Supporting Information

Structural, Mechanistic and Ultra-dilute Catalysis Portrayal of Substrate Inhibition in the TAML–Hydrogen Peroxide Catalytic Oxidation of the Persistent Drug and Micropollutant, Propranolol

Yogesh Somasundar,[1] Longzhu Q. Shen,[2] Alexis G. Hoane,[1] Liang L. Tang,[1] Matthew R. Mills,[1] Abigail E. Burton,[1] Alexander D. Ryabov,[1]* and Terrence J. Collins[1]*

[1]Department of Chemistry, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, Pennsylvania 15213, United States

[2]Department of Zoology, University of Cambridge, Downing Street, Cambridge CB2 3EJ, UK

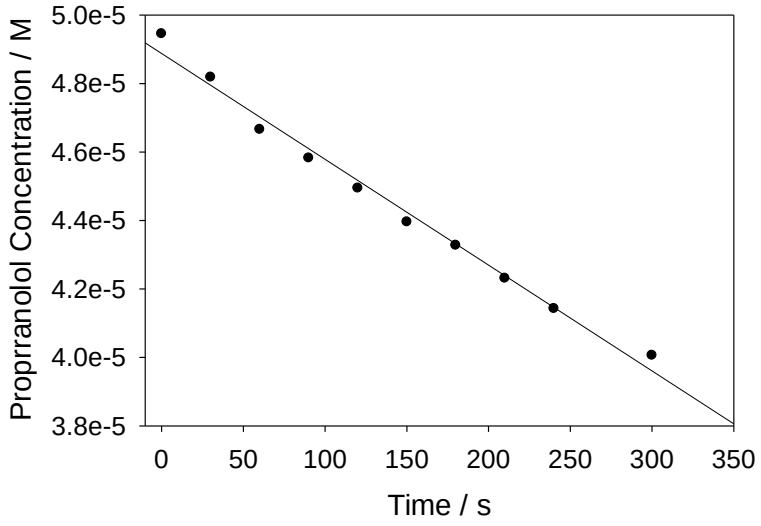


Figure S1: Determination of initial rate (slope of the line) when ≤ 20% reaction is completed. Conditions: [**1a**] 1×10^{-6} M, [propranolol] 5×10^{-5} M, [H_2O_2] 1×10^{-3} M, pH 9 (0.01 M phosphate), 25 °C.

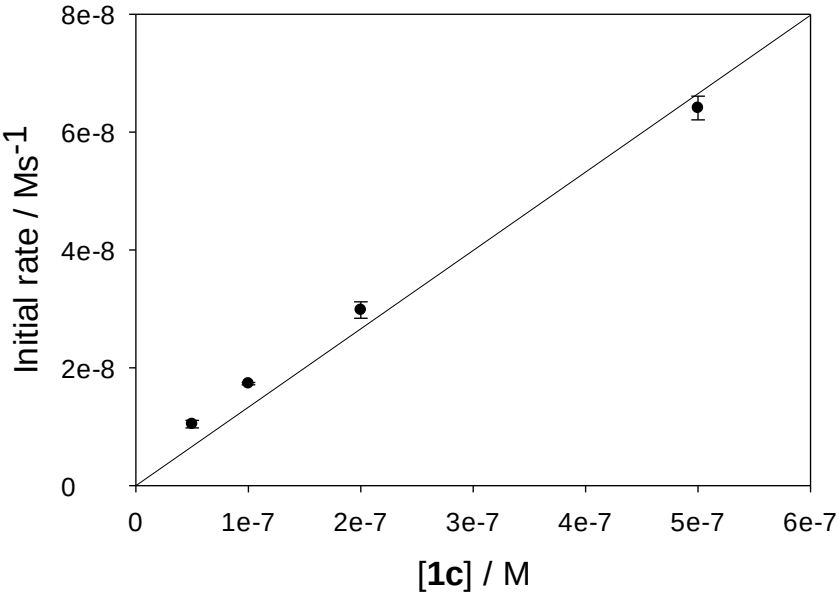


Figure S2. Initial rate of propranolol degradation by H_2O_2 catalyzed by **1c** as a function of [**1c**]. Conditions: [**1c**] = (5-50) $\times 10^{-8}$ M, [propranolol] = 5×10^{-5} M, [H_2O_2] 3×10^{-3} M, pH 7 (0.01 M phosphate).

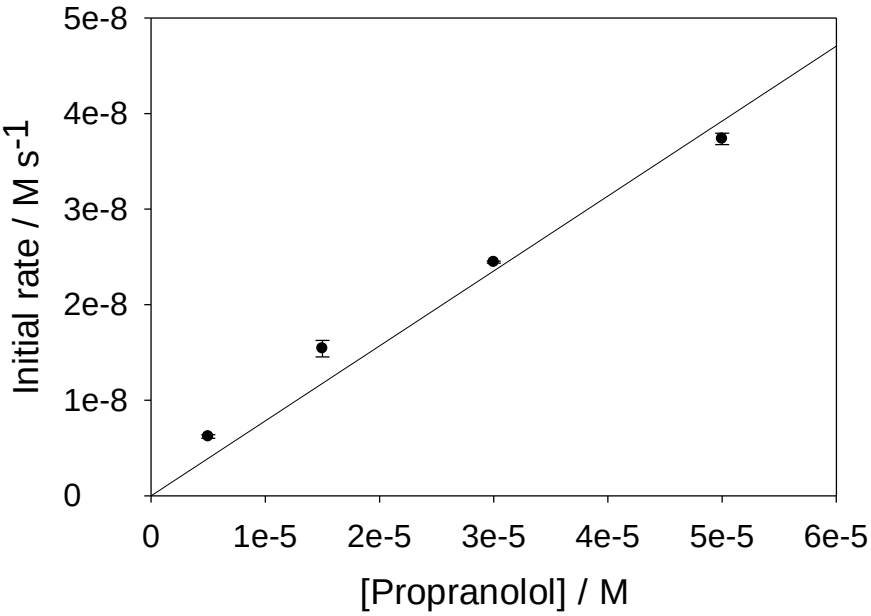
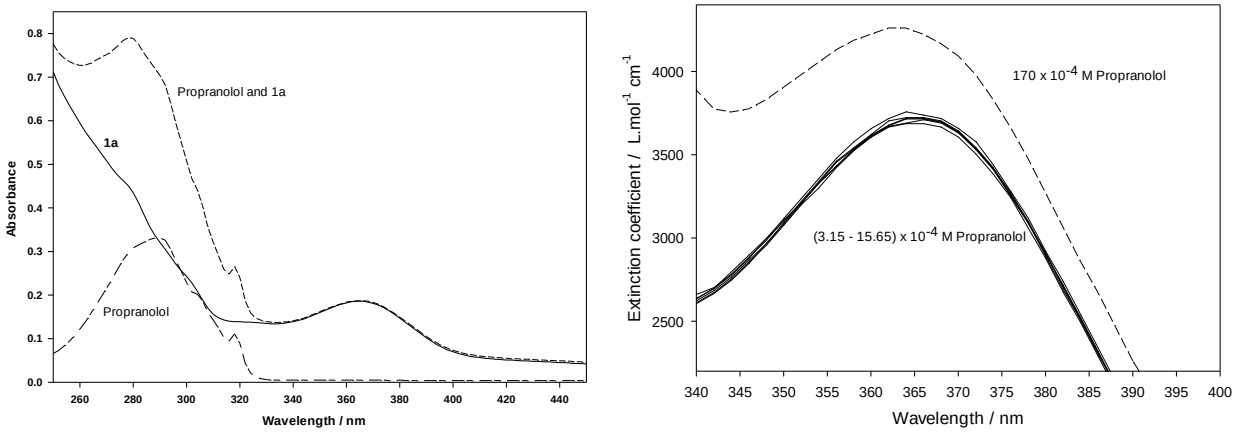


Figure S3. Initial rate of propranolol degradation by H_2O_2 catalyzed by **1a** as a function of [propranolol]. Conditions: [**1a**] 1×10^{-6} M, [propranolol] (5-50) $\times$ 10^{-6} M, [H_2O_2] 4.25×10^{-3} M, pH 9 (0.01 M phosphate).



(A) (B)

Figure S4. (A) UV-vis spectrum of propranolol (5×10^{-5} M), **1a** (5×10^{-5} M), and propranolol and **1a** (5×10^{-5} M each), in pH 7 0.01 M phosphate buffer. (B) the variation of extinction coefficient of **1a** (5×10^{-5} M) upon titration with propranolol. Solid lines represent propranolol (3.2 - 15.7) $\times10^{-4}$ M and the dotted line represents propranolol (170×10^{-4} M).

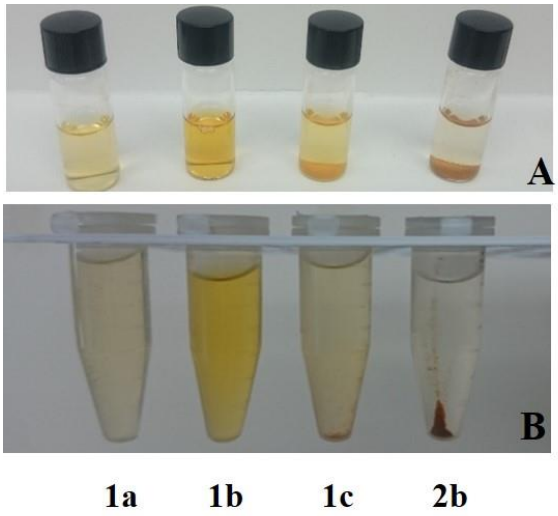


Figure S5: Mixtures of propranolol with TAMLs (left to right: **1a**, **1b**, **1c**, **2b**) showing the formation of precipitates for **1c** and **2b** before (A) and after (B) centrifugation. Conditions: propranolol (7.5×10^{-2} M), TAMLs (4.5×10^{-4} M), pH 7.0, room temperature.

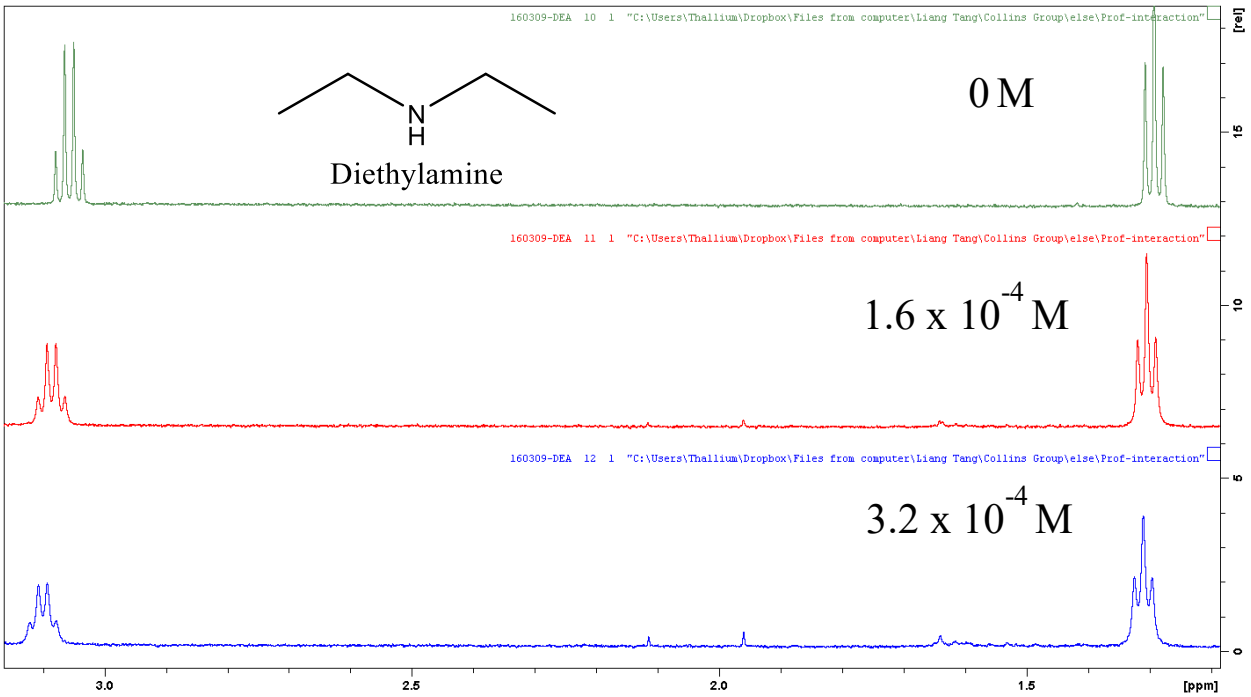


Figure S6. ^{1}H NMR spectra of diethylamine alone (0.015 M, top) and in the presence of **1b** (1.6×10^{-4} and 3.2×10^{-4} M, middle and bottom, respectively). Conditions: D_2O, 25 °C.

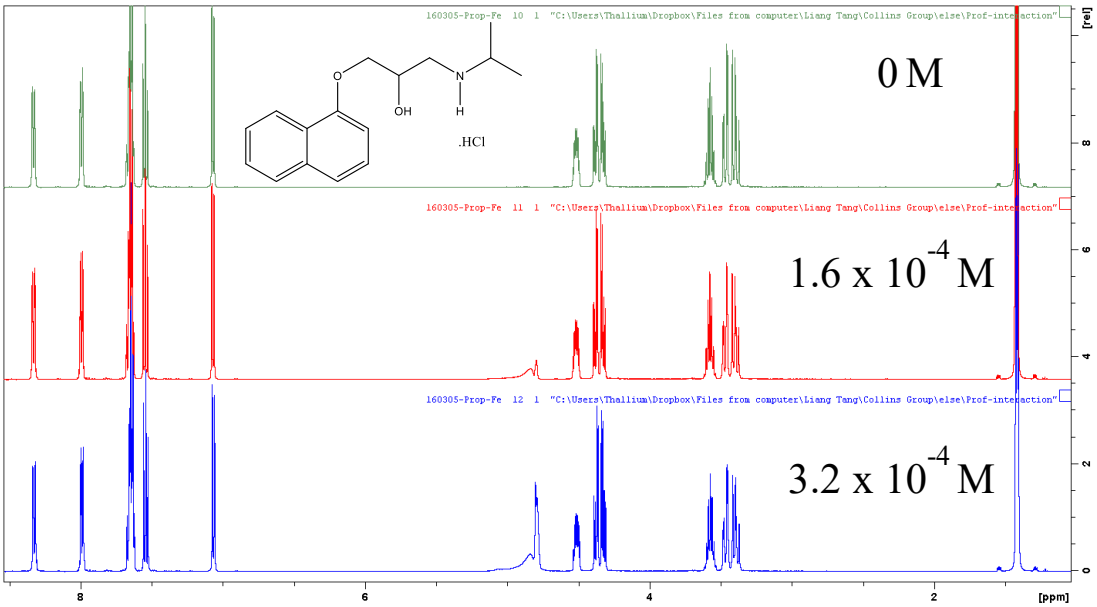


Figure S7. ^{1}H NMR spectra of propranolol alone (0.015 M, top) and in the presence of $FeCl_3$ (1.6×10^{-4} and 3.2×10^{-4} M, middle and bottom, respectively). Conditions: D_2O, 25 °C.

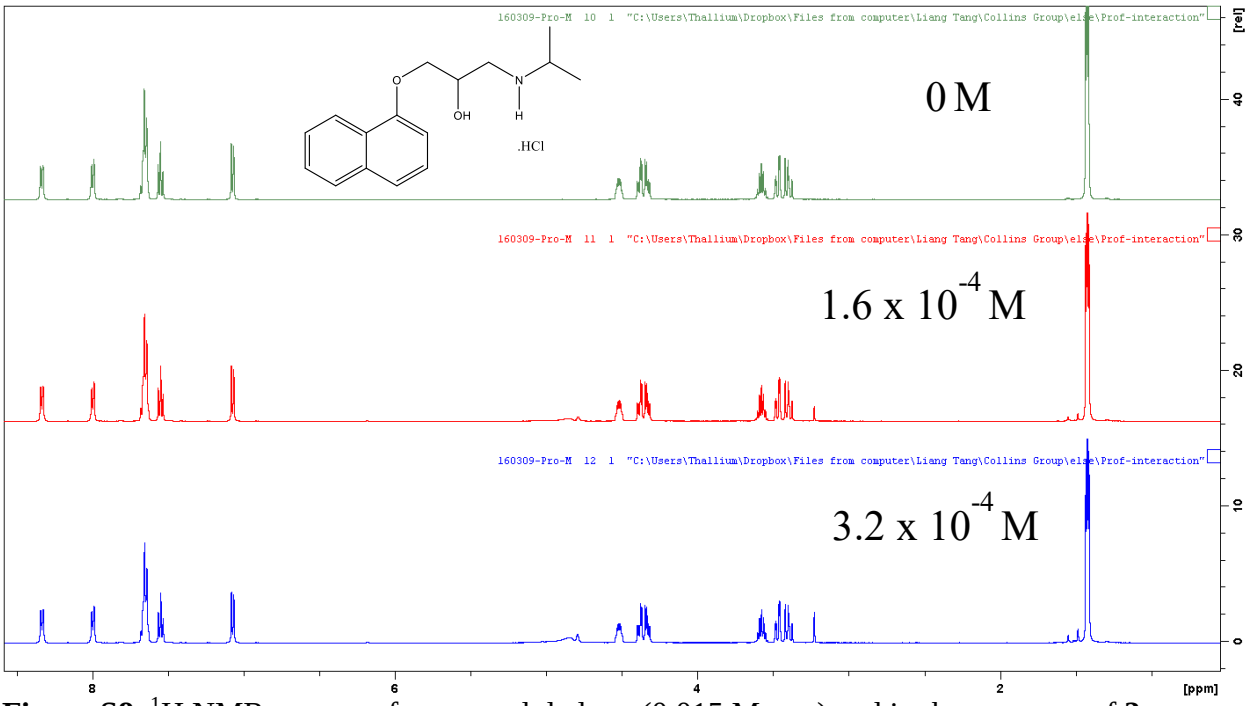


Figure S8. ^{1}H NMR spectra of propranolol alone (0.015 M, top) and in the presence of **3** (1.6×10^{-4} and 3.2×10^{-4} M, middle and bottom, respectively). Conditions: D_2O, 25 °C.

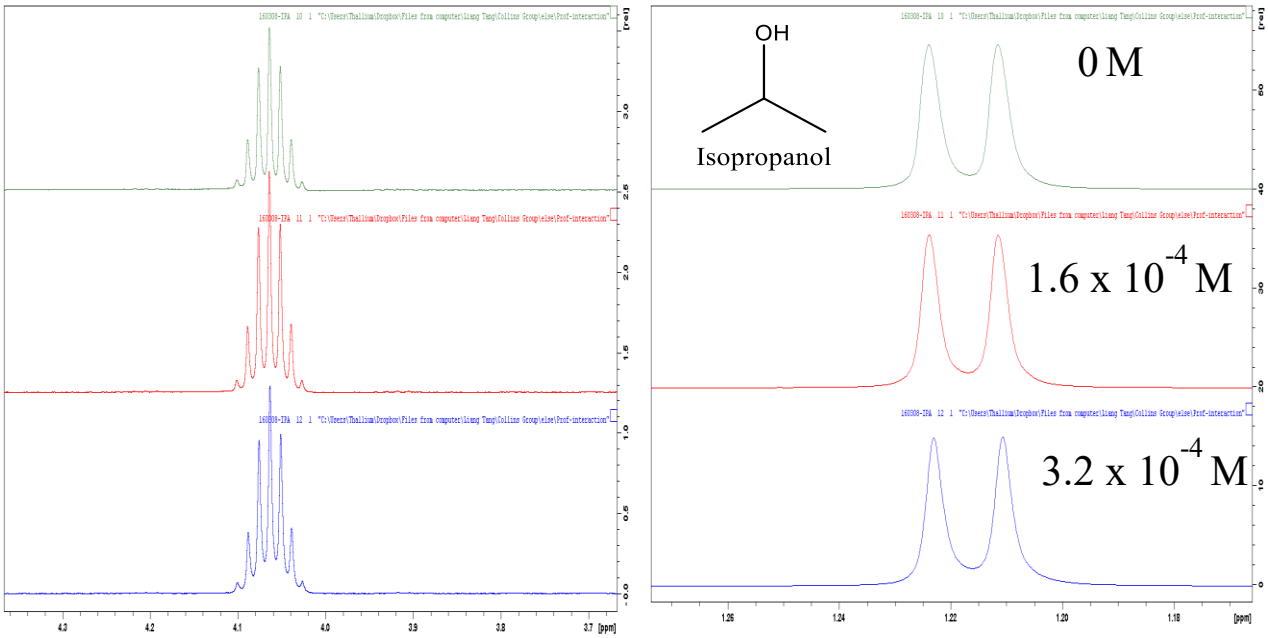


Figure S9. ^{1}H NMR spectra of isopropanol alone (0.015 M, top) and in the presence of **1b** (1.6×10^{-4} and 3.2×10^{-4} M, middle and bottom, respectively). Conditions: D_2O, 25 °C.

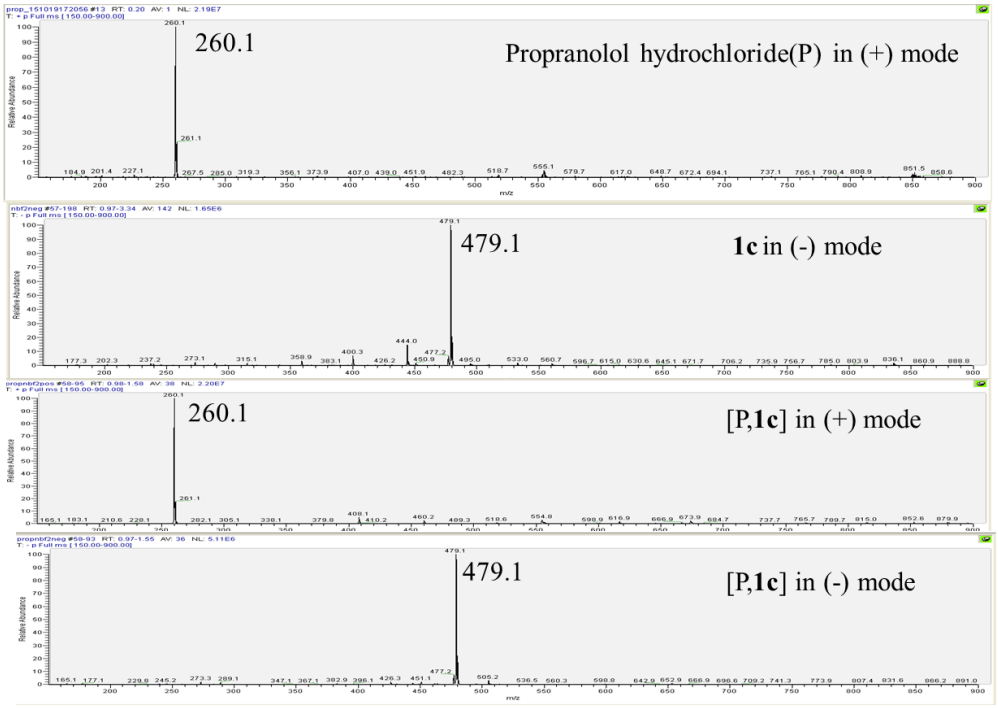


Figure S10. ESI-MS of propranolol, **1c** and [P,**1c**] in methanol. Conditions: 10 μL injection, 25 °C.

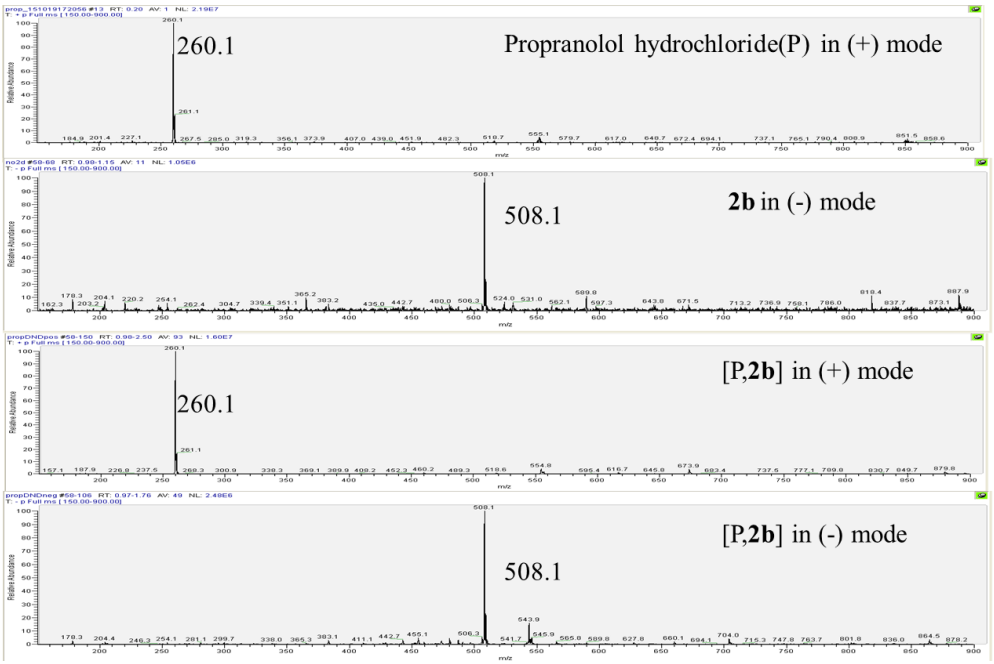


Figure S11. ESI-MS of propranolol, **2b** and [P,**2b**] in methanol. Conditions: 10 μL injection, 25 °C.

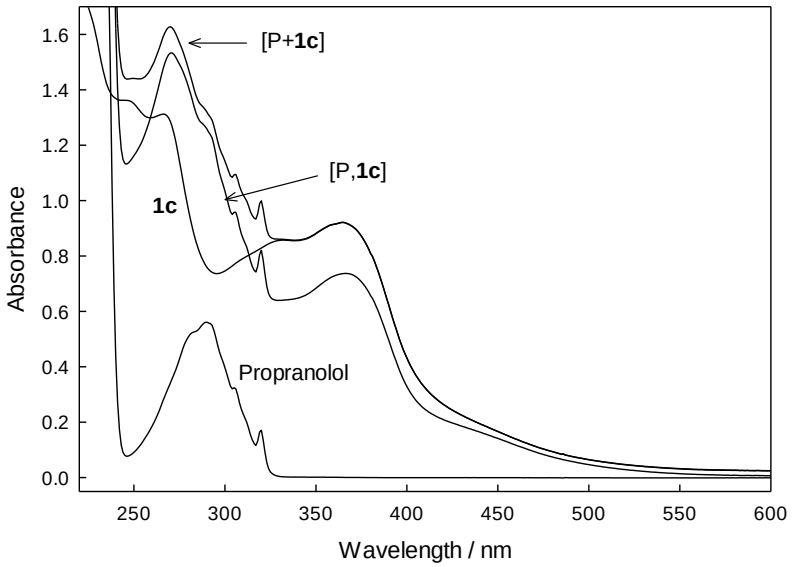


Figure S12. UV-vis spectra of propranolol (9×10^{-5} M), **1c** (9×10^{-5} M), [P,**1c**] adduct (ca. 8×10^{-5} M) and the sum of the spectra of propranolol and **1c** (both 9×10^{-5} M, P + **1c**). All spectra are in methanol.

Propranolol does not absorb light at 365 nm and therefore the concentration of **1c** in solution can be calculated from absorbance at 365 nm. At 290 nm (maximum for propranolol), the absorbance

$A = c_p\varepsilon_p + c_{1c}\varepsilon_{1c}$ and the concentration of propranolol c_p is easy to find since the extinction coefficients ε_p and ε_{1c} for propranolol and **1c**, respectively, and the concentration of **1c** (c_{1c}) are known. This routine confirmed an approximate 1:1 stoichiometry of the [P,TAML] adducts (Table S1). The exact P:TAML ratio was found to be 1.2 and 1.4 for **1c** and **2b**, respectively. Based on these stoichiometries, the isolated yields of the adducts equal 42% and 124% for **1c** and **2b**, respectively.

Table S1. Stoichiometry of [P,TAML] adducts.

Adduct type	Concentration of TAML x 10^4 M		Average concentration of Propranolol x 10^4 M			Ratio of Propranolol : TAML	
	365nm	445nm	280nm	290nm	300nm		
P+1c	0.79	-	1.02	0.95	0.90	0.95(3)	1.2 (3)
P+2	-	0.84	1.25	1.18	1.08	1.17 (3)	1.4 (3)

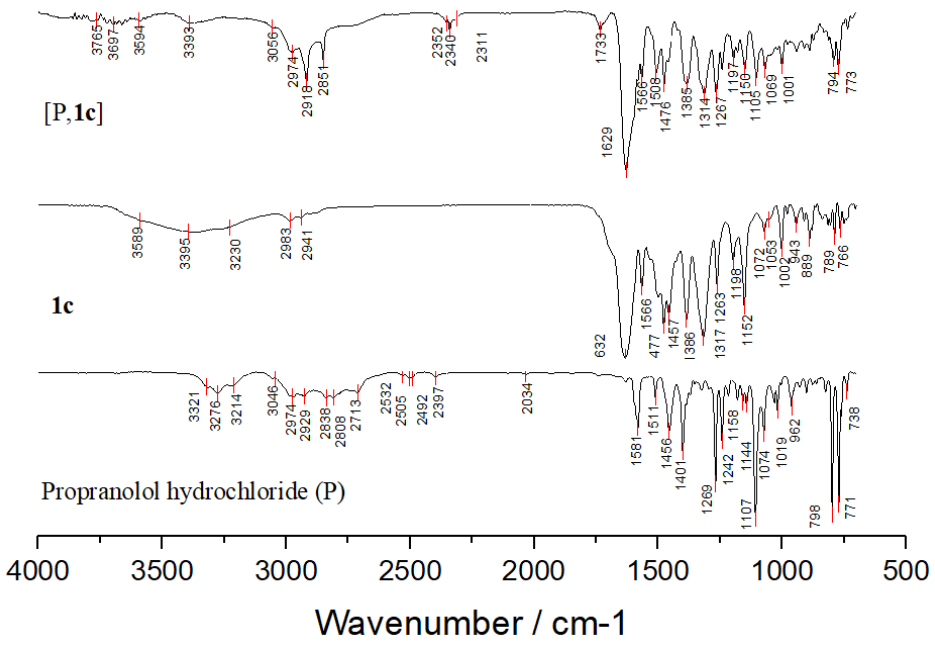


Figure S13. Infrared spectra of propranolol (P), **1c** and [P,**1c**]. Conditions: ATR accessory, germanium crystal, 25 °C. (All the spectra are scaled differently).

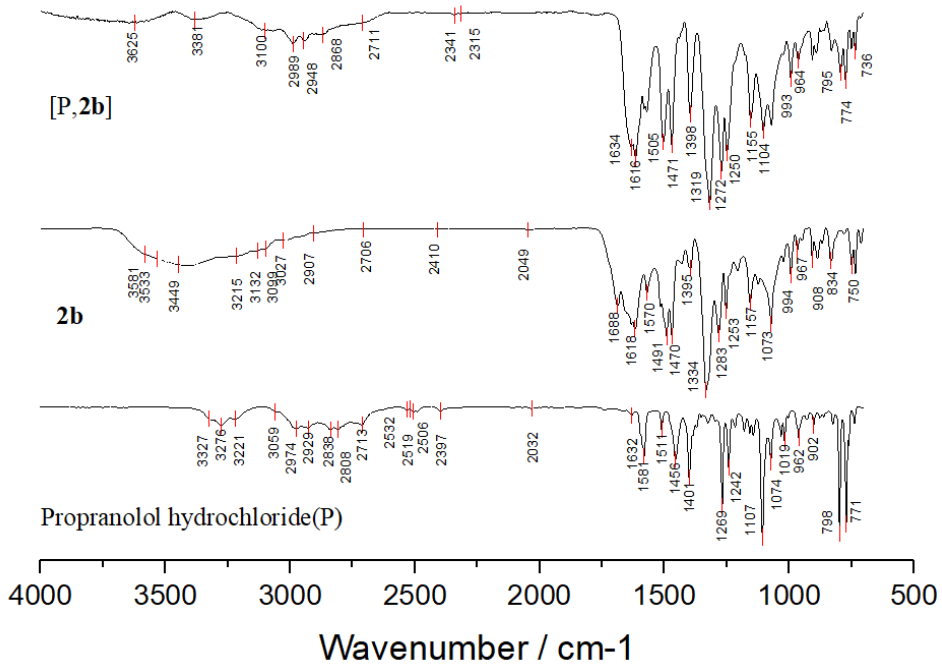


Figure S14. Infrared spectra of propranolol (P), **2b** and [P,**2b**]. Conditions: ATR accessory, germanium crystal, 25 °C. (All the spectra are scaled differently).

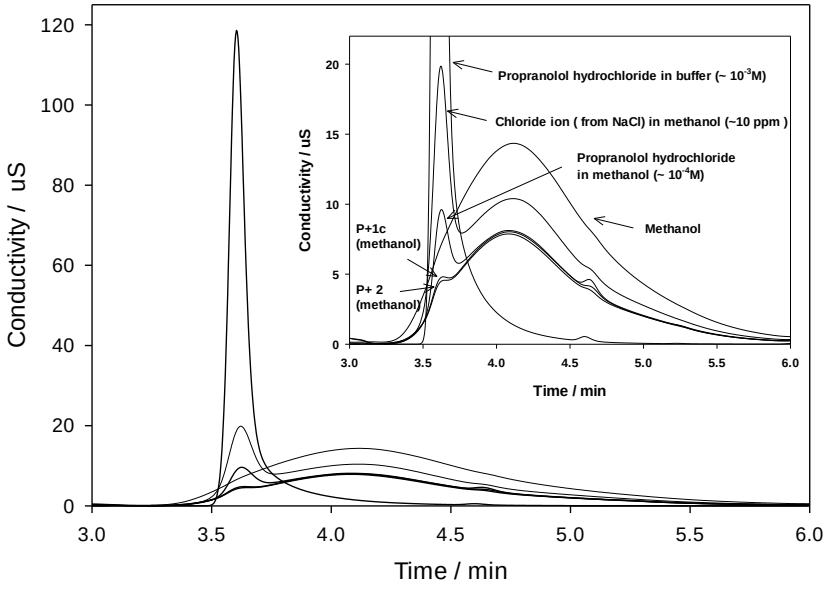


Figure S15. Ion chromatogram for the anionic component of [P,**1c**] and [P,**2b**] in methanol. Inset: zoomed in area between 0-20 μS. Conditions: Sample prepared at 25 °C, 25 μL injection. A trace of chloride remains in the isolated adducts as seen in the peak at 3.6 min.

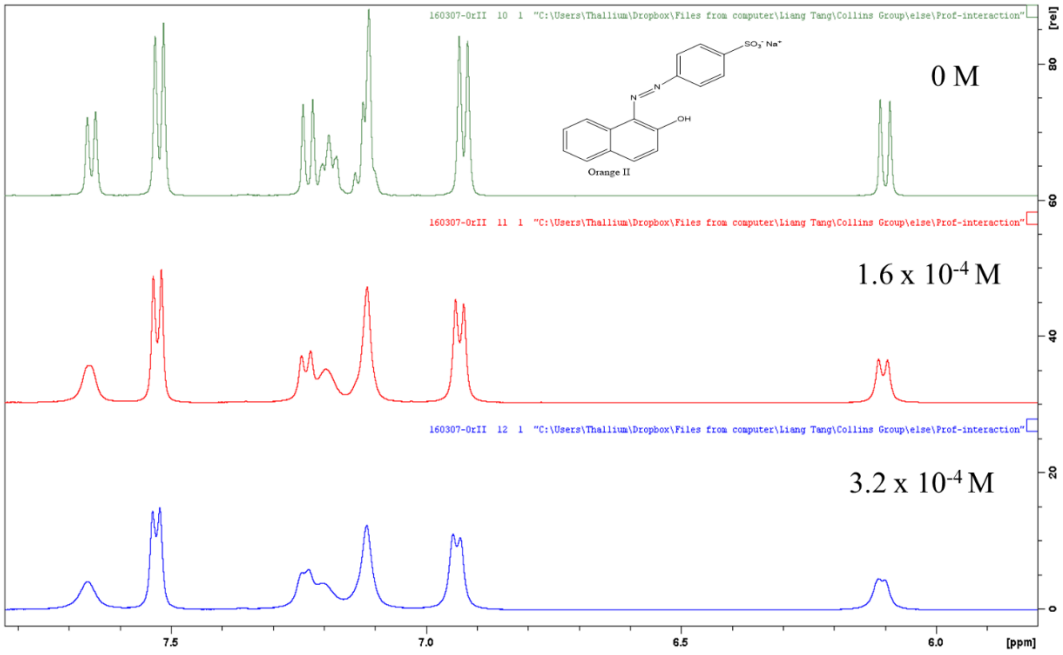


Figure S16. ^{1}H NMR spectra of OrangeII alone (0.015 M, top) and in the presence of **1b** (1.6×10^{-4} and 3.2×10^{-4} M, middle and bottom, respectively). Conditions: D_2O, 25 °C.

Table S2. Rate constants k_I and k_{II} for Propranolol at 25 °C compared with k_I values reported previously using other test substrates; calculated equilibrium constants, K and corresponding free energy change, $\Delta G°$.

TAML	pH	k_I M^{-1} s^{-1}	$10^{-2}\times k_{II}$ M^{-1} s^{-1}	k_I^{OrII} or $\boldsymbol{k_I^{Ru}}$ M^{-1} s^{-1}	k_I^{OrII}/k_I or $\boldsymbol{k_I^{Ru}/k_I}$	$10^{-5}\times K$ [e] M	$\Delta G°$ kcal mol^{-1}
1a	7.0	2.0±0.1	0.7±0.2	31.4±0.1 [a]	16	3	-7.5
	7.0			**52±2** [c]	**26**	**5**	**-7.8**
	9.0	74±3	8.0±0.3	1400±10 [b]	19	3.6	-7.6
	9.0			**2400±300** [c]	**32**	**6.2**	**-7.9**
1b	7.0	5.0±0.2	1.4±0.2	152±5 [a]	30	5.8	-7.9
	9.0	149±5	35±1				
1c	7.0	90±10	146±2	350±2 [a]	4	0.6	-6.5
	9.0	2990±50	680±10				
2b	7.0	200±10	53±24	1900±100 [a]	9.5	1.7	-7.1
	9.0	4200±400	500±40	16,000±2000 [d]	4	0.6	-6.5

[a] Orange II; from ref.[72] [b] Orange II; from ref.[80] [c] Cyclometalated ruthenium(II) dye $[Ru^{II}(o\text{-}C_6H_4\text{-}2\text{-}py)(phen)_2]^+$ [83]; from ref.[81] [d] Orange II; from ref.[70]