Synthesis and Structure−Activity Relationships of 2-Pyrazinylcarboxamidobenzoates and β-Ionylideneacetamidobenzoates with Retinoidal Activity

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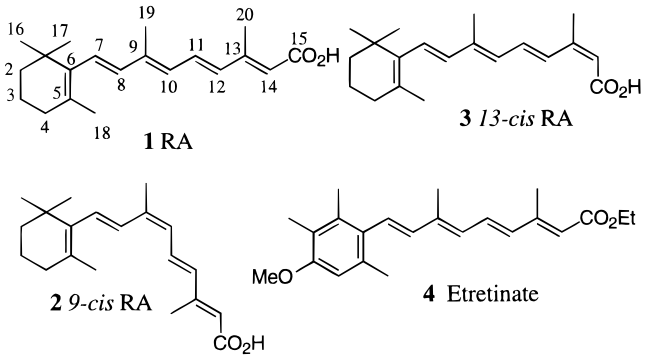
The structure−activity relationships of two series of novel retinoids (2-pyrazinylcarboxamidobenzoates and β-ionylideneacetamidobenzoates) have been investigated by evaluating their ability to induce differentiation in both human promyelocytic leukemia (HL60) cells and mouse embryonal carcinoma (P19) cells. The most active compound ($ED_{50} = 8.3 \times 10^{-9}$ M) of the 2-pyrazinylcarboxamidobenzoates is 4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethylquinoxalyl)-carboxamido]benzoic acid (**9u**), while the most active analogue of the β-ionylideneacetamidobenzoates is 4-[3-methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexen-1′-yl)-(2*E*,4*E*)-pentadienamido]-benzoic acid (**10a**, $ED_{50} = 3.2 \times 10^{-8}$ M). Our studies identify an absolute requirement for the carboxylic acid moiety on the aromatic ring to be *para* relative to the amide linkage for activity. Benzoate substitutions in the *ortho* position relative to the terminal carboxylate (**9d**,**k**,**r**) are well-tolerated; however, a methoxy substituent *meta* relative to the terminal carboxylate gives rise to only weakly active analogues (**9x**). Conformational studies (NMR, X-ray crystallography) of the 2-pyrazinylcarboxamidobenzoates indicate that the preferred conformation exhibits a *trans*-amide bond and an internal hydrogen bond between the quinoxaline N1 and HN amide which locks the torsional angle between C2 and CO in the *s-trans* conformation. N-Methylation (**9y**) results in loss of activity. Studies indicate that there is now a *cis*-amide bond present which redirects the carboxylate toward the pharmacophoric *gem*-dimethyl groups. The distance between the *gem*-dimethyl group and the terminal carboxylate appears to be too short to activate the retinoid receptor. N-Methylation in the β-ionylideneacetamidobenzoate series (**10c**) also results in the formation of a *cis*-amide bond and loss of activity.

Introduction

all-trans-Retinoic acid (RA) (**1**), its biological geometrical isomer 9-*cis*-retinoic acid (9-*cis*-RA) (**2**), and 13-*cis*-retinoic acid (13-*cis*-RA) (**3**) as well as a wide variety of synthetic analogues (retinoids) elicit profound effects in diverse biological processes. Their ability to regulate differentiation and proliferation of both preneoplastic and neoplastic cells[1,2] has resulted in the development of new pharmaceuticals for the treatment of dermatological diseases[3] as well as the development of novel chemotherapeutic and chemopreventive agents.[4,5] Retinoic acid and etretinate (**4**) have been recognized for their usefulness in the treatment of leukemia[6−9] and psoriasis.[10] Clinical trials with RA and its isomers are evaluating the usefulness of these compounds in head and neck[5,11] and skin cancers[10,12] as well as a potential treatment for cancer of the cervix.[13,14]



Nuclear receptors for retinoids are members of a receptor superfamily which includes the thyroid hormone receptor, vitamin D receptor, and steroid receptors. The retinoid receptors fall into two main categories: the retinoic acid receptors (RARα, RARβ, and RARγ) and the retinoid X receptors (RXRα, RXRβ, and RXRγ) with various isoforms of each receptor being generated by alternate splicing.[15] The RARs bind both RA and 9-*cis*-RA, while the RXRs bind only 9-*cis*-RA.[16] In the presence of ligand, these receptors stimulate transcription by binding to specific response elements in the promoters of RA-regulated genes.[17] The transcription of such genes is required to initiate RA-mediated cellular differentiation. These retinoid recep-

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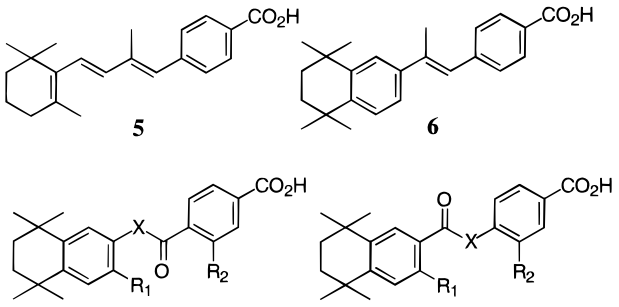
tors can also inhibit the activity of another transcription factor, AP-1, resulting in growth inhibition.[18] Whereas the naturally occurring RA acts via both these mechanisms, synthetic analogues have been developed which can independently activate these two pathways.[18,19] In addition, synthetic analogues have been identified which show significant selectivity toward the α, *β*, and *γ* receptor subtypes or which preferentially activate the RAR or RXR responsive pathway.[20−26] The identification of new analogues with specific binding and/or transactivation patterns is critical for the development of retinoids with specific biological activities.

Successful analogue design based on lead compounds should include skeletal changes in order to obtain different physicochemical characteristics from those leads. On the basis of this rationale, a range of benzoic acid derivatives have been designed. Aromatization of the polyene chain was shown to be a successful approach for obtaining new retinoids. The aromatic retinoid **5**, in which the benzene ring replaces the 11*E*,13*E*-double-bond system, had significant biological activity.[27,28] Aromatization at C8−C18 and at C12−C14 gave rise to the stilbenecarboxylic acids such as **6**[29,30] (5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalenyl)propenylbenzoic acid, TTNPB, called "arotinoid") which also exhibited strong biological activity. As a further extension the double bond of **6** was replaced by an amide bond (Am580, **8**)[31] or a retroamide bond (Am80, **7**).[31] The



5 **6**

7 R_1 = H, R_2 = H, X = NH Am80

8 R_1 = H, R_2 = H, X = NH Am580

electronic effects of the amide group on the two aromatic rings as well as on the acidity of the carboxylic group are different in the two compounds.[31] Both compounds, however, are potent differentiators of human leukemia cells to granulocytes, and their analogues exhibit similar structure−activity relationships. N-Methylation of these compounds results in a loss of activity due to the conformational change about the amide bond from *trans* to *cis*[32] which appears not to be recognized by the retinoic acid receptor. In a similar vein, Shimasazi et al.[33] introduced amide or retroamide bonds into the 9, 10-position of retinoic acid in an attempt to yield analogues of 9-*cis*-RA. Secondary amide compounds exhibited differentiating activity at concentrations > 10^{-7} M, while the tertiary amides, which they had hoped would mimic 9-*cis*-RA (**2**) in activity, were inactive at concentrations below 10^{-6} M. Amide or retroamide bonds have also been introduced into retinoid **5** resulting this time in fairly active compounds in HL60 differentiation assay. Once again, *N*-amide methylation resulted in loss of activity. Replacement of the *cis*-olefinic bond of 9-*cis*-RA with a *cis*-amide bond appears to result in loss of retinoidal activity.[33]

Rotatable bonds in retinoids are always in conjugation; therefore, they can adopt either an antiperiplanar or so-called *s-trans* conformation or a synperiplanar or so-called *s-cis* conformation.[36] In the case of compounds **6**−**8**, the *s-cis* and the *s-trans* conformations for the bonds connecting the naphthalenyl C2 to the amide or to the double bond are sterically equivalent. To investigate which conformation was preferred by the retinoic acid receptors, conformationally restrained *s-cis* and *s-trans* analogues have been studied. The *s-trans* model compound [37] shows potency similar to TTNPB (**6**), whereas the conformationally restrained *s-cis* model[38] was even more potent in the same assay of differentiation of HL60 cells. Interestingly, *s-cis* and *s-trans* conformationally restricted retinoid amides show parallel results,[35] which suggest that the *s-cis* form of Am80 (**7**) and the *s-trans* form of Am580 (**8**) are the active conformers.

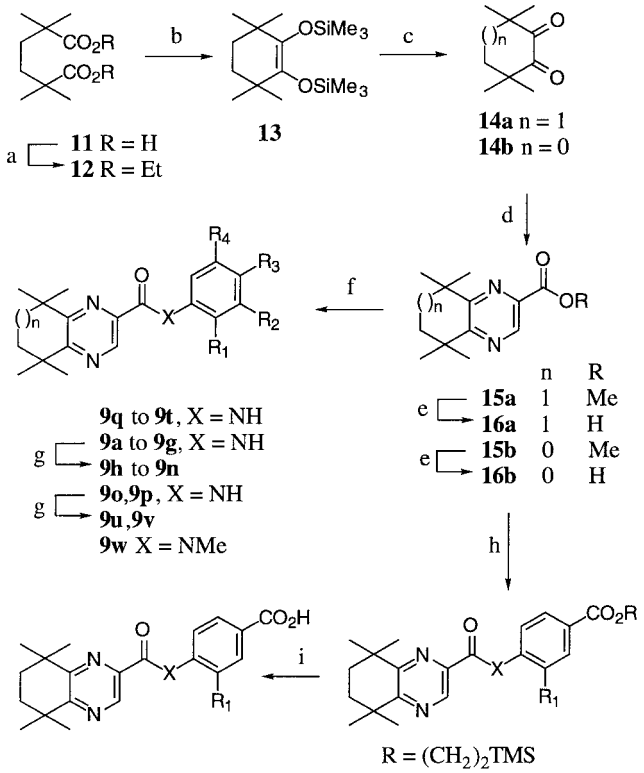
As an extension of this work we have undertaken the synthesis, conformational analysis, and screening of two novel amide series modeled on the highly potent **8**. In our first series **9**, 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-quinoxaline replaces the 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene of **8**. Introduction of the nitrogen atoms should enhance the water solubility of these compounds and may be used to probe the binding of the retinoids within the receptor sites through H-bonding. The second series of *β*-ionylideneacetamidobenzoates **10** is a two-carbon homologue of **5**. In both series the effect of *N*-amide methylation as well as the effects of substitution on the terminal benzoate ring have been investigated. In series **9** we have also studied the effects of ring size on differentiation ability. The biological results have been correlated with conformation using molecular modeling, X-ray crystallography, and ^{1}H NMR solution studies.

Results

Synthesis. The preparation of compounds **9** is outlined in Scheme 1. After conversion of hexanedioic acid **11** to its ethyl ester **12**, ring closure was effected under acyloin conditions with concomitant silyl ether formation according to the procedure described by Cookson and Smith.[39] Silyl deprotection and oxidation to the diketone **14** were carried out using bromine in carbon tetrachloride.[40] Condensation of either the 6-membered cyclic diketone **14a** or the commercially available 5-membered ring diketone **14b** with methyl 2,3-diaminopropionate was accompanied by spontaneous aromatization to yield the desired 2-methoxycarbonylalkanopyrazines **15**. Hydrolysis of the methyl esters provided the acids **16** which were then coupled to the appropriate aminobenzoates using (benzotriazolyloxy)-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) in methylene chloride[41] yielding the desired retinamides **9a**−**g,o**−**t** directly. Retinamides **9h**−**n,u,v** were obtained after cleavage of the methyl ester functionality. Due to the sensitivity of the amide linkage to cleavage, the ester linkages were cleaved using potassium *tert*-butoxide in refluxing dimethoxyethane—a modification of the procedure described by Gassman and Schenk.[42]

Problems with the above procedure were encountered during the synthesis of the *N*-methyl analogues. The

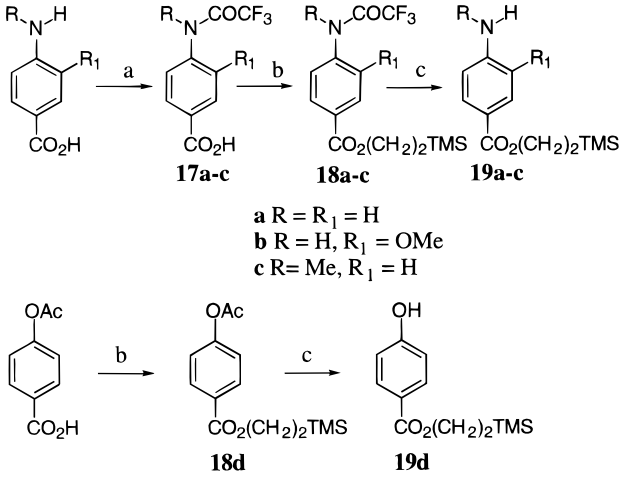
Scheme 1[a]



[a] (a) Benzene, EtOH, cat. H_2SO_4, reflux; (b) Na, toluene, Me_3SiCl, reflux; (c) Br_2, CCl_4; (d) methyl 2,3-diaminopropionate, MeOH, reflux; (e) NaOH, H_2O/MeOH (1:2); (f) methyl aminobenzoates, CH_2Cl_2, BOP, NEt_3; (g) 8 equiv of *t*-BuOK, 2 equiv of H_2O, DME, reflux; (h) PPh_3, $(CCl_3)_2CO$, 10 °C, **19a**−**d,** pyridine, 0 °C; (i) Bu_4NF, THF, DMF.

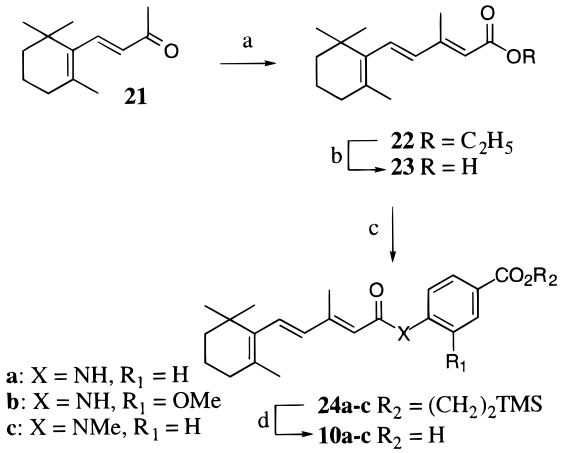
final cleavage of the methyl ester of **9w** could not be accomplished without damage to the activated tertiary amide. The 2′-(trimethylsilyl)ethyl protecting group to the carboxylate function[43] was used as a viable alternative to the previously employed methyl esters. To introduce this group, the aminobenzoic acids were protected as outlined in Scheme 2. They were first N-protected as the trifluoroacetamides **17a**−**c** and then converted to the acid chlorides using triphenylphosphine/carbon tetrachloride in acetonitrile.[44] Refluxing with 2-(trimethylsilyl)ethanol in dichloromethane provided the esters **18a**−**c**. After removal of the trifluoroacetyl N-protecting group with aqueous sodium carbonate, the desired esters **19a**−**c** were obtained. The protected hydroxybenzoate (**19d**) needed for the synthesis of **9z** was synthesized in an analogous manner. Coupling to **16a** could be accomplished using BOP; however, our new coupling method using triphenylphosphine/hexachloroacetone increased the yields dramatically. Triphenylphosphine/hexachloroacetone is known to convert alcohols to chlorides at low temperature (10 °C),[45] but until now this method had not been employed for the production of acid chlorides. These conditions smoothly converted **16a** to its acid chloride and subsequent coupling to the various aminobenzoates in pyridine at 0 °C can be carried out in nearly quantitative yields.[46] The 2′-(trimethylsilyl)ethyl protecting group

Scheme 2[a]



[a] (a) $(CF_3CO)_2O$, CF_3CO_2H, 0 °C; (b) PPh_3, CCl_4, CH_3CN then $HO(CH_2)_2TMS$, reflux; (c) Na_2CO_3 1%, H_2O/MeOH/THF.

Scheme 3[a]



[a] (a) $(EtO)_2P(O)CH_2CO_2Et$, benzene, NaOMe, MeOH, 40 °C; (b) KOH, H_2O/MeOH/THF (1:2:2), H_3O^+; (c) PPh_3, $(CCl_3)_2CO$, 10 °C, **19a**−**c**, pyridine, 0 °C; (d) Bu_4NF, THF, DMF.

could be removed quantitatively using tetrabutylammonium fluoride in DMF[43] to yield **9u**,**x**,**y**. Despite the mild basic conditions used, considerable cleavage of the highly activated phenol ester of **20d** was observed. Nevertheless, low yields of the desired compound **9z** were obtained.

The preparation of compounds **10** is outlined in Scheme 3. *β*-Ionone **21** was condensed with ethyl diethylphosphonoacetate following the procedure of Andrewes and Liaaen-Jensen,[47] to provide the 2*E*,4*E* and 2*E*,4*Z* isomers of the cyclohexenyl pentadienoate **22** in a 2:1 ratio. The mixture of esters was hydrolyzed to the corresponding acids **23** which yielded the pure 2*E*,4*E* isomer when recrystallized from hot acetonitrile. Coupling of this acid to the aminobenzoates proved to be very difficult. Coupling after generation of the acid chloride from **23** using oxalyl chloride/DMF resulted in less than 15% yield of the desired product. Attempts to use coupling reagents such as diphenylphosphoryl azide (DPPA)[48] or *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihyroquinone (EEDQ)[49] were abortive; the corresponding isocyanate and ethyl esters, respectively, were obtained. The use of bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[50] gave the desired coupling product in about

5% yield, leading mainly to the formation of the symmetrical anhydride of **23** which proved not to be reactive enough to couple with the aminobenzoate derivatives. The acid fluoride of **23** could be prepared and isolated in good yields using the procedure of Olah *et al.*[51] Unfortunately, the coupling to the aminobenzoates was very slow and led to several reaction products. Standard methods[44] used to form the acid chloride (triphenylphosphine/CCl_4 in acetonitrile) formed intractable mixtures. However, formation of the acid chloride at low temperatures using our new procedure with triphenylphosphine/hexachloroacetone[46] followed by coupling to the appropriate aniline derivatives yielded compounds **24** in good yields. The only minor side product resulted from the trichloroacetylation of the amines.[52] Removal of the 2′-(trimethylsilyl)ethyl protecting group yielded the β-ionylideneacetamidobenzoates **10**.

Biological Activities. The biological activity of these novel retinamides was examined by determining their ability to induce differentiation using two separate cell systems (HL60, P19), together with a resistant variant of the second system (RAC65).

Our novel retinoids were first evaluated for their ability to induce differentiation of the human promyelocytic leukemia cell line (HL60). HL60 cells differentiate into functionally mature granulocytes after exposure to RA,[53,54] acquiring the ability to produce superoxide anions when stimulated with PMA. When nitroblue tetrazolium (NBT) is added to the cells, it is reduced into an insoluble diformazan product only in differentiated cells. This NBT reduction assay[55,56] was used to quantitate the extent of differentiation after exposure to our novel retinoids. The second assay system monitors the differentiation of P19 mouse embryonal carcinoma cells.[57−59] These cells can be stimulated to develop along a neuroectodermal pathway by growing them as suspended aggregates in the presence of RA (**1**), followed by attachment and outgrowth of cells from the aggregates. Cells with neuronal characteristics appear, extending neurites over an underlying layer of glial cells. The extent of the differentiation in the population is determined by calculating the percentage of aggregates with neural outgrowth. As mentioned previously, resistance to retinoids has often been encountered in the clinical setting; resistance has also been experienced in long-term cell culture (HL60R[60] and RAC65 cells[61]). We utilized the RAC65 cell line to determine whether our novel retinoids could bypass the classical RA differentiation pathway. The RAC65 cell line is derived from P19 cells and is resistant to the differentiating effects of RA (**1**). In this case, the retinoid resistance has been associated with a mutation in the RARα gene which transcribes a RAR receptor truncated at the C-terminal end.[61] As a result, this mutant receptor was found to be a dominant repressor of transcription from an RA-responsive gene.

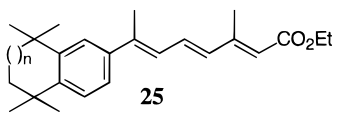
The results of the cell differentiation abilities of the 2-pyrazinylcarboxamidobenzoates **9** and the β-ionylideneacetamidobenzoates **10** are given in Table 1. None of the above compounds exhibited any activity in the resistant RAC65 cell line. ED_{50} values were determined from the dose−response curves in the P19 cell line for the active analogues **9h**,**u** and **10a**.

Computational and X-ray Crystallographic Studies. Conformational analyses were conducted on retinoids **9** and **10** as described in the Experimental Section. Low-energy conformations of the 2-pyrazinylcarboxamidobenzoate **9u**, the *N*-methyl derivative **9y**, and the corresponding ester **9z** were performed. In each case, four starting conformations resulting from the combination of either an *s-cis* or *s-trans* conformation for the bond linking the pyrazine C2 to the carbonyl with either a *cis*- or *trans*-amide bond were used. To complement this study, X-ray crystallography was used to determine the solid-state structure of **9y** as well as **20a**, the trimethylsilylethyl ester of **9u** (Figure 1). The low-energy conformations of the β-ionylideneacetamidobenzoates **10a**−**c** were also explored. In this case 16 starting conformations allowing the three single bonds in the chain to adopt either *s-cis* or *s-trans* conformations in combination with a *cis*- or *trans*-amide bond were explored. Again, to complement these calculations, the solid-state structures of **10b**,**c** were obtained by X-ray crystallography. The activity profiles for these compounds were found to strongly correlate with the distances between carbon C5 and the terminal carboxylate group in the case of the 2-pyrazinylcarboxamidobenzoates **9** and between carbon C6′ and the terminal carboxylate for the β-ionylideneacetamidobenzoates **10**.

Discussion

All active analogues contained a carboxylic acid functionality on the aromatic ring in a position *para* to the amide group. All analogues carrying the carboxylic acid *meta* to the amide functionality were found to be inactive. For the 2-pyrazinylcarboxamidobenzoates, the biological activity was unaffected by the presence of a chlorine substituent in the *ortho* position relative to the carboxylic acid **(9d,k,r)**. However, the presence of a methoxy substituent *ortho* to the amide linkage **(9g,n,x)** eliminated all activity in the P19 cells and substantially reduced or eliminated activity in the HL60 cell line.

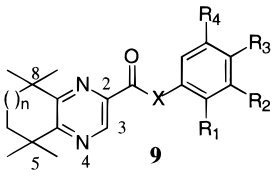
Compound **25** ($n = 0$) can be regarded as a compound with a new bond between C18 and C8 of RA (**1**) as well as a compound resulting from conformational restriction of the *s-cis* bond at C6.[29] While the five-membered ring analogue exhibited a clear activity, the corresponding six-membered ring compound ($n = 1$) was far more active.[29] For all derivatives in the 2-pyrazinylcarboxamidobenzoate **9** series, the size of the ring encompassing the *gem*-dimethyl group does not have a dramatic affect on activity (**9h**, $ED_{50} = 8.5 \times 10^{-9}$ M; **9u**, $ED_{50} = 8.3 \times 10^{-9}$ M; RA, $ED_{50} = 1.7 \times 10^{-8}$ M). Modifications to the amide linkage were also explored, and the *N*-methyl-substituted amides **9w,y** were found to be inactive in both cell lines. However, the ester derivative **9z** exhibited activity in the HL60 cell line but not in P19 cells.



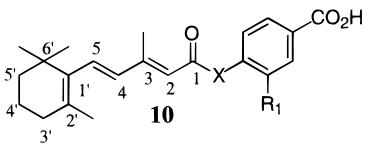
25

Activity modulation within the β-ionylideneacetamidobenzoate series **10** parallels that found for the 2-pyrazinylcarboxamidobenzoates **9**. The parent compound **10a**, bearing a *para*-carboxylic acid group relative to the amide linkage is active in both cell lines, while the

Table 1. Cell Differentiating Abilities of the 2-Pyrazinylcarboxamidobenzoates **9** and β-Ionylideneacetamidobenzoates **10**



9



10

compd	*n*	R_1	R_2	R_3	R_4	X	HL60[a]	P19[b]
9a	0	H	H	CO_2Me	H	NH	43 ± 6	52 ± 4
9b	0	H	CO_2Me	H	H	NH	0 ± 4	2 ± 1
9c	0	H	CO_2Me		CO_2Me	NH	4 ± 5	1 ± 1
9d	0	H	Cl	CO_2Me	H	NH	69 ± 2	50 ± 2
9e	0	Cl	H	H	CO_2Me	NH	4 ± 5	0 ± 0
9f	0	OCH_3	H	H	CO_2Me	NH	1 ± 3	0 ± 0
9g	0	OCH_3	H	CO_2Me	H	NH	13 ± 4	0 ± 0
9h	0	H	H	CO_2H	H	NH	46 ± 4	67 ± 5
9i	0	H	CO_2H	H	H	NH	0 ± 5	0 ± 0
9j	0	H	CO_2H	H	CO_2H	NH	2 ± 3	2 ± 2
9k	0	H	Cl	CO_2H	H	NH	67 ± 4	60 ± 5
9l	0	Cl	H	H	CO_2H	NH	20 ± 5	2 ± 2
9m	0	OCH_3	H	H	CO_2H	NH	3 ± 3	0 ± 0
9n	0	OCH_3	H	CO_2H	H	NH	6 ± 3	0 ± 0
9o	1	H	H	CO_2Me	H	NH	76 ± 4	75 ± 5
9p	1	H	CO_2Me	H	H	NH	6 ± 3	0 ± 0
9q	1	H	CO_2Me	H	CO_2Me	NH	2 ± 2	0 ± 0
9r	1	H	Cl	CO_2Me	H	NH	47 ± 3	74 ± 6
9s	1	Cl	H	H	CO_2Me	NH	7 ± 4	0 ± 0
9t	1	OCH_3	H	H	CO_2Me	NH	0 ± 2	0 ± 0
9u	1	H	H	CO_2H	H	NH	73 ± 3	70 ± 2
9v	1	H	CO_2H	H	H	NH	2 ± 3	1 ± 1
9w	0	H	H	CO_2Me	H	NMe	7 ± 5	0 ± 2
9x	1	OCH_3	H	CO_2H	H	NH	30 ± 3	0 ± 0
9y	1	H	H	CO_2H	H	NMe	15 ± 5	0 ± 0
9z	1	H	H	CO_2H	H	O	47 ± 6	0 ± 0
10a		H				NH	79 ± 2	68 ± 2
10b		OCH_3				NH	9 ± 3	2 ± 4
10c		H				N CH_3	4 ± 4	1 ± 2
RA (**1**)							91 ± 3	86 ± 6

[a] All values are given as percent differentiation of cells (as measured by NBT reduction) with compound **9** or **10** present at 10^{-6} M concentration in the culture medium. [b] All values are given as percent of aggregates with neurite formation with compound **9** or **10** present at 10^{-6} M concentration.

introduction of an *ortho*-methoxy relative to the amide bond (**10b**) abolishes activity in both cell lines. Once again, as in the 2-pyrazinylcarboxamidobenzoate series **9**, *N*-methyl substitution of the amide linkage as in **10c** also results in the loss of activity.

Energy calculations for compound **9u**, the parent six-membered ring 2-pyrazinylcarboxamidobenzoic acid, show that the global energy minimum matches the *s-trans,trans* (*tt*)-amide conformation observed in the solid state. This conformer is 2.06 kcal/mol more stable than the corresponding *s-cis,trans* (*ct*)-amide combination. NMR solution studies of **9u** also suggest a preference for the *s-trans,trans*-amide conformation involving an internal hydrogen bond. The NOESY spectrum clearly indicates the absence of a cross-peak between the NH amide and the H3 of the quinoxaline ring, thereby ruling out the *s-cis,trans*-amide conformation. More significantly there is a weak NOE between the NH and the *gem*-dimethyl at 1.41 ppm in accordance with the relatively short distance observed (3.0 Å) between the C8 dimethyl protons and the NH in the *s-trans,trans*-amide conformation of **9u**. An attempt was made to establish the presence of the intramolecular H-bond in **9u** by measuring the slope of the chemical shift of the NH proton with temperature in DMSO. This value has been used successfully in the study of peptide conformations (values lower than 3 ppb/K are associated with NH's involved in internal hydrogen bonds).[62] In the present situation a value of 3.1 ± 0.1 ppb/K was obtained, and no clear-cut conclusions can be made. However, it should be pointed out that the limiting value of 3 ppb/K was established in a study of peptide conformations in which the amide carbonyl acted as the H-bond acceptor. In the present situation the acceptor is a pyridine nitrogen, and to our knowledge no temperature coefficients have been compiled for that kind of acceptor. NMR solution studies of **9a** also suggest a preference for the *s-trans,trans*-amide conformation involving an internal hydrogen bond.

Conformational studies of *all-trans*-RA[21] indicate that there are two energetically equivalent low-energy conformers that differ only in the torsional angle connecting the 11*E*,13*E*-double-bond system with one being *s-trans* and the other *s-cis*. The C1−C15 distances for these two conformers were 12.3 and 11.6 Å respectively. In the case of compound **9u**, the C8−COOH distance in the lowest-energy *s-trans,trans*-amide conformer is 10.1 Å which would seem inappropriate for recognition by retinoic acid receptors. The higher-energy conformer (2.06 kcal/mol) *s-cis,trans*-amide however possesses a more consistent C8−COOH distance (11.4 Å) with that found for *all-trans*-RA (**1**). The NMR studies, however, indicated that essentially none of this conformation is present in solution. It is therefore difficult to believe that the higher-energy conformer contributes to the high potency of **9u** ($ED_{50} = 8.3 \times 10^{-9}$). An alternative

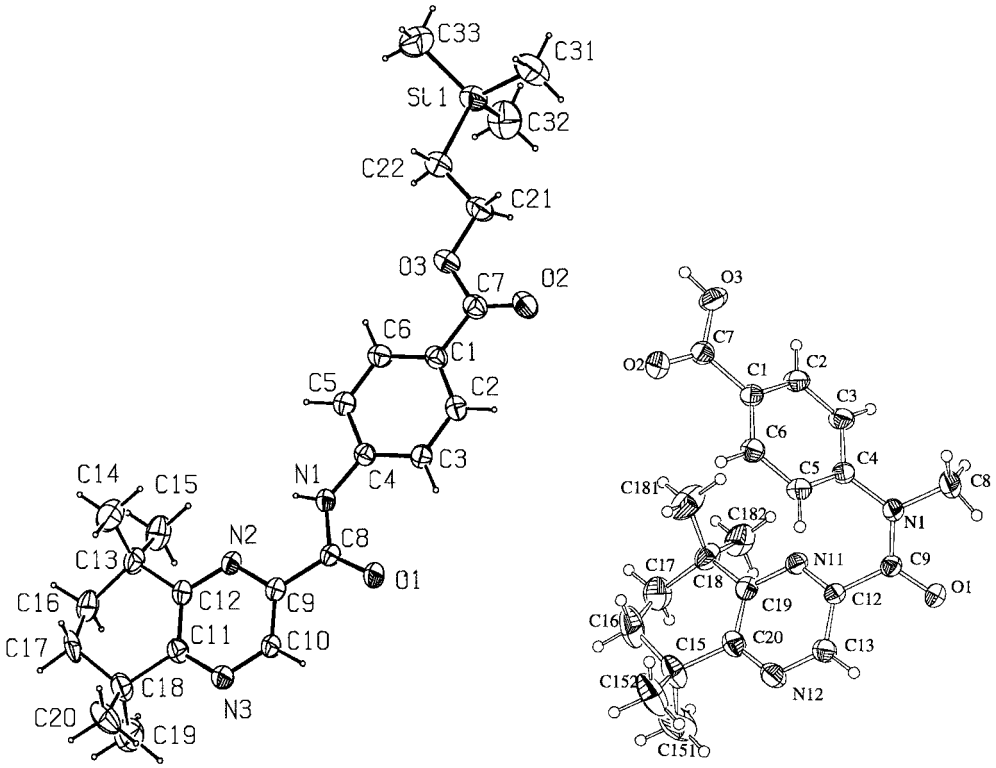


Figure 1. ORTEP diagram of the solid-state structures of 2-pyrazinylcarboxamidobenzoate **9y** with the PLATON diagram of the solid-state structure of the trimethylsilylethyl ester of **9u (20a)**.

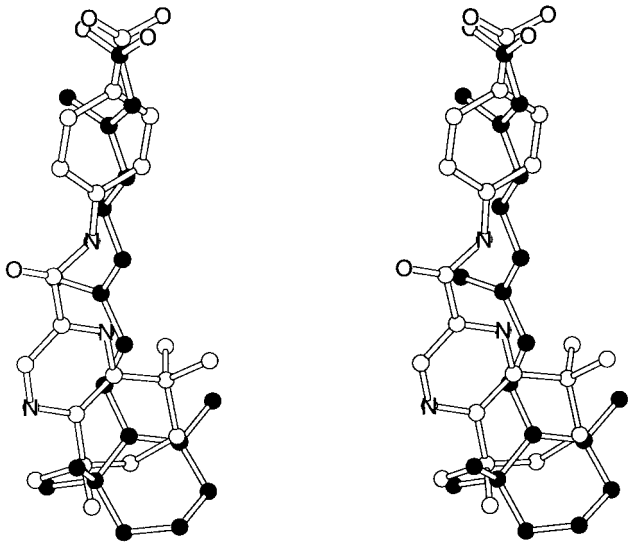


Figure 2. Stereoview of the superimposition of the favored conformer of **9u** (white balls) with *all-trans*-retinoic acid (black balls) assuming the *gem*-dimethyl group of C5 in **9u** overlaps with the *gem*-dimethyl group on C1 of *all-trans*-retinoic acid.

explanation for the high activity of the *s-trans,trans*-amide conformer presents itself if the *gem*-dimethyl group on C5 instead of those on C8 are used as an overlap point with the *gem*-dimethyl group on C1 of *all-trans*-RA. Superimposition of the favored conformer of **9u** with *all-trans*-RA assuming this alignment (Figure 2) indicates that the C5−COOH distance is a characteristic 12.1 Å, in good agreement with accepted values for *all-trans*-RA.

Results from the NMR solution study of the conformation of **9y** match that found in the solid state (Figure 1) as much as those obtained in the molecular modeling study. The minimum energy-folded *s-trans,cis*-amide structure is supported by the observation of a weak NOE between the *gem*-dimethyl protons at 0.75 ppm with those of the benzoate aromatic protons in accordance with a predicted distance of 3.2 Å. Moreover, no NOE is detected either between the NMe and the quinoxaline H3 or between benzoate protons and H3 which rules out any significant presence of either the *s-cis,trans*-amide or the *s-cis,cis*-amide conformers, respectively. The conformational change occurring between **9y** and **9u** is also manifested when comparing the ^{1}H NMR spectra: the signal of H3 in the pyrazine ring is ∼0.4 ppm higher field in **9y** (δ 8.84) than in **9u** (δ 9.23); a similar observation stands with the methylene and *gem*-dimethyl protons. The amide configuration inversion is also confirmed by the IR carbonyl frequency which occurred at 1697 cm^{-1} for **9u** and at 1625 cm^{-1} for **9y**. The *cis*-amide bond causes the benzoate ring to redirect itself so that it bends back toward the 5,5-*gem*-dimethyl group, thus reducing the distance between C5 and the carboxylate carbon to 7.9 Å from the 12.1 Å found for **9u** and explaining the total loss of cell differentiation ability (Table 1).

Shudo and Kagechika[32] have shown that the amide moiety of Am80 (**7**) and Am580 (**8**) can be replaced by an ester group and that both types of esters (**7**, **8**; $R_1 = R_2 = H$, X = O) corresponding to the carboxamide and the carbamoylbenzoic acids are strongly active in the HL60 assay. In fact, they exhibit structure−activity relationship similar to that of the amides.[31,32] In principle, esters can also exist in *cis* and *trans* conformations. However, it has been shown that they exist in the *trans* conformation predominantly.[36] Therefore, to investigate a compound which may allow the existence of the *s-cis* conformation between C2 and the

carbonyl carbon, the ester **9z** corresponding to the amide **9u** was synthesized. The energy minimization studies support the hypothesis of a favorable *s-cis,trans* (*ct*) ester conformer which possesses an identical steric energy to that of the *s-trans,trans* (*tt*) ester. Both of these conformers also exhibit a characteristic pharmacophore distance of 12.1 Å and are expected to be active in cell differentiation. Indeed **9z** was found to be active in the HL60 cell line but not in P19 cells. This apparent discrepancy is in our opinion due to divergent drug process in P19 compared to HL60 cell lines. As mentioned earlier, this ester linkage is very susceptible to cleavage. It is therefore likely that the medium of P19 cells cleaves the drug before cell differentiation can occur, whereas this process is slow enough in HL60 cell medium so as to permit cell differentiation to occur.

Steric energy calculations of the 16 potential conformers for **10a** indicate that it is the C1′−C5 *s-cis*-amide, C4−C3 *s-trans*-amide, and C2−C1 *s-cis,trans*-amide conformations (abbreviated *ctct*) which exhibit the global energy minimum at 11.4 kcal/mol. Unfortunately, crystals suitable for X-ray diffraction studies could not be obtained for **10a**, but the solid-state structure for **10b** was determined. Indeed the solid-state conformation of **10b** (*ctct*) matches the global minimum calculated for **10a**. When the characteristic pharmacophoric distance is considered, it appear that the *ctct* conformer gives rise to an extremely long pharmacophoric distance (13.9 Å) which is at departure from the one observed with *all-trans*-RA in its most extended conformation. A more favorable characteristic distance of 12.8 Å is obtained with the higher-energy (11.7 kcal/mol) *cttt* conformer. The calculation let however supposed that a significant dynamic equilibrium must exist between the *cttt* and *ctct* conformations. Inspection of the conformation with the NOESY spectrum[63,64] for **10a** tends to indicate that the lowest-energy *ctct* conformer is predominant in solution. The strong negative NOE cross-peaks observed between H2 and both H4 and NH are consistent with the presence of an *s-trans* conformation around C3−C4, an *s-cis* conformation around C2−C1, and a *trans*-amide bond. Further support for this conformation results from the observation of a medium strength NOE between Me(C3) and H5.[65] However, no NOEs were observed between NH and Me(C3) which tends to indicate that the population of the *cttt* conformer is below the limits of detection of this experiment. Nevertheless the *cttt* conformer exhibits the most favorable interatomic distance between the lipophilic terminus and the carboxyl group, and Figure 3 shows an overlap of **10a** in its putative active conformation and *all-trans*-RA (**1**) in its fully extended form. It is worth mentioning that there is essentially no chemical shift difference in the ^{1}H NMR spectrum for the ionylideneacetate moiety of **10a** when compared with **10b** which supports the absence of conformational change created when introducing the *o*-OMe substituent on the benzoic acid ring. It is then likely that **10b**'s inability to induce cell differentiation is due solely to the steric effect of the *ortho*-methoxy substituent on the retinoic acid receptor and not to a different conformational preference when compared to **10a**.

As with the 2-pyrazinylcarboxamidobenzoate series, N-methylation of **10a** results in the loss of all cell differentiating activity. Energy minimization of the 16 potential conformers of **10c** indicates that the global energy minimum possesses a *cis*-amide bond (*cttc*). The solid-state structure for **10c** indeed presents a *cis*-amide bond (the global conformation can be coded *ctcc*), except that an *s-cis* conformation is found for the C2−C1 bond whereas the *s-trans* conformation is predicted by calculation. The X-ray structure (*ctcc*) was calculated to be about 1 kcal/mol higher in energy than the most stable *cttc* conformation. Such a difference may result from intermolecular packing forces in the crystal, which of course cannot be taken into account in the calculation. The solution data are however consistent with a predominant *cttc* conformation for **10c**. Medium strength positive NOEs are observed between H4 and H2 and between Me(C3) and H5, but no NOEs are observed between the NMe and H2 nor between the NMe and Me(C3). These observations are consistent with an *s-trans* conformation around C4−C3 and with an *s-cis* conformation around C2−C1, along with a *cis*-amide bond. The folding induced by this conformation redirects the benzoate toward the cyclohexenyl moiety such that a small NOE is observed between the *gem*-dimethyl protons and the aromatic protons at 7.92 ppm (*meta* to the carboxylic acid) consistent with a distance of 2.7 Å observed in the modeled *cttc* structure. As for the pyrazinylcarboxamidobenzoates, significant ^{1}H chemical shift differences occur upon N-methylation of **10a** to form **10c**: olefinic protons are 0.2 ppm downfield in **10c** compared to **10a** with all other resonances being affected. Moreover, the IR carbonyl frequency of the amide moves from 1684 cm^{-1} in **10a** to 1627 cm^{-1} in **10c** consistent with a conformational change from a *trans*- to a *cis*-amide linkage.[32] The preferred *cttc* conformer for **10c** exhibits a characteristic distance between C6′ and the carboxylate carbon of only 8.7 Å, which is below the shortest characteristic pharmacophore distance reported up to now for retinoids.

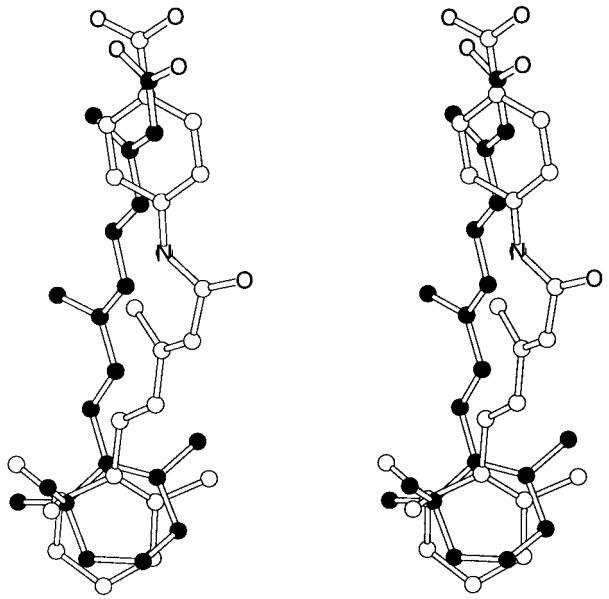


Figure 3. Stereoview of the superimposition of the putative active conformer for **10a** (white balls) with *all-trans*-retinoic acid (black balls) in its fully extended form.

Although for both Am80 (**7**) and Am580 (**8**) modification of the carboxylic acid to an ester decreased the

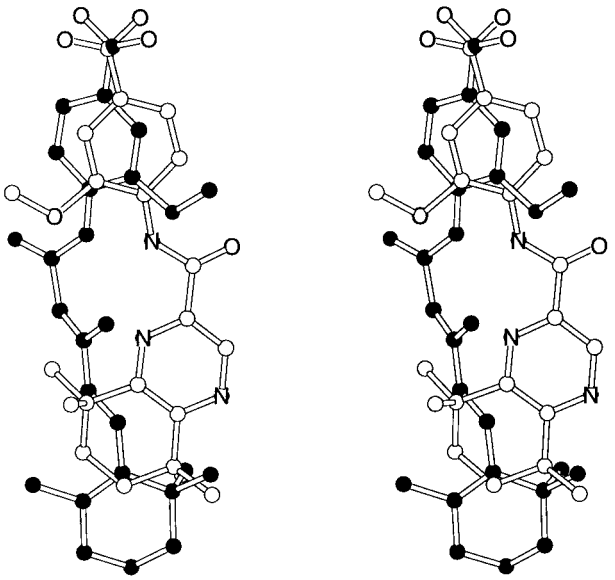


Figure 4. Stereoview of the superimposition of the putative active conformer of **9x** (white balls) and the preferred conformer of **10b** (black balls).

activity to about one-tenth of that of the parent acid, our methyl ester derivatives induced differentiation like the parent acid. It is likely that the terminal esters are hydrolyzed in the culture medium or by endogenous esterases which results in the generation of the corresponding active acids. The esters could therefore act as effective prodrugs for either in vivo experiments or clinical trials.

In both Am80 and Am580 the torsional angles between N and Ph or CO and Ph affect the relative orientation of the substituted cyclohexyl ring and the carboxyl group. For example, if one adds a methyl substituent *ortho* to the amide N atom (**7**: R_1 = Me, R_2 = H, X = NH) in Am80, which alters the torsion angle along the aryl−nitrogen bond, the activity is decreased 2 or 3 orders of magnitude.[31] A methyl substituent *ortho* to the amide N in Am580 (**8**: R_1 = H, R_2 = Me, X = NH) also results in a loss of activity. If the substitution in the *ortho* position is an amino (**7**; R_1 = H, R_1 = NH_2, X = NH) or hydroxyl group (**7**, **8**: R_1 = H, R_2 = OH, X = NH), there does not appear to be serious twisting of the amide−aryl bond and there is very little activity loss.[31] Both our X-ray diffraction data and our molecular mechanics calculations indicate that the *ortho*-methoxy substituent acts similarly to an amino or hydroxyl substituent in that it can act as a hydrogen bond acceptor for the proton on the nitrogen of the amide linkage. In addition the methyl group of the methoxy substituent, being in the same plane as the aromatic ring, is at a sufficient distance from the amide linkage so as not to cause any distortions from planarity. Despite the similarity in substitution patterns, **9x** exhibits low but significant activity in the differentiation of HL60 cells to granulocytes; however, **10b** is completely inactive. Assuming the *s-trans*,*trans*-amide conformation as the active conformation of **9x** and the *cttt* structure as the active conformation of **10b**, one can see from the overlay in Figure 4 that the methyl groups of the methoxy functionalities occupy very different locations and may account for the differences in observed biological activity. It is also important to point out that the mouse and human retinoic acid receptors may have sufficiently different topologies to account for the differences in activity in the two cell lines.

Experimental Section

Cell Culture. HL60 human promyelocytic leukemia cells[53,54] were obtained from NCI, DCT Tumor Repository, NCI-FCRF, Frederick, MD. They were maintained as suspension cultures in RPMI-1640 supplemented with 10% fetal bovine serum, 2 mM L-glutamine, and 5 μg/mL gentamycin (RPMI-complete). P19 mouse embryonal carcinoma cells were cultured in α-MEM containing 7.5% calf serum, 2.5% fetal calf serum, and 5 μg/mL gentamycin. All cells were incubated in a 5% CO_2 humidified atmosphere at 37 °C.

Test Compound Preparation. *all-trans*-Retinoic acid (RA, **1**) was included in all assays as a positive control. Compounds were stored frozen in vials covered in aluminum foil. Stock solutions were prepared in DMSO and stored frozen at −80 °C in eppendorf tubes covered with aluminum foil. All solutions were used within 9 days of preparation. Stock solutions were diluted in culture medium to the final concentration required. Addition of the test compounds to cells was performed under subdued lighting. DMSO (final concentration of 1×10^{-3}%) served as a negative control.

Differentiation of HL60 Cells. Test compounds were added to cells in 12-well plates (1×10^5 cells/mL or 1.5×10^5 cells/well). After 4 days, the extent of differentiation into granulocytes was assessed using the nitroblue tetrazolium (NBT) reduction assay.[55,56] Briefly, cells were incubated for 30 min at 37 °C in RPMI-complete containing 0.2% NBT and 200 ng/mL PMA (phorbol 12-myristrate 13-acetate). Counts were performed using light microscopy on a minimum of 200 cells (blue = differentiated, clear = undifferentiated).

Differentiation of P19 cells. Mouse P19 cells[57−59] were added to α-MEM media (10 mL) and incubated in tissue culture Petri dishes for 2 days at 37 °C. The α-MEM was removed, and each Petri dish was rinsed with phosphate-buffered saline (PBS) (2 mL). The PBS was removed, and the plates were incubated in trypsin (1 mL) at 37 °C for 10 min at which time α-MEM media (4 mL) was added. The suspension was transferred to a tissue culture flask, the concentration of the cells was calculated, and the cells were replated in new tissue culture Petri dishes at a concentration of 2×10^5 cells/mL. The test compounds (10 μL) were added to each plate and the Petri dishes incubated for 2 days at 37 °C. Fresh media (10 mL) was added followed by another addition of drug (10 μL). Three days later, the tissue culture (5 mL) was added to fresh media (5 mL), and 2 days after that the differentiated cells were counted. All assays were run in triplicate and compared to both a blank and a well containing only DMSO (1×10^{-6} M) in media (10 μL/mL). For the dose-response curves the test compound was evaluated from 1×10^{-11} to 5×10^{-6} M and the EC_{50}s were determined.

Synthetic Methods. Chemistry. Benzene, toluene, tetrahydrofuran, and dimethoxyethane were dried by distillation from sodium/benzophenone. Dry methanol was obtained from distillation over magnesium, dichloromethane from distillation over calcium hydride, and dry pyridine from distillation over sodium. Carbon tetrachloride, hexachloroacetone, and absolute ethanol were used as supplied unless otherwise stated. Triethylamine was stored over potassium hydroxide pellets. High-purity potassium *tert*-butoxide was obtained by sublimation under high vacuum. All other reagents were used without further purification except trimethylsilyl chloride which was freshly distilled from phosphorus pentoxide before use. Silica gel 60 (230−400 mesh; E. Merck) was used for flash chromatography. Reactions were monitored using analytical thin-layer chromatography plates coated with silica gel F_{254} (polyester-backed). Compounds were visualized with short wavelength UV light, cerium sulfate/ammonium molybdate spray, or ninhydrin as was appropriate.

Melting points were recorded on a Gallenkamp capillary apparatus, and the temperature was read with a type T thermocouple thermometer (Cole-Parmer 8110-25). Infrared

spectra were recorded on a Analect AQS-20 FTIR instrument. ^{1}H and ^{13}C NMR were recorded with either a Gemini-200, a JEOL 270 CPF, or a UNITY 500 and are referenced to the residual solvent peak ($CDCl_3$ ^{1}H 7.26 ppm, ^{13}C 77.0 ppm, DMSO-d_6 ^{1}H 2.49 ppm, ^{13}C 39.5 ppm). Mass and exact mass were determined with a Kratos MS25RFA. Elemental analysis was performed at the Canadian microanalytical service, Delta BC, and were within ±0.4% of the calculated value.

Diethyl 2,2,5,5-Tetramethylhexanedioate (12). 2,2,5,5-Tetramethylhexanedioic acid (**11**) (3.02 g, 14.93 mmol) was added to anhydrous ethanol (10 mL), dry benzene (60 mL), and a catalytic amount of concentrated H_2SO_4. The solution was refluxed under Dean−Stark conditions for 12 h and then concentrated under reduced pressure. The residue was dissolved in ether and washed with water, 10% sodium bicarbonate solution, and again with water. The resulting solution was dried ($MgSO_4$) and filtered and the solvent removed *in vacuo* to yield a clear oil (3.32 g, 83.2% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 12H), 1.21 (t, J = 7.1 Hz, 6H), 1.41 (s, 4H), 4.08 (q, J = 7.1 Hz, 4H).

3,3,6,6-Tetramethyl-1,2-bis(trimethylsilyloxy)cyclohexene (13).[39] Sodium (1.05 g, 45.6 mmol) was added to dry toluene (125 mL) and heated at reflux with stirring until a fine dispersion of sodium was obtained. The suspension was cooled to 90 °C, and dimethyl 2,2,5,5-tetramethylhexanedioate (**12**) (2.36 g, 9.1 mmol) was added followed by chlorotrimethylsilane (4.97 g, 45.75 mmol). The mixture was heated at 90 °C for 20 h and cooled, and the contents were filtered under nitrogen. The precipitate was washed with dry THF and the filtrate concentrated *in vacuo*. Purification of the resulting yellow liquid by Kugelrohr distillation gave the desired compound as a colorless oil (2.41 g, 77% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.18 (s, 18H), 1.00 (s, 12H), 1.42 (s, 4H).

1,2-Dioxo-3,3,6,6-tetramethylcyclohexane (14a).[40] To a stirred solution of 3,3,6,6-tetramethyl-1,2-bis(trimethylsilyloxy)cyclohexene **(13)** (2.75 g, 8.7 mmol) in carbon tetrachloride (distilled over P_2O_5) was added dropwise bromine (1.39 g, 8.7 mmol) under nitrogen atmosphere. The solvent was removed *in vacuo* yielding a yellow solid which was recrystallized from methylene chloride (1.32 g, 89% yield): mp 114−115 °C (lit.[40] mp 113.5−115 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (s, 12H), 1.84 (s, 4H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 23.2, 34.9, 48.9, 207.6.

Methyl 2,3-Diaminopropionate Dihydrochloride. 2,3-Diaminopropionic acid monohydrochloride (2.8 g, 20 mmol) was suspended in dry methanol (100 mL) and cooled to 0 °C, and dry HCl gas was bubbled through until all the solid had disappeared (ca. 30 min). After stirring at room temperature for an additional 3 h, the solvent was evaporated *in vacuo* yielding a white solid (3.0 g, 99%): mp 172 °C; IR (KBr) 3200−2500 (br), 1735 (CO), 1598, 1525, 1455, 1255, 1145, 1050 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.33 (d, J = 6 Hz, 2H), 3.77 (s, 3H), 4.43 (t, J = 6 Hz, 1H), 8.89 (br s, 6H); ^{13}C NMR (DMSO-d_6) δ 38.3, 49.9, 53.3, 165.4 (CO).

Methyl 5,6,7,8-Tetrahydo-5,5,8,8-tetramethylquinoxalinecarboxylate (15a). Potassium hydroxide (150 mg) dissolved in methanol (1 mL) was added to a suspension of methyl 2,3-diaminopropionate dihydrochloride (191 mg, 1.0 mmol) in dry methanol (1 mL). That mixture was shaken vigorously for 5 min, and the potassium chloride which had formed was filtered quickly over a cotton pad. The freshly prepared free diamine solution was added to a solution of 1,2-dioxo-3,3,6,6-tetramethylcyclohexane **(14a)** (168 mg, 1.0 mmol) in methanol (2 mL). A few beads of molecular sieves (3 Å) were added, and the reaction was heated at reflux for 5 h. After cooling, the sieves were filtered off, and the solvent was removed *in vacuo*. Water was added (2 mL) and the suspension extracted several times with diethyl ether (5 × 5 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (hexane/EtOAc, 98:2) to yield a thick colorless oil which crystallized upon standing (104 mg, 45%): mp 39−40 °C; IR (KBr) 2960, 2864, 1724 (CO), 1259, 1238, 1146 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 6H), 1.34 (s, 6H), 1.80 (s, 4H), 3.96 (s, 3H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.3 (4×), 33.4, 33.5, 37.1, 37.3, 52.3, 139.8, 142.3, 158.2, 161.9, 164.9; MS (EI) m/z 248 (M^+, 100), 233 (80), 190 (28); HRMS $C_{14}H_{20}N_2O_2$ calcd 248.1525 (M^+), found 248.1521.

Methyl 5,6-(1,1,3,3-Tetramethylcyclopentano)-2-pyrazinecarboxylate (15b). To a solution of dry triethylamine (1.8 mL, 12.9 mmol) and methyl 2,3-diaminoproprionate dihydrochloride (2.49 g, 12.9 mmol) in methylene chloride (175 mL) at 0 °C was added 1,2-dioxo-3,3,5,5-tetramethylcyclopentane (2.0 g, 12.9 mmol). The reaction was stirred for 72 h after which it was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting solid was purified by flash chromatography (hexane/CH_2Cl_2, 98:2) yielding a white solid (561 mg, 75%): mp 71.5−73 °C; IR (KBr) 2961, 2864, 1744 (CO), 1266, 1213, 1149, 772 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.39 (s, 6H), 2.02 (s, 2H), 3.99 (s, 3H), 9.05 (s, 1H); ^{13}C NMR (67.8 MHz, CDCl3) δ 29.2 (2×), 29.3 (2×), 40.1, 40.2, 52.5, 52.9, 141.7, 144.6, 163.7, 165.0, 167.4; MS (EI) m/z 234 (M^+, 33), 219 (100), 204 (11), 187 (18), 176 (99), 159 (68); HRMS $C_{13}H_{18}N_2O_2$ calcd 234.1368 (M^+), found 234.1362.

5,6,7,8-Tetrahydo-5,5,8,8-tetramethylquinoxalinecarboxylic Acid (16a). To a solution of **15a** (51.3 mg, 0.2 mmol) in methanol (3 mL) was added NaOH (16.6 mg, 0.42 mmol) in water (1 mL). The solution was stirred at room temperature for 2 h after which HCl (1 N, 0.42 mL) was added followed by sufficient water to turn the solution cloudy. The methanol was evaporated *in vacuo* and the solution extracted with ether (3 × 5 mL). The organic phase was dried, filtered, and concentrated *in vacuo* to yield **16a** (46.6 mg, 96%): mp 77−78 °C; IR ($CHCl_3$) 3400−2500 (br, COOH), 2969, 2868, 1768 (CO), 1389, 1346, 1268 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 12H), 1.83 (s, 4H), 9.17 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 30.5, 30.6, 34.3, 34.4, 38.0, 38.8, 138.1, 142.9, 158.1, 164.1, 165.5; MS (EI) m/z 234 (M^+, 100), 219 (77), 173 (77): HRMS $C_{13}H_{18}N_2O_2$ calcd 234.1368 (M^+), found 234.1365.

5,6-(1,1,3,3-Tetramethylcyclopentano)-2-pyrazinecarboxylic Acid (16b). This compound was synthesized using the procedure described for **16a**: mp 145−147 °C; IR (KBr) 3200−2400 (br, COOH), 2966, 2871, 1736 (CO), 1386, 1286, 1200, 746 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 12H), 2.07 (s, 2H), 9.21 (s, 1H); ^{13}C NMR (67.8 MHz, CDCl3) δ 29.1, 29.1, 39.8, 40.5, 52.5, 139.1, 143.8, 162.4, 163.4, 169.1; MS (EI) m/z 220 (M^+, 38), 205 (100), 187 (16), 176 (6), 159 (48); HRMS $C_{12}H_{16}N_2O_2$ calcd 220.1212 (M^+), found 220.1220.

General Procedure for the Coupling of the Pyrazinecarboxylic Acids 16a,b with Methyl Aminobenzoate Derivatives Using BOP. One equivalent of the pyrazinecarboxylic acid (**16a** or **16b**), 1.2 equiv of the methyl benzoate, 2.4 equiv of dry TEA, and 1.1 equiv of BOP were dissolved in dichloromethane, and the solution was stirred for 12 h. Saturated aqueous sodium chloride solution was added and the resultant solution stirred for 30 min. After extraction with ethyl acetate, the organic phase was washed with hydrochloric acid (1 M), saturated $NaHCO_3$ solution, and finally with saturated sodium chloride solution. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude products were purified by flash chromatography using MeOH/CH_2Cl_2 (0.5%) to give the desired retinamides which usually solidified on standing. Yields varied from 62% to 71% depending upon the amino benzoate used.

Methyl 4-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoate (9a): mp 177−178 °C; IR (KBr) 3354 (NH), 2961, 2865, 1714 (CO), 1699 (CO), 1606, 1592, 1534, 1276, 1185, 1114, 768 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.41 (s, 6H), 2.07 (s, 2H), 3.91 (s, 3H), 7.84 (d, J = 8.8 Hz, 2H), 8.07 (d, J = 8.8 Hz, 2H), 9.27 (s, 1H), 9.87 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.6, 29.7, 40.2, 40.7, 52.1, 53.2, 119.1, 126.0, 131.0, 141.6, 142.5, 143.2, 161.7, 162.2, 166.6, 168.1; MS (EI) m/z 353 (M^+, 100), 203 (19), 175 (96); HRMS $C_{20}H_{23}N_3O_3$ calcd 353.1739 (M^+), found 353.1732.

Methyl 3-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoate (9b): mp 113−114 °C; IR (KBr) 3360 (NH), 2961, 2865, 1721 (CO), 1699 (CO), 1550,

1300, 1280, 1223, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.42 (s, 6H), 2.07 (s, 2H), 3.93 (s, 3H), 7.47 (t, $J = 7.8$ Hz, 1H), 7.82 (dt, $J = 7.8$, 1.4 Hz, 1H), 8.19 (m, 2H), 9.27 (s, 1H), 9.80 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.6, 29.7, 40.2, 40.7, 52.3, 53.2, 120.7, 124.3, 125.6, 129.4, 131.0, 137.7 (2×), 142.6, 143.2, 161.7, 166.7, 168.0; MS (EI) *m/z* 353 (M^+, 100), 203 (15), 175 (83); HRMS C20H23N3O3 calcd 353.1739 (M^+), found 353.1743.

Dimethyl 3-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]isophthalate (9c): mp 168−169 °C; IR (KBr) 2956, 2870, 1730 (CO), 1694 (CO), 1540, 1436, 1248, 1240, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 6H), 1.43 (s, 6H), 2.08 (s, 2H), 3.96 (s, 6H), 8.84 (t, $J = 1.5$ Hz, 1H), 8.63 (d, $J = 1.5$ Hz, 2H), 9.28 (s, 1H), 9.89 (s, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 29.6, 29.7, 40.3, 40.7, 52.5, 53.2, 124.7, 126.6, 131.6, 138.1, 142.3, 143.2, 161.9, 162.4, 166.0, 168.3; MS (EI) *m/z* 411 (M^+, 97), 203 (21), 175 (100); HRMS $C_{22}H_{25}N_3O_5$ calcd 411.1794 (M^+), found 411.1797.

Methyl 2-chloro-4-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoate (9d): mp 143.5−144.5 °C; IR (KBr) 3340 (NH), 2964, 2867, 1728 (CO), 1701 (CO), 1581, 1519, 1396, 1252, 1119, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.41 (s, 6H), 2.07 (s, 2H), 3.91 (s, 3H), 7.75 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.56 (d, $J = 2.0$ Hz, 1H), 7.94 (d, $J = 8.4$ Hz, 1H), 9.26 (s, 1H), 9.83 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.6, 29.7, 40.3, 40.7, 52.3, 53.2, 117.3, 121.6, 125.0, 132.9, 135.3, 141.2, 142.1, 143.3, 161.8, 162.3, 165.4, 168.5; MS (EI) *m/z* 389 ($M^+ + 2$, 22), 387 (M^+, 65), 203 (25), 175 (100); HRMS $C_{20}H_{22}ClN_3O_3$ calcd 387.1350 (M^+), found 387.1354.

Methyl 4-chloro-3-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoate (9e): mp 130−131 °C; IR (KBr) 3350 (NH), 2965, 2862, 1721 (CO), 1708 (CO), 1589, 1531, 1307, 1252, 1259, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 6H), 1.41 (s, 6H), 2.08 (s, 2H), 3.93 (s, 3H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.78 (dd, $J = 8.4$, 2.0 Hz, 1H), 9.27 (s, 1H) 9.28 (d, $J = 2.0$ Hz, 1H), 10.59 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.6, 29.7, 40.2, 40.8, 52.4, 53.1, 121.7, 125.9, 127.9, 129.3, 130.0, 134.6, 142.6, 143.0, 161.7, 162.3, 166.2, 168.2; MS (EI) *m/z* 389 ($M^+ + 2$, 8), 387 (M^+, 22), 352 (100), 203 (5), 175 (58); HRMS $C_{20}H_{22}ClN_3O_3$ calcd 387.1350 (M^+), found 387.1345.

Methyl 4-methoxy-3-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoate (9f): mp 198−200 °C; IR (KBr) 3350 (NH), 2964, 2864, 1713 (CO), 1696 (CO), 1606, 1548, 1268, 764 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.40 (s, 6H), 2.06 (s, 2H), 3.89 (s, 3H), 4.01 (s, 3H), 6.95 (d, $J = 8.7$ Hz, 1H), 7.85 (dd, $J = 8.7$, 2.1 Hz, 1H), 9.20 (d, $J = 2.1$ Hz, 1H), 9.26 (s, 1H), 10.42 (s, 1H); ^{13}C NMR (67.8 MHz, CDCl3) δ 29.6, 29.7, 40.1, 40.7, 52.0, 53.2, 56.2, 109.6, 120.8, 123.2, 126.6, 127.1, 143.0, 143.2, 152.2, 161.5, 162.1, 166.9, 167.5; MS (EI) *m/z* 383 (M^+, 100), 352 (22), 203 (6), 190 (17), 175 (56); HRMS $C_{21}H_{25}N_3O_4$ calcd 383.1845 (M^+), found 383.1849.

Methyl 3-methoxy-4-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoate (9g): mp 219−219.5 °C; IR (KBr) 3328 (NH), 2963, 2867, 1702 (CO), 1697 (CO), 1606, 1545, 1451, 1286, 1278, 761 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (s, 6H), 1.40 (s, 6H), 2.07 (s, 2H), 3.90 (s, 3H), 4.01 (s, 3H), 7.59 (d, $J = 1.6$ Hz, 1H), 7.74 (dd, $J = 1.6$, 8.4 Hz, 1H), 8.64 (d, $J = 8.4$ Hz, 1H), 9.24 (s, 1H), 10.62 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.6, 29.7, 40.1, 40.7, 52.1, 53.1, 56.3, 111.0, 118.6, 123.5, 125.4, 131.7, 143.0 (2×), 148.2, 161.7, 162.2, 166.8, 167.7; MS (EI) *m/z* 383 (M^+, 100), 352 (20), 203 (7), 190 (15), 175 (67); HRMS $C_{21}H_{25}N_3O_4$ calcd 383.1845 (M^+), found 383.1848.

Methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoate (9o): mp 125−126 °C; IR (KBr) 3350 (NH), 2929, 2867, 1716 (CO), 1712 (CO), 1591, 1532, 1275, 768 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.39 (s, 6H), 1.84 (s, 4H), 3.90 (s, 3H), 7.81 (d, $J = 8.7$ Hz, 2H), 8.07 (d, $J = 8.7$ Hz, 2H), 9.22 (s, 1H), 9.82 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 30.5, 30.7, 34.4, 34.5, 38.0, 38.6, 52.8, 119.7, 126.7, 131.7, 141.1, 141.9, 142.3, 157.5, 162.4, 163.8, 167.3; MS (EI) *m/z* 367 (M^+, 100), 248 (19), 189 (83), 173 (30); HRMS $C_{21}H_{25}N_3O_3$ calcd 367.1896 (M^+), found 367.1916.

Methyl 3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoate (9p): mp 107−108 °C; IR (KBr) 3357 (NH), 2952, 2867, 1716 (CO), 1697 (CO), 1539, 1426, 1226, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.39 (s, 6H), 1.83 (s, 4H), 3.92 (s, 3H), 7.45 (t, $J = 7.9$ Hz, 1H), 7.80 (dt, $J = 7.9$, 1.1 Hz, 1H), 8.13 (ddd, $J = 7.9$, 2.2, 1.1 Hz, 1H), 8.19 (m, 1H), 9.21 (s, 1H), 9.72 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.8, 30.0, 33.7, 33.8, 37.2, 37.8, 52.3, 120.5, 124.1, 125.6, 129.4, 131.1, 137.7, 140.5, 141.1, 156.7, 161.7, 162.8, 166.7; MS (EI) *m/z* 367 (M^+, 21), 189 (100), 173 (18); HRMS $C_{21}H_{25}N_3O_3$ calcd 367.1896 (M^+), found 367.1911.

Dimethyl 3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]isophthalate (9q): mp 143−145 °C; IR (KBr) 3346 (NH), 2961, 2867, 1730 (CO), 1693 (CO), 1539, 1245, 1140, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 6H), 1.40 (s, 6H), 1.84 (s, 4H), 3.95 (s, 6H), 8.46 (t, $J = 1.5$ Hz, 1H), 8.59 (d, $J = 1.5$ Hz, 2H), 9.23 (s, 1H), 9.80 (br s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.7, 30.0, 33.7, 33.8, 37.2, 37.8, 52.5, 124.6, 126.5, 131.5, 138.0, 140.2, 141.1, 156.8, 161.8, 163.1, 165.9; MS (EI) *m/z* 425 (M^+, 13), 189 (100), 173 (20); HRMS $C_{23}H_{27}N_3O_5$ calcd 425.1951 (M^+), found 425.1952.

Methyl 2-chloro-4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoate (9r): mp 159−161 °C; IR (KBr) 3346 (NH), 2867, 1733 (CO), 1701 (CO), 1576, 1508, 1121, 774 cm^{-1}; ^1H NMR (200 MHz, CDCl3) δ 1.35 (s, 6H), 1.38 (s, 6H), 1.84 (s, 4H), 3.90 (s, 3H), 7.70 (dd, $J = 8.6$, 2.3 Hz, 1H), 7.89 (d, $J = 2.3$ Hz, 1H), 7.91 (d, $J = 8.6$ Hz, 1H), 9.20 (s, 1H), 9.76 (br s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.7, 29.9, 33.6, 33.7, 37.2, 37.8, 52.3, 117.1, 121.4, 124.8, 132.8, 135.3, 140.0, 141.1 (2×), 156.8, 161.7, 163.3, 165.3; MS (EI) *m/z* 403 ($M^+ + 2$, 31) 401 (M^+, 92), 366 (18), 189 (100), 173 (17); HRMS $C_{21}H_{24}ClN_3O_3$ calcd 401.1506 (M^+), found 401.1514.

Methyl 4-chloro-3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoate (9s): mp 95−97 °C; IR (KBr) 3339 (NH), 2957, 2927, 1722 (s, CO), 1585, 1530, 1304, 1230, 1107 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.40 (s, 6H), 1.85 (s, 4H), 3.92 (s, 3H), 7.50 (d, $J = 8.4$ Hz, 1H), 7.76 (dd, $J = 8.4$, 2.4 Hz, 1H), 9.22 (s, 1H), 9.29 (d, $J = 2.4$ Hz, 1H), 10.60 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.7, 29.9, 33.6, 33.9, 37.3, 37.8, 52.4, 121.5, 125.7, 127.6, 129.2, 130.0, 134.6, 140.4, 140.9, 156.9, 161.6, 163.1, 166.1; MS (EI) *m/z* 403 ($M^+ + 2$, 10) 401 (M^+, 29), 366 (100), 189 (47); HRMS $C_{21}H_{24}ClN_3O_3$ calcd 401.1506 (M^+), found 401.1514.

Methyl 4-methoxy-3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoate (9t): mp 197−198 °C; IR (KBr) 3350 (NH), 2918, 2867, 1716 (CO), 1694 (CO), 1545, 1129, 1213, 764 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.39 (s, 6H), 1.85 (s, 4H), 3.89 (s, 3H), 4.01 (s, 3H), 6.96 (d, $J = 8.5$ Hz, 1H), 7.85 (dd, $J = 8.5$, 2.1 Hz, 1H), 9.20 (d, $J = 2.1$ Hz, 1H), 9.21 (s, 1H), 10.48 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.7, 29.8, 33.6, 33.9, 37.2, 37.7, 52.0, 56.2, 109.5, 120.4, 123.2, 126.5, 127.2, 140.8, 141.0, 152.0, 156.6, 161.4, 162.5, 166.9; MS (EI) *m/z* 397 (M^+, 100), 366 (23), 190 (71), 189 (50), 173 (17); HRMS $C_{22}H_{27}O_4N_3$ calcd 397.2001 (M^+), found 397.2003.

General Method for Methyl Ester Cleavage.[42] To a suspension of 1 equiv of methyl benzoates in anhydrous dimethoxyethane were added 8.6 equiv of potassium *tert*-butoxide and 2.2 equiv of water. The suspension was refluxed for 12 h and then cooled and water added. The aqueous layer was washed with ether, acidified with concentrated HCl, and then extracted with ether. The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. Purification was accomplished by flash chromatography using CH_2Cl_2/MeOH: AcOH; 200:4:0.5. Yields varied between 82 and 97%.

4-[(5,6-(1,1,3,3-Tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoic acid (9h): mp 243.5−245 °C dec; IR (KBr) 3300 (NH), 3200−2400 (br, COOH), 2964, 2852, 1684 (s, CO), 1592, 1527, 1297, 1171 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 6H), 1.41 (s, 6H), 2.07 (s, 2H), 7.88 (d, $J = 8.5$ Hz, 2H,), 8.13 (d, $J = 8.5$ Hz, 2H), 9.28 (s, 1H), 9.91 (s,

1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.1, 30.3, 40.7, 41.1, 53.5, 118.6, 124.41, 131.0, 141.5, 141.6, 142.4, 160.72, 161.25, 167.1, 169.7; MS (EI) *m/z* 339 (M^+, 80), 203 (25), 175 (100); HRMS $C_{19}H_{21}N_3O_3$ calcd 339.1583 (M^+), found 339.1580.

3-[(5,6-(1,1,3,3-Tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoic acid (9i): mp 229−231 °C dec; IR (KBr) 3313 (NH), 3250−2400 (br, COOH), 2964, 2866, 1723 (CO), 1674 (CO), 1593, 1543, 1281, 1169, 1147 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.33 (s, 6H), 1.41 (s, 6H), 2.04 (s, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.47 (s, 1H), 9.07 (s, 1H), 10.59 (s, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 29.1 (2×), 39.7, 40.0, 52.2 (CH_2), 121.4, 124.6, 124.8, 128.7, 131.1, 138.1, 142.2, 143.4, 161.7, 162.1, 166.4, 166.9; MS (EI) *m/z* 339 (M^+, 87), 203 (23), 175 (100); HRMS $C_{19}H_{21}N_3O_3$ calcd 339.1583 (M^+), found 339.1586.

3-[(5,6-(1,1,3,3-Tetramethylcyclopentano)-2-pyrazinyl)carboxamido]isophthalic acid (9j): mp > 300 °C; IR (KBr) 3355 (NH), 3250−2400 (br, COOH), 2966, 2868, 1699 (s, CO), 1534, 1435, 1275, 1168 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.33 (s, 6H), 1.41 (s, 6H), 2.04 (s, 2H), 8.23 (s, 1H), 8.60 (s, 2H), 9.07 (s, 1H), 10.68 (s, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 30.3 (2×), 40.9, 41.2, 53.3 (CH_2), 126.0 (2×), 126.6, 139.5, 143.5, 144.5, 163.0, 163.5, 167.6, 167.8; MS (EI) *m/z* 383 (100, M^+) 203 (28), 175 (88); HRMS $C_{20}H_{21}N_3O_5$ calcd 383.1481 (M^+), found 383.1488.

2-Chloro-4-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoic acid (9k): mp 228−229 °C dec; IR (KBr) 3406 (NH), 3300−2400 (br, COOH), 2964, 2929, 1700 (s, CO), 1581, 1522, 1391, 1289, 1119 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.34 (s, 6H), 1.42 (s, 6H), 2.05 (s, 2H), 7.88 (d, J = 8.4 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H), 9.07 (s, 1H), 10.68 (s, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 29.6 (2×), 40.3, 40.6, 52.7 (CH_2), 118.9, 122.1, 132.4, 133.0, 141.9, 143.0 (2×), 143.6, 162.38, 163.0, 167.3 (2×); MS (EI) *m/z* 375 (M^+ + 2, 14), 373 (M^+, 43), 338 (43), 203 (24), 175 (100); HRMS $C_{19}H_{20}ClN_3O_3$ calcd 373.1193 (M^+), found 373.1194.

4-Chloro-3-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoic acid (9l): mp 249−250 °C dec; IR (KBr) 3337 (NH), 3300−2400 (br, COOH), 2964, 2862, 1718 (s, CO), 1586, 1532, 1367, 1245, 1113 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.35 (s, 6H), 1.39 (s, 6H), 2.07 (s, 2H), 7.74 (s, 2H), 8.90 (s, 1H), 9.13 (s, 1H), 10.59 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.8 (2×), 39.2, 40.8, 52.7, 123.2, 126.9, 128.9, 130.2, 134.8, 142.7, 142.8 (2×), 161.8, 162.5, 168.3 (2×); MS (EI) *m/z* 375 (M^+ + 2, 8), 373 (M^+, 24), 338 (100), 203 (8), 175 (59); HRMS $C_{19}H_{20}ClN_3O_3$ calcd 373.1193 (M^+), found 373.1189.

4-Methoxy-3-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoic acid (9m): mp 277−279 °C dec; IR (KBr) 3350 (NH), 3300−2500 (br, COOH), 2963, 2860, 1692 (s, CO), 1600, 1542, 1267, 1143 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.34 (s, 6H), 1.38 (s, 6H), 2.06 (s, 2H), 4.01 (s, 3H), 7.23 (d, J = 8.7 Hz, 1H), 7.77 (d, J = 8.7 Hz, 1H), 8.97 (s, 1H), 9.11 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (67.8 MHz, DMSO-d_6) δ 29.1 (2×), 40.1 (2×), 52.0, 56.5, 110.5, 120.0, 123.1, 126.2, 126.3, 142.0, 142.4, 151.8, 160.6, 161.7, 166.8, 167.3; MS (EI) *m/z* 369 (M^+, 100), 338 (19), 203 (9), 175 (77); HRMS $C_{20}H_{23}N_3O_4$ calcd 369.1689 (M^+), found 369.1681.

3-Methoxy-4-[(5,6-(1,1,3,3-tetramethylcyclopentano)-2-pyrazinyl)carboxamido]benzoic acid (9n): mp 268−269 °C dec; IR (KBr) 3350 (NH), 3300−2500 (br, COOH), 2963, 2870, 1712 (CO), 1690 (CO), 1601, 1549, 1463, 1267, 1164 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.37 (s, 6H), 1.41 (s, 6H), 2.09 (s, 2H), 4.04 (s, 3H), 7.62 (d, J = 1.8 Hz, 1H), 7.69 (dd, J = 8.3, 1.8 Hz, 1H), 8.52 (d, J = 8.3 Hz, 1H), 9.16 (s, 1H), 10.58 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 30.2, 30.3, 40.6, 41.2, 53.5, 56.6, 110.9, 118.2, 123.8, 123.9, 131.8, 142.2 (2×), 147.4, 160.8, 161.3, 166.7, 169.8; MS (EI) *m/z* 369 (M^+, 100), 338 (11), 203 (7), 175 (61); HRMS $C_{20}H_{23}N_3O_4$ calcd 369.1689 (M^+), found 369.1694.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoic acid (9u): mp 258−259 °C dec; IR (KBr) 3343 (NH), 3300−2500 (br, COOH), 2960, 2866, 1697 (s, CO), 1609, 1589, 1536, 1420, 1289, 1175 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.40 (s, 6H), 1.85 (s, 4H), 7.85 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 8.5 Hz, 2H), 9.23 (s, 1H), 9.86 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.8, 29.9, 33.7, 33.8, 37.2, 37.8, 119.0, 124.9, 131.7, 140.3, 141.2, 142.3, 156.8, 161.7, 163.1, 170.6; MS (EI) *m/z* 353 (M^+, 100), 189 (80); HRMS $C_{20}H_{23}N_3O_3$ calcd 353.1739 (M^+), found 353.1734. Anal. ($C_{20}H_{23}N_3O_3$) C, H, N.

3-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoic acid (9v): mp 211−213 °C dec; IR (KBr) 3350 (NH), 3300−2500 (br, COOH), 2959, 2861, 1694 (s, CO), 1538, 1454, 1291, 1141 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.32 (s, 6H), 1.42 (s, 6H), 1.82 (s, 4H), 7.52 (t, J = 7.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 8.44 (s, 1H), 9.05 (s, 1H), 10.43 (s, 1H); ^{13}C NMR (50 MHz, DMSO-d6) δ 30.4, 30.6, 34.3, 34.4, 37.7, 38.3, 120.6, 124.5, 125.6, 128.9, 129.5, 137.1, 139.7, 140.3, 155.8, 160.7, 161.8, 169.5; MS (EI) *m/z* 353 (M^+, 100), 189 (67); HRMS $C_{20}H_{23}N_3O_3$ calcd 353.1739 (M^+), found 353.1736.

Methyl 4-(Methylamino)benzoate. 4-(Methylamino)benzoic acid (0.15 g, 1 mmol) and *p*-toluenesulfonic acid monohydrate (0.076 g, 0.4 mmol) were dissolved in methanol (15 mL) and refluxed for 72 h. Chloroform was added (50 mL), and the solution was filtered. The solvent was removed *in vacuo* to give a quantitative yield of methyl 4-(methylamino)benzoate as a yellow powder: mp 83−85 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.89 (s, 3H), 3.84 (s, 3H), 6.92 (d, J = 8.6 Hz, 2H), 7.86 (d, J = 8.6 Hz, 2H).

Methyl 4-[(5,6-(1,1,3,3-Tetramethylcyclopenteno)-2-pyrazinyl)methylcarboxamido]benzoate (9w). Compound **16b** (110 mg, 0.5 mmol), methyl 4-(methylamino)benzoate (80 mg, 0.5 mmol), 4-(dimethylamino)pyridine (60 mg, 0.5 mmol), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide methiodide (190 mg, 1 mmol) were dissolved in dried CH_2Cl_2 (25 mL). The reaction mixture was stirred at ambient temperature for 72 h after which it was washed with 1 N HCl, 10% $NaHCO_3$ solution, and finally brine. The organic layer was dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was subjected to column chromatography (10% EtOAc in hexanes) to give a white powder (62 mg, 34%): mp 108−110 °C; IR ($CHCl_3$) 2960, 1719 (CO), 1645 (CO), 1603, 1283, 1238, 1115 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.9 (s, 6H), 1.26 (s, 6H), 1.83 (s, 2H), 3.53 (s, 3H), 3.87 (s, 3H), 7.10 (d, J = 8.6 Hz, 2H), 7.78 (d, J = 8.6 Hz, 2H), 8.74 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.1, 29.4, 38.2, 39.8, 40.4, 52.2, 52.9, 126.6, 128.0, 130.3, 143.8, 146.8, 149.0, 161.6, 164.6, 166.2, 167.0; MS (EI) *m/z* 367 (M^+, 34), 176 (100), 175 (28); HRMS $C_{21}H_{25}N_3O_3$ calcd 367.1896 (M^+), found 367.1892.

General Procedure for Trifluoroacetamide Formation. The commercially available aminobenzoic acids (10.0 mmol) were dissolved in neat trifluoroacetic acid (10 mL) and cooled to 0 °C at which point trifluoroacetic anhydride (3 mL) was added. After stirring for 10 min a precipitate usually formed. The reaction was checked for completion and more trifluoroacetic anhydride added if required. Upon completion, the reaction mixture was poured over crushed ice (150 mL) whereupon a voluminous white precipitate formed. After 30 min the solid was filtered, washed with copious amounts of water, and allowed to air-dry at 50 °C for 12 h. Yields exceeded 90%.

4-(Trifluoroacetamido)benzoic acid (17a): mp 281−282 °C; IR (KBr) 3319 (NH), 3300−2300 (br, COOH), 1705 (CO), 1678 (CO), 1543, 1292, 1194 (s), 1187 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H), 10.67 (s, 1H), 11.0−11.8 (s, 1H, COOH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 116.3 (q, $^1J_{^{13}C,^{19}F}$ = 285.2 Hz), 120.3, 127.8 (C_{quat}), 130.7, 140.8 (C_{quat}), 155.3 (q, $^2J_{^{13}C,^{19}F}$ = 37.1 Hz), 167.5.

3-Methoxy-4-(trifluoroacetamido)benzoic acid (17b): mp 173−174 °C; IR (KBr) 3413 (w, NH), 3394 (w, NH), 3200−2500 (br, COOH), 1746 (CO), 1688 (CO), 1604, 1310, 1277, 1223, 1171, 1150 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.63 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 8.4 Hz, 1H), 8.70 (s, 1H, NH), 11.6−12.4 (br s, 1H, COOH); ^{13}C NMR (50 MHz, $(CD_3)_2CO$) δ 57.7, 112.9, 117.0 (q, $^1J_{^{13}C,^{19}F}$ = 284.2

Hz), 122.0, 123.6, 129.4 (C_{quat}), 130.0 (C_{quat}), 150.4 (C_{quat}), 155.4 (q, $^2J_{^{13}C,^{19}F}$ = 37.1 Hz), 171.1.

4-(Methyltrifluoroacetamido)benzoic acid (17c): mp 168−169 °C; IR (KBr) 3300−2400 (br, COOH), 1709 (s, CO), 1605, 1429, 1287, 1221, 1202, 1149 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.42 (s, 3H), 7.39 (d, J = 8.5 Hz, 2H), 8.20 (d, J = 8.5 Hz, 2H), 12.0 (s, 1H, COOH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 40.7 (br, NMe), 116.7 (q, $^1J_{^{13}C,^{19}F}$ = 284.6 Hz), 127.7 (br, N−C−(*C*H)$_2$), 130.3 (br, C_{quat}), 131.9, 145.6 (C_{quat}), 157.7 (q, $^2J_{^{13}C,^{19}F}$ = 36.2 Hz), 170.6.

General Procedure for 2-(Trimethylsilyl)ethyl Ester Formation. The benzoic acid derivative (9.0 mmol) was suspended in acetonitrile (4 mL). Carbon tetrachloride (2 mL) was added and the thick paste shaken vigorously. Finely ground triphenylphosphine (2.80 g, 10.0 mmol) was added in one portion and the flask shaken vigorously for 5 min. The mixture slowly liquefied, and little heat was generated. After the complete disappearance of all solids, stirring was continued for 15 min at which point trimethylsilylethanol (1.16 g, 10.0 mmol) was added and the reaction mixture refluxed for 15 min. Upon cooling, the reaction mixture was poured into rapidly stirring diethyl ether (200 mL), and triphenylphosphine oxide precipitated out. After filtration and drying ($MgSO_4$), the solvent was removed *in vacuo* and the crude product purified by column chromatography (hexane/EtOAc (95:5)) yielding between 60% and 70% of the desired product.

2′-(Trimethylsilyl)ethyl 4-(trifluoroacetamido)benzoate (18a): mp 93−94 °C; IR (KBr) 3316 (w, NH), 2957 (CH), 1743 (CO), 1678 (CO), 1606, 1293, 1149, cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 9H), 1.13 (m, 2H), 4.41, (m, 2H), 7.73 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H), 8.99 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.3, 19.0, 64.7, 116.0 (q, $^1J_{^{13}C,^{19}F}$ = 285.1 Hz), 120.5, 128.3 (C_{quat}), 131.0, 139.7 (C_{quat}), 155.3 (q, $^2J_{^{13}C,^{19}F}$ = 37.4 Hz), 166.1.

2′-(Trimethylsilyl)ethyl 3-methoxy-4-(trifluoroacetamido)benzoate (18b): mp 37−38 °C; IR (KBr) 3402 (NH), 2955 (CH), 1741 (CO), 1711 (CO), 1542, 1281, 1154 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 9H), 1.14 (m, 2H), 4.00 (s, 3H), 4.31, (m, 2H), 7.61 (d, J = 1.8 Hz, 1H), 7.73 (dd, J = 8.5, 1.8 Hz, 1H), 8.40 (d, J = 8.5 Hz, 1H), 8.68 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 19.0, 57.4, 64.6, 111.5, 116.0 (q, $^1J_{^{13}C,^{19}F}$ = 285.0 Hz), 119.7, 123.5, 128.3 (C_{quat}), 129.2 (C_{quat}), 147.9 (C_{quat}), 154.5 (q, $^2J_{^{13}C,^{19}F}$ = 37.4), 165.7.

2′-(Trimethylsilyl)ethyl 4-(methyltrifluoroacetamido)-benzoate (18c). mp 28−29 °C; IR (KBr) 2957 (CH), 1701 (s, CO), 1276, 1224, 1197, 1154, 1114, 865, 839 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.14 (m, 2H), 3.39 (br s, 3H), 4.43, (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 19.1, 40.7 (br, NMe), 64.8, 116.9 (q, $^1J_{^{13}C,^{19}F}$ = 284.5 Hz), 127.6 (br, N−C−(*C*H)$_2$), 131.1, 131.5 (C_{quat}), 144.6 (br, C_{quat}), 156.6 (q, $^2J_{^{13}C,^{19}F}$ = 35.8 Hz), 165.4.

2′-(Trimethylsilyl)ethyl 4-acetoxybenzoate (18d): colorless oil; IR (neat) 2955 (CH), 1764 (CO), 1718 (CO), 1274, 1196, 1160, 1112, 860, 839 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9H), 1.13 (m, 2H), 2.32 (s, 3H), 4.41 (m, 2H), 7.16 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.0, 18.7, 22.4, 64.3, 121.9, 128.6 (C_{quat}), 131.4, 154.3 (C_{quat}), 165.9 (CO), 168.8 (CO).

General Procedure for *N*-Trifluoroacetyl and Phenol Acetyl Removal. An aqueous solution of sodium carbonate (1%, 60 mL) was added slowly to compounds **18a**−**d** (5.5 mmol) which were previously dissolved in a 50:50 mixture of THF/methanol (40 mL). The solution was stirred at room temperature until the reaction was judged complete by TLC (30 min−60 h). The methanol and THF were removed in vacuo, and the remaining aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic phase was dried ($MgSO_4$), the solvent removed, and the thick oil crystallized under high vacuum to give the desired compounds in 80−90% yield.

2′-(Trimethylsilyl)ethyl 4-aminobenzoate (19a): mp 64−65 °C; IR (KBr) 3454 (NH), 3353 (NH), 2954 (CH), 1678 (CO), 1598, 1274 (s), 1170, 849 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9H), 1.10 (m, 2H), 4.07 (br s, 2H, NH), 4.36, (m, 2H), 6.62 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 19.1, 63.6, 114.2, 120.5 (C_{quat}), 131.8, 150.9 (C_{quat}), 166.7.

2′-(Trimethylsilyl)ethyl 4-amino-3-methoxybenzoate (19b): mp 79−80 °C; IR (KBr) 3457 (NH), 3345 (s, NH), 2952 (CH), 1679 (CO), 1622, 1588, 1521, 1428, 1310, 1287, 1264 (s), 1223, 1106, 854, 767 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9H), 1.10 (m, 2H), 3.86 (s, 3H), 4.17 (br s, 2H), 4.36, (m, 2H), 6.64 (d, J = 8.1 Hz, 1H), 7.45 (d, J = 1.7 Hz, 1H), 7.53 (dd, J = 8.1, 1.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 19.1, 56.7, 63.6, 111.7, 113.6, 120.3 (C_{quat}), 124.3, 141.2 (C_{quat}), 146.2 (C_{quat}), 166.8.

2′-(Trimethylsilyl)ethyl 4-(methylamino)benzoate (19c): mp 53−54 °C; IR (KBr) 3372 (s, NH), 2953 (CH), 2896, 1683 (CO), 1598, 1534, 1344, 1275 (s), 1171 (s), 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.11 (m, 2H), 2.88 (s, 3H), 4.05 (br s, 1H), 4.36, (m, 2H), 6.55 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 19.1, 31.7, 63.5, 111.6, 119.2 (C_{quat}), 131.7, 152.7 (C_{quat}), 166.7.

2′-(Trimethylsilyl)ethyl 4-hydroxybenzoate (19d): mp 102−103 °C; IR (KBr) 3354 (br, OH), 2955 (CH), 2900, 1678 (CO), 1591, 1512, 1296 (s), 1275, 1165, 840 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9H), 1.12 (m, 2H), 4.40 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.05 (br s, 1H), 7.95 (d, J = 8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.3, 18.4, 64.2, 115.8, 122.9 (C_{quat}), 132.3, 160.7 (C_{quat}), 167.6.

General Procedure for Amide or Ester Formation Using Triphenylphosphine/Hexachloroacetone. Finely ground triphenylphosphine (280 mg, 1.1 mmol) was added in one portion to a rapidly stirred mixture of either carboxylic acid **16a** or **23** (1 mmol) suspended in hexachloroacetone (1 mL) at 10 °C. The progress of the acyl chloride formation could be followed by both the development of a faint yellow color and the disappearance of the solid. This was generally followed by precipitation of triphenylphosphine oxide (ca. 30 min). The acyl chloride so formed was then added dropwise to a rapidly stirred solution of the appropriate amine **19a**−**c** or phenol **19d** (1.0 mmol) in dry pyridine (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min and the pyridine/hexachloroacetone removed under high vacuum at room temperature (usually overnight). The crude brownish mixture was then treated with water (5 mL) and extracted several times with diethyl ether (5 × 5 mL). The combined organic phases were dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography using a gradient elution from 100% hexane to hexane/EtOAc (9:1). Yields varied from 60% to 80%, and the reaction could be used successfully down to a 0.1-mmol scale.

2′-(Trimethylsilyl)ethyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoate (20a): mp 142−143 °C; IR (KBr) 3310 (w, NH), 2958 (CH), 2921, 1712 (s, CO), 1651, 1597, 1543, 1267, 1110, 834 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.15 (m, 2H), 1.37 (s, 6H), 1.41 (s, 6H), 1.86 (s, 4H), 4.42, (m, 2H), 7.82 (d, J = 8.6 Hz, 2H), 8.08 (d, J = 8.6 Hz, 2H), 9.25 (s, 1H), 9.84 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.0, 18.0, 30.3, 30.5, 34.2, 34.4, 37.8, 38.4, 63.7, 112.8 (C_{quat}), 119.4, 126.9 (C_{quat}), 131.3, 140.8 (C_{quat}), 141.6 (CH), 141.8 (C_{quat}), 162.1 (C_{quat}), 163.4, 166.7.

2′-(Trimethylsilyl)ethyl 3-methoxy-4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoate (20b): mp 200−201 °C; IR (KBr) 3311 (NH), 2963 (CH), 2926, 2926, 2863, 1701 (s, CO), 1605, 1554, 1247, 1215, 833 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.15 (m, 2H), 1.37 (s, 6H), 1.41 (s, 6H), 1.86 (s, 4H), 4.03 (s, 3H), 4.42, (m, 2H), 7.61 (d, J = 1.7 Hz, 1H), 7.75 (dd, J = 8.4, 1.7 Hz, 1H), 8.63 (d, J = 8.4 Hz, 1H), 9.21 (s, 1H), 10.68 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 19.1, 31.2, 31.3, 35.0, 35.3, 38.6, 39.1, 57.4, 64.3, 111.34, 118.8, 123.8, 126.2 (C_{quat}), 131.8 (C_{quat}), 140.97, 141.0 (C_{quat}), 148.1 (C_{quat}), 156.6 (C_{quat}), 161.5 (C_{quat}), 162.5, 166.3.

2′-(Trimethylsilyl)ethyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)methylcarboxamido]benzoate (20c): mp 97−98 °C; IR (KBr) 2958 (CH), 2930, 1715 (s, CO), 1652 (CO), 1272, 1099, 864, 839 cm^{-1}; ^{1}H NMR (200 MHz,

$CDCl_3$) δ 0.07 (s, 9H), 0.78 (s, 6H), 1.05-1.15 (m, 2H), 1.25 (s, 6H), 1.50−1.75 (m, 4H), 3.53 (s, 3H), 4.39, (m, 2H), 7.09 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H), 8.80 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 18.9, 30.6, 31.1, 35.0, 35.2, 38.2, 38.7, 39.8, 64.4, 126.7, 128.7 (C_{quat}), 130.7, 142.3, 144.9 (C_{quat}), 149.1 (C_{quat}), 156.2 (C_{quat}), 159.5 (C_{quat}), 165.7, 166.9.

2′-(Trimethylsilyl)ethyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carbonyloxy]benzoate (20d): colorless oil; IR (KBr) 2957 (CH), 1769 (CO), 1742 (CO), 1273, 1095, 838 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.09 (s, 9H), 1.15 (m, 2H), 1.38 (s, 6H), 1.40 (s, 6H), 1.85 (s, 4H), 4.44, (m, 2H), 7.34 (d, J = 8.6 Hz, 2H), 8.13 (d, J = 8.6 Hz, 2H), 9.16 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 1.0, 17.7, 29.9 (2×), 33.9, 34.0, 37.8, 38.0, 63.4, 121.2 (C_{quat}), 128.0 (C_{quat}), 130.6, 138.8 (C_{quat}), 142.6, 153.6 (C_{quat}), 158.4 (C_{quat}), 162.1, 162.5, 165.0.

General Procedure for the Cleavage of the 2-(Trimethylsilyl)ethyl Ester. The 2-(trimethylsilyl)ethyl ester (0.2 mmol) was dissolved in dimethylformamide (1 mL), and a solution of tetrabutylammonium fluoride in THF (1.0 M, 0.2 mL) was added. The reaction was monitored by TLC, and more reagent was added until all the starting material had been consumed. After acidification (1 M HCl, 1 mL), the reaction mixture was evaporated to dryness under high vacuum. Water was added to the residue and the evaporation repeated in order to eliminate all traces of dimethylformamide. Water was added to the residue (2 mL) and the desired compound extracted with diethyl ether (6 × 7 mL). The organic layer was dried ($MgSO_4$), the solvent removed, and the crude product purified by recrystallization in hot acetonitrile followed by cooling to either room temperature or −20 °C. Yields were almost quantitative for reaction scales from 0.01 to 0.5 mmol.

3-Methoxy-4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carboxamido]benzoic acid (9x). mp 260−261 °C; IR (KBr) 3360 (NH), 3300−2400 (br, COOH), 2965 (CH), 2934, 2867, 1690 (CO), 1537, 1490, 1460, 1277, 1253, 1136 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (s, 6H), 1.43 (s, 6H), 1.88 (s, 4H), 4.06 (s, 3H), 7.67 (d, J = 1.7 Hz, 1H), 7.87 (dd, J = 8.4, 1.7 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H), 9.23 (s, 1H), 10.75 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.2, 31.3, 35.0, 35.3, 38.6, 39.1, 57.4, 111.8 (CH), 118.8 (CH), 124.6, 124.9 (CH), 132.8, 141.0 (2×), 148.2, 156.7, 161.6, 162.6, 170.7 (CO); MS (EI) m/z 383 (M^+, 100), 368 (7), 352 (13), 203 (22), 189 (73); HRMS $C_{21}H_{25}N_3O_4$ calcd 383.1845 (M^+), found 383.1841. Anal. ($C_{21}H_{25}N_3O_4 \cdot 2H_2O$) C, N; H: calcd, 6.97; found, 6.21.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)methylcarboxamido]benzoic acid (9y): mp 229−230 °C; IR (KBr) 3300−2500 (br, COOH), 2964 (CH), 2929, 1724 (CO), 1625 (CO), 1602, 1221 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79 (s, 6H), 1.26 (s, 6H), 1.55−1.75 (m, 4H), 3.56 (s, 3H), 7.14 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 8.84 (s, 1H), 9.5−10.0 (br s, 1H, COOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.75 (s, 6H, Me_2C_8), 1.20 (s, 6H, Me_2C_5), 1.59 (m, 2H), 1.64 (m, 2H) 3.44 (s, 3H, NMe), 7.24 (d, J = 8.5 Hz, 2H, NMe-C−(CH)$_2$), 7.79 (d, J = 8.5 Hz, 2H, CO_2H−C−(CH)$_2$), 8.72 (s, 1H, H3), 12 (br s, 1H, COOH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.5, 31.1, 35.0, 35.2, 38.3, 38.8, 39.8, 126.8 (CH), 127.4, 131.4 (CH), 142.4, 144.8, 150.0, 156.3, 159.7, 166.9 (CO), 170.4 (CO); MS (EI) m/z 367 (M^+, 27), 235 (14), 190 (100); HRMS $C_{21}H_{25}N_3O_3$ calcd 367.1896 (M^+), found 367.1894. Anal. ($C_{21}H_{25}N_3O_3$) C, H, N.

4-[(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-quinoxalinyl)carbonyloxy]benzoic acid (9z): mp 209−210 °C; IR (KBr) 3300−2500 (br, COOH), 2964 (CH), 1764 (CO), 1687 (CO), 1605, 1296, 1204, 1165 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 6H), 1.39 (s, 6H), 1.84 (s, 4H), 7.38 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H), 9.16 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.4, 29.7, 33.6, 33.9, 37.5, 37.7, 121.9, 126.8, 131.3, 139.1, 143.1, 154.9, 159.0, 162,5, 163.2 (CO), 169.3 (CO); MS (EI) m/z 354 (M^+, 11), 234 (14), 217 (54), 189 (100); HRMS $C_{20}H_{22}N_2O_4$ calcd 354.1580 (M^+), found 354.1581.

***β*-Ionylideneacetic Acid (23).** *β*-Ionone (**21**) (15.1 g, 78.3 mmol), ethyl diethylphosphonoacetate (18.0 g, 94 mmol), and freshly distilled benzene (40 mL) were placed in a flame-dried 500-mL three-neck flask equipped with a condenser and a dropping funnel under positive argon pressure. The dropping funnel was charged with a solution of sodium methoxide in methanol (prepared from 4.6 g of freshly cut sodium added to 100 mL of vigorously stirred methanol at 0 °C). Dropwise addition was continued for 1 h, after which the reaction mixture was heated at 40 °C for 9 h, cooled, and poured slowly over crushed ice (200 mL) and the aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water to neutrality and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The crude product was distilled under vacuum (bp 118 °C, P = 0.3 mmHg) to yield the methyl ester (2:1 ratio of the 2*E*,4*E*:2*E*,4*Z* isomers) as a thick yellow oil (17.3 g, 90%). The ester **22** (5.0 g, 21.3 mmol) was saponified by dissolving it in a 1:1 mixture of THF/methanol (100 mL) followed by the addition of aqueous potassium hydroxide (2 M, 25 mL). After stirring for 12 h at room temperature, the organic solvents were removed under reduced pressure. Water was added to the residue until a volume of 100 mL was reached and the aqueous layer extracted with diethyl ether (2 × 100 mL) to remove impurities. The aqueous layer was acidified (pH 2) with concentrated hydrochloric acid (ca. 5 mL), and the crude acid **23** was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with water (1 × 75 mL) and dried (MgSO4), and the was solvent removed. The resulting yellow oil was dried under high vacuum (12 h) and the pure 2*E*,4*E* isomer obtained by recrystallization of the isomeric mixture in the minimum volume of boiling acetonitrile (ca. 15 mL). Acid **23** was obtained as white platelets (1.75 g, 37%): mp 121−122 °C; IR (KBr) 3200−2400 (br, COOH), 1685 (CO), 1597, 1253, 1185 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 6H), 1.45−1.50 (m, 2H), 1.59−1.66 (m, 2H), 1.71 (s, 3H), 2.03 (m, 2H), 2.35 (s, 3H), 5.77 (s, 1H), 6.13 (d, J = 16.1 Hz, 1H), 6.63 (d, J = 16.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.5, 20.7, 23.2, 30.4 ((CH_3)$_2$), 34.5, 35.6 (C_{quat}), 40.9, 117.7, 131.9 (C_{quat}), 134.9, 136.2, 137.3 (C_{quat}), 155.4 (C_{quat}), 172.5; MS (EI) m/z 234 (M^+, 85), 219 (42), 173 (40), 119 (100); HRMS $C_{15}H_{22}O_2$ calcd 234.1620 (M^+), found 234.1622.

2′-(Trimethylsilyl)ethyl 4-[3-methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexenyl)-(2*E*,4*E*)-pentanamido]benzoate (24a): mp 122−123 °C; IR (KBr) 3309 (NH), 2956 (CH), 1722 (CO), 1651, 1599, 1527, 1269 (s), 1104, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.02 (s, 6H), 1.13 (m, 2H), 1.43-1.50 (m, 2H), 1.55−1.65 (m, 2H), 1.69 (s, 3H), 1.95−2.10 (m, 2H), 2.40 (s, 3H), 4.41, (m, 2H), 5.81 (s, 1H), 6.06 (d, J = 16.0 Hz, 1H), 6.57 (d, J = 16.0 Hz, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.97 (d, J = 8.6 Hz, 2H), 8.62 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 15.3, 19.0, 20.7, 23.2, 30.4 ((CH_3)$_2$), 34.5, 35.6 (C_{quat}), 40.8, 64.2, 119.1, 120.6, 126.0, 131.0, 131.1, 133.9, 136.2, 137.4, 142.7, 151.7, 165.3 (CO), 166.3 (CO).

2′-(Trimethylsilyl)ethyl 3-methoxy-4-[3-methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexenyl)-(2*E*,4*E*)-pentanamido]benzoic acid (24b): yellow foam; IR (KBr) 3376 (br, NH), 2955 (CH), 1713 (s, CO), 1601, 1525, 1278, 1245, 1219, 859, 837 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.03 (s, 6H), 1.13 (m, 2H), 1.42−1.52 (m, 2H), 1.55−1.70 (m, 2H), 1.71 (s, 3H), 1.95−2.10 (m, 2H), 2.41 (s, 3H), 3.93 (s, 3H), 4.41, (m, 2H), 5.83 (s, 1H), 6.11 (d, J = 16.1 Hz, 1H), 6.58 (d, J = 16.1 Hz, 1H), 7.53 (d, J = 1.7 Hz, 1H), 7.68 (d, J = 8.5, 1.7 Hz, 1H), 7.96 (br s, 1H, NH), 8.56 (d, J = 8.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 15.2, 19.0, 20.7, 23.3, 30.4 ((CH_3)$_2$), 34.5, 35.6 (C_{quat}), 40.9, 57.1, 64.2, 111.0, 118.7, 121.2, 123.7, 125.4 (C_{quat}), 131.3 (C_{quat}), 132.6 (C_{quat}), 133.7, 136.4, 137.4 (C_{quat}), 147.1 (C_{quat}), 151.2 (C_{quat}), 165.1 (CO), 166.3 (CO).

2′-(Trimethylsilyl)ethyl 4-[3-methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexenyl)-*N*-methyl-(2*E*,4*E*)-pentanamido]benzoic acid (24c): thick oil; IR (neat) 2905 (CH), 2866, 1717 (CO), 1649, 1602, 1101, 838 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9H), 0.95 (s, 6H), 1.12 (m, 2H), 1.37−1.43 (m, 2H), 1.51−1.57 (m, 2H), 1.59 (s, 3H), 1.90−1.97 (m, 2H), 2.28 (s, 3H), 3.36 (s, 3H), 4.41, (m, 2H), 5.55 (s, 1H), 5.80 (d, J = 16.0 Hz, 1H), 6.39 (d, J = 16.0 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 8.02 (d, J = 8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.4, 15.6, 19.0,

20.7, 23.1, 30.3 ($(CH_3)_2$), 34.4, 35.6, 38.2, 40.8, 64.5, 120.4 (CH), 126.7 (CH_{arom}), 129.1, 130.7, 130.9 (CH_{arom}), 132.4 (CH), 136.7 (CH), 137.4, 148.2, 148.7, 165.8 (CO), 167.1 (CO).

4-[3-Methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexenyl)-(2*E*,4*E*)-pentanamido] benzoic acid (10a): mp 186−188 °C; IR (KBr) 3299 (w, NH), 3400−2400 (br, COOH), 2929 (CH), 1684 (CO), 1596, 1529, 1412, 1257 1164 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.04 (s, 6H), 1.45−1.51 (m, 2H), 1.57−1.70 (m, 2H), 1.72 (s, 3H), 2.01−2.07 (m, 2H), 2.42 (s, 3H), 5.79 (s, 1H), 6.10 (d, J = 16.0 Hz, 1H), 6.61 (d, J = 16.0 Hz, 1H), 7.43 (br s, 1H, NH), 7.67 (d, J = 8.7 Hz, 2H), 8.07 (d, J = 8.7, 2H); ^1H NMR (500 MHz, DMSO-d_6) d 1.02 (s, 6H, *Me*$_2$(C6′)), 1.45 (m, 2H, H5′), 1.57 (m, 2H, H4′), 1.70 (s, 3H, *Me*(C2′)), 2.02 (m, 2H, H3′), 2.32 (s, 3H, *Me*(C_3)), 6.02 (s, 1H, H2), 6.11 (d, J = 16.0 Hz, 1H, H4), 6.53 (d, J = 16.0 Hz, 1H, H5), 7.74 (d, J = 8.7 Hz, 2H, NH−C−(*CH*)$_2$), 7.84 (d, J = 8.7, 2H, CO_2H−C−(*CH*)$_2$), 10.27 (s, 1H, NH), 12 (br, s, COOH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.4, 20.7, 23.3, 30.4 ($(CH_3)_2$), 34.5, 35.7, 40.9, 118.8, 120.1, 124.2, 131.2, 131.4, 133.7, 136.0, 137.2, 143.3, 151.9, 166.0 (CO), 171.3 (CO); MS (EI) *m*/*z* 353 (M^+, 22), 217 (21), 189 (8), 161 (100); HRMS $C_{22}H_{27}NO_3$ calcd 353.1991 (M^+), found 353.1995. Anal. ($C_{22}H_{27}NO_3 \cdot H_2O$) C, H, N.

3-Methoxy-4-[3-methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexenyl)-(2*E*,4*E*)-pentanoamido]benzoic acid (10b): mp 187−188 °C; IR (KBr) 3417 (w, NH), 3300−2500 (br, COOH), 2956 (CH), 2926, 1680 (s, CO), 1598, 1523, 1279, 1249 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 6H), 1.45−1.55 (m, 2H), 1.55−1.75 (m, 2H), 1.73 (s, 3H), 1.96−2.12 (m, 2H), 2.43 (s, 3H), 3.97 (s, 3H), 5.85 (s, 1H), 6.13 (d, J = 16.1 Hz, 1H), 6.60 (d, J = 16.1 Hz, 1H), 7.59 (d, J = 1.7 Hz, 1H), 7.80 (d, J = 8.5, 1.7 Hz, 1H), 8.00 (br s, 1H, NH), 8.62 (d, J = 8.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.2, 20.7, 23.3, 30.4 ($(CH_3)_2$), 34.5, 35.7 (C_{quat}), 40.9, 57.1, 111.4, 118.7, 121.0, 123.8 (C_{quat}), 124.8, 131.4 (C_{quat}), 133.6 (C_{quat}), 133.9, 136.3, 137.4 (C_{quat}), 147.1 (C_{quat}), 151.6 (C_{quat}), 165.1 (CO), 171.2 (CO); MS (EI) *m*/*z* 383 (M^+, 29), 217 (20), 167 (18), 161 (100); HRMS $C_{23}H_{29}NO_4$ calcd 383.2097 (M^+), found 383.2091. Anal. ($C_{23}H_{29}NO_4 \cdot 0.25H_2O$) C, H, N.

4-[3-Methyl-5-(2′,6′,6′-trimethyl-1′-cyclohexenyl)-*N*-methyl-(2*E*,4*E*)-pentanamido]benzoic acid (10c): mp 198−199 °C; IR (KBr) 3300−2500 (br, COOH), 2965 (CH), 2928, 1717 (CO), 1627, 1592 (s), 1371, 1218, 1124 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 6H), 1.37−1.50 (m, 2H), 1.50−1.65 (m, 2H), 1.61 (s, 3H), 1.90−2.02 (m, 2H), 2.31 (s, 3H), 3.41 (s, 3H), 5.59 (s, 1H), 5.84 (d, J = 16.1 Hz, 1H), 6.43 (d, J = 16.1 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H); ^1H NMR (500 MHz, DMSO-d_6) δ 0.93 (s, 6H, Me_2(C6′)), 1.38 (m, 2H, H5′), 1.51 (m, 2H, H4′), 1.56 (s, 3H, *Me*C2′), 1.93 (m, 2H, H3′), 2.12 (s, 3H, MeC_3), 3.26 (s, 3H, NMe), 5.68 (s, 1H, H2), 5.87 (d, J = 16.1 Hz, 1H, H4), 6.33 (d, J = 16.1 Hz, 1H, H5), 7.36 (d, J = 1.7 Hz, 2H, NH−C−(*CH*)$_2$), 7.92 (d, J = 8.5, 1.7 Hz, 2H, CO_2H−C−(*CH*)$_2$), 12 (br s, COOH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 19.7, 22.2, 29.4 ($(CH_3)_2$), 33.5, 34.7, 37.4 (C_{quat}), 39.9, 120.4, 127.0, 128.0 (C_{quat}), 131.1 (C_{quat}), 131.8, 132.9, 136.8, 137.6 (C_{quat}), 149.5 (C_{quat}), 149.6 (C_{quat}), 167.9 (CO), 171.2 (CO); MS (EI) *m*/*z* 367 (M^+, 23), 352 (4), 217 (20), 161 (100), 151 (15); HRMS $C_{23}H_{29}NO_3$ calcd 367.2147 (M^+), found 367.2143. Anal. ($C_{23}H_{29}NO_3$) H, N, C: calcd, 75.17; found, 75.87.

NMR Solution Studies of Compounds 9u,y and 10a,c. Solutions (1 mM) of compounds in DMSO-d_6 were degassed by two successive freezing and pumping cycles under high vacuum (5 μmHg). The NMR tubes were filled with argon and flame-sealed. 1D and 2D ^1H NMR spectra were recorded at 499.83 MHz with a Varian Unity 500 equipped with a temperature controller. 2D NOE spectra[63] were recorded at 298.0 K in the phase-sensitive mode using the phase cycling method of States−Haberkorn.[64] A relaxation delay of 1 s was used with a mixing time of 0.5 s; 2K data points were acquired in F2 dimension and 256 t_1 in F1. A total of 64 transients were accumulated for each t_1. Relative cross-peak amplitudes were estimated from cross sections taken at maximum diagonal peak amplitudes. Several cross sections were taken within the 2D spectra where no diagonal peak appeared in order to estimate the amplitude of the background. The variation of the chemical shift of the NH signal with temperature for **9u** was measured by 5° intervals from 298 to 318 K. A minimum of 10 min of equilibration was allowed between each measurement. The chemical shifts were referenced to the DMSO-d_5 residual signal which remained constant at 2.49 ppm at all temperatures studied.

Computational Methods. Computational analysis was performed using CSC Chem 3D Plus 3.1.1 from Cambridge Scientific Computing running on a Macintosh IIx. The program used MM2 parameters and algorithm. The force field allows for delocalization to be taken into account by implementing a special torsional component to the total steric energy. Structures for the β-ionylideneacetamidobenzoates **10** were built assuming all *E*-double bonds and a symmetrically charged terminal carboxylate. Two half-chair conformations are possible for the cyclohexenyl group, but as they exhibited essentially the same steric energy, calculations were pursued using the *exo* half-chair conformation. The 16 starting conformations for the β-ionylideneacetamidobenzoates **10** contained all possible combinations of conformations (*s-cis* or *s-trans*) for the C1′−C5, C4−C3, and C2−C1 bonds as well as both possible conformations for the amide bond (*cis* or *trans*). For the pyrazinecarboxamidobenzoates **9**, the four starting conformations allowed for the single bond between C2 and the carbonyl group to be either *s-cis* or *s-trans* and again allowed for the two possible amide bond conformations. All torsional angles were reset at 0° or 180° before minimization. Energy minimizations were performed by allowing bond lengths, bond angles, and dihedral angles to vary until the rms gradient deviation fell below 0.1. All molecular mechanic parameters needed for the calculations were used as supplied by the Chem 3D Plus software. Supplementary torsional parameters had to be included in order to carry out the energy minimization for **9x** and **10b.** The V_1, V_2, and V_3 barriers were set at −0.1, 15.0, and 0.0, respectively, for the torsion Nam-Csp2-Csp2-Oether. These values were estimated from the values used for the torsion N_{am}−Csp2−Csp2−N_{am} and O_{ether}−Csp2−Csp2−O_{ether}. For *ortho*-methoxy derivatives (**9x**, **10b**), the initial conformation was built such that the *ortho*-oxygen atom assumed an internal hydrogen bond with HN amide which by the same token minimized crowding; the methyl of the methoxy was oriented to the side of the molecule in order to minimize steric repulsions. The initial torsion for the bond C_{ar}−O was set at 180° according to known crystallographic data for **10b**. Molecular superimpositions were realized by using the overlay option of Chem 3D by setting the optimal distance to 0 Å for the aligned atoms. The two carbons of the *gem*-dimethyl, the quaternary carbon, and the carbon of the end carboxylate were used as anchoring points for the superimpositions.

X-ray Crystallographic Studies. Crystals were obtained by slow cooling to room temperature of hot dilute solutions of the desired compound in acetonitrile. For **10c** hot ethanol was used instead of acetonitrile. Intensity data were collected on a Rigaku AFC6S automatic diffractometer for **9y** and a P4 diffractometer equipped with a Siemens Smart Charge-Coupled Device (CCD) area detector for the others. With the P4 diffractometer, the crystal to detector distance was 3.991 cm and the data collection was carried out in 512 × 512 pixel mode, utilizing 2 × 2 pixel binning. One complete hemisphere of data was collected to better than 0.8 Å resolution. Upon completion of data collection, the first 50 frames were recollected in order to improve decay correction analysis. Processing was carried out using the program SAINT[66] which applied Lorentz and polarization corrections to three-dimensionally integrated diffraction spots. The program SADABS[67] was utilized for the scaling of diffraction data, the decay correction, and the empirical absorption correction-based redundant reflections. Details of crystal data and data collection are given as Supporting Information. All structures were solved by direct methods (SHELX-86)[68] and difmap synthesis using SHELX-93.[69] Weighting scheme was based on the measured esd. Non-hydrogen atoms were refined anisotropically. Hy-

drogen atoms were calculated at idealized positions using a riding model with C−H distances of 0.93 Å (aromatic), 0.97 Å (methylene), and 0.96 Å (methyl). The U_{iso} values for hydrogen atoms were adjusted to 20% more than the value of the bonded carbon and to 50% for hydrogen atoms on methyl groups; OH and NH were refined isotropically for **10c** and **20a**. Details of the structure refinement are given as Supporting Information. These compounds exhibit two mirror image conformations for either the tetramethylcyclohexyl or the trimethylcyclohexenyl groups. The two orientations were refined as separate parts with the two orientations restrained to have similar geometries using SAME and SADI commands. Thermal parameters in disordered regions were constrained to be identical for atoms closer than 0.4 Å and restrained to similar values for other disordered atoms. For compound **9y** the occupancies refined to 0.60 and 0.40. An intermolecular hydrogen bond is found between O(3)−H of the acid group and carbonyl O(1) of a neighboring molecule. For compound **10b** the occupancies refined to 0.53 and 0.47. An intramolecular hydrogen bond is found between O(4) and H1−N1 with a *d* H1···O4 of 2.070(27) Å. One of the hydrogens on C(12) was found oriented toward O1 such that the internuclear distance is 2.294(6) which falls in the hydrogen-bonding range. Molecules within the crystal formed dimers through carboxylic groups (*d* O(3)H···O(2) = 1.652(43) Å). For compound **10c** the occupancies refined to 0.70 and 0.30. An intermolecular hydrogen bond is found between O(3)−H of the acid group and the carbonyl O(1) of a neighboring molecule (*d* O(3)H(3)···O(2) = 1.977 Å). For compound **20a** the occupancies refined to 0.52 and 0.48. An intramolecular hydrogen bond is found between N(1)−H and N(2) with a *d* H···N(2) of 2.150 (33) Å.

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Supporting Information Available: Crystal data and data collection and details of the structure refinement (20 pages). Ordering information is given on any current masthead page.

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