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SYNTHESIS OF NEW 1-BENZYL-4-(((2,2-DIMETHYLCHROMAN-4-YL)OXY)METHYL)-1H-1,2,3-TRIAZOLES AND 4-(((2,2-DIMETHYLCHROMAN-4-YL)OXY)METHYL)-1-PHENYL-1H-1,2,3-TRIAZOLES

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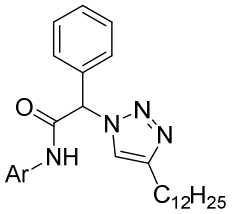
Abstract:
A new series of 1-benzyl-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazoles, 4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1-phenyl-1H-1,2,3-triazoles were synthesized by the reaction of 2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman and substituted benzyl and phenyl azides. The products were purified by column chromatography and structures of these compounds are established by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

Keywords: Chromanone, Triazoles

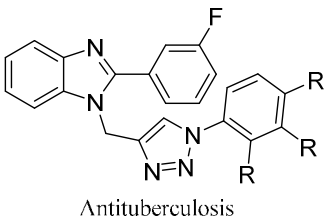
Introduction:

Triazoles constitute an important class of nitrogen heterocycles in the field of organic and medicinal chemistry. Medicinally, they have been shown to possess a wide range of diverse pharmacological properties such as antituberculosis,[i] antibacterial,[ii,iii] antimalarial,[iv] antiepileptic,[v] antileishmanial,[vi] antiallergic,[vii] antifungal,[viii,ix] anticancer[x,xi] and anti-HIV[xii] activities. Triazoles have been utilized as proton transport facilitators,[xiii] glycoside cluster arrays,[xiv,xv] spacers or linkers to dendrimers,[xvi,xvii] DNA cleaving agents,[xviii] structural components in hyper branched polymers[xix] and most importantly in liquid crystals.[xx] In the present article, we report the synthesis of new 1-benzyl-5-(((2,2-dimethylchroman-4-yl)oxy)mehyl)-1*h*-1,2,3-triazoles and 4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1-phenyl-1H-1,2,3-triazoles derivatives.



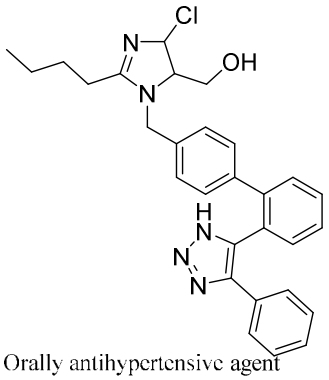
Hypocholesterolemic activity

1



Antituberculosis

2



Orally antihypertensive agent

3

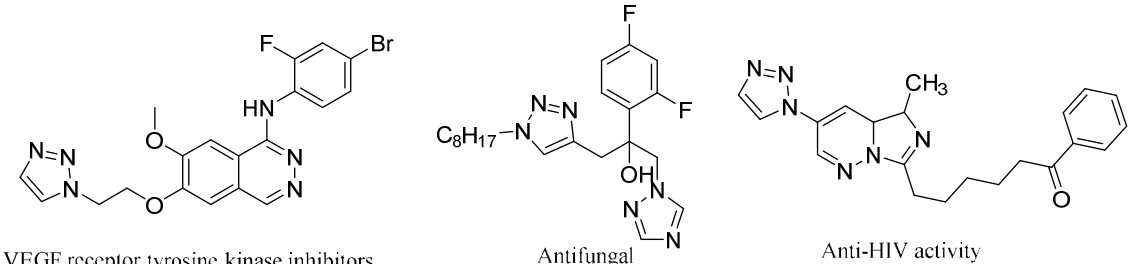
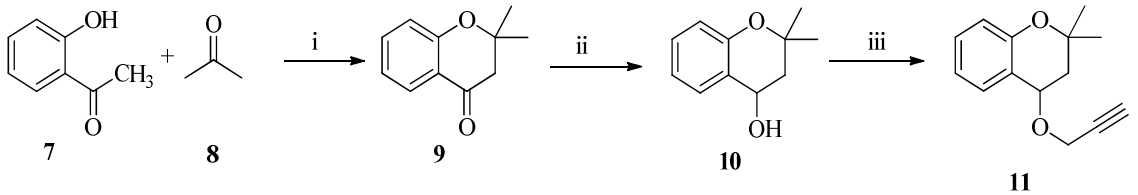


Figure 2: 1,2,3-Triazole containing molecules with different biological activities

Result and discussion:

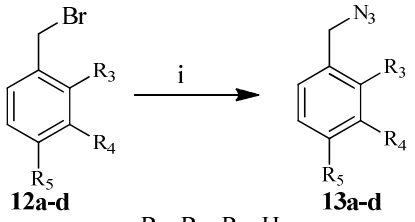
Synthesis of 1-benzyl-5-(((2,2-dimethylchroman-4-yl)oxy)mehyl)-1*H*-1,2,3-triazoles

The reaction of 2-hydroxy acetophenone (**7**) with acetone (**8**) in the presence of piperidine resulted in 2,2-dimethylchroman-4-one[xxi] (**9**). These chromanone on reduction with $NaBH_4$ led to 2,2-dimethylchroman-4-ol[xxii] (**10**). 2,2-dimethylchroman-4-ol on alkylation with propargylbromide in the presence of NaH in THF led to 2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman[xxiii] (**11**).



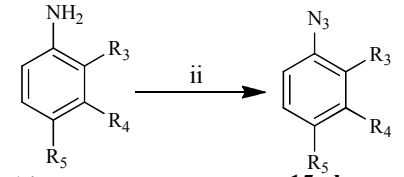
Reagents and conditions: i. piperidine, EtOH ii. $NaBH_4$, CH_3OH iii. NaH, Propargyl bromide, dry THF

Benzyl bromide on reaction with sodium azide in DMF solvent led to benzyl azides and aniline dissolved in con HCl reacted with $NaNO_2$ followed by reaction with NaN_3 furnish phenyl azides[xxiv].



a= R_3=R_4=R_5=H
b= R_3=R_4=H, R_5=Cl
c= R_3=R_5=Cl, R_4=H
d= R_3=H, R_4=R_5=Cl

Reagents and conditions: NaN_3, DMF, rt, 6 h

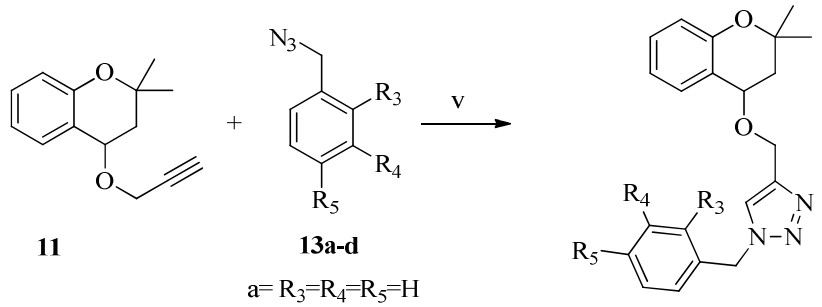


14 e-k **15e-k**

e=R_3=R_4=R_5=H i=R_3=R_5=H R_4=Cl
f=R_3=R_4=H, R_5=Br j=R_3=R_5=H R_4=OCH_3
g=R_3=R_4=H, R_5=Cl k=R_3=Cl, R_4=R_5=H
h=R_3=R_4=H, R_5=F

Reagents and conditions: Con HCl, $NaNO_2$, NaN_3

2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman (**11**) reacted with different benzyl azides (**13a-d**) furnish 1-benzyl-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole[xxiv] (**16a-d**).

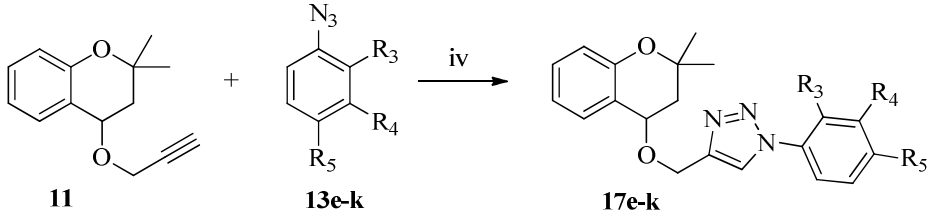


11 **13a-d** **16a-d**

a= R_3=R_4=R_5=H
b= R_3=R_4=H, R_5=Cl
c= R_3=R_5=Cl, R_4=H
d= R_3=H, R_4=R_5=Cl

Reagents and conditions: v. $CuSO_4.5H_2O$, Sodium ascorbate, DMF

2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman (**11**) reacted with substituted phenyl azides (**13e-k**) furnish 4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1-phenyl-1H-1,2,3-triazole[xxiv] (**17e-k**).



11 **13e-k** **17e-k**

e=R_3=R_4=R_5=H i=R_3=R_5=H R_4=Cl
f=R_3=R_4=H, R_5=Br j=R_3=R_5=H R_4=OCH_3
g=R_3=R_4=H, R_5=Cl k=R_3=Cl, R_4=R_5=H
h=R_3=R_4=H, R_5=F

Reagents and conditions: iv. $CuSO_4.5H_2O$, Sodium ascorbate, DMF

Conclusion

We have synthesized novel 1-benzyl-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazoles, 4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1-phenyl-1H-1,2,3-triazoles in excel lent yields employing click chemistry approach.

Experimental section:

General remarks

Air or/and moisture sensitive reactions were carried out in anhydrous solvents under an argon atmosphere in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2. Commercial reagents were used without purification. Column chromatography was carried out by using ACME silica gel (60-120 mesh). Infrared spectra were recorded on Perkin-Elmer 683 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-500 or Varian INOVA 400 MHz or a Bruker-300 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) in Hz. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of doublet, q = quartet, m = multiplet, br = broad. Mass spectra were obtained on an Exactive Thermo Scientific Orbit rap Mass Spectrometer.

Synthesis of 2,2-dimethylchroman-4-one (9):

To a well stirred solution of *o*-hydroxyacetophenone (5 g, 36.7 mmol) and propan-2-one (2.35 g, 40.4 mmol) in ethanol (30 mL), pyrrolidine (3.13 g, 44.1 mmol) was added at room temperature. The reaction mixture was refluxed for 3 h. The completion of the reaction was monitored by TLC. The reaction mixture was quenched by crushed ice and extracted with ethyl acetate. The organic layer was washed by brine (2×25 mL) and dried over anhydrous sodium sulfate, and the solvent was removed under pressure to obtain the crude product. The obtained residues were purified by column chromatography on silica gel, ethylacetate and pet ether as eluent to give product **9** 6.08 g, 94% yield. Physical state: white solid. m.p: 85-87 ^oC. IR: 2977, 2932, 1690, 1603, 1573, 1456, 1372, 1329, 1304, 1257, 1202, 1169, 1117, 768 cm^{-1}. ^1H-NMR (500 MHz, $CDCl_3$): δ 7.84 (dd, J=1.5 Hz, 1.5 Hz H-7), 7.44 (t, H-5), 6.94 (t, H-6), 6.90 (d, J=8.3 Hz, H-8), 2.72 (s, 3-CH_2), 1.46 (s, 6H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 192.4, 159.8, 136.0, 126.3, 120.5, 120.0, 118.2, 79.0, 48.7, 26.5 ppm. ESI-MS: 177 $[M+H]^+$.

Synthesis of 2,2-dimethylchroman-4-ol (10):

A stirred solution of 2,2-dimethylchromanone (2 g, 1eq, 11.36 mmol) in absolute ethanol was treated with $NaBH_4$ (0.516 g, 1.2 eq) and stirred at room temperature 2 h. The reaction mixture was then quenched with 3 mL H_2O, then 3 mL brine, extracted with EtOAc (4×3 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and then evaporated to dryness. The resulting residue was purified by column chromatography (silica gel, ethyl acetate: pet ether) as eluent to give product **10**(1.82 g) 90% yield.

Physical state: pale yellow liquid. IR: 3195, 2965, 1610, 1584, 1487, 1226, 1038, 1019, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.6 Hz, 1H), 7.17 (s, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 4.82 (s, 1H), 2.14 (ddd, *J* = 13.3, 6.0, 2.4 Hz, 2H), 1.89 – 1.79 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 129.1, 127.5, 124.2, 120.2, 117.1, 75.2, 63.5, 42.5, 28.8, 25.7 ppm. ESI-MS: 179 $[M+H]^+$.

Synthesis of 2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman (11):

To a solution of 2,2-dimethylchroman-4-ol (550 mg, 1.09 mmol) in dry THF (5 mL) was added solid NaH (60%, 123 mg, 3.08 mmol) at 0 ^oC under argon. The reaction mixture was stirred at room temperature for 1h. Then propargyl bromide (0.3 mL, 3.33 mmol) was added. The reaction mixture was stirred for 3 h at room temperature. Then it was quenched with sat.aq.NH_4Cl at 0 ^oC and extracted with ethyl acetate. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4. After concentration under vacuum, the residue was purified by flash chromatography using hexane/ethyl acetate as an eluent to give 2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman (**11**) (576 mg, yield 97%) as colorless oil.

Physical state: yellow liquid. IR: 3442, 1635, 1528, 1483, 1456, 1379, 1303, 1243, 1188, 1033, 753 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50 – 7.00 (m, 2H), 7.05 – 6.65 (m, 2H), 4.78 (t, *J* = 6.4 Hz, 2H), 4.45 – 4.17 (m, 2H), 2.48 (s, 1H), 2.22 – 1.87 (m, 2H), 1.50 – 1.27 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 129.4, 128.9, 121.3, 120.0, 117.2, 80.1, 74.8, 74.6, 69.5, 55.6, 37.8, 28.1, 27.0 ppm. ESI-MS: 217 $[M+H]^+$.

Synthesis of benzyl azides (13a-d):

Sodium azide (715 mg, 11.0 mmol) was dissolved in 20 mL DMSO and benzyl bromide (1.71 g, 1.19 mL, 10 mmol) was added to the solution. The reaction mixture was stirred for 2 h at room temperature. 200 mL H_2O were added and after cooling to room temperature, the aqueous solution was extracted with diethyl ether (3×100 mL). The combined organic layers were washed with water (2×100 mL) and brine (100 mL). After drying over Na_2SO_4 the ether was removed under reduced pressure to yield the pure azide in a yield[49] of 90% as colourless oil. These are used without characterization.

Synthesis of phenyl azides (13e-k):

The aniline (1 g, 10.7 mmol) was suspended in 30 mL hydrochloric acid (17%) at room temperature and then ethanol was added until a clear solution was obtained. The solution was cooled to 0 °C and $NaNO_2$ (1.1 g, 1.5 eq.) was added in small portions. After stirring at 0 °C for 15-30 min. NaN_3 (1.05 g, 1.5 eq.) was slowly added and the mixture was stirred for additional 2 h at room temperature. The reaction mixture was extracted with diethyl ether (3×80 mL) and the combined organic fractions were washed with saturated $NaHCO_3$ solution (3×50 mL) and with brine (50 mL). After drying over Na_2SO_4 the ether was removed under reduced pressure and the desired azides were used without further purification and characterization.

Synthesis of 1-(4-chlorobenzyl)-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (16a):

To a solution of 2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman (0.2g, 1eq) in DMF was added 4-chloro benzyl azide (0.17 g, 1.1 eq) to this solution aq solution of copper sulphate and sodium ascorbate was added and stirred for 10 h at room temperature. After completion of reaction monitored by TLC cold water was added and extracted with ethylacetate (3×50 mL). Organic fractions are dried over Na_2SO_4 and concentrated and purified by column chromatography by eluting with pet ether and ethylacetate.

Physical state: yellow liquid. IR: 3128, 3090, 2921, 2872, 2358, 1595, 1550, 1484, 1340, 1216, 1129, 1109, 1094 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.38 – 7.31 (m, 2H), 7.31 – 7.23 (m, 1H), 7.19 (dd, *J* = 8.2, 5.8 Hz, 2H), 7.18 – 7.11 (m, 1H), 6.85 (td, *J* = 7.5, 1.1 Hz, 1H), 6.77 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.48 (s, 2H), 4.85 – 4.72 (m, 2H), 4.70 – 4.63 (m, 1H), 2.13 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.00 (dd, *J* = 13.6, 7.5 Hz, 1H), 1.41 (s, 3H), 1.32 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.6, 146.3, 134.8, 133.2, 129.4, 128.7, 122.4, 121.6, 120.0, 117.3, 78.0, 76.7, 75.0, 70.6, 62.1, 53.4, 38.0, 28.4, 26.8 ppm. ESI-MS: 484 $[M+H]^+$, 486$[M+H+2]^+$.

Compounds **16b**, **16c**, **16d** were similarly prepared.

1-Benzyl-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (16b):

Physical state: colourless liquid. IR: 3130, 3093, 2925, 2876, 2361, 2339, 1619, 1592, 1563, 1475, 1455, 1384, 1332, 1218, 1132, 1110, 1090 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (s, 1H), 7.44 – 7.31 (m, 3H), 7.31 – 7.23 (m, 3H), 7.15 (s, 1H), 6.85 (d, *J* = 1.0 Hz, 1H), 6.77 (dd, *J* = 8.2, 0.9 Hz, 1H), 5.53 (s, 2H), 4.79 (q, *J* = 12.2 Hz, 2H), 4.70 – 4.64 (m, 1H), 2.13 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.00 (dd, *J* = 13.6, 7.5 Hz, 1H), 1.41 (s, 3H), 1.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 146.2, 129.2, 128.7, 128.1, 122.4, 121.6, 120.0, 117.3, 77.4, 77.0, 76.7, 75.0, 70.6, 62.1, 54.2, 38.0, 28.4, 26.8, 14.2 ppm. ESI-MS: 350 $[M+H]^+$.

1-(2,4-Dichlorobenzyl)-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (16c):

Physical state: white solid. m.p. 121-123 ^{o}C. IR: 3130, 3093, 2925, 2876, 2361, 2339, 1619, 1599, 1578, 1472, 1294, 1270, 1218, 1132, 1110, 1090 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.46 (d, *J* = 2.1 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.19 – 7.10 (m, 2H), 6.86 (td, *J* = 7.5, 1.1 Hz, 1H), 6.78 (dd, *J* = 8.2, 1.0 Hz, 1H), 5.63 (s, 2H), 4.80 (q, *J* = 12.2 Hz, 2H), 4.70 – 4.65 (m, 1H), 2.15 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.02 (dd, *J* = 13.6, 7.5 Hz, 1H), 1.42 (s, 3H), 1.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 146.3, 131.2, 129.8, 129.3, 128.7, 128.0, 122.7, 120.0, 117.3, 75.0, 70.7, 62.0, 60.4, 50.9, 38.0, 28.4, 26.8, 14.2 ppm. ESI-MS: 418$[M+H]^+$, 420$[M+2+H]^+$.

1-(3,4-Dichlorobenzyl)-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (16d):

Physical state: white solid. m.p. 132-134 ^{o}C. IR: 3134, 3094, 2994, 2920, 2875, 2361, 2060, 1639, 1607, 1563, 1473, 1453, 1403, 1368, 1334, 1283, 1214, 1192, 1114, 1089, 1051, 1032, 1007 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.37 (s, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.48 (s, 2H), 4.80 (q, *J* = 12.2 Hz, 2H), 4.68 (t, *J* = 6.5 Hz, 1H), 2.15 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.02 (dd, *J* = 13.6, 7.5 Hz, 1H), 1.42 (s, 3H), 1.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6, 146.2, 135.6, 134.1, 131.1, 129.8, 129.3, 128.6, 128.0, 122.6, 121.5, 120.0, 117.3, 75.0, 70.6, 62.0, 50.8, 38.0, 28.3, 26.8 ppm. ESI-MS: 418$[M+H]^+$, 420$[M+H+2]^+$.

Synthesis of 1-(4-bromophenyl)-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (17e):

To a solution of 2,2-dimethyl-4-(prop-2-yn-1-yloxy)chroman (0.2 g, 1eq) in DMF was added 4-bromo phenyl azide (0.16 g, 1.1eq) to this solution aq solution of copper sulphate and sodium ascorbate was added and stirred for 10 h at room temperature. After completion of reaction monitored by TLC cold water was added and extracted with ethylacetate (3×50 mL). Organic fractions are dried over Na_2SO_4 and concentrated and purified by column chromatography by eluting with pet ether and ethylacetate (0.34 g, 90% yield).

Physical state: white solid. m.p. 85-87 ^{o}C. IR: 3135, 3093, 2997, 2918, 2877, 2364, 1639, 1617, 1594, 1523, 1490, 1319, 1284, 1192, 1114, 1089, 1051, 1032, 1007 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 5'-H), 7.61 (m, 2'-H, 3'-H, 5'-H, 6'-H), 7.36 (m, H-5), 7.15 (m, H-7), 6.87 (m, H-6), 6.79 (m, H-8), 4.83 (dd, J=12.4 Hz, 12.0 Hz OCH_2), 4.72 (t,H-4), 2.17 (dd, J=5.6 Hz, 5.6 Hz 3-Ha), 2.04 (dd, J=7.3 Hz, 7.3 Hz 3-Hb), 1.46 (s, 2-CH_3),1.36 (s, 2-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 144.4, 135.8, 131.6, 128.1, 127.3, 126.4, 125.5, 123.0, 120.1, 119.1, 112.2, 79.7, 78.2, 65.8, 27.2 ppm. ESI-MS: 414 $[M+H]^+$, 416 $[M+H+2]^+$.

Compounds **17f**, **17g**, **17h**, **17i**, **17j**, **17k** were similarly prepared.

4-(((2,2-Dimethylchroman-4-yl)oxy)methyl)-1-phenyl-1H-1,2,3-triazole (17f):

Physical state: yellow solid. m.p. 79-81 ^{o}C. IR: 3131, 3090, 2996, 2925, 2878, 2360, 2060, 1634, 1607, 1561, 1493, 1309, 1276, 1130, 1114, 1095 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.77 – 7.71 (m, 2H), 7.55 – 7.50 (m, 2H), 7.47 – 7.41 (m, 1H), 7.39 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.92 – 6.86 (m, 1H), 6.80 (dd, *J* = 8.2, 1.1 Hz, 1H), 4.92 (dd, *J* = 12.2, 3.8 Hz, 1H), 4.86 (dd, *J* = 12.3, 4.9 Hz, 1H), 4.75 (t, *J* = 6.5 Hz, 1H), 2.20 (ddd, *J* = 13.6, 5.7, 1.9 Hz, 1H), 2.08 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.46 (s, 3H), 1.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 146.6, 137.9, 135.6, 130.9, 129.8, 129.4, 128.8, 121.5, 120.8, 120.5, 120.1, 118.5, 117.3, 75.1, 70.9, 62.0, 38.0, 28.4, 26.9 ppm. ESI-MS: 336 $[M+H]^+$.

1-(4-Chlorophenyl)-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (17g):
Physical state: white solid. m.p. 112-114 ^{o}C. IR: 3447, 3118, 2974, 2928, 2781, 1607, 1562, 1502, 1484, 1364, 1325, 1269, 1225, 1132, 1056, 1023, 827, 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 5'-H), 7.61 (m, 2' -H, 3'-H, 5'-H, 6'-H), 7.36 (m, H-5), 7.15 (m, H-7), 6.87 (m, H-6), 6.79 (m, H-8), 4.83 (dd, J=12.4 Hz, 12.0 Hz OCH_2), 4.72 (t,H-4), 2.17 (dd, J=5.6 Hz, 5.6 Hz 3-Ha), 2.04 (dd, J=7.3 Hz, 7.3 Hz 3-Hb), 1.46 (s, 2-CH_3), 1.36 (s, 2-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 144.6, 134.9, 134.3, 128.9, 127.5, 126.5, 125.6, 122.2, 120.1, 119.2, 112.4, 79.7, 78.3, 65.8, 27.3, 24.6 ppm. ESI-MS: 370 $[M+H]^+$, 372 $[M+H+2]^+$.

4-(((2,2-Dimethylchroman-4-yl)oxy)methyl)-1-(4-fluorophenyl)-1H-1,2,3-triazole (17h):
Physical state: yellow liquid. IR: 3128, 3084, 2976, 2927, 1609, 1516, 1484, 1453, 1372, 1272, 1226, 1206, 1126, 1100, 1042, 931, 829, 747 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (s, 5'-H), 7.61 (m, 2' -H, 3'-H, 5'-H, 6'-H), 7.36 (m, H-5), 7.15 (m, H-7), 6.87 (m, H-6), 6.79 (m, H-8), 4.83 (dd, J=12.4 Hz, 12.0 Hz OCH_2), 4.72 (t,H-4), 2.17 (dd, J=5.6 Hz, 5.6 Hz 3-Ha), 2.04 (dd, J=7.3 Hz, 7.3 Hz 3-Hb), 1.46 (s, 2-CH_3), 1.36 (s, 2-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 153.2, 144.4, 132.4, 127.4, 126.5, 125.6, 122.5, 120.2, 119.2, 115.4, 112.3, 79.6, 78.1, 65.8, 27.2, 24.6 ppm. ESI-MS: 354 $[M+H]^+$.

1-(3-Chlorophenyl)-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (17i):
Physical state: yellow liquid. IR: 3125, 3081, 2973, 2926, 1600, 1561, 1469, 1352, 1226, 1206, 1126, 1100, 1042, 931, 829, 747, 524 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.80 (t, *J* = 2.0 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.50 – 7.40 (m, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.90 (td, *J* = 7.5, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.89 (q, *J* = 12.3 Hz, 2H), 4.78 – 4.72 (m, 1H), 2.20 (dt, *J* = 10.5, 5.3 Hz, 1H), 2.08 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.46 (s, 3H), 1.36 (s, 3H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 198.3, 143.5, 198.3, 136.5, 121.5, 120.8, 120.5, 120.1, 118.5, 117.4, 75.0, 71.0, 62.0, 38.0, 28.4, 26.9 ppm. ESI-MS: 370 $[M+H]^+$, 372 $[M+H+2]^+$.

4-(((2,2-Dimethylchroman-4-yl)oxy)methyl)-1-(3-methoxyphenyl)-1H-1,2,3-triazole (17j):
Physical state: yellow liquid. IR: 3126, 3082, 2973, 2924, 1601, 1598, 1581,1470,1383,1213, 1206, 1126, 1100, 1042, 931, 829, 747, 524 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.80 (t, *J* = 2.0 Hz, 1H), 7.68 – 7.62 (m, 1H), 7.50 – 7.40 (m, 2H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.21 – 7.15 (m, 1H), 6.90 (td, *J* = 7.5, 1.1 Hz, 1H), 6.81 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.89 (q, *J* = 12.3 Hz, 2H), 4.78 – 4.72 (m, 1H),3.88 (s,3H), 2.20 (dt, *J* = 10.5, 5.3 Hz, 1H), 2.08 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.46 (s, 3H), 1.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 153.3, 144.4, 142.6, 131.3, 129.5, 127.4, 126.5, 125.5, 121.9, 120.1, 119.1, 114.4, 112.3, 108.4, 79.6, 78.2, 65.8, 55.6, 27.2, 27.1, 24.6 ppm. ESI-MS: 366 $[M+H]^+$.

1-(2-Chlorophenyl)-4-(((2,2-dimethylchroman-4-yl)oxy)methyl)-1H-1,2,3-triazole (17k):
Physical state: yellow liquid. IR: 3129, 3086, 2974, 2922, 1601, 1595, 1565, 1467, 1325, 1213, 1206, 1126, 1100, 1042, 931, 829, 747, 524 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.66 – 7.61 (m, 1H), 7.61 – 7.56 (m, 1H), 7.51 – 7.42 (m, 2H), 7.40 – 7.35 (m, 1H), 7.20 – 7.14 (m, 1H), 6.89 (td, *J* = 7.5, 1.1 Hz, 1H), 6.80 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.93 (q, *J* = 12.3 Hz, 2H), 4.80 – 4.73 (m, 1H), 2.20 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.08 (dd, *J* = 13.6, 7.4 Hz, 1H), 1.46 (s, 3H), 1.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 198.3, 143.2, 142.3, 136.4, 121.3, 120.6, 120.2, 120.0, 118.6, 117.1, 75.1, 71.4, 62.0, 38.0, 28.3, 26.8 ppm. ESI-MS: 370 $[M+H]^+$, 372 $[M+H+2]^+$.

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