Synthesis of chromeno[2,3-*b*]carbazole and chromeno[3,2-*f*]indazole derivatives. A new class of indole- and pyrazole-fused polycyclic compounds using *o*-quinodimethane chemistry. A reactivity and regioselectivity computational study

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Abstract

An efficient route to the new classes of derivatives tetrahydrochromeno[2,3-*b*]carbazoles and tetrahydrochromeno[3,2-*f*]indazoles has been developed. The cycloaddition reactions of chromones **3** and **4** with indole-*o*-quinodimethane **2** gave a diastereomeric mixture of Diels–Alder cycloadducts **5**–**8** in good yields, whereas the corresponding reactions of chromones **3** with pyrazole-*o*-quinodimethane **10** were more regioselective giving only cycloadducts **11** and **12** along with a small amount of the oxidation product **14**, which, however, was the main reaction product in the case of formylchromone. Frontier Molecular Orbital theory (FMO) predicted in all cases a $HOMO_{(QDM)}$–$LUMO_{(chromone)}$ controlled reaction. The observed regioselectivity was explained on account of the Δc difference in absolute values of the p_z orbital coefficients of the terminal reacting atoms in HOMO and LUMO, and also from the activation parameters calculated after locating the several transition states (TS) involved. The structure of all new compounds was confirmed by using 1D and 2D NMR data (COSY H-H, NOESY H-H, COSY C-H and COLOC C-H), ms and elemental analysis. Full assignment of all ^{1}H and ^{13}C NMR chemical shifts has been unambiguously achieved.

Keywords: Carbazoles, chromones, Diels–Alder reactions, indazoles, pyrazole*s*, *o*-quino-dimethanes

Introduction

Condensed heterocyclic systems are of considerable interest not only because of their potential biological activity but also because of their versatility as synthons in organic transformations.

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Concerning the chromone moiety, besides forming the basic nucleus of an entire class of natural products, i.e. flavones,[1] it also forms the important component of pharmacophores of a large number of molecules of medicinal significance.[2] Consequently, considerable attention is being devoted to isolation from natural resources, chemistry and synthesis of chromone derivatives, and evaluation of their biological activity with emphasis on their potential medicinal applications.[2–5] Moreover, chromone-fused heterocyclic derivatives have attracted a great deal of interest due to their wide applications in the field of pharmaceuticals.[6] Because 3-formylchromone has been extensively used in the formation of various heterocyclic systems, since its convenient synthesis was reported in the 1970s, the synthesis and reactivity of this versatile compound has been the subject of numerous reviews.[5,7,8a] 3-Formylchromone represents a very reactive system due to the presence of an *α,β*-unsaturated keto function, a conjugated second formyl group at C-3 and a center at C-2, which is very reactive towards Michael addition of nucleophiles with opening of the *γ*-pyrone ring followed by a new cyclization. Although 3-formylchromone has emerged as a valuable synthon for incorporation of the chromone moiety into a number of molecular frameworks,[8] its synthetic utility is limited due to the facile opening of the chromone ring[8,9] and strategies are being developed to circumvent it.[10] On the other hand, indoles and pyrazoles have attracted considerable attention from both synthetic organic and medicinal chemists due to their biological activity covering a wide range of medicinal applications.[6–9]

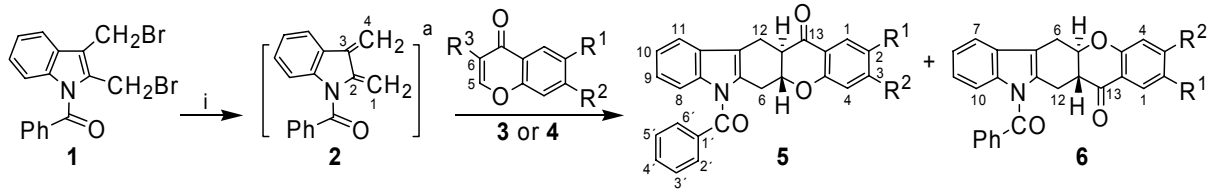
Recently, a synthetic approach involving the reaction of 3-formylchromone with *o*-benzoquinodimethane, formed *in situ* by sulfur dioxide extraction from 1,3-dihydrobenzo-[*c*]thiophene and leading to benzo[*b*]xanthones appeared in the literature.[11a–b] These results in combination with our continuous interest in the chemistry of *o*-quinodimethanes[12] (*o*-QDMs) encouraged us to investigate further utilizations of formylchromones through reactions with heterocyclic *o*-QDMs, in order to obtain a variety of chromanoheterocycles, novel macrocycles having an intact chromone moiety at the periphery with potential biological applications. So, the possibility of incorporating the chromone moiety into the indole and also into the pyrazole nucleus was examined. Moreover, the study concerning the influence on the reaction regiochemistry by incorporating two different heterocyclic rings into the chromone moiety seemed of interest. In this work we wish to present a full report of our results.[13]

Results and Discussion

Our experiments considered the Diels–Alder reactions of 3-formylchromones **3a**–**3e** with two heterocyclic *o*-QDMs, namely indole *o*-QDM **2**, containing a five-membered ring with one nitrogen heteroatom, and pyrazole *o*-QDM **10**, a heterocycle with two nitrogen heteroatoms in the five-membered ring.

Compounds **2** and **10** were generated *in situ* through reaction of sodium iodide to the appropriate dibromo-derivatives **1** and **9**, respectively, which were prepared by reaction

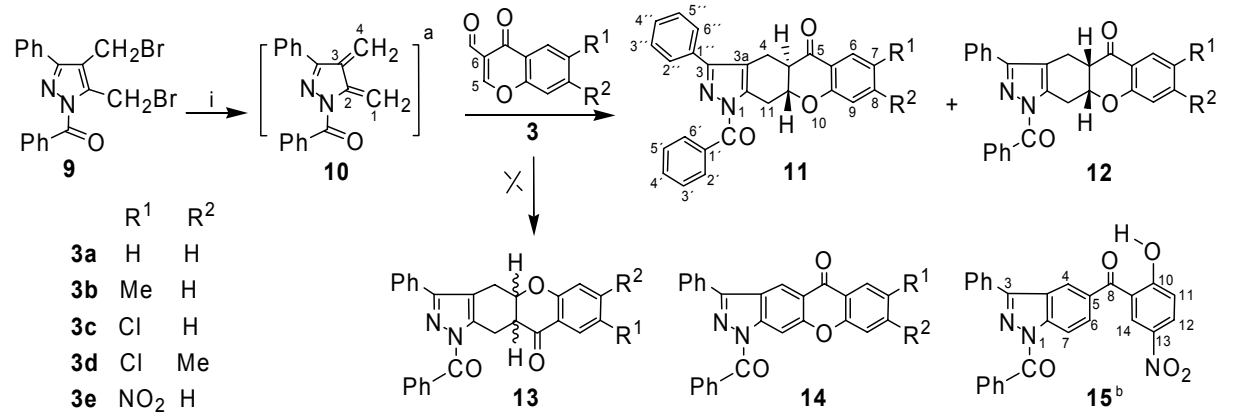
sequences reported in the literature.[14,15] Initially, the Diels–Alder reaction of **3a** with *o*-QDM **2** was carried out by the usual procedure, namely in refluxing DMF for 45 min, whereupon from the reaction mixture after separation with column chromatography two fractions of products were isolated. The first fraction contained an inseparable on TLC mixture of the two diastereomers, which proved to be (see Structure Assignments section) the two possible *tran*s diastereomers, **5a** and **6a** (12% overall yield) in a 10:1 ratio. From this mixture a pure sample of compound **5a** was obtained by recrystallization from CH_2Cl_2–Et_2O. The second fraction was shown to be a 2:1, inseparable on TLC mixture of the two possible *cis* diastereomers, **7a** and **8a** (7% overall yield, Scheme 1). Because the yields were considerably low, the reaction was repeated by modifying the reaction method. So, the reaction was repeated in boiling toluene for 10 h, using 18-crown-6 ether as a phase transfer catalyst, whereupon substantial improvement was achieved and the same products were isolated in good yields. The **5a**–**6a** mixture was isolated in 31% and the **7a**–**8a** mixture in 26% overall yield, respectively. Therefore, the reactions with substituted 3-formylchromones, **3b**–**3e**, were performed under the same conditions and the results are presented in Table 1. The reaction was also carried out in boiling benzene, where no reaction was observed and also in boiling xylene, whereupon in this higher temperature polymerization of the quinodimethane took place and no addition products were isolated. Attention should also be drawn to the fact that under the reaction conditions deformylation of the expected cycloadducts always occurred[11,16] yielding the products **5**–**8**.



	R^1	R^2	R^3		R^1	R^2	R^3
3a	H	H	CHO	**4a**	H	H	H
3b	Me	H	CHO	**4b**	NO_2	H	H
3c	Cl	H	CHO				
3d	Cl	Me	CHO				
3e	NO_2	H	CHO				

[a] The position numbering in the reactants **2** and **3** or **4** is arbitrary, used only for the computational study and the notation of transition states during the Diels-Alder reactions.

Scheme 1. Synthesis of indole *o*-QDM **2** and its reaction with some substituted chromenones **3** or **4**. Reaction conditions: (i) NaI, 18-crown-6, toluene, reflux 10 h under N_2.



[a] Same as in Scheme 1. [b] The position numbering of 5-benzoyl group is arbitrary.

Scheme 2. Synthesis of pyrazole *o*-QDM **10** and its reaction with some substituted chromenones **3**. Reaction conditions: (i) NaI, 18-crown-6, toluene, reflux 10 h under N_2.

Table 1. Reaction products for compounds **5–8** and **11–12**

	5 + 6	**7 + 8**	**11 + 12**	Dehydrogenated
a	31% (10:1)	26% (2:1)	20%[a]	**14** 35%
b	3% (10:1)	44% (2.5:1)	42% (1:2)	[b]
c	29% (10:1)	34% (4:1)	51% (2:3)	[b]
d	23% (10:1)	32% (2.5:1)	48% (2:3)	[b]
e	27% (10:1)	59% (3:1)	31% (1:2)	[b]

[a] Only the *cis* isomer **12a** is present. [b] In all cases compound **14** is present in ~3%.

Moreover, experiments involving reactions of chromones **4** with indole *o*-QDM **2**, generated *in situ* through the action of sodium iodide on compound **1** either in dry refluxing DMF for 30 min or in dry refluxing toluene for 20 h in the presence of 18-crown-6 ether were carried out. However, in all cases low yields (2–4%) of the corresponding mixture of *cis* and *trans* cycloaddition products, tetrahydrochromeno[2,3-*b*]carbazoles **5**–**8** were isolated, proving thus that the presence of the formyl group enhances considerably the dienophilicity of the chromone moiety (see Theoretical Calculations section).

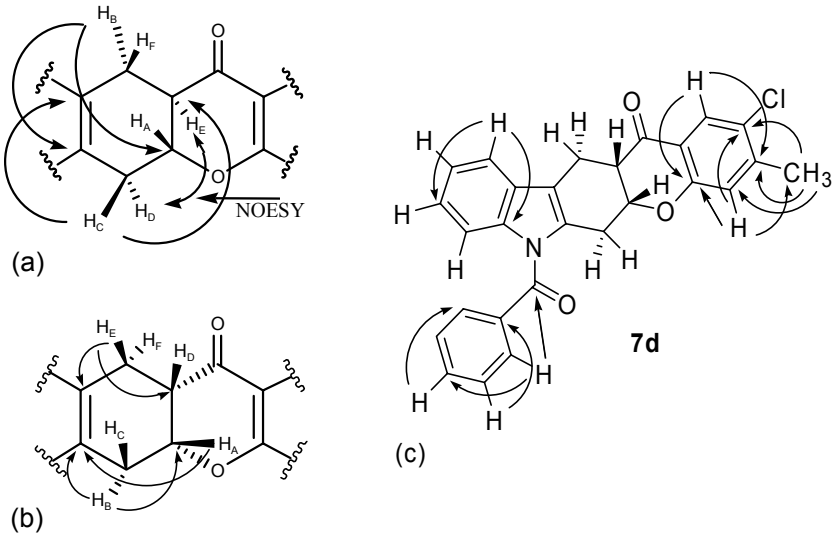


Figure 1. NOESY and COLOC correlations between protons and carbons in the saturated part of fused rings of compounds **5a** (a) and **7d** (b). (c) COLOC correlations in the aromatic rings in compound **7d**.

Next, the reaction of 3-formylchromones **3a**–**3e** with pyrazole-*o*-quinodimethane **10** were studied in boiling toluene for 10 h using 18-crown-6 ether. It is remarkable that in this case the reaction was highly regioselective and mixtures of only two diastereomers **11b**–**11e** and **12b**–**12e**, were isolated in good yields by column chromatography, with the benzoyl group being always on the same side with the pyrane oxygen (Scheme 2, Table 1). The possible regio isomers **13** were never isolated, although small amounts less than 2% were formed, as was observed from ^{1}H nmr spectra of the crude reaction mixtures. In most cases this mixture was accompanied with small amounts (2–5% yield) of the corresponding oxidation products **14**. However, in the case of **3a** the oxidation product **14a** was isolated as the main reaction product (35% yield) together with **12a** (20% yield). Compound **14a** most probably is formed by the dehydrogenation of the *trans* bridgehead hydrogens (4a-H and 10a-H). All formed products were again prone to deformylation under the reaction conditions. It is also notable that in the reactions studied in this work opening of the pyran ring was never observed. However, upon purification of **11e** on prep. TLC cleavage of the pyran ring occurred resulting to the hydroxy derivative **15**.

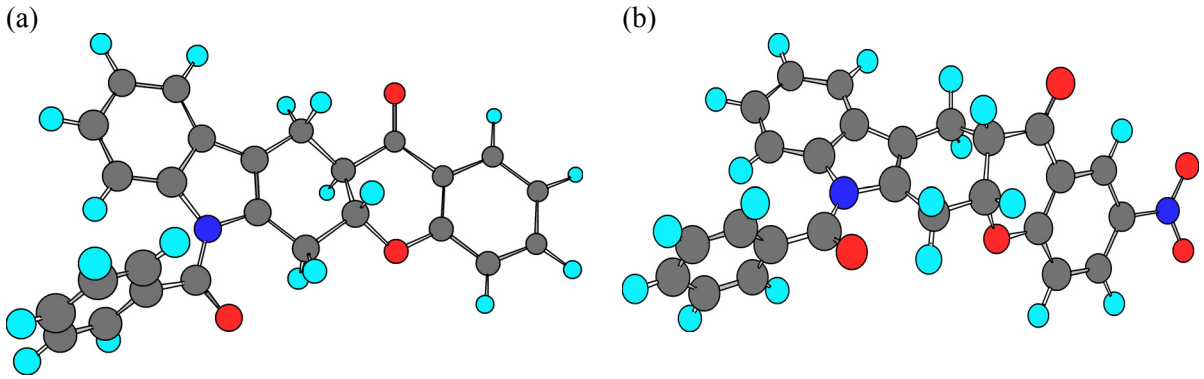


Figure 2. Minimum energy conformations of compounds **5a** (a) and **7e** (b) calculated by AM1 method.

Structure assignments

Concerning the stereochemistry of the cycloaddition products the structure of **5a** will be analysed. This structure was deduced on account of the following data. For the saturated protons H_A-H_F (Figure 1a) one proton multiplets at 4.622, 3.499, 3.460, 3.306, 3.102 and 2.824 δ were observed in the ^{1}H nmr spectrum, correspondingly. The most downfield multiplet at 4.622 δ was attributed to the H_A proton next to the chromone oxygen. This proton shows COSY correlations with the 3.102 δ proton and also with the 3.460 and 3.306 δ protons belonging to the 32.07 ppm carbon (C-6), whereas the 3.102 δ proton shows correlations with the 4.622 δ proton and also with the 3.499 and 2.824 δ protons belonging to the 19.82 ppm carbon (C-12). In this way the arrangement of the methylene groups was deduced.

Moreover, from the coupling constants of J_{AD} = 9.6 Hz, J_{AE} = 13.3 Hz and J_{EF} = 10.8 Hz the conclusion of an *axial–axial* (*trans*) configuration between these protons could be drawn, whereas the coupling constants of J_{AC} = 6.1 Hz και J_{BE} = 6.1 Hz indicated an *axial–equatorial* configuration of these protons.[17] On the other hand, COLOC correlations between H_C with carbons at 45.67 (C-12a) and 115.87 ppm (C-11b), and between H_B with carbons at 131.55 (C-6a) and 77.72 ppm (C-5a) indicated that these protons occupy equatorial positions in the cyclohexene ring justifying thus their favorable dihedral angles. The more downfield shift of H_C compared to H_D and of H_B compared to H_F can be attributed to the fact that equatorial protons in cyclohexane rings resonate at about 0.5 ppm more downfield than their axial counterparts and also to a small extent to their vicinity with the NCOPh and pyrane carbonyls, the NCOPh group causing also a slight broadening to the H_C multiplet. Moreover, the homoallylic coupling constant J_{DF} between the C-6 and C-12 axial protons varies between 2.5 to 3.3 Hz, whereas in the case of axial-equatorial protons is ~1.7 Hz. The minimized energy conformation of compound **5a** calculated by AM1 is depicted in Figure 2a. To the minor component the **6a** structure was deduced.

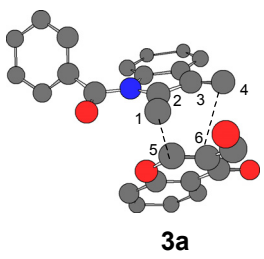
Concerning the two *cis* addition products **7** and **8** the structure of **7e** was analysed based on the following data. The chemical shift of the carbon at 76.58 ppm with its proton H_A resonating at 5.168 δ reveals its neighborhood to the ether oxygen. This proton shows a ddd multiplet with smaller coupling with its neighbors (J_{AB} = 4.5 Hz, J_{AC} = 4.2 Hz and J_{AD} = 2.7 Hz, Figure 1b). The small coupling constants reveal a chair instead of a boat conformation of the cyclohexene ring, H_A having an equatorial configuration. This configuration is also in agreement with the fact that H_A shows COLOC correlation with the quaternary carbon C-6a at 131.33 ppm. On the other hand, H_D shows a ddd multiplet at 3.222 δ with J_{DF} = 9.4 Hz, J_{DE} = 6.7 Hz and J_{AD} = 2.7 Hz and no COLOC correlation with C-11b. This conformation is more flexible than that of the *trans* adduct **5**; as a result, the methylene protons H_B, H_C at 6- and H_E, H_F at 12-positions are not diversified in their chemical shifts as it happens in **5**. All COLOC correlations in the aromatic rings are depicted in Figure 1c. The structure which is in agreement with these data most probably has the chromone moiety almost perpendicular to the indole–cyclohexene moiety (Figure 2b).

Theoretical calculations

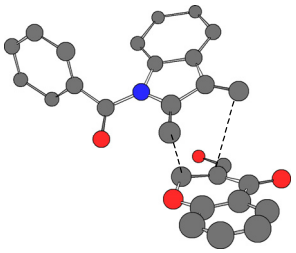
In order to investigate the reactivity of the reacting species and the regioselectivity of the products **5**–**8** and **11**–**12** we have studied the frontier molecular orbital (FMO) interactions of the reactants and the transition structures (TS) of the intermediates involved. Full geometry optimizations were carried out for *o*-QDMs **2** and **10** and chromones **3** and **4** as well as for the possible adducts and the corresponding transition structures (**TS1**–**TS12**) at the AM1 level of theory (Figures 3, 4 and 5). For each located TS after complete optimization with the keywords LET and PRECISE only one imaginary frequency was calculated assigned to the shorter new forming bond.[18] The activation energy of almost any reaction is influenced by the polarity of the solvent used. In the present case, since in all studied reactions the conditions are similar, the solvent effects can be ignored, as long as the differences of activation parameters are calculated.

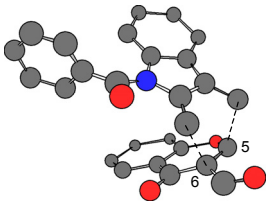
In Table 2 the calculated HOMO–LUMO energies (eigenvalues) and the orbital coefficients (eigenvectors) for the atoms of all compounds involved in the [4+2] cycloaddition reaction are presented. According to FMO interactions the energy difference between the two orbitals involved is essential, the smaller the better, so the reaction of the indolo-*o*-QDMs **2** and pyrazolo-*o*-QDMs **10** with 3-formylchromones **3** and with chromones **4** are predicted to be $HOMO_{(QDM)} - LUMO_{(chromone)}$ controlled (Figure 6a). The opposite attacking process is predicted to be energetically disfavored by 29 to 81 kcal/mol (Table 3).

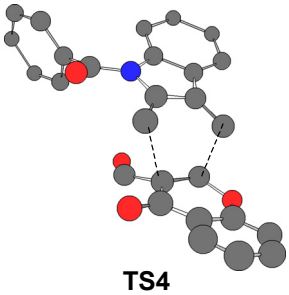
Examining the MO coefficients in Table 2 the first attacking position of chromone can be predicted. In all cases the chromone position 5 (see Schemes 1 and 2 for the arbitrary numbering) has the larger coefficient and consequently the new forming bond begins there.



3a

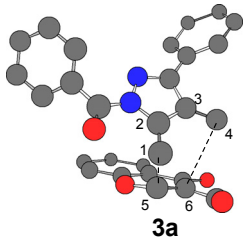




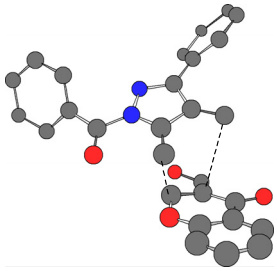


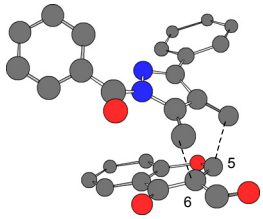
TS1	**TS2**	**TS3**	**TS4**
C_1–C_2 = 1.406	C_1–C_2 = 1.408	C_1–C_2 = 1.374	C_1–C_2 = 1.374
C_2–C_3 = 1.481	C_2–C_3 = 1.482	C_2–C_3 = 1.448	C_2–C_3 = 1.450
C_3–C_4 = 1.341	C_3–C_4 = 1.341	C_3–C_4 = 1.388	C_3–C_4 = 1.388
C_5–C_6 = 1.421	C_5–C_6 = 1.421	C_5–C_6 = 1.416	C_5–C_6 = 1.418
C_1–C_5 = 1.806	C_1–C_5 = 1.803	C_1–C_6 = 2.369	C_1–C_6 = 2.372
C_4–C_6 = 3.075	C_4–C_6 = 3.154	C_4–C_5 = 1.963	C_4–C_5 = 1.955
E_{TS} = 63.99	E_{TS} = 64.07	E_{TS} = 67.30	E_{TS} = 66.68
$\bar{\nu}$ = –624	$\bar{\nu}$ = –639	$\bar{\nu}$ = –791	$\bar{\nu}$ = –791

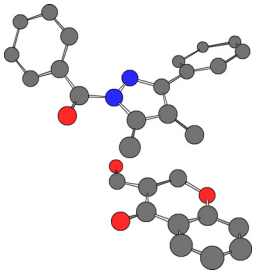
Figure 3. Transition structures optimized at AM1 level for the interaction of *o*-QDM **2** with chromone **3a** for *endo* or *exo* approaching leading to product **7** (**TS1**, **TS2**) and **8** (**TS3**, **TS4**). The values of bond lengths involved in the new cyclohexene ring along with the heats of formation of the activated complex at TS and the vibrating frequency of the shorter new forming bond at 383 K are given. All bond lengths are in angstroms (Å) and energies in kcal/mol. For the numbering of reacting atoms see Scheme 1.



3a







TS5	**TS6**	**TS7**	**TS8**
C_1–C_2 = 1.401	C_1–C_2 = 1.402	C_1–C_2 = 1.378	C_1–C_2 = 1.379
C_2–C_3 = 1.477	C_2–C_3 = 1.478	C_2–C_3 = 1.446	C_2–C_3 = 1.445
C_3–C_4 = 1.340	C_3–C_4 = 1.339	C_3–C_4 = 1.382	C_3–C_4 = 1.381
C_5–C_6 = 1.420	C_5–C_6 = 1.420	C_5–C_6 = 1.414	C_5–C_6 = 1.415
C_1–C_5 = 1.817	C_1–C_5 = 1.816	C_1–C_6 = 2.295	C_1–C_6 = 2.272
C_4–C_6 = 3.079	C_4–C_6 = 3.130	C_4–C_5 = 2.028	C_4–C_5 = 2.037
E_{TS} = 105.39	E_{TS} = 105.55	E_{TS} = 108.41	E_{TS} = 108.33
$\bar{\nu}$ = –653	$\bar{\nu}$ = –663	$\bar{\nu}$ = –816	$\bar{\nu}$ = –832

Figure 4. Transition structures for the interaction of *o*-QDM **10** with chromone **3a** for *endo* or *exo* approaching leading to product **12** (**TS5**, **TS6**) and **13** (**TS7**, **TS8**). For the numbering of reacting atoms see Scheme 2.

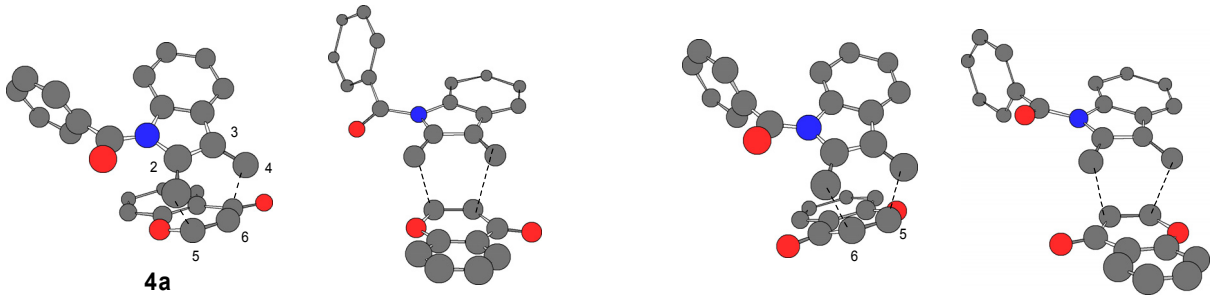


Figure 5. Transition structures for the interaction of *o*-QDM **2** with chromone **4a** for *endo* or *exo* approaching leading to product **7** (**TS9**, **TS10**) and **8** (**TS11**, **TS12**). For the numbering of reacting atoms see Scheme 1.

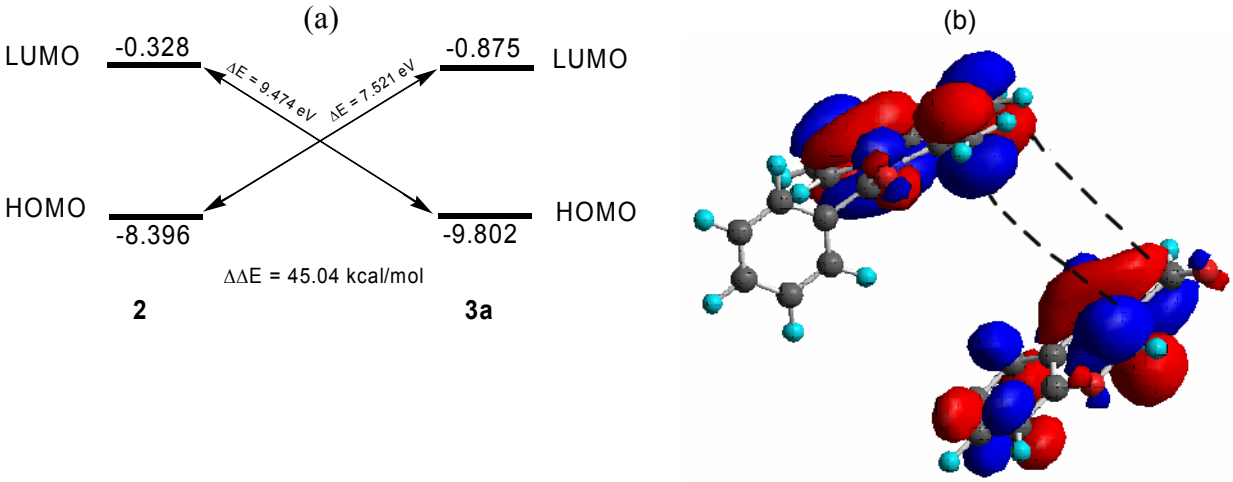


Figure 6. (a) Molecular orbital correlation diagram for the interaction of *o*-QDM **2** with chromone **3a** in the *endo* approaching **TS1** calculated by AM1. (b) HOMO-LUMO interaction of **2** and **3a** in the endo transition state **TS1**.

In order to examine the regioselectivity of the reactions both the coefficients of the reacting MO and the energetically favored TS were examined. The reactions can proceed either by *endo* or by *exo* approach of the reacting species. So, all the possible TS were located and the heats of formation $E_{TS}^{\#}$ at the reaction temperature (110 ^{o}C, 383 K) were calculated.

According to FMO theory the reaction progress depends on the orbital overlapping in the TS,

the larger overlap giving the better yield. In asymmetric π systems, as in our case, the regioselectivity depends on the difference of size of the mutual overlapping orbitals as well as on steric effects, which affect the easy proximity of the reacting species. As a measure for the first factor the difference of the vectors of p_z orbitals can be used, whereas for the steric effects the energy of formation of the transition structure (or the free energy of activation $\Delta G^{\#}$) is a good tool. As a result, in the transition state complex the corresponding bond is always shorter. This means that even if the reaction is believed to be concerted, it is slightly asynchronous. In favor of this statement is the fact that both *cis* and *trans* isomeric products are present in the crude reaction mixture, exluding the isomerisation induced by the silica gel. In Table 2 Δc represents the difference in absolute values of the p_z orbital coefficients of terminal reacting atoms. The bigger the difference the better regioselectivity can be achieved. So, the fact that the Δc value (Table 2) of the reacting HOMO of the pyrazole *o*-QDM **10** is almost double than the corresponding of indole *o*-QDM **2** is in agreement with the experimental results (Table 1), where in the case of **10** only one regio isomer was isolated.

Table 2. Calculated HOMO–LUMO energies (eV) and orbital coefficients (eigenvectors) for the atoms involved in new bond formations[a] for the reaction of *o*-QDMs **2** and **10** with chromones **3** and **4** (in gas phase at 298 K, AM1)

Comp.	HOMO	LUMO	Δc	Comp.	HOMO	LUMO	Δc
2	–8.396[b]	–0.328		**10**	–8.602	–0.580	
C-1	0.4242[c]	0.2708	0.0596[d]	C-1	–0.4610	0.2793	0.0996
C-2	0.2163	–0.1508		C-2	–0.2437	–0.1473	
C-3	–0.1838	–0.2996		C-3	0.1823	–0.2631	
C-4	–0.3646	0.4812		C-4	0.3614	0.4509	
3a	–9.802	–0.875		**3e**	–10.531	–1.722	
C-5	0.1302	–0.5722	0.2972[e]	C-5	0.2054	–0.2543	0.0255
C-6	0.3719	0.2750		C-8	0.4386	0.2288	
3b	–9.581	–0.837		**4a**	–9.472	–0.547	
C-5	–0.0810	–0.5896	0.3000	C-5	0.1572	–0.3379	0.2062
C-6	–0.3066	0.2896		C-6	0.3633	0.1317	
3c	–9.765	–1.044		**4b**	–10.241	–1.174[f]	
C-5	0.0839	0.5229	0.2837	C-5	0.2252	–0.3357	0.1741
C-6	0.3003	–0.2392		C-6	0.4210	0.1616	
3d	–9.700	–1.003					
C-5	–0.0723	–0.4820	0.2769				
C-6	–0.2833	0.2051					

[a]For atom numbering of the diene moieties and chromones see Schemes 1 and 2. [b]HOMO–LUMO energies (eigenvalues, in eV). [c]Orbital coefficients (eigenvectors). [d]Δc is the difference in absolute values of the p_z orbital coefficients of the terminal reacting atoms 1–4 (HOMO). [e]As above, for 5–6 (LUMO). [f]*N*–LUMO.

Table 3. Energy differences for the various HOMO–LUMO interactions between quinodimethanes (**2** and **10**) and chromones **3a**–**e** and **4a**–**b** (in gas phase at 298 ^{o}K, AM1)

Reaction	with **2**					with **10**		
	HOMO	LUMO	$\Delta E(L_{chr})$[a]	$\Delta E(L_{qdm})$	$\Delta\Delta E$[b]	$\Delta E(L_{chr})$	$\Delta E(H_{chr})$	$\Delta\Delta E$
3a	–9.802	–0.875	7.521	9.474	45.04	7.727	9.222	34.47
3b	–9.581	–0.837	7.559	9.253	39.06	7.765	9.001	28.50
3c	–9.765	–1.044	7.352	9.437	48.08	7.558	9.185	37.52
3d	–9.700	–1.003	7.393	9.372	45.64	7.599	9.120	35.07
3e	–10.531	–1.722	6.674	10.203	81.38	6.880	9.951	70.82
4a	–9.472	–0.547	7.849	9.144	29.86	8.055	8.892	19.30
4b	–10.241	–1.174[c]	7.222	9.913	62.05	7.428	9.661	51.49

[a] $\Delta E(L_{chr}) = E(LUMO_{chromone}) - E(HOMO_{qdm})$; $\Delta E(L_{qdm}) = E(LUMO_{qdm}) - E(HOMO_{chromone})$, (in eV/mol). [b] $\Delta\Delta E = \Delta E(L_{qdm}) - \Delta E(L_{chromone})$, (in kcal/mol). [c] *N*–LUMO.

The activation energy factor is also very important. When two possible TS can be involved, the one with the lower activation energy is considered to be kinetically favored. In Tables 4 and 5 the calculated ratio of the intermediate adducts, before formyl elimination, resulting from *endo/exo* approach[19] of the reacting species is shown in the last column. Since these approaches afford the same products the comparison has only theoretical interest. The selected, from Tables 4 and 5, TS with the lower activation energies corresponding to the favored approach for each one of the studied reactions are given in Table 6. The comparison of these activation parameters showed that in all cases products **7** and **12** are predicted to be favored over **8** and **13**, respectively. In Figure 6b the HOMO-LUMO interaction of compounds **2** and **3a** in the *endo* approaching transition state **TS1** is depicted. All isolated products resulted after deformylation of the primarily formed cycloaddition products. By adding up the yields given in Table 1 for **5**+**7**, and **6**+**8** a ratio of approximately 13:2 (or 86:14 %) is obtained, a value very close to the theoretical prediction of 97:3 given in Table 6, calculated *in vacuo* without solvent effects. On the other hand, products **12** are predicted to be favored over **13** in a ratio of 99:1, which is practically the same with the one found experimentally (98:2) by ^{1}H nmr of the crude reaction mixture.

Table 4. Calculated energies of formation ΔH_f[a] and activation parameters for the *endo* and *exo* transition structures and corresponding adducts for the reactions of *o*-QDMs **2** with chromones **3a**–**e** and **4a**–**b** leading: (a) to compounds **7** and (b) to compounds **8** (in gas phase, 383 °K, AM1)[b]

(a)	*Endo* approach					*Exo* approach				
	$\Sigma\Delta H_{f(r)}$ [c]	$\Delta H_{f(p)}$	ΔH^o [d]	E_{TS} [e]	$\Delta H^{\#}_{(endo)}$ [f]	E_{TS}	$\Delta H^{\#}_{(exo)}$	$\Delta\Delta H^{\#}$ [g,h]	C_{endo}/C_{exo} [i]	C_{endo}/C_{exo} [j]
3a	36.63	2.99	–33.64	63.99	27.36	64.07	27.44	–0.08	1.111	53/47
3b	29.42	–4.07	–33.49	56.98	27.56	57.05	27.63	–0.07	1.096	52/48
3c	30.99	–2.93	–33.92	57.42	26.43	60.59	29.60	–3.17	64.43	98/2
3d	24.31	–9.60	–33.91	53.81	29.50	51.09	26.78	2.72	0.028	3/97
3e	43.64	8.59	–35.05	67.69	24.05	67.89	24.25	–0.20	1.301	57/43
4a	68.11	24.48	–43.63	97.00	28.89	95.13	27.02	1.87	0.086	8/92
4b	74.03	29.19	–44.84	101.33	27.30	99.93	25.90	1.40	0.159	14/86

(b)	*Endo* approach					*Exo* approach				
	$\Sigma\Delta H_{f(r)}$ [c]	$\Delta H_{f(p)}$	ΔH^o [d]	E_{TS} [e]	$\Delta H^{\#}_{(endo)}$ [f]	E_{TS}	$\Delta H^{\#}_{(exo)}$	$\Delta\Delta H^{\#}$ [g,h]	C_{endo}/C_{exo} [i]	C_{endo}/C_{exo} [j]
3a	36.63	2.89	–33.74	67.30	30.67	66.68	30.05	0.62	0.443	31/69
3b	29.42	–4.14	–33.56	60.13	30.71	59.61	30.19	0.52	0.505	34/66
3c	30.99	–3.14	–34.13	60.93	29.94	60.63	29.64	0.30	0.674	40/60
3d	24.31	–9.79	–35.58	54.41	30.10	54.05	29.74	0.36	0.623	38/62
3e	43.64	8.06	–35.58	71.59	27.95	72.00	28.36	–0.41	1.714	63/37
4a	68.11	24.05	–44.06	98.88	30.77	96.63	28.52	2.25	0.052	5/95
4b	74.03	28.80	–45.23	102.80	28.77	101.62	27.59	1.18	0.212	18/82

[a] ΔH_f for the reactants(at 383 °K, in kcal/mol): **2** = 87.17; **3a** = –50.54; **3b** = –57.75; **3c** = –56.18; **3d** = –62.86; **3e** = –43.53; **4a** = –19.06; **4b** = –13.14. [b] The boiling temperature of toluene. [c] $\Sigma\Delta H_{f(r)} = \Delta H_{f(chr)} + \Delta H_{f(QDM)}$, (p = products, r = reactants, chr = chromone). [d] $\Delta H^o = \Delta H_{f(p)} - \Sigma\Delta H_{f(r)}$ [e] E_{TS} is the calculated ΔH_f for the transition state. [f] $\Delta H^{\#} = E_{TS} - \Sigma\Delta H_{f(r)}$. [g] $\Delta\Delta H^{\#} = \Delta H^{\#}_{(endo)} - \Delta H^{\#}_{(exo)}$ is the relative activation energy. [h] A negative value means a more stable TS for *endo* approach, the corresponding adduct being kinetically favored. [i] C_{endo}/C_{exo} is the relative calculated ratio of products **7** derived from *endo* versus that of *exo* approach by the Boltzmann equation for equilibrium distribution. [j] C_{endo}/C_{exo} is the corresponding calculated % ratio of products.

Table 5. Calculated energies of formation ΔH_f[a] and activation parameters for the *endo* and *exo* transition structures and corresponding adducts for the reactions of *o*-QDMs **10** with chromones **3a**–**e** leading: (a) to compounds **12** and (b) to compounds **13** (in gas phase, 383 °K, AM1)[b]

(a)	*Endo* approach					*Exo* approach				
	$\Sigma\Delta H_{f(r)}$[c]	$\Delta H_{f(p)}$	ΔH^o[d]	E_{TS}[e]	$\Delta H^{\#}_{(endo)}$[f]	E_{TS}	$\Delta H^{\#}_{(exo)}$	$\Delta\Delta H^{\#}$[g,h]	C_{endo}/C_{exo}[i]	C_{endo}/C_{exo}[j]
3a	78.13	42.90	−35.23	105.39	27.26	105.55	27.42	–0.16	1.234	55/45
3b	70.92	35.84	−35.08	98.35	27.43	98.52	27.60	–0.17	1.250	56/44
3c	72.49	36.96	−35.53	98.95	28.03	99.12	26.63	1.40	0.159	14/86
3d	65.81	30.30	−35.51	92.51	26.70	92.64	26.83	–0.13	1.186	54/46
3e	85.14	48.40	−36.74	109.58	24.44	109.71	24.57	–0.13	1.186	54/46
(b)	*Endo* approach					*Exo* approach				
	$\Sigma\Delta H_{f(r)}$[c]	$\Delta H_{f(p)}$	ΔH^o[d]	E_{TS}[e]	$\Delta H^{\#}_{(endo}$[f]	E_{TS}	$\Delta H^{\#}_{(exo)}$	$\Delta\Delta H^{\#}$[g,h]	C_{endo}/C_{exo}[i]	C_{endo}/C_{exo}[j]
3a	78.13	40.49	–37.64	108.41	30.28	108.33	30.20	0.08	0.900	47/53
3b	70.92	33.45	–37.47	101.36	30.44	101.23	30.31	0.13	0.843	46/54
3c	72.49	34.53	–37.96	102.28	29.79	102.39	29.90	–0.11	1.156	54/46
3d	65.81	27.85	–37.96	95.72	29.91	95.77	29.96	–0.05	1.068	52/48
3e	85.14	45.90	–39.24	113.35	28.21	114.03	28.89	–0.68	2.444	71/29

[a] ΔH_f for the reactants(at 383 °K, in kcal/mol): **10** = 128.67; **3a** = –50.54; **3b** = –57.75; **3c** = –56.18; **3d** = –62.86; **3e** = –43.53; **4a** = –19.06; **4b** = –13.14. [b] The symbols have the same meaning as in Table 4.

Table 6. Calculated product ratio **7**/**8** and **12**/**13** according to their lower calculated activation parameters for *endo* or *exo* approach (in gas phase, 383 °K, AM1)

Reaction	$E_{(7)TS}$[a]	$E_{(8)TS}$	ΔE_{TS}	**7/8**	Reaction	$E_{(12)TS}$	$E_{(14)TS}$	ΔE_{TS}	**12/13**
3a+**2**	63.99	66.68	–2.69	97/3	**3a**+**10**	105.39	108.33	–2.94	98/2
3b+**2**	56.98	59.61	–2.63	97/3	**3b**+**10**	98.35	101.23	–2.88	98/2
3c+**2**	57.42	60.63	–3.21	98/2	**3c**+**10**	98.95	102.28	–3.33	99/1
3d+**2**	51.09	54.05	–2.96	98/2	**3d**+**10**	92.51	95.72	–3.21	99/1
3e+**2**	67.69	71.59	–3.90	99/1	**3e**+**10**	109.58	113.75	–4.17	99/1
4a+**2**	95.13	96.63	–1.50	88/12					
4b+**2**	99.93	101.62	–1.69	90/10					

[a] E_{TS} is the lower transition state energy of the activated complex leading after deformylation to compound **7**, **8**, **12** or **13**, correspondingly.

The smaller reactivity of chromones **4** can be attributed mainly to the higher activation energy required to reach the TS. The computed activation energies $E_{TS}^{\#}$ of reactions between **2**+**4a** and **2**+**4b** for *endo* approach are ~33 kcal/mol higher than the corresponding ones for **2**+**3a** and **2**+**3e**. To overcome this additional energy the temperature of the reaction must be increased. However, as mentioned earlier, by using boiling xylene as solvent only resinous material was formed.

Conclusions

In conclusion, an efficient route for the synthesis of new classes of fused tetrahydrochromeno carbazoles and indazoles has been described by incorporating the chromone moiety into the indole and pyrazole nuclei, respectively. The new products are formed by the combination of two extremely active biological components and such polycyclic molecules are known to display substantial biological activities.[20] In all cases *in situ* deformylation of chromenone Diels–Alder adducts was observed. Frontier Molecular Orbital theory (FMO) predicted the reaction in all cases to be $HOMO_{(qdm)}$–$LUMO_{(chromone)}$ controlled. The observed regioselectivity is a result of the Δc difererence in absolute values of the p_z orbital coefficients of the terminal reacting atoms in HOMO and LUMO and of the activation parameters calculated after locating the several TS involved. In addition, the theoretical prediction for the product ratio is in excellent agreement with the experimental results.

Experimental Section

General Procedures. Melting points were measured on a Kofler hot-stage and are uncorrected. Column chromatography was carried out using Merck silica gel. TLC was performed using precoated silica gel glass plates of 0.25 mm containing fluorescent indicator UV254 purchased from Macherey–Nagel using a 3:1 mixture of petroleum ether–ethyl acetate. Petroleum ether refers to the fraction boiling between 60 and 80°C. NMR spectra were recorded on a Bruker AM 300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively, using $CDCl_3$ as solvent. Coupling constants ^nJ are reported in Hz and chemical shifts are expressed in δ values (ppm) relative to TMS as internal standard for ^{1}H and relative to TMS (0.00 ppm) or to $CDCl_3$ (77.05 ppm) for ^{13}C NMR spectra. Second order ^{1}H NMR spectra were analysed by simulation.[17] IR spectra were recorded on a Perkin–Elmer 1600 series FTIR spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution electron impact mass spectra (EIMS) were obtained either on a VG TS-250 instrument or on a 6890N GC/MS system (Agilent Technology) and elemental analyses performed with a Perkin–Elmer 2400-II CHN analyzer. The MO calculations for minimum energy conformation of compounds were computed with the AM1 method as implemented in the MOPAC package.[21] All stationary points were refined by minimization of

the gradient norm of the energy to at least 0.005 kcal/mol. Structural assignments of the derived compounds were established by analysis of their elemental analyses, IR, MS, and NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HETCOR, and COLOC).

General procedure for the Diels–Alder reactions of 3-formylchromones (3a–3e) with indole *o*-quinodimethane 2

To a stirred solution of **3** (5.0 mmol) in dry toluene (25 mL), 18-crown-6 ether was added (0.581 g, 2.2 mmol) followed by the addition of 1-benzoyl-2,3-bisbromomethylindole (**1**) (0.407 g, 1.0 mmol) and finally sodium iodide (0.33 g, 2.2 mmol). The reaction mixture was stirred at reflux under nitrogen for 10 h. The solvent was distilled off and the resulting residue was subjected to the following procedure in order to remove the excess of chromone, except in the case of nitro derivative. The residue was dissolved in 10 mL of dichoromethane and washed initially with 2×10 mL of 5% sodium hydroxide, then with 5% ammonium chloride and finally with water. The organic phase was dried with anhydrous sodium sulphate, the solvent was distilled off and the residue was subjected to column chromatography on silica gel using petroleum ether/EtOAc (7:1) as eluent, to give in order of elution an inseparable mixture of **5** and **6** and a second inseparable mixture of **7** and **8**.

From compound 3a

(5a*R*,12a*R* or 5a*S*,12a*S*)-7-Benzoyl-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (5a) and (5a*R*,12a*R* or 5a*S*,12a*S*)-11-Benzoyl-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (6a) in a 10:1 ratio**.** Overal yield 0.122 g, 31%. From this mixture a pure sample of the **major isomer 5a** was obtained after recrystallization from CH_2Cl_2–Et_2O as a white solid, mp 235–237 °C; IR (KBr) ν_{max}: 1682, 1606 cm^{-1}. ^{1}H NMR δ 2.824 (dddd, J = 17.2, 10.8, 3.3, 1.7 Hz, 1H, 12-H$_{ax}$),[17] 3.102 (ddd, J = 13.3, 10.8, 6.1 Hz, 1 H, 12a-H$_{ax}$), 3.306 (dddd, J = 17.0, 9.6, 3.3, 1.7 Hz, 1H, 6-H$_{ax}$), 3.460 (dddd, J = 17.0, 6.1, 1.7, 0.5 Hz, 1H, 6-H$_{eq}$), 3.499 (dddd, J = 17.2, 6.1, 1.7, 0.5 Hz, 1H, 12-H$_{eq}$), 4.622 (ddd, J = 13.3, 9.6, 6.1 Hz, 1H, 5a-H$_{ax}$), 6.99 (dd, J = 8.3, 1.1 Hz, 1H, 8-H),[17] 7.02 (ddd, J = 8.0, 1.1, 0.4 Hz, 1H, 4-H), 7.06 (ddd, J = 7.9, 7.2, 1.1 Hz, 1H, 2-H), 7.08 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H, 9-H), 7.222 (ddd, J = 8.2, 7.1, 1.1 Hz, 1H, 10-H), 7.48–7.52 (m, 2H, 3,11-H), 7.52–7.56 (m, 2H, 3',5'-H), 7.667 (tt, J = 7.45, 1.6 Hz, 1H, 4'-H), 7.72–7.76 (m, 2H, 2',6'-H), 7.965 (ddd, J = 7.9, 1.8, 0.4 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.82 (C-12), 32.07 (C-6), 45.67 (C-12a), 77.72 (C-5a), 114.72 (C-8), 115.87 (C-11b), 117.91 (C-4), 118.37 (C-11), 120.72 (C-13a), 121.69 (C-2), 123.05 (C-10), 123.78 (C-9), 127.25 (C-1), 128.88 (C-3',5'), 128.94 (C-11a), 129.48 (C-2',6'), 131.55 (C-6a), 132.83 (C-4'), 135.42 (C-1'), 136.24 (C-3), 137.06 (C-7a), 161.27 (C-4a), 169.00 (NCO), 193.49 (C-13). EIMS m/z (%) 393 (4, M$^{+\cdot}$), 392 (57), 373 (8), 288 (40), 269 (45), 166 (95), 143 (27), 130 (35), 105 (45), 104 (62), 77 (100). Anal. calcd for $C_{26}H_{19}NO_3$ (393.43): C, 79.37; H, 4.87; N, 3.56. Found: C, 79.25; H, 4.92; N. 3.50%.

After isolation of **5a** some NMR data[21] of **the minor isomer 6a** were also deduced: ^{1}H NMR δ 4.714 (ddd, J = 13.4, 9.6, 6.3 Hz, 1H, 5a-H), 7.915 (dd, J = 8.0, 1.7 Hz, 1H, 1-H). ^{13}C NMR (75

MHz, $CDCl_3$) δ 24.24 (C-12), 28.08 (C-6), 46.55 (C-12a), 77.33 (C-5a), 114.83 (C-10), 115.82 (C-6a), 118.00 (C-4), 118.52 (C-7), 120.32 (C-13a), 121.34 (C-2), 122.43 (C-8), 123.54 (C-9), 127.33 (C-1), 128.80 (C-3',5'), 129.31 (C-11a), 129.40 (C-2',6'), 130.80 (C-6a), 133.38 (C-4'), 135.35 (C-1'), 136.04 (C-3), 136.95 (C-10a).

(5a*R*,12a*S* or 5a*S*,12a*R*)-7-Benzoyl-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (7a) and (5a*S*,12a*R* or 5a*R*,12a*S*)-11-benzoyl-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (8a) in a 2:1 ratio**.** 0.102 g, 26% Yield, white solid, mp 254–258 °C (CH_2Cl_2–pet. ether); IR (KBr) ν_{max}: 1687, 1606, 1457, 1300 cm^{-1}. EIMS m/z (%) 393 (60, $M^{+\cdot}$), 374 (8), 288 (10), 270 (15), 246 (8), 167 (15), 105 (100), 77 (35). Anal. calcd for $C_{26}H_{19}NO_3$ (393.43): C, 79.37; H, 4.87; N, 3.56. Found: C, 79.52; H, 4.72; N. 3.67%.

Major isomer 7a. ^{1}H NMR δ 2.98–3.03 (m, 2H, 12-H), 3.04–3.09 (m, 1 H, 12a-H), 3.33–3.38 (m, 2H, 6-H), 5.00–5.05 (m, 1H, 5a-H), 6.87 (dd, J = 8.4, 1.0 Hz, 1H, 8-H), 6.96 (dd, J = 8.4, 1.0 Hz, 1H, 4-H), 7.00–7.08 (m, 2H, 2,9-H), 7.17 (ddd, J = 7.9, 7.2, 1.0 Hz, 1H, 10-H), 7.48 (ddd, J = 8.4, 7.1, 1.8 Hz, 1H, 3-H), 7.49–7.55 (m, 3H, 11,3',5'-H), 7.646 (tt, J = 7.5, 1.4 Hz, 1H, 4'-H), 7.71–7.76 (m, 2H, 2',6'-H), 7.951 (dd, J = 7.9, 1.8 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.27 (C-12), 30.00 (C-6), 44.26 (C-12a), 75.10 (C-5a), 114.70 (C-8), 115.90 (C-11b), 117.91 (C-13a), 118.00, 118.10 (C-4, C-11), 121.72 (C-2), 122.90 (C-10), 123.55 (C-9), 127.58 (C-1), 128.78 (C-3',5'), 129.14 (C-11a), 129.45 (C-2',6'), 131.89 (C-6a), 132.73 (C-4'), 135.41 (C-1'), 136.17 (C-3), 136.58 (C-7a), 160.86 (C-4a), 169.15 (7-CO), 194.62 (C-13).

Some NMR data for the **minor isomer 8a** were also deduced: ^{1}H NMR δ 5.07–5.12 (m, 1H, 5a-H), 7.18 (ddd, J = 7.9, 7.2, 1.0 Hz, 1H, 8-H), 7.68–7.72 (m, 2H, 2',6'-H), 7.897 (dd, J = 7.9, 1.8 Hz, 1H, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.70 (C-12), 25.64 (C-6), 45.38 (C-12a), 74.93 (C-5a), 114.72 (C-10), 115.85 (C-6a), 118.03 (C-7), 119.33 (C-4), 119.60 (C-13a), 121.60 (C-2), 122.78 (C-8), 123.59 (C-9), 127.59 (C-1), 128.88 (C-3',5'), 129.16 (C-6b), 129.45 (C-2',6'), 131.52 (C-11a), 132.85 (C-4'), 135.31 (C-1'), 136.17 (C-3), 136.74 (C-10a), 160.64 (C-4a), 169.06 (7-CO), 193.67 (C-13).

From compound 3b

(5a*R*,12a*S* or 5a*S*,12a*R*)-7-Benzoyl-2-methyl-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (7b) and (5a*S*,12a*R* or 5a*R*,12a*S*)-11-benzoyl-2-methyl-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (8b) in a 2:1 ratio**.** 0.179 g, 44% Yield, white solid, mp 154–158 °C (CH_2Cl_2–pet. ether); IR (KBr) ν_{max}: 1684, 1644 cm^{-1}. The ^{1}H NMR of the mixture consists of overlapping multiplets. Only the protons H_{5a} of both compounds are well discriminated, giving multiplets at 4.97–5.01 and 5.04–5.10 ppm, and allowing the measurement of the mixture composition.

Major isomer 7b. ^{1}H NMR δ 2.326 (s, 3H, 2-CH_3), 2.94–3.30 (m, 3H, 12-H, 12a-H), 3.32–3.37 (m, 2H, 6-H), 4.97–5.01 (m, 1H, 5a-H), 6.857 (d, J = 8.5 Hz, 1H, 4-H), 6.881 (dd, J = 8.3, 1.1 Hz, 1H, 8-H), 7.031 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H, 9-H), 7.167 (ddd, J = 7.7, 7.3, 1.0 Hz, 1H, 10-H), 7.388 (dd, J = 8.5, 1.3 Hz, 1H, 3-H), 7.40–7.44 (m, 1H, 11-H),7.50–7.55 (m, 2H, 3',5'-H), 7.61–7.69 (m, 1H, 4'-H), 7.67–7.73 (m, 2H, 2',6'-H), 7.750 (d, J = 1.3 Hz, 1H, 1-H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 19.36 (C-12), 20.48 (2-CH_3), 30.09 (C-6), 44.28 (C-12a), 75.32 (C-5a), 114.70 (C-8), 115.99 (C-11b), 117.77 (C-4), 118.10 (C-11), 118.87 (C-13a), 122.91 (C-10), 123.55 (C-9), 127.15 (C-1), 128.84 (C-3',5'), 129.18 (C-11a), 129.47 (C-2',6'), 131.22 (C-2), 131.98 (C-6a), 132.75 (C-4'), 135.42 (C-1'), 136.73 (C-7a), 137.31 (C-3), 158.94 (C-4a), 169.18 (7-CO), 195.02 (C-13). EIMS m/z (%) 407 (1, $M^{+\cdot}$), 389 (2), 284 (10), 268 (7), 254 (5), 217 (15), 167 (8), 143 (8), 127 (10), 115 (10), 105 (55), 77 (100). Anal. calcd for $C_{27}H_{21}NO_3$ (407.46): C, 79.59; H, 5.19; N, 3.44. Found: C, 79.72; H, 4.99; N. 3.57%.

Some NMR data for the **minor isomer 8b** were also deduced: ^{1}H NMR δ 2.315 (s, 3H, 2-CH_3), 5.04–5.10 (m, 1H, 5a-H), 6.892 (d, J = 8.6 Hz, 1H, 4-H), 7.031 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H, 9-H), 7.185 (ddd, J = 7.7, 7.3, 1.0 Hz, 1H, 10-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.78 (C-12), 25.45 (2-CH_3), 29.74 (C-6), 45.33 (C-12a), 74.84 (C-5a), 114.50 (C-10), 116.13 (C-6a), 117.63 (C-4), 117.91 (C-7), 118.32 (C-13a), 122.79 (C-8), 123.58 (C-9), 127.08 (C-1), 128.81 (C-3',5'), 129.24 (C-6b), 129.47 (C-2',6'), 131.12 (C-2), 132.48 (C-11a), 132.78 (C-4'), 135.32 (C-1'), 136.35 (C-10a), 137.31 (C-3), 158.73 (C-4a), 168.96 (11-CO), 194.04 (C-13).

From compound 3c

(5a*R*,12a*R* or 5a*S*,12a*S*)-7-Benzoyl-2-chloro-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (5c) and (5a*R*,12a*R* or 5a*S*,12a*S*)-11-benzoyl-2-chloro-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (6c) in a 3.5:1 ratio**.** 0.124 g, 29% Yield. White solid (CH_2Cl_2–Et_2O), mp 270–274 °C; IR (KBr) ν_{max}: 1690, 1679, 1602, 1471, 1353 cm^{-1}. EIMS m/z (%) 427/429 (4, $M^{+\cdot}$), 323/325 (10), 304/306 (18), 168 (23), 167 (66), 166 (33), 164 (11), 139 (22), 130 (15), 115 (12), 105 (75), 77 (100). Anal. calcd for $C_{26}H_{18}ClNO_3$ (427.88): C, 72.78; H, 4.24; N, 3.27. Found: C, 72.69; H, 4.42; N. 3.23%.

Major isomer 5c. ^{1}H NMR δ 2.819 (dddd, J = 17.2, 10.8, 3.2, 1.7 Hz, 1H, 12-H_{ax}), 3.098 (ddd, J = 13.4, 10.8, 6.1 Hz, 1H, 12a-H_{ax}), 3.326 (dddd, J = 17.0, 9.5, 3.2, 1.7 Hz, 1H, 6-H_{ax}), 3.45–3.55 (m, 2H, 6-H_{eq}, 12-H_{eq}), 4.623 (ddd, J = 13.4, 9.6, 6.2 Hz, 1H, 5a-H_{ax}), 6.962 (ddd, J = 8.3, 1.2, 0.5 Hz, 1H, 8-H), 6.980 (d, J = 8.9 Hz. 1H, 4-H), 7.085 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H, 9-H), 7.226 (ddd, J = 8.3, 7.3, 1.0 Hz, 1H, 10-H), 7.448 (dd, J = 9.0, 2.6 Hz, 1H, 3-H), 7.505 (dd, J = 7.4, 1.1 Hz, 1H, 11-H), 7.49–7.57 (m, 2H, 3',5'-H), 7.64–7.70 (m, 1H, 4'-H), 7.72–7.76 (m, 2H, 2',6'-H), 7.915 (d, J = 2.6 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.79 (C-12), 31.95 (C-6), 45.49 (C-12a), 77.98 (C-5a), 114.74 (C-8), 115.70 (C-11b), 118.01 (C-13a), 118.39 (C-11), 119.69 (C-4), 123.11 (C-10), 123.86 (C-9), 126.56 (C-1), 127.28 (C-2), 128.84 (C-11a), 128.92 (C-3',5'), 129.51 (C-2',6'), 131.39 (C-6a), 132.92 (C-4'), 135.31 (C-1'), 136.02 (C-3), 137.01 (C-7a), 159.71 (C-4a), 169.03 (7-CO), 192.50 (C-13).

Some NMR data of the **minor isomer 6c** were also deduced: ^{1}H NMR δ 4.706 (ddd, J = 13.3, 9.6, 6.1 Hz, 1H, H-5a), 7.100 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H, 9-H), 7.867 (d, J = 2.6 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.16 (C-12), 27.97 (C-6), 46.38 (C-12a), 77.47 (C-5a), 114.82 (C-10), 118.00 (C-7), 119.59 (C-4), 122.94 (C-8), 126.63 (C-1), 128.92 (C-3',5'), 129.51 (C-2',6'), 128.78 (C-11a), 132.96 (C-4'), 135.96 (C-3), 159.60 (C-4a), 169.00 (7-CO), 192.50 (C-13).

(5a*R*,12a*S* or 5a*S*,12a*R*)-7-Benzoyl-2-chloro-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (7c) and (5a*S*,12a*R* or 5a*R*,12a*S*)-11-benzoyl-2-chloro-6,11,12,12a-

tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (8c) in a 4:1 ratio**.** 0.145 g, 34% Yield, white solid, mp 200–204 °C (CH_2Cl_2–pet. ether); IR (KBr) ν_{max}: 1688, 1603 cm^{-1}. EIMS m/z (%) 427/429 (10, $M^{+\cdot}$), 411/413 (10), 322 (5), 304 (3), 271 (3), 263 (10), 246 (5), 220 (10), 209 (8), 167 (8), 105 (100), 77 (80). Anal. calcd for $C_{26}H_{18}ClNO_3$ (427.88): C, 72.98; H, 4.24; N, 3.27. Found: C, 73.09; H, 4.35; N. 3.15%.

Major isomer 7c. ^{1}H NMR δ 2.94–3.02 (m, 2H, 12-H), 3.05–3.12 (m, 1H, 12a-H), 3.34–3.39 (m, 2H, 6-H), 5.014 (ddd, J = 4.1, 4.0, 2.4 Hz, 1H, 5a-H_{eq}), 6.850 (ddd, J = 8.3, 1.2, 0.6 Hz, 1H, 8-H), 6.917 (d, J = 8.9 Hz, 1H, 4-H), 7.031 (ddd, J = 8.3, 7.2, 1.0 Hz, 1H, 9-H), 7.170 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H, 10-H), 7.387 (ddd, J = 7.8, 1.0, 0.6 Hz, 1H, 11-H), 7.415 (dd, J = 8.9, 2.7 Hz, 1H, 3-H), 7.48–7.55 (m, 2H, 3',5'-H), 7.648 (tt, J = 7.5, 2.0 Hz, 1H, 4'-H), 7.71–7.75 (m, 2H, 2',6'-H), 7.900 (d, J = 2.7 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.19 (C-12), 29.83 (C-6), 44.02 (C-12a), 75.70 (C-5a), 114.69 (C-8), 115.68 (C-11b), 117.91 (C-13a), 118.13 (C-11), 119.75 (C-4), 122.97 (C-10), 123.67 (C-9), 126.92 (C-1), 127.29 (C-2), 128.87 (C-3',5'), 129.06 (C-11a), 129.47 (C-2',6'), 131.73 (C-6a), 132.80 (C-4'), 135.38 (C-1'), 136.01 (C-3), 136.61 (C-7a), 159.30 (C-4a), 169.13 (7-CO), 193.38 (C-13).

Some NMR data for the **minor isomer 8c** were also deduced: ^{1}H NMR δ 3.13–3.23 (m, 1H, 12a-H), 5.090 (ddd, J = 4.1, 4.0, 2.4 Hz, 1H, 5a-H), 6.861 (ddd, J = 8.3, 1.2, 0.6 Hz, 1H, 10-H), 7.041 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H, 9-H), 7.181 (ddd, J = 7.8, 7.2, 1.2 Hz, 1H, 8-H), 7.437 (dd, J = 8.8, 2.8 Hz, 1H, 3-H), 7.848 (d, J = 2.8 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.61 (C-12), 25.26 (C-6), 45.05 (C-12a), 75.24 (C-5a), 113.29 (C-6a), 114.83 (C-10), 118.14 (C-7), 118.38 (C-13a), 119.79 (C-4), 122.84 (C-8), 123.70 (C-9), 126.83 (C-1), 127.17 (C-2), 128.83 (C-3',5'), 128.95 (C-6b), 129.47 (C-2',6'), 131.37 (C-11a), 132.84 (C-4'), 135.28 (C-1'), 136.01 (C-3), 136.77 (C-10a), 159.10 (C-4a), 169.03 (7-CO), 192.50 (C-13).

From compound 3d

(5a*R*,12a*R* or 5a*S*,12a*S*)-7-Benzoyl-2-chloro-3-methyl-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (5d) and (5a*R*,12a*R* or 5a*S*,12a*S*)-11-benzoyl-2-chloro-3-methyl-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (6d) in a 10:1 ratio**.** 0.102 g, 23% Yield. White solid (CH_2Cl_2–Et_2O), mp 243–245 °C; IR (KBr) ν_{max}: 1686, 1611, 1457, 1357 cm^{-1}. EIMS m/z (%) 441/443 (4, $M^{+\cdot}$), 390 (2), 337 (2), 318 (2), 247 (3), 207 (2), 167 (10), 140 (8), 127 (5), 105 (100), 77 (60). Anal. calcd for $C_{27}H_{20}ClNO_3$ (441.91): C, 73.38; H, 4.56; N, 3.17. Found: C, 73.51; H, 4.62; N. 3.02%.

Major isomer 5d. ^{1}H NMR δ 2.389 (s, 3H, CH_3), 2.796 (dddd, J = 17.2, 10.8, 3.3, 1.7 Hz, 1H, 12-H_{ax}), 3.058 (ddd, J = 13.3, 10.8, 6.1 Hz, 1H, 12a-H_{ax}), 3.300 (dddd, J = 17.0, 9.6, 3.3, 1.7 Hz, 1H, 6-H_{ax}), 3.456 (ddd, J = 17.0, 6.1, 1.7 Hz, 1H, 6-H_{eq}), 3.485 (ddd, J = 17.2, 6.1, 1.7 Hz, 1H, 12-H_{eq}), 4.584 (ddd, J = 13.3, 9.6, 6.1 Hz, 1H, 5a-H_{ax}), 6.908 (s, 1H, 4-H), 6.962 (dd, J = 8.4, 1.1 Hz, 1H, 8-H), 7.075 (ddd, J = 8.4, 7.1, 1.1 Hz, 1H, 9-H), 7.217 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H, 10-H), 7.498 (dd, J = 8.1, 1.1 Hz, 1H, 11-H), 7.50–7.56 (m, 2H, 3',5'-H), 7.668 (tt, J = 8.1, 1.7 Hz, 1H, 4'-H), 7.71–7.76 (m, 2H, 2',6'-H), 7.897 (s, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.80 (C-12), 20.87 (3-CH_3), 31.97 (C-6), 45.42 (C-12a), 77.93 (C-5a), 114.72 (C-8), 115.79 (C-11b),

117.98 (C-13a), 118.38 (C-11), 119.98 (C-4), 123.08 (C-10), 123.81 (C-9), 126.87 (C-1), 126.94 (C-2), 128.80 (C-11a), 128.90 (C-3',5'), 129.50 (C-2',6'), 131.45 (C-6a), 132.88 (C-4'), 135.32 (C-1'), 136.99 (C-7a), 145.27 (C-3), 159.53 (C-4a), 169.01 (7-CO), 192.32 (C-13).

Some NMR data of the **minor isomer 6d** were also deduced: ^{1}H NMR δ 2.40 (s, 3H, CH_3), 4.60–4.73 (m, 1H, H-5a), 6.94 (s, 1H, H-4), 7.85 (s, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.64 (C-12), 24.18 (CH_3-2), 31.60 (C-6), 46.30 (C-12a), 114.80 (C-10), 115.83 (C-6a), 122.92 (C-8), 128.90 (C-3',5'), 129.50 (C-2',6'), 133.02 (C-11a), 133.41 (C-4'), 135.29 (C-1'), 137.05 (C-10a), 145.18 (C-3), 159.42 (C-4a), 169.05 (11-CO), 191.52 (C-13).

(5a*R*,12a*S* or 5a*S*,12a*R*)-7-Benzoyl-2-chloro-3-methyl-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (7d) and (5a*S*,12a*R* or 5a*R*,12a*S*)-11-benzoyl-2-chloro-3-methyl-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (8d) in a 2.5:1 ratio**.** 0.141 g, 32% Yield, white solid, mp 180–185 °C (CH_2Cl_2–pet. ether); IR (KBr) ν_{max}: 1693, 1655, 1609, 1456, 1355 cm^{-1}. EIMS m/z (%) 441/443 (25, $M^{+\cdot}$), 422 (2), 336 (2), 318 (5), 281 (2), 207 (5), 167 (10), 140 (1), 105 (100), 77 (30). Anal. calcd for $C_{27}H_{20}ClNO_3$ (441.91): C, 73.38; H, 4.56; N, 3.17. Found: C, 73.22; H, 4.41; N. 3.31%.

Major isomer 7d. ^{1}H NMR δ 2.35 (s, 3H, CH_3), 2.97–3.10 (m, 2H, 12-H), 3.15–3.23 (m, 1H, 12a-H), 3.35–3.40 (m, 2H, 6-H), 4.98–5.02 (m, 1H, 5a-H), 6.85 (d, J = 0.4 Hz, 1H, 4-H), 6.854 (ddd, J = 8.4, 1.0, 0.5 Hz, 1H, 8-H), 7.031 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H, 9-H), 7.168 (ddd, J = 7.7, 7.3, 1.0 Hz, 1H, 10-H), 7.386 (ddd, J = 7.7, 1.3, 0.5 Hz, 1H, 11-H), 7.51–7.55 (m, 2H, 3',5'-H), 7.62–7.69 (m, 1H, 4'-H), 7.71–7.75 (m, 2H, 2',6'-H), 7.891 (d, J = 0.4 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.25 (C-12), 20.87 (3-CH_3), 29.88 (C-6), 44.01 (C-12a), 75.64 (C-5a), 114.69 (C-8), 115.74 (C-11b), 117.88 (C-13a), 118.11 (C-11), 120.07 (C-4), 122.95 (C-10), 123.62 (C-9), 127.24 (C-1), 127.97 (C-2), 128.83 (C-3',5'), 129.08 (C-11a), 129.13 (C-2',6'), 131.79 (C-6a), 132.75 (C-4'), 135.41 (C-1'), 136.59 (C-7a), 145.26 (C-3), 159.11 (C-4a), 169.11 (7-CO), 193.30 (C-13).

Some NMR data for the **minor isomer 8d** were also deduced: ^{1}H NMR δ 2.37 (s, 1H, CH_3), 5.05–5.10 (m, 1H, 5a-H), 6.88 (d, J = 0.45 Hz, 1H, 4-H), 7.05 (ddd, J = 8.4, 7.3, 1.3 Hz, 1H, 9-H), 7.18 (ddd, J = 7.7, 7.3, 1.0 Hz, 1H, 8-H), 7.84 (s, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.94 (C-12), 22.68 (3-CH_3), 25.27 (C-6), 45.04 (C-12a), 75.19 (C-5a), 113.35 (C-10), 114.70 (C-6a), 118.41 (C-7), 118.64 (C-13a), 120.12 (C-4), 122.81 (C-8), 123.67 (C-9), 127.15 (C-1), 127.84 (C-2), 128.80 (C-3',5'), 129.10 (C-6b), 129.15 (C-2',6'), 132.42 (C-11a), 132.80 (C-4'), 135.31 (C-1'), 136.78 (C-10a), 145.25 (C-3), 159.11 (C-4a), 169.11 (7-CO), 193.30 (C-13).

From compound 3e

(5a*R*,12a*R* or 5a*S*,12a*S*)-7-Benzoyl-2-nitro-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (5e) and (5a*R*,12a*R* or 5a*S*,12a*S*)-11-benzoyl-2-nitro-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (6e) in a 10:1 ratio**.** 0.118 g, 27% Yield, white solid, mp 236–242 °C (EtOH); IR (KBr) ν_{max}: 1698, 1681, 1615, 1519, 1343, 1278 cm^{-1}. EIMS m/z (%) 393 (4, $M^{+\cdot}$), 288 (40), 105 (45), 104 (62), 77 (100). Anal. calcd for $C_{26}H_{18}N_2O_5$ (438.43): C, 71.23; H, 4.14; N, 6.39. Found: C, 71.49; H, 4.02; N. 6.25%.

Major isomer 5e: ^{1}H NMR δ 2.885 (dddd, J = 17.2, 10.7, 3.0, 1.7 Hz, 1H, 12-H$_{ax}$), 3.159 (ddd, J = 13.3, 10.7, 6.1, Hz, 1H, 12a-H$_{ax}$), 3.405 (dddd, J = 17.1, 9.3, 3.0, 1.7 Hz, 1H, 6-H$_{ax}$), 3.524 (dddd, J = 17.2, 6.1, 1.7, 0.5 Hz, 1H, 12-H$_{eq}$), 3.609 (dddd, J = 17.1, 6.1, 1.7, 0.5 Hz, 1H, 6-H$_{eq}$), 4.751 (ddd, J = 13.3, 9.3, 6.1 Hz, 1H, 5a-H$_{ax}$), 6.906 (ddd, J = 8.4, 1.1, 0.4 Hz, 1H, 8-H), 7.068 (ddd, J = 8.4, 7.3, 1.2 Hz, 1H, 9-H), 7.139 (dd, J = 9.1, 0.4 Hz, 1H, 4-H), 7.215 (ddd, J = 7.8, 7.3, 1.0 Hz, 1H, 10-H), 7.508 (ddd, J = 7.8, 1.2, 0.4 Hz, 1H, 11-H), 7.49–7.56 (m, 2H, 3',5'-H), 7.661 (tt, J = 7.5, 1.35 Hz, 1H, 4'-H), 7.71–7.75 (m, 2H, 2',6'-H), 8.344 (dd, J = 9.1, 2.85 Hz, 1H, 3-H), 8.835 (dd, J = 2.85, 0.4 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.76 (C-12), 31.96 (C-6), 45.73 (C-12a), 78.90 (C-5a), 114.83 (C-8), 115.63 (C-11b), 118.49 (C-11), 119.31 (C-4), 120.46 (C-13a), 123.23 (C-10), 123.88 (C-9), 124.05 (C-1), 128.86 (C-11a), 128.99 (C-3',5'), 129.57 (C-2',6'), 130.46 (C-3), 131.20 (C-6a), 132.96 (C-4'), 135.52 (C-1'), 137.28 (C-7a), 142.77 (C-2), 165.09 (C-4a), 169.01 (7-CO), 191.38 (C-13).

Some NMR data of the **minor isomer 6e** were also deduced: ^{1}H NMR δ 7.03 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H, 9-H), 7.166 (dd, J = 9.1, 0.38 Hz, 1H, 4-H), 8.351 (dd, J = 9.1, 2.85 Hz, 1H, 3-H), 8.793 (dd, J = 2.85, 0.38 Hz, 1H, 1-H),. ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.09 (C-12), 28.08 (C-6), 46.54 (C-12a), 78.58 (C-5a), 114.92 (C-10), 116.20 (C-6a), 118.04 (C-7), 119.20 (C-4), 123.07 (C-8), 123.95 (C-9), 124.05 (C-1), 128.99 (C-3',5'), 129.57 (C-2',6'), 130.30 (C-3), 133.00 (C-4'), 142.30 (C-2), 168.5 (7-CO).

(5a*R*,12a*S* or 5a*S*,12a*R*)-7-Benzoyl-5-nitro-6,7,12,12a-tetrahydrochromeno[2,3-*b*]carbazol-13(5a*H*)-one (7e) and (5a*S*,12a*R* or 5a*R*,12a*S*)-11-benzoyl-5-nitro-6,11,12,12a-tetrahydrochromeno[3,2-*b*]carbazol-13(5a*H*)-one (8e) in a 3:1 ratio**.** 0.259 g, 59% Yield, white solid, mp 227–232 ^{o}C (EtOH); IR (KBr) ν_{max}: 1705, 1683, 1614, 1585, 1515, 1338, 1273 cm^{-1}. EIMS m/z (%) 393 (4, $M^{+\cdot}$), 288 (40), 105 (45), 104 (62), 77 (100). Anal. calcd for $C_{26}H_{18}N_2O_5$ (438.43): C, 71.23; H, 4.14; N, 6.39. Found: C, 71.39; H, 4.22; N. 6.47%.

Major isomer 7e. mp 234–236 ^{o}C (EtOH); ^{1}H NMR δ 3.010 (ddd, J = 9.4, 1.3, 0.5 Hz, 1H, 12-H$_{ax}$), 3.040 (ddd, J = 6.7, 1.3, 0.5 Hz, 1H, 12-H$_{eq}$), 3.222 (ddd, J = 9.4, 6.7, 2.7 Hz, 1H, 12a-H$_{ax}$), 3.443 (ddd, J = 4.2, 1.3, 0.5 Hz, 1H, 6-H$_{ax}$), 3.451 (ddd, J = 4.5, 1.3, 0.5 Hz, 1H, 6-H$_{eq}$), 5.168 (ddd, J = 4.5, 4.2, 2.7 Hz, 1H, 5a-H$_{eq}$), 6.812 (ddd, J = 8.4, 1.0, 0.6 Hz, 1H, 8-H), 7.042 (ddd, J = 8.4, 7.2, 1.1 Hz, 1H, 9-H), 7.103 (d, J = 9.1, 1H, 4-H), 7.183 (ddd, J = 7.9, 7.2, 1.0 Hz, 1H, 10-H), 7.402 (ddd, J = 7.9, 1.1, 0.6 Hz, 1H, 11-H), 7.529 (ddd, J = 8.2, 7.4, 1.5 Hz, 2H, 3',5'-H), 7.663 (tt, J = 7.4, 1.5 Hz, 1H, 4'-H), 7.741 (ddd, J = 8.2, 2.0, 1.3 Hz, 2H, 2',6'-H), 8.345 (dd, J = 9.1, 2.8 Hz, 1H, 3-H), 8.848 (d, J = 2.8 Hz, 1H, 1-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.05 (C-12), 29.58 (C-6), 43.96 (C-12a), 76.58 (C-5a), 114.75 (C-8), 115.32 (C-11b), 118.18 (C-11), 118.44 (C-13a), 119.18 (C-11a), 119.38 (C-4), 123.08 (C-9), 123.86 (C-10), 124.20 (C-1), 128.92 (C-3',5'), 129.51 (C-2',6'), 130.50 (C-3), 131.33 (C-6a), 132.92 (C-4'), 135.30 (C-1'), 136.67 (C-7a), 142.58 (C-2), 164.72 (C-4a), 169.12 (7-CO), 192.19 (C-13).

General procedure for the Diels–Alder reactions of 3-formylchromones (3a–3e) with pyrazole o-quinodimethane 10

To a stirred solution of the chromone **3** (5.0 mmol) in dry toluene (25 mL), 18-crown-6 ether was added (0.581 g, 2.2 mmol) followed by the addition of 1-benzoyl-3-phenyl-4,5-

bis(bromomethyl)pyrazole (**9**) (0.434 g, 1.0 mmol) and finally sodium iodide (0.33 g, 2.2 mmol) and the reaction mixture was stirred at reflux under nitrogen for 10 h. The solvent was distilled off and from the resulting residue the excess of chromone was removed, as described previously. The residue was finally purified by column chromatography on silica gel using petroleum ether/EtOAc (7:1) as eluent, to give in order of elution the chromenoindazole **13**, the *trans* tetrahydrochromenoindazole **11** followed by the *cis* isomer **12**.

From compound 3a

1-Benzoyl-3-phenylchromeno[3,2-*f*]indazol-5(1*H*)-one (14a). 0.146 g, 35% Yield. White solid (CH_2Cl_2–Et_2O), mp 232–234 °C; IR (KBr) ν_{max}: 1691, 1654, 1623, 1469, 1339 cm^{-1}. ^1H NMR δ 7.442 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H, 7-H), 7.53–7.63 (m, 6H, 3',4',5',3",4",5"-H), 7.639 (dd, J = 8.4, 1.1 Hz, 1H, 9-H), 7.805 (ddd, J = 8.4, 7.1, 1.7 Hz, 1H, 8-H), 8.06–8.10 (m, 2H, 2",6"-H), 8.22–8.26 (m, 2H, 2',6'-H), 8.407 (ddd, J = 8.0, 1.7, 0.4 Hz, 1H, 6-H), 8.790 (d, J = 0.6 Hz, 1H, 4-H), 9.099 (d, J = 0.6 Hz, 1H, 11-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.44 (C-11), 118.13 (C-9), 120.18 (C-3a), 121.23 (C-4a), 121.39 (C-7), 121.90 (C-5a), 124.21 (C-4), 127.00 (C-6), 128.10 (C-3",5"), 128.37 (C-3',5'), 129.22 (C-2",6"), 130.22 (C-4"), 130.92 (C-1"), 131.49 (C-2',6'), 132.65 (C-4'), 132.88 (C-1'), 135.42 (C-8), 144.22 (C-11a), 151.30 (C-3), 156.59 (C-10a), 156.69 (C-9a), 168.22 (1-CO), 177.42 (C-5). EIMS m/z (%) 416 (40, $M^{+\cdot}$), 388 (2), 339 (2), 311 (5), 283 (8), 255 (4), 226 (12), 200 (3), 105 (100), 77 (30). Anal. calcd for $C_{27}H_{16}N_2O_3$ (416.43): C, 77.87; H, 3.87; N, 6.73. Found: C, 77.69; H, 4.01; N. 6.85%.

(4a*S*,10a*R* or 4a*R*,10a*S*)-1-Benzoyl-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (12a). 0.084 g, 20% Yield. White solid (CH_2Cl_2–Et_2O), mp 234–236 °C; IR (KBr) ν_{max}: 1682, 1661, 1620 cm^{-1}. ^1H NMR δ 2.95–3.06 (m, 2H, 4-H), 3.30–3.40 (m, 1H, 4a-H), 3.73 (dm, J = 18.2 Hz, 1H, 11-H_{ax}), 4.768 (dm, J = 18.2 Hz, 1H, 11-H_{eq}), 5.22–5.23 (m, 1H, 10a-H), 7.39–7.51 (m, 6H, 9,3', 5',3",4",5"-H), 7.51–7.66 (m, 2H, 6,4'), 7.784 (ddd, J = 8.4, 7.2, 1.7 Hz, 1H, 7-H), 7.78–7.83 (m, 1H, 8-H), 7.87–7.90 (m, 2H, 2",6"-H), 8.13–8.16 (m, 2H, 2',6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.90 (C-4), 31.55 (C-11), 45.82 (C-4a), 65.88 (C-10a), 116.84 (C-9), 119.61 (C-5a), 119.78 (C-3a), 120.08 (C-7), 126.92 (C-6), 127.48 (C-2",6"), 127.97 (C-3',5'), 128.33 (C-3",5"), 128.81 (C-4"), 131.48 (C-1"), 131.75 (C-2',6'), 131.96 (C-1'), 132.79 (C-4'), 140.25 (C-11a), 140.25 (C-8), 152.16 (C-3), 159.53 (C-9a), 168.00 (1-CO), 191.88 (C-5). EIMS m/z (%) 420 (22, $M^{+\cdot}$), 402 (5), 388 (2), 339 (5), 315 (18), 297 (14), 281 (4), 207 (12), 195 (10), 165 (9), 121 (4), 105 (100), 77 (50). Anal. calcd for $C_{27}H_{20}N_2O_3$ (420.46): C, 77.13; H, 4.79; N, 6.66. Found: C, 77.39; H, 4.91; N. 6.80%.

From compound 3b

(4a*R*,10a*R* or 4a*S*,10a*S*)-1-Benzoyl-7-methyl-3-phenyl-4,4a,10a,11-tetrahydro chromeno[3,2-*f*]indazol-5(1*H*)-one (11b). 0.126 g, 29% Yield. White solid (CH_2Cl_2–Et_2O), mp 240–242 °C; IR (KBr) ν_{max}: 1680, 1620, 1606 cm^{-1}. ^1H NMR δ 2.370 (s, 3H, 7-CH_3), 2.870 (dddd, J = 17.7, 10.9, 3.3, 1.1 Hz, 1H, 4-H_{ax}), 3.028 (ddd, J = 13.1, 10.9, 6.5 Hz, 1H, 4a-H), 3.46–3.52 (m, 1H, 11-H_{ax}), 3.52–3.56 (m, 1H, 4-H_{eq}), 4.090 (ddd, J = 17.7, 6.1, 1.7 Hz, 1H, 11-H_{eq}), 4.694

(ddd, *J* = 13.1, 9.4, 6.1 Hz, 1H, 10a-H), 6.981 (d, *J* = 8.5 Hz, 1H, 9-H), 7.359 (dd, *J* = 8.5, 2.7 Hz, 1H, 8-H), 7.40–7.49 (m, 3H, 3",4",5"-H), 7.50–7.54 (m, 2H, 3',5'-H), 7.615 (tt, *J* = 7.5, 1.4 Hz, 1H, 4'-H), 7.753 (dd, *J* = 2.2, 0.5 Hz, 1H, 6-H), 7.78–7.82 (m, 2H, 2",6"-H), 8.13–8.17 (m, 2H, 2',6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.36 (C-4), 20.49 (7-CH_3), 31.62 (C-11), 44.94 (C-4a), 78.10 (C-10a), 116.70 (C-3a), 117.86 (C-9), 119.82 (C-5a), 127.21 (C-6), 127.50 (C-2",6"), 127.95 (C-3',5'), 128.69 (C-3",5"), 129.01 (C-4"), 131.36 (C-7), 131.50 (C-1"), 131.71 (C-2',6'), 132.73 (C-4'), 132.80 (C-1'), 137.40 (C-8), 140.46 (C-11a), 152.15 (C-3), 159.35 (C-9a), 168.20 (1-CO), 192.02 (C-5). EIMS m/z (%) 430 (25, $M^{+\cdot} - 2H_2$),[23] 325 (2), 297 (5), 281 (3), 239 (6), 207 (5), 105 (100), 77 (35). Anal. calcd for $C_{28}H_{22}N_2O_3$ (434.49): C, 77.40; H, 5.10; N, 6.45. Found: C, 77.27; H, 5.12; N. 6.42%.

(4a*S*,10a*R* or 4a*R*,10a*S*)-1-Benzoyl-7-methyl-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (12b). 0.056 g, 13% Yield. White solid (CH_2Cl_2–Et_2O), mp 236–238 °C; IR (KBr) ν_{max}: 1684, 1644, 1605, 1477, 1457, 1359 cm^{-1}. ^{1}H NMR δ 2.342 (s, 3H, CH_3), 2.93–3.02 (m, 2H, 4-H), 3.03–3.05 (m, 1H, 4a-H), 3.590 (dd, *J* = 19.3, 5.2 Hz, 1H, 11-H), 3.837 (dd, *J* = 19.3, 2.5 Hz, 1H, 11-H), 5.060 (ddd, *J* = 5.2, 2.8, 2.5 Hz,1H, 10a-H), 6.930 (d, *J* = 8.5 Hz, 1H, 9-H), 7.344 (dd, *J* = 8.3, 2.0 Hz, 1H, 8-H), 7.35–7.40 (m, 2H, 3",5"-H), 7.43–7.48 (m, 1H, 4"-H), 7.48–7.54 (m, 2H, 3',5'-H), 7.612 (tt, *J* = 7.4, 1.4 Hz,1H, 4'-H), 7.68–7.71 (m, 2H, 2",6"-H), 7.750 (d, *J* = 2.0 Hz, 1H, 6-H), 8.13–8.17 (m, 2H, 2',6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.50 (C-4), 20.75 (CH_3), 29.73 (C-11), 46.07 (C-4a), 75.86 (C-10a), 116.85 (C-3a), 117.87 (C-9), 121.02 (C-5a), 127.21 (C-6), 127.52 (C-2",6"), 127.95 (C-3',5'), 128.08 (C-1"), 128.80 (C-3",5"), 129.02 (C-4"), 131.45 (C-7), 131.71 (C-2',6'), 132.61 (C-4'), 132.75 (C-1'), 137.47 (C-8), 140.42 (C-11a), 152.13 (C-3), 159.40 (C-9a), 171.80 (1-CO), 193.20 (C-5). EIMS m/z (%) 434 (25, $M^{+\cdot}$), 329 (60), 311 (30), 239 (5), 195 (7), 165 (12), 135 (10), 105 (100), 77 (40). Anal. calcd for $C_{28}H_{22}N_2O_3$ (434.49): C, 77.40; H, 5.10; N, 6.45. Found: C, 77.27; H, 5.12; N. 6.42.

From compound 3c

(4a*R*,10a*R* or 4a*S*,10a*S*)-1-Benzoyl-7-chloro-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (11c). 0.091 g, 20% Yield. White solid (CH_2Cl_2–Et_2O), mp 226–228 °C. IR (KBr) ν_{max}: 1681, 1636, 1465 cm^{-1}. ^{1}H NMR δ 2.871 (dddd, *J* = 16.4, 10.5, 2.5, 1.6 Hz, 1H, 4-H_{ax}), 3.034 (ddd, *J* = 13.3, 11.0, 5.4 Hz, 1H, 4a-H_{ax}), 3.48–3.56 (m, 2H, 4-H_{eq},11-H_{ax}), 4.098 (ddd, *J* = 17.7, 6.4, 1.6 Hz, 1H, 11-H_{eq}), 4.714 (ddd, *J* = 13.3, 9.7, 6.4 Hz, 1H, 10a-H_{ax}), 7.042 (d, *J* = 9.1 Hz, 1H, 9-H), 7.40–7.65 (m, 6H, 8,3',5',3",4",5"-H), 7.75–7.83 (m, 2H, 2",6"-H), 7.914 (d, *J* = 2.9 Hz, 1H, 6-H), 8.03–8.12 (m, 1H, 4'-H), 8.13–8.20 (m, 2H, 2',6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.66 (C-4), 31.54 (C-11), 45.90 (C-4a), 77.33 (C-10a), 116.74 (C-3a), 119.79 (C-9), 121.20 (C-5a), 126.61 (C-6), 127.50 (C-2",6"), 127.99 (C-3',5'), 128.20 (C-7), 128.84 (C-3",5"), 129.10 (C-4"), 131.50 (C-1"), 131.75 (C-2',6'), 131.98 (C-1'), 132.81 (C-4'), 136.16 (C-8), 140.20 (C-11a), 152.17 (C-3), 159.72 (C-9a), 168.05 (1-CO), 192.06 (C-5). EIMS m/z (%) 454/456 (10, $M^{+\cdot}$), 349/351 (16), 105 (100). Anal. calcd for $C_{27}H_{19}ClN_2O_3$ (454.90): C, 71.29; H, 4.21; N, 6.16. Found: C, 71.51; H, 4.35; N, 6.19%.

(4a*S*,10a*R* or 4a*R*,10a*S*)-1-Benzoyl-7-chloro-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (12c). 0.141 g, 31% Yield. White solid (CH_2Cl_2–Et_2O), mp 202–204 °C; IR (KBr) ν_{max}: 1684, 1632 cm^{-1}. ^1H NMR δ 2.95–3.06 (m, 3H, 4,4a-H), 3.603 (ddd, J = 19.2, 4.8, 0.8 Hz, 1H, 11-H_{ax}), 3.842 (ddd, J = 19.2, 1.4, 1.0 Hz, 1H, 11-H_{eq}), 5.081 (ddd, J = 4.8, 3.5, 1.4 Hz, 1H, 10a-H), 6.993 (d, J = 8.9 Hz, 1H, 9-H), 7.37–7.53 (m, 1H, 9-H), 7.38–7.42 (m, 3H, 3",4",5"-H), 7.465 (dd, J = 8.9, 2.4 Hz, 1H, 8-H), 7.48–7.53 (m, 2H, 3',5'-H), 7.611 (tt, J = 7.5, 1.3 Hz, 1H, 4'-H), 7.65–7.71 (m, 2H, 2",6"-H), 7.912 (d, J = 2.4 Hz, 1H, 6-H), 8.13–8.16 (m, 2H, 2',6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.20 (C-4), 31.01 (C-11), 44.63 (C-4a), 75.06 (C-10a), 116.61 (C-3a), 119.84 (C-9), 120.18 (C-5a), 126.99 (C-6), 127.52 (C-2",6"), 127.67 (C-7), 127.98 (C-3',5'), 128.74 (C-3",5"), 129.04 (C-4"), 131.67 (C-2',6'), 131.96 (C-1"), 132.54 (C-1'), 132.81 (C-4'), 136.22 (C-8), 140.00 (C-11a), 152.21 (C-3), 159.20 (C-9a), 168.08 (1-CO), 193.12 (C-5). EIMS m/z (%) 454/456 (5, $M^{+\cdot}$), 349/351 (8), 331/333 (3), 281 (4), 207 (8), 165 (5), 105 (100). Anal. calcd for $C_{27}H_{19}ClN_2O_3$ (454.90): C, 71.29; H, 4.21; N, 6.16. Found: C, 71.55; H, 4.10; N, 6.27.

From compound 3d

(4a*R*,10a*R* or 4a*S*,10a*S*)-1-Benzoyl-7-chloro-8-methyl-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (11d). 0.084 g, 18% Yield. White solid (CH_2Cl_2–Et_2O), mp 219–221 °C; IR (KBr) ν_{max}: 1688, 1661, 1622, 1466, 1335 cm^{-1}. ^1H NMR δ 2.418 (s, 3H, 8-CH_3), 2.865 (dddd, J = 16.3, 10.9, 2.8, 1.0 Hz, 1H, 4-H_{ax}), 3.009 (ddd, J = 13.3, 10.9, 5.1 Hz, 1H, 4a-H_{ax}), 3.510 (dddd, J = 17.5, 9.6, 2.8, 0.5 Hz, 1H, 11-H_{ax}), 3.514 (ddd, J = 16.3, 5.1, 0.5 Hz, 1H, 4-H_{eq}), 4.081 (ddd, J = 17.5, 6.3, 1.0 Hz, 1H, 11-H_{eq}), 4.688 (ddd, J = 13.3, 9.6, 6.3 Hz, 1H, 10a-H), 6.975 (d, J = 0.5 Hz, 1H, 9-H), 7.42-7.50 (m, 3H, 3",4",5"-H), 7.51–7.55 (m, 2H, 3',5'-H), 7.619 (tt, J = 7.6, 1.8 Hz, 1H, 4'-H), 7.77–7.82 (m, 2H, 2",6"-H), 7.902 (d, J = 0.5 Hz, 1H, 6-H), 8.13–8.17 (m, 2H, 2',6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.66 (C-4), 20.87 (8-CH_3), 31.53 (C-11), 45.79 (C-4a), 77.26 (C-10a), 116.81 (C-3a), 119.74 (C-5a), 120.04 (C-9), 126.87 (C-6), 127.44 (C-2",6"), 127.92 (C-3',5'), 128.07 (C-4"), 128.31 (C-7), 128.79 (C-3",5"), 129.03 (C-4"), 131.50 (C-1"), 131.70 (C-2',6'), 131.94 (C-1'), 132.93 (C-4"), 140.20 (C-11a), 145.41 (C-8), 152.12 (C-3), 159.49 (C-9a), 167.80 (1-CO), 191.84 (C-5). EIMS m/z (%) 464/466 (16, $M^{+\cdot}$-$2H_2$),[23] 359/361 (2), 331/333 (4), 302/304 (2), 281 (4), 266 (2), 239 (5), 207 (6), 105 (100). Anal. calcd for $C_{28}H_{21}ClN_2O_3$ (468.93): C, 71.72; H, 4.51; N, 5.97. Found: C, 71.89; H, 4.60; N, 6.12%.

(4a*S*,10a*R* or 4a*R*,10a*S*)-1-Benzoyl-7-chloro-8-methyl-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (12d). 0.141 g, 30% Yield. White solid (CH_2Cl_2–Et_2O), mp 217–219 °C; IR (KBr) ν_{max}: 1690, 1647, 1629, 1604, 1451, 1360 cm^{-1}. ^1H NMR δ 2.39 (s, 3H, 8-CH_3), 2.95-3.05 (m, 1 H, 4a-H), 2.90-3.10 (m, 3H, 4,4a-H), 3.59 (dd, J = 19.2, 4.4 Hz, 1H, 11-H_{ax}), 3.825 (dd, J = 19.2, 2.5 Hz, 1H, 11-H_{eq}), 5.02–5.10 (m, 1H, 10a-H), 6.919 (s, 1H, 9-H), 7.34–7.46 (m, 3H, 3",4',5"-H), 7.46–7.53 (m, 2H, 3',5'-H), 7.58–7.63 (m, 1H, 4"-H), 7.67–7.71 (m, 2H, 2",6"-H), 7.897 (s, 1H, 6-H), 8.13–8.17 (m, 2H, 2',6'-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.31 (C-4), 20.88 (8-CH_3), 30.06 (C-11), 44.64 (C-5a), 75.01 (C-10a), 116.71 (C-3a), 118.37

(C-5a), 120.15 (C-9), 127.32 (C-6), 127.50 (C-2",6"), 127.96 (C-3',5'), 128.27 (C-7), 128.73 (C-3",5"), 129.01 (C-4"), 131.74 (C-2',6'), 132.02 (C-1"), 132.60 (C-1'), 132.77 (C-4'), 140.08 (C-11a), 145.53 (C-8), 152.19 (C-3), 159.01 (C-9a), 168.06 (1-CO), 192.99 (C-5). EIMS m/z (%) 464/466 (12, $M^{+\cdot}$), 331 (4), 281 (6), 239 (10), 207 (8), 105 (100). Anal. calcd for $C_{28}H_{21}ClN_2O_3$ (468.93): C, 71.72; H, 4.51; N, 5.97. Found: C, 71.59; H, 4.67; N, 6.13%.

From compound 3e

(4a*R*,10a*R* or 4a*S*,10a*S*)-1-Benzoyl-7-nitro-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (11e). 10% Yield.[24] ^{1}H NMR δ 2.85–3.01 (m, 1H, 4-H_{ax}), 3.10–3.20 (m, 1H, 4a-H_{ax}), 3.75–3.85 (m, 1H, 11-H_{eq}), 3.77 (dd, J = 19.1, 4.8 Hz, 1H, 4-H), 4.176 (dd, J = 17.5, 6.3 Hz, 1H, 11-H_{eq}), 4.859 (ddd, J = 13.1, 9.6, 6.6 Hz, 1H, 10a-H), 7.224 (d, J = 9.1 Hz, 1H, 9-H), 7.40-7.65 (m, 6H, 3', 4',5',3",4",5"-H), 7.75–7.82 (m, 2H, 2",6"-H), 8.16–8.18 (m, 2H, 2',6'-H), 8.408 (dd, J = 9.1, 2.6 Hz, 1H, 6-H), 8.85 (d, J = 2.6 Hz, 1H, 6-H). No other experimental data are available due to transformation to **15** upon purification on prep. TLC.

1-Benzoyl-5-(2-hydroxy-5-nitrobenzoyl)-3-phenyl-1*H*-indazole (15). White solid (CH_2Cl_2–Et_2O), mp 232–235 ^{o}C; ^{1}H NMR δ 7.24 (d, J = 9.2 Hz, 1H, 11-H), 7.52–7.61 (m, 5H, 3',5',3",4",5"-H), 7.662 (tt, J = 7.6, 1.6 Hz, 1H, 4'-H), 7.95–7.99 (m, 2H, 2",6"-H), 8.032 (dd, J = 8.8, 1.85 Hz, 1H, 6-H), 8.21–8.26 (m, 2H, 2',6'-H), 8.436 (dd, J = 9.2, 2.8 Hz, 1H, 12-H), 8.450 (dd, J = 1.85, 0.7 Hz, 1H, 4-H), 8.706 (d, J = 2.8 Hz, 1H, 14-H), 8.846 (dd, J = 8.8, 0.7 Hz, 1H, 7-H), 12.6 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 116.89 (C-7), 118.10 (C-9), 119.83 (CH), 123.33, 123.95, 124.62, 129.52 (CH), 128.15 (C-3',5'), 128.32 (C-3",5"), 129.28 (C-2",6"), 130.05 (C-4"), 130.11 (CH), 130.90 (C-1"), 131.08 (C-12), 131.57 (C-2',6'), 132.84 (C-4'), 133.15 (C-1'), 136.05 (C-5), 139.63 (C-13), 143.70 (C-7a), 151.92 (C-3), 163.20 (C-10), 168.03 (1-CO), 199.43 (C-8). Anal. calcd for $C_{27}H_{17}N_3O_5$ (463.441): C, 69.97; H, 3.70; N, 9.07. Found: C, 70.31; H, 3.82; N, 8.92%.

(4a*S*,10a*R* or 4a*R*,10a*S*)-1-Benzoyl-7-nitro-3-phenyl-4,4a,10a,11-tetrahydrochromeno[3,2-*f*]indazol-5(1*H*)-one (12e). 0.098 g, 21% Yield. White solid (CH_2Cl_2–Et_2O), mp 228–230 ^{o}C; IR (KBr) ν_{max}: 1695, 1616, 1585, 1526, 1350, 1279 cm^{-1}. ^{1}H NMR δ 2.99–3.05 (m, 1H, 4-H_{ax}), 3.05–3.11 (m, 1H, 4-H_{eq}), 3.125 (td, J = 5.8, 2.5 Hz, 1H, 4a-H), 3.663 (dd, J = 19.3, 4.8 Hz, 1H, 11-H_{ax}), 3.87 (dd, J = 19.3, 2.8 Hz, 1H, 11-H_{eq}), 5.20 (ddd, J = 4.8, 2.8, 2.5 Hz,1H, 10a-H), 7.168 (d, J = 9.15 Hz, 1H, 9-H), 7.37–7.45 (m, 3H, 3",4",5"-H), 7.47–7.55 (m, 2H, 3',5'-H), 7.620 (tt, J = 7.4, 1.3 Hz, 1H, 4'-H), 7.67–7.71 (m, 2H, 2",6"-H), 8.13–8.18 (m, 2H, 2',6'-H), 8.375 (dd, J = 9.15, 2.85 Hz, 1H, 8-H), 8.846 (d, J = 2.85 Hz, 1H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.99 (C-4), 29.74 (C-11), 44.45 (C-4a), 75.84 (C-10a), 116.15 (C-3a), 119.48 (C-9), 124.21 (C-6), 127.45 (C-2",6"), 127.99 (C-3',5'), 128.48 (C-5a), 128.78 (C-3",5"), 129.12 (C-4"), 130.62 (C-8), 131.55 (C-1"), 131.73 (C-2',6'), 132.36 (C-1'), 132.90 (C-4'), 139.52 (C-11a), 142.62 (C-7), 152.16 (C-3), 164.56 (C-9a), 168.00 (1-CO), 191.92 (C-5). EIMS m/z (%) 461 (9, $M^{+\cdot} - 2H_2$),[23] 431 (27), 355 (5), 327 (6), 298 (7), 281 (25), 224 (5), 207 (55), 191 (7), 133 (5), 105 (100). Anal. calcd for $C_{27}H_{19}N_3O_5$ (465.46): C, 69.67; H, 4.11; N, 9.03. Found: C, 69.54; H, 4.23; N, 9.20%.

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