Molecular Modeling of Allosteric Site of Isoform-Specific Inhibition of the Peroxisome Proliferator-activated Receptor PPARγ

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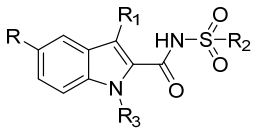
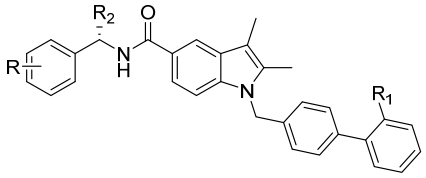
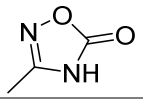
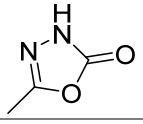
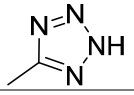
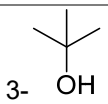
Table S1. The chemical structures of PPARγ antagonists taken from Hopkins' paper [1].

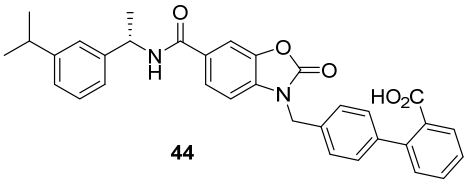


Compound	R	R_1	R_2	R_3
NSI	H	4-CH_3OPh	Ph	3-CF_3Bn
1	H	4-CH_3OPh	4-F-Ph	3-CF_3Bn
2	H	4-CH_3OPh	2-CO_2MePh	3-CF_3Bn
3	H	4-CH_3OPh	2-CH_3Ph	3-CF_3Bn
4	H	4-CH_3OPh	Me	3-CF_3Bn
5	H	H	Ph	3-CF_3Bn
6	H	H	4-F-Ph	3-CF_3Bn
7	H	H	4-Cl-Ph	3-CF_3Bn
8	H	H	3-CF_3-Ph	3-CF_3Bn
9	H	H	4-CH_3Ph	3-CF_3Bn
10	H	H	2-CH_3Ph	3-CF_3Bn
11	H	H	2-Naphthyl	3-CF_3Bn
12	H	H	2-CF_3-Ph	3-CF_3Bn
13	H	H	2-(5-Chlorothiophene)	3-CF_3Bn
14	H	H	Me	3-CF_3Bn
15	H	H	4-CF_3-Ph	4-CF_3Bn
16	H	H	3-CF_3-Ph	3-CH_3OBn
17	H	H	3-CF_3-Ph	3-CF_3OBn
18	H	H	3-CF_3-Ph	Et
19	H	H	3-CF_3-Ph	4-CF_3Bn
20	H	H	3-CF_3-Ph	3-BnOBn
21	H	H	3-CF_3-Ph	Bn
22	H	H	3-CF_3-Ph	2,5-DiClBn
23	H	H	3-CF_3-Ph	4-*t*-BuBn
24	Cl	H	3-CF_3-Ph	3-CF_3Bn
25	OBn	H	3-CF_3-Ph	3-CF_3Bn
26	OH	H	3-CF_3-Ph	3-CF_3Bn

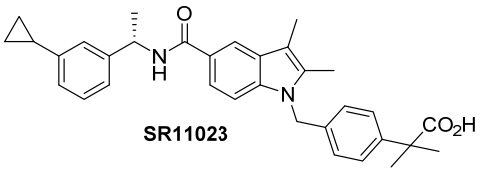
Table S2. The chemical structures of PPARγ antagonists taken from Asteian's paper [2].



Compound	R	R_1	R2	Compound	R	R_1	R2
27	2-CH_3	COOH	H	**SR1664**	4-NO_2	COOH	CH_3
28	2-NH_2	COOH	H	**36**	3-iPr		CH_3
29	2-NO_2	COOH	H	**37**	3-iPr		CH_3
30	3-iPr	COOH	CH_3	**38**	3-iPr		CH_3
31	3- 	COOH	CH_3	**39**	3-iPr	CONHOH	CH_3
32	3-tBu	COOH	CH_3	**40**	3-iPr	$CONH_2$	CH_3
33	4-iPr	COOH	CH_3	**41**	3-iPr	$CON(CH_3)_2$	CH_3
34	4-tBu	COOH	CH_3	**42**	3-iPr	COOH	CF_3
35	3- 	COOH	CH_3	**43**	3-iPr	COOH	3-iPr



44



SR11023

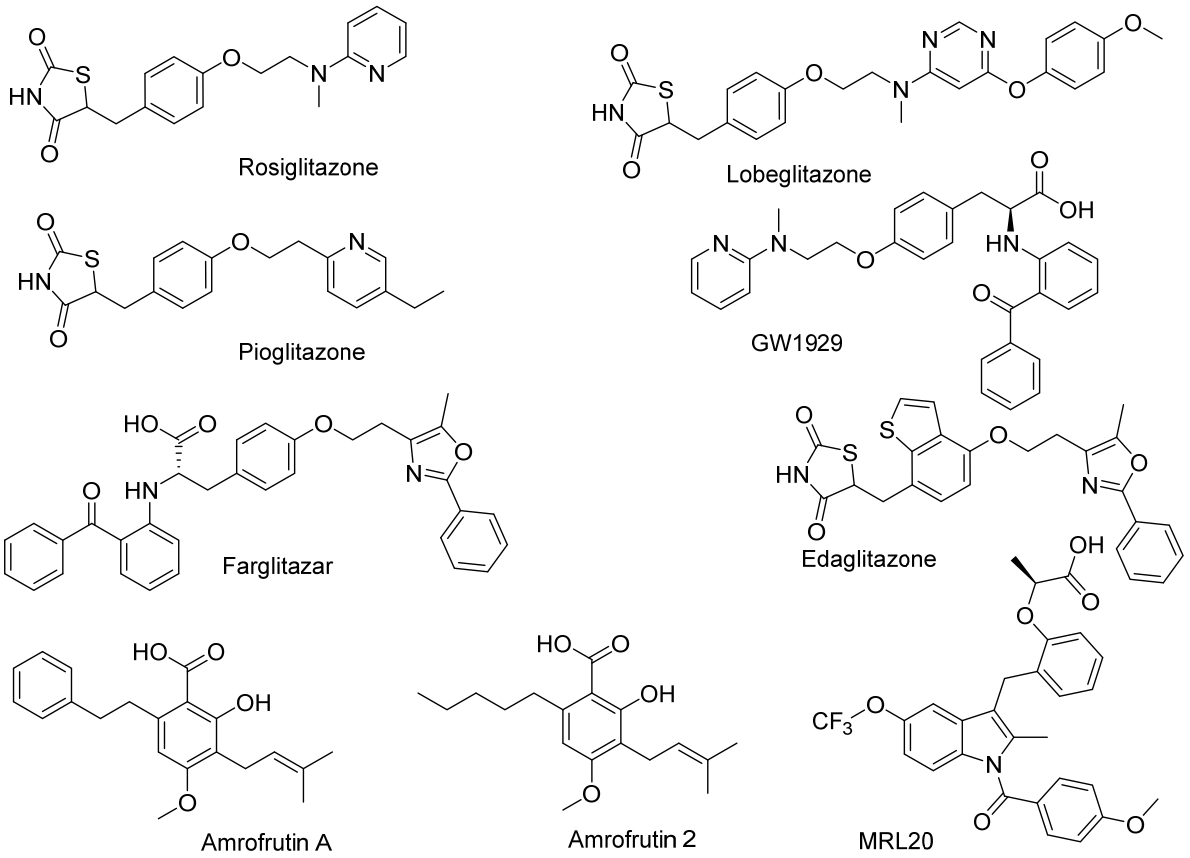


Figure S1. The chemical structures of PPARγ agonists.

Table S3. Glide docking scores (GScore, kcal/mol) of drug-like molecules extracted from a NCI database Against the PPARγ (2HFP) at allosteric site.

NCI ID	GScore	NCI ID	GScore	NCI ID	GScore	NCI ID	GScore	NCI ID	GScore
116	-6.57	**47742**	-8.92	**95895**	-5.44	**130813**	-8.28	**171538**	-6.30
153	-6.13	**48151**	-7.65	**99547**	-8.54	**130842**	-5.41	**172540**	-7.21
3098	-3.65	**49628**	-6.92	**101523**	-8.59	**131366**	-8.68	**172846**	-7.50
6918	-5.84	**51478**	-5.27	**101672**	-6.10	**131367**	-8.92	**177363**	-7.99
7579	-7.68	**52003**	-6.80	**101793**	-8.08	**132263**	-7.31	**178023**	-7.99
8008	-7.78	**53199**	-5.51	**103843**	-7.19	**132898**	-7.22	**178889**	-6.78
8490	-5.87	**54906**	-6.76	**105274**	-2.80	**134118**	-6.13	**180617**	-7.27
8609	-8.76	**56243**	-8.84	**105337**	-6.56	**135634**	-6.89	**180627**	-7.71
8611	-9.12	**57034**	-10.75	**106156**	-9.66	**135848**	-9.42	**180642**	-6.90
9011	-4.64	**60616**	-7.64	**106221**	-6.73	**139461**	-7.25	**180648**	-7.63
9349	-7.28	**62571**	-5.89	**110347**	-8.63	**141337**	-5.53	**180661**	-7.17
10406	-6.33	**63837**	-7.31	**110559**	-3.91	**142333**	-7.60	**190528**	-6.80
10671	-9.92	**66072**	-4.71	**111593**	-5.81	**143351**	-7.88	**190748**	-6.50
12985	-7.19	**69584**	-9.17	**112828**	-7.57	**143748**	-8.31	**201618**	-7.27
13481	-8.36	**70824**	-6.88	**113311**	-6.99	**144441**	-6.86	**201666**	-7.58
13843	-8.52	**70914**	-10.38	**113915**	-6.69	**146005**	-5.81	**202677**	-7.88
14013	-9.08	**70972**	-6.44	**114133**	-6.67	**147980**	-6.70	**204583**	-6.64
15285	-8.80	**71012**	-5.49	**114631**	-8.18	**148001**	-6.77	**204590**	-6.52
15903	-6.04	**71682**	-7.25	**114673**	-6.33	**149543**	-5.98	**205546**	-7.69
16764	-8.15	**71790**	-6.86	**114819**	-7.01	**150206**	-5.53	**205684**	-8.44
16765	-8.15	**72559**	-8.90	**117195**	-6.40	**150386**	-8.82	**205811**	-9.58
16768	-9.63	**74975**	-5.98	**117777**	-4.40	**151215**	-7.83	**210344**	-9.86
19223	-6.33	**77700**	-4.04	**119707**	-7.51	**152426**	-8.00	**211226**	-8.04
21312	-7.07	**77720**	-6.21	**119765**	-6.67	**155243**	-8.07	**211831**	-7.32
24914	-6.17	**79023**	-9.82	**120183**	-8.89	**156601**	-9.99	**212018**	-8.10
26870	-8.66	**79566**	-5.62	**122309**	-6.98	**156773**	-7.17	**212032**	-9.16
27265	-7.41	**81129**	-5.22	**122514**	-6.38	**157402**	-4.63	**212112**	-5.07
30019	-8.80	**84538**	-7.53	**123112**	-7.94	**157967**	-6.14	**213899**	-7.67
30967	-8.94	**85154**	-6.82	**123222**	-6.57	**161387**	-7.11	**215556**	-9.97
31546	-6.82	**85267**	-7.91	**123247**	-5.06	**162183**	-6.11	**216451**	-7.77
33408	-6.04	**85410**	-6.26	**123976**	-8.04	**162501**	-9.45	**216506**	-6.50
34567	-7.56	**85518**	-7.29	**124442**	-8.51	**162765**	-6.29	**216694**	-7.70
36487	-6.69	**85679**	-7.80	**125281**	-7.81	**163369**	-4.53	**217080**	-7.22
36506	-10.26	**85740**	-5.44	**125661**	-5.16	**164089**	-10.94	**226116**	-7.55
37117	-7.73	**86711**	-8.34	**126424**	-5.30	**164113**	-5.63	**226178**	-8.16
37815	-8.77	**88972**	-5.92	**127678**	-8.73	**164377**	-7.48	**226517**	-9.62
39006	-6.08	**89808**	-8.49	**127690**	-6.39	**164929**	-6.86	**227395**	-4.90
39612	-8.07	**91332**	-10.58	**128094**	-4.94	**165995**	-5.63	**230297**	-11.56
42399	-3.86	**91397**	-8.77	**128583**	-6.90	**167739**	-6.07	**231315**	-9.15
44491	-8.35	**92204**	-7.31	**128594**	-9.96	**167819**	-7.97	**231923**	-6.49
45093	-5.71	**92228**	-6.56	**130101**	-8.92	**170757**	-7.31	**232022**	-7.76
234698	-9.18	**341661**	-10.03	**515421**	-6.74	**630981**	-4.02	**667386**	-6.67
240360	-7.78	**343544**	-8.27	**523235**	-6.63	**632016**	-7.68	**667708**	-8.21
244974	-8.87	**344240**	-9.77	**527570**	-5.76	**632242**	-7.23	**671438**	-7.18
254681	-9.24	**345725**	-6.28	**529321**	-8.55	**633057**	-8.81	**672084**	-9.87
269193	-5.06	**346878**	-7.48	**602681**	-7.58	**633971**	-6.54	**672293**	-6.93
270150	-7.33	**349963**	-8.74	**603656**	-6.02	**637660**	-5.35	**674002**	-6.56
270734	-7.73	**350111**	-7.52	**608550**	-6.07	**638038**	-8.44	**674012**	-7.49
273905	-9.93	**350986**	-6.01	**609357**	-6.18	**639829**	-7.75	**674612**	-6.47

277480	-6.71	**353485**	-7.82	**609523**	-7.09	**640341**	-8.46	**675766**	-7.19
279829	-8.74	**356465**	-8.40	**610540**	-6.14	**640991**	-7.84	**675767**	-7.98
281299	-6.16	**356785**	-6.84	**612475**	-11.78	**640996**	-8.47	**676464**	-6.49
284669	-6.31	**357681**	-7.99	**612977**	-6.44	**641217**	-7.11	**676607**	-10.51
289626	-8.76	**359827**	-7.77	**613586**	-9.79	**641250**	-9.53	**677157**	-8.56
291629	-7.83	**363784**	-8.54	**613748**	-9.15	**641602**	-8.05	**679497**	-8.87
292943	-8.22	**363918**	-7.99	**617013**	-7.05	**642075**	-9.13	**679513**	-7.98
294866	-6.30	**364069**	-5.18	**618178**	-9.15	**642305**	-9.36	**680329**	-6.28
296242	-7.28	**364385**	-6.65	**618443**	-8.03	**642324**	-9.54	**681170**	-7.55
298141	-6.91	**365357**	-9.29	**618449**	-7.27	**643509**	-8.32	**681536**	-6.23
299208	-6.69	**366098**	-10.03	**618555**	-7.66	**644965**	-8.06	**681633**	-9.27
299236	-6.60	**367933**	-9.70	**618660**	-6.12	**645168**	-7.72	**681958**	-8.38
300910	-5.19	**368279**	-9.58	**618682**	-7.14	**645980**	-7.98	**682500**	-5.65
304891	-8.56	**371012**	-7.01	**618688**	-7.39	**646474**	-8.47	**682506**	-9.00
308001	-12.89	**371194**	-9.22	**619196**	-8.95	**647592**	-7.47	**683237**	-6.63
309842	-6.26	**371488**	-6.25	**620478**	-5.46	**648635**	-7.81	**683711**	-5.60
310324	-7.03	**372059**	-6.86	**622586**	-6.06	**648639**	-6.49	**685509**	-8.20
310361	-6.11	**372302**	-8.31	**622958**	-7.87	**648650**	-8.51	**685706**	-7.53
310835	-6.76	**372523**	-6.23	**623091**	-7.44	**648689**	-4.84	**687105**	-5.60
313957	-7.85	**372642**	-7.95	**623712**	-6.35	**651331**	-2.48	**687524**	-7.88
317877	-6.57	**374682**	-6.69	**623768**	-8.57	**652035**	-6.80	**687739**	-7.86
318822	-6.85	**375722**	-8.47	**624333**	-6.88	**652861**	-8.23	**687869**	-8.80
319112	-6.44	**379100**	-11.92	**624425**	-8.16	**652900**	-7.40	**688818**	-9.21
319688	-6.66	**379472**	-6.59	**624454**	-8.06	**654387**	-5.83	**690564**	-8.85
320204	-6.91	**380509**	-6.54	**624546**	-7.25	**655041**	-5.69	**691348**	-7.57
320212	-7.15	**381584**	-7.28	**624547**	-7.74	**656455**	-7.52	**691350**	-7.51
320562	-7.93	**400063**	-6.50	**624548**	-6.76	**657990**	-7.19	**691424**	-8.98
320864	-7.16	**401688**	-7.98	**627785**	-5.81	**658262**	-11.55	**691578**	-6.86
325304	-10.66	**401696**	-9.32	**627889**	-7.93	**658994**	-9.12	**693055**	-5.53
328102	-7.03	**401828**	-6.81	**629819**	-11.91	**659343**	-8.01	**693123**	-6.76
331921	-7.88	**403031**	-4.68	**629827**	-6.15	**661081**	-7.54	**694919**	-6.36
333346	-5.14	**405904**	-8.03	**630312**	-6.25	**662564**	-5.93	**695857**	-6.62
335415	-7.73	**406369**	-6.67	**630321**	-7.18	**664889**	-6.47	**731365**	-7.04
335994	-10.45	**408562**	-9.79	**630373**	-9.79	**665312**	-7.94	**338620**	-7.10
337738	-8.06	**409253**	-6.93	**512601**	-5.48	**666613**	-7.16		
338540	-8.51	**409615**	-7.79	**514213**	-6.78	**666714**	-7.03		

Table S4. Interacting residues of PPARγ antagonists at the orthosteric site.

Compound	Interacting Residues	Compound	Interacting Residues
NSI	Phe282, Phe363, Lys367, His449	**22**	Phe282, Phe363, Lys367
SR1664	Lys265, Ser289, Ser342, Lys367	**23**	Phe363
SR11023	Lys265, Ser289, Ser342	**24**	Phe282, Lys367, His449
1	Phe282, Phe363, Lys367, His449	**25**	Phe363
2	Phe282, His449	**26**	Phe282, Lys367
3	Phe282, Phe363, His449	**27**	Lys265, Ser289, Ser342
4	Lys367, His449	**28**	Lys265, Ser342
5	Lys367	**29**	Lys265, Ser289, Ser342
6	His449	**30**	Lys265, Ser289, Ser342
7	Phe282, Lys367, His449	**31**	Lys265, Phe282, Ser342
8	Phe282, Lys367, His449	**32**	Lys265, Phe282, Ser342
9	Phe282, His449	**33**	Lys265
10	Phe363, Lys367, His449	**34**	Lys265, Phe282, Ser289, Ser342
11	Phe282, Lys367	**35**	Lys265, Ser342, Tyr473
12	Lys367	**36**	Lys265, Ser342
13	Lys367, His449	**37**	Lys265, Phe282
14	Phe282, Lys367, His449	**38**	Lys265
15	Phe282, Lys367, His449	**39**	Lys265, Ser342
16	Phe282, Phe363, Lys367	**40**	Lys265, Glu291
17	Phe282, Lys367	**41**	Lys265, Gly284, Tyr327
18	Phe282, Lys367	**42**	Lys265
19	Phe282, Lys367	**43**	Lys265
20	NA	**44**	NA
21	Phe282, Phe363, Lys367		

Table S5. Interacting residues of PPARγ agonists at the orthosteric site and the allosteric site based on the Induced-Fit Docking.

Title	Ortho	Allo
Rosiglitazone	Ser289, His323, Gln286, Lys367	His323, Tyr327, Tyr473
Lobeglitazone	Ser289, His323, Gln286, Lys367	Lys265, Tyr473, Tyr327
Pioglitazone	Ser289, His323, Gln286, Lys367	His323, Tyr327, Tyr473, Leu340
GW1929	Leu340, Glu343, Lys265	HIE266, LYS265, Ser342
Farglitazar	Ser342	HIE266, LYS265, Ser342
Edaglitazone	Ser342	His323, Tyr327, Tyr473
Amorfrutin 1	Ser342, Glu343, Arg288	Glu343, Lys265
Amorfrutin 2	Ser342, Glu343, Arg288	Ser342
MRL20	Ser342	Ser342

References

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