XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery (BCADD-2025)

X-ray crystallographic analysis of 17-pyridin-2-yl estrane derivatives: lead-like compounds against breast and cervical cancer

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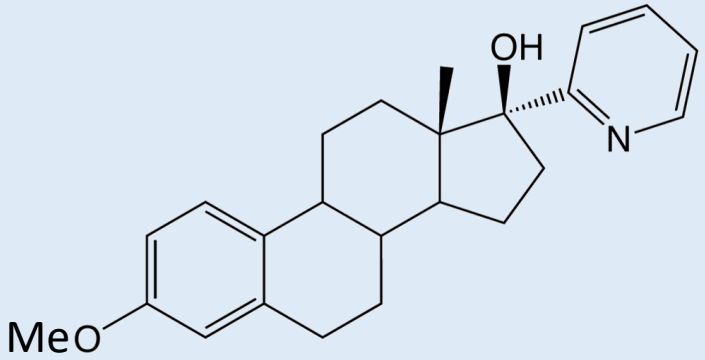
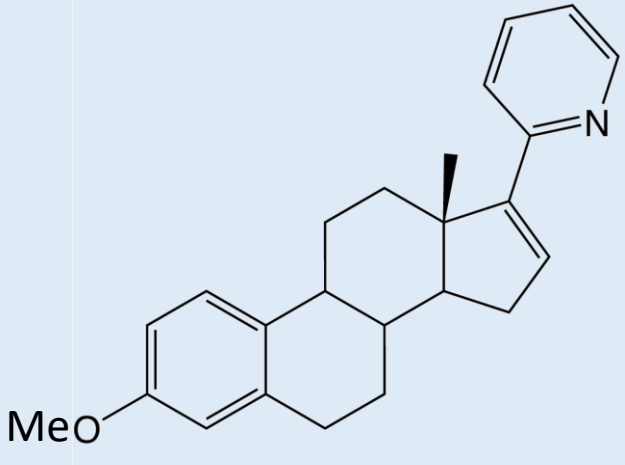
- Previously synthesized novel 3-methoxy-17α-(pyridin-2-yl)estra-1,3,5(10)-trien-17β-ol (**1**) and 3-methoxy-17-(pyridin-2-yl)estra-1,3,5(10),16-tetraen (**2**) showed notable antiproliferative activity against MCF-7 breast cancer cells[1]

- Molecular structures and absolute configurations of compounds of **1** and **2** were confirmed by single X-ray diffraction.



1



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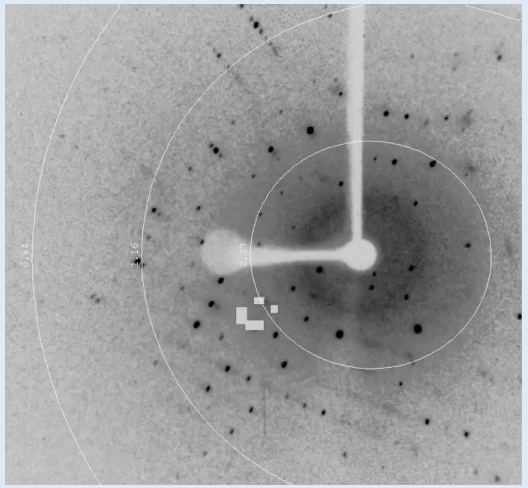


[1]Stevanović, M. Z. *et al.* (2024). *Future Med Chem* 16, 1127–1145.

- Oxford Diffraction Gemini S diffractometer

- *CrysAlisPro* software packages were used for data collection

- *ShelXle* as a GUI for solving crystal structures

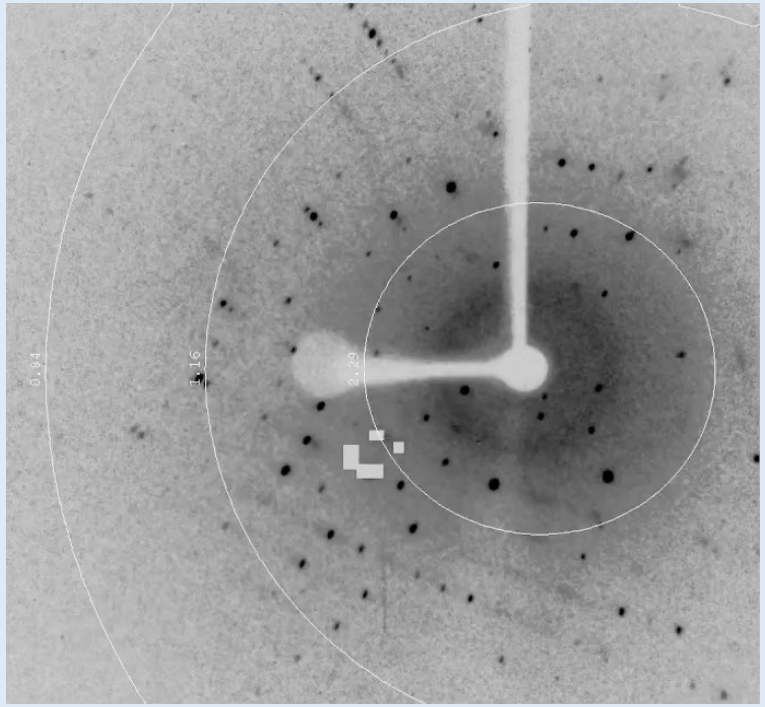
CIF file

- *Mercury CSD* for external validation

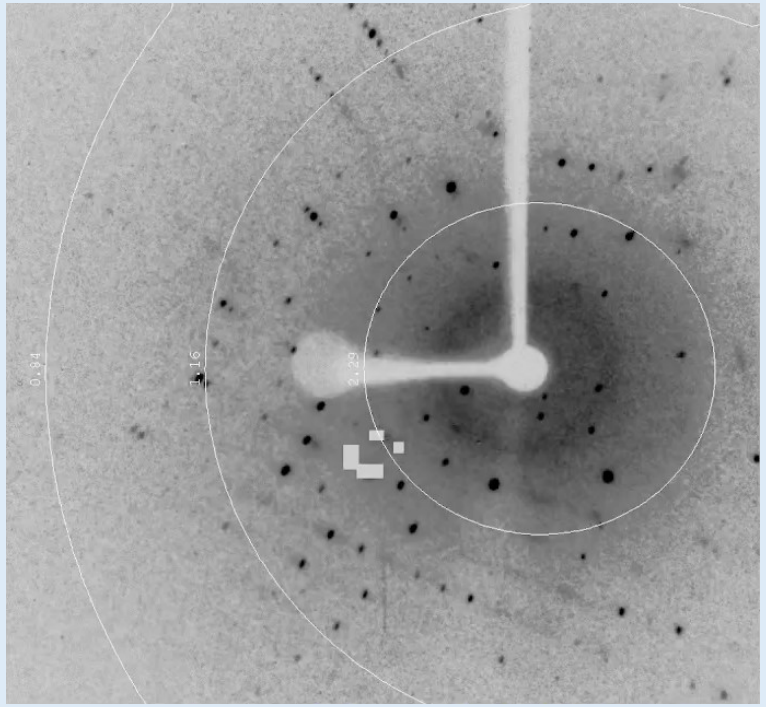
- *PLATON* for internal validation

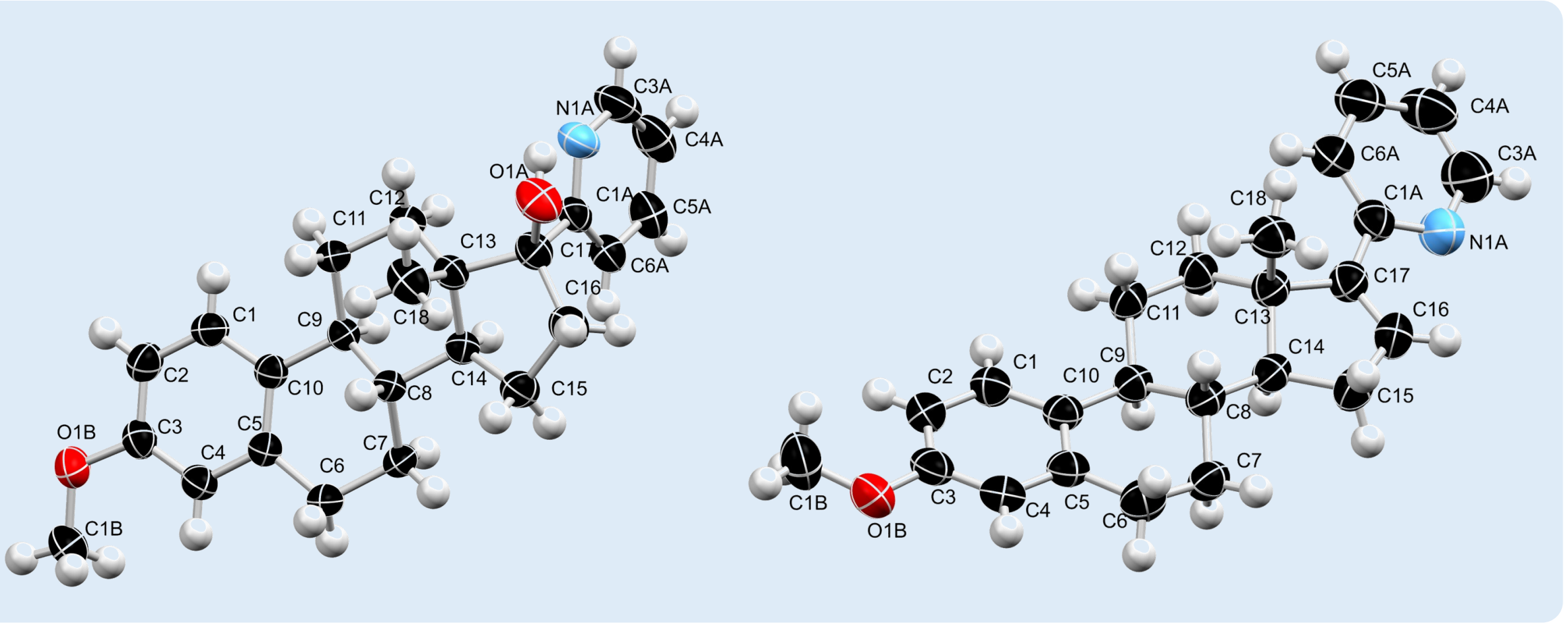
- *CrystalExplorer* for calculating intermolecular interaction energies

	1	2
Crystal Data		
Chemical formula	$C_{24}H_{29}NO_2$	$C_{24}H_{27}NO$
M_r	363.48	345.46
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$
a / Å	9.75529(16)	7.02510(8)
b / Å	7.44286(13)	30.3381(4)
c / Å	13.6837(2)	8.93115(9)
α / °	90	90
β / °	100.0734(15)	90
γ / °	90	90
V / Å^3	978.22(3)	1903.48 (4)
Z	2	
Radiation type	Cu $K\alpha$	Cu $K\alpha$
μ / mm^{-1}	0.61	0.56
Crystal size, mm	0.46 × 0.36 × 0.21	0.58 × 0.27 × 0.11



	1	2
Data collection		
Absorption correction	Analytical	Analytical
T_{min}	0.824	0.806
T_{max}	0.904	0.942
Measured reflections	14731	10499
Independent reflections	3726	3673
Observed reflections [$I > 2\sigma(I)$]	3588	3480
R_{int}	0.033	0.036
$(\sin \theta/\lambda)_{max}$ / Å^{-1}	1.339	1.339
Refinement		
R [$F^2 > 2\sigma(F^2)$]	0.037	0.039
wR [F^2]	0.094	0.103
S	1.06	1.05
Reflections	3726	3673
Parameters	249	237
H-atom treatment	Mixed	Constrained
$\Delta\rho_{max}$ / e Å^{-3}	0.12	0.12
$\Delta\rho_{min}$ / e Å^{-3}	−0.20	−0.22

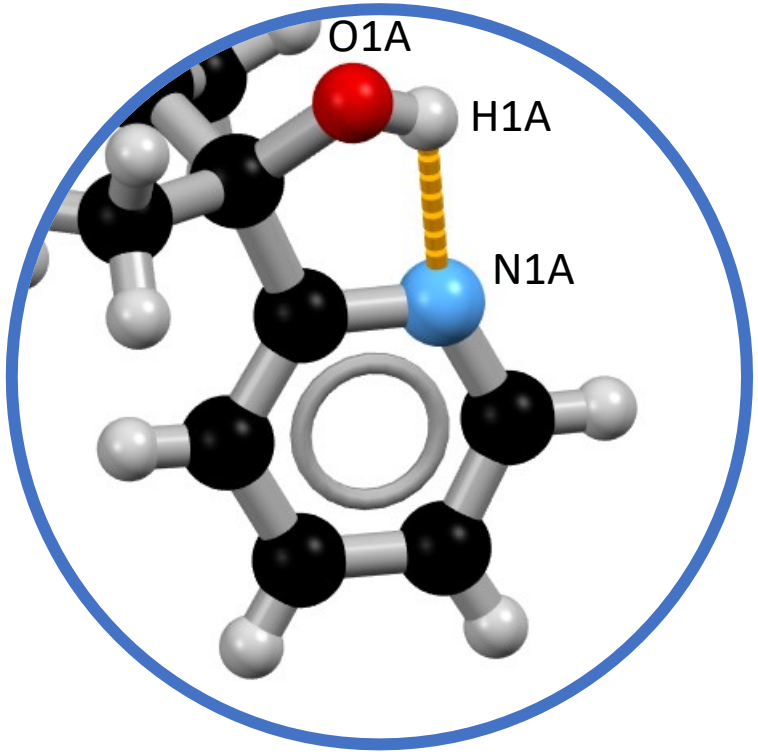




- ORTEP drawings of the molecular structure of compounds **1** and **2** with labeled non-hydrogen atoms

- Intramolecular hydrogen bond parameters for compound **1**

Bond	Distance, Å			Angle, °	Symmetry Operation on A
D—H···A	D—H	H···A	D···A	D—H···A	
O1A—H1A···N1A	0.83(2)	2.04(4)	2.553(3)	120(4)	*x*, *y*, *z*



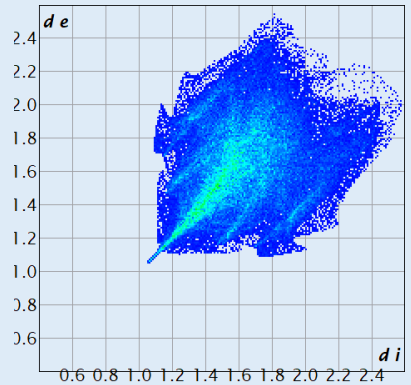
- Structural parameters of π···π interactions in the crystal structures of **1** and **2**.

Cg(m)···Cg(n)	d(Cg···Cg) / Å	*α* / °	*β* / °	*γ* / °	Score according to Atomic Analyser	Assessment	Symmetry operation on Cg(n)
1							
Cg(1)···Cg(1)	4.9863(16)	77.65(13)	8.0	83.9	8.3	Strong	–1/2+*x*, 3/2–*y*, 1–*z*
2							
Cg(1)···Cg(1)	4.9762(15)	85.33(12)	9.9	88.4	8.7	Strong	2–*x*, –1/2+*y*, 2–*z*
Cg(2)···Cg(2)	5.0596(13)	39.03(10)	31.7	68.9	7.4	Strong	–*x*, –1/2+*y*, 1–*z*
Cg(2)···Cg(1)	5.8428(13)	76.37(11)	48.4	85.8	4.9	Moderate	1–*x*, 1/2+*y*, 1–*z*

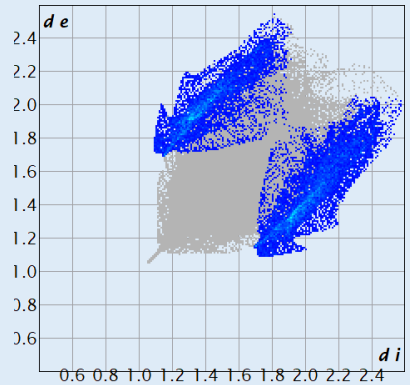
Cg = geometric center of a ring; *α* = dihedral angle between mean planes of rings m and n; *β* = angle between Cg(m)→Cg(n) vector and normal to mean plane of ring m; *γ* = angle between Cg(m)→Cg(n) vector and normal to mean plane of ring n. Ring numbering: (1) N1A, C1A, C3A, C4A C5A, C6A; (2) C1, C2, C3, C4, C5, C10.

- The overall two-dimensional fingerprint plots for compound **1**(a) and **2**(b), and plots delineated into C···H, H···H, N···H and O···H interactions

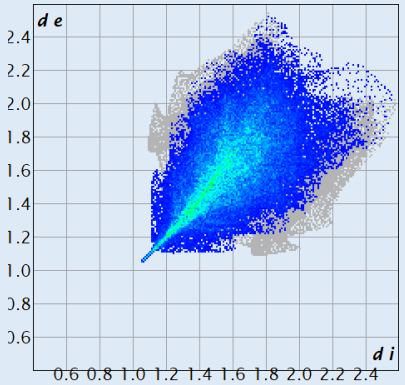
(a)



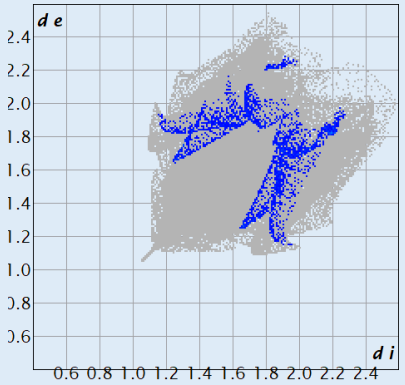
All



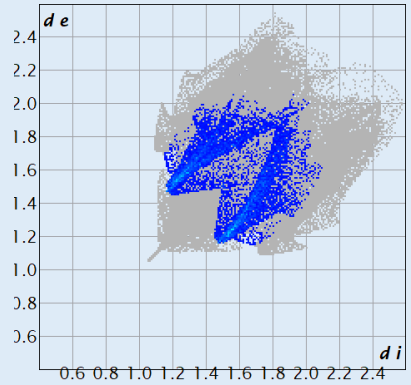
C···H (18%)



H···H (71%)

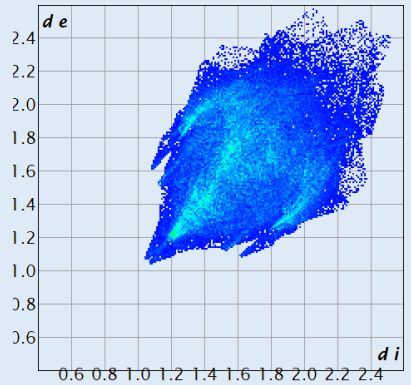


N···H (3%)



O···H (9%)

(b)



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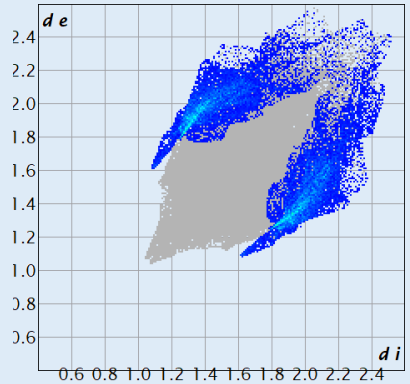
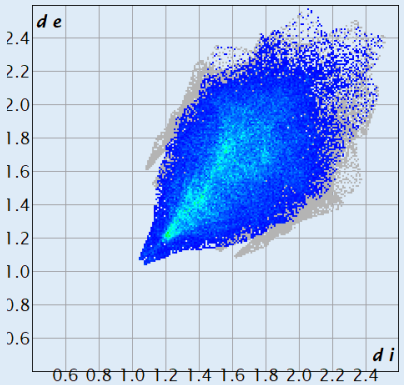
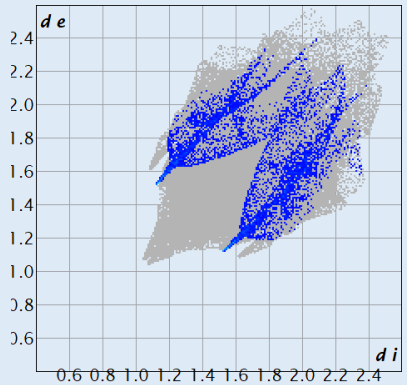


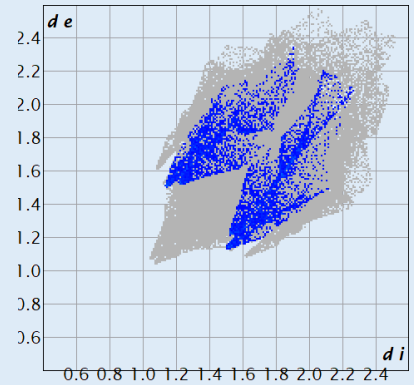
C···H (22%)



H···H (68%)



N···H (5%)

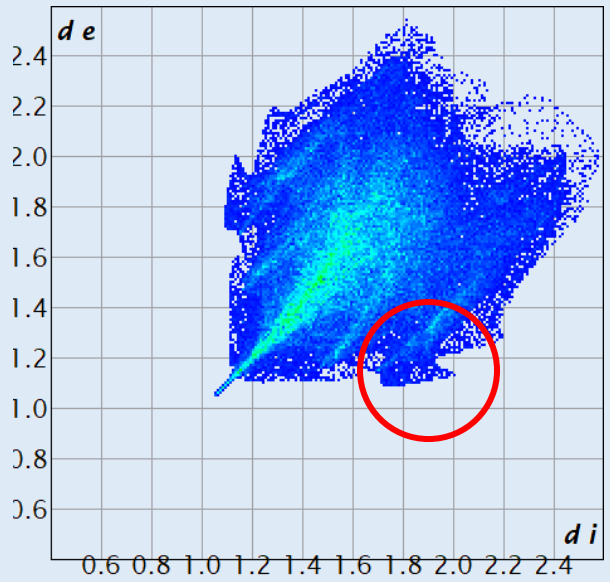


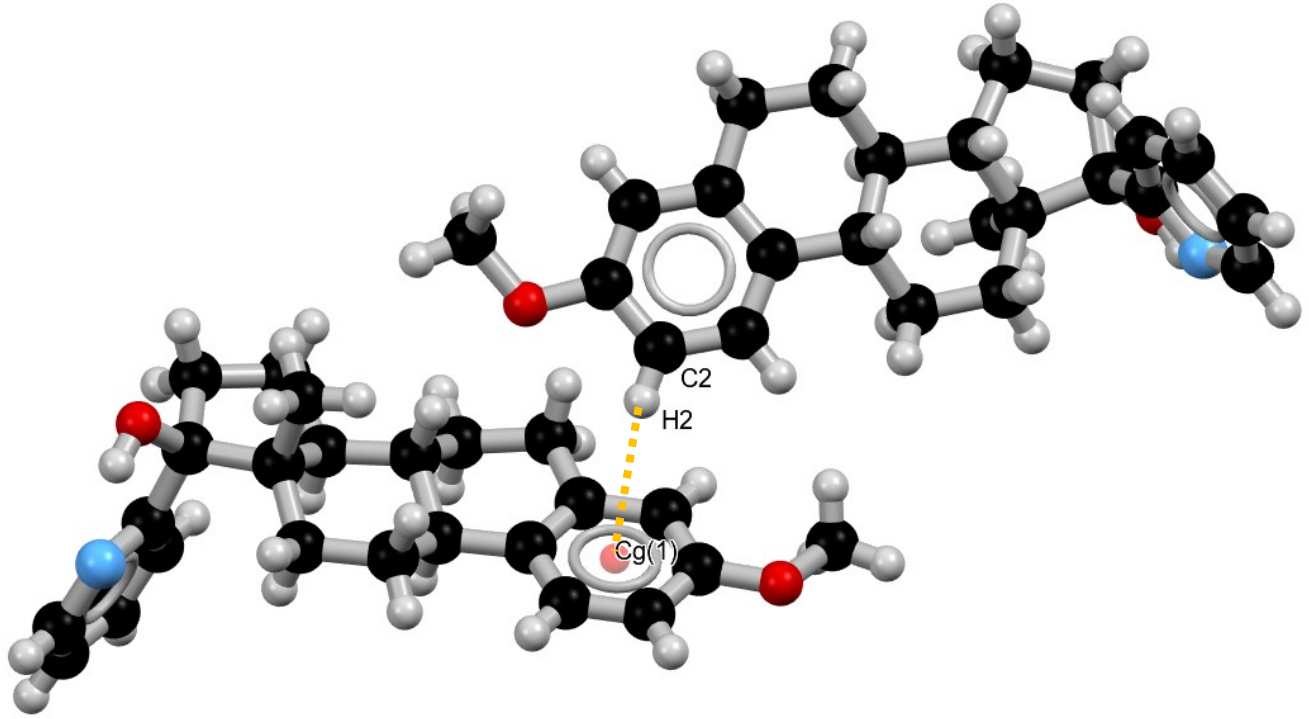
O···H (5%)

- . Structural parameters of C–H···π interactions in the crystal structures of **1**

C–H···Cg(n)	d(C···Cg) / Å	d(H···Cg) / Å	∠(C–H···Cg) / °	*δ* / °	Symmetry operation on Cg(n)
C3A–H3A···Cg(1)	3.680(3)	2.78	162	7.00	2–*x*, 1/2+*y*, 2–*z*

δ = angle between Cg(n)→H vector and normal to mean plane of ring n. Ring numbering: (1) N1A, C1A, C3A, C4A C5A, C6A.

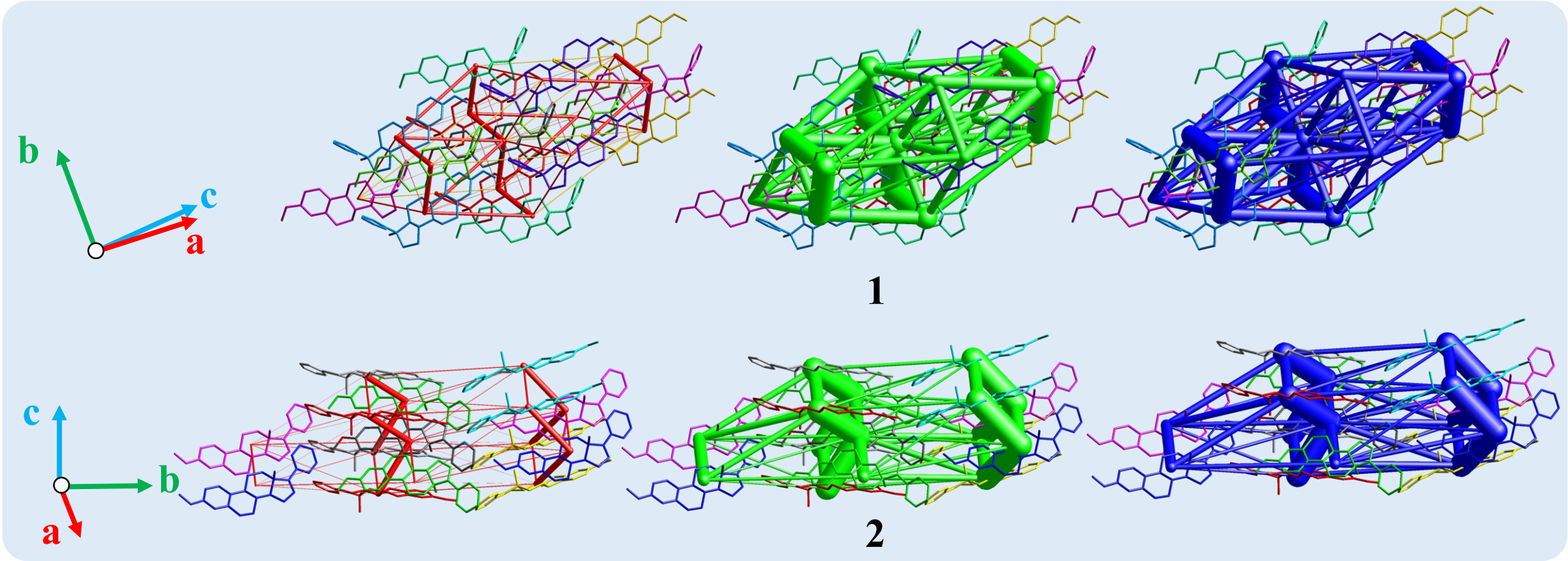




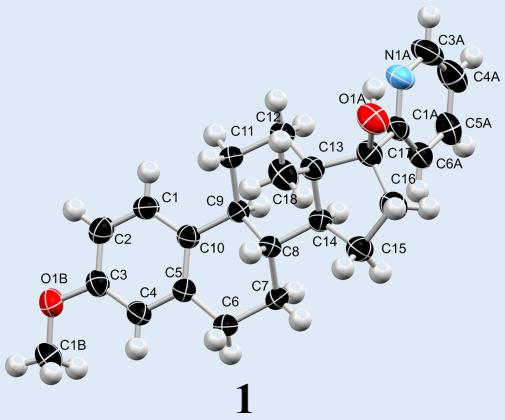
- Summary of intermolecular interaction energies of the unique molecular pairs constituting the first coordination sphere for **1** and **2** calculated using the B3LYP/6-31G(d,p)

				E/kJ mol^{-1}				
Label	N	Symmetry operation	R/Å	E_{ele}	E_{pol}	E_{dis}	E_{rep}	E_{tot}
1								
1	2	$-x, y+1/2, -z$	6.43	−11.6	−2.6	−62.3	33.7	−47.6
2	2	$-x, y+1/2, -z$	12.86	2.5	−1.6	−21.4	0.0	−17.2
3	2	x, y, z	9.76	−0.8	−0.6	−12.5	3.3	−10.1
4	2	x, y, z	7.44	−1.6	−0.3	−26.3	8.9	−19.3
5	2	$-x, y+1/2, -z$	10.29	−7.1	−2.0	−37.4	20.5	−28.9
6	2	$-x, y+1/2, -z$	9.29	−3.5	−2.3	−22.6	12.6	−17.2
7	2	x, y, z	15.35	0.8	−0.5	−8.4	0.0	−6.8
2								
1	2	$-x+1/2, -y, z+1/2$	6.01	−14.3	−2.8	−65.9	32.3	−54.6
2	2	$x+1/2, -y+1/2, -z$	12.69	−0.4	−0.7	−18.1	0.0	−16.6
3	2	x, y, z	7.03	−4.4	−0.6	−35.0	15.1	−26.1
4	2	$x+1/2, -y+1/2, -z$	12.88	−1.3	−0.4	−6.5	0.0	−7.3
5	2	$-x, y+1/2, -z+1/2$	15.98	−1.4	−0.3	−7.2	0.0	−8.0
6	2	$-x, y+1/2, -z+1/2$	15.30	−2.1	−1.3	−9.6	0.0	−11.5

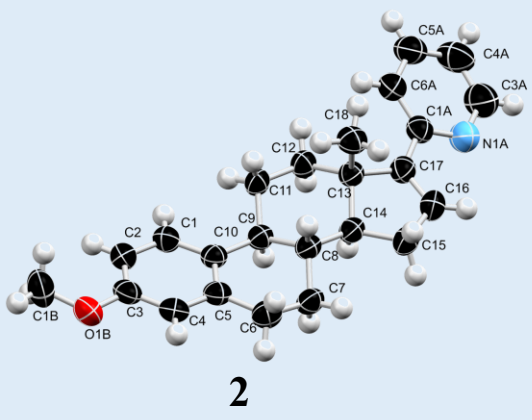
- Energy frameworks for separate electrostatic (red) and dispersion (green) contributions to the total nearest neighbour pairwise interaction energies (blue) for **1** and **2**. The cylinders link molecular centroids, and their thickness is proportional to the magnitude of the energy.The scaling of framework cylinders is the same in all three diagrams, and for subsequent figures



- A detailed analysis of the crystal structures of **1** and **2** is presented in this study.
- The presence of a hydroxyl group at the 17β-position in **2** does not result in intermolecular hydrogen bond formation. However, it alters the orientation of the pyridine ring through the formation of an intramolecular hydrogen bond, leading to a distinct packing arrangement compared to **1**.
- In both structures, besides C–H···π and π···π stacking interactions, dispersion forces are the most dominant, as confirmed by calculations at the CE-B3LYP level of theory implemented in *CrystalExplorer*.
- The combination of classical single-crystal X-ray diffraction and computational energy analysis provides deeper insight into the interaction patterns within the crystal lattice and offers a valuable foundation for understanding potential interaction modes in molecular docking studies.



1



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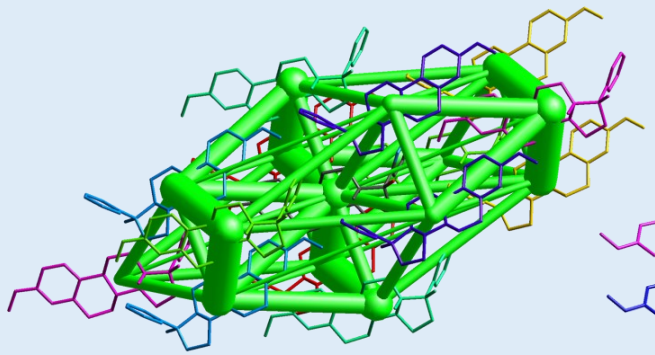
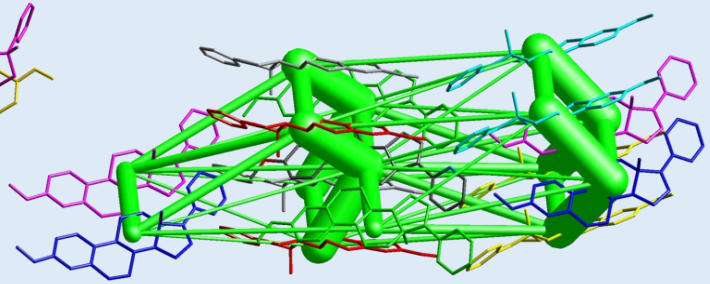


1



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Acknowledgments

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