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Original article

Synthesis and evaluation of a series of benzopyran derivatives as PPAR α/γ agonists

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Abstract

A series of benzopyran derivatives were synthesized and evaluated for PPAR α/γ agonist activities. Most of the compounds exhibit reasonable PPAR α and PPAR γ agonist activities. In particular, compounds **7b**, **8b**, **8e** and **8h** with remarkable PPARg EC_{50} values of 0.001 μM are excellent full PPAR γ agonists with the functional potency about 130, 20 times stronger than that of leading compound **5** and rosiglitazone, respectively. Compounds **7a**, **7c**, **7d** and **8a** are dual PPAR α/γ agonists, and all of them gave comparable or stronger PPAR α/γ agonist efficacy than that of the corresponding positive control.

1. Introduction

The peroxisome proliferator-activated receptors (PPARs) are a subfamily of ligand-activated nuclear hormone transcription factors. By governing lipid and glucose homeostasis, PPARs (PPAR α, PPAR γ, and PPAR δ) play a central role in cardiovascular diseases, obesity and diabetes. PPAR γ is highly distributed in skeletal muscle, liver and adipose tissue which is important for insulin action. Activation of PPAR γ improves glycemic control by improving insulin sensitivity, via activation of genes involved in the control of glucose production, transportation and utilization [1]. Alternatively, PPAR α is localized in tissues of the heart, liver and muscle, where it plays an important role in lipid metabolism by controlling genes relating to cellular free fatty acid metabolism and cholesterol trafficking. PPAR α activation decreases serum triglycerides (TGs) and increases levels of serum high-density lipoprotein (HDL)-cholesterol [2]. In addition, both PPAR γ and PPAR α selective activators have been demonstrated to suppress vessel wall inflammatory activity and reduce atherosclerosis in animal models through complementary mechanisms [3]. Since most of type 2 diabetic patients suffer from insulin resistance in addition to atherogenic lipid abnormalities, an agent that simultaneously activates both PPAR α and PPAR γ has the potential advantage over the single selective PPAR α or PPAR γ agonist for the treatment of diabetic patients with the additional risk factor of dyslipidemia. In the recent decades, much attention has been paid to the development of PPAR α/γ dual agonists [4–14]. Compound **1** (farglitazar) [5], a potent PPAR γ agonist with moderate PPAR α relative activity, was developed as a clinical candidate but was dropped due to the emergence of edema at phase III. Two dual agonists **2** (ragaglitazar or **DRF2725**) [6] and **3** (**MK-767** or **KRP-297**) [4] with more substantial PPAR α activity also discontinued the development in the late clinical stage due to carcinogenicity in rodent toxicity models. Compound **4** (muraglitazar) [10], also a dual PPAR α/γ agonist, was abandoned after phase III because of the possibility of increasing incidence of adverse cardiovascular events. Though suffered so much frustration, the work to investigate PPAR α/γ dual agonists with novel biological profiles and structural diversity still remains attractive [15,16].

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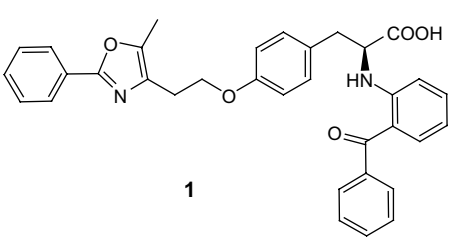

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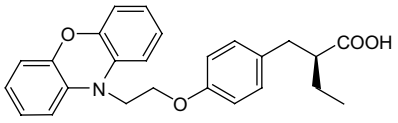

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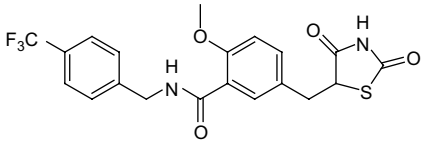

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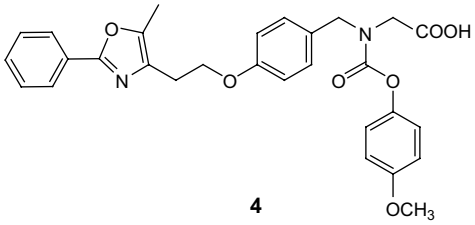

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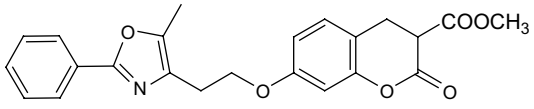
We previously reported the synthesis and insulin sensitizing activity of a novel kind of benzopyran derivatives [17], the representative compound **5**, which is now under preclinical research as a candidate for treatment of type 2 diabetes, exhibited more potent insulin sensitizing activity than that of positive control rosiglitazone. However, the molecular target of the novel kind of benzopyran derivatives is not clear. As part of our continuing research directed toward the structural development of dual PPAR α/γ agonists, we subsequently found that compound **5** is a selective potent dual PPAR α/γ agonist. In this article, we report our efforts related to the synthesis of a series novel benzopyran-based dual PPAR α/γ agonists, and evaluations of their *in vitro* PPAR α and PPAR γ transactivation activity. The putative pharmacophore 2-(5-methyl-2-phenyloxazol-4-yl)ethanol, originally reported by Sohda et al. [18] was the most effective block selected in our previous investigation [17]. The oxobenzopyran-3-methyl carboxylate was retained as a core skeleton to keep the functional activity and various substitutions on the phenyl ring of the 2-(5-methyl-2-aryloxazol-4-yl)ethanol block were designed as modification to develop more potent PPAR agonists.



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2. Chemistry

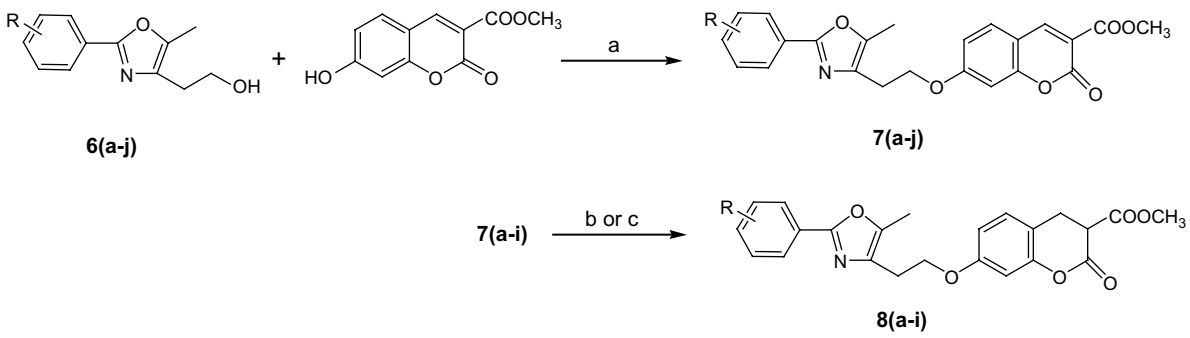
Condensation of methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate with substituted 2-(5-methyl-2-aryloxazol-4-yl)ethanols **6**(**a**-−**j**) via Mitsunobu reaction yield compounds **7**(**a**−**j**). Catalytic hydration of **7**(**a**−**i**) with palladium on carbon gave compounds **8**(**a**−**i**) (Scheme 1). The desired heterocyclic alcohols **6**(**a**−**c**), **6e** and **6f** were synthesized as previously reported [11,19] and alcohols **6d**, **6**(**g**−**j**) were prepared similarly to the reported literature [19]. The sequence involved acylation to incorporate variety of substituted aryl ring, Darkin−West conversion to form methyl ketoamide, cyclodehydration to the oxazole ring and reduction of the ester side chain (Scheme 2). The compounds obtained are summarized in Table 1.

3. Biological evaluation

All compounds prepared were evaluated for activity at each of the human PPAR subtypes by using an established cell-based transactivation assay in U2OS cells [20]. The results obtained (Table 1) were compared with the corresponding data for WY14643 and rosiglitazone, used as reference compounds in the PPAR α and PPAR γ transactivation assays, respectively. The activating efficacy of the test compound was judged by the maximal activation and given as the percentage of the corresponding result obtained with the reference compounds. The activating potency of the test compound was expressed as EC_{50} (the concentration at which 50% of the maximum activation was observed).

4. Results and discussion

As described in Table 1, modification on the phenyl ring of phenyloxazol resulted in significant fluctuation in both PPAR α and PPAR γ transactivation activity. It is encouraging that compounds listed in Table 1, except **7f** and **7j**, all showed stronger PPAR α agonist potency than that of WY14643. Compounds **7a**, **7c**, **7d** and **8a**, showing EC_{50} values for both PPAR α and γ in almost the same rank, were defined as dual PPAR α/γ agonists, and all of them gave comparable or stronger PPAR α/γ agonist efficacy than that of the corresponding positive control. For the other compounds listed in Table 1, all exhibited selective PPAR γ agonist activity 100 to 1000-fold stronger than that of PPAR α agonist activity. Compounds **7b**, **8b**, **8e** and **8h** are full PPAR γ agonists, all exhibited the functional potency about 130, 20 times stronger



Scheme 1. Reagents and conditions: (a) Ph_3P, DEAD, THF; (b) H_2, 10% Pd/C, MeOH/dioxane (1:3); (c) H_2, 5% Pd/C, EtOAc/dioxane (1:1).

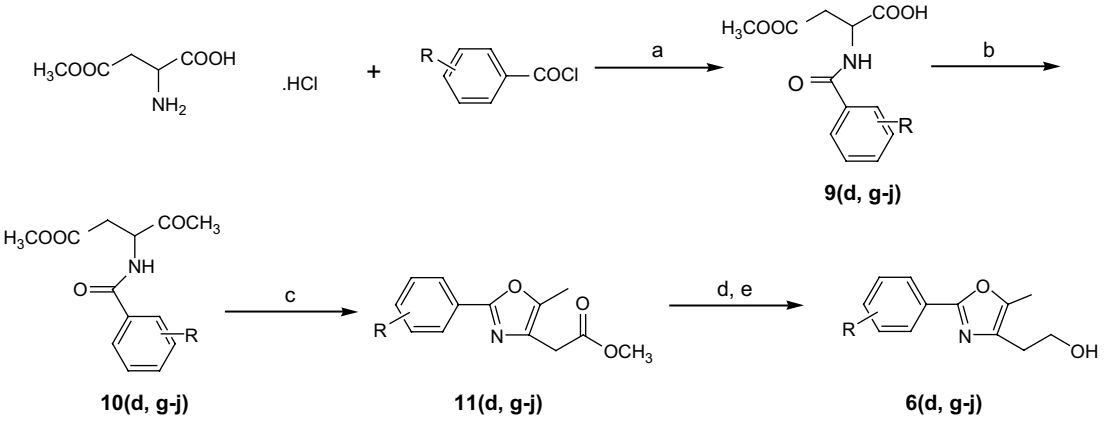
than that of leading compound **5** and rosiglitazone, respectively. In addition, these compounds also displayed noticeable agonist potency and efficacy on PPAR α. It is interesting that the compounds showing good PPAR γ agonist activity also possess good PPAR α agonist activity judged by their maximum activity. It might imply that these two types of agonists may exhibit similar structure–activity relationship, thus many group-replacement operations in the search of PPAR γ agonists, may be applicable in the design of selective PPAR α or dual PPAR α/γ agonists. With the comparison of **7b** and **7c**, **8b** and **8c**, **7e** and **7f**, **8e** and **8f**, **7h** and **7i**, **8h** and **8i**, compounds with *para* substitutions on the phenyl ring showed more potent PPAR α and γ agonist efficacy than that of the compounds with *meta* substitutions judged by EC_{50}. Introduction of strong electron-withdrawing trifluoromethyl group provided compounds **7g** and **8g** with relatively low PPAR α and PPAR γ efficacy (E_{max}). Similar result was obtained in compound **7j**, also, with the introduction of a nitro group, with electron-withdrawing and poor lipophilicity characteristics, and even no activation of PPAR α was produced. A significant improvement in PPAR γ efficacy was obtained with the more bulky phenyl (**7a**) or *tert*-butyl (**7d**) groups as substituent on the phenyl ring. There is no obvious trend of transactivation activity for most of the double-bond and single-bond congeners, though the unsaturated compounds **7**(**a**–**d**) have more effective maximal activity (E_{max}) than their saturated congeners **8**(**a**–**d**).

In conclusion, we prepared a new series of benzopyran derivatives and primarily investigated their structure and activity relationships (SAR). All compounds, except **7f** and **7j**, exhibited stronger PPAR α agonist potency than that of WY14643. Compounds **7a**, **7c**, **7d** and **8a** are dual agonists with comparable or stronger activating efficacy for both PPAR α and PPAR γ isomers than that of the positive control, respectively. Compounds **7b**, **8b**, **8e** and **8h** are full PPAR γ agonists with about 130, 20 times stronger agonist potency than that of leading compound **5** and rosiglitazone, respectively. Further pharmacological studies on these compounds are ongoing in our lab.

5. Experimental

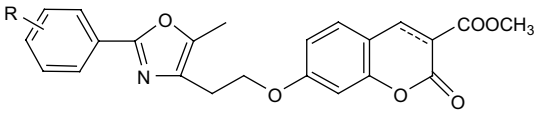
5.1. General methods

Tetrahydrofuran was dried by distillation from sodium/benzophenone. *N*,*N*-Dimethylformamide was dried by distillation *in vacuo* from calcium hydride. Other commercially available chemicals and solvents were used without further purification. NMR spectra were recorded on a Varian Mercury-400 MHz spectrometer. Low resolution mass spectra were obtained using a Finnigan MAT 95 mass spectrometer. Elemental analysis for carbon, hydrogen, and nitrogen was determined on a Vario EL elemental analyzer.



Scheme 2. Reagents and conditions: (a) Na_2CO_3, acetone, H_2O, 0 °C; (b) acetic anhydride, pyridine, 90 °C; (c) $POCl_3$, DMF, 90 °C; (d) NaOH, MeOH; (e) BH_3–THF, MeOH, 50 °C.

Table 1
Structure and transactivation activity of the compounds



Compound	R	Double bond[a]	PPAR α		PPAR γ	
			EC_{50} (μM)	% max	EC_{50} (μM)	% max
7a	*p*-Ph	Yes	1.23	116	1.26	263
8a	*p*-Ph	No	0.91	68	1.12	164
7b	*p*-OMe	Yes	5.25	163	0.001	122
8b	*p*-OMe	No	1.74	96	0.001	101
7c	*m*-OMe	Yes	1.62	100	0.35	109
8c	*m*-OMe	No	1.20	23	0.1	75
7d	*p*-^{t}Bu	Yes	2.29	90	1.74	239
8d	*p*-^{t}Bu	No	0.10	26	0.25	84
7e	*p*-Me	Yes	0.001	65	0.001	89
8e	*p*-Me	No	0.91	94	0.001	101
7f	*m*-Me	Yes	ia[b]	ia	0.001	76
8f	*m*-Me	No	1.55	83	0.001	88
7g	*m*-CF_3	Yes	1.20	21	0.42	72
8g	*m*-CF_3	No	0.17	23	0.16	75
7h	*p*-F	Yes	0.07	44	1.62	89
8h	*p*-F	No	0.1	98	0.001	173
7i	*m*-F	Yes	1.29	38	0.96	65
8i	*m*-F	No	0.72	30	0.17	78
7j	*m*-NO_2	Yes	ia	ia	3.55	62
5	H	No	0.14	42	0.13	96
Rosiglitazone			–	–	0.02	100
WY14643			12	100	–	–

[a] Yes: 3,4-double bond; No: 3,4-single bond.
[b] ia: Inactive.

5.2. 2-(2-(4-tert-Butylphenyl)-5-methyloxazol-4-yl)ethanol (**6d**)

5.2.1. Step 1: Methyl 3-(4-tert-butylbenzamido)-4-oxopentanoate (**10d**)

A mixture of 2-(4-*tert*-butylbenzamido)-4-methoxy-4-oxobutanoic acid (**9d**) (6.3 g, 20.5 mmol), pyridine (20.8 ml), and acetic anhydride (12.5 ml) was heated at 90 °C for 1.5 h. Excess acetic anhydride and pyridine were evaporated in vacuum and the residue was diluted with ether (200 ml). The organic phase was washed with 1.0 M HCl (100 ml), water (150 ml) and brine (150 ml), then dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield the desired product 4.20 g (67.1%) as a pale yellow oil. The residue was used in the next reaction without purification.

5.2.2. Step 2: Methyl 2-(2-(4-tert-butylphenyl)-5-methyloxazol-4-yl)acetate (**11d**)

Phosphorus oxychloride (1.0 ml) was added dropwise to a solution of methyl 3-(4-*tert*-butylbenzamido)-4-oxopentanoate (1.11 g, 3.64 mmol) in DMF (8 ml). The mixture was heated to 90 °C for 0.5 h and then cooled to ambient temperature before being poured into an ice-water bath. The mixture was extracted with ethyl ether (3 ml) after the ice melted. The combined organic phases were washed with water (30 ml) and brine (30 ml), dried, and concentrated to obtain a brown oil. The residue was purified by column chromatography (EtOAc/hexane) to provide 0.75 g (72.1%) of the desired product as a white solid.

5.2.3. Step 3: 2-(2-(4-tert-Butylphenyl)-5-methyloxazol-4-yl)ethanol (**6d**)

Methyl 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)acetate (0.75 g, 2.61 mmol), methanol (8 ml), water (2 ml), and NaOH (0.2 g) were stirred at 40 °C for 1 h. The reaction mixture was concentrated, diluted with water (10 ml), extracted two times with ethyl ether. The combined organic phases were discarded. The aqueous layer was acidified and extracted with EtOAc (2 × 15 ml). The combined organic layers were washed with water, brine and concentrated to obtain 0.71 g of 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)acetic acid.

BH_3–THF complex (6.5 ml, 6.5 mmol) was added dropwise to a solution of 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)acetic acid (0.71 g, 2.6 mmol) in THF. The reaction mixture was stirred for 0.5 h, quenched by saturated sodium bicarbonate aqueous and concentrated. The residue was dissolved in EtOAc (20 ml), washed by water (10 ml) and brine (10 ml), dried over anhydrous sodium sulfate and concentrated to obtain 0.66 g (98.5%) 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)ethanol as a white solid. Mp 124–125 °C. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9H), 2.32 (s, 3H), 2.71 (t, $J = 5.49$ Hz, 2H), 3.92 (t, $J = 5.49$ Hz, 2H), 7.44 (dd, $J = 6.77$ Hz, $J = 2.01$ Hz, 2H), 7.90(dd, $J = 6.77$ Hz, $J = 2.01$ Hz, 2H).

5.3. 2-(5-Methyl-2-(4-(trifluoromethyl)phenyl)oxazol-4-yl)ethanol (**6g**)

The title compound was prepared as a white solid from 4-methoxy-4-oxo-2-(4-(trifluoromethyl)benzamido)butanoic acid according to the procedure described for 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)ethanol (**6d**). ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.74 (t, $J = 5.50$ Hz, 2H), 3.94 (t, $J = 5.50$ Hz, 2H), 7.56 (m, 1H), 7.65 (d, $J = 7.51$ Hz, 1H), 8.15 (d, $J = J = 7.51$ Hz, 1H), 8.23 (s, 1H).

5.4. 2-(2-(4-Fluorophenyl)-5-methyloxazol-4-yl)ethanol (**6h**)

The title compound was prepared as a white solid from 2-(4-fluorobenzamido)-4-methoxy-4-oxobutanoic acid according to the procedure described for 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)ethanol (**6d**). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.74 (t, $J = 5.50$ Hz, 2H), 3.86 (t, $J = 5.50$ Hz, 2H), 7.44 (m, 2H), 8.29 (m, 2H).

5.5. 2-(2-(3-Fluorophenyl)-5-methyloxazol-4-yl)ethanol (**6i**)

The title compound was prepared as a white solid from 2-(3-fluorobenzamido)-4-methoxy-4-oxobutanoic acid according to the procedure described for 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)ethanol (**6d**). ^{1}H NMR ($CDCl_3$): δ 2.35 (s,

3H), 2.74 (t, $J = 5.50$ Hz, 2H), 3.86 (t, $J = 5.50$ Hz, 2H), 6.93 (m, 1H), 7.19 (m, 1H), 7.25 (m, 1H), 7.30 (m, 1H).

5.6. 2-(5-Methyl-2-(3-nitrophenyl)oxazol-4-yl)ethanol (6j)

The title compound was prepared as a white solid from 2-(4-fluorobenzamido)-4-methoxy-4-oxobutanoic acid according to the procedure described for 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)ethanol (**6d**). ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.74 (t, $J = 5.50$ Hz, 2H), 3.86 (t, $J = 5.50$ Hz, 2H), 6.93 (m, 1H), 7.19 (m, 1H), 7.25 (m, 1H), 7.30 (m, 1H).

5.7. Methyl 7-(2-(2-(biphenyl-4-yl)-5-methyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (7a)

Diethyl azodicarboxylate (0.50 ml, 3.20 mmol) was added dropwise into a cold (0 °C) solution of 2-(2-(biphenyl-4-yl)-5-methyloxazol-4-yl)ethanol (**6a**) (0.90 g, 3.20 mmol), triphenylphosphine(0.84 g, 3.20 mmol), and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate (0.70 g, 3.20 mmol) in anhydrous THF (50 ml). The reaction temperature was allowed to come to room temperature, and the mixture was stirred for 12 h. Solvent was evaporated in vacuo. The residue was crystallized in methanol to give the title compound **7a** 0.80 g (51.6%) as a white solid. Mp 159–160 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.04 (t, $J = 6.30$ Hz, 2H), 3.94 (s, 3H), 4.36 (t, $J = 6.30$ Hz, 2H), 6.88 (m, 2H), 7.37 (m, 5H), 7.60 (m, 4H), 8.04 (dd, $J = 8.41$ Hz, 1H), 8.54 (s, 1H). MS (EI) *m/z* 481 $[M]^+$. Anal. Calcd for $C_{29}H_{23}NO_6$: C, 72.34; H, 4.81; N, 2.91. Found: C, 72.23; H, 4.92; N, 2.88.

5.8. Methyl 7-(2-(2-(biphenyl-4-yl)-5-methyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (8a)

A solution of compound **7a** (0.07 g, 0.14 mmol) in a mixture of methanol (5 ml) and dioxane (15 ml) was stirred in the presence of 10% Pd–C (10 mg) under 5 atm of hydrogen at room temperature until hydrogen uptake ceased. The solution was filtered and the filtrate was evaporated under vacuum. The residue was crystallized in methanol to give the title compound **8a** 0.06 g (85.4%) as a white solid. Mp 122–123 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.03 (t, $J = 6.30$ Hz, 2H), 3.29 (dd, $J = 15.80$ Hz, $J = 6.05$ Hz, 1H), 3.54 (dd, $J = 15.80$ Hz, $J = 8.66$ Hz, 1H), 3.93 (m, 4H), 4.35 (t, $J = 6.30$ Hz, 2H), 6.86 (m, 2H), 7.02 (d, $J = 8.65$ Hz, 1H), 7.37 (m, 5H), 7.59 (m, 4H). MS (EI) *m/z* 483 $[M]^+$. Anal. Calcd for $C_{29}H_{25}NO_6$: C, 72.04; H, 5.21; N, 2.90. Found: C, 72.13; H, 5.12; N, 2.82.

5.9. Methyl 7-(2-(2-(4-methoxyphenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (7b)

The title compound was prepared according to the procedure described for compound **7a** from 2-(2-(4-methoxyphenyl)-5-methyloxazol-4-yl)ethanol (**6b**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid. Yield 54.5%. Mp 161–162 °C. ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H), 3.01 (t, $J = 6.74$ Hz, 2H), 3.85 (s, 3H), 3.93 (s, 3H), 4.34 (t, $J = 6.74$ Hz, 3H), 6.83 (d, $J = 2.25$ Hz, 1H), 6.88 (dd, $J = 8.60$ Hz, $J = 2.34$ Hz, 1H), 6.94 (m, 2H), 7.48 (d, $J = 8.69$ Hz, 1H), 7.91 (dd, $J = 6.84$ Hz, $J = 2.15$ Hz, 2H), 8.53 (s, 1H). MS (EI) *m/z* 435 $[M]^+$. Anal. Calcd for $C_{24}H_{21}NO_7$: C, 66.20; H, 4.86; N, 3.22. Found: C, 66.25; H, 4.77; N, 3.32.

5.10. Methyl 7-(2-(2-(4-methoxyphenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (8b)

The title compound was prepared according to the procedure described for compound **8a** from compound **7b** as a white solid. Yield 92.4%. Mp 132–133 °C. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.95 (t, $J = 6.72$ Hz, 2H), 3.09 (dd, $J = 15.61$ Hz, $J = 5.87$ Hz, 1H), 3.36 (dd, $J = 15.61$ Hz, $J = 8.56$ Hz, 1H), 3.74 (m, 4H), 3.85 (s, 3H), 4.21 (t, $J = 6.72$ Hz, 2H), 6.63 (d, $J = 2.52$ Hz, 1H), 6.67 (dd, $J = 8.39$ Hz, $J = 2.52$ Hz, 1H), 6.94 (m, 2H), 7.07 (d, $J = 8.23$ Hz, 1H), 7.91 (m, 2H). MS (EI) *m/z* 437 $[M]^+$. Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20. Found: C, 66.02; H, 5.25; N, 3.25.

5.11. Methyl 7-(2-(2-(3-methoxyphenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (7c)

The title compound was prepared in 70.0% yield from 2-(2-(3-methoxyphenyl)-5-methyloxazol-4-yl)ethanol (**6c**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **7a**. Mp 142–143 °C. ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H), 3.02 (t, $J = 6.60$ Hz, 2H), 3.89 (s, 3H), 3.93 (s, 3H), 4.34 (t, $J = 6.60$ Hz, 2H), 6.84 (d, $J = 2.33$ Hz, 1H), 6.88 (dd, $J = 8.65$ Hz, $J = 2.47$ Hz, 1H), 6.96 (m, 1H), 7.34 (t, $J = 8.11$ Hz, 1H), 7.48 (s, 1H), 7.50 (d, $J = 2.74$ Hz, 1H), 7.56 (m, 1H), 8.53 (s, 1H). MS (EI) *m/z* 435 $[M]^+$. Anal. Calcd for $C_{24}H_{21}NO_7$: C, 66.20; H, 4.86; N, 3.22. Found: C, 65.97; H, 4.99; N, 3.19.

5.12. Methyl 7-(2-(2-(3-methoxyphenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (8c)

The title compound was prepared in 92.4% yield from compound **7c** as a white solid according to the procedure described for **8a**. Mp 88–89 °C. ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.97 (t, $J = 6.46$ Hz, 2H), 3.09 (dd, $J = 15.79$ Hz, $J = 6.04$ Hz, 1H), 3.34 (dd, $J = 15.79$ Hz, $J = 8.20$ Hz, 1H), 3.74 (m, 4H), 3.87 (s, 3H), 4.22 (t, $J = 6.46$ Hz, 2H), 6.63 (d, $J = 2.34$ Hz, 1H), 6.67 (dd, $J = 8.37$ Hz, $J = 2.47$ Hz, 1H), 6.96 (dd, $J = 7.96$ Hz, $J = 2.06$ Hz, 1H), 7.08 (d, $J = 8.53$ Hz, 1H), 7.33 (m, 1H), 7.50 (s, 1H), 7.57 (d, $J = 7.70$ Hz, 1H). MS (EI) *m/z* 437 $[M]^+$. Anal. Calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20. Found: C, 65.63; H, 5.31; N, 3.14.

*5.13. Methyl 7-(2-(2-(4-tert-butylphenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (**7d**)*

The title compound was prepared in 61.6% yield from 2-(2-(4-*tert*-butylphenyl)-5-methyloxazol-4-yl)ethanol (**6d**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **7a**. Mp 168–169 °C. ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 9H), 2.38 (s, 3H), 3.02 (t, $J = 6.88$ Hz, 2H), 3.93 (s, 3H), 4.34 (t, $J = 6.88$ Hz, 2H), 6.83 (d, $J = 2.18$ Hz, 2H), 6.88 (m, 3H), 7.90 (d, $J = 8.38$ Hz, 2H), 8.53 (s, 1H). MS (EI) *m/z* 461 $[M]^+$. Anal. Calcd for $C_{27}H_{27}NO_6$: C, 70.21; H, 5.90; N, 3.03. Found: C, 70.21; H, 5.80; N, 3.03.

*5.14. Methyl 7-(2-(2-(4-tert-butylphenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (**8d**)*

The title compound was prepared in 81.5% yield from compound **7d** as a white solid according to the procedure described for **8a**. Mp 101–102 °C. ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H), 2.17 (s, 3H), 2.97 (t, $J = 6.74$ Hz, 2H), 3.11 (dd, $J = 15.60$ Hz, $J = 6.70$ Hz, 1H), 3.32 (dd, $J = 15.60$ Hz, $J = 8.59$ Hz, 1H), 3.74 (m, 4H), 4.21 (t, J = 6.74 Hz, 2H), 6.62 (d, $J = J = 2.34$ Hz, 1H), 6.66 (dd, J = 8.38 Hz, $J = 2.48$ Hz, 1H), 7.07 (d, J = 8.25 Hz, 1H), 7.44 (dd, $J = 6.74$ Hz, $J = 2.06$ Hz, 2H), 7.89 (dd, $J = 6.73$ Hz, $J = 1.92$ Hz, 2H). MS (EI) *m/z* 463 $[M]^+$. Anal. Calcd for $C_{27}H_{29}NO_6$: C, 69.96; H, 6.31; N, 3.02. Found: C, 70.00; H, 6.26; N, 3.10.

*5.15. Methyl 7-(2-(5-methyl-2-p-tolyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (**7e**)*

The title compound was prepared in 38.0% yield from 2-(5-methyl-2-*p*-tolyloxazol-4-yl)ethanol (**6e**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **7a**. Mp 166–167 °C. ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 2.39 (s, 3H), 3.02 (t, $J = 6.55$ Hz, 2H), 3.93 (s, 3H), 4.34 (t, $J = 6.55$ Hz, 2H), 6.83 (d, $J = 2.35$ Hz, 1H), 6.88 (dd, $J = 8.73$ Hz, $J = 2.35$ Hz, 1H), 7.24 (d, $J = 8.39$ Hz, 2H), 7.48 (d, $J = 9.06$ Hz, 1H), 7.86 (d, $J = 8.39$ Hz, 2H), 8.53 (s, 1H). MS (EI) *m/z* 419 $[M]^+$. Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.42; H, 4.92; N, 3.30.

*5.16. Methyl 7-(2-(5-methyl-2-p-tolyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (**8e**)*

The title compound was prepared in 87.1% yield from compound **7e** as a white solid according to the procedure described for **8a**. Mp 136–137 °C. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.39 (s, 3H), 2.97 (t, $J = 6.59$ Hz, 2H), 3.09 (dd, $J = 15.90$ Hz, $J = 6.04$ Hz, 1H), 3.34 (dd, $J = 15.90$ Hz, $J = 8.65$ Hz, 1H), 3.73 (m, 4H), 4.21 (t, $J = 6.59$ Hz, 2H), 6.63 (d, $J = 2.33$ Hz, 1H), 6.67 (dd, $J = 8.24$ Hz, $J = 2.47$ Hz, 1H), 7.07 (d, $J = 8.38$ Hz, 1H), 7.23 (d, $J = 7.97$ Hz, 2H), 7.86 (d, $J = 8.24$ Hz, 2H). MS (EI) *m/z* 421 $[M]^+$. Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.32. Found: C, 68.33; H, 5.32; N, 3.17.

*5.17. Methyl 7-(2-(5-methyl-2-m-tolyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (**7f**)*

The title compound was prepared in 58.3% yield from 2-(5-methyl-2-*m*-tolyloxazol-4-yl)ethanol (**6f**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **7a**. Mp 134–134.5 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 2.38 (s, 3H), 3.02 (t, $J = 6.59$ Hz, 2H), 3.93 (s, 3H), 4.34 (t, $J = 6.59$ Hz, 2H), 6.83 (d, $J = 2.33$ Hz, 1H), 6.88 (dd, $J = 8.66$ Hz, $J = 2.34$ Hz, 1H), 7.22 (d, $J = 7.70$ Hz, 1H), 7.32 (t, $J = 7.69$ Hz, 1H), 7.48 (d, $J = 8.79$ Hz, 1H), 7.76 (d, $J = 7.69$ Hz, 1H), 7.81 (s, 1H), 8.53 (s, 1H). MS (EI) *m/z* 419 $[M]^+$. Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.61; H, 4.89; N, 3.34.

*5.18. Methyl 7-(2-(5-methyl-2-m-tolyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (**8f**)*

The title compound was prepared in 94.5% yield from compound **2f** as a white solid according to the procedure described for **8a**. Mp 129–130 °C. ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H), 2.40 (s, 3H), 2.97 (t, $J = 6.60$ Hz, 2H), 3.09 (dd, $J = 15.80$ Hz, $J = 6.05$ Hz, 1H), 3.34 (dd, $J = 15.80$ Hz, $J = 8.66$ Hz, 1H), 3.74 (m, 4H), 4.21 (t, $J = 6.60$ Hz, 2H), 6.23 (d, $J = 2.34$ Hz, 1H), 6.67 (dd, $J = 8.24$ Hz, $J = 2.47$ Hz, 1H), 7.08 (d, $J = 8.24$ Hz, 1H), 7.22 (d, $J = 7.55$ Hz, 1H), 7.32 (m, 1H), 7.77 (d, $J = 7.69$ Hz, 1H), 7.82 (s, 1H). MS (EI) *m/z* 421 $[M]^+$. Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.32. Found: C, 68.48; H, 5.42; N, 3.52.

*5.19. Methyl 7-(2-(5-methyl-2-(3-(trifluoromethyl)phenyl)oxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (**7g**)*

The title compound was prepared in 63.8% yield from 2-(5-methyl-2-(3-(trifluoromethyl)phenyl)-oxazol-4-yl)ethanol (**6g**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **7a**. Mp 187–188 °C. ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H), 3.04 (t, $J = 6.19$ Hz, 2H), 3.93 (s, 3H), 4.34 (t, $J = 6.19$ Hz, 2H), 6.83 (d, $J = 2.06$ Hz, 1H), 6.89 (dd, $J = 8.80$ Hz, $J = 2.62$ Hz, 1H), 7.50 (d, $J = 8.80$ Hz, 1H), 7.57 (t, $J = 7.98$ Hz, 1H), 7.66 (d, $J = 7.15$ Hz, 1H), 8.16 (d, $J = 8.12$ Hz, 1H), 8.24 (s, 1H), 8.54 (s, 1H). MS (EI) *m/z* 473 $[M]^+$. Anal. Calcd for $C_{24}H_{18}F_3NO_6$: C, 60.89; H, 3.83; N, 2.96. Found: C, 60.67; H, 3.85; N, 2.74.

*5.20. Methyl 7-(2-(5-methyl-2-(3-(trifluoromethyl)phenyl)oxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (**8g**)*

The title compound was prepared in 85.0% yield from compound **7g** as a white solid according to the procedure

described for **8a**. Mp 118–119 °C. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 2.98 (t, $J = 6.74$ Hz, 2H), 3.10 (dd, $J = 15.81$ Hz, $J = 5.91$ Hz, 1H), 3.34 (dd, $J = 15.81$ Hz, $J = 8.66$ Hz, 1H), 3.75 (m, 4H), 4.22 (t, $J = 6.74$ Hz, 2H), 6.63 (d, $J = 2.47$ Hz, 1H), 6.67 (dd, $J = 8.24$ Hz, $J = 2.33$ Hz, 1H), 7.08 (d, $J = 8.52$ Hz, 1H), 7.57 (d, $J = 7.69$ Hz, 1H), 7.66 (d, $J = 7.84$ Hz, 1H), 8.16 (d, $J = 7.84$ Hz, 1H), 8.24 (s, 1H). MS (EI) *m/z* 437 $[M]^+$. Anal. Calcd for $C_{24}H_{20}F_3NO_6$: C, 60.63; H, 4.24; N, 2.95. Found: C, 60.36; H, 4.35; N, 2.68.

5.21. Methyl 7-(2-(2-(4-fluorophenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (**7h**)

The title compound was prepared in 74.7% yield from 2-(2-(4-fluorophenyl)-5-methyloxazol-4-yl)ethanol (**6h**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **7a**. Mp 168–169 °C. ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.02 (t, $J = 6.74$ Hz, 2H), 3.93 (s, 3H), 4.34 (t, $J = 6.74$ Hz, 2H), 6.83 (d, $J = 2.33$ Hz, 1H), 6.88 (dd, $J = 8.66$ Hz, $J = 2.48$ Hz, 1H), 7.11 (m, 2H), 7.49 (d, $J = 8.67$ Hz, 1H), 7.96 (m, 2H), 8.53 (s, 1H). MS (EI) *m/z* 423 $[M]^+$. Anal. Calcd for $C_{23}H_{18}FNO_6$: C, 65.25; H, 4.29; N, 3.31. Found: C, 65.27; H, 4.17; N, 3.09.

5.22. Methyl 7-(2-(2-(4-fluorophenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (**8h**)

The title compound was prepared in 89.9% yield from compound **7h** as a white solid according to the procedure described for **8a**. Mp 149–150 °C. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.96 (t, $J = 6.59$ Hz, 2H), 3.09 (dd, $J = 15.93$ Hz, $J = 6.05$ Hz, 1H), 2.34 (dd, $J = 15.93$ Hz, $J = 8.52$ Hz, 1H), 3.74 (m, 4H), 4.21 (t, $J = 6.59$ Hz, 2H), 6.62 (d, $J = 2.48$ Hz, 1H), 6.67 (dd, $J = 8.52$ Hz, $J = 2.61$ Hz, 1H), 7.10 (m, 3H), 7.96 (m, 2H). MS (EI) *m/z* 425 $[M]^+$. Anal. Calcd for $C_{23}H_{20}FNO_6$: C, 64.94; H, 4.74; N, 3.29. Found: C, 65.08; H, 4.71; N, 3.10.

5.23. Methyl 7-(2-(2-(3-fluorophenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (**7i**)

The title compound was prepared in 78.4% yield from 2-(2-(3-fluorophenyl)-5-methyloxazol-4-yl)ethanol (**6i**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **7a**. Mp 179–180 °C. ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H), 3.02 (t, $J = 6.33$ Hz, 2H), 3.93 (s, 3H), 4.34 (t, $J = 6.33$ Hz, 2H), 6.83 (d, $J = 2.20$ Hz, 1H), 6.88 (dd, $J = 8.66$ Hz, $J = 2.34$ Hz, 1H), 7.11 (m, 1H), 7.39 (m, 1H), 7.49 (d, $J = 8.66$ Hz, 1H), 7.67 (m, 1H), 7.77 (d, $J = 7.70$ Hz, 1H), 8.53 (s, 1H). MS (EI) *m/z* 423 $[M]^+$. Anal. Calcd for $C_{23}H_{18}FNO_6$: C, 65.25; H, 4.29; N, 3.31. Found: C, 65.28; H, 4.28; N, 3.20.

5.24. Methyl 7-(2-(2-(3-fluorophenyl)-5-methyloxazol-4-yl)ethoxy)-2-oxochroman-3-carboxylate (**8i**)

The title compound was prepared in 90.2% yield from compound **7i** as a white solid according to the procedure described for **8a**. Mp 124–125 °C. ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H), 2.97 (t, $J = 5.87$ Hz, 2H), 3.10 (dd, $J = 15.65$ Hz, $J = 8.41$ Hz, 1H), 3.34 (dd, $J = 15.65$ Hz, $J = 8.41$ Hz, 1H), 3.74 (m, 4H), 4.22 (t, $J = 5.87$ Hz, 2H), 6.63 (d, $J = 2.15$ Hz, 1H), 7.10 (m, 2H), 7.40 (dd, $J = 13.89$ Hz, $J = 7.83$ Hz, 1H), 7.67 (d, $J = 9.59$ Hz, 1H), 7.77 (d, $J = 7.63$ Hz, 1H). MS (EI) *m/z* 425 $[M]^+$. Anal. Calcd for $C_{23}H_{20}FNO_6$: C, 64.94; H, 4.74; N, 3.29. Found: C, 64.77; H, 4.74; N, 3.17.

5.25. Methyl 7-(2-(5-methyl-2-(3-nitrophenyl)oxazol-4-yl)ethoxy)-2-oxo-2H-chromene-3-carboxylate (**7j**)

The title compound was prepared in 57.1% yield from 2-(5-methyl-2-(3-nitrophenyl)oxazol-4-yl)ethanol (**6j**) and methyl 7-hydroxy-2-oxo-2*H*-chromene-3-carboxylate as a white solid according to the procedure described for **2a**. Mp 189–190 °C. ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 3H), 3.04 (t, $J = 6.45$ Hz, 2H), 3.93 (s, 3H), 4.36 (t, $J = 6.45$ Hz, 2H), 6.83 (d, $J = 2.19$ Hz, 1H), 6.88 (dd, $J = 8.66$ Hz, $J = 2.48$ Hz, 1H), 7.49 (d, $J = 8.65$ Hz, 1H), 7.63 (t, $J = 8.10$ Hz, 1H), 8.28 (m, 2H), 8.53 (s, 1H), 8.80 (t, $J = 1.93$ Hz, 1H). MS (EI) *m/z* 450 $[M]^+$. Anal. Calcd for $C_{23}H_{18}N_2O_8$: C, 61.33; H, 4.03; N, 6.22. Found: C, 61.51; H, 4.03; N, 6.11.

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