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Research paper

New, highly potent and non-toxic, chromone inhibitors of the human breast cancer resistance protein ABCG2

Amanda do Rocio Andrade Pires [a, 1], Florine Lecerf-Schmidt [b, 1], Nathalie Guragossian [a], Jaqueline Pazinato [a], Gustavo Jabor Gozzi [a], Evelyn Winter [a], Glaucio Valdameri [a], Alexander Veale [b], Ahcène Boumendjel [b], Attilio Di Pietro [a, 2], Basile Pérès [b, *, 2]

[a] Equipe Labellisée Ligue 2014 "Mécanisme et Modulation de la Résistance aux Médicaments", Université Lyon 1, Univ. Lyon, CNRS UMR 5086 Bases Moléculaires et Structurales des Systèmes Infectieux, IBCP, 7 Passage du Vercors, 69367 Lyon Cedex 07, France
[b] Université Grenoble-Alpes/CNRS, Département de Pharmacochimie Moléculaire UMR 5063, F-38041 Grenoble, France

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ABSTRACT

Breast cancer resistance protein (BCRP/ABCG2) is one of the major transporters involved in the efflux of anticancer compounds, contributing to multidrug resistance (MDR). Inhibition of ABCG2-mediated transport is then considered a promising strategy for overcoming MDR in tumors. We recently identified a chromone derivative, namely MBL-II-141 as a selective ABCG2 inhibitor, with relevant *in vivo* activity. Here, we report the pharmacomodulation of MBL-II-141, with the aim of identifying key pharmacophoric elements to design more potent selective and non-toxic inhibitors. Through rational structural modifications of MBL-II-141, using simple and affordable chemistry, we obtained highly active and easily-made inhibitors of ABCG2. Among the investigated compounds, derivative **4a**, was found to be 3-fold more potent than MBL-II-141. It was similarly efficient as the reference inhibitor Ko143 but with the advantage of a lower intrinsic cytotoxicity, and therefore constitutes the best ABCG2 inhibitor ever reported displaying a very high therapeutic ratio.

1. Introduction

ATP-Binding Cassette (ABC) transporters belong to one of the largest membrane protein superfamily expressed in both prokaryotic and eukaryotic cells. Acting as ATP-powered pumps, ABC transporters are able to extrude a wide variety of structurally-unrelated compounds from the cells. As expressed in major physiological barriers, ABC transporters are crucial for cell detoxification and survival, by effluxing exogenous toxic substances outside the cell. Their overexpression in tumor cells contributes to chemoresistance through the efflux of anticancer drugs. P-glycoprotein (Pgp/ABCB1) [1], multidrug resistance protein 1 (MRP1/ABCC1) [2] and breast cancer resistance protein (BCRP/ABCG2) [3–5] are so far the three major ABC proteins recognized to strongly contribute to the multidrug resistance developed by cancer cells against cytotoxic drugs. ABCG2 is the most recently ABC transporter identified to be involved in cross-resistance to a wide panel of structurally-unrelated anticancer drugs and other compounds. As opposed to Pgp and MRP1, ABCG2 is a half-transporter which requires at least dimerization [6], or even tetramerization [7,8], to be functional. Since its discovery, ABCG2 has attracted intense interest in the MDR context, particularly as a target for the development of new inhibitors to be used in combination with conventional anticancer drugs for restoring their efficacy. In the absence of high-resolution structural information regarding ABCG2, the design of new inhibitors is exclusively based on ligand-based drug design [9,10].

Fumitremorgin C (FTC) [11] was the first selective inhibitor reported for ABCG2. Unfortunately, it was found to be clinically unusable due to its high neurotoxicity. Targeting powerful, selective and less toxic inhibitors has led to the design and development of FTC synthetic analogues. In this regard, Ko143 was considered as a reference ABCG2 inhibitor on the basis of its high potency [12,13]; however, its selectivity for ABCG2 *versus* ABCB1 (P-gp) was recently challenged [14]. Despite the number of known ABCG2 inhibitors [15–22], only very few of them were evaluated *in vivo*, in animal-

* Corresponding author.
E-mail address: Basile.Peres@univ-grenoble-alpes.fr (B. Pérès).
[1] First co-authors.
[2] Last co-authors.

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based models to assess the restoration of antitumor activity of conventional anticancer drugs. Pursuing our efforts to develop effective modulators of ABC proteins, we recently reported that a chromone-derived compound, namely MBL-II-141 (Fig. 1) was an excellent *in vivo* ABCG2 inhibitor, based on its potency, high selectivity, lack of transport and very low toxicity [19,22].

With the aim to establish structure-activity relationships governing MBL-II-141 inhibition and obtain more potent ABCG2 inhibitors, we targeted its pharmacomodulation (Fig. 1). We especially investigated: a) the nature and position of the halogen present within the benzyloxy group (series I), b) the influence of the methoxy group on the indole ring (series II), and c) the variation of the linker between the chromone and indole moieties through the insertion of an amino acid residue (series III).

2. Chemistry

The synthesis of series I compounds is shown in Scheme 1. The chromone moiety was prepared according to our previously described process, starting from 2,6-dihydroxyacetophenone and the corresponding benzylbromide derivatives [19,23]. **3a**–**g** acids were stepped into a peptide coupling reaction with 5-methoxytryptamine, using 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide (EDCI) and hydroxybenzotriazole (HOBt) as coupling agent, in the presence of triethylamine to give target analogues **4a**–**g** with 5–50% yields [24].

The synthesis of series II compounds (**5a**–**e**) is shown in Scheme 2. Starting from previously described derivative **3g**, a peptide coupling reaction was performed with either serotonin or tryptamine to provide **5a** and **5e**, respectively. Finally, compound **5a** was alkylated with different alkyl iodide in refluxing acetone to afford compounds **5b**–**d** with a 17–31% yield.

The synthetic pathway for compounds **8a**–**c** (series III) is shown in Scheme 3. Starting from **3g**, a classical peptide-coupling reaction was performed with the corresponding protected amino acid to give derivatives **6a**–**d**. This time, the peptide-coupling reaction was performed in DMF with *O*-(Benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate (TBTU) in the presence of *N,N*-diisopropylethylamine (DIEA). The mild hydrolysis of the ester function was performed with lithium hydroxide at room temperature in a mixture of water/ethanol/tetrahydrofuran to afford carboxylic acids **7a**–**c** which were engaged in a classic peptide coupling reaction (TBTU, DIEA) with 5-methoxytryptamine to give the desired final compounds **8a**–**c** with a 7–29% yield.

3. Results and discussion

The newly synthesized compounds were evaluated for their ability to inhibit the efflux of mitoxantrone (an anticancer drug and substrate of ABCG2) in *ABCG2*-transfected HEK293 cells and for their cytotoxicity (Table 1). The inhibition results underline that compound **4a,** bearing a 2-bromine atom on the benzyloxy moiety, was 3-fold more potent than **MBL-II-141** where the bromine atom is at C-4 position (EC_{50} = 0.086 μM *versus* 0.26 μM), reaching the same potency as **Ko143** (0.074 μM). In contrast, bromine shift to the C-3 position in **4b** was detrimental to inhibition (0.54 μM). Interestingly, substitution of the bromine by fluorine induced different types of effects (**4c-f** compounds). There was no effect at C-4 position as compared to **MBL-II-141**, whereas negative effects were observed at all other positions including C-2 as compared to **4a**. Such an influence of halogen nature and position may indicate potential Hammet contribution at the benzyl group. This is consistent with previous observations that replacement of the **MBL-II-141** bromine with a methoxy group or its omission led to less active derivatives [19].

The modulation performed with **5a**–**e** derivatives (Series II) showed the beneficial presence of a hydrophobic 5-alkoxy group on the indole ring of chromones **5b**–**d**. Indeed, the dealkylation or the suppression of the alkyloxy group led to a sharp decrease of activity in **5a** (4.35 μM) and **5e** (1.05 μM) as compared to **MBL-II-141**. This is consistent with previous observation that a methoxy group was important at either position C-5 or C-6 [22].

Series III was targeted to explore if the presence of an amino acid residue might impact the inhibitory activity. This pharmacomodulation was inspired from the chemical structures of FTC and Ko143, considered as reference inhibitors of ABCG2, in which the presence of an isobutyl moiety was found to be important for inhibition. A shown in Table 1, we noticed a slight decrease in potency for the **8b** derivative bearing a leucine residue, while a valine residue in **8a** had no effect. Finally, mono methylation at one of the

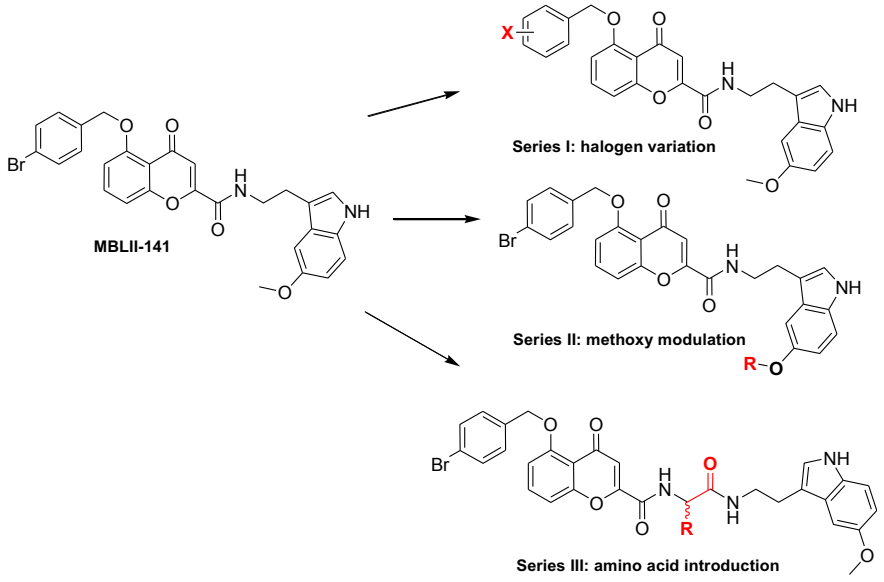
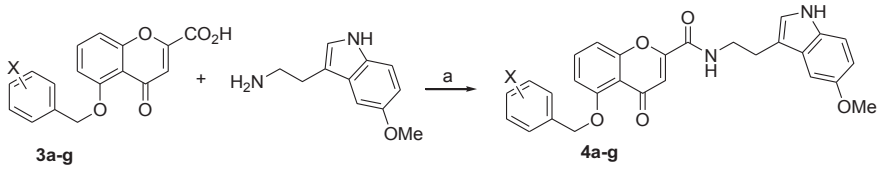
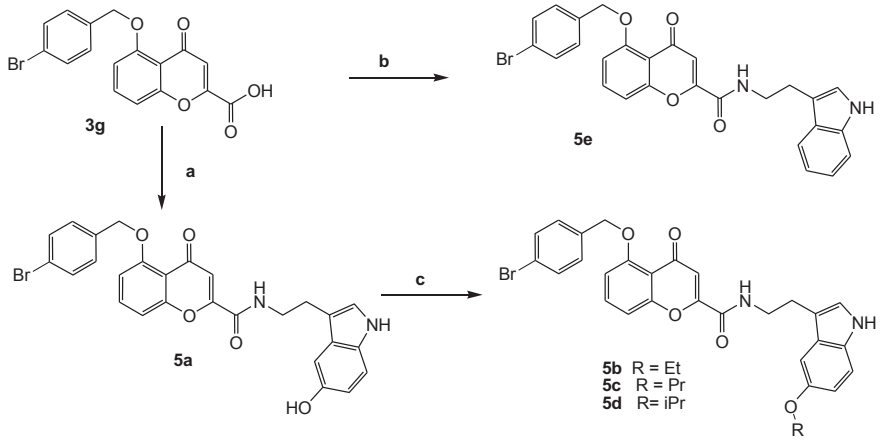


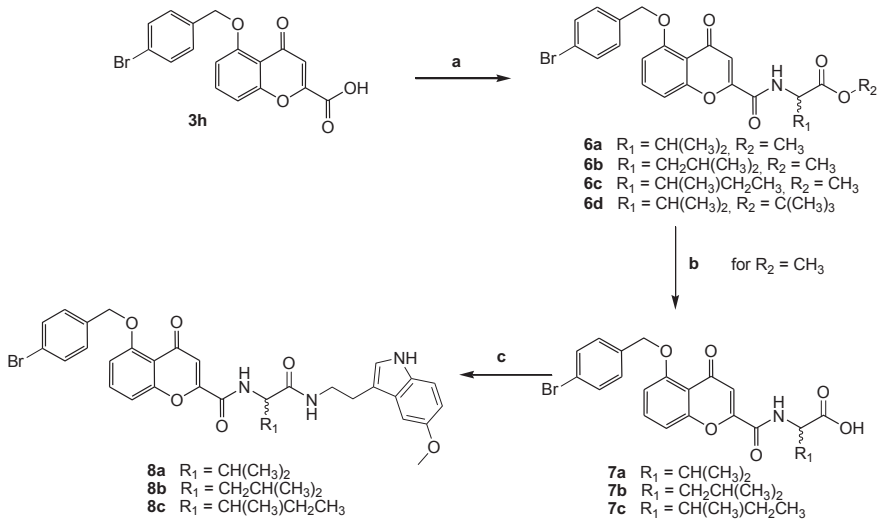
Fig. 1. Structure of MBL-II-141 and different types of modulations.



Scheme 1. Reagents and conditions: **(a)** K_2CO_3, $Bu_4N^+Br^-$, acetone, reflux; **(b)** (i) EtO^-Na^+, Ethyl oxalate, THF-EtOH, reflux, (ii) HCl 37%, THF-EtOH, reflux; **(c)** $NaHCO_3$, EtOH-THF-H_2O, reflux; **(d)** EDCI, HOBt, Et_3N, DMF, rt, overnight.



Scheme 2. Reagents and conditions: **(a)** 5-hydroxytryptamine, EDCI, HOBt, ET_3N, DMF, rt, overnight; **(b)** tryptamine, EDCI, HOBt, ET_3N, DMF, rt, overnight; **(c)** corresponding alkyl iodide, K_2CO_3, $Bu_4N^+Br^-$, acetone, reflux (4–5 h).

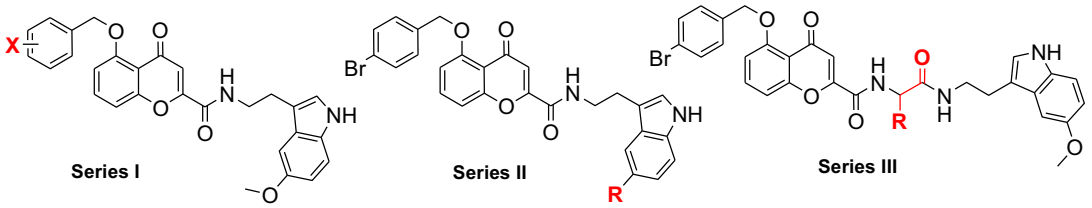


Scheme 3. Reagents and conditions: **(a)** corresponding protect racemic amino acid, TBTU, DIEA, DMF, rt, overnight; **(b)** LiOH, THF-MeOH-H_2O, rt, 1 h; **(c)** 5-methoxytryptamine, TBTU, DIEA, DMF, rt, overnight.

two nitrogen atoms or dimethylation of MBL-II-141 altered the inhibitory activity (results not shown here, in agreement with previous observations on other derivatives [22]).

Cell cytotoxicity assays were performed on control, untransfected, HEK293 cells. As shown in Table 1, **4a** displayed a very low cytotoxicity (IG_{50} > 100 μM), similarly to **MBL-II-141**, leading to a very high TR value (>1163). It is worth mentioning that **Ko143** was significantly more toxic (IG_{50} = 60.2 μM), then resulting in a lower TR value. This makes the new chromone derivative **4a** the most potent and promising ABCG2 inhibitor reported to date. Whereas a bromine substituent at either position C-2 (**4a**), C-3 (**4b**) or C-4 (**MBL-II-141**) did not induce cytotoxicity, the presence of two fluorines in **4f** was quite detrimental (IG_{50} = 10.2 μM and TR = 16). Similarly, the introduction of a valine residue (**8a**) within the linker chain markedly increased cytotoxicity (IG_{50} = 7.6 μM) giving low TR value (TR = 22). Such increased cytotoxicity might be related to additional interaction of the chromone derivative with unknown cellular target(s) important for cell survival. When ABCG2-transfected HEK293 cells were used (not shown here), the same cytotoxicity values as in control cells were observed for all compounds, suggesting that none of these chromone derivatives was transported by ABCG2. This confirms the lack of transport

Table 1
Inhibition of mitoxantrone efflux, and cytotoxicity.



Compound	EC_{50} (μM)[b]	(%) Maximal inhibition at 10 μM[a]	IG_{50} for cytotoxicity (μM)[c]	Therapeutic ratio (TR)[d]
Series I				
4a X = 2-Br	0.086 ± 0.02	102 ± 8	>100	>1163
4b X = 3-Br	0.54 ± 0.05	98 ± 8	>100	>185
4c X = 2-F	0.55 ± 0.01	131 ± 3	94 ± 1	171
4d X = 3-F	0.38 ± 0.06	107 ± 3	>100	>263
4e X = 4-F	0.26 ± 0.06	106 ± 4	>100	>385
4f X = 3,4-difluoro	0.63 ± 0.02	140 ± 3	10.2 ± 0.4	16
Series II				
5a R = OH	4.35 ± 0.47	104 ± 7	61.2 ± 7.6	14
5b R = OC_2H_5	0.36 ± 0.02	ND	>80	>222
5c R = OC_3H_7	0.28 ± 0.04	ND	>60	>214
5d R = $OCH(CH_3)_2$	0.36 ± 0.2	ND	>100	>278
5e R = H	1.05 ± 0.2	97 ± 10	>100	>95
Series III				
8a R = $CH(CH_3)_2$	0.34 ± 0.02	101 ± 7	7.6 ± 0.2	22
8b R = $CH_2CH(CH_3)_2$	0.91 ± 0.06	105 ± 9	>100	>110
Reference inhibitors				
Ko143	0.074 ± 0.01	99 ± 5[e]	60.2 ± 1	814
MBL-II-141 (4g)	0.26 ± 0.02	133 ± 11[f]	>100	>385

[a] The percent inhibition of ABCG2 transport activity was studied by comparison with the reference inhibitor Ko143, which fully inhibited; the maximal inhibition for each derivative was measured at 10 μM.
[b] The affinity of inhibitor interaction was expressed as EC_{50} values (compound concentrations giving a half-maximal inhibition).
[c] The cytotoxicity of inhibitors was evaluated by IG_{50} (concentration producing 50% inhibition of cell growth) values on control HEK293 cells using the MTT test.
[d] The therapeutic ratio (TR) was calculated as the ratio between IG_{50} and EC_{50} values.
[e] The maximal inhibition with **Ko143** was measured at 1 μM.
[f] The maximal inhibition with **MBL-II-141** was measured at 5 μM.

previously reported for MBL-II-141 [19] and other derivatives [22].

4. Conclusion

The new chromone derivative **4a**, with a 2-bromine atom on the benzyloxy group appears a quite promising compound since it is: i) 3-fold more potent that **MBL-II-141**, ii) better than the reference **Ko143** inhibitor based on its a remarkably low cytotoxicity, and iii) available through an easy synthesis process [25]. It therefore constitutes the best, non-transported, ABCG2 inhibitor ever reported. Although introduction of amino acids residues into the structure did not provide more active modulators, it indicated that further efforts could be spent, for example by investigating other amino acids residues, and introducing D-amino acids, or even dipeptides, in the structure.

5. Experimental section

5.1. Chemistry

NMR spectra were recorded on a 400 MHz Bruker Avance-400 instrument (400 MHz). Chemical shifts (δ) are reported in ppm relatively to Me_4Si used as an internal standard. Electrospray ionization (ESI) mass spectra were acquired by the Analytical Department of Grenoble University on an Esquire 300 Plus Bruker Daltonis instrument with a nanospray inlet. Combustion analyses were performed in the same Analytical Department, and all the tested compounds had a purity of at least 95%. Thin-layer chromatography (TLC) used Merck silica gel F-254 plates (thickness 0.25 mm), and flash chromatography used Merck silica gel 60, 0.04–0.063 mesh. Unless otherwise stated, reagents were obtained from commercial sources (Alpha Aesar and Sigma-Aldrich) and were used without further purification.

5.1.1. Synthesis of alkylated compounds *1a–g*

5.1.1.1. General procedure A. A solution of dihydroxyacetophenone (1 equiv.), potassium carbonate (3 equiv.) and tetrabutylammonium bromide (0.35 equiv.) in acetone (7 mL/mmol) was refluxed for 20 min. A solution of halogenated derivative (1.2 equiv.) in acetone (3 mL/mmol) was added dropwise and the resulting mixture was refluxed for 2–6 h (the end of the reaction was controlled by TLC using acetone/cyclohexane 25:75). The resulting solution was cooled to room temperature and concentrated under reduced pressure. The residue was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

*5.1.1.2. 6-(2′-Bromobenzyloxy)-2-hydroxyacetophenone **(1a)**.* The crude was prepared according to general procedure A starting from 2,6-dihydroxyacetophenone (2 g, 13 mmol) and 2-bromobenzylbromide (4 g, 16 mmol) and was purified by flash silica column chromatography, using cyclohexane/ethyl acetate (100:0 to 98:2) as eluent to afford **1a** as a yellow solid (1.5 g, 36%). $C_{15}H_{13}BrO_3$. **m.p.** 68–70 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.45 (s, 3H, $COCH_3$), 5.17 (s, 2H, OCH_2), 6.54 (dd, 1H, J = 0.7 Hz,

J = 8.3 Hz, ArH), 6.64 (m, 1H, ArH), 7.28–7.37 (m, 2H, ArH), 7.44 (m, 1H, ArH), 7.59 (dd, 1H, J = 1.7 Hz, J = 7.6 Hz, ArH), 7.69 (dd, 1H, J = 1.1 Hz, J = 7.9 Hz, ArH), 11.67 (s, 1H, OH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 32.9, 70.0, 103.2, 109.8, 114.7, 123.1, 128.0, 130.4, 130.7, 132.7, 133.9, 135.3, 157.9, 159.6, 203.3. **MS** (ESI) m/z 321 (^{79}Br), 323 (^{81}Br) $[M+H]^+$.

5.1.1.3. 6-(3′-Bromobenzyloxy)-2-hydroxyacetophenone ***(1b)***. The crude was prepared according to general procedure A starting from 2,6-dihydroxyacetophenone (2 g, 13 mmol) and 3-bromobenzylbromide (4 g, 16 mmol) and was washed with diethyl ether to afford **1b** as a beige solid (3 g, 73%). $C_{15}H_{13}BrO_3$. **m.p.** 131–133 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.49 (s, 3H, $COCH_3$), 5.17 (s, 2H, OCH_2), 6.52 (d, 1H, J = 8.2 Hz, ArH), 6.61 (d, 1H, J = 8.3 Hz, ArH), 7.29 (m, 1H, ArH), 7.37 (m, 1H, ArH), 7.46–7.55 (m, 2H, ArH), 7.68 (m, 1H, ArH), 13.58 (s, 1H, OH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 33.0, 69.1, 103.5, 109.7, 115.0, 121.7, 126.7, 130.4, 130.7, 130.8, 133.7, 139.4, 157.8, 159.3, 203.4. **MS** (ESI) m/z 321 (^{79}Br), 323 (^{81}Br) $[M+H]^+$.

5.1.1.4. 6-(2′-Fluorobenzyloxy)-2-hydroxyacetophenone ***(1c)***. The crude was prepared according to general procedure A starting from 2,6-dihydroxyacetophenone (2 g, 13 mmol) and 2-fluorobenzylbromide (3 g, 16 mmol) and was washed with diethyl ether to afford **1c** as a white solid (1.3 g, 39%). $C_{15}H_{13}FO_3$. **m.p.** 106–108 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.43 (s, 3H, $COCH_3$), 5.20 (s, 2H, OCH_2), 6.52 (dd, 1H, J = 0.8 Hz, J = 8.3 Hz, ArH), 6.69 (d, 1H, J = 7.8 Hz, ArH), 7.23–7.29 (m, 2H, ArH), 7.32 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.57 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 32.8, 64.5 (d, $J_{C\text{-}F}$ = 3.7 Hz), 103.3, 109.8, 114.7, 115.5 (d, $J_{C\text{-}F}$ = 21.9 Hz), 123.2 (d, $J_{C\text{-}F}$ = 14.5 Hz), 124.6 (d, $J_{C\text{-}F}$ = 3.5 Hz), 130.6 (d, $J_{C\text{-}F}$ = 8.3 Hz), 130.9 (d, $J_{C\text{-}F}$ = 3.9 Hz), 133.9, 158.0, 159.6, 160.4 (d, $J_{C\text{-}F}$ = 246.4 Hz), 203.4. **MS** (ESI) m/z 283 $[M+Na]^+$.

5.1.1.5. 6-(3′-Fluorobenzyloxy)-2-hydroxyacetophenone ***(1d)***. The crude was prepared according to general procedure A starting from 2,6-dihydroxyacetophenone (2 g, 13 mmol) and 3-fluorobenzylbromide (2.8 g, 15 mmol) and recrystallized with cyclohexane/ethyl acetate (3:1) to afford **1d** as a white solid (1.7 g, 50%). $C_{15}H_{13}FO_3$. **m.p.** 123–124 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.5 (s, 3H, $COCH_3$), 5.18 (s, 2H, OCH_2), 6.52 (d, 1H, J = 8.3 Hz, ArH), 6.62 (d, 1H, J = 7.9 Hz, ArH), 7.17 (m, 1H, ArH), 7.27–7.31 (m, 2H, ArH), 7.42–7.48 (m, 2H, ArH), 11.62 (s, 1H, OH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 33.0, 69.3, 103.4, 109.7, 114.4 (d, $J_{C\text{-}F}$ = 21.9 Hz), 114.6, 114.8 (d, $J_{C\text{-}F}$ = 5.1 Hz), 123.6 (d, $J_{C\text{-}F}$ = 3 Hz), 130.5 (d, $J_{C\text{-}F}$ = 8.3 Hz), 133.7, 139.4 (d, $J_{C\text{-}F}$ = 7.6 Hz), 157.8, 159.4, 162.1 (d, $J_{C\text{-}F}$ = 243.7 Hz), 203.4. **MS** (ESI) m/z 259 $[M-H]^-$.

5.1.1.6. 6-(4′-Fluorobenzyloxy)-2-hydroxyacetophenone ***(1e)***. The crude was prepared according to general procedure A starting from 2,6-dihydroxyacetophenone (2 g, 13 mmol) and 4-fluorobenzylbromide (3 g, 16 mmol) and was washed with diethyl ether to afford **1e** as a beige solid (1.7 g, 50%). $C_{15}H_{13}FO_3$. **m.p.** 137–139 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.47 (s, 3H, $COCH_3$), 5.14 (s, 2H, OCH_2), 6.51 (dd, 1H, J = 0.8 Hz, J = 8.3 Hz, ArH), 6.65 (dd, 1H, J = 0.8 Hz, J = 8.4 Hz, ArH), 7.19–27 (m, 2H), 7.31 (m, 1H), 7.49–7.56 (m, 2H), 11.69 (s, 1H, OH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 33.1, 69.4, 103.4, 109.6, 114.7, 115.3 (d, $J_{C\text{-}F}$ = 21.4 Hz), 130.1 (d, $J_{C\text{-}F}$ = 8.4 Hz), 132.7 (d, $J_{C\text{-}F}$ = 2.9 Hz), 133.9, 158.1, 159.7, 161.8 (d, $J_{C\text{-}F}$ = 243.9 Hz), 203.5. **MS** (ESI) m/z 259 $[M-H]^-$.

5.1.1.7. 6-(3′,4′-Difluorobenzyloxy)-2-hydroxyacetophenone ***(1f)***. The crude was prepared according to general procedure A starting from 2,6-dihydroxyacetophenone (5 g, 33 mmol) and 3,4-difluorobenzylbromide (8.2 g, 40 mmol) and was washed with diethyl ether to afford **1f** as a white solid (2.5 g, 27%). $C_{15}H_{12}F_2O_3$. **m.p.** 127–128 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.48 (s, 3H, $COCH_3$), 5.14 (s, 2H, OCH_2), 6.52 (dd, 1H, J = 0.8 Hz, J = 8.3 Hz, ArH), 6.62 (dd, 1H, J = 0.8 Hz, J = 8.3 Hz, ArH), 7.30 (m, 1H, ArH), 7.34 (m, 1H, ArH), 7.50 (m, 1H, ArH), 7.56 (m, 1H, ArH), 11.62 (s, 1H, OH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 33.0, 68.8, 103.4, 109.7, 114.9, 116.9 (d, $J_{C\text{-}F}$ = 17.5 Hz), 117.5 (d, $J_{C\text{-}F}$ = 17.1 Hz), 124.7 (m) 133.7, 134.3 (m), 147.9 (m), 150.4 (m), 157.8, 159.4, 203.4. **MS** (ESI) m/z 277 $[M-H]^-$.

5.1.1.8. 6-(4′-Bromobenzyloxy)-2-hydroxyacetophenone ***(1g)***. The crude was prepared according to general procedure A starting from commercially available 2,6-dihydroxyacetophenone (2 g, 13 mmol) and 4-bromobenzylbromide (4 g, 16 mmol) and was triturated in diethyl ether to afford **1h** as a white solid (2.8 g, 68%). $C_{15}H_{13}BrO_3$. **m.p.** 116–117 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.48 (s, 3H, $COCH_3$), 5.14 (s, 2H, OCH_2), 6.54 (d, 1H, J = 8.0 Hz, ArH), 6.63 (d, 1H, J = 8.0 Hz, ArH), 7.31 (m, 1H, ArH), 7.44 (d, 2H, J = 8.0 Hz, ArH), 7.61 (d, 2H, J = 8.0 Hz, ArH), 11.69 (s, 1H, OH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 33.0, 69.3, 103.4, 109.7, 114.6, 121.2, 130.0, 131.4, 133.8, 135.9, 158.0, 159.7, 203.4. **MS** (ESI) m/z 321 (^{79}Br), 323 (^{81}Br) $[M+H]^+$.

5.1.2. Synthesis of chromones ***2a–g***

5.1.2.1. General procedure B. To a solution of sodium (6 equiv.) in a mixture of anhydrous THF/EtOH (1/1, 10 mL/mmol) under argon were added alkylated derivative **1a–g** (1 equiv.) and diethyloxalate (4 equiv.) at O°C. The resulting mixture was warmed to room temperature and refluxed for 2–4 h (the end of the reaction was controlled by TLC using acetone/cyclohexane 30:70). The solution was cooled to room temperature and concentrated under reduced pressure. The residue was poured into 1 M hydrochloric acid and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in THF/EtOH (1/1, 10 mL/mmol) and 37% hydrochloric acid (1 mL/mmol) was added dropwise. The resulting mixture was refluxed for 2–4 h (the end of the reaction was controlled by TLC using acetone/cyclohexane 30:70). The solution was cooled to room temperature and concentrated under reduced pressure. The residue was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

5.1.2.2. 5-(2′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid ethyl ester ***(2a)***. The crude was prepared according to general procedure B starting from **1a** (273 mg, 0.8 mmol) and was purified by flash silica column chromatography using cyclohexane/ethyl acetate (9:1 to 8:2) as eluent to afford **2a** as a beige solid (150 mg, 44%). $C_{19}H_{15}BrO_5$. **m.p.** 155–157 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.35 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.39 (q, 2H, J = 7.1 Hz, $CO_2CH_2CH_3$), 5.23 (s, 2H, OCH_2), 6.80 (s, 1H, COCH), 7.15 (d, 1H, J = 8.0 Hz, ArH), 7.25–7.35 (m, 2H, ArH), 7.50 (m, 1H, ArH), 7.67 (dd, 1H, J = 1.1 Hz, J = 7.1 Hz, ArH), 7.79 (m, 1H, ArH), 8.10 (dd, 1H, J = 1.5 Hz, J = 7.7 Hz, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 62.6, 69.8, 108.9, 110.8, 114.7, 115.5, 121.1, 127.9, 129.2, 129.6, 132.2, 135.5, 135.7, 150.3, 157.3, 157.5, 160.0, 176.5. **MS** (ESI) m/z 403 (^{79}Br), 405 (^{81}Br) $[M+H]^+$.

5.1.2.3. 5-(3′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid ethyl ester ***(2b)***. The crude was prepared according to general procedure B starting from **1b** (3 g, 9.4 mmol) and washed with diethyl ether to afford **2b** as a yellow solid (2 g, 50%). $C_{19}H_{15}BrO_5$. **m.p.** 147–149 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.75 (t, 3H, J = 7.2 Hz, $CO_2CH_2CH_3$), 4.80 (q, 2H, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.69 (s, 2H, OCH_2), 7.22 (s, 1H, COCH), 7.12 (d, 1H, J = 8.0 Hz, ArH), 7.25 (d, 1H, J = 8.0 Hz, ArH), 7.38 (m, 1H, ArH), 7.50–7.65 (m, 2H, ArH), 7.77

(m, 1H, ArH), 7.92 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 62.6, 69.0, 109.0, 110.6, 114.7, 115.5, 121.7, 125.6, 129.4, 130.3, 130.5, 135.3, 139.6, 150.2, 157.3, 157.6, 160.0, 176.5. **MS** (ESI) *m/z* 425 (^{79}Br), 427 (^{81}Br) $[M+Na]^+$.

*5.1.2.4. 5-(2′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid ethyl ester **(2c)**.* The crude was prepared according to general procedure B starting from **1c** (900 mg, 3.5 mmol) and was purified by flash silica column chromatography using cyclohexane/ethyl acetate (1:0 to 8:2) as eluent to afford **2c** as a white solid (265 mg, 24%). $C_{19}H_{15}FO_5$. **m.p** 156–157 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.38 (q, 2H, J = 7.1 Hz, $CO_2CH_2CH_3$), 5.29 (s, 2H, OCH_2), 6.76 (s, 1H, COCH), 7.16–7.32 (m, 4H, ArH), 7.42 (m, 1H, ArH), 7.76 (m, 1H, ArH), 7.92 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 62.6, 64.5 (d, $J_{C\text{-}F}$ = 4.2 Hz), 109.1, 110.7, 114.7, 115.0 (d, $J_{C\text{-}F}$ = 20.5 Hz), 115.4, 123.7 (d, $J_{C\text{-}F}$ = 14.1 Hz), 124.5 (d, $J_{C\text{-}F}$ = 3.2 Hz), 129.6 (d, $J_{C\text{-}F}$ = 4.0 Hz), 129.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 135.4, 150.2, 157.3, 157.7, 159.6 (d, $J_{C\text{-}F}$ = 245.1 Hz), 160.0, 176.4. **MS** (ESI) *m/z* 343 $[M+H]^+$, 365 $[M+Na]^+$.

*5.1.2.5. 5-(3′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid ethyl ester **(2d)**.* The crude was prepared according to general procedure B starting from **1d** (1.5 g, 5.7 mmol) and was washed with diethyl ether to afford **2d** as white solid (1.7 g, 87%). $C_{19}H_{15}FO_5$. **m.p.** 108–109 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.38 (q, 2H, J = 7.1 Hz, $CO_2CH_2CH_3$), 5.30 (s, 2H, OCH_2), 6.80 (s, 1H, COCH), 7.11–7.26(m, 2H, ArH), 7.26 (d, 1H, J = 8.4 Hz, ArH), 7.41–7.47 (m, 2H, ArH), 7.56 (m, 1H, ArH), 7.76 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 62.6, 69.1, 109.0, 110.6, 113.4 (d, $J_{C\text{-}F}$ = 22.5 Hz), 114.2 (d, $J_{C\text{-}F}$ = 20.9 Hz), 114.7, 115.5, 122.4 (d, $J_{C\text{-}F}$ = 2.6 Hz), 130.2 (d, $J_{C\text{-}F}$ = 8.4 Hz), 135.3, 139.8 (d, $J_{C\text{-}F}$ = 7.8 Hz), 150.2, 157.2, 157.6, 160.0, 162.3 (d, $J_{C\text{-}F}$ = 242.9 Hz), 176.5. **MS** (ESI) *m/z* 343 $[M+H]^+$.

*5.1.2.6. 5-(4′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid ethyl ester **(2e)**.* The crude was prepared according to general procedure B starting from **1e** (1.2 g, 4.6 mmol) and was washed with diethyl ether to afford **2e** as a yellowish solid (590 mg, 39%). $C_{19}H_{15}FO_5$. **m.p.** 125–126 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.38 (q, 2H, J = 7.2 Hz, $CO_2CH_2CH_3$), 5.25 (s, 2H, OCH_2), 6.77 (s, 1H, COCH), 7.13 (d, 1H, J = 7.7 Hz, ArH), 7.21–7.29 (m, 3H, ArH), 7.62–7.69 (m, 2H, ArH), 7.75 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 62.6, 69.4, 109.1, 110.5, 114.7, 115.1 (d, $J_{C\text{-}F}$ = 21.4 Hz), 115.5, 128.9 (d, $J_{C\text{-}F}$ = 8.2 Hz), 132.9, 135.3, 150.2, 157.3, 157.8, 160.1, 161.6 (d, $J_{C\text{-}F}$ = 243.2 Hz), 176.4. **MS** (ESI) *m/z* 343 $[M+H]^+$, 365 $[M+Na]^+$.

*5.1.2.7. 5-(3′,4′-Difluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid ethyl ester **(2f)**.* The crude was prepared according to general procedure B starting from **1f** (900 mg, 3.2 mmol) and was purified by flash silica column chromatography using cyclohexane/ethyl acetate (100:0 to 50:50) as eluent to afford **2f** as a white solid (200 mg, 18%). $C_{19}H_{14}F_2O_5$. **m.p.** 145–146 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.38 (q, 2H, J = 7.1 Hz, $CO_2CH_2CH_3$), 5.26 (s, 2H, OCH_2), 6.80 (s, 1H, COCH), 7.12 (d, 1H, J = 8.0 Hz, ArH), 7.25 (d, 1H, J = 7.9 Hz, ArH), 7.46–7.50 (m, 2H, ArH), 7.73–7.82 (m, 2H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 62.6, 68.7, 109.0, 110.7, 114.7, 115.4, 115.8 (d, $J_{C\text{-}F}$ = 18.2 Hz), 117.4 (d, $J_{C\text{-}F}$ = 17.2 Hz), 123.2 (m), 134.6 (m), 135.4, 147.8 (m), 150.1 (m), 150.2, 157.2, 157.5, 160.0, 176.5. **MS** (ESI) *m/z* 361 $[M+H]^+$, 383 $[M+Na]^+$.

*5.1.2.8. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid ethyl ester **(2g)**.* The crude was prepared according to general procedure B from **1g** (2 g, 6.2 mmol) and was washed with diethyl ether to afford **2g** as a yellow solid (1.7 g, 69%). $C_{19}H_{15}BrO_5$. **m.p.** 151–153 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.34 (t, 3H, J = 7.1 Hz, $CO_2CH_2CH_3$), 4.38 (q, 2H, J = 7.1 Hz, $CO_2CH_2CH_3$), 5.25 (s, 2H, OCH_2), 6.79 (s, 1H, COCH), 7.13 (m, 1H, ArH), 7.24 (dd, 1H, J = 0.8 Hz, J = 8.5 Hz, ArH), 7.55–7.65 (m, 4H, ArH), 7.75 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 13.9, 62.6, 69.2, 109.0, 110.5, 114.7, 115.4, 120.6, 128.9, 131.2, 135,2, 136.2, 150.1, 157.2, 157.7, 160.0, 176.4. **MS** (ESI) *m/z* 403 (^{79}Br), 405 (^{81}Br) $[M+H]^+$.

*5.1.3. Synthesis of chromones-2-carboxylic acids **3a–g***

5.1.3.1. General procedure C. To a solution of ethyl ester **2a–g** (1 equiv.) in THF/EtOH (1/1, 9 mL/mmol) were added a solution of sodium bicarbonate (7% in water, 4 mL/mmol) and water (4 mL/mmol). The resulting mixture was refluxed for 2 h (the end of the reaction was controlled by TLC using acetone/cyclohexane 50:50). The solution was cooled to room temperature and poured into 1 M hydrochloric acid in order to form a solid which was filtered and washed with diethyl ether.

*5.1.3.2. 5-(2′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid **(3a)**.* The crude was prepared according to general procedure C starting from **2a** (150 mg, 0.4 mmol) to afford **3a** as a white solid (103 mg, 74%). $C_{17}H_{11}BrO_5$. **m.p.** 244–245 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 5.22 (s, 2H, OCH_2), 6.74 (s, 1H, COCH), 7.13 (d, 1H, J = 8.2 Hz, ArH), 7.25 (d, 1H, J = 8.1 Hz, ArH), 7.30 (m, 1H, ArH), 7.49 (m, 1H, ArH), 7.67 (dd, 1H, J = 0.9 Hz, J = 7.9 Hz, ArH), 7.77 (m, 1H, ArH), 8.11 (d, 1H, J = 7.6 Hz, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 69.8, 108.7, 110.9, 114.7, 115.0, 121.1, 127.9, 129.2, 129.6, 132.2, 135.3, 135.8, 157.4, 157.5, 161.4, 176.9. **MS** (ESI) *m/z* 373 (^{79}Br), 375 (^{81}Br) $[M-H]^-$.

*5.1.3.3. 5-(3′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid **(3b)**.* The crude was prepared according to general procedure C starting from **2b** (1.8 mg, 4.5 mmol) to afford **3b** as a beige solid (821 mg, 49%). $C_{17}H_{11}BrO_5$. Decomposition at 230 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 5.26 (s, 2H, OCH_2), 6.74 (s, 1H, COCH), 7.07 (d, 1H, J = 8.2 Hz, ArH), 7.20 (d, 1H, J = 8.4 Hz, ArH), 7.37 (m, 1H, ArH), 7.51 (d, 1H, J = 7.8 Hz, ArH), 7.60 (d, 1H, J = 7.8 Hz, ArH), 7.72 (m, 1H, ArH), 7.92 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 69.0, 108.7, 110.7, 114.4, 114.7, 121.8, 125.6, 129.4, 130.3, 130.5, 134.9, 139.7, 157.5, 157.6, 161.5, 177.2. **MS** (ESI) *m/z* 373 (^{79}Br), 375 (^{81}Br) $[M-H]^-$, 397 (^{79}Br), 399 (^{81}Br) $[M+Na]^+$.

*5.1.3.4. 5-(2′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid **(3c)**.* The crude was prepared according to general procedure C starting from **2c** (265 mg, 0.8 mmol) to afford **3c** as a white solid (157 mg, 65%). $C_{17}H_{11}FO_5$. **m.p.** 213–214 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 5.29 (s, 2H, OCH_2), 6.73 (s, 1H, COCH), 7.14–7.32 (m, 4H, ArH), 7.40 (m, 1H, ArH), 7.75 (m, 1H, ArH), 7.93 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 64.5 (d, $J_{C\text{-}F}$ = 3.7 Hz), 108.9, 110.8, 114.8, 115.1 (d, $J_{C\text{-}F}$ = 21.9 Hz), 115.2, 123.7 (d, $J_{C\text{-}F}$ = 14.1 Hz), 124.5 (d, $J_{C\text{-}F}$ = 3.3 Hz), 129.7 (d, $J_{C\text{-}F}$ = 3 Hz), 129.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 135.3, 151.3, 157.4, 157.7, 159.6 (d, $J_{C\text{-}F}$ = 245.3 Hz), 161.5, 176.8. **MS** (ESI) *m/z* 313 $[M-H]^-$, 337 $[M+Na]^+$.

*5.1.3.5. 5-(3′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid **(3d)**.* The crude was prepared according to general procedure C starting from **2d** (1.2 g, 3.5 mmol) to afford **3d** as a white solid (840 mg, 76%). $C_{17}H_{11}FO_5$. **m.p.** 241–242 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 5.29 (s, 2H, OCH_2), 6.76 (s, 1H, COCH), 7.05–7.18 (m, 2H, ArH), 7.22 (d, 1H, J = 8.5 Hz, ArH), 7.38–7.50 (m, 2H, ArH), 7.56 (d, 1H, J = 10.2 Hz, ArH), 7.77 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 69.1, 108.8, 110.6, 113.4 (d, $J_{C\text{-}F}$ = 22.5 Hz), 114.1 (d, $J_{C\text{-}F}$ = 21 Hz), 114.7, 115.2, 122.4, 130.2, 135.2, 138.8 (d, $J_{C\text{-}F}$ = 7.8 Hz), 151.2, 157.4, 157.6, 161.5, 162.3 (d, $J_{C\text{-}F}$ = 242.7 Hz), 176.8. **MS** (ESI) *m/z* 313

$[M - H]^-$, 337 $[M+Na]^+$.

*5.1.3.6. 5-(4′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid **(3e)**.* The crude was prepared according to general procedure C starting from **2e** (500 mg, 1.5 mmol) to afford **3e** as a yellowish solid (220 mg, 47%). **m.p**. 178–179 °C. $C_{17}H_{11}FO_5$. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 5.24 (s, 2H, OCH_2), 6.69 (s, 1H, COCH), 7.10 (d, 1H, $J = 8.3$ Hz, ArH), 7.20 (d, 1H, $J = 8.5$ Hz, ArH), 7.18–7.28 (m, 2H, ArH), 7.63–7.77 (m, 2H, ArH), 7.72 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 69.3, 108.7, 110.6, 114.3, 114.7, 115.1 (d, $J_{C\text{-}F} = 21.3$ Hz), 128.9 (d, $J_{C\text{-}F} = 8.1$ Hz), 133.0 (d, $J_{C\text{-}F} = 2.8$ Hz), 134.8, 157.5, 157.8, 158.6, 161.3, 161.6 (d, $J_{C\text{-}F} = 242.9$ Hz), 177.1. **MS** (ESI) *m/z* 313 $[M - H]^-$.

*5.1.3.7. 5-(3′,4′-Difluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid **(3f)**.* The crude was prepared according to general procedure C starting from **2f** (196 mg, 0.5 mmol) to afford **3f** as a white solid (142 mg, 79%). $C_{17}H_{10}F_2O_5$. **m.p.** 198–199 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 5.25 (s, 2H, OCH_2), 6.74 (s, 1H, COCH), 7.10 (d, 1H, $J = 7.9$ Hz, ArH), 7.23 (d, 1H, $J = 7.7$ Hz, ArH), 7.42–7.54 (m, 2H, ArH), 7.73–7.84 (m, 2H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 68.6, 108.9, 110.7, 114.7, 115.1, 115.8 (d, $J_{C\text{-}F} = 18.1$ Hz), 117.4 (d, $J_{C\text{-}F} = 17.1$ Hz), 123.2 (m), 134.7, 135.2, 148.0 (m), 150.0, 151.5, 157.4, 157.5, 161.5, 176.9. **MS** (ESI) *m/z* 331 $[M - H]^-$.

*5.1.3.8. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid **(3g)**.* The crude was prepared according to general procedure B from **2g** (1.7 g, 4.3 mmol) to afford **3g** as a white solid (1.5 g, 90%). $C_{17}H_{11}BrO_5$. Decomposition at 200 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 4.79 (s, 2H, OCH_2), 6.29 (s, 1H, COCH), 6.64 (d, 1H, $J = 8.2$ Hz, ArH), 6.76 (d, 1H, $J = 8.0$ Hz, ArH), 7.08–7.20 (m, 4H, ArH), 7.28 (m, 1H, ArH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 69.2, 108.9, 110.6, 114.7, 115.2, 120.6, 128.9, 131.2, 135.1, 136.3, 151.2, 157.4, 157.7, 161.4, 176.7. **MS** (ESI) *m/z* 374 (^{79}Br), 476 (^{81}Br) $[M]^+$.

*5.1.4. Synthesis of targeted compounds **4a–g***

5.1.4.1. General procedure D. To a solution of tryptamine derivative (1 equiv.) in DMF (10 mL/mmol) were added successively a solution of acid derivative **3a–g** (1 equiv.) in DMF (10 mL/mmol), HOBt (2 equiv.), triethylamine (4 equiv.) and EDCI (2 equiv.). The mixture was stirred overnight at room temperature. The resulting mixture was poured into 1 M hydrochloric acid and extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate and water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

*5.1.4.2. 5-(2′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(4a)**.* The crude was prepared according to general procedure D starting from **3a** (103 mg, 0.3 mmol) and 5-methoxytryptamine hydrochloride (105 mg, 0.55 mmol) and was purified by flash silica column chromatography, using dichloromethane/methanol (95:5) as eluent to afford **4a** as a white solid (36 mg, 24%). $C_{28}H_{23}BrN_2O_5$. **m.p.** 204–205 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.95 (t, 2H, $J = 7.6$ Hz, CH_2CH_2NH), 3.56 (m, 2H, CH_2CH_2NH), 3.74 (s, 3H, OCH_3), 5.23 (s, 2H, OCH_2), 6.69 (s, 1H, COCH), 6.71 (dd, 1H, $J = 2.4$ Hz, $J = 8.8$ Hz, ArH), 7.08 (d, 1H, $J = 2.3$ Hz, ArH), 7.12–7.18 (m, 2H, ArH), 7.23 (d, 1H, $J = 8.6$ Hz), 7.26–7.35 (m, 2H, ArH), 7.50 (m, 1H, ArH), 7.67 (m, 1H, ArH), 7.80 (m, 1H, ArH), 8.12 (m, 1H, ArH), 9.20 (t, 1H, $J = 5.7$ Hz, CONH), 10.7 (s, 1H, NH). **^{13}C NMR** (500 MHz, DMSO-d_6) δ 24.9, *CH_2 under DMSO*, 55.3, 69.7, 100.1, 108.8, 110.8, 111.1, 111.2, 112.0, 112.1, 114.5, 121.1, 123.4, 127.6, 127.9, 129.2, 129.6, 131.4, 132.2, 135.2, 135.8, 153.0, 153.7, 157.1, 157.5, 158.9, 176.6. **MS** (ESI) *m/z* 547 (^{79}Br), 549 (^{81}Br) $[M+H]^+$, 545 (^{79}Br), 547 (^{81}Br) $[M - H]^-$. **Anal. Calcd for $C_{28}H_{23}BrN_2O_5$**, C, 61.43; H, 4.24; N, 5.12; Found: C, 61.74; H, 4.22; N, 5.12.

*5.1.4.3. 5-(3′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-methoxy-1H-indol 3-yl)-ethyl]-amide **(4b)**.* The crude was prepared according to general procedure D starting from **3b** (0.6 g, 1.7 mmol) and 5-methoxytryptamine hydrochloride (323 mg, 1.7 mmol) and was recrystallized in ethyl acetate/toluene (9:1) to afford **4b** as a cream solid (456 mg, 49%). $C_{28}H_{23}BrN_2O_5$. **m.p.** 199–200 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.95 (t, 2H, $J = 6.8$ Hz, CH_2CH_2NH), 3.57 (m, 2H, CH_2CH_2NH), 3.74 (s, 3H, OCH_3), 5.27 (s, 2H, OCH_2), 6.69 (s, 1H, COCH), 6.73 (dd, 1H, $J = 2.4$ Hz, $J = 8.7$ Hz, ArH), 7.08 (d, 1H, $J = 1.8$ Hz, ArH), 7.10 (d, 1H, $J = 8.3$ Hz, ArH), 7.17 (d, 1H, $J = 1.7$ Hz, ArH), 7.23 (d, 1H, $J = 8.7$ Hz, ArH), 7.26 (d, 1H, $J = 8.3$ Hz, ArH), 7.38 (m, 1H, ArH), 7.52 (d, 1H, $J = 8.0$ Hz, ArH), 7.60 (d, 1H, $J = 7.6$ Hz, ArH), 7.77 (m, 1H, ArH), 7.91 (m, 1H), 9.19 (t, 1H, $J = 5.2$ Hz, CONH), 10.68 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 24.9, *CH_2 under DMSO*, 55.2, 69.0, 100.2, 108.9, 110.7, 111.1, 111.2, 112.0, 112.1, 114.5, 121.7, 123.4, 125.6, 127.5, 129.4, 130.3, 130.5, 131.4, 135.0, 139.7, 153.0, 153.6, 157.0, 157.6, 158.9, 176.6. **MS** (ESI) *m/z* 569 (^{79}Br), 571 (^{81}Br) $[M+Na]^+$; **Anal. Calcd for $C_{28}H_{23}BrN_2O_5$, H_2O:** C, 59.48; H, 4.46; N, 4.95; Found: C, 59.73; H, 4.29; N, 4.82.

*5.1.4.4. 5-(2′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(4c)**.* The crude was prepared according to general procedure D starting from **3c** (157 mg, 0.5 mmol) and was recrystallized in acetonitrile to afford **4c** as a white solid (18 mg, 7%). $C_{28}H_{23}FN_2O_5$. **m.p.** 216–217 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.95 (t, 2H, $J = 7.5$ Hz, CH_2CH_2NH), 3.56 (m, 2H, CH_2CH_2NH), 3.73 (s, 3H, OCH_3), 5.29 (s, 2H, OCH_2), 6.66 (s, 1H, COCH), 6.71 (m, 1H, ArH), 7.07 (m, 1H, ArH), 7.17–7.29 (m, 6H, ArH), 7.41 (m, 1H), 7.78 (m, 1H, ArH), 7.95 (m, 1H, ArH), 9.21 (t, 1H, $J = 5.5$ Hz, CONH), 10.69 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 24.9, *CH_2 under DMSO*, 55.3, 64.5 (d, $J_{C\text{-}F} = 4.0$ Hz), 100.1, 108.9, 110.7, 111.1, 111.2, 112.1, 114.5, 115.0 (d, $J_{C\text{-}F} = 14.2$ Hz), 123.4, 123.8 (d, $J_{C\text{-}F} = 14.2$ Hz), 124.5 (d, $J_{C\text{-}F} = 2.9$ Hz), 127.5, 129.6 (d, $J_{C\text{-}F} = 4.3$ Hz), 129.8 (d, $J_{C\text{-}F} = 8.3$ Hz), 131.4, 135.0, 153.0, 153.6, 157.0, 157.7, 158.9, 159.6 (d, $J_{C\text{-}F} = 245.2$ Hz), 176.5. **MS** (ESI) *m/z* 485 $[M - H]^-$, 487 $[M+H]^+$, 509 $[M+Na]^+$. **Anal. Calcd for $C_{28}H_{23}FN_2O_5$**, C, 69.13; H, 4.77; N, 5.76; Found: C, 69.09; H, 4.81; N, 6.13.

*5.1.4.5. 5-(3′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(4d)**.* The crude was prepared according to general procedure D starting from **3d** (370 mg, 1.2 mmol) and was washed with diethyl ether to afford **4d** as a white solid (300 mg, 51%). $C_{28}H_{23}FN_2O_5$. Decomposition at 260 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.95 (t, 2H, $J = 7.6$ Hz, CH_2CH_2NH), 3.57 (m, 2H, CH_2CH_2NH), 3.75 (s, 3H, OCH_3), 5.29 (s, 2H, OCH_2), 6.69 (s, 1H, COCH), 6.71 (dd, 1H, $J = 2.4$ Hz, $J = 8.7$ Hz, ArH), 7.08 (d, 1H, $J = 2.3$ Hz, ArH), 7.11 (d, 1H, $J = 8.3$ Hz, ArH), 7.15 (m, 1H, ArH), 7.17 (d, 1H, $J = 2.2$ Hz, ArH), 7.23 (d, 1H, $J = 8.8$ Hz, ArH), 7.26 (d, 1H, $J = 8.0$ Hz, ArH), 7.41–7.49 (m, 2H, ArH), 7.57 (m, 1H, ArH), 7.77 (m, 1H, ArH), 9.19 (t, 1H, $J = 5.8$ Hz, CONH), 10.68 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 24.9, *CH_2 under DMSO*, 55.3, 69.1, 100.1, 108.8, 110.6, 111.0, 111.1, 112.0, 112.1, 113.4 (d, $J_{C\text{-}F} = 22.6$ Hz), 114.1 (d, $J_{C\text{-}F} = 21$ Hz), 114.5, 122.4 (d, $J_{C\text{-}F} = 2.6$ Hz), 123.4, 127.5, 130.2 (d, $J_{C\text{-}F} = 8.4$ Hz), 131.4, 135.0, 139.8 (d, $J_{C\text{-}F} = 7.9$ Hz), 153.0, 153.6, 157.0, 157.6, 158.9, 161.3 (d, $J_{C\text{-}F} = 242.9$ Hz), 176.6. **MS** (ESI) *m/z* 487 $[M+H]^+$.

*5.1.4.6. 5-(4′-Fluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(4e)**.* The crude was prepared according to general procedure D starting from **3e** (180 mg, 0.6 mmol) and 5-methoxytryptamine hydrochloride (114 mg, 0.6 mmol) and was precipitated with diethyl ether to afford **4e** as a yellow solid (118 mg, 50%). $C_{28}H_{23}FN_2O_5$. **m.p.**

234–236 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.95 (t, 2H, J = 7.8 Hz, CH_2CH$_2$NH), 3.56 (m, 2H, CH$_2$CH_2NH), 3.74 (s, 3H, OCH$_3$), 5.24 (s, 2H, OCH$_2$), 6.67 (s, 1H, COCH), 6.72 (dd, 1H, J = 2.4 Hz, J = 8.7 Hz, ArH), 7.07 (d, 1H, J = 2.4 Hz, ArH), 7.12 (d, 1H, J = 8.0 Hz, ArH), 7.17 (d, 1H, J = 2.3 Hz, ArH), 7.20–7.30 (m, 4H, ArH), 7.60–7.75 (m, 2H, ArH), 7.76 (m, 1H, ArH), 9.18 (t, 1H, J = 5.8 Hz, CONH), 10.7 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 24.8, *CH$_2$ under DMSO*, 55.3, 69.3, 100.1, 109.0, 110.5, 111.1, 111.2, 112.0, 112.1, 114.5, 115.1 (d, $J_{C\text{-}F}$ = 21.5 Hz), 123.4, 127.5, 128.9 (d, $J_{C\text{-}F}$ = 8.3 Hz), 131.4, 133.0 (d, $J_{C\text{-}F}$ = 2.9 Hz), 134.9, 153.0, 153.6, 157.0, 157.8, 158.9, 161.6 (d, $J_{C\text{-}F}$ = 243.0 Hz), 176.5. **MS** (ESI) *m/z* 487 [M+H]$^+$, 509 [M+Na]$^+$. **Anal. Calcd for C$_{28}$H$_{23}$FN$_2$O$_5$, 1/3 H$_2$O:** C, 68.29; H, 4.84; N, 5.69; Found: C, 68.63; H, 4.63; N, 5.66.

*5.1.4.7. 5-(3′,4′-Difluorobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(4f)**.* The crude was prepared according to general procedure D starting from **3f** (142 mg, 0.4 mmol) and was recrystallized in acetonitrile to afford **4f** as a white solid (13.5 mg, 5%). C$_{28}$H$_{22}$F$_2$N$_2$O$_5$. **m.p.** 234–236 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.95 (t, 2H, J = 7.7 Hz, CH_2CH$_2$NH), 3.57 (m, 2H, CH$_2$CH_2NH), 3.74 (s, 3H, OCH$_3$), 5.25 (s, 2H, OCH$_2$), 6.69 (s, 1H, COCH), 6.71 (dd, 1H, J = 2.4 Hz, J = 8.7 Hz, ArH), 7.08 (d, 1H, J = 2.3 Hz, ArH), 7.10 (d, 1H, J = 8.3 Hz, ArH), 7.17 (d, 1H, J = 2.2 Hz, ArH), 7.20–7.30 (m, 2H, ArH), 7.40–7.55 (m, 2H, ArH), 7.73–7.83 (m, 2H, ArH), 9.19 (t, 1H, J = 5.8 Hz, CONH), 10.7 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 24.9, *CH$_2$ under DMSO*, 55.3, 68.6, 100.1, 108.9, 110.7, 111.0, 111.2, 112.0, 112.1, 114.5, 115.8 (d, $J_{C\text{-}F}$ = 18.1 Hz), 117.4 (d, $J_{C\text{-}F}$ = 17.1 Hz), 123.3 (m), 123.4, 127.5, 131.4, 134.7 (m), 135.0, 147.8 (m), 150.3 (m), 153.0, 153.7, 157.0, 157.5, 158.9, 176.5. **MS** (ESI) *m/z* 505 [M+H]$^+$, 527 [M+Na]$^+$. **Anal. Calcd for C$_{28}$H$_{22}$F$_2$N$_2$O$_5$**: C, 66.65; H, 4.40; N, 5.55. Found: C, 66.57; H, 4.36; N, 5.49.

*5.1.4.8. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(4g or MBL-II-141)**.* The crude was prepared according to general procedure D from **3g** (860 mg, 2.3 mmol) and 5-methoxytryptamine hydrochloride (430 g, 2.3 mmol) and was purified by flash silica column chromatography using dichloromethane/ethyl acetate (9:1) as eluent to afford **MBL-II-141** as a beige powder (566 mg, 45%). C$_{28}$H$_{23}$BrN$_2$O$_5$. **mp** 159–160 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.95 (t, 2H, J = 7.8 Hz, CH_2CH$_2$NH), 3.56 (m, 2H, CH$_2$CH_2NH), 3.74 (s, 3H, OCH$_3$), 5.25 (s, 2H, OCH$_2$), 6.67 (s, 1H, COCH), 6.71 (dd, 1H, J = 2.4 Hz, J = 8 Hz, ArH), 7.06–7.29 (m, 5H, ArH), 7.55–7.65 (m, 4H, ArH), 7.76 (m, 1H, ArH), 9.18 (t, 1H, J = 5.8 Hz, CONH), 10.68 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 24.8, *CH$_2$ under DMSO*, 55.3, 69.2, 100.1, 108.9, 110.6, 111.0, 111.2, 112.0, 114.5, 120.6, 123.4, 127.5, 128.9, 131.2, 131.4, 134.9, 136.3, 153.0, 153.6, 157.0, 157.7, 158.9, 176.6. **MS** (ESI) *m/z* 546 (^{79}Br), 548 (^{81}Br) [M]$^+$. **Anal. Calcd for C$_{28}$H$_{23}$BrN$_2$O$_5$**: C, 61.44; H, 4.24; N, 5.12. Found C, 61.38; H, 4.23; N, 5.10.

*5.1.5. Synthesis of compounds **5a–e** belonging to the second type of modulation*

*5.1.5.1. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-hydroxy-1H-indol-3-yl)-ethyl]-amide **(5a)**.* The crude was prepared according to general procedure D starting from **3g** (1 g, 2.66 mmol) and commercially available serotonine hydrochloride (567 mg, 2.7 mmol) and was washed with diethylether to afford **5a** as a white solid (794 mg, 56%). C$_{27}$H$_{21}$BrN$_2$O$_5$. **m.p.** 222–225 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.88 (t, 2H, J = 8 Hz, CH_2CH$_2$NH), 3.53 (m, 2H, CH$_2$CH_2NH), 5.24 (s, 2H, OCH$_2$), 6.59 (dd, 1H, J = 2.4 Hz, J = 8.8 Hz, ArH), 6.68 (s, 1H, COCH), 6.89 (d, 1H, J = 2.4 Hz, ArH), 7.05–7.17 (m, 3H, ArH), 7.25 (d, 1H, J = 8.4 Hz, ArH), 7.55–7.67 (m, 4H, ArH), 7.76 (m, 1H, ArH), 8.60 (s, 1H, OH), 9.17 (t, 1H, J = 5.7 Hz, CONH), 10.5 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 25.0, *CH$_2$ under DMSO*, 69.2, 102.2, 108.9, 110.5, 110.6, 111.4, 111.7, 112.1, 114.5, 120.6, 123.2, 127.9, 128.9, 130.8, 131.2, 134.9, 136.3, 150.3, 153.6, 157.0, 157.7, 158.9, 176.6. **MS** (ESI) *m/z* 533 (^{79}Br), 535 (^{81}Br) [M+H]$^+$. **Anal. Calcd for C$_{27}$H$_{21}$BrN$_2$O$_4$, 1/2 H$_2$O:** C, 59.79; H, 4.09; N, 5.16. Found: C, 59.66; H, 3.76; N, 5.41.

5.1.5.2. General procedure E. A solution of **5a** (1 equiv.), potassium carbonate (6 equiv.) and tetrabutylammonium bromide (0.35 equiv.) in acetone (10 mL/mmol) was refluxed for 20 min. A solution of the corresponding alkyl iodide (1.2 equiv.) in acetone (3 mL/mmol) was added dropwise and the resulting mixture was refluxed for 2–6 h (the end of the reaction was controlled by TLC using acetone/cyclohexane 40:60). The resulting solution was cooled to room temperature and concentrated under reduced pressure. The residue was poured into water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

*5.1.5.3. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-ethoxy-1H-indol-3-yl)-ethyl]-amide **(5b)**.* The crude was prepared according to general procedure E starting from **5a** (200 mg, 0.4 mmol) and iodoethane (56 mg, 0.4 mmol) and was purified by flash silica column chromatography, using dichloromethane/methanol (99:1) as eluent to afford **5b** as a white solid (36.5 mg, 17%). C$_{29}$H$_{25}$BrN$_2$O$_5$. **m.p.** 234–236 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 1.28 (t, 3H, J = 6.8 Hz, OCH$_2$CH_3), 2.92 (t, 2H, J = 7.2 Hz, CH_2CH$_2$NH), 3.53 (m, 2H, CH$_2$CH_2NH), 3.94 (q, 2H, J = 6.8 Hz, OCH_2CH$_3$), 5.23 (s, 2H, OCH$_2$), 6.64 (s, 1H, COCH), 6.68 (dd, 1H, J = 2.0 Hz, J = 8.4 Hz, ArH), 7.06–7.24 (m, 5H, ArH), 7.55–7.66 (m, 4H, ArH), 7.74 (m, 1H, ArH), 9.15 (t, 1H, J = 5.6 Hz, CONH), 10.64 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 14.9, 24.8, *CH$_2$ under DMSO*, 63.3, 69.2, 101.2, 109.0, 110.6, 111.2, 111.5, 112.0, 112.1, 114.5, 120.6, 123.5, 127.6, 128.9, 131.2, 131.4, 134.9, 136.3, 152.1, 153.6, 157.0, 157.7, 158.9, 176.5. **MS** (ESI) *m/z* 561 (^{79}Br), 563 (^{81}Br) [M+H]$^+$; 583 (^{79}Br), 585 (^{81}Br) [M+Na]$^+$. **Anal. Calcd for C$_{29}$H$_{25}$BrN$_2$O$_5$**: C, 62.04; H, 4.49; N, 4.99. Found: C, 61.82; H, 4.28; N, 4.75.

*5.1.5.4. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-propyloxy-1H-indol-3-yl)-ethyl]-amide **(5c)**.* The crude was prepared according to general procedure E starting from **5a** (200 mg, 0.4 mmol) and 1-iodopropane (60 mg, 0.4 mmol) and was purified by flash silica column chromatography using dichloromethane/methanol (99:1) as eluent to afford **5c** as a white solid (67 mg, 31%). C$_{30}$H$_{27}$BrN$_2$O$_5$. **m.p.** 203–206 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.94 (t, 3H, J = 8 Hz, CH$_3$), 1.66 (m, 2H, OCH$_2$CH_2CH$_3$), 2.93 (t, 2H, J = 8 Hz, CH_2CH$_2$NH), 3.55 (m, 2H, CH$_2$CH_2NH), 3.86 (t, 2H, J = 6.4 Hz, OCH_2CH$_2$CH$_3$), 5.23 (s, 2H, OCH$_2$), 6.66 (s, 1H, COCH), 6.70 (dd, 1H, J = 2.0 Hz, J = 8.8 Hz, ArH), 7.02–7.31 (m, 5H, ArH), 7.55–7.68 (m, 4H, ArH), 7.76 (m, 1H, ArH), 9.17 (t, 1H, J = 5.6 Hz, CONH), 10.66 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 10.5, 22.3, 24.8, *CH$_2$ under DMSO*, 69.2, 69.4, 101.2, 109.0, 110.6, 111.3, 111.5, 112.0, 112.1, 114.5, 120.6, 123.4, 127.6, 128.9, 131.2, 131.4, 134.9, 136.3, 152.3, 153.6, 157.0, 157.7, 158.9, 176.5. **MS** (ESI) *m/z* 575 (^{79}Br), 577 (^{81}Br) [M+H]$^+$; 597 (^{79}Br), 599 (^{81}Br) [M+Na]$^+$. **Anal. Calcd for C$_{30}$H$_{27}$BrN$_2$O$_5$, 1/2 H$_2$O:** C, 61.65; H, 4.83; N, 4.79. Found: C, 61.92; H, 4.77; N, 4.97.

*5.1.5.5. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(5-isopropyloxy-1H-indol-3-yl)-ethyl]-amide **(5d)**.* The crude was prepared according to general procedure E starting from **5a** (280 mg, 0.5 mmol) and 2-iodopropane (89 mg, 0.5 mmol) and was purified by flash silica column chromatography using dichloromethane/methanol (99:1) as eluent to afford **5d** as a white solid (90 mg, 30%). C$_{30}$H$_{27}$BrN$_2$O$_5$. **m.p**. 240–243 °C. **^{1}H NMR** (400 MHz,

DMSO-d_6) δ 1.21 (d, 6H, J = 6.0 Hz, CH(CH_3)$_2$), 2.93 (t, 2H, J = 7.5 Hz, CH_2CH$_2$NH), 3.54 (m, 2H, CH$_2$$CH_2$NH), 4.46 (septuplet, 1H, J = 6.0 Hz, CH(CH_3)$_2$), 5.24 (s, 2H, OCH$_2$), 6.66 (s, 1H, COCH), 6.69 (dd, 1H, J = 2.3 Hz, J = 8.7 Hz, ArH), 7.00–7.30 (m, 5H, ArH), 7.53–7.65 (m, 4H, ArH), 7.76 (t, 1H, J = 8.4 Hz, ArH), 9.17 (t, 1H, J = 5.9 Hz, CONH), 10.65 (s, 1H, NH). **^{13}C NMR** (125 MHz, DMSO-d_6) δ 22.0, 24.8, *CH_2 under DMSO*, 69.2, 70.1, 104.0, 109.0, 110.6, 111.2, 111.9, 112.0, 112.9, 120.6, 123.5, 127.7, 128.9, 131.2, 131.6, 134.9, 136.3, 150.7, 152.6, 153.6, 157.7, 158.9, 176.7. **MS** (ESI) *m/z* 575 (^{79}Br), 576 (^{81}Br) [M+H]$^+$. **Anal. Calcd for $C_{30}H_{27}BrN_2O_5$**: C, 62.62; H, 4.73; N, 4.87. Found: C, 64.16; H, 4.75; N, 4.85.

*5.1.5.6. 5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carboxylic acid [2-(1H-indol-3-yl)-ethyl]-amide **(5e)**.* The crude was prepared according to general procedure D starting from **3g** (200 mg, 0.5 mmol) and commercially available tryptamine hydrochloride (98 mg, 0.5 mmol) and was purified by flash silica column chromatography using dichloromethane/methanol (95:5) as eluent to afford to afford **5e** as a white solid (80 mg, 31%). $C_{27}H_{21}BrN_2O_4$. **m.p.** 221 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 2.99 (t, 2H, J = 7.5 Hz, CH_2CH$_2$NH), 3.58 (m, 2H, CH$_2$$CH_2$NH), 5.24 (s, 2H, OCH$_2$), 6.68 (s, 1H, COCH), 6.92–7.40 (m, 6H, ArH), 7.52–7.68 (m, 5H, ArH), 7.77 (m, 1H, ArH), 9.20 (t, 1H, J = 5.7 Hz, CONH), 10.8 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 24.8, *CH_2 under DMSO*, 69.2, 109.0, 110.6, 111.4, 112.0, 114.5, 118.2, 118.3, 120.6, 121.0, 122.7, 127.2, 128.9, 131.2, 135.0, 136.2, 136.3, 153.6, 157.0, 157.7, 158.9, 162.3, 176.6. **MS** (ESI) *m/z* 539 (^{79}Br), 541 (^{81}Br) [M+Na]$^+$. **Anal. Calcd for $C_{27}H_{21}BrN_2O_4$**: C, 62.67; H, 4.10; N, 5.41. Found: C, 62.45; H, 4.12; N, 5.48.

*5.1.6. Synthesis of esters **6a–b***

5.1.6.1. General procedure F. To a solution of acid **3g** (1 equiv.) in DMF (10 mL/mmol) were added successively a solution of corresponding protected amino-acid derivative or 5-methoxytryptamine hydrochloride (2 equiv.) in DMF (10 mL/mmol), TBTU (1.5 equiv.) and DIEA (5 equiv.). The mixture was stirred overnight at room temperature. The resulting mixture was poured into sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

*5.1.6.2. 2-[(5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carbonyl)-amino]-3-methylbutyric acid methyl ester **(6a)**.* The crude was prepared according to general procedure F starting from **3g** (500 mg, 1.3 mmol) and L-valine methylester hydrochloride (446 mg, 2.7 mmol) and was washed with diethyl ether to afford **6a** as a white solid (540 mg, 83%). $C_{23}H_{22}BrNO_6$. **m.p.** 151–152 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.95 (d, 3H, J = 6.7 Hz, CH_3), 0.98 (d, 3H, J = 6.8 Hz, CH_3), 2.23 (m, 1H, CHC*H*(CH$_3$)$_2$), 3.69 (s, 3H, OCH$_3$), 4.30 (m, 1H, *C*HCH(CH$_3$)$_2$), 5.25 (s, 2H, OCH$_2$), 6.70 (s, 1H, COCH), 7.11 (d, 1H, J = 8.3 Hz, ArH), 7.34 (d, 1H, J = 8.3 Hz, ArH), 7.55–7.68 (m, 4H, ArH), 7.77 (m, 1H, ArH), 9.16 (d, 1H, J = 7.9 Hz, CONH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 19.0, 19.1, 29.5, 51.9, 58.6, 69.2, 109.0, 110.9, 112.7, 114.6, 120.6, 129.0, 131.2, 135.0, 136.3, 153.0, 157.0, 157.7, 159.7, 171.4, 176.4. **MS** (ESI) *m/z* 488 (^{79}Br), 490 (^{81}Br) [M+H]$^+$. **Anal. Calcd for $C_{23}H_{22}BrNO_6$**: C, 56.57; H, 4.54; N, 2.87. Found: C, 56.42; H, 4.49; N, 3.01.

*5.1.6.3. 2-[(5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carbonyl)-amino]-4-methylpentanoic acid methyl ester **(6b)**.* The crude was prepared according to general procedure F starting from **3g** (500 mg, 1.3 mmol) and L-leucine methylester hydrochloride (484 mg, 2.7 mmol) and was purified by flash silica column chromatography, using cyclohexane:acetone (8:2 to 5:5) as eluent to afford **6b** as a white solid (531 mg, 79%). $C_{24}H_{24}BrNO_6$. **m.p.** 135–138 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.89 (d, 3H, J = 4.3 Hz, CH_3), 0.92 (d, 3H, J = 4.4 Hz, CH_3), 1.64 (m, 2H, CHCH_2CH(CH$_3$)$_2$), 1.84 (m, 1H, CHCH$_2$C*H*(CH$_3$)$_2$), 3.67 (s, 3H, OCH$_3$), 4.53 (m, 1H, *C*HCH$_2$CH(CH$_3$)$_2$), 5.25 (s, 2H, OCH$_2$), 6.70 (s, 1H, COCH), 7.11 (d, 1H, J = 8.4 Hz, ArH), 7.30 (d, 1H, J = 8.2 Hz, ArH), 7.55–7.68 (m, 4H, ArH), 7.77 (m, 1H, ArH), 9.33 (d, 1H, J = 7.3 Hz, CONH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 21.1, 22.8, 24.3, *signal under DMSO*, 50.9, 52.1, 69.2, 109.1, 110.7, 112.7, 114.6, 120.6, 128.9, 131.2, 135.0, 136.3, 152.8, 157.0, 157.7, 159.4, 172.1, 176.4. **MS** (ESI) *m/z* 502 (^{79}Br), 504 (^{81}Br) [M+H]$^+$. **Anal. Calcd for $C_{24}H_{24}BrNO_6$**: C, 57.38; H, 4.82; N, 2.79. Found: C, 57.00; H, 5.12; N, 2.87.

*5.1.7. Synthesis of **7a–b** acids*

5.1.7.1. General procedure G. To a solution of methyl ester **6a–d** (1 equiv.) in tetrahydrofuran/methanol (1/1) (10 mL/mmol) was added a solution of lithium hydroxide (1 equiv.) in water (5 mL/mmol). The resulting mixture was stirred at room temperature for 1 h. The solution was poured into 1 M hydrochloric acid and extracted with dichloromethane. The combined organic layers were washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

*5.1.7.2. 2-[(5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carbonyl)-amino]-3-methylbutyric acid **(7a)**.* The crude was prepared according to general procedure G starting from **6a** (400 mg, 0.8 mmol) and recrystallized in acetonitrile to afford **7a** as a white solid (282 mg, 72%). $C_{22}H_{20}BrNO_6$. **m.p.** 250–251 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.97 (m, 6H, CH(CH_3)$_2$), 2.24 (m, 1H, CHC*H*(CH$_3$)$_2$), 4.25 (m, 1H, *C*HCH(CH$_3$)$_2$), 5.25 (s, 2H, OCH$_2$), 6.70 (s, 1H, COCH), 7.11 (d, 1H, J = 8.3 Hz, ArH), 7.34 (d, 1H, J = 8.4 Hz, ArH), 7.54–7.69 (m, 4H, ArH), 7.77 (m, 1H, ArH), 8.89 (d, 1H, J = 7.8 Hz, CONH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 19.0, 19.5, 29.8, 58.9, 69.5, 109.3, 111.2, 112.8, 114.7, 120.9, 129.3, 131.5, 135.3, 136.5, 153.5, 157.3, 157.9, 159.7, 172.5, 176.9. **MS** (ESI) *m/z* 472 (^{79}Br), 474 (^{81}Br) [M – H]$^-$, 496 (^{79}Br), 498 (^{81}Br) [M+Na]$^+$. **Anal. Calcd for $C_{22}H_{20}BrNO_6$**: C, 55.70; H, 4.26; N, 2.95. Found: C, 55.54; H, 4.16; N, 3.06.

*5.1.7.3. 2-[(5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carbonyl)-amino]-3-methylpentanoic acid **(7b)**.* The crude was prepared according to general procedure G starting from **6b** (450 mg, 0.9 mmol) and recrystallized in acetonitrile to afford **7b** as a white solid (163 mg, 37%). $C_{23}H_{22}BrNO_6$. **m.p.** 258–259 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.88 (d, 3H, J = 6.1 Hz, CH_3), 0.93 (d, 3H, J = 6.2 Hz, CH_3), 1.66 (m, 2H, CHCH_2CH(CH$_3$)$_2$), 1.81 (m, 1H, CHCH$_2$C*H*(CH$_3$)$_2$), 4.45 (m, 1H, *C*HCH$_2$CH(CH$_3$)$_2$), 5.25 (s, 2H, OCH$_2$), 6.70 (s, 1H, COCH), 7.11 (d, 1H, J = 8.0 Hz, ArH), 7.30 (dd, 1H, J = 0.8 Hz, J = 8.5 Hz, ArH), 7.55–7.65 (m, 4H, ArH), 7.77 (m, 1H, ArH), 9.33 (d, 1H, J = 7.6 Hz, CONH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 21.1, 22.9, 24.5, *signal under DMSO*, 50.9, 69.3, 109.0, 110.8, 112.6, 114.6, 120.6, 129.0, 131.2, 135.0, 136.3, 153.1, 157.1, 157.7, 159.3, 173.2, 176.5. **MS** (ESI) *m/z* 486 (^{79}Br), 488 (^{81}Br) [M – H]$^-$, 488 (^{79}Br), 490 (^{81}Br) [M+H]$^+$. **Anal. Calcd for $C_{23}H_{22}BrNO_6$**: C, 56.57; H, 4.54; N, 2.87. Found: C, 56.54; H, 4.65; N, 3.06.

*5.1.8. Synthesis of targeted compounds **8a–b***

*5.1.8.1. 2-[(5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carbonyl)-amino]-3-methylbutyric acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(8a)**.* The crude was prepared according to general procedure F starting from **7a** (263 mg, 0.55 mmol) and 5-methoxytryptamine hydrochloride (211 mg, 1.1 mmol) and was purified by flash silica column chromatography using cyclohexane/acetone (8:2 to 5:5) as eluent to afford **8a** as a white solid (62.5 mg, 18%). $C_{33}H_{32}BrN_3O_6$. **m.p.** 170–171 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.90 (d, 6H, J = 6.7 Hz, CH(CH_3)$_2$), 2.14 (m, 1H, CHC*H*(CH$_3$)$_2$),

2.81 (t, 2H, $J = 7.2$ Hz, CH_2CH_2NH), 3.42 (m, 2H, CH_2CH_2NH), 3.75 (s, 3H, OCH_3), 4.26 (m, 1H, $CHCH(CH_3)_2$), 5.25 (s, 2H, OCH_2), 6.67–6,73 (m, 2H, ArH), 7.01 (d, 1H, $J = 2.3$ Hz, ArH), 7.07–7.13 (m, 2H, ArH), 7.20 (d, 1H, $J = 8.8$ Hz, ArH), 7.35 (d, 1H, $J = 7.9$ Hz, ArH), 7.55–7.65 (m, 4H, ArH), 7.77 (m, 1H), 8.32 (t, 1H, $J = 5.6$ Hz, $CONHCH_2$), 8.77 (d, 1H, $J = 4.8$ Hz, CONHCH), 10.64 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 19.2, 19.7, 25.4, 30.7, *CH_2 under DMSO*, 55.9, 59.8, 69.8, 100.6, 109.6, 111.4, 111.6, 111.9, 112.7, 113.0, 114.9, 121.3, 124.0, 128.0, 129.6, 131.8, 131,9, 135.8, 136.7, 153.5, 153.8, 157.6, 158.1, 159.7, 171.0, 177.6. **MS** (ESI) *m/z* 644 (^{79}Br), 646 (^{81}Br) $[M - H]^-$, 646 (^{79}Br), 648 (^{81}Br) $[M+H]^+$. **Anal. Calcd for $C_{33}H_{32}BrN_2O_6$**: C, 61.31; H, 4.99; N, 6.50. Found: C, 61.27; H, 5.48; N, 5.81.

*5.1.8.2. 2-[(5-(4′-Bromobenzyloxy)-4-oxo-4H-chromene-2-carbonyl)-amino]-3-methylpentanoic acid [2-(5-methoxy-1H-indol-3-yl)-ethyl]-amide **(8b)**.* The crude was prepared according to general procedure E starting from **7b** (163 mg, 0.3 mmol) and 5-methoxytryptamine hydrochloride (127 mg, 0.7 mmol) and was washed with diethyl ether to afford **8b** as a white solid (64 mg, 29%). $C_{34}H_{34}BrN_3O_6$. **m.p.** 130–131 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 0.86 (d, 3H, $J = 5.7$ Hz, CH_3), 0.90 (d, 3H, $J = 5.8$ Hz, CH_3), 1.58 (m, 2H, $CHCH_2CH(CH_3)_2$), 1.71 (m, 1H, $CHCH_2CH(CH_3)_2$), 2.80 (t, 2H, $J = 7.3$ Hz, CH_2CH_2NH), 3.39 (m, 2H, CH_2CH_2NH), 3.75 (s, 3H, OCH_3), 4.48 (m, 1H, $CHCH_2CH(CH_3)_2$), 5.25 (s, 2H, OCH_2), 6.66–6.75 (m, 2H, ArH), 7.02 (m, 1H, ArH), 7.07–7.15 (m, 2H, ArH), 7.21 (d, 1H, $J = 8.7$ Hz, ArH), 7.33 (d, 1H, $J = 8.5$ Hz, ArH), 7.55–7.65 (m, 4H, ArH), 7.77 (m, 1H, ArH), 8.22 (m, 1H, $CONHCH_2$), 9.00 (d, 1H, $J = 8.3$ Hz, CONHCH), 10.63 (s, 1H, NH). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 21.4, 23.0, 24.4, 25.1, *2 signals under DMSO*, 51.9, 55.4, 69.2, 100.1, 109.0, 110.9, 111.0, 111.4, 112.0, 112.5, 114.6, 120.6, 123.4, 127.5, 129.0, 131.3, 131.4, 135.0, 136.4, 153.0, 153.3, 157.1, 157.7, 159.1, 171.1, 176.6. **MS** (ESI) *m/z* 658 (^{79}Br), 660 (^{81}Br) $[M - H]^-$, 660 (^{79}Br), 662 (^{81}Br) $[M+H]^+$. **Anal. Calcd for $C_{34}H_{34}BrN_3O_6$**: C, 61.81; H, 5.20; N, 6.36. Found: C, 60.49; H, 5.22; N, 6.16.

5.2. Biology

5.2.1. Materials

High-glucose Dulbecco's modified Eagle's medium (DMEM high glucose) and fetal bovine serum were purchased from Gibco. The penicillin/streptomycin (10 000 unit/10 mg), G418 phosphate, trypsine and PBS solution were purchased from Sigma Aldrich (France). Mitoxantrone, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) were purchased from Sigma Aldrich (France). All commercial products were of the highest available purity grade.

5.2.2. Compounds

All chromone derivatives were dissolved in DMSO, and then diluted in DMEM high glucose medium. The stock solutions were stored at −20 °C, and warmed to 25 °C just before use.

5.2.3. Cell cultures

The human embryonic kidney HEK293 cells transfected with *ABCG2* (HEK293-ABCG2) or the non-transfected (wild-type) control cells were obtained and studied as previously described [22,26] for other inhibitor derivatives. They were maintained in Dulbecco's modified Eagle's medium (DMEM high glucose), supplemented with 10% fetal bovine serum (FBS), 1% penicillin/streptomycin, and supplemented with 0.75 mg/mL G418.

5.2.4. ABCG2-mediated drug transport

The efflux assays were determined according to ref [19] with minor modifications. HEK293-ABCG2 cells and control cells were seeded at a density of 1×10^5 cells/well into 24-well culture plates. After 48-h incubation, the cells were exposed to 5 μM mitoxantrone for 30 min at 37 °C (HEK293-ABCG2 cells), in the presence or absence of compounds at various concentrations. After cell washing with phosphate buffer saline (PBS), the cells were trypsinized and subsequently resuspended in ice-cold PBS for analysis by flow cytometry. The intracellular drug fluorescence was monitored with a FACS Calibur cytometer (Becton Dickinson). At least 5000–10,000 events were collected, for which the maximal fluorescence (taken as 100%) was the difference between the geometric mean fluorescence of cells incubated with 1 μM Ko143 and without inhibitor.

5.2.5. Cytotoxicity assays

HEK293-ABCG2 and wild-type (control) cells were seeded into 96-well culture plates at a 1×10^4 cells/well density. After overnight incubation, the cells were treated with increasing concentrations of compounds for 72 h, at 37 °C under 5% CO_2. Cell viability was then evaluated with a MTT colorimetric assay [27]. Control experiments were performed with DMEM high glucose containing 0.1% DMSO (v/v). The results were expressed as percentage of viable cells *versus* initial control cells taken as 100%.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.05.053.

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