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Aminimides as Potential CNS Acting Agents. I. Design, Synthesis, and Receptor Binding of 4′-Aryl Aminimide Analogues of Clozapine as Prospective Novel Antipsychotics

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A series of substituted 1-[4-(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-aminimide derivatives were designed on the basis of the physicochemical properties of the aminimide functional group and synthesized as potential antipsychotic agents for the treatment of schizophrenia. The target compounds were readily prepared in two steps from clozapine (8-chloro-11-(4-methylpiperazino)-5*H*-dibenzo[*b*,*e*][1,4]diazepine) and involved *N*-acylation of a common hydrazinium salt intermediate by an acyl chloride or activated ester in the presence of a strong base. The aminimides were tested for in vitro activity at the dopamine D_4 and serotonin 5-HT_{2A} receptors and were found to possess modest affinity for both receptor systems.

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Introduction

Schizophrenia is a debilitating mental illness that severely impairs one's perception of reality, and damages a variety of emotional, behavioural, and cognitive functions.[1] This most common form of psychosis afflicts about 1% of the population. The symptoms of schizophrenia are divided into two distinct classifications; positive (delusions, hallucinations, and disorganized behaviour) and negative (social and emotional withdrawal, affective flattening).[2] For further elaboration on the complex disease state of schizophrenia, see cited reviews.[2–4]

Antipsychotic drugs are divided into two clinical classes, namely; *typical* (effective in treating positive symptoms and tend to induce Parkinsonian type side-effects) and *atypical* (effective in treating both positive and negative symptoms, and are virtually devoid of dose-limiting side-effects).[5] Fig. 1 depicts four commercially available antipsychotic agents commonly prescribed for the treatment of schizophrenia.

Clozapine, the prototype atypical antipsychotic, causes no extrapyramidal side effects (EPS) and is effective against both positive and negative symptoms. Clozapine has weak dopamine D_2 receptor affinity, and significantly greater dopamine $D_{4.4}$ (the most common polymorphic variant of the D_4 receptor) and serotonin 5-HT_{2A} receptor affinities. Clozapine is unfortunately hampered by a 1–2% incidence of agranulocytosis[2] (a life-threatening blood disorder) which mandates expensive hematological monitoring. As a consequence, clozapine is generally administered for the treatment of refractory schizophrenia.

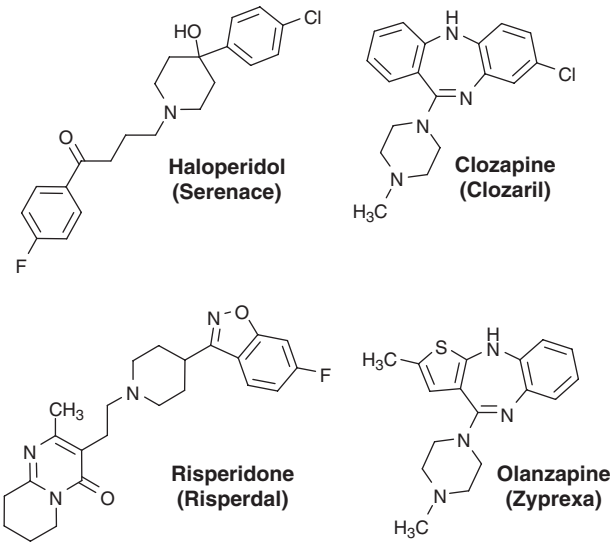

Fig. 1. Clinically prescribed antipsychotic agents.

The clinical model for antipsychotic activity we have selected is directed towards compounds with a potential dual action.

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Primarily, the clozapine-like profile of high $D_{4.4}$ and 5-HT_{2A} receptor affinity is postulated for the improvement of positive and negative symptoms, respectively, and reduced striatal D_2 affinity to minimize EPS liability. Because of clozapine's almost ideal therapeutic profile, structural analogues have been synthesized as biological probes to further explore this model.[2,6]

In a previous study, the synthesis of a series of 4′-arylmethyl clozapine analogues of general structure **1** (Fig. 2), were reported along with their affinities at the $D_{4.4}$ and 5-HT_{2A} receptors.[6] From this research, it was concluded that the introduction of an *N*-arylmethyl group into the structure of clozapine, although affording compounds with respectable affinity, appears not to have a superior effect on binding at the receptors of interest compared with clozapine. In addition, incorporation of a substituted arylmethyl group into the structure of clozapine increased the lipophilicity and reduced the aqueous solubility to a level difficult to use in assays, therefore indicating potential bioavailability issues. Recently, there have been reports describing the use of the aminimide moiety in azole antifungals,[7] and peptidomimetic inhibitors of elastase[8] and HIV-1 protease.[9] The zwitterionic character of aminimides is reported to result in enhanced solubility in protic, aprotic, and non-polar media.[9,10] This interesting property led us to consider the use of aminimides in clozapine-like molecules of general structure **2** (Fig. 2), in order to address some of the limitations of our compounds. Here we report the design, synthesis, and preliminary pharmacological evaluation of these aminimide-based clozapine analogues.

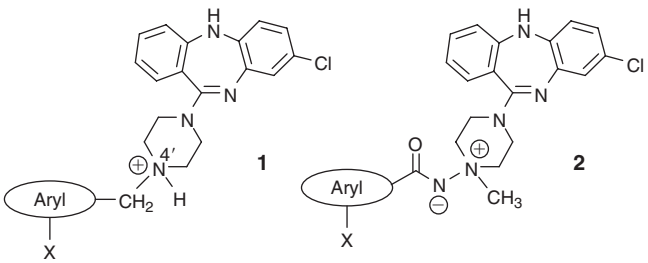


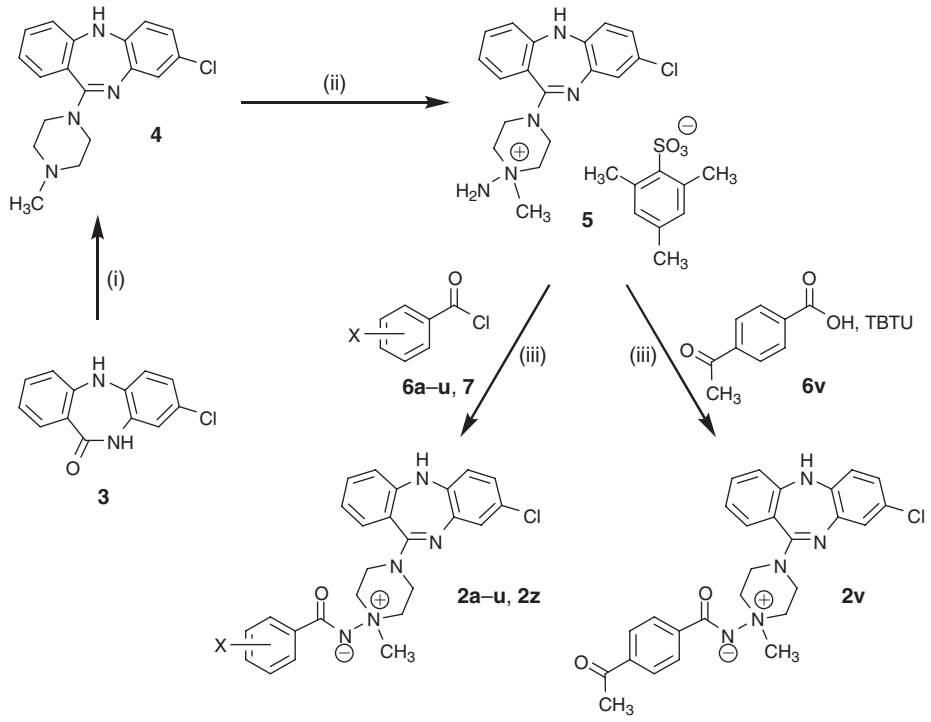
Fig. 2. General substituted arylmethyl (**1**) and aryl aminimide analogues (**2**) of clozapine at physiological pH.

The general structure (**1**) for the 4′-arylmethyl clozapine analogues investigated in the previous study[6] essentially contains the tricyclic nucleus of clozapine and an additional substituted aromatic ring attached to the distal nitrogen by a methylene spacer. The reported analogues (**2**) have replaced the methylene spacer with an aminimide functional group and the aryl portion (Ar) of the aminimide acyl moiety is represented by: (a) a monosubstituted phenyl ring that includes a variety of electron-withdrawing and electron-releasing groups (phenyl analogues, **2a–y**); (b) a catechol-based moiety (**2z** and **2aa**); and (c) a 5-substituted indol-2-yl group connected by the 2-position (**9**, **10**).

Chemistry

Our recent communication on the chemistry of benzoyl azides[11] showed that direct synthesis of the desired series of aminimide analogues from clozapine was not feasible. A convenient and flexible synthesis was consequently developed for all of the target aminimides, in two steps from clozapine (**4**). Clozapine (**4**) was readily synthesized from the key intermediate lactam (**3**) and *N*-methylpiperazine in the presence of the Lewis acid, titanium tetrachloride (Scheme 1).

The general approach used for all aminimides involved initial *N*-amination of **4** with *O*-mesitylenesulfonylhydroxylamine[12] to produce the hydrazinium salt (**5**), followed by *N*-acylation of **5** with an appropriate acylating agent (Scheme 1). Compounds **2a–u** and **2z** were formed by *N*-acylation of **5** with the



Scheme 1. *Reagents and conditions*: (i) $TiCl_4$, *N*-methylpiperazine, 1,4-dioxan, reflux, 2 h. (ii) $MesSO_3NH_2$, CH_2Cl_2, 0°C, 10 min. (iii) NaH, DMF, −15°C to room temp., 8 h.

appropriately substituted benzoyl chloride (**6a–u**, **7**, Scheme 1) in 33–64% yield. Compound **2v** was synthesized in 38% yield by *N*-acylation of **5** with an activated (hydroxybenzotriazolyl, HOBt) ester (**6v**) prepared from 4-acetylbenzoic acid and *O*-benzotriazol-1yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU). The 5-methoxyindolyl aminimide analogue (**9**) was prepared from **5** and the corresponding indolecarboxylic acid and TBTU (Scheme 2, 34% yield). The hydroxy analogues **2w–y**, **2aa**, and **10** were prepared by BBr_3-mediated deetherification of their corresponding methoxyphenyl analogues (**2q–s**), the methylenedioxy ether (**2z**), and 5-methoxyindolyl compounds (**9**), respectively (Scheme 3) in 42–79% yield.

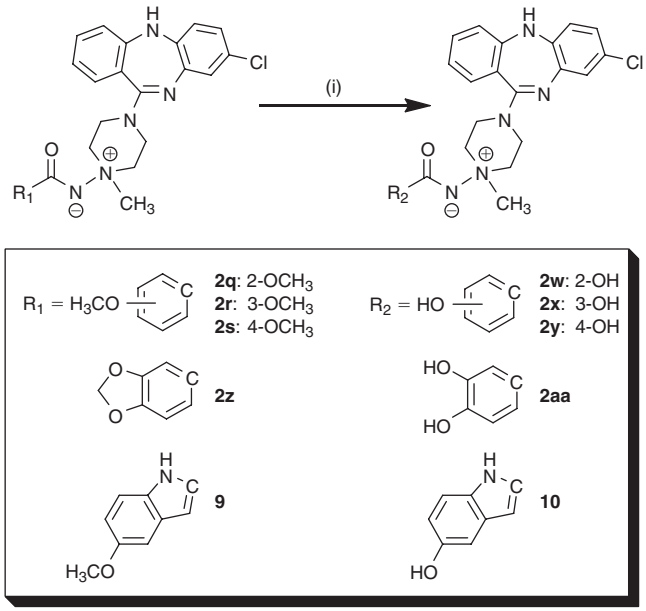
Structural assignment of the aminimides was achieved from their NMR analyses and mass spectrometric data. The X-ray crystal structure of **2g** (Fig. 3) has also been published,[13] which gave insight into structural features associated with the aminimide functional group (a group not well parameterized in molecular modelling packages) and its incorporation into the structure of clozapine.

Our interest in the crystal structure of **2g** was to examine the effect of the aminimide substituent on the geometries of the piperazine ring and the tricyclic nucleus, relative to clozapine. The tricyclic portion of **2g** is in a similar conformation to that observed for the parent compound, clozapine (**4**),[14] which shows the buckled nature of the dibenzodiazepine nucleus with the central seven-membered heterocycle in a boat conformation. As was observed for clozapine (**4**), the piperazine ring of **2g** adopts a chair conformation. The methyl group of **2g** assumes an *equatorial* orientation as is observed with clozapine. This observation supports the *axial* orientation of the 4-chlorobenzimide group for the solution structure, which was deduced by the correlations observed in the nuclear Overhauser effect (NOESY) spectrum of **2g** (Fig. 4). NOes are observed between the ^{+}N-methyl proton resonance and both the *axial* and *equatorial* H2′ and H6′ proton resonances, which indicates that the methyl group lies *equatorial* and the (4-chlorobenzoyl)amide group *axial*. A further nOe observed between the H2″/H6″ proton resonance (δ 7.93) and resonances of H2′b/H6′b (δ 4.43) and H3′/H5′ (δ 3.87) provides further evidence for the axial 4-chlorobenzimide group. The 4-chlorobenzimide moiety also shows features similar to those reported for other aminimides.[15,16] The N–N bond is similar to a single bond in length. There is also charge delocalization from the nitrogen onto the carbonyl oxygen atom of the molecule, which is supported by the characteristic aminimide infrared resonance ($^{-}$OC=N) at 1554 cm^{-1}.

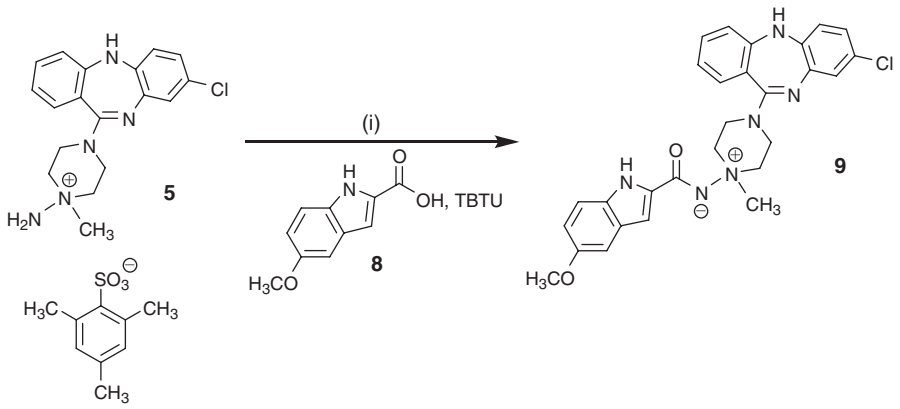
Receptor Binding Studies

Details of the in vitro assays for the synthesized compounds are described in the Experimental section. Tables 1 and 2 list preliminary percentage inhibition of radioligand at a compound concentration of 10^{-6} M for the dopamine $D_{4.4}$ and serotonin 5-HT_{2A} receptors for all test compounds. All affinities were below that of clozapine, which recorded 54 and 90% inhibition at $D_{4.4}$ and 5-HT_{2A} receptors, respectively, at a concentration of 10^{-6} M.

The affinities of the phenyl analogues for $D_{4.4}$ receptors in mammalian CHO-K_1 cells, calculated as a percentage inhibition using [^{3}H]spiperone as the competing radioligand, ranged from −14 to 40% at 10^{-6} M (Table 1), with the 4-fluorophenyl compound (**2d**) displaying the greatest affinity. The affinities of the phenyl analogues for 5-HT_{2A} receptors in rat cerebral cortex (percentage inhibition, [^{3}H]ketanserin) ranged from 6 to 53% at 10^{-6} M (Table 1), with the 3,4-dihydroxyphenyl (catechol) compound **2aa** exhibiting the highest affinity. The affinities for the indolyl analogues **8**, **9** for the $D_{4.4}$ receptor were poor with 9 and 14% inhibition, respectively (Table 2).



Scheme 3. *Reagents and conditions*: (i) BBr_3, CH_2Cl_2, −78°C, 1 h, room temp.



Scheme 2. *Reagents and conditions*: (i) NaH, DMF, −15°C to room temp., 8 h.

Similarly, compound **8** showed poor dopaminergic affinity at the $D_{4.4}$ receptor. A notable result was the 5-HT_{2A} receptor affinity of compound **9**, which showed a very respectable affinity corresponding to 67% inhibition. This result is gratifying as it demonstrates relatively enhanced recognition of the 5-HT_{2A} receptor by the incorporation of a serotonin-like moiety (5-hydroxyindol-2-yl), and may be useful in establishing further structure–activity relationships. Overall, the synthesized compounds all showed mild binding affinity for both the $D_{4.4}$ and 5-HT_{2A} receptors with none exhibiting affinity superior to that of clozapine, or the corresponding substituted arylmethyl compounds published previously.[6] As a result, no compounds assayed met the criteria of greater than 50% inhibition at both receptors, to warrant K_i determination.

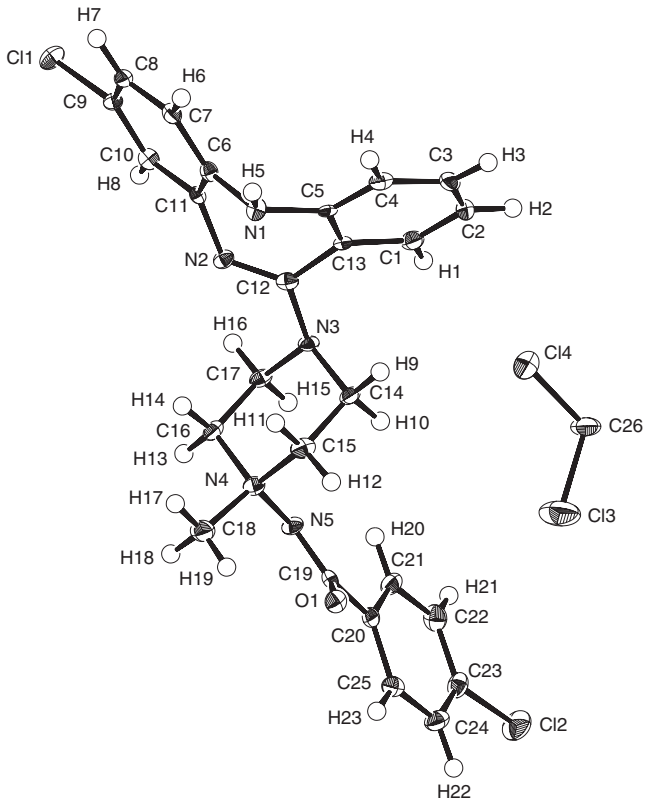


Fig. 3. ORTEP view of **2g** (50% probability displacement ellipsoids).

Conclusions

Several aminimide analogues of clozapine were synthesized and evaluated in vitro for their affinity for the dopamine $D_{4.4}$ and serotonin 5-HT_{2A} receptors. All of the compounds showed a marked reduction in binding at the two receptor systems when compared with clozapine, thus indicating minimal potential for atypical antipsychotic activity. The reduced affinities, in general for the aminimide analogues, may reflect the introduced aromatic moiety's *axial* disposition in contrast to the *equatorial* disposition of the original series. Further work will focus on the biochemical effects of extending the alkyl spacer between the aminimide functional group and the newly introduced aryl moiety.

Experimental

General

Melting points were determined using a Reichert Micro-melting point apparatus and are uncorrected. Microanalyses were carried out by Chemical and Micro Analytical Services Pty Ltd, Melbourne, Australia, or the Chemistry Department, University of Queensland. Infrared spectra were recorded using a Hitachi 270-30 infrared spectrometer as potassium bromide

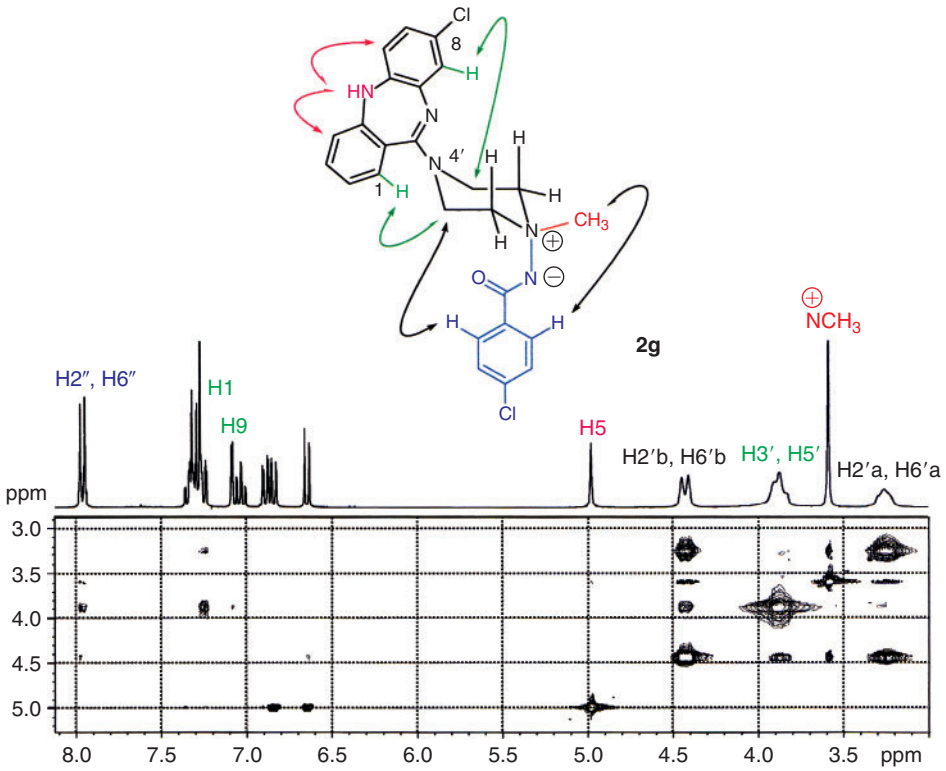
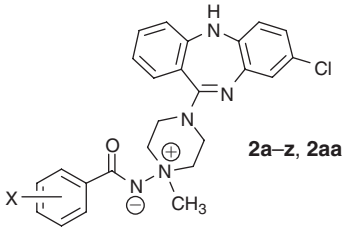


Fig. 4. 300 MHz ^{1}H–^{1}H NOESY spectrum of **2g**. Some nOe correlations (arrows) have been omitted for clarity.

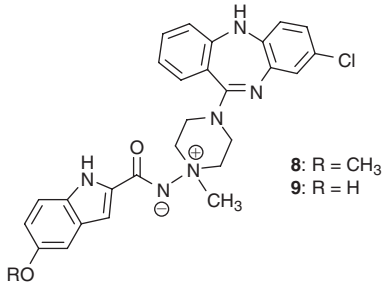
Table 1. Preliminary binding studies



Compound	X	Binding affinity percentage inhibition [% I] at 10^{-6} M	
		$D_{4.4}$[A] [^{3}H]spiperone	5-HT_{2A}[A] [^{3}H]ketanserin
Clozapine	—	54	90
2a	H	−14	47
2b	2-F	3	3
2c	3-F	2	12
2d	4-F	40	34
2e	2-Cl	−13	21
2f	3-Cl	20	19
2g	4-Cl	14	12
2h	2-Br	17	42
2i	3-Br	5	18
2j	4-Br	−13	21
2k	2-CH_3	3	14
2l	3-CH_3	2	24
2m	4-CH_3	12	9
2n	2-CF_3	−1	29
2o	3-CF_3	3	16
2p	4-CF_3	−18	8
2q	2-OCH_3	25	33
2r	3-OCH_3	12	10
2s	4-OCH_3	28	13
2t	2-$COCH_3$	−7	29
2u	3-$COCH_3$	10	22
2v	4-$COCH_3$	14	26
2w	2-OH	28	22
2x	3-OH	11	6
2y	4-OH	23	8
2z	3,4-OCH_2O–	33	13
2aa	3,4-diOH	17	53

[A]Determined in duplicate by MDS PANLABS (Taiwan).

Table 2. Preliminary binding studies



Compound	R	Binding affinity percentage inhibition [% I] at 10^{-6} M	
		$D_{4.4}$[A] [^{3}H]spiperone	5-HT_{2A}[A] [^{3}H]ketanserin
Clozapine	—	54	90
8	CH_3	14	17
9	H	9	67

[A]Determined in duplicate by MDS PANLABS (Taiwan).

(KBr) disks for solids, as thin films of liquids (neat) between sodium chloride plates, and as chloroform ($CHCl_3$) solutions of gums. UV-Vis spectra were recorded as ethanolic solutions with a Pharmacia Biotech Ultraspec 2000 UV-VIS spectrometer utilising *Swift II* software. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX-300 and a Bruker DRX-500 spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane (TMS) or the deuterated solvent. ^{13}C NMR spectra were recorded at 75.5 MHz on a Bruker DPX-300 spectrometer or, where stated, at 125.72 MHz on a Bruker DRX-500 spectrometer. The NOESY, homonuclear (^{1}H/^{1}H) correlation spectroscopy (DQFCOSY and gradient COSY), and inverse heteronuclear (^{1}H/^{13}C) correlation spectroscopy (HMQC and gradient HMBC) were obtained by the standard Bruker pulse sequences for the structural assignment of some NMR spectra. Mass spectra were recorded on a JEOL JMS-DX300 or a Micromass platform II mass spectrometer in positive ion electrospray mode. High-resolution mass spectra (HRMS) were recorded with a Bruker Bio Apex II FTICR mass spectrometer. Silica gel (Kieselgel 60 silica gel 230–400 mesh) was used for column chromatography. Preparative TLC was performed on glass plates (Merck ART 5717). Solvents were purified by literature methods.[17,18] Hexane refers to the hydrocarbon fraction boiling between 60 and 80°C.

*8-Chloro-11-(4-methylpiperazino)-5*H*-dibenzo[*b,e*][1,4]diazepine* ***4***

To a solution of 1-methylpiperazine (3.43 mL, 3.10 g, 30.8 mmol) in anhydrous dioxan (30 mL) under nitrogen was added a solution of titanium tetrachloride in toluene (1.0 M, 6.76 mL, 6.76 mmol), which resulted in an immediate deep green coloration (titanium–amine complex). The reaction mixture was heated to 50–55°C and a hot solution of **17** (1.50 g, 6.15 mmol) in anhydrous dioxan (20 mL) was added. The mixture was heated to reflux for 2 h, cooled, and evaporated to dryness. The brown coloured residue was partitioned between ethyl acetate (200 mL) and aqueous sodium hydroxide (2 M, 50 mL) and filtered through a bed of Celite. The organic layer was separated and the aqueous phase extracted with ethyl acetate (2 × 100 mL). The organic fractions were combined, washed with water (2 × 50 mL), dried over anhydrous sodium sulfate, and evaporated to dryness. The resulting oily yellow residue was purified by flash chromatography (ethyl acetate followed by 85/15 ethyl acetate/methanol) to afford a bright yellow foam (1.97 g, 98%), which recrystallized from acetone/water to afford **4** (1.76 g, 88%) as brilliant yellow prisms, mp 181–183°C [lit.[19] 183–184°C]. δ_H ($CDCl_3$) 2.35 (3H, s, CH_3N), 2.52 (4H, br s, H3′, H5′), 3.49 (4H, br s, H2′, H6′), 5.00 (1H, s, H5), 6.61 (1H, d, *J* 8.5, H6), 6.80–6.83 (2H, m, H4, H7), 7.01 (1H, app td, *J* 7.5, 1, H2), 7.07 (1H, d, *J* 2.5, H9), 7.24–7.30 (2H, m, H1, H3). δ_C ($CDCl_3$) 46.0 (CH_3N), 47.2 (C2′, C6′), 55.0 (C3′, C5′), 120.0 (C6), 120.1 (C4), 123.0 (C2), 123.1 (C7), 123.5 (C11a), 126.8 (C9), 129.1 (C8), 130.3 (C1), 131.9 (C3), 140.4 (C5a), 141.8 (C9a), 152.8 (C4a), 162.8 (C11). *m/z* (+ESI, 30 V) 329 (35%, M[^{37}Cl]H$^+$), 327 (100%, MH$^+$).

*1-Amino-4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium-2,4,6-trimethyl-1-benzenesulfonate* ***5***

A solution of *O*-mesitylenesulfonylhydroxylamine[20] (0.66 g, 3.1 mmol) was added dropwise to a solution of **4** (1.0 g,

3.1 mmol) in dichloromethane (15 mL) in ice and after the addition was complete the mixture was left to stir for a further 20 min. Hexane (20 mL) was added to precipitate the product (1.59 g, 95%), which was collected by filtration. Recrystallization from ethyl acetate/methanol gave **5** as bright yellow needles (1.36 g, 82%), mp 183–184°C. (Found: C 59.4, H 6.2, N 13.0. $C_{27}H_{32}ClN_5O_3S$ requires C 59.8, H 6.0, N 12.9%.) ν_{max} (KBr)/cm^{-1} 3312, 1568. λ_{max}/nm (ε/M^{-1} cm^{-1}) 205 (77 600), 226 (74 100), 260 (18 200), 296 (9330). δ_H (d_4-methanol) 2.27 (3H, s, ArCH_3), 2.67 (6H, s, 2 × ArCH_3), 3.47 (3H, s, CH_3N^+), 3.55–3.63 (2H, m, H3′a, H5′a), 3.71–3.76 (2H, m, H3′b, H5′b), 3.80–3.84 (2H, m, H2′a, H6′a), 3.93 (2H, br m, H2′b, H6′b), 6.88 (1H, d, *J* 8.5, 1H, H6), 6.92 (2H, s, H3″, H5″), 6.95 (1H, dd, *J* 8.5, 2.5, H7), 7.03 (1H, d, *J* 2.5, H9), 7.07 (1H, br d, *J* 8, H4), 7.12 (1H, app br t, *J* 8, H2), 7.38 (1H, br d, *J* 7.5, H1), 7.43 (1H, app td, *J* 8, 1.5, H3). δ_C (d_4-methanol) 21.0 (Ar*C*H$_3$), 24.4 (2 × Ar*C*H$_3$), 42.9 (C3′, C5′), 58.4 (CH_3N^+), 64.3 (C2′, C6′), 121.7 (C4), 121.8 (C6), 123.6 (C11a), 124.5 (C2), 125.4 (C7), 127.5 (C9), 129.8 (C8), 131.1 (C1), 131.9 (C3″, C5″), 134.1 (C3), 138.3 (C2″, C6″), 140.3 (C1″), 141.0 (C4″), 142.6 (C5a), 143.2 (C9a), 155.6 (C4a), 164.0 (C11). *m*/*z* (+ESI, 70 V) 344 (13%, M[^{37}Cl]$^+$), 342 (40%, M$^+$), 272 (28), 270 (80), 258 (20), 256 (60), 245 (25), 243 (100), 229 (20), 227 (60).

General Procedure for the Synthesis of Aminimides: N-Acylation Using Acid Chlorides

The aminimides **2a–u** and **2z** were prepared from 1-amino-4-(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium-2,4,6-trimethyl-1-benzenesulfonate **5** (100 mg, 0.18 mmol) and the corresponding substituted acyl chloride (0.22 mmol) in the presence of sodium hydride (0.74 mmol), and isolated as yellow crystalline solids. The general method exemplified for the synthesis of 1-[4-(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-benzimide **2a** is described below.

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-benzimide* ***2a***

Sodium hydride (29.8 mg, 0.74 mmol, 60% dispersion in oil) was washed with anhydrous hexane, dried under a continuous stream of dry nitrogen and cooled to −15°C (dry ice-benzyl alcohol). A cooled solution of 1-amino-4-(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium 2,4,6-trimethyl-1-benzenesulfonate **5** (100 mg, 0.18 mmol), and benzoyl chloride (25.7 μL, 0.22 mmol) in anhydrous *N*,*N*-dimethylformamide (4 mL) was added dropwise to the dry sodium hydride with stirring over 5 min. The mixture was then maintained at −15°C for 7 h and then allowed to warm to room temperature overnight. The solvent was removed under vacuum to afford an orange solid, which was resuspended in ethyl acetate, and a white solid removed by filtration. The filtrate was concentrated and the resulting residue purified by flash chromatography (10/1, ethyl acetate/methanol) to afford a bright yellow solid (68.2 mg, 85%). Recrystallization from acetone/water gave **2a** (51 mg, 64%) as bright yellow microneedles, mp 229–230°C. (Found: C 67.4, H 5.5, N 15.4, MH$^+$ 446.1745. $C_{25}H_{24}ClN_5O$ requires C 67.3, H 5.4, N 15.7%, MH$^+$ 446.1742.) ν_{max} (KBr)/cm^{-1} 3264, 1586, 1560. λ_{max}/nm (ε/M^{-1} cm^{-1}) 226 (30 900), 259 (19 100), 297 (9300). δ_H ($CDCl_3$) 3.24 (2H, br m, H2′a, H6′a), 3.59 (3H, s, CH_3N^+), 3.91 (4H, br m, H3′, H5′), 4.45 (2H, m, H2′b, H6′b), 4.93 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.01 (1H, app td, *J* 7.5, 1, H2), 7.07 (1H, d, *J* 2.5, H9), 7.25 (1H, dd, *J* 7.5, 1.5, H1), 7.30–7.38 (4H, m, H3, H3″, H4″, H5″), 8.00 (2H, dd, *J* 7, 2, H2″, H6″). δ_C ($CDCl_3$) 42.7 (C3′, C5′), 53.5 (CH_3N^+), 62.1 (C2′, C6′), 120.46 (C4), 120.51 (C6), 122.9 (C11a), 123.6 (C2), 124.2 (C7), 127.2 (C9), 127.7 (C2″, C6″), 127.9 (C3″, C5″), 129.5 (C8), 129.7 (C4″), 130.2 (C1), 132.8 (C3), 139.0 (C1″), 140.6 (C5a), 141.4 (C9a), 153.3 (C4a), 162.3 (C11), 170.4 (CO). *m*/*z* (+ESI, 70 V) 448 (35%, M[^{37}Cl]H$^+$), 446 (100%, MH$^+$), 402 (10), 400 (30), 329 (12), 327 (40), 298 (30), 296 (100), 272 (27), 270 (80).

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2-fluoro)benzimide* ***2b***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), yellow needles ($CHCl_3$), yield 48%, mp 226–227°C. (Found: C 63.6, H 4.9, N 14.7, MH$^+$ 464.1647. $C_{25}H_{23}ClFN_5O{\cdot}0.5H_2O$ requires C 63.5, H 5.1, N 14.8%, MH$^+$ 464.1648.) ν_{max} (KBr)/cm^{-1} 3268, 1608, 1560. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (32 400), 259 (20 400), 295 (10 700). δ_H ($CDCl_3$) 3.25 (2H, m, H2′a, H6′a), 3.60 (3H, s, CH_3N^+), 3.96 (4H, br m, H3′, H5′), 4.45 (2H, m, H2′b, H6′b), 4.99 (1H, br s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.83 (1H, br d, *J* 8, H4), 6.88 (1H, dd, *J* 8.5, 2.5, H7), 7.03 (1H, ddd, *J* 8, 7.5, 1, H2), 7.00–7.05 (1H, m, H3″), 7.07 (1H, d, *J* 2.5, H9), 7.11 (1H, app td, *J* 7.5, 1, H5″), 7.26 (1H, dd, *J* 8, 1, H1), 7.25–7.27 (1H, m, H4″), 7.32 (1H, app td, *J* 7.5, 1.5, H3), 7.69 (1H, ddd, *J* 7.5, 6, 1.5, H6″). δ_C ($CDCl_3$) 42.6 (C3′, C5′), 53.4 (CH_3N^+), 61.8 (C2′, C6′), 116.2 (d, *J* 23, C3″), 120.49 (C6), 120.52 (C4), 122.8 (C11a), 123.5 (C2), 123.8 (d, *J* 4, C5″), 124.1 (C7), 127.0 (C9), 128.0 (d, *J* 15, C1″), 129.3 (C8), 130.1 (C1), 130.2 (d, *J* 9, C4″), 130.5 (d, *J* 4, C6″), 132.7 (C3), 140.6 (C5a), 141.4 (C9a), 153.2 (C4a), 160.5 (d, *J* 252, C2″), 162.2 (C11), 169.2 (d, *J* 11.5, CO). *m*/*z* (+ESI, 70 V) 466 (35%, M[^{37}Cl]H$^+$), 464 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3-fluoro)benzimide* ***2c***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), yellow needles ($CHCl_3$), yield 48%, mp 193–194°C. (Found: C 64.6, H 5.1, N 14.7. $C_{25}H_{23}ClFN_5O$ requires C 64.7, H 5.0, N 15.1%.) ν_{max} (KBr)/cm^{-1} 3262, 1605, 1566. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (32 400), 261 (21 400), 295 (10 700). δ_H (d_6-DMSO) 3.48 (2H, br m, H2′a, H6′a), 3.50 (2H, br m, H3′a, H5′a), 3.50 (3H, s, CH_3N^+), 3.77 (2H, br m, H3′b, H5′b), 4.21 (2H, m, H2′b, H6′b), 6.87–6.90 (3H, m, H6, H7, H9), 7.00 (1H, app t, *J* 7.5, H2), 7.01 (1H, d, *J* 8, H4), 7.04 (1H, s, H5), 7.14 (1H, ddd, *J* 9, 7.5, 2.5, H4″), 7.28–7.31 (1H, m, H1, H5″), 7.36 (1H, app t, *J* 8, H3), 7.58 (1H, dd, *J* 10.5, 1.5, H2″), 7.71 (1H, d, *J* 7.5, H6″). δ_C (d_6-DMSO) 42.0 (C3′, C5′), 51.7 (CH_3N^+), 60.7 (C2′, C6′), 113.7 (d, *J* 22, C2″), 115.6 (d, *J* 21, C4″), 120.4 (C4), 120.7 (C6), 122.4 (C11a), 122.5 (C2), 123.1 (C7), 123.2 (C6″), 125.7 (C9), 126.7 (C8), 129.2 (d, *J* 8, C5″), 129.9 (C1), 132.4 (C3), 141.4 (C5a), 142.3 (C9a), 142.3 (d, *J* 6, C1″), 154.1 (C4a), 161.8 (d, *J* 242, C3″), 162.2 (C11), 166.2 (CO). *m*/*z* (+ESI, 30 V) 466 (35%, M[^{37}Cl]H$^+$), 464 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-fluoro)benzimide* ***2d***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), fine yellow needles ($CHCl_3$/hexane), yield 46%, mp

219–220°C. (Found: C 64.8, H 5.0, N 14.9. $C_{25}H_{23}ClFN_5O$ requires C 64.7, H 5.0, N 15.1%.) ν_{max} (KBr)/cm^{-1} 3274, 1605, 1572. λ_{max}/nm (ε/M^{-1} cm^{-1}) 228 (3600), 260 (23 400), 296 (11 500). δ_H ($CDCl_3$) 3.27 (2H, br m, H2′a, H6′a), 3.58 (3H, s, CH_3N^+), 3.88 (4H, br m, H3′, H5′), 4.41 (2H, m, H2′b, H6′b), 4.94 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, dd, *J* 8, 1, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.00 (2H, br d, *J* 9, H3″, H5″), 7.03 (app td, *J* 7.5, 1, H2), 7.07 (1H, d, *J* 2.5, H9), 7.24 (1H, dd, *J* 8, 1.5, H1), 7.32 (1H, app td, *J* 8, 1, H3), 8.00 (2H, dd, *J* 7.5, 5, H2″, H6″). δ_C ($CDCl_3$) 42.8 (C3′, C5′), 53.5 (CH_3N^+), 62.2 (C2′, C6′), 114.7 (d, *J* 22, C3″, C5″), 120.6 (C4, C6), 123.0 (C11a), 123.7 (C2), 124.3 (C7), 127.3 (C9), 129.5 (C8), 129.8 (d, *J* 8, C2″, C6″), 130.2 (C1), 132.9 (C3), 135.2 (C1″), 140.8 (C5a), 141.5 (C9a), 153.5 (C4a), 162.5 (C11), 164.2 (d, *J* 256, C4″), 169.5 (CO). *m*/*z* (+ESI, 30 V) 466 (33%, M[^{37}Cl]H$^+$), 464 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2-chloro)benzimide* ***2e***

Purified by flash chromatography (10/1, ethyl acetate/methanol), yellow rosettes ($CHCl_3$/hexane), yield 39%, mp 158–159°C. (Found: C 61.5, H 4.8, N 14.0, MH$^+$ 480.1370. $C_{25}H_{23}Cl_2N_5O{\cdot}0.5H_2O$ requires C 61.4, H 4.9, N 14.3%, MH$^+$ 480.1370.) ν_{max} (KBr)/cm^{-1} 3308, 1604, 1560. λ_{max}/nm (ε/M^{-1} cm^{-1}) 231 (20 400), 260 (12 600), 295 (7100). δ_H ($CDCl_3$) 3.22 (2H, br m, H2′a, H6′a), 3.57 (3H, s, CH_3N^+), 3.97 (4H, m, H3′, H5′), 4.41 (2H, m, H2′b, H6′b), 5.04 (1H, br s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.83 (1H, d, *J* 8, H4), 6.86 (1H, dd, *J* 8.5, 2.5, H7), 7.03 (1H, app t, *J* 7.5, H2), 7.06 (1H, d, *J* 2.5, H9), 7.16–7.22 (2H, m, H3″, H5″), 7.26 (1H, dd, *J* 7.5, 1, H1), 7.29–7.34 (2H, m, H3, H4″), 7.47–7.50 (1H, m, H6″). δ_C ($CDCl_3$) 42.8 (C3′, C5′), 53.5 (CH_3N^+), 62.1 (C2′, C6′), 120.47 (C4), 120.52 (C6), 122.9 (C11a), 123.6 (C2), 124.2 (C7), 126.7 (C5″), 127.1 (C9), 129.1 (C3″), 129.5 (C8), 129.7 (C6″), 130.0 (C4″), 130.2 (C1), 131.6 (C1″), 132.8 (C3), 139.8 (C2″), 140.6 (C5a), 141.4 (C9a), 153.3 (C4a), 162.2 (C11), 171.6 (CO). *m*/*z* (+ESI, 30 V) 484 (15%, M[^{37}Cl, ^{37}Cl]H$^+$), 482 (70%, M[^{37}Cl, ^{35}Cl]H$^+$), 480 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3-chloro)benzimide* ***2f***

Purified by flash chromatography (95/5/1, dichloromethane/ethanol/ammonia), yellow rosettes ($CHCl_3$/hexane), yield 44%, mp 218–218.5°C. (Found: C 62.2, H 4.9, N 14.5. $C_{25}H_{23}Cl_2N_5O$ requires C 62.5, H 4.8, N 14.6%.) ν_{max} (KBr)/cm^{-1} 3280, 1604, 1562. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (21 900), 260 (18 600), 299 (8700). δ_H ($CDCl_3$) 3.25 (2H, br m, H2′a, H6′a), 3.57 (3H, s, CH_3N^+), 3.89 (4H, m, H3′, H5′), 4.45 (2H, m, H2′b, H6′b), 4.94 (1H, br s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.83 (1H, d, *J* 8, H4), 6.88 (1H, dd, *J* 8.5, 2.5, H7), 7.02 (1H, br app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.25 (1H, br d, *J* 7.5, H1), 7.29–7.35 (3H, m, H3, H4″, H5″), 7.88 (1H, br d, *J* 7.5, H6″), 8.00 (1H, br s, H2″). δ_C ($CDCl_3$) 42.6 (C3′, C5′), 53.3 (CH_3N^+), 62.2 (C2′, C6′), 120.5 (C4, C6), 122.8 (C11a), 123.4 (C2), 124.2 (C7), 125.9 (C2″), 127.1 (C9), 128.0 (C6″), 129.1 (C5″), 129.3 (C8), 129.5 (C4″), 130.1 (C1), 132.7 (C3), 133.8 (C3″), 134.2 (C1″), 140.8 (C5a), 141.3 (C9a), 153.4 (C4a), 162.3 (C11), 168.7 (CO). *m*/*z* (+ESI, 30 V) 484 (14%, M[^{37}Cl, ^{37}Cl]H$^+$), 482 (67%, M[^{37}Cl, ^{35}Cl]H$^+$), 480 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-chloro)benzimide* ***2g***

Purified by flash chromatography (10/1, ethyl acetate/methanol), fine yellow needles ($CHCl_3$/hexane), yield 40%, mp 168–170°C. (Found: C 61.4, H 4.8, N 14.0, MH$^+$ 480.1358. $C_{25}H_{23}Cl_2N_5O$ requires C 61.4, H 4.9, N 14.3%, MH$^+$ 480.1352.) ν_{max} (KBr)/cm^{-1} 3264, 1600, 1554. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (22 400), 259 (15 100), 294 (6800). δ_H ($CDCl_3$) 3.23 (2H, br m, H2′a, H6′a), 3.54 (3H, s, CH_3N^+), 3.87 (4H, m, H3′, H5′), 4.43 (2H, m, H2′b, H6′b), 4.98 (1H, br s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.86 (1H, dd, *J* 8.5, 2.5, H7), 7.01 (1H, app t, *J* 8, H2), 7.06 (1H, d, *J* 2.5, H9), 7.23 (1H, d, *J* 8, H1), 7.28 (2H, d, *J* 8.5, H3″, H5″), 7.31 (1H, app t, *J* 8, H3), 7.93 (2H, d, *J* 8.5, H2″, H6″). δ_C ($CDCl_3$) 42.6 (C3′, C5′), 53.4 (CH_3N^+), 62.1 (C2′, C6′), 120.5 (C4), 120.6 (C6), 122.8 (C11a), 123.6 (C2), 124.3 (C7), 127.2 (C9), 128.0 (C3″, C5″), 129.2 (C2″, C6″), 129.5 (C8), 130.1 (C1), 132.8 (C3), 135.7 (C4″), 137.2 (C1″), 140.6 (C5a), 141.3 (C9a), 153.3 (C4a), 162.3 (C11), 169.1 (CO). *m*/*z* (+ESI, 30 V) 484 (15%, M[^{37}Cl, ^{37}Cl]H$^+$), 482 (70%, M[^{37}Cl, ^{35}Cl]H$^+$), 480 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2-bromo)benzimide* ***2h***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), fine yellow needles ($CHCl_3$), yield 36%, mp 203–204°C. (Found: C 57.2, H 4.5, N 13.2, MH$^+$ 524.0847. $C_{25}H_{23}ClBrN_5O$ requires C 57.2, H 4.4, N 13.3%, MH$^+$ 523.0848.) ν_{max} (KBr)/cm^{-1} 3256, 1614, 1550. λ_{max}/nm (ε/M^{-1} cm^{-1}) 228 (32 400), 260 (17 400), 295 (9800). δ_H ($CDCl_3$) 3.24 (2H, br m, H2′a, H6′a), 3.60 (3H, s, CH_3N^+), 4.01 (4H, m, H3′, H5′), 4.43 (2H, m, H2′b, H6′b), 4.96 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.83 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.04 (1H, app t, *J* 8, H2), 7.07 (1H, d, *J* 2.5, H9), 7.12 (1H, app td, *J* 8, 2, H5″), 7.23–7.29 (2H, m, H1, H4″), 7.32 (1H, app td, *J* 8, 1.5, H3), 7.47 (1H, dd, *J* 7.5, 1.5, H3″), 7.52 (1H, dd, *J* 8, 1, H6″). δ_C ($CDCl_3$) 42.9 (C3′, C5′), 53.4 (CH_3N^+), 62.1 (C2′, C6′), 120.5 (C4), 120.6 (C6), 120.8 (C2″), 123.0 (C11a), 123.8 (C2), 124.3 (C7), 127.3 (C9, C5″), 129.3 (C6″), 129.6 (C8), 129.8 (C3″), 130.3 (C1), 132.2 (C1″), 132.9 (C3), 133.2 (C4″), 140.7 (C5a), 141.5 (C9a), 153.5 (C4a), 162.3 (C11), 172.6 (CO). *m*/*z* (+ESI, 30 V) 528 (30%, M[^{81}Br, ^{37}Cl]H$^+$), 526 (100%, M[^{81}Br, ^{35}Cl]H$^+$; M[^{79}Br, ^{37}Cl]H$^+$), 524 (70%, MH$^+$), 329 (10), 327 (30), 263 (40).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3-bromo)benzimide* ***2i***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), yellow needles ($CHCl_3$/hexane), yield 33%, mp 213–214°C. (Found: C 57.0, H 4.4, N 13.0. $C_{25}H_{23}ClBrN_5O$ requires C 57.2, H 4.4, N 13.3%.) ν_{max} (KBr)/cm^{-1} 3276, 1604, 1554. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (35 500), 262 (22 400), 300 (10 200). δ_H ($CDCl_3$) 3.25 (2H, br m, H2′a, H6′a), 3.56 (3H, s, CH_3N^+), 3.86 (4H, br m, H3′, H5′), 4.41 (2H, m, H2′b, H6′b), 4.96 (1H, br s, H5), 6.62 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.01 (1H, app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.18–7.25 (2H, m, H1, H5″), 7.31 (1H, br app t, *J* 7.5, H3), 7.48 (1H, br d, *J* 7, H4″), 7.93 (1H, d, *J* 7, H6″), 8.16 (1H, s, H2″). δ_C ($CDCl_3$) 42.7 (C3′, C5′), 53.4 (CH_3N^+), 62.1 (C2′,

C6′), 120.5 (C4, C6), 122.2 (C3″), 122.9 (C11a), 123.6 (C2), 124.3 (C7), 126.4 (C6″), 127.2 (C9), 129.5 (C8, C5″), 130.2 (C1), 130.9 (C2″), 132.6 (C4″), 132.8 (C3), 140.6 (C5a), 141.1 (C1″), 141.4 (C9a), 153.3 (C4a), 162.3 (C11), 168.8 (CO). *m/z* (+ESI, 30 V) 528 (30%, M[^{81}Br, ^{37}Cl]H$^+$), 526 (100%, M[^{81}Br, ^{35}Cl]H$^+$; M[^{79}Br, ^{37}Cl]H$^+$), 524 (80%, MH$^+$), 264 (80).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-bromo)benzimide* ***2j***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), yellow needles ($CHCl_3$/hexane), yield 44%, mp 176.5–178°C. (Found: C 53.7, H 4.4, N 12.2, MH$^+$ 524.0851. $C_{25}H_{23}ClBrN_5O{\cdot}2H_2O$ requires C 53.5, H 4.8, N 12.5%, MH$^+$ 524.0848.) ν_{max} (KBr)/cm^{-1} 3228, 1604, 1584, 1544. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (30 200), 261 (21 400), 299 (8700). δ_H ($CDCl_3$) 3.25 (2H, br m, H2′a, H6′a), 3.57 (3H, s, CH_3N^+), 3.85 (4H, m, H3′, H5′), 4.41 (2H, m, H2′b, H6′b), 4.94 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, dd, *J* 8, 1, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.02 (1H, app td, *J* 8, 1, H2), 7.07 (1H, d, *J* 2.5, H9), 7.24 (1H, dd, *J* 8, 1.5, H1), 7.32 (1H, app td, *J* 8, 1.5, H3), 7.45 (2H, d, *J* 8.5, H3″, H5″), 7.88 (1H, d, *J* 8.5, H2″, H6″). δ_C ($CDCl_3$) 42.5 (C3′, C5′), 53.4 (CH_3N^+), 62.0 (C2′, C6′), 120.5 (C4, C6), 122.8 (C11a), 123.6 (C2), 124.1 (C4″), 124.3 (C7), 127.1 (C9), 129.5 (C8, C2″, C6″), 130.2 (C1), 131.0 (C3″, C5″), 132.8 (C3), 137.8 (C1″), 140.6 (C5a), 141.3 (C9a), 153.3 (C4a), 162.3 (C11), 169.3 (CO). *m/z* (+ESI, 30 V) 528 (30%, M[^{81}Br, ^{37}Cl]H$^+$), 526 (100%, M[^{81}Br, ^{35}Cl]H$^+$; M[^{79}Br, ^{37}Cl]H$^+$), 524 (80%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydro-pyrazin-1-ium]-1-(2-methyl)benzimide* ***2k***

Purified by flash chromatography (9/1, chloroform/propan-2-ol), bright yellow needles ($CHCl_3$/hexane), yield 56%, mp 144–145°C. (Found: C 65.1, H 5.8, N 14.3, MH$^+$ 460.1898. $C_{26}H_{26}ClN_5O{\cdot}H_2O$ requires C 65.3, H 5.9, N 14.6%, MH$^+$ 460.1899.) ν_{max} (KBr)/cm^{-1} 3224, 1604, 1564. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (25 700), 259 (15 100), 298 (8100). δ_H ($CDCl_3$) 2.51 (3H, s, $ArCH_3$), 3.26 (2H, br m, H2′a, H6′a), 3.62 (3H, s, CH_3N^+), 3.92 (4H, m, H3′, H5′), 4.48 (2H, m, H2′b, H6′b), 4.96 (1H, br s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.83 (1H, d, *J* 8, H4), 6.88 (1H, dd, *J* 8.5, 2.5, H7), 7.04 (1H, app t, *J* 7.5, H2), 7.05 (1H, d, *J* 2.5, H9), 7.13–7.17 (3H, m, H3″, H4″, H5″), 7.25 (1H, d, *J* 7.5, H1), 7.31 (1H, app t, *J* 7.5, H3), 7.50 (1H, br d, *J* 7, H6″). δ_C ($CDCl_3$) 20.6 ($ArCH_3$), 42.8 (C3′, C5′), 53.3 (CH_3N^+), 61.9 (C2′, C6′), 120.5 (C4, C6), 122.9 (C11a), 123.6 (C2), 124.3 (C7), 125.5 (C5″), 127.2 (C9), 128.3 (C3″, C6″), 129.5 (C8), 130.2 (C1), 130.7 (C4″), 132.8 (C3), 135.8 (C2″), 139.8 (C1″), 140.7 (C5a), 141.4 (C9a), 153.4 (C4a), 162.2 (C11), 174.3 (CO). *m/z* (+ESI, 30 V) 462 (30%, M[^{37}Cl]H$^+$), 460 (100%, MH$^+$), 327 (30).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium-1]-1-(3-methyl)benzimide* ***2l***

Purified by flash chromatography (4/1, chloroform/propan-2-ol), bright yellow needles ($CHCl_3$/hexane), yield 55%, mp 214–215°C. (Found: C 67.7, H 5.7, N 15.0, MH$^+$ 460.1898. $C_{26}H_{26}ClN_5O$ requires C 67.9, H 5.7, N 15.2%, MH$^+$ 460.1899.) ν_{max} (KBr)/cm^{-1} 3284, 1610, 1564. λ_{max}/nm (ε/M^{-1} cm^{-1}) 228 (30 200), 261 (19 100), 294 (9500). δ_H ($CDCl_3$) 2.36 (3H, s, $ArCH_3$), 3.25 (2H, br m, H2′a, H6′a), 3.59 (3H, s, CH_3N^+), 3.91 (4H, m, H3′, H5′), 4.47 (2H, m, H2′b, H6′b), 4.93 (1H, br s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.83 (1H, br d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.02 (1H, app td, *J* 7.5, 1, H2), 7.07 (1H, d, *J* 2.5, H9), 7.18 (1H, app t, *J* 7.5, H5″), 7.21 (1H, br d, *J* 7.5, H4″), 7.24 (1H, dd, *J* 8, 1.5, H1), 7.32 (1H, app td, *J* 8, 1.5, H3), 7.79–7.82 (2H, m, H2″, H6″). δ_C ($CDCl_3$) 21.6 ($ArCH_3$), 42.7 (C3′, C5′), 53.5 (CH_3N^+), 62.2 (C2′, C6′), 120.5 (C4, C6), 122.8 (C11a), 123.5 (C2), 124.2 (C7), 125.0 (C6″), 127.1 (C9), 127.9 (C2″), 128.4 (C5″), 129.4 (C8), 130.1 (C1), 132.7 (C3), 133.7 (C4″), 137.4 (C3″), 138.3 (C1″), 140.7 (C5a), 141.3 (C9a), 153.3 (C4a), 162.3 (C11), 170.6 (CO). *m/z* (+ESI, 30 V) 462 (35%, M[^{37}Cl]H$^+$), 460 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-methyl)benzimide* ***2m***

Purified by flash chromatography (95/5/0.1, ethyl acetate/methanol/triethylamine), bright yellow needles ($CHCl_3$/hexane), yield 47%, mp 162–164°C. (Found: C 66.7, H 5.7, N 14.4, MH$^+$ 460.1901. $C_{26}H_{26}ClN_5O{\cdot}0.5H_2O$ requires C 66.6, H 5.7, N 14.4%, MH$^+$ 460.1899.) ν_{max} (KBr)/cm^{-1} 3220, 1614, 1554. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (25 700), 262 (13 500), 295 (6500). δ_H ($CDCl_3$) 2.35 (3H, s, $ArCH_3$), 3.22 (2H, br m, H2′a, H6′a), 3.58 (3H, s, CH_3N^+), 3.90 (4H, m, H3′, H5′), 4.44 (2H, m, H2′b, H6′b), 4.99 (1H, br s, H5), 6.62 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.00 (1H, app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.13 (2H, d, *J* 8, H3″, H5″), 7.22 (1H, d, *J* 7.5, H1), 7.32 (1H, app t, *J* 7.5, H3), 7.90 (2H, d, *J* 8, H2″, H6″). δ_C ($CDCl_3$) 21.5 ($ArCH_3$), 42.7 (C3′, C5′), 53.5 (CH_3N^+), 62.1 (C2′, C6′), 120.5 (C4, C6), 122.9 (C11a), 123.6 (C2), 124.2 (C7), 127.3 (C9), 127.8 (C2″, C6″), 128.6 (C3″, C5″), 129.5 (C8), 130.2 (C1), 132.7 (C3), 136.2 (C1″), 139.5 (C4″), 140.7 (C5a), 141.4 (C9a), 153.4 (C4a), 162.3 (C11), 170.3 (CO). *m/z* (+ESI, 30 V) 462 (35%, M[^{37}Cl]H$^+$), 460 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2-trifluoromethyl)benzimide* ***2n***

Purified by flash chromatography (4/1, chloroform/propan-2-ol), yellow/orange needles ($CHCl_3$/hexane), yield 51%, mp 206–208°C. (Found: MH$^+$ 514.1612. $C_{26}H_{23}ClF_3N_5O$ requires MH$^+$ 524.1616.) ν_{max} (KBr)/cm^{-1} 3260, 1612, 1570. λ_{max}/nm (ε/M^{-1} cm^{-1}) 228 (27 500), 261 (17 000), 295 (9100). δ_H ($CDCl_3$) 3.28 (2H, br m, H2′a, H6′a), 3.58 (3H, s, CH_3N^+), 3.91 (4H, br m, H3′, H5′), 4.41 (2H, m, H2′b, H6′b), 4.97 (1H, s, H5), 6.65 (1H, d, *J* 8, H6), 6.85 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2, H7), 7.06 (1H, app t, *J* 7.5, H2), 7.08 (1H, d, *J* 2, H9), 7.28 (1H, d, *J* 7.5, H1), 7.33 (1H, app td, *J* 7.5, 1, H3), 7.39 (1H, app t, *J* 8, H4″), 7.51 (1H, app t, *J* 7.5, H5″), 7.61 (1H, br d, *J* 8, H6″), 7.64 (1H, br d, *J* 8, H3″). δ_C ($CDCl_3$) 42.8 (C3′, C5′), 52.8 (CH_3N^+), 61.8 (C2′, C6′), 120.5 (C4, C6), 122.6 (C11a), 123.5 (C2), 124.1 (C7), 125.1 (q, *J* 277, CF_3), 126.3 (q, *J* 4, C3″), 127.0 (C9), 127.2 (q, *J* 30, C2″), 128.0 (C4″), 129.2 (C8), 129.6 (C6″), 130.0 (C1), 131.7 (C5″), 132.7 (C3), 139.7 (C1″), 140.7 (C5a), 141.3 (C9a), 153.3 (C4a), 162.1 (C11), 172.2 (CO). *m/z* (+ESI, 30 V) 536 (20%, MNa$^+$), 516 (33%, M[^{37}Cl]H$^+$), 514 (100%, MH$^+$), 327 (50).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3-trifluoromethyl)benzimide* ***2o***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), yellow/orange needles ($CHCl_3$/hexane), yield 61%, mp

181–183°C. (Found: C 60.5, H 4.8, N 13.6. $C_{26}H_{23}ClF_3N_5O$ requires C 60.8, H 4.5, N 13.6%.) ν_{max} (KBr)/cm^{-1} 3216, 1604, 1566. λ_{max}/nm (ε/M^{-1} cm^{-1}) 227 (27 500), 257 (11 700), 296 (5500). δ_H ($CDCl_3$) 3.27 (2H, br m, H2′a, H6′a), 3.58 (3H, s, CH_3N^+), 3.87 (4H, br m, H3′, H5′), 4.42 (2H, m, H2′b, H6′b), 4.97 (1H, s, H5), 6.62 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.02 (1H, app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.24 (1H, dd, *J* 7.5, 1, H1), 7.33 (1H, app td, *J* 7.5, 1, H3), 7.44 (1H, app t, *J* 7.5, H5″), 7.60 (1H, d, *J* 7.5, H4″), 8.18 (1H, d, *J* 7.5, H6″), 8.29 (1H, br s, H2″). δ_C ($CDCl_3$) 42.6 (C3′, C5′), 53.3 (CH_3N^+), 62.0 (C2′, C6′), 120.48 (C4), 120.54 (C6), 122.7 (C11a), 123.6 (C2), 124.2 (C7), 124.5 (q, *J* 278, CF_3), 124.6 (C2″), 126.3 (C4″), 127.1 (C9), 128.3 (C5″), 129.4 (C8), 130.1 (C1), 130.5 (q, *J* 32, C3″), 131.0 (C6″), 132.8 (C3), 139.6 (C1″), 140.7 (C5a), 141.2 (C9a), 153.3 (C4a), 162.3 (C11), 168.6 (CO). *m*/*z* (+ESI, 30 V) 516 (35%, M[^{37}Cl]H$^+$), 514 (100%, MH$^+$), 501 (28), 499 (70).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-trifluoromethyl)benzimide* ***2p***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), yellow/orange rosettes ($CHCl_3$/hexane), yield 45%, mp 159–161°C. (Found: C 58.5, H 4.6, N 13.1, MH$^+$ 514.1613. $C_{26}H_{23}ClF_3N_5O{\cdot}H_2O$ requires C 58.7, H 4.7, N 13.2%, MH$^+$ 514.1616.) ν_{max} (KBr)/cm^{-1} 3288, 1604, 1552. λ_{max}/nm (ε/M^{-1} cm^{-1}) 228 (28 800), 260 (20 400), 299 (9100). δ_H ($CDCl_3$) 3.27 (2H, br m, H2′a, H6′a), 3.57 (3H, s, CH_3N^+), 3.87 (4H, br m, H3′, H5′), 4.41 (2H, m, H2′b, H6′b), 5.00 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.01 (1H, app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.23 (1H, d, *J* 8, H1), 7.31 (1H, app td, *J* 7.5, 1.5, H3), 7.58 (2H, d, *J* 8, H3″, H5″), 8.11 (2H, d, *J* 8, H2″, H6″). δ_C ($CDCl_3$) 42.7 (C3′, C5′), 53.4 (CH_3N^+), 62.1 (C2′, C6′), 120.5 (C4, C6), 122.9 (C11a), 123.6 (C2), 124.3 (C7), 124.6 (q, *J* 274, CF_3), 124.8 (C3″, C5″), 127.2 (C9), 128.1 (C2″, C6″), 129.5 (C8), 130.1 (C1), 131.4 (q, *J* 32, C4″), 132.8 (C3), 140.6 (C5a), 141.3 (C9a), 142.5 (C1″), 153.3 (C4a), 162.3 (C11), 168.9 (CO). *m*/*z* (+ESI, 30 V) 516 (35%, M[^{37}Cl]H$^+$), 514 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2-methoxy)benzimide* ***2q***

Purified by flash chromatography (4/1, chloroform/propan-2-ol), yellow needles ($CHCl_3$/hexane), yield 48%, mp 163.5–165°C. (Found: C 65.8, H 5.5, N 14.5. $C_{26}H_{26}ClN_5O_2$ requires C 65.6, H 5.6, N 14.7%.) ν_{max} (KBr)/cm^{-1} 3262, 1614, 1587, 1563. λ_{max}/nm (ε/M^{-1} cm^{-1}) 226 (24 500), 260 (13 500), 299 (7400). δ_H ($CDCl_3$) 3.16 (2H, br m, H2′a, H6′a), 3.59 (3H, s, CH_3N^+), 3.85 (3H, s, OCH_3), 4.03 (4H, m, H3′, H5′), 4.46 (2H, m, H2′b, H6′b), 4.95 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.85 (1H, dd, *J* 8.5, 2.5, H7), 6.86 (1H, d, *J* 8, H3″), 6.89 (1H, app t, *J* 8, H5″), 7.03 (1H, app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.23 (1H, app td, *J* 8, 1.5, H4″), 7.25 (1H, br d, *J* 8, H1), 7.32 (1H, app td, *J* 8, 1.5, H3), 7.43 (1H, dd, *J* 7.5, 1.5, H6″). δ_C ($CDCl_3$) 42.8 (C3′, C5′), 53.5 (CH_3N^+), 56.1 (OCH_3), 61.9 (C2′, C6′), 111.8 (C3″), 120.6 (C4, C6, C1″, C5″), 123.1 (C11a), 123.7 (C2), 124.2 (C7), 127.3 (C9), 129.3 (C6″), 129.5 (C8, C4″), 130.3 (C1), 132.8 (C3), 140.7 (C5a), 141.5 (C9a), 153.4 (C4a), 157.2 (C2″), 162.3 (C11), 170 (CO). *m*/*z* (+ESI, 30 V) 478 (35%, M[^{37}Cl]H$^+$), 476 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3-methoxy)benzimide* ***2r***

Purified by flash chromatography (9/1, chloroform/propan-2-ol), yellow rosettes ($CHCl_3$/hexane), yield 61%, mp 208–209°C. (Found: C 65.6, H 5.6, N 14.5, MH$^+$ 476.1854. $C_{26}H_{26}ClN_5O_2$ requires C 65.6, H 5.5, N 14.7%, MH$^+$ 476.1848.) ν_{max} (KBr)/cm^{-1} 3296, 1602, 1564. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (24 500), 262 (17 000), 299 (9500). δ_H ($CDCl_3$, 500 MHz) 3.28 (2H, br m, H2′a, H6′a), 3.61 (3H, s, CH_3N^+), 3.84 (3H, s, OCH_3), 3.91 (4H, m, H3′, H5′), 4.48 (2H, m, H2′b, H6′b), 4.99 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 6.93 (1H, br dd, *J* 8, 2, H4″), 7.01 (1H, app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.23 (1H, d, *J* 7.5, H1), 7.34 (1H, br app t, *J* 8, H3), 7.43 (1H, app t, *J* 8, H5″), 7.60 (1H, br s, H2″), 7.68 (1H, br d, *J* 7.5, H6″). δ_C ($CDCl_3$) 42.8 (C3′, C5′), 53.6 (CH_3N^+), 55.7 (OCH_3), 62.4 (C2′, C6′), 112.9 (C2″), 116.5 (C4″), 120.2 (C6″), 120.6 (C4, C6), 123.1 (C11a), 123.7 (C2), 124.3 (C7), 127.3 (C9), 128.9 (C5″), 129.4 (C8), 130.3 (C1), 132.9 (C3), 139.9 (C1″), 140.7 (C5a), 141.6 (C9a), 153.4 (C4a), 159.7 (C3″), 162.2 (C11), 170.6 (CO). *m*/*z* (+ESI, 30 V) 498 (20%, MNa$^+$), 478 (38%, M[^{37}Cl]H$^+$), 476 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-methoxy)benzimide* ***2s***

Purified by flash chromatography (4/1, chloroform/propan-2-ol), yellow needles ($CHCl_3$/hexane), yield 45%, mp 159–160°C. (Found: C 64.0, H 5.4, N 14.3, MH$^+$ 476.1848. $C_{26}H_{26}ClN_5O_2$ requires C 64.4, H 5.6, N 14.4%, MH$^+$ 476.1848.) ν_{max} (KBr)/cm^{-1} 3224, 1606, 1566. λ_{max}/nm (ε/M^{-1} cm^{-1}) 231 (20 400), 258 (19 100), 297 (7100). δ_H ($CDCl_3$) 3.23 (2H, br m, H2′a, H6′a), 3.58 (3H, s, CH_3N^+), 3.90 (3H, s, OCH_3), 3.90 (4H, br m, H3′, H5′), 4.43 (2H, m, H2′b, H6′b), 4.92 (1H, s, H5), 6.62 (1H, d, *J* 8.5, H6), 6.82 (1H, br d, *J* 8, H4), 6.84 (2H, d, *J* 9, H3″, H5″), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.01 (1H, app td, *J* 8, 1, H2), 7.07 (1H, d, *J* 2.5, H9), 7.23 (1H, dd, *J* 8, 1.5, H1), 7.31 (1H, app td, *J* 8, 1.5, H3), 7.96 (2H, d, *J* 9, H2″, H6″). δ_C ($CDCl_3$) 42.3 (C3′, C5′), 53.2 (CH_3N^+), 55.2 (OCH_3), 61.7 (C2′, C6′), 112.9 (C3″, C5″), 120.2 (C4, C6), 122.5 (C11a), 123.3 (C2), 123.9 (C7), 126.8 (C9), 128.9 (C2″, C6″), 129.1 (C8), 129.9 (C1), 131.1 (C1″), 132.5 (C3), 140.3 (C5a), 141.0 (C9a), 152.9 (C4a), 160.7 (C4″), 162.0 (C11), 169.8 (CO). *m*/*z* (+ESI, 30 V) 478 (35%, M[^{37}Cl]H$^+$), 476 (100%, MH$^+$).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2-acetyl)benzimide* ***2t***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), pale yellow needles ($CHCl_3$/hexane), yield 43%, mp 221–222°C. (Found: C 66.4, H 5.3, N 14.2. $C_{27}H_{26}ClN_5O_2$ requires C 66.5, H 5.4, N 14.4%.) ν_{max} (KBr)/cm^{-1} 3364, 1680, 1604, 1552. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (30 200), 261 (17 800), 299 (9100). δ_H ($CDCl_3$, 500 MHz) 2.56 (3H, s, $COCH_3$), 3.25 (2H, br m, H2′a, H6′a), 3.57 (3H, s, CH_3N^+), 3.88 (4H, m, H3′, H5′), 4.36 (2H, m, H2′b, H6′b), 4.94 (1H, s, H5), 6.65 (1H, d, *J* 8.5, H6), 6.84 (1H, br d, *J* 7.5, H4), 6.88 (1H, dd, *J* 8.5, 2.5, H7), 7.04 (1H, app td, *J* 7.5, 1, H2), 7.07 (1H, d, *J* 2.5, H9), 7.26 (1H, dd, *J* 7.5, 1, H1), 7.33 (1H, app td, *J* 7.5, 1, H3), 7.35–7.39 (2H, m, H4″, H6″), 7.41 (1H, app td, *J* 7, 2, H5″), 7.80 (1H,

dd, *J* 7, 2, H3″). δ_C ($CDCl_3$) 26.7 ($COCH_3$), 42.0 (C3′, C5′), 53.0 (CH_3N^+), 61.8 (C2′, C6′), 120.3 (C4, C6), 122.5 (C11a), 123.4 (C2), 124.0 (C7), 126.2 (C6″), 126.8 (C9), 128.6 (C3″), 128.7 (C4″), 129.1 (C8), 129.7 (C5″), 129.9 (C1), 132.5 (C3), 137.8 (C1″), 138.0 (C2″), 140.2 (C5a), 141.0 (C9a), 153.0 (C4a), 161.9 (C11), 170.9 (CO), 198.2 (CH_3CO). *m/z* (+ESI, 30 V) 510 (30%, MNa^+) 490 (35%, $M[^{37}Cl]H^+$), 488 (100%, MH^+).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3-acetyl)benzimide* ***2u***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), pale yellow needles ($CHCl_3$/hexane), yield 50%, mp 159–160°C. (Found: C 63.0, H 5.5, N 13.3, MH^+ 488.1848. $C_{27}H_{26}ClN_5O_2 \cdot 1.5H_2O$ requires C 63.0, H 5.7, N 13.6%, MH^+ 488.1848.) ν_{max} (KBr)/cm^{-1} 3364, 1680, 1604, 1552. λ_{max}/nm (ε/M^{-1} cm^{-1}) 230 (17 800), 260 (17 000), 298 (14 100). δ_H ($CDCl_3$) 2.65 (3H, s, $COCH_3$), 3.28 (2H, br m, H2′a, H6′a), 3.60 (3H, s, CH_3N^+), 3.89 (4H, m, H3′, H5′), 4.44 (2H, m, H2′b, H6′b), 5.00 (1H, s, H5), 6.65 (1H, d, *J* 8.5, H6), 6.84 (1H, d, *J* 8, H4), 6.86 (1H, dd, *J* 8.5, 2.5, H7), 7.02 (1H, app t, *J* 7.5, H2), 7.06 (1H, d, *J* 2.5, H9), 7.25 (1H, d, *J* 7.5, H1), 7.33 (1H, app t, *J* 8, H3), 7.44 (1H, app t, *J* 7.5, H5″), 7.99 (1H, d, *J* 7.5, H6″), 8.24 (1H, d, *J* 7.5, H4″), 8.59 (1H, s, H2″). δ_C ($CDCl_3$) 27.0 ($COCH_3$), 42.6 (C3′, C5′), 53.3 (CH_3N^+), 62.0 (C2′, C6′), 120.5 (C4, C6), 123.3 (C11a), 123.5 (C2), 124.2 (C7), 127.0 (C9), 127.9 (C2″), 128.2 (C5″), 129.2 (C6″), 129.3 (C8), 130.1 (C1), 132.1 (C4″), 132.7 (C3), 136.9 (C1″), 139.3 (C3″), 140.7 (C5a), 141.2 (C9a), 153.3 (C4a), 162.2 (C11), 169.1 (CO), 198.7 (CH_3CO). *m/z* (+ESI, 30 V) 490 (35%, $M[^{37}Cl]H^+$), 488 (100%, MH^+).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3,4-methylenedioxy)benzimide* ***2z***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), yellow micro-needles ($CHCl_3$/hexane), yield 48%, mp 165–167°C. (Found: C 63.4, H 4.9, N 14.3. $C_{26}H_{24}ClN_5O_3$ requires C 63.7, H 4.9, N 14.3%.) ν_{max} (KBr)/cm^{-1} 3348, 1608, 1566, 1548. λ_{max}/nm (ε/M^{-1} cm^{-1}) 231 (26 900), 260 (22 400), 295 (14 800). δ_H ($CDCl_3$) 3.27 (2H, br m, H2′a, H6′a), 3.57 (3H, s, CH_3N^+), 3.88 (4H, br m, H3′, H5′), 4.42 (2H, m, H2′b, H6′b), 4.91 (1H, s, H5), 5.94 (2H, s, H2″), 6.62 (1H, d, *J* 8.5, H6), 6.77 (1H, d, *J* 8, H7″), 6.82 (1H, d, *J* 8, H4), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 7.02 (1H, app t, *J* 7.5, H2), 7.07 (1H, d, *J* 2.5, H9), 7.23 (1H, br d, *J* 7.5, H1), 7.32 (1H, app td, *J* 7.5, 1, H3), 7.51 (1H, br s, H4″), 7.58 (1H, dd, *J* 8, 1, H6″). δ_C ($CDCl_3$) 42.8 (C3′, C5′), 53.6 (CH_3N^+), 62.2 (C2′, C6′), 101.3 (C2″), 107.7 (C4″), 108.5 (C7″), 120.6 (C4, C6), 122.1 (C6″), 123.0 (C11a), 123.6 (C2), 124.3 (C7), 127.2 (C9), 130.2 (C1), 132.8 (C3), 133.5 (C5″), 140.9 (C5a), 141.5 (C9a), 147.4 (C3″a), 149.0 (C7″a), 153.5 (C4a), 162.4 (C11), 169.8 (CO). *m/z* (+ESI, 30 V) 492 (35%, $M[^{37}Cl]H^+$), 490 (100%, MH^+), 329 (20), 327 (60).

General Method: N*-Acylation Using Acyl Acids (***2v, 9***)*

The following compounds were prepared by acylation of 1-amino-4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium 2,4,6-trimethyl-1-benzenesulfonate (**5**), in the presence of sodium hydride, with a hydroxybenzotriazolyl active ester. The activated ester was prepared from TBTU and the appropriate carboxylic acid. The general method exemplified for the synthesis of 1-[(4-acetyl)benzimide]-4-(8-chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium (**2v**) is described below.

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-acetyl)benzimide* ***2v***

A solution of **5** (167 mg, 0.31 mmol), 4-acetylbenzoic acid (46 mg, 0.28 mmol), and TBTU (108 mg, 0.34 mmol) in anhydrous *N*,*N*-dimethylformamide (4 mL) was stirred at room temperature for 1 h under an atmosphere of nitrogen. The reaction mixture was cooled to −15°C and then added to sodium hydride (45 mg, 1.1 mmol, 60% dispersion in oil), which had been previously washed with anhydrous hexane and cooled to −15°C. The reaction mixture was maintained at −15°C for a further 2 h and then allowed to warm to room temperature overnight. The solvent was removed under vacuum to afford a brown gum, which was resuspended in ethyl acetate, and a brown solid removed by filtration. The filtrate was concentrated and the resulting residue purified by flash chromatography (9/1, chloroform/propan-2-ol) to afford a bright yellow powder (70 mg, 50%). Recrystallization from dichloromethane/hexane gave **2v** (52 mg, 38%) as yellow micro-needles, mp 178–180°C. (Found: C 66.4, H 5.6, N 14.0, MH^+ 488.1849. $C_{27}H_{26}ClN_5O_2$ requires C 66.4, H 5.4, N 14.4%, MH^+ 488.1848.) ν_{max} (KBr)/cm^{-1} 3464, 1680, 1606, 1564. λ_{max}/nm (ε/M^{-1} cm^{-1}) 232 (32 400), 261 (19 100), 295 (9500). δ_H ($CDCl_3$) 2.60 (3H, s, $COCH_3$), 3.27 (2H, br m, H2′a, H6′a), 3.57 (3H, s, CH_3N^+), 3.85 (4H, br m, H3′, H5′), 4.42 (2H, m, H2′b, H6′b), 4.96 (1H, s, H5), 6.65 (1H, d, *J* 8, H6), 6.83–6.88 (2H, m, H4, H7), 7.00 (1H, app t, *J* 7.5, H2), 7.06 (1H, d, *J* 2.5, H9), 7.23 (1H, br d, *J* 7.5, H1), 7.31 (1H, app td, *J* 8, 1.5, H3), 7.92 (2H, d, *J* 8, H3″, H5″), 8.08 (2H, d, *J* 8, H2″, H6″). δ_C ($CDCl_3$) 26.7 ($COCH_3$), 42.2 (C3′, C5′), 53.0 (CH_3N^+), 61.8 (C2′, C6′), 120.3 (C4, C6), 122.4 (C11a), 123.3 (C2), 124.0 (C7), 126.8 (C9), 127.6, 127.8 (C2″, C3″, C5″, C6″), 129.1 (C8), 129.8 (C1), 132.5 (C3), 137.9 (C1″), 140.4 (C5a), 141.0 (C9a), 143.1 (C4″), 153.1 (C4a), 162.2 (C11), 168.9 (CO), 198.2 (CH_3CO). *m/z* (+ESI, 30 V) 490 (40%, $M[^{37}Cl]H^+$), 488 (100%, MH^+).

*1-[4-(8-Chloro-5*H*-dibenzo[*b,e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(5-methoxy-1*H*-indol-2-yl)carbonylimide* ***9***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), fine yellow micro-crystals (CH_2Cl_2/hexane), yield 34%, mp 209–212°C. (Found: C 63.3, H 5.4, N 15.2, MH^+ 515.1962. $C_{28}H_{27}ClN_6O_2 \cdot H_2O$ requires C 63.3, H 5.4, N 15.2%, MH^+ 515.1597.) ν_{max} (KBr)/cm^{-1} 3446, 1611, 1572. λ_{max}/nm (ε/M^{-1} cm^{-1}) 232 (30 900), 264 (15 800), 295 (22 900). δ_H ($CDCl_3$) 3.16 (2H, br m, H2′a, H6′a), 3.60 (3H, s, CH_3N^+), 3.83 (4H, br m, H3′, H5′), 3.83 (3H, s, OCH_3), 4.32 (2H, m, H2′b, H6′b), 5.03 (1H, s, H5), 6.63 (1H, d, *J* 8.5, H6), 6.82 (1H, dd, *J* 8, 1, H4), 6.84 (1H, dd, *J* 8.5, 2.5, H7), 6.86 (1H, dd, *J* 9, 2.5, H6″), 6.90 (1H, d, *J* 2.5, H3″), 7.00 (1H, app td, *J* 7.5, 1, H2), 7.06 (1H, d, *J* 2.5, H4″), 7.08 (1H, d, *J* 2.5, H9), 7.18 (1H, br d, *J* 8, H1), 7.22 (1H, d, *J* 9, H7″), 7.30 (1H, app td, *J* 7.5, 1.5, H3), 9.28 (1H, br s, H1″). δ_C ($CDCl_3$) 42.2 (C3′, C5′), 53.6 (CH_3N^+), 55.9 (OCH_3), 62.1 (C2′, C6′), 102.4 (C3″), 102.7 (C4″), 112.2 (C7″), 113.6 (C6″), 120.6 (C4, C6), 122.7 (C11a), 123.5 (C2), 124.2 (C7), 127.0 (C9), 128.8 (C3″a), 129.2 (C8), 130.4 (C1), 131.1 (C2″), 132.7 (C3), 136.8 (C7″a), 140.7 (C5a), 141.2 (C9a), 153.2 (C4a), 154.1 (C5″), 162.3 (C11), 165.3 (CO). *m/z* (+ESI,

30 V) 537 (45%, MNa^+) 517 (35%, $M[^{37}Cl]H^+$), 515 (100%, MH^+).

*General Method: De-etherification of Aminimides **2w–y**, **2aa**, **10***

The following hydroxy-substituted aminimides were prepared from their respective methyl ethers (100 mg, 0.21 mmol) by boron tribromide (4 equiv.) in dichloromethane and isolated as yellow crystalline solids. The general method exemplified for the synthesis of 1-[4-(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2- hydroxy)benzimide **2w** is described below.

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2-hydroxy)benzimide **2w***

A solution of boron tribromide in dichloromethane (1.0 M, 850 μL, 0.85 mmol) was added at −78°C, under an atmosphere of nitrogen, to a solution of 1-[4-(8-chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(2- methoxy)benzimide **2q** (100 mg, 0.21 mmol) in anhydrous dichloromethane (10 mL). The reaction mixture was maintained at −78°C for 1 h and then allowed to warm to room temperature overnight. Saturated brine solution (10 mL) was added and the reaction mixture stirred for a further 20 min. Saturated sodium bicarbonate solution (50 mL) was then added and the reaction mixture extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (50 mL), dried over anhydrous sodium sulfate, and concentrated under vacuum. The resulting residue was purified by flash chromatography (85/15, chloroform/propan-2-ol) to afford a bright yellow foam (81 mg, 81%). Recrystallization from chloroform/hexane gave **2w** (61 mg, 63%) as yellow rosettes, mp 184–186°C. (Found: MH^+ 462.1696. $C_{25}H_{24}ClN_5O_2$ requires MH^+ 462.1691.) ν_{max} (KBr)/cm^{-1} 3600–3100, 3286, 1608, 1563. λ_{max}/nm (ε/M^{-1} cm^{-1}) 231 (29 500), 263 (17 000), 297 (12 600). δ_H ($CDCl_3$) 3.30 (2H, m, H2′a, H6′a), 3.60 (3H, s, CH_3N^+), 3.79 (4H, m, H3′, H5′), 4.38 (2H, m, H2′b, H6′b), 4.91 (1H, s, H5), 6.62 (1H, d, *J* 8.5, H6), 6.80 (1H, br d, *J* 8, H3″), 6.81 (1H, d, *J* 8, H4), 6.86–6.89 (2H, m, H7, H5″), 7.00 (1H, app t, *J* 7.5, H2), 7.05 (1H, d, *J* 2.5, H9), 7.21 (1H, br d, *J* 7.5, H1), 7.26 (1H, app td, *J* 8, 2, H4″), 7.31 (1H, app td, *J* 7.5, 1.5, H3), 7.91 (1H, dd, *J* 8, 2, H6″), 12.64 (1H, br s, OH). δ_C ($CDCl_3$) 42.3 (C3′, C5′), 54.1 (CH_3N^+), 62.2 (C2′, C6′), 116.4 (C3″), 118.4 (C5″), 120.3 (C1″), 120.6 (C4, C6), 122.5 (C11a), 123.6 (C2), 124.3 (C7), 127.0 (C9), 129.1 (C6″), 129.3 (C8), 130.0 (C1), 132.0 (C4″), 132.8 (C3), 140.7 (C5a), 141.1 (C9a), 153.3 (C4a), 159.5 (C2″), 162.1 (C11), 171.0 (CO). *m*/*z* (+ESI, 30 V) 464 (35%, $M[^{37}Cl]H^+$), 462 (100%, MH^+).

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3-hydroxy)benzimide **2x***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), fine yellow needles ($CHCl_3$/MeOH), yield 66%, mp 236–237°C. (Found: C 62.7, H 5.3, N 14.3, MH^+ 462.2697. $C_{25}H_{24}ClN_5O_2{\cdot}H_2O$ requires C 62.6, H 5.5, N 14.6, MH^+ 462.1691.) ν_{max} (KBr)/cm^{-1} 3328, 3250, 1614, 1554. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (15 800), 261 (9800), 295 (6200). δ_H (d_6-DMSO) 3.48 (6H, br m, H3′, H5′, H2′a, H6′a), 3.48 (3H, s, CH_3N^+), 4.21 (2H, m, H2′b, H6′b), 6.68 (1H, br dd, *J* 8, 1.5, H4″), 6.87–6.90 (3H, m, H6, H7, H9), 7.00 (1H, s, H5), 7.01 (1H, app td, *J* 8, 1.5, H2), 7.05 (1H, br d, *J* 8, H4), 7.27–7.32 (4H, m, H1, H2″, H5″, H6″), 7.35 (1H, br app t, *J* 8, H3), 9.09 (1H, br s, OH). δ_C (d_6-DMSO) 42.3 (C3′, C5′), 51.7 (CH_3N^+), 60.6 (C2′, C6′), 114.4 (C2″), 115.8 (C4″), 117.9 (C6″), 120.5 (C4), 120.8 (C6), 122.4 (C11a), 122.5 (C2), 123.1 (C7), 125.7 (C9), 126.7 (C8), 128.0 (C5″), 129.9 (C1), 132.4 (C3), 141.0 (C1″), 141.4 (C5a), 142.3 (C9a), 154.1 (C4a), 156.9 (C3″), 162.3 (C11), 167.9 (CO). *m*/*z* (+ESI, 30 V) 464 (35%, $M[^{37}Cl]H^+$), 462 (100%, MH^+).

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(4-hydroxy)benzimide **2y***

Purified by flash chromatography (85/15, chloroform/propan-2-ol), fine yellow needles ($CHCl_3$), yield 42%, mp 195–196°C. (Found: MH^+ 462.1693. $C_{25}H_{24}ClN_5O_2$ requires MH^+ 462.1691.) ν_{max} (KBr)/cm^{-1} 3328, 1716, 1614, 1548. λ_{max}/nm (ε/M^{-1} cm^{-1}) 232 (23 400), 254 (22 400), 298 (7600). δ_H (d_4-methanol) 3.47 (2H, br m, H2′a, H6′a), 3.53 (3H, s, CH_3N^+), 3.69 (2H, br m, H3′b, H5′b), 3.87 (2H, br m, H3′a, H5′a), 4.28 (2H, m, H2′b, H6′b), 6.74 (2H, d, *J* 8.5, H3″, H5″), 6.81 (1H, d, *J* 8.5, H6), 6.87 (1H, dd, *J* 8.5, 2.5, H7), 6.99 (1H, d, *J* 2.5, H9), 7.00 (1H, d, *J* 7.5, H4), 7.05 (1H, app t, *J* 7.5, H2), 7.31 (1H, br d, *J* 7.5, H1), 7.35 (1H, app td, *J* 7.5, 1.5, H3), 7.76 (2H, d, *J* 8.5, H2″, H6″). δ_C (d_4-methanol) 43.8 (C3′, C5′), 56.0 (CH_3N^+), 63.0 (C2′, C6′), 115.5 (C3″, C5″), 121.6 (C4), 121.7 (C6), 124.0 (C11a), 124.4 (C2), 125.1 (C7), 127.5 (C9), 129.8 (C1″), 130.4 (C2″, C6″), 130.9 (C8), 131.3 (C1), 133.9 (C3), 142.9 (C5a), 143.4 (C9a), 155.5 (C4a), 160.5 (C4″), 164.5 (C11), 172.3 (CO). *m*/*z* (+ESI, 30 V) 464 (35%, $M[^{37}Cl]H^+$), 462 (100%, MH^+).

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(3,4-dihydroxy)benzimide **2aa***

Purified by flash chromatography (9/1, ethyl acetate/methanol), yellow-brown foam, yield 79%, mp 194–198°C (dec.). (Found: MH^+ 478.1645. $C_{25}H_{24}ClN_5O_3$ requires MH^+ 478.1640.) ν_{max} (KBr)/cm^{-1} 3464, 3364, 1614, 1566. λ_{max}/nm (ε/M^{-1} cm^{-1}) 232 (19 100), 258 (15 800), 295 (9100). δ_H (d_4-methanol) 3.55 (2H, br m, H2′a, H6′a), 3.55 (3H, s, CH_3N^+), 3.69 (4H, br m, H3′, H5′), 4.34 (2H, m, H2′b, H6′b), 6.78 (1H, d, *J* 8.5, H5″), 6.83 (1H, d, *J* 8.5, H6), 6.89 (1H, dd, *J* 8.5, 2.5, H7), 7.02 (1H, d, *J* 2.5, H9), 7.06–7.16 (2H, m, H2, H4), 7.29 (1H, dd, *J* 8.5, 2, H6″), 7.36–7.40 (2H, m, H1, H3), 7.42 (1H, d, *J* 2, H2″). δ_C (d_4-methanol) 43.2 (C3′, C5′), 53.6 (CH_3N^+), 63.0 (C2′, C6′), 115.3 (C2″), 115.6 (C5″), 121.0 (C6″), 121.6 (C4), 121.8 (C6), 124.0 (C11a), 124.4 (C2), 125.0 (C7), 127.5 (C9), 129.4 (C8), 131.3 (C1), 131.5 (C1″), 133.9 (C3), 142.9 (C5a), 143.4 (C9a), 145.6 (C3″), 148.5 (C4″), 155.6 (C4a), 164.6 (C11), 171.1 (CO). *m*/*z* (+ESI, 30 V) 480 (35%, $M[^{37}Cl]H^+$), 478 (100%, MH^+).

*1-[4-(8-Chloro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-yl)-1-methylhexahydropyrazin-1-ium]-1-(5-hydroxyindol-1*H*-2-yl)carbonylimide **10***

Purified by flash chromatography (4/1, chloroform/propan-2-ol), amorphous tan coloured solid, yield 60%, mp 184–186°C (dec.). (Found: MH^+ 501.1781. $C_{27}H_{25}ClN_6O_2$ requires MH^+ 501.1800.) ν_{max} (KBr)/cm^{-1} 3464, 3364, 1614, 1566. λ_{max}/nm (ε/M^{-1} cm^{-1}) 229 (31 600), 263 (18 200), 297 (20 400). δ_H (d_4-methanol) 3.46 (2H, m, H2′a, H6′a), 3.55 (3H, s, CH_3N^+), 3.78 (2H, m, H3′, H5′), 4.26 (2H, m, H2′b, H6′b), 6.72 (1H, dd, *J* 9, 2.5, H6″), 6.74 (1H, br s, H3″), 6.80 (1H, d, *J* 8.5, H6), 6.86 (1H,

dd, *J* 8.5, 2.5, H7), 6.91 (1H, d, *J* 2.5, H4″), 6.99 (1H, d, *J* 2.5, H9), 6.99 (1H, br d, *J* 7.5, H4), 7.04 (1H, br app t, *J* 7.5, H2), 7.22 (1H, d, *J* 9, H7″), 7.30 (1H, br d, *J* 8, H1), 7.35 (1H, app td, *J* 7.5, 1, H3). δ_C (d_4-methanol) 43.2 (C3′, C5′), 53.8 (CH_3N^+), 63.2 (C2′, C6′), 103.4 (C3″), 105.8 (C4″), 113.2 (C7″), 114.5 (C6″), 121.6 (C4), 121.7 (C6), 124.0 (C11a), 124.4 (C2), 125.0 (C7), 127.5 (C9), 129.8 (C8), 130.0 (C3″a), 131.3 (C1), 133.0 (C7″a), 133.9 (C3), 137.5 (C2″), 142.9 (C5a), 143.3 (C9a), 151.7 (C5″), 155.5 (C4a), 164.5 (C11), 167.0 (CO). *m*/*z* (+ESI, 30 V) 503 (35%, M[^{37}Cl]H$^+$), 501 (100%, MH$^+$), 327 (20), 225 (20), 126 (35).

Receptor Binding Assays

Receptor affinities were determined by MDS Panlabs, Taiwan, by the ability of the tested compounds to displace selective radioligands. All assayed compounds were dissolved in dimethyl sulfoxide to a stock concentration of 10×10^{-3} M, and then diluted with assay buffer to a final concentration of 10^{-6} M. The assays were carried out using the following: (i) for dopamine $D_{4.4}$; human recombinant (mammalian CHO-K_1 cells), [^{3}H]spiperone (0.3×10^{-9} M) as radioligand, and haloperidol (10×10^{-6} M) as reference compound for non-specific binding; (ii) for serotonin 5-HT_{2A}; rat cortex, [^{3}H]ketanserin (0.5×10^{-9} M) as radioligand, and ketanserin (1×10^{-6} M) as reference compound for non-specific binding. The binding results are expressed as the percentage inhibition of specific binding at a concentration of 1×10^{-6} M for the tested compound and represent the mean of duplicate tubes with a maximum standard error in the mean of ±5.

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