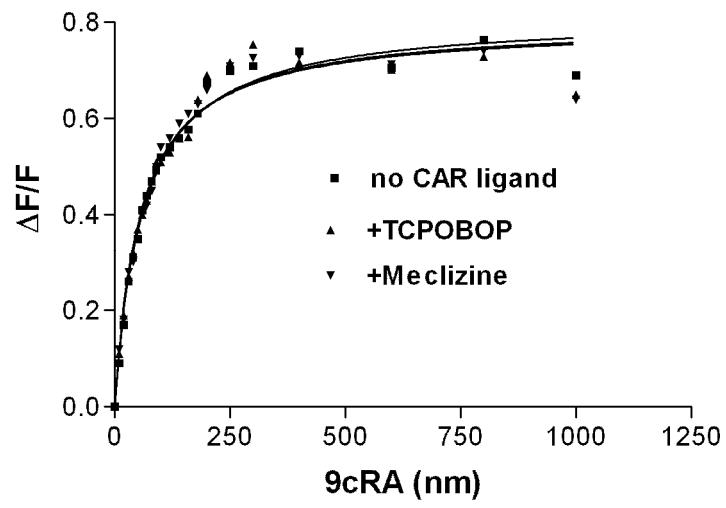
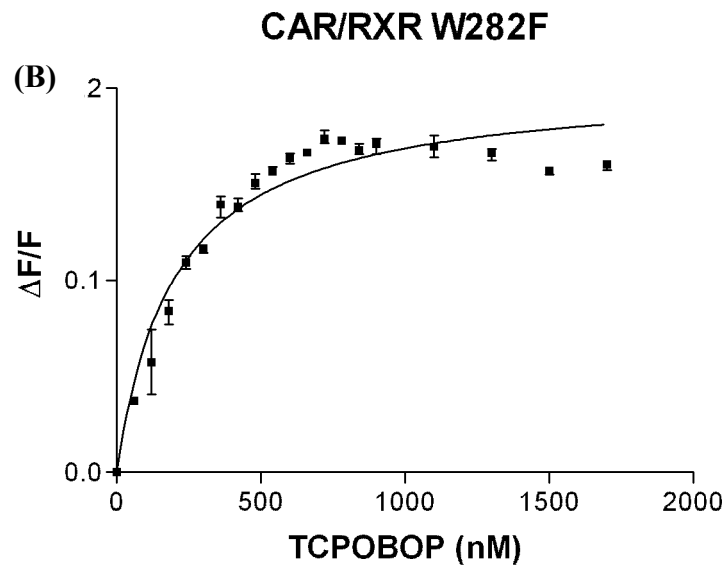
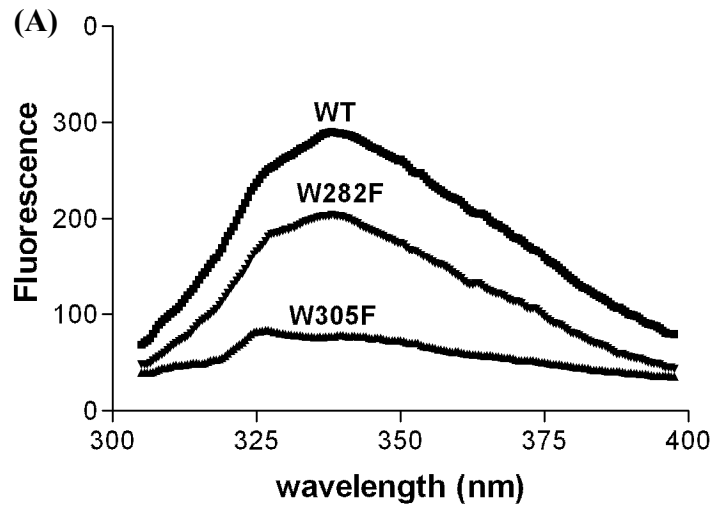


Supplemental Figure S1, related to Figure 2: **CAR ligands do not significantly affect 9c (9cRA) binding to CAR:RXR.** Steady-state fluorescence quenching measured at 340 nm upon titrating 9c into 250 nM CAR:RXR (■), CAR(TCPOBOP):RXR (▲) and CAR(meclizine):RXR.

Supplemental Figure S2, related to Figure 2: **Emission spectra of 1.0 μM CAR:RXR, CAR:(W282F)RXR and CAR:(W305F)RXR.** (A). The majority steady-state fluorescence quenching within the CAR:RXR heterodimer arises from W305. Mutation of W305 results in an almost complete loss of fluorescence signal. The W282F mutant still retains approximately 75% of its fluorescence at the emission maximum of 340 nm. (B). Titration of TCPOBOP into CAR:(W282F)RXR shows that there is a dose-dependent quenching of RXR W305 fluorescence.

Supplemental Figure S3, related to Figure 3: **Comparison of changes in HDX rates in regions of liganded CAR and RXR vs. unliganded CAR:RXR.** (A). Comparison of differences in deuterium exchange for CAR from CAR(TCPOBOP):RXR and CAR(meclizine)RXR compared to unliganded receptor. (B). Comparison of differences in deuterium exchange for RXR from CAR(TCPOBOP):RXR and CAR(meclizine)RXR compared to unliganded receptor. Increasing protections from deuterium exchange compared to unliganded receptor are represented as color gradient from light to dark blue. Gray indicates no significant change in exchange between ligand bound and unliganded receptor.

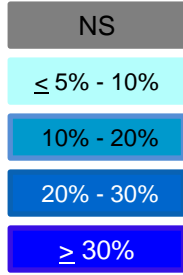




Supplemental Text & Figures

A

	Meclizine	TCPOBOP		Meclizine	TCPOBOP		Meclizine	TCPOBOP
115-125 (+2)	0%	2%	205-216 (+2)	0%	-3%	318-329 (+2)	0%	-2%
140-151 (+2)	1%	-3%	209-216 (+2)	0%	0%	319-325 (+2)	-2%	-2%
143-150 (+2)	1%	-7%	211-216 (+2)	0%	0%	319-326 (+2)	-1%	0%
151-171 (+3)	-1%	-5%	228-245 (+3)	-5%	-7%	327-339 (+2)	-7%	-28%
152-176 (+3)	1%	-5%	234-244 (+2)	-4%	-11%	330-337 (+2)	-9%	-36%
166-176 (+2)	-1%	-11%	234-245 (+3)	-4%	-5%	330-339 (+2)	-10%	-32%
166-178 (+2)	0%	-4%	234-249 (+3)	-3%	-5%	330-343 (+3)	-11%	-14%
177-185 (+2)	0%	0%	235-245 (+2)	-3%	-5%	330-346 (+2)	-8%	-29%
177-191 (+2)	0%	0%	235-247 (+2)	-3%	-6%	330-358 (+3)	-11%	-18%
177-192 (+2)	0%	0%	239-249 (+2)	-3%	-8%	338-343 (+2)	-11%	-54%
177-192 (+3)	0%	0%	248-269 (+3)	0%	-2%	340-358 (+2)	-21%	-12%
177-196 (+2)	0%	0%	248-271 (+3)	0%	0%	346-358 (+1)	-13%	-9%
177-198 (+2)	-1%	-2%	249-269 (+3)	0%	0%			
177-198 (+3)	-1%	0%	249-271 (+3)	0%	-1%			
177-199 (+3)	-1%	-1%	250-269 (+2)	0%	0%			
178-185 (+2)	0%	1%	250-269 (+3)	0%	0%			
178-192 (+2)	0%	0%	250-271 (+3)	0%	0%			
178-192 (+3)	0%	0%	250-272 (+3)	0%	0%			
178-198 (+3)	-1%	0%	256-269 (+3)	0%	0%			
178-203 (+3)	0%	1%	273-294 (+3)	-1%	1%			
179-185 (+2)	0%	0%	274-294 (+3)	-1%	-2%			
179-196 (+3)	-1%	0%	278-294 (+3)	-1%	-2%			
179-198 (+2)	0%	0%	278-297 (+2)	-1%	-2%			
179-198 (+3)	-1%	0%	278-299 (+2)	-1%	-2%			
179-203 (+3)	0%	0%	278-299 (+3)	-1%	-2%			
179-208 (+3)	0%	2%	299-317 (+3)	-1%	0%			
186-197 (+2)	4%	2%	300-308 (+2)	-2%	0%			
186-198 (+2)	-1%	0%	300-313 (+2)	0%	1%			
193-204 (+2)	-1%	3%	300-318 (+3)	-2%	1%			
199-208 (+2)	-1%	-6%	301-313 (+2)	-1%	-1%			
201-208 (+2)	0%	-5%	301-318 (+3)	-1%	0%			
201-210 (+2)	0%	-6%	314-322 (+3)	-2%	0%			



B	Meclizine		TCPOBOP		Meclizine		TCPOBOP	
	Meclizine	TCPOBOP	Meclizine	TCPOBOP	Meclizine	TCPOBOP	Meclizine	TCPOBOP
240-248 (+2)	-2%	0%	331-347 (+3)	2%	0%	419-427 (+3)	-1%	-5%
240-251 (+2)	-1%	-3%	353-362 (+2)	1%	0%	419-429 (+2)	0%	-3%
241-251 (+2)	-1%	-1%	353-362 (+3)	1%	-1%	419-430 (+2)	0%	-4%
249-270 (+2)	-1%	-3%	354-362 (+2)	1%	0%	419-430 (+3)	0%	-4%
249-278 (+2)	1%	1%	354-367 (+2)	0%	1%	419-438 (+2)	0%	-4%
249-279 (+3)	0%	-1%	354-370 (+2)	0%	3%	419-438 (+3)	0%	-5%
252-270 (+2)	-2%	2%	354-372 (+2)	0%	0%	420-432 (+2)	-1%	-5%
252-278 (+3)	1%	-1%	354-372 (+3)	0%	1%	420-432 (+3)	0%	-5%
271-278 (+2)	2%	1%	371-390 (+2)	-1%	0%	420-430 (+2)	0%	-4%
279-292 (+2)	0%	0%	371-390 (+3)	-1%	1%	423-432 (+3)	0%	-5%
279-292 (+3)	0%	0%	371-391 (+3)	0%	0%	423-432 (+3)	-1%	-4%
279-296 (+2)	0%	1%	373-388 (+2)	-1%	1%	423-430 (+3)	-1%	-4%
279-296 (+3)	0%	1%	373-390 (+2)	-1%	-1%	426-432 (+2)	0%	-4%
279-297 (+2)	0%	1%	373-391 (+2)	-1%	1%	426-438 (+2)	1%	-1%
279-297 (+3)	0%	1%	376-390 (+2)	-1%	1%	426-438 (+3)	1%	0%
280-296 (+2)	-1%	1%	376-392 (+2)	-2%	0%	438-451 (+2)	1%	0%
280-297 (+2)	0%	1%	376-400 (+3)	-1%	0%	439-451 (+2)	1%	1%
282-296 (+2)	-1%	1%	389-400 (+2)	-1%	0%	451-462 (+2)	-1%	2%
282-297 (+2)	-1%	0%	389-400 (+3)	0%	-2%	454-462 (+2)	0%	0%
283-297 (+3)	1%	-1%	390-400 (+2)	0%	0%	455-462 (+1)	1%	2%
298-308 (+2)	-1%	0%	391-397 (+2)	0%	0%			
301-304 (+2)	0%	1%	391-400 (+3)	-1%	0%			
301-305 (+2)	0%	1%	392-400 (+2)	0%	0%			
309-325 (+2)	0%	-1%	392-402 (+3)	0%	-1%			
310-325 (+2)	0%	-1%	393-400 (+2)	0%	0%			
310-325 (+3)	0%	-1%	401-415 (+3)	-1%	1%			
313-325 (+2)	1%	1%	401-418 (+3)	0%	1%			
326-343 (+2)	1%	-2%	403-415 (+2)	-1%	2%			
326-346 (+2)	1%	1%	403-415 (+3)	-1%	1%			
326-347 (+3)	1%	0%	416-432 (+3)	-1%	-4%			
326-353 (+3)	2%	-3%	419-425 (+2)	0%	-4%			
331-346 (+2)	0%	1%	419-427 (+2)	0%	-5%			

