Electronic Supplementary Material (ESI) for Toxicology Research.

Supplementary Information

QSAR Modeling for Predicting Reproductive Toxicity of Chemicals in Rat for Regulatory Purposes

Nikita Basant[1], Shikha Gupta[2], Kunwar P. Singh*[2]

[1]ETRC, Gomtinagar, Lucknow- 226010, India

[2]Environmental Chemistry Division

CSIR-Indian Institute of Toxicology Research

Post Box 80, Mahatma Gandhi Marg, Lucknow-226 001, India

***Author for all correspondance :** kpsingh_52@yahoo.com; kunwarpsingh@gmail.com

Table S1: Data set used in QSAR modeling

S.No.	Chemical name	CAS no.	loael_dose
1	(+-)-Indoxacarb	144171-61-9	3.91
2	1,3-Dichloro-5,5-dimethylhydantoin	118-52-5	1322.00
3	1,3-Propanediamine, N-(3-aminopropyl)-N-dodecyl-	2372-82-9	30.00
4	1,4-Dichlorobenzene	106-46-7	90.00
5	1,6-Hexanediamine	124-09-4	500.00
6	1H-1,2,4-Triazole-1-ethanol, .alpha.-(1-chlorocyclopropyl)-.alpha.-[(2-chlorophenyl)methyl]-	120983-64-4	39.60
7	2-(Thiocyanomethylthio)benzothiazole	21564-17-0	38.40
8	2,2-Dibromo-3-nitrilopropionamide	10222-01-2	15.00
9	2,4-Dichlorophenol	120-83-2	543.00
10	2,4-Dichlorophenoxyacetic acid	94-75-7	20.00
11	2-Methyl-4-chlorophenoxyacetic acid	94-74-6	22.50
12	2-Phenylphenol	90-43-7	140.00
13	3-(3-Chloro-p-tolyl)-1,1-dimethylurea	15545-48-9	50.00
14	3-(Dichloroacetyl)-5-(2-furanyl)-2,2-dimethyloxazolidine	121776-33-8	92.39
15	3-Iodo-2-propynyl-N-butylcarbamate	55406-53-6	37.50
16	4-(2,4-Dichlorophenoxy)butyric acid	94-82-6	112.00
17	4-(2-Nitrobutyl)morpholine	2224-44-4	20.00

18	4,5-Dichloro-2-octyl-3(2H)-isothiazolone	64359-81-5	20.00
19	4-Nitrotoluene	99-99-0	160.00
20	5-Chloro-2-methyl-3(2H)-isothiazolone	26172-55-4	8.50
21	Abamectin	71751-41-2	0.40
22	Acephate	30560-19-1	25.00
23	Acequinocyl	57960-19-7	65.50
24	Acetamiprid	135410-20-7	51.00
25	Acetochlor	34256-82-1	29.90
26	Acibenzolar-S-methyl	135158-54-2	100.00
27	Acrolein	107-02-8	3.00
28	Alachlor	15972-60-8	30.00
29	Aldicarb	116-06-3	0.90
30	Ametryn	834-12-8	131.00
31	Amitraz	33089-61-1	4.36
32	Asulam	3337-71-1	250.00
33	Atrazine	1912-24-9	39.00
34	Azafenidin	68049-83-2	10.10
35	Azamethiphos	35575-96-3	10.00
36	Azoxystrobin	131860-33-8	165.40
37	Bendiocarb	22781-23-3	12.50
38	Benfluralin	1861-40-1	68.10
39	Benomyl	17804-35-2	25.00
40	Benoxacor	98730-04-2	34.84
41	Bensulide	741-58-2	86.50
42	Bentazone	25057-89-0	62.00
43	Benzophenone	119-61-9	8.78
44	Bethoxazin	163269-30-5	70.00
45	Bifenazate	149877-41-8	6.90
46	Bifenthrin	82657-04-3	5.00
47	Bis(tributyltin)oxide	56-35-9	2.95
48	Bitertanol	55179-31-2	5.00
49	Boscalid	188425-85-6	123.90
50	Bromacil	314-40-9	125.00
51	Bromuconazole	116255-48-2	141.20
52	Bronopol	52-51-7	50.00
53	Buprofezin	69327-76-0	81.47
54	Butachlor	23184-66-9	50.00
55	Butafenacil	134605-64-4	23.80
56	Butyl benzyl phthalate	85-68-7	100.00
57	Butylate	2008-41-5	50.00
58	Butylbenzene	104-51-8	100.00

59	Captafol	01-06-2425	60.00
60	Captan	133-06-2	25.00
61	Carbaryl	63-25-2	31.34
62	Carbendazim	10605-21-7	250.00
63	Carbofuran	1563-66-2	5.00
64	Carbophenothion	786-19-6	0.50
65	Carboxin	5234-68-4	10.00
66	Carfentrazone-ethyl	128639-02-1	343.00
67	Chlorethoxyfos	54593-83-8	0.78
68	Chlorfenapyr	122453-73-0	22.00
69	Chlorothalonil	1897-45-6	30.80
70	Chlorpropham	101-21-3	150.00
71	Chlorpyrifos-methyl	5598-13-0	3.00
72	Chlorsulfuron	64902-72-3	541.00
73	Chlorthal-dimethyl	1861-32-1	233.00
74	Clethodim	99129-21-2	263.00
75	Clodinafop-propargyl	105512-06-9	31.69
76	Clofencet	82697-71-0	393.00
77	Clofentezine	74115-24-5	20.00
78	Clomazone	81777-89-1	100.00
79	Cloprop	101-10-0	250.00
80	Clopyralid	1702-17-6	1500.00
81	Cloquintocet-mexyl	99607-70-2	721.65
82	Cloransulam-methyl	147150-35-4	100.00
83	Clothianidin	210880-92-5	31.20
84	Copper-8-hydroxyquinoline	10380-28-6	196.00
85	Coumaphos	56-72-4	0.30
86	Cumyluron	99485-76-4	297.40
87	Cyanamide	420-04-2	1.25
88	Cyanazine	21725-46-2	1.43
89	Cyclanilide	113136-77-9	2.00
90	Cycloate	1134-23-2	20.00
91	Cyfluthrin	68359-37-5	9.00
92	Cyhalofop-butyl	122008-85-9	51.10
93	Cyhalothrin	68085-85-8	5.00
94	Cyhexatin	13121-70-5	2.40
95	Cymoxanil	57966-95-7	32.10
96	Cypermethrin	52315-07-8	27.60
97	Cyproconazole	94361-06-5	8.29
98	Cyprodinil	121552-61-2	326.40
99	Cyromazine	66215-27-8	50.00

100	Daminozide	1596-84-5	500.00
101	Dazomet	533-74-4	2.78
102	Deltamethrin	52918-63-5	21.20
103	Desmedipham	13684-56-5	20.00
104	Diazinon	333-41-5	6.69
105	Dicamba	1918-00-9	122.00
106	Dichlobenil	1194-65-6	17.50
107	Dichlorprop	120-36-5	25.00
108	Dichlorvos	62-73-7	7.20
109	Diclofop-methyl	51338-27-3	2.10
110	Dicloran	99-30-9	87.00
111	Dicofol	115-32-2	1.90
112	Dicrotophos	141-66-2	0.49
113	Dicyclohexyl phthalate	84-61-7	17.84
114	Diethyl phthalate	84-66-2	197.00
115	Difenoconazole	119446-68-3	12.50
116	Diflubenzuron	35367-38-5	36.00
117	Diflufenzopyr	109293-97-2	113.10
118	Dimethenamid	87674-68-8	150.00
119	Dimethipin	55290-64-7	40.00
120	Dimethoate	60-51-5	1.00
121	Dimethomorph	110488-70-5	50.00
122	Dimethylarsinic acid	75-60-5	17.86
123	Dinotefuran	165252-70-0	822.10
124	Diphenylamine	122-39-4	40.00
125	Dipropyl pyridine-2,5-dicarboxylate	136-45-8	289.40
126	Disulfoton	298-04-4	0.12
127	Dithiopyr	97886-45-8	16.40
128	Diuron	330-54-1	101.00
129	Endosulfan	115-29-7	6.18
130	Epoxiconazole	106325-08-0	22.12
131	Esfenvalerate	66230-04-4	5.10
132	Ethalfluralin	55283-68-6	37.50
133	Ethametsulfuron methyl	97780-06-8	1582.00
134	Ethephon	16672-87-0	198.10
135	Ethoprop	13194-48-4	13.00
136	Etofenprox	80844-07-1	35.00
137	Etoxazole	153233-91-1	100.00
138	Etridiazole	2593-15-9	32.00
139	Famoxadone	131807-57-3	44.70
140	Fenamidone	161326-34-7	89.20

141	Fenamiphos	22224-92-6	0.65
142	Fenarimol	60168-88-9	1.20
143	Fenbuconazole	114369-43-6	40.00
144	Fenbutatin Oxide	13356-08-6	17.40
145	Fenhexamid	126833-17-8	406.00
146	Fenitrothion	122-14-5	0.68
147	Fenoxaprop-ethyl	66441-23-4	0.25
148	Fenoxycarb	72490-01-8	16.00
149	Fenpropathrin	39515-41-8	8.90
150	Fenpyroximate (Z,E)	111812-58-9	6.59
151	Fenthion	55-38-9	0.70
152	Fipronil	120068-37-3	2.54
153	Florasulam	145701-23-1	500.00
154	Fluazifop-butyl	69806-50-4	5.80
155	Fluazinam	79622-59-6	9.70
156	Flucycloxuron	113036-88-7	374.50
157	Fludioxonil	131341-86-1	221.61
158	Flufenacet	142459-58-3	7.30
159	Flufenpyr-ethyl	188489-07-8	16.00
160	Flumiclorac-pentyl	87546-18-7	829.00
161	Flumioxazin	103361-09-7	12.70
162	Fluometuron	2164-17-2	15.00
163	Fluopicolide	239110-15-7	144.60
164	Fluoxastrobin	361377-29-9	665.00
165	Fluroxypyr	69377-81-7	500.00
166	Flusilazole	85509-19-9	0.85
167	Fluthiacet-methyl	117337-19-6	31.80
168	Fluvalinate	69409-94-5	5.00
169	Folpet	133-07-3	180.00
170	Forchlorfenuron	68157-60-8	144.00
171	Fosthiazate	98886-44-3	2.09
172	Glutaraldehyde	111-30-8	19.50
173	Glyphosate	1071-83-6	30.00
174	Halosulfuron-methyl	100784-20-1	223.20
175	Hexachlorobenzene	118-74-1	4.00
176	Hexaconazole	79983-71-4	50.00
177	Hexazinone	51235-04-2	143.00
178	Hexythiazox	78587-05-0	180.67
179	Hydramethylnon	67485-29-4	3.32
180	Imazalil	35554-44-0	80.00
181	Imidacloprid	138261-41-3	47.30

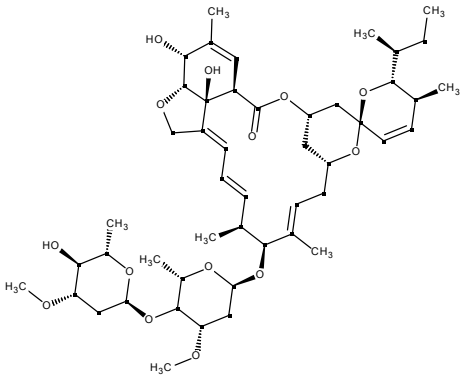
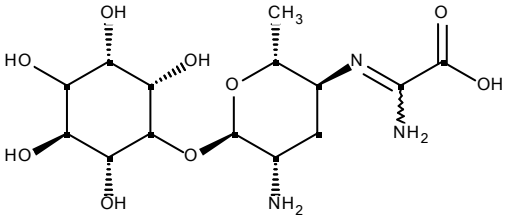
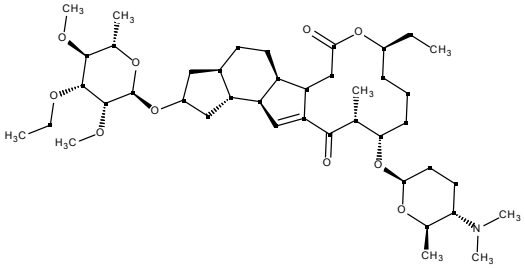
182	Imiprothrin	72963-72-5	143.50
183	Iprodione	36734-19-7	54.70
184	Isazofos	42509-80-8	6.25
185	Isofenphos	25311-71-1	0.44
186	Isoxaben	82558-50-7	200.00
187	Isoxadifen-ethyl	163520-33-0	249.80
188	Isoxaflutole	141112-29-0	17.40
189	Kasugamycin	6980-18-3	70.30
190	Kresoxim-methyl	143390-89-0	362.70
191	Lactofen	77501-63-4	26.20
192	lambda-Cyhalothrin	91465-08-6	5.00
193	Lindane	58-89-9	1.71
194	Linuron	330-55-2	5.83
195	Malathion	121-75-5	394.00
196	Mecoprop	93-65-2	50.00
197	Mefenpyr-diethyl	135590-91-9	250.00
198	Mesotrione	104206-82-8	0.30
199	Metaflumizone	139968-49-3	50.00
200	Metalaxyl	57837-19-1	62.50
201	Metaldehyde	108-62-3	133.53
202	Metasystox R	301-12-2	2.10
203	Metconazole	125116-23-6	32.00
204	Methamidophos	10265-92-6	0.08
205	Methidathion	950-37-8	1.25
206	Methomyl	16752-77-5	36.90
207	Methoxyfenozide	161050-58-4	1551.90
208	Methyl isothiocyanate	556-61-6	3.40
209	Methyl parathion	298-00-0	2.00
210	Methyl salicylate	119-36-8	150.00
211	Methylene bis(thiocyanate)	6317-18-6	2.50
212	Metobenzuron	111578-32-6	18.75
213	Metolachlor	51218-45-2	76.60
214	Metribuzin	21087-64-9	7.50
215	Metsulfuron-methyl	74223-64-6	250.00
216	Mevinphos	7786-34-7	0.50
217	MGK-264	113-48-4	61.00
218	Molinate	2212-67-1	0.80
219	Myclobutanil	88671-89-0	10.00
220	N,N-Diethyl-3-methylbenzamide	134-62-3	25.00
221	Naled	300-76-5	18.00
222	Napropamide	15299-99-7	100.00

223	Neodecanamide, N-methyl-	105726-67-8	25.10
224	Nitrapyrin	1929-82-4	20.00
225	Nonylphenol	25154-52-3	15.00
226	Norflurazon	27314-13-2	50.80
227	Novaluron	116714-46-6	74.00
228	Orthosulfamuron	213464-77-8	635.00
229	Oryzalin	19044-88-3	19.40
230	Oxamyl	23135-22-0	5.20
231	Oxasulfuron	144651-06-9	377.00
232	Oxyfluorfen	42874-03-3	120.00
233	Paclobutrazol	76738-62-0	12.50
234	Parathion	56-38-2	1.00
235	Pendimethalin	40487-42-1	173.00
236	Penoxsulam	219714-96-2	100.00
237	Pentachloronitrobenzene	82-68-8	100.00
238	Permethrin	52645-53-1	125.00
239	Phenmedipham	13684-63-4	50.00
240	Phorate	298-02-2	0.36
241	Phosalone	2310-17-0	29.40
242	Picloram	01-02-1918	1000.00
243	Picolinafen	137641-05-5	19.00
244	Pinoxaden	243973-20-8	500.00
245	Piperonyl butoxide	51-03-6	469.00
246	Pirimicarb	23103-98-2	88.00
247	Polihexanide	32289-58-0	238.90
248	Prallethrin	23031-36-9	156.00
249	Primisulfuron-methyl	86209-51-0	250.00
250	Prochloraz	67747-09-5	31.25
251	Procymidone	32809-16-8	12.50
252	Profenofos	41198-08-7	29.00
253	Prometon	1610-18-0	35.08
254	Prometryn	7287-19-6	47.80
255	Propachlor	1918-16-7	69.60
256	Propanil	709-98-8	43.00
257	Propargite	2312-35-8	20.00
258	Propazine	139-40-2	50.00
259	Propetamphos	31218-83-4	5.50
260	Propiconazole	60207-90-1	42.00
261	Propyzamide	23950-58-5	114.00
262	Prosulfuron	94125-34-5	136.00
263	Prothioconazole	178928-70-6	750.00

264	Pymetrozine	123312-89-0	10.00
265	Pyraclostrobin	175013-18-0	20.50
266	Pyraflufen-ethyl	129630-19-9	721.00
267	Pyrasulfotole	365400-11-9	2.50
268	Pyridaben	96489-71-3	6.31
269	Pyridalyl	179101-81-6	68.70
270	Pyrimethanil	53112-28-0	294.00
271	Pyriproxyfen	95737-68-1	453.00
272	Quinclorac	84087-01-4	480.00
273	Quinoxyfen	124495-18-7	100.00
274	Quizalofop-ethyl	76578-14-8	1.25
275	Resmethrin	10453-86-8	25.00
276	Rimsulfuron	122931-48-0	830.00
277	Rotenone	83-79-4	3.00
278	S-Bioallethrin	28434-00-6	150.00
279	Sethoxydim	74051-80-2	150.00
280	S-Ethyl dipropylthiocarbamate	759-94-4	10.00
281	Simazine	122-34-9	5.61
282	Spinetoram (major component)	187166-40-1	74.84
283	Spiromesifen	283594-90-1	13.20
284	Spirotetramat	203313-25-1	419.30
285	Spiroxamine	118134-30-8	11.90
286	Sulfentrazone	122836-35-5	33.00
287	Sulfluramid	4151-50-2	1.34
288	Sulfosulfuron	141776-32-1	1312.80
289	Tebufenozide	112410-23-8	11.50
290	Tebufenpyrad	119168-77-3	16.80
291	Tebupirimfos	96182-53-5	1.25
292	Tebuthiuron	34014-18-1	31.00
293	Tefluthrin	79538-32-2	2.50
294	Tembotrione	335104-84-2	1.30
295	Temephos	3383-96-8	25.00
296	Tepraloxydim	149979-41-9	253.10
297	Terbufos	13071-79-9	0.18
298	Tetraconazole	112281-77-3	6.00
299	Tetramethrin	7696-12-0	150.00
300	Thiabendazole	148-79-8	28.10
301	Thiacloprid	111988-49-9	21.00
302	Thiamethoxam	153719-23-4	1.84
303	Thiazopyr	117718-60-2	5.00
304	Thidiazuron	51707-55-2	108.50

305	Thiobencarb	28249-77-6	2.00
306	Thiodicarb	59669-26-0	5.00
307	Thiophanate-methyl	23564-05-8	13.70
308	Thiram	137-26-8	4.70
309	Tolylfluanid	731-27-1	57.50
310	Topramezone	210631-68-8	4.20
311	Tralkoxydim	87820-88-0	100.00
312	Tralomethrin	66841-25-6	0.75
313	Triadimefon	43121-43-3	90.00
314	Triadimenol	55219-65-3	25.00
315	Tri-allate	2303-17-5	30.00
316	Triasulfuron	82097-50-5	250.00
317	Triazamate	112143-82-5	101.40
318	Tribenuron-methyl	101200-48-0	19.00
319	Tribufos	78-48-8	15.00
320	Tributyltin chloride	1461-22-9	0.25
321	Trichlorfon	52-68-6	175.00
322	Triclopyr	55335-06-3	25.00
323	Triclosan	3380-34-5	150.00
324	Trifloxystrobin	141517-21-7	55.30
325	Triflumizole	68694-11-1	1.50
326	Trifluralin	1582-09-8	47.00
327	Triflusulfuron-methyl	126535-15-7	44.00
328	Triforine	26644-46-2	226.00
329	Trinexapac-ethyl	95266-40-3	593.50
330	Triphenyltin hydroxide	76-87-9	1.40
331	Triticonazole	131983-72-7	250.00
332	Uniconazole-P	83657-17-4	75.00
333	Vinclozolin	50471-44-8	4.90
334	Zoxamide	156052-68-5	1624.40

Table S2: Out of AD compounds in QSAR models by leverage approach

S.No.	Model	Data set	Chemical name	Chemical structure
High Leverage Compounds				
1.	DTF, DTB	Training	Abamectin	
2	DTF, DTB	Training	Kasugamycin	
3	DTF, DTB	Training	Spinetoram (major component)	

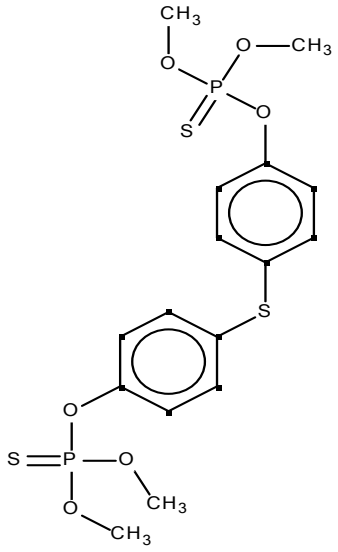
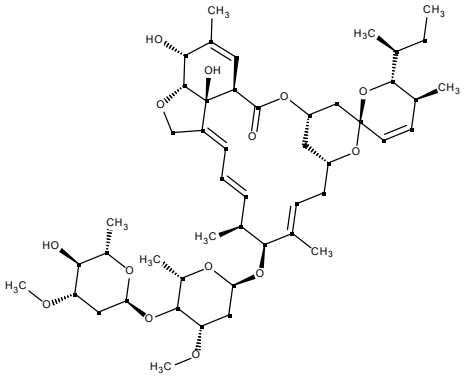
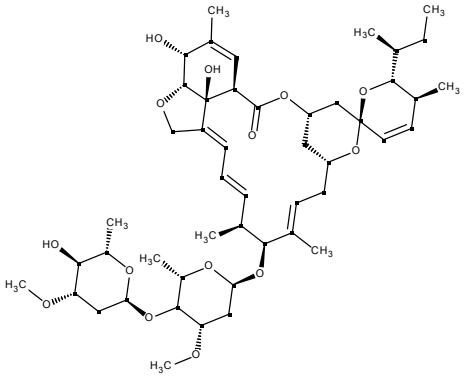
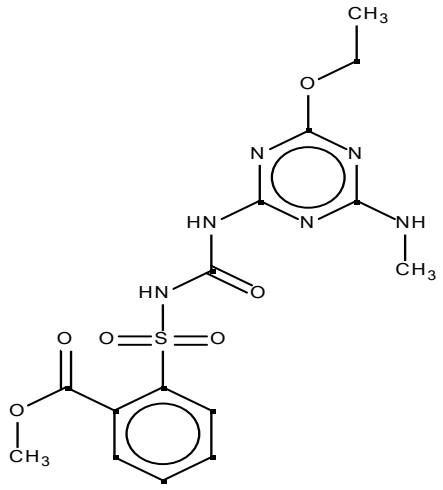
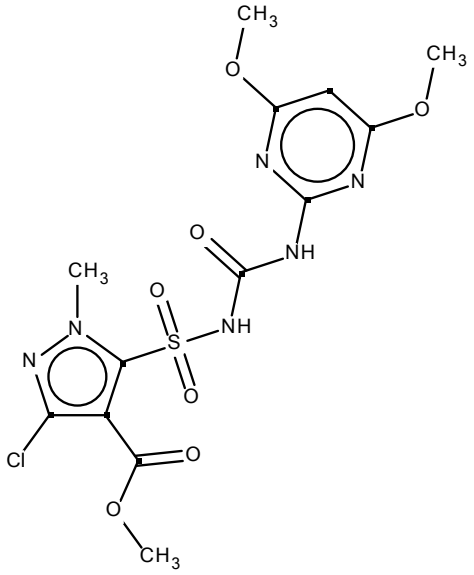
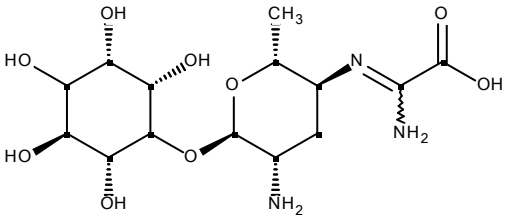
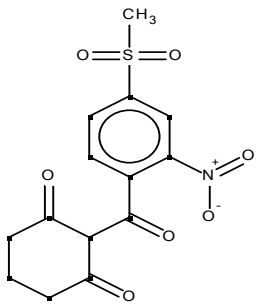
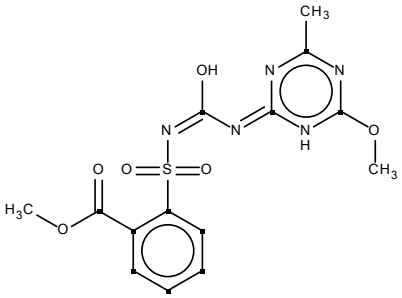
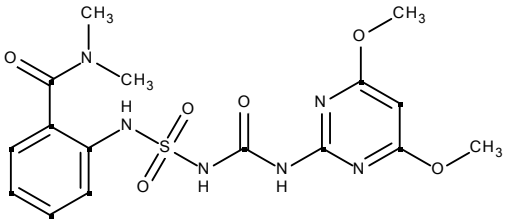
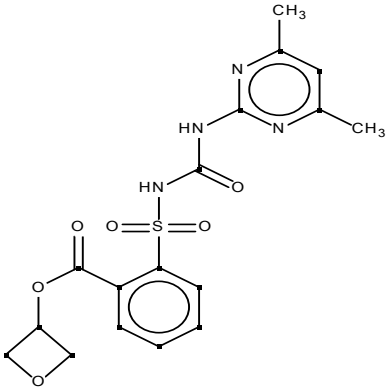
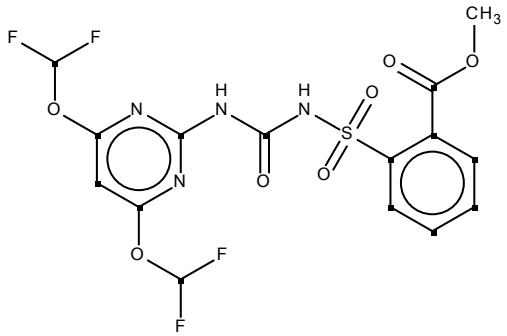
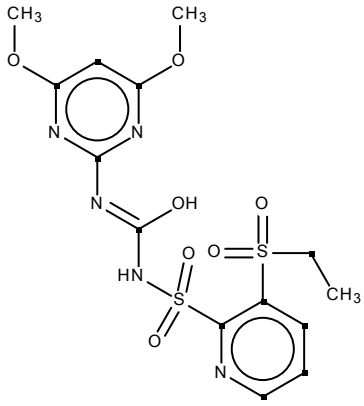
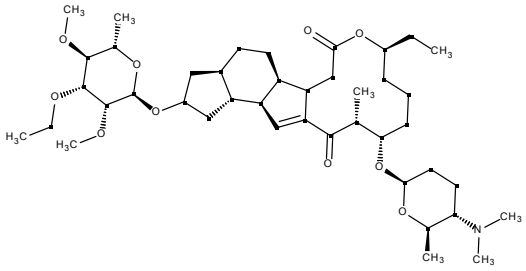
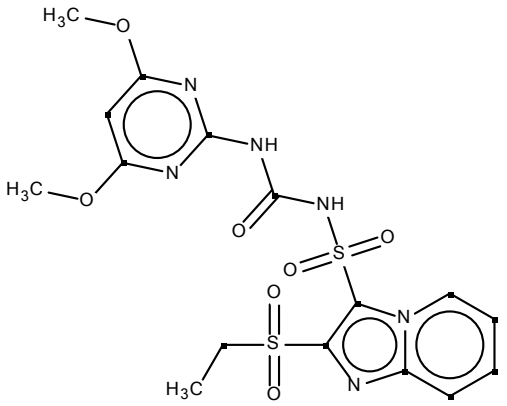
4	DTB	Training	Temephos	
High Standardized Residual Compounds				
1.	DTF	Training	Abamectin	

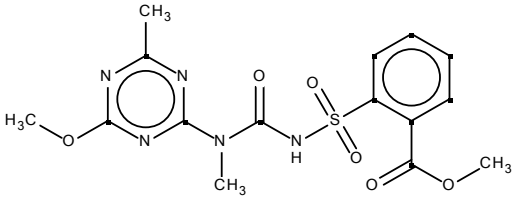
Table S3: Out of AD compounds in QSAR models by standardization approach

S.No.	Model	Data set	Chemical name	Chemical structure
1.	DTF, DTB	Training	Abamectin	

2	DTF, DTB	Training	Ethametsulfuron methyl	
3	DTF, DTB	Test	Halosulfuron-methyl	
4	DTF, DTB	Training	Kasugamycin	

5	DTF	Training	Mesotrione	
6	DTB	Training	Metsulfuron-methyl	
7	DTF	Training	Orthosulfamuron	
8	DTF	Training	Oxasulfuron	

9	DTF	Training	Primisulfuron-methyl	
10	DTF, DTB	Test	Rimsulfuron	
11	DTF, DTB	Training	Spinetoram (major component)	
12	DTF, DTB	Training	Sulfosulfuron	

13	DTF	Training	Tribenuron-methyl	
14	DTF, DTB	Training	Triflusulfuron-methyl