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多种类杂环化合物的药理和毒理活性系数构效关系

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Structure-Property Relationship for the Pharmacological and Toxicological Activity of Heterocyclic Compounds

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Table S1 Experimental and predicted AH receptor binding affinity pEC_{50} based on our model eq. (1) and Basak et al.' method, for the set of 32 dibenzofurans compounds

Chemical	exp. pEC_{50}[26]	Basak *et al.*' Method[16]		This work	
		pred. pEC_{50}	AD [a]	pred. pEC_{50}	AD
2-Cl	3.553	3.169	0.384	3.665	0.112
3-Cl	4.377	4.199	0.178	4.506	0.129
4-Cl	3.000	3.692	-0.692	3.270	0.270
2,3-diCl	5.326	4.964	0.362	5.346	0.020
2,6-diCl	3.609	4.279	-0.67	4.958	1.349
2,8-diCl [b]	3.590	4.251	-0.661	4.128	0.538
1,2,7-trCl	6.347	5.646	0.701	6.436	0.089
1,3,6-trCl	5.357	4.705	0.652	5.265	0.093
1,3,8-trCl [b]	4.071	5.330	-1.259	4.806	0.735
2,3,8-trCl	6.000	6.394	-0.394	6.471	0.471
1,2,3,6-teCl	6.456	6.480	-0.024	6.922	0.466
1,2,3,7-teCl	6.959	7.066	-0.107	7.769	0.810
1,2,4,8-teCl	5.000	4.715	0.285	5.381	0.381
2,3,4,6-teCl [b]	6.456	7.321	-0.865	6.991	0.535
2,3,4,7-teCl	7.602	7.496	0.106	7.917	0.315
2,3,4,8-teCl	6.699	6.976	-0.277	7.266	0.567
2,3,6,8-teCl	6.658	6.008	0.650	6.224	0.434
2,3,7,8-teCl	7.387	7.139	0.248	7.774	0.387
1,2,3,4,8-peCl [b]	6.921	6.293	0.628	6.822	0.099
1,2,3,7,8-peCl	7.128	7.213	-0.085	7.598	0.470
1,2,3,7,9-peCl	6.398	5.724	0.674	6.723	0.325
1,2,4,6,7-peCl	7.169	6.135	1.035	7.015	0.154
1,2,4,7,8-peCl	5.886	6.607	-0.720	6.136	0.250
1,2,4,7,9-peCl	4.699	4.937	-0.238	5.454	0.755
1,3,4,7,8-peCl	6.699	6.513	0.186	6.607	0.092

2,3,4,7,8-peCl	7.824	7.479	0.345	8.194	0.370
2,3,4,7,9-peCl	6.699	6.509	0.190	6.919	0.220
1,2,3,4,7,8-heCl	6.638	6.802	-0.164	7.029	0.391
1,2,3,6,7,8-heCl [b]	6.569	7.124	-0.555	7.469	0.900
1,2,4,6,7,8-heCl	5.081	5.672	-0.591	5.648	0.567
2,3,4,6,7,8-heCl	7.328	7.019	0.309	7.513	0.185
Dibenzofuran	3.000	2.765	0.235	3.422	0.422

[a] AD: the absolute difference

[b] Compounds for the testing set members

Table S2 Experimental and predicted mutagenic activity ln*R* based on our model eq. (2) and Basak et al.' method for the set of 95 aromatic and heteroaromatic amines

Chemicals	exp. ln*R* [27]	Basak SC et al. Method[17]		This work	
		pred. ln*R*	AD [a]	pred. ln*R*	AD
2-Bromo-7-aminofluorene	2.62	1.99	0.63	2.58	0.04
2-Methoxy-5-methylaniline(*p*-cresidine)	-2.05	-2.82	0.77	-2.74	0.69
5-Aminoquinoline [b]	-2.00	-1.85	0.15	-1.87	0.13
4-Ethoxyaniline(*p*-phenetidine)	-2.30	-3.26	0.96	-2.27	0.03
1-Aminonaphthalene [b]	-0.60	-0.61	0.01	-2.01	1.41
4-Aminofluorene	1.13	1.14	0.01	0.25	0.88
2-Aminoanthracene [b]	2.62	1.34	1.28	1.20	1.42
7-Aminofluoranthene	2.88	3.10	0.22	2.44	0.44
8-Aminoquinoline	-1.14	-1.76	0.62	-1.21	0.07
1,7-Diaminophenazine	0.75	0.88	0.13	1.07	0.32
2-Aminonaphthalene	-0.67	-0.32	0.35	-1.42	0.75
4-Aminopyrene	3.16	2.57	0.59	2.91	0.25
3-Amino-3_-nitrobiphenyl [b]	-0.55	0.07	0.62	-0.50	0.05
2,4,5-Trimethylaniline	-1.32	-1.18	0.14	-1.52	0.20

3-Aminofluorene	0.89	1.25	0.36	0.80	0.09
3,3_-Dichlorobenzidine [b]	0.81	-0.17	0.98	1.12	0.31
2,4-Dimethylaniline(2,4-xylidine)	-2.22	-2.17	0.05	-2.13	0.09
2,7-Diaminofluorene	0.48	1.11	0.63	1.91	1.43
3-Aminofluoranthene	3.31	2.65	0.66	2.86	0.45
2-Aminofluorene	1.93	1.03	0.90	1.07	0.86
2-Amino-4_-nitrobiphenyl [b]	-0.62	-0.27	0.35	-0.27	0.35
4-Aminobiphenyl	-0.14	-0.34	0.20	-0.81	0.67
3-Methoxy-4-methylaniline(*o*-cresidine)	-1.96	-2.84	0.88	-2.66	0.70
2-Aminocarbazole	0.60	0.69	0.09	1.19	0.59
2-Amino-5-nitrophenol	-2.52	-2.86	0.34	-1.63	0.89
2,2_-Diaminobiphenyl [b]	-1.52	-0.15	1.37	-1.08	0.44
2-Hydroxy-7-aminofluorene	0.41	1.13	0.72	2.09	1.68
1-Aminophenanthrene	2.38	1.19	1.19	0.93	1.45
2,5-Dimethylaniline	-2.40	-1.98	0.42	-3.06	0.66
4-Amino-2_-nitrobiphenyl [b]	-0.92	-0.05	0.87	0.11	1.03
2-Amino-4-methylphenol	-2.10	-4.05	1.95	-2.12	0.02
2-Aminophenazine [b]	0.55	1.54	0.99	1.17	0.62
4, 4_-Diaminophenyl	0.31	-0.62	0.93	0.27	0.04
2,4-Dinitroaniline	-2.00	-2.07	0.07	-1.78	0.22
2,4-Diaminoisopropylbenzene	-3.00	-2.56	0.45	-3.21	0.21
2,4-Difluoroaniline [b]	-2.70	-2.43	0.27	-2.19	0.51
4,4_-Methylenedianiline	-1.60	-0.96	0.64	-0.44	1.16
3,3_-Dimethylbenzidine [b]	0.01	0.28	0.27	0.72	0.71
2-Aminofluoranthene	3.23	3.27	0.04	2.83	0.40
2-Amino-3-nitrobiphenyl	-0.89	-0.64	0.25	-0.44	0.45
1-Aminofluoranthene	3.35	3.00	0.35	2.36	0.99
4,4_-Ethylenebis(aniline)	-2.15	-1.10	1.05	-1.87	0.28
4-Chloroaniline [b]	-2.52	-2.60	0.08	-2.74	0.22

2-Aminophenanthrene	2.46	1.45	1.01	1.55	0.91
4-Fluoroaniline	-3.32	-3.26	0.06	-3.00	0.32
9-Aminophenanthrene [b]	2.98	1.36	1.62	0.63	2.35
3,3_-Diaminobiphenyl	-1.30	-1.14	0.16	-0.40	0.90
2-Aminopyrene	3.50	2.69	0.81	2.92	0.58
2,6-Dichloro-1,4-phenylenediamine	-0.69	-1.02	0.33	-1.54	0.85
2-Amino-7-acetamidofluorene	1.18	0.37	0.81	1.20	0.02
2,8-Diaminophenazine [b]	1.12	0.77	0.35	1.57	0.45
6-Aminoquinoline	-2.67	-1.52	1.15	-0.66	2.01
4-Methoxy-2-methylaniline(m-cresidine)	-3.00	-2.65	0.35	-2.37	0.63
3-Amino-2_-nitrobiphenyl	-1.30	-0.38	0.92	-0.55	0.75
2,4_-Diamino-biphenyl [b]	-0.92	-0.72	0.20	-0.18	0.74
1,6-Diaminophenazine	0.20	-0.34	0.54	0.15	0.05
4-Aminophenyldisulfide	-1.03	0.91	1.94	-1.29	0.26
2-Bromo-4,6-dinitroaniline	-0.54	-1.06	0.52	-0.58	0.04
2,4-Diamino-*n*-butylbenzene	-2.70	-2.36	0.34	-2.08	0.62
4-Aminophenyl ether [b]	-1.14	-0.45	0.69	-0.11	1.03
2-Aminobiphenyl	-1.49	-0.27	1.22	-1.30	0.19
1,9-Diaminophenazine	0.04	0.00	0.04	0.62	0.58
1-Aminofluorene	0.43	1.25	0.82	0.42	0.01
8-Aminofluoranthene	3.80	3.05	0.75	3.47	0.33
2-Chloroaniline	-3.00	-2.43	0.57	-3.14	0.14
2-Amino-*ααα*-trifluorotoluene	-0.80	-1.88	1.08	-1.96	1.16
2-Amino-1-nitronaphthalene	-1.17	-0.25	0.92	-1.09	0.08
3-Amino-4_-nitrobiphenyl	0.69	0.43	0.26	-0.59	1.28
4-Bromoaniline [b]	-2.70	-1.48	1.22	-2.19	0.51
2-Amino-4-chlorophenol	-3.00	-1.57	1.43	-2.43	0.57
3,3_-Dimethoxybenzidine	0.15	1.11	0.96	-0.04	0.19
4-Cyclohexylaniline	-1.24	-1.75	0.51	-0.99	0.25

4-Phenoxyaniline	0.38	-0.72	1.10	0.01	0.37
4,4_-Methylenebis(*o*-ethylaniline) [b]	-0.99	-0.78	0.21	-0.67	0.32
2-Amino-7-nitrofluorene	3.00	1.87	1.13	1.98	1.02
Benzidine	-0.39	0.20	0.59	-0.21	0.18
1-Amino-4-nitronaphthalene	-1.77	-0.23	1.54	-1.10	0.67
4-Amino-3_-nitrobiphenyl	1.02	0.45	0.57	-0.23	1.25
4-Amino-4_-nitrobiphenyl [b]	1.04	-0.80	1.84	0.19	0.85
1-Aminophenazine	-0.01	1.32	1.33	0.46	0.47
4,4_-Methylenebis(*o*-fluoroaniline)	0.23	0.28	0.05	-0.64	0.87
4-Chloro-2-nitroaniline	-2.22	-2.12	0.10	-1.76	0.46
3-Aminoquinoline	-3.14	-1.26	1.88	-0.66	2.48
3-Aminocarbazole	-0.48	-0.55	0.07	0.83	1.31
4-Chloro-1,2-phenylenediamine [b]	-0.49	-2.21	1.72	-2.58	2.09
3-Aminophenanthrene	3.77	1.36	2.41	1.55	2.22
3,4_-Diaminobiphenyl	0.20	-0.46	0.66	-0.15	0.35
1-Aminoanthracene	1.18	1.42	0.24	0.48	0.70
1-Aminocarbazole	-1.04	-0.54	0.50	0.49	1.53
9-Aminoanthracene	0.87	1.08	0.21	0.64	0.23
4-Aminocarbazole	-1.42	-0.32	1.10	0.44	1.86
6-Aminochrysene [b]	1.83	3.35	1.52	3.29	1.46
1-Aminopyrene	1.43	3.72	2.29	2.79	1.36
4-4_-Methylenebis(*o*-isopropylaniline)	-1.77	-0.34	1.43	-1.45	0.32
2,7-Diaminophenazine	3.97	0.87	3.10	1.64	2.33

[a] AD: the absolute difference

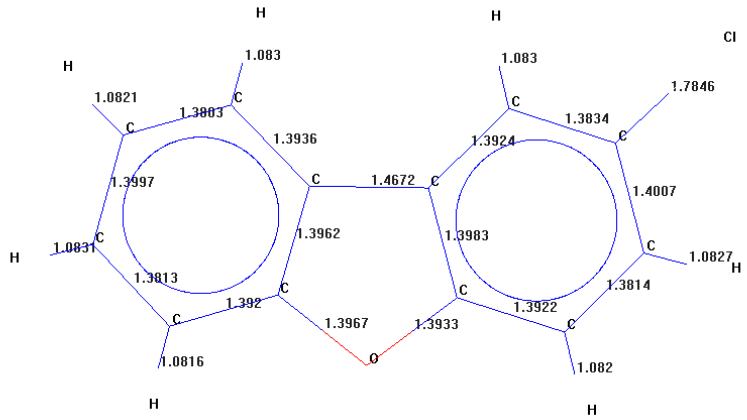
[b] Compounds for the testing set members

Example:

Prediction of the aryl hydrocarbon (AH) receptor binding affinity (described as pEC_{50}) of 2-Cl-dibenzofuran is exampled as follows. For this compound, the total number of

group N is 21, and molecular weight M is 202.56.

Firstly, the structure for the 2-Cl-dibenzofuran is drawn and optimized by Gaussian software.



Secondly, the distant matrix $\boldsymbol{M}_{\mathrm{d}}$, and the extended matrix $\boldsymbol{M}_{\mathrm{e}}$ is described as below.

$$M_d = \begin{bmatrix} 0 & 1 & 2 & 3 & 2 & 1 & 2 & 3 & 4 & 5 & 4 & 3 & 3 & 2 \\ 1 & 0 & 1 & 2 & 3 & 2 & 3 & 4 & 5 & 6 & 5 & 4 & 4 & 1 \\ 2 & 1 & 0 & 1 & 2 & 3 & 4 & 4 & 5 & 6 & 6 & 5 & 3 & 2 \\ 3 & 2 & 1 & 0 & 1 & 2 & 3 & 3 & 4 & 5 & 5 & 4 & 2 & 3 \\ 2 & 3 & 2 & 1 & 0 & 1 & 2 & 2 & 3 & 4 & 4 & 3 & 1 & 4 \\ 1 & 2 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 4 & 3 & 2 & 2 & 3 \\ 2 & 3 & 4 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 2 & 1 & 2 & 4 \\ 3 & 4 & 4 & 3 & 2 & 2 & 1 & 0 & 1 & 2 & 3 & 2 & 1 & 5 \\ 4 & 5 & 5 & 4 & 3 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 2 & 6 \\ 5 & 6 & 6 & 5 & 4 & 4 & 3 & 2 & 1 & 0 & 1 & 2 & 3 & 7 \\ 4 & 5 & 6 & 5 & 4 & 3 & 2 & 3 & 2 & 1 & 0 & 1 & 4 & 6 \\ 3 & 4 & 5 & 4 & 3 & 2 & 1 & 2 & 3 & 2 & 1 & 0 & 3 & 5 \\ 3 & 4 & 3 & 2 & 1 & 2 & 2 & 1 & 2 & 3 & 4 & 3 & 0 & 5 \\ 2 & 1 & 2 & 3 & 4 & 3 & 4 & 5 & 6 & 7 & 6 & 5 & 5 & 0 \end{bmatrix}$$

$$Me = \begin{bmatrix} 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 3.44 & 3.16 \\ 1.75 & 1.60 & 1.75 & 1.75 & 1.60 & 1.60 & 1.60 & 1.60 & 1.75 & 1.75 & 1.75 & 1.75 & 1.42 & 1.80 \\ 1.3834 & 1.3834 & 1.3814 & 1.3814 & 1.3922 & 1.3924 & 1.3936 & 1.392 & 1.3813 & 1.3813 & 1.3803 & 1.3803 & 1.3933 & 1.7846 \\ 2 & 3 & 2 & 2 & 3 & 3 & 3 & 3 & 2 & 2 & 2 & 2 & 2 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 \end{bmatrix}$$

$$Me = \begin{bmatrix} 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 2.55 & 3.44 & 3.16 \\ 1.75 & 1.60 & 1.75 & 1.75 & 1.60 & 1.60 & 1.60 & 1.60 & 1.75 & 1.75 & 1.75 & 1.75 & 1.42 & 1.80 \\ 1.3834 & 1.3834 & 1.3814 & 1.3814 & 1.3922 & 1.3924 & 1.3936 & 1.392 & 1.3813 & 1.3813 & 1.3803 & 1.3803 & 1.3933 & 1.7846 \\ 2 & 3 & 2 & 2 & 3 & 3 & 3 & 3 & 2 & 2 & 2 & 2 & 2 & 1 \\ 1 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & 0 & 0 \end{bmatrix}$$

Thirdly, in this work, the norm values of the extended matrix are calculated and shown as in Table S3.

Table S3 Norm values of extended matrix for 2-Cl-dibenzofuran

extended matrix	norm(M,1)	norm(M,2)	norm(M,fro)	norm(M,inf)
M_D	57.6696	41.6355	46.7410	53
M_A	9.0621	12.3061	13.5912	32
M_B	11.06215	12.5624	14.0968	
M_C	10.2020	12.4590	13.9542	

Lastly, from parameters in Table 3, the pEC_{50} of 2-Cl-dibenzofuran is predicted by Eq. (1):

$$\begin{aligned} pEC_{50} = {} & 0.2730\times 57.6696 - 18.5465\times 41.6355 + 14.0124\times 46.7410 - 0.1447\times 53 - 22.7744\times 9.0621 \\ & -48.5409\times 12.3061 - 462.3183\times 13.5912 - 5.9163\times 32 - 0.1887\times 11.0625 \\ & +156.6532\times 12.5624 + 428.6100\times 14.0970 + 0.2801\times 10.2020 - 55.6900\times 12.4590 \\ & +16.3321\times 13.9542 + 3544.4709\exp(\frac{1}{21}) + 10679.1349\exp(\frac{1}{202.56}) - 14604.7935 \\ & = 3.665 \end{aligned}$$

The calculated result is 3.665 while the experimental pEC_{50} is 3.553.