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Synthesis and cytotoxicity of novel (E)-2-phenylchroman-4-one-*O*-((1-substituted-1*H*-1,2,3-triazol-4-yl)methyl) oxime derivatives

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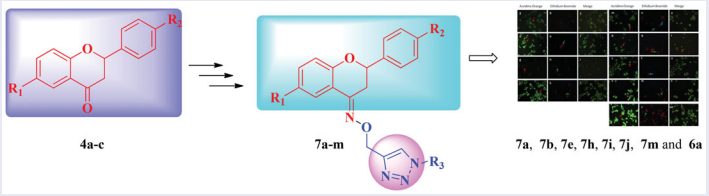
ABSTRACT

A series of new flavanone-triazole hybrids (**7a–m**) were synthesized from flavanone oximes (**6a–c)** via multistep synthetic strategy, involving Cu (I) catalyzed azide, alkyne 1,3-dipolar cycloaddition by Click reaction. All the synthesized compounds were tested for their cytotoxicity against HCT-15, HeLa, NCI-H522, and HEK-293 (normal cell line) cell lines. Compounds **6a**, **7a**, **7b**, **7d**, **7e**, **7j,** and **7m** showed the significant cytotoxicity, wherein compound **7b** showed potential cytotoxicity against NCI-H522 cell line and compounds **6a** and **7a** were offensive with HEK-293 in their toxicity profile.

GRAPHICAL ABSTRACT



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KEYWORDS
Cytotoxicity; 13-dipolar cycloaddition; flavanone; 123-triazoles

Introduction

New-fangled medicinal chemistry faces various tasks from numerous directions, as well as the need for both potency and specificity of any therapeutic agent. Flavanone is an important natural secondary metabolite with significance to cure and prevent tumor, senescence and cardiovascular diseases.[1,2] Flavanone is a member of the flavonoids, which are polyphenols found in plant kingdom. On an average, people intake of flavonoids is about 50–150 mg per day from vegetables, fruits, and other food sources.[3] Flavanones are potential source for the discovery of biologically active lead compounds and therefore have been focused in research and development in the last three decades.[4] The flavanone scaffold is an important intermediate and building block in

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organic synthesis in the design of new lead compounds.[5] The 1,2,3-triazole moiety does not occur in nature, even though triazole derivatives are known to exhibit various pharmacological properties such as anticancer,[6,7] antimicrobial,[8,9] anticonvulsant,[10] antitubercular,[11] analgesic,[12] and antiviral activities.[13] The major problem commonly associated with 1,2,3-triazole synthetic methodology,[14] including the need for long reaction time and high temperature, as well as the formation of regioisomeric mixture of products when unsymmetrical alkynes are involved.[15] To avoid the regioisomeric mixture, Sharpless pioneered Cu (I) catalyzed Click reaction between organic azides and alkynes resulted regioselective-1,4-disubstituted-1,2,3-triazoles with good yields.[16] In view of several applications of flavanones and triazoles, we planned to synthesize novel 1,2,3-triazoles on flavanone skeleton adopting Click chemistry.

Results and discussion

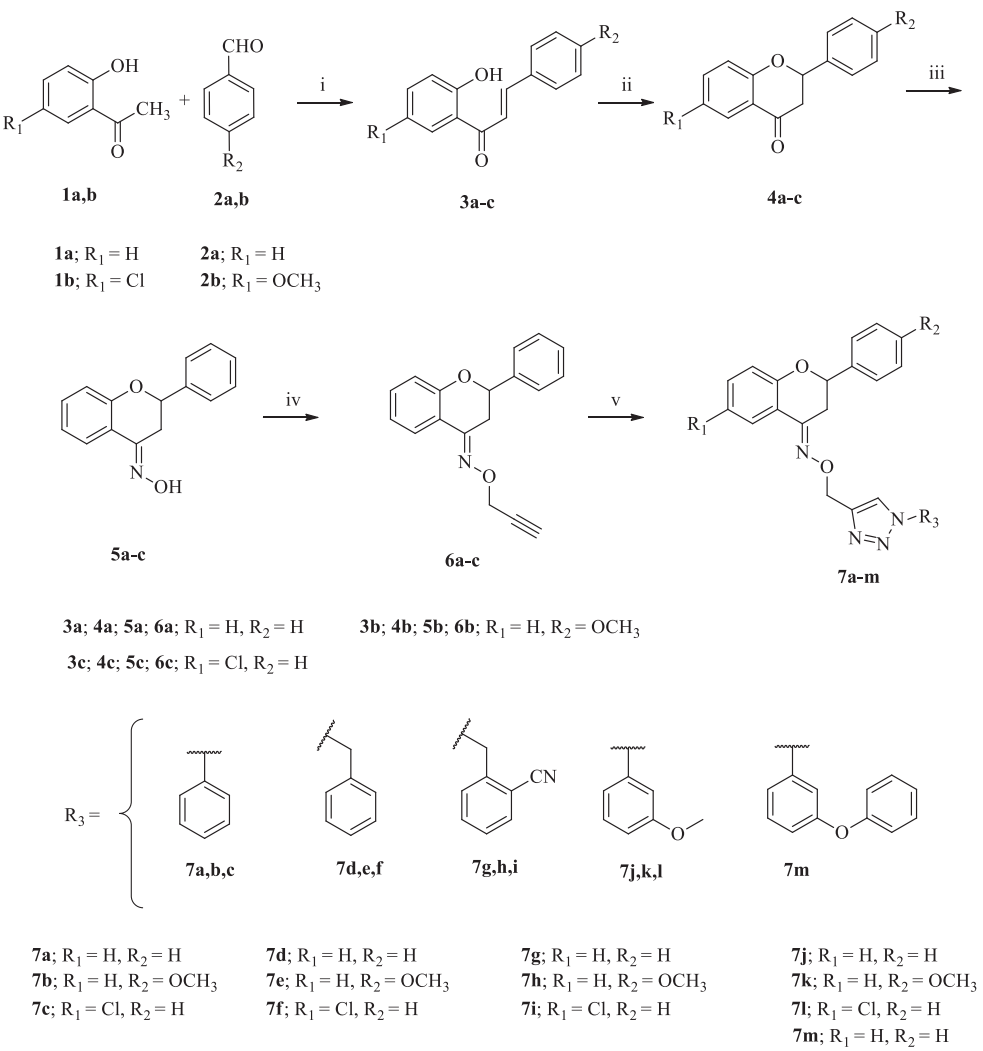
Chemistry

The synthetic outline for the synthesis of novel flavanone-triazole hybrids (**7a–m**) is shown in Scheme 1. The key intermediates, (E)-2-phenylchroman-4-one O-prop-2-yn-1-yl oxime derivatives (**6a–c**) were prepared by four steps methodology. Initially, aldehydes (**2a**,**b**) condensed with 2-hydroxy acetophenones (**1a**,**b**) in basic medium to afforded corresponding chalcones (**3a–c**). Subsequently, cyclization of intermediates **3a–c** in the presence of hydrochloric acid in ethanol under reflux condition gave respective flavanone derivatives (**4a–c**).[17] Furthermore, compounds **4a–c** were treated with hydroxylamine hydrochloride in the presence of sodium acetate in THF, methanol, and water in 1:1:1 ratio under reflux to give exclusively (E)-2-phenylchroman-4-one oxime derivatives (**5a–c**) respectively.[18] The propargylation of compounds **5a–c** with propagyl bromide and potassium carbonate in acetone under reflux condition gave the desired precursors (E)-2-phenylchroman-4-one O-prop-2-yn-1-yl oxime derivatives (**6a–c**).

Finally, compounds **6a–c** undergo regioselective 1,3-dipolar cycloaddition with eagerly prepared substituted phenyl/benzyl azides in the presence sodium ascorbate and $CuSO_4{\cdot}5H_2O$ under Click reaction condition to give selectively 1,4-isomer of corresponding (E)-2-phenylchroman-4-one-O-((1-substituted-1*H*-1,2,3-triazol-4-yl)methyl) oximes (**7a–m**) with good yields. These results were shown in (Table 1). All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and ESI-MS.

Cytotoxic evaluation

Initially, all 16 compounds were tested for their cytotoxicity against three cancerous cell lines such as HCT-15, HeLa, NCI-H522 and one normal cell line HEK-29 IC_{50} values were shown in Table 2. The synthesized compounds showed diverse effect on the three cell lines tested. Descriptively **7k** compound have moderate cytotoxic effect on only HCT-15 cell line, **6b** and **7l** have mild cytotoxic effect on only Hela cell line while **6a**, **7j,** and **7m** showed moderate cytotoxic effect on NCI-H522 cell line only. The compounds **7d**, **7f**, and **7g** showed moderate cytotoxicity against HCT-15 and HeLa cell lines both while **7i** showed moderate cytotoxicity against HeLa and NCI-H522 cell line and **7b** against HCT-15 and NCI-H522 cell lines. **7a**, **7e,** and **7h** are three synthesized



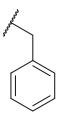
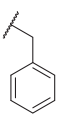
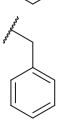
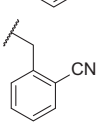
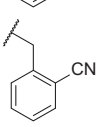
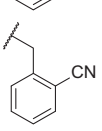
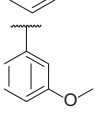
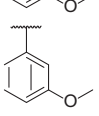
Scheme 1. Reagents and conditions: (i) KOH, EtOH, rt, 12 h, 60%; (ii) EtOH, HCl, reflux, 24 h, 70%; (iii) $NH_2OH{\cdot}HCl$, CH_3COONa,THF:CH_3OH:H_2O (1:1:1), 80 °C, 3 h, 80–82%; (iv) Propargyl bromide, acetone, K_2CO_3, 70 °C, 3 h, 80–85%; (v) R_3–N_3, sodium ascorbate, $CuSO_4{\cdot}5H_2O$, DMF, H_2O, rt, 4 h, 80–85%.

compounds among all which have mild to moderate cytotoxicity against all three cell lines tested. Specific among all, the compound **7b** has found to have high cytotoxicity against NCI-H522 cell line. Interestingly, all the compounds showing anti-cancer activity did not affect HEK-293 cell line, except **6a** and **7a**.

Evaluation of apoptosis by using acridine orange/ethidium bromide (AO/EB) staining

HCT-15, HeLa and NCI-H522 cells were again treated for 24 hours with synthesized compounds at IC_{50} value. The double staining was executed using equimolar mixture of AO/EB. The stained cells were analyzed by fluorescent microscopy. The captured images

Table 1. Synthesis of title compounds.

Entry	R_3	Yield(%)	mp(°C)
7a		80	165
7b		82	168
7c		85	170
7d		80	155
7e		84	170
7f		80	173
7g		82	155
7h		80	156
7i		84	164
7j		83	152
7k		80	155

shows early apoptosis (yellow arrow), late apoptosis (blue arrow) and necrosis condition (green arrows) in cells treated with compounds found effective in MTT assay. Unaffected cells are represented with red arrow in the images. In brief AO is absorbed by live cells and dead cells both, whereas EB is absorbed by dead cells only when the cytoplasmic membrane integrity is lost as in case of apoptosis or necrosis. The staining images of HCT-15, HeLa and NCI-H522 cell lines are shown in Figures 1–3, respectively.

Table 2. IC_{50}[a] values of synthesized compounds in μM[b].

Entry	Compound	HCT-15	HeLa	NCI-H522	HEK-293
1.	6a	>100	>100	14.2 ± 2.1	81.9 ± 4.9
2.	6b	>100	31.0 ± 17.7	>100	118.7 ± 0.7
3.	6c	>100	>100	>100	369.2 ± 0.5
4.	7a	34.5 ± 4.9	11.4 ± 1.5	28.2 ± 16.7	61.4 ± 3.7
5.	7b	32.9 ± 4.6	>100	5.4 ± 2.7	n.s
6.	7c	>100	>100	>100	426.1 ± 2.9
7.	7d	19.4 ± 8	18.9 ± 5.6	>100	n.s
8.	7e	17.4 ± 5.9	15.6 ± 2.4	16.1 ± 1.6	662.1 ± 11.9
9.	7f	36.5 ± 18.8	36.0 ± 14.4	>100	189.0 ± 1.3
10.	7g	25.4 ± 4.2	46.6 ± 15.6	>100	127.4 ± 1.4
11.	7h	34.3 ± 16.6	38.1 ± 13.7	42.5 ± 9.7	967.2 ± 15.8
12.	7i	>100	23.1 ± 11.2	31.6 ± 12.8	145.3 ± 1.5
13.	7j	>100	>100	20.8 ± 1.3	619.6 ± 4.6
14.	7k	30.1 ± 7.6	>100	>100	n.s
15.	7l	>100	25.4 ± 6.8	>100	n.s
16.	7m	>100	>100	16.8 ± 2.1	n.s
17.	Cyclophosphamide	11.18 ± 0.22	3.63 ± 0.19	13.47 ± 0.87	>100
18.	5-Fluorouracil	22.86 ± 1.2	5.18 ± 0.51	26.54 ± 3.2	>100

[a]50% growth inhibition as determined by MTT assay (24 hour drug exposure).
[b]Compounds tested in triplicate, data expressed as mean value ± SEM of three independent experiment.
n.s.: describes non-significant value; drug whose IC_{50} values found non-convergent for HEK-293 cells only.

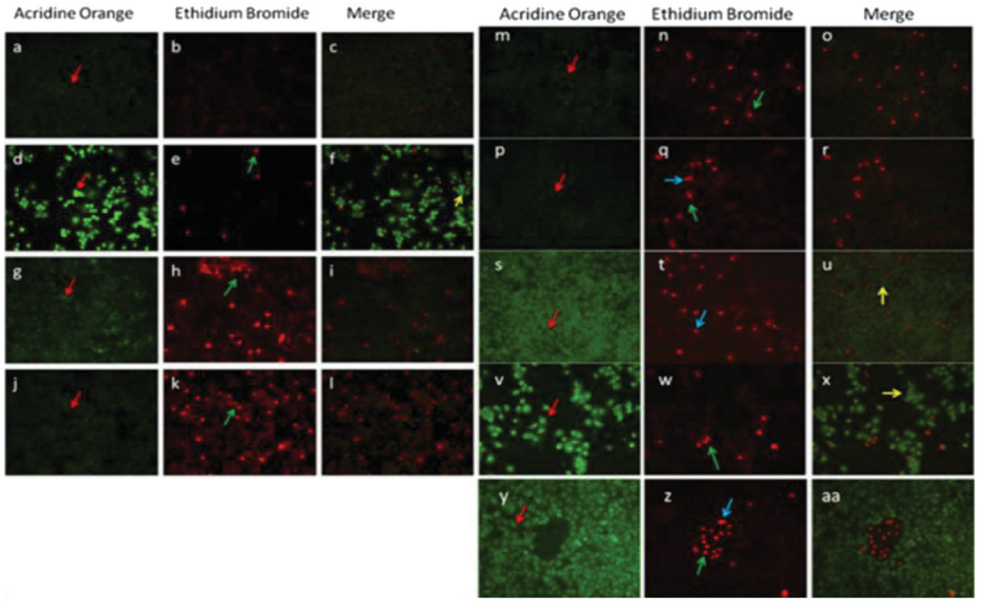


Figure 1. Fluorescent micrographs of AO/EB stained HCT-15 cells incubated for 24 hours. (a–c) Vehicle treated cells, (d–f) cells treated with compound **7a**, (g–i) with compound **7b**, (j–l) with compound **7d**, (m–o) with compound **7e**, (p–r) with compound **7f**, (s–u) with compound **7g**, (v–x) with compound **7h** and (y–aa) with compound **7k**.

Conclusion

In summary, we developed an efficient and facile protocol for the synthesis of regioselective novel flavanone-triazole derivatives via Cu(I) catalyzed 1,3-dipolar cycloaddition of (E)-2-phenylchroman-4-one O-prop-2-yn-1-yl oxime derivatives (**6a–c**) and phenyl/

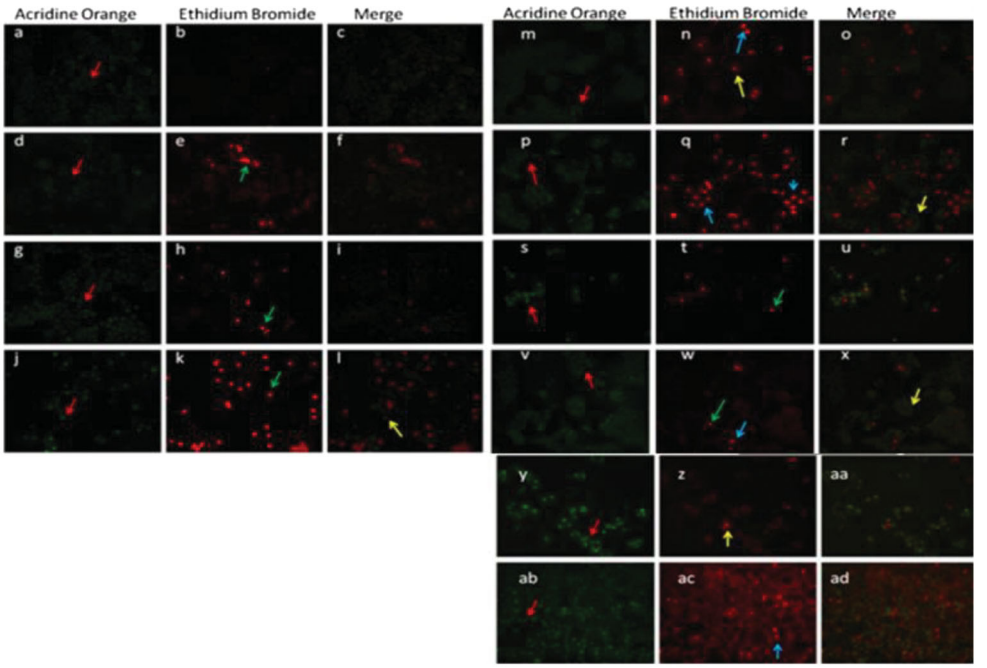


Figure 2. Fluorescent micrographs of AO/EB stained HeLa cells incubated for 24 hours. (a–c) Vehicle treated cells, (d–f) cells treated with compound **7a**, (g–i) with compound **7d**, (j–l) with compound **7e**, (m–o) with compound **7f**, (p–r) with compound **7g**, (s–u) with compound **7h**, (v–x) with compound **7i**, (y–aa) with compound **7l**, and (ab–ad) with compound **6b**.

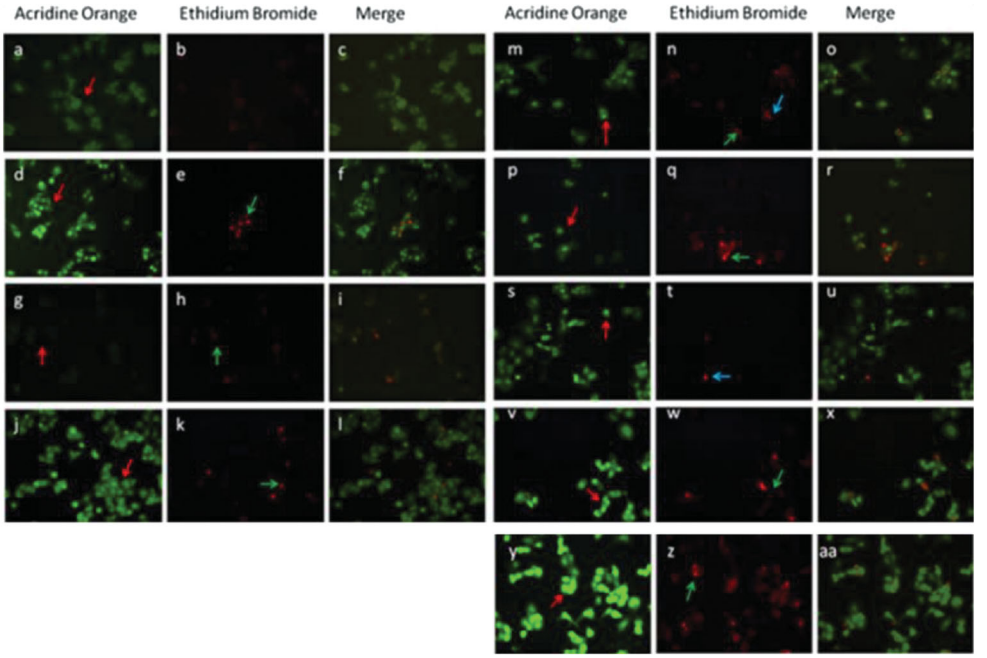


Figure 3. Fluorescent micrographs of AO/EB stained NCI-H522 cells incubated for 24 hours. (a–c) Vehicle treated cells, (d–f) cells treated with compound **7a**, (g–i) with compound **7b**, (j–l) with compound **7e**, (m–o) with compound **7h**, (p–r) with compound **7i**, (s–u) with compound **7j**, (v–x) with compound **7m,** and (y–aa) with compound **6a**.

aryl azides. The entire synthesized compounds showed cell line subjective but diverse cytotoxic effect against the HCT-15, HeLa and NCI-H522 cell line. Compound **7b** is most vivid cytotoxicity against NCI-H522, in addition to better safety profile; these results are fortified to further research on these flavanone based triazole derivatives.

Experimental

Instrumentation and chemicals

All chemicals were purchased from Sigma-Aldrich and solvents from SD Fine Chemicals Pvt. Ltd. Solvents were purified as per the procedures given in the "Text book of practical organic chemistry" by Vogel (6th Edition). Silica gel pre-coated aluminum sheets (60F254, Merck) were used for monitoring the progress of reaction and purity of final products. The spots on TLC plates were visualized by exposure to ultraviolet light (UV) at 254 nm. Column chromatography was performed using Merck silica gel 60–120 mesh. ^{1}H NMR spectra were recorded on Bruker spectrometer at 400 MHz spectrometer, ^{13}C NMR spectra were acquired on 100 MHz with tetramethylsilane as an internal standard, chemical shift (δ) are reported in ppm. (δ) Shift (multiplicity, coupling constant, proton count). Mass spectral analysis was accomplished using electro spray ionization (ESI) techniques.

General method for the synthesis of substituted oximes (5a–c)

Hydroxylamine hydrochloride (1.11 g, 16 mmol) was added to flavanone (2.0 g, 9 mmol) (**4a**) which is dissolved in THF (15 mL) solvent in presence of sodium acetate (1.28 g, 16 mmol), methanol and water (1:1:1) and the mixture was stirred at reflux temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water and extracted with ethylacetate (150 mL). The organic layer was washed with water (3 × 150 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane: ethylacetate (7:3) to obtain the pure product (**5a**).

Synthesis of (E)-2-phenylchroman-4-one oxime (5a)

Yield: 80%, White solid, mp: 165 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (s), 7.86 (dd, J = 8.2, 1.5 Hz, 1H), 7.51 (m, 2H), 7.44 (m, 2H), 7.38 (m, 1H), 7.36–7.28 (m, 1H), 7.00 (m, 2H), 5.13 (dd, J = 12.5, 3.2 Hz, 1H), 3.61 (dd, J = 17.3, 3.0 Hz, 1H), 2.80 (dd, J = 17.3, 12.5 Hz, 1H).^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.7, 150.2, 139.7, 131.3, 128.7, 128.4, 126.2, 123.8, 121.7, 118.1, 117.9, 77.1, 30.4. MS (ESI): m/z 240 $[M+H]^+$. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48. Found: C, 75.16, H, 5.55%.

General method for the synthesis of (E)-2-arylchroman-4-one O-prop-2-yn-1-yl oximes (6a-c)

Propargyl bromide (0.89 g, 7.53 mmol) was added slowly to a stirring mixture of the Oxime (**5a**) (1.5 g, 6.27 mmol) and anhydrous K_2CO_3 (1.040 g, 7.53 mmol) in Acetone

(15 mL), and the stirring continued at reflux temperature for 3 h. After completion of the reaction (monitored by TLC), solvent was removed under reduced pressure and water was added (50 mL) into the reaction mixture. The reaction mixture was extracted with ethylacetate (150 mL). The combined organic layer was washed with water (3 × 150 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography using hexane: ethylacetate (9:1) to obtain the pure product (**6a**).

Synthesis of (E)-2-phenylchroman-4-one O-prop-2-yn-1-yl oxime (6a)

Yield: 85%, Yellow solid, mp: 155 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J = 7.5$ Hz, 1H), 7.45–7.25 (m, 6H), 6.97 (m, 2H), 5.06 (brd, $J = 12.5$ Hz, 1H), 4.76 (brs, 2H), 3.49 (brd, $J = 17.6$ Hz, 1H), 2.75 (m, 1H), 2.47 (brs, ≡CH, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.8, 150.1, 139.8, 131.4, 128.7, 128.5, 126.2, 124.4, 121.6, 118.0, 117.9, 79.8, 77.1, 74.6, 61.8, 31.3. MS (ESI): *m/z* 278 $[M + H]^+$. Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45. Found: C, 77.66, H, 5.27%.

General methods for the synthesis of (E)-2-arylchroman-4-one O-((1-aryl-1H-1,2,3-trizol-5yl)methyl) oximes (7a–m)

(E)-2-phenylchroman-4-one O-prop-2-yn-1-yl oxime (**6a**) (0.1 g, 0.36 mmol) and various phenyl/benzyl azides (0.04 g, 0.43 mmol) were dissolved in DMF (5 mL) then sodium ascorbate (0.3 mmol, 300 µL of freshly prepared 1 M solution in water) and copper (II) sulfate pentahydrate (7.5 mg, 0.03 mmol, in 100 µL of water) was added. The homogeneous mixture was stirred vigorously for 4 h, until to become clear solution and TLC analysis indicated complete consumption of the reactants. The reaction mixture was diluted with water (50 mL), cooled in ice, and the precipitate was collected by filtration. After washing the precipitate with cold water (2 × 25 mL), the crude product was purified by column chromatography using hexane: ethylacetate (8:2) to obtain the pure product (**7a**).

(E)-2-phenylchroman-4-one O-((1-phenyl-1H-1,2,3-trizol-5yl)methyl) oxime (7a)

Yield: 80%, White solid, mp: 165 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.96 (dd, $J = 8.5$, 1.6 Hz, 1H), 7.74 (dd, $J = 8.6$, 1.3 Hz, 2H), 7.53 (m, 2H), 7.45 (m, 3H), 7.40 (m, 2H), 7.35 (m, 1H), 7.29 (m, 1H), 7.00 (m, 2H), 5.41 (s, 2H), 5.08 (dd, $J = 2.3$, 3.0 Hz, 1H), 3.52 (dd, $J = 17.3$, 3.0 Hz, 1H), 2.77 (dd, $J = 17.3$, 12.3 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.7, 149.7, 145.3, 139.7, 137.0, 131.3, 129.7, 128.8, 128.4, 126.2, 124.1, 121.5, 121.3, 120.6, 118.7, 118.0, 76.9, 67.6, 31.2. MS (ESI): *m/z* 397 $[M + H]^+$. Anal. Calcd for $C_{24}H_{20}N_4O_2$: C, 72.21; H, 5.09. Found: C, 72.09, H, 5.19%.

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