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[1,3]Diazaheterofused isoindolol derivatives displaying anxiolytic-like effects on mice

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Abstract—Anxiolytic-like effects induced on mice by several compounds with imidazo[2,1-*a*]isoindolol (**II**), pyrimido[2,1-*a*]isoindolol (**III**) and [1,3]diazepino[2,1-*a*]isoindolol (**IV**) structures have been evaluated through the elevated plus-maze test. The evaluation has been based on measuring the spent time and counting the number of entries of mice in the open arms of the maze. Single intraperitoneal administration of imidazoisoindolol **IIe** and pyrimidoisoindolols **IIIa**, **IIIe** and **IIIg** induced significant increments in these behavioural parameters.

Anxiety is a normal reaction to stress that in many cases can become an important pathological disabling and lasting disorder.[1,2] Pharmacological treatment of anxiety is principally based on the 1,4-benzodiazepines (BDZ), such as diazepam (DZP) and related drugs, though for anxiety disorders associated to depression, 5-HT_{1A} receptor agonists and selective 5-HT reuptake inhibitors (SSRIs) are often prescribed.[3] In a previous paper dealing with the search for new types of anxiolytic agents we reported the evaluation of the effects induced by some benzalphthalides (**I**),[4] which were easily prepared by condensation of phthalic anhydride with differently substituted phenylacetic acids. Two benzalphthalides, **Ia** (*p*-methoxybenzalphthalide) and **Ii** (*p*-methylsulfonylbenzalphthalide), induced significant increments in the two main parameters considered as those most relevant for testing anxiety in the elevated plus-maze test,[5] namely, the relative spent time on the open arms (STOA %) and the relative number of entries into the open arms (NEOA %). The 3D structures of the most stable conformers calculated for the phthalides **Ia** and **Ii** could be practically superimposable with those of the previously reported anxiolytic flavonoids apigenin and 6-bromo-3′-nitroflavone, respectively.[4,6]

As a part of our ongoing study aiming to discover novel anxiolytic compounds, we report in this article the preliminary evaluation of the anxiolytic-like effects displayed by other heterocyclic compounds derived from benzalphthalides, including imidazo[2,1-*a*]isoindolol (**II**), pyrimido[2,1-*a*]isoindolol (**III**) and [1,3]diazepino[2,1-*a*]isoindolol (**IV**) derivatives.

The general procedure to obtain the intermediate benzalphthalides (**I**) was previously described by us.[7] These compounds were subsequently treated with either, ethylenediamine, 1,3-propylenediamine or 1,4-butylenediamine to obtain, respectively, the corresponding imidazoisoindolol (**II**), pyrimidoisoindolol (**III**) and diazepinoisoindolol (**IV**) derivatives, in good to excellent yields (65–99%, Scheme 1), with the exception of compound **IIIa** (25%).[8–10] A representative selection of natural and not natural, electron-donating and electron-withdrawing, bulky and small volume substituents were introduced on ring B, aiming to analyse their respective influences on the activity.

The evaluation of anxiolytic effects was performed on albino ICR mice, through their behaviour in the mentioned elevated plus-maze test.[4] In this assay anxiolytic drugs prolong the spent time and the number of entries into the open arms of the maze, whereas anxiogenic

Keywords: Benzalphthalides; Imidazo-isoindole; Pyrimido-isoindole; Diazepino-isoindole; Structural–activity relationship (SAR); Anxiolytic effects; Mice experiments; Open arms test; Elevated plus-maze test.
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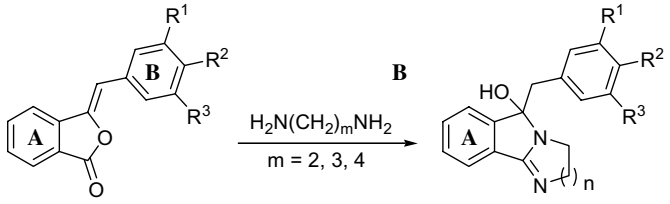


Benzalphthalides (**I**)	n	yield
Ia: R^1, R^3 = H, R^2= OCH_3	Imidazoisoindolols (**II**) 1	71-99 %
Ib: R^1, R^2 = OCH_2O, R^3= H	pyrimidoisoindolols (**III**) 2	25-95 %
Ie: R^1, R^3 = H, R^2= Cl	[1,3]diazepinoisoindolols (**IV**) 3	65-96 %
Ig: R^1, R^3 = H, R^2= OCH_3		
Ii: R^1, R^3 = H, R^2 = SO_2CH_3		

Scheme 1. The synthesis of fused [1,3]diazaheterocycle[2,1-*a*]isoindolols.

compounds produced a fair reduction of these parameters. The test group was treated with compounds **IIa**–**IIi**; **IIIa**–**IIIi**; **IVa**, **IVd** and **IVe** (15 mg/kg, single dose, ip); three other groups were, respectively, treated with either, the anxiolytic reference drug (diazepam, DZP, 1 mg/kg, ip), the anxiogenic reference drug (picrotoxin, PTX, 2 mg/kg, ip) or vehicle (Tween 20, 5%, ip).[11] Doses were selected according to our previous experience in this field. Tests began 1 h after administration and mice evolutions were recorded for 5 min using a video camera. The anxiolytic effect was evaluated through counting the number of entries and measuring the times spent on the open or in the closed arms of the maze, among other parameters.[12]

Table 1 shows the structures and the experimental values of the spent time by mice on the open arms (STOA) and of the number of entries in the open arms (NEOA). Percent STOA values were calculated considering the time spent by the animal in the closed arms and also the time spent in the central zone (dead time). Two other columns have also been implemented in order to facilitate data comparisons. They correspond to normalised percent data *n*STOA and *n*NEOA, calculated, respectively, by means of Eqs. 1 and 2, and whose values are equivalent to consider the anxiolytic responses to DZP and the control (vehicle) as 100% and 0% in each parameter, respectively. Thus, compounds with significant positive values in these *n* columns could be considered as anxiolytics, while those with fair negative values could be considered as anxiogenics.

$$n\mathrm{STOA} = 100 \times [\mathrm{STOA}(\%)_{\mathrm{compd}} - \mathrm{STOA}(\%)_{\mathrm{control}}]/[\mathrm{STOA}(\%)_{\mathrm{DZP}} - \mathrm{STOA}(\%)_{\mathrm{control}}] \quad (1)$$

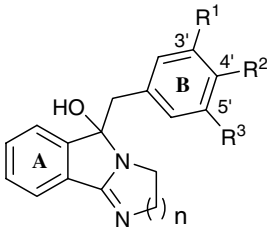
$$n\mathrm{NEOA} = 100 \times [\mathrm{NEOA}(\%)_{\mathrm{compd}} - \mathrm{NEOA}(\%)_{\mathrm{control}}]/[\mathrm{NEOA}(\%)_{\mathrm{DZP}} - \mathrm{NEOA}(\%)_{\mathrm{control}}] \quad (2)$$

In a first overall comparison, it is observed (Table 1) that all of the tested pyrimidoisoindolols (**III**) and almost all the tested imidazoisoindolols (**II**) increased the *n*STOA parameter with respect to control, whereas the few diazepinoisoindolols (**IV**) tested induced low increments or even decreased (**IVa**) the value of this parameter. These facts can be analysed by comparison within the groups of chloro (**IIIe** ~ **IIe** > **IVe**) or methoxy (**IIIa** > **IIa** ≫ **IVa**) derivatives. Similarly, pyrimidoisoindolols increased the *n*NEOA values, becoming higher than 60% for compounds **IIIa** and **IIIg**, thus confirming the fair anxiolytic-like activity of compounds of this series, whereas imidazo (**II**) and diazepino (**IV**) derivatives gave lower *n*NEOA values, below 50% of that of DZP in all the cases.

Almost half of the tested pyrimidoisoindolols induced differences greater than 20% between the relative times spent on the open and in the closed arms. The effects of compounds **IIIe** and **IIIg** were significant, the last one corresponding to the highest potency observed through this parameter. Imidazo derivatives (**II**), though less potent, behaved similarly, with only two compounds (**IIb** and **IIe**) inducing a fair difference and only one (**IIe**) doing it significantly. It is interesting to note that, while a certain parallelism was observed for the influence of most substituents in both series **II** and **III**, it happened differently in relation with the increase induced by the methylsulfanyl group in series **III**, that was practically absent in series **II**. Also it can be noted the anxiogenic-like effect induced by the bulky trimethoxyphenyl group in series **II**, while being almost insignificant in series **III**.

The observation of data related to the number of entries denotes that only two compounds, **IIIg** and **IIIa**, displayed a significant increase of the NEOA parameter. These two compounds also belong to the group of pyrimidoisoindolols, thus reinforcing the interest of this structural group. Compound **IIIg**, at the dose regime applied in the experiments, attained up to the 73.8% of the *n*STOA and 66.0% of the *n*NEOA values of DZP, thus becoming a new anxiolytic drug lead, which would merit further research.

Table 1. Structures and anxiolytic-like effects of benzyl derivatives of imidazo, pyrimido and [1,3]diazepino[2,1-*a*]isoindolols



	n
imidazoisoindolols (**II**)	1
pyrimidoisoindolols (**III**)	2
[1,3]diazepinoisoindolols (**IV**)	3

Chemical data				Plus-maze evaluation data					
				Spent time			Number of entries		
Compound	R^1	R^2	R^3	STOA[a]	STOA (%)	*n*STOA	NEOA[b]	NEOA (%)	*n*NEOA
IIa	H	OCH_3	H	145.1 ± 39.0	59.2	48.9	9.1 ± 3.4	52.8	34.6
IIb	OCH_2O		H	**126.0 ± 50.5**	**60.3**	**51.3**	12.5 ± 5.7	56.3	44.8
IIc	OCH_3	OCH_3	OCH_3	79.0 ± 46.0	33.4	−7.9	6.1 ± 3.4	35.4	*−16.0*
IId	H	F	H	99.3 ± 36.3	47.4	22.9	10.1 ± 4.5	42.8	5.5
IIe	H	Cl	H	**166.8 ± 35.7***	**65.4***	**62.6**	9.8 ± 4.0	55.3	41.9
IIf	H	NO_2	H	115.9 ± 17.0	53.4	36.1	12.7 ± 1.8	52.3	33.1
IIg	H	SCH_3	H	139.4 ± 26.7	58.7	47.8	9.6 ± 3.2	53.4	36.3
IIh	H	$SOCH_3$	H	122.7 ± 15.2	57.0	44.0	9.7 ± 2.7	49.6	25.3
IIi	H	SO_2CH_3	H	106.5 ± 53.2	57.0	44.0	11.9 ± 6.2	50.3	27.3
IIIa	H	OCH_3	H	**152.6 ± 58.1**	**60.5**	**51.8**	**10.1 ± 3.1***	**61.6***	**60.2**
IIIb	OCH_2O		H	126.8 ± 14.0	59.1	48.7	13.7 ± 4.2	56.7	45.9
IIIc	OCH_3	OCH_3	OCH_3	143.2 ± 41.4	57.1	44.2	13.0 ± 5.2	57.0	46.8
IIId	H	F	H	125.3 ± 35.0	57.3	44.7	8.7 ± 2.3	49.4	24.7
IIIe	H	Cl	H	**143.2 ± 15.5***	**65.4***	**62.6**	8.3 ± 2.9	57.2	47.4
IIIf	H	NO_2	H	**135.3 ± 65.7**	**63.8**	**59.0**	12.5 ± 2.7	56.1	44.2
IIIg	H	SCH_3	H	**177.0 ± 25.6***	**70.5***	**73.8**	**13.2 ± 4.5***	**63.6***	**66.0**
IIIh	H	$SOCH_3$	H	96.1 ± 45.3	44.4	16.3	9.8 ± 3.3	50.4	27.6
IIIi	H	SO_2CH_3	H	98.8 ± 33.2	43.3	13.9	8.3 ± 3.1	38.4	*−7.3*
IVa	H	OCH_3	H	77.2 ± 62.9	32.9	*−9.0*	6.0 ± 4.5	32.5	*−24.4*
IVd	H	F	H	120.2 ± 33.8	52.2	33.5	10.5 ± 4.6	53.4	36.3
IVe	H	Cl	H	132.2 ± 44.3	56.4	42.7	9.5 ± 3.3	55.0	41.0
DZP				**218.1 ± 32.1***	**82.4***	**100.0**	**14.6 ± 5.2****	**75.3****	**100.0**
VEH				85.3 ± 26.2	37.0	0.0	8.0 ± 2.2	40.9	0.0
PTX				52.2 ± 34.0	22.8	*−31.8*	2.8 ± 1.8	27.9	*−37.8*

In bold, data for compounds attaining *n*STOA and *n*NEOA values >50% of DZP values. In italic, anxiogenic-like data. Other explanations, see text and references and notes.[5]

[a] Data represent means (seconds/5 min) ± SEM.

[b] Data represent means (number of entries/5 min) ± SEM ($n = 8$). Dose for compounds **II**, **III**, and **IV**: 15 mg/kg, ip; DZP, diazepam (1 mg/kg, ip); VEH, Tween 20 (5%); PTX, picrotoxin (2 mg/kg, ip).

* $p < 0.05$.

** $p < 0.001$.

In attempts at justifying the potency variations observed for the sulfide (**IIIg**), sulfoxide (**IIIh**), sulfone (**IIIi**) derivatives as well as, for the oxygenated derivatives (types **a**, **b**, **c**), the electronic (σ_p), lipophilic (πar) and size (E_s, L_{ster}) aspects of the substituents at the benzylic moiety were examined as possible structure–activity relationship (SAR) influencing factors. No one of these parameters can be considered as a main determinant of the activity. Similarly, not a fair linear dependence, but a certain correlation was found between the *n*STOA and *n*NEOA values of pyrimidoisoindolols and lipophilicity factors of the whole molecules. The most potent compounds displayed log *P*[13] values around 4.4 and milog *P*[14] values near 2.8. These facts and, particularly, the lack of a well-defined lipophilia–activity correlation would suggest the existence of a specific compound–biotarget interaction to be ascertained, rather than that of an unspecific action.

In spite of the appreciable structural difference between pyrimidoisoindolols and the most typical BDZ anxiolytics, we detected several features shared by both types of molecules. Thus, *p*-chloro- and *p*-nitrophenyl substituents, present in the structures of those more potent pyrimidoisoindolols, can be recognised as parts of the structure of common BDZs, most of which contain chloro or nitro groups at position C-7 of the BDZ system (Fig. 1A). This analogy moved us to carry out other structural comparisons between both types of molecules. With this aim, MM and ab initio calculations of conformational energies and electrostatic charge distribution were performed for the most potent compounds of those tested, **IIIe** and **IIIg**. Conformational calculations led to several conformers displaying energy differences lesser than 1.5 kcal/mol, with respect to that of the most stable one, for both compounds. Two of the main conformers of compound **IIIe** were superimposed to the most stable conformer of

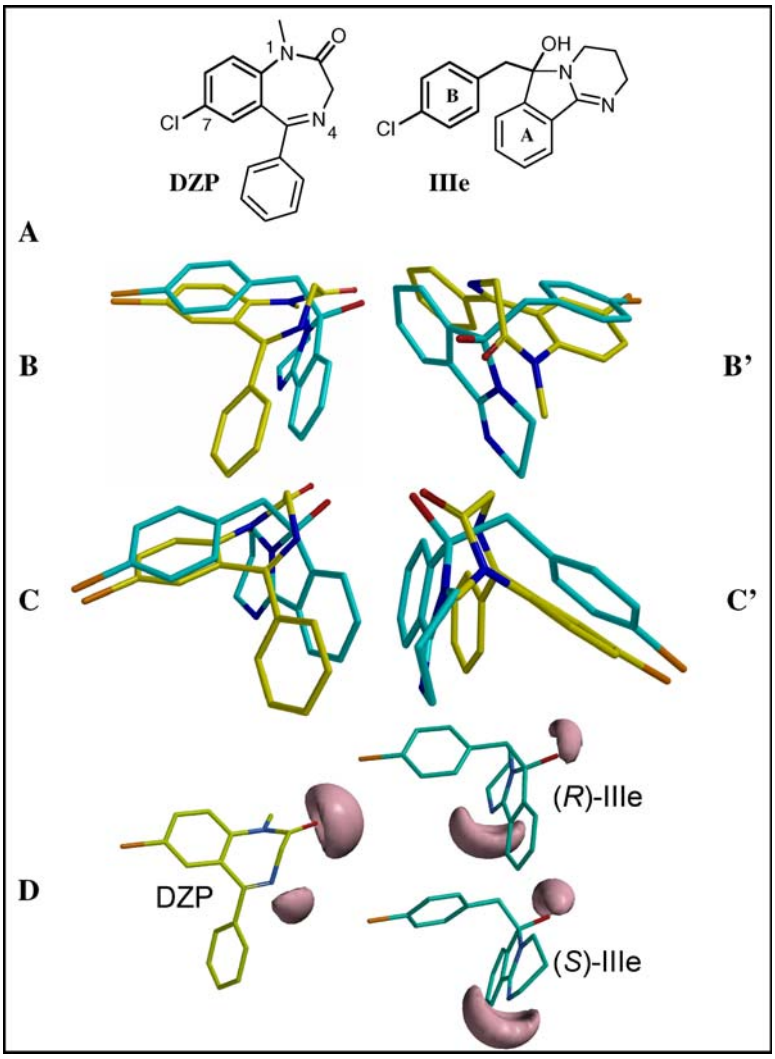


Figure 1. Comparisons of structures (A), main conformations (B and C) and 3D contours of molecular electrostatic isopotentials (D, pink-purple) between diazepam (DZP, yellowish) and pyrimidoisoindolol **IIIe** (blue-green).

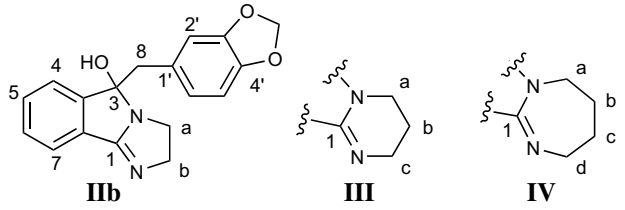
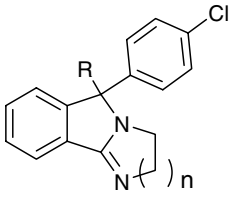


Figure 2. Numbering used for NMR data assignment.

DZP, allowing us to confirm the a priori non expected global structure similarity between both compounds (Fig. 1A–C). In the figure, B/B′ and C/C′ pairs correspond to superimpositions of two stable conformers of **IIIe** with the most stable conformer of DZP, each one being observed from two different orientations. It can be seen that actually, in spatial and geometric terms, compound **IIIe** is not too far from DZP and, consequently, could be able to interact with BZD receptors (Fig. 2).

Complementarily, calculations for analysing the charge distribution in both molecules were also carried out.[15,16] The comparison of 3D contours of molecular electrostatic potentials (MEP), at the −35 kcal/mol isopotential level for DZP and **IIIe** (Fig. 1D, pink-purple colour zones), also revealed, particularly for the *S*-**IIIe** enantiomer, a similar spatial distribution of the electrostatic charge[17] and, consequently, of the sites for molecular recognition and binding to the target biomolecules. All these favourable comparisons seem to justify the observed parallelism of the anxiolytic-like effects of pyrimidoisoindolols with those of DZP. However, it remains to be ascertained experimentally whether or not they act by the same mechanism. In this respect, more compounds are being prepared and the effect of pyrimidoisoindolols on the $GABA_A$ receptor–benzodiazepine receptor–chloride ion channel complex, as well as their potential interaction with 5-HT receptors and its transporter protein, will be evaluated. The close structural similarity between compounds **IIe** and **IIIe** and the approved antiobesity agent and anorexogenic drug mazindol, as well as the reported ability of mazindane group of compounds for inhibiting cocaine binding to the DA transporter,[18] will also be considered for future mechanistic studies.



mazindane	n = 1, R = H
mazindol	n = 1, R = OH
cyclazindol	n = 2, R = OH

As a global conclusion, though much chemical and pharmacological research must be done, it can be stated that the pyrimido[2,1-*a*]isoindolol fragment constitutes a new scaffold and the structural basis for the development of new anxiolytic drugs.

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5. A description of the elevated plus-maze apparatus was included in the previous paper of this series.[4] The animals were administered intraperitoneally (ip) 30 min before the test with the different treatments (DZP, 1 mg/kg; PTX, 2 mg/kg; compounds, 15 mg/kg). Test began with the mice placed singly in the centre of plus-maze facing a closed arm. The number of entries and the time spent in closed and open arms were recorded for 5 min. Entry into an arm was defined as the animal placing all four paws onto the arm. Total exploratory activity (number of entries) and other ethologically derived measures (grooming, rearing, stretched attend postures and head dipping) were also registered. All tests were taped by using a video camera. After each test, the maze was carefully cleaned up with a wet tissue paper (10% EtOH solution). Groups of 8 male Albino ICR mice (32–38 g) were conditioned to laboratory environment (12 h light and 12 h dark), with free access to water and food. Data obtained in the test were compared against the control group by using the ANOVA method and followed by a post-hoc Dunnett test. Probability values less than 5% ($p < 0.05$) were considered significant. Statistical analysis was performed using the SPSS software package.
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8. Example of synthesis and characterisation of imidazoisoindolols: 5-(benzo[*d*][1,3]dioxol-5-ylmethyl)-3,5-dihydro-2*H*-imidazo[2,1-*a*]isoindol-5-ol (**IIb**). To 3-(benzo[*d*]-[1,3]dioxol-5-ylmethylene)isobenzofuran-1(3*H*)-one (**Ib**) (266 mg, 1 mmol) in dichloromethane (5 mL) at room temperature was added dropwise 0.34 mL (5 mmol) of ethylenediamine (99%) and maintained for 9 h. After reaction completion (TLC control), the mixture was poured into water (100 mL) and extracted two times with EtOAc. Standard workup and chromatography on silica gel gave 253 mg (82%) of **IIb**, as a yellowish viscous oil. IR ν_{max}: 3359, 2927, 1687, 1598, 1492, 1249, 1194, 928, 880, 814, 767 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.78–3.02 (2H, m, H-b+b′), 3.09 (1H, d, J = 13.9 Hz, H-8a), 3.12 (1H, m, H-a), 3.32 (1H, d, J = 13.9 Hz, H-8b), 3.75 (1H, bs, OH), 4.06 (1H, dt, J = 14.6, 2.6 Hz, H-a′), 5.80 (2H, s, OCH_2O), 6.27 (1H, dd, J = 8.0, 1.8 Hz, H-6′), 6.30 (1H, d, J = 1.8, H-2′), 6.50 (1H, d, J = 8.0, H-5′), 7.36 (1H, dt, J = 7.3, 1.2 Hz, H-6), 7.39 (1H, dd, J = 7.3, 1.2 Hz, H-4), 7.49 (1H, dt, J = 7.3, 1.1 Hz, H-5), and 7.58 (1H, bd, J = 7.3 Hz, H-7) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: (C-assignment): 39.5 (a), 41.8 (b), 44.1 (8), 89.4(3), 100.8 (acetalic), 107.7 (5′), 110.2 (2′), 122.4 (6′), 123.0 (4), 123.3 (7), 128.7 (7a), 129.0 (6), 130.8 (1′), 132.0 (5), 146.3 (3a), 147.2 (4′), 147.8 (3′) and 167.7 (1) ppm. MW: 308.33; EIMS *m/z*(%): 308 (2)M^+, 266 (6), 173 (100). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09; found: C, 70.22; H, 5.20; N, 8.97.
9. Example of synthesis and characterisation of pyrimidoisoindolols: 6-(4-methylthiobenzyl)-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ol (**IIIg**). 3-(4-Methylthiobenzylidene)-isobenzofuran-1(3*H*)-one (**Ig**) (268 mg, 1 mmol) and 0.42 mL (5 mmol) of 1,3-diaminopropane (99%) were refluxed in dry dichloromethane (5 mL) for 90 min until phthalide disappearance on TLC. Then, the reaction mixture was poured into water (100 mL) and extracted two times with EtOAc. Routine workup and crystallisation from methanol afforded 285 mg (88%) of **IIIg**, as a white powder; mp = 135–136 °C. IR ν_{max}: 3359, 2927, 1687, 1598, 1492, 1083, 819, 762, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.71 (1H, m, H-b), 2.20 (1H, m, H-b′), 2.43 (3H, s, SCH_3), 2.83 (2H, m, H-c+c′), 3.11 (1H, d, J = 13.8 Hz, H-8a), 3.38 (1H, d, J = 13.8 Hz, H-8b), 3.39 (1H, m, H-a), 3.88 (1H, m, H-a′), 6.70 (2H, d, J = 8.4 Hz, H-3′ + H-5′), 6.93 (2H, d, J = 8.4, H-2′ + H-6′), 7.31–7.50 (3H, m, H-4 + H-5 + H-6) and 7.51 (1H, bd, J = 7.3, H-7) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (C-assignment): 15.1 (MeS), 27.7 (b), 37.5 (a), 39.4 (c), 43.1 (8), 90.5 (3), 121.2 (4), 122.1 (7), 125.4 (3′, 5′), 128.2 (6), 129.8 (2′, 6′), 130.6 (7a), 131.0 (5, 1′), 135.6 (4′), 147.1 (3a) and 166.7 (1) ppm. MW: 324.44; MS (FAB) *m/z* 325.14 $(M+H)^+$. Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63; S, 9.88; found: C, 70.42; H, 6.18; N, 8.59; S, 9.78.
10. Example of synthesis and characterisation of [1,3]diazepinoisoindolols: 7-(4-chlorobenzyl)-3,4,5,7-tetrahydro-2*H*-[1,3]diazepino[2,1-*a*]isoindol-7-ol (**IVe**): to 3-(4-chlorobenzylidene)isobenzofuran-1(3*H*)-one (**Ie**) (258 mg, 1 mmol) in dichloromethane (5 mL) at room temperature was added dropwise 0.50 mL (5 mmol) of 1,4-butylenediamine and maintained for 3 h. After completion of the reaction, similar workup and crystallisation from methanol afforded 293 mg (94%) of **IVe**, as a white powder; mp = 148–149 °C; IR ν_{max}: 3360, 2926, 1687, 1595, 1492, 1085, 820, 762, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.51 (2H, m, H-c + H-c′), 1.73 (1H, m, H-b), 1.88 (1H, m, H-b′), 2.50 (1H, bs, OH), 2.59 (2H, m, H-d + H-d′), 3.12 (1H, d, J = 13.5 Hz, H-8a), 3.33 (1H, m, H-a), 3.40 (1H, d, J = 13.5 Hz, H-8b), 3.77 (1H, m, H-a′), 6.74 (2H, d,

J = 8.4 Hz, H-2′,6′), 7.03 (2H, d, J = 8.4, H-3′ + H-5′), 7.22 (1H, d, J = 7.4 Hz, H-4), 7.36 (1H, bt, J = 7.4, H-6), 7.45 (1H, bt, J = 7.5, H-5) and 7.56 (1H, d, J = 7.5, H-7) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (C-assignment): 26.0 (b), 29.0 (c), 39.0 (a), 40.6 (d), 42.6 (8), 91.2 (3), 122.4 (4), 122.8 (7), 127.9 (3′, 5′, 6), 129.2 (7a), 131.3 (2′, 6′), 131.5 (4′), 132.6 (5), 133.3 (1′), 146.7 (3a) and 167.2 (1) ppm. MW: 326.82; Anal. Calcd for $C_{19}H_{19}ClN_2O$: C, 69.83; H, 5.86; Cl, 10.85; N, 8.57; found: C, 69.97; H, 5.78; Cl, 10.76; N, 8.56.

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