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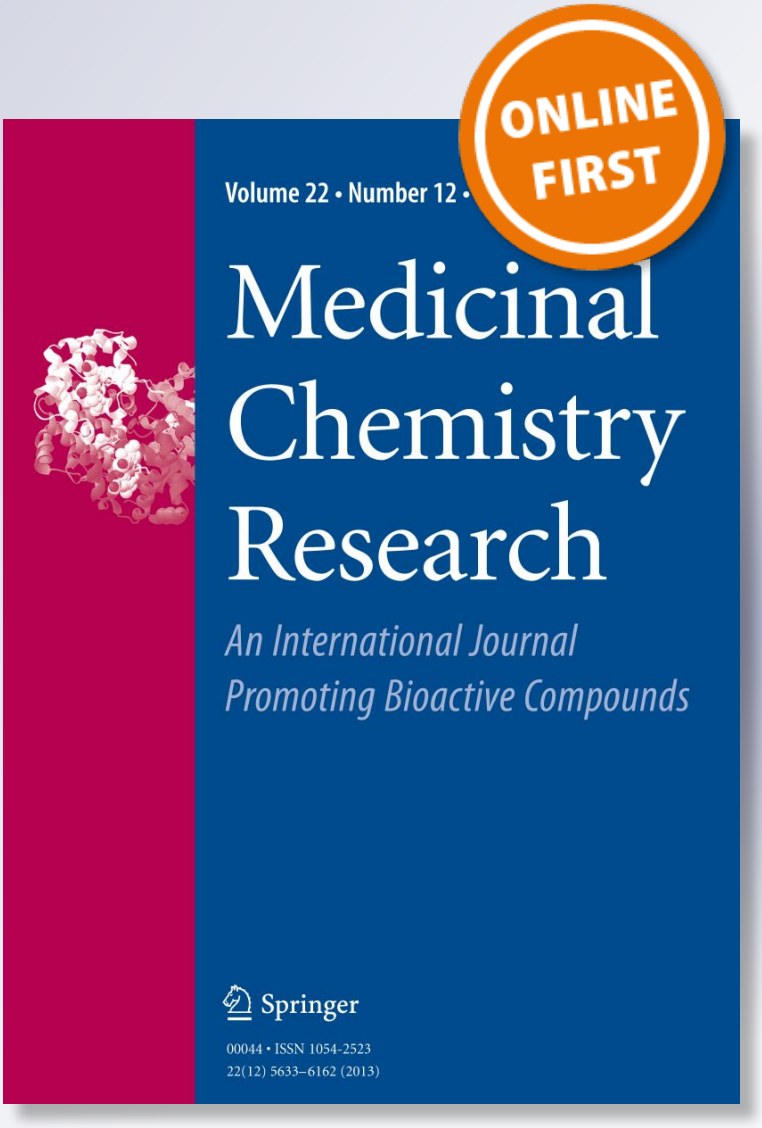

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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, anti-parasitic activity and QSAR study of a new library of polysubstituted tetrahydronaphtho[1,2-*b*]azepines

Andrés Felipe Yépes[1] · Alí Bahsas[2] · Patricia Escobar[3] · Justo Cobo[4] · Alirio Palma[1] · Juan C. Garro Martinez[5] · Ricardo Enriz[5]

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Abstract

A new series of twenty two 2-*exo*-aryl(heteroaryl)-1,4-epoxytetrahydronaphtho[1,2-*b*]azepines **8–10** and eighteen *cis*-2-aryl (heteroaryl)-4-hydroxytetrahydronaphtho[1,2-b]azepines **11–13** were synthesized, and most of them were tested for their ability to inhibit the in vitro growth of the extracellular forms of *Trypanosoma cruzi* and *Leishmania infantum* parasites. Cell toxicity was also determined on Vero and THP-1 mammalian cells. Seventeen compounds exhibited potent activity against the epimastigotes (IC_{50} lower than 20 μM), without cytotoxicity on Vero cells. Ten compounds also showed remarkable anti-leishmanial properties against the promastigote form of the parasite (IC_{50} lower than 20 μM), but most of them were found cytotoxic for HTP-1 cells. We have also performed a quantitative structure activity relationship analysis by means of the multivariate lineal regression (MLR) technique with a family of ninety-four tetrahydro-1-benzazepine and tetrahydronaphtho [1,2-*b*]azepine derivatives with anti-parasitic activity. The aim of this study is to develop a tool that permits us to elucidate the structural features, which influence in the bioactivity of these compounds. The QSAR prediction models for *Trypanosoma cruzi* and *Leishmania infantum* were acceptable with a correlation coefficient values (R) of 0.668 and 0.852, respectively, in the prediction of those activities.

Keywords 2-*exo*-aryl(heteroaryl)-1,4-epoxytetrahydronaphtho[1,2-b]azepines · *cis*-2-aryl(heteroaryl)-4-hydroxytetrahydronaphtho[1,2-*b*]azepines · Anti-parasitic activity · Structure activity relationship (SAR) · Quantitative structure-activity relationship (QSAR)

Introduction

Chagas disease and leishmaniasis remain a major public health problem due to the inadequate therapy, and because there are no vaccines available (Hotez et al. 2011; Diniz et al. 2013). Chagas disease (American trypanosomiasis) is caused by the flagellate protozoan *Trypanosoma cruzi*, mainly transmitted by the infected feces of triatomine bugs. Nevertheless, it could also be transmitted by blood transfusions and organs transplant, as well as congenitally and orally from contaminated food. Chagas disease is a devastating and neglected disease, which affects about 6 million to 7 million people worldwide, mostly in Latin America, and causes approximately 10,000 deaths annually, and it is responsible for 89% of death from tropical-clustered

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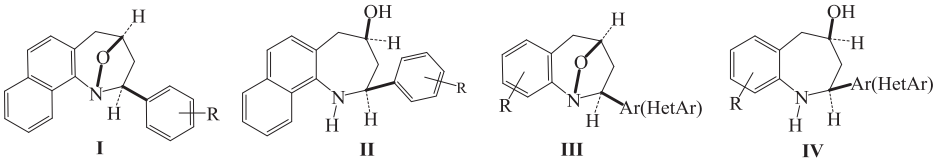


Fig. 1 The 2-aryltetrahydronaphtho[1,2-b] azepine series and 2-aryl (heteroaryl)tetrahydro-1-benzazepine series

diseases in the region. In addition, Chagas disease causes over US$ 1.2 billion/year of productivity loss in seven of the countries where it is endemic (Rodrigues-Coura and Albajar-Viñas 2010; Crompton et al. 2010; Ayo et al. 2013; Jackson et al. 2013; World Health Organization 2016). 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 (Rodrigues–Coura and Albajar–Viñas 2010). Nifurtimox (recently discontinued) and benznidazole are the two drugs available for treatment during the acute and asymptomatic chronic phases of disease. Unfortunately, these drugs have poor efficacy in the chronic stage of the disease and are related to several side effects (Rodriques–Coura and de Castro 2002; Urbina 2010; Olivieri et al. 2010; Pinazo et al. 2010), and drug resistant strains have been observed (Kessler et al. 2013, Wiggers et al. 2013, Serafim et al. 2014).

Leishmaniasis is a poverty-related group of diseases caused by several species of protozoan parasites belonging to the family *Trypanosomatidae* and genus *Leishmania*, and transmitted by the bite of more than 30 different species of sand flies (Mishra et al. 2007, World Health Organization 2012). They are digenetic parasites that proliferate as motile promastigotes in the gut of sand flies and as amastigotes inside vertebrate-host macrophages. There are two main forms of leishmaniasis, cutaneous (the most common), and visceral leishmaniasis, also known as Kala-azar (the most severe form, fatal in 85–90% of untreated cases). Leishmaniasis is currently prevalent in four continents, being endemic in 98 countries, leading to about 5,00,000 new cases and 50,000 annual deaths, mostly due to the visceral form (Alvar et al. 2012). In most of the developing countries the therapy is still based on pentavalent antimonials, sodium stibogluconate (Pentostam), and meglumine antimoniate (Glucantime), developed more than 50 years ago as first-line drugs, whereas amphotericin B (both the free and liposomal amphotericin B), pentamidine isothionate, paromomycin, and miltefosine are used as second-line chemotherapy. Unfortunately, all these drugs present several side-effects and are toxic and expensive, and have low availability, variable effectiveness, and high risk of resistance (Croft and Yardley 2002; Sundar and Chakravarty 2013; Perez-Victoria et al. 2003).

Although some progress has been made in the development of alternative drugs to treat these two diseases, efforts directed toward the discovery of non-toxic, safer, cheaper, and more effective chemotherapeutic agents are urgently needed (Barrett and Croft 2012; Molina et al. 2014; Espuelas et al. 2012; Marín et al. 2013; Chauhan et al. 2013; Galiana-Roselló et al. 2013).

The tetrahydro-1-benzazepine nucleus is frequently encountered as scaffold in medicinal chemistry (Bankir et al. 2001; Abraham 1994; Morita et al. 2003; Barberis et al. 1999; Decaux 2001), as this heterocyclic unit is present in an extensively studied class of potent and orally active non-peptide arginine-vasopressin antagonists for both V_{1A} and V_2 receptors, (Shimada et al. 2000; Kakefuda et al. 2002; Tsunoda et al. 2003 2005; Matthews et al. 2003; Yea et al. 2008) as potent inhibitors of cyclin-dependent kinases Schultz et al. 1999; Sielecki et al. 2000; Kunick et al. 2000, 2006), as potent and orally bioavailable growth hormone secretagogue (Schoen et al. 1994; De Vita and Wyvratt 1996; De Vita et al. 1998; Ankersen 2002), and as agents against HIV-1 infection (Seto et al. 2005). Furthermore, some molecules containing this frame have been described as promising anti-leishmanicidal and anti-chagasic agents (Knockaert et al. 2002; Zuccotto et al. 2001).

In preceding studies, we have established that compounds bearing a substituted 2-aryltetrahydronaphtho[1,2-*b*]azepine scaffold, like in compounds I and II (Fig. 1), possess remarkable anti-parasitic activity against both the extracellular and intracellular forms of *T. cruzi* and *L. infantum* parasites (Palma et al. 2009a, 2009b). Moreover, we have also synthetized series of compounds of the types III and IV (Fig. 1), in which the naphthalene ring of the tetrahydronaphtho[1,2-*b*]azepine system was replaced by benzene, and have analyzed the consequences of such structural modification, as well as the role of the substituents attached at C–2 position for their anti-chagasic and anti-leishmanicidal activities (Gómez–Ayala et al. 2010; Blanco et al. 2014).

In order to determine the anti-parasitic activity of new compounds, containing the structural scaffolds I and II, we describe the syntheses of 22 new 2-*exo*-aryl(heteroaryl)-1,4-epoxytetrahydronaphtho[1,2-*b*]azepines **8**–**10** and 18 new *cis*-2-aryl(heteroaryl)-4-hydroxy-tetrahydronaphtho[1,2-*b*] azepines **11**–**13**. We have also carried out the corresponding bio-assays to check their ability to inhibit the in vitro growth of the extracellular forms of *T. cruzi* and *L. infantum*

parasites along with an in vitro cytotoxicity evaluation on Vero and THP-1 mammalian cells. The choice of substituents presented in compounds **8**–**10** and **11**–**13** at C-2 position was considered in the previously described structure-activity relationships on compounds of the series III and IV (Gómez–Ayala et al. 2010; Blanco et al. 2014). On the other hand, taking the advantage to obtain a relatively extended library, formed by more than 90 compounds, we have developed a quantitative structure activity relationship (QSAR) analysis by means of the Multivariate lineal regression (MLR) technique, with the aim to elucidate the structural features, which influence in the bioactivity of these compounds to attempt predictive models able to orientate the synthesis of new derivatives with even greater anti-parasitic activity.

Results and discussion

Chemistry

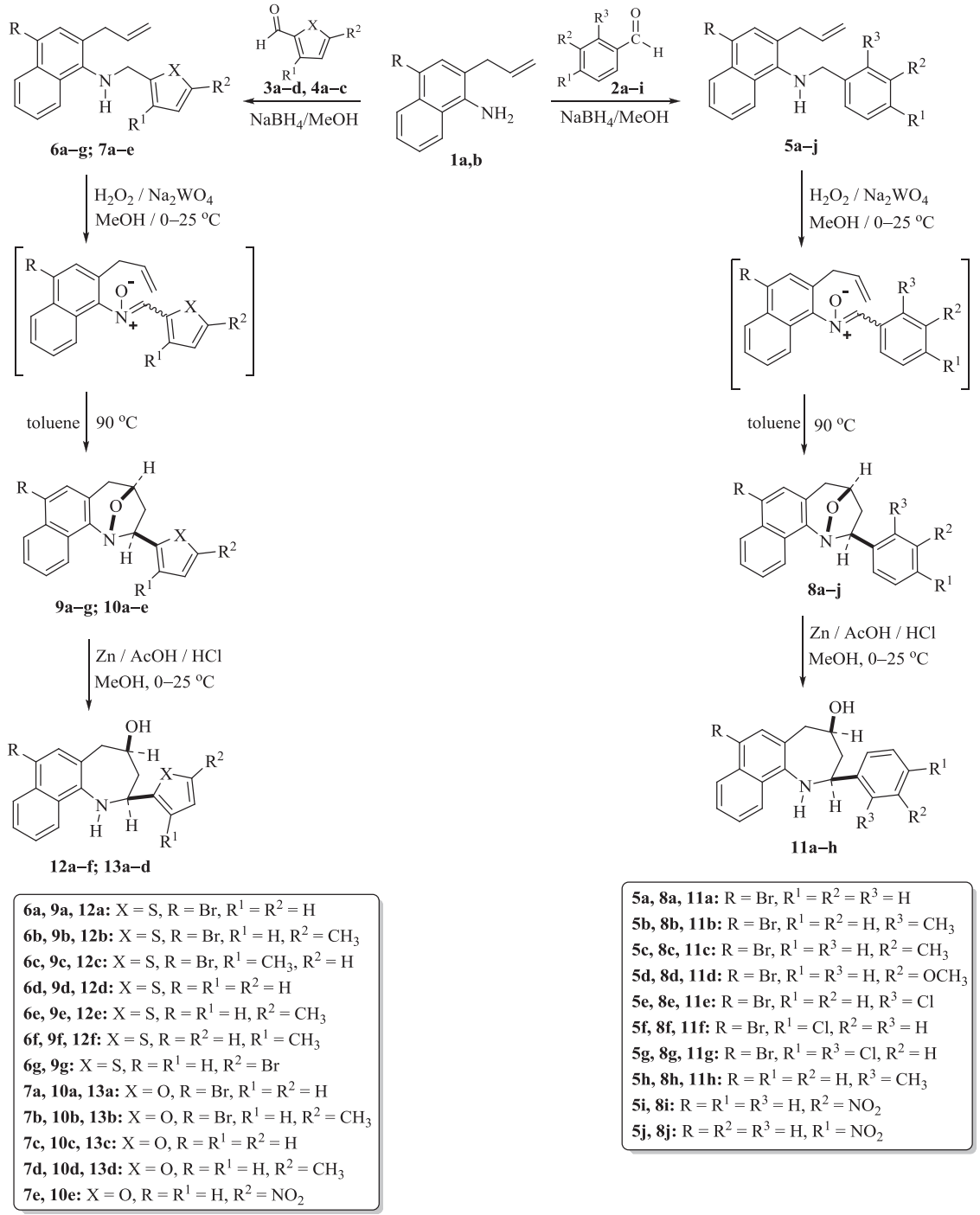
The diastereoselective synthesis of the target compounds **8**–**10** and **11**–**13** was achieved employing the synthetic routes, previously described by our group (Palma et al. 2009a, 2009b; Gómez-Ayala et al. 2010; Blanco et al. 2014) and are illustrated in Scheme 1. Synthetically available 2-allyl-α-naphthylamines (Palma et al. 2009a, 2009b) **1a,b** were condensed with substituted benzaldehydes **2a**–**i**, 2-thiophenecarboxaldehydes **3a**–**d** and 2-furancarboxaldehydes **4a**–**c** in refluxing methanol to afford the corresponding imine intermediates, which were further reduced with sodium borohydride to give key intermediates **5a**–**j**, **6a**–**g**, and **7a**–**c**. These key intermediates were oxidized with an excess of hydrogen peroxide (30% H_2O_2) in the presence of sodium tungstate ($Na_2WO_4{\cdot}2H_2O$) to afford the corresponding nitrones, which then undergo an internal 1,3-dipolar cycloaddition to generate the targeted 2-*exo*-aryl(heteroaryl)-1,4-epoxycycloadducts **8a**–**j**, **9a**–**g**, and **10a**–**e**. Finally, reductive cleavage of the N–O bond of **8**, **9**, and **10** by treatment with an excess of zinc in a mixture of glacial acetic acid and concentrated hydrochloric acid at temperature ranging from 0–25 °C afforded the target *cis*-2-aryl(heteroaryl)-4-hydroxytetrahydronaphtho[1,2-*b*]azepines **11a**–**h**, **12a**–**f**, and **13a**–**d**. As it was previously observed with other structural analogs (Blanco et al. 2014), the reductive cleavage of bromo-substituted cycloadduct **9g** also afforded the debrominated tetrahydronaphtho[1,2-*b*]azepin-4-ol **12a** instead of the expected 5-bromo-substituted tetrahydronaphtho[1,2-*b*]azepin-4-ol. Additionally, all attempts to furnish the reductive cleavage of nitro-substituted 1,4-epoxy-cycloadducts **8i, 8j**, and **10e** resulted in the formation of a very complex mixture of non-identifiable degradation products. The chemical structures of all the synthesized compounds were then fully characterized on the basis of their physicochemical and spectral data (see Experimental section), and the relative configurations of tertiary methynic C–2 and C–4 carbons and the conformation of the tetrahydroazepine ring in compounds **8**–**12** were unambiguously determined on the basis of single-crystal X-ray analysis, which confirmed what we had deduced by means of ^{1}H NMR experiments (Palma et al. 2009a, 2009b; Yépes et al. 2013a, 2013b).

Anti-parasitic activity and cytotoxicity for the newly synthetized compounds

Anti-parasitic activity in vitro assays with *T. cruzi* epimastigotes and *L. infantum* promastigotes, as well as cytotoxicity with Vero epithelial cells (the host cells of *T. cruzi*) and THP-1 transformed human macrophages (the host cells of *L. infantum*) were conducted, as previously reported (Gómez-Ayala et al. 2010; Blanco et al. 2014). Nifurtimox and amphotericin B were used as control under the same assay conditions. Considering the low antiparasitic activity that revealed compounds of the type IV bearing a substituted furan ring at C-2 position (Blanco et al. 2014), in this work compounds 13 were not evaluated. The obtained results are listed in Tables 1 and 2. From the results observed in both tables, it is clear that some of these new compounds displayed a significant anti-parasitic activity. Unfortunately, we do not know the mechanism of action (at molecular level) for compounds reported here. Therefore, indirect approaches are the only option we have in order to better understand the structural requirements to produce the biological response; thus, in the next sections we present the results obtained by using both techniques SAR and QSAR analysis.

Qualitative structure-activity relationship analysis (SAR)

As observed from Table 1, the anti-parasitic activity and cytotoxicity of the tested 1,4-epoxycycloadducts depend on the presence or absence of bromine atom at C–6 position and upon the nature and the substitution pattern of the aromatic rings at C–2 position. These results indicated that most of the 6-bromo substituted derivatives of the series **8** did not display any activity against epimastigotes of *T. cruzi* and promastigotes of *L. infantum*; only compounds **8c** and **8d** showed moderate and good anti-epimastigote activity with IC_{50} values of 29.7 µM and 11.9 µM, respectively. Non-brominated compounds **8i** and **8j**, bearing *meta*- and *para*-nitrophenyl groups at C–2, also displayed good anti-parasitic activity. The nitro derivative **8i** was inactive against promastigotes ($IC_{50} = 98.6$ µM), but it is active against epimastigotes ($IC_{50} = 17.5$ µM). While, the compounds **8j** has the best activity of the series **8** against the



Scheme 1 Synthesis of the target compounds **8**–**13**

epimastigotes ($IC_{50} = 8.6\,\mu M$) and promastigotes ($IC_{50} = 5.0\,\mu M$).

From the series **9**, bearing a substituted thiophene ring at C–2 position, derivatives **9a**, **9b**, **9e**, and **9g** showed low to high anti-parasitic activity with IC_{50} values ranging from 54.1 to 8.3 μM against epimastigotes, and 29.3 to 10.9 μM against promastigotes. The compound **9g** is the most active against epimastigotes ($IC_{50} = 8.3\,\mu M$) and **9e** the most active against promastigotes ($IC_{50} = 10.9\,\mu M$).

Out of four compounds of the series **10**, bearing a substituted furan ring at C–2 position, only derivatives **10d** and **10e** displayed a good anti-parasitic activity with IC_{50} values of 9.6 and 8.6 μM against epimastigotes, and 15.4 μM and 13.9 μM against promastigotes, respectively.

Table 1 In vitro activity of tested compounds **8–10** (2-*exo*-aryl(heteroaryl)-1,4-epoxytetrahydronaphtho[1,2-*b*] azepines) against extracellular forms of *T. cruzi* and *L. infantum* parasites and mammalian cells expressed as IC_{50} and CC_{50}

Comp.	X	R	R^1	R^2	R^3	*T. cruzi* epimastigotes IC_{50} (μM)	Vero cells CC_{50} (μM)	*L. infantum* promastigotes IC_{50} (μM)	THP-1 cells CC_{50} (μM)
8a	–	Br	H	H	H	>821.8	1543.7	485.1	1293.8
8b	–	Br	H	H	CH_3	107.7	1431.5	>787.2	100.0
8c	–	Br	H	CH_3	H	29.7	>1574.6	117.4	29.7
8d	–	Br	H	OCH_3	H	11.9	>1518.8	40.1	>1518.8
8e	–	Br	H	H	Cl	591.3	140.6	>751.9	591.3
8f	–	Br	Cl	H	H	>751.9	344.9	116.4	1101.2
8g	–	Br	Cl	H	Cl	>692.9	121.6	692.9	1212.3
8h	–	H	H	H	CH_3	>996.18	260.30	604.45	1083.15
8i	–	H	H	NO_2	H	17.5	>903.3	98.6	>903.3
8j	–	H	NO_2	H	H	8.6	>903.3	5.0	>903.3
9a	S	Br	H	H	–	27.8	>808.6	20.1	>808.6
9b	S	Br	H	CH_3	–	54.1	>779.2	29.3	>779.2
9d	S	H	H	H	–	338.8	1295.0	777.5	338.8
9e	S	H	H	CH_3	–	11.3	497.5	10.9	>976.9
9f	S	H	CH_3	H	–	314.5	>1953.8	590.4	314.5
9g	S	H	H	Br	–	8.3	>808.6	21.6	>808.6
10a	O	Br	H	H	–	54.5	>845.0	142.7	845.0
10c	O	H	H	H	–	60.0	50.9	60.3	1082.6
10d	O	H	H	CH_3	–	9.6	94.5	15.4	22.5
10e	O	H	H	NO_2	–	8.6	85.4	13.9	931.4
Nif.						4.0	67.5	–	–
Amph. B						–	–	0.01	29.7

With respect to the tested 2-aryl(thiophen-2-yl)-substituted 4-hydroxytetrahydronaphtho[1,2-*b*]azepines **11** and **12** (Table 2), only compounds **11a** and **12f** were inactive against promastigotes. The rest of the analogs of these two series showed low to remarkable activity against epimastigotes (IC_{50} values ranging from 42.2 to 2.47 μM), and promastigotes (IC_{50} values ranging from 48.2 to 7.7 μM). Among the active compounds, derivatives **11b** ($IC_{50} = 7.1$ μM), **11f** ($IC_{50} = 6.3$ μM), **11g** ($IC_{50} = 3.3$ μM) and **11h** ($IC_{50} = 2.47$ μM) exhibited the highest anti-epimastigote activity, whereas derivatives **11b** ($IC_{50} = 7.7$ μM), **11d** ($IC_{50} = 9.6$ μM), and **11e** ($IC_{50} = 8.9$ μM) were the most active against promastigotes.

Cytotoxic assays showed that most of the tested compounds of the series **8–10** have CC_{50} values higher than 100 μM, demonstrating that all of the active compounds were far less cytotoxic (excepting **8c** and **10d**, which displayed a limited cytotoxicity on HTP-1 cells) than the reference drugs, nifurtimox and amphotericin B. In majority of the cases the tested compounds of the series **11** and **12** were more cytotoxic for Vero and HTP-1 cells than their precursors **8–10**.

The structure-activity relationships (SARs) analysis showed that *meta* substitution of benzene ring with a methoxyl group render a compound with better anti-epimastigote activity than substitutions with methyl and nitro groups, as was observed in compounds **8d**, **8c**, and **8i**, respectively. However, the *para* substitution of benzene ring with a nitro group (**8j**) resulted in the most active compound of the series **8** for both the epimastigote and promastigote forms of the parasites. The IC_{50} values **8i** and **8j** indicated that the *para* position is more favorable than the *meta* position for providing anti-parasitic activity on nitro-derivatives. Other substitution patterns led to total loss of anti-parasitic activity, as was observed in compounds **8a**, **8b**, **8e**, **8f**, **8g**, and **8h**.

The introduction of methyl (**9e**) and bromo (**9g**) substituents on the position 5 of thiophene ring in compounds of the series **9**, resulted in increased anti-epimastigote and anti-promastigote activities. In addition, there is an emerging pattern of decreasing anti-parasitic activity when the methyl group is changed from position 5 to 3 on the thiophene ring (**9f**), or when the bromine atom is incorporated at C–7 position of the base nucleus (**9b**).

Within the series **10**, the substitution of furan ring on position 5 with methyl (**10d**) and nitro (**10e**) groups also rendered compounds with improved anti-epimastigote and anti-promastigote activities as compared to the non-substituted analogs **10a** and **10c**.

Table 2 In vitro activity of tested compounds **11**–**12** (*cis*-2-aryl(heteroaryl)-4-hydroxy-tetrahydronaphtho[1,2-*b*] azepines) against extracellular forms of *T. cruzi* and *L. infantum* parasites and mammalian cells expressed as IC_{50} and CC_{50}

Comp.	X	R	R^1	R^2	R^3	*T. cruzi* epimastigotes[a] IC_{50} (μM)[b]	Vero cells[c] CC_{50} (μM)[d]	*L. infantum* promastigotes[e] IC_{50} (μM)	THP-1 cells[f] CC_{50} (μM)
11a	–	Br	H	H	H	12.2	25.3	617.1	24.0
11b	–	Br	H	H	CH_3	7.1	113.2	7.7	7.1
11c	–	Br	H	CH_3	H	20.0	46.9	12.6	20.0
11d	–	Br	H	OCH_3	H	11.7	54.4	9.6	178.5
11e	–	Br	H	H	Cl	11.1	16.0	8.9	11.1
11f	–	Br	Cl	H	H	6.3	10.0	48.2	45.1
11g	–	Br	Cl	H	Cl	3.3	40.1	11.8	59.8
11h	–	H	H	H	CH_3	2.47	36.05	36.19	41.60
12d	S	H	H	H	–	42.2	74.0	42.5	67.2
12e	S	H	H	CH_3	–	17.0	65.9	16.6	192.3
12f	S	H	CH_3	H	–	10.0	>970.5	58.5	ND
Nif.[g]						4.0	67.5	–	–
Amph. B[g]						–	–	0.01	29.7

N.D. not determined

[a]*Trypanosoma cruzi* strain 320I04 were treated for 72 h at 27 °C with tested compounds

[b]Inhibitory concentration IC_{50} was the concentration required for 50% growth inhibition

[c]African green monkey kidney cell line (Vero, ATCC) were treated for 72 h at 37 °C with tested compounds

[d]Cytotoxic concentration CC_{50} was the concentration required for 50% mammalian cell killing

[e]*Leishmania infantum* strain MHOM/BR/74/PP75 were treated for 72 h at 27 °C with tested compounds

[f]Transformed human acute monocytic leukemia cell line (THP-1, ATCC) were treated for 72 h at 37 °C with tested compounds

[g]Reference drugs (nifurtimox and amphotericin B)

In the compounds of the series **11**, the most potent compounds against epimastigotes (even more active than nifurtimox) were the 7-bromo-substituted derivatives **11f** and **11g**, bearing 4-chloro- and 2,4-dichlorophenyl moieties at C–2, respectively. Whereas the derivatives **11b**, **11d**, and **11e**, bearing 2-methyl-, 3-methoxy- and 2-chlorophenyl moieties at C–2, respectively, emerged as the most active compounds against *L. infantum* promastigotes. Finally, the non-bromo-substituted derivative **11h** in which the benzene ring at C–2 is 2-methylphenyl is the most active compounds against *T. cruzi* epimastigotes.

Unfortunately, the above molecules have significant cytotoxicity on both the Vero and THP-1 cells. As shown by the comparison of the activities of derivatives **11h** and **11b**, the incorporation of a bromine atom at C–7 position slightly reduced the anti-epimastigote activity (from 2.47 to 7.1 μM), but substantially enhanced the anti-promastigote activity (from 36.19 to 7.1 μM); similar effect on the activities was observed when the chlorine atom is changed from position 4 (**11f**) to position 2 (**11e**) on the phenyl moiety. Moreover, the 7-bromo-substituted derivatives **11d** and **11e**, bearing 3-methoxy- and 2-chlorophenyl moieties at C–2, demonstrated a strong affinity for the extracellular parasite forms with IC_{50} values of 11.7 and 11.1 μM against epimastigotes, and IC_{50} values of 9.6 μM and 8.9 μM against promastigotes, respectively. Although being inactive against promastigotes ($IC_{50} = 617.1$ μM), compound **11a** was active against epimastigotes ($IC_{50} = 12.2$ μM). Finally, the IC_{50} values of compounds of the series **12** show that the anti-parasitic activity did not improve by the replacement of the substituted benzene ring by a substituted thiophene ring. In this series of compounds, the presence of a 5-methyl-2-thiophenyl moiety (**12e**) is more favorable than the presence of a 3-methyl-2-thiophenyl moiety (**12f**) for enhancing the anti-epimastigote and anti-promastigote activities.

Quantitative structure-activity relationship analysis (QSAR)

At this step of our study, we were interested in obtaining a model that allowed us to predict the potential anti-parasitic activity of these compounds. Thus, a QSAR analysis was carried out by searching the optimal linear regression equations by means of the Replacement Method (RM) approach (Duchowicz et al. 2006; Mercader et al. 2010), which minimizes their standard deviation (S). A total of 94 compounds, tables 5S-10S, previously described (Palma et al. 2009a, 2009b; Gómez-Ayala et al. 2010; Blanco et al. 2014), were included in the dataset. In these tables the

compounds are identified as I, II, III, and IV, which corresponds to each type of compound in Fig. 1.

We analyzed the regression that includes the most "representative" d = 1–10 molecular descriptors. To define the maximum number of molecular descriptors in the lineal regression we consider the "rule of thumb", which states that at least six data points should be present per fitting parameter, i.e., ($N_{train}/d \geq 6$), where N_{train} is the number of compounds of training set and d is the number of molecular descriptors.

QSAR for the growth inhibition of Trypanosoma cruzi epimastigotes Table 1S of the supplementary material summarized the main statistical parameters of the QSAR model for the inhibition of *Trypanosoma cruzi* epimastigotes. We considered that a model with five molecular descriptors shows an acceptable quality in accordance with the number of independent variables. The equation of selected QSAR model is:

$$-\log(IC_{50}) = -27.533 + 0.09(ATSC1i) - 0.185(nBondsM) + 6.458(SpMax3\_Bhv) + 0.098(RDF45v) + 2.773(Di)$$

$$N = 71 \quad d = 5 \quad N_{train}/d = 14.2$$

$$R_{train} = 0.828 \quad R^2_{train} = 0.686 \quad S_{train} = 0.291 \quad RMS = 0.278$$

$$R_{val} = 0.499 \quad S_{val} = 0.495 \quad R_{loo} = 0.785 \quad S_{loo} = 0.323$$
$$R_{lmo} = 0.694 \quad S_{lmo} = 0.376 \quad S_{rand} = 0.434$$

The results of the validation reveal that model have an acceptable predictive capacity, according to the known criterions ($R_{val} \geq 0.500$ and $S_{rand} > S_{train}$). Figure 2a shows the linear trend of the relationship of the predicted and experimental values. The residuals values are plotted in the Fig. 2b. From this figure it can be appreciated that compounds IId and IIId present a residual value close to the 2.5 S limit (dotted line). However, these compounds were not considered outliers. Within the validation set, only compounds Ii and IVaa exhibit a residual value higher than the limit of deviation standard.

The molecular descriptors involved in the QSAR model are listed in Table 2S. The table presents the maximum correlation, the standardized regression coefficients of the molecular descriptors and a brief description of them. The maximum correlation between the descriptors of the model is 0.825, given by nBondsM and SpMax3_Bhv. The standardized coefficient specifies the importance of the descriptor on the biological activity, and the sign indicates whether the relationship is direct or indirect. The standardized regression coefficients values plot is presented in the Fig. 3.

The most important descriptor for the activity is SpMax3_Bhv (0.910), whole positive value expresses a direct relationship of this descriptor with the –log(IC_{50}). This descriptor is defined as the average centered Broto-Moreau autocorrelation–lag 1/weighted by first ionization potential, and to have strong empirical relationship to electron distribution of the molecule as a whole (Todeschini and Consonni 2009). The standardized regression coefficients magnitudes for the rest of the molecular descriptors (0.516, −0.428, 0.375, 0.313) suggest that they complement each other in QSAR equation and the negative values in nBondsM indicate its indirect relationship with the –log (IC_{50}).

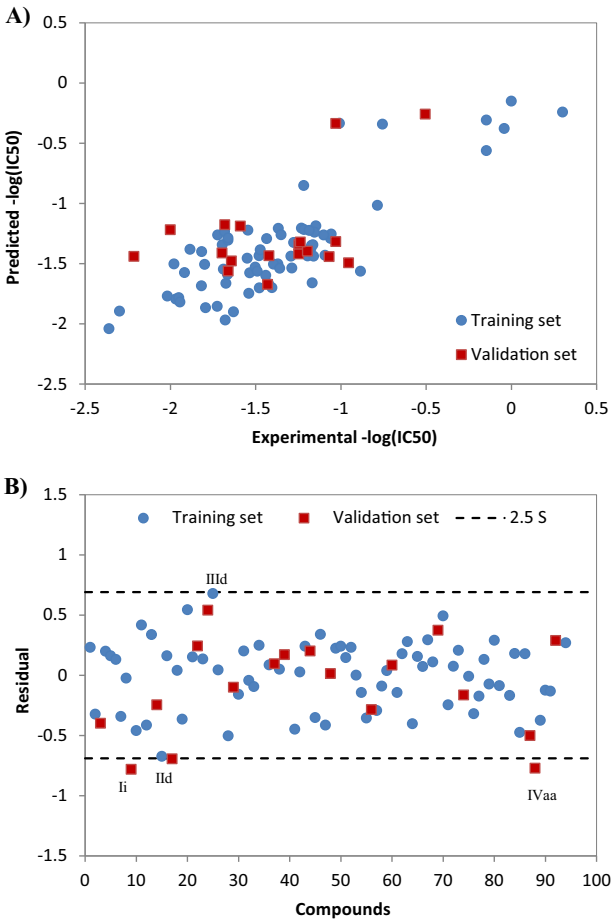


Fig. 2 *Trypanosoma cruzi* Epimastigote QSAR model. **a** Predicted versus Experimental values of −log(IC_{50}). **b** Residual of predicted values

QSAR for the growth inhibition of Leishmania infantum promastigotes The statistical parameters of QSAR models (from 1 to 10 descriptors) for the inhibition of *Leishmania infantum* promastigotes are listed in the Table 3S. In this case, the model containing six molecular descriptors was considered appropriate, with an acceptable quality for the training and validation sets. The mathematical equation of

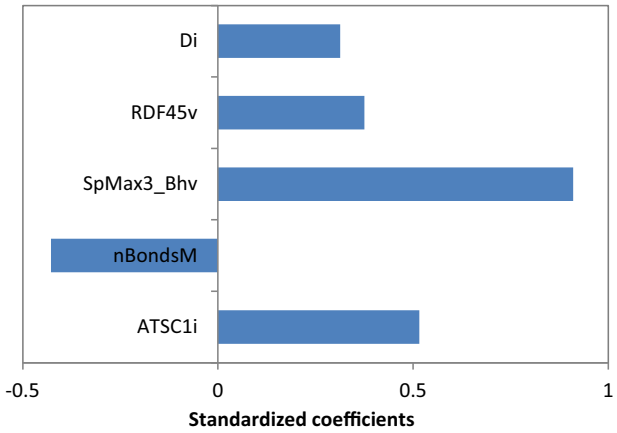


Fig. 3 Standardized regression coefficients values of the molecular descriptors for *Trypanosoma cruzi* Epimastigote QSAR model

selected QSAR model is:

$$-\log(\mathrm{IC50}) = 3.224 - 2.35 \times 10^{-4}(VR1\_Dzi) - 0.633(SpMax5\_Bhm) - 1.170(SpMax6\_Bhv) - 0.044(RDF35u) + 0.041(RDF60s) + 0.014(Vm)$$

$$N = 67 \quad d = 6 \quad N_{train}/d = 11.1$$

$$R_{train} = 0.757 \quad R^2_{train} = 0.572 \quad S_{train} = 0.218 \quad RMS = 0.206$$

$$R_{val} = 0.589 \quad S_{val} = 0.301 \quad R_{loo} = 0.650 \quad S_{loo} = 0.279$$
$$R_{lmo} = 0.554 \quad S_{lmo} = 0.392 \quad S_{rand} = 0.278$$

The statistical parameters indicate that model has a suitable predictive power for both, the training set ($R_{train} = 0.757$, $S_{train} = 0.218$) and the validation set ($R_{val} = 0.589$, $S_{val} = 0.301$). Figure 3 shows the predicted and experimental –log(IC_{50}) values plot and the residual values graphic. Figure 4a suggests the existence of a linear trend between the predicted and experimental values, while Fig. 4b indicates that there are no compounds outside the 2.5 S limit (dotted line).

Table 4S presents the maximum correlation, the standardized regression coefficients of the molecular descriptors and a brief description of molecular descriptors involved in the QSAR model. The maximum correlation value (0.684) indicates that there is a low relationship between the descriptors of model and the information is not overlapping. Figure 5 shows the standardized regression coefficients values plot.

The two most important descriptors for the activity present positive values of the standardized regression coefficients and a direct relationship with the –log(IC_{50}); Vm (0.816) and RDF60s (0.679). The Vm descriptor is one of the most used in the QSAR model and it is relate to the molecular volume.[58] While RDF60s is a radial distribution

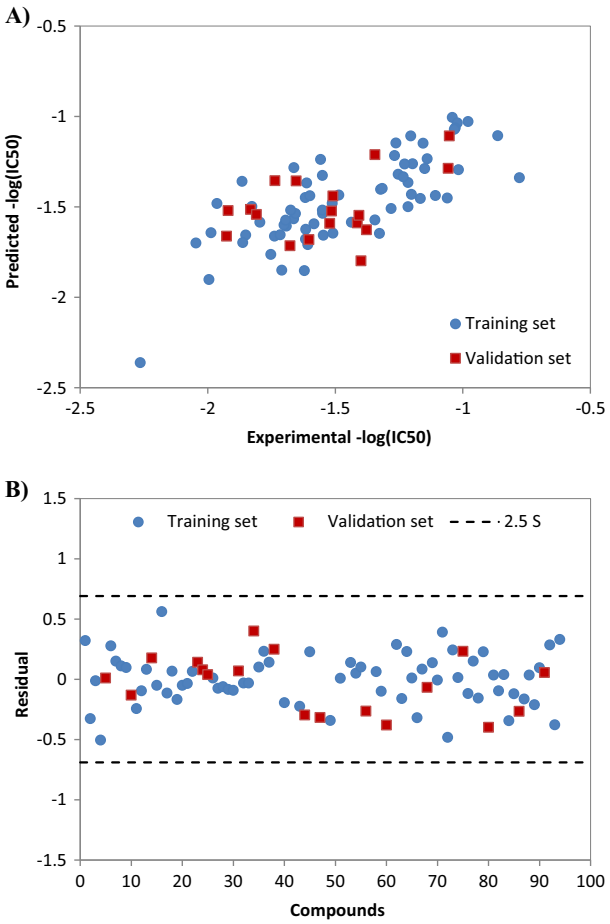


Fig. 4 *Leishmania infantum* Promastigote QSAR model. **a** Predicted versus Experimental values of −log(IC_{50}). **b** Residual of predicted values

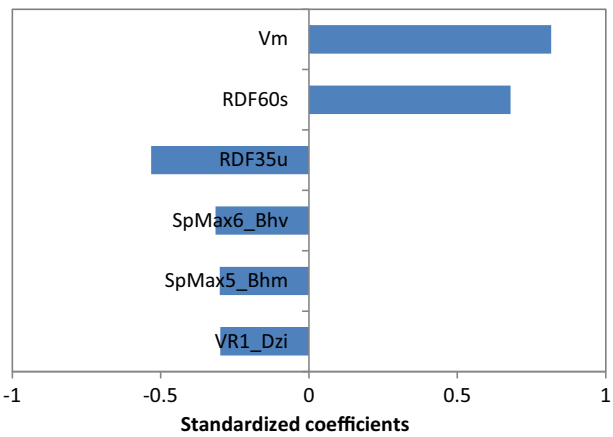


Fig. 5 Standardized regression coefficients values of the molecular descriptors for *Trypanosoma cruzi* Epimastigote QSAR model

function at 6.0 Å inter-atomic distances weighted by relative I-state.[57] The rest of the molecular descriptors have negative standardized regression coefficients values (−0.299,

Table 3 Experimental anti-parasitic activity and QSAR prediction

	Trypanosoma cruzi epimastigotes $-\log(IC_{50})$		*Leishmania infantum* promastigotes $-\log(IC_{50})$	
	Experimental	Predicted	Experimental	Predicted
8a	−2.915	−2.454	−2.686	−1.708
8b	−2.032	−1.272	−2.896	−1.395
8c	−1.473	−2.722	−2.070	−1.580
8d	−1.076	−1.443	−1.603	−1.149
8e	−2.772	−2.298	−2.876	−1.816
8f	−2.876	−2.290	−2.066	−1.609
8g	−2.841	−2.204	−2.841	−1.520
8h	−2.998	−2.599	−2.781	−1.610
8i	−1.243	−0.735	−1.994	−1.257
8j	−0.934	−0.875	−0.699	−1.426
9a	−1.444	−0.766	−1.303	−1.498
9b	−1.733	−0.730	−1.467	−1.509
9d	−2.530	−0.889	−2.891	−1.491
9e	−1.053	−0.862	−1.037	−1.451
9f	−2.497	−0.679	−2.771	−1.633
9g	−0.919	−0.883	−1.334	−1.261
10a	−1.736	−0.841	−2.154	−1.665
10c	−1.778	−0.995	−1.780	−1.681
10e	−0.934	−0.403	−1.143	−1.260
10d	−0.982	−1.024	−1.188	−1.810
11a	−1.086	−0.313	−2.790	−1.266
11b	−0.851	−0.475	−0.886	−1.212
11c	−1.301	−2.461	−1.100	−1.128
11d	−1.068	−1.100	−0.982	−0.932
11e	−1.045	−0.211	−0.949	−1.241
11f	−0.799	−0.219	−1.683	−0.785
11g	−0.519	−0.118	−1.072	−0.859
11h	−0.393	−0.510	−1.559	−1.601
12d	−1.625	−0.507	−1.628	−1.898
12e	−1.230	−0.853	−1.220	−1.813
12f	−1.000	−0.378	−1.767	−1.870

−0.301, −0.315, −0.532), indicating an indirect relationship of these descriptors with the $-\log(IC_{50})$.

Anti-parasitic activity prediction for the newly synthetized compounds We apply the established QSAR models to predict the anti-parasitic activity of the newly synthesized compounds. These results are presented in Table 3. The *Trypanosoma cruzi* model presents a correlation coefficient (R) of 0.668, a standard deviation of 0.852 and the residue average is −0.430. Both models show acceptable values for QSAR prediction. However, same compounds accuse a poor prediction. The compounds **8c**, **9f**, **11a**, **11c**, **11e**, and **11f** show an error in the prediction higher than 60% for *Trypanosoma cruzi*. While for *Leishmania infantum* this percentage is achieve only for the compound **8j**. It is clear that *Trypanosoma cruzi* model has problem to predict correctly the activity of compounds of the series **11**. This may be due to they have a molecular structure different to the ones investigated in the training set.

Conclusions

We report here a new library of twenty two 2-*exo*-aryl (heteroaryl)-1,4-epoxytetrahydronaphtho[1,2-*b*]azepines and eighteen *cis*-2-aryl(heteroaryl)-4-hydroxytetrahydronaphtho[1,2-*b*]azepines. Seventeen compounds exhibited potent activity against the *T. cruzi* epimastigotes (IC_{50} lower than 20 μM), without cytotoxicity or with just limited effect on Vero cells. In addition, ten compounds also showed remarkable anti-leishmanial properties against the *L. infantum* promastigotes (IC_{50} lower than 20 μM), however in some of them were found cytotoxic effects for HTP-1 cells.

Both SAR and QSAR analyses were carried out for the compounds reported here. Thus, we performed a quantitative structure activity relationship analysis by means of the multivariate lineal regression (MLR) technique for a family of ninety four tetrahydro-1-benzazepine and tetrahydronaphtho[1,2-*b*]azepine derivatives. The QSAR prediction models obtained for the extracellular forms of *Trypanosoma cruzi* and *Leishmania infantum* parasites were acceptable with a correlation coefficient values (R) of 0.668 and 0.852, respectively. From our results, it is clear that the QSAR study reported here might predict the potential anti-parasitic effect of non-synthesized compounds with an acceptable degree of accuracy. Such information could be useful in order to know a priori the putative activity of new anti-parasitic compounds structurally related to these series.

Materials and methods

General

All the reagents and solvents were purchased from commercial suppliers (Aldrich, Merck), and used without further purification. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Column chromatography purification was performed on Merck Kieselgel 230–400 mesh (ASTM). Melting points were determined with a MEL–TEMP 1201D capillary apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 spectrometer (equipped with a platinum ATR cell). ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM–400 spectrometer, using $CDCl_3$ as the solvent. Chemical shifts (δ) and coupling constants (J) values are

reported in ppm and hertz, respectively. Chemical shifts are relative to the solvent peaks used as reference [$CDCl_3$: $\delta_H = 7.26$, and $\delta_C = 77.0$]. A Hewlett–Packard (HP) 5890 A series II Gas Chromatograph interfaced to a HP 5972 Mass Selective Detector with a HP MS ChemStation Data system, and a High Resolution Mass Spectrometer Waters Micromass AutoSpect NT (equipped with a direct inlet probe) operating at 70 eV were used for MS identification. All the compounds described here were synthetized according to the experimental conditions reported in previous related works (Gómez-Ayala et al. 2010; Blanco et al. 2014).

Physicochemical and spectral data for 2–allyl–N–aryl(heteroaryl)methylnaphthylamines (5a–j), (6a–g), and (7a–e)

2–Allyl–N–benzyl–4–bromo–1–naphthylamine (5a)

Colorless viscous oil. Yield: 93%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3361 (N–H), 1636 (C=C_{allyl}), 916 (=C–H_{allyl}). ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (dd, $J = 7.5$, 2.2 Hz, 1H, H–8), 8.26 (dd, $J = 7.5$, 2.3 Hz, 1H, H–5), 7.54–7.62 (m, 2H, H–6, H–7), 7.62 (s, 1H, H–3), 7.32–7.42 (m, 5H, H–2', H–3', H–4', H–5', H–6'), 5.94 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1 H, =CH), 5.14 (dq, $J = 10.1$, 1.5 Hz, 1H, =$CH_{2(H-cis)}$), 5.03 (dq, $J = 17.1$, 1.5 Hz, 1H, =$CH_{2(H-trans)}$), 4.35 (s, 2H, N–CH_2), 3.34 (dt, $J = 6.0$, 1.5 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6 (C1), 139.8 (C1'), 136.0 (=CH), 132.2 (C3), 132.1 (C4a), 130.4 (C8a), 128.9 (C2), 128.0 (C3', C5'), 127.9 (C8), 127.7 (C4'), 127.6 (C2', C6'), 126.7 (C6), 126.4 (C7), 123.9 (C5), 117.0 (C4), 116.7 (=CH_2), 55.1 (N–CH_2), 36.1 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 351 ($M^{+\bullet}$, ^{79}Br, 31), 274 (2), 260 (10), 246 (1), 180 (100), 91 (55).

2–Allyl–4–bromo–N–(2–methylbenzyl)–1–naphthylamine (5b)

Colorless viscous oil. Yield: 92%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3363 (N–H), 1637 (C=C_{allyl}), 916 (=C–H_{allyl}). ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd, $J = 8.0$, 1.7 Hz, 1H, H–8), 8.27 (dd, $J = 8.0$, 1.8 Hz, 1H, H–5), 8.00 (td, $J = 8.0$, 1.7 Hz, 1H, H–6), 7.65 (s, 1H, H–3), 7.61 (td, $J = 8.0$, 1.8 Hz, 1H, H–7), 7.50–7.54 (m, 1H, H–6'), 7.21–7.34 (m, 3H, H–3', H–4', H–5'), 5.97 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.17 (dq, $J = 10.1$, 1.6 Hz, 1H, =$CH_{2(H-cis)}$), 5.05 (dq, $J = 17.1$, 1.6 Hz, 1H, =$CH_{2(H-trans)}$), 4.35 (s, 2H, N–CH_2), 3.42 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–), 2.35 (s, 3H, 2'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9 (C1), 137.9 (C1'), 136.0 (=CH), 132.2 (C3, C4a), 132.1 (C2'), 130.6 (C3'), 130.5 (C8a), 130.4 (C5'), 128.9 (C2), 128.4 (C6'), 127.7 (C8), 127.6 (C4'), 126.8 (C6), 126.4 (C7), 124.0 (C5), 117.0 (C4), 116.7 (=CH_2), 52.5 (N–CH_2), 35.7 (–CH_2–), 19.4 (2'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 365 ($M^{+\bullet}$, ^{79}Br, 18), 274 (2), 260 (10), 246 (4), 180 (70), 105 (100).

2–Allyl–4–bromo–N–(3–methylbenzyl)–1–naphthylamine (5c)

Colorless viscous oil. Yield: 88%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3361 (N–H), 1637 (C=C_{allyl}), 916 (=C–H_{allyl}). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (dd, $J = 7.1$, 2.1 Hz, 1H, H–8), 8.24 (dd, $J = 8.0$, 1.6 Hz, 1H, H–5), 7.62 (s, 1H, H–3), 7.54–7.60 (m, 2H, H–6, H–7), 7.28 (t, $J = 7.5$ Hz, 1H, H–5'), 7.24 (s, 1H, H–2'), 7.18–7.22 (m, 1H, H–4'), 7.14–7.18 (m, 1H, H–6'), 5.94 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.14 (dq, $J = 10.1$, 1.6 Hz, 1H, =$CH_{2(H-cis)}$), 5.03 (dq, $J = 17.1$, 1.6 Hz, 1H, =$CH_{2(H-trans)}$), 4.28 (s, 2H, N–CH_2), 3.40 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–), 2.40 (s, 3H, 3'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.5 (C1), 139.6 (C1'), 138.4 (C3'), 136.0 (=CH), 132.2 (C3), 132.1 (C4a), 130.4 (C8a), 129.0 (C2), 128.7 (C5'), 128.4 (C2'), 127.8 (C4'), 126.8 (C6), 126.4 (C7), 125.1 (C6'), 124.0 (C5, C8), 117.6 (C4), 116.7 (=CH_2), 55.2 (N–CH_2), 36.1 (–CH_2–), 21.5 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 365 ($M^{+\bullet}$, ^{79}Br, 7), 274 (2), 260 (5), 246 (2), 180 (100), 105 (92).

2–Allyl–4–bromo–N–(3–methoxybenzyl)–1–naphthylamine (5d)

Colorless viscous oil. Yield: 90%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3361 (N–H), 1635 (C=C_{allyl}), 915 (=C–H_{allyl}). ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, $J = 8.0$, 1.6 Hz, 1H, H–8), 8.22 (dd, $J = 8.0$, 1.6 Hz, 1H, H–5), 7.60 (s, 1H, H–3), 7.58 (td, $J = 8.0$, 1.6 Hz, 1H, H–7), 7.55 (td, $J = 8.0$, 1.6 Hz, 1H, H–6), 7.29 (t, $J = 7.8$ Hz, 1H, H–5'), 6.96 (d, $J = 7.8$ Hz, 1H, H–6'), 6.94 (d, $J = 2.2$ Hz, 1H, H–2'), 6.87 (dd, $J = 7.8$, 2.2 Hz, 1H, H–4'), 5.93 (ddt, $J = 17.2$, 10.1, 6.0 Hz, 1H, =CH), 5.13 (dq, $J = 10.1$, 1.7 Hz, 1H, =$CH_{2(H-cis)}$), 5.02 (dq, $J = 17.2$, 1.7 Hz, 1H, =$CH_{2(H-trans)}$), 4.29 (s, 2H, N–CH_2), 3.38 (dt, $J = 6.0$, 1.7 Hz, 2H, –CH_2–), 3.30 (s, 3H, 3'–OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1 (C3'), 142.3 (C1), 141.3 (C1'), 136.1 (=CH), 132.3 (C3), 132.1 (C4a), 130.4 (C8a), 129.8 (C5'), 129.2 (C2), 127.8 (C8), 126.8 (C6), 126.5 (C7), 123.9 (C5), 120.3 (C2'), 120.2 (C4'), 117.1 (C4), 116.8 (=CH_2), 113.3 (C6'), 55.3 (OCH_3), 55.0 (N–CH_2), 36.1 (–CH_2–).GC–MS (EI, 70 eV): *m/z* (%) 381 ($M^{+\bullet}$, ^{79}Br, 20), 274 (2), 260 (14), 246 (1), 180 (100), 121 (74).

2–Allyl–4–bromo–N–(2–chlorobenzyl)–1–naphthylamine (5e)

Colorless viscous oil. Yield: 90%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3367 (N–H), 1636 (C=C_{allyl}), 916 (=C–H_{allyl}). ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, $J = 7.5$, 2.6 Hz, 1H, H–8),

8.24 (dd, $J = 7.5$, 2.6 Hz, 1H, H–5), 7.55–7.62 (m, 2H, H–6, H–7), 7.59 (s, 1H, H–3), 7.45 (dd, $J = 7.0$, 1.2 Hz, 1H, H–3'), 7.30 (td, $J = 7.0$, 1.2 Hz, 1H, H–5'), 7.27 (td, $J = 7.0$, 1.8 Hz, 1H, H–6'), 7.23 (td, $J = 7.0$, 1.8 Hz, 1H, H–4'), 5.92 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.13 (dq, $J = 10.1$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.06 (dq, $J = 17.1$, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.43 (s, 2H, N–CH_2), 3.37 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2 (C1), 137.4 (C1'), 136.0 (=CH), 133.7 (C2'), 132.1 (C3, C4a), 130.2 (C8a, C6'), 129.7 (C3'), 129.0 (C2, C5'), 127.8 (C8), 127.1 (C4'), 126.8 (C6), 126.5 (C7), 123.9 (C5), 117.2 (C4), 116.7 (=CH_2), 52.5 (N–CH_2), 36.0 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 385 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 15), 274 (3), 260 (10), 246 (2), 180 (100), 125 (20).

2–Allyl–4–bromo–N–(4–chlorobenzyl)–1–naphthylamine (5f)

Colorless viscous oil. Yield: 90%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3361 (N–H), 1635 (C=C_{allyl}), 916 (=C–H_{allyl}). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, $J = 8.4$, 1.6 Hz, 1H, H–8), 8.20 (dd, $J = 7.6$, 1.6 Hz, 1H, H–5), 7.59 (s, 1H, H–3), 7.57 (td, $J = 7.6$, 1.6 Hz, 1H, H–7), 7.55 (td, $J = 7.6$, 1.6 Hz, 1H, H–6), 7.33 (d, $J = 8.5$ Hz, 2H, H–3', H–5'), 7.28 (d, $J = 8.5$ Hz, 2H, H–2', H–6'), 5.91 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.12 (dq, $J = 10.1$, 1.5 Hz, 1H, $=CH_{2(H-cis)}$), 5.00 (dq, $J = 17.1$, 1.5 Hz, 1H, $=CH_{2(H-trans)}$), 4.27 (s, 2H, N–CH_2), 3.35 (dt, $J = 6.0$, 1.5 Hz, 2H, –CH_2–).^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8 (C1), 138.1 (C1'), 136.0 (=CH), 133.5 (C4'), 132.2 (C3), 132.1 (C4a), 130.2 (C8a), 129.1 (C2), 129.4 (C3', C5'), 128.9 (C2', C6'), 127.8 (C8), 126.8 (C6), 126.6 (C7), 123.8 (C5), 117.3 (C4), 116.5 (=CH_2), 55.1 (N–CH_2), 36.3 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 385 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 14), 274 (1), 260 (7), 246 (3), 180 (100), 125 (43).

2–Allyl–4–bromo–N–(2,4–dichlorobenzyl)–1–naphthylamine (5g)

Yellow viscous oil. Yield: 88%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3363 (N–H), 1637 (C=C_{allyl}), 914 (=C–H_{allyl}). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, $J = 7.5$, 1.5 Hz, 1H, H–8), 8.17 (dd, $J = 7.5$, 1.5 Hz, 1H, H–5), 7.57 (td, $J = 7.5$, 1.5 Hz, 1H, H–7), 7.54 (td, $J = 7.5$, 1.5 Hz, 1H, H–6), 7.53 (s, 1H, H–3), 7.43 (d, $J = 2.0$ Hz, 1H, H–3'), 7.18 (dd, $J = 8.1$, 2.0 Hz, 1H, H–5'), 7.25 (d, $J = 8.1$ Hz, 1H, H–6'), 5.90 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.12 (dq, $J = 10.1$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.03 (dq, $J = 17.1$, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.37 (s, 2H, N–CH_2), 3.35 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0 (C1), 135.8 (=CH), 135.6 (C1'), 134.4 (C2'), 134.1 (C4'), 132.2 (C3, C6'), 132.0 (C4a), 130.4 (C8a), 129.5 (C3'), 129.4 (C2), 127.8 (C5'), 127.4 (C8), 126.8 (C6), 126.6 (C7), 123.8 (C5), 117.5 (C4), 116.7 (=CH_2), 51.5 (N–CH_2), 36.2 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 421 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 10), 274 (1), 260 (7), 246 (2), 180 (100), 159 (20).

4.2.8. 2–Allyl–N–(2–methylbenzyl)–1–naphthylamine (5h)

Pale Yellow viscous oil. Yield: 78%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3363 (N–H), 1635 (C=C_{allyl}), 915 (=C–H_{allyl}). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (dd, $J = 9.0$, 1.0 Hz, 1H, H–8), 7.87 (dd, $J = 7.6$, 2.0 Hz, 1H, H–5), 7.59 (d, $J = 8.4$ Hz, 1H, H–4), 7.58 (dd, $J = 7.6$, 1.6 Hz, 1H, H–6'), 7.33 (d, $J = 8.4$ Hz, 1H, H–3), 7.43–7.49 (m, 2H, H–6, H–7), 7.27–7.30 (m, 3H, H–3', H–4', H–5'), 5.98–6.05 (m, 1H, =CH), 5.01–5.15 (m, 2H, =CH_2), 4.36 (s, 2H, N–CH_2), 3.59 (dt, $J = 6.4$, 1.6 Hz, 2H, –CH_2–), 2.36 (s, 3H, 2'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0 (C1), 138.4 (C1'), 136.9 (C2', =CH), 134.0 (C4a), 130.5 (C5'), 129.3 (C8a), 128.7 (C5), 128.5 (C6'), 128.3 (C3), 127.9 (C2), 127.5 (C4'), 126.4 (C3'), 125.7 (C7), 125.4 (C6), 123.4 (C4, C8), 116.1 (=CH_2), 52.7 (N–CH_2), 36.5 (–CH_2–), 19.2 (2'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 318 ($M^{+\bullet}$, 31), 277 (1), 274 (2), 196 (1), 182 (100), 136 (3).

2–Allyl–N–(3–nitrobenzyl)–1–naphthylamine (5i)

Yellow viscous oil. Yield: 78%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3360 (N–H), 1641(C=C_{allyl}), 1528 (–NO_2), 1348 (–NO_2), 919 (=C–H_{allyl}). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H, H–2'), 8.18 (dd, $J = 8.3$, 1.1 Hz, 1H, H–8), 8.13 (dd, $J = 8.2$, 0.4 Hz, 1H, H–5), 7.73 (d, $J = 8.4$ Hz, 1H, H–6'), 7.65 (d, $J = 7.0$ Hz, 1H, H–4), 7.57 (t, $J = 8.4$ Hz, 1H, H–5'), 7.43–7.52 (m, 2H, H–6, H–7), 7.47 (d, $J = 7.0$ Hz, 1H, H–3), 7.30 (d, $J = 8.4$ Hz, 1H, H–4'), 6.00 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.12 (dq, $J = 10.1$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.01 (dq, $J = 17.1$, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.41 (s, 2H, N–CH_2), 3.47 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6 (C1'), 142.0 (C3'), 141.7 (C1), 136.7 (=CH_2), 134.0 (C4a), 133.9 (C6'), 129.3 (C8a), 128.6 (C4'), 128.1 (C2, C4), 125.9 (C3, C6), 125.5 (C7), 123.9 (C5'), 123.0 (C5), 122.7 (C8), 122.4 (C2'), 116.3 (=CH_2), 53.8 (N–CH_2), 36.5 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 318 ($M^{+\bullet}$, 36), 196 (6), 182 (100), 168 (1), 136 (11).

2–Allyl–N–(4–nitrobenzyl)–1–naphthylamine (5j)

Yellow viscous oil. Yield: 79%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3354 (N–H), 1522 (–NO_2), 1350 (–NO_2), 1637 (C=C_{allyl}), 917 (=C–H_{allyl}). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, $J = 8.4$ Hz, 2H, H–3', H–5'), 8.10 (dd, $J = 7.1$, 1.9 Hz, 1H, H–8), 7.84 (dd, $J = 7.8$, 2.3 Hz, 1H, H–5), 7.58 (d, $J = 8.4$ Hz, 2H, H–2', H–6'), 7.57 (d, $J = 8.3$ Hz, 1H, H–4), 7.42–7.51 (m, 2H, H–6, H–7), 7.29 (d, $J = 8.3$ Hz, 1H, H–3),

5.99 (ddt, $J = 17.1$, 10.2, 6.0 Hz, 1H, =CH), 5.10 (dq, $J =$ 10.1, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 4.99 (dq, $J = 17.1$, 1.5 Hz, 1H, $=CH_{2(H-trans)}$), 4.41 (s, 2H, N–CH_2), 3.44 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8 (C1'), 147.4 (C4'), 141.9 (C1), 136.6 (=CH), 134.0 (C4a), 129.0 (C8a), 128.7 (C4), 128.6 (C3), 128.5 (C5), 128.0 (C2), 125.9 (C6), 125.5 (C7), 124.0 (C3', C5'), 123.9 (C2', C6'), 122.9 (C8), 116.2 ($=CH_2$), 54.2 (N–CH_2), 36.8 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 318 ($M^{+\bullet}$, 29), 196 (5), 182 (100), 168 (1), 136 (7).

2–Allyl–4–bromo–N–(thiophen–2–ylmethyl)–1–naphthylamine (6a)

Colorless viscous oil. Yield: 75%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3360 (N–H), 1635 ($C{=}C_{allyl}$), 916 ($=C–H_{allyl}$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, $J = 8.7$, 1.2 Hz, 1H, H–8), 7.57 (dd, $J = 8.4$, 1.5 Hz, 1H, H–5), 7.53 (ddd, $J = 8.7$, 7.2, 1.5 Hz, 1H, H–7), 7.51 (ddd, $J = 8.4$, 7.2, 1.2 Hz, 1H, H–6), 7.23 (s, 1H, H–3), 7.19 (dd, $J = 3.2$, 0.7 Hz, 1H, H–5'), 6.95 (dd, $J = 3.5$, 3.5 Hz, 1H, H–4'), 6.91 (dd, $J = 3.5$, 0.7 Hz, 1H, H–3'), 5.88 (ddt, $J = 17.1$, 10.2, 6.1 Hz, 1H, =CH), 5.07 (dq, $J = 10.2$, 1.8 Hz, 1H, $=CH_{2(H-cis)}$), 4.97 (dq, $J =$ 17.1, 1.8 Hz, 1H, $=CH_{2(H-trans)}$), 4.40 (s, 2H, N–CH_2), 3.39 (dt, $J = 6.1$, 1.8 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9 (C1), 141.3 (C2'), 136.0 (=CH), 131.7 (C4a), 128.7 (C8a), 128.4 (C3), 127.8 (C2), 127.8 (C5), 126.8 (C7), 126.6 (C5'), 126.5 (C6), 125.2 (C4'), 124.9 (C3'), 123.8 (C8), 117.2 (C4), 116.6 ($=CH_2$), 49.4 (N–CH_2), 36.3 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 357 ($M^{+\bullet}$, ^{79}Br, 6), 274 (1), 260 (3), 246 (2), 97 (100).

2–Allyl–4–bromo–N–(5–methylthiophen–2–ylmethyl)–1–naphthylamine (6b)

Colorless viscous oil. Yield: 78%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3362 (N–H), 1635 ($C{=}C_{allyl}$), 915 ($=C–H_{allyl}$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, $J = 7.1$, 2.2 Hz, 1H, H–8), 8.20 (dd, $J = 7.1$, 2.3 Hz, 1H, H–5), 7.60 (s, 1H, H–3), 7.56 (td, $J = 7.1$, 2.3 Hz, 1H, H–7), 7.55 (td, $J = 7.1$, 2.2 Hz, 1H, H–6), 6.61 (dd, $J = 3.3$, 1.0 Hz, 1H, H–4'), 6.68 (d, $J = 3.3$ Hz, 1H, H–3'), 5.94 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.13 (dq, $J = 10.1$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.03 (dq, $J =$ 17.1, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.37 (s, 2H, N–CH_2), 3.40 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–), 2.48 (s, 3H, 5'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3 (C1), 140.6 (C2'), 139.4 (C5'), 136.3 (=CH), 132.2 (C3, C4a), 130.4 (C8a), 129.2 (C2), 127.7 (C5), 126.8 (C7), 126.4 (C6), 125.3 (C3'), 125.0 (C4'), 124.0 (C8), 117.3 (C4), 115.2 ($=CH_2$), 49.5 (N–CH_2), 35.8 (–CH_2–), 15.5 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 371 ($M^{+\bullet}$, ^{79}Br, 3), 274 (2), 182 (4), 260 (4), 111 (100).

2–Allyl–4–bromo–N–(3–methylthiophen–2–ylmethyl)–1–naphthylamine (6c)

Colorless viscous oil. Yield: 70%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3360 (N–H), 1636 ($C{=}C_{allyl}$), 916 ($=C–H_{allyl}$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, $J = 7.0$, 2.1 Hz, 1H, H–8), 8.20 (dd, $J = 7.0$, 2.0 Hz, 1H, H–5), 7.58 (s, 1H, H–3), 7.56 (td, $J = 7.0$, 2.1 Hz, 1H, H–7), 7.55 (td, $J = 7.0$, 2.1 Hz, 1H, H–6), 7.16 (d, $J = 5.1$ Hz, 1H, H–5'), 6.82 (d, $J = 5.1$ Hz, 1H, H–4'), 5.91 (ddt, $J = 17.0$, 10.2, 6.0 Hz, 1H, =CH), 5.12 (dq, $J = 10.2$, 1.5 Hz, 1H, $=CH_{2(H-cis)}$), 5.02 (dq, $J =$ 17.0, 1.5 Hz, 1H, $=CH_{2(H-trans)}$), 4.36 (s, 2H, N–CH_2), 3.35 (dt, $J = 6.0$, 1.5 Hz, 2H, –CH_2–), 2.01 (s, 3H, 3'–CH_3).^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4 (C1), 136.1 (C2'), 136.0 (=CH), 134.2 (C3'), 132.2 (C3), 132.1 (C4a), 130.5 (C8a), 130.3 (C5'), 129.2 (C2), 127.7 (C5), 126.8 (C7), 126.5 (C6), 123.2 (C8, C4'), 117.3 (C4), 116.9 ($=CH_2$), 47.3 (N–CH_2), 36.1 (–CH_2–), 13.6 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 371 ($M^{+\bullet}$, ^{79}Br, 2), 274 (3), 260 (3), 246 (2), 180 (14), 111 (100).

2–Allyl–N–(thiophen–2–ylmethyl)–1–naphthylamine (6d)

Colorless viscous oil. Yield: 76%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3361 (N–H), 1629 ($C{=}C_{allyl}$), 916 ($=C–H_{allyl}$).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, $J = 8.4$, 1.2 Hz, 1H, H–8), 7.87 (dd, $J = 8.4$, 1.2 Hz, 1H, H–5), 7.55 (ddd, $J = 8.4$, 7.0, 1.2 Hz, 1H, H–7), 7.50 (ddd, $J = 8.4$, 7.0, 1.2 Hz, 1H, H–6), 7.33 (d, $J = 8.4$ Hz, 1H, H–3), 7.29 (dd, $J = 5.2$, 1.2 Hz, 1H, H–5'), 7.02 (d, $J = 5.2$, 3.2 Hz, 1H, H–4'), 6.99 (dd, J $= 3.2$, 0.8 Hz, 1H, H–3'), 6.02 (ddt, $J = 17.2$, 10.2, 6.0 Hz, 1H, =CH), 5.14 (dq, $J = 10.2$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.07 (dq, $J = 17.2$, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.55 (s, 2H, N–CH_2), 3.38 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3 (C1), 141.9 (C2'), 137.1 (=CH), 134.3 (C4a), 129.5 (C8a), 128.9 (C3), 128.8 (C2), 127.3 (C7, C4'), 126.2 (C3'), 125.8 (C6), 125.7 (C5), 124.2 (C4), 123.6 (C8), 116.5 ($=CH_2$), 49.7 (N–CH_2), 36.8 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 279 ($M^{+\bullet}$, 40), 196 (1), 182 (36), 168 (6), 97 (100).

2–Allyl–N–(5–methylthiophen–2–ylmethyl)–1–naphthylamine (6e)

Colorless viscous oil. Yield: 80%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3361 (N–H), 1636 ($C{=}C_{allyl}$), 915 ($=C–H_{allyl}$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 30 (br d, $J = 8.8$ Hz, 1H, H–8), 7.90 (br d, $J = 8.4$ Hz, 1H, H–5), 7.62 (d, $J = 8.4$ Hz, 1H, H–4), 7.58 (ddd, $J = 8.4$, 7.0, 1.2 Hz, 1H, H–7), 7.52 (ddd, $J =$ 8.0, 7.0, 1.2 Hz, 1H, H–6), 7.36 (d, $J = 8.4$ Hz, 1H, H–3), 6.80 (d, $J = 3.2$ Hz, 1H, H–4'), 6.70 (dd, $J = 3.2$, 1.0 Hz, 1H, H–3'), 6.07 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.18 (dq, $J = 10.1$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.12 (dq, $J =$

17.1, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.48 (s, 2H, N–CH_2), 3.55 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–), 2.57 (s, 3H, 5'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6 (C1), 141.4 (C2'), 139.7 (C5'), 137.2 (=CH), 134.3 (C4a), 129.6 (C8a), 129.0 (C5), 128.8 (C3), 128.5 (C2), 126.1 (C7), 125.7 (C6), 125.4 (C4'), 125.3 (C3'), 123.9 (C4), 123.7 (C8), 116.5 ($=CH_2$), 50.1 (N–CH_2), 36.9 (–CH_2–), 15.9 (5'–CH_3). GC–MS (EI, 70 eV): m/z (%) 293 ($M^{+\bullet}$, 10), 196 (1), 182 (4), 168 (4), 111 (100).

2–Allyl–N–(3–methylthiophen–2–ylmethyl)–1–naphthylamine (6f)

Colorless viscous oil. Yield: 81%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3360 (N–H), 1635 ($C{=}C_{allyl}$), 915 ($=C–H_{allyl}$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (dd, $J = 8.4$, 1.2 Hz, 1H, H–8), 7.86 (br d, $J = 7.2$ Hz, 1H, H–5), 7.58 (br d, $J = 8.4$ Hz, 1H, H–4), 7.54 (ddd, $J = 8.4$, 7.0, 1.4 Hz, 1H, H–7), 7.48 (ddd, $J = 7.2$, 7.0, 1.2 Hz, 1H, H–6), 7.31 (br d, $J = 8.4$ Hz, 1H, H–3), 7.19 (d, $J = 5.2$ Hz, 1H, H–5'), 6.86 (d, $J = 5.2$ Hz, 1H, H–4'), 6.00 (ddt, $J = 17.2$, 10.0, 6.4 Hz, 1H, =CH), 5.13 (dq, $J = 10.2$, 1.5 Hz, 1H, $=CH_{2(H-cis)}$), 5.06 (dq, $J = 17.2$, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.43 (s, 2H, N–CH_2), 3.46 (dt, $J = 6.4$, 1.6 Hz, 2H, –CH_2–), 2.08 (s, 3H, 3'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.6 (C1), 137.1 (=CH), 136.9 (C2'), 134.3 (C4a, C3'), 130.6 (C5'), (129.7 (C8a), 128.9 (C5), 128.8 (C3), 128.6 (C2), 126.1 (C7), 125.7 (C6), 124.0 (C4), 123.7 (C8), 123.4 (C4'), 116.4 ($=CH_2$), 47.8 (N–CH_2), 36.8 (–CH_2–), 14.0 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 357 ($M^{+\bullet}$, 3), 274 (2), 260 (4), 246 (1), 180 (12), 111 (100).

2–Allyl–N–(5–bromothiophen–2–ylmethyl)–1–naphthylamine (6g)

Colorless viscous oil. Yield: 78%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3360 (N–H), 1628 ($C{=}C_{allyl}$), 915 ($=C–H_{allyl}$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (br d, $J = 8.4$ Hz, 1H, H–8), 7.86 (br d, $J = 8.4$ Hz, 1H, H–5), 7.59 (d, $J = 8.4$ Hz, 1H, H–4), 7.53 (ddd, $J = 8.4$, 7.0, 1.2 Hz, 1H, H–7), 7.49 (ddd, $J = 8.4$, 7.0, 1.2 Hz, 1H, H–6), 7.32 (d, $J = 8.4$ Hz, 1H, H–3), 6.96 (d, $J = 3.8$ Hz, 1H, H–4'), 6.71 (dd, $J = 3.8$, 1.0 Hz, 1H, H–3'), 6.02 (ddt, $J = 16.8$, 10.2, 6.0 Hz, 1H, =CH), 5.14 (dq, $J = 10.2$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.05 (dq, $J = 16.8$, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.43 (s, 2H, N–CH_2), 3.50 (dt, $J = 6.0$, 1.6 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0 (C1), 145.6 (C2'), 137.0 (=CH), 134.3 (C4a), 130.0 (C4'), 129.5 (C8a), 129.0 (C3), 128.8 (C5), 128.7 (C2), 126.2 (C7), 125.8 (C6), 125.4 (C3'), 124.3 (C4), 123.4 (C8), 116.5 ($=CH_2$), 111.5, (C5'), 50.0 (N–CH_2), 36.9 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 357 ($M^{+\bullet}$, ^{79}Br, 8), 196 (1), 182 (39), 175 (100).

2–Allyl–4–bromo–N–(furan–2–ylmethyl)–1–naphthylamine (7a)

Colorless viscous oil. Yield: 74%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3370 (N–H), 1636 ($C{=}C_{allyl}$), 916 ($=C–H_{allyl}$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, $J = 7.0$, 1.6 Hz, 1H, H–8), 8.20 (dd, $J = 7.0$, 1.5 Hz, 1H, H–5), 7.58 (s, 1H, H–3), 7.57 (td, $J = 7.0$, 1.5 Hz, 1H, H–7), 7.55 (td, $J = 7.0$, 1.6 Hz, 1H, H–6), 7.41 (dd, $J = 1.9$, 0.8 Hz, 1H, H–5'), 6.31 (dd, $J = 3.1$, 1.9 Hz, 1H, H–4'), 6.06 (dd, $J = 3.1$, 0.8 Hz, 1H, H–3'), 5.93 (ddt, $J = 17.1$, 10.0, 6.1 Hz, 1H, =CH), 5.15 (dq, $J = 10.0$, 1.5 Hz, 1H, $=CH_{2(H-cis)}$), 5.05 (dq, $J = 17.1$, 1.5 Hz, 1H, $=CH_{2(H-trans)}$), 4.28 (s, 2H, N–CH_2), 3.33 (dt, $J = 6.1$, 1.5 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.6 (C2'), 142.2 (C5'), 142.1 (C1), 136.3 (=CH), 132.2 (C3), 132.1 (C4a), 129.2 (C2), 129.1 (C8a), 127.4 (C5), 126.7 (C7), 126.4 (C6), 124.0 (C8), 117.0 (C4), 116.4 ($=CH_2$), 110.6 (C4'), 107.2 (C3'), 47.4 (N–CH_2), 35.8 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 341 ($M^{+\bullet}$, ^{79}Br, 8), 274 (1), 260 (6), 246 (1), 81 (100).

2–Allyl–4–bromo–N–(5–methylfuran–2–ylmethyl)–1–naphthylamine (7b)

Colorless viscous oil. Yield: 82%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3369 (N–H), 1635 ($C{=}C_{allyl}$), 917 ($=C–H_{allyl}$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, $J = 8.5$, 2.0 Hz, 1H, H–8), 8.20 (dd, $J = 8.6$, 1.0 Hz, 1H, H–5), 7.57 (s, 1H, H–3), 7.56 (td, $J = 8.6$, 1.0 Hz, 1H, H–7), 7.54 (td, $J = 8.6$, 2.0 Hz, 1H, H–6), 5.93 (ddt, $J = 17.1$, 10.0, 6.1 Hz, 1H, =CH), 5.92 (d, $J = 3.2$ Hz, 1H, H–3'), 5.87 (d, $J = 3.2$ Hz, 1H, H–4'), 5.13 (dq, $J = 10.0$, 1.6 Hz, 1H, $=CH_{2(H-cis)}$), 5.06 (dq, $J = 17.1$, 1.6 Hz, 1H, $=CH_{2(H-trans)}$), 4.20 (s, 2H, N–CH_2), 3.35 (dt, $J = 6.1$, 1.6 Hz, 2H, –CH_2–), 2.31 (s, 3H, 5'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.8 (C2'), 151.6 (C5'),142.4 (C1), 136.2 (=CH), 132.1 (C3), 130.4 (C8a), 132.0 (C4a), 129.0 (C2), 127.7 (C5), 126.7 (C7), 126.4 (C6), 124.0 (C8), 117.0 (C4), 116.6 ($=CH_2$), 108.1 (C3'), 106.3 (C4'), 47.6 (N–CH_2), 35.9 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 355 ($M^{+\bullet}$, ^{79}Br, 4), 274 (1), 260 (2), 246 (2), 95 (100).

2–Allyl–N–(furan–2–ylmethyl)–1–naphthylamine (7c)

Colorless viscous oil. Yield: 77%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3369 (N–H), 1634 ($C{=}C_{allyl}$), 915 ($=C–H_{allyl}$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (br d, $J = 8.4$ Hz, 1H, H–8), 7.84 (br d, $J = 8.1$ Hz, 1H, H–5), 7.55 (d, $J = 8.4$ Hz, 1H, H–4), 7.51 (ddd, $J = 8.4$, 8.1, 1.5 Hz, 1H, H–7), 7.47 (td, $J = 8.1$, 1.2 Hz, 1H, H–6), 7.43 (dd, $J = 3.0$, 0.7 Hz, 1H, H–5'), 7.28 (d, $J = 8.4$ Hz, 1H, H–3), 6.33 (dd, $J = 3.0$, 1.8 Hz, 1H, H–4'), 6.11 (d, $J = 3.0$ Hz, 1H, H–3'), 5.99 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.12 (dq, $J = 10.1$, 1.5 Hz, 1H,

$=CH_{2(H-cis)}$), 5.06 (dq, $J = 17.1$, 1.5 Hz, 1H, $=CH_{2(H-trans)}$), 4.32 (s, 2H, N–CH_2), 3.41 (dt, $J = 6.0$, 1.5Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7 (C2'), 142.2 (C5'), 142.0 (C1), 136.9 (=CH), 133.9 (C4a), 128.6 (C8a), 128.4 (C3, C5), 128.1 (C2), 125.7 (C7), 125.4 (C6), 123.6 (C8), 123.4 (C4), 116.1 (=CH_2), 107.2 (C3'), 47.0 (N–CH_2), 36.6 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 263 ($M^{+\bullet}$, 28), 196 (1), 182 (34), 168 (60), 81 (100).

2–Allyl–N–(5–methylfuran–2–ylmethyl)–1–naphthylamine (7d)

Colorless viscous oil. Yield: 76%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3369 (N–H), 1635 (C=C_{allyl}), 917 (=C–H_{allyl}). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (br d, $J = 8.4$ Hz, 1H, H–8), 7.84 (br d, $J = 8.4$ Hz, 1H, H–5), 7.55 (d, $J = 8.2$ Hz, 1H, H–4), 7.51 (td, $J = 8.4$, 1.4 Hz, 1H, H–7), 7.45 (td, $J = 8.4$, 1.1 Hz, 1H, H–6), 7.29 (d, $J = 8.2$ Hz, 1H, H–3), 6.01 (ddt, $J = 17.1$, 10.1, 6.0 Hz, 1H, =CH), 5.99 (d, $J = 3.0$ Hz, 1H, H–3'), 5.91 (dd, $J = 3.0$, 1.0 Hz, 1H, H–4'), 5.14 (dq, $J = 10.1$, 1.2 Hz, 1H, $=CH_{2(H-cis)}$), 5.09 (dq, $J = 17.1$, 1.2 Hz, 1H, $=CH_{2(H-trans)}$), 4.26 (s, 2H, N–CH_2), 3.46 (dt, $J = 6.0$, 1.2 Hz, 2H, –CH_2–), 2.35 (s, 3H, 5'-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9 (C2'), 151.7 (C5'), 142.3 (C1), 136.9 (=CH), 133.9 (C4a), 129.3 (C8a), 128.5 (C3), 128.4 (C5), 128.0 (C2), 125.6 (C7), 125.3 (C6), 123.5 (C4, C8), 115.9 (=CH_2), 108.1 (C3'), 106.2 (C4'), 47.0 (N–CH_2), 36.2 (–CH_2–), 13.9 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 277 ($M^{+\bullet}$, 8), 196 (1), 182 (3), 168 (6), 95 (100).

2–Allyl–N–(5–nitrofuran–2–ylmethyl)–1–naphthylamine (7e)

Colorless viscous oil. Yield: 70%. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3373 (N–H), 1636 (C=C_{allyl}), 1497 (–NO_2), 1356 (–NO_2), 918 (=C–H_{allyl}). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, $J = 8.3$, 1.1 Hz, 1H, H–8), 7.85 (dd, $J = 7.4$, 1.2 Hz, 1H, H–5), 7.59 (d, $J = 8.5$ Hz, 1H, H–4), 7.52 (td, $J = 8.3$, 1.2 Hz, 1H, H–7), 7.47 (td, $J = 7.4$, 1.1 Hz, 1H, H–6), 7.29 (d, $J = 8.5$ Hz, 1H, H–3), 7.24 (d, $J = 3.6$ Hz, 1H, H–4'), 6.33 (d, $J = 3.6$ Hz, 1H, H–3'), 6.01 (ddt, $J = 17.1$, 10.1, 5.9 Hz, 1H, =CH), 5.15 (dq, $J = 10.1$, 1.7 Hz, 1H, $=CH_{2(H-cis)}$), 5.06 (dq, $J = 17.1$, 1.7 Hz, 1H, $=CH_{2(H-trans)}$), 4.41 (s, 2H, N–CH_2), 3.48 (dt, $J = 5.9$, 1.7 Hz, 2H, –CH_2–). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6 (C5'), 151.9 (C2'), 141.0 (C1), 136.5 (=CH), 134.0 (C4a), 129.0 (C8a), 128.7 (C5), 128.6 (C3), 128.5 (C2), 126.1 (C7), 125.6 (C6), 124.3 (C4), 122.7 (C8), 116.2 (=CH_2), 112.8 (C4'), 110.7 (C3'), 47.0 (N–CH_2), 36.6 (–CH_2–). GC–MS (EI, 70 eV): *m/z* (%) 308 ($M^{+\bullet}$, 34), 196 (14), 182 (74), 167 (100), 126 (20).

Physicochemical and spectral data for (2SR,4RS)–2–aryl(heteroaryl)–1,4–epoxy–2,3,4,5–tetrahydro–naphtho[1,2–b]azepines (8a–j), (9a–g), and (10a–e)

(2SR,4SR)–7–Bromo–2–phenyl–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8a)

Reaction time: 35 h. Yield: 49%. White solid, mp 123 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1044 (C–O), 996, (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (br d, $J = 8.2$ Hz, 1H, H–11), 8.19 (br d, $J = 8.2$ Hz, 1H, H–8), 7.58 (td, $J = 8.2$, 1.0 Hz, 1H, H–9), 7.57 (d, $J = 7.6$ Hz, 2H, H–2', H–6'), 7.56 (s, 1H, H–6), 7.51 (td, $J = 8.2$, 1.1 Hz, 1H, H–10), 7.44 (t, $J = 7.6$ Hz, 2H, H–3', H–5'), 7.34 (t, $J = 7.6$ Hz, 1H, H–4'), 5.07 (ddd, $J = 7.2$, 5.3, 1.9 Hz, 1H, H–4), 4.73 (dd, $J = 8.3$, 2.8 Hz, 1H, H–2), 3.55 (dd, $J = 16.8$, 5.3 Hz, 1H, H_B–5), 2.69 (dddd, $J = 12.6$, 7.2, 2.8, 0.8 Hz, 1H, H_B–3), 2.63 (ddd, $J = 12.6$, 8.3, 1.9 Hz, 1H, H_A–3), 2.61 (br d, $J = 16.8$ Hz, 1H, H_A–5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6 (C11b), 143.6 (C1'), 131.1 (C6), 131.0 (C7a), 128.9 (C11a), 128.8 (C3', C5'), 127.3 (C4'), 127.2 (C8), 127.1 (C9, C2', C6'), 126.4 (C10), 122.6 (C11), 122.1 (C5a), 119.6 (C7), 75.4 (C4), 74.5 (C2), 43.2 (C3), 35.0 (C5). GC–MS (EI, 70 eV): *m/z* (%) 365 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 10), 335 (7), 322 (5), 257 (9), 231 (2), 220 (100), 193 (2). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{16}BrNO$, 365.0415; found, 365.0421.

(2SR,4SR)–7–Bromo–2–(o–tolyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8b)

Reaction time: 60 h. Yield: 50%. Pale yellow solid, mp 177 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1048 (C–O), 1000 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (br d, $J = 7.3$ Hz, 1H, H–11), 8.19 (br d, $J = 8.0$ Hz, 1H, H–8), 8.09 (br d, $J = 7.7$ Hz, 1H, H–6'), 7.58 (s, 1H, H–6), 7.56 (td, $J = 8.2$, 1.1 Hz, 1H, H–9), 7.48 (td, $J = 8.2$, 0.9 Hz, 1H, H–10), 7.37 (t, $J = 7.7$ Hz, 1H, H–5'), 7.25 (td, $J = 7.6$, 1.1 Hz, 1H, H–4'), 7.19 (br d, $J = 7.6$ Hz, 1H, H–3'), 5.02 (ddd, $J = 7.9$, 5.4, 1.5 Hz, 1H, H–4), 4.80 (dd, $J = 8.6$, 2.9 Hz, 1H, H–2), 3.55 (dd, $J = 16.9$, 5.4 Hz, 1H, H_B–5), 2.70 (ddd, $J = 12.2$, 8.6, 1.5 Hz, 1H, H_A–3), 2.63 (br d, $J = 16.9$ Hz, 1H, H_A–5), 2.47 (dddd, $J = 12.2$, 7.9, 2.9, 1.2 Hz, 1H, H_B–3), 2.17 (s, 3H, 2'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9 (C11b), 141.8 (C1'), 133.9 (C2'), 131.0 (C6), 130.3 (C7a, C3'), 128.9 (C11a), 127.4 (C9), 127.3 (C4'), 127.2 (C10), 127.0 (C8), 126.5 (C5'), 125.7 (C6'), 122.6 (C11), 122.3 (C5a), 119.6 (C7), 75.4 (C4), 72.0 (C2), 43.4 (C3), 35.1 (C5), 19.7 (2'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 379 ($M^{+\bullet}$, ^{79}Br, 8), 349 (3), 336 (6), 220 (100), 193 (4). HR–MS (EI–MS) *m/z* calcd. for $C_{21}H_{18}BrNO$, 379.0566; found, 379.0572.

(2SR,4SR)–7–Bromo–2–(m–tolyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8c)

Reaction time: 58 h. Yield: 51%. Yellow solid, mp 80 °C (heptane). IR (KBr, cm^{-1}): ṽ 1046 (C–O), 992 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (br d, $J = 8.3$ Hz, 1H, H–11), 8.19 (br d, $J = 8.3$ Hz, 1H, H–8), 7.59 (d, $J = 7.7$ Hz, 1H, H–6'), 7.58 (td, $J = 8.3$, 0.8 Hz, 1H, H–9), 7.55 (s, 1 H, H–6), 7.50 (td, $J = 8.2$, 0.8 Hz, 1H, H–10), 7.41 (s, 1H, H–2'), 7.33 (t, $J = 7.7$ Hz, 1H, H–5'), 7.16 (br d, $J = 7.7$ Hz, 1H, H–4'), 5.07 (ddd, $J = 7.0$, 5.4, 1.6 Hz, 1H, H–4), 4.70 (dd, $J = 8.3$, 2.8 Hz, 1H, H–2), 3.55 (dd, $J = 16.8$, 5.3 Hz, 1H, H_B–5), 2.68 (dddd, $J = 12.5$, 7.0, 2.8, 0.9 Hz, 1H, H_B–3), 2.63 (ddd, $J = 12.5$, 8.3, 1.6 Hz, 1H, H_A–3), 2.60 (br d, $J = 16.8$ Hz, 1H, H_A–5), 2.44 (s, 3H, 3'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7 (C11b), 143.3 (C1'), 138.4 (C3'), 131.0 (C6), 130.1 (C7a), 128.8 (C11a), 128.0 (C4'), 127.3 (C10, C6'), 127.2 (C8), 127.1 (C9), 127.0 (C2'), 123.6 (C5'), 122.5 (C11), 122.1 (C5a), 119.5 (C7), 75.3 (C4), 74.6 (C2), 43.0 (C3), 34.7 (C5), 21.6 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 379 ($M^{+\bullet}$, ^{79}Br, 11), 349 (4), 336 (4), 220 (100), 193 (3). HR–MS (EI–MS) *m/z* calcd. for $C_{21}H_{18}BrNO$, 379.0563; found, 379.0572.

(2SR,4SR)–7–Bromo–2–(3–methoxyphenyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8d)

Reaction time: 57 h. Yield: 48%. Viscous yellow oil. IR (liquid film, cm^{-1}): ṽ 1048 (C–O), 991 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (br d, $J = 8.3$ Hz, 1H, H–11), 8.18 (br d, $J = 8.3$ Hz, 1H, H–8), 7.87 (dd, $J = 8.0$, 2.3 Hz, 1H, H–4'), 7.58 (td, $J = 8.1$, 1.0 Hz, 1H, H–9), 7.55 (s, 1H, H–6), 7.50 (td, $J = 8.2$, 1.1 Hz, 1H, H–10), 7.34 (t, $J = 7.9$ Hz, 1H, H–5'), 7.18 (br d, $J = 2.3$ Hz, 1H, H–2'), 7.10 (d, $J = 7.9$ Hz, 1H, H–6'), 5.06 (ddd, $J = 7.0$, 5.4, 1.5 Hz, 1H, H–4), 4.89 (dd, $J = 8.3$, 2.8 Hz, 1H, H–2), 3.87 (s, 3H, 3'–OCH_3), 3.54 (dd, $J = 16.8$, 5.4 Hz, 1H, H_B–5), 2.66 (dddd, $J = 12.5$, 7.0, 2.8, 1.0 Hz, 1H, H_B–3), 2.61 (ddd, $J = 12.5$, 8.3, 1.5 Hz, 1H, H_A–3), 2.60 (br d, $J = 16.8$ Hz, 1H, H_A–5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (C3'), 145.6 (C11b), 145.2 (C1'), 131.1 (C6), 131.0 (C7a), 129.8 (C5'), 128.8 (C11a), 127.3 (C10), 127.2 (C9, C8), 122.5 (C11), 122.2 (C5a), 119.6 (C7), 118.8 (C6'), 112.5 (C4'), 112.1 (C2'), 75.4 (C4), 74.2 (C2), 43.4 (C3), 34.7 (C5), 55.5 (3'–OCH_3). GC–MS (EI, 70 eV): *m/z* (%) 395 ($M^{+\bullet}$, ^{79}Br, 3), 365 (1), 352 (1), 220 (100), 193 (1). HR–MS (EI–MS) *m/z* calcd. for $C_{21}H_{18}BrNO_2$, 395.0509; found, 395.0521.

(2SR,4SR)–7–Bromo–2–(2–chlorophenyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8e)

Reaction time: 61 h. Yield: 48%. Pale yellow solid, mp 17 °C (heptane). IR (KBr, cm^{-1}): ṽ 1054 (C–O), 955 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (br d, $J = 7.2$ Hz, 1H, H–11), 8.17 (dd, $J = 7.3$, 1.1 Hz, 1H, H–8), 8.16 (dd, $J = 7.8$, 1.3 Hz, 1H, H–6'), 7.60 (s, 1H, H–6), 7.58 (td, $J = 7.2$, 1.3 Hz, 1H, H–9), 7.49 (td, $J = 7.2$, 1.3 Hz, 1H, H–10), 7.43 (td, $J = 7.8$, 1.3 Hz, 1H, H–5'), 7.39 (td, $J = 8.0$, 1.3 Hz, 1H, H–4'), 7.29 (dd, $J = 7.9$, 1.6 Hz, 1H, H–3'), 5.03 (ddd, $J = 7.7$, 5.4, 1.5 Hz, 1H, H–4), 4.96 (dd, $J = 8.6$, 2.7 Hz, 1H, H–2), 3.57 (dd, $J = 16.9$, 5.4 Hz, 1H, H_B–5), 2.81 (ddd, $J = 12.8$, 8.6, 1.5 Hz, 1H, H_A–3), 2.54 (dddd, $J = 12.8$, 7.7, 2.7, 0.9 Hz, 1H, H_B–3), 2.65 (br d, $J = 16.9$ Hz, 1H, H_A–5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3 (C11b), 140.9 (C1'), 132.0 (C2'), 131.1 (C7a), 131.0 (C6), 129.4 (C4'), 128.8 (C11a), 128.3 (C3'), 127.8 (C9), 127.4 (C10), 127.3 (C5'), 127.2 (C8), 122.5 (C11), 122.4 (C5a, C6'), 119.8 (C7), 75.3 (C4), 71.8 (C2), 43.4 (C3), 34.8 (C5). GC–MS (EI, 70 eV): *m/z* (%) 399 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 1), 365 (100), 348 (6), 335 (4), 322 (2). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{15}BrClNO$, 399.0022; found, 399.0026.

(2SR,4SR)–7–Bromo–2–(4–chlorophenyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8f)

Reaction time: 61 h. Yield: 48%. Yellow solid, mp 181 °C (heptane). IR (KBr, cm^{-1}): ṽ 1047 (C–O), 958 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (br d, $J = 8.5$ Hz, 1H, H–11), 8.18 (br d, $J = 8.5$ Hz, 1H, H–8), 7.52–7.58 (m, 2H, H–9, H–10), 7.55 (s, 1H, H–6), 7.48 (d, $J = 7.6$ Hz, 2H, H–2', H–6'), 7.38 (d, $J = 7.6$ Hz, 2H, H–3', H–5'), 5.06 (ddd, $J = 8.0$, 5.1, 1.4 Hz, 1H, H–4), 4.66 (dd, $J = 8.4$, 2.0 Hz, 1H, H–2), 3.53 (dd, $J = 16.7$, 5.1 Hz, 1H, H_B–5), 2.69 (m, 2H, H_A–3, H_B–3), 2.70 (br d, $J = 16.7$ Hz, 1H, H_A–5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2 (C11b), 142.0 (C1'), 133.0 (C4'), 131.0 (C6, C7a), 128.9 (C3', C5'), 128.8 (C11a), 127.7 (C2', C6'), 127.3 (C8), 127.2 (C9, C10), 122.3 (C11), 122.1 (C5a), 119.8 (C7), 75.4 (C4), 73.8 (C2), 43.1 (C3), 34.8 (C5). GC–MS (EI, 70 eV): *m/z* (%) 399 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 5), 369 (3), 356 (2), 220 (100), 193 (3). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{15}BrClNO$, 399.0008; found, 399.0021.

(2SR,4SR)–7–Bromo–2–(2,4–dichlorophenyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8g)

Reaction time: 60 h. Yield: 49%. White solid, mp 192 °C (heptane). IR (KBr, cm^{-1}): ṽ 1045 (C–O), 993 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (br d, $J = 8.3$ Hz, 1H, H–11), 8.11 (br d, $J = 8.7$ Hz, 1H, H–8), 8.09 (d, $J = 8.9$ Hz, 1H, H–6'), 7.57 (s, 1H, H–6), 7.56 (td, $J = 8.7$, 1.2 Hz, 1H, H–9), 7.47 (td, $J = 8.3$, 1.2 Hz, 1H, H–10), 7.40 (dd, $J = 8.9$, 2.0 Hz, 1H, H–5'), 7.39 (d, $J = 2.0$ Hz, 1H, H–3'), 5.00 (ddd, $J = 7.9$, 5.4, 1.5 Hz, 1H, H–4), 4.87 (dd, $J = 8.6$, 2.8 Hz, 1H, H–2), 3.54 (dd, $J = 16.9$, 5.4 Hz, 1H, H_B–5), 2.76 (ddd, $J = 12.8$, 8.6, 1.5 Hz, 1H, H_A–3), 2.62 (br d, $J = 16.9$

Hz, 1H, H_A–5), 2.50 (dddd, $J = 12.8$, 7.9, 2.8, 1.3 Hz, 1H, H_B–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3 (C11b), 139.9 (C1'), 133.7 (C4'), 133.0 (C2'), 131.3 (C7a), 131.2 (C6), 129.2 (C6'), 129.0 (C11a), 127.8 (C9, C5'), 127.7 (C10), 127.6 (C8, C3'), 122.6 (C5a), 122.5 (C11), 120.4 (C7), 75.7 (C4), 71.9 (C2), 43.9 (C3), 35.3 (C5). GC–MS (EI, 70 eV): *m/z* (%) 432 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 1), 399 (100), 382 (5), 369 (3), 356 (1). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{14}BrCl_2NO$, 432.9639; found, 432.9636.

(2SR,4SR)–2–(o–Tolyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8h)

Reaction time: 58 h. Yield: 47%. Pale yellow solid, mp 198 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1046 (C–O), 995 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (dd, $J = 8.0$, 1.0 Hz, 1H, H–11), 8.10 (dd, $J = 8.0$, 1.3 Hz, 1H, H–8), 7.79 (dd, $J = 7.2$, 1.5 Hz, 1H, H–6'), 7.64 (d, $J = 8.5$ Hz, 1H, H–7), 7.44 (td, $J = 8.0$, 1.3 Hz, 1H, H–10), 7.40 (td, $J = 8.0$, 1.0 Hz, 1H, H–9), 7.35 (t, $J = 7.2$ Hz, 1H, H–5'), 7.24 (d, $J = 7.2$ Hz, 1H, H–3'), 7.22 (td, $J = 7.2$, 1.0 Hz, 1H, H–4'), 7.16 (d, $J = 8.5$ Hz, 1H, H–6), 5.03 (ddd, $J = 8.2$, 5.2, 1.8 Hz, 1H, H–4), 4.81 (dd, $J = 8.8$, 2.8 Hz, 1H, H–2), 3.59 (dd, $J = 16.8$, 5.2 Hz, 1H, H_B–5), 2.73 (ddd, $J = 12.0$, 8.8, 1.8 Hz, 1H, H_A–3), 2.64 (d, $J = 16.8$, 1H, H_A–5), 2.47 (dddd, $J = 12.0$, 7.2, 2.8, 0.8 Hz, 1H, H_B–3), 2.16 (s, 3H, 2'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9 (C11b), 142.2 (C1'), 134.0 (C2'), 132.7 (C7a), 130.2 (C3'), 127.8 (C8), 127.7 (C11a), 127.4 (C6), 126.9 (C4'), 126.4 (C10, C6'), 126.0 (C5'), 125.8 (C9), 125.6 (C7), 122.3 (C11), 121.1 (C5a), 75.7 (C4), 72.0 (C2), 43.7 (C3), 35.3 (C5), 19.6 (2'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 301 ($M^{+\bullet}$, 41), 272 (7), 258 (21), 142 (80), 115 (100). HR–MS (EI–MS) *m/z* calcd. for $C_{21}H_{19}NO$, 301.1473; found, 301.1467.

(2SR,4SR)–2–(3–Nitrophenyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8i)

Reaction time: 58 h.Yield: 48%. Pale yellow solid. mp 137 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1525 (–NO_2), 1325 (–NO_2), 1046 (C–O), 1004 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H, H–2'), 8.16 (ddd, $J = 8.0$, 2.0, 0.8 Hz, 1H, H–4'), 7.95 (ddd, $J = 8.0$, 2.0, 0.8, Hz, 1H, H–6'), 7.81 (dd, $J = 7.0$, 2.7 Hz, 1H, H–11), 7.79 (dd, $J = 7.0$, 2.5 Hz, 1H, H–8), 7.64 (d, $J = 8.4$ Hz, 1H, H–7), 7.57 (t, $J = 7.6$ Hz, 1H, H–5'), 7.41–7.47 (m, 2H, H–9, H–10), 7.21 (d, $J = 8.4$ Hz, 1H, H–6), 5.09 (ddd, $J = 7.3$, 5.5, 1.8 Hz, 1H, H–4), 4.80 (dd, $J = 8.6$, 2.8 Hz, 1H, H–2), 3.57 (dd, $J = 16.7$, 5.5 Hz, 1H, H_B–5), 2.70 (ddd, $J = 12.5$, 8.6, 1.8 Hz, 1H, H_A–3), 2.63 (br d, $J = 16.7$ Hz, 1H, H_A–5), 2.60 (dddd, $J = 12.5$, 7.3, 2.8, 1.0 Hz, 1H, H_B–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6 (C3'), 145.9 (C1'), 144.7 (C11b), 132.9 (C6'), 132.7 (C7a), 129.7 (C5'), 128.0 (C8), 127.5 (C11a), 127.4 (C6), 126.6 (C9), 126.0 (C10, C7), 122.2 (C11), 121.7 (C4'), 121.1 (C2'), 120.9 (C5a), 75.8 (C4), 73.6 (C2), 43.3 (C3), 35.2 (C5). GC–MS (EI, 70 eV): *m/z* (%) 332 ($M^{+\bullet}$, 10), 302 (1), 289 (7), 142 (100), 115 (31). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{16}N_2O_3$, 332.1160; found, 332.1161.

(2SR,4SR)–2–(4–Nitrophenyl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (8j)

Reaction time: 58 h. Yield: 50%. Yellow solid, mp 64 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1519 (–NO_2), 1342 (–NO_2), 1048 (C–O), 960 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, $J = 8.5$ Hz, 2H, H–3', H–5'), 8.11 (dd, $J = 7.6$, 1.8 Hz, 1H, H–11), 7.81 (dd, $J = 7.6$, 1.7 Hz, 1H, H–8), 7.75 (d, $J = 8.5$ Hz, 2H, H–2', H–6'), 7.66 (d, $J = 8.3$ Hz, 1H, H–7), 7.47 (td, $J = 7.6$, 1.8 Hz, 1H, H–10), 7.44 (td, $J = 7.6$, 1.8 Hz, 1H, H–9), 7.23 (d, $J = 8.3$ Hz, 1H, H–6), 5.09 (ddd, $J = 6.9$, 5.2, 1.4 Hz, 1H, H–4), 4.81 (dd, $J = 8.7$, 2.5 Hz, 1H, H–2), 3.59 (dd, $J = 16.9$, 5.2 Hz, 1H, H_B–5), 2.72 (ddd, $J = 12.4$, 8.7, 1.4 Hz, 1H, H_A–3), 2.65 (br d, $J = 16.9$ Hz, 1H, H_A–5), 2.60 (dddd, $J = 12.4$, 6.9, 2.5, 1.0 Hz, 1H, H_B–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0 (C4'), 147.2 (C1'), 144.7 (C11b), 132.7 (C7a), 128.0 (C8), 127.4 (C6), 127.3 (C11a, C2', C6'), 126.7 (C9), 126.3 (C10), 126.1 (C7), 124.1 (C3', C5'), 121.6 (C11), 121.0 (C5a), 75.9 (C4), 73.7 (C2), 43.2 (C3), 35.1 (C5). GC–MS (EI, 70 eV): *m/z* (%) 332 ($M^{+\bullet}$, 12), 302 (1), 289 (7), 142 (100), 115 (31). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{16}N_2O_3$, 332.1158; found, 332.1161.

(2SR,4SR)–7–Bromo–2–(thiophen–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (9a)

Reaction time: 39 h. Yield: 52%. Pale Yellow solid, mp 139 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1044 (C–O), 996 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (dd, $J = 7.3$, 2.4 Hz, 1H, H–11), 8.18 (dd, $J = 7.3$, 2.1 Hz, 1H, H–8), 7.59 (td, $J = 7.3$, 2.4 Hz, 1H, H–9), 7.57 (td, $J = 7.3$, 2.1 Hz, 1H, H–10), 7.54 (s, 1H, H–6), 7.30 (dd, $J = 4.2$, 2.0 Hz, 1H, H–5'), 7.02 (dd, $J = 4.3$, 2.0 Hz, 1H, H–3'), 7.00 (dd, $J = 4.2$, 4.3 Hz, 1H, H–4'), 5.12 (ddd, $J = 7.7$, 5.3, 1.8 Hz, 1H, H–4), 4.94 (dd, $J = 8.3$, 2.0 Hz, 1H, H–2), 3.56 (dd, $J = 16.9$, 5.3 Hz, 1H, H_B–5), 2.81 (dddd, $J = 12.6$, 7.7, 2.0, 1.0 Hz, 1H, H_B–3), 2.60 (br d, $J = 16.9$ Hz, 1H, H_A–5), 2.56 (ddd, $J = 12.6$, 8.3, 1.8 Hz, 1H, H_A–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3 (C2'), 144.7 (C11b), 133.1 (C7a), 131.0 (C6), 128.0 (C11a), 127.4 (C8, C10), 127.3 (C9), 126.9 (C5'), 125.0 (C4'), 124.1 (C3'), 122.6 (C11), 121.0 (C5a), 120.0 (C7), 75.6 (C4), 70.9 (C2), 42.7 (C3), 35.1 (C5). GC–MS (EI, 70 eV): *m/z* (%) 371 ($M^{+\bullet}$, ^{79}Br, 18), 341 (5), 328 (7), 257 (4), 231 (2), 220 (100), 193 (1). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{14}BrNOS$, 370.9976; found, 370.9979.

(2SR,4SR)–7–Bromo–2–(5–methylthiophen–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (9b)

Reaction time: 40 h. Yield: 47%. White solid, mp 122 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1050 (C–O), 989 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37–8.41 (m, 1H, H–11), 8.15–8.22 (m, 1H, H–8), 7.54–7.63 (m, 2H, H–9, H–10), 7.53 (s, 1H, H–6), 6.79 (d, $J = 3.4$ Hz, 1H, H–3'), 6.65 (dd, $J = 3.2$, 0.8 Hz, 1H, H–4'), 5.06–5.12 (m, 1H, H–4), 4.97 (br d, $J = 7.9$ Hz, 1H, H–2), 3.54 (dd, $J = 16.8$, 5.3 Hz, 1H, H_B–5), 2.77 (dddd, $J = 12.0$, 7.5, 2.0, 1.0 Hz, 1H, H_B–3), 2.62 (br d, $J = 16.8$ Hz, 1H, H_A–5), 2.51 (s, 3H, 5'–CH_3), 2.43–2.53 (m, 1H, H_A–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8 (C11b), 144.2 (C2'), 139.5 (C5'), 132.0 (C7a), 131.0 (C6), 128.9 (C11a), 127.4 (C9, C10), 127.3 (C8), 124.8 (C4'), 124.0 (C3'), 122.7 (C11), 122.0 (C5a), 119.9 (C7), 75.2 (C4), 70.9 (C2), 42.4 (C3), 34.9 (C5), 15.4 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 385 ($M^{+\bullet}$, ^{79}Br, 8), 355 (3), 342 (6), 257 (4), 231 (3), 220 (100), 193 (3). HR–MS (EI–MS) *m/z* calcd. for $C_{19}H_{16}BrNOS$, 385.0134; found, 385.0136.

(2SR,4SR)–7–Bromo–2–(3–methylthiophen–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (9c)

Reaction time: 34 h. Yield: 44%. Pale yellow solid, mp 145 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1041 (C–O), 988 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (dd, $J = 8.4$, 0.7 Hz, 1H, H–11), 8.18 (dd, $J = 8.3$, 1.0 Hz, 1H, H–8), 7.59 (td, $J = 8.3$, 0.7 Hz, 1H, H–9), 7.55 (s, 1H, H–6), 7.51 (td, $J = 8.4$, 1.0 Hz, 1H, H–10), 7.20 (d, $J = 5.1$ Hz, 1H, H–5'), 6.82 (dd, $J = 5.1$, 0.8 Hz, 1H, H–4'), 5.12 (ddd, $J = 7.5$, 5.5, 2.1 Hz, 1H, H–4), 4.95 (dd, $J = 8.0$, 2.6 Hz, 1H, H–2), 3.56 (dd, $J = 16.9$, 5.5 Hz, 1H, H_B–5), 2.67 (dddd, $J = 12.5$, 7.5, 2.6, 1.2 Hz, 1H, H_B–3), 2.62 (ddd, $J = 12.5$, 8.0, 2.1 Hz, 1H, H_A–3), 2.60 (br d, $J = 16.9$ Hz, 1H, H_A–5), 2.14 (s, 3H, 3'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9 (C11b), 140.7 (C2'), 132.3 (C3'), 131.0 (C6, C7a), 129.8 (C5'), 128.7 (C11a), 127.4 (C8), 127.3 (C10), 127.2 (C9), 122.6 (C4'), 122.0 (C5a), 121.9 (C11), 119.9 (C7), 75.3 (C4), 69.8 (C2), 43.2 (C3), 34.9 (C5), 14.2 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 385 ($M^{+\bullet}$, ^{79}Br, 14), 355 (5), 342 (7), 257 (1), 231 (1), 220 (100), 193 (1). HR–MS (EI–MS) *m/z* calcd. for $C_{19}H_{16}BrNOS$, 385.0137; found, 385.0136.

(2SR,4SR)–2–(Thiophen–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (9d)

Reaction time: 34 h. Yield: 48%. Pale yellow solid, mp 134 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1041 (C–O), 986 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (br d, $J = 8.2$ Hz, 1H, H–11), 7.81 (br d, $J = 8.2$ Hz, 1H, H–8), 7.65 (d, $J = 8.4$ Hz, 1H, H–7), 7.53 (ddd, $J = 8.2$, 6.8, 1.4 Hz, 1H, H–10), 7.49 (ddd, $J = 8.2$, 6.8, 1.4 Hz, 1H, H–9), 7.29 (dd, $J = 4.5$, 1.7 Hz, 1H, H–5'), 7.21 (d, $J = 8.4$ Hz, 1H, H–6), 7.04 (dd, $J = 4.6$, 1.7 Hz, 1H, H–3'), 7.02 (td, $J = 4.6$, 4.5 Hz, 1H, H–4'), 5.12 (ddd, $J = 7.8$, 5.2, 2.0 Hz, 1H, H–4), 4.97 (dd, $J = 8.2$, 1.8 Hz, 1H, H–2), 3.58 (dd, $J = 16.8$, 5.2 Hz, 1H, H_B–5), 2.77–2.83 (m, 1H, H_B–3), 2.62 (br d, $J = 16.8$ Hz, 1H, H_A–5), 2.56–2.61 (m, 1H, H_A–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8 (C2'), 144.7 (C11b), 132.7 (C7a), 127.9 (C8), 127.6 (C11a), 127.3 (C6), 126.8 (C5'), 126.5 (C10), 126.0 (C9), 125.9 (C7), 124.8 (C4'), 124.0 (C3'), 122.2 (C11), 120.9 (C5a), 75.5 (C4), 70.9 (C2), 42.9 (C3), 35.3 (C5). GC–MS (EI, 70 eV): *m/z* (%) 293 ($M^{+\bullet}$, 18), 263 (3), 250 (24), 180 (6), 142 (100), 115 (26). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{15}NOS$, 293.0868; found, 293.0874.

(2SR,4SR)–2–(5–Methylthiophen–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (9e)

Reaction time: 36 h. Yield: 50%. Pale yellow solid, mp 132 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1048 (C–O), 991 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (br d, $J = 8.4$ Hz, 1H, H–11), 7.80 (br d, $J = 8.4$ Hz, 1H, H–8), 7.63 (d, $J = 8.4$ Hz, 1H, H–7), 7.53 (ddd, $J = 8.4$, 6.8, 1.4 Hz, 1H, H–10), 7.47 (ddd, $J = 8.4$, 6.8, 1.4 Hz, 1H, H–9), 7.20 (d, $J = 8.4$ Hz, 1H, H–6), 6.81 (dd, $J = 3.2$, 0.4 Hz, 1H, H–4'), 6.66 (dd, $J = 3.2$, 1.0 Hz, 1H, H–3'), 5.10 (ddd, $J = 7.6$, 5.2, 2.0 Hz, 1H, H–4), 4.89 (br d, $J = 8.4$ Hz, 1H, H–2), 3.57 (dd, $J = 16.8$, 5.2 Hz, 1H, H_B–5), 2.78 (dddd, $J = 12.8$, 7.6, 2.0, 1.2 Hz, 1H, H_B–3), 2.60 (br d, $J = 16.8$ Hz, 1H, H_A–5), 2.54 (ddd, $J = 12.8$, 8.4, 1.6 Hz, 1H, H_A–3), 2.52 (s, 3H, 5'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (C11b), 145.1 (C2'), 139.7 (C5'), 133.0 (C7a), 128.2 (C8), 127.9 (C11a), 127.6 (C6), 126.7 (C9), 126.2 (C10), 126.1 (C7), 125.0 (C4'), 124.1 (C3'), 122.5 (C11), 121.1 (C5a), 75.7 (C4), 71.4 (C2), 42.8 (C3), 35.6 (C5), 15.7 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 307 ($M^{+\bullet}$, 18), 277 (4), 264 (30), 180 (8), 142 (100), 115 (25). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{17}NOS$, 307.1033; found, 307.1031.

(2SR,4SR)–2–(3–Methylthiophen–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (9f)

Reaction time: 28 h. Yield: 50%. Pale yellow solid, mp 149 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1045 (C–O), 986 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26–8.29 (m, 1H, H–11), 7.79–7.81 (m, 1H, H–8), 7.64 (d, $J = 8.4$ Hz, 1H, H–7), 7.44–7.49 (m, 2H, H–9, H–10), 7.21 (d, $J = 8.4$ Hz, 1H, H–6), 7.20 (d, $J = 5.0$ Hz, 1H, H–5'), 6.82 (d, $J = 5.0$ Hz, 1H, H–4'), 5.13 (ddd, $J = 7.2$, 5.2, 2.0 Hz, 1H, H–4), 4.99 (dd, $J = 8.0$, 2.8 Hz, 1H, H–2), 3.59 (dd, $J = 16.8$, 5.2 Hz, 1H, H_B–5), 2.68 (dddd, $J = 12.4$, 7.2, 2.8, 0.8 Hz, 1H, H_B–3), 2.62 (br d, $J = 16.8$ Hz, 1H, H_A–5), 2.59–2.65 (m, 1H, H_A–3), 2.15 (s, 3H, 3'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ

145.3 (C11b), 141.4 (C2'), 132.9 (C7a), 132.4 (C3'), 130.0 (C5'), 128.2 (C8), 127.9 (C11a), 127.6 (C6), 126.7 (C9), 126.3 (C10), 126.1 (C7), 123.5 (C4'), 122.6 (C11), 121.0 (C5a), 75.8 (C4), 70.0 (C2), 43.7 (C3), 35.5 (C5), 14.5 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 307 ($M^{+\bullet}$, 14), 277 (3), 264 (14), 180 (9), 142 (100), 115 (31). HR–MS (EI–MS) *m/z* calcd. for $C_{19}H_{17}NOS$, 307.1019; found, 307.1031.

(2SR,4SR)–2–(5–bromothiophen–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (9g)

Reaction time: 20 h. Yield: 49%. Pale yellow solid, mp 135 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1044 (C–O), 981 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (br d, $J = 8.4$ Hz, 1H, H–11), 7.82 (br d, $J = 8.4$ Hz, 1H, H–8), 7.66 (d, $J = 8.4$ Hz, 1H, H–7), 7.55 (ddd, $J = 8.4$, 7.0, 1.4 Hz, 1H, H–10), 7.50 (ddd, $J = 8.4$, 7.0, 1.4 Hz, 1H, H–9), 7.21 (d, $J = 8.4$ Hz, 1H, H–6), 6.97 (d, $J = 3.8$ Hz, 1H, H–4'), 6.76 (dd, $J = 3.8$, 1.0 Hz, 1H, H–3'), 5.11 (ddd, $J = 7.6$, 5.2, 2.0 Hz, 1H, H–4), 4.88 (dd, $J = 8.4$, 2.0 Hz, 1H, H–2), 3.59 (dd, $J = 16.8$, 5.2 Hz, 1H, H_B–5), 2.75 (dddd, $J = 12.4$, 7.6, 2.0, 0.8 Hz, 1H, H_B–3), 2.63 (br d, $J = 16.8$ Hz, 1H, H_A–5), 2.57 (ddd, $J = 12.4$, 8.4, 2.0 Hz, 1H, H_A–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7 (C2'), 144.5 (C11b), 133.0 (C7a), 129.8 (C4'), 128.3 (C8), 127.8 (C11a), 127.6 (C6), 126.9 (C10), 126.4 (C9), 126.3 (C7), 124.3 (C3'), 122.2 (C11), 121.1 (C5a), 112.0 (C5'), 75.8 (C4), 71.3 (C2), 42.8 (C3), 35.6 (C5). GC–MS (EI, 70 eV): *m/z* (%) 371 ($M^{+\bullet}$, ^{79}Br, 8), 341 (4), 328 (7), 180 (5), 154 (2), 142 (100), 115 (27). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{14}BrNOS$, 370.9980; found, 370.9979.

(2SR,4SR)–7–Bromo–2–(furan–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (10a)

Reaction time: 39 h. Yield: 50%. Pale yellow solid, mp 187 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1049 (C–O), 993 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (dd, $J = 7.6$, 2.0 Hz, 1H, H–11), 8.20 (dd, $J = 7.6$, 2.1 Hz, 1H, H–8), 7.61 (td, $J = 7.6$, 2.1 Hz, 1H, H–10), 7.59 (td, $J = 7.6$, 2.0 Hz, 1H, H–9), 7.53 (s, 1H, H–6), 7.48 (dd, $J = 3.2$, 1.8 Hz, 1H, H–5'), 6.44 (d, $J = 3.2$ Hz, 1H, H–4'), 6.41 (dd, $J = 3.2$, 1.8 Hz, 1H, H–3'), 5.09 (ddd, $J = 7.8$, 5.3, 1.8 Hz, 1H, H–4), 4.73 (dd, $J = 8.6$, 2.5 Hz, 1H, H–2), 3.54 (dd, $J = 16.8$, 5.3 Hz, 1H, H_B–5), 2.85 (dddd, $J = 12.6$, 7.8, 2.5, 1.1 Hz, 1H, H_B–3), 2.60 (br d, $J = 16.8$ Hz, 1H, H_A–5), 2.42 (ddd, $J = 12.6$, 8.6, 1.8 Hz, 1H, H_A–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1 (C2'), 144.9 (C11b), 142.4 (C5'), 131.1 (C7a), 130.9 (C6), 128.7 (C11a), 127.4 (C8, C9), 127.3 (C10), 122.7 (C11), 122.0 (C5a), 119.0 (C7), 110.5 (C3'), 106.8 (C4'), 74.9 (C4), 68.9 (C2), 38.7 (C3), 34.9 (C5). GC–MS (EI, 70 eV): *m/z* (%) 355 ($M^{+\bullet}$, ^{79}Br, 12), 325 (6), 312 (7), 257 (2), 231 (2), 220 (100), 193 (3). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{14}BrNO_2$, 355.0207, found, 355.0208.

(2SR,4SR)–7–Bromo–2–(5–methylfuran–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (10b)

Reaction time: 39 h. Yield: 48%. Pale Yellow solid, mp 123 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1054 (C–O), 989 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (dd, $J = 7.7$, 2.2 Hz, 1H, H–11), 8.18 (dd, $J = 7.7$, 2.2 Hz, 1H, H–8), 7.60 (td, $J = 7.7$, 2.2 Hz, 1H, H–10), 7.59 (td, $J = 7.7$, 2.2 Hz, 1H, H–9), 7.53 (s, 1H, H–6), 6.29 (dd, $J = 3.0$ Hz, 1H, H–3'), 5.98 (dd, $J = 3.0$, 2.8 Hz, 1H, H–4'), 5.08 (ddd, $J = 7.8$, 5.3, 1.6 Hz, 1H, H–4), 4.68 (dd, $J = 8.6$, 2.2 Hz, 1H, H–2), 3.54 (dd, $J = 16.7$, 5.3 Hz, 1H, H_B–5), 2.85 (dddd, $J = 12.6$, 7.8, 2.2, 1.0 Hz, 1H, H_B–3), 2.59 (br d, $J = 16.7$ Hz, 1H, H_A–5), 2.40 (ddd, $J = 12.6$, 8.6, 1.6 Hz, 1H, H_A–3), 2.36 (s, 3H, 5'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (C2'), 152.1 (C5'), 144.9 (C11b), 130.9 (C7a), 130.8 (C6), 127.9 (C11a), 127.2 (C8, C9), 127.1 (C10), 122.6 (C11), 122.0 (C5a), 119.7 (C7), 107.6 (C3'), 106.1 (C4'), 74.7 (C4), 68.6 (C2), 38.3 (C3), 34.5 (C5), 13.7 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 369 ($M^{+\bullet}$, ^{79}Br, 13), 339 (3), 326 (9), 231 (4), 220 (100), 193 (4). HR–MS (EI–MS) *m/z* calcd. for $C_{19}H_{16}BrNO_2$, 369.0363; found, 369.0364.

(2SR,4SR)–2–(Furan–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (10c)

Reaction time: 36 h. Yield: 51%. White solid, mp 96 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 1051 (C–O), 996 (N–O). ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (dd, $J = 8.4$, 0.9 Hz, 1H, H–11), 7.81 (dd, $J = 8.4$, 1.1 Hz, 1H, H–8), 7.64 (d, $J = 8.4$ Hz, 1H, H–7), 7.56 (td, $J = 8.4$, 1.1 Hz, 1H, H–10), 7.50 (td, $J = 8.4$, 0.9 Hz, 1H, H–9), 7.48 (dd, $J = 3.3$, 1.9 Hz, 1H, H–5'), 7.20 (d, $J = 8.4$ Hz, 1H, H–6), 6.45 (dd, $J = 3.1$, 3.3 Hz, 1H, H–4'), 6.42 (dd, $J = 3.1$, 1.9 Hz, 1H, H–3'), 5.10 (ddd, $J = 7.9$, 5.3, 1.7 Hz, 1H, H–4), 4.77 (dd, $J = 8.6$, 2.3 Hz, 1H, H–2), 3.57 (dd, $J = 16.7$, 5.3 Hz, 1H, H_B–5), 2.87 (dddd, $J = 12.7$, 7.9, 2.3, 1.5 Hz, 1H, H_B–3), 2.62 (br d, $J = 16.7$ Hz, 1H, H_A–5), 2.44 (ddd, $J = 12.7$, 8.6, 1.7 Hz, 1H, H_A–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7 (C2'), 144.9 (C11b), 142.6 (C5'), 132.6 (C7a), 127.9 (C8), 127.6 (C11a), 127.3 (C6), 126.5 (C9), 125.9 (C10), 125.8 (C7), 122.9 (C11), 120.9 (C5a), 110.4 (C4'), 106.6 (C3'), 75.5 (C4), 68.7 (C2), 38.8 (C3), 35.1 (C5). GC–MS (EI, 70 eV): *m/z* (%) 277 ($M^{+\bullet}$, 27), 247 (4), 234 (25), 180 (4), 142 (100), 115 (22). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{15}NO_2$, 277.1097; found, 277.1103.

(2SR,4SR)–2–(5–Methylfuran–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (10d)

Reaction time: 31 h. Yield: 50%. White solid, mp 117 °C (heptane). IR (KBr, cm^{-1}): ṽ 1054 (C–O), 991 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (dd, $J = 8.1$, 1.2 Hz, 1H, H–11), 7.80 (dd, $J = 8.1$, 1.2 Hz, 1H, H–8), 7.63 (d, $J = 8.4$ Hz, 1H, H–7), 7.56 (td, $J = 8.1$, 1.2 Hz, 1H, H–10), 7.48 (td, $J = 8.1$, 1.0 Hz, 1H, H–9), 7.19 (d, $J = 8.4$ Hz, 1H, H–6), 6.31 (d, $J = 2.9$ Hz, 1H, H–3'), 5.99 (dd, $J = 2.9$, 0.8 Hz, 1H, H–4'), 5.11 (ddd, $J = 7.8$, 5.3, 1.8 Hz, 1H, H–4), 4.71 (dd, $J = 8.5$, 2.2 Hz, 1H, H–2), 3.57 (dd, $J = 16.7$, 5.3 Hz, 1H, H_B–5), 2.87 (dddd, $J = 12.8$, 7.8, 2.2, 1.1 Hz, 1H, H_B–3), 2.61 (br d, $J = 16.7$ Hz, 1H, H_A–5), 2.41 (ddd, $J = 12.8$, 8.5, 1.8 Hz, 1H, H_A–3), 2.37 (s, 3H, 5'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5 (C2'), 152.2 (C5'), 145.1 (C11b), 132.7 (C7a), 127.9 (C8), 127.6 (C11a), 127.3 (C6), 126.4 (C9), 125.9 (C10), 125.8 (C7), 122.3 (C11), 120.9 (C5a), 107.4 (C3'), 106.4 (C4'), 75.1 (C4), 68.7 (C2), 38.6 (C3), 35.2 (C5), 14.0 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 291 ($M^{+\bullet}$, 20), 261 (3), 248 (22), 180 (7), 142 (100), 115 (26). HR–MS (EI–MS) *m/z* calcd. for $C_{19}H_{17}NO_2$, 291.1261; found, 291.1259.

(2SR,4SR)–2–(5–Nitrofuran–2–yl)–2,3,4,5–tetrahydro–1,4–epoxynaphtho[1,2–b]azepine (10e)

Reaction time: 34 h. Yield: 51%. Pale yellow solid, mp 147 °C (heptane/ethyl acetate 2:1). IR (KBr, cm^{-1}): ṽ 1494 (–NO_2), 1356 (–NO_2), 1048 (C–O), 993 (N–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (dd, $J = 8.2$, 1.0 Hz, 1H, H–11), 7.81 (dd, $J = 8.2$, 1.2 Hz, 1H, H–8), 7.66 (d, $J = 8.4$ Hz, 1H, H–7), 7.54 (td, $J = 8.2$, 1.2 Hz, 1H, H–10), 7.48 (td, $J = 8.2$, 1.0 Hz, 1H, H–9), 7.36 (d, $J = 3.7$ Hz, 1H, H–4'), 7.20 (d, $J = 8.4$ Hz, 1H, H–6), 6.84 (d, $J = 3.7$ Hz, 1H, H–3'), 5.09 (ddd, $J = 7.8$, 5.3, 1.6 Hz, 1H, H–4), 4.77 (dd, $J = 8.4$, 1.3 Hz, 1H, H–2), 3.57 (dd, $J = 16.9$, 5.3 Hz, 1H, H_B–5), 2.87 (dddd, $J = 12.9$, 7.8, 1.3, 1.1 Hz, 1H, H_B–3), 2.64 (br d, $J = 16.9$ Hz, 1H, H_A–5), 2.53 (ddd, $J = 12.9$, 8.4, 1.6 Hz, 1H, H_A–3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2 (C2'), 151.7 (C5'), 143.9 (C11b), 132.7 (C7a), 128.1 (C8), 127.3 (C11a), 127.2 (C6), 126.8 (C9), 126.5 (C10), 126.2 (C7), 121.5 (C11), 120.9 (C5a), 112.9 (C4'), 109.9 (C3'), 75.6 (C4), 68.4 (C2), 39.1 (C3), 34.9 (C5). GC–MS (EI, 70 eV): *m/z* (%) 322 ($M^{+\bullet}$, 10), 292 (2), 279 (4), 180 (10), 142 (100), 115 (38). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{14}N_2O_2$, 322.0958; found, 322.0954.

Physicochemical and spectral data for cis–2–aryl (heteroaryl)–4–hydroxy–2,3,4,5–tetrahydronaphtho [1,2–b]azepines (11a–h), (12a–f), and (13a–d)

7–Bromo–cis–2–phenyl–2,3,4,5–tetrahydro–1H–naphtho [1,2–b]azepin–4–ol (11a)

Reaction time: 12 h. Yield: 70%. White solid, mp 147 °C (heptane). IR (KBr, cm^{-1}): ṽ 3322 (N–H, O–H), 1267 (C–N), 1013 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br d, $J = 8.3$ Hz, 1H, H–11), 7.66 (s, 1H, H–6), 7.61 (br d, $J = 8.3$ Hz, 1H, H–8), 7.53 (td, $J = 8.3$, 1.0 Hz, 1H, H–9), 7.48 (t, $J = 8.3$ Hz, 1H, H–4'), 7.45 (t, $J = 8.3$ Hz, 2H, H–3', H–5'), 7.44 (t, $J = 8.3$ Hz, 1H, H–10), 7.42 (dd, $J = 8.3$, 1.6 Hz, 2H, H–2', H–6'), 4.40 (br s, 1H, NH), 4.01 (dd, $J = 12.0$, 6.3 Hz, 1H, H_{ax}–2), 3.94 (tdd, $J = 9.8$, 3.4, 1.8 Hz, 1H, H_{ax}–4), 3.28 (dd, $J = 16.6$, 9.8 Hz, 1H, H_{ax}–5), 3.12 (dt, $J = 13.6$, 1.8 Hz, 1H, H_{eq}–5), 2.16–2.33 (m, 2H, H_{ax}–3, H_{eq}–3), 2.01 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4 (C11b), 144.1 (C1'), 133.4 (C6), 131.7 (C7a), 128.3 (C4'), 128.1 (C3', C5'), 128.0 (C8), 127.5 (C11a), 126.8 (C10), 126.7 (C2', C6'), 126.5 (C9), 125.3 (C5a), 120.6 (C11), 114.1 (C7), 69.7 (C4), 61.3 (C2), 47.4 (C3), 44.1 (C5). GC–MS (EI, 70 eV): *m/z* (%) 367 ($M^{+\bullet}$, ^{79}Br, 78), 323 (25), 290 (2), 246 (7), 234 (100), 219 (2). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{18}BrNO$, 367.0559; found, 367.0572.

7–Bromo–cis–2–(o–tolyl)–2,3,4,5–tetrahydro–1H–naphtho [1,2–b]azepin–4–ol (11b)

Reaction time: 12 h. Yield: 79%. White solid, mp 147 °C (heptane). IR (KBr, cm^{-1}): ṽ 3377 (N–H, O–H), 1267 (C–N), 1027 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (br d, $J = 8.3$ Hz, 1H, H–11), 7.70 (br d, $J = 7.5$ Hz, 2H, H–6'), 7.66 (s, 1H, H–6), 7.61 (br d, $J = 8.3$ Hz, 1H, H–8), 7.53 (t, $J = 8.3$ Hz, 1H, H–9), 7.43 (td, $J = 8.3$, 1.0 Hz, 1H, H–10), 7.24 (dd, $J = 7.5$, 0.9 Hz, 1H, H–3'), 7.33 (td, $J = 7.5$, 1.5 Hz, 1H, H–5'), 7.28 (td, $J = 7.5$, 1.5 Hz, 1H, H–4'), 4.64 (br s, 1H, NH), 4.25 (dd, $J = 11.3$, 1.7 Hz, 1H, H_{ax}–2), 3.95 (tdd, $J = 10.1$, 4.1, 1.7 Hz, 1H, H_{ax}–4), 3.36 (dd, $J = 13.5$, 10.1 Hz, 1H, H_{ax}–5), 3.14 (br d, $J = 13.5$ Hz, 1H, H_{eq}–5), 2.28 (ddd, $J = 13.0$, 11.3, 10.1 Hz, 1H, H_{ax}–3), 2.22 (ddt, $J = 13.0$, 4.1, 1.7 Hz, 1H, H_{eq}–3), 2.28 (s, 3H, 2'–CH_3), 2.00 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (C11b), 142.0 (C1'), 134.8 (C2'), 133.6 (C6), 131.6 (C7a), 131.0 (C4'), 128.0 (C8, C3',C5'), 127.5 (C11a), 126.8 (C10), 126.7 (C9), 125.8 (C6'), 125.6 (C5a), 120.4 (C11), 115.3 (C7), 69.9 (C4), 57.2 (C2), 46.2 (C3), 44.1 (C5), 19.8 (2'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 381 ($M^{+\bullet}$, ^{79}Br, 26), 337 (8), 290 (1), 246 (6), 234 (100), 219 (1). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{18}BrNO$, 381.0732; found, 381.0728.

7–Bromo–cis–2–(m–tolyl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (11c)

Reaction time: 10 h. Yield: 82%. Yellow solid, mp 80 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3306 (N–H, O–H), 1242 (C–N), 1015 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 8.3, 1.2 Hz, 1H, H–11), 7.65 (s, 1H, H–6), 7.63 (dd, J = 8.3, 1.0 Hz, 1H, H–8), 7.53 (td, J = 8.3, 1.0 Hz, 1H, H–9), 7.44 (td, J = 8.3, 1.2 Hz, 1H, H–10), 7.33 (t, J = 7.6 Hz, 1H, H–5'), 7.31 (s, 1H, H–2'), 7.28 (d, J = 7.6 Hz, 1H, H–6'), 7.21 (d, J = 7.6 Hz, 1H, H–4'), 4.50 (br s, 1H, NH), 3.97 (dd, J = 10.2, 3.8 Hz, 1H, H_{ax}–2), 3.91 (tdd, J = 9.9, 3.5, 2.2 Hz, 1H, H_{ax}–4), 3.30 (dd, J = 13.5, 9.9 Hz, 1H, H_{ax}–5), 3.11 (dd, J = 13.5, 2.2 Hz, 1H, H_{eq}–5), 2.20–2.31 (m, 2H, H_{ax}–3, H_{eq}–3), 2.42 (s, 3H, 3'–CH_3), 2.11 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1 (C11b), 143.8 (C1'), 139.0 (C3'), 133.5 (C6), 131.6 (C7a), 129.2 (C6'), 129.0 (C4'), 128.1 (C8, C5'), 127.7 (C11a), 127.3 (C2'), 126.7 (C10), 126.5 (C9), 125.5 (C5a), 120.5 (C11), 114.9 (C7), 69.6 (C4), 61.7 (C2), 47.1 (C3), 44.3 (C5), 21.6 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 381 ($M^{+\bullet}$, ^{79}Br, 50), 337 (18), 290 (1), 246 (10), 234 (100), 219 (1). HR–MS (EI–MS) *m/z* calcd. for $C_{21}H_{20}BrNO$, 381.0735; found, 381.0733.

7–Bromo–cis–2–(3–methoxyphenyl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (11d)

Reaction time: 12 h. Yield: 77%. Viscous yellow oil. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3382 (N–H, O–H), 1265 (C–N), 1038 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, J = 8.2, 1.1 Hz, 1H, H–11), 7.65 (s, 1H, H–6), 7.64 (dd, J = 8.2, 0.7 Hz, 1H, H–8), 7.53 (td, J = 8.2, 0.7 Hz, 1H, H–9), 7.45 (td, J = 8.2, 1.1 Hz, 1H, H–10), 7.35 (t, J = 8.1 Hz, 1H, H–5'), 7.06 (d, J = 2.4 Hz, 1H, H–2'), 7.05 (dd, J = 8.1, 0.7 Hz, 1H, H–6'), 6.92 (ddd, J = 8.1, 2.4, 0.7 Hz, 1H, H–4'), 4.67 (br s, 1H, NH), 4.01 (dd, J = 10.0, 4.3 Hz, 1H, H_{ax}–2), 3.93 (tdd, J = 9.9, 3.6, 2.3 Hz, 1H, H_{ax}–4), 3.84 (s, 3H, 3'–OCH_3), 3.33 (dd, J = 13.5, 9.9 Hz, 1H, H_{ax}–5), 3.12 (dt, J = 13.5, 2.3 Hz, 1H, H_{eq}–5), 2.29–2.33 (m, 2H, H_{ax}–3, H_{eq}–3), 2.10 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3 (C3'), 145.4 (C1'), 143.2 (C11b), 133.4 (C6), 131.6 (C7a), 130.4 (C5'), 128.2 (C8), 127.7 (C11a), 126.8 (C10), 126.7 (C9), 125.7 (C5a), 120.6 (C11), 119.1 (C2'), 115.3 (C7), 113.8 (C4'), 112.3 (C6'), 69.6 (C4), 61.6 (C2), 55.6 (3'–OCH_3), 46.9 (C3), 44.0 (C5). GC–MS (EI, 70 eV): *m/z* (%) 397 ($M^{+\bullet}$, ^{79}Br, 28), 353 (8), 290 (1), 246 (9), 234 (100), 219 (1).

7–Bromo–cis–2–(2–chlorophenyl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (11e)

Reaction time: 8 h. Yield: 80%. Pale Yellow solid, mp 84 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3376 (N–H, O–H), 1268 (C–N), 1038 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br d, J = 8.4 Hz, 1H, H–11), 7.75 (dd, J = 7.7, 1.2 Hz, 1H, H–6'), 7.66 (br d, J = 8.4 Hz, 1H, H–8), 7.66 (s, 1H, H–6), 7.53 (t, J = 8.4 Hz, 1H, H–9), 7.43 (t, J = 8.4 Hz, 1H, H–10), 7.41 (br d, J = 7.7 Hz, 1H, H–3'), 7.40 (t, J = 7.7 Hz, 1H, H–5'), 7.31 (td, J = 7.7, 1.2 Hz, 1H, H–4'), 4.55 (dd, J = 11.3, 1.6 Hz, 1H, H_{ax}–2), 4.23 (br s, 1H, NH), 3.99 (tdd, J = 9.8, 3.5, 1.8 Hz, 1H, H_{ax}–4), 3.27 (dd, J = 13.6, 9.8 Hz, 1H, H_{ax}–5), 3.14 (br d, J = 13.6 Hz, 1H, H_{eq}–5), 2.27 (ddt, J = 12.7, 3.5, 1.6 Hz, 1H, H_{eq}–3), 2.18 (ddd, J = 12.7, 11.3, 9.8 Hz, 1H, H_{ax}–3), 2.04 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0 (C11b), 141.6 (C1'), 133.5 (C6), 132.8 (C2'), 131.6 (C7a), 129.2 (C4'), 128.0 (C3', C5'), 127.9 (C8), 127.8 (C11a), 127.2 (C10), 126.8 (C6'), 126.5 (C9), 125.4 (C5a), 120.7 (C11), 114.9 (C7), 69.6 (C4), 56.5 (C2), 46.0 (C3), 44.3 (C5). GC–MS (EI, 70 eV): *m/z* (%) 401 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 98), 357 (30), 290 (3), 246 (11), 234 (100), 219 (2). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{17}BrClNO$, 401.0180; found, 401.0182.

7–Bromo–cis–2–(4–chlorophenyl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (11f)

Reaction time: 12 h. Yield: 75%. Yellow solid, mp 109 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3354 (N–H, O–H), 1267 (C–N), 1013 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (br d, J = 8.3 Hz, 1H, H–11), 7.64 (s, 1H, H–6), 7.58 (br d, J = 8.3 Hz, 1H, H–8), 7.53 (t, J = 8.3 Hz, 1H, H–9), 7.45 (t, J = 8.3 Hz, 1H, H–10), 7.40–7.42 (m, 4H, H–2', H–3', H–5', H–6'), 4.31 (br s, 1H, NH), 3.95–3.99 (m, 1H, H_{ax}–2), 3.87–3.94 (m, 1H, H_{ax}–4), 3.25 (dd, J = 13.5, 9.9 Hz, 1H, H_{ax}–5), 2.61 (br d, J = 13.5 Hz, 1H, H_{eq}–5), 2.17–2.22 (m, 2H, H_{ax}–3, H_{eq}–3), 2.05 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8 (C11b), 142.7 (C1'), 134.0 (C4'), 133.5 (C6), 131.6 (C7a), 129.5 (C3', C5'), 128.2 (C2', C6'), 128.1 (C8), 127.7 (C11a), 126.7 (C10), 126.6 (C9), 125.5 (C5a), 120.3 (C11), 115.1 (C7), 69.7 (C4), 60.6 (C2), 47.3 (C3), 44.1 (C5). GC–MS (EI, 70 eV): *m/z* (%) 401 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 20), 357 (9), 290 (1), 246 (6), 234 (100), 219 (1).

7–Bromo–cis–2–(2,4–dichlorophenyl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (11g)

Reaction time: 12 h. Yield: 72%. Pale yellow solid, mp 80 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3354 (N–H, O–H), 1267 (C–N), 1040 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, J = 8.4, 1.2 Hz, 1H, H–11), 7.72 (d, J = 8.4 Hz, 1H,

H–6'), 7.68 (br d, $J = 8.4$ Hz, 1H, H–8), 7.65 (s, 1H, H–6), 7.55 (td, $J = 8.4$, 1.2 Hz, 1H, H–9), 7.47 (td, $J = 8.4$, 1.2 Hz, 1H, H–10), 7.47 (d, $J = 2.1$ Hz, 1H, H–3'), 7.36 (dd, $J = 8.4$, 2.1 Hz, 1H, H–5'), 4.51 (dd, $J = 10.2$, 3.3 Hz, 1H, H_{ax}–2), 4.45 (br s, 1H, NH), 3.96 (tdd, $J = 10.1$, 4.6, 2.3 Hz, 1H, H_{ax}–4), 3.34 (dd, $J = 13.5$, 10.1 Hz, 1H, H_{ax}–5), 3.11 (br d, $J = 13.5$ Hz, 1H, H_{eq}–5), 2.09–2.30 (m, 2H, H_{eq}–3, H_{ax}–3), 2.07 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1 (C11b), 139.2 (C1'), 133.8 (C4'), 133.5 (C6), 133.0 (C2'), 131.6 (C7a), 129.9 (C3'), 128.8 (C6'), 128.3 (C5'), 128.1 (C8), 127.6 (C11a), 127.0 (C10), 126.9 (C9), 125.7 (C5a), 120.7 (C7, C11), 69.1 (C4), 56.8 (C2), 45.6 (C3), 44.0 (C5). GC–MS (EI, 70 eV): *m/z* (%) 437 ($M^{+\bullet}$, ^{79}Br, ^{35}Cl, 14), 393 (10), 290 (1), 246 (8), 234 (100), 219 (1). HR–MS (EI–MS) *m/z* calcd. for $C_{20}H_{16}BrCl_2NO$, 434.9795; found, 434.9792.

cis–2–(o–Tolyl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (11h)

Reaction time: 12 h. Yield: 65%. Pale yellow solid, mp 116 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3322 (N–H, O–H), 1278 (C–N), 1025 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, $J = 7.6$, 1.1 Hz, 1H, H–11), 7.73 (d, $J = 8.0$ Hz, 1H, H–6'), 7.62 (dd, $J = 8.0$, 1.0 Hz, 1H, H–8), 7.48 (d, $J = 8.4$ Hz, 1H, H–7), 7.40–7.42 (m, 2H, H–9, H–10), 7.35 (d, $J = 8.4$ Hz, 1H, H–6), 7.28–7.36 (m, 1H, H–5'), 7.25–7.28 (m, 2H, H–3', H–4'), 4.37 (br s, 1H, NH), 4.27 (dd, $J = 11.2$, 2.0 Hz, 1H, H_{ax}–2), 3.96 (tdd, $J = 10.0$, 4.4, 2.6 Hz, 1H, H_{ax}–4), 3.39 (dd, $J = 13.2$, 10.0 Hz, 1H, H_{ax}–5), 3.20 (dt, $J = 13.2$, 1.6 Hz, 1H, H_{eq}–5), 2.19–2.32 (m, 2H, H_{ax}–3, H_{eq}–3), 2.29 (s, 3H, 2'–CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9 (C11b), 142.5 (C1'), 134.8 (C2'), 133.6 (C7a), 131.0 (C3'), 130.1 (C6), 128.9 (C8), 127.8 (C4'), 127.1 (C11a), 126.3 (C6'), 125.9 (C5'), 125.8 (C10), 125.4 (C9), 124.5 (C5a), 122.0 (C7), 119.9 (C11), 70.1 (C4), 57.0 (C2), 46.7 (C3), 44.8 (C5), 19.6 (2'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 303 ($M^{+\bullet}$, 60), 259 (22), 168 (29), 156 (100), 141 (8). HR–MS (EI–MS) *m/z* calcd. for $C_{21}H_{21}NO$, 303.1622; found, 303.1623.

7–Bromo–cis–2–(thiophen–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (12a)

Reaction time: 3 h. Yield: 82%. Pale yellow solid, mp 66 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3349 (N–H, O–H), 1268 (C–N), 1023 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (dd, $J = 8.4$, 1.5 Hz, 1H, H–11), 7.75 (br d, $J = 8.4$ Hz, 1H, H–8), 7.66 (s, 1H, H–6), 7.56 (td, $J = 8.4$, 1.2 Hz, 1H, H–9), 7.51 (td, $J = 8.4$, 1.5 Hz, 1H, H–10), 7.34 (dd, $J = 5.1$, 1.1 Hz, 1H, H–5'), 7.14 (dd, $J = 3.5$, 1.1 Hz, 1H, H–3'), 7.07 (dd, $J = 5.1$, 3.5 Hz, 1H, H–4'), 4.43 (br s, 1H, NH), 4.34 (dd, $J = 11.7$, 1.9 Hz, 1H, H_{ax}–2), 3.95 (tdd, $J = 10.0$, 4.1, 2.0 Hz, 1H, H_{ax}–4), 3.29 (dd, $J = 13.6$, 10.0 Hz, 1H, H_{ax}–5), 3.11 (dt, $J = 13.6$, 2.0 Hz, 1H, H_{eq}–5), 2.46 (ddt, $J = 12.2$, 4.1, 1.9 Hz, 1H, H_{eq}–3), 2.30 (ddd, $J = 12.2$, 11.7, 10.0 Hz, 1H, H_{ax}–3), 1.96 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2 (C2'), 143.5 (C11b), 133.4 (C6), 131.5 (C7a), 128.0 (C8), 127.9 (C11a), 127.1 (C5'), 126.8 (C10), 126.7 (C9), 125.7 (C5a), 124.8 (C4'), 124.3 (C3'), 120.7 (C11), 115.2 (C7), 69.5 (C4), 55.7 (C2), 47.8 (C3), 43.9 (C5). GC–MS (EI, 70 eV): *m/z* (%) 373 ($M^{+\bullet}$, ^{79}Br, 11), 329 (2), 290 (1), 246 (4), 234 (100), 219 (5). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{14}BrNOS$, 370.9976; found, 370.9979.

7–Bromo–cis–2–(5–methylthiophen–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (12b)

Reaction time: 2 h. Yield: 70%. Pale yellow solid, mp 53 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3364 (N–H, O–H), 1268 (C–N), 1022 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, $J = 8.0$, 1.3 Hz, 1H, H–11), 7.76 (dd, $J = 8.0$, 1.1 Hz, 1H, H–8), 7.63 (s, 1H, H–6), 7.54 (td, $J = 8.0$, 1.1 Hz, 1H, H–9), 7.51 (td, $J = 8.0$, 1.1 Hz, 1H, H–10), 6.89 (d, $J = 3.4$ Hz, 1H, H–3'), 6.68 (dd, $J = 3.4$, 1.0 Hz, 1H, H–4'), 4.41 (br s, 1H, NH), 4.22 (dd, $J = 11.6$, 2.0 Hz, 1H, H_{ax}–2), 3.91 (tdd, $J = 9.9$, 4.0, 2.0 Hz, 1H, H_{ax}–4), 3.26 (dd, $J = 13.6$, 9.9 Hz, 1H, H_{ax}–5), 3.08 (dt, $J = 13.6$, 2.0 Hz, 1H, H_{eq}–5), 2.42 (ddt, $J = 12.6$, 4.0, 2.0 Hz, 1H, H_{eq}–3), 2.25 (ddd, $J = 12.6$, 11.6, 9.9 Hz, 1H, H_{ax}–3), 2.53 (s, 3H, 5'–CH_3), 2.03 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.8 (C2'), 143.6 (C11b), 139.4 (C5'), 133.5 (C6), 131.6 (C7a), 128.1 (C8), 127.8 (C11a), 126.8 (C10), 126.7 (C9), 125.6 (C5a), 125.0 (C4'), 124.3 (C3'), 120.7 (C11), 115.0 (C7), 69.7 (C4), 56.1 (C2), 47.7 (C3), 43.9 (C5), 15.6 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 387 ($M^{+\bullet}$, ^{79}Br, 10), 343 (4), 290 (2), 246 (3), 234 (100), 219 (2). HR–MS (EI–MS) *m/z* calcd. for $C_{19}H_{18}BrNOS$, 387.0305; found, 387.0292.

7–Bromo–cis–2–(3–methylthiophen–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (12c)

Reaction time: 2 h. Yield: 85%. Yellow solid, mp 65 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3352 (N–H, O–H), 1269 (C–N), 1039 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (dd, $J = 8.4$, 1.4 Hz, 1H, H–11), 7.66 (s, 1H, H–6), 7.65 (br d, $J = 8.4$ Hz, 1H, H–8), 7.54 (td, $J = 8.4$, 1.1 Hz, 1H, H–9), 7.48 (td, $J = 8.4$, 1.4 Hz, 1H, H–10), 7.24 (d, $J = 5.1$ Hz, 1H, H–5'), 6.89 (d, $J = 5.1$ Hz, 1H, H–4'), 4.36 (br s, 1H, NH), 4.34 (dd, $J = 11.1$, 2.5 Hz, 1H, H_{ax}–2), 3.90–3.99 (m, 1H, H_{ax}–4), 3.29 (dd, $J = 13.5$, 10.0 Hz, 1H, H_{ax}–5), 3.12 (dt, $J = 13.5$, 2.0 Hz, 1H, H_{eq}–5), 2.36 (ddt, $J = 12.1$, 3.5, 2.5 Hz, 1H, H_{eq}–3), 2.29 (ddd, $J = 12.1$, 11.1, 10.0 Hz, 1H, H_{ax}–3), 2.20 (s, 3H, 3'–CH_3), 1.93 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7 (C11b), 140.5 (C2'), 133.6 (C7a, C3'), 133.5 (C6), 130.3 (C5'), 128.3 (C8),

127.6 (C11a), 126.8 (C10), 126.6 (C9), 125.4 (C5a), 123.4 (C4'), 120.4 (C11), 115.0 (C7), 69.8 (C4), 54.3 (C2), 47.9 (C3), 44.1 (C5), 13.9 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 387 ($M^{+\bullet}$, ^{79}Br, 8), 343 (1), 290 (1), 246 (4), 234 (100), 219 (1).

cis–2–(Thiophen–2–yl)–2,3,4,5–tetrahydro–1H–naphtho [1,2–b]azepin–4–ol (12d)

Reaction time: 2 h. Yield: 77%. Pale brown oil. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3357 (N–H, O–H), 1273 (C–N), 1025 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, $J = 7.4$, 2.0 Hz, 1H, H–11), 7.75–7.77 (m, 1H, H–8), 7.44–7.50 (m, 2H, H–9, H–10), 7.49 (br d, $J = 8.0$ Hz, 1H, H–7), 7.35 (br d, $J = 8.0$ Hz, 1H, H–6), 7.32 (dd, $J = 5.1$, 1.4 Hz, 1H, H–5'), 7.14 (dd, $J = 3.5$, 1.4 Hz, 1H, H–3'), 7.06 (dd, $J = 5.1$, 3.5 Hz, 1H, H–4'), 4.44 (br s, 1H, NH), 4.36 (dd, $J = 11.6$, 2.0 Hz, 1H, H_{ax}–2), 3.96 (tdd, $J = 10.0$, 3.5, 1.8 Hz, 1H, H_{ax}–4), 3.27 (dd, $J = 13.6$, 10.0 Hz, 1H, H_{ax}–5), 3.17 (dt, $J = 13.6$, 1.8 Hz, 1H, H_{eq}–5), 2.48 (ddt, $J = 12.4$, 4.0, 2.0 Hz, 1H, H_{eq}–3), 2.34 (ddd, $J = 12.4$, 11.6, 10.0 Hz, 1H, H_{ax}–3), 2.16 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9 (C2'), 143.9 (C11b), 133.9 (C7a), 130.0 (C6), 129.1 (C8), 127.3 (C5'), 127.0 (C11a, C4'), 126.3 (C10), 125.7 (C9), 125.1 (C5a), 124.3 (C3'), 122.5 (C7), 120.6 (C11), 70.0 (C4), 56.3 (C2), 48.5 (C3), 44.7 (C5). GC–MS (EI, 70 eV): *m/z* (%) 295 ($M^{+\bullet}$, 22), 251 (4), 212 (1), 168 (6), 156 (100), 141 (5).

cis–2–(5–Methylthiophen–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (12e)

Reaction time: 2 h. Yield: 79%. Viscous brown oil. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3359 (N–H, O–H), 1276 (C–N), 1022 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, $J = 7.0$, 2.6 Hz, 1H, H–11), 7.78 (dd, $J = 7.2$, 2.0 Hz, 1H, H–8), 7.42–7.48 (m, 2H, H–9, H–10), 7.46 (br d, $J = 8.4$ Hz, 1H, H–7), 7.32 (br d, $J = 8.4$ Hz, 1H, H–6), 7.26 (d, $J = 5.2$ Hz, 1H, H–3'), 6.92 (d, $J = 5.2$ Hz, 1H, H–4'), 4.44 (br s, 1H, NH), 4.23 (dd, $J = 11.6$, 2.0 Hz, 1H, H_{ax}–2), 3.93 (tdd, $J = 10.0$, 4.0, 2.0 Hz, 1H, H_{ax}–4), 3.31 (dd, $J = 13.2$, 10.0 Hz, 1H, H_{ax}–5), 3.14 (dt, $J = 13.2$, 2.0 Hz, 1H, H_{eq}–5), 2.54 (s, 3H, 5'–CH_3), 2.42 (ddt, $J = 12.4$, 4.0, 2.0 Hz, 1H, H_{eq}–3), 2.27 (ddd, $J = 12.4$, 11.6, 10.0 Hz, 1H, H_{ax}–3), 2.08 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5 (C2'), 144.0 (C11b), 139.5 (C5'), 133.9 (C7a), 130.2 (C6), 129.1 (C8), 126.9 (C11a), 126.2 (C10), 125.7 (C9), 125.3 (C4'), 124.9 (C5a), 124.4 (C3'), 122.3 (C7), 120.5 (C11), 70.1 (C4), 56.5 (C2), 48.2 (C3), 44.7 (C5), 15.8 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 309 ($M^{+\bullet}$, 26), 265 (5), 212 (1), 168 (7), 156 (100), 141 (4).

cis–2–(3–Methylthiophen–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (12f)

Reaction time: 2 h. Yield: 80%. Yellow solid, mp 160 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3300 (N–H, O–H), 1273 (C–N), 1032 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (dd, $J = 7.0$, 2.8 Hz, 1H, H–11), 7.70 (dd, $J = 7.0$, 2.4 Hz, 1H, H–8), 7.49 (br d, $J = 8.4$, 1H, H–7), 7.43–7.47 (m, 2H, H–9, H–10), 7.36 (br d, $J = 8.4$, 1H, H–6), 6.90 (d, $J = 3.2$ Hz, 1H, H–5'), 6.69 (dd, $J = 3.2$, 0,8 Hz, 1H, H–4'), 4.40 (br s, 1H, NH), 4.38 (dd, $J = 11.2$, 2.4 Hz, 1H, H_{ax}–2), 3.96–4.00 (m, 1H, H_{ax}–4), 3.36 (dd, $J = 13.6$, 10.0 Hz, 1H, H_{ax}–5), 3.19 (dt, $J = 13.6$, 2.4 Hz, 1H, H_{eq}–5), 2.29–2.41 (m, 2H, H_{ax}–3, H_{eq}–3), 2.23 (s, 3H, 3'–CH_3), 2.24 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0 (C11b), 141.1 (C2'), 133.8 (C7a), 133.7 (C3'), 130.4 (C5'), 130.3 (C6), 129.1 (C8), 126.6 (C11a), 126.2 (C10), 125.6 (C9), 124.7 (C5a), 123.5 (C4'), 122.2 (C7), 120.2 (C11), 70.1 (C4), 54.6 (C2), 48.4 (C3), 44.8 (C5), 14.4 (3'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 309 ($M^{+\bullet}$, 14), 265 (1), 212 (1), 168 (6), 156 (100), 141 (7). HR–MS (EI–MS) *m/z* calcd. for $C_{19}H_{19}NOS$, 309.1194; found, 309.1187.

7–Bromo–cis–2–(furan–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (13a)

Reaction time: 0.7 h. Yield: 72%. Yellow solid, mp 58 °C (heptane). IR (KBr, cm^{-1}): $\tilde{\nu}$ 3344 (N–H, O–H), 1271 (C–N), 1015 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, $J = 7.0$, 2.8 Hz, 1H, H–11), 7.93 (dd, $J = 7.5$, 1.9 Hz, 1H, H–8), 7.64 (s, 1H, H–6), 7.52–7.60 (m, 2H, H–9, H–10), 7.51 (dd, $J = 1.9$, 0.7 Hz, 1H, H–5'), 6.42 (dd, $J = 3.2$, 1.9 Hz, 1H, H–4'), 6.34 (dd, $J = 3.2$, 0.8 Hz, 1H, H–3'), 4.73 (br s, 1H, NH), 4.13 (dd, $J = 11.8$, 2.0 Hz, 1H, H_{ax}–2), 3.94 (tdd, $J = 9.8$, 4.1, 2.0 Hz, 1H, H_{ax}–4), 3.26 (dd, $J = 13.5$, 9.8 Hz, 1H, H_{ax}–5), 3.08 (dt, $J = 13.5$, 2.0 Hz, 1H, H_{eq}–5), 2.46 (ddt, $J = 12.7$, 4.1, 2.0 Hz, 1H, H_{eq}–3), 2.22 (ddd, $J = 12.7$, 11.8, 9.8 Hz, 1H, H_{ax}–3), 2.01 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9 (C2'), 143.4 (C11b), 142.4 (C5'), 133.5 (C6), 131.7 (C7a), 128.1 (C11a), 128.0 (C8), 126.8 (C10), 126.7 (C9), 126.0 (C5a), 120.7 (C11), 115.3 (C7), 110.8 (C4'), 106.0 (C3'), 69.3 (C4), 53.7 (C2), 44.0 (C3), 43.4 (C5). GC–MS (EI, 70 eV): *m/z* (%) 357 ($M^{+\bullet}$, ^{79}Br, 20), 313 (5), 290 (1), 246 (4), 234 (100), 219 (3).

7–Bromo–cis–2–(5–methylfuran–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (13b)

Reaction time: 1.5 h. Yield: 82%. Viscous yellow oil. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3351 (N–H, O–H), 1271 (C–N), 1023 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (dd, $J = 7.2$, 2.0 Hz, 1H, H–11), 7.90 (dd, $J = 8.0$, 2.2 Hz, 1H, H–8), 7.64 (s, 1H, H–6), 7.51–7.60 (m, 2H, H–9, H–10), 6.20 (d,

$J = 3.0$ Hz, 1H, H–3'), 5.99 (dd, $J = 3.0$, 0.9 Hz, 1H, H–4'), 4.70 (br s, 1H, NH), 4.07 (dd, $J = 11.5$, 2.0 Hz, 1H, H_{ax}–2), 3.93 (tdd, $J = 9.8$, 4.0, 2.0 Hz, 1H, H_{ax}–4), 3.25 (dd, $J =$ 13.6, 9.8 Hz, 1H, H_{ax}–5), 3.08 (dt, $J = 13.6$, 2.0 Hz, 1H, H_{eq}–5), 2.42 (ddt, $J = 12.4$, 4.0, 2.0 Hz, 1H, H_{eq}–3), 2.37 (s, 3H, 5'–CH_3), 2.21 (ddd, $J = 12.4$, 11.5, 9.8 Hz, 1H, H_{ax}–3), 2.02 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0 (C2'), 152.0 (C5'), 143.7 (C11b), 133.4 (C6), 131.6 (C7a), 128.0 (C8, C11a), 126.7 (C10), 126.6 (C9), 125.8 (C5a), 120.6 (C11), 115.0 (C7), 106.7 (C4'), 106.4 (C3'), 69.3 (C4), 53.9 (C2), 44.0 (C3), 43.4 (C5), 13.8 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 371 ($M^{+\bullet}$, ^{79}Br, 6), 327 (1), 290 (1), 246 (20), 234 (100), 219 (2).

cis–2–(Furan–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (13c)

Reaction time: 0.5 h. Yield: 77%. Viscous yellow oil. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3359 (N–H, O–H), 1285 (C–N), 1031 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (br d, $J = 8.2$ Hz, 1H, H–11), 7.84 (br d, $J = 8.2$ Hz, 1H, H–8), 7.53 (td, $J = 8.2$, 1.2 Hz, 1H, H–9), 7.51 (dd, $J = 1.9$, 0.8 Hz, 1H, H–5'), 7.47 (d, $J = 8.3$ Hz, 1H, H–7), 7.46 (td, $J = 8.2$, 1.3 Hz, 1H, H–10), 7.32 (d, $J = 8.3$ Hz, 1H, H–6), 6.43 (dd, $J = 3.1$, 1.9 Hz, 1H, H–4'), 6.35 (dd, $J = 3.1$, 0.8 Hz, 1H, H–3'), 4.75 (br s, 1H, NH), 4.15 (dd, $J = 11.6$, 2.0 Hz, 1H, H_{ax}–2), 3.95 (tdd, $J = 10.0$, 4.0, 2.0 Hz, 1H, H_{ax}–4), 3.31 (dd, $J =$ 13.5, 10.0 Hz, 1H, H_{ax}–5), 3.14 (dt, $J = 13.5$, 2.0 Hz, 1H, H_{eq}–5), 2.47 (ddt, $J = 12.5$, 4.0, 2.0 Hz, 1H, H_{eq}–3), 2.25 (ddd, $J = 12.5$, 11.6, 10.0 Hz, 1H, H_{ax}–3), 1.83 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4 (C2'), 143.7 (C11b), 142.1 (C5'), 133.7 (C7a), 129.8 (C6), 128.9 (C8), 126.9 (C11a), 126.2 (C10), 125.5 (C9), 125.0 (C5a), 122.2 (C7), 120.2 (C11), 110.7 (C4'), 105.8 (C3'), 69.5 (C4), 54.0 (C2), 44.6 (C3), 43.8 (C5). GC–MS (EI, 70 eV): *m/z* (%) 279 ($M^{+\bullet}$, 28), 235 (4), 212 (1), 168 (7), 156 (100), 141 (4). HR–MS (EI–MS) *m/z* calcd. for $C_{18}H_{17}NO_2$, 279.1246; found, 279.1259.

cis–2–(5–Methylfuran–2–yl)–2,3,4,5–tetrahydro–1H–naphtho[1,2–b]azepin–4–ol (13d)

Reaction time: 1.5 h. Yield: 78%. Viscous yellow oil. IR (liquid film, cm^{-1}): $\tilde{\nu}$ 3395 (N–H, O–H), 1276 (C–N), 1022 (C–O). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (br d, $J = 8.2$ Hz, 1H, H–11), 7.84 (br d, $J = 8.2$ Hz, 1H, H–8), 7.50 (td, $J = 8.2$, 1.0 Hz, 1H, H–9), 7.46 (d, $J = 8.3$ Hz, 1H, H–7), 7.45 (td, $J = 8.2$, 1.3 Hz, 1H, H–10), 7.31 (d, $J = 8.3$ Hz, 1H, H–6), 6.20 (d, $J = 3.0$ Hz, 1H, H–3'), 5.99 (dd, $J = 3.0$, 1.0 Hz, 1H, H–4'), 4.74 (br s, 1H, NH), 4.09 (dd, $J = 11.6$, 2.0 Hz, 1H, H_{ax}–2), 3.94 (tdd, $J = 9.9$, 4.1, 2.2 Hz, 1H, H_{ax}–4), 3.30 (dd, $J = 13.7$, 9.9 Hz, 1H, H_{ax}–5), 3.13 (dt, $J =$ 13.7, 2.2 Hz, 1H, H_{eq}–5), 2.43 (ddt, $J = 12.1$, 4.1, 2.2 Hz, 1H, H_{eq}–3), 2.24 (ddd, $J = 12.1$, 11.6, 9.9 Hz, 1H, H_{ax}–3), 2.38 (s, 3H, 5'–CH_3), 1.72 (br s, 1H, 4–OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9 (C5'), 154.4 (C2'), 143.7 (C11b), 133.5 (C7a), 129.9 (C6), 128.8 (C8), 126.7 (C11a), 125.8 (C10), 125.4 (C9), 124.9 (C5a), 122.0 (C7), 120.1 (C11), 106.4 (C3'), 105.5 (C4'), 69.7 (C4), 54.2 (C2), 44.4 (C3), 43.8 (C5), 14.1 (5'–CH_3). GC–MS (EI, 70 eV): *m/z* (%) 293 ($M^{+\bullet}$, 14), 249 (1), 212 (1), 168 (17), 156 (100), 141 (6).

QSAR analysis

Dataset and biological activity

A total of 94 compounds, synthetized in our laboratory and previously published (Palma et al. 2009a, 2009b; Gómez-Ayala et al. 2010; Blanco et al. 2014), were included in the dataset. Their anti-parasitic activity (IC_{50}) evaluated against the extracellular form of *Trypanosoma cruzi* and *Leishmania infantum* parasites were converted to $-\log(IC_{50})$ and used as depended variable in two different QSAR models. The biological activity was evaluated by a single protocol at the same laboratory in identical experimental conditions (Gómez-Ayala et al. 2010; Blanco et al. 2014). The compounds with IC_{50} identified in the Tables as >100 were consider outlier to QSAR models, due they do not have a defined IC_{50} value. The Tables 5S–10S in the Supplementary Material display a listing of the compounds used to develop the QSAR models and their experimental biological activities. The dataset was divided into training set and validation set with a percentage of 80/20. To setup the sets we used the k-means clustering technique (Mamy et al. 2015). Thus, we performed a rational sets partition avoiding the random selection which is sometimes inappropriate (Andrada et al. 2015).

Structure and molecular descriptors

The molecular structures were optimized with MOPAC 09 software (Stewart 2008) using the semiempirical PM6 (parametric method-6) method (Stewart 2007). Then, a set of 1875 molecular descriptors of different types were calculated by PaDEL software (Yap 2011). They included, acidic group count, ALOGP, APol, Aromatic atoms count, Aromatic bonds count, Atom count, Autocorrelation, Barysz matrix, Basic group count, BCUT, Bond count, BPol, Burden modified eigenvalues, Carbon types, Chi, Constitutional, Crippen logP and MR, Detour matrix, Eccentric connectivity index, Atom type electrotopological state, Extended topochemical atom, FMFDescriptor, Fragment complexity, Hbond acceptor count, Hbond donor count, Hybridization ratio, Information content, Kappa shape indices, Largest chain, Largest Pi

system, Longest aliphatic chain, Mannhold LogP, McGowan volume, Molecular distance edge, Molecular linear free energy relation, Path counts, Petitjean number, Ring count, Rotatable bonds count, Rule of five, Topological, Van der Waals volume, Vertex adjacency information (magnitude), Walk counts, Weight, Weighted path, Wiener numbers, XLogP, Zagreb index, 3D autocorrelation, Charged partial surface area, Gravitational index, Length over breadth, Moment of inertia, Petitjean shape index, RDF, and WHIM. To avoid redundant information, the descriptors with a correlation higher than 0.9 were removed from the total set.

QSAR modeling

The Replacement Method (RM) (Duchowicz et al. 2006; Mercader et al. 2010), implemented in Matlab software (Matlab 2014), was used as the variable selection procedure in the search of the best Multivariate lineal regression (MLR) equations. The RM is an optimization tool, which generates multivariate linear equation for the QSAR models by searching an optimal subset of descriptors from the total set descriptors (1875) with minimum standard deviation (S) of the model. The quality of the model and the validation was quantified with the traditional statistic parameters: the regression coefficient (R), the determination coefficient (R^2), Root-mean-square (RMS) and the standard deviation (S).

To validate the developed QSAR models, we used a validation set containing about a 20% of the total set of compounds. In addition, we used the internal-validation procedures; the leave-one-out (loo) and the leave-more-out (lmo). We selected about the 10% of the compounds and generated a million cases of random data removal. Finally, 100,000 cases of y-randomization validation were performed. The y-randomization consists in the interchange of the experimental property such that property value and the compound do not match. Thus, it is demonstrated that the best model was not found by chance.

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Compliance with ethical standards

Conflicts of interest The authors declare that there is no conflict of interest.

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