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Intermolecular interactions in the crystal structures of potential HIV-1 integrase inhibitors

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Abstract—2-[(2,5-dichloro-4-nitro-phenylamino)-methoxy-methyl]-8-hydroxy-quinoline **1** and 2-methyl-quinoline-5,8-dione-5-oxime **2** were obtained as potential HIV-1 integrase inhibitors and analyzed by X-ray crystallography. Semiempirical theoretical calculations of energy preferred conformations were also carried out. The crystal structures of both compounds are stabilized via hydrogen bonds and π–π stacking interactions. The planarity of compound **1** is caused by intramolecular hydrogen bonds.

HIV-1 integrase (IN) is the third main HIV enzyme that inserts the viral DNA into the host chromosome. The first two, i.e., reverse transcriptase and protease, are used as targets in highly active antiretroviral therapy (HAART). The anti-HIV drugs most often investigated have been mainly the inhibitors of these two enzymes, while only few inhibitors of the integrase are until now under clinical trials.[1] Since no similar protein exists in humans, inhibitors of integrase may be used as selective anti-HIV-1 drugs.[2]

Diketoacid compounds (DKA) are a promising class of HIV IN inhibitors with in vivo antiviral activity.[3,4] Styrylquinolines (SQ) are another group that is also capable of IN inhibition.[5a,b] Several compounds of both classes are under clinical trials, S-1360 or L-870810 (DKA), or earlier stages of drug development projects, FZ-41(SQ). Comparison of these two classes reveals clear molecular similarities, but they differ in the inhibition activity. An attempt to mimic the DKA pharmacophore in the styrylquinoline series resulted in compound SQ1 which appeared to be inactive in vitro against IN[6] (shown in Fig. 1). On the other hand, this compound exhibited a significant antiviral activity in the in vivo experiment.[7] This is still to be understood and explained.

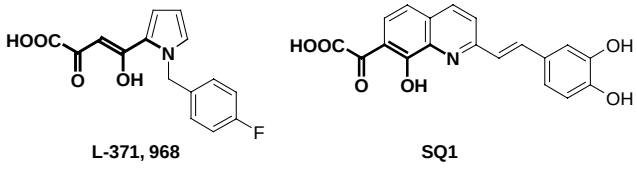

Figure 1. Styrylquinoline designed to mimic DKA pharmacophore.

The so-called fragment based discovery is one of the recent ideas among different drug discovery concepts.[8] In this approach, the interactions of protein inhibitors are investigated by probing the interaction capability and measuring the affinity of small ligand fragments. Although the affinity of such scaffolds is a much lower, and usually screening in a much higher concentration (250–1000 μM) is necessary, such fragments can be efficiently converted into hits and leads.[9]

In a search for the new HIV-1 integrase inhibitors, we have recently designed and synthesized a series of quinoline scaffolds.[10] Among these compounds 6-carboxy-5-hydroxyquinaldic acid was identified as the most active inhibitor, while the affinity of 5-nitroso-8-hydroxyquinaldine appeared to be unexpectedly low.

Keywords: Crystal structure; HIV-1 integrase inhibitor; Quinoline.
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In the current paper, we report a study aimed at the possible explanation of this fact using X-ray diffraction data. Moreover, the analysis of several styrylquinoline like compounds seems to identify possible styryl moiety scaffolds. In order to investigate the relationship between molecular structure and anti-HIV activity of these interesting compounds, the X-ray diffraction measurements and structure analysis were carried out for their single crystals. Molecular mechanics and semi-empirical calculations were performed to explain some relevant features of these compounds, such as planarity of molecule **1**.

Synthetic problems are the main obstacles in the design of new potent styrylquinoline integrase inhibitors.[11] For this reason new insight into specific properties of these analogues could be of great importance for organic chemists. Terms of reactions leading to compounds obtained during this study are presented in Supplementary material.

Single crystals of compound **1** (CCDC 276710) and compound **2** (CCDC 276711) (in the form of picrate) were obtained from ethanol solution. All the crystals were grown by slow evaporation of the solvent, at a temperature of about 293 K. The phase problem was solved by direct methods using SIR–DEF2 and SIR–DEF3[12] for structures **1** and **2**, (Fig. 2) respectively, and refined by full matrix least-squares method using SHELXL97.[13]

All hydrogen atoms were located in difference Fourier maps and refined isotropically, using a riding model. The details of the crystal data, data collection, and refinement are listed in Table 1.

The asymmetric units with atom numbering of both structures investigated are shown in Figure 3. All these projections were generated using ORTEP.[14]

The asymmetric unit of **1** consists of one molecule (Fig. 3 (**1**)). The bond lengths, bond angles, and torsion angles are comparable to those typical for similar compounds.[15] Quinoline and benzene rings are approximately planar with the greatest deviations, 0.023(2) Å for C2 and 0.020(2) Å for C16, from the best planes of quinoline and benzene rings, respectively. The angle between these planes is 8.7(1)°. The atoms C12 and N15, which form 'a bridge' between the rings, are approximately coplanar with both of them. The deviations for the atoms C12 and N15 from the benzene plane are 0.32(5) Å and 0.07(4) Å, while those from the quinoline plane are −0.13(3) Å and −0.18(4) Å, respectively. An angle between the plane consisting of the mentioned

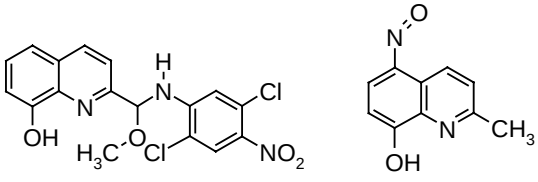

Figure 2. Structural formulae of compounds **1** and **2**.

Table 1. Crystal data, the measurement, and calculation details

	Structure **1**	Structure **2**
Chemical formula:	$C_{17}H_{13}N_3O_4$	$C_{10}H_9N_2O_2$
	Crystal data	
M (g mol^{-1})	394.48	188.064
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a (Å)	7.4535(1)	8.1544(1)
b (Å)	9.0693(2)	10.3611(2)
c (Å)	13.3801(3)	12.8440(3)
α (°)	92.904(1)	97.4773(8)
β (°)	100.943(1)	103.4752(8)
γ (°)	106.015(1)	97.4017(8)
V (Å^3)	848.46(3)	1031.97(3)
Z	2	2
D (mg m^{-3})	1.418	1.343
$F(000)$	404	480
μ (mm^{-1})	3.47	0.858
T (K)	293(3)	293(3)
Radiation	MoKα	MoKα
	Data collection	
Diffractometer	Bruker Nonius KappaCCD	Bruker Nonius KappaCCD
h_{min}	−11	−11
h_{max}	10	10
k_{min}	−14	−14
k_{max}	14	12
l_{min}	−21	−18
l_{max}	21	18
Θ_{min} (°)	0.998	0.998
Θ_{max} (°)	34.338	30.07
Unique reflections	6695	5981
Reflns $F_0 > 4\delta$ (Fo)	4226	4565
	Refinement	
R1 for $F_0 > 4\delta$ (Fo)	0.0559	0.0592
R1 for all data	0.0944	0.0781
wR2 for $F_0 > 4\delta$ (Fo)	0.1714	0.1694
GooF on F^2	1.021	1.001

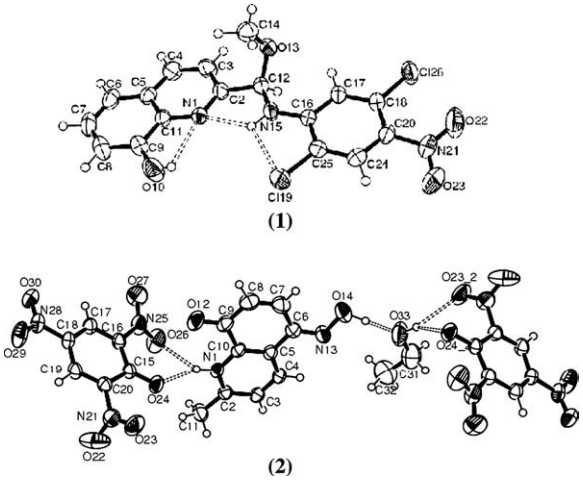

Figure 3. ORTEP projections of the asymmetric units of structures **1** and **2** with hydrogen bonds shown by dashed lines. In (2), the picrate anion transformed by $-x-1$, $-y$, $-z+1$ is added to show the intermolecular hydrogen bonds.

atoms and the phenyl ring is 10.4(2)°, while an angle between the same plane and the quinoline ring is 2.3(2)°.

The overall molecular conformation can be described as transoidal with the torsion angle C2–C12–N15–C16 = 168.9(2)°. The methoxy group adopts a synclinal conformation in relation to the quinoline fragment, with the torsion angle C2–C12–O13–C14 = 63.7(3)°. The nitro group is not coplanar with the benzene ring and it shows a disorder, which seems to be connected with free rotation around the C20–N21 bond.

Although in the molecule **1** there are potential proton donors, O10, N15, and acceptors N1, O10, Cl19, and O13, no intermolecular hydrogen bonds are formed in the structure. An explanation for that situation may be found by considering the intramolecular interactions (see Fig. 3), which are rather strained intramolecular hydrogen bonds with the geometry parameters listed in Table 2. They are in agreement with the data found in the literature for *N*-(4-methoxyphenyl)quinoline-2-carboxamide and *N*-(4-iodophenyl)quinoline-2-carboxamide.[16,17] It is plausible that these bonds are responsible for the planarity of the molecule.

The crystal structure is stabilized by intermolecular head-to-tail (between phenyl and quinoline substituents) and head-to-head (between nitrobenzene moieties) π–π interactions. The distance between C6 (quinoline ring) and the center of the benzene ring of a neighboring molecule is 3.346 Å, while in the head-to-head interaction the distance between C20 and C20_2 (both in phenyl substituents) is 3.581 Å.

The asymmetric unit of **2** consists of one cation formed by protonation of N1, picrate anion, and one molecule of ethanol used as solvent (Fig. 3 (**2**)). The bond lengths and angles are comparable to those typical for similar compounds.[9] The only exception is the relatively short N21–O23 bond, which may be the effect of high values of atomic displacement parameters of O23. The atomic distances C6–N13 and C9–O12, being 1.303(3) Å and 1.218(2) Å, respectively, agree well with the double character of these bonds. The bonds C7–C8 and C5–C10 are shorter than C5–C6, C6–C7, C8–C9, and C9–C10, which suggests electron localization of quinone-like character.

The high values of the atomic displacement parameters for O23, O26, O27, and O30 of the nitro groups, as well as for C32, O33 of ethanol and for hydrogen atoms of methyl and hydroxyl groups can be explained by the rotational freedom and certain possibility of disorder.

Molecule **2** is almost planar, the greatest distortion, 0.052(2) Å, being that of the C9 atom. The approximate coplanarity of the substituents with the quinoline ring plane is shown by the values of the torsion angles: C5–C6–N13–O14 = −179.75(2)° and O12–C9–C10–N1 = −3.47(3)°.

The benzene ring of the picrate anion is also planar with the greatest deviation, 0.027(1) Å, shown by C15. The nitro groups are not coplanar with the ring as demonstrated by the torsion angles C15–C20–N21–O23 = 69.27(4)°, C15–C16–N25–O26 = 29.75(3)°, and C17–C18–N28–O30 = 9.32(3)°.

The packing of the molecules in the unit cell is dominated mainly by intermolecular hydrogen bonds. The details of their geometry are given in Table 3. The proton of N1 is shared by two oxygen atoms, O24 and O26, of the picrate anion and forms a bifurcated hydrogen bond (Fig. 3). A similar situation occurs for the proton of the alcohol OH group (Fig. 3). The H330 proton is shared by oxygen atoms O23(i) and O24(i) of the picrate anion.

The molecule structure of **1** found in the crystal was optimized with the semiempirical method using Mopac program with AM1 parameterization.[18] As shown in Table 4 there are no significant differences between optimized and crystal structures (see Fig. 4).

The grid search method incorporated to the Sybyl program[19] was used to investigate conformational flexibility and global minimum using the structure optimized by AM1 as the initial model. The calculations were performed for the torsion angles τ_1 = N1–C2–C12–N15 and τ_2 = C16–N15–C12–C2 with the grid

Table 2. Intramolecular hydrogen-bonding geometry in **1**

D-H	A	d(D-H) (Å)	d(H..A) (Å)	∠DHA (°)	d(H..A) (Å)
N15–H15	N1	0.865(3)	2.207	112.96	2.666
O10–H10	N1	0.741(4)	2.373	117.49	2.720
N15–H15	Cl19	0.865(3)	2.614	105.19	2.969

Table 3. Intermolecular hydrogen-bonding geometry in the crystal structure of **2**

D-H	A	d(D-H) (Å)	d(H..A) (Å)	∠DHA (°)	d(H..A) (Å)
N1–H13	O24	0.884	1.945	154.80	2.770
N1–H13	O26	0.884	2.451	126.14	3.057
O14–H141	O33	1.035	1.605	165.74	2.621
O33–H330	O24(i)	0.894	2.147	152.75	2.970
O33–H330	O23(i)	0.894	2.448	123.27	3.032

Symmetry codes (i) $-x-1, -y, -z+1$.

Table 4. Selected torsion angles for the crystal and optimized structure

Conformer	τ_1 (°)	τ_2 (°)
In crystal structure	0.8	164
Corresponding to the global minimum (AM1)	21	169

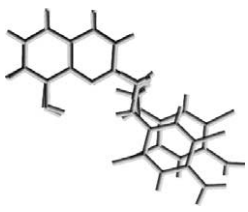

Figure 4. Superposition of the calculated (upper) and the X-ray crystal structure molecules of compound **1**.

increment 15° for both angles. Figure 5 shows conformational energy map plotted as a function of the torsion angles τ_1 and τ_2. According to Figure 5, the conformers corresponding to the crystal and AM1-optimized molecular structures are located in global minimum and there is no significant difference in the energy between the optimized and crystal structure. The superposition (Fig. 4) of the quinoline rings of the two conformers indicates the similarity of their shapes. Performed analysis of occupied orbitals does not explain the planarity of the molecule, which suggests no conjugation of the two π-systems *via* the C12–N15 bridge.

These results confirm the idea that the molecular conformation is determined mainly by the intramolecular hydrogen bonds (Fig. 3 (**1**)).

All antiviral assays were performed in the presence of Mg^{2+} as described previously.[5b] The IC_{50} values of specific compounds are listed in Table 5.

Compound **1** has weak activity against HIV-1 integrase, while compound **2** should be considered as inactive.

Interestingly, the same weak activity could be observed in a group of compounds (**1**, **3**, and **4**; Fig. 6).

In Figure 7, we present a relationship between IC_{50} and molar refractivity for a series of 5-substituted SQ compounds extracted from the literature data.

This proves the importance of polar interactions between drug and receptor, thus further proving a previous hypothesis of the Mg^{2+} complexing during DKA IN inhibition. The comparison of a series of active structures bearing 8-hydroxyquinoline moiety indicates that the IN affinity seems to be strongly connected with the

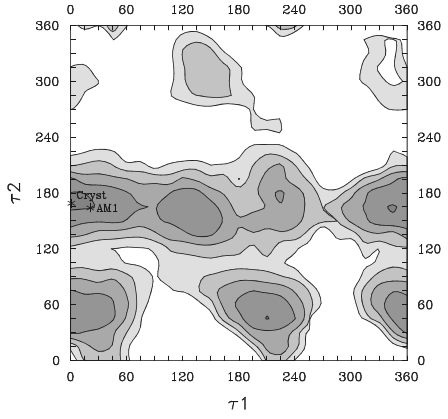

Figure 5. Conformational energy map calculated using Sybyl.

Table 5. Antiviral activity

Compound	IC_{50} (μM)
1	230
2	>333
3[20]	230
4[20]	230

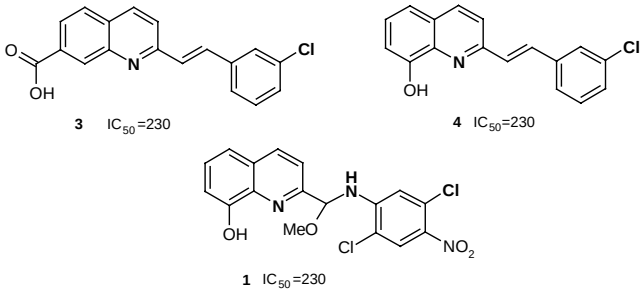

Figure 6. Structural formulae of compounds revealing fragmental similarities.[21]

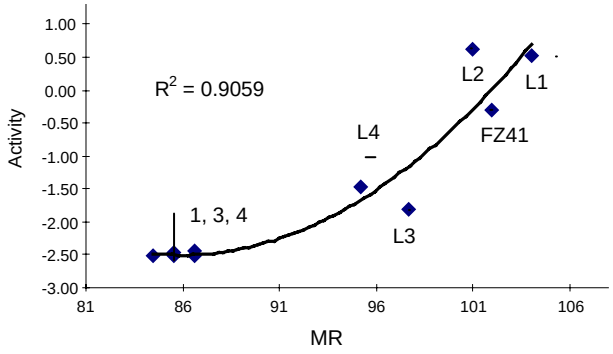

Figure 7. Relationship between molar refractivity MR and activity ($-\log IC_{50}$) of some SQ-like compounds[21].

acidity of the 8-OH group.[10,20] This can enhance the Mg^{2+} complexing ability which is important for the IN inhibition. Thus, a quinon-like form of **2** can disturb the Mg^{2+} complexing ability, which probably explains the lack of IN affinity.

The comparison of compounds **1**, **3**, and **4** reveals an interesting partial similarity for the styryl moiety of SQ compounds, i.e., 3-chlorostyryl group. This is an interesting information for further fragmental approach projects.

The structures of integrase–inhibitor complexes deposited with PDB show that hydrogen bonds and stacking interactions are crucial for the inhibitor anchoring at the enzyme. Our investigations show that both compounds **1** and **2** are capable of forming those kind of interactions. However, in compound **1** conformation should be changed to make hydrogen bond donors and acceptors more available for integrase hydrogen bond acceptors and donors. This fact probably implies a relatively weak activity of this compound. Furthermore, the structure of compound **2** indicates the higher stability of the presented mesomeric quinonoxime structure in comparison to that of nitroso-form, known from the literature.

This observation is of high importance in organic synthesis of quinoline-like structures because modifications of quinoline derivatives at position 5 may introduce additional proton donors to their molecules. The potential interactions of these protons with enzyme would be helpful in understanding the anti-HIV properties of quinolines.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2005.10.083.

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