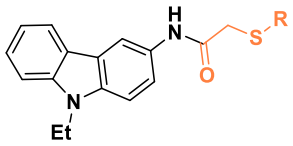
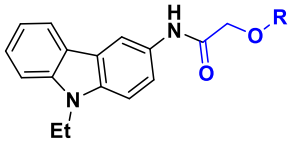
Table S1. Carbazole derivatives, see **Figure 3** (TYRIs bearing the carbazole scaffold).



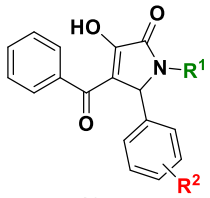
10



11

Compound	R	*Ki* (μM ± SEM)
10a	2-benzimidazole	1.64
10b	2-thiazole	3.46
10c	2-benzoxazole	4.34
10d	2-benzothiazole	6.87
11a	3-nitrobenzene	5.41
11b	4-ethylbenzene	6.73
11c	4-chlorobenzene	7.48
kojic acid (**5**)		4.43

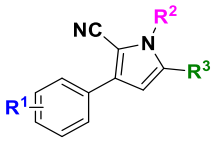
Table S2. 3-Hydroxy-1*H*-pyrrol-2(5*H*)-one derivatives, see **Figure 4** (3-Hydroxy-1*H*-pyrrol-2(5*H*)-one derivatives and their inhibitory activity).



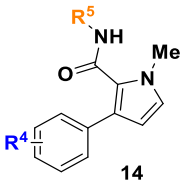
12

Compound	R^1	R^2	IC_{50} (μM ± SE)
12a	phenyl	H	6.98
12b	phenyl	2-F	8.12
12c	phenyl	2-Cl	-
12d	phenyl	3-Br	-
12e	phenyl	4-NO_2	-
12f	phenyl	4-OMe	-
12g	2-propenyl	2-F	9.77
12h	2-propenyl	2-Cl	-
12i	2-propenyl	4-Cl	-
12j	2-propenyl	2-Br	-
12k	2-propenyl	3-Br	-
12l	2-propenyl	4-NO_2	26.73
12m	2-propenyl	4-OMe	-
12n	2-F-phenyl	H	-
12o	4-Cl-Phenyl	H	-
12p	4-Cl-Phenyl	4-OMe	-
12q	4-Br-Phenyl	H	-
12r	4-ethyl-phenyl	H	-
12s	4-ethyl-phenyl	2-F	-
kojic acid (**5**)			18.56

Table S3. 2-Cyanopyrrole derivatives, see **Figure 5** (Derivatives of 2-cyanopyrrole and their inhibitory activities).



13



14

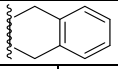
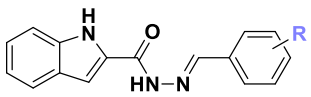
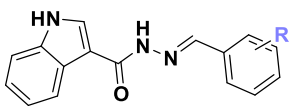
Compound	R^1	R^2	R^3	R^4	R^5	IC_{50} (μM)
13a	2-vinyl	Me	H	-	-	0.97
13b	2-OMe; 5-Br	Me	H	-	-	2.11
13c	2,3-diCl	Me	H	-	-	4.83
13d	H	Me	H	-	-	7.42
13e	4-Br	Me	H	-	-	8.17
13f	2-Br	Me	H	-	-	8.47
13g	2-F	Me	H	-	-	8.72
13h	4-CF_3	Me	H	-	-	12.44
13i	3-Br	Me	H	-	-	16.52
13j	3-F	Me	H	-	-	21.43
13k	2-OMe	Me	H	-	-	23.57
13l	4-OMe	Me	H	-	-	89.15
13m	H	Et	Me	-	-	4.46
13n	4-Cl			-	-	5.06
13o	4-Cl			-	-	5.57
13p	4-Cl	benzyl	H	-	-	80.46
13q	4-Cl	Me	phenyl	-	-	87.32
14a	-	-	-	3-Br	H	>200
14b	-	-	-	3-Br	CO_2t-Bu	>200
14c	-	-	-	4-Br	H	>200
14d	-	-	-	4-Br	CO_2t-Bu	>200
14e	-	-	-	3-F	CO_2t-Bu	>200
14f	-	-	-	H	CO_2t-Bu	>200
14g	-	-	-	4-CF_3	CO_2t-Bu	>200
14h	-	-	-	2-F	CO_2t-Bu	>200
kojic acid (**5**)						28.72

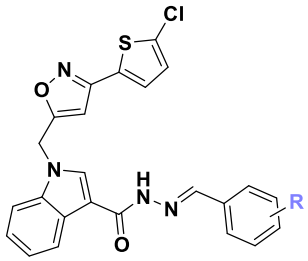
Table S4. Indole-carbohydrazide derivatives, see **Figure 6** (Indole-carbohydrazide derivatives).



15



16

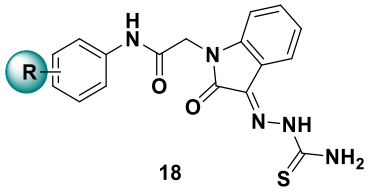


17

Compound	R	IC_{50} (μM)
15a	4-OH	0.070
15b	2,4-diCl	61.52

15c	3-F	69.66
15d	4-OMe	72.94
15e	3-Cl	78.52
15f	H	79.43
15g	2,3-diOH	80.72
15h	2,4-diOH	-
16a	4-OH	0.072
16b	2,4-diCl	94.84
16c	3-F	-
16d	3-Cl	-
16e	4-OMe	-
16f	H	-
16g	2,4-diOH	-
16h	2,3-diOH	-
17a	4-OH	0.19
17b	4-OMe	2.96
17c	2,4-diOH	3.30
17d	2,3-diOH	3.40
17e	2,5-diOH	4.62
17f	3-Cl	47.42
17g	H	95.06
17h	3-F	-
17i	2,3-diOMe	-
kojic acid (**5**)		9.28

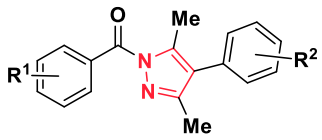
Table S5. *N*-Phenylacetamide-oxindole-thiosemicarbazide hybrids, see **Figure 7** (*N*-Phenylacetamide-oxindole-thiosemicarbazide hybrids (**18**) and their activities).



18

Compound	R	IC_{50} (µM)
18a	2-Me; 4-NO_2	0.80
18b	2-F	0.84
18c	4-Br	0.89
18d	4-F	0.97
18e	4-Me	1.06
18f	4-Cl	1.21
18g	3-F	1.44
18h	2-Me	1.73
18i	4-NO2	2.14
18l	2-Cl	2.17
18m	H	2.30
18n	2,3-diCl	2.47
18o	3-Cl	2.85
18p	4-OMe	3.40
18q	2,6-diCl	3.88
kojic acid (**5**)		36.32

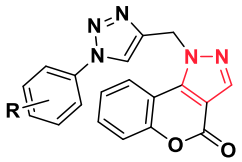
Table S6. Aryl pyrazole derivatives, see **Figure 8** (TYRIs bearing an aryl pyrazole moiety).



19

Compound	R^1	R^2	IC_{50} (μM)
19a	2,4-diOMe	4-NH_2	1.56
19b	3-Me	4-NO_2	2.12
19c	4-NO_2	4-OMe	2.31
19d	2,4-diOMe	4-NO_2	3.37
19e	4-OMe	4-NH_2	6.46
19f	4-Me	4-NH_2	7.75
19g	4-NO_2	3-NH_2	7.89
19h	3-Me	4-OMe	10.07
19i	4-OMe	4-NO_2	15.13
19j	4-Me	4-OMe	16.59
19k	3-Me	4-NH_2	19.53
19l	4-NO_2	4-NH_2	19.65
kojic acid (**5**)			16.05

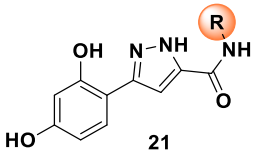
Table S7. 1,2,3-Triazolo-coumarino[4,3-*c*]pyrazole derivatives, see **Figure 9** (Inhibitory effects of 1,2,3-triazolo-coumarino[4,3-*c*]pyrazole derivatives).



20

Compound	R	PI (%)
20a	H	85.0
20b	2,4,6-triCl	72.0
20c	3-Me	66.0
20d	4-Cl	46.0
20e	phenyl	-
kojic acid (**5**)		85.2

Table S8. Pyrazole-resorcinol derivatives, see **Figure 10** (Pyrazole-resorcinol derivatives with promising biological profiles).

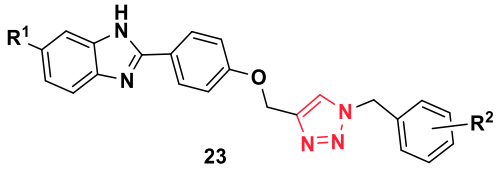


21

Compound	R	IC_{50} monophenolase (μM)	IC_{50} diphenolase (μM)
21a	3,4,5-triOMe-phenyl	0.006	0.64

22b	4-CO_2Me-phenyl	0.02	0.45
22c	4-OMe-phenyl	0.03	-
22d	4-F-phenyl	0.03	0.97
22e	naphthalen-2-yl	0.04	2.88
22f	2-Me-phenyl	0.06	3.55
22g	4-Cl-phenyl	0.06	1.69
22h	naphthalen-1-yl	0.07	6.19
22i	2-OMe-phenyl	0.07	11.25
22j	2,6-diOMe-phenyl	0.08	10.70
22k	4-Br-phenyl	0.11	4.21
22l	4-Me-phenyl	0.11	2.23
22m	4-CN-phenyl	0.12	6.51
22n	4-*i*Pr-phenyl	0.14	0.14
22o	3-OMe-phenyl	0.26	10.14
22p	3-Me-phenyl	0.33	0.45
22q	phenyl	0.33	5.23
22r	6-methylpyridin-2-yl	0.73	6.86
22s	3-F-phenyl	0.79	7.23
kojic acid (**5**)		21.58	17.76

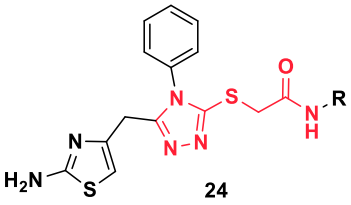
Table S9. Benzimidazole-1,2,3-triazole derivatives, see **Figure 12** (Benzimidazole-1,2,3-triazole hybrids).



23

Compound	R^1	R^2	IC_{50} (μM)
23a	H	3,4-diCl	9.42
23b	H	4-Br	10.34
23c	H	2-F	45.22
23d	H	4-F	46.89
23e	H	4-NO_2	48.00
23f	H	Phenyl	>50
23g	H	4-Me	>50
23h	H	2-Cl	>50
23i	H	2,3-diCl	>50
23j	Me	4-F	29.31
23k	Me	H	43.30
23l	Me	2-Cl	>50
23m	Me	3-Cl	>50
23n	Me	2,3-diCl	>50
23o	Me	3,4-diCl	>50
23p	Me	4-Br	>50
23q	Me	4-NO_2	>50
23r	Me	4-Me	>50
koji acid (**5**)			9.28

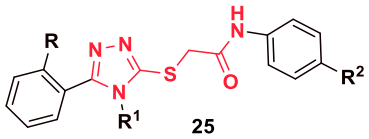
Table S10. 1,2,4-Triazol-3-ylthio-*N*-phenyl acetamide derivatives, see **Figure 13a** (1,2,4-Triazol-3-ylthio-*N*-phenyl acetamide derivatives (**24**) containing the 2-aminothiazole moiety (a) in the position five of the triazole ring).



24

Compound	R	IC_{50} (µM)
24a	2-Me-phenyl	0.0156
24b	ethyl phenyl	0.0161
24c	2,6-diMe-phenyl	0.0513
24d	2,4-diMe-phenyl	0.0547
24e	2,5-diMe-phenyl	0.0589
24f	2-Et-phenyl	0.0652
24g	3,4-diMe-phenyl	0.1133
24h	4-Et-phenyl	0.1224
24i	phenyl	0.1330
24j	4-OEt-phenyl	0.1726
24k	2-Et,6-Me-phenyl	0.1943
24l	3,5-diMe-phenyl	0.2465
24m	benzyl	1.0108
24n	2,3-diMe-phenyl	2.0181
kojic acid (**5**)		16.8320

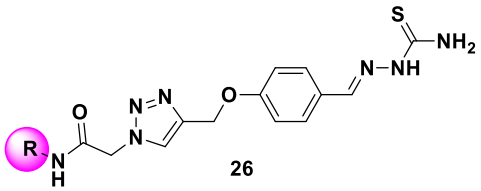
Table S11. 1,2,4-Triazol-3-ylthio-*N*-phenyl acetamide derivatives, see **Figure 13b** (1,2,4-Triazol-3-ylthio-*N*-phenyl acetamide derivatives containing a phenyl ring (**25**) (b) in the position five of the triazole ring).



25

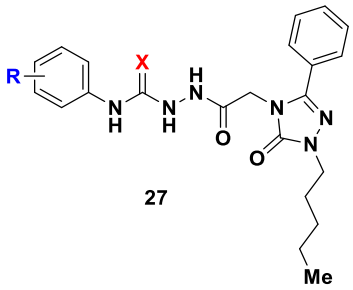
Compound	R	R^1	R^2	IC_{50} (µM)
25a	H	2-OMe-phenyl	Br	0.0048
25b	H	2-OMe-phenyl	H	0.0238
25c	H	2-OMe-phenyl	F	0.0802
25d	H	2-OMe-phenyl	I	0.6545
25e	F	2-OMe-phenyl	I	0.0605
25f	F	2-OMe-phenyl	Br	0.1537
25d	F	2-OMe-phenyl	F	0.1691
25h	F	2-OMe-phenyl	H	0.5425
25i	H	*n*-Bu	H	0.2144
25j	H	*n*-Bu	I	0.2179
25k	H	*n*-Bu	Br	0.3431
25l	H	*n*-Bu	F	0.3696
kojic acid (**5**)				16.8320

Table S12. Triazoles derivatives, see **Figure 14** (Aryl phenoxy methyl triazoles conjugated with thiosemicarbazides derivatives).



Compound	R	IC_{50} monophenolase (µM)	IC_{50} diphenolase (µM)
26a	benzyl	0.11	0.17
26b	4-OMe-phenyl	0.12	0.52
26c	4-F-phenyl	0.14	0.60
26d	3-OMe-phenyl	0.22	0.84
26e	2-Me,3-NO_2-phenyl	0.25	0.56
26f	4-Br-phenyl	0.35	0.21
26g	2,3-diCl-phenyl	0.42	0.42
26h	4-NO_2-phenyl	0.42	0.68
26i	2-Me,3-Cl-phenyl	0.46	0.26
26j	4-Cl-phenyl	0.50	0.14
26k	3-Br-phenyl	0.51	0.31
26l	3-Cl-phenyl	0.51	0.50
26m	phenyl	0.79	2.18
26n	4-F-benzyl	0.83	0.43
kojic acid (**5**)		9.28	9.30

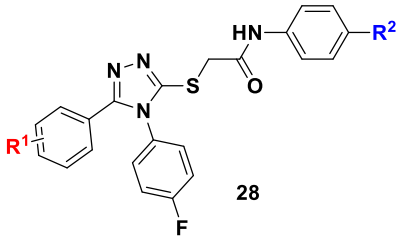
Table S13. 1,2,4-Triazole-thiosemicarbazide derivatives, see **Figure 15** (1,2,4-Triazole-thiosemicarbazide hybrid molecules).



Compound	R	X	IC_{50} (µM)
27a	2,4-diCl	O	0.00162
27b	2-CF_3	O	0.00166
27c	3-CF_3	O	0.00165
27d	3,5-diCF_3	O	0.00197
27e	2-F	O	>20
27f	3-F	O	>20
27g	4-F	O	>20
27h	2,4-diF	O	>20
27i	2-Cl	O	>20
27j	3-Cl	O	>20
27k	4-Cl	O	>20
27l	3,5-diCl	O	>20
27m	2-Br	O	>20
27n	3-Br	O	>20

27o	4-Br	O	>20
27p	4-CF_3	O	>20
27q	4-F	S	0.0145
27r	2,4-diF	S	0.019
27s	4-Br	S	0.0199
27t	3,5-diCl	S	0.17
27u	4-Cl	S	0.1885
27v	4-CF_3	S	1.49
27w	2-Cl	S	4.68
27x	3-Cl	S	5.4
27y	2-CF_3	S	5.62
27z	3-F	S	15.2
27aa	2,4-diCl	S	>20
27bb	2-F	S	>20
27cc	2-Br	S	>20
27dd	3-Br	S	>20
27ee	3-CF_3	S	>20
27ff	3,5-diCF_3	S	>20
kojic acid (**5**)			14.09

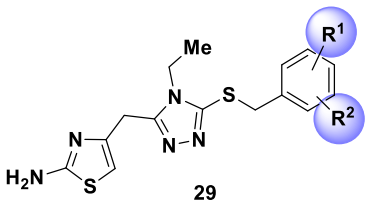
Table S14. 1,2,4-Triazole based compounds, see **Figure 16** (1,2,4-Triazole based compounds (**28**) and their inhibitory activities).



28

Compound	R^1	R^2	IC_{50} (μM)
28a	2-F	4-F	0.098
28b	2-F	H	0.111
28c	4-F	H	0.124
28d	H	4-Br	0.142
28e	H	H	0.219
28f	H	4-F	0.379
28g	4-F	4-F	-
28h	4-F	4-Br	-
28i	2-F	4-Br	-
kojic acid (**5**)			16.832

Table S15. Thiazole-triazole based compounds, see **Figure 17** (Thiazole-triazole hybrids as TYRIs).

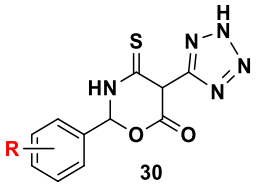


29

Compound	R^1	R^2	IC_{50} (μM)

29a	2-Cl	4-Cl	0.0018
29b	H	3-Br	0.0021
29c	2-Cl	H	0.0059
29d	H	4-Cl	0.0066
29e	H	4-F	0.0115
29f	3-Cl	4-Cl	0.0142
29g	2-Br	H	0.0157
29h	H	4-Br	0.0243
29i	H	3-Me	0.0341
29j	2-Me	H	0.0713
29k	H	4-Me	0.0782
29l	H	H	0.0896
kojic acid (**5**)			16.8320

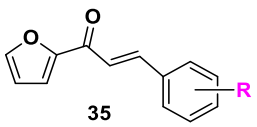
Table S16. Tetrazole based compounds, see **Figure 18** (Tetrazole-containing TYRIs **30**).



30

Compound	R	IC_{50} (µM)
30a	2-Br	0.0371
30b	2,4-diCl	0.0472
30c	3-NO_2	0.0601
30d	3-Cl	0.0715
30e	4-OMe	0.0728
30f	3,5-diNO_2	0.0758
30g	4-NO_2	0.0815
30h	2-Cl	0.0883
30i	2,6-diOMe	0.1992
30j	4-Cl	0.2941
30k	4-Me	0.3080
kojic acid (**5**)		16.832

Table S17. Chalcone derivatives, see **Figure 20** (TYRIs combining chalcone and furan moieties).

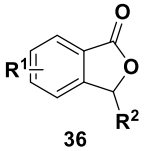


35

Compound	R	IC_{50} (µM)
35a	2,4-diOH	0.28
35b	3,4-diOH	24.86
35c	3,5-diBr,4-OH	27.17
35d	3-OH,4-OMe	37.36
35e	3-OMe,4-OH	>200
35f	3,5-diOMe,4-OH	>200
35g	3-Br,4-OH	>200
35h	4-OH	>200

kojic acid (**5**)		33.47

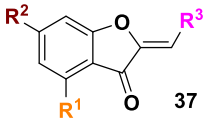
Table S18. Isobenzofuran-1(3*H*)-one derivatives, see **Figure 21** (Derivatives of isobenzofuran-1(3*H*)-one (**36a**) and their inhibitory profile).



36

Compound	R^1	R^2	IC_{50} (µM)
36a	H	OH	156.03
36b	H	2,6-diCO_2Me-phenyl	194.01
36c	H	2,6-diOH,4-*i*Pr-phenyl	255.23
36d	5-OMe	H	-
36e	5-OH	H	-
36f	H	2,6-diOH,4-Me-phenyl	-
36g	H	2,6-diOH-phenyl	-
36h	H	2,6-diCO_2Me,4-Me-phenyl	-
36i	H	2,6-diCO_2Me,4-*i*Pr-phenyl	-
36j	6-OMe	H	-
36k	6-OH	H	-
kojic acid (**5**)			5.71

Table S19. Aurone derivatives, see **Figure 22**(Chemical structures of aurone derivatives **37** and their activities as AbTYRIs).

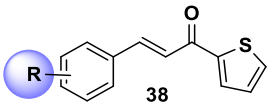


37

Compound	R^1	R^2	R^3	IC_{50} (µM)
37a	H	H	4-Me-phenyl	7.12
37b	H	H	3-OMe,4-OPr-phenyl	9.94
37c	H	H	5-OMe-2-naphtyl	10.12
37d	H	H	3-OMe,4-OBu-phenyl	10.56
37e	H	H	4-OMe-phenyl	10.65
37f	H	H	4-OEt-phenyl	12.52
37g	H	H	3-OMe,4-OHex-phenyl	13.35
37h	H	H	4-COOH-phenyl	14.23
37i	H	H	4-CHO-phenyl	15.24
37k	H	H	3-OMe,4-OBn-phenyl	20.82
37l	H	H	4-Cl-phenyl	34.31
37m	H	H	2-CF_3-phenyl	44.21
37n	H	H	2-thiophenyl	54.51
37o	H	H	4-F-phenyl	66.82
37p	Br	Br	4-Cl-phenyl	16.54
37q	Br	Br	4-CF_3-phenyl	19.76
37r	Br	Br	2-furanyl	39.45
37s	NO_2	Cl	3-OMe,4-OBn-phenyl	8.25
37t	NO_2	Cl	3-OMe,4-OPr-phenyl	9.55

37u	NO_2	Cl	2,4-diMe-phenyl	10.34
37v	NO_2	Cl	4-OMe-phenyl	13.10
37w	NO_2	Cl	4-Cl-phenyl	15.23
37x	NO_2	Cl	4-F-phenyl	16.33
37y	NO_2	Cl	4-$N(CH_3)_2$-phenyl	25.31
37z	NO_2	Cl	2-thiophenyl	26.90
kojic acid (**5**)				16.69

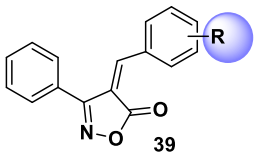
Table S20. Thiophene derivatives, see **Figure 23** (Thiophene derivatives).



38

Compound	R	IC_{50} (µM)
38a	2,4-diOH	0.93
38b	3-OH,4-OMe	28.72
38c	4-OH	60.05
38d	3,4-diOH	103.44
38e	3-Br,4-OH	112.09
38f	3-OMe,4-OH	>200
38g	2,5-diBr,4-OH	>200
38h	3,5-diOMe,4-OH	>200
kojic acid (**5**)		0.93

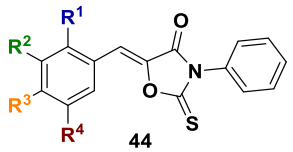
Table S21. Isoxazole derivatives, see **Figure 24** ((*Z*)-4-(Substituted benzylidene)-3-phenylisoxazol-5(4*H*)-one derivatives).



39

Compound	R	PI (%)	IC_{50} (µM)
39a	3-Br,4-OH	70.22	14.62
39b	2,4-diOH	72.73	-
39c	3,5-diOH,4-OH	47.29	-
39d	3-OEt,4-OH	44.52	-
39e	3-OH,4-OMe	42.03	-
39f	3,4-diOMe	40.02	
39g	4-OMe	28.45	-
39h	4-OH	24.60	-
39i	3-OMe,4-OH	-	-
39j	3,4-diOH	-	-
39k	3,4,5-triOMe	-	-
39l	2,4-diOH	-	-
39m	2-OH	-	-
kojic acid (**5**)		-	58.44

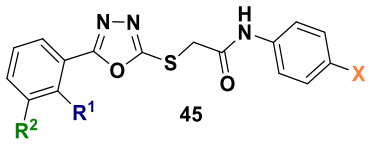
Table S22. 2-Thioxooxazoline-4-one derivatives, see **Figure 25** (2-Thioxooxazoline-4-one derivatives **44** as tyrosinase inhibitors).



44

Compound	R^1	R^2	R^3	R^4	PI (%)	IC_{50} (μM)
44a	OH	H	OH	H	78.05	4.70
44b	OH	H	H	H	71.12	11.18
44c	H	OH	OH	H	30.57	-
44d	H	Br	OH	H	24.96	-
44e	H	OH	OMe	H	13.39	-
44f	H	H	OH	H	10.25	-
44g	H	OMe	OH	OMe	10.22	-
44h	H	*t*-Bu	OH	*t*-Bu	8.53	-
44i	H	OMe	OMe	H	7.47	-
44j	OMe	H	OMe	H	4.09	-
44j	H	Br	OH	Br	-	-
44l	F	H	F	H	-	-
44m	H	OMe	OH	H	-	-
44n	H	OEt	OH	H	-	-
44o	H	H	OMe	H	-	-
44p	H	OMe	OMe	OMe	-	-
kojic acid (**5**)					58.09	23.18

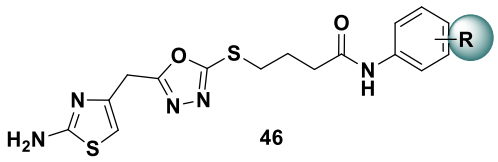
Table S23. 1,3,4-Oxadiazoles derivatives, see **Figure 26** (The tyrosinase inhibition potential of 1,3,4-oxadiazoles derivatives **45**).



45

Compound	R^1	R^2	X	IC_{50} (μM)
45a	OMe	H	H	0.003
45b	OMe	H	F	0.018
45c	H	OMe	H	0.019
45d	OMe	H	I	0.023
45e	H	OMe	F	0.027
45f	H	H	Br	0.039
45g	OMe	H	Br	0.046
45h	H	H	I	0.085
45i	H	OMe	I	0.088
45j	H	OMe	Br	0.145
45k	H	H	H	0.231
45l	H	H	F	0.396
kojic acid (**5**)				16.832

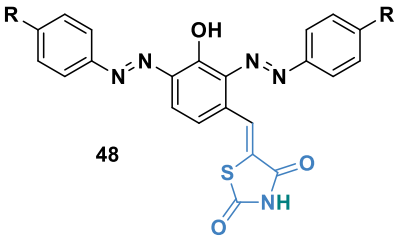
Table S24. 2-Aminothiazole-oxadiazole derivatives, see **Figure 27** (2-Aminothiazole-oxadiazole bi-heterocyclic hybrids **46** and their potential as AbTYR inhibitors).



46

Compound	R	IC_{50} (µM)
46a	2-Me	0.0311
46b	2-Et	0.0349
46c	2,5-diMe	0.1987
46d	3,5-diMe	0.4611
46e	2,4-diMe	0.6524
46f	2,3-diMe	0.7379
46g	3-Me	1.0103
46h	2,6-diMe	1.6139
kojic acid (**5**)		16.8319

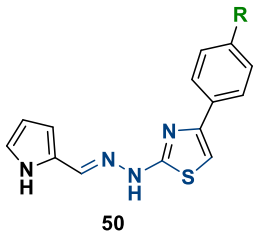
Table S25. Thiazolidinone derivatives, see **Figure 29** (Azo-hydrazone tautomeric dyes bearing a thiazolidinone moiety derivatives).



48

Compound	R	IC_{50} (µM)
48a	OMe	37.59
48b	NO_2	42.31
48c	Me	45.83
48d	CN	61.92
48e	Br	140.25
kojic acid (**5**)		29.44

Table S26. Thiazole derivatives, see **Figure 31a** (TYRIs containing hydrazinyl thiazole moieties).

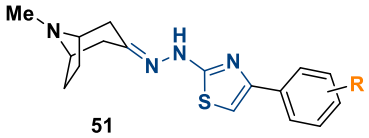


50

Compound	R	IC_{50} (µM)
50a	F	21.45
50b	Br	6.06
50c	OMe	5.94
50d	H	5.81
50e	Cl	4.95

kojic acid (**5**)		4.43

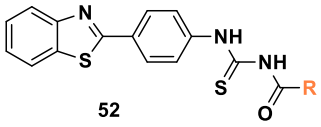
Table S27. Thiazole derivatives, see **Figure 31b** (TYRIs containing hydrazinyl thiazole moieties).



51

Compound	R	IC_{50} (μM)
51a	3,4-diCl-phenyl	3.22
51b	2,4-diCl-phenyl	3.51
51c	4-CF_3-phenyl	33.74
51d	N_3-phenyl	72.30
51e	4-Br-phenyl	84.97
51f	4-Me-phenyl	101.2
51g	4-NH_2-phenyl	118.06
51h	NHCOMe-phenyl	120.71
51i	4-F-phenyl	123.1
51j	4-Cl-phenyl	132.7
51k	4-NO_2-phenyl	140.21
51l	4-I-phenyl	151.44
51m	4-$NHSO_2$Me-phenyl	152.04
51n	4-CN-phenyl	153.04
51o	4-OMe-phenyl	165.38
51p	2*H*-chromen-2-one	183.34
Ascorbic acid (**7**)		386.5
kojic acid (**5**)		72.27

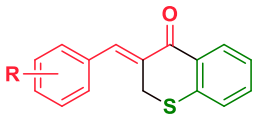
Table S28. 2-Benzothiazole-linked thiourea derivatives, see **Figure 32** (2-Benzothiazole-linked thioureas with inhibitory activity towards TYR).



52

Compound	R	IC_{50} (μM)
52a	nonyl	1.3431
52b	heptyl	1.3526
52c	pentyl	2.6841
52d	octyl	4.1576
52e	3,5-diNO_2-phenyl	4.7745
52f	propyl	6.0986
52g	*t*-Bu	7.8319
52h	2,4-diCl-phenyl	19.0153
52i	4-OMe-phenyl	54.6311
kojic acid (**5**)		16.8320

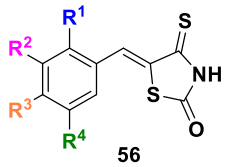
Table S29. Benzylidenethiochroman-4-one derivatives, see **Figure 33** (Rational design of TYRIs bearing the benzylidenethiochroman-4-one scaffold).



53

Compound	R	PI (%)	IC_{50} (μM)
53a	3-OH,4-OMe	91.5	4.1
53b	3-Br,4-OH	90.7	-
53c	3,4-diOH	45.0	-
53d	3-OMe,4-OH	25.8	-
53e	2,4-diOMe	20.3	-
53f	3,5-diOMe,4-OH	15.6	-
53g	3,5-diBr,4-OH	8.5	-
kojic acid (**5**)		77.5	22.0

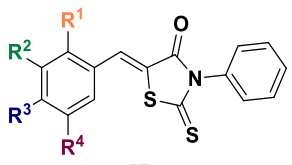
Table S30. ((*Z*)-5-(Substituted benzylidene)-4-thioxothiazolidin-2-one derivatives, see **Figure 34** ((*Z*)-5-(Substituted benzylidene)-4-thioxothiazolidin-2-one derivatives (**56**) as tyrosinase inhibitors).



56

Compound	R^1	R^2	R^3	R^4	IC_{50} (μM)
56a	OH	H	OH	H	0.47
56b	H	OH	OMe	H	15.24
56c	H	OMe	OMe	H	23.31
56d	H	Br	OH	H	26.27
56e	H	H	OH	H	28.05
56f	H	H	OMe	H	30.83
56g	H	OH	OH	H	47.41
56h	H	OMe	OH	H	70.75
56i	H	OMe	OH	OMe	82.39
56l	H	OEt	OH	H	92.81
56m	OMe	H	OMe	H	126.35
56n	OH	H	H	H	147.61
kojic acid (**5**)					66.30

Table S31. (*Z*)-5-(Substituted benzylidene)-3-phenyl-2-thioxothiazolidin-4-one derivatives, see **Figure 35** (*Z*)-5-(Substituted benzylidene)-3-phenyl-2-thioxothiazolidin-4-one derivatives **57**, that showed promising inhibitory characteristics).

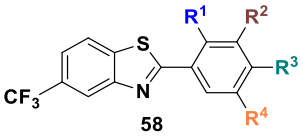


57

Compound	R^1	R^2	R^3	R^4	IC_{50} (μM)

57a	OH	H	OH	H	0.59
57b	H	OH	OH	H	1.38
57c	H	H	OH	H	1.45
57d	H	OH	OMe	H	1.88
57e	OMe	H	OMe	H	22.15
57f	H	Br	OH	H	65.54
57g	H	Br	OH	Br	78.75
57h	H	OMe	OH	H	80.03
57i	H	OMe	OMe	H	94.29
57j	H	H	OMe	H	>200
57k	H	OMe	OMe	OMe	>200
57l	H	OMe	OH	OMe	>200
57m	H	OEt	OH	H	>200
kojic acid (**5**)					17.05

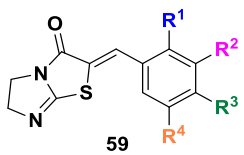
Table S32. 2-(Aryl)-5-(trifluoromethyl)benzo[*d*]thiazoles, see **Figure 36** (Inhibitory activities towards TYR of 2-(aryl)-5-(trifluoromethyl)benzo[*d*]thiazoles **58**).



58

Compound	R^1	R^2	R^3	R^4	IC_{50} (μM)
58a	OH	H	OH	H	0.2
58b	H	H	OH	H	52.4
58c	H	Br	OH	H	101.9
58d	H	Me	OH	Me	128.9
58e	H	OH	H	OH	216.5
58f	H	OMe	OMe	H	263.9
58g	H	OMe	OH	H	291.1
58h	H	OH	OMe	H	>300
58i	OH	H	H	H	>300
58j	H	H	OMe	H	>300
58k	OMe	H	OMe	H	>300
58l	H	Br	OH	Br	>300
58m	H	OEt	OH	H	>300
58n	H	OMe	OMe	OMe	>300
58o	H	OMe	OH	OMe	>300
58p	H	OH	OH	H	>300
kojic acid (**5**)					12.6

Table S33. ((*Z*)-2-Benzylidene-dihydroimidazothiazolone derivatives, see **Figure 37a** ((*Z*)-2-Benzylidene-dihydroimidazothiazolone derivatives (**59**) (a)).

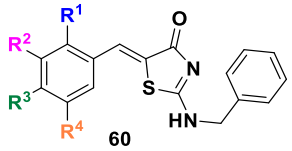


59

Compound	R^1	R^2	R^3	R^4	IC_{50} (μM)
59a	OH	H	OH	H	0.88

59b	H	OH	OMe	H	17.10
59c	H	H	OH	H	36.14
59d	H	OH	OH	H	>100
59e	H	OMe	OH	H	>100
59f	H	OEt	OH	H	>100
59g	H	H	OMe	H	>100
59h	OMe	H	OMe	H	>100
59i	H	OMe	OMe	H	>100
59j	H	OMe	OH	OMe	>100
59k	H	OMe	OMe	OMe	>100
kojic acid (**5**)					84.41

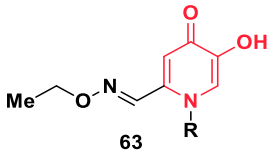
Table S34. ((*Z*)-2-(Benzylamino)-5-benzylidenethiazol-4(5*H*)-one derivatives, see **Figure 37b** ((*Z*)-2-(Benzylamino)-5-benzylidenethiazol-4(5*H*)-one derivatives (**60**) (b)).



60

Compound	R^1	R^2	R^3	R^4	IC_{50} (µM)	
60a	OH	H	OH	H	0.27	1.04
60b	H	OH	OMe	H	10.0	10.3
60c	H	H	OH	H	27.5	65.1
60d	OMe	H	OMe	H	293.3	213.6
60e	H	OMe	OMe	OMe	192.4	231.1
60f	H	H	OMe	H	125.5	239.4
60g	H	OEt	OH	H	198.9	248.1
60h	F	H	F	H	>300	>300
60i	H	F	F	H	288.7	>300
60j	H	OMe	OH	H	148.3	>300
60k	H	OMe	OMe	H	>300	>300
60l	H	OMe	OH	OMe	166.0	>300
60m	H	t-Bu	OH	t-Bu	136.7	>300
60n	H	OH	OH	H	>300	>300
kojic acid (**5**)					28.6	20.1

Table S35. Hydroxypyridinone derivatives, see **Figure 39** (Hydroxypyridinone-based TYRIs (**63**) bearing an oxime moiety).

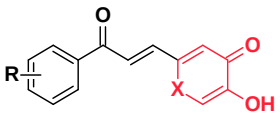


63

Compound	R	IC_{50} monophenolase (µM)	IC_{50} diphenolase (µM)
63a	*n*-Octyl	1.60	7.99
63b	*n*-Hexyl	2.04	13.89
63c	*n*-Bu	4.78	-
63d	Et	7.45	-
63e	Me	19.65	-

63f	H	22.87	-
kojic acid (**5**)		12.24	-

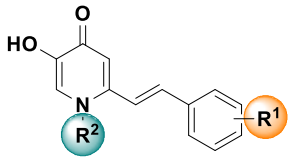
Table S36. Hydroxypyridinones, see **Figure 40** (TYRIs bearing a chalcone-hydroxypyridinone scaffold)



64

Compound	R	X	PI (%)	IC_{50} monophenolase (μM)	IC_{50} diphenolase (μM)
64a	4-F	NH	89.5	2.25	11.7
64b	3,4-diOCH_3	NH	87.6	2.75	19.3
64c	4-F	NCH_3	85.3	3.07	17.1
64d	3,4-diOH	NC_2H_5	78.8	8.11	-
64e	H	NCH_3	72.8	-	-
64f	2-OH, 4-OCH_3	NC_2H_5	71.4	-	-
64g	3,4-diOH	NC_4H_9	69.4	-	-
64h	2-OH, 4-OCH_3	NCH_3	66.7	-	-
64i	H	NH	66.7	-	-
64j	2-OH, 4-OCH_3	NC_4H_9	64.6	-	-
64k	H	NC_2H_5	63.3	-	-
64l	3,4-diOCH_3	NH	63.3	-	-
64m	4-F	NC_2H_5	57.8	-	-
64n	2,4-diOCH_3	O	50.3	-	-
64o	4-F	NC_4H_9	50.3	-	-
kojic acid (**5**)			75.4	-	-

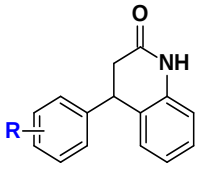
Table S37. Hydroxypyridinones, see **Figure 41** (TYR-inhibitory profile of stilbene-hydroxypyridinone hybrids).



65

Compound	R^1	R^2	IC_{50} monophenolase (μM)	IC_{50} diphenolase (μM)
65a	3,5-diOH	*n*-C_6H_{13}	2.72	15.86
65b	3,4-di-OH	*n*-C_6H_{13}	3.83	-
65c	4-OH	*n*-C_6H_{13}	5.27	-
65d	3,5-diOH	*n*-C_4H_9	6.35	-
65e	3,4-diOH	*n*-C_4H_9	7.45	-
65f	4-OH	*n*-C_4H_9	7.62	-
65g	3,5-diOH	*n*-C_8H_{17}	9.31	-
65h	3,4-diOH	*n*-C_8H_{17}	12.26	-
65i	4-OH	*n*-C_8H_{17}	16.32	-
kojic acid (**5**)			12.52	-

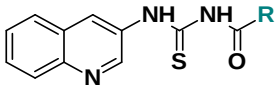
Table S38. Quinoline derivatives, see **Figure 42** (Dihydroquinolinones and their TYR inhibitory behavior).



66

Compound	R	PI (%)
66a	3-OH,4-OMe	25.94
66b	4-OH	-
66c	3,4-diOH	-
66d	3-OMe,4-OH	-
kojic acid (**5**)		21.39

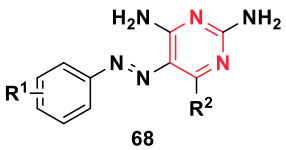
Table S39. Quinoline derivatives, see **Figure 44** (Quinolinyl based acyl thiourea derivatives).



67

Compound	R	IC_{50} (µM)
67a	*n*-pentyl	0.0070
67b	phenyl	0.0148
67c	3,5-diNO_2-Ph	0.1099
67d	*n*-hexyl	0.1105
67e	*n*-heptyl	0.1149
67f	4-Me-Ph	0.1275
67g	*n*-nonyl	0.2685
67h	*n*-butyl	0.4196
67i	2,4-diCl-Ph	0.7656
67j	*n*-propyl	1.9737
kojic acid (**5**)		16.8320

Table S40. Pyrimidine-based derivatives, see **Figure 44** (Azo-pyrimidine derivatives that were tested on their inhibitory activity on TYR).

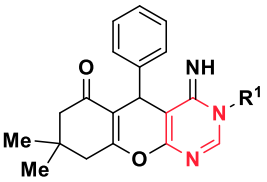


68

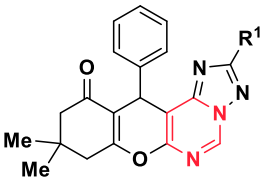
Compound	R^1	R^2	IC_{50} (µM)
68a	4-NHCOMe	Cl	24.45
68b	2-NO_2	Cl	24.68
68c	4-OMe	Cl	28.01
68d	4-NHCOMe	NH_2	29.77
68e	2-NO_2	NH_2	34.06
68f	4-NO_2	Cl	37.191
68g	4-NO_2	NH_2	40.62
68h	4-Me	NH_2	41.4

68i	4-Me	Cl	42.04
68j	4-OMe	NH_2	43.8
kojic acid (**5**)			25.24

Table S41. Pyrimidine-based derivatives, see **Figure 45** (TYRIs bearing the pyranopyrimidine and the pyranotriazolopyrimidine scaffolds).



69



70

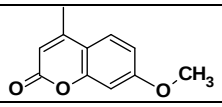
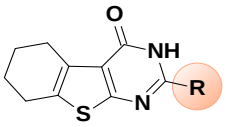
Compound	R^1	PI (%)
69a	3-Cl-Ph	94.23
69b	Ph	91.35
69c	4-C_2H_5-Ph	84.14
69d	4-Me-Ph	-
69e	1-naphtyl	-
69f	4-OMe-Ph	-
70a	CH_2CN	93.94
70b		90.12
70c	H	78.09
70d	Me	-
kojic acid (**5**)		85.50

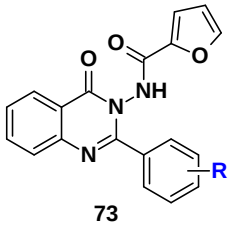
Table S42. Pyrimidine-based derivatives, see **Figure 47** (Tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidine-4(3*H*)-one derivatives **72**, which are substituted in the 2-position).



72

Compound	R	IC_{50} (mM)
72a	2,4-diOH-Ph	0.51
72b	4-OH-Ph	0.70
72c	2-OH-Ph	0.87
72d	Ph	1.11
72e	2-OH,3-OMe-Ph4	1.57
72f	3-OMe,4-OH	2.04
72g	3-Me-furan	2.10
72h	*t*Bu-Ph	2.11
72i	4-Me-Ph	2.25
72j	4-OMe-Ph	2.34
72k	4-OMe,3-OH	2.45
72l	furan	3.03
kojic acid (**5**)		0.32

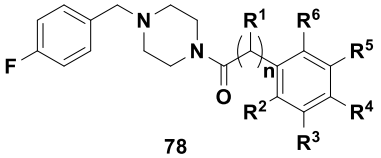
Table S43. Oxoquinazoline derivatives, see **Figure 48** (Oxoquinazoline derivatives **73** and their potential in inhibition of TYR).



73

Compound	R	IC_{50} (μM)
73a	2-OH,3,5-diBr	0.028
73b	2-OH,3-NO_2	0.031
73c	2-OH,5-Cl	0.052
73d	2-OH,3,5diI	0.055
73e	2,4-diOH	0.056
73f	2-OH,5-br	0.063
73g	2-OH	0.499
73h	2-OH,3,5-diCl	0.627
73i	2-OH,4-$(CH_3CH_2)_2NH$	1.218
73j	2-OH,5-OMe	1.775
kojic acid (**5**)		16.832

Table S44. Piperazines, see **Figure 50** (Further 4-fluorobenzylpiperazine derivatives (**78**) which were identified as TYRIs).

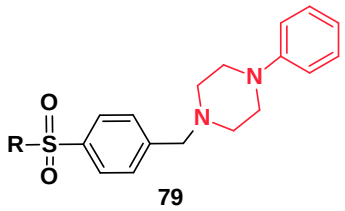


78

Compound	*n*	R^1	R^2	R^3	R^4	R^5	R^6	IC_{50} (μM)
78a	0	H	NO_2	Cl	H	H	H	0.18
78b	0	H	CF_3	H	H	F	H	0.24
78c	0	H	CF_3	F	H	H	H	0.45
78d	0	H	CF_3	H	F	H	H	0.87
78e	0	H	NO_2	H	H	OMe	H	1.11
78f	0	H	NO_2	H	H	H	Cl	1.17
78g	1	H	H	H	NO_2	H	H	1.71
78h	0	H	NO_2	H	OMe	H	H	1.80
78i	0	H	NO_2	H	H	Cl	H	2.01
78j	0	H	NO_2	OMe	H	H	H	2.09
78k	0	H	NO_2	H	Cl	H	H	2.27
78l	1	H	H	H	NO_2	H	H	3.74
78m	1	H	H	H	H	H	H	4.28
78n	1	H	H	Cl	H	H	H	4.66
78o	1	H	Br	H	H	H	H	4.70
78p	1	H	H	H	Cl	H	H	4.71
78q	1	H	H	H	Br	H	H	7.66
78r	1	H	NO_2	H	H	H	H	8.31
78s	1	H	H	NO_2	H	H	H	8.66

78t	1	H	Cl	H	H	H	H	8.70
78u	1	H	H	NH_2	H	H	H	9.36
78v	2	H	H	H	H	H	H	13.17
78w	1	H	H	Br	H	H	H	15.74
78x	1	H	H	H	NH_2	H	H	16.73
78y	1	H	H	H	OMe	H	H	19.63
78z	1	Ph	H	H	H	H	H	40.43
kojic acid (**5**)								17.76

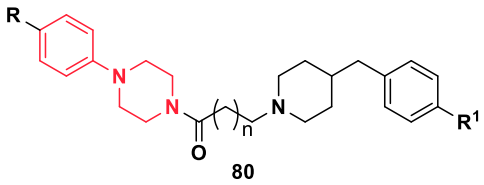
Table S45. Piperazines, see **Figure 51a** (Phenylpiperazine TYRIs (**79** - **81**) from various studies).



79

Compound	R	IC_{50} (µM)
79a	1-piperidinyl	0.06
79b	3,5-dimethyl-1-piperidinyl	0.07
79c	4-methyl-1-piperidinyl	0.14
79d	4-morpholinyl	0.41
kojic acid (**5**)		16.83

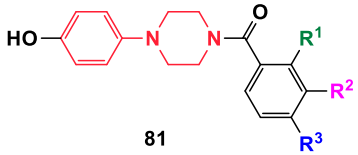
Table S46. Piperazines, see **Figure 51b** (Phenylpiperazine TYRIs (**79** - **81**) from various studies).



80

Compound	*n*	R	R^1	IC_{50} (µM)
80a	0	OH	H	3.80
80b	1	OH	H	4.03
80c	0	OH	F	4.49
80d	1	OH	F	6.06
80e	0	H	F	9.60
80f	1	F	F	23.36
80g	1	H	H	57.50
80h	0	H	H	80.86
kojic acid (**5**)				17.76

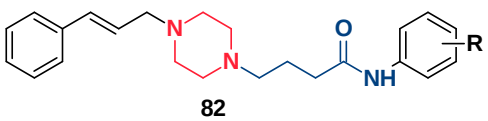
Table S47. Piperazines, see **Figure 51c** (Phenylpiperazine TYRIs (**79** - **81**) from various studies).



81

Compound	R^1	R^2	R^3	IC_{50} (μM)
81a	Cl	H	Cl	1.5
81b	Cl	H	H	2.6
81c	OMe	H	H	3.5
81d	Br	H	H	4.5
81e	CF_3	H	H	4.6
81f	H	CF_3	H	5.5
81g	NO_2	H	H	7.4
81h	NO_2	H	NO_2	7.6
81i	H	H	Cl	8.9
81l	H	Cl	H	9.0
81j	Br	H	Br	9.5
81m	H	OMe	H	9.8
81n	H	H	OMe	14.9
81o	F	H	H	15.2
81p	H	Br	H	16.4
81q	OMe	H	OMe	16.7
81r	F	H	F	17.5
81s	CF_3	H	CF_3	18.2
81t	H	H	F	21.7
81u	H	NO_2	H	21.8
81v	H	F	H	22.6
81w	H	H	NO_2	23.2
81x	Me	H	H	29.9
81y	H	Me	H	31.7
81z	Me	H	Me	33.7
81aa	H	H	Me	34.4
81bb	H	H	CF_3	35.1
81cc	H	NH_2	H	35.7
81dd	H	H	Br	39.6
81ee	H	H	NH_2	43.9
81ff	NH_2	H	H	66.4
81gg	H	H	H	73.2
81hh	NH_2	H	NH_2	82.4
81ii	H	H	Ph	128.3
kojic acid (**5**)				17.76

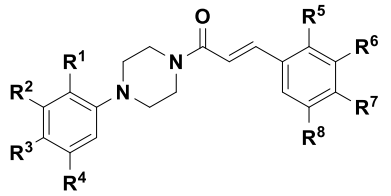
Table S48. Piperazines, see **Figure 52** (Piperazinyl butanamide-containing TYRIs).



82

Compound	R	IC_{50} (μM)
79a	2,4-diMe	0.01
79b	2,3-diMe	0.02
79c	3-Me	0.04
79d	4-Me	0.05
79e	4-Et	0.68
kojic acid (**5**)		16.84

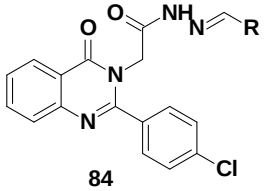
Table S49. Piperazines, see **Figure 53** (Cinnamic acid derivatives linked to aryl piperazines).



83

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	IC_{50} (μM)
83a	H	Cl	F	H	H	NO_2	H	H	0.16
83b	H	Cl	F	H	Cl	OMe	H	H	0.12
83c	H	Cl	F	H	NO_2	OMe	H	H	0.51
83d	H	Cl	F	H	H	OMe	H	H	0.25
83e	H	Cl	F	H	H	H	Cl	H	0.33
83f	H	Cl	F	H	H	H	NO_2	H	0.35
83g	H	Cl	F	H	OMe	H	H	Cl	0.46
83h	H	Cl	F	H	H	NH_2	OMe	H	0.53
83i	H	F	F	H	H	NH_2	OMe	H	6.84
83j	H	H	F	H	H	OMe	H	H	9.96
83k	H	H	F	H	H	H	Cl	H	14.09
83l	H	F	F	H	H	NH_2	OMe	H	15.47
83m	H	H	F	H	H	NH_2	OMe	H	17.85
83n	H	H	F	H	H	NO_2	H	H	23.32
83o	OMe	H	H	H	H	H	H	Cl	27.40
83p	H	Cl	H	H	H	OCH_2O	OCH_2O	H	34.25
83q	H	F	H	H	H	NH_2	OMe	H	>100
83r	H	H	F	H	H	H	NO_2	H	NI
83s	H	H	F	H	H	OCH_2O	OCH_2O	H	NI
83t	H	H	F	H	H	OBn	NO_2	H	NI
83u	H	H	F	H	H	NO_2	OMe	H	NI
83v	H	F	H	H	H	NO_2	OMe	H	NI
83w	H	F	H	F	H	NO_2	OMe	H	NI
83x	F	H	Cl	H	H	NH_2	OMe	H	NI
83y	H	OMe	H	H	H	OBn	H	H	NI
83z	Cl	H	H	H	OMe	H	H	Cl	NI
kojic acid (**5**)									17.76

Table S50. Quinazolines, see **Figure 54** (Chlorophenylquinazolin-4(3*H*)-one derivatives **84** with inhibitory potential of TYR).

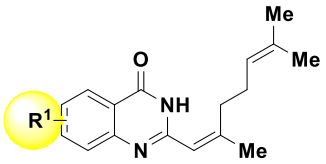


84

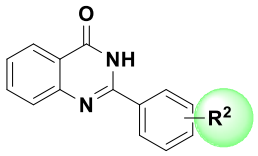
Compound	R	PI (%)	IC_{50} (μM)
84a	Ph-O-Ph	63.68	25.48
84b	4-Me-Ph	53.84	-
84c	2-NO_2,3-OMe-Ph	49.77	-

84d	3-OMe-Ph	41.78	-
84e	2-F-Ph	38.58	-
84f	3-NO_2-Ph	29.28	-
84g	4-OMe-Ph	29.22	-
84h	2-Me-Ph	25.64	-
84i	2-naphtyl	24.61	-
84j	4-NO_2-Ph	22.60	-
84k	2-Cl-Ph	22.37	-
84l	2-thienyl	17.17	-
84m	Ph	7.30	-
84n	2-Cl,5-NO_2	1.02	-
kojic acid (**5**)			9.30

Table S51. Quinazolines, see **Figure 55** (Quinazoline derivatives **85** and **86** in three-digit micromolar range of TYR inhibition).



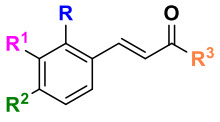
85



86

Compound	R^1	R^2	IC_{50} (μM)
85a	H	-	103
85b	5-F	-	105
85c	6-Cl	-	168
85d	7-Me	-	253
86a	-	H	-
86b	-	4-Me	-
86c	-	4-OMe	-
arbutin (**6**)			180

Table S52. Miscellaneous, see **Figure 56** (Cinnamide derivatives and their percentage of inhibition of monophenolase).

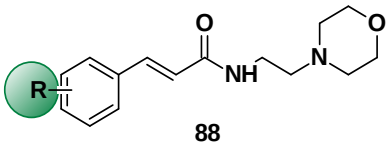


87

Compound	R	R^1	R^2	R^3	PI (%)
87a	OH	H	OH	pyrrolidine	93.72
87b	OH	H	OH	piperidine	78.97
87c	OH	H	OH	1-methyl-piperazine	94.39
87d	OH	H	OH	morpholine	95.74
87e	H	OMe	OH	piperidine	59.09
87f	H	OH	OMe	1-methyl-piperazine	40.22
87f	H	OH	OMe	piperidine	36.70
87g	H	OH	OMe	morpholine	31.12
87h	H	OH	OMe	pyrrolidine	26.42

87i	H	OMe	OH	pyrrolidine	24.00
87i	H	OMe	OH	morpholine	21.28
87j	H	OMe	OH	1-methyl-piperazine	19.33
87k	H	H	OH	piperidine	19.07
87l	H	H	OH	pyrrolidine	13.65
87m	H	OH	OH	piperidine	12.43
87n	H	OH	OH	pyrrolidine	3.41
87o	H	H	OH	1-methyl-piperazine	-
87p	H	OH	OH	1-methyl-piperazine	-
87q	H	H	OH	morpholine	-
87r	H	OH	OH	morpholine	-
kojic acid (**5**)					20.57

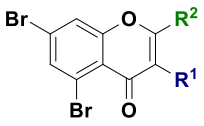
Table S53. Miscellaneous, see **Figure 57** (Morpholine containing cinnamides and inhibition of TYR thereof).



88

Compound	R	IC_{50} (μM)
88a	3-Cl	15.2
88b	3-Me	21.3
88c	4-NO_2	25.2
88d	4-Cl	28.6
88e	3-NO_2	35.5
88f	2-NO_2	36.0
88g	4-F	40.6
88h	3,4,5-OMe	50.0
88i	H	75.8
88j	2F	>100
88k	3-F	>100
88l	2-Cl	>100
88m	2-OMe	>100
88n	3-OMe	>100
88o	4-OMe	>100
88p	3,4-diOMe	>100
88q	2-Me	>100
88r	4-Me	>100
88s	4-OH,3-OMe	>100
kojic acid (**5**)		14.4

Table S54. Chromone derivatives, see **Figure 59** (Chromone derivatives and their inhibition of TYR).

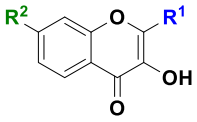


90

Compound	R^1	R^2	IC_{50} (μM)
90a	OH	3,4-diOMe-Ph	0.093

90b	OH	3-NO_2-Ph	0.15
90c	H	indole	0.22
90d	OH	4-Me-Ph	0.126
90e	OH	4-NO_2-Ph	0.27
90f	H	4-NO_2-Ph	0.27
90g	H	3,4-diOMe-Ph	0.49
90h	OH	4-$N(Me)_2$-Ph	0.50
90i	OH	1-naphtyl	0.564
90j	H	4-$N(Me)_2$-Ph	0.57
90k	H	2-thienyl	0.68
90l	OH	4-Cl-Ph	0.71
90m	H	2-furyl	2.07
90n	OH	4-F-Ph	2.36
90o	OH	2-furyl	2.5
90p	OH	2-thienyl	3.01
90q	H	3-NO_2-Ph	3.28
90r	H	1-naphtyl	3.41
90s	H	4-Cl-Ph	4.2
90t	OH	4-CO_2H-Ph	4.26
90u	H	4-Me-Ph	7.2
90v	7	2,4-diMe-Ph	7.57
90w	H	4-CO_2H-Ph	9.7
90x	H	2,4-diOMe-Ph	11.33
90y	H	4-F-Ph	20.5
90z	OH	indole	23.58
kojic acid (**5**)			1.79

Table S55. Chromone derivatives, see **Figure 60** (3-Hydroxyflavone derivatives **91** as TYRIs).

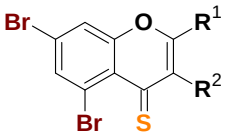


91

Compound	R^1	R^2	IC_{50} (μM)
91a	4-Cl-Ph	OH	0.23
91b	4-NO_2-Ph	OH	0.28
91c	2-thienyl	OH	0.35
91d	4-NO_2-Ph	H	0.284
91e	$N(Ph)_3$	H	0.327
91f	2-thienyl	H	0.347
91g	4-F-Ph	H	0.799
91h	4-OMe-Ph	H	1.787
91i	4-OMe-Ph	Br	2.236
91j	3-NO2-Ph	H	2.564
91k	1-naphtyl	H	2.90
91l	Ph	H	4.268
91m	4-Br-Ph	H	4.437
91n	4-*i*Bu-Ph	H	4.844
91o	3-Br-Ph	Cl	5.783
91p	4-Br-ph	Br	7.226

91q	4-Me	H	14.171
91r	4-*i*Bu-Ph	Br	19.595
91s	4-CO_2H-Ph	H	35.189
kojic acid (**5**)			1.79

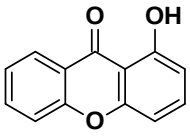
Table S56. Chromone derivatives, see **Figure 61** (Thioflavones and thioflavonols derivatives and their activities on TYR inhibition).



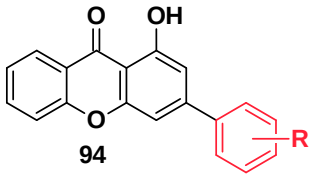
92

Compound	R^1	R^2	IC_{50} (µM)
92a	3-NO_2-Ph	OH	1.12
92b	4-Cl-Ph	OH	1.16
92c	4-$N(Me)_2$-Ph	OH	1.37
92d	4-NO_2-Ph	OH	1.45
92e	3,4-diOMe-Ph	OH	1.49
92f	2-naphtyl	OH	1.55
92g	2,4-diMe-Ph	OH	1.70
92h	4-Cl-Ph	H	3.46
92i	2-naphtyl	H	3.90
92j	2,4-diMe-Ph	H	3.96
92k	4-Me-Ph	OH	4.60
92l	3-NO_2-Ph	H	4.94
92m	2-thienyl	H	5.06
92n	3,4-diOMe-Ph	H	5.68
kojic acid (**5**)			12.6

Table S57. Xanthone derivatives, see **Figure 62** (1-hydroxyl xanthone (**93**), and derived 3-aryl substituted xanthone derivatives and their TYR inhibitory potencies).



93

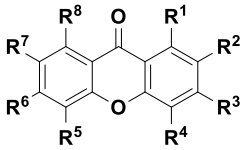


94

Compound	R	IC_{50} (µM)
93	-	>150
94a	4-OH	11.3
94b	2-OH	14.1
94c	3-OH	16.2
94d	3,4-diOMe	34.8
94e	3,4,5-*tri*OMe	35.2
94f	4-OMe	36.5
94g	2,4-diOMe	37.4
94h	3,5-diOMe	39.8
94i	4-CHO	42.1

94j	4-CO_2H	44.2
94k	4-COMe	45.1
94l	2-CHO	45.6
94m	3,4-diOH	50.7
94n	3,4,5-*tri*OH	52.6
94o	2,4-diOH	53.6
94p	3-CHO	54.1
94q	2-CO_2H	55.1
94r	4-COOMe	56.1
94s	2-CO_2H	73.9
94t	2-COOMe	78.1
94u	2-OMe	82.2
94v	3,5-diOH	92.6
94w	3-OMe	109.1
94x	3-COOMe	115.8
kojic acid (**5**)		17.3

Table S58. Xanthone derivatives, see **Figure 64** (Further xanthone derivatives with promising inhibitory activity of TYR).



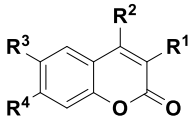
98

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	IC_{50} (µM)
98a	Me	Cl	OMe	OMe	H	OMe	H	H	1.9
98b	Me	H	OMe	OMe	H	H	H	H	2.0
98c	Me	H	OMe	OMe	H	OMe	H	H	2.24
98d	OH	OMe	OH	H	H	H	H	H	3.01
98e	CHO	H	OMe	OMe	H	OMe	H	H	3.16
98f	Me	H	OH	OH	H	OH	H	H	3.28
98g	CH_2Br	H	OMe	OMe	H	H	H	H	3.37
98h	H	H	OH	OMe	H	H	H	H	3.81
98i	OMe	OMe	H	H	H	H	H	H	4.02
98j	H	H	OH	H	H	OH	H	H	4.42
98k	OH	H	H	H	H	H	OH	H	4.52
98l	H	H	OMe	OMe	H	H	H	H	5.12
98m	H	H	OH	OH	H	H	H	H	5.12
98n	H	H	OMe	H	H	H	H	H	5.14
98o	OMe	H	H	H	H	H	H	H	5.14
98p	H	H	OMe	OH	H	H	H	H	5.2
98q	H	H	H	OMe	H	H	H	H	5.33
98r	Me	Br	OMe	OMe	H	H	H	H	5.57
98s	H	OH	H	H	H	H	H	H	5.60
98t	H	OH	OH	H	H	H	H	H	5.70
98u	OH	OH	H	H	H	H	H	H	7.8
98v	H	OMe	OMe	H	H	H	H	H	8.29
98w	H	H	H	OH	H	H	H	H	8.46

98x	H	OMe	H	H	H	H	H	H	8.47
98y	OH	H	H	H	H	H	H	H	8.83
98z	H	H	H	H	H	H	H	H	8.84
98aa	Me	H	OH	OH	H	H	H	H	8.93
98bb	H	H	OH	H	H	H	H	H	9.26
98cc	CHO	H	OMe	OMe	H	H	H	H	29.13
98dd	CHO	H	OH	OH	H	H	H	H	89.37
kojic acid (**5**)									12.81

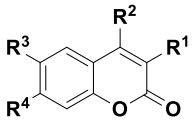
Table S59. Coumarin derivatives, see **Figure 65** (Coumarin derivatives **99** and **100** as TYRIs).

Hydroxycoumarin derivatives



99

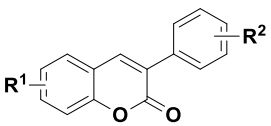
Geranyloxycoumarin derivatives



100

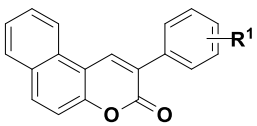
Compound	R^1	R^2	R^3	R^4	PI (%)	IC_{50} (μM)
99a	H	H	OH	H	191	-
99b	CN	H	H	OH	158	-
99c	H	Me	OH	H	102	-
99d	H	Me	Cl	OH	101	-
99e	OH	H	H	H	81	-
99f	Cl	Me	H	OH	79	-
99g	NO_2	OH	H	H	68	-
99h	H	Me	OH	OH	35	-
99i	H	H	H	OH	15	-
99j	H	CH_2CO_2H	H	OH	14	-
100a	H	Me	geranyloxy	geranyloxy	200	0.67
100b	H	Me	Cl	geranyloxy	137	-
100c	H	H	H	geranyloxy	132	-
100d	H	CF_3	H	geranyloxy	127	-
100e	H	Me	H	geranyloxy	121	-
100f	geranyloxy	H	H	H	107	-
100g	H	Me	H	geranyloxy	97	-
100h	Ph	H	H	geranyloxy	79	-
arbutin (**6**)					100	-

Table S60. Coumarin derivatives, see **Figure 66a** (Coumarin derivatives with either aryl groups, **101** and **102**).



101

or

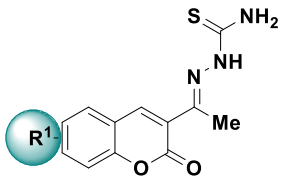


102

Compound	R_1	R_2	IC_{50} (μM)
101a	2,4-diOH	4-Br	1.05
101b	5,7-diOH	3-Br	7.0
101c	6,7-diOH	3-Br	8.3

101d	6,7-diOH	4-Br	39.9
101e	7-OH	3-Br	42.0
101f	5,7-diOH	2-Br	>50
101g	6,7-diOH	2-Br	>50
101h	7,8-diOH	4-Br	>50
101i	7,8-diOH	3-Br	>50
101j	7,8-diOH	2-Br	>50
101k	6,7-diOH	3-OH	>50
101l	6,7-diOH	2-OH	>50
102a	4-OH	-	>50
102b	3-OH	-	>50
102c	2-OH	-	>50
102d	3,4-diOH	-	>50
102e	3,5-diOH	-	>50
kojic acid (**5**)			17.9

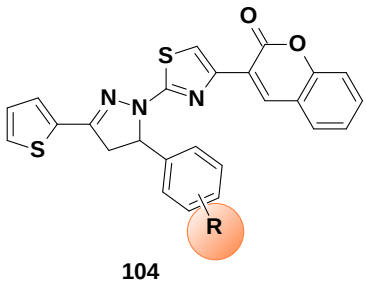
Table S61. Coumarin derivatives, see **Figure 66b** (Coumarin derivatives with thiosemicarbazone (**103**, b) group in the 3-position).



103

Compound	R^1	IC_{50} (μM)
103a	H	4.0
103b	7,8-diOH	4.1
103c	7-OH	5.0
103d	8-OH	5.7
103e	6,7-diOH	6
103f	6-OH	14
kojic acid (**5**)		18.1

Table S62. Coumarin derivatives, see **Figure 67** (Coumarin-based thiophenyl-pyrazolylthiazole hybrids which show good activity in TYR inhibition.).

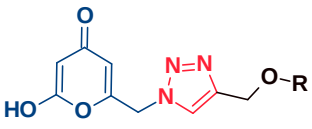


104

Compound	R	IC_{50} (μM)
104a	3-OMe,4-OBn	0.043
104b	4-OMe	0.278
104c	4-Br	0.809

104d	H	1.206
104e	4-F	1.946
104f	4-Cl	2.028
104g	4-Me	4.071
104h	4-OPh	4.508
kojic acid (**5**)		18.521

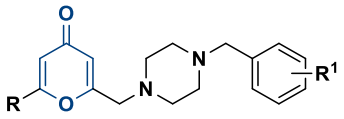
Table S63. Kojic acid derivatives, see **Figure 68** (Triazole-based kojic acid derivatives **107** and their inhibitory profile on TYR.).



107

Compound	R	IC_{50} (µM)
107a	1-naphtyl	0.06
107b	4-hydroxycoumarin	0.02
107c	2-naphtyl	0.30
107d	4-NO_2-Ph	0.52
107e	4-Cl-Ph	0.69
107f	3,5-diMe-Ph	0.74
107g	3,4,5-*tri*OMe-Ph	0.87
107h	4-F-Ph	0.88
107i	3-Cl-Ph	0.99
107j	3-F-Ph	1.07
107k	2,4-diCl	1.12
107l	4-OMe-Ph	1.24
107m	4-CH_2OH-Ph	1.32
107n	Ph	1.33
107o	4-CH_3CONHPh	2.64
107p	4-CN-Ph	6.29
kojic acid (**5**)		9.28

Table S64. Kojic acid derivatives, see **Figure 69** (Kojic acid derivatives containing a benzylpiperazine portion (**108**) and their TYR inhibition).

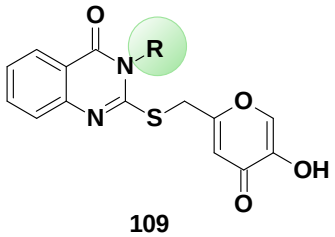


108

Compound	R	R^1	IC_{50} (µM)
108a	hydroxymethyl	3,4-diCl	86.2
108b	pirrolidinylmethyl	3,4-diCl	94.1
108c	methyl	3,4-diCl	123.7
108d	methyl	3-Cl	198.7
108e	piperidinylmethyl	3,4-diCl	204.1
108f	hydroxymethyl	3-Cl	223.2
108g	pirrolidinylmethyl	4-F	225.5

108h	piperidinylmethyl	4-F	232.3
108i	hydroxymethyl	4-F	264.2
108j	methyl	4-F	362.1
108k	methyl	4-Cl	438.8
108l	piperidinylmethyl	3-Cl	493.8
108m	pirrolidinylmethyl	3-Cl	588.2
108n	chloromethyl	4-F	618.6
108o	hydroxymethyl	4-Cl	710.0
108p	piperidinylmethyl	4-Cl	746.0
108q	chloromethyl	3-Cl	990.7
108r	morpholinylmethyl	3-Cl	1105
108s	hydroxymethyl	2,5-diF	1564
108t	pirrolidinylmethyl	2,5-diF	1616
108u	morpholinylmethyl	4-Cl	1759
108v	morpholinylmethyl	4-F	1847
108w	morpholinylmethyl	2,5-diF	1900
108x	chloromethyl	4-Cl	1900
108y	chloromethyl	2,5-dF	>2000
108z	morpholinylmethyl	3,4-diCl	>2000
108aa	piperidinylmethyl	2,5-dF	>2000
kojic acid (**5**)			418.2

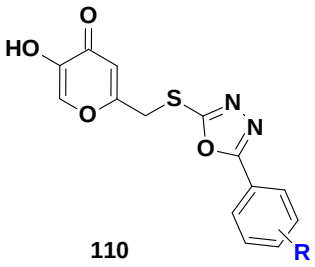
Table S65. Kojic acid derivatives, see **Figure 70** (Thioquinazolinones conjugated to kojic acid derivatives (**109**) showing medium 3-digit nanomolar activity as TYRIs).



109

Compound	R	IC_{50} (μM)
109a	pyridin-2-ylmethyl	0.46
109b	pyridin-2-yl	0.50
109c	4-Cl-Ph	0.50
109d	Bn	1.42
109e	*i*-Pr	1.44
109f	4-Br-Ph	1.48
109g	4-F-Bn	1.56
109h	allyl	1.56
109i	Ph	1.88
109j	cyclopropyl	2.10
109k	3,4-diOMe-Ph	2.12
109l	pyridin-4-ylmethyl	2.20
109m	*n*-butyl	2.31
109n	4-OMe-Ph	2.40
109o	4-Me-Ph	5.32
kojic acid (**5**)		9.30

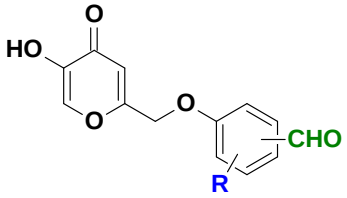
Table S66. Kojic acid derivatives, see **Figure 71a** (Kojic acid derivatives).



110

Compound	R	IC_{50} (μM)
110a	4-F	5.32
110b	4-Me	6.17
110c	4-OMe	9.57
110d	Ph	10.24
110e	3-Cl	10.24
110f	3,4-diOH	10.67
110g	4-*t*Bu	11.34
110h	4-Br	11.47
110i	4-Cl	11.88
110j	4-OH	14.43
110k	2-OH	14.79
110l	3-Me	17.36
110m	3-OH	19.30
110n	2-NO_2	19.45
kojic acid (**5**)		49.77

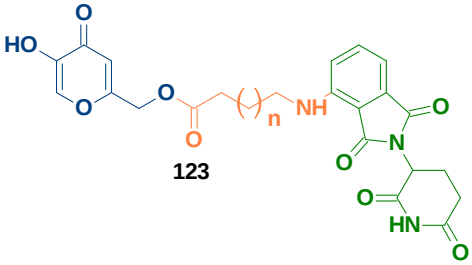
Table S67. Kojic acid derivatives, see **Figure 71b** (Kojic acid derivatives).



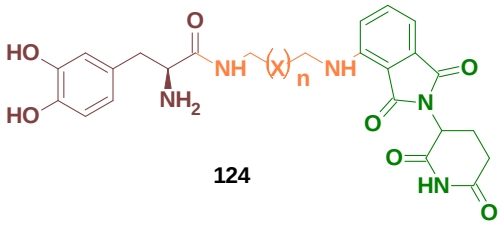
111

Compound	R	CHO	IC_{50} (μM)
111a	3-F	*para*	5.32
111b	H	*para*	5.98
111c	2-F	*para*	9.78
111d	3,5-diMe	*para*	12.39
111e	2-Cl	*para*	12.75
111f	5-OMe	*meta*	25.31
111g	2-OMe	*para*	26.44
111h	2-C_2H_5O	*para*	37.34
111i	2,6-diMe	*para*	77.18
111j	2-OMe,6-Br	*para*	77.89
111k	2,6-diOMe	*para*	>100
111l	6-OMe	*ortho*	>100
111m	6-C_2H_5O	*ortho*	>100
kojic acid (**5**)			48.05

Table S68. Human tyrosinase inhibitors, see **Figure 73** (PROTACs as human tyrosinase degraders).



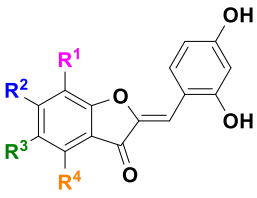
123



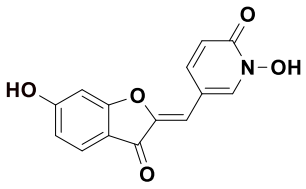
124

Compound	*n*	X	Reduction (%)	IC_{50} (μM)
123a	3	-	-	-
123b	5	-	-	-
123c	6	-	-	-
123d	8	-	-	-
124a	3	CH_2	46	112.7
124b	6	CH_2	38	-
124c	5	CH_2	37	-
124d	8	CH_2	37	-
124e	4	CH_2	33	-
124f	1	CH_2	25	-
124g	2	CH_2	19	-
124h	0	CH_2	14	-
124i	1	CH_2-O-CH_2	7	-
124j	2	CH_2-O-CH_2	7	-

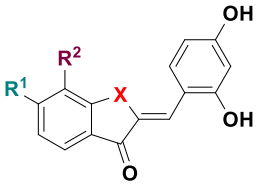
Table S69. Human tyrosinase inhibitors, see **Figure 75** (Resorcinol-based hemiindigoid derivatives).



125



125f



126

Compound	R^1	R^2	R^3	R^4	X	MNT-1 lysate IC_{50} (μM)	MNT-1 whole cells IC_{50} (μM)	MNT-1 whole cells CC_{50} (μM)
125a	H	H	H	OH	-	1.57	32	108
125b	H	OH	H	H	-	6.4	-	-
125c	H	OMe	H	H	-	6.9	-	-
125d	H	OH	H	OH	-	7.7	-	-
125e	OH	OH	H	H	-	11.8	-	-
125f	-	-	-	-	-	15.0	-	-
125g	H	H	H	H	-	18.0	-	-
125h	H	$N(Me)_2$	H	OH	-	18.4	-	-
125i	H	H	OH	H	-	19.0	-	-
125j	H	H	H	OH	-	25.0	-	-
125k	I	OH	H	H	-	32.0	-	-
125l	Me	OH	H	H	-	80.0	-	-

125m	OMe	H	H	H	-	80.0	-	-
125n	H	F	H	F	-	88.0	-	-
125o	H	OBu	H	H	-	>100	-	-
125p	H	Cl	H	H	-	>100	-	-
125q	H	$N(Me)_2$	H	H	-	>100	-	-
125r	H	OMe	H	OMe	-	>100	-	-
125s	Me	OMe	-	-	-	>100	-	-
125t	OMe	OMe	-	-	-	>100	-	-
126a	H	OH	-	-	CH_2	1.6	29	91
126b	OH	H	-	-	NH	2.3	-	-
126c	OH	H	-	-	CH_2	3.4	-	-
126d	H	H	-	-	CH_2	5.8	-	-
126e	OH	H	-	-	S	5.8	-	-
126f	H	H	-	-	S	5.9	-	-
126g	H	H	-	-	CHMe	8.2	-	-
126h	H	H	-	-	NH	12.7	-	-
126i	H	OH	-	-	S	48.0	-	-
126j	H	H	-	-	C=O	>100	-	-
rucinol **(9)**						8.3	-	-