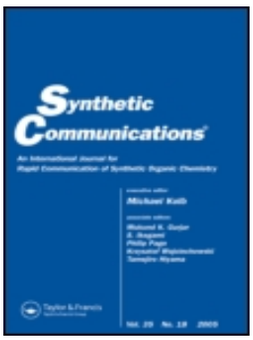

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SYNTHESIS OF DEUTERIUM-LABELED ANTIHYPERTENSIVE 3-(4'-PHENYL-1'-PIPERAZINYL)-PROPYL-2,4-QUINAZOLINEDIONE

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Abstract: Synthesis of deuterium-labeled 3-(4'-phenyl-1'-piperazinyl)-propyl-2,4-quinazolinedione (Pelanserine) an anti-hypertensive agent.

Pelanserine (TR2515) (**1a**), a quinazolinedione, is a well established potent antihypertensive agent, having activity comparable to the clinically used ketanserine[1-4]. In order to study its metabolic breakdown *in vivo*, we needed radioactively labeled Pelanserine to follow its reaction path. For making the labeled Pelanserine, we selected the method we recently reported, starting from phenylpiperazine and acrylonitrile[5]. Using this route, we targeted the Michael addition product (**2**) as the potential candidate for introducing the radioactive label. Although carbon-14 labeled acrylonitrile is commercially available, we needed an inexpensive method to introduce the radioactive label and also one that would have a short life time.

As a model route to the radiactive labeled pelanserine, we initially explored the synthesis of the deuterium labeled equivalent (**1b**), reducing the intermediate (**2**) with $LiAlD_4$, to give the primary amine (**3**) in 72% with 87% deuterium incorporation. We were also able to reduce the nitrile (**2**) to the amine (**3**) using deuterium gas and nickel as catalyst. However, in this case, the final yield of the primary amine was low due to secondary amine formation.

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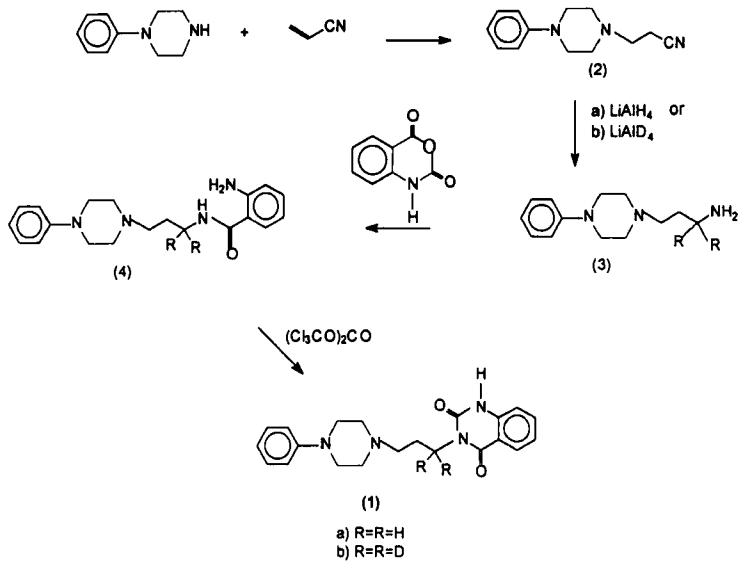
The deuterated amine (**3**) was then treated with isatoic anhydride and subsequently ring closed with triphosgene to give the desired deuterium-labeled Pelanserine (**1b**). (Scheme-1). Thus we have developed a simple and efficient route to making deuterium-labeled Pelanserine.



(Scheme-1)

Experimental: Melting points were obtained on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR 1600 spectrophotometer. Nuclear magnetic resonance ^{1}H spectra were recorded on a Varian 200 MHz Spectrometer with TMS as internal standard. ^{13}C spectra were recorded on a Varian Gemini 200 Spectrometer at 50.289 Hz in $CDCl_3$. Mass spectra were obtained on a Hewlett-Packard 5989 by EI at 70 eV by direct insertion. High resolution mass spectra were obtained at the University of California Mass Spectra Facility (Riverside), on a VG 7070.

1-(2-Cyanoethyl)-4-phenylpiperazine (2)[5]

mp 67-68 °C, yield 96%, IR (KBr): 3047, 2944, 2818, 1597, 1499, 1442, 1379,

1338, 1279, 1231, 1137, 1017, 926, 869, 755, 684 cm^{-1}. ^1H NMR($CDCl_3$): δ 7.3 (m, 2H, Ar-H), 6.95 (m, 3H, Ar-H), 3.28 (t, 4H, J=4.8 Hz, piper-H), 2.80(t, 2H, J= 6.0 Hz, N-CH_2-), 2.72(t, 4H, J= 4.8 Hz, piper-H), 2.60(t, 2H, J= 6.0 Hz, CH_2-CN). ^{13} C NMR ($CDCl_3$): δ 129, 120, 116, 57, 53, 49, 41. EIMS (m/z): 215 [M^+, 48], 175 (33), 161(5), 147(6), 104 (70).

1-(3-Aminopropyl)-4-phenylpiperazine (3a)[5]

mp 43-44 °C, yield 52%, IR(KBr): 3305, 2940, 2821, 1598, 1499, 1382, 1342, 1236, 1134, 1004, 922, 811, 757, 691 cm^{-1}. ^1H NMR($CDCl_3$): δ 7.25(m, 2H, Ar-H), 6.90 (m, 3H, Ar-H), 3.20 (t, 4H, J= 4.8 Hz, piper-H), 2.85(t, 2H, J= 6.0 Hz, CH_2-NH_2), 2.63(t, 4H, J= 4.8 Hz, piper-H), 2.50(t, 2H, J= 6.0 Hz, N-CH_2), 2.40 (s, 2H, NH_2), 1.75 (q, 2H, J= 6.0 Hz, -CH_2-). ^{13}C NMR ($CDCl_3$): δ 129, 120, 116, 57, 53, 49, 41. EIMS (m/z): 219 [M^+, 6], 204 (6), 189 (5), 175 (18), 161 (14).

1-(3-Amino-3',3'-dideuteropropyl)-4-phenylpiperazine (3b)

mp 43-45 °C, yield 48%, IR(KBr): 3305, 2942, 2824, 1586, 1460, 1354, 1242, 1135, 1002, 922, 755, 688 cm^{-1}. ^1H NMR($CDCl_3$): δ 7.25(m, 2H, Ar-H), 6.90 (m, 3H, Ar-H), 3.20 (m, 4H, piper-H), 2.60(m, 4H, piper-H), 2.50(t, 2H, J= 6.0 Hz, N-CH_2), 1.68 (t, 2H, J= 6.0 Hz, -CH_2-). ^{13} C NMR ($CDCl_3$): δ 129, 120, 116, 57, 53, 49, 30. EIMS (m/z): 221 [M^+, 10], 206 (10), 189 (6), 175 (24), 161 (18). HRMS 221.1883 (calcd. for $C_{13}H_{19}D_2N_3$, 221.1861).

GENERAL METHOD FOR MAKING o-AMINOBENZAMIDE[5].

A solution of 1-(3-aminopropyl)-4-phenylpiperazine (5.0 g, 23 mmol) in DMF (50 ml) was stirred and isatoic anhydride (4.09 g, 25 mmol) was added portionwise over a period of 30min.The temperature was maintained at approx. 50 °C, CO_2 gas evolved. The mixture was stirred at room temperature for additional 2 hrs, water was added and the solid collected by filtration and recristallized from ethanol to give (**4a**).

1-(3'-o-Amino-N-benzamido)-propyl-4-phenylpiperazine (4a)[5]

mp 115-117 °C, yield 85%, IR(KBr): 3449, 3334, 3059, 2944, 2822, 1708, 1634, 1590, 1583, 1529, 1490, 1450, 1264, 1238, 1157, 991, 926, 753, 693 cm^{-1}. ^1H

NMR($CDCl_3$): δ 8.04(s, 1H, N-H), 7.40 (d, 1H, J= 8.0 Hz, Ar-H), 7.34-7.22(m, 2H, Ar-H), 7.14(t, 1H, J= 8.0 Hz, Ar-H), 6.96-6.84(m, 3H, Ar-H), 6.65(d, 1H, J= 8.0 Hz, Ar-H), 6.52(t, 1H, J= 8.0 Hz, Ar-H), 3.54(c, 2H, J= 5.0 Hz, NH_2), 3.22(t, 4H, J=4.8 Hz, piper-H), 2.70(m, 6H, piper-H y CH_2-N), 1.84(q, 2H, J= 6.0 Hz, CH_2-).^{13}C ($CDCl_3$): 132, 129, 127, 120, 117, 116, 58, 53, 49, 40, 24. EIMS (m/z): 338 [M^+, 16], 323 (17), 296 (6), 219 (20), 206 (47), 189 (59), 175 (32), 161 (15), 147 (16), 132(31), 120 (100). Anal. Calcd for $C_{20}H_{26}N_4O$; C, 71.00, H, 7.69, found, C, 71.31, H, 7.65.

1-(3'-o-Amino-N-benzamido-3',3'-dideutero)-propyl-4 phenylpiperazine (4b). mp 115-118 °C, yield 76%, IR(KBr): 3444, 3339, 2931, 2822, 1723, 1632, 1588, 1519, 1450, 1266, 1233, 1153, 927, 753, 688 cm^{-1}. ^{1}H NMR($CDCl_3$): δ 8.0(s, 1H, N-H), 7.40 (d, 1H, J= 8.0 Hz, Ar-H), 7.34-7.22(m, 2H, Ar-H), 7.14(t, 1H, J= 8.0 Hz, Ar-H), 6.96-6.84(m, 3H, Ar-H), 6.65(d, 1H, J= 8.0 Hz, Ar-H), 6.62 (t, 1H, J= 8.0 Hz, Ar-H) 3.20 (m, 4H, piper-H), 2.70(m, 6H, piper-H y CH_2N), 1.84(t, 2H, J= 6.0 Hz, -CH_2-). EIMS (m/z): 340 [M^+, 21], 325 (23), 298 (7), 221 (22), 208 (53), 191 (56), 175 (34), 161 (13), 147 (14), 132(31), 120 (100).

GENERAL METHOD FOR MAKING THE QUINAZOLINEDIONE[5].

A solution of o-aminobenzamide (1.2 g, 5 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature, and triphosgene (0.5 g, 1.7 mmol) in CH_2Cl_2 (10 ml) was added. The mixture was refluxed for 2 h. The organic phase was washed with water and dried over $MgSO_4$. Removal of solvents under reduced pressure gave a solid. The solid was then recristallized from ethanol to give (**1a**).

3-(4'-Phenyl-1'-piperazinyl)-propyl-2,4-quinazolinedione (1a)[5]

mp 190-192 °C, yield 88% IR(KBr): 3358(NH), 2982, 1737 (C=O), 1638(NHCO), 1528, 1208, 1021, 986, 751cm^{-1}. ^{1}H NMR($CDCl_3$): δ 10.7 (s, 1H, N-H), 8.1(d, 1H, J= 8.0 Hz), 7.6(t, 1H, J=8.0 Hz), 7.2(m, 4H), 6.85(m, 3H), 4.2(t, 2H, J=6.0 Hz), 3.12(t, 4H, J= 6.0 Hz), 2.60(m, 6H), 1.95(q, 2H, J= 6.0 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 135, 129, 128, 123, 119, 116, 114, 56, 53, 49, 40, 25. EIMS (m/z): 364 [M^+, 36], 349 (8), 258 (8), 232 (16), 175 (100). Anal. Calcd for $C_{21}H_{24}N_4O_2$; C, 69.23, H, 6.59, found C, 69.23, H, 6.58.

3-(4'-Phenyl-1'-piperazinyl))-1'1'-dideuteropropyl-2,4-quinazolinedione (1b). mp 190-193 ^{0}C, yield 84 %, IR(KBr): 3052, 2939, 2817, 1715, 1653, 1599, 1493, 1454, 1294, 1226, 1143, 1023, 757, 690 cm^{-1}. ^{1}H NMR($CDCl_3$): δ 9.6(s, 1H, NH), 8.12(d, 1H, J=8.0 Hz, ArH), 7.60(t, 1H, J=8.0 Hz, ArH), 7.2(m, 4H, ArH), 7.05(d, 1H, J=8.0 Hz, ArH), 6.85(m, 2H, ArH), 3.15(t, 4H, J=6.0 Hz, piper-H), 2.60(m, 6H), 1.95(t, 2H, J=6.0 Hz). ^{13}C NMR ($CDCl_3$): δ 135, 129, 128, 123, 120, 116, 114, 56, 53, 49, 24. EIMS (m/z): 366 [M$^+$, 26], 351 (6), 260 (3), 234 (14), 205 (20), 175 (100). HRMS 366.2046 (calcd. for $C_{21}H_{22}D_2N_4O_2$, 366.2024).

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