

Electronic Supplementary Information

Nitrogen atoms in the following groups were not counted as acceptors: nitro, amide, amidine, sulphonamide, aniline, pyrrol, N=O, quaternary N, positive aromatic N and vinylamine.

- 5 The following bonds were not counted as rotatable bonds: bonds to terminal triple bonds, C-N bond in amide groups and amidine groups, N-S bond in sulphonamide groups, bonds between an aromatic ring and a nitro group, carboxylate group, amide group and an anilinic or anilidic nitrogen atom, vinylic amide bonds, vinylic carbonyl bonds, bonds between aromatic atoms (e.g. biphenyl), styrol bonds, conjugated double bonds, diphenylmethylene bonds, bonds to trihalogenated atoms and trimethylated atoms, as well as bonds to SO_3^- and PO_3^{2-} groups.

10

Table S1 Influence of hydrogen bond donors (Hdon), hydrogen bond acceptors (Hacc), the number of rotatable bonds (Nrot) and the calculated octanol-water partition coefficient (ClogP) on the T_m under the constraint that only the descriptors of interest is increased while the respective other descriptors remain constant.

In-house								
descriptors	const	Δdescr^a	ΔT_m^b	SD ^c	signif ^d	%<0 ^e	%>0 ^f	n ^g
Hdon	Hacc, ClogP, Nrot	1.1	48	46	yes***	16.7	80.6	36
Hacc	Hdon, ClogP, Nrot	1	36	45	yes*	18.8	81.3	16
ClogP	Hdon, Hacc, Nrot	0.5	3	40	no(0.14)	43.1	54.5	167
Nrot	Hdon, Hacc, ClogP	1.2	-21	36	yes***	74.2	24.2	66
Karthikeyan								
descriptors	const	Δdescr^a	ΔT_m^b	SD ^c	signif ^d	%<0 ^e	%>0 ^f	n ^g
Hdon	Hacc, ClogP, Nrot	1.1	30	61	yes*	28.0	70.0	50
Hacc	Hdon, ClogP, Nrot	1.7	19	51	yes***	32.6	67.0	270
ClogP	Hdon, Hacc, Nrot	0.6	6	46	yes***	41.3	58.0	828
Nrot	Hdon, Hacc, ClogP	2.0	-11	58	yes*	63.7	34.6	182

^a mean change of the descriptor of interest. ^b mean change of the T_m . ^c standard deviation of T_m changes. ^d significance, 'yes' if ΔT_m significantly deviates from zero ($p < 0.05$), 'no' if ΔT_m does not significantly deviate from zero ($p > 0.05$), p-values are classified (* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$) or written in brackets. ^e frequency T_m is decreased. ^f frequency T_m is increased. ^g number of MMPs.

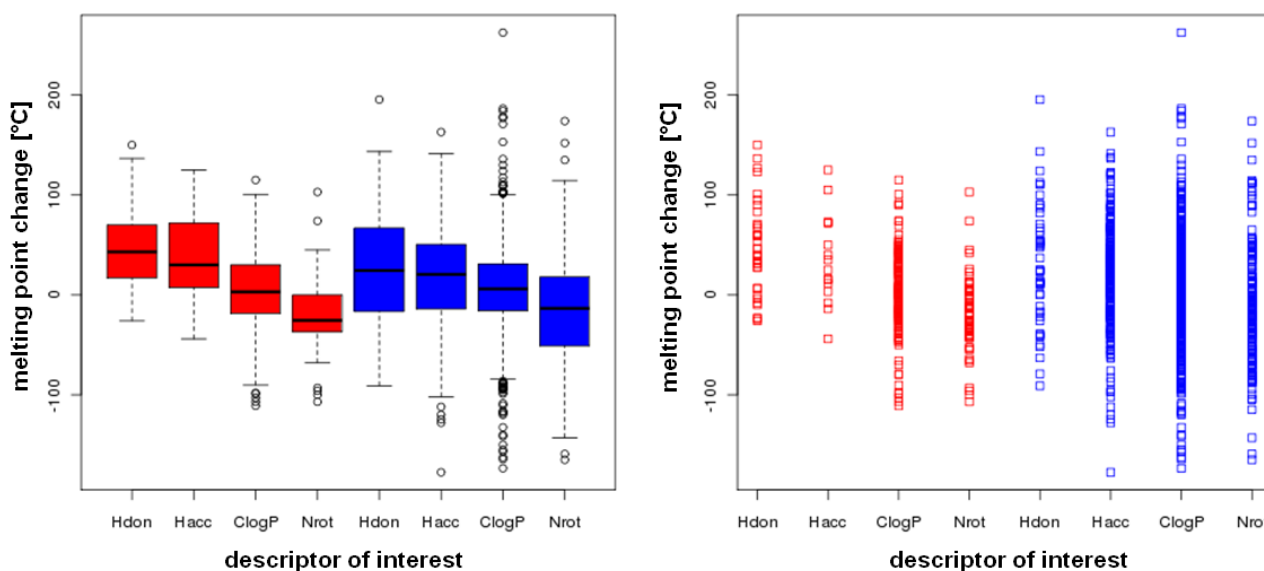


Fig. S1 Box plots (left) and strip plots (right) of the T_m changes if the descriptor of interest (number of hydrogen bond donors (Hdon), number of hydrogen bond acceptors (Hacc), calculated octanol-water partition coefficient (ClogP), number of rotatable bonds (Nrot)) is increased while the respective other descriptors remain constant. In-house data are shown in red, Karthikeyan data are shown in blue.

Table S2 Influence of hydrogen bond donors (Hdon), hydrogen bond acceptors (Hacc) and the number of rotatable bonds (Nrot) on the T_m under the constraint that only the descriptor of interest is increased while the respective other descriptors, as well as the number of each halogen atom type (nX), remain constant.

In-house								
descriptors	const	Δ descr ^a	ΔT_m ^b	SD ^c	signif ^d	%<0 ^e	%>0 ^f	n ^g
Hdon	Hacc, Nrot, nX	1.1	53	45	yes***	13.5	82.7	52
Hacc	Hdon, Nrot, nX	1.0	22	38	yes***	24.6	70.5	61
Nrot	Hdon, Hacc, nX	1.4	-24	39	yes***	75.7	23.2	177
Karthikeyan								
descriptors	const	Δ descr ^a	ΔT_m ^b	SD ^c	signif ^d	%<0 ^e	%>0 ^f	n ^g
Hdon	Hacc, Nrot, nX	1.1	33	59	yes***	27.3	68.0	128
Hacc	Hdon, Nrot, nX	1.5	16	51	yes***	35.8	63.6	505
Nrot	Hdon, Hacc, nX	2.1	-16	50	yes***	67.5	31.5	495

^a mean change of the descriptor of interest. ^b mean change of the T_m . ^c standard deviation of T_m changes. ^d significance, 'yes' if ΔT_m significantly deviates from zero ($p < 0.05$), 'no' if ΔT_m does not significantly deviate from zero ($p > 0.05$), p-values are classified (* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$) or written in brackets. ^e frequency T_m is decreased. ^f frequency T_m is increased. ^g number of MMPs.

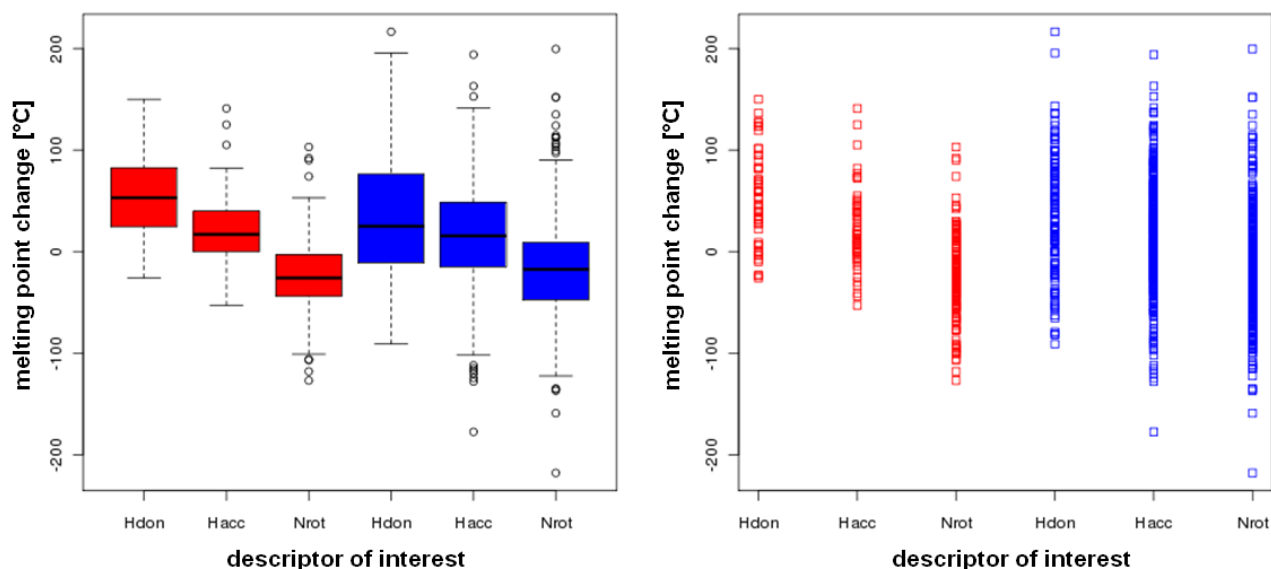


Fig. S2 Box plots (left) and strip plots (right) of the T_m change if the descriptors of interest (number of hydrogen bond donors (Hdon), number of hydrogen bond acceptors (Hacc), number of rotatable bonds (Nrot)) is increased while the respective other descriptors, as well as the number of each halogen atom type, remain constant. In-house data are shown in red, Karthikeyan data are shown in blue.

Table S3 Influence on the T_m if the number of hydrogen bond donors (Hdon) and hydrogen bond acceptors (Hacc) is decreased and the number of rotatable bonds (Nrot) is increased while the number of each halogen atom type (nX) remains constant.

In-house							
descriptors	const	ΔT_m^a	SD ^b	signif ^c	%<0 ^d	%>0 ^e	n ^f
Hdon↓ Hacc↓ Nrot↑	nX	-63	27	yes*	100	0	4
Karthikeyan							
descriptors	const	ΔT_m^a	SD ^b	signif ^c	%<0 ^d	%>0 ^e	n ^f
Hdon↓ Hacc↓ Nrot↑	nX	-57	61	yes***	83.2	16.8	250

^a mean change of the T_m . ^b standard deviation of T_m changes. ^c significance, 'yes' if ΔT_m significantly deviates from zero ($p < 0.05$), 'no' if ΔT_m does not significantly deviate from zero ($p > 0.05$), p-values are classified (* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$) or written in brackets. ^d frequency T_m is decreased. ^e frequency T_m is increased. ^f number of MMPs.

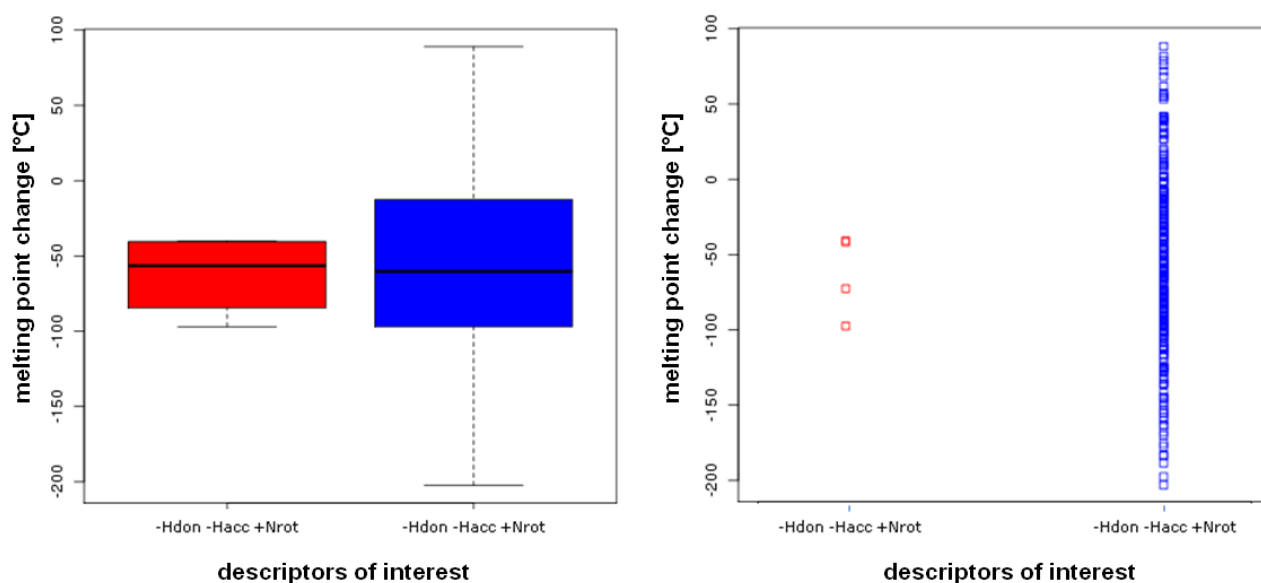


Fig. S3 Box plots (left) and strip plots (right) of the T_m changes if the number of hydrogen bond donors (Hdon) and hydrogen bond acceptors (Hacc) is decreased and the number of rotatable bonds (Nrot) is increased while the number of each halogen atom type remains constant. In-house data are shown in red, Karthikeyan data are shown in blue.

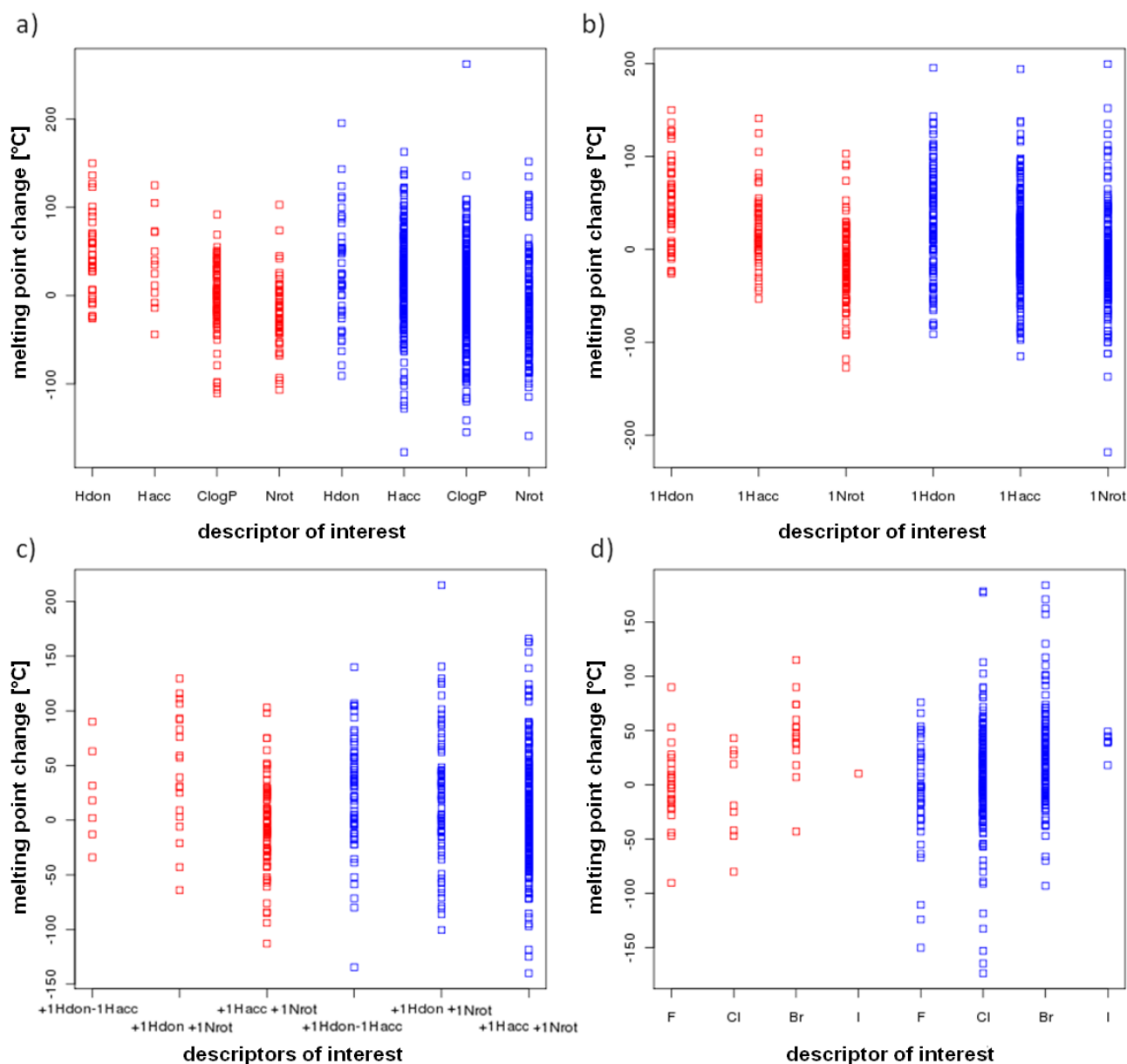
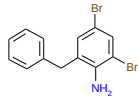
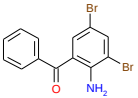
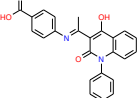
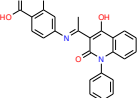


Fig. S4 a) Strip plots of the T_m changes if the descriptor of interest (number of hydrogen bond donors (Hdon), number of hydrogen bond acceptors (Hacc), calculated octanol-water partition coefficient (ClogP), number of rotatable bonds (Nrot)) is increased while the respective other descriptors, as well as the number of each halogen atom type, remain constant. b) Strip plots of the T_m changes if the descriptor of interest is increased exactly by one while the respective other descriptors, as well as the number of each halogen atom type, remain constant. c) Strip plots of the T_m changes if two descriptors of interest (out of hydrogen bond donors, hydrogen bond acceptors or the number of rotatable bonds) are changed exactly by one while the remaining descriptor, as well as the number of each halogen atom type, remains constant. d) Strip plots of the T_m changes if the number of one halogen atom type (F, Cl, Br, I) is increased while the number of the respective other halogen atom types, as well as the number of hydrogen bond donors, the number of hydrogen bond acceptors and the number of rotatable bonds, remains constant. In-house data are shown in red, Karthikeyan data are shown in blue.

Table S4 Examples of MMPs of the Karthikeyan dataset where the addition of a hydrogen bond donor and/or hydrogen bond acceptor leads to a T_m decrease.

QUERY	HIT	$T_m(Q)^a$	$T_m(H)^b$	ΔT_m^c	$\Delta desc^b$
		195	98	-97	+1Hacc
		237	177	-60	+1Hdon +1Hacc

^a T_m of the QUERY compound. ^b T_m of the HIT compound. ^c T_m change ($T_m(H)-T_m(Q)$). ^d change of descriptors (hydrogen bond donor (Hdon), hydrogen bond acceptor (Hacc))