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Short communication

Structure–activity relationship of selected polyphenol derivatives as inhibitors of Bax/Bcl-xL interaction

Duc Duy Vo [a], Fabien Gautier [b,c], Philippe Juin [b], René Grée [a,*]

[a] Université de Rennes1, Laboratoire Sciences Chimiques de Rennes, CNRS UMR 6226, Avenue du Général Leclerc, 35042 Rennes Cedex, France
[b] Université de Nantes, CRCNA INSERM U892, 8 quai Moncousu, 44007 Nantes Cedex 1, France
[c] Institut de Cancérologie de l'Ouest, Centre de Recherche en Cancérologie, Bd Jacques Monod 44805 Saint Herblain, Nantes Cedex, France

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ABSTRACT

This paper describes the synthesis of nine selected diaryl/heteroaryl-containing phenol and polyphenol derivatives which have been evaluated against Bax/Bcl-xL interaction in comparison with ABT-737. Using a BRET assay, six of these derivatives exhibit activity comparable to ABT-737 to disrupt Bax/Bcl-xL interaction. These preliminary results demonstrate that such polyphenol-derived molecules are attractive compounds regarding anticancer activity and that the phenol at position 3 is important regarding disruption of Bax/Bcl-xL interaction.

1. Introduction

Apoptosis is one of the major cell death pathways involved in maintaining cell homeostasis, and escape from apoptosis is understood to contribute to carcinogenesis [1]. The anti-apoptotic Bcl-2 family of proteins (especially Bcl-2, Bcl-xL, Mcl-1) are frequently overexpressed in cancer cells, including solid tumors. Therefore, they prevent death in corresponding cells and increase resistance to traditional treatments [2]. Current data indicate that they contribute to the aberrant survival and/or maintenance of cancer cells by counteracting death signals triggered by oncogenic lesions and/or therapy. Anti-apoptotic Bcl-2 proteins homologs exert their survival activity by engaging inhibitory protein–protein interactions. They are known, in particular, to exert an anti-apoptotic effect by engaging the BH3 domain of pro-apoptotic members of the Bcl-2 family, Bax, Bak, and their upstream effectors the BH3-only proteins (e.g. Bad, Bid, Bim and PUMA) via a well characterized binding interface. Thus, anti-apoptotic Bcl-2 proteins inhibitory strategies, aiming at disrupting these heterodimers, are of therapeutic interest [3]. ABT-737 is a representative example of a small molecule inhibitor, called "BH3-mimetic", that binds to the BH3-binding site of Bcl-2/Bcl-xL proteins at nanomolar concentration and inhibits their survival activity [4]. This molecule also induces apoptosis in some cancer cell as a single agent or enhances the pro-apoptotic activity of other drugs, both *in vitro* and *in vivo* [4]. However it is not binding efficiently to Mcl-1, a Bcl-2 homolog which is also overexpressed in many cancer cells, and therefore resistance to ABT-737 used as a single agent have appeared [5].

The polyphenol core is widely recognized as an attractive structure-target towards new anticancer agents [6]. For instance, gossypol showed good activities towards Bcl-2, Bcl-xL and Mcl-1 with K_i at submicromolar level and it has entered into clinical trials [7]. Various molecules based on the gossypol structure were designed [8]. In particular the benzophenone analog **1**, developed by the group of Wang, is a simplified pyrogallol-based analog which showed good activities against Bcl-2 and Mcl-1 [8d]. Further, **1** induced apoptosis and cell death in the MDA-MB-231 and PC-3 cell lines at IC_{50} values of 12.9 μM and 12.4 μM respectively. Later developments from the same group showed that the isopropyl group of **1** can be modified into more bulky hydrophobic groups to improve activity [8d]. Fig. 1.

* Corresponding author. Tel.: +33 0 2 23 23 57 15; fax: +33 0 2 23 23 69 78.
E-mail address: rene.gree@univ-rennes1.fr (R. Grée).

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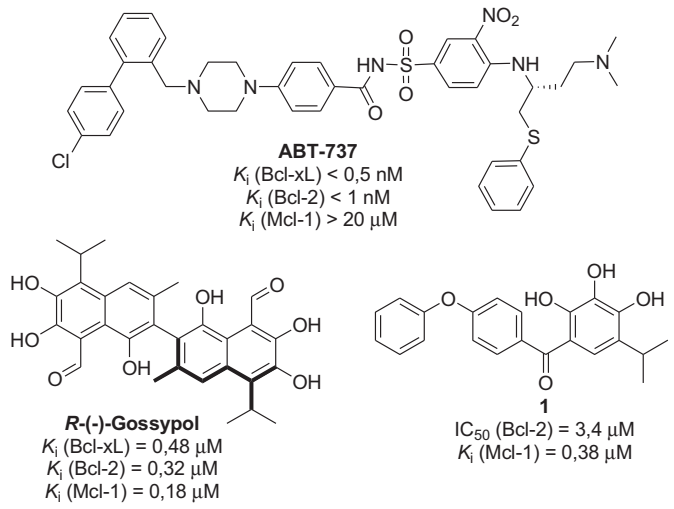


Fig. 1. Selected inhibitors of Bcl-2 proteins.

As part of our ongoing programme on the development of anticancer molecules based on reinduction of apoptosis in cancer cells [9], we started a preliminary structure–activity relationship study on selected polyphenol-derived molecules. In particular, based on previous data, we intend to synthesize some selected polyphenol compounds, analogous to **1** (Fig. 2), in which:

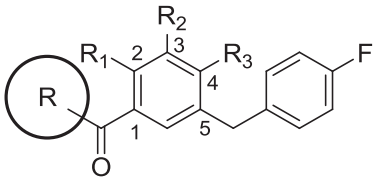


Fig. 2. General structure for our target molecules.

- we used *p*-fluorobenzyl group to replace isopropyl substituent and,
- we selected a few aromatic/heteroaromatic R groups and,
- on an active model compound, we modified the number and position of the three OH phenolic groups (R_1, R_2 and R_3) in order to study their effect regarding Bax/Bcl-xL interaction.

We chose to study this key protein–protein interaction for two reasons. First, we wanted to investigate whether the new polyphenol derivatives retained the ability to interfere with the BH3-binding activity of the anti-apoptotic Bcl-xL protein previously reported for gossypol. Second, we recently reported that disruption of the specific interaction that this protein engages with the multi-domain pro-apoptotic protein Bax is necessary and may be a sufficient requirement for BH3-mimetic Bcl-xL inhibitors to promote cell death [10]. This point appeared to us as a key issue for the future development of new molecules in this area.

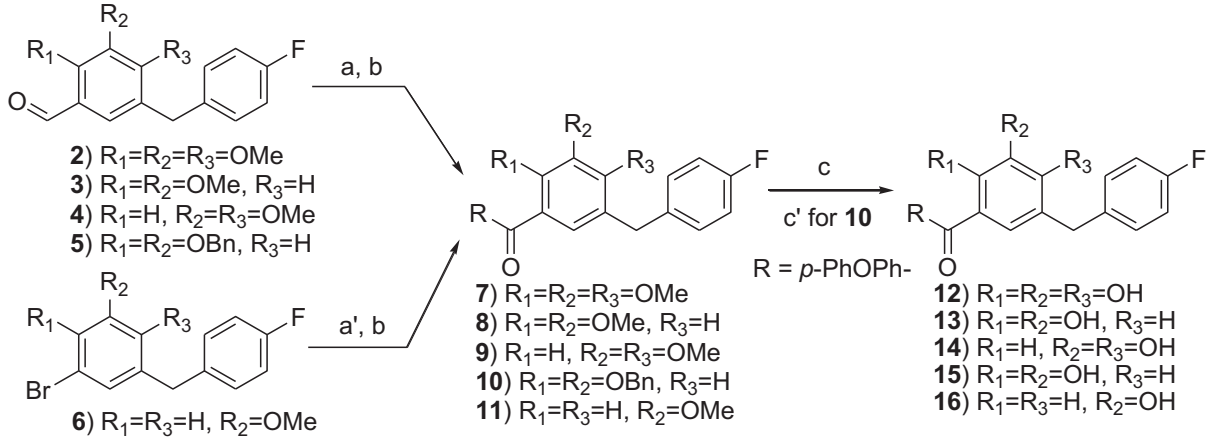
2. Results and discussion

2.1. Chemistry

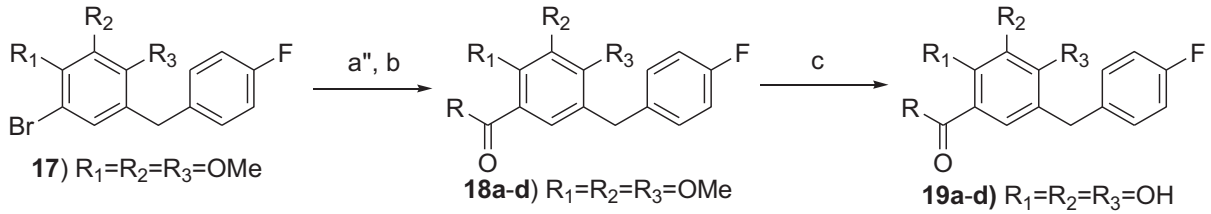
In the present work, a series of selected diaryl/heteroaryl-containing phenol and polyphenol derivatives was prepared, starting from aromatic aldehydes **2**–**5** or bromo aromatic compounds **6** and **17**. The synthesis of our target molecules is described in Scheme 1 (compounds **12**–**16**) and Scheme 2 (compounds **19a**–**d**). First, a series of ketones **7**–**10** was prepared in a two-step sequence starting from aldehydes **2**–**5**. On reaction with *p*-PhOPhMgBr, latter compounds gave corresponding alcohols which were immediately oxidized with IBX to afford the target intermediates **7**–**10**. The last target ketone **11** was obtained in a three-steps sequence: metalation of bromo aromatic compound **6** with *t*-BuLi, followed by reaction with the required aldehyde to an alcohol which was immediately oxidized with IBX. A similar strategy (metalation/trapping by aldehyde and then oxidation) was followed for the preparation of ketones **18a**–**d**, starting from bromo aromatic compound **17** (Scheme 2). The final deprotection step was successfully performed, with excess BBr_3, for all derivatives having methoxy-protected polyphenols. In the case of benzyl-protected intermediate **10**, deprotection was performed by hydrogenation to give the target ketone **15**. The structures and overall yields of final molecules **12**–**16**, **19a**–**d** are given in Fig. 2 and Table 1.

2.2. Biological evaluation: Bax/Bcl-xL disruption

The nine final molecules (**12**–**16** and **19a**–**d**) were tested for their ability to disrupt Bax/Bcl-xL interactions and to do so in a whole cell configuration. For these studies, we used a method which allows to monitor in-cell interactions between one transiently transfected luciferase tagged protein [Bax in this work



Scheme 1. Synthesis of target molecules **12**–**16**. Reagents and conditions: (a) p-PhOPhMgBr, THF, 0°C-rt; (a') t-BuLi, Et_2O, -78°C, then p- PhOPhCHO, -78°C – rt; (b) IBX, THF/DMSO, reflux; (c) BBr_3, CH2Cl2, 0°C – rt; (c') H2, Pd/C, CH_2Cl_2, rt; overall yields are given in Table 1.



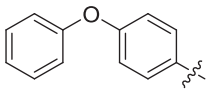
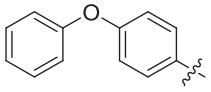
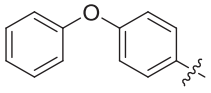
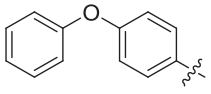
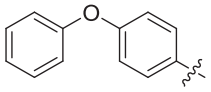
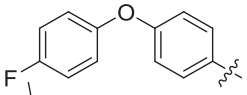
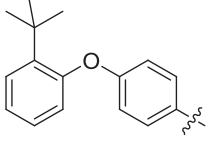
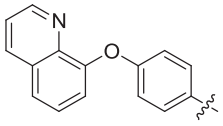
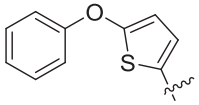
Scheme 2. Synthesis of target molecules **19a**–**d** (R see Table 1). Reagents and conditions: (a") t-BuLi, Et_2O, -78°C, then RCHO, -78°C – rt; (b) IBX, THF/DMSO, reflux; (c) BBr_3, CH_2Cl_2, 0°C – rt; overall yields are given in Table 1.

(Rluc-Bax)] and a second, yellow fluorescent tagged protein [Bcl-xL in this work (eYFP-Bcl-xL)] by Bioluminescence Resonance Energy Transfer (BRET). This method provides robust and reliable signals. It allows to study directly the effects of compounds added in the culture medium on intracellular interactions. Validation of this BRET model is described in Fig. 3. Expression and interaction between the two BRET partners was confirmed in co-immunoprecipitation assays, followed by Western blotting (Fig. 3a). Importantly, BRET signals between RLuc-Bax and eYFP-Bcl-xL, and not between Rluc-Bax and eYFP, were found saturable, demonstrating the specificity of the interaction (Fig. 3b). ABT-737 was used as a reference compound, and its observed ability to decrease BRET signals also confirmed the specificity of the interaction evaluated by BRET analysis.

The results obtained with our new derivatives are given in Fig. 4, and their analysis has to be done along three lines:

- First, regarding the choice of the alkyl/aryl-alkyl substituent on the right part of polyphenol: the compound **1** has only half activity compared to ABT-737 while molecule **12**, in which the isopropyl group was replaced by a *p*-fluorobenzyl, showed similar activity to this reference compound. This result is in agreement with literature data [8d] and therefore the molecule **12** appears as

Table 1
Structure and overall yields for final compounds.

Entry	Compound	R	R_1	R_2	R_3	Yield (%)[a]
1	**12**		OH	OH	OH	59
2	**13**		OH	OH	H	66
3	**14**		H	OH	OH	53
4	**15**		OH	H	OH	34
5	**16**		H	OH	H	13
6	**19a**		OH	OH	OH	21
7	**19b**		OH	OH	OH	22
8	**19c**		OH	OH	OH	36
9	**19d**		OH	OH	OH	44

[a] overall yields for isolated compounds, after the 3 steps sequence.

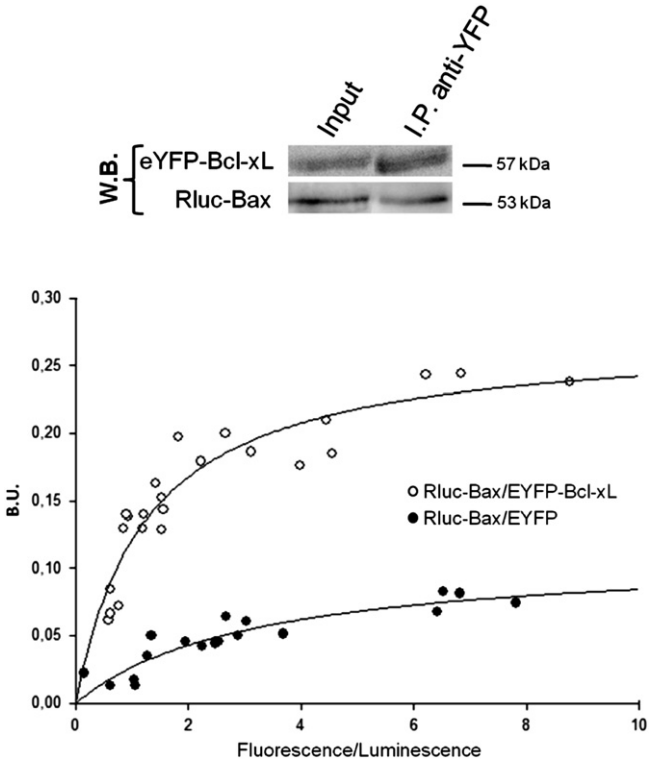


Fig. 3. (a) Co-immunoprecipitation of eYFP-Bcl-xL and Rluc-Bax: Protein lysate was prepared in CHAPS buffer (PBS, CHAPS 1%, proteases inhibitors) on HeLa cells cultured in 12 wells plate and transfected with 100 ng of pRluc-Bax and 500 ng of peYFP-Bcl-xL vectors. Co-immunoprecipitation was performed using anti-eYFP antibody (Santa Cruz Biotechnology) and 500 μg of protein lysate with the Catch and Release immunoprecipitation system (Upstate) according to the manufacturer's recommendations. (b) BRET Saturation curves: Saturation curves were performed on Hela cells using increasing amount of vectors encoding eYFP (black circles) alone, or eYFP-Bcl-xL (white circles) in the presence of a fixed amount of the vector encoding Rluc-Bax. The logarithmic shape of the regression curve for Rluc-Bax/eYFP-Bcl-xL complexes indicates a specific interaction between the two proteins.

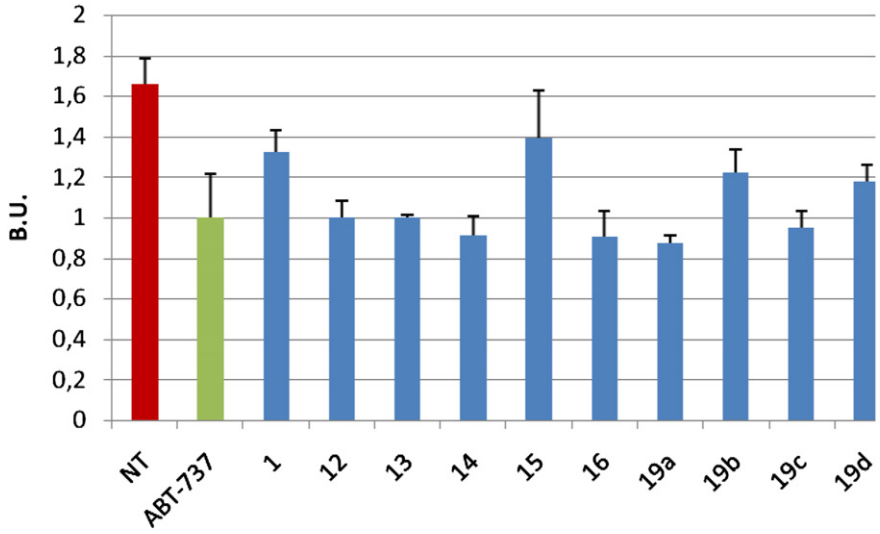


Fig. 4. BRET assay on Bax/Bcl-xL interaction NT: non treated, ABT-737 used as positive control.

a good starting point for developing structure–activity relationships on the other side of this skeleton.

- Second, regarding the nature of the aromatic/heteroaromatic substituents on the left part of the core structure: compounds **19a**–**d** showed various activities against Bax/Bcl-xL interactions. The fluorine atom in para position (compound **19a**) slightly improved activity while the *t*-butyl group at ortho position (compound **19b**) lost near half of activity. Compound **19c** showed an activity equivalent to ABT-737, indicating that a quinoline ring can replace the corresponding benzene ring. However, in this skeleton the replacement of the first benzene ring by a thiophene group (compound **19d**) reduces activity to near half.
- Third, concerning the number and position of the phenol groups: the 2,3-diphenolic compound **13** exhibit the same activity as **12** while the 3,4-diphenolic compound **14** and the 3-monophenolic compound **16** showed slightly better activity than **12** and ABT-737. In contrast, the 2,4-diphenolic compound **15** was found inactive in this assay. These results concerning this series of compounds containing different number and position of the OH phenolic groups are particularly interesting: they indicate that, for this type of molecules, three OH groups are not absolutely required for disruption of Bax/Bcl-xL interaction. However the OH at position 3 is very important for corresponding bioactivity.

3. Conclusion

The synthesis of a few selected diaryl/heteroaryl-containing phenol and polyphenol derivatives was achieved. Six of these new compounds showed activity comparable to ABT-737 with regard to their ability to disrupt Bax/Bcl-xL interactions in a BRET-based assay. These preliminary results indicate that molecules in these series represent attractive hit compounds for further optimization to develop new drugs that can overcome resistance of cancer cells to apoptosis. It should nevertheless be noted that our preliminary data suggests that these molecules exhibit much less cytotoxic activity against reference cell lines than ABT-737 (data not shown). This suggests that these tool compounds may not interfere efficiently with all the protein–protein interactions engaged by Bcl-xL (such as those involving BH3-only proteins) or by other targets of ABT-737 such as Bcl-2. Further study of this family of compounds and their activity on other members of anti-apoptotic Bcl-2 proteins (especially Bcl-2, Mcl-1) will be presented in due course.

4. Experimental section

All reagents were obtained commercially and used without further purification. All reactions have been carried out under a nitrogen atmosphere and anhydrous conditions. The solvents used were freshly distilled under anhydrous conditions, unless otherwise specified. The reaction mixtures have been magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. Reactions that require anhydrous conditions have been carried out by using oven dried (120 °C, 24 h) glassware. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, and the reactions have been monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of pentane and ethyl acetate (EA), with detection by UV light, or a *p*-anisaldehyde staining solution. Acros silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Nuclear magnetic resonance (NMR) spectra have been recorded with Bruker Avance 400 and 300 spectrometers. ^{1}H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS), using [δ (C***H***Cl$_3$) = 7.26 ppm] as internal reference. ^{13}C NMR spectra: δ (C) are given in ppm relative to TMS, using [δ (**C**DCl$_3$) = 77.0 ppm] as internal reference. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m) or br (broad). Mass spectral analyses have been performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO) in Rennes (France).

4.1. Chemistry

4.1.1. General procedure for synthesis of compounds 7–10, example: synthesis of compound 7

First, to a stirred solution of *p*-phenoxyphenyl magnesium bromide, prepared from *p*-bromodiphenylether (0.43 ml, 2 eq.) and Mg (87.1 mg, 3 eq.) in THF (15 ml), cooled at 0 °C under argon, was added 5-(4-fluorobenzyl)-2,3,4-trimethoxybenzaldehyde **2** (368 mg, 1.21 mmol). The reaction mixture was allowed to come back to rt and it was stirred for 2 h before quenching with saturated ammonium chloride solution and extraction with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated

under reduced pressure. The crude product was purified by flash column chromatography using a mixture pentane/EA 8/2 as eluent to afford the alcohol intermediate (495 mg, 86%) as a colorless viscous oil. A solution of alcohol obtained in this first step (326 mg, 0.69 mmol) and IBX (291 mg, 1.5 eq.) in a 3/1 mixture of THF/DMSO (4 ml) were heated under reflux for 1 h, until total consumption of alcohol. After cooling down to rt, the mixture was poured into water and filtered on celite. The solution was then extracted with Et_2O, washed with water and brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column using the 9/1 mixture pentane/EA as eluent to afford **7** (291 mg, 89%) as a light yellow viscous oil.

*4.1.1.1. (5-(4-Fluorobenzyl)-2,3,4-trimethoxyphenyl)(4-phenoxyphenyl)methanone (**7**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.9 Hz, 2H), 7.40 (dd, J = 7.5, 8.3 Hz, 2H), 7.20 (tt, J = 1.1, 7.4 Hz, 1H), 7.14 (dd, J = 5.5, 8.4 Hz, 2H), 7.10–7.05 (m, 2H), 7.00–6.94 (m, 4H), 6.85 (s, 1H), 3.90 (s, 3H), 3.89 (s, 2H), 3.78 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.1, 162.0, 161.3 (d, J = 243.9 Hz), 155.4, 153.9, 151.0, 146.2, 136.2 (d, J = 3.2 Hz), 132.2, 130.1 (d, J = 7.8 Hz), 130.0, 129.9, 128.8, 124.7, 124.6, 120.2, 117.0, 115.1 (d, J = 21.2 Hz), 61.9, 60.8, 60.7, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.4. HRMS [ESI (+) -MS]: $C_{29}H_{25}FO_5Na$ $[M + Na]^+$ m/z, calc. 495.1584 found. 495.1584.

*4.1.1.2. (5-(4-Fluorobenzyl)-2,3-dimethoxyphenyl)(4-phenoxyphenyl) methanone (**8**).* First, the reaction was performed with *p*-bromodiphenylether (0.26 ml, 2 eq.), Mg (38.5 mg, 2.2 eq.), 5-(4-fluorobenzyl)-2,3-dimethoxybenzaldehyde **3** (200 mg, 0.73 mmol) and THF (10 ml) to afford the alcohol as a crude product. Then, this alcohol (<0.73 mmol) was oxidized with IBX (306.6 mg, 1.5 eq.) in the mixture THF/DMSO 4/1 (10 ml) to afford ketone **8** (248 mg, 77% yield over 2 steps) as a light yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 8.9 Hz, 2H), 7.39 (dd, J = 7.5, 8.4 Hz, 2H), 7.19 (tt, J = 1.1, 7.4 Hz, 1H), 7.14 (dd, J = 5.4, 8.7 Hz, 2H), 7.08–7.05 (m, 2H), 6.98 (d, J = 8.9 Hz, 4H), 6.80 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 3.92 (s, 2H), 3.84 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.8, 162.2, 161.5 (d, J = 244.4 Hz), 155.4, 152.6, 145.0, 137.0, 136.1 (d, J = 3.2 Hz), 131.1, 132.3, 131.9, 130.2 (d, J = 7.9 Hz), 130.0, 124.6, 120.3, 120.2, 117.0, 115.3 (d, J = 21.3 Hz), 114.6, 61.7, 55.9, 40.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −116.9. HRMS [ESI (+) -MS]: $C_{28}H_{23}FO_4Na$ $[M + Na]^+$ m/z, calc. 465.1478 found. 465.1477.

*4.1.1.3. (3-(4-Fluorobenzyl)-4,5-dimethoxyphenyl)(4-phenoxyphenyl) methanone (**9**).* First, the reaction was performed with *p*-bromodiphenylether (0.26 ml, 2 eq.), Mg (38.5 mg, 2.2 eq.), 3-(4-fluorobenzyl)-4,5-dimethoxybenzaldehyde **4** (200 mg, 0.73 mmol) and THF (10 ml) to afford the alcohol as a crude product. Then, this alcohol (<0.73 mmol) was oxidized with IBX (306.6 mg, 1.5 eq.) in the mixture THF/DMSO 4/1 (10 ml) to afford ketone **9** (256 mg, 79% yield over 2 steps) as a light yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.76 (d, J = 8.9 Hz, 2H), 7.41 (dd, J = 7.5, 8.5 Hz, 2H), 7.32 (d, J = 2.0 Hz, 1H), 7.21 (tt, J = 1.1, 7.4 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.14 (dd, J = 5.4, 8.7 Hz, 2H), 7.11–7.08 (m, 2H), 7.00 (d, J = 8.9 Hz, 2H), 6.94 (t, J = 8.7 Hz, 2H), 3.97 (s, 2H), 3.90 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.5, 161.4, 161.3 (d, J = 244.0 Hz), 155.5, 152.7, 150.7, 136.2 (d, J = 3.2 Hz), 134.3, 133.2, 132.3, 132.1, 130.2, 130.1 (d, J = 8.1 Hz), 125.4, 124.6, 120.3, 117.0, 115.1 (d, J = 21.1 Hz), 112.1, 60.6, 55.9, 35.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.3. HRMS [ESI (+) -MS]: $C_{28}H_{23}FO_4Na$ $[M + Na]^+$ m/z, calc. 465.1478 found. 465.1478.

*4.1.1.4. (2,4-Bis(benzyloxy)-5-(4-fluorobenzyl)phenyl)(4-phenoxyphenyl)methanone (**10**).* First, the reaction was performed with *p*-bromodiphenylether (0.2 ml, 2 eq.), Mg (34.8 mg, 2.5 eq.), 2,4-bis(benzyloxy)-5-(4-fluorobenzyl)benzaldehyde **5** (249 mg, 0.58 mmol) and THF (10 ml) to afford the alcohol as a crude product. Then, 7/10 of this alcohol crude product (<0.4 mmol) was oxidized by using procedure 2 with IBX (168 mg, 1.5 eq.) in the mixture THF/DMSO 5/1 (12 ml) to afford ketone **10** (167 mg, 70% yield over 2 steps) as a light yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 8.8 Hz, 2H), 7.43–7.34 (m, 5H), 7.34 (s, 1H), 7.30–7.26 (m, 5H), 7.20 (tt, J = 1.1, 7.4 Hz, 1H), 7.16 (dd, J = 5.5, 8.7 Hz, 2H), 7.08–7.04 (m, 4H), 6.98 (d, J = 8.8 Hz, 2H), 6.95 (t, J = 8.8 Hz, 2H), 6.61 (s, 1H), 5.08 (s, 2H), 4.97 (s, 2H), 3.95 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.4, 161.3, 161.2 (d, J = 243.5 Hz), 159.5, 157.0, 155.8, 136.4, 136.3 (d, J = 3.2 Hz), 136.2, 133.7, 132.3, 131.9, 130.1 (d, J = 8.1 Hz), 128.5, 128.3, 128.1, 127.7, 127.3, 126.6, 124.2, 122.6, 121.6, 119.8, 117.1, 114.9 (d, J = 21.1 Hz), 98.3, 70.7, 70.3, 34.9. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −116.9. HRMS [ESI (+) -MS]: $C_{40}H_{31}FO_5Na$ $[M + Na]^+$ m/z, calc. 617.2104 found. 617.2103.

*4.1.2. General procedure for synthesis of compounds **11**, **18a–d**, exemple: synthesis of compound **11***

To a solution of bromo compound 1-bromo-3-(4-fluorobenzyl)-5-methoxybenzene **6** (464 mg, 1.57 mmol) in Et_2O (10 ml) under argon, was added dropwise *t*-BuLi (2.16 ml, 2.2 eq.) at. −78 °C. The mixture was stirred for 30 min at −78 °C before adding a solution of *p*-phenoxybenzaldehyde (373.7 mg, 1.2 eq.) in Et_2O (3 ml). The reaction mixture was allowed to come back to rt and stirred for 4 h and then quenched with saturated ammonium chloride solution and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the alcohol as a crude product. Then, this alcohol (<1.57 mmol) was oxidized with IBX (659 mg, 1.5 eq.) in the mixture THF/DMSO 3/1 (8 ml) to afford ketone **11** (150 mg, 23%) as a light yellow viscous oil.

*4.1.2.1. (3-(4-Fluorobenzyl)-5-methoxyphenyl)(4-phenoxyphenyl)methanone (**11**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.80 (d, J = 8.9 Hz, 2H), (dd, J = 7.6, 8.4 Hz, 2H), 7.21 (tt, J = 1.1, 7.4 Hz, 1H), 7.17–7.08 (m, 6H), 7.04–6.93 (m, 4H), 6.91 (t, J = 2.0 Hz, 1H), 3.97 (s, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.1, 161.6, 161.5 (d, J = 244.5 Hz), 159.6, 155.4, 142.5, 139.4, 135.9 (d, J = 3.3 Hz), 132.4, 131.8, 130.2 (d, J = 7.9 Hz), 130.0, 124.6, 122.9, 120.1, 118.9, 117.0, 115.3 (d, J = 21.3 Hz), 112.1, 55.4, 40.9. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −116.8. HRMS [ESI (+) -MS]: $C_{27}H_{21}FO_3Na$ $[M + Na]^+$ m/z, calc. 435.1372 found. 435.1373.

*4.1.2.2. (5-(4-Fluorobenzyl)-2,3,4-trimethoxyphenyl)(4-(4-fluorophenoxy)phenyl)methanone (**18a**).* First, the reaction was performed with bromo compound 1-bromo-5-(4-fluorobenzyl)-2,3,4-trimethoxybenzene **17** (405 mg, 1.14 mmol), *t*-BuLi (1.57 ml, 2.2 eq.), *p*-(4-fluorophenoxy)benzaldehyde (370 mg, 1.5 eq.) and Et_2O (10 ml) to afford the alcohol intermediate (306 mg, 54%) as a colorless viscous oil. Then, this alcohol (306 mg, 0.62 mmol) was oxidized with IBX (261 mg, 1.5 eq.) in the mixture THF/DMSO 5/1 (9 ml) to afford ketone **18a** (231 mg, 76%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (d, J = 8.9 Hz, 2H), (dd, J = 5.4, 8.7 Hz, 2H), 7.10–7.02 (m, 4H), 6.98–6.90 (m, 4H), 6.86 (s, 1H), 3.90 (s, 3H), 3.89 (s, 2H), 3.79 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.0, 162.2, 161.4 (d, J = 243.9 Hz), 159.5 (d, J = 243.5 Hz), 153.9, 151.1 (d, J = 2.7 Hz), 151.0, 146.2, 136.2 (d, J = 3.2 Hz), 132.3, 132.2, 130.1 (d, J = 7.8 Hz), 130.0, 128.8, 124.7, 121.8 (d, J = 8.4 Hz), 116.7 (d, J = 23.4 Hz), 116.6, 115.1 (d, J = 21.2 Hz), 61.9, 60.8, 60.7, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.3, −118.1. HRMS [ESI (+) -MS]: $C_{29}H_{24}F_2O_5Na$ $[M + Na]^+$ m/z, calc. 513.1489 found. 513.1488.

*4.1.2.3. (4-(2-Tert-butylphenoxy)phenyl)(5-(4-fluorobenzyl)-2,3,4-trimethoxyphenyl)methanone (**18b**).* First, the reaction was performed

with bromo compound 1-bromo-5-(4-fluorobenzyl)-2,3,4-trimethoxybenzene **17** (110 mg, 0.31 mmol), *t*-BuLi (0.43 ml, 2.2 eq.), *p*-(2-*t*-butylphenoxy)benzaldehyde (86.6 mg, 1.1 eq.) and Et_2O (5 ml) to afford the alcohol intermediate (61 mg, 37%) as a colorless viscous oil. Then, this alcohol (61 mg, 0.11 mmol) was oxidized with IBX (48 mg, 1.5 eq.) in the mixture THF/DMSO 4/1 (2.5 ml) to afford ketone **18b** (40 mg, 66%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.81 (d, J = 8.7 Hz, 2H), 7.44 (dd, J = 1.9, 7.6 Hz, 1H), 7.24–7.10 (m, 4H), 6.99–6.88 (m, 6H), 3.92 (s, 3H), 3.91 (s, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 194.0, 162.3, 161.3 (d, J = 244.0 Hz), 154.2153.8, 151.0, 146.6, 141.6, 136.2 (d, J = 3.2 Hz), 132.2, 131.9, 130.1 (d, J = 7.8 Hz), 129.8, 128.9, 127.6, 127.3, 124.7, 124.5, 121.4, 117.1, 115.1 (d, J = 21.2 Hz), 61.9, 60.8, 60.7, 35.2, 34.7, 30.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.3. HRMS [ESI (+) -MS]: $C_{33}H_{35}FO_5Na$ $[M + Na]^+$ m/z, calc. 551.2210 found. 551.2210.

*4.1.2.4. (5-(4-Fluorobenzyl)-2,3,4-trimethoxyphenyl)(4-(quinolin-8-yloxy)phenyl)methanone (**18c**).* First, the reaction was performed with bromo compound 1-bromo-5-(4-fluorobenzyl)-2,3,4-trimethoxybenzene **17** (355 mg, 1 mmol), *t*-BuLi (1.38 ml, 2.2 eq.), *p*-quinolin-8-yloxy-benzaldehyde (274 mg, 1.1 eq.) and Et_2O (10 ml) to afford the alcohol intermediate (258 mg, 49%) as a colorless viscous oil. Then, this alcohol (258 mg, 0.49 mmol) was oxidized with IBX (207 mg, 1.5 eq.) in the mixture THF/DMSO 4/1 (5 ml) to afford ketone **18c** (212 mg, 82%) as a light yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.93 (d, J = 3.9 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.55–7.45 (m, 3H), 7.32 (d, J = 7.5 Hz, 1H), 7.16–7.11 (m, 1H), 7.05 (d, J = 8.7 Hz, 2H), 6.93 (d, J = 8.7 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 3.89 (s, 5H), 3.77 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.2, 162.3, 161.3 (d, J = 244.0 Hz), 159.7, 153.9, 151.6, 151.0, 150.4, 146.1, 141.1, 136.2 (d, J = 3.2 Hz), 132.5, 132.2, 130.1 (d, J = 7.8 Hz), 129.9, 129.8, 128.8, 126.6, 124.7, 124.2, 121.9, 118.7, 117.5, 115.1 (d, J = 21.2 Hz), 61.8, 60.8, 60.7, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.4. HRMS [ESI (+) -MS]: $C_{32}H_{26}FNO_5Na$ $[M + Na]^+$ m/z, calc. 546.1693 found. 546.1691.

*4.1.2.5. (5-(4-Fluorobenzyl)-2,3,4-trimethoxyphenyl)(5-phenoxythiophen-2-yl)methanone (**18d**).* First, the reaction was performed with bromo compound 1-bromo-5-(4-fluorobenzyl)-2,3,4-trimethoxybenzene **17** (329 mg, 0.93 mmol), *t*-BuLi (1.27 ml, 2.2 eq.), 5-phenoxythiophene-2-carbaldehyde (209 mg, 1.1 eq.) and Et_2O (5 ml) to afford the alcohol intermediate (299 mg, 67%) as a light yellow viscous oil. Then, this alcohol (258 mg, 0.54 mmol) was oxidized with IBX (226 mg, 1.5 eq.) in the mixture THF/DMSO 5/1 (6 ml) to afford ketone **18d** (223 mg, 87%) as a light yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40 (dd, J = 7.5, 8.4 Hz, 2H), 7.23 (tt, J = 1.1, 7.4 Hz, 1H), 7.21–7.17 (m, 3H), 7.14 (dd, J = 5.4, 8.7 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 6.90 (s, 1H), 6.41 (d, J = 4.2 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 2H), 3.85 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 186.6, 171.5, 161.3 (d, J = 243.9 Hz), 157.1, 153.8, 150.9, 146.4, 136.2 (d, J = 3.2 Hz), 135.2, 133.3, 130.1 (d, J = 7.9 Hz), 130.0, 129.8, 128.2, 125.5, 124.5, 119.1, 115.1 (d, J = 21.2 Hz), 111.5, 62.2, 60.8, 60.7, 35.2. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.2. HRMS [ESI (+) -MS]: $C_{27}H_{23}FO_5SNa$ $[M + Na]^+$ m/z, calc. 501.1148 found. 501.1148.

*4.1.3. General procedure for synthesis of compounds **12**–**14**, **16**, **19a**–**d**, example: synthesis of compound **12***

To a stirred solution of compound **7** (243 mg, 0.51 mmol) was added dropwise BBr_3 (4.6 ml, 9 eq., 1 M in CH_2Cl_2) in CH_2Cl_2 (5 ml) at 0 °C under nitrogen. The reaction mixture was allowed to warm up to rt and stirred overnight. The mixture was then cooled again at 0 °C and water was added, then CH_2Cl_2, and the mixture was stirred for 1 h before extracting with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified on a silica gel column using the mixture pentane/AE 7/3 as eluent to afford compound **12** (170 mg, 77%) as a light yellow solid. Mp: 139–141 °C.

*4.1.3.1. (5-(4-Fluorobenzyl)-2,3,4-trihydroxyphenyl)(4-phenoxyphenyl)methanone (**12**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12,63 (br s, 1H): 7.61 (d, J = 8.6 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.26–6.91 (m, 9H), 6.02 (br s, 2H), 3.89 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 199.0, 161.3 (d, J = 243.9 Hz), 161.1, 159.7, 115.5, 149.9, 148.2, 135.6 (d, J = 3.2 Hz), 132.0, 131.5, 131.2, 130.1 (d, J = 7.8 Hz), 130.0, 126.3, 124.6, 120.1, 119.2, 117.1, 115.1 (d, J = 21.2 Hz), 112.6, 34.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.1. HRMS [ESI (+) -MS]: $C_{26}H_{19}FO_5Na$ $[M + Na]^+$ m/z, calc. 453.1109 found. 453.1112.

*4.1.3.2. (5-(4-Fluorobenzyl)-2,3-dihydroxyphenyl)(4-phenoxyphenyl)methanone (**13**).* The reaction was performed with **8** (230 mg, 0.52 mmol), a 1M solution of BBr_3 in DCM (3.1 ml, 6 eq.) and DCM (10 ml) to afford **13** (186 mg, 86%) as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.01 (br, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.43 (dd, J = 7.4, 8.2 Hz, 2H), 7.23 (tt, J = 1.1, 7.4 Hz, 1H), 7.13–7.06 (m, 4H), 7.03 (d, J = 8.8 Hz, 2H), 7.00–6.92 (m, 4H), 5.76 (br, 1H), 3.84 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 199.8, 161.6, 161.5 (d, J = 244.5 Hz), 155.4, 148.6, 145.6, 136.3 (d, J = 3.2 Hz), 131.8, 131.5, 130.2, 130.1 (d, J = 8.1 Hz), 124.7, 123.7, 120.7, 120.2, 118.8, 117.1, 115.3 (d, J = 21.2 Hz), 40.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −116.9. HRMS [ESI (+) -MS]: $C_{26}H_{19}FO_4Na$ $[M + Na]^+$ m/z, calc. 437.1165 found. 437.1162.

*4.1.3.3. (3-(4-Fluorobenzyl)-4,5-dihydroxyphenyl)(4-phenoxyphenyl)methanone (**14**).* The reaction was performed with **9** (247 mg, 0.56 mmol), a 1M solution of BBr_3 in DCM (5.6 ml, 10 eq.) and DCM (10 ml) to afford **14** (156 mg, 67%) as a light orange solid. Mp: 171–173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.72 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 7.5, 8.4 Hz, 2H), 7.21 (tt, J = 1.1, 7.4 Hz, 1H), 7.18 (dd, J = 5.4, 8.7 Hz, 2H), 7.11 (d, J = 1.9 Hz, 1H), 7.11–7.07 (m, 2H), 6.99 (d, J = 8.8 Hz, 2H), 6.94 (t, J = 8.7 Hz, 2H), 6.04 (br, 1H), 3.98 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 195.1, 161.5 (d, J = 244.5 Hz), 161.4, 155.5, 147.3, 143.3, 135.5 (d, J = 3.2 Hz), 132.3, 132.1, 130.2, 130.1 (d, J = 8.1 Hz), 129.4, 126.8, 126.4, 124.6, 123.7, 120.3, 120.1, 118.8, 117.1, 115.2 (d, J = 21.1 Hz), 35.0. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −116.9. HRMS [ESI (+) -MS]: $C_{26}H_{19}FO_4Na$ $[M + Na]^+$ m/z, calc. 437.1165 found. 437.1166.

*4.1.3.4. (3-(4-Fluorobenzyl)-5-hydroxyphenyl)(4-phenoxyphenyl)methanone (**16**).* The reaction was performed with **11** (50 mg, 0.12 mmol), a 1 M solution of BBr_3 in DCM (0.36 ml, 3 eq.) and DCM (3 ml) to afford **16** (26.5 mg, 55%) as a white solid. Mp: 120–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.77 (d, J = 8.8 Hz, 2H), 7.41 (t, J = 8.1 Hz, 2H), 7.22 (tt, J = 1.1, 7.4 Hz, 1H), 7.15–7.06 (m, 6H), 7.01–6.91 (m, 4H), 6.86 (t, J = 1.5 Hz, 1H), 6.34 (br s, 1H), 3.92 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 195.7, 161.9, 161.5 (d, J = 244.5 Hz), 156.1, 155.4, 143.0, 139.3, 135.8 (d, J = 3.3 Hz), 135.6, 131.5, 130.3 (d, J = 7.9 Hz), 130.1, 124.7, 122.8, 120.2, 119.9, 117.0, 115.3 (d, J = 21.3 Hz), 114.6, 40.7. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −116.8. HRMS [ESI (+) -MS]: $C_{26}H_{19}FO_3Na$ $[M + Na]^+$ m/z, calc. 399.1396 found. 399.1396.

*4.1.3.5. (5-(4-Fluorobenzyl)-2,3,4-trihydroxyphenyl)(4-(4-fluorophenoxy)phenyl)methanone (**19a**).* The reaction was performed with **18a** (231 mg, 0.47 mmol), a 1 M solution of BBr_3 in DCM (4.23 ml, 9 eq.) and DCM (5 ml) to afford **19a** (109 mg, 51%) as a yellow solid. Mp: 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 12.48 (br s, 1H), 7.59 (d, J = 8.9 Hz, 2H), 7.17–7.03 (m, 6H), 6.99–6.90 (m, 5H),

6.09 (br s, 1H), 5.66 (br s, 1H), 3.88 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 198.8, 161.4 (d, J = 244.1 Hz), 161.3, 159.5 (d, J = 243.4 Hz), 151.2 (d, J = 2.7 Hz), 149.8, 147.9, 135.7 (d, J = 3.3 Hz), 132.1, 131.5, 131.1, 130.1 (d, J = 7.8 Hz), 126.2, 121.8 (d, J = 8.4 Hz), 119.1, 116.7 (d, J = 23.4 Hz), 116.6, 115.1 (d, J = 21.2 Hz), 112.6, 34.4. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.2, −118.1. HRMS [ESI (+) -MS]: $C_{26}H_{18}F_2O_5Na$ $[M + Na]^+$ m/z, calc. 471.1020 found. 471.1019.

*4.1.3.6. (4-(2-Tert-butylphenoxy)phenyl)(5-(4-fluorobenzyl)-2,3,4-trihydroxyphenyl)methanone (**19b**).* The reaction was performed with **18b** (40 mg, 0.08 mmol), a 1 M solution of BBr_3 in DCM (0.7 ml, 9 eq.) and DCM (5 ml) to afford **19b** (33 mg, 90%) as a yellow solid. Mp: 89–91 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.92 (br s, 3H), 7.59 (d, J = 8.6 Hz, 2H), 7.45 (dd, J = 1.7, 7.8 Hz, 1H), 7.22 (dt, J = 1.8, 7.4 Hz, 1H), 7.17–7.11 (m, 3H), 6.98 (d, J = 8.6 Hz, 2H), 6.96–6.85 (m, 4H), 3.88 (s, 2H), 1.41 (s, 9H). ^{13}C NMR [75 MHz, $(CD_3)_2CO$)] δ (ppm): 200.3, 163.1 (d, J = 241.8 Hz), 162.7, 156.3, 153.1, 153.0, 140.1, 138.7 (d, J = 3.0 Hz), 134.5, 133.4, 132.4 (d, J = 7.8 Hz), 129.4, 129.3, 127.3, 126.4, 123.1, 121.8, 118.9, 116.6 (d, J = 21.2 Hz), 113.6, 36.3, 36.1, 31.6. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.5. HRMS [ESI (+) -MS]: $C_{30}H_{27}FO_5Na$ $[M + Na]^+$ m/z, calc. 509.1740 found. 509.1741.

*4.1.3.7. (5-(4-Fluorobenzyl)-2,3,4-trihydroxyphenyl)(4-(quinolin-8-yloxy)phenyl)methanone (**19c**).* The reaction was performed with **18c** (182 mg, 0.35 mmol), a 1 M solution of BBr_3 in DCM (3.5 ml, 10 eq.) and DCM (7 ml) to afford **19c** (155 mg, 89%) as a yellow solid. Mp: 69–71 °C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$)] δ (ppm): 12.17 (br s, 1H), 9.83 (br s, 1H), 9.05 (br s, 1H), 8.87 (dd, J = 1.4, 4.1 Hz, 1H), 8.50 (dd, J = 1.3, 8.3 Hz, 1H), 7.95 (d, J = 7.4 Hz, 1H), 7.70 (t, J = 8.0 Hz, 2H), 7.62 (dd, J = 4.2, 8.3 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.00 (t, J = 8.8 Hz, 2H), 6.94 (d, J = 8.7 Hz, 2H), 6.81 (s, 1H), 3.78 (s, 2H). ^{13}C NMR [75 MHz, $(CD_3)_2SO$)] δ (ppm): 197.8, 160.8 (d, J = 244.0 Hz), 159.6, 158.9, 150.9, 150.8, 148.3, 148.1, 142.0, 136.6 (d, J = 3.2 Hz), 135.2, 133.1, 132.3, 131.4, 130.2 (d, J = 7.8 Hz), 129.9, 128.6, 125.0, 124.7, 122.7, 120.6, 119.7, 117.4, 114.7 (d, J = 21.2 Hz), 111.8, 34.0. ^{19}F NMR [282.4 MHz, $(CD_3)_2SO$)] δ (ppm): −117.6. HRMS [ESI (+) -MS]: $C_{29}H_{20}FNO_5Na$ $[M + Na]^+$ m/z, calc. 504.1223 found. 504.1223.

*4.1.3.8. (5-(4-Fluorobenzyl)-2,3,4-trihydroxyphenyl)(5-phenoxythiophen-2-yl)methanone (**19d**).* According to procedure 3, the reaction was performed with **18d** (198 mg, 0.41 mmol),a 1*M* solution of BBr_3 in DCM (3.73 ml, 9 eq.) and DCM (10 ml) to afford **19d** (137 mg, 76%) as a yellow solid. Mp: 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.10 (br s, 1H), 7.42 (dd, J = 7.5, 8.5 Hz, 2H), 7.35 (d, J = 4.3 Hz, 1H), 7.28–7.16 (m, 6H), 6.97 (t, J = 8.7 Hz, 2H), 6.46 (d, J = 4.3 Hz, 1H), 6.10 (br s, 1H), 5.71 (br s, 1H), 3.94 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 188.7, 170.7, 161.4 (d, J = 243.9 Hz), 157.1, 149.0, 147.6, 135.8 (d, J = 3.2 Hz), 134.1, 131.2, 130.9, 130.2 (d, J = 7.9 Hz), 130.1125.5, 124.1, 119.5, 119.0, 115.2 (d, J = 21.2 Hz), 112.5, 111.6, 34.3. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −117.1. HRMS [ESI (+) -MS]: $C_{24}H_{17}FO_5SNa$ $[M + Na]^+$ m/z, calc. 459.0678 found. 459.0677.

*4.1.4. Synthesis of (5-(4-Fluorobenzyl)-2,4-dihydroxyphenyl)(4-phenoxyphenyl)methanone (**15**)*

A solution of **10** (100 mg, 0.17 mmol), Pd on C (20 mg, 7%) in EtOH (5 ml) was stirred under hydrogen atmosphere overnight at rt. The reaction mixture was then filtered on celite. The residue was purified by flash chromatography using a pentane/EA 7/3 mixture to afford **15** (34 mg, 49%) as a light green solid. Mp: 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 12.50 (br, 1H), 7.57 (d, J = 8.7 Hz, 2H), 7.43 (dd, J = 7.6, 8.3 Hz, 2H), 7.30 (s, 1H), 7.22 (tt, J = 1.1, 7.4 Hz, 1H), 7.15–7.06 (m, 4H), 7.05 (d, J = 8.7 Hz, 2H), 6.95 (t, J = 8.7 Hz, 2H), 6.43 (s, 1H), 6.39 (br, 1H), 3.85 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 198.7, 164.5, 161.4 (d, J = 244.4 Hz), 161.0, 160.9, 155.5, 135.8, 135.4 (d, J = 3.2 Hz), 132.2, 131.3, 130.1, 130.0 (d, J = 7.8 Hz), 124.6, 120.1, 119.4, 117.2, 115.3 (d, J = 21.2 Hz), 113.2, 34.5. ^{19}F NMR (282.4 MHz, $CDCl_3$) δ (ppm): −116.8. HRMS [ESI (+) -MS]: $C_{26}H_{19}FO_4Na$ $[M + Na]^+$ m/z, calc. 437.1165 found. 437.1166.

4.2. BRET assay

Briefly, Hela cells were seeded on 6-well plates and transfected with 200°ng/well of plasmid pRLuc-Bax coding for BRET donor and 1μg/well of peYFP-Bcl-xL coding for BRET acceptor (or with pCMV-Bcl-xL for control). Twenty-four hours after transfection, cells were trypsinized and re-seeded into white 96 flat well plate, incubated for another day, and then treated with drugs for 16 h at 10 μM. Light emission at 485 nm and 530 nm was measured consecutively by using the Mithras fluorescence-luminescence detector LB 940 (Berthold) after adding the luciferase substrate, coelenterazine H (Uptima) at a final concentration of 5 μM. BRET ratios were calculated as described [11].

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Appendix. Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejmech.2012.02.036.

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