PR05.01.16 STRUCTURE OF THREE BIOACTIVE FURANIC BIDERIVATIVES. Julio Duque Rodríguez*, Ramón Pomés Hernández, National Center for Scientific Research. P.O.Box 6990. Havana. Cuba, Hector Novoa de Armas, Center of Pharmaceutical Chemistry. P.O.Box 16042, Havana, Cuba, Raúl Alfredo Toscano, Institute of Chemistry, UNAM. 04510, México, D.F.

1-Furfuryl-(6-Amino-3-Cyano-4-Methyithio)-5NFurfurylamidePridin-2-One.H_2O,$C_{20}H_{20}O_4N_4S.H_2O$, Mr= 252.3, Triclinic, P-1, a= 7.406(2), b= 11.473(2), c= 12.543(4) Å, α= 81.76(3), β= 79.62(3), γ= 71.20(3)o,V= 7996.1(5) Å^3, Z=2, Dx= 1.37 mg/m^{-3}, μ= 1.70 mm^{-1}, R=0.06; N-Bencyl-(2-Cyano-3-(2' Furyl)-Acrylamide), $C_{15}H_{12}N_2O_2$, Mr= 252.3, Triclinic, P-1, a= 9.805(2), b= 27.542(3), c= 5.010(4) Å, α= 95.64(2), β= 104.83(2), γ= 88.52(2)°, V= 1301.5(2) Å^3, Z=4, Dx= 1.29 mg/m^{-3} , μ= 0.67 mm^{-1}, R= 0.074 and Furfuryl-[2-Cyano-3-Furfuryliden]-Acrylamide, $C_{13}H_{10}N_2O_3$, Mr= 242.23, Triclinic, P-1, a= 5.311(1), b= 9.495(1), c= 11.442(2) Å, α= 94.13(2), β= 93.79(2), γ= 93.60(2)o, V= 572.9(3) Å^3, Z= 2, Dx= 1.39 mg/m^{-3}, μ= 0.10 mm^{-1}, R= 0.041. Have been investigated by single crystal and obtained by synthetic procedures or as constituents of naturally occurring molecules, have been studied and used as drugs showing antimicrobiotic hypotensive and antitumor activity (Bartroli, Lami, Quincoses & Peseke, 1984). The chemical and biological characteristics of these substances can be directry related to the conformation of their molecules and the presents sustituents. The structures were solved used SHELXTL-Plus (Direct Methods) and refinement by full-matrix least-squares.

Bartroli, R., Lami, L., Quincoses, J. & Peseke, K. Cuban Patent. No 21789, Havana, Cuba, 1984

PS05.01.17 X-RAY AND MOLECULAR MODELLING STUDIES OF NEW POTENTIAL ALDOSE REDUCTASE INHIBITORS. D. Tranqui(1), M. Cussac(2), P. Fresneau(2), G. Leclerc(2), and A.Vegas(3), (1)Lab. de Cristallographie-CNRS associé à l' UJF, BP 166, 38042 Grenoble Cedex, France, (2)Lab. de Chimie Therapeutique et Organique - Groupe. de Pharmacochimie Moléculaire, UFR de Pharmacie de Grenoble, UJF, BP 138, 38243 Meylan, France. (3)Instituto Rocasolano, CSIC, Serrano, 119, E-28006, Madrid, Spain

Several derivatives of 5-(2-Naphtylmethylene)-4-oxo-2-thioxothiazolidin-3-yl acetic, NOTA, were identified as potential inhibitors of aldose reductase. The 1-OCH_3 substituted form of NOTA have been observed to have an inhibitor-aldose-reductase activity one order better than that of the non-substituted derivative. Attempts to model inhibitor-enzyme interaction using the geometry-and-energy-optimised atomic coordinates of NOTA, showed the non-substituted form of NOTA fitted snugly in the hydrophobic active site of aldose reductase while binding of the substituted form and aldose reductase may require substantial conformational changes of the latter.

These results incite us to verify the geometry of NOTA molecules used in the previous modelling studies. Single crystals of NOTA were grown and their crystal and molecular structure determined(*). X-ray structural features of both forms of NOTA are reported and their marked differences with those of molecular mechanic models are highlighted and discussed in terms of molecular packing force and molecule-solvent interaction.

Calculated (ΔH) for both models shows that they are each other energetically accessible suggesting our docking results using the molecular mechanic model of NOTA remain valid. Preliminary modelling results of inhibitor-enzyme interaction using the X-ray structure model of NOTA appear to confirm this point. Possible hydrophobic interaction scheme of NOTA with aldose reductase is proposed. (*)Space group P1 a = 7.320(5), b = 8.307(5), c = 16.399(6) Å, α = 81.23(7)°, β = 98.52(6)°, γ = 104.46(8)°, R-factor = 0.05 and Space group C2/c, a = 34.199(9), b = 5.222(3), c = 23.178(8) Å, β = 98.51(6)°, R-factor = 0.06 for substituted and non-substituted derivatives, respectively.

PS05.01.18 DIPROLINE ß-TURN MIMICS: SUBSTITUTION EFFECTS ON ALLOWED CONFORMATIONS. William H. Ojala[a], Paul W. Baures[b], Rodney L. Johnson[b], William B. Gleason[b], [a]University of St. Thomas, St. Paul, MN 55105, USA, [b]University of Minnesota, Minneapolis, MN 55455, USA

Diproline segments have the potential to serve as ß-turn mimics with substitution at the α- and ß- positions providing a means of mimicking the side-chains of turn residues. Although the ß-turn conformations of unsubstituted diprolyl segments have previously been explored, the effect of prolyl ring substituents upon the conformational preferences of diprolyl templates has not been studied. To address this issue the diproline peptides tosyl-*trans*-3-Me-D-Pro-D-Pro-NH_2 (**I**), tosyl-*cis*-3-Me-D-Pro-D-Pro-NH_2 (**II**), and Boc-L-Pro-*trans*-3-Me-L-Pro-D-Pro-NH_2 (**III**) have been synthesized and their crystal structures determined. In addition, the crystal structure of Boc-L-Tic-D-Pro-NH_2 (**IV**), where a Tic (1,2,3,4-tetrahydro-3-isoquinolinyl) residue is substituted for a prolyl residue, has also been studied. The results show that in homochiral diprolines a 3-methyl group in a *cis* relationship with the carbonyl group induces a conformation which is different from that favored in the corresponding unsubstituted diproline.

Crystal Data: (**I**): $C_{18}H_{25}O_4N_3S$, $P2_1$, a=7.652(3), b=13.400(5), c=9.725(3) Å, ß=108.06(3)°, R=0.074; (**II**): $C_{18}H_{25}O_4N_3S$, $P2_1$, a=8.781(2), b=6.107(2), c=17.374(1) Å, ß=91.38(1)°, R=0.040; (**III**): $C_{21}H_{34}O_5N_4 \cdot 1/2H_2O$, $P2_1$, a=14.675(3), b=10.106(5), c=15.994(5) Å, ß=99.64(2)°, R=0.050; (**IV**): $C_{20}H_{27}O_4N_3$, $P2_12_12_1$, a=10.598(3), b=29.245(2), c=6.517(2) Å, R=0.036.

PS05.01.19 BIPHALIN, A HIGHLY POTENT DIMERIC ENKEPHALIN ANALOG. Judith. L. Flippen-Anderson, Jeffrey Deschamps and Clifford George, Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D. C. 20375-5341; Victor J. Hruby, Guigen Li, Andrzej W. Lipkowski, and Aleksandra Misicka, Department of Chemistry, University of Arizona, Tucson, AZ 85721

One of the major achievements in the area of opioid research in the past twenty years has been the elucidation of multiple opioid receptors (μ, κ, δ) In the absence of direct structural information for these receptors current structure activity studies still center on understanding the effects of conformational changes on the opioid ligands. Structural modifications of endogenous ligands such as enkephalin have produced compounds with enhanced receptor selectivity, biological stability and antinociceptive potency. Most modifications of the opioid ligands have involved changes which reduce the flexibility of the molecule thereby significantly lowering the number of possible conformations to be studied. Combining X-ray results with modeling and NMR studies can provide a more reliable picture of the biological conformation of a highly potent ligand than one could get from any single analytical method.

In this paper we are reporting the solid state structure of biphalin [(Tyr-DAla-Gly-Phe-NH)2], a highly potent site specific dimeric enkephalin analog. Biphalin is formed by replacing the Gly 2 residue in enkephalin with a D-Ala residue and replacing the C-terminal residue by a second identical enkephalin fragment connected by a hydrazine bridge. Biphalin displays an unusual activity profile in that it shows similar binding affinity at both μ and δ receptor sites. When administered i.c.v. it is more than 200 times as potent as morphine in antinociception. However, both μ and δ antagonists can block its antinociceptive effects. The X-ray structure revealed distinctly different conformations for the two halves of the dimer which is consistent with its activity profile. Comparison with the structures of known μ and δ agonists clearly reveals which half of the molecule binds at each receptor site.

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