Structural chemometrics applied to small bioactive molecules complexed with their protein receptors (The examples)

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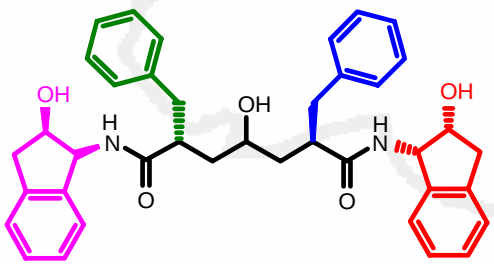
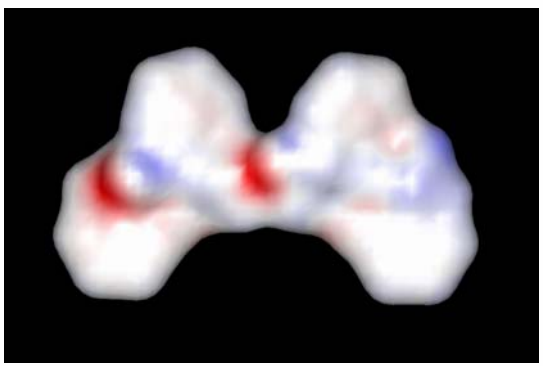
EXAMPLE 1: A PEPTIDIC HIV-1 PROTEASE INHIBITOR L-700,417 IN INTERACTION WITH THE PROTEASE

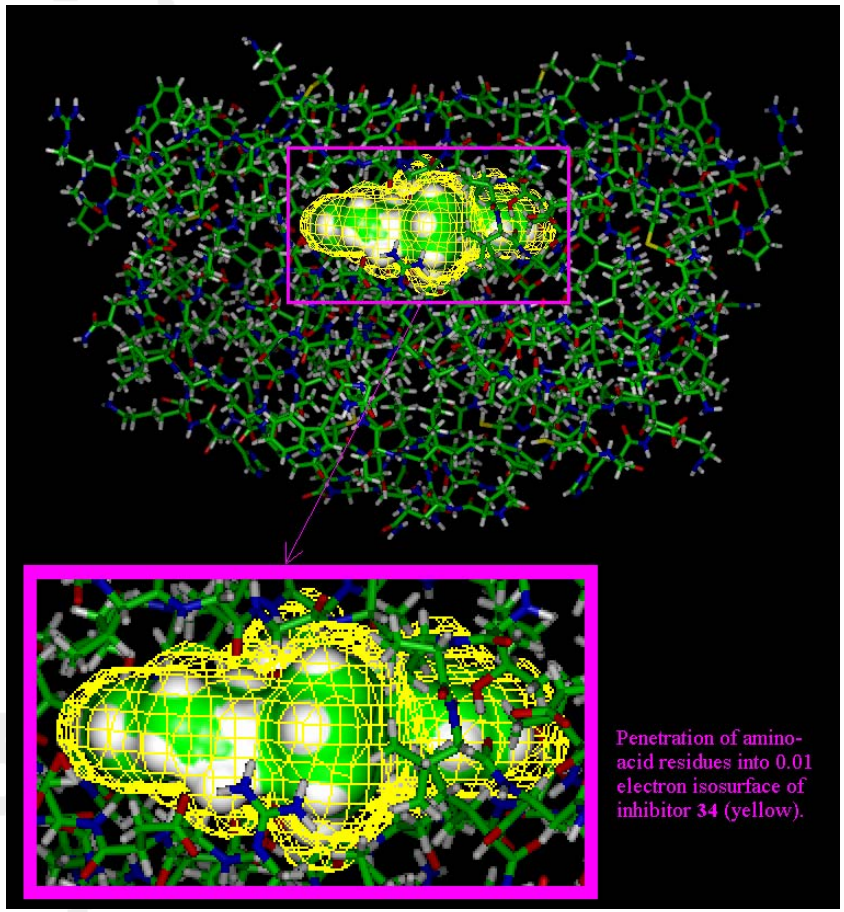
R. Kiralj, M. M. C. Ferreira, *J. Mol. Graph. Mod*., 21, 2003, 499.

[PDB: 4PHV]





INHIBITOR L-700,417



HIV-1 PROTEASE/L-700,417 COMPLEX

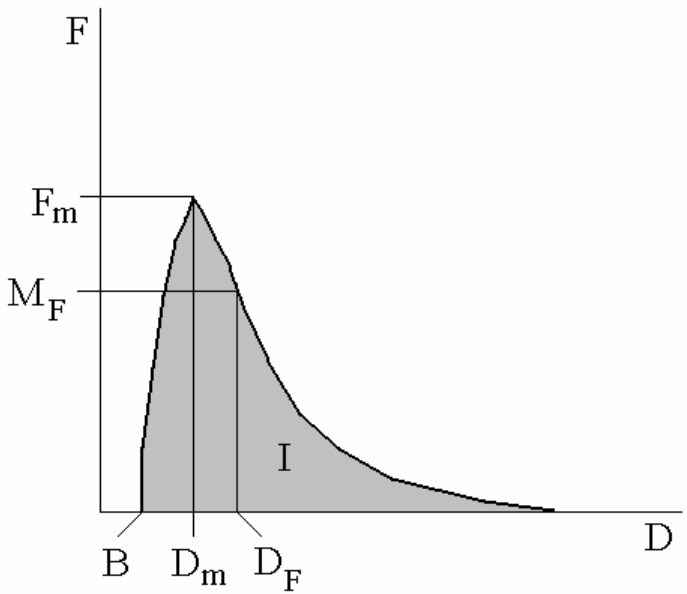
Groups	F_m	D_m/Å	I	M_F	D_F/Å	B/Å
All groups	100%	1.6	100%	82%	3.1	3.1
H-bond groups	66%	2.3	47%	45%	2.8	1.6
Hydrophobic groups	82%	2.7	80%	82%	3.2	1.7
Aromatic groups	60%	3.1	62%	56%	3.4	1.8
Benzene carbons	29%	3.5	28%	17%	4.0	2.5
Polar groups	82%	2.4	70%	54%	3.0	1.6

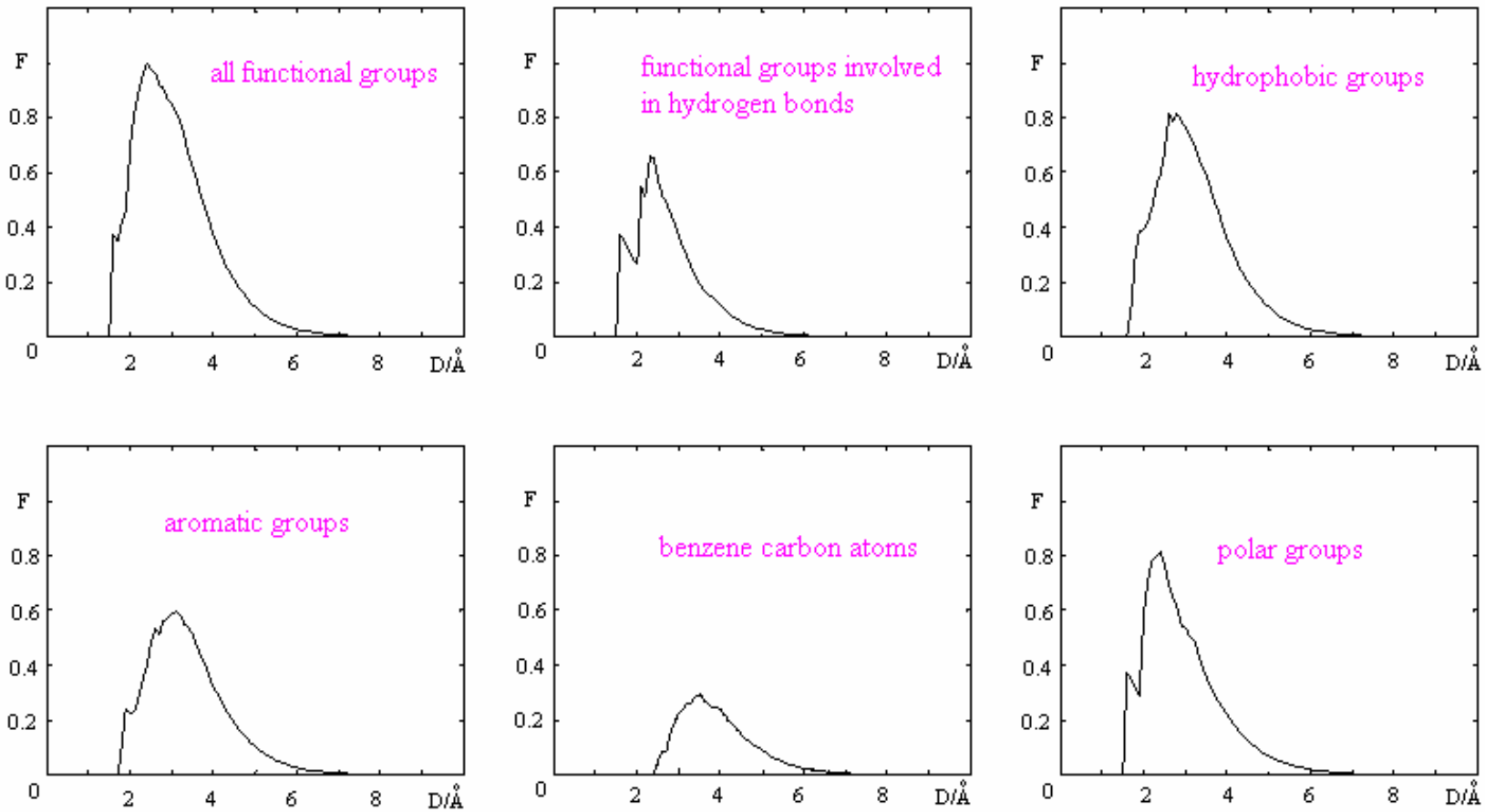
$\rho = a_1 + b_1 \log D$

$V^{1/3} = a_2 + b_2 \log \rho$

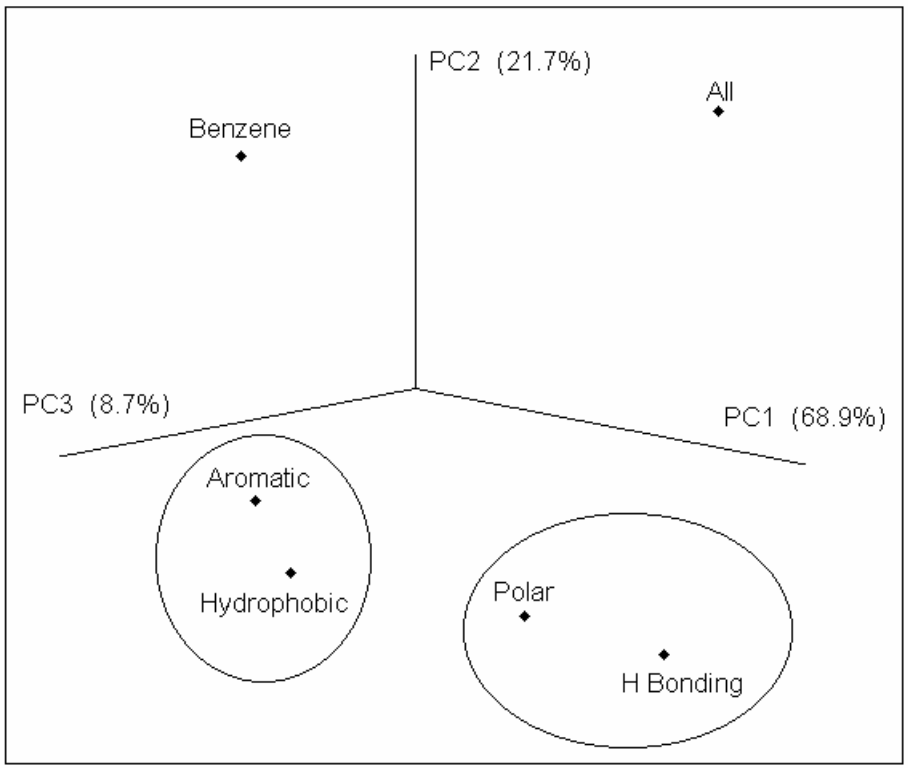
$F = (\rho\tau)^{1/2} (V - V_0), \quad \tau = N_{ve} (V - V_0),$

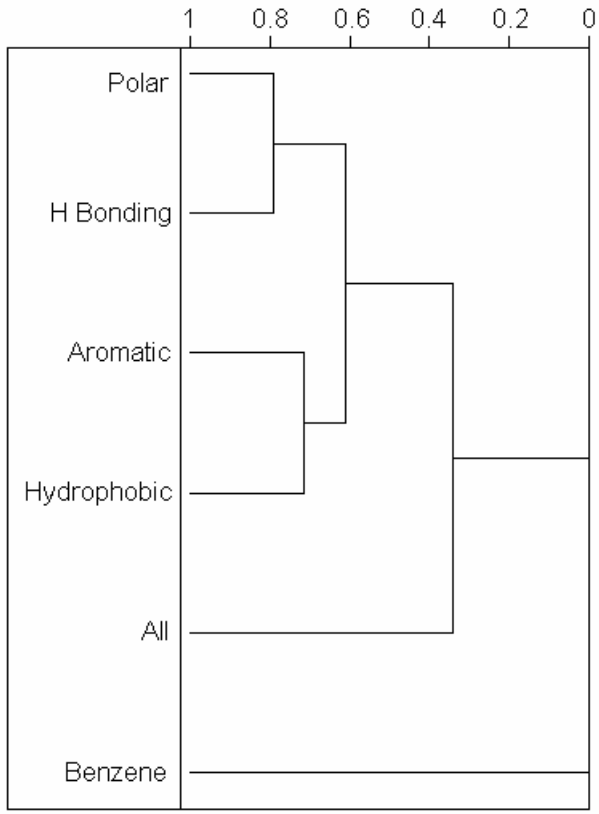
ρ – overall ligand elec. density at D
V_0 – ligand molecular volume
V – volume inside D
N_{ve} – No. val. electrons (protein+H_2O)
D – cut-off from the inhibitor surface





Function F as a measure of the overlap of the electron densities of the inhibitor and protease

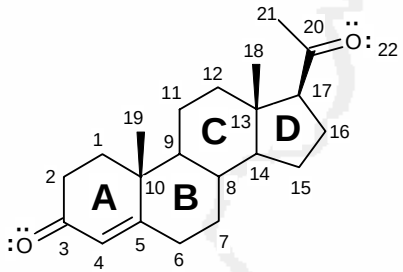


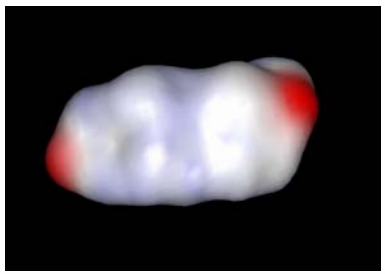


The 3D scores plot from Principal Component Analysis (PCA, left) and the dendogram with samples from Hierarchical Cluster Analysis (HCA, right) applied to variables F_m, D_m, I, M_F, D_F and B.

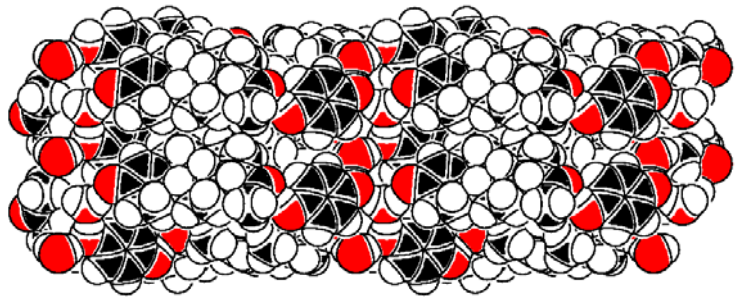
EXAMPLE 2: PROGESTERONE IN INTERACTION WITH PROGESTERONE RECEPTOR

R. Kiralj, M. M. C. Ferreira, *QSAR Comb. Sci*., 22, 2003, 430.

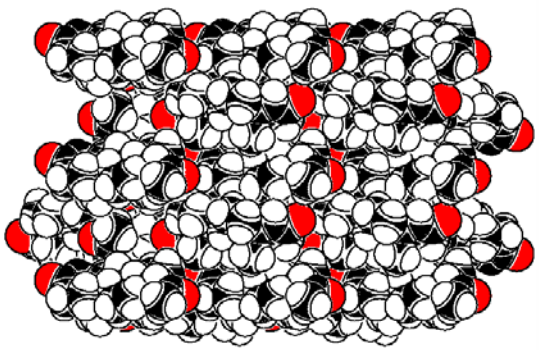




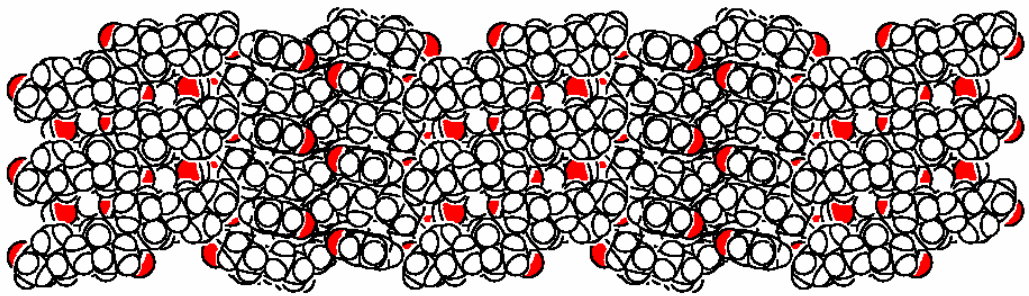
PROGESTERONE



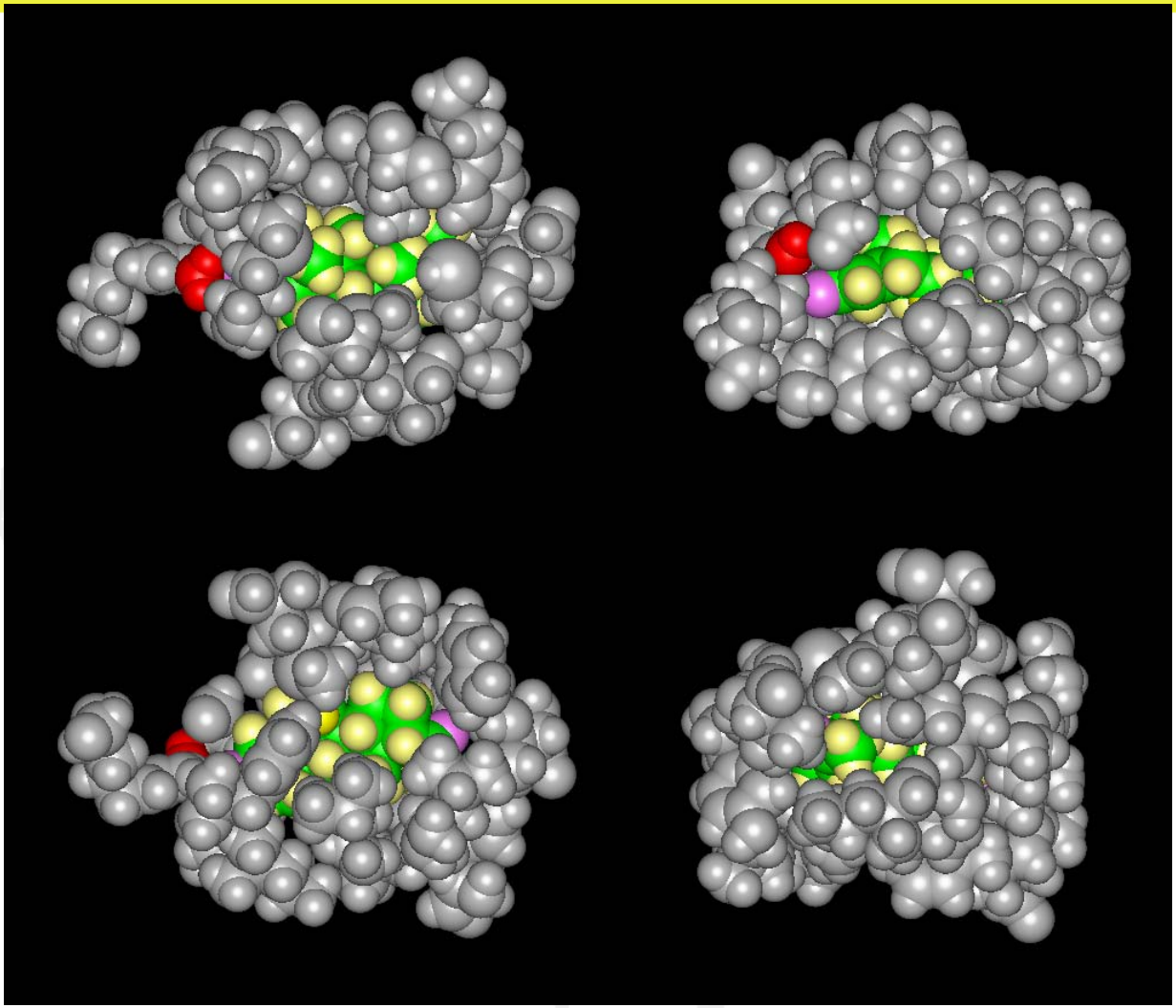
Progesterone -hydroquinone complex hydrate:
CSD – PRORES



Progesterone:
CSD – PROGST10



Progesterone-resorcionol complex:
CSD – KEFBEC



Progesterone (C: green; H: yellow; O; pink) at the active site of progesterone receptor (PR, gray; water: red). Four free pockets are visible - hydrogen substitution possible. [PDB: 1A28]

H	D_H/Å	D/Å	η	η_H	H	D_H/Å	D/Å	η	η_H
H4	2.5	3.3	55	143	H21a	2.2	3.0	62	147
H6-β	3.1	3.5	52	139	H12-α	2.4	3.0	44	116
H6-α	2.9	3.6	53	135	H12-β	2.3	2.3	43	118
H7-β	2.7	3.4	43	94	H11-β	2.5	3.3	32	98
H7-α	2.8	3.2	37	79	H11-α	2.5	2.5	46	126
H8	3.0	3.0	29	56	H1-α	2.9	3.4	47	161
H9	3.0	3.9	30	68	H1-β	2.8	2.8	56	161
H14	3.5	4.4	32	74	H2-β	2.4	2.5	55	154
H15-β	3.1	3.6	47	120	H19a	2.4	2.6	49	146
H15-α	2.4	3.0	51	119	H18b	2.4	3.1	36	97
H16-β	2.4	3.1	50	130	H18a	2.7	3.2	29	82
H16-α	2.5	2.8	53	132	H18c	2.6	3.1	41	113
H17	2.7	3.5	43	95	H19b	2.8	3.4	43	117
H21c	2.5	3.3	62	168	H2-α	2.3	3.0	69	184
H21-β	2.2	2.2	58	139	H19c	2.7	3.5	41	110

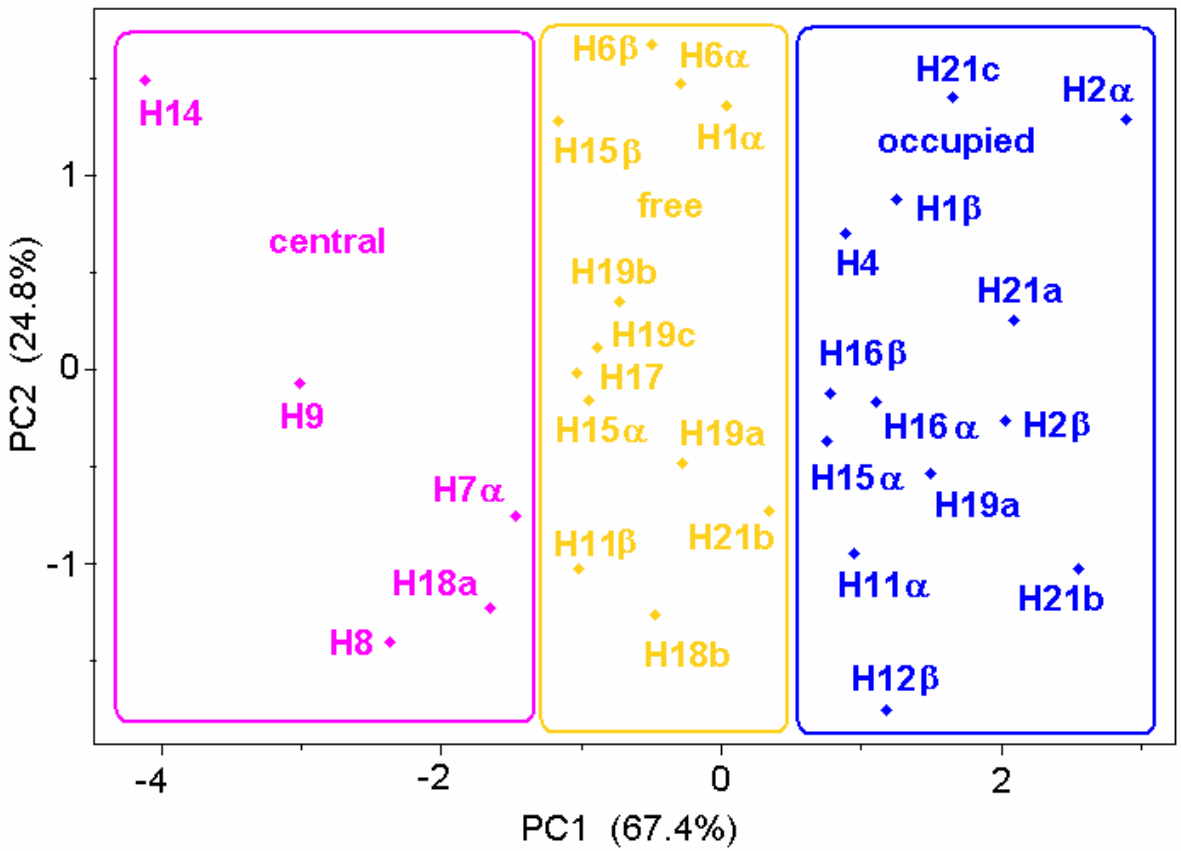
Four variables were generated using a monomer unit of PR complexed with a progesterone molecule (PDB: 1A28), inside 5.5 Å cut-off distance from progesterone molecular surface:

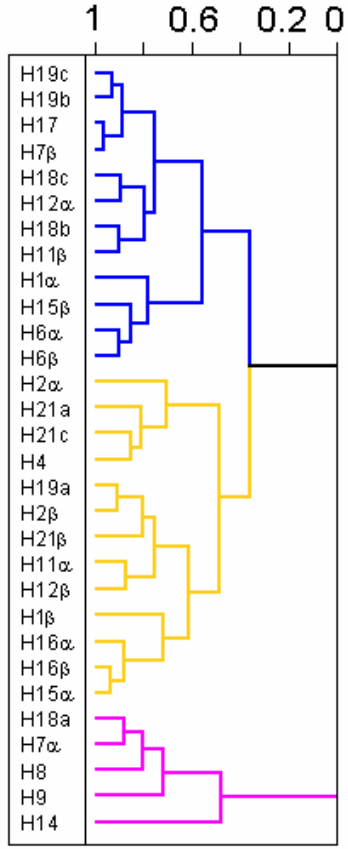
D_H – No. all PR+water atoms

D – No. non-H PR+water atoms

η_H – No. valence electrons from all PR+water atoms

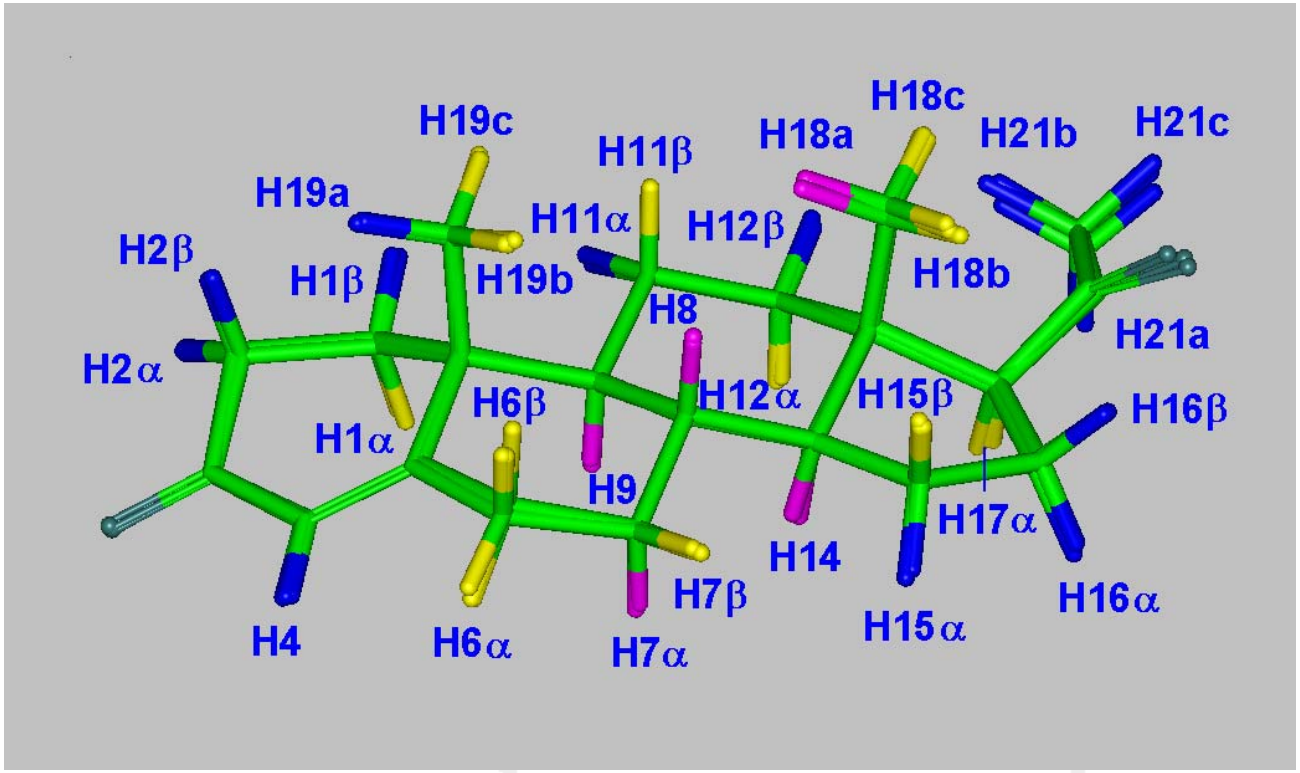
η – No. valence electrons from non-H PR+water atoms





Principal Component Analysis (left) and Hierarchical Cluster Analysis (right) – three clusters of progesterone hydrogens:

-central (hidden,non-accessible, at ring junction) → substitution ???
-occupied (no free space around) → substitution ?
-and free (there is a free space around) → substitution



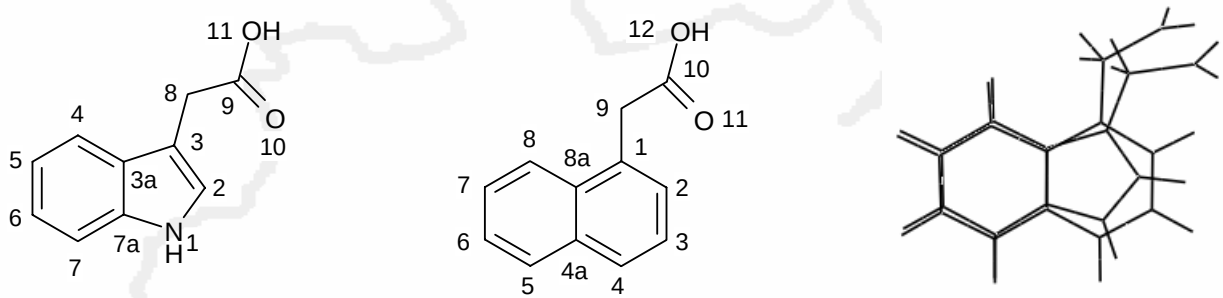
Superimposed X-ray (PDB: 1A28) and *ab initio* geometries - high degree of rigidity;

Central (pink), occupied (blue) and free (yellow) hydrogens;

Substitution of hydrogens H6α, H6β, H11(α, β), H17α, H18(a-c) → variation of progestational activity → treatment of diseases, post-menopausal difficulties and hormonal disorders

EXAMPLE 3: 1-NAPHTHALENIC ACID (NAA) IN INTERACTION WITH AUXIN BINDING PROTEIN 1 (ABP1)

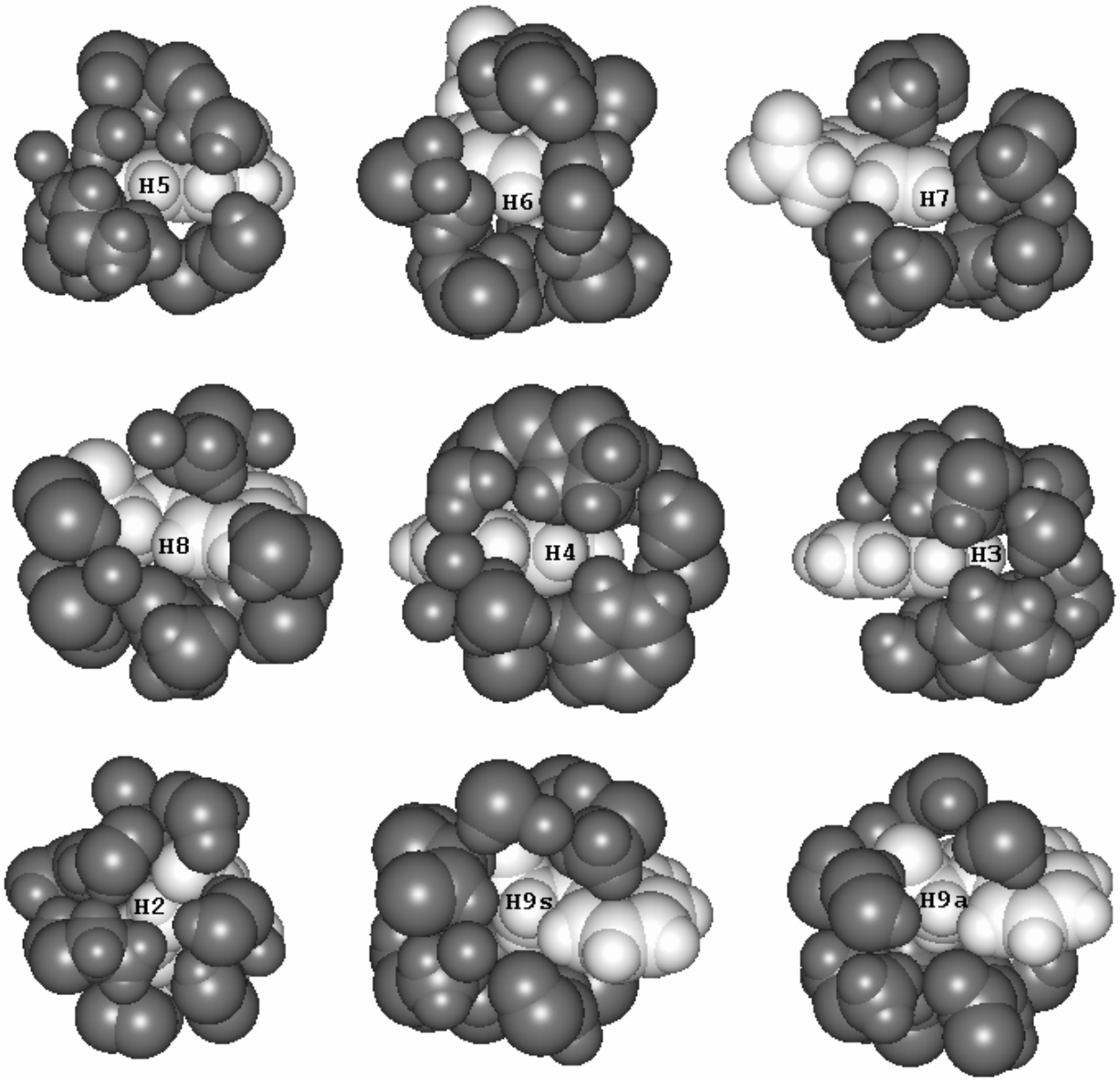
M. M. C. Ferreira, R. Kiralj, *Croat. Chem. Acta*, submitted.



Indole-3-acetic acid (IAA, left), NAA (middle) and superimposition.

Substitution	Higher activity (5.6)	IAA like activity (5.4 – 5.5)	Lower activity (≤ 5.3)	Pocket size
2	–	–	Me	small
4	F, Me	Et, Cl	–	medium
5	–	F, Cl, Me, Et, Pr, Bu	Br	large
6	–	F, Me, Et	–	medium
7	–	F, Cl, N, Me, Et	–	medium or large

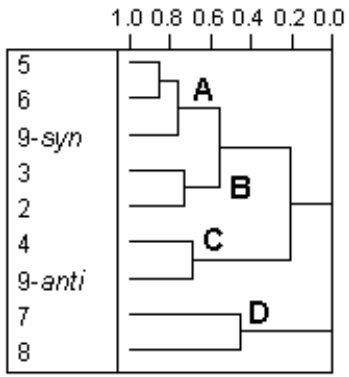
Biological activity of auxins (IAAs) and probable size of pockets in ABP1.

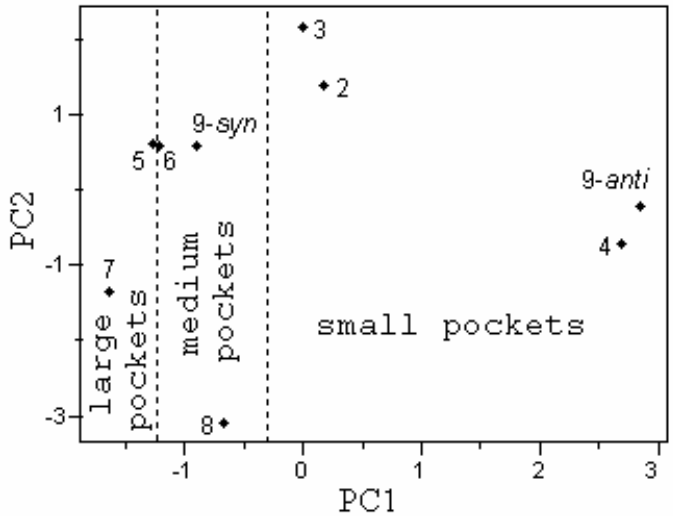


NAA at the active cavity of ABP1 [PDB: 1LRH].

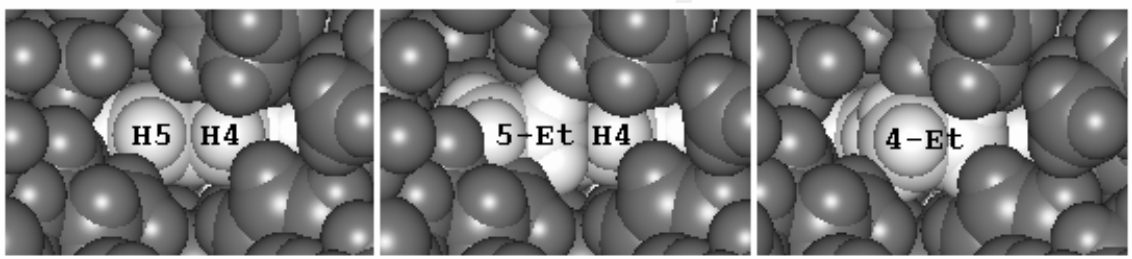
NAA[b]	IAA eq.[c]	Count1	Count2	Min. d	Count3	Non-H	Count4	Pocket size[d]
9 *anti*	8 *anti*	2	1	2.90	27	0.54	21	very small
9 *syn*	8 *syn*	0	0	3.43	23	0.46	17	medium
2	[2][e]	0	0	3.35	26	0.48	20	small
3	[2][e]	0	0	3.70	27	0.44	22	small
4	1	3	1	2.91	27	0.46	11	small
8	4	1	1	2.68	17	0.38	15	medium
7	5	2	0	3.31	19	0.35	16	large
6	6	0	0	3.46	24	0.39	18	medium
5	7	0	0	3.54	22	0.42	18	large

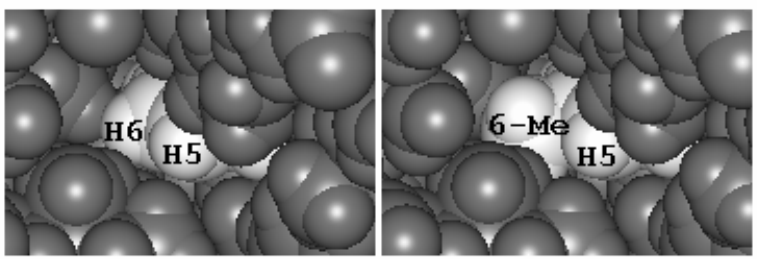
[a]Steric descriptors inside 5.5 Å: Count1, Count2 – No. vdW contacts with all/non-H atoms; Min. d – min. distance for vdW contacts; Count3 – No. non-H atoms; Non-H – number fraction of non-H atoms count; Count4 – No. C atoms. [b]NAA H atoms. [c]IAA H atoms. [d]From molecular graphics. [e]This IAA H is in the mid-way between two NAA H atoms.





HCA (left): very small (B), small (C), medium (A) and large (D) pockets. PCA (right): small, medium and large pockets.





Larger pockets allow placement of Me and Et at C4 and C5 of NAA.