Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 20 Aug 2006.

To cite this article: I. A. Rivero , R. Somanathan & L. H. Hellberg (1998) Synthesis of 3-Dipeptidyl-2,4(1H,3H)-Quinazolinediones as Potential Anti-Hypertensive Agents, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:11, 2077-2086, DOI: 10.1080/00397919808007184

To link to this article: http://dx.doi.org/10.1080/00397919808007184

SYNTHETIC COMMUNICATIONS, 28(11), 2077-2086 (1998)

SYNTHESIS OF 3-DIPEPTIDYL-2,4(1H,3H)-QUINAZOLINEDIONES AS POTENTIAL ANTI-HYPERTENSIVE AGENTS

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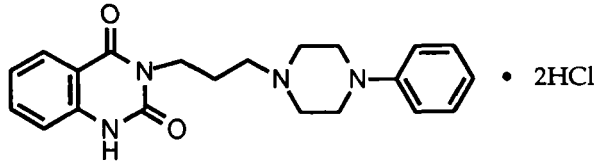
Abstract: Quinazolinediones bearing a dipeptide side chain have been synthesized as potential anti-hypertensive agents.

Numerous quinazolinedione molecules have been prepared over the years to serve as potential anti-hypertensive agents[1,4]. Pelanserine TR-2515 **(1)** is one such potent molecule[5,6], structurally similar to the clinically used ketanserine[7,8].



(1)

In our studies of synthesis of new anti-hypertensive agents, we have focused on modifying the N-phenyl-piperazine

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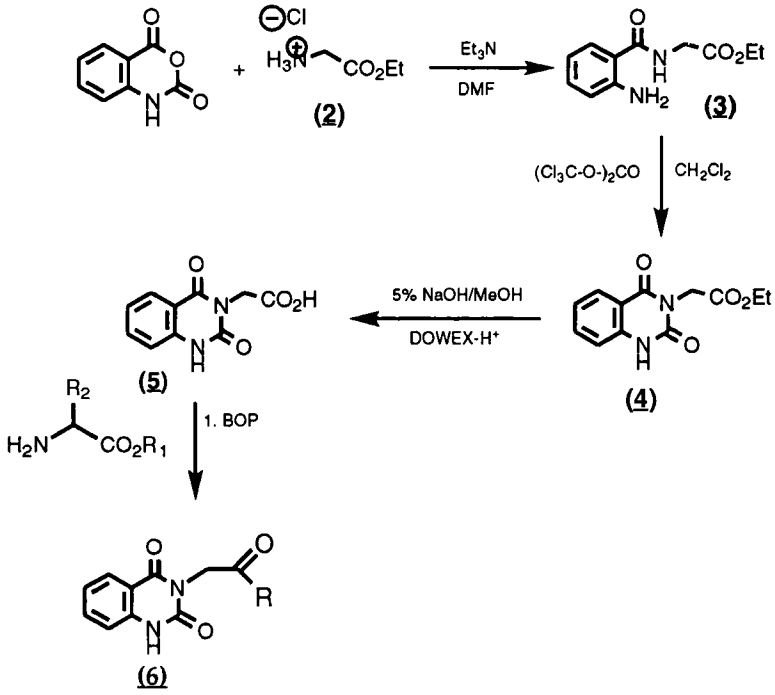
portion of the pelanserine molecule **(1)**. This led us to incorporate simple heterocyclic systems such as azaspirans and oxazolines[9]. These derived quinazolinedione systems showed mild to no activity compared to the parent pelanserine. Continuing in this context, we have synthesized several of quinazolinediones with a dipeptide side chain to examine as potential anti-hypertensive agents.

Rather than use synthetic route earlier reported[10,11], the amino acid ester **(2)** was treated with isatoic anhydride to give the amide **(3)**, followed by ring closure to the desired quinazolenediones **(4)** with triphosgene in 70% overall yield. The second amino acid, as its methyl ester, was coupled to **(5)** using benzotriazoloxy tris [dimethylamino] phosphonium hexafluorophosphate(BOP)[12] reagent to give the 3-dipeptidyl-quinazolinediones **(6).**

Although peptides have long been recognized as a useful diverse class of biologically agents, their limited stability and absence of oral activity has limited their potential therapeutic application[13]. However, captopril and enalaprilat, both proline derived dipeptides, have shown great promise as inhibitors of angiotensin converting-enzyme in controlling hypertension[10,11,14-16]. Considering this observation, we have prepared a number of quinazolinediones-dipeptides **(6a-e)** for a preliminary study of anti-hypertensive effects.



R: **6a)** N-L-TRYPTOPHANE METHYL ESTER **6b)** N-GLYCINE ETHYL ESTER
6c) N-L-PHENYL ALANINE ETHYL ESTER **6d)** N-DL-ALANINE METHYL ESTER
6e) N-L-PROLINE METHYL ESTER

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 Chemagnetic 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. Elemental analysis for carbon and hydrogen were performed by Galbraith Laboratories, Incorporated (Knoxville, TN).

2-Aminobenzamido-N-glycine ethyl ester (3). To a stirred and warm solution of glycine ethyl ester.HCl (15.02 g, 18 mmol) and triethylamine (10.86 g, 18 mmol) in dry DMF (50 mL) at 55 °C, isatoic anhydride (20.01 g, 123 mmol) was added portion-wise over a period of 20 minutes. During this addition evolution of carbon dioxide was observed; after complete addition the mixture was stirred at 55-60 °C for an additional two hours. The organic layer was extracted into methylene chloride (2X50 mL) and washed with sodium bicarbonate (5%, 50 mL) and water (2X50 mL). The methylene chloride solution was dried (sodium sulfate) and evaporation in vacuo gave 19.97g (84%) yield, a white residue, which was recrystallized from ethanol to give **(3).** mp 141-143°C, IR(KBr): 3358(NH), 2982, 1737 (C=O), 1638(NHCO), 1528, 1208, 1021, 986, 751cm^{-1}. ^{1}H NMR($CDCl_3$): δ 7.45(d, 1H, J= 8.0 Hz, ArH), 7.26(m, 1H, ArH), 6.85(brs, 1H, CONH), 6.75(m, 2H, ArH), 5.26(brs, 2H, $ArNH_2$), 4.23(q, 2H, J= 7.0 Hz, O-CH_2), 4.13(d, 2H, J= 5.4 Hz, CH_2-N), 1.26(t, 3H, J= 7.3 Hz, CH_3) ppm. MS m/e: 222 (M-160), 120.

Anal. Calcd. for $C_{11}H_{14}N_2O_3$; C, 59.45; H, 6.30. Found: C, 59.93; H, 6.38.

Ethyl α-(3N-1,2,3,4-tetrahydro-2,4-dioxoquinazoline) -acetate (4). To a stirred solution of o-aminobenzamido-N-

glycine ethyl ester **(3)**, (23.4 g, 94.9 mmol) in methylene chloride (100 mL) at room temperature was added triphosgene (9.34 g, 31.46 mmol) in methylene chloride (50 mL). The mixture was stirred at room temperature for 1 hour and under reflux for an additional hour. The reaction mixture was cooled to room temperature and washed with sodium bicarbonate (5%, 2X50 mL). The organic layer was dried (sodium sulfate) and removal of solvent under reduced pressure gave a crystalline solid, 18.2 g (70%) of (**4**). mp 223-225°C; IR (KBr): 1745, 1719 (-C=O), 1668 (NHCO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 9.84(brs, 1H, CONH), 8.12(d, 1H, J=8.0 Hz, ArH), 7.65(m, 2H, ArH), 7.06(d, 1H, J= 8.2 Hz, ArH), 4.93(s, 1H, $-CH_2N$), 4.24(q, 2H, J= 7.0 Hz, $-OCH_2$), 1.29(t, 3H, J= 7.0 Hz, CH_3) ppm. MS m/e 248(M^+) 203, 175, 146.

Anal calcd. for $C_{12}H_{12}N_2O_4$; C, 58.06; H, 4.83. Found: C, 58.18; H, 5.10.

α-(3N-[1,2,3,4-tetrahydro-2,4-dioxoquinazoline])-acetic acid (5). The ethyl ester **(4)** (11.20 g, 45 mmol) was stirred with a solution of sodium hydroxide (5%) in methanol (100 mL) at room temperature for 6 hours. The final mixture was neutralized with Dowex 50w-x8 H^+ resin and filtered. The methanolic solution was concentrated at low pressure and the residue was redisolved in a solution of sodium hydroxide (5%) in water (50mL) and the impurities extracted with ethyl acetate (2x50mL). The basic solution was neutralized with Conc. Hcl, and gave a white solid that was dried with hot air,

8.45 g (85%) of **(5)**. mp 156-160°C; IR (KBr): 3284, (NH), 1745(-COOH), 1713(N-CO-N), 1657(NHCO) cm^{-1}; ^1H NMR ($CDCl_3$): δ 11.10(brs, 1H, COOH), 10.99 (brs, 1H, NH), 7.88(d, 1H, J= 8.0 Hz, ArH), 7.02(m, 2H, ArH), 4.58(s, 1H, $-CH_2N$) ppm. MS m/e: 220 (M^+), 176, 146, 119.

General method for the coupling of acid **(5)** with an amino acid ester to give the dipeptide **(6)**.

N'-1,2,3,4-tetrahydro-2,4-dioxoquinazolin-3N-ylacetyl tryptophan methyl ester (6a). To a solution of acid **(5)** (1.0 g, 4.55 mmol) in dry DMF was added BOP (2.01 g, 4.55 mmol), L-tryptophane methyl ester (1.57 g, 4.55 mmol) and stirred at room temperature for 3 hours. The final mixture was diluted with water (100 mL) and extracted with ethyl acetate (3X50 ml). The combined organic phases was washed with HCl (5%, 50 mL), $NaHCO_3$ (5%, 50 mL) and water (50mL), respectively. The organic layer was dried over sodium sulfate and removal of solvent under vacuo gave 1.86 (94%) of **(6a)** as colorless crystals. mp156-158°C; IR (KBr): 3383(NH), 1736($COCH_3$), 1639(NHCO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.02(brs, 1H, CONH-Ar), 9.83(brs, 1H, CH-NH-CO), 7.99 (d, 1H, J= 8.0 Hz, ArH), 7.65-7.05(m, 8H, ArH), 5.07(m, 1H, N-CH-CO), 4.74(dd, 2H, $J_1=J_2=15.9$ Hz, CH_2N), 3.60(s, 3H, OCH_3), 3.28(d, 2H, J= 5.8 Hz, CH_2-indol) ppm. ^{13}C NMR ($CDCl_3$): δ 176.2 (C=O), 167.4 (C=O), 151.1 (C=O), 139.9 (C=O), 136.6, 135.2, 128.2, 124.2, 123.0, 121.7, 119.3, 118.6, 115.8, 111.8, 109.3, 53.6, 52.6, 43.4, 28.1

ppm. ^{13}C-DEPT NMR ($CDCl_3$): δ 136.6, 135.2, 128.2, 124.2, 123.0, 121.7, 119.3, 118.6, 115.8, 111.8, 53.6 (CH); 43.4, 28.1 (CH_2); 52.6 (CH_3). MS m/e: 420 (M+), 219, 201, 130.

High resolution m/e: found 420.1425; calculated for $C_{22}H_{20}N_4O_5$ 420.1435.

N'-(1,2,3,4-tetrahydro-2-4-dioxoquinazolin-3N-ylacetyl) glycine ethyl ester (6b). (88%). mp 223-225°C. IR (KBr): 3422, 3250, 1743, 1638 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 11.02(brs, 1H, CONH), 8.15(brs, 1H, CH-NH-CO), 8.03(d, 1H, J= 8.1 Hz, ArH), 7.56-7.09 (m, 3H, ArH), 4.76(s, 2H, CH_2N), 4.18(q, 2H, OCH_2), 3.99(d, 2H, J= 5.6 Hz, CH_2-NH), 1.26 (t, 3H J= 7.0 Hz, -CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 176.1 (C=O), 158.5 (C=O), 152.3 (C=O), 144.6 (C=O), 135.0, 128.0, 122.7, 115.6, 61.1, 43.1, 41.4, 14.5 ppm. ^{13}C-DEPT NMR ($CDCl_3$): δ 135.0, 128.0, 122.7, 115.6 (CH); 61.1, 43.1, 41.4 (CH_2);14.5 (CH_3). MS m/e: 305 (M^+), 259, 203, 176, 146, 119.

High resolution m/e: found 305.1015; calculated for $C_{14}H_{15}N_3O_5$ 305.103.

N'-(1,2,3,4-tetrahydro-2-4-dioxoquinazolin-3N-ylacetyl)-phenyl alanine ethyl ester (6c). (91%), mp 208-210°C. IR (KBr): 3318, 3246 , 2965, 1733, 1674, cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.03(d, 1H, J= 8.7 Hz, ArH), 7.77(d, 1H, J= 8.0 Hz, ArH), 7.75(brs, 1H, CONH-Ar), 7.75-7.23(m, 7H, ArH), 7.25(brs, 1H, CH-NH-CO), 4.79 (dd, 2H, J_1=J_2= 18.0 Hz, CH_2N), 4.75(m, 1H, N-CH), 4.12(q, 2H, J= 7.3 Hz, O-CH_2), 1.38(t, 3H, J= 7.3 Hz, CH_2Ar), 1.19(t, 3H, J= 7.3 Hz, CH_2-CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ

181.1 (C=O), 168.2 (C=O), 150.4 (C=O), 139.9 (C=O), 135.0, 129.5, 128.5, 128.0, 126.9, 122.7, 115.2, 61.3, 54.1, 43.0, 38.0, 14.4. ^{13}C-DEPT ($CDCl_3$): δ 135.0, 129.5, 128.5, 128.0, 126.9, 122.7, 115.2, 54.1 (CH); 61.3, 43.0, 38.0 (CH_2); 14.4 (CH_3). MS m/e : 395 (M^+), 321, 219, 203, 176.

High resolution m/e: found 395.1481; calculated for $C_{21}H_{21}N_3O_5$ 395.1482.

N'-(1,2,3,4-tetrahydro-2-4-dioxoquinazolin-3N-ylacetyl) alanine methyl ester (6d). (81%), mp 256-258°C. IR (KBr): 3260, 3253, 2965, 1741, 1637, 1451 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.25(brs, 1H, CONH), 7.99(d, 1H, J= 8.0 Hz, ArH), 7.75(brs, 1H, -CONH), 7.55(dd, 1H, J_1=J_2= 7.8 Hz, ArH), 7.18(m, 2H, ArH), 4.69(dd, 2H, J_1=J_2= 15.6 Hz, CH_2N), 4.42(q, 2H, J= 7.0 Hz, -NCH), 4.14(q, 2H, J= 7.0 Hz, OCH_2), 1.39(d, 3H, J= 7.3 Hz, CH_3), 1.26(t, 3H, J= 7.3 Hz, C-CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ 191.2 (C=O), 167.5 (C=O), 151.2 (C=O), 139.8 (C=O), 135.0, 128.0, 122.7, 115.6, 61.2, 48.4, 43.0, 18.2, 14.9. ^{13}C-DEPT NMR ($CDCl_3$): δ 135.0, 128.0, 122.7, 115.6, 48.4(CH); 61.2, 43.0 (CH_2); 18.2, 14.9 (CH_3). MS m/e: 319 (M^+), 246, 175, 146, 119.

High resolution m/e: found 319.1160; calculated for $C_{15}H_{17}N_5O_3$ 319.1169.

N'-(1,2,3,4-tetrahydro-2-4-dioxoquinazolin-3N-ylacetyl) proline methyl ester (6e). (78%), mp 178-180°C. IR (KBr): 3439, 3197, 2955, 1734, 1672 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 10.34(brs, 1H, CONH), 7.99(d, 1H, J= 8.0 Hz, ArH), 7.45-7.05(m, 3H, ArH), 5.03(dd, 2H, J_1=J_2= 15.7 Hz, CH_2N), 4.60(m, 1H,

NCHCO-proline), 3.69(s, 3H, OCH_3), 2.26-1.96(m, 6H, CH_2 proline ring) ppm. ^{13}C NMR ($CDCl_3$): δ 173.6 (C=O), 167.4 (C=O), 151.3 (C=O), 139.2 (C=O), 135.4, 128.6, 123.4, 115.8, 59.2, 52.9, 47.0, 42.7 (32.1), 29.7, 25.47 (23.0). ^{13}C-DEPT NMR ($CDCl_3$): δ 135.4, 128.6, 123.4, 115.8, 59.2(CH); 47.0, 42.7 (32.1), 29.6, 25.5 (23.0) (CH_2); 52.9 (CH_3). MS m/e: 331 (M^+), 203, 175, 146.

High resolution m/e: found 331.1156; calculated for $C_{16}H_{17}N_3O_5$ 331.1169.

Acknowledgement: We gratefully acknowledge support of this project by CONACYT (GRANTS No.1528-E9207 and No. 1502-E9201) and thank San Diego State University for Spectral Data. We thank Dr. R. Wandler, Aldrich Chemical Co., for the IUPAC nomenclature.

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(Received in the USA 11 December 1997)