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New Potent Fluorescent Analogues of Strigolactones: Synthesis and Biological Activity in Parasitic Weed Germination and Fungal Branching

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In this work we report the synthesis of new fluorescent analogues of strigolactones, their spectroscopic properties and the evaluation of their biological activity both on seeds of *Orobanche aegyptiaca* and on the AM fungus *Gigaspora margarita*. The synthesis has been accomplished according to two different synthetic plans and allows the introduction of various substituents on the A and C rings of the framework, thus enabling access to bioactive molecules with different spectroscopic properties.

Introduction

Several hundreds of organic compounds released from plants, insects, animals and microbes are known to affect the growth, development and distribution of the receiving organism. Among them are signalling molecules, which play key roles in the intricate communication network within the soil. Very recently a new class of signalling molecules, the strigolactones (SLs), has garnered particular interest both by biologists and chemists.[1–5] SLs were originally isolated from plant root exudates as germination stimulants for root parasitic plants of the family Orobanchaceae, including witchweeds (*Striga* spp.), boomrapes (*Orobanche* and *Phelipanche* spp.) and *Alectra* spp. and so were regarded as detrimental to the producing plants.[6–8] Subsequently, their role as indispensable chemical signals for the establishment of arbuscular mycorrhizas (AM), the widespread symbiosis between most land plants and a small group of soil fungi, was unveiled.[9–13] In addition to these functions in the rizosphere, it has recently been shown that SLs represent a new class of plant hormones that inhibit shoot branching.[14–18] Extensive structure-activity relationship studies have been conducted both for natural and synthetic SLs analogues.[7,19–26] Very recently Akiyama demonstrated that the structural features needed to achieve biological activity in AM fungi are very similar but not identical to those observed in root parasitic weeds, especially with respect to the enol ether bridge linking the C and D rings.[9] The production of signalling molecules and the elicitation of responses in either partner represent the first steps in the cascade of events that lead to the biological effect. With respect to this, increasing evidence suggests that the induction of seed germination in parasitic weeds or hyphal branching in AM fungi proceeds through a receptor-mediated mechanism. Thus far very little is known about the protein structure or location of this hypothetical receptor.[27–30] Detailed knowledge of the receptor protein would provide insight into the mechanisms responsible for the biological effects. Moreover, such information would enable the design of perfectly fitting non-natural stimulants or inhibitors that may be used to control parasitic weeds or to develop new green and white biotechnologies exploiting AM fungi as biofertilizers in agriculture. In this sense labelled synthetic active SLs can be considered useful tools for the detection of the receptor in vivo or for protein identification experiments.

We recently reported the synthesis of a new class of SL analogues (PL series, Figure 1) featuring an unprecedented extended conjugated system and whose bioactiphore is an α,β-unsaturated ketone instead of the more common α,β-unsaturated lactone. All of these new molecules showed remarkable activity in *Orobanche aegyptiaca* seed germination tests.[31] Furthermore, some of these molecules showed interesting luminescent properties that prompted us to design and develop new fluorescent analogues whose spectroscopic properties could be exploited in bioimaging studies. In this work we report the synthesis of new fluorescent ana-

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logues of SLs, their spectroscopic properties and the evaluation of their biological activity both on seeds of *Orobanche aegyptiaca* and on the AM fungus *Gigaspora margarita*.

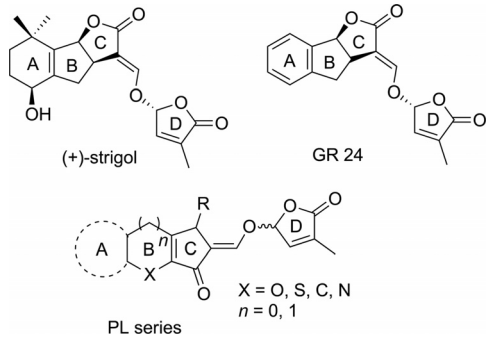
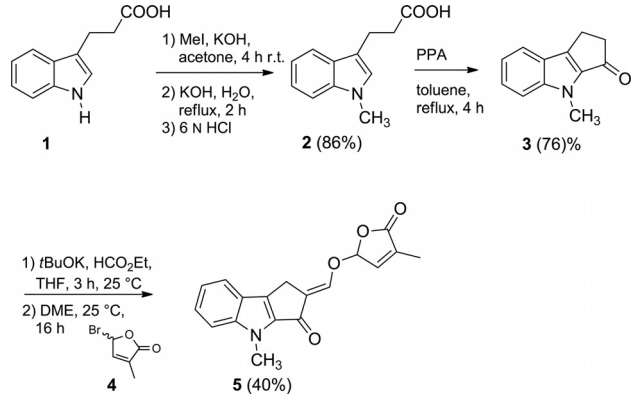


Figure 1. Natural strigol, synthetic GR 24 and synthetic PL series.

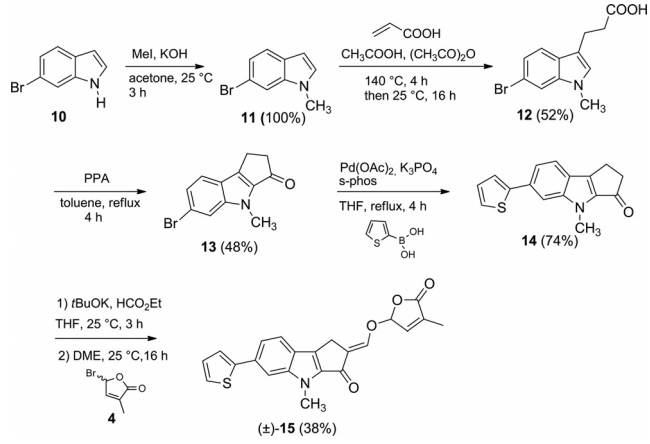
Results and Discussion

Synthesis

In our previous work,[31] nitrogen-derived SL analogues showed the most promising fluorescent properties associated with a remarkable biological activity. We then decided to focus our efforts on the synthesis of highly conjugated nitrogen derivatives with different patterns of substitution on the A ring in order to accurately tune the spectroscopic behavior while sparing the majority of biological activity thus allowing us to attain SL-like molecules for use as fluorescent probes. Towards this purpose, two main synthetic pathways were designed. The first, leading to the EGO series (Scheme 1, Schemes 2 and 3), was specifically designed for large scale synthesis applications; this approach required few steps, cheap reagents and feasible reaction conditions.[32] The EGO-derived molecules were obtained as racemates and the enantiomers separated by chiral High Performance Liquid Chromatography (HPLC). The second pathway, leading to the ST series (Scheme 4 and 5), was intended to be more versatile as it allows the introduction of substituents on the C ring. In this case, the molecules were obtained as diastereomeric mixtures and, at this stage, could be tested directly in biological assays.

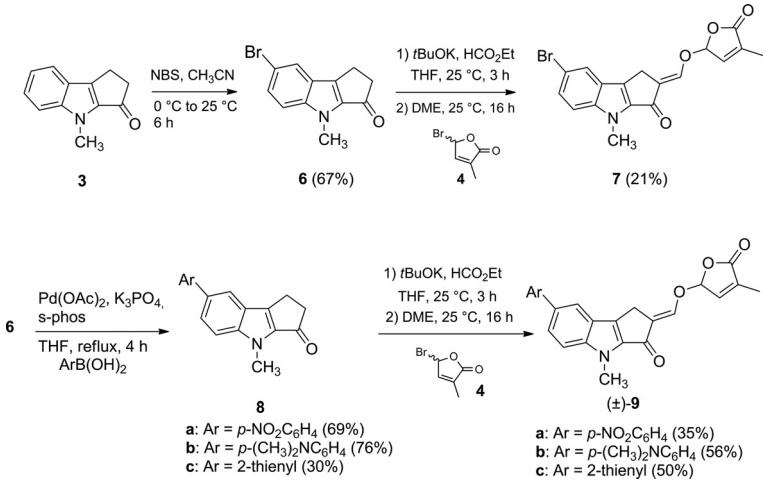


Scheme 1. Synthesis of unsubstituted EGO **5**.

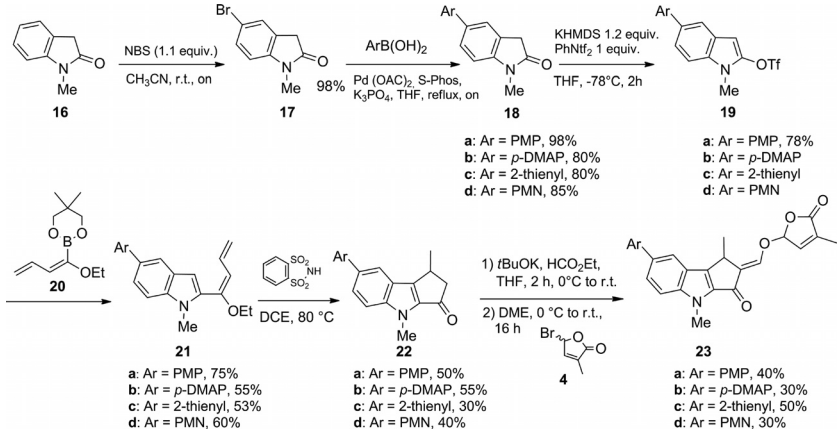


Scheme 3. Synthesis of 6-thienyl EGO molecule **15**.

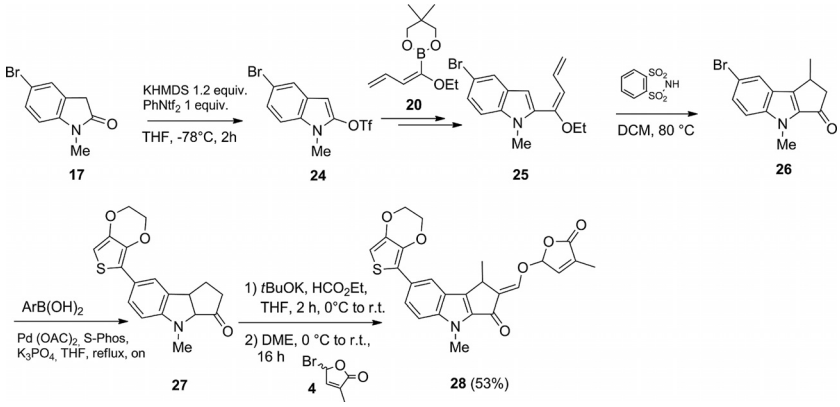
According to Scheme 1, the ABC nucleus of the molecules was easily obtained in two steps starting from commercially available 3-(indol-3-yl)propanoic acid **1**, after *N*-



Scheme 2. Synthesis of 7-functionalized EGO molecules **7**, **9a**–**c**.



Scheme 4. Synthesis of the ST derivatives.



Scheme 5. Synthesis of SL derivative **28**.

methylation (**2**, 86% yield) and subsequent cyclization with PPA (polyphosphoric acid) in refluxing toluene (**3**, 76% yield). Ultimately, the D ring was introduced using previously reported conditions.[31] The final molecule was thereby obtained in only three steps (**5**, 40%) as a racemate. The enantiomers were then easily separated by chiral HPLC (see Exp. Section) and their biological activities determined (vide infra).

In order to obtain EGO derivatives functionalized at the 7-position of the A ring, a slight modification of the proposed sequence was accomplished (Scheme 2). 4-Methyl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one **3** obtained according to Scheme 1 was reacted with NBS to selectively produce 7-bromo analogue **6** in 67% yield and then functionalized with bromobutenolide **4** to yield corresponding SL analogue **7**. Interestingly, intermediate **6** could also be used as a substrate for Suzuki–Miyaura cross-coupling reactions in order to introduce *p*-nitrophenyl, *p*-(dimethylamino)phenyl, or 2-thienyl substituents specifically at the 7-position of ring A. The corresponding boronic acids were properly chosen with the aim of introducing substituents with different electronic properties – electron-withdrawing for *p*-nitrophenyl and electron-donating for *p*-(dimethylamino)phenyl and thienyl – that might influence spectroscopic behavior. The last step, linkage of the D ring, was performed under the usual conditions and led to SL analogues **9a**–**c** in 35, 56 and 50% overall yields, respectively.

The presence of an unsaturated substituent in the 6-position of ring A would allow a more extended conjugate system which might have consequences on the luminescent behavior of these molecules. To this purpose we planned the synthetic path represented in Scheme 3. Commercially available 6-bromoindole **10** was *N*-protected as methyl derivative **11** and successively treated with acrylic acid at high temperature to give **12** (52%). Usual cyclization of the C ring with polyphosphoric acid gave **13** as a key intermediate. For the following step, a Suzuki–Miyaura cross coupling, 2-thienylboronic acid was chosen as the cross coupling partner due to the well documented luminescent properties of the thiophene moiety and its wide use in the synthesis of fluorescent probes.[33] Compound **14** was obtained in 74% yield and then coupled with bromobutenolide **4** as usual to obtain the final SL-like molecule **15** (38%) as the racemate.

The ST series of molecules was synthesized according to a more versatile synthetic plan which, in principle, allows the introduction of substituents on the C ring. In this case all SL analogues were isolated as diastereomeric mix-

tures. Commercially available 1-methylindolin-2-one **16** (Scheme 4) was selectively brominated with NBS to afford 5-bromo-1-methylindolin-2-one **17**. Compound **17** was then used as a coupling partner in a Suzuki–Miyaura reaction in order to functionalize the A ring of the final molecule with various substituents. Coupling partners *p*-methoxyphenyl- (PMP), *p*-(dimethylamino)phenyl- (*p*-DMAP), 2-thienyl-, 6-methoxy-2-naphthyl-boronic acids (PMN) were used, and corresponding coupling products **18a**–**d** were obtained in good yields. The corresponding triflates **19a**–**d** were then generated in the presence of KHMDS and *N*-phenyl-triflimide, and coupled with the ethoxy dienyl boronic ester **20** to afford compounds **21a**–**d** which were then cyclized according to a Nazarov electrocyclic process catalyzed by *o*-benzenedisulfonimide,[34] and finally coupled with bromobutenolide **4** under the usual conditions.[31]

The synthesis of derivative **28** required a different sequence of synthetic steps due to the acid lability of the 2,3-dihydrothieno[3,4-*b*][1,4]dioxin moiety which was incapable of surviving Nazarov reaction conditions. Consequently, 5-bromo-1-methylindolin-2-one (**17**) was directly converted into triflate **24** and then coupled with the alkoxydienyl boronate **20** to give product **25** in 77% yield (Scheme 5). Electrocyclization using *o*-benzenedisulfonimide gave 7-bromo-1,4-dimethyl-1,2-dihydrocyclopenta[*b*]indol-3(4*H*)-one (**26**) which was then coupled with 2-(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-7-yl)-5,5-dimethyl-1,3,2-dioxaborinane to provide the corresponding adduct **27**. The final step, coupling to bromobutenolide **4**, performed under the usual conditions provided SL derivative **28** in 53% yield.

Spectroscopic Properties

In Figure 2 absorption and emission spectra of ST **23 a**–**d**, EGO **9c** and **15** derivatives are reported. Solutions of the molecules in dichloromethane, isoabsorbent at the selected excitation wavelength, were prepared and emission spectra were acquired. In Table 1 selected photophysical properties of interest for future imaging application (e.g., fluorescence quantum yields and lifetimes) are displayed. The molecules

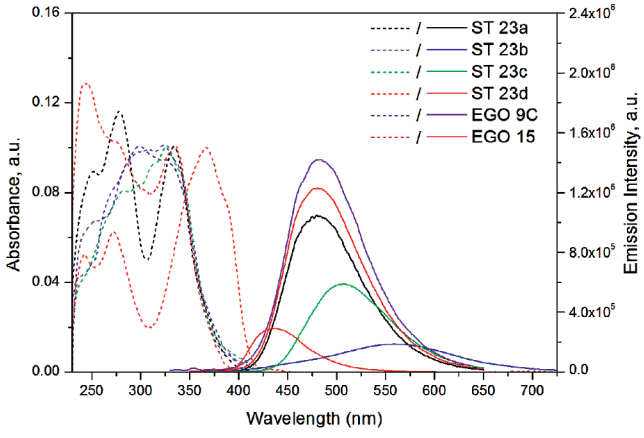


Figure 2. Absorption (dashed lines) and emission (solid lines) spectra of selected ST and EGO derivatives.

of the ST **23 a**–**d** series were characterized by intense absorption bands in the 200–400 nm range, with relative maxima, ranging from 300 to 335 nm, chosen as the λ_{ex}. The effects of substituents on the A ring were evaluated, showing that the PMP and the PMN groups similarly affect the photoemission properties of the molecules, with emission bands centered at ca. 480 nm and fluorescence quantum yields of 0.10 (ST **23a**) and 0.12 (ST **23d**). A strong reduction of the quantum yield (0.03), along with a significant red-shift of the emission band (560 nm), was found for the *p*-DMAP-substituted ST molecule (ST **23b**), whereas the thienyl-substituted molecule (ST **23c**) was characterized by an emission band centered at ca. 506 nm and a quantum yield of about 0.06.

Table 1. Selected photophysical properties of ST and EGO derivatives.

Entry	Sample	λ_{ex}/nm	λ_{em}/nm	Φ_f[a]	τ_1/ns	τ_2/ns
1	ST **23a**	335	480	0.10	7.26 (100%)	–
2	ST **23b**	300	560	0.03	4.37 (56%)	11.9 (44%)
3	ST **23c**	325	506	0.06	4.69 (47%)	5.78 (53%)
4	ST **23d**	335	480	0.12	5.99 (57%)	7.96 (43%)
5	EGO **15**	365	437	0.02	0.80 (100%)	–
6	EGO **9c**	320	484	0.14	4.64 (100%)	–

[a] Fluorescence quantum yields (Φ_f) were determined at 25 °C using anthracene as the standard, upon selection of λ_{ex} and λ_{em} and the excitation and emission wavelengths.

With respect to the EGO **9c** and **15** molecules the effect of the position of the thienyl substituent on photophysical properties was investigated. The 7-substituted EGO molecule (EGO **9c**) was characterized by a broad absorption band in the 220–400 nm range, with a maximum at 320 nm, which is the wavelength chosen as the λ_{ex}. The emission band was found to be 164 nm red-shifted, being centered at 484 nm; this molecule was characterized by a good fluorescence quantum yield (ca. 0.14).

The corresponding 6-substituted EGO derivative (EGO **15**) was characterized by an absorption band different in both shape and position, with a maximum at 365 nm, which was the wavelength chosen as the λ_{ex}. The emission band was found to be only 72 nm red-shifted, being centered at 437 nm and the fluorescence quantum yield was strongly reduced (ca. 0.02) The position of the thienyl substituent on the A ring of the molecule was found to dramatically affect the photophysical properties of the resulting EGO derivative. The 7-substituted derivative showed more interesting properties including a larger Stokes shift (e.g., the shift between absorption and emission band) and significantly higher quantum yield than observed for the corresponding 6-substituted derivative.

Due to the large Stokes shift and the high quantum yield the EGO **9c** and ST **23d** molecules appear to be the most promising derivatives to be used in fluorescence imaging applications. Further studies may focus on the evaluation of their photophysical properties in complex media (e.g., in the presence of seeds studied for germination), since these features, in particular fluorescence lifetimes, can be highly affected by external environmental factors.

Biological Activity

Bioassays were carried out according to the standard procedures (see Exp. Section). Water and acetone were used as negative controls and a diastereomeric mixture of GR **24** (10^{-7} M) served as a positive control. The results obtained with the EGO **5** and **15**, both as racemic mixtures, are represented as a bar graph in Figure 3. The bioassays revealed that racemic **5** had remarkable activity in stimulating the germination of *Orobanche* seeds. As can be deduced from the data, at all the concentrations tested EGO **5** possessed a germination stimulant activity higher than those obtained with GR **24**, the positive control. EGO **15**, possessing a thienyl group in the 6 position of ring A proved to be less active with germination percentages lower than those obtained with EGO **5** and statistically similar to those obtained with water, even though at 10^{-6} M data generated with **15** was statistically similar to that obtained with GR **24**. Based on these data EGO **15** can be considered active.

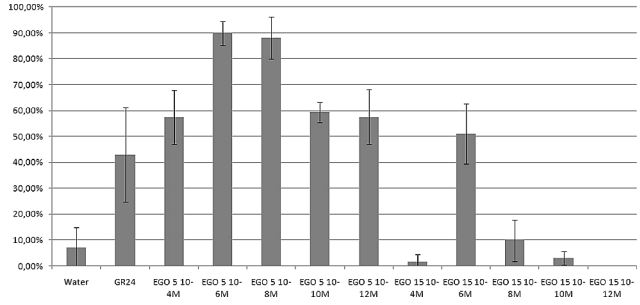


Figure 3. Bar graph representation of percentages of germinated seeds of *Orobanche aegyptiaca* after exposure to various concentrations of racemic EGO series members **5** and **15**.

On the basis of literature data indicating that enantiomers with the same configuration at C2′ of the D ring as the natural strigol are more biologically active, we separated the racemic mixtures of EGO **5** by semipreparative chiral HPLC and tested each optically pure enantiomer in seed germination bioassays. We exploited those concentrations that had previously given the best results with racemates; in the case of EGO **5** the concentration was set to 10^{-8} M. As can be deduced from the bar chart reported in Figure 4, we could not observe a statistically significant difference in the activity between the two enantiomers of **5**.

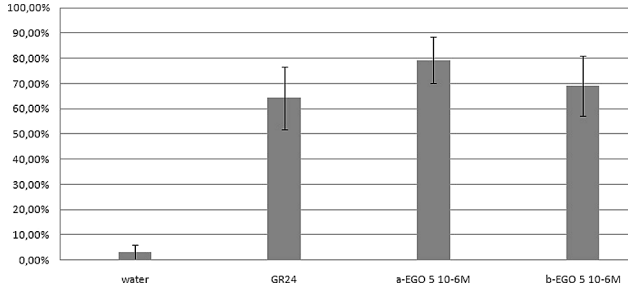


Figure 4. Bar graph representation of percentages of germinated seeds of *Orobanche aegyptiaca* after exposure to each optically pure enantiomer of EGO **5**.

The ST series of molecules, whose main differentiating feature with respect to the EGO series is the substituent on C1 of the ABC nucleus were tested in similar assays of seed germination. The results are represented as a bar chart in Figure 5. Compounds **23d** (Ar = 6-methoxy-2-naphthyl) and **23a** (Ar = *p*-methoxyphenyl) showed stimulant activity on germination at 10^{-6} M (**23a** and **23d**) and at 10^{-4} M (**23a**). These data were statistically different from water and similar to GR **24**. Remarkable activity was also displayed by **23b** [Ar = *p*-(dimethylamino)phenyl)]; its activity was higher than that of GR **24** in four out of the five concentrations examined. Compound **23c** (Ar = 2-thienyl) was found to be the less active compound; only at a concentration of 10^{-6} M could it can be considered active even though the value was lower than obtained with the other compounds, thus confirming the similar trend observed in the EGO series for compound EGO **15**. ST series member **22c** deserves a deeper discussion. Since recent data have spurred questions about the effective role of the enol ether bridge,[35] as well as the D ring itself[9] in determining the biological activity, we decided to test **22c**, a molecule lacking both functionalities.

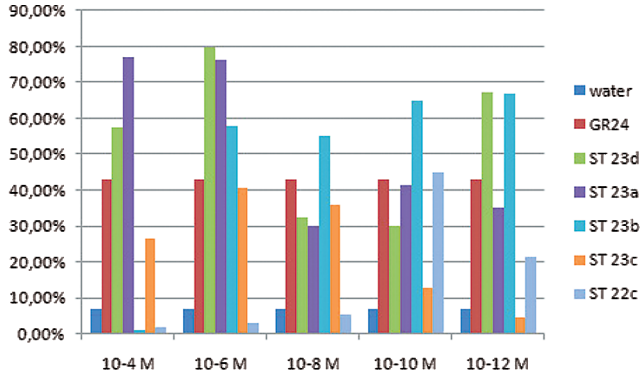


Figure 5. Bar graph representation of percentages of germinated seeds of *Orobanche aegyptiaca* after exposure to diastereomeric mixtures of ST **23a**–**d** and to ST **22c**.

As can be deduced from the bar chart reported in Figure 5, a remarkable activity, statistically comparable to GR **24**, has been observed at 10^{-10} M. This result seems to confirm that, lacking specific information about the receptor active site, further structure-activity investigations are required to undoubtedly assess the role of each functional group in the molecular structure.

As a further step, we tested some of the more promising molecules in seed germination tests, as inducers of hyphal branching in the fungus *Gigaspora margarita*. The results are represented in Figure 6. ST series members **23a** and **23d** which proved to be so active on *Orobanche*, lacked activity on *Gigaspora*; data were found to be statistically different from GR **24** data and similar to water data. EGO series member **5** retained an activity statistically comparable with GR **24**, even though much weaker than its previously determined activity on *Orobanche*. Remarkably and in disagree-

ment with what we had observed in seed assays, the two pure enantiomers of EGO **5** showed different levels of activity in the hyphal branching assay.

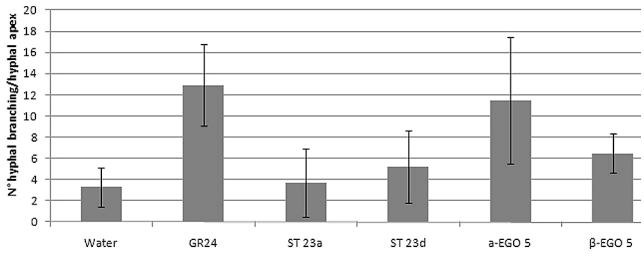


Figure 6. Bar graph representation of percentages of hyphal branching of *Gigaspora margarita* after exposure to diastereomeric mixtures of ST **23a**,**b**,**d** and to the two pure enantiomers of EGO **5**.

In Figure 7 the results concerning molecules with a thienyl group in the 6- or 7-positions of the A ring both for the EGO and ST series are reported. As usual, the concentrations of the bioactive molecule that gave the best result in the seed germination assays were chosen to test bioactivity on *Gigaspora margarita*. On the basis of the statistical analysis we determined that only GR **24**, ST **23c**, and ST **23b** acted as hyphal branching inducers showing an enhanced bioactivity with respect to water. Both EGO **15** and ST **22c** (lacking the D ring) were found to not be statistically different from water and thus can not be considered active branching factors.

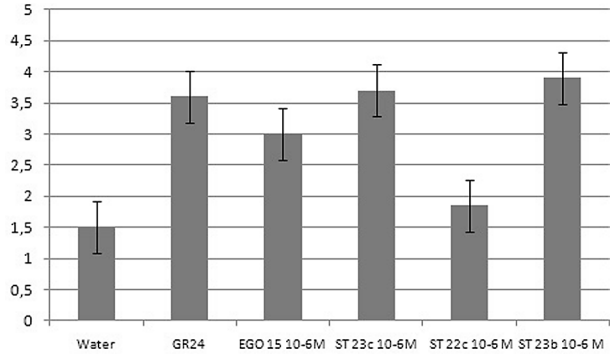


Figure 7. Bar graph representation of percentages of hyphal branching of *Gigaspora margarita* after exposure to diastereomeric mixtures of EGO **15**, ST series members **22c**, and **23b**,**c**.

These data confirm the results of Akiyama and coworkers[9] in that they demonstrate divergent structural requirements for achieving biological activity in seed germination and fungal hyphal branching processes.

Conclusions

In this work we accomplished the synthesis of new SL-like molecules with the specific aim of obtaining potent new germination or hyphal branching stimulants which can be exploited both in field applications and as probes to identify the SL receptor in vivo. The synthesis has been designed according to two main paths, the first of which is mainly focused on providing a rapid and feasible route to bioactive compounds starting from commercially available and cheap reagents (EGO series). This sequence should provide bioactive compounds in large amounts for agricultural applications. The second set of molecules (the ST series) can be obtained using a more versatile synthetic approach which

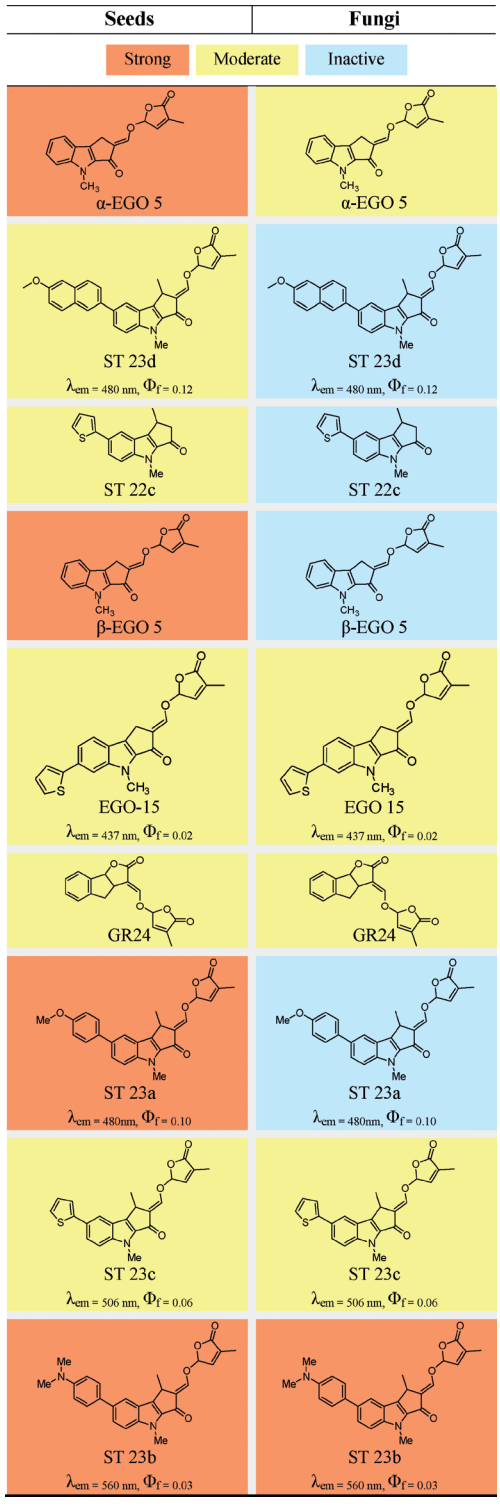


Figure 8. Bioactivity of the ST and EGO series of molecules with respect to GR **24**.

can, in principle, allow the introduction of various functional groups in different positions of the ABC nucleus. All new molecules have been tested on *Orobanche aegyptiaca* seeds and on *Gigaspora margarita* spores in order to evaluate their bioactivity and to decipher possible structure-activity relationships.

The results are summarized in Figure 8, where a red colour indicates an activity superior to the universal standard GR **24**, yellow indicates comparable activity and blue indicates an activity not statistically different from water which served as negative control in these experiments. As can be deduced from the Figure it is quite evident that there is no direct correlation between bioactivity in seeds and fungi, since molecules with a strong activity on seeds [(–)-β-EGO **5**, ST **23a**,**d**] are not active on fungi. Interestingly, the bioactivity on fungi seems to be strongly dependent on the configuration at C2′ of the D ring, since (+)-α-EGO **5** was found to be much more active than (–)-β-EGO **5**. Even more intriguing was the behaviour of ST **22c** lacking the enol ether and the D ring, as this compound retained activity comparable to GR **24** in seeds but was completely inactive in fungi. Furthermore, all molecules herein synthesized and tested were found to be fluorescent with UV light irradiation, inspiring us to investigate their spectroscopic properties. This property will allow us to finely tune the role of the substituents on the ABC core and to identify a putative SL-like probe to be used in the identification the SL receptor in vivo. Due to their large Stokes shifts and to the high quantum yields EGO **9c** and ST **23d** appear to be the most promising candidates for use in future fluorescence imaging applications.

Experimental Section

General Remarks: Chromatographic separations were carried out on silica gel using flash-column techniques; R_f values refer to TLC carried out on 0.25-mm silica gel plates (Merck F254), with the same eluent indicated for the column chromatography. Unless indicated otherwise ^{1}H NMR spectra and NOESY 2D experiments were recorded at 200 and 400 MHz and ^{13}C NMR spectra were recorded at 50 and 100 MHz. MS spectra were recorded at an ionizing voltage of 70 eV. For the determination of optical rotations a Jasco P-2000 polarimeter was used. The enantiomers were separated on a semi-preparative Chiralpak IC column (Φ 10 × 250 mm, Daicel, Osaka, Japan) employing an isocratic elution with CH_2Cl_2 and 1% EtOH at a flow rate of 4.7 mL/min. Absorption UV/Vis spectra were collected with a Cary 300 instrument. Fluorescence spectra were acquired with a Horiba Jobin Yvon Fluorolog3 TCSPC spectrofluorimeter equipped with a 450 W Xenon lamp and a Hamamatsu R928 photomultiplier. The spectral response was corrected for the spectral sensitivity of the photomultiplier. Fluorescence lifetimes were measured using a time-correlated single photon counting (TCSPC) technique (Horiba Jobin Yvon) with excitation source NanoLed at 297 nm (Horiba) and impulse repetition rate of 1 MHz at 90° to a TBX-4 detector. The detector was set to the emission wavelength indicated in Table 1 for each sample. The instrument was set in the Reverse TAC mode, where the first detected photon represented the start signal by the time-to-amplitude converter (TAC), and the excitation pulse triggered the stop signal. DAS6 decay analysis software was used for lifetime calculation.

Biological Test: Plant material. Seeds of *Orobanche aegyptiaca* were collected from field-grown tomato in the West Galilli of Israel. The seeds were stored in glass vials in the dark at room temperature until use in germination tests. Preparation of test solutions: the compound to be tested was weighted out very accurately and dissolved in 1 mL of EtOH and then diluted with sterile distilled water to reach the desired concentrations. All solutions were prepared just before use.

Seeds were surface-sterilized and preconditioned according to the experimental procedure indicated in ref.[31] Briefly seeds were exposed for 5 min to 50% (v/v) aqueous solutions of commercial bleach (2% hypochlorite) and rinsed with sterile distilled water. For preconditioning seeds were sown by using a sterile toothpick on a glass fiber filter paper disc (approximately 20 seeds per disc), the glass fiber discs were placed on 2 filter paper discs, wetted with sterile distilled water and incubated at 25 °C in the dark for 6 days. The preconditioned seeds were then allowed to dry completely in the laminar flow hoods, treated with the SL analogue solutions at 5 different concentrations: 10^{-4}, 10^{-6}, 10^{-8}, 10^{-10} and 10^{-12} M and the germination rates were evaluated under a stereomicroscope 7 days after treatment. For each concentration at least 100 seeds were analyzed, synthetic SL GR **24** 10^{-7} M was included as a positive control, while an aqueous solution of 0.1% EtOH and sterile distilled water was included as a negative control. Seeds were considered to be germinated if the radicle protruded through the seed coat.

Fungal Material: Spores of *Gigaspora margarita* Becker and Hall were collected form already established trap culture of clover, sterilized with a solution of chloramine T (3% P/V) and streptomycine sulfate (0.03% P/V), rinsed with distilled water and placed in a Petri plate filled with 0.2% Phytagel gel (Sigma–Aldrich) containing 3 mM $MgSO_4$. The plates were incubated vertically for 5 days at 30 °C in the dark. Paper discs (6 mm diameter) impregnated with the strigolactone analogues were positioned on either side of the germinating hyphae tips. The number of newly formed hyphal apex were recorded 24 h after treatment. GR **24** 10^{-7} M was included as a positive control whereas an aqueous solution of 0.1% acetone and sterile distilled water was included as a negative control.

3-(1-Methyl-1*H*-indol-3-yl)propionic Acid (2):[36] To a solution of 3-(1*H*-indol-3-yl)propionic acid **1** (1.21 g, 6.40 mmol) in acetone (60 mL), cooled to 0 °C, were added powdered KOH (2.15 g, 38.26 mmol) and, dropwise, MeI (1.99 mL, 31.99 mmol). The resulting pale yellow reaction mixture was left under vigorous stirring at 25 °C for 4 h. After evaporation of the solvent, the residue was dissolved in water (130 mL) and KOH (1.79 g, 31.87 mmol) was added. The mixture was then heated to reflux while stirring for 2 h and, after cooling, 6 N HCl was added until complete precipitation of a white solid which was filtered and washed with heptane, thus obtaining acid **2** (1.12 g) in 86% yield. Analytical and spectroscopic data as reported.[1] ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 12.04 (s, 1 H), 7.52 (d, J = 7.7 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 1 H), 7.21–7.00 (m, 3 H), 3.72 (s, 3 H), 2.92 (t, J = 7.2 Hz, 2 H), 2.57 (t, J = 7.2 Hz, 2 H) ppm.

4-Methyl-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (3): Warm polyphosphoric acid (115% in H_3PO_4, 3.65 mL, 66.77 mmol) was added by a graduated pipette to 3-(1-methyl-1*H*-indol-3-yl)propionic acid **2** (0.90 g, 4.47 mmol) followed by toluene (45 mL). The mixture was refluxed for 4 h, during which time it turned brown. After cooling to room temp. a mixture of ice and water (90 g) was added, followed by extraction with CH_2Cl_2 (4 × 80 mL). The com-

bined organic layers were dried with Na_2SO_4, filtered and the solvents evaporated. The residue was chromatographed (*n*-hexane/EtOAc, 3:1, R_f = 0.38) to afford compound **3** (0.63 g) as a solid in 76% yield. Analytical and spectroscopic data as reported;[1] m.p. 135.1–136.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, J = 7.9 Hz, 1 H), 7.45–7.35 (m, 2 H), 7.21–7.16 (m, 1 H), 3.92 (s, 3 H), 3.09–3.05 (m, 2 H), 3.01–2.97 (m, 2 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 194.8 (s), 145.0 (s), 144.8 (s), 138.9 (s), 126.8 (d), 123.1 (s), 121.7 (d), 120.2 (d), 110.9 (d), 41.2 (t), 30.0 (q), 19.6 (t) ppm. MS (EI): *m*/*z* (%) = 185 (100) $[M]^+$, 157 (53), 142 (13).

(±)4-Methyl-2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yloxymethylene)-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (5): To a solution of compound **3** (0.29 g, 1.07 mmol) in anhydrous THF (18 mL), cooled to 0 °C and under nitrogen atmosphere, were added ethyl formate (0.86 mL, 10.7 mmol) and, dropwise, a 1 M solution of *t*BuOK (2.14 mL, 2.14 mmol) in THF. The pink reaction mixture was left stirring at room temp. with monitoring by TLC (*n*-hexane/EtOAc, 3:2). After complete consumption of the substrate (3 h), the solvent was evaporated under strong nitrogen flow rendering a solid residue to which were added anhydrous DME (16 mL) and, after cooling to 0 °C, bromobutenolide **4** (0.21 g, 1.18 mmol). The resulting dark green mixture was left while stirring at room temp. for 16 h and then quenched by addition of a saturated NH_4Cl aqueous solution (15 mL). The mixture was extracted with Et_2O (5 × 10 mL), the combined organic layers washed with brine (2 × 15 mL) and dried with K_2CO_3. After filtration and evaporation of the solvent, chromatography (*n*-hexane/EtOAc, 1:1, 1% Et_3N, R_f = 0.39) gave compound **5** (136 mg) as a solid in 40% yield; m.p. 176.2–176.8 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.2 Hz, 1 H), 7.43 (s, 1 H), 7.41–7.30 (m, 2 H), 7.17 (pseudo t, J = 8.0 Hz, 1 H), 6.99–6.95 (m, 1 H), 6.22–6.18 (m, 1 H), 3.94 (s, 3 H), 3.59 (s, 2 H), 2.03 (s, 3 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 184.8 (s), 170.5 (s), 145.9 (d), 144.5 (s), 141.3 (d), 140.7 (s), 136.9 (s), 135.6 (s), 126.6 (d), 124.0 (s), 122.7 (s), 121.6 (d), 120.4 (d), 110.9 (d), 100.6 (d), 30.2 (q), 22.4 (t), 10.7 (q) ppm. MS (ESI): *m*/*z* (%) = 310.07 (8) $[M + H]^+$, 264 (81), 213 (100). $C_{18}H_{15}NO_4$ (309.32): calcd. C 69.89, H 4.89, N 4.53; found C 69.77, H 4.61, N 4.18.

7-Bromo-4-methyl-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (6): To a solution of **3** (0.10 g, 0.54 mmol) in anhydrous CH_3CN (15 mL), cooled to 0 °C, was added NBS (0.11 g, 0.65 mmol) while stirring under a nitrogen atmosphere. The resulting green solution was gradually heated and left 1 h at room temp. with monitoring by TLC (*n*-hexane/EtOAc, 2.5:1. Compound **3** had R_f = 0.48, and gave a red spot with *p*-anisaldehyde stain, and was fluorescent at 254 nm under the UV lamp; reaction product **6** has R_f = 0.51, gave a red spot with *p*-anisaldehyde stain, but was not fluorescent at 254 nm). After 1 h, the reaction mixture was cooled to 0 °C again and further NBS (0.05 g, 0.27 mmol) was added. The mixture was heated to room temp. and allowed to stir for 1.5 h, after which time the consumption of the starting material was complete (total reaction time: 6 h). The reaction mixture was diluted with H_2O (15 mL), extracted with Et_2O (4 × 15 mL) and the combined organic layers dried with Na_2SO_4. After filtration and evaporation of the solvent, chromatography (*n*-hexane/EtOAc, 2.5:1, R_f = 0.51) gave compound **6** (95 mg) as a solid in 67% yield; m.p. 124.4–126.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 1.9 Hz, 1 H), 7.47 (dd, J = 8.8, 1.9 Hz, 1 H), 7.24 (dd, J = 8.8, 0.4 Hz, 1 H), 3.89 (s, 3 H), 3.02–2.93 (m, 2 H), 2.91–2.82 (m, 4 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 194.4 (s), 143.3 (s), 143.2 (s), 139.5 (s), 129.4 (d), 124.4 (s), 124.1 (d), 113.4 (s), 112.4 (d), 41.5 (t), 30.3 (q), 19.6 (t) ppm. MS (ESI): *m*/*z* (%) = 266 (97) and 264 (100) $[M + H]^+$, 151(27). $C_{12}H_{10}BrNO$ (264.12): calcd. C 54.57, H 3.82, N 5.30; found C 54.62, H 3.65, N 5.01.

7-Bromo-4-methyl-2-(4-methyl-5-oxo-2,5-dihydrofuran-2-yloxymethylene)-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (7): Prepared as reported for compound **5**. Starting from 7-bromo-4-methyl-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one **6** (158 mg, 0.6 mmol), compound **7** (48 mg) was obtained after chromatography (CH_2Cl_2/MeOH, 30:1, 1% Et_3N, R_f = 0.41) as a solid in 21% yield; m.p. 167.1–180.0 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 1.9 Hz, 1 H), 7.47 (dd, J = 8.9, 1.9 Hz, 1 H), 7.45 (s, 1 H), 7.27–7.23 (m, 1 H), 6.99–6.96 (m, 1 H), 6.22–6.19 (m, 1 H), 3.95 (s, 3 H), 3.56 (s, 2 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 183.0 (s), 170.5 (s), 146.5 (d), 142.9 (s), 141.5 (s), 141.2 (d), 135.7 (s), 135.5 (s), 129.2 (d), 124.2 (s), 124.0 (d), 123.5 (s), 113.6 (s), 112.4 (d), 100.6 (d), 30.3 (q), 22.3 (t), 10.7 (q) ppm. MS (ESI): *m*/*z* (%) = M^+ not found. $C_{18}H_{14}BrNO_4$ (388.21): calcd. C 55.69, H 3.63, N 3.61; found C 55.87, H 3.46, N 3.28.

4-Methyl-7-(4-nitrophenyl)-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (8a): Starting from **6** (221 mg, 0.84 mmol) and (*p*-nitrophenyl)boronic acid (419 mg, 2.51 mmol), compound **9** (176 mg) was obtained after chromatography (CH_2Cl_2/MeOH, 60:1, R_f = 0.41, red spot with *p*-anisaldehyde stain) as a solid in 69% yield; m.p. 198.4–200.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, J = 9.0 Hz, 2 H), 7.96 (d, J = 1.8 Hz, 1 H), 7.79 (d, J = 9.0 Hz, 2 H), 7.69 (dd, J = 8.8, 1.8 Hz, 1 H), 7.48 (d, J = 8.8 Hz, 1 H), 3.97 (s, 3 H), 3.15–3.10 (m, 2 H), 3.05–3.01 (m, 2 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 194.7 (s), 148.1 (s), 146.7 (s), 145.0 (s), 144.9 (s), 140.0 (s), 131.1 (s), 127.7 (d, 2 C), 126.1 (d), 124.2 (d, 2 C), 123.6 (s), 120.8 (d), 111.7 (d), 41.4 (t), 30.3 (q), 19.6 (t) ppm. MS (ESI): *m*/*z* (%) = 329 (100) $[M + Na]^+$. $C_{18}H_{14}N_2O_3$ (306.32): calcd. C 70.58, H 4.61, N 9.15; found C 70.76, H 4.60, N 9.02.

4-Methyl-2-(4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-7-(4-nitrophenyl)-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (9a): Prepared as reported for compound **5**. Starting from **8** (157 mg, 0.51 mmol), compound **9a** (77 mg) was obtained after chromatography (CH_2Cl_2/MeOH, 50:1, 1% Et_3N, R_f = 0.32, red spot with *p*-anisaldehyde stain) as a solid in 35% yield; m.p. 245.1–247.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 9.0 Hz, 2 H), 7.93 (d, J = 1.4 Hz, 1 H), 7.79 (d, J = 9.0 Hz, 1 H), 7.68 (dd, J = 8.8, 1.4 Hz, 2 H), 7.49 (d, J = 8.8 Hz, 1 H), 7.48 (s, 1 H), 7.00–6.98 (m, 1 H), 6.24–6.21 (m, 1 H), 4.02 (s, 3 H), 3.66 (s, 2 H), 2.05 (s, 3 H) ppm. ^{13}C NMR (100.4 MHz, [D$_6$]DMSO): δ = 182.2 (s), 170.9 (s), 147.9 (s), 147.2 (s), 146.1 (d), 144.1 (s), 143.4 (d), 141.2 (s), 136.8 (s), 133.7 (s), 130.1 (s), 127.6 (d, 2 C), 125.7 (d), 124.1 (d, 2 C), 122.8 (s), 122.3 (s), 120.7 (d), 112.5 (d), 101.2 (d), 30.3 (q), 22.1 (t), 10.2 (q) ppm. MS (ESI): *m*/*z* (%) = 431 (17) $[M + H]^+$, 239 (100). $C_{24}H_{18}N_2O_6$ (430.41): calcd. C 66.97, H 4.22, N 6.51; found C 67.12, H 3.93, N 6.40.

7-[4-(Dimethylamino)phenyl]-4-methyl-1,4-dihydro-2*H*-cyclopenta-[*b*]indol-3-one (8b): A solution of **6** (0.07 g, 0.28 mmol) in anhydrous THF (6 mL) was added to a mixture of K_3PO_4 (0.24 g, 1.12 mmol), [4-(dimethylamino)phenyl]boronic acid (0.14 g, 0.84 mmol) and 2-dicyclohexylphosphanyl-2′,6′-dimethoxybiphenyl (S-Phos, 0.01 g, 0.028 mmol) under nitrogen atmosphere, followed by $Pd(OAc)_2$ (0.003 g, 0.014 mmol). The mixture was refluxed while stirring and monitored by TLC (*n*-hexane/EtOAc, 2.5:1, R_f = 0.25, red spot with *p*-anisaldehyde stain). After 4 h, the mixture was cooled to room temp. and diluted with H_2O (25 mL), extracted with Et_2O (5 × 25 mL) and the combined organic layers dried with Na_2SO_4. After filtration and evaporation of the solvent, chromatography (*n*-hexane/EtOAc, 3:1, 1% Et_3N, R_f = 0.28) gave **8** (0.065 g) as a solid in 76% yield; m.p. 212.6–214.2 °C. ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 7.82 (d, J = 1.6 Hz, 1 H), 7.65 (dd, J = 8.6, 1.6 Hz, 1 H), 7.55 (d, J = 8.8 Hz, 2 H), 7.37 (d, J = 8.6 Hz, 1 H), 6.84 (d, J = 8.8 Hz, 2 H), 3.92 (s, 3 H), 3.10–3.06 (m, 2 H), 3.02–2.97 (m, 2 H + 6 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 194.7 (s), 149.7 (s), 145.0 (s), 144.0 (s), 139.2 (s), 133.9 (s), 129.7 (s), 127.8 (d, 2 C), 126.4 (d), 123.5 (s), 118.6 (d), 112.9 (d, 2 C), 111.0 (d), 41.5 (t), 40.6 (q, 2 C), 30.1 (q), 19.6 (t) ppm. MS (ESI): m/z (%) = 305 (7) $[M + H]^+$, 290 (100). $C_{20}H_{20}N_2O$ (304.39): calcd. C 78.92, H 6.62, N 9.20; found C 79.03, H 6.44, N 8.87.

7-[4-(Dimethylamino)phenyl]-4-methyl-2-(4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (9b): Prepared as reported for compound **5**. Starting from **8** (0.095 g, 0.31 mmol), compound **9b** (75 mg) was obtained after chromatography (CH_2Cl_2/MeOH, 40:1, 1% Et_3N, R_f = 0.43, wine-colored spot with *p*-anisaldehyde stain) as a solid in 56% yield; m.p. 202.7 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 1.4 Hz, 1 H), 7.60 (dd, J = 8.6, 1.4 Hz, 1 H), 7.51 (d, J = 8.8 Hz, 2 H), 7.42–7.40 (m, 1 H), 7.35 (d, J = 8.6 Hz, 1 H), 6.95–6.92 (m, 1 H), 6.81 (d, J = 8.8 Hz, 2 H), 6.18–6.15 (m, 1 H), 3.93 (s, 3 H), 3.58 (s, 2 H), 2.98 (s, 6 H), 2.01 (s, 3 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 182.9 (s), 170.5 (s), 149.7 (s), 145.9 (d), 143.5 (s), 141.4 (d), 141.1 (s), 137.0 (s), 135.5 (s), 134.1 (s), 129.7 (s), 127.8 (d, 2 C), 126.2 (s), 124.0 (d), 123.2 (s), 118.5 (d), 112.9 (d, 2 C), 111.0 (d), 100.6 (d), 40.6 (q, 2 C), 30.3 (q), 22.4 (t), 10.7 (q) ppm. MS (ESI): m/z (%) = 429.14 (5) $[M^+ + H]^+$, 414 (17), 401 (31), 332 (100), 303 (18). $C_{26}H_{24}N_2O_4$ (428.48): calcd. C 72.88, H 5.65, N 6.54; found C 73.09, H 5.31, N 6.28.

1,2-Dihydro-4-methyl-7-(thiophen-2-yl)cyclopenta[*b*]indol-3(4*H*)-one (8c): Prepared as reported for compound **8a**. Starting from **6** (264 mg, 1 mmol) and 2-thienylboronic acid (384 mg, 3 mmol), compound **8c** (215 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, R_f = 0.48, blue spot with *p*-anisaldehyde stain) as a yellow oil in 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 7.51 (d, J = 10.6 Hz, 1 H), 7.13 (m, 3 H), 6.94 (m, 1 H), 3.73 (s, 3 H), 2.83 (m, 4 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.5 (s), 144.8 (s), 144.7 (s), 144.1 (s), 139.4 (s), 127.9 (d), 125.4 (d), 123.9 (d), 123.1 (s), 122.3 (d), 121.5 (s), 118.5 (d), 111.1 (d), 41.2 (t), 29.9 (q), 19.4 (t) ppm. $C_{16}H_{15}NOS$ (269.09): calcd. C 71.34, H 5.61, N 5.20; found C 72.06, H 5.83, N 5.88.

(±) (2*E*)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-1,2-dihydro-4-methyl-7-(thiophen-2-yl)cyclopenta[*b*]indol-3(4*H*)-one (9c): Prepared as reported for compound **5**. Starting from **8c** (0.215 g, 0.8 mmol), compound **9c** (74 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, 1% Et_3N, R_f = 0.20, grey spot with *p*-anisaldehyde stain) as a solid in 24% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.60 (d, J = 10.5 Hz, 1 H), 7.36 (s, 1 H), 7.29–7.17 (m, 3 H), 7.04–7.02 (m, 1 H), 6.89 (br. s, 1 H), 6.13 (br. s, 1 H), 3.87 (s, 3 H), 3.51 (br. s, 2 H), 1.99 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.8 (s), 170.4 (s), 146.0 (d), 144.8 (s), 143.7 (s), 141.3 (s), 141.1 (d), 136.8 (s), 135.4 (s), 127.9 (d), 127.1 (s), 125.3 (d), 124.0 (d), 123.6 (s), 122.9 (s), 122.4 (d), 118.4 (d), 111.1 (d), 100.4 (d), 30.2 (q), 22.3 (t), 10.6 (q) ppm. MS/MS (ESI): m/z (%) = 392 (7) $[M + H]^+$, 374 (4), 346 (10), 330 (7), 295 (100). $C_{22}H_{17}NO_4S$ (391.4): calcd. C 67.53, H 4.38, N 3.58; found C 67.55, H 4.30, N 3.25.

6-Bromo-1-methyl-1*H*-indole (11):[37] To a solution of 6-bromoindole **12** (1.0 g, 5.1 mmol) in acetone (26 mL), cooled to 0 °C, were added powdered KOH (1.71 g, 30.5 mmol) and, dropwise, MeI (1.59 mL, 25.5 mmol). The mixture stirred vigorously for 4 h at room temp. and solvent then was evaporated and the residue diluted with H_2O (20 mL). The aqueous phase was extracted with Et_2O (4 × 20 mL) and the combined organic layers were dried with Na_2SO_4. After filtration and evaporation of the solvent, compound **11** (1.071 g, 100%) was obtained in a sufficiently pure form for the next step. Analytical and spectroscopic data as reported.[2] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (br. s, 1 H), 7.48 (d, J = 8.4 Hz, 1 H), 7.21 (dd, J = 8.4, 1.8 Hz, 1 H), 7.02 (d, J = 3.1 Hz, 2 H), 6.46 (dd, J = 3.1, 0.8 Hz, 1 H), 3.76 (s, 3 H) ppm.

3-(6-Bromo-1-methyl-1*H*-indol-3-yl)propionic Acid (12):[38] To compound **11** (1.07 g, 5.1 mmol) were added in sequence acetic acid (2.5 mL), acrylic acid (0.929 mL, 14.3 mmol) and acetic anhydride (0.9 mL) under nitrogen atmosphere. The mixture was left whilst stirring at 140 °C for 4 h and then at room temp. for 16 h. Acetic acid was then removed by distillation and the residue was diluted with H_2O (10 mL), the organic phase was extracted with Et_2O (5 × 10 mL) and the combined organic layers were dried with Na_2SO_4. After filtration and evaporation of the solvent, chromatography (*n*-hexane/EtOAc, 4:1, R_f = 0.23, fuchsia-colored spot with *p*-anisaldehyde stain) gave acid **12** (0.75 g) as a solid in 52% yield; m.p. 128.5–137.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 1.9 Hz, 1 H), 7.43 (d, J = 8.2 Hz, 1 H), 7.20 (dd, J = 8.2, 1.9 Hz, 1 H), 6.84 (s, 1 H), 3.69 (s, 3 H), 3.06 (t, J = 7.6 Hz, 2 H), 2.74 (t, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 179.2 (s), 137.8 (s), 126.9 (d), 126.4 (s), 122.0 (d), 120.0 (d), 115.4 (s), 113.4 (s), 112.3 (d), 34.7 (t), 32.7 (q), 20.0 (t) ppm. MS (ESI): m/z (%) = 282 (3) $[M + H]^+$, 264 (13), 222 (100), 203 (32). $C_{12}H_{12}BrNO_2$ (282.13): calcd. C 51.09, H 4.29, N 4.96; found C 51.33, H 4.17, N 4.58.

6-Bromo-4-methyl-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (13): Prepared as reported for compound **3**. Starting from **12** (0.75 g, 2.67 mmol), compound **13** (337 mg) was obtained after chromatography (*n*-hexane/EtOAc, 3:1, R_f = 0.36) as a solid in 48% yield; m.p. 161.7–163.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, J = 8.6 Hz, 1 H), 7.51 (d, J = 1.8 Hz, 1 H), 7.26 (dd, J = 8.6, 1.8 Hz, 1 H), 3.86 (s, 3 H), 3.05–3.00 (m, 2 H), 2.98–2.94 (m, 2 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 194.6 (s), 145.4 (s), 144.5 (s), 139.3 (s), 123.7 (d), 122.8 (d), 121.8 (s), 120.5 (s), 114.0 (d), 41.4 (t), 30.1 (q), 19.4 (t) ppm. MS (ESI): m/z (%) = 264 (14) $[M + H]^+$, 222 (100). $C_{12}H_{10}BrNO$ (264.12): calcd. C 54.57, H 3.82, N 5.30; found C 54.86, H 3.55, N 5.02.

4-Methyl-6-thiophen-2-yl-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (14): Prepared as reported for compound **8** but by using 10 mol-% of $Pd(OAc)_2$. Starting from **13** (337 mg, 1.28 mmol) and from 2-thienylboronic acid (490 mg, 3.83 mmol), compound **14** (254 mg) was obtained after chromatography (*n*-hexane/EtOAc, 6:1, R_f = 0.25, blue, then green spot with *p*-anisaldehyde stain) as a solid in 74% yield; m.p. 161.8–163.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (dd, J = 8.4, 0.6 Hz, 1 H), 7.52 (bs s, 1 H), 7.45 (dd, J = 8.4, 1.6 Hz, 1 H), 7.40 (dd, J = 3.7, 1.2 Hz, 1 H), 7.32 (dd, J = 5.0, 1.2 Hz, 1 H), 7.11 (dd, J = 5.0, 3.7 Hz, 1 H), 3.92 (s, 3 H), 3.06–3.01 (m, 2 H), 2.99–2.96 (m, 2 H) ppm. ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 194.4 (s), 145.3 (s), 144.9 (s), 144.7 (s), 139.4 (s), 133.0 (s), 128.1 (d), 125.0 (d), 123.5 (d), 122.4 (s), 122.0 (d), 119.1 (d), 107.6 (d), 41.4 (t), 30.0 (q), 19.5 (t) ppm. MS (ESI): m/z (%) = 268 (6) $[M + H]^+$, 253 (11), 226 (100). $C_{16}H_{13}NOS$ (267.35): calcd. C 71.88, H 4.90, N 5.24; found C 71.92, H 4.76, N 4.99.

(±) 4-Methyl-2-(4-methyl-5-oxo-2,5-dihydro-furan-2-yloxymethylene)-6-thiophen-2-yl-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one (15): Prepared as reported for compound **5**. Starting from **14** (317 mg, 1.19 mmol), compound **15** (182 mg) was obtained after chromatography (CH_2Cl_2/MeOH, 80:1, 1% Et_3N, R_f = 0.27, blue spot with *p*-anisaldehyde stain) as a solid in 38% yield; m.p. 189.7–192.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.4 Hz, 1 H), 7.55 (br. s, 1 H), 7.47 (dd, J = 8.4, 1.4 Hz, 1 H), 7.44 (br. s, 1 H), 7.40

(d, J = 3.5 Hz, 1 H); 7.32 (d, J = 4.9 Hz, 1 H), 7.12 (dd, J = 4.9, 3.5 Hz, 1 H), 6.98–6.96 (m, 1 H), 6.2 (br. s, 1 H), 3.99 (s, 3 H), 3.56 (s, 2 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 182.5 (s), 170.5 (s), 145.9 (d), 144.8 (s), 144.7 (s), 141.4 (d), 141.3 (s), 136.7 (s), 135.5 (s), 132.8 (s), 128.1 (d), 125.0 (d), 123.9 (s), 123.4 (d), 122.0 (s), 121.9 (d), 119.2 (d), 107.5 (d), 100.6 (d), 30.2 (q), 22.3 (t), 10.7 (q) ppm. MS (ESI): m/z (%) = 392 (11) $[M + H]^+$, 295 (100). $C_{22}H_{17}NO_4S$ (391.44): calcd. C 67.50, H 4.38, N 3.58; found C 67.74, H 4.31, N 3.47.

5-Bromo-1-methylindolin-2-one (17): NBS (1.2 equiv., 12 mmol, 2.14 g) was recrystallized from water and added to a solution of compound **16** (10 mmol, 1.47 g) in CH_3CN at 0 °C. The reaction mixture was then brought to room temp. and left stirring overnight. Et_2O was added to the solution and it was washed with water. The aqueous phase was extracted three times with Et_2O (20 mL). The combined organic phases were dried with Na_2SO_4 anhydrous and the solvent was evaporated under reduced pressure, to afford, without any further purification, 2.15 g (9.5 mmol, 95%) of the product as a pink solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.29 (m, 2 H), 6.63 (d, J = 8.2 Hz, 1 H), 3.46 (s, 2 H), 3.13 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.1 (s), 144.0 (s), 130.5 (d), 127.1 (d), 126.2 (s), 114.7 (s), 109.2 (d), 35.3 (t), 26.1 (q) ppm. C_9H_8BrNO (224.98): calcd. C 47.80, H 3.59, N 6.21; found C 47.81, H 3.57, N 6.20.

General Procedure for the Synthesis of 18a–d: To a degassed solution of Pd_2OAc_2 (5%), S-Phos (10%), K_3PO_4 (3 equiv.), and 3 equiv. of the corresponding boronic acid, in THF (20 mL), 2 mmol (0.452 g) of 5-bromo-1-methylindolin-2-one (**17**) were added. The reaction was then left stirring at reflux overnight. Water (25 mL) was then added, the mixture was extracted with Et_2O (3 × 20 mL), and dried with anhydrous K_2CO_3. Evaporation of the solvent afforded the crude mixture of solid products which were purified by chromatography.

5-(4-Methoxyphenyl)-1-methylindolin-2-one (18a): Starting from **17** (452 mg, 2 mmol), compound **18a** (500 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, R_f = 0.12, brown spot with *p*-anisaldehyde stain) as an orange solid in 98% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.15 (d, J = 6.8 Hz, 2 H), 7.45 (m, 3 H), 6.95 (t, J = 6.2 Hz, 2 H), 3.90 (s, 3 H), 3.76 (s, 2 H), 3.25 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175 (s), 158.7 (s), 149.3 (s), 143.9 (s), 138.5 (s), 134 (s), 133.3 (s), 128.1 (d, 2 C), 126.2 (d), 122.9 (s), 119.3 (d), 114.1 (d, 2 C), 111 (d), 55.2 (q), 36.4 (t), 35.1 (q) ppm. $C_{16}H_{15}NO_2$ (253.11): calcd. C 75.87, H 5.97, N 5.53; found C 76.78, H 6.02, N 5.73.

5-[4-(Dimethylamino)phenyl]-1-methylindolin-2-one (18b): Starting from **17** (452 mg, 2 mmol), compound **18b** (425 mg) was obtained after chromatography (petroleum ether/EtOAc, 9:1, R_f = 0.20, brown spot with *p*-anisaldehyde stain) as an orange solid in 98% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.96 (m, 7 H), 3.45 (s, 2 H), 3.12 (s, 3 H), 2.88 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.9 (s), 149.6 (s), 143.4 (s), 135.9 (s), 128.8 (s), 127.2 (d, 2 C), 125.5 (d), 124.8 (s), 122.4 (d), 112.7 (d, 2 C), 108.0 (d), 40.4 (q, 2 C), 35.8 (t), 26.1 (q) ppm. $C_{17}H_{18}N_2O$ (266.14): calcd. C 76.66, H 6.81, N 10.52; found C 77.80, H 6.40, N 10.84.

1-Methyl-5-(thiophen-2-yl)indolin-2-one (18c): Starting from **17** (452 mg, 2 mmol), compound **18c** (366 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, R_f = 0.50, blue spot with *p*-anisaldehyde stain) as an orange solid in 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (m, 2 H), 7.14 (m, 2 H), 6.98 (m, 3 H), 6.71 (d, J = 8 Hz, 2 H), 3.88 (s, 3 H), 3.44 (s, 2 H), 3.13 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.7 (s), 144.4 (s), 144.1 (s), 128.9 (s), 127.9 (d), 125.4 (d), 125.0 (s), 124.0 (d), 122.1 (d), 122.0 (d), 108.1 (d), 35.5 (q), 26.1 (d) ppm. $C_{13}H_{11}NOS$ (229.06): calcd. C 68.09, H 4.84, N 6.11; found C 68.85, H 5.04, N 6.67.

5-(2-Methoxynaphthalen-6-yl)-1-methylindolin-2-one (18d): Starting from **17** (452 mg, 2 mmol), compound **18d** (519 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, R_f = 0.10, brown spot with *p*-anisaldehyde stain) as an orange solid in 85% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.73 (m, 2 H), 7.57 (m, 3 H), 7.11 (m, 2 H), 6.84 (d, J = 7.6 Hz, 1 H), 3.88 (s, 3 H), 3.54 (s, 2 H), 3.19 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.9 (s), 157.5 (s), 144.2 (s), 135.8 (s), 135.6 (s), 133.4 (s), 129.4 (d), 129.0 (s), 127.1 (d), 126.6 (d), 125.6 (d), 125.0 (d), 124.9 (s), 123.1 (d), 119.1 (d), 108.1 (d), 105.4 (d), 55.1 (q), 35.7 (t), 26.1 (q) ppm. $C_{20}H_{17}NO_2$ (303.13): calcd. C 79.19, H 5.65, N 4.62; found C 79.79, H 5.83, N 4.94.

General Procedure for the Synthesis of Compounds 19a–d and 24: Triflates **19a–d** have been prepared as previously reported.[39]

General Procedure for the Synthesis of Compounds 21a–d and 25: To a solution of the corresponding crude triflate in THF, under a nitrogen atmosphere, $(Ph_3P)_2PdCl_2$ (0.05 equiv.), (*E*)-2-(1-ethoxybuta-1,3-dienyl)-5,5-dimethyl-1,3,2-dioxaborinane (1.2 equiv.), and a 2 M aqueous K_2CO_3 solution (1 mL) were added. The mixture was stirred for 3 h at room temp. H_2O (25 mL) was then added, the mixture extracted with Et_2O (3 x 20 mL) and dried with anhydrous Na_2CO_3. Evaporation of the solvent afforded a yellow oil which was purified by chromatography.

2-[(*E*)-1-Ethoxybuta-1,3-dienyl]-5-(4-methoxyphenyl)-1-methyl-1*H*-indole (21a): Compound **21a** (405 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1% Et_3N, R_f = 0.7, brown spot with *p*-anisaldehyde stain) as a yellow oil in 75% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 751 (d, J = 8.5 Hz, 2 H), 7.37 (d, J = 8.6 Hz, 1 H), 7.29 (d, J = 8.6 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 2 H), 6.54 (s, 1 H), 6.35 (dt, J = 16.0, 10.8 Hz, 1 H), 5.79 (d, J = 10.8 Hz, 1 H), 5.15 (dd, J = 16.0, 1.5 Hz, 1 H), 4.82 (dd, J = 10.8, 1.5 Hz, 1 H), 3.88 (q, J = 6.8 Hz, 2 H), 3.79 (s, 3 H), 3.65 (s, 3 H), 1.32 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.2 (s), 149.8 (s), 136.7 (s), 134.9 (s), 134.1 (s), 133.5 (d), 132.7 (s), 128.0 (d, 2 C), 127.4 (s), 121.8 (d), 118.7 (d), 113.9 (d, 2 C), 113.1 (t), 109.4 (d), 108.5 (d), 104.8 (d), 65.7 (t), 55.2 (q), 30.7 (q), 14.0 (q) ppm. $C_{22}H_{23}NO_2$ (333.17): calcd. C 79.25, H 6.95, N 4.20; found C 80.05, H 6.73, N 4.48.

4-{2-[(*E*)-1-Ethoxybuta-1,3-dienyl]-1-methyl-1*H*-indol-5-yl}-*N*,*N*-dimethylbenzenamine (21b): Compound **21b** (191 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1% Et_3N, R_f = 0.6, brown spot with *p*-anisaldehyde stain), as a yellow oil in 55% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.23 (m, 7 H), 6.53 (s, 1 H), 6.36 (dt, J = 17, 10.6 Hz, 1 H), 5.80 (d, J = 10.6 Hz, 1 H), 5.09 (dd, J = 17, 1.8 Hz, 1 H), 4.95 (dd, J = 10.1, 1.8 Hz, 1 H), 3.89 (q, J = 7 Hz, 2 H), 3.65 (s, 3 H), 2.93 (s, 6 H), 1.32 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 150.1 (s), 149.4 (s), 136.7 (s), 134.0 (s), 133.7 (s), 133.3 (d), 130.8 (s), 127.8 (d, 2 C), 127.6 (s), 121.8 (d), 118.2 (d), 113.2 (t), 112.9 (d, 2 C), 109.5 (d), 108.5 (d), 104.9 (d), 63.5 (t), 40.6 (q, 2 C), 30.8 (q), 14.6 (q) ppm. $C_{23}H_{26}N_2O$ (346.20): calcd. C 79.73, H 7.56, N 8.09; found C 79.50, H 7.43, N 8.16.

2-[(*E*)-1-Ethoxybuta-1,3-dienyl]-1-methyl-5-(thiophen-2-yl)-1*H*-indole (21c): Compound **21c** (243 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, 1% Et_3N, R_f = 0.50, blue spot with *p*-anisaldehyde stain), as a yellow oil in 53% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.50 (d, J = 14.0 Hz, 1 H), 7.22 (m, 3 H), 7.02 (m, 1 H), 6.54 (s, 1 H) 6.35 (dt,

J = 16.0, 10.5 Hz, 1 H), 5.83 (d, J = 10.5 Hz, 1 H), 5.10 (dd, J = 16.0, 1.5 Hz, 1 H), 4.83 (dd, J = 10.5, 1.5 Hz, 1 H), 3.90 (q, J = 7 Hz, 2 H), 3.66 (s, 3 H), 1.33 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.6 (s), 145.9 (s), 137.1 (s) 133.4 (d) 127.7 (d), 127.3 (s), 126.3 (s), 123.3 (d), 121.8 (d), 121.1 (d), 118.2 (d), 113.3 (t), 109.6 (d), 108.5 (d), 104.9 (d), 63.5 (t), 30.8 (q), 14.5 (q) ppm. $C_{19}H_{19}NOS$ (309.12): calcd. C 73.75, H 6.19, N 4.53; found C 74.05, H 6.27, N 4.60.

2-[(*E*)-1-Ethoxybuta-1,3-dienyl]-5-(2-methoxynaphthalen-6-yl)-1-methyl-1*H*-indole (21d): Compound **21d** (384 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1% Et_3N, R_f = 0.65, brown spot with *p*-anisaldehyde stain), as a yellow oil in 60% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.96 (s, 1 H), 7.89 (s, 1 H), 7.75 (m, 3 H), 7.56 (d, J = 8.6 Hz, 1 H), 7.36 (d, J = 8.6 Hz, 1 H), 7.12 (m, 2 H), 6.60 (s, 1 H), 6.41 (dt, J = 17.0, 10.6 Hz, 1 H), 5.82 (d, J = 10.6 Hz, 1 H), 5.11 (dd, J = 17.0, 1.7 Hz, 1 H), 4.81 (dd, J = 10.6, 1.7 Hz), 3.88 (m, 5 H), 3.68 (s, 3 H), 1.26 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.2 (s), 137.5 (s), 137.0 (s), 134.2 (s), 133.5 (s), 133.1 (d), 133.0 (s), 129.4 (d), 129.2 (s), 128.9 (d), 127.6 (d), 126.9 (d), 126.5 (d), 125.2 (d), 122.1 (d), 119.3 (d), 118.8 (t), 113.2 (d), 109.6 (d), 108.5 (d), 105.4 (d), 104.9 (d), 63.5 (t), 55.4 (q), 30.8 (q), 14.5 (q) ppm. $C_{26}H_{25}NO_2$ (383.19): calcd. C 81.43, H 6.57, N 3.65; found C 81.85, H 6.48, N 3.58.

5-Bromo-2-[(*E*)-1-ethoxybuta-1,3-dienyl]-1-methyl-1*H*-indole (25): Compound **25** (700 mg) was obtained after chromatography (petroleum ether/EtOAc, 9:1, 1% Et_3N, R_f = 0.43, brown spot with *p*-anisaldehyde stain), as a yellow oil in 77% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.46–7.25 (m, 3 H), 7.18 (d, J = 8.6 Hz, 1 H), 6.66 (s, 1 H), 6.56 (dt, J = 17.0, 10.4 Hz, 1 H), 5.82 (d, J = 10.4 Hz, 1 H), 5.34 (dd, J = 17.0, 1.2 Hz, 1 H), 5.05 (dd, J = 10.4, 1.2 Hz), 4.00 (q, J = 7 Hz, 2 H), 3.70 (s, 3 H), 1.48 (t, J = 7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 157.6 (s), 136.8 (s), 135.7 (s), 130.4 (s), 121.3 (d), 121.1 (d), 118.8 (t), 117.8 (s), 106.4 (d), 102.8 (d), 63.8 (t), 36.4 (q), 14.8 (q) ppm. $C_{15}H_{16}BrNO$ (305.04): calcd. C 58.84, H 5.27, N 4.57; found C 59.05, H 5.47, N 4.52.

General Procedure for the Synthesis of Compounds 22a–d and 26: To a solution of **21** in 4 mL of DCE *o*-benzenedisulfonimide was added (30 mol-%) and the reaction mixture was stirred in an open air vessel at 80 °C until TLC analyses showed no further reaction progress. The crude reaction mixture was treated with CH_2Cl_2/H_2O (1:1, 20 mL) and the aqueous phase extracted with CH_2Cl_2 (20 mL); combined organic extracts were dried with anhydrous Na_2CO_3. Evaporation of the solvent afforded the crude products, which were purified by flash chromatography.

(±)-1,2-Dihydro-7-(4-methoxyphenyl)-1,4-dimethylcyclopenta[*b*]-indol-3(4*H*)-one (22a): Compound **22a** (61 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1% Et_3N, R_f = 0.32, brown spot with *p*-anisaldehyde stain), as an orange waxy solid in 50% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.48 (m, 2 H), 7.30 (d, J = 8.8 Hz, 2 H), 6.91 (d, J = 8.8 Hz, 2 H), 3.82 (t, 3 H), 3.77 (t, 3 H), 3.51–3.49 (m, 1 H), 3.15 (dd, J = 18.0, 5.9 Hz, 1 H), 2.45 (dd, J = 18.0 Hz, 1 H, 1.8 Hz), 1.41 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.1 (s), 158.7 (s), 149.3 (s), 143.9 (s), 138.5 (s), 134.0 (s), 133.3 (s), 128.1 (d, 2 C), 126.2 (d), 122.9 (s), 119.3 (d), 114.1 (d, 2 C), 111.0 (d), 55.2 (q), 50.5 (q), 30.0 (t), 27.9 (d), 20.9 (q) ppm. $C_{20}H_{19}NO_2$ (305.14): calcd. C 78.66, H 6.27, N 4.59; found C 78.75, H 6.32, N 4.63.

(±)-7-[4-(Dimethylamino)phenyl]-1,2-dihydro-1,4-dimethylcyclopenta[*b*]indol-3(4*H*)-one (22b): Compound **22b** (117 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1% Et_3N, R_f = 0.60, brown spot with *p*-anisaldehyde stain), as an orange waxy solid in 55% yield ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18 (m, 7 H) 3.86 (s, 3 H), 3.51–3.49 (m, 1 H), 3.17 (dd, J = 18.2, 6.2 Hz, 1 H), 2.95 (s, 6 H), 2.48 (dd, J = 18.2, 2 Hz, 1 H), 1.44 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.1 (s), 149.6 (s), 149.3 (s), 143.7 (s), 138.3 (s), 133.8 (s) 129.5 (s), 127.7 (d, 2 C), 126.1 (d), 122.9 (s), 118.6 (d), 112.8 (d, 2 C), 111.0 (d), 503.5 (t), 40.5 (q, 2 C), 29.9 (d), 27.9 (q), 20.9 (q) ppm. $C_{21}H_{22}N_2O$ (318.17): calcd. C 79.21, H 6.96, N 8.80; found C 79.25, H 6.88, N 8.58.

(±)-1,2-Dihydro-1,4-dimethyl-7-(thiophen-2-yl)cyclopenta[*b*]indol-3(4*H*)-one (22c): Compound **22c** (139 mg) was obtained after chromatography (CH_2Cl_2, 1% Et_3N, R_f 0.30, blue spot with *p*-anisaldehyde stain), as an orange waxy solid in 30% yield ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.58 (d, J = 13.8 Hz, 1 H), 7.24–7.19 (m, 3 H), 7.06–7.01 (m, 1 H), 3.83 (s, 3 H), 3.48–3.46 (m, 1 H), 3.15 (dd, J = 18.4, 6.2 Hz, 1 H), 2.47 (dd, J = 18.4, 2.0 Hz), 1.44 (d, J = 7 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.1 (s), 149.2 (s), 144.8 (s), 144.1 (s), 138.7 (s), 127.8 (d), 126.9 (d), 125.4 (d), 124.0 (d), 122.7 (s), 122.4 (s), 118.7 (d), 111.2 (d), 50.4 (t), 30.0 (q), 27.9 (d), 20.9 (q) ppm. $C_{17}H_{15}NOS$ (281.09): calcd. C 72.57, H 5.37, N 4.98; found C 72.05, H 5.27, N 4.60.

(±)-1,2-Dihydro-7-(2-methoxynaphthalen-6-yl)-1,4-dimethylcyclopenta[*b*]indol-3(4*H*)-one (22d): Compound **22d** (76 mg) was obtained after chromatography (petroleum ether/EtOAc, 9:1, 1% Et_3N, R_f = 0.20, brown spot with *p*-anisaldehyde stain), as an orange waxy solid in 40% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.98 (s, 2 H), 7.75–7.69 (m, 4 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.20–7.11 (m, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.51–3.49 (m, 1 H), 3.19 (dd, J = 18.2, 6.2 Hz, 1 H), 2.51 (dd, J = 18.2, 1.8 Hz, 1 H), 1.47 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.2 (s), 157.5 (s), 149.4 (s), 144.1 (s), 138.6 (s), 136.6 (s), 133.6 (s), 133.3 (s), 129.4 (d), 129.1 (s), 127.1 (d), 126.5 (d), 126.2 (d), 125.3 (d), 122.9 (s), 119.9 (d), 119.0 (d), 111.2 (d), 105.4 (d), 55.2 (q), 50.5 (t), 30.0 (q), 27.9 (d), 21.0 (q) ppm. $C_{24}H_{21}NO_2$ (355.16): calcd. C 81.10, H 5.96, N 3.94; found C 81.35, H 5.42, N 3.83.

(±)-7-Bromo-1,2-dihydro-1,4-dimethylcyclopenta[*b*]indol-3(4*H*)-one (26): Compound **26** (140 mg) was obtained after chromatography (CH_2Cl_2, 1% Et_3N, R_f 0.20, brown spot with *p*-anisaldehyde stain), as brown oil in 22% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.77 (s, 1 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.16 (d, J = J = 8.8 Hz, 1 H), 3.80 (s, 3 H), 3.48–3.32 (m, 1 H), 3.13 (dd, J = 18.4, 6.2 Hz), 2.45 (dd, J = 18.4, 2.0 Hz), 1.38 (d, J = 7 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.1 (s), 147.8 (s), 143.1 (s), 138.8 (s), 129.1 (d), 124.1 (d), 113.2 (s), 112.4 (d), 50.4 (t), 30.0 (s), 27.8 (d), 20.8 (q) ppm.

2-(2,3-Dihydrothieno[3,4-*b*][1,4]dioxin-7-yl)-5,5-dimethyl-1,3,2-dioxaborinane: A solution of 3,4-ethylenedioxythiophene (1.14 g, 8 mmol) in dry THF (20 mL), was cooled to –78 °C under N_2 and treated with 1.6 M solution of *n*BuLi (5.5 mL). The temperature was slowly raised to 0 °C and the mixture was stirred at the same temperature for 20 min. The reaction mixture was recooled to –78 °C and treated with triisopropyl borate (3 g, 16 mmol) and stirred for 2.5 h, then NH_4Cl was added and the crude product was extracted into (3 × 20 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude product was dissolved in anhydrous toluene (30 mL) and 2,2-dimethyl-1,3-propanediol (0.83 g, 8 mmol) was added under N_2. The mixture was stirred at room temp. overnight, washed with water (30 mL), extracted with Et_2O (3 × 30 mL) and dried with anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the product was obtained as a white solid 1.94 g (95%). ^{1}H NMR (200 MHz,

$CDCl_3$): δ = 7.20 (s, 1 H), 4.20 (s, 4 H), 3.87 (s, 4 H), 1.12 (s, 6 H) ppm.

1,2-Dihydro-7-(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-7-yl)-1,4-dimethylcyclopenta[*b*]indol-3(4*H*)-one (27): Prepared as reported for compounds **22**. Starting from **26** (140 mg, 0.50 mmol), compound **27** (65 mg) was obtained after chromatography (CH_2Cl_2, 1% Et_3N, R_f = 0.18, blue spot with *p*-anisaldehyde stain) as a yellow waxy solid in 38% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.70 (d, J = 8.8 Hz, 1 H), 7.27 (d, J = 8.8 Hz, 1 H), 6.22 (s, 1 H), 4.28–4.19 (m, 4 H), 3.83 (s, 3 H), 3.55–3.43 (m, 1 H), 3.15 (dd, J = 18.4, 6.2 Hz), 2.46 (dd, J = 18.4, 2.8 Hz), 1.42 (d, J = 7 Hz) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 194.1 (s), 149.3 (s), 143.6 (s), 142.1 (s), 138.5 (s), 137.2 (s), 125.6 (d), 125.4 (s), 122.6 (s), 119.0 (d), 117.7 (s), 110.9 (d), 96.6 (d), 64.6 (t), 64.3 (t), 50.4 (t), 29.9 (d), 27.9 (q), 25.4 (q) ppm. $C_{19}H_{17}NO_3S$ (339.09): calcd. C 67.24, H 5.05, N 4.13; found C 67.37, H 5.49, N 4.63.

(2*E*)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-1,2-dihydro-7-(4-methoxyphenyl)-1,4-dimethylcyclopenta[*b*]indol-3(4*H*)-one (23a): Prepared as reported for compound **5**. Starting from **22a** (61 mg, 0.20 mmol), compound **23a** (34 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, 1% Et_3N, R_f = 0.40, orange spot with *p*-anisaldehyde stain) as a yellow solid in 40% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.55 (d, J = 8.78 Hz, 3 H), 7.34 (m, 2 H), 6.93 (d, J = 8.78 Hz, 3 H), 6.15 (s, 1 H), 3.92–4.05 (m, 1 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 1.98 (s, 3 H), 1.48 (two d superimposed, J = 6.75 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.6 (s), 170.4 (s), 158.6 (s), 145.9 (s), 143.5 (d), 142.9 (d), 141.2 (s), 139.9 (s), 135.5 (s), 134.0 (s), 129.4 (s), 129.3 (s), 128.1, 102 (d, 2 C), 126.12 (d), 122.5 (s), 119.1 (d), 114.0 (d, 2 C), 111.0 (d), 100.6 (d), 55.2 (q), 30.6 (d), 30.2 (q), 18.4 (q), 10.6 (q) ppm. MS (ESI): m/z (%) = 430 (71) $[M + H]^+$, 359 (77), 214 (100). $C_{26}H_{23}NO_5$ (429.16): calcd. C 72.71, H 5.42, N 3.42; found C 72.88, H 5.94, N 3.80.

(2*E*)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-7-[4-(dimethylamino)phenyl]-1,2-dihydro-1,4-dimethylcyclopenta[*b*]-indol-3(4*H*)-one (23b): Prepared as reported for compound **5**. Starting from **22b** (117 mg, 0.37 mmol), compound **23b** (49 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, 1% Et_3N, R_f = 0.42, orange spot with *p*-anisaldehyde stain) as a yellow solid in 30% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.59–6.76 (m, 3 H), 7.48 (d, J = 8.9 Hz, 2 H), 7.31 (s, 1 H), 6.92 (br. s, 1 H), 6.78 (d, J = 8.9 Hz, 2 H), 6.14 (br. s, 1 H), 4.04–3.90 (m, 1 H), 3.91 (s, 3 H), 2.95 (s, 6 H), 1.99 (s, 3 H), 1.49 (2d superimposed, J = 3.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.6 (s), 170.4 (s), 149.5 (s), 145.8 (d), 143.4 (s), 142.9 (s), 141.2 (d), 139.8 (s), 135.5 (s), 134.0 (s), 129.6 (s), 129.5 (s), 127.7 (d, 2 C), 126.1 (d), 122.5 (s), 118.5 (d), 112.7 (d, 2 C), 110.9 (d), 100.5 (d), 40.5 (q, 2 C), 30.6 (d), 30.2 (q), 18.4 (q), 10.6 (q) ppm. MS/MS (ESI): m/z (%) = 443 (11) $[M + H]^+$, 415 (38), 346 (100), 317 (52), 302 (28). $C_{27}H_{26}N_2O_4$ (442.19): calcd. C 76.66, H 6.81, N 10.52; found C 76.58, H 6.84, N 10.70.

(2*E*)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-1,2-dihydro-1,4-dimethyl-7-(thiophen-2-yl)cyclopenta[*b*]indol-3(4*H*)-one (23c): Prepared as reported for compound **5**. Starting from **22c** (139 mg, 0.49 mmol), compound **23c** (69 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, 1% Et_3N, R_f = 0.30, orange spot with *p*-anisaldehyde stain) as a yellow solid in 50% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.60 (d, J = 8.6 Hz, 1 H), 7.32–7.15 (m, 4 H), 7.06–6.97 (m, 2 H), 6.92 (s, 1 H), 6.14 (s, 1 H), 4.04–3.97 (m, 1 H), 3.93 (s, 3 H), 1.91 (s, 3 H), 1.49 (two d superimposed, J = 7.00 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.6 (s), 170.5 (s), 146.2 (s), 144.7 (s), 143.7 (s), 142.8 (s), 141.3 (s), 140.2 (s), 135.4 (s), 129.3 (d), 127.9 (d), 127.1 (d), 125.3 (d), 124.0 (s), 122.5 (d), 118.4 (d), 111.2 (d), 100.6 (d), 30.6 (d), 30.1 (q), 18.6 (q), 10.6 (q) ppm. MS/MS (ESI): m/z (%) = 406 (5) $[M + H]^+$, 360 (4), 309 (100). $C_{23}H_{19}NO_4S$ (405.10): calcd. C 68.13, H 4.72, N 3.45; found C 68.25, H 4.47, N 3.61.

(2*E*)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-1,2-dihydro-7-(2-methoxynaphthalen-6-yl)-1,4-dimethylcyclopenta[*b*]-indol-3(4*H*)-one (23d): Prepared as reported for compound **5**. Starting from **22d** (76 mg, 0.21 mmol), compound **23d** (30 mg) was obtained after chromatography (petroleum ether/EtOAc, 6:4, 1% Et_3N, R_f = 0.36, orange spot with *p*-anisaldehyde stain) as a yellow solid in 30% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.94–7.90 (m, 2 H), 7.79–7.63 (m, 4 H), 7.42–7.35 (m, 2 H), 7.12–7.11 (m, 2 H), 6.93 (s, 1 H), 6.14 (s, 1 H), 4.08–4.10 (m, 1 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 1.99 (s, 3 H), 1.52 (two d superimposed, J = 7.99 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.7 (s), 170.4 (s), 167.6 (s), 157.4 (s), 146.0 (d), 143.7 (s), 143.0 (s), 141.1 (d), 140.05 (s), 136.6 (s), 135.4 (s), 133.8 (s), 130.7 (d), 129.4 (d), 129.3 (s), 129.0 (s), 128.6 (d), 127.1 (d), 126.2 (d), 125.4 (d), 122.6 (s), 119.8 (d), 119.1 (d), 111.2 (d), 105.4 (d), 100.6 (d), 55.2 (q), 30.3 (d), 30.1 (q), 18.6 (q) ppm. MS (ESI): m/z (%) = 981 (100) $[2M + Na]^+$, 480 (29) $[M + H]^+$. $C_{30}H_{25}NO_5$ (479.17): calcd. C 75.14, H 5.25, N 2.92; found C 74.88, H 5.30, N 3.02.

(2*E*)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-1,2-dihydro-7-(2,3-dihydrothieno[3,4-*b*][1,4]dioxin-7-yl)-1,4-dimethylcyclopenta[*b*]indol-3(4*H*)-one (28): Prepared as reported for compound **5**. Starting from **27** (65 mg, 0.19 mmol), compound **28** (50 mg) was obtained after chromatography (petroleum ether/EtOAc, 6:4, 1% Et_3N, R_f = 0.16, grey spot with *p*-anisaldehyde stain) as an orange solid in 56% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.69 (d, J = 10.4 Hz, 1 H), 7.32–7.25 (m, 2 H), 6.91 (s, 1 H), 6.22 (s, 1 H), 6.13 (s, 1 H), 4.28–4.19 (m, 4 H), 4.04–3.94 (m, 1 H), 3.88 (s, 3 H), 1.98 (s, 3 H), 1.20 (2d superimposed, J = 4.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 182.6 (s), 170.4 (s), 145.9 (s), 143.2 (s), 143.0 (s), 142.1 (s), 141.2 (s), 140.0 (s), 137.2 (s), 135.5 (s), 135.4 (s), 129.5 (d), 125.6 (d), 122.2 (d), 118.8 (s), 117.6 (d), 110.9 (d), 100.6 (d), 96.7 (d), 64.6 (t), 64.3 (t), 30.6 (d), 30.1 (q), 18.5 (q), 10.6 (q) ppm. MS/MS (ESI): m/z (%) = 464 (6) $[M + H]^+$, 436 (12), 366 (100), 323 (11). $C_{25}H_{21}NO_6S$ (463.11): calcd. C 64.80, H 4.58, N 3.04; found C 64.85, H 4.62, N 3.37.

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