Electronic Supplementary Information for

Ecotoxicity studies of glycerol ethers in *Vibrio fischeri*: checking the greenness of glycerol-derived solvents

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Content

Table S1. Topological parameters of 20 glycerol-derived solvents.

Code	HBA	HBD	RB	φ	Bal^{JX}	Bal^{JY}	W	Z	κ_1^{am}	κ_2^{am}	κ_3^{am}	SC_p^0	SC_p^1	SC_p^2	SC_p^3	SC_c^3	$^0\chi$	$^1\chi$	$^2\chi$	$^3\chi_p$	$^3\chi_{cl}$	$^0\chi^{vm}$	$^1\chi^{vm}$	$^2\chi^{vm}$	$^3\chi_p^{vm}$	$^3\chi_{cl}^{vm}$
000	3	3	5	3.02	2.572	2.814	31	20	5.88	3.08	2.88	6	5	5	4	1	4.99	2.81	1.92	1.39	0.29	3.33	1.71	1.02	0.42	0.13
100	3	2	5	3.98	2.620	2.901	50	24	6.88	4.05	3.72	7	6	6	5	1	5.70	3.31	2.30	1.48	0.29	4.29	2.09	1.29	0.57	0.13
200	3	2	6	4.95	2.665	2.926	76	28	7.88	5.03	4.88	8	7	7	6	1	6.41	3.81	2.66	1.75	0.29	5.00	2.68	1.50	0.73	0.13
400	3	2	8	6.91	2.723	2.939	153	36	9.88	6.99	6.88	10	9	9	8	1	7.82	4.81	3.36	2.25	0.29	6.42	3.68	2.26	1.16	0.13
101	3	1	5	4.95	2.686	2.996	75	28	7.88	5.03	4.88	8	7	7	6	1	6.41	3.81	2.68	1.56	0.29	5.26	2.47	1.56	0.72	0.13
103i	3	1	6	5.58	2.915	3.193	143	38	9.88	5.65	6.88	10	9	10	8	2	7.98	4.66	3.87	2.02	0.70	6.83	3.45	2.49	0.98	0.37
104	3	1	8	7.89	2.788	3.033	202	40	10.88	7.98	7.78	11	10	10	9	1	8.53	5.31	3.74	2.33	0.29	7.38	4.06	2.54	1.31	0.13
104i	3	1	7	6.51	2.909	3.162	194	42	10.88	6.58	7.78	11	10	11	9	2	8.69	5.16	4.22	2.26	0.70	7.54	3.91	3.04	1.12	0.54
104t	3	1	6	4.65	3.173	3.444	180	46	10.88	4.70	7.78	11	10	13	9	5	8.91	4.96	4.99	2.17	1.85	7.76	3.76	3.53	1.07	1.24
202	3	1	7	6.91	2.792	3.066	149	36	9.88	6.99	6.88	9.88	9	9	8	1	7.82	4.81	3.39	2.10	0.29	6.67	3.64	1.97	1.03	0.13
3i03i	3	1	7	6.34	3.079	3.334	243	48	11.88	6.40	8.88	12	11	13	10	3	9.56	5.52	5.05	2.47	1.11	8.41	4.43	3.42	1.24	0.60
404	3	1	11	10.86	2.907	3.121	419	52	13.88	10.96	10.88	14	13	13	12	1	10.65	6.81	4.80	3.10	0.29	9.50	5.64	3.51	1.91	0.13
404t	3	1	9	7.15	3.152	3.380	388	58	13.88	7.21	10.88	14	13	16	12	5	11.03	6.46	6.05	2.94	1.85	9.88	5.35	4.51	1.66	1.24
111	3	0	5	5.93	2.907	3.263	102	32	8.88	6.01	4.39	9	8	8	8	1	7.11	4.35	2.85	1.97	0.20	6.22	2.85	1.77	1.04	0.12
114	3	0	8	8.88	2.974	3.260	250	44	11.88	8.97	7.32	12	11	11	11	1	9.23	5.85	3.91	2.74	0.20	8.34	4.44	2.74	1.63	0.12
114i	3	0	7	7.46	3.089	3.383	241	46	11.88	7.53	7.32	12	11	12	11	2	9.40	5.70	4.39	2.67	0.61	8.50	4.30	3.24	1.44	0.53
414	3	0	11	11.86	3.105	3.357	488	56	14.88	11.95	10.17	15	14	14	14	1	11.36	7.35	4.97	3.51	0.20	10.46	6.03	3.72	2.23	0.12
444	3	0	14	14.84	3.443	3.683	789	68	17.88	14.94	13.17	18	17	17	17	1	13.48	8.85	6.06	4.15	0.20	12.58	7.62	4.70	2.74	0.12
3F03F	9	1	7	6.05	3.136	3.615	557	72	15.46	6.26	12.46	16	15	21	14	9	12.82	7.10	8.01	3.25	3.41	7.94	4.07	2.91	1.15	0.49
3F13F	9	0	7	6.80	3.325	3.835	638	76	16.46	7.02	11.72	17	16	22	16	9	13.53	7.64	8.18	3.66	3.33	8.90	4.46	3.12	1.47	0.48

Table S2. DARC/PELCO parameters of 20 glycerol-derived solvents.[a]

Code	A_1	A_2	B_1	B_2	$^{F}B_2$	C_1	C_2	D_1	D_2
000	0	0	0	0	0	0	0	0	0
100	0	1	0	0	0	0	0	0	0
200	0	1	0	1	0	0	0	0	0
400	0	1	0	1	0	0	1	0	1
101	0	2	0	0	0	0	0	0	0
103i	0	2	0	2	0	0	0	0	0
104	0	2	0	1	0	0	1	0	1
104i	0	2	0	1	0	0	2	0	0
104t	0	2	0	3	0	0	0	0	0
202	0	2	0	2	0	0	0	0	0
3i03i	0	2	0	4	0	0	0	0	0
404	0	2	0	2	0	0	2	0	2
404t	0	2	0	4	0	0	1	0	1
111	1	2	0	0	0	0	0	0	0
114	1	2	0	1	0	0	1	0	1
114i	1	2	0	1	0	0	2	0	0
414	1	2	0	2	0	0	2	0	2
444	1	2	1	2	0	1	2	1	2
3F03F	0	2	0	0	2	0	0	0	0
3F13F	1	2	0	0	2	0	0	0	0

[a] Note that B_1. C_1 and D_1 columns are identical. because there is a single compound with a substituent at 2-position longer than methyl (444). As a consequence. the coefficient for B1 in any regression model will account for the contribution of the whole butyl group. and not only for that of a single carbon at that position.

Table S3. Experimental EC_{50} values for *V. fischeri* expressed in mM units and calculated logP for the solvent set used.[a]

Code	EC_{50} (mM)	$logEC_{50}$	logP
000	1177.34	1177.34	–1.33
100	198.38	198.38	–0.97
200	35.29	35.29	–0.63
400	6.35	6.35	0.28
101	114.04	114.04	–0.60
103i	14.76	14.76	0.05
104	2.86	2.86	0.64
104i	0.88	0.88	0.62
104t	1.17	1.17	0.27
202	8.20	8.20	0.07
3i03i	6.04	6.04	0.71
404	0.05	0.05	1.88
404t	0.08	0.08	1.51
111	7.22	7.22	–0.24
114	2.57	2.57	1.00
114i	1.46	1.46	0.98
414	0.27	0.27	2.24
444	1.82	1.82	3.48
3F03F	6.23	6.23	1.35
3F13F	14.93	14.93	1.71

[a] A. K. Ghose and G. M. Crippen. *J. Chem. Inf. Comput. Sci.*. 1987. **27**. 21–35.

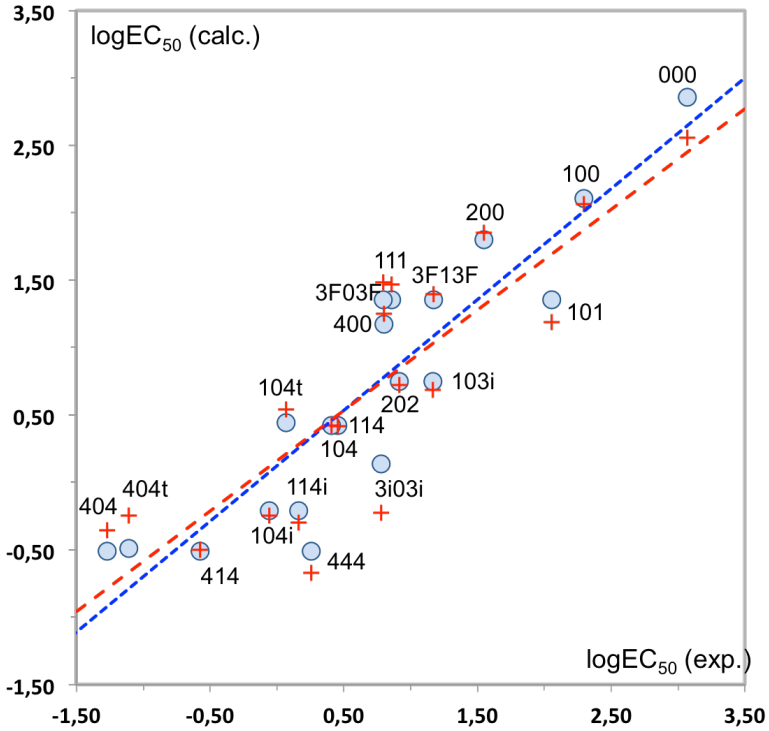

Figure S1. Plots of predicted *vs.* experimental values of $logEC_{50}$ (EC_{50} expressed in mM units) as calculated through MLR analysis using the DARC/PELCO model. Circles represent the predictions made with the plain regression equation and crosses are the cross-validated predictions. Blue and red lines represent the least squares fit between both sets of data, respectively.

$$logEC_{50} = 2.856(\pm 0.374) - 0.751(\pm 0.225)\cdot A_2 - 0.304(\pm 0.0.096)\cdot B_2 - 0.630(\pm 0.136)\cdot C_2$$

$$logEC_{50} = -0.387\cdot A_2 - 0.361\cdot B_2 - 0.510\cdot C_2 \qquad \text{Standardized coefficients}$$

$N = 20$, $R = 0.91$, $R_{CV} = 0.84$, $\sigma(y) = 0.490$

$F = 24.7$ ($F_{(3,16,\ 0,05)} = 3.2$)

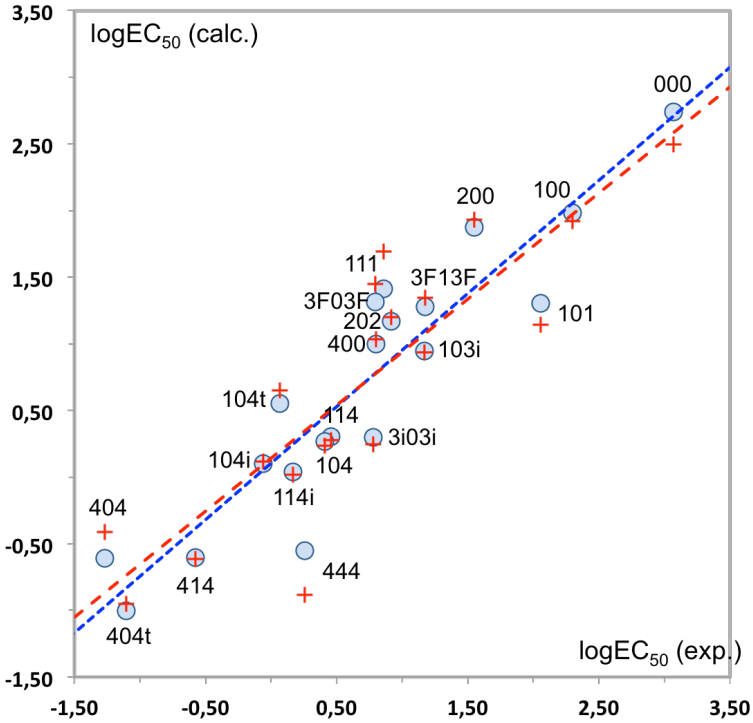

Figure S2. Plots of predicted *vs.* experimental values of $logEC_{50}$ (EC_{50} expressed in mM units) as calculated through MLR analysis using topological descriptors. Circles represent the predictions made with the plain regression equation and crosses are the cross-validated predictions. Blue and red lines represent the least squares fit between both sets of data, respectively.

$$logEC_{50} = -9.000(\pm 2.811) - 1.492(\pm 0.208)\cdot\ {}^{v}\chi_2 + 4.491(\pm 1.061)\cdot Bal^{JX} + 0.571(\pm 0.187)\cdot HBD_{count}$$

$$logEC_{50} = -1.434\cdot\ {}^{v}\chi_2 + 1.004\cdot Bal^{JX} + 0.442\cdot HBD_{count} \qquad \text{Standardized coefficients}$$

$N = 20$, $R = 0.92$, $R_{CV} = 0.85$, $\sigma(y) = 0.452$

$F = 29.9$ ($F_{(3,16,\ 0,05)} = 3.2$)

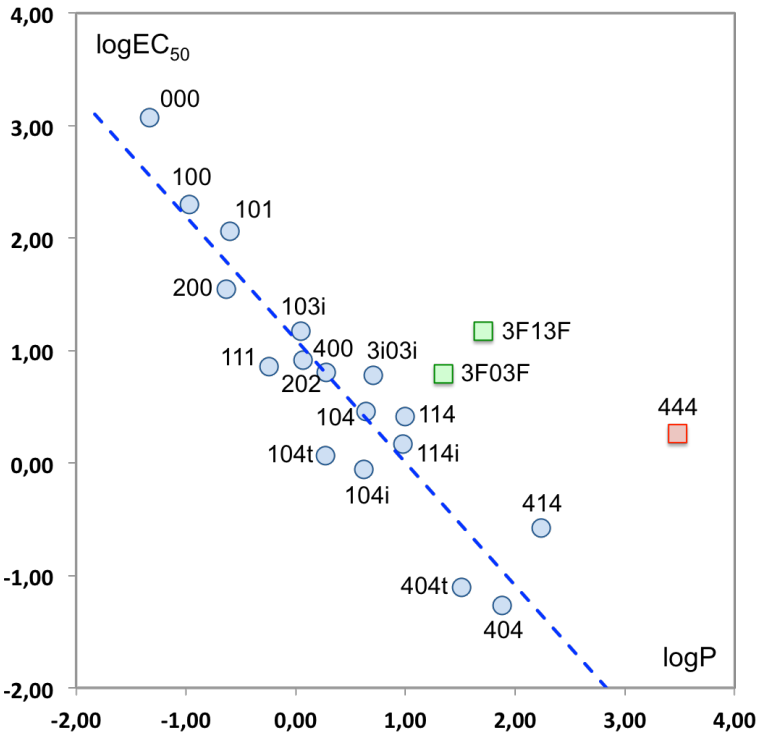

Figure S3. Plot of $logEC_{50}$ (EC_{50} expressed in mM units) *vs.* logP. Only the solvents represented with circles have been used to obtain the least-squares fitting line.

$logEC_{50} = 1.099(\pm 0.115) - 1.094(\pm 0.112) \cdot logP$

$N = 17$, $R = 0.93$, $R_{CV} = 0.90$, $\sigma(y) = 0.439$

$F = 95.1$ ($F_{(1,15,\ 0,05)} = 4.5$)

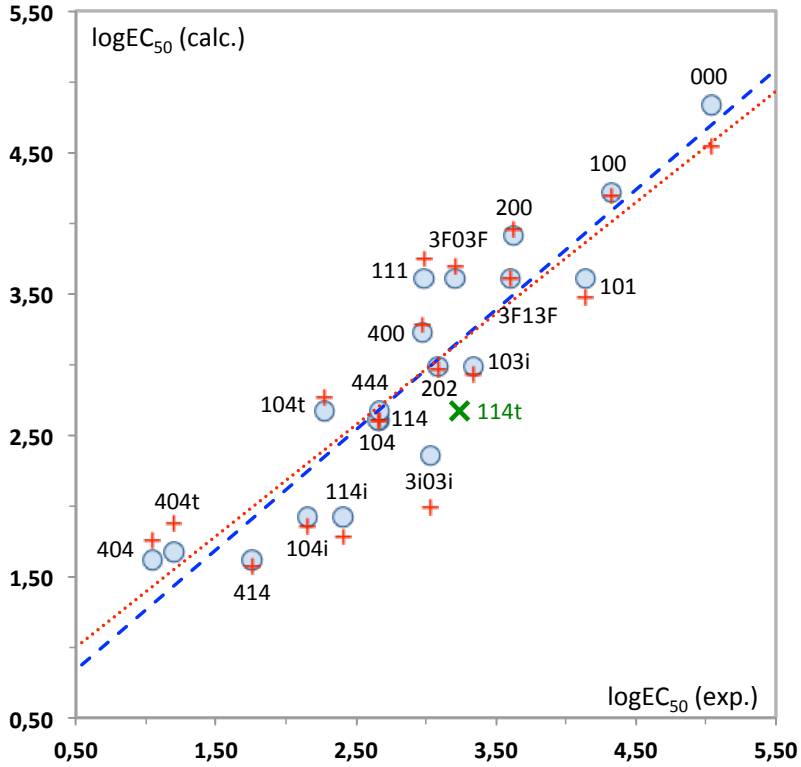

Figure S4. Plots of predicted *vs.* experimental values of $logEC_{50}$ (EC_{50} expressed in $mg \cdot L^{-1}$ units) as calculated through MLR analysis using the DARC/PELCO model. Circles represent the predictions made with the plain regression equation and crosses are the cross-validated predictions. Blue and red lines represent the least squares fit between both sets of data, respectively. Green cross represents the pure prediction of the toxicity of compound 114t made with the same MRL equation.

MLR equation derived with the initial 20 solvent set:

$$logEC_{50} = 4.828(\pm0.320) + 1.064(\pm0.460)\cdot B_1 - 0.614(\pm0.192)\cdot A_2 - 0.310(\pm0.0.082)\cdot B_2 - 0.685(\pm0.123)\cdot C_2$$

N = 20, R = 0.93, $\sigma(y)$ = 0.418
F = 22.6 ($F_{(4,15,\,0,05)}$ = 3.1)

MLR equation derived including the experimental value of 114t (21 solvent set):

$$logEC_{50} = 4.816(\pm0.325) + 1.062(\pm0.467)\cdot B_1 - 0.602(\pm0.195)\cdot A_2 - 0.282(\pm0.0.080)\cdot B_2 - 0.718(\pm0.122)\cdot C_2$$

N = 21, R = 0.92, $\sigma(y)$ = 0.425
F = 21.7 ($F_{(4,16,\,0,05)}$ = 3.0)

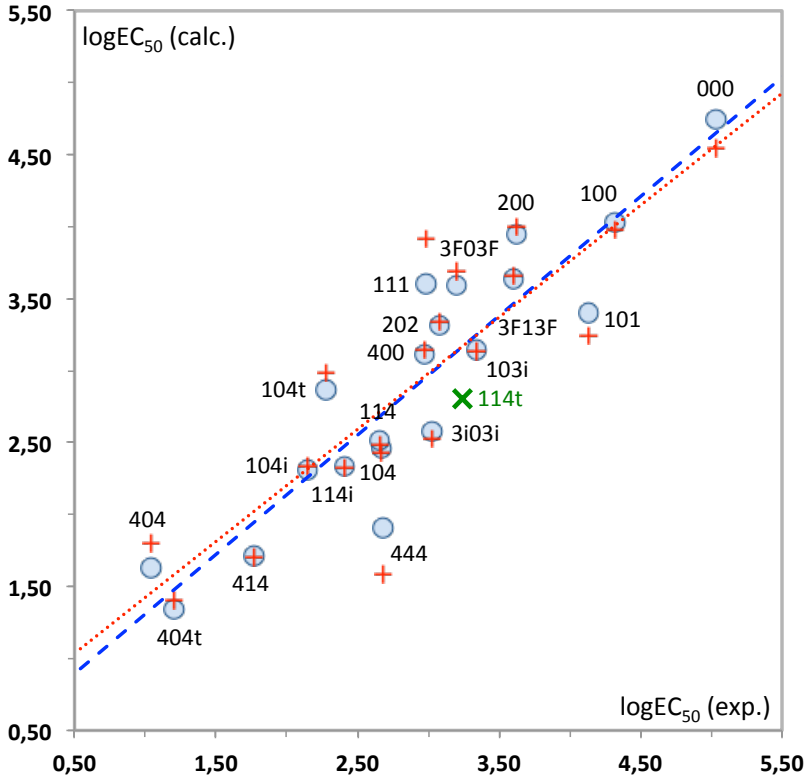

Figure S5. Plots of predicted *vs.* experimental values of $logEC_{50}$ (EC_{50} expressed in $mg \cdot L^{-1}$ units) as calculated through MLR analysis using topological descriptord. Circles represent the predictions made with the plain regression equation and crosses are the cross-validated predictions. Blue and red lines represent the least squares fit between both sets of data, respectively. Green cross represents the pure prediction of the toxicity of compound 114t made with the same MRL equation.

MLR equation derived with the initial 20 solvent set:

$$logEC_{50} = -7.715(\pm 2.710) - 1.455(\pm 0.200) \cdot {}^{v}\chi_2 + 4.779(\pm 1.023) \cdot Bal^{JX} + 0.553(\pm 0.180) \cdot HBD_{count}$$

N = 20, R = 0.91, $\sigma(y) = 0.436$
$F = 27.0$ ($F_{(3,16,\,0,05)} = 3.2$)

MLR equation derived including the experimental value of 114t (21 solvent set):

$$logEC_{50} = -8.421(\pm 2.576) - 1.490(\pm 0.195) \cdot {}^{v}\chi_2 + 5.054(\pm 0.970) \cdot Bal^{JX} + 0.560(\pm 0.179) \cdot HBD_{count}$$

N = 21, R = 0.91, $\sigma(y) = 0.434$
$F = 27.3$ ($F_{(3,17,\,0,05)} = 3.2$)

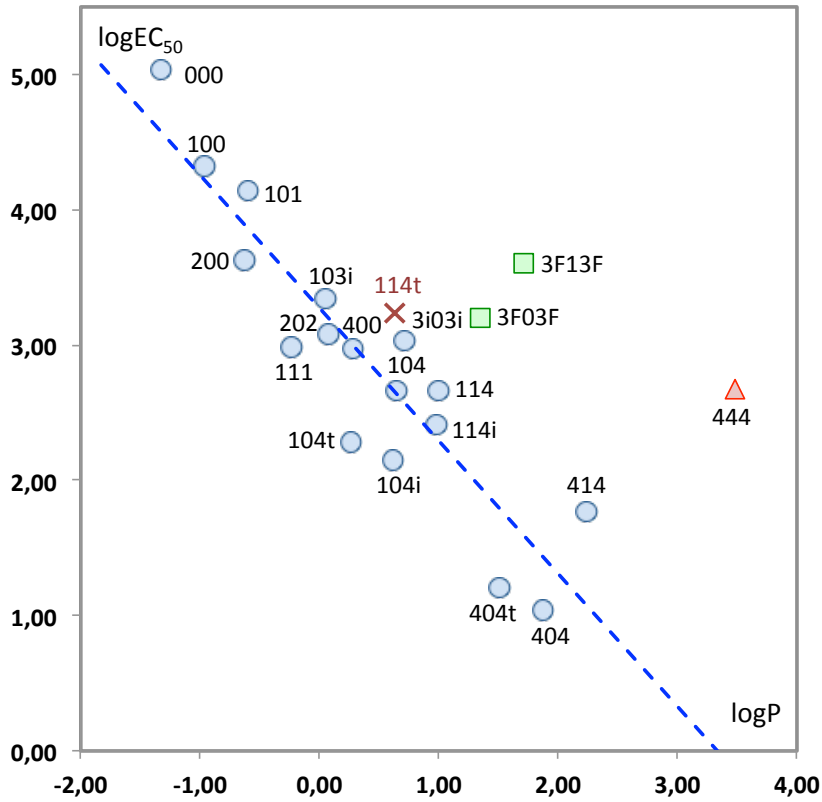

Figure S6. Plot of $logEC_{50}$ (EC_{50} expressed in $mg \cdot L^{-1}$ units) *vs.* logP. Only the solvents represented with circles have been used to obtain the least-squares fitting line. Red cross represents the pure prediction of the toxicity of compound 114t made with the same MRL equation.

MLR equation derived with the initial 20 solvent set:

$$logEC_{50} = 3.243(\pm 0.112) - 0.992(\pm 0.110) \cdot logP$$

$N = 17$, $R = 0.92$, $\sigma(y) = 0.429$
$F = 81.9$ ($F_{(1,16,\,0,05)} = 4.5$)

MLR equation derived including the experimental value of 114t (21 solvent set):

$$logEC_{50} = 3.274(\pm 0.113) - 0.982(\pm 0.113) \cdot logP$$

$N = 18$, $R = 0.91$, $\sigma(y) = 0.441$
$F = 76.0$ ($F_{(1,17,\,0,05)} = 4.5$)

General procedure for the synthesis of non-fluorinated 1-alkylglycerols ($R^1$00) from glycidol.

3.28 mol of R^1OH (R^1 =Me, Et, ^{i}Pr, ^{n}Bu) and 0.1 mol of KOH were placed in a round bottom flask. The mixture was heated at 70 ºC and 0.5 mol (34 g) of glycidol were added dropwise to the reaction mixture. The reaction was monitored by gas chromatography until no signal of glycidol was observed. After 1 hour the reaction was completed and after cooling down the reaction mixture to room temperature, HCl was added dropwise until neutrality. Salts were filtered off and the excess of alcohol was removed under vacuum. The product was purified by vacuum distillation.

General procedure for the synthesis of fluorinated 1-alkylglycerol (R^f00) from glycidol.

1.1 mol of R^fOH (R^f = CF_3CH_2) and 1 mol (140 g) of potassium carbonate were placed in a round bottom flask. The flask was heated up at 70 ºC, and 1 mol of glycidol was added dropwise to the reaction mixture. The reaction was monitored by gas chromatography until no signal of glycidol was observed. After 1 hour the reaction was completed and after cooling down, the reaction was filtered off in order to remove potassium carbonate. The reaction mixture was diluted with 75 mL of water and then extracted with dichloromethane‡ (3 x 50 mL). The organic phase was washed with 50 mL of a saturated solution of NaCl, dried with $MgSO_4$ and the solvent was removed under vacuum. Finally the product was purified by vacuum distillation.

General procedure for the synthesis of non-fluorinated symmetric 1,3-dialkylglycerols ($R^1$0R^1) from epichlorohydrin.

300 mL of R^1OH (R^1 = Me, Et, ^{i}Pr, nBu) were placed in a round bottom flask and cooled in an ice bath. Then 1 mol (24 g) of sodium was added to generate the corresponding alkoxide. When the sodium reacted completely, the flask was heated up to 70 ºC, and 1 mol of epichlorohydrin (94 g) was added dropwise to the reaction mixture. The reaction was monitored by gas chromatography until no signal of epichlorohydrin was observed. After 1 hour, the reaction was completed. The solvent was removed under vacuum, the reaction was cooled down in an ice bath and 25 mL of water were added. Extractions with dichloromethane‡ (3 x 50 mL) were carried out. The organic phase was washed with 50 mL of saturated solution of NaCl and finally dried with $MgSO_4$. The solvent was removed under vacuum. Non-fluorinated 1,3-dialkoxyglycerols were purified by vacuum distillation.

General procedure for the synthesis of fluorinated symmetric 1,3-dialkylglycerols (R^f0R^f) from epichlorohydrin

2.2 mol of R^fOH (R = CF_3CH_2) and 1 mol (140 g) of potassium carbonate were placed in a round bottom flask. The flask was heated up at 70 ºC, and 1 mol of epichlorohydrin (94g) was then added dropwise to the reaction mixture. The reaction was monitored by gas chromatography until no signal of epichlorohydrin was observed. After 1 hour the reaction was completed and after cooling down, the reaction was filtered off in order to remove potassium carbonate. The reaction mixture was diluted with 75 mL of water and then extracted with dichloromethane‡ (3 x 50 mL). The organic phase was washed with 50 mL of a saturated solution of NaCl, dried with $MgSO_4$ and the solvent was removed under vacuum. Finally the product was purified by vacuum distillation.

General procedure for the synthesis of non-fluorinated non-symmetric 1,3-dialkylglycerols ($R^1$0R^3) from glycidol ethers

3.28 mol of R^1OH (R^1 =Me, Et, ^{i}Pr, nBu) and 0.1 mol of KOH were placed in a round-bottomed flask. The mixture was heated at 70 ºC and then 0.5 mol of the corresponding glycidol ether were added dropwise to the reaction mixture (glycidyl isopropyl ether (R^3 = iPr) 59 g; butyl glycidyl ether (R^3 = nBu) 68.5 g; glycidyl isobutyl ether (R^3 = iBu) 67.5 g; tert-butyl glycidyl ether (R^3 = tBu), 67 g). The reaction was monitored by gas chromatography until no signal of glycidol was observed. After 1 hour the reaction was completed and after cooling down the reaction mixture to room temperature, HCl was added dropwise until neutrality. Salts were filtered off and the excess of alcohol was removed under vacuum. The product was purified by vacuum distillation.

General procedure for the synthesis of 1,2,3-trialkylglycerols ($R^1R^2R^3$) from 1,3-dialkylglycerols

1.8 mol of NaH were placed in a round bottom flask together with 250 mL of anhydrous THF. Then 1.8 mol of 1,3-dialkylglycerols (R^10R^1 or R^10R^3) diluted in 50 mL of THF were added dropwise to the reaction flask. The reaction was heated at 40 ºC and then 2.2 mol of R^2I were slowly added. When finished, the reaction was cooled down in an ice bath, quenched with 200 mL of water and neutralized with HCl. The organic phase was separated and the water phase was extracted with ether (4 x 100 mL). The combined organic phase was dried with $MgSO_4$ and the solvent was removed under vacuum. The product was purified by vacuum distillation.

‡NOTE ABOUT THE USE OF DICHLOROMETHANE IN THE SYNTHETIC PROCEDURES

As a referee noted, although dichloromethane is a very convenient solvent for the purification steps of some of the glycerol derivatives described, allowing easy phase separation and subsequent elimination in a rotary evaporator, its use is not desirable in the context of a green strategy. In this regard, ethyl acetate has been successfully tested with the same purpose, so the experimental procedure can be modified accordingly. We have, however, maintained the description of the original procedure for the sake of truthfulness.