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Synthesis, crystal structure, and spectroscopic characterization of a new non-centrosymmetric compound, 1-(2-chloroquinolin-3-yl)-*N*-(4-fluorobenzyl)methanimine

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RESEARCH ARTICLE

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ABSTRACT

In this work, we report the synthesis and characterization of a new condensed aromatic heterocycle (1-(2-chloroquinolin-3-yl)-*N*-(4-fluorobenzyl)methanimine) useful in various fields, mainly in medicinal and therapeutic chemistry, with interesting biological properties. Characterization of the title compound was carried out by ^{1}H, ^{13}C, ^{19}F nuclear magnetic resonance and X-ray diffraction techniques. The crystal structure reveals that title compound crystallizes in the monoclinic system and crystal data for $C_{17}H_{12}ClFN_2$: monoclinic, space group $P2_1$ (no. 4), a = 7.2253(10) Å, b = 5.7720(10) Å, c = 17.105(2) Å, β = 95.338(10)°, V = 710.26(18) Å^3, Z = 2, T = 298(2) K, μ(MoKα) = 0.274 mm^{-1}, *Dcalc* = 1.397 g/cm^3, 5010 reflections measured (4.784° ≤ 2Θ ≤ 54.324°), 3160 unique (R_{int} = 0.0501, R_{sigma} = 0.0506) which were used in all calculations. The final R_1 was 0.0339 (I > 2σ(I)) and wR_2 was 0.0907 (all data). The obtained molecular structure has an antiparallel arrangement of the molecular unit leading to a one-dimensional framework.

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1. Introduction

Heterocyclic chemistry is an essential section of chemistry that offers powerful synthetic tools for the search for biologically active molecules. Indeed, the majority of biologically active compounds contain a heterocyclic profile, and, therefore, heterocyclic chemistry has taken on an important place in organic and inorganic synthesis. Heterocycles occupy a predominant place in the dye industry, pharmaceuticals, and their roles are constantly increasing in the field of plastics, agricultural chemicals, and various other sectors. The development of new methods to obtain heterocycles of biological active compounds is one of the main objectives of chemists. Quinoline derivatives have been studied as antibacterial, antifungal, antimycobacterial, antiviral, anti SARS-Cov-2 Target, antimalarial, anticancer, antioxidant, anticonvulsant, analgesic, anti-inflammatory, anthelmintic and cardiovascular protective, in addition to being beneficial against diseases affecting the nervous system [1-9]. These compounds are also widely used for their optical properties [10]. The importance of quinoline derivatives in biological systems has encouraged researchers to use this molecular framework to develop new potential drugs. On these days, the discovery of new compounds of this family is becoming increasingly observed. We are interested in the synthesis of a new compound containing the quinoline nucleus with a highly sought-after pharmacological profile and an important area of interesting biological activity. In this study, we synthesized 1-(2-chloroquinolin-3-yl)-*N*-(4-fluorobenzyl) methanimine (3) by a Vilsmeier-Haack reaction and an aromatic nucleophilic addition. The structure of the compound (3) obtained was confirmed and analyzed using ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy and X-ray diffraction techniques.

2. Experimental

2.1. Instrumentation

The melting points were measured with a Koffler hot-staged apparatus and were not corrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with $CDCl_3$ as the solvent on a Bruker-300 spectrometer. Chemical shifts δ are reported in ppm relative to TMS as an internal reference.

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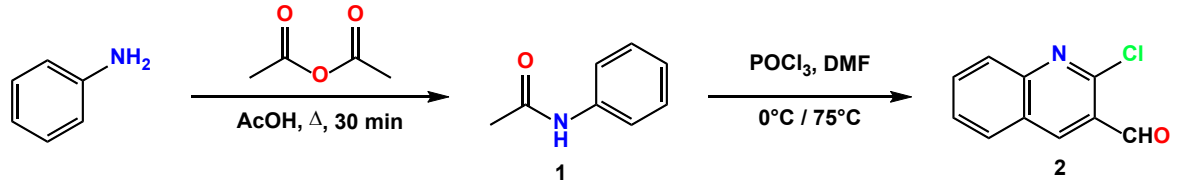
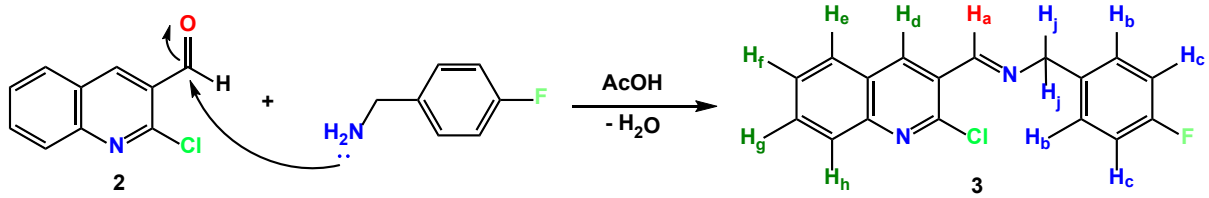
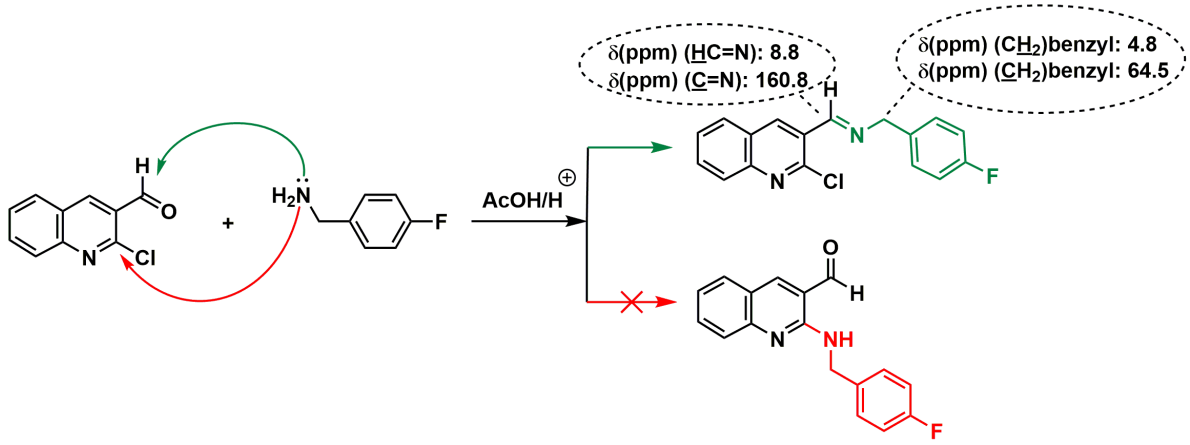


Scheme 1. Synthesis of 2-chloro-3-formylquinoline (**2**).



Scheme 2. Synthesis of 1-(2-chloroquinolin-3-yl)-*N*-(4-fluorobenzyl)methanimine (**3**).



Scheme 3. Correlations observed on the HMBC spectrum for compound **3**.

The progress of the reactions was monitored by TLC. The purification of the synthesized products was performed by recrystallisation and column chromatography.

2.2. Synthesis

2.2.1. Synthesis of 2-chloro-3-formylquinoline

To a solution of *N*-phenylacetamide (**1**) (5 mmoles, 1 equiv.) in dry DMF (15 mmoles, 2.5 equiv.) at 0 °C with stirring, $POCl_3$ (60 mmoles, 7 equiv.) was added dropwise. The reaction mixture was then warmed to 75 °C. After stirring for 5 hours, the mixture was poured into crushed ice, stirred for 5 minutes, and the resulting solid was filtered, washed well with water, and dried. The compound was purified by recrystallisation from ethyl acetate (Scheme 1). Yield: 50%. M.p.: 150-152 °C. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 10.5 (s, 1H, CHO), 8.8 (s, 1H, H-1), 8.1 (m, 1H, H-5), 8.0 (m, 1H, H-2), 7.9 (m, 1H, H-3), 7.7 (m, 1H, H-4). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 189.0 (HC=O), 127.3-134.5 (Ar-C).

2.2.2. Synthesis of 1-(2-chloroquinolin-3-yl)-N-(4-fluoro benzyl)methanimine (3)

A solution of 2-chloro-3-formylquinoline (**2**) (2.60 mmol, 1 equiv.) in methanol (10 mL) was added dropwise to 4-benzylamine fluorine (2.60 mmol, 1.0 equiv.) in the presence of a catalytic amount of acetic acid. The reaction mixture was then heated to 60 °C for 12 hours with stirring. After evaporation, the residue is dried and recrystallized from petroleum ether. (Scheme 2). Color: Yellow crystals. M.p.: 83-85 °C. Yield: 80%. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 4.80 (s, 2H, H_j), 7.12 (s, 2H, H_c), 7.21 (s, 2H, H_b), 7.60 (s, 1H, H_f), 7.80 (s, 1H, H_g), 7.88 (s, 1H, H_h), 7.92 (s, 1H, H_e), 8.71 (s, 1H, H_d), 8.8 (s, 1H, H_a). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 160.8 (*H*C=N), 121.1-161.5 (Ar-C), 64.5 (*C*H_2-N). ^{19}F NMR (282 MHz, $CDCl_3$, δ, ppm): -115.35.

2.3. X-ray diffraction study

A yellow single crystal of compound **3** was selected and used for X-ray diffraction experiment. Intensity data were collected using an Enraf-Nonius CAD-4 diffractometer equipped with graphite monochromatic MoKα (λ = 0.71073 Å). Data reduction was processed with XCAD4 [11] included in the WINGX software package [12]. The structure was solved by direct method using the SHELXS-97 program [13] and refinements were performed by the full matrix least squares technique on all (F^2) data using the program SHELXL-2014 [14]. Correction by psi-scan absorption was achieved [15]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters and refined against F^2 data using the SHELXS-97 program [13]. All hydrogen atoms were fixed using the HFIX instruction authorized by SHELXL-2014 [14]. The structure representation was prepared using DIAMOND 3.1 [16]. Crystal data for compound **3** are summarized in Table 1.

Table 1. Crystal data and structure refinement for the title compound.

Empirical formula	$C_{17}H_{12}ClFN_2$
Formula weight (g/mol)	298.74
Temperature (K)	298(2)
Crystal system	Monoclinic
Space group	$P2_1$
a, (Å)	7.2253(10)
b, (Å)	5.7720(10)
c, (Å)	17.105(2)
β (°)	95.338(10)
Volume (Å^3)	710.26(18)
Z	2
ρ_{calc} (g/cm^3)	1.397
μ (mm^{-1})	0.274
F(000)	308.0
Crystal size (mm^3)	0.35 × 0.29 × 0.25
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection (°)	4.784 to 54.324
Index ranges	$-9 \le h \le 4$, $-7 \le k \le 7$, $-21 \le l \le 21$
Reflections collected	5010
Independent reflections	3160 [R_{int} = 0.0501, R_{sigma} = 0.0506]
Data/restraints/parameters	3160/1/239
Goodness-of-fit on F^2	1.038
Final R indexes [I≥2σ (I)]	R_1 = 0.0339, wR_2 = 0.0851
Final R indexes [all data]	R_1 = 0.0432, wR_2 = 0.0907
Largest diff. peak/hole (e.Å^{-3})	0.24/-0.13
Flack parameter	0.02(4)
CCDC number	2091684

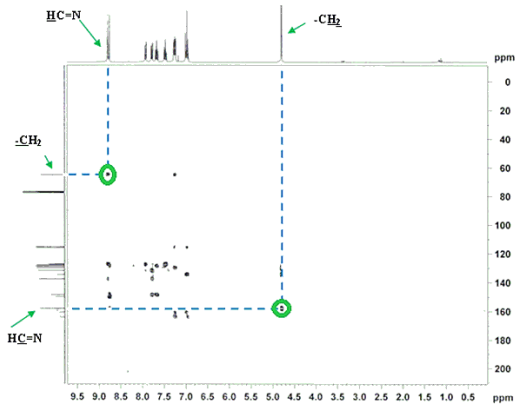


Figure 1. Spectrum HMBC in $CDCl_3$ of compound 3.

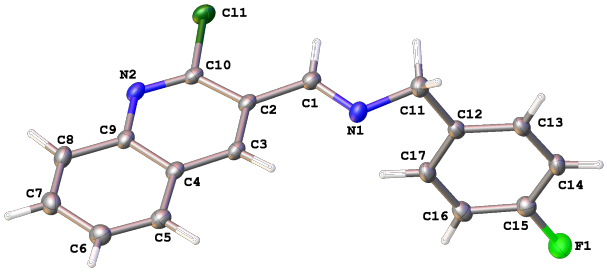


Figure 2. The asymmetric unit of compound 3.

3. Results and discussion

3.1. Synthesis

The required acetanilide (**1**) was readily prepared from the reaction of the corresponding aniline with acetic anhydride in acetic acid. Vilsmeier cyclization of acetanilide (**1**) was carried out by adding $POCl_3$ to the substrate in DMF at 0 ° C followed by heating to 75 ° C to obtain 2-chloro-3-formylquinoline (**2**) with good yield [1] (Scheme 1). The chemical shifts and scalar coupling constants of the different types of protons and carbon of compound **2** are given in the experimental part.

To access the desired compound **3**, we react *p*-fluoro-benzylamine with quinoline **2** in the presence of a few drops of acetic acid in methanol, which allowed us to isolate a functionalized quinoline **3** (Scheme 2). Identification of this product was performed by 1D and 2D NMR (^{1}H, ^{13}C, HMBC). In particular, a detailed study of the HMBC spectrum unambiguously confirms the structure of compound **3** (Figure 1). On the HMBC spectrum, we observed the presence of a heteronuclear correlation between the protons of the CH_2 unit in the benzyl group and the imine carbon (Scheme 3). No correlation was observed between the carbon that carries the chlorine atom and the CH_2 of the benzyl group.

Table 2. Bond lengths, bond angles and torsion angles for the title compound.

Atom	Atom	Length (Å)	Atom	Atom	Length (Å)
C1	N1	1.257(3)	C5	C6	1.354(5)
C1	C2	1.470(4)	C6	C7	1.413(5)
Cl1	C10	1.749(3)	C7	C8	1.346(5)
F1	C15	1.364(3)	C8	C9	1.414(4)
N1	C11	1.450(4)	C11	C12	1.511(4)
C2	C3	1.369(4)	C12	C13	1.391(4)
C2	C10	1.420(3)	C12	C17	1.387(4)
N2	C9	1.370(3)	C13	C14	1.378(4)
N2	C10	1.294(4)	C14	C15	1.367(4)
C3	C4	1.402(4)	C15	C16	1.366(4)
C4	C5	1.410(4)	C16	C17	1.384(4)
C4	C9	1.418(3)			

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
N1	C1	C2	120.8(2)	C8	C9	C4	118.9(2)
C1	N1	C11	117.7(2)	C2	C10	Cl1	118.5(2)
C3	C2	C1	121.5(2)	N2	C10	Cl1	115.20(19)
C3	C2	C10	115.7(2)	N2	C10	C2	126.3(2)
C10	C2	C1	122.8(2)	N1	C11	C12	111.5(2)
C10	N2	C9	117.3(2)	C13	C12	C11	119.7(2)
C2	C3	C4	121.5(2)	C17	C12	C11	122.0(2)
C3	C4	C5	124.0(2)	C17	C12	C13	118.3(2)
C3	C4	C9	117.0(2)	C14	C13	C12	121.6(3)
C5	C4	C9	119.0(2)	C15	C14	C13	118.0(3)
C6	C5	C4	120.6(3)	F1	C15	C14	119.2(3)
C5	C6	C7	120.2(3)	F1	C15	C16	118.1(3)
C8	C7	C6	120.9(3)	C16	C15	C14	122.7(3)
C7	C8	C9	120.4(3)	C15	C16	C17	118.7(3)
N2	C9	C4	122.2(2)	C16	C17	C12	120.7(2)
N2	C9	C8	118.9(2)				

A	B	C	D	Angle (°)	A	B	C	D	Angle (°)
C1	N1	C11	C12	-118.2(3)	C5	C6	C7	C8	0.3(5)
C1	C2	C3	C4	178.0(2)	C6	C7	C8	C9	0.0(5)
C1	C2	C10	Cl1	1.6(3)	C7	C8	C9	N2	-179.7(3)
C1	C2	C10	N2	-178.4(2)	C7	C8	C9	C4	-0.3(4)
F1	C15	C16	C17	178.7(2)	C9	N2	C10	Cl1	-179.52(18)
N1	C1	C2	C3	13.7(4)	C9	N2	C10	C2	0.5(4)
N1	C1	C2	C10	-167.9(2)	C9	C4	C5	C6	-0.1(4)
N1	C11	C12	C13	-156.8(2)	C10	C2	C3	C4	-0.5(3)
N1	C11	C12	C17	23.2(4)	C10	N2	C9	C4	-0.7(3)
C2	C1	N1	C11	-179.3(2)	C10	N2	C9	C8	178.6(2)
C2	C3	C4	C5	-179.0(2)	C11	C12	C13	C14	-179.7(3)
C2	C3	C4	C9	0.3(3)	C11	C12	C17	C16	-179.9(3)
C3	C2	C10	Cl1	-179.87(18)	C12	C13	C14	C15	-0.8(4)
C3	C2	C10	N2	0.1(4)	C13	C12	C17	C16	0.1(4)
C3	C4	C5	C6	179.2(3)	C13	C14	C15	F1	-178.3(2)
C3	C4	C9	N2	0.4(3)	C13	C14	C15	C16	0.9(4)
C3	C4	C9	C8	-179.0(2)	C14	C15	C16	C17	-0.6(4)
C4	C5	C6	C7	-0.2(5)	C15	C16	C17	C12	0.0(4)
C5	C4	C9	N2	179.7(2)	C17	C12	C13	C14	0.3(4)
C5	C4	C9	C8	0.4(4)					

3.2. Crystal structure

The crystal structure determination reveals that compound **3** ($C_{17}H_{12}ClFN_2$) crystallizes in the monoclinic system with the $P2_1$ space group. The lattices parameters are a = 7.2253(10) Å, b = 5.7720(10) Å, c = 17.105(2) Å, β = 95.338(10)°. Single-crystal XRD analysis shows that the formula unit of $C_{17}H_{12}ClFN_2$ consists of two aromatic rings that contain an N and Cl atom linked to another aromatic ring, which contains an F atom (Figure 2).

The structure of the title compound can be described by the antiparallel arrangement of the molecular units (Figure 3). In this structure, the double bonds C-N in the imine functions: C10-N2 and C1-N1 are 1.294(4) and 1.257(3) Å, respectively. The average of the C-C bond distances in the aromatic ring is equal to 1.419(3) Å. Furthermore, the values of C15-F1 and C10-Cl1 are 1.364(3) and 1.749(3) Å, respectively (Table 2). These values are consistent with those reported in the literature [17-20]. Intramolecular interactions determine the supramolecular structure of the title compound (Table 3). Noncovalent interactions between hydrocarbons (C–H···π interaction) and aromatic ring (Cg(3)) form one-dimensional framework in compound **3**, and play an essential role in maintaining the stability of the crystal (Figure 4).

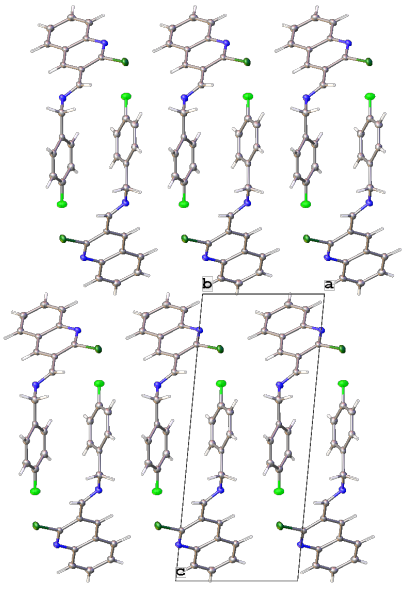


Figure 3. Projection of the structure of compound 3 along *b* direction.

Table 3. Intramolecular hydrogen bonding interactions and the geometric parameters of C–H···π contact for title compound.

Donor-H···Acceptor	D-H, Å	H···A, Å	D···A, Å	D-H···A, °			
C(1)-H(1)···Cl(1)	0.93(3)	2.69(3)	3.066(2)	105(2)			
C(3)-H(3)···N(1)	0.94(3)	2.53(3)	2.844(4)	100(2)			
X--H(I)···Cg(J)	**X-H, Å**	**H···Cg, Å**	**X···Cg, Å**	**X-H···Cg , °**	**H-Perp, Å**	**γ, °**	**Symmetry**
C(13)-H(13)···Cg(3) *	0.92(3)	2.78(3)	3.452(3)	132(2)	2.75	7.99	1-*x*,1/2+*y*,1-*z*

* Cg(3): C12-C17 ring.

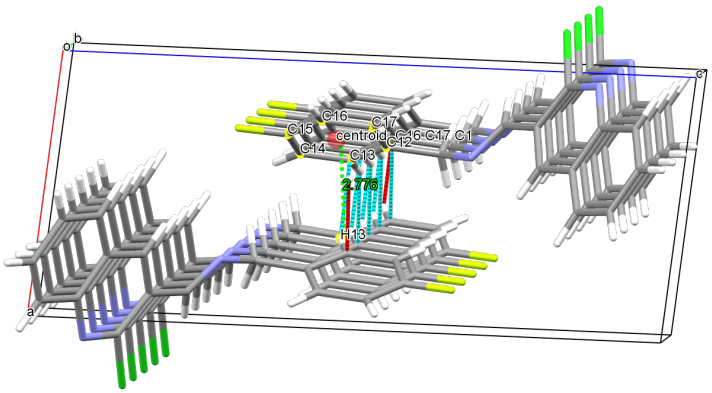


Figure 4. C–H···π contact for title compound.

4. Conclusions

1-(2-Chloroquinolin-3-yl)-*N*-(4-fluorobenzyl)methanimine (3) was successfully synthesized in three steps and the compound obtained was characterized by ^{1}H, ^{13}C and ^{19}F NMR techniques. In addition, the obtained molecular structure by the single crystal X-ray diffraction study of the title compound confirms the suggested molecular structure. The obtained molecular structure has an antiparallel arrangement of the molecular unit leading to a one-dimensional framework.

Acknowledgements

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Supporting information

CCDC-2091684 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: A sample of the compound is available from the author.

CRediT authorship contribution statement

Conceptualization: Rawia Nasri, Maha Hachicha; Methodology: Rawia Nasri, Maha Hachicha; Validation: Rawia Nasri, Maha Hachicha; Mohamed Faouzi Zid; Hédi Mrabet; Formal Analysis: Rawia Nasri, Mohamed Faouzi Zid; Investigation: Rawia Nasri, Maha Hachicha; Mohamed Faouzi Zid; Data Curation: Rawia Nasri, Maha Hachicha; Writing - Original Draft: Rawia Nasri, Maha Hachicha; Writing - Review and Editing: Rawia Nasri, Maha Hachicha; Visualization: Rawia Nasri, Mohamed Faouzi Zid; Supervision: Mohamed Faouzi Zid, Hédi Mrabet; Project Administration: Ministry of Higher Education and Scientific Research of Tunisia.

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