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Mosquito repellency data on acylpiperidines derived from the U.S. Department of Agriculture archives were modeled by using molecular descriptors calculated by CODESSA PRO software. An artificial neural network model was developed for the correlation of these archival results and used to predict the repellent activity of novel compounds of similar structures. A series of 34 promising *N*-acylpiperidine mosquito repellent candidates (4a–4q′) were synthesized by reactions of acylbenzotriazoles 2a–2p with piperidines 3a–3f. Compounds (4a–4q′) were screened as topically applied mosquito repellents by measuring the duration of repellency after application to cloth patches worn on the arms of human volunteers. Some compounds that were evaluated repelled mosquitoes as much as three times longer than *N*,*N*-diethyl-*m*-toluamide (DEET), the most widely used repellent throughout the world. The newly measured durations of repellency were used to obtain a superior correlation equation relating mosquito repellency to molecular structure.

N-acylpiperidine | quantitative structure–activity relationship | CODESSA PRO | artificial neural network | *Aedes aegypti*

Mosquito-borne diseases such as malaria, arboviral encephalitis, dengue fever, Rift Valley fever, and yellow fever produce significant morbidity and mortality in humans and livestock in many parts of the world (1). Pathogens that cause these diseases are transmitted by injection of saliva into susceptible hosts by female mosquitoes needing protein from a blood meal to develop their eggs. Repellents play a vital role in interrupting this mosquito/human interaction by serving as a means of personal protection by reducing bites from mosquitoes. Although vaccines and genetically modified mosquitoes are under development for prevention of mosquito-borne diseases, new and improved topical repellents are needed to provide alternatives that are safer, effective for a longer duration, and more efficacious against mosquitoes and a wide range of arthropods.

Some repellents that are applied to the skin or clothing are highly effective but only of limited duration because of evaporative loss, dermal absorption, abrasive loss, or dissolution in water and perspiration (2, 3). Furthermore, some compounds cause skin irritation or a stinging sensation when they contact eyelids or lips. Finally, several are successful at preventing bites only when they are present on the skin or clothing in relatively large quantities. Thus, the current research is driven by the need to discover a new generation of repellents that overcome these limitations and supplement or replace today's standard repellent (*N*,*N*-diethyl-*m*-toluamide, DEET).

Insects are believed to detect repellents through receptor uptake of molecules with specific chemical characteristics (4–7). Therefore, we have conducted extensive studies of the relationship between molecular structure and the observed biological property of repellency. Our approach is based on a rational design similar to that used by the pharmaceutical industry for drug development but, in this case, is specifically aimed at products that interfere with mosquito olfaction and/or deter biting of a host. The use of quantitative structure–activity relationship (QSAR) approaches to repellent discovery is relatively uncommon (8). In one of the most recent studies, three-dimensional (3D)-QSAR was used successfully with CATALYST software to develop models for repellents based on pharmacophores (8). We have chosen to use artificial neural network (ANN) modeling because it is one of the most efficient QSAR approaches. Neural networks have been applied in many diverse scientific endeavors, including economics, engineering, physics, chemistry, and medical science (9). A particular advantage of ANNs is their inherent ability to incorporate nonlinear dependencies between the dependent and independent variables without using an explicit mathematical function.

Methodology for a general QSAR approach has been developed and coded as the CODESSA PRO software package (10). We previously examined 31 repellents by using CODESSA PRO (11) and here extend this research by examining available data on *N*-acylpiperidines, calculating their structure–activity relationships, synthesizing novel compounds, and performing repellency assays with human volunteers (12).

Results and Discussion

Correlation of Existing Mosquito Repellency Data for *N*-acylpiperidines with Chemical Structures. ***Dataset.*** Early investigations on the synthesis of insect repellents and their practical tests on skin and cloth against mosquitoes and other biting Diptera have been well documented (13–24). In the present work, nonlinear QSAR modeling based on the ANN approach was performed using available data for 200 *N*-acylpiperidines. The efficacy of these compounds was determined by a "time point of failure" defined as a specified number of bites (usually a low number) by female *Aedes aegypti* (L.) mosquitoes through cloth treated with each candidate piperidine and fixed on the arm of a volunteer (12). The original data on piperidines were obtained from U.S. Department of Agriculture (USDA) records collected and compiled over the past 50 years (25–27). Historically, the level of repellency was divided into five classes, as defined by "the time to first bite." This classification system placed all repellents that were efficacious for >21 d into class 5, the top tier. The remaining classes were divided as class 4 for 10- to 21-d protection, class 3 for 5- to 10-d protection, class 2 for 1- to 5-d protection, and class 1 as ineffective (<1-d protection).

Nonlinear QSAR modeling. The objective of these calculations was to build a predictive ANN model able to classify the duration of

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repellent efficacy and use this information to predict structures of novel repellents. The data set was divided into training (150 repellents) and validation (50 repellents) subsets. The main model is based on the back propagation learning algorithm for optimization of the ANN (28, 29). To obtain good generalization of the ANN, the following factors were taken into account:

(*i*) To build a general model, 150 of the 200 compounds [see supporting information (SI) Table S1 for details] were randomly selected to form the training set.

(*ii*) The preferred architecture of the ANN model (by rms error) was 8-7-1 (i.e., 8 neurons in the input layer, 7 neurons in the hidden layer, and 1 neuron in the output) representing the time class of the repellent.

(*iii*) A sensitivity analysis was done by building 1-1-1 ANN models, and the descriptors that showed lowest error at the output were selected. In addition, scatter plot analysis between the descriptors and the time classes was carried out to reveal the variability of the classes with respect to the descriptors. Finally, a combination of eight descriptors was selected as inputs for the ANN: total number of bonds, molecular weight, Kier and Hall index (order 3), molecular surface area, total dipole of the molecule, total molecular electrostatic interaction, surface area for atom C, and surface area for atom N.

The training procedure of the ANN was stopped when the rms error of the validation set started to increase. The final results for the coefficient of determination and rms error for the training set were 0.73 and 0.87, respectively. The calculated rms error of the validation set was 1.4. As expected, the rms error of the validation set was bigger than that of the training subset.

Utilization of the ANN Model to Design and Select New Compounds for Synthesis. ***Discussion of the ANN model.*** Based on the results obtained by the ANN model, the repellent time classes for additional compounds were predicted. The expected accuracy of prediction of the repellency class for a new compound by using the results on measured compounds is given by N_s/N, where N_s is the number of the repellents predicted by the network at this particular class and N is the total number of the repellents in a given experimental class. Thus, the accuracies of each class are as follows (see Fig. S1 for more information): class 1, 0.76; class 2, 0.69; class 3, 0.50; class 4, 0.25; and class 5, 0.35. If classes 4 and 5 are combined into a single class, the exact number of compounds predicted from class 4 and class 5 combined is 39. Therefore, the predicted accuracy for class 4 and class 5 compounds is 71% (39/55). This prediction accuracy is quite high, considering the distribution of the class values. Therefore, this ANN model can be used with some confidence to predict novel candidate repellents.

Selecting compounds for synthesis. Good correlation existed between the experimental and predicted values of the repellent efficacy. Of the 34 compounds selected for synthesis, 11 of these (see Table 1 and Table S2 for more details and refs. 20 and 30–33) were chosen from those examined previously. The repellency of these 11 compounds was reassessed to (*i*) compare results obtained from the biological test procedure to experimental results of those conducted and reported previously (26); (*ii*) conduct a rigorous assessment of the testing protocol using new analogs and thereby to gain confidence in the utility of the output data; and (*iii*) increase predictive ability and accuracy by reexamination of the most effective repellent candidates identified as class 4 and class 5 from previous assays and then use the protocols to further divide the repellency of these compounds into additional subclasses.

At present, the activities of ≈2,000 untested analogs have been predicted. A total of 23 were selected from this set for synthesis. Using the ANN model, we predicted these compounds to be principally members of repellent classes 3, 4, and 5 (see Table 1 and Table S3 for details, and refs. 15, 20, and 33–38). Thus, together with the 11 compounds previously examined (see Table 1) with activity predicted by the ANN as classes 4 and 5, we synthesized a total of 34 compounds of general structure **4** as shown in Fig. 1.

Synthesis of Additional *N*-acylpiperidines. ***Introduction.*** *N*-acylpiperidines have generally been synthesized by reaction of acid chlorides with amines (either the amine itself or pyridine was used as a hydrochloric acid scavenger). The product amides are then isolated by routine extraction procedures and purified by crystallization, chromatography, or distillation under high vacuum.

The high reactivity of acid halides and their incompatibility with acid-sensitive functionalities prompted efforts to find alternative methods. A benzotriazolyl group is easily introduced, activates molecules toward numerous transformations, and can be removed easily at the end of each reaction sequence (39–44). 1-Acylbenzotriazoles are advantageous carboxylic acid derivatives because they are stable and readily available in one step from carboxylic acids even where an acid-sensitive functionality is present (45–47). We report herein the use of this method in the synthesis of *N*-acylpiperidines as candidates for mosquito repellents.

Synthetic results and discussion. 1-Acylbenzotriazoles **2** (Fig. 1) were produced by treatment of the corresponding carboxylic acids **1** at 25°C with thionyl chloride and benzotriazole in methylene chloride in 1:1:3 mole ratio (48).

Reaction of 1-acylbenzotriazoles **2** with 1 eq of piperidines **3** in THF at 20°C or in toluene under reflux resulted in formation of *N*-acylpiperidines **4** by our modified procedure (46). Subsequent evaporation of the solvent, addition of methylene chloride, and washing with aqueous sodium carbonate solution gave *N*-acylpiperidines **4a**–**4q′** in 71–100% yield (Tables S2 and S3).

Experimental (if available) and predicted classes of repellency according to the ANN model are given in Table S1. From these data, the 11 candidates reselected for synthesis are listed in Table 1 and Table S2. These compounds have the highest measured activity (i.e., class 5) and also possess high activities predicted by the ANN model.

Another 23 compounds were synthesized as repellent candidates (Table 1 and Table S3). Of these, 17 (74%) were predicted by ANN as highly active repellents falling in classes 4 and 5, which in theory provide protection from mosquito bites for >10 d when applied to cloth worn over the skin. For controls, we also synthesized six compounds with relatively poor (classes 1 and 2) predicted repellency (**4a**–**4f**, Table 1, Table S3). Measurements of the biological activity of all these compounds are described in the section on biological testing.

NMR Spectra of *N*-acylpiperidines. The proton spectra of the unsymmetrical amides **4a**, **4c**, **4h**, **4i**, **4l**, **4p**, **4q**, **4c′**, **4h′**–**k′**, **4n′**, and **4o′** all revealed hindered rotation about the N–CO bond on the NMR time scale. Detailed variable temperature NMR spectra of **4c**, **4p′**, and **4q′** gave $\Delta G^{\ddagger}$ values of 16.2 ± 0.3 kcal·mol^{-1} for interconversion of the rotamers, corresponding to a first-order rate constant of ≈30 s^{-1} at ambient temperature. Thus, hindered rotation is not expected to influence the biological activity (see *SI Text*, Figs. S2–S5, and Table S4 for more details).

Biological Testing. Initially, mass concentrations (12) were used at the start of experiments, but a modification of the initial experimental setting was necessary so that the current modeling scheme would meet one of the following QSAR conditions (*i*) measurement of the induced biological effect at a constant concentration or (*ii*) measurement of the concentration that causes a constant biological effect. The first condition is closer to the actual application rate of repellents in the field and thus was chosen for further study. The experimental determination of repellency was based on

Table 1. Predicted ANN class, averaged experimental protection time (PT) from tests 1 and 2, standard deviation of the data, and converted class

Compound			Predicted		PT, d, at 25 μmol/cm^2			Conv.	PT, d, at 2.5 μmol/cm^2			Conv.
ID no.	R	R′	ANN class*		Test 1	Test 2	Average	class	Test 1	Test 2	Average	class
DEET					14	21	17.5	4	2	3	2.5	2
4a	Me	2-Me	4.82	5	1	3	2	2	1	3	2	2
4b	Et	H	4.56	5	7	3	5	2	1	7	4	2
4c	Et	2-Et	4.10	4	3	7	5	2	3	3	3	2
4d	*n*-C_6H_{13}	2-Me	3.14	3	17	17	17	4	3	7	5	2
4e	*n*-C_6H_{13}	3-Me	3.11	3	14	17	15.5	4	7	8	7.5	3
4f	*n*-C_7H_{15}	4-Me	2.69	3	43	53	48	5	9	7	8	3
4g	*n*-C_7H_{15}	4-Bn	1.82	2	9	17	13	4	7	7	7	3
4h	*n*-C_8H_{17}	2-Et	3.01	3	23	63	43	5	10	9	9.5	3
4i	*n*-C_9H_{19}	2-Me	2.85	3	21	78	49.5	5	9	7	8	3
4j	*n*-C_9H_{19}	4-Me	2.78	3	23	59	41	5	9	14	11.5	4
4k†	$CH_2{=}CH(CH_2)_8$	H	3.87	4	37	63	50	5	10	17	13.5	4
4l	$CH_2{=}CH(CH_2)_8$	2-Et	1.56	2	21	85	53	5	9	9	9	3
4m	$CH_2{=}CH(CH_2)_8$	4-Bn	1.11	1	7	10	8.5	3	7	9	8	3
4n	$CH_2{=}CH(CH_2)_8$	4-Me	2.26	2	73	73	73	5	0	21	10.5	4
4o	*n*-$C_{10}H_{21}$	H	2.12	2	23	56	39.5	5	9	17	13	4
4p	*n*-$C_{11}H_{23}$	2-Me	3.63	4	7	22	14.5	4	3	7	5	2
4q	*n*-$C_{11}H_{23}$	3-Me	1.64	2	10	29	19.5	4	3	8	5.5	3
4a′†	1-*c*-C_6H_9	H	4.87	5	17	17	17	4	3	7	5	2
4b′†	*c*-C_6H_{11}	H	5.21	5	14	14	14	4	7	9	8	3
4c′†	*c*-C_6H_{11}	3-Me	5.01	5	17	17	17	4	3	9	6	3
4d′†	*c*-C_6H_{11}	4-Me	5.02	5	28	21	24.5	5	7	10	8.5	3
4e′†	*c*-$C_5H_9(CH_2)_2$	H	4.33	4	28	42	35	5	9	9	9	3
4f′†	1-Me-*c*-C_6H_{10}	3-Me	3.98	4	10	14	12	4	7	7	7	3
4g′	4-Me-*c*-C_6H_{10}	2-Me	4.98	5	28	38	33	5	8	9	8.5	3
4h′†	*c*-C_6H_{11}	2-Et	5.23	5	21	22	21.5	5	7	7	7	3
4i′†	*c*-$C_6H_{11}CH_2$	2-Me	4.55	5	24	35	29.5	5	7	8	7.5	3
4j′†	*c*-$C_6H_{11}(CH_2)_2$	2-Me	3.56	4	29	66	47.5	5	10	10	10	3
4k′†	*c*-$C_6H_{11}(CH_2)_2$	3-Me	3.62	4	14	56	35	5	7	11	9	3
4l′	*c*-$C_6H_{11}(CH_2)_2$	4-Me	4.03	4	28	63	45.5	5	7	9	8	3
4m′	*c*-$C_6H_{11}(CH_2)_3$	4-Me	3.66	4	10	56	33	5	3	3	3	2
4n′	*c*-$C_5H_9(CH_2)_2$	2-Et	4.74	5	23	58	40.5	5	7	10	8.5	3
4o′	*c*-$C_6H_{11}(CH_2)_2$	2-Et	4.34	4	21	63	42	5	0	21	10.5	4
4p′	*c*-$C_6H_{11}CH_2$	4-Bn	3.56	4	3	3	3	2	0	3	1.5	2
4q′	*c*-$C_6H_{11}(CH_2)_2$	4-Bn	2.98	3	7	17	12	4	1	1	1	1

Bn, benzyl.

*ANN predicted class, three significant figures on the left, rounded on the right.

†Repellents that had previously been evaluated for repellent classes; all others are candidate repellents synthesized for this study.

two tests per compound performed at 2.5 and 25 μmol/cm^2 concentrations, and average protection times (d) were derived from the two tests (see Table 1).

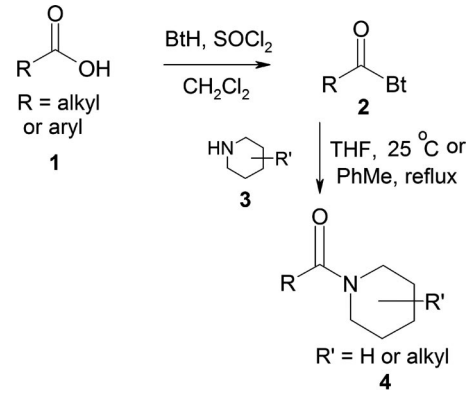

Fig. 1. Synthetic scheme for the preparation of *N*-acylpiperidines **4**. Bt, benzotriazolyl.

The repellent 4-methyl-1-(1-oxooctyl)piperidine (**4f**) (at 25 μmol/cm^2) failed on day 43 for the female volunteer, whereas the male had a repellent, 2-ethyl-1-(1-oxo-10-undecylenyl)piperidine (**4l**) that provided protection for 85 d. With both the male and female volunteers repellency persisted for 73 d at 25 μmol/cm^2 with 4-methyl-1-(1-oxo-10-undecylenyl)piperidine (**4n**). Repellent **4l** was the most potent toxicant as measured by LD_{50} of the repellents examined by Pridgeon *et al.* (49). For comparison, and highly illustrative of the efficacy of these candidate repellents, the failure point (protection time) for 25 μmol/cm^2 DEET on cloth averaged 17.5 d for this screening assay. At the low dose of 2.5 μmol/cm^2, repellent **4k,** 1-(1-oxo-10-undecylenyl)piperidine, averaged 13.5-d protection compared with only 2.5-d protection for the 2.5 μmol/cm^2 DEET standard.

Statistical examination of the average protection times (PT) revealed several important characteristics.

(*i*) The distribution of the data at 2.5 μmol/cm^2 is close to normal (Gaussian), whereas the one at 25 μmol/cm^2 deviates slightly (see Fig. 2).

2) Perhaps because most of the compounds measured were highly active, the experimental PT values at the lower concen-

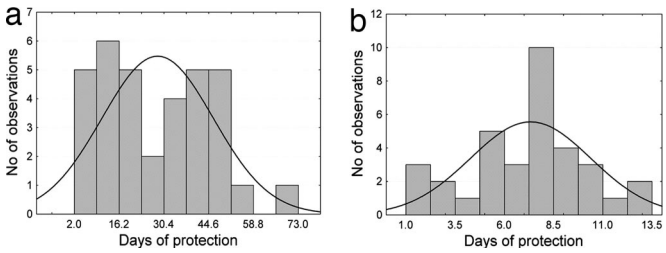

Fig. 2. Histograms and probability density functions of the averaged protection time (PT) at 25 μmol/cm^2 (*a*) and 2.5 μmol/cm^2 (*b*).

tration of 2.5 μmol/cm^2 are more precise than those at 25 μmol/cm^2. Hence, the QSAR modeling results at the lower concentration are expected to be more reliable.

Comparison of the Present Bioassay Values with the Archival Data. The dataset of 34 *N*-acylpiperidines with averaged PT transformed into classes was used to estimate the predictive power of ANN. No significant correlation was found between the experimental PT values and those predicted by ANN at either 25 or 2.5 μmol/cm^2 (columns 5 vs. 10 and 5 vs. 15 produced $R^2 = 0.007$ and $R^2 = 0.06$, respectively). The possible mismatch between the ANN-predicted classes (based on archival data) and those measured in the present work could be due to the significant difference in the experimental settings: mass instead of molar concentrations used, fewer mosquitoes tested (500 instead of 2,000–4,000), different cage size, and use of a new PT definition (see *Methods*).

We conclude that the use of classes as such is not appropriate and does not provide sufficient levels to clearly discriminate the repellency effectiveness of these compounds. We now use the average days of protection (duration) as a more precise basis for QSAR modeling.

New QSAR Modeling. By using the Best Multilinear Regression (BMLR) algorithm integrated into CODESSA PRO [CODESSA PRO Software, University of Florida (2002), www.codessa-pro.com], QSAR models with up to seven descriptors [the maximum allowed by "5-to-1" rule of thumb (50)] were generated for both concentrations of the candidate repellents. As can be seen from Fig. 3, the models with four and more descriptors are characterized by very close statistical parameters. Following the "Occam's Razor" rule of simplicity, QSAR models with four descriptors were preferred and considered further (Table 2 and Fig. 4), thus making the comparison of the two models easier. Using four descriptors, we obtain superior R^2 values of 0.729 and 0.689 for the 25 μmol/cm^2 and 2.5 μmol/cm^2 concentration data sets, respectively.

As can be seen from Table 2, the statistical parameters obtained in both cases are close, whereas the descriptors that appear in the two models are quite different. The reasons for such behavior may be as follows:

(*i*) Data distribution: a subtle distinction in the data distribution could lead to selection of a different descriptor set that fits the experimental data best.

(*ii*) High intercorrelation: at each consecutive step the BLMR algorithm selects only one of a pair or a set of highly intercorrelated descriptors, which is considered further. Thus, depending on the data set, different but physically similar and highly intercorrelated descriptors (Table S5) may appear in the different models.

The descriptors introduced into the two models (Table 2) may be classified as (*i*) electrostatic interaction-related descriptors: RNCG relative negative charge (QMNEG/QTMINUS), minimum e–n attraction for bond C–O, WPSA-2 weighted PPSA

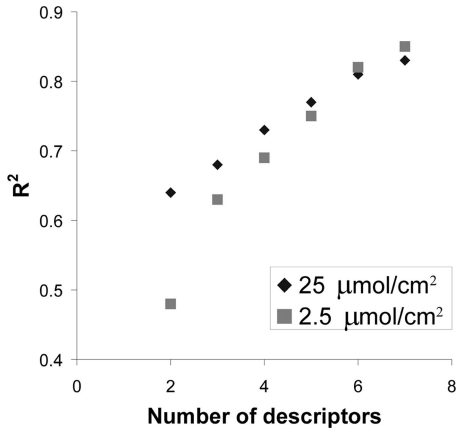

Fig. 3. Plot of R^2 vs. number of descriptors used.

(PPSA2*TMSA/1000), maximum 1-electron reactivity index for atom C, and maximum e–e repulsion for bond C–C; and (*ii*) steric interactions-related descriptors: YZ shadow/YZ rectangle, molecular volume/XYZ box, principal moment of inertia *Z*.

The mechanism of repellent action is known to be receptor-based, possibly involving the GPRor7 receptor (until recently, it was designated as AgOR7) on mosquito antennae as a target for the bioactive molecules (51). The first class of descriptors could be related to orientation effects and to the possibility of ligand–receptor noncovalent bonds. Most of the electrostatic descriptors depict the distribution of negative charge within the molecule and are probably connected to the heteroatoms present, such as oxygen and nitrogen. Especially the "Minimum e–n attraction for bond C–O" descriptor shows how important the presence of a carbonyl group is for the repellent effect and indicates that the stronger the –C=O bond the longer the protection time.

The second set of descriptors encoding the mass distribution and the size of the molecules probably depict the steric interactions that are responsible for the surface recognition between the ligand and receptor. The structures identified on the basis of our models as highly active at both concentrations (**4k**, **4j**, **4i**, **4o**, **4n**, **4o′**, **4f**, **4l**, **4j′**, and **4h**) (Table 1 and Table S6) probably include all the structural features essential for repellency.

Conclusion

This report documents significant findings in the area of repellent research through the application of a combination of techniques and methods from the disciplines of medical entomology and synthetic and theoretical chemistry. Models were constructed by using a subset of 30,000 chemicals accumulated in the USDA archives over the last 60 years. The repellency assays originally used to study these archived chemicals were the

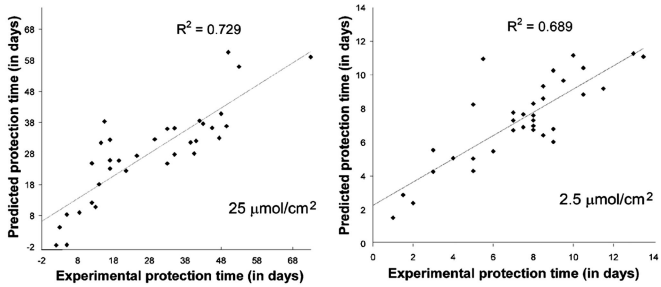

Fig. 4. Predicted vs. observed protection time values at concentrations 25 and 2.5 μmol/cm^2.

Table 2. Best four descriptors models and their statistical parameters

Conc., μmol/cm²	No. of descriptors	*B*	*S*	*t*	IC	Name of descriptor
25†	0	−188.8	84.08	−2.246		Intercept
	1	−2686	461.3	−5.823	0.09647	Maximum 1-electron reactivity index for atom C
	2	−2616	488.2	−5.359	0.7253	Principal moment of inertia *C*
	3	2.040	0.6920	2.948	0.3632	Maximum e–e repulsion for bond C–C
	4	−0.02195	0.009215	−2.382	0.7759	WPSA-2 weighted PPSA (PPSA2*TMSA/1000)
2.5‡	0	−726.1	329.3	−2.205		Intercept
	1	−68.13	9.393	−7.254	0.5248	YZ shadow/YZ rectangle
	2	58.50	13.22	4.426	0.7120	Molecular volume/XYZ box
	3	−71.37	16.41	−4.350	0.5696	RNCG relative negative charge (QMNEG/QTMINUS)
	4	1.870	0.8053	2.321	0.2822	Minimum e–n attraction for bond C–O

B, regression coefficient; S, regression coefficient error; *t*, Student criterion; IC, partial intercorrelation; PPSA, partial positively charged molecular surface area; WPSA, weighted PPSA; RNCG relative negative charge, ratio between the maximum atomic negative charge and sum of the negative atomic charges in the molecule.

†$N = 4$; $n = 34$; $R^2 = 0.729$; $R^2_{cvOO} = 0.638$; $R^2_{cvMO} = 0.628$; $F = 19.50$; $s = 9.769$.

‡$N = 4$; $n = 34$; $R^2 = 0.689$; $R^2_{cvOO} = 0.608$; $R^2_{cvMO} = 0.582$; $F = 16.05$; $s = 1.815$.

same as those that led to the discovery of DEET in 1953, the most widely used repellent in the United States. The appeal of DEET as the "gold standard" is based on its excellent human-use safety record, its ability to protect humans from bites of a wide range of hematophagous arthropods, and its duration of protection on the skin—the measure of merit for the original repellency assays and for those used in the current study. While some newer commercial repellents are nearly as efficacious as DEET-based repellents with respect to their protection from insect bites, to the best of our knowledge, none protect users for significantly longer than equivalent stoichiometric or gravimetric amounts of DEET.

In this study, we performed a successful closing of the "QSAR–synthesis–bioassay" cycle. Using the original data, linear and nonlinear QSAR approaches were applied consecutively to two series of 200 and 34 compounds, respectively. On the basis of this model, we identified 23 compounds for synthesis and study that we expected to be as efficacious as DEET. Modification of the original repellency assays, including application of chemicals in stoichiometrically equivalent amounts and converting from a class system to recording of actual days of protection, confirmed that most of these novel acylpiperidines were equivalent to or better than DEET in duration of protection. Astonishingly, a number of these protected >3 times as long as DEET. Finally, the new repellency data were incorporated into structure–activity models and produced exceptional correlation coefficients. Modifications and retraining of the model will be expected as we assess the chemical-structural impact of new classes of compounds on mosquito repellent efficacy.

Methods

Synthesis. See *SI Text*.

Biological Testing. Laboratory-reared *Aedes aegypti* mosquitoes (Orlando strain, 1952) were obtained from the USDA-Agricultural Research Service Gainesville colony. Adults were provided with sugar and water and maintained nulliparous in laboratory cages at an ambient temperature of 28 ± 1°C and relative humidity of 35–60%. Repellency assays were conducted in 45 cm × 37.5 cm × 35 cm (≈59,000 cm³) cages containing 500 ± 50 mosquitoes (5–10 d old). Female mosquitoes were preselected from those that did not display host-seeking behavior and from males by capture in a trap after anemotaxis toward odors from a human hand in a draw box (52) and then were transferred to a test cage for acclimatization for 15–20 min before bioassays.

Two concentrations of each candidate repellent were prepared in a 2-dram vial with acetone (1 ml) as the solvent. An appropriate amount of each piperidine was added to the vials to produce a deposition of 25 μmol and 2.5 μmol of each piperidine, respectively, per cm² on a 50 cm²-section of muslin cloth that was inserted into the vial. Each cloth and solution were kept sealed in vials and stored in a freezer at −4°C until used on "day 0." On day 0, each cloth was removed from its vial and mounted on two sections of 5 cm × 2.5 cm card stock. Masking tape was applied to the card stock edges and the assembly was hung from a rack and allowed to dry for at least 1 h.

Two volunteers (one male and one female) participated in this study. The protocol was approved as project 636-2005 by the University of Florida Human Use Institutional Review Board-01. Informed consent was obtained for subjects before participation in this study. Bioassays were conducted by covering the volunteer's hand with a soft-embossed long cuff poly glove (Atlantis Products) and then covering the same hand with a powder-free latex glove (Diamond Grip, Microflex). A stocking (Leggs everyday knee highs) was then pulled over the hand and arm to cover the skin surface of the arm. A polyvinyl plastic sleeve, with a Velcro seam to seal the edges around the arm, and with a 3 × 8 cm opening (i.e., window) cut into the plastic approximately half way between the wrist and elbow end of the sleeve, was fastened around the arm. Each cloth patch assembly was affixed, one at a time, over the open window with masking tape to hold it in place on the sleeve. This allowed volatile kairomones to pass from the skin surface through the window opening and attract mosquitoes which might, if the treatment was not sufficiently repellent, bite through the cloth in the open window. All 2.5 μmol/cm² samples were assayed before the 25 μmol/cm²-treated patches; however, the order within each concentration group was random, differing not only for the individual volunteers but also day-to-day for a single individual.

The arm and affixed cloth patch were inserted into the cage of mosquitoes and held stationary for 1 min to determine whether the cloth patch was repellent. The number of feeding mosquitoes was counted before removal of the arm with a quick, brisk shaking movement. This procedure was repeated daily until the failure threshold was reached. Feeding mosquitoes that remained on the window were considered to be biting. A maximum of 10 different repellents were assayed with the same group of preselected mosquitoes. Each additional set of 10 candidate repellents was run in a separate cage of ≈500 mosquitoes. This procedure minimizes the fatigue and attenuated response of mosquitoes subjected to repeated exposures to repellents, it and avoids depletion of sufficient numbers of fresh mosquitoes to conduct bioassays with all compounds at both concentrations from day 0 onward.

The failure threshold for repellency for these experiments was established as 1% biting (5 bites) and confirmed by achievement of two consecutive days of 5 or more bites. The failure point was ultimately recorded as the first day, rather than the second day, that 5 bites were achieved through a repellent-treated cloth.

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Supporting Information

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SI Text

^{1}H NMR Spectra. Examination of the ^{1}H/^{13}C NMR spectra reveals that the coalescence temperatures (T_c) for all of the carboxamide-piperidines are above room temperature. Due to the partial double character of C–N bonds, amides **4a**, **c**–**e**, **h**, **i**, **l**, **p**, **q**, **c′**, **h′**–**k′**, **n′**, and **4o′** exist as mixtures of two rotamers in almost equal proportions at 20°C as depicted in Fig. S2. Amide **4g′** is a mixture of *cis* and *trans* isomers (1:1), each of which exists also as a mixture of the two rotamers. Because of the symmetrical structures in the piperidine rings, molecules **4b**, **f**, **g**, **j**, **k**, **m**–**o**, **a′**, **b′**, **d′**, **e′**, **l′**, **m′**, **p′** , and **q′** are observed as single rotamers at 20°C. The population ratio of the two rotamers was found to be 1:1 in different solvents, such as $CDCl_3$, $CDBr_3$, $C_6D_5CD_3$, and C_6D_6. In the case of amide **4f′** only one rotamer is observed even though it is unsymmetrical.

The ^{1}H NMR spectra (Figs. S3–S5) of **4c, e**, and **k′** reveal two sets of signals for the CH_3 protons at room temperature. Similarly, the protons at C-2 and C-6 of the piperidine rings have different chemical shifts due to differing environments. When the NMR spectra of **4 c**, **e**, and **k′** were observed at higher temperatures, the two sets of signals (CH_3, H-2 and H-6, O=C–CH_2) were seen to coalesce into a single set. This corresponds to an increase in the rate of rotation around the C–N amide bond causing the environments of CH_3, H-2, and H-6 to become equivalent.

Variable-temperature ^{1}H NMR (Figs. S3-S5) was used to investigate the amide rotation barriers in all three acylpiperidines **4c**, **e**, and **k′**.

Barriers to Rotation. The equation used to calculate free energies of activation at coalescence (Table S4), $\Delta G^{\ddagger}$ (kcal·mol^{-1}) = $4.58 \times 10^{-3}\ T_c[10.32 + \log(T_c/2.22\Delta\nu)]$, assumes exchange between equally populated sites with no coupling. For an AB system, with coupling between the sites, the mean lifetime when A and B signals coalesce is given by $\tau_c = 2^{1/2}[\pi(\Delta\nu^2 + 6J^2)]^{-1/2}$. In general, the effect of coupling to other nuclei on the exchange rate required to cause coalescence cannot easily be estimated.

The free energy of activation, $\Delta G^{\ddagger}$, was obtained from the exchange rate at the coalescence temperature, T_c, by application of the Eyring equation. Ignoring the couplings between the exchanging sites means that the estimated $\Delta G^{\ddagger}$ are lower than the true values. The precision, for the exchange when the couplings are also accounted for, is ±0.3 kcal·mol^{-1}. The relative values will be more accurate because the error due to neglect of coupling is always in the same direction.

General Methods and Materials. Melting points were determined on a hot-stage apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (300 MHz) or $CDCl_3$ as the internal standard on a Varian Mercury 300 for ^{13}C (75 MHz), unless otherwise specified. Elemental and mass spectrometry analyses were performed by Analytical Laboratories, Department of Chemistry, University of Florida in Gainesville. All reactions were carried out under an atmosphere of nitrogen. Anhydrous THF was obtained by distillation immediately before use, from sodium/benzophenone ketyl. Column chromatography was performed with S733–1 silica gel (200–425 mesh; Fisher Scientific).

General Procedure for the Preparation of *N*-acylpiperidines 4a–4q′. 1-Acylbenzotriazole (**2a**–**2q**, 38.0 mmol) was stirred with a piperidine (**3a**–**3f**, 38.0 mmol) in THF (200 ml) at room temperature for 4–72 h or in dry toluene (200 ml) under reflux for 8–24 h. After evaporation of solvent in a vacuum, the residue was added to 1 M Na_2CO_3 (100 ml) and the mixture was extracted with ethyl acetate (120 ml). The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent gave pure *N*-acylpiperidines (**4b**–**g**, **i**–**k**, **m**–**e′**, **j′**–**n′**, **p′**, **q′**). Further purification of the residues of the remaining compounds by column chromatography on silica gel using a mixture of hexanes and ethyl acetate as gradient eluant gave the corresponding *N*-acylpiperidines (**4a**, **h**, **l**, **f′**, **g′**, **h′**, **i′**, **o′**).

N*-acylpiperidines 4a–4q′.** ***1-Acetyl -2-methylpiperidine (4a). Colorless oil (1); after chromatography on silica gel using hexanes/ethyl acetate as eluant (100/1 to 2/1, vol/vol); yield 71%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.91 (br s, 1H), 4.49 (d, J = 13.3 Hz, 1H), 4.08 (br s, 1H), 3.58 (d, J = 13.5, 1H), 3.15 (t, J = 13.3 Hz, 1H), 2.63 (t, J = 13.4 Hz, 1H), 2.07 (d, J = 7.6 Hz, 6H), 1.69–1.12 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 168.8, 49.0, 43.4, 41.5, 36.0, 30.6, 29.7, 26.1, 25.3, 21.9, 21.3, 18.6, 16.4, 15.4. Anal. Calcd for $C_8H_{15}NO$: C, 68.05; H, 10.71; N, 9.92. Found: C, 67.68; H, 10.97; N, 10.18.

1-(1-Oxopropyl)piperidine (4b). Colorless oil (2); yield 84%; ^{1}H NMR ($CDCl_3$) δ 3.55 (t, J = 5.4 Hz, 2H), 3.39 (t, J = 5.4 Hz, 2H), 2.34 (q, J = 7.5, 2H), 1.64–1.53 (m, 6H), 1.14 (t, J = 7.5, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 46.4, 42.5, 26.5, 26.4, 25.5, 24.5, 9.5.

2-Ethyl-1-(1-oxopropyl)piperidine (4c). Colorless oil (3); yield 75%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.71 (br s, 1H), 4.57–4.53 (m, 1H), 3.81 (br s, 1H), 3.65–3.60 (m, 1H), 3.09–3.00 (m, 1H), 2.62–2.52 (m, 1H), 2.40–2.29 (m, 4H), 1.79–1.31 (m, 16H), 1.17–1.08 (m, 6H), 0.98–0.82 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 172.3, 54.1, 49.1, 40.7, 36.2, 28.7, 27.5, 26.9, 26.5, 26.3, 25.4, 22.8, 22.1, 19.0, 10.8, 10.6, 9.7, 9.7. Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.97; H, 11.44; N, 8.75.

2-Methyl-1-(1-oxoheptyl)-piperidine (4d). colorless oil (4); yield 88%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.93 (br s, 1H), 4.51 (d, J = 13.5 Hz, 1H), 4.14 (br s, 1H), 3.63 (d, J = 13.0 Hz, 1H), 3.11 (t, J = 12.5 Hz, 1H), 2.64 (t, J = 12.6 Hz, 1H), 2.37–2.26 (m, 4H), 1.69–1.46 (m, 14H), 1.38–1.10 (m, 20H), 0.91–0.86 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 171.3, 53.2, 47.9, 43.1, 40.5, 35.7, 33.7, 33.1, 31.4, 30.5, 29.5, 28.9, 26.1, 25.3, 22.3, 18.5, 16.4, 15.2, 13.8. Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.88; H, 12.34; N, 6.93.

3-Methyl-1-(1-oxoheptyl)piperidine (4e). colorless oil (4); yield 76%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.44 (d, J = 12.6 Hz, 2H), 3.79–3.66 (m, 2H), 2.99–2.90 (m, 1H), 2.70–2.55 (m, 2H), 2.34–2.17 (m, 5H), 1.84–1.80 (m, 2H), 1.75–1.22 (m, 22H), 1.20–1.05 (m, 2H), 0.96–0.82 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 171.3, 171.2, 53.1, 48.8, 46.0, 41.9, 33.4, 33.2, 32.9, 32.9, 31.7, 31.5, 31.5, 30.8, 29.0, 25.9, 25.3, 25.3, 24.6, 22.4, 18.9, 18.8, 13.9, 13.9.

4-Methyl-1-(1-oxooctyl)piperidine (4f). Colorless oil (4); yield 77%; ^{1}H NMR ($CDCl_3$) δ 4.64–4.53 (m, 1H), 3.86–3.76 (m, 1H), 2.98 (td, J = 12.9, 2.4 Hz, 1H), 2.52 (td, J = 12.9, 2.3 Hz, 1H), 2.31 (t, J = 7.7 Hz, 2H), 1.73–1.51 (m, 5H), 1.37–1.22 (m, 8H), 1.15–1.00 (m, 2H), 0.95 (d, J = 6.3 Hz, 3H), 0.90–0.84 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 46.0, 41.9, 34.7, 33.8, 33.5, 31.7, 31.1, 29.5, 29.1, 25.5, 22.6, 21.7, 14.1. Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.07; N, 6.21. Found: C, 74.56; H, 12.44; N, 6.65.

1-(1-Oxooctyl)-4-(phenylmethyl)piperidine (4g). Colorless oil; yield 76%; ^{1}H NMR ($CDCl_3$) δ 7.32–7.26 (m, 2H), 7.23–7.17 (m, 1H), 7.15–7.12 (m, 2H), 4.61 (dt, J = 13.2, 1.9 Hz, 1H), 3.8 (d, 13.5, 1H), 2.93 (td, J = 13.0, 2.0 Hz, 1H), 2.56–2.42 (m, 3H) 2.32–2.27

(m, 2H), 1.79–1.55 (m, 5H), 1.30–1.07 (m, 10H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 139.9, 129.0, 128.2, 126.0, 45.9, 42.9, 41.8, 38.3, 33.5, 32.6, 31.8, 31.7, 29.4, 29.0, 25.4, 22.6, 14.1. Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found: C, 79.94; H, 10.77; N, 5.01.

2-Ethyl-1-(1-oxononyl)piperidine (4h). Colorless oil (4) after chromatography on silica gel using hexanes/ethyl acetate as eluant (80/1 to 40/1, vol/vol); yield 83%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.71 (br s, 1H), 4.55 (dd, J = 13.2, 3.4 Hz, 1H), 3.81 (br s, 1H), 3.65–3.61 (m, 1H), 3.09–3.00 (m, 1H), 2.60–2.51 (m, 1H), 2.40–2.21 (m, 4H), 1.81–1.47 (m, 16H), 1.44–1.27 (m, 24H), 0.98–0.81 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 171.9, 54.3, 49.0, 41.0, 36.2, 33.9, 33.4, 31.8, 29.5, 29.3, 29.1, 28.8, 27.6, 26.4, 25.5, 25.4, 22.9, 22.6, 22.1, 19.0, 14.0, 10.8, 10.6.

2-Methyl-1-(1-oxodecyl)piperidine (4i). Colorless oil (5); yield 92%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.94 (br s, 1H), 4.52 (d, J = 11.9 Hz, 1H), 4.14 (br s, 1H), 3.62 (d, J = 13.0 Hz, 1H), 3.11 (t, J = 13.1, 1H), 2.64 (t, J = 12.6 Hz, 1H), 2.36–2.25 (m, 4H), 1.72–1.48 (m, 14H), 1.45–1.12 (m, 32H), 0.90-O.85 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 17.6, 171.5, 146.1, 130.2, 126.0, 120.0, 114.4, 48.1, 43.3, 40.7, 35.9, 35.4, 33.9, 33.4, 31.8, 31.8, 30.7, 29.7, 29.5, 29.4, 29.3, 29.2, 29.2, 29.0, 26.3, 25.5, 24.3, 22.6, 18.7, 15.4, 14.0.

4-Methyl-1-(1-oxodecyl)piperidine (4j). Colorless oil (4); yield 83%; ^{1}H NMR ($CDCl_3$) δ 4.62 (dd, J = 13.2, 1.8 Hz, 1H), 3.85 (d, J = 12.1 Hz, 1H), 3.01 (td, J = 12.8, 2.3 Hz, 1H), 2.55 (td, J = 12.8, 2.3 Hz, 1H), 2.34 (t, J = 7.8 Hz, 2H), 1.73–1.58 (m, 5H), 1.33–1.30 (m, 12H), 1.18–0.89 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 171.5, 45.9, 41.9, 34.7, 33.8, 33.5, 31.8, 31.1, 29.5, 29.4, 29.4, 29.2, 25.5, 22.6, 21.7, 14.1.

1-(1-Oxo-10-undecylenyl)piperidine (4k). Colorless oil (6); yield 83%; ^{1}H NMR ($CDCl_3$) δ 5.88–5.75 (m, 1H), 5.02–4.91 (m, 2H), 3.55 (t, J = 5.4 Hz, 2H), 3.39 (t, J = 5.3 Hz, 2H), 2.31 (t, J = 7.8 Hz, 2H), 2.07–2.00 (m, 2H), 1.67–1.50 (m, 8H), 1.39–1.23 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 171.5, 139.2, 114.1, 46.7, 42.5, 33.7, 33.4, 29.5, 29.4, 29.3, 29.0, 28.9, 26.5, 25.5, 25.4, 24.6. Anal. Calcd for $C_{16}H_{29}NO$: C, 76.44; H, 11.63; N, 5.57. Found: C, 76.58; H, 12.02; H, 5.85.

2-Ethyl-1-(1-oxo-10-undecylenyl)piperidine (4l). Colorless oil after chromatography on silica gel using hexanes/ethyl acetate as eluant (80/1 to 40/1, vol/vol); yield 90%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 5.88–5.74 (m, 2H), 5.03–4.91 (m, 4H), 4.51 (d, J = 12.8 Hz, 1H), 4.14 (br s, 1H), 3.62 (d, J = 12.8 Hz, 1H), 3.11 (t, J = 12.6 Hz, 1H), 2.64 (t, J = 12.6 Hz, 1H), 2.42–2.20 (m, 4H), 2.04 (q, J = 7.0 Hz, 4H), 1.69–1.52 (m, 16H), 1.42–1.12 (m, 31H); ^{13}C NMR ($CDCl_3$) δ 171.5, 139.1, 114.0, 48.1, 43.3, 40.7, 36.0, 33.9, 33.7, 33.4, 30.7, 29.7, 29.5, 29.3, 29.3, 29.0, 28.8, 26.3, 25.5, 25.4, 18.7, 16.6, 15.4. Anal. Calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 77.58; H, 12.29; N, 5.49.

1-(1-Oxo-10-undecylenyl)-4-(phenylmethyl)piperidine (4m). Colorless oil; yield 76%; ^{1}H NMR ($CDCl_3$) δ 7.37–7.17 (m, 5H), 5.93–5.79 (m, 1H), 5.08–4.96 (m, 2H), 4.66 (d, J = 11.4 Hz, 1H), 3.87 (d, J = 13.5 Hz, 1H), 3.02–2.93 (m, 1H), 2.61–2.47 (m, 3H), 2.35 (t, J = 7.7 Hz, 2H), 2.09 (q, J = 7.0 Hz, 2H), 1.84–1.60 (m, 5H), 1.44–1.12 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 171.4, 139.9, 139.2, 129.0, 128.2, 126.0, 114.1, 45.9, 42.9, 41.8, 38.2, 33.7, 33.5, 32.6, 31.8, 29.5, 29.3, 29.3, 29.0, 28.8, 25.4. Anal. Calcd for $C_{23}H_{35}NO$: C, 80.88; H, 10.33; N, 4.10. Found: C, 81.25; H, 10.71; N, 4.49.

4-Methyl-1-(1-oxo-10-undecylenyl)piperidine (4n). Colorless oil; yield 76%; ^{1}H NMR ($CDCl_3$) δ 5.87–5.74 (m, 1H), 5.03–4.91 (m, 2H), 4.61–4.56 (m, 1H), 3.84–3.79 (m, 1H), 2.98 (td, J = 13.0, 2.4 Hz, 1H), 2.52 (td, J = 12.8, 2.4 Hz, 1H), 2.31 (t, J = 7.8 Hz, 2H), 2.03 (q, J = 7.0 Hz, 2H), 1.73–1.51 (m, 5H), 1.42–1.23 (m, 10H), 1.15–0.99 (m, 2H), 0.95 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.4, 139.1, 114.1, 45.9, 41.9, 34.7, 33.8, 33.7, 33.5, 31.1, 29.4, 29.3, 29.3, 29.0, 28.8, 25.4, 21.7. Anal. Calcd for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.85; H, 11.91; N, 5.58.

1-(1-Oxoundecyl)piperidine (4o). Colorless oil (7); yield 92%; ^{1}H NMR ($CDCl_3$) δ 3.57–3.53 (m, 2H), 3.41–3.38 (m, 2H), 2.31 (t, J = 7.8 Hz, 2H), 1.64–1.53 (m, 8H) 1.38–1.18 (m, 14H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5, 46.7, 42.5, 33.5, 31.8, 29.5, 29.5, 29.5, 29.4, 29.3, 26.5, 25.5, 25.5, 24.5, 22.6, 14.1.

2-Methyl-1-(1-oxododecyl)piperidine (4p). Colorless oil (8); yield 77%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.94 (br s, 1H), 4.51 (d, J = 12.9 Hz, 1H), 4.14 (br s, 1H), 3.63 (d, J = 11.9 Hz, 1H), 3.11 (t, J = 13.0 Hz, 1H), 2.64 (t, J = 13.3 Hz, 1H), 2.34–2.26 (m, 4H), 1.70–1.50 (m, 14H), 1.40–1.12 (m, 40H), 0.88 (t, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 171.4, 48.0, 43.2, 40.6, 35.8, 33.7, 33.2, 31.7, 30.6, 29.4, 29.3, 29.3, 29.1, 26.2, 25.3, 22.5, 18.6, 16.4, 15.3, 13.9.

3-Methyl-1-(1-oxododecanyl)piperidine (4q). Colorless oil (8); yield 92%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.49–4.38 (m, 2H), 3.80–3.63 (m, 2H), 2.99–2.88 (m, 1H), 2.69–2.54 (m, 2H), 2.31 (t, J = 7.8 Hz, 4H), 2.25–2.17 (m, 1H), 1.90–1.78 (m, 2H), 1.76–1.50 (m, 8H), 1.50–1.05 (m, 36H), 0.93–0.84 (m, 12H); ^{13}C NMR ($CDCl_3$) δ 171.4, 171.4, 53.2, 48.9, 46.1, 42.0, 33.5, 33.4, 33.1, 33.0, 31.8, 31.8, 30.9, 29.5, 29.4, 29.4, 29.3, 26.0, 25.5, 25.4, 24.7, 22.6, 19.0, 18.9, 14.0. Anal. Calcd for $C_{18}H_{35}NO$: C, 76.80; H, 12.53; N, 4.98. Found: C, 76.95; H, 12.96; N, 5.27.

1-(1-Cyclohexen-1-ylcarbonyl)piperidine (4a′). Colorless oil (9); yield 98%; ^{1}H NMR ($CDCl_3$) δ 5.78–5.75 (m, 1H), 3.49 (br s, 4H), 2.18–2.08 (m, 4H), 1.74–1.54 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 171.7, 134.7, 126.6, 47.9 (br), 42.6 (br), 26.0, 24.7, 24.5, 22.1, 21.6. Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.18; H, 10.16; N, 7.68.

1-(Cyclohexylcarbonyl)piperidine (4b′). Colorless oil (10); yield 97%; ^{1}H NMR ($CDCl_3$) δ 3.55 (t, J = 5.3 Hz, 2H), 3.43 (t, J = 4.8 Hz, 2H), 2.52–2.42 (m, 1H), 1.85–1.45 (m, 13H), 1.35–1.18 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 46.3, 42.6, 40.4, 29.4 (2C), 26.8, 25.9 (2C), 25.8, 25.6, 24.6.

1-(Cyclohexylcarbonyl)-3-methylpiperidine (4c′). Yellow oil (11); yield 100%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.49–4.42 (m, 2H), 3.84–3.71 (m, 2H), 2.99–2.90 (m, 1H), 2.68–2.43 (m, 4H), 2.25–2.18 (m, 1H), 1.85–1.06 (m, 30H), 0.94–0.88 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 168.8, 49.0, 43.4, 41.5, 36.0, 30.6, 29.7, 26.1, 25.3, 21.9, 21.3, 18.6, 16.4, 15.4. Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.23; H, 11.41; N, 7.01.

1-(Cyclohexylcarbonyl)-4-methylpiperidine (4d′). Yellow oil (11); yield 99%; ^{1}H NMR ($CDCl_3$) δ 4.60 (d, J = 13.3 Hz, 1H), 3.88 (d, J = 13.9 Hz, 1H), 2.97 (td, J = 12.9, 2.1 Hz, 1H), 2.58–2.40 (m, 2H), 1.88–1.40 (m, 10H), 1.36–1.18 (m, 3H), 1.16–1.00 (m, 2H), 0.99–0.88 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3, 45.6, 41.9, 40.4, 35.0, 33.8, 31.2, 29.5, 29.2, 25.8, 25.8, 21.7.

1-(3-Cyclopentyl-1-oxopropyl)piperidine (4e′). Yellow oil (8); yield 97%; ^{1}H NMR ($CDCl_3$) δ 3.56–3.53 (m, 2H), 3.42–3.38 (m, 2H), 2.36–2.30 (m, 2H), 1.82–1.72 (m, 3H), 1.69–1.45 (m, 12H), 1.20–1.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.5, 46.7, 42.5, 39.9, 32.7, 32.5, 31.7, 26.5, 25.5, 25.1, 24.6.

1-(1-Methylcyclohexylcarbonyl)-3-methylpiperidine (4f′). Colorless oil after chromatography on silica gel using hexanes/ethyl acetate as eluant (80/1 to 5/1, vol/vol); yield 71%; ^{1}H NMR ($CDCl_3$) δ 4.30 (t, J = 16.2 Hz, 2H), 2.71 (t, J = 12.6 Hz, 1H), 2.39 (t, J = 11.7 Hz, 1H), 2.05–1.99 (m, 2H), 1.86–1.80 (m, 1H), 1.70–0.91 (m, 12H), 1.23 (s, 3H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.4, 52.7, 46.0, 42.6, 37.2 (2C), 33.4, 31.5, 25.9, 25.7, 24.3, 23.1 (2C), 19.0. Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 74.97; H, 11.69; N, 6.54.

2-Methyl-1-[(4-methylcyclohexyl)carbonyl]piperidine (4g′). Mixture of *cis* and *trans*; colorless oil (8) after chromatography on silica gel using hexanes/ethyl acetate as eluant (100/1 to 9/1, vol/vol); yield 86%; (mixture of two rotamers for each geometric isomer): ^{1}H NMR ($CDCl_3$) δ 4.94 (br s, 1H), 4.60–4.42 (m, 1H), 4.19 (br s, 1H), 3.74–3.59 (m, 1H), 3.10 (t, J = 12.0 Hz, 1H), 2.74–2.30 (m, 3H), 1.90–1.04 (m, 34H), 1.02–0.84 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 174.6, 174.6, 174.5, 174.5, 174.4, 47.8, 43.3, 40.4, 39.2, 36.0, 34.5,

32.0, 31.1, 30.9, 30.1, 29.8, 29.4, 29.2, 29.0, 28.3, 26.6, 25.6, 25.0, 24.5, 22.6, 18.8, 17.0, 15.4.

1-(Cyclohexylcarbonyl)-2-ethylpiperididne (4h′). Colorless oil (11) after chromatography on silica gel using hexanes/ethyl acetate as eluant (80/1 to 8/1, vol/vol); yield 75%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.72 (br s, 1H), 4.55 (d, J = 13.3 Hz, 1H), 3.87 (br s, 1H), 3.70 (d, J = 12.9 Hz, 1H), 3.04 (t, J = 11.7 Hz, 1H), 2.58–2.43 (m, 3H), 1.90–1.20 (m, 36H), 0.92–0.79 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 175.1, 174.7, 53.8, 48.9, 40.7, 40.6, 40.5, 36.2, 30.2, 29.5, 29.3, 29.1, 29.0, 28.9, 27.7, 26.6, 26.1, 25.9, 25.8, 25.7, 25.5, 25.4, 23.0, 22.2, 19.1, 10.8, 10.5. Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.59; H, 11.65; N, 6.67.

1-(Cyclohexylacetyl)-2-methylpiperidine (4i′). Colorless oil (11) after chromatography on silica gel using hexanes/ethyl acetate as eluant (80/1–9/1, vol/vol); yield 72%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.96 (br s, 1H), 4.53 (d, J = 12.8 Hz, 1H), 4.17 (br s, 1H), 3.66 (d, J = 12.8 Hz, 1H), 3.11 (t, J = 13.5 Hz, 1H), 2.64 (t, J = 12.8 Hz, 1H), 2.33–2.06 (m, 4H), 1.88–1.46 (m, 22H), 1.45–1.05 (m, 14H), 1.04–0.90 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 170.8, 48.3, 43.3, 41.2, 41.0, 40.8, 36.0, 35.2, 33.3, 30.8, 29.8, 26.4, 26.2, 26.1, 26.1, 25.6, 18.7, 16.7, 15.5. Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.39; H, 11.67; N, 6.68.

1-(3-Cyclohexyl-1-oxopropyl)-2-methylpiperidine (4j′). Yellow oil (11); yield 94%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.92 (br s, 1H), 4.51 (d, J = 10.7 Hz, 1H), 4.14 (br s, 1H), 3.62 (d, J = 13.5 Hz, 1H), 3.11 (t, J = 12.0 Hz, 1H), 2.64 (t, J = 13.1 Hz, 1H), 2.44–2.20 (m, 4H), 1.78–1.06 (m, 40H), 0.99–0.83 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 171.8, 48.2, 43.3, 40.7, 37.5, 36.0, 33.1, 33.1, 32.8, 31.4, 30.9, 30.7, 29.7, 26.5, 26.3, 26.2, 25.5, 18.7, 16.6, 15.4.

1-(3-Cyclohexyl-1-oxopropyl)-3-methylpiperidine (4k′). Colorless oil (11); yield 100%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.44 (d, J = 12.8 Hz, 2H), 3.77–3.65 (m, 2H), 2.98–2.89 (m, 1H), 2.69–2.53 (m, 2H), 2.53–2.30 (m, 4H), 2.21 (t, J = 11.9 Hz, 1H), 1.86–1.32 (m 22H), 1.31–1.03 (m 10H), 0.97–0.88 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.6, 53.2, 48.9, 46.1, 42.0, 37.4, 37.4, 33.0, 33.0, 32.9, 32.8, 31.8, 31.0, 30.9, 30.8, 26.5, 26.2, 26.0, 24.7, 19.0, 18.9.

1-(3-Cyclohexyl-1-oxopropyl)-4-methylpiperidine (4l′). Yellow oil (11); yield 96%; ^{1}H NMR ($CDCl_3$) δ 4.61 (d, J = 11.8 Hz, 1H), 3.84 (d, J = 13.0 Hz, 1H), 3.01 (t, J = 11.6 Hz, 1H), 2.55 (t, J = 12.6 Hz, 1H), 2.38–2.33 (m, 2H), 1.80–1.48 (m, 10H), 1.35–0.85 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 171.8, 45.9, 41.9, 37.5, 34.7, 33.8, 33.1, 32.9, 31.1, 31.0, 26.5, 26.2, 21.7.

1-(3-Cyclohexyl-1-oxopropyl)-4-methylpiperidine (4m′). Colorless oil (11); yield 100%; ^{1}H NMR ($CDCl_3$) δ 4.61 (d, J = 11.8 Hz, 1H), 3.84 (d, J = 13.0 Hz, 1H), 3.01 (t, J = 11.6 Hz, 1H), 2.55 (t, J = 12.6 Hz, 1H), 2.38–2.33 (m, 2H), 1.80–1.48 (m, 10H), 1.35–0.85 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 171.8, 45.9, 41.9, 37.5, 34.7, 33.8, 33.1, 32.9, 31.1, 31.0, 26.5, 26.2, 21.7.

1-(3-Cyclopentyl-1-oxopropyl)-2-ethylpiperidine (4n′). Brown oil; yield 98%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.90 (br s, 1H), 4.74 (dd, J = 14.7, 3.3 Hz, 1H), 4.01 (br s, 1H), 3.82 (d, J = 11.2 Hz, 1H), 3.24 (td, J = 13.0, 1.8 Hz, 1H), 2.74 (t, J = 13.0 Hz, 1H), 2.64–2.40 (m, 4H), 2.10–1.42 (m, 34H), 1.40–1.18 (m, 4H), 1.15–1.00 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 172.0, 171.9, 54.3, 49.0, 41.0, 39.9, 36.2, 33.2, 32.7, 32.5, 31.8, 31.8, 28.8, 27.6, 26.4, 25.4, 25.1, 22.9, 22.1, 19.0, 10.8, 10.6. Direct insertion probe/chemical ionization/mass spectrometry (DIP-CI-MS), Calcd for $C_{15}H_{28}ON$ $[M+H]^+$ using methane as a chemical ionization reagent: m/z 238.2171. Found: 238.2159.

1-(3-Cyclohexyl-1-oxopropyl)-2-ethylpiperidine (4o′). Yellow oil (11); yield 93%; (mixture of two rotamers): ^{1}H NMR ($CDCl_3$) δ 4.70 (br s, 1H), 4.55 (dd, J = 13.2, 3.0 Hz, 1H), 3.81 (br s, 1H), 3.62 (d, J = 11.1 Hz, 1H), 3.05 (t, J = 13.5, 2.4 Hz, 1H), 2.55 (t, J = 12.6 Hz, 1H), 2.43–2.22 (m, 4H), 1.85–1.36 (m, 30H), 1.32–1.08 (m, 8H), 1.05–0.81 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 172.2, 172.1, 54.3, 49.0, 41.0, 37.5, 36.2, 33.2, 33.1, 33.0, 31.4, 31.0, 28.8, 27.6, 26.5, 26.4, 26.2, 25.5, 22.9, 22.2, 19.0, 10.9, 10.6.

1-(Cyclohexylacetyl)-4-(phenylmethyl)piperidine (4p′). Off-white microcrystals; mp 50–52°C; yield 100%; ^{1}H NMR ($CDCl_3$) δ 7.29 (t, J = 7.1 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 7.13 (d, J = 7.0 Hz, 2H), 4.63 (d, J = 13.5 Hz, 1H), 3.84 (d, J = 13.5 Hz, 1H), 2.97–2.88 (m, 1H), 2.60–2.42 (m, 3H), 2.20 (d, J = 6.7 Hz, 2H), 1.85–1.55 (m, 9H), 1.33–1.05 (m, 5H), 1.03–0.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.7, 139.9, 129.0, 128.2, 125.9, 46.2, 42.9, 41.8, 40.8, 38.2, 38.2, 35.1, 33.4, 33.3, 32.7, 31.8, 26.2, 26.1. Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.65. Found: C, 79.85; H, 9.92; N, 5.10.

1-(3-Cyclohexyl-1-oxopropyl)-4-(phenylmethyl)piperidine (4q′). Yellow oil; yield 99%; ^{1}H NMR ($CDCl_3$) δ 7.32–7.24 (m, 2H), 7.23–7.16 (m, 1H), 7.16–7.10 (m, 2H) 4.60 (d, J = 13.4 Hz, 1H), 3.81 (d, J = 13.9 Hz, 1H), 2.93 (td, J = 13.1, 2.3 Hz, 1H), 2.60–2.40 (m, 3H), 2.34–2.28 (m, 2H), 1.80–1.60 (m, 8H), 1.54–1.46 (m, 2H), 1.30–1.08 (m, 6H), 0.95–0.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.8, 139.9, 129.0, 128.2, 125.9, 45.9, 42.9, 41.8, 38.2, 37.4, 33.1, 32.8, 32.6, 31.7, 31.0, 26.5, 26.2. Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.61; H, 10.29; N, 4.73.

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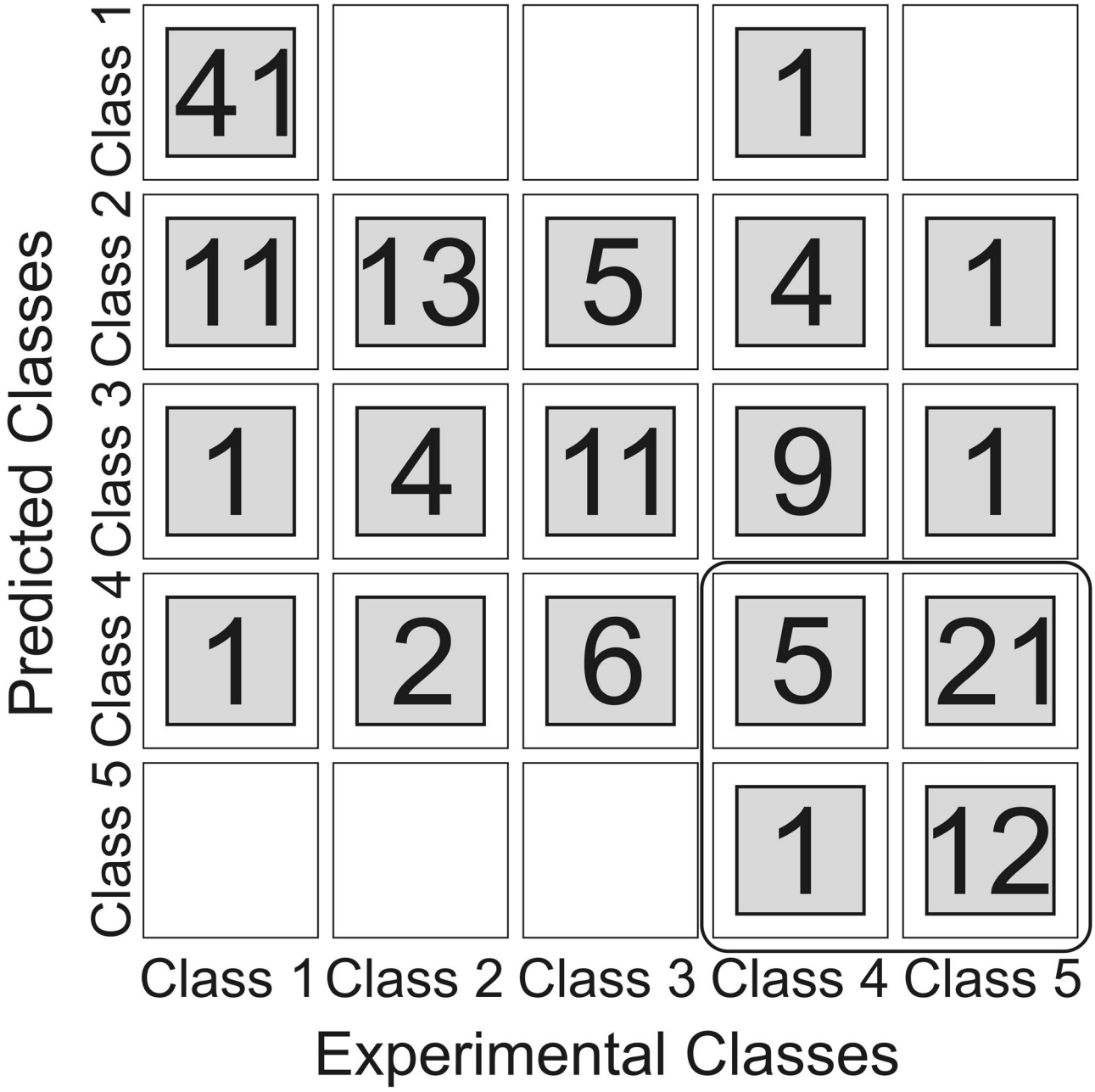

Fig. S1. Confusion matrix of predicted versus experimental classes using ANN model for the training subset.

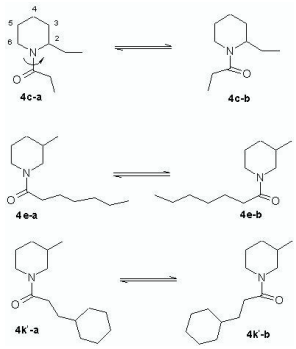

Fig. S2. Amide rotation in acylpiperidines **4c**, **4e**, and **4k'**.

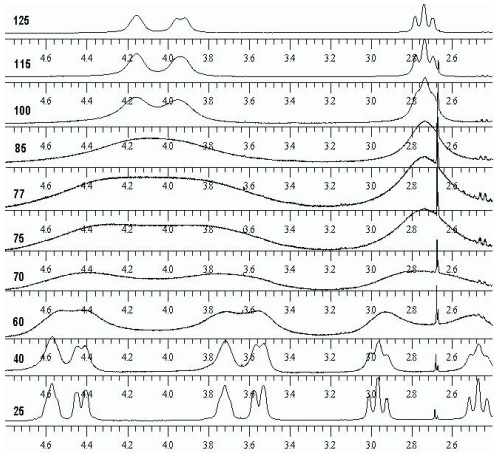

Fig. S3. Temperature-dependent ^{1}H NMR spectra of **4c**.

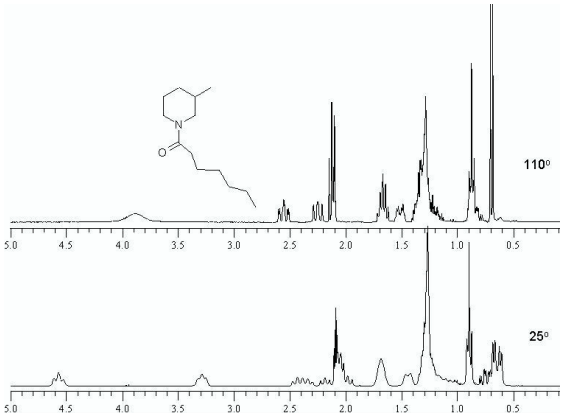

Fig. S4. Temperature-dependent ^{1}H NMR spectra of **4e**.

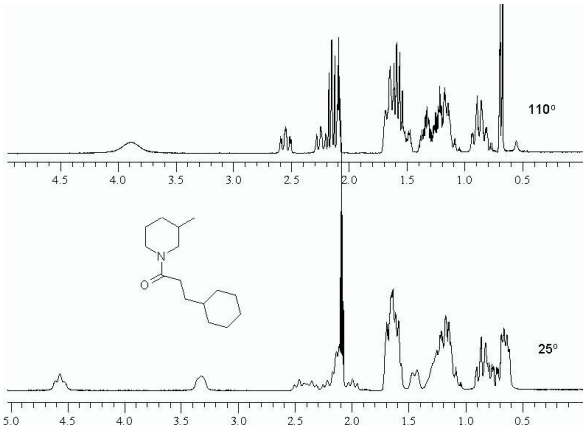

Fig. S5. Temperature-dependent ^{1}H NMR spectra of **4k′**.

Table S1. Experimental and predicted classes of repellency according to the ANN model (see Fig. S1)

ID	Entry	R	R′	Experimental class	Predicted class
37495	1	$C_{10}H_{21}$	2-CH_3	1	1
05550*	2	C_6H_5	H	5	4
06328*	3	$(CH_3)_2CHCH_2OOC(CH_2)_2$	H	1	1
08009*	4	$C_{11}H_{23}$	H	1	1
11533*	5	CH_3	H	2	2
14061*	6	2-Cl-C_6H_4	H	1	1
15132*	7	$C_6H_5CH_2$	H	2	5
15202*	8	3,4-Cl-C_6H_3	H	1	1
15496*	9	2,4-Cl-C_6H_3	H	1	1
16139*	10	C_2H_5O	H	2	2
17017*	11	4-CH_3O-C_6H_4	H	1	2
20364*	12	2-$CH_3C(O)$-C_6H_4	H	1	1
20365*	13	4-$CH_3C(O)$-C_6H_4	H	1	1
23151*	14	$(CH_3)_2C(H)O$	H	1	2
23545*	15	$ClCH_2$	H	3	3
25921*	16	$C_5H_{11}CH(C_2H_5)$	H	1	4
26189*	17	C_2H_5OOC	H	2	4
26783*	18	3,5-CH_3-C_6H_3	H	1	3
26785*	19	3-PiperidinoC(O)-C_6H_4	H	1	1
26948*	20	3-CH_3-C_6H_4	2-C_2H_5	1	2
26953*	21	$(CH_3)_3C$	H	1	4
26959*	22	3-CH_3O-C_6H_4	H	1	2
28563*	23	3-CH_3-C_6H_4	2-C_3H_7	1	1
28564*	24	3-CH_3-C_6H_4	4-C_3H_7	1	1
28800*	25	C_6H_5	2-CH_3	1	4
28801*	26	C_6H_5	4-CH_3	1	4
30566*	27	$C_6H_5CH_2O$	H	1	3
30720*	28	Naphth-1-yl	H	1	1
31640*	29	4-CH_3-C_6H_4	H	1	4
31641*	30	2-CH_3-C_6H_4	H	2	4
31642*	31	3-CH_3-C_6H_4	H	4	4
32826*	32	C_7H_{15}	H	5	5
32827*	33	C_8H_{17}	H	5	5
32828*	34	$C_{13}H_{27}$	H	1	1
32829*	35	$C_8H_{17}CH{=}CHC_7H_{14}$	H	1	1
32830	36	PiperidinoC(O)-C_8H_{16}	H	1	1
32831	37	PiperidinoC(O)-C_7H_{14}	H	1	1
32837	38	PiperidinoC(O)-C_4H_8	H	1	1
32848	39	C_5H_{11}	H	4	3
32850	40	$C_{15}H_{31}$	H	1	1
33510	41	C_6H_{13}	H	5	4
33511	42	C_9H_{19}	H	5	5
35462	43	C_4H_9	H	3	3
35468	44	C_3H_7	H	2	2
35643	45	C_5H_{11}	2-C_2H_5	5	5
35644	46	C_6H_{13}	2-C_2H_5	5	4
35645	47	C_7H_{15}	2-C_2H_5	5	4
35646	48	C_8H_{17}	2-C_2H_5	2	4
35647	49	C_9H_{19}	2-C_2H_5	1	1
35759	50	$ClCH_2(CH_2)_2$	H	2	3
35765	51	3-Cyclohexenyl	H	5	4
36156	52	(*E*)-$CH_3CH{=}C(CH_3)$	H	3	2
36158	53	(*E*)-$CH_3CH{=}C(CH_3)$	2-CH_3	4	3
36159	54	(*E*)-$CH_3CH{=}C(CH_3)$	3-CH_3	3	3
36160	55	(*E*)-$CH_3CH{=}C(CH_3)$	4-CH_3	3	3
36161	56	(*E*)-$CH_3CH{=}C(CH_3)$	2-C_2H_5	4	4
36170	57	$(CH_3)_2C{=}CH$	H	2	2
36172	58	$(CH_3)_2C{=}CH$	2-CH_3	3	3
36173	59	$(CH_3)_2C{=}CH$	3-CH_3	3	3
36174	60	$(CH_3)_2C{=}CH$	4-CH_3	3	2
36175	61	$(CH_3)_2C{=}CH$	2-C_2H_5	4	4
36302	62	$ClCH_2$	2-CH_3	3	3
36303	63	$ClCH_2$	3-CH_3	3	3
36304	64	$ClCH_2$	4-CH_3	3	2

ID	Entry	R	R′	Experimental class	Predicted class
36305	65	$ClCH_2$	2-C_2H_5	3	3
36324	66	*c*-C_6H_{11}	H	5	5
36335	67	2-C_2H_5O-C_6H_4	2-C_2H_5	4	2
36337	68	2-C_2H_5O-C_6H_4	4-CH_3	2	2
36338	69	2-C_2H_5O-C_6H_4	2-CH_3	1	2
36340	70	2-C_2H_5O-C_6H_4	3-CH_3	3	3
36392	71	$CH_3CH(OH)$	4-CH_3	4	3
36536	72	*c*-C_6H_{11}	2-CH_3	5	5
36537	73	*c*-C_6H_{11}	3-CH_3	5	5
36538	74	*c*-C_6H_{11}	4-CH_3	5	5
36539	75	*c*-C_6H_{11}	2-C_2H_5	5	5
36693	76	C_3H_7	3-$C(O)N(C_2H_5)_2$	1	1
36702	77	*c*-C_6H_{11}	3-$C(O)N(C_2H_5)_2$	1	1
36746	78	CH_3	4-CH_2-C_6H_5	5	5
36747	79	C_2H_5	4-CH_2-C_6H_5	5	4
37086	80	$C_2H_5CH(CH_3)$	H	2	2
37090	81	$C_2H_5CH(CH_3)$	4-CH_3	2	3
37128	82	$C_3H_7CH(CH_3)$	H	4	3
37132	83	$C_3H_7CH(CH_3)$	4-CH_3	2	4
37156	84	C_3H_7	4-CH_2-C_6H_5	4	4
37157	85	$(CH_3)_2CH$	4-CH_2-C_6H_5	2	2
37158	86	C_4H_9	4-CH_2-C_6H_5	2	2
37159	87	$(CH_3)_2CHCH_2$	4-CH_2-C_6H_5	2	2
37160	88	$C_2H_5CH(CH_3)$	4-CH_2-C_6H_5	3	2
37161	89	C_5H_{11}	4-CH_2-C_6H_5	1	2
37162	90	*c*-C_6H_{11}	4-CH_2-C_6H_5	1	1
37222	91	3-Cyclohexenyl	4-CH_3	4	4
37407	92	*c*-$C_6H_{11}CH_2$	H	5	5
37409	93	*c*-$C_6H_{11}CH_2$	2-CH_3	5	5
37410	94	*c*-$C_6H_{11}CH_2$	3-CH_3	5	5
37411	95	*c*-$C_6H_{11}CH_2$	4-CH_3	5	4
37412	96	*c*-$C_6H_{11}CH_2$	2-C_2H_5	5	4
37422	97	*c*-$C_6H_{11}(CH_2)_2$	H	5	4
37424	98	*c*-$C_6H_{11}(CH_2)_2$	2-CH_3	5	4
37425	99	*c*-$C_6H_{11}(CH_2)_2$	3-CH_3	5	4
37426	100	*c*-$C_6H_{11}(CH_2)_2$	4-CH_3	3	3
37427	101	*c*-$C_6H_{11}(CH_2)_2$	2-C_2H_5	4	1
37436	102	*c*-$C_6H_{11}(CH_2)_3$	H	5	4
37438	103	*c*-$C_6H_{11}(CH_2)_3$	2-CH_3	1	2
37439	104	*c*-$C_6H_{11}(CH_2)_3$	3-CH_3	2	2
37440	105	*c*-$C_6H_{11}(CH_2)_3$	4-CH_3	1	2
37441	106	*c*-$C_6H_{11}(CH_2)_3$	2-C_2H_5	4	2
37453	107	$C_{17}H_{35}$	2-CH_3	1	1
37454	108	$C_{17}H_{35}$	3-CH_3	1	1
37455	109	$C_{17}H_{35}$	4-CH_3	1	1
37456	110	$C_{17}H_{35}$	2-C_2H_5	1	1
37462	111	$C_{12}H_{25}$	2-CH_3	1	1
37463	112	$C_{12}H_{25}$	3-CH_3	1	1
37464	113	$C_{12}H_{25}$	4-CH_3	1	1
37465	114	$C_{12}H_{25}$	2-C_2H_5	1	1
37470	115	$C_{13}H_{27}$	2-CH_3	1	1
37471	116	$C_{13}H_{27}$	3-CH_3	1	1
37472	117	$C_{13}H_{27}$	4-CH_3	1	1
37473	118	$C_{13}H_{27}$	2-C_2H_5	1	1
37478	119	$C_{15}H_{31}$	2-CH_3	1	1
37479	120	$C_{15}H_{31}$	3-CH_3	1	1
37480	121	$C_{15}H_{31}$	4-CH_3	1	1
37481	122	$C_{15}H_{31}$	2-C_2H_5	1	1
37489	123	$C_{10}H_{21}$	2-CH_3	5	3
37490	124	$C_{10}H_{21}$	3-CH_3	5	4
37492	125	$C_{10}H_{21}$	2-C_2H_5	1	1
37496	126	$C_{11}H_{23}$	3-CH_3	1	1
37497	127	$C_{11}H_{23}$	4-CH_3	1	1
37498	128	$C_{11}H_{23}$	2-C_2H_5	1	1
37771	129	C_4H_9O	H	1	1

ID	Entry	R	R′	Experimental class	Predicted class
37774	130	$C_6H_{13}O$	H	1	1
37989	131	*c*-$C_6H_{11}NH$	H	1	1
37992	132	$C_5H_{11}O$	H	3	3
38140	133	*c*-$C_6H_{11}CH_2$	H	4	5
38142	134	*c*-$C_5H_9CH_2$	H	5	4
38423	135	*c*-$C_5H_9(CH_2)_2$	H	5	4
38739	136	1-Cyclohexenyl	H	5	4
38816	137	2-Thiophenyl-CH_2	H	4	2
38822	138	*c*-C_6H_{10}(1-CH_3)	H	5	4
38861	139	*c*-$C_5H_9CH_2$	H	5	4
38871	140	2-Cyclopenten-1-yl-CH_2	H	5	4
39008	141	*c*-C_6H_{10}(4-CH_3)	H	5	5
39012	142	*c*-C_6H_{10}(4-CH_3)	2-CH_3	5	4
39049	143	$H_2C{=}CH(CH_2)_8$	H	5	4
39177	144	*c*-$C_5H_9(CH_2)_2$	2-CH_3	5	4
39178	145	*c*-$C_5H_9(CH_2)_2$	3-CH_3	1	1
39179	146	*c*-$C_5H_9(CH_2)_2$	4-CH_3	1	4
39180	147	*c*-$C_5H_9(CH_2)_2$	2-C_2H_5	1	3
39239	148	*c*-C_5H_9	H	3	4
39680	149	*c*-C_3H_5	H	4	3
39754	150	*c*-C_3H_5	2-CH_3	2	2
39755	151	*c*-C_3H_5	4-CH_3	2	2
39765	152	*c*-C_3H_5	2-C_2H_5	2	3
39775	153	*c*-C_3H_5	4-C_6H_5	1	1
39781	154	*c*-C_5H_9	2-CH_3	3	4
39782	155	*c*-C_5H_9	3-CH_3	3	4
39783	156	*c*-C_5H_9	4-CH_3	3	4
39784	157	*c*-C_5H_9	2-C_2H_5	3	4
54017	158	*c*-C_4H_7	H	4	3
54422	159	CH_3	3,3-$(CH_3)_2$	2	3
54456	160	2-Furanyl	H	2	2
54458	161	2-Furanyl	2-CH_3	4	4
54459	162	2-Furanyl	3-CH_3	4	3
54460	163	2-Furanyl	4-CH_3	4	2
54461	164	2-Furanyl	2-C_2H_5	4	3
54514	165	2-Thiophenyl	H	1	2
54516	166	2-Thiophenyl	2-CH_3	1	1
54917	167	2-Thiophenyl	3-CH_3	1	2
54918	168	2-Thiophenyl	4-CH_3	1	1
54919	169	2-Thiophenyl	2-C_2H_5	1	2
55059	170	2-CH_3-3-furanyl	2-CH_3	1	2
55070	171	2-CH_3-3-furanyl	4-CH_3	5	2
55127	172	3-Furanyl	2-CH_3	1	2
55134	173	5-CH_3-2-furanyl	H	1	2
55166	174	3-CH_3-C_6H_4	3-CH_2OH	1	2
70312	175	5,5-Di-CH_3-1,3,6-*c*-heptatrienyl	H	1	1
70339	176	$(CH_3)_2C{=}CH(CH_2)_2(CH_3)C{=}CHCH_2O(CH_2)_2$	H	1	1
02746*	177	2-NO_2-C_6H_4	H	1	1
02748*	178	4-NO_2-C_6H_4	H	1	1
06539*	179	$C_4H_9OOCCH_2$	H	2	4
06544*	180	*c*-$C_6H_{11}OOCCH_2$	H	5	5
07695*	181	$(C_2H_5)_2NSO_2$	H	5	4
08183*	182	$C_{12}H_{25}$	H	1	4
11524*	183	$NH_2(CH_2)_2$	H	2	1
11531*	184	$C_6H_5(CH_2)_2$	H	3	2
11580*	185	Piperidinyl-$(CH_2)_6$	H	1	5
11727*	186	Piperidinyl-$(CH_2)_{10}$	H	1	1
11737*	187	$HO(CH_2)_2$	H	1	1
15112*	188	C_7H_{15}	H	2	2
15117*	189	4-CH_3-3-NO_2-$C_6H_3SO_2$	2-O	1	1
15234*	190	$CNCH_2$	H	1	1
15238*	191	OHC	H	3	1
30839*	192	4-CH_3-$C_6H_4SO_2$	H	1	2
32882	193	4-C_2H_5O-$C_6H_4SO_2$	H	1	1
32884	194	4-CH_3O-$C_6H_4SO_2$	H	1	1

ID	Entry	R	R′	Experimental class	Predicted class
34692	195	$C_2H_5SO_2$	H	2	2
34693	196	$C_3H_7SO_2$	H	2	2
34696	197	$C_5H_{11}SO_2$	H	3	4
35719	198	$ClCH_2(CH_2)_2SO_2$	H	3	2
36253	199	$C_2H_5SO_2$	2-C_2H_5	4	3
37916	200	$C_2H_5OOCCH_2$	4-C_2H_5OOC	1	1

*Compounds used for validation.

Table S2. Eleven *N*-acylpiperidines for which the repellent classes were previously measured

	Reagents				Conditions		Products				Literature	
No.	**2**	R	**3**	R′	Solvent	Time, h	**4**	Yield, %	State/mp, °C	ID	State/mp, °C	Ref.
1	**2g**	$CH_2{=}CH(CH_2)_8$	**3b**	H	bTHF	5	**4k**	96	Oil	39049	Oil	1
2	**2j**	1-*c*-C_6H_9	**3b**	H	THF	24	**4a′**	98	Oil	38739	Oil	2
3	**2k**	*c*-C_6H_{11}	**3b**	H	THF	14.5	**4b′**	97	Oil	36324	Oil	3
4	**2k**	*c*-C_6H_{11}	**3d**	3-Me	THF	24	**4c′**	100	Oil	36537	Oil	4
5	**2k**	*c*-C_6H_{11}	**3e**	4-Me	THF	24	**4d′**	99	Oil	36538	Oil	4
6	**2l**	*c*-$C_5H_9(CH_2)_2$	**3b**	H	THF	24	**4e′**	97	Oil	38423	Oil	5
7	**2m**	1-Me-*c*-C_6H_{10}	**3d**	3-Me	THF	16.7	**4f′**	71*	Oil	39012		Novel
8	**2k**	*c*-C_6H_{11}	**3c**	2-Et	PhMe	8	**4h′**	75*	Oil	36539	Oil	4
9	**2o**	*c*-$C_6H_{11}CH_2$	**3a**	2-Me	PhMe	24	**4i′**	72*	Oil	37409	Oil	4
10	**2p**	*c*-$C_6H_{11}(CH_2)_2$	**3a**	2-Me	PhMe	24	**4j′**	94	Oil	37424	Oil	4
11	**2p**	*c*-$C_6H_{11}(CH_2)_2$	**3d**	3-Me	THF	17.5	**4k′**	100	Oil	37425	Oil	4

*Purification by column chromatography.

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3. Yoshifuji S, Arakawa Y, Nitta Y (1985) Ruthenium tetroxide oxidation of 1-azabicycloalkan-2-ones. *Chem Pharm Bull* 33:5042–5047.
4. McGovern TP, Schreck CE, Jackson J, Beroza M (1975) *n*-Acylamides and *n*-alkylsulfonamides from heterocyclic amines as repellents for yellow fever mosquitoes. *Mosq News* 35(2):204–210.
5. Skau EL, Mod RR, Magne FC (1967) N-Acyl derivatives of cyclic imines as poly(vinyl chloride) polymer plasticizer. US Patent 3,309,332.
6. Nambu H, Hata K, Matsugi M, Kita Y (2005) Efficient synthesis of thioesters and amides from aldehydes by using an intermolecular radical reaction in water. *Chem Eur J* 11:719–727.
7. McGovern TP, Burden GS (1984) Cockroach repellents. US Patent 6,625,329; (1985) *Chem Abstr* 102:144859.
8. McGovern TP, Schreck CE (1981) Alicyclic piperidine derivatives as insect repellents. US Patent 4,291,041.

Table S3. Twenty-three *N*-acylpiperidines as novel candidate repellents

	Reagents				Conditions		Products			Literature	
No.	**2**	R	**3**	R′	Solvent	Time, h	**4**	Yield, %	State/mp, °C	State/mp, °C	Ref.
1	**2a**	Me	**3a**	2-Me	THF	4	**4a**	71*	Oil	Oil	1
2	**2b**	Et	**3b**	H	THF	4	**4b**	84	Oil	Oil	2
3	**2b**	Et	**3c**	2-Et	THF	4	**4c**	75	Oil	Oil	3
4	**2c**	*n*-C_6H_{13}	**3a**	2-Me	THF	72	**4d**	88	Oil	Oil	4
5	**2c**	*n*-C_6H_{13}	**3d**	3-Me	THF	4	**4e**	76	Oil	Oil	4
6	**2d**	*n*-C_7H_{15}	**3e**	4-Me	THF	5	**4f**	77	Oil	Oil	4
7	**2d**	*n*-C_7H_{15}	**3f**	4-Bn	THF	4	**4g**	76	Oil		Novel
8	**2e**	*n*-C_8H_{17}	**3c**	2-Et	THF	4	**4h**	83*	Oil	Oil	4
9	**2f**	*n*-C_9H_{19}	**3a**	2-Me	PhMe	24	**4i**	92	Oil	Oil	5
10	**2f**	*n*-C_9H_{19}	**3e**	4-Me	THF	4	**4j**	83	Oil	Oil	4
11	**2 g**	$CH_2{=}CH(CH_2)_8$	**3c**	2-Et	THF	72	**4l**	90*	Oil		Novel
12	**2 g**	$CH_2{=}CH(CH_2)_8$	**3f**	4-Bn	THF	4	**4m**	76	Oil		Novel
13	**2 g**	$CH_2{=}CH(CH_2)_8$	**3e**	4-Me	THF	4	**4n**	95	Oil		Novel
14	**2 h**	*n*-$C_{10}H_{21}$	**3b**	H	THF	4	**4o**	92	Oil	Oil	6
15	**2i**	*n*-$C_{11}H_{23}$	**3a**	2-Me	THF	4	**4p**	77	Oil	Oil	7
16	**2i**	*n*-$C_{11}H_{23}$	**3d**	3-Me	THF	5	**4q**	92	Oil	Oil	7
17	**2n**	4-Me-*c*-C_6H_{10}	**3a**	2-Me	PhMe	24	**4g′**	86*†	Oil	Oil	7
18	**2p**	*c*-$C_6H_{11}(CH_2)_2$	**3e**	4-Me	THF	24	**4l′**	96	Oil	Oil	8
19	**2q**	*c*-$C_6H_{11}(CH_2)_3$	**3e**	4-Me	THF	18.5	**4m′**	100	Oil	Oil	8
20	**2l**	*c*-$C_5H_9(CH_2)_2$	**3c**	2-Et	PhMe	24	**4n′**	98	Oil		Novel
21	**2p**	*c*-$C_6H_{11}(CH_2)_2$	**3c**	2-Et	PhMe	24	**4o′**	93*	Oil	Oil	8
22	**2o**	*c*-$C_6H_{11}CH_2$	**3f**	4-Bn	THF	18	**4p′**	100	50–52		Novel
23	**2p**	*c*-$C_6H_{11}(CH_2)_2$	**3f**	4-Bn	THF	24	**4q′**	99	Oil		Novel

*Purification by column chromatography.
†Mixture of *cis* and *trans* (1:1).

Table S4. Calculated free energies of activation at coalescence

Comp.	Rotamers*	Protons	δ, ppm	$\Delta\nu$, Hz	T_c, °C	k, s^{-1}	$\Delta G^{\ddagger}$, kcal·mol^{-1}
4p′	a	H-2eq	4.58	375	80	832.5	16.1
4p′	b	H-2eq	3.33				
4p′	a	CH_3	0.67	15	30	33.3	16.1
4p′	b	CH_3	0.62				
4q′	a	H-2eq	4.58	375	80	832.5	16.1
4q′	b	H-6eq	3.33				
4q′	a	CH_3	0.68	15	30	33.3	16.1
4q′	b	CH_3	0.63				
4c	a	H-2eq	4.57	252	77	559.4	16.2
4c	b	H-2eq	3.73				
4c	a	H-6eq	4.43	264	77	586.1	16.2
4c	b	H-6eq	3.55				
4c	a	H-6ax	2.97	150	65	333	16.5
4c	b	H-6ax	2.47				
4c	a	CH_2CH_3	0.81	15	37	33.3	16.0
4c	b	CH_2CH_3	0.76				

*Assignments a and b are nominal.

Table S5. Intercorrelation matrix

Descriptor	No.	1	2	3	4	5	6	7	8
WPSA-2 weighted PPSA (PPSA2*TMSA/1000)	1	1							
Maximum 1-electron reactivity index for atom C	2	0.08	1.00						
Maximum e–e repulsion for bond C–C	3	0.14	0.01	1.00					
Principal moment of inertia C	4	0.63	0.03	0.00	1.00				
YZ shadow/YZ rectangle	5	0.08	0.03	0.00	0.16	1.00			
Molecular volume/XYZ box	6	0.50	0.13	0.05	0.53	0.41	1.00		
RNCG relative negative charge (QMNEG/QTMINUS)	7	0.78	0.08	0.02	0.92	0.10	0.52	1.00	
Minimum e–n attraction for bond C–O	8	0.00	0.05	0.03	0.09	0.28	0.16	0.04	1.00

Table S6. Predicted and observed PT values and the most active compounds selected

	25 μmol/liter			2.5 μmol/liter		
ID	Experimental	Predicted	Difference	Experimental	Predicted	Difference
4a*	2.00	−1.50	3.50	2.00	2.40	−0.40
4b*	5.00	−1.40	6.40	4.00	5.06	−1.06
4c	5.00	8.36	−3.36	3.00	4.26	−1.26
4d	17.00	32.43	−15.43	5.00	4.30	0.70
4e	15.50	38.34	−22.84	7.50	6.90	0.60
4f	48.00	40.84	7.16	8.00	7.31	0.69
4g	13.00	10.79	2.21	7.00	6.72	0.28
4h	43.00	37.59	5.41	9.50	9.66	−0.16
4i	49.50	36.83	12.67	8.00	7.60	0.40
4j	41.00	32.07	8.93	11.50	9.19	2.31
4k	50.00	60.63	−10.63	13.50	11.08	2.42
4l	53.00	55.96	−2.96	9.00	10.26	−1.26
4m	8.50	8.99	−0.49	8.00	6.74	1.26
4n	73.00	59.08	13.92	10.50	8.84	1.66
4o	39.50	31.59	7.91	13.00	11.27	1.73
4p	14.50	31.45	−16.95	5.00	8.24	−3.24
4q	19.50	25.73	−6.23	5.50	10.95	−5.45
4a′	17.00	23.19	−6.19	5.00	5.04	−0.04
4b′	14.00	18.12	−4.12	8.00	8.30	−0.30
4c′	17.00	25.83	−8.83	6.00	5.47	0.53
4d′	24.50	27.29	−2.79	8.50	8.60	−0.10
4e′	35.00	27.74	7.26	9.00	6.03	2.97
4f′	12.00	24.86	−12.86	7.00	7.76	−0.76
4g′	33.00	24.79	8.21	8.50	9.33	−0.83
4h′	21.50	22.45	−0.95	7.00	7.30	−0.30
4i′	29.50	32.58	−3.08	7.50	7.66	−0.16
4j′	47.50	33.00	14.50	10.00	11.16	−1.16
4k′	35.00	36.16	−1.16	9.00	6.79	2.21
4l′	45.50	36.25	9.25	8.00	6.98	1.02
4m′	33.00	35.97	−2.97	3.00	5.54	−2.54
4n′	40.50	28.00	12.50	8.50	6.42	2.08
4o′	42.00	38.56	3.44	10.50	10.41	0.09
4p′	3.00	4.26	−1.26	1.50	2.88	−1.38
4q′	12.00	12.17	−0.17	1.00	1.53	−0.53

*Predicted as having negative PT at 25 μmol/cm^2.

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