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Short Communication

Structure–activity relationships for the analgesic activity of gallic acid derivatives

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Abstract

Values of ID_{50} for a collection of structurally-related gallic acid derivatives have been employed to create a predictive quantitative structure–activity relationship (QSAR) which links structure to values of analgesic activity. The QSAR model developed has substantial predictive power for the design of novel gallic acid derivatives having improved analgesic potency.

Keywords: Analgesic activity; Gallic acid; Structure–activity relationships; QSAR models

1. Introduction

The ability to discover, or to design efficiently, novel, patentable molecules that are potent specific inhibitors of enzymes, or potent specific agonists or antagonists of biological receptors, is of great importance. Many such molecules contribute to the prevention of, or are used as therapy for, human diseases [1].

Quantitative structure–activity relationships (QSAR) have been employed — and continue to be developed and employed — both to correlate information in data sets and as a tool to facilitate, for example, the discovery of new molecules with increased biological potency. A very large number of such QSAR models have been developed for an amazing variety of properties [2,3]. Recently, we have reported the development of useful QSAR models for enzyme inhibition [1,4], and analgesic activity [5].

As part of our efforts to create QSAR models that show substantial predictive promise for the design of new compounds with improved pharmacological activity, we have previously synthesized and evaluated the analgesic activity of a large group of gallic acid derivatives [6]. Among these are compounds which have potencies in standard biological assays of analgesia comparable to, or greater than, that of substances employed in clinical medicine, such as aspirin and acetaminophen. This communication reports the results of a promising effort to create a QSAR model employing the structure/potency data collected for this series of gallic acid derivatives.

2. Results

Structures of gallic acid derivatives employed in this study and corresponding values of their analgesic activity are collected in Table 1. The data set to be modeled includes 49 compounds that have an analgesic activity spanning about two and a half orders of magnitude. The group of gallic acid derivatives examined has moderate structural diversity.

For statistical modeling of the values of log ID_{50}, the data set was divided into three arbitrary subsets, two of which each contained sixteen and the third of which contained seventeen compounds. The first subset contained those compounds numbered **001**, **004**, **007**, **010**, . . . in Table 1; the second contained those compounds numbered **002**, **005**, **008**, **011**, . . . , and so forth.

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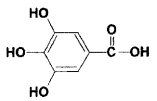
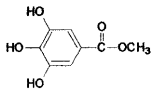
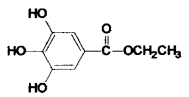
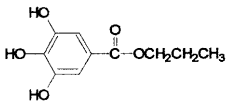
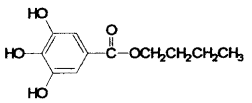
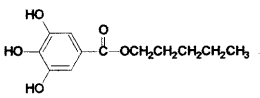
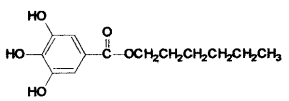
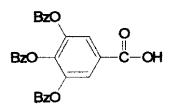
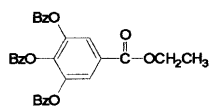
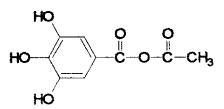
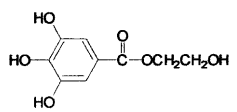
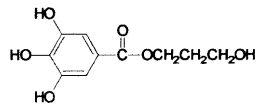
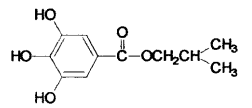
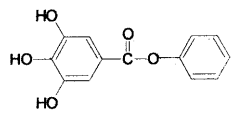
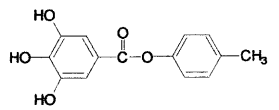
Table 1
Measured, estimated, and predicted values of analgesic potency for a series of gallic acid derivatives

Comp.	Structure	ID_{50} (μmol/kg)	log ID_{50} measured [a]	log ID_{50} estimated	log ID_{50} predicted	Δ estimated [b]	Δ predicted [c]
001		30.4	1.48	1.51	1.50	−0.03	−0.02
002		242.0	2.38	2.31	2.27	0.07	0.11
003		175.1	2.24	2.22	2.21	0.02	0.03
004		190.6	2.28	2.25	2.32	0.03	0.03
005		30.97	1.49	1.70	1.76	−0.21	−0.21
006		223.84	2.35	2.26	2.07	0.09	0.28
007		307	2.49	2.35	2.17	0.14	0.32
008		999	3.00	2.95	2.97	0.05	0.03
009		999	3.00	2.99	2.81	0.01	0.19
010		229.8	2.36	2.23	2.13	0.13	0.23
011		28.7	1.46	1.63	1.56	−0.23	−0.10
012		73.45	1.86	1.95	1.86	−0.09	0
013		89.42	1.95	2.04	2.04	−0.09	−0.09
014		46.2	1.66	1.65	1.64	0.01	0.02
015		43.26	1.63	1.56	1.59	0.07	0.04

(*Continued on next page*)

Table 1 (*Continued*)

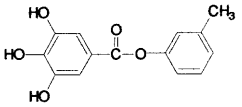
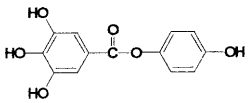
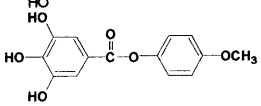
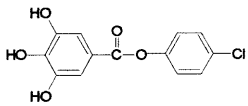
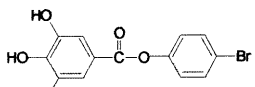
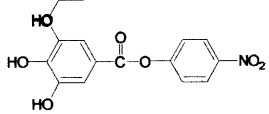
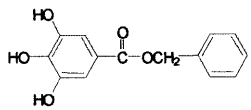
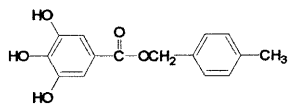
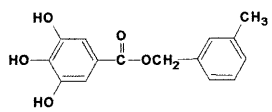
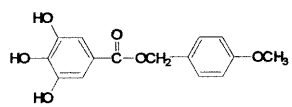
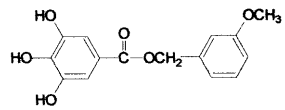
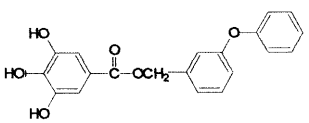
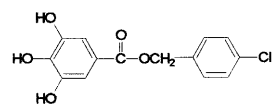
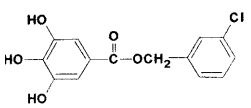
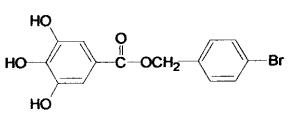
Comp.	Structure	ID_{50} (μmol/kg)	log ID_{50} measured [a]	log ID_{50} estimated	log ID_{50} predicted	Δ estimated [b]	Δ predicted [c]
016		39.48	1.60	1.48	1.47	0.12	0.13
017		22.59	0.96	1.18	1.15	−0.22	−0.19
018		43.76	1.64	1.55	1.61	0.09	0.03
019		39.26	1.59	1.47	1.36	0.12	0.23
020		17.51	1.24	1.41	1.23	−0.17	0.01
021		17.96	1.25	1.31	1.26	−0.06	−0.01
022		31.16	1.49	1.58	1.55	−0.09	−0.06
023		15.55	1.19	1.41	1.44	−0.22	−0.25
024		20.15	1.30	1.46	1.46	−0.16	−0.16
025		15.14	1.18	1.35	1.39	−0.17	−0.21
026		39.50	1.60	1.47	1.41	0.13	0.19
027		10.85	1.03	1.08	0.98	−0.05	0.05
028		21.05	1.32	1.43	1.49	−0.11	−0.17
029		17.62	1.25	1.36	1.43	−0.11	−0.18
030		12.62	1.10	1.32	1.38	−0.22	−0.28

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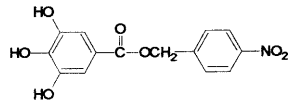
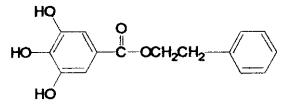
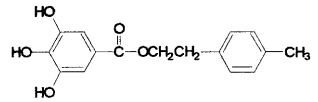
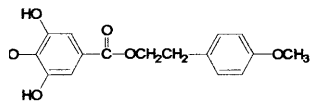
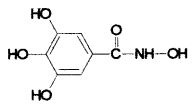
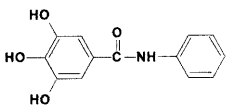
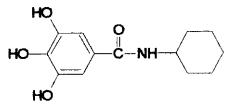
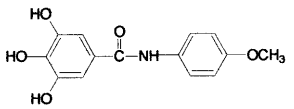
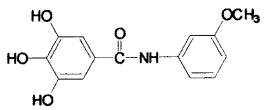
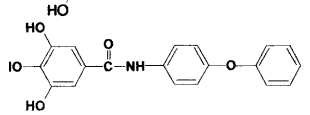
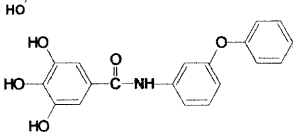
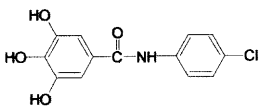
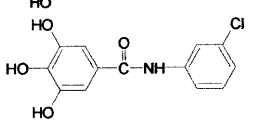
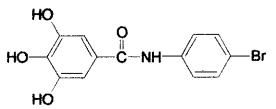
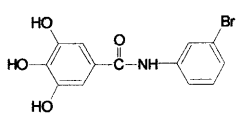
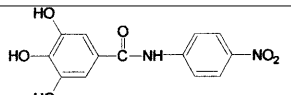
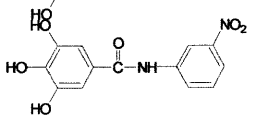
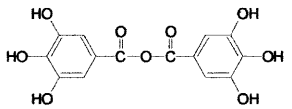
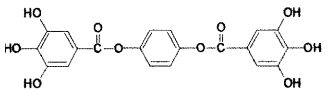
Table 1 (*Continued*)

Comp.	Structure	ID_{50} (μmol/kg)	log ID_{50} measured [a]	log ID_{50} estimated	log ID_{50} predicted	Δ estimated [b]	Δ predicted [c]
031		24.5	1.39	1.29	1.37	0.10	0.02
032		171.67	2.23	1.95	1.90	0.28	0.33
033		37.87	1.58	1.66	1.58	−0.08	0
034		46.93	1.67	1.67	1.51	0	0.16
035		23.60	1.37	1.36	1.37	0.01	0
036		27.79	1.44	1.33	1.33	0.11	0.11
037		15.20	1.18	1.22	1.37	−0.04	−0.19
038		29.17	1.46	1.59	1.59	−0.13	−0.13
039		17.16	1.23	1.27	1.32	−0.04	−0.09
040		11.66	1.07	1.01	0.95	0.06	0.12
041		6.63	0.82	0.84	0.96	−0.02	−0.14
042		35.50	1.55	1.35	1.27	0.20	0.28
043		11.46	1.06	1.10	1.11	−0.05	−0.05
044		12.73	1.10	1.10	1.23	0	−0.12
045		11.24	1.05	1.11	1.04	−0.06	0.01

(*Continued on next page*)

Table 1 (*Continued*)

Comp.	Structure	ID_{50} (μmol/kg)	log ID_{50} measured [a]	log ID_{50} estimated	log ID_{50} predicted	Δ estimated [b]	Δ predicted [c]
046		14.28	1.15	1.06	1.09	0.09	0.06
047		4.90	0.69	0.91	0.91	−0.22	−0.22
048		14.23	1.15	1.14	0.86	0.01	0.29
049		3.91	0.59	0.57	0.57	0.02	0.02

[a] Averages of two estimates.
[b] The difference between logarithms of measured and estimated values.
[c] The difference between logarithms of measured and predicted values.

The property value modeled was the logarithm of the analgesic potency. Three fractional QSAR modeling runs were computed, each employing as the training set one of the three possible combinations of two of the three subsets. The remaining subset was, in each case, employed as the test set. Thus, either 32 or 33 compounds were employed as training sets to predict values of ID_{50} for either 16 or 17 test compounds. At the completion of the three modeling runs, values for analgesic activity had been estimated twice for each compound as a member of a training set and predicted once for each compound as a member of a test set. The standard error of the measured analgesic potencies is taken to be ± 0.20 logarithm units.

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 two estimates and one single prediction. The differences between the measured and estimated or predicted values are also included in Table 1. Results of the modeling effort are presented graphically in Fig. 1 as a plot of the logarithms of the measured values of analgesic potency against the corresponding estimated and predicted values.

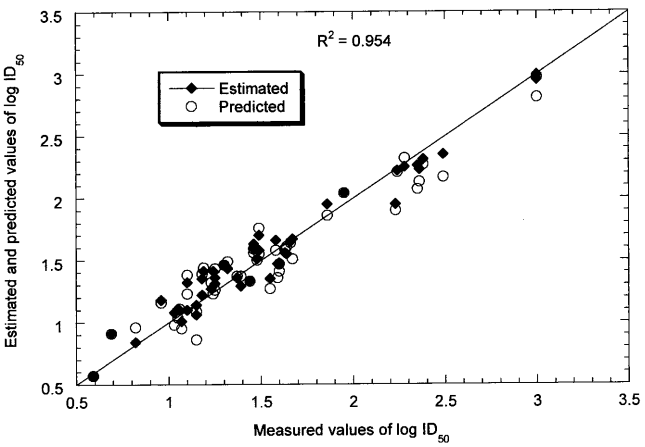


Fig. 1. Logarithms of measured values of analgesic potency plotted against the logarithms of estimated (diamonds) and predicted (circles) values.

3. Discussion

The QSAR model created in this study is highly satisfactory (see Table 1 and Fig. 1). The model correlates the data very well: for all 49 compounds in the data set, all estimates of analgesic potency for members of training sets differ from measured values by less than 1.5 standard deviations of the estimated experimental error (0.2 log units). The model also predicts analgesic potency very well when compounds are members of test set: predictions for only two compounds (**007** and **032**) out of the 49 differ from the measured value by more than 1.5 standard deviations of the estimated experimental error. These two compounds fall close to this limit: 1.60 standard deviations for compound **007** and 1.65 standard deviations for compound **032**. There are no outliers.

In principle, this is a difficult data set to model satisfactorily. Firstly, the data refer to an in vivo assay of analgesic potency and therefore suffer from animal-to-animal variability and, hence, a substantial experimental error. Secondly, the mechanism of analgesia for the gallic acid analogs is unknown; indeed, it is possible that there is more than one mechanism. Thirdly, these compounds are either esters, amides, or anhydrides of gallic acid. As such, they are susceptible to enzymatic or non-enzymatic hydrolysis, yielding gallic acid, an active anal-

gesic. Therefore, these compounds have analgesic activity in their own right (note that several are substantially more potent than gallic acid itself) and additionally act as prodrugs for gallic acid. The rate and extent of hydrolysis to gallic acid may well differ from compound to compound. Finally, the accessibility of each compound to the site of analgesic activity may vary from compound to compound.

Despite the challenges of this data set, the modeling process has, as noted above, been quite successful. This is the second example of successful QSAR modeling for in vivo analgesic activity of a family of structurally-related compounds [5]. The QSAR model developed in this work shows substantial promise in the prediction of the analgesic potency of novel gallic acid analogs, as we search for more potent compounds.

4. Experimental

The synthesis and characterization of all gallic acid derivatives employed in this study have been previously described, as have measures of their analgesic potency in the murine writhing test [6].

Statistical modeling was carried out as previously described [1,4,5,7]. A set of molecular descriptors was calculated for a single optimized conformation of each molecule in the data set. This set of descriptors employed in the modeling include those traditional 2D and 3D QSAR descriptors, a set of quantum-mechanical descriptors [9,10], a number of descriptors which identify structural elements within each molecule, as well as a collection of novel descriptors based on transferable atom equivalent (TAE) technology [8,11]. The data set modeled was divided into a large number of overlapping subsets, employing a mixture of regression models algorithm [8]. Several linear subset QSAR models were constructed for each subset. Those subsets were then qualified for their ability to generate QSAR models which predict the property value for molecules outside the subset but within the training set to within 1–2 standard deviations of the experimental error of measurements. Only those subsets passing this criterion were retained. Partial least-squares (PLS) statistical models were then developed and optimized for each qualified subset. The final QSAR model employed in this work contained several thousand qualified subsets, each containing 3 to 5 subset QSAR models. Thus, the final QSAR model contained approximately 10 000 subset QSAR models. Finally, the descriptors for each of the molecules in the test set were compared with the average of the descriptors for all molecules in each subset. For those cases in which these descriptors for the test set molecule and those in the subset are adequately concordant (indicating that the structure/descriptor space occupied by the test set molecules falls within that spanned by the subset), the subset QSAR models for that subset were employed to make predictions for the property value of the test set molecule. This procedure was continued until all subsets within the final QSAR molecule have been so examined. Thus, at the end of the procedure, each molecule in the test set will have multiple predictions. The number of such predictions varies from several hundred for some molecules in test set to perhaps 10 for other molecules. The reported predictions are the simple numerical average of these predictions.

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