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Photoreversible Zn^{2+} Ion Transportation Across an Interface Using Ion-Chelating Substituted Photochromic 3,3′-Indolospirobenzopyrans: Steric and Electronic Controlling Effects

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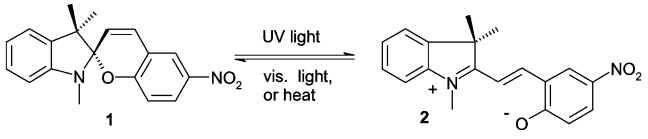
The photoreversible transportation of Zn^{2+} ions across an interface using photochromic substituted-spirobenzopyrans has been demonstrated. The inclusion of strategically placed sterically influencing 3′-methyl-**3b** and 3-spirocyclohexyl-**3c** groupings is investigated and compared to the unsubstituted analogue **3a**. Significant control over the spiropyran ring-opening↔closing reaction, and hence Zn^{2+} ion transportation has been realised. Additionally, the spiropyran ring-opening↔closing reactions of two skeletally identical spirobenzopyrans **4** and **5**, but possessing "electronically-modifying" 5-trifluoromethyl-substitutents have been studied by ^1H NMR spectroscopy: this has enabled us to realise the additional biasing, on the ring-opening↔closing process, excerpted on these systems through both selectively placed, inductively controlling functional-group substitution and/or, simultaneously, sterically influencing group substitution.

Introduction

There is ongoing interest in the development of reversible metal-chelating agents in which chelation can be switched on and off by exposure to light of different wavelengths.[1] Several groups have made contributions to this area.[2] A popular substrate for such studies is the 6-nitrospiro[chromene-2,2′-indole] system **1**↔**2** and its analogues since these have well-documented photochemical properties.[3] Photoirradiation with UV light centred at λ = 380 nm leads to the ring-opened zwitterionic (merocyanine or quinonic) form **2**, which can be converted back into the ring-closed form, either by photoirradiation with visible light, or thermally. This process may be repeated many times and has formed the basis of light-induced ionic switches. The photoreversible chelation of specific metal ions has been reported in other systems.[4–7]



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Zinc is a vital element essential for all life forms. It is present in all human body tissues and fluids, and stabilises the molecular structure of cellular components and membranes thus contributing to their maintenance and integrity. It is found in over three hundred enzymes and participates in the synthesis and degradation of carbohydrates, lipids, proteins, and nucleic acids as well as in the metabolism of other micronutrients: in particular it plays an essential role in polynucleotide transcription and thus the process of genetic expression. Consequently the development of a photoreversible zinc ion chelating system could, indirectly, potentially offer the possibility of acting as a cellular probe; help elucidate metabolic pathways, and ultimately lead to the development of new drug candidates aimed at treatment of ailments associated with abnormalities of the above classes of structures. A system such as this could be utilised in the presence of a specific and selective compound which modulates the transportation of metal ions through cellular ion-channels (i.e. when cell membranes are exposed to certain molecular structures metal ions are expelled, commonly through cellular ion-channels), the subsequent introduction of the type of structures described here to the solution could, thus, potentially act as a zinc ion probe. This could potentially be achieved by the treatment of a cellular structure with a suitable ion-releasing compound. Subsequent addition or, indeed, in vitro introduction of a solution containing the spirobenzopyran, followed by photoirriatiation would allow, by UV spectrophotometry, detection and measurement of the zinc ion complexed merocyanine form. Alternatively, cellular structures could be lysed and sub-

sequently treated with the spirobenzopyran etc., as described above.

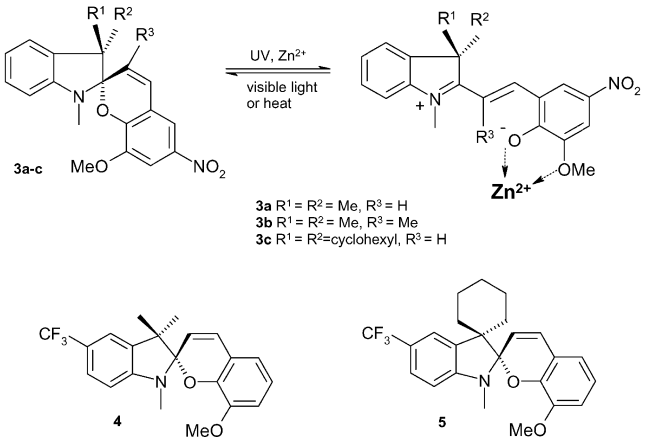
Compounds possessing structural and functional groups similar to those in structures **3a**–**c**, **4** and **5** below are known for their general ability to sequester metal ions; however, no photoreversible Zn^{2+} ion chelating systems, in which Zn^{2+} ions have photoreversibly been transported across a solvent interface have been reported. Further, no mention of steric and electronically biasing substituent effects on photoreversible Zn^{2+} ion transportation has been reported. We were interested in developing this capability by devising some new photochromic spirobenzopyrans since these could be used to photoreversibly transport metal ions i.e. Zn^{2+} ions across an interface; and thus, potentially, offer the ultimate capability of through cellular membrane-transportation.

In theory, a truly clean, on-off photoreversible system would ideally extract zero Zn^{2+} ions from the aqueous layer (or other medium) in the "dark"; on photoirradiation with UV light it would extract, by chelation, 100% of the Zn^{2+} ions, and on photoirradiation with a different wavelength light (in our case visible light) "un-chelate" the Zn^{2+} ions, thus allowing them to return to the water layer: This is practically extremely difficult to achieve, and in reality a photoreversible ion-chelating system will probably lie somewhere in-between these two extremes.

Discussion

We previously reported that the spirobenzopyran↔merocyanine equilibrium position in crown-containing systems, under photolysis, could be influenced by the use of appropriately placed "electronically-controlling" substituents; specifically in the 5-position of the indole ring.[8a,8b]

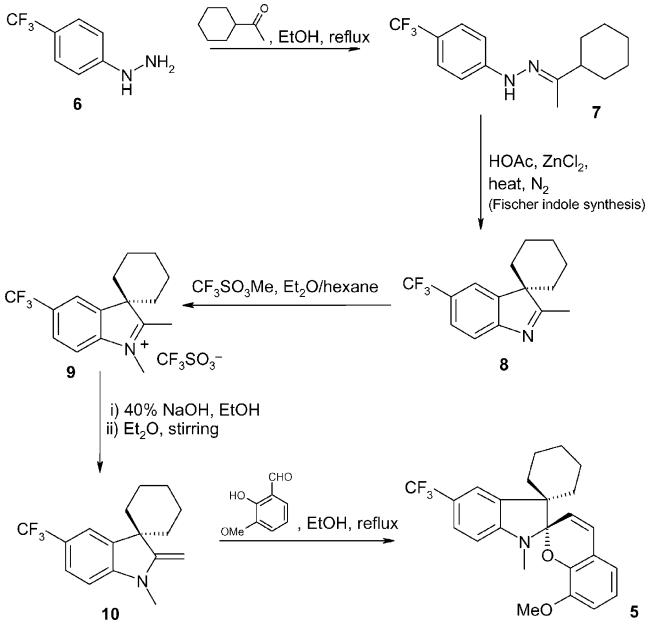
Reported here are the syntheses of some new photoreversible zinc ion chelating indolobenzospiropyrans, containing substituents that through specific and selective steric interactions, inhibit, bias, and thus offer "steric-tuning" of the photochromic ring-opening↔closing process: Specifically, **3b** and **3c** containing 3′-methyl (in the pyran ring) and 3,3′-cyclohexyl (in the indole ring) groups, respectively; these are compared and contrasted to the unsubstituted parent structure **3a**. Additionally, and importantly, demonstration that these structures photoreversibly transport Zn^{2+} ions across an interface is made. Further, some new compounds, **4** and **5**, both possessing electronically-modifying substitutents, and in the case of **5**, simultaneously, a sterically influencing group, are reported; these have been synthesised and photochemically evaluated. In detail, compounds **4** and **5**, possess a trifluoromethyl group in the 5-position of the indole ring, and in the case of structure **5** an additional bulky sterically-biasing 3,3′-cyclohexyl group: in the latter case the simultaneous effects of these two types of functionalities, on the spirocyclic ring-opening↔closing process, are tested, and compared and contrasted against structure **4**, not possessing such a bulky sterically modifying group (cyclohexyl vs. *geminal* dimethyl substitution).



Some qualitative experiments were conducted with the compounds **3a**–**c**, **4** and **5** in the presence of Li^+, Na^+, Ba^{2+}, Mg^{2+} and Ca^{2+} ions to ascertain if these systems exhibited a similar magnitude of interaction towards these metal ions, as Zn^{2+}; relatively little interaction, and hence selectivity, in comparison to that with Zn^{2+} ions was observed.

Typical Syntheses of Spiro[chromene-2,2′-indoles] as Exemplified for Compound 5

The syntheses of the spiro[chromene-2,2′-indoles] **3a**–**c**, **4** and **5** were undertaken using standard methods, or slight modifications thereof. Typically, the appropriately substituted hydrazines and ketones were condensed together to yield the corresponding hydrazones; these were then cyclised using variations on the Fischer indole synthesis. Quaternisation of the indoles were affected using various *N*-alkylating agents, from which the indolenines were obtained, after treatment with aqueous sodium hydroxide. The



Scheme 1. Synthesis of the dispiro compound **5**; typical synthetic procedure for compounds **3a**–**c** and **4**.

final spiro[chromene-2,2′-indoles] were obtained in good to excellent yields – ranging from 59 to 91% – by condensation between the appropriate indolenines and salicylaldehydes. A "typical" synthesis is exemplified in Scheme 1 for the new compound **5**.

Demonstration of Zn^{2+} Ion Transportation in Compounds 3a–c Using Quantitative Inductively Coupled Plasma-Mass Spectrometry

Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) is a reliable, widely used and accurate routine industrial analysis technique for the quantification of metal species. This was thus applied to quantify zinc ion concentrations in the aqueous layers of the following test system, and thus as a demonstration that photo-controlled metal ion transport is taking place. The transport system (Test System in Figure 1) previously devised and utilised by us was used to test whether, for the above compounds **3a**–**c**, Zn^{2+} ions were photoreversibly transported across a barrier (two immiscible layers of water and 1,2-dichloroethane).[9]

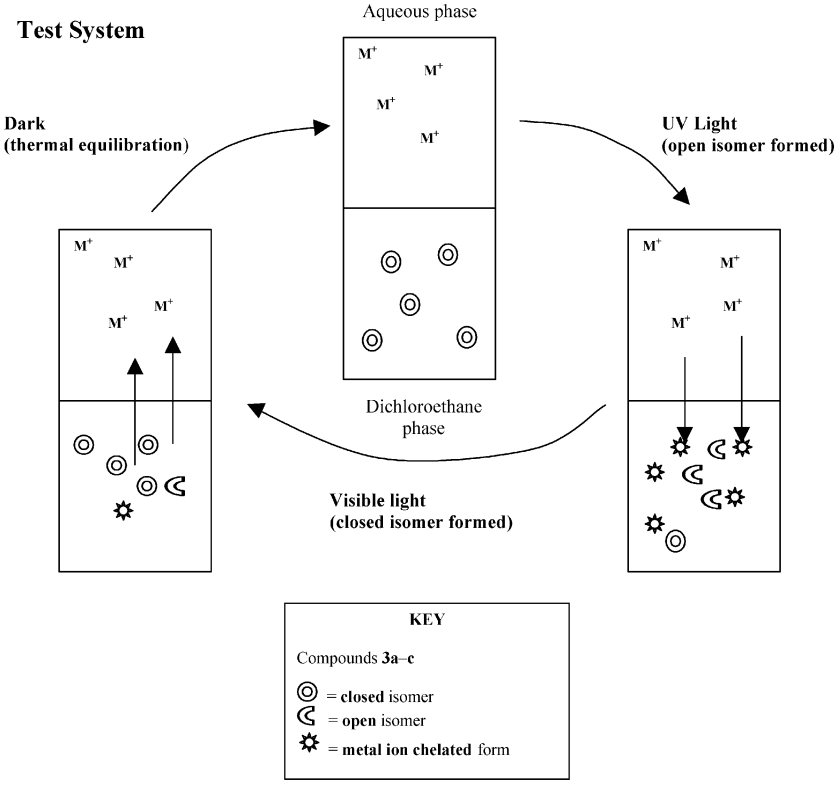
The bottom layer consisted of the compounds **3a**–**c** (2×10^{-4} M) in 1,2-dichloroethane, and the top layer zinc perchlorate (2×10^{-4} M) in water (1:1 ratio). The position of the spirocyclic↔merocyanine equilibrium was measured by UV spectroscopy for compounds **3a**–**c**: (a) before adding the metal salt (control); (b) after adding the metal salt in the dark; (c) after photoirradiation of the solution with UV light, allowing remeasurement of the UV spectrum; and finally (d) on exposure to visible light, and remeasuring the spectrum.

The experiments were repeated four times with 3 mL aliquots of the aqueous layers collected, for each of the compounds **3a**–**c**. The metal ion concentrations were quantified using ICP-MS analysis, with the measurements (parts per million, ppm) observed for each system given in Table 1, with the corresponding percentages in Figure 2.

Table 1. Zinc ion concentrations (ppm) in the aqueous layer (starting with a control solution of 2×10^{-4} M).

	3a	3b	3c
Control (Std)	10.988	10.606	11.929
Dark	8.450	6.477	11.236
Irradiated (UV)	5.288	7.114	8.854
Visible light	8.399	9.778	10.266

A decrease in the aqueous layer metal ion concentration is observed between the dark equilibrium state before and after photoirradiating it with UV light (migration of Zn^{2+} ions into the organic layer), as indicated in Table 1. An in-



(Note: under applied photoirradiation an equilibrium position is established in which there is a subsequent major predominance of the open or closed forms; however as pictorially shown above a small percentage of the minor form ultimately remains since photochemical conversion is not totally quantitative).

Figure 1. Metal ion transportation system.

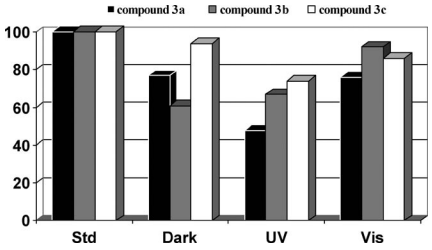


Figure 2. Compounds **3a**–**c**: percentage Zn^{2+} ions left in the aqueous layer at 2×10^{-4} M.

crease in the aqueous layer zinc ion concentration was measured on exposure to visible light as the reverse – migration of the zinc ions back into the water layer occurred (Table 1).

Results

As can been seen from Figures 2 and 3, compounds **3a** and **3c** produced the predicted trends, i.e. Zn^{2+} ions were photoreversibly transported across a solvent interface using two, appropriately different wavelength light sources (UV $\lambda \approx 365$, Vis $\lambda \approx 550$ nm): the degree of extraction, unsurprisingly, varied with the structure of the compound. In the "dark" compounds **3a** and **3c** extracted, by chelation, almost 23 and 5% Zn^{2+} ions respectively. The unsubstituted compound **3a** extracted 4.6 times the quantity of Zn^{2+} ions, under "dark" conditions, as **3c**, which is probably due to the larger thermodynamic barrier to spirocyclic ring-opening, due to incorporation of the sterically bulky spirocyclic-cyclohexyl group. Subsequent phoroirradiation of **3a** with UV light increased the quantity of the open form and hence the degree of Zn^{2+} ion chelation (23→55%), whilst irradiation with visible light, caused a reduction in the amount of open form, resulting in a concomitant loss of chelated Zn^{2+} ions (55→30%): this effect was photoreversible. Thus compound **3a** possess useable potential as a photoreversible Zn^{2+} ion chelating agent.

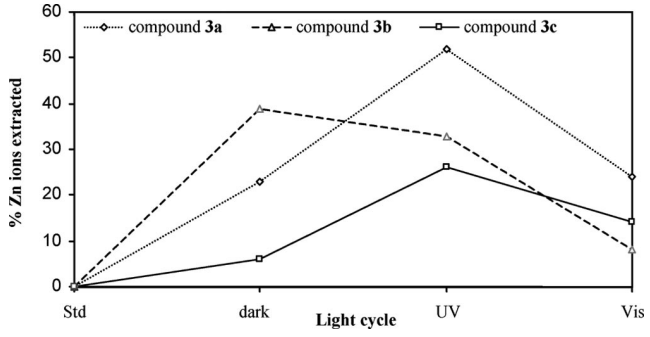


Figure 3. Compounds **3a**–**c**: percentage zinc ions extracted from the aqueous layer (2×10^{-4} M).

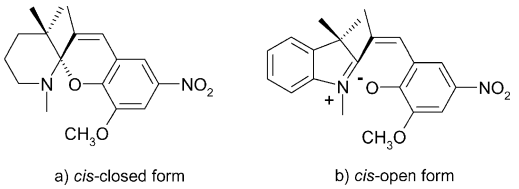
The spirocyclohexane-containing system **3c** extracted only 5% (one-quarter of that extracted by **3a**) of the Zn^{2+} ions, as quantified by ICP-MS. Photoirradiation of **3c** with UV light resulted in the extraction of almost 25% of the Zn^{2+} ions from the water layer; subsequent photoirradiation with visible light, accompanied by a concomitant reduction in the amount of open form, resulted in a reduction of the extracted Zn^{2+} ions to 15%: this effect was photoreversible. Thus compound **3c** also possesses the ability to photoreversibly chelate Zn^{2+} ions, albeit with a reduced magnitude, compared to compound **3a**. However, compound **3a**, under "dark" conditions yields significantly more of the open-chelated form than structure **3c**, but is photodynamically more receptive, producing relatively larger changes in the concentrations of extracted Zn^{2+} ions under the "dark"↔UV↔visible irradiation sequence.

Overall, structure **3c** therefore exhibits "cleaner" on↔off photoreversible Zn^{2+} ion chelating properties than structure **3a**, as there is significantly less metal ion extraction (5% vs. 20%) under "dark" conditions; however, a far greater enhancement of photo-induced Zn^{2+} ion transportation is exhibited by structure **3a**.

In conclusion, the above demonstrates that the considered placement of suitable sterically modifying substituents can be used to "sterically tune" the photoreversible chelating properties of spirobenzopyrans: this, together with the control that has been demonstrated to occur on substitution with "purely" electronically modifying groups, enables one to exert significant influences on the photoreversible chelating properties of these spirobenzopyrans.

The results for compound **3b** initially suggest that almost 40% of the Zn^{2+} ions are extracted from the aqueous layer under "dark" conditions; however, the UV spectroscopic data did not support the presence of the expected *trans*-zwitterionic open form (merocyanine) – i.e. there was no UV absorption (λ_{max} = 550 nm). We previously reported[8b] that it was possible to study the ring-opening reaction of spiro[chromene-2,2′-indoles] by treatment with deuteriotrifluoroacetic acid, and subsequently, the ring-closing reaction, using sodium deuterioxide (we have found ^{1}H NMR spectroscopy to be clear and unambiguous with regard to assigning the exact stereochemistry of the products, whereas gross UV spectroscopy was less so). We therefore applied this methodology to a range of compounds, including **3b**;[9b] the ^{1}H NMR spectrum clearly indicated that solely the *cis*-open form was generated (see Supporting Information for spectra); in this *cis*-open form the geminal dimethyl group possesses different absorbance shifts, whereas in the *trans*-open form, due to the overall planar spatial stereochemical orientation, they become equivalent. Further, treatment of the acid-generated *cis*-open form, with sodium deuterioxide, produces a yellow colourisation – consistent with lower wavelength absorption – whereas the *trans*-open forms tend to produce deep purple/red colourisations (higher wavelength) when treated with sodium deuterioxide. It is possible that the 3-alkenic methyl group weakens the spirocyclic carbon–oxygen bond creating a more facile cleavage to the *cis*-open form; however, by far, the relatively greatest, and additional effects in this system, comes from the steric interactions between the 3-alkenic methyl group and the 3,3′-geminal dimethyl groups: once the spirocyclic C–O bond has broken, rotation about the remnant single carbon–oxygen bond [C–C(Me)] must take place for isomerisation to the *trans*-open isomer to occur. In the *cis*-open

form (Figure 4, b) the alkenic-methyl group sits above (or, equally, below) the 3,3′-geminal dimethyl groups; rotation about the remnant spirocyclic carbon–carbon single bond, necessary for formation of the *trans*-open isomer (cf. 2), is thus greatly restricted by steric hindrance. Therefore it is postulated that Zn^{2+} ion chelation is occurring within both the *cis*-closed form and, to a relatively far greater extent than the *cis*-closed form, the *cis*-open form. In both cases, however, chelation to the Zn^{2+} ions would be significantly lower than to the "possible" *trans*-open form. UV irradiation of the "dark equilibrium" state produces little change in the quantity of Zn^{2+} ions extracted: indicating that a near maximal Zn^{2+} ion chelation, for this state/system has occurred. The above would tend to indicate a binding of the Zn^{2+} ions to the *cis*-open form (cf. part b of Figure 4) with perhaps some, but relatively less, to the *cis*-closed form. The relatively small quantity of *cis*-closed isomer would be expected to form the *cis*-open isomer when subjected to UV irradiation; this is perhaps why little increase in Zn^{2+} ion chelation takes place. A relatively higher degree of binding to the *cis*-open form, than the *cis*-closed form would be expected; however, as mentioned above, the degree of chelation to both of these two forms would be significantly less than to the *trans*-open form. Interestingly, the UV spectroscopic data of structure **3b** indicates, relatively, significant Zn^{2+} ion release on exposure to visible light (approximately 40%→10%) indicating interaction of the chelated form with the "broad spectrum" visible light. This result would also suggest that the main "dark-structural isomer" associated with compound **3b** is the *cis*-open form, which can interact with the "broad band" visible light, whilst the pure *cis*-closed form, being far less conjugated, would be less likely to do so. We believe the presence of the Zn^{2+} ions, in this particular system, are promoting negative photochromism. Thus, interaction of structure of **3b** with Zn^{2+} ions produces, almost entirely, the *cis*-open form, which interacts to a small degree, and is sterically unchanged, by photoirradiation with UV light. Therefore this compound offers little potential as a truly photoreversible Zn^{2+} ion chelating system: however, it offers potential as a more "general" chelating system that can be, to a significant degree, used to chelate, under "dark" conditions, and release, on exposure to visible light, Zn^{2+} ions.



a) *cis*-closed form b) *cis*-open form

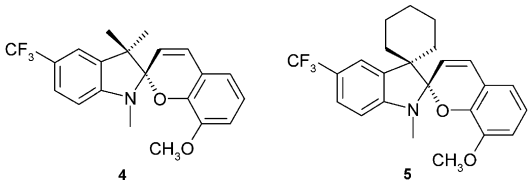
Figure 4. a) *cis*-closed form b) *cis*-open form.

The above findings are, in part, supported by the work of Guglielmetti[10] and co-workers who elucidated these findings on the closely related structure shown in part a of Figure 4. Guglielmetti confirmed the lack of the formation of the deeply coloured *trans* isomer, which he also ascribed to steric hindrance: the most stable isomer in this case was assigned to the *cis*-open form ($t_{1/2}$ = 3 s, λ_{max} = 440 nm).

It was summarised, that the introduction of a 3-alkenic methyl substituent into the benzospiropyran skeleton of these molecules causes a major perturbation in their photochromic properties by creating a significant thermodynamic barrier to *trans*-merocyanine formation. The 3-alkenic methyl group sits above (or, equally, below) the geminal dimethyl groups; rotation about the spirocyclic carbon–carbon [C–C(Me)] bond (cf. Figure 4, b) is thus sterically inhibited: as a consequence little light-induced photochromacity is observed.

As mentioned earlier our aim was to design a totally "clean", on/off photoreversible ion-chelating system. All three compounds **3a**–**c**, to varying degrees, existed, under "dark" conditions, in an "open" state; as our aim was to design a totally "clean", on/off photoreversible chelating system we thus attempted to inhibit "dark" ring-opening such that Zn^{2+} ion chelation could be entirely controlled by photoirradiations. In our previous reports for other systems[8,9] we a found control i.e. significant limitation of ring-opening, could be achieved by the addition of selectively placed electron-withdrawing substituents into the benzospiropyran skeleton – introduction of a 5-trifluoromethyl substituent produced the most photo-responsive and controllable systems.[8,9] As **3a** and **3c** demonstrated the greatest photoreversibility we synthesised and investigated the two structures **4** and **5** below: these were identical in skeletal structure, and the nearest in overall structure, to **3a** and **3c** it was possible to readily synthesise, but possessed the required 5-trifluoromethyl substituent (**5** is a new compound). In theory, addition of an electron-withdrawing substituent would, as mentioned previously, potentially allow one to excerpt additional control over the Zn^{2+} ion sequestering process by inhibiting ring-opening (destabilisation of the open-zwitterionic form). These structures were studied using ^1H NMR spectroscopy, both, in the presence, and absence, of Zn^{2+} ions [see Supporting Information for high resolution ^1H NMR spectra of compound **4** and **5** in both the presence, and absence, of Zn^{2+} ions]: in the absence of Zn^{2+} ions both systems existed entirely in the closed-spirocyclic form demonstrating the effectiveness of the 5-trifluoromethyl substituent in "holding" the closed form. Experiments involving the addition of one-equivalent, and subsequently five-equivalents of $Zn(ClO_4)_2$ in CD_3CN caused the following effects: for compound **4** a new set of aromatic signals appeared; the doublet associated with the *gem*-dimethyl group broadened and a new singlet associated with the N^+–CH_3 of the *trans*-open form appeared. In the case of structure **5** the general ^1H NMR spectra broadened; the vinylic protons retained their *cis* coupling of 10 Hz; in addition to the singlet associated with the N–CH_3 grouping at 2.7 ppm there appeared a second singlet due to the N^+–CH_3 of the open form. Thus, in the presence of zinc ions a simultaneous dynamic equilibrium mixture of both the *cis*-closed and *trans*-open forms exists – this observation in the ^1H NMR spectra can only be explained by interaction of the Zn^{2+} ions with the open-zwitterionic form. Thus for

compounds **4** and **5** the thermodyanamic binding of the Zn^{2+} ion chelated species was strong enough to overcome the powerful destabilising electron-withdrawing inductive effect of the 5-trifluoromethyl substituent – which destabilises the quaternary imminium ion present in the open-zwitterionic structure (cf. structure **2**).



In both systems, even in the presence of five-equivalents Zn^{2+} ions there was a predominance of the closed form.

In conclusion it can be deduced that the introduction of electronically modifying (withdrawing) substituents allows further biasing of the fluxional open↔closed equilibria in these dynamic systems (in this case a biasing towards the closed form). In the absence of the trifluoromethyl group both systems existed, in the presence of Zn^{2+} ions, entirely in the open form.

In summary – we have synthesised, in good to excellent yields, several new substituted-spiropyrans: demonstrated Zn^{2+} ion chelation; photoreversible Zn^{2+} ion-transportation across an interface, and the control and biasing of this transportation effect utilising both steric and electronic substituents.

Note: Whilst we have qualified and quantified the main observations and results described here, we believe that the metal ion binding interactions, and subsequent equilibrium positions, in these systems are multifactorial and probably involve an extremely complex set of interactions and theoretical parameters: The detailed discussion of which is outside the scope of this report being more applicable to individual studies in theoretical journals. We believe that they are comprised of, but not limited to, the following: 1) the type and nature of the substituent in the 3-position of the pyran ring, 2) the type and nature of the substituent in the 3,3′-position of the indole-ring, 3) the type and nature of the substituent in the 5-position (through inductive effects, when present), 4) the 8-benzo substituent or group, 5) the size of the metal ion, 6) the charge density of the metal ion, 7) the distribution of charge throughout the zwitterionic structure (in particular that of the phenoxide anion, 8) solvent interactions (or non-interaction) and 9) the conformation of the overall system in solution.

Experimental Section

Photoirradiation Studies: The photochromic properties of these compounds were evaluated by preparing solutions (2×10^{-5} mol dm^{-3} unless otherwise stated), in the "dark", in freshly dried and redistilled solvents [generally tetrahydrofuran (THF), acetonitrile, dichloroethane (DCE) or methanol]. Perchlorate salts were dried with P_2O_5 for several days before use. Solutions were placed in a stoppered 1-cm path length cuvette at room temperature (20–25 °C) and allowed to equilibrate for 1 h before measurement of their UV/Vis absorption curves ("dark" curves). The solutions were then irradiated for 1 min with UV light of λ = 365 nm generated from a steady power source. The UV light source was a 200-W mercury/xenon lamp, focussed in a LOT-Oriel air-cooled lamp housing, with solution filters (for details see below) to eliminate light of $320 < \lambda > 400$ nm (this allows maximal photoirradiation with a λ_{max} centred at 365 nm, the absorption wavelength of the spirobenzopyrans, and additionally avoids photoirradiation of the formed merocyanine, which has a λ_{max} centred at 550 nm). The UV absorption spectra (UV curve) were measured; this was followed by exposure of the cuvette to a visible-light source (3 min: 100-W tungsten spotlight) and the UV absorption spectrum remeasured.

Solution filters used: A 1 M cobalt and copper sulfate solution (1:1) contained within a 2-mm walled Pyrex glass cuvette was prepared. This combination of solution filter and Pyrex glass possesses an irradiation window of between 450–650 nm with unwanted wavelengths outside this range effectively filtered out.

The equilibrium positions for the dynamic systems were measured by UV and visible light spectroscopy according to the following protocol:

(a) before adding the metal salt, in the "dark" for 1 h,

(b) after adding the metal salt, in the "dark" for 1 h,

(c) exposure of the solution to UV light using a focused 200-W high-pressure mercury/xenon light source, for 1 min, and remeasuring the spectrum. Photoirradiations were carried out in the UV range of 365 nm using a focussed LOT-Oriel air-cooled lamp housing,

(d) in the visible region photoirradiations were carried out by exposing the solution to a 100-W tungsten spotlight for 3 min and remeasuring the UV spectrum,

(e) the reversibility of the examined systems was ascertained by repetition of the above light cycles (at least three times).

^{1}H NMR Spectroscopy: Studies were carried out with a JEOL FX2000 spectrometer using deuteriochloroform of [D_6]DMSO as the solvent with tetramethylsilane (TMS) as the internal reference. Multiplicities are reported as (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. Assignments of hydroxy and ammonium protons were checked by deuterium exchange. Mass spectra were recorded with a VG 7070H mass spectrometer interfaced with a Finnigan Incos data system. Accurate mass measurements were carried out at the EPSRC mass spectrometry service at the University of Wales, Swansea. UV spectroscopy was carried out using Perkin–Elmer Lambda 5 and Lambda 9 spectrophotometers; both instruments are double-beamed with thermostatically controlled cell blocks. The Lambda 9 is also fitted with an digital RS232 port, which allows remote control by PC. All UV measurements were taken at 25 °C using 3-mL quartz cells with a 1-cm path length and are referenced against air. IR spectra were recorded with a Perkin–Elmer 983 spectrophotometer. Melting points were determined in open capillary tubes with an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were carried out by MEDAC Ltd., Brunel Science Centre, Egham, Surrey, UK. Thin-layer chromatography was performed over glass plates coated with Merck silica gel 60 F254; flash chromatography was performed using Merck 7734 silica gel (20–63 μm).

Zinc ion concentrations were measured using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS).

Chemical intermediates were purchased from the Aldrich Chemical Company unless otherwise stated.

8-Methoxy-1′,3′,3′-trimethyl-6-nitro-1′,3′-dihydrospiro[chromene-2,2′-indole] (3a): 2-Hydroxy-3-methoxy-5-nitrobenzaldehyde (0.4 g, 2.03 mmol) and 1,3,3-trimethyl-2-methyleneindolenine (0.35 g, 2.02 mmol) were dissolved in ethanol (10 mL) and the resulting solution heated under reflux for 8 h. Reduction of the solvent volume to approximately one-quarter of the original amount and cooling in an ice box yielded a pink solid. One recrystallisation from ethanol yielded the **3a** as a pink powder (0.42 g, 59%), m.p. 166–168 °C (ref.[11] 159–161 °C, 167 °C). ^{1}H NMR ($CDCl_3$): δ = 7.7 (d, J = 3 Hz, 1 H, ArH), 7.63 (d, J = 3 Hz, 1 H, ArH), 7.19 (t, 1 H, ArH), 7.07 (d, J = 7 Hz, 1 H, ArH), 6.87 (d, J = 10 Hz, 1 H, CH=CH), 6.85 (t, 1 H, ArH), 6.55 (d, J = 7 Hz, 1 H, ArH), 5.83 (d, 1 H, J = 10, CH=CH), 3.81 (s, 3 H, OCH_3), 2.75 (s, 3 H, N-CH_3), 1.22, 1.18 ppm (6 H, *gem* dimethyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3018, 2970 (satd. CH), 1606 (C=C), 1334 (NO_2), 1216 (C–N), 1092 (C–C), 954 (C–O spiro), 771 cm^{-1} (4 adj. H). MS: *m*/*z* 354 [M^+ + 2, 4.8], 253 [M^+ + 1, 21.5], 352 [M^+, 8.6], 351 [M^+ – 1, 20.0], 158 (100% base peak). $C_{20}H_{20}N_2O_4$ (352.385): calcd. C 62.12, H 4.66, N 11.43; found C 62.19, H 4.58, N 11.22.

8-Methoxy-1′,3′,3′,3-tetramethyl-6-nitro-1′,3′-dihydrospiro[chromene-2,2′-indole] (3b): 2-Ethyl-1,3,3-trimethylindolium triflate (1.00 g, 2.97 mmol) was dissolved in a 40% sodium hydroxide solution (10 mL) and the resulting mixture stirred for 5 min. Then diethyl ether (10 mL) was added. The ether layer was separated from the reaction mixture, dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The resulting yellow/orange oil obtained was isolated (0.44 g, 2.34 mmol, 79%) and dissolved in ethanol (5 mL). 2-Hydroxy-3-methoxy-5-nitrobenzaldehyde (0.46 g, 2.43 mmol) in ethanol (5 mL) was added, and the resulting mixture heated under reflux for 8 h. Partial removal of the ethanol under reduced pressure produced a yellow/orange precipitate, which was filtered off and recrystallised from chloroform/ethanol to yield **3b** as yellow/orange needles (0.57 g, 67%), m.p. 165–167 °C. ^{1}H NMR ($CDCl_3$): δ = 7.59 (d, J = 7 Hz, 1 H, ArH), 7.57 (d, J = 7 Hz, 1 H, ArH), 7.17 (t, J = 8, 1 Hz, 1 H, ArH), 7.0 (d, 1 H, ArH), 6.99 (d, J = 7 Hz, 1 H, ArH), 6.55 (s, 1 H, CH=C), 3.7 (s, 3 H, OCH_3), 2.83 (s, 3 H, NCH_3), 1.96 (s, 3 H, CH_3), 1.14 ppm (6 H, *gem* dimethyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3018 (satd. CH), 1533 (C=C), 1210 (C–C), 1190, 1350 (NO_2), 954 (C–O spiro), 771 cm^{-1} (4 adj H's). MS: *m*/*z* 368 [M^+ + 2, 5.9], 367 [M^+ + 1, 35.7], 366 (M^+, 87.5), 351 (100% base peak). $C_{21}H_{22}N_2O_4$ Acc (FAB): calcd. 366.1579; found M^+ = 366.4103 (4.4 ppm), M^+ + 1 = 366.4104 (3.5 ppm).

8-Methoxy-1′-methyl-6-nitro-1′*H*-dispiro[chromene-2,2′-indole-3′,1′′-cyclohexane] (3c): 1′,2′-Dimethyl-5′-(trifluoromethyl)spiro-[cyclohexane-1,3′-indolium] triflate (1.45 g, 3.99 mmol) was dissolved in a 40% sodium hydroxide solution (10 mL). The resulting solution was stirred for 5 min and diethyl ether (15 mL) was added. The ether layer was separated from the reaction mixture, dried (anhydrous sodium sulfate) and evaporated under reduced pressure to produce an yellow/orange oil. The oil that remained was isolated (0.75 g, 3.50 mmol), dissolved in ethanol (3 mL), added to 2-hydroxy-3-methoxy-4-nitrobenzaldehyde (0.69 g, 3.50 mmol) in ethanol (25 mL); the resulting mixture was heated under reflux for 24 h. Removal of the solvent under reduced pressure yielded a brown coloured solid which was broken up and recrystallised from ethanol to yield **3c** as a dark beige/pale brown coloured precipitate (1.25 g, 91%), m.p. 196–198 °C. ^{1}H NMR ($CDCl_3$): δ = 7.68, 7.69 (d, J = 7 Hz, 1 H, ArH), 7.62, 7.61 (d, J = 7 Hz, 1 H, ArH), 7.41, 7.39 (d, J = 7 Hz, 1 H, ArH), 7.21–7.17 (t, 1 H, ArH), 6.86, 6.83 (d, J = 10 Hz, 1 H, CH=CH), 6.85–6.81 (t, 1 H, ArH), 6.56, 6.54 (d, J = 7 Hz, 1 H, ArH), 5.88, 5.85 (d, J = 10 Hz, 1 H, CH=CH), 3.81 (s, 3 H, OCH_3), 2.74 (s, 3 H, NCH_3), 1.95–1.22 ppm (m, 10 H, cyclohexyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3020, 2936 (satd. CH), 1604 (C=C), 1450, 1334 (NO_2), 1216 (C–N), 1092 (C–C), 954 (C–O spiro), 771 cm^{-1} (ArH, 4 adj H). MS: *m*/*z* 393 [M^+ + 1, 13.6], 392 (M^+, 54.4), 83 (100% base peak). $C_{23}H_{24}N_2O_4$ Acc (CI): calcd. 392.1736; found M^+ = 392.1736.

8-Methoxy-1′,3′,3′-trimethyl-5′-(trifluoromethyl)-1′,3′-dihydrospiro-[chromene-2,2′-indole] (4): 1,3,3-Trimethyl-2-methylene-5-(trifluoromethyl)indolenine (0.47 g, 0.20 mmol) was dissolved in ethanol (10 mL), to which was added to 2-hydroxy-3-methoxybenzaldehyde (0.30 g, 0.20 mmol) in ethanol (10 mL); and the resulting solution heated under reflux for 24 h. Removal of the solvent under reduced pressure produced a brown coloured solid which was recrystallised from ethanol to yield **4** as a tan coloured crystalline solid (0.41 g, 68%), m.p. 126–128 °C (ref.[1] 125–127 °C). ^{1}H NMR ($CDCl_3$): δ = 7.49 (d, J = 7 Hz, 1 H, ArH), 7.36 (s, 1 H, ArH), 6.95 (d, J = 7 Hz, 1 H, ArH), 6.83–6.72 (m, 3 H, ArH), 6.62 (d, J = 7 Hz, 1 H, ArH), 5.71 (d, J = 10 Hz, 1 H, CH=CH), 3.72 (s, 3 H, OCH_3), 2.8 (s, 3 H, CH_3), 1.13, 1.06 ppm (6 H, *gem* dimethyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3100 (satd. CH), 1600 (C=C), 1210 (C–N), 1400 (C–O), 1100 (C–C), 954 (C–O spiro), 758 cm^{-1} (C–F). MS: *m*/*z* 376 [M^+ + 1, 12], 375 [M^+, 50], 374 [M^+ – 1, 10], 360 (M^+ – 15). $C_{21}H_{20}NO_2F_3$ Acc (EI): calcd. 375.1759; found M^+ = 375.1759.

8-Methoxy-1′-methyl-5′-(trifluoromethyl)-1′*H*-dispiro[chromene-2,2′-indole-3′,1′′-cyclohexane] (5): 1′,2′-Dimethyl-5′-(trifluoromethyl)spiro[cyclohexane-1,3′-indolium] triflate (0.61 g, 1.42 mmol) was dissolved in a stirred 40% sodium hydroxide solution (15 mL) for 5 min, after which time diethyl ether (15 mL) was added. The ether layer was separated from the reaction mixture, dried (anhydrous sodium sulfate) and evaporated under reduced pressure to yield an orange/yellow oil: The oil was isolated (0.19 g, 0.68 mmol), dissolved in ethanol (3 mL), and added to 2-hydroxy-3-methoxybenzaldehyde (0.10 g, 0.66 mmol) in ethanol (25 mL); and the resulting solution heated under reflux for 24 h. Partial removal of the solvent under reduced pressure yielded the title compound as a brown coloured solid. The solid was recrystallised from ethanol to yield **5** as a beige/brown coloured precipitate (0.19 g, 70%). m.p. 129–131 °C. ^{1}H NMR ($CDCl_3$): δ = 7.57 (s, 1 H, ArH), 7.48 (d, J = 8 Hz, 1 H, ArH), 6.9 (d, J = 10 Hz, 1 H, ArH), 6.83 (d, J = 8 Hz, 1 H, ArH), 6.80 (d, J = 8 Hz, 1 H, ArH), 6.74 (t, J = 7 Hz, 1 H, ArH), 6.51 (d, J = 8 Hz, 1 H, ArH), 5.77 (d, J = 10 Hz, 1 H, CH=CH), 3.72 (s, 3 H, OCH_3), 2.80 (s, 3 H, NCH_3), 2.1–1.3 ppm (m, 10 H, cyclohexyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3150 (satd. CH), 1608 (C=C), 1384 (C–O), 1210 (C–N), 1000 (C–C), 954 (C–O spiro), 755 cm^{-1} (C–F). MS: *m*/*z* 416 [M^+ + 1, 20], 415 (M^+, 100% base peak). $C_{24}H_{24}NO_2F_3$ Acc (EI): calcd. 415.1759; found M^+ = 415.1759.

Isopropyl Ethyl Ketone Phenylhydrazone: Phenylhydrazine (2.68 g, 24.81 mmol) was added to 2-methyl-3-pentanone (2.48 g, 24.80 mmol) in ethanol (10 mL) and the resulting solution heated under reflux for 5 h. Removal of the ethanol under reduced pressure yielded the title compound as a mobile, slightly red oil (3.20 g, 68%). ^{1}H NMR (TCE): δ = 6.8–7.3 (m, J = 8 Hz, 5 H, ArH), 2.6 (q, 1 H, C*H*), 2.2–2.3 (q, 2 H, CH_2CH_3), 1.2 (t, 6 H, 2 $ArCH_3$), 1.1 ppm (t, 3 H, CH_2CH_3). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3300–3500 (C=N–H), 3100 (C–H), 1650 (C=C), 1530 cm^{-1} (C=N). MS: *m*/*z* 191 [M^+ + 1, 16.7], 190 (M^+, 100%, base peak), 175 (M^+, – CH_3, 3.6). $C_{12}H_{18}N_2$ Acc (EI): calcd. 190.1470; found M^+ = 190.1470.

2-Ethyl-3,3-dimethyl-3*H*-indole: Isopropyl ethyl ketone phenylhydrazone (2.88 g, 15.16 mmol) was added to zinc chloride (0.50 g, 3.66 mmol) in glacial acetic acid (50 mL) and the resulting mixture heated on a steam bath, under nitrogen, for 4 h. The title compound, obtained as a yellow/orange oil, after removal of the solvent under reduced pressure, was purified over flash chromatography

using chloroform as the elutant (2.29 g, 87%). ^{1}H NMR ($CDCl_3$): δ = 6.90–7.30 (m, 4 H, ArH), 2.60 (q, 2 H, CH_2CH$_3$), 1.49 (t, 3 H, CH$_2$CH_3), 1.47 ppm [s, 6 H, *gem* –C(CH$_3$)$_2$]. IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3018 (satd. C–H), 1450 (C=N), 1533 (C=C), 1010 (C–C), 1190 (C–N), 771 cm^{-1} (Ar-H, 4 adj. H). MS: *m*/*z* 174 [M$^+$ + 1, 8.9], 173 (M$^+$, 62.5), 158 (base peak, 100%). $C_{12}H_{15}N$ Acc (EI): calcd. 173.1204; found 173.12040.

2-Ethyl-1,3,3-trimethylindolium Triflate: 2-Ethyl-3,3-dimethyl-3*H*-indole (2.08 g, 12.02 mmol) was added to methyl trifluoromethanesulfonate (1.96 g, 12.02 mmol) in hexane (5 mL) and diethyl ether (5 mL), the resulting solution was stirred at room temperature. Instantly, a yellow precipitate formed, which was filtered off and recrystallized from ethanol to yield the title compound as deep golden coloured crystals (3.81 g, 89%), m.p. 134–136 °C. ^{1}H NMR ($CDCl_3$): δ = 7.20–7.69 (m, 4 H, ArH), 4.15 [s, 3 H, N$^+$–CH$_3$ (CF$_3$SO$_3^-$)], 3.22–3.28 (q, 2 H, CH_2CH$_3$), 1.63 [s, 6 H, *gem* ArC(CH$_3$)$_2$], 1.41–1.45 ppm (t, 3 H, CH$_2$CH_3). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 2982 (satd. C–H), 1632 (C=C), 1630 (C=N), 1264 (C–F), 1154 (SO$_2$-O), 1032 (C–N), 736 cm^{-1} (Ar-H, 4 adj. H). MS: *m*/*z* 187 [M$^+$ –149 (SO$_3$CF$_3$), 78.7], 173 (4.11), 172 (base peak 100%), 203 (M$^+$ – SO$_3$CF$_3$ – 2 × 15, 4.2). $C_{14}H_{18}F_3NO_3S\cdot0.75H_2O$ (350.87): calcd. C 49.84, H 5.38, N 4.15; found C 49.72, H 5.38, N 4.20].

1,3,3-Trimethyl-2-ethyleneindolene: 2-Ethyl-1,3,3-trimethylindolium triflate (0.51 g, 1.51 mmol) was dissolved in a 40% sodium hydroxide solution (5 mL). Diethyl ether (10 mL) was added and the resultant solution vigorously stirred for 5 min. After this period the ether layer was separated from the reaction mixture, dried (anhydrous sodium sulfate) and evaporated under reduced pressure to yield the pure title compound as a pale yellow/orange oil (0.22 g, 79%). ^{1}H NMR ($CDCl_3$): δ = 6.38–7.09 (m, 4 H, ArH), 4.30–4.33 [q, 1 H, C=CH(CH$_3$)], 2.93 (s, 3 H, NCH$_3$), 1.88–1.92 (d, 3 H, C=CHCH_3), 1.13 ppm [s, 6 H, *gem* C(CH$_3$)$_2$]. IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 2982 (satd. C–H), 1632 (C=C), 1630 (C=N), 1032 (C–N), 735 cm^{-1} (Ar-H, 4 adj. H). MS: *m*/*z* 188 [M$^+$ + 1, 3.8], 175 (base peak, 100%), 306 [M$^+$ – 1, 15.8].

Cyclohexyl Methyl Ketone: A dry 100-mL three-necked round-bottomed flask was fitted with a reflux condenser, a pressure-equalising dropping funnel, a mechanical stirrer, and an inlet tube to maintain a static nitrogen atmosphere in the reaction vessel throughout the reaction. In the flask were placed powdered lithium hydride (0.69 g, 0.087 mol) and anhydrous predistilled 1,2-dimethoxyethane (50 mL). While this solution was being stirred vigorously, a solution of cyclohexanecarboxylic acid (9.62 g, 0.075 mol) in anhydrous 1,2-dimethoxyethane (50 mL) was added over a 10 min period. The resulting mixture was heated to reflux while stirring for 2 h, at which time the hydrogen evolution and the formation of lithium cyclohexanecarboxylate was complete. The resulting suspension was cooled to approximately 10 °C with an ice-bath and stirred vigorously while an ethereal solution containing methyllithium (1.6 M, 62 mL, 0.085 mol) was added dropwise over 30 min. After complete addition, the ice-bath was removed and the resulting suspension was stirred at room temperature for 2 h. The fine suspension in the reaction flask was agitated and siphoned into a vigorously stirred solution of concentrated hydrochloric acid (13.5 mL, 0.16 mol) and water (200 mL). The reaction flask was rinsed with an additional amount of ether (60 mL), which was also added to the aqueous solution. After the resulting mixture was saturated with sodium chloride, the organic phase was separated and the alkaline aqueous phase extracted with diethyl ether (3 × 100 mL). The organic solutions were combined and dried with magnesium sulfate, the bulk of the ether was distilled from the mixture through a Vigreux column. Distillation under vacuum provided the title compound as a pale yellow liquid (8.85 g, 94%).

Cyclohexyl Ketone Phenylhydrazone:[12] Phenylhydrazine (3.00 g, 27.77 mmol) was added to cyclohexyl methyl ketone (3.50 g, 27.77 mmol) in ethanol (100 mL) and the resulting solution heated under reflux for 0.5 h. Removal of the solvent under reduced pressure yielded the title compound as a deep orange mobile oil (4.78 g, 79%). ^{1}H NMR ($CDCl_3$): δ = 11.0 (s, 1 H, NH, exchangeable D_2O), 7.25 (t, 2 H, ArH), 7.03, 7.05 (dd, 2 H, ArH), 6.79, 6.83 (t, *J* = 8 Hz, 1 H, ArH), 1.90 [m, 1 H, (CH$_2$)$_2$CHC], 1.82 (s, 3 H, N=C–CH$_3$), 1.17–1.78 ppm (m, 10 H, cyclohexyl, 5 CH$_2$). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3650 (N–H), 3020 (C–H), 1616 (C=C), 1520 (C–N), 1020 (C–C), 760 cm^{-1} (ArH). MS: *m*/*z* 216 [M$^+$, 6.6], 215 (M$^+$ – 1, 8.1), 18 (base peak, 100%).

3-Cyclohexyl-2-methyl-3*H*-indole: Cyclohexyl methyl ketone phenylhydrazone (4.65 g, 21.53 mmol) was added to zinc chloride (1.00 g, 7.35 mmol) in glacial acetic acid (100 mL), and the resulting solution heated on a steam bath, under nitrogen, for 3 h. Filtration and removal of the glacial acetic acid under reduced pressure yielded the title compound as an orange oil (3.25 g, 76%). ^{1}H NMR ($CDCl_3$): δ = 7.51–7.53 (d, *J* = 7 Hz, 1 H, ArH), 7.31 (d, *J* = 7 Hz, 1 H, ArH), 7.15, 6.99 (m, 2 H, ArH), 2.7 (s, 3 H, CH$_3$), 1.25–2.31 ppm (m, 10 H, cyclohexyl, 5 CH$_2$). IR ($CDCl_3$, film): $\tilde{\nu}_{(max)}$ ($CDCl_3$) 2932 (satd. C–H), 1688 (C=N), 1598 (C=C, Ar), 1216 (C–N), 1026 cm^{-1} (C–C). MS: *m*/*z* 200 [M$^+$ + 1, 27.6], 199 (M$^+$, base peak, 100%), 198 [M$^+$ – 1, 4.2]. $C_{14}H_{17}N$ Acc (EI) calcd. 199.1361; found 199.1361.

1′,2′-Dimethylspiro[cyclohexane-1,3′-indolium] Triflate: 2′-Methylspiro[cyclohexane-1,3′-indole] (3.22 g, 16.18 mmol) was added to methyltrifluoromethane sulfonate (2.66 g, 16.22 mmol) in hexane (20 mL) and diethyl ether (30 mL). Instantly a canary yellow precipitate formed which was filtered off and washed with diethyl ether to yield the title compound as pale yellow coloured crystals (4.59 g, 78%), m.p. 126–128 °C. ^{1}H NMR ($CDCl_3$): δ = 7.91, 7.93 (d, 1 H, ArH), 7.66–7.68 (d, 1 H, ArH), 7.62 (t, *J* = 8 Hz, 1 H, ArH), 7.56 (t, *J* = 8 Hz, 1 H, ArH), 4.12 (s, 3 H, N$^+$-CH$_3$), 2.88 (s, 3 H, N$^+$=C–CH$_3$), 1.54, 2.08 ppm (m, 10 H, cyclohexyl, 5 CH$_2$). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3020 (satd. C–H), 1590 (C=C), 1325 (C–C), 1210 (C–N), ArH (760), 758 cm^{-1} (C–F). MS: *m*/*z* 233 [M$^+$ – (SO$_3$CF$_3$), 6.7], 323 (M$^+$ – SO$_3$CF$_3$ – 1, 41.7), 218 (M$^+$ – SO$_3$CF$_3$ – 15, 17.7), 217 (base peak, 100%) 203 (M$^+$ – SO$_3$CF$_3$ – 2 × 15, 4.2). $C_{16}H_{20}F_3NO_3S$ (363.397): calcd. C 52.88, H 5.55, N 3.86; found C 52.50, H 5.36, N 3.88.

1′-Methyl-2′-methylidene-5′-(trifluoromethyl)-1′,2′-dihydrospiro[cyclohexane-1,3′-indole]: 1′,2′-Dimethylspiro[cyclohexane-1,3′-indolium] triflate (1.02 g, 2.81 mmol) was dissolved in a 40% sodium hydroxide solution (10 mL) and stirred for ten minutes. Then diethyl ether (10 mL) was added to the solution, stirring was continued for a further 5 min. The ether layer was separated from the reaction mixture, dried (anhydrous sodium sulfate), filtered, and removed under reduced pressure to yield the title compound as a yellow/orange oil (0.45 g, 75%). ^{1}H NMR ($CDCl_3$): δ = 7.44 (d, *J* = 7 Hz, 1 H, ArH), 7.14 (t, 1 H, ArH), 6.74 (t, 1 H, ArH), 6.56 (d, *J* = 7 Hz, 1 H, ArH), 3.88 (dd, *J* = 10, 10 Hz, 2 H, C=CH$_2$), 3.02 (s, 3 H, N-CH$_3$), 1.83 ppm (m, 10 H, cyclohexyl, 5 CH$_2$). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 2934 (satd. C–H), 1644 (C=N), 1604 (C=C), 1908 (C–C), 908 (C–C), 775 cm^{-1} (Ar-H, 4 adj. H). MS: *m*/*z* 215 [M$^+$ + 1, 18.5], 214 (M$^+$, 46.9), 213 [M$^+$ – 1, 80.0], 158 (base peak, 100%), 306 [M$^+$ – 1, 15.8]. $C_{15}H_{19}N$ Acc (EI): calcd. 213.1517; found 213.1517.

Cyclohexyl Methyl Ketone [4-(Trifluoromethyl)phenyl]hydrazone (7): [4-(Trifluoromethyl)phenyl]hydrazine (2.45 g, 13.92 mmol) was

added to cyclohexyl methyl ketone (1.75 g, 13.89 mmol) in ethanol (50 mL) and the resulting solution heated under reflux for 7 h. Removal of the solvent under reduced pressure yielded **7** as a burgundy red mobile oil (2.45 g, 62%). ^{1}H NMR ($CDCl_3$): δ = 7.47, 7.44 (t, J = 7 Hz, 2 H, ArH), 7.09, 7.06 (d, J = 7 Hz, 2 H, ArH), 1.9 (m, 1 H, C*H*), 1.84 (s, 3 H, -CH_3), 1.78–1.17 ppm (m, 10 H, CH_2, 5 cyclohexyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3650 (N–H), 3020 (satd. CH), 1616 (C=C), 1525 (C–N), 1020 (C–C), 785 (C–F), 760 cm^{-1} (ArH). MS: *m*/*z* 286 [M^+ + 2, 4.6], 285 [M^+ + 1, 4.7], 284 [M^+, 5.4], 145 (100% base peak).

2′-Methyl-5′-(trifluoromethyl)spiro[cyclohexane-1,3′-indole] (8): Hydrazone **7** (3.30 g, 5.05 mmol) was added to zinc dichloride (0.25 g, 1.83 mmol) in acetic acid (100 mL), and the resulting solution heated on a steam bath, under nitrogen, for 3 h. Filtration and removal of the solvent under reduced pressure yielded **8** as an orange oil (1.52 g, 70%). ^{1}H NMR ($CDCl_3$): δ = 7.92 (d, J = 7 Hz, 1 H, ArH), 7.62 (s, 1 H, ArH), 7.26 (d, J = 7 Hz, 1 H, ArH), 2.32 (s, 3 H, -CH_3), 1.83–1.21 ppm (m, 10 H, CH_2, 5 cyclohexyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 2932 (satd. CH), 1688 (C=N), 1598 (C=C), 1216, 1026 (C–C), 778 cm^{-1} (C–F). MS: *m*/*z* 268 [M^+ + 1, 35.1], 267 (M^+, 91.6), 266 [M^+ – 1, 49.8], 252 (100% base peak). $C_{15}H_{16}NF_3$ Acc (CI): calcd. 267.1235; found 267.1235.

1′,2′-Dimethyl-5′-(trifluoromethyl)spiro[cyclohexane-1,3′-indolium] Triflate (9): Indole **8** (0.50 g, 1.86 mmol) was dissolved in diethyl ether (15 mL) and hexane (10 mL); methyltrifluoromethane sulfonate (0.32 g, 1.95 mmol) was added in one portion to the stirred reaction mixture at room temperature. A tan coloured precipitate instantly formed which was broken up and recrystallised from ethanol to yield **9** as pale yellow crystals (0.65 g, 80%), m.p. 112–114 °C. ^{1}H NMR ($CDCl_3$): δ = 8.12 (s, J = 7 Hz, 1 H, ArH), 7.91 (d, J = 7 Hz, 1 H, ArH), 7.84 (d, J = 7 Hz, 1 H, ArH), 4.17 (s, 3 H, N-CH_3), 2.89 (s, 3 H, -CH_3), 2.00–1.16 ppm (m, 10 H, CH_2, 5 cyclohexyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3020 (satd. CH), 1590 (C=C), 1325 (C–C), 1210 (C–N), 760 (ArH), 758 cm^{-1} (C–F). MS: *m*/*z* 370 (M^+ – CF_3, 7.7), 282 (M^+ – SO_3CF_3, 9.4) 83 (100% base peak), 203 (M^+ – SO_3CF_3 – 2×15, 4.2). $C_{17}H_{19}F_6NO_3S{\cdot}H_2O$: calcd. C 45.43, H 4.68, N 3.12; found C 45.12, H 4.68, N 3.12. $C_{17}H_{19}F_6NO_3S$ Acc FAB (M^+ – SO_3CF_3) calcd. 282.146960; found 282.147906 (–3.4 ppm).

1′-Methyl-2′-methylidene-5′-(trifluoromethyl)-1′,2′-dihydrospiro[cyclohexane-1,3′-indole] (10): Triflate **9** (0.61 g, 1.42 mmol) was dissolved in a 40% sodium hydroxide solution (10 mL) suspended under diethyl ether (10 mL), and vigorously stirred for 5 min. The ether layer was separated, dried (anhydrous sodium sulfate), and filtered to yield **10** as an yellow/orange oil (0.19 g, 48%). ^{1}H NMR ($CDCl_3$): δ = 7.65 (s, 1 H, ArH), 7.55 (d, J = 7 Hz, 1 H, ArH), 6.83 (d, J = 7 Hz, 1 H, ArH), 3.88 (dd, J = 10, 10 Hz, 2 H, C=CH_2), 2.8 (s, 3 H, N-CH_3), 2.1–1.3 ppm (m, 10 H, CH_2, 5 cyclohexyl). IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3100, 2935 (satd. CH), 1605 (C=C), 1210 (C–N), 1400 (C–O), 1100 (C–C), 750 cm^{-1} (C–F). MS: *m*/*z* 282 [M^+ + 1, 12], 281 (M^+, 100%, base peak).

Isopropyl Methyl Ketone [4-(Trifluoromethyl)phenyl]hydrazone: [4-(Trifluoromethyl)phenyl]hydrazine (2.47 g, 14.03 mmol) was added to 3-methylbutan-2-one (1.19 g, 14.00 mmol) in ethanol (20 mL) and the resulting solution heated under reflux for 1.5 h. Removal of solvent under reduced pressure yielded the title compound as a mobile, slightly brown oil (3.09 g, 90%). ^{1}H NMR ($CDCl_3$): δ = 7.45 (br. d, J = 8, 2 H, ArH), 7.07 (br. d, J = 8, 2 H, ArH), 4.77 (br. s, 1 H, NH), 2.55 [hept, 1 H, $(CH_3)_2CH$], 1.91 (s, 3 H, N=C–CH_3), 1.14 ppm [d, 6 H, $CH(CH_3)_2$]. IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 3300–3500 (C=N–H, weak), 3100 (C–H), 1650 (C=C), 1530 (C=N), 1150–1300 cm^{-1} (C–F). MS: *m*/*z* 244 [M^+, 8.3], 201 [M^+ – $C(CH_3)_2$-H, 9.2], 186 [M^+ – $CH_3C(CH_3)_2H$, 8.2], 172 [M^+ – N=$CCH_3(CH_3)_2$-H, 4.5], 171 [–HN=$CCH_3(CH_3)_2H$, 3.1], 145 (base peak, 100%), 69 (CF_3 fragment, 17.4).

2,3,3-Trimethyl-5-(trifluoromethyl)-3*H*-indole: Isopropyl methyl ketone [4-(trifluoromethyl)phenyl]hydrazone (2.68 g, 10.98 mmol) and boron trifluoride–diethyl ether (1.56 g, 10.99 mmol), in acetic acid (30 mL), were heated under reflux for 1 h prior to stirring at room temperature for 3 h. After this period the resulting mixture was filtered and the acetic acid removed under reduced pressure to yield a light brown oil. Column chromatography of the oil was carried out over silica, using ethyl acetate as the eluent, to yield the title compound as a reddish oil (1.65 g, 54%). ^{1}H NMR ($CDCl_3$): δ = 7.5–7.7 (m, 3 H, ArH), 2.3 (s, 3 H, N=CCH_3), 1.3 ppm [s, 6 H, *gem* $C(CH_3)_2$]. IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 2900–3000 (satd. C–H), 1600 (C=C), 1530 (C=N), 1250 cm^{-1} (C–F). MS: *m*/*z* 228 [M^+ + 1, 20.6], 227 (M^+, 98.1), 226 [M^+ – 1, 69.3], 212 (base peak, 100%).

Tetramethyl-5-(trifluoromethyl)indolium Iodide: 2,3,3-Trimethyl-5-(trifluoromethyl)-3*H*-indole (1.60 g, 7.05 mmol) and methyl iodide (0.96 g, 7.06 mmol) in diethyl ether (50 mL) were heated under reflux for 26 h. Removal of the solvent and excess methyl iodide under reduced pressure yielded a white solid. The solid was recrystallised from ethanol to yield the title compound as a white solid (1.39 g, 51%), m.p. 206–208 °C. ^{1}H NMR ($CDCl_3$): δ = 8.1–8.4 (m, 3 H, ArH), 4.02 (s, 3 H, N^+–CH_3), 2.8 (s, 3 H, N^+=C–CH_3), 1.6 ppm [s, 6 H, *gem* Ar-$C(CH_3)_2$]. IR ($CDCl_3$, film): $\tilde{\nu}_{max}$ = 1500–1450 (C=N), 1660, 1610 (C=C), 1400 (C–N), 1300–1150 (C–F), 1100 cm^{-1} (C–C). MS: *m*/*z* 242 (M^+ – H1, 10.0), 18 (base peak, 100%). (M – HI) Acc EI $C_{13}H_{14}NF_3$ calcd. 241.1078; found 241.1078.

1,3,3-Trimethyl-2-methylene-5-(trifluoromethyl)indolenine: 1,2,3,3-Tetramethyl-5-(trifluoromethyl)indolium iodide (1.15 g, 3.17 mmol) was dissolved in a 40% sodium hydroxide solution (25 mL) and the resulting solution vigorously stirred, under a diethyl ether layer, until the disappearance of the methiodide (24 h, detected by TLC). A further quantity of diethyl ether (10 mL) was added, with stirring continued for a further 4 h. The ether layer was separated, dried (anhydrous sodium sulfate), and filtered to yield a yellow oil, which quickly darkened on exposure to air (the extremely unstable oil was stored under nitrogen at 0 °C, wrapped in silver foil). The oil was triturated with cold diethyl ether (10 mL) to leave behind the pure title compound as a yellow solid (0.26 g, 34%). ^{1}H NMR: No data available (the solid is not sufficiently soluble in any common solvent). IR (Nujol): $\tilde{\nu}_{max}$ = 2750 (satd. C–H), 1650 (C=C), 1240 (C–N), 720 cm^{-1} (C–F). MS: *m*/*z* 244 (M^+ + 3, 27), 243 [M^+ + 2, 40], 242 [M^+ + 1, 22], 241 [M^+, 12], 183 (base peak, 100%).

Supporting Information (see also the footnote on the first page of this article): Typical UV-Vis absorption spectra of **1** and **2**, ^{1}H NMR spectra for compounds of type **3**, **4** and **5**.

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[1] a) I. Willner, B. Wilner, "Chemistry of Photobiological Switches", in *Biological Applications of Photochemical Switches* (Ed.: H. Morrison), John Wiley & Sons, New York, **1993**, pp. 1–110; b) J. D. Winkler, K. Deshayes, B. Shao, "Photochemical Binding, Release and Transport of Metal Ions", in *Biological Applications of Photochemical Switches* (Ed.: H. Morrison), John Wiley & Sons, New York, **1993**, pp. 171–196.

[2] a) M. Inouye, *Coord. Chem. Rev.* **1996**, *148*, 265–283; b) M. Inouye, K. Akanatsu, H. Nakazumi, *Chem. Commun.* **1997**, *119*, 9160; c) J. Zhou, F. Zhao, Y. Li, F. Zha, X. Song, *J. Photochem. Photobiol. A: Chem.* **1995**, *92*, 193; d) M. V. Alfimov, Y. V. Fedorov, O. A. Fedorova, S. P. Gromov, R. E. Hester, I. K. Lednev, J. N. Moore, V. P. Oleshko, A. I. Vedernikov, *J. Chem. Soc. Perkin Trans. 2* **1996**, 1441; e) M. V. Alfimov, A. V. Churakov, Y. V. Fedorov, S. P. Gromov, R. E. Hester, A. K. Howard, L. G. Kuzimina, I. K. Lednev, J. N. Moore, *J. Chem. Soc. Perkin Trans. 2* **1997**, 2249; f) O. A. Fedorova, Y. P. Strokach, S. P. Gromov, A. V. Koshkin, T. M. Valova, M. V. Alfimov, A. V. Feofanov, I. S. Alaverdian, V. A. Lokshin, A. Samat, R. Guglielmetti, R. B. Girling, J. N. Moore, R. E. Hester, *New J. Chem.* **2002**, *26*, 1137.

[3] a) R. C. Bertleson, "Photochromism", in *Techniques of Organic Chemistry* (Ed.: G. H. Brown), Wiley Interscience, New York, **1971**, chapter 3, pp. 45–294; b) R. Guglielmetti in *Photochromism Molecules and Systems* (Eds.: H. Dürr, H. Bouas-Laurent), Elsevier, Amsterdam, **1990**, chapter 8, pp. 314–466.

[4] a) K. Kimura, T. Yamashita, M. Yokoyama, *J. Chem. Soc., Chem. Commun.* **1991**, 147; b) K. Kimura, T. Yamashita, M. Yokoyama, *J. Chem. Soc. Perkin Trans. 2 Trans. 2* **1992**, 613.

[5] K. Kimura, *Coord. Chem. Rev.* **1996**, *148*, 41.

[6] K. Kimura, M. Kaneshiga, T. Yamashita, M. Yokoyama, *J. Org. Chem.* **1994**, *59*, 1521.

[7] M. Tanaka, K. Kamada, H. Ando, T. Kitagako, Y. Shibutani, S. Yajima, H. Sakamoto, K. Kimura, *Chem. Commun.* **1999**, 1453.

[8] a) C. J. Roxburgh, P. G. Sammes, *Eur. J. Org. Chem.* **2006**, *4*, 1050–1056; b) C. J. Roxburgh, P. G. Sammes, *Dyes Pigm.* **1995**, *28*, 317–325.

[9] a) C. J. Roxburgh, A. Abdullah, P. G. Sammes, *Dyes and Pigments*, **2008**, *76*(2), 319–326: C. J. Roxburgh, A. Abdullah, P. G. Sammes, *Dyes and Pigments*, **2006** (published online), 10.1016/j.dyepig.2006.09.002 (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TFY-4M7DRYF-1&_user=10&_coverDate=10%2F30%2F2006&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=b642c38d9c143eef32289a920df8b35f)); b) C. J. Roxburgh, P. G. Sammes, see ref.[8b], and unpublished observations/spectra.

[10] R. Guglielmetti, A. Kellmann, L. Lindqvist, S. Monti, F. Tfibel, *J. Photochem.* **1985**, *28*, 547–558; **1986**, *35*, 155–167.

[11] E. Berman, R. E. Fox, F. D. Thompson, *J. Am. Chem. Soc.* **1959**, *81*, 5605.

[12] R. E. Lyle, L. Skarlos, *J. Chem. Soc., Chem. Commun.* **1966**, 644–646.

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