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Supplementary Material

Mutagenicity of *N*-acyloxy-*N*-alkoxyamides – QSAR determination of factors controlling activity

Stephen A. Glover[A,*]

[A]Department of Chemistry, School of Physical Sciences, University of New England, NSW 2350, Australia

*Correspondence to: Email: sglover@une.edu.au

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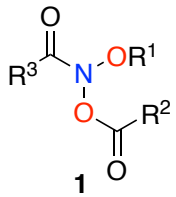
Stephen A. Glover

Chemistry Department, School of Science and Technology, University of New England, Armidale New South Wales 2351, Australia.

Supplementary Data

Table 1. QSAR parameters Log*P*, pK_A, E_S^1, E_S^2, E_S^3, *I* and Log TA100 data for *N*-acyloxy-*N*-alkoxyamides used in derivation of Eqn. 3, 4, 6, 7 and 10.[a]



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	R^1, R^2, R^3	Log*P*[b]	pK_A[c]	E_S^1[d]	E_s^2[e]	E_S^3[f]	*I*[g]	LogTA100[h]
1	Et, Me, Ph	1.54	4.76	0	0	0	0	2.49
2	Pr, Me, Ph	2.02	4.76	0	0	0	0	2.53
3	Oct, Me, Ph	4.11	4.76	0	0	0	0	2.88
4	Pr^i, Me, Ph	1.86	4.76	0	0	0	0	2.40
5	Bu, Me, Ph	2.44	4.76	0	0	0	0	2.50
6	Bu, Me, (4-MeO)Ph	2.32	4.76	-0.55	0	0	0	2.73
7	Bu, Me, (4-Ph)Ph	4.12	4.76	-2.41	0	0	0	2.92
8	Bu, Me, (4-Me)Ph	2.93	4.76	-1.24	0	0	0	2.48
9	Bu, Me, (4-Cl)Ph	3.00	4.76	-0.97	0	0	0	2.54
10	Bu, Me, (4-Br)Ph	3.27	4.76	-1.16	0	0	0	2.69
11	Bu, Me, (4-NO_2)Ph	2.48	4.76	-1.76	0	0	0	2.16
12	Bu, Me, (3-NO_2)Ph	2.48	4.76	0	0	0	0	2.45
13	Bu, Me, (4-Bu^t)Ph	4.15	4.76	-2.78	0	0	0	2.37
14	Bn, Me, Ph	2.93	4.76	0	0	0	0	2.63
15	(4-MeO)Bn, Me, Ph	2.81	4.76	0	-0.55	0	0	2.70
16	(4-PhO)Bn, Me, Ph	3.96	4.76	0	-0.55	0	0	3.06
17	(4-Ph)Bn, Me, Ph	4.61	4.76	0	-2.41	0	0	3.09
18	(4-Me)Bn, Me, Ph	3.42	4.76	0	-1.24	0	0	2.78
19	(4-Cl)Bn, Me, Ph	3.49	4.76	0	-0.97	0	0	2.76

20	(4-Br)Bn, Me, Ph	3.76	4.76	0	-1.16	0	0	2.74
21	(4-Bu^t)Bn, Me, Ph	4.64	4.76	0	-2.78	0	0	2.60
22	Bn, Ph, Ph	4.83	4.20	0	0	0	0	3.22
23	Bn, (4-MeO)Ph, Ph	4.70	4.31	0	0	-0.55	0	3.06
24	Bn, (4-Ph)Ph, Ph	6.51	4.21	0	0	-2.41	0	3.70
25	Bn, (4-Me)Ph, Ph	5.32	4.37	0	0	-1.24	0	3.29
26	Bn, (4-Cl)Ph, Ph	5.39	3.99	0	0	-0.97	0	3.12
27	Bn, (4-CHO)Ph, Ph	4.58	3.73	0	0	-1.01	0	2.87
28	Bn, (4-CN)Ph, Ph	4.86	3.55	0	0	-0.51	0	2.96
29	Bn, (4-NO_2)Ph, Ph	4.86	3.42	0	0	-1.76	0	2.69
30	Bn, (4-Bu^t)Ph, Ph	6.54	4.35	0	0	-2.78	0	3.20
31	Bn, (3-NO_2)Bn, Ph	4.86	3.45	0	0	0	0	2.94
32	Bn, (3-MeO)Bn, Ph	4.70	4.09	0	0	0	0	3.23
33	-$(CH_2)_6$-, Me, Ph	3.55	4.76	0	0	0	0	2.96
34	Bu, Ph, Ph	4.34	4.20	0	0	0	0	2.70
35	Bu, Me, Me	0.54	4.76	0	0	0	0	1.94
36	Bu, Ph, Me	2.44	4.20	0	0	0	0	2.65
37	Bn, Me, Me	1.04	4.76	0	0	0	0	2.22
38	Bn, Ph, Me	2.93	4.20	0	0	0	0	2.90
39	(2,6-diMe)Bn, Me, Ph	3.91	4.76	0	0	0	0	3.04
40	Bu, Me, (3,5-diMe)Ph	3.42	4.76	0	0	0	0	2.74
41	Bn, Ph, (4-Bu^t)Ph	6.54	4.20	-2.78	0	0	0	3.50
42	(4-Bu^t)Bn, Ph, Ph	6.54	4.20	0	-2.78	0	0	3.05
43	(4-Bu^t)Bn, Me, (4-Bu^t)Ph	6.31	4.76	-2.78	-2.78	0	0	2.89
44	2-Bu, Me, Ph	2.07	4.76	0	0	0	0	2.59
45	Bu^t, Me, Ph	2.34	4.76	0	0	0	0	2.47
46	(2-Me)Bn, Me, Ph	3.42	4.76	0	0	0	0	2.71
47	(3-Me)Bn, Me, Ph	3.42	4.76	0	0	0	0	2.86
48	(3,5-diMe)Bn, Me, Ph	3.91	4.76	0	0	0	0	2.95
49	Bu, (4-Me)Ph, Ph	4.83	4.37	0	0	-1.24	0	2.91
50	Bu, (4-MeO)Ph, Ph	4.21	4.47	0	0	-0.55	0	2.87
51	Bu, Me, 2-Np	3.44	4.76	0	0	0	1	3.59
52	Bu, 2-Np, Me	3.44	4.16	0	0	0	1	3.64
53	Bu,2-NpCH_2, Me	3.38	4.24	0	0	0	1	3.4
54	Bu, 2-Np$(CH_2)_2$, Me	3.8	4.57	0	0	0	1	3.46
55	1-NpCH_2, Me, Me	2.03	4.76	0	0	0	1	3.53
56	2-NpCH_2, Me, Me	2.03	4.76	0	0	0	1	3.57
57	2-Np$(CH_2)_2$, Me, Me	2.31	4.76	0	0	0	1	3.41
58	2-Np$(CH_2)_3$, Me, Me	2.73	4.76	0	0	0	1	3.48
59	Bu, Me,1-Fl	4.18	4.76	0	0	0	0	2.71
60	Bu, 1-Fl, Me	4.18	4.11	0	0	0	0	3.04

61	Bu, 4-Fl, Me	4.18	3.97	0	0	0	0	3.05
62	Bu, Me, 2-Fn	3.29	4.76	0	0	0	1	3.37
63	Bu, 1-Fn, Me	3.29	3.48	0	0	0	1	3.57
64	Bu, Me, 4-Fn	3.29	4.76	0	0	0	0	2.62
65	Bu, 2-Fn, Me	3.29	3.85	0	0	0	0	2.64
66	Bu, 4-Fn, Me	3.29	3.46	0	0	0	0	2.57
67	Bu, Pr, Ph	3.51	4.82	0	0	0	0	2.56
68	Hexyl, Pentyl, Ph	5.18	4.86	0	0	0	0	3.42
69	Heptyl, Hexyl, Ph	6.02	4.78	0	0	0	0	3.25
70	Octyl, Heptyl, Ph	6.85	4.78	0	0	0	0	3.02
71	Nonyl, Octyl, Ph	7.69	4.78	0	0	0	0	2.95
72	Decyl, Nonyl,Ph	8.52	4.79	0	0	0	0	2.88
73	Octyl, Heptyl, 2-Np	7.85	4.78	0	0	0	0	3.00

[a] Data for structures 1-50 used for Eqn. 3; 1-58 used for Eqn. 6, 1-67 used for Equation 10; 1-50 with 68-72 used for bilinear Eqn. 4; 1-58 with 68-72 used for bilinear Eqn. 7.

[b] Log *P* calculated according to Ghose-Crippen;

[c] pK_A of the carboxylic acid corresponding to the acyloxyl group;

[d] E_s^1 Taft steric parameter for *para* –substituent on a benzamide side chain;

[e] E_s^2 Taft steric parameter for *para* –substituent on a benzyloxyl side chain;

[f] E_s^3 Taft steric parameter for *para* –substituent on a benzoyloxyl side chain;

[g] Indicator variable *I*=1 for mutagens bearing intercalating PAH otherwise 0;

[h] Experimental LogTA100 ($\log_{10}$[induced revertants at 1μmol/plate]).

1. Regression analysis for Table entries 1-50 of Supplementary Table 1 — linear Eqn. 3.

Regression Statistics	
Multiple R	0.89262161
R Square	0.79677334
Adjusted R^2	0.7736794
Standard Error	0.15722872
Observations	50

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	5	4.26452373	0.85290475	34.5014054	3.6368E-14
Residual	44	1.08771827	0.02472087		
Total	49	5.352242			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	1.02256821	0.41453685	2.46677276	0.0175985	0.1871241	1.85801233	0.1871241	1.85801233
Log*P*	0.27993978	0.02697906	10.3761875	2.1127E-13	0.22556706	0.33431251	0.22556706	0.33431251
pKa	0.1838004	0.07986506	2.30138693	0.02616442	0.02284295	0.34475784	0.02284295	0.34475784
Es1	0.13415203	0.0325755	4.1181881	0.00016549	0.06850043	0.19980363	0.06850043	0.19980363
Es2	0.15011275	0.0373256	4.02171069	0.00022346	0.07488796	0.22533755	0.07488796	0.22533755
Es3	0.1072062	0.04987034	2.14969868	0.03711663	0.00669914	0.20771326	0.00669914	0.20771326

$$\text{LogTA100} = 1.02\ (\pm 0.41) + 0.28\ (\pm 0.03)\log P + 0.18\ (\pm 0.08)\text{p}K_a + 0.13\ (\pm 0.03)E_s^1 + 0.15\ (\pm 0.04)E_s^2 + 0.11\ (\pm 0.05)E_s^3 \quad (3)$$

$n = 50, r = 0.89, s = 0.16, F = 34, \text{LOOCV } Q^2 = 0.70$

2. Regression analysis for Table entries 1-50 with 68-72 of Supplementary Table 1 — bilinear Eqn. 4.

Regression Statistics	
Multiple R	0.86361164
R Square	0.74582507
Adjusted R Sq	0.7140532
Standard Erro	0.17809047
Observations	55

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	6	4.46711248	0.63815893	19.7017174	9.8214E-13
Residual	48	1.52237843	0.03239103		
Total	54	5.98949091			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	1.46266824	0.41072345	3.56119975	0.00084522	0.63685341	2.28848307	0.63685341	2.28848307
LogP	0.24345135	0.02461222	9.89148238	3.6159E-13	0.19396516	0.29293754	0.19396516	0.29293754
Log(BP+1)	-0.6665206	0.12099345	-5.5087327	1.3982E-06	-0.9097942	-0.4232469	-0.9097942	-0.4232469
pKa	0.10693304	0.08129531	1.31536536	0.19463599	-0.0565221	0.27038821	-0.0565221	0.27038821
ES1	0.08812842	0.03351647	2.62940659	0.011458	0.02073905	0.15551779	0.02073905	0.15551779
ES2	0.09193746	0.03673316	2.50284609	0.01577745	0.01808048	0.16579444	0.01808048	0.16579444
ES3	0.02196228	0.05028411	0.43676381	0.6642412	-0.0791407	0.12306526	-0.0791407	0.12306526

$\text{LogTA100} = 0.243\ (\pm 0.02)\ \text{Log}P - 0.667\ (\pm 0.12)\ \text{Log}(\beta P + 1) + 0.107\ (\pm 0.08)\ pK_A + 0.088\ (\pm 0.03)\ E_S^1 + 0.091\ (\pm 0.04)\ E_S^2 + 0.022\ (\pm 0.05)\ E_S^3 + 1.463\ (\pm 0.41)$

$\text{Log}\beta = -6.639,\ n = 55,\ R^2 = 0.7458,\ \text{Adj. } R^2 = 0.714,\ s = 0.18,\ F = 19.7017$ (4)

3. Regression analysis for Table entries 1-58 of Supplementary Table 1 — Linear Eqn. 6.

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.921933905
R Square	0.849962125
Adjusted R^2	0.832310611
Standard Error	0.16202119
Observations	58

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	6	7.58424722	1.2640412	48.1523621	2.6258E-19
Residual	51	1.33879416	0.02625087		
Total	57	8.92304138			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	1.118776251	0.41240451	2.71281282	0.00907408	0.29083966	1.94671284	0.29083966	1.94671284
Log*P*	0.26194125	0.02691708	9.7314154	3.2364E-13	0.20790297	0.31597953	0.20790297	0.31597953
pK_a	0.174568394	0.07933588	2.20037135	0.03233554	0.01529498	0.33384181	0.01529498	0.33384181
E_s^1	0.12494227	0.03334112	3.74739243	0.00045642	0.05800718	0.19187737	0.05800718	0.19187737
E_s^2	0.135844783	0.03802586	3.57243179	0.000783	0.05950469	0.21218488	0.05950469	0.21218488
E_s^3	0.083226995	0.05058788	1.64519633	0.1060797	-0.0183324	0.1847864	-0.0183324	0.1847864
I	0.829293849	0.06437014	12.883208	1.1647E-17	0.70006541	0.95852229	0.70006541	0.95852229

Log TA100 = 0.26 (±0.03) Log$P$ + 0.17 (±0.08) pK_A + 0.12 (±0.03) E_S^1 + 0.14 (±0.04) E_s^2 + 0.08 (±0.05) E_S^3 + 0.83 (±0.06) I + 1.12 (±0.41) (6)

n = 58, R^2 = 0.85, adj. R^2 = 0.83, s = 0.16, F = 48.2; LOO CV Q^2 = 0.85

4. Regression analysis for Table entries 1-58 with 68-72 of Supplementary Table 1 — bilinear Eqn. 7.

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.90213051
R Square	0.81383946
Adjusted R^2	0.7901463
Standard Error	0.17770552
Observations	63

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	7	7.59303949	1.08471993	34.3491318	7.0867E-18
Residual	55	1.73685892	0.03157925		
Total	62	9.32989841			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	1.48587254	0.39687319	3.74394791	0.00043504	0.6905209	2.28122417	0.6905209	2.28122417
Log$P$	0.23082845	0.02381244	9.69360697	1.681E-13	0.18310725	0.27854965	0.18310725	0.27854965
Log(βP+1)	0.65178502	0.12363469	5.27186185	2.3337E-06	0.40401556	0.89955448	0.40401556	0.89955448
pK_A	0.11079818	0.07836737	1.4138306	0.1630472	-0.0462535	0.26784989	-0.0462535	0.26784989
E_S^1	0.08549174	0.03342251	2.55790886	0.01331587	0.01851153	0.15247195	0.01851153	0.15247195
E_s^2	0.08600219	0.03654818	2.35311799	0.02221999	0.01275799	0.15924639	0.01275799	0.15924639
E_S^3	0.00938502	0.04966188	0.1889784	0.85080538	-0.0901396	0.10890966	-0.0901396	0.10890966
I	0.84547887	0.07033057	12.0214994	5.0994E-17	0.70453327	0.98642448	0.70453327	0.98642448

LogTA100 = 0.23 (±0.02) Log$P$ - 0.65 (±0.12) Log(βP + 1) + 0.11 (±0.08) pK_A + 0.09 (±0.03) E_S^1 + 0.09 (±0.04) E_S^2 + 0.01 (±0.05) E_S^3 + 0.85 (±0.07) I + 1.48 (±0.40) (7)

Logβ = -6.705, n = 63, R^2 = 0.81, adj. R^2 = 0.79, s = 0.18, F = 29.6; LOO CV Q^2= 0.76

5. Regression analyses for entries 1-67 of Supplementary Table 1 — Eqn. 10.

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.9139022

R Square	0.835217231
Adjusted R Square	0.818738954
Standard Error	0.166071815
Observations	67

ANOVA

	df	*SS*	*MS*	*F*	*Significance F*
Regression	6	8.38746584	1.39791097	50.6859567	1.1271E-21
Residual	60	1.65479087	0.02757985		
Total	66	10.0422567			

	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	1.546117772	0.32308669	4.78545801	1.152E-05	0.89984818	2.19238737	0.89984818	2.19238737
Log*P*	0.240729006	0.02528326	9.52128198	1.324E-13	0.19015496	0.29130305	0.19015496	0.29130305
pK_A	0.090803585	0.06149222	1.47666783	0.14499429	-0.0321992	0.21380634	-0.0321992	0.21380634
E_S^1	0.104256863	0.03290904	3.16803148	0.00241455	0.03842899	0.17008474	0.03842899	0.17008474
E_s^2	0.10968138	0.03710353	2.95609041	0.00444871	0.03546328	0.18389948	0.03546328	0.18389948
E_S^3	0.063736289	0.049411	1.28992103	0.20202778	-0.0351004	0.16257301	-0.0351004	0.16257301
I	0.830247229	0.05921779	14.0202328	1.3655E-20	0.71179401	0.94870045	0.71179401	0.94870045

Log TA100 = 0.24 (±0.03) Log*P* + 0.09 (±0.06) pK_A + 0.10 (±0.03) E_S^1 + 0.11 (±0.04) E_s^2 + 0.06 (±0.05) E_S^3 + 0.83 (±0.06) *I* + 1.55(±0.32) 10)

n = 67, R^2 = 0.84, adj. R^2 = 0.82, s = 0.17, F = 50.7, LOOCV Q^2 = 0.83