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Synthesis of novel polysubstituted (2*SR*,4*RS*)-2-heteroaryltetrahydro-1,4-epoxy-1-benzazepines and *cis*-2-heteroaryl-4-hydroxytetrahydro-1*H*-1-benzazepines as antiparasitic agents

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ABSTRACT

New series of polysubstituted (2*SR*,4*RS*)-2-heteroaryltetrahydro-1,4-epoxy-1-benzazepines and *cis*-2-heteroaryl-4-hydroxytetrahydro-1*H*-1-benzazepines were designed and synthesized in moderate to high yields using a three-step procedure from *ortho*-allylanilines. Their antiparasitic activity was evaluated against the extracellular and intracellular forms of *Trypanosoma cruzi* and *Leishmania (Leishmania) infantum* parasites. Their cytotoxicity was also determined on Vero and THP-1 mammalian cells. Many of the tested compounds inhibited significantly the growth of extracellular forms of *T. cruzi* and *L. (L.) infantum* without showing cytotoxicity on Vero and HTP-1 cells. Only compounds **10h** and **14f** demonstrated good activity against amastigotes of *T. cruzi*, but none was able to inhibit the growth of *L. (L.) infantum* amastigotes.

1. Introduction

Chagas disease and leishmaniasis remain a major public health problem due to the inadequate therapy, and to the ineffective vaccines available [1]. Chagas disease is caused by the flagellate protozoan *Trypanosoma cruzi* mainly transmitted by the infected faeces of triatomine bugs. Nevertheless, it could also be transmitted by blood transfusions and organs transplants, as well as, congenitally and orally from contaminated food. It has been estimated that about 7–8 million people worldwide are infected, spreading from Latin America to non-endemic countries [2]. In Colombia, it has been assessed that about 1 million people are infected and 3 million are at risk of acquiring the infection [3]. Chagas disease presents an initial acute phase with a high number of parasites circulating the blood followed by a chronic phase which, in approximately 30% of the infected people, leads after several years to cardiac, digestive, neurological or mixed clinical alterations [2]. Nifurtimox (Nfx) and benznidazole are drugs currently recommended mainly for the treatment during the acute and early chronic phase, along with immunoreactive diseases or congenital infections. Unfortunately, these drugs are related to significant side effects such as edema, fever, skin rash, articular and muscular pain, peripheral neuropathy, neutropenia, sore throat, fever, septicemia, thrombocytopenic purpura, nausea and vomiting [4].

Leishmaniasis is a poverty-related group of diseases caused by several species of protozoan parasites belonging to the genus *Leishmania* and transmitted by the bite of a female phlebotomine sandfly [5]. They are digenetic parasites that proliferate as motile promastigotes in the gut of sandflies and as amastigotes inside vertebrate-host macrophages. There are two main forms of leishmaniasis, cutaneous (the most common), and visceral leishmaniasis (fatal in 85–90% of untreated cases). Currently, leishmaniasis is endemic in 98 countries, and approximately 58,000 cases of

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visceral leishmaniasis (VL) and 220,000 cases of cutaneous leishmaniasis (CL) are officially reported each year. Based on under-reporting assessments, 0.2–0.4 million new cases of VL and 0.7–1.2 million new cases of CL are estimated to occur every year [6]. Pentavalent antimony compounds (sodium stibogluconate and meglumine antimoniate) followed by amphotericin B (both the free and liposomal amphotericin B), pentamidine isothionate, paromomycin and miltefosine constitute the major drug options for the disease. These drugs present significant side-effects, such as toxicity, expensiveness, low availability, variable effectiveness and high risk of resistance. It is clear that alternative drugs are desperately needed to treat Chagas disease and leishmaniasis [5,7].

The tetrahydro-1-benzazepine nucleus has attracted wide interest since several derivatives bearing this heterocyclic unit have shown useful pharmaceutical applications [8–12]. Many tetrahydro-1-benzazepine derivatives were developed and evaluated as potent and orally active non-peptide arginine vasopressin antagonists for both V_{1A} and V_2 receptors [13–18], as potent inhibitors of cyclin-dependent kinases [19–22], as potent and orally bioavailable growth hormone secretagogue [23–26], and as agents against HIV-1 infection [27]. Some derivatives containing this frame, such as paullones, completely inhibit the growth of *Leishmania mexicana* promastigotes *in vitro* [28], and others are considered as promising inhibitors of *T. cruzi* dihydrofolate reductase [29].

In a previous work we presented the synthesis and biological evaluation against the extracellular and intracellular forms of *T. cruzi* and *L. (L.) infantum* parasites of a series of diverse functionalized 2-aryltetrahydro-1-benzazepines of the types **I** and **II** (Fig. 1). While these compounds were inactive or displayed only limited activity against the intracellular forms of the parasites, several showed a high level of activity against the extracellular epimastigotes (IC_{50} = 6.1–35.4 μM) and promastigotes (IC_{50} = 9.5–49.1 μM). Structure–activity relationship (SAR) studies showed that the antiparasitic properties of these compounds greatly depended on the number and the chemical nature of the substituents on the aromatic rings (benzene-fused ring, and pendant aryl moiety at C-2), being the halogen-substituted and the methyl-substituted derivatives the most promising [30]. With the aim of synthesizing new analogues with comparable or better antiparasitic activity and taking into account the flexibility of our synthetic approach to incorporate moieties other than aryl into the final products, we centered our efforts on the replacement of aryl moiety at C-2 in compounds **I** and **II** by an isosteric thiophene ring and its closely related furan and pyrrole nuclei, while at the same time maintaining a similar halogen substitution pattern at C-7 position of the benzene-fused ring. The halogen-substitution pattern in this study was selected not only taking into account the fact that in medicinal chemistry the halogenation of molecules allows the modulation of their physicochemical properties, such as free energy of binding, selectivity, lipophilicity and pharmacokinetics [31–33], but also based on the previously obtained results, where a remarkable activity against the extracellular forms of parasites was observed (I: R = F, $R^1 = R^2 = R^3 = R^4$ = H, IC_{50} (epimastigotes *T. cruzi*) = 7.7 μM; R = Cl, $R^1 = R^2 = R^3 = R^4$ = H, IC_{50} (epimastigotes *T. cruzi*) = 9.0 μM; II: R = Cl, R^1 = Br, $R^2 = R^3 = R^4$ = H, IC_{50} (promastigotes *L. (L.) infantum*) = 9.5 μM) [30]. By the same manner, the incorporation of thiophene, furan and pyrrole nuclei in the molecules is in concordance with the several examples reported of antiparasitic agents possessing this substitution [34–38].

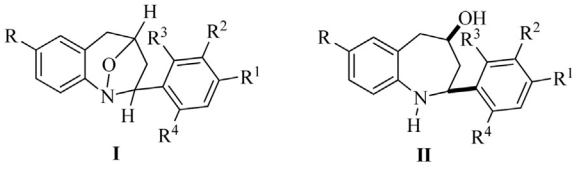


Fig. 1. Potential antichagasic and antileishmanial agents of the series 2-aryltetrahydro-1,4-epoxy-benzo[*b*]azepines **I** and *cis*-2-aryl-4-hydroxytetrahydro-1*H*-1-benzazepines **II**.

In the present study, we report the synthesis and antiparasitic activity of new series of polysubstituted (2*SR*,4*RS*)-2-heteroaryltetrahydro-1,4-epoxy-1-benzazepines and *cis*-2-heteroaryl-4-hydroxytetrahydro-1*H*-1-benzazepines, resulting from the replacement of the aryl moiety at C-2 by substituted thiophene, furan and pyrrole rings. The results obtained in the evaluation of new compounds were compared to those of the parent compounds **I** and **II** and of control drugs. We also theoretically determined the octanol/water partition coefficients (log *P*) and dipoles (D) and tried to find a relationship between these two quantitative parameters and antiparasitic activity presented by active compounds.

2. Results and discussion

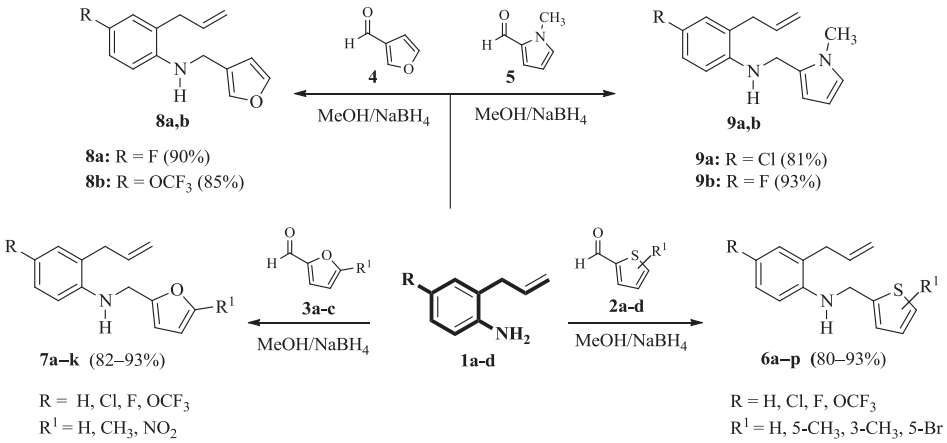
2.1. Chemistry

The investigation started with the synthesis of *ortho*-allyl-*N*-(heteroarylmethyl)anilines **6**–**9**, which are the building blocks to the target heterocycles. For this task, the *ortho*-allylanilines **1a**–**d** were treated with 2-thiophene-carboxaldehydes **2a**–**d**, 2-furaldehydes **3a**–**c**, 3-furaldehyde **4**, and *N*-methyl-2-pyrrolecarboxaldehyde **5** in methanol to generate the corresponding imine intermediates. The imines were easily transformed *in situ* in very high yields to the secondary aromatic amines **6a**–**p**, **7a**–**k**, **8a,b** and **9a,b** by reduction with a threefold excess of sodium borohydride (Scheme 1).

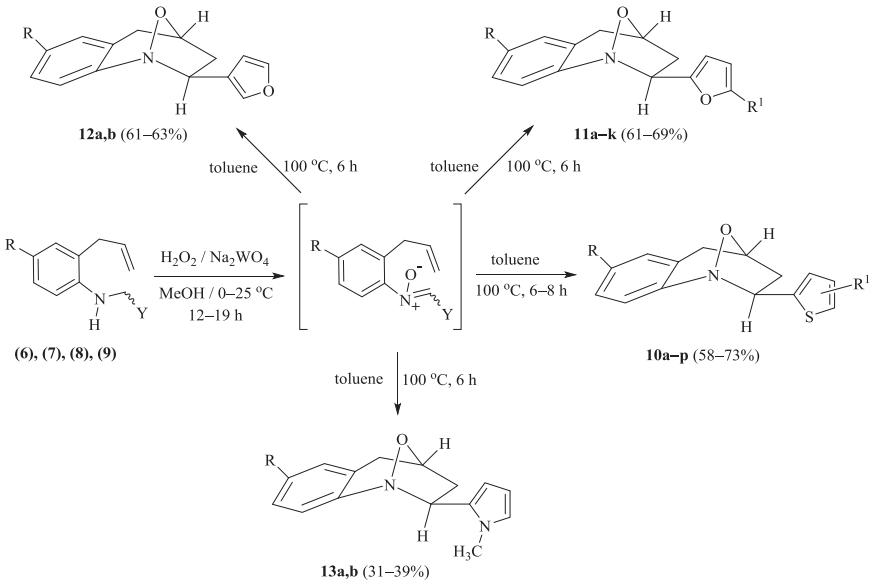
As we have already demonstrated, the intramolecular 1,3-dipolar cycloaddition of nitrones derived from *ortho*-allyl-*N*-benzyl(alkenyl)anilines is a versatile route to effectively build the tetrahydro-1-benzazepine ring [39–41]. Using this methodology, key precursors **6**–**9** were transformed into the target 2-heteroaryltetrahydro-1,4-epoxy-1-benzazepines **10**–**12** in moderate to good yields (Scheme 2). The low yields obtained for 1,4-epoxycycloadducts **13** can be explained considering the concomitant oxidation of the π-electron rich pyrrole nucleus, which is probably carried out by hydrogen peroxide, leading to the formation of considerable amounts of no identifiable degradation products.

In all the cases, the intramolecular 1,3-dipolar cycloaddition of the intermediate nitrones was entirely stereoselective leading to the exclusive formation of 2-*exo*-heteroaryl-1,4-epoxycycloadducts. It was unambiguously determined by the chemical shifts and coupling constant values of the 1,4-epoxytetrahydroazepine ring protons (see Experimental Section), and specially by the absence of NOE cross-signal between tertiary 2–H and 4–H protons in their NOESY spectra. Definitive structural elucidation was achieved by single-crystal X-ray analysis on compounds type **10**, **11**, and **13** [42–44]. The molecular structures of **10j**, **11g** and **13b** (see Fig. 2), are in agreement with the stereochemistry deduced from NMR analysis.

Finally, most of the obtained 1,4-epoxycycloadducts were subjected to N–O bond reductive cleavage using an excess of zinc in a mixture of glacial acetic acid and concentrated hydrochloric acid at temperature ranging from 0 to 25 °C (Scheme 3). Under such conditions, the reductive cleavage of **10a**–**c**, **10e**–**g**, **10i**–**k**, **10m**–**o**, **11a,b**, **11d**–**g**, **11i,j**, and **12a,b** proceeded smoothly and was completed within 0.5–1 h affording the desired 2-heteroaryl-4-



Scheme 1. Synthesis of key precursors **6a**–**p**, **7a**–**k**, **8a,b** and **9a,b.**



Scheme 2. Oxidation and subsequent intramolecular 1,3-dipolar cycloaddition of key precursors **6**–**9.**

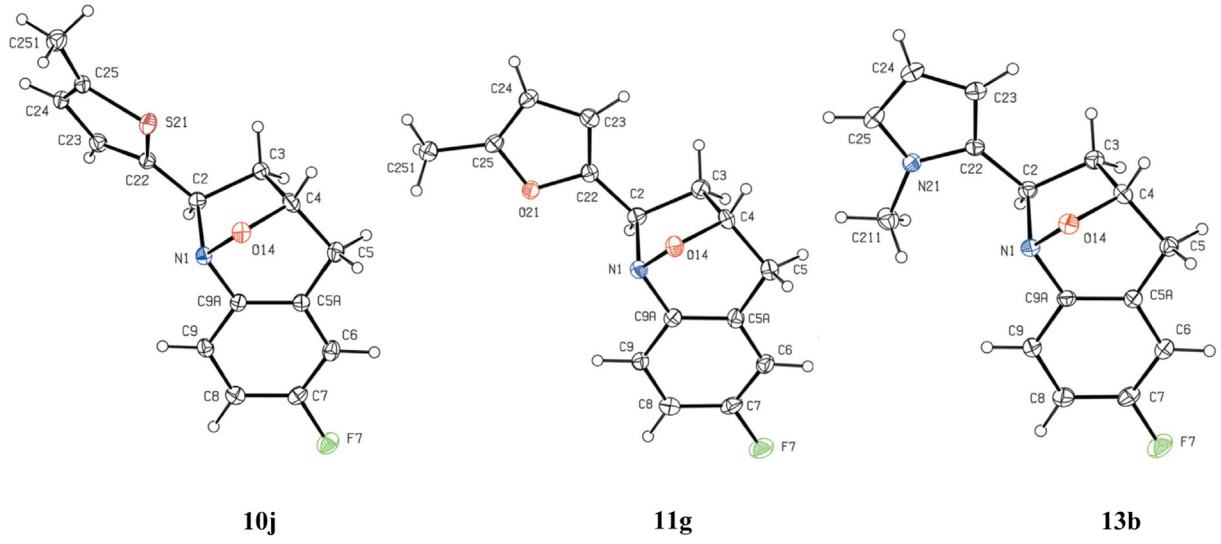
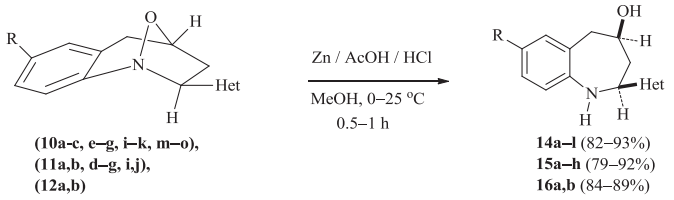


Fig. 2. Single crystal X-ray structures of **10j**, **11g** and **13b** (ORTEP views).



(10a-c, e–g, i–k, m–o), (11a,b, d–g, i,j), (12a,b)

14a–l (82–93%) **15a–h** (79–92%) **16a,b** (84–89%)

Scheme 3. N–O bond reductive cleavage in 1,4-epoxycycloadducts **10**–**12.**

hydroxytetrahydro-1-benzazepines **14a**–**l**, **15a**–**h**, and **16a,b**, respectively, in good to excellent yields.

The reductive cleavage of the bromo-substituted cycloadducts **10d,h,l,p** also proceeded very easy affording, in these cases, the debrominated amino-alcohols **14a,d,g,j** instead of the expected 5-bromothiophene substituted amino-alcohols. These results were deduced from NMR and MS analysis. The formation of **14a,d,g,j** (84–92% yields) can be explained by the concomitant generation of thienylzinc bromide intermediate and its subsequent hydrolysis. Unfortunately, the reductive cleavage of the 5-nitrofuran-2-yl and the *N*-methylpyrrolo-substituted cycloadducts **11c,h,k**, and **13a,b** gave a very complex mixture of no identifiable degradation products.

The structures and stereochemistry of these novel compounds were determined mainly by 1D and 2D NMR spectroscopy. As expected, the reductive cleavage of the 1,4-epoxycycloadducts **10**–**12** afforded stereospecifically the 2,4-*cis* stereoisomeric amino-alcohols **14**–**16** with the tetrahydroazepine ring adopting a chair conformation. The stereochemistry and conformation were unambiguously determined by the chemical shifts and coupling constant values of the six tetrahydroazepine ring protons (see Experimental Section), and, specially, by the NOE cross-signal between the double doublet (dd) of proton at position C-2 (3.91–4.32 ppm) and the triple double doublet (tdd) of proton at position C-4 (3.82–4.07 ppm). Confirmation of this structural assignment was made by single-crystal X-ray analysis of **14a** and **14b** [45]. The X-ray crystal structures of these compounds with the atomic numbering scheme are shown in Fig. 3, and are in agreement with the stereochemistry deduced from NMR analysis.

2.2. Antiparasitic activity

The majority of the synthesized compounds were *in vitro* screened against the extracellular and intracellular forms of *T. cruzi* and *L. (L.) infantum* parasites. The cytotoxicity of compounds was also evaluated on Vero epithelial cells (the host cells of *T. cruzi*) and on THP-1 transformed human macrophages (the host cells of *L. (L.) infantum*) in parallel with the antiparasitic activity. To study the effects of structural modifications on inhibitory activity and cytotoxicity, different substituents (R = H, Cl, F, OCF_3) were introduced at the C-7 position of the benzene-fused ring, and an appropriate substituted thiophene, furan and pyrrole rings were also linked to tetrahydro-1-benzazepine nucleus at the C-2 position. Complete data concerning anti-trypanosomal, anti-leishmanial and cytotoxic activities as well as the calculated octanol/water partition coefficients (log *P*) and dipoles (D) of the active compounds are reported in Tables 1–3.

From the forty nine compounds evaluated in the *T. cruzi* assays, eighteen [nine of the 2-(thiophen-2-yl)-1,4-epoxytetrahydro-1-benzazepine series **10**, three of the 2-(furan-2-yl)-1,4-epoxytetrahydro-1-benzazepine series **11**, five of the 2-(thiophen-2-yl)-4-hydroxytetrahydro-1-benzazepine series **14**, and one of the 2-(furan-2-yl)-4-hydroxy-tetrahydro-1-benzazepine series **15**] were active against epimastigostes with IC_{50} values lying in the 10.7–47.9 μM range (Table 1). Compounds **14l** (amino-alcohol bearing a trifluoromethoxy group at C-7 and a 3-methylthiophen-2-yl-moiety at C-2), **10g** (1,4-epoxycycloadduct bearing a chlorine atom at C-7 and a 3-methylthiophen-2-yl-moiety at C-2), **14e** (amino-alcohol bearing a chlorine atom at C-7 and a 5-methylthiophen-2-yl-moiety at C-2), and **10h** (1,4-epoxycycloadduct bearing a chlorine atom at C-7 and a 5-bromothiophen-2-yl-moiety at C-2), showed the best activities with IC_{50} values of 10.7, 11.7, 14.6 and 14.7 μM, respectively. These IC_{50s} are quite similar to that measured for the most active members of the series **I** and **II** [30], and only 2.7–3.7 times higher than that of nifurtimox, found to be 4.0 μM in the same assay. However, the most active compound **14l** was also toxic for Vero cells, with a CC_{50} = 26.7 μM and a SI = 2.5. On the contrary, compound **10h** possesses the highest CC_{50} value of 1664.2 μM and has the maximum SI value of 113.4, which are several folds better than that measured for the most active members of the series **I** and **II** and nifurtimox (CC_{50} = 67.5 μM and SI = 17.0).

Unfortunately, the majority of the evaluated compounds were unable to inhibit the growth of amastigotes, due, may be, to the difficult to penetrate the cell membrane of parasite (see data in Supplementary material). Only two compounds, the 1,4-epoxycycloadduct **10h** and the amino-alcohol **14f** (this last bearing a chlorine atom at C-7 and a 3-methylthiophen-2-yl-moiety at C-2), exhibited considerable (IC_{50} = 23.9 μM) or limited

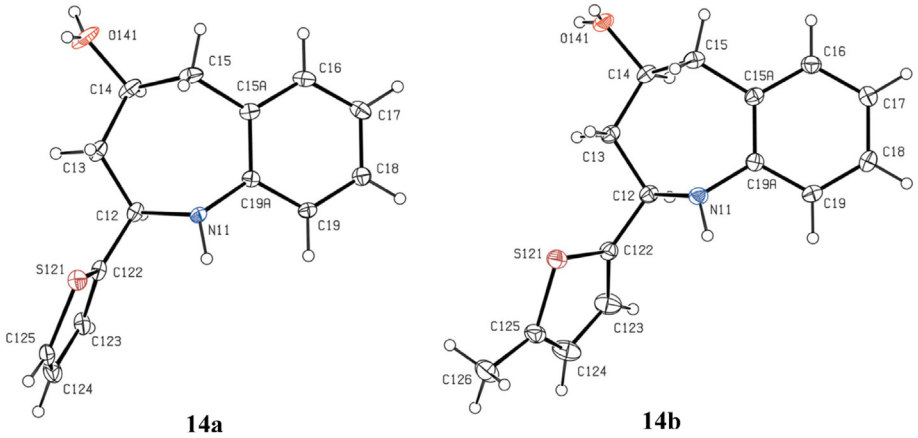
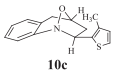
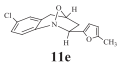
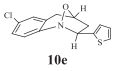
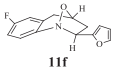
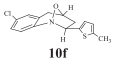
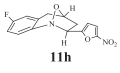
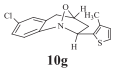
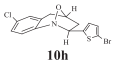
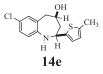
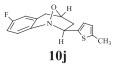
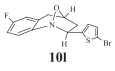
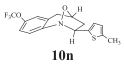
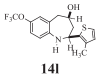
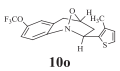
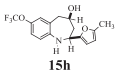


Fig. 3. Single crystal X-ray structures of **14a** and **14b** (ORTEP views, atom-labeling schemes were numbered as 1× and 2× for the two independent molecules appear in asymmetric unit in both cases, representing here just one of them).

Table 1
In vitro antiparasitic activity and cytotoxicity of active 2-*exo*-heteroaryltetrahydro-1,4-epoxy- (**10**, **11**) and *cis*-2-heteroaryl-4-hydroxytetrahydro-1-benzazepines (**14**, **15**) against *T. cruzi* parasite and Vero cells.

Compound	Epimastigotes/Amastigotes	SI	Vero cells	Compound	Epimastigotes/Amastigotes	SI	Vero cells
	IC_{50} (μM)		CC_{50} (μM)		IC_{50} (μM)		CC_{50} (μM)
 **10c**	27.6 ± 2.1/NA	16.4	452.7 ± 2.4	 **11e**	46.2 ± 2.4/NA	25.1	1158.7 ± 12.6
 **10e**	25.4 ± 0.2/NA	>14.2	>361.0	 **11f**	47.7 ± 3.2/NA	>8.6	>408.0
 **10f**	24.8 ± 1.2/NA	46.1	1144.7 ± 19.4	 **11h**	29.7 ± 1.4/NA	14.2	421.5 ± 5.1
 **10g**	11.7 ± 0.9/NA	15.6	182.9 ± 7.5	 **14b**	22.8 ± 0.9/NA	41.9	956.4 ± 7.5
 **10h**	14.7 ± 0.1/23.9 ± 0.0	113.4/69.8	1664.2 ± 3.5	 **14e**	14.6 ± 0.6/NA	10.5	153.7 ± 3.8
 **10j**	30.9 ± 0.4/NA	30.6	944.0 ± 0.0	 **14f**	47.9 ± 2.2/41.5 ± 0.4	4.2/4.8	200.3 ± 6.6
 **10l**	34.7 ± 0.1/NA	>8.5	>295.0	 **14i**	45.9 ± 1.4/NA	5.3	243.1 ± 0.6
 **10n**	43.9 ± 3.4/NA	3.9	169.9 ± 20.1	 **14l**	10.7 ± 0.2/NA	2.5	26.7 ± 2.9
 **10o**	47.2 ± 0.9/NA	1.3	61.7 ± 3.8	 **15h**	42.7 ± 2.3/NA	1.9	82.1 ± 1.5
Nfx	4.0 ± 0.0/1.6 ± 0.0	17.0/43.0	67.5 ± 4.0				

IC: inhibitory concentration; CC: cytotoxic concentration; SI: selectivity index; Nfx: nifurtimox; NA: compounds that were inactive at the lowest tested concentration.
Note: Data for non-active compounds can be seen in the Supporting material.

activity (IC_{50} = 41.5 μM), respectively, against amastigotes without showing toxicity on Vero cells. It is interesting to note that **10h** also demonstrated a noteworthy inhibitory activity against epimastigotes. In comparison to inhibitory activity of the most prominent members of the series **I** and **II**, compound **10h** exhibited an improved activity.

In the cytotoxicity assays, with the exception of **10o**, **11c**, **11i**, **14j**, **14k**, **14l**, **15h** and **16b**, the compounds did not show toxicity on Vero cells at the CC_{50} level (see data in Supplementary material). As a result, 34 of the examined compounds have SI higher than 3, indicating that such compounds were more active against the parasite than against the Vero cells.

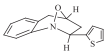
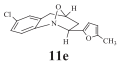
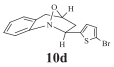
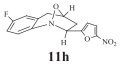
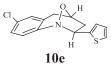
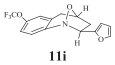
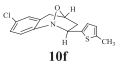
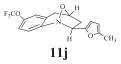
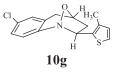
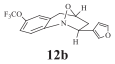
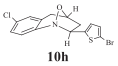
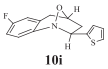
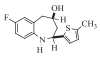
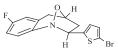
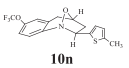
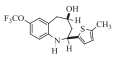
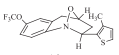
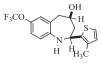
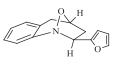
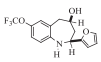
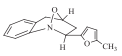
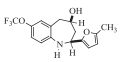
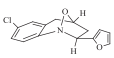
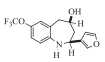
Of all the evaluated compounds in the *L. (L.) infantum* assays, twenty six (ten of the series **10**, seven of the series **11**, one of the 2-(furan-3-yl)-1,4-epoxytetrahydro-1-benzazepine series **12**, five of the series **14**, two of the series **15**, and one of the 2-(furan-3-yl)-4-hydroxytetrahydro-1-benzazepine series **16**), showed inhibitory activity of less than 50 μM (Table 2). Compounds **10l** (1,4-epoxycycloadduct bearing a fluorine atom at C-7 and a 5-bromothiophen-2-yl-moiety at C-2), **10n** (1,4-epoxycycloadduct bearing a trifluoromethoxy group at C-7 and a 5-methylthiophen-2-yl-moiety at C-2), **11h** (1,4-epoxycycloadduct bearing a fluorine atom at C-7 and a 5-nitrofuran-2-yl-moiety at C-2), **11j** (1,4-epoxycycloadduct bearing a trifluoromethoxy group at C-7 and a 5-methylfuran-2-yl-moiety at C-2), **14k** (amino-alcohol bearing a trifluoromethoxy group at C-7 and a 5-methylthiophen-2-yl-moiety at C-2), **10o** (1,4-epoxy-cycloadduct bearing a trifluoromethoxy group at C-7 and a 3-methylthiophen-2-yl-moiety at C-2), and **10i** (1,4-epoxycycloadduct bearing a fluorine atom at C-7 and a thiophen-2-yl-moiety at C-2), exhibited the best activities with IC_{50} values of 7.3, 10.5, 10.7, 10.8, 11.3, 11.4 and 11.5 μM, respectively. These IC_{50s} are similar or only slightly better than that measured for the most active members of the series **I** and **II** [30]; in comparison with amphotericin B (IC_{50} = 0.03 μM), the above compounds are far less active. In addition, compound **10o** has shown the lowest cytotoxicity with a CC_{50} > 1759.2 μM and has the maximum SI value of >153.9, which are more than three folds better than that measured for compound **10l** and at least six folds lower than that measured for amphotericin B (CC_{50} = 29.7 μM and SI = 927.5).

Analogously to compounds of the series **I** and **II**, none of the examined compounds inhibited the growth of *L. (L.) infantum* amastigotes at the concentrations employed.

In the cytotoxicity assays, with the exception of **14j**, **14k** and **14l**, the compounds were nontoxic to THP-1 cells at the CC_{50} level (see data in Supplementary material). As a result, 38 of the examined compounds have SI higher than 3, indicating that such compounds were more active against the parasite than against the HTP-1 cells. As shown above, these three compounds were also toxic to Vero cells.

The lack of or the limited *in vitro* inhibitory activity of compounds against the intracellular form of *T. cruzi* or *Leishmania*

Table 2
In vitro antiparasitic activity and cytotoxicity of active 2-*exo*-heteroaryltetrahydro-1,4-epoxy- (**10**–**12**) and *cis*-2-heteroaryl-4-hydroxytetrahydro-1-benzazepines (**14**–**16**) against *L. (L.) infantum* promastigotes and THP-1 cells.

Compound	Promastigotes IC_{50} (μM)	SI	HTP-1 cells CC_{50} (μM)	Compound	Promastigotes IC_{50} (μM)	SI	HTP-1 cells CC_{50} (μM)
 **10a**	15.9 ± 1.4	45.7	727.44 ± 8.0	 **11e**	19.1 ± 1.4	19.6	374.4 ± 1.5
 **10d**	36.1 ± 0.6	34.7	1251.9 ± 24.9	 **11h**	10.7 ± 0.1	50.4	538.9 ± 1.3
 **10e**	20.7 ± 0.2	>17.5	>361.0	 **11i**	16.0 ± 0.7	19.9	318.9 ± 5.2
 **10f**	32.3 ± 5.2	>63.8	>2061.5	 **11j**	10.8 ± 0.0	16.3	175.8 ± 19.6
 **10g**	32.3 ± 5.2	7.7	250.2 ± 18.1	 **12b**	25.2 ± 0.5	>76.6	>1928.8
 **10h**	14.3 ± 0.7	>117.9	>1690.4	 **14d**	49.5 ± 0.5	2.3	114.9 ± 5.5
 **10i**	11.5 ± 0.4	86.6	991.3 ± 2.2	 **14h**	16.9 ± 0.1	18.5	311.5 ± 16.8
 **10l**	7.3 ± 0.3	>40.6	>295.0	 **14j**	13.8 ± 0.2	4.4	61.5 ± 0.7
 **10n**	10.5 ± 0.1	26.8	282.0 ± 2.0	 **14k**	11.3 ± 0.1	8.6	98.0 ± 3.5
 **10o**	11.4 ± 0.1	>153.9	>1759.2	 **14l**	16.4 ± 0.2	5.5	89.7 ± 2.5
 **11a**	45.3 ± 6.5	14.7	663.1 ± 24.5	 **15g**	45.9 ± 0.8	2.9	134.5 ± 13.4
 **11b**	27.3 ± 1.6	14.5	394.5 ± 14.1	 **15h**	12.8 ± 0.1	9.7	124.1 ± 9.1
 **11d**	47.3 ± 0.1	>24.3	>114 ± 9.2	 **16b**	43.1 ± 1.3	10.7	460.4 ± 4.2
AmB.	0.03 ± 0.00001	927.5	29.7 ± 3.6				

IC: inhibitory concentration; CC: cytotoxic concentration; SI: selectivity index; AmB: amphotericin B.
Note: Data for non-active compounds can be seen in the Supporting material.

(compared with the inhibitory activity of the active compounds against the extracellular forms) could be due to an unsuccessful cooperation between compounds and the host–parasite cell. Though the mechanism of action of the tested compounds is not known, the active compounds could be able to activate different mechanism, such as elicit of death intracellular signals, enzymatic transformation of prodrugs in active ones or penetration inside the cells, reaching the infected cellular compartments and expressing their activity in the corresponding environment [46]. The intracellular environmental circumstances where the parasite survives are complex and not always well understood. In *T. cruzi*, the infective trypomastigotes, after reaching the cell lysosomal compartment of the host cell, are released into cytosol where transformation and replication of intracellular amastigotes occur [47]. In *Leishmania*, once the promastigotes are phagocytosed by mammalian host macrophages, they are transformed into amastigotes which multiplies within the phagolysosome of the host cell. Intracellular amastigotes must grow continuously and released after destruction of highly infected macrophages to enter into uninfected macrophages and get again a parasitophorous vacuole throughout a progressive infection [48].

Finding active compounds in the process of small molecule drug discovery against the intracellular forms of the parasite is more complicated than in promastigotes or axenic amastigotes [49]. The promastigotes are easily cultivated in culture medium, but are the form of the parasite in the insect vector. In addition, although

Table 3
Anti-trypanosomal and anti-leishmanial *in vitro* activities of active 2-*exo*-heteroaryltetrahydro-1,4-epoxy- (**10**, **11**, **12**) and *cis*-2-heteroaryl-4-hydroxytetrahydro-1-benzazepines (**14**, **15**, **16**), and their calculated log *P* and dipole.

Compound	Epimastigotes	Promastigotes	Log *P*	Dipole (D)
	IC_{50} (μM)	IC_{50} (μM)		
10a	–	15.9 ± 1.4	2.71	2.26
10c	27.6 ± 2.1	–	3.17	2.12
10d	–	36.1 ± 0.6	3.56	2.59
10e	25.4 ± 0.2	20.7 ± 0.2	3.54	2.42
10f	24.8 ± 1.2	32.3 ± 5.2	4.00	2.36
10g	11.7 ± 0.9	32.3 ± 5.2	4.00	2.13
10h	14.7 ± 0.1	14.3 ± 0.7	4.39	2.29
10i	–	11.5 ± 0.4	3.00	2.62
10j	30.9 ± 0.4	–	3.46	2.49
10l	34.7 ± 0.1	7.3 ± 0.3	3.85	2.33
10n	43.9 ± 3.4	10.5 ± 0.1	3.29	3.18
10o	47.2 ± 0.9	11.4 ± 0.1	3.13	3.09
11a	–	45.3 ± 6.5	2.19	2.70
11b	–	27.3 ± 1.6	2.65	2.66
11d	–	47.3 ± 0.1	3.02	2.55
11e	46.2 ± 2.4	19.1 ± 1.4	3.48	2.52
11f	47.7 ± 3.2	–	2.48	2.52
11h	29.7 ± 1.4	10.7 ± 0.1	1.88	5.03
11i	–	16.0 ± 0.7	2.32	3.00
11j	–	10.8 ± 0.0	2.78	3.18
12b	–	25.2 ± 0.5	2.33	3.037
14b	22.8 ± 0.9	–	2.46	3.28
14d	–	49.5 ± 0.5	2.78	3.58
14e	14.6 ± 0.6	–	3.48	3.78
14f	47.9 ± 2.2	–	3.24	3.79
14h	–	16.9 ± 0.1	2.90	4.21
14i	45.9 ± 1.4	–	2.90	4.14
14j	–	13.8 ± 0.2	2.85	4.63
14k	–	11.3 ± 0.1	3.31	4.90
14l	10.7 ± 0.2	16.4 ± 0.2	3.31	4.73
15g	–	45.9 ± 0.8	2.33	4.26
15h	42.7 ± 2.3	12.8 ± 0.1	2.79	4.75
16b	–	43.1 ± 1.3	2.35	4.20

axenic amastigotes clearly resembled intracellular amastigotes in their ultra-structural, biological, biochemical, and immunological properties [50], they have shown differences in several cellular processes [51]. The intracellular forms are dependent on energy and nutrients produced by the host cells. They could adapt to the particular environmental conditions by activating some additional genes present in their genome. In amastigotes of *Leishmania* main variation have been found in genes involved in metabolism, cellular organization, biogenesis and transport, as well as in genes encoding unknown functions [51]. However, the promastigote or axenic amastigote assays not always serve to identify active compounds and, generally, they lead to a rate of high percent of false positives because such compounds, in fact, kill the parasite. In a screening approach (as is the case of the present work), different aspects related with host cell: parasite interactions such as parasite target, cell toxicity, ability to cross host cell membranes, stability under low pH, accumulation or intracellular distribution are unknown. However, the data of antiparasitic activity and cytotoxicity obtained in this work are necessary to progress to new stages of drug-discovery. In fact, the levels of mammalian cell toxicity compared with the antiparasitic activities calculated as SI on free forms were very encouraging.

From the antiparasitic and cytotoxic data reported in Tables 1 and 2, it can be observed that, of all active compounds against *T. cruzi* and *L. (L.) infantum* parasites, eleven compounds (**10e**, **10f**, **10g**, **10h**, **10l**, **10n**, **10o**, **11e**, **11h**, **14l** and **15h**) demonstrated a noteworthy or a moderate affinity for both extracellular epimastigote and promastigote forms of parasites with the compounds **10h** and **14l** being the most active. Interestingly, compound **10h** also exerted a remarkable inhibitory activity against *T. cruzi* amastigotes. Due to its lower cytotoxicity on Vero and THP-1 cells (CC_{50} = 1664.2 and >1690.4 μM, respectively) and better selectivity indexes (SI = 113.4 and >117.9, respectively), this compound can serve as a promising candidate for further development of more potent antichagasic and antileishmanial agents. Although no treatment for leishmaniasis is used to treat Chagas disease, susceptibility of parasites *in vitro* and in experimental models to the same drug has been demonstrated. Both parasites have been susceptible *in vitro* to different drugs such as miltefosine, ketoconazole, AmB (both the free and liposomal AmB) and tafenoquine [52–55]. This could be explained by the existing similarity between both parasites; both are flagellated protozoa belonging to the same Trypanosomatidae family, share biological and genetic features such as the presence of a single mitochondrion where the genetic material is packaged (kinetoplast), both are transmitted by insect vectors and both have an intracellular cycle where the parasites are transformed in a replicative amastigote forms.

In terms of the structure–activity relationships, the presence of halogen atoms, especially a chlorine atom, or a trifluoromethoxy group at the C-7 position and a 3(5)-methyl- or 5-bromothiophen-2-yl-moiety at the C-2 position (series **10** and **14**) positively influenced the activity against epimastigotes and amastigotes of *T. cruzi*, prominent examples being the 7-chloro-2-(3(5)-methylthiophen-2-yl)-substituted derivatives **10g** and **14e**, the 7-chloro-2-(5-bromothiophen-2-yl)-substituted derivative **10h**, and the 7-trifluoromethoxy-2-(3-methylthiophen-2-yl)-substituted derivative **14l**; compounds **10n**, **10o** and **14f** are the exception. On the contrary, the anti-*T. cruzi* activity is reduced (*e.g.,* compounds **11e**, **11f**, **11h**, and **15h**) or eliminated (most of the compounds of the series **11**, **12**, **13**, **15** and **16**) by replacing the thiophen-2-yl-moiety with furan-2-yl- (series **11** and **15**), furan-3-yl- (series **12** and **16**) and N-methylpyrrol-2-yl- (series **13**) moieties. Similar reduction (*e.g.,* compounds **10c** and **14b**) or loss (*e.g.*, compounds **10a**, **10b**, **10d**, **11a**, **11b**, **11c**, **14a**, **14c**, **15a** and **15b**) of activity was also observed for all non-substituted (R = H), at the C-7 position compounds.

On the other hand, the presence of a fluorine atom or a trifluoromethoxy group at the C-7 position and 5-bromothiophen-2-yl-, 3(5)-methyl- or thiophen-2-yl-moieties at the C-2 position appeared to be the best combinations to enhance the inhibitory activity against *L. (L.) infantum* promastigotes, prominent examples being the 7-fluoro-2-(5-bromothiophen-2-yl)-substituted derivative **10l**, the 7-fluoro-2-(thiophen-2-yl)-substituted derivative **10i**, the 7-trifluoromethoxy-2-(3-methylthiophen-2-yl)-substituted derivative **10o**, and the 7-trifluoromethoxy-2-(5-methyl-thiophen-2-yl)-substituted derivatives **10n** and **14k**. In addition, the presence of the above two substituents at the C-7 position and a 5-nitro(5-methyl)furan-2-yl-moiety at the C-2 position also produced compounds with remarkable inhibitory activity, prominent examples being the 7-fluoro-2-(5-nitrofuran-2-yl)-substituted derivative **11h**, and the 7-trifluoro-2-(5-methylfuran-2-yl)-substituted derivatives **11j** and **15h**. Other combinations between the substituents at the C-7 position and the heterocyclic moieties at the C-2 position generally reduced or eliminated the activity.

The data reported in Tables 1 and 2 also indicated that, in most of the cases, compounds of the series **10** tended to show better activity than compounds of the series **11**, **14** and **15**. The data also revealed that the incorporation of a furan-3-yl-moiety at C-2 did not exert influence on anti-*T. cruzi* activity, but exerted only a modest influence on anti-*L. (L.) infantum* activity (compounds **12b** and **16b**). Similarly, the incorporation of a N-methylpyrrol-2-yl-moiety at C-2 did not exert influence on both anti-*T. cruzi* and anti-*L. (L.) infantum* activities (compound **13b**).

In order to correlate the structure–activity relationships described above with quantitative parameters, we theoretically determined the octanol/water partition coefficients (log *P*) and dipole (D) for the 1,4-epoxy-tetrahydro-1-benzazepines (**10**, **11**, **12**) and 4-hydroxytetrahydro-1-benzazepines (**14**, **15**, **16**) that were active against epimastigostes of *T. cruzi* and promastigotes of *L. (L.) infantum* (Table 3), and tried to establish a relationship between their IC_{50} (μM) and values of these two parameters (Figs. 4 and 5). For the calculation of log *P* and dipole, the geometries for all molecules studied were fully optimized with the parametric method 3 (PM3) implemented in MOPAC2012 program [56–58]. The models were minimized until the root mean square (RMS) gradient value reached a value smaller than 0.0001 kcal/mol. Frequency calculations were performed in order to determine the character of the stationary point: zero imaginary frequency for minima. The lowest energy structure was used for each molecule to calculate dipole moment. Theoretical log *P* (octanol/water partition coefficient) values were obtained using Advanced Chemistry Development Inc. (ACD/Labs) software, version 14.01 (1994–2013).

From the data consigned in Table 3 and Figs. 3 and 4, it can be observed that there is not a clear correlation between IC_{50} values of all active compounds and their lipophilicities and dipoles. However, the high inhibitory activity against epimastigotes of *T. cruzi* of compounds **10h**, **10g**, **14e** and **14l** with IC_{50} values of 14.7, 11.7, 14.6 and 10.7 μM, respectively, positively correlated with the values of Log *P* (Fig. 4). Similarly, compounds **10l**, **10i**, **10o**, **10n** and **14k**, which showed the best inhibitory activities against *L. (L.) infantum* promastigotes with IC_{50} values of 7.3, 11.5, 11.4, 10.5, 11.4 μM, respectively, also presented appropriate values of Log *P* higher than 3.0 (Fig. 5). On the contrary, the Log *P* and dipole values for compound **11h** disagree with its high antileishmanial activity (IC_{50} = 10.7 μM), what can be attributed to the presence of the nitro group in the molecule. It is important to note, that compound **10h**, which not only possesses the highest CC_{50} value of 1664.2 μM and has the maximum SI value of 113.4, but also demonstrated a noteworthy inhibitory activity against epimastigotes and was one of the few compounds who exhibited activity against amastigotes of *T. cruzi*, presented the highest Log *P* value of all the evaluated compounds, thus validating the importance of this property in the process of small molecule drug discovery. Finally, the remaining compounds presented lower values of Log *P* and higher values of dipole which agree with the moderate or limited antiparasitic activity observed against *T. cruzi* and *L. (L.) infantum* parasites (Figs. 4 and 5).

3. Conclusion

In summary, we have designed and synthesized small libraries of structurally diverse and novel (2*SR*,4*RS*)-2-heteroaryl-1,4-epoxytetrahydro-1-benzazepines and *cis*-2-heteroaryl-4-hydroxytetrahydro-1-benzazepines, starting from readily available and highly economical substrates and reagents following simple protocols. In the present study, we identified several compounds with high affinity for the extracellular forms of both *T. cruzi* and *L. (L.) infantum* parasites without showing toxicity on Vero and THP-1 cells. We also found that compound **10h** possessed the most promising activity against amastigotes of *T. cruzi* with an IC_{50} value of 23.9 μM. Due to its lower cytotoxicity on Vero and THP-1 cells (CC_{50} = 1664.2 and >1690.4 μM, respectively) and better selectivity indexes (SI = 113.4 and >117.9, respectively), this compound can serve as a promising candidate for further development of more potent antichagasic and antileishmanial agents. This conclusion is also supported by the fact that this compound is fully compatible with Lipinski's rules. Structure–activity relationships established that the inhibitory activity against epimastigotes and amastigotes of *T. cruzi* was greatly enhanced by the presence of a chlorine atom or a trifluoromethoxy group at the C-7 position and a 3(5)-methyl- or 5-bromothiophen-2-yl-moiety at the C-2 position, while the presence of a fluorine atom or a trifluoromethoxy group at the C-7 position and 5-bromothiophen-2-yl-, 3(5)-methyl-, or thiophen-2-yl-moieties at the C-2 position enhanced the inhibitory activity of the molecules against *L. (L.) infantum* promastigotes. Experiments aimed at improving the activity of these classes of compounds and determining their modes of action are underway, and the results from these studies will be published in the near future.

4. Experimental section

4.1. General

All the reagents and solvents were purchased from Sigma–Aldrich or Merck companies, and used without further purification. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualized by UV light at 254 and 365 nm. Column chromatography was performed on Merck Kieselgel 60–230 mesh (ASTM). All the chromatographic solvent proportions were volume to volume. Melting points were determined with a MEL-TEMP 1201D capillary apparatus and were not corrected. IR spectra were recorded on a Nicolet Avatar 360-

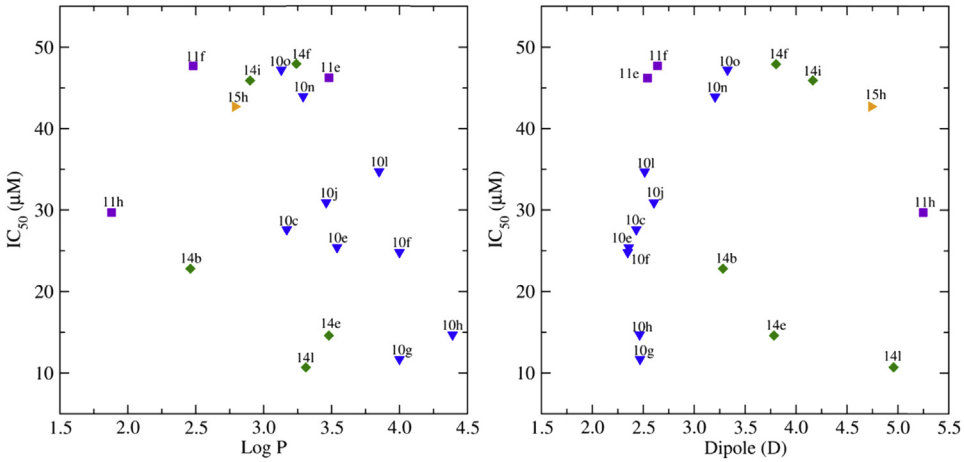


Fig. 4. Log *P* and dipole vs. *in vitro* anti-trypanosomal activity against epimastigotes of active 2-*exo*-heteroaryltetrahydro-1,4-epoxy- (**10**, **11**) and *cis*-2-heteroaryl-4-hydroxytetrahydro-1-benzazepines (**14**, **15**).

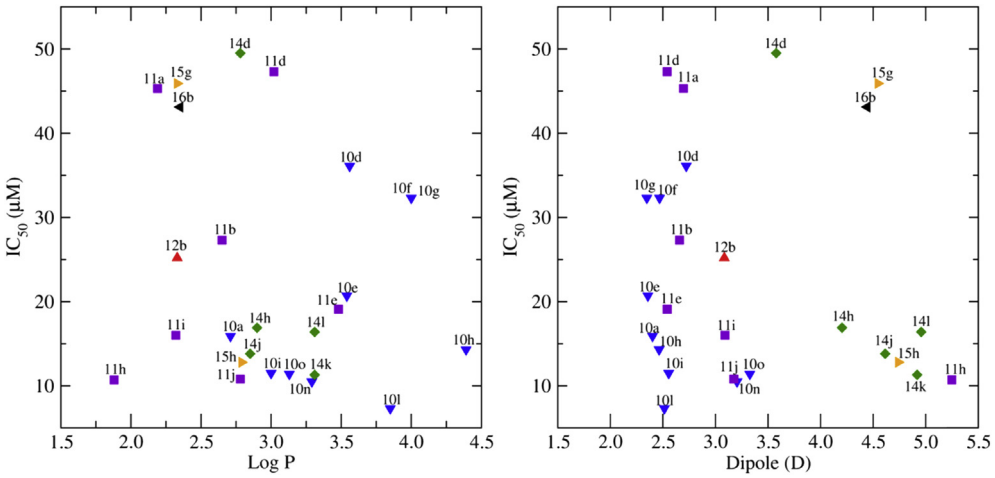


Fig. 5. Log *P* and dipole vs. *in vitro* anti-leishmanial activity against promastigotes of active 2-*exo*-heteroaryltetrahydro-1,4-epoxy- (**10**, **11**, **12**) and *cis*-2-heteroaryl-4-hydroxytetrahydro-1-benzazepines (**14**, **15**, **16**).

FTIR spectrometer and were referenced to polystyrene standard, using cells equipped with potassium bromide windows. ^{1}H and ^{13}C NMR spectra were measured at 25 °C on a Bruker Avance III-400 spectrometer, using $CDCl_3$ as the solvent. Chemical shifts (δ) and coupling constant (J) values are reported in ppm and Hz, respectively. Chemical shifts are relative to the solvent peaks used as reference [$CDCl_3$: δ_H = 7.26, and δ_C = 77.0]. For ^{1}H NMR, the assignments are: q = quartet, t = triplet, d = doublet, s = singlet, br = broad and m = multiplet. A Hewlett Packard HP 5890 A series II Gas Chromatograph interfaced to a Hewlett Packard 5972 Mass Selective Detector with a HP MS ChemStation Data system, and High Resolution Mass Spectrometer Waters Micromass AutoSpect NT (equipped with a direct inlet probe) operating at 70 eV were used for MS identification. Compounds of **1** were prepared according to our previously established experimental conditions [40].

4.1.1. General procedure for the preparation of 2-allyl-N-(heteroarylmethyl)anilines ***6–9***

To a stirred solution of the appropriately N-substituted *ortho*-allylanilines **1** (6 mmol) in methanol (50 mL) was added the respective heteroaromatic aldehydes **2–5** (6.2 mmol). The reaction mixtures were heated at 40–50 °C for 4–6 h. Once the corresponding imines were formed (TLC monitoring), to these methanolic solutions sodium borohydride (18 mmol) was slowly added in small portions at 0 °C. After adding the reductive agent, the reaction mixtures were stirred at room temperature for further 6 h. Finally, water (60 mL) was added and the reaction mixtures were heated at 45–50 °C for 4 h. Each mixture was extracted with chloroform (2 × 100 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and then concentrated under reduced pressure. The resulting crude products were purified by silica gel column chromatography using heptane–ethyl acetate (compositions ranged from 30:1 to 15:1 *v*/*v*) as eluent to give **6a–p**, **7a–k**, **8a,b** and **9a,b** as viscous pale yellow oils. The spectroscopic data of these compounds are reported in the Supporting material.

4.1.2. General procedure for the synthesis of (2SR,4RS)-2-heteroaryl-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepines ***10–13***

To a stirred and cooled (ice-bath) solution of the appropriately N-substituted *ortho*-allylanilines (**6a–p**), (**7a–k**), (**8a,b**) and (**9a,b**), (4 mmol), in methanol (20 mL), were added sodium tungstate dihydrate (10 molar%) and 30% aqueous hydrogen peroxide solution (12 mmol). The resulting mixtures were stirred at 0 °C during 30 min and then at room temperature for further 11.5–18.5 h. Each mixture was filtered, extracted with ethyl acetate, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and toluene (30 mL) was added to the organic black residue. The resulting solution was heated at 100 °C for 6–8 h. After cooling each solution to ambient temperature, the solvent was removed under reduced pressure and the crude product was purified on silica gel column chromatography using heptane–ethyl acetate (compositions in the range from 15:1 to 10:1 *v*/*v*) as eluent, to give the expected compounds as yellow viscous oils or colorless crystalline substances.

4.1.2.1. (2SR,4RS)-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10a***. Reaction time: 20 h. Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, J = 4.8, 1.5 Hz, 1H, H5′), 7.17 (dd, J = 7.4, 2.0 Hz, 1H, H6), 7.15 (td, J = 7.4, 2.0 Hz, 1H, H8), 7.15 (td, J = 7.4, 2.0 Hz, 1H, H7), 7.14 (dd, J = 7.4, 2.0 Hz, 1H, H9), 6.97 (dd, J = 4.8, 1.5 Hz, 1H, H3′), 6.96 (dd, J = 4.8, 4.8 Hz, 1H, 4′-H), 5.01 (ddd, J = 7.7, 5.3, 2.0 Hz, 1H, H4), 4.86 (dd, J = 8.2, 2.2 Hz, 1H, H2), 3.42 (dd, J = 16.5, 5.3 Hz, 1H, HB5), 2.72 (dddd, J = 12.6, 7.7, 2.2, 1.2 Hz, 1H, HB3), 2.56 (ddd, J = 12.6, 8.2, 2.0 Hz, 1H, H_A3), 2.55 (br d, J = 16.5 Hz, 1H, H_A5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1 (C9a), 146.9 (C2′), 129.3 (C6), 126.2 (C8), 126.0 (C7), 125.7 (C5′), 124.5 (C5a), 124.3 (C4′), 123.4 (C3′), 121.6 (C9), 74.5 (C4), 71.3 (C2), 41.9 (C3), 34.2 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 1048 (C–O), 980 (N–O). GC–MS (EI, 70 eV): m/z (%) = 243 (M^{+}•, 41), 226 (29), 213 (18), 130 (12), 110 (29), 105 (53), 104 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{13}NOS$: 243.0718; found: 243.0719.

4.1.2.2. (2SR,4RS)-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10b***. Reaction time: 23 h. Yield: 61%. White solid. mp 85 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (dd, J = 8.4, 1.5 Hz, 1H, H6), 7.14 (td, J = 8.4, 1.5 Hz, 1H, H8), 7.13 (td, J = 8.4, 2.0 Hz, 1H, H7), 7.11 (dd, J = 8.4, 2.0 Hz, 1H, H9), 6.75 (d, J = 3.4 Hz, 1H, H3′), 6.60 (d, J = 3.4 Hz, 1H, H4′), 4.99 (ddd, J = 7.8, 5.2, 2.0 Hz, 1H, H4), 4.78 (dd, J = 8.3, 2.0 Hz, 1H, H2), 3.41 (dd, J = 16.5, 5.2 Hz, 1H, HB5), 2.70 (dddd, J = 12.6, 7.8, 2.0, 1.0 Hz, 1H, HB3), 2.53 (br d, J = 16.5 Hz, 1H, H_A5), 2.51 (ddd, J = 12.6, 8.3, 2.0 Hz, 1H, H_A3), 2.50 (s, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1 (C9a), 144.3 (C2′), 138.9 (C5′), 129.3 (C6), 126.2 (C8), 125.7 (C7), 124.5 (C5a), 123.9 (C4′), 123.3 (C3′), 121.6 (C9), 74.5 (C4), 71.6 (C2), 41.5 (C3), 34.2 (C5), 14.8 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1053 (C–O),

990 (N–O). GC–MS (EI, 70 eV): m/z (%) = 257 (M^{+}•, 59), 240 (58), 227 (12), 130 (12), 124 (100), 105 (50), 104 (78). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{15}H_{15}NOS$: 257.0874; found: 257.0873.

4.1.2.3. (2SR,4RS)-2-(3-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10c***. Reaction time: 21 h. Yield: 58%. White solid. mp 54 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.16 (m, 2H, H7, H8), 7.15–7.12 (m, 3H, H5′, H6, H9), 6.80 (d, J = 5.0 Hz, 1H, H4′), 5.04 (ddd, J = 7.5, 5.4, 2.1 Hz, 1H, H4), 4.90 (dd, J = 8.2, 2.5 Hz, 1H, H2), 3.44 (dd, J = 16.7, 5.4 Hz, 1H, HB5), 2.65 (dddd, J = 12.6, 7.5, 2.5, 1.1 Hz, 1H, HB3), 2.58 (ddd, J = 12.6, 8.2, 2.1 Hz, 1H, H_A3), 2.55 (br d, J = 16.7 Hz, 1H, H_A5), 2.24 (s, 3H, 3′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9 (C9a), 140.4 (C2′), 132.9 (C3′), 130.0 (C6), 129.8 (C4′), 126.8 (C8), 126.3 (C7), 125.2 (C5a), 123.2 (C5′), 122.1 (C9), 75.2 (C4), 70.4 (C2), 42.5 (C3), 34.7 (C5), 14.3 (3′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1050 (C–O), 977 (N–O). GC–MS (EI, 70 eV): m/z (%) = 257 (M^{+}•, 39), 240 (30), 227 (9), 130 (18), 124 (67), 105 (67), 104 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{15}H_{15}NOS$: 257.0874; found: 257.0878.

4.1.2.4. (2SR,4RS)-2-(5-bromothiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10d***. Reaction time: 23 h. Yield: 68%. White solid. mp 106 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.15 (m, 2H, H7, H8), 7.12 (dd, J = 7.4, 1.8 Hz, 1H, H6), 7.10 (dd, J = 7.4, 2.3 Hz, 1H, H9), 6.89 (d, J = 3.7 Hz, 1H, H4′), 6.69 (d, J = 3.7 Hz, 1H, H3′), 4.98 (ddd, J = 7.6, 5.2, 2.0 Hz, 1H, H4), 4.75 (dd, J = 8.1, 2.0 Hz, 1H, H2), 3.42 (dd, J = 16.6, 5.2 Hz, 1H, HB5), 2.66 (dddd, J = 12.6, 7.6, 2.0, 1.0 Hz, 1H, HB3), 2.53 (br d, J = 16.6 Hz, 1H, H_A5), 2.52 (ddd, J = 12.6, 8.1, 2.0 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3 (C9a), 149.3 (C2′), 130.0 (C6), 129.3 (C4′), 126.9 (C8), 126.5 (C7), 125.1 (C5a), 124.1 (C3′), 122.2 (C9), 111.9 (C5′), 75.2 (C4), 72.1 (C2), 42.1 (C3), 34.7 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1028 (C–O), 993 (N–O). GC–MS (EI, 70 eV): m/z (%) = 321 (M^{+}•, ^{79}Br, 15), 304 (12), 291 (6), 188 (30), 130 (12), 105 (70), 104 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{12}BrNOS$: 320.9823; found: 320.9818.

4.1.2.5. (2SR,4RS)-7-chloro-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10e***. Reaction time: 22 h. Yield: 62%. White solid. mp 73 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, J = 4.4, 4.0 Hz, 1H, H5′), 7.15 (dd, J = 8.4, 2.0 Hz, 1H, H8), 7.12 (d, J = 2.0 Hz, 1H, H6), 7.07 (d, J = 8.4 Hz, 1H, H9), 6.96 (d, J = 4.4 Hz, 1H, H3′), 6.95 (d, J = 4.0 Hz, 1H, H4′), 4.98 (ddd, J = 7.4, 5.6, 2.0 Hz, 1H, H4), 4.81 (dd, J = 8.4, 2.0 Hz, 1H, H2), 3.39 (dd, J = 16.8, 5.6 Hz, 1H, HB5), 2.73 (dddd, J = 13.0, 7.4, 2.0, 1.0 Hz, 1H, HB3), 2.53 (ddd, J = 13.0, 8.4, 2.0 Hz, 1H, H_A3), 2.52 (br d, J = 16.8 Hz, 1H, H_A5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3 (C9a), 147.2 (C2′), 131.5 (C7), 129.9 (C6), 127.1 (C5a), 127.0 (C8), 126.7 (C5′), 125.0 (C4′), 124.1 (C3′), 123.6 (C9), 74.6 (C4), 71.9 (C2), 42.4 (C3), 34.6 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1048 (C–O), 979 (N–O). GC–MS (EI, 70 eV): m/z (%) = 277 (M^{+}•, ^{35}Cl, 37), 260 (16), 247 (10), 164 (5), 139 (73), 138 (100), 110 (44). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{12}ClNOS$: 277.0328; found: 277.0328.

4.1.2.6. (2SR,4RS)-7-chloro-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10f***. Reaction time: 23 h. Yield: 63%. White solid. mp 106 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, J = 8.4, 2.2 Hz, 1H, H8), 7.11 (d, J = 2.2 Hz, 1H, H6), 7.06 (d, J = 8.4 Hz, 1H, H9), 6.73 (d, J = 3.4 Hz, 1H, H3′), 6.59 (d, J = 3.4 Hz, 1H, H4′), 4.97 (ddd, J = 7.8, 5.1, 2.0 Hz, 1H, H4), 4.72 (dd, J = 8.2, 2.0 Hz, 1H, H2), 3.38 (dd, J = 16.6, 5.1 Hz, 1H, HB5), 2.70 (dddd, J = 12.6, 7.8, 2.0, 1.2 Hz, 1H, HB3), 2.50 (br d, J = 16.6 Hz, 1H, H_A5), 2.48 (ddd, J = 12.6, 8.2, 2.0 Hz, 1H, H_A3), 2.46 (s, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1 (C9a), 144.3 (C2′), 139.5 (C5′), 131.3 (C7), 127.6 (C6), 127.0 (C5a), 126.8 (C8), 124.4 (C4′), 123.8 (C3′), 123.5 (C9), 74.4 (C4), 71.9 (C2), 41.9 (C3), 34.5 (C5), 15.2 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1049 (C–O), 971 (N–O). GC–MS (EI, 70 eV): m/z (%) = 291 (M^{+}•, ^{35}Cl, 27), 274 (21), 261 (5), 164 (6), 139 (34), 138 (40), 124 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{15}H_{14}ClNOS$: 291.0485; found: 291.0490.

4.1.2.7. (2SR,4RS)-7-chloro-2-(3-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10g***. Reaction time: 20 h. Yield: 73%. White solid. mp 125 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (dd, J = 8.4, 2.4 Hz, 1H, H8), 7.14 (d, J = 5.2 Hz, 1H, H5′), 7.13 (d, J = 2.4 Hz, 1H, H6), 7.06 (d, J = 8.4 Hz, 1H, H9), 6.80 (d, J = 5.2 Hz, 1H, H4′), 5.00 (ddd, J = 7.6, 5.2, 2.0 Hz, 1H, H4), 4.80 (dd, J = 8.4, 2.4 Hz, 1H, H2), 3.40 (dd, J = 16.8, 5.2 Hz, 1H, HB5), 2.60 (dddd, J = 12.8, 7.6, 2.4, 1.6 Hz, 1H, HB3), 2.55 (ddd, J = 12.8, 8.4, 2.0 Hz, 1H, H_A3), 2.52 (br d, J = 16.8 Hz, 1H, H_A5), 2.23 (s, 3H, 3′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6 (C9a), 140.2 (C2′), 132.8 (C3′), 131.5 (C7), 129.8 (C6), 129.8 (C4′), 127.1 (C5a), 126.9 (C8), 123.5 (C9), 123.2 (C5′), 74.6 (C4), 70.4 (C2), 42.5 (C3), 34.6 (C5), 14.2 (3′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1050 (C–O), 973 (N–O). GC–MS (EI, 70 eV): m/z (%) = 291 (M^{+}•, ^{35}Cl, 41), 274 (22), 261 (7), 164 (10), 139 (68), 138 (87), 124 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{15}H_{14}ClNOS$: 291.0485; found: 291.0482.

4.1.2.8. (2SR,4RS)-7-chloro-2-(5-bromothiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10h***. Reaction time: 21 h. Yield: 64%. White solid. mp 89 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, J = 8.4, 2.2 Hz, 1H, H8), 7.11 (d, J = 2.2 Hz, 1H, H6), 7.03 (d, J = 8.4 Hz, 1H, H9), 6.89 (d, J = 4.0 Hz, 1H, H4′), 6.68 (d, J = 4.0 Hz, 1H, H3′), 4.95 (ddd, J = 7.6, 5.6, 2.2 Hz, 1H, H4), 4.70 (dd, J = 8.4, 1.8 Hz, 1H, H2), 3.37 (dd, J = 16.8, 5.6 Hz, 1H, HB5), 2.65 (dddd, J = 13.0, 7.6, 1.8, 1.0 Hz, 1H, HB3), 2.50 (br d, J = 16.8 Hz, 1H, H_A5), 2.49 (ddd, J = 13.0, 8.4, 2.2 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8 (C2′), 147.8 (C9a), 131.7 (C7), 129.8 (C6), 129.3 (C4′), 127.1 (C5a), 127.0 (C8), 124.1 (C3′), 123.6 (C9), 111.9 (C5′), 74.7 (C4), 72.0 (C2), 42.1 (C3), 34.6 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1047 (C–O), 967 (N–O). GC–MS (EI, 70 eV): m/z (%) = 355 (M^{+}•, ^{35}Cl, ^{79}Br, 10), 338 (6), 325 (2), 188 (31), 164 (7), 139 (81), 138 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{11}BrClNOS$: 354.9433; found: 354.9448.

4.1.2.9. (2SR,4RS)-7-fluoro-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10i***. Reaction time: 22 h. Yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (dd, J = 4.4, 4.0 Hz, 1H, H5′), 7.10 (dd, J = 8.8, 5.2 Hz, 1H, H9), 6.96 (d, J = 4.4 Hz, 1H, H3′), 6.95 (d, J = 4.0 Hz, 1H, H4′), 6.88 (td, J = 8.8, 3.3 Hz, 1H, H8), 6.83 (dd, J = 9.1, 3.3 Hz, 1H, H6), 4.98 (ddd, J = 7.0, 5.2, 2.0 Hz, 1H, H4), 4.80 (dd, J = 8.2, 2.2 Hz, 1H, H2), 3.40 (dd, J = 16.8, 5.2 Hz, 1H, HB5), 2.73 (dddd, J = 13.0, 7.0, 2.2, 1.0 Hz, 1H, HB3), 2.54 (ddd, J = 13.0, 8.2, 2.0 Hz, 1H, H_A3), 2.53 (br d, J = 16.8 Hz, 1H, H_A5). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8 (d, $^{1}J_{C,F}$ = 248.8 Hz, C7), 147.4 (C2′), 145.7 (C9a), 127.3 (d, $^{3}J_{C,F}$ = 7.8 Hz, C5a), 126.7 (C5′), 125.0 (C4′), 124.0 (C3′), 123.9 (d, $^{3}J_{C,F}$ = 8.4 Hz, C9), 116.3 (d, $^{2}J_{C,F}$ = 22.6 Hz, C6), 113.7 (d, $^{2}J_{C,F}$ = 22.2 Hz, C8), 74.5 (C4), 71.9 (C2), 42.5 (C3), 34.9 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 1048 (C–O), 965 (N–O). GC–MS (EI, 70 eV): m/z (%) = 261 (M^{+}•, 32), 244 (15), 231 (11), 148 (7), 123 (56), 122 (100), 110 (32). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{12}FNOS$: 261.0624; found: 261.0623.

4.1.2.10. (2SR,4RS)-7-fluoro-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10j***. Reaction time: 23 h. Yield: 64%. White solid. mp 103 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (dd, J = 8.6, 5.3 Hz, 1H, H9), 6.87 (td, J = 8.6, 2.8 Hz, 1H, H8), 6.82 (dd, J = 9.0, 2.8 Hz, 1H, H6), 6.74 (d, J = 3.4 Hz, 1H, H3′), 6.60 (d, J = 3.4 Hz, 1H, H4′), 4.96 (ddd, J = 7.6, 5.3, 1.6 Hz, 1H, H4), 4.72 (dd, J = 8.3, 2.0 Hz, 1H, H2), 3.39 (dd, J = 16.6, 5.3 Hz, 1H, HB5), 2.70

(dddd, J = 12.6, 7.6, 2.0, 1.2 Hz, 1H, HB3), 2.52 (br d, J = 16.6 Hz, 1H, H_A5), 2.48 (ddd, J = 12.6, 8.3, 1.6 Hz, 1H, H_A3), 2.46 (s, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (d, $^1J_{C,F}$ = 244.3 Hz, C7), 145.6 (d, $^4J_{C,F}$ = 2.7 Hz, C9a), 144.6 (C2′), 139.0 (C5′), 127.2 (d, $^3J_{C,F}$ = 8.3 Hz, C5a), 124.5 (C4′), 123.8 (C3′), 123.7 (d, $^3J_{C,F}$ = 8.5 Hz, C9), 116.2 (d, $^2J_{C,F}$ = 22.4 Hz, C6), 113.6 (d, $^2J_{C,F}$ = 22.6 Hz, C8), 74.4 (C4), 72.0 (C2), 42.0 (C3), 34.9 (C5), 15.4 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1043 (C–O), 978 (N–O). GC–MS (EI, 70 eV): m/z (%) = 275 ($M^{+\bullet}$, 52), 258 (36), 245 (12), 148 (12), 123 (82), 122 (79), 124 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{14}FNOS$: 275.0780; found: 275.0784.

4.1.2.11. (2SR,4RS)-7-fluoro-2-(3-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10k***. Reaction time: 20 h. Yield: 66%. White solid. mp 126 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 5.1 Hz, 1H, H5′), 7.04 (dd, J = 8.6, 5.2 Hz, 1H, H9), 6.88 (td, J = 8.6, 2.8 Hz, 1H, H8), 6.84 (dd, J = 9.0, 2.8 Hz, 1H, H6), 6.80 (d, J = 5.1 Hz, 1H, H4′), 5.00 (ddd, J = 7.2, 5.4, 1.8 Hz, 1H, H4), 4.84 (dd, J = 8.1, 2.6 Hz, 1H, H2), 3.40 (dd, J = 16.8, 5.4 Hz, 1H, HB5), 2.65 (dddd, J = 12.5, 7.2, 2.6, 1.2 Hz, 1H, HB3), 2.58 (ddd, J = 12.5, 8.1, 1.8 Hz, 1H, H_A3), 2.54 (br d, J = 16.8 Hz, 1H, H_A5), 2.24 (s, 3H, 3′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (d, $^1J_{C,F}$ = 244.4 Hz, C7), 145.8 (d, $^4J_{C,F}$ = 2.7 Hz, C9a), 140.3 (C2′), 132.7 (C3′), 129.7 (C4′), 127.2 (d, $^3J_{C,F}$ = 8.2 Hz, C5a), 123.6 (d, $^3J_{C,F}$ = 8.5 Hz, C9), 123.1 (C5′), 116.3 (d, $^2J_{C,F}$ = 22.4 Hz, C6), 113.6 (d, $^2J_{C,F}$ = 22.6 Hz, C8), 74.5 (C4), 70.3 (C2), 42.4 (C3), 34.8 (C5), 14.2 (3′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1036 (C–O), 977 (N–O). GC–MS (EI, 70 eV): m/z (%) = 275 ($M^{+\bullet}$, 52), 258 (30), 245 (9), 148 (15), 124 (79), 123 (91), 122 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{14}FNOS$: 275.0780; found: 275.0782.

4.1.2.12. (2SR,4RS)-7-fluoro-2-(5-bromothiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10l***. Reaction time: 21 h. Yield: 61%. White solid. mp 107 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (dd, J = 8.6, 5.2 Hz, 1H, H9), 6.89 (d, J = 4.0 Hz, 1H, H4′), 6.87 (td, J = 8.6, 3.3 Hz, 1H, H8), 6.83 (dd, J = 9.0, 3.3 Hz, 1H, H6), 6.68 (d, J = 4.0 Hz, 1H, H3′), 4.95 (ddd, J = 7.2, 5.2, 2.0 Hz, 1H, H4), 4.70 (dd, J = 8.2, 2.0 Hz, 1H, H2), 3.38 (dd, J = 16.8, 5.2 Hz, 1H, HB5), 2.66 (dddd, J = 12.0, 7.2, 2.0, 1.0 Hz, 1H, HB3), 2.52 (br d, J = 16.8 Hz, 1H, H_A5), 2.50 (ddd, J = 12.0, 8.2, 2.0 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (d, $^1J_{C,F}$ = 243.8 Hz, C7), 149.0 (C2′), 145.2 (C9a), 129.3 (C4′), 127.2 (d, $^3J_{C,F}$ = 8.1 Hz, C5a), 124.1 (C3′), 123.8 (d, $^3J_{C,F}$ = 8.7 Hz, C9), 116.3 (d, $^2J_{C,F}$ = 22.8 Hz, C6), 113.8 (d, $^2J_{C,F}$ = 22.5 Hz, C8), 111.9 (C5′), 74.6 (C4), 72.1 (C2), 42.1 (C3), 34.9 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1051 (C–O), 979 (N–O). GC–MS (EI, 70 eV): m/z (%) = 339 ($M^{+\bullet}$, ^{79}Br, 13), 322 (6), 309 (3), 188 (27), 148 (9), 123 (76), 122 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{14}H_{11}BrFNOS$: 338.9729; found: 338.9740.

4.1.2.13. (2SR,4RS)-7-trifluoromethoxy-2-exo-(thiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10m***. Reaction time: 23 h. Yield: 67%. White solid. mp 90 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, J = 4.8, 4.8 Hz, 1H, H5′), 7.16 (d, J = 8.8 Hz, 1H, H9), 7.04 (d, J = 8.8 Hz, 1H, H8), 7.00 (s, 1H, H6), 6.97 (d, J = 4.8 Hz, 1H, H3′), 6.96 (d, J = 4.8 Hz, 1H, H4′), 5.00 (ddd, J = 7.2, 5.2, 2.2 Hz, 1H, H4), 4.84 (dd, J = 8.4, 2.0 Hz, 1H, H2), 3.42 (dd, J = 16.8, 5.2 Hz, 1H, HB5), 2.75 (dddd, J = 13.2, 7.2, 2.0, 1.2 Hz, 1H, HB3), 2.56 (br d, J = 16.8 Hz, 1H, H_A5), 2.55 (ddd, J = 13.2, 8.4, 2.2 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2 (C9a), 147.2 (C7), 147.1 (C2′), 127.2 (C5a), 126.7 (C5′), 125.0 (C4′), 124.1 (C3′), 123.7 (C9), 122.4 (C6), 120.6 (q, $^1J_{C,F}$ = 258.2 Hz, 7-OCF_3), 119.6 (C8), 74.5 (C4), 71.9 (C2), 42.5 (C3), 34.8 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1045 (C–O), 968 (N–O). GC–MS (EI, 70 eV): m/z (%) = 327 ($M^{+\bullet}$, 42), 310 (21), 297 (14), 214 (7), 189 (61), 188 (100), 110 (28). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{12}F_3NO_2S$: 327.0538; found: 327.0533.

4.1.2.14. (2SR,4RS)-7-trifluoromethoxy-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10n***. Reaction time: 26 h. Yield: 62%. White solid. mp 96 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 8.7 Hz, 1H, H9), 7.04 (dd, J = 8.7, 2.4 Hz, 1H, H8), 6.99 (d, J = 2.4 Hz, 1H, H6), 6.75 (d, J = 3.4 Hz, 1H, H3′), 6.60 (d, J = 3.4 Hz, 1H, H4′), 4.98 (ddd, J = 7.7, 5.2, 2.0 Hz, 1H, H4), 4.75 (dd, J = 8.4, 2.0 Hz, 1H, H2), 3.41 (dd, J = 16.8, 5.2 Hz, 1H, HB5), 2.72 (dddd, J = 12.6, 7.7, 2.0, 1.2 Hz, 1H, HB3), 2.54 (br d, J = 16.8 Hz, 1H, H_A5), 2.51 (ddd, J = 12.6, 8.4, 2.0 Hz, 1H, H_A3), 2.47 (s, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2 (C9a), 147.0 (C7), 144.4 (C2′), 139.6 (C5′), 127.1 (C5a), 124.5 (C4′), 123.9 (C3′), 123.6 (C9), 122.3 (C6), 120.5 (q, $^1J_{C,F}$ = 257.6 Hz, 7-OCF_3), 119.5 (C8), 74.4 (C4), 72.0 (C2), 42.1 (C3), 34.7 (C5), 15.3 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1050 (C–O), 991 (N–O). GC–MS (EI, 70 eV): m/z (%) = 341 ($M^{+\bullet}$, 21), 324 (18), 311 (3), 214 (6), 189 (39), 188 (61), 124 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{16}H_{14}F_3NO_2S$: 341.0697; found: 341.0704.

4.1.2.15. (2SR,4RS)-7-trifluoromethoxy-2-(3-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10o***. Reaction time: 23 h. Yield: 69%. White solid. mp 78 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 8.7 Hz, 1H, H9), 7.14 (d, J = 5.1 Hz, 1H, H5′), 7.05 (dd, J = 8.7, 1.7 Hz, 1H, H8), 7.01 (d, J = 1.7 Hz, 1H, H6), 6.81 (d, J = 5.1 Hz, 1H, H4′), 5.02 (ddd, J = 7.5, 5.4, 2.0 Hz, 1H, H4), 4.87 (dd, J = 8.4, 2.6 Hz, 1H, H2), 3.43 (dd, J = 16.8, 5.4 Hz, 1H, HB5), 2.67 (dddd, J = 12.8, 7.5, 2.6, 1.2 Hz, 1H, HB3), 2.59 (ddd, J = 12.8, 8.4, 2.0 Hz, 1H, H_A3), 2.56 (br d, J = 16.8 Hz, 1H, H_A5), 2.24 (s, 3H, 3′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4 (C9a), 146.0 (C7), 143.0 (C2′), 132.9 (C3′), 129.7 (C4′), 127.1 (C5a), 123.4 (C5′), 123.2 (C9), 122.4 (C6), 120.5 (q, $^1J_{C,F}$ = 257.5 Hz, 7-OCF_3), 119.5 (C8), 74.4 (C4), 70.2 (C2), 42.2 (C3), 34.7 (C5), 14.2 (3′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1053 (C–O), 975 (N–O). GC–MS (EI, 70 eV): m/z (%) = 341 ($M^{+\bullet}$, 30), 324 (21), 311 (6), 214 (9), 189 (67), 188 (100), 124 (70). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{16}H_{14}F_3NO_2S$: 341.0697; found: 341.0709.

4.1.2.16. (2SR,4RS)-7-trifluoromethoxy-2-(5-bromothiophen-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***10p***. Reaction time: 24 h. Yield: 61%. White solid. mp 99 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, J = 8.4 Hz, 1H, H9), 7.03 (d, J = 8.4 Hz, 1H, H8), 6.99 (s, 1H, H6), 6.89 (d, J = 3.6 Hz, 1H, H4′), 6.69 (d, J = 3.6 Hz, 1H, H3′), 4.97 (ddd, J = 7.2, 5.2, 1.6 Hz, 1H, H4), 4.73 (dd, J = 8.4, 1.2 Hz, 1H, H2), 3.41 (dd, J = 16.8, 5.2 Hz, 1H, HB5), 2.68 (dddd, J = 12.8, 7.2, 1.2, 0.8 Hz, 1H, HB3), 2.54 (br d, J = 16.8 Hz, 1H, H_A5), 2.51 (ddd, J = 12.8, 8.4, 1.6 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8 (C2′), 147.8 (C9a), 147.3 (C7), 129.3 (C4′), 127.1 (C5a), 124.2 (C3′), 123.6 (C9), 122.4 (C6), 120.6 (q, $^1J_{C,F}$ = 257.5 Hz, 7-OCF_3), 119.7 (C8), 112.0 (C5′), 74.6 (C4), 72.0 (C2), 42.1 (C3), 34.8 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1046 (C–O), 963 (N–O). GC–MS (EI, 70 eV): m/z (%) = 405 ($M^{+\bullet}$, ^{79}Br, 19), 388 (13), 375 (7), 214 (6), 189 (60), 188 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{11}BrF_3NO_2S$: 404.9646; found: 404.9656.

4.1.2.17. (2SR,4RS)-2-(furan-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11a***. Reaction time: 18 h. Yield: 69%. White solid. mp 86 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, J = 3.2 Hz, 1H, H5′), 7.21–7.17 (m, 2H, H7, H8), 7.16–7.14 (m, 2H, H6, H9), 6.36 (dd, J = 3.3, 3.2 Hz, 1H, H4′), 6.34 (d, J = 3.3 Hz, 1H, H3′), 4.99 (ddd, J = 7.8, 5.8, 1.7 Hz, 1H, H4), 4.65 (dd, J = 8.7, 2.4 Hz, 1H, H2), 3.42 (dd, J = 16.5, 5.8 Hz, 1H, HB5), 2.79 (dddd, J = 12.7, 7.8, 2.4, 1.1 Hz, 1H, HB3), 2.55 (br d, J = 16.5 Hz, 1H, H_A5), 2.42 (ddd, J = 12.7, 8.7, 1.7 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3 (C2′), 149.9 (C9a), 143.1 (C5′), 129.9 (C6), 126.8 (C8), 126.3 (C7), 125.3 (C5a), 122.2 (C9), 110.5 (C4′), 106.6 (C3′), 74.9 (C4), 69.7 (C2), 38.7 (C3), 34.7 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1015 (C–O), 980 (N–O). GC–MS (EI, 70 eV): m/z (%) = 227 ($M^{+\bullet}$, 47), 210 (18), 197 (18), 130 (12), 105 (59), 104 (100),

94 (29). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{14}H_{13}NO_2$: 227.0946; found: 227.0943.

4.1.2.18. (2SR,4RS)-2-(5-methylfuran-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11b***. Reaction time: 19 h. Yield: 61%. White solid. mp 102 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.10 (m, 4H, H6, H7, H8, H9), 6.20 (d, *J* = 3.0 Hz, 1H, H3′), 5.93 (d, *J* = 3.0 Hz, 1H, H4′), 4.98 (ddd, *J* = 7.8, 5.3, 1.6 Hz, 1H, H4), 4.59 (dd, *J* = 8.7, 2.3 Hz, 1H, H2), 3.41 (dd, *J* = 16.6, 5.3 Hz, 1H, HB5), 2.76 (dddd, *J* = 12.6, 7.8, 2.3, 1.0 Hz, 1H, HB3), 2.54 (br d, *J* = 16.6 Hz, 1H, H_A5), 2.39 (ddd, *J* = 12.6, 8.7, 1.6 Hz, 1H, H_A3), 2.31 (s, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4 (C2′), 151.9 (C5′), 150.1 (C9a), 129.9 (C6), 126.8 (C8), 126.3 (C7), 125.3 (C5a), 122.3 (C9), 107.5 (C3′), 106.4 (C4′), 74.9 (C4), 69.8 (C2), 38.5 (C3), 34.7 (C5), 13.8 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1019 (C–O), 953 (N–O). GC–MS (EI, 70 eV): *m/z* (%) = 241 (M^+•, 36), 224 (24), 211 (9), 130 (12), 108 (100), 105 (42), 104 (73). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{15}H_{15}NO_2$: 241.1103; found: 241.1106.

4.1.2.19. (2SR,4RS)-2-(5-nitrofuran-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11c***. Reaction time: 19 h. Yield: 64%. White solid. mp 138 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 3.7 Hz, 1H, H4′), 7.22–7.18 (m, 2H, H7, H8), 7.16–7.10 (m, 2H, H6, H9), 6.71 (d, *J* = 3.7 Hz, 1H, H3′), 4.98 (ddd, *J* = 7.8, 5.3, 2.0 Hz, 1H, H4), 4.68 (dd, *J* = 8.6, 1.8 Hz, 1H, H2), 3.43 (dd, *J* = 16.8, 5.3 Hz, 1H, HB5), 2.82 (ddd, *J* = 12.8, 7.8, 1.8 Hz, 1H, HB3), 2.57 (br d, *J* = 16.8 Hz, 1H, H_A5), 2.52 (ddd, *J* = 12.8, 8.6, 2.0 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (C2′), 151.3 (C5′), 149.2 (C9a), 130.3 (C6), 127.4 (C8), 127.2 (C7), 125.3 (C5a), 122.4 (C9), 113.3 (C4′), 110.3 (C3′), 75.4 (C4), 69.7 (C2), 39.4 (C3), 34.8 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1561 (–NO_2), 1318 (–NO_2), 1021 (C–O), 980 (N–O). GC–MS (EI, 70 eV): *m/z* (%) = 272 (M^+•, 30), 255 (3), 242 (3), 130 (10), 105 (67), 104 (100). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{14}H_{12}N_2O_4$: 272.0797; found: 272.0791.

4.1.2.20. (2SR,4RS)-7-chloro-2-(furan-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11d***. Reaction time: 23 h. Yield: 65%. White solid. mp 95 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (br s, 1H, H5′), 7.15 (dd, *J* = 8.4, 1.6 Hz, 1H, H8), 7.11 (s, 1H, H6), 7.07 (d, *J* = 8.4 Hz, 1H, H9), 6.36–6.35 (m, 1H, H4′), 6.32 (d, *J* = 3.2 Hz, 1H, H3′), 4.96 (ddd, *J* = 7.6, 5.2, 1.6 Hz, 1H, H4), 4.58 (dd, *J* = 8.8, 2.4 Hz, 1H, H2), 3.37 (dd, *J* = 16.8, 5.2 Hz, 1H, HB5), 2.78 (dddd, *J* = 12.8, 7.6, 2.4, 1.2 Hz, 1H, HB3), 2.50 (br d, *J* = 16.8 Hz, 1H, H_A5), 2.38 (ddd, *J* = 12.8, 8.8, 1.6 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0 (C2′), 148.5 (C9a), 142.2 (C5′), 131.5 (C6), 129.7 (C7), 127.2 (C5a), 126.9 (C8), 123.6 (C9), 110.5 (C4′), 106.7 (C3′), 74.4 (C4), 69.6 (C2), 38.6 (C3), 34.6 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1015 (C–O), 982 (N–O). GC–MS (EI, 70 eV): *m/z* (%) = 261 (M^+•, ^{35}Cl, 35), 244 (10), 231 (8), 164 (8), 139 (63), 138 (100), 94 (36). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{14}H_{12}ClNO_2$: 261.0557; found: 261.0563.

4.1.2.21. (2SR,4RS)-7-chloro-2-(5-methylfuran-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11e***. Reaction time: 20 h. Yield: 67%. White solid. mp 113 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, *J* = 8.6, 2.2 Hz, 1H, H8), 7.11 (d, *J* = 2.2 Hz, 1H, H6), 7.10 (d, *J* = 8.6 Hz, 1H, H9), 6.18 (d, *J* = 3.0 Hz, 1H, H3′), 5.93 (d, *J* = 3.0 Hz, 1H, H4′), 4.96 (ddd, *J* = 7.4, 5.2, 1.6 Hz, 1H, H4), 4.54 (dd, *J* = 8.6, 2.3 Hz, 1H, H2), 3.38 (dd, *J* = 16.8, 5.2 Hz, 1H, HB5), 2.76 (dddd, *J* = 12.8, 7.4, 2.3, 1.2 Hz, 1H, HB3), 2.51 (br d, *J* = 16.8 Hz, 1H, H_A5), 2.36 (ddd, *J* = 12.8, 8.6, 1.6 Hz, 1H, H_A3), 2.30 (s, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0 (C2′), 152.1 (C5′), 148.6 (C9a), 131.5 (C7), 129.8 (C6), 127.3 (C5a), 127.0 (C8), 123.7 (C9), 107.7 (C3′), 106.4 (C4′), 74.4 (C4), 69.8 (C2), 38.5 (C3), 34.6 (C5), 13.8 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1013 (C–O), 971 (N–O). GC–MS (EI, 70 eV): *m/z* (%) = 275 (M^+•, ^{35}Cl, 18), 258 (12), 245 (3), 164 (6), 139 (27), 138 (33), 108 (100). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{15}H_{14}ClNO_2$: 275.0713; found: 275.0716.

4.1.2.22. (2SR,4RS)-7-fluoro-2-(furan-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11f***. Reaction time: 22 h. Yield: 65%. White solid. mp 84 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 2.0 Hz, 1H, H5′), 7.11 (dd, *J* = 8.8, 5.2 Hz, 1H, H9), 6.88 (td, *J* = 8.8, 3.0 Hz, 1H, H8), 6.83 (dd, *J* = 9.0, 3.0 Hz, 1H, H6), 6.36 (dd, *J* = 3.0, 2.0 Hz, 1H, H4′), 6.33 (d, *J* = 3.0 Hz, 1H, H3′), 4.95 (ddd, *J* = 7.2, 5.2, 1.6 Hz, 1H, H4), 4.60 (dd, *J* = 8.8, 2.2 Hz, 1H, H2), 3.40 (dd, *J* = 16.8, 5.2 Hz, 1H, HB5), 2.78 (dddd, *J* = 12.8, 7.2, 2.2, 1.0 Hz, 1H, HB3), 2.53 (br d, *J* = 16.8 Hz, 1H, H_A5), 2.41 (ddd, *J* = 12.8, 8.8, 1.6 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9 (d, $^1J_{C,F}$ = 243.8 Hz, C7), 155.2 (C2′), 145.9 (C9a), 142.2 (C5′), 127.3 (d, $^3J_{C,F}$ = 7.8 Hz, C5a), 123.9 (d, $^3J_{C,F}$ = 8.3 Hz, C9), 116.3 (d, $^2J_{C,F}$ = 22.4 Hz, C6), 113.7 (d, $^2J_{C,F}$ = 22.1 Hz, C8), 110.5 (C4′), 106.7 (C3′), 74.4 (C4), 69.7 (C2), 36.7 (C3), 34.9 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1014 (C–O), 979 (N–O). GC–MS (EI, 70 eV): *m/z* (%) = 245 (M^+•, 32), 228 (9), 215 (10), 148 (8), 123 (52), 122 (100), 94 (32). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{14}H_{12}FNO_2$: 245.0852; found: 245.0849.

4.1.2.23. (2SR,4RS)-7-fluoro-2-(5-methylfuran-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11g***. Reaction time: 24 h. Yield: 63%. White solid. mp 102 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (dd, *J* = 8.6, 5.3 Hz, 1H, H9), 6.87 (td, *J* = 8.6, 2.8 Hz, 1H, H8), 6.82 (dd, *J* = 9.0, 2.8 Hz, 1H, H6), 6.18 (d, *J* = 3.1 Hz, 1H, H3′), 5.92 (dd, *J* = 3.1, 0.8 Hz, 1H, H4′), 4.95 (ddd, *J* = 7.5, 5.4, 1.8 Hz, 1H, H4), 4.52 (dd, *J* = 8.6, 2.6 Hz, 1H, H2), 3.38 (dd, *J* = 16.8, 5.4 Hz, 1H, HB5), 2.76 (dddd, *J* = 12.8, 7.5, 2.6, 1.3 Hz, 1H, HB3), 2.52 (br d, *J* = 16.8 Hz, 1H, H_A5), 2.37 (ddd, *J* = 12.8, 8.6, 1.8 Hz, 1H, H_A3), 2.30 (d, *J* = 0.8 Hz, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (d, $^1J_{C,F}$ = 244.3 Hz, C7), 153.1 (C2′), 151.9 (C5′), 145.9 (d, $^4J_{C,F}$ = 2.6 Hz, C9a), 127.3 (d, $^3J_{C,F}$ = 8.2 Hz, C5a), 123.7 (d, $^3J_{C,F}$ = 8.5 Hz, C9), 116.2 (d, $^2J_{C,F}$ = 22.5 Hz, C6), 113.6 (d, $^2J_{C,F}$ = 22.6 Hz, C8), 107.5 (C3′), 106.3 (C4′), 74.2 (C4), 69.6 (C2), 38.4 (C3), 34.7 (C5), 13.7 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1024 (C–O), 955 (N–O). GC–MS (EI, 70 eV): *m/z* (%) = 259 (M^+•, 33), 242 (18), 229 (6), 148 (9), 123 (27), 122 (52), 108 (100). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{15}H_{14}FNO_2$: 259.1009; found: 259.1007.

4.1.2.24. (2SR,4RS)-7-fluoro-2-(5-nitrofuran-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11h***. Reaction time: 25 h. Yield: 63%. White solid. mp 168 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 3.7 Hz, 1H, H4′), 7.09 (dd, *J* = 8.6, 5.2 Hz, 1H, H9), 6.89 (td, *J* = 8.6, 2.8 Hz, 1H, H8), 6.85 (dd, *J* = 9.0, 2.8 Hz, 1H, H6), 6.69 (d, *J* = 3.7 Hz, 1H, H3′), 4.96 (ddd, *J* = 7.9, 5.4, 1.9 Hz, 1H, H4), 4.63 (dd, *J* = 8.6, 2.3 Hz, 1H, H2), 3.40 (dd, *J* = 16.9, 5.4 Hz, 1H, HB5), 2.82 (dddd, *J* = 12.9, 7.9, 2.3, 1.1 Hz, 1H, HB3), 2.57 (br d, *J* = 16.9 Hz, 1H, H_A5), 2.51 (ddd, *J* = 12.9, 8.6, 1.9 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0 (d, $^1J_{C,F}$ = 245.5 Hz, C7), 159.0 (C2′), 151.5 (C5′), 144.7 (d, $^4J_{C,F}$ = 2.8 Hz, C9a), 127.1 (d, $^3J_{C,F}$ = 8.3 Hz, C5a), 123.7 (d, $^3J_{C,F}$ = 8.6 Hz, C9), 116.4 (d, $^2J_{C,F}$ = 22.7 Hz, C6), 113.9 (d, $^2J_{C,F}$ = 22.7 Hz, C8), 112.9 (C4′), 109.9 (C3′), 74.4 (C4), 69.2 (C2), 38.9 (C3), 34.6 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1522 (–NO_2), 1315 (–NO_2), 1024 (C–O), 968 (N–O). GC–MS (EI, 70 eV): *m/z* (%) = 290 (M^+•, 15), 273 (1), 260 (1), 148 (6), 123 (67), 122 (100). HRMS (EI, 70 eV): *m/z* $[M]^+$ calcd for $C_{14}H_{11}FN_2O_4$: 290.0703; found: 290.0707.

4.1.2.25. (2SR,4RS)-7-trifluoromethoxy-2-(furan-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11i***. Reaction time: 23 h. Yield: 60%. White solid. mp 79 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 1.0 Hz, 1H, H5′), 7.17 (d, *J* = 8.6 Hz, 1H, H9), 7.04 (dd, *J* = 8.6, 1.8 Hz, 1H, H8), 6.99 (d, *J* = 1.8 Hz, 1H, H6), 6.36 (dd, *J* = 3.2, 1.0 Hz, 1H, H4′), 6.33 (d, *J* = 3.2 Hz, 1H, H3′), 4.99 (ddd, *J* = 8.1, 5.6, 1.2 Hz, 1H, H4), 4.62 (dd, *J* = 8.7, 2.4 Hz, 1H, H2), 3.42 (dd, *J* = 16.8,

5.6 Hz, 1H, HB5), 2.81 (dddd, J = 12.8, 8.1, 2.4, 1.0 Hz, 1H, HB3), 2.56 (br d, J = 16.8 Hz, 1H, H_A5), 2.42 (ddd, J = 12.8, 8.7, 1.2 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8 (C2′), 148.4 (C9a), 147.0 (C7), 142.2 (C5′), 127.2 (C5a), 123.5 (C9), 122.3 (C6), 120.5 (q, $^1J_{C,F}$ = 257.1 Hz, 7-OCF_3), 119.5 (C8), 110.4 (C4′), 105.7 (C3′), 74.3 (C4), 69.5 (C2), 38.6 (C3), 34.6 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1019 (C—O), 985 (N—O). GC—MS (EI, 70 eV): m/z (%) = 311 (M^{+}•, 21), 294 (6), 281 (6), 214 (6), 189 (55), 188 (100), 94 (33). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{12}F_3NO_3$: 311.0769; found: 311.0767.

4.1.2.26. (2SR,4RS)-7-trifluoromethoxy-2-(5-methylfuran-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11j***. Reaction time: 22 h. Yield: 67%. White solid. mp 93 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 8.6 Hz, 1H, H9), 7.04 (dd, J = 8.6, 2.1 Hz, 1H, H8), 6.98 (d, J = 2.1 Hz, 1H, H6), 6.19 (d, J = 3.1 Hz, 1H, H3′), 5.93 (d, J = 3.1 Hz, 1H, H4′), 4.97 (ddd, J = 7.9, 5.3, 1.8 Hz, 1H, H4), 4.56 (dd, J = 8.6, 2.4 Hz, 1H, H2), 3.40 (dd, J = 16.8, 5.3 Hz, 1H, HB5), 2.77 (dddd, J = 12.9, 7.9, 2.4, 1.2 Hz, 1H, HB3), 2.54 (br d, J = 16.8 Hz, 1H, H_A5), 2.38 (ddd, J = 12.9, 8.6, 1.8 Hz, 1H, H_A3), 2.31 (s, 3H, 5′-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9 (C2′), 152.0 (C5′), 148.5 (C9a), 146.0 (C7), 127.2 (C5a), 123.6 (C9), 122.3 (C6), 120.5 (q, $^1J_{C,F}$ = 256.9 Hz, 7-OCF_3), 119.5 (C8), 107.6 (C3′), 106.3 (C4′), 74.2 (C4), 69.5 (C2), 38.4 (C3), 34.6 (C5), 13.7 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1021 (C—O), 983 (N—O). GC—MS (EI, 70 eV): m/z (%) = 325 (M^{+}•, 18), 308 (12), 295 (3), 214 (6), 189 (27), 188 (45), 108 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{16}H_{14}F_3NO_3$: 325.0926; found: 325.0919.

4.1.2.27. (2SR,4RS)-7-trifluoromethoxy-2-(5-nitrofuran-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***11k***. Reaction time: 25 h. Yield: 66%. White solid. mp 165 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, J = 3.7 Hz, 1H, H4′), 7.15 (d, J = 8.6 Hz, 1H, H9), 7.06 (dd, J = 8.6, 1.7 Hz, 1H, H8), 7.02 (d, J = 1.7 Hz, 1H, H6), 6.69 (d, J = 3.7 Hz, 1H, H3′), 4.99 (ddd, J = 7.8, 5.4, 2.0 Hz, 1H, H4), 4.66 (dd, J = 8.6, 2.2 Hz, 1H, H2), 3.43 (dd, J = 16.8, 5.4 Hz, 1H, HB5), 2.85 (dddd, J = 12.9, 7.8, 2.2, 1.2 Hz, 1H, HB3), 2.60 (br d, J = 16.8 Hz, 1H, H_A5), 2.52 (ddd, J = 12.9, 8.6, 2.0 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (C2′), 151.5 (C5′), 147.4 (C7), 147.2 (C9a), 127.0 (C5a), 123.5 (C9), 122.4 (C6), 120.4 (q, $^1J_{C,F}$ = 257.4 Hz, 7-OCF_3), 119.8 (C8), 112.9 (C4′), 110.0 (C3′), 74.4 (C4), 69.2 (C2), 38.9 (C3), 34.5 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1527 (−NO_2), 1356 (−NO_2), 1023 (C—O), 964 (N—O). GC—MS (EI, 70 eV): m/z (%) = 356 (M^{+}•, 9), 339 (1), 326 (1), 214 (12), 189 (70), 188 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{11}F_3N_2O_5$: 356.0620; found: 356.0630.

4.1.2.28. (2SR,4RS)-7-fluoro-2-(furan-3-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***12a***. Reaction time: 18 h. Yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (dd, J = 1.7, 0.6 Hz, 1H, H2′), 7.39 (*t*, J = 1.7 Hz, 1H, H5′), 7.05 (dd, J = 8.4, 5.3 Hz, 1H, H9), 6.86 (td, J = 8.4, 2.8 Hz, 1H, H8), 6.82 (dd, J = 9.2, 2.8 Hz, 1H, H6), 6.47 (dd, J = 1.7, 0.6 Hz, 1H, H4′), 4.93 (ddd, J = 7.2, 5.3, 1.2 Hz, 1H, H4), 4.48 (dd, J = 8.3, 2.4 Hz, 1H, H2), 3.38 (dd, J = 16.8, 5.3 Hz, 1H, HB5), 2.54 (dddd, J = 12.4, 7.2, 2.4, 1.2 Hz, 1H, HB3), 2.51 (br d, J = 16.8 Hz, 1H, H_A5), 2.43 (ddd, J = 12.4, 8.3, 1.2 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6 (d, $^1J_{C,F}$ = 244.2 Hz, C7), 146.0 (d, $^4J_{C,F}$ = 2.6 Hz, C9a), 143.4 (C5′), 139.1 (C2′), 127.2 (d, $^3J_{C,F}$ = 8.2 Hz, C5a), 123.6 (d, $^3J_{C,F}$ = 8.5 Hz, C9), 128.2 (C3′), 116.2 (d, $^2J_{C,F}$ = 22.4 Hz, C6), 113.5 (d, $^2J_{C,F}$ = 22.5 Hz, C8), 109.6 (C4′), 74.2 (C4), 68.3 (C2), 41.1 (C3), 34.9 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 1024 (C—O), 985 (N—O). GC—MS (EI, 70 eV): m/z (%) = 245 (M^{+}•, 21), 228 (6), 215 (1), 148 (6), 123 (45), 122 (100), 94 (12). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{14}H_{12}FNO_2$: 245.0852; found: 245.0841.

4.1.2.29. (2SR,4RS)-7-trifluoromethoxy-2-(furan-3-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***12b***. Reaction time: 20 h. Yield: 63%. White solid. mp 72 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dd, J = 1.6, 0.9 Hz, 1H, H2′), 7.40 (t, J = 1.6 Hz, 1H, H5′), 7.11 (d, J = 8.6 Hz, 1H, H9), 7.03 (dd, J = 8.6, 1.7 Hz, 1H, H8), 6.99 (d, J = 1.7 Hz, 1H, H6), 6.48 (dd, J = 1.6, 0.9 Hz, 1H, H4′), 4.95 (ddd, J = 7.6, 5.4, 2.1 Hz, 1H, H4), 4.52 (dd, J = 8.3, 2.4 Hz, 1H, H2), 3.40 (dd, J = 16.8, 5.4 Hz, 1H, HB5), 2.55 (dddd, J = 12.6, 7.6, 2.4, 1.2 Hz, 1H, HB3), 2.54 (br d, J = 16.8 Hz, 1H, H_A5), 2.44 (ddd, J = 12.6, 8.3, 2.1 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9 (C7), 143.4 (C5′), 142.6 (C9a), 139.2 (C2′), 128.1 (C3′), 127.1 (C5a), 123.4 (C9), 122.3 (C6), 120.5 (q, $^1J_{C,F}$ = 257.0 Hz, 7-OCF_3), 119.4 (C8), 109.5 (C4′), 74.2 (C4), 68.2 (C2), 41.2 (C3), 34.8 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1035 (C—O), 989 (N—O). GC—MS (EI, 70 eV): m/z (%) = 311 (M^{+}•, 20), 294 (6), 281 (1), 214 (3), 189 (52), 188 (100), 94 (12). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{12}F_3NO_3$: 311.0769; found: 311.0766.

4.1.2.30. (2SR,4RS)-7-chloro-2-(1-methyl-1H-pyrrol-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***13a***. Reaction time: 20 h. Yield: 39%. White solid. mp 170 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (dd, J = 8.3, 2.2 Hz, 1H, H8), 7.13 (d, J = 2.2 Hz, 1H, H6), 7.07 (d, J = 8.3 Hz, 1H, H9), 6.64 (dd, J = 3.2, 1.6 Hz, 1H, H5′), 6.13 (dd, J = 3.2, 1.6 Hz, 1H, H3′), 6.08 (t, J = 3.2 Hz, 1H, H4′), 4.99 (ddd, J = 7.3, 5.3, 2.0 Hz, 1H, H4), 4.60 (dd, J = 8.5, 2.1 Hz, 1H, H2), 3.80 (s, 3H, N—CH_3), 3.38 (dd, J = 16.6, 5.3 Hz, 1H, HB5), 2.86 (dddd, J = 12.9, 7.3, 2.1, 1.2 Hz, 1H, HB3), 2.53 (br d, J = 16.6 Hz, 1H, H_A5), 2.38 (ddd, J = 12.9, 8.5, 2.0 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1 (C9a), 132.6 (C2′), 131.7 (C7), 130.3 (C6), 128.0 (C5a), 127.1 (C8), 123.7 (C9), 123.4 (C5′), 108.2 (C3′), 107.0 (C4′), 74.7 (C4), 68.9 (C2), 38.8 (C3), 35.2 (C5), 34.9 (N—CH_3). IR (KBr, cm−1): $\tilde{\nu}$ = 1026 (C—O), 977 (N—O). GC—MS (EI, 70 eV): m/z (%) = 274 (M^{+}•, ^{35}Cl, 24), 257 (15), 244 (1), 164 (3), 139 (6), 138 (12), 107 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{15}ClN_2O$: 274.0873; found: 274.0879.

4.1.2.31. (2SR,4RS)-7-fluoro-2-(1-methyl-1H-pyrrol-2-yl)-2,3,4,5-tetrahydro-1,4-epoxy-1-benzazepine ***13b***. Reaction time: 20 h. Yield: 31%. White solid. mp 154 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, J = 8.6, 5.2 Hz, 1H, H9), 6.89 (td, J = 8.6, 2.7 Hz, 1H, H8), 6.85 (dd, J = 9.3, 2.7 Hz, 1H, H6), 6.64 (dd, J = 2.8, 1.2 Hz, 1H, H5′), 6.14 (dd, J = 3.2, 1.2 Hz, 1H, H3′), 6.09 (dd, J = 3.2, 2.8 Hz, 1H, H 4′), 4.99 (ddd, J = 8.0, 5.2, 1.9 Hz, 1H, H4), 4.60 (dd, J = 8.4, 1.9 Hz, 1H, H2), 3.81 (s, 3H, N—CH_3), 3.39 (dd, J = 16.7, 5.2 Hz, 1H, HB5), 2.86 (dddd, J = 12.8, 8.0, 1.9, 1.0 Hz, 1H, HB3), 2.54 (br d, J = 16.7 Hz, 1H, H_A5), 2.40 (ddd, J = 12.8, 8.4, 1.9 Hz, 1H, H_A3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0 (d, $^1J_{C,F}$ = 244.3 Hz, C7), 146.5 (d, $^4J_{C,F}$ = 2.8 Hz, C9a), 132.8 (C2′), 128.0 (d, $^3J_{C,F}$ = 8.1 Hz, C5a), 123.6 (C5′), 123.5 (d, $^3J_{C,F}$ = 8.5 Hz, C9), 116.8 (d, $^2J_{C,F}$ = 22.4 Hz, C6), 113.9 (d, $^2J_{C,F}$ = 22.5 Hz, C8), 108.1 (C3′), 107.0 (C4′), 74.6 (C4), 68.9 (C2), 38.8 (C3), 35.4 (C5), 34.9 (N—CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1023 (C—O), 976 (N—O). GC—MS (EI, 70 eV): m/z (%) = 258 (M^{+}•, 30), 241 (18), 228 (1), 148 (9), 123 (9), 122 (15), 107 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{15}FN_2O$: 258.1168; found: 258.1157.

4.1.3. General procedure for the synthesis of cis-2-heteroaryl-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ols ***14***–***16***

To a stirred and cooled (ice-bath) solution of the appropriately 2-substituted 1,4-epoxytetrahydro-1-benzazepines (**10a**–**c**, **10e**–**g**, **10i**–**k**, **10m**–**o**), (**11a,b**, **11d**–**g**, **11i,j**), and (**12a,b**), (1.5 mmol), in methanol (10 mL) were added zinc powder (15.0 mmol), glacial acetic acid (7.5 mmol) and hydrochloric acid (37%, 7.5 mmol). The resulting mixtures were stirred at 0 °C during 20–30 min and then at room temperature for further 10–30 min (TLC monitoring). Each mixture was filtered, neutralized with a 25% ammonium hydroxide solution to pH = 8, and then extracted with ethyl acetate (2 × 100 mL). The organic layer was dried over anhydrous sodium sulfate, and concentrated in vacuum to give crude products which were purified on silica gel column chromatography using

heptane–ethyl acetate (compositions in the range from 5:1 to 2:1 *v*/*v*) as eluent; the expected compounds were obtained as yellow viscous oils or crystalline substances.

4.1.3.1. cis-2-(Thiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14a***. Reaction time: 30 min. Yield: 84%. White solid. mp 122 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (d, J = 5.0 Hz, 1H, H5′), 7.17 (br d, J = 7.4 Hz, 1H, H6), 7.10 (td, J = 7.4, 0.7 Hz, 1H, H8), 7.06 (d, J = 3.4 Hz, 1H, H3′), 7.00 (dd, J = 5.0, 3.4 Hz, 1H, H4′), 6.92 (t, J = 7.4 Hz, 1H, H7), 6.74 (d, J = 7.4 Hz, 1H, H9), 4.32 (dd, J = 11.4, 2.0 Hz, 1H, H_{ax}2), 3.88 (tdd, J = 10.0, 3.8, 2.0 Hz, 1H, H_{ax}4), 3.74 (br s, 1H, N–H), 3.12 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 3.01 (dt, J = 13.6, 2.0 Hz, 1H, H_{eq}5), 2.36 (ddd, J = 12.8, 3.8, 2.0 Hz, 1H, H_{eq}3), 2.19 (ddd, J = 12.8, 11.4, 10.0 Hz, 1H, H_{ax}3), 1.97 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6 (C9a), 147.7 (C2′), 131.8 (C6), 128.2 (C5a), 128.2 (8-C), 126.8 (C5′), 124.5 (C4′), 124.0 (C3′), 122.3 (C7), 120.5 (C9), 69.8 (C4), 56.3 (C2), 49.2 (C3), 44.4 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3301 (N–H, O–H), 1246 (C–N), 1016 (C–O). GC–MS (EI, 70 eV): m/z (%) = 245 ($M^{+\bullet}$, 64), 227 (3), 199 (21), 139 (52), 118 (21), 107 (82), 106 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{14}H_{15}NOS$: 245.0874; found: 245.0874.

4.1.3.2. cis-2-(5-Methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14b***. Reaction time: 45 min. Yield: 93%. Pale yellow solid. mp 93 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, J = 7.4, 1.1 Hz, 1H, H6), 7.09 (td, J = 7.4, 1.1 Hz, 1H, H8), 6.91 (td, J = 7.4, 1.1 Hz, 1H, H7), 6.81 (d, J = 3.4 Hz, 1H, H3′), 6.72 (dd, J = 7.4, 1.1 Hz, 1H, H9), 6.62 (dd, J = 3.4, 1.0 Hz, 1H, H4′), 4.21 (dd, J = 11.5, 2.0 Hz, 1H, H_{ax}2), 3.86 (tdd, J = 10.0, 3.8, 2.0 Hz, 1H, H_{ax}4), 3.71 (br s, 1H, N–H), 3.09 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 3.00 (dt, J = 13.6, 2.0 Hz, 1H, H_{eq}5), 2.49 (d, J = 1.0 Hz, 3H, 5′-CH_3), 2.34 (ddd, J = 12.8, 3.8, 2.0 Hz, 1H, H_{eq}3), 2.14 (ddd, J = 12.8, 11.5, 10.0 Hz, 1H, H_{ax}3), 1.99 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9 (C9a), 145.6 (C2′), 139.3 (C5′), 132.0 (C6), 128.5 (C5a), 127.9 (C8), 125.0 (C4′), 124.1 (C3′), 122.5 (C7), 120.7 (C9), 70.1 (C4), 56.8 (C2), 49.3 (C3), 44.7 (C5), 15.8 (5′-CH_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3342 (N–H, O–H), 1251 (C–N), 1025 (C–O). GC–MS (EI, 70 eV): m/z (%) = 259 ($M^{+\bullet}$, 42), 241 (1), 215 (9), 153 (100), 118 (15), 107 (70), 106 (67). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{17}NOS$: 259.1031; found: 259.1034.

4.1.3.3. cis-2-(3-Methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14c***. Reaction time: 30 min. Yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (dd, J = 7.4, 1.1 Hz, 1H, H6), 7.17 (d, J = 5.1 Hz, 1H, H5′), 7.10 (td, J = 7.4, 1.1 Hz, 1H, H8), 6.93 (td, J = 7.4, 1.1 Hz, 1H, H7), 6.84 (d, J = 5.1 Hz, 1H, H4′), 6.73 (dd, J = 7.4, 1.1 Hz, 1H, H9), 4.31 (dd, J = 11.4, 2.1 Hz, 1H, H_{ax}2), 3.88 (tdd, J = 10.1, 3.8, 2.1 Hz, 1H, H_{ax}4), 3.66 (br s, 1H, N–H), 3.13 (dd, J = 13.5, 10.1 Hz, 1H, H_{ax}5), 3.01 (dt, J = 13.5, 2.1 Hz, 1H, H_{eq}5), 2.30 (ddd, J = 12.7, 3.8, 2.1 Hz, 1H, H_{eq}3), 2.23 (s, 3H, 3′-CH_3), 2.18 (ddd, J = 12.7, 11.4, 10.1 Hz, 1H, H_{ax}3), 1.96 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.1 (C9a), 141.3 (C2′), 133.4 (C3′), 132.0 (C6), 130.3 (C4′), 128.1 (C5a), 127.9 (C8), 123.4 (C5′), 122.6 (C7), 120.7 (C9), 70.3 (C4), 54.6 (C2), 48.7 (C3), 44.8 (C5), 14.4 (3′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3342 (N–H, O–H), 1249 (C–N), 1029 (C–O). GC–MS (EI, 70 eV): m/z (%) = 259 ($M^{+\bullet}$, 52), 241 (1), 215 (12), 153 (100), 118 (18), 107 (99), 106 (91). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{17}NOS$: 259.1031; found: 259.1027.

4.1.3.4. 7-Chloro-cis-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14d***. Reaction time: 60 min. Yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (dd, J = 4.0, 1.0 Hz, 1H, H5′), 7.13 (d, J = 2.4 Hz, 1H, H6), 7.03 (dd, J = 5.2, 1.0 Hz, 1H, H3′), 7.03 (dd, J = 8.0, 2.4 Hz, 1H, H8), 6.98 (dd, J = 5.2, 4.0 Hz, 1H, H4′), 6.66 (d, J = 8.0 Hz, 1H, H9), 4.27 (dd, J = 11.6, 2.0 Hz, 1H, H_{ax}2), 3.84 (tdd, J = 10.4, 4.0, 2.0 Hz, 1H, H_{ax}4), 3.06 (dd, J = 13.8, 10.4 Hz, 1H, H_{ax}5), 2.94 (dt, J = 13.8, 2.0 Hz, 1H, H_{eq}5), 2.34 (ddd, J = 12.9, 4.0, 2.0 Hz, 1H, H_{eq}3), 2.16 (ddd, J = 12.9, 11.6, 10.4 Hz, 1H, H_{ax}3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2 (C9a), 147.0 (C2′), 131.3 (C6), 130.1 (C5a), 127.4 (C8), 127.0 (C7), 126.8 (C5′), 124.6 (C4′), 124.2 (C3′), 121.7 (C9), 69.4 (C4), 56.3 (C2), 49.3 (C3), 44.0 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3347 (N–H, O–H), 1250 (C–N), 1024 (C–O). GC–MS (EI, 70 eV): m/z (%) = 279 ($M^{+\bullet}$, ^{35}Cl, 23), 261 (1), 235 (7), 152 (8), 151 (10), 141 (58), 140 (62), 139 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{14}H_{14}ClNOS$: 279.0485; found: 279.0484.

4.1.3.5. 7-Chloro-cis-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14e***. Reaction time: 60 min. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, J = 2.5 Hz, 1H, H6), 7.03 (dd, J = 8.3, 2.5 Hz, 1H, H8), 6.80 (d, J = 3.4 Hz, 1H, H3′), 6.64 (d, J = 8.3 Hz, 1H, H9), 6.62 (d, J = 3.4 Hz, 1H, H4′), 4.17 (dd, J = 11.4, 2.0 Hz, 1H, H_{ax}2), 3.83 (tdd, J = 10.0, 3.8, 2.0 Hz, 1H, H_{ax}4), 3.72 (br s, 1H, N–H), 3.04 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 2.93 (dt, J = 13.6, 2.0 Hz, 1H, H_{eq}5), 2.48 (s, 3H, 5′-CH_3), 2.32 (ddd, J = 12.8, 3.8, 2.0 Hz, 1H, H_{eq}3), 2.11 (ddd, J = 12.8, 11.4, 10.0 Hz, 1H, H_{ax}3), 1.95 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.2 (C9a), 144.9 (C2′), 139.2 (C5′), 131.3 (C6), 129.9 (C5a), 127.3 (C8), 126.7 (C7), 124.7 (C4′), 123.9 (C3′), 121.6 (C9), 69.5 (C4), 56.4 (C2), 48.7 (C3), 44.0 (C5). 15.5 (5′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3348 (N–H, O–H), 1250 (C–N), 1025 (C–O). GC–MS (EI, 70 eV): m/z (%) = 293 ($M^{+\bullet}$, ^{35}Cl, 18), 275 (1), 249 (3), 153 (100), 152 (6), 141 (24), 140 (21). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{16}ClNOS$: 293.0641; found: 293.0630.

4.1.3.6. 7-Chloro-cis-2-(3-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14f***. Reaction time: 30 min. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, J = 5.1 Hz, 1H, H5′), 7.15 (d, J = 2.5 Hz, 1H, H6), 7.04 (dd, J = 8.3, 2.5 Hz, 1H, H8), 6.83 (d, J = 5.1 Hz, 1H, H4′), 6.64 (d, J = 8.3 Hz, 1H, H9), 4.26 (dd, J = 11.5, 2.0 Hz, 1H, H_{ax}2), 3.86 (tdd, J = 10.0, 4.0, 2.1 Hz, 1H, H_{ax}4), 3.70 (br s, 1H, N–H), 3.08 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 2.95 (dt, J = 13.6, 2.1 Hz, 1H, H_{eq}5), 2.29 (ddd, J = 12.8, 4.0, 2.0 Hz, 1H, H_{eq}3), 2.22 (s, 3H, 3′-CH_3), 2.15 (ddd, J = 12.8, 11.5, 10.0 Hz, 1H, H_{ax}3), 1.90 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5 (C9a), 140.6 (C2′), 133.3 (C3′), 131.3 (C6), 130.1 (C4′), 130.0 (C5a), 127.4 (C8), 126.8 (C7), 123.2 (C5′), 121.5 (C9), 69.7 (C4), 54.3 (C2), 48.2 (C3), 44.1 (C5). 14.0 (3′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3347 (N–H, O–H), 1249 (C–N), 1030 (C–O). GC–MS (EI, 70 eV): m/z (%) = 293 ($M^{+\bullet}$, ^{35}Cl, 24), 275 (1), 249 (3), 153 (100), 152 (6), 141 (3), 140 (27). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{16}ClNOS$: 293.0641; found: 293.0636.

4.1.3.7. 7-Fluoro-cis-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14g***. Reaction time: 30 min. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, J = 5.2, 0.6 Hz, 1H, H5′), 7.04 (dd, J = 3.6, 0.6 Hz, 1H, H3′), 6.98 (dd, J = 5.2, 3.6 Hz, 1H, H4′), 6.87 (dd, J = 9.2, 2.8 Hz, 1H, H6), 6.78 (td, J = 8.8, 2.8 Hz, 1H, H8), 6.67 (dd, J = 8.8, 5.2 Hz, 1H, H9), 4.24 (dd, J = 11.6, 1.6 Hz, 1H, H_{ax}2), 3.83 (tdd, J = 10.0, 4.0, 2.0 Hz, 1H, H_{ax}4), 3.11 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 2.92 (dt, J = 13.6, 2.0 Hz, 1H, H_{eq}5), 2.34 (ddd, J = 12.9, 4.0, 1.6 Hz, 1H, H_{eq}3), 2.15 (ddd, J = 12.9, 11.6, 10.0 Hz, 1H, H_{ax}3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (d, $^1J_{C,F}$ = 245.2 Hz, C7), 147.3 (C2′), 144.5 (d, $^4J_{C,F}$ = 2.6 Hz, C9a), 130.5 (d, $^3J_{C,F}$ = 8.0 Hz, C5a), 126.8 (C5′), 124.5 (C4′), 124.0 (C3′), 121.7 (d, $^3J_{C,F}$ = 8.8 Hz, C9), 117.9 (d, $^2J_{C,F}$ = 22.6 Hz, C6), 113.8 (d, $^2J_{C,F}$ = 22.4 Hz, C8), 69.5 (C4), 56.5 (C2), 49.1 (C3), 44.2 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3346 (N–H, O–H), 1245 (C–N), 1023 (C–O). GC–MS (EI, 70 eV): m/z (%) = 263 ($M^{+\bullet}$, 30), 245 (1), 219 (12), 139 (96), 136 (22), 135 (23), 125 (96), 124 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{14}H_{14}FNOS$: 263.0780; found: 263.0781.

4.1.3.8. 7-Fluoro-cis-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14h***. Reaction time: 30 min. Yield: 88%. ^{1}H

NMR (400 MHz, $CDCl_3$): $\delta = 6.87$ (dd, $J = 8.8$, 2.9 Hz, 1H, H6), 6.80 (d, $J = 3.4$ Hz, 1H, H3′), 6.76 (td, $J = 8.5$, 2.9 Hz, 1H, H8), 6.66 (dd, $J = 8.5$, 5.0 Hz, 1H, H9), 6.62 (dd, $J = 3.4$, 1.0 Hz, 1H, H4′), 4.13 (dd, $J = 11.5$, 2.0 Hz, 1H, $H_{ax}2$), 3.82 (tdd, $J = 10.3$, 3.9, 2.0 Hz, 1H, $H_{ax}4$), 3.63 (br s, 1H, N–H), 3.08 (dd, $J = 13.6$, 10.3 Hz, 1H, $H_{ax}5$), 2.91 (dt, $J = 13.6$, 2.0 Hz, 1H, $H_{eq}5$), 2.42 (d, $J = 1.0$ Hz, 3H, 5′-CH_3), 2.32 (ddd, $J = 12.8$, 3.9, 2.0 Hz, 1H, $H_{eq}3$), 2.11 (ddd, $J = 12.8$, 11.5, 10.3 Hz, 1H, $H_{ax}3$), 1.87 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2 (d, $^1J_{C,F} = 244.6$ Hz, C7), 144.9 (C2′), 144.6 (d, $^4J_{C,F} = 2.4$ Hz, C9a), 139.0 (C5′), 130.3 (d, $^3J_{C,F} = 7.4$ Hz, C5a), 124.6 (C4′), 123.7 (C3′), 121.4 (d, $^3J_{C,F}$ = 8.4 Hz, C9), 117.8 (d, $^2J_{C,F}$ = 22.1 Hz, C6), 113.7 (d, $^2J_{C,F} = 21.9$ Hz, C8), 69.4 (C4), 56.6 (C2), 48.9 (C3), 44.1 (C5), 15.4 (5′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu} = 3345$ (N–H, O–H), 1251 (C–N), 1025 (C–O). GC–MS (EI, 70 eV): m/z (%) = 277 (M^+•, 18), 259 (1), 233 (3), 153 (100), 136 (9), 125 (39), 124 (45). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{16}FNOS$: 277.0937; found: 277.0936.

4.1.3.9. 7-Fluoro-cis-2-(3-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14i***. Reaction time: 45 min. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.17$ (d, $J = 5.1$ Hz, 1H, H5′), 6.89 (dd, $J = 8.8$, 2.8 Hz, 1H, H6), 6.83 (d, $J = 5.1$ Hz, 1H, H4′), 6.78 (td, $J = 8.5$, 2.8 Hz, 1H, H8), 6.67 (dd, $J = 8.5$, 5.0 Hz, 1H, H9), 4.24 (dd, $J = 11.4$, 1.8 Hz, 1H, $H_{ax}2$), 3.84 (tdd, $J = 10.2$, 3.4, 2.5 Hz, 1H, $H_{ax}4$), 3.55 (br s, 1H, N–H), 3.12 (dd, $J = 13.8$, 10.2 Hz, 1H, $H_{ax}5$), 2.93 (dt, $J = 13.8$, 2.5 Hz, 1H, $H_{eq}5$), 2.29 (ddd, $J = 12.8$, 3.4, 1.8 Hz, 1H, $H_{eq}3$), 2.23 (s, 3H, 3′-CH_3), 2.15 (ddd, $J = 12.8$, 11.4, 10.2 Hz, 1H, $H_{ax}3$), 1.95 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.3$ (d, $^1J_{C,F} = 244.6$ Hz, C7), 145.0 (d, $^4J_{C,F}$ = 2.4 Hz, C9a), 140.8 (C2′), 133.1 (C3′), 130.5 (d, $^3J_{C,F}$ = 7.0 Hz, C5a), 130.0 (C4′), 123.1 (C5′), 121.4 (d, $^3J_{C,F}$ = 8.0 Hz, C9), 115.9 (d, $^2J_{C,F}$ = 22.8 Hz, C6), 113.9 (d, $^2J_{C,F} = 22.6$ Hz, C8), 69.8 (C4), 54.6 (C2), 48.4 (C3), 44.3 (C5), 14.0 (3′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu} = 3345$ (N–H, O–H), 1251 (C–N), 1029 (C–O), GC–MS (EI, 70 eV): m/z (%) = 277 (M^+•, 21), 259 (1), 233 (6), 153 (100), 136 (9), 125 (52), 124 (48). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{16}FNOS$: 277.0937; found: 277.0947.

4.1.3.10. 7-Trifluoromethoxy-cis-2-(thiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14j***. Reaction time: 60 min. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$ (dd, $J = 4.8$, 1.2 Hz, 1H, H5′), 7.05 (dd, $J = 3.6$, 1.2 Hz, 1H, H3′), 7.03 (d, $J = 2.0$ Hz, 1H, H6), 6.99 (dd, $J = 4.8$, 3.6 Hz, 1H, H4′), 6.94 (dd, $J = 8.4$, 2.0 Hz, 1H, H8), 6.74 (d, $J = 8.4$ Hz, 1H, H9), 4.30 (dd, $J = 11.6$, 2.0 Hz, 1H, $H_{ax}2$), 3.88 (tdd, $J = 10.0$, 4.0, 2.0 Hz, 1H, $H_{ax}4$), 3.11 (dd, $J = 13.6$, 10.0 Hz, 1H, $H_{ax}5$), 2.98 (dt, $J = 13.6$, 2.0 Hz, 1H, $H_{eq}5$), 2.36 (ddd, $J = 12.8$, 4.0, 2.0 Hz, 1H, $H_{eq}3$), 2.20 (ddd, $J = 12.8$, 11.6, 10.0 Hz, 1H, $H_{ax}3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0 (C7), 147.0 (C2′), 144.0 (C9a), 129.9 (C5a), 126.9 (C5′), 124.7 (C6), 124.3 (C4′), 124.3 (C3′), 121.4 (C9), 120.7 (q, $^1J_{C,F} = 255.6$ Hz, 7-OCF_3), 120.2 (C8), 69.4 (C4), 56.3 (C2), 48.8 (C3), 44.1 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu} = 3351$ (N–H, O–H), 1248 (C–N), 1024 (C–O). GC–MS (EI, 70 eV): m/z (%) = 329 (M^+•, 61), 311 (1), 285 (13), 202 (9), 201 (14), 191 (68), 190 (63), 139 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{14}F_3NO_2S$: 329.0697; found: 329.0709.

4.1.3.11. 7-Trifluoromethoxy-cis-2-(5-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14k***. Reaction time: 30 min. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.01$ (d, $J = 2.3$ Hz, 1H, H6), 6.93 (dd, $J = 8.4$, 2.3 Hz, 1H, H8), 6.81 (d, $J = 3.4$ Hz, 1H, H3′), 6.69 (d, $J = 8.4$ Hz, 1H, H9), 6.62 (dd, $J = 3.4$, 1.1 Hz, 1H, H4′), 4.19 (dd, $J = 11.5$, 2.0 Hz, 1H, $H_{ax}2$), 3.85 (tdd, $J = 10.0$, 3.9, 2.0 Hz, 1H, $H_{ax}4$), 3.74 (br s, 1H, N–H), 3.07 (dd, $J = 13.7$, 10.0 Hz, 1H, $H_{ax}5$), 2.96 (dt, $J = 13.7$, 2.0 Hz, 1H, $H_{eq}5$), 2.48 (d, $J = 1.1$ Hz, 3H, 5′-CH_3), 2.33 (ddd, $J = 12.9$, 3.9, 2.0 Hz, 1H, $H_{eq}3$), 2.13 (ddd, $J = 12.9$, 11.5, 10.0 Hz, 1H, $H_{ax}3$), 1.95 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3 (C9a), 144.7 (C2′), 143.6 (C7), 139.1 (C5′), 129.6 (C5a), 124.6 (C4′), 124.1 (C6), 123.9 (C3′), 121.0 (C9), 120.6 (q, $^1J_{C,F} = 256.1$ Hz, 7-OCF_3), 120.1 (C8), 69.3 (C4), 56.3 (C2), 48.6 (C3), 44.0 (C5), 15.4 (5′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu} = 3352$ (N–H, O–H), 1245 (C–N), 1027 (C–O). GC–MS (EI, 70 eV): m/z (%) = 343 (M^+•, 12), 325 (1), 299 (3), 202 (6), 191 (21), 190 (24), 153 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{16}H_{16}F_3NO_2S$: 343.0854; found: 343.0844.

4.1.3.12. 7-Trifluoromethoxy-cis-2-(3-methylthiophen-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***14l***. Reaction time: 45 min. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.18$ (d, $J = 5.1$ Hz, 1H, H5′), 7.04 (d, $J = 2.0$ Hz, 1H, H6), 6.94 (dd, $J = 8.4$, 2.0 Hz, 1H, H8), 6.84 (d, $J = 5.1$ Hz, 1H, H4′), 6.70 (d, $J = 8.4$ Hz, 1H, H9), 4.30 (dd, $J = 11.4$, 2.0 Hz, 1H, $H_{ax}2$), 3.88 (tdd, $J = 10.0$, 4.0, 2.0 Hz, 1H, $H_{ax}4$), 3.68 (br s, 1H, N–H), 3.11 (dd, $J = 13.6$, 10.0 Hz, 1H, $H_{ax}5$), 2.98 (dt, $J = 13.6$, 2.0 Hz, 1H, $H_{eq}5$), 2.48 (s, 3H, 3′-CH_3), 2.30 (ddd, $J = 12.8$, 4.0, 2.0 Hz, 1H, $H_{eq}3$), 2.17 (ddd, $J = 12.8$, 11.4, 10.0 Hz, 1H, $H_{ax}3$), 1.99 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.8$ (C9a), 144.1 (C7), 140.8 (C2′), 133.5 (C3′), 130.3 (C4′), 130.1 (C5a), 124.6 (C6), 123.5 (C5′), 121.3 (C9), 120.6 (q, $^1J_{C,F} = 256.0$ Hz, 7-OCF_3), 120.5 (C8), 69.7 (C4), 54.5 (C2), 48.4 (C3), 44.4 (C5), 14.3 (3′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu} = 3356$ (N–H, O–H), 1244 (C–N), 1032 (C–O). GC–MS (EI, 70 eV): m/z (%) = 343 (M^+•, 15), 325 (1), 299 (3), 202 (6), 191 (30), 190 (30), 153 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{16}H_{16}F_3NO_2S$: 343.0854; found: 343.0865.

4.1.3.13. cis-2-(Furan-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15a***. Reaction time: 30 min. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$ (dd, $J = 1.9$, 0.7 Hz, 1H, H5′), 7.16 (dd, $J = 7.4$, 1.5 Hz, 1H, H6), 7.11 (td, $J = 7.4$, 1.5 Hz, 1H, H8), 6.92 (td, $J = 7.4$, 1.0 Hz, 1H, H7), 6.81 (dd, $J = 7.4$, 1.0 Hz, 1H, H9), 6.37 (dd, $J = 3.3$, 1.9 Hz, 1H, H4′), 6.27 (dd, $J = 3.3$, 0.7 Hz, 1H, H3′), 4.11 (dd, $J = 11.4$, 1.9 Hz, 1H, $H_{ax}2$), 3.89 (tdd, $J = 10.0$, 4.0, 2.3 Hz, 1H, $H_{ax}4$), 3.93 (br s, 1H, N–H), 3.10 (dd, $J = 13.8$, 10.0 Hz, 1H, $H_{ax}5$), 3.01 (dt, $J = 13.8$, 2.3 Hz, 1H, $H_{eq}5$), 2.39 (ddd, $J = 12.8$, 4.0, 1.9 Hz, 1H, $H_{eq}3$), 2.16 (ddd, $J = 12.8$, 11.4, 10.0 Hz, 1H, $H_{ax}3$), 1.75 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.0$ (C2′), 148.6 (C9a), 141.9 (C5′), 131.6 (C6), 128.3 (C5a), 127.5 (C8), 122.2 (C7), 120.4 (C9), 110.4 (C4′), 105.5 (C3′), 69.6 (C4), 53.8 (C2), 44.3 (C3), 44.2 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3360 (N–H, O–H), 1253 (C–N), 1012 (C–O). GC–MS (EI, 70 eV): m/z (%) = 229 (M^+•, 52), 211 (1), 185 (18), 123 (36), 118 (15), 107 (67), 106 (100). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{14}H_{15}NO_2$: 229.1103; found: 229.1098.

4.1.3.14. cis-2-(5-Methylfuran-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15b***. Reaction time: 30 min. Yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, J = 7.5, 1.0 Hz, 1H, H6), 7.11 (td, J = 7.5, 1.0 Hz, 1H, H8), 6.91 (td, J = 7.5, 1.0 Hz, 1H, H7), 6.81 (dd, J = 7.5, 1.0 Hz, 1H, H9), 6.12 (d, J = 3.1 Hz, 1H, H3′), 5.93 (dd, J = 3.1, 1.0 Hz, 1H, H4′), 4.03 (dd, J = 11.4, 2.0 Hz, 1H, $H_{ax}2$), 3.86 (tdd, J = 10.0, 3.9, 2.2 Hz, 1H, $H_{ax}4$), 3.09 (dd, J = 13.6, 10.0 Hz, 1H, $H_{ax}5$), 2.99 (dt, J = 13.6, 2.2 Hz, 1H, $H_{eq}5$), 2.36 (ddd, J = 12.8, 3.9, 2.0 Hz, 1H, $H_{eq}3$), 2.31 (d, J = 1.0 Hz, 3H, 5′-CH_3), 2.14 (ddd, J = 12.8, 11.4, 10.0 Hz, 1H, $H_{ax}3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2 (C2′), 151.6 (C5′), 148.7 (C9a), 131.6 (C6), 128.3 (C5a), 127.5 (C8), 122.1 (C7), 120.4 (C9), 106.2 (C4′), 106.2 (C3′), 69.6 (C4), 53.9 (C2), 44.3 (C3), 44.2 (C5), 13.6 (5′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3359 (N–H, O–H), 1254 (C–N), 1023 (C–O). GC–MS (EI, 70 eV): m/z (%) = 243 (M^+•, 30), 225 (1), 199 (6), 137 (100), 118 (12), 107 (58), 106 (55). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{17}NO_2$: 243.1259; found: 243.1251.

4.1.3.15. 7-Chloro-cis-2-(furan-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15c***. Reaction time: 60 min. Yield: 81%. White solid. mp 109–110 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 1.2$ Hz, 1H, H5′), 7.11 (d, $J = 2.0$ Hz, 1H, H6), 7.04 (dd, J = 8.4,

2.0 Hz, 1H, H8), 6.71 (d, J = 8.4 Hz, 1H, H9), 6.35 (dd, J = 3.2, 1.2 Hz, 1H, H4′), 6.25 (d, J = 3.2 Hz, 1H, H3′), 4.03 (dd, J = 11.2, 1.2 Hz, 1H, H_{ax}2), 3.84 (tdd, J = 10.0, 3.6, 2.2 Hz, 1H, H_{ax}4), 3.03 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 2.93 (dt, J = 13.6, 2.2 Hz, 1H, H_{eq}5), 2.36 (ddd, J = 12.8, 3.6, 1.2 Hz, 1H, H_{eq}3), 2.12 (ddd, J = 12.8, 11.2, 10.0 Hz, 1H, H_{ax}3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8 (C2′), 147.2 (C9a), 142.2 (C5′), 131.3 (C6), 130.2 (C5a), 127.3 (C8), 126.8 (C7), 121.7 (C9), 110.5 (C4′), 105.7 (C3′), 69.3 (C4), 53.9 (C2), 44.0 (C3), 44.0 (C5). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3296 (N–H, O–H), 1245 (C–N), 1019 (C–O). GC–MS (EI, 70 eV): m/z (%) = 263 (M^{+}•, ^{35}Cl, 55), 219 (15), 218 (13), 190 (27), 152 (11), 151 (15), 141 (65), 140 (70), 123 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{14}ClNO_2$: 263.0713; found: 263.0719.

4.1.3.16. 7-Chloro-cis-2-(5-methylfuran-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15d***. Reaction time: 60 min. Yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, J = 2.4 Hz, 1H, H6), 7.04 (dd, J = 8.4, 2.4 Hz, 1H, H8), 6.73 (d, J = 8.4 Hz, 1H, H9), 6.11 (d, J = 3.1 Hz, 1H, H3′), 5.93 (d, J = 3.1 Hz, 1H, H4′), 4.00 (dd, J = 11.4, 2.0 Hz, 1H, H_{ax}2), 3.84 (tdd, J = 10.0, 4.0, 2.0 Hz, 1H, H_{ax}4), 3.03 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 2.93 (dt, J = 13.6, 2.0 Hz, 1H, H_{eq}5), 2.34 (ddd, J = 12.8, 4.0, 2.0 Hz, 1H, H_{eq}3), 2.30 (s, 3H, 5′-CH_3), 2.11 (ddd, J = 12.8, 11.4, 10.0 Hz, 1H, H_{ax}3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8 (C2′), 151.6 (C5′), 147.2 (C9a), 131.1 (C6), 129.9 (C5a), 127.1 (C8), 126.5 (C7), 121.4 (C9), 106.3 (C3′), 106.2 (C4′), 69.2 (C4), 53.8 (C2), 43.9 (C3), 43.8 (C5). 13.5 (5′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3364 (N–H, O–H), 1252 (C–N), 1024 (C–O). GC–MS (EI, 70 eV): m/z (%) = 277 (M^{+}•, ^{35}Cl, 12), 259 (1), 233 (3), 152 (3), 141 (18), 140 (18), 137 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{15}H_{16}ClNO_2$: 277.0870; found: 277.0874.

4.1.3.17. 7-Fluoro-cis-2-(furan-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15e***. Reaction time: 30 min. Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, J = 1.6 Hz, 1H, H5′), 6.86 (dd, J = 9.2, 2.8 Hz, 1H, H6), 6.79 (td, J = 8.8, 2.8 Hz, 1H, H8), 6.74 (dd, J = 8.8, 5.0 Hz, 1H, H9), 6.36 (dd, J = 3.2, 1.6 Hz, 1H, H4′), 6.25 (d, J = 3.2 Hz, 1H, H3′), 4.02 (dd, J = 11.4, 1.2 Hz, 1H, H_{ax}2), 3.85 (tdd, J = 10.0, 4.0, 2.0 Hz, 1H, H_{ax}4), 3.06 (dd, J = 13.6, 10.0 Hz, 1H, H_{ax}5), 2.91 (dd, J = 13.6, 2.0 Hz, 1H, H_{eq}5), 2.36 (ddd, J = 12.8, 4.0, 1.2 Hz, 1H, H_{eq}3), 2.12 (ddd, J = 12.8, 11.4, 10.0 Hz, 1H, H_{ax}3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (d, $^1J_{C,F}$ = 244.8 Hz, C7), 155.9 (C2′), 144.7 (d, $^4J_{F,C}$ = 2.8 Hz, C9a), 141.9 (C5′), 130.7 (d, $^3J_{C,F}$ = 8.2 Hz, C5a), 121.6 (d, $^3J_{C,F}$ = 8.8 Hz, C9), 117.9 (d, $^2J_{C,F}$ = 22.8 Hz, C6), 113.8 (d, $^2J_{C,F}$ = 22.6 Hz, C8), 110.5 (C4′), 105.6 (C3′), 69.3 (C4), 54.2 (C2), 44.2 (C3), 44.1 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3358 (N–H, O–H), 1248 (C–N), 1016 (C–O). GC–MS (EI, 70 eV): m/z (%) = 247 (M^{+}•, 56), 203 (16), 202 (16), 174 (33), 136 (18), 135 (18), 125 (83), 124 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{14}FNO_2$: 247.1009; found: 247.1012.

4.1.3.18. 7-Fluoro-cis-2-(5-methylfuran-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15f***. Reaction time: 45 min. Yield: 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (dd, J = 9.2, 2.8 Hz, 1H, H6), 6.77 (td, J = 8.8, 2.8 Hz, 1H, H8), 6.75 (dd, J = 8.8, 5.2 Hz, 1H, H9), 6.11 (d, J = 3.1 Hz, 1H, H3′), 5.93 (d, J = 3.1 Hz, 1H, H4′), 3.96 (dd, J = 11.4, 1.9 Hz, 1H, H_{ax}2), 3.83 (tdd, J = 10.1, 3.9, 2.4 Hz, 1H, H_{ax}4), 3.07 (dd, J = 13.6, 10.1 Hz, 1H, H_{ax}5), 2.91 (dt, J = 13.6, 2.4 Hz, 1H, H_{eq}5), 2.35 (ddd, J = 12.7, 3.9, 1.9 Hz, 1H, H_{eq}3), 2.30 (s, 3H, 5′-CH_3), 2.11 (ddd, J = 12.7, 11.4, 10.1 Hz, 1H, H_{ax}3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2 (d, $^1J_{C,F}$ = 243.8 Hz, C7), 154.2 (C2′), 151.7 (C5′), 144.9 (d, $^4J_{C,F}$ = 2.8 Hz, C9a), 130.5 (d, $^3J_{C,F}$ = 8.4 Hz, C5a), 121.5 (d, $^3J_{C,F}$ = 8.8 Hz, C9), 117.9 (d, $^2J_{C,F}$ = 22.6 Hz, C6), 113.8 (d, $^2J_{C,F}$ = 22.4 Hz, C8), 106.3 (C4′), 106.3 (C3′), 69.5 (C4), 54.3 (C2), 44.3 (C3), 44.2 (C5), 13.6 (5′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3361 (N–H, O–H), 1252 (C–N), 1022 (C–O). GC–MS (EI, 70 eV): m/z (%) = 261 (M^{+}•, 18), 243 (1), 217 (3), 137 (100), 136 (9), 125 (30), 124 (33). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{15}H_{16}FNO_2$: 261.1165; found: 261.1156.

4.1.3.19. 7-Trifluoromethoxy-cis-2-(furan-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15g***. Reaction time: 45 min. Yield: 79%. Pale yellow solid. mp 85 °C (heptane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, J = 1.9, 0.7 Hz, 1H, H5′), 7.02 (d, J = 2.1 Hz, 1H, H6), 6.96 (dd, J = 8.5, 2.1 Hz, 1H, H8), 6.78 (d, J = 8.5 Hz, 1H, H9), 6.37 (dd, J = 3.2, 1.9 Hz, 1H, H4′), 6.27 (dd, J = 3.2, 0.7 Hz, 1H, H3′), 4.10 (dd, J = 11.6, 1.9 Hz, 1H, H_{ax}2), 3.96 (br s, 1H, N–H), 3.89 (tdd, J = 9.9, 3.7, 2.1 Hz, 1H, H_{ax}4), 3.07 (dd, J = 13.7, 9.9 Hz, 1H, H_{ax}5), 2.97 (dt, J = 13.7, 2.1 Hz, 1H, H_{eq}5), 2.39 (ddd, J = 12.8, 3.7, 1.9 Hz, 1H, H_{eq}3), 2.15 (ddd, J = 12.8, 11.6, 9.9 Hz, 1H, H_{ax}3), 2.07 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6 (C2′), 147.3 (C9a), 143.7 (C7), 142.0 (C5′), 129.8 (C5a), 124.2 (C6), 121.1 (C9), 120.6 (q, $^1J_{C,F}$ = 256.1 Hz, 7-OCF_3), 120.1 (C8), 110.5 (C4′), 105.7 (C3′), 69.2 (C4), 53.7 (C2), 44.0 (C5),43.9 (C3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3362 (N–H, O–H), 1248 (C–N), 1013 (C–O). GC–MS (EI, 70 eV): m/z (%) = 313 (M^{+}•, 36), 295 (1), 269 (12), 202 (6), 191 (52), 190 (67), 123 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{15}H_{14}F_3NO_3$: 313.0926; found: 313.0921.

4.1.3.20. 7-Trifluoromethoxy-cis-2-(5-methylfuran-2-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***15h***. Reaction time: 60 min. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, J = 1.9 Hz, 1H, H6), 6.95 (dd, J = 8.5, 1.9 Hz, 1H, H8), 6.78 (d, J = 8.5 Hz, 1H, H9), 6.12 (d, J = 3.1 Hz, 1H, H3′), 5.93 (d, J = 3.1 Hz, 1H, H4′), 4.04 (dd, J = 11.4, 1.9 Hz, 1H, H_{ax}2), 3.96 (br s, 1H, N–H), 3.89 (tdd, J = 9.8, 3.8, 2.7 Hz, 1H, H_{ax}4), 3.07 (dd, J = 13.7, 9.8 Hz, 1H, H_{ax}5), 2.97 (dt, J = 13.7, 2.7 Hz, 1H, H_{eq}5), 2.36 (ddd, J = 12.8, 3.8, 1.9 Hz, 1H, H_{eq}3), 2.30 (s, 3H, 5′-CH_3), 2.14 (ddd, J = 12.8, 11.4, 9.8 Hz, 1H, H_{ax}3), 2.07 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2 (C2′), 152.1 (C5′), 147.8 (C9a), 144.1 (C7), 130.0 (C5a), 124.6 (C6), 121.4 (C9), 121.0 (q, $^1J_{C,F}$ = 257.5 Hz, 7-OCF_3), 120.4 (C8), 106.7 (C3′), 106.6 (C4′), 69.6 (C4), 54.2 (C2), 44.3 (C5), 44.3 (C3), 14.0 (5′-CH_3). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3366 (N–H, O–H), 1246 (C–N), 1023 (C–O). GC–MS (EI, 70 eV): m/z (%) = 327 (M^{+}•, 12), 309 (1), 283 (3), 202 (6), 191 (18), 190 (24), 137 (100). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{16}H_{16}F_3NO_3$: 327.1082; found: 327.1092.

4.1.3.21. 7-Fluoro-cis-2-(furan-3-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***16a***. Reaction time: 60 min. Yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (dd, J = 1.7, 0.8 Hz, 1H, H2′), 7.42 (*t*, J = 1.7 Hz, 1H, H5′), 6.87 (dd, J = 9.0, 2.9 Hz, 1H, H6), 6.77 (td, J = 8.5, 2.9 Hz, 1H, H8), 6.65 (dd, J = 8.5, 5.0 Hz, 1H, H9), 6.48 (dd, J = 1.7, 0.8 Hz, 1H, H4′), 3.91 (dd, J = 11.4, 2.0 Hz, 1H, H_{ax}2), 3.82 (tdd, J = 10.3, 4.0, 2.2 Hz, 1H, H_{ax}4), 3.50 (br s, 1H, N–H), 3.07 (dd, J = 13.6, 10.3 Hz, 1H, H_{ax}5), 2.91 (dt, J = 13.6, 2.2 Hz, 1H, H_{eq}5), 2.21 (ddd, J = 12.9, 4.0, 2.0 Hz, 1H, H_{eq}3), 2.12 (br s, 1H, 4-OH), 2.05 (ddd, J = 12.9, 11.4, 10.3 Hz, 1H, H_{ax}3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1 (d, $^1J_{C,F}$ = 239.8 Hz, C7), 145.0 (d, $^4J_{C,F}$ = 2.3 Hz, C9a), 143.6 (C5′), 138.7 (C2′), 130.2 (d, $^3J_{C,F}$ = 7.4 Hz, C5a), 128.8 (C3′), 121.3 (d, $^3J_{C,F}$ = 8.0 Hz, C9), 117.9 (d, $^2J_{C,F}$ = 22.1 Hz, C6), 113.7 (d, $^2J_{C,F}$ = 22.0 Hz, C8), 108.7 (C4′), 69.6 (C4), 52.6 (C2), 47.5 (C3), 44.2 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3358 (N–H, O–H), 1252 (C–N), 1023 (C–O). GC–MS (EI, 70 eV): m/z (%) = 247 (M^{+}•, 94), 229 (3), 203 (36), 136 (27), 125 (79), 124 (100), 123 (42). HRMS (EI, 70 eV): m/z $[M]^{+}$ calcd for $C_{14}H_{14}FNO_2$: 247.1009; found: 247.1014.

4.1.3.22. 7-Trifluoromethoxy-cis-2-(furan-3-yl)-2,3,4,5-tetrahydro-1H-1-benzazepin-4-ol ***16b***. Reaction time: 60 min. Yield: 84%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (dd, J = 1.5, 0.8 Hz, 1H, H2′), 7.43 (*t*, J = 1.5 Hz, 1H, H5′), 7.01 (d, J = 1.8 Hz, 1H, H6), 6.93 (dd, J = 8.4, 1.8 Hz, 1H, H8), 6.69 (d, J = 8.4 Hz, 1H, H9), 6.48 (dd, J = 1.5, 0.8 Hz, 1H, H4′), 3.97 (dd, J = 11.5, 2.0 Hz, 1H, H_{ax}2), 3.85 (tdd, J = 9.9, 4.0, 2.1 Hz, 1H, H_{ax}4), 3.62 (br s, 1H, N–H), 3.06 (dd, J = 13.7, 9.9 Hz, 1H,

$H_{ax}5$), 2.95 (dt, J = 13.7, 2.1 Hz, 1H, $H_{eq}5$), 2.22 (ddd, J = 12.9, 4.0, 2.0 Hz, 1H, $H_{eq}3$), 2.07 (ddd, J = 12.9, 11.5, 9.9 Hz, 1H, $H_{ax}3$), 2.05 (br s, 1H, 4-OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6 (C9a), 143.6 (C5′), 143.6 (C7), 138.8 (C2′), 129.5 (C5a), 128.6 (C3′), 124.3 (C6), 120.9 (C9), 120.6 (q, $^1J_{C,F}$ = 256.1 Hz, 7-OCF_3), 120.1 (C8), 108.6 (C4′), 69.4 (C4), 52.3 (C2), 47.2 (C3), 44.2 (C5). IR (liquid film, cm^{-1}): $\tilde{\nu}$ = 3359 (N–H, O–H), 1249 (C–N), 1024 (C–O). GC–MS (EI, 70 eV): m/z (%) = 313 ($M^{+\bullet}$, 94), 295 (1), 269 (42), 202 (21), 191 (70), 190 (100), 123 (76). HRMS (EI, 70 eV): m/z $[M]^+$ calcd for $C_{15}H_{14}F_3NO_3$: 313.0926; found: 313.0914.

4.2. Biological screening

4.2.1. Materials and methods

4.2.1.1. Parasites and cells. Epimastigotes of *T. cruzi* (Sylvio X10 strain, ATCC-50823) were cultured in Liver Infusion Tryptose (LIT) medium supplemented with heat inactivated fetal calf serum (hiFCS, Gibco, Grand Island, NY, USA) at 28 °C. Promastigotes of *Leishmania chagasi* (MHOM/BR/74/PP75), actually classified as *Leishmania (L.) infantum*, were maintained at 28 °C in RPMI 1640 medium (Gibco) containing hemin (Sigma Chemical Company, St. Louis, MO, USA), HEPES (Gibco) and 10% of hiFCS. Vero (ATCC, CCL81) and THP-1 (ATCC-TIB202) mammalian cells were cultured in RPMI 1640 medium supplemented with 10% of hiFCS, at 37 °C, 5% CO_2 and 95% of humidity.

4.2.1.2. Reference drugs and stock solutions. Nifurtimox (Nfx, kindly donated by Professor Simon Croft from the LSHTM) and Amphotericin B (AmB, from Sigma) were used as reference drugs. Stock solutions of each evaluated compound and parasite reference drugs were prepared in dimethyl sulfoxide (DMSO, Carlo Erba Reagenti Rodano, Italy) at a final concentration of 0.1% v/v. Work solutions were prepared in RPMI 1640 culture medium immediately before assays. DMSO was not toxic for the cells at the working concentrations.

4.2.1.3. Mammalian cell toxicities assays. Vero monolayers and THP-1 cells (this last transformed to its adherent phenotype with 10 ng/mL of phorbol myristate acetate (PMA, from Sigma) were incubated with each new compound (0.3–300 μg/mL) or with reference drugs (0.1–100 μM) 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 colorimetrically using tetrazolium salt (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, MTT, from Sigma). The optical density (OD) of the formazan crystals dissolved with DMSO was measured using a microplate reader at a wavelength of 580 nm. The percentage of cytotoxicity was calculated using the following equation:

$$\text{Cytotoxicity } (\%) = 100 \times (\text{OD control group} - \text{OD treatment group})/\text{OD control group}.$$

4.2.1.4. Parasites assays. Epimastigotes of *T. cruzi* and promastigotes of *L. (L.) infantum* in exponential phase of growth were treated with threefold serial dilutions of each new compound (0.3–300 μg/mL) or reference drugs for 72 h at 28 °C. Control parasites were maintained without compound. The inhibition of parasite growth was microscopically determined by counting parasite numbers in a hemocytometer using eosin yellow 0.25%, as a vital dye.

For *T. cruzi* tissue derived trypomastigotes test (TDT), 7×10^5 TDT/mL were diluted in LIT-hiFCS medium and incubated with serial dilutions of each evaluated compound (0.3–300 μg/mL) and reference drugs at 37 °C, 5% CO_2, and 95% of humidity for 24 h. Control parasites were maintained without compound. The inhibition of parasite growth was microscopically determined by counting parasite numbers in a hemocytometer as above.

For intracellular amastigote test, both *T. cruzi* and *L. (L.) infantum* parasites were used. Vero cells were infected with *T. cruzi* TDT, and THP-1 transformed cells were infected with late phase growth promastigotes of *L. (L.) infantum* in a 1:10 ratio cell: parasite for 24 h. The infected cells were treated with two doses of serial dilutions of each evaluated compound and reference drugs. A second dose was added on the third day of treatment with medium change. Control cells were maintained without compound. The percentage of infected cells was determined by counting infected and non-infected cells on methanol fixed and Giemsa-stained slides on 300 cells. Each parasite experiment was tested in duplicate and each concentration for triplicate.

4.2.1.5. Analysis of results. The antiparasitic activity was expressed as the concentration of compound that inhibited 50% of parasites (IC_{50}), and the mammalian cell toxicity was expressed as the concentration of compound required for 50% cell killing (CC_{50}). They were calculated by sigmoidal regression analysis (Msxlfit™; ID Business Solution, Guildford, UK).The obtained results were expressed as mean ± standard deviation (SD). In this work, a compound with an IC_{50} > 50 μM and a CC_{50} < 100 μM was considered as inactive for parasites and toxic for the mammalian cell lines used. In order to compare the concentration of compound that causes cell toxicity with the concentration that causes the antichagasic or antileishmanial effect, the Selectivity Index (SI) was determined. They were calculated using the following ratio: SI = CC_{50} in Vero (THP-1) cells/IC_{50} in parasites. SI ≥ 3 were arbitrarily defined as parasite-selective compound. A higher therapeutic index is preferable to a lower one; consequently, lower SI values indicate a narrow therapeutic range.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.08.055.

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