Brief Articles

1,5-Diarylpyrrole-3-acetic Acids and Esters as Novel Classes of Potent and Highly Selective Cyclooxygenase-2 Inhibitors

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A small set of substituted 1,5-diarylpyrrole-3-acetic and -glyoxylic acid derivatives have been synthesized, and their cyclooxygenase (COX-1 and COX-2) inhibiting properties have been evaluated. Some compounds proved to be highly selective COX-2 inhibitors, and their affinity data have been rationalized through docking simulations in terms of interactions with a crystallographic model of the COX-2 binding site.

Introduction

Nonsteroidal antiinflammatory drugs (NSAIDs) represent the standard therapy for the management of inflammation and pain. However, because NSAIDs indiscriminately inhibit both isoforms of cyclooxygenase (COX) (constitutive COX-1, responsible for cytoprotective effects; inducible COX-2, responsible for inflammatory effects), they are associated with well-known side effects at the gastrointestinal level (mucosal damage, bleeding) and less frequently at the renal level.[1] On the other hand, it is known that selective inhibitors of COX-2 can provide antiinflammatory agents devoid of the undesirable effects associated with classical, nonselective NSAIDs.[2] As a consequence, the search for specific inhibitors of COX-2 by means of modifications of well-known nonselective agents has been largely pursued and increasing interest has been devoted to the synthesis of the diaryl heterocyclic class.[3] In fact, DUP-697 (**1**, Chart 1) and NS398 (**2**) were the first COX-2 selective compounds identified[4] and the structure of **1** was the starting point for the synthesis of selective inhibitors, which include recently marketed celecoxib[5] (SC58635, Celebrex, **3**), rofecoxib[6] (MK-966, Vioxx, **4**), valdecoxib[7] (**5**) (and its water-soluble prodrug parecoxib,[8] **6**), and etoricoxib[9] (**7**). As part of our research program, aimed at discovering new pyrrole-containing antiinflammatory agents, we focused our attention on the synthesis of 1,5-diarylpyrrole-3-acetic acids and esters (**8**−**10**) as new COX-2 selective inhibitors in which the pyrroleacetic and vicinal diaryl heterocyclic moieties were reminiscent of indometacin (**11**) and of the above "coxib" family, respectively (Chart 1).

Discussion

The synthesis of the target compounds is shown in Scheme 1. Briefly, the reaction of 4-(methylthio)benzaldehyde with methyl vinyl ketone[10] was shown to be very versatile and high-yielding in the preparation of the 1,4-diketone **12**, which was transformed into the corresponding 4-methylsulfonyl derivative **13** by means of Oxone oxidation.[11] Compound **13**, heated in the presence of the appropriate amine according to the usual Paal−Knoor (thermal) condensation, cyclized to yield the expected 3-unsubstituted 1,5-diarylpyrrole **14** in satisfactory yield after prolonged reflux. The construction of the acetic acid chain was achieved by regioselective acylation[12] of **14** with ethoxalyl chloride in the presence of pyridine to give derivatives **8**. The α-keto esters (**8**) were reduced by means of triethylsilane[13] in trifluoroacetic acid to give pyrroleacetic esters (**9**), which in turn were hydrolyzed with a solution of potassium hydroxide in methanol/THF/H_2O to afford the expected acids (**10**) in good yields.

Biological evaluation of the title compounds showed that the insertion of the acetic moiety in the coxib-like scaffold gives rise to very potent and selective COX-2 inhibitors, the activities of which are presented in Table 1. Among them, three compounds (namely, **9a**, **9c**, and **10c**) showed very interesting biological activity profiles, their affinity toward COX-2 being comparable to that of **3** (0.04, 0.06, and 0.11 μM versus 0.079 μM, respectively) and COX-1/COX-2 selectivity ranging from >900 to >2500, even better than **4** (>800).

To rationalize the results obtained, the new pyrrole derivatives were submitted to a two-step computational protocol consisting of molecular docking calculations and structural optimization of the complexes obtained, with the aim of investigating the possible interaction modes

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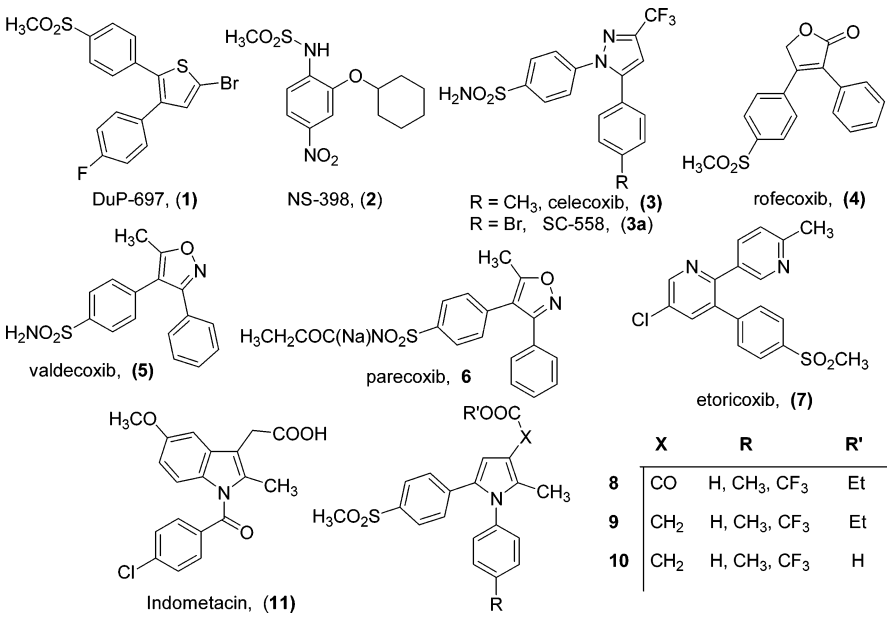
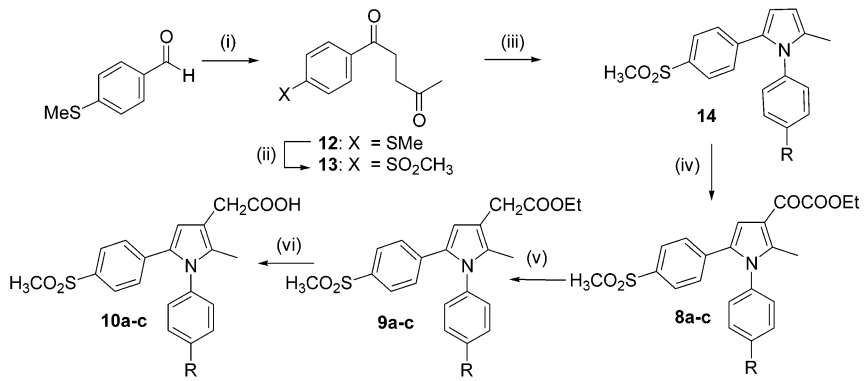
Chart 1



Scheme 1[a]



[a] Compounds: **8a**, R = H; **8b**, R = Me; **8c**, R = CF_3; **9a**, R = H; **9b**, R = Me; **9c**, R = CF_3; **10a**, R = H; **10b**, R = Me; **10c**, R = CF_3. Reagents and conditions: (i) CH_2=$CHCOCH_3$, NEt_3, EtOH, 75−80 °C, 20 h, thiazolium; (ii) Oxone, MeOH/H_2O, room temp, 2 h; (iii) $RPhNH_2$, $TiCl_4$, toluene, room temp, 10 h; (iv) EtOCOCOCl, Pyr, CH_2Cl_2, 0 °C, 4 h; (v) Et_3SiH, CF_3COOH, room temp, 24 h; (vi) KOH, EtOH, reflux, 2 h.

Table 1. In Vitro Inhibition of COX-1 and COX-2 by Compounds **8**−**10**

compd	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	% inhib of COX-2 (10 μM)[a]	% inhib of COX-2 (1 μM)[a]	COX-1/COX-2 (SI)[b]
8a	>100	4.3	54	43	>23
8b	>100	1.9	77	33	>92
8c	>100	9.9	51	33	>10
9a	>100	0.04	84	79	>2500
9b	>100	0.48	81	67	>208
9c	>100	0.06	87	80	>1600
10a	>100	1.0	100	43	>100
10b	>100	0.43	100	74	>200
10c	>100	0.11	100	69	>900
celecoxib[c]	5.1	0.079	96.4	67	64.5
rofecoxib[c]	>10	0.012	100	84.1	>800
indometacin[c]	0.002	0.009	100	67.9	0.22

[a] Results are expressed as the mean of three experiments, of the % inhibition of PGE_2 production by test compounds with respect to control samples. [b] In vitro COX-2 selectivity index [IC_{50}(COX-1)/IC_{50}(COX-2)]. [c] See ref 20.

of such inhibitors within the COX-2 binding site. Moreover, Grid maps[14] were calculated for some probe atoms or groups to evaluate the regions of best interaction between inhibitors and macromolecule. A preliminary calculation was set to check if the program Autodock[15] could be considered as a reliable tool for investigating the binding mode of the diaryl five-membered compounds into the binding site of COX-2. In particular, to set the optimal run parameters of Autodock and to verify that they could be used to successfully dock flexible diaryl five-membered inhibitors within the COX-2 active site, the crystallographic complex between COX-2 and SC-558[16] (**3a**) was used as a control structure. A total of 10 Autodock runs were performed with different parameter sets (the optimal run parameters are reported in the Supporting Information). As a result, the first ranked cluster (among a total number of 17 clusters) contained 43 conformations in the same orientation within the binding site, with respect to **3a**, and the first conformation of the inhibitor was characterized by a root-mean-square deviation of 0.27 Å (calculated on the heavy atoms) with respect to the crystal structure, showing a very good agreement between the experimental and the calculated coordinates. Considering that the control docking trial was a success, Autodock was thus used to find the best orientations and conformations of the new inhibitors

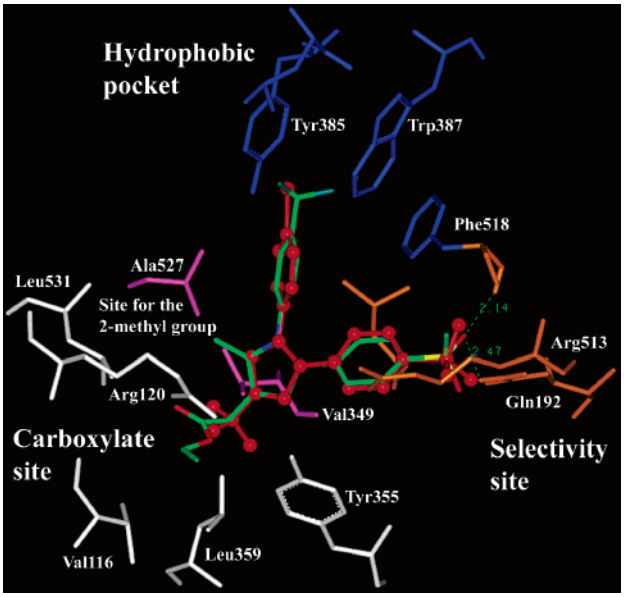


Figure 1. Orientation of the optimized first ranked conformation (belonging to the first of 53 clusters) of **9c** (displayed following the atom type color codes) in comparison with the cocrystallized inhibitor SC-558 (red, ball-and-stick) within the COX-2 binding site. Three major regions of interactions between **9c** and the macromolecule can be discerned: (1) the "hydrophobic pocket"[16] (blue), (2) the "selectivity site" (orange), and (3) the "classical NSAID's carboxylate binding site" (white). An accessory hydrophobic site (pink) can profitably interact with the methyl group at position 2 of **9c**. For the sake of clarity, only a few amino acid residues of the COX-2 binding site are represented while the hydrogen bonds involving the ester side chain of **9c** are omitted.

within the COX-2 binding site. The complexes obtained from Autodock calculations and subsequent structural optimization showed that the five-membered ring and the diaryl systems of **9c** and **3a** are oriented in a similar way (Figure 1). As previously reported,[11] the vicinal diaryl arrangement was responsible for the optimal effectiveness in this series of compounds. In agreement with this statement, computational simulations showed that the two benzene rings were located within two of the three most important binding pockets of the COX-2 binding site. In particular, the *p*-trifluorophenyl moiety at position 1 of the pyrrole ring of **9c** was found to be superimposed on the *p*-bromophenyl group at position 1 of the co-crystallized inihibitor, occupying the "hydrophobic pocket" (following the notation used by Kurumbail and co-workers)[16] delimited by the lipophilic and aromatic side chains of Leu384, Tyr385, Trp387, and Phe518. The side chain of the last residue formed the wall separating the hydrophobic site from the "selectivity site" (see below). Moreover, the *p*-methylsulfonylphenyl moiety of **9c** corresponded to the *p*-sulfonamidophenyl of **3a**, filling a region of space called the selectivity site.[16] The oxygen atoms of the methylsulfone group of **9c** interacted by means of hydrogen bonds with the backbone NH group of Phe518 (2.14 Å) and with the NH_2 group of the Gln192 side chain (2.47 Å), while the phenyl ring at position 5 was embedded in a hydrophobic region, making lipophilic contacts with the side chains of both Leu352 and Val523 possible. Finally, the ester chain of **9c**, superimposed to the trifluoromethyl group of **3a**, was involved with its oxygen atoms in a network of three hydrogen bonds with the guanidino group of Arg120 in a portion of the COX-2 binding site, referred to as the "classical NSAID's carboxylate binding site".[16] The ethyl group pointed toward the solvent-accessible surface and made hydrophobic contacts with Val116 and Tyr355 possible. Finally, the methyl substituent at position 2 of the pyrrole ring was sandwiched between the side chains of Val349 and Ala527 with positive hydrophobic interactions. Details of computer simulations on **9a** and **9b** have been reported in the Supporting Information, as well as the results from Grid calculations. Transformation of the ethyl ester side chain into the corresponding acidic derivatives did not significantly influence the activity of the methyl and trifluoromethyl derivatives, in agreement with what was previously reported, suggesting that position 3 of pyrrole seemed much more permissive and tolerant to a number of substituents and functional groups.[11] In fact, **10c** showed an activity only twice lower than the corresponding ester, while the activities of **10b** and **9b** were comparable to each other. In contrast, **10a** was found to be 25 times less active than the corresponding ester derivative **9a**. Inspection of the alignment mode of **3a** and the new pyrrole derivatives within the COX-2 binding site suggested that the CF_3 group, crucial for the binding of **3** and **3a**,[17] could be replaced among pyrrole derivatives by larger substituents (i.e., an acidic function and the corresponding ethyl ester) without affecting the activity, as shown by the affinity and selectivity data of the new pyrrole compounds. Moreover, literature reports showed that pyrrole derivatives bearing small substituents (such as Br and F) also retained high affinity for COX-2 but with a large decrease in selectivity because of the higher COX-1 affinity.[11] Taken together, these findings suggested that the role of CF_3 in the binding of coxib derivatives was carried out by the ester (or acidic) function and by the methyl substituent at position 2 of the new pyrroles, as shown by docking simulations and Grid maps.

Conclusions

Two computational approaches were applied to the new inhibitors, based on molecular docking/structural optimization and on the generation of Grid maps for different probes. Results from calculations led to the identification of a binding mode for the pyrrole derivatives, to the rationalization of their major structure–activity relationships, and finally to the suggestion of structural modifications of the compounds studied with the aim of obtaining new derivatives with higher affinity for COX-2. For this purpose, the synthesis and biological evaluation of new compounds are now being carried out and definitive results will be reported in due course.

Experimental Section

Chemistry. All chemicals used were of reagent grade. Yields refer to purified products and are not optimized. Melting points were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. Microanalyses were carried out by means of a Perkin-Elmer 240C or a Perkin-Elmer series II CHNS/O analyzer, model 2400. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Merck TLC plates and silica gel 60 F_{254} were used for TLC. ^{1}H NMR spectra were recorded with a Bruker AC 200 spectrometer in the indicated solvent (TMS as internal standard). The values of the chemical shifts are expressed in ppm, and the coupling

constants (*J*) are expressed in Hz. Mass spectra were recorded on a Varian Saturn 3 or a ThermoFinnigan LCQ-deca spectrometer.

1-[4-(Methylthio)phenyl]pentane-1,4-dione (12). To a solution of 4-(methylthio)benzaldehyde (12 mL, 0.09 mol) in ethanol (30 mL) were added triethylamine (19.5 mL, 0.14 mol), methyl vinyl ketone (5.8 mL, 0.07 mol), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (3.53 g, 0.014 mol). The mixture was heated at 75−80 °C for 20 h under nitrogen and then cooled. The solvent was removed under reduced pressure, and the residue was treated with 2 N HCl (300 mL). After extraction with dichloromethane, the organic layer was washed with aqueous sodium hydrogen carbonate and water. The organic fractions were dried over Na_2SO_4, filtered, and concentrated to give a crude orange liquid (16.2 g). After chromatography on silica gel (hexane/ethyl acetate, 7/3 v/v), the desired **12** was isolated (yield 70%) as a light-yellow solid that after recrystallization from hexane gave an analytical sample as light-yellow needles. The analytical data, melting point, and ^{1}H NMR spectrum were consistent with those reported in the literature.[11]

1-[4-(Methylsulfonyl)phenyl]pentane-1,4-dione (13). To a solution of **12** (7.8 g, 35 mmol) in methanol (150 mL), Oxone (37.7 g, 61.4 mmol) dissolved in water (150 mL) was added over 5 min. After the mixture was stirred at 25 °C for 2 h, the reaction mixture was diluted with water (400 mL) and extracted with CH_2Cl_2 (3 × 400 mL). The organic layer was washed with brine (200 mL) and water (200 mL) and dried (Na_2SO_4). After filtration and concentration, the crude material was chromatographed (silica gel; hexane/ethyl acetate, 3/1) to give **13** (yield 90%) as a yellowish solid that after recrystallization from hexane/ethyl acetate gave an analytical sample as white needles. The analytical data, melting point, and NMR spectrum were consistent with those reported in the literature.[11]

General Procedure for the Preparation of 1,5-Diarylpyrroles 14a−c. These compounds were prepared by means of the Paal−Knorr reaction as shown in Scheme 1 by condensing a 1,4-diketone with the appropriate amine. Briefly, a mixture of diketone **13** (2.28 mmol) and the suitable amine (2.5 mmol) in the presence of *p*-toluenesulfonic acid (30 mg) in dry toluene (50 mL) was refluxed for 20 h using a Dean−Stark apparatus. The reaction mixture was cooled, filtered, and concentrated. The crude material was purified by flash chromatography with a hexane/ethyl acetate (7/3 v/v) mixture as the eluent to give the expected 1,5-diarylpyrrole as a solid in satisfactory yield. Recrystallization from hexane/ethyl acetate gave the required product.

General Procedure for the Preparation of Ethyl 1,5-Diarylpyrrole-3-ylglyoxylic Esters (8a−c). These compounds were prepared by reaction of ethoxalyl chloride with the appropriate pyrrole in the presence of pyridine, as previously reported.[12] A solution of pyridine (11 mmol) in CH_2Cl_2 was added to a strirred solution of ethoxalyl chloride (1.22 mL, 10 mmol) in CH_2Cl_2 (15 mL) at a rate that allowed the temperature to be kept between −20 and −25 °C. Immediately after, a solution of the pyrrole derivative (10 mmol) in CH_2Cl_2 (15 mL) at the same temperature was added. The solution was stirred for 4 h at 0 °C, then washed sequentially with dilute HCl and saturated aqueous NaCl solution. The organic solution was dried and evaporated in vacuo. Purification of the residue by flash chromatography with ethyl acetate as eluent gave a solid that after recrystallization from hexane/ethyl acetate afforded the expected product.

General Procedure for the Preparation of Ethyl 1,5-Diarylpyrrole-3-acetic Esters (9a−c). These compounds were prepared by reduction of the appropriate glyoxylic derivative by means of triethylsilane in trifluoroacetic acid (TFA)[13] under nitrogen atmosphere at 0 °C. The procedure for the synthesis of **9a−c** is as follows. To a solution of the suitable α-keto ester (2.3 mmol) in trifluoroacetic acid (TFA) (9 mL) stirred at 0 °C under nitrogen, triethylsilane (0.75 mL, 4.7 mmol) was slowly added, and the mixture was stirred for 30 min at room temperature. At the end of the reaction, the mixture was made alkaline with 40% aqueous ammonia (10 mL) and extracted with $CHCl_3$ (250 mL). The organic solution was dried and evaporated in vacuo. The resulting residue was chromatographed on silica gel, eluting with $CHCl_3$ to give a solid that after recrystallization from hexane/ethyl acetate afforded the required product.

General Procedure for the Preparation of 1,5-Diarylpyrrole-3-acetic Acids (10a−c). These compounds were prepared from the appropriate pyrroleacetic ester by alkaline hydrolysis in a solution of 2 M KOH. The synthetic procedure is described below. To a solution of 2 M KOH (20 mL) in EtOH (15 mL), the suitable 1,5-diarylpyrrole-3-acetic ester (1.5 mmol) was added. The reaction mixture was refluxed for 2 h. The solution was then cooled and acidified with 3 N HCl (10 mL) and extracted with dichloroethane (20 mL). The organic solution was dried and evaporated in vacuo. The resulting residue was recrystallized with ethanol to afford the expected acid in good yields.

Biology. Arachidonic acid was obtained from SPIBIO, Paris, France. [^{3}H-PGE_2] was from Perkin-Elmer Life Sciences (Milan, Italy). All other reagents and compounds used were obtained from Sigma-Aldrich, Milan, Italy.

Cell Culture. The murine monocyte/macrophage J774 cell line was grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 2 mM glutamine, 25 mM Hepes, penicillin (100 u/mL), streptomycin (100 μg/mL), 10% foetal bovine serum (FBS), and 1.2% Na pyruvate (Bio Whittaker, Europe). Cells were plated in 24-well culture plates at a density of 2.5 × 10^5 cells/mL or in 10 cm diameter culture dishes (1 × 10^7 cells/10 mL per dish) and allowed to adhere at 37 °C in 5% CO_2/95% O_2 for 2 h. Immediately before the experiments, the culture medium was replaced by a fresh medium without FBS in order to avoid interference with radioimmunoassay,[18] and cells were stimulated as described.

COX-1 Activity. Cells were pretreated with the reference standard or the test compounds (0.01−10 μM) for 15 min and incubated at 37 °C for 30 min with 15 μM arachidonic acid in order to activate the constitutive COX.[18] Stock solutions of the reference standard or test compounds were prepared in dimethyl sulfoxide, and an equivalent amount of dimethyl sulfoxide was included in control samples. At the end of the incubation the supernatants were collected for the measurement of PGE_2 by radioimmunoassay.

COX-2 Activity. Cells were stimulated for 24 h with *E. coli* lipopolysaccharide (LPS, 10 μg/mL) to induce COX-2 in the absence or presence of the test compounds at the concentrations previously reported. The supernatants were collected for the measurement of PGE_2 by radioimmunoassay.

Statistical Analysis. Triplicate wells were used for the various conditions of the treatment throughout the experiments. Results are expressed as the mean, of three experiments, of the % inhibition of PGE_2 production by test compounds with respect to control samples. Data fit was obtained using the sigmoidal dose−response equation (variable slope) (GraphPad software). The IC_{50} values were calculated by the GraphPad Instat program (GraphPad software).

Computational Details. All calculations and graphical manipulations were performed on Silicon Graphics computers (Origin 300 server and Octane workstations) using the software package Autodock 3.0.5,[15] Grid 21,[14] and MacroModel 8.5[19] (equipped with the AMBER94 and OPLS-AA force field). The program Autodock was used to evaluate the binding mode of the new inhibitors and to explore their binding conformations within the COX-2 structure. Because Autodock does not perform any structural optimization and energy minimization of the complexes found, a molecular mechanics/energy minimization (MM/EM) approach was applied to refine the Autodock output. Program Grid was used to map the COX-2 binding site onto a three-dimensional grid and to calculate for each grid point the interaction energy (including contributions from the van der Waals, electrostatic, and hydrogen bond interactions) between a probe and all the protein atoms.

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Supporting Information Available: Experimental details (chemistry, pharmacology, and molecular modeling) and results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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