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# Synthesis of novel 1,2,3-triazole/isoxazole functionalized 2*H*-Chromene derivatives and their cytotoxic activity

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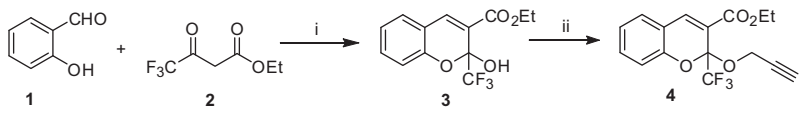
ABSTRACT

A series of novel 2-(1,2,3-triazolylmethoxy) **5a–q** and isoxazole tagged **6a–g** 2*H*-Chromene derivatives were prepared starting from salicylaldehyde and ethyl-4,4,4-trifluoroacetoacetate via cyclization to form ethyl 2-hydroxy-2-(trifluoromethyl)-2*H*-Chromene-3-carboxylate **3**. Compound **3** on reaction with propargyl bromide resulted compound **4** and was independently reacted with aryl/alkyl azides and aryl aldoximes obtained 2-(1,2,3-triazolylmethoxy) and isoxazole tagged 2*H*-Chromene derivatives **5a–q**, **6a–i**, respectively. Compounds **6** were further hydrolysed to acid derivatives **7a–g**. All the products **5a–q**, **6a–i**, **7a–g** were screened for cytotoxic activity against four human cancer cell lines and among all the compounds, **5f**, **5g**, **5l**, **5q** showed promising activity at <20 μM concentration.



2*H*-Chromene derivatives are an important class of heterocyclic compounds[1] used as substrates for the synthesis of antitumor,[2,3] antimicrobial,[4] fungicidal,[5] insecticidal[6] and anti HIV agents.[7] The 2*H*-Chromene nucleus also present in health promoting agents like antioxidants,[8] polyphenols,[9] and is a privileged scaffold found in many biologically active molecules,[10–12] including natural products.[13,14] Several reports are available on synthesis of Chromene derivatives and efficient strategies are based on salicylaldehyde.[15–19] Recent reports on synthesis of 2*H*-Chromene derivatives are mainly from salicylaldehyde and ethyl-4,4,4-trifluoroacetoacetate,[20] α,β-unsaturated cyclic ketones,[21] 1*H*-indene-1,3(2*H*)dione.[22] Similarly, 1,2,3-triazoles and isoxazoles due to their unique chemical and structural properties received much attention over the past decade and found wide application in medicinal chemistry.[23–28] In order to construct 1,2,3-triazole and isoxazole ring systems, several synthetic methods have been developed.[29–32] Based on the importance of 2*H*-Chromenes, 1,2,3-triazole and isoxazole, it was envisaged that hybrid molecules would display promising activity.

In continuation of our efforts on the synthesis of potential molecules,[33–35] we have prepared a series of novel 1,2,3-triazole and isoxazole functionalized chromene derivatives. Thus, the salicylaldehyde **1** on reaction with ethyl-4,4,4-trifluoroaceto acetate **2** in dichloromethane using piperidine as a base yielded 2-hydroxy-2-trifluoromethyl chromene-3-carboxylate ethyl ester **3**. Compound **3** was reacted with propargyl bromide in acetone using $K_2CO_3$ as a base and obtained O-propargylated chromene derivative **4** which was further reacted with diverse substituted azides




**Scheme 1.** Preparation of ethyl-2-(prop-2-ynyloxy)-2(trifluoromethyl)-2*H*-Chromene-3-carboxylate (**4**). Reagents and conditions: (i) piperidine/ethanol, reflux, 5 h. (ii) Propargyl bromide (1.0 equiv)/acetone, $K_2CO_3$ (1.0 equiv), KI (5 mol %), 4 h, reflux.

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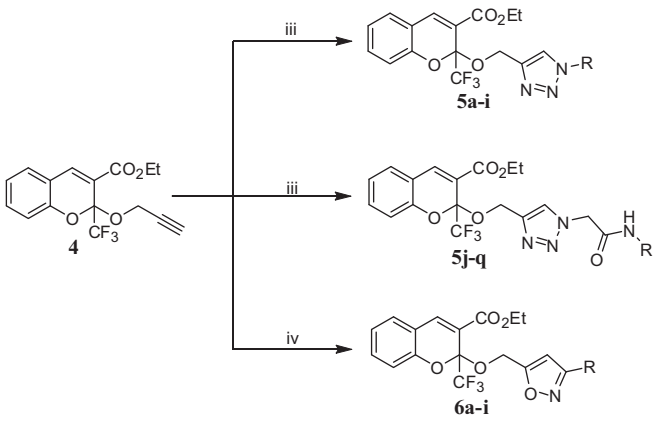
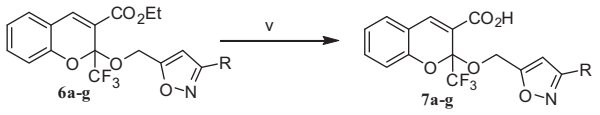
like aryl azides or alkyl amide azides[37,38] in THF using CuI as catalyst under Sharpless conditions yielded **5a–i** and **5j–q**, respectively, in high yield. Similarly, compound **4** on reaction with aryl aldoximes[39,40] yielded isoxazole functionalized 2*H*-Chromene derivatives **6a–i**. Compounds **6a–i** were further hydrolyzed to acid derivatives **7a–g**. All the products **5a–q**, **6a–i**, **7a–g** were screened for anticancer activity against four human cancer cell lines using 5-Fluorouracil as control. Compounds **5f**, **5g**, **5l**, **5q**, **6a**, **6b**, **6i**, **7a** and **7f** which showed promising activity at micro molar concentration have been identified. The sequence of reactions outlined in Schemes 1–3 and the resulting products are tabulated in Table 1.




**Scheme 2.** Synthesis of 1,2,3-triazole/isoxazole functionalized 2*H*-Chromene derivatives. Reagents and conditions: (iii). Aryl or alkyl amide azide/CuI, THF, rt, 15–20 h, (iv) R–CH=NOH/NaOCl, DCM, rt, 6–8 h.




**Scheme 3.** 2-((3-Arylisoxazole-5-yl)methoxy)-2-trifluoromethyl)-2*H*-Chromene-3-carboxylic acid (**7a–g**). Reagents and conditions: (v) 10% NaOH/EtOH, reflux 1 h.

**Table 1**
Preparation of compounds **5a–q**, **6a–i and 7a–g**

| Compound | R | Yield[a] | Mp (°C) |
|---|---|---|---|
| **5a** | 4-$CH_3C_6H_4$ | 85 | 155–157 |
| **5b** | 4-$NO_2C_6H_4$ | 83 | 122–124 |
| **5c** | $C_6H_5$ | 90 | 136–138 |
| **5d** | 3,4-ClF-$C_6H_3$ | 80 | 103–105 |
| **5e′** | 3-$CF_3C_6H_4$ | 82 | 102–104 |
| **5f** | 4-$FC_6H_4$ | 83 | 125–127 |
| **5g** | 3,4-$NO_2FC_6H_3$ | 82 | 92–93 |
| **5h** | 3-$OCH_3C_6H_4$ | 84 | 74–75 |
| **5i** | $-(CH_2)_7-CH_3$ | 85 | Liquid |
| **5j** | 4-$CH_3C_6H_4$ | 75 | 86–88 |
| **5k** | 4-$OCH_3C_6H_4$ | 78 | 84–86 |
| **5l** | 3-$ClC_6H_5$ | 80 | 68–70 |
| **5m** | 3-$FC_6H_4$ | 81 | 83–85 |
| **5n** | 2-$FC_6H_4$ | 75 | 92–93 |
| **5o** | 2-$BrC_6H_4$ | 70 | 120–122 |
| **5p** | 2-Cl,4-$IC_6H_3$ | 80 | 67–69 |
| **5q** | 3-$C_6H_{11}$ | 70 | 75–76 |
| **6a** | 4-$FC_6H_4$ | 87 | 119–122 |
| **6b** | 3-$CF_3C_6H_4$ | 85 | 108–109 |
| **6c** | 2-$C_9H_8$ | 90 | 123–124 |
| **6d** | 4-$CH_3C_6H_4$ | 80 | 115–116 |
| **6e′** | 4-$NO_2C_6H_4$ | 82 | 135–136 |
| **6f** | 2,4-$DiFC_6H_4$ | 83 | 117–118 |
| **6g** | 4-$OCH_3C_6H_4$ | 84 | 118–120 |
| **6h** | 4-$BrC_6H_4$ | 85 | 122–123 |
| **6i** | 4-$ClC_6H_4$ | 82 | 132–135 |
| **7a** | 4-$CH_3C_6H_4$ | 76 | 137–138 |
| **7b** | 2,4-$DiFC_6H_4$ | 75 | 166–167 |
| **7c** | 4-$FC_6H_4$ | 80 | 157–158 |
| **7d** | 3-$CF_3C_6H_4$ | 81 | 158–159 |
| **7e** | 2-$C_9H_8$ | 80 | 160–161 |
| **7f** | 4-$OCH_3C_6H_4$ | 60 | 154–156 |
| **7g** | 4-$NO_2C_6H_4$ | 65 | 162–163 |

[a] Isolated yields.

**Table 2**
Cytotoxic activity of compounds **5a–q**, **6a–i** and **7a–g**[a]

| Compound | $IC_{50}$ values[b] (in μM) | | | |
|---|---|---|---|---|
| | A549 | DU145 | HeLa | MCF7 |
| **5a** | 19.7 ± 0.11 | 30.2 ± 0.21 | 25.1 ± 0.32 | 26.7 ± 0.22 |
| **5b** | — | — | — | — |
| **5c** | — | — | — | — |
| **5d** | 26.3 ± 0.22 | 21.5 ± 0.28 | 22.7 ± 0.18 | 25.3 ± 0.16 |
| **5e** | — | — | — | — |
| **5f** | 7.3 ± 0.14 | 8.9 ± 0.09 | 8.4 ± 0.20 | 9.1 ± 0.15 |
| **5g** | 11.9 ± 0.16 | 13.2 ± 0.11 | 15.6 ± 0.14 | 16.2 ± 0.21 |
| **5h** | — | — | — | — |
| **5i** | — | — | — | — |
| **5j** | 54.3 ± 0.36 | — | 67.4 ± 0.48 | — |
| **5k** | 29.4 ± 0.24 | 32.7 ± 0.36 | 31.9 ± 0.28 | 28.1 ± 0.16 |
| **5l** | 12.8 ± 0.18 | 10.1 ± 0.42 | 12.3 ± 0.12 | 11.6 ± 0.23 |
| **5m** | — | — | — | — |
| **5n** | 50.1 ± 0.48 | 33.9 ± 0.37 | 49.9 ± 0.34 | 42.1 ± 0.21 |
| **5o** | — | — | — | — |
| **5p** | 22.3 ± 0.11 | 24.4 ± 0.23 | 26.1 ± 0.31 | 28.1 ± 0.14 |
| **5q** | 9.9 ± 0.14 | 10.2 ± 0.08 | 11.4 ± 0.22 | 12.1 ± 019 |
| **6a** | 35.5 ± 0.24 | 53.5 ± 0.36 | 42.3 ± 0.21 | 48.2 ± 0.14 |
| **6b** | 48.6 ± 0.32 | 57.3 ± 0.33 | 21.4 ± 0.11 | 22.1 ± 0.22 |
| **6c** | — | 71.8 ± 0.48 | — | 65.4 ± 0.48 |
| **6d** | — | — | — | — |
| **6e** | — | — | — | — |
| **6f** | — | — | — | — |
| **6g** | — | — | — | — |
| **6h** | — | 71.7 ± 0.42 | 52.3 ± 0.32 | — |
| **6i** | 19.1 ± 0.18 | 18.2 ± 0.30 | 12.3 ± 0.35 | 18.2 ± 0.12 |
| **7a** | 51.2 ± 0.24 | 41.4 ± 0.32 | 33.4 ± 0.23 | 30.1 ± 0.16 |
| **7b** | — | — | — | — |
| **7c** | — | 168.0 ± 0.41 | — | 64.2 ± 0.32 |
| **7d** | — | 155.0 ± 0.52 | — | — |
| **7e** | — | 140.5 ± 0.35 | — | — |
| **7f** | 36.2 ± 0.24 | 42.0 ± 0.48 | — | 35.2 ± 0.25 |
| **7g** | — | 100.2 ± 0.28 | — | — |
| 5-Fluoro uracil[c] | 1.9 ± 0.09 | 1.9 ± 0.17 | 1.8 ± 0.08 | 1.8 ± 0.17 |

[a] Exponentially growing cells were treated with different concentrations of compounds **5a–q**, **6a–i and 7a–g** for 24 h and cell growth inhibition was analyzed through MTT assay.

[b] $IC_{50}$ is defined as the concentration, which results in a 50% decrease in cell number as compared with that of the control cultures in the absence of an inhibitor. The values represent the mean ± SE of three individual observations.

[c] 5-Fluorouracil was employed as positive control, — indicates $IC_{50}$ value >150 μM.

Compounds **5a–q**, **6a–i and 7a–g** were screened against four human cancer cell lines namely A549-Lung Cancer (CCL-185), MCF7—Breast cancer (HTB-22), DU145—Prostate cancer (HTB-81), HeLa—Cervical cancer (CCL-2) using 5-Fluorouracil as positive control by MTT assay.[36] The $IC_{50}$ values of the test compounds for 24 h were calculated and presented in Table 2. It is evident from the results that, most of the compounds showed significant decrease in cell viability in all the tested cell lines in a concentration-dependent manner. Among all the compounds, **5f**, **5g**, **5l**, **5q** found to show promising activity at <20 μM against all the cell lines whereas compounds **6a**, **6b**, **6i**, **7a** and **7f** showed moderate activity at <50 μM concentration. The activity is attributed to the presence of fluorine or chlorine or nitro group on phenyl at fourth position of triazole ring, whereas in presence of chlorine along with fluorine on phenyl of triazole ring reducing activity. Isoxazole functionalized 2*H*-Chromene derivatives **6a–i** and **7a–g** showed minute decrease in cell viability of the tested cell lines even after 100 μM

concentration. Slight structural modification of these active derivatives may yield prospective anticancer drugs.

In conclusion, A series of novel 2*H*-Chromene derivatives were prepared and screened for cytotoxic activity against four human cancer cell lines and triazole tagged 2*H*-Chromene derivatives showed better cytotoxic activity than isoxazole tagged 2*H*-Chromene derivatives. Among all the compounds **5f**, **5g**, **5l** and **5q** are identified as promising compounds.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.02.069.

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