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# UNIVERSITÀ DEGLI STUDI DI TORINO

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

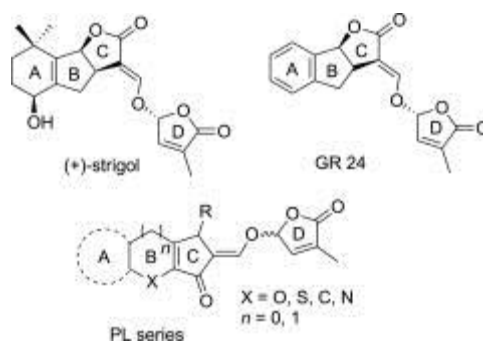
Cristina Prandi, Ernesto G. Occhiato, Silvia Tabasso, Paola Bonfante, Mara Novero, Dina Scarpi,  
Maria Elena Bova, Ivana Miletto

**Abstract:** 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.<sup>1-5</sup> 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.<sup>6-8</sup> 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.<sup>9-13</sup> In addition to these functions in the rhizosphere, it has recently been shown that SLs represent a new class of plant hormones that inhibit shoot branching.<sup>14-18</sup> Extensive structure-activity relationship studies have been conducted both for natural and synthetic SLs analogues.<sup>7,19-26</sup> 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.<sup>9</sup> 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.<sup>27-30</sup> 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 bioactive part is an  $\alpha,\beta$ -unsaturated ketone instead of the more common  $\alpha,\beta$ -unsaturated lactone. All of these new molecules showed remarkable activity in *Orobanche aegyptiaca* seed germination tests.<sup>31</sup> 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 analogues 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*.

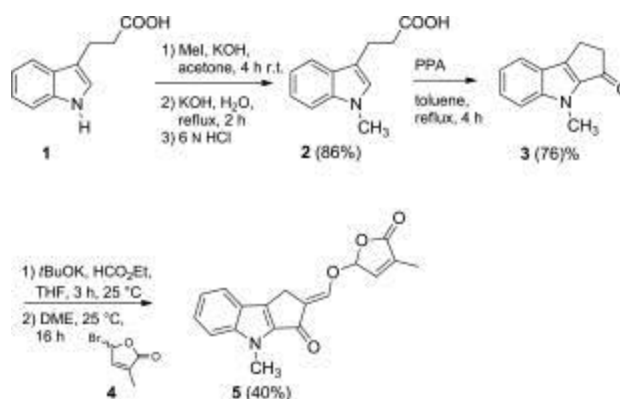


**Figure. 1** Natural strigol, synthetic GR 24 and synthetic PL series.

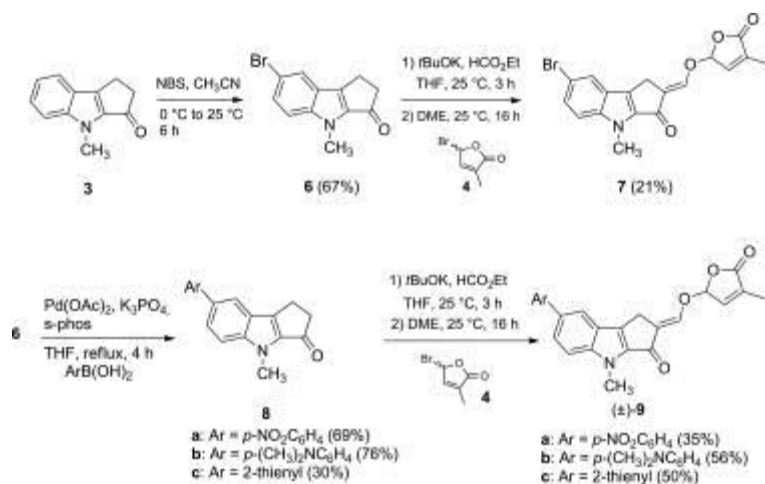
## RESULTS AND DISCUSSION

### Synthesis

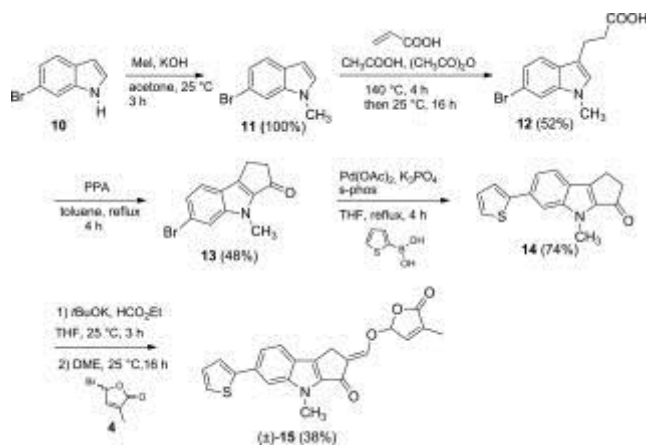
In our previous work,<sup>31</sup> nitrogen-derived SL analogues showed the most promising fluorescent properties associated with a remarkable biological activity. We then decided to focus our efforts on the synthesis of highly conjugated nitrogen derivatives with different patterns of substitution on 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.<sup>32</sup> 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.



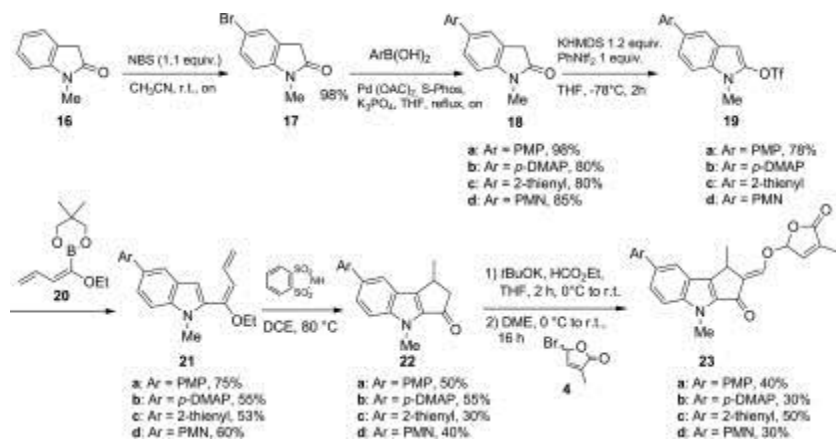
**Scheme 1** Synthesis of unsubstituted EGO 5.



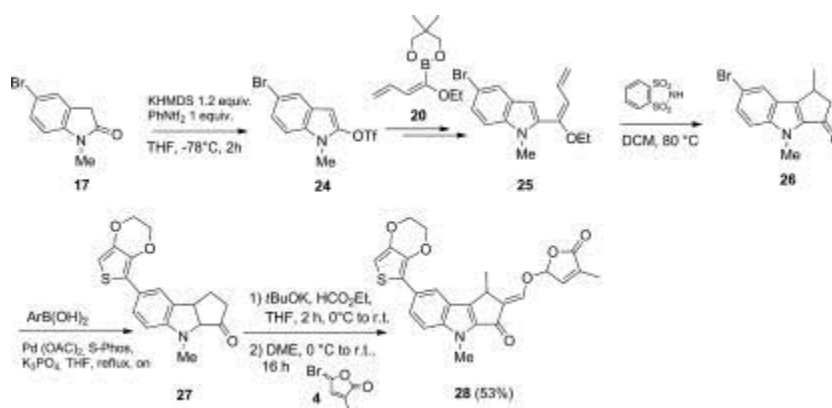
**Scheme 2** Synthesis of 7-functionalized EGO molecules 7, 9a–c.



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



**Scheme 4** Synthesis of the ST derivatives.



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

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*-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.<sup>31</sup> 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(4H)-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.<sup>33</sup> 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.

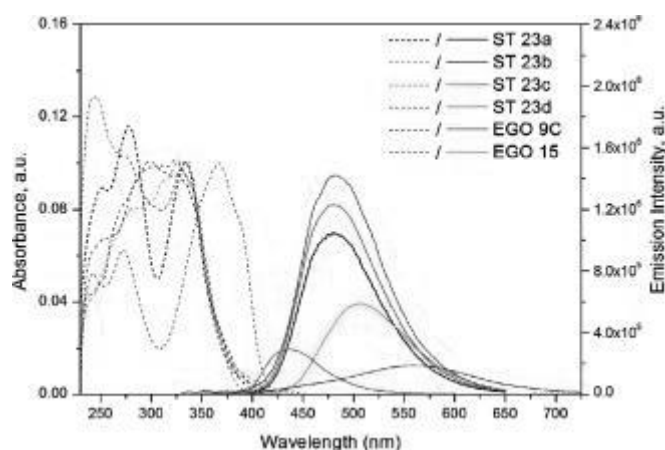
The ST series of molecules was synthesized according to a more versatile synthetic plan which, in principle, allows the introduction of substituents on the C ring. In this case all SL analogues were isolated as diastereomeric mixtures. Commercially available 1-methylindolin-2-one 16 (Scheme 4) was selectively 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*-phenyltriflimide, 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,<sup>34</sup> and finally coupled with bromobutenolide 4 under the usual conditions.<sup>31</sup>

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(4H)-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 of the ST 23a–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  $\lambda_{\text{ex}}$ . 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.





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

Entry	Sample	$\lambda_{\text{ex}}/\text{nm}$	$\lambda_{\text{em}}/\text{nm}$	$\Phi_f^{[a]}$	$\tau_1/\text{ns}$	$\tau_2/\text{ns}$
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 ( $\Phi_f$ ) were determined at 25 °C using anthracene as the standard, upon selection of  $\lambda_{\text{ex}}$  and  $\lambda_{\text{em}}$  and the excitation and emission wavelengths.

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

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  $\lambda_{\text{ex}}$ . 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).

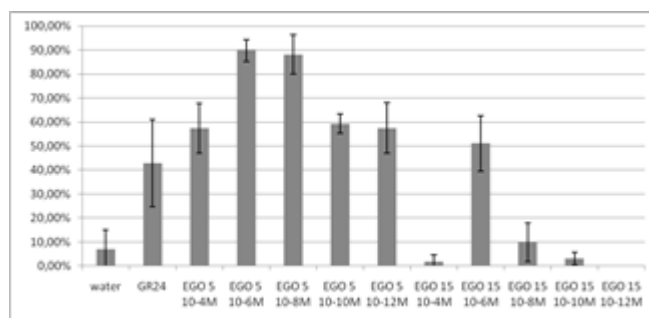
The corresponding 6-substituted EGO derivative (EGO 15) was characterized by an absorption band different in both shape and position, with a maximum at 365 nm, which was the wavelength chosen as the  $\lambda_{\text{ex}}$ . The emission band was found to be only 72 nm red-shifted, being centered at 437 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

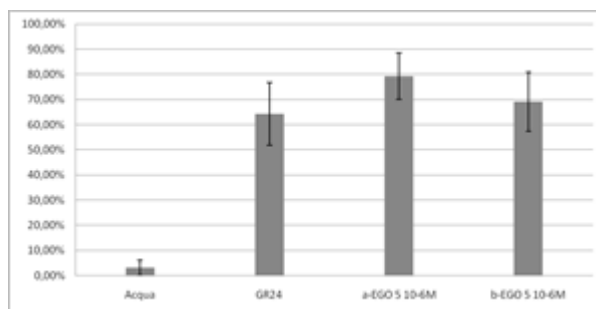
Bioassays were carried out according to the standard procedures (see Exp. Section). Water and acetone were used as negative controls and a diastereomeric mixture of GR 24 ( $10^{-7}$ M) served as a positive control. The results obtained with the EGO 5 and 15, both as racemic mixtures, are represented as a bar graph in Figure 3. The bioassays revealed that racemic 5 had remarkable activity in stimulating the germination of *Orobanchae* 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 *Orobanchae aegyptiaca* after exposure to various concentrations of racemic EGO series members 5 and 15.

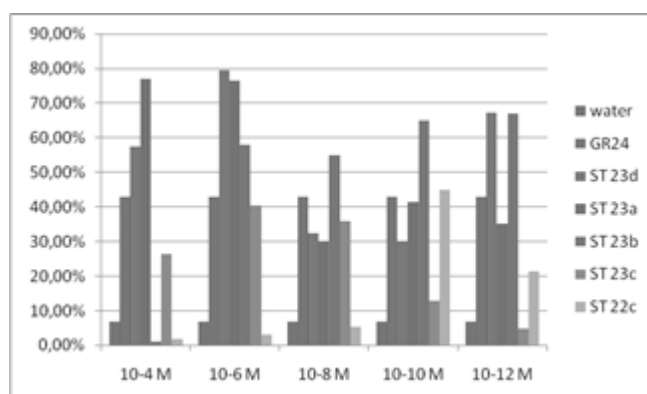
On the basis of literature data indicating that enantiomers with the same configuration at C2' of the D ring as the natural strigol are more biologically active, we separated the racemic mixtures of EGO 5 by semipreparative chiral HPLC and tested each optically pure enantiomer in seed germination bioassays. 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.

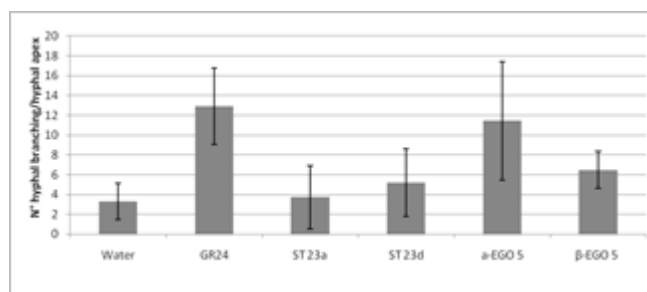
The ST series of molecules, whose main differentiating feature with respect to the EGO series is the substituent on C1 of the ABC nucleus were tested in similar assays of seed germination. The results are represented as a bar chart in Figure 5. Compounds 23d (Ar = 6-methoxy-2-naphthyl) and 23a (Ar = *p*-methoxyphenyl) showed stimulant activity on germination at 10<sup>-6</sup>M (23a and 23d) and at 10<sup>-4</sup>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<sup>-6</sup>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,<sup>35</sup> as well as the D ring itself<sup>9</sup> 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.

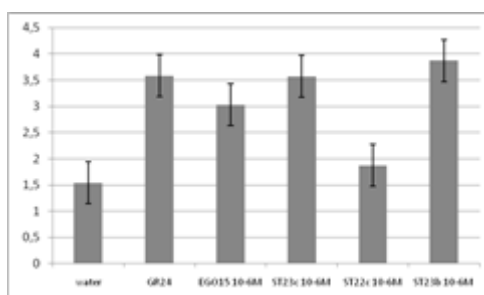
As can be deduced from the bar chart reported in Figure 5, a remarkable activity, statistically comparable to GR 24, has been observed at  $10^{-10}$ M. This result seems to confirm that, lacking specific information about the receptor active site, further structure-activity investigations are required 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 *Orobanch*e, 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 *Orobanch*e. Remarkably and in disagreement 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.



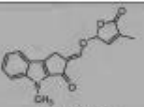
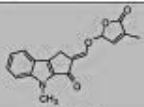
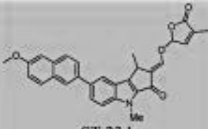
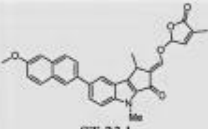
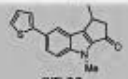
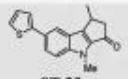
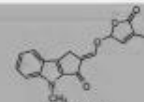
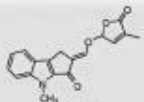
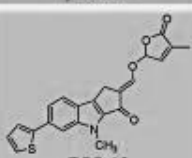
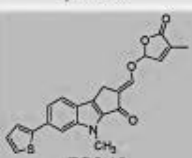
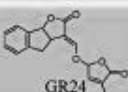
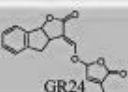
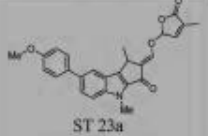
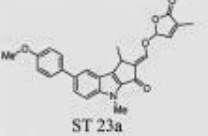
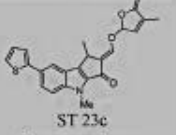
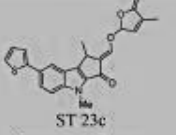
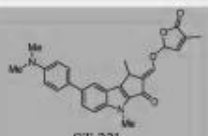
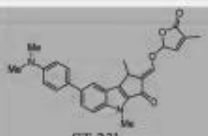
**Figure 7** Bar graph representation of percentages of hyphal branching of *Gigaspora margarita* after exposure to diastereomeric mixtures of EGO 15, ST series members 22c, and 23b,c.

These data confirm the results of Akiyama and co-workers<sup>9</sup> 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 can, in principle, allow the introduction of various functional groups in different positions of the ABC nucleus. All new molecules have been tested on *Orobanchae 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.

Seeds	Fungi
Strong	Moderate
 $\alpha$ -EGO 5	 $\alpha$ -EGO 5
 ST 23d $\lambda_{\text{cat}} = 480 \text{ nm}$ , $\Phi_f = 0.12$	 ST 23d $\lambda_{\text{cat}} = 480 \text{ nm}$ , $\Phi_f = 0.12$
 ST 22c	 ST 22c
 $\beta$ -EGO 5	 $\beta$ -EGO 5
 EGO-15 $\lambda_{\text{cat}} = 437 \text{ nm}$ , $\Phi_f = 0.02$	 EGO 15 $\lambda_{\text{cat}} = 437 \text{ nm}$ , $\Phi_f = 0.02$
 GR24	 GR24
 ST 23a $\lambda_{\text{cat}} = 480 \text{ nm}$ , $\Phi_f = 0.10$	 ST 23a $\lambda_{\text{cat}} = 480 \text{ nm}$ , $\Phi_f = 0.10$
 ST 23c $\lambda_{\text{cat}} = 506 \text{ nm}$ , $\Phi_f = 0.06$	 ST 23c $\lambda_{\text{cat}} = 506 \text{ nm}$ , $\Phi_f = 0.06$
 ST 23b $\lambda_{\text{cat}} = 560 \text{ nm}$ , $\Phi_f = 0.03$	 ST 23b $\lambda_{\text{cat}} = 560 \text{ nm}$ , $\Phi_f = 0.03$

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

## 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  $^1\text{H}$  NMR

spectra and NOESY 2D experiments were recorded at 200 and 400 MHz and  $^{13}\text{C}$  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 ( $\Phi$  10  $\times$  250 mm, Daicel, Osaka, Japan) employing an isocratic elution with  $\text{CH}_2\text{Cl}_2$  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 *Orobanchae 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.<sup>31</sup> 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 from 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  $\text{MgSO}_4$ . 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):**<sup>36</sup> 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.<sup>1</sup> <sup>1</sup>H NMR (400 MHz, [D<sub>6</sub>]DMSO):  $\delta$  = 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<sub>3</sub>PO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> (4 × 80 mL). The combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvents evaporated. The residue was chromatographed (*n*-hexane/EtOAc, 3:1, *R<sub>f</sub>* = 0.38) to afford compound 3 (0.63 g) as a solid in 76 % yield. Analytical and spectroscopic data as reported;<sup>1</sup> m.p. 135.1–136.1 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 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. <sup>13</sup>C NMR (100.4 MHz, CDCl<sub>3</sub>):  $\delta$  = 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]<sup>+</sup>, 157 (53), 142 (13).

**(±)4-Methyl-2-(4-methyl-5-oxo-2,5-dihydrofuran-2-ylloxymethylene)-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  $\text{NH}_4\text{Cl}$  aqueous solution (15 mL). The mixture was extracted with  $\text{Et}_2\text{O}$  ( $5 \times 10$  mL), the combined organic layers washed with brine ( $2 \times 15$  mL) and dried with  $\text{K}_2\text{CO}_3$ . After filtration and evaporation of the solvent, chromatography (*n*-hexane/ $\text{EtOAc}$ , 1:1, 1 %  $\text{Et}_3\text{N}$ ,  $R_f = 0.39$ ) gave compound 5 (136 mg) as a solid in 40 % yield; m.p. 176.2–176.8 °C (dec).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.66$  (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.  $^{13}\text{C}$  NMR (100.4 MHz,  $\text{CDCl}_3$ ):  $\delta = 184.8$  (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) [ $\text{M} + \text{H}$ ] $^+$ , 264 (81), 213 (100).  $\text{C}_{18}\text{H}_{15}\text{NO}_4$  (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-2H-cyclopenta[*b*]indol-3-one (6):** To a solution of 3 (0.10 g, 0.54 mmol) in anhydrous  $\text{CH}_3\text{CN}$  (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/ $\text{EtOAc}$ , 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  $\text{H}_2\text{O}$  (15 mL), extracted with  $\text{Et}_2\text{O}$  ( $4 \times 15$  mL) and the combined organic layers dried with  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent, chromatography (*n*-hexane/ $\text{EtOAc}$ , 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.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.82$  (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.  $^{13}\text{C}$  NMR (100.4 MHz,  $\text{CDCl}_3$ ):  $\delta = 194.4$  (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) [ $\text{M} + \text{H}$ ] $^+$ , 151(27).  $\text{C}_{12}\text{H}_{10}\text{BrNO}$  (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-2H-cyclopenta[*b*]indol-3-one (7):** Prepared as reported for compound 5. Starting from 7-bromo-4-methyl-1,4-dihydro-2H-cyclopenta[*b*]indol-3-one 6 (158 mg, 0.6 mmol), compound 7 (48 mg) was obtained after chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 30:1, 1 %  $\text{Et}_3\text{N}$ ,  $R_f = 0.41$ ) as a solid in 21 % yield; m.p. 167.1–180.0 °C (dec).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.80$  (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.  $^{13}\text{C}$  NMR (100.4 MHz,  $\text{CDCl}_3$ ):  $\delta = 183.0$  (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-2H-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.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 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,  $CDCl_3$ ):  $\delta$  = 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-2H-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.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 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,  $[D_6]DMSO$ ):  $\delta$  = 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-2H-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.  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 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,  $CDCl_3$ ):  $\delta$  = 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) [ $M + H$ ]<sup>+</sup>, 290 (100). C<sub>20</sub>H<sub>20</sub>N<sub>2</sub>O (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-2H-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<sub>2</sub>Cl<sub>2</sub>/MeOH, 40:1, 1 % Et<sub>3</sub>N, R<sub>f</sub> = 0.43, wine-colored spot with *p*-anisaldehyde stain) as a solid in 56 % yield; m.p. 202.7 °C (dec). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (100.4 MHz, CDCl<sub>3</sub>): 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) [ $M^+ + H$ ]<sup>+</sup>, 414 (17), 401 (31), 332 (100), 303 (18). C<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub> (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(4H)-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<sub>f</sub> = 0.48, blue spot with *p*-anisaldehyde stain) as a yellow oil in 80 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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<sub>16</sub>H<sub>15</sub>NOS (269.09): calcd. C 71.34, H 5.61, N 5.20; found C 72.06, H 5.83, N 5.88.

**(±)(2E)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-1,2-dihydro-4-methyl-7-(thiophen-2-yl)cyclopenta[*b*]indol-3(4H)-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<sub>3</sub>N, R<sub>f</sub> = 0.20, grey spot with *p*-anisaldehyde stain) as a solid in 24 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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) [ $M + H$ ]<sup>+</sup>, 374 (4), 346 (10), 330 (7), 295 (100). C<sub>22</sub>H<sub>17</sub>NO<sub>4</sub>S (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-1H-indole (11):**<sup>37</sup> 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<sub>2</sub>O (20 mL). The aqueous phase was extracted with Et<sub>2</sub>O (4 × 20 mL) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>. 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.<sup>2</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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-1H-indol-3-yl)propionic Acid (12):**<sup>38</sup> 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<sub>2</sub>O (10 mL), the organic phase was extracted with Et<sub>2</sub>O (5 × 10 mL) and the combined organic layers were dried with Na<sub>2</sub>SO<sub>4</sub>. After filtration and evaporation of the solvent, chromatography (*n*-hexane/EtOAc, 4:1, R<sub>f</sub> = 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. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (100.4 MHz, CDCl<sub>3</sub>): 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]<sup>+</sup>, 264 (13), 222 (100), 203 (32). C<sub>12</sub>H<sub>12</sub>BrNO<sub>2</sub> (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-2H-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<sub>f</sub> = 0.36) as a solid in 48 % yield; m.p. 161.7–163.2 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (100.4 MHz, CDCl<sub>3</sub>): 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]<sup>+</sup>, 222 (100). C<sub>12</sub>H<sub>10</sub>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-2H-cyclopenta[*b*]indol-3-one (14):** Prepared as reported for compound 8 but by using 10 mol-% of Pd(OAc)<sub>2</sub>. 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<sub>f</sub> = 0.25, blue, then green spot with *p*-anisaldehyde stain) as a solid in 74 % yield; m.p. 161.8–163.9 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 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.  $^{13}\text{C}$  NMR (100.4 MHz,  $\text{CDCl}_3$ ):  $\delta = 194.4$  (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)  $[\text{M} + \text{H}]^+$ , 253 (11), 226 (100).  $\text{C}_{16}\text{H}_{13}\text{NOS}$  (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-2H-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 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$ , 80:1, 1 %  $\text{Et}_3\text{N}$ ,  $R_f = 0.27$ , blue spot with *p*-anisaldehyde stain) as a solid in 38 % yield; m.p. 189.7–192.8 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.65$  (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.  $^{13}\text{C}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta = 182.5$  (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)  $[\text{M} + \text{H}]^+$ , 295 (100).  $\text{C}_{22}\text{H}_{17}\text{NO}_4\text{S}$  (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  $\text{CH}_3\text{CN}$  at 0 °C. The reaction mixture was then brought to room temp. and left stirring overnight.  $\text{Et}_2\text{O}$  was added to the solution and it was washed with water. The aqueous phase was extracted three times with  $\text{Et}_2\text{O}$  (20 mL). The combined organic phases were dried with  $\text{Na}_2\text{SO}_4$  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.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.29$  (m, 2 H), 6.63 (d,  $J = 8.2$  Hz, 1 H), 3.46 (s, 2 H), 3.13 (s, 3 H) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 174.1$  (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.  $\text{C}_9\text{H}_8\text{BrNO}$  (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  $\text{Pd}_2\text{OAc}_2$  (5 %), S-Phos (10 %),  $\text{K}_3\text{PO}_4$  (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  $\text{Et}_2\text{O}$  (3 × 20 mL), and dried with anhydrous  $\text{K}_2\text{CO}_3$ . 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.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{16}\text{H}_{15}\text{NO}_2$  (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.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 6.96 (m, 7 H), 3.45 (s, 2 H), 3.12 (s, 3 H), 2.88 (s, 6 H) ppm.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$  (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.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{13}\text{H}_{11}\text{NOS}$  (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.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{20}\text{H}_{17}\text{NO}_2$  (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.<sup>39</sup>

**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,  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  (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  $\text{K}_2\text{CO}_3$  solution (1 mL) were added. The mixture was stirred for 3 h at room temp.  $\text{H}_2\text{O}$  (25 mL) was then added, the mixture extracted with  $\text{Et}_2\text{O}$  (3 x 20 mL) and dried with anhydrous  $\text{Na}_2\text{CO}_3$ . 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-1H-indole (21a):** Compound 21a (405 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1 %  $\text{Et}_3\text{N}$ ,  $R_f$  = 0.7, brown spot with *p*-anisaldehyde stain) as a yellow oil in 75 % yield.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.71 (s, 1 H), 7.51 (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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{22}\text{H}_{23}\text{NO}_2$  (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-1H-indol-5-yl}-N,N-dimethylbenzenamine (21b):** Compound 21b (191 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1 %  $\text{Et}_3\text{N}$ ,  $R_f$  = 0.6, brown spot with *p*-anisaldehyde stain), as a yellow oil in 55 % yield.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}$  (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)-1H-indole (21c):** Compound 21c (243 mg) was obtained after chromatography (petroleum ether/EtOAc, 7:3, 1 %  $\text{Et}_3\text{N}$ ,  $R_f$  = 0.50, blue spot with *p*-anisaldehyde stain), as a yellow oil in 53 % yield.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{19}\text{H}_{19}\text{NOS}$  (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-1H-indole (21d):**

Compound 21d (384 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1 % Et<sub>3</sub>N, R<sub>f</sub> = 0.65, brown spot with *p*-anisaldehyde stain), as a yellow oil in 60 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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<sub>26</sub>H<sub>25</sub>NO<sub>2</sub> (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-1H-indole (25):** Compound 25 (700 mg) was obtained after chromatography (petroleum ether/EtOAc, 9:1, 1 % Et<sub>3</sub>N, R<sub>f</sub> = 0.43, brown spot with *p*-anisaldehyde stain), as a yellow oil in 77 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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<sub>15</sub>H<sub>16</sub>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<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (1:1, 20 mL) and the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL); combined organic extracts were dried with anhydrous Na<sub>2</sub>CO<sub>3</sub>. 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(4H)-one (22a):**

Compound 22a (61 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1 % Et<sub>3</sub>N, R<sub>f</sub> = 0.32, brown spot with *p*-anisaldehyde stain), as an orange waxy solid in 50 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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<sub>20</sub>H<sub>19</sub>NO<sub>2</sub> (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(4H)-one (22b):**

Compound 22b (117 mg) was obtained after chromatography (petroleum ether/EtOAc, 8:2, 1 % Et<sub>3</sub>N, R<sub>f</sub> = 0.60, brown spot with *p*-anisaldehyde stain), as an orange waxy solid in 55 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O (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(4H)-one (22c):**

Compound 22c (139 mg) was obtained after chromatography (CH<sub>2</sub>Cl<sub>2</sub>, 1 % c12, R<sub>f</sub> 0.30, blue spot with *p*-anisaldehyde stain), as an orange waxy solid in 30 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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<sub>17</sub>H<sub>15</sub>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(4H)-one (22d):**

Compound 22d (76 mg) was obtained after chromatography (petroleum ether/EtOAc, 9:1, 1 % Et<sub>3</sub>N, R<sub>f</sub> = 0.20, brown spot with *p*-anisaldehyde stain), as an orange waxy solid in 40 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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<sub>24</sub>H<sub>21</sub>NO<sub>2</sub> (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(4H)-one (26):**

Compound 26 (140 mg) was obtained after chromatography (CH<sub>2</sub>Cl<sub>2</sub>, 1 % Et<sub>3</sub>N, R<sub>f</sub> 0.20, brown spot with *p*-anisaldehyde stain), as brown oil in 22 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ = 7.77 (s, 1 H), 7.39 (d, J = 8.8 Hz, 1 H), 7.16 (d, 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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  $-78^{\circ}\text{C}$  under  $\text{N}_2$  and treated with 1.6 M solution of *n*BuLi (5.5 mL). The temperature was slowly raised to  $0^{\circ}\text{C}$  and the mixture was stirred at the same temperature for 20 min. The reaction mixture was recooled to  $-78^{\circ}\text{C}$  and treated with triisopropyl borate (3 g, 16 mmol) and stirred for 2.5 h, then  $\text{NH}_4\text{Cl}$  was added and the crude product was extracted into ( $3 \times 20$  mL) and dried with anhydrous  $\text{Na}_2\text{SO}_4$ . 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  $\text{N}_2$ . The mixture was stirred at room temp. overnight, washed with water (30 mL), extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL) and dried with anhydrous  $\text{Na}_2\text{SO}_4$ . After filtration and evaporation of the solvent, the product was obtained as a white solid 1.94 g (95 %).  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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(4H)-one (27):** Prepared as reported for compounds 22. Starting from 26 (140 mg, 0.50 mmol), compound 27 (65 mg) was obtained after chromatography ( $\text{CH}_2\text{Cl}_2$ , 1 %  $\text{Et}_3\text{N}$ ,  $R_f$  = 0.18, blue spot with *p*-anisaldehyde stain) as a yellow waxy solid in 38 % yield.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $\text{C}_{19}\text{H}_{17}\text{NO}_3\text{S}$  (339.09): calcd. C 67.24, H 5.05, N 4.13; found C 67.37, H 5.49, N 4.63.

**(2E)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-1,2-dihydro-7-(4-methoxyphenyl)-1,4-dimethylcyclopenta[b]indol-3(4H)-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/ $\text{EtOAc}$ , 7:3, 1 %  $\text{Et}_3\text{N}$ ,  $R_f$  = 0.40, orange spot with *p*-anisaldehyde stain) as a yellow solid in 40 % yield.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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.  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 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)  $[\text{M} + \text{H}]^+$ , 359 (77), 214 (100).  $\text{C}_{26}\text{H}_{23}\text{NO}_5$  (429.16): calcd. C 72.71, H 5.42, N 3.42; found C 72.88, H 5.94, N 3.80.

**(2E)-2-[(2,5-Dihydro-4-methyl-5-oxofuran-2-yloxy)methylene]-7-[4-(dimethylamino)phenyl]-1,2-dihydro-1,4-dimethylcyclopenta[b]indol-3(4H)-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<sub>3</sub>N, R<sub>f</sub> = 0.42, orange spot with *p*-anisaldehyde stain) as a yellow solid in 30 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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]<sup>+</sup>, 415 (38), 346 (100), 317 (52), 302 (28). C<sub>27</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub> (442.19): calcd. C 76.66, H 6.81, N 10.52; found C 76.58, H 6.84, N 10.70.

**(2E)-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(4H)-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<sub>3</sub>N, R<sub>f</sub> = 0.30, orange spot with *p*-anisaldehyde stain) as a yellow solid in 50 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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]<sup>+</sup>, 360 (4), 309 (100). C<sub>23</sub>H<sub>19</sub>NO<sub>4</sub>S (405.10): calcd. C 68.13, H 4.72, N 3.45; found C 68.25, H 4.47, N 3.61.

**(2E)-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(4H)-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<sub>3</sub>N, R<sub>f</sub> = 0.36, orange spot with *p*-anisaldehyde stain) as a yellow solid in 30 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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]<sup>+</sup>, 480 (29) [M + H]<sup>+</sup>. C<sub>30</sub>H<sub>25</sub>NO<sub>5</sub> (479.17): calcd. C 75.14, H 5.25, N 2.92; found C 74.88, H 5.30, N 3.02.

**(2E)-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(4H)-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<sub>3</sub>N, R<sub>f</sub> = 0.16, grey spot with *p*-anisaldehyde stain) as an orange solid in 56 % yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): 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. <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): 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]<sup>+</sup>, 436 (12), 366 (100), 323 (11). C<sub>25</sub>H<sub>21</sub>NO<sub>6</sub>S (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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