Supporting Information:

Figure SI-1

Raw data evaluation and primary data evaluation in Kinspec

SI-2

Equations for transforming nominal concentrations to aqueous and membrane concentrations

Figure SI-3

Structures of 35 uncouplers used in this study.

SI-4

Equations of nonlinear model implemented in the R environment and language

SI-5

Additional experimental data used to select descriptor calculation methods.

SI-6

A) SMILES-Code of structures of Table 1
B) SMILES-Code of structures of SI-5
The SMILES are codes as unique smiles as implemented in Cactvs (Manual and free academic versions under http://www.xemistry.com/). The 3D-structures from the DFT-studies are available from the authors upon request.

SI-7

Calculated descriptors of 35 uncouplers.

SI-8

Plots of regression models R2-R6 for EC_w with training set (circles) and test set (triangles).

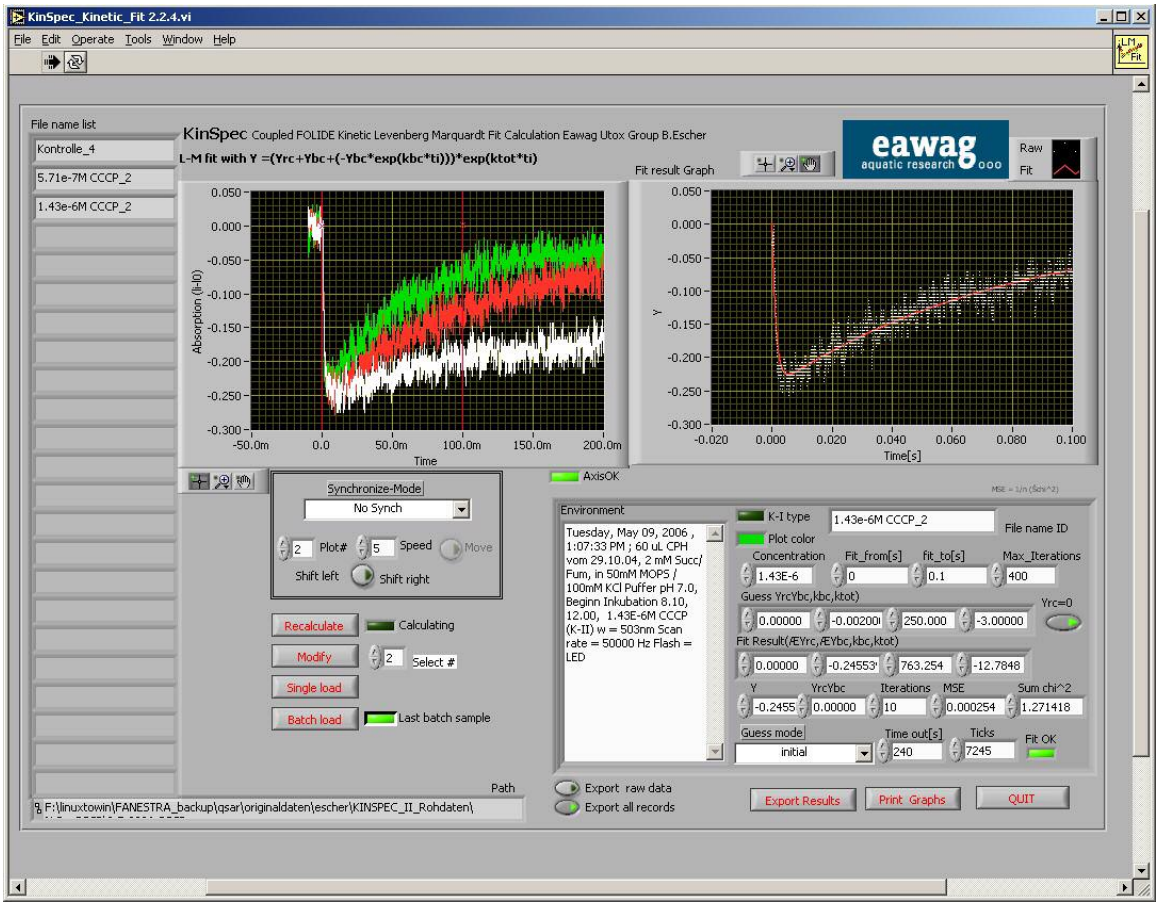
SI-9

Plots of regression models R7-R10 for EC_{tot} with training set (circles) and test set (triangles). The plots of models R8-R10 show all 35 compounds used in this study.

SI-10

Predicted versus experimental EC_w for nonlinear model.

Figure SI-1



Left hand side: Plot of typical membrane decay in Kinspec experiment for the control (white curve), EC_{tot} = 0.57 µl (red curve) and EC_{tot} = 1.43 µl (green curve).

The changes in the membrane potential, are proportional to an electrochromic shift of the absorption band of the carotenoids in the light-harvesting antennae. After a flash of light the potential builds up rapidly and the subsequent decay of the potential is measured and evaluated over 0.1ms using the following equation

$$Y = \Delta Y_{rc} + \Delta Ybc_1 - (\Delta Ybc_1 \cdot \exp(kbc_1 \cdot t)) \cdot \exp(k_{tot} \cdot t)$$

In all evaluations ΔYrc and ΔYbc_1 were combined and refer to the build-up of the initial membrane potential after the flash and the electronic filtering of the signal, kbc_1 is the rate of potential build-up, k_{tot} is a pseudo-first-order decay constant of the potential and t is the time. The right hand side of the Figure shows the fitted curve for EC_{tot} = 1.43 µl. The $k_{uncoupling}$ for a given concentration is obtained by subtracting the k_{tot} of the control from the k_{tot} at this given concentration.

SI-2

The effect concentrations determined with in vitro test systems generally are nominal concentrations. This means, one has only data of the total concentration EC_{tot} in the system and not measured aqueous concentrations, EC_w nor measured concentrations in the membrane, EC_m. However, EC_m and EC_w can be derived from EC_{tot} if the system is in equilibrium and the partition coefficients between aqueous phase and membrane are known. The absolute values of EC_w can be orders of magnitude lower than EC_{tot}, especially in case of very hydrophobic compounds with high fractions of the compound partitioned into the membrane. However, they are in most cases well correlated, i.e., for the 25 compounds used for the models for EC_w the aqueous concentration correlates with EC_{tot} with an r^2 of 0.93 and the *sd* would be 0.42. Nevertheless, modeling the activity under the assumption that EC_w and EC_{tot} are equal would be an additional source of error and would lead to misleading coefficients in regression models which can easily be avoided using the formulas derived below.

As EC_w is just one specific concentration, i.e., the endpoint in vitro test system Kinspec, the general notation of concentrations will be use here. For the concentration of a compound in water this will be C_{tot_w} (referring to EC_w) and for the concentration in the membrane C_{tot_m} (referring to EC_m).

Speciation in the Aqueous Phase (w): The dissociation of an acid in aqueous solution can be written as

$$HA_w \underset{\leftarrow}{\overset{\rightarrow}{}} H^+ + A^- \quad \text{SI-2.1}$$

where HA_w presents the neutral form, A_w^- the acid anion and H^+ the aqueous hydrogen ion.

Following the notation used in similar studies (*1,2*) the representation of the positive charge of the proton and the negative charge of the acid anion will be omitted in this section from now on.

The mass law expression for the reaction in water is

$$K_{aq} = \frac{C_{A_w} \cdot a_H}{C_{HA_w}} \quad \text{SI-2.2}$$

where C_{A_w} and C_{HA_w} [mol·L^{-1}] represent the concentrations of A and HA in the aqueous phase and a_H the hydrogen activity. The total concentration of toxicant in the aqueous phase C_{tot_w} is defined by

$$C_{tot_w} = C_{HA_w} + C_{A_w} \quad \text{SI-2.3}$$

Concentration and Speciation in the Membrane (m): Both species HA and A partition between the aqueous phase and the membrane phase. This effect can be described by the membrane-water partition coefficients of the neutral species and the anion, $K_{mw,HA}$ and $K_{mw,A}$ and the mass law equations for the partitioning processes are

$$K_{mw,HA} = \frac{C_{HA_m}}{C_{HA_w}} \quad \text{SI-2.4}$$

$$K_{mw,A} = \frac{C_{A_m}}{C_{A_w}} \qquad \text{SI-2.5}$$

where C_{HA_m} and C_{A_m} are the concentrations of the neutral species and of the anion, respectively, in the membrane phase. As in the aqueous phase C_{tot_m} is defined by

$$C_{tot_m} = C_{HA_m} + C_{A_m} \qquad \text{SI-2.6}$$

Mass balance: In a system containing water and a given mass of membranes the total concentration of a weak acid is

$$C_{tot} = C_{tot_m} \cdot [m] + C_{tot_w} \qquad \text{SI-2.7}$$

where [m] is the mass to volume ratio given by m_{lip}/V_w. The concentration in the membrane C_{tot_m}, or EC_m in the case of the effect concentration, are given in units of mol per kg phospholipid in the membrane and [m] takes the unit of g phospholipid per liter given in Table 1 of the paper. For a given pH and a given total concentration in the system it is now possible to calculate the concentration of each species in each compartment using the mass law expressions of Equations SI-2.2, SI-2.4, and SI-2.5 and the mass balance of Equation SI-2.7. In other words it is necessary to know – or in the case of a QSAR model to estimate – a compounds pK_a and the membrane-water partition coefficients of both neutral species and anion, $K_{mw,HA}$ and $K_{mw,A}$.

As an example the equation for the total concentration of acid in the membrane, C_{tot_m} (or EC_m in the case of the toxic effect concentration) is subsequently derived. Equation SI-2.6 is transformed into an expression containing only C_{HA_w} by combining Equations SI-2.4, SI-2.5, and SI-2.2

$$C_{tot_m} = C_{HA_m} + C_{A_m} = K_{mw,HA} \cdot C_{HA_w} + K_{mw,A} \cdot C_{A_w} = K_{mw,HA} \cdot C_{HA_w} + K_{mw,A} \cdot C_{HA_w}/a_H \qquad \text{SI-2.8}$$

In order to arrange the formulas in a clearer form the notion of the fraction of the neutral species, f_{HA} and the charged species, f_A present in the aqueous phase at a given pH are introduced

$$f_{HA_w} = \frac{C_{HA_w}}{C_{tot_w}} = \frac{C_{HA_w}}{C_{HA_w} + C_{A_w}} = \frac{1}{1 + 10^{pH - pK_a}} \qquad \text{SI-2.9}$$

$$f_{A_w} = \frac{C_{A_w}}{C_{tot_w}} = \frac{C_{A_w}}{C_{HA_w} + C_{A_w}} = \frac{1}{1 + 10^{pK_a - pH}} = 1 - f_{HA_w} \qquad \text{SI-2.10}$$

Using the notion of species fractions Equation SI-2.8 can then be rewritten as

$$C_{tot_m} = C_{HA_w} \cdot (K_{mw,HA} + K_{mw,A} \cdot (\frac{1}{f_{HA_w}} - 1)) \qquad \text{SI-2.11}$$

Then, the mass balance of Equation SI-2.7 is used to substitute C_{HA_w} with the total concentration of toxicant in the system, C_{tot} using the relationship

$$C_{HA_w} = \frac{C_{tot}}{[m] \cdot (K_{mw,HA} + K_{mw,A} \cdot \frac{f_{A_w}}{f_{HAw}}) + \frac{1}{f_{HA_w}}} \qquad \text{SI-2.12}$$

and putting it into the Equation SI-2.11 yields the final pH-dependent expression for C_{tot_m}

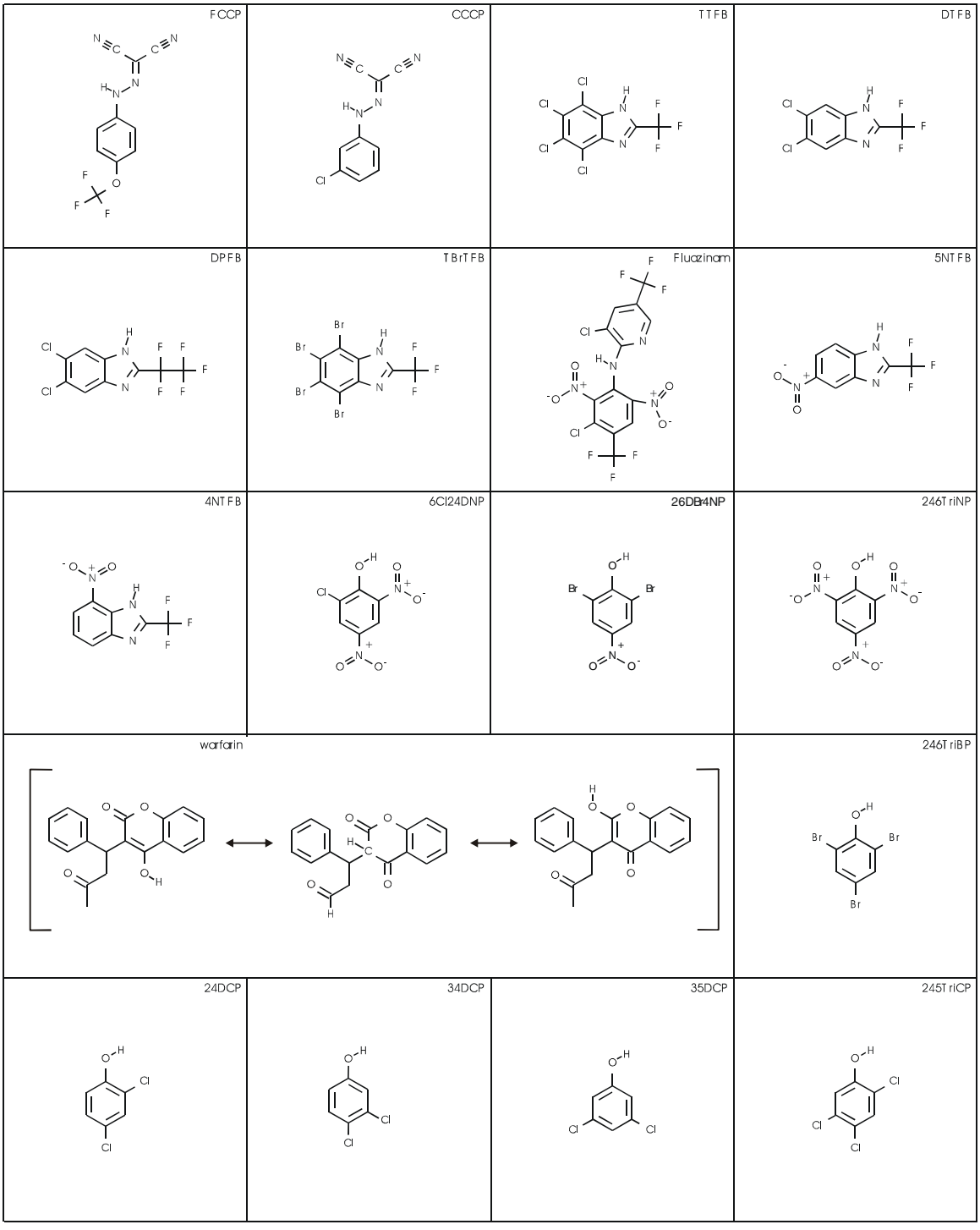
$$C_{tot_m} = \frac{C_{tot}}{[m] + \frac{1}{f_{HA_w} \cdot K_{mw,HA} + f_{A_w} \cdot K_{mw,A}}} = \frac{C_{tot}}{[m] + \frac{1}{D_{mw}}} \qquad \text{SI-2.13}$$

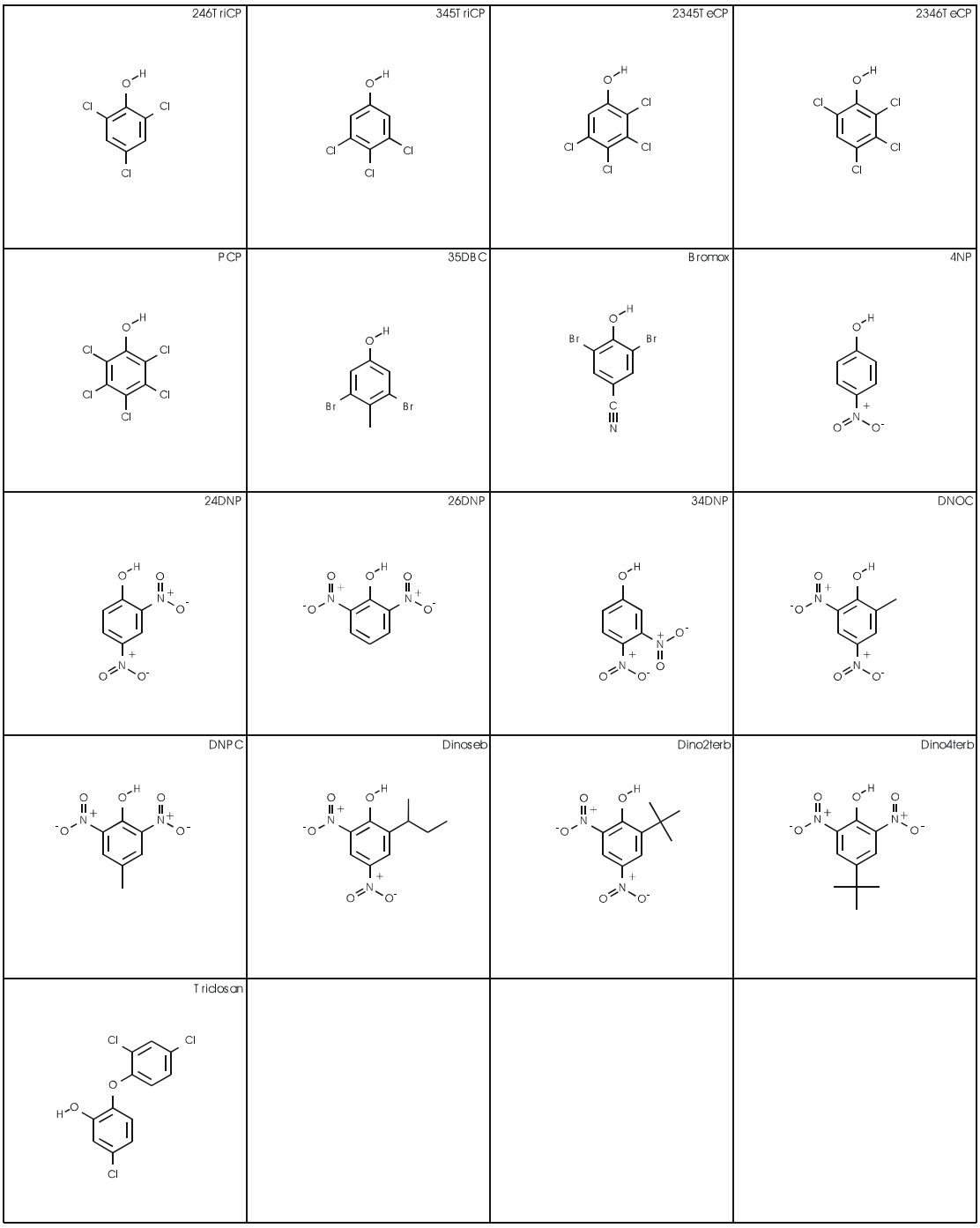
which can be transformed into an expression for C_{tot_w} by using the mass balance of Eq. SI-2.7

$$C_{tot_w} = C_{tot} - [m]\frac{C_{tot}}{[m] + \frac{1}{D_{mw}}} = \frac{C_{tot}}{[m] \cdot D_{mw} + 1} \qquad \text{SI-2.14}$$

(1) Escher, B. I., Hunziker, R., Schwarzenbach, R. P., and Westall, J. C. (1999) Kinetic model to describe the intrinsic uncoupling activity of substituted phenols in energy transducing membranes. *Environ. Sci. Technol. 33,* 560-570.
(2) Escher, B. I., and Schwarzenbach, R. P. (2000) Evaluation of Liposome-Water Partitioning of Organic Acids and Bases. 1. Development of a Sorption Model. *Environ. Sci. Technol. 34,* 3954-3961.

SI-3


FCCP
CCCP
TTFB
DTFB
DPFB
TBrTFB
Fluazinam
5NTFB
4NTFB
6Cl24DNP
26DBr4NP
246TriNP
warfarin
246TriBP
24DCP
34DCP
35DCP
245TriCP



Structures of 35 uncouplers measured in the Kinspec system. The first 14 uncouplers cover the extremely diverse structural range of protonophoric uncouplers measured in this study while the last 21 compounds consist of phenols measured in earlier studies. In the case of warfarin the anion has several tautomers with comparable energies which needed to be considered in the descriptor calculations (cf. Minxia H. *et al.* (1999) Structural forms of phenprocoumon and warfarin that are metabolized at the active site of CYP2C9. *Arch. Biochem. Biophys. 372,* 16–28.).

SI-4

The functions below define the nonlinear equations for the uncoupling process as defined by Escher *et al.* (1999) Environ. Sci. Technol. 33, 560-570. The model is implemented in R (www.R-project.org) a Free Software under the terms of the Free Software Foundation's GNU General Public License.

Function block

```
lambda12 <- function(Ctot, pK.w.a, K.mw.HA, K.mw.A, k.HA, k.A,
k.AHA, lip.conc, K.m.AHA=1, pH=7, Temperature=298) {
  # Definition of constants
    Faraday <- 96485.3383 #coulomb/mole equivalent to s A / mol
    R <-  8.3144 # J mol-1 K-1
    Capacitance <- 8.3e-3 # F m-2, Eq. 24    value taken from Benz, R. and
McLaughlin, S. (1983) Biophys. J. 41, 381-398. Table III
#  Capacitance <- 5.5e-3 # F m-2, Eq. 24    value used by Escher et al. taken from Casadio et al.
(1988) Eur Biophys J, 16, 243-253.
  s <- 7.0e5 # m^2 kg-1  Text after Eq. 18 (value in study of Escher et al. was 4.4e5, but
higher value seems more appropriate, cf. Biophys. J., (2000), 79, 3172-3192.

  # Eq. 14
    Ka_aH <- 10^(-pK.w.a + pH) # Ka / aH
    a <- 2 * K.mw.A * K.mw.HA * Ka_aH  * K.m.AHA * lip.conc #
corrected for Typo
#  a <- 2 * K.mw.HA * Ka_aH  * K.m.AHA * m  #original

    b <- 1 + Ka_aH + K.mw.HA * lip.conc + K.mw.A * Ka_aH *
lip.conc
    d <- - Ctot
    C.w.HA <- (-b + sqrt(b^2 - 4*a*d))/(2*a)

    C.m.HA <- K.mw.HA * C.w.HA      # Eq. 6
    C.w.A <- Ka_aH * C.w.HA       # Eq. 2
    C.m.A <- K.mw.A * C.w.A       # Eq. 7
    C.m.AHA <- K.m.AHA * C.m.HA * C.m.A  # Eq. 9
    C.m.tot <- C.m.HA + C.m.A + 2*C.m.AHA # Eq. 10

    a.m.HA <- C.m.HA / C.m.tot      # Eq. 13
    a.m.A <- C.m.A / C.m.tot       # Eq. 13
    a.m.AHA <- C.m.AHA / C.m.tot     # Eq. 13

    Gamma0 <- (C.m.HA + C.m.A + 2*C.m.AHA) / s # Eqns. 17, 18, 36

    B <- Faraday^2 / (Capacitance * R * Temperature) # Eq. 44

    k.AHA <- k.AHA / K.m.AHA  # see comment i in Table 1of Escher et al.
    k <- c(k.HA, k.A, k.AHA)
    n <- c(1, 1, 2) # HA, A, AHA
```

```
   z <- c(0, -1, -1) # HA, A, AHA
 # Eq. 47:
   alpha <- c(a.m.HA, a.m.A, a.m.AHA)
   t1 <- -2 * sum(n * k * alpha)
   t2 <- B * sum(k * alpha * z^2) * Gamma0
   t3 <- 8 * B * sum(n*k*alpha*z) * sum(k * alpha * z)* Gamma0
   tmp <- sqrt((t1 + t2)^2 + t3)
   0.5 * (t1 - t2 + c(tmp, -tmp))
}


foo2 <- function(x, lambda1crit = 0.5, pK.w.a, K.mw.HA, K.mw.A,
k.HA, k.A, k.AHA, lip.conc, K.m.AHA=1, pH=7, Temperature=298) {
   (-lambda1crit - lambda12(Ctot = x, pK.w.a = pK.w.a, K.mw.HA =
K.mw.HA, K.mw.A = K.mw.A, k.HA = k.HA, k.A = k.A,
                      k.AHA = k.AHA, lip.conc=lip.conc,
K.m.AHA=K.m.AHA, pH=pH, Temperature=Temperature)[1])
}


opttot2ECw <- function(Ctot, pK.w.a, K.mw.HA, K.mw.A, k.HA, k.A,
k.AHA, lip.conc, K.m.AHA=1, pH=7, Temperature=298) {
  # Eq. 14
   Ka_aH <- 10^(-pK.w.a + pH) # Ka / aH
   a <- 2 * K.mw.A * K.mw.HA * Ka_aH  * K.m.AHA * lip.conc #
corrected
#  a <- 2 * K.mw.HA * Ka_aH  * K.m.AHA * m  #original

   b <- 1 + Ka_aH + K.mw.HA * lip.conc + K.mw.A * Ka_aH *
lip.conc
   d <- - Ctot
   C.w.HA <- (-b + sqrt(b^2 - 4*a*d))/(2*a)

   C.m.HA <- K.mw.HA * C.w.HA             # Eq. 6
   C.w.A <- Ka_aH * C.w.HA                # Eq. 2
   C.m.A <- K.mw.A * C.w.A                # Eq. 7
   C.m.AHA <- K.m.AHA * C.m.HA * C.m.A    # Eq. 9
   C.m.tot <- C.m.HA + C.m.A + 2*C.m.AHA # Eq. 10

   C.w.tot <- Ctot - C.m.tot * lip.conc         # Eq. 11
   -log10(C.w.tot)
}
```

Model block

```
# 1. Create data.frame "inp.data.calc" with the following columns:
# names(inp.data.calc) <-
c("Abbr","pK.w.a","K.mw.HA","K.mw.A","k.HA","k.A","k.AHA","lip.co
nc","logECw.meas","logECtot.meas")
# 2. Run the function foo2 (for predicted effect concentrations, ECtot)
# Note: K.m.AHA=1 is used by Escher et al., see middle of left column, p. 565,
```

but lower values of K.m.AHA=1e-04 used here (otherwise C.m.AHA can become very large in Eq. 10)

```
ECtot.mod <- vector(length=nrow(inp.data.calc))
for(i in (1:nrow(inp.data.calc))) {
ECtot.mod[i] <- uniroot(foo2, low = 1e-10, up = 1e-1, tol = 1e-
10, pK.w.a=inp.data.calc$pK.w.a[i],
K.mw.HA=inp.data.calc$K.mw.HA[i], K.mw.A=inp.data.calc$K.mw.A[i],

k.HA=inp.data.calc$k.HA[i], k.A=inp.data.calc$k.A[i],
k.AHA=inp.data.calc$k.AHA[i], lip.conc=inp.data.calc$lip.conc[i],
K.m.AHA=0.0001)$root
}
```

3. Transfor ECtot to ECw with the function opttot2ECw

```
ECw.mod <- vector(length=nrow(inp.data.calc))
for(i in (1:nrow(inp.data.calc))) {
ECw.mod[i] <- opttot2ECw(ECtot.mod[i],
pK.w.a=inp.data.calc$pK.w.a[i],
K.mw.HA=inp.data.calc$K.mw.HA[i], K.mw.A=inp.data.calc$K.mw.A[i],
k.HA=inp.data.calc$k.HA[i],

k.A=inp.data.calc$k.A[i], k.AHA=inp.data.calc$k.AHA[i],
lip.conc=inp.data.calc$lip.conc[i], K.m.AHA=0.0001)
}
```

SI-5

Additional experimental data used to find optimal descriptor calculation methods. The last column to the right (Tr) indicates the division into training (1) and test set (0) which was used to evaluate the models for $K_{mw,HA}$ and K_{mw,A^-}. Only the training set data have been used because further modifications of COSMOmic are planned. In case the readers use these data develop new QSARs for $K_{mw,HA}$ or K_{mw,A^-} it would make sense to keep the same split because it would allow model comparisons. For cations only the partition coefficient of the neutral species (in the column log $K_{mw,HA}$) is given and the original works need to be consulted for the partition coefficients of the charged species, i.e., log K_{mw,HB^+}. The evaluation of the predictive power of the tools for pK_a and log K_{ow} was made with compounds 1-25 of this table plus the 35 compounds of Table 1 of the paper, because these compounds had the strongest structural similarity to uncouplers.

Number	CAS	Compoundname	pKa	s1	logKow	s2	logKm,HA	s3	logKmw,A	Tr
1	312-73-2	2-trifluoromethylbenzimidazole	8.8	a	2.67	b	NA	NA	NA	NA
2	530-78-9	flufenamic acid	4.53	c	5.25	b	NA	NA	NA	NA
3	79-94-7	3,5,3',5'-Tetrabromobisphenol A (TBBPA)	7.5	d	4.8	d	NA	NA	NA	NA
4	2138-22-9	4-chlorocatechol	8.2	e	NA	NA	NA	NA	NA	NA
5	13673-92-2	3,5-dichlorocatechol	7.78	e	NA	NA	NA	NA	NA	NA
6	56961-20-7	3,4,5-trichlorocatechol	6.95	e	3.71	b	NA	NA	NA	NA
7	1198-55-6	tetrachlorocatechol	5.97	e	4.057	e	4.41	e	2.63	0
8	16128-96-4	5-chloro-3-tert-butyl-2'-chloro-4'-nitrosalicylanilide (S-13)	5.8	f	NA	NA	6.44	f	5.05	1
9	95-57-8	2-Chlorophenol	8.56	j	2.15	h	2.79	j	0.92	0
10	87-65-0	2,6-Dichlorophenol	6.97	j	2.64	h	2.87	j	1.43	1
11	106-48-9	4-Chlorophenol	9.38	j	2.39	j	2.96	j	2.51	1
12	103-90-2	acetaminophen	10.1	q	0.46	b	NA	NA	NA	NA
13	15307-86-5	diclofenac	3.99	p	4.51	b	4.45	p	2.64	1
14	57-63-6	ethinylestradiol	NA	NA	3.67	b	4.20	t	NA	1
15	15687-27-1	ibuprofen	4.45	p	3.97	b	3.8	p	1.81	1
16	88-75-5	2-nitrophenol	7.23	h	1.89	h	1.89	j	0.69	1
17	120-80-9	catechol	9.25	e	0.895	e	NA	NA	NA	NA
18	527-54-8	3,4,5-trimethylphenol	10.25	i	NA	NA	2.66	i	NA	1
19	108-95-2	phenol	9.86	o	1.46	b	1.97	g	NA	1
20	14938-35-3	4-n-pentylphenol	NA	NA	4.24	m	4.31	m	NA	1
21	59-50-7	4-chloro-3-methylphenol	9.55	o	3.1	m	3.34	m	NA	0
22	90-43-7	2-phenylphenol	10.01	o	3.09	m	3.46	m	NA	1
23	1745-81-9	2-allylphenol	10.29	o	NA	NA	3.06	m	NA	1

24	2270-20-4	5-phenylvaleric_acid	4.88	k	2.94	b	3.06	k,A	1.08	0
25	69-72-7	salicylic_acid	2.98	s	2.26	b	2.5	s	1.04	0
26	95-51-2	2-chloroaniline	2.661	b	1.91	g	1.53	g		1
27	106-47-8	4-chloroaniline	3.982	b	1.88	g	1.53	g		0
28	439-14-5	diazepam	3.31	s	2.82	b	2.992	s		1
29	525-66-6	propranolol	9.24	s	3.48	b	3.24	s		1
30	95-68-1	3,4-dimethylaniline	5.23	j	1.87	j	2.11	j		1
31	88-05-1	2,4,6-trimethylaniline	4.38	j	2.35	j	2.38	j		0
32	13214-66-9	4-phenylbutylamine	10.54	k	NA	NA	2.41	k		0
33	88150-42-9	amlodipine	9.02	k	NA	NA	3.75	k		1
34	699-04-7	(p-methylbenzyl)methylamine	9.93	r	1.96	r	3.09	r		0
35	39190-96-0	(p-methylbenzyl)propylamine	9.98	r	2.96	r	3.07	r		1
36	170303-38-5	(p-methylbenzyl)pentylamine	10.08	r	4.26	r	3.5	r		0
37	215177-24-5	(p-methylbenzyl)heptylamine	10.02	r	5.12	r	4.4	r		1
38	137-58-6	lidocaine	7.86	s	NA	NA	2.06	s		1
39	94-24-6	tetracaine	8.49	p	3.51	p	3.23	p		1
40	108-90-7	monochlorobenzene	NA	NA	2.98	n	3.00	n	NA	1
41	95-50-1	1,2-dichlorobenzene	NA	NA	3.38	n	3.64	n	NA	1
42	541-73-1	1,3-dichlorobenzene	NA	NA	3.48	n	3.71	n	NA	0
43	106-46-7	1,4-dichlorobenzene	NA	NA	3.38	n	3.57	n	NA	0
44	87-61-6	1,2,3-trichlorobenzene	NA	NA	4.04	n	4.16	n	NA	1
45	120-82-1	1,2,4-trichlorobenzene	NA	NA	3.98	n	4.20	n	NA	1
46	108-70-3	1,3,5-trichlorobenzene	NA	NA	4.02	n	4.32	n	NA	1
47	634-90-2	1,2,3,5-tetrachlorobenzene	NA	NA	4.65	n	4.91	n	NA	1
48	95-94-3	1,2,4,5-tetrachlorobenzene	NA	NA	4.51	n	4.87	n	NA	0
49	608-93-5	pentachlorobenzene	NA	NA	5.03	n	5.26	n	NA	0
50	118-74-1	hexachlorobenzene	NA	NA	5.47	n	5.43	n	NA	1
51	106-37-6	1,4-dibromobenzene	NA	NA	3.89	n	4.30	n	NA	1
52	626-39-1	1,3,5-tribromobenzene	NA	NA	5.26	n	5.21	n	NA	0
53	71-36-3	butanol	NA	NA	0.88	k	0.54	q	NA	1
54	71-41-0	pentanol	NA	NA	1.51	k	1.08	q	NA	1
55	111-27-3	hexanol	NA	NA	2.03	k	1.72	q	NA	1
56	111-70-6	1-heptanol	NA	NA	2.62	k	2.38	q	NA	0
57	111-87-5	octanol	NA	NA	3	k	2.66	q	NA	1
58	96-41-3	cyclopentanol	NA	NA	NA	NA	0.76	q	NA	0
59	108-93-0	cyclohexanol	NA	NA	1.23	k	1.03	q	NA	1
60	502-41-	cycloheptanol	NA	NA	NA	NA	1.27	q	NA	1

61	696-71-9	cyclooctanol	NA	NA	NA	NA	1.61	q	NA	0
62	504-02-9	1,3-cyclohexanedione	NA	NA	NA	NA	0.49	q	NA	0
63	120-92-3	cyclopentanone	NA	NA	NA	NA	0.30	q	NA	1
64	108-94-1	cyclohexanone	NA	NA	0.81	k	0.54	q	NA	1
65	502-42-1	cycloheptanone	NA	NA	NA	NA	0.98	q	NA	0
66	502-49-8	cyclooctanone	NA	NA	NA	NA	1.40	q	NA	1
67	27522-11-8	2-ethyl-1-pentanol	NA	NA	NA	NA	1.81	q	NA	0
68	600-36-2	2,4-dimethyl-3-pentanol	NA	NA	NA	NA	1.71	q	NA	0
69	928-97-2	trans-3-hexen-1-ol	NA	NA	NA	NA	1.23	q	NA	1
70	928-95-0	trans-2-hexen-1-ol	NA	NA	NA	NA	1.36	q	NA	1
71	928-96-1	cis-3-hexen-1-ol	NA	NA	NA	NA	1.20	q	NA	1
72	821-41-0	5-hexen-1-ol	NA	NA	NA	NA	1.20	q	NA	1
73	4938-52-7	1-hepten-3-ol	NA	NA	NA	NA	1.61	q	NA	1
74	3031-66-1	3-hexyne-2,5-diol	NA	NA	NA	NA	-0.22	q	NA	1
75	928-90-5	5-hexyn-1-ol	NA	NA	NA	NA	0.78	q	NA	0
76	5343-92-0	1,2-pentanediol	NA	NA	NA	NA	0.26	q	NA	1
77	111-29-5	1,5-pentanediol	NA	NA	NA	NA	-0.70	q	NA	1
78	625-69-4	2,4-pentanediol	NA	NA	NA	NA	-0.30	q	NA	0
79	6920-22-5	1,2-hexanediol	NA	NA	NA	NA	0.81	q	NA	0
80	928-40-5	1,5-hexanediol	NA	NA	NA	NA	-0.22	q	NA	0
81	629-11-8	1,6-hexanediol	NA	NA	NA	NA	-0.10	q	NA	1
82	629-30-1	1,7-heptanediol	NA	NA	NA	NA	0.32	q	NA	0
83	1117-86-8	1,2-octanediol	NA	NA	NA	NA	1.93	q	NA	1
84	629-41-4	1,8-octanediol	NA	NA	NA	NA	0.81	q	NA	1
85	1460-57-7	trans-1,2-cyclohexanediol	NA	NA	0.08	NA	0.23	q	NA	1
86	42565-22-0	trans-1,2-cyclooctanediol	NA	NA	NA	NA	1.11	q	NA	0
87	123-07-9	4-ethylphenol	10.17	t	2.58	k	2.85	q	NA	0
88	371-41-5	4-fluorophenol	NA	NA	1.77	k	2.32	q	NA	0
89	99-89-8	4-isopropylphenol	NA	NA	2.9	k	3.25	q	NA	1
90	98-54-4	4-tert-butylphenol	NA	NA	3.31	k	3.53	q	NA	1
91	95-48-7	o-cresol	10.24	l	1.97	l	2.45	l	NA	1
92	108-39-4	m-cresol	10.04	l	2.02	l	2.34	l	NA	1

93	106-44-5	p-cresol	10.1	l	1.94	l	2.42	l	NA	1
94	90-00-6	2-ethylphenol	10.16	l	2.47	l	2.81	l	NA	0
95	644-35-9	2-n-propylphenol	10.3	l	2.93	l	3.13	l	NA	1
96	645-56-7	4-n-propylphenol	10.17	l	3.06	l	3.07	l	NA	1
97	89-72-5	2-sec-butylphenol	10.3	l	3.27	l	3.47	l	NA	1
98	99-71-8	4-sec-butylphenol	10.19	l	3.08	t	3.43	l	NA	1
99	88-18-6	2-tert-butylphenol	11.12	l	3.31	l	3.51	l	NA	1
100	585-34-2	3-t-butylphenol	10.08	l	3.31	l	3.25	l	NA	0
101	92-69-3	4-phenylphenol	9.506	l	3.2	l	3.24	l	NA	1
102	80-46-6	4-tert-pentylphenol	10.19	l	3.87	l	3.64	l	NA	1
103	576-26-1	2,6-dimethylphenol	10.58	l	2.3	l	2.47	l	NA	0
104	1006-59-3	2,6-diethylphenol	10.53	l	3.03	l	2.73	l	NA	1
105	108-43-0	3-chlorophenol	8.976	l	2.5	l	2.78	l	NA	1
106	14763-60-1	4-(methylsulfonyl)phenol	7.786	l	0.58	l	1.27	l	NA	1
107	767-00-0	4-hydroxybenzonitrile	7.906	l	1.6	l	2.11	l	NA	1
108	98-17-9	3-(Trifluoromethyl)phenol	8.906	l	2.95	l	3.25	l	NA	1
109	554-84-7	3-nitrophenol	8.356	l	2	l	2.56	l	NA	0
110	4099-71-2	2-ethyl-4,6-dinitrophenol	4.386	l	2.67	l	3.02	l	NA	1
111	118-95-6	2-iso-propyl-4,6-dinitrophenol	4.426	l	3.1	l	3.14	l	NA	1
112	111-76-2	2-butoxyethanol	NA	NA	0.83	m	0.59	m	NA	1
113	6639-30-1	2,4,5-trichlorotoluene	NA	NA	4.78	m	4.77	m	NA	0
114	584-02-1	3-pentanol	NA	NA	1.21	m	0.99	m	NA	0
115	106-42-3	p-xylene	NA	NA	3.15	m	2.98	m	NA	0
116	88-72-2	2-nitrotoluene	NA	NA	2.3	m	2.41	m	NA	0
117	98-95-3	nitrobenzene	NA	NA	1.85	m	2.01	m	NA	1
118	99-09-2	3-nitroaniline	NA	NA	1.37	m	2.17	m	NA	1
119	636-30-6	2,4,5-trichloroaniline	NA	NA	3.69	m	4.16	m	NA	1
120	62-53-3	aniline	4.6	b	0.9	m	1.63	m	NA	1
121	91-22-5	quinoline	4.9	b	2.03	m	1.67	m	NA	1
122	121-69-7	dimethylaniline	5.15	b	2.31	m	2.33	m	NA	0
123	5372-81-6	dimethyl-2-amino-p-phthalate	NA	NA	2.28	m	2.53	m	NA	0
124	42087-80-9	methyl-4-chloro-2-nitrobenzoate	NA	NA	2.35	m	2.45	m	NA	1
125	141-03-7	dibutylsuccinate	NA	NA	3.65	m	2.40	m	NA	1
126	141-28-6	diethyl_adipate	NA	NA	1.8	m	1.66	m	NA	0
127	109-60-4	1-propyl_acetate	NA	NA	1.25	m	1.01	m	NA	0
128	105-53-3	diethylmalonate	NA	NA	1.19	m	0.50	m	NA	1
129	50-28-2	17beta-estradiol	10.23	t	4.01	t	3.79	t	NA	0
130	53-16-7	estrone	10.34	t	3.13	t	3.92	t	NA	0

131	50-27-1	estriol	10.21	t	2.45	t	1.96	t	NA	1
132	104-40-5	4-nonylphenol	10.43	t	5.76	t	5.50	t	NA	1
133	140-66-9	4-tert-octylphenol	10.21	t	NA	NA	5.61	t	NA	1
134	80-05-7	bisphenol A	9.28	t	3.32	t	4.46	t	NA	1
135	85-68-7	butylbenzylphthalate	NA	NA	4.91	t	4.68	t	NA	1
136	84-74-2	1,2-dibutyl-1,2-benzenedicarboxylic_acid-ester	NA	NA	4.57	t	4.19	t	NA	1
137	56-53-1	diethylstilbestrol	9.56	t	5.07	t	4.98	t	NA	1
138	84-16-2	hexestrol	10.34	t	NA	NA	4.58	t	NA	0
139	84-17-3	dienestrol	9.56	t	NA	NA	5.45	t	NA	0
140	94-26-8	butyl-4-hydroxybenzoate	8.92	t	3.57	t	3.54	t	NA	1
141	94-18-8	benzyl-4-hydroxybenzoate	8.94	t	NA	NA	3.84	t	NA	1
142	611-99-4	4,4'-dihydroxybenzophenone		t	NA	NA	2.70	t	NA	1
143	84-66-2	diethylphthalate	NA	NA	2.42	t	1.77	t	NA	1
144	57-83-0	progesterone	NA	NA	3.87	t	3.28	t	NA	1

[a] Ref (*1*). [b] PhysProp-Database (http://www.syrres.com/esc/physdemo.htm) or KowWin-Demo-Database (http://www.syrres.com/esc/kowdemo.htm). [c] pK_a taken as average from refs (*2*) (3.9), (*3*) (3.36), (*4*) (5.0), and (*5*) (5.84). [d] Ref (*6*). Value for K_{ow} questionable [e] Ref (*7*). [f] Ref (*8*) (defined for surface of 0.7 nm^2 per lipid molecule and MW 760 g/mol lipid). [g] Ref (*9*). [h] Ref (*10*). [i] Ref (*11*). [j] Ref (*12*). [k] Ref (*13*). [l] Ref (*14*) (cpds 106, 107, 110, 111 have pK_a less than 2 units away from pH of measurement, but error of assuming $K_{mw} = D_{mw} < 10\%$ in all cases). [m] Ref (*15*). [n] Ref (*16*) (no values with log $K_{ow} > 5.5$ used from this source). [o] SPARC pK_a-Database (http://ibmlc2.chem.uga.edu/sparc/index.cfm). [p] Ref (*17*). [q] Ref (*18*). No description of experimental method used, but six compounds measured in other studies had very small differences (< factor 1.5) [r] Ref (*19*). [s] Ref (*20*). [t] Ref (*21*).

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SI-6 A) and B)

	A)
1	N#CC(C#N)=NNC1=CC=C(OC(F)(F)(F))C=C1
2	N#C\C(=N\NC1=CC(=CC=C1)Cl)C#N
3	ClC1=C2NC(C(F)(F)(F))=NC2=C(Cl)C(Cl)=C1(Cl)
4	C1=C2C(=CC(=C1Cl)Cl)N=C([NH]2)C(F)(F)F
5	ClC1=C(Cl)C=C2C(=C1)N=C([NH]2)C(F)(F)C(F)(F)F
6	BrC1=C(Br)C(=C2C(=C1Br)N=C([NH]2)C(F)(F)F)Br
7	C1=NC(=C(C=C1C(F)(F)F)Cl)NC2=C(C(=C(C=C2[N+](=O)[O-])C(F)(F)F)Cl)[N+](=O)[O-]
8	C1=C2C(=CC(=C1)[N+](=O)[O-])N=C([NH]2)C(F)(F)F
9	C2(=C1[NH]C(=NC1=CC=C2)C(F)(F)F)[N+]([O-])=O
10	C1(=C(C=C(C=C1Cl)[N+]([O-])=O)[N+](=O)[O-])O
11	C1(=C(C=C(C=C1Br)[N+]([O-])=O)Br)O
12	C1(=C(C=C(C=C1[N+](=O)[O-])[N+]([O-])=O)[N+](=O)[O-])O
13	CC(CC(C1=CC=CC=C1)C3=C(O)C2=C(C=CC=C2)OC3=O)=O
14	C1(=C(C=C(C=C1Br)Br)Br)O
15	OC1=C(Cl)C=C(C=C1)Cl
16	ClC1=C(Cl)C=CC(=C1)O
17	ClC1=CC(=CC(=C1)O)Cl
18	ClC1=C(Cl)C=C(O)C(=C1)Cl
19	OC1=C(Cl)C=C(Cl)C=C1Cl
20	ClC1=C(Cl)C=C(O)C=C1Cl
21	OC1=C(Cl)C(Cl)=C(Cl)C(Cl)=C1
22	ClC1=C(Cl)C(=C(Cl)C=C1Cl)O
23	ClC1=C(Cl)C(=C(O)C(=C1Cl)Cl)Cl
24	OC1=CC(Br)=C(C)C(Br)=C1
25	OC1=C(Br)C=C(C#N)C=C1(Br)
26	[O-][N+](=O)C1=CC=C(O)C=C1
27	[O-][N+](=O)C1=CC(=CC=C1O)[N+](=O)[O-]
28	[O-][N+](=O)C1=C(O)C(=CC=C1)[N+](=O)[O-]
29	OC1=CC([N+](=O)[O-])=C([N+](=O)[O-])C=C1
30	[O-][N+](=O)C1=CC(=CC(=C1O)C)[N+](=O)[O-]
31	[O-][N+](=O)C1=C(O)C(=CC(=C1)C)[N+](=O)[O-]
32	CC(CC)C1=C(O)C(=CC(=C1)[N+](=O)[O-])[N+](=O)[O-]
33	CC(C)(C)C1=C(O)C(=CC(=C1)[N+](=O)[O-])[N+](=O)[O-]
34	[O-][N+](=O)C1=C(O)C(=CC(=C1)C(C)(C)C)[N+](=O)[O-]
35	C1(Cl)=CC(Cl)=CC=C1OC2=C(O)C=C(Cl)C=C2

	B)
1	C1=C2C(=CC=C1)N=C([NH]2)C(F)(F)F
2	C1=C(C(=CC=C1)C(=O)O)NC2=CC=CC(=C2)C(F)(F)F
3	C1(=C(C=C(C=C1Br)C(C2=CC(=C(C(=C2)Br)O)Br)(C)C)Br)O

4	OC1=C(O)C=C(Cl)C=C1
5	OC1=C(O)C(Cl)=CC(Cl)=C1
6	OC1=C(O)C(Cl)=C(Cl)C(Cl)=C1
7	ClC1=C(Cl)C(=C(O)C(=C1Cl)O)Cl
8	[O-][N+](=O)C1=CC(Cl)=C(NC(=O)C2=C(O)C(C(C)(C)C)=CC(Cl)=C2)C=C1
9	OC1=C(Cl)C=CC=C1
10	OC1=C(Cl)C=CC=C1Cl
11	OC1=CC=C(Cl)C=C1
12	CC(NC1=CC=C(O)C=C1)=O
13	ClC1=C(NC2=C(CC(=O)O)C=CC=C2)C(Cl)=CC=C1
14	C1=C2C(=CC(=C1)O)CC[C@@H]3[C@@H]2CC[C@]4([C@H]3CC[C@@]4(O)C#C)C
15	CC(C(=O)O)C1=CC=C(CC(C)C)C=C1
16	[O-][N+](=O)C1=C(O)C=CC=C1
17	OC1=C(O)C=CC=C1
18	CC1=C(C)C=C(O)C=C1C
19	OC1=CC=CC=C1
20	C1(=CC=C(C=C1)CCCCC)O
21	CC1=C(Cl)C=CC(=C1)O
22	C1=CC(=C(C=C1)O)C2=CC=CC=C2
23	C=CCC1=C(C=CC=C1)O
24	C1(=CC=CC=C1)CCCCC(=O)O
25	OC(=O)C1=C(O)C=CC=C1
26	NC1=C(Cl)C=CC=C1
27	NC1=CC=C(Cl)C=C1
28	N1=C(C2=CC=CC=C2)C3=CC(Cl)=CC=C3N(C)C(=O)C1
29	C1=CC2=C(OCC(O)CNC(C)(C))C=CC=C2C=C1
30	NC1=CC(=C(C=C1)C)C
31	NC1=C(C)C=C(C)C=C1(C)
32	NCCCCC1=CC=CC=C1
33	ClC1=C(C2C(C(=O)OC)=C(C)NC(COCCN)=C2(C(=O)OCC))C=CC=C1
34	CNCC1=CC=C(C)C=C1
35	C1=CC(C)=CC=C1CNCCC
36	C(NCCCCC)C1=CC=C(C)C=C1
37	C(NCCCCCCCC)C1=CC=C(C)C=C1
38	O=C(NC1=C(C=CC=C1C)C)CN(CC)CC
39	CCCCNC1=CC=C(C(=O)OCCN(C)C)C=C1
40	C1(=CC=CC=C1)Cl
41	C1(=C(C=CC=C1)Cl)Cl
42	C1(=CC(=CC=C1)Cl)Cl
43	C1(=CC=C(C=C1)Cl)Cl
44	C1=C(C(=C(C=C1)Cl)Cl)Cl
45	C1(=C(C=C(C=C1)Cl)Cl)Cl
46	C1(=CC(=CC(=C1)Cl)Cl)Cl
47	C1=C(C(=C(C=C1Cl)Cl)Cl)Cl

48	C1(=CC(=C(C=C1Cl)Cl)Cl)Cl
49	C1(=C(C(=C(C=C1Cl)Cl)Cl)Cl)Cl
50	C1(=C(C(=C(C(=C1Cl)Cl)Cl)Cl)Cl)Cl
51	C1(=CC=C(C=C1)Br)Br
52	C1(=CC(=CC(=C1)Br)Br)Br
53	OCCCC
54	OCCCCC
55	OCCCCCC
56	OCCCCCCC
57	OCCCCCCCC
58	OC1CCCC1
59	OC1CCCCC1
60	OC1CCCCCC1
61	OC1CCCCCCC1
62	C1(=O)CC(=O)CCC1
63	C1(=O)CCCC1
64	C1(=O)CCCCC1
65	C1(=O)CCCCCC1
66	C1(=O)CCCCCCC1
67	OCC(CC)CCC
68	CC(C)C(O)C(C)C
69	C(C/C=C/CC)O
70	OC\C=C\CCC
71	C(C/C=C\CC)O
72	C=CCCCCO
73	C=CC(O)CCCC
74	CC(O)C#CC(O)C
75	OCCCCC#C
76	OCC(O)CCC
77	OCCCCCO
78	CC(O)CC(O)C
79	OCC(O)CCCC
80	OCCCCC(O)C
81	OCCCCCCO
82	OCCCCCCCCO
83	OCC(O)CCCCCC
84	OCCCCCCCCO
85	O[C@H]1CCCC[C@@H]1O
86	O[C@H]1[C@@H](CCCCCC1)O
87	C1(=CC=C(C=C1)CC)O
88	C1(=CC=C(C=C1)F)O
89	C1(=CC=C(C=C1)C(C)C)O
90	C1(=CC=C(C=C1)C(C)(C)C)O
91	C1(=C(C=CC=C1)C)O
92	C1=C(C=CC=C1O)C

93	C1=C(C=CC(=C1)O)C
94	C1=CC=CC(=C1CC)O
95	C1=CC=CC(=C1CCC)O
96	C1=CC(=CC=C1CCC)O
97	C1(=CC=CC=C1C(CC)C)O
98	C1=CC(=CC=C1C(CC)C)O
99	C1(=CC=CC=C1C(C)(C)C)O
100	C1=C(C=CC=C1C(C)(C)C)O
101	C1=CC(=CC=C1O)C2=CC=CC=C2
102	C1(=CC=C(C=C1)C(C)(C)CC)O
103	C1(=C(C=CC=C1C)C)O
104	C1(=C(C=CC=C1CC)CC)O
105	C1(=CC(=CC=C1)Cl)O
106	C1(=CC=C(C=C1)S(=O)(=O)C)O
107	C1(=CC=C(C=C1)C#N)O
108	C1(=CC(=CC=C1)C(F)(F)F)O
109	C1(=CC(=CC=C1)[N+]([O-])=O)O
110	C1(=C(C=C(C=C1[N+]([O-])=O)[N+]([O-])=O)CC)O
111	C1(=C(C=C(C=C1[N+]([O-])=O)[N+]([O-])=O)C(C)C)O
112	CCCCOCCO
113	C1(=C(C=C(C(=C1)Cl)Cl)Cl)C
114	CCC(O)CC
115	C1(=CC=C(C=C1)C)C
116	C1(=C(C=CC=C1)[N+](=O)[O-])C
117	C1=C(C=CC=C1)[N+](=O)[O-]
118	C1=C(C=CC=C1N)[N+](=O)[O-]
119	C1=C(C(=CC(=C1Cl)Cl)Cl)N
120	C1(=CC=CC=C1)N
121	C1=CC=CC2=C1N=CC=C2
122	C1(=CC=CC=C1)N(C)C
123	C1=CC(=C(C=C1C(OC)=O)N)C(OC)=O
124	C1(=C(C=C(C=C1)Cl)[N+](=O)[O-])C(=O)OC
125	C(C(=O)OCCCC)CC(=O)OCCCC
126	CCOC(=O)CCCCC(=O)OCC
127	CCCOC(=O)C
128	CCOC(=O)CC(=O)OCC
129	C1=C2C(=CC(=C1)O)CC[C@@H]3[C@@H]2CC[C@]4([C@H]3CC[C@@H]4O)C
130	C1=C2C(=CC(=C1)O)CC[C@@H]3[C@@H]2CC[C@]4([C@H]3CCC4=O)C
131	C2=C1[C@@H]3[C@@H](CCC1=CC(=C2)O)[C@H]4[C@](CC3)([C@H]([C@@H](C4)O)O)C
132	C1=C(C=CC(=C1)O)CCCCCCCCC
133	C1=C(C=CC(=C1)O)C(CCCCC)(C)C
134	C1=C(C=CC(=C1)O)C(C2=CC=C(C=C2)O)(C)C
135	C1=C(C(=CC=C1)C(=O)OCC2=CC=CC=C2)C(=O)OCCCC

136	C1=C(C(=CC=C1)C(=O)OCCCC)C(=O)OCCCC
137	C1=C(C=CC(=C1)O)\C(CC)=C(/CC)C2=CC=C(C=C2)O
138	C1=CC(=CC=C1O)[C@@H](CC)[C@@H](CC)C2=CC=C(C=C2)O
139	C1=C(C=CC(=C1)O)C(=CC)C(=CC)C2=CC=C(C=C2)O
140	C1=C(C=CC(=C1)O)C(=O)OCCCC
141	C1=C(C=CC(=C1)O)C(=O)OCC2=CC=CC=C2
142	C1=C(C=CC(=C1)O)C(=O)C2=CC=C(C=C2)O
143	C1=C(C(=CC=C1)C(=O)OCC)C(=O)OCC
144	C1CC(C=C2[C@]1([C@@H]3[C@@H](CC2)[C@H]4[C@](CC3)([C@H](CC4)C(C)=O)C)C)=O

SI-7

Abbr	pK_a QC [a]	pK_a SPARC [b]	log $K_{mw,HA}$ QC [c]	log $K_{mw,HA}$ Kowexp [d]	log $K_{mw,HA}$ KowWin [e]	log K_{mw,A^-} QC [f]	ΔG_{HA} [g]	ΔG_{A^-} [h]	log K_{ow} KowWin [i]	logKow QC [j]	log$K_{19decadiene\text{-}octanol,A^-}$ [k]	log$K_{19decadiene\text{-}water,A^-}$ [l]
FCCP	6.32	3.56	2.80	3.74	3.62	3.51	3.29	7.28	3.55	2.63	-0.63	-3.50
CCCP	6.00	3.48	2.35	3.47	3.26	3.32	3.28	7.76	3.15	2.16	-0.64	-3.90
TTFB	6.26	8.81	4.07	4.70	4.75	4.15	3.00	5.18	4.78	4.17	-1.06	-1.80
DTFB	8.01	10.27	2.95	3.57	3.57	3.34	3.72	8.27	3.49	2.94	-2.05	-4.40
DPFB	8.37	10.32	3.89	NA	4.45	3.91	3.77	6.07	4.45	3.92	-1.34	-2.58
TBrTFB	6.45	8.76	4.40	4.78	5.65	4.75	2.43	4.87	5.76	4.60	-0.36	-0.41
Fluazinam	7.42	6.85	6.29	3.50	4.05	6.24	0.09	1.90	4.02	6.02	0.44	2.01
5NTFB	7.15	9.82	2.09	2.83	2.22	2.89	5.09	9.15	2.02	1.87	-1.69	-5.22
4NTFB	6.92	10.07	2.21	NA	2.22	2.65	2.33	10.22	2.02	2.24	-1.98	-6.15
6Cl24DNP	2.74	2.47	3.00	NA	2.54	2.53	0.97	9.91	2.37	2.89	-1.34	-6.00
26DBr4NP	2.76	3.61	3.13	3.64	3.75	2.79	1.84	9.46	3.69	3.16	-1.45	-5.24
246TriNP	0.71	0.53	2.74	2.23	1.78	2.83	1.76	9.09	1.54	2.46	-0.62	-4.99
warfarin	4.89	6.20	3.35	2.75	2.41	2.86	1.15	10.98	2.23	3.49	-3.37	-7.64
246TriBP	6.36	6.18	3.86	4.21	4.20	3.22	0.96	11.39	4.18	3.91	-3.31	-5.84
24DCP	7.78	7.74	3.04	3.33	2.94	2.26	1.40	15.17	2.80	2.91	-5.59	-9.72
34DCP	8.60	8.52	2.86	3.16	2.94	2.26	3.77	15.62	2.80	2.55	-6.06	-10.10
35DCP	8.12	8.27	3.04	3.69	2.94	2.40	3.95	14.54	2.80	2.75	-5.39	-9.23
245TriCP	6.85	6.87	3.54	4.21	3.53	2.72	1.51	12.90	3.45	3.49	-4.57	-7.91
246TriCP	6.34	6.12	3.52	3.78	3.53	2.72	1.57	12.52	3.45	3.48	-4.14	-7.55
345TriCP	7.83	7.65	3.36	4.41	3.53	2.70	4.08	13.39	3.45	3.14	-5.07	-8.34
2345TeCP	6.28	6.01	3.98	4.83	4.12	3.04	1.44	11.31	4.09	3.97	-3.94	-6.66
2346TeCP	5.71	5.26	3.92	4.42	4.12	3.08	1.58	10.87	4.09	3.91	-3.50	-6.23
PCP	5.05	4.39	4.36	5.17	4.71	3.38	1.50	9.41	4.74	4.37	-3.01	-5.10
35DBC	8.48	8.58	3.56	5.35	3.89	2.78	3.46	14.21	3.84	3.43	-5.47	-8.47
Bromox	4.22	4.14	2.38	3.09	3.48	2.54	2.20	11.21	3.39	2.40	-2.47	-6.60
4NP	5.53	6.74	1.78	2.24	2.12	1.45	5.24	15.51	1.91	1.16	-3.90	-10.78
24DNP	4.01	4.04	2.42	1.90	1.96	1.99	1.09	12.26	1.73	2.22	-2.09	-8.08
26DNP	3.63	3.35	2.17	1.49	1.96	1.85	1.20	13.37	1.73	1.93	-2.18	-8.86
34DNP	4.46	5.32	2.59	2.41	1.96	2.28	6.42	11.91	1.73	1.85	-2.19	-7.53
DNOC	4.29	4.50	2.92	2.31	2.45	2.21	0.71	11.21	2.27	2.82	-1.90	-7.34
DNPC	4.23	3.67	2.63	NA	2.45	1.80	0.84	13.55	2.27	2.50	-2.73	-9.35

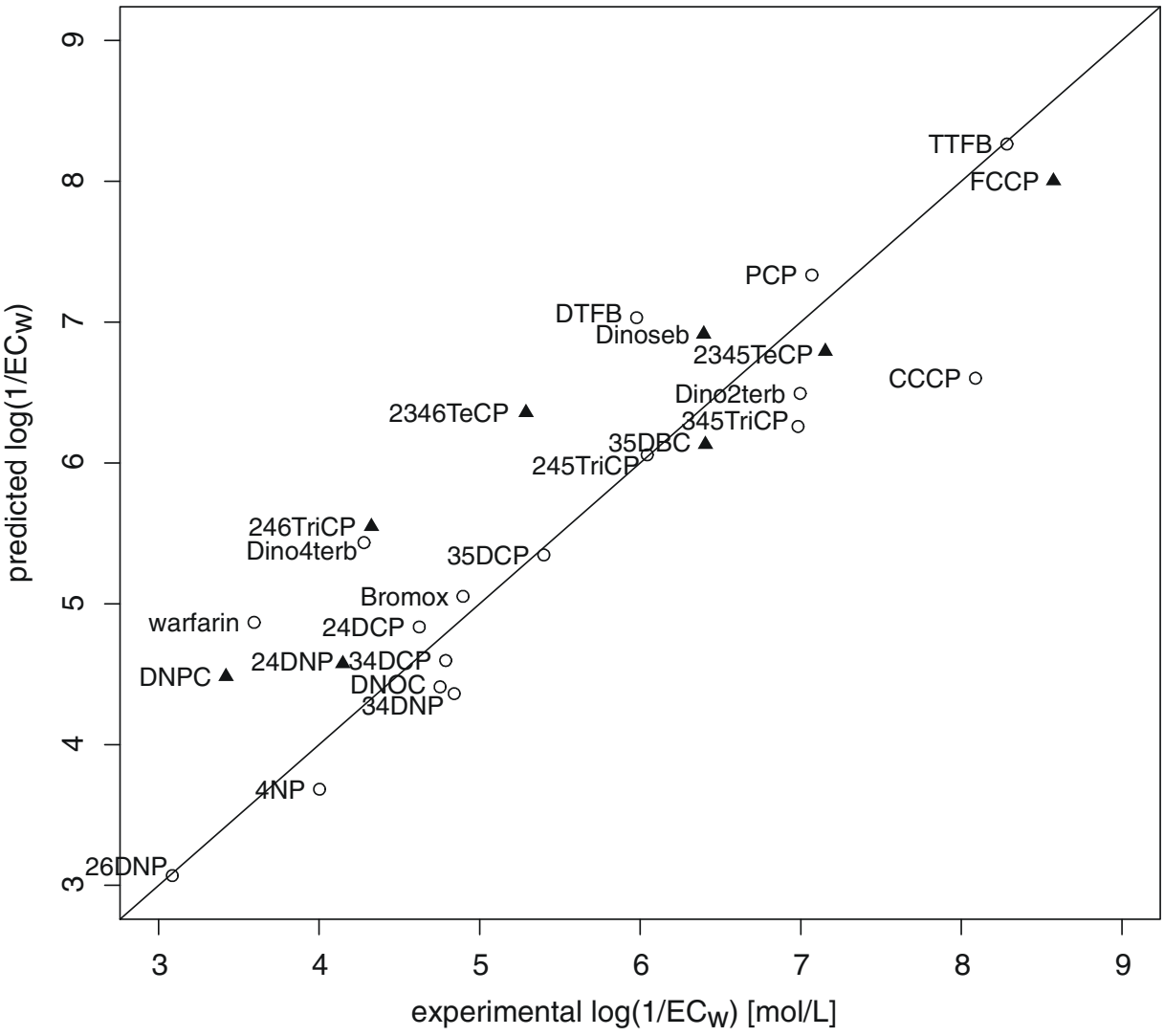
Dinoseb	4.32	5.47	4.42	3.63	3.73	2.90	0.40	8.50	3.67	4.33	-1.49	-5.28
Dino2terb	4.73	5.51	4.30	NA	3.71	2.99	0.34	8.31	3.64	4.21	-1.36	-5.01
Dino4terb	4.25	3.65	3.94	NA	3.71	2.42	0.56	11.76	3.64	3.87	-2.69	-7.93
Triclosan	7.78	7.99	5.11	4.73	4.64	3.70	1.30	10.05	4.66	5.16	-4.26	-5.65

[a] acid dissociation constant in pure water at 298 K (calculated with COSMOtherm Version C2.1 Release 01.06). Two compounds (246TriNP and 34DNP) were determined with several conformers weighted by their energy [b] acid dissociation constant in pure water at 298 K (calculated with SPARC Version 3.1 - Accessed on 02-08-2007). [c] liposome-water partition coefficient of neutral species (HA) calculated with COSMOmic-long with EPOT=0.0 (COSMOtherm Version C2.1 Release 01.06; COSMOmic V2 (Feb 07)). The results of the COSMOmic calculations were fitted with the experimental partition coefficients by log $K_{mw,HA}$ (exp) = 1.02·log $K_{mw,HA}$ (COSMOmic) – 3.93·Volume + 9.52 with the volume taken from the cosmo-files generated by Turbomole. The fit equation without this volume correction was used for Table 3 and is log $K_{mw,HA}$ (exp) = 0.77·log $K_{mw,HA}$ (COSMOmic) – 1.42 [d] liposome-water partition coefficient calculated by empirical relationship between experimental log K_{ow} and experimental log $K_{mw,HA}$: Eq. 4 of paper. For compounds without experimental K_{ow} (NA) the value calculated with KowWin was used. [e] same approach as in [d], but K_{ow} calculated with KowWin. [f] liposome-water partition coefficient of anions (A^-) calculated with COSMOmic-dl with EPOT=0.02 (COSMOtherm Version C2.1 Release 01.06; COSMOmic V2 (Feb 07)). The results of the COSMOmic calculations were fitted with the experimental partition coefficients by log K_{mw,A^-} (exp) = 0.90·log K_{mw,A^-} (COSMOmic) – 1.84 [g] energy difference between energy well and lipophilic barrier for neutral species (HA), $\Delta G_{well\text{-}barrier,HA}$ calculated with COSMOmic-dl (cf. [f]): Eq. 12 of paper. [h] energy difference between energy well and lipophilic barrier for charged species (A-), $\Delta G_{well\text{-}barrier,A^-}$ calculated with COSMOmic (cf. [f]). [i] octanol-water partition coefficient calculated with KOWWin (v 1.67). [j] octanol-water partition coefficient (calculated with COSMOtherm Version C2.1 Release 01.06). [k] 1,9-decadiene-octanol partition coefficient of anion (calculated with COSMOtherm Version C2.1 Release 01.06). [l] 1,9-decadiene-water partition coefficient of anion (calculated with COSMOtherm Version C2.1 Release 01.06).

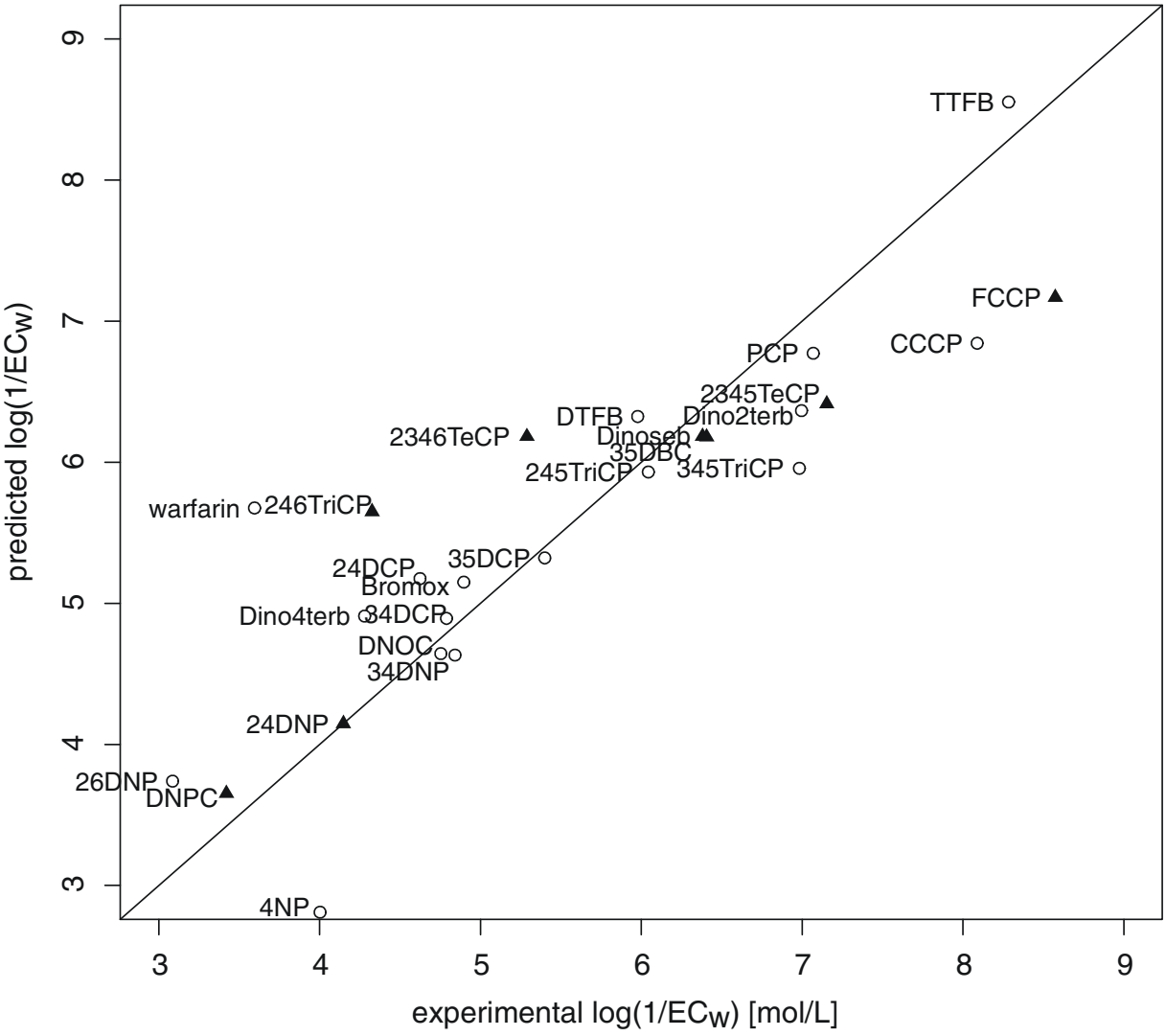
Note about EPOT in COSMOmic calculations (cf. [c,f,g]): COSMOmic allows the application of a scaling factor for the electrostatic potential caused by the dipole (positive in the membrane interior) of the phosphatidylcholine molecules (Parameter: EPOT). Increasing EPOT showed little effect on the calculated $K_{mw,HA}$, but a strong effect on the calculated K_{mw,A^-}. The analysis of the calculated distributions of anions over the membrane revealed that choosing high values for EPOT drives the anionic solutes towards the polar head groups. A series of EPOT values were tested with external data from SI-5 in terms of the correlation and standard deviation of the difference between calculated and predicted log K_{mw,A^-} (as defined by Eq. 14). A low EPOT value of 0.02 performed best and was used in this study. All other parameters were kept at their default values.

SI-8

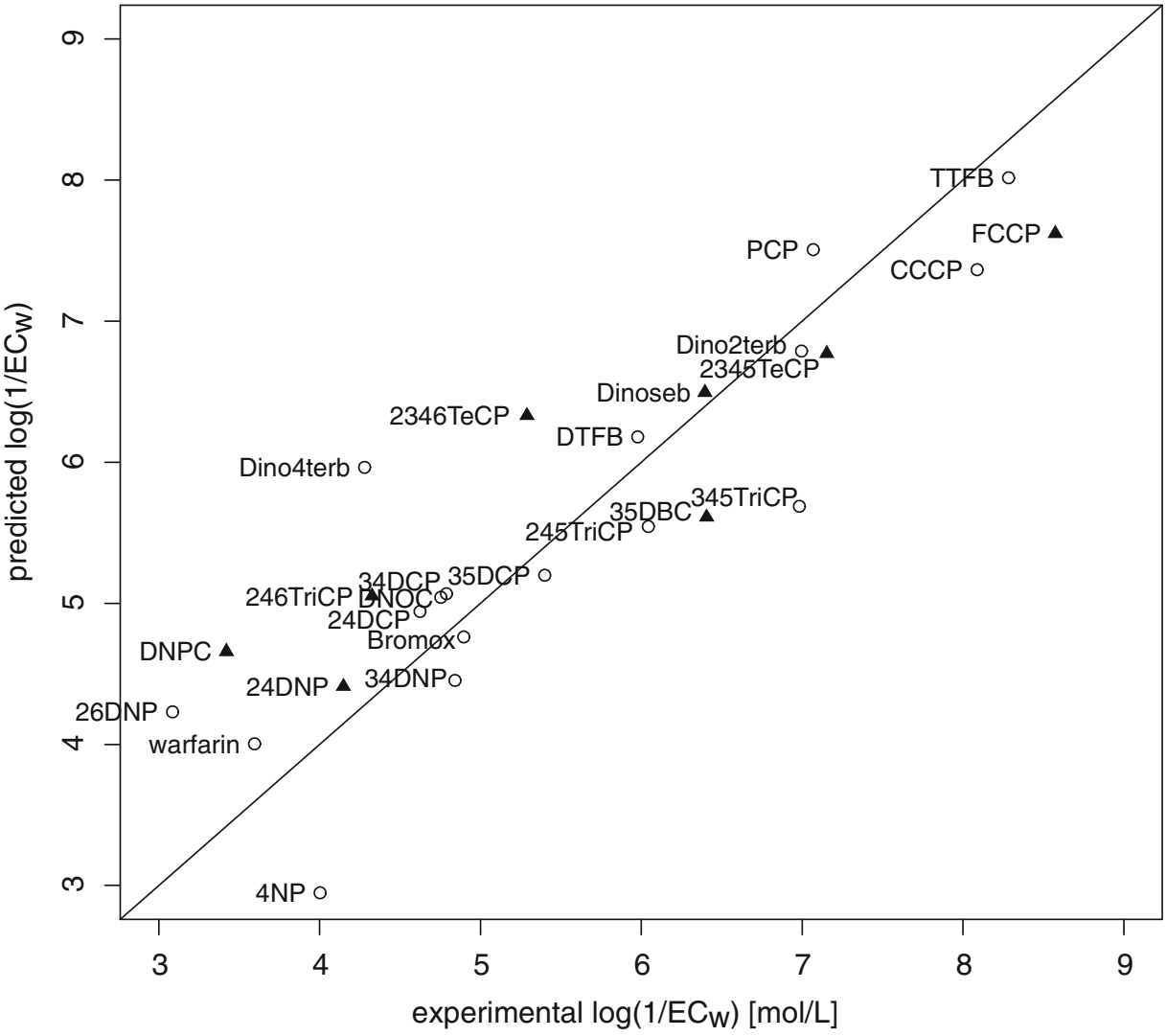
Regression Model R2:



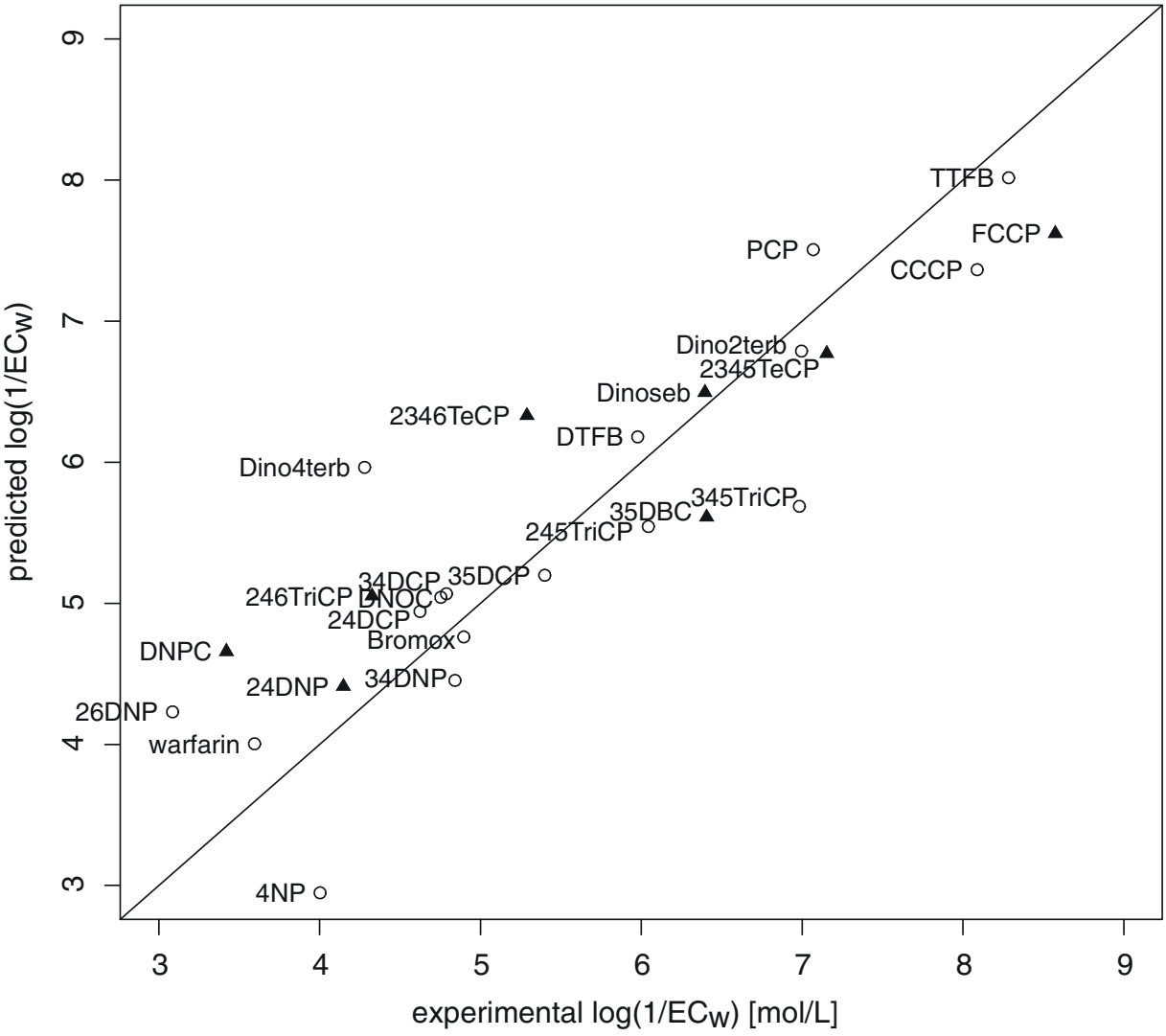
Regression Model R3:



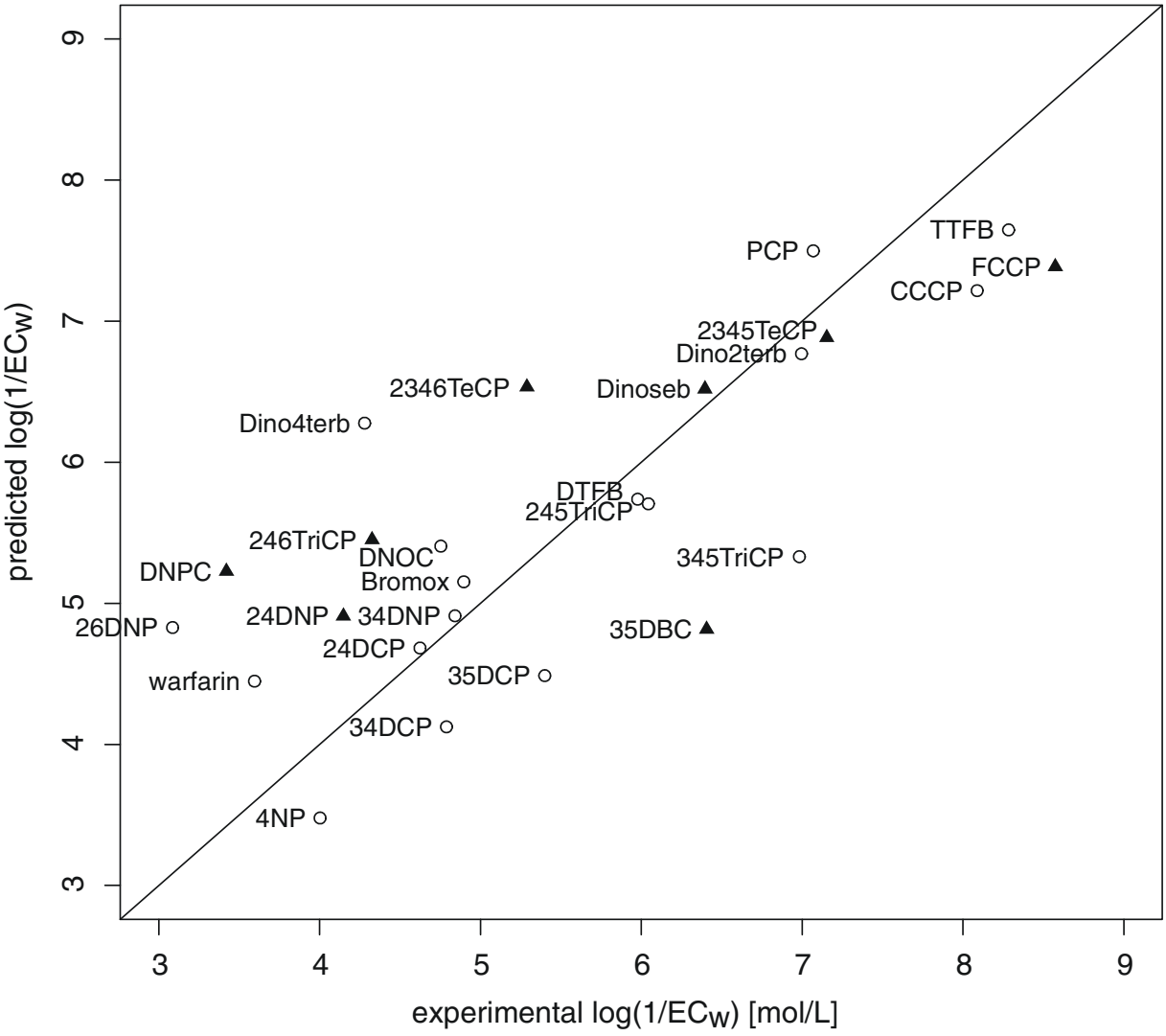
Regression Model R4:



Regression Model R5:

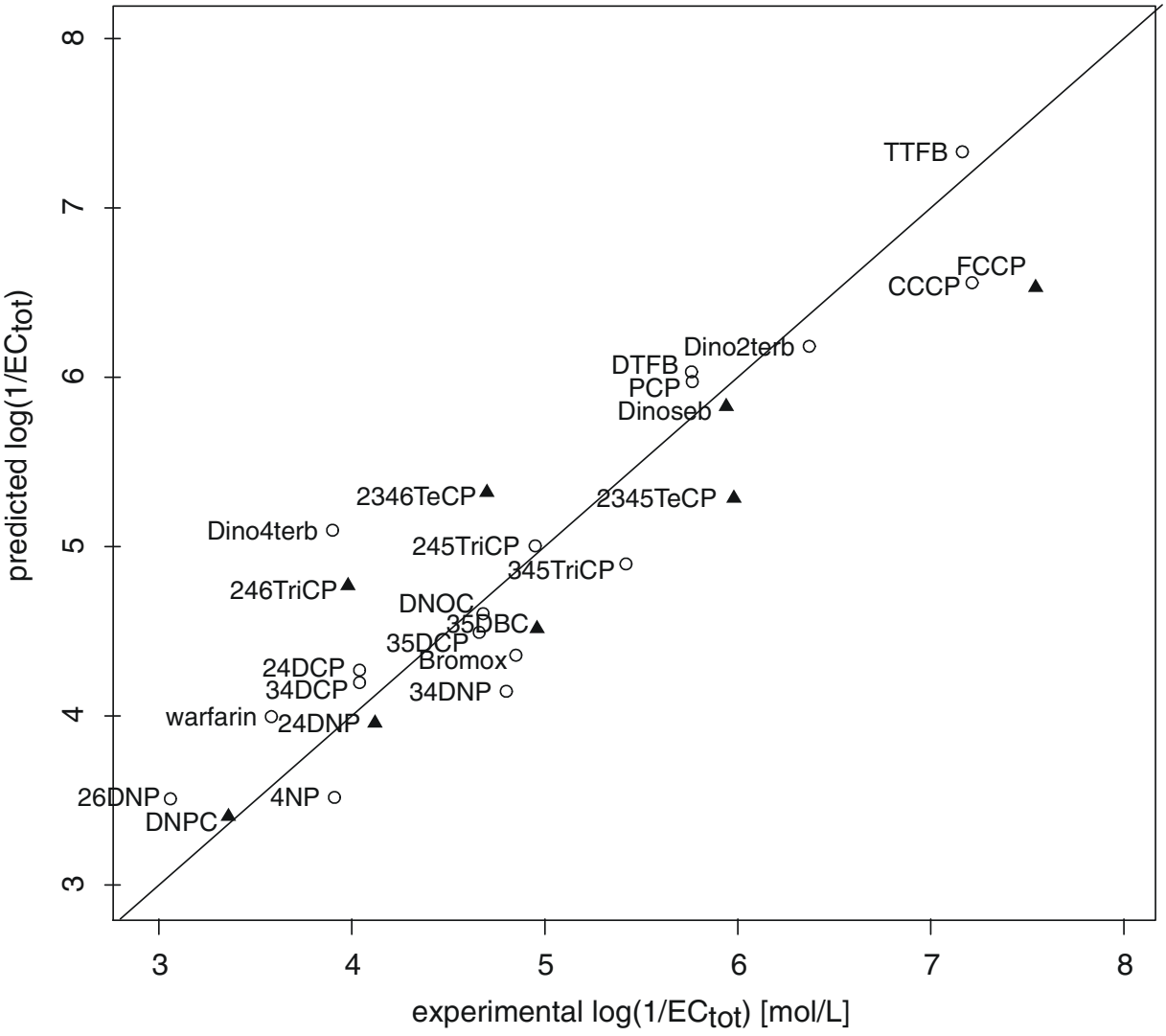


Regression Model R6:

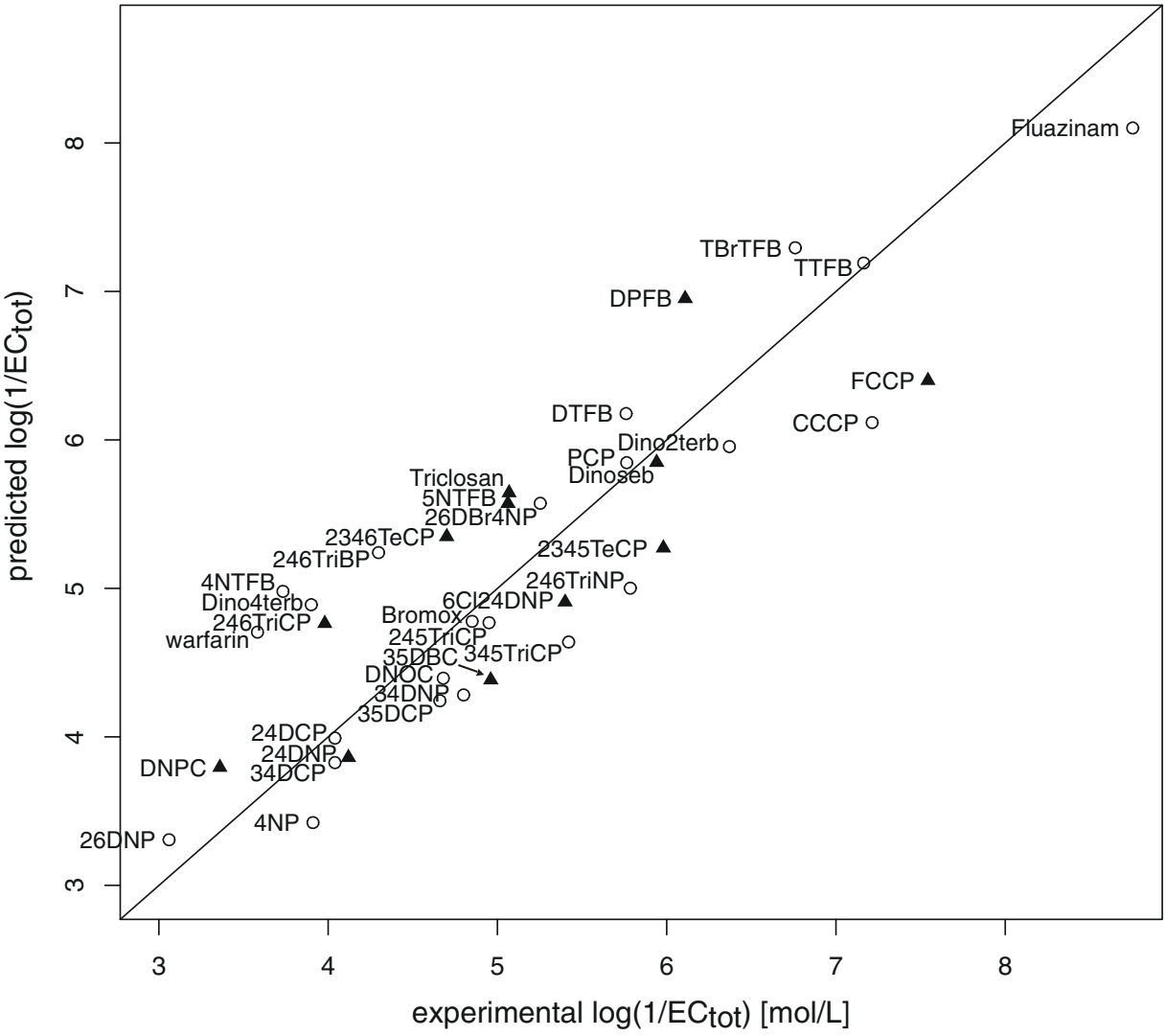


SI-9

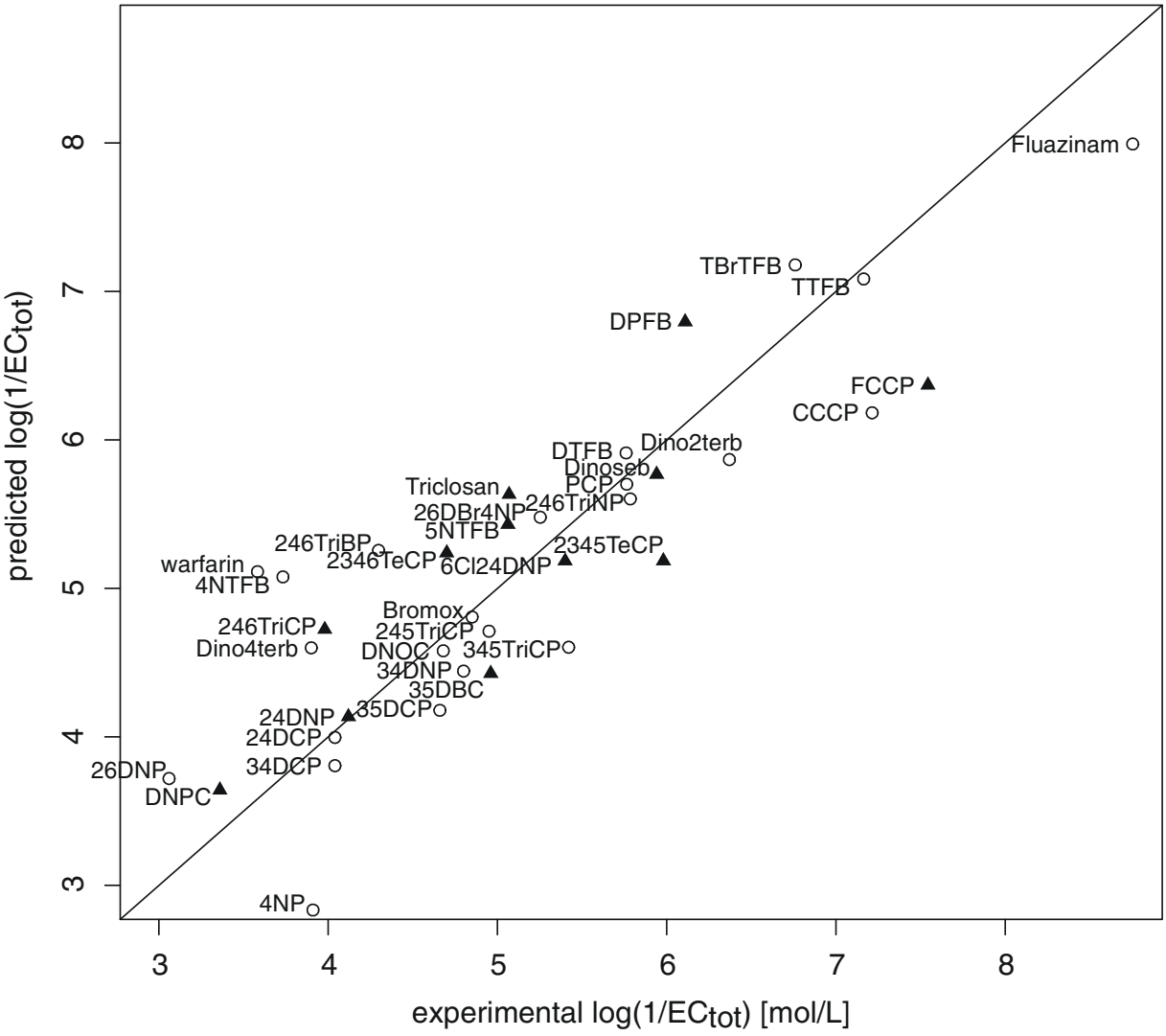
Regression Model R7:



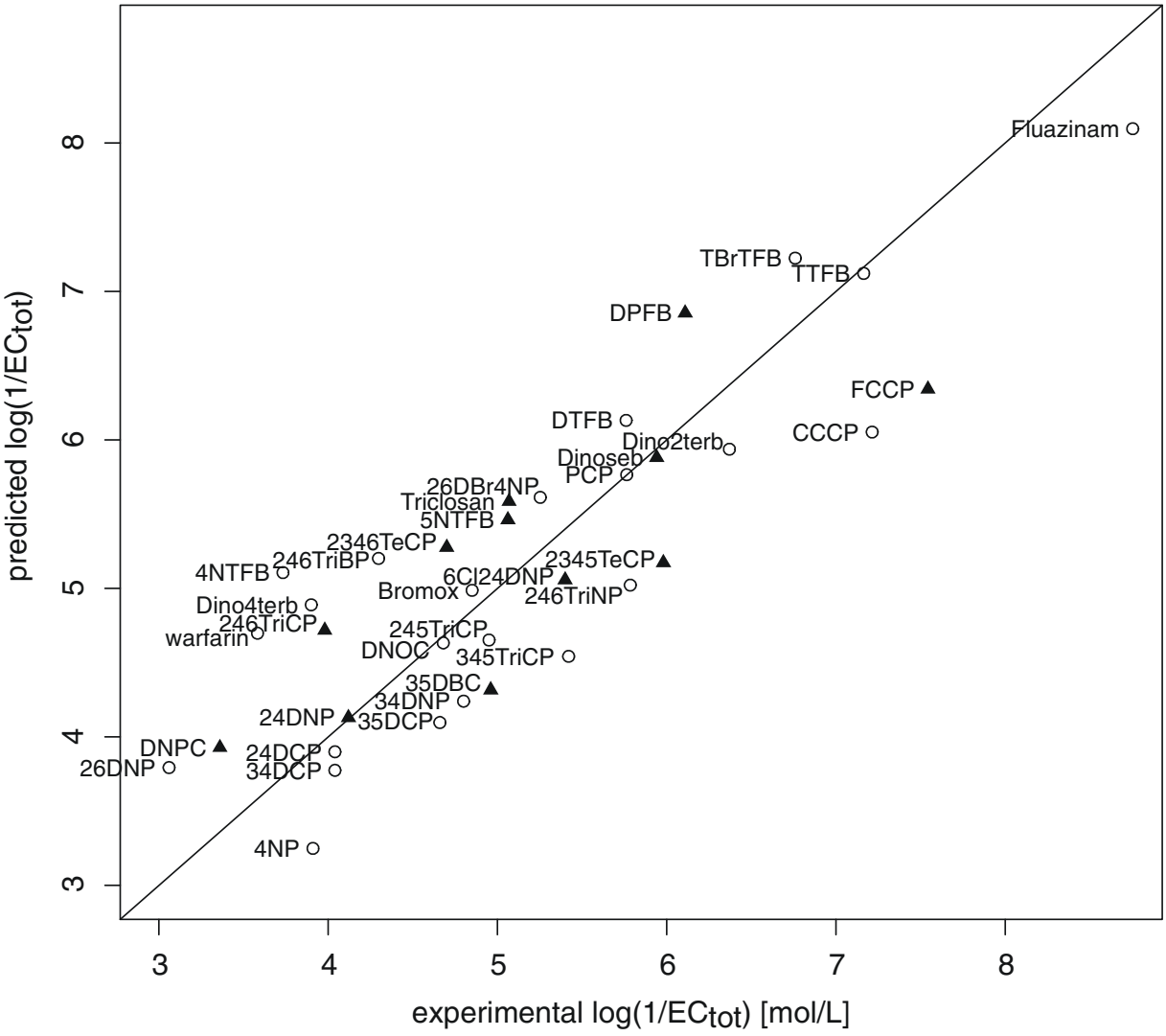
Regression Model R8:

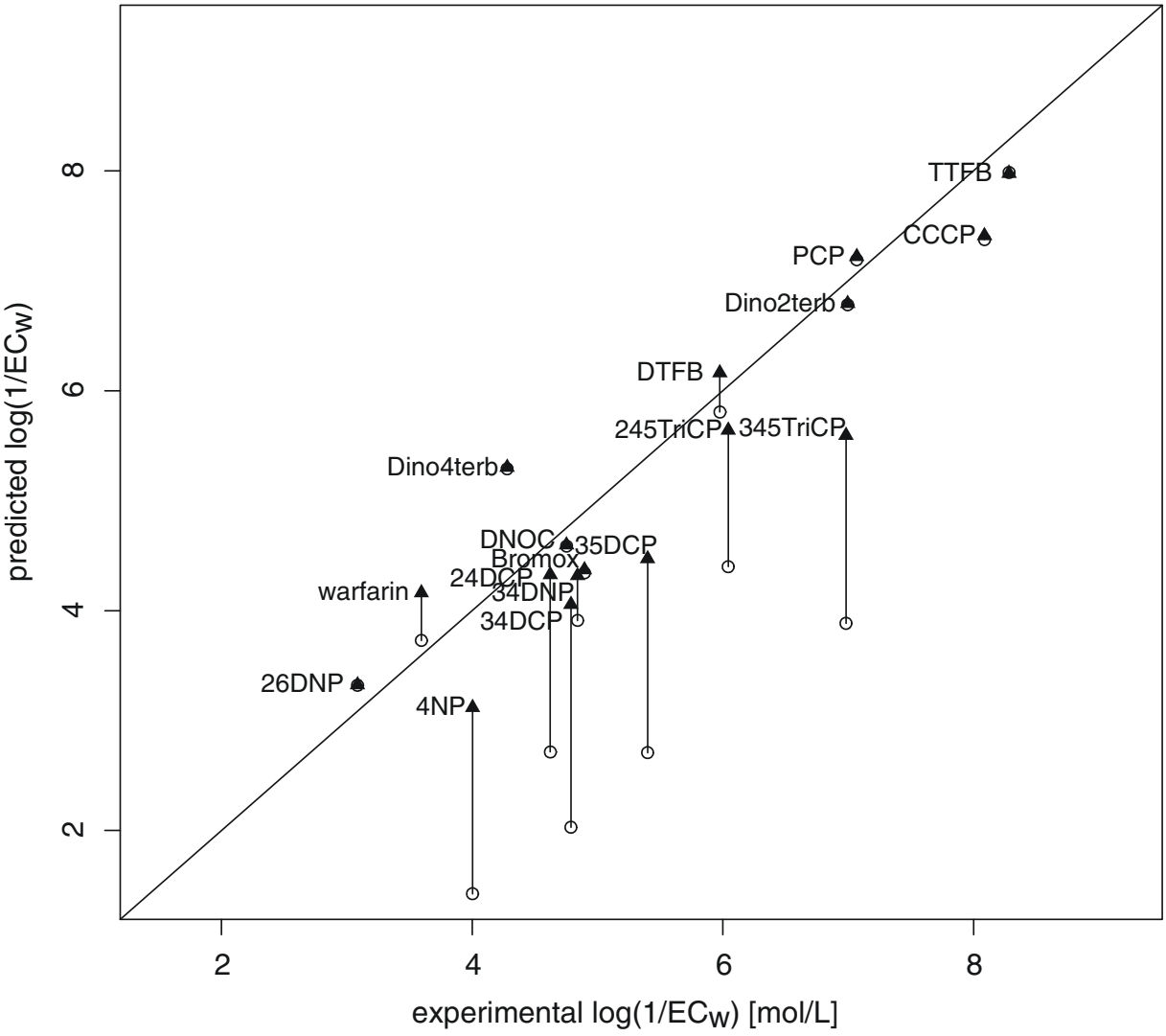


Regression Model R9:



Regression Model R10:





Predicted versus experimental EC_w for nonlinear model. Empty circles are the values obtained with k_{AHA}- = 0 and the full circles with k_{AHA}- estimated by the approach described in the section on nonlinear models for EC_w. The lines connect the predictions for the same compound. Compounds without connecting lines are compounds where k_{AHA}- has no influence at pH = 7 and thus the empty circle and the full circle overlap.