Title: *In silico* optimization of pharmacokinetic properties and receptor binding affinity simultaneously: a “parallel progression approach to drug design” applied to β -blockers

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Supporting information: The supporting information includes Table S1: PK data for β -blockers, Table S2: pK_i values of β -blockers determined using ICYP as the radiolabelled substrate, Table S3: pK_i values of β -blockers determined with CGP12177 as the radiolabelled substrate, Table S4: Validation sets for pharmacokinetic and pharmacodynamic models, Table S5: Results of toxicity studies performed with ADMET Predictor and references.

Table S1: Pharmacokinetic data for β -blockers:

S. No.	Name	V _d (L/Kg)	logV _d (L/Kg)	Cl (mL/min/kg)	logCl (mL/min/kg)
1	Acebutalol ^(Obach, Lombardo & Waters 2008)	1.70	0.23	10.00	1.00
2	Alprenolol ^(Obach et al. 2008)	3.20	0.51	15.00	1.18
3	Amosulalol ^(Nakashima et al. 1984)	0.75	-0.13	1.90	0.28
4	Atenolol ^(Obach et al. 2008)	0.95	-0.022	2.50	0.40
5	Betaxolol ^(Obach et al. 2008)	4.80	0.68	3.40	0.53
6	Bevantolol ^(Obach et al. 2008)	0.67	-0.17	5.50	0.74
7	Bisoprolol ^(Obach et al. 2008)	2.40	0.38	3.70	0.57
8	Bufuralol ^(Hinderling, Schmidlin & Seydel 1984; Obach et al. 2008)	1.86	0.27	8.90	0.95
9	Bunitrolol ^(Yamada, Ito, Nakamura, Sawada & Iga 1993)	5.00	0.70	-	-
10	Carteolol ^(Ishizaki et al. 1983)	4.00	0.60	10.13	1.01
11	Carvedilol ^(Obach et al. 2008)	1.30	0.11	7.80	0.89
12	Celiprolol	4.50	0.65	7.14	0.85
13	Cetamolol ^(Campese & Tanasescu 2004)	2.50	0.40	5.00	0.70
14	Deacetylmepipranolol ^(Abshagen, Betzien, Kaufmann & Endeke 1982)	3.50	0.54	17.67	1.25
15	Dilevalol ^(Obach et al. 2008)	4.80	0.68	29.00	1.46
16	Esmolol ^(Obach et al. 2008)	1.20	0.08	290.00	2.46
17	Flestolol ^(Achari et al. 1987)	1.89	0.28	181.00	2.26
18	Landiolol ^(Honda et al. 2008)	0.16	-0.79	36.60	1.56
19	Levobunolol	5.50	0.74	0.16	-0.80
20	Metipranolol ^(Abshagen et al. 1982)	3.50	0.54	15.70	1.20
21	Metoprolol ^(Obach et al. 2008)	3.10	0.49	13.00	1.11
22	Nadolol ^(Obach et al. 2008)	1.90	0.28	2.90	0.46
23	Nebivolol ^(Obach et al. 2008)	11.00	1.04	14.00	1.15
24	Oxprenolol ^(Yamada et al. 1993; Anderson 2008)	1.30	0.11	3.10	0.49

25	Pafenolol ^(Regårdh, Heggelund, Kylberg-Hanssen & Lundborg 1990)	1.10	0.04	4.29	0.63
26	Pindolol ^(Obach et al. 2008)	1.20	0.08	7.70	0.89
27	Practolol ^(Yamada et al. 1993)	1.70	0.230	1.830	0.26
28	Propranolol ^(Obach et al. 2008)	3.10	0.491	12.000	1.08
29	Sotalol ^(Obach et al. 2008)	1.30	0.114	2.000	0.30
30	Talinolol ^(Obach et al. 2008)	3.300	0.519	4.900	0.690
31	Timolol ^(Obach et al. 2008)	1.500	0.176	8.500	0.929
32	Tolamolol ^(Obach et al. 2008)	4.000	0.602	14.000	1.146

Table S2: pK_i values of β -blockers determined using ICYP as the radiolabelled substrate.

S. No	Compound	pK _i	S. No	Compound	pK _i
1	CHEMBL442225 ^(Sawa et al. 2004)	7.47	23	Cicloprolol ^(Louis, Nero, Iakovidis, Jackman & Louis 1999)	7.97
2	CHEMBL361505 ^(Kazuhiro Mizuno et al. 2004)	7.37	24	H87_07 ^(Louis et al. 1999)	7.00
3	CHEMBL250760 ^(Lafontaine et al. 2007)	7.30	25	Isoproterenol ^(Hoffmann, Leitz, Oberdorf-Maass, Lohse & Klotz 2004)	6.65
4	CHEMBL184407 ^(Kazuhiro Mizuno et al. 2004)	7.18	26	NIHP ^(Louis et al. 1999)	7.07
5	CHEMBL251600 ^(Lafontaine et al. 2007)	7.00	27	Xamoterol ^(Joseph, Lynham, Grace, Colledge & Kaumann 2004)	6.77
6	CHEMBL400392 ^(Lafontaine et al. 2007)	6.89	28	ICI118551 ^(Fraundorfer, Fertel, Miller & Feller 1994; Louis et al. 1999; Hoffmann et al. 2004)	7.19
7	CHEMBL251392 ^(Lafontaine et al. 2007)	6.85	29	CGP_20712A ^(Hoffmann et al. 2004; Baker 2005)	8.57
8	CHEMBL250144 ^(Lafontaine et al. 2007)	6.82	30	SR59230A ^(Candelore et al. 1999; Hoffmann et al. 2004)	8.09
9	CHEMBL399440 ^(Lafontaine et al. 2007)	6.77	31	Alprenolol ^(Hoffmann et al. 2004)	8.24
10	CHEMBL249336 ^(Lafontaine et al. 2007)	6.70	32	Atenolol ^(Louis et al. 1999; Hoffmann et al. 2004)	6.65
11	CHEMBL250559 ^(Lafontaine et al. 2007)	6.68	33	Betaxolol ^(Louis et al. 1999)	8.75
12	CHEMBL188622 ^(Sawa et al. 2004)	6.64	34	Bisoprolol ^(Hoffmann et al. 2004; Joseph et al. 2004)	7.33
13	CHEMBL317003 ^(Steffan et al. 2002)	6.62	35	Carvedilol ^(Candelore et al. 1999; Hoffmann et al. 2004; Joseph et al. 2004)	9.08
14	CHEMBL251180 ^(Lafontaine et al. 2007)	6.57	36	Metoprolol ^(Hoffmann et al. 2004; Joseph et al. 2004)	7.10
15	CHEMBL250352 ^(Lafontaine et al. 2007)	6.44	37	Nadolol ^(Candelore et al. 1999; Joseph et al. 2004)	7.26
16	CHEMBL249534 ^(Lafontaine et al. 2007)	6.40	38	Oxprenolol ^(Joseph et al. 2004)	8.41
17	CHEMBL400049 ^(Lafontaine et al. 2007)	6.40	39	Pindolol ^(Fraundorfer et al. 1994; Hoffmann et al. 2004)	8.65
18	CHEMBL188196 ^(Kazuhiro Mizuno et al. 2004)	6.32	40	Practolol ^(Louis et al. 1999)	6.78
19	CHEMBL12998 ^(Hu et al. 2001)	6.24	41	Propranolol ^(Fraundorfer et al. 1994; Schotte et al. 1996; Louis et al. 1999)	9.39
20	Bupranolol ^(Candelore et al. 1999; Louis et al. 1999)	8.17	42	Sotalol ^(Joseph et al. 2004)	5.34
21	CGP12177 ^(Louis et al. 1999; Hu et al. 2001; Hoffmann et al. 2004)	9.10	43	Timolol ^(Joseph et al. 2004)	8.36
22	NIP ^(Louis et al. 1999)	8.42			

Table S3: pK_i values of β -blockers determined with CGP12177 as the radiolabelled substrate.

S. No.	Compound	pK _i	S. No.	Compound	pK _i
1	Formoterol ^(Beattie et al. 2010)	6.50	28	Salmeterol ^(Beattie et al. 2010)	6.10
2	Carazolol ^(Baker 2010)	9.69	30	Xamoterol ^(Baker 2005; Baker et al. 2011)	7.15
3	ICI118551 ^(Baker et al. 2011)	6.63	31	Indacaterol ^(Beattie et al. 2010)	7.04
4	Pronethalol ^(Baker 2005; Baker et al. 2011)	6.55	32	CHEMBL29141_R ^(Beattie et al. 2010)	7.22
5	Cyanopindolol ^(Baker 2010)	10.39	33	CHEMBL1221679 ^(Beattie et al. 2010)	7.10
6	Bucindolol ^(Baker 2010; Baker et al. 2011)	9.39	34	CHEMBL1221735 ^(Beattie et al. 2010)	6.35
7	ZD7114 ^(Baker 2010)	7.61	35	CHEMBL1221801 ^(Beattie et al. 2010)	6.18
8	CHEMBL1221542 ^(Beattie et al. 2010)	7.41	36	CHEMBL1221862 ^(Beattie et al. 2010)	7.51
9	CHEMBL1221543 ^(Beattie et al. 2010)	8.04	37	Metoprolol ^(Joseph, Lynham, Colledge & Kaumann 2004; Baker 2005)	7.56
10	CHEMBL1221540 ^(Beattie et al. 2010)	6.77	38	Nebivolol ^(Baker 2010; Baker et al. 2011)	8.93
11	CHEMBL1221634 ^(Beattie et al. 2010)	6.95	39	CHEMBL1221803 ^(Beattie et al. 2010)	7.75
12	CHEMBL1221637 ^(Beattie et al. 2010)	8.85	40	CHEMBL1221586 ^(Beattie et al. 2010)	7.45
13	CHEMBL1221732 ^(Beattie et al. 2010)	7.39	41	Acebutalol ^(Baker 2005; Baker et al. 2011)	6.52
14	CHEMBL1221736 ^(Beattie et al. 2010)	6.91	42	CHEMBL1221590 ^(Beattie et al. 2010)	8.74
15	CHEMBL1221802 ^(Beattie et al. 2010)	6.73	43	CHEMBL1221587 ^(Beattie et al. 2010)	8.42
16	CHEMBL1221861 ^(Beattie et al. 2010)	8.77	44	CHEMBL1221680 ^(Beattie et al. 2010)	9.05

17	Alprenolol ^(Joseph et al. 2004; Baker 2005)	8.12	45	CHEMBL1221588 ^(Beattie et al. 2010)	6.04
18	Atenolol ^(Baker 2005; Dolusic et al. 2011)	6.71	46	CHEMBL1221636 ^(Beattie et al. 2010)	7.82
19	Betaxolol ^(Baker 2005)	8.21	47	CGP20712A ^(Baker 2005; Baker et al. 2011)	8.72
20	Bisoprolol ^(Bundkirchen, Brixius, Bölck, Nguyen & Schwinger 2003; Joseph et al. 2004; Baker 2005; Baker et al. 2011)	7.79	48	CHEMBL1221589 ^(Beattie et al. 2010)	8.70
21	Carvedilol ^(Joseph et al. 2004; Baker 2005; Baker et al. 2011)	9.14	49	ICI89406 ^(Baker 2005)	8.91
22	Dilevalol ^(Baker 2005; Baker et al. 2011)	7.81	50	Practolol_S ^(Baker 2005)	6.14
23	Nadolol ^(Joseph et al. 2004; Baker 2005)	7.63	51	CHEMBL1221804 ^(Beattie et al. 2010)	8.08
24	Oxprenolol ^(Joseph et al. 2004; Baker 2010)	8.05	52	CGP12177 ^(Baker 2005)	9.21
25	Pindolol ^(Baker 2010)	8.57	53	ICI215001 ^(Baker 2005)	6.37
26	Propranolol ^(Smith & Teitler 1999; Baker 2005)	8.30			
27	Sotalol ^(Joseph et al. 2004; Baker 2005)	6.03			
28	Timolol ^(Baker 2005)	8.27			

Table S4: Validation sets for pharmacokinetic and pharmacodynamic models

	Molecule	Experimental log V _d	Predicted log V _d		Molecule	Experimental log Cl	Predicted log Cl
Validation set for log V_d	Alprenolol	0.51	0.45	Validation set for log Cl	Nebivolol	1.15	1.38
	Levobunolol	0.74	0.42		Sotalol	0.30	0.23
	Bufuralol	0.27	0.02		Talinolol	0.69	0.71
	Metipranolol	0.54	0.40		Timolol	0.93	1.18
	Talinolol	0.52	0.20				
	Molecule	Experimental pK _i	Predicted pK _i		Molecule	Experimental pK _i	Predicted pK _i
Validation set for pK_i PD Dataset I	CHEMBL 400392	6.89	6.81	Validation set for pK_i PD Dataset II	Indacaterol	7.04	6.98
	CHEMBL 250559	6.68	6.46		CHEMBL 29141	7.22	7.36
	CHEMBL 188622	6.64	7.18		CHEMBL 1221679	7.10	7.46
	CHEMBL 317003	6.62	6.78		CHEMBL 1221735	6.35	4.94
	CHEMBL 12998	6.24	5.89		CHEMBL 1221801	6.18	7.07
	NIP	8.42	7.66		CHEMBL 1221862	7.50	7.23
	CGP_20712A	8.57	8.16		Metoprolol	7.56	7.99
					Nebivolol	8.93	8.38

Table S5: Results of toxicity studies performed with ADMET Predictor*

Parameters	Carvedilol	Cetamolol	ECC 4	ECC 19	ECC 46	ECC 56
CYP_Risk	2	0	0	0	0	0
TOX_ER	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic
TOX_ER_Filter	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic
TOX_AR	0.0117	0.0064	0.0058	0.004	0.0049	0.0155
TOX_AR_Filter	Toxic	Toxic	Toxic	Toxic	Toxic	Toxic
TOX_SKIN	Sensitizer	Sensitizer	Sensitizer	Nonsensitizer	Sensitizer	Sensitizer
TOX_RESP	Sensitizer	Nonsensitizer	Nonsensitizer	Nonsensitizer	Sensitizer	Nonsensitizer
TOX_FHM	0.04	277.51	509.2	27.7	85.41	1.23
TOX_hERG_Filter	Toxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Toxic
TOX_hERG	6.41	4.16	4.04	3.92	4.22	5.38
TOX_RAT	858.89	656.98	913.62	691.25	1715.06	929.7
TOX_BRM_Rat	19.56	23.57	15.83	59.67	4.24	62.96
TOX_BRM_Mouse	152.61	329.13	342.23	207.49	235.21	118.51
TOX_CABR	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic
TOX_REPR	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic
TOX_AlkPhos	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic
TOX_GGT	Nontoxic	Toxic	Toxic	Toxic	Toxic	Nontoxic
TOX_LDH	Nontoxic	Nontoxic	Undecided	Nontoxic	Nontoxic	Nontoxic
TOX_SGOT	Nontoxic	Toxic	Toxic	Toxic	Toxic	Nontoxic

TOX_SGPT	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic
TOX_MUT_Risk	0	0	0	0	0	0
TOX_Risk	1	1	1	1	1	0

* ADMET predictor v6.0 implemented in the Simulation plus, Inc software
The parameters are described below.

Toxicity parameter description:

CYP_Risk: computational filter for metabolic liability

TOX_ER_Filter: prediction of whether the molecule will have a detectable affinity for the estrogen receptor at all, to cause endocrine toxicity by binding to the receptor.

TOX_ER: predicts the degree of binding for those compounds that are identified by the filter as “Toxic”. Higher values indicate greater binding affinity and likelihood for endocrine-related toxicity.

TOX_AR_Filter: prediction of whether the molecule will have a detectable affinity for the androgen receptor at all, to cause endocrine toxicity by binding to the receptor. Compounds with LC25 less than or equal to 10 µmol/L were labeled “**Toxic**” (likely to bind) while those greater than 10 µmol/L are considered “**Nontoxic**”.

TOX_AR: predicts the degree of binding for those compounds that are identified by the filter as “Toxic”

TOX_SKIN: qualitative assessment of allergenic skin sensitization in mouse.

TOX_RESP: qualitative assessment of allergenic respiratory sensitization in rat.

TOX_FHM: [mg/L] LC50 for fathead minnow lethal toxicity after 96 hours of exposure.

TOX_hERG_Filter:

TOX_hERG [mol/L]: pIC50 as a measure of affinity towards hERG K⁺ channel and potential for cardiac toxicity.

TOX_RAT: [mg/kg] LD50 for lethal rat acute toxicity.

TOX_BRM_Rat: [mg/kg/day] TD50, which is defined as the oral dose of a compound required to induce tumors in 50 percent of a rat population after exposure over a standard lifetime

TOX_BRM_Mouse: [mg/kg/day] TD50, as above, but for mouse

TOX_CABR: qualitative estimation of triggering the mutagenic chromosomal aberrations

TOX_REPR: qualitative estimation of reproductive / developmental toxicity

TOX_AlkPhos: human liver adverse effect as the likelihood of causing elevation in the levels of Alkaline Phosphatase enzyme

TOX_GGT: human liver adverse effect as the likelihood of causing elevation in the levels of GGT enzyme

TOX_LDH: human liver adverse effect as the likelihood of causing elevation in the levels of LDH enzyme

TOX_SGOT: human liver adverse effect as the likelihood of causing elevation in the levels of SGOT enzyme

TOX_SGPT: human liver adverse effect as the likelihood of causing elevation in the levels of SGPT enzyme

TOX_MUT_Risk: a computational filter to assess risk of mutagenicity in *S. typhimurium*

TOX_Risk: a computational filter to assess toxic liability

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