Efficient Synthesis and Spectroscopy of 3,3-Dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1 *H*-dibezo-[*b*,*e*][1,4]diazepin-1-ones

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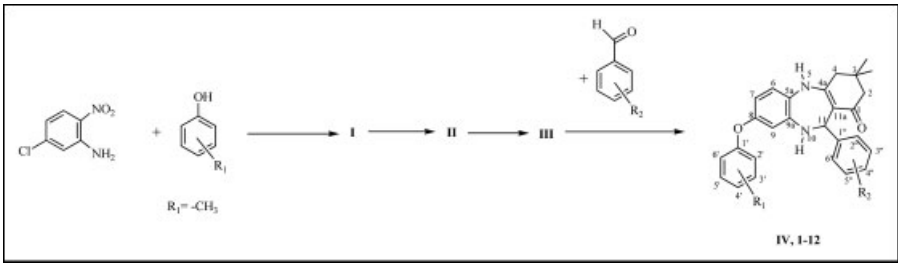

An easy synthesis of four steps to afforded 12 new derivatives of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)phenoxy]-11-[(o-; and *p*-substituted)phenyl]-1H-dibezo-[b,e][1,4]diazep-in-1-ones **IV**, **1-12** with potential biological and pharmacological activity as sedative, hypnotic-muscular relaxing, anticonvulsant, and schizophrenia treatment of the central nervous system (CNS). The final products have been obtained with good yields, by condensation and cyclization between 3-{4-[(*o*-; and *p*-methyl)phenoxy]-1,2-phenylendiamine}-5,5-dimethyl-2-cyclohexanone **III**, with the corresponding (*o*-; and *p*-R)benzaldehyde. The structure of all derivatives was corroborated by spectroscopy of ir, ^{1}H, and ^{13}C NMR, with bi-dimensional experiments and EI-MS in low and high resolution with collision-induced dissociation experiments (CID).

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INTRODUCTION

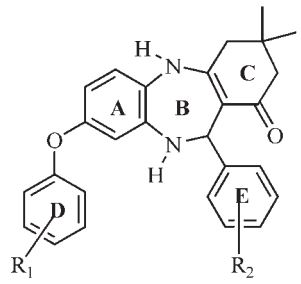
The first 1,4- and 1,5-benzodiazepines appeared in the pharmaceutical industry as tranquilizers in the 1970's, their use and interest in recent years has been broader in areas such as tranquilizer, sedative, hypnotic, muscular relaxant, anticonvulsant, and schizophrenia treatment in the central nervous system. The development of new research projects using benzodiazepines and their application has great importance because these types of compounds have been used as antipsycotic drugs [1,2] and also for their antianaphylactic activity [3].

RESULTS AND DISCUSSION

To continue with our research program on the synthesis and determination of biological activity in different 1,4 and 1,5-benzodiazepines [4–7], we described in this report the synthesis of 12 new derivatives of 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)-phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1*H*-dibezo-[*b*,*e*][1,4]di-azepin-1-ones **IV**, **1-12** (Fig. 1). The synthesis of the dibenzo[*b*,*e*][1,4]diazepin-1-ones **IV**, **1-12** derivatives was carried out in four steps as shown in the Scheme 1.

The reaction mixture of 5-chloro-2-nitroaniline with the (*o*- and *p*-methyl)phenol in presence of anhydrous potassium carbonate at reflux in anhydrous dimethylformamide was heated for 5 h. After cooling, the reaction mixture was diluted with cold water, the 3-amine-4-nitrophenyl-[(*o*-; and *p*-methyl)phenyl]ether **I** that was precipitated and collected by filtration with suction was obtained in a 90–93% yield [8].

Hydrogenation of the corresponding ether **I** in ethanol in presence of Pd/C 10% under a pressure of 60 pounds/inch^2 at room temperature with magnetic stirring for 22 h, we reduced the nitro group to amine. When the reaction was finished, the catalyst Pd/C 10% was removed



IV, 1-12

	R_1	R_2
1	o-CH_3	o-CH_3
2	o-CH_3	p-CH_3
3	o-CH_3	o-Cl
4	o-CH_3	p-Cl
5	o-CH_3	o-Br
6	o-CH_3	p-Br
7	p-CH_3	o-CH_3
8	p-CH_3	p-CH_3
9	p-CH_3	o-Cl
10	p-CH_3	p-Cl
11	p-CH_3	o-Br
12	p-CH_3	p-Br

Figure 1. Compounds **IV**, **1–12**.

by filtration through celite and ethanol solution was evaporated under reduced pressure. The 3,4-diaminophenyl-[(*o*-; and *p*-methyl)phenyl]ether **II** [9] was obtained in very good yield of 95–98%.

Condensation of the derivatives **II** with 5,5-dimethyl-1,3-cyclohexanedione at reflux in anhydrous benzene with a Dean-Stark trap to eliminate the water produced; afforded after evaporated the ethanol under reduced pressure, the 3-{4-[(*o*-; and *p*-methyl)phenoxy]-1,2-phenylendiamine}-5,5-dimethyl-2-cyclohexenone **III** [10,11], almost pure in 70–75% yield.

Treatment of 1 equiv. of the corresponding 5,5-dimethyl-2-cyclohexenone **III**, with 1 equiv. of the corresponding (*o*-; and *p*-R_2)benzaldehyde in the presence of 0.5 mL of glacial acetic acid at reflux in 10 mL of ethanol with magnetic stirring for 2–4 h afforded the 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)-phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1H-dibezo-[*b*,*e*][1,4]diazepin-1-ones **IV**, **1-12** in 54–75% yields.

The infrared spectra of compounds **IV**, **1-12** displayed absorptions at 3415–3299 cm^{-1} for N—H stretching; at 1700–1600 cm^{-1} for C=O stretching; at 1377–1369 and 1266–1263 cm^{-1} for C—N stretching; at 1187–1171 and 1114–1012 cm^{-1} for C—O stretching and the corresponding absorptions for aromatic and R-substituents.

In the ^{1}H NMR spectra the presence of two singlet signals (2X3H) at δ 1.01–1.12 and 1.11–1.15 were assigned to the methyl protons joined at C-3. The presence of a doublet at δ 2.18–2.31 and 2.28–2.34 was consistent with the methylene protons at C-2; other doublet signals at δ 2.40–2.57 and 2.54–2.64 was assigned to the methylene protons on C-4. The singlet signal at δ 5.84–6.21 was consistent with methine proton on C-11.

The presence of a broad signal deuterium oxide exchangeable proton a δ 6.45–7.76 was consistent with the N—H. The other signals corresponding at the aromatic protons of the aromatic ring of dibenzodiazepin-1-one appears as a doublet at δ 5.60–6.12 and was consistent with the proton at C-9; the presence of a signal doublet of doublet at δ 6.26–6.40 correspond at the proton on C-7 and the signal doublet at δ 6.66–6.90 was assigned at the proton on C-6.

The other aromatic protons of the rings phenoxy and phenyl substituent on the framework of the dibenzodiazepin-1-one appears as multiplet and as AA′BB′ systems at δ 6.00–7.47. The signals for the methyl substituent in the aromatic rings were also observed as a singlet signal at δ 2.03–2.51.

The ^{13}C NMR spectra data for compounds **IV**, **1-12** are given in Table 1. The signals were confirmed by

Scheme 1

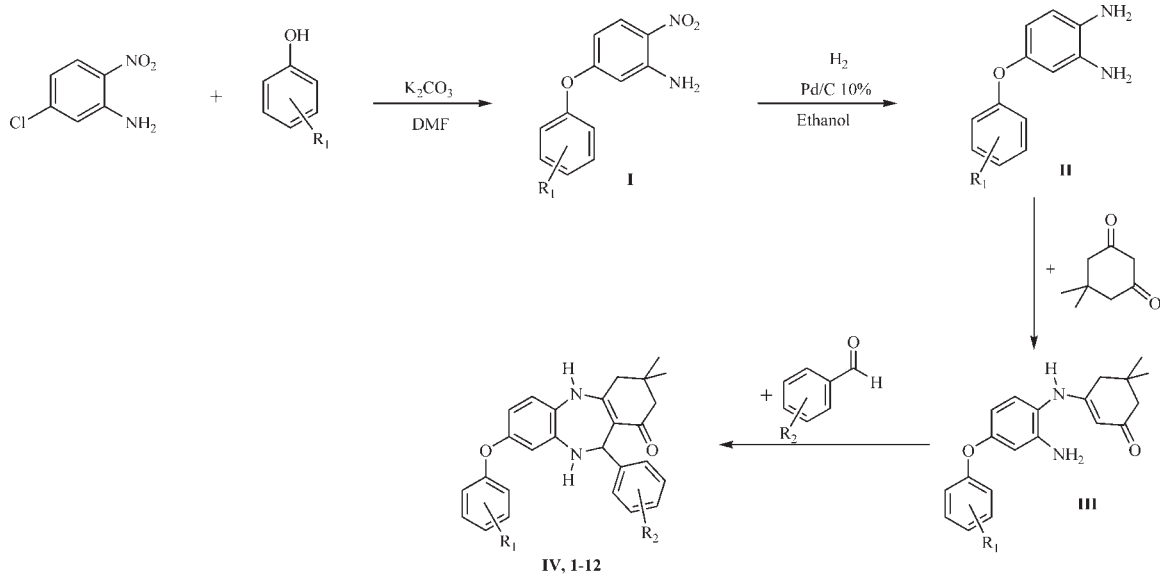
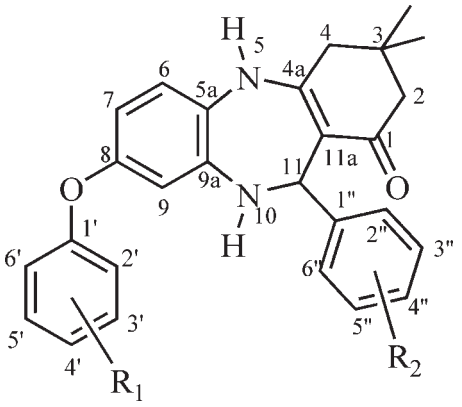


Table 1

^{13}C NMR spectral data for compounds **1–12**.



Compounds	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
R_1	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*o*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3	*p*-CH_3
R_2	*o*-CH_3	*p*-CH_3	*o*-Cl	*p*-Cl	*o*-Br	*p*-Br	*o*-CH_3	*p*-CH_3	*o*-Cl	*p*-Cl	*o*-Br	*p*-Br
C-1	193.8	193.6	193.6	193.7	193.2	193.3	193.6	193.7	192.7	193.6	193.6	193.8
C-2	49.8	49.7	49.7	49.7	49.7	49.6	49.6	49.7	49.2	49.7	49.7	49.7
C-3	32.3	32.3	32.3	32.3	32.3	32.0	32.4	32.3	32.3	32.3	32.4	32.3
C-4	46.1	46.4	46.1	46.5	46.2	45.4	46.2	46.3	46.0	46.2	46.3	46.4
C-4a	153.8	153.0	153.8	153.1	154.7	154.8	153.8	153.2	156.0	153.5	153.4	153.3
C-5a	127.3	126.5	127.1	126.4	127.0	127.0	127.8	127.0	126.8	126.9	127.4	126.8
C-6	120.9	120.9	120.9	121.0	121.0	121.6	121.1	121.0	122.0	121.4	120.9	121.1
C-7	111.5	111.0	111.6	111.3	111.6	111.6	111.9	112.2	112.9	112.4	112.7	112.4
C-8	153.6	153.7	154.7	154.2	154.0	153.6	153.3	153.3	153.7	153.7	154.4	153.8
C-9	111.0	110.9	111.0	110.9	111.1	110.9	111.3	111.0	112.0	112.1	112.3	112.1
C-9a	138.5	138.8	138.9	138.4	138.8	137.7	138.6	138.5	139.7	138.3	138.7	138.3
C-11	55.4	57.8	56.1	57.6	58.3	57.6	55.5	57.8	56.1	57.6	58.3	57.7
C-11a	110.9	118.5	109.2	110.5	109.5	109.4	111.9	111.0	109.2	110.3	109.6	110.4
C-1′	155.0	154.9	154.9	154.8	154.9	154.2	155.3	155.3	155.2	155.1	155.2	155.1
C-2′	129.0	140.7	129.1	129.4	129.1	129.1	130.2	130.0	129.9	130.1	130.0	130.1
C-3′	130.5	131.3	131.2	131.4	131.3	131.2	117.7	118.0	117.8	118.1	117.7	118.2
C-4′	123.2	123.5	123.4	123.7	123.5	123.3	129.9	132.3	132.3	132.3	132.6	132.6
C-5′	126.8	126.8	128.1	127.0	126.7	126.9	117.7	118.0	117.8	118.1	117.7	118.2
C-6′	118.2	118.6	118.3	118.9	118.4	118.5	130.2	130.0	129.9	130.1	130.0	130.1
C-1″	141.2	135.9	133.5	132.3	129.1	129.1	130.4	136.0	133.6	132.5	132.6	129.0
C-2″	135.1	128.8	139.9	128.4	141.4	128.9	135.5	127.0	139.7	128.3	142.5	131.2
C-3″	131.2	127.0	129.6	128.3	132.9	130.9	132.2	128.8	129.6	128.2	133.0	128.9
C-4″	126.7	129.2	126.8	142.2	128.4	142.4	126.9	140.5	128.2	142.2	128.4	142.8
C-5″	125.2	127.0	126.1	128.3	126.8	130.9	125.4	128.8	126.2	128.5	126.7	128.9
C-6″	125.7	128.8	127.6	128.4	127.7	128.9	125.8	127.0	127.6	128.3	127.7	131.2
C-3(CH_3)	27.9	27.8	28.2	27.9	28.2	27.6	27.8	27.8	28.1	27.8	28.2	27.9
C-3(CH_3)	28.6	28.7	28.5	28.6	28.4	28.6	28.6	28.8	28.4	28.7	28.5	28.6
$C_{2'}$-CH_3	16.0	16.0	16.0	16.0	16.0	15.9	–	–	–	–	–	–
$C_{4'}$-CH_3						–	20.6	21.0	20.6	20.6	20.6	20.7
$C_{2''}$-CH_3	19.5	–	–	–	–	–	19.6	–	–	–	–	–
$C_{4''}$-CH_3	–	20.9	–	–	–	–	–	20.6	–	–	–	–

The numbering of the phenyl ring is only for the assignment of the chemical shifts of the carbon in ^{13}C NMR spectra.

using HETCOR, FLOCK, COSY, NOESY, and DEPT NMR experiments operating at 300 and 500 MHz. The mass spectra of compounds **IV**, **1-12** exhibit a stable molecular ion with a relative abundance of 24–55%. The base peak is the ion at m/z $[M-(76 + R_2)]^+$. The main fragmentation pathway was consistent with the assigned structures and the mass spectra of the compounds **IV**, **1-12** includes ions of m/z corresponding to molecular ion $[M]^+$; $[M-CH_3]^+$; $[M-CH_4]^+$; $[M-R_2]^+$; $[M-(R_2+ CH_4)]^+$; $[M-28]^+$; $[M-57]^+$; $[M-84]^+$; $[M-85]^+$; $[M-(76 + R_2)]^+$ (the base peak); m/z 363 and 83. The proposed fragmentation pathways leading to the

formation of a number of important daughter ions have been confirmed by the corresponding parent ion spectra, using collision-induced dissociation experiments (CID). The elemental composition of the molecular ion and the principal fragment ion were determined by exact mass measurements.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet Magna TR-750 spectrophotometer in chloroform. The ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer operating at 300 MHz and the ^{13}C NMR spectra were recorded on a Varian Unity 500 spectrometer operating at 125 MHz in deuterochloroform solution containing tetramethylsilane as the internal standard with chemical shifts δ (ppm) expressed downfield from tetramethylsilane. The mass spectra were measured on a JEOL JMS-AC505 and JEOL MS-SX 102A high-resolution mass spectrometer with accurate mass determination of the molecular ion and the principal fragment ions, using the direct inlet system. The spectra were recorded by electron impact at an ionization chamber temperature of 190°C and ionizing electron energy of 70 eV, using electronic ionization. The compounds **I**, **II**, and **III** were prepared following methods developed by us with modifications [8,9,12].

General procedure for the synthesis of the 3,3-dimethyl-2,3,4,5,10,11-hexahydro-8-[(*o*-; and *p*-methyl)phenoxy]-11-[(*o*-; and *p*-substituted)phenyl]-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-ones IV, 1-12. A mixture of 1 equiv. of the corresponding 3-{4-[(*o*-; and *p*-methyl)phenoxy]-1,2-phenylendiamine}-5,5-dimethyl-2-cyclo-hexenone III; 1 equiv. of the corresponding (*o*-; and *p*-substituted)benzaldehyde, 0.5 mL of acetic acid glacial in 10 mL ethanol was heated at reflux for 2–4 h. The reaction mixture was cooled to room temperature and evaporated *in vacuo* to yield a semisolid. The residual semisolid was purified on a silica gel by choromatography in column and elution with hexane-ethyl acetate (95:5) to yield the compounds **IV**, **1–12**, in 54–75%.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*o*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 1). This compound was obtained as an orange solid in 70% yield; mp 135–136°; ir (chloroform): ν N—H 3415, C=O 1619, C—N 1369 and 1264, C—O 1287 and 1113 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.05 and 1.11 (s, 6H, C_3—$(CH_3)_2$); 2.05 (s, 3H, $C_{2'}$—CH_3); 2.18 (d, 1H, J = 16.4 Hz, 2-Ha); and 2.28 (d, 1H, J = 16.4 Hz, 2-Hb); 2.43 (d, 1H, J = 15.8 Hz, 4-Ha); and 2.56 (d, 1H, J = 15.8 Hz, 4-Hb); 2.50 (s, 3H, $C_{2''}$—CH_3); 5.88 (d, 1H, J = 2.6 Hz, 9-H); 6.11 (s, 1H, 11-H); 6.27 (dd, 1H, J = 2.6, 8.6 Hz, 7-H); 6.43 (dd, 1H, J = 1.5, 7.8 Hz, 6′-H); 6.64 (dd, 1H, J = 1.1, 7.7 Hz, 6″-H); 6.72 (d, 1H, J = 8.6 Hz, 6-H); 6.81 (dt, 1H, J = 1.0, 7.2 Hz, 5″-H); 6.96 (dt, 1H, J = 1.4, 6.2 Hz, 4′-H); 6.98 (dt, 1H, J = 1.5, 6.2 Hz, 4″-H); 7.0 (bs, 2H, N—H, deuterium oxide exchangeable); 7.05 (dt, 1H, J = 2.1; 6.3 Hz, 5′-H); 7.06 (dd, 1H, J = 1.2, 8.0 Hz, 3′-H); 7.14 (dd, 1H, J = 1.7, 6.6 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 438 (55) [M$^+$]; 423 (24) [M-R_1]$^+$ [M-(CH_3)]$^+$; 422 (14); 381 (4); 354 (6); 347 (100) [M-(76 + R_1)]$^+$; 83 (5). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.50; H, 6.80; N, 6.49.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*p*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 2). This compound was obtained as an orange solid in 70% yield; mp 240°; ir (chloroform): ν N—H 3301, C=O 1600, C—N 1376 and 1263, C—O 1185 and 1114 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.08 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.08 (s, 3H, $C_{2'}$—CH_3); 2.22 (s, 3H, $C_{4''}$—CH_3); 2.22 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.5 Hz, 2-Hb); 2.40 (d, 1H, J = 15.6 Hz, 4-Ha); and 2.57 (d, 1H, J = 15.6 Hz, 4-Hb); 5.86 (s, 1H, 11-H); 5.96 (d, 1H, J = 2.4 Hz, 9-H); 6.32 (dd, 1H, J = 2.7, 8.7 Hz, 7-H); 6.53 (bs, 2H, N—H, deuterium oxide exchangeable); 6.57 (dd, 1H, J = 1.2, 8.1 Hz, 6′-H); 6.66 (d, 1H, J = 8.7 Hz, 6-H); 6.92 (s, 4H, phenyl protons of "E" ring); 6.99 (dt, 1H, J = 1.5, 7.3 Hz, 4′-H); 7.06 (dt, 1H, J = 1.5, 7.4 Hz, 5′-H); 7.16 (dd, 1H, J = 1.2, 6.3 Hz, 3′-H); ms (IE = 70 eV): m/z (%) 438 (49) [M$^+$]; 423 (6) [M-R_1]$^+$ [M-(CH_3)]$^+$; 422 (9); 381 (6); 354 (7); 353 (6); 347 (100) [M-(76 + R_1)]$^+$; 83 (4). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.55; H, 6.76; N, 6.31.

3,3-Dimethyl-8-[(o-methyl)phenoxy]-11-[(*o*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (IV, 3). This compound was obtained as an orange solid in 75% yield; mp 105–107°; ir (chloroform): ν N—H 3299, C=O 1620, C—N 1376 and 1265, C—O 1186 and 1113 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.12 and 1.15 (s, 6H, C_3—$(CH_3)_2$); 2.04 (s, 3H, $C_{2'}$—CH_3); 2.23 (d, 1H, J = 16.2 Hz, 2-Ha); and 2.32 (d, 1H, J = 16.2 Hz, 2-Hb); 2.50 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.61 (d, 1H, J = 15.9 Hz, 4-Hb); 6.0 (dt, 1H, J = 1.2; 7.8 Hz, 5″-H); 6.01 (d, 1H, J = 2.4 Hz, 9-H); 6.21 (s, 1H, 11-H); 6.26 (dd, 1H, J = 2.3, 8.8 Hz, 7-H); 6.43 (dd, 1H, J = 1.0, 7.8 Hz, 6′-H); 6.67 (d, 1H, J = 8.7 Hz, 6-H); 6.78 (dd, 1H, J = 1.3, 7.6 Hz, 6″-H); 6.88 (bs, 2H, N—H, deuterium oxide exchangeable); 7.01 (dt, 1H, J = 1.2, 6.6 Hz, 4′-H); 7.02 (dt, 1H, J = 1.2, 7.8 Hz, 5′-H); 7.03 (dt, 1H, J = 1.5, 7.3 Hz, 4″-H); 7.16 (dd, 1H, J = 1.5, 6.5 Hz, 3′-H); 7.27 (dd, 1H, J = 1.2, 6.6 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 460 (15) [M + 2]$^+$; 458 (38) [M$^+$]; 443 (5) [M-(CH_3)]$^+$; 442 (9); 423 (20) [M-R_1]$^+$; 401 (4); 374 (5); 373 (4); 347 (100) [M-(76+ R_1)]$^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.59; H, 5.81; N, 6.25.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*p*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1H-dibenzo[b,e][1,4]diazepin-1-one (IV, 4). This compound was obtained as a yellow solid in 70% yield; mp 220–222°; ir (chloroform): ν N—H 3301, C=O 1585, C—N 1377 and 1264, C—O 1185 and 1114 cm^{-1}; ^{1}H NMR (deuterochloroform): δ 1.08 and 1.14 (s, 6H, C_3—$(CH_3)_2$); 2.08 (s, 3H, $C_{2'}$—CH_3); 2.22 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.5 Hz, 2-Hb); 2.42 (d, 1H, J = 16.2 Hz, 4-Ha); and 2.58 (d, 1H, J = 16.2 Hz, 4-Hb); 5.85 (s, 1H, 11-H); 5.94 (d, 1H, J = 2.7 Hz, 9-H); 6.36 (dd, 1H, J = 2.4, 8.8 Hz, 7-H); 6.45 (bs, 2H, N—H, deuterium oxide exchangeable); 6.58 (dd, 1H, J = 1.2, 7.8 Hz, 6′-H); 6.68 (d, 1H, J = 8.7 Hz, 6-H); 6.96 and 7.10 (AA′BB′, 4H, J = 8.7 Hz, phenyl protons of "E" ring); 7.0 (dt, 1H, J = 1.2, 6.6 Hz, 4′-H); 7.11 (dt, 1H, J = 1.2, 6.6 Hz, 5′-H); 7.17 (dd, 1H, J = 1.2, 7.5 Hz, 3′-H); ms (IE = 70 eV): m/z (%) 460 (16) [M+2]$^+$; 458 (40) [M$^+$]; 443 (4) [M-(CH_3)]$^+$; 442 (6); 401 (6); 374 (6); 373 (6); 347 (100) [M-(76 + R_1)]$^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.15; H, 5.80; N, 6.19.

3,3-Dimethyl-8-[(o-methyl)phenoxy]-11-[(*o*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 5). This compound was obtained as an orange solid in 60% yield; mp 72–74°; ir (chloroform): ν N—H 3413, C=O 1700, C—N 1371 and 1266, C—O 1285 and 1113 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.09 and 1.12 (s, 6H, C_3—$(CH_3)_2$); 2.03 (s, 3H, $C_{2'}$—CH_3); 2.21 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.30 (d, 1H, J = 16.5 Hz, 2-Hb); 2.51 (d, 1H, J = 15.3 Hz, 4-Ha); and 2.62 (d, 1H, J = 15.3 Hz, 4-Hb); 6.01 (d, 1H, J = 2.4 Hz, 9-H); 6.14 (s, 1H, 11-H); 6.26 (dd, 1H, J = 2.3, 8.8 Hz, 7-H); 6.43 (dd, 1H, J = 1.8, 7.8 Hz, 6′-H); 6.72 (d, 1H, J = 8.1 Hz, 6-H); 6.77 (dd, 1H, J = 1.8, 6.8 Hz, 6″-H); 6.78 (bs, 2H, N—H, deuterium oxide exchangeable); 6.91 (dt, 1H, J = 1.8, 6.6 Hz, 4″-H); 6.94 (dt, 1H, J = 1.8; 6.3 Hz, 5″-H); 6.97 (dt, 1H, J = 1.8, 7.2 Hz, 4′-H); 7.03 (dt, 1H, J = 2.1, 7.5 Hz, 5′-H); 7.15 (dd, 1H, J = 1.5, 7.2 Hz, 3′-H); 7.44 (dd, 1H, J = 1.5, 6.6 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 504 (24) $[M + 2]^+$; 502 (24) $[M^+]$; 487 (5) $[M\text{-}(CH_3)]^+$; 486 (8); 423 (36) $[M\text{-}R_1]^+$; 407 (7) $[M\text{-}(R_1 + CH_4)]^+$; 445 (3); 418 (3); 417 (3); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.92; H, 5.33 N, 5.50.

3,3-Dimethyl-8-[(*o*-methyl)phenoxy]-11-[(*p*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 6). This compound was obtained as a brown solid in 73% yield; mp 208–210°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1266, C—O 1185 and 1112 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.07 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.08 (s, 3H, $C_{2'}$—CH_3); 2.20 (d, 1H, J = 16.4 Hz, 2-Ha); and 2.29 (d, 1H, J = 16.4 Hz, 2-Hb); 2.49 (d, 1H, J = 16.0 Hz, 4-Ha); and 2.58 (d, 1H, J = 16.0 Hz, 4-Hb); 5.60 (d, 1H, J = 2.4 Hz, 9-H); 5.9 (s, 1H, 11-H); 6.37 (dd, 1H, J = 2.5, 8.7 Hz, 7-H); 6.54 (dd, 1H, J = 1.5, 7.5 Hz, 6′-H); 6.9 (d, 1H, J = 8.4 Hz, 6-H); 6.93 and 7.24 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of ''E'' ring); 7.0 (dt, 1H, J = 1.5, 7.4 Hz, 4′-H); 7.14 (dt, 1H, J = 1.6, 7.5 Hz, 5′-H); 7.18 (dd, 1H, J = 1.5, 7.5 Hz, 3′-H); 7.76 (bs, 2H, N—H, deuterium oxide exchangeable);; ms (IE = 70 eV): m/z (%) 504 (31) $[M + 2]^+$; 502 (32) $[M^+]$; 487 (3) $[M\text{-}(CH_3)]^+$; 486 (4); 445 (4); 418 (5); 417 (4); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (4). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.70; H, 5.50; N, 5.68.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*o*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 7). This compound was obtained as a yellow solid in 51% yield; mp 102–104°; ir (chloroform): ν N—H 3414, C=O 1617, C—N 1369 and 1263, C—O 1171 and 1016 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.01 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.19 (d, 1H, J = 16.2 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.2 Hz, 2-Hb); 2.28 (s, 3H, $C_{4'}$—CH_3); 2.48 (d, 1H, J = 16.2 Hz, 4-Ha); and 2.54 (d, 1H, J = 16.2 Hz, 4-Hb); 2.51 (s, 3H, $C_{2''}$—CH_3); 6.00 (d, 1H, J = 2.1 Hz, 9-H); 6.14 (s, 1H, 11-H); 6.39 (dd, 1H, J = 2.4, 8.7 Hz, 7-H); 6.55 and 7.01 (AA′BB′, 4H, J = 8.7 Hz, phenyl protons of ''D'' ring); 6.75 (bs, 2H, N—H, deuterium oxide exchangeable); 6.80 (dd, 1H, J = 1.3, 7.6 Hz, 6″-H); 6.81 (d, 1H, J = 7.8 Hz, 6-H); 6.82 (dt, 1H, J = 1.6, 7.6 Hz, 5″-H);6.99 (dt, 1H, J = 1.5, 6.2 Hz, 4″-H); 7.08 (dd, 1H, J = 1.6, 8.1 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 438 (52) $[M^+]$; 423 (19) $[M\text{-}R_1]^+$ $[M\text{-}(CH_3)]^+$; 422 (12); 381 (3); 354 (5); 353 (4); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (5). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.51; H, 6.79; N, 6.52.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*p*-methyl)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 8). This compound was obtained as a yellow solid in 54% yield; mp 47-49°; ir (chloroform): ν N—H 3415, C=O 1618, C—N 1369 and 1264, C—O 1172 and 1016 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.08 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.21 (d, 1H, J = 16.2 Hz, 2-Ha); and 2.30 (d, 1H, J = 16.2 Hz, 2-Hb); 2.23 (s, 3H, $C_{4'}$—CH_3); 2.29 (s, 3H, $C_{4''}$—CH_3); 2.42 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.57 (d, 1H, J = 15.9 Hz, 4-Hb); 5.88 (s, 1H, 11-H); 6.08 (d, 1H, J = 2.5 Hz, 9-H); 6.38 (dd, 1H, J = 2.5, 8.6 Hz, 7-H); 6.64 and 7.03 (AA′BB′, 4H, J = 8.8 Hz, phenyl protons of ''D'' ring); 6.72 (d, 1H, J = 8.8 Hz, 6-H); 6.75 (bs, 2H, N—H, deuterium oxide exchangeable); 6.93 (s, 4H, phenyl protons of ''E'' ring); ms (IE = 70 eV): m/z (%) 438 (44) $[M^+]$; 423 (8) $[M\text{-}R_1]^+$ $[M\text{-}(CH_3)]^+$; 422 (6); 381 (8); 354 (10); 353 (9); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{29}H_{30}N_2O_2$: (438.55): C, 79.42; H, 6.90; N, 6.40; Found: C, 79.51; H, 6.79; N, 6.52.

3,3-Dimethyl-8-[(p-methyl)phenoxy]-11-[(*o*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 9). This compound was obtained as a yellow solid in 70% yield; mp 42-44°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1265, C—O 1172 and 1117 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.12 and 1.14 (s, 6H, C_3—$(CH_3)_2$); 2.29 (s, 3H, $C_{4'}$—CH_3); 2.22 (d, 1H, J = 16.4 Hz, 2-Ha); and 2.31 (d, 1H, J = 16.4 Hz, 2-Hb); 2.57 (d, 1H, J = 16.2 Hz, 4-Ha); and 2.64 (d, 1H, J = 16.2 Hz, 4-Hb); 6.11 (d, 1H, J = 2.7 Hz, 9-H); 6.20 (s, 1H, 11-H); 6.33 (dd, 1H, J = 2.7, 8.4 Hz, 7-H); 6.56 and 7.02 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of ''D'' ring); 6.74 (bs, 2H, N—H, deuterium oxide exchangeable); 6.77 (dd, 1H, J = 1.3, 7.5 Hz, 6″-H); 6.82 (d, 1H, J = 8.7 Hz, 6-H); 6.92 (dt, 1H, J = 1.2; 7.5 Hz, 5″-H); 7.04 (dt, 1H, J = 1.8, 7.7 Hz, 4″-H); 7.28 (dd, 1H, J = 1.5, 7.2 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 460 (16) $[M+2]^+$; 458 (40) $[M^+]$; 443 (3) $[M\text{-}(CH_3)]^+$; 442 (5); 423 (20) $[M\text{-}R_1]^+$; 401 (5); 374 (6); 373 (5); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.33; H, 5.84; N, 6.22.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*p*-chloro)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 10). This compound was obtained as an orange solid in 54% yield; mp 87–88°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1266, C—O 1173 and 1016 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.06 and 1.12 (s, 6H, C_3—$(CH_3)_2$); 2.20 (d, 1H, J = 16.1 Hz, 2-Ha); and 2.30 (d, 1H, J = 16.1 Hz, 2-Hb); 2.30 (s, 3H, $C_{4'}$—CH_3); 2.41 (d, 1H, J = 15.8 Hz, 4-Ha); and 2.56 (d, 1H, J = 15.8 Hz, 4-Hb); 5.87 (s, 1H, 11-H); 6.05 (d, 1H, J = 2.6 Hz, 9-H); 6.39 (dd, 1H, J = 2.5, 8.6 Hz, 7-H); 6.5 (bs, 2H, N—H, deuterium oxide exchangeable); 6.63 and 7.06 (AA′BB′, 4H, J = 8.5 Hz, phenyl protons of ''D'' ring); 6.71 (d, 1H, J = 8.5 Hz, 6-H); 6.96 and 7.10 (AA′BB′, 4H, J = 8.5 Hz, phenyl protons of ''E'' ring); ms (IE = 70 eV): m/z (%) 460 (12) $[M + 2]^+$; 458 (36) $[M^+]$; 443 (3) $[M\text{-}(CH_3)]^+$; 442 (5); 401 (5); 374 (6); 373 (5); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (4). Anal. Calcd. for $C_{28}H_{27}ClN_2O_2$: (458.97): C, 73.27; H, 5.93; N, 6.10; Found: C, 73.39; H, 6.03; N, 6.02.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*o*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 11). This compound was obtained as an orange solid in 68% yield; mp 99–101°; ir (chloroform): ν N—H 3413, C=O

1619, C—N 1369 and 1264, C—O 1172 and 1023 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.12 and 1.15 (s, 6H, C_3—$(CH_3)_2$); 2.22 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.34 (d, 1H, J = 16.5 Hz, 2-Hb); 2.29 (s, 3H, $C_{4'}$—CH_3); 2.50 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.62 (d, 1H, J = 15.9 Hz, 4-Hb); 6.12 (d, 1H, J = 2.4 Hz, 9-H); 6.16 (s, 1H, 11-H); 6.34 (dd, 1H, J = 2.5, 8.5 Hz, 7-H); 6.55 (dt, 1H, J = 1.2; 6.3 Hz, 5″-H); 6.71 (d, 1H, J = 8.7 Hz, 6-H); 6.78 (dd, 1H, J = 2.1, 7.8 Hz, 6″-H); 6.80 (bs, 2H, N—H, deuterium oxide exchangeable); 6.96 (dt, 1H, J = 1.2, 6.3 Hz, 4″-H); 7.26 (s, 4H, phenyl protons of ''D'' ring); 7.47 (dd, 1H, J = 2.7, 6.2 Hz, 3″-H); ms (IE = 70 eV): m/z (%) 504 (26) $[M + 2]^+$; 502 (25) $[M^+]$; 487 (8) $[M\text{-}(CH_3)]^+$; 486 (8); 423 (34) $[M\text{-}R_1]^+$; 407 (14) $[M\text{-}(R_1 + CH_4)]^+$; 445 (3); 418 (4); 417 (3); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (5). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.73; H, 5.32 N, 5.49.

3,3-Dimethyl-8-[(*p*-methyl)phenoxy]-11-[(*p*-bromo)phenyl]-2,3,4,5,10,11-hexahydro-1*H*-dibenzo[*b*,*e*][1,4]diazepin-1-one (IV, 12). This compound was obtained as a brown solid in 52% yield; mp 170–172°; ir (chloroform): ν N—H 3413, C=O 1618, C—N 1369 and 1266, C—O 1173 and 1012 cm^{-1}; ^1H NMR (deuterochloroform): δ 1.07 and 1.13 (s, 6H, C_3—$(CH_3)_2$); 2.21 (d, 1H, J = 16.5 Hz, 2-Ha); and 2.309 (d, 1H, J = 16.5 Hz, 2-Hb); 2.30 (s, 3H, $C_{4'}$—CH_3); 2.43 (d, 1H, J = 15.9 Hz, 4-Ha); and 2.58 (d, 1H, J = 15.9 Hz, 4-Hb); 5.84 (s, 1H, 11-H); 6.05 (d, 1H, J = 2.4 Hz, 9-H); 6.64 and 7.07 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of ''D'' ring); 6.40 (dd, 1H, J = 2.6, 8.8 Hz, 7-H); 6.58 (bs, 2H, N—H, deuterium oxide exchangeable); 6.71 (d, 1H, J = 8.7 Hz, 6-H); 6.91 and 7.25 (AA′BB′, 4H, J = 8.4 Hz, phenyl protons of ''E'' ring); ms (IE = 70 eV): m/z (%) 504 (23) $[M + 2]^+$; 502 (24) $[M^+]$; 487 (3) $[M\text{-}(CH_3)]^+$; 486 (3); 445 (3); 418 (4); 417 (3); 347 (100) $[M\text{-}(76 + R_1)]^+$; 83 (3). Anal. Calcd. for $C_{28}H_{27}BrN_2O_2$: (503.34): C, 66.81; H, 5.41; N, 5.57; Found: C, 66.95; H, 5.28; N, 5.68.

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