Synthesis and Spectral Properties of Methyl 5-[(*o*-, *m*-, and *p*-R)-Phenoxy]-2-benzimidazolecarbamate

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The preparation of eleven novel methyl 5-[(*o*-, *m*-, *p*-R)-phenoxy-2-benzimidazolecarbamates with possible pharmacological activity as anthelmintics is described. The structure of all products was corroborated by ir, ^{1}H-nmr, ^{13}C-nmr and mass spectra.

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There have been several reports concerning pharmacological interest of benzimidazolecarbamate derivatives as anthelmintics which have good efficacy against gastrointestinal nematodes of laboratory and domestic animals, for which the addition of a phenoxy group to a chemotherapeutically active molecule can considerably increase its efficacy [3-8]. Recently, it has been reported that benzimidazole anthelmintics are useful for the treatment of cryptococcal infection, including meningitis, in particular for AIDS patients [9].

As a part of a program directed towards the synthesis and the spectral property determination of heterocyclic derivatives with possible pharmacological activity, we describe in this report the synthesis of compounds **III**, **1-11** (Scheme 1), following the steps indicated in Scheme 2.

5-Chloro-2-nitroaniline was heated for five hours under reflux in dimethylformamide with the corresponding R-phenol in the presence of anhydrous potassium carbonate. After cooling, the reaction mixture was diluted with water, the 3-amino-4-nitrophenyl-R-phenyl ether, **I**, that had precipitated was filtered off with suction; the corresponding derivatives have been obtained in 70-98% yield.

To prepare the 3,4-diaminophenyl-R-phenyl ethers we followed two routes:

Route 1.

This route was used when the R-substituted are H-, CH_3-, and CH_3O-.

The 3-amino-4-nitrophenyl-R-phenyl ether was hydrogenated in ethanol in presence of Pd/C 10% under a pressure of 4.2 atmospheres at room temperature, the catalyst was then removed by filtration and the solution was evaporated under reduced pressure.

The 3,4-diaminophenyl-R-phenyl ethers have been obtained in 77-98% yield.

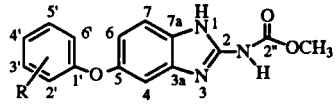
Route 2.

This route was used when the R-substitutents are Cl, and Br.

The 3-amino-R-nitrophenyl-R-phenyl ether was dissolved in ethanol, subsequently was added tin(II) chloride, sodium borohydride and the mixture was stirred and heated at 60° for three hours. After the reaction mixture was cooled with ice-water, subsequently cold water and aqueous sodium hydroxide solution until neutral *p*H was attained. The ethanol was evaporated *in vacuo* and the residual was filtered, the solution was extracted with methylene chloride, the organic solution was dried (sodium sulfate) and evaporated to yield the 3,4-diaminophenyl-R-phenyl ethers in 40-50% yield.

S-Methylthiourea sulfate was dissolved in water and then chloroformic acid methyl ester and an aqueous sodium hydroxide solution were added dropwise, while stirring at a temperature of 3° to 6°, in the mixture cooled with ice-water. After having stirred for forty minutes, the reaction mixture was combined with glacial acetic acid solution and the 3,4-diaminophenyl-R-phenyl ether was dissolved in ethanol. The mixture was stirred and heated for twenty hours, during which time methylmercaptan separated. After having allowed the entire reaction mixture to cool with ice-water, the methyl 5-[(*o*-, *m*-, and *p*-R)-phenoxy]-2-benzimidazolecarbamate that had formed was filtered to yield **III**, **1-11** (48-95%).

Scheme 1

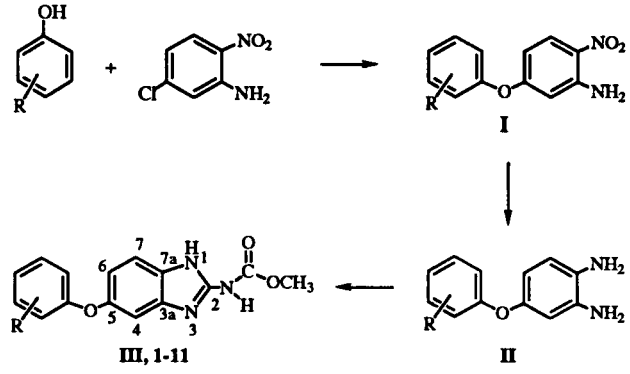


III, **1-11**

	R		R
1	H	**7**	*p*-OCH_3
2	*o*-CH_3	**8**	*o*-Cl
3	*m*-CH_3	**9**	*p*-Cl
4	*p*-CH_3	**10**	*o*-Br
5	*o*-OCH_3	**11**	*p*-Br
6	*m*-OCH_3		

The infrared spectrum of compounds **1-11** displayed absorptions at 3410-3345 for N-H stretching, at 2850-2734 cm^{-1} for NH-CO stretching, at 1739-1710 cm^{-1} for C=O stretching, at 1650-1628 cm^{-1} for C=N stretching, at 1275-1263 cm^{-1} and 1070-1020 cm^{-1} for C-O stretching; at 1196-1135 cm^{-1} and 1130-1060 cm^{-1} for C-N stretching and the corresponding absorptions for the R-substituent. In the ^{1}H-nmr spectra of derivatives **1-11** the presence of

Scheme 2



two-proton broad signal at δ 11.6 with exchanges with deuterium oxide, was consistent with the presence of two amine groups. One other proton signal at δ 7.4 as a doublet was assigned to the proton joined to C-7. One proton signal at δ 6.9-7.2, a doublet, was assigned to the proton joined to C-4; one proton signal at δ 6.8, a doublet of doublets was assigned to the proton joined to C-6. The presence of two proton signals at δ 7.7-6.8 as a triplet were assigned to the aromatic protons of the C-3' and C-5' positions. One proton signal at δ 6.6-7.1 as a triplet was assigned to the aromatic proton at C-4' and the presence of a one proton signal at δ 7.5-6.5 as a doublet of doublets was assigned to the aromatic proton at C-6'. A three proton signal at δ 3.7 as a singlet was assigned to the methoxy protons joined to C-2" of the ester group.

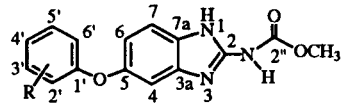
The ^{13}C nmr spectra of compounds **1-3** and **5-11** are given in Table 1, and the signals were confirmed by using HETCOR, longe range HETCOR, COSY and NOESY nmr experiments operating at 500 MHz.

The mass spectra of the compounds **1-11** exhibit a stable molecular ion and is the base peak for the compounds **1-9** and **11**; for compound **10** the ion at m/z 250 is the base peak. The relative abundance of the principal fragment ions have some common features and was confirmed by using tandem ms/ms technics, and high resolution with accurate mass determination of the molecular ion and the principal fragment ions.

The main fragmentation pathways of **1-11** include ions at m/z $[M-32]^+$, m/z $[M-58]^+$, m/z $[M-59]^+$, m/z $[M-60]^+$, m/z $[M-61]^+$, m/z $[M-74]^+$, m/z $[M-75]^+$, m/z [76+R]+, m/z $[92+R]^+$, m/z 174, and the ions at m/z $[M-R]^+$, m/z 250, 223 and 222 for the compounds **1**, **5**, **8** and **10**. The ions at m/z 204 and 172 are present only in the compound **5**; the ions at m/z 191 and 159 appear only in the compound **2** and are characteristic of compounds *ortho*-substituted with methoxy and methyl. All the fragments ions were consistent with the assigned structures.

Table 1

^{13}C NMR Spectral Data for Compounds **1-3** and **5-11**



III, 1-11

Compounds	1	2	3	5	6	7	8	9	10	11
R	H	*o*-CH_3	*m*-CH_3	*o*-CH_3O	*m*-CH_3O	*p*-CH_3O	*o*-Cl	*p*-Cl	*o*-Br	*p*-Br
C-2	147.9	147.8	147.8	147.8	147.8	147.9	148.0	147.8	147.9	148.0
C-3a	136.8	137.0	137.9	136.7	136.9	137.5	137.0	137.5	137.0	137.2
C-4	104.8	103.4	104.8	102.2	104.9	103.9	104.0	104.9	104.0	105.2
C-5	150.7	151.8	150.8	152.7	150.4	152.2	150.6	150.2	150.7	150.1
C-6	113.4	112.2	113.4	111.6	113.5	113.0	112.5	113.4	112.6	113.5
C-7	114.0	114.2	114.2	114.4	114.4	114.2	114.0	114.1	114.0	114.3
C-7a	132.0	132.0	132.9	131.9	132.0	132.5	132.0	132.5	132.0	132.5
C-1'	158.0	155.6	158.3	145.4	159.7	147.6	153.4	157.2	154.6	157.9
C-2'	117.0	128.2	117.8	151.0	103.4	119.8	123.4	118.6	112.9	119.3
C-3'	129.8	131.4	139.3	113.6	160.5	115.5	130.5	129.2	133.5	132.5
C-4'	122.4	123.1	123.1	124.6	108.0	152.3	124.1	126.0	124.5	113.8
C-5'	129.8	127.2	129.4	121.0	130.2	115.5	128.5	129.2	129.1	132.5
C-6'	117.0	117.9	114.4	120.4	109.2	119.8	119.3	118.6	119.1	119.3
C-2"	154.7	154.8	154.6	154.9	154.6	154.5	154.7	154.5	154.4	154.6
$COOCH_3$	52.4	52.4	52.3	52.4	52.4	52.4	52.4	52.4	52.4	52.4
R	-	15.8	20.8	55.6	55.1	55.1	-	-	-	-

Note: The numbering of the phenyl ring is only for the assignment of the chemical shifts of the carbons in ^{13}C nmr spectra.

EXPERIMENTAL

The ir spectra were recorded on a Nicolet Magna TR-750 spectrophotometer. 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 Plus-500 spectrometer operating at 500 MHz in deuteriochloroform solution or deuteriodimethyl sulfoxide solution containing tetramethylsilane as the internal standard with chemical shifts δ (ppm) expressed downfiled from TMS. The mass spectra were measured on a Jeol JMS-AX505 and Jeol MS-SX 102A high resolution mass spectrometer with accurate mass determination of the molecular ion and the principal fragments ions, using the direct inlet system. The spectra were recorded by electron impact at an ionization chamber temperature of 190° and ionizing electron energy of 70 eV.

General Procedure for the Synthesis of the Methyl 5-[(*o*-, *m*-, and *p*-R)-Phenoxy]-2-benzimidazolecarbamates, **III, 1-11.**

S-Methylthiourea sulfate (2.5 x 10^{-3} mole) was dissolved in water (3.0 ml) and then chloroformic acid methyl ester (4.6 x 10^{-3} mole) and a 25% aqueous sodium hydroxide solution (1.0 ml) were added dropwise, while stirring at a temperature of 3° to 6° cooling with an ice-water bath. After having stirred for forty minutes the reaction mixture was combined with aqueous glacial acetic acid solution (0.6 ml in 5.0 ml of water) at room temperature and subsequently was added the 3,4-diaminophenyl-R-phenyl ether (1.8 x 10^{-3} mole) dissolved in ethanol (5.0 ml). The mixture was stirred and heated at 95° for twenty hours, during which time methylmercaptan separated. The entire reaction mixture was cooled with ice-water, then the methyl 5-[(*o*-, *m*-, and *p*-R)-phenoxy]-2-benzimidazolecarbamate that had formed was filtered to yield **III, 1-11** (48-95%).

Methyl 5-Phenoxy-2-benzimidazolecarbamate (**1**).

This compound was obtained as whitish needles in 48% yield, mp 230°; ir (chloroform): ν NH 3345, NH-CO 2847-2734, C=O 1712, C=N 1628, C-O 1263 and 1020, C-N 1194 and 1130 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.7 (s, 3H, $COOCH_3$), 6.8 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 6.9 (dd, 2H, J = 0.9, 8.5 Hz, 2'-H and 6'-H), 7.0 (dt, 1H, J = 0.9, 6.6 Hz, 4'-H), 7.05 (d, 1H, J = 2.1 Hz, 4-H), 7.3 (dt, 2H, J = 0.9, 7.5 Hz, 3'-H and 5'-H), 7.4 (d, 1H, J = 8.7 Hz, 7-H), 11.7 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 283 (M^+).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.84. Found: C, 63.50; H, 4.70; N, 14.93.

Methyl 5-[(*o*-Methyl)phenoxy]-2-benzimidazolecarbamate (**2**).

This compound was obtained as whitish needles in 70% yield, mp 200°; ir (chloroform); ν NH 3362, NH-CO 2842-2736, C=O 1715, C=N 1631, C-O 1264 and 1042, C-N 1196 and 1154 cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.2 (s, 3H, CH_3-), 3.7 (s, 3H, $COOCH_3$), 6.7 (dd, 1H, J = 2.4, 8.7 Hz, 6-H), 6.8 (dd, 1H, J = 1.2, 8.1 Hz, 6'-H), 6.9 (d, 1H, J = 2.1 Hz, 4-H), 7.0 (dt, 1H, J = 1.2, 7.5 Hz, 4'-H), 7.1 (dt, 1H, J = 1.2, 7.5 Hz, 5'-H), 7.3 (dd, 1H, J = 1.2, 7.5 Hz, 3'-H), 7.4 (d, 1H, J = 8.7 Hz, 7-H), 11.5 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 297 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.56; H, 5.19; N, 14.03.

Methyl 5-[(*m*-Methyl)phenoxy]-2-benzimidazolecarbamate (**3**).

This compound was obtained as whitish needles in 49% yield, mp 210°; ir (chloroform): ν NH 3343, NH-CO 2840-2739, C=O 1717, C=N 1639, C-O 1265 and 1042, C-N 1195 and 1060 cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.2 (s, 3H, CH_3-), 3.7 (s, 3H, $COOCH_3$), 6.7 (ddd, 1H, J = 0.9, 1.2, 8.7 Hz, 6'-H), 6.74 (dd, 1H, J = 0.8, 1.2 Hz, 2'-H), 6.8 (dd, 1H, J = 1.5, 8.5 Hz, 6-H), 6.9 (ddd, 1H, J = 0.8, 1.2, 7.2 Hz, 4'-H), 7.0 (d, 1H, J = 2.1 Hz, 4-H), 7.2 (t, 1H, J = 7.5 Hz, 5'-H), 7.4 (d, 1H, J = 8.4 Hz, 7-H), 11.7 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 297 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.70; H, 5.01; N, 14.21.

Methyl 5-[(*p*-Methyl)phenoxy]-2-benzimidazolecarbamate (**4**).

This compound was obtained as whitish needles in 95% yield, mp 275°; ir (chloroform): ν NH 3358, NH-CO 2858-2740, C=O 1739, C=N 1685, C-O 1261 and 1052, C-N 1174 and 1114 cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.3 (s, 3H, CH_3-), 3.7 (s, 3H, $COOCH_3$), 6.7 (dd, 1H, J = 2.8, 8.7 Hz, 6-H), 6.9 and 7.2 (AA'BB', 4H, J = 8.6 Hz, phenyl protons), 7.25 (d, 1H, J = 2.8 Hz, 4-H), 7.35 (d, 1H, J = 8.8 Hz, 7-H), 11.6 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 297 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.56; H, 5.16; N, 14.07.

Methyl-5-[(*o*-Methoxy)phenoxy]-2-benzimidazolecarbamate (**5**).

This compound was obtained as brownish needles in 50% yield, mp > 280° dec; ir (chloroform): ν NH 3399, NH-CO 2838-2760, C=O 1734, C=N 1649, C-O 1257 and 1024; C-N 1176 and 1157 cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.69 (s, 3H, $COOCH_3$), 3.74 (s, 3H, $-OCH_3$), 6.74 (dd, 1H, J = 2.4, 6.3 Hz, 6-H), 6.87 (d, 1H, J = 2.4 Hz, 4-H), 6.91 (dt, 1H, J = 0.6, 3.3 Hz, 5'-H), 6.92 (dd, 1H, J = 2.1, 3.3 Hz, 6'-H), 7.11 (dt, 1H, J = 0.6, 3.2 Hz, 4'-H), 7.12 (dd, 1H, J = 2.0, 3.2 Hz, 3'-H), 7.4 (d, 1H, J = 8.4 Hz, 7-H), 11.8 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.26; H, 4.75; N, 13.51.

Methyl 5-[(*m*-Methoxy)phenoxy]-2-benzimidazolecarbamate (**6**).

This compound was obtained as brownish needles in 70% yield, mp 190°; ir (chloroform): ν NH 3399, NH-CO 2835-2738, C=O 1720, C=N 1648, C-O 1265 and 1042, C-N 1995 and 1150 cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.70 (s, 3H, $COOCH_3$), 3.74 (s, 3H, $-OCH_3$), 6.45 (ddd, 1H, J = 0.6, 1.5, 7.8 Hz, 6'-H), 6.50 (t, 1H, J = 2.1 Hz, 2'-H), 6.63 (ddd, 1H, J = 0.6, 1.5, 1.8, 7.8 Hz, 4'-H), 6.80 (dd, 1H, J = 2.1, 8.4 Hz, 6-H), 7.05 (d, 1H, J = 2.4 Hz, 4-H), 7.21 (t, 1H, J = 8.4 Hz, 5'-H), 7.4 (d, 1H, J = 8.4 Hz, 7-H), 11.6 (bs, 2H, N-H deuterium oxide exchangeable); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.39; H, 4.71; N, 13.49.

Methyl 5-[(*p*-Methoxy)phenoxy]-2-benzimidazolecarbamate (**7**).

This compound was obtained as white needles in 60% yield, mp 225°; ir (potassium bromide): ν NH 3359, NH-CO 2837-2775, C=O 1709, C=N, 1631, C-O 1265 and 1030, C-N 1194 and 1151 cm^{-1}; ^{1}H nmr (deuteriodimethyl sulfoxide): δ 3.71 (s, 3H, $COOCH_3$), 3.72 (s, 3H, OCH_3), 6.92 (s, 4H, phenyl protons), 6.8 (dd, 1H, J = 2.4, 8.7 Hz, 6-H), 6.95 (d, 1H, J = 2.4 Hz, 4-H), 7.35 (d, 1H, J = 8.7 Hz, 7-H), 11.6 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 313 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.41; H, 4.75; N, 13.34.

Methyl 5-[(*o*-Chloro)phenoxy]-2-benzimidazolecarbamate (**8**).

This compound was obtained as yellowish needles in 50% yield, mp > 280° dec; ir (potassium bromide): ν NH 3358, NH-CO 2840-2750, C=O 1715, C=N 1640, C-O 1265 and 1035, C-N 1150 and 1117 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 3.7 (s, 3H, $COOCH_3$), 6.78 (dd, 1H, J = 2.4, 8.7 Hz, 6-H), 6.92 (dd, 1H, J = 2.4, 8.1 Hz, 6'-H), 7.0 (d, 1H, J = 2.4 Hz, 4-H), 7.14 (dt, 1H, J = 1.5, 7.8 Hz, 4'-H), 7.28 (dt, 1H, J = 1.5, 7.5 Hz, 5'-H), 7.39 (d, 1H, J = 8.4 Hz, 7-H), 7.56 (dd, 1H, J = 1.5, 7.8 Hz, 3'-H), 11.6 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 317 (M^+), 319 $[M+2]^+$.

Anal. Calcd. for $C_{15}H_{12}N_3O_3Cl$: C, 56.70; H, 3.81; N, 13.23. Found: C, 56.63; H, 3.86; N, 13.29.

Methyl 5-[(*p*-Chloro)phenoxy]-2-benzimidazolecarbamate (**9**).

This compound was obtained as yellowish needles in 52% yield, mp 215°; ir (potassium bromide): ν NH 3358, NH-CO 2836-2735, C=O 1712, C=N 1639, C-O 1274 and 1010, C-N 1139 and 1092 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 3.7 (s, 3H, $COOCH_3$), 6.78 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 6.92 and 7.32 (AA'BB', 4H, J = 6.9, 7.6 Hz, phenyl protons), 7.07 (d, 1H, J = 2.4 Hz, 4-H), 7.4 (d, 1H, J = 8.4 Hz, 7-H), 11.6 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 317 (M^+), 319 $[M+2]^+$.

Anal. Calcd. for $C_{15}H_{12}N_3O_3Cl$: C, 56.70; H, 3.81; N, 13.23. Found: C, 56.78; H, 3.76; N, 13.17.

Methyl 5-[(*o*-Bromo)phenoxy]-2-benzimidazolecarbamate (**10**).

This compound was obtained as whitish needles in 51% yield, mp 205°; ir (chloroform): ν NH 3407, NH-CO 2832-2758, C=O 1711, C=N 1650, C-O 1263 and 1028, C-N 1140 and 1039 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 3.7 (s, 3H, $COOCH_3$), 6.8 (dd, 1H, J = 2.4, 8.4 Hz, 6-H), 6.9 (dd, 1H, J = 1.2, 8.2 Hz, 6'-H), 6.99 (d, 1H, J = 2.4 Hz, 4-H), 7.05 (dt, 1H, J = 1.5, 8.7 Hz, 4'-H), 7.3 (dt, 1H, J = 1.5, 7.8 Hz, 5'-H), 7.4 (d, 1H, J = 8.4 Hz, 7-H), 7.7 (dd, 1H, J = 1.5, 8.1 Hz, 3'-H), 11.6 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 361 (M^+), 363 $[M+2]^+$.

Anal. Calcd. for $C_{15}H_{12}N_3O_3Br$: C, 49.74; H, 3.34; N, 11.60. Found: C, 49.85; H, 3.27; N, 11.68.

Methyl 5-[(*p*-Bromo)phenoxy]-2-benzimidazolecarbamate (**11**).

This compound was obtained as whitish needles in 60% yield, mp > 280° dec; ir (potassium bromide): ν NH 3392, NH-CO 2846-2738, C=O 1716, C=N 1634, C-O 1273 and 1069, C-N 1139 and 1065 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 3.7 (s, 3H, $COOCH_3$), 6.81 (dd, 1H, J = 2.4, 8.7 Hz, 6-H), 6.9 and 7.5 (AA'BB', 4H, J = 9.0 Hz, phenyl protons), 7.08 (d, 1H, J = 2.4 Hz, 4-H), 7.4 (d, 1H, J = 8.4 Hz, 7-H), 11.6 (bs, 2H, N-H, deuterium oxide exchangeable); ms: m/z 361 (M^+), 363 $[M+2]^+$.

Anal. Calcd. for $C_{15}H_{12}N_3O_3Br$: C, 49.74; H, 3.34; N, 11.60. Found: C, 49.81; H, 3.42; N, 11.54.

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