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Synthesis of New 1*H*-Indazoles through Diels–Alder Transformations of 4-Styrylpyrazoles under Microwave Irradiation Conditions

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Microwave irradiation under solvent-free conditions induces 1-acetyl-4-styrylpyrazoles to undergo Diels–Alder cycloaddition reactions with *N*-methyl- or *N*-phenylmaleimide to give tetrahydroindazoles in good yields and with high selectivities. With conventional heating, these reactions either do not occur or afford only traces of the cycloadducts. These cycloadducts were then converted into the corresponding 1*H*-indazoles by dehydrogenation with DDQ in dry 1,2,4-trichlorobenzene under microwave irradiation or classical heating conditions. The structures of all new derivatives and the stereochemistries of the cycloadducts were assigned by NMR spectroscopy.

Introduction

Natural products containing indazole moieties are rare and at present only three examples are known: nigellicine, nigeglanine and nigellidine.[1–6] Many synthetic indazoles, however, are known and recognized by their pharmaceutical activity, which has inspired the development of a number of new syntheses for the indazole ring system.[7–10] Certain indazoles act as dopamine D2 receptor antagonists,[11–13] antipyretic and anti-inflammatory agents (bendazac and benzidamine),[14] analgesics[15,16] or anti-HIV protease[17,18] and Rho kinase inhibitors[19,20] and are used in the treatment of diabetes[7,21,22] and obesity.[23] Other derivatives exhibit antitumour (combretastatin),[24–28] CNS (granisetron),[8] bronchodilatory, vasodilatory or neuroprotectant activities.[29] 1-Benzyl-1*H*-indazole-3-carboxylic acids display antispermatogenetic[30] and anticancer activity,[24,28] whereas 4-(indazol-3-yl)phenols behave as anti-arthritic drugs.[31,32] Indazoles also have agrochemical applications as herbicides, bactericides, fungicides (fluconazole)[33] and plant growth inhibitors.[7] In the food industry they (mainly guanidino-1*H*-indazoles) are used as sweeteners.[7] Indazole-type compounds also have a wide range of applications in analytical determinations and in industry. Arylazoindazoles are used as reagents for the determination of vanadium,[7,34] whereas others are formulated in photographic materials and as components of adhesives, with applications in polyimide films and as corrosion inhibitors.[7]

There are several methods for the synthesis of indazoles;[8,9,35] most of them start from benzene derivatives, with the pyrazole ring being formed by ring closure. Most indazole ring-closure procedures involve bond formation between the two nitrogen atoms (N–N) as the last step;[36] nevertheless, ring-closure through N–C bond formation through the creation of N2–C3[37] or N1–C7a bonds[38] [numbering of 1*H*-indazole (**1**); Figure 1] is also common. A few examples involving C3–C3a ring-closure have also been reported.[39] There are also, however, some examples that start from pyrazoles, involving cycloaddition reactions between 1-phenyl-5-vinylpyrazole,[40] 1-aryl-3-phenyl-1,6-dihydropyrano[2,3-*c*]pyrazoles[41] or *N*-unsubstituted pyrazole *ortho*-quinodimethanes[42] and several dienophiles. As part of our continuing work on the synthesis and transformation of styrylpyrazoles we have studied Diels–Alder reactions between 1-acetyl-4-styrylpyrazoles and (mainly) *N*-methylmaleimide, as well as the oxidation of the obtained cycloadducts, thus developing a method for the synthesis of fused 1*H*-indazoles.

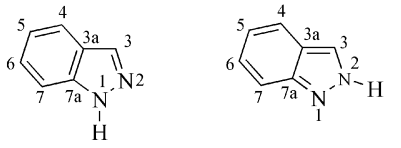

Figure 1. Structures of 1*H*- and 2*H*-indazoles.

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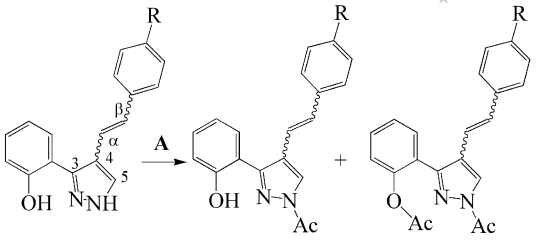
Results and Discussion

Chemistry

Vinylpyrazoles are very reluctant to participate as dienes in cycloaddition reactions involving their pyrazole rings, owing to the loss of aromaticity involved in these reactions.[40] Cycloaddition reactions of vinylpyrazoles require very reactive dienophiles and high temperatures and pressures (120–140 °C and 8–10 atm) and are usually slow reactions giving rise to adducts in moderate to low yields.[40,43] Obviously these conditions are not compatible with sensitive or unstable compounds, and retro Diels–Alder reactions can occur when the cycloadditions require long reaction times. In spite of vinylpyrazoles being very unreactive we decided to study the reactivities of styrylpyrazoles as dienes under classical heating or microwave irradiation conditions, following our previous work with compounds of this type.[44]

All attempts to achieve reactions between (*E*)-5(3)-(2-hydroxyphenyl)-3(5)-styrylpyrazoles or their *N*-methyl derivatives and either electron-rich or electron-poor dienophiles in 1,2,4-trichlorobenzene at reflux or under microwave irradiation conditions, in solvent or under solvent-free conditions, had previously been unsuccessful; the expected adducts either were obtained only in small yields or were not obtained at all.[45] In that prior study, however, we also showed that (*E*)-1-acetyl-3-(2-hydroxyphenyl)-5-styrylpyrazole can react with *N*-methylmaleimide to give the expected cycloadduct, though in less than 20% yield, together with other products.[45]

In our ongoing research into the synthesis and transformation of (*E*)- and (*Z*)-3-styrylchromones[46] we have synthesized several (*E*)- and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a**–**e** and **4a**–**c**[47] (Scheme 1) in order to study their reactivities in cycloaddition reactions. As we have previously shown in the Diels–Alder reactions of (*E*)-5(3)-(2-hydroxyphenyl)-3(5)-styrylpyrazoles, it is necessary to carry out *N*-derivatisation to avoid conjugate additions to dienophiles,[45] so the 4-styrylpyrazoles **3a**–**e** and **4a**–**c** were acetylated with acetyl chloride in dry pyridine (Scheme 1). These acetylation reactions are dependent on the substituents on the aryl rings of the styryl groups and on the stereochemistries of the styryl groups (Table 1). Acetylation of the (*E*)-styrylpyrazoles **3a**–**e** with excess acetyl chloride led to the diacetylated pyrazoles **7a**, **7b** and **7d**, except in the case of the compound bearing an electron-donating group on the aryl ring of the styryl group (derivative **3c**), which also requires an excess of acetylation agent to yield the monoacetyl derivative **5c**. The (*Z*)-4-styrylpyrazoles **4a**–**c** seem to be more reactive than the corresponding diastereomers **3a**–**c**, because smaller amounts of acetylating agent or shorter reaction times are required to provide similar results (Table 1). Although some indication about the acetylation sites of some asymmetric pyrazoles can be found in the literature, acetylation generally occurs at N-1 in the starting material because the resulting product is the less hindered one;[48] in the present case N1-acetylation is probably reinforced by the hydrogen bond between the 2′-hydroxy proton and N-2.



E-isomers: **3a–e** *Z*-isomers: **4a–c** | *E*-isomers: **5a–e** *Z*-isomers: **6a–c** | *E*-isomers: **7a**,**b**,**d** *Z*-isomers: **8c**

a) R = H, b) R = Cl, c) R = OC_2H_5, d) R = NO_2, e) R = CF_3
A: dry pyridine, AcCl, room temperature

Scheme 1. Acetylation of (*E*)- and (*Z*)-3(5)-(2-hydroxyphenyl)-4-styrylpyrazoles **3a**–**e** and **4a**–**c**.

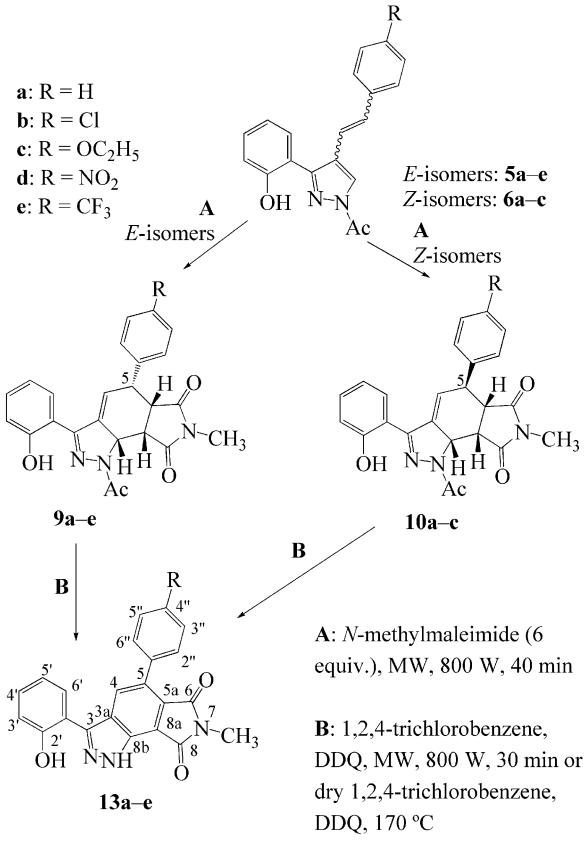
Table 1. Results and conditions for *N*-acetylation of (*E*)- and (*Z*)-3-(2-hydroxyphenyl)-4-styrylpyrazoles **3a**–**e** and **4a**–**c**.

	R	AcCl (molar equiv.)	Reaction time [h]	Yield of **5/6** (%)	Yield of **7/8** (%)
3a	H	1.1	70	**5a** (75)	–
3a	H	3.5	24	–	**7a** (79)
3b	Cl	1.1	24	**5b** (77)	–
3b	Cl	3.2	24	–	**7b** (80)
3c	OC_2H_5	3	70	**5c** (72)	–
3d	NO_2	1.1	24	**5d** (45)	–
3d	NO_2	3.2	66	–	**7d** (92)
3e	CF_3	1.1	24	**5e** (60)	–
4a	H	1.5	24	**6a** (59)	–
4b	Cl	1.5	24	**6b** (62)	–
4c	OC_2H_5	2.4	48	**6c** (70)	–
4c	OC_2H_5	3.0	72	**6c** (56)	**8c** (28)

In continuation of our previous work on microwave-assisted Diels–Alder cycloaddition reactions under solvent-free conditions,[49] mixtures of each one of the 1-acetyl-4-styrylpyrazoles **5a**–**e** or **6a**–**c** and *N*-methylmaleimide were subjected to microwave irradiation under solvent-free conditions[45] (Scheme 2) and the desired cycloadducts **9a**–**e** or **10a**–**c** were obtained in moderate to very good yields (**9a**–**e**, 68–95%; **10a**–**c**, 54–60%).

We tried to improve the yield of cycloadduct **9a** by changing the reaction time. The reaction between **5a** and *N*-methylmaleimide in a shorter reaction time (20 min) afforded **9a** in 12% yield, whereas a longer reaction time (1 h) gives **9a** in 34% yield with the recovery of starting material **5a** (17%), probably due to a retro-Diels–Alder reaction. We thus concluded that the best yield was achieved after 40 min of irradiation, and therefore all the cycloaddition reactions were conducted with this period of time. The *Z* isomers **6a**–**c** seem to be less reactive than the corresponding *E* isomers **5a**–**c**, because the adducts **10a**–**c** were obtained in lower yields (54–60% for **10a**–**c**, in comparison with 68–95% for **9a**–**c**) under the same experimental conditions (800 W for 40 min).

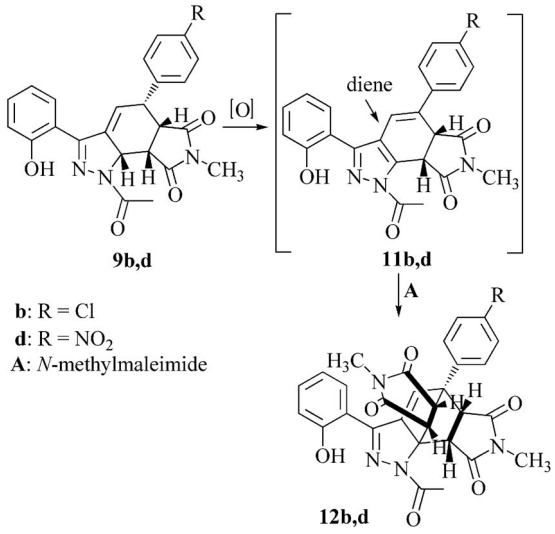
In the reactions between *N*-methylmaleimide and **5b** or **5d**, another compound besides the expected adducts **9b** and **9d** was isolated in each case (7–10%). The formation of this compound can be explained by partial oxidation of the



Scheme 2. Synthesis of indazoles **13a**–**e**.

formed adducts **9b** or **9d** in the reaction medium, giving the intermediates **11b** or **11d**. Cycloadditions between the formed diene moieties in these intermediates with another molecule of *N*-methylmaleimide, which was used in excess, afforded compounds **12b** or **12d** (Scheme 3). Probably the presence of a 5-aryl ring bearing electron-withdrawing substituents increases the acidity of proton H-5, facilitating the oxidation of **9b** and **9d** into **11b** and **11d**, which further react with the excess *N*-methylmaleimide to give **12b** and **12d** (Scheme 3). The literature reports the formation of compounds of this type in the reactions between vinylic derivatives of [1]benzothieno[3,2-*b*]furan and DMAD.[50]

In order to determine the scope of these reactions and their utility as a new synthetic methodology for the synthesis of novel indazole-type compounds, with complete and extended aromatic structures, we studied the oxidation of the cycloadducts by our recently published methodology using DDQ as dehydrogenation agent and microwave irradiation as an alternative to conventional heating (Scheme 2).[49] The 1-acetyl-5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]-indazoles **9a**–**e** and **10a**–**c** were oxidised with DDQ (3 molar equiv., excess) in 1,2,4-trichlorobenzene under microwave irradiation at 170 °C for 30 min, and the 5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazoles **13a**–**e** (Scheme 2) were obtained in moderate to low yields (Table 2).[45]



Scheme 3. Synthesis of compounds **12b** and **12d**.

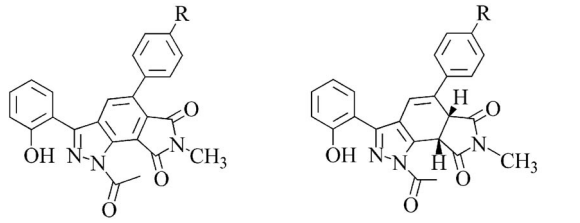
Table 2. Results and conditions for the dehydrogenation of adducts **9a**–**e** and **10a**–**c** with DDQ under microwave and conventional heating conditions.[a]

	R	Microwave/conventional heating conditions Reaction time [h]	Yield of **13** (%)	Yield of **14** (%)	Yield of **15** (%)
9a	H	6	85/31	13/–	–/–
9b	Cl	4	32/60	–/–	13/–
9c	OC_2H_5	6	36/36	–/–	4/–
9d	NO_2	4	34/73	–/20	20/–
9e	CF_3	4	11*/68	–/–	6/–
10a	H	4	22**/56	–/–	25/–
10b	Cl	3	6***/55	–/–	–/–
10c	OC_2H_5	8	31/36	–/–	–/–
		3	–/49	–/–	–/–

[a] Recovered starting material: * 7%, ** 25%, *** 18%.

These results indicate that the dehydrogenation was accompanied by *N*-deacetylation.[51] The yields, however, were low to moderate, due to extensive degradation occurring in the reaction mixtures. In some cases we also recovered small amounts of the starting cycloadducts and we isolated the partially oxidised compounds **15a**–**e** (Figure 2, Table 2). By dehydrogenation of tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole **9a** we obtained **14a** (13%), whereas from the dehydrogenation of adducts **9b**–**e** and **10a** we also isolated the partially oxidised compounds **15a**–**e**. From the dehydrogenation of adduct **9d** under conventional heating conditions we also isolated **14d** (20%). In order to improve the yields of compounds **13a**–**e** we studied the dehydrogenation of **9b** over a longer reaction time (1 h) but we only obtained unknown compounds (decomposition products).

Because the above results were not satisfactory we decided to investigate the dehydrogenation of the 1-acetyl-5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazoles **9a**–**e** and **10a**–**c** under classical heating conditions. The dehydrogenation of adducts **9a**–**e** and **10a**–**c** in the presence of DDQ (3 molar



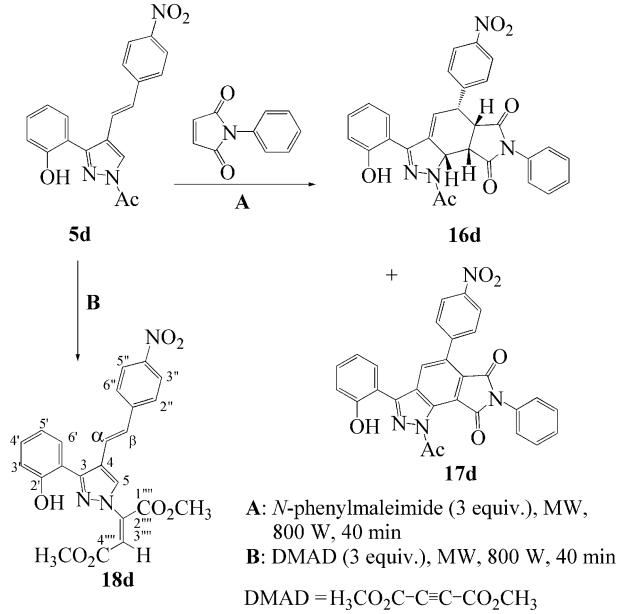
14a: R = H **15b–e**: R = Cl, OC_2H_5, NO_2, CF_3

Figure 2. Structures of compounds **14a**, **14d** and **15a–e**.

equiv., excess) in dry 1,2,4-trichlorobenzene at 170 °C, until the consumption of the starting material, gave the expected indazoles **13a–e** in moderate to good yields (Table 2).

In an attempt to improve the yields we investigated the dehydrogenation of cycloadduct **9b** under classical heating conditions in the presence of chloranil instead of DDQ, expecting to minimize the degradation of the reaction mixture. The reaction between **9b** and chloranil (3 molar equiv.) in dry 1,2,4-trichlorobenzene at 170 °C over 17 h led to the corresponding indazole **13b** in 27% yield and to decomposition products. These results suggested that the best conditions for the dehydrogenation under classical heating conditions involve the use of a stronger oxidant such as DDQ during a short period of time.

Indazoles **13a–e** were obtained in better yields when the dehydrogenation of adducts **9a–e** and **10a–c** was performed under classical heating conditions; probably the hard conditions used under microwave irradiation are responsible for the observed radical degradation and consequently for the low obtained yields. Our results also suggested that the dehydrogenation of the cycloadducts **9a–e** and **10a–c** is easy to perform when there is an electron-withdrawing substituent in the 5-aryl ring.



A: *N*-phenylmaleimide (3 equiv.), MW, 800 W, 40 min
B: DMAD (3 equiv.), MW, 800 W, 40 min

DMAD = $H_3CO_2C{-}C{\equiv}C{-}CO_2CH_3$

Scheme 4. Reactions of (*E*)-1-acetyl-3-(2-hydroxyphenyl)-4-(4-nitrostyryl)-1*H*-pyrazole (**5d**) with *N*-phenylmaleimide and DMAD.

It was also decided to study cycloadditions between the (*E*)-1-acetyl-4-nitrostyrylpyrazole **5d** and the other electron-deficient dienophiles *N*-phenylmaleimide and dimethyl acetylenedicarboxylate (DMAD) (Scheme 4). Treatment of **5d** with an excess of *N*-phenylmaleimide (3 molar equiv.) under microwave irradiation and solvent-free conditions for 40 min led to the formation of the cycloadduct **16d** in 49% yield and to the oxidised indazole **17d** in 5% yield, without recovery of any starting material. We examined the cycloaddition reaction between **5d** and *N*-phenylmaleimide in a shorter reaction time (20 min) in an attempt to improve the yield of the adduct **16d** and to avoid its oxidation, but a mixture of compounds that was difficult to separate was obtained and no pure compound was isolated or identified.

The cycloaddition reaction between **5d** and an excess of DMAD (3 molar equiv.) under microwave irradiation in solvent-free conditions for 40 min yielded traces of compound **18d**, obtained from the conjugate addition of the pyrazole nitrogen of **5d** to DMAD (Scheme 4).[52]

Nuclear Magnetic Resonance

The ^{1}H NMR spectra of the 1-acetyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazoles **5a–e** and **6a–c** each show a singlet at δ = 2.71–2.78 ppm corresponding to the COCH_3 protons and a deshielded singlet at δ = 9.66–10.32 ppm due to the resonance of the 2′-O*H* proton. The high frequency value of this proton is due to the intramolecular hydrogen bond with N-2. Other important features of the NMR spectra of pyrazoles **5a–e** and **6a–c** are the presence in each of a singlet due to the resonance of 5-H (δ = 8.00–8.55 ppm) and doublets due to the resonances of H-α and H-β. Protons 5-H and H-α can appear as a doublet and a double doublet, respectively, when they are coupled to each other (J = 0.6–1.2 Hz). The coupling constant values of $^3J_{H\alpha,H\beta}$ are the main criteria to distinguish between pyrazoles **5a–e** and **6a–c**: $^3J_{H\alpha,H\beta} \approx$ 16–18 Hz indicates a *trans* configuration of the vinylic moiety whereas a value of $^3J_{H\alpha,H\beta} \approx$ 11–12 Hz indicates a *cis* configuration. Because of the non-coplanarity between ring B and the rest of the structure in the cases of pyrazoles **6a–c** the resonances of the 5-H, H-α and H-β protons appear at lower frequencies than in the cases of pyrazoles **5a–e**.

The ^{13}C NMR spectra of pyrazoles **5a–e** and **6a–c** each presented two characteristic signals at δ = 21.6 and 167.8–168.1 ppm due to the resonance of methyl and carbonyl group, respectively. The identification of the other carbons was done on the basis of two-dimensional HSQC and HMBC spectroscopic experiments [the main connectivities of the HMBC spectra are (CH_3→C=O); (H-α→C-3, C-4, C-5, C-1′′, C-β); (H-β→C-α, C-4, C-2′′,6′′, C-1′′); (5-H→C-3, C-4, C-α); (6′-H→C-2′, C-3, C-4′); (3′-H→C-2′, C-1′, C-4′ e C-5′); (2′′,6′′-H→C-4′′); (3′′,5′′-H→C-1′′)].

In the spectra of the diacetylated pyrazoles **7a**, **7b**, **7d** and **8c** one can in each case observe the singlet due to the resonance of the methyl protons of the *O*-acetyl group (CO_2CH_3) at δ = 2.07–2.20 ppm and the singlet due to the

resonance of the methyl protons of the *N*-acetyl group ($NCOCH_3$) at a higher frequency (δ = 2.68–2.75 ppm). Also characteristic of these compounds are the signals observed in the ^{13}C NMR spectra corresponding to the resonance of two CO_2CH_3 groups (at δ = 20.8–21.1 and 21.4–21.6 ppm and also at δ = 168.9–169.1 and 169.2–169.4 ppm).

The main feature in each of the ^1H NMR spectra of cycloadducts **9a**–**e** and **10a**–**c** is the presence in the aliphatic region of signals due to the proton resonances of the tetrahydro-aromatic ring and the absence of H-α and H-β resonances. Other spectroscopic characteristics are: i) the presence of the hydroxy group involved in a hydrogen bond (δ_H = 9.73–9.85 ppm), ii) the presence of the acetyl group, apparent in the ^1H NMR spectra from the signal corresponding to the methyl group (δ_H = 2.46–2.55 ppm) and in the ^{13}C NMR spectra due to the signals corresponding to the methyl group at (δ_C = 21.4–21.5 ppm) and the carbonyl group at (δ_C = 168.4–168.6 ppm), and iii) the presence of an *N*-methyl group (δ_H = 2.76–2.77 ppm; δ_C = 25.0–25.4 ppm). These data are consistent with the proposed cycloadduct structures **9a**–**e** and **10a**–**c**.[45] The *cis* configurations of protons 5-H, 5a-H, 8a-H and 8b-H in adducts **9a**–**e** and of protons 5a-H, 8a-H and 8b-H in adducts **10a**–**c**, confirmed by NOE cross peaks observed in the NOESY spectra[45] and also by detailed analysis of the coupling constants of some protons ($J_{H8a,H8b} \approx 7$–8 Hz for both isomers; $J_{H5,H5a} \approx 8$ Hz for **9a**–**e**; $J_{H5,H5a} \approx 0$ Hz for **10a**–**c**) indicate that the reaction selectively afforded the *endo* adduct in both cases. No traces of the *exo* adduct were detected.

In the aliphatic region of the ^{13}C NMR spectra, several signals due to the newly formed tetrahydro-aromatic ring are observed at δ = 40.3–57.6 ppm. The signals due to the carbonyl groups of the *N*-methylmaleimide moiety in these compounds were assigned at δ = 172.9–173.9 ppm (C-6) and δ = 174.1–174.7 ppm (C-8). Another characteristic signal is the resonance of C-4 appearing at δ = 123.3–126.2 ppm. Unambiguous assignment of the carbons was carried out on the basis of the correlations observed in HSQC and HMBC spectra [the main connectivities of the HMBC spectra are ($COCH_3 \rightarrow COCH_3$); ($NCH_3 \rightarrow$C-6 and C-8); (2′-O*H*→C-2′ and C-1′); (6′-H→C-2′, C-3 and C-4′); (5a-H→C-8a, C-8); (8a-H→C-3a, C-6); (3′-H and 5′-H→C-1′); (3′′,5′′-H→C-1′′); (2′′,6′′-H→C-4′′)].

The main features of the ^1H NMR spectra of compounds **13a**–**e** are the singlets at δ = 8.40–8.44 ppm, each corresponding to the resonance of proton 4-H, and δ = 10.33–10.50 ppm, due to the resonance of the N*H* proton and confirming the absence of the acetyl group. The signal due to the resonance of 2′-O*H* proton appears in each case as a broad singlet, which means that the hydrogen bond between the 2′-O*H* proton and N-2 is less strong in these oxidised derivatives due to the possible prototropy. The ^1H NMR spectra of **14a** and **14d** are similar to those of **13a** and **13d**, save for the singlets due to the resonance of the $NCOCH_3$ protons at $\delta \approx 2.10$ ppm.

The structures of compounds **12b** and **12d** are supported by the presence in their ^1H NMR spectra of: i) singlets at δ = 2.64 ppm, due to the resonance of the $COCH_3$ protons, and at δ = 2.71 ppm, due to the resonance of the six protons of the two NCH_3 groups, ii) pairs of doublets at δ = 3.52 and 4.34 ppm, due to the resonance of two protons from sp^3 carbons from two *N*-methylmaleimide units, and iii) singlets at δ = 7.21 ppm, due to the resonance of 4-H.

The NMR spectroscopic data for cycloadducts **16d** and **17d** are similar to those for **9d** and **13d**, except for the presence in each case of an extra multiplet due to the resonance of the phenyl ring of the *N*-phenylmaleimide unit in the aromatic region. The structure **18d** is supported by the presence in the ^1H NMR spectrum of two singlets at δ = 3.85 ppm and 4.10 ppm, due to the resonance of the methoxy groups (CO_2CH_3) of the dienophile, the absence of the singlet characteristic of the acetyl group resonance and the presence of a singlet due to the resonance of H-3′′′. We also observed some typical signals of compound **18d** in the ^{13}C NMR spectrum, such as i) the signals due to the resonance of the methoxy groups of DMAD at δ = 52.4 and 53.9 ppm, ii) the signals due to the resonance of vinylic carbons at δ = 105.9 ppm (C-3′′′) and δ = 141.8 ppm (C-2′′′), and iii) the signals due to the resonances of the DMAD carbonyl groups at δ = 162.7 and 165.0 ppm.

Conclusions

We have established a new and efficient methodology for the synthesis of novel indazole-type compounds. Our results indicate that the (*Z*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles **6a**–**c** are less reactive than the (*E*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles **5a**–**e**, probably due to the steric hindrance caused by the phenyl ring at the β position. The Diels–Alder cycloadditions described here were stereoselective and gave the expected *endo* cycloadducts, which were dehydrogenated to the indazole-type compounds **13a**–**e**. Under microwave conditions, however, indazoles **13a**–**e** were obtained in better yields by the dehydrogenation of cycloadducts **9a**–**c**. This result can be explained by considering the dehydrogenation mechanism and the structures of the isomer cycloadducts, because the DDQ-mediated dehydrogenation of hydroaromatic compounds involves the parallel approach of the DDQ to the cyclohexene moiety of the cycloadduct in order to produce a 1,4-*cis* elimination.[53] This kind of elimination is easier for cycloadducts **9a**–**c**, in which the protons 5-H and 8b-H are in a *cis* configuration, because in the isomers **10a**–**c** there is higher steric hindrance and the protons 5-H and 8b-H are in a *trans* configuration.

Experimental Section

General Remarks: Melting points were measured in a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. NMR spectra were recorded on a Bruker Avance 300 spectrometer (300.13 MHz for ^1H and 75.47 MHz for ^{13}C), with $CDCl_3$ used as solvent if not stated otherwise. Chemical shifts (δ) are reported in ppm values and coupling constants (*J*) in Hz. The internal standard was TMS. ^1H assignments were made by use of 2D *g*COSY spectra, whereas unequivocal ^{13}C assignments were made

with the aid of 2D *g*HSQC (or HETCOR) and *g*HMBC experiments (delays for one-bond and long-range *J* C/H couplings were optimised for 145 and 7 Hz, respectively). Mass spectra (EI, 70 eV) were measured on VG Autospec Q and M mass spectrometers, whereas mass spectra (ESI^+) were measured on a Micromass Q-TOF-2TH spectrometer [dilution of 1 μL of the sample chloroform solution (≈ 10^{-5} M) in 200 μL of 0.1% trifluoroacetic acid/methanol solution; nitrogen was used as nebulizer gas and argon as collision gas; the needle voltage was set at 3000 V, with the ion source set at 80 °C and desolvation temperature at 150 °C; cone voltage was 35 V]. Mass spectra (MALDI TOF/TOF) were measured on a 4800 MALDI TOF/TOF Analyzer, MDS (Applied Biosystems) with α-cyano-4-hydroxycinnamic acid as matrix. Elemental analyses were obtained with Carlo Erba 1108 and LECO 932 instruments. Preparative thin-layer chromatography was carried out with Merck silica gel (60 DGF_{254}) and column chromatography with Merck silica gel 60 (70–230 mesh). All other chemicals and solvents used were obtained from commercial sources and were either used as received or dried by standard procedures.

Syntheses of the (*E*)- and (*Z*)-1-Acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles 5a–e and 6a–c: An appropriate amount of acetyl chloride was added to a stirred solution of the (*E*)- or (*Z*)-3-(2-hydroxyphenyl)-4-styrylpyrazole **3a**–**e** or **4a**–**c** (0.76 mmol) in dry pyridine (20 mL). The mixture was stirred at room temperature under nitrogen until complete consumption of the starting material **3a**–**e** or **4a**–**c**. The reaction mixture was then poured onto ice and water and acidified to pH 2–3 with hydrochloric acid (20%). The resulting mixture was extracted with chloroform and dried with anhydrous sodium sulfate. The solvent was evaporated to dryness and the residue was purified by thin layer chromatography with CH_2Cl_2 as eluent, giving the expected (*E*)- or (*Z*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazole [**5a** 173 mg (75%), **5b** 198 mg (77%), **5c** 191 mg (72%), **5d** 119 mg (45%), **5e** 170 mg (60%), **6a** 136 mg (59%), **6b** 160 mg (62%), **6c** 185 mg (70%)]. Compounds **5a**–**c**, **5e** and **6a**–**c** were obtained as white solids and compound **5d** was obtained as a yellow solid, all of them recrystallized from ethanol.

(*E*)-1-Acetyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazole (5a): M.p. 124–126 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.75 (s, 3 H, 1-COCH_3), 6.98 (ddd, *J* = 7.5, 7.7, 1.3 Hz, 1 H, 5′-H), 6.98 (d, *J* = 16.8 Hz, 1 H, Hβ), 7.07 (dd, *J* = 16.8, 0.4 Hz, 1 H, Hα), 7.11 (dd, *J* = 8.2, 1.3 Hz, 3′-H), 7.28–7.34 (m, 4′-,4′′-H), 7.39 (dt, *J* = 7.0, 7.5 Hz, 2 H, 3′′-,5′′-H), 7.49 (dd, *J* = 7.0, 1.6 Hz, 2 H, 2′′-,6′′-H), 7.66 (dd, *J* = 7.7, 1.6 Hz, 1 H, 6′-H), 8.47 (s, 1 H, 5-H), 9.87 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.6 (1-CO*C*H_3), 115.9 (C-1′), 117.3 (C-α,3′), 119.8 (C-5′), 123.2 (C-4), 126.1 (C-5), 126.6 (C-2′′,-6′′), 128.3 (C-4′′), 128.85 (C-3′′,-5′′), 128.99 (C-6′), 130.9 (C-4′), 132.7 (C-β), 136.5 (C-1′′), 152.5 (C-3), 156.1 (C-2′), 168.1 (1-*C*OCH$_3$) ppm. EI-MS: *m*/*z* (%) = 304 (80) $[M]^{+\cdot}$, 262 (73), 202 (6), 185 (21), 171 (100), 115 (23), 89 (5), 77 (8), 65 (4). $C_{19}H_{16}N_2O_2$ (304.3): calcd. C 74.98, H 5.30, N 9.20; found C 75.01, H 5.26, N 9.05.

(*E*)-1-Acetyl-4-(4-chlorostyryl)-3-(2-hydroxyphenyl)-1*H*-pyrazole (5b): This compound was shown to possess spectroscopic and analytical data identical to those previously reported.[45]

(*E*)-1-Acetyl-4-(4-ethoxystyryl)-3-(2-hydroxyphenyl)-1*H*-pyrazole (5c): M.p. 138–139 °C (recrystallized from ethanol). ^{1}H NMR: δ = 1.44 (t, *J* = 7.0 Hz, 3 H, 4′′-OCH$_2$CH_3), 2.75 (s, 3 H, 1-COCH_3), 4.07 (q, *J* = 7.0 Hz, 2 H, 4′′-OCH_2CH$_3$), 6.89 (d, *J* = 16.4 Hz, 1 H, Hβ), 6.91 (d, *J* = 8.6 Hz, 2 H, 3′′-,5′′-H), 6.95 (d, *J* = 16.4 Hz, 1 H, Hα), 6.98 (ddd, *J* = 7.4, 7.7, 1.2 Hz, 1 H, 5′-H), 7.10 (dd, *J* = 8.3, 1.2 Hz, 1 H, 3′-H), 7.34 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1 H, 4′-H), 7.42 (d, *J* = 8.6 Hz, 2 H, 2′′-,6′′-H), 7.68 (dd, *J* = 7.7, 1.6 Hz, 1 H, 6′-H), 8.43 (s, 1 H, 5-H), 9.91 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 14.8 (4′′-OCH$_2$*C*H$_3$), 21.6 (1-CO*C*H$_3$), 63.5 (4′′-O*C*H$_2$CH$_3$), 114.7 (C-3′′,-5′′), 114.9 (C-α), 116.0 (C-1′), 117.2 (C-3′), 119.7 (C-5′), 123.5 (C-4), 125.7 (C-5), 127.9 (C-2′′,-6′′), 128.9 (C-6′), 129.1 (C-1′′), 130.8 (C-4′), 132.3 (C-β), 152.3 (C-3), 156.0 (C-2′), 159.1 (C-4′′), 168.1 (1-*C*OCH$_3$) ppm. EI-MS: *m*/*z* (%) = 349 (75) $[M]^{+\cdot}$, 319 (5) $[M - C_2H_5]^+$, 307 (91), 290 (12), 260 (31), 247 (8), 185 (19), 171 (100), 115 (8), 91 (11), 77 (4), 65 (3). $C_{21}H_{20}N_2O_3$ (348.4): calcd. C 72.40, H 5.79, N 8.04; found C 72.20, H 6.14, N 7.68.

(*E*)-1-Acetyl-3-(2-hydroxyphenyl)-4-(4-nitrostyryl)-1*H*-pyrazole (5d): M.p. 178–180 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.78 (s, 3 H, 1-COCH_3), 7.02 (ddd, *J* = 7.5, 7.7, 1.1 Hz, 1 H, 5′-H), 7.05 (d, *J* = 16.0 Hz, 1 H, Hβ), 7.13 (dd, *J* = 8.1, 1.1 Hz, 3′-H), 7.25 (dd, *J* = 16.0, 0.6 Hz, 1 H, Hα), 7.38 (ddd, *J* = 8.1, 7.5, 1.6 Hz, 1 H, 4′-H), 7.57 (dd, *J* = 7.7, 1.6 Hz, 1 H, 6′-H), 7.62 (d, *J* = 8.8 Hz, 2 H, 2′′-,6′′-H), 8.25 (d, *J* = 8.8 Hz, 2 H, 3′′-,5′′-H), 8.55 (d, *J* = 0.6 Hz, 1 H, 5-H), 9.66 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.6 (1-CO*C*H$_3$), 115.7 (C-1′), 117.5 (C-3′), 119.9 (C-5′), 121.9 (C-α), 122.2 (C-4), 124.3 (C-3′′,-5′′), 126.6 (C-5), 127.0 (C-2′′,-6′′), 128.8 (C-6′), 130.1 (C-β), 131.2 (C-4′), 142.8 (C-1′′), 147.2 (C-4′′), 152.5 (C-3), 156.0 (C-2′), 168.1 (1-*C*OCH$_3$) ppm. EI-MS: *m*/*z* (%) = 349 (86) $[M]^{+\cdot}$, 319 (4) $[M - NO]^+$, 307 (100) $[M - C_2H_2O]^+$, 290 (21), 260 (43), 231 (8), 185 (30), 171 (98), 115 (13), 102 (6), 91 (3), 77 (5); 65 (4). $C_{19}H_{15}N_3O_4$ (349.3): calcd. C 65.32, H 4.33, N 12.03; found C 64.97, H 4.23, N 11.86.

(*E*)-1-Acetyl-3-(2-hydroxyphenyl)-4-(4-trifluoromethylstyryl)-1*H*-pyrazole (5e): M.p. 164–166 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.77 (s, 3 H, 1-COCH_3), 7.00 (ddd, *J* = 7.8, 7.4, 1.1 Hz, 1 H, 5′-H), 7.02 (d, *J* = 16.3 Hz, 1 H, Hβ), 7.13 (dd, *J* = 8.0, 1.1 Hz, 1 H, 3′-H), 7.17 (d, *J* = 16.3 Hz, 1 H, Hα), 7.36 (ddd, *J* = 8.0, 7.8, 1.7 Hz, 4′-H), 7.58 (d, *J* = 8.2 Hz, 2 H, 2′′-,6′′-H), 7.60 (dd, *J* = 7.4, 1.7 Hz, 1 H, 6′-H), 7.64 (d, *J* = 8.2 Hz, 2 H, 3′′-,5′′-H), 8.51 (s, 1 H, 5-H), 9.76 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.6 (1-CO*C*H$_3$), 115.8 (C-1′), 117.4 (C-3′), 119.8 (C-5′), 119.9 (C-α), 122.5 (C-4), 123.6 (q, *J* = 273.5 Hz, 4′′-*C*F$_3$), 125.8 (q, *J* = 3.8 Hz, C-3′′,-5′′), 126.7 (C-5), 128.9 (C-2′′,-6′′), 129.9 (q, *J* = 32.4 Hz, C-4′′), 130.1 (C-6′), 131.0 (C-4′,-β), 139.9 (C-1′′), 152.5 (C-3), 156.0 (C-2′), 168.1 (1-*C*OCH$_3$) ppm. EI-MS: *m*/*z* (%) = 372 (66) $[M]^{+\cdot}$, 353 (8), 330 (73), 185 (24), 171 (100), 115 (10), 102 (5), 91 (3), 77 (5). $C_{20}H_{15}F_3N_2O_2$ (372.3): calcd. C 64.51, H 4.06, N 7.52; found C 64.89, H 4.18, N 7.25.

(*Z*)-1-Acetyl-3-(2-hydroxyphenyl)-4-styryl-1*H*-pyrazole (6a): M.p. 151–153 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.71 (s, 3 H, 1-COCH_3), 6.48 (dd, *J* = 11.9, 1.2 Hz, 1 H, Hα), 6.81 (d, *J* = 11.9 Hz, 1 H, Hβ), 6.96 (ddd, *J* = 7.9, 7.5, 1.2 Hz, 1 H, 5′-H), 7.09 (dd, *J* = 8.2, 1.2 Hz, 1 H, 3′-H), 7.21–7.39 (m, 5 H, 2′′-,3′′-,4′-,5′′-,6′′-H), 7.33 (tt, *J* = 7.8, 1.6 Hz, 1 H, 4′′-H), 7.91 (dd, *J* = 7.9, 1.6 Hz, 1 H, 6′-H), 8.00 (d, *J* = 1.2 Hz, 1 H, 5-H), 10.26 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.6 (1-CO*C*H$_3$), 115.9 (C-1′), 117.2 (C-3′), 119.2 (C-α), 119.6 (C-5′), 120.4 (C-4), 127.6 (C-5), 128.3 (C-4′′), 128.5 (C-2′′,-6′′,-3′′,-5′′), 128.7 (C-6′), 130.9 (C-4′), 133.7 (C-β), 136.0 (C-1′′), 153.2 (C-3), 156.3 (C-2′), 167.9 (1-*C*OCH$_3$) ppm. MALDI TOF/TOF-MS: *m*/*z* (%) = 304.3 (23) $[M + H]^+$. $C_{19}H_{16}N_2O_2$ (304.3): calcd. C 74.98, H 5.30, N 9.20; found C 74.76, H 5.38, N 8.97.

(*Z*)-1-Acetyl-4-(4-chlorostyryl)-3-(2-hydroxyphenyl)-1*H*-pyrazole (6b): This compound was shown to possess spectroscopic and analytical data identical to those previously reported.[45]

(*Z*)-1-Acetyl-4-(4-ethoxystyryl)-3-(2-hydroxyphenyl)-1*H*-pyrazole (6c): M.p. 132–133 °C (recrystallized from ethanol). ^{1}H NMR: δ = 1.39 (t, *J* = 7.0 Hz, 3 H, 4′′-OCH$_2$CH_3), 2.72 (s, 3 H, 1-COCH_3), 4.00 (q, *J* = 7.0 Hz, 2 H, 4′′-OCH_2CH$_3$), 6.35 (dd, *J* = 11.8, 1.2 Hz,

Hα), 6.73 (d, *J* = 11.8 Hz, 1 H, Hβ), 6.75 (d, *J* = 8.7 Hz, 2 H, 3′′-,5′′-H), 6.94 (ddd, *J* = 7.9, 7.2, 1.2 Hz, 1 H, 5′-H), 7.08 (dd, *J* = 7.9, 1.2 Hz, 1 H, 3′-H), 7.19 (d, *J* = 8.7 Hz, 2 H, 2′′-,6′′-H), 7.32 (ddd, *J* = 7.9, 7.2, 1.6 Hz, 1 H, 4′-H), 7.94 (dd, *J* = 7.9, 1.6 Hz, 1 H, 6′-H), 8.06 (d, *J* = 1.2 Hz, 1 H, 5-H), 10.32 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 14.8 (4′′-OCH$_2$*C*H$_3$), 21.6 (1-CO*C*H$_3$), 63.4 (4′′-O*C*H$_2$CH$_3$), 114.4 (C-3′′,-5′′), 116.0 (C-1′), 117.16 (C-3′), 117.18 (C-α), 119.5 (C-5′), 120.7 (C-4), 127.6 (C-5), 128.3 (C-1′′), 128.7 (C-6′), 129.9 (C-2′′,-6′′), 130.8 (C-4′), 133.3 (C-β), 153.2 (C-3), 156.3 (C-2′), 158.5 (C-4′′), 167.8 (1-*C*OCH$_3$) ppm. EI-MS: *m*/*z* (%) = 348 (100) [M]$^{+\cdot}$, 320 (2), 306 (73), 291 (3), 277 (27), 260 (3), 247 (6), 185 (8), 171 (59), 155 (5), 131 (7), 115 (8), 102 (7), 91 (4), 77 (8), 65 (5). $C_{21}H_{20}N_2O_3$ (348.4): calcd. C 72.40, H 5.79, N 8.04; found C 72.21, H 5.75, N 7.65.

(*E*)-1-Acetyl-3-(2-acetyloxyphenyl)-4-styryl-1*H*-pyrazole (7a): Yield 621 mg (79%), yellow oil. ^{1}H NMR: δ = 2.07 (s, 3 H, OCOC*H*$_3$), 2.71 (s, 3 H, NCOC*H*$_3$), 6.72 (d, *J* = 16.4 Hz, 1 H, Hα), 6.93 (d, *J* = 16.4 Hz, 1 H, Hβ), 7.21–7.23 (m, 1 H, 4′′-H), 7.26 (dd, *J* = 8.0, 1.0 Hz, 1 H, 3′-H), 7.30 (dd, *J* = 7.3, 7.6 Hz, 2 H, 3′′-,5′′-H), 7.34–7.38 (m, 1 H, 5′-H), 7.37 (d, *J* = 7.3 Hz, 2 H, 2′′-,6′′-H), 7.49 (ddd, *J* = 7.7, 8.0, 1.7 Hz, 1 H, 4′-H), 7.57 (dd, *J* = 7.5, 1.7 Hz, 1 H, 6′-H), 8.49 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 20.8 (OCO*C*H$_3$), 21.4 (NCO*C*H$_3$), 116.9 (C-α), 123.1 (C-3′), 123.2 (C-4), 124.1 (C-5), 124.7 (C-1′), 126.1 (C-5′), 126.2 (C-2′′,-6′′), 127.8 (C-4′′), 128.5 (C-3′′,-5′′), 130.2 (C-4′), 130.7 (C-β), 131.3 (C-6′), 136.5 (C-1′′), 148.4 (C-2′), 151.3 (C-3), 168.9 (O*C*OCH$_3$), 169.2 (N*C*OCH$_3$) ppm. ESI$^+$-MS: *m*/*z* (%) = 369.1 (37) [M + Na$^+$]. HRMS (ESI$^+$): calcd. ($C_{21}H_{18}N_2O_3Na$) 369.12096; found 369.12072.

(*E*)-1-Acetyl-3-(2-acetyloxyphenyl)-4-(4-chlorostyryl)-1*H*-pyrazole (7b): Yield 1.10 g (80%), M.p. 124–126 °C, yellow solid (recrystallized from ethanol). ^{1}H NMR: δ = 2.08 (s, 3 H, OCOC*H*$_3$), 2.74 (s, 3 H, NCOC*H*$_3$), 6.69 (dd, *J* = 16.6, 0.5 Hz, 1 H, Hα), 6.87 (d, *J* = 16.6 Hz, 1 H, Hβ), 7.27–7.33 (m, 4 H, 2′′-,3′′-,5′′-,6′′-H), 7.34 (dd, *J* = 7.7, 1.2 Hz, 1 H, 3′-H), 7.38 (ddd, *J* = 7.2, 7.6, 1.2 Hz, 1 H, 5′-H), 7.52 (ddd, *J* = 7.2, 7.7, 1.8 Hz, 1 H, 4′-H), 7.57 (dd, *J* = 7.6, 1.8 Hz, 1 H, 6′-H), 8.49 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 21.0 (OCO*C*H$_3$), 21.6 (NCO*C*H$_3$), 117.7 (C-α), 123.1 (C-4), 123.2 (C-3′), 124.3 (C-5), 124.7 (C-1′), 126.3 (C-5′), 127.5 (C-2′′,-6′′), 128.9 (C-3′′,-5′′), 129.5 (C-β), 130.5 (C-4′), 131.4 (C-6′), 133.5 (C-4′′), 135.1 (C-1′′), 148.6 (C-3), 151.5 (C-2′), 169.1 (O*C*OCH$_3$), 169.4 (N*C*OCH$_3$) ppm. ESI$^+$-MS: *m*/*z* (%) = 403.1 (100) [M + Na$^+$], 381.1 (5) [M + H$^+$]. $C_{21}H_{17}ClN_2O_3$ (380.8): calcd. C 66.23, H 4.50, N 7.36; found C 66.21, H 4.66, N 7.26.

(*E*)-1-Acetyl-3-(2-acetyloxyphenyl)-4-(4-nitrostyryl)-1*H*-pyrazole (7d): Yield 844 mg (92%), M.p. 171–174 °C, yellow solid (recrystallized from ethanol). ^{1}H NMR: δ = 2.08 (s, 3 H, OCOC*H*$_3$), 2.75 (s, 3 H, NCOC*H*$_3$), 6.90 (d, *J* = 16.5 Hz, 1 H, Hα), 6.97 (d, *J* = 16.5 Hz, 1 H, Hβ), 7.29 (dd, *J* = 8.0, 0.6 Hz, 1 H, 3′-H), 7.40 (ddd, *J* = 7.5, 7.8, 0.6 Hz, 1 H, 5′-H), 7.51 (d, *J* = 8.9 Hz, 2 H, 3′′-,5′′-H), 7.55 (ddd, *J* = 7.5, 8.0, 1.7 Hz, 1 H, 4′-H), 7.57 (dd, *J* = 7.8, 1.7 Hz, 1 H, 6′-H), 8.18 (d, *J* = 8.9 Hz, 2 H, 2′′-,6′′-H), 8.56 (s, 1 H, 5-H) ppm. ^{13}C NMR: δ = 21.0 (OCO*C*H$_3$), 21.6 (NCO*C*H$_3$), 121.8 (C-α), 122.4 (C-4), 123.3 (C-3′), 124.2 (C-3′′,-5′′), 124.6 (C-1′), 125.1 (C-5), 126.4 (C-5′), 126.8 (C-2′′,-6′′), 128.3 (C-β), 130.7 (C-4′), 131.4 (C-6′), 143.1 (C-1′′), 146.9 (C-4′′), 148.6 (C-2′), 151.6 (C-3), 169.0 (O*C*OCH$_3$), 169.4 (N*C*OCH$_3$) ppm. EI-MS: *m*/*z* (%) = 391 (57) [M]$^{+\cdot}$, 361 (2) [M – NO]$^+$, 349 (73), 307 (100), 290 (16), 277 (49), 260 (33), 231 (5), 202 (6), 185 (16), 171 (75), 155 (2), 140 (2), 115 (6), 102 (2), 91 (2), 77 (2). $C_{21}H_{17}N_3O_5$ (391.4): calcd. C 64.45, H 4.38, N 10.74; found C 64.85, H 4.50, N 10.80.

(*Z*)-1-Acetyl-3-(2-acetyloxyphenyl)-4-(4-ethoxystyryl)-1*H*-pyrazole (8c): Yield 590 mg (92%), yellow oil. ^{1}H NMR: δ = 1.43 (t, *J* = 7.0 Hz, 3 H, 4′′-OCH$_2$C*H*$_3$), 2.20 (s, 3 H, OCOC*H*$_3$), 2.68 (s, 3 H, NCOC*H*$_3$), 4.04 (q, *J* = 7.0 Hz, 2 H, 4′′-OC*H*$_2$CH$_3$), 6.03 (dd, *J* = 12.1, 0.7 Hz, 1 H, Hα), 6.52 (d, *J* = 12.1 Hz, 1 H, Hβ), 6.81 (d, *J* = 8.8 Hz, 2 H, 3′′-,5′′-H), 7.22 (d, *J* = 8.8 Hz, 2 H, 2′′-,6′′-H), 7.22 (dd, *J* = 7.8, 1.1 Hz, 1 H, 3′-H), 7.31 (dt, *J* = 7.6, 1.1 Hz, 1 H, 5′-H), 7.46 (ddd, *J* = 7.6, 7.8, 1.7 Hz, 1 H, 4′-H), 7.56 (dd, *J* = 7.6, 1.7 Hz, 1 H, 6′-H), 8.12 (d, *J* = 0.7 Hz, 1 H, 5-H) ppm. ^{13}C NMR: δ = 14.8 (4′′-OCH$_2$*C*H$_3$), 21.1 (OCO*C*H$_3$), 21.6 (NCO*C*H$_3$), 63.4 (4′′-O*C*H$_2$CH$_3$), 114.5 (C-3′′,-5′′), 117.2 (C-α), 121.0 (C-4), 123.1 (C-3′), 124.6 (C-1′), 125.96 (C-5′), 126.04 (C-5), 129.0 (C-1′′), 129.4 (C-2′′,-6′′), 130.2 (C-4′), 131.4 (C-6′), 131.6 (C-β), 148.4 (C-2′), 152.5 (C-3), 158.4 (C-4′′), 169.1 (O*C*OCH$_3$), 169.2 (N*C*OCH$_3$) ppm. EI-MS: *m*/*z* (%) = 390 (16) [M]$^{+\cdot}$, 348 (100) [M – C_2H_2O]$^+$, 319 (1), 306 (99), 291 (3), 277 (42), 260 (3), 247 (8), 229 (1), 222 (3), 205 (4), 185 (8), 171 (69), 155 (5), 139 (3), 131 (7), 115 (7), 102 (5), 89 (2), 77 (6), 65 (3). HRMS (ESI$^+$): calcd. ($C_{23}H_{22}N_2O_4Na$) 413.14718; found 413.14685.

Synthesis of *endo*-1-Acetyl-5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazoles 9a-e and 10a-c: A mixture of each one of the (*E* or *Z*)-1-acetyl-3-(2-hydroxyphenyl)-4-styrylpyrazoles **5a**–**e** or **6a**–**c** (0.16 mmol) and *N*-methylmaleimide (0.11 g, 0.96 mmol) was irradiated at atmospheric pressure in an Ethos SYNTH microwave (Milestone Inc.) at 802 W for 40 min. The crude product was dissolved in chloroform and purified by thin layer chromatography with a mixture of CHCl$_3$/EtOAc (8:2) as eluent. The residue was crystallised from ethanol to give the *endo*-1-acetyl-5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole [**9a** 58.5 mg (88%), **9b** 49.0 mg (68%), **9c** 69.8 mg (95%), **9d** 62.6 mg (85%), **9e** 60.3 mg (78%), **10a** 40.0 mg (60%), **10b** 38.9 mg (54%), **10c** 39.7 mg (54%)]. Compounds **9a**–**c**, **9e** and **10a**–**c** were obtained as white solids and compound **9d** was obtained as a yellow solid.

(5*S,5a*S**,8a*S**,8b*S**)-1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole (9a):** M.p. 227–229 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.54 (s, 3 H, 1-COC*H*$_3$), 2.76 (s, 3 H, 7-NC*H*$_3$), 3.42 (dd, *J* = 7.1, 7.9 Hz, 1 H, 5a-H), 3.59 (ddd, *J* = 7.1, 4.0, 3.6 Hz, 1 H, 5-H), 4.48 (dd, *J* = 7.2, 7.9 Hz, 1 H, 8a-H), 4.98 (ddd, *J* = 7.2, 3.6, 3.7 Hz, 1 H, 8b-H), 6.94–7.00 (m, 1 H, 5′-H), 6.99 (dd, *J* = 4.0, 3.7 Hz, 1 H, 4-H), 7.11 (dd, *J* = 8.3, 1.1 Hz, 1 H, 3′-H), 7.26 (d, *J* = 8.5 Hz, 2 H, 2′′-,6′′-H), 7.31–7.49 (m, 1 H, 4′-H), 7.38–7.42 (m, 1 H, 4′′-H), 7.42 (t, *J* = 8.5 Hz, 2 H, 3′′-,5′′-H), 7.65 (dd, *J* = 7.9, 1.6 Hz, 1 H, 6′-H), 9.80 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.5 (1-CO*C*H$_3$), 25.0 (7-N*C*H$_3$), 40.6 (C-8a), 42.0 (C-5a), 45.0 (C-5), 57.6 (C-8b), 114.4 (C-1′), 117.7 (C-3′), 119.7 (C-5′), 125.6 (C-4), 127.5 (C-6′), 127.9 (C-4′′), 128.6 (C-3′′,-5′′), 128.8 (C-2′′,-6′′), 131.9 (C-4′), 137.2 (C-1′′), 138.0 (C-3a), 149.2 (C-3), 157.1 (C-2′), 168.6 (1-*C*OCH$_3$), 173.4 (C-6), 174.4 (C-8) ppm. EI-MS: *m*/*z* (%) = 415 (70) [M]$^{+\cdot}$, 373 (42), 304 (47), 286 (15), 262 (100), 202 (7), 185 (16), 171 (91), 149 (14), 128 (8), 115 (19), 91 (40), 83 (66), 69 (11), 57 (17). $C_{24}H_{21}N_3O_4$ (415.4): calcd. C 69.39, H 5.10, N 10.11; found C 68.98, H 4.92, N 10.39.

(5*S,5a*S**,8a*S**,8b*S**)-1-Acetyl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]-indazole (9b):** M.p. 209–210 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.54 (s, 3 H, 1-COC*H*$_3$), 2.76 (s, 3 H, 7-NC*H*$_3$), 3.39 (dd, *J* = 6.9, 8.0 Hz, 1 H, 5a-H), 3.59 (ddd, *J* = 6.9, 4.0, 3.4 Hz, 1 H, 5-H), 4.48 (dd, *J* = 8.0, 7.1 Hz, 1 H, 8a-H), 4.97 (ddd, *J* = 7.1, 3.9, 3.4 Hz, 1 H, 8b-H), 6.90 (dd, *J* = 4.0, 3.9 Hz, 1 H, 4-H), 6.98 (ddd, *J* = 7.9, 7.4, 1.1 Hz, 5′-H), 7.11 (dd, *J* = 8.1, 1.1 Hz, 1 H, 3′-H), 7.26 (d, *J* = 8.5 Hz, 2 H, 2′′-,6′′-H), 7.38 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1 H, 4′-H), 7.42 (d, *J* = 8.5 Hz, 2 H, 3′′-,5′′-H), 7.65 (dd,

J = 7.9, 1.6 Hz, 1 H, 6′-H), 9.80 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.5 (1-CO*C*H$_3$), 25.0 (7-N*C*H$_3$), 40.4 (C-8a), 41.8 (C-5a), 44.4 (C-5), 57.5 (C-8b), 114.3 (C-1′), 117.7 (C-3′), 119.8 (C-5′), 124.9 (C-4), 127.4 (C-6′), 128.8 (C-3′′,-5′′), 130.1 (C-2′′,-6′′), 131.9 (C-4′), 133.8 (C-4′′), 135.8 (C-1′′), 138.3 (C-3a), 149.1 (C-3), 157.0 (C-2′), 168.6 (1-*C*OCH$_3$), 173.2 (C-6), 174.3 (C-8) ppm. EI-MS: *m*/*z* (%) = 451 (29) [M]$^{+\cdot}$ (^{37}Cl), 449 (75) [M]$^{+\cdot}$ (^{35}Cl), 407 (64), 338 (34), 321 (10), 296 (91), 257 (7), 202 (16), 188 (14), 171 (100), 160 (35), 152 (11), 131 (10), 115 (16), 102 (6), 78 (8); 55 (4). HRMS (FAB$^+$-LR): calcd. ($C_{24}H_{21}N_3O_4{}^{35}Cl$) 450.1221; found 450.1220.

(5*S,5a*S**,8a*S**,8b*S**)-1-Acetyl-5-(4-ethoxyphenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole (9c):** This compound was shown to possess spectroscopic and analytical data identical to those previously reported.[45]

(5*S,5a*S**,8a*S**,8b*S**)-1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-(4-nitrophenyl)-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole (9d):** M.p. 229–231 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.55 (s, 3 H, 1-COC*H*$_3$), 2.77 (s, 3 H, 7-NC*H*$_3$), 3.47 (dd, *J* = 8.6, 6.9 Hz, 1 H, 5a-H), 3.68 (ddd, *J* = 6.9, 4.0, 3.6 Hz, 1 H, 5-H), 4.53 (dd, *J* = 8.6, 7.3 Hz, 1 H, 8a-H), 5.00 (ddd, *J* = 7.3, 4.0, 3.6 Hz, 1 H, 8b-H), 6.94 (t, *J* = 4.0 Hz, 1 H, 4-H), 7.00 (ddd, *J* = 7.5, 7.8, 1.0 Hz, 1 H, 5′-H), 7.12 (dd, *J* = 8.1, 1.0 Hz, 1 H, 3′-H), 7.40 (ddd, *J* = 8.1, 7.5, 1.5 Hz, 1 H, 4′-H), 7.52 (d, *J* = 8.7 Hz, 2 H, 2′′-,6′′-H), 7.65 (d, *J* = 7.8 Hz, 1 H, 6′-H), 8.32 (d, *J* = 8.7 Hz, 2 H, 3′′-,5′′-H), 9.73 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.5 (1-CO*C*H$_3$), 25.1 (7-N*C*H$_3$), 40.3 (C-8a), 41.8 (C-5a), 44.5 (C-5), 57.6 (C-8b), 114.2 (C-1′), 117.8 (C-3′), 119.8 (C-5′), 123.3 (C-4), 123.8 (C-3′′,-5′′), 127.3 (C-6′), 129.8 (C-2′′,-6′′), 132.1 (C-4′), 138.8 (C-3a), 144.7 (C-1′′), 147.5 (C-4′′), 148.9 (C-3), 157.0 (C-2′), 168.6 (1-*C*OCH$_3$), 172.9 (C-6), 174.1 (C-8) ppm. EI-MS: *m*/*z* (%) = 460 (54) [M]$^{+\cdot}$, 430 (9), 418 (61), 386 (17), 349 (26), 331 (16), 319 (19), 307 (81), 296 (11), 277 (21), 255 (24), 220 (13), 205 (36), 185 (20), 171 (100), 160 (19), 149 (22), 137 (12), 123 (16), 109 (38), 97 (68), 65 (63), 57 (71). $C_{24}H_{20}N_4O_6$ (460.4): calcd. C 62.60, H 4.38, N 12.17; found C 62.96, H 4.50, N 12.43.

(5*S,5a*S**,8a*S**,8b*S**)-1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-(4-trifluoromethylphenyl)-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo-[3,4-*g*]indazole (9e):** M.p. 208–209 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.54 (s, 3 H, 1-COC*H*$_3$), 2.77 (s, 3 H, 7-NC*H*$_3$), 3.45 (broad dd, *J* = 8.0, 7.3 Hz, 1 H, 5a-H), 3.63 (ddd, *J* = 7.3, 4.0, 3.6 Hz, 5-H), 4.50 (dd, *J* = 8.0, 7.5 Hz, 1 H, 8a-H), 4.98 (ddd, *J* = 7.5, 3.9, 3.6 Hz, 8b-H), 6.94 (dd, *J* = 4.0, 3.9 Hz, 4-H), 6.98 (ddd, *J* = 7.9, 7.5, 1.0 Hz, 1 H, 5′-H), 7.11 (dd, *J* = 8.1, 1.0 Hz, 1 H, 3′-H), 7.39 (ddd, *J* = 8.1, 7.5, 1.5 Hz, 1 H, 4′-H), 7.46 (d, *J* = 8.2 Hz, 2 H, 2′′-,6′′-H), 7.65 (dd, *J* = 7.9, 1.5 Hz, 1 H, 6′-H), 7.71 (d, *J* = 8.2 Hz, 2 H, 3′′-,5′′-H), 9.78 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.5 (1-CO*C*H$_3$), 25.0 (7-N*C*H$_3$), 40.4 (C-8a), 41.7 (C-5a), 44.7 (C-5), 57.6 (C-8b), 114.2 (C-1′), 117.7 (C-3′), 119.8 (C-5′), 123.9 (q, *J* = 270.0 Hz, *C*F$_3$), 124.3 (C-4), 125.6 (q, *J* = 3.7 Hz, C-3′′,-5′′), 127.4 (C-6′), 129.2 (C-2′′,-6′′), 130.0 (q, *J* = 32.4 Hz, C-4′′), 132.0 (C-4′), 138.5 (C-3a), 141.3 (C-1′′), 149.0 (C-3), 157.0 (C-2′), 168.6 (1-*C*OCH$_3$), 173.1 (C-6), 174.2 (C-8) ppm. ^{19}F NMR (300.13 MHz, CDCl$_3$, ref. C$_6$F$_6$): δ = –85.5 (s, C*F*$_3$) ppm. EI-MS: *m*/*z* (%) = 483 (71) [M]$^{+\cdot}$, 441 (65) [M – C$_2$H$_2$O]$^+$, 372 (22), 354 (11), 330 (100), 211 (6), 185 (15), 171 (81), 160 (23), 115 (6), 77 (5). $C_{25}H_{20}F_3N_3O_4$ (483.4): calcd. C 62.11, H 4.17, N 8.69; found C 62.31, H 4.17, N 8.85.

(5*R,5a*S**,8a*S**,8b*S**)-1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole (10a):** M.p. 223–224 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.46 (s, 3 H, 1-COC*H*$_3$), 2.88 (s, 3 H, 7-NC*H*$_3$), 3.60 (dd, *J* = 8.7, 1.3 Hz, 1 H, 5a-H), 4.43 (dd, *J* = 8.2, 8.7 Hz, 1 H, 8a-H), 4.76 (dd, *J* = 8.2, 2.8 Hz, 1 H, 5-H), 4.79 (ddd, *J* = 8.2, 3.2, 2.8 Hz, 1 H, 8b-H), 6.96 (dd, *J* = 3.2, 1.3 Hz, 1 H, 4-H), 6.98 (ddd, *J* = 7.9, 7.8, 1.2 Hz, 1 H, 5′-H), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1 H, 3′-H), 7.31–7.39 (m, 6 H, 2′′-,3′′-,4′′-,5′′-,6′′-,4′-H), 7.70 (dd, *J* = 7.9, 1.6 Hz, 1 H, 6′-H), 9.79 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.4 (1-CO*C*H$_3$), 25.4 (7-N*C*H$_3$), 41.5 (C-8a), 42.5 (C-5), 42.8 (C-5a), 55.6 (C-8b), 114.2 (C-1′), 117.6 (C-3′), 119.7 (C-5′), 125.4 (C-4), 126.8 (C-2′′,-6′′), 127.5 (C-6′), 127.7 (C-4′), 129.3 (C-3′′,-5′′), 131.8 (C-4′′), 136.8 (C-1′′), 138.4 (C-3a), 149.5 (C-3), 157.0 (C-2′), 168.4 (1-*C*OCH$_3$), 173.8 (C-6), 177.6 (C-8) ppm. EI-MS: *m*/*z* (%) = 415 (93) [M]$^{+\cdot}$, 373 (100) [M – CH$_2$CO]$^+$, 304 (24), 296 (8), 282 (46), 262 (88), 239 (6), 231 (6), 210 (7), 202 (9), 185 (16), 171 (90), 160 (7), 152 (11), 141 (6), 131 (8), 128 (10), 115 (24), 102 (8), 91 (11), 77 (14), 63 (10). HRMS (FAB$^+$-LR) ($C_{24}H_{22}N_3O_4$): calcd. 416.1610; found 416.1617.

(5*R,5a*S**,8a*S**,8b*S**)-1-Acetyl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo-[3,4-*g*]indazole (10b):** M.p. 136–137 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.46 (s, 3 H, 1-COC*H*$_3$), 2.88 (s, 3 H, 7-NC*H*$_3$), 3.55 (d, *J* = 8.6 Hz, 5a-H), 4.43 (dd, *J* = 8.1, 8.6 Hz, 1 H, 8a-H), 4.72 (d, *J* = 7.7 Hz, 1 H, 5-H), 4.73 (ddd, *J* = 8.1, 3.9, 3.9 Hz, 1 H, 8b-H), 6.93 (dd, *J* = 3.9, 4.1 Hz, 1 H, 4-H), 6.98 (ddd, *J* = 7.5, 7.7, 0.9 Hz, 1 H, 5′-H), 7.09 (dd, *J* = 8.6, 0.9 Hz, 1 H, 3′-H), 7.35 (d, *J* = 8.6 Hz, 2 H, 2′′-,6′′-H), 7.37 (ddd, *J* = 8.6, 7.5, 1.5 Hz, 1 H, 4′-H), 7.68 (dd, *J* = 7.7, 1.5 Hz, 1 H, 6′-H), 8.63 (d, *J* = 8.6 Hz, 2 H, 3′′-,5′′-H), 9.74 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 21.4 (1-CO*C*H$_3$), 25.4 (7-N*C*H$_3$), 41.4 (C-8a), 41.9 (C-5), 42.7 (C-5a), 55.6 (C-8b), 114.1 (C-1′), 117.7 (C-3′), 119.7 (C-5′), 124.8 (C-4), 127.5 (C-6′), 128.2 (C-3′′,-5′′), 129.4 (C-2′′,-6′′), 131.9 (C-4′), 133.6 (C-4′′), 135.3 (C-1′′), 138.8 (C-3a), 149.4 (C-3), 157.0 (C-2′), 168.4 (1-*C*OCH$_3$), 173.6 (C-6), 177.3 (C-8) ppm. EI-MS: *m*/*z* (%) = 449 (91) [M]$^{+\cdot}$, 407 (100), 338 (17), 321 (15), 296 (92), 282 (41), 257 (7), 239 (6), 228 (6), 213 (5), 211 (8), 202 (9), 185 (15), 171 (84), 160 (5), 152 (9), 127 (5), 115 (14), 102 (6), 77 (6). HRMS (FAB$^+$-LR) ($C_{24}H_{21}N_3O_4{}^{35}Cl$): calcd. 450.1221; found 450.1201.

(5*R,5a*S**,8a*S**,8b*S**)-1-Acetyl-5-(4-ethoxyphenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo-[3,4-*g*]indazole (10c):** This compound was shown to possess spectroscopic and analytical data identical to those previously reported.[45]

1-Acetyl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-7-methyl-5,8b-(1-methylsuccinimido)-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo-[3,4-*g*]indazole (12b): M.p. 222–223 °C (10%), white solid (recrystallized from ethanol). ^{1}H NMR**:** δ = 2.64 (s, 3 H, 1-COC*H*$_3$), 2.71 (s, 6 H, 2 × NC*H*$_3$), 3.52 (d, *J* = 8.5 Hz, 2 H, 8a-,8a′-H), 4.34 (d, *J* = 8.5 Hz, 2 H, 5a-,5a′-H), 7.00 (ddd, *J* = 8.1, 7.7, 1.1 Hz, 1 H, 5′-H), 7.10 (dd, *J* = 8.1, 1.1 Hz, 1 H, 3′-H), 7.21 (s, 1 H, 4-H), 7.40 (ddd, *J* = 8.1, 7.7, 2.0 Hz, 1 H, 4′-H), 7.47–7.57 (m, 4 H, 2′′-,3′′-,5′′-,6′′-H), 7.67 (dd, *J* = 8.1, 2.0 Hz, 6′-H), 9.75 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 22.2 (1-CO*C*H$_3$), 25.0 (2 × N*C*H$_3$), 29.2 (C-5), 43.0 (C-5a,-5a′), 46.1 (C-8a,-8a′), 66.4 (C-8b), 114.0 (C-1′), 118.0 (C-3′), 119.8 (C-5′), 121.8 (C-4), 126.7 and 128.6 (C-3′′ and C-5′′), 128.1 (C-6′), 128.9 and 129.5 (C-2′′ and C-6′′), 132.3 (C-4′), 134.36 (C-4′′), 134.40 (C-3a), 139.4 (C-1′′), 146.4 (C-3), 157.1 (C-2′), 169.6 (1-*C*OCH$_3$), 171.6 (C-6,6′), 172.8 (C-8,8′) ppm. FAB$^+$-MS: *m*/*z* (%) = 559 (8) [M + H]$^+$, 558 (16), 460 (4), 452 (6), 406 (4), 307 (30), 289 (17), 288 (10), 244 (7), 219 (6), 176 (6), 155 (31), 154 (100). HRMS (FAB$^+$-LR) ($C_{29}H_{24}N_4O_6{}^{35}Cl$): calcd. 559.1384; found 559.1364.

1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5,8b-(1-methylsuccinimido)-5-(4-nitrophenyl)-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]-indazole (12d): 7%, oil. ^{1}H NMR: δ = 2.64 (s, 3 H, 1-COC*H*$_3$), 2.71 (s, 6 H, 2 × NC*H*$_3$), 3.61 (d, *J* = 8.5 Hz, 2 H, 8a-,8a′-H), 4.38 (d,

J = 8.5 Hz, 2 H, 5a-,5a′-H), 7.02 (ddd, J = 8.1, 7.5, 0.8 Hz, 1 H, 5′-H), 7.11 (dd, J = 7.9, 0.8 Hz, 1 H, 3′-H), 7.24 (s, 1 H, 4-H), 7.42 (ddd, J = 7.9, 7.5, 1.4 Hz, 4′-H), 7.52 (dd, J = 8.1, 1.4 Hz, 1 H, 6′-H), 7.75 (dd, J = 8.2, 1.8 Hz, 1 H, 2′′-H), 7.94 (dd, J = 8.3, 1.8 Hz, 1 H, 6′′-H), 8.40 (dd, J = 8.3, 2.3 Hz, 1 H, 5′′-H), 8.45 (dd, J = 8.2, 2.3 Hz, 1 H, 3′′-H), 9.67 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 22.2 (1-CO*C*H$_3$), 25.1 (2 × N*C*H$_3$), 29.2 (C-5), 42.9 (C-5a,-5a′), 46.1 (C-8a,-8a′), 66.5 (C-8b), 113.9 (C-1′), 118.0 (C-3′), 120.0 (C-5′), 120.8 (C-4), 123.6 and 124.2 (C-3′′,-5′′), 126.7 (C-6′), 127.9 and 128.7 (C-2′′,-6′′), 132.4 (C-4′), 139.9 (C-1′′), 143.5 (C-4′′), 146.3 (C-3a), 147.5 (C-3), 157.1 (C-2′), 169.7 (1-*C*OCH$_3$), 171.4 (C-6,6′), 172.7 (C-8,8′) ppm. HRMS (ESI$^+$) ($C_{29}H_{23}N_5O_8Na$): calcd. 592.1418; found 592.1436.

Synthesis of 5-Aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazoles 13a–e under Microwave Irradiation Conditions: A mixture of each of the appropriate *endo*-1-acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazoles **9a**–**e** or **10a**–**c** (0.12 mmol) and DDQ (0.082 g, 0.36 mmol) in 1,2,4-trichlorobenzene (20 mL) was irradiated at atmospheric pressure and 170 °C in an Ethos SYNTH microwave (Milestone Inc.) at 800 W for 30 min. The crude product was purified by column chromatography, with light petroleum as eluent, to remove the 1,2,4-trichlorobenzene, followed by ethyl acetate to remove the reaction product, which was further purified by thin layer chromatography with a mixture of $CHCl_3$/EtOAc (9:1) as eluent. The residue was recrystallized from ethanol to give the 5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]-indazole [**13a** from **9a**, 37.6 mg (85%); **13b** from **9b**, 15.5 mg (32%); **13c** from **9c**, 17.9 mg (36%), **13d** from **9d**, 16.9 mg (34%), **13e** from **9e**, 5.8 mg (11%); **13a** from **10a**, 9.7 mg (22%); **13b** from **10b**, 2.9 mg (6%); **13c** from **10c**, 15.4 mg (31%)]. In the purification of compound **13a** obtained from **9a** we also isolated a spot with lower R_f value that was identified as compound **14a**, obtained as a yellow residue (6.42 mg, 13%). Compounds **15a**–**e** were identified, in each case, as a spot with a lower R_f value than the indazole **13a**–**e** (**15b**–**e** from the dehydrogenation of **9b**–**e** and **15a** from **10a**): **15a** 12.4 mg (25%), **15b** 7.0 mg (13%), **15c** 2.2 mg (4%), **15d** 11.0 mg (20%), **15e** 3.5 mg (6%).

Synthesis of 5-Aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazoles 13a–e under Classical Heating Conditions: A mixture of each one of the appropriate *endo*-1-acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazoles **9a**–**e** or **10a**–**c** (0.12 mmol) and DDQ (0.082 g, 0.36 mmol) in 1,2,4-trichlorobenzene (20 mL) was heated at 170 °C until the consumption of the starting material. The reaction progress was monitored by tlc. After that, the crude product was purified by column chromatography, with light petroleum as eluent to remove the 1,2,4-trichlorobenzene, followed by elution with a mixture of ethyl acetate/light petroleum (3:2) to remove the reaction product, which in some cases was further purified by thin layer chromatography with the same mixture of ethyl acetate/light petroleum (3:2) as eluent. The residue was recrystallized from ethanol to give the 5-aryl-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole [**13a** from **9a** (13.7 mg, 31%), **13b** from **9b** (29.1 mg, 60%), **13c** from **9c** (17.8 mg, 36%), **13d** from **9d** (36.3 mg, 73%), **13e** from **9e** (35.7 mg, 68%), **13a** from **10a** (24.8 mg, 56%), **13b** from **10b** (26.6 mg, 55%), **13c** from **10c** (24.3 mg, 49%)]. In the dehydrogenation of compound **9d** into **13d** we also isolated a compound **14d** (10.9 mg, 20%) with a lower R_f value than **13d**.

3-(2-Hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]-indazole (13a): This compound was shown to possess spectroscopic and analytical data identical to those previously reported.[45]

5-(4-Chlorophenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole (13b): M.p. > 275 °C (recrystallized from ethanol). ^{1}H NMR: δ = 3.21 (s, 3 H, 7-NC*H*$_3$), 7.06 (ddd, J = 7.8, 7.4, 1.0 Hz, 1 H, 5′-H), 7.17 (dd, J = 8.1, 1.0 Hz, 1 H, 3′-H), 7.37 (ddd, J = 8.1, 7.4, 1.5 Hz, 1 H, 4′-H), 7.47–7.57 (m, 4 H, 2′′-,3′′-, 5′′-,6′′-H), 7.99 (dd, J = 7.8, 1.5 Hz, 1 H, 6′-H), 8.40 (s, 1 H, 4-H), 10.43 (s, 1 H, N*H*), 11.37 (brs, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 24.0 (7-N*C*H$_3$), 115.5 (C-8a), 116.1 (C-1′), 117.7 (C-3′), 119.8 (C-5′), 126.1 (C-5a), 127.2 (C-6′), 128.4 (C-3′′,-5′′), 130.0 (C-4), 130.6 (C-4′), 131.0 (C-2′′,-6′′), 132.7 (C-8b), 133.2 (C-5), 133.5 (C-3a), 134.7 (C-4′′), 135.0 (C-1′′), 145.7 (C-3), 156.2 (C-2′), 167.6 (C-6,-8) ppm. FAB$^+$-MS: m/z (%) = 404 (13), 338 (11), 289 (16), 273 (3), 242 (2), 212 (7), 195 (3), 165 (6). (FAB$^+$-LR)-HRMS: ($C_{22}H_{15}N_3O_3{}^{35}Cl$): calcd. 404.0802; found 404.0813.

5-(4-Ethoxyphenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole (13c): M.p. 258–260 °C (recrystallized from ethanol). ^{1}H NMR: δ = 1.47 (t, J = 7.0 Hz, 3 H, 4′′-OCH$_2$C*H*$_3$), 3.20 (s, 3 H, 7-NC*H*$_3$), 4.13 (q, J = 7.0 Hz, 2 H, 4′′-OC*H*$_2$CH$_3$), 7.03 (d, J = 8.7 Hz, 2 H, 3′′-,5′′-H), 7.05 (ddd, J = 7.8, 7.3, 1.2 Hz, 1 H, 5′-H), 7.16 (dd, J = 8.3, 1.2 Hz, 1 H, 3′-H), 7.35 (ddd, J = 8.3, 7.3, 1.6 Hz, 1 H, 4′-H), 7.50 (d, J = 8.7 Hz, 2 H, 2′′-,6′′-H), 8.01 (dd, J = 7.8, 1.6 Hz, 1 H, 6′-H), 8.41 (s, 1 H, 4-H), 10.50 (s, 1 H, N*H*), 11.34 (brs, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 14.9 (4′′-OCH$_2$*C*H$_3$), 24.0 (7-N*C*H$_3$), 63.5 (4′′-O*C*H$_2$CH$_3$), 114.1 (C-3′′, -5′′), 115.3 (C-8a), 116.2 (C-1′), 117.6 (C-3′), 119.8 (C-5′), 127.3 (C-6′), 128.1 (C-5a), 128.7 (C-1′′), 130.0 (C-4), 130.4 (C-4′), 130.9 (C-2′′,-6′′), 133.0 (C-8b,-3a), 134.0 (C-5), 145.5 (C-3), 156.2 (C-2′), 159.3 (C-4′′), 168.2 (C-6,-8) ppm. EI-MS: m/z (%) = 413 (100) [M]$^{+\cdot}$, 385 (22) [M – CO]$^+$, 356 (5), 300 (3), 271 (2), 119 (1), 69 (5). (FAB$^+$-LR)-HRMS: ($C_{24}H_{20}N_3O_4$): calcd. 414.1454; found 414.1462.

3-(2-Hydroxyphenyl)-7-methyl-5-(4-nitrophenyl)-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole (13d): M.p. >275 °C (recrystallized from ethanol). ^{1}H NMR: δ = 3.20 (s, 3 H, 7-NC*H*$_3$), 7.07 (ddd, J = 7.8, 7.5, 1.1 Hz, 5′-H), 7.18 (dd, J = 8.3, 1.1 Hz, 1 H, 3′-H), 7.38 (ddd, J = 8.3, 7.8, 1.5 Hz, 1 H, 4′-H), 7.76 (d, J = 8.8 Hz, 2 H, 2′′-,6′′-H), 7.98 (dd, J = 7.5, 1.5 Hz, 1 H, 6′-H), 8.38 (d, J = 8.8 Hz, 2 H, 3′′-, 5′′-H), 8.44 (s, 1 H, 4-H), 10.33 (s, 1 H, N*H*), 11.30 (brs, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 24.1 (7-*N*CH$_3$), 117.9 (C-3′), 120.0 (C-5′), 123.4 (C-3′′,-5′′), 127.3 (C-6′), 128.8 (C-5a), 130.1 (C-4), 130.7 (C-4′,-2′′,-6′′), 133.3 (C-8b), 133.5 (C-3a), 134.7 (C-5), 137.1 (C-1′′), 142.3 (C-4′′), 143.4 (C-3), 156.0 (C-2′), 167.8 (C-6,-8) ppm. FAB$^+$-MS: m/z (%) = 415 (5) [M + H]$^+$, 391 (12), 355 (2), 338 (14), 242 (3), 212 (7), 195 (5), 180 (10), 123 (17). (FAB$^+$-LR)-HRMS: ($C_{22}H_{15}N_4O_5$): calcd. 415.1042; found 415.1049.

3-(2-Hydroxyphenyl)-7-methyl-5-(4-trifluoromethylphenyl)-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole (13e): M.p. >275 °C (recrystallized from ethanol). ^{1}H NMR: δ = 3.07 (s, 3 H, 7-NC*H*$_3$), 6.98 (dd, J = 8.0, 7.2 Hz, 1 H, 5′-H), 7.06 (d, J = 8.0 Hz, 1 H, 3′-H), 7.25–7.38 (m, 1 H, 4′-H), 7.59 (dd, J = 8.0, 1.5 Hz, 1 H, 6′-H), 7.68 (d, J = 8.5 Hz, 2 H, 3′′-,5′′-H), 7.73 (d, J = 8.5 Hz, 2 H, 2′′-,6′′-H), 8.43 (s, 1 H, 4-H), 9.95 (brs, 1 H, N*H*) ppm. ^{13}C NMR: δ = 24.5 (7-N*C*H$_3$), 117.3 (C-3′), 119.8 (C-5′), 127.5 (C-6′), 125.6 (C-3′′,-5′′), 126.6 (C-2′′,-6′′), 130.0 (C-4′), 133.4 (C-8b), 133.9 (C-3a), 134.4 (C-5), 143.0 (C-3), 152.0 (C-2′), 162.6 (C-6,-8) ppm. MS (ESI $^+$): m/z (%) = 438.1 (6) [M + H]$^+$. $C_{23}H_{14}F_3N_3O_3$ (437.4): calcd. C 63.16, H 3.23; N 9.61: found C 62.91, H 3.45, N 9.11.

1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole (14a): ^{1}H NMR: δ = 2.10 (s, 3 H, 1-COC*H*$_3$), 3.20 (s, 3 H, NC*H*$_3$), 7.39–7.54 (m, 8 H, 3′-,4′-,5′-,2′′-,3′′-,4′′-, 5′′-,6′′-H), 7.78 (dd, J = 7.5, 1.6 Hz, 1 H, 6′-H), 8.07 (s, 1 H, 4-H), 11.23 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 20.9 (1-CO*C*H$_3$),

23.9 (N*C*H$_3$), 127.2 (C-5a), 128.1 (C-2′′,-6′′), 128.3 (C-6′), 129.3 (C-4′′), 129.5 (C-3′′,-5′′), 130.2 (C-4), 131.0 (C-4′), 133.3 (C-5), 133.6 (C-3a), 136.7 (C-1′′), 155.0 (C-2′), 168.0 (1-*C*OCH$_3$), 168.4 (C-6), 169.3 (C-8) ppm.

1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-(4-nitrophenyl)-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole (14d): ^{1}H NMR: δ = 2.09 (s, 3 H, 1-COC*H*$_3$), 3.21 (s, 3 H, NC*H*$_3$), 7.16–7.26 (m, 1 H, 5′-H), 7.29 (d, *J* = 8.1, 1.1 Hz, 1 H, 3′-H), 7.36–7.54 (m, 2 H, 4′,6′-H), 7.70 (d, *J* = 8.8 Hz, 2 H, 2′′-,6′′-H), 8.07 (s, 1 H, 4-H), 8.33 (d, *J* = 8.8 Hz, 2 H, 3′′-,5′′-H) ppm.

(5a*R,8a*S**)-1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-phenyl-6,8-dioxo-5a,8a-dihydro-1*H*-pyrrolo[3,4-*g*]indazole (15a):** ^{1}H NMR: δ = 2.83 (s, 3 H, 1-COC*H*$_3$), 2.98 (s, 3 H, NC*H*$_3$), 4.71 (dd, *J* = 11.3, 2.2 Hz, 1 H, 5a-H), 5.51 (d, *J* = 11.3 Hz, 1 H, 8a-H), 6.91 (d, *J* = 2.2 Hz, 1 H, 4-H), 6.97 (ddd, *J* = 7.7, 7.4, 1.2 Hz, 1 H, 5′-H), 7.09 (dd, *J* = 8.3, 1.2 Hz, 1 H, 3′-H), 7.33 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1 H, 4′-H), 7.38–7.52 (m, 5 H, 2′′-, 3′′-,4′′-,5′′-,6′′-H), 7.60 (dd, *J* = 7.7, 1.6 Hz, 1 H, 6′-H), 9.90 (s, 1 H, 2′-O*H*) ppm.

(5a*R,8a*S**)-1-Acetyl-5-(4-chlorophenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5a,8a-dihydro-1*H*-pyrrolo[3,4-*g*]indazole (15b):** ^{1}H NMR: δ = 2.83 (s, 3 H, 1-COC*H*$_3$), 2.98 (s, 3 H, NC*H*$_3$), 4.66 (dd, *J* = 11.3, 2.0 Hz, 1 H, 5a-H), 5.51 (d, *J* = 11.3 Hz, 1 H, 8a-H), 6.89 (d, *J* = 2.0 Hz, 4-H), 6.98 (ddd, *J* = 7.8, 7.4, 1.0 Hz, 1 H, 5′-H), 7.10 (dd, *J* = 8.3, 1.0 Hz, 3′-H), 7.34 (ddd, *J* = 8.3, 7.4, 1.5 Hz, 1 H, 4′-H), 7.39 (d, *J* = 8.6 Hz, 2 H, 2′′-,6′′-H), 7.44 (d, *J* = 8.6 Hz, 2 H, 3′′-,5′′-H), 7.58 (dd, *J* = 7.8, 1.5 Hz, 1 H, 6′-H), 9.85 (s, 1 H, 2′-O*H*) ppm.

(5a*R,8a*S**)-1-Acetyl-5-(4-ethoxyphenyl)-3-(2-hydroxyphenyl)-7-methyl-6,8-dioxo-5a,8a-dihydro-1*H*-pyrrolo[3,4-*g*]indazole (15c):** ^{1}H NMR: δ = 1.44 (t, *J* = 7.0 Hz, 3 H, 4′′-OCH$_2$C*H*$_3$), 2.83 (s, 3 H, 1-COC*H*$_3$), 2.98 (s, 3 H, NC*H*$_3$), 4.09 (q, *J* = 7.0 Hz, 2 H, 4′′-OC*H*$_2$CH$_3$), 4.66 (dd, *J* = 11.4, 2.1 Hz, 1 H, 5a-H), 5.49 (d, *J* = 11.4 Hz, 1 H, 8a-H), 6.84 (d, *J* = 2.1 Hz, 1 H, 4-H), 6.92–7.10 (m, 2 H, 3′-,5′-H), 7.03 (d, *J* = 8.7 Hz, 2 H, 3′′-,5′′-H), 7.33 (ddd, *J* = 7.8, 7.7, 1.5 Hz, 1 H, 4′-H), 7.44 (d, *J* = 8.7 Hz, 2 H, 2′′-,6′′-H), 7.61 (dd, *J* = 7.9, 1.5 Hz, 1 H, 6′-H), 9.92 (s, 1 H, 2′-O*H*) ppm.

(5a*R,8a*S**)-1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-(4-nitrophenyl)-6,8-dioxo-5a,8a-dihydro-1*H*-pyrrolo[3,4-*g*]indazole (15d):** ^{1}H NMR: δ = 2.85 (s, 3 H, 1-COC*H*$_3$), 3.00 (s, 3 H, NC*H*$_3$), 4.74 (dd, *J* = 11.4, 2.0 Hz, 1 H, 5a-H), 5.58 (d, *J* = 11.4 Hz, 1 H, 8a-H), 7.03 (ddd, *J* = 7.8, 7.5, 1.0 Hz, 1 H, 5′-H), 7.04 (d, *J* = 2.0 Hz, 1 H, 4-H), 7.11 (dd, *J* = 8.2, 1.0 Hz, 1 H, 3′-H), 7.35 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 4′-H), 7.58 (dd, *J* = 7.8, 1.5 Hz, 6′-H), 7.67 (d, *J* = 8.6 Hz, 2 H, 2′′-,6′′-H), 8.29 (d, *J* = 8.6 Hz, 2 H, 3′′-,5′′-H), 9.74 (s, 1 H, 2′-O*H*) ppm.

(5a*R,8a*S**)-1-Acetyl-3-(2-hydroxyphenyl)-7-methyl-5-(4-trifluoromethylphenyl)-6,8-dioxo-5a,8a-dihydro-1*H*-pyrrolo[3,4-*g*]indazole (15e):** ^{1}H NMR: δ = 2.84 (s, 3 H, 1-COC*H*$_3$), 2.99 (s, 3 H, NC*H*$_3$), 4.72 (dd, *J* = 11.4, 2.3 Hz, 1 H, 5a-H), 5.55 (d, *J* = 11.4 Hz, 1 H, 8a-H), 6.96 (d, *J* = 2.3 Hz, 1 H, 4-H), 6.98 (ddd, *J* = 8.1, 7.4, 1.4 Hz, 1 H, 5′-H), 7.10 (dd, *J* = 8.1, 1.4 Hz, 1 H, 3′-H), 7.34 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1 H, 4′-H), 7.57 (dd, *J* = 8.1, 1.6 Hz, 1 H, 6′-H), 7.61 (d, *J* = 8.2 Hz, 2 H, 2′′-,6′′-H), 7.68 (d, *J* = 8.2 Hz, 2 H, 3′′-,5′′-H), 9.81 (s, 1 H, 2′-O*H*) ppm.

Synthesis of *endo*-1-Acetyl-3-(2-hydroxyphenyl)-5-(4-nitrophenyl)-7-phenyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole (16d): A mixture of (*E*)-1-acetyl-3-(2-hydroxyphenyl)-4-(4-nitrostyryl)-1*H*-pyrazole (**5d**, 0.040 g; 0.11 mmol) and *N*-phenylmaleimide (0.060 g, 0.33 mmol) was irradiated at atmospheric pressure in a Ethos SYNTH microwave (Milestone Inc.) at 802 W for 40 min. The crude product was dissolved in chloroform and purified by thin layer chromatography with a mixture of CHCl$_3$/EtOAc (9:1) as eluent. The residue was crystallised from ethanol to give *endo*-1-acetyl-3-(2-hydroxyphenyl)-5-(4-nitrophenyl)-7-phenyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole (**16d**), obtained as a yellow solid (49%, 29.2 mg).

(5*S,5a*S**,8a*S**,8b*S**)-1-Acetyl-3-(2-hydroxyphenyl)-5-(4-nitrophenyl)-7-phenyl-6,8-dioxo-5,5a,8a,8b-tetrahydro-1*H*-pyrrolo[3,4-*g*]indazole (16d):** M.p. 229–231 °C (recrystallized from ethanol). ^{1}H NMR: δ = 2.48 (s, 3 H, 1-COC*H*$_3$), 3.61 (dd, *J* = 7.5, 5.3 Hz, 1 H, 5a-H), 3.73 (ddd, *J* = 2.8, 3.2, 5.3 Hz, 1 H, 5-H), 4.63 (dd, *J* = 7.5, 7.8 Hz, 1 H, 8a-H), 5.09 (ddd, *J* = 2.8, 3.9, 7.8 Hz, 1 H, 8b-H), 6.54 (dd, *J* = 3.2, 3.9 Hz, 1 H, 4-H), 7.10 (dd, *J* = 7.9, 1.6 Hz, 2 H, 2′′′-,6′′′-H), 7.24 (dd, *J* = 8.6, 1.6 Hz, 1 H, 3′-H), 7.31–7.39 (m, 4 H, 5′-,3′′′-,4′′′-,5′′′-H), 7.48–7.56 (m, 4 H, 4′-,2′′-,6′′-,6′-H), 8.22 (d, *J* = 8.7 Hz, 2 H, 3′′-,5′′-H) ppm. ^{13}C NMR: δ = 21.2 (1-CO*C*H$_3$), 40.4 (C-8a), 42.6 (C-5a), 44.3 (C-5), 58.3 (C-8b), 120.0 (C-4), 122.8 (C-1′), 123.6 (C-3′′,-5′′), 123.9 (C-3′), 126.4 (C-5′), 126.5 (C-2′′′,-6′′′), 128.7 (C-4′′′), 128.9 (C-3′′′,-5′′′), 129.7 (C-2′′,-6′′), 129.8 (C-4′), 131.3 (C-6′), 140.1 (C-3a), 144.9 (C-1′′), 147.2 (C-4′′), 147.7 (C-3), 148.5 (C-2′), 169.5 (1-*C*OCH$_3$), 172.0 (C-6), 173.4 (C-8) ppm. FAB$^+$-MS: *m*/*z* (%) = 523 (30) [M + H]$^+$, 522 (10), 479 (7), 391 (7), 349 (6), 307 (32), 289 (16), 273 (7), 219 (7), 174 (10), 155 (30), 154 (100). HRMS (FAB$^+$-LR) (C$_{29}$H$_{23}$N$_4$O$_6$): calcd. 523.1618; found 523.1618.

1-Acetyl-3-(2-hydroxyphenyl)-5-(4-nitrophenyl)-7-phenyl-6,8-dioxo-1*H*-pyrrolo[3,4-*g*]indazole (17d): Yellow oil (5%). ^{1}H NMR: δ = 2.75 (s, 3 H, 1-COC*H*$_3$), 6.98–6.95 (m, 2 H, 3′-,5′-H), 7.20–7.61 (m, 6 H, NC$_6$*H*$_5$, 4′-H), 7.51 (d, *J* = 8.8 Hz, 2 H, 2′′-,6′′-H), 7.97 (d, *J* = 8.7 Hz, 1 H, 6′-H), 8.18 (d, *J* = 8.8 Hz, 2 H, 3′′-,5′′-H), 8.56 (s, 1 H, 4-H) ppm. MS (ESI$^+$): *m*/*z* (%) = 478.1 (20) [M + H]$^+$, 500.1 (73) [M + Na]$^+$.

Synthesis of 1-[1,2-Bis(methoxycarbonyl)ethenyl]-3-(2-hydroxyphenyl)-4-(4-nitrostyryl)-1*H*-pyrazole (18d): A mixture of (*E*)-1-acetyl-3-(2-hydroxyphenyl)-4-(4-nitrostyryl)-1*H*-pyrazole (**5d**, 0.040 g; 0.11 mmol) and DMAD (0.049 g, 0.33 mmol) was irradiated at atmospheric pressure in an Ethos SYNTH microwave (Milestone Inc.) at 802 W for 40 min. The crude product was dissolved in chloroform and purified by thin layer chromatography with chloroform as eluent. The residue was isolated in a trace amount and identified by NMR as **18d**. ^{1}H NMR: δ = 3.85 (s, 3 H, 1′′′-CO$_2$C*H*$_3$), 4.10 (s, 3 H, 4′′′-CO$_2$C*H*$_3$), 6.48 (s, 1 H, 3′′′-H), 6.51 (s, 1 H, 4-H), 7.02 (dd, *J* = 7.0, 7.8 Hz, 1 H, 5′-H), 7.03 (d, *J* = 16.4 Hz, 1 H, Hβ), 7.12 (d, *J* = 8.0 Hz, 1 H, 3′-H), 7.26 (d, *J* = 16.4 Hz, 1 H, Hα), 7.38 (ddd, *J* = 8.0, 7.0, 1.4 Hz, 1 H, 4′-H), 7.55 (d, *J* = 7.8 Hz, 1 H, 6′-H), 7.63 (d, *J* = 8.8 Hz, 2 H, 2′′-,6′′-H), 7.96 (s, 1 H, 5-H), 8.27 (d, *J* = 8.8 Hz, 2 H, 3′′-,5′′-H), 9.45 (s, 1 H, 2′-O*H*) ppm. ^{13}C NMR: δ = 52.4 (1′′′-CO$_2$*C*H$_3$), 53.9 (4′′′-CO$_2$*C*H$_3$), 105.9 (C-3′′′), 115.6 (C-1′), 117.6 (C-3′), 119.8 (C-5′), 121.8 (C-α), 124.3 (C-3′′,-5′′), 127.0 (C-2′′,-6′′), 127.2 (C-5), 128.7 (C-6′), 129.6 (C-β), 131.1 (C-4′), 141.8 (C-2′′′), 142.9 (C-1′′), 147.2 (C-3), 152.1 (C-4′′), 155.9 (C-2′), 162.7 (1′′′-*C*O$_2$CH$_3$), 165.0 (4′′′-*C*O$_2$CH$_3$) ppm. FAB$^+$-MS: *m*/*z* (%) = 451 (5) [M + H]$^+$, 450 (18), 391 (29), 313 (13), 307 (20), 289 (15), 259 (10), 219 (17), 203 (8), 191 (9), 176 (9), 167 (18), 165 (12), 163 (10), 156 (10). HRMS (FAB$^+$-LR) (C$_{23}$H$_{20}$N$_3$O$_7$): calcd. 450.1301; found 450.1292.

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[1] A. Schmidt, *Adv. Heterocycl. Chem.* **2003**, *85*, 67–171.
[2] Atta-ur-Rahman, S. Malik, H. Cun-Heng, J. Clardy, *Tetrahedron Lett.* **1985**, *26*, 2759–2762.
[3] A. Schmidt, *Curr. Org. Chem.* **2004**, *8*, 653–670.
[4] Y.-M. Liu, J.-S. Yang, Q.-H. Liu, *Chem. Pharm. Bull.* **2004**, *52*, 454–455.
[5] Atta-ur-Rahman, S. Malik, S. S. Hasan, M. I. Choudhary, C.-Z. Ni, J. Clardy, *Tetrahedron Lett.* **1995**, *36*, 1993–1996.
[6] E. L. Elliot, S. M. Bushell, M. Cavero, B. Tolan, T. R. Kelly, *Org. Lett.* **2005**, *7*, 2449–2451.
[7] W. Stadlbauer, in: *1H- and 2H-Indazoles*, in *Science of Synthesis* (Ed.: R. Neier), *Five-Membered Hetarenes with Two Nitrogen or Phosphorus Atoms*, Thieme, Stuttgart, **2004**, vol. 12, pp. 227–324.
[8] a) J. Elguero, in: *Pyrazoles and their Benzo Derivatives* (Ed.: K. T. Potts), in: *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford, **1984**, vol. 5, pp. 167–303; b) J. Elguero, in: *Pyrazoles* (Ed.: I. Shinkai), in: *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. Scriven), Pergamon Press, Oxford, **1996**, vol. 3, pp. 1–75; c) L. Yet, *Pyrazoles*, in: *Comprehensive Heterocyclic Chemistry III* (Eds.: A. R. Katritzky, R. J. K. Taylor, C. A. Ramsden, E. F. Scriven), Elsevier, Oxford, **2008**, vol. 4, pp. 1–141.
[9] A. Schmidt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, 4073–4095.
[10] H. Cerecetto, A. Gerpe, M. González, V. J. Arán, C. O. Ocáriz, *Mini-Rev. Med. Chem.* **2005**, *5*, 869–878.
[11] P. J. Connoly, S. K. Wetter, K. N. Beers, S. C. Hamel, D. Haynes-Johnson, M. Kiddoe, P. Kraft, M. T. Lai, C. Campen, S. Palmer, A. Phillips, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2551–2556.
[12] P. Grundt, S. L. J. Husband, R. R. Luedtke, M. Taylor, A. H. Newman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 745–749.
[13] J. Sakaguchi, N. Iwasaki, Y. Iwanaga, T. Saito, E. Takahara, H. Kato, M. Hanaoka, *Chem. Pharm. Bull.* **2001**, *49*, 424–436.
[14] J. M. Jez, J. M. Vanderkooi, A. M. Laties, *Biochem. Biophys. Res. Commun.* **1996**, *221*, 266–270.
[15] S. Schenone, O. Bruno, A. Ranise, C. Brullo, F. Bondavalli, W. Filippelli, F. Mazzeo, A. Capuano, G. Falcone, *Farmaco* **2003**, *58*, 845–849.
[16] K. W. Locke, R. W. Dunn, J. W. Hubbard, C. L. Vanselous, M. Cornfeldt, S. Fielding, J. T. Strupczewski, *Drug Dev. Res.* **1990**, *19*, 239–256.
[17] a) J.-H. Sun, C. A. Teleha, J.-S. Yan, J. D. Rodgers, D. A. Nugiel, *J. Org. Chem.* **1997**, *62*, 5627–5629; b) J. D. Rodgers, B. L. Johnson, H. Wang, R. A. Greenberg, S. Erickson-Viitanen, R. M. Klabe, B. C. Cordova, M. M. Rayner, G. N. Lam, C.-H. Chang, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2919–2924.
[18] a) W. Han, J. C. Pelletier, C. N. Hodge, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3615–3620; b) M. Patel, J. D. Rodgers, R. J. McHugh Jr., B. L. Johnson, B. C. Cordova, R. M. Klaba, L. T. Bacheler, S. Erickson-Viitanen, S. S. Ko, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3217–3220.
[19] M. Iwakubo, A. Takami, Y. Okada, T. Kawata, Y. Tagami, H. Ohashi, M. Sato, T. Sugiyama, K. Fukushima, H. Iijima, *Bioorg. Med. Chem.* **2007**, *15*, 350–367.
[20] K. B. Goodman, H. Cui, S. E. Dowdell, D. E. Gaitanopoulos, R. L. Ivy, C. A. Sehon, R. A. Stavenger, G. Z. Wang, A. Q. Viet, W. Xu, G. Ye, S. F. Semus, C. Evans, H. E. Fries, L. J. Jolivette, R. B. Kirkpatrick, E. Dul, S. S. Khandekar, T. Yi, D. K. Jung, L. L. Wright, G. K. Smith, D. J. Behm, R. Bentley, C. P. Doe, E. Hu, D. Lee, *J. Med. Chem.* **2007**, *50*, 6–9.
[21] A. Walser, T. Flynn, C. Mason, *J. Heterocycl. Chem.* **1991**, *28*, 1121–1125.
[22] H. Harada, Y. Hirokawa, K. Suzuki, Y. Hiyama, M. Oue, H. Kawashima, H. Kato, N. Yoshida, Y. Furutani, S. Kato, *Chem. Pharm. Bull.* **2005**, *53*, 184–198.
[23] A. J. Souers, J. Gao, M. Brune, E. Bush, D. Wodka, A. Vasudevan, A. S. Judd, M. Mulhern, S. Brodjian, B. Dayton, R. Shapiro, L. E. Hernandez, K. C. Marsh, H. L. Sham, C. A. Collins, P. R. Kym, *J. Med. Chem.* **2005**, *48*, 1318–1321.
[24] B. K. Keppler, M. Hartmann, *Met.-Based Drugs* **1994**, *1*, 145–150.
[25] J.-X. Duan, X. Cai, F. Meng, L. Lan, C. Hart, M. Matteucci, *J. Med. Chem.* **2007**, *50*, 1001–1006.
[26] G. Daidone, D. Raffa, B. Maggio, M. V. Raimondi, F. Plescia, D. Schillaci, *Eur. J. Med. Chem.* **2004**, *39*, 219–224.
[27] D. Simoni, R. Romagnoli, R. Baruchello, R. Rondanin, M. Rizzi, M. G. Pavani, D. Alloati, G. Giannini, M. Marcellini, T. Riccioni, M. Castorina, M. B. Guglielmi, F. Bucci, P. Carminati, C. Pisano, *J. Med. Chem.* **2006**, *49*, 3143–3152.
[28] G. A. Pina, M. A. Pirisi, J.-M. Mussinu, G. Murineddu, G. Loriga, A. Pau, G. E. Grella, *Farmaco* **2003**, *58*, 749–763.
[29] F. Saczewski, A. L. Hudson, R. J. Tyacke, D. J. Nutt, J. Man, P. Tabin, J. Saczewski, *Eur. J. Pharm. Sci.* **2003**, *20*, 201–208.
[30] a) M. Bonanomi, G. Lucente, B. Silvestrini, *Contraception* **2002**, *65*, 317–320; b) C. Y. Cheng, M. Mo, J. Grima, L. Saso, B. Tita, D. Mruk, B. Silvestrini, *Contraception* **2002**, *65*, 265–268.
[31] R. J. Steffan, E. Matelan, M. A. Ashwell, W. J. Moore, W. R. Solvibile, E. Trybulski, C. C. Chadwick, S. Chippari, T. Kenney, A. Eckert, L. Borges-Marcucci, J. C. Keith, Z. Xu, L. Mosyak, D. C. Harnish, *J. Med. Chem.* **2004**, *47*, 6435–6438.
[32] S. T. Wrobleski, P. Chen, J. Hynes Jr., S. Lin, D. J. Norris, C. R. Pandit, S. Spergel, H. Wu, J. S. Tokarski, X. Chen, K. M. Gillooly, P. A. Kiener, K. W. McIntyre, V. Patilkoota, D. J. Shuster, L. A. Turk, G. Yang, K. Leftheris, *J. Med. Chem.* **2003**, *46*, 2110–2116.
[33] N. Lebouvier, F. Pagniez, M. Duflos, P. Le Pape, Y. M. Na, G. Le Baut, M. Le Borgne, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3686–3689.
[34] M. E. Moustafa, E. H. El-Mossalamy, A. S. Amin, *Monatsh. Chem.* **1995**, *126*, 901–908.
[35] a) L. C. Behr, R. Fusco, C. H. Jarboe, in: *Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings* (Ed.: R. H. Wiley), Interscience, New York, **1967**; b) L. Baiocchi, G. Corsi, G. Palazzo, *Synthesis* **1978**, 633–648.
[36] a) M.-A. Armour, J. I. G. Cadogan, D. S. B. Grace, *J. Chem. Soc. Perkin Trans. 2* **1975**, 1185–1189; b) M. A. Ardakani, R. K. Smalley, R. H. Smith, *Synthesis* **1979**, 308–309; c) M. Akazome, T. Kondo, Y. Watanabe, *J. Org. Chem.* **1994**, *59*, 3375–3380; d) B. A. Frontana-Uribe, C. Moinet, *Tetrahedron* **1998**, *54*, 3197–3206; e) D. K. O'Dell, K. M. Nicholas, *Heterocycles* **2004**, *63*, 373–382.
[37] a) A. Alberti, N. Bedogni, M. Benaglia, R. Leardini, D. Nanni, G. F. Pedulli, A. Tundo, G. J. Zanardi, *J. Org. Chem.* **1992**, *57*, 607–613; b) C. Dell'Erba, M. Novi, G. Petrillo, C. Tavani, *Tetrahedron* **1994**, *50*, 3529–3536.
[38] a) Z. Zhenqi, X. Tongsheng, C. Xiaonai, Q. Yuzhu, Z. Zheng, H. J. Hongwen, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1279–1280; b) F. Halley, X. Sava, *Synth. Commun.* **1997**, *27*, 1199–1207; c) K. Lukin, M. C. Hsu, D. Fernando, M. R. Leanna, *J. Org. Chem.* **2006**, *71*, 8166–8172.
[39] a) N. Vivona, G. Macaluso, G. Cusmano, V. Frenna, *J. Chem. Soc. Perkin Trans. 1* **1982**, 165–167; b) T. G. Miller, R. C. Hollander, *J. Org. Chem.* **1980**, *45*, 1334–1336; c) R. Richter, H. Ulrich, *J. Org. Chem.* **1978**, *43*, 3060–3063.
[40] a) M. Medio-Simón, M. J. A. Laviada, J. Sepúlveda-Arques, *J. Chem. Soc. Perkin Trans. 1* **1990**, 2749–2750; b) J. Sepúlveda-Arques, B. Abarca-González, M. Medio-Simón, *Adv. Heterocycl. Chem.* **1995**, *63*, 339–401.
[41] S. Matsugo, A. Takamizawa, *Synthesis* **1983**, 852.

[42] A. C. Tomé, J. A. S. Cavaleiro, R. C. Storr, *Synlett* **1996**, 531–532.
[43] a) M. Médio-Simon, J. Sepúlveda-Arques, *Tetrahedron* **1986**, *42*, 6683–6686; b) B. Abarca González, R. A. Jones, M. Medio-Simón, J. Sepúlveda-Arques, H. M. Dawes, M. B. Hursthouse, *J. Chem. Res. (S)* **1985**, 84–85.
[44] a) D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, *Heterocycl. Commun.* **1997**, *3*, 433–436; b) D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, C. Foces-Foces, A. L. Llamas-Saiz, N. Jagerovic, J. Elguero, *Tetrahedron* **1999**, *55*, 10187–10200; c) D. C. G. A. Pinto, A. M. S. Silva, A. Levai, J. A. S. Cavaleiro, T. Patonay, J. Elguero, *Eur. J. Org. Chem.* **2000**, 2593–2599; d) D. C. G. A. Pinto, A. M. S. Silva, J. A. S. Cavaleiro, *J. Heterocycl. Chem.* **2000**, *37*, 1629–1634; e) A. Levai, T. Patonay, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, *J. Heterocycl. Chem.* **2002**, *39*, 751–758; f) V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, J. Elguero, *Eur. J. Org. Chem.* **2004**, 4348–4356.
[45] V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, *Synlett* **2006**, 1369–1373.
[46] a) A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, A. Levai, T. Patonay, *Arkivoc* **2004**, *7*, 106–123; b) V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, T. Patonay, *Synlett* **2004**, *15*, 2717–2720; c) V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, A. Vasas, T. Patonay, *Monatsh. Chem.* **2008**, *139*, 1307–1315; d) T. Patonay, A. Kiss-Szikszai, V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, J. Jekő, *Eur. J. Org. Chem.* **2008**, 1937–1946.
[47] a) V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, J. Elguero, *Tetrahedron Lett.* **2007**, *48*, 3859–3862; b) V. L. M. Silva, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, J. Elguero, *Monatsh. Chem.* **2009**, *140*, 87–95.
[48] a) H. Sauvaitre, J. Teysseyre, J. Elguero, *Bull. Soc. Chim. Fr.* **1976**, 635–641; b) J. Elguero, C. Foces-Foces, D. Sanz, R. M. Claramunt, in: *Advances in Nitrogen Heterocycles* (Ed.: C. J. Moody), Jay Press Inc., Stamford, **2000**, vol. 4, pp. 295–367.
[49] a) D. C. G. A. Pinto, A. M. S. Silva, L. M. P. M. Almeida, J. R. Carrillo, A. Díaz-Ortiz, A. de la Hoz, J. A. S. Cavaleiro, *Synlett* **2003**, 1415–1418; b) D. C. G. A. Pinto, A. M. S. Silva, C. M. Brito, A. Sandulache, J. R. Carrillo, P. Prieto, A. Díaz-Ortiz, A. de la Hoz, J. A. S. Cavaleiro, *Eur. J. Org. Chem.* **2005**, 2973–2986.
[50] P. Pihera, H. Dvořáková, J. Svoboda, *Collect. Czech. Chem. Commun.* **1999**, *64*, 389–407.
[51] A. Levai, A. M. S. Silva, D. C. G. A. Pinto, J. A. S. Cavaleiro, I. Alkorta, J. Elguero, J. Jekő, *Eur. J. Org. Chem.* **2004**, 4672–4679.
[52] J. Elguero, A. de la Hoz, C. Pardo, *J. Chem. Soc. Perkin Trans. 2* **1985**, 427–431.
[53] M. C. Carreño, S. García-Cerrada, A. Urbano, *Chem. Eur. J.* **2003**, *9*, 4118–4131.

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