Supporting Information for:

Towards discovery of new leishmanicidal scaffolds able to inhibit *Leishmania* GSK-3

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Contents:

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sp|P49841|GSK3B_HUMAN   MSGRPRTTSFAESCKPVQQPSAFGSMKVSRDKDGSKVTTVVATPGQGPDRPQEVSYTDTK 60
tr|Q4QE15|Q4QE15_LEIMA  -----------------------------------MSLNAAAAADERSRKEMDRFQVER 24
                                                  ::  .*  .:  .* :   :   :

sp|P49841|GSK3B_HUMAN   VIGNGSFGVVYQAKLCDSGELVAIKKVLQDKRFKNRELQIMRKL---DHCNIVRLRYFFY 117
tr|Q4QE15|Q4QE15_LEIMA  MAGQGTFGTVQLGKEKSTGMSVAIKKVIQDPRFRNRELQIMQDLAVLHHPNIVQLQSYFY 84
                        : *:*:**.*  .*  .:*  ******:** **:*******:.*   .* ***:*: :**

sp|P49841|GSK3B_HUMAN   SSGEK-KDEVYLNLVLDYVPETVYRVARHYSRAKQTLPVIYVKLYMYQLFRSLAYIH--S 174
tr|Q4QE15|Q4QE15_LEIMA  TLGERDRRDIYLNVVMEYVPDTLHRCCRNYYRRQVAPPPILIKVFLFQLIRSIGCLHLPS 144
                        : **: : ::***:*::***:*::* .*:* * : : * * :*::::**:**:. :*  *

sp|P49841|GSK3B_HUMAN   FGICHRDIKPQNLLLDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRYYRAPELIFGATDY 234
tr|Q4QE15|Q4QE15_LEIMA  VNVCHRDIKPHNVLVNEADGTLKLCDFGSAKKLSPSEPNVAYICSRYYRAPELIFGNQHY 204
                        ..:*******:*:*::   ..**********:*  .****:***************  .*

sp|P49841|GSK3B_HUMAN   TSSIDVWSAGCVLAELLLGQPIFPGDSGVDQLVEIIKVLGTPTREQIREMNPNYTEFKFP 294
tr|Q4QE15|Q4QE15_LEIMA  TTAVDIWSVGCIFAEMMLGEPIFRGDNSAGQLHEIVRVLGCPSREVLRKLNPSHTDVDLY 264
                        *:::*:**.**::**::**:*** **....** **::*** *:** :*::**.:*:..:

sp|P49841|GSK3B_HUMAN   QIKAHPWTKVFRPRT---PPEAIALCSRLLEYTPTARLTPLEACAHSFFDELRDPNVKLP 351
tr|Q4QE15|Q4QE15_LEIMA  NSKGIPWSNVFSDHSLKDAKEAYDLLSALLQYLPEERMKPYEALCHPYFDELHDPATKLP 324
                        : *. **:.**  ::     **  * * **:* *  *:.* ** .* :****:*  .***

sp|P49841|GSK3B_HUMAN   NGRDTPA-LFNFTTQELSSNPPLATILIPPHARIQAAASTPTNATAASDANTGDRGQTNN 410
tr|Q4QE15|Q4QE15_LEIMA  NNKDLPEDLFRFLPNEIEVMSEAQKAKLVRK---------------------------- 355
                        *.:* *  **.*  .*:.      .  :  :

sp|P49841|GSK3B_HUMAN   AASASASNST 420
tr|Q4QE15|Q4QE15_LEIMA  ---------- 355
```

Figure S1. Sequence alignment of the GSK-3 structures of *Leishmania major* (Q4QE15) and *Homo sapiens* (P49841).

```
tr|A0A088RMG0_9TRYP  MSLNAADAADDRSRKEMDRFQVERMAGQGTFGTVQLGKEKSTGMSVAIKKVIQDPRFRNR   60
tr|Q4QE15_LEIMA      MSLNAAAAADERSRKEMDRFQVERMAGQGTFGTVQLGKEKSTGMSVAIKKVIQDPRFRNR   60
tr|A6N857_LEIDO      MSLNAADAADERSRKEMDRFQVERMAGQGTFGTVQLGKEKSTGMSVAIKKVIQDPRFRNR   60
tr|A4HXQ3_LEIIN      MSLNAADAADERSRKEMDRFQVERMAGQGTFGTVQLGKEKSTGMSVAIKKVIQDPRFRNR   60
tr|Q0PKV3_LEIME      MSLNAADAADERSRKEMDRFLVERMAGQGTFGTVQLGKEKSTGMSVAIKKVIQDPRFRNR   60
                     ****** ***:********* ****************************************

tr|A0A088RMG0_9TRYP  ELQIMQDLAVLHHPNIVQLQSYFYTLGERDRRDIYLNVVMEYVPDTLHRCCRNYYRRQTT   120
tr|Q4QE15_LEIMA      ELQIMQDLAVLHHPNIVQLQSYFYTLGERDRRDIYLNVVMEYVPDTLHRCCRNYYRRQVA   120
tr|A6N857_LEIDO      ELQIMQDLAVLHHPNIVQLQSYFYTLGERDRRDIYLNVVMEYVPDTLHRCCRNYYRRQVA   120
tr|A4HXQ3_LEIIN      ELQIMQDLAVLHHPNIVQLQSYFYTLGERDRRDIYLNVVMEYVPDTLHRCCRNYYRRQVA   120
tr|Q0PKV3_LEIME      ELQIMQDLAVLHHPNIVQLQSYFYTLGERDRRDIYLNVVMEYVPDTLHRCCRNYYRRQVA   120
                     ************************************************************.:

tr|A0A088RMG0_9TRYP  PPPILIKVFLFQLIRSIGCLHLPSVNVCHRDIKPHNVLVNEAEGTLKLCDFGSAKKLSPS   180
tr|Q4QE15_LEIMA      PPPILIKVFLFQLIRSIGCLHLPSVNVCHRDIKPHNVLVNEADGTLKLCDFGSAKKLSPS   180
tr|A6N857_LEIDO      PPPILIKVFLFQLIRSIGCLHLPSVNVCHRDIKPHNVLVNEADGTLKLCDFGSAKKLSPS   180
tr|A4HXQ3_LEIIN      PPPILIKVFLFQLIRSIGCLHLPSVNVCHRDIKPHNVLVNEADGTLKLCDFGSAKKLSPS   180
tr|Q0PKV3_LEIME      PPPILIKVFLFQLIRSIGCLHLPSVNVCHRDIKPHNVLVNEAEGTLKLCDFGSAKKLSPS   180
                     ******************************************:*****************

tr|A0A088RMG0_9TRYP  EPNVAYICSRYYRAPELIFGNQHYTTAVDIWSVGCIFAEMMLGEPIFRGDNSAGQLHEIV   240
tr|Q4QE15_LEIMA      EPNVAYICSRYYRAPELIFGNQHYTTAVDIWSVGCIFAEMMLGEPIFRGDNSAGQLHEIV   240
tr|A6N857_LEIDO      EPNVAYICSRYYRAPELIFGNQHYTTSVDIWSVGCIFAEMMLGEPIFRGDNSAGQLHEIV   240
tr|A4HXQ3_LEIIN      EPNVAYICSRYYRAPELIFGNQHYTTSVDIWSVGCIFAEMMLGEPIFRGDNSAGQLHEIV   240
tr|Q0PKV3_LEIME      EPNVAYICSRYYRAPELIFGNQHYTTSVDIWSVGCIFAEMMLGEPIFRGDNSAGQLHEIV   240
                     *************************:**********************************

tr|A0A088RMG0_9TRYP  RVLGCPPREVLRKLNPSHTDVDLYNSKGIPWSNVFCDQSLKDAKEAHDLLSGLLQYLPEE   300
tr|Q4QE15_LEIMA      RVLGCPSREVLRKLNPSHTDVDLYNSKGIPWSNVFSDHSLKDAKEAYDLLSALLQYLPEE   300
tr|A6N857_LEIDO      RVLGCPSREVLRKLNPSHTDVDLYNSKGIPWSSVFCDHSLKDAKEAYDLLSALLQYLPED   300
tr|A4HXQ3_LEIIN      RVLGCPSREVLRKLNPSHTDVDLYNSKGIPWSSVFCDHSLKDAKEAYDLLSALLQYLPED   300
tr|Q0PKV3_LEIME      RVLGCPSREVLRKLNPSHTDVDLYNSKGIPWSTVFCDHSLKDAKEAYDLLSALLQYLPED   300
                     ****** *************************.**.*:********:****.*******:

tr|A0A088RMG0_9TRYP  RTKPYEALCHPYFDELRDSATKLPNNKDLPDDLFHFLPAEVEIMTDVQKGKLIRK   355
tr|Q4QE15_LEIMA      RMKPYEALCHPYFDELHDPATKLPNNKDLPEDLFRFLPNEIEVMSEAQKAKLVRK   355
tr|A6N857_LEIDO      RMKPYEALCHPYFDELHDSATKLPNNKDLPEDLFRFLPSEIEVMSEAQKAKLVRK   355
tr|A4HXQ3_LEIIN      RMKPYEALCHPYFDELHDSATKLPNNKDLPEDLFRFLPSEIEVMSEAQKAKLVRK   355
tr|Q0PKV3_LEIME      RMKPYEALCHPYFDELHDSATKLPNHKNLPEDLFRFLPSEIEVMSEAQKAKLVRK   355
                     * ***************:* ******:*:**:***:*** *:*:*::.**.**:**


#  Percent Identity  Matrix
#
#

     1: tr|A0A088RMG0|A0A088RMG0_9TRYP  100.00   93.52   93.52   93.52   92.96
     2: tr|Q4QE15|Q4QE15_LEIMA           93.52  100.00   98.03   98.03   96.90
     3: tr|A6N857|A6N857_LEIDO           93.52   98.03  100.00  100.00   98.59
     4: tr|A4HXQ3|A4HXQ3_LEIIN           93.52   98.03  100.00  100.00   98.59
     5: tr|Q0PKV3|Q0PKV3_LEIME           92.96   96.90   98.59   98.59  100.00
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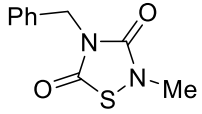
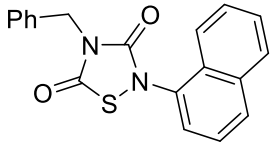
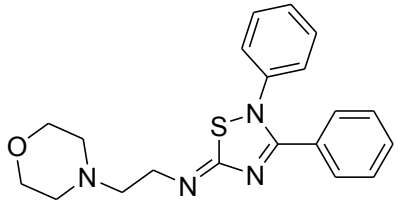
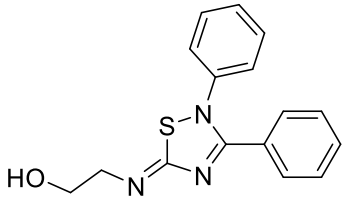
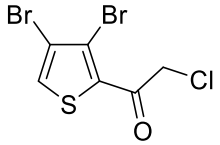
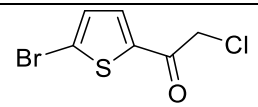
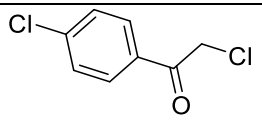
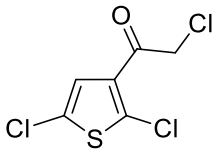
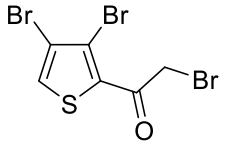
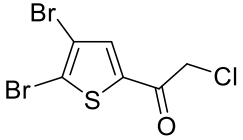
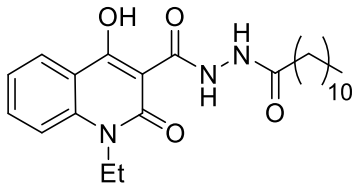
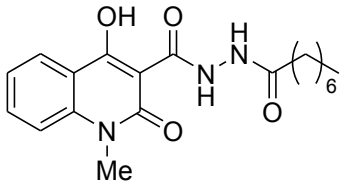
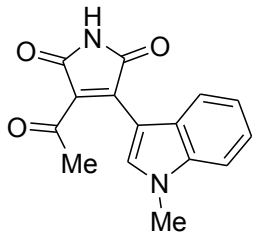
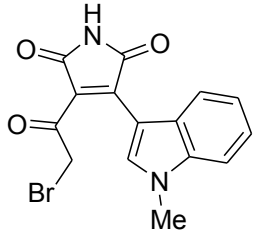
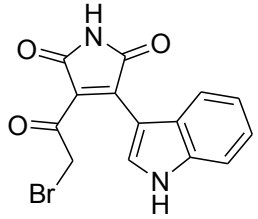
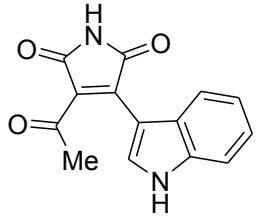
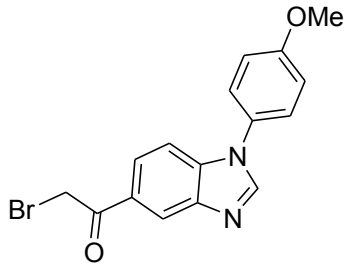
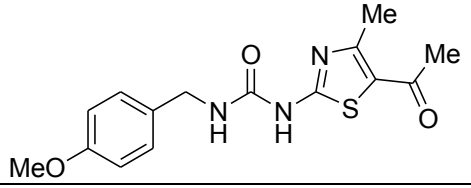
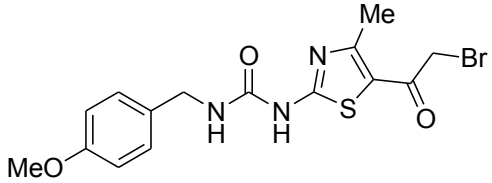
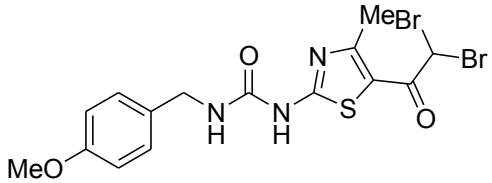
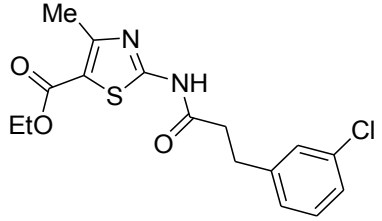
Figure S2. Sequence alignment of *Leishmania spp.* GSK-3 sequences available in the Uniprot database. The identity index among the sequences is also included. *L. panamensis* (A0A088RMG0)*, L. major* (Q4QE15)*, L. donovani* (A6N857)*, L. infantum* (A4HXQ3) and *L. mexicana* (Q0PKV3).

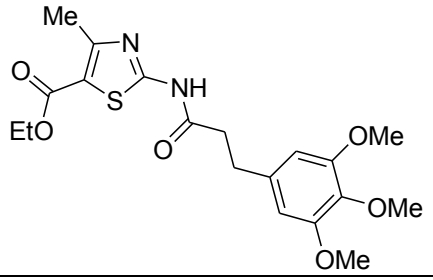
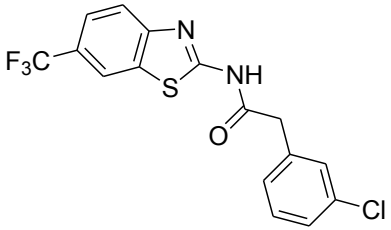
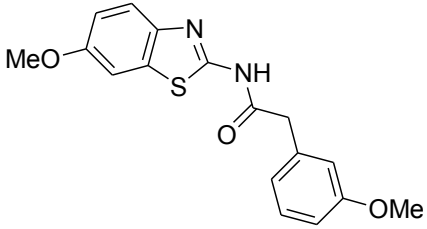
Table S1. *In vitro* enzymatic and antiparasitic activities of first selection of hGSK-3β inhibitors (**1-24**).[a]

Compound	Chemical structure	hGSK-3β IC_{50} (μM)	LdGSK-3[b] IC_{50} (μM)	*L. infantum* promastigotes EC_{50} (μM)	*L. pifanoi* amast. ax EC_{50} (μM)	PMM[c] EC_{50} (μM)	SI[d]
1		2[1]	1.1±0.2	10.9±0.4	2.0±1.9	32.9±3.5	16.5
2		0.005[2]	0.32±0.05	17.6±2.3	7.1±1.8	>50	>7.0
3	 2HBr	0.9±0.1[3]	0.24±0.00	>25	>50	-	-
4	 HBr	2.0±0.4[3]	0.17±0.00	>25	>50	-	-
5		0.5[4]	1.8±0.3	4.6±0.2	2.2±0.6	6.3±1.2	2.9

6		10^{4}	12.5±2.4	0.9±0.1	1.7±0.1	6.8±0.4	4.0
7		2.5^{4}	7.5±1.4	6.6±0.5	0.5±0.1	7.3±1.0	14.6
8		5^{4}	10.3±2.0	4.4±0.1	2.4±0.4	3.6±0.5	1.5
9		1.0^{5}	74.3%@10 μM	>50	>50	-	-
10		1^{4}	3.0±0.4	8.6±0.3	1.2±0.2	7.9±0.6	6.6
11		3.01 ± 0.14^{6}	<20%@10 μM	>50	3.6±1.3	9.9±0.9	2.8
12		8.7 ± 0.4^{7}	<20%@10 μM	>50	20.8±0.0	-	-

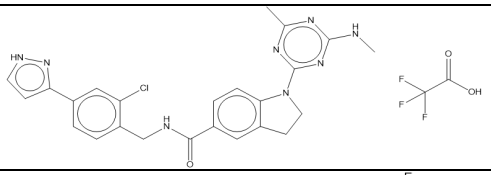
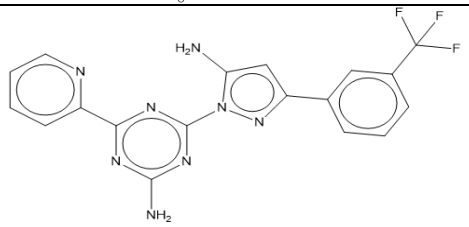
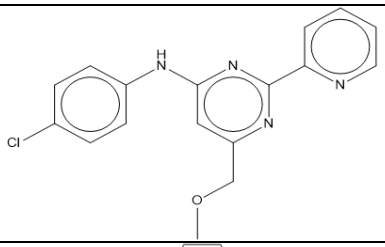
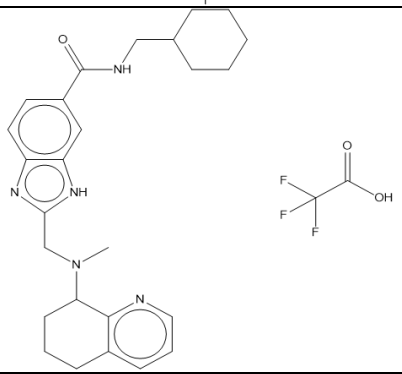
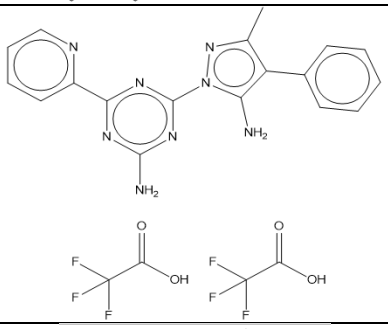
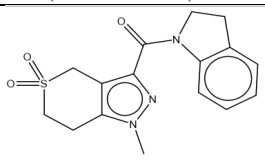
13		0.89±0.19[8]	<20%@10 μM	>50	>25	-	-
14		0.005±0.001[8]	1.6±0.2 μM	>50	6.5±2.0	>25	>3.8
15		0.047±0.007[8]	17.7±2.7	>50	>50	-	-
16		4.47±0.35[8]	<20%@10 μM	>50	2.5±2.7	>50	>20.0

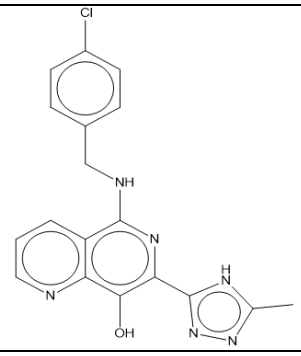
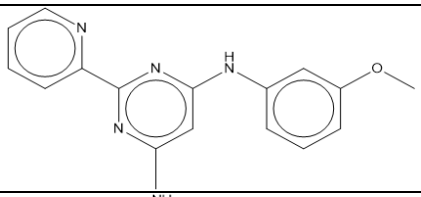
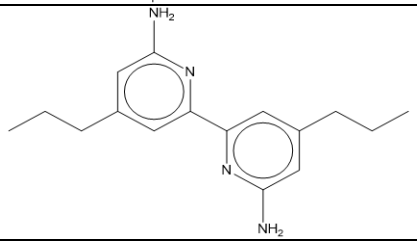
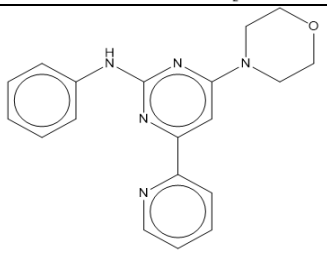
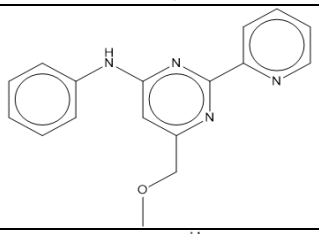
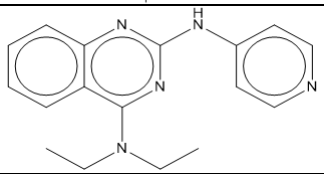
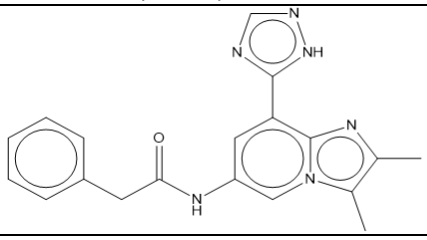
17		0.58±0.07[8]	35.5%@10 μM	3.4±0.5	4.5±0.2	>25	>5.6
18		0.8[9]	<20%@10 μM	>50	>50	-	-
19		9.72±0.57	<20%@10 μM	>25	14.4±2.6	32.0±3.1	2.2
20		6.22±0.20	<20%@10 μM	>50	>50	-	-
21		7.23±0.26	<20%@10 μM	>50	>50	-	-

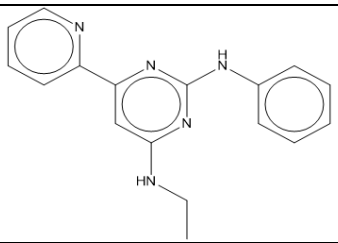
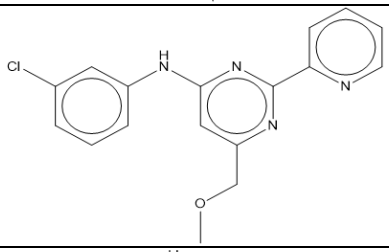
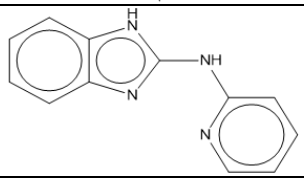
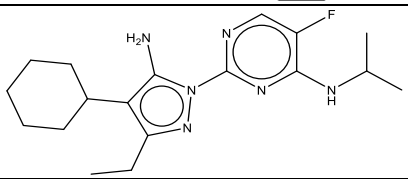
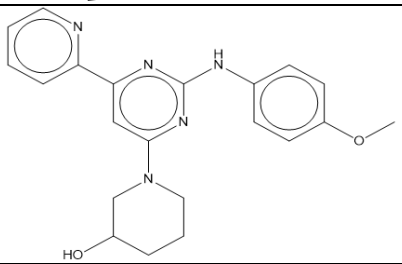
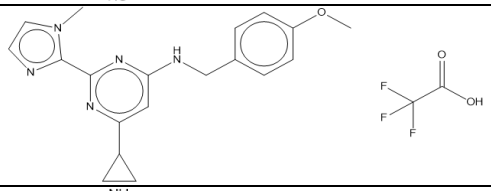
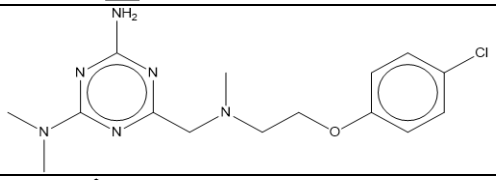
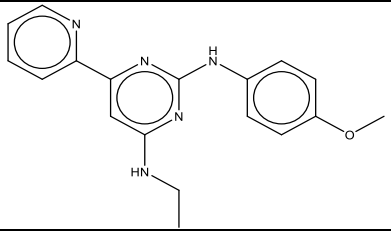
22		7.04±0.27	<20%@10 μM	>50	>50	-	-
23		9.75±0.26	<20%@10 μM	>50	>50	-	-
24		7.33±0.15	<20%@10 μM	>50	>50	-	-

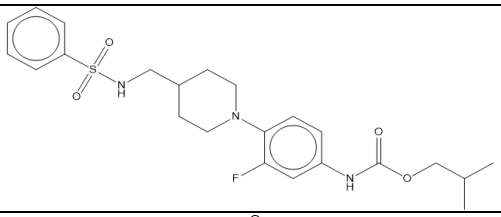
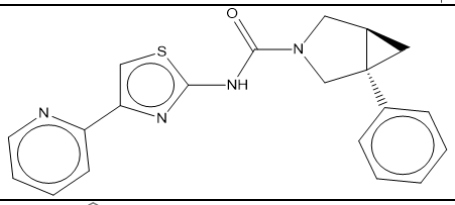
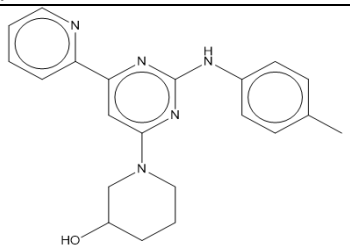
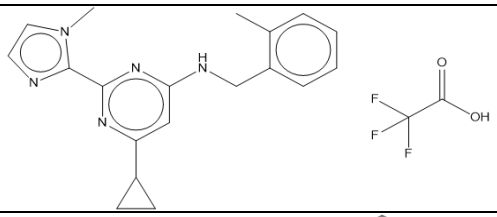
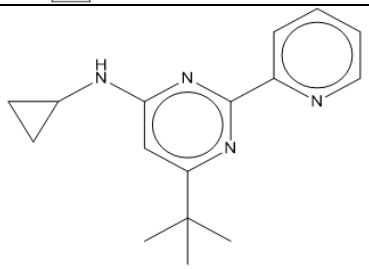
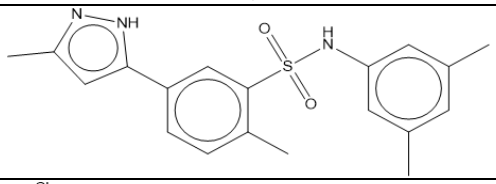
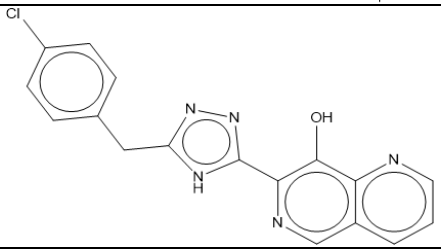
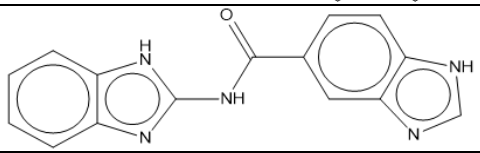
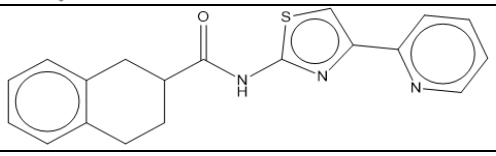
[a]IC_{50}: 50% inhibitory concentration; EC_{50}: 50% effective concentration.
[b]Indirubin-3'-monoxime-5-sulphonic acid was used as reference of the assay: IC_{50} (LdGSK-3)= 2.4±0.2 μM.
[c]PMM: peritoneal murine macrophages.
[d]SI: Specificity Index (EC_{50} PMM/EC_{50} amas. ax).

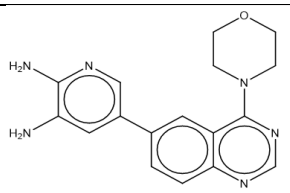
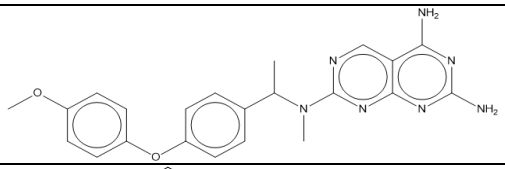
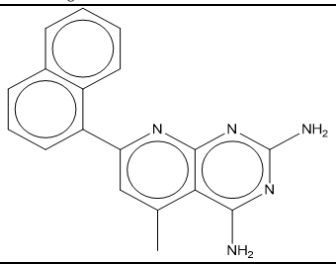
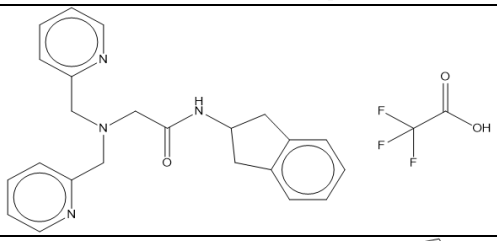
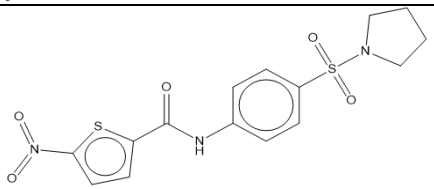
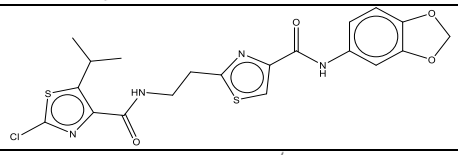
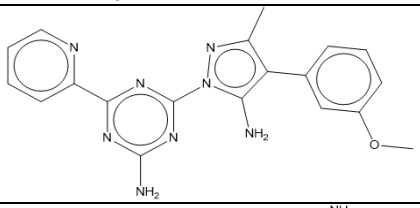
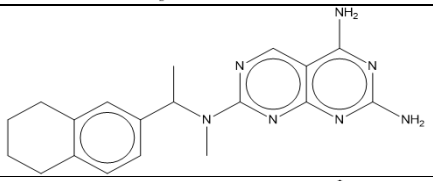
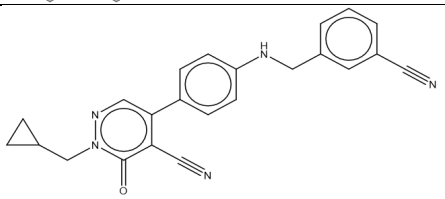
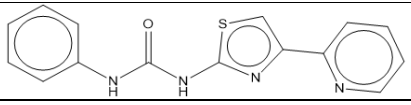
Table S2. Chemical structure of the Leishbox compounds (**25-210**) and the initial screening on LdGSK3.

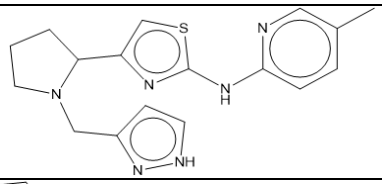
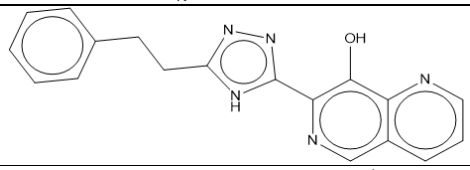
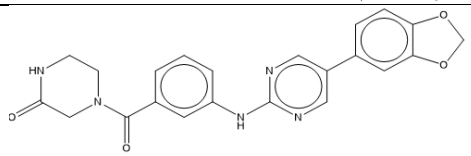
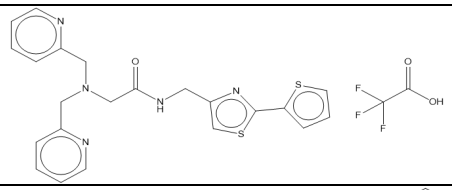
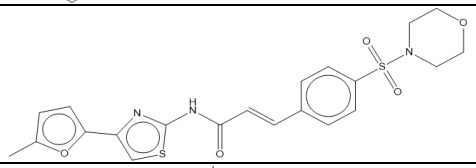
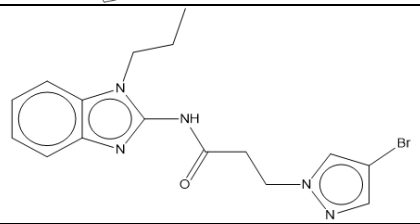
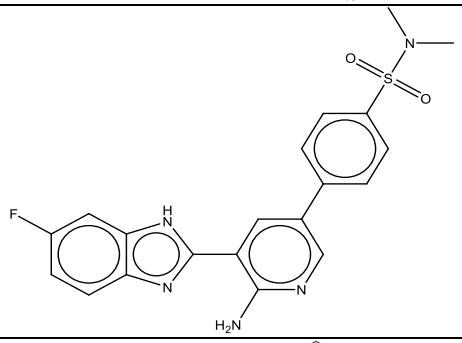
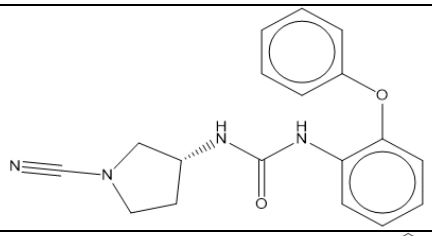
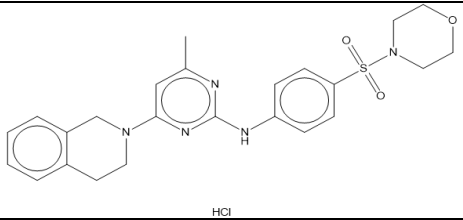
Compd.	Leishbox ID	Chemical structure	% inhibition @ 10μM
25	TCMDC-143347		-13.55±3.90
26	TCMDC-134026		4.75±1.20
27	TCMDC-143077		6.35±5.75
28	TCMDC-143512		1.15±1.75
29	TCMDC-143217		3.80±1.90
30	TCMDC-143442		5.20±1.90

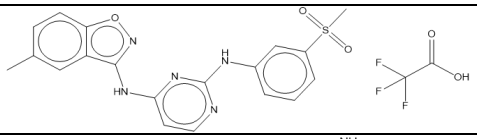
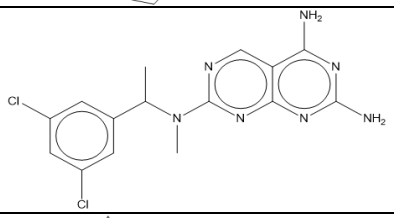
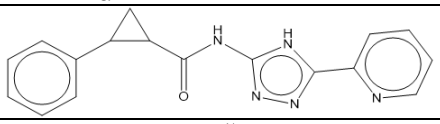
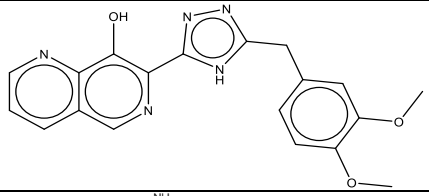
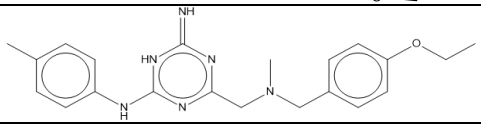
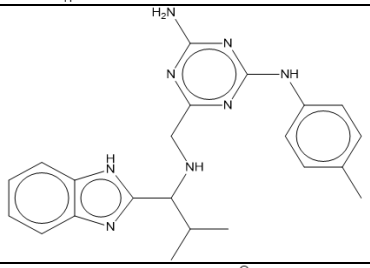
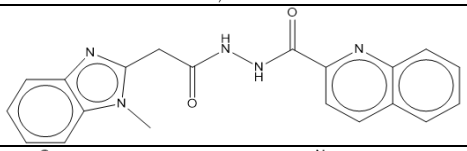
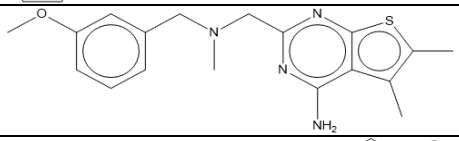
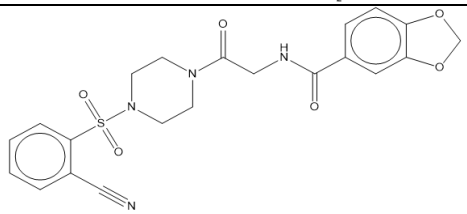
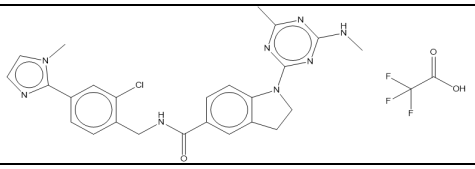
31	TCMDC-143180		8.20±1.70
32	TCMDC-143621		8.80±4.10
33	TCMDC-143600		-0.35±3.85
34	TCMDC-143211		-2.00±2.70
35	TCMDC-143078		2.90±4.05
36	TCMDC-143136		7.10±1.90
37	TCMDC-143459		5.90±4.55

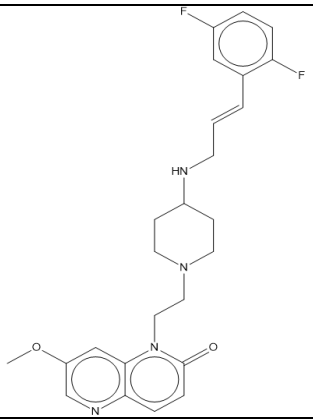
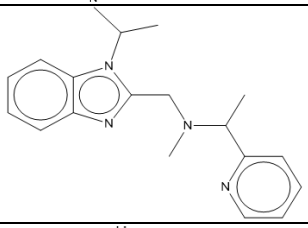
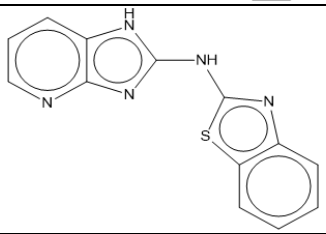
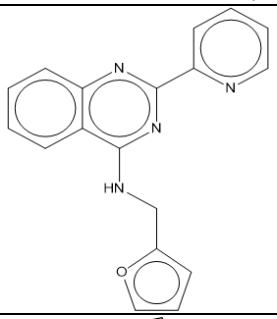
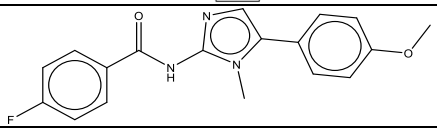
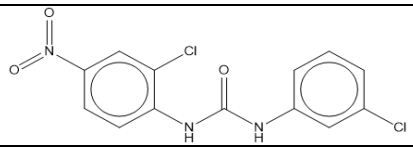
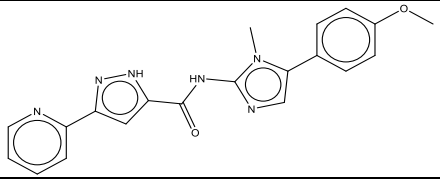
38	TCMDC-143212		7.10±1.40
39	TCMDC-143076		9.00±3.05
40	TCMDC-143554		13.50±3.10
41	TCMDC-143443		7.05±1.35
42	TCMDC-143216		5.30±2.55
43	TCMDC-143486		15.30±1.60
44	TCMDC-143427		-2.45±1.00
45	TCMDC-143213		-2.50±5.50

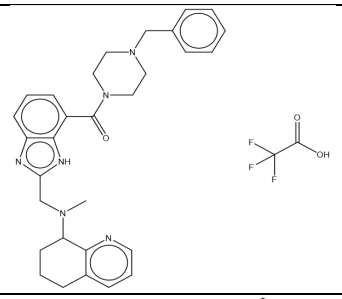
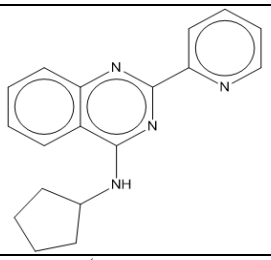
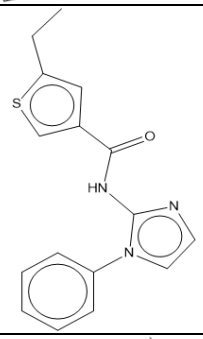
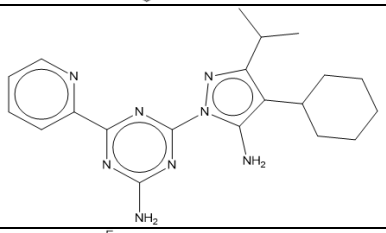
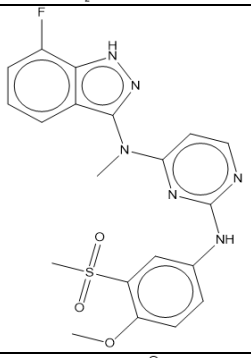
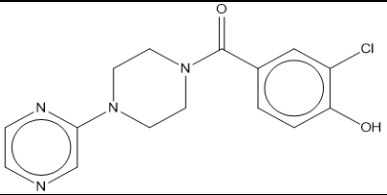
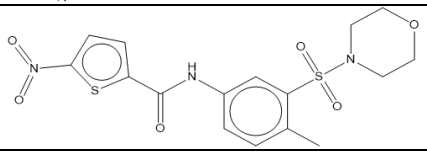
46	TCMDC-143260		4.95±4.45
47	TCMDC-143122		1.55±0.55
48	TCMDC-143215		3.25±2.75
49	TCMDC-143487		5.60±2.35
50	TCMDC-125826		4.70±2.30
51	TCMDC-143196		5.95±1.25
52	TCMDC-143630		5.05±2.35
53	TCMDC-143350		-1.60±1.50
54	TCMDC-143113		0.10±1.10

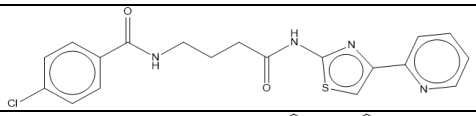
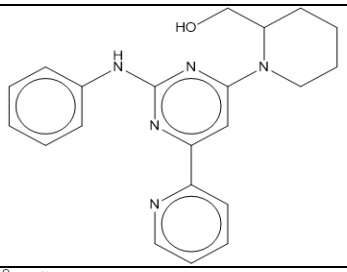
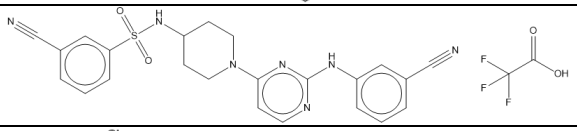
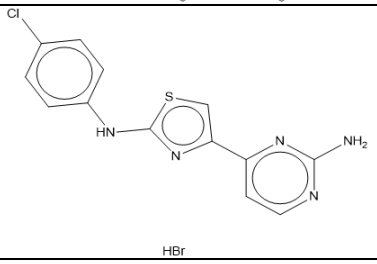
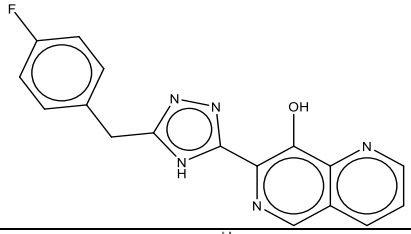
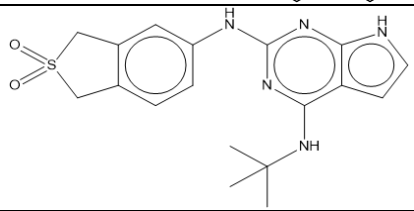
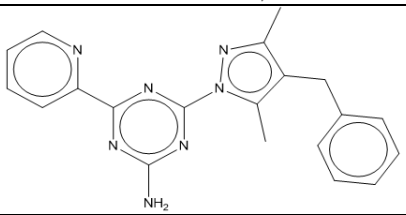
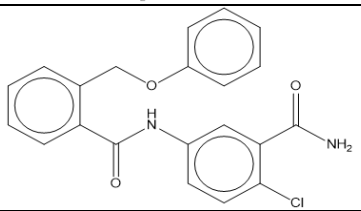
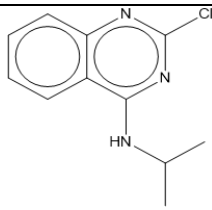
55	TCMDC-143397		0.55±3.00
56	TCMDC-143295		0.50±2.95
57	TCMDC-143607		6.10±3.15
58	TCMDC-143091		3.75±2.40
59	TCMDC-143169		16.15±4.10
60	TCMDC-143245		0.20±2.80
61	TCMDC-143404		-2.20±1.15
62	TCMDC-143296		12.10±2.40
63	TCMDC-143388		-3.20±0.80
64	TCMDC-143133		1.40±0.95

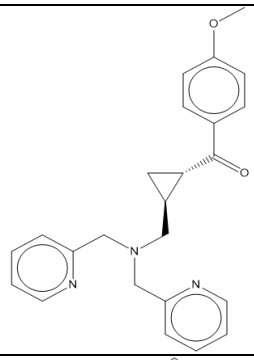
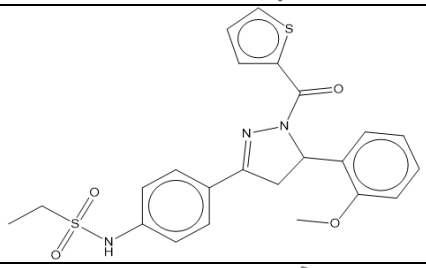
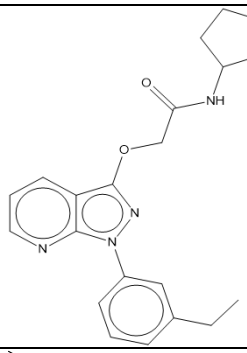
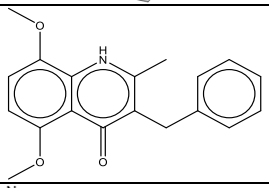
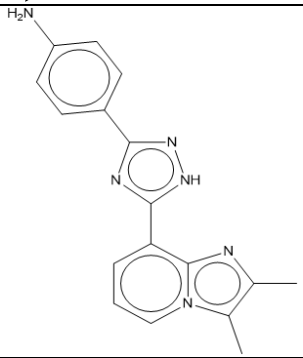
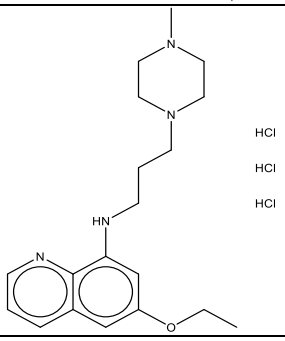
65	TCMDC-143501		-0.35±2.35
66	TCMDC-143633		0.90±0.90
67	TCMDC-143349		5.65±3.60
68	TCMDC-143094		6.80±1.95
69	TCMDC-143171		64.27±2.13
70	TCMDC-143277		3.80±1.25
71	TCMDC-143396		74.63±1.76
72	TCMDC-143238		7.40±4.30
73	TCMDC-143246		-3.05±0.35

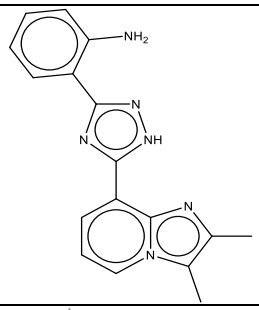
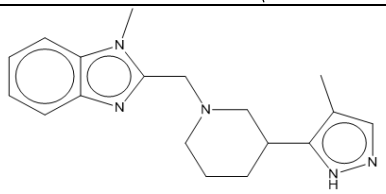
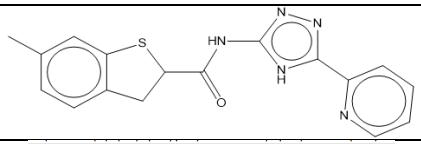
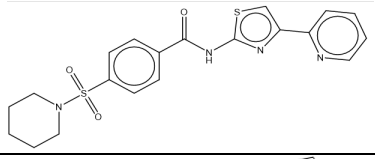
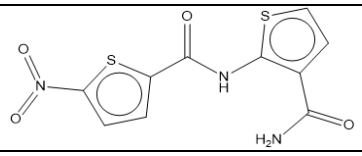
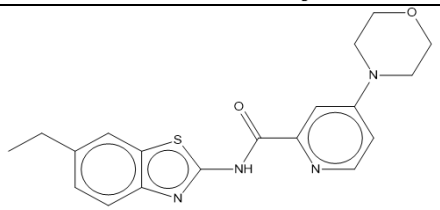
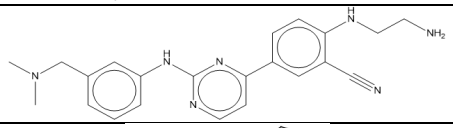
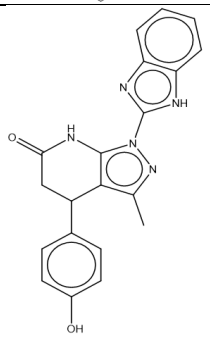
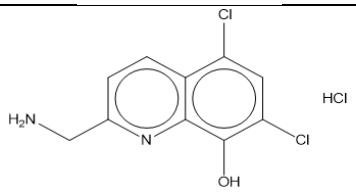
74	TCMDC-143451		10.00±0.75
75	TCMDC-143297		10.05±1.10
76	TCMDC-143491		5.70±0.50
77	TCMDC-143629		4.60±0.95
78	TCMDC-143144		4.90±1.45
79	TCMDC-143168		6.40±1.30
80	TCMDC-143261		7.95±1.65
81	TCMDC-143418		6.35±3.00
82	TCMDC-143099		1.90±2.60
83	TCMDC-143351		-5.05±0.45

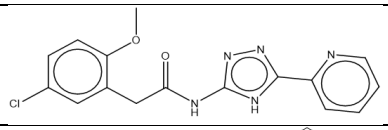
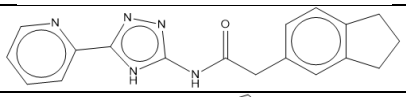
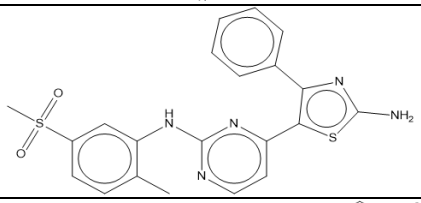
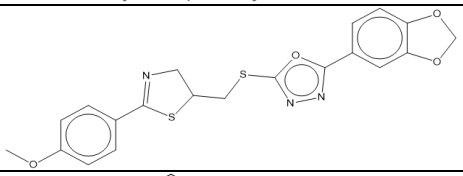
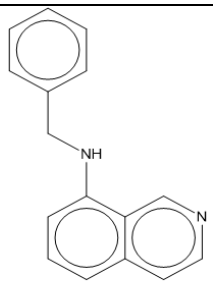
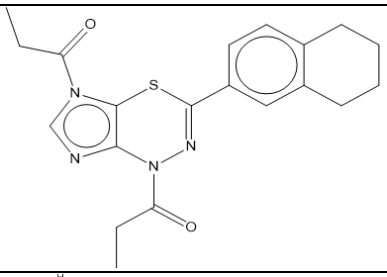
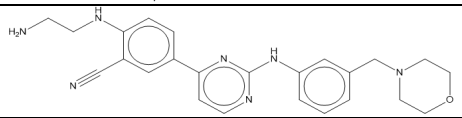
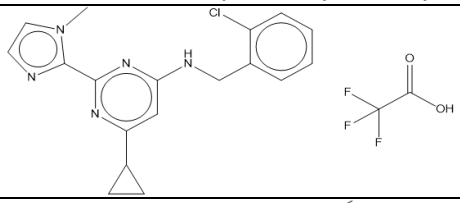
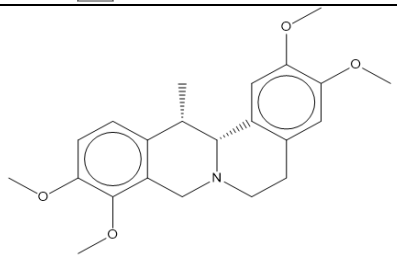
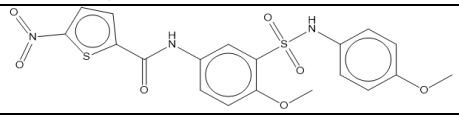
84	TCMDC-143285		3.55±2.20
85	TCMDC-143503		3.45±4.90
86	TCMDC-143072		6.55±2.70
87	TCMDC-143145		-0.05±0.95
88	TCMDC-143115		2.00±1.95
89	TCMDC-143175		4.80±2.05
90	TCMDC-143305		6.40±2.45

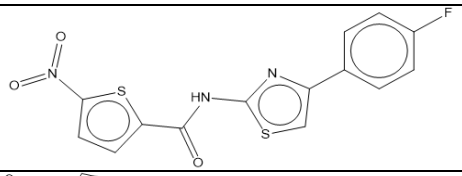
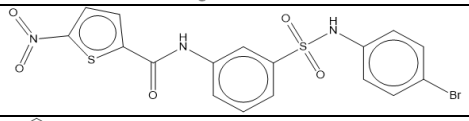
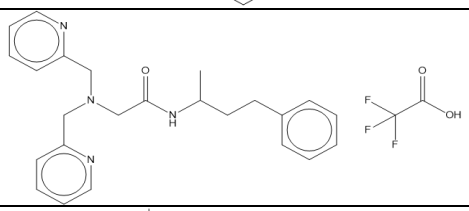
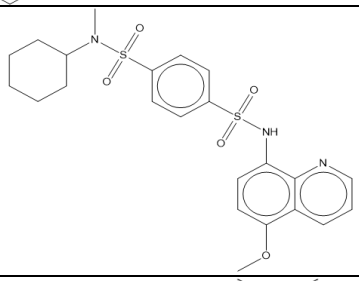
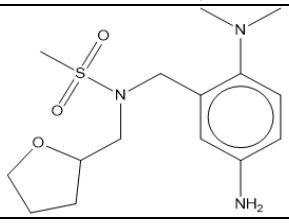
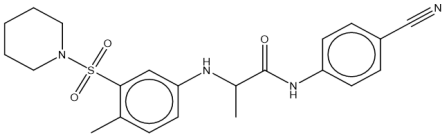
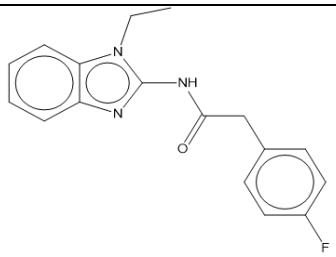
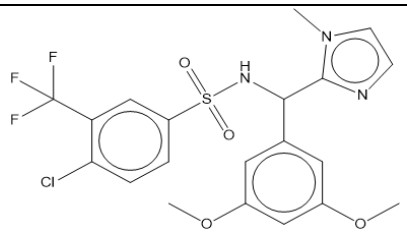
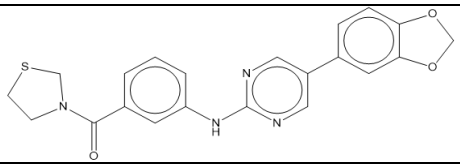
91	TCMDC-143524		12.65±6.10
92	TCMDC-143509		-0.55±1.25
93	TCMDC-143375		-2.35±1.95
94	TCMDC-143406		10.45±0.55
95	TCMDC-143483		90.25±1.12
96	TCMDC-143431		1.65±2.40
97	TCMDC-143577		6.15±1.05

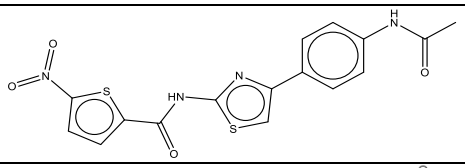
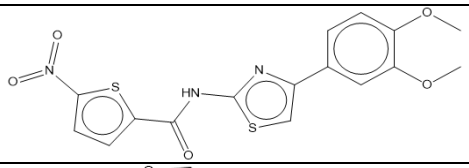
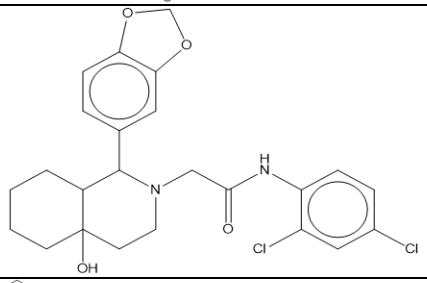
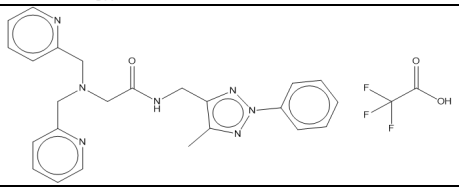
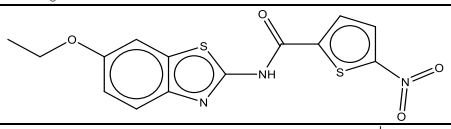
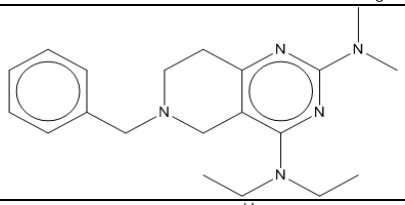
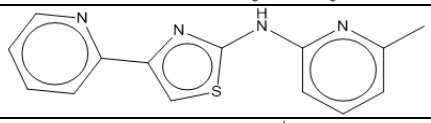
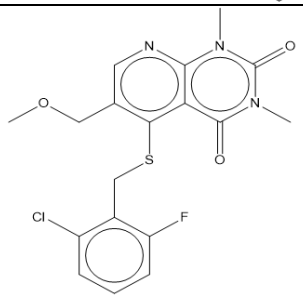
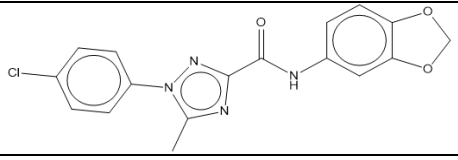
98	TCMDC-143124		8.50±1.10
99	TCMDC-143214		0.60±0.60
100	TCMDC-143249		37.05±1.50
101	TCMDC-143628		16.40±2.40
102	TCMDC-143627		4.05±3.10
103	TCMDC-143086		25.85±1.25
104	TCMDC-143407		-0.75±1.55
105	TCMDC-143398		-0.45±1.10
106	TCMDC-143419		-4.60±0.90

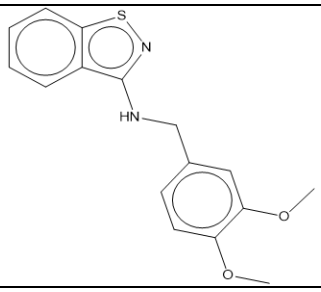
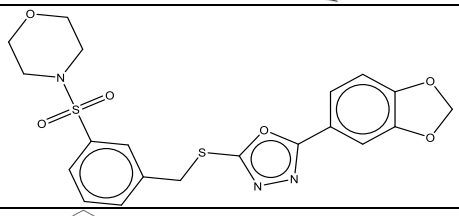
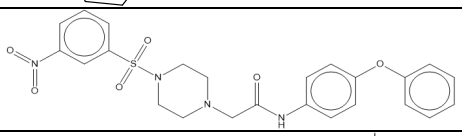
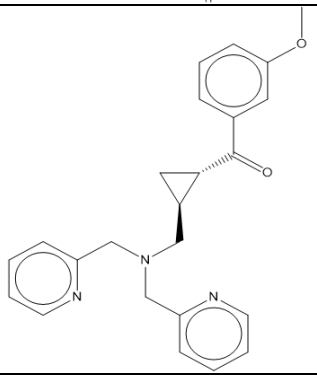
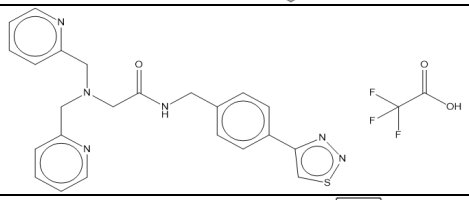
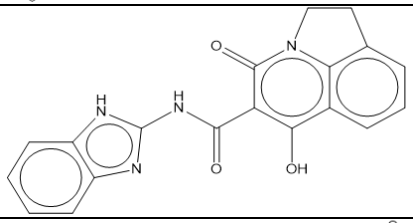
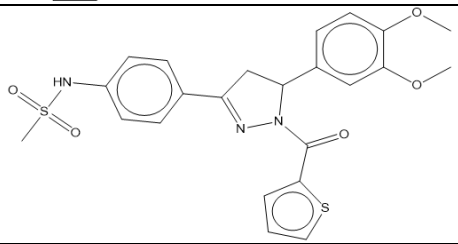
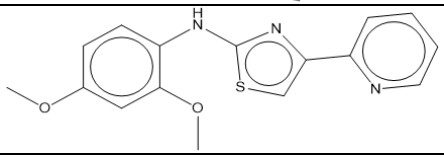
107	TCMDC-142900		-4.05±3.20
108	TCMDC-143141		5.15±1.90
109	TCMDC-125160		-4.55±1.90
110	TCMDC-143274		-0.10±5.35
111	TCMDC-143448		7.35±4.65
112	TCMDC-143603		7.50±0.65

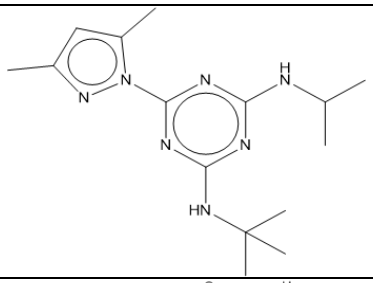
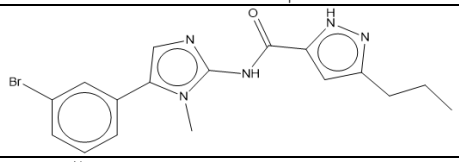
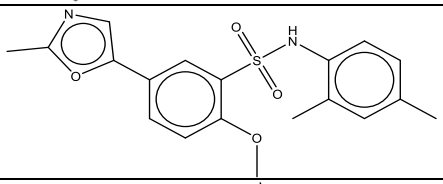
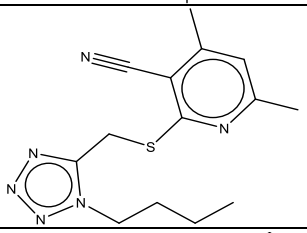
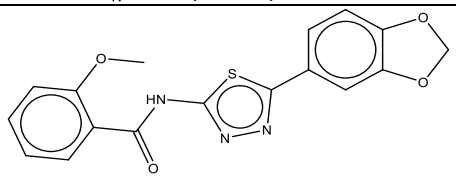
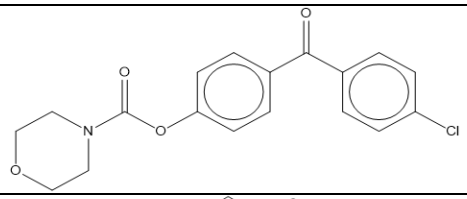
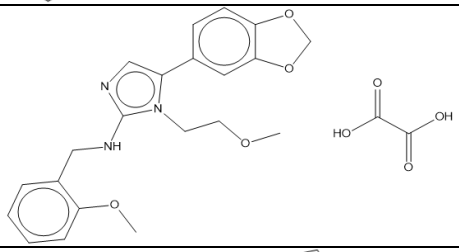
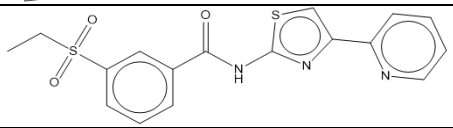
113	TCMDC-143447		1.40±0.50
114	TCMDC-143478		2.85±0.45
115	TCMDC-143473		3.20±0.80
116	TCMDC-143584		7.05±1.35
117	TCMDC-143571		6.20±1.15
118	TCMDC-143239		22.80±3.55
119	TCMDC-143281		100.29±1.24
120	TCMDC-143429		18.15±1.70
121	TCMDC-143647		14.80±1.70

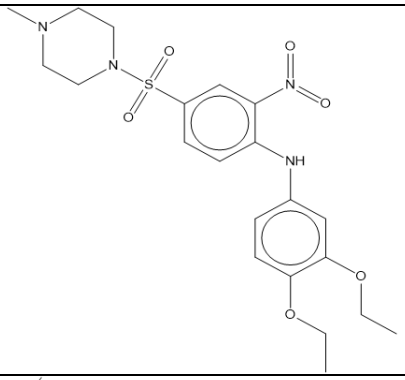
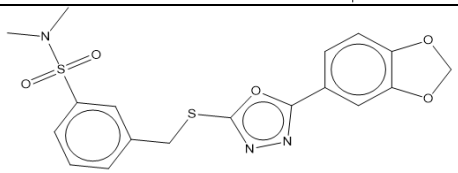
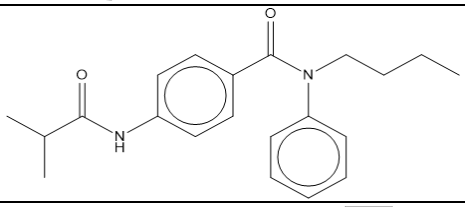
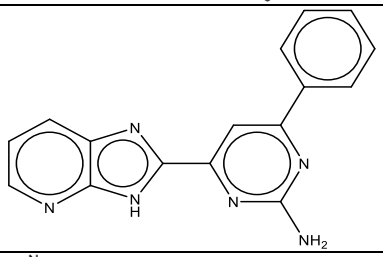
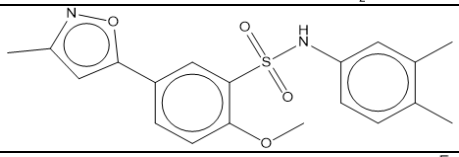
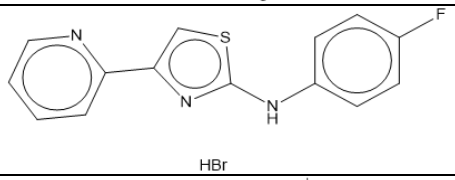
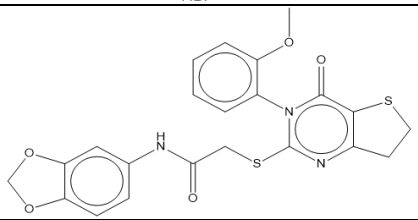
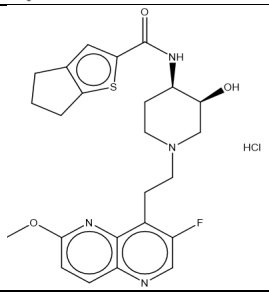
122	TCMDC-143480		3.95±2.45
123	TCMDC-143482		12.15±3.90
124	TCMDC-143391		70.59±3.12
125	TCMDC-143594		10.60±1.00
126	TCMDC-143576	 HCl	17.10±1.10
127	TCMDC-143208		9.65±3.70
128	TCMDC-143280		99.46±0.78
129	TCMDC-143488		8.90±6.75
130	TCMDC-143075		12.85±2.80
131	TCMDC-143163		19.75±3.70

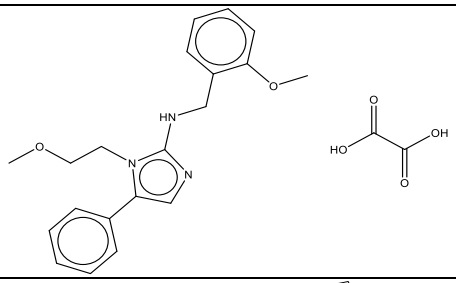
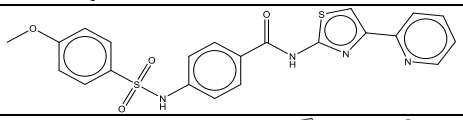
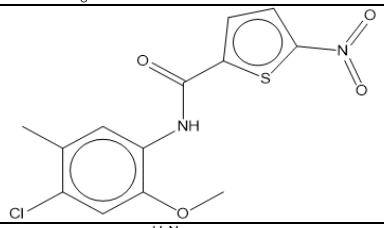
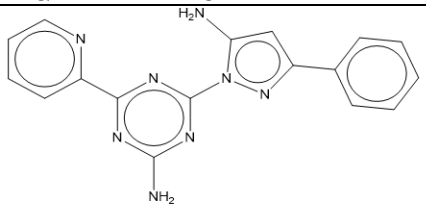
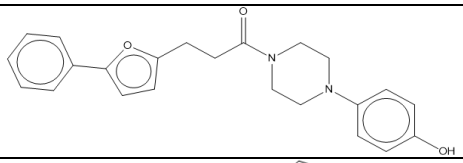
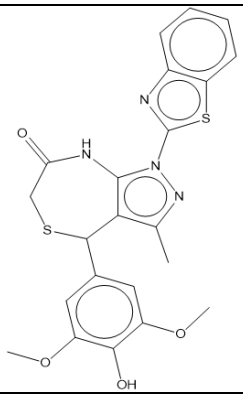
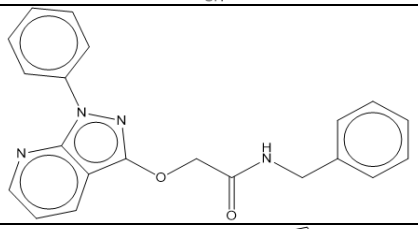
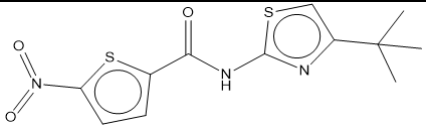
132	TCMDC-143521		8.15±0.95
133	TCMDC-143563		15.75±4.25
134	TCMDC-143092		5.25±1.70
135	TCMDC-143106		6.85±1.55
136	TCMDC-143129		13.95±3.25
137	TCMDC-124508		9.35±1.30
138	TCMDC-143278		13.00±3.55
139	TCMDC-143269		15.95±1.70
140	TCMDC-143367		18.20±7.00

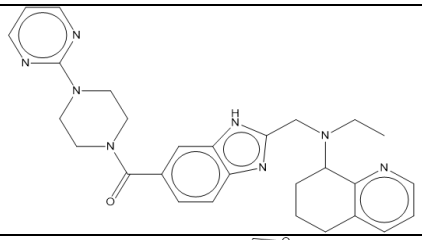
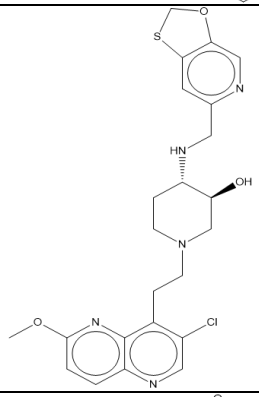
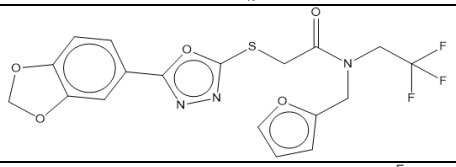
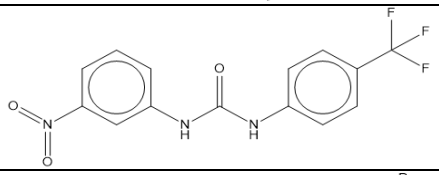
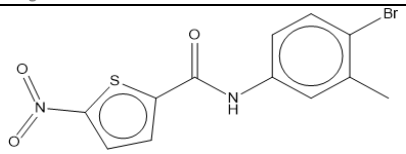
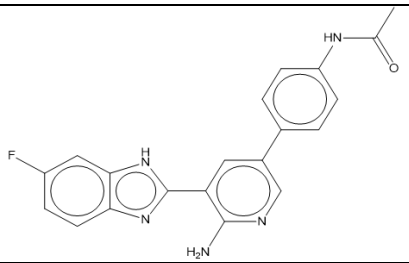
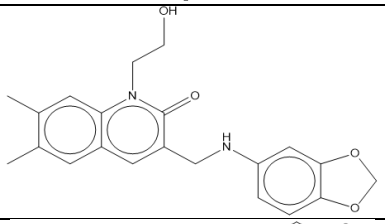
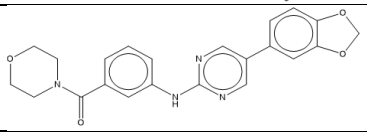
141	TCMDC-143164		8.55±0.55
142	TCMDC-143534		7.95±2.05
143	TCMDC-143567		2.25±0.35
144	TCMDC-143095		9.10±1.75
145	TCMDC-143110		9.25±0.40
146	TCMDC-143147		11.85±0.55
147	TCMDC-143558		13.40±2.35
148	TCMDC-143223		9.60±3.10
149	TCMDC-143266		8.90±2.10

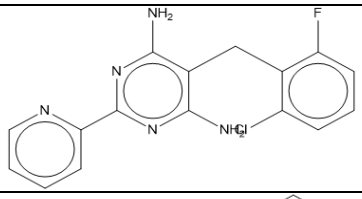
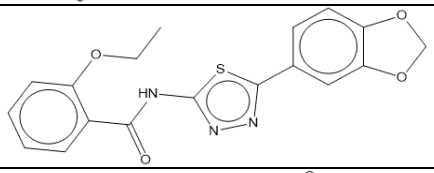
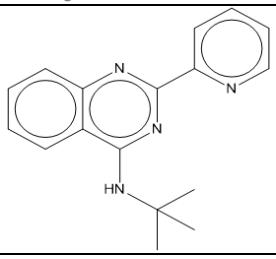
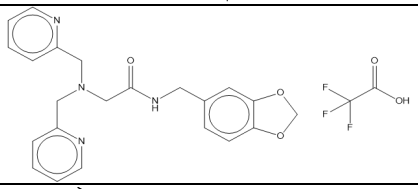
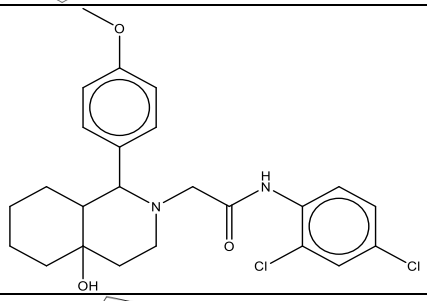
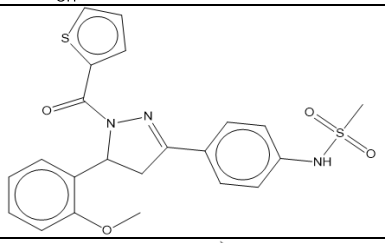
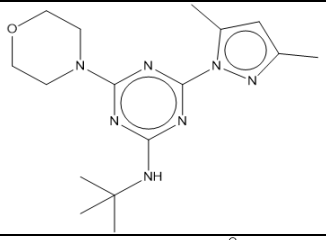
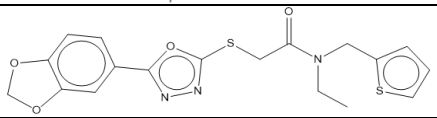
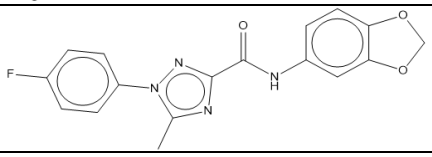
150	TCMDC-143353		13.55±4.65
151	TCMDC-143197		61.89±2.34
152	TCMDC-143536		-2.95±1.70
153	TCMDC-143586		-5.50±2.15
154	TCMDC-143096		2.50±1.45
155	TCMDC-143119		7.50±1.00
156	TCMDC-143139		11.90±1.75
157	TCMDC-143557		4.50±4.45

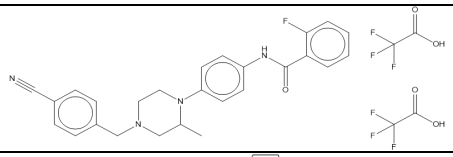
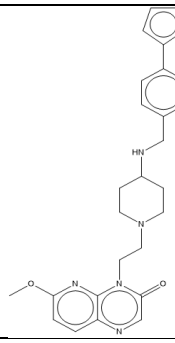
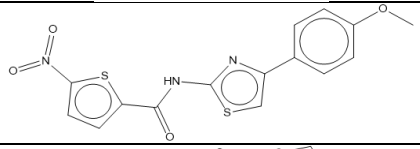
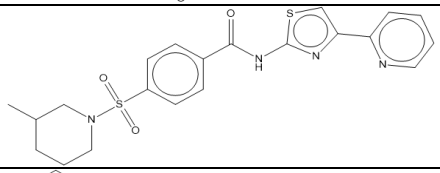
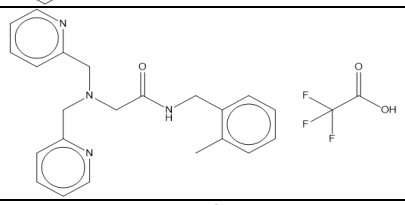
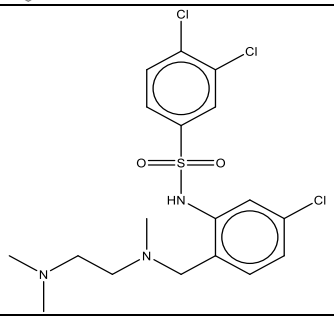
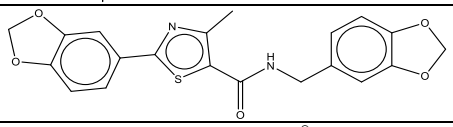
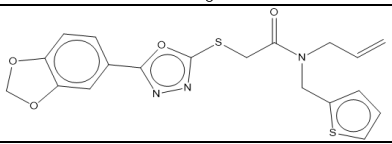
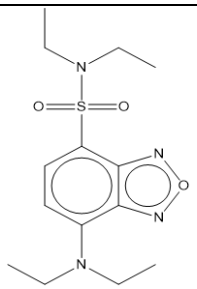
158	TCMDC-143170		7.85±3.95
159	TCMDC-143306		8.80±2.70
160	TCMDC-143345		12.60±3.50
161	TCMDC-143315		3.00±3.05
162	TCMDC-143532		9.20±3.30
163	TCMDC-143591		3.10±0.70
164	TCMDC-143573		1.15±1.40
165	TCMDC-142704		4.70±0.85

166	TCMDC-143174		18.60±2.15
167	TCMDC-143237		38.45±1.35
168	TCMDC-143252		14.15±2.15
169	TCMDC-143236		32.90±2.70
170	TCMDC-143344		13.20±1.65
171	TCMDC-143639		4.25±2.30
172	TCMDC-143523		5.20±2.65
173	TCMDC-143538		8.60±2.90

174	TCMDC-143574		6.00±1.50
175	TCMDC-143101		16.65±1.70
176	TCMDC-143165		8.55±1.75
177	TCMDC-143218		17.70±1.20
178	TCMDC-143255		28.65±1.95
179	TCMDC-143327		29.35±2.80
180	TCMDC-143358		17.50±3.45
181	TCMDC-143517		5.90±2.90

182	TCMDC-143518		9.60±1.20
183	TCMDC-143514		14.80±2.25
184	TCMDC-143098		53.23±3.29
185	TCMDC-125387		1.70±0.75
186	TCMDC-143166		3.65±2.60
187	TCMDC-143181		67.81±1.17
188	TCMDC-143287		20.90±4.45
189	TCMDC-143348		12.20±0.75

190	TCMDC-143508		8.15±3.40
191	TCMDC-143531		12.20±2.70
192	TCMDC-143568		-2.40±2.70
193	TCMDC-143093		2.65±4.15
194	TCMDC-143566		0.90±4.25
195	TCMDC-143140		16.55±4.05
196	TCMDC-143188		-2.80±6.35
197	TCMDC-143201		10.05±1.90
198	TCMDC-143268		7.15±1.10

199	TCMDC-143355		8.70±1.75
200	TCMDC-143383		20.95±1.30
201	TCMDC-143522		18.65±3.35
202	TCMDC-143570		6.50±2.15
203	TCMDC-143090		4.90±2.30
204	TCMDC-143117		8.00±4.85
205	TCMDC-143184		14.00±2.25
206	TCMDC-143202		10.00±0.90
207	TCMDC-143271		8.90±5.85

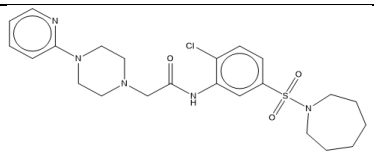
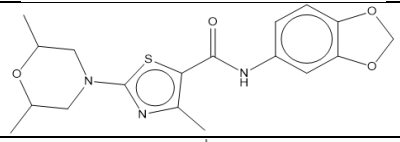
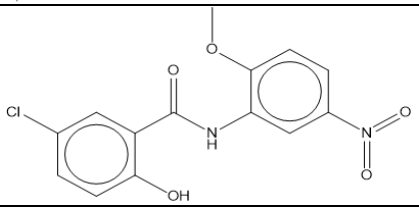
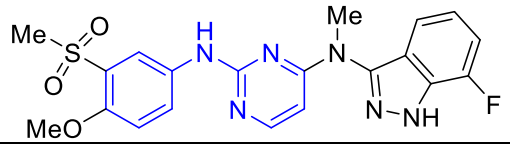
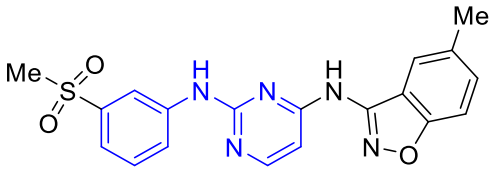
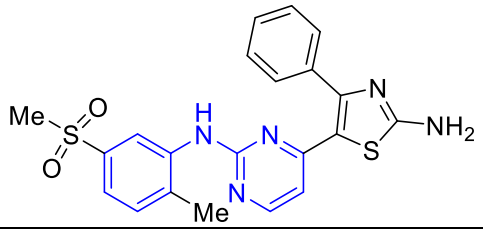
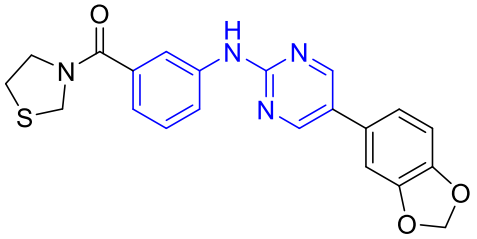
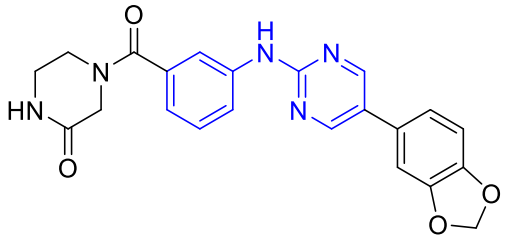
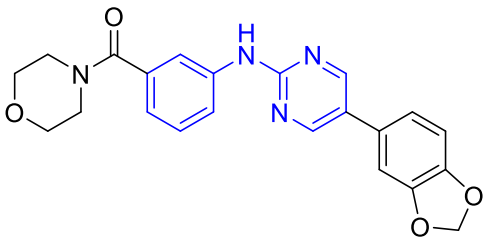
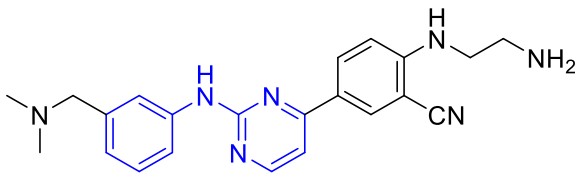
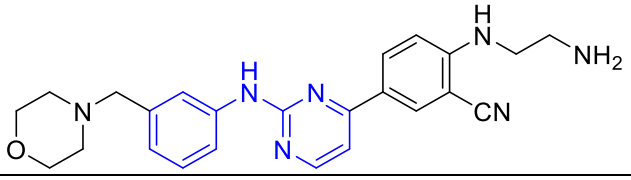
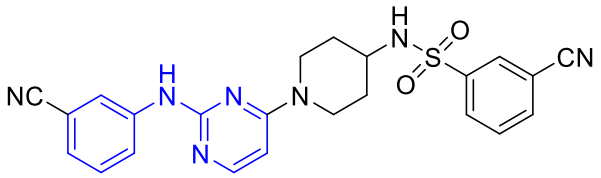
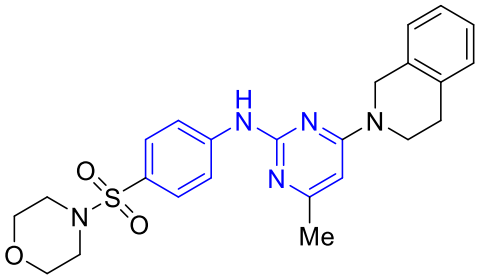
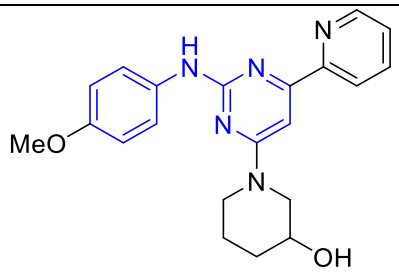
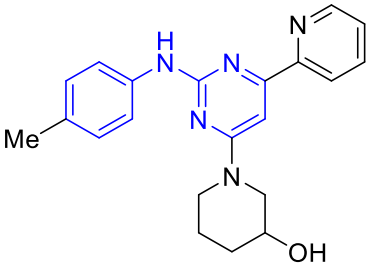
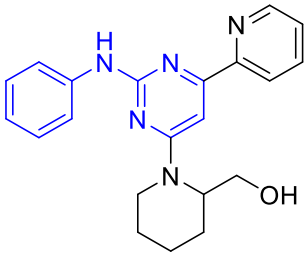
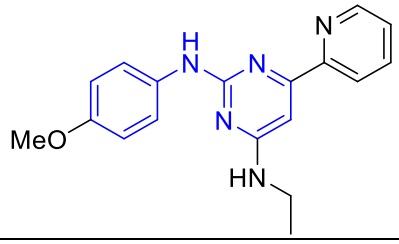
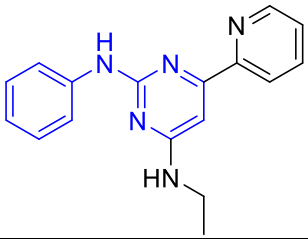
208	TCMDC-143259		10.20±3.25
209	TCMDC-143340		16.10±4.80
210	TCMDC-143618		17.65±3.55

Table S3. LdGSK-3 inhibition for *N*-phenylpyrimidine-2-amines from the Leishbox.

Compound	Leishbox ID	Chemical Structure	%inhibition @10μM
95	TCMDC-143483		90.25±1.12
74	TCMDC-143451		10.00±0.75
124	TCMDC-143391		70.59±3.12
140	TCMDC-143367		18.20±7.00
67	TCMDC-143349		5.65±3.60
189	TCMDC-143348		12.20±0.75
119	TCMDC-143281		100.29±1.24
128	TCMDC-143280		99.46±0.78

100	TCMDC-143249		37.05±1.50
73	TCMDC-143246		-3.05±0.35
42	TCMDC-143216		5.30±2.55
48	TCMDC-143215		3.25±2.75
99	TCMDC-143214		0.60±0.60
45	TCMDC-143213		-2.50±5.50
38	TCMDC-143212		7.10±1.40

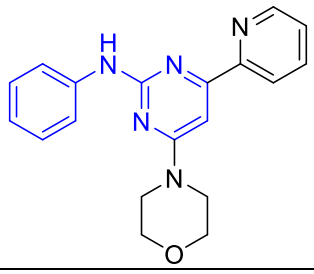
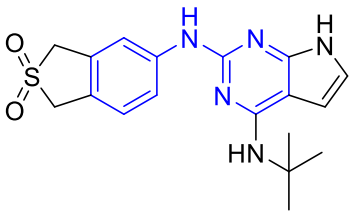
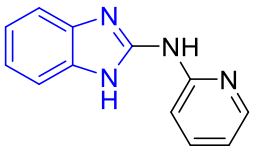
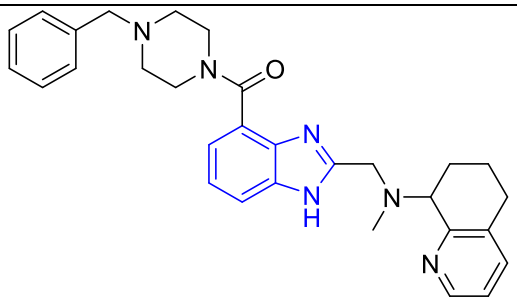
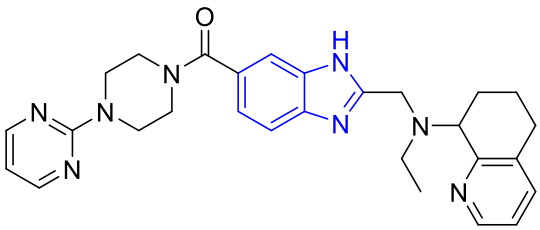
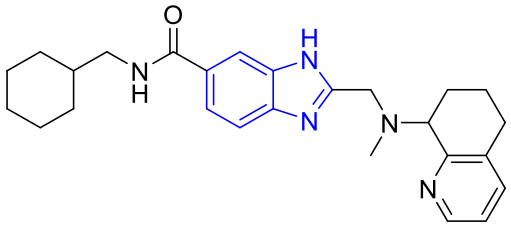
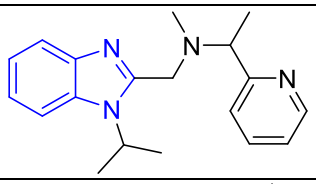
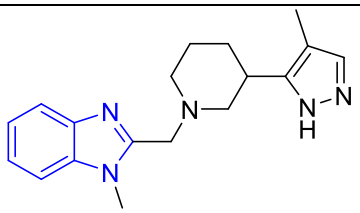
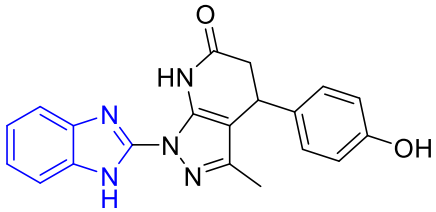
34	TCMDC-143211		-2.00±2.70
103	TCMDC-143086		25.85±1.25

Table S4. LdGSK-3 inhibition for benzoimidazoles from the Leishbox

Compound	Leishbox ID	Chemical Structure	%inhibition @10μM
40	TCMDC-143554		13.50±3.10
91	TCMDC-143524		12.65±6.10
182	TCMDC-143518		9.60±1.20
28	TCMDC-143512		1.15±1.75
85	TCMDC-143503		3.45±4.90
114	TCMDC-143478		2.85±0.45
120	TCMDC-143429		18.15±1.70

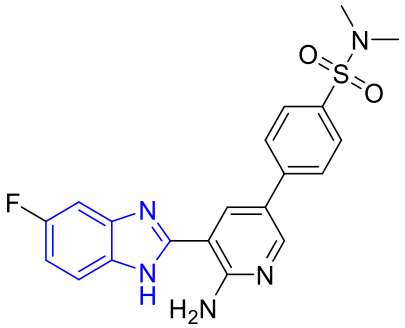
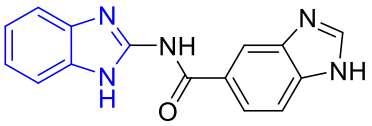
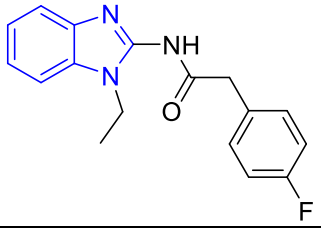
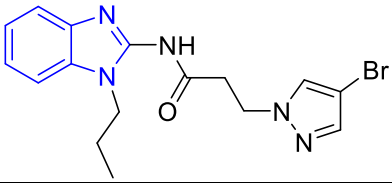
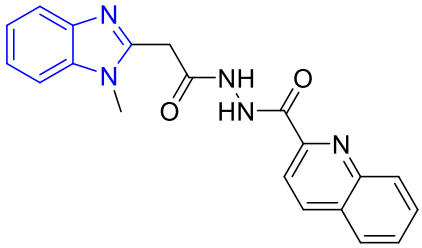
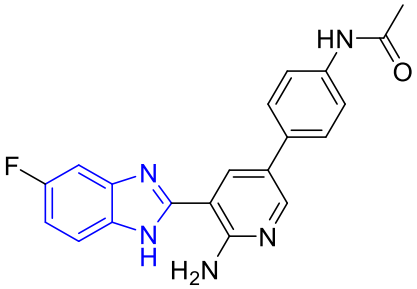
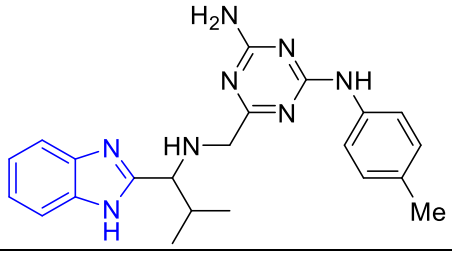
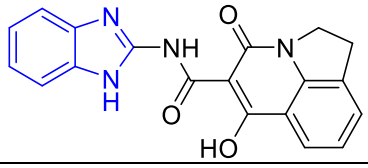
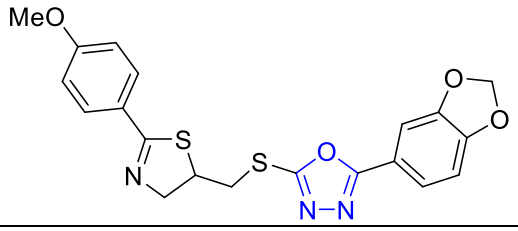
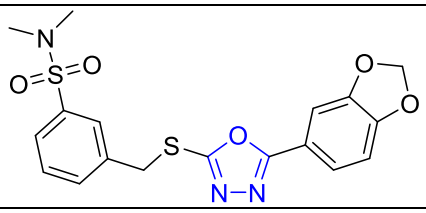
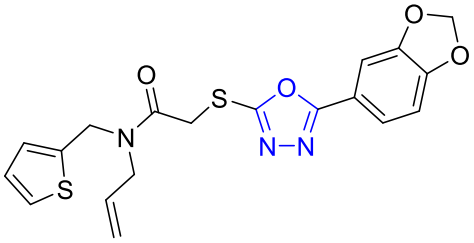
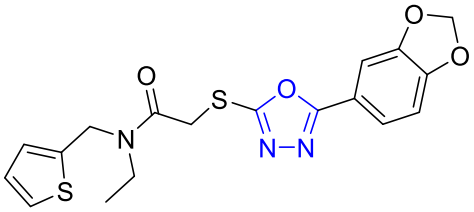
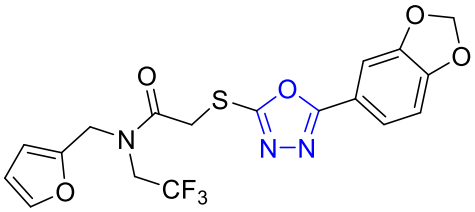
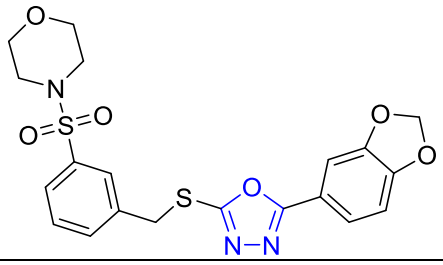
71	TCMDC-143396		74.63±1.76
53	TCMDC-143350		-1.60±1.50
138	TCMDC-143278		13.0±3.55
70	TCMDC-143277		3.80±1.25
80	TCMDC-143261		7.95±1.65
187	TCMDC-143181		67.81±1.17
79	TCMDC-143168		6.40±1.30
155	TCMDC-143119		7.50±1.00

Table S5. LdGSK-3 inhibition for oxadiazole from the Leishbox

Compound	Leishbox ID	Chemical Structure	%inhibition @10μM
125	TCMDC-143594		10.60±1.00
167	TCMDC-143237		38.45±1.35
206	TCMDC-143202		10±0.90
197	TCMDC-143201		10.05±1.90
184	TCMDC-143098		53.23±3.29
151	TCMDC-143197		61.89±2.34

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