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QSAR STUDY OF A SERIES OF QUINOLINE DERIVATIVES ACTIVE ON THE ALPHA2 ADRENERGIC RECEPTOR SUBTYPES

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A QSAR study using multiple linear regression (MLR) is reported for a series of 43 ligands of the alpha2 adrenergic receptor subtypes. For the alpha2A adrenoceptor the majority of models are based on topological, constitutional, and aromaticity descriptors. Affinity to alpha2B adrenoceptor depends on topological, radial distribution functions, and 3D-MoRSE descriptors, while the affinity for alpha2C adrenoceptor depends on topological, molecular walk count, RDF and GETAWAY descriptors. The topological descriptors correlating significantly with Ki of alpha2A or alpha2B adrenoceptor are different of those descriptors correlating significantly with Ki of the alpha2B or alpha2C adrenoceptors. Only for alpha2B and alpha2C regressions with predictive value have been obtained. The binding affinities of quinoline derivatives to alpha2B-AR subtype depend on molecular conformation (3D-MoRSE), molecular symmetry (HVcpx), and molecular size and shape (RDF) while the binding affinities to alpha2C adrenoceptor depend on molecular conformation and electrostatic properties.

INTRODUCTION

Adrenergic receptors (ARs) are members of the G protein-coupled receptor (GPCR) superfamily, and belong to the biogenic amine receptors of the rhodopsin-like class. Various subtypes of adrenergic receptors distributed all over the body, are critical in the normal fulfillment of many physiological functions such as peripheral excitation or inhibition of certain types of smooth muscles, cardiac excitation, central nervous system (CNS) modulation, metabolic and endocrine regulations. They are involved in the occurrence of many clinical disorders such as hypertension, cardiovascular shock, arrhythmias, ocular hypertension, glaucoma, asthma, migraine headaches, or anaphylactic reactions.[1]

The alpha2-AR class has three subtypes (alpha2A, alpha2B, alpha2C)[2], which share many common structural and functional[1-3] properties. However, due to their different tissue distribution they mediate different physiological and pharmacological effects. The alpha2A-AR subtype is responsible for most of the major pharmacological actions of the alpha2-AR ligands, such as the central regulation of blood pressure and sympathetic nerve activity, nociceptive processing, and the control of alertness and attention.[4] The alpha2B-AR subtype mediates vasoconstriction and the alpha2C-AR subtype is involved in sensorimotor integration.[4,5]

Although highly potent agonists and antagonists for all three alpha2-AR subtypes are known, selective agonists and antagonists for alpha2-AR subtypes are still needed.[6] In searching selective and potent ligands for alpha2-AR subtypes, different classes of compounds have been synthesized and tested.[7-11] Of them some have nano or subnanomolar affinities to alpha2A and alpha2C-AR. A series of 4-quinoline-4-phenyl derivatives have been shown to be selective on alpha2C subtype.[11] To find out which properties of the quinoline derivatives are important for their affinity to each of the three alpha2-AR subtypes a classical QSAR study was performed.

METHODS

Gas phase geometries of the quinoline derivatives have been optimized using the AMBER99 force field. The optimization was performed with the Polak-Ribiere conjugate gradient algorithm. All methods are implemented in the HyperChem7.52 package.[12] A RMS gradient of 0.01 kcal/Å·mol was used in all optimization runs. For some representative structures a conformational search was carried out with the Conformational Search module from HyperChem7.52. An energy criterion of 10 kcal/mol above the lowest energy conformer was used. Maximum number of optimization cycles was 3000 and the lowest 100 conformers above the best conformer were kept.

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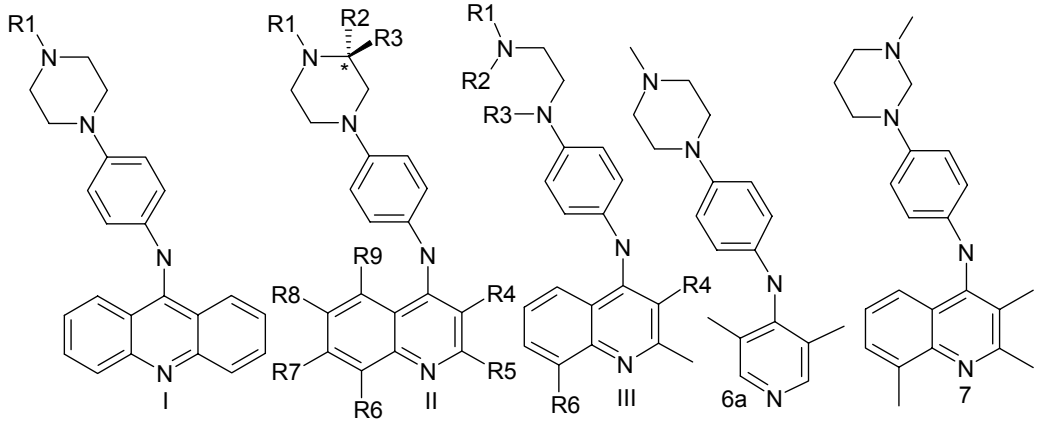
Table 1

Ligand structure and affinity to alpha2-AR subtypes



No	No/ref	Str	R1	R2	R3	R4	R5	R6	R7	R8	R9	pKi_{a2C}	pKi_{a2A}	pKi_{a2B}
1	1	I	Me									7.55	5.49	5.82
2	2	I	Et									7.43	5.44	5.92
3	5a	II	Me									5.77	6.14	5.42
4	5b	II	Me			Me	Me					7.46	5.66	5.30
5	5c	II	Me			Et	Me					7.60	5.96	5.00
6	5d	II	Me			iPr	Me					7.28	5.77	5.41
7	5e	II	Me			Ph	Me					7.46	5.77	5.00
8	5f	II	Me			Bn	Me					7.46	6.24	7.02
9	5g	II	Me				Me					6.16	6.30	5.43
10	7	-										5.30	5.44	4.52
11	8	II*,[a]	Me	Me		Et	Me					6.96	6.20	5.53
12	5h	II*	Me	Me		Ph	Me					8.30	5.85	5.77
13	5i	II*	-(CH2)4-			Me	Me					8.64	6.15	5.88
14	5j	II	Me	Me	Me	Me						8.27	6.05	5.90
15	5k	II*	Me	Me		Me						8.07	5.85	5.46
16	5l	II*	Me	Me		Me	Me	Me	Me			8.30	5.73	6.24
17	5m	II	Me	Me		Me	Me	Me	Me			8.11	6.10	6.22
18	5n	II	Me		Me	Me	Me	Me	Me			7.08	6.07	5.88
19	5o	II*	Me	Me		Me	Me		Me			7.82	6.08	5.89
20	5p	II	Me	Me		Me	Me		Me			8.08	6.04	5.94
21	5q	II	Me		Me	Me	Me		Me			7.12	5.98	5.59
22	5r	II*	Me	Me		Me	Me	Me				8.16	5.72	5.96
23	5s	II*	Me	Me		Me	Me				Me	7.06	6.17	5.69
24	5t	II*	Me	Me		Me	Me		Me		Me	6.88	6.19	6.04
25	5u	II*	Me	Me		Me	Me	Me			Me	6.41	5.64	5.44
26	5v	II*	Me	Me		Me	Me		Cl			8.08	5.84	6.06
27	5w	II*	Me	Me		Me	Me				Cl	6.87	6.11	5.95
28	5x	II*	Me	Me		Me	Me			F		7.80	5.91	5.46
29	6a	-										6.11	5.00	5.60
30	6b	III	Et	Et		Et		Me				7.09	6.05	5.54
31	6c	III	-(CH2)4-			Me						7.00	6.00	5.77
32	6d	III	Me	-(CH2)3-		Et		Me				8.07	5.10	5.59
33	6e	II*	Me	Me		-CH2OH	Me					8.12	5.51	5.00
34	6f	II	Me	Me	Me	-CH2OH	Me					8.42	5.93	5.83
35	6g	II*	Me	Me		-CH(Me)-OH	Me					8.31	5.51	5.29
36	6h	II	Me	Me		Me	-CH2OH					8.05	5.73	5.74
37	6i	II	Me	Me	Me	-CH2OH						8.19	5.73	5.72
38	6j	II	Me	Me		-CH2OH						8.04	5.66	5.59
39	6k	II		Me		-CH2OH						6.69	5.02	4.75
40	6l	II	Me	Me	Me	-CH2OH			Cl			8.23	6.02	6.38
41	6m	II*	Me	Me		-CH2OH				F		7.37	5.86	5.00
42	6n	II	Me	Me	Me	-CH2OH				F		7.30	5.88	5.76
43	6o	II	Me	Me		-CH2OH				F		7.42	6.01	5.50

II* - the chiral center marked with asterisk in structure II is racemic; II[a] - 5,6,7,8-tetrahydroquinoline instead of quinoline; experimental data are taken from ref. 11 (Kallatsa and all., *J. Med. Chem*., **2006**, *49*, 6351-6363).

Using the AMBER99 optimized geometry a set of descriptors: total AMBER energy and its terms, stretching energy, E_{BOND}, bending energy, E_{BEND}, torsion energy, E_{TORS}, and van der Waals energy, E_{VDW} were calculated. The QSAR properties module from HyperChem7.52 was used to calculate: molar polarizability, MPol, the molar refractivity, MRefr, logP (partition coefficient octanol/water), hydration energy, E_{Hy}, van der Waals area, A_{VDW}, and volume, V_{VDW}, solvent accessible surface area, SASA, solvent-accessible surface-bound molecular volume, SASV. Constitutional, topological and other descriptors were calculated with the DRAGON3.0[13] software using the AMBER99 geometries having Gasteiger-Marsili atomic partial charges. Variable selection was performed with the forward stepwise method on a set of 11 descriptors or a subset of descriptors mediated by a certain atomic property.

The structure and biological activities of a series of 43 quinoline derivatives synthesized and tested by Kallatsa and coll.[11] on human cloned alpha2-AR subtypes are presented in Table 1. Biological activity is expressed as pKi (-log of inhibition constant, Ki).

RESULTS

The cross-correlation coefficients (Table 2) between the binding affinities to the alpha2-AR subtypes are not statistically significant. This suggests that different properties should model the binding affinities of quinoline derivatives to each alpha2-AR subtype.

Table 2

Cross-correlation coefficients of dependent variables pKi_{a2A}, pKi_{a2B}, pKi_{a2C}, and their variance

	pKi_{a2A}	pKi_{a2B}	pKi_{a2C}
pKi_{a2A}	1		
pKi_{a2B}	0.423	1	
pKi_{a2C}	0.056	0.394	1
Minimum	5.00	4.52	5.30
Maximum	6.30	7.02	8.64

a2A, a2B, a2C stand for alpha2A-, alpha2B-, and alpha2C-AR subtypes, respectively

Alpha2A-AR

Of 1171 calculated descriptors only 104 correlate significantly with pKi alpha2A (pKi_{a2A}). The descriptor ICR (radial centric information index) has the highest correlation coefficient (r=0.592).

Some multiple linear models resulted, but with low statistical significance. They contain MoRSE descriptors, constitutional descriptors such as the number of benzene-like rings (NBNZ), the number of multiple bonds (NBM) and topological descriptors such as X2Av (average valence connectivity index $\chi 2$) and AROM (aromaticity descriptor). After eliminating the outliers 2, 9, 14, 16, 25, 32, 34 the best biparameter model obtained is:

pKi_{a2A}=5.19629(0.42286)ICR-
21.98040(2.93120)AROM +12.01059(2.55823)
n=36 r^2=0.828 r^2_{adj}=0.818 s=0.128 F=79.44.

Although the statistical significance of the regressions is low, some qualitative information related to the ligand properties important for their biological activity can be obtained from the type of descriptors correlating with pKi together with ICR. The ligand affinity to the alpha2A-AR depends, beside ICR, on the number of multiple bonds, the number of benzene-like rings, aromaticity, and the presence of H atoms bound at C(sp3) in the sequence -C(sp3)-CX2-, where X are halogen atoms. These descriptors suggest that the shape (ICR) and the unsaturation and aromaticity of the quinoline derivatives are important properties for the affinity to alpha2A-AR.

Alpha2B-AR

Of 1171 descriptors 629, are statistical significant. HVcpx (graph vertex complexity index) has the best statistical parameters:
pKi_{a2B}=6.28221(0.9538354)HVcpx-
15.7798(3.25351)

n=43 r^2=0.514 s=0.316 F=43.38.

HVcpx can be associated with topological descriptors (Qindex, ZM2v, X1, X2, X2v, X2sol, RDSQ), 2D-autocorrelation (ATS6e, ATS3p), RDF (RDF120m), GETAWAY (H6u, HGM, HATS5m, H4m), descriptors of functional groups (nCrR2, nHdon), descriptors of molecular properties (Avdw, SASV, Pol).

Families of descriptors such as BCUT, 2D-autocorrelation, RDF, 3D-MoRSE, WHIM, GETAWAY, have subsets which can be unweighted or weighted by atomic masses, atomic van der Waals volumes, atomic polarizabilities, or atomic Sanderson electronegativities. For this type of descriptors a subset was considered in variable selection. To evaluate 3D-MoRSE descriptors all 32 descriptors contained in a subset were taken in a run.

Of 30 possible radial distribution function (RDF) descriptors only 29 could be calculated for quinoline derivatives. The 29 RDF descriptor subset weighted by atomic masses was evaluated in a single run. Thus, after eliminating three outliers (observables 25, 29 and 37) regression (1) was obtained:

pKi_{a2B}=0.10474(0.01828)RDF025m
-0.11522(0.03221)RDF030m
+0.09981(0.02178)RDF040m
-0.08490(0.02069)RDF060m
+0.12243(0.02725)RDF110m
+0.21834(0.03245)RDF120m
+2.32823(0.33177) (1)
n=40 r^2=0.881 r^2adj=0.859 s=0.174 F=40.67
$r^2_{cv(LOO)}$=0.777 press=1.626 SDEP=0.202
Spress=0.222

According to the above type of statistical parameters, regression (1) is the best regression (with 6 descriptors) that can be obtained from the family of descriptors weighted by different physico-chemical properties. This model is able to describe around 88% of the variance in the experimental activity. Cross-correlation coefficients between the descriptors of regression (1) are low, but there is a high cross-correlation between RDF025m and RDF030m (0.785). RDF descriptors correlate with size and shape descriptors.

The best regression containing a subset of descriptors weighted by different physico-chemical properties and HVcpx is regression (2). It was obtained by correlating pKi_{a2B} with a subset of unweighted 3D-MoRSE signals and HVcpx. After eliminating three outliers (compounds 8, 29 and 41) the following regression resulted:

pKi_{a2B}=5.05388(0.55258)HVcpx
-0.30036(0.02922)MoR07u
+0.29717(0.07443)MoR13u
-0.41898(0.09112) MoR15u
-0.26629(0.09112)MoR18u
-0.71141(0.14724)MoR23u
+1.21423(0.17735)MoR24u
-0.80793(0.15784) MoR26u
-11.21090(1.79205) (2)
n=40 r^2= 0.899 r^2adj= 0.873 s = 0.141 F=34.44
$r^2_{cv(LOO)}$=0.803 press=1.077 SDEP=0.164
Spress=0.186

Model (2) is statistically similar to model (1) and can explain around 90% of the variance in the experimental activity. The cross-correlation coefficients between the descriptors of regression (2) are low, but there is a high cross-correlation between MoR13u and MoR26u (0.682).

From these two regressions it results that the affinity of quinoline derivatives to alpha2B-AR subtype depends on molecular conformation (3D-MoRSE), molecular symmetry (HVcpx), molecular size and shape (RDF).

Alpha2C-AR

The variance of the pKi alpha2C (pKi_{a2C}) is 3.34. Of 1171 descriptors 527 have statistical significance. Similarly to the affinity to alpha2B-AR, the affinity of quinoline derivatives to alpha2C-AR gives many statistically significant multiple regressions, but their statistical indices are not sufficiently high for predictive objectives. Only by eliminating outliers resulted regressions with acceptable statistical indices. For example, the best regression obtained after eliminating the outliers 5, 18, 21, 25, 27, 29 and 42 contains five types of descriptors: a topological index, IC3 (information content index (neighborhood symmetry of 3-order)), a 3D-MoRSE descriptor, MoR32v (3D-MoRSE - signal 32 / weighted by atomic van der Waals volumes), a GETAWAY descriptor R5p (R autocorrelation of lag - 5 / weighted by atomic polarizabilities), a 2D-autocorrelation descriptor, GATS5v (Geary autocorrelation - lag 5 / weighted by atomic van der Waals volumes), and a RDF descriptor, RDF055p (radial distribution function 5.5 / weighted by atomic polarizabilities). Regression (3) has the following coefficients and statistical parameters:

pKi_{a2C}=0.70554(0.23480)IC3
-3.39690(0.61686)MoR32v
+5.28879(1.45681)R5p
-4.14468(0.94393) GATS5v
+0.11369(0.03376) RDF055p
+3.00061(1.57853) (3)
n=36 r^2=0.892 r^2_{adj}=0.874 s=0.271 F(5,30)=49.488
$r^2_{cv(LOO)}$=0.860 press=3.012 SDEP=0.289
Spress=0.317

There are no high cross-correlations between the descriptors of regression (3). This can be seen from Table 3 where the cross-correlation coefficients between the descriptors together with their partial correlation coefficients are displayed.

In regression (3), which explains around 88% of data variance, all partial correlation coefficients are highly significant (Table 3, values in the last row). All the above statistical tests suggest that regression (3) has predictive value.

The plot of experimental vs. calculated pKi_{a2C} values using regression (3) is shown in Fig 1. The maximum and minimum residuals between experimental and calculated pKi_{a2C} values are 0.468 and -0.452, respectively. One can conclude that the model predicts slightly higher values for low pKi_{a2C} and slightly lower values for high pKi_{a2C}.

Table 3

Cross-correlation (off-diagonal values) and partial correlation coefficients (last raw) for regression (3)

	RDF055p	IC3	GATS5v	MoR32v	R5p
RDF055p	1.000				
IC3	0.542	1.000			
GATS5v	-0.217	-0.298	1.000		
MoR32v	-0.201	-0.312	0.298	1.000	
R5p	0.535	0.399	-0.295	-0.176	1.000
pKi_{a2C}	0.664	0.673	-0.599	-0.614	0.646

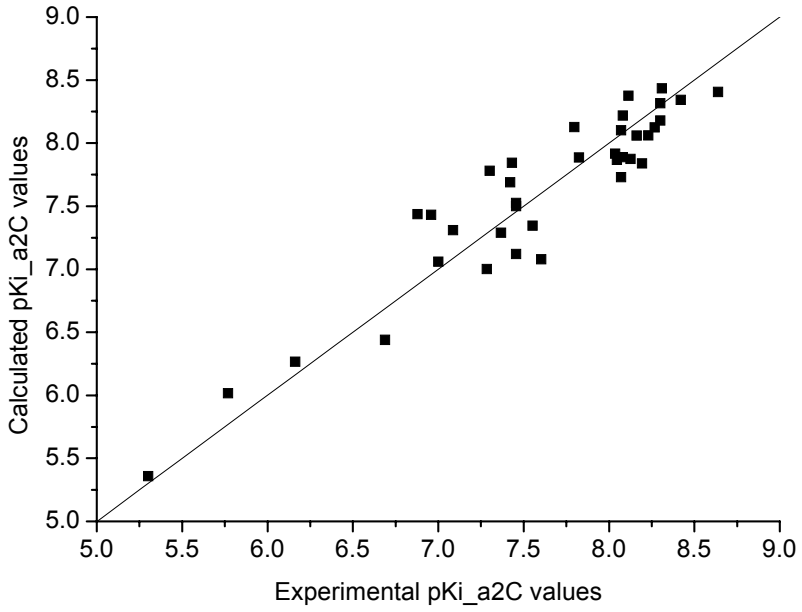


Fig. 1 – Plot of experimental versus pKi_{a2C} values calculated with regression (3).

For validating a model, beside the correlation coefficient, Fisher test, and standard error of estimation, an important test is the cross-validation. The leave-one-out cross-validation coefficient, r^2cv_{LOO}, for the regression (3) is 0.860 and the prediction error sum of squares, press, is 3.012.

Another validation test is the internal validation. The 36 compounds were divided in a learning set of 30 compounds and a test set of 6 compounds. Two variants of dividing the 36 compounds were tested. In the first variant, the learning set contained compounds with the extreme pKi values. Next compounds to those with maximum variance were chosen for the test set. Thus, the pKi variance in the learning set is between 5.3 and 8.64 and in the test set between 5.77 and 8.42, respectively. In this variant, compounds 1, 3, 17, 30, 34, 39 were chosen in the test set. In the second variant the learning set contained compounds with pKi values between 5.77 and 8.64, while the test set contained compounds with pKi values between 5.3 and 8.42. In the second variant the test set contained compounds 6, 10, 11, 28, 32, 34. For the first learning set the following regression was obtained:

pKi_{a2C}=0.72168(0.31176)IC3
-4.18857(1.34271)GATS5v
+0.11300(0.04813)RDF055p
-3.36333(0.72471)MoR32v
+5.55134(1.82821)R5p
+2.81379(2.19384) (4)
n=30 r²=0.860 r²adj=0.831 s=0.294 F=29.55
$r^2_{cv(LOO)}$=0.601 press=5.916 SDEP=0.444
Spress=0.496

The regression resulted from the second learning set is:
pKi_{a2C}=0.84856(0.31535)IC3
-4.05516(1.25351)GATS5v
+0.11127(0.03833)RDF055p
-3.23879(0.73442)MOR32v
+4.93525(1.72535)R5p
+2.47879(1.93796) (5)

n=30 r^2= 0.855 r^2_{adj}= 0.825 s = 0.286 F=28.28
$r^2_{cv(LOO)}$=0.783 press=2.928 SDEP=0.312
Spress=0.349

The differences between the experimental and calculated pKi values using the regressions (4) and (5) are in experimental error limits (Table 4). The statistical and validation tests applied to regression (3) suggest that this regression is not obtained by chance correlation and it can be used in designing new compounds of the quinoline class with affinity and selectivity for the alpha2C-AR subtype.

Table 4

Predicted (pred) pKi_{a2C} and residuals towards experimental (exp) pKi_{a2C} for test compounds

Regression (4)				Regression (5)			
No	Exp	Pred	Residual	No	Exp	Pred	Residual
1	7.553	7.314	0.238	6	7.284	7.086	0.198
3	5.770	5.751	0.019	10	5.301	5.285	0.016
17	8.114	8.267	-0.154	11	6.959	7.331	-0.372
30	7.086	7.143	-0.057	28	7.796	8.029	-0.233
34	8.420	8.255	0.165	32	8.071	8.147	-0.076
39	6.688	6.541	0.147	34	8.420	8.241	0.180

Descriptors of regression (3) encode properties related to atomic van der Waals volumes and polarizabilities, thus suggesting that beside the molecular dimension and conformation, the electrostatic properties are important for the binding affinity of the quinoline derivatives to the alpha2C-AR.

CONCLUSIONS

A set of 1171 descriptors have been tested in multiple linear regressions for binding affinities of 43 quinoline derivatives towards alpha2A-, alpha2B-, and alpha2C-AR subtypes.

Correlations resulted for pKi alpha2A-AR, although with low significance, suggest that the binding affinities of quinoline derivatives to alpha2A-AR are influenced by the molecular shape (ICR), aromaticity and the number of multiple bonds.

For pKi alpha2B, significant correlations have been obtained with topologic descriptors (HVcpx), comparative molecular moments analysis descriptors (QZZM), Randič molecular profile descriptors (DP02 - DP05), subsets of radial distribution functions (RDF) and 3D-MoRSE descriptors. These descriptors can be associated with other topological descriptors or with 2D-autocorrelation, functional group descriptors, van der Waals area or solvent accessible area or volume. The best regressions containing RDF descriptors weighted by atomic masses and unmediated 3D MoRSE descriptors indicate that the binding affinity of quinoline derivatives to alpha2B-AR depends on molecular shape (RDF) and conformation (MoRSE).

pKi alpha2C, which has a variance over three log units, can be modeled by many multiple linear regressions. The best regression obtained after eliminating outliers contains five descriptors: a topological index, IC3, a 3D-MoRSE descriptor, MoR32v, a GETAWAY descriptor R5p, a 2D-autocorrelation descriptor, GATS5v, and a RDF descriptor, RDF055p. These descriptors suggest that the binding affinity of quinoline derivatives to alpha2C-AR depends on molecular conformation and electrostatic properties.

Supplementary Information contains correlation coefficients of all monoparametric regressions, values of descriptors, cross correlation coefficients and residuals (pKi_exp – pKi_calc) for regressions (1-3).

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