-5″), 64.3 (C-2), 57.7 (CH$_2$—O—C═O), 45.8 (C-2″), 45.5 (C-6″), 41.9 (N—CH$_2$—Ph), 32.9 (CH$_2$—C═O); ESIMS: $m/z$ 433[M + H]$^+$ and 434[M + H + 2]; *Anal.* Calc. for $C_{20}H_{21}ClN_4O_5$: C, 55.50; H, 4.89; N, 12.94. Found: C, 55.64; H, 4.72; N, 12.89%.

### *2.3.10. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 6-methoxy-2H-3-chromenecrboxylate (**4di**)*

Yield: 88%; white solid; Mp: 109–111 °C; IR (KBr): 1685 cm$^{-1}$ (C═O); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 8.28 (1H, s, H-5′), 7.50 (1H, m, H-7), 7.35–7.33 (5H, m, H-2″,3″,4″, 5″,6″), 7.01 (1H, s, H-4), 6.83 (1H, d, $J$ = 8.3 Hz, H-8), 5.61 (2H, s, N—CH$_2$), 5.28 (2H, s, COOCH$_2$), 4.85 (2H, s, OCH$_2$), 3.69 (3H, s, 6-OCH$_3$); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): $\delta$ 164.0 (C═O), 154.1 (C-8(a), 142.7 (C-4′), 134.2 (C-3″, C-5″), 128.9 (C-2″), (C-6″), 128.6 (C-4″), 127.9 (C-5′), 123.7 (C-4), 122.5 (C-3, C-1″), 121.1 (C-4(a), 117.7 (C-7), 116.6 (C-5), 112.9 (C-8), 64.0 (C-2), 57.6 (CH$_2$—O—C═O), 55.5 (O—CH$_3$), 54.0 (N—CH$_2$—Ph); ESIMS: $m/z$ 378[M + H]$^+$; *Anal.* Calc. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.90; H, 5.01; N, 11.19%.

### *2.3.11. [1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl]methyl 6-methoxy-2H-3-chromenecarboxylate (**4dii**)*

Yield: 90%; Yellow solid; Mp: 167–169 °C; IR (KBr): 1690 cm$^{-1}$ (CON), 1715 cm$^{-1}$ (COO); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 8.11 (1H, s, H-5′), 7.51 (1H, s, H-4), 7.01 (1H, dd, $J$ = 7.8 Hz, $J$ = 2.1 Hz, H-7), 7.01–6.87 (2H, m, H-8, H-6), 5.49 (2H, s, N—CH$_2$), 5.31 (2H, s, COOCH$_2$), 4.91 (2H, s, OCH$_2$), 3.76 (3H, s, 6-OCH$_3$), 3.65–3.57 (4H, 2t, $J$ = 4.2 Hz, O(CH$_2$)$_2$), 3.52–3.38 (4H, 2t, $J$ = 4.2 Hz, N(CH$_2$)$_2$); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): $\delta$ 164.2 (N—C═0), 163.3 (O—C═O), 154.2 (C-8(a), 149.1 (C-6), 134.4 (C-4), (C-5′), 125.9 (C-4′), 122.6 (C-3), 121.3 (C-4(a), 117.9 (C-7), 116.7 (C-5), 113.0 (C-8), 66.4 (C-3″), 66.2 (C-5″), 64.2 C-2), 57.7 (—CH$_2$—O—C═O), 55.6 (6-OCH$_3$), 50.7 (N—CH$_2$—Ph), 45.6 (C-2″), 42.4 (C-6″); ESIMS: $m/z$ 415[M + H]$^+$; *Anal.* Calc. for $C_{20}H_{22}N_4O_6$: C, 57.97; H, 5.35; N, 13.52. Found: C, 57.86; H, 5.42; N, 13.47%.

### *2.3.12. [1-(3-Morpholino-3-oxopropyl)-1H-1,2,3-triazol-4-yl]methyl 6-methoxy-2H-3-chromenecarboxylate (**4diii**)*

Yield: 87%; Yellow solid; Mp: 98–100 °C; IR (KBr): 1690 cm$^{-1}$ (CON), 1730 cm$^{-1}$ (COO); $^1$H NMR (DMSO-d$_6$, 300 MHz): $\delta$ 8.20 (1H, s, H-5′), 7.49 (1H, s, H-4), 7.01 (1H, d, $J$ = 2.9 Hz, H-5), 6.86 (1H, dd, $J$ = 2.7 Hz, $J$ = 8.4 Hz, H-7), 6.80 (1H, d, $J$ = 8.4 Hz, H-8), 5.36 (2H, s, COOCH$_2$), 4.85 (2H, s, OCH$_2$), 4.58 (2H, t, $J$ = 5.9 Hz, N—CH$_2$), 3.52 (4H, m, 3″,5″-(CH$_2$)$_2$), 3.41 (4H, m, 2″,6″-(CH$_2$)$_2$), 3.0 (2H, t, $J$ = 5.9 Hz, CH$_2$CO); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): $\delta$ 167.7 (N—C═O), 164.0 (O—C═O), 154.1 (C-8(a), 148.9 (C-6), 142.1 (C-4′), 134.1 (C-4), 125.2 (C-5′), 122.5 (C-3), 121.1 (C-4(a), 117.7 (C-7), 116.6 (C-5), 112.9 (C-8), 66.4 (C-3″), 66.1 (C-5″), 64.0 (C-2), 57.5 (CH$_2$—O—C═O), 55.5 (6-OCH$_3$), 45.7 (C-2″), 45.4 (C-6″), 41.8 (N—CH$_2$—Ph), 32.9 (CH$_2$—C═O); ESIMS: $m/z$ 429[M + H]$^+$; *Anal.* Calc. for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08. Found: C, 58.98; H, 5.59; N, 13.21%.

### *2.3.13. (1-Benzyl-1H-1,2,3-triazol-4-yl)methyl 8-methoxy-2H-3-chromenecarboxylate (**4ei**)*

Yield: 90%; white solid; Mp: 139–141 °C; IR (KBr): 1690 cm$^{-1}$ (C═O); $^1$H NMR (DMSO-d$_6$, 400 MHz): $\delta$ 8.24 (1H, s, H-5′), 7.45 (1H, s, H-4), 7.38–7.31 (5H, m, H-2″,3″,4″,5″,6″), 7.02 (1H, d, $J$ = 7.4 Hz, H-5), 6.95–6.87 (2H, m, H-6, H-7), 5.61 (2H, s, N—CH$_2$), 5.24 (2H, s,COOCH$_2$), 4.90 (2H, s, OCH$_2$), 3.78 (3H, s, 8-OCH$_3$); $^{13}$C NMR (CDCl$_3$, 75.5 MHz): $\delta$ 164.0 (C═O),147.7 (C-8, C-8(a),142.8 (C-4′), 134.2 (C-6, C-3, C-1″), 129.0 (C-3″, C-5″), 128.7 (C-2″, C-6″), 128.0 (C-4″), 123.7 (C-5′), 121.7 (C-4(a), 121.3 (C-4), 120.8 (C-5), 114.5 (C-7), 64.4 (C-2), 57.6 (CH$_2$—O—C═O), 55.9 (8-OCH$_3$), 54.0 (N—CH$_2$—Ph); ESIMS: $m/z$ 377[M + H]$^+$; *Anal.* Calc. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.87; H, 5.14; N, 11.06%.

*2.3.14. [1-(2-Morpholino-2-oxoethyl)-1H-1,2,3-triazol-4-yl]methyl 8-methoxy-2H-3-chromenecarboxylate (**4eii**)*

Yield: 92%; yellow solid; Mp: 146–148 °C; IR (KBr): 1690 $cm^{-1}$ (CON), 1725 $cm^{-1}$ (COO); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.87 (1H, s, H-5′), 7.46 (1H, s, H-4), 6.88 (1H, m, H-7, H-5), 6.77 (1H, m, H-6), 5.38 (2H, s, N—$CH_2$), 5.24 (2H, s, $COOCH_2$), 5.04 (2H, s, $OCH_2$), 3.87 (3H, s, 8-$OCH_3$), 3.64–3.56 (4H, 2t, $J$ = 4.1 Hz, $O(CH_2)_2$), 3.53–3.41 (4H, 2t, $N(CH_2)_2$); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): $\delta$ 163.7 (N—C═O), 163.2 (O—C═O), 147.4 (C-8, C-8(a), 143.5 (C-4′), 133.8 (C-3), 121.4 (C-5′), 121.1 (C-6, C-4), 121.0 (C-4(a), 120.6 (C-5), 114.3 (C-7), 66.0 (C-3″), 65.8 (C-5″), 64.1 (C-2), 57.4 ($CH_2COO$), 55.6 (8-$OCH_3$), 50.4 (N—$CH_2$), 45.0(C-2″), 42.0 (C-6″); ESIMS: $m/z$ 415$[M+H]^+$; *Anal.* Calc. for $C_{20}H_{22}N_4O_6$: C, 57.97; H, 5.35; N, 13.52. Found: C, 57.89; H, 5.28; N, 13.61%.

*2.3.15. [1-(3-Morpholino-3-oxopropyl)-1H-1,2,3-triazol-4-yl]methyl 8-methoxy-2H-3-chromenecarboxylate (**4eiii**)*

Yield: 86%; yellow solid; Mp: 88–90 °C; IR (KBr): 1685 $cm^{-1}$ (CON), 1720 $cm^{-1}$ (COO); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.81 (1H, s, H-5′), 7.45 (1H, s, H-4), 6.91 (2H, m, H-7, H-5), 6.77 (1H, m, H-6), 5.34 (2H, s, $COOCH_2$), 4.97 (2H, s, $OCH_2$), 4.72 (2H, t, $J$ = 5.9 Hz, N—$CH_2$), 3.65 (3H, s, 8-$OCH_3$), 3.40 (4H, t, $J$ = 4.4 Hz, 3″,5″-$(CH_2)_2$), 2.99 (4H, t, $J$ = 4.4 Hz, 2″,6″-$(CH_2)_2$), 2.56 (2H, t, $J$ = 5.9 Hz, $CH_2CO$); $^{13}C$ NMR ($CDCl_3$, 75.5 MHz): $\delta$ 168.0 (N—C═O), 164.1 (O—C═O), 149.3(C-8, C-8(a), 142.2 (C-4′), 134.6(C-3), 124.9 (C-5′), 121.8 (C-6), 120.7 (C-4), 117.7 (C-4(a), 116.6 (C-5), 116.0 (C-7), 66.5 (C-3″), 66.3 (C-5″), 64.2 (C-2), 58.5 ($\underline{C}H_2COO$), 57.7 (8-$OCH_3$), 45.9 (C-2″), 45.6 (C-6″), 42.0(N—$CH_2$), 33.0 ($\underline{C}H_2CO$); ESI MS: $m/z$ 429$[M+H]^+$; *Anal.* Calc. for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08. Found: C, 58.93; H, 5.70; N, 13.17%.

## 3. Results and discussion

### *3.1. Chemistry*

The aim of present work was to develop simple and efficient procedure for the preparation of new chromene derivatives bearing substituted 1,2,3-triazole moiety. 3-Cyano-2H-chromenes **1a–e** and 2H-chromene-3-carboxylic acids **2a–e** prepared according to literature procedure (Subramanian, 2001), the key intermediates 2-propynyl-2H-chromene-3-carboxylates **3a–e** obtained by treating **2a–e** with $SOCl_2$ and propargyl alchol (Scheme 1).The structures of **3a–e** characterized by spectral analysis. Compound **3a** in its IR showed peaks at 2150 $cm^{-1}$ (C≡C) and 1685 $cm^{-1}$ (CO). In the $^1H$ NMR of **3a** the characteristic protons of propargyl group appeared at $\delta$ 4.79 (d, $J$ = 2.4 Hz, $COOCH_2$), $\delta$ 2.77 (d, $J$ = 2.4 Hz, C≡C—H), the chromene protons resonated at $\delta$ 7.53 (s H-4), 7.12 (d, $J$ = 7.5 Hz, H-5), $\delta$ 6.97 (ddd, $J$ = 7.5 Hz, $J$ = 7.3 Hz, $J$ = 1.3 Hz, H-6), $\delta$ 6.82 (d, $J$ = 8.1 Hz, H-8), $\delta$ 4.99 (s, $OCH_2$). In **$^{13}C$ NMR** of **3a** the signals due to propargyl moiety are at $\delta$ 77.4 (C-4′), $\delta$ 75.1(C-5′), the ester carbonyl appeared at $\delta$ 163.4 and the signals due to chromene moiety appeared at $\delta$ 52.0, ($OCH_2$), 155.1 (C-8(a), 134.5 (C-7), 132.1 (C-4), 128.9 (C-5), 121.6 (C-6), 121.3 (C-3), 120.5 (C-4(a), 116.0 (C-8), 64.1 (C-2). MS $m/z$ 215$[M+H]^+$.

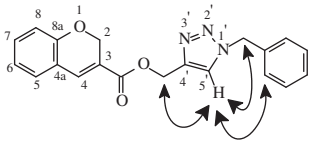
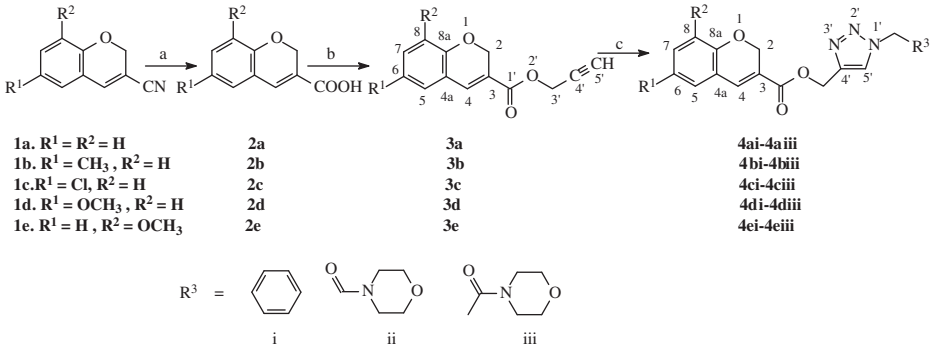


**Figure 1** NOE representation of triazole proton.

The azides (**i–iii**) are prepared by the reaction of substituted alkyl halides with sodium azide in DMF medium (Escaicu et al., 2008).

2-Propynyl-2H-chromene-3-carboxylates **3a–e** on reaction with different azides in the presence of $CuSO_4.5H_2O$ and sodium ascorbate in water and *t*-BuOH affords exclusively 1,4-regioisomers of 1H-1,2,3-triazol-4-yl)methyl 2H-chromene-3-carboxylates (**4ai–4eiii**) in good yields (Scheme 1). The 1,5-regioisomer formation not observed. The compounds (**4ai–4eiii**) were characterized from IR, $^1H$ NMR, $^{13}C$ NMR, NOESY and MS data. In the IR of (1-benzyl-1H-1,2,3-triazol-4-yl)methyl 2H-chromene-3-carboxylate **4ai**, the peak observed at 1725 $cm^{-1}$ is due to CO of ester. In the $^1H$ NMR of **4ai**, the proton of the newly formed triazole ring, H-5′ appeared at $\delta$ 8.30 as singlet. The benzyl $CH_2$ protons appeared as a singlet at $\delta$ 5.61, aromatic protons of phenyl appeared at $\delta$ 7.38–7.33 (H-2″, H-6″, H-3″, H-4″, H-5″, H-5), the $COOCH_2$ appeared as a singlet at $\delta$ 5.28. The chromene protons appeared at $\delta$ 7.52 (s, H-4), $\delta$ 7.28 (ddd, $J$ = 7.6 Hz, $J$ = 8.0 Hz, $J$ = 1.6 Hz, H-7), $\delta$ 6.86 (d, $J$ = 8.0 Hz, H-8), $\delta$ 6.96 (ddd, $J$ = 7.6 Hz, $J$ = 7.2 Hz, $J$ = 1.6 Hz, H-6) and $\delta$ 4.93 (s, 2-$OCH_2$). The regioselective formation of 1,4-regioisomer, (1-benzyl-1H-1,2,3-triazol-4-yl)methyl 2H-chromene-3-carboxylate **4ai** rather than 1,5-regioisomer (1-benzyl-1H-1,2,3-triazol-5-yl) methyl




**Scheme 1** Synthesis of (1-alkyl-1*H*-1,2,3-triazol-4-yl) methyl-2*H*-chromene-3-carboxylates. Reagents and conditions: (a) 10% NaOH, 100 °C; (b) $SOCl_2$ , propargyl alchol , TEA; (c) $R^3CH_2N_3$ , $CuSO_4{\cdot}5H_2O$, sodium ascorbate , *t*-BuOH/H2O.

**Table 1** Antibacterial activity.

| Bacillus subtilis (Gram-positive) (Conc. μg/mL) zone of inhibition mm) | | | | Pseudomonas aerogenosa (Gram-negative) (Conc. μg/mL) zone of inhibition mm | | | | Staphylococus aureus (Gram-positive) (Conc. μg/mL) zone of inhibition mm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Comp | 200 | 100 | 50 | Comp | 200 | 100 | 50 | Comp | 200 | 100 | 50 |
| **4ai** | 14.0 | 12.0 | 9.0 | **4ai** | 12.5 | 8.5 | 6.0 | **4ai** | 29.5 | 16.0 | 11.0 |
| **4aiii** | 22.0 | 16.0 | – | **4aiii** | 19.5 | – | 13.5 | **4aii** | 32.5 | 14.0 | 8.0 |
| **4biii** | 20.0 | 12.0 | 7.0 | **4biii** | 28.0 | 21.0 | 13.0 | **4bii** | 29.5 | 19.5 | 12.5 |
| **4ci** | 11.0 | 12.5 | – | **4ci** | 19.5 | – | 16.5 | **4biii** | 21.5 | 12.5 | 8.0 |
| **4ciii** | 17.5 | 20.0 | 7.5 | **4cii** | – | 10.5 | – | **4ci** | 12.5 | – | 14.0 |
| **4dii** | 27.0 | 21.0 | 19.0 | **4ciii** | – | 5.0 | 4.0 | **4dii** | 18.0 | 14.5 | – |
| **4diii** | – | 11.0 | – | **4diii** | 14.0 | 7.0 | 5.0 | **4diii** | 14.5 | 10.0 | 5.0 |
| **4eii** | 15.0 | 12.0 | 9.0 | **4ei** | 26.0 | 18.0 | 11.0 | **4ei** | 22.0 | 12.5 | 4.0 |
| **4eiii** | 13.5 | 20.5 | 10.0 | **4eiii** | 17.0 | – | 10.0 | **4eiii** | 19.0 | 13.0 | – |
| Ref. | 31.0 | 25.0 | 20.0 | Ref. | 32.0 | 22.0 | 14.5 | Ref. | 34.0 | 30.0 | 25.0 |

**Table 2** Antifungal activity.

| Aspergillus niger (Conc. μg/mL) zone of inhibition mm | | | | Rhizoctonia solani (Conc. μg/mL) zone of inhibition mm | | | | Aspergillus terreus (Conc. μg/mL) zone of inhibition mm | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Comp | 200 | 100 | 50 | Comp | 200 | 100 | 50 | Comp | 200 | 100 | 50 |
| **4aii** | 17.5 | 8.0 | 04.0 | **4aiii** | 16.5 | 09.0 | 06.0 | **4ai** | 22.0 | 13.0 | 04.0 |
| **4aiii** | – | 12.0 | 09.0 | **4bi** | 15.0 | 11.0 | 11.5 | **4aiii** | 14.0 | 09.5 | 08.0 |
| **4bi** | 32.0 | 19.0 | 05.0 | **4bii** | – | 06.0 | 03.5 | **4bi** | 16.0 | 09.0 | 04.0 |
| **4bii** | 21.0 | – | – | **4biii** | 23.0 | 09.5 | 04.5 | **4bii** | 24.0 | – | – |
| **4cii** | 24.0 | 19.0 | 14.0 | **4ci** | 17.5 | 10.5 | 08.0 | **4ci** | 25.0 | 19.0 | 14.0 |
| **4ciii** | – | – | 07.0 | **4ciii** | 18.0 | – | – | **4cii** | 15.0 | 12.0 | – |
| **4diii** | 16.0 | 22.0 | 04.0 | **4dii** | 15.0 | 04.0 | – | **4ciii** | 12.5 | 11.0 | 04.0 |
| **4ei** | 15.0 | – | 05.0 | **4diii** | 23.0 | 18.0 | 12.0 | **4dii** | 21.0 | – | – |
| **4eii** | 28.0 | 20.0 | – | **4eiii** | 22.0 | – | 08.5 | **4eiii** | 15.0 | 11.5 | 10.0 |
| Ref. | 32.0 | 23.5 | 17.0 | Ref. | 30.0 | 22.0 | 15.0 | Ref. | 30.0 | 22.0 | 24.0 |

2H-chromene-3-carboxylate is confirmed from the analysis of NOESY spectrum (Fig. 1). The triazole proton at $\delta$ 8.30 showed a strong NOE with the N—$CH_2$ at $\delta$ 5.61 and $COOCH_2$ at $\delta$ 5.28 and a medium NOE with the protons of the phenyl ring. The H-4 at $\delta$ 7.52 showed a weak NOE with 2-$OCH_2$ at $\delta$ 4.93 and $COOCH_2$ at $\delta$ 5.28. These NOE values are possible only for the 1,4-regioisomer. In the **$^{13}$C NMR** the 4′-$OCH_2$ appeared at $\delta$ 57.6 and the two triazole carbons at $\delta$ 142.8 (C-4′, C-1″), $\delta$ 123.7 (C-5′), the benzylic carbon at $\delta$ 54.0 and the ester carbonyl at $\delta$164.1. The chromenyl moiety carbons appeared as follows $\delta$ 154.9 (C-8(a), 134.2 (C-7), 131.9 (C-4),128.9 (C-5),128.8 (C-3″),(C-5″),128.6 (C-2″),(C-6″), 127.9 (C-4″), 121.6(C-6),120.5 (C-3),(C-4(a),115.9 (C-8) and 64.1 (C-2). In the ESIMS of **4ai** the quasimolecular ion peak was observed at $m/z$ 348$[M + H]^+$.

### *3.2. Antimicrobial activity*

The *in vitro* antimicrobial activity (Atwal et al., 1993; Pfefferle et al., 1990; Ayer and Nozawa, 1990) of all the synthesized compounds were carried out using paper disk method, the compounds screened against *Bacillus subtilis* (Gram-positive), *Staphylococus aureus* (Gram-positive), *Pseudomonas aerogenosa* (Gram-negative) antibacterial as well as *Aspergillus niger*, *Rhizoctonia solani* and *Aspergillus terreus* antifungal strains. The strains used for the activity procured from IMT, Chandigarah. Cultures of test organisms were maintained on nutrient agar (bacterial) and potato dextrose agar (fungal) media and subcultured in petri dishes prior to testing. The compounds are tested at concentrations 200 μg/mL, 100 μg/mL, 50 μg/mL using DMSO as solvent. After solidification of media, petri plates inoculated with actively growing cultures of *B. subtilis* (Gram-positive), *S. aureus* (Gram-positive), *P. aerogenosa* (Gram-negaitive) and *A. niger*, *R. solani*, *A. terreus* separately. Filter paper disks of 5 mm diameter dipped in the test solution of different concentrations. After drying the disk, kept on nutrient agar broth. Potato dextrose broth in petri plates seeded with 1 mL culture of *B. subtilis* (Gram-positive), *P. aerogenosa* (Gram-negative), *S. aureus* (Gram-positive) and *A. niger*, *R. solani*, *A. terreus* incubated for 24 h at 27 °C. After 2 h the petri dishes were tested for growth of inhibition. The presence of clear zone of growth inhibition around the paper disk indicated the inhibition of growth of organisms. The diameter of zone of inhibition was calculated in millimeters, ampicillin is used as standard antibacterial drug, where as clotrimazole used as standard antifungal drug.

The examination of data (Tables 1 and 2) reveals that compound **4biii**, **4ei** having comparable activity with standard drug against *P. aerogenosa* at 200 μg/mL, 100 μg/mL compound

**4dii** shown high activity at 50 μg/mL against *B. subtilis* and **4ai, 4aii, 4bii** showed high activity against *S. aureus* at 200 μg/mL. Compounds **4bi, 4eii** exhibited activity against *A. niger* comparable to that of reference drugs at 200 μg/mL, 100 μg/mL, remaining all the other compounds showed low to moderate activity.

## 4. Conclusion

Herewith, we report the simple and efficient method of synthesis of novel mixed heterocyclic compounds, (1-alkyl-1H-1,2,3-triazol-4-yl)methyl-2H-chromene-3-carboxylates (**4ai–4eiii**). Some of these compounds have shown good antimicrobial activity. Hence chromene – triazole derivatives can be used in future for drug designing and development.

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