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Steric and electronically biasing substituent effects on the Photoreversibility of novel, 3′-, 5′- and 3-substituted indolospirobenzopyrans. Thermal evaluation using ^{1}H NMR spectroscopy and Overhauser enhancement studies

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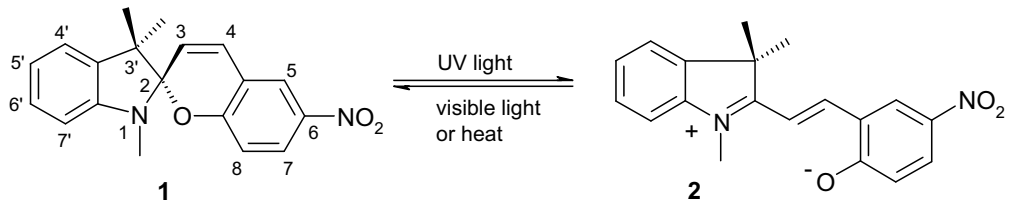
ABSTRACT

Several, novel, 3′-, 5- and 3-substituted indolospirobenzopyrans were prepared and their reversible thermochromic equilibria were investigated by synthesising derivatives with appropriately placed "electronically" modifying substituents in both the indole and benzopyran rings as well as by synthesising structural variants that contained sterically hindering (with regard to spiropyran-opening ↔ closing) groups, within the spirocyclic ring-system. In addition, structural combinations of the above, involving the syntheses of sterically restricted and electronically biasing substituents were prepared and their effects upon the spiropyran ring-opening ↔ closing process investigated. The influence of these steric and electronic substituent effects on the relative quantities of the open- and closed-forms was established using ^{1}H NMR at six temperature intervals (298, 320, 340, 360, 380 and 410 K). Further elucidation of the stereochemical conformation in these systems was undertaken using nuclear Overhauser enhancement (nOe) studies.

1. Introduction

Currently, there is significant research 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 research groups have made contributions to this area [2]. A popular substrate for such studies is the 6-nitrospiro[1-benzopyran-2,2′-indole] system **1** and its analogues since these have well-documented photochemical properties [3]. Photoirradiation with UV light centred around 360–380 nm (see typical UV–VIS absorption spectra-(a)) leads to the formation of the ring-opened zwitterionic (-merocyanine) form **2**, which can be converted back to the ring-closed spirocyclic structure **1**, either by photoirradiation with visible light centred around 520–570 nm (see typical UV–VIS absorption spectra-(b)), or thermally. This process may be repeated many times and has formed the basis of light-induced ionic switches. The reversible chelation of specific metal-ions has been reported in other systems.[4–7]



1 **2**

UV/Vis Light Equilibrium for Indolospirobenzopyrans

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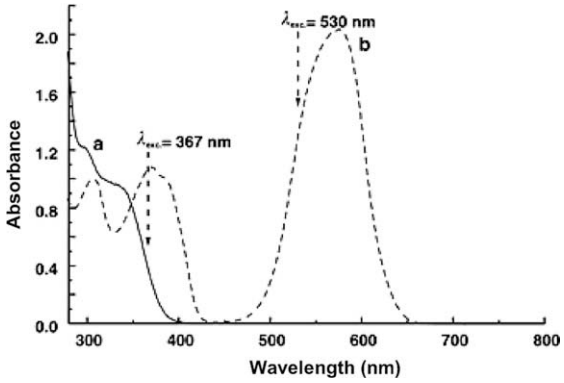
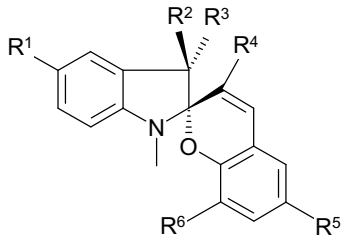


Typical UV-VIS Absorption Spectra of the closed- **(a)**, and open- **(b)** Indolospiropyrans



3 R^1=H, R^2=R^3=CH_3, R^4=H, R^5=NO_2, R^6=NO_2
4 R^1=H, R^2=R^3=CH_3, R^4=CH_3, R^5=NO_2, R^6=NO_2
5 R^1=H, R^2=R^3=cyclohexyl, R^4=H, R^5=NO_2, R^6=NO_2
6 R^1=CF_3, R^2=R^3=CH_3, R^4=H, R^5=H, R^6=OMe
7 R^1=CF_3, R^2=R^3=cyclohexyl, R^4=H, R^5=H, R^6=OMe
8 R^1=H, R^2=R^3=CH_3, R^4=CH_3, R^5=NO_2, R^6=OMe

2. Results and discussion

2.1. Steric biasing: variable temperature studies using ^{1}H NMR spectroscopy

In order to study the effect that steric interactions exert on the biasing of the open ↔ closed equilibrium in indolospirobenzopyrans (*cf.* 1 ↔ 2), variable temperature ^{1}H NMR spectroscopy studies were undertaken on the compounds **3**–**5** depicted above. [Note: these studies were conducted in d_6-dimethyl sulfoxide (DMSO): In some instances, particularly noticeable in structures **6** and **7**, the incompletely deuterated methyl group (centred at $\delta\sim=2.5$ ppm), and the absorbed water peak (variably centred at $\delta\sim3.3$ ppm) were evident. This was the case even when utilising "the best" commercially available deuterated solvents]. In particular, the group was interested in investigating the effects of alkyl group substitution (both position and type), since these interactions could be beneficially used in the design of "tuneable" photoreversible systems; and ultimately possess the potential to be utilised in other photochromic systems.

In theory, if a pure, clean on/off switchable photoreversible ion-chelating system is to be achieved facile room-temperature ring-opening of the spirobenzopyran requires thermodynamic modification such that it does not too readily occur: An argument therefore exists that the presence of appropriately placed groupings (*i.e.* in the 3-position of the pyran-ring **4**, and in the 3′-position of the indole-ring), would generate significant steric hindrance in the open-form, effectively offering control by thermodynamic inhibition over the spiropyran ring-opening ↔ closing process. The two compounds, **4** (possessing a methyl group in the 3-position of the pyran-ring) and **5** (possessing a 3′-cyclohexyl group in place of the *geminal*-dimethyl functionality) were synthesised; together with the known unsubstituted compound **3**, which additionally acted as a "reference structure". Furthermore, the ability, through further functional group control, to bias the ring-opening ↔ closing equilibrium, was investigated using a combination of "electronically-modifying" and "sterically biasing" substituent control ("tuning"). This was achieved and investigated through the synthesis of compounds **6** and **7**. On the observation (see later) that incorporation of a 3-methyl group into the pyran-ring, and a 3′-cyclohexyl grouping, into the indole-ring produced large biasing effects on the ring-opening ↔ closing equilibrium, a 5-trifluoromethyl grouping was additionally investigated in the presence of these functionalities, and its resultant effects studied (Note: compounds possessing the exact same functionality in the benzene-portion of the benzopyran-ring were not directly synthetically accessible, however this was not entirely necessary in order to investigate the relative equilibrium effects associated with the introduction of a trifluoromethyl substituent in these structures). Lastly, we have attempted to qualify and quantify these steric interactions through nOe spectroscopic studies.

Evaluation of the substituent effects were undertaken using ^{1}H NMR spectroscopy at six temperatures (increasing at regular defined intervals from 298 to 410 K) which are detailed, along with a summary of the ^{1}H NMR results, in Table 1: By varying the temperature and monitoring the spiropyran equilibrium position, we have been able to ascertain a relative indication of the equilibrium-biasing (between the open ↔ closed states), thus enabling the thermal stability of the benzospiropyrans to be ascertained. The results are compared and contrasted to the unsubstituted control reference system **3**. By verification of the relative quantities of open- and closed- forms we have been able to establish the usefulness, in the biasing of the spiropyran ring-opening ↔ closing equilibrium, and subsequently, potential utilisation in other spirobenzopyrans systems, of substituent steric control.

This study potentially allows a further understanding of the changes in the photoequilibrium positions, produced upon functional group substitution. Ultimately, the use of these "controlling groups" may enable one to design and "fine-tune" photoreversible systems which are of benefit in the production of cleaner on ↔ off photochemical switching devices. This, in turn, has wider additional implications in the design of photoreversible ion-chelating applications.

2.2. Typical syntheses of indolospirobenzopyrans exemplified for compound **7**

The syntheses of the indolospiropyrans **3**–**8** were undertaken using standard methods, or slight modifications as indicted in Scheme 1 below. Typically, the appropriately substituted hydrazines and ketones were condensed together to yield the corresponding hydrazones, which were cyclised using the appropriate variations of the Fischer indole synthesis. N-Alkylation of the indoles was affected using various N-alkylating agents, from which the indolenines were obtained, after treatment with ethanolic sodium hydroxide. The final indolospirobenzopyrans were obtained in very good yields by condensation between the appropriate indolenes and salicaldehydes. A typical synthesis is exemplified in Scheme 1 for the novel spiropyran **7**.

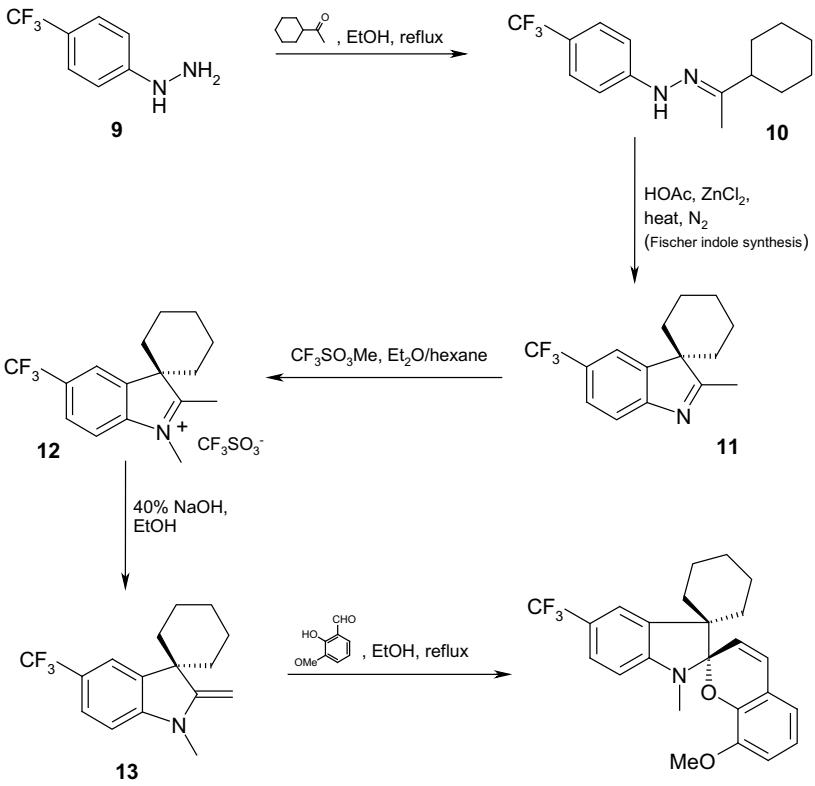
2.3. Discussion for the control reference system **3**

Studies, at predefined temperatures, showed that at room temperature (298 K) the open ↔ closed equilibrium of the control

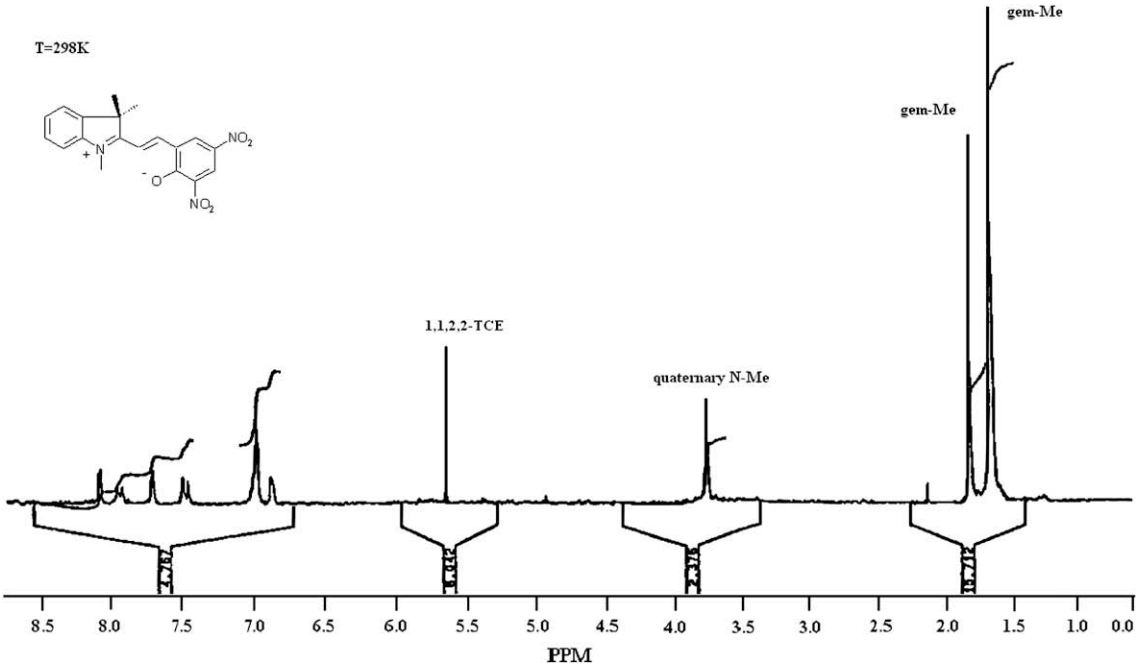
Table 1
Summary of the variable temperature (K) ^{1}H NMR spectral data for systems **3**, **4** and **5**.

	System **3** (R^1 = H, R^2 = R^3 = CH_3, R^4 = H, R^5 = NO_2, R^6 = NO_2)	System **4** (R^1 = H, R^2 = R^3 = CH_3, R^4 = CH_3, R^5 = NO_2, R^6 = NO_2)	System **5** (R^1 = H, R^2 = R^3 = Cyclohexyl, R^4 = H, R^5 = NO_2, R^6 = NO_2)
298 K	Only open-isomer present	Only closed-isomer present	Mixture of closed- and open-isomers present.
Observation	N–CH_3 (s) 3.8 ppm, geminal CH_3 (s) 1.7 & 1.85 ppm, olefinic proton (d, J 15) 8.23 ppm (*trans*).	N–CH_3 2.7 ppm, geminal CH_3 (d) 1.13, 1.16 ppm.	N–CH_3 3.8 ppm (*trans*), N–CH_3 2.78 ppm (*cis*), olefinic proton (d, J 15) 7.3, 8.3 ppm (*trans*), olefinic proton 5.89 ppm, (d, J 10) (*cis*).
320 K	Only open-isomer present	Only closed-isomer present	Mixture of closed- and open-isomers present (increasing amount of closed- form over that at 298 K).
Observation	N–CH_3 3.8 ppm, geminal CH_3 (s) 1.7 & 1.85 ppm, olefinic proton (d, J 15) 8.23 ppm (*trans*).	N–CH_3 2.7 ppm, geminal CH_3 (d) 1.13, 1.16 ppm.	N–CH_3 3.8 ppm (*trans*), N–CH_3 2.78 ppm (*cis*), olefinic proton (d, J 15) 7.3, 8.3 ppm (*trans*), olefinic proton 5.89 ppm, (d, J 10) (*cis*).
340 K	Mixture of closed- and open-isomers present.	Only closed-isomer present	Mixture of closed- and open-isomers present (increasing amount of closed- form over that at 320 K).
Observation	N–CH_3 3.8 ppm, (*trans*), N–CH_3 (s) 2.6 ppm (*cis*), geminal CH_3 (s) 1.3 & 1.6 ppm, (*trans*). [Geminal CH_3 (br) 1.3 (*cis*)]. Olefinic proton (d, J 15) 8.23 ppm (*trans*).	N–CH_3 2.7 ppm, geminal CH_3 (d) 1.13, 1.16 ppm.	N–CH_3 3.8 ppm (*trans*), N–CH_3 2.7 ppm (*cis*), olefinic proton (d, J 15) 8.22, 8.6 ppm (*trans*), olefinic proton 5.7, 6.3 ppm, (d, J 10) (*cis*).
360 K	Mixture of closed- and open-isomers present.	Only closed-isomer present	Mixture of closed- and open-isomers present (increasing amount of closed- form over that at 340K).
Observation	N–CH_3 3.8 ppm, (*trans*) N–CH_3 (s) 2.6 ppm (*cis*), geminal CH_3 (s) 1.3 & 1.6 ppm, (*trans*). [Geminal CH_3 (br) 1.3]. (*cis*) olefinic proton (d, J 15) 8.23 ppm (*trans*) & 6.02 ppm (d, J 10) (*cis*).	N–CH_3 2.7 ppm, geminal CH_3 (d) 1.13, 1.16 ppm.	N–CH_3 3.8 ppm (*trans*), N–CH_3 2.6 ppm (*cis*), olefinic proton (d, J 15) 8.22, 8.6 ppm (*trans*), olefinic proton 5.7, 6.3 ppm, (d, J 10) (*cis*).
380K	Mixture of closed- and open-isomers present.	Only closed-isomer present	Mixture of closed- and open-isomers present (increasing amount of closed- form over that at 360K).
Observation	N–CH_3 3.8 ppm, (*trans*) N–CH_3 (s) 2.6 ppm (*cis*), geminal CH_3 (s) 1.3 & 1.6 ppm (*trans*). [Geminal CH_3 (br) 1.3]. (*cis*) olefinic proton (d, J 15) 8.23 ppm (*trans*) & 6.30 ppm (d, J 10) (*cis*)	N–CH_3 2.7 ppm, geminal CH_3 (d) 1.13, 1.16 ppm.	N–CH_3 3.8 ppm (*trans*), N–CH_3 2.6 ppm (*cis*), olefinic proton (d, J 15) 8.22, 8.6 ppm (*trans*), olefinic proton 5.7, 6.3 ppm, (d, J 10) (*cis*).
410 K	Mixture of closed- and open-isomers present.	Only closed-isomer present	Mixture of closed- and open-isomers present (increasing amount of closed- form over that at 380 K).
Observation	N–CH_3 3.8 ppm, (*trans*) N–CH_3 (s) 2.6 ppm (*cis*), geminal CH_3 (s) 1.5 & 1.8 ppm (*trans*). [Geminal CH_3 (br) 1.3–1.4 (*cis*) olefinic proton (d, J 15) 8.23 ppm (*trans*) & 6.4 ppm (d, J 10) (*cis*).	N–CH_3 2.7 ppm, geminal CH_3 (d) 1.13, 1.16 ppm.	N–CH_3 3.8 ppm (*trans*), N–CH_3 2.7 ppm (*cis*), olefinic proton (d, J 15) 8.22, 8.5 ppm (*trans*), olefinic proton 5.7, 6.3 ppm, (d, J 10) (*cis*).

reference spiropyran system **3** lies entirely towards the *trans*- open-isomer (-merocyanine); this indicates a very facile ring-opening (Spectrum 1, Table 1). [Note: The pyran-ring alkenic protons possess a *cis*- coupling of $J \sim 10$ Hz (closed-form), whilst the same protons, in the *trans*- open-form exhibit a coupling of $J \sim 16$ Hz. A small impurity/solvent peak exists under the most upfield geminal methyl group explaining its slightly enhanced integral]. Elevation of the temperature to 320 K fails to produce any detectable amounts of the closed-form (thermal ring-closure is expected): It is not until 340 K is reached (Spectrum 2, Table 1) before the presence of the



Scheme 1. Synthesis of 1-methyl-8-methoxy-5′-trifluoromethyl-3′-spirocyclohexylspiro-[2*H*-1-benzopyran-2,2′-indoline] **7** – (and typical synthetic procedure for compounds **3**–**8**).



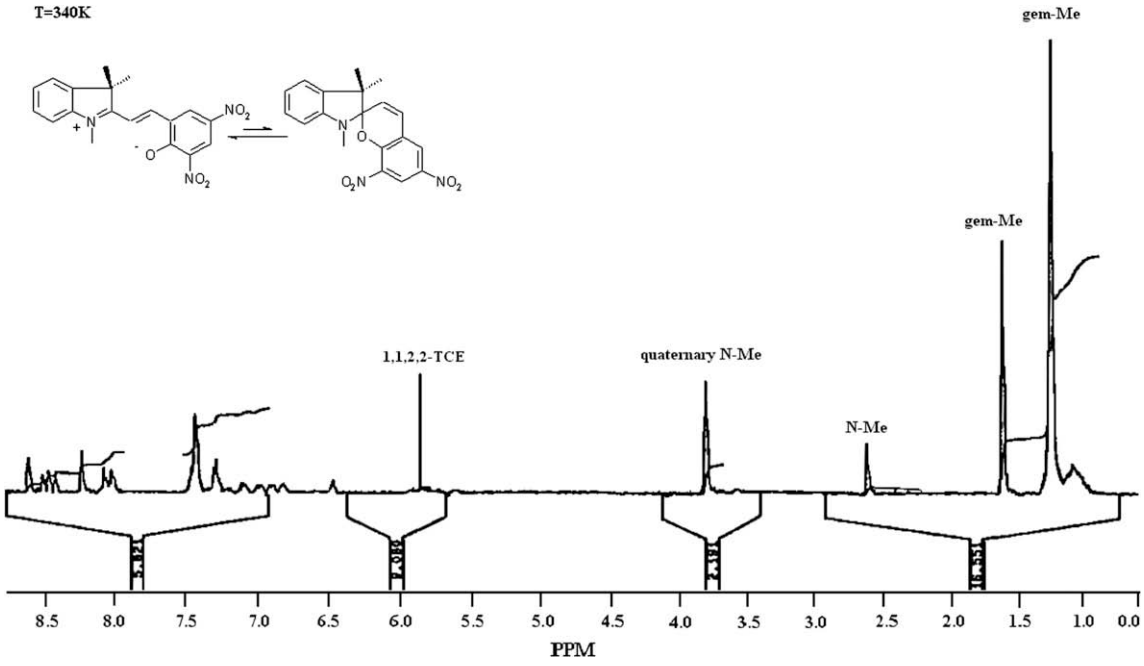
Spectrum 1. [1]H NMR of compound **3** at 298 K.

closed-form (by the known thermal ring-closure mechanism) is observed. Further increases of the temperature, through additional increments to 360 K and 380 K, continue to produce additional quantities of the closed-form (Table 1), until, at 410 K, a steady state equilibrium forms between the closed- and open-forms (Spectrum 3, Table 1). It was not possible to elevate the temperature above 410 K due to the physical limitations of the solvent.

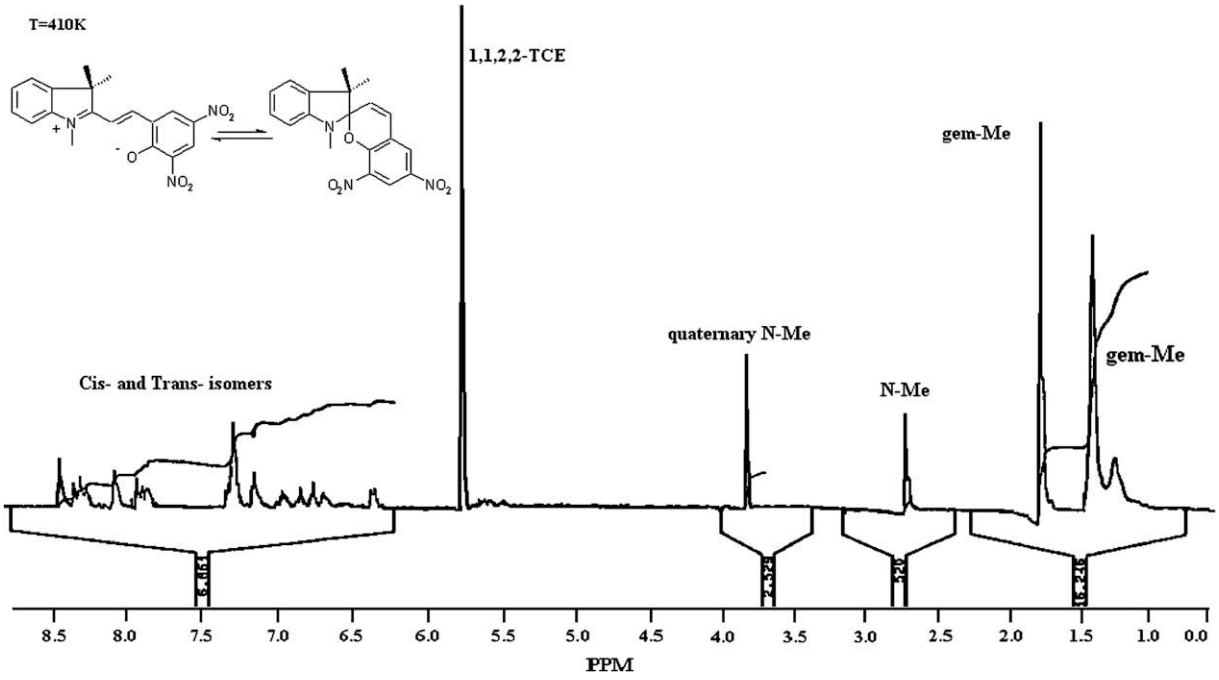
In order to devise a room temperature activated switchable system this facile ring-opening needs to be thermodynamically constrained. The results for this compound therefore clearly demonstrate that increased thermodynamic inhibition of the ring-opening is required in order to produce a room temperature "photocontrollable" system.

*2.4. Discussion for the sterically restricted 3-methyl substituted system **4***

Following the observations above, for the unsubstituted system **3**, that thermal biasing (ring-opening) was occurring too readily at room temperature we decided to investigate the 3-methyl substituted system **4**; A sterically hindering group present in the pyran-ring of the spiropyran was hypothesised to greatly increase the thermal energy



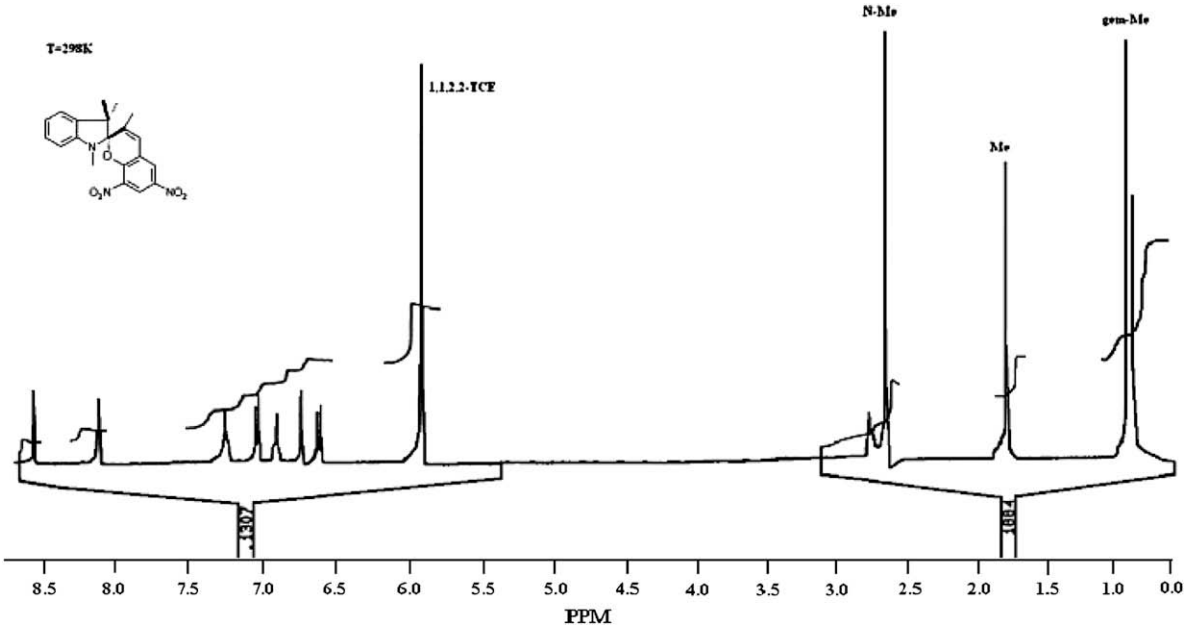
Spectrum 2. [1]H NMR of compound **3** at 340 K.



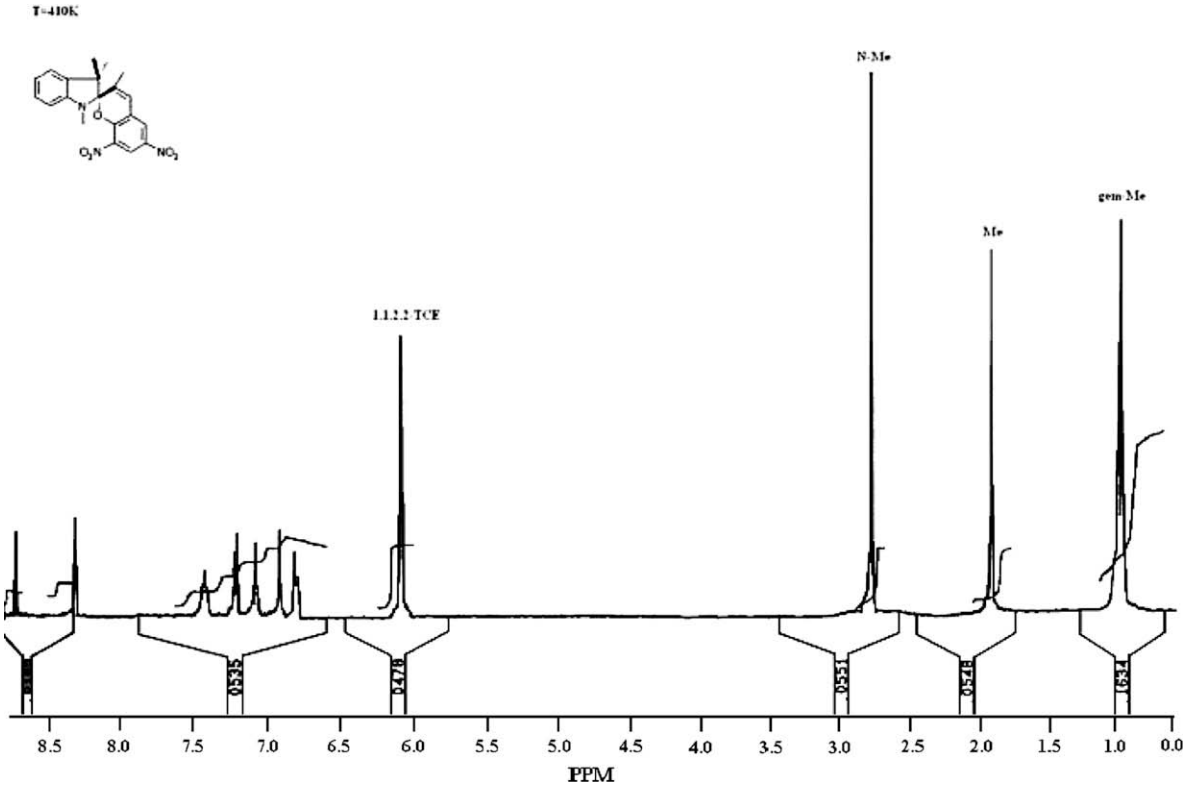
Spectrum 3. ^{1}H NMR of compound **3** at 410 K.

barrier to room temperature ring-opening, and therefore create a system which possessed greater room temperature thermodynamic stability. The synthesis was achieved *via* modified standard methods (*cf.* Scheme 1), the final condensation step being affected by condensation between the appropriate methyl-substituted indolene and the dinitro-salicaldehyde, to produce the required indolospirobenzopyran **4** in an excellent 84% yield (see Experimental for full details).

The variable temperature studies indicate that at room temperature (298 K) (Spectrum 4, Table 1) system **4** exists entirely as the closed-isomer, indicating the 3-methyl group is quantitatively effective in preventing ring-opening; confirming our hypothesis. Increasing the temperature by 112 °C to 410 K failed to bias the equilibrium (produce any measurable quantity of the open-*trans*-isomer: Spectrum 5, Table 1) as expected. Thus it is concluded that the introduction of a 3-methyl substituent into the pyran-ring causes a major perturbation in the thermochromic property of this system by creating a large thermodynamic barrier to *trans*-merocyanine formation: Consequently no light-induced photochromic properties were observed. In the light of the above observations we turned our attention to the investigation of a system which would potentially possess a significant and controllable, but not totally overpowering, biasing effect on the dynamic room temperature equilibrium position. Since 3-methyl substitution obviously produces very large thermodynamic effects, we decided to investigate the introduction



Spectrum 4. ^{1}H NMR of compound **4** at 298 K.



Spectrum 5. ^{1}H NMR of compound **4** at 410 K.

of a significantly sterically bulky large grouping, but in the 3′-position of the indole-ring, since this could potentially generate a fluxional system which is, at room temperature, dynamically balanced, but also controllable. To this end we decided to synthesise the 3′-cyclohexyl-substituted indolospirobenzopyran **5**.

*2.5. Discussion for the sterically restricted 3′-cyclohexyl substituted system **5***

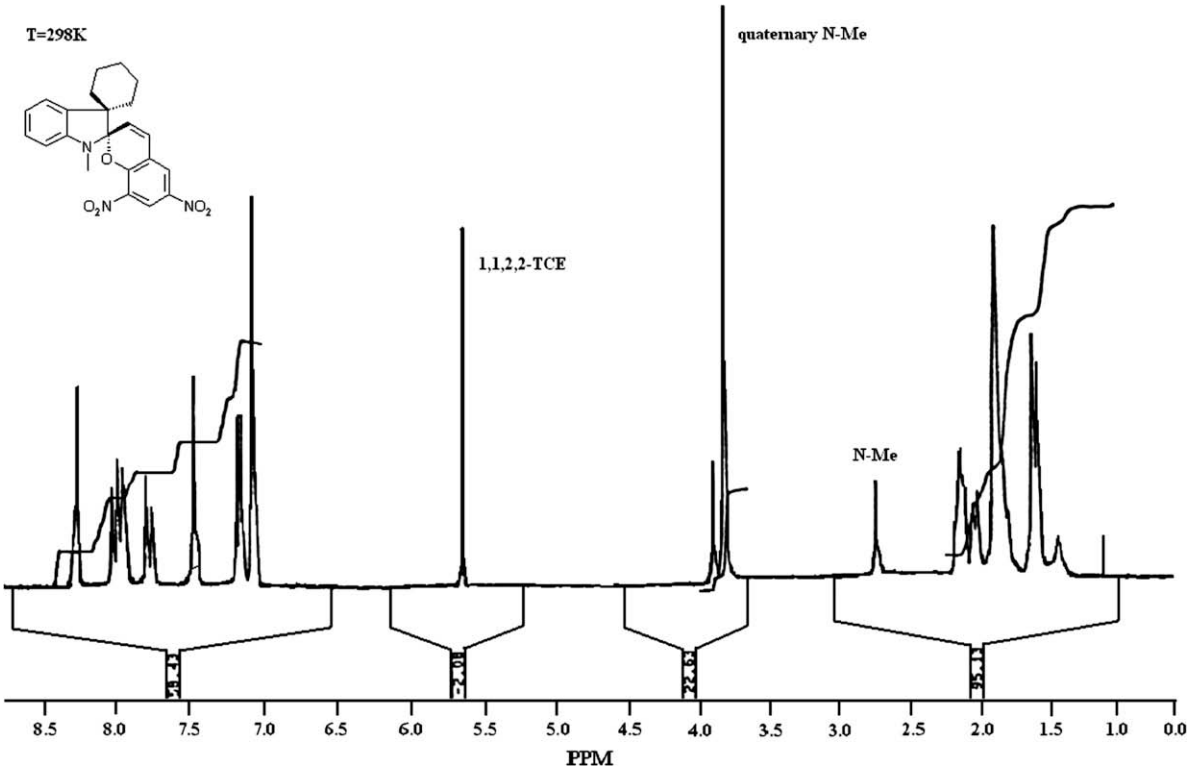
^{1}H NMR spectroscopy studies for the structure **5**, possessing a sterically "bulky" and restricting 3′-cyclohexyl indolic moiety, indicate that at room temperature (298 K) it existed as a mixture of open- and closed-forms. At this temperature it possesses a predominance of the *trans*-open-merocyanine form as evidenced by the indicated absorption strength of the quaternary N-methyl ^{1}H NMR absorption signal (Spectrum 6, Table 1). As the temperature was raised to 320 K (Spectrum 7, Table 1) the quantity of *trans*-open-form decreased (and the associated quantity of the closed-form increased); this trend continued through 320 K and 360 K (Spectrum 8, Table 1) until a temperature of 410 K was attained (Spectrum 9, Table 1). At this temperature a steady state equilibrium was reached in which both the *trans*-open- and *cis*-closed-forms co-existed, but possessed a predominance of the *cis*-closed form (this would be expected since thermal ring-cyclisation is increasingly favoured at elevated temperatures). In conclusion, the introduction of a sterically bulky 3′-cyclohexyl grouping demonstrates that one can exert considerable influence on the thermochromic spiropyran ring-opening ↔ closing process, and consequently potentially influence the photochromic properties of indolospirobenzopyrans. In conclusion we have produced a system which is 'thermodynamically controllable'; particularly, and importantly, at room temperature, and which has potentially useable and transferable properties in the design and build of future photochromic systems.

In summary, of the three foregoing systems: at room temperature, the open ↔ closed equilibrium position of **5** lies further towards that of the closed-form than **3**, and thus offers increased photodynamic control, particularly with regard to "clean" on/off "photocontrollable" switching. Conversely, compound **4** exists entirely in the closed-form at room temperature (see above), it not being possible to bias the equilibrium; thus, this system, as a stand-alone structure, does not exhibit or offer useable photoreversible properties – however, in the presence of a crown, or other intramolecular lariate ether-containing systems, which greatly influences the thermodynamic balance in these systems (often biasing the equilibrium towards the open-form), this substitution may ultimately prove, practically, very useful and useable.

2.6. Steric and electronic biasing: variable temperature studies using ^{1}H NMR spectroscopy

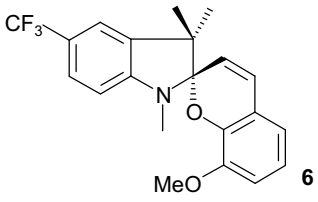
To further investigate functional group substitution, and potential substitutent control/biasing, some further comparative studies were additionally performed on the 5′-trifluoro-substituted system **6**, and the new sterically restricted, 5′-trifluoromethyl-3′-cyclohexyl substituted system **7**. The latter was to investigate the relative and simultaneous effects of the substitution of electronically and sterically influencing functional groups, and their subsequent role in the potential biasing of the dynamic open ↔ closed spiropyran equilibrium. [Note: the "identical" skeletal structures to compounds **3**–**5**, possessing 6,8-nitro-group substitutents, were not synthetically readily accessible. But as mentioned earlier this was not totally necessary in order to substantiate the overall relative biasing effects].

As discussed above, some variable temperature studies, using ^{1}H NMR spectroscopy, were additionally performed on the known structure **6**, which also acted as a reference control compound to compound **7**, and structure **7** (Table 2, Spectra 10–14 below).



Spectrum 6. ^{1}H NMR of compound **5** at 298 K.

*2.7. Discussion for the electronically biased 5′-trifluoromethyl substituted system **6***



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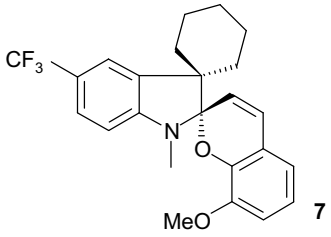
In mind of the observation that compound **3** existed entirely in the *trans*-open-form, at room temperature, it was evident that an appropriate grouping, capable of inhibiting the spirocyclic ring-opening, was required in order to produce an enhanced room temperature photo-labile and controllable system. Thus, a destabilising effect, affected by the introduction of a 5′-trifluoromethyl substituent, potentially enables one to favour the closed-form, which further demonstrates substituent, particularly electronic, control. If one is aiming to produce a room temperature photo-activated and reversible ion-chelating system then a closed-spirocyclic form is initially required: photoirradiation with UV light generates the open-form, whilst photoirradiation with visible light regenerates the closed-form. [Note: this is the traditional photo-irradiation sequence however, it is also possible to start with the open-ion chelated form and 'unchelate' by photoirradiation with visible light; however, this would not be truly photoreversible as removal of the visible light source would allow re-isomerisation to the open-form. Thus, this is effectively a thermochromic ↔ photochromic sequence and not strictly a photoreversible system]. To this end we synthesised the 5′-trifluro-substituted variant, since it is known that this inhibits ring-opening in other similar systems.[8] Variable temperature studies; monitoring using ^{1}H NMR spectroscopy were consequently performed on system **6** (Table 2 – ^{1}H NMR data). At 298 K structure **6** existed entirely in the closed-form (Spectrum 10, Table 2). Elevation of the temperature 62° to 360 K failed to bias the equilibrium position, as expected (Spectrum 11, Table 2). Thus, one can conclude that in this system the powerfully electronegative inductive effect from the trifluoromethyl group results in the equilibrium lying entirely towards the closed-spirocyclic-form, it not being possible to, in any way, bias this potentially dynamic equilibrium.

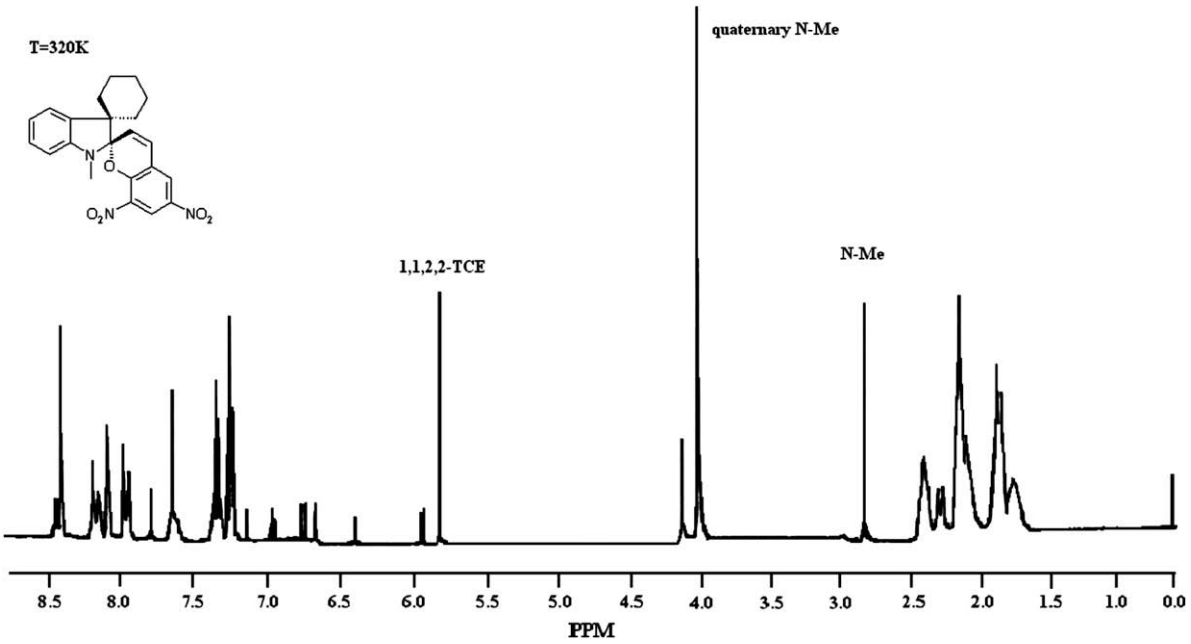
In conclusion, the introduction of a 5′-trifluoromethyl group allows one to produce a system possessing an equilibrium position that lies entirely toward the closed-form; as opposed to the unsubstituted parent structure, which exists as an equilibrium mixture under identical physical conditions.

*2.8. Discussion for the electronically biased and sterically restricted 5′-trifluoromethyl-3-cyclohexyl substituted system **7***



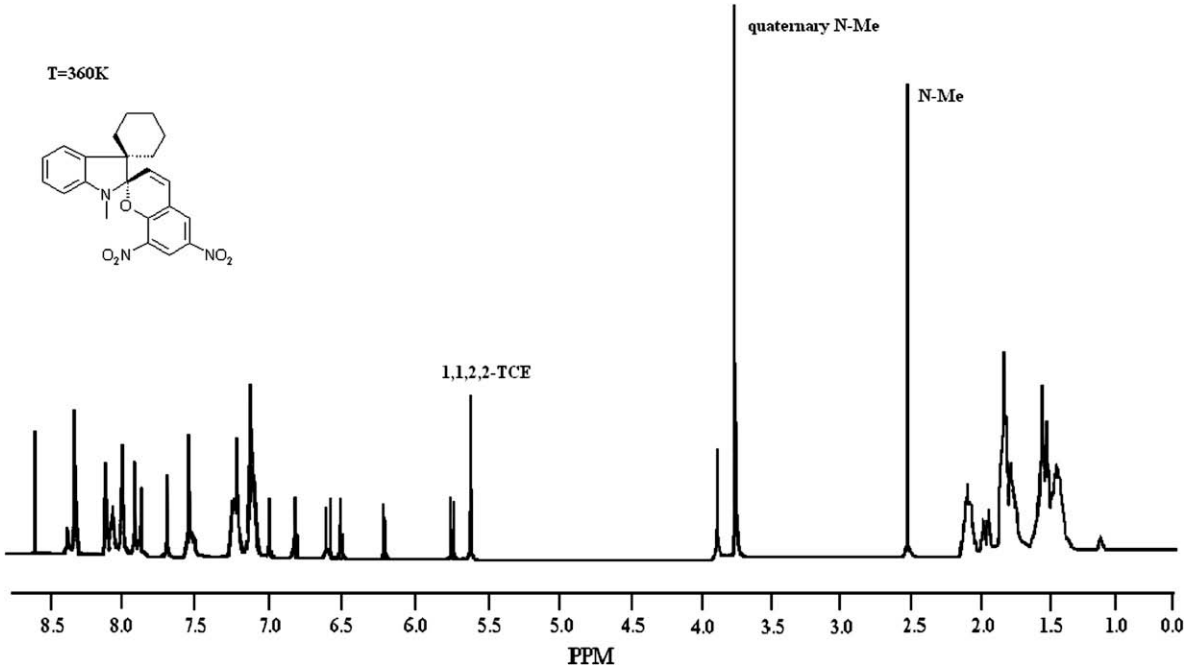
7

In the light of the observations for compounds **5** and **6**, and in particular the fact that **5** existed in a "biasable" and "controllable-equilibrium", possessing a mixture of both open- and closed-forms, we investigated whether it was possible to further bias and

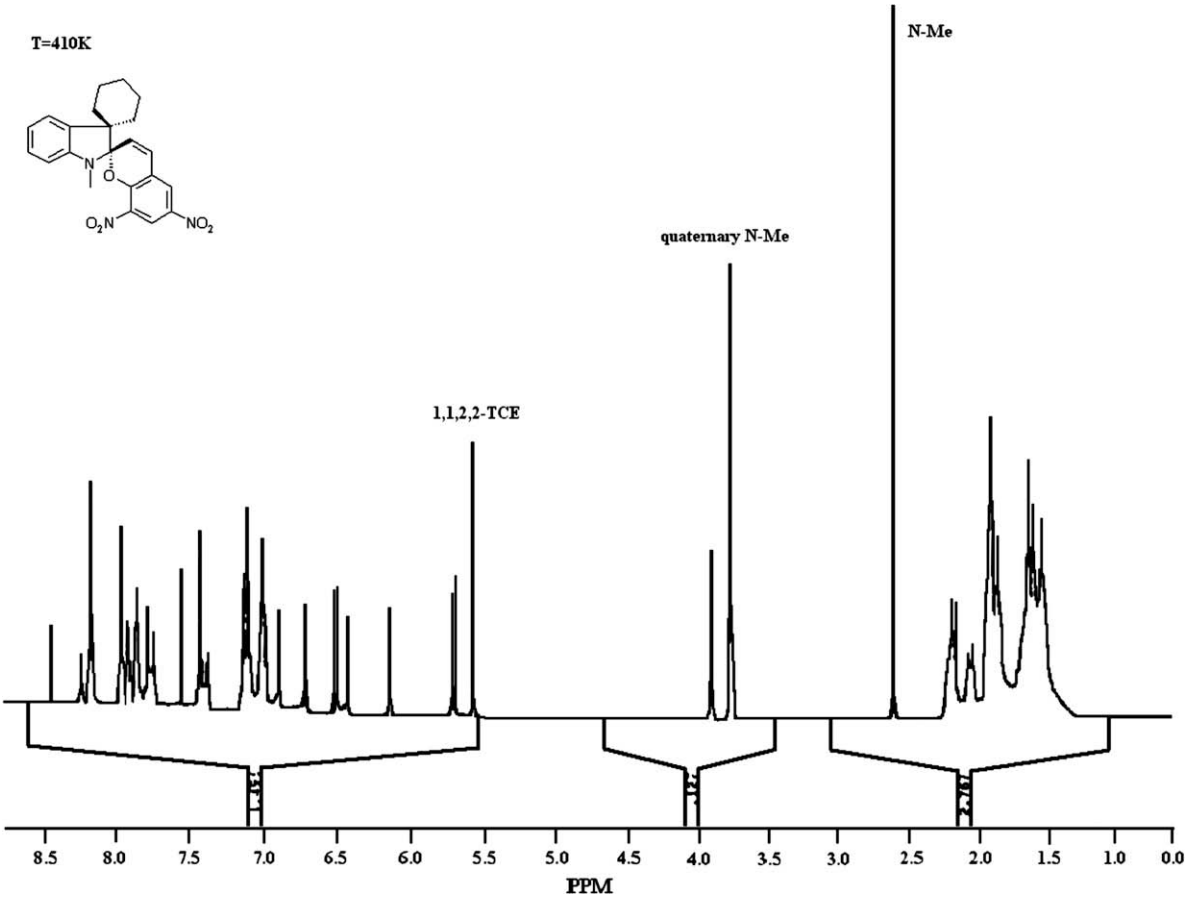


Spectrum 7. ^{1}H NMR of compound **5** at 320 K.

"fine-tune" the dynamic equilibrium position *via* the introduction of a 5′-trifluoromethyl substituent – structure **6** was used as an additional reference. Some variable temperature studies using ^{1}H NMR spectroscopy were thus performed on system **7** depicted above (Table 2). At room temperature (Table 2) **7** existed entirely in the closed-spirocyclic form with no measurable amount of the open-merocyanine detected. Subsequent elevation of the temperature 62° to 360 K produced no thermal biasing of the equilibrium position as expected, as shown in (Spectra 11, Table 2). Thus, unlike **5**, in which it was possible to thermally bias the quantities of open- and closed-forms, it was not possible to influence the equilibrium position, even under photoirradiation with UV light centred at 380 nm. This result clearly indicates that the 5′-trifluoromethyl substituent exerts a powerful negative inductive effect, destabilising production of the open-form (stabilising the closed-form), totally negating its formation. Clearly, the above observations further demonstrate the influence that sterically and electronically modifying substituents exert on the dynamic equilibrium in these systems. In this case the effects were too pronounced; however, to reiterate previous comments, this type of substitution could well prove useful in other systems, particularly when the basic skeleton of **7** is incorporated into a more complex system such as a metal-ion



Spectrum 8. ^{1}H NMR of compound **5** at 360 K.



Spectrum 9. ^{1}H NMR of compound **5** at 410 K.

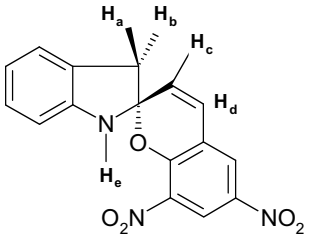
binding, crown ether-containing, structure (or other ion-chelating congeners). Here the combined thermodynamics of the lariate ether's, and open-zwitterionic structures', ion-chelating, which promote formation of the *trans*-open-form, effects counteract those of the electron-withdrawing group, which tends to favour the production of the *cis*-closed form. This results in the production of an overall, more thermodynamically balanced system, which is more readily controlled and biased.

2.9. ^{1}H NMR nOe spectroscopic studies

As the steric effects of introducing a methyl group into the 3-position of the pyran-ring of **4** are so marked, and clearly not fully understood or evaluated, we sought to further investigate this phenomena, on some similarly substituted compounds, using ^{1}H NMR nOe spectroscopic studies.

Previous studies undertaken by Guglielmetti [9] and co-workers on the skeletally similar compound below (Fig. 1) also observed a striking lack of formation of the *trans*-open-form: they ascribed this as possibly due to steric hindrance arising from the 3-methyl-groups substituent; in this particular case Gugliemetti assigned the most stable -isomer as the *cis*-open-form ($t_{1/2}$ = 3 s, λ_{max} at 440 nm).

We therefore decided to investigate structure **4**, and additionally synthesised the new 3-methyl-substituted structure **8** (below) since this not only structurally resembled the substituted indolo-spirobenzopyrans described here, but also, closely skeletally resembled Gugliemetti's structure depicted in Fig. 1 (with respect to substitution in the benzopyran-rings).



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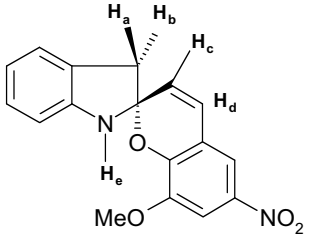


8

The various functionality producing immediate and direct steric interactions, associated with, and affecting the spirocyclic

Table 2
Summary of the variable temperature (K) ^{1}H NMR spectral data for systems **6** and **7**.

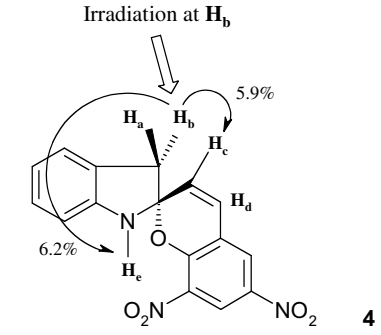
	System **6**	System **7**
298 K	Only closed-isomer present	Only closed-isomer present
Observation	N–CH_3 2.78 ppm, olefinic proton 6.9 ppm (d) J 10, geminal CH_3 (d) 2.2, 1.9 ppm.	N–CH_3 2.77 ppm, olefinic proton 6.8 ppm (d) J 10, geminal CH_3 (d) 2.2–2.8 ppm.
360K	Only closed-isomer present	Only closed-isomer present
Observation	N–CH_3 2.78 ppm, olefinic proton 6.9 ppm (d) J 10, geminal CH_3 (d) 2.2, 1.9 ppm.	N–CH_3 2.77 ppm, olefinic proton 5.8 ppm (d) J 10, geminal CH_3 (d) 2.2–2.8 ppm.

ring-opening ↔ closing reaction was subjected to individual irradiations, and the nOe spectra recorded.

The ^{1}H NMR nOe's are reproduced in Spectra 12–17 below, however, for ease of comparison and immediacy the signal enhancement data are summarised in Tables 3,4 and 5 below.

2.10. nOe studies of compound **4**

nOe studies were initially performed, with irradiations affected as indicated in the diagrams below, on structure **4** (see Table 3 for summary signal enhancement data).



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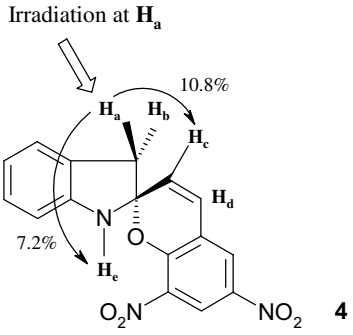

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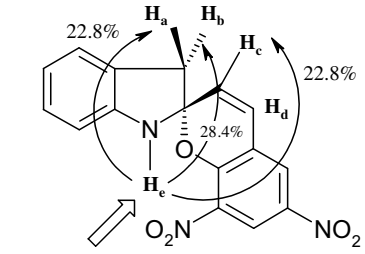

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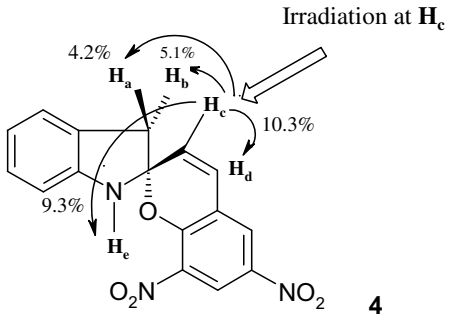
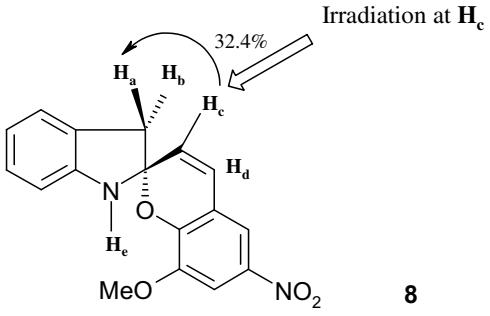


4

In summary, the effect of irradiating the 3-methyl group protons (***H*c**) resulted in a 4.2% and 5.1% through-space changes in the absorbance values of the geminal-dimethyl group protons (***H*a**) and (***H*b**), respectively: conversely irradiation of the geminal-dimethyl group protons ***H*a** and ***H*b** of **4** produce absorbance changes of 10.8% and 5.9%, respectively, in the absorbance shift values of ***H*c**.

2.11. nOe studies of compound **8**

nOe studies were subsequently performed, on structure **8**, with irradiations affected as indicated in the two diagrams below (see Table 4 for summary signal enhancement data).



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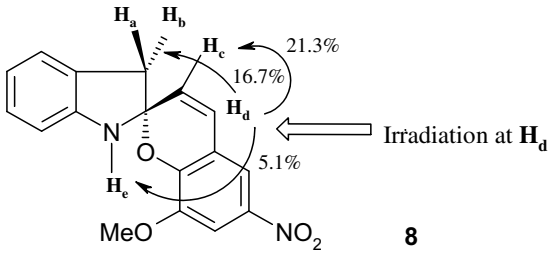

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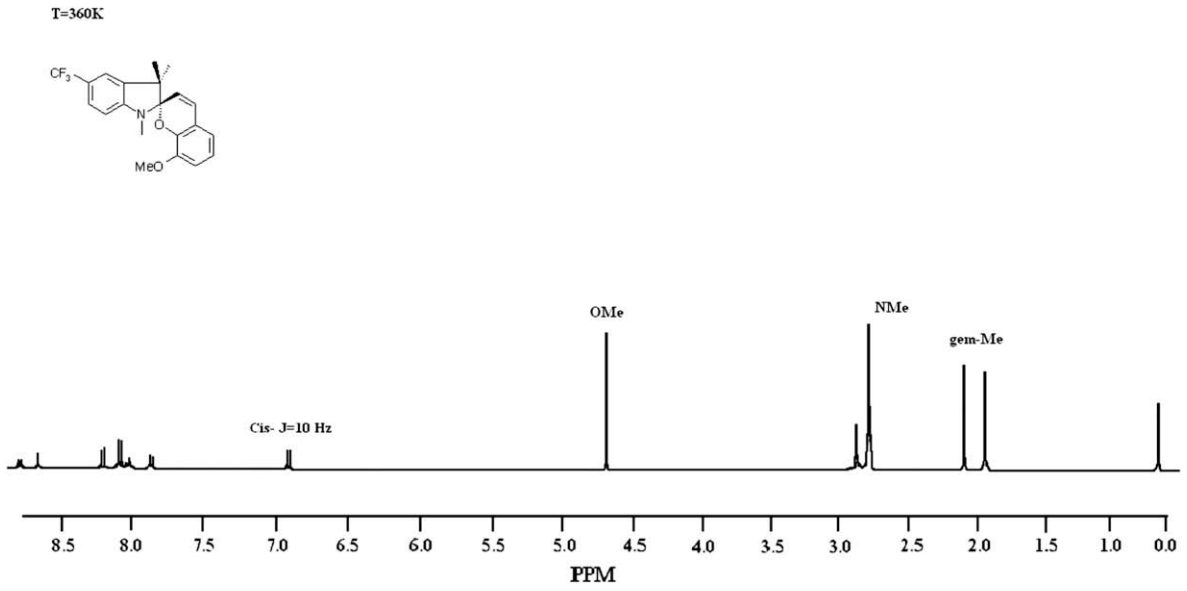
Irradiation of the 3-methyl protons (***H*c**) induces a 32.4% change in the absorbance resonance values of protons ***H*a** and ***H*b**; irradiation of the alkenic proton ***H*d** induces a much reduced, as expected, 16.7% change in the absorbance value of the geminal-dimethyl protons (***H*a**, ***H*b**) and an associated absorbance change of the



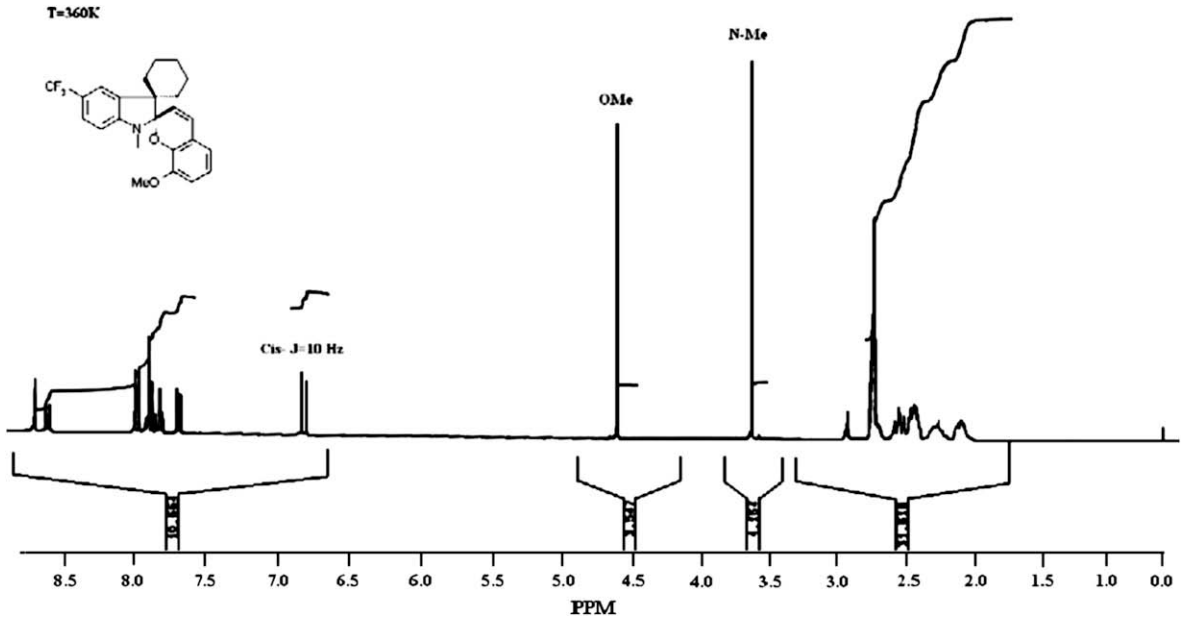
Spectrum 10. ^{1}H NMR of compound **6** at 360 K.

N-methyl protons at $\boldsymbol{H_e}$ of 5.1% due to increased distance effects. Additionally, irradiation of the $\boldsymbol{H_d}$ proton is also informative in that it enforces the fact that there is a larger interaction between itself and the $\boldsymbol{H_c}$ protons (21.3%), than the $\boldsymbol{H_a}$/$\boldsymbol{H_b}$ protons (16.7%), which would also be expected due to increased distance.

[Note: in the case of compound **4**, irradiation at $\boldsymbol{H_c}$ produces an enhancement of 10.3% at $\boldsymbol{H_d}$. This value is reproduced for academic completeness; however, as mentioned previously we were only interested in the magnitude of interactions between the groups that directly play a role in the ring-opening ↔ closing sequence. Thus, in the case of compound **8**, although irradiation of the protons at $\boldsymbol{H_c}$ would certainly produce an effect at the proton $\boldsymbol{H_d}$, it is academic and superfluous to our argument, and thus, is not measured].

From the nOe data it is therefore clear that there are large through-space interactions between the 3-methyl and geminal-dimethyl groups, confirming the observation that the 3-methy groups produce a major influence on the spirobenzopyran ring-opening process. The relatively large coupled-effect existing between the alkenic $\boldsymbol{H_d}$ proton and the methyl ($\boldsymbol{H_c}$, $\boldsymbol{H_a}$/$\boldsymbol{H_b}$), and even $\boldsymbol{H_e}$ protons is perhaps a little surprising; the latter two obviously occurring largely *via* a "through-space", rather than a "through-bond" effect, since these are separated by five covalent bonds (through-bond ^{1}H NMR chemical shift changes are unusual through more than four covalent bonds).

In summary, the groups that produced the most pronounced biasing effects on the spiropyran ring-opening ↔ closing process, in compounds **4** and **8**, are those that directly sterically interfere *i.e.* the pyran-3-methyl and geminal-dimethyl groups: From this



Spectrum 11. ^{1}H NMR of compound **7** at 360 K.

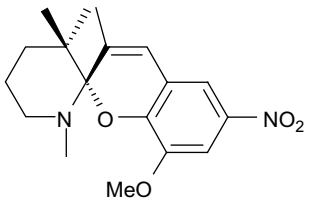


Fig. 1.

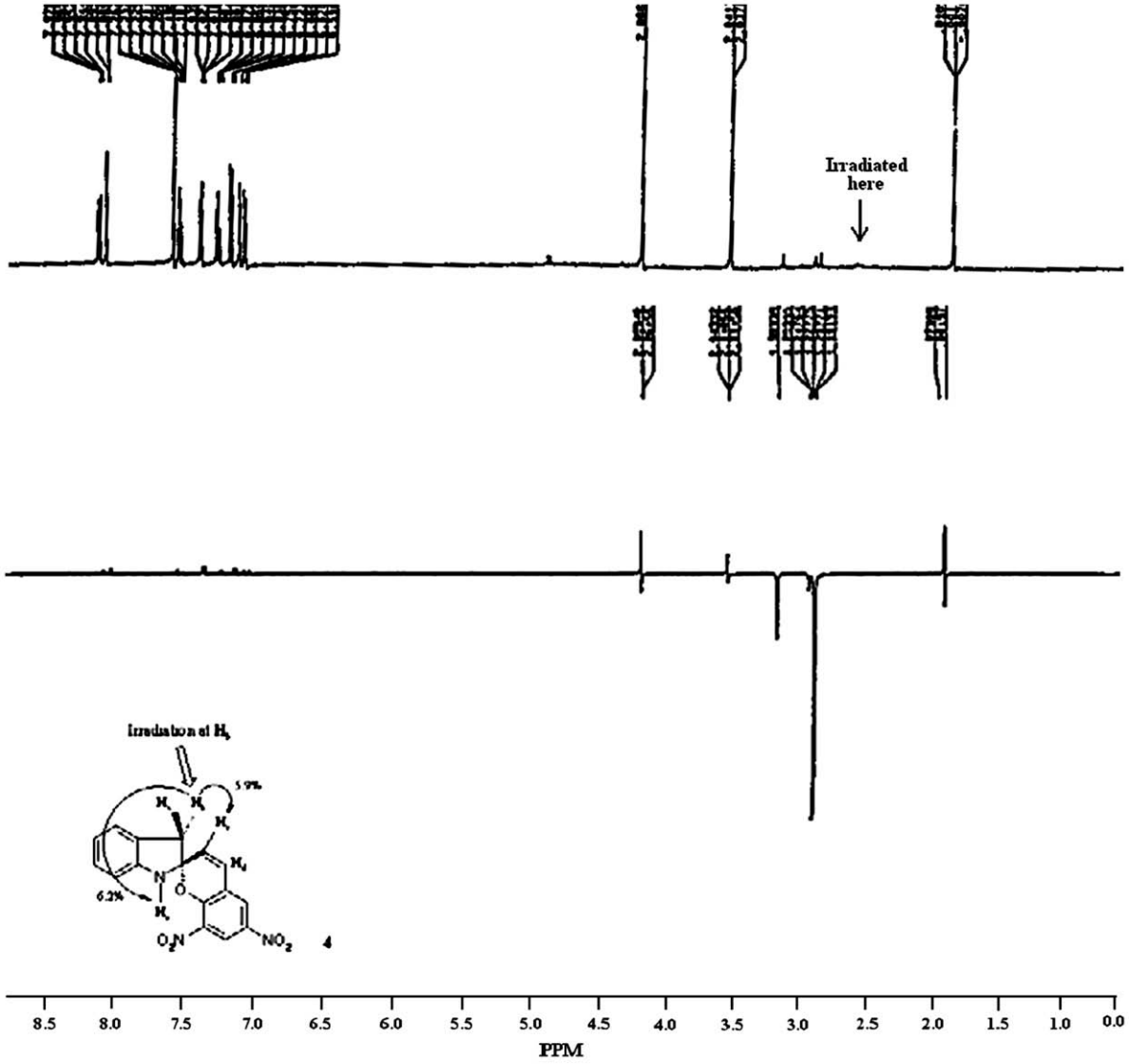
perspective, the peak enhancement values, on irradiation of these groups are the most pertinent to consider in detail.

For compound **4**: the effect of irradiating the 3-methyl group protons ($\boldsymbol{H_c}$) resulted in a 4.2% and 5.1% changes in the peak absorbance values of the geminal-dimethyl group protons ($\boldsymbol{H_a}$) and ($\boldsymbol{H_b}$), respectively – conversely irradiation of the geminal-dimethyl group protons $\boldsymbol{H_a}$ and $\boldsymbol{H_b}$ produce changes of 10.8% and 5.9% respectively in the absorbance values of the $\boldsymbol{H_c}$ protons.

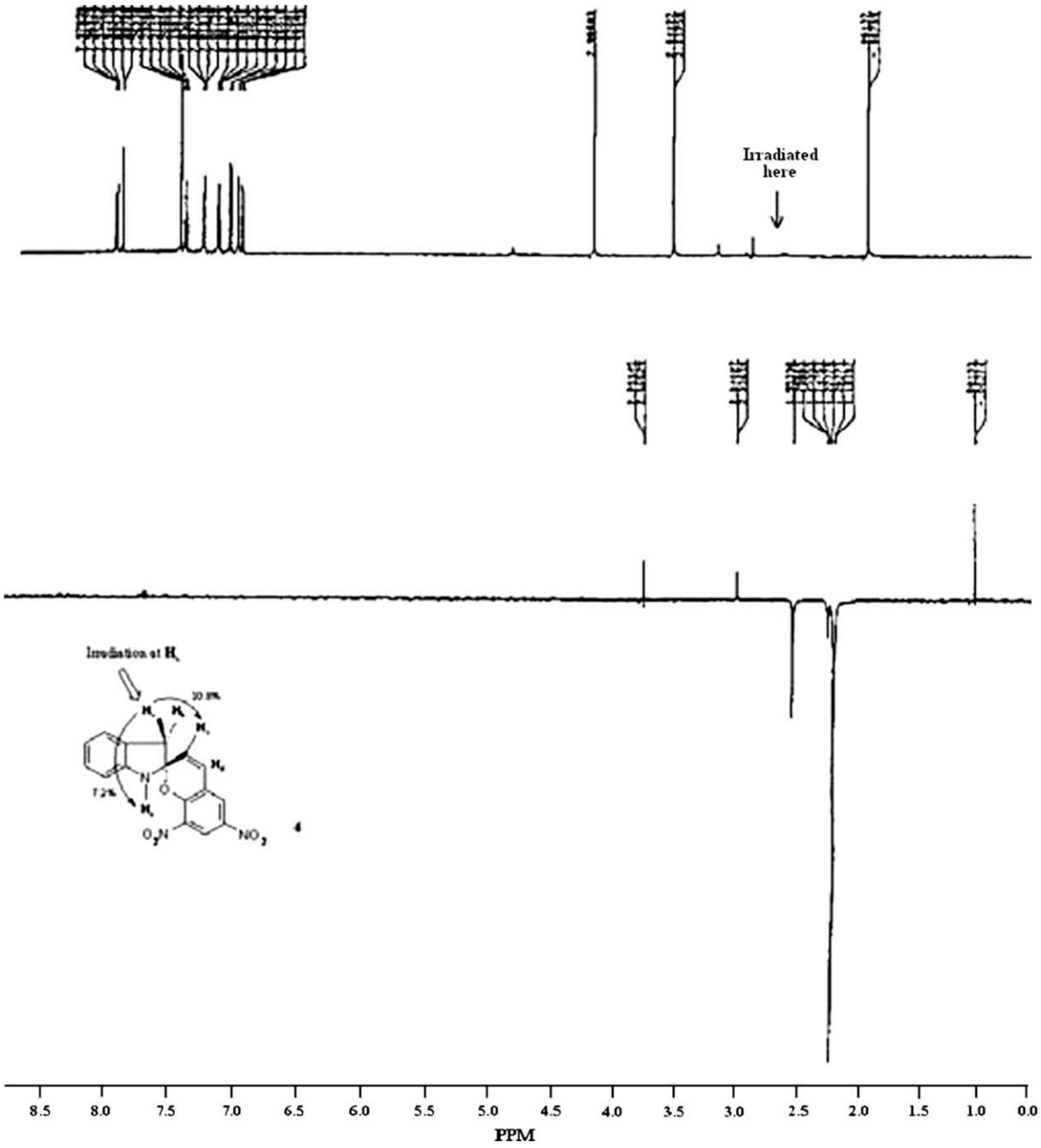
For compound **8**: the effect of irradiating the 3-methyl group protons ($\boldsymbol{H_c}$) resulted in a 32% absorbance change of the geminal-dimethyl group protons ($\boldsymbol{H_b}$ and $\boldsymbol{H_c}$), thus indicating a significant and greater relative interaction than for compound **4**. Therefore, there is a dramatic measured difference in the degree of intramolecular interaction between the 3-methyl and geminal-dimethyl groups, not only within compounds **4** and **8**, but, and particularly, between them: This is exemplified in Table 5, which indicates the relative percentage difference is 671%. This result is surprising since the Dreiding models of both compounds indicate similar steric interactions; the only difference between these two compounds being the 8-methoxy-group of **8**, as opposed to the 8-nitro-substituent of **4**.

We believe that there are two possible explanations for these large differences, the latter being the more plausible.

Firstly; the 8-methoxy-group of **8**, being significantly more electron-donating (by mesomeric effects) than the corresponding nitro- group of **4**, influences the electron density (and thus absorbance values), and hence the magnitude of interactions between of the protons at $\boldsymbol{H_c}$ (and thus, indirectly, $\boldsymbol{H_a}$/$\boldsymbol{H_b}$ – by through-space effects) by through-the-bonds mesomeric effects, which become evident on nOe irradiation [Note: this positive mesomeric effect would largely reside at the base of the 3-methyl-group's bond



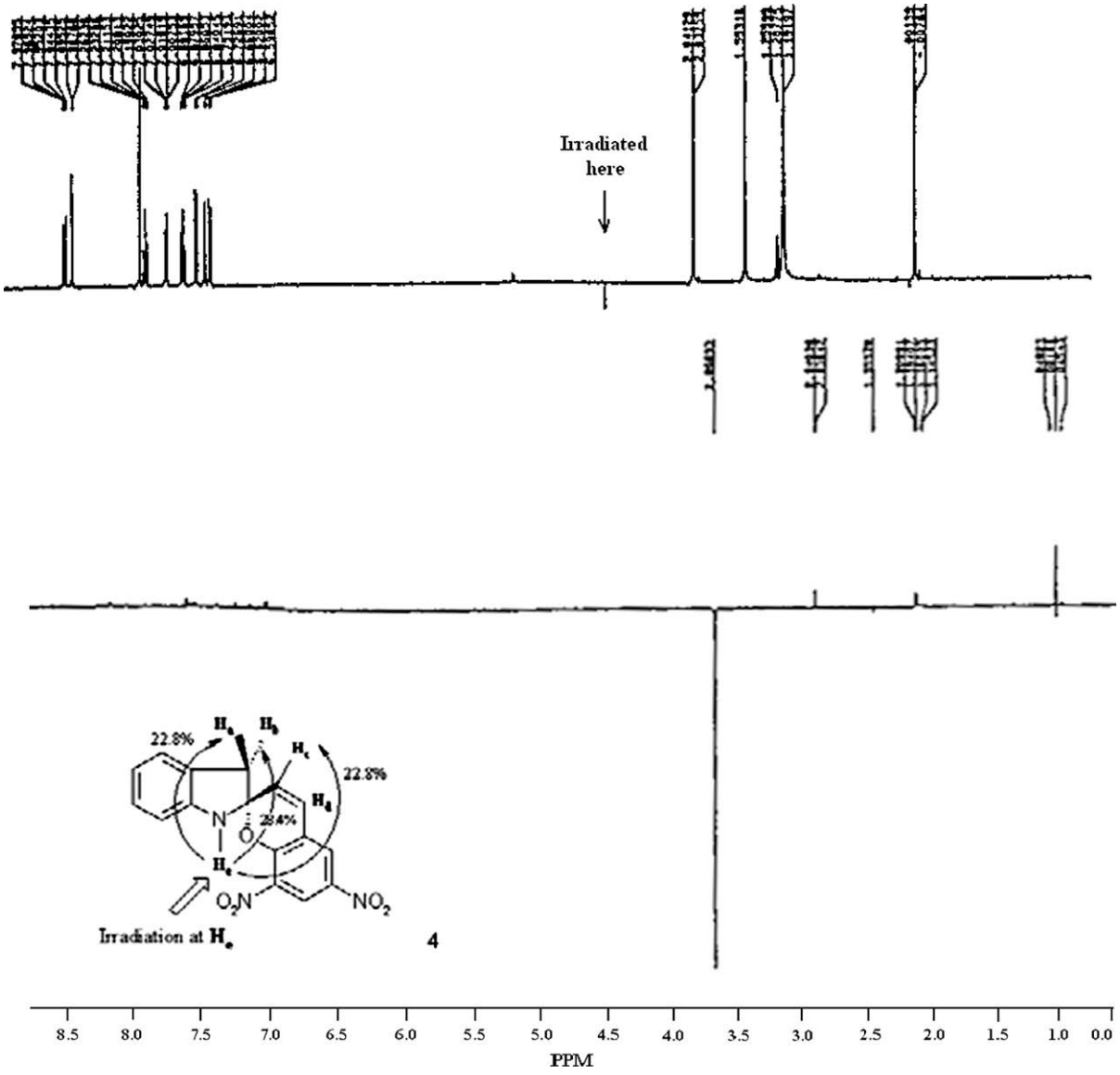
Spectrum 12. nOe spectrum of **4** during irradiation of the methyl protons at $\boldsymbol{H_b}$.



Spectrum 13. nOe spectrum of **4** during irradiation of methyl protons at H_a.

through increased electron density, thus affecting the H_c protons. This is possible since there is direct five-bond covalent conjugation, through the aromatics, right up to the base of the methyl group's bond (an "electron-push" mechanism is in operation at this point)]. This change in the relative electron density of H_c will lead to a changed interaction at the methyl protons of H_a/H_b.

Secondly, and, we feel, more probable: there are significant relative differences in the degrees of interactions between the *ortho*-nitro-group of **4**, and the *ortho*-methoxy group of **8**, with their corresponding pyran-oxygen lone pairs; both sterically and mesomerically (through the benzene ring). These interactions will subsequently, collectively, and differently, affect the interactions of the pyran-ring oxygen lone-pairs with their corresponding indolic-nitrogen atoms lone pair – for **4** and **8** respectively. The result of this is likely to affect the stereospatial orientation of corresponding N-methyl groups leading to different steric and/or electronic effects in the spirocyclic indolic and pyran rings: the consequence of this may lead to different, relatively slightly distorted, spirocyclic structures (the two rings not being equally "perpendicular", or disposed). The overall effect of this leads to differences in the internuclear distance between the 3′-geminal methyl protons (of the indole) and those of the 3-methyl (pyran) protons. As the nuclear Overhauser enhancements are directly proportional to the sixth power of the distance (r^{-6}) between the interacting nuclei, a very small change in the through-space distance will produce very large changes in the degree of nuclear interactions. Thus the above may therefore explain why a simple substitutional change in a "distant" part of the molecule, interestingly, produces a large change in the relative interactions between the 3-methyl and 3′-geminal-dimethyl protons in these two systems.



Spectrum 14. nOe spectrum of **4** during irradiation of the N-methyl protons at H_e.

3. Conclusions

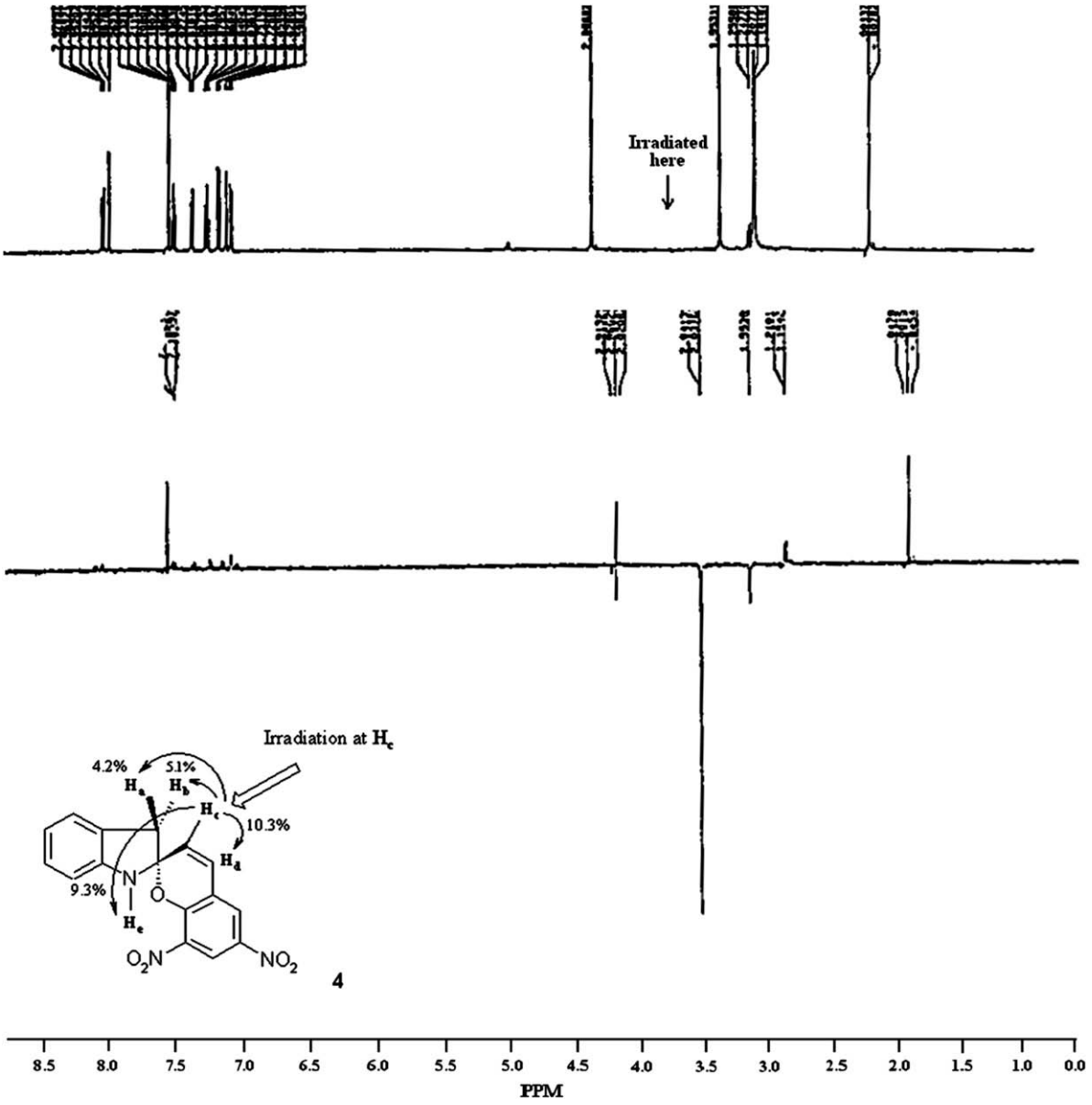
This investigation of substituent control has led to a much greater understanding of the potential ability to bias the general spiropyran ring-opening ↔ closing processes. In particular, the above results allow us to conclude that by using either, or both, appropriately placed "electronically biasing" substitutents and "sterically-controlling" groups, suitably placed in the benzospiropyran skeleton, we can effectively exert significant biasing over the open ↔ closed equilibrium position in these systems. The thermodynamics of the above interactions can be effectively utilised, in whole, or in part, to design, and to "tune" truly clean 'on-off' photoreversible systems. These observations also have further implications in the future design of selective metal-ion chelating systems.

Whilst we have qualified and quantified the main observations and results described here, we believe that the interactions, and subsequent equilibrium position in these systems are multifactorial and probably involve an extremely complex set of interactions and theoretical parameters. The detailed discussion of these are outside the scope of this report and 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′-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 distribution of charge throughout the zwitterionic structure (in particular that on the phenoxide anion; 6), solvent interactions through solvation effects (or non-interaction); 7), the conformation of the overall system in solution.

4. Experimental

4.1. ^1H NMR spectroscopic studies

These were carried out with a JEOL FX2000 spectrometer using deuteriochloroform or [D_6]dimethyl sulfoxide as the solvent with tetramethylsilane (TMS) as the internal reference. [For the variable temperature studies deuterated 1,1,2,2-tetrachloroethane and



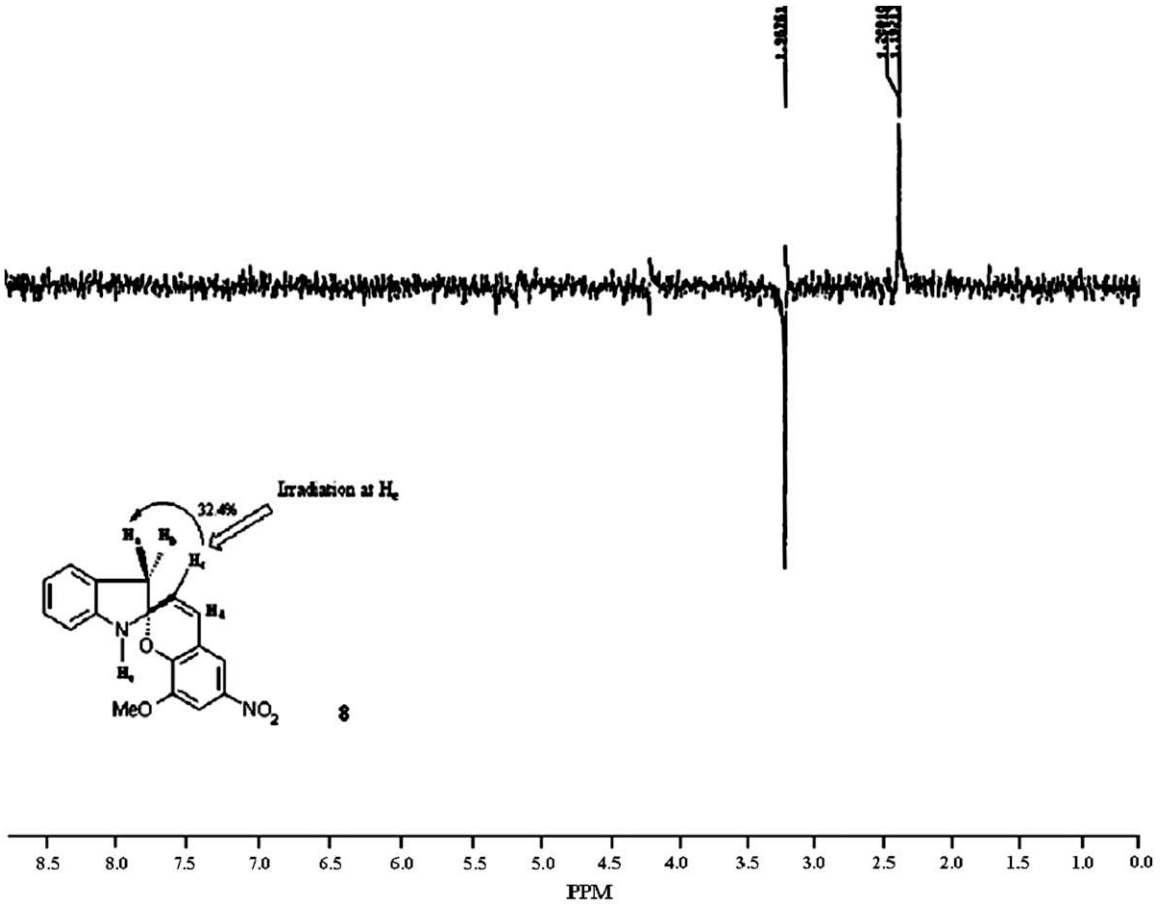
Spectrum 15. nOe spectrum of **4** during irradiation of the 3-methyl protons at H_c.

acetonitrile were used]. Multiplicities are reported as (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. Assignments of hydroxyl and ammonium protons were checked by deuterium exchange. Mass spectra were recorded with a VG 7070H mass spectrometer interfaced with a Finnegan 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 as RS 232 port, which allows remote control by PC. All UV measurements were taken at 25 °C using 3 cm^3 quartz cells with a 1 cm path length and are referenced against air. IR spectra were recorded with a Perkin–Elmer 983 spectrometer. Melting points were determined in open capillary tubes with an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were carried out in-house 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).

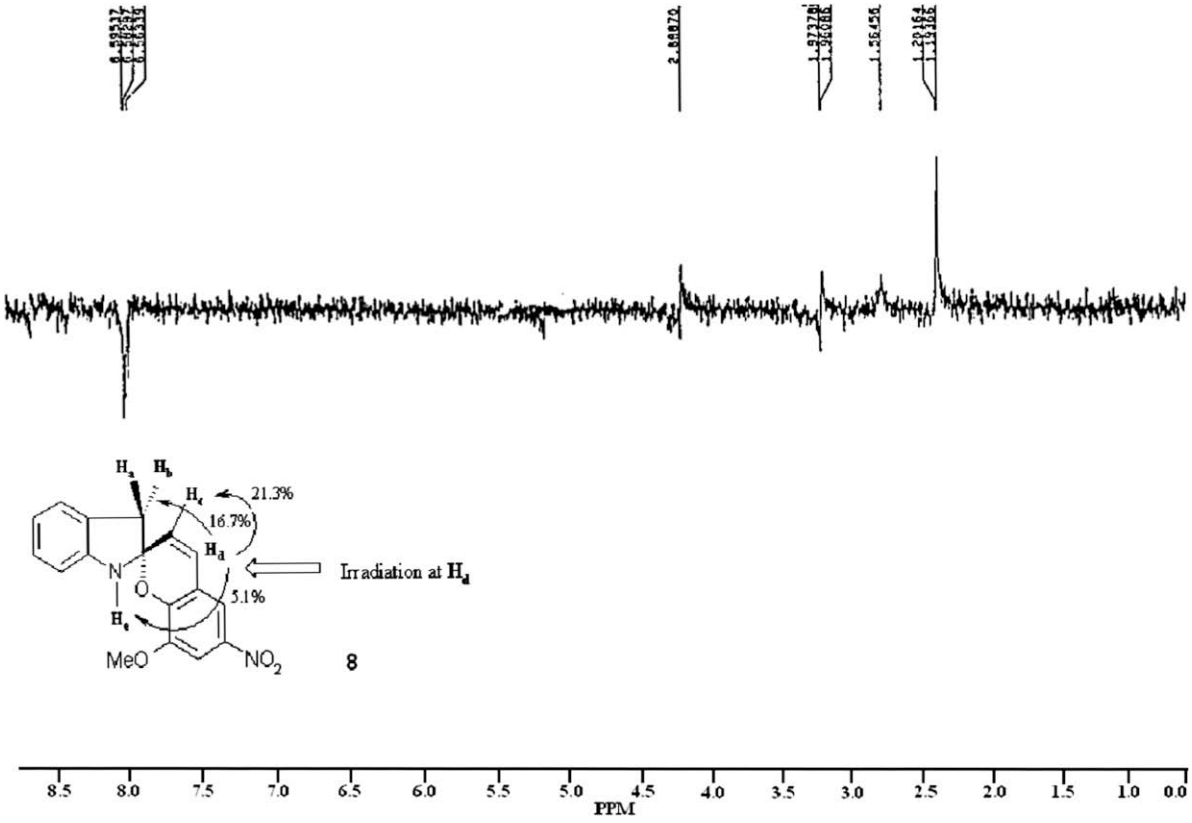
Chemical intermediates were purchased from the Aldrich Chemical Company unless otherwise stated.

4.1.1. Synthesis of spirobenzopyrans

*4.1.1.1. 6,8-Dinitro-1,3′-trimethylspiro-[2*H*-1-benzopyran-2,2′-indoline] (**3**).* 2-Hydroxy-3,5-dinitrobenzaldehyde (0.20 g, 0.094 mmol) and 1,3,3-trimethyl-2-methylene indolenine (0.16 g, 0.92 mmol) were dissolved in ethanol (10 cm^3), and the resulting solution heated under reflux for 24 h. After this period the solvent was removed under reduced pressure, yielding an oil. The oil was dissolved in a little ethanol and cooled overnight in a refrigerator, yielding a crystalline solid. The crystalline solid was broken up and recrystallised from ethanol to yield the title compound as a bottle green crystalline solid (0.22 g, 63%). M.p. 278–280 °C. Lit 280–283 °C.[10] δ_H ($CDCl_3$) 8.0–7.6 (6H, m, ArH), 6.8 (1H, d, CH═CH $J = 10$), 5.83 (1H, d, CH═CH $J = 10$), 2.75 (3H, s, N–CH_3), 1.33 (3H, s, –CH_3),



Spectrum 16. nOe spectrum of **8** during irradiation of the 3′-methyl protons of H_c.



Spectrum 17. nOe spectrum of **8** during irradiation of the alkenic proton H_d.

Table 3
Summary of the nOe ^{1}H NMR spectral peak enhancement data for compound **4**.

Compound **4**	H_a	H_b	H_c	H_d	H_e
Irradiation of proton(s)		H_b			
% Peak enhancements			5.9		6.2
Irradiation of proton(s)	H_a				
% Peak enhancements			10.8		7.2
Irradiation of proton(s)					H_e
% Peak enhancements	22.8	22.8	28.4		
Irradiation of proton(s)			H_c		
% Peak enhancements	4.2	5.1		10.3	9.3

1.35 (3H, s, $-CH_3$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3020 (sat C–H), 1600 (C=C), 1540 (C=O), 1220 (C–C), 1200 (C–N), 1450 (NO_2), 954 (C–O spiro), 771 (ArH, 4 adjacent H's). M/e 308 ($M^+ + 1$, 24.5), 307 (M^+, base peak 100%), 306 ($M^+ - 1$, 15.8). (Found: C 61.19, H 4.58, N 11.22. $C_{19}H_{17}N_3O_5.0.4H_2O$ requires C 62.12, H 4.66, N 11.43).

*4.1.1.2. 6,8-Dinitro-1,3′,3-tetramethylspiro-[2*H*-1-benzopyran-2,2′-indoline] (**4**).* 2-Ethyl-1,3,3-trimethyl indolium triflate (1.00 g, 2.97 mmol) was dissolved in a 40% sodium hydroxide solution (10 cm^3) and stirred for 5 min; after this period diethylether (10 cm^3) was then added. The diethylether layer was separated from the reaction mixture, dried (anhydrous sodium sulphate) and evaporated under reduced pressure to give an yellow-orange oil (0.44 g, 2.34 mmol (70%)). The oil that remained was taken up in ethanol (3 cm^3), added to 2-hydroxy-3,5-dinitrobenzaldehyde (0.49 g, 2.31 mmol) in ethanol (10 cm^3), and the resulting mixture heated under reflux for 24 h. Evaporation of the solvent under reduced pressure yielded a red solid which was recrystallised from ethanol/chloroform to yield the title compound as a deep red crystalline solid (74 mg, 83%). M.p. 144–146 °C. δ_H ($CDCl_3$) 8.5 (1H, s, ArH), 8.01 (1H, s, ArH), 7.2 (1H, t, ArH $J = 8$), 7.0 (1H, d, ArH $J = 7$), 6.90 (1H, t, ArH $J = 8$), 6.7 (1H, bs, ArC<u>H</u>=CCH_3)), 6.6 (1H, d, ArH $J = 7$), 2.83 (3H, s, N–CH_3), 1.17, 1.18 (6H, d, *gem* C–(CH_3)$_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3018 (sat C–H), 1533 (C=C), 1400 (C–O), 1210 (C–C), 1190 (C–N), 1450, 1350 (NO_2), 954 (C–O spiro), 771 (ArH, 4 adj H's). M/e 383 ($M^+ + 2$, 4.0), 382 ($M^+ + 1$, 4.1), 381 (M^+, 381), 366 ($M^+ - 15$, 97.2), 83 (base peak, 100%). (Found: C 60.87, H 4.92, N 10.29. $C_{20}H_{19}N_3O_5.0.75H_2O$ requires C 60.87, H 4.92, N 10.29). ($C_{20}H_{19}N_3O_5$. Acc. FAB requires 381.1325, found $M^+ = 381.1325$ (−0.1 ppm) $M^+ + 1 = 382.1399$ (1.0 ppm)).

*4.1.1.3. 1-Methyl-6,8-dinitro-3′-spirocyclohexylspiro-[2*H*-1-benzopyran-2,2′-indoline] (**5**).* 1,2-Dimethyl-3′-spirocyclohexyl indolium triflate (1.02 g, 2.81 mmol) was dissolved in a 40% sodium hydroxide solution (10 cm^3) and stirred for 5 min. Diethylether (15 cm^3) was then added with stirring for a further 10 min. After this period the diethylether layer was separated from the reaction mixture, dried (anhydrous sodium sulphate) and evaporated under reduced pressure. The yellow/orange oil that remained was isolated (0.44 g, 2.06 mmol), dissolved in ethanol (3 cm^3), added to 2-hydroxy-3,5-dinitrobenzaldehyde (0.44 g, 2.07 mmol) in ethanol (20 cm^3), and the resulting solution heated under reflux for 24 h. Cooling yielded the pure title compound as a dark red coloured precipitate (0.45 g, 58%). M.p. 209–211 °C. δ_H (TCE (tetrachloroethylene)) 8.4–8.42 (1H, d, ArH $J = 8$), 8.22–8.24 (1H, d, ArH $J = 8$), 7.65, 7.67 (1H, d, ArH $J = 8$), 7.39–7.41 (1H, t, ArH), 6.88, 6.90 (1H, d, CH=CH $J = 10$), 6.85–6.87 (1H, t, ArH), 6.74, 6.76 (1H, d, ArH $J = 8$), 6.20, 6.22 (1H, d, CH=CH $J = 10$), 2.78 (3H, s, N–CH_3), 1.22–1.95 (10H, m, cyclohexyl 5 × CH_2). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3020, 2930 (sat C–H), 1602 (C=C), 1430, 1330 (NO_2), 1376 (C–O), 1216 (C–N), 1092 (C–C), 774 (Ar–H, 4 adj H's). M/e 379 ($M^+ + 2$, 13.3), 378 ($M^+ + 1$, 15.7), 377 (M^+, 15.7), 362 ($M^+ - 15$, 5.5), 352 (base peak, 100%), 306 ($M^+ - 1$, 15.8). $C_{22}H_{21}N_3O_5$ Acc.(CI) requires: 407.1481 Found: 407.1481.

Table 4
Summary of the nOe ^{1}H NMR spectral peak enhancement data for compound **8**.

Compound **8**	H_a	H_b	H_c	H_d	H_e
Irradiation of proton(s)			H_c		
% Peak enhancements	32.4				
Irradiation of proton(s)				H_d	
% Peak enhancements		16.7	21.3		5.1

Table 5
Change in percentage (and relative percentage) peak enhancements, on irradiation of corresponding proton(s) for compounds **4** and **8**.

Proton(s)	H_a	H_c
Irradiation of proton(s)		H_c
Δ% Peak enhancement (between **4** and **8**)	28.2	
Relative percentage Δ% peak enhancement (between **4** and **8**)[a]	671	

[a] [Note: Irradiation of H_c methyl protons in compound **4** produces a 4.2% change in the peak enhancement of the H_a methyl protons. Irradiation of the corresponding H_c methyl protons of compound **8** produces a 32.4% change in the peak enhancement of its H_a methyl proton. The absolute difference percentage peak enhancement (Δ% peak enhancement) between these two compound's H_a methyl protons is thus 28.2, and thus the relative percentage change in peak enhancement (relative percentage Δ% peak enhancement) between compounds **4** and **8** is a massive 671%].

*4.1.1.4. 8-Methoxy-5′-trifluoromethyl-1′,3′-trimethylspiro-[2*H*-1-benzopyran-2,2′-indoline] (**6**).* 1,3,3-Trimethyl-5-trifluoromethyl-2-methylene indolenine (0.47 g, 0.20 mmol) was dissolved in ethanol (10 cm^3), added to 2-hydroxy-3methoxy-benzaldehyde (0.30 g, 0.20 mmol) in ethanol (10 cm^3), and the resulting solution heated under reflux for 24 h. Partial removal of the solvent under reduced pressure, and cooling, yielded a powdery solid. The solid was recrystallised from ethanol to yield the title compound as a tan coloured powdery precipitate (0.41 g, 68%). M.p. 126–128 °C., Lit[1] 125–127 °C, δ_H ($CDCl_3$) 7.49 (1H, d, ArH $J = 7$), 7.36 (1H, s, ArH), 6.95 (1H, d, ArH, $J = 7$), 6.83–6.72 (3H, m, ArH), 6.62 (1H, d, ArH, $J = 7$), 5.71 (1H, d, CH=CH $J = 10$ Hz), 3.72 (3H, s, OCH_3), 2.8 (3H, s, CH_3), 1.13, 1.06 (6H, *gem* dimethyl). $\nu_{(max)}$ ($CDCl_3$ film)/cm^{-1} 3100 (sat CH), 1600 (C=C), 1210 (C–N), 1400 (C–O), 1100 (C–C), 954 (C–O spiro), 758 (C–F). M/e 376 ($M^+ + 1$, 12), 375 (M^+, 50), 374 ($M^+ - 1$, 10), 360 ($M^+ - 15$). ($C_{21}H_{20}NO_2F_3$ Acc (EI) requires 375.1759, found $M^+ = 375.1759$).

*4.1.1.5. 1-Methyl-8-methoxy-5′-trifluoromethyl-3′-spirocyclohexylspiro-[2*H*-1-benzopyran-2,2′-indoline] (**7**).* 1,2-Dimethyl-3-spirocyclohexyl-5-trifluoromethyl indolium triflate (0.61 g, 1.42 mmol) was dissolved in 40% sodium hydroxide (15 cm^3). The resultant reaction mixture was then stirred for 5 min and diethylether (15 cm^3) added. The diethylether layer was separated from the reaction mixture, dried (anhydrous sodium sulphate) and evaporated under reduced pressure to yield an orange/yellow oil. The resultant isolated oil (0.19 g, 0.68 mmol) was dissolved in ethanol (3 cm^3); added to 2-hydroxy-3-methoxy-benzaldehyde (0.10 g, 0.66 mmol) in ethanol (25 cm^3), and the resulting solution heated under reflux for 24 h. Removal of the solvent under reduced pressure yielded a solid which was broken up and recrystallised from ethanol/ethylacetate (1/1) to yield the title compound as a beige/brown coloured solid precipitate (0.19 g, 70%). M.p. 129–131 °C, δ_H ($CDCl_3$) 7.57 (1H, s, ArH), 7.48 (1H, d, ArH $J = 8$), 6.9 (1H, d, ArH, $J = 10$), 6.83 (1H, d, ArH $J = 8$), 6.80 (1H, d, ArH $J = 8$), 6.74 (1H, t, ArH, $J = 7$), 6.51 (1H, d, ArH, $J = 8$), 5.77 (1H, d, CH=CH $J = 10$), 3.72 (3H, s, OCH_3), 2.80 (3H, s, NCH_3), 2.1–1.3 (10H, m, cyclohexyl). $\nu_{(max)}$ ($CDCl_3$ film)/cm^{-1} 3150 (sat C–H), 1608 (C=C), 1384 (C–O), 1210 (C–N), 1000 (C–C), 954 (C–O spiro), 755 (C–F). M/e 416 ($M^+ + 1$, 20), 415 (M^+, 100% base peak). ($C_{24}H_{24}NO_2F_3$ Acc (EI) requires 415.1759, found $M^+ = 415.1759$).

*4.1.1.6. 8-Methoxy-6-nitro-1,3′,3-tetramethylspiro-[2*H*-1-benzopyran-2,2′-indoline] (**8**).* 2-Ethyl-1,3,3-trimethyl indolium triflate (1.00 g, 2.97 mmol) was dissolved in 40% sodium hydroxide solution (10 cm^3) and the resulting mixture stirred for 5 min. After this period, diethylether (10 cm^3), was added and the resulting solution vigorously stirred for an hour. The diethylether layer was subsequently separated from the reaction mixture, dried (anhydrous sodium sulphate) and evaporated under reduced pressure. The yellow/orange oil that remained was isolated (0.44 g, 79%), dissolved in ethanol (5 cm^3), and added to 2-hydroxy-3-methoxy-5-nitrobenzaldehyde (0.46 g, 2.34 mmol) in ethanol (5 cm^3); the resulting mixture was then heated under reflux for 8 h. After this period the ethanol was removed under reduced pressure, producing a yellow/orange precipitate. The precipitate was broken up and recrystallised from a (1/1) mixture of ethanol/chloroform to yield the title compound as yellow/orange needles (0.57 g, 67%). M.p. 165–167 °C. δ_H ($CDCl_3$) 7.59 (1H, d, ArH $J = 7$), 7.57 (1H, d, ArH $J = 7$), 7.17 (1H, t, ArH $J = 8{,}1$), 7.0 (1H, d, ArH $J = 8$), 6.99 (1H, d, ArH $J = 7$), 6.55 (1H, s, CH═C), 3.7 (3H, s, OCH_3), 2.83 (3H, s, NCH_3), 1.96 (3H, s, CH_3), 1.14 (6H, d, 2 × $-CH_3$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3018 (sat C–H), 1554 (C–O), 1533 (C═C), 1350 (NO_2), 1210 (C–C), 1190 (C–N), 954 (C–O spiro), 771 (ArH, 4 adjacent H's). M/e 368 ($M^+ + 2$, 5.9), 367 ($M^+ + 1$, 35.7), 366 (M^+, 87.5), 351 (base peak, 100%). $C_{21}H_{22}N_2O_4$ Acc FAB requires: 366.1579 Found: $M^+ = 366.1563$ (4.4 ppm), $M^+ + 1 = 367.1645$ (3.5 ppm).

4.1.2. Syntheses of indolenines

4.1.2.1. 1-Methyl-3′-spirocyclohexyl-2-methylene indolenine. 1,2-Dimethyl-3′-spirocyclohexyl indolium triflate (1.02 g, 2.81 mmol) was dissolved in a 40% sodium hydroxide solution (10 cm^3) and stirred for 10 min. After this period diethylether (10 cm^3) was added to this solution, and stirred for a further 5 min. The diethylether layer was separated from the reaction mixture, dried (anhydrous sodium sulphate), filtered, and removed under reduced pressure to yield the pure title compound as a yellow/orange oil (0.45 g, 75%). δ_H ($CDCl_3$) 7.44 (1H, d, ArH $J = 7$), 7.14 (1H, t, ArH), 6.74 (1H, t, ArH), 6.56 (1H, d, ArH $J = 7$), 3.88 (2H, dd, C═CH_2 $J = 10, 10$), 3.02 (3H, s, N–CH_3), 1.83 (10H, m, cyclohexyl 5 × CH_2). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 2934 (sat C–H), 1644 (C═N), 1604 (C═C), 1908 (C–C), 908 (C–C), 775 (Ar–H, 4 adj H's). M/e 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) requires: 213.1517 Found: 213.1517.

4.1.2.2. 1,3′-Trimethyl-2-methylene-5′-trifluoromethyl indolenine. 1,2,3′-Tetramethyl-5′-trifluoromethyl indolium iodide (1.15 g, 3.17 mmol) was dissolved in a 40% sodium hydroxide solution (25 cm^3), suspended under a diethyl ether layer; the resulting solution was vigorously stirred, until the disappearance, by TLC, of the methiodide (24 h). A further quantity of diethylether (10 cm^3) was added with stirring continued for a further 4 h. The diethylether layer was separated, dried (anhydrous sodium sulphate), and filtered to yield a yellow oil, which quickly darkened on exposure to air (the extremely unstable oil was stored under nitrogen at −15 °C, wrapped in silver foil). The oil was triturated with cold diethylether (10 cm^3) to leave behind the pure title compound as a yellow oil (0.26 g, 34%). δ_H (Not sufficiently soluble in any common solvent). $\nu_{(max)}$ (Nujol)/cm^{-1} 2750 (sat C–H), 1650 (C═C), 1240 (C–N), 720 (C–F). M/e 244 ($M^+ + 3$, 27), 243 ($M^+ + 2$, 40), 242 ($M^+ + 1$, 22), 241 (M^+, 12), 183 (base peak, 100%).

*4.1.2.3. 1-Methyl-3′-spirocyclohexyl-5′-trifluoromethyl-2-methylene indolenine (**13**).* 1,2-Dimethyl-3′-spirocyclohexyl-5′-trifluoromethyl indolium triflate (0.61 g, 1.42 mmol) was dissolved in 40% sodium hydroxide solution (10 cm^3). Diethylether (10 cm^3) was added and the resultant mixture stirred for 5 min. The diethylether layer was separated from the reaction mixture, dried (anhydrous sodium sulphate), and evaporated under reduced pressure to yield the title compound as a yellow/orange oil (0.19 g, 48%).δ_H ($CDCl_3$) 7.65 (1H, s, ArH), 7.55 (1H, d, ArH, $J = 7$), 6.83 (1H, d, ArH, $J = 7$), 3.88 (2H, dd, C═CH_2, $J = 10, 10$), 2.8 (3H, s, N–CH_3), 2.1–1.3 (10H, m, CH_2 × 5 cyclohexyl). $\nu_{(max)}$ ($CDCl_3$ film)/cm^{-1} 3100, 2935 (sat C–H), 1605 (C═C), 1210 (C–N), 1400 (C–O), 1100 (C–C), 750 (C–F). M/e 282 ($M^+ + 1$, 12), 281 (M^+, 100%, base peak).

4.1.2.4. 1,3,3-Trimethyl-2-ethylene indolene. 2-Ethyl-1,3,3-trimethyl indolium triflate (0.51 g, 1.51 mmol) was dissolved in a 40% sodium hydroxide solution (5 cm^3). Diethylether (10 cm^3) was added and the resultant reaction mixture vigorously stirred for 5 min. After this period the diethylether layer was separated from the reaction mixture, dried (anhydrous sodium sulphate), and evaporated under reduced pressure to yield the pure title compound as a pale yellow/orange oil (0.22 g, 79%). δ_H ($CDCl_3$) 6.38–7.09 (4H, m, ArH), 4.30–4.33 (1H, q, C═C<u>H</u>(CH_3)), 2.93 (3H, s, NCH_3), 1.88–1.92 (3H, d, C═CHC<u>H</u>$_3$), 1.13 (6H, 2 × s, *gem* –$C(CH_3)_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 2982 (sat C–H), 1632 (C═C), 1630 (C═N), 1032 (C–N), 735 (Ar–H, 4 adj H's). M/e 188 ($M^+ + 1$, 3.8), 175 (base peak, 100%), 306 ($M^+ - 1$, 15.8).

4.1.3. Syntheses of N-alkyl indoles

4.1.3.1. 2-Ethyl-1,3,3-trimethyl indolium triflate. 2-Ethyl 3,3-dimethyl-3*H*-indole (2.08 g, 12.02 mmol) was added to methyl trifluoromethanesulphonate (1.96 g, 12.02 mmol) in a 1/1 hexane/diethylether mixture (10 cm^3), and the resulting solution 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. δ_H ($CDCl_3$) 7.20–7.69 (4H, m, ArH), 4.15 (3H, s, N^+–CH_3 ($CF_3SO_3^-$)), 3.22–3.28 (2H, q, <u>C</u>H$_2$CH$_3$), 1.63 (6H, s, *gem* Ar$C(CH_3)_2$), 1.41–1.45 (3H, t, CH$_2$C<u>H</u>$_3$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 2982 (sat C–H), 1632 (C═C), 1630 (C═N), 1264 (C–F), 1154 (SO_2–O), 1032 (C–N), 736 (ArH, 4 adj H's). M/e 187 ($M^+ - 149$ (SO_3CF_3), 78.7), 173 (4.11). 172 (base peak 100%), 203 (M^+–SO_3CF_3 – 2 × 15, 4.2). (Found: C 49.72, H 5.38, N 4.20. $C_{14}H_{18}NO_3F_3S$ .0.75H_2O requires C 49.84, H 5.38, N 4.15).

4.1.3.2. Tetramethyl-5′-trifluoromethyl indolium iodide. 2,3′-Trimethyl-5′-trifluoromethyl-3*H*-indole (1.60 g, 7.05 mmol) and methyl iodide (0.96 g, 7.06 mmol), in diethylether (50 ml), were heated under reflux for 26 h. Removal of the diethylether under reduced pressure yielded a solid which was broken up and washed with cold diethylether to yield the title compound as a white solid (1.39 g, 51%). M.p. 206–208 °C. δ_H ($CDCl_3$) 8.1–8.4 (3H, m, ArH), 4.02 (3H, s, N^+–CH_3), 2.8 (3H, s, N^+═C–CH_3), 1.6 (6H, s, *gem* Ar–$C(CH_3)_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 1500–1450 (C═N), 1660, 1610 (C═C), 1400 (C–N), 1300–1150 (C–F), 1100 (C–C). M/e 242 ($M^+ -$ H1, 10.0), 18 (base peak, 100%). ((M − HI) Acc.EI. $C_{13}H_{14}NF_3$. Measured: 241.1078 found: 241.1078).

*4.1.3.3. 1,2-Dimethyl-3′-spirocyclohexyl-5′-trifluoromethyl indolium triflate (**12**).* 2-Methyl-3′-spirocyclohexyl-5′-trifluoromethyl-indole (0.50 g, 1.86 mmol) was dissolved in diethylether (15 cm^3) and hexane (10 cm^3). Methyltrifluoromethane sulphonate (0.32 g, 1.95 mmol) was added in a single portion to the stirred mixture at room temperature, instantly, a tan coloured precipitate formed. The solvents were removed under reduced pressure to yield a yellow crystalline solid. The solid was broken up and recrystallised from ethanol/ethylacetate (1/1) to yield the title compound as pale yellow coloured crystals (0.65 g, 80%). M.p. 112–114 °C, δ_H ($CDCl_3$) 8.12 (1H, s, ArH $J = 7$), 7.91 (1H, d, ArH, $J = 7$), 7.84 (1H, d, ArH $J = 7$), 4.17 (3H, s, N–CH_3), 2.89 (3H, s, –CH_3), 2.00–1.16 (10H, m, CH_2 × 5 cyclohexyl). $\nu_{(max)}$ ($CDCl_3$ film)/cm^{-1} 3020 (sat CH), 1590 (C═C), 1325 (C–C), 1210 (C–N), 760 (ArH), 758 (C–F). M/e 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). (Found: C 45.12, H 4.68, N 3.12. $C_{17}H_{19}NO_3SF_6.H_2O$ requires C 45.43, H 4.68, N 3.12). ($C_{17}H_{19}NO_3SF_6$ Acc FAB M^+ –SO_3CF_3 requires 282.146960, found 282.147906 (−3.4 ppm).

4.1.3.4. 2-Ethyl-1,3,3-trimethyl indolium triflate. 2-Ethyl 3,3-dimethyl-3*H*-indole (2.08 g, 12.02 mmol) was added to methyltrifluoromethanesulphonate (1.96 g, 12.02 mmol) in a mixture of hexane (5 cm^3) and diethylether (5 cm^3) (1/1). The stirred, room temperature, solution instantly formed a yellow precipitate, which was filtered off and washed with cold diethylether. Recrystallisation from ethanol yielded the title compound as deep golden coloured crystals (3.81 g, 89%). M.p. 134–136 °C. δ_H ($CDCl_3$) 7.20–7.69 (4H, m, ArH), 4.15 (3H, s, N^+–CH_3 ($CF_3SO_3^-$)), 3.22–3.28 (2H, q, $C\underline{H}_2CH_3$), 1.63 (6H, 2 × s, *gem* –$C(CH_3)_2$), 1.41–1.45 (3H, t, $CH_2C\underline{H}_3$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 2982 (sat C–H), 1632 (C═C), 1630 (C═N), 1264 (C–F), 1154 (SO_2–O), 1032 (C–N), 736 (ArH, 4 adj H's). M/e 187 (M^+ − 149 (SO_3CF_3), 78.7), 173 (4.11). 172 (base peak 100%), 203 (M^+–SO_3CF_3 – 2 × 15, 4.2). (Found: C 49.72, H 5.38, N 4.20. $C_{14}H_{18}NO_3F_3S$ .0.75H_2O requires C 49.84, H 5.38, N 4.15).

4.1.3.5. 1,2-Dimethyl-3-spirocyclohexyl indolium triflate. 2-Methyl-3-spirocyclohexyl-3*H*-indole (3.22 g, 16.18 mmol) was added to methyltrifluoromethane sulphonate (2.66 g, 16.22 mmol) in a mixture of hexane (20 cm^3) and diethylether (30 cm^3). The canary yellow precipitate which instantly formed was filtered off and washed with cold diethylether to yield the title compound as pale yellow coloured crystals (4.59 g, 78%). M.p. 126–128 °C. δ_H ($CDCl_3$) 7.91, 7.93 (1H, d, ArH), 7.66–7.68 (1H, d, ArH), 7.62 (1H, t, Ar $J = 8$), 7.56 (1H, t, ArH $J = 8$), 4.12 (3H, s, N^+–CH_3), 2.88 (3H, s, N^+═C–CH_3), 1.54, 2.08 (10H, m, cyclohexyl 5 × CH_2). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3020 (sat C–H), 1590 (C═C), 1325 (C–C), 1210 (C–N), ArH (760), 758 (C–F). M/e 233 (M^+ − (SO_3CF_3), 6.7), 323 (M^+–SO_3CF_3-1, 41.7), 218 (M^+–SO_3CF_3–15, 17.7), 217 (base peak, 100%) 203 (M^+–SO_3CF_3 – 2 × 15, 4.2). (Found: C 52.50, H 5.36, N 3.88. $C_{16}H_{20}NO_3F_3S$ requires C 52.88, H 5.55, N 3.86).

4.1.4. Syntheses of 3H-indoles

*4.1.4.1. 2,3′-Trimethyl-5′-trifluoromethyl-3*H*-indole.* Isopropyl methyl ketone 4-trifluoromethylphenylhydrazone (2.68 g, 10.98 mmol) and boron trifluoride etherate (1.56 g, 10.99 mmol), in acetic acid (30 cm^3), 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%). δ_H ($CDCl_3$) 7.5–7.7 (3H, m, ArH), 2.3 (3H, s, N═CCH_3), 1.3 (6H, s, *gem* $C(CH_3)_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 2900–3000 (sat C–H), 1600 (C═C), 1530 (C═N), 1250 (C–F). M/e 228 (M^+ + 1, 20.6), 227 (M^+, 98.1), 226 (M^+ − 1, 69.3), 212 (base peak, 100%).

*4.1.4.2. 1-Methyl-3′-spirocyclohexyl-5′-trifluoromethyl-3*H*-indole (**11**).* Cyclohexylmethyl ketone-4-trifluoromethylphenylhydrazone (3.30 g, 5.05 mmol) was added to a solution of zinc dichloride (0.25 g, 1.83 mmol) in acetic acid (100 cm^3), and the resulting solution heated on a steam bath, under nitrogen for 3 h. Filtration, followed by removal of the acetic acid under reduced pressure, yielded the title compound as an orange oil (1.52 g, 70%). δ_H ($CDCl_3$) 7.92 (1H, d, ArH $J = 7$), 7.62 (1H, s, ArH), 7.26 (1H, d, ArH $J = 7$), 2.32 (3H, s, –CH_3), 1.83–1.21 (10H, m, CH_2 × 5 cyclohexyl). $\nu_{(max)}$ ($CDCl_3$ film)/cm^{-1} 2932 (sat CH), 1688 (C═N), 1598 (C═C), 1216, 1026 (C–C), 778 (C–F). M/e 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) requires 267.1235, found 267.1235).

*4.1.4.3. 2-Ethyl-5-nitro-3,3-dimethyl-3*H*-indole.* Isopropyl ethyl ketone phenylhydrazone (2.88 g, 15.16 mmol) was added to zinc chloride (0.5 g, 3.66 mmol) in glacial acetic acid (50 cm^3), and the resulting mixture heated on a steam bath, under nitrogen, for 4 h. Filtration of the solution and removal of the solvent under reduced pressure yielded an oil. The oil was purified using flash chromatography, with chloroform as the eluent, to yield title compound as an yellow/orange oil (2.29 g, 87%). δ_H (TCE) 6.9–7.3 (4H, m, ArH $J = 8$), 2.6 (2H, q, $C\underline{H}_2CH_3$), 1.49 (3H, t, CH_3 of $CH_2C\underline{H}_3$), 1.47 (6H, s, 2 × $ArCH_3$); $\nu_{(max)}$ ($C\underline{D}Cl_3$)/cm^{-1} 3018 (C–H), 1450 (C═N), 1533 (C═C), 1210 (C–C), 1190 (C–N), 771 (ArH, 4 adj H, s). M/e 174 (M^+ + 1, 8.9), 173 (M^+, 62.5), 158 (M^+, 100%, base peak). $C_{12}H_{15}N$ Acc. (EI) requires: 173.1204 Found: 173.12040.

*4.1.4.4. 3-Cyclohexyl-2-methyl-3*H*-indole.* Cyclohexylmethyl ketone phenylhydrazone (4.65 g, 21.53 mmol) was added to a mixture of zinc chloride (1.00 g, 7.35 mmol) in glacial acetic acid (100 cm^3), and the resulting solution heated on a steam bath, under nitrogen, for 3 h. Filtration of the resulting solution and removal of the glacial acetic acid under reduced pressure yielded the title compound as an orange oil (3.25 g, 76%). δ_H ($CDCl_3$) 7.51–7.53 (1H, d, ArH $J = 7$), 7.31 (1H, d, ArH $J = 7$), 7.15, 6.99 (2H, m, ArH), 2.7 (3H, s, CH_3), 1.25–2.31 (10H, m, cyclohexyl 5 × CH_2). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 2932 (sat C–H), 1688 (C═N), 1598 (C═C, Ar), 1216 (C–N), 1026(C–C). M/e 200 (M^+ + 1, 27.6), 199 (M^+, base peak, 100%), 198 (M^+ − 1, 4.2). $C_{14}H_{17}N$ Acc.(EI) requires: 199.1361 Found: 199.1361.

*4.1.4.5. 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 cm^3), and the resulting mixture heated on a steam bath, under nitrogen, for 4 h. The cooled solution was filtered and the glacial acetic acid removed under reduced pressure to yield an oil. The oil was purified using flash chromatography, with chloroform as the eluant, to yield the title compound as a yellow/orange oil (2.29 g, 87%). δ_H ($CDCl_3$) 6.90–7.30 (4H, m, ArH), 2.60 (2H, q, $C\underline{H}_2CH_3$), 1.49 (3H, t, $CH_2C\underline{H}_3$), 1.47 (6H, 2 × s, *gem* –$C(CH_3)_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3018 (sat C–H), 1450 (C═N), 1533 (C═C), 1010 (C–C), 1190 (C–N), 771 (Ar–H, 4 adj H's). M/e 174 (M^+ + 1, 8.9), 173 (M^+, 62.5), 158 (base peak, 100%). $C_{12}H_{15}N$ Acc.(EI) requires: 173.1204 Found: 173.12040.

4.1.5. Syntheses of hydrazones

*4.1.5.1. Cyclohexyl methyl ketone-4-trifluoromethylphenylhydrazone (**10**).* 4-Trifluoromethylphenylhydrazine (2.45 g, 13.92 mmol) was added to cyclohexylmethyl ketone (1.75 g, 13.89 mmol) in ethanol (50 cm^3) and the resulting mixture heated under reflux for 7 h. Removal of the ethanol under reduced pressure yielded the title compound as a burgundy red mobile oil (2.45 g, 62%). δ_H ($CDCl_3$) 7.47, 7.44 (2H, t, ArH $J = 7$), 7.09, 7.06 (2H, d, ArH, $J = 7$), 1.9 (1H, m, C-H), 1.84 (3H, s, -CH_3), 1.78–1.17 (10H, m, CH_2 × 5 cyclohexyl). $\nu_{(max)}$ ($CDCl_3$ film)/cm^{-1} 3650 (N–H), 3020 (sat CH), 1616 (C═C), 1525 (C–N), 1020 (C–C), 785 (C–F), 760 (ArH). M/e 286 (M^+ + 2, 4.6), 285 (M^+ + 1, 4.7), 284 (M^+, 5.4), 145 (100% base peak).

4.1.5.2. 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 cm^3) 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%). δ_H (TCE) 6.8–7.3 (5H, m, ArH $J = 8$), 2.6 (1H, q, C<u>H</u>), 2.2–2.3 (2H, q, $C\underline{H}_2CH_3$), 1.2 (6H, t, 2 × $ArCH_3$), 1.1 (3H, t, $CH_2C\underline{H}_3$), $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3300–3500 (C═N–H), 3100 (C–H), 1650 (C═C), 1530 (C═N) M/e 191 (M^+ + 1, 16.7), 190 (M^+, 100%, base peak), 175 (M^+,–CH_3, 3.6). $C_{12}H_{18}N_2$ Acc.(EI) requires: 190.1470 Found: 190.1470.

4.1.5.3. Cyclohexyl ketone phenylhydrazone. Phenylhydrazine (3.00 g, 27.77 mmol) was added to a mixture of cyclohexylmethyl ketone

(3.50 g, 27.77 mmol) in ethanol (100 cm^3), and the resulting solution heated under reflux for 0.5 h. Removal of the solvent under reduced pressure yielded the title compound [11] as a deep orange mobile oil (4.78 g, 79%). δ_H ($CDCl_3$) 11.0 (1H, s, NH, exchangeable D_2O), 7.25 (2H, t, ArH), 7.03, 7.05 (2H, dd, ArH), 6.79, 6.83 (1H, t, ArH $J = 8$), 1.90 (1H, m, $(CH_2)_2C\underline{H}C$), 1.82 (3H, s, N=C–CH_3), 1.17–1.78 (10H, m, cyclohexyl $5 \times CH_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3650 (N–H), 3020 (C–H), 1616 (C=C), 1520 (C–N), 1020 (C–C), 760 (ArH). M/e 216 (M^+, 6.6), 215 ($M^+ - 1$, 8.1), 18 (base peak, 100%).

4.1.5.4. Isopropyl methyl ketone 4-trifluoromethylphenylhydrazone. 4-Trifluoromethylphenylhydrazine (2.47 g, 14.03 mmol) was added to 3-methylbutan-2-one (1.19 g, 14.00 mmol) in ethanol (20 cm^3), and the resulting solution heated under reflux for 1.5 h. Removal of the solvent under reduced pressure yielded the title compound as a mobile, slightly brown oil (3.09 g, 90%). δ_H ($CDCl_3$) 7.45 (2H, bd, ArH, $J = 8$), 7.07 (2H, bd, ArH $J = 8$), 4.77 (1H, bs, NH), 2.55 (1H, hept, $(CH_3)_2C\underline{H}$), 1.91 (3H, s, N=C–CH_3), 1.14 (6H, d, $CH(C\underline{H}_3)_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3300–3500 (C=N–H, weak), 3100 (C–H), 1650 (C=C), 1530 (C=N), 1150–1300 (C–F). M/e 244 (M^+, 8.3), 201 (M^+–$C(CH_3)_2H$, 9.2), 186 (M^+–$CH_3C(CH_3)_2H$, 8.2), 172 (M^+–N=$CCH_3(CH_3)_2H$, 4.5), 171 (–HN=$CCH_3(CH_3)_2H$, 3.1), 145 (base peak, 100%), 69 (CF_3 fragment, 17.4).

4.1.6. Salicaldehyde synthesis

4.1.6.1. 2-Hydroxy-3,5-dinitrobenzaldehyde. 2-Hydroxy-5-nitrobenzaldehyde (0.50 g, 2.99 mmol) was stirred with fuming nitric acid (0.19 g, 3.02 mmol) in sulphuric acid (25 cm^3) for 3 h at room temperature. The solution was then added to ice (50 g), stirred for a further 10 min and left standing overnight whereupon pale yellow coloured crystals formed. These were filtered off and washed with water to yield the title compound as a yellow crystalline solid (0.36 g, 57%). M.p. 68–70 °C. Lit 69–72 °C [12]. δ_H ($CDCl_3$) 7.7 (1H, d, ArH $J = 3$), 7.63 (1H, d, ArH $J = 3$), 7.19 (1H, t, ArH), 7.07 (1H, d, ArH $J = 7$), 6.87 (1H, d, CH=CH $J = 10$), 6.85 (1H, t, ArH), 6.55 (1H, d, ArH $J = 7$), 5.83 (1H, d, CH=CH $J = 10$), 3.81 (3H, s, OCH_3), 2.75 (3H, s, N–CH_3), 1.22, 1.18 (6H, $2 \times$ s, *gem* $C(CH_3)_2$). $\nu_{(max)}$ ($CDCl_3$)/cm^{-1} 3018, 2970 (sat C–H), 1606 (C=C), 1334 (NO_2), 1216 (C–N), 1092 (C–C), 771 (ArH, 4 adj H's), 954 (C–O spiro). M/e 354 ($M^+ + 2$, 4.8), 353 ($M^+ + 1$, 21.5), 352 (M^+, 8.6), 351 ($M^+ - 1$, 20.0), 158 (base peak 100%). (Found: C 37.46, H 1.97, N 12.40. $C_7H_4N_2O_6$. $0.75H_2O$ requires C 37.25, H 2.44, N 12.41).

4.1.7. Cyclohexylmethylketone preparation

A dry 100 cm^3 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 cm^3). While this solution was being stirred vigorously, a solution of cyclohexane carboxylic acid (9.62 g, 0.075 mol) in anhydrous 1,2-dimethoxyethane (50 cm^3) 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 methyl lithium (1.6 M, 62 cm^3, 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 cm^3, 0.16 mol) and water (200 cm^3). The reaction flask was rinsed with an additional amount of diethylether (60 cm^3), 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 diethylether (3×100 cm^3). The organic solutions were combined and dried over magnesium sulphate; the bulk of the diethylether 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%).

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