Supplementary Information (SI) for RSC Advances. This journal is © The Royal Society of Chemistry 2024

Design, synthesis, *in vitro*, and *in silico* study of 1-benzyl-indole hybrid thiosemicarbazones as competitive tyrosinase inhibitors

Dose Curve response for compounds 5a-5r4
Figure S1. Dose curve response for compounds 5a- 5r against tyrosinase
Glide molecular docking studies
Table S1. Glide Score, H-Bonding Interactions with Distances in Å, Polar, and Hydrophobic Interacting Residues for Investigated Ligands with target protein possessing tyrosinase activity (PDB ID: 2Y9W)
Figure S2. 3D and 2D representation of interaction with tyrosinase target protein (PDB ID: 2Y9W)
Table S2. Docking Score, glide Score, and glide emodel values of all investigated ligands withtarget protein possessing tyrosinase activity (PDB ID: 2Y9W)
Figure S3. The boiled-egg plot (plot of WLOGP against TPSA) of all investigated compounds from SwissADME web tool
1H NMR and 13C NMR Spectra of 5a20
1H NMR and 13C NMR Spectra of 5b
1H NMR and 13C NMR Spectra of 5c23
1H NMR and 13C NMR Spectra of 5d24
1H NMR and 13C NMR Spectra of 5e25
1H NMR and 13C NMR Spectra of 5f26
H NMR and 13C NMR Spectra of 5g27
H NMR and 13C NMR Spectra of 5h
1H NMR and 13C NMR Spectra of 5i
1H NMR and 13C NMR Spectra of 5j
¹ H NMR and ¹³ C NMR Spectra of 5k
1H NMR and 13C NMR Spectra of 51
1H NMR and 13C NMR Spectra of 5m
1H NMR and 13C NMR Spectra of 5n
¹ H NMR and ¹³ C NMR Spectra of 50
1H NMR and 13C NMR Spectra of 5p
1H NMR and 13C NMR Spectra of 5q

1H NMR and 13C NMR Spectra of 5r	
HPLC chromatogram of 5a	
HPLC chromatogram of 5b	
HPLC chromatogram of 5c	40
HPLC chromatogram of 5d	40
HPLC chromatogram of 5e	40
HPLC chromatogram of 5f	41
HPLC chromatogram of 5g	41
HPLC chromatogram of 5h	42
HPLC chromatogram of 5i	42
HPLC chromatogram of 5j	43
HPLC chromatogram of 5k	44
HPLC chromatogram of 51	44
HPLC chromatogram of 5m	44
HPLC chromatogram of 5n	45
HPLC chromatogram of 50	45
HPLC chromatogram of 5p	46
HPLC chromatogram of 5q	46
HPLC chromatogram of 5r	47
Mass spectrum of 5a	48
Mass spectrum of 5b	48
Mass spectrum of 5c	49
Mass spectrum of 5d	49
Mass spectrum of 5e	50
Mass spectrum of 5f	50
Mass spectrum of 5g	51
Mass spectrum of 5h	51
Mass spectrum of 5i	52
Mass spectrum of 5j	52
Mass spectrum of 5k	53
Mass spectrum of 51	53
Mass spectrum of 5m	54

Mass spectrum of 5n	54
Mass spectrum of 50	55
Mass spectrum of 5p	55
Mass spectrum of 5q	56
Mass spectrum of 5r	56

Dose Curve response for compounds 5a-5r



















Figure S1. Dose curve response for compounds 5a- 5r against tyrosinase.

Glide molecular docking studies

The compounds 5c and 5b demonstrated strong binding interactions with tyrosinase target protein with gScores values even much better than the co-crystallized ligand and the kojic acid. Table S1 details the gScore, emodel, H-bonding, and hydrophobic interacting residues for the ligands 5c and 5b. Gln307, Thr308, and Thr360 are the common amino acid residue involved in polar contacts. Ile17, Tyr311, and Trp358 are showing common hydrophobic interacting residues as shown in **Figure S2**.

Table S1. Glide Score, H-Bonding Interactions with Distances in Å, Polar, and Hydrophobic Interacting Residues for Investigated Ligands with target protein possessing tyrosinase activity (PDB ID: 2Y9W).

Lignd	gScore (kcal/mol)	Emodel (kcal/mol)	HBI residue (distance Å)	Polar interacting amino acid residues	Hydrophobic interacting residues				
5c	-5.033	-60.546	Asp357 (1.97)	Gln307, Thr308, Thr360, Ser364	Ile17, Tyr311, Trp358, Phe368, Val371				
5b	-5.005	-54.341	Glu359 (1.72, 2.02)	Gln307, Thr308, Thr360, Ser380	Ile17, Tyr311, Trp358				

Abbreviation: HBI, hydrogen bonding interactions.



Figure S2. 3D and 2D representation of interaction with tyrosinase target protein (PDB ID: 2Y9W).

Table S2. Docking Score, glide Score, and glide emodel values of all investigated ligands with target protein possessing tyrosinase activity (PDB ID: 2Y9W).

Ligand	docking score (kcal/mol)	glide gscore (kcal/mol)	glide emodel (kcal/mol)
5k	-5.157	-5.157	-63.013
5c	-5.033	-5.033	-60.546
5b	-5.005	-5.005	-54.341
5a	-4.666	-4.666	-55.237
kojic acid	-4.416	-4.549	-34.051
5p	-4.313	-4.313	-45.738
5m	-4.236	-4.236	-47.798
5f	-4.129	-4.129	-54.012
5q	-4.033	-4.033	-55.055
5d	-3.876	-3.876	-42.321
5e	-3.815	-3.815	-46.426
5i	-3.778	-3.778	-49.164

5h	-3.554	-3.554	-49.496
50	-3.454	-3.454	-48.434
51	-3.311	-3.311	-48.872
5n	-3.183	-3.183	-46.608
5g	-3.085	-3.085	-42.012
5r	-2.983	-2.983	-42.112
5j	-2.185	-2.185	-34.915
co-crystallized- ligand-2Y9W	-0.129	-0.129	-19.187

Table S3. The ADMET Properties of all investigated ligands.

Ligand	Canonical SMILES	Formula	ŇW	#Heavy atoms	#Aromatic heavy atoms	Fraction Csp3	#Rotatabl e bonds	#H-bond acceptors	#H-bond donors	MR	TPSA	ilogp	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P
5a	COc1ccc(cc1)NC(= S)N/N=C /c1cn(c2 c1cccc2) Cc1ccccc 1	C24 H22 N4O S	414.52	30	21	0.08	8	2	2	127.06	82.67	3.9	4.8	4.83	3.28	5.19
5b	S=C(Nc1 cccc1) N/N=C/ c1cn(c2 c1cccc2) Cc1cccc c1	C23 H20 N4S	384.5	28	21	0.04	7	1	2	120.5 6	73.44	3.59	4.83	4.82	3.63	5.12
5c	S=C(Nc1c (C)cccc1 C)N/N=C /c1cn(c2 c1cccc2) Cc1ccccc 1	C25 H24 N4S	412.55	30	21	0.12	7	1	2	130.5	73.44	3.95	5.56	5.44	4.04	6.18
5d	S=C(Nc1c cc(cc1)F) N/N=C/c 1cn(c2c1 cccc2)Cc 1ccccc1	C23 H19 FN4 S	402.49	29	21	0.04	7	2	2	120.52	73.44	3.73	4.93	5.38	4	5.54
5e	S=C(NCc 1ccc(cc1)	C24 H21	432.97	30	21	0.08	8	1	2	128.84	73.44	4.2	5.4	5.19	4.04	6.16

	CI)N/N=C /c1cn(c2 c1cccc2) Cc1ccccc	CIN4 S														
5f	S=C(Nc1c ccc(c1Cl) Cl)N/N=C /c1cn(c2 c1cccc2) Cc1ccccc 1	C23 H18 Cl2N 45	453.39	30	21	0.04	7	1	2	130.58	73.44	4.05	6.09	6.13	4.58	6.4
5g	S=C(Nc1c cccc1)N/ N=C/c1c n(c2c1cc cc2)Cc1c cccc1	C23 H20 N45	384.5	28	21	0.04	7	1	2	120.56	73.44	3.59	4.83	4.82	3.63	5.12
55	S=C(Nc1c cc(cc1C) C)N/N=C /c1cn(c2 c1cccc2) Cc1ccccc	C25 H24	412 55	20	24	0.04				120.50	73.44	3.00	T.05	F. 44	4.04	5.12
5n 5i	1 S=C(NCc 1ccccc1) N/N=C/c 1cn(c2c1 cccc2)Cc 1ccccc1	N45 C24 H22 N45	398.52	30	21	0.12	8	1	2	130.5	73.44	3.82	4.77	4.54	3.57	5.52
5i	S=C(Nc1c cc(cc1)Br)N/N=C/c 1cn(c2c1 cccc2)Cc 1ccccc1	C23 H19 BrN4 S	463.39	29	21	0.04	7	1	2	128.26	73.44	4.09	5.52	5.58	4.21	5.8
5k	S=C(NCc 1ccc(cc1) C)N/N=C /c1cn(c2 c1cccc2) Cc1ccccc 1	C25 H24 N4S	412.55	30	21	0.12	8	1	2	128.8	73.44	4.12	5.13	4.84	3.78	6.05
	COc1cccc (c1)NC(= S)N/N=C /c1cn(c2 c1cccc2) Cc1ccccc	C24 H22 N40				0.00				127.05	00.57			4.00	2.22	- 10
51 5	1 COc1cccc	S C25	414.52 444.55	30 32	21 21	0.08	8	2	2	127.06 133.55	82.67 91.9	3.94 4.02	4.8 4.78	4.83 4.84	3.28 2.94	5.19 5.26
-							-	-						·		

m	(c1NC(=)N/N=C/ 1cn(c2c: cccc2)Cc 1ccccc1) OC	S F /c N 1 2 c	124 140 25															
5n	S=C(Nc1 cc(cc1)C N/N=C/c 1cn(c2c2 cccc2)Cc 1ccccc1	.c ;) c 1 C c F	24 122 145	398.52		29	21	0.08	7	1	2	125.53	73.44	3.94	5.2	5.13	3.84	5.65
	S=C(Nc1 ccc(c1)[I +](=O)[C])N/N=C c1cn(c2c 1cccc2)C	.c N D- C/ C F C N	223 119 150										119.2					
50 5n	c1ccccc CNC(=S) N/N=C/c 1cn(c2c2 cccc2)Cc	1 2 c 1 C c F	2S C18 H18	429.49		23	21	0.04	8	3	2	99 35	73 44	2.91	4.66	4.73	2.67	2.96
50	S=C(Nc1 cc(cc1)[i +](=O)[C])N/N=C c1cn(c2) c1cccc2)(.c N D- C/ C C H C N	223 119 150	429.49		31	21	0.04	8		2	129 39	119.2	3 27	4.66	4.73	2.40	2.96
5r	S=C(Nc1 cc2c(c1) ccc2)N/I =C/c1cn c2c1cccc 2)Cc1ccc	.c c N (c C c H	227 122	434 56		32	25	0.04	7	1	2	138.07	73 44	4.08	6.08	5.97	4.28	6.15
Kojic acid	OCc1occ c(=O)c1) O	c() C	C6H 504	142.11		10	6	0.17	1	4	2	33.13	70.67	1.12	-0.64	-0.31	- 1.69	0.74
Ligand	Consensus Log P	ESOL Log S	ESOL	solubility ESOL Solubility	(I/Iom)	ESOL Class	Ali Log S	Ali Solubility (mg/ml)	Ali	solubility Ali Clace	Silicos-IT	Silicos-IT Solubility	(mg/ml) Silicos-IT	Solubility (mol/l)	Silicos-IT class GI	absorptio n	BBB permeant	Pgp substrate
5a	4.4	- 5. 42	1.50 E-03	5 3 3.77E	-06	Mode rately solubl e	- 6. 27	2.24E-04	5.39 E-0	Poo ly 9 solu 7 ble	r -8.2	8 2.17E	-06	5.22E- 09	Poor ly solu ble	High	No	No

					Mod											
					erate				Роо				Роо			
		-			ly	-			rly				rly			
		5.	1.68	4.37E-	solub	6.	3.02E-	7.84	solu	-	2.54E-	6.61E-	solu			
	4.4	36	E-03	06	le	11	04	E-07	ble	8.18	06	09	ble	High	No	No
5b					Mada				Deer				Deer			
		_			rately	_			Poor				Poor			
		5.	4.56		solubl	6.		1.37	solu			1.17F-	solu			
5c	5.03	96	E-04	1.11E-06	e	86	5.65E-05	E-07	ble	-8.93	4.84E-07	09	ble	High	No	Yes
					Mode				Poor				Poor			
		-			rately	-			ly				ly			
		5.	1.23		solubl	6.		6.18	solu			3.60E-	solu			
5d	4.72	52	E-03	3.05E-06	e	21	2.49E-04	E-07	ble	-8.44	1.45E-06	09	ble	High	No	No
		_			rately	_			Poor				Poor			
		5.	5.25		solubl	6.		2.01	solu			6.95E-	solu			
5e	5	92	E-04	1.21E-06	e	7	8.70E-05	E-07	ble	-9.16	3.01E-07	10	ble	High	No	Yes
					Poorl				Poor				Poor			
		-			У	-			ly				ly			
		6.	1.30		solubl	7.		3.86	solu			4.48E-	solu			
5t	5.45	54	E-04	2.86E-07	e Mada	41	1.75E-05	E-08	ble	-9.35	2.03E-07	10	ble	High	No	No
					rately				POOr				POOr			
		5.	1.68		solubl	6.		7.84	solu			6.61F-	solu			
5g	4.4	36	E-03	4.37E-06	e	11	3.02E-04	E-07	ble	-8.18	2.54E-06	09	ble	High	No	No
					Mode				Poor				Poor			
		-			rately	-			ly				ly			
-1	5.04	5.	4.56	4.445.00	solubl	6.		1.37	solu	0.00	4 9 4 5 9 7	1.17E-	solu			
5n	5.01	96	E-04	1.11E-06	e Modo	86	5.65E-05	E-07	Die	-8.93	4.84E-07	09	Die	High	INO	res
		_			rately	_			lv				lv			
		5.	1.89		solubl	6.		9.05	solu			2.67E-	solu			
5i	4.47	32	E-03	4.74E-06	е	04	3.61E-04	E-07	ble	-8.57	1.07E-06	09	ble	High	No	Yes
					Poorl				Poor				Poor			
		-			У	-			ly .				ly .			
c :	E 04	6. 26	2.52		solubi	6. 02		1.51	solu	8 OC		1.10E-	solu	High	No	No
ЭJ	5.04	20	E-04	5.44E-07	e Mode	02	0.992-05	E-07	Poor	-0.90	5.09E-07	09	Poor	півіі	NO	NO
		_			rately	_			ly				ly			
		5.	9.90		, solubl	6.		3.83	solu			1.13E-	solu			
5k	4.78	62	E-04	2.40E-06	е	42	1.58E-04	E-07	ble	-8.95	4.65E-07	09	ble	High	No	Yes
					Mode				Poor				Poor			
			1 5 6		rately	-		F 20	ly solu			ГЭЭГ	ly colu			
51	<u>д</u> л1	5. 42	1.50 F-U3	3 775-06	SOIUDI	0. 27	2 24F-01	5.39 F_07	solu hle	-8.28	2 17F-06	5.22E- NQ	solu hle	High	No	No
	7.41	72	L-03	5.772-00	Mode	21	2.27L-04	L-07	Poor	-0.20	2.17 L-00	09	Poor	111611		
		-			rately	-			ly				ly			
		5.	1.41		solubl	6.		3.62	solu			4.16E-	solu			
5m	4.37	5	E-03	3.17E-06	е	44	1.61E-04	E-07	ble	-8.38	1.85E-06	09	ble	High	No	No
5n	4.75	-	8.70	2.18E-06	Mode	-	1.29E-04	3.24	Poor	-8.56	1.11E-06	2.78E-	Poor	High	No	No

			5. 66	E-04	4		rately solubl	6. 49			E-07	ly solu			09	ly solu			
							e de la					ble				ble			
			-				rately	-				Poor ly				ly			
			5.	1.6	6		solubl	6.			1.28	solu			3.02E-	solu			
50	3	.66	41	E-03	3 3.8	7E-06	e	89	5.52	E-05	E-07	ble	-7.52	1.30E-05	08	ble	Low	No	No
												erat				Poor			
			-					-				ely				ly			
			3.	3.33	3		Solubl	4.			3.26	solu			8.07E-	solu			
5p	3	.16	99	E-02	2 1.0	3E-04	e Modo	49	1.05	E-02	E-05	ble	-6.09	2.60E-04	07	ble	High	Yes	No
			_				rately	-				lv				lv			
			5.	1.6	6		solubl	6.			1.28	solu			3.02E-	solu			
5q	3	.66	41	E-03	3 3.8	7E-06	e	89	5.52	E-05	E-07	ble	-7.52	1.30E-05	08	ble	Low	No	No
							Poorl	_				Poor				Poor			
			6.	1.44	4		y solubl	7.			3.96	solu			1.55E-	solu			
5r	5	.31	48	E-04	4 3.3	1E-07	e	4	1.72	E-05	E-08	ble	-9.81	6.71E-08	10	ble	High	No	No
σ																			
c aci			-				Very	-				Very							
(ojic			0.	2.80	6		solubl	0.			4.25	solu			6.84E-	Solu			
-	0-	.16		E+01	1 2.0	1E-01	e	37	6.05	E+01	E-01	ble	-1.17	9.72E+00	02	ble	High	No	No
										s	5	S	0	2				ess S	<u>₹</u>
		. 5	6	2	- 5		- 5			u	l	u no		a 5	e lat			u u	bili
	-igand	CYP1A2 nhibitor	CYP2C19	nhibitor	CYP2C9 nhibitor	CYP2D6 nhibitor	CYP3A4 nhibitor	og Kp	cm/s)	.ipinski ‡violation	Shose tviolation	/eber #violation	Egan #violation	Muegge #violation	3ioavailak Y Score	AINS #alerts	3renk ¢alerts	eadliken. tviolation	synthetic Accessibili
50	Ligand	CYP1A2 inhibitor	< CYP2C19	inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	n log Kp	cm/s)	Lipinski #violation	Ghose #violation	Veber #violation	Egan #violation	Muegge #violation	Bioavailat ty Score	PAINS #alerts	Brenk #alerts	Leadliken , #violation	Synthetic Accessibili
5a	Ligand	CVP1A2 Aes Aes	CVP2C19	es es	CVP2C9 Acvection CVP2C9 Acvection Ac	CVP2D6 Acvector Acvec	Yes Yes	dy 80 -5	(cm/s) .42	0 C Huriolation	Ghose (hose) (Veber #violation	C C Egan	Muegge	Bioavailat th Score	BAINS #alerts	Brenk #alerts	Leadliken 8 #violation	Synthetic 3.7 3.14
5a 5b	Ligand	Yes Yes	A CYP2C19	es es	Yes Yes	CXP2D6 Anibitor Acvector	Yes Yes Yes	dy 80 -5 -5.	(s/w) .42 22	0 0 H H Violation	Ghose () () () () () () () () () () () () ()	Contraction Contraction Contraction	Egan	Muegge	Bioavailat ty Score	PAINS 1 1	Brenk #alerts	Leadliken 3 5	Synthetic 3.5 3.14
5a 5b 5c	Ligand	Yes Yes Yes	0Y 0Y 0Y 0Y 0Y	es es es	Yes Yes Yes	Yes Yes Yes	Acceleration of the second sec	dy 80 -5 -5. -4.	(s/uc) .42 22 .87	0 0 C #violation	Ghose Chose))) ())) ())	Egan	Muegge #violation	Bioavailat 1 X Score	1 1 1 1	Brenk alerts 2 2 2	Leadliken 3 5 2 2	3.14 3.38 3.12
5a 5b 5c 5d 5e	Ligand	Yes Yes Yes Yes	0Y 0Y 0Y 0Y 0Y 0Y	es es es es	Yes Yes Yes Yes Yes	Yes Yes Yes Yes	Yes Yes Yes Yes Yes	dy 80 -5 -5. -4 -5	(s/w) .42 22 .87 .25 .11	0 0 0 0 0 0 0 0 0 0 0 0 0	Ghose	0 0 0 0 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 1 0 0 0 0 1 0 0 0 0 1 0 0 0 0 1 0 0 0 0 1 0 0 0 0 0 1 0 0 0 0 0 1 0 0 0 0 0	(((((((((((((((((((massing	Bioavailat 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	BAINS 1 1 1 1 0	Halerts 2 2 2 2 2 2 2 2 2	Leadliken 3 2 2 3	3.2 3.14 3.38 3.12 3.2
5a 5b 5c 5d 5e 5f	Ligand	Yes Yes Yes Yes Yes No	97 97 97 97 97 97 97	es es es es es es es es	Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes No	Yes Yes Yes Yes Yes Yes	dy sol -5 -5. -5. -5 -5 -5	(%) (42) (42) (22) (87) (25) (11) (74)	Lipinski 0 0 0 0 0 0 0 0	() () () () () () () () () () () () () (0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 Neber 0 0	() () () () () () () () () () () () () (main main <td< th=""><th>Bioavailat 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55</th><th>BAINS 1 1 1 1 1 1 1 1 1 1</th><th>Brenk kare kare kare kare kare kare kare kar</th><th>readliken 3 2 2 2 3 3 2 2 2 2 3 3</th><th>3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2</th></td<>	Bioavailat 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55	BAINS 1 1 1 1 1 1 1 1 1 1	Brenk kare kare kare kare kare kare kare kar	readliken 3 2 2 2 3 3 2 2 2 2 3 3	3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2
5a 5b 5c 5d 5e 5f 5g	Ligand	Yes Yes Yes Yes No Yes	97 97 97 97 97 97 97	es es es es es es es es es es es	Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes No Yes	Yes Yes Yes Yes Yes Yes Yes	dy 80 -5 -5. -5 -5 -4 -4 -5	(\$/wo) .42 22 .87 .25 .11 .74 .22	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Ghose	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	() () () () () () () () () () () () () (# Muses 0 </th <th>Bioavailat 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55</th> <th>BAINS 1 1 1 1 1 1 1 1 1 1</th> <th>Brenk Brenk 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2</th> <th><pre>readilitien</pre></th> <th>3.2 3.14 3.38 3.12 3.2 3.2 3.26 3.14</th>	Bioavailat 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55 0.55	BAINS 1 1 1 1 1 1 1 1 1 1	Brenk Brenk 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	<pre>readilitien</pre>	3.2 3.14 3.38 3.12 3.2 3.2 3.26 3.14
5a 5b 5c 5d 5e 5f 5g 5h	Ligand	Yes Yes Yes Yes Yes Yes Yes Yes	947 CAP2C19 947 947 944 944 944 944 944 944 944 944	es es es es es es es es es es es es	Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes	VesYesYesYesYesYesYesYesYesYesYesYes	dy 80 -5 -5. -5 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5	(\$/w5) .42 .22 .87 .25 .11 .74 .22 .87	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Ghose	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Egan ()	meesse 0 meesse 0 meesse 0 meesse 0	Bioavailat 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55	# bains 1 1 1 1 1 1 1 1 1 1 1	Brenk 2	<pre>readilitien</pre>	3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.2 3.14 3.2 3.2 3.14 3.39
5a 5b 5c 5d 5e 5f 5g 5h 5i	Ligand	yes Yes Yes Yes Yes Yes No Yes Yes Yes	97 CVP2C19	es es es es es es es es es es es es es	Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes No Yes Yes Yes	VesYesYesYesYesYesYesYesYesYesYesYes	9 1 1 1 1 1 1 1 1	(\$\u00ed{s}\u0ed{s}\u0ed{	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Ghose	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		# Wneesse 0	Bioasailat 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55 0 0.55	#alerts 0 0 0 0 0	generation generation 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2	Tead like 3 2 2 2 3 2 2 3 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3	3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.26 3.14 3.39 3.19
5a 5b 5c 5d 5e 5f 5g 5h 5i 5j	Ligand	VesYesYesYesYesYesYesYesYesYesYesYesYesYes	94 94 00 00 00 00 00 00 00 00 00 00 00 00 00	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes	VesYesYesYesYesYesYesYesYesYesYesYesYesYesYesYes	\$ 6 5 5 5 5 5 5 1 1 1 1 1 1 1 1 1 1	(\$/w5) .42 .22 .87 .25 .11 .74 .22 .87 .34 .21	C C C C C C C C C C C C C C C C C C C	() () () () () () () () () () () () () (0 0 0 0 0 0 0 0 0 0	Egan Hviolation Hviolation	meesse 0 0 meesse 0 0 0 meesse 0 0 0 0 meesse 0 0 0 0 0 meesse 0 </th <th>Bioasailat 0 0.55 0 <</th> <th># bains 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</th> <th>Brenk 2</th> <th>Teadlife 3 2 2 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 3 2</th> <th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.14 3.39 3.19 3.19 3.2</th>	Bioasailat 0 0.55 0 <	# bains 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Brenk 2	Teadlife 3 2 2 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 3 2	3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.14 3.39 3.19 3.19 3.2
5a 5b 5c 5d 5d 5f 5g 5h 5i 5j 5k	Ligand	VesYesYesYesYesYesYesYesYesYesYesYesYesYesYesYesYes	947 947 947 947 947 947 947 947 947 947	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes	9 1 1 1 1 1 1 1 1	(\$/w5) .42 .22 .87 .25 .11 .74 .22 .87 .34 .21 .17	Lipinski 1 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Comparison C	0 0 0 0 0 0 0 0 0 0		# Wneek 0 </th <th>Answer Answer <thanswe< th=""> <thanswe< th=""> Answe</thanswe<></thanswe<></th> <th>#alerts #alerts #alerts 0 1 1 1 1 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0</th> <th>generation 2 <</th> <th>Tead like 3 2 2 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 3 3 3</th> <th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.2 3.14 3.39 3.19 3.2 3.2 3.3</th>	Answer Answer <thanswe< th=""> <thanswe< th=""> Answe</thanswe<></thanswe<>	#alerts #alerts #alerts 0 1 1 1 1 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	generation 2 <	Tead like 3 2 2 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 2 3 3 3 3	3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.2 3.14 3.39 3.19 3.2 3.2 3.3
5a 5b 5c 5d 5g 5f 5g 5h 5i 5j 5k 5l		VesYesYesYesYesYesYesYesYesYesYesYesYesYesYesYesYes	94 94 94 94 94 94 94 94 94 94 94 94 94 94 94	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes	9 1 1 1 1 1 1 1 1	(\$/w) .42 .22 .87 .25 .11 .74 .22 .87 .34 .21 .17 .42	C C C C C C C C C C C C C C C C C C C	() () () () () () () () () () () () () (0 0 0 0 0 0 0 0 0 0	Egan Egan Egan	# W G	Biogramital 0.55	# bains # alerts # alerts 0 1 1 0 0 1 1 0 0 1 1 0 0 1 1	gradient 2 <th>Teadlife 3 2 2 2 2 2 3 2 3 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3</th> <th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.14 3.2 3.2 3.14 3.39 3.19 3.19 3.19 3.2 3.2 3.3 3.29</th>	Teadlife 3 2 2 2 2 2 3 2 3 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3	3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.14 3.2 3.2 3.14 3.39 3.19 3.19 3.19 3.2 3.2 3.3 3.29
5a 5b 5c 5d 5d 5f 5g 5h 5i 5j 5k 5l 5k 5l		VesYes	97 97 97 97 97 97 97 97 97 97 97 97 97 97 97	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes	\$ -5 -5 -5 -4 -5 -4 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5	(\$/w) .42 .22 .87 .25 .11 .74 .22 .87 .34 .21 .42 .42 .62	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	Comparison C	1 0 0 0 0 0		# Wneekee 0	Align and ali	#alerts #alerts #alerts #alerts #alerts 1 1 1 1 1 1 1 1 1 1 1 1 1	generation 2 <	Tead like 3 2 2 2 3 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 3 3	Jumphetic 3.2 3.14 3.38 3.12 3.26 3.14 3.32 3.26 3.14 3.39 3.19 3.20 3.19 3.20 3.31 3.29 3.51
5a 5b 5c 5d 5g 5f 5g 5h 5i 5j 5k 5j 5k 5l 5m 5n	Ligand	CAPAPA Yes	94 94 94 94 94 94 94 94 94 94 94 94 94 94 94	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes	9 1 1 1 1 1 1 1 1	(\$/w) .42 .22 .87 .25 .11 .74 .22 .87 .34 .21 .42 .42 .42 .42 .42 .42 .42 .42 .42 .42 .42 .42 .44 .44	C C C C C C C C C C C C C C C C C C C	Comparison C	1 0 0 1 0 1 <th>Egan Egan Egan Egan</th> <th># W 0</th> <th>Big Big Big<th># bains # bains # alerts 1 1 1 1 1 1 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1</th><th>gradient 2 <th>Teadlife 3 2 2 2 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 2</th><th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.12 3.2 3.14 3.29 3.19 3.19 3.19 3.2 3.2 3.3 3.29 3.51 3.26</th></th></th>	Egan Egan Egan Egan	# W 0	Big Big <th># bains # bains # alerts 1 1 1 1 1 1 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1</th> <th>gradient 2 <th>Teadlife 3 2 2 2 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 2</th><th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.12 3.2 3.14 3.29 3.19 3.19 3.19 3.2 3.2 3.3 3.29 3.51 3.26</th></th>	# bains # bains # alerts 1 1 1 1 1 1 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	gradient 2 <th>Teadlife 3 2 2 2 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 2</th> <th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.12 3.2 3.14 3.29 3.19 3.19 3.19 3.2 3.2 3.3 3.29 3.51 3.26</th>	Teadlife 3 2 2 2 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 2	3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.12 3.2 3.14 3.29 3.19 3.19 3.19 3.2 3.2 3.3 3.29 3.51 3.26
5a 5b 5c 5d 5d 5f 5g 5h 5i 5j 5k 5i 5k 5l 5m 5n 5n 5o	Ligand	CADATA Yes No Yes No Yes	94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	9 -5 -5 -5 -4 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5	(\$/w) .42 .22 .87 .25 .11 .74 .22 .87 .34 .21 .42 .62 .04 .61	C C C C C C C C C C C C C C C C C C C	Company C	1 1 1 <th></th> <th># Wneek 0<!--</th--><th>A O</th><th># BAINS 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</th><th>generation 2 <</th><th>Tead like 3 2 2 2 3 2 3 2 3 2 3 2 3</th><th>Jumph 3.2 3.14 3.38 3.12 3.26 3.14 3.26 3.14 3.39 3.19 3.21 3.26 3.14 3.39 3.19 3.20 3.19 3.20 3.21 3.22 3.33 3.29 3.51 3.26 3.49</th></th>		# Wneek 0 </th <th>A O</th> <th># BAINS 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</th> <th>generation 2 <</th> <th>Tead like 3 2 2 2 3 2 3 2 3 2 3 2 3</th> <th>Jumph 3.2 3.14 3.38 3.12 3.26 3.14 3.26 3.14 3.39 3.19 3.21 3.26 3.14 3.39 3.19 3.20 3.19 3.20 3.21 3.22 3.33 3.29 3.51 3.26 3.49</th>	A O	# BAINS 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	generation 2 <	Tead like 3 2 2 2 3 2 3 2 3 2 3 2 3	Jumph 3.2 3.14 3.38 3.12 3.26 3.14 3.26 3.14 3.39 3.19 3.21 3.26 3.14 3.39 3.19 3.20 3.19 3.20 3.21 3.22 3.33 3.29 3.51 3.26 3.49
5a 5b 5c 5d 5g 5f 5g 5h 5i 5j 5k 5l 5n 5n 5o 5p	Ligand	Katal Yes	94 94 94 94 94 94 94 94 94 94 94 94 94 94 94	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	9 1 1 1 1 1 1 1 1	(\$/w) .42 .22 .87 .25 .11 .74 .25 .34 .21 .42 .42 .42 .42 .42 .42 .42 .42 .42 .42 .42 .42 .42 .61 .95	C C C C C C C C C C C C C C C C C C C	0 0	1 0 0 1 0 1 <th>1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1</th> <th># Wreek 0 0 1 1 0 0 1 1 0 0 0 1 1 0 0 0 0 1 1 1 0<!--</th--><th>Big Big <thbig< th=""> <thbig< th=""> <thbig< th=""></thbig<></thbig<></thbig<></th><th># bains # bains 1 1 1 1 1 1 1 1 1 1 1 1 1</th><th>generation 2 <</th><th>Tead like 3 2 2 2 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 0</th><th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.14 3.2 3.2 3.14 3.39 3.19 3.19 3.19 3.2 3.3 3.29 3.51 3.26 3.51 3.26 3.49 2.75</th></th>	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	# Wreek 0 0 1 1 0 0 1 1 0 0 0 1 1 0 0 0 0 1 1 1 0 </th <th>Big Big <thbig< th=""> <thbig< th=""> <thbig< th=""></thbig<></thbig<></thbig<></th> <th># bains # bains 1 1 1 1 1 1 1 1 1 1 1 1 1</th> <th>generation 2 <</th> <th>Tead like 3 2 2 2 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 0</th> <th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.14 3.2 3.2 3.14 3.39 3.19 3.19 3.19 3.2 3.3 3.29 3.51 3.26 3.51 3.26 3.49 2.75</th>	Big Big <thbig< th=""> <thbig< th=""> <thbig< th=""></thbig<></thbig<></thbig<>	# bains # bains 1 1 1 1 1 1 1 1 1 1 1 1 1	generation 2 <	Tead like 3 2 2 2 2 3 2 3 2 3 2 3 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 0	3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.14 3.2 3.2 3.14 3.39 3.19 3.19 3.19 3.2 3.3 3.29 3.51 3.26 3.51 3.26 3.49 2.75
5a 5b 5c 5d 5d 5g 5f 5g 5j 5j 5j 5k 5j 5k 5j 5k 5j 5k 5j 5g 5p 5q	Ligand	CADADA Yes No Yes	by Y c <thc< th=""> <thc< th=""> <thc< th=""> <thc< th=""></thc<></thc<></thc<></thc<>	es es es es es es es es es es es es es e	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes Yes Yes Yes Yes Yes Yes Yes Yes Yes	Yes	g 80 -5 -5. -5. -5 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5 -5	(\$/w) .42 .22 .87 .25 .11 .74 .22 .87 .34 .21 .42 .62 .04 .95 .61	C C C C C C C C C C C C C C C C C C C	0 0	** Control <	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	# Wneek 0 0 1 1 0 0 1 1 0 0 0 1 1 1 0 0 0 1 1 1 1 1 0 </th <th>Big Big <thbig< th=""> <thbig< th=""> <thbig< th=""></thbig<></thbig<></thbig<></th> <th># bains 1 1 1 1 1 1 1 1 1 1 1 1 1</th> <th>gradient gradient 2 2 3 3 4 2 4 3</th> <th>Image: second system Image: second system 3 2 2 2 3 2 2 3 2 2 3 2 3 2 3 3 3 3 2 3 3 3 2 3 3 3 3 3 0 3 0 3</th> <th>3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.14 3.29 3.19 3.29 3.19 3.2 3.3 3.29 3.51 3.26 3.49 2.75 3.3</th>	Big Big <thbig< th=""> <thbig< th=""> <thbig< th=""></thbig<></thbig<></thbig<>	# bains 1 1 1 1 1 1 1 1 1 1 1 1 1	gradient gradient 2 2 3 3 4 2 4 3	Image: second system Image: second system 3 2 2 2 3 2 2 3 2 2 3 2 3 2 3 3 3 3 2 3 3 3 2 3 3 3 3 3 0 3 0 3	3.2 3.14 3.38 3.12 3.2 3.2 3.2 3.2 3.2 3.2 3.2 3.14 3.29 3.19 3.29 3.19 3.2 3.3 3.29 3.51 3.26 3.49 2.75 3.3





from SwissADME web tool.



1H NMR and 13C NMR Spectra of 5a



1H NMR and 13C NMR Spectra of 5b



1H NMR and 13C NMR Spectra of 5c



1H NMR and 13C NMR Spectra of 5d



1H NMR and 13C NMR Spectra of 5e



1H NMR and 13C NMR Spectra of 5f



H NMR and 13C NMR Spectra of 5g



H NMR and 13C NMR Spectra of 5h



1H NMR and 13C NMR Spectra of 5i





¹H NMR and ¹³C NMR Spectra of 5k

1H NMR and 13C NMR Spectra of 5l



1H NMR and 13C NMR Spectra of 5m





1H NMR and 13C NMR Spectra of 5n



¹H NMR and ¹³C NMR Spectra of 50



1H NMR and 13C NMR Spectra of 5p



1H NMR and 13C NMR Spectra of 5q

1H NMR and 13C NMR Spectra of 5r



HPLC chromatogram of 5a



HPLC chromatogram of 5b





HPLC chromatogram of 5d



HPLC chromatogram of 5e



HPLC chromatogram of 5f



HPLC chromatogram of 5g



HPLC chromatogram of 5h







HPLC chromatogram of 5j



HPLC chromatogram of 5k



HPLC chromatogram of 51







HPLC chromatogram of 5n



HPLC chromatogram of 50



HPLC chromatogram of 5p



HPLC chromatogram of 5q



HPLC chromatogram of 5r



Mass spectrum of 5a



Mass spectrum of 5b



Mass spectrum of 5c







Mass spectrum of 5e







Mass spectrum of 5g



Mass spectrum of 5h



Mass spectrum of 5i







Mass spectrum of 5k



Mass spectrum of 5l



Mass spectrum of 5m



Mass spectrum of 5n



Mass spectrum of 50

Mass spectrum of 5p







Mass spectrum of 5r

