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In order to make clear the structural function of C-terminal amide group of endomorphin-2(EM2:YPFF-NH_2) the conformations of EM2 and its C-terminal free acid (EM2OH:YPFF-OH) were analyzed by ^{1}H-NMR spectroscopy and X-ray crystal analysis.

The NMR spectra in trifluoroethanol(TFE) and water solvents indicated that both peptides were in equilibrium between the *cis*- and *trans*-rotamer around Tyr-Pro peptide bond, respectively. However they take almost trans rotmer in dodecylphosphocholine(DodPCho), micells, except for the EM2OH in water solvent at pH5.2. With the use of the proton-proton distance derived from ROESY cross peaks, possible fifty 3D structures are generated by dynamical simulated annealing method and were classified in four groups of two open and two fold conformers according to the folding of backbone structure.

On the other hand, two independent conformational isomers per asymmetric unit and seven water molecules were existed in the crystal structure of EM2OH. Both conformers were crystallized as neutral zwitterionic forms and took a folded-form with *cis*-configuration in around Tyr-Pro peptide bond.

Based on the conformational features of EM2 and EM2OH in solution and solid state, we would like to discuss the possible function of C-terminal amide group.

Keywords: NMR, X-ray conformation analysis, molecular conformation

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New Monocyclic and Acyclic hNK-2 Antagonists Retaining the β-turn Feature

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The human tachykinin NK-2 receptor is a promising target for important pathologies at respiratory, gastrointestinal and genitourinary level, where this receptor is mainly localized. Several peptidic and non-peptidic antagonists to this receptor are known, and a few of them are undergoing clinical studies. The bicyclic peptide MEN10627 [1] is one of the most potent antagonists for the neurokinin NK-2 receptor. However its low bioavailability prevents it to be used as a drug. We have already shown how, by selecting a proper part of its structure, i.e. that featuring the β-turn, it is possible to obtain simpler peptides still retaining their activity. The monocyclic series which originated was designed on the basis of theoretical assumptions with the support of modeling [2]. In the present contribution we show how subsequently that rationale has been experimentally validated through X-ray structure determination of a novel monocyclic hNK-2 antagonist (MEN13365). Moreover the same structural features have been retained in MEN15596, which belongs to a new non cyclic series of hNK-2 antagonists developed to circumvent the low oral bioavailability. Antagonists from this last series are presently undergoing preclinical development.

[1] Pavone V., Lombardi A., Nastri F., Saviano M., Maglio O., D'Auria G., Quartara L., Maggi C.A., Pedone C., *J. Chem. Soc. Perkin Trans. 2*, 1995, 987, *and references therein*. [2] Fedi V., Altamura M., Balacco G., Canfarini F., Criscuoli M., Giannotti D., Giolitti A., Giuliani S., Guidi A., Harmat N.J.S., Nannicini R., Pasqui F., Patacchini R., Perrotta E., Tramontana M., Triolo A., Maggi C.A., *J. Med. Chem.*, 2004, **47**, 6935, *and references therein*.

Keywords: molecular scaffold, β-turn, tachykinin

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Absolute Configuration of the κ-Agonist Salvinicin A

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Salvinorin A and B are potent κ selective opioid receptor agonists from *Salvia divinorum*. An infusion prepared from fresh or dried leaves is used by the Mazatec Indians to stop diarrhea, relieve headache and rheumatism, and is also used in traditional spiritual practices to produce "mystical" or hallucinogenic experiences.[1] Young adults and adolescents have begun to smoke the leaves and leaf extracts of the plants to induce powerful hallucinations.[2] The stereochemistry of Salvinorin has not previously been determined. In an effort to determine the sterochemistry of this opioid agonist a 3,4-dichlorobenzoyl derivative was prepared. Single crystal x-ray diffraction was able to unambiguously determine the absolute configuration of this dichloro derivative and by extension that of Salvinorin A.

[1] Valdes III L. J., Diaz, J. L., Paul A. G., *J. Ethnopharmacol.*, 1983, **7**, 287-312. [2] Hazelden Foundation, *www.research.hazelden.org* , 2004.

Keywords: κ-opioid receptor, structure, stereochemistry

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Crystal Structures of Cholesterol Derivatives

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We have undertaken a series of crystal structures of the esters, carbonates and ethers of cholesterol. These are cholesteryl formate, pentanoate, hexanoate, heptanoate, crotonate, isobutyrate, aniline, 2,4-dichlorobenzoate and hemisuccinate, cholesteryl phenyl acetate, methyl carbonate, ethyl carbonate, propyl carbonate, butyl carbonate, isobutyl carbonate, isopropyl carbonate, pentyl carbonate, hexyl carbonate, crotyl carbonate, cholesteryl ethyl ether, isopropyl ether and methyl ether.

Among these structures, (1) cholesteryl ethyl carbonate, propyl carbonate, crotyl carbonate, crotonate are isostructure each other, (2) cholesteryl pentyl carbonate, hexyl carbonate, hexanoate, heptanoate are also isostructural,

These structures are remarkable in forming layer structures in which the central region of the layers, composed largely of semi-rigid cholesteryl groups is closely packed and the packing of the flexible fatty acid or carbonate chains and the isoprenoid tail of the cholesterol form the interface region between layers. Some of the crystals show the liquid crystalline states. Typical packing modes will be discussed.

Keywords: cholesteryl ester, cholesteryl carbonate, cholesteryl ether

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Structure and Tautomerism of Mercapto-1,2,4-triazole Derivatives in the Solid State

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Molecular and crystal structures and tautomerism of new mercapto-1,2,4-triazole derivatives, which are structurally labile compounds capable to exist in different tautomeric forms, are discussed. X-Ray single crystal diffraction experiments show the existence of only 1*H*-triazole tautomer in crystal. As a result of our investigations it can be concluded, that for 3,5-substituted 1,2,4-triazoles usually crystallizes the tautomer, where hydrogen atom is bonded with the nitrogen (one of two neighbouring) situated near the electronodonor group, that is 3-R_A-5-R_D-1,2,4-(1*H*)-triazole. For 3-phenyl-5-mercap-to-1,2,4-triazole two thion-thiolic tautomers were found in one crystal: two molecules of four symmetrically independent ones are 3-phenyl-4,5-dihydro-(1*H*)-1,2,4-triazole-5-tion tautomers, and the rest are 3-phenyl-5-mercapto-(1*H*)-1,2,4-triazole. The asymmetric part of the unit cell of 3(5)-(2-hydroxyethyl)thio-1,2,4-triazolinium oxalate consists of two cation-anion pairs. The two cations are the endocyclic tautomers: one of them is 3-(2-hydroxyethyl)thio-(1*H*),(4*H*)-1,2,4-triazolinium cation and the other is 5-(2-hydroxyethyl)thio-(1*H*),(4*H*)-1,2,4-triazolinium cation. The

hydrogen bonds system (intra- and intermolecular ones) and crystal packing are also discussed. The crystal packing are stabilized by π-π-interactions between benzene rings and/or triazole heterocycles. The packing coefficient and solvent accessible potential area in crystal were also analyzed.
Keywords: triazoles, X-ray structure, tautomerism

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An Investigation of Interactions in Barakol Complexes
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Barakol has various interactions that contribute to its biological activities. This work presents the first successful crystal structure determination of anhydrobarakol and its analogues. Anhydrobarakol and anhydrobarakol hydrochloride were crystallized in a monoclinic system, space group $P2_1/c$ and $P2_1/n$, $Z = 4$ with unit cell parameters a = 13.2280(7), b= 6.8738(2) , c = 19.7879(9) Å, β = 127.013(2)° and a = 12.2547(2), b = 8.051(2) , c = 12.8133(2) Å, β = 99.514(1)°, respectively. The novel 1:1 molecular complexes of barakol and carboxylic acid (phthalic acid and 3-hydroxybenzoic acid) were synthesized and charactherized by spectroscopic and X-ray crystallographic techniques. Electrostatic effects, electron delocalization, and intermolecular interactions in the barakol ring system were investigated. The X-ray crystallographic studies revealed that the barakol-phthalate complex exists in an ion-pair complex. The formation of barakol-phthalate ion-pair complex is stabilized by the complementary of ion-ion interaction,π-π interaction and hydrogen bonding. The barakol-3-hydroxybenzoic acid complex is a π-π molecular complex. The co-crystallization of barakol- 3-hydroxybenzoic acid complex is solely stabilized by π-π interactions. The spectroscopic studies including IR, ^{1}H-NMR and UV-visible are consistent with the results from the X-ray analysis.
Keywords: barakol, X-ray diffraction, spectroscopic method

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Amino Acids at High Pressure
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The use of pressure to perform structural studies has been of important use to many areas of research, from Physics to Geochemistry. However, pressure studies have become a new notable tool in Chemistry and Biology to study the structure of small compounds. The main reason for this is the necessity of a better understanding of different processes, which happen even at extreme conditions of pressure, such as the existence of life in the deep ocean. Thus, small molecules may play important roles in these biological processes and therefore, a good knowledge of their structural features could be essential to explain how they happen.

In this work we are exploring the behaviour of amino acids structures at high pressure. Changes in pressure have been known to induce conformational changes in small molecules. We are trying to extend this research to the larger amino acids.

We have been working, principally, with L-glutamine, L-asparagine monohydrate, L- glutamic acid and L-aspartic acid. It was found that by applying pressure the cell parameters were reduced but no structural rearrangement was found up to pressures of 50-60 kbar. *Ab initio* computational studies were then performed to establish a possible relationship between the energetics of the hydrogen bonding with their compressibility.
Keywords: high-pressure crystallography, amino acids, *ab initio* calculations

P.05.05.4
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Structural Studies on ST1481, Gimatecan, a 7-substituted Camptothecin with Anti-tumor Activity
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Camptothecins are a class of of active antitumor agents that target the nuclear enzyme DNA topoisomerase I, inhibiting single strand religation. Several camptothecin derivatives are in clinical trials [1]. The substitution of position 7 by lipophilic side chains seems to be important as it increases cytotoxic potency, helps in the drug delivery and in stabilizing the DNA-topoisomerase I cleavable complex that forms in ST1481 presence and is is as part of its mechanism of action. Of 44 compounds synthesized [1] the most potent derivative contains a $CH{=}NOC(CH_3)_3$ substituent and its X-ray crystal structure has been determined. The unit cell parameters are space group: $\boldsymbol{P2_1}$, a = 12.131(8)Å, b = 6.712(5)Å, c = 13.817(8)Å, β = 96.05(3). This derivative (gimatecan) is orally administered, and thus, represents a significant advantage compared to other camptothecins. *Ab initio* studies have been performed using Density Functional Theory to analyze the lactone ring opening, a critical step in the interaction with topoisomerase I.

[1] Dallavalle S., Ferrari A., Biasotti B., Merlini L., Penco S., Gallo G., Marzi M., Tinti M. O., Martinelli R., Pisano C., Carminati P., Carenini N., Beretta G., Perego P., De Cesare M., Pratesi G., Zunino F., *J. Med. Chem.*, 2001, **44**, 3264.
Keywords: camptothecin, anti-tumor, topoisomerase I inhibitor

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Hydrogen Bonding and Absolute Configuration in Manzamine Alkaloids
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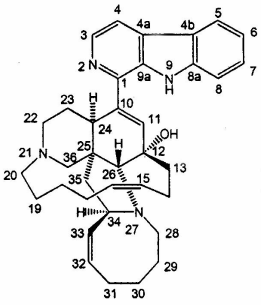
The manzamines, a class of sponge-derived alkaloids, have a complex polycyclic system with 5, 6, 8, and 13-membered rings and a β-carboline substituent. They show promising antibacterial, antitumor, and antimalarial activities, and moderate activity against HIV-1. Manzamine A (**1**) forms solvates with MeOH and acetone. Formation of the hydrochloride of 8-OH manzamine A (**2**) by N27 protonation allows absolute configuration determination. The Cl^- accepts hydrogen bonds from all four donors of one cation. Manzamine F (**3**) also has an 8-OH group and C31=O rather than C32=C33, and forms a mixed solvate with H_2O and MeCN. Ircinol A (**4**) lacks the β-carboline group, but has CH_2OH at C10, and crystallizes with Z'=3.



Keywords: marine natural products, absolute structure, hydrogen bonding

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The Structure of Protocyanin, a Complex Pigment from Blue Cornflower
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