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(*E*)-3-Halo-2-styryl-4*H*-chromen-4-ones: synthesis and transformation to novel pyrazoles

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ABSTRACT

New methods for the synthesis of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones were established. The reaction of these compounds with hydrazine hydrate afforded new and unexpected 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-1*H*-pyrazoles, which upon acid hydrolysis gave 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1*H*-pyrazoles. The reaction mechanisms for these transformations, involving 1,6- followed by 1,4-conjugate additions, are discussed and the structures of all new compounds were established by NMR studies.

1. Introduction

(*E*)-3-Halo-2-styryl-4*H*-chromen-4-ones can be valuable intermediates to be converted into other functionalities by simple chemical transformations,[1] however there are only few methods to prepare this type of compounds.[1,2] These compounds can be synthesized by direct C-3 halogenation of (*E*)-2-styryl-4*H*-chromen-4-ones or indirectly by halogenation of their intermediates, which will then be cyclized to the desired (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones. Some typical halogenation methods of chromen-4-ones, flavones or 2-styryl-4*H*-chromen-4-ones, involve the use of molecular halogens (Br_2 in CCl_4 or Br_2 in AcOH, I_2–CAN/CH_3CN or I_2/NEt_3).[3–6] However, molecular halogens have environmental drawbacks and in particular bromine is hazardous and difficult to manipulate. To overcome these problems other methodologies have been developed involving the in situ generation of halogen or halogen cationic species, which are used for the halogenation of other organic substrates, such as PTB/AcOH, or $R_4NBr/PhI(OAc)_2$.[7,8] Recent reports describe the synthesis of (*E*)-3-bromo-2-styryl-4*H*-chromen-4-ones through Baker–Venkataraman rearrangement of 2-acetylphenyl cinnamates, followed by one-pot bromination/cyclization with phenyltrimethylammonium tribromide in THF at room temperature.[1] Further disadvantages of these established methods involve the use of hazardous and expensive chemicals, complicated work-up procedures, and solvents. Thus, the development of new halogenation methods focused on environmentally friendly methods and materials with improved yields is highly desirable.

Pyrazoles have been extensively studied and several routes for their synthesis have been developed due to their widespread applications in the fields of agriculture, industry, and medicine.[9–15] Over the past two decades, pyrazole-containing compounds have been highlighted by their remarkable anticancer effects through inhibiting different types of enzymes that play important roles in cell division. Therefore, certain pyrazoles have been implemented as antileukemic, antitumor, and antiproliferative agents,[16,17] while other have demonstrated to possess significant monoamine oxidase and HMG-CoA reductase inhibitory activity, making them good candidates for the treatment of neurodegenerative diseases (such as Parkinson's and Alzheimer's disease)[18,19] and hypercholesterolemia.[20] *N*-Substituted pyrazoles have been used as non-steroidal anti-inflammatory agents and in the treatment of rheumatoid arthritis. Some well-known drugs, such as Sildenafil (Viagra®), Celecoxib (Celebrex®), and Rimonabant (Acomplia®) are also pyrazole derivatives.[9] Arylpyrazoles are also key structures in a large variety of compounds having important medicinal and pesticidal properties. For instance, 1,5-diarylpyrazoles were identified as potent and selective cyclooxygenase 2 inhibitors[21] and the

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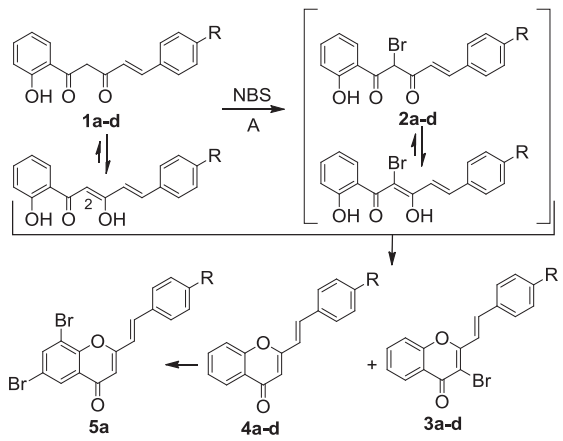
use of *C*- and/or *N*-(2-hydroxyphenyl)pyrazoles as ultraviolet stabilizers,[22,23] as analytical reagents in the chelation of transition metal ions,[24] analgesic agents, platelet aggregation inhibitors,[25] and also potent inhibitors of Hsp90 ATP-ase activity[26–30] highlight these particular compounds as targets for the preparation of new derivatives or/and to develop new strategies for their synthesis.

Previously our group studied the synthesis of 3(5)-(2-hydroxyphenyl)pyrazoles through the reaction of hydrazines with several chromone derivatives, including 2- and 3-styryl-4*H*-chromen-4-ones,[31,32] 2-(methyl- and phenyl)-4*H*-chromen-4-ones,[33] 3-aroyl-5-hydroxyflavones,[34] 3-(3-aryl-3-oxopropenyl)chromen-4-ones,[35] 3-benzylchromen-4-ones, and their thio analogues[36] and isoflavones.[37] With these procedures, 3,4- and 3,5-disubstituted and 3,4,5-trisubstituted pyrazoles were obtained. These results lead us to study the reaction of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones with hydrazine hydrate in order to prepare similar pyrazoles. Herein we describe our results in the synthesis of 3-bromo- and 3-iodo-2-styryl-4*H*-chromen-4-ones and in their reaction with hydrazine hydrate, leading to new 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-1*H*-pyrazoles.

2. Results and discussion

2.1. Synthesis of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones

Due to the high reactivity of 2-bromo-1,3-dicarbonyl compounds they are valuable building blocks in organic synthesis.[38] Thus we thought to prepare (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones by cyclodehydration of 2-bromo-1-(2-hydroxyphenyl)-5-phenylpent-4-ene-1,3-dione (**2a**, Scheme 1). On the other hand, NXS (X=Br or I) are easily accessible halogenating agents and easy to handle, being appropriate for the halogenation of 1,3-dicarbonyl compounds. A major advantage of using NXS is that the by-product succinimide can be easily filtered and recycled to NXS. Moreover 3-bromo-2-vinylchromen-4-ones can be prepared by cyclization of 2-bromo-1,3-diones using Br_2 in dioxane or NBS in CCl_4. However, the products were obtained as mixtures that could not be separated even after repeated crystallization.[39] Aware of these advantages and limitations, we decided to investigate a better methodology for the halogenation of 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones **1a**–**d** using NBS as halogenating agent.



a) R=H, **b)** R = OMe, **c)** R = Cl, **d)** R = NO_2

A: NBS (1.5 equiv), MW 800 W, 40 min.

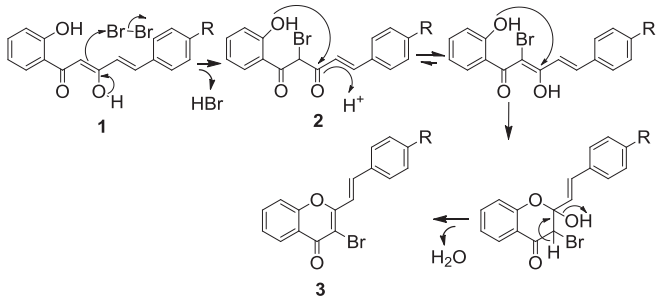
Scheme 1. Synthesis of (*E*)-3-bromo-2-styryl-4*H*-chromen-4-ones **3a**–**d**.

Solvent-free strategies are an important alternative to the use of organic solvents in organic transformations considering the demands for sustainable and ecologically friendly organic syntheses. Solvent-free halogenation of aromatic compounds has not been extensively studied but it is known that some brominations can be carried out under such conditions.[40] Based on the work of Pravst et al.[40] we studied the solvent-free bromination of 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones **1a**–**d** with NBS under microwave irradiation (Scheme 1). After an accurate study (Table 1), the optimal results were obtained in the reaction of diketone **1a** with NBS (1.5 molar equiv) at 800 W power in an open vessel after 40 min of irradiation (Table 1, entry 6). Under these conditions the TLC revealed the presence of two new major products and a very small amount of the starting material. After purification, the NMR spectra of the two major isolated products confirmed the presence of (*E*)-3-bromo-2-styryl-4*H*-chromen-4-one **3a** (78%) with high R_f and (*E*)-2-styryl-4*H*-chromen-4-one **4a** (16%). Increasing the amount of NBS (2.2 equiv) at 800 W in order to ensure the quantitative bromination of the diketone **1a** and to avoid the formation of (*E*)-2-styryl-4*H*-chromen-4-one **4a** (Table 1, entry 7), C-6 and C-8 bromination occurs and 6,8-dibromo-2-styryl-4*H*-chromen-4-one **5a** was obtained in 12% yield (one can see the signals of H-5 and H-7 as two doublets at 8.27 and 8.02 ppm, with a ^4J=2.2 Hz). (*E*)-2-Styryl-4*H*-chromen-4-one **4a** is probably formed by cyclodehydration of the non-brominated diketone **1a**, which can be promoted by the high microwave power used. The formation of (*E*)-3-bromo-2-styrylchromone **3a** occurs via the cyclodehydration of the halogenated diketone **2a**, which is promoted by the HBr generated in the reaction media (Scheme 2). The formation of **5a** is the result of an electrophilic aromatic substitution at the most activated positions of the formed chromone **4a**.

Table 1
Bromination of 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones **1a**–**d** with NBS under microwave irradiation in open vessel conditions

Entry	Compound	NBS (molar equiv)	Solvent	Power MW (W)	Time (min)	Yield (%)/ product[b]
1	**1a**	1.1	—	800	40	31/**3a** 30/**4a**
2	**1a**[a]	1.1	—	800	10	39/**3a** 4/**4a**
3	**1a**	1.1	—	300	30+30	36/**3a** 27/**4a**
4	**1a**	1.5	—	300	45	21/**3a**
5	**1a**	1.5	—	450	40	37/**3a**
6	**1a**	1.5	—	800	30+10	78/**3a** 16/**4a**
7	**1a**	2.2	—	800	17	21/**4a** 12/**5a**
8	**1a**	2.2	—	600	40	7/**3a** 16/**4a**
9	**1a**	1.5	DMF	600	40	High degradation
10	**1a**	1.1	DMF	600	30	High degradation
11	**1a**	1.1	DMF	300	10+30	34/**3a** 41/**4a**
12	**1b**	1.5	—	800	40	88/**3b** 7/**4b**
13	**1c**	1.5	—	800	40	51/**3c** 5/**4c**
14	**1d**	1.5	—	800	40	31/**3d** 42/**4d**
15	**1e**	1.5	—	800	40	21/**3e** 42/**3f**

[a] 3-Bromo-2-phenethyl-4*H*-chromen-4-one (13% yield) was also isolated.
[b] Yields determined on isolated products.

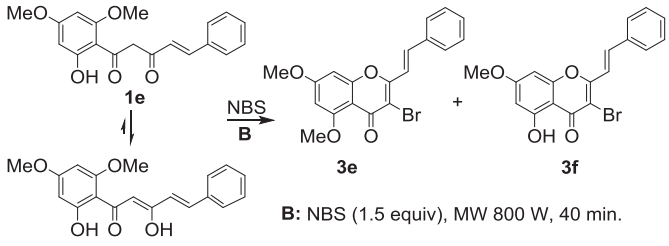


Scheme 2. Proposed mechanism for the formation of (*E*)-3-bromo-2-styryl-4*H*-chromen-4-ones **3a**–**d**.

Using DMF as solvent and buffer for the formed HBr, to prevent the cyclodehydration reaction, a high degradation of the reaction mixture was observed with 600 W irradiation power (Table 1, entries 9, 10). At 300 W the desired (*E*)-3-bromo-2-styryl-4*H*-chromen-4-one **3a** was obtained in low yield (34%) together with (*E*)-2-styryl-4*H*-chromen-4-one **4a** (41%) (Table 1, entry 11).

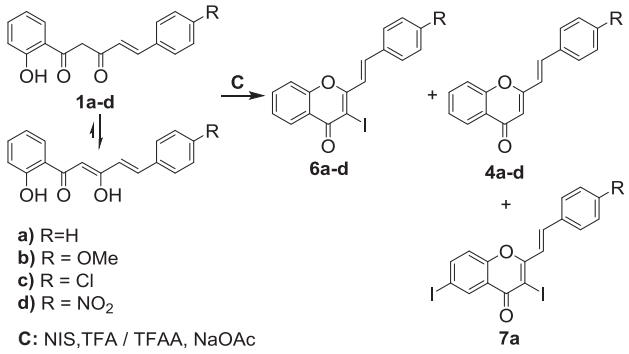
The optimal conditions established for **1a** were applied to the halogenation of diketones **1b**–**d** and the obtained results highlight the effect of the *p*-substituent of the styryl group in the yield of the C-2 bromination reaction. The high yield was obtained in the case of electron donating substituents, which increase the nucleophilicity of C-2 (see Table 1 and the structure of the enolic form of **1a**–**d**).

The bromination of diketone **1e** was studied under the optimal conditions described above to evaluate the method selectivity (Scheme 3). After the reaction workup, two products **3e** (21%) and **3f** (42%) were isolated (Table 1, entry 15). This result indicates that this method is selective for the bromination at C-3 position and the formation of compound **3f** may be explained by the cleavage of the 5-OMe group due to the HBr formation in the reaction medium.



Scheme 3. Selective C-2 bromination of 1-(2-hydroxy-4,6-dimethoxyphenyl)-5-phenylpent-4-ene-1,3-dione **1e** and cyclization into (*E*)-3-bromo-2-styryl-4*H*-chromen-4-ones **3e** and **3f**.

Based on the obtained results we tried the synthesis of (*E*)-3-iodo-2-styryl-4*H*-chromen-4-ones by using NIS as iodination agent. Firstly 1-(2-hydroxyphenyl)-5-phenylpent-4-ene-1,3-dione **1a** was reacted with NIS at room temperature, under solvent-free conditions during 5 days. After TLC purification three main compounds (*E*)-3-iodo-2-styryl-4*H*-chromen-4-one **6a** (11%), (*E*)-2-styryl-4*H*-chromen-4-one **4a** (32%), and (*E*)-3,6-diiodo-2-styryl-4*H*-chromen-4-one **7a** (24%) were identified. The 6-iodination of the activated phenolic ring is not surprising, since similar results were reported in the bromination of 5-hydroxy-2,7-dimethylchromone with NBS under weakly acidic media.[41] However in the presence of a strongly acidic medium, using the catalytic system of TFA/TFAA, NaOAc it was possible to regioselectively halogenate the 3-position of (*E*)-2-styryl-4*H*-chromen-4-ones.[41] So we performed the iodination of 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones **1a**–**d** with 1.5 molar equiv of NIS, in the presence of TFA/TFAA, NaOAc (Scheme 4). The reaction was followed by TLC and, after consumption of the starting material, (*E*)-3-iodo-2-styryl-4*H*-chromen-4-ones **6a**–**d** were obtained in good yields (59–70%) (Table 2). We also observed the formation of (*E*)-2-styryl-4*H*-chromen-4-ones **4a**–**d** as minor compounds (10–32% yield).



Scheme 4. Synthesis of (*E*)-3-iodo-2-styryl-4*H*-chromen-4-ones **6a**–**d** starting from 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones **1a**–**d** and NIS in TFA/TFAA and NaOAc.

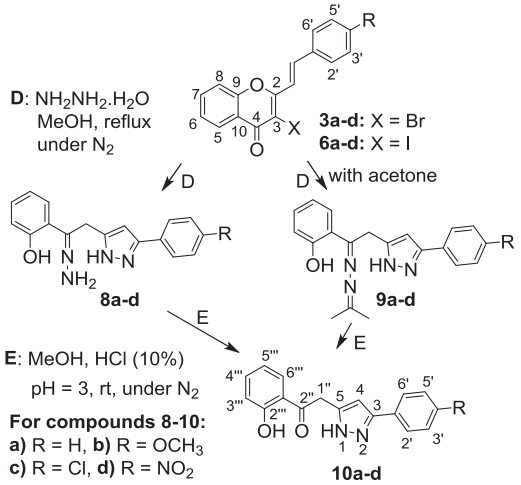
Table 2
Yields obtained in the synthesis of (*E*)-3-iodo-2-styryl-4*H*-chromen-4-ones **6a**–**d** from the reaction of 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones **1a**–**d** with NIS in the presence of TFA/TFAA and NaOAc

Starting material	R	Reaction time (h)	Yield[a] of **6a**–**d** (%)	Yield[a] of **4a**–**d** (%)
1a	H	6	70	23
1b	OMe	3	62	11
1c	Cl	4	61	10
1d	NO_2	6	59	32

[a] Yields determined on isolated products.

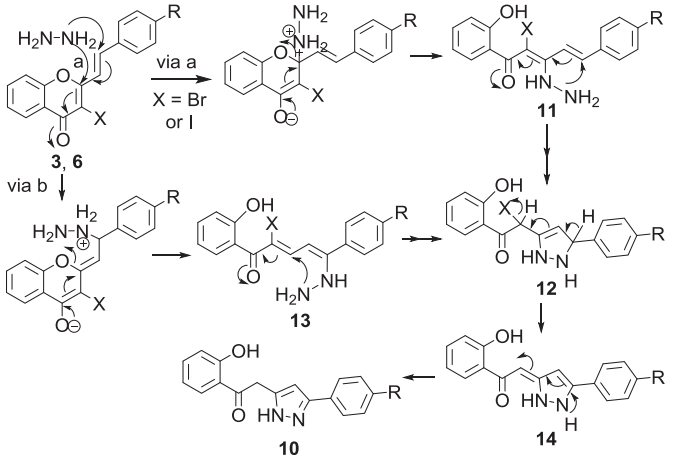
2.2. Transformation of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones into pyrazoles

This study started with the reaction of (*E*)-3-bromo-2-styryl-4*H*-chromen-4-one **3a** with an excess of hydrazine hydrate in refluxing methanol. Thin layer chromatography analysis revealed that after 24 h the starting material was completely consumed and 5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-3(5)-phenyl-1*H*-pyrazole **8a** was obtained (63%) (Scheme 5). The obtained pyrazole **8a** is not the expected reaction product based on our previous work.[31–33,42] Its formation results from pyrazole **10a** (Scheme 6) after the nucleophilic attack of hydrazine, present in excess in the



Scheme 5. Synthesis of 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1*H*-pyrazoles **10a**–**d** through the reaction of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones **3a**–**d** and **6a**–**d** with hydrazine hydrate.

reaction medium, on the carbonyl group at 2″-position. The formation of pyrazole **10a** can be explained by the two possible reaction mechanisms proposed in Scheme 6. The first one (via a, Scheme 6) involves the 1,4-conjugate addition of hydrazine to the C-2 of chromone **3a** and subsequent ring-opening, followed by an intramolecular 1,6-conjugate addition of the hydrazine to the α,β,γ,δ-diunsaturated carbonyl system of **11a** to afford pyrazoline **12a**, which is facilitated by the presence of the halogen atom. Therefore this compound can be obtained by another way (via b, Scheme 6), first there is a 1,6-conjugate addition of hydrazine to the C-β of chromone **3a**, subsequent ring-opening and then an intramolecular 1,4-conjugate addition. If the mechanism follows via a, we should observe the formation of two pyrazoles, and not only the formation of pyrazole **10a**. Since we have not found any pyrazole resulting from the expected intramolecular reaction of the hydrazino and carbonyl group of the possible intermediate **11a**[31,32] we suppose that the reaction mechanism must follow via b depicted in Scheme 6.



Scheme 6. Proposed mechanism for the formation of 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1*H*-pyrazoles **10a**–**d**, based on those already described for similar compounds.[31–37]

Pyrazoline **12a** underwent a dehalogenation process and then a 1,5-proton shift to afford pyrazole **10a** (Scheme 6). Since there is an excess of hydrazine in the reaction medium, there is an addition of hydrazine to the free carbonyl group of **10a** to give compound **8a** (Scheme 5). To avoid the second addition of hydrazine and the formation of **8a**, (*E*)-3-bromo-2-styryl-4*H*-chromen-4-one **3a** was left reacted with 1.5 molar equiv of hydrazine in methanol at reflux during 24 h. After that period, an extra 1.5 molar equiv of hydrazine was added to the reaction mixture since the starting material was not totally consumed, and the reaction stirring at reflux for more 24 h. This reaction revealed a high degradation and a complicated mixture of compounds.

When a small amount of acetone is present as contaminant in the solvents, an extra hydrazone is formed by the reaction of hydrazine moiety of **8a** with the acetone carbonyl group leading to the azine **9a** (Scheme 5). We have recently discussed the stereochemistry of azines.[43]

Finally the 5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-3(5)-phenyl-1*H*-pyrazole **10a** was obtained from compounds **8a** and **9a** by hydrolysis of the hydrazone moiety under acidic conditions (Scheme 5). Very similar pyrazoles have been reported by Errington et al. but the synthesis differs greatly from our synthetic protocol.[44]

A study to establish the optimal conditions (different temperatures, reaction times, solvents, and amounts of hydrazine) for the synthesis of pyrazoles **8a** and **9a** was carried out (Table 3). Considering that the best yields were obtained using 5 molar equiv of hydrazine hydrate, in refluxing methanol, these conditions were used in the reaction of 3-bromochromones **3b**–**d** and 3-iodochromones **6a**–**d** with hydrazine hydrate (Table 3).

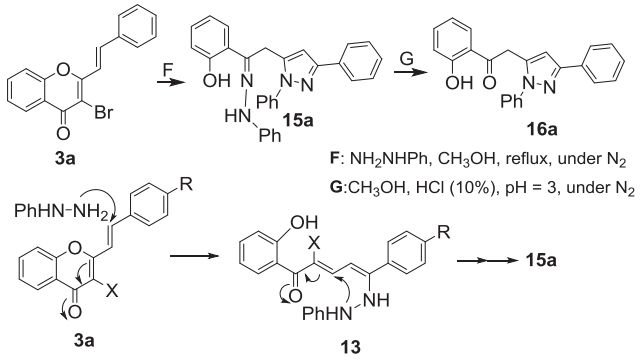
Table 3
Reaction conditions and yields in the reaction of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones **3a**–**d** and **6a**–**d** with hydrazine hydrate in methanol

Starting material	R	Hydrazine (molar equiv)	Reaction time (h)	Temperature (°C)	Yield[b] **8** (%)	Yield[b] **9** (%)
3a	H	5	3	Reflux	—	13
3a	H	2.5	48	rt	—	48
3a[a]	H	3	4	Reflux	—	20
3a	H	5	24	Reflux	75	78
3b	OMe	5	16	Reflux	69	51
3c	Cl	5	24	Reflux	62	43
3d	NO_2	5	24	Reflux	50	49
6a	H	5	24	Reflux	—	65
6b	OMe	5	24	Reflux	—	43
6c	Cl	5	24	Reflux	—	44
6d	NO_2	5	24	Reflux	—	40

[a] Ethanol was used as solvent.
[b] Yields determined on isolated products.

Pyrazoles **10b**–**d** were obtained by the hydrazone moieties cleavage under acidic conditions, by treating methanolic solutions of hydrazones **8b**–**d** and **9a**–**d**, at room temperature, with 1 molar equiv of hydrochloric acid (10%).

In order to confirm the proposed reaction mechanism (Scheme 6) (*E*)-3-bromo-2-styryl-4*H*-chromen-4-one **3a** was reacted with phenylhydrazine, using the optimal conditions found previously, and hydrazonopyrazole **15a** was obtained (66%) (Scheme 7). Pyrazole **16a** was obtained with 70% yield after acidic hydrolysis of the hydrazone moiety of **15a** in the conditions previously described.



Scheme 7. Synthesis of 5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-3(5)-phenyl-1-phenyl-1*H*-pyrazole **16a** and proposed mechanism for the formation of the hydrazonopyrazole **15a**.

The structure of pyrazole **16a** was unequivocally established based in 1D and 2D NMR, mainly in the NOE cross peaks found in the NOESY spectrum (H-4→CH_2; H-4→C-6‴; H-4→C-2′,6′; CH_2→H-2⁗,6⁗; CH_2→H-6‴) (Fig. 1).

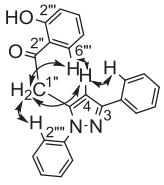


Fig. 1. Correlations observed in the NOESY spectrum of pyrazole **16a**.

The formation of pyrazole **15a** confirms that via b depicted in Scheme 6 is the most probably mechanism, since in this case we must have an initial 1,6-conjugate addition of the most nucleophilic amino group of the hydrazine (Scheme 7), followed by the proposed sequence depicted in Scheme 6.

2.3. NMR spectroscopy

All the synthesized compounds have been characterized by NMR, MS, and high resolution mass spectrometry. The most noticeable features in the ^{1}H and ^{13}C NMR spectra of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones **3a**–**d** and **6a**–**d** are: (i) the resonances assigned to H-β/C-β (d, δ_H 7.66–7.76 ppm/δ_C 135.6–139.6 ppm for **3a**–**d**; δ_H 7.66–7.75 ppm/δ_C 137.4–140.2 ppm for **6a**–**d**), which appear at high frequency values than those of H-α/C-α (d, δ_H 7.33–7.65 ppm/δ_C 116.6–123.5 ppm for **3a**–**d**; d, δ_H 7.32–7.65 ppm/δ_C 113.5–125.5 ppm for **6a**–**d**) due to the mesomeric deshielding effect of the carbonyl group. The coupling constants $^{3}J_{H\alpha-H\beta} \sim 16$ Hz indicates a trans-configuration for these vinylic systems; (ii) the absence of the singlet corresponding to the resonance of H-3 and the resonance of C-3 at low frequencies (108.8–111.6 ppm for **3a**–**d**; 89.8–90.2 ppm for **6a**–**d**). The shielding effect on C-3 carbon of **6a**–**d** is due to the effect of heavy atoms, which confirms the substitution with a halogen at this position; and (iii) the resonance of the carbonyl group at δ_C 172.7–172.8 ppm for **3a**–**d** and 172.6–174.3 ppm for **6a**–**d**.

The main features in the ^{1}H NMR spectra of 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-(propan-2-ylidenehydrazono)ethyl]-1*H*-pyrazoles **9a**–**d** are: (i) two singlets corresponding to the resonance of the methyl groups of the hydrazone moiety at δ_H 2.02–2.31 and 2.19–2.39 ppm; (ii) the singlet at δ_H 4.42–4.43 ppm due to the resonance of the methylene group; (iii) the resonance of H-4 appearing as a singlet at δ_H 6.26–6.61 ppm; (iv) the high frequency broad singlet due to the 2‴-OH resonance at 13.20–13.50 ppm. The characteristic signals in the ^{13}C NMR spectra of compounds **9a**–**d** are: (i) the signals due to the methyl groups of the hydrazone moiety at δ_C 19.3–19.4 ppm and 25.8–26.1 ppm; (ii) the signal at δ_C 24.5–25.0 ppm due to the methylene group (CH_2); (iii) the carbon resonances of the pyrazole moiety C-5 (δ_C 141.3–143.5 ppm) and C-3 (δ_C 148.8–149.5 ppm), which were confirmed by the connectivities found in their HMBC spectra (C-2′,6′→C-3); (iv) the resonances of C-2‴–OH at δ_C 160.9–161.1 ppm, C-2″=NNH_2 at δ_C 165.9–166.1 ppm and that of the other hydrazine moiety at δ_C 168.2–169.3 ppm.

The absence of the two singlets in the aliphatic region of the spectra, due to the resonance of the methyl groups of the hydrazone moiety is the main characteristic to distinguish compounds **8a**–**d** (hydrazones) from **9a**–**d** (azines). There are only small differences in the resonance of some characteristic signals in the ^{1}H and ^{13}C NMR spectra of compounds **8a**–**d** compared with those of **9a**–**d**.

The most typical signals in the ^{13}C NMR spectra of 5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1*H*-pyrazoles **10a**–**d** are the signal of the CH_2 at δ_C 37.3–37.9 ppm and that of the carbonyl group at δ_C 201.2–202.1 ppm. This indicates that we are not in the presence of any keto-enol tautomerism, all the reported pyrazole compounds exist as keto tautomers ($ArCOCH_2$–). We have represented all pyrazoles as 3-aryl tautomers although they are probably mixtures of 3- and 5-aryl tautomers.

3. Conclusions

(*E*)-3-Bromo-2-styryl-4*H*-chromen-4-ones were obtained through a selective 2-bromination of 1,3-diketones followed by the in situ cyclization under microwave irradiation with NBS in solvent-free conditions. This green protocol affords (*E*)-3-bromo-2-styryl-4*H*-chromen-4-ones in moderate to very good yields, depending on the substituents of the starting 1,3-diketones.

(*E*)-3-Iodo-2-styryl-4*H*-chromen-4-ones were prepared in good yields by the regioselective 2-iodination of 5-aryl-1-(2-hydroxyphenyl)pent-4-ene-1,3-diones with NIS in the presence of the catalytic system TFA/TFAA and NaOAc.

3(5)-Aryl-5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-1*H*-pyrazoles were obtained from the unexpected reaction of (*E*)-3-halo-2-styryl-4*H*-chromen-4-ones with hydrazine hydrate in methanol. This study demonstrates the influence of the 3-halogen atom on the reactivity of this type of chromones with hydrazine, which involves a 1,6- followed by a 1,4-conjugate additions. Finally, after the hydrazone moiety hydrolysis 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1*H*-pyrazoles have been obtained. Some structural features of these new pyrazole derivatives, such as the presence of the carbonyl group and the 2-hydroxyphenyl ring as well as the other aromatic ring, highlight their potential medicinal application.

4. Experimental section

4.1. General

Melting points were determined on a Buchi Melting point B-545 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or 500 [300.13 MHz (^{1}H), 75.47 MHz (^{13}C) or 500.13 MHz (^{1}H), 125.77 MHz (^{13}C)] spectrometers, using TMS as internal reference and $CDCl_3$ as solvent, if not stated otherwise. Chemical shifts (δ) are reported in parts per million values and coupling constants (*J*) in Hertz. Unequivocal ^{1}H assignments were made using 2D gCOSY (^{1}H/^{1}H) and NOESY experiments (800 ms of mixing time), while ^{13}C assignments were made on the basis of 2D gHSQC (^{1}H/^{13}C) and gHMBC (delays for one bond and long-range $J_{C/H}$ couplings were optimized for 145 and 7 Hz, respectively) experiments. Positive-ion ESI mass spectra were acquired using a Q-TOF 2 instrument [Nitrogen was used as nebulizer gas and argon as collision gas. The needle voltage was set at 3000 V, with the ion source at 80 °C and desolvation temperature at 150 °C. Cone voltage was 35 V]. High resolution mass spectra analysis (HRMS-ESI^{+}) were performed on a microTOF (focus) mass spectrometer. Ions were generated using an ApolloII (ESI) source. Ionization was achieved by electrospray, using a voltage of 4500 V applied to the needle, and a counter voltage between 100 and 150 V applied to the capillary. High resolution mass spectra analysis (HRMS-EI, 70 eV) were measured with VG Autospec M spectrometer. Preparative thin layer chromatography was carried out with Riedel silica gel 60 DGF_{254}, and column chromatography using Merck silica gel 60, 70–230 mesh. All other chemicals and solvents used were obtained from commercial sources and used as received or dried using standard procedures.

4.2. General procedure for the synthesis of (*E*)-3-bromo-2-styryl-4*H*-chromen-4-ones 3a–e

A mixture of the appropriate 5-aryl-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-diene-1-one **1a**–**e** (0.37 mmol) and *N*-bromosuccinimide (100 mg, 0.56 mmol) was irradiated in open vessel in an Ethos SYNHT microwave instrument (Milestone Inc.) for 40 min at 800 W, under nitrogen. After that, the mixture was taken in chloroform (20 mL) and washed with an aqueous solution of sodium thiosulfate (3×20 mL) and dried over anhydrous sodium sulfate. The obtained crude oil was purified by thin layer chromatography using dichloromethane as eluent. (*E*)-3-Bromo-2-styryl-4*H*-chromen-4-ones **3a**–**e** were recrystallized in ethanol and obtained as yellow to orange solids in moderate to good yields: **3a**, 94.42 mg, 78%; **3b**, 116.30 mg, 88%; **3c**, 68.24 mg, 51%; **3d**, 42.68 mg,

31%; **3e**, 30.09 mg, 21% and **3f**, which was also obtained in the reaction of **1e** with NBS, 57.99 mg, 42%.

*4.2.1. (E)-3-Bromo-2-styryl-4H-chromen-4-one (**3a**).* Yellow solid. Mp 169–170 °C. δ_H (300.13 MHz, $CDCl_3$) 7.38–7.47 (4H, m, H-6, H-3′,4′,5′), 7.50 (1H, d, *J* 16.0 Hz, H-α), 7.55 (1H, d, *J* 7.9 Hz, H-8), 7.64–7.69 (2H, m, H-2′,6′), 7.72 (1H, dt, *J* 7.9 and 1.8 Hz, H-7), 7.74 (1H, d, *J* 16.0 Hz, H-β), 8.27 (1H, dd, *J* 8.0 and 1.8 Hz, H-5); δ_C (75.47 MHz, $CDCl_3$) 109.8 (C-3), 117.5 (C-8), 119.1 (C-α), 122.0 (C-10), 125.4 (C-6), 126.5 (C-5), 128.1 (C-2′,6′), 129.1 (C-3′,5′), 130.3 (C-4′), 134.1 (C-7), 134.9 (C-1′), 139.6 (C-β), 154.7 (C-9), 158.4 (C-2), 172.8 (C-4). EI-MS, *m*/*z* 328 (22, $M^{+\bullet}$, ^{81}Br), 326 (22, $M^{+\bullet}$, ^{79}Br), 282 (10), 247 (100), 218 (12), 191 (11), 189 (12), 165 (4), 127 (24), 109 (7), 101 (3), 92 (10), 77 (9), 63 (6), 51 (4%); HR-EIMS: $M^{+\bullet}$, $C_{17}H_{11}{}^{81}BrO_2$ requires 327.9911, found 327.9901; $C_{17}H_{11}{}^{79}BrO_2$ requires 325.9942, found 325.9927.

*4.2.2. (E)-3-Bromo-2-(4-methoxystyryl)-4H-chromen-4-one (**3b**).* Yellow solid. Mp 141–142 °C. δ_H (300.13 MHz, $CDCl_3$) 3.86 (3H, s, 4′-OC*H*$_3$), 6.94 (2H, d, *J* 8.6 Hz, H-3′,5′), 7.33 (1H, d, *J* 16.0 Hz, H-α), 7.40 (1H, ddd, *J* 8.5, 8.0, and 0.8 Hz, H-6), 7.52 (1H, d, *J* 8.0 Hz, H-8), 7.59 (2H, d, *J* 8.6 Hz, H-2′,6′), 7.66 (1H, d, *J* 16.0 Hz, H-β), 7.71 (1H, ddd, *J* 8.5, 8.0, and 1.6 Hz, H-7), 8.20 (1H, dd, *J* 8.0 and 1.6 Hz, H-5); δ_C (75.47 MHz, $CDCl_3$) 55.3 (4′-O*C*H$_3$), 108.8 (C-3), 114.5 (C-3′,5′), 116.6 (C-α), 117.6 (C-8), 122.0 (C-10), 125.1 (C-6), 126.5 (C-5), 127.7 (C-1′) 129.6 (C-2′,6′), 134.0 (C-7), 139.6 (C-β), 154.7 (C-9), 158.7 (C-2), 161.5 (C-4′), 172.8 (C-4). EI-MS, *m*/*z* 358 (32, $M^{+\bullet}$, ^{81}Br), 356 (21, $M^{+\bullet}$, ^{79}Br), 325 (7), 323 (10), 277 (100), 247 (12), 245 (11), 223 (4), 145 (5%); HR-EIMS: $M^{+\bullet}$, $C_{18}H_{13}{}^{81}BrO_3$ requires 358.0016, found 358.0000; $C_{18}H_{13}{}^{79}BrO_3$ requires, 356.0048, found 356.0034.

*4.2.3. (E)-3-Bromo-2-(4-chlorostyryl)-4H-chromen-4-one (**3c**).* Orange solid. Mp 154–155 °C. δ_H (300.13 MHz, $CDCl_3$) 7.43 (3H, m, H-6 and H-3′,5′), 7.46 (1H, d, *J* 16.0 Hz, H-α), 7.54 (1H, d, *J* 8.4 Hz, H-8), 7.58 (2H, d, *J* 8.5 Hz, H-2′,6′), 7.66 (1H, d, *J* 16.0 Hz, H-β), 7.72 (1H, dt, *J* 8.4 and 1.6 Hz, H-7), 8.24 (1H, dd, *J* 8.0 and 1.6 Hz, H-5); δ_C (75.47 MHz, $CDCl_3$) 109.8 (C-3), 117.5 (C-8), 120.1 (C-α), 122.0 (C-10), 125.1 (C-3′,5′), 125.7 (C-6), 126.5 (C-5), 128.1 (C-2′,6′), 134.6 (C-7), 134.9 (C-1′), 135.6 (C-β), 138.3 (C-4′), 154.7 (C-9), 158.4 (C-2), 172.8 (C-4). EI-MS, *m*/*z* 364 (8, $M^{+\bullet}$, ^{81}Br, ^{37}Cl), 362 (18, $M^{+\bullet}$, ^{79}Br, ^{37}Cl or ^{81}Br, ^{35}Cl), 360 (24, $M^{+\bullet}$, ^{79}Br, ^{35}Cl), 325 (5), 281 (8), 223 (4), 248 (100%); HR-EIMS: $M^{+\bullet}$, $C_{17}H_{10}{}^{81}Br^{37}ClO_2$ requires 363.9433, found 363.9416; $C_{17}H_{10}{}^{79}Br^{37}ClO_2$ requires 361.9521, found 361.9506; $C_{17}H_{10}{}^{81}Br^{35}ClO_2$ requires 361.9519, found 361.9504; $C_{17}H_{10}{}^{79}Br^{35}ClO_2$ requires 359.9553, found 359.9541.

*4.2.4. (E)-3-Bromo-2-(4-nitrostyryl)-4H-chromen-4-one (**3d**).* Orange solid. Mp 184–185 °C. δ_H (500.13 MHz, $CDCl_3$) 7.47 (1H, dt, *J* 7.6 and 0.9 Hz, H-6), 7.58 (1H, dd, *J* 8.1 and 0.9 Hz, H-8), 7.65 (1H, d, *J* 15.8 Hz, H-α), 7.76 (1H, d, *J* 15.8 Hz, H-β), 7.77 (1H, ddd, *J* 8.1, 7.6, and 1.5 Hz, H-7), 7.81 (2H, dd, *J* 8.8 Hz, H-2′,6′), 8.27 (1H, dd, *J* 8.0 and 1.5 Hz, H-5), 8.31 (2H, d, *J* 8.8 Hz, H-3′,5′); δ_C (75.47 MHz, $CDCl_3$) 111.6 (C-3), 117.6 (C-8), 122.0 (C-10), 123.5 (C-α), 124.4 (C-3′,5′), 125.8 (C-6), 126.6 (C-5), 128.6 (C-2′,6′), 134.5 (C-7), 136.4 (C-β), 141.0 (C-1′), 148.3 (C-4′), 154.9 (C-9), 157.2 (C-2), 172.7 (C-4). EI-MS, *m*/*z* 373 (24, $M^{+\bullet}$, ^{81}Br), 371 (28, $M^{+\bullet}$, ^{79}Br), 325 (7), 323 (10), 248 (100), 250 (11), 223 (5), 125 (5%); HR-EIMS: $M^{+\bullet}$, $C_{17}H_{10}{}^{81}BrNO_4$ requires 372.9763, found 372.9745; $C_{17}H_{10}{}^{79}BrNO_4$ requires 370.9793, found 370.9779.

*4.2.5. (E)-3-Bromo-5,7-dimethoxy-2-styryl-4H-chromen-4-one (**3e**).* Yellow solid. Mp 179–181 °C. δ_H (300.13 MHz, $CDCl_3$) 3.82 (3H, s, 7-OC*H*$_3$), 3.83 (3H, s, 5-OC*H*$_3$), 6.38 (1H, d, *J* 2.3 Hz, H-8), 6.55 (1H, d, *J* 2.3 Hz, H-6), 7.43 (1H, d, *J* 16.2 Hz, H-α), 7.43 (2H, d, *J* 8.8 Hz, H-2′,6′), 7.61 (1H, d, *J* 16.2 Hz, H-β), 7.63 (2H, dd, *J* 8.8 and 1.8 Hz, H-3′,5′); δ_C (125.77 MHz, $CDCl_3$) 55.8 (5-O*C*H$_3$), 58.9 (7-O*C*H$_3$), 92.8 (C-8), 98.7 (C-6), 104.3 (C-10), 109.5 (C-3), 119.1 (C-α), 127.5 (C-2′, 6′), 129.0 (C-3′,5′), 130.1 (C-4′), 134.9 (C-1′), 139.5 (C-β), 156.9 (C-9), 158.9 (C-5), 159.2 (C-2), 165.0 (C-7), 182.0 (C-4). EI-MS, *m*/*z* 388 (18, $M^{+\bullet}$, ^{81}Br), 386 (25, $M^{+\bullet}$, ^{79}Br), 355 (8), 325 (10), 277 (11), 248 (100), 247 (12%); HR-EIMS: $M^{+\bullet}$, $C_{19}H_{15}{}^{81}BrO_4$ requires 388.0125, found 388.0108; $C_{19}H_{15}{}^{79}BrO_4$ requires 386.0155, found 386.0166.

*4.2.6. (E)-5-Hydroxy-7-methoxy-2-styryl-4H-chromen-4-one (**3f**).* Pale yellow solid. Mp 180–181 °C. δ_H (300.13 MHz, $CDCl_3$) 3.89 (3H, s, 7-OC*H*$_3$), 6.18 (1H, s, H-3), 6.36 (1H, d, *J* 2.2 Hz, H-6), 6.48 (1H, d, *J* 2.2 Hz, H-8), 6.74 (1H, d, *J* 16.1 Hz, H-α), 7.39–7.46 (3H, m, H-3′,4′,5′), 7.57–7.60 (2H, m, H-2′,6′), 7.58 (1H, d, *J* 16.1 Hz, H-β), 12.75 (1H, br s, 5-O*H*); δ_C (125.77 MHz, $CDCl_3$), 56.4 (7-O*C*H$_3$), 93.2 (C-8), 98.5 (C-6), 106.4 (C-10), 109.5 (C-3), 120.2 (C-α), 128.3 (C-2′,6′), 129.6 (C-3′,5′), 130.6 (C-4′), 135.4 (C-1′), 137.9 (C-β), 158.1 (C-9), 162.0 (C-5), 162.8 (C-2), 166.2 (C-7), 183.1 (C-4). EI-MS, *m*/*z* 293 (42, $M^{+\bullet}$), 277 (11), 264 (12), 248 (100%). HR-EIMS: $M^{+\bullet}$, $C_{18}H_{14}O_4$ requires 294.0890, found 294.0894.

*4.2.7. (E)-6,8-Dibromo-2-styryl-4H-chromen-4-one (**5a**).* Yellow residue. δ_H (300.13 MHz, $CDCl_3$) 6.35 (1H, s, H-3), 6.81 (d, 1H, *J* 16.0 Hz, H-α), 7.41–7.45 (m, 3H, H-3′,4′,5′), 7.60–7.63 (m, 2H, H-2′,6′), 7.75 (d, 1H, *J* 16.0 Hz, H-β), 8.02 (d, 1H, *J* 2.2 Hz, H-7), 8.27 (d, 1H, *J* 2.2 Hz, H-5); δ_C (75.47 MHz, $CDCl_3$) 110.3 (C-3), 112.8 (C-8), 118.2 (C-6), 119.4 (C-α), 126.1 (C-10), 127.8 (C-7), 127.9 (C-3′,5′), 129.0 (C-2′,6′), 130.2 (C-4′), 134.7 (C-1′), 138.8 (C-β), 139.3 (C-5), 151.5 (C-9), 162.1 (C-2), 176.4 (C-4). ESI^+-MS, *m*/*z* 409 [31, $(M+H)^+$, ^{81}Br], 407 [31%, $(M+H)^+$, ^{79}Br].

4.3. General procedure for the synthesis of (*E*)-3-iodo-2-styryl-4*H*-chromen-4-ones 6a–d

NaOAc (121 mg, 1.48 mmol) was added to a mixture of trifluoroacetic acid (0.43 μL, 5.6×10^{-3} mmol) and trifluoroacetic anhydride (0.79 μL, 5.6×10^{-3} mmol) at 0 °C. Then the appropriate 5-aryl-3-hydroxy-1-(2-hydroxyphenyl)penta-2,4-diene-1-one **1a–d** (0.37 mmol) was added and the mixture was stirred at room temperature for 30 min. After the addition of *N*-iodosuccinimide (124.9 mg, 0.56 mmol) the stirring was continued over 24 h. After that period the reaction mixture was poured into ice (20 g) and water (20 mL) and brought to pH 5 with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic fractions were washed with water (20 mL) and brine (20 mL). After drying over anhydrous sodium sulfate, the solvent was evaporated to dryness. Purification was accomplished by thin layer chromatography using dichloromethane as eluent. (*E*)-3-Iodo-2-styryl-4*H*-chromen-4-ones **6a–d** were recrystallized from ethanol and obtained as yellow to orange solids in good yields: **6a**, 96.91 mg, 70%; **6b**, 92.72 mg, 62%; **6c**, 92.22 mg, 61%; **6d**, 91.50 mg, 59%.

*4.3.1. (E)-3-Iodo-2-styryl-4H-chromen-4-one (**6a**).* Yellow solid. Mp 174–176 °C. δ_H (300.13 MHz, $CDCl_3$) 7.40–7.46 (4H, m, H-6 and H-3′,4′,5′), 7.56 (1H, d, *J* 15.8 Hz, H-α), 7.57 (1H, dd, *J* 8.0 and 1.1 Hz, H-8), 7.66 (2H, d, *J* 8.4 Hz, H-2′,6′), 7.71 (1H, d, *J* 15.8 Hz, H-β), 7.73 (1H, dt, *J* 8.0 and 1.7 Hz, H-7), 8.24 (1H, dd, *J* 8.0 and 1.7 Hz, H-5); δ_C (75.47 MHz, $CDCl_3$) 89.9 (C-3), 117.3 (C-8), 120.4 (C-10), 123.4 (C-α), 125.5 (C-6), 126.7 (C-5), 128.1 (C-2′,6′), 129.1 (C-3′,5′), 130.3 (C-4′), 134.1 (C-7), 134.8 (C-1′), 140.2 (C-β), 155.1 (C-9), 160.0 (C-2), 174.3 (C-4); EI-MS, *m*/*z* 374 (18, $M^{+\bullet}$), 247 [100, $(M-I)^+$], 218 (10), 189 (13), 127 (12%); HRMS (EI): $M^{+\bullet}$, $C_{17}H_{11}IO_2$ requires 373.9804, found 373.9805.

*4.3.2. (E)-3-Iodo-2-(4-methoxystyryl)-4H-chromen-4-one (**6b**).* Orange solid. Mp 156–157 °C. δ_H (300.13 MHz, $CDCl_3$) 3.88 (3H, s, 4′-OC*H*$_3$), 6.98 (2H, d, *J* 8.5 Hz, H-3′,5′), 7.32 (1H, d, *J* 15.9 Hz,

H-α), 7.38 (1H, ddd, *J* 8.5, 8.0, and 1.0 Hz, H-6), 7.50 (1H, d, *J* 8.0 Hz, H-8), 7.57 (2H, d, *J* 8.5 Hz, H-2′,6′), 7.66 (1H, d, *J* 15.9 Hz, H-β), 7.73 (1H, ddd, *J* 8.5, 8.0, and 1.6 Hz, H-7), 8.22 (1H, dd, *J* 8.0, 1.6 Hz, H-5); δ_C (75.47 MHz, $CDCl_3$) 55.3 (4′-OCH_3), 90.2 (C-3), 113.5 (C-α), 114.9 (C-3′,5′), 117.7 (C-8), 121.2 (C-10), 125.0 (C-6), 126.5 (C-5), 127.4 (C-1′) 129.2 (C-2′,6′), 134.3 (C-7), 139.6 (C-β), 154.6 (C-9), 159.0 (C-2), 161.5 (C-4′), 172.7 (C-4); EI-MS, *m*/*z* 404 (60, $M^{+\bullet}$), 392 (21), 324 (33), 309 (97), 278 (22), 277 [100, $(M-I)^+$], 262 (72), 234 (83), 205 (35%); HR-EIMS: $M^{+\bullet}$, $C_{18}H_{13}IO_3$ requires 403.9909, found 403.9911.

*4.3.3. (E)-3-Iodo-2-(4-chlorostyryl)-4H-chromen-4-one (**6c**).* Yellow solid. Mp 165–166 °C. δ_H (300.13 MHz, $CDCl_3$) 7.44–7.51 (4H, m, H-6, H-α, and H-3′,5′), 7.60 (1H, d, *J* 7.9 Hz, H-8), 7.64 (2H, d, *J* 8.5 Hz, H-2′,6′), 7.73 (1H, d, *J* 16.0 Hz, H-β), 7.77 (1H, dt, *J* 7.9 and 1.7 Hz, H-7), 8.30 (1H, dd, *J* 8.0 and 1.7 Hz, H-5); δ_C (75.47 MHz, $CDCl_3$) 90.2 (C-3), 117.5 (C-α), 117.6 (C-8), 122.6 (C-10), 125.4 (C-6), 126.3 (C-5), 129.2 (C-3′,5′), 129.4 (C-2′,6′), 133.5 (C-1′), 134.2 (C-7), 136.2 (C-4′), 137.6 (C-β), 154.8 (C-9), 157.3 (C-2), 172.6 (C-4); EI-MS, *m*/*z*: 410 (0.07, $M^{+\bullet}$, ^{37}Cl), 408 (0.24, $M^{+\bullet}$, ^{35}Cl), 281 [100, $(M-I)^+$, ^{35}Cl], 283 [28, $(M-I)^+$, ^{37}Cl], 262 (72), 245 (29), 247 (5), 218 (14), 126 (16%); HR-EIMS: $M^{+\bullet}$, $C_{17}H_{10}I^{37}ClO_2$ requires 409.9385, found 409.9370; $C_{17}H_{10}I^{35}ClO_2$ requires 407.9414, found 407.9398.

*4.3.4. (E)-3-Iodo-2-(4-nitrostyryl)-4H-chromen-4-one (**6d**).* Light yellow solid. Mp 190–192 °C. δ_H (300.13 MHz, $CDCl_3$) 7.46 (1H, dt, *J* 8.1 and 1.1 Hz, H-6), 7.58 (1H, dd, *J* 8.1 and 1.1 Hz, H-8), 7.65 (1H, d, *J* 16.0 Hz, H-α), 7.75 (1H, d, *J* 16.0 Hz, H-β), 7.79 (1H, dt, *J* 8.1 and 1.1 Hz, H-7), 7.81 (2H, dd, *J* 8.6 Hz, H-2′,6′), 8.26 (1H, dd, *J* 8.1 and 1.1 Hz, H-5), 8.31 (2H, d, *J* 8.6 Hz, H-3′,5′); δ_C (75.47 MHz, $CDCl_3$) 89.8 (C-3), 117.7 (C-8), 122.1 (C-10), 124.5 (C-3′,5′), 125.5 (C-α), 125.6 (C-6), 126.8 (C-5), 128.9 (C-2′,6′), 134.5 (C-7), 137.4 (C-β), 141.2 (C-1′), 148.0 (C-4′), 154.6 (C-9), 156.9 (C-2), 172.6 (C-4); EI-MS, *m*/*z* 419 (69, $M^{+\bullet}$), 293 [100%, $(M-I)^+$]; HR-EIMS: $M^{+\bullet}$, $C_{17}H_{10}INO_4$ requires 418.9655, found 418.9666.

4.4. General procedure for the synthesis of 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-(propan-2-ylidenehydrazono)ethyl]-1*H*-pyrazoles 9a–d

Hydrazine hydrate (72.8 μL, 1.50 mmol) was added to a solution of the appropriate (*E*)-3-halo-2-styryl-4*H*-chromen-4-one **3a**–**d** or **6a**–**d** (0.30 mmol) in methanol (15 mL). The reaction mixture was stirred at reflux, under nitrogen atmosphere, until the disappearance of the starting material. The mixture was then poured into chloroform (20 mL) and washed with acidified water (2×20 mL, pH 5). The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated to dryness, and the solid residue was purified by thin layer chromatography using a 2:3 mixture of light petroleum/ethyl acetate as eluent. The residue obtained after solvent evaporation was recrystallized from a mixture of dichloromethane/light petroleum, giving 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-(propan-2-ylidenehydrazono)ethyl]-1*H*-pyrazoles **9a**–**d** in moderate yields: **9a** from **3a**, 77.78 mg, 78%; **9b** from **3b**, 55.45 mg, 51%; **9c** from **3c**, 47.32 mg, 43%, **9d** from **3d**, 55.48 mg, 49%, **9a** from **6a**, 64.82 mg, 65%; **9b** from **6b**, 46.75 mg, 43%; **9c** from **6c**, 48.42 mg, 44%; **9d** from **6d**, 45.29 mg, 40%.

*4.4.1. 5(3)-[2-(2-Hydroxyphenyl)-2-(propan-2-ylidenehydrazono) ethyl]-3(5)-phenyl-1H-pyrazole (**9a**).* Light yellow solid. Mp 180–181 °C. δ_H (300.13 MHz, $CDCl_3$) 2.10 and 2.23 [2× 3H, 2s, NC(CH_3)$_2$], 4.43 (2H, s, H-1″), 6.43 (1H, s, H-4), 6.90 (1H, dt, *J* 7.8 and 1.2 Hz, H-5‴), 6.99 (1H, dd, *J* 8.3 and 1.2 Hz, H-3‴), 7.29–7.40 (4H, m, H-4‴, H-4′ and H-3′,5′), 7.67 (2H, d, *J* 7.1 Hz, H-2′,6′), 7.74 (1H, dd, *J* 7.8 and 1.5 Hz, H-6‴), 13.40 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 19.3 and 25.9 [NC(CH_3)$_2$], 24.9 (C-1″), 102.0 (C-4), 117.9 (C-3‴), 118.0 (C-1‴), 118.8 (C-5‴), 125.5 (C-2′,6′), 125.7 (C-6‴), 128.0 (C-4′), 128.7 (C-3′,5′), 132.0 (C-1′), 132.4 (C-4‴), 142.4 (C-5), 149.5 (C-3), 160.9 (C-2‴), 165.9 (C-2″), 168.3 [N*C*(CH$_3$)$_2$]; EI-MS, *m*/*z* 332 (7, $M^{+\bullet}$), 278 (52), 261 (31), 158 (90), 149 (53), 127 (15), 121 (100%); HR-EIMS: $M^{+\bullet}$, $C_{20}H_{20}N_4O$ requires 332.1637, found 332.1634.

*4.4.2. 5(3)-[2-(2-Hydroxyphenyl)-2-(propan-2-ylidenehydrazono) ethyl]-3(5)-(4-methoxyphenyl)-1H-pyrazole (**9b**).* Light yellow solid. Mp 163–164 °C. δ_H (300.13 MHz, $CDCl_3$) 2.02 and 2.19 [2× 3H, 2s, NC(CH_3)$_2$], 3.81 (3H, s, 4′-OCH_3), 4.43 (2H, s, H-1″), 6.26 (1H, s, H-4), 6.90 (2H, d, *J* 8.7 Hz, H-3′,5′), 6.86–6.96 (1H, m, H-5‴), 6.98 (1H, dd, *J* 7.8 and 1.1 Hz, H-3‴), 7.31 (1H, t, *J* 7.8 Hz, H-4‴), 7.55 (1H, d, *J* 8.7 Hz, H-2′,6′), 7.71 (1H, dd, *J* 8.0 and 1.1 Hz, H-6‴), 13.50 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 19.3 and 25.9 [NC(CH_3)$_2$], 25.0 (C-1″), 55.3 (OCH_3), 101.5 (C-4), 114.1 (C-3′,5′), 117.9 (C-3‴), 118.0 (C-1‴), 118.8 (C-5‴), 124.6 (C-1′), 126.8 (C-2′,6′), 127.9 (C-4′), 128.8 (C-6‴), 132.4 (C-4‴), 143.5 (C-5), 148.8 (C-3), 159.5 (C-4′), 160.9 (C-2‴), 166.0 (C-2″), 168.2 [N*C*(CH$_3$)$_2$]; ESI-MS, *m*/*z* 363 [100%, $(M+H)^+$]; HR-ESI$^+$MS: $(M+H)^+$, $(C_{21}H_{22}N_4O_2+H)^+$ requires 363.18155, found 363.18138.

*4.4.3. 3(5)-(4-Chlorophenyl)-5(3)-[2-(2-hydroxyphenyl)-2-(propan-2-ylidenehydrazono)ethyl]-1H-pyrazole (**9c**).* Light orange solid. Mp 173–174 °C. δ_H (300.13 MHz, $CDCl_3$) 2.12 and 2.25 [2× 3H, 2s, NC(CH_3)$_2$], 4.42 (2H, s, H-1″), 6.44 (1H, s, H-4), 6.91 (1H, dt, *J* 8.0 and 1.2 Hz, H-5‴), 6.99 (1H, dd, *J* 8.0 and 1.2 Hz, H-3‴), 7.33 (2H, d, *J* 8.7 Hz, H-3′,5′), 7.35 (1H, t, *J* 8.0 Hz, H-4‴), 7.63 (1H, d, *J* 8.7 Hz, H-2′,6′), 7.72 (1H, dd, *J* 8.0 and 1.6 Hz, H-6‴), 13.30 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 19.4 and 26.1 [NC(CH_3)$_2$], 24.5 (C-1″), 102.0 (C-4), 117.7 (C-1‴), 118.0 (C-3‴), 118.9 (C-5‴), 126.7 (C-2′,6′), 128.5 (C-6‴), 128.8 (C-3′,5′), 131.1 (C-1′), 132.6 (C-4‴), 133.6 (C-4′), 141.3 (C-5), 149.0 (C-3), 161.1 (C-2‴), 166.1 (C-2″), 169.3 [N*C*(CH$_3$)$_2$]; ESI-MS, *m*/*z* 367 [100%, $(M+H)^+$]; HR-ESI$^+$MS: $(M+H)^+$, $(C_{20}H_{19}ClN_4O+H)^+$ requires 367.13202, found 367.13182.

*4.4.4. 5(3)-[2-(2-Hydroxyphenyl)-2-(propan-2-ylidenehydrazono) ethyl]-3(5)-(4-nitrophenyl)-1H-pyrazole (**9d**).* Orange solid. Mp 197–198 °C. δ_H (300.13 MHz, $CDCl_3$) 2.31 and 2.39 [2× 3H, 2s, NC(CH_3)$_2$], 4.43 (2H, s, H-1″), 6.61 (1H, s, H-4), 6.96 (1H, t, *J* 8.0 Hz, H-5‴), 7.00 (1H, d, *J* 8.0 Hz, H-3‴), 7.36 (1H, dt, *J* 8.0 and 1.3 Hz, H-4‴), 7.73 (1H, dd, *J* 8.0 and 1.3 Hz, H-6‴), 7.91 (1H, d, *J* 8.9 Hz, H-2′,6′), 8.24 (2H, d, *J* 8.9 Hz, H-3′,5′), 13.20 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 19.3 and 25.8 [NC(CH_3)$_2$], 24.8 (C-1″), 102.3 (C-4), 117.9 (C-1‴), 118.0 (C-3‴), 118.9 (C-5‴), 124.8 (C-3′,5′), 128.3 (C-2′,6′), 128.5 (C-6‴), 132.6 (C-4‴), 136.3 (C-1′), 141.3 (C-5), 148.6 (C-4′), 149.3 (C-3), 161.0 (C-2‴), 165.9 (C-2″), 169.0 [N*C*(CH$_3$)$_2$]; ESI-MS, *m*/*z* 378 [100%, $(M+H)^+$]; HR-ESI$^+$MS: $(M+H)^+$, $(C_{20}H_{19}N_5O_3+H)^+$ requires 378.15607, found 378.15685.

4.5. General procedure for the synthesis of 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-1*H*-pyrazoles 8a–d

Hydrazine hydrate (72.8 μL, 1.50 mmol) was added to a solution of the appropriate (*E*)-3-halo-2-styryl-4*H*-chromen-4-one **3a**–**d** (0.30 mmol) in methanol (15 mL). The reaction mixture was stirred at reflux under nitrogen atmosphere, until the disappearance of the starting material. The mixture was then poured into chloroform (20 mL) and washed with acidified water (2×20 ml, pH 5). The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated to dryness, and the solid residue was purified by thin layer chromatography using a 2:3 mixture of hexane/ethyl acetate as eluent. The residue obtained after solvent evaporation was recrystallized from a mixture of dichloromethane/light petroleum, giving 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-1*H*-pyrazole **8a**–**d** in good yields: **8a**, 65.77 mg, 75%; **8b**, 66.73 mg, 69%; **8c**, 60.78 mg, 62%; **8d**, 50.57 mg, 50%.

*4.5.1. 5(3)-[2-(2-Hydroxyphenyl)-2-hydrazonoethyl]-3(5)-phenyl-1H-pyrazole (**8a**).* White solid. Mp 185–185 °C. δ_H (300.13 MHz, $CDCl_3$) 4.10 (2H, s, H-1″), 6.40 (1H, s, H-4), 6.87 (1H, dt, *J* 7.7 and 1.1 Hz, H-5‴), 6.97 (1H, dd, *J* 7.7 and 1.1 Hz, H-3‴), 7.22 (1H, dt, *J* 7.7 and 1.4 Hz, H-4‴), 7.32–7.40 (3H, m, H-4′ and H-3′,5′), 7.48 (3H, m, H-6‴ and H-2′,6′), 12.90 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 24.5 (C-1″), 102.1 (C-4), 117.4 (C-3‴), 118.7 (C-5‴), 119.3 (C-1‴), 125.4 (C-2′,6′), 126.6 (C-6‴), 128.6 (C-4′), 128.8 (C-3′,5′), 129.5 (C-1′), 130.0 (C-4‴), 145.9 and 146.5 (C-3,5), 153.1 (C-2‴), 158.7 (C-2″); ESI^+-MS, *m*/*z* 293 [100%, $(M+H)^+$]; HR-EIMS: $M^{+\bullet}$, $C_{17}H_{16}N_4O$ requires 292.1324, found 292.1315.

*4.5.2. 5(3)-[2-(2-Hydroxyphenyl)-2-hydrazonoethyl]-3(5)-(4-methoxyphenyl)-1H-pyrazole (**8b**).* Light yellow solid. Mp 160–161 °C. δ_H (300.13 MHz, $CDCl_3$) 3.88 (s, 3H, O*CH*$_3$), 4.13 (2H, s, H-1″), 6.26 (1H, s, H-4), 6.90 (2H, d, *J* 8.7 Hz, H-3′,5′), 6.94–6.96 (1H, m, H-5‴), 6.98 (1H, dd, *J* 7.8 and 1.1 Hz, H-3‴), 7.29 (1H, t, *J* 7.8 Hz, H-4‴), 7.50 (1H, d, *J* 8.7 Hz, H-2′,6′), 7.71 (1H, dd, *J* 8.0 and 1.0 Hz, H-6‴), 13.50 (1H, s, 2‴-O*H*); δ_C (125.77 MHz, $CDCl_3$) 24.9 (C-1″), 55.3 (OCH_3), 101.5 (C-4), 114.1 (C-3′,5′), 117.4 (C-3‴), 118.8 (C-5‴), 119.0 (C-1‴), 124.5 (C-1′), 126.8 (C-2′,6′), 129.0 (C-6‴), 130.0 (C-4′), 131.0 (C-4‴), 147.5 (C-5), 155.1 (C-3), 158.1 (C-2‴), 159.5 (C-2″); ESI^+-MS, *m*/*z* 323 [100%, $(M+H)^+$]; HR-EIMS: $M^{+\bullet}$, $C_{18}H_{18}N_4O_2$ requires 322.1430, found 322.1422.

*4.5.3. 3(5)-(4-Chlorophenyl)-5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-1H-pyrazole (**8c**).* Light yellow solid. Mp 170–171 °C. δ_H (300.13 MHz, $CDCl_3$) 4.10 (2H, s, H-1″), 6.41 (1H, s, H-4), 6.90 (1H, dt, *J* 8.0 and 1.2 Hz, H-5‴), 6.98 (1H, dd, *J* 8.0 and 1.2 Hz, H-3‴), 7.32 (2H, d, *J* 8.8 Hz, H-3′,5′), 7.35 (1H, t, *J* 8.0 Hz, H-4‴), 7.62 (1H, d, *J* 8.8 Hz, H-2′,6′), 7.72 (1H, dd, *J* 8.0 and 1.6 Hz, H-6‴), 12.90 (1H, s, 2‴-O*H*); δ_C (125.77 MHz, $CDCl_3$) 24.5 (C-1″), 102.0 (C-4), 117.8 (C-1‴), 118.0 (C-3‴), 118.9 (C-5‴), 126.7 (C-2′,6′), 128.8 (C-3′,5′), 128.9 (C-6‴), 130.5 (C-1′), 132.0 (C-4‴), 133.6 (C-4′), 146.3 (C-5), 150.3 (C-3), 155.5 (C-2‴), 159.9 (C-2″); ESI^+-MS, *m*/*z* 329 [56, $(M+H)^+$, ^{37}Cl], 327 [100, $(M+H)^+$, ^{35}Cl]; HR-EIMS: $M^{+\bullet}$, $C_{17}H_{15}{}^{37}ClN_4O$ requires 328.0910, found 328.0897; $C_{17}H_{15}{}^{35}ClN_4O$ requires, 326.0934found 326.0918.

*4.5.4. 5(3)-[2-(2-Hydroxyphenyl)-2-hydrazonoethyl]-3(5)-(4-nitrophenyl)-1H-pyrazole (**8d**).* Orange solid. Mp 191–192 °C. δ_H (300.13 MHz, $CDCl_3$) 4.13 (2H, s, H-1″), 6.43 (1H, s, H-4), 6.98 (1H, t, *J* 7.8 Hz, H-5‴), 7.08 (1H, d, *J* 8.2 Hz, H-3‴), 7.36 (1H, ddd, *J* 8.2, 7.8, and 1.4 Hz, H-4‴), 7.73 (1H, dd, *J* 7.8 and 1.4 Hz, H-6‴), 7.91 (1H, d, *J* 8.6 Hz, H-2′,6′), 8.24 (2H, d, *J* 8.6 Hz, H-3′,5′), 13.20 (1H, s, 2‴-O*H*); δ_C (125.77 MHz, $CDCl_3$) 24.9 (C-1″), 102.1 (C-4), 117.9 (C-1‴), 118.2 (C-3‴), 118.3 (C-5‴), 124.8 (C-3′,5′), 127.9 (C-6‴), 128.9 (C-2′,6′), 132.6 (C-4‴), 136.3 (C-1′), 141.3 (C-5), 143.6 (C-4′), 149.6 (C-3), 159.6 (C-2″), 161.5 (C-2‴); ESI^+-MS, *m*/*z* 337 [100%, $(M+H)^+$]; HRMS (ESI): $(M+H)^+$, found 337.1161. $C_{17}H_{15}N_5O_3$ requires 337.1175.

4.6. General procedure for the synthesis of 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1*H*-pyrazoles 10a–d

To a solution of the appropriate 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-hydrazonoethyl]-1*H*-pyrazole **8a–d** (0.15 mmol) in methanol (10 mL) was added 1 molar equiv of a HCl solution (10%, 52.3 μL, 0.15 mmol). The mixture was stirred at room temperature for 48 h. After that period the reaction mixture was extracted with chloroform and dried over anhydrous sodium sulfate and the solvent was evaporated to dryness. The solid residue was purified by thin layer chromatography, using a mixture of light petroleum/ethyl acetate (2:3) as eluent. The 3(5)-aryl-5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1*H*-pyrazoles **10a–d** were obtained in moderate yields: **10a**, 29.64 mg, 71%; **10b**, 22.20 mg, 48% **10c**, 23.46 mg, 50%; **10d**, 24.73 mg, 51%.

*4.6.1. 5(3)-[2-(2-Hydroxyphenyl)-2-oxoethyl]-3(5)-phenyl-1H-pyrazole (**10a**).* Yellow solid. Mp 189–190 °C. δ_H (300.13 MHz, $CDCl_3$) 4.43 (2H, s, H-1″), 6.53 (1H, s, H-4), 6.93 (1H, ddd, *J* 7.6, 6.3, and 1.1 Hz, H-5‴), 7.01 (1H, dd, *J* 8.0 and 1.1 Hz, H-3‴), 7.35–7.46 (3H, m, H-4′ and H-3′,5′), 7.51 (1H, ddd, *J* 8.0, 6.3, and 1.5 Hz, H-4‴), 7.63 (2H, dd, *J* 8.2, 1.2 Hz, H-2′,6′), 7.91 (1H, dd, *J* 7.6, 1.1 Hz, H-6‴), 12.10 (1H, s, 2‴-OH); δ_C (75.47 MHz, $CDCl_3$) 37.3 (C-1″), 103.2 (C-4), 118.7 (C-3‴), 118.8 (C-1‴), 119.2 (C-5‴), 125.5 (C-2′,6′), 128.5 (C-4′), 129.0 (C-3′,5′), 130.3 (C-1′), 130.4 (C-6‴), 136.9 (C-4‴), 143.1 (C-5), 146.8 (C-3), 162.9 (C-2‴), 202.1 (C-2″). ESI-MS, *m*/*z*: 279 [100%, $(M+H)^+$]; HRMS (ESI): $(M+H)^+$, found 279.11259. $C_{17}H_{14}N_2O_2$ requires 279.11280.

*4.6.2. 5(3)-[2-(2-Hydroxyphenyl)-2-oxoethyl]-3(5)-(4-methoxyphenyl)-1H-pyrazole (**10b**).* Orange oil. Mp 170–170 °C. δ_H (300.13 MHz, $CDCl_3$) 3.88 (3H, s, 4′-O*CH*$_3$), 4.42 (2H, s, H-1″), 6.62 (1H, s, H-4), 6.85–6.96 (4H, m, H-3‴, H-5‴ and H-3′,5′) 7.51 (1H, d, *J* 8.6 Hz, H-2′,6′), 7.68 (1H, dd, *J* 8.1 and 1.1 Hz, H-6‴), 7.97 (1H, dt, *J* 7.0 and 1.1 Hz, H-4‴), 12.10 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 37.9 (C-1″), 55.4 (4′-OCH_3), 101.7 (C-4), 116.7 (C-3′,5′), 118.0 (C-3‴), 118.2 (C-1‴), 119.0 (C-5‴), 124.8 (C-1′), 126.9 (C-2′,6′), 130.4 (C-6‴), 136.7 (C-4‴), 140.9 (C-5), 142.3 (C-3), 159.6 (C-4′), 162.8 (C-2‴), 201.2 (C-2″); ESI^+-MS, *m*/*z* 309 [100%, $(M+H)^+$]; HR-ESI^+MS: $C_{18}H_{16}N_2O_3$ requires 309.1171, found 309.1190.

*4.6.3. 3(5)-(4-Chlorophenyl)-5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-1H-pyrazole (**10c**).* Yellow oil. Mp 180–182 °C. δ_H (300.13 MHz, $CDCl_3$) 4.42 (2H, s, H-1″), 6.64 (1H, s, H-4), 6.92 (1H, dt, *J* 8.4 and 1.2 Hz, H-5‴), 7.00 (1H, dd, *J* 8.4 and 1.2 Hz, H-3‴), 7.30–7.38 (3H, m, H-4‴ and H-3′,5′), 7.64 (2H, dd, *J* 8.5 and 1.2 Hz, H-2′,6′), 7.73 (1H, dd, *J* 8.4 and 1.2 Hz, H-6‴), 13.30 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 37.6 (C-1″), 102.6 (C-4), 118.6 (C-3‴), 118.9 (C-1‴), 119.2 (C-5‴), 125.2 (C-2′,6′), 128.0 (C-3′,5′), 130.3 (C-1′,6‴), 132.3 (C-4′), 132.8 (C-4‴), 140.2 (C-5), 149.1 (C-3), 161.3 (C-2‴), 202.0 (C-2″); ESI-MS, *m*/*z* 315 [100, $(M+H)^+$, ^{37}Cl], 313 [35%, $(M+H)^+$, ^{35}Cl]; HR-ESI^+MS: $(M+H)^+$, $(C_{17}H_{13}{}^{37}ClN_2O_2+H)^+$ requires 315.07100, found 315.06901; $(C_{17}H_{13}{}^{35}ClN_2O_2+H)^+$ requires 313.07383, found 313.07384.

*4.6.4. 5(3)-[2-(2-Hydroxyphenyl)-2-oxoethyl]-3(5)-(4-nitrophenyl)-1H-pyrazole (**10d**).* Orange solid. Mp 208–209 °C. δ_H (300.13 MHz, $CDCl_3$) 4.46 (2H, s, H-1″), 6.69 (1H, s, H-4), 6.95 (1H, dt, *J* 8.0 and 0.9 Hz, H-5‴), 6.99 (1H, dd, *J* 7.8 and 0.9 Hz, H-3‴), 7.36 (1H, dt, *J* 7.8 and 1.3 Hz, H-4‴), 7.73 (1H, dd, *J* 8.0 and 1.3 Hz, H-6‴), 7.91 (1H, d, *J* 8.1 Hz, H-3′,5′), 8.21 (2H, d, *J* 8.1 Hz, H-2′,6′), 13.20 (s, 1 H, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 37.4 (C-1″), 102.6 (C-4), 118.5 (C-3‴), 118.6 (C-1‴), 118.8 (C-5‴), 125.5 (C-2′,6′), 128.0 (C-3′,5′), 130.4 (C-6‴), 130.6 (C-1′), 136.9 (C-4‴), 138.8 (C-4′), 140.9 (C-5), 148.1 (C-3), 162.6 (C-2‴), 201.6 (C-2″). ESI^+-MS, *m*/*z* 309 [100%, $(M+H)^+$]; HR-ESI^+MS: $(M+H)^+$, $C_{16}H_{11}N_3O_4$ requires 309.0755, found 309.0759.

4.7. General procedure for the synthesis of 5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-3(5)-phenyl-1-phenyl-1*H*-pyrazole 16a

Phenylhydrazine (0.15 mL, 1.50 mmol) was added to a solution of the (*E*)-3-bromo-2-styryl-4*H*-chromen-4-one **3a** (0.30 mmol) in methanol (15 mL). The reaction mixture was stirred at reflux under nitrogen atmosphere, until the disappearance of the starting material. The mixture was then poured into chloroform (20 mL) and washed with acidified water (2×20 ml, pH 5). The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated to dryness, and the solid residue was purified by thin layer chromatography using a 2:3 mixture of hexane/ethyl acetate as eluent. The hydrazonopyrazole **15a** (88.02 mg, 66% yield), obtained after solvent evaporation, was dissolved in methanol (10 mL) and 1 molar

equiv of an HCl solution (10%, 69.69 μL; 0.20 mmol) was added to the methanolic solution. The mixture was stirred at room temperature for 48 h. After that period the reaction mixture was extracted with chloroform and dried over anhydrous sodium sulfate and the solvent was evaporated to dryness. The solid residue was purified by thin layer chromatography, using a mixture of light petroleum/ethyl acetate (2:3) as eluent. After solvent evaporation 5(3)-[2-(2-hydroxyphenyl)-2-oxoethyl]-3(5)-phenyl-1*H*-pyrazole (**16a**) was obtained in good yield (49.62 mg; 70%).

*4.7.1. 5(3)-[2-(2-Hydroxyphenyl)-2-oxoethyl]-3(5)-phenyl-1-phenyl-1H-pyrazole (**16a**).* Yellow residue. δ_H (300.13 MHz, $CDCl_3$) 4.40 (2H, s, H-1″), 6.67 (1H, s, H-4), 6.87 (1H, ddd, *J* 8.1, 7.1, and 1.1 Hz, H-5‴), 7.01 (1H, dd, *J* 8.4 and 1.1 Hz, H-3‴), 7.31–7.52 (9H, m, H-3′,4′,5′, H-2‴,3‴,4‴,5‴,6‴ and H-4‴), 7.60 (1H, dd, *J* 8.1 and 1.6 Hz, H-6‴), 7.86 (2H, dd, *J* 8.4, 1.3 Hz, H-2′,6′), 11.96 (1H, s, 2‴-O*H*); δ_C (75.47 MHz, $CDCl_3$) 36.2 (C-1″), 105.4 (C-4), 118.5 (C-1‴), 118.8 (C-3‴), 119.2 (C-5‴), 125.7 and 125.8 (C-2′,6′, 2‴,6‴), 128.0 (C-4′), 128.6 (C-3′,5′), 129.4 (C-3‴,5‴), 129.9 (C-6‴), 132.8 (C-1′), 136.6 (C-3), 137.0 (C-4‴), 139.3 (C-1‴), 152.0 (C-5), 162.8 (C-2‴), 200.8 (C-2″). ESI-MS, *m*/*z*: 355 [100%, $(M+H)^+$]; HRMS (ESI): $(M+H)^+$, found 355.14479. $C_{17}H_{14}N_2O_2$ requires 355.14481.

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Supplementary data

Spectroscopic data of all reported compounds are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.028.

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