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Development of a predictive statistical model for the analgesic activity of a family of imides

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Quantitative structure-activity relationship (QSAR) studies were done with a family of cyclic imides. Promising efforts to create a QSAR model with substantial predictive power for the design of novel cyclic imides with improved analgesic activity are reported.

1. Introduction

We have previously reported the synthesis and analgesic activity of a family of cyclic imides [1–6]. Among these are compounds having potency in a standard biological assay of analgesia comparable to or greater than that of agents, including aspirin and paracetamol, employed in clinical medicine. Within this family of imides, sufficient structure/potency data have been collected to permit the development of a quantitative structure-activity relationship (QSAR) [7, 8]. A QSAR with substantial predictive power would obviously be useful for the design of novel cyclic imides having improved analgesic activity. This communication reports results of a promising effort to create such a QSAR model.

2. Investigations, results and discussion

Structures of imides examined in this study and measures of their analgesic activity are collected in the Table. The data set to be modeled includes 34 imides of moderate structural diversity having analgesic activity spanning about two orders of magnitude. The standard error of the measured analgesic potencies is taken to be ± 0.2 logarithm units.

For modeling purposes, the data set was divided into five arbitrary subsets, four of which contained seven imides and the fifth of which contained six. Ten fractional QSAR models were computed, each employing as training set one of the ten possible combinations of three of the five subsets. The two remaining subsets were, in each case, employed as the test set. Thus, in each fractional modeling effort, 20 or 21 compounds in the training set were employed to predict values for 13 or 14 compounds in the test set. At completion of the ten modeling runs, values for analgesic activity had been estimated six times for each compound as a member of a training set and predicted four times for each compound as a member of a test set. The property value modeled was the logarithm of the analgesic potency.

For each compound in the data set, measured, estimated, and predicted values of logarithms of analgesic potency are collected in Table 1. These values are presented as averages of the six estimates and four predictions, together with their standard deviations. The differences between the measured and estimated or predicted values are also included in the Table. In the Fig., the data are presented graphically as a plot of the logarithms of the measured values of analgesic potency against the corresponding estimated and predicted values.

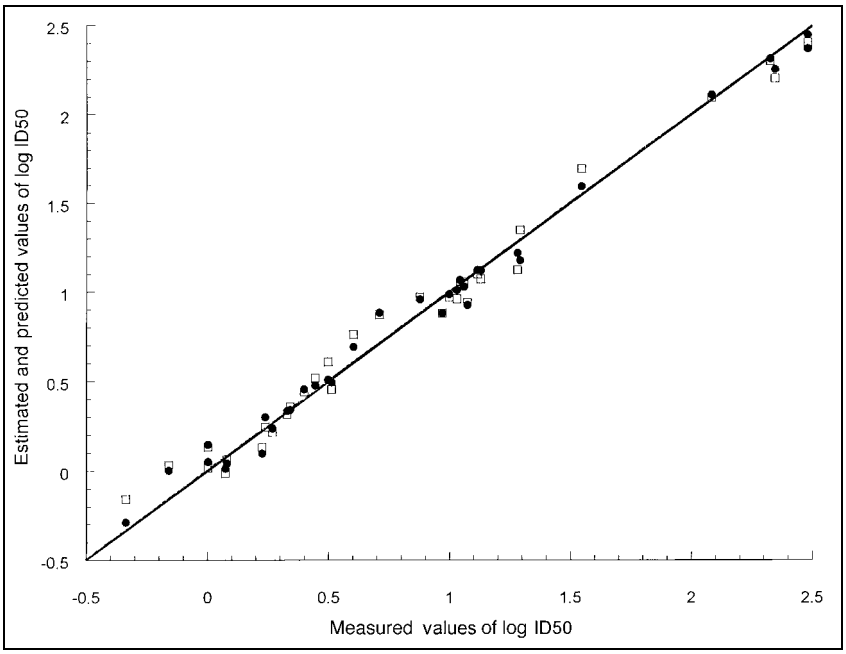


Fig.: Logarithms of measured values of analgesic potency plotted against the logarithms of estimated (circles) and predicted (squares) values

Table: Measured, estimated, and predicted values of analgesic potency for a family of cyclic imides

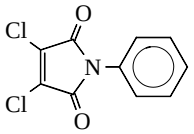
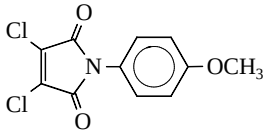
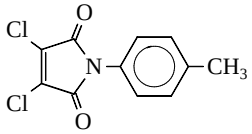
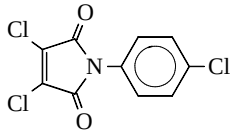
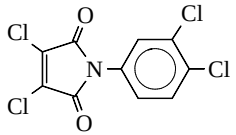
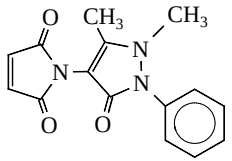
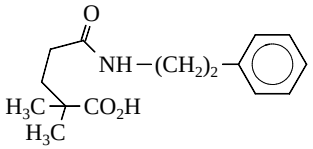
Compd.	Structure	ID_{50} ($\mu mol\ kg^{-1}$)	log ID_{50} Measured	log ID_{50}[a] Estimated	log ID_{50}[b] Predicted	Δ Estimated [c]	Δ Predicted[d]
1		2.78	0.444	0.478 ± 0.04	0.519 ± 0.04	−0.034	−0.075
2		11.81	1.072	0.926 ± 0.05	0.940 ± 0.04	0.146	0.132
3		10.67	1.028	1.009 ± 0.03	0.961 ± 0.05	0.019	0.067
4		9.31	0.969	0.881 ± 0.04	0.885 ± 0.07	0.088	0.084
5		3.14	0.497	0.509 ± 0.04	0.610 ± 0.04	−0.012	−0.113
6		2.5	0.398	0.457 ± 0.04	0.443 ± 0.03	−0.059	−0.045
7		11	1.01	1.066 ± 0.06	1.040 ± 0.05	−0.025	0.001

Table continued

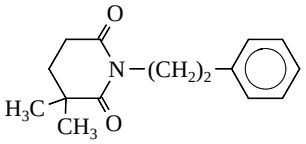
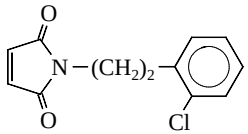
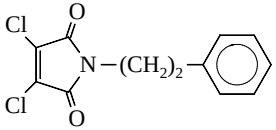
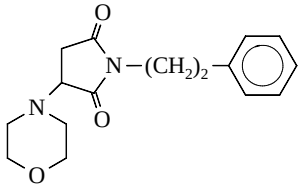
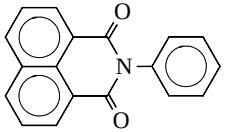
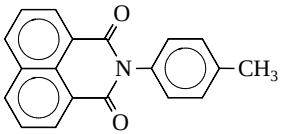
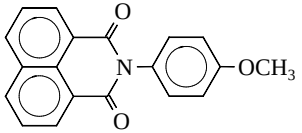
Compd.	Structure	ID_{50} ($\mu mol\ kg^{-1}$)	log ID_{50} Measured	log ID_{50}[a] Estimated	log ID_{50}[b] Predicted	Δ Estimated [c]	Δ Predicted[d]
8		123	2.081	2.112 ± 0.06	2.095 ± 0.03	−0.031	−0.014
9		13	1.114	1.122 ± 0.03	1.100 ± 0.07	−0.008	0.014
10		4	0.602	0.693 ± 0.04	0.760 ± 0.02	−0.091	−0.158
11		35	1.544	1.595 ± 0.07	1.695 ± 0.11	−0.051	−0.151
12		1.72	0.236	0.301 ± 0.04	0.245 ± 0.04	−0.065	−0.009
13		2.19	0.340	0.340 ± 0.06	0.358 ± 0.04	0	−0.018
14		0.69	−0.1612	0.002 ± 0.04	0.032 ± 0.07	−0.163	−0.193

Table continued

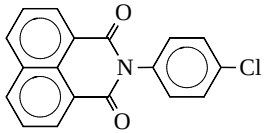
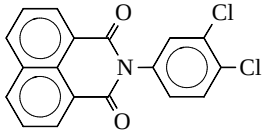
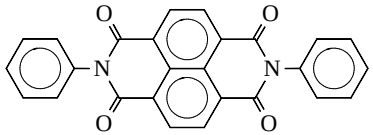
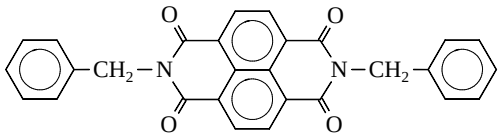
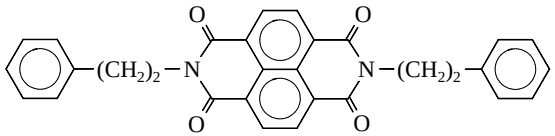
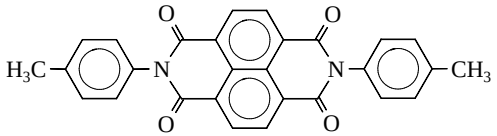
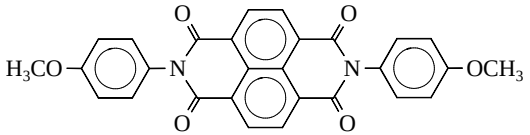
Compd.	Structure	ID_{50} ($\mu mol\ kg^{-1}$)	log ID_{50} Measured	log ID_{50}[a] Estimated	log ID_{50}[b] Predicted	Δ Estimated [c]	Δ Predicted[d]
15		3.25	0.512	0.494 ± 0.04	0.455 ± 0.05	0.018	0.057
16		1.0	0.001	0.147 ± 0.02	0.135 ± 0.09	−0.146	−0.134
17		1.0	0.001	0.051 ± 0.04	0.017 ± 0.01	−0.050	−0.016
18		2.13	0.328	0.335 ± 0.02	0.317 ± 0.05	−0.007	0.011
19		1.85	0.267	0.237 ± 0.02	0.218 ± 0.05	0.030	0.049
20		1.2	0.079	0.042 ± 0.05	0.064 ± 0.02	0.037	0.015
21		0.46	−0.337	−0.287 ± 0.07	−0.156 ± 0.01	−0.050	−0.181

Table continued

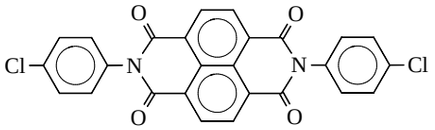
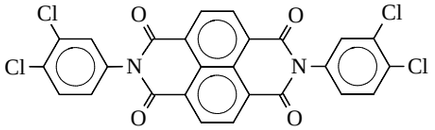
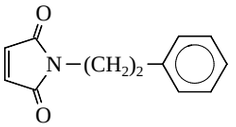
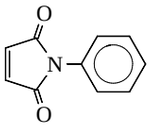
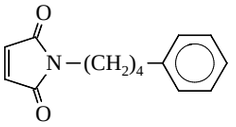
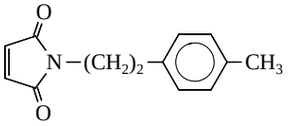
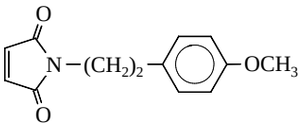
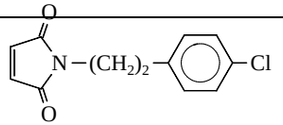
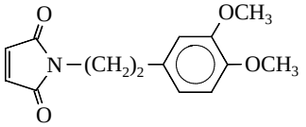
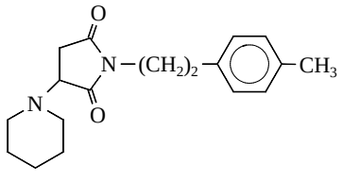
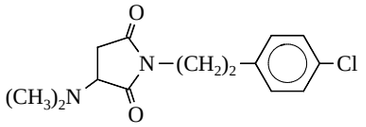
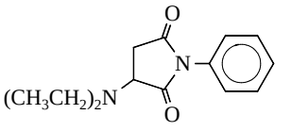
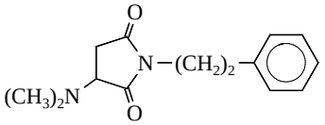
Compd.	Structure	ID_{50} (μmol kg^{-1})	log ID_{50} Measured	log ID_{50}[a] Estimated	log ID_{50}[b] Predicted	Δ Estimated[c]	Δ Predicted[d]
22		1.68	0.225	0.098 ± 0.05	0.134 ± 0.04	0.127	0.091
23		1.18	0.072	0.014 ± 0.05	-0.013 ± 0.05	0.058	0.085
24		13.4	1.127	1.120 ± 0.04	1.073 ± 0.05	0.007	0.054
25		19	1.279	1.219 ± 0.02	1.123 ± 0.03	0.060	0.156
26		7.5	0.875	0.959 ± 0.04	0.970 ± 0.04	-0.084	-0.095
27		5.1	0.709	0.884 ± 0.04	0.874 ± 0.06	-0.175	-0.165
28		9.9	0.996	0.988 ± 0.03	0.971 ± 0.04	0.008	0.025

Table continued

Compd.	Structure	ID_{50} (μmol kg^{-1})	log ID_{50} Measured	log ID_{50}[a] Estimated	log ID_{50}[b] Predicted	Δ Estimated[c]	Δ Predicted[d]
29		19.5	1.290	1.177 ± 0.03	1.348 ± 0.40	0.113	-0.058
30		11.4	1.057	1.029 ± 0.04	1.055 ± 0.03	0.028	0.002
31		210	2.322	2.315 ± 0.04	2.300 ± 0.07	0.007	0.022
32		220	2.342	2.255 ± 0.05	2.205 ± 0.02	0.087	0.137
33		300	2.477	2.372 ± 0.04	2.385 ± 0.06	0.105	0.092
34		300	2.477	2.450 ± 0.05	2.408 ± 0.03	0.027	0.069

[a] Averages of six estimates. [b] Averages of four predictions. [c] The difference between logarithms of measured and esitimated values. [d] The difference between logarithms of measured and predicted values.

The data establish three points. First, the QSAR models developed in this work do an excellent job of characterizing the data set. The estimated values of analgesic potency mirror the measured values within the estimated experimental error for all compounds in the data set. Beyond that, the difference between measured and estimated values is less than one-half the measurement error for 27 of the 34 compounds. Second, these QSAR models to an excellent job of predicting values of logarithms of analgesic activity for compounds in the test sets. Here too, all predicted values reflect measured values within the estimated experimental error for all compounds in the data set. For 24 of the 34 compounds, the difference between measured and predicted values is less than one-half of the experimental error. Third, the estimated and predicted values are largely independent of the nature of the training set, as evidenced by the modest standard deviations reported in the Table. Finally, it is worth noting that the strategy of creating several QSAR models based on different subsets of the data set as training sets has the merit of providing a sensible estimate of the error of predicted values. The QSAR models developed in this work have substantial promise in guiding future efforts to synthesize cyclic imides having improved analgesic potency.

3. Experimental

The synthesis and characterization of all imides employed in this study have been previously reported, as have measures of their analgesic potency in the murine writhing test [1–6].

Statistical modeling studies have been conducted employing novel QSAR technology. This technology includes the use of traditional QSAR molecular descriptors as well as a collection of surface electron density-based molecular descriptors developed employing transferable atom equivalent (TAE) technology [9]. The data set was decomposed into a large number of overlapping subsets employing these descriptors and a mixture of regression models algorithm [10]. Each subset was examined for its ability to create models which made qualified predictions for analgesic activity for compounds outside the subset but within the data set. Those subsets which met this standard were retained and refined QSAR models were created based upon them. This procedure created a large number of subsets (although more than 95% of subsets tested failed to meet the statistical standard for inclusion in the final QSAR model) and a larger number of models (3 to 5 for each subset). These models were employed for calculating values of analgesic activity for compounds outside the subset whose set of molecular descriptors reflected those of the molecules creating the subset. Reported values are averages of the family of predictions based upon these models.

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