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Synthesis, structural elucidation and in vitro antiparasitic activity against *Trypanosoma cruzi* and *Leishmania chagasi* parasites of novel tetrahydro-1-benzazepine derivatives

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ABSTRACT

Forty six new 1,4-epoxy-2-*exo*-aryl- and *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepine derivatives were synthesized and fully characterized. All compounds were tested in vitro against both *Trypanosoma cruzi* and *Leishmania chagasi* parasites and also for cytotoxicity using Vero and THP-1 mammalian cell lines. Many of the evaluated compounds showed remarkable activity against the epimastigote and intracellular amastigote forms of *T. cruzi*, with IC_{50} values comparable with that of control drug nifurtimox, a nitrofuran derivative currently used in the treatment of Chagas' disease. Other derivatives were found to have good activity against *L. chagasi* promastigotes, with low toxicity against the mammalian cells, but neither of them was active on intracellular amastigotes of *L. chagasi* infecting THP-1 macrophages.

1. Introduction

Leishmaniasis and Chagas' disease are two parasitic infections that constitute a serious public health problem in many tropical and subtropical countries and that affect million people living mainly in poor rural areas. Leishmaniasis is a group of diseases caused by different species and subspecies of *Leishmania*, and transmitted to humans by the phlebotomine sandfly belonged from the *Phlebotumus* genus. It is estimated that 12 million people are infected worldwide, particularly in the developing countries, with 2 million new incidences occurring yearly.[1] For many years, the classic treatment of leishmaniasis has been based on the use of pentavalent antimonial drugs. Amphotericin B, aminosidine (paromomycin), pentamidine and miltefosine have been introduced as second-line therapy.[2–7]

Chagas' disease is caused by the infection with the *Trypanosoma cruzi* parasite, and transmitted to humans through the feces of infected triatomines insects or by blood transfusions, organ transplantation, placental and orally routes. It is estimated that between 18 and 20 million people are infected and around 40 million people are at risk of infection in almost all Latin-American countries. The treatments of Chagaś disease are based on the use of nifurtimox and benznidazole, compounds that are effective only in the acute phase of the disease.[8]

Unfortunately, the current treatments against these both parasitic diseases have a number of severe limitations such as parenteral administration, poor efficacy, toxic side effects, long course of treatment, high treatment cost and loss of effectiveness due to parasites resistance.[8–15] Consequently, the development of novel, safe and affordable compounds with potent anti-leishmanial and anti-trypanocidal activities are urgently needed. It remains an important challenge for synthetic and medicinal chemists.

In this context, tetrahydro-1-benzazepine ring system is an important core in the structures of many biologically active compounds.[16–23] Different tetrahydro-1-benzazepines have been reported as potent and orally active non-peptide arginine vasopressin antagonists for both V_{1A} and V_2 receptors,[24–28] potent inhibitors of cyclin-dependent kinases,[29–32] potent and orally bioavailable growth hormone secretagogue,[33–36] agents against HIV-1 infection,[37,38] and as antipsychotics.[39,40] Moreover, some tetrahydro-1-benzazepine derivatives such as paullones also exhibited potent activity against the parasites which cause the leishmaniasis and Chagas' disease, especially as inhibitors of CRK3 cyclin-dependent kinase of *Leishmania mexicana* promastigotes,[41] and *T. cruzi* dihydrofolate reductase.[42] This broad spectrum

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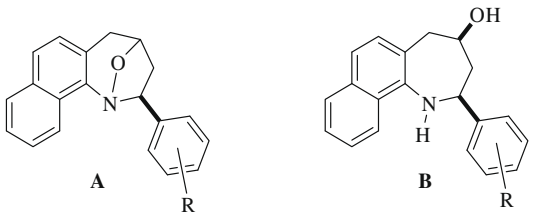


Figure 1. General structures of the novel tetrahydronaphtho[1,2-*b*]azepine derivatives with antiparasitic activity.

of biological activity has encouraged research regarding the methodologies to synthesize many derivatives of this heterocyclic system.[43–49]

In our group, we have been working on the synthesis and evaluation of novel tetrahydronaphtho[1,2-*b*]azepine derivatives with the general structures **A** and **B** as antiparasitics (Figure 1).[50] We noticed that many of these compounds were active against the epimastigote and promastigote forms of *T. cruzi* and *L. chagasi* parasites, respectively, with IC_{50} values between 0.50 and 38.77 μM. Three of these compounds were also active against the intracellular amastigotes of *T. cruzi* with IC_{50} values between 9.89 and 18.35 μM, and with slight or without toxicity on Vero mammalian cells.[50]

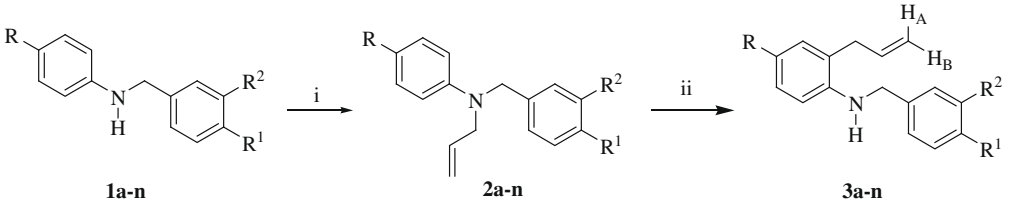
Encouraged by such positive results, we focused on the replacement of naphthalene ring of compounds **A** and **B** by an isostere benzene ring with the aim of synthesizing new analogues with comparable or better antiparasitic activity. The purpose of this paper is to report the synthesis, the spectroscopic characterization, and the antiparasitic activity of two new series of 1,4-epoxy-2-*exo*-aryl- and *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepines, as well as the determination of their cytotoxicity against the Vero and THP-1 mammalian cell lines. The present work is a continuation of a structural study of this class of 1,4-epoxybenzazepines and tetrahydro-1-benzazepin-4-oles, which is itself part of a wider program aimed at the identification of novel antiparasitic agents.

2. Results and discussion

2.1. Chemistry

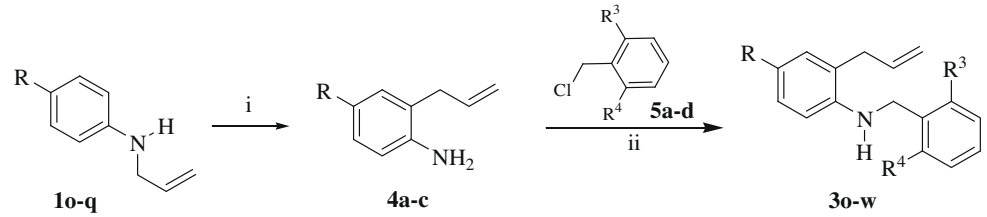
Target tetrahydro-1-benzazepine derivatives **6a–w** and **7a–w** were prepared following a multi-step reaction pathways outlined in Schemes 1–3, a synthetic strategy used previously in our laboratory.[51,52] Initially, the required key intermediates, substituted *ortho*-allyl-*N*-benzylanilines **3a–w**, were easily obtained either by thermal induced aromatic amino-Claisen rearrangement of the corresponding *N*-allyl-*N*-benzyl-anilines using our previous experimental conditions with minor modifications (Scheme 1),[51] or by N-benzylation reaction of the appropriate *ortho*-allylanilines (Scheme 2). Thus, N-allylation of *N*-benzylanilines **1a–n** with excess of allyl bromide (2 equiv) in the presence of sodium carbonate in dry acetone over reflux gave *N*-allyl derivatives **2a–n**, which were transformed into the *ortho*-allylanilines **3a–n** by aromatic amino-Claisen rearrangement using boron trifluoride diethyl ether complex ($BF_3{\cdot}OEt_2$) as catalyst.[53] Optimal conditions were determined to be excess of $BF_3{\cdot}OEt_2$ (1.2–1.5 equiv) and heating at 125–150 °C for periods ranging from 3 to 5 h. The yields of the rearranged products **3a–n** (67–88%) were not significantly affected by the nature and positions of the substituents on both the benzene rings of **2a–n** precursors.

However, we found that in the conditions employed for **2a–n**, the amino-Claisen rearrangement of *N*-allyl-*N*-benzylanilines



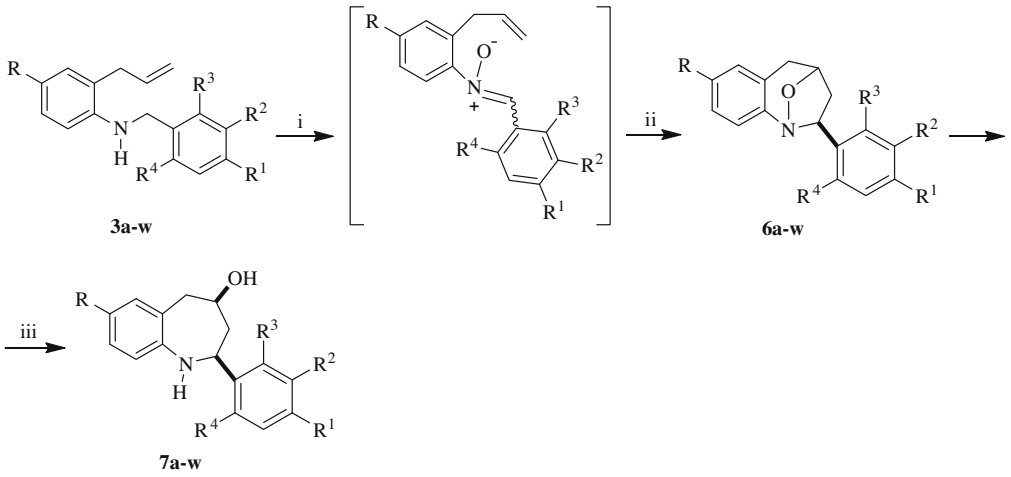
a : R = R¹ = R² = H; b : R = OCF₃, R¹ = R² = H; c : R = Br, R¹ = R² = H; d : R = Cl, R¹ = R² = H;
e : R = F, R¹ = R² = H; f : R = R² = H, R¹ = Cl; g : R = R² = H, R¹ = F; h : R = R¹ = H, R² = OCH₃;
i : R = R¹ = H, R² = CH₃; j : R = R¹ = H, R² = Cl; k : R = R¹ = Me, R² = H; l : R = R¹ = Cl, R² = H;
m : R = Cl, R¹ = Br, R² = H; n : R = F, R¹ = Cl, R² = H

Scheme 1. Preparation of substituted 2-allyl-*N*-benzylanilines **3a–n**. Reagents and conditions: (i) allyl bromide (0.02 mol), Na_2CO_3 (0.03 mol), dry acetone, reflux, 4–7 h; (ii) $BF_3{\cdot}OEt_2$ (0.012–0.015 equiv), 125–150 °C, 3–5 h.



o : R = R⁴ = H, R³ = Cl; p : R = R⁴ = H, R³ = F; q : R = Me, R³ = Cl, R⁴ = H; r : R = R³ = Cl, R⁴ = H;
s : R = Cl, R³ = F, R⁴ = H; t : R = H, R³ = R⁴ = Cl; u : R = H, R³ = Cl, R⁴ = F; v : R = R³ = R⁴ = Cl;
w : R = R³ = Cl, R⁴ = F

Scheme 2. Preparation of substituted 2-allyl-*N*-benzylanilines **3o–w**. Reagents and reaction conditions: (i) $BF_3{\cdot}OEt_2$ (0.015 equiv), 130–140 °C, 4–6 h. (ii) Benzyl chloride 5a–d (0.011 mol), Na_2CO_3 (0.025 mol), DMF, 0 to 25 °C, 3–4 h.



Scheme 3. Preparation of target compounds **6a–w** and **7a–w**. Reagents and reaction conditions: (i) $Na_2WO_4{\cdot}2H_2O$ (8–10 mol %), 30% H_2O_2 (0.03 mol), MeOH, 0–25 °C, 36–72 h; (ii) toluene, 70–90 °C, 3–7 h; (iii) Zn (0.06–0.08 mol), 80% CH_3CO_2H (excess), 70–90 °C, 4–12 h. or Zn (0.08 mol), glacial CH_3CO_2H (excess), 37% HCl (0.04 mol), rt, 10–14 h.

substituted at the *ortho*-positions of the benzyl fragment with chlorine and/or fluorine atoms take place with formation of a very complex mixture of products. As was evidenced by TLC, neither of them was formed in quantities justifying their isolation and identification.

In the light of these results, we planned to synthesize the other key intermediates **3o–w** through the alternative route depicted in Scheme 2, starting from the corresponding substituted mono *N*-allylanilines **1o–q**. This way, the amino-Claisen rearrangement of **1o–q**, followed by treatment of the resultant *ortho*-allylanilines **4a–c** with equimolar amounts of *ortho*-substituted benzyl chlorides **5a–d** at 0 °C to room temperature in dry *N*,*N*-dimethylformamide (DMF) and in the presence of sodium carbonate provided the desired intermediates **3o–w** in good to excellent yields (73–84%).

Having in hand the required precursors **3**, we then turned our attention to the synthesis of the target 1,4-epoxy-cycloadducts **6** and their reduced 2-aryltetrahydro-1-benzazepin-4-oles **7** (Scheme 3). Thus, selective oxidation of *ortho*-allyl-*N*-benzyl-anilines **3** with 3 fold-excess of hydrogen peroxide (30% H_2O_2) in the presence of catalytic amounts of sodium tungstate (8–10 mol %, $Na_2WO_4{\cdot}2H_2O$)[54,55] in methanol at 0 °C to room temperature, and subsequent thermal induced intramolecular 1,3-dipolar cycloaddition of the generated nitrones gave the expected 1,4-epoxy-2-aryltetrahydro-1-benzazepines **6** in moderate to good yields (55–76%).

The structures and stereochemistry of all the obtained 1,4-epoxy-cycloadducts **6a–w** were determined by means of one and two dimensional NMR spectroscopy. The assignments of all the signals to individual H- and C-atoms (see Section 4) have been made from their chemical shift values, coupling constants, and confirmed on the basis of COSY, HSQC and HMBC spectra as well as by comparing with the reference spectra of previously reported analogues.[51] The data derived from these experiments along with the coupling constants values of the azepinic protons were used to identify the isolated 1,4-epoxy-cycloadducts as the *exo*-isomer

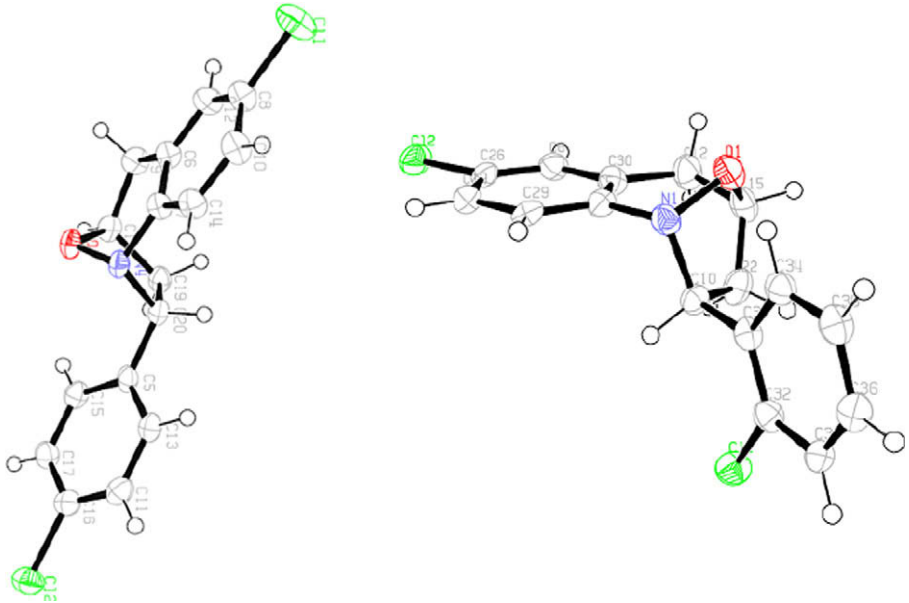


Figure 2. X-ray crystal structure of 7-chloro-1,4-epoxy-2-*exo*-(4′-chlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine **6l** and 7-chloro-1,4-epoxy-2-*exo*-(2′-chlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine **6r** (ORTEP views).[56]

in all the cases. Furthermore, single crystal X-ray diffraction of 1,4-epoxy-cycloadducts **6k**, **6l**, **6o**, **6r**, **6u** and **6w** (each recrystallized from heptane) unambiguously confirmed the stereochemical assignment for these compounds.[56,57] The single crystal X-ray structure of 1,4-epoxy-cycloadducts **6l** and **6r** are shown in Figure 2.

Finally, the compounds **6** were readily converted into the corresponding 2-aryl-4-hydroxytetrahydro-1-benzazepines **7** as exclusively *cis* diastereoisomers, by reductive cleavage of the N–O bond with zinc powder in acetic acid at 70–90 °C (for compounds 6a–**s**) or with zinc powder and hydrochloric acid in glacial acetic acid at room temperature (for compounds **6t–w**). After completion of the reactions, usually in 4–14 h, the amino-alcohols **7a–w** were isolated by silica gel column chromatography in excellent yields (76–93%) as high-viscosity yellow oils or crystalline substances.

The structures and stereochemistry of these novel compounds were determined by ^{1}H NMR and ^{13}C NMR spectroscopy in $CDCl_3$ solution, and all the signals for each individual H- and C-atoms (see Section 4) were also unambiguously assigned on the basis of their COSY, HSQC and HMBC spectra as well as by comparing with the reference spectra of previously reported analogues.[51] The *cis* stereochemistry at the stereogenic centers 2-C and 4-C of the tetrahydroazepine ring was established based on its 2D-NOESY spectra, in which the tertiary proton 2-H at 3.86–5.06 ppm demonstrates unambiguous NOE cross peak with the stereogenic 4-H proton at 3.76–4.03 ppm, indicating that both tertiary protons are oriented in the same side of the heterocyclic ring. Consequently, the 2-phenyl (aryl) group is oriented equatorially, since the proton 2-H appears as a doublets of doublets (dd) with $J_1 \approx 11$ Hz and $J_2 \approx 2$ Hz and therefore having exactly one *trans*-axial and one *cis*-equatorial coupling partners, namely 3-H_{ax} and 3-H_{eq}. The 4-hydroxy group is also oriented equatorially, since proton 4-H appears as triplets of doublets of doublets (tdd) with $J_1 \approx 11$ Hz, $J_2 \approx 4$ Hz and $J_3 \approx 2$ Hz and therefore having two *trans*-axial coupling partners (3-H_{ax} and 5-H_{ax}) and two *cis*-equatorial coupling partners (3-H_{eq} and 5-H_{eq}). The data derived from NOESY experiments along with the coupling constants values of

Table 1
In vitro antiparasitic activity and cytotoxicity of 1,4-epoxy-2-*exo*-aryl- (**6a–w**) and *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepines **7a–w** against *T. cruzi* and Vero cells

Compd	R	R^1	R^2	R^3	R^4	μM				
						Epimastigotes		Intracellular amastigotes		Vero cells
						IC_{50}/IC_{90}	SI	IC_{50}/IC_{90}	SI	CC_{50}/CC_{90}
6a	H	H	H	H	H	>100/>100	>3	>100/>100	>3	>300/>300
6b	OCF_3	H	H	H	H	26.94/>100	>11	>100/>100	>3	>300/>300
6c	Br	H	H	H	H	23.4/>100	>12	56.38/43.58	>5	>300/>300
6d	Cl	H	H	H	H	9.0/35.3	>33	>100/>100	>3	>300/>300
6e	F	H	H	H	H	7.68/54.13	>39	>100/>100	>3	>300/>300
6f	H	Cl	H	H	H	34.23/89.38	>8	45.37/66.84	>6	>300/>300
6g	H	F	H	H	H	>100/>100	>3	>100/>100	>3	>300/>300
6h	H	H	OMe	H	H	>100/>100	>3	>100/>100	>3	>300/>300
6i	H	H	Me	H	H	76.73/>100	>4	>100/>100	>3	>300/>300
6j	H	H	Cl	H	H	45.82/>100	>6	>100/>100	>3	>300/>300
6k	Me	Me	H	H	H	23.23/85.42	8.97	45.28/90.03	4.60	208.3/>300
6l	Cl	Cl	H	H	H	14.98/>100	>20	>100/>100	>3	>300/>300
6m	Cl	Br	H	H	H	30.12/>100	>10	60.62/>95.42	>4	>300/>286.54
6n	F	Cl	H	H	H	35.39/85.76	>8	40.16/103.61	>7	>300/>300
6o	H	H	H	Cl	H	19.4/57.77	5.71	>100/>100	>1	110.89/>300
6p	H	H	H	F	H	>100/>100	>3	58.58/96.35	>5	>300/>300
6q	Me	H	H	Cl	H	14.28/30.45	3.51	51.94/>100	0.96	50.23/>300
6r	Cl	H	H	Cl	H	17.6/43.9	6.17	>100/>100	>1	108.64/>300
6s	Cl	H	H	F	H	18.92/38.1	6.51	>100/>100	>1	123.19/>300
6t	H	H	H	Cl	Cl	>100/>100	>3	>100/>100	>3	>300/>300
6u	H	H	H	Cl	F	17.68/>100	>17	>100/>100	>3	>300/>300
6v	Cl	H	H	Cl	Cl	>100/>100	>0.56	>98.23/>98.23	>0.58	56.99/>294.99
6w	Cl	H	H	Cl	F	48.08/>100	>6	>100/>100	>3	>300/>300
7a	H	H	H	H	H	31.82/>100	>9	>100/>100	>3	>300/>300
7b	OCF_3	H	H	H	H	26.59/60.35	4.64	>100/>100	>1	123.55/262.64
7c	Br	H	H	H	H	15.71/57.41	2.68	97.78/99.36	0.43	42.14/>300
7d	Cl	H	H	H	H	49.58/>100	3.85	>100/>100	>2	190.89/>300
7e	F	H	H	H	H	12.37/>100	>24	>100/>100	>3	>300/>300
7f	H	Cl	H	H	H	65.44/>100	>4	41.82/>100	>7	>300/>300
7g	H	F	H	H	H	26.37/57.56	>11	>100/>100	>3	>300/>300
7h	H	H	OMe	H	H	30.06/70.19	>10	>100/>100	>3	>300/>300
7i	H	H	Me	H	H	15.64/54.87	>19	97.97/>100	>3	>300/>300
7j	H	H	Cl	H	H	19.62/>100	15.05	>100/>100	>3	295.36/>300
7k	Me	Me	H	H	H	6.1/35.33	>49	50.53/>100	>6	>300/>300
7l	Cl	Cl	H	H	H	16.45/29.7	4.65	>100/>100	>0.8	76.6/>300
7m	Cl	Br	H	H	H	27.21/54.36	2.12	>94.87/>94.87	>0.6	57.69/163.9
7n	F	Cl	H	H	H	45.93/>100	4.21	>100/>100	>1.9	193.8/>300
7o	H	H	H	Cl	H	49.73/>100	>6	>100/>100	>3	>300/>300
7p	H	H	H	F	H	62.97/>100	>4	>100/>100	>3	>300/>300
7q	Me	H	H	Cl	H	22.43/67.19	3.67	45.8/73.56	1.8	82.37/>300
7r	Cl	H	H	Cl	H	15.34/35.73	6.91	>100/>36.15	>1	106.01/>300
7s	Cl	H	H	F	H	17.31/79.94	10.53	>38.13/>38.13	>4	182.39/>300
7t	H	H	H	Cl	Cl	48.88/>100	>6	69.92/>100	>4	>300/>300
7u	H	H	H	Cl	F	>100/>100	>3	>100/>100	>3	>300/>300
7v	Cl	H	H	Cl	Cl	14.84/53.02	3.36	>32.55 />32.55	>1	49.91/176.01
7w	Cl	H	H	Cl	F	14.46/34.76	6.36	>34.15/>34.15	>2	92.02/182.44
Nfx						2.33/23.41	26.36	2.3/9.06	26.70	61.42/>300

SI: selectivity index; IC: inhibitory concentration; CC: cytotoxic concentration; Nfx: nifurtimox.

the azepinic protons were used to identify the isolated 2-aryltetrahydro-1-benzazepin-4-oles as the *cis*-isomer with the tetrahydroazepine ring in the chair conformation and consequently proves that their precursors **6** are *exo* adducts.

2.2. Biological activity

All the target compounds described in this work were initially synthesized and further evaluated in vitro assays against the free and intracellular forms of *T. cruzi* and *L. chagasi* parasites as well as on Vero epithelial cells (the host cells of *T. cruzi*) and THP-1 transformed human macrophages (the host cells of *L. chagasi*). In order to study the effects of structural modifications on inhibitory activity and cytotoxicity, substituents with different electronic characteristics have been introduced at the C-7 (*para*), C-4′ (*para*′-), C-3′ (*meta*′-), C-2′ (*ortho*′-), and C-6′ (*ortho*″-) positions of the target compounds. The antiparasitic activity and cytotoxicity of the compounds evaluated were expressed as the concentration required to inhibit 50% and 90% of parasites (IC_{50} and IC_{90}), and the concentration required to kill 50% and 90% of the mammalian cells (CC_{50} and CC_{90}). The results are summarized in Tables 1 and 2, along with the analogous data for the reference drugs nifurtimox and amphotericin B and the data of the selectivity index (SI), which were obtained by dividing the activity of one compound on mammalian cells CC_{50} by the activity of the same compound (IC_{50}) on parasites. In this work, compounds with IC_{50} >50 μM and IC_{90} >100 μM were classified as inactive, and compounds with CC_{50} <100 μM were classified as toxic for the mammalian cell lines.

The analysis of the antiparasitic activities of the 1,4-epoxy-cycloadducts **6** and their corresponding amino-alcohols **7** did not showed a statistical difference between them (p >0.05). The results also clearly indicate that the substitution pattern on both benzene rings (benzene of the 1-benzazepine skeleton and benzene as substituent at the C-2 position) markedly influenced the antiparasitic activity as well as the cytotoxicity of **6** and **7**.

As can be seen from the data in Tables 1 and 2, many of the tested compounds exhibited remarkable inhibitory activity against the epimastigote and promastigote forms of *T. cruzi* and *L. chagasi*

Table 2
In vitro antiparasitic activity and cytotoxicity of 1,4-epoxy-2-*exo*-aryl- (**6a**–**w**) and *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepines **7a**–**w** against *L. chagasi* and THP-1 cells

Compd	R	R^1	R^2	R^3	R^4	μM				
						Promastigotes		Intracellular amastigotes		THP-1 cells
						IC_{50}/IC_{90}	SI	IC_{50}/IC_{90}	SI	CC_{50}/CC_{90}
6a	H	H	H	H	H	>100/>100	>3	>100/>100	>3	>300/>300
6b	OCF_3	H	H	H	H	15.73/34.73	>19	>100/>100	>3	>300/>300
6c	Br	H	H	H	H	25.52/54.88	>11	>100/>100	>3	>300/>300
6d	Cl	H	H	H	H	40.1/55.44	>7	>100/>100	>3	>300/>300
6e	F	H	H	H	H	47.55/>100	>6	>100/>100	>3	>300/>300
6f	H	Cl	H	H	H	38.33/67.54	>7	>100/>100	>3	>300/>300
6g	H	F	H	H	H	>100/>100	>1	>100/>100	>1	182.86/>300
6h	H	H	OMe	H	H	54.73/>100	>5	>100/>100	>3	>300/>300
6i	H	H	Me	H	H	52/>100	>5	>100/>100	>3	>300/>300
6j	H	H	Cl	H	H	49.14/70.72	2.73	>100/>100	>1	133.98/>300
6k	Me	Me	H	H	H	98.96/>100	0.75	>100/>100	>0.74	74.0/125.74
6l	Cl	Cl	H	H	H	33.24/50.09	>9	>100/>100	>3	>300/>300
6m	Cl	Br	H	H	H	32.52/42.21	7.24	>95.42 />95.42	>2	235.54/>286.54
6n	F	Cl	H	H	H	35.18/41.79	>8	>100/>100	>3	>300/>300
6o	H	H	H	Cl	H	25.08/>100	4.37	>100/>100	>1	109.67/211.45
6p	H	H	H	F	H	40.53/47	4.93	>100/>100	>2	199.99/>300
6q	Me	H	H	Cl	H	41.74/49.46	1.6	>100/>100	>0.66	66.75/108.63
6r	Cl	H	H	Cl	H	51.27/>100	>5	>100/>100	>3	>300/>300
6s	Cl	H	H	F	H	23.84/67.28	>12	>100/>100	>3	>300/>300
6t	H	H	H	Cl	Cl	>100/>100	>3	>100/>100	>3	>300/>300
6u	H	H	H	Cl	F	>100/>100	>3	>100/>100	>3	>300/>300
6v	Cl	H	H	Cl	Cl	71.0/>100	4.15	>98.23/>98.23	>3	>294.99/>294.99
6w	Cl	H	H	Cl	F	>100/>100	>3	>100/>100	>3	>300/>300
7a	H	H	H	H	H	>100/>100	>3	>100/>100	>3	>300/>300
7b	OCF_3	H	H	H	H	35.5/43.21	2.92	>100/>100	>1	103.59/>300
7c	Br	H	H	H	H	45.04/>100	4.10	97.65/>100	>1	184.52/>300
7d	Cl	H	H	H	H	22.12/90.56	8.50	>100/>100	>1	188.07/>300
7e	F	H	H	H	H	>100/>100	>3	>100/>100	>3	>300/>300
7f	H	Cl	H	H	H	67.89/>100	1.68	>100/>100	>1	113.85/>300
7g	H	F	H	H	H	>100/>100	>3	>100/>100	>3	>300/>300
7h	H	H	OMe	H	H	97.09/>100	>3	>100/>100	>3	>300/>300
7i	H	H	Me	H	H	>100/>100	>1	>100/>100	>1	176.38/>300
7j	H	H	Cl	H	H	41.23/47.02	4.04	>100/>100	>1	166.58/>300
7k	Me	Me	H	H	H	>100/>100	>1	>100/>100	>1	171.66/>300
7l	Cl	Cl	H	H	H	14.1/41	3.49	>100/>100	>0.49	49.21/>300
7m	Cl	Br	H	H	H	9.54/11.74	16.05	>94.87/>94.87	>1.61	153.11/279.77
7n	F	Cl	H	H	H	17.11/77.74	5.86	>100/>100	>1	100.32/>300
7o	H	H	H	Cl	H	84.44/>100	>3	>100/>100	>3	>300/>300
7p	H	H	H	F	H	>100/>100	>3	>100/>100	>3	>300/>300
7q	Me	H	H	Cl	H	41.34/49.35	2.06	>100/>100	>0.85	85.19/>300
7r	Cl	H	H	Cl	H	50.22/>100	1.5	>100/>100	>0.75	75.53/>300
7s	Cl	H	H	F	H	54.45/>100	2.02	>100/>100	>1	110.21/273.12
7t	H	H	H	Cl	Cl	>100/>100	>3	>100/>100	>3	>300/>300
7u	H	H	H	Cl	F	>100/>100	>3	>100/>100	>3	>300/>300
7v	Cl	H	H	Cl	Cl	14.66/30.29	4.06	>32.55/>32.55	>1	59.59/>293.25
7w	Cl	H	H	Cl	F	39.75/78.51	2.76	73.22/>100	>1	109.77/213.67
AmB						0.02/0.02	439.5	0.08/0.14	109.87	8.79/34.88

SI: selectivity index; IC: inhibitory concentration; CC: cytotoxic concentration; AmB: amphotericin B.

parasites, respectively. On *T. cruzi* assays, nine 1,4-epoxy-cycloadducts (**6d–f**,**k**,**n**,**o**,**q–s**), with IC_{50} values of 7.68–35.39 μM and IC_{90} values of 30.45–89.38 μM, and thirteen amino-alcohols (**7b**,**c**,**g–i**, **k–m**,**q–s**,**v**,**w**), with IC_{50} values of 6.10–30.06 μM and IC_{90} values of 29.70–79.94 μM, were active against the epimastigote form of *T. cruzi*, being the *para*,*para*′-dimethyl substituted amino-alcohol **7k**, with IC_{50} = 6.10 μM, the most active compound, followed by 1,4-epoxy-cycloadducts **6e** and **6d**, the *para*-fluoro and *para*-chloro substituted, with IC_{50} = 7.68 and 9.00 μM, respectively. Only three compounds were active against the amastigote form of *T. cruzi*, the *para*′-chloro-1,4-epoxy-cycloadduct **6f**, the *para*-*para*′-dimethyl-1,4-epoxy-cycloadduct **6k**, and the *para*-methyl-*ortho*′-chloro disubstituted amino-alcohol **7q**, with IC_{50} values of 45.28–45.80 μM and IC_{90} values of 66.84–90.03 μM. These three compounds were also active against the epimastigote form of *T. cruzi*.

On *L. chagasi* assays, eleven 1,4-epoxy-cycloadducts (**6b–d**,**f**,**j**,**l–n**,**p**,**q**,**s**), with IC_{50} values of 15.73–49.14 μM and IC_{90} values of 34.73–70.72 μM, and nine amino-alcohols (**7b**,**d**,**j**,**l–n**,**q**,**v**,**w**), with IC_{50} values of 9.54–41.34 μM and IC_{90} values between 11.74 and 90.56 μM, were active against the promastigote form of *L. chagasi*. In these series of compounds, the *para*-chloro-*para*′-bromo disubstituted amino-alcohol **7m** displayed the most remarkable inhibitory activity (IC_{50} = 9.54 μM), followed by amino-alcohols **7l** and **7v** with IC_{50} = 14.10 and 14.66 μM, respectively. We also found that none of the compounds evaluated was active against the intracellular amastigote form of *L. chagasi* at any of the concentrations tested (Table 2). It is also important to note that the 1,4-epoxy-cycloadducts **6d**,**f**,**n**,**q**,**s**, and the amino-alcohols **7b**,**l**,**m**,**q**,**v**,**w**, proved to have inhibitory properties against the epimastigote and promastigote forms of both *T. cruzi* and *L. chagasi* parasites, respectively.

On mammalian cell assays, only eight compounds (**6q**,**v** and **7c**,**l**,**m**,**q**,**v**,**w**) were toxics for the Vero cells, and six compounds (**6k**,**q** and **7l**,**q**,**r**,**v**) were also toxics for the THP-1 mammalian cells. These results suggest that the *para*-*para*′-dimethyl, *para*-methyl-*ortho*′-chloro- and *para*-*ortho*′-*ortho*″-trichloro substitution patterns in the **6a-w** series, as well as the *para*-bromo-, *para*-*para*′-dichloro-, *para*-chloro-*para*′-bromo-, *para*-methyl-*ortho*′-chloro-, *para*-*ortho*′-dichloro-, *para*-*ortho*′-*ortho*″-trichloro- and *para*-*ortho*′-dichloro-*ortho*″-fluoro substitution patterns increase their cytotoxicity against both mammalian cell lines.

3. Conclusion

In an attempt to find novel antiparasitic agents, we have synthesized and fully characterized two new series of 1,4-epoxy-2-*exo*-aryl- (**6a–w**) and *cis*-2-aryl-4-hydroxytetrahydro-1-benzazepine (**7a–w**) derivatives that showed relevant inhibitory activity against the epimastigote and promastigote forms of *T. cruzi* and *L. chagasi* parasites, respectively. Taking into account the inhibitory activity against both the epimastigote and amastigote forms of *T. cruzi* observed during the present study, compounds **6f**, **6k** and **7q** revealed the most promising. However, considering the cytotoxic profile to Vero cells, only the *para*′-chloro-1,4-epoxy-cycloadduct **6f** as well as the *para*-*para*′-dimethyl-1,4-epoxy-cycloadduct **6k** may serve as possible candidates for further structural modifications in order to improve their antitrypanosomal activity.

4. Experimental

4.1. Chemistry

4.1.1. General

All the reagents and solvents were purchased from commercial suppliers (Aldrich, Merck), and used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck precoated Silica Gel (60 F_{254}) plates and column chromatography was accomplished on Merck Kieselgel 60 70–230 mesh (ASTM). All the chromatographic solvent proportions were volume to volume. Melting points were determined with a MEL-TEMP 1201D capillary apparatus and are uncorrected. IR spectra were recorded on a Nicolet Avatar 360-FTIR spectrometer and referenced to polystyrene standard, using cells equipped with potassium bromide windows. ^1H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer, using $CDCl_3$ as the solvent. Chemical shifts (δ) and coupling constants (J) values are reported in ppm and hertz, respectively. Chemical shifts are relative to the solvent peaks used as reference [$CDCl_3$: δ_H = 7.26, and δ_C = 77.0]. A Hewlett–Packard (HP) 5890 A series II Gas Chromatograph interfaced to a HP 5972 Mass Selective Detector with a HP MS ChemStation Data system was used for MS identification. Elemental analyses (C, H, N) were performed on a Perkin–Elmer 2400 Series II analyzer.

Compounds **2a**,**b**,**d**,**e**,**f**,**i**, **3a**,**b**,**d**,**e**,**f**,**i**, **6a**,**b**,**d**,**e**,**f**,**i**, and **7a**,**b**,**d**,**e**,**f**,**i** were previously synthesized and characterized.[51]

4.2. General procedure for the synthesis of *N*-allyl-*N*-benzylanilines 2a–n

To a stirred solution of *N*-benzylanilines **1a–n** (0.01 mol) and anhydrous sodium carbonate (0.03 mol) in dry acetone (50 mL) was slowly added allyl bromide (0.02 mol). The reaction mixture was then stirred at reflux for 4–7 h (TLC control). Each mixture was filtered and the filtrate was concentrated under reduced pressure. The remaining organic residue was purified by column chromatography on silica gel using heptane–ethyl acetate (compositions ranged from 70:1 to 30:1 v/v) as eluent to give compounds **2a–n** as low-viscosity colorless oils.

4.2.1. *N*-Allyl-*N*-benzylaniline (2a)

1.83 g (82%). IR (liquid film): ν = 1643 (C=C allyl), 919 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.08 (2H, dd, J = 6.8, 2.0 Hz, –C*H*$_2$–CH=), 4.61 (2H, s, –N–C*H*$_2$–), 5.23–5.29 (2H, m, =C*H*$_2$), 5.91–6.00 (1H, m, –C*H*=), 6.76 (1H, t, J = 7.8 Hz, 4-H), 6.79 (2H, d, J = 8.0 Hz, 2-H, 6-H), 7.25 (2H, dd, J = 7.8, 0.8 Hz, 3-H, 5-H), 7.32 (3H, t, J = 7.6 Hz, 2′-H, 4′-H, 6′-H), 7.38 (2H, t, J = 7.6 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1 (–*C*H$_2$–CH=), 54.1 (–N–*C*H$_2$–), 112.5 (2-C, 6-C), 116.4 (=*C*H$_2$), 116.6 (4-C), 126.7 (2′-C, 4′-C, 6′-C), 129.2 (3́-C, 5′-C), 129.3 (3-C, 5-C), 133.8 (–*C*H=), 139.1 (1′-C), 149.1 (1-C). MS (EI): m/z (%) = 223 (51) [M^+], 197 (2), 196 (11), 182 (3), 180 (8), 91 (100), 77 (32), 65 (15).

4.2.2. *N*-Allyl-*N*-benzyl-4-trifluoromethoxyaniline (2b)

2.46 g (80%). IR (liquid film): ν = 1642 (C=C allyl), 919 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.04 (2H, d, J = 4.8 Hz, –C*H*$_2$–CH=), 4.57 (2H, s, –N–C*H*$_2$–), 5.23–5.29 (2H, m, =C*H*$_2$), 5.90–5.98 (1H, m, –C*H*=), 6.67 (2H, d, J = 9.2 Hz, 2-H, 6-H), 7.05 (2H, d, J = 9.2 Hz, 3-H, 5-H), 7.26 (2H, d, J = 7.6 Hz, 2′-H, 6′-H), 7.28 (1H, t, J = 7.2 Hz, 4′-H), 7.36 (2H, t, J = 7.2 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.6 (–*C*H$_2$–CH=), 54.5 (–N–*C*H$_2$–), 112.9 (2-C, 6-C), 116.8 (=*C*H$_2$), 118.4 (q, J = 250.0 Hz, 4-O*C*F$_3$), 122.2 (3-C, 5-C), 126.7 (2′-C, 6′-C), 127.2 (4′-C), 128.9 (3′-C, 5′-C), 133.3 (–*C*H=), 138.5 (1′-C), 140.1 (4-C), 147.80 (1-C). MS (EI): m/z (%) = 307 (38) [M^+], 280 (3), 266 (2), 264 (4), 91 (100), 161 (5), 65 (16).

4.2.3. *N*-Allyl-*N*-benzyl-4-bromoaniline (2c)

2.41 g (80%). IR (liquid film): ν = 1642 (C=C allyl), 919 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.01 (2H, dd, J = 4.8, 2.4 Hz, –C*H*$_2$–CH=), 4.54 (2H, s, –N–C*H*$_2$–), 5.18–5.24 (2H, m, =C*H*$_2$), 5.84–5.94 (1H, m, –C*H*=), 6.60 (2H, d, J = 8.8 Hz, 2-H, 6-H), 7.24 (2H, dd, J = 7.6, 2.2 Hz, 2′-H, 6′-H), 7.25 (2H, d,

J = 8.8 Hz, 3-H, 5-H), 7.27 (1H, td, J = 8.0, 2.2 Hz, 4′-H), 7.35 (2H, t, J = 7.6 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5 (–CH_2–CH=), 54.4 (–N–CH_2–), 108.8 (4-C), 114.5 (2-C, 6-C), 116.8 (=CH_2), 126.7 (3-C, 5-C), 127.2 (4′-C), 128.8 (2′-H, 6′-H), 131.9 (3′-H, 5′-H), 133.2 (–CH=), 138.3 (1′-C), 147.9 (1-C). MS (EI): m/z (%) = 301 (^{79}Br, 30) [M^+], 260 (3), 258 (3), 130 (20), 155 (13), 91 (100), 76 (10).

4.2.4. *N*-Allyl-*N*-benzyl-4-chloroaniline (2d)

2.00 g (78%). IR (liquid film): ν = 1643 (C=C allyl), 921 (=C-H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (2H, dd, J = 6.0, 2.0 Hz, –CH_2–CH=), 4.54 (2H, s, –N–CH_2–), 5.18–5.23 (2H, m, =CH_2), 5.83–5.93 (1H, m, –CH=), 6.64 (2H, d, J = 8.8 Hz, 2-H, 6-H), 7.13 (2H, d, J = 8.8 Hz, 3-H, 5-H), 7.23 (2H, d, J = 7.6 Hz, 2′-H, 6′-H), 7.26 (1H, d, J = 7.4 Hz, 4′-H), 7.34 (2H, t, J = 7.4 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5 (–CH_2–CH=), 54.4 (–N–CH_2–), 113.8 (2-C, 6-C), 116.7 (=CH_2), 122.0 (4-C), 126.6 (2′-C, 6′-C), 127.1 (4′-C), 128.8 (3′-C, 5′-C), 129.0 (3-C, 5-C), 133.3 (–CH=), 138.5 (1′-C), 147.6 (1-C). MS (EI): m/z (%) = 257 (^{35}Cl, 42) [M^+], 230 (6), 216 (3), 214 (4), 91 (100), 111 (15), 65 (18).

4.2.5. *N*-Allyl-*N*-benzyl-4-fluoroaniline (2e)

1.95 g (81%). IR (liquid film): ν = 1643 (C=C allyl), 920 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.01 (2H, dd, J = 6.4, 1.2 Hz, –CH_2–CH=), 4.54 (2H, s, –N–CH_2–), 5.19–5.26 (2H, m, =CH_2), 5.86–5.96 (1H, m, –CH=), 6.65–6.69 (2H, m, 2-H, 6-H), 6.90–6.94 (2H, m, 3-H, 5-H), 7.26 (2H, dd, J = 7.6, 1.2 Hz, 2′-H, 6′-H), 7.28 (1H, t, J = 7.6 Hz, 4′-H), 7.36 (2H, td, J = 7.6, 1.2 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.9 (–CH_2–CH=), 54.9 (–N–CH_2–), 113.8 (d, J = 10.0 Hz, 2-C, 6-C), 115.6 (d, J = 20.0 Hz, 3-C, 5-C), 116.6 (=CH_2), 126.8 (2′-C, 6′-C), 127.0 (4′-C), 128.7 (3′-C, 5′-C), 133.8 (–CH=), 139.0 (1′-C), 145.7 (1-C), 155.9 (d, J = 230.0 Hz, 4-C). MS (EI): m/z (%) = 241 (44) [M^+], 164 (12), 150 (80), 148 (24), 135 (23), 91 (100), 95 (3).

4.2.6. *N*-Allyl-*N*-(4′-chlorobenzyl)aniline (2f)

2.14 g (83%). IR (liquid film): ν = 1643 (C=C allyl), 920 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (2H, dd, J = 5.0, 1.5 Hz, –CH_2–CH=), 4.57 (2H, s, –N–CH_2–), 5.23–5.30 (2H, m, =CH_2), 5.91–6.00 (1H, m, –CH=), 6.77 (2H, dd, J = 8.0, 2.0 Hz, 2-H, 6-H), 6.81 (1H, t, J = 8.0 Hz, 4-H), 7.25 (2H, t, J = 8.0 Hz, 3-H, 5-H), 7.29 (2H, d, J = 9.0 Hz, 2′-H, 6′-H), 7.35 (2H, d, J = 9.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1 (–CH_2–CH=), 53.4 (–N–CH_2–), 112.5 (2-C, 6-C), 116.5 (=CH_2), 116.8 (4-C), 128.0 (2′-C, 6′-C), 128.7 (3′-C, 5′-C), 129.1 (3-C, 5-C), 132.4 (4′-C), 133.5 (–CH=), 137.5 (1′-C), 148.7 (1-C). MS (EI): m/z (%) = 257 (^{35}Cl, 35) [M^+], 231 (2), 230 (8), 125 (100), 99 (3), 77 (33), 51 (10).

4.2.7. *N*-Allyl-*N*-(4′-fluorobenzyl)aniline (2g)

1.86 g (77%). IR (liquid film): ν = 1642 (C=C allyl), 924 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.03 (2H, d, J = 4.9 Hz, –CH_2–CH=), 4.54 (2H, s, –N–CH_2–), 5.21–5.26 (2H, m, –CH_2=), 5.89–5.96 (1H, m, –CH=), 6.75–6.77 (3H, m, 2-H, 4-H, 6-H), 7.04 (2H, tt, J = 8.7, 2.0 Hz, 3′-H, 5′-H), 7.21–7.28 (4H, m, 3-H, 5-H, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.2 (CH_2–CH=), 53.6 (–N–CH_2–), 112.7 (2-C, 6-C), 115.5 (d, J = 21.2 Hz, 3′-C, 5′-C), 116.6 (=CH_2), 116.9 (4-C), 128.3 (d, J = 10.0 Hz, 2′-C, 6′-C), 129.3 (3-C, 5-C), 133.7 (–CH=), 134.6 (1′-C), 148.9 (1-C), 162.0 (d, J = 243.1 Hz, 4′-C). MS (EI): m/z (%) = 241 (37) [M^+], 215 (2), 214 (6), 109 (100), 83 (11), 77 (22), 51 (5).

4.2.8. *N*-Allyl-*N*-(3′-methoxybenzyl)aniline (2h)

1.82 g (72%). IR (liquid film): ν = 1641 (C=C allyl), 920 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (3H, s, 3′-OCH_3), 4.02 (2H, d, J = 5.0 Hz, –CH_2–CH=), 4.53 (2H, s, –N–CH_2–), 5.18–5.23 (2H, m, =CH_2), 5.86–5.95 (1H, m, –CH=), 6.70 (1H, t, J = 8.0 Hz, 4-H), 6.73 (2H, d, J = 8.4 Hz, 2-H, 6-H), 6.79 (1H, dd, J = 7.8, 2.3 Hz, 4′-H), 6.82 (1H, br s, 2′-H), 6.85 (1H, d, J = 7.8 Hz, 6′-H), 7.19 (2H, t, J = 8.0 Hz, 3-H, 5-H), 7.25 (1H, t, J = 7.8 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.2 (–CH_2–CH=), 54.2 (–N–CH_2–), 55.3 (3′-OCH_3), 112.2 (2′-C), 112.5 (4′-C), 112.6 (2-C, 6-C), 116.5 (=CH_2), 116.7 (4-C), 119.0 (6′-C), 129.3 (3-C, 5-C), 129.8 (5′-C), 133.8 (–CH=), 141.0 (1′-C), 149.1 (1-C), 160.1 (3′-C). MS (EI): m/z (%) = 253 (66) [M^+], 227 (3), 226 (10), 121 (100), 104 (20), 91 (23), 77 (30).

4.2.9. *N*-Allyl-*N*-(3′-methylbenzyl)aniline (2i)

1.66 g (70%). IR (liquid film): ν = 1640 (C=C allyl), 918 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (3H, s, 3′-CH_3), 4.11 (2H, dd, J = 6.0, 1.5 Hz, –CH_2–CH=), 4.61 (2H, s, –N–CH_2–), 5.27–5.32 (2H, m, =CH_2), 5.94–6.03 (1H, m, –CH=), 6.79 (1H, t, J = 8.4 Hz, 4-H), 6.82 (2H, d, J = 8.4 Hz, 2-H, 6-H), 7.15 (2H, d, J = 8.0 Hz, 4′-H, 6′-H), 7.17 (1H, s, 2′-H), 7.29 (2H, t, J = 8.4 Hz, 3-H, 5-H), 7.32 (1H, t, J = 8.0 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (3′-CH_3), 53.1 (–CH_2–CH=), 54.1 (–N–CH_2–), 112.5 (2-C, 6-C), 116.4 (=CH_2), 116.6 (4-C), 123.8 (6′-C), 127.3 (2′-C), 127.7 (4′-C), 128.6 (5′-C), 129.2 (3-C, 5-C), 133.8 (–CH=), 138.3 (3′-C), 139.1 (1′-C), 149.2 (1-C). MS (EI): m/z (%) = 237 (51) [M^+], 210 (8), 196 (3), 194 (8), 105 (100), 77 (49), 51 (12).

4.2.10. *N*-Allyl-*N*-(3′-chlorobenzyl)aniline (2j)

2.19 g (85%). IR (liquid film): ν = 1641 (C=C allyl), 921 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (2H, dd, J = 5.8, 1.5 Hz, –CH_2–CH=), 4.57 (2H, s, –N–CH_2–), 5.23–5.28 (2H, m, =CH_2), 5.90–5.99 (1H, m, –CH=), 6.76 (2H, dd, J = 8.0, 2.0 Hz, 2-H, 6-H), 6.78 (1H, td, J = 8.0, 2.0 Hz, 4-H), 7.19 (1H, dd, J = 8.0, 2.0 Hz, 6′-H), 7.26 (2H, t, J = 8.0 Hz, 3-H, 5-H), 7.28 (1H, d, J = 8.0 Hz, 4′-H), 7.29 (1H, t, J = 8.0 Hz, 5′-H), 7.31 (1H, s, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.3 (–CH_2–CH=), 53.8 (–N–CH_2–), 112.6 (2-H, 6-C), 116.7 (=CH_2), 117.1 (4-C), 124.8 (6′-C), 126.8 (4′-C), 127.2 (2′-C), 129.3 (3-C, 5-C), 130.0 (5′-C), 133.5 (–CH=), 134.7 (3′-C), 141.5 (1′-C), 148.8 (1-C). MS (EI): m/z (%) = 257 (^{35}Cl, 63) [M^+], 230 (22), 216 (6), 214 (8), 125 (100), 77 (68), 99 (3).

4.2.11. *N*-Allyl-*N*-(4′-methylbenzyl)-4-methylaniline (2k)

2.13 g (90%). IR (liquid film): ν = 1641 (C=C allyl), 917 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (3H, s, 4-CH_3), 2.44 (3H, s, 4′-CH_3), 4.07 (2H, d, J = 5.0 Hz, –CH_2–CH=), 4.59 (2H, s, –N–CH_2–), 5.25–5.32 (2H, m, =CH_2), 5.95–6.02 (1H, m, –CH=), 6.76 (2H, d, J = 8.0 Hz, 2-H, 6-H), 7.11 (2H, d, J = 8.0 Hz, 3-H, 5-H), 7.22 (2H, d, J = 8.0 Hz, 2′-H, 6′-H), 7.25 (2H, d, J = 8.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (4-CH_3), 21.2 (4′-CH_3), 53.3 (–N–CH_2–), 54.1 (–CH_2–CH=), 112.8 (2-C, 6-C), 116.3 (=CH_2), 125.7 (4-C), 126.8 (2′-C, 6′-C), 129.3 (3′-C, 5′-C), 129.8 (3-C, 5-C), 134.1 (–CH=), 136.2 (1′-C), 136.4 (4′-C), 147.0 (1-C). MS (EI): m/z (%) = 237 (63) [M^+], 210 (13), 160 (17), 146 (9), 118 (21), 91 (100), 65 (22).

4.2.12. *N*-Allyl-*N*-(4′-chlorobenzyl)-4-chloroaniline (2l)

2.42 g (83%). IR (liquid film): ν = 1638 (C=C allyl), 922 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.99 (2H, dd, J = 5.6, 1.6 Hz, –CH_2–CH=), 4.49 (2H, s, –N–CH_2–), 5.17–5.24 (2H, m, =CH_2), 5.83–5.92 (1H, m, –CH=), 6.62 (2H, d, J = 9.2 Hz, 2-H, 6-H), 7.14 (2H, d, J = 9.2 Hz, 3-H, 5-H), 7.17 (2H, d, J = 8.6 Hz, 2′-H, 6′-H), 7.31 (2H, d, J = 8.6 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.5 (–CH_2–CH=), 53.9 (–N–CH_2–), 113.9 (2-C, 6-C), 116.9 (=CH_2), 122.8 (4-C), 128.0 (2′-C, 6′-C), 128.9 (3-C, 5-C), 129.1 (3′-C, 5′-C), 132.8 (4′-C), 133.1 (–CH=), 137.1 (1′-C), 147.4 (1-C). MS (EI): m/z (%) = 291 (^{35}Cl, 35) [M^+], 264 (4), 250 (3), 248 (3), 125 (100), 111 (14), 99 (4).

4.2.13. *N*-Allyl-*N*-(4′-bromobenzyl)-4-chloroaniline (2m)

2.99 g (89%). IR (liquid film): ν = 1641 (C=C allyl), 921 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.98 (2H, dd, J = 4.8, 1.7 Hz, –C*H*$_2$–CH=), 4.47 (2H, s, –N–C*H*$_2$–), 5.16–5.23 (2H, m, =C*H*$_2$), 5.83–5.90 (1H, m, –CH=), 6.61 (2H, d, J = 8.9 Hz, 2-H, 6-H), 7.10 (2H, d, J = 8.4 Hz, 2′-H, 6′-H), 7.13 (2H, d, J = 8.9 Hz, 3-H, 5-H), 7.44 (2H, d, J = 8.4 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.7 (–*C*H$_2$–CH=), 54.0 (–N–*C*H$_2$–), 114.0 (2-C, 6-C), 117.0 (=*C*H$_2$), 120.9 (4′-C), 122.2 (4-C), 128.5 (3-C, 5-C), 129.1 (2′-C, 6′-C), 131.9 (3′-C, 5′-C), 133.1 (–CH=), 138.2 (1′-C), 144.2 (1-C). MS (EI): m/z (%) = 337 (^{79}Br, ^{35}Cl, 43) [M^+], 310 (10), 294 (7), 169 (100), 111 (23), 89 (27), 63 (10).

4.2.14. *N*-Allyl-*N*-(4′-chlorobenzyl)-4-fluoroaniline (2n)

2.29 g (83%). IR (liquid film): ν = 1642 (C=C allyl), 923 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.97 (2H, d, J = 5.2 Hz, –C*H*$_2$–CH=), 4.47 (2H, s, –N–C*H*$_2$–), 5.18–5.23 (2H, m, =C*H*$_2$), 5.84–5.93 (1H, m, –CH=), 6.62–6.66 (2H, m, 2-H, 6-H), 6.91 (2H, td, J = 9.2, 2.2 Hz, 3-H, 5-H), 7.19 (2H, d, J = 8.4 Hz, 2′-H, 6′-H), 7.30 (2H, d, J = 8.4 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0 (–*C*H$_2$–CH=), 54.4 (–N–*C*H$_2$–), 114.0 (d, J = 10.0 Hz, 2-C, 6-C), 115.6 (d, J = 30.0 Hz, 3-C, 5-C), 116.9 (=*C*H$_2$), 128.2 (2′-C, 6′-C), 128.9 (3′-C, 5′-C), 132.7 (4′-C), 133.6 (–CH=), 137.5 (1′-C), 145.4 (1-C), 155.7 (d, J = 240.0 Hz, 4-C). MS (EI): m/z (%) = 275 (^{35}Cl, 34) [M^+], 248 (4), 232 (4), 125 (100), 99 (5), 95 (26), 69 (2).

4.3. General procedures for the synthesis of 2-allyl-*N*-benzylanilines 3a–w

Procedure 1: A mixture of substituted *N*-allyl-*N*-benzylanilines **2a–n** (0.01 mol) and boron trifluoride diethyl ether complex, (BF_3·OEt_2, 0.012–0.015 equiv), was heated at 125–150 °C for 3–5 h. After cooling to room temperature, the reaction mixture was neutralized with a saturated sodium carbonate solution to pH 8 and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and then concentrated under reduced pressure. The remaining organic residue was purified by column chromatography on silica gel using heptane–ethyl acetate (compositions ranged from 50:1 to 20:1) as eluent to yield compounds **3a–n** as low-viscosity maroon oils.

Procedure 2: To an ice-cooled and stirred solution of substituted *ortho*-allylanilines **4a–c** (0.010 mol) and anhydrous sodium carbonate (0.025 mol) in dry *N*,*N*-dimethylformamide (20 mL), was slowly added the corresponding substituted benzyl chloride **5a–d** (0.011 mol) in *N*,*N*-dimethylformamide (3 mL). Each mixture was stirred at 0 °C for 3–4 h and allowed to reach room temperature (TLC control). The mixture was poured onto water (100 mL) and then extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and then concentrated under reduced pressure. The remaining organic residue was purified by column chromatography on silica gel using heptane–ethyl acetate (compositions ranged from 50:1 to 20:1) as eluent to yield compounds **3o–w** as low-viscosity maroon oils or maroon crystals (compound **3v**).

4.3.1. 2-Allyl-*N*-benzylaniline (3a)

1.60 g (72%). IR (liquid film): ν = 3438 (N–H), 1634 (C=C allyl), 915 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.37 (2H, d, J = 6.0 Hz, –C*H*$_2$–), 4.16 (1H, br s, NH), 4.40 (2H, s, –N–C*H*$_2$–), 5.12 (1H, dq, J = 16.0, 1.6 Hz, =C*H*$_A$H$_B$), 5.17 (1H, dq, J = 10.0, 1.6 Hz, =CH$_A$*H*$_B$), 6.02 (1H, ddt, J = 16.0, 10.0, 6.0 Hz, =CH–), 6.69 (1H, dd, J = 7.2, 0.8 Hz, 6-H), 6.77 (1H, td, J = 7.2, 0.8 Hz, 4-H), 7.13 (1H, dd, J = 7.2, 1.4 Hz, 3-H), 7.18 (1H, td, J = 7.6, 1.4 Hz, 5-H), 7.30–7.42 (5H, m, 2′-H. 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5 (–*C*H$_2$–), 48.2 (–N–*C*H$_2$–), 110.7 (6-C), 116.3 (=*C*H$_2$), 117.4 (4-C), 123.5 (2-C), 127.1 (5-C), 127.4 (2′-C, 6′-C), 127.7 (4′-C), 128.6 (3′-C, 5′-C), 129.8 (3-C), 136.0 (–CH=), 139.5 (1′-C), 146.1 (1-C). MS (EI): m/z (%) = 223 (47) [M^+], 195 (4), 194 (15), 132 (100), 130 (30), 117 (26), 91 (86).

4.3.2. 2-Allyl-*N*-benzyl-4-trifluoromethoxyaniline (3b)

2.15 g (70%). IR (liquid film): ν = 3444 (N–H), 1637 (C=C allyl), 920 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32 (2H, d, J = 6.4 Hz, –C*H*$_2$–), 4.22 (1H, br s, NH), 4.36 (2H, s, –N–C*H*$_2$–), 5.13 (1H, dq, J = 17.0, 1.6 Hz, =C*H*$_A$H$_B$), 5.20 (1H, dq, J = 10.0, 1.6 Hz, =CH$_A$*H*$_B$), 5.96 (1H, ddt, J = 17.0, 10.0, 6.0 Hz, –CH=), 6.58 (1H, d, J = 8.4 Hz, 6-H), 6.99 (1H, s, 3-H), 7.00 (1H, d, J = 8.4 Hz, 5-H), 7.31–7.38 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.3 (–*C*H$_2$–), 48.5 (–N–*C*H$_2$–), 111.0 (6-C), 117.2 (=*C*H$_2$), 120.5 (5-C), 120.9 (q, J = 260.0 Hz, 4-O*C*F$_3$), 123.0 (3-C), 124.9 (2-C), 127.5 (2′-C, 4′-C, 6′-C), 128.9 (3′-C, 5′-C), 135.0 (–CH=), 139.0 (1′-C), 140.6 (4-C), 144.9 (1-C). MS (EI): m/z (%) = 307 (23) [M^+], 266 (1), 230 (8), 216 (48), 214 (12), 201 (5), 91 (100).

4.3.3. 2-Allyl-*N*-benzyl-4-bromoaniline (3c)

2.20 g (73%). IR (liquid film): ν = 3438 (N–H), 1634 (C=C allyl), 919 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.28 (2H, d, J = 6.1 Hz, –C*H*$_2$–), 4.12 (1H, br s, NH), 4.32 (2H, s, –N–C*H*$_2$–), 5.10 (1H, dq, J = 17.2, 1.5 Hz, =C*H*$_A$H$_B$), 5.16 (1H, dq, J = 10.2, 1.5 Hz, =CH$_A$*H*$_B$), 5.93 (1H, ddt, J = 17.2, 10.2, 6.1 Hz, =CH–), 6.48 (1H, d, J = 8.4 Hz, 6-H), 7.17 (1H, d, J = 2.3 Hz, 3-H), 7.20 (1H, dd, J = 8.4, 2.3 Hz, 5-H), 7.27–7.37 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.2 (–*C*H$_2$–), 48.3 (–N–*C*H$_2$–), 109.3 (4-C), 112.5 (6-C), 117.1 (=*C*H$_2$), 125.8 (2-C), 127.5 (2′-C, 6′-C), 127.5 (4′-C), 128.8 (3′-C, 5′-C), 130.4 (5-C), 132.4 (3-C), 135.2 (–CH=), 139.1 (1′-C), 145.3 (1-C). MS (EI): m/z (%) = 301 (^{79}Br, 17) [M^+], 210 (10), 211 (3), 209 (3), 131 (37), 91 (100), 65 (30).

4.3.4. 2-Allyl-*N*-benzyl-4-chloroaniline (3d)

2.27 g (88%). IR (liquid film): ν = 3444 (N-H), 1636 (C=C allyl), 920 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32 (2H, d, J = 6.0 Hz, –C*H*$_2$–), 4.12 (1H, br s, NH), 4.37 (2H, s, –N–C*H*$_2$–), 5.11 (1H, dq, J = 17.0, 1.6 Hz, =C*H*$_A$H$_B$), 5.17 (1H, dq, J = 10.0, 1.6 Hz, =CH$_A$*H*$_B$), 5.95 (1H, ddt, J = 17.0, 10.0, 6.0 Hz, =CH–), 6.57 (1H, d, J = 8.4 Hz, 6-H), 7.11 (1H, d, J = 2.4 Hz, 3-H), 7.12 (1H, dd, J = 8.4, 2.4 Hz, 5-H), 7.31–7.43 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.2 (–*C*H$_2$–), 48.3 (–N–*C*H$_2$–), 112.0 (6-C), 117.1 (=*C*H$_2$), 122.1 (4-C), 125.4 (2-C), 127.4 (5-C, 2′-C, 4′-C, 6′-C), 128.8 (3′-C, 5′-C), 129.6 (3-C), 135.2 (–CH=), 139.1 (1′-C), 144.7 (1-C). MS (EI): m/z (%) = 257 (^{35}Cl, 24) [M^+], 229 (2), 228 (4), 214 (2), 166 (29), 164 (9), 91 (100).

4.3.5. 2-Allyl-*N*-benzyl-4-fluoroaniline (3e)

2.10 g (86%). IR (liquid film): ν = 3440 (N–H), 1636 (C=C allyl), 917 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.32 (2H, d, J = 6.4 Hz, –C*H*$_2$–), 4.06 (1H, br s, NH), 4.34 (2H, s, –N–C*H*$_2$–), 5.12 (1H, dq, J = 17.0, 1.6 Hz, =C*H*$_A$H$_B$), 5.19 (1H, dq, J = 10.0, 1.6 Hz, =CH$_A$*H*$_B$), 5.97 (1H, ddt, J = 17.0, 10.0, 6.4 Hz, =CH–), 6.57 (1H, dd, J = 8.0, 8.0 Hz, 6-H), 6.83 (1H, td, J = 8.0, 3.0 Hz, 5-H), 6.85 (1H, d, J = 8.0 Hz, 3-H), 7.29–7.37 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.7 (–*C*H$_2$–), 48.3 (–N–*C*H$_2$–), 111.1 (6-C), 113.0 (d, J = 30.0 Hz, 5-C), 116.1 (d, J = 30.0 Hz, 3-C), 116.4 (=*C*H$_2$), 125.0 (d, J = 10.0 Hz, 2-C), 126.8 (4′-C), 126.9 (2′-C, 6′-C), 128.2 (3′-C, 5′-C), 134.6 (–CH=), 138.8 (1′-C), 141.8 (1-C), 155.3 (d, J = 240.0 Hz, 4-C). MS (EI): m/z (%) = 241 (44) [M^+], 164 (12), 150 (80), 148 (24), 135 (23), 91 (100), 95 (3).

4.3.6. 2-Allyl-*N*-(4′-chlorobenzyl)aniline (3f)

1.93 g (75%). IR (liquid film): ν = 3439 (N–H), 1635 (C=C allyl), 917 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.36 (2H, d, J = 6.0 Hz, $-CH_2-$), 4.12 (1H, br s, NH), 4.35 (2H, s, $-N-CH_2-$), 5.12 (1H, dq, J = 17.0, 1.6 Hz, $=CH_AH_B$), 5.17 (1H, dq, J = 10.0, 1.6 Hz, $=CH_AH_B$), 6.00 (1H, ddt, J = 17.0, 10.0, 6.0 Hz, –CH=), 6.59 (1H, d, J = 8.0 Hz, 6-H), 6.76 (1H, t, J = 8.0 Hz, 4-H), 7.11 (1H, dd, J = 8.0, 1.6 Hz, 3-H), 7.15 (1H, td, J = 8.0, 1.6 Hz, 5-H), 7.31 (2H, d, J = 8.4 Hz, 2′-H, 6′-H), 7.34 (2H, d, J = 8.4 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5 ($-CH_2-$), 47.4 ($-N-CH_2-$), 110.8 (6-C), 116.6 ($=CH_2$), 117.6 (4-C), 123.6 (2-C), 127.7 (2′-C, 6′-C), 128.6 (3′-C, 5′-C), 128.7 (5-C), 129.9 (3-C), 132.8 (4′-C), 135.9 (–CH=), 138.0 (1′-C), 145.8 (1-C). MS (EI): m/z (%) = 257 (^{35}Cl, 32) [M^+], 229 (2), 228 (6), 132 (100), 130 (26), 117 (21), 125 (75).

4.3.7. 2-Allyl-*N*-(4′-fluorobenzyl)aniline (3g)

1.83 g (76%). IR (liquid film): ν = 3437 (N–H), 1634 (C=C allyl), 917 (=C-H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.36 (2H, d, J = 6.2 Hz, $-CH_2-$), 4.08 (1H, br s, NH), 4.34 (2H, s, $-N-CH_2-$), 5.11 (1H, dq, J = 17.1, 1.6 Hz, $=CH_AH_B$), 5.16 (1H, dq, J = 10.1, 1.6 Hz, $=CH_AH_B$), 5.99 (1H, ddt, J = 17.1, 10.1, 6.2 Hz, –CH=), 6.64 (1H, d, J = 8.0 Hz, 6-H), 6.77 (1H, t, J = 7.4 Hz, 4-H), 7.05 (2H, tt, J = 8.6, 2.0 Hz, 3′-H, 5′-H), 7.11 (1H, dd, J = 7.4, 1.5 Hz, 3-H), 7.16 (1H, td, J = 8.0, 1.5 Hz, 5-H), 7.34 (2H, dd, J = 8.4, 8.5 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5 ($-CH_2-$), 47.6 ($-N-CH_2-$), 111.1 (6-C), 115.4 (d, J = 21.2 Hz, 3′-C, 5′-C), 116.3 ($=CH_2$), 117.8 (4-C), 123.8 (2-C), 127.7 (5-C), 129.0 (d, J = 8.0 Hz, 2′-C, 6′-C), 129.9 (3-C), 134.9 (1′-C), 136.0 (–CH=), 145.6 (1-C), 162.0 (d, J = 243.5 Hz, 4′-C). MS (EI): m/z (%) = 241 (42) [M^+], 132 (86), 117 (19), 109 (100), 91 (6), 77 (8), 65 (4).

4.3.8. 2-Allyl-*N*-(3′-methoxybenzyl)aniline (3h)

1.70 g (67%). IR (liquid film): ν = 3438 (N-H), 1634 (C=C allyl), 916 (=C-H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.36 (2H, d, J = 6.2 Hz, $-CH_2-$), 3.82 (3H, s, 3′-OCH_3), 4.35 (2H, s, $-N-CH_2-$), 5.12 (1H, dq, J = 17.1, 1.5 Hz, $=CH_AH_B$), 5.15 (1H, dq, J = 10.2, 1.5 Hz, $=CH_AH_B$), 6.00 (1H, ddt, J = 17.1, 10.2, 6.2 Hz, –CH=), 6.65 (1H, d, J = 8.0 Hz, 6-H), 6.74 (1H, td, J = 7.3, 1.0 Hz, 4-H), 6.84 (1H, dd, J = 8.2, 2.4 Hz, 4′-H), 6.94 (1H, br s, 2′-H), 6.97 (1H, d, J = 8.0 Hz, 6′-H), 7.10 (1H, dd, J = 7.3, 1.6 Hz, 3-H), 7.15 (1H, td, J = 8.0, 1.6 Hz, 5-H), 7.28 (1H, t, J = 8.0 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.8 ($-CH_2-$), 48.4 ($-N-CH_2-$), 55.4 (3′-OCH_3), 111.0 (6-C), 112.8 (4′-C), 113.2 (2′-C), 116.5 ($=CH_2$), 117.6 (4-C), 119.9 (6′-C), 123.8 (2-C), 128.0 (5-C), 129.9 (5′-C), 130.1 (3-C), 136.3 (–CH=), 141.4 (1′-C), 146.4 (1-C), 160.2 (3′-C). MS (EI): m/z (%) = 253 (33) [M^+], 224 (10), 146 (17), 132 (100), 121 (67), 91 (23), 77 (13).

4.3.9. 2-Allyl-*N*-(3′-methylbenzyl)aniline (3i)

1.75 g (74%). IR (liquid film): ν = 3439 (N–H), 1635 (C=C allyl), 914 (=C-H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.45 (3H, s, 3′-CH_3), 3.41 (2H, d, J = 6.0 Hz, $-CH_2-$), 4.21 (1H, br s, NH), 4.39 (2H, s, $-N-CH_2-$), 5.17 (1H, dq, J = 17.0, 1.6 Hz, $=CH_AH_B$), 5.20 (1H, dq, J = 10.0, 1.6 Hz, $=CH_AH_B$), 6.05 (1H, ddt, J = 17.0, 10.0, 6.0 Hz, –CH=), 6.74 (1H, d, J = 8.0 Hz, 6-H), 6.82 (1H, td, J = 8.0, 1.0 Hz, 4-H), 7.16 (1H, dd, J = 8.0, 1.0 Hz, 3-H), 7.17 (1H, d, J = 1.6 Hz, 2′-H), 7.23 (1H, dd, J = 8.0, 1.6 Hz, 4′-H), 7.25 (1H, dd, J = 8.0, 1.6 Hz, 6′-H), 7.27 (1H, td, J = 8.0, 1.0 Hz, 5-H), 7.30 (1H, t, J = 8.0 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (3′-CH_3), 36.6 ($-CH_2-$), 48.3 ($-N-CH_2-$), 110.9 (6-C), 116.4 ($=CH_2$), 117.5 (4-C), 123.7 (2-C), 124.6 (6′-C), 127.8 (2′-C), 128.0 (4′-C), 128.3 (5′-C), 128.6 (5-C), 129.9 (3-C), 136.1 (–CH=), 138.3 (3′-C), 139.5 (1′-C), 146.3 (1-C). MS (EI): m/z (%) = 237 (41) [M^+], 209 (4), 208 (11), 132 (100), 130 (24), 117 (17), 105 (64).

4.3.10. 2-Allyl-*N*-(3′-chlorobenzyl)aniline (3j)

1.93 g (75%). IR (liquid film): ν = 3440 (N-H), 1636 (C=C allyl), 918 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.44 (2H, d, J = 6.0 Hz, $-CH_2-$), 4.43 (2H, s, $-N-CH_2-$), 5.21 (1H, dq, J = 17.0, 1.6 Hz, $=CH_AH_B$), 5.25 (1H, dq, J = 10.0, 1.6 Hz, $=CH_AH_B$), 6.07 (1H, ddt, J = 17.0, 10.0, 6.0 Hz, –CH=), 6.65 (1H, d, J = 8.0 Hz, 6-H), 6.83 (1H, t, J = 8.0 Hz, 4-H), 7.19 (1H, t, J = 8.0 Hz, 5-H), 7.21 (1H, d, J = 8.0 Hz, 3-H), 7.44 (1H, s, 2′-H), 7.30–7.35 (3H, m, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.7 ($-CH_2-$), 47.7 ($-N-CH_2-$), 110.9 (6-C), 116.5 ($=CH_2$), 117.8 (4-C), 123.8 (2-C), 125.4 (6′-C), 127.4 (2′-C), 127.5 (4′-C), 127.9 (5-C), 130.0 (5′-C), 130.1 (3-C), 134.6 (3′-C), 136.1 (–CH=), 141.9 (1′-C), 145.9 (1-C). MS (EI): m/z (%) = 257 (^{35}Cl, 22) [M^+], 229 (22), 228 (4), 132 (100), 130 (29), 117 (25), 125 (26).

4.3.11. 2-Allyl-*N*-(4′-methylbenzyl)-4-methylaniline (3k)

2.18 g (87%). IR (liquid film): ν = 3431 (N–H), 1634 (C=C allyl), 921 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.33 (3H, s, 4-CH_3), 2.42 (3H, s, 4′-CH_3), 3.37 (2H, d, J = 6.0 Hz, $-CH_2-$), 4.36 (2H, s, $-N-CH_2-$), 5.15 (1H, dq, J = 17.2, 1.6 Hz, $=CH_AH_B$), 5.19 (1H, dq, J = 10.0, 1.6 Hz, $=CH_AH_B$), 6.03 (1H, ddt, J = 17.2, 10.0, 6.0 Hz, =CH–), 6.65 (1H, d, J = 8.0 Hz, 6-H), 6.97 (1H, d, J = 1.6 Hz, 3-H), 7.02 (1H, dd, J = 8.0, 1.6 Hz, 5-H), 7.22 (2H, d, J = 8.0 Hz, 3′-H, 5′-H), 7.32 (2H, d, J = 8.0 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (4-CH_3), 21.2 (4′-CH_3), 36.6 ($-CH_2-$), 48.4 ($-N-CH_2-$), 111.2 (6-C), 116.3 ($=CH_2$), 123.9 (2-C), 126.7 (4-C), 127.6 (2′-C, 6′-C), 128.1 (5-C), 129.4 (3′-C, 5′-C), 130.7 (3-C), 136.3 (–CH=), 136.6 (1′-C), 136.8 (4′-C), 144.0 (1-C). MS (EI): m/z (%) = 251 (56) [M^+], 222 (9), 160 (7), 146 (72), 132 (17), 131 (23), 105 (100), 91 (8).

4.3.12. 2-Allyl-*N*-(4′-chlorobenzyl)-4-chloroaniline (3l)

2.15 g (74%). IR (liquid film): ν = 3444 (N–H), 1635 (C=C allyl), 920 (=C-H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.30 (2H, d, J = 6.0 Hz, $-CH_2-$), 4.15 (1H, br s, NH), 4.32 (2H, s, $-N-CH_2-$), 5.12 (1H, dq, J = 17.0, 1.7 Hz, $=CH_AH_B$), 5.19 (1H, dq, J = 10.0, 1.7 Hz, $=CH_AH_B$), 5.95 (1H, ddt, J = 17.0, 10.0, 6.0 Hz, =CH–), 6.48 (1H, d, J = 9.0 Hz, 6-H), 7.07 (1H, dd, J = 9.0, 2.8 Hz, 5-H), 7.07 (1H, d, J = 2.8 Hz, 3-H), 7.27 (2H, d, J = 8.4 Hz, 2′-H, 6′-H), 7.33 (2H, d, J = 8.4 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.3 ($-CH_2-$), 47.6 ($-N-CH_2-$), 112.0 (6-C), 117.1 ($=CH_2$), 122.4 (4-C), 125.5 (2-C), 127.4 (5-C), 128.7 (2′-C, 6′-C), 128.9 (3′-C, 5′-C), 129.7 (3-C), 133.1 (4′-C), 135.1 (–CH=), 137.6 (1′-C), 144.5 (1-C). MS (EI): m/z (%) = 291 (^{35}Cl, 29) [M^+], 180 (7), 166 (38), 164 (11), 152 (9), 125 (100), 111 (2).

4.3.13. 2-Allyl-*N*-(4′-bromobenzyl)-4-chloroaniline (3m)

2.52 g (75%). IR (liquid film): ν = 3444 (N–H), 1634 (C=C allyl), 920 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.29 (2H, d, J = 6.1 Hz, $-CH_2-$), 4.29 (2H, s, $-N-CH_2-$), 5.10 (1H, dq, J = 17.1, 1.7 Hz, $=CH_AH_B$), 5.17 (1H, dq, J = 10.1, 1.7 Hz, $=CH_AH_B$), 5.93 (1H, ddt, J = 17.1, 10.1, 6.1 Hz, =CH–), 6.46 (1H, d, J = 9.3 Hz, 6-H), 7.06 (1H, d, J = 2.5 Hz, 3-H), 7.06 (1H, dd, J = 9.3, 2.5 Hz, 5-H), 7.21 (2H, d, J = 8.4 Hz, 2′-H, 6′-H), 7.46 (2H, d, J = 8.4 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.3 ($-CH_2-$), 47.7 ($-N-CH_2-$), 112.1 (6-C), 117.1 ($=CH_2$), 121.2 (4′-C), 122.5 (4-C), 125.5 (2-C), 127.4 (5-C), 129.1 (2′-C, 6′-C), 129.8 (3-C), 131.9 (3′-C, 5′-C), 135.2 (–CH=), 138.1 (1′-C), 144.8 (1-C). MS (EI): m/z (%) = 337 (^{79}Br, ^{35}Cl, 33) [M^+], 180 (13), 169 (100), 131 (57), 89 (37), 77 (20), 63 (20).

4.3.14. 2-Allyl-*N*-(4′-chlorobenzyl)-4-fluoroaniline (3n)

1.98 g (72%). IR (liquid film): ν = 3441 (N–H), 1638 (C=C allyl), 918 (=C–H allyl) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.31 (2H, d, J = 6.0 Hz, $-CH_2-$), 4.0 (1H, br s, NH), 4.30 (2H, s, $-N-CH_2-$),

5.11 (1H, dq, J = 17.0, 1.7 Hz, =CH_AH$_B$), 5.18 (1H, dq, J = 10.0, 1.7 Hz, =CH$_A$$H_B$), 5.95 (1H, ddt, J = 17.0, 10.0, 6.0 Hz, =CH–), 6.49 (1H, dd, J = 9.0, 8.0 Hz, 6-H), 6.82 (1H, td, J = 9.0, 3.0 Hz, 5-H), 6.85 (1H, dd, J = 8.0, 3.0 Hz, 3-H), 7.28 (2H, d, J = 8.6 Hz, 2′-H, 6′-H), 7.32 (2H, d, J = 8.6 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.3 (–CH_2–), 48.1 (–N–CH_2–), 111.7 (d, J = 10.0 Hz, 6-C), 113.6 (d, J = 20.0 Hz, 5-C), 116.8 (d, J = 20.0 Hz, 3-C), 117.0 (=CH_2), 125.7 (d, J = 10.0 Hz, 2-C), 128.8 (2′-C, 6′-C), 128.9 (3′-C, 5′-C), 133.1 (4′-C), 135.2 (–CH=), 137.9 (1′-C), 142.1 (1-C), 156.0 (d, J = 240.0 Hz, 4-C). MS (EI): m/z (%) = 275 (^{35}Cl, 30) [M$^+$], 246 (5), 164 (8), 150 (83), 148 (22), 135 (19), 125 (100).

4.3.15. 2-Allyl-*N*-(2′-chlorobenzyl)aniline (3o)

2.03 g (79%). IR (liquid film): ν = 3440 (N–H), 1634 (C=C allyl), 916 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (2H, d, J = 6.1 Hz, –CH_2–), 4.51 (2H, s, –N–CH_2–), 5.16 (1H, dq, J = 17.0, 1.7 Hz, =CH_AH$_B$), 5.20 (1H, dq, J = 10.2, 1.7 Hz, =CH$_A$$H_B$), 6.04 (1H, ddt, J = 17.0, 10.2, 6.1 Hz, =CH–), 6.62 (1H, d, J = 8.0 Hz, 6-H), 6.78 (1H, td, J = 7.4, 1.0 Hz, 4-H), 7.14 (1H, dd, J = 7.4, 1.6 Hz, 3-H), 7.17 (1H, td, J = 8.0, 1.6 Hz, 5-H), 7.23–7.28 (2H, m, 3′-H, 5′-H), 7.40–7.45 (2H, m, 4′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5 (–CH_2–), 45.7 (–N–CH_2–), 111.0 (6-C), 116.4 (=CH_2), 117.7 (4-C), 123.8 (2-C), 126.9 (3′-C), 127.7 (5-C), 128.3 (5′-C), 128.9 (6′-C), 129.5 (4′-C), 129.9 (3-C), 133.2 (2′-C), 135.9 (–CH=), 136.6 (1′-C), 145.5 (1-C). MS (EI): m/z (%) = 257 (^{35}Cl, 32) [M$^+$], 229 (1), 146 (16), 132 (100), 130 (25), 117 (22), 115 (34).

4.3.16. 2-Allyl-*N*-(2′-fluorobenzyl)aniline (3p)

1.95 g (81%). IR (liquid film): ν = 3439 (N–H), 1634 (C=C allyl), 916 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.37 (2H, d, J = 6.2 Hz, –CH_2–), 4.46 (2H, s, –N–CH_2–), 5.14 (1H, dq, J = 16.8, 1.6 Hz, =CH_AH$_B$), 5.17 (1H, dq, J = 10.2, 1.6 Hz, =CH$_A$$H_B$), 6.01 (1H, ddt, J = 16.8, 10.2, 6.2 Hz, =CH–), 6.67 (1H, d, J = 7.8 Hz, 6-H), 6.76 (1H, td, J = 7.4, 1.0 Hz, 4-H), 7.07–7.11 (2H, m, 3′-H, 5′-H), 7.12 (1H, dd, J = 7.4, 1.4 Hz, 3-H), 7.17 (1H, td, J = 7.8, 1.4 Hz, 5-H), 7.25–7.28 (1H, m, 4′-H), 7.38 (1H, td, J = 7.6, 1.4 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.6 (–CH_2–), 41.9 (d, J = 4.3 Hz, –N–CH_2–), 111.1 (6-C), 115.4 (d, J = 21.3 Hz, 3′-C), 116.5 (=CH_2), 117.9 (4-C), 124.0 (2-C), 124.3 (d, J = 3.6 Hz, 5′-C), 126.4 (d, J = 14.4 Hz, 1′-C), 127.9 (5-C), 128.9 (d, J = 8.1 Hz, 6′-C), 129.5 (d, J = 4.4 Hz, 4′-C), 130.1 (3-C), 136.1 (–CH=), 145.9 (1-C), 161.0 (d, J = 244.3 Hz, 2′-C). MS (EI): m/z (%) = 241 (42) [M$^+$], 213 (2), 146 (8), 132 (100), 130 (23), 117 (23), 109 (51).

4.3.17. 2-Allyl-*N*-(2′-chlorobenzyl)-4-methylaniline (3q)

2.28 g (84%). IR (liquid film): ν = 3437 (N–H), 1634 (C=C allyl), 914 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (3H, s, 4-CH_3), 3.36 (2H, d, J = 6.2 Hz, –CH_2–), 4.47 (2H, s, –N–CH_2–), 5.09 (1H, dq, J = 17.0, 1.4 Hz, =CH_AH$_B$), 5.17 (1H, dq, J = 10.1, 1.4 Hz, =CH$_A$$H_B$), 6.01 (1H, ddt, J = 17.0, 10.1, 6.2 Hz, =CH–), 6.52 (1H, d, J = 8.7 Hz, 6-H), 6.94 (1H, d, J = 2.0 Hz, 3-H), 6.97 (1H, dd, J = 8.7, 2.0 Hz, 5-H), 7.21–7.24 (2H, m, 3′-H, 5′-H), 7.38–7.41 (2H, m, 4′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.5 (4-CH_3), 36.6 (–CH_2–), 46.2 (–N–CH_2–), 111.5 (6-C), 116.4 (=CH_2), 124.2 (2-C), 127.0 (3′-C), 127.2 (4-C), 128.1 (5-C), 128.4 (5′-C), 129.1 (6′-C), 129.6 (4′-C), 130.9 (3-C), 134.4 (2′-C), 136.2 (–CH=), 137.6 (1′-C), 143.3 (1-C). MS (EI): m/z (%) = 271 (^{35}Cl, 42) [M$^+$], 243 (1), 160 (10), 146 (100), 144 (24), 131 (51), 125 (29).

4.3.18. 2-Allyl-*N*-(2′-chlorobenzyl)-4-chloroaniline (3r)

2.33 g (80%). IR (liquid film): ν = 3444 (N–H), 1635 (C=C allyl), 919 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (2H, d, J = 6.2 Hz, –CH_2–), 4.44 (2H, s, –N–CH_2–), 5.13 (1H, dq, J = 17.1, 1.7 Hz, =CH_AH$_B$), 5.17 (1H, dq, J = 10.2, 1.7 Hz, =CH$_A$$H_B$), 5.96 (1H, ddt, J = 17.1, 10.2, 6.2 Hz, =CH–), 6.47 (1H, d, J = 8.3 Hz, 6-H), 7.05 (1H, dd, J = 8.3, 2.3 Hz, 5-H), 7.06 (1H, d, J = 2.3 Hz, 3-H), 7.21–7.25 (2H, m, 3′-H, 5′-H), 7.38–7.41 (2H, m, 4′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.2 (–CH_2–), 46.5 (–N–CH_2–), 111.9 (6-C), 117.2 (=CH_2), 122.2 (4-C), 124.9 (2-C), 127.1 (3′-C), 127.5 (5-C), 128.8 (5′-C), 129.0 (6′-C), 129.5 (4′-C), 129.8 (3-C), 133.6 (2′-C), 135.2 (–CH=), 137.2 (1′-C), 144.6 (1-C). MS (EI): m/z (%) = 291 (^{35}Cl, 77) [M$^+$], 263 (2), 180 (13), 166 (67), 164 (16), 151 (6), 131 (100), 125 (91).

4.3.19. 2-Allyl-4-chloro-*N*-(2′-fluorobenzyl)aniline (3s)

2.29 g (83%). IR (liquid film): ν = 3443 (N–H), 1628 (C=C allyl), 920 (=C-H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 (2H, d, J = 6.1 Hz, –CH_2–), 4.41 (2H, s, –N–CH_2–), 5.11 (1H, dq, J = 17.1, 1.6 Hz, =CH_AH$_B$), 5.17 (1H, dq, J = 10.1, 1.6 Hz, =CH$_A$$H_B$), 5.94 (1H, ddt, J = 17.1, 10.1, 6.1 Hz, =CH–), 6.56 (1H, d, J = 8.4 Hz, 6-H), 7.05–7.12 (4H, m, 3-H, 5-H, 3′-H, 5′-H), 7.24–7.34 (2H, m, 4′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.1 (–CH_2–), 41.8 (d, J = 4.4 Hz, –N–CH_2–), 112.1 (6-C), 115.4 (d, J = 21.2 Hz, 3′-C), 117.0 (=CH_2), 122.4 (4-C), 124.2 (d, J = 3.56 Hz, 5′-C), 125.6 (2-C), 125.7 (d, J = 16.0 Hz, 1′-C), 127.3 (5-C), 128.9 (d, J = 8.0 Hz, 6′-C), 129.2 (d, J = 5.0 Hz, 4′-C), 129.6 (3-C), 135.0 (–CH=), 144.1 (1-C), 160.9 (d, J = 244.4 Hz, 2′-C). MS (EI): m/z (%) = 275 (^{35}Cl, 15) [M$^+$], 180 (2), 166 (100), 164 (9), 151 (12), 131 (74), 109 (58).

4.3.20. 2-Allyl-*N*-(2′,6′-dichlorobenzyl)aniline (3t)

2.33 g (80%). IR (liquid film): ν = 3394 (N–H), 1634 (C=C allyl), 915 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (2H, d, J = 6.2 Hz, –CH_2–), 4.60 (2H, s, –N–CH_2–), 5.06 (1H, dq, J = 17.3, 1.6 Hz, =CH_AH$_B$), 5.10 (1H, dq, J = 10.1, 1.6 Hz, =CH$_A$$H_B$), 5.95 (1H, ddt, J = 17.3, 10.1, 1.6 Hz, =CH–), 6.78 (1H, td, J = 7.4, 0.9 Hz, 4-H), 6.94 (1H, d, J = 8.0 Hz, 6-H), 7.09 (1H, dd, J = 7.4, 1.2 Hz, 3-H), 7.20 (1H, t, J = 8.0 Hz, 4′-H), 7.24 (1H, td, J = 7.9, 1.2 Hz, 5-H), 7.35 (2H, d, J = 8.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5 (–CH_2–), 44.1 (–N–CH_2–), 111.6 (6-C), 116.5 (=CH_2), 118.1 (4-C), 124.6 (2-C), 127.8 (5-C), 128.7 (3′-C, 5′-C), 129.5 (3-C), 130.0 (4′-C), 134.9 (1′-C), 136.0 (–CH=), 136.3 (2′-C, 6′-C), 146.1 (1-C). MS (EI): m/z (%) = 291 (^{35}Cl, 13) [M$^+$], 263 (1), 146 (5), 132 (100), 130 (25), 117 (22), 159 (23).

4.3.21. 2-Allyl-*N*-(6′-chloro-2′-fluorobenzyl)aniline (3u)

2.12 g (77%). IR (liquid film): ν = 3419 (N–H), 1634 (C=C allyl), 916 (=C-H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (2H, d, J = 6.2 Hz, –CH_2–), 4.25 (1H, br s, NH), 4.53 (2H, s, –N–CH_2–), 5.08 (1H, dq, J = 17.2, 1.6 Hz, =CH_AH$_B$), 5.12 (1H, dq, J = 10.2, 1.6 Hz, =CH$_A$$H_B$), 5.96 (1H, ddt, J = 17.2, 10.2, 6.2 Hz, =CH–), 6.76 (1H, t, J = 7.4 Hz, 4-H), 6.94 (1H, d, J = 8.1 Hz, 6-H), 7.00–7.05 (1H, m, 3′-H), 7.08 (1H, dd, J = 7.4, 0.6 Hz, 3-H), 7.19–7.24 (3H, m, 5-H, 4′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.5 (–CH_2–), 39.6 (d, J = 3.4 Hz, –N–CH_2–), 111.3 (6-C), 114.4 (d, J = 23.2 Hz, 3′-H), 116.5 (=CH_2), 118.0 (4-C), 124.5 (2-C), 125.1 (d, J = 18.0 Hz, 1′-C), 125.7 (d, J = 3.5 Hz, 5′-C), 127.8 (5-C), 129.5 (d, J = 9.7 Hz, 4′-C), 130.0 (3-C), 135.8 (d, J = 5.0 Hz, 6′-C), 136.0 (–CH=), 145.7 (1-C), 161.8 (d, J = 247.5 Hz, 2′-C). MS (EI): m/z (%) = 291 (^{35}Cl, 29) [M$^+$], 180 (7), 166 (38), 164 (11), 152 (9), 125 (100), 111 (2).

4.3.22. 2-Allyl-4-chloro-*N*-(2′,6′-dichlorobenzyl)aniline (3v)

Maroon crystals, 2.38 g (73%), mp: 70–71 °C (from heptane). IR (KBr): ν = 3399 (N–H), 1629 (C=C allyl), 912 (=C–H allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (2H, d, J = 6.2 Hz, –CH_2–), 4.56 (2H, s, –N–CH_2–), 5.05 (1H, dq, J = 17.1, 1.6 Hz, =CH_AH$_B$), 5.12 (1H, dq, J = 10.1, 1.6 Hz, =CH$_A$$H_B$), 5.87 (1H, ddt, J = 17.1, 10.1, 6.2 Hz, =CH–), 6.84 (1H, d, J = 8.6 Hz, 6-H), 7.04 (1H, d, J = 2.5 Hz, 3-H), 7.16 (1H, dd, J = 8.6, 2.5 Hz, 5-H), 7.19 (1H, t, J = 8.0 Hz, 4′-H), 7.34 (2H, d, J = 8.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.1 (–CH_2–), 44.2 (–N–CH_2–), 112.9 (6-C), 117.2 (=CH_2), 122.9 (4-C), 126.4 (2-C), 127.4 (5-C), 128.7 (3′-C, 5′-C), 129.6

(4′-C), 129.7 (3-C), 134.5 (1′-C), 135.1 (–CH=), 136.2 (2′-C, 6′-C), 144.4 (1-C). MS (EI): *m*/*z* (%) = 325 (^{35}Cl, 14) [M$^+$], 180 (8), 166 (71), 164 (14), 159 (44), 151 (5), 131 (100).

4.3.23. 2-Allyl-4-chloro-*N*-(6′-chloro-2′-fluorobenzyl)aniline (3w)

2.50 g (81%). IR (liquid film): ν = 3422 (NH), 1637 (C=C allyl), 920 (allyl) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (2H, d, *J* = 6.2 Hz, –CH_2–), 4.48 (2H, d, *J* = 1.2 Hz, –N–CH_2–), 5.06 (1H, dq, *J* = 17.1, 1.4 Hz, =CH_AH$_B$), 5.14 (1H, dq, *J* = 10.1, 1.4 Hz, =CH$_A$$H_B$), 5.89 (1H, ddt, *J* = 17.1, 10.1, 6.2 Hz, =CH–), 6.82 (1H, d, *J* = 8.6 Hz, 6-H), 7.01 (1H, dd, *J* = 9.3, 5.0 Hz, 3′-H), 7.03 (1H, d, *J* = 2.6 Hz, 3-H), 7.14 (1H, dd, *J* = 8.6, 2.6 Hz, 5-H), 7.19–7.23 (2H, m, 4′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.1 (–CH_2–), 39.7 (d, *J* = 3.0 Hz, –N–CH_2–), 112.5 (6-C), 114.5 (d, *J* = 24.0 Hz, 3′-H), 117.1 (=CH_2), 124.7 (d, *J* = 18.0 Hz, 1′-C), 125.7 (4-C), 125.8 (2-C), 126.3 (5-C), 127.4 (d, *J* = 3.5 Hz, 5′-C), 129.6 (3-C), 129.7 (d, *J* = 4.0 Hz, 4′-C), 135.0 (–CH=), 135.7 (d, *J* = 6.0 Hz, 6′-C), 144.1 (1-C), 161.7 (d, *J* = 247.0 Hz, 2′-C). MS (EI): *m*/*z* (%) = 309 (^{35}Cl, 25) [M$^+$], 180 (6), 166 (54), 164 (15), 151 (6), 131 (100), 143 (68).

4.4. General procedure for the synthesis of 2-*exo*-aryl-1,4-epoxytetrahydro-1-benzazepines 6a–w

To an ice-cooled and stirred solution of substituted *ortho*-allyl-*N*-benzylanilines **3a–w** (0.010 mol) and catalytic amounts of sodium tungstate dehydrated (8–10 mol %) in methanol (40 mL), was added dropwise 30% aqueous hydrogen peroxide solution (0.030 mol). The resulting mixture was then stirred at room temperature for 36–72 h. Each mixture was filtered and the filtrate concentrated under reduced pressure. Toluene (50 mL) was added to the remaining organic residue and the resulting solution was heated at 70–90 °C for 3–7 h. After cooling to room temperature, toluene was removed under reduced pressure and the crude material was purified by column chromatography on silica gel using heptane–ethyl acetate (compositions ranged from 40:1 to 10:1 v/v) as eluent to give compounds **6a–w**.

4.4.1. 1,4-Epoxy-2-*exo*-phenyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6a)

Maroon viscous oil, 1.45 g (61%). IR (liquid film): ν = 1026 (–C–O–), 997 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.58 (1H, d, *J* = 16.5 Hz, 5-H$_A$), 2.61–2.69 (2H, m, 3-H$_A$H$_B$), 3.45 (1H, dd, *J* = 16.5, 5.4 Hz, 5-H$_B$), 4.62 (1H, dd, *J* = 11.2, 4.4 Hz, 2-H), 4.99 (1H, ddd, *J* = 6.4, 5.6, 2.4 Hz, 4-H), 7.12 (1H, dd, *J* = 6.6, 2.1 Hz, 9-H), 7.15–7.24 (3H, m, 6-H, 7-H, 8-H), 7.30 (1H, t, *J* = 7.6 Hz, 4′-H), 7.39 (2H, t, *J* = 7.6 Hz, 3′-H, 5′-H), 7.50 (2H, d, *J* = 7.2 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (5-C), 42.7 (3-C), 75.1 (4-C), 75.3 (2-C), 121.9 (9-C), 125.2 (5a-C), 125.9 (7-C), 126.4 (2′-C, 6′-C), 126.5 (8-C), 126.9 (4′-C), 128.4 (3′-C, 5′-C), 129.8 (6-C), 143.8 (1′-C), 150.9 (9a-C). MS (EI): *m*/*z* (%) = 237 (40) [M$^+$], 220 (24), 208 (7), 194 (14), 130 (7), 104 (100), 91 (25), 77 (31). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.08; H, 6.24; N, 5.82.

4.4.2. 1,4-Epoxy-2-*exo*-phenyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6b)

White crystals, 1.77 g (55%), mp: 63–64 °C (from heptane). IR (KBr): ν = 1026 (–C–O–), 998 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.57 (1H, d, *J* = 16.8 Hz, 5-H$_A$), 2.58–2.70 (2H, m, 3-H$_A$H$_B$), 3.43 (1H, dd, *J* = 16.8, 5.4 Hz, 5-H$_B$), 4.62 (1H, dd, *J* = 8.2, 3.3 Hz, 2-H), 4.97 (1H, ddd, *J* = 7.6, 5.4, 2.3 Hz, 4-H), 7.03 (1H, s, 6-H), 7.05 (1H, d, *J* = 8.4 Hz, 8-H), 7.12 (1H, d, *J* = 8.4 Hz, 9-H), 7.29 (1H, t, *J* = 7.3 Hz, 4′-H), 7.38 (2H, t, *J* = 8.0 Hz, 3′-H, 5′-H), 7.47 (2H, d, *J* = 8.0 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 42.7 (3-C), 74.5 (2-C), 75.3 (4-C), 119.4 (8-C), 120.1 (q, *J* = 257.0 Hz, 7-OCF_3), 122.2 (6-C), 123.3 (9-C), 126.3 (2′-C, 6′-C), 127.1 (4′-C), 127.3 (5a-C), 128.5 (3′-C, 5′-C), 143.3 (1′-C), 146.8 (d, *J* = 1.9 Hz, 7-C), 149.1 (9a-C). MS (EI): *m*/*z* (%) = 321 (22) [M$^+$], 304 (13), 292 (2), 278 (4), 214 (5), 188 (100), 175 (2), 161 (1). Anal. Calcd for $C_{17}H_{14}F_3NO_2$: C, 63.55; H, 4.39; N, 4.36. Found: C, 63.42; H, 4.50; N, 4.28.

4.4.3. 7-Bromo-1,4-epoxy-2-*exo*-phenyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6c)

White crystals, 1.99 g (63%), mp: 83–85 °C (from heptane). IR (KBr): ν = 1024 (–C–O–), 975 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (1H, d, *J* = 16.8 Hz, 5-H$_A$), 2.57–2.67 (2H, m, 3-H$_A$H$_B$), 3.40 (1H, dd, *J* = 16.8, 5.3 Hz, 5-H$_B$), 4.58 (1H, dd, *J* = 8.3, 2.9 Hz, 2-H), 4.96 (1H, ddd, *J* = 7.1, 5.2, 1.9 Hz, 4-H), 6.97 (1H, d, *J* = 8.0 Hz, 9-H), 7.27 (1H, t, *J* = 8.0 Hz, 4′-H), 7.29 (1H, s, 6-H), 7.30 (1H, d, *J* = 8.0 Hz, 8-H), 7.36 (2H, t, *J* = 8.0 Hz, 3′-H, 5′-H), 7.45 (2H, d, *J* = 8.0 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 42.7 (3-C), 74.8 (4-C), 75.5 (2-C), 119.1 (7-C), 123.9 (9-C), 126.5 (2′-C, 6′-C), 127.2 (4′-C), 127.9 (5a-C), 128.7 (3′-C, 5′-C), 129.9 (8-C), 132.8 (6-C), 143.5 (1′-C), 149.8 (9a-C). MS (EI): *m*/*z* (%) = 315 (^{79}Br, 31) [M$^+$], 298 (11), 286 (6), 208 (11), 184 (100), 132 (40), 104 (54), 77 (80). Anal. Calcd for $C_{16}H_{14}BrNO$: C, 60.78; H, 4.46; N, 4.43. Found: C, 60.91; H, 4.21; N, 4.57.

4.4.4. 7-Chloro-1,4-epoxy-2-*exo*-phenyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6d)

Maroon viscous oil, 1.76 g (65%). IR (liquid film): ν = 1026 (–C–O–), 997 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (1H, d, *J* = 16.8 Hz, 5-H$_A$), 2.57–2.68 (2H, m, 3-H$_A$H$_B$), 3.39 (1H, dd, *J* = 16.8, 5.4 Hz, 5-H$_B$), 4.59 (1H, dd, *J* = 8.3, 3.0 Hz, 2-H), 4.95 (1H, ddd, *J* = 6.0, 5.4, 2.0 Hz, 4-H), 7.03 (1H, d, *J* = 8.2 Hz, 9-H), 7.14 (1H, s, 6-H), 7.15 (1H, d, *J* = 8.2 Hz, 8-H), 7.29 (1H, t, *J* = 7.4 Hz, 4′-H), 7.38 (2H, t, *J* = 7.4 Hz, 3′-H, 5′-H), 7.47 (2H, d, *J* = 7.6 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.5 (5-C), 42.4 (3-C), 74.5 (2-C), 75.3 (4-C), 123.3 (9-C), 126.7 (2′-C, 6′-C), 126.9 (8-C), 127.0 (4′-C), 127.2 (5a-C), 128.5 (3′-C, 5′-C), 129.7 (6-C), 131.1 (7-C), 143.7 (1′-C), 149.3 (9a-C). MS (EI): *m*/*z* (%) = 271 (^{35}Cl, 34) [M$^+$], 254 (13), 242 (4), 228 (3), 164 (6), 138 (100), 125 (6), 111 (3). Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.81; H, 5.35; N, 5.02.

4.4.5. 1,4-Epoxy-2-*exo*-phenyl-7-fluoro-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6e)

Maroon viscous oil, 1.50 g (59%). IR (liquid film): ν = 1027 (–C-O–), 998 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.55 (1H, d, *J* = 16.9 Hz, 5-H$_A$), 2.58–2.68 (2H, m, 3-H$_A$H$_B$), 3.41 (1H, dd, *J* = 16.9, 5.5 Hz, 5-H$_B$), 4.59 (1H, dd, *J* = 8.0, 3.6 Hz, 2-H), 4.95 (1H, ddd, *J* = 7.2, 5.2, 2.6 Hz, 4-H), 6.86 (1H, d, *J* = 9.2 Hz, 6-H), 6.88 (1H, td, *J* = 8.6, 2.0 Hz, 8-H), 7.07 (1H, dd, *J* = 8.4, 5.2 Hz, 9-H), 7.28 (1H, t, *J* = 7.6 Hz, 4′-H), 7.38 (2H, t, *J* = 7.6 Hz, 3′-H, 5′-H), 7.47 (2H, d, *J* = 7.6 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.8 (5-C), 42.5 (3-C), 74.4 (4-C), 75.3 (2-C), 113.4 (d, *J* = 21.0 Hz, 8-C), 116.1 (d, *J* = 21.0 Hz, 6-C), 123.5 (d, *J* = 8.6 Hz, 9-C), 126.3 (2′-C, 6′-C), 127.0 (4′-C), 127.3 (d, *J* = 8.3 Hz, 5a-C), 128.5 (3′-C, 5′-C), 143.5 (1′-C), 146.5 (d, *J* = 3.0 Hz, 9a-C), 161.0 (d, *J* = 244.0 Hz, 7-C). MS (EI): *m*/*z* (%) = 255 (40) [M$^+$], 238 (17), 226 (5), 212 (6), 148 (7), 122 (100), 109 (9), 95 (5). Anal. Calcd for $C_{16}H_{14}FNO$: C, 75.28; H, 5.53; N, 5.49. Found: C, 75.11; H, 5.76; N, 5.62.

4.4.6. 1,4-Epoxy-2-*exo*-(4′-chlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6f)

Maroon viscous oil, 1.71 g (63%). IR (liquid film): ν = 1013 (–C–O–), 984 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (1H, d, *J* = 16.6 Hz, 5-H$_A$), 2.52–2.64 (2H, m, 3-H$_A$H$_B$), 3.42 (1H, dd, *J* = 16.6, 5.5 Hz, 5-H$_B$), 4.59 (1H, dd, *J* = 8.0, 3.2 Hz, 2-H), 4.96

(1H, ddd, J = 6.0, 5.4, 2.0 Hz, 4-H), 7.07 (1H, dd, J = 6.2, 2.1 Hz, 9-H), 7.12–7.22 (3H, m, 6-H, 7-H, 8-H), 7.33 (2H, d, J = 8.6 Hz, 3′-H, 5′-H), 7.42 (2H, d, J = 8.4 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 42.7 (3-C), 74.8 (2-C), 75.2 (4-C), 121.9 (9-C), 125.2 (5a-C), 126.1 (7-C), 126.7 (8-C), 127.9 (2′-C, 6′-C), 128.6 (3′-C, 5′-C), 129.8 (6-C), 132.6 (4′-C), 142.3 (1′-C), 150.3 (9a-C). MS (EI): m/z (%) = 271 (^{35}Cl, 21) [M$^+$], 254 (13), 242 (3), 228 (3), 130 (5), 104 (100), 91 (14), 77 (25). Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.90; H, 5.35; N, 5.08.

4.4.7. 1,4-Epoxy-2-*exo*-(4′-fluorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6g)

Maroon viscous oil, 1.61 g (63%). IR (liquid film): ν = 1015 (–C–O–), 999 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (1H, d, J = 16.6 Hz, 5-H$_A$), 2.56–2.61 (2H, m, 3-H$_A$H$_B$), 3.43 (1H, dd, J = 16.6, 5.4 Hz, 5-H$_B$), 4.61 (1H, dd, J = 8.0, 3.0 Hz, 2-H), 4.98 (1H, ddd, J = 6.0, 5.4, 2.3 Hz, 4-H), 7.05 (2H, t, J = 8.7 Hz, 3′-H, 5′-H), 7.10 (1H, dd, J = 8.2, 2.1 Hz, 9-H), 7.15–7.21 (3H, m, 6-H, 7-H, 8-H), 7.43–7.47 (2H, m, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 42.6 (3-C), 74.9 (2-C), 75.3 (4-C), 115.3 (d, J = 22.0 Hz, 3′-C, 5′-C), 122.0 (9-C), 125.3 (5a-C), 126.2 (7-C), 126.7 (8-C), 128.3 (d, J = 7.0 Hz, 2′-C, 6′-C), 130.0 (6-C), 139.6 (d, J = 3.0 Hz, 1′-C), 150.4 (9a-C), 162.0 (d, J = 244.0 Hz, 4′-C). MS (EI): m/z (%) = 255 (^{35}Cl, 37) [M$^+$], 238 (21), 225 (7), 133 (14), 104 (100), 91 (14), 78 (25), 65 (12). Anal. Calcd for $C_{16}H_{14}FNO$: C, 75.28; H, 5.53; N, 5.49. Found: C, 75.14; H, 5.67; N, 5.57.

4.4.8. 1,4-Epoxy-2-*exo*-(3′-methoxyphenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6h)

Maroon viscous oil, 1.73 g (65%). IR (liquid film): ν = 1031 (–C–O–), 999 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (1H, d, J = 16.6 Hz, 5-H$_A$), 2.60–2.67 (2H, m, 3-H$_A$H$_B$), 3.43 (1H, dd, J = 16.6, 5.3 Hz, 5-H$_B$), 3.85 (3H, s, 3′-OCH$_3$), 4.62 (1H, dd, J = 7.8, 3.9 Hz, 2-H), 4.98 (1H, ddd, J = 6.5, 5.3, 2.5 Hz, 4-H), 6.83 (1H, dd, J = 8.2, 2.4 Hz, 4′-H), 7.03 (1H, d, J = 7.6 Hz, 6′-H), 7.11 (1H, d, J = 2.4 Hz, 2′-H), 7.11–7.22 (4H, m, 6-H, 7-H, 8-H, 9-H), 7.29 (1H, t, J = 7.9 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 42.7 (3-C), 55.4 (3′-OCH$_3$), 75.2 (2-C), 75.5 (4-C), 112.2 (2′-C), 112.7 (4′-C), 118.9 (6′-C), 122.1 (9-C), 125.4 (5a-C), 126.2 (7-C), 126.7 (8-C), 129.6 (5′-C), 129.9 (6-C), 145.3 (1′-C), 150.5 (9a-C), 159.9 (3′-C). MS (EI): m/z (%) = 267 (^{35}Cl, 90) [M$^+$], 250 (40), 224 (20), 134 (60), 104 (100), 91 (33), 78 (30), 65 (20). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.22; H, 6.19; N, 5.34.

4.4.9. 1,4-Epoxy-2-*exo*-(3′-methylphenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6i)

Maroon viscous oil, 1.68 g (67%). IR (liquid film): ν = 1034 (–C–O–), 997 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (3H, s, 3′-CH$_3$), 2.58 (1H, d, J = 16.8 Hz, 5-H$_A$), 2.57–2.69 (2H, m, 3-H$_A$H$_B$), 3.45 (1H, dd, J = 16.8, 5.4 Hz, 5-H$_B$), 4.63 (1H, dd, J = 7.9, 3.4 Hz, 2-H), 4.99 (1H, ddd, J = 7.6, 5.9, 2.8 Hz, 4-H), 7.12 (2H, dd, J = 8.0, 1.6 Hz, 9-H, 6′-H), 7.16–7.24 (3H, m, 6-H, 7-H, 8-H), 7.25–7.30 (2H, m, 4′-H, 5′-H), 7.38 (1H, br s, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (3′-CH$_3$), 34.8 (5-C), 42.6 (3-C), 75.2 (2-C), 75.5 (4-C), 122.0 (9-C), 123.6 (4′-C), 125.4 (5a-C), 125.9 (8-C), 126.5 (7-C), 127.0 (2′-C), 127.7 (6′-C), 128.3 (5′-C), 129.9 (6-C), 138.6 (3′-C), 143.7 (1′-C), 150.8 (9a-C). MS (EI): m/z (%) = 251 (55) [M$^+$], 234 (36), 222 (10), 208 (12), 130 (8), 104 (100), 91 (33), 77 (22). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.39; H, 6.69; N, 5.49.

4.4.10. 1,4-Epoxy-2-*exo*-(3′-chlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6j)

Maroon viscous oil, 1.71 g (63%). IR (liquid film): ν = 1024 (–C–O–), 1000 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (1H, d, J = 16.4 Hz, 5-H$_A$), 2.55–2.65 (2H, m, 3-H$_A$H$_B$), 3.42 (1H, dd, J = 16.4, 5.6 Hz, 5-H$_B$), 4.59 (1H, dd, J = 7.6, 4.0 Hz, 2-H), 4.96 (1H, ddd, J = 6.8, 5.6, 2.4 Hz, 4-H), 7.08 (1H, dd, J = 8.0, 2.0 Hz, 9-H), 7.15–7.20 (3H, m, 6-H, 7-H, 8-H), 7.27 (1H, t, J = 8.4 Hz, 5′-H), 7.31 (1H, d, J = 8.4 Hz, 6′-H), 7.53 (1H, s, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 42.6 (3-C), 74.9 (2-C), 75.2 (4-C), 122.0 (9-C), 124.7 (6′-C), 125.3 (5a-C), 126.3 (7-C), 126.8 (8-C, 4′-C), 127.2 (2′-C), 129.8 (5′-C), 130.0 (6-C), 134.5 (3′-C), 145.9 (1′-C), 150.3 (9a-C). MS (EI): m/z (%) = 271 (^{35}Cl, 32) [M$^+$], 254 (18), 242 (4), 228 (9), 130 (6), 104 (100), 91 (15), 77 (24). Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.60; H, 5.12; N, 5.26.

4.4.11. 1,4-Epoxy-2-*exo*-(4′-methylphenyl)-7-methyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6k)

White crystals, 1.72 g (65%), mp: 101–103 °C (from heptane). IR (KBr): ν = 1022 (–C–O–), 979 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (3H, s, 7-CH$_3$), 2.35 (3H, s, 4′-CH$_3$), 2.51 (1H, d, J = 16.5 Hz, 5-H$_A$), 2.57–2.64 (2H, m, 3-H$_A$H$_B$), 3.39 (1H, dd, J = 16.5, 4.6 Hz, 5-H$_B$), 4.57 (1H, dd, J = 7.1, 3.5 Hz, 2-H), 4.96 (1H, ddd, J = 6.8, 5.0, 2.6 Hz, 4-H), 6.98 (1H, d, J = 8.2 Hz, 8-H), 6.95 (1H, br s, 6-H), 7.00 (1H, d, J = 8.2 Hz, 9-H), 7.17 (2H, d, J = 7.9 Hz, 3′-H, 5′-H), 7.35 (2H, d, J = 7.9 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (7-CH$_3$), 21.2 (4′-CH$_3$), 34.9 (5-C), 42.6 (3-C), 75.3 (4-C), 75.6 (2-C), 121.9 (9-C), 125.0 (5a-C), 126.6 (2′-C, 6′-C), 127.4 (8-C), 129.3 (3′-C, 5′-C), 130.4 (6-C), 135.7 (7-C), 136.8 (4′-C), 140.9 (1′-C), 148.2 (9a-C). MS (EI): m/z (%) = 265 (35) [M$^+$], 248 (18), 222 (10), 207 (5), 146 (7), 132 (23), 118 (100), 103 (12), 91 (30), 77 (18), 65 (9), 51 (5). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.40; H, 7.28; N, 5.22.

4.4.12. 7-Chloro-1,4-epoxy-2-*exo*-(4′-chlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6l)

White crystals, 2.32 g (76%), mp: 133–134 °C (from heptane). IR (KBr): ν = 1024 (–C–O–), 982 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54 (1H, d, J = 16.8 Hz, 5-H$_A$), 2.54–2.61 (2H, m, 3-H$_A$H$_B$), 3.38 (1H, d, J = 16.8, 5.6 Hz, 5-H$_B$), 4.54 (1H, dd, J = 7.4, 3.6 Hz, 2-H), 4.93 (1H, dd, J = 6.5, 4.8, Hz, 4-H), 7.00 (1H, d, J = 8.4 Hz, 9-H), 7.14 (1H, d, J = 8.4 Hz, 8-H), 7.16 (1H, d, J = 2.4 Hz, 6-H), 7.32 (2H, d, J = 8.4 Hz, 3′-H, 5′-H), 7.38 (2H, d, J = 8.4 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (5-C), 42.6 (3-C), 74.8 (2-C, 4-C), 123.4 (9-C), 127.0 (8-C), 127.3 (5a-C), 127.9 (2′-C, 6′-C), 128.7 (3′-C, 5′-C), 129.8 (6-C), 131.4 (7-C), 132.9 (4′-C), 142.0 (1′-C), 148.9 (9a-C). MS (EI): m/z (%) = 305 (^{35}Cl, 31) [M$^+$], 288 (12), 276 (3), 262 (5), 164 (7), 138 (100), 125 (13), 111 (5). Anal. Calcd for $C_{16}H^{13}C\ l_2NO$: C, 62.76; H, 4.28; N, 4.57. Found: C, 62.88; H, 4.20; N, 4.50.

4.4.13. 7-Chloro-1,4-epoxy-2-*exo*-(4′-bromophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6m)

White crystals, 2.66 g (76%), mp: 144–146 °C (from heptane). IR (KBr): ν = 1020 (–C–O–), 983 (–N–O–) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52 (1H, d, J = 16.9 Hz, 5-H$_A$), 2.53–2.59 (2H, m, 3-H$_A$H$_B$), 3.38 (1H, dd, J = 16.9, 5.4 Hz, 5-H$_B$), 4.52 (1H, dd, J = 7.5, 3.8 Hz, 2-H), 4.93 (1H, ddd, J = 7.2, 5.4, 2.8 Hz, 4-H), 7.00 (1H, d, J = 8.3 Hz, 9-H), 7.13 (1H, br s, 6-H), 7.14 (1H, dd, J = 8.3, 2.2 Hz, 8-H), 7.33 (2H, d, J = 8.5 Hz, 3′-H, 5′-H), 7.47 (2H, d, J = 8.5 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (5-C), 42.6 (3-C), 74.8 (2-C, 4-C), 121.1 (4′-C), 123.4 (9-C), 127.0 (8-C), 127.3 (5a-C), 128.3 (2′-C, 6′-C), 129.8 (6-C), 131.5 (7-C), 131.7 (3′-C, 5′-C), 142.5 (1′-C), 148.9 (9a-C). MS (EI): m/z (%) = 351 (^{79}Br, ^{35}Cl, 20) [M$^+$], 334 (10), 182 (13), 152 (13), 139 (100), 102 (23), 89 (30), 77 (30). Anal. Calcd for $C_{16}H_{13}BrClNO$: C, 54.81; H, 3.74; N, 3.99. Found: C, 54.77; H, 3.81; N, 3.90.

4.4.14. 1,4-Epoxy-2-*exo*-(4′-chlorophenyl)-7-fluoro-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6n)

Maroon viscous oil, 1.94 g (67%). IR (liquid film): ν = 1015 (–C–O–), 998 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.53 (1H, d, J = 16.8 Hz, 5-H_A), 2.53–2.62 (2H, m, 3-H_AH_B), 3.39 (1H, dd, J = 16.8, 5.6 Hz, 5-H_B), 4.53 (1H, dd, J = 7.2, 4.0 Hz, 2-H), 4.93 (1H, ddd, J = 6.4, 5.6, 2.6 Hz, 4-H), 6.83–6.88 (2H, m, 6-H, 8-H), 7.03 (1H, dd, J = 8.4, 5.2 Hz, 9-H), 7.32 (2H, d, J = 8.0 Hz, 3′-H, 5′-H), 7.39 (2H, d, J = 8.0 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.9 (5-C), 42.7 (3-C), 74.6 (2-C), 74.8 (4-C), 113.7 (8-C), 116.3 (d, J = 20.0 Hz, 6-C), 123.5 (d, J = 10.0 Hz, 9-C), 127.4 (5a-C), 127.9 (2′-C, 6′-C), 128.7 (3′-C, 5′-C), 132.9 (4′-C), 142.2 (1′-C), 146.3 (9a-C), 160.8 (d, J = 250.0 Hz, 7-C). MS (EI): m/z (%) = 289 (^{35}Cl, 20) [M^+], 272 (8), 260 (2), 246 (2), 148 (5), 122 (100), 109 (9), 95 (5). Anal. Calcd for $C_{16}H^{13}C$ lFNO: C, 66.33; H, 4.52; N, 4.83. Found: C, 66.19; H, 4.59; N, 4.88.

4.4.15. 1,4-Epoxy-2-*exo*-(2′-chlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6o)

White crystals, 1.71 g (63%), mp: 112–114 °C (from heptane). IR (KBr): ν = 1033 (–C–O–), 999 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.50 (1H, dddd, J = 12.7, 7.7, 2.8, 1.2 Hz, 3-H_B), 2.58 (1H, d, J = 16.6 Hz, 5-H_A), 2.74 (1H, ddd, J = 12.7, 8.7, 1.6 Hz, 3-H_A), 3.44 (1H, dd, J = 16.6, 5.3 Hz, 5-H_B), 4.91–4.94 (2H, m, 2-H, 4-H), 7.10 (1H, dd, J = 8.1, 2.0 Hz, 9-H), 7.16–7.21 (3H, m, 6-H, 7-H, 8-H), 7.22 (1H, td, J = 7.5, 1.5 Hz, 4′-H), 7.32 (1H, dd, J = 7.5, 1.1 Hz, 3′-H), 7.35 (1H, td, J = 7.7, 1.1 Hz, 5′-H), 7.90 (1H, dd, J = 7.7, 1.5 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (5-C), 42.4 (3-C), 72.5 (2-C), 75.0 (4-C), 122.0 (9-C), 125.3 (5a-C), 126.1 (7-C), 126.6 (8-C), 126.9 (3′-C), 127.8 (6′-C), 128.0 (4′-C), 129.1 (5′-C), 129.8 (6-C), 132.0 (2′-C), 141.1 (1′-C), 150.3 (9a-C). MS (EI): m/z (%) = 271 (^{35}Cl, 50) [M^+], 254 (19), 242 (2), 228 (2), 130 (4), 104 (100), 91 (25), 77 (26). Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.15. Found: C, 70.81; H, 5.28; N, 5.08.

4.4.16. 1,4-Epoxy-2-*exo*-(2′-fluorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6p)

Yellow crystals, 1.61 g (63%), mp: 54–55 °C (from heptane). IR (KBr): ν = 1029 (–C-O–), 998 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.55 (1H, dddd, J = 12.7, 7.7, 2.8, 1.4 Hz, 3-H_B), 2.57 (1H, d, J = 16.6 Hz, 5-H_A), 2.66 (1H, ddd, J = 12.7, 8.5, 1.9 Hz, 3-H_A), 3.44 (1H, dd, J = 16.6, 5.4 Hz, 5-H_B), 4.91 (1H, br d, J = 7.8 Hz, 2-H), 4.96 (1H, ddd, J = 7.5, 5.6, 1.2 Hz, 4-H), 7.04 (1H, ddd, J = 8.2, 8.0, 1.2 Hz, 3′-H), 7.10 (1H, dd, J = 6.4, 1.7 Hz, 9-H), 7.15–7.27 (5H, m, 6-H, 7-H, 8-H, 4′-H, 5′-H), 7.80 (1H, td, J = 7.6, 1.7 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.8 (5-C), 42.1 (3-C), 69.0 (d, J = 2.5 Hz, 2-C), 75.1 (4-C), 115.0 (d, J = 21.3 Hz, 3′-C), 122.1 (9-C), 124.3 (d, J = 3.4 Hz, 5′-C), 125.4 (5a-C), 126.2 (7-C), 126.8 (8-C), 128.0 (d, J = 4.0 Hz, 6′-C), 128.6 (d, J = 8.1 Hz, 4′-C), 129.9 (6-C), 130.8 (d, J = 13.2 Hz, 1′-C), 150.4 (9a-C), 159.9 (d, J = 243.4 Hz, 2′-C). MS (EI): m/z (%) = 255 (43) [M^+], 238 (15), 226 (4), 212 (5), 130 (4), 104 (100), 91 (17), 77 (15). Anal. Calcd for $C_{16}H_{14}FNO$: C, 75.28; H, 5.53; N, 5.49. Found: C, 75.14; H, 5.62; N, 5.42.

4.4.17. 1,4-Epoxy-2-*exo*-(2′-chlorophenyl)-7-methyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6q)

White crystals, 2.03 g (71%), mp: 122–124 °C (from heptane). IR (KBr): ν = 1017 (–C–O–), 969 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (3H, s, 7-CH_3), 2.48 (1H, dddd, J = 12.8, 7.7, 2.8, 1.5 Hz, 3-H_B), 2.54 (1H, d, J = 16.7 Hz, 5-H_A), 2.73 (1H, ddd, J = 12.8, 8.7, 1.8 Hz, 3-H_A), 3.39 (1H, dd, J = 16.7, 5.4 Hz, 5-H_B), 4.89 (1H, dd, J = 8.7, 2.8 Hz, 2-H), 4.90 (1H, ddd, J = 6.9, 5.4, 1.8 Hz, 4-H), 6.98 (2H, d, J = 6.4 Hz, 8-H, 9-H), 6.99 (1H, br s, 6-H), 7.22 (1H, td, J = 7.7, 1.6 Hz, 4′-H), 7.33 (1H, td, J = 7.7, 1.2 Hz, 5′-H), 7.36 (1H, dd, J = 7.7, 1.2 Hz, 3′-H), 7.89 (1H, dd, J = 7.7, 1.6 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.8 (5-C), 42.6 (3-C), 72.7 (2-C), 75.2 (4-C), 122.0 (9-C), 125.1 (5a-C), 127.0 (5′-C), 127.4 (8-C), 128.0 (6′-C), 128.1 (4′-C), 129.2 (3′-C), 130.4 (6-C), 132.2 (2′-C), 135.8 (7-C), 141.4 (1′-C), 148.0 (9a-C). MS (EI): m/z (%) = 285 (^{35}Cl, 51) [M^+], 268 (18), 256 (2), 242 (4), 144 (4), 118 (100), 91 (18), 77 (19). Anal. Calcd for $C_{17}H_{16}ClNO$: C, 71.45; H, 5.64; N, 4.90. Found: C, 71.56; H, 5.60; N, 4.81.

4.4.18. 7-Chloro-1,4-epoxy-2-*exo*-(2′-chlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6r)

White crystals, 2.14 g (70%), mp: 167–169 °C (from heptane). IR (KBr): ν = 1030 (–C–O–), 1000 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.49 (1H, dddd, J = 12.8, 7.7, 2.8, 1.2 Hz, 3-H_B), 2.55 (1H, d, J = 16.8 Hz, 5-H_A), 2.70 (1H, ddd, J = 12.8, 8.6, 1.6 Hz, 3-H_A), 3.39 (1H, dd, J = 16.8, 5.4 Hz, 5-H_B), 4.86 (1H, dd, J = 8.6, 2.8 Hz, 2-H), 4.90 (1H, ddd, J = 7.1, 5.4, 0.8 Hz, 4-H), 7.03 (1H, d, J = 8.2 Hz, 9-H), 7.15 (1H, s, 6-H), 7.16 (1H, d, J = 8.2 Hz, 8-H), 7.22 (1H, td, J = 7.7, 1.6 Hz, 4′-H), 7.31 (1H, dd, J = 7.7, 0.9 Hz, 3′-H), 7.34 (1H, td, J = 7.8, 0.9 Hz, 5′-H), 7.84 (1H, dd, J = 7.8, 1.6 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.5 (5-C), 42.4 (3-C), 72.4 (2-C), 74.6 (4-C), 123.4 (9-C), 126.8 (8-C), 126.9 (3′-C), 127.2 (4′-C), 127.3 (5a-C), 127.7 (6′-C), 129.1 (5′-C), 129.6 (6-C), 131.3 (7-C), 132.0 (2′-C), 140.7 (1′-C), 148.8 (9a-C). MS (EI): m/z (%) = 305 (^{35}Cl, 20) [M^+], 288 (7), 276 (1), 262 (1), 164 (5), 138 (100), 125 (12), 111 (4). Anal. Calcd for $C_{16}H^{13}C$ I_2NO: C, 62.76; H, 4.28; N, 4.57. Found: C, 62.65; H, 4.20; N, 4.65.

4.4.19. 7-Chloro-1,4-epoxy-2-*exo*-(2′-fluorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6s)

Yellow crystals, 1.91 g (66%), mp: 86–87 °C (from heptane). IR (KBr): ν = 1027 (–C–O–), 999 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.55 (1H, d, J = 16.8 Hz, 5-H_A), 2.54–2.61 (1H, m, 3-H_B), 2.64 (1H, ddd, J = 12.9, 8.4, 2.0 Hz, 3-H_A), 3.40 (1H, dd, J = 16.8, 5.4 Hz, 5-H_A), 4.84 (1H, d, J = 6.4 Hz, 2-H), 4.93 (1H, ddd, J = 7.1, 5.4, 1.8 Hz, 4-H), 7.03 (1H, td, J = 7.8, 1.0 Hz, 3′-H), 7.04 (1H, d, J = 7.8 Hz, 9-H), 7.14 (1H, br s, 6-H), 7.15 (1H, d, J = 7.8 Hz, 8-H), 7.18 (1H, td, J = 7.7, 1.0 Hz, 5′-H), 7.24–7.28 (1H, m, 4′-H), 7.44 (1H, td, J = 7.7, 1.6 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 42.0 (3-C), 69.0 (d, J = 2.0 Hz, 2-C), 74.8 (4-C), 115.2 (d, J = 21.0 Hz, 3′-C), 123.5 (9-C), 124.3 (d, J = 4.0 Hz, 5′-C), 127.0 (8-C), 127.3 (5a-C), 127.9 (d, J = 4.0 Hz, 6′-C), 128.7 (d, J = 8.0 Hz, 4′-C), 129.8 (6-C), 130.5 (d, J = 14.0 Hz, 1′-C), 131.5 (7-C), 149.0 (9a-C), 159.9 (d, J = 244.0 Hz, 2′-C). MS (EI): m/z (%) = 289 (^{35}Cl, 32) [M^+], 272 (8), 260 (4), 246 (3), 164 (3), 138 (100), 125 (6), 111 (2). Anal. Calcd for $C_{16}H^{13}C$ lFNO: C, 66.33; H, 4.52; N, 4.83. Found: C, 66.27; H, 4.60; N, 4.89.

4.4.20. 1,4-Epoxy-2-*exo*-(2′,6′-dichlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6t)

White crystals, 1.98 g (65%), mp: 171–172 °C (from heptane). IR (KBr): ν = 1022 (–C–O–), 996 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (1H, ddd, J = 12.9, 9.3, 1.9 Hz, 3-H_A), 2.61 (1H, d, J = 16.6 Hz, 5-H_A), 3.37 (1H, dddd, J = 12.9, 7.6, 3.0, 1.0 Hz, 3-H_B), 3.47 (1H, dd, J = 16.6, 5.4 Hz, 5-H_B), 5.15 (1H, ddd, J = 7.4, 5.4, 1.9 Hz, 4-H), 5.41 (1H, dd, J = 9.3, 3.0 Hz, 2-H), 7.13–7.19 (3H, m, 6-H, 7-H, 4′-H), 7.20 (1H, td, J = 8.0, 2.5 Hz, 8-H), 7.25 (1H, dd, J = 8.0, 1.0 Hz, 9-H), 7.37 (2H, d, J = 8.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.7 (5-C), 38.4 (3-C), 72.2 (2-C), 76.2 (4-C), 122.2 (9-C), 125.6 (5a-C), 126.2 (7-C), 126.7 (8-C), 129.1 (6-C), 129.9 (4′-C), 130.1 (3′-C, 5′-C), 135.9 (1′-C), 136.1 (2′-C, 6′-C), 151.3 (9a-C). MS (EI): m/z (%) = 305 (^{35}Cl, 8) [M^+], 288 (4), 276 (1), 262 (2), 130 (1), 104 (100), 91 (25), 77 (18). Anal. Calcd for $C_{16}H^{13}C$ I_2NO: C, 62.76; H, 4.28; N, 4.57. Found: C, 62.85; H, 4.19; N, 4.51.

4.4.21. 1,4-Epoxy-2-*exo*-(6′-chloro-2′-fluorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6u)

White crystals, 1.88 g (65%), mp: 160–161 °C (from heptane). IR (KBr): ν = 1025 (–C–O–), 991 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (1H, dddd, J = 12.6, 8.8, 4.7, 2.2 Hz, 3-H_B), 2.58 (1H, d, J = 16.4 Hz, 5-H_A), 3.07 (1H, ddd, J = 12.6, 7.7, 0.8 Hz, 3-H_A), 3.45 (1H, dd, J = 16.4, 5.1 Hz, 5-H_B), 5.11 (1H, ddd, J = 7.3, 5.1, 2.0 Hz, 4-H), 5.17 (1H, dd, J = 8.8, 0.9 Hz, 2-H), 7.00 (1H, ddd, J = 8.2, 8.0, 1.4 Hz, 3′-H), 7.12–7.25 (6H, m, 6-H, 7-H, 8-H, 9-H, 4′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.1 (5-C), 38.2 (d, J = 6.2 Hz, 3-C), 70.8 (d, J = 2.7 Hz, 2-C), 75.8 (d, J = 1.8 Hz, 4-C), 115.9 (d, J = 25.0 Hz, 3′-C), 122.1 (9-C), 125.5 (5a-C), 125.8 (d, J = 3.3 Hz, 5′-C), 126.2 (7-C), 126.7 (8-C), 127.1 (d, J = 14.5 Hz, 1′-C), 129.5 (d, J = 10.4 Hz, 4′-C), 129.9 (6-C), 136.1 (d, J = 6.7 Hz, 6′-C), 150.3 (9a-C), 161.9 (d, J = 248.0 Hz, 2′-C). MS (EI): m/z (%) = 289 (^{35}Cl, 32) [M^+], 272 (7), 260 (1), 246 (3), 130 (4), 104 (100), 91 (10), 77 (10). Anal. Calcd for $C_{16}H^{13}C$ lFNO: C, 66.33; H, 4.52; N, 4.83. Found: C, 66.22; H, 4.59; N, 4.88.

4.4.22. 7-Chloro-1,4-epoxy-2-*exo*-(2′,6′-dichlorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6v)

Yellow crystals, 2.14 g (63%), mp: 60–61 °C (from heptane). IR (KBr): ν = 1024 (–C–O–), 977 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.41 (1H, ddd, J = 12.9, 9.3, 1.9 Hz, 3-H_A), 2.59 (1H, d, J = 16.7 Hz, 5-H_A), 3.37 (1H, dddd, J = 12.9, 7.5, 3.1, 1.2 Hz, 3-H_B), 3.42 (1H, dd, J = 16.7, 5.3 Hz, 5-H_B), 5.13 (1H, ddd, J = 7.4, 5.3, 1.8 Hz, 4-H), 5.36 (1H, dd, J = 9.3, 3.1 Hz, 2-H), 7.13–7.17 (3H, m, 6-H, 8-H, 4′-H), 7.18 (1H, dd, J = 7.9, 0.6 Hz, 9-H), 7.36 (2H, d, J = 8.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.6 (5-C), 38.4 (3-C), 72.2 (2-C), 75.7 (4-C), 123.6 (9-C), 126.9 (8-C), 127.6 (5a-C), 129.3 (6-C), 129.8 (4′-C), 130.1 (3′-C, 5′-C), 135.5 (1′-C), 131.5 (7-C), 136.1 (2′-C, 6′-C), 149.7 (9a-C). MS (EI): m/z (%) = 339 (^{35}Cl, 9) [M^+], 324 (2), 312 (1), 298 (1), 164 (4), 138 (100), 125 (9), 111 (4). Anal. Calcd for $C_{16}H_{12}Cl_3NO$: C, 56.42; H, 3.55; N, 4.11. Found: C, 56.50; H, 3.62; N, 4.03.

4.4.23. 7-Chloro-1,4-epoxy-2-*exo*-(6′-chloro-2′-fluorophenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (6w)

White crystals, 1.97 g (61%), mp: 156–157 °C (from heptane). IR (KBr): ν = 1024 (–C–O–), 973 (–N–O–) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (1H, dddd, J = 12.7, 8.8, 4.7, 2.3 Hz, 3-H_B), 2.56 (1H, d, J = 16.6 Hz, 5-H_A), 3.09 (1H, ddd, J = 12.7, 7.6, 0.8 Hz, 3-H_A), 3.42 (1H, dd, J = 16.6, 5.1 Hz, 5-H_B), 5.08–5.13 (2H, m, 2-H, 4-H), 7.01 (1H, ddd, J = 8.1, 7.7, 1.7 Hz, 3′-H), 7.13 (1H, s, 6-H), 7.15–7.25 (3H, m, 8-H, 9-H, 4′-H), 7.26 (1H, dd, J = 8.4, 1.7 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.2 (5-C), 38.4 (d, J = 6.2 Hz, 3-C), 71.2 (d, J = 2.7 Hz, 2-C), 75.8 (d, J = 1.8 Hz, 4-C), 116.6 (d, J = 25.0 Hz, 3′-C), 124.3 (9-C), 126.6 (d, J = 3.4 Hz, 5′-C), 127.5 (d, J = 14.6 Hz, 1′-C), 127.7 (8-C), 128.2 (5a-C), 130.5 (d, J = 10.5 Hz, 4′-C), 130.6 (6-C), 132.2 (7-C), 136.9 (d, J = 6.7 Hz, 6′-C), 149.7 (9a-C), 162.9 (d, J = 252.1 Hz, 2′-C). MS (EI): m/z (%) = 323 (^{35}Cl, 17) [M^+], 306 (3), 294 (1), 280 (1), 164 (3), 138 (100), 125 (6), 111 (4). Anal. Calcd for $C_{16}H_{12}Cl_2FNO$: C, 59.28; H, 3.73; N, 4.32. Found: C, 59.16; H, 3.60; N, 4.21.

4.5. General procedures for the synthesis of *cis*-2-aryl-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepines 7a–w

Procedure 1: To a stirred solution of the appropriately substituted 1,4-epoxy-cycloadducts **6a–s** (0.010 mol) in 80% acetic acid (10–30 mL) was added zinc powder (0.060–0.080 mol). The resulting mixture was then stirred at 70–90 °C for 4–12 h (TLC control). After cooling to room temperature, each mixture was filtered and the filtrate was neutralized with a 25% ammonium hydroxide solution to pH 8, and then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and then concentrated under reduced pressure. The remaining crude material was purified by column chromatography on silica gel using heptane–ethyl acetate (compositions ranged from 15:1 to 1:1 v/v) as eluent to give amino-alcohols **7a–s**.

Procedure 2: To a stirred solution of the appropriately substituted 1,4-epoxy-cycloadducts **6t–w** (0.010 mol) in glacial acetic acid (10–15 mL) was added zinc powder (0.080 mol) and hydrochloric acid (37% HCl, 0.040 mol). The resulting mixture was then stirred at room temperature for 10–14 h (TLC control). Each mixture was filtered and the filtrate was neutralized with a 25% ammonium hydroxide solution to pH 8, and then extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and then concentrated under reduced pressure. The remaining crude material was purified by column chromatography on silica gel using heptane–ethyl acetate (compositions ranged from 15:1 to 1:1 v/v) as eluent to give amino-alcohols **7t–w**.

4.5.1. *cis*-4-Hydroxy-2-phenyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7a)

White crystals, 2.15 g (90%), mp: 97–99 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3341 (NH, OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.14 (1H, ddd, J = 11.1, 10.7, 10.5 Hz, 3-H_{ax}), 2.22 (1H, ddt, J = 10.7, 2.9, 1.9 Hz, 3-H_{eq}), 3.03 (1H, dt, J = 13.6, 1.9 Hz, 5-H_{eq}), 3.13 (1H, dd, J = 13.6, 10.5 Hz, 5-H_{ax}), 3.88 (1H, tdd, J = 10.2, 2.9, 1.9 Hz, 4-H_{ax}), 3.98 (1H, dd, J = 11.1, 1.9 Hz, 2-H_{ax}), 6.70 (1H, d, J = 7.6 Hz, 9-H), 6.92 (1H, t, J = 7.6 Hz, 7-H), 7.10 (1H, t, J = 7.6 Hz, 8-H), 7.18 (1H, d, J = 7.6 Hz, 6-H), 7.35 (1H, t, J = 6.9 Hz, 4′-H), 7.39 (2H, d, J = 6.9 Hz, 2′-H, 6′-H), 7.43 (2H, t, J = 7.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (5-C), 48.5 (3-C), 61.3 (2-C), 70.0 (4-C), 120.1 (9-C), 121.8 (7-C), 126.6 (2′-C, 6′-C), 127.4 (8-C), 127.8 (4′-C), 128.0 (5a-C), 129.9 (3′-C, 5′-C), 131.6 (6-C), 145.1 (1′-C), 149.4 (9a-C). MS (EI): m/z (%) = 239 (100) [M^+], 221 (3), 220 (16), 195 (72), 194 (94), 118 (98), 106 (57), 91 (30), 77 (27). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.44; H, 7.03; N, 5.76.

4.5.2. *cis*-4-Hydroxy-2-phenyl-7-trifluoromethoxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7b)

Maroon viscous oil, 2.49 g (77%). IR (liquid film): ν = 3354 (NH, OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.13 (1H, ddd, J = 12.9, 11.2, 9.9 Hz, 3-H_{ax}), 2.20 (1H, ddt, J = 12.9, 4.2, 2.0 Hz, 3-H_{eq}), 2.98 (1H, dt, J = 13.6, 2.2 Hz, 5-H_{eq}), 3.01 (1H, dd, J = 13.6, 10.1 Hz, 5-H_{ax}), 3.88 (1H, tdd, J = 10.0, 4.1, 1.6 Hz, 4-H_{ax}), 3.96 (1H, dd, J = 11.2, 2.3 Hz, 2-H_{ax}), 6.67 (1H, d, J = 8.4 Hz, 9-H), 6.93 (1H, dd, J = 8.4, 2.4 Hz, 8-H), 7.04 (1H, d, J = 2.4 Hz, 6-H), 7.31–7.45 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.4 (5-C), 48.1 (3-C), 61.1 (2-C), 69.5 (4-C), 120.0 (8-C), 120.6 (q, J = 256.0 Hz, 7-OCF_3), 120.8 (9-C), 124.2 (6-C), 126.4 (2′-C, 6′-C), 128.0 (4′-C), 129.0 (3′-C, 5′-C), 129.5 (5a-C), 143.5 (7-C), 144.3 (1′-C), 147.8 (9a-C). MS (EI): m/z (%) = 323 (80) [M^+], 305 (3), 304 (10), 279 (67), 278 (73), 202 (100), 190 (55), 175 (4), 161 (1). Anal. Calcd for $C_{17}H_{16}F_3NO_2$: C, 63.15; H, 4.99; N, 4.33. Found: C, 63.07; H, 4.87; N, 4.41.

4.5.3. 7-Bromo-*cis*-4-hydroxy-2-phenyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7c)

Maroon viscous oil, 2.73 g (86%). IR (liquid film): ν = 3346 (NH, OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (1H, ddd, J = 12.9, 11.3, 10.45 Hz, 3-H_{ax}), 2.20 (1H, ddt, J = 12.9, 4.1, 2.0 Hz, 3-H_{eq}), 2.95 (1H, dt, J = 13.6, 1.9 Hz, 5-H_{eq}), 3.06 (1H, dd, J = 13.6, 10.0 Hz, 5-H_{ax}), 3.86 (1H, tdd, J = 10.0, 4.1, 2.0 Hz, 4-H_{ax}), 3.94 (1H, dd, J = 11.3, 2.0 Hz, 2-H_{ax}), 6.56 (1H, d, J = 8.3 Hz, 9-H), 7.16 (1H, dd, J = 8.3, 2.2 Hz, 8-H), 7.29 (1H, d, J = 2.2 Hz, 6-H), 7.32–7.41 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$):

δ = 44.2 (5-C), 48.2 (3-C), 61.2 (2-C), 69.8 (4-C), 113.9 (7-C), 121.8 (9-C), 126.5 (2′-C, 6′-C), 128.1 (4′-C), 129.2 (3′-C, 5′-C), 130.2 (5a-C), 130.3 (8-C), 134.2 (6-C), 144.5 (1′-C), 148.4 (9a-C). MS (EI): *m*/*z* (%) = 317 (^{79}Br, 80) [M$^+$], 300 (10), 299 (7), 273 (40), 272 (23), 193 (60), 117 (100), 105 (57), 89 (50). Anal. Calcd for $C_{16}H_{16}BrNO$: C, 60.39; H, 5.07; N, 4.40. Found: C, 60.27; H, 5.17; N, 4.36.

4.5.4. 7-Chloro-*cis*-4-hydroxy-2-phenyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7d)

Maroon viscous oil, 2.22 g (81%). IR (liquid film): ν = 3350 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (1H, ddd, *J* = 13.1, 11.3, 10.0 Hz, 3-H$_{ax}$), 2.19 (1H, ddt, *J* = 13.1, 4.2, 2.1 Hz, 3-H$_{eq}$), 2.95 (1H, dt, *J* = 13.5, 1.9 Hz, 5-H$_{eq}$), 3.10 (1H, dd, *J* = 13.5, 10.2 Hz, 5-H$_{ax}$), 3.85 (1H, tdd, *J* = 10.0, 4.0, 1.5 Hz, 4-H$_{ax}$), 3.92 (1H, dd, *J* = 11.3, 2.2 Hz, 2-H$_{ax}$), 6.61 (1H, d, *J* = 8.3 Hz, 9-H), 7.03 (1H, dd, *J* = 8.3, 2.5 Hz, 8-H), 7.14 (1H, d, *J* = 2.4 Hz, 6-H), 7.31–7.43 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.1 (5-C), 48.1 (3-C), 61.2 (2-C), 69.6 (4-C), 121.4 (9-C), 126.5 (2′-C, 6′-C), 127.3 (7-C, 8-C), 128.1 (4′-C), 129.9 (3′-C, 5′-C), 129.9 (5a-C), 131.3 (6-C), 144.5 (1′-C), 147.8 (9a-C). MS (EI): *m*/*z* (%) = 273 (^{35}Cl, 100) [M$^+$], 255 (3), 254 (12), 229 (86), 228 (72), 152 (90), 140 (66), 125 (11), 111 (4), 99 (7). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.32; H, 5.78; N, 5.21.

4.5.5. 7-Fluoro-*cis*-4-hydroxy-2-phenyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7e)

Maroon viscous oil, 2.39 g (93%). IR (liquid film): ν = 3355 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (1H, ddd, *J* = 12.9, 11.2, 10.1 Hz, 3-H$_{ax}$), 2.19 (1H, ddt, *J* = 12.9, 4.0, 2.2 Hz, 3-H$_{eq}$), 2.93 (1H, dt, *J* = 13.5, 2.0 Hz, 5-H$_{eq}$), 3.11 (1H, dd, *J* = 13.5, 10.5 Hz, 5-H$_{ax}$), 3.76 (1H, tdd, *J* = 10.1, 3.8, 1.3 Hz, 4-H$_{ax}$), 3.89 (1H, dd, *J* = 11.2, 2.2 Hz, 2-H$_{ax}$), 6.63 (1H, dd, *J* = 8.4, 5.2 Hz, 9-H), 6.77 (1H, td, *J* = 8.3, 3.1 Hz, 8-H), 7.14 (1H, dd, *J* = 9.2, 3.1 Hz, 6-H), 7.33–7.42 (5H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3 (5-C), 48.3 (3-C), 61.4 (2-C), 69.6 (4-C), 113.6 (d, *J* = 22.0 Hz, 8-C), 117.7 (d, *J* = 22.0 Hz, 6-C), 121.1 (d, *J* = 8.1 Hz, 9-C), 126.3 (2′-C, 6′-C), 127.8 (4′-C), 128.9 (3′-C, 5′-C), 130.1 (d, *J* = 7.4 Hz, 5a-C), 144.4 (1′-C), 145.2 (9a-C), 158.0 (d, *J* = 239.9 Hz, 7-C). MS (EI): *m*/*z* (%) = 257 (57) [M$^+$], 239 (2), 238 (9), 213 (47), 212 (64), 136 (100), 124 (53), 109 (24), 95 (8), 83 (14). Anal. Calcd for $C_{16}H_{16}FNO$: C, 74.69; H, 6.27; N, 5.44. Found: C, 74.60; H, 6.33; N, 5.48.

4.5.6. *cis*-2-(4′-Chlorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7f)

Maroon viscous oil, 2.41 g (88%). IR (liquid film): ν = 3348 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08 (1H, ddd, *J* = 12.9, 11.2, 10.0 Hz, 3-H$_{ax}$), 2.13 (1H, ddt, *J* = 12.9, 4.2, 2.0 Hz, 3-H$_{eq}$), 3.00 (1H, dt, *J* = 13.4, 2.1 Hz, 5-H$_{eq}$), 3.10 (1H, dd, *J* = 13.4, 10.2 Hz, 5-H$_{ax}$), 3.85 (1H, tdd, *J* = 10.0, 4.1, 1.6 Hz, 4-H$_{ax}$), 3.93 (1H, dd, *J* = 11.2, 2.3 Hz, 2-H$_{ax}$), 6.70 (1H, dd, *J* = 7.8, 0.8 Hz, 9-H), 6.92 (1H, td, *J* = 7.4, 1.0 Hz, 7-H), 7.09 (1H, td, *J* = 7.7, 1.4 Hz, 8-H), 7.16 (1H, d, *J* = 7.4 Hz, 6-H), 7.35 (4H, d, *J* = 8.0 Hz, 2′-H, 3′-H, 5′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.5 (5-C), 48.3 (3-C), 60.5 (2-C), 69.8 (4-C), 120.2 (9-C), 122.0 (7-C), 127.5 (8-C), 127.8 (2′-C, 6′-C), 128.0 (5a-C), 129.0 (3′-C, 5′-C), 131.6 (6-C), 133.4 (4′-C), 143.0 (1′-C), 148.8 (9a-C). MS (EI): *m*/*z* (%) = 273 (^{35}Cl, 78) [M$^+$], 255 (10), 254 (12), 229 (68), 228 (63), 118 (100), 106 (89), 91 (33), 77 (45), 65 (19). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.31; H, 6.02; N, 5.01.

4.5.7. *cis*-2-(4′-Fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7g)

Maroon viscous oil, 2.34 g (91%). IR (liquid film): ν = 3340 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.01–2.21 (2H, m, 3-H$_{ax}$-H$_{eq}$), 3.01 (1H, d, *J* = 13.6 Hz, 5-H$_{eq}$), 3.13 (1H, dd, *J* = 13.6, 10.5 Hz, 5-H$_{ax}$), 3.86 (1H, tdd, *J* = 10.1, 4.4, 1.5 Hz, 4-H$_{ax}$), 3.95 (1H, dd, *J* = 10.8, 2.6 Hz, 2-H$_{ax}$), 6.74 (1H, d, *J* = 7.7 Hz, 9-H), 6.93 (1H, t, *J* = 7.6 Hz, 7-H), 7.06 (2H, t, *J* = 8.6 Hz, 3′-H, 5′-H), 7.10 (1H, td, *J* = 7.7, 1.2 Hz, 8-H), 7.17 (1H, d, *J* = 7.6 Hz, 6-H), 7.34–7.43 (2H, m, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.6 (3-C), 48.5 (5-C), 60.8 (2-C), 70.0 (4-C), 115.6 (d, *J* = 21.2 Hz, 3′-C, 5′-C), 120.5 (9-C), 122.4 (7-C, 5a-C), 127.8 (8-C), 128.2 (d, *J* = 7.9 Hz, 2′-C, 6′-C), 131.8 (6-C), 140.4 (1′-C), 148.7 (9a-C), 162.4 (d, *J* = 244.7 Hz, 4′-C). MS (EI): *m*/*z* (%) = 257 (63) [M$^+$], 239 (7), 238 (13), 213 (63), 212 (80), 118 (90), 106 (100), 91 (37), 77 (33), 65 (17). Anal. Calcd for $C_{16}H_{16}FNO$: C, 74.69; H, 6.27; N, 5.44. Found: C, 74.77; H, 6.18; N, 5.36.

4.5.8. *cis*-4-Hydroxy-2-(3′-methoxyphenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7h)

Yellow crystals, 2.42 g (90%), mp: 95–96 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3337 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (1H, ddd, *J* = 12.8, 11.3, 10.0 Hz, 3-H$_{ax}$), 2.21 (1H, ddt, *J* = 12.8, 4.1, 2.0 Hz, 3-H$_{eq}$), 3.02 (1H, dt, *J* = 13.5, 2.2 Hz, 5-H$_{eq}$), 3.11 (1H, dd, *J* = 13.5, 10.1 Hz, 5-H$_{ax}$), 3.85 (3H, s, 3′-OCH$_3$), 3.88 (1H, tdd, *J* = 9.9, 4.0, 1.2 Hz, 4-H$_{ax}$), 3.95 (1H, dd, *J* = 11.3, 2.0 Hz, 2-H$_{ax}$), 6.70 (1H, dd, *J* = 8.0, 1.0 Hz, 9-H), 6.87 (1H, dd, *J* = 8.1, 1.6 Hz, 4′-H), 6.91 (1H, td, *J* = 8.0, 1.0 Hz, 7-H), 6.98 (1H, d, *J* = 1.6 Hz, 2′-H), 6.99 (1H, d, *J* = 8.1 Hz, 6′-H), 7.08 (1H, td, *J* = 8.0, 1.0 Hz, 8-H), 7.17 (1H, dd, *J* = 8.0, 1.0 Hz, 6-H), 7.30 (1H, t, *J* = 8.1 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (5-C), 48.6 (3-C), 55.4 (3′-O*C*H$_3$), 61.3 (2-C), 70.1 (4-C), 112.1 (2′-C), 113.4 (4′-C), 118.9 (6′-C), 120.3 (9-C), 121.9 (7-C), 127.6 (8-C), 128.1 (5a-C), 130.1 (5′-C), 131.8 (6-C), 146.5 (1′-C), 149.3 (9a-C), 160.2 (3′-C). MS (EI): *m*/*z* (%) = 269 (90) [M$^+$], 251 (3), 250 (7), 225 (63), 224 (70), 145 (7), 118 (100), 106 (57), 91 (33), 77 (23). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.92; H, 7.00; N, 5.28.

4.5.9. *cis*-4-Hydroxy-2-(3′-methylphenyl)-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7i)

Maroon viscous oil, 2.30 g (91%). IR (liquid film): ν = 3356 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (1H, ddd, *J* = 12.9, 11.0, 10.4 Hz, 3-H$_{ax}$), 2.21 (1H, ddt, *J* = 12.9, 4.1, 2.1 Hz, 3-H$_{eq}$), 2.41 (3H, s, 3′-CH$_3$), 3.03 (1H, dt, *J* = 13.5, 2.0 Hz, 5-H$_{eq}$), 3.13 (1H, dd, *J* = 13.5, 10.2 Hz, 5-H$_{ax}$), 3.88 (1H, tdd, *J* = 9.9, 4.1, 1.5 Hz, 4-H$_{ax}$), 3.94 (1H, dd, *J* = 11.0, 2.3 Hz, 2-H$_{ax}$), 6.70 (1H, d, *J* = 7.8 Hz, 9-H), 6.92 (1H, td, *J* = 7.5, 0.9 Hz, 7-H), 7.10 (1H, td, *J* = 7.6, 0.8 Hz, 8-H), 7.17 (1H, br d, *J* = 7.5 Hz, 4′-H), 7.18 (1H, d, *J* = 7.6 Hz, 6-H), 7.23 (1H, d, *J* = 7.4 Hz, 6′-H), 7.27 (1H, br s, 2′-H), 7.30 (1H, t, *J* = 7.4 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (3′-*C*H$_3$), 44.5 (5-C), 48.3 (3-C), 61.1 (2-C), 70.0 (4-C), 120.1 (9-C), 121.7 (7-C), 123.4 (6′-C), 127.1 (2′-C), 127.4 (8-C), 128.0 (5a-C), 128.5 (4′-C), 128.8 (5′-C), 131.6 (6-C), 138.6 (3′-C), 144.6 (1′-C), 149.2 (9a-C). MS (EI): *m*/*z* (%) = 253 (87) [M$^+$], 235 (2), 234 (9), 209 (70), 208 (88), 118 (100), 106 (55), 91 (50), 77 (29), 65 (21). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.73; H, 7.50; N, 5.61.

4.5.10. *cis*-2-(3′-Chlorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7j)

Maroon viscous oil, 2.34 g (87%). IR (liquid film): ν = 3347 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08 (1H, ddd, *J* = 13.0, 11.2, 10.2 Hz, 3-H$_{ax}$), 2.17 (1H, ddt, *J* = 13.0, 4.0, 2.0 Hz, 3-H$_{eq}$), 3.00 (1H, dt, *J* = 13.5, 1.9 Hz, 5-H$_{eq}$), 3.11 (1H, dd, *J* = 13.5, 10.2 Hz, 5-H$_{ax}$), 3.85 (1H, tdd, *J* = 10.2, 3.6, 2.8 Hz, 4-H$_{ax}$), 3.93 (1H, dd, *J* = 11.2, 1.6 Hz, 2-H$_{ax}$), 6.70 (1H, d, *J* = 8.0 Hz, 9-H), 6.93 (1H, t, *J* = 8.0 Hz, 7-H), 7.10 (1H, td, *J* = 8.0, 1.0 Hz, 8-H), 7.16 (1H, d, *J* = 8.0 Hz, 6-H), 7.29–7.32 (3H, m, 4′-H, 5′-H, 6′-H), 7.44 (1H, s, 2′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.5 (5-C), 48.2 (3-C), 60.7

(2-C), 69.7 (4-C), 120.2 (9-C), 122.0 (7-C), 124.6 (6′-C), 126.0 (2′-C), 127.5 (5′-C), 127.9 (5a-C), 128.0 (4′-C), 130.2 (8-C), 131.6 (6-C), 134.6 (3′-C), 146.5 (1′-C), 148.7 (9a-C). MS (EI): *m*/*z* (%) = 273 (^{35}Cl, 45) [M$^+$], 255 (2), 254 (9), 229 (35), 228 (30), 118 (100), 106 (49), 91 (27), 77 (32), 65 (13). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.32; H, 5.82; N, 5.20.

4.5.11. *cis*-4-Hydroxy-2-(4′-methylphenyl)-7-methyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7k)

Maroon viscous oil, 2.32 g (87%). IR (liquid film): ν = 3340 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (1H, ddd, *J* = 13.4, 11.1, 10.2 Hz, 3-H$_{ax}$), 2.18 (1H, ddt, *J* = 13.4, 4.0, 2.0 Hz, 3-H$_{eq}$), 2.28 (3H, s, 7-CH$_3$), 2.35 (3H, s, 4′-CH$_3$), 2.96 (1H, dt, *J* = 13.6, 1.95 Hz, 5-H$_{eq}$), 3.10 (1H, dd, *J* = 13.6, 10.2 Hz, 5-H$_{ax}$), 3.85 (1H, tdd, *J* = 10.1, 4.1, 2.5 Hz, 4-H$_{ax}$), 3.90 (1H, dd, *J* = 11.1, 2.3 Hz, 2-H$_{ax}$), 6.59 (1H, d, *J* = 7.8 Hz, 9-H), 6.88 (1H, dd, *J* = 7.8, 1.4 Hz, 8-H), 6.99 (1H, s, 6-H), 7.19 (2H, d, *J* = 8.0 Hz, 3′-H, 5′-H), 7.31 (2H, d, *J* = 8.0 Hz, 2′-H, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (7-CH$_3$), 21.3 (4′-CH$_3$), 44.6 (5-C), 48.8 (3-C), 61.3 (2-C), 70.3 (4-C), 120.2 (9-C), 126.5 (2′-C, 6′-C), 128.0 (5a-C, 8-C), 129.7 (3′-C, 5′-C), 131.2 (7-C), 132.4 (6-C), 137.6 (4′-C), 142.1 (1′-C), 147.0 (9a-C). MS (EI): *m*/*z* (%) = 267 (100) [M$^+$], 249 (2), 248 (7), 223 (71), 222 (65), 132 (51), 120 (73), 91 (27), 77 (18), 65 (7). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.80; H, 8.03; N, 5.15.

4.5.12. 7-Chloro-*cis*-2-(4′-chlorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)- benzazepine (7l)

White crystals, 2.70 g (88%), mp: 106–107 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3354 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.04 (1H, dd, *J* = 12.8, 11.6 Hz, 3-H$_{ax}$), 2.14 (1H, ddt, *J* = 12.8, 4.0, 1.8 Hz, 3-H$_{eq}$), 2.93 (1H, d, *J* = 13.6 Hz, 5-H$_{eq}$), 3.05 (1H, dd, *J* = 13.6, 10.5 Hz, 5-H$_{ax}$), 3.82 (1H, tdd, *J* = 10.1, 4.4, 2.2 Hz, 4-H$_{ax}$), 3.89 (1H, dd, *J* = 11.6, 2.0 Hz, 2-H$_{ax}$), 6.61 (1H, d, *J* = 8.0 Hz, 9-H), 7.03 (1H, dd, *J* = 8.0, 2.4 Hz, 8-H), 7.13 (1H, d, *J* = 2.4 Hz, 6-H), 7.34 (2H, d, *J* = 7.6 Hz, 2′-H, 6′-H), 7.36 (2H, d, *J* = 7.6 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.3 (5-C), 48.2 (3-C), 60.6 (2-C), 69.2 (4-C), 121.5 (9-C), 126.7 (7-C), 127.3 (8-C), 127.9 (2′-C, 6′-C), 129.3 (3′-C, 5′-C), 129.8 (5a-C), 131.3 (6-C), 133.7 (4′-C), 142.9 (1′-C), 147.5 (9a-C). MS (EI): *m*/*z* (%) = 307 (^{35}Cl, 62) [M$^+$], 289 (2), 288 (7), 263 (54), 262 (34), 152 (72), 140 (100), 125 (29), 111 (9), 99 (9). Anal. Calcd for $C_{16}H_{15}Cl_2NO$: C, 62.35; H, 4.91; N, 4.54. Found: C, 62.40; H, 4.98; N, 4.51.

4.5.13. *cis*-2-(4′-Bromophenyl)-7-chloro-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7m)

White crystals, 3.10 g (88%), mp: 150–151 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3352 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (1H, ddd, *J* = 12.9, 11.3, 10.6 Hz, 3-H$_{ax}$), 2.15 (1H, ddt, *J* = 12.9, 3.9, 1.9 Hz, 3-H$_{eq}$), 2.94 (1H, d, *J* = 13.6 Hz, 5-H$_{eq}$), 3.07 (1H, dd, *J* = 13.6, 10.5 Hz, 5-H$_{ax}$), 3.83 (1H, tdd, *J* = 10.5, 4.0, 2.6 Hz, 4-H$_{ax}$), 3.89 (1H, dd, *J* = 11.2, 2.1 Hz, 2-H$_{ax}$), 6.95 (1H, d, *J* = 8.0 Hz, 9-H), 7.03 (1H, dd, *J* = 8.0, 2.3 Hz, 8-H), 7.14 (1H, d, *J* = 2.3 Hz, 6-H), 7.29 (2H, d, *J* = 8.4 Hz, 2′-H, 6′-H), 7.36 (2H, d, *J* = 8.4 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.2 (5-C), 48.1 (3-C), 60.8 (2-C), 69.6 (4-C), 121.7 (9-C), 121.9 (4′-C), 127.3 (8-C), 127.4 (7-C), 128.3 (2′-C, 6′-C), 129.8 (5a-C), 131.4 (6-C), 132.3 (3′-C, 5′-C), 142.9 (1′-C), 147.5 (9a-C). MS (EI): *m*/*z* (%) = 353 (^{79}Br, ^{35}Cl, 77) [M$^+$], 335 (13), 334 (17), 309 (57), 308 (43), 182 (40), 140 (100), 104 (30), 89 (30), 77 (43). Anal. Calcd for $C_{16}H_{15}BrClNO$: C, 54.49; H, 4.29; N, 3.97. Found: C, 54.61; H, 4.20; N, 4.05.

4.5.14. *cis*-2-(4′-Chlorophenyl)-7-fluoro-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7n)

White crystals, 2.57 g (88%), mp: 130–132 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3358 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (1H, ddd, *J* = 12.9, 11.8, 10.5 Hz, 3-H$_{ax}$), 2.14 (1H, ddt, *J* = 12.9, 4.0, 2.0 Hz, 3-H$_{eq}$), 2.91 (1H, dt, *J* = 13.5, 2.0 Hz, 5-H$_{eq}$), 3.09 (1H, dd, *J* = 13.5, 10.0 Hz, 5-H$_{ax}$), 3.81 (1H, tdd, *J* = 10.0, 4.0, 2.0 Hz, 4-H$_{ax}$), 3.86 (1H, dd, *J* = 11.8, 2.0 Hz, 2-H$_{ax}$), 6.64 (1H, dd, *J* = 8.8, 5.2 Hz, 9-H), 6.77 (1H, td, *J* = 8.8, 3.2 Hz, 8-H), 6.87 (1H, dd, *J* = 9.6, 3.2 Hz, 6-H), 7.33 (2H, d, *J* = 8.8 Hz, 2′-H, 6′-H), 7.35 (2H, d, *J* = 8.8 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.4 (5-C), 48.5 (3-C), 60.9 (2-C), 69.5 (4-C), 113.8 (d, *J* = 20.0 Hz, 8-C), 117.9 (d, *J* = 20.0 Hz, 6-C), 121.4 (9-C), 127.9 (2′-C, 6′-C), 129.2 (3′-C, 5′-C), 130.3 (d, *J* = 10.0 Hz, 5a-C), 133.7 (4′-C), 143.0 (1′-C), 145.0 (9a-C), 158.3 (d, *J* = 230.0 Hz, 7-C). MS (EI): *m*/*z* (%) = 291 (^{35}Cl, 78) [M$^+$], 273 (2), 272 (9), 247 (1), 246 (50), 136 (100), 124 (82), 109 (27), 95 (8), 83 (16). Anal. Calcd for $C_{16}H_{15}ClFNO$: C, 65.87; H, 5.18; N, 4.80. Found: C, 65.81; H, 5.23; N, 4.73.

4.5.15. *cis*-2-(2′-Chlorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7o)

White crystals, 2.35 g (86%), mp: 141–142 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3278 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (1H, ddd, *J* = 12.7, 11.4, 10.0 Hz, 3-H$_{ax}$), 2.26 (1H, ddt, *J* = 12.7, 3.7, 1.9 Hz, 3-H$_{eq}$), 3.02 (1H, dt, *J* = 13.5, 2.0 Hz, 5-H$_{eq}$), 3.15 (1H, dd, *J* = 13.5, 10.0 Hz, 5-H$_{ax}$), 3.92 (1H, tdd, *J* = 10.2, 3.5, 2.9 Hz, 4-H$_{ax}$), 4.45 (1H, br d, *J* = 11.4 Hz, 2-H$_{ax}$), 6.80 (1H, br s, 9-H), 6.95 (1H, t, *J* = 7.5 Hz, 7-H), 7.13 (1H, td, *J* = 7.5, 1.1 Hz, 8-H), 7.20 (1H, dd, *J* = 7.5, 1.1 Hz, 6-H), 7.26 (1H, td, *J* = 7.6, 1.3 Hz, 4′-H), 7.33 (1H, t, *J* = 7.6 Hz, 5′-H), 7.41 (1H, dd, *J* = 7.8, 1.3 Hz, 3′-H), 7.69 (1H, dd, *J* = 7.6, 1.3 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.7 (5-C), 46.6 (3-C), 56.3 (2-C), 70.0 (4-C), 120.5 (9-C), 122.0 (7-C), 127.1 (6′-C), 127.5 (5′-C, 8-C), 128.2 (5a-C), 128.8 (4′-C), 129.8 (3′-C), 131.5 (6-C), 132.7 (2′-C), 141.9 (1′-C), 149.0 (9a-C). MS (EI): *m*/*z* (%) = 273 (^{35}Cl, 73) [M$^+$], 256 (11), 254 (10), 229 (39), 228 (29), 118 (100), 106 (48), 91 (26), 77 (33), 65 (15). Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.33; H, 5.80; N, 5.18.

4.5.16. *cis*-2-(2′-Fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7p)

White crystals, 2.26 g (88%), mp: 89–90 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3356 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (1H, ddd, *J* = 12.7, 11.5, 10.2 Hz, 3-H$_{ax}$), 2.21 (1H, ddt, *J* = 12.7, 4.0, 2.4 Hz, 3-H$_{eq}$), 3.02 (1H, dt, *J* = 13.5, 2.0 Hz, 5-H$_{eq}$), 3.14 (1H, dd, *J* = 13.5, 10.3 Hz, 5-H$_{ax}$), 3.89 (1H, tdd, *J* = 10.2, 4.0, 2.0 Hz, 4-H$_{ax}$), 4.36 (1H, dd, *J* = 11.5, 2.4 Hz, 2-H$_{ax}$), 6.74 (1H, d, *J* = 7.6 Hz, 9-H), 6.93 (1H, td, *J* = 7.6, 1.0 Hz, 7-H), 7.07–7.12 (1H, m, 8-H), 7.18 (1H, d, *J* = 7.6 Hz, 6-H), 7.28–7.34 (3H, m, 3′-H, 4′-H, 5′-H), 7.61 (1H, td, *J* = 7.5, 1.6 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.6 (5-C), 47.1 (3-C), 53.2 (d, *J* = 2.5 Hz, 2-C), 70.0 (4-C), 115.8 (d, *J* = 22.2 Hz, 3′-C), 120.5 (9-C), 122.2 (7-C), 124.8 (d, *J* = 3.6 Hz, 5′-C), 127.4 (d, *J* = 3.9 Hz, 6′-C), 127.6 (8-C), 128.3 (5a-C), 129.3 (d, *J* = 8.3 Hz, 4′-C), 131.4 (d, *J* = 13.6 Hz, 1′-C), 131.7 (6-C), 149.1 (9a-C), 159.5 (d, *J* = 245.1 Hz, 2′-C). MS (EI): *m*/*z* (%) = 257 (83) [M$^+$], 239 (3), 238 (16), 213 (78), 212 (100), 118 (87), 106 (48), 91 (19), 77 (13), 65 (5). Anal. Calcd for $C_{16}H_{16}FNO$: C, 74.69; H, 6.27; N, 5.44. Found: C, 74.80; H, 6.35; N, 5.32.

4.5.17. *cis*-2-(2′-Chlorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7q)

White crystal, 2.56 g (89%), mp: 128–130 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3284 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (1H, ddd, *J* = 12.3, 11.3, 10.3 Hz, 3-H$_{ax}$), 2.24 (1H, ddt, *J* = 12.3, 3.5, 1.3 Hz, 3-H$_{eq}$), 2.27 (3H, s, 7-CH$_3$), 2.96 (1H, dt, *J* = 13.5, 2.7 Hz, 5-H$_{eq}$), 3.12 (1H, dd, *J* = 13.5, 10.6 Hz, 5-H$_{ax}$), 3.89 (1H, tdd, *J* = 10.3, 3.5, 2.7 Hz, 4-H$_{ax}$), 4.39 (1H, dd, *J* = 11.3, 1.3 Hz, 2-H$_{ax}$), 6.68 (1H, d, *J* = 7.7 Hz, 9-H), 6.92

(1H, d, J = 7.7 Hz, 8-H), 7.00 (1H, s, 6-H), 7.26 (1H, td, J = 7.9, 1.4 Hz, 4′-H), 7.34 (1H, td, J = 7.9, 1.0 Hz, 5′-H), 7.41 (1H, dd, J = 7.9, 1.0 Hz, 3′-H), 7.67 (1H, dd, J = 7.9, 1.4 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (7-*C*H$_3$), 44.8 (5-C), 46.8 (3-C), 56.6 (2-C), 70.2 (4-C), 120.6 (9-C), 127.3 (6′-C), 127.6 (5′-C), 128.1 (8-C), 128.4 (5a-C), 128.8 (4′-C), 129.9 (3′-C), 131.5 (7-C), 132.3 (6-C), 132.8 (2′-C), 141.9 (1′-C), 146.9 (9a-C). MS (EI): m/z (%) = 287 (^{35}Cl, 85) [M$^+$], 270 (9), 268 (8), 243 (44), 242 (27), 132 (100), 120 (60), 105 (9), 91 (4), 79 (6). Anal. Calcd for $C_{17}H_{18}ClNO$: C, 70.

4.5.18. 7-Chloro-*cis*-2-(2′-chlorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7r)

White crystals, 2.67 g (87%), mp: 132–134 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3280 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.07 (1H, dd, J = 12.7, 11.3 Hz, 3-H$_{ax}$), 2.24 (1H, ddt, J = 12.7, 3.8, 1.9 Hz, 3-H$_{eq}$), 2.95 (1H, dt, J = 13.6, 2.0 Hz, 5-H$_{eq}$), 3.09 (1H, dd, J = 13.6, 10.2 Hz, 5-H$_{ax}$), 3.89 (1H, tdd, J = 10.2, 3.8, 1.0 Hz, 4-H$_{ax}$), 4.39 (1H, dd, J = 11.3, 1.9 Hz, 2-H$_{ax}$), 6.71 (1H, d, J = 8.3 Hz, 9-H), 7.05 (1H, dd, J = 8.3, 2.4 Hz, 8-H), 7.16 (1H, d, J = 2.4 Hz, 6-H), 7.27 (1H, td, J = 7.8, 2.0 Hz, 4′-H), 7.33 (1H, td, J = 7.8, 1.2 Hz, 5′-H), 7.41 (1H, dd, J = 7.8, 1.2 Hz, 3′-H), 7.64 (1H, dd, J = 7.8, 2.0 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.4 (5-C), 46.3 (3-C), 56.5 (2-C), 69.8 (4-C), 121.8 (9-C), 127.0 (7-C), 127.2 (8-C), 127.4 (6′-C), 127.7 (5′-C), 129.1 (4′-C), 130.0 (3′-C), 130.2 (5a-C), 131.3 (6-C), 132.8 (2′-C), 141.6 (1′-C), 148.0 (9a-C). MS (EI): m/z (%) = 307 (^{35}Cl, 79) [M$^+$], 290 (12), 288 (8), 263 (69), 262 (23), 152 (100), 140 (69), 125 (24), 111 (5), 99 (7). Anal. Calcd for $C_{16}H_{15}Cl_2NO$: C, 62.35; H, 4.91; N, 4.54. Found: C, 62.27; H, 5.03; N, 4.61.

4.5.19. 7-Chloro-*cis*-2-(2′-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7s)

White crystals, 2.42 g (83%), mp: 124–125 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3289 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13–2.21 (2H, m, 3-H$_{ax}$H$_{eq}$), 2.96 (1H, d, J = 13.6 Hz, 5-H$_{eq}$), 3.43 (1H, dd, J = 13.6, 10.5 Hz, 5-H$_{ax}$), 3.87 (1H, tdd, J = 10.5, 3.0, 2.1 Hz, 4-H$_{ax}$), 4.31 (1H, dd, J = 10.7, 2.4 Hz, 2-H$_{ax}$), 6.69 (1H, d, J = 8.0 Hz, 9-H), 7.04 (1H, dd, J = 8.0, 2.0 Hz, 8-H), 7.10 (1H, d, J = 9.8 Hz, 3′-H), 7.15 (1H, d, J = 2.0 Hz, 6-H), 7.18 (1H, t, J = 7.5 Hz, 5′-H), 7.28–7.33 (1H, m, 4′-H), 7.58 (1H, td, J = 7.5, 1.6 Hz, 6′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.2 (5-C), 46.7 (3-C), 53.3 (2-C), 69.7 (4-C), 115.9 (d, J = 22.0 Hz, 3′-C), 121.8 (9-C), 124.9 (d, J = 3.5 Hz, 5′-C), 127.1 (7-C), 127.4 (d, J = 4.4 Hz, 6′-C), 127.4 (8-C), 129.5 (d, J = 8.3 Hz, 4′-C), 130.2 (5a-C), 130.8 (1′-C), 131.3 (6-C), 147.8 (9a-C), 159.5 (d, J = 245.2 Hz, 2′-C). MS (EI): m/z (%) = 291 (^{35}Cl, 100) [M$^+$], 273 (2), 272 (12), 246 (85), 245 (64), 152 (68), 140 (48), 125 (9), 111 (3), 99 (4). Anal. Calcd for $C_{16}H_{15}ClFNO$: C, 65.87; H, 5.18; N, 4.80. Found: C, 65.80; H, 5.25; N, 4.77.

4.5.20. *cis*-2-(2′,6′-Dichlorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7t)

Maroon crystals, 2.61 g (85%), mp: 67–68 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3351 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.02 (1H, ddd, J = 13.1, 11.7, 9.6 Hz, 3-H$_{ax}$), 2.77 (1H, ddt, J = 13.1, 4.1, 1.2 Hz, 3-H$_{eq}$), 3.12 (1H, dd, J = 14.1, 2.0 Hz, 5-H$_{eq}$), 3.16 (1H, dd, J = 14.1, 8.2 Hz, 5-H$_{ax}$), 4.03 (1H, tdd, J = 8.4, 5.0, 1.4 Hz, 4-H$_{ax}$), 5.06 (1H, dd, J = 11.7, 2.2 Hz, 2-H$_{ax}$), 6.69 (1H, d, J = 7.8 Hz, 9-H), 6.89 (1H, td, J = 7.4, 1.0 Hz, 7-H), 7.08 (1H, td, J = 7.6, 1.4 Hz, 8-H), 7.16 (1H, d, J = 7.4 Hz, 6-H), 7.17 (1H, t, J = 8.0 Hz, 4′-H), 7.40 (2H, d, J = 8.0 Hz, 3′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.5 (3-C), 43.5 (5-C), 57.2 (2-C), 70.5 (4-C), 119.9 (9-C), 121.6 (7-C), 127.3 (5a-C), 127.6 (8-C), 128.9 (3′-C, 5′-C), 129.2 (4′-C), 131.9 (6-C), 135.0 (2′-C, 6′-C), 138.1 (1′-C), 148.9 (9a-C). MS (EI): m/z (%) = 307 (^{35}Cl, 18) [M$^+$], 289 (1), 288 (4), 263 (13), 262 (5), 118 (100), 106 (22), 91 (23), 77 (15), 65 (10). Anal. Calcd for $C_{16}H_{15}Cl_2NO$: C, 62.35; H, 4.91; N, 4.54. Found: C, 62.27; H, 5.03; N, 4.61.

4.5.21. *cis*-2-(6′-Chloro-2′-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)- benzazepine (7u)

Maroon crystals, 2.45 g (84%), mp: 55–56 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3349 (NH, OH) cm^{-1}. H NMR (400 MHz, $CDCl_3$): δ = 2.10 (1H, ddd, J = 12.7, 11.4, 9.9 Hz, 3-H$_{ax}$), 2.26 (1H, ddt, J = 12.7, 3.7, 1.9 Hz, 3-H$_{eq}$), 3.02 (1H, dt, J = 13.5, 2.0 Hz, 5-H$_{eq}$), 3.15 (1H, dd, J = 13.5, 9.9 Hz, 5-H$_{ax}$), 3.92 (1H, tt, J = 9.9, 2.9 Hz, 4-H$_{ax}$), 4.45 (1H, d, J = 11.4 Hz, 2-H$_{ax}$), 6.80 (1H, br. s, 9-H), 6.95 (1H, t, J = 7.4 Hz, 7-H), 7.13 (1H, td, J = 7.5, 1.1 Hz, 8-H), 7.26 (1H, td, J = 7.4, 1.3 Hz, 4′-H), 7.20 (1H, dd, J = 7.4, 1.1 Hz, 6-H), 7.69 (1H, dd, J = 7.8, 1.3 Hz, 3′-H), 7.33 (1H, d, J = 7.6 Hz, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.2 (5-C), 46.6 (3-C), 55.5 (2-C), 70.3 (4-C), 115.8 (d, J = 22.1 Hz, 3′-C), 120.6 (9-C), 122.1 (7-C), 126.1 (5′-C), 127.5 (8-C), 128.0 (d, J = 14.0 Hz, 1′-C), 128.6 (5a-C), 129.6 (4′-C), 131.8 (6-C), 134.2 (d, J = 8.0 Hz, 6′-C), 148.6 (9a-C), 163.3 (d, J = 245.0 Hz, 2′-C). MS (EI): m/z (%) = 291 (^{35}Cl, 38) [M$^+$], 273 (1), 272 (5), 247 (28), 246 (19), 118 (100), 106 (34), 91 (24), 77 (15), 65 (10). Anal. Calcd for $C_{16}H_{15}ClFNO$: C, 65.87; H, 5.18; N, 4.80. Found: C, 65.81; H, 5.24; N, 4.84.

4.5.22. 7-Chloro-*cis*-2-(2′,6′-dichlorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7v)

Yellow crystals, 2.90 g (85%), mp: 60–61 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3361 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.15 (1H, ddt, J = 13.0, 3.8, 1.2 Hz, 3-H$_{eq}$), 2.55 (1H, ddd, J = 13.0, 11.7, 10.0 Hz, 3-H$_{ax}$), 3.08 (1H, dt, J = 13.5, 2.0 Hz, 5-H$_{eq}$), 3.17 (1H, dd, J = 13.5, 9.0 Hz, 5-H$_{ax}$), 3.89 (1H, tdd, J = 8.5, 4.1, 2.5 Hz, 4-H$_{ax}$), 4.67 (1H, d, J = 11.7 Hz, 2-H$_{ax}$), 6.73 (1H, d, J = 7.7 Hz, 9-H), 6.93 (1H, td, J = 7.5, 1.0 Hz, 7-H), 7.08 (1H, dd, J = 8.0, 1.7 Hz, 3′-H), 7.10 (1H, td, J = 7.5, 1.7 Hz, 8-H), 7.18 (1H, dd, J = 7.3, 1.7 Hz, 6-H), 7.21–7.24 (2H, m, 4′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1 (3-C), 43.0 (5-C), 57.1 (2-C), 70.1 (4-C), 121.0 (9-C), 126.1 (7-C), 127.3 (8-C), 129.0 (3′-C, 5′-C), 129.3 (5a-C, 4′-C), 131.4 (6-C), 135.0 (2′-C, 6′-C), 137.9 (1′-C), 147.5 (9a-C). MS (EI): m/z (%) = 341 (^{35}Cl, 31) [M$^+$], 324 (6), 322 (4), 297 (25), 296 (5), 152 (100), 140 (31), 125 (13), 111 (10), 99 (11). Anal. Calcd for $C_{16}H_{14}Cl_3NO$: C, 56.08; H, 4.12; N, 4.09. Found: C, 56.16; H, 4.20; N, 3.99.

4.5.23. 7-Chloro-*cis*-2-(6′-chloro-2′-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydro-1(1*H*)-benzazepine (7w)

Maroon crystals, 2.47 g (76%), mp: 111–112 °C (from heptane–ethyl acetate, 20:1). IR (KBr): ν = 3355 (NH, OH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (1H, ddt, J = 12.7, 3.3, 1.6 Hz, 3-H$_{eq}$), 2.53 (1H, ddd, J = 12.7, 11.7, 10.2 Hz, 3-H$_{ax}$), 3.02–3.11 (2H, m, 5-H$_{eq}$H$_{ax}$), 3.94 (1H, tdd, J = 8.9, 4.7, 0.2 Hz, 4-H$_{ax}$), 4.65 (1H, d, J = 11.7 Hz, 2-H$_{ax}$), 6.64 (1H, d, J = 8.4 Hz, 9-H), 7.03 (1H, dd, J = 8.4, 2.1 Hz, 8-H), 7.07 (1H, dd, J = 7.2, 3.3 Hz, 3′-H), 7.15 (1H, d, J = 2.1 Hz, 6-H), 7.22–7.25 (2H, m, 4′-H, 5′-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 43.4 (5-C), 43.7 (3-C), 55.3 (2-C), 70.0 (4-C), 115.8 (d, J = 23.5 Hz, 3′-C), 121.4 (9-C), 126.2 (5′-C), 126.6 (7-C), 127.3 (8-C), 128.7 (d, J = 16.0 Hz, 1′-C), 129.7 (d, J = 4.0 Hz, 4′-C), 129.8 (5a-C), 131.4 (6-C), 134.3 (d, J = 7.1 Hz, 6′-C), 147.7 (9a-C), 161.2 (d, J = 244.0 Hz, 2′-C). MS (EI): m/z (%) = 325 (^{35}Cl, 72) [M$^+$], 307 (2), 306 (7), 281 (58), 280 (21), 152 (100), 140 (44), 125 (10), 111 (4), 99 (9). Anal. Calcd for $C_{16}H_{14}Cl_2FNO$: C, 58.91; H, 4.33; N, 4.29. Found: C, 58.80; H, 4.42; N, 4.18.

4.6. Biological assays

4.6.1. Parasites, cells and compounds

Epimastigotes of *T. cruzi* (strain 320I01 isolated and characterized by Katerine Luna, CINTROP-UIS)[58] were cultured in infusion

tryptose liver (LIT) medium supplemented with heat inactivated fetal calf serum (hiFCS) at 28 °C. Promastigotes of *L. chagasi* (MHOM/BR/74/PP75) were maintained at 28 °C in RPMI 1640 medium (Gibco) containing hemin (Sigma), HEPES (Gibco) and 10% of hiSBF.

The Vero (ATCC) and THP-1 (ATCC) cells were cultured in RPMI medium plus 5% of hiSBF at 37 °C, 5% CO_2 and 95% of humidity. Nifurtimox (Nfx) and amphotericin B (AmB) were used as reference drugs.

Stock solutions of the tested compounds and reference drugs were prepared in dimethyl sulfoxide (DMSO, Sigma) 100 × concentrated. Work solutions were prepared on culture medium before the experiment.

4.6.2. Parasite assays

Late phase growth *T. cruzi* epimastigotes or *L. chagasi* promastigotes were treated with a three fold serial dilutions of each compound (0.3–100 μM) or reference drugs for 72 h at 28 °C. Control cells were maintained without compound. The inhibition of parasite growth was microscopically determined by counting parasite numbers in a haemocytometer.

For intracellular amastigotes assays, Vero cells were infected with tissue derived trypomastigotes of *T. cruzi* and THP-1 transformed cells were infected with late phase growth promastigotes of *Leishmania* at a parasite: cell ratio of 10:1 for 24 h. The infected cells were treated with each compound and reference drug dilutions for a total of 5 days at 37 °C and 5% CO_2; the medium was changed once after 3 days. Control cells were maintained without compound. The percentage of parasite inhibition was calculated microscopically by counting infected cells on 300 cells in methanol fixed and Giemsa stained preparations.

All the experiments were repeated twice. The top concentration for the tested compounds was 100 μM, and all concentrations were carried out in triplicate.

4.6.3. Mammalian cell assays

Vero and transformed THP-1 cells were incubated with each compound (0.3–300 μM) or reference drugs for 72 h at 37 °C in a 5% CO_2-95% air mixture. Control cells were maintained without compound. The cell toxicity was determined using the MTT colorimetric method described by Mosmann.[59] The optical density (OD) of the dissolved formazan crystals was measured using a microplate reader at a wavelength of 580 nm. The percentage of cytotoxicity was calculated using the following equation: cytotoxicity (%) = 100 × (OD control group − OD treatment group)/OD control group.

All the experiments were repeated twice. The top concentration for the tested compounds was 300 μM, and all concentrations were carried out in triplicate.

4.6.4. Analysis of results

The antiparasitic activity was expressed as the concentration that inhibited 50% and 90% (IC_{50} and IC_{90}) of parasites, and the mammalian cell toxicity was expressed as the concentration required for 50% and 90% (CC_{50} and CC_{90}) cell killing. They were calculated by sigmoidal regression analysis (Msxlfit™; ID Business Solution, Guildford, UK). The selectivity index (SI) was calculated by dividing CC_{50} Vero cells/IC_{50} *T. cruzi*, or CC_{50} THP-1 cells/IC_{50} *L. chagasi*. The results were expressed as mean ± standard deviation (SD), and statistical significance was determined by Student's *t*-tests (p <0.05 were considered as statistically significant).

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Supplementary data

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