

Izicopan, a second-generation oral C5a receptor 1 (C5aR1) antagonist, demonstrates promising therapeutic potential in kidney disease models

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Background: Izicopan is a next-generation small-molecule C5aR1 antagonist developed to provide improved pharmacologic properties compared with avacopan, the first-in-class oral C5aR1 inhibitor. Izicopan achieves therapeutic exposure within days in humans, compared with weeks for avacopan, and demonstrates improved metabolic stability without evidence of time-dependent CYP3A4 inhibition. Together, these properties support a differentiated pharmacokinetic profile with potentially reduced drug–drug interaction liability.

Methods: C5a–C5aR1 signaling promotes neutrophil activation and recruitment and contributes to inflammatory kidney injury across diverse disease settings, including immune complex–mediated disease, ischemia–reperfusion injury (IRI), and unilateral ureteral obstruction (UUO). In the immune complex assay, levels of the neutrophil activation marker CD11b were measured using flow cytometry. In the IRI and UUO models, changes in whole blood cell counts (WBC), renal function indicators including creatinine (CREA) and blood urea nitrogen (BUN) were evaluated, and histopathological investigation were performed on kidney tissue samples.

Izicopan Demonstrated Improved Chemistry, Metabolic and Safety features

Feature	Avacopan	Izicopan	Key differentiation for izicopan
Medicinal chemistry	Used as a lead compound series	Further structure-activity optimization performed	Improved PK/PD and safety profiles
Chirality	2 chiral centers	3 chiral centers	Enhanced conformational control and druggability
Solid-state form	Crystalline	Amorphous	Faster absorption (therapeutic levels in days for izicopan vs. in 13 weeks for avacopan)
CYP inhibition	TDI of CYP3A4	No TDI of CYP3A4	Low risk of drug–drug interactions
Metabolic stability	Rapid CYP3A4-mediated metabolism in HLM and HH.	Slow CYP3A4-mediated turnover in HLM and HH	High metabolic stability and reduced risk of reactive metabolite formation
Reactive metabolites	Avacopan showed more extensive and diverse thiol-conjugate formation through both oxidative dealkylation-associated and non-dealkylation bioactivation pathways	Izicopan showed limited formation of low-abundance GSH-conjugated metabolites via oxidative dealkylation-associated pathways	Significantly lower reactive metabolite potential and lower risk of liver toxicity

CYP = cytochrome P450, HLM = human liver microsome, HH=human hepatocyte, TDI= time dependent inhibition.

Izicopan Maintains Avacopan-Like C5aR1 Potency with Differentiated CYP3A4 Metabolism

Izicopan preserves the structural features required for high-affinity C5aR1 binding, while its trifluoromethyl substituent minimized CYP3A4/5 interaction and prevents clinically relevant TDI.

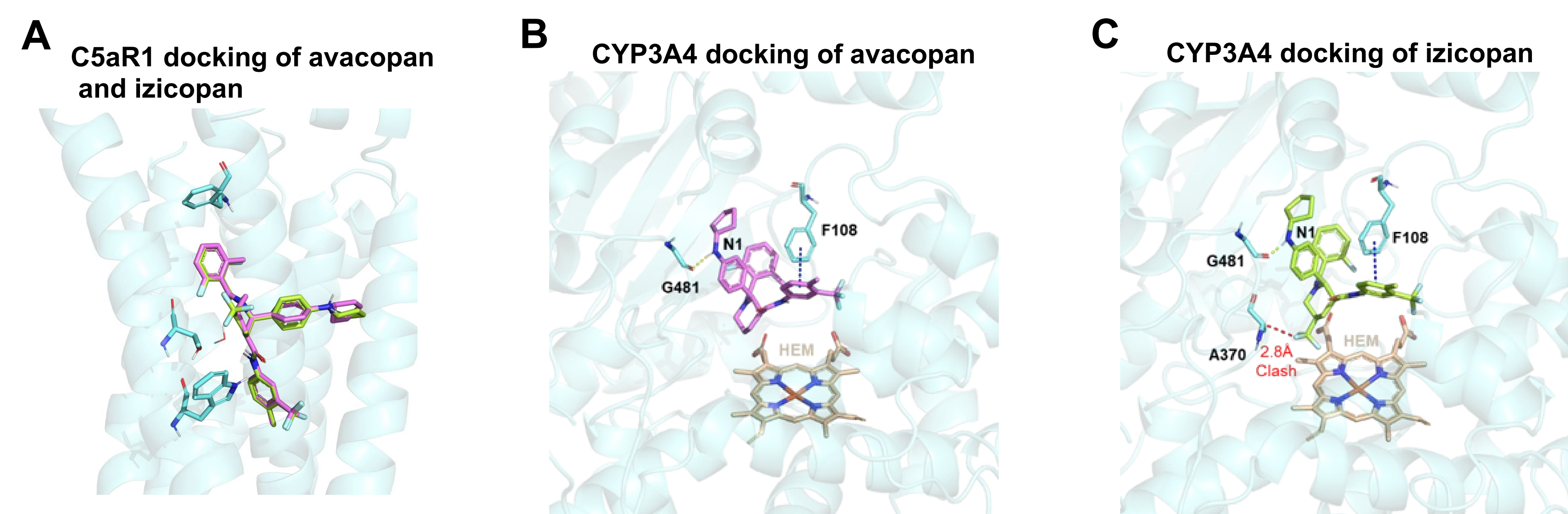


Figure 1. C5aR1 and CYP3A4 docking of izicopan and avacopan. (A) Superimposition of the C5aR1 docking pose of izicopan (green) and avacopan (purple). Cyan: C5aR1. (B–C) Molecular docking simulations of avacopan (B) and izicopan (C) with CYP3A4. Cyan: CYP3A4; Wheat: HEM; Purple: Avacopan; Green: Izicopan; Yellow dash lines: hydrogen bonds; Blue dash line: pi-pi stacking.

Efficacy of izicopan in a Hamster Renal Ischemia-reperfusion Injury Model (IRI)

The efficacy of izicopan was evaluated in a renal IRI model in LVG hamsters. Animals received a single oral dose of 100 mg/kg izicopan via oral gavage, 4 hours before surgery. Comparison of the vehicle-treated and izicopan-treated IRI groups showed that izicopan significantly reduced plasma CREA and BUN levels following IRI surgery, indicating that izicopan may be able to prevent kidney injury induced by ischemic reperfusion. Izicopan treatment significantly improved overall histological scores, as well as infarction and necrosis scores, compared with vehicle-treated controls.

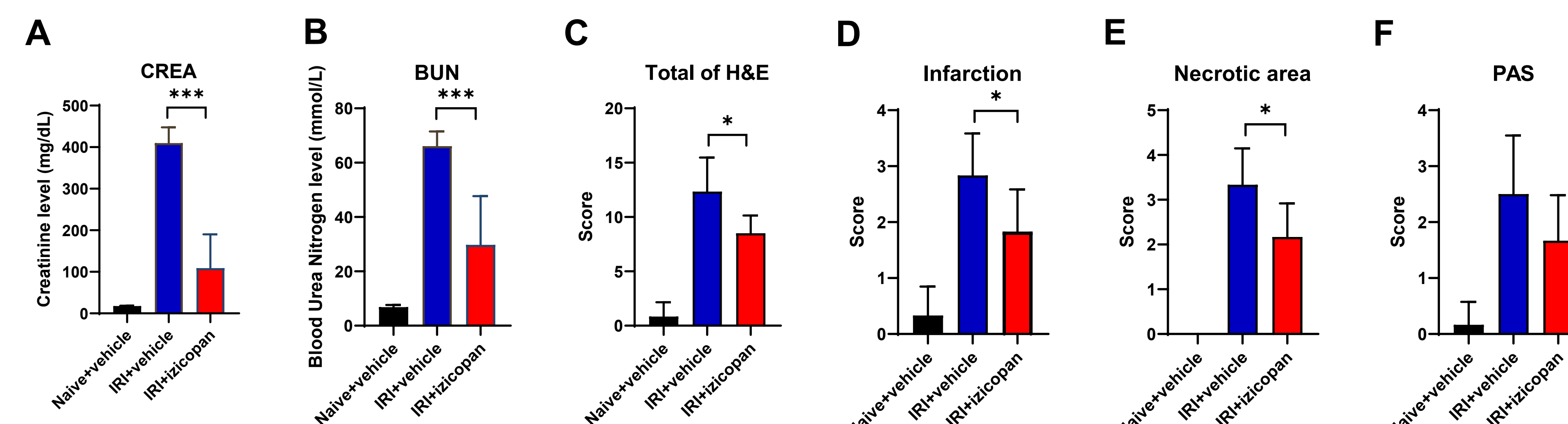


Figure 2. Effect of izicopan on blood biochemistry and histopathological scoring after IRI in hamsters. Izicopan significantly reduced plasma levels of creatine and blood urea nitrogen and improved histological of total score after the ischemia reperfusion surgery in comparison to vehicle treatment; *** $p < 0.001$, * $p < 0.05$.

Efficacy of Izicopan in a Hamster Unilateral Ureteral Obstruction-induced Nephropathy

The efficacy of izicopan was also evaluated in a UUO-induced nephropathy model in LVG hamsters. The first dose of izicopan or vehicle was given orally 5 hours before surgery, following 14 days QD dosing. The plasma level of CREA in the izicopan treated group was similar to that in the UUO model group during the study, and the serum levels of BUN in the izicopan treated group on day 14 after surgery was relatively low. Izicopan treatment significantly attenuated the total score of H&E staining compared to the vehicle group. Izicopan decreased the fibrosis score by Masson's staining and the score of α -smooth muscle actin (SMA)-positive cells but did not reach a statistically significant difference.

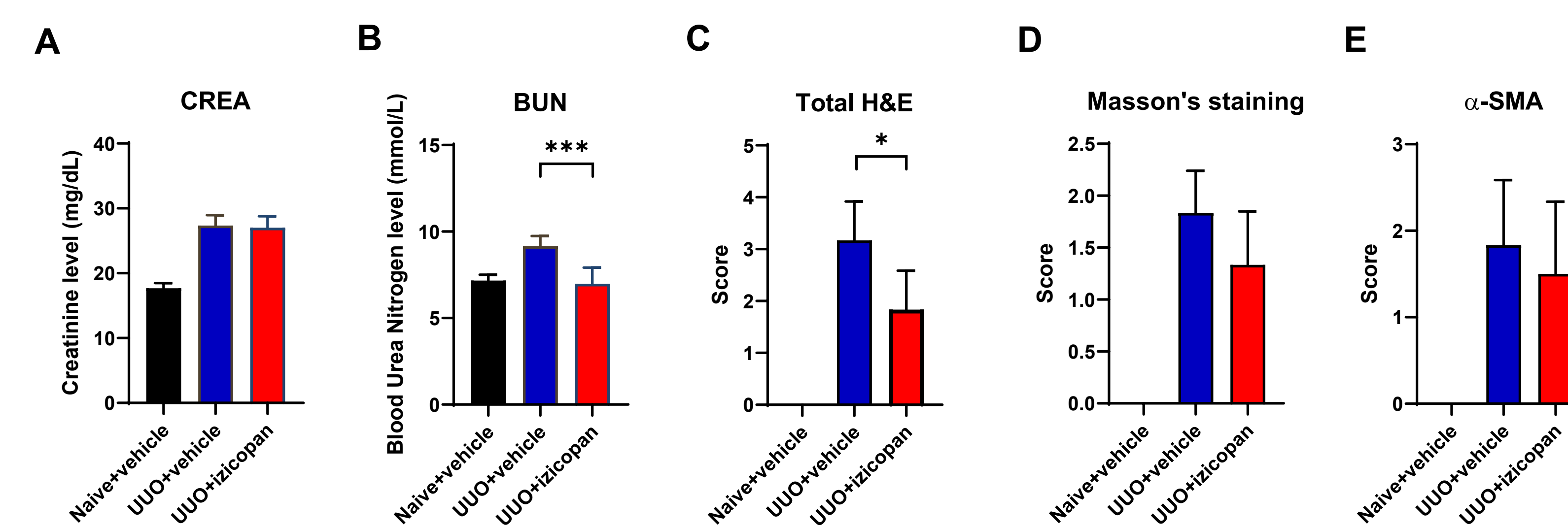


Figure 3. Effect of izicopan on blood biochemistry and renal histopathology in UUO-induced nephropathy. Izicopan significantly reduced blood urea nitrogen and improved histological of total score after the surgery in comparison to vehicle treatment; *** $p < 0.001$, * $p < 0.05$.

Conclusion: Across complementary *in vitro* immune complex model (data not shown) and *in vivo* models of renal injury, izicopan demonstrated robust inhibition of C5aR1-mediated inflammatory responses and renal protection, supporting it as a therapeutic candidate for complement-driven kidney diseases.

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