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(54) Title: HETEROCYCLE ANALOGS OF CAI-1 AS AGONISTS OF QUORUM SENSING IN VIBRIO

(57) Abstract: A structurally distinct and potent series of synthetic small molecule activators of *Vibrio cholerae* quorum sensing have been chemically synthesized. The small molecule activators reduce virulence in *V. cholerae*. Acyl pyrrole molecules displayed strong potency and stability, particularly 1-(1H-pyrrol-3-yl)decan-1-one.



HETEROCYCLE ANALOGS OF CAI-1 AS AGONISTS OF QUORUM SENSING IN *VIBRIO*

Cross-Reference To Related Applications

[0001] This application claims priority to U.S. Provisional Application No. 61/867,831, filed August 20, 2013, which is herein incorporated by reference in its entirety.

Statement Regarding Federally Sponsored Research Or Development

[0002] This invention was made with government support under National Institutes of Health (NIH) grants R01 AI 054442 and R01 GM 065859, and National Science Foundation (NSF) grant MCB-0948112. The government has certain rights in this invention.

Background

[0003] Quorum sensing (QS) is a process of bacterial cell-cell communication that allows populations of bacteria to act like multicellular organisms by carrying out tasks in synchrony. The process involves secreted signaling molecules called autoinducers that the bacteria produce and release. Specifically, autoinducers accumulate at high cell densities, and when the concentration reaches a critical level, their detection drives synchronous group-wide changes in gene expression.

[0004] QS controls collective behaviors including bioluminescence, sporulation, biofilm formation, and virulence factor production. Quorum sensing plays a vital role in the pathogenicity of many bacteria because the ability to act as a coordinated group is essential for bacteria to successfully infect host organisms. Modulation of either the production or the detection of autoinducer molecules can abolish bacterial communication and render bacteria non-pathogenic.

[0005] The primary QS autoinducer in *V. cholerae* is known as CAI-1, which is the small molecule (S)-3-hydroxytridecan-4-one. CqsA synthase produces CAI-1 and CqsS is a membrane-spanning receptor that detects CAI-1. *V. cholerae* use a CqsA/CqsS quorum sensing circuit to control the production of virulence factors and require repression of this quorum sensing system to establish an infection in its host.

[0006] Typically in pathogenic bacteria that cause persistent infection, the accumulation of autoinducers at high cell densities triggers QS-mediated virulence factor production and biofilm formation. By contrast, *Vibrio cholerae*, which causes the acute intestinal disease cholera, displays an unusual QS profile: at high population density, QS initiates a cascade that *suppresses* virulence factor production (PCT/US2013/026837).

[0007] The distinct QS behavior exhibited by *V. cholerae* is attributed to its life cycle. Successful infection by *V. cholerae* leads to profuse diarrhea, which washes huge numbers of bacteria from the human intestine into the environment. Thus, at low cell density, the expression of genes for virulence and biofilm formation promotes establishment of infection in the host, while at high cell density, autoinducer-dependent repression of these traits promotes dissemination.

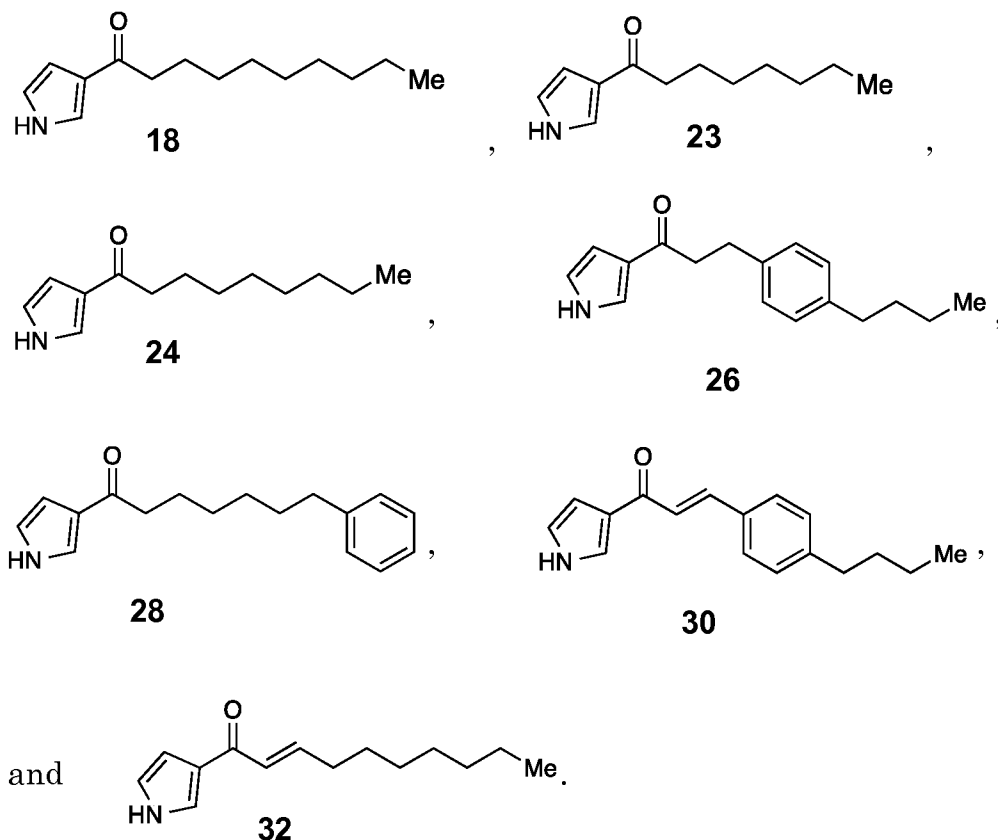
[0008] Several other clinically relevant bacteria are known to use a CqsA/CqsS quorum sensing circuit (e.g., *V. parahaemolyticus* and *V. vulnificus*). A homologous quorum sensing circuit identified in certain bacteria uses homologs of CqsA and CqsS found in e.g., *Legionella* species and in *Nitrococcus mobilis*, *Burkholderia xenovorans*, and *Polaromonas* spp.

Summary of the Invention

[0009] Disclosed herein are novel strategies directed at the activation of quorum sensing in *Vibrio* species, thereby inhibiting the virulence of these bacteria and diminishing the likelihood of infection. Small-molecule modulators of quorum sensing pathways represent promising lead compounds en route to novel anti-bacterial therapeutics.

[0010] The invention encompasses the prevention, inhibition and control of bacterial diseases, including, but not limited to infections caused by *Vibrio* species and *Legionella* species. For this reason, the novel strategies described herein that activate quorum sensing in *V. cholerae*, thereby inhibiting its virulence and diminishing infection, have a broad range of clinical applications. The strategies may be applied, as well, to environmental applications such as affecting biofilms.

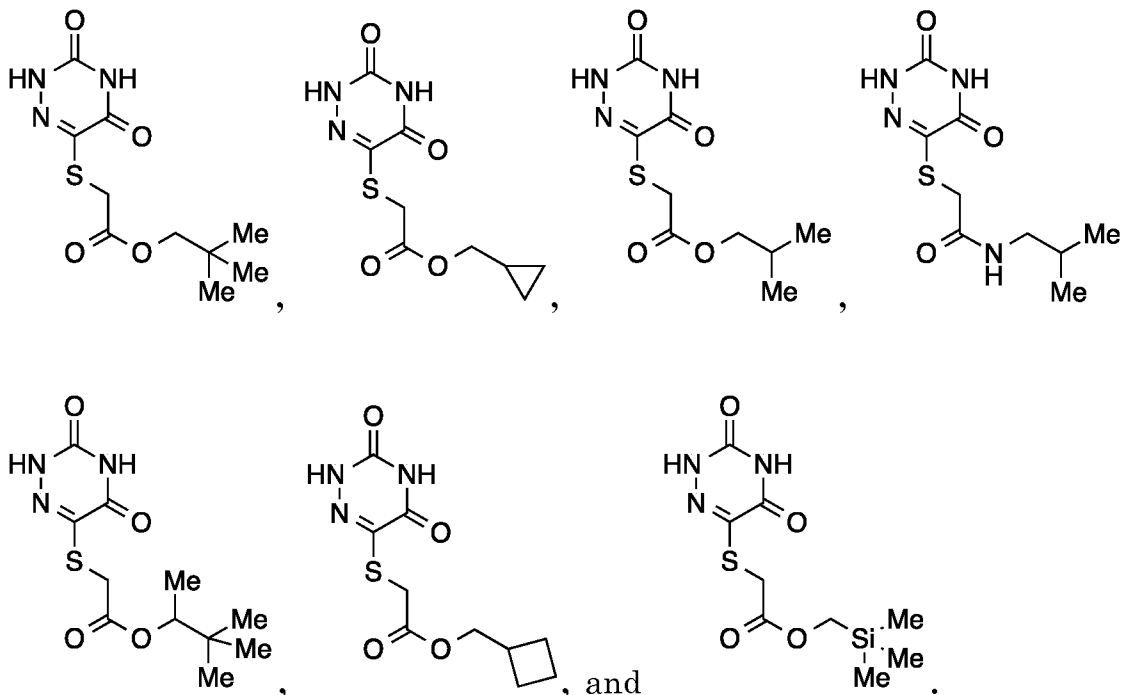
[0011] In a first aspect, the invention is a compound from the group consisting of:



[0012] In a second aspect, the invention is a pharmaceutical composition comprising one or more of the inventive pyrrole compounds and a pharmaceutically acceptable carrier, excipient or diluent.

[0013] In another aspect, the invention is a method of treating a bacterial infection of Gram-negative quorum sensing bacteria, comprising administering to a subject a therapeutically effective amount of one or more of the inventive pyrrole compounds. The bacteria have a cholera-type QS circuit. One embodiment is directed to prophylactic treatment prior to bacterial infection. Another embodiment is directed to active treatment of bacterial infection. Yet another embodiment comprises administering to the subject a therapeutically effective amount of one or more of the inventive pyrrole compounds and an antibiotic. Still another embodiment comprises administering to the subject a therapeutically effective amount of one or more of the inventive pyrrole compounds and one or more LuxO inhibitory molecules. LuxO inhibitory molecules

inhibit bacterial virulence by a mechanism that is different from that of the pyrrole compounds of the present invention. LuxO inhibitory molecules are described in PCT Application No. PCT/US2013/026837. Examples of the LuxO inhibitory molecules are:



[0014] In yet another aspect, the invention is a method of inhibiting virulence in Gram-negative bacteria comprising contacting the bacteria with one or more of the inventive pyrrole compounds. In another embodiment of this method, the bacteria are pathogenic to marine life and the compound or compounds are administered to the marine life as a feed additive.

[0015] In another aspect, the invention is a bacterial biofilm-inhibiting composition comprising one or more of the inventive pyrrole compounds.

[0016] In another aspect, the invention is a method of controlling quorum sensing Gram-negative bacteria on a surface, comprising exposing the bacteria to one or more of the inventive pyrrole compounds, in an amount that affects biofilm formation. In one embodiment of this method, the surface is a solid.

[0017] In yet another aspect, the invention is a device that is coated or embedded with one or more of the inventive pyrrole compounds to prevent bacterial biofilm

formation or bacterial transmission.

Brief Description of the Drawings

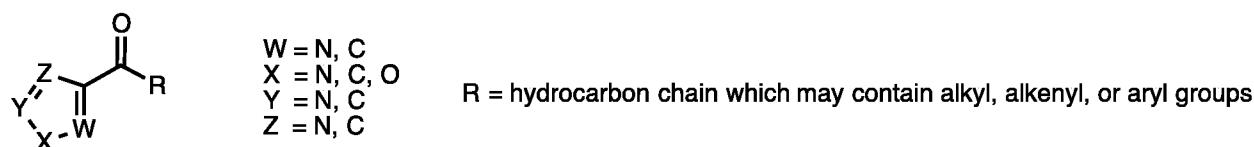
- [0018] Fig. 1. Structure of CAI-1 and Ea-CAI-1 and design of agonist.
- [0019] Fig. 2. Modified tail structures in the 2- and 3-acylpyrrole motif.
- [0020] Fig. 3. CAI-1 and Compound **18** repress production of the *V. cholerae* toxin-correlated pilus TcpA and activate production of HapR. DMSO is used as control.
- [0021] Fig. 4. Murine 3T3 fibroblast cell toxicity assay. Effects of different concentrations of Compound **18** on 3T3 cells.
- [0022] Fig. 5. Dose-response curves from bioassays. In 5A, the error bars represent the 95% confidence intervals; In 5B the standard deviation is shown.
- [0023] Fig. 6. Compounds that activate Quorum Sensing. A. General structural features of QS analog compounds. B. Examples of compounds.
- [0024] Fig. 7. Four general synthesis strategies for acyl pyrroles shown in Fig. 6.
- [0025] Fig. 8. Bioassay data for compounds tested for agonist activity. Superscript a indicates this is preliminary bioassay data for compounds **17**, **18**, **19** and **20**. Superscript b indicates this value is at 50000 nM concentration.
- [0026] Fig. 9. Compound **18** has no effect on growth of *V. cholerae* strain MM920.

Detailed Description of the Invention

- [0027] In *V. cholerae*, the native QS signal is CAI-1 ((S)-3-hydroxytridecan-4-one). Ea-CAI-1 is an intermediate in the CAI-1 biosynthetic pathway. Ea-CAI-1 is less chemically stable than CAI-1 but is an order of magnitude more potent as a QS agonist than the native, longer-lived CAI-1. With an aim to determine target structures that achieve higher potency and improved chemical stability over the native QS signal in *V. cholerae*, a series of analogs of Ea-CAI-1 were synthesized (Fig. 1).
- [0028] Using rational molecule design principles based on a wealth of structure-activity relationships (SAR), a structurally distinct and potent series of synthetic small molecule modulators of quorum sensing were identified which cause repression of virulence factor expression and biofilm formation in pathogenic bacteria. The molecules may be employed to affect QS behaviors of *V. cholerae* or other pathogenic bacteria that

utilize *V. cholerae*-type quorum sensing circuits such as *Legionella* species. (e.g., *L. pneumophila*) and *Vibrio* species. (e.g., *V. cholera*, *V. vulnificus*, *V. parahaemolyticus*, *V. alginolyticus*, *V. anguillarum*, *V. carchariae*, *V. damsela*, *V. ordalii*).

[0029] The general structure of compounds that were synthesized can be described as follows:



[0030] The series of agonists described herein were designed and assayed with the goal of identifying molecules that, like Ea-CAI-1, demonstrate high QS agonist activity and, in an improvement over Ea-CAI-1, possess the chemical stability of a useful probe or drug candidate. Compounds were synthesized and assayed for activity and are shown in Scheme 1 and Scheme 2 and also in Figures 2, 6, and 8.

[0031] Ea-CAI-1, a delicate biosynthetic intermediate and the most potent natural agonist of QS in *V. cholerae*, was used as a starting point in designing chemically stable analogs with high potency in activating the CqsS receptor. Several derivatives of the 3-acylpyrrole structure have activities equivalent to Ea-CAI-1 and are promising leads for developing new therapeutics to control *V. cholerae* infection, for example the 3-acylpyrrole with the C9 alkyl tail, compound **18**.

[0032] The agonists that were synthesized ("pro-QS" molecules) induced *V. cholerae* cells to exhibit high cell density behaviors regardless of their actual cell density. Most notable of these behaviors is repression of genes encoding virulence factors and those required for biofilm formation. Numerous human pathogens from the *Vibrio* genus have been shown to operate under this system wherein QS represses virulence and biofilm traits at high cell density (e.g., *V. parahaemolyticus*, *V. alginolyticus*, and *V. vulnificus*).

[0033] Molecules that activate the QS system of *V. cholerae* are referred to as pro-QS agents, of which there are two varieties that are especially suited to therapeutic uses. The first is the set of small molecules identified herein which may be classified as QS receptor agonists. The second is a set of small molecules that have been previously

identified and classified as LuxO inhibitors (PCT/US2013/026837) that function uncompetitively to perturb LuxO ATPase activity. The inhibitors broadly activate different *Vibrio* QS circuits and, in turn, repress virulence factor production and reduce cytotoxicity. The present invention encompasses combined administration of molecules from the first set of QS receptor agonists and the second set of LuxO inhibitors for the treatment of bacterial pathogenicity.

[0034] The invention encompasses use of LuxO inhibitors and QS receptor agonists to treat active infection and for prophylactic measures. Use of these molecules as prophylactics serves to prevent *V. cholerae* or other pathogenic vibrios from initiating the low cell density virulence gene expression program that is required for colonization. In this embodiment, inhibiting the launch of virulence factors would provide sufficient time for the host immune system to eliminate the pathogen. In contrast to traditional antibiotics that target essential bacterial processes, growth is not affected by interfering with QS, so development of bacterial resistance could potentially be minimized. Thus, just as antagonizing QS in bacteria is an alternative to traditional antibiotics, so is the use of pro-QS agents.

[0035] Some of the uses for the inventive molecules are herein described. In one embodiment, the invention provides a pharmaceutical composition comprising one or more compounds of the present invention or a pharmaceutically-acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle. Treatment comprises administering to the host of the bacteria a therapeutically effective amount of the pharmaceutical composition of this invention. A skilled artisan can determine which form of administration is best and the therapeutic amount for balancing the dose versus periodic delivery.

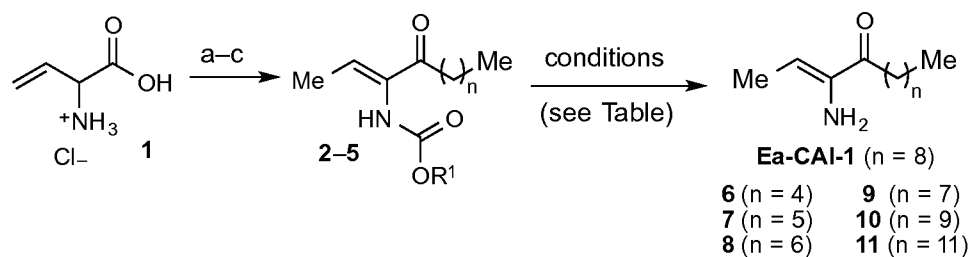
[0036] Infectious bacteria that use quorum sensing strategies to produce virulence include pathogens to humans, animals, and plants. Some pathogens infect marine life and thereafter cause disease in humans who eat or otherwise come into contact with the marine life. *Vibrio* species may contaminate shellfish and cause food poisoning. The methods described herein to inhibit bacterial infection include methods to inhibit

bacterial infection of marine life such as by administering the inventive compounds as feed supplements or by applying the compounds to devices or cages to prevent growth of bacteria or formation of bacterial biofilms.

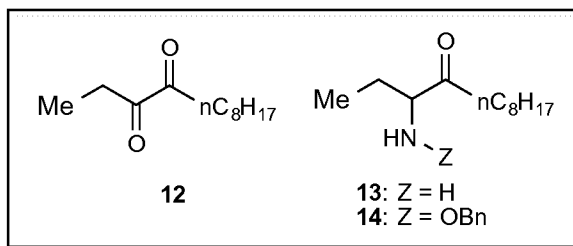
[0037] The following examples set forth the general procedures involved in practicing the present invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention.

EXPERIMENTAL

[0038] Ea-CAI-1 Analogs of Varying Tail lengths



R ¹	conditions	yield
2 , <i>t</i> -Bu	TFA, CH ₂ Cl ₂ or 1 N HCl	0%
3 , Bn	H ₂ , Pd, EtOH	0%
4 , (CH ₂) ₂ TES	TASF, DMSO	N/A [†]
5 , allyl	Pd(OAc) ₂ , dppe, Et ₂ NH, THF	55–65%



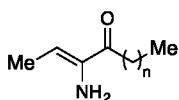
Scheme 1. Synthesis of Ea-CAI-1 and tail length–modified analogs. Reagents and conditions: (a) Amine protection; (b) HNMe(OMe)•HCl, EDC, HOBT, Et₃N, THF (42–58% from **1**); (c) R²MgX (71–93%). [†]These conditions led to quantitative consumption of the starting material and slow formation of the desired product along with inseparable silyl byproducts.

[0039] Synthesis of the Ea-CAI-1 analogs of varying tail lengths required

development of an effective enamine protecting group strategy. Deprotection of the enamino ketone functionality (**2–5**) is significantly complicated by the high propensity of the product (Ea-CAI-1) to undergo hydrolysis to the α -diketone **12**. As shown in Scheme 1, efforts to employ a *t*-Boc protecting group strategy (**2**, R¹ = *t*Bu) were unsuccessful; this functionality could not be removed under standard conditions. Similarly, attempts to reductively remove the Cbz group of **3** (R¹ = Bn) through exposure to H₂ and Pd led to two major products, which were tentatively identified as aminoketone **13** and N-Cbz analog **14**; these compounds presumably arise via preferential reduction of the alkene unit prior to benzyl cleavage. Although the *N*-Teoc protecting group (**4**) could be removed by treatment with excess TASF in DMSO, this transformation was very slow and yielded the desired adduct along with inseparable silyl-byproducts. The *N*-Alloc protecting group (**5**, R = allyl) was most effective; upon exposure to Pd(PPh₃)₄ and Et₂NH, **5** was rapidly deprotected to deliver Ea-CAI-1 in good yield. Importantly, the product was isolated in pure form after passage through a short plug of silica gel deactivated with Et₃N. Using this Alloc protecting group strategy, a series of tail-length modified Ea-CAI-1 analogs (**6–11**) was prepared.

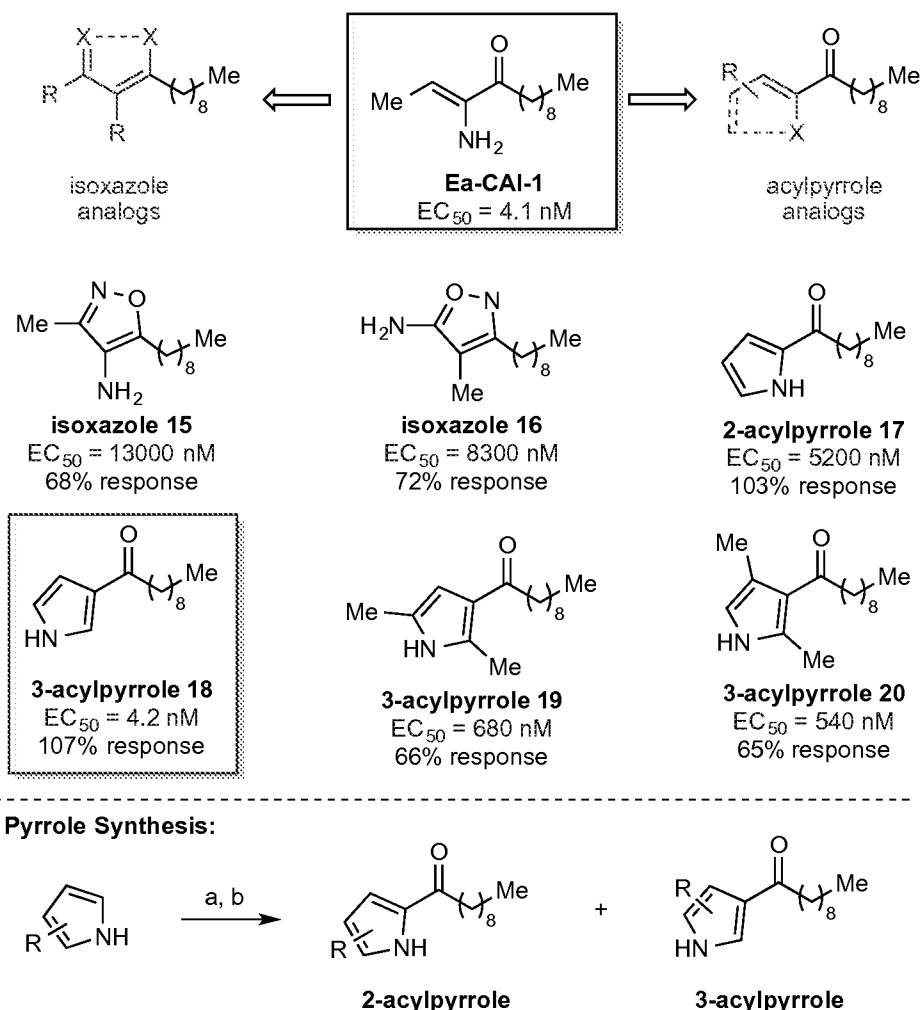
[0040] The “tail-modified” analogs (**6–11**) were evaluated in a CqsS agonist bioassay (Table 1). The *V. cholerae* CqsS receptor was somewhat promiscuous with respect to variations in tail length. (This observation is consistent with similar evaluation of tail-length modified CAI-1 analogs). The parent compound (Ea-CAI-1, n = 8) and the analog bearing a one-carbon truncated tail (**9**, n = 7) show low nM activity and full activation (entries 4 and 5). Other analogs with shorter (**6–8**) or longer (**10**) tail lengths were 1–2 orders of magnitude less potent, but nonetheless promoted full activation (entries 1–3 and 6). Only a very long tail gave an analog (**11**, n = 11) that was much less active, even at high concentrations. There was no observed direct correlation between maximum % response and EC₅₀. Small perturbations in the structure of the ligand or binding site can presumably disrupt the balance between kinase and phosphatase activity. In all cases, the Ea-CAI-1 analogs were more active by an order of magnitude compared to the related examples from a native CAI-1 series.

Table 1. Effect of Ea-CAI-1 tail length on QS agonist activity.

Entry		EC ₅₀ (nM) ^a	% Response ^b
1	6 , n = 4	590	100
2	7 , n = 5	290	120
3	8 , n = 6	40	109
4	9 , n = 7	2.6	112
5	Ea-CAI-1 , n = 8	4.1	100
6	10 , n = 9	170	105
7	11 , n = 11	>5000	38

Values were determined using the CqsS agonist bioassay. *a.* All EC₅₀ values are the mean of triplicate analyses. *b.* Percent maximal bioluminescence with respect to Ea-CAI-1, which is set at 100%.

[0041] Ea-CAI-1 Analogs of Substitute Head Domain and Diverse Tail Structure



Scheme 2. Variation of the Ea-CAI-1 head group: isoxazole and acylpyrrole analogs. Reagents and conditions: (a) MeMgBr, Et₂O; (b) *n*-C₉H₁₉COCl.

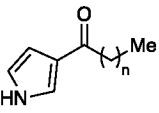
[0042] The next set of Ea-CAI-1 analogs that were created can be generally described as having replaced the enamino ketone “head” domain with more stable functionality, and of having installed greater structural diversity onto the “tail” sector.

[0043] The effects of head group variation on agonist activity was examined first. Attempts to mimic the stereoelectronic features of the enamino ketone motif of the parent compound were made through substitution with more stable isoxazole or acylpyrrole functional motifs (Scheme 2). A series of analogs was synthesized and evaluated for agonist activity. Neither of the isoxazole analogs showed significant activity (**15** and **16**, $EC_{50} > 8000 \text{ nM}$). However, promising results were obtained with

the series of analogs bearing acyl pyrrole head groups; importantly, these motifs retain both ketone and α -heteroatom hydrogen bond donor functionality. For the initial analysis, compounds **17** and **18** were prepared as a readily separable mixture of isomers for biological evaluation (Scheme 2). While both analogs elicit the full level of QS response, the 3-acyl isomer **18** exhibits an EC_{50} >1000-fold more potent than the 2-acyl isomer. The EC_{50} value of 4.2 nM identifies **18** as comparable in activity to the parent compound, Ea-CAI-1. Incorporation of additional substituents onto the 3-acyl pyrrole (**19** and **20**) resulted in lower agonist activity, as indicated by the higher EC_{50} and lower % response.

[0044] The 3-acylpyrrole heterocyclic motif has therefore been identified as a viable, chemically stable bioisostere of the native Ea-CAI-1 head group. The next set of analogs probed the effect of variations in the tail structure on CqsS agonist activity (Table 2). Analogs bearing a C9 or a C10 fatty acid tail were most potent and provided full activation (entries 4 and 5); these findings are comparable to the structure-activity relationships observed in the α -enamino ketone series. The other tail lengths were less potent and gave no more than 50% activation.

Table 2. Effect of 3-acylpyrrole tail length on QS agonist activity.

Entry		EC_{50} (nM) ^a	% Response ^b
1	21 , n = 4	1200	14
2	22 , n = 5	740	43
3	23 , n = 6	51	50
4	24 , n = 7	8.2	100
5	18 , n = 8	4.2	110
6	25 , n = 9	300	29

Values were determined using the CqsS agonist bioassay. *a.* All EC_{50} values are the mean of triplicate analyses. *b.* Percent maximal bioluminescence with respect to Ea-CAI-1, which is set at 100%.

[0045] Further probing of the effect of tail structure involved introduction of simple *E*-alkene units and benzene rings, with the goal of examining the effects of conformational restriction and steric perturbation within the acyl tail (Figure 2). In all cases in which significant activity was observed (EC_{50} values <5000 nM), the 3-acyl pyrrole analogs were much more potent than the corresponding 2-acyl pyrrole analogs. Introduction of a benzene ring in the 3-acylpyrrole series produced highly active analogs; compounds **26** and **28** show activities only 3- to 10-fold lower than the best agonists (Ea-CAI-1 and acylpyrrole **18**). This result suggests substantial steric flexibility in the presumed hydrophobic binding site for the tail group and expands the design opportunities for further exploration of the tail structure. However, the maximum percent activation is lower for these benzyl analogs (54–75%). In previous SAR work focused on the structure of the fatty acid tail of CAI-1, the conformational restriction provided by incorporation of an *E*-alkene unit conferred enhanced potency over the corresponding fully saturated analog. Similarly, in the 3-acylpyrrole Ea-CAI-1 series, incorporation of an *E*-alkene moiety (**32**) leads to the one of the most potent agonists of *V. cholerae* QS yet discovered; compound **32**, with an EC_{50} of 3.8 nM, is slightly more potent than both Ea-CAI-1 (4.1 nM) and acyl-pyrrole **18** (4.2 nM). Yet, incorporation of a biphenyl unit in the acyl chain leads to essentially inactive analogs (**34** and **35**).

[0046] Effect of Compound **18** on the QS Circuit

[0047] Having identified a stable and highly potent lead compound (**18**), examination proceeded on its effect on the QS circuit in *V. cholerae*. In vivo, HapR is a transcription factor that functions as one of two master QS regulators in *V. cholerae*. Agonism of CqsS leads to increased production of HapR and HapR, in turn, drives the high-cell density gene expression program, which leads to repression of the expression of genes required for virulence and biofilm formation. Figure 3 shows that production of HapR increased in response to 1 μ M of the 3-acyl pyrrole **18** to a level similar to that achieved from exposure to 10 μ M of the native ligand, CAI-1. Conversely, production the major *V. cholerae* virulence factor, TcpA, (toxin-co-regulated pilis protein subunit A), is

repressed by both CAI-1 and compound **18**. These results are consistent with the heterocyclic analog **18** acting on CqsS in a manner similar to CAI-1.

[0048] Effect of Compound **18** on Cytotoxicity

[0049] Given the possibility for further development of the 3-acylpyrrole **18** as a potential anti-virulence agent, a preliminary investigation was made of the cytotoxicity of this analog in bacteria and in a murine 3D3 fibroblast cell line. Consistent with our proposal that the molecule functions by influencing QS-controlled behaviors and not by altering growth, compound **18** was not toxic to bacteria. No decrease in OD₆₀₀ occurred when *V. cholerae* was treated with **18** at concentrations up to 25,000 nM (i.e. levels more than 5000-fold higher than the EC₅₀ for **18**). Likewise, **18** was tolerated by murine 3T3 fibroblast cells at concentrations up to 23,000 nM, as assessed by optical microscopy (Figure 4).

[0050] Compound **18** functions analogously to the native signal, CAI-1, in regulating production of the transcription factor HapR and the virulence factor, TcpA (Fig. 3). Compound **18** does not inhibit bacterial growth (Fig. 9) nor does it show toxicity toward a mammalian cell line (Fig. 4), and is therefore a promising candidate.

[0051] Effect of Compound **18** on *V. Harveyi*

[0052] Despite the high activity of this class of molecules with respect to the *V. cholerae* CqsS receptor, none of the 3-acyl pyrrole analogs showed significant activity against the *Vibrio harveyi* CqsS receptor. This result is perhaps surprising, given the high homology between these two QS receptors; however, it is consistent with earlier observations that, compared to the *V. cholerae* receptor, the *V. harveyi* receptor is less tolerant of structural perturbations to the cognate ligand.

[0053] Bioassay data

[0054] *Vibrio cholerae* Agonism Bioassay

[0055] The molecules were bioassayed in a system that exploits the *V. cholerae* quorum sensing circuit. The bioassay used a bacterial reporter strain to measure the QS response. Values for percent of activation correspond to the level of bioluminescence produced in the bacterial reporter strain at saturating concentrations of molecule

compared to the maximal levels produced in the presence of a native autoinducer molecule (Ea-CAI-1). In the activity assay, activation of quorum sensing, as reported by induction of bioluminescence, tracks with *in vivo* repression of virulence factor production and biofilm formation in *V. cholerae*. The EC₅₀ values correspond to the concentrations that are required to activate quorum sensing to its half-maximal level.

[0056] Reporter strain MM920 (*V. cholerae* $\Delta cqsA \Delta luxQ$ carrying pBB1 cosmid, which contains the *V. harveyi luxCDABE* luciferase operon) was used to assay agonist activity of each synthetic compound. This strain was grown in LB medium containing 10 μ g/mL tetracycline at 30°C for >16 hours and diluted 20-fold with the same medium. Two μ L of each synthetic compound dissolved in DMSO in various concentrations was added to 200 μ L of the diluted reporter strain in triplicate in a 96-well plate. Bioluminescence and OD₆₀₀ were measured in a PerkinElmer EnVision Multilabel Reader following 4-hour incubation at 30°C with shaking. DMSO was used as the negative control.

[0057] Example of dose-response curves from bioassay and data extracted

[0058] Fig. 5 is an example of typical dose response curves highlighting the data that is represented in the Tables. Both of the dose-response curves were generated using GraphPad Prism 5 from the identical primary luminescence measurements.

[0059] The dose-response curve in Fig. 5A displays error bars that represent the 95% confidence intervals for each of the luminescence measurements. The curve in Fig. 5B displays the standard deviation of the data.

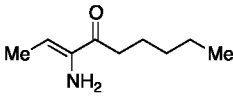
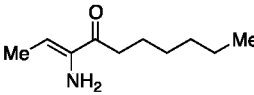
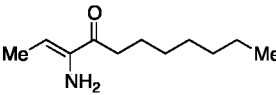
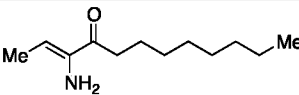
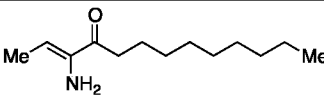
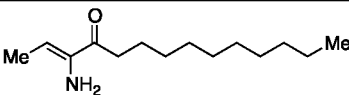
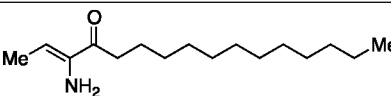
[0060] EC₅₀ values were calculated by Prism 5 using standard settings and are described in the Tables and text with the error representing the 95% confidence interval for the calculated EC₅₀ value.

[0061] The values for % response described in the Tables and text describe the maximal luminescence change for each of the analogs as a percent of EaCAI-1 or **18** (set at 100%). One of these molecules was included as a positive standard of activity for each of the assays. The error described within the tables represents the 95% confidence intervals for this data expressed as a percentage. While there is typically little variation

in the maximal luminescence at saturation, there is some noise at low concentrations; compare for example the 95% confidence intervals for the points of low compound concentration and the points of high concentration on the left.

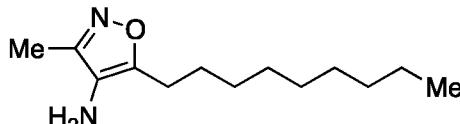
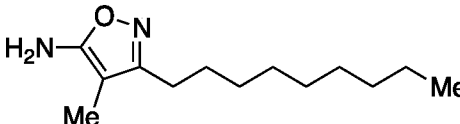
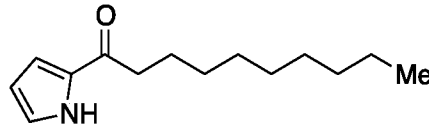
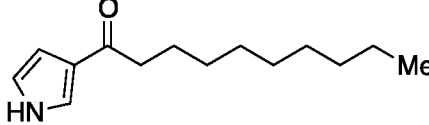
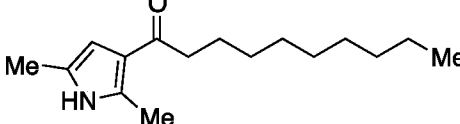
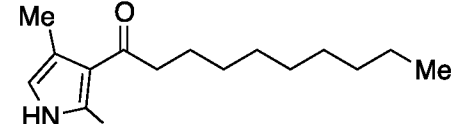
[0062] Complete Bioassay Data and 95% Confidence Intervals for all Compounds

[0063] Tabulated bioassay data for the compounds in Table 1

Entry	Compound	<i>Vibrio cholerae</i>	
		EC ₅₀ (nM) ^a	% Response ^b
1	 6	594±319	100±57
2	 7	286±240	120±117
3	 8	40±14.5	109±25
4	 9	2.6±0.32	112±7.0
5	 Ea-CAI-1	4.1±0.45	100±6.6
6	 10	169±32	105±11
7	 11	>5000	38

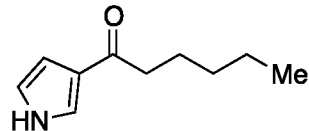
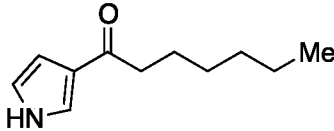
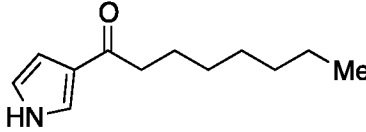
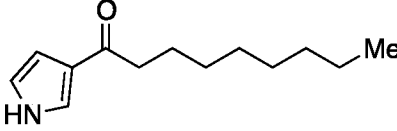
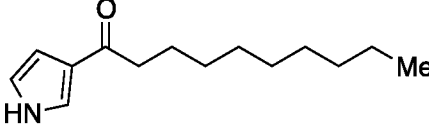
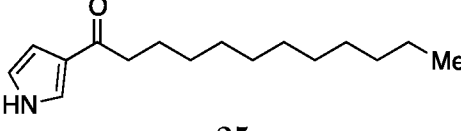
a. All EC₅₀ values are the mean of triplicate analyses. *b.* Percent maximal bioluminescence with respect to Ea-CAI-1, which is set at 100%.

[0064] Tabulated bioassay data for the compounds in Scheme 2 and Figure 2.

Entry	Compound	EC ₅₀ (nM) ^a	% Response ^b
1	 15	13,090±5,765	68±52
2	 16	8,263±4,870	72±56
3	 17	5,166±2,174	103±91
4	 18	4.2±0.8	107±10
6	 19	679±92	66±14
7	 20	536±80	65±16

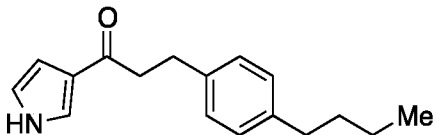
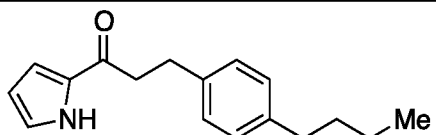
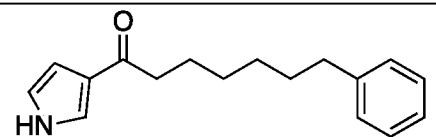
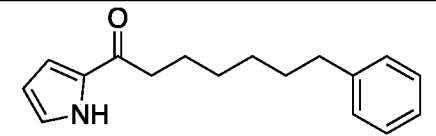
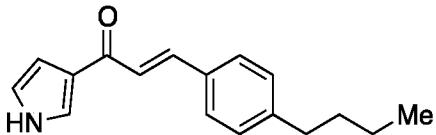
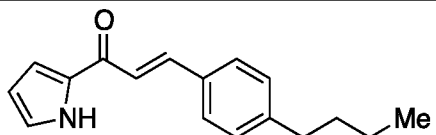
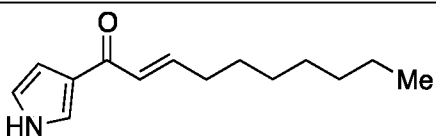
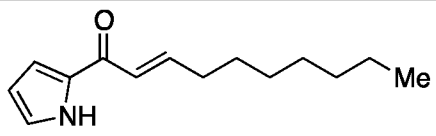
a. All EC₅₀ values are the mean of triplicate analyses. b. Percent maximal bioluminescence with respect to Ea-CAI-1, which is set at 100%.

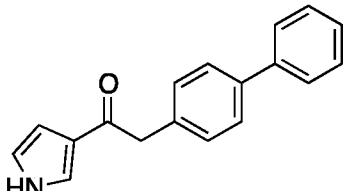
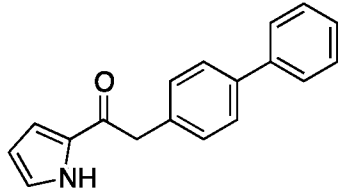
[0065] Tabulated bioassay data for the compounds in Table 2.

Entry	Compound	EC ₅₀ (nM) ^a	% Response ^b
1	 21	1152±247	14±50
2	 22	737±472	43±42
3	 23	51±15	50±15
4	 24	8.2±2.0	101±14
5	 18	4.2±0.8	107±10
6	 25	301±98	29±45

a. All EC₅₀ values are the mean of triplicate analyses. b. Percent maximal bioluminescence with respect to Ea-CAI-1, which is set at 100%.

[0066] Tabulated bioassay data for the compounds in Figure 3.

Entry	Compound	EC ₅₀ (nM) ^a	% Response ^b
1	 26	10.9±4.8	64±42
2	 27	2017±1681	75±45
3	 28	35.8±6.1	75±10
4	 29	>5000	60
5	 30	88.4±24.9	54±29
6	 31	731±686	45±62
7	 32	3.8±0.4	97±5
8	 33	288±92	109±31

Entry	Compound	EC ₅₀ (nM) ^a	% Response ^b
9	 34	>5000	25
10	 35	>5000	26

a. All EC₅₀ values are the mean of triplicate analyses. *b.* Percent maximal bioluminescence with respect to Ea-CAI-1, which is set at 100%.

[0067] General Structures and Additional Examples of Compounds

[0068] Figure 6A provides the general structure of the synthetic compounds contemplated as QS agonists. Figure 6B provides further examples of the synthetic compounds as well as the structures of compounds 18, 19, 20. Figure 7 shows general synthesis strategies that were employed to synthesize 3-acyl pyrroles shown in Fig. 6. Bioassay data for some of the compounds is shown in Figure 8.

[0069] Western Blot Analysis

[0070] Overnight cultures of *V. cholerae* CqsA- LuxQ- were diluted 1000-fold in AKI medium containing the indicated compounds. The cultures were grown under static conditions at 37°C for 4h and then were shaken for 18h at 37°C. Cells were collected by centrifugation, TcpA and HapR from different samples were analyzed by Western Blot as described in references [4, 5].

[0071] Murine 3T3 Fibroblast Cell Toxicity Assay

[0072] 3T3 cells were prepared in a 24-well plate and incubated for 24h at 37°C as described in NIH Publication No. 07-4518. Reference [6]. The culture media was replaced by media containing the compound 18 at the indicated concentrations and the plates were visually examined using a microscope for cytotoxicity after incubation in the

presence of the compound for 24h. Figure 4 shows representative images displaying the effects of different concentrations of compound **18** on 3T3 cells.

[0073] Cytotoxicity of Compound **18** in *V. cholerae* as assessed by OD₆₀₀

[0074] Figure 9 is a plot showing the no effect on growth of *Vibrio cholerae* strain MM920 under the conditions described for biological assay. Diamonds represent luminescence measurements in the presence of varying concentrations of compound **18**. Circles represent the OD₆₀₀ at each of the concentrations of **18**.

[0075] General Experimental

[0076] Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of nitrogen or argon using dried reagents and solvents. All chemicals were purchased from commercial vendors and used without further purification. Anhydrous solvents were purchased from commercial vendors.

[0077] Flash chromatography was performed using standard grade silica gel 60 230-400 mesh from SORBENT Technologies. Silica gel was loaded into glass columns as a slurry. Analytical thin-layer chromatography was carried out using Silica G TLC plates, 200 µm with UV₂₅₄ fluorescent indicator (SORBENT Technologies), and visualization was performed by staining and/or by absorbance of UV light.

[0078] NMR spectra were recorded using a Bruker Avance II (500 MHz for ¹H; 125 MHz for ¹³C) spectrometer fitted with either a ¹H-optimized TCI (H/C/N) cryoprobe or a ¹³C-optimized dual C/H cryoprobe. Chemical shifts are reported in parts per million (ppm) and were calibrated according to residual protonated solvent. High-resolution mass spectral analysis was performed using an Agilent 1200-series electrospray ionization – time-of-flight (ESI-TOF) mass spectrometer in the positive ESI mode.

[0079] Compound Synthesis

[0080] **(Z)-benzyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate, 3a.** To a solution of (Z)-2-(benzyloxycarbonylamino)but-2-enoic acid^[1] (800 mg, 3.4 mmol) in DMF (16.7 mL) at ambient temperature and was treated with HOBt (1.2 g, 9.17 mmol), HNMe(OMe)-HCl (814 mg, 8.3 mmol), EDC (2.4 g, 12.5 mmol), and Et₃N (2.3 mL, 16.7 mmol) sequentially and the mixture was allowed to stir for 10h

at ambient temperature. The crude mixture was filtered through a plug of celite and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluting with a gradient from hexanes to 60%EtOAc/hexanes. Fractions containing the desired product were combined and concentrated *in vacuo* to provide (Z)-benzyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (100 mg, 11%). ¹H-NMR (500MHz, CDCl₃) δ 7.39-7.21 (m, 5H); 6.99 (s, 1H); 5.69 (bs, 1H); 5.05 (s, 2H); 3.62 (s, 3H); 3.22 (s, 3H); 1.66 (d, *J*=7.1Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 167.1, 153.7, 135.9, 128.5, 128.2, 128.2, 128.1, 121.7, 67.1, 60.8, 34.6, 12.5. HRMS (ESI-TOF) 279.1351 [M+H]⁺ (calculated for C₁₄H₁₉N₂O₄ = 279.1345).

[0081] **(Z)-benzyl (4-oxotridec-2-en-3-yl)carbamate, 3.** To a solution of (Z)-benzyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (100 mg, 0.359 mmol) in THF (3.6 mL) at 0°C was added nonyl-MgBr (1.0M in Et₂O, 1.8 mL, 1.8 mmol) and the mixture was stirred at 0°C for 5h. The reaction was quenched with sat. NH₄Cl, extracted with Et₂O (3 x 10 mL), the combined organics were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to 40% EtOAc/hexanes to provide (Z)-benzyl (4-oxotridec-2-en-3-yl)carbamate (72 mg, 58%) ¹H-NMR (500MHz, CDCl₃) δ 7.45-7.29 (m, 5H); 6.66 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.11 (s, 2H); 2.64 (t, *J*=7.5Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.56-1.51 (m, 2H); 1.37-1.14 (m, 12H); 0.85 (t, *J*=6.9Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 197.7, 153.9, 136.2, 134.9, 131.4, 128.8, 128.5, 128.4, 67.5, 36.8, 31.9, 29.9, 29.4, 29.3, 25.8, 24.8, 22.8, 15.4, 14.3. HRMS (ESI-TOF) 346.2388 [M+H]⁺ (calculated for C₂₁H₃₂NO₃ = 346.2382).

[0082] **(Z)-2-(trimethylsilyl)ethyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate, 4a.** L-Vinylglycine hydrochloride^[1] (320 mg, 2.33 mmol) was dissolved in dioxane/H₂O (26 mL, 0.017M, 1:1 dioxane:H₂O) and was treated with NaHCO₃ (391 mg, 4.66 mmol) and *N*-[2-(Trimethylsilyl)ethoxycarbonyloxy]succinimide (633 mg, 2.44 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for 24h and was then concentrated *in vacuo* to a volume of ca. 10 mL. The resulting solution was acidified with 10% KHSO₄ to ~pH6.5, was

extracted with DCM (3 x 50 mL), dried over Na₂SO₄ and concentrated to dryness. The resulting oil was dissolved in THF (23 mL) at ambient temperature and was treated with HOBt (944 mg, 6.99 mmol, 3.0 eq to VGly-HCl), HNMe(OMe)-HCl (341 mg, 3.5 mmol, 1.15 eq to VGly-HCl), EDC (671 mg, 3.5 mmol, 1.15 eq to VGly-HCl), and Et₃N (975 μ L, 6.99 mmol, 3.0 eq to VGly-HCl) sequentially and the mixture was allowed to stir for 10h at ambient temperature. The crude mixture was filtered through a plug of celite and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluting with a gradient from hexanes to 60%EtOAc/hexanes. Fractions containing the desired product were combined and concentrated *in vacuo* to provide (Z)-2-(trimethylsilyl)ethyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate as a pale yellow oil (280 mg, 42% from VGly-HCl). ¹H-NMR (500MHz, CDCl₃) δ 6.28 (s, 1H); 5.81-5.68 (m, 1H); 4.19-4.10 (m, 2H); 3.67 (s, 3H); 3.24 (s, 3H); 1.70 (d, *J*=7.0Hz, 3H); 1.03-0.91 (m, 2H); -0.01 (s, 9H). ¹³C-NMR (125MHz, CDCl₃) δ 167.2, 154.2, 130.1, 121.2, 64.1, 61.1, 34.3, 17.8, 12.6, -1.34. HRMS (ESI-TOF) 289.1578 [M+H]⁺ (calculated for C₁₂H₂₅N₂O₄Si = 289.1584).

[0083] **(Z)-2-(trimethylsilyl)ethyl (4-oxotridec-2-en-3-yl)carbamate, 4.** To a solution of (Z)-2-(trimethylsilyl)ethyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (115.3 mg, 0.40 mmol) in THF (4 mL) at 0°C was added nonyl-MgBr (1.0M in Et₂O, 2 mL, 2 mmol) and the mixture was stirred at 0°C for 2 h. The reaction was quenched with 10% KHSO₄, extracted with Et₂O (3 x 10 mL), the combined organics were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to 40% EtOAc/hexanes to provide (Z)-2-(trimethylsilyl)ethyl (4-oxotridec-2-en-3-yl)carbamate (132.1 mg, 93%) ¹H-NMR (500MHz, CDCl₃) δ 6.55 (q, *J*=7.1Hz, 1H); 6.53 (s, 1H); 4.19-4.12 (m, 2H); 2.64 (t, *J*=7.5Hz, 2H); 1.86 (d, *J*=7.1Hz, 3H); 1.64-1.51 (m, 2H); 1.33-1.17 (m, 12H); 0.94-0.86 (m, 2H); 0.85 (t, *J*=7.0Hz, 3H), 0.01 (s, 9H). ¹³C-NMR (125MHz, CDCl₃) δ 197.8, 154.3, 135.1, 131.2, 64.0, 36.8, 32.1, 29.6, 29.6, 29.5, 29.5, 24.8, 22.9, 17.8, 15.3, 14.3, -1.3. HRMS (ESI-TOF) 356.2623 [M+H]⁺ (calculated for C₁₉H₃₈NO₃Si = 356.2621).

[0084] **(Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate, 5a.** To a solution of VGly-HCl^[1] (284.9 mg, 2.07 mmol) was dissolved in dioxane/H₂O (20 mL, 0.02M, 1:1 dioxane:H₂O) and was treated with NaHCO₃ (348 mg, 4.14 mmol) and allyl chloroformate (240 μ L, 2.28 mmol) sequentially at room temperature. The resulting mixture was stirred at room temperature for 24 h and was then concentrated *in vacuo* to a volume of ca. 10 mL. The resulting solution was acidified with 10% KHSO₄ to ~pH6.5, was extracted with DCM (3 x 50mL), dried over Na₂SO₄ and concentrated to dryness. The resulting oil was dissolved in THF (20.7 mL) at ambient temperature and was treated with HOBt (839 mg, 6.21 mmol), HNMe(OMe)-HCl (232 mg, 2.38 mmol), EDC (456 mg, 2.38 mmol), and Et₃N (1.4 mL, 10.35 mmol) sequentially and the mixture was allowed to stir overnight at ambient temperature. The crude mixture was filtered through a plug of celite and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography eluting with a gradient from hexanes to 60% EtOAc/hexanes. Fractions containing the desired product were combined and concentrated *in vacuo* to provide (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate as a pale yellow oil (200 mg, 42% from VGly-HCl). ¹H-NMR (500MHz, CDCl₃) δ 6.29 (s, 1H); 5.97-5.78 (m, 2H); 5.31 (d, *J*=17.3Hz, 1H); 5.22 (d, *J*=10.4Hz, 1H); 4.58 (d, *J*=5.7Hz, 2H); 3.67 (s, 3H); 3.25 (s, 3H); 1.73 (d, *J*=7.1Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 167.1, 153.8, 132.5, 128.1, 118.5, 118.1, 61.2, 60.6, 34.2, 14.4. HRMS (ESI-TOF) 229.1192 [M+H]⁺ (calculated for C₁₀H₁₇N₂O₄ = 229.1188).

[0085] **(Z)-allyl (4-oxotridec-2-en-3-yl)carbamate, 5.** To a solution of (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate (91.3 mg, 0.40 mmol) in THF (4 mL) at 0°C was added nonyl-MgBr (1.0M in Et₂O, 2 mL, 2 mmol) and the mixture was stirred at 0°C for 2 h. The reaction was quenched with 10% KHSO₄, extracted with Et₂O (3 x 10 mL), the combined organics were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with 10% EtOAc/hexanes to 40% EtOAc/hexanes to provide (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (98.3 mg, 83%) ¹H-NMR (500MHz, CDCl₃) δ 6.63 (s, 1H); 6.57 (q, *J*=7.1Hz, 1H); 5.96-5.84 (m, 1H); 5.31 (dd, *J*=17.2, 1.4Hz, 1H); 5.21 (dd, *J*=10.5, 1.3Hz, 1H); 4.57

(d, $J=5.6\text{Hz}$, 2H); 2.64 (t, $J=7.6\text{Hz}$, 2H); 1.86 (d, $J=7.1\text{Hz}$, 3H); 1.65-1.51 (m, 2H); 1.35-1.15 (m, 12H); 0.85 (t, $J=7.0\text{Hz}$, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.7, 153.7, 134.9, 132.6, 131.4, 118.2, 66.3, 36.8, 32.1, 29.6, 29.6, 29.5, 29.5, 24.8, 22.9, 15.3, 14.3. HRMS (ESI-TOF) 296.2230 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{17}\text{H}_{30}\text{NO}_3 = 296.2226$).

[0086] **(Z)-allyl (4-oxonon-2-en-3-yl)carbamate, 6a.** Prepared in a manner analogous to (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and pentyl-MgBr to provide (Z)-allyl (4-oxonon-2-en-3-yl)carbamate (21.1 mg, 67%). ^1H -NMR (500MHz, CDCl_3) δ 6.62 (s, 1H); 6.57 (q, $J=7.1\text{Hz}$, 1H); 5.98-5.81 (m, 1H); 5.31 (d, $J=17.2\text{Hz}$, 1H); 5.21 (d, $J=11.6\text{Hz}$, 1H); 4.57 (d, $J=5.6\text{Hz}$, 2H); 2.65 (t, $J=7.51\text{Hz}$, 2H); 1.86 (d, $J=7.1\text{Hz}$, 3H); 1.68-1.51 (m, 2H); 1.34-1.15 (m, 4H); 0.86 (t, $J=6.9\text{Hz}$, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.7, 153.8, 134.9, 132.6, 131.5, 118.3, 66.3, 36.7, 31.7, 24.5, 22.7, 15.3, 14.2. HRMS (ESI-TOF) 240.1602 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{13}\text{H}_{22}\text{NO}_3 = 240.1600$).

[0087] **(Z)-allyl (4-oxodec-2-en-3-yl)carbamate, 7a.** Prepared in a manner analogous to (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and hexyl-MgBr to provide (Z)-allyl (4-oxodec-2-en-3-yl)carbamate (27 mg, 81%). ^1H -NMR (500MHz, CDCl_3) δ 6.63 (s, 1H); 6.56 (q, $J=7.1\text{Hz}$, 1H); 5.96-5.83 (m, 1H); 5.30 (d, $J=17.2\text{Hz}$, 1H); 5.21 (d, $J=11.6\text{Hz}$, 1H); 4.56 (d, $J=5.6\text{Hz}$, 2H); 2.64 (t, $J=7.6\text{Hz}$, 2H); 1.85 (d, $J=7.1\text{Hz}$, 3H); 1.64-1.48 (m, 2H); 1.35-1.16 (m, 6H); 0.85 (t, $J=6.9\text{Hz}$, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.4, 153.9, 134.8, 132.6, 131.5, 118.3, 66.2, 36.8, 32.0, 29.3, 24.8, 22.8, 15.4, 14.3. HRMS (ESI-TOF) 254.1756 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{14}\text{H}_{24}\text{NO}_3 = 254.1756$).

[0088] **(Z)-allyl (4-oxoundec-2-en-3-yl)carbamate, 8a.** Prepared in a manner analogous to (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and heptyl-MgBr to provide (Z)-allyl (4-oxoundec-2-en-3-yl)carbamate (26.6 mg, 76%). ^1H -NMR (500MHz, CDCl_3) δ 6.64 (s, 1H); 6.56 (q, $J=7.1\text{Hz}$, 1H); 5.96-5.83 (m, 1H); 5.30 (d, $J=18.2\text{Hz}$, 1H); 5.20 (d, $J=10.4\text{Hz}$, 1H); 4.56 (d, $J=5.6\text{Hz}$, 2H); 2.64 (t, $J=7.5\text{Hz}$, 2H); 1.85 (d, $J=7.5\text{Hz}$, 3H); 1.63-

1.48 (m, 2H); 1.36-1.15 (m, 8H); 0.84 (t, $J=6.8\text{Hz}$, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.1, 153.8, 134.9, 132.6, 131.5, 118.3, 66.3, 36.8, 31.9, 29.5, 29.3, 24.8, 22.8, 15.4, 14.3. HRMS (ESI-TOF) 268.1913 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{15}\text{H}_{26}\text{NO}_3 = 268.1913$).

[0089] **(Z)-allyl (4-oxododec-2-en-3-yl)carbamate, 9a.** Prepared in a manner analogous to (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and octyl-MgBr to provide (Z)-allyl (4-oxododec-2-en-3-yl)carbamate (27.9 mg, 78%). ^1H -NMR (500MHz, CDCl_3) δ 6.64 (s, 1H); 6.57 (q, $J=7.1\text{Hz}$, 1H); 5.96-5.85 (m, 1H); 5.31 (d, $J=17.2\text{Hz}$, 1H); 5.21 (d, $J=10.4\text{Hz}$, 1H); 4.57 (d, $J=5.6\text{Hz}$, 2H); 2.65 (t, $J=7.5\text{Hz}$, 2H); 1.86 (d, $J=7.1\text{Hz}$, 3H); 1.60-1.48 (m, 2H); 1.38-1.18 (m, 10H); 0.85 (t, $J=6.8\text{Hz}$, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.7, 153.8, 134.9, 132.6, 131.5, 118.3, 63.3, 32.9, 32.0, 29.6, 29.5, 25.9, 24.8, 22.9, 15.4, 14.3. HRMS (ESI-TOF) 282.2065 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{16}\text{H}_{28}\text{NO}_3 = 282.2069$).

[0090] **(Z)-allyl (4-oxotetradec-2-en-3-yl)carbamate, 10a.** Prepared in a manner analogous to (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and decyl-MgBr to provide (Z)-allyl (4-oxotetradec-2-en-3-yl)carbamate (12.9 mg, 32%). ^1H -NMR (500MHz, CDCl_3) δ 6.64 (s, 1H); 6.57 (q, $J=7.1\text{Hz}$, 1H); 5.97-5.84 (m, 1H); 5.31 (dd, $J=17.2, 1.4\text{Hz}$, 1H); 5.21 (dd, $J=10.4, 1.2\text{Hz}$, 1H); 4.57 (d, $J=5.6\text{Hz}$, 2H); 2.65 (t, $J=7.5\text{Hz}$, 2H); 1.86 (d, $J=7.1\text{Hz}$, 3H); 1.66-1.50 (m, 2H); 1.37-1.16 (m, 14H); 0.85 (t, $J=6.9\text{Hz}$, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.7, 153.8, 134.9, 132.6, 131.5, 118.2, 63.3, 37.6, 32.9, 32.1, 29.8, 29.8, 29.6, 29.5, 25.9, 22.9, 15.3, 14.3. HRMS (ESI-TOF) 310.2378 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{18}\text{H}_{32}\text{NO}_3 = 310.2382$).

[0091] **(Z)-allyl (4-oxohexadec-2-en-3-yl)carbamate, 11a.** Prepared in a manner analogous to (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) from (Z)-allyl (1-(methoxy(methyl)amino)-1-oxobut-2-en-2-yl)carbamate and dodecyl-MgBr to provide (Z)-allyl (4-oxohexadec-2-en-3-yl)carbamate (28.9 mg, 65%). ^1H -NMR (500MHz, CDCl_3) δ 6.63 (s, 1H); 6.57 (q, $J=7.1\text{Hz}$, 1H); 5.97-5.85 (m, 1H); 5.31 (d, $J=17.2\text{Hz}$, 1H); 5.21 (d, $J=10.4\text{Hz}$, 1H); 4.57 (d, $J=5.6\text{Hz}$, 2H); 2.65 (t, $J=7.5\text{Hz}$, 2H); 1.86 (d, $J=7.1\text{Hz}$, 3H); 1.66-1.51 (m, 2H); 1.36-1.15 (m, 18H); 0.85 (t, $J=6.9\text{Hz}$, 3H). ^{13}C -NMR (125MHz, CDCl_3)

δ 197.7, 153.8, 134.9, 132.6, 131.4, 118.2, 63.3, 36.8, 33.0, 32.1, 29.9, 29.9, 29.8, 29.8, 29.6, 29.6, 24.8, 22.9, 15.4, 14.3. HRMS (ESI-TOF) 338.2696 $[M+H]^+$ (calculated for $C_{20}H_{36}NO_3 = 338.2695$).

[0092] **(Z)-3-aminotridec-2-en-4-one, Ea-CAI-1.** To a solution of (Z)-allyl (4-oxotridec-2-en-3-yl)carbamate (**5**) (8.6 mg, 0.029 mmol) in THF (300 μ L) was added Et_2NH (45 μ L, 0.435 mmol) followed by $Pd(PPh_3)_4$ (5.1 mg, 0.0044 mmol) and the mixture was allowed to stir at room temperature for 4 h in a flask shielded from light. The mixture was diluted with heptane (~1.5 mL) and concentrated to remove the THF. The remaining solution (~1 mL) was loaded onto a short plug of SiO_2 pre-equilibrated in hexane containing 1% Et_3N . The product was eluted with one column volume of hexane (1% Et_3N), 2 column volumes of 4:1 hexane: CH_2Cl_2 (1% Et_3N), 2 column volumes of 1:1 hexane: CH_2Cl_2 (1% Et_3N), 2 column volumes of 1:4 hexane: CH_2Cl_2 (1% Et_3N) and 1 column volume of CH_2Cl_2 (1% Et_3N). Fractions containing the desired product ($R_f \sim 0.4$, 20% EtOAc/hexane, CAM stain) were combined to provide (Z)-3-aminotridec-2-en-4-one (2.9 mg, 47%) The product was typically immediately dissolved in anhydrous DMSO and was stored frozen. ^1H -NMR (500MHz, d_6 -DMSO) δ 5.53 (q, $J=7.1$ Hz, 1H); 4.31 (s, 2H); 2.60 (t, $J=7.4$ Hz, 2H); 1.65 (d, $J=7.1$ Hz, 3H); 1.51-1.43 (m, 2H); 1.29-1.16 (m, 12H); 0.85 (t, $J=6.8$ Hz, 3H). ^{13}C -NMR (125MHz, d_6 -DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.3, 29.0, 28.9, 28.7 (2C), 25.0, 22.2, 14.0, 12.1. HRMS (ESI-TOF) 212.2010 $[M+H]^+$ (calculated for $C_{13}H_{26}NO = 212.2014$).

[0093] **(Z)-3-aminonon-2-en-4-one, 6.** Prepared in an analogous manner to (Z)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (Z)-allyl (4-oxonon-2-en-3-yl)carbamate to provide (Z)-3-aminonon-2-en-4-one (4.7 mg, 66%). ^1H -NMR (500MHz, d_6 -DMSO) δ 5.53 (q, $J=7.1$ Hz, 1H); 4.31 (s, 2H); 2.61 (t, $J=7.4$ Hz, 2H); 1.65 (d, $J=7.1$ Hz, 3H); 1.48 (pentet, $J=7.4$ Hz, 2H); 1.33-1.14 (m, 4H); 0.85 (t, $J=7.1$ Hz, 3H). ^{13}C -NMR (125MHz, d_6 -DMSO) δ 197.1, 141.8, 106.7, 35.1, 30.9, 24.7, 22.0, 13.9, 12.1. HRMS (ESI-TOF) 156.1386 $[M+H]^+$ (calculated for $C_9H_{18}NO = 156.1388$).

[0094] **(Z)-3-aminodec-2-en-4-one, 7.** Prepared in an analogous manner to (Z)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (Z)-allyl (4-oxodec-2-en-3-yl)carbamate to

provide (*Z*)-3-aminodec-2-en-4-one (5.9 mg, 66%). ¹H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.61 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.52-1.44 (m, 2H); 1.31-1.18 (m, 6H); 0.85 (t, *J*=6.8 Hz, 3H). ¹³C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.1, 31.2, 28.4, 25.0, 22.1, 14.0, 12.1. HRMS (ESI-TOF) 170.1539 [M+H]⁺ (calculated for C₁₀H₂₀NO = 170.1545).

[0095] **(*Z*)-3-aminoundec-2-en-4-one, 8.** Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxoundec-2-en-3-yl)carbamate to provide (*Z*)-3-aminoundec-2-en-4-one (3.9 mg, 34%). ¹H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.61 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.51-1.43 (m, 2H); 1.30-1.18 (m, 8H); 0.85 (t, *J*=6.9 Hz, 3H). ¹³C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.2, 28.7, 28.6, 25.0, 22.1, 14.0, 12.1. HRMS (ESI-TOF) 184.1699 [M+H]⁺ (calculated for C₁₁H₂₂NO = 184.1701).

[0096] **(*Z*)-3-aminododec-2-en-4-one, 9.** Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxododec-2-en-3-yl)carbamate to provide (*Z*)-3-aminododec-2-en-4-one (2.8 mg, 59%). ¹H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.61 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.52-1.43 (m, 2H); 1.32-1.16 (m, 10H); 0.85 (t, *J*=6.8 Hz, 3H). ¹³C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.3, 28.9, 28.7, 28.7, 25.0, 22.1, 14.0, 12.1. HRMS (ESI-TOF) 198.1853 [M+H]⁺ (calculated for C₁₂H₂₄NO = 198.1858).

[0097] **(*Z*)-3-aminotetradec-2-en-4-one, 10.** Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxotetradec-2-en-3-yl)carbamate to provide (*Z*)-3-aminotetradec-2-en-4-one (4.4 mg, 51%). ¹H-NMR (500MHz, d6-DMSO) δ 5.53 (q, *J*=7.1 Hz, 1H); 4.30 (s, 2H); 2.60 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.53-1.43 (m, 2H); 1.36-1.14 (m, 14H); 0.85 (t, *J*=6.8 Hz, 3H). ¹³C-NMR (125MHz, d6-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.3, 29.0, 28.9, 28.8, 28.8, 28.7, 25.0, 22.2, 14.0, 12.1. HRMS (ESI-TOF) 226.2166 [M+H]⁺ (calculated for C₁₄H₂₈NO = 226.2171).

[0098] **(*Z*)-3-aminohexadec-2-en-4-one, 11.** Prepared in an analogous manner to (*Z*)-3-aminotridec-2-en-4-one (**Ea-CAI1**) from (*Z*)-allyl (4-oxohexadec-2-en-3-

yl)carbamate to provide (*Z*)-3-aminohexadec-2-en-4-one (7.5 mg, 67%). ¹H-NMR (500MHz, d₆-DMSO) δ 5.52 (q, *J*=7.1 Hz, 1H); 4.31 (s, 2H); 2.60 (t, *J*=7.4 Hz, 2H); 1.65 (d, *J*= 7.1 Hz, 3H); 1.53-1.43 (m, 2H); 1.33-1.15 (m, 18H); 0.85 (t, *J*=6.8 Hz, 3H). ¹³C-NMR (125MHz, d₆-DMSO) δ 197.1, 141.8, 106.7, 35.2, 31.4, 29.2, 29.1, 29.0, 29.0, 28.9, 28.8, 28.7, 25.0, 22.2, 14.0, 12.1. HRMS (ESI-TOF) 254.2481 [M+H]⁺ (calculated for C₁₆H₃₂NO = 254.2484).

[0099] ***tert*-butyl (2-oxoundecyl)carbonate.** Prepared using a modification of a reported procedure.^[2] To a solution of *tert*-Butyl (2-(methoxy(methyl)amino)-2-oxoethyl)carbamate (500 mg, 2.29mmol) in THF (23 mL) at 0°C was added nonyl-MgBr (1.0M in Et₂O, 11.5 mL, 11.5 mmol) and the mixture was allowed to stir at 0°C for 4 h. The mixture was quenched with sat. NH₄Cl (50 mL), extract with Et₂O (2 x 50 mL), dry over Na₂SO₄ and concentrate *in vacuo*. The mixture was purified by silica gel chromatography (20% to 40% EtOAc/hexanes) to provide *tert*-butyl (2-oxoundecyl)carbonate as a clear colorless oil (510 mg, 78%). ¹H-NMR (500MHz, CDCl₃) δ 5.22 (s, 1H); 4.00 (d, *J*=4.7Hz, 1H); 3.62 (m, 1H); 2.39 (t, *J*=7.5Hz, 2H); 1.63-1.50 (m, 2H); 1.39 (s, 9H); 1.36-1.17 (m, 12H); 0.85 (t, *J*=7.0Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 206.2, 155.8, 79.9, 50.4, 40.3, 32.1, 29.5, 29.5, 29.5, 29.4, 28.5, 23.9, 22.9, 14.3.

[00100] **3-methyl-5-nonylisoxazol-4-amine, 15.** To a solution of acetaldehyde oxime (1 g, 16.9 mmol) in DMF (34 mL) at room temperature was added *N*-chloro succinimide (2.9 g, 21.9 mmol) and the mixture was allowed to stir for 3.5 h. The reaction was quenched with H₂O (40 mL), extracted with EtOAc (3 x 40 mL), dried over MgSO₄, filtered and concentrated *in vacuo* to yield *N*-hydroxyacetimidoyl chloride as a clear, colorless oil that was used without further purification. To *tert*-butyl (2-oxoundecyl)carbonate (510 mg, 1.78 mmol) in THF (3.6 mL) at -78°C was added *tert*-butyl lithium (1.7M in pentane, 2.1 mL, 3.56 mmol). The resulting mixture was allowed to stir at -78°C for 20 min and was treated with the above prepared *N*-hydroxyacetimidoyl chloride (166.4 mg, 1.78 mmol) as a solution in THF (1.8 mL). The resulting mixture was allowed to warm slowly to room temperature and was stirred at room temperature overnight. The reaction was quenched with sat. NH₄Cl (10 mL),

extracted with Et₂O (3 x 10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue (300 mg) was dissolved in CH₂Cl₂ (9.3 mL) and H₂O (140 µL) at room temperature and was treated with TFA (700 µL, 9.25 mmol). The mixture was allowed to stir overnight, was concentrated to dryness and the residue was purified by silica gel chromatography (40% EtOAc/hexanes to 100% EtOAc) to yield 3-methyl-5-nonylisoxazol-4-amine as a yellow solid (48 mg, 12% over two steps). ¹H-NMR (500MHz, CDCl₃) δ 8.18 (bs, 2H); 2.72 (t, *J*= 7.6 Hz, 2H); 2.25 (s, 3H); 1.69-1.55 (m, 2H); 1.34-1.15 (m, 12H); 0.86 (t, *J*= 6.9 Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 165.1, 155.2, 111.0, 32.0, 29.5, 29.4, 29.3, 29.3, 27.2, 25.0, 22.8, 14.2, 9.1. HRMS (ESI-TOF) 225.1961 [M+H]⁺ (calculated for C₁₃H₂₅N₂O = 225.1967).

[00101] **4-methyl-3-nonylisoxazol-5-amine, 16.** To a solution of decanal oxime^[3] (2 g, 11.67 mmol) in CH₂Cl₂ (58 mL) at room temperature was added benzyltrimethylammonium tetrachloroiodate (4.89 g, 11.67 mmol) and the mixture was allowed to stir for 1 h before dilution with Et₂O (280 mL). The resulting precipitate was removed by filtration and the filtrate was concentrated to dryness to provide *N*-hydroxydecanimidoyl chloride which was used without further purification. To propionitrile (1.22 mL, 17.49 mmol) in THF (35 mL) at -78 °C was added *tert*-butyl lithium (1.7M in pentane, 10.3 mL, 17.5 mmol) and the mixture was allowed to react at -78 °C for 40 min before the addition of a solution of *N*-hydroxydecanimidoyl chloride (1.0M solution in Et₂O, 5.83 mL). The mixture was allowed to stir at -78 °C for 4 h. The reaction was quenched with sat. NH₄Cl (70 mL), extracted with Et₂O (3 x 70 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (40% EtOAc/hexanes to 100% EtOAc) to yield 4-methyl-3-nonylisoxazol-5-amine as a white solid (116 mg, 9% over two steps). ¹H-NMR (500MHz, CDCl₃) δ 4.16-4.05 (m, 2H); 2.47 (t, *J*= 7.9 Hz, 2H); 1.76 (s, 3H); 1.66-1.54 (m, 2H); 1.41-1.17 (m, 12H); 0.87 (t, *J*= 6.8 Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 165.1, 164.5, 87.5, 32.0, 29.6, 29.5, 29.5, 27.6, 25.7, 22.8, 21.2, 14.3, 6.2. HRMS (ESI-TOF) 225.1966 [M+H]⁺ (calculated for C₁₃H₂₅N₂O = 225.1967).

[00102] **General Procedure A. Synthesis of Acylated Pyrrole Analogs**

(Compounds 17, 18 and 21-35). To a solution of the pyrrole (1.0 eq) in Et₂O (1.4M) was added MeMgBr (1.0 eq) and the mixture is stirred at reflux for 30 minutes before cooling to 0 °C. The cooled solution is treated with the appropriate acid chloride (1.0 eq) as a solution in PhMe (1.0M) and the mixture is allowed to warm slowly to room temperature and stirred overnight. The reaction is quenched with sat. NH₄Cl (double reaction volume), extracted with Et₂O (3 x double reaction volume), dried over Na₂SO₄ and concentrated *in vacuo* before purification by silica gel chromatography. Both regioisomers of the acylated pyrrole are readily accessible in this manner. The 3-acylated pyrrole analogs typically eluted after the 2-acylated analogs.

[00103] **1-(1*H*-pyrrol-2-yl)decan-1-one, 17.** Prepared according to general procedure A to provide 1-(1*H*-pyrrol-2-yl)decan-1-one as an off-white solid (1.8 g, 28%). ¹H-NMR (500MHz, CDCl₃) δ 10.5 (s, 1H); 7.04 (s, 1H); 6.92 (s, 1H); 6.25 (s, 1H); 2.76 (t, *J*=7.5Hz, 2H); 1.80-1.65 (m, 2H); 1.45-1.14 (m, 12H); 0.86 (t, *J*=6.8Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 191.8, 132.1, 125.3, 116.7, 110.5, 38.2, 32.0, 29.6, 29.5, 25.6, 22.8, 14.3. HRMS (ESI-TOF) 222.1852 [M+H]⁺ (calculated for C₁₄H₂₄NO = 222.1858).

[00104] **1-(1*H*-pyrrol-3-yl)decan-1-one, 18.** Prepared according to general procedure A to provide 1-(1*H*-pyrrol-2-yl)decan-1-one as an off-white solid (1.3 g, 20%). ¹H-NMR (500MHz, CDCl₃) δ 9.32 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.63 (s, 1H); 2.73 (t, *J*=7.6Hz, 2H); 1.75-1.62 (m, 2H); 1.39-1.12 (m, 12H); 0.85 (t, *J*=6.8Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 197.7, 126.0, 123.6, 119.8, 108.8, 40.0, 32.1, 29.7, 29.7, 29.5, 25.4, 22.9, 14.3. HRMS (ESI-TOF) 222.1854 [M+H]⁺ (calculated for C₁₄H₂₄NO = 222.1858).

[00105] **1-(2,5-dimethyl-1*H*-pyrrol-3-yl)decan-1-one, 19.** To a solution of 2,5-dimethyl pyrrole (500 μL, 4.91mmol) in CH₂Cl₂ (5 mL) at 0 °C was added decanoyl chloride (1.0 mL, 4.91mmol). Aluminum (III) chloride (654.7 mg, 4.91 mmol) was added portion wise to the resulting solution and the mixture was allowed to stir at 0 °C for 1 h. The mixture was quenched by the addition of sat. NaHCO₃ (10 mL), extracted with CH₂Cl₂ (3 x 10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes to 40%EtOAc/hexane) to provide 1-(2,5-dimethyl-1*H*-pyrrol-3-yl)decan-1-one (153 mg, 13%). ¹H-NMR (500MHz, CDCl₃) δ 7.90 (s,

1H); 6.17 (s, 1H); 2.68 (t, J = 7.6 Hz, 2H); 2.51 (s, 3H); 2.22 (s, 3H); 1.71-1.59 (m, 2H); 1.39-1.18 (m, 12H); 0.87 (t, J = 6.8 Hz, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 198.0, 134.0, 125.4, 120.6, 107.6, 40.6, 31.9, 29.7, 29.7, 29.7, 29.5, 24.9, 22.7, 14.3, 14.1, 12.8. HRMS (ESI-TOF) 250.2161 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{16}\text{H}_{28}\text{NO}$ = 250.2171).

[00106] **1-(2,4-dimethyl-1H-pyrrol-3-yl)decan-1-one, 20.** To a solution of 2,4-dimethyl pyrrole (500 μL , 4.91 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added decanoyl chloride (1.0 mL, 4.91 mmol). Aluminum (III) chloride (654.7 mg, 4.91 mmol) was added portion wise to the resulting solution and the mixture was allowed to stir at 0 °C for 1 h. The mixture was quenched by the addition of sat. NaHCO_3 (10 mL), extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes to 40% EtOAc/hexane) to provide 1-(2,4-dimethyl-1H-pyrrol-3-yl)decan-1-one as an off white solid (82 mg, 7%). ^1H -NMR (500MHz, CDCl_3) δ 7.85 (s, 1H); 6.17 (s, 1H); 2.68 (t, J = 7.5 Hz, 2H); 2.51 (s, 3H); 2.22 (s, 3H); 1.72-1.60 (m, 2H); 1.39-1.18 (m, 12H); 0.87 (t, J = 6.7 Hz, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.9, 134.0, 125.3, 120.6, 107.6, 40.6, 32.0, 29.7, 29.7, 29.7, 29.5, 24.9, 22.7, 14.3, 14.1, 12.8. HRMS (ESI-TOF) 250.2160 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{16}\text{H}_{28}\text{NO}$ = 250.2171).

[00107] **1-(1H-pyrrol-3-yl)hexan-1-one, 21.** Prepared according to general procedure A to provide 1-(1H-pyrrol-3-yl)hexan-1-one as an off-white solid (387 mg, 16%). ^1H -NMR (500MHz, CDCl_3) δ 8.55 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.65 (s, 1H); 2.73 (t, J = 7.6 Hz, 2H); 1.76-1.64 (m, 2H); 1.38-1.28 (m, 4H); 0.87 (t, J = 6.7 Hz, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.0, 126.3, 123.0, 119.4, 109.1, 40.0, 31.9, 24.9, 22.8, 14.2. HRMS (ESI-TOF) 166.1232 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{10}\text{H}_{16}\text{NO}$ = 166.1232).

[00108] **1-(1H-pyrrol-3-yl)heptan-1-one, 22.** Prepared according to general procedure A to provide 1-(1H-pyrrol-3-yl)heptan-1-one as an off-white solid (121 mg, 5%). ^1H -NMR (500MHz, CDCl_3) δ 8.71 (s, 1H); 7.41 (s, 1H); 6.96 (s, 1H); 6.65 (s, 1H); 2.73 (t, J = 7.6 Hz, 2H); 1.74-1.56 (m, 2H); 1.39-1.18 (m, 6H); 0.86 (t, J = 6.9 Hz, 3H). ^{13}C -NMR (125MHz, CDCl_3) δ 197.1, 126.2, 123.2, 119.5, 109.0, 40.0, 31.9, 29.4, 25.2, 22.8, 14.3. HRMS (ESI-TOF) 180.1384 $[\text{M}+\text{H}]^+$ (calculated for $\text{C}_{11}\text{H}_{18}\text{NO}$ = 180.1388).

[00109] **1-(1*H*-pyrrol-3-yl)octan-1-one, 23.** Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)octan-1-one as an off-white solid (92 mg, 33%). ¹H-NMR (500MHz, CDCl₃) δ 8.47 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.65 (s, 1H); 2.72 (t, *J*=7.4Hz, 2H); 1.73-1.57 (m, 2H); 1.38-1.17 (m, 8H); 0.85 (t, *J*=6.8Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 196.7, 126.4, 123.0, 119.4, 109.1, 40.0, 32.0, 29.7, 29.4, 25.3, 22.9, 14.3. HRMS (ESI-TOF) 194.1545 [M+H]⁺ (calculated for C₁₂H₂₀NO = 194.1545).

[00110] **1-(1*H*-pyrrol-3-yl)nonan-1-one, 24.** Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)nonan-1-one as an off-white solid (431 mg, 14%). ¹H-NMR (500MHz, CDCl₃) δ 9.32 (s, 1H); 7.41 (s, 1H); 6.76 (s, 1H); 6.63 (s, 1H); 2.73 (t, *J*=7.4Hz, 2H); 1.75-1.62 (m, 2H); 1.39-1.12 (m, 10H); 0.85 (t, *J*=6.8Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 196.7, 126.0, 123.6, 119.7, 108.8, 40.0, 32.0, 29.7, 29.7, 29.5, 25.4, 22.9, 14.3. HRMS (ESI-TOF) 208.1703 [M+H]⁺ (calculated for C₁₃H₂₂NO = 208.1701).

[00111] **1-(1*H*-pyrrol-3-yl)dodecan-1-one, 25.** Prepared according to general procedure A to provide 1-(1*H*-pyrrol-3-yl)dodecan-1-one as an off-white solid (108 mg, 3%). ¹H-NMR (500MHz, CDCl₃) δ 8.50 (s, 1H); 7.41 (s, 1H); 6.77 (s, 1H); 6.65 (s, 1H); 2.72 (t, *J*=7.4Hz, 2H); 1.73-1.62 (m, 2H); 1.37-1.16 (m, 16H); 0.85 (t, *J*=6.7Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 196.9, 126.3, 123.0, 119.4, 109.1, 40.0, 32.1, 29.9, 29.8, 29.7, 29.6, 25.2, 22.9, 14.4. HRMS (ESI-TOF) 250.2167 [M+H]⁺ (calculated for C₁₆H₂₈NO = 250.2171).

[00112] **3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)propan-1-one, 26.** Prepared according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)propan-1-one as an off-white solid (62.7 mg, 4%). ¹H-NMR (500MHz, CDCl₃) δ 8.55 (s, 1H), 7.42-7.41 (m, 1H), 7.17-7.09 (m, 4H), 6.78-6.77 (m, 1H), 6.68-6.67 (m, 1H), 3.09-3.06 (m, 2H), 3.02-2.99 (m, 2H), 2.57 (t, *J*=7.8 Hz, 2H), 1.61-1.55 (m, 4H), 1.39-1.31 (m, 2H), 0.93-0.91 (t, *J*=7.3 Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 195.4, 140.7, 139.0, 128.5, 128.3, 126.0, 123.0, 119.4, 109.0, 41.8, 35.4, 33.9, 30.3, 22.5, 14.1. HRMS (ESI-TOF) 256.1701 [M+H]⁺ (calculated for C₁₇H₂₂NO = 256.1701).

[00113] **3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)propan-1-one, 27.** Prepared

according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)propan-1-one as an off-white solid (190.3 mg, 11%) ¹H-NMR (500MHz, CDCl₃) δ 9.60 (s, 1H), 7.17-7.10 (m, 4H), 7.03-7.02 (m, 1H), 6.91-6.90 (m, 1H), 6.28-6.26 (m, 1H), 3.12-3.07 (m, 2H), 3.04-3.00 (m, 2H), 2.58 (t, *J*=7.77, 2H), 1.62-1.56 (m, 2H), 1.39-1.32 (m, 2H), 0.93 (t, *J*=7.35, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 190.0, 140.8, 138.5, 132.0, 128.7, 128.3, 124.7, 116.3, 110.8, 39.9, 35.4, 33.9, 30.5, 22.5, 14.1. HRMS (ESI-TOF) 256.1701 [M+H]⁺ (calculated for C₁₇H₂₂NO = 256.1701).

[00114] **7-phenyl-1-(1*H*-pyrrol-3-yl)heptan-1-one, 28.** Prepared according to general procedure A to provide 7-phenyl-1-(1*H*-pyrrol-2-yl)heptan-1-one as an off-white solid (69.8 mg, 3%) ¹H-NMR (500MHz, CDCl₃) δ 8.67 (s, 1H), 7.42-7.41 (m, 1H), 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 6.79-6.77 (dd, *J*=2.4 Hz, 1H), 6.67-6.66 (dd, *J*=2.6, 1.5 Hz, 1H), 2.74 (t, *J*=7.5 Hz, 2H), 2.59 (t, *J*=7.8 Hz, 2H), 1.74-1.68 (m, 2H), 1.65-1.59 (m, 2H), 1.42-1.33 (m, 4H). ¹³C-NMR (125MHz, CDCl₃) δ 197.4, 142.9, 128.5, 128.3, 125.8, 125.7, 123.5, 119.7, 108.7, 39.8, 36.0, 31.5, 29.4, 29.2, 25.1. HRMS (ESI-TOF) 256.1700 [M+H]⁺ (calculated for C₁₇H₂₂NO = 256.1701).

[00115] **7-phenyl-1-(1*H*-pyrrol-2-yl)heptan-1-one, 29.** Prepared according to general procedure A to provide 7-phenyl-1-(1*H*-pyrrol-2-yl)heptan-1-one as an off-white solid (267 mg, 13%) ¹H-NMR (500MHz, CDCl₃) δ 9.48 (s, 1H), 7.32-7.28 (m, 2H), 7.22-7.19 (m, 3H), 7.05-7.04 (m, 1H), 6.93-6.92 (m, 1H), 6.31-6.29 (m, 1H), 2.78 (t, *J*=7.5 Hz, 2H), 2.63 (t, *J*=7.7 Hz, 2H), 1.77-1.70 (m, 2H), 1.68-1.62 (m, 2H), 1.46-1.36 (m, 4H). ¹³C-NMR (125MHz, CDCl₃) δ 191.2, 142.9, 132.2, 128.5, 128.4, 125.7, 124.4, 116.1, 110.7, 38.1, 36.0, 31.5, 29.4, 29.2, 25.3. HRMS (ESI-TOF) 256.1713 [M+H]⁺ (calculated for C₁₇H₂₂NO = 256.1701).

[00116] **3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)prop-2-en-1-one, 30.** Prepared according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-3-yl)prop-2-en-1-one as an off-white solid (62.7 mg, 4%) ¹H-NMR (500MHz, CDCl₃) δ 8.73 (s, 1H), 7.78 (d, *J*=15.6 Hz, 1H), 7.59 (s, 1H), 7.54 (d, *J*=7.8 Hz, 2H), 7.27 (d, *J*=15.6 Hz, 1H), 7.21 (d, *J*=7.7 Hz, 2H), 6.83 (d, *J*=14.2, 2H), 2.63 (t, *J*=7.7 Hz, 2H), 1.64-1.58 (m, 2H), 1.36 (h, *J*=7.4 Hz, 2H), 0.93 (t, *J*=7.3 Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 185.25, 145.60,

142.31, 132.77, 129.09, 128.48, 127.00, 123.69, 122.70, 119.74, 109.40, 35.74, 33.59, 22.50, 14.11. HRMS (ESI-TOF) 254.1554 [M+H]⁺ (calculated for C₁₇H₂₀NO = 254.1545).

[00117] **3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one, 31.** Prepared according to general procedure A to provide 3-(4-butylphenyl)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one as an off-white solid (18.6 mg, 5%) ¹H-NMR (500MHz, CDCl₃) δ 10.86 (s, 1H), 7.94 (d, *J*=15.7 Hz, 1H), 7.63 (d, *J*=8.3 Hz, 2H), 7.44 (d, *J*=15.7 Hz, 1H), 7.29 (d, *J*=8.3 Hz, 2H), 7.24-7.23 (m, 1H), 7.20-7.18 (m, 1H), 6.44-6.41 (m, 1H), 2.70 (t, *J*=7.9 Hz, 2H), 1.70-1.65 (m, 2H), 1.43 (h, *J*=7.3 Hz, 2H), 1.01 (t, *J*=7.5 Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 179.14, 145.84, 142.55, 133.28, 132.53, 129.11, 128.48, 125.75, 121.03, 116.55, 111.03, 35.72, 33.54, 22.46, 14.08. HRMS (ESI-TOF) 254.1564 [M+H]⁺ (calculated for C₁₇H₂₀NO = 254.1545).

[00118] **(*E*)-1-(1*H*-pyrrol-3-yl)dec-2-en-1-one, 32.** Prepared according to general procedure A to provide (*E*)-1-(1*H*-pyrrol-3-yl)dec-2-en-1-one as an off-white solid (14.6 mg, 1%) ¹H-NMR (500MHz, CDCl₃) δ 8.64 (s, 1H), 7.49 (m, 1H), 7.05-6.99 (dt, *J*=15.3, 7.0 Hz, 1H), 6.81-6.78 (m, 1H), 6.75-6.73 (m, 1H), 6.68-6.64 (dt, *J*=15.3, 1.5 Hz, 1H), 2.29-2.24 (m, 2H), 1.51-1.46 (m, 2H), 1.29-1.26 (m, 8H), 0.89-0.83 (m, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 185.6, 147.0, 127.0, 126.6, 123.5, 119.6, 109.4, 32.8, 31.9, 29.4, 29.3, 28.5, 22.8, 14.3. HRMS (ESI-TOF) 220.1700 [M+H]⁺ (calculated for C₁₄H₂₂NO = 220.1701).

[00119] **(*E*)-1-(1*H*-pyrrol-2-yl)dec-2-en-1-one, 33.** Prepared according to general procedure A to provide (*E*)-1-(1*H*-pyrrol-2-yl)dec-2-en-1-one as an off-white solid (42.1 mg, 2%). ¹H-NMR (500MHz, CDCl₃) δ 10.13 (s, 1H), 7.13-7.07 (m, 2H), 6.98-6.96 (m, 1H), 6.73 (d, *J*=15.6, 1H), 6.31-6.29 (m, 1H), 2.32-2.27 (m, 2H), 1.54-1.48 (m, 2H), 1.38-1.23 (m, 8H), 0.89 (t, *J*=6.7 Hz, 3H). ¹³C-NMR (125MHz, CDCl₃) δ 179.5, 147.5, 132.8, 125.4, 116.5, 110.8, 32.8, 32.0, 29.4, 29.2, 28.4, 22.8, 14.2. HRMS (ESI-TOF) 220.1723 [M+H]⁺ (calculated for C₁₄H₂₂NO = 220.1701).

[00120] **2-([1,1'-biphenyl]-4-yl)-1-(1*H*-pyrrol-3-yl)ethanone, 34.** Prepared according to general procedure A to provide 2-([1,1'-biphenyl]-4-yl)-1-(1*H*-pyrrol-3-yl)ethanone as an off-white solid (13.4 mg, 2%) ¹H-NMR (500MHz, CDCl₃) δ 8.60 (s, 1H), 7.59-7.53 (m, 4H), 7.49-7.48 (m, 1H), 7.44-7.40 (m, 2H), 7.38-7.31 (m, 3H), 6.79-6.78 (m,

1H), 6.73-6.72 (m, 1H), 4.10 (s, 2H). ¹³C-NMR (125MHz, CDCl₃) δ 193.4, 141.0, 139.7, 134.7, 129.9, 128.9, 127.4, 127.2, 125.7, 123.8, 119.6, 109.5, 46.6. HRMS (ESI-TOF) 262.1228 [M+H]⁺ (calculated for C₁₈H₁₆NO = 262.1232).

[00121] **2-([1,1'-biphenyl]-4-yl)-1-(1H-pyrrol-2-yl)ethanone, 35.** Prepared according to general procedure A to provide 2-([1,1'-biphenyl]-4-yl)-1-(1H-pyrrol-2-yl)ethanone as an off-white solid (175 mg, 20%) ¹H-NMR (500MHz, CDCl₃) δ 9.60 (s, 1H), 7.58-7.54 (m, 4H), 7.45-7.32 (m, 4H), 7.36-7.32 (m, 1H), 7.06-7.04 (dd, *J*=4.5, 2.5 Hz, 2H), 6.32-6.30 (m, 1H), 4.11 (s, 2H). ¹³C-NMR (125MHz, CDCl₃) δ 187.8, 141.0, 139.9, 134.2, 131.7, 129.9, 128.9, 127.5, 127.3, 127.2, 125.1, 117.1, 111.1, 44.6. HRMS (ESI-TOF) 262.1235 [M+H]⁺ (calculated for C₁₈H₁₆NO = 262.1232).

[00122] References

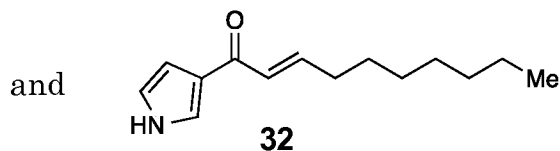
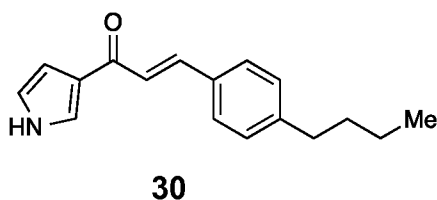
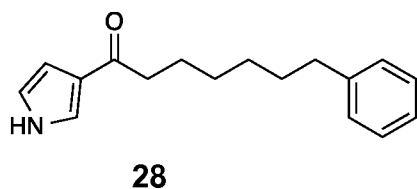
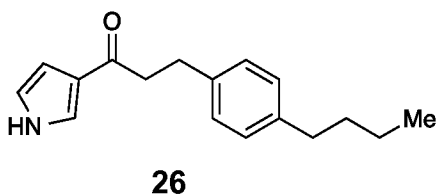
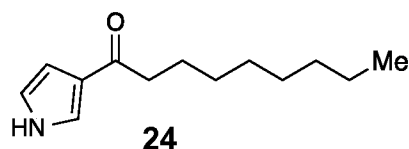
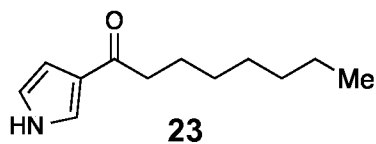
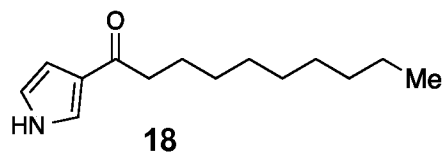
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[00123] Various modifications and variations of the invention in addition to those shown and described herein will be apparent to those skilled in the art without departing from the scope and spirit of the invention and fall within the scope of the appended claims. Although the invention has been described in connection with specific

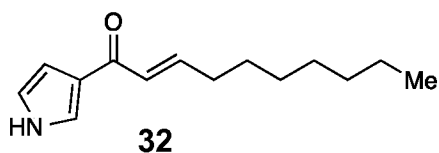
preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. All publications and patents mentioned in the above specification are incorporated in their entirety by reference.

CLAIMS

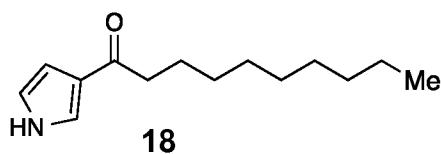
1. A 3-acyl pyrrole compound having one of the structures of the group consisting of:



2. The compound of claim 1 that is



3. The compound of claim 1 that is



4. A pharmaceutical composition comprising one or more compounds of claim 1 and a pharmaceutically acceptable carrier, excipient or diluent.

5. A method of treating a bacterial infection of Gram-negative quorum sensing bacteria, comprising administering to a subject one or more compounds of claim 1.

6. The method of claim 5 that is prophylactic treatment prior to bacterial infection.

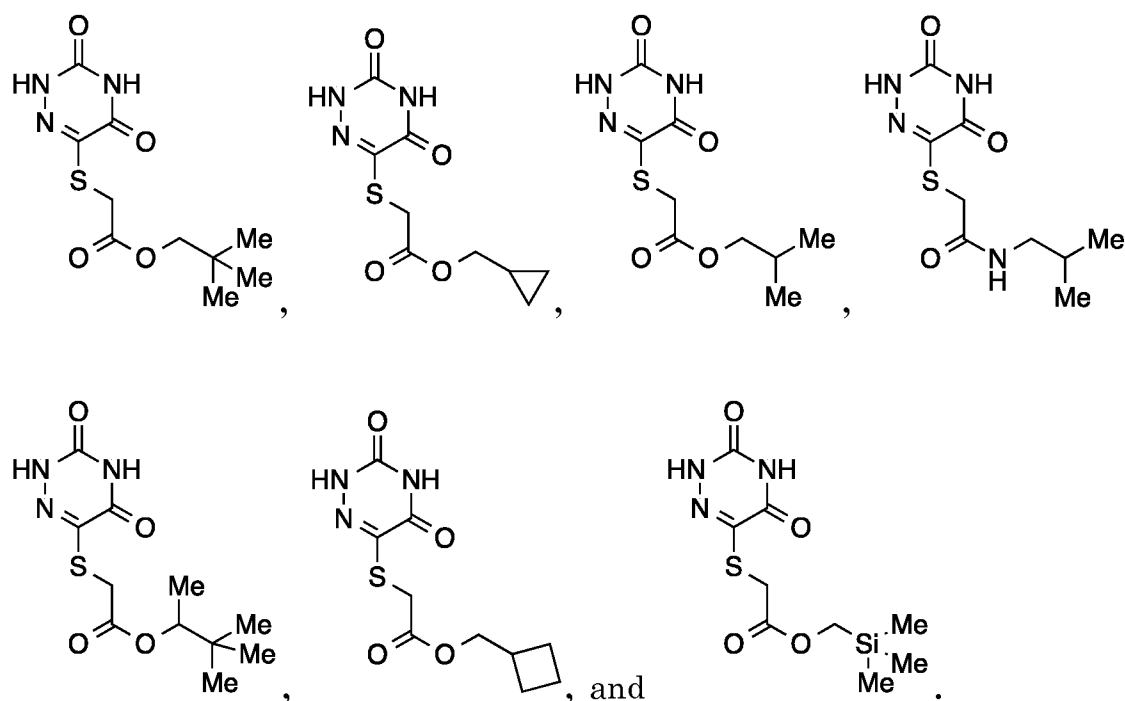
7. The method of claim 5 that is active treatment of bacterial infection.

8. The method of claim 5 also comprising the step of contacting the bacteria with an

antibiotic.

9. The method of claim 5 also comprising the step of contacting the bacteria with a LuxO inhibitory molecule.

10. The method of claim 9 wherein the LuxO inhibitory molecule is a compound from the group consisting of:



11. A method of inhibiting virulence in Gram-negative bacteria comprising contacting the bacteria with one or more compounds of claim 1.

12. The method of claim 11 wherein the bacteria are pathogenic to marine life and the compound or compounds are administered to the marine life as a feed additive.

13. A bacterial biofilm-inhibiting composition comprising one or more compounds of claim 1.

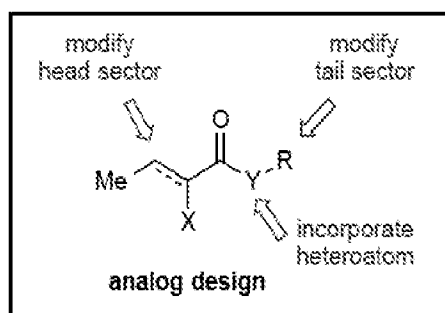
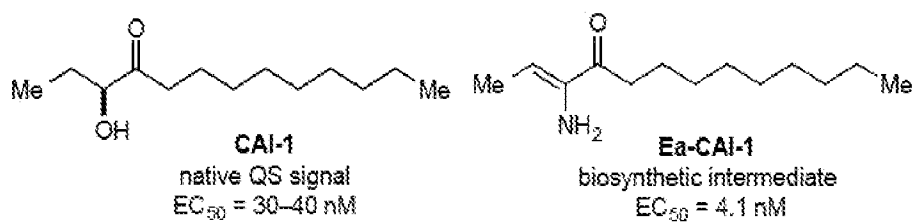
14. A method of controlling quorum sensing Gram-negative bacteria on a surface, comprising exposing the bacteria to one or more compounds of claim 1, in an amount that affects biofilm formation.

15. The method of claim 14 wherein the surface is a solid.

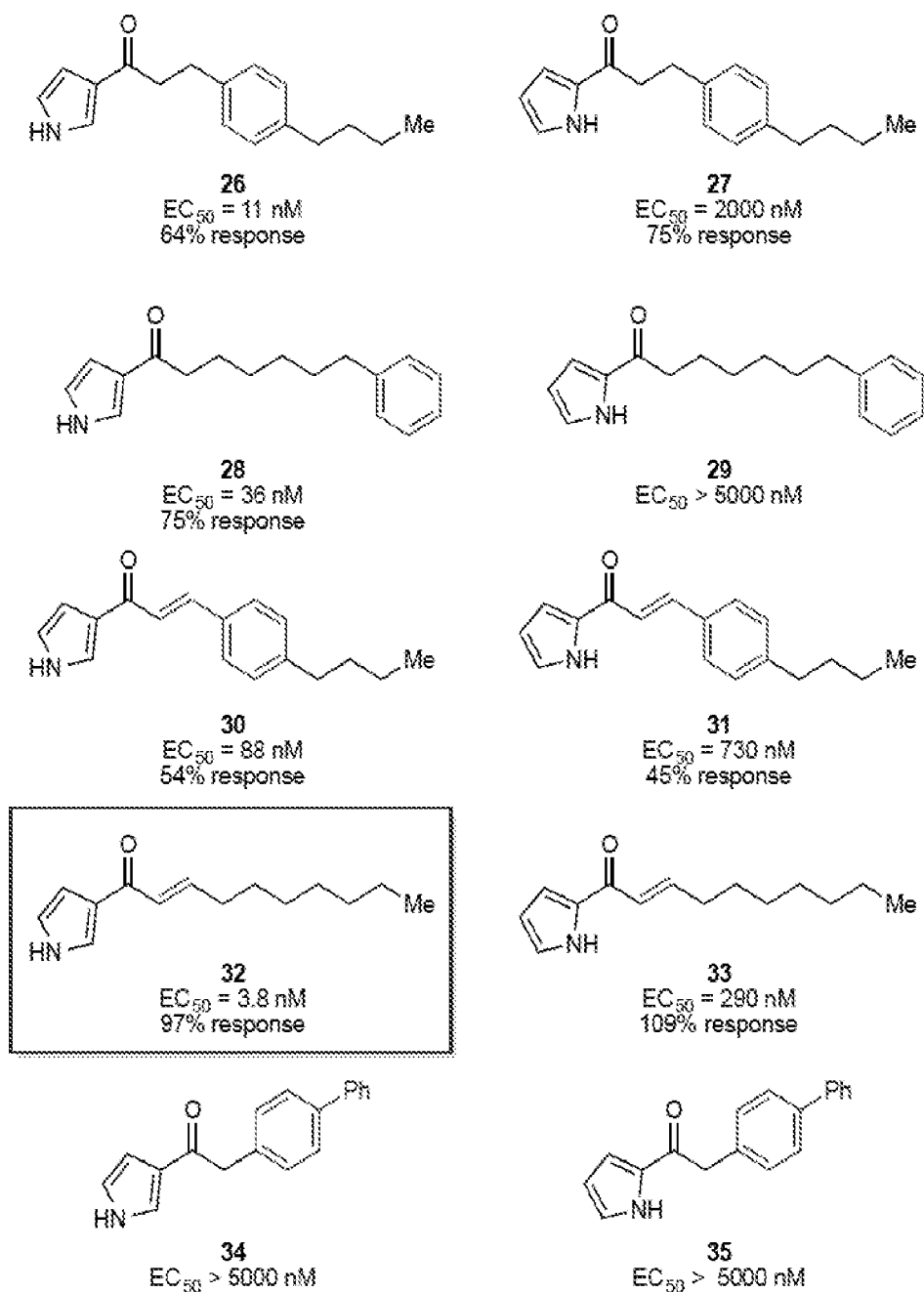
16. A device that is coated or embedded with one or more compounds of claim 1 to

prevent bacterial biofilm formation or bacterial transmission.

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**Figure 1.**

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**Figure 2.**

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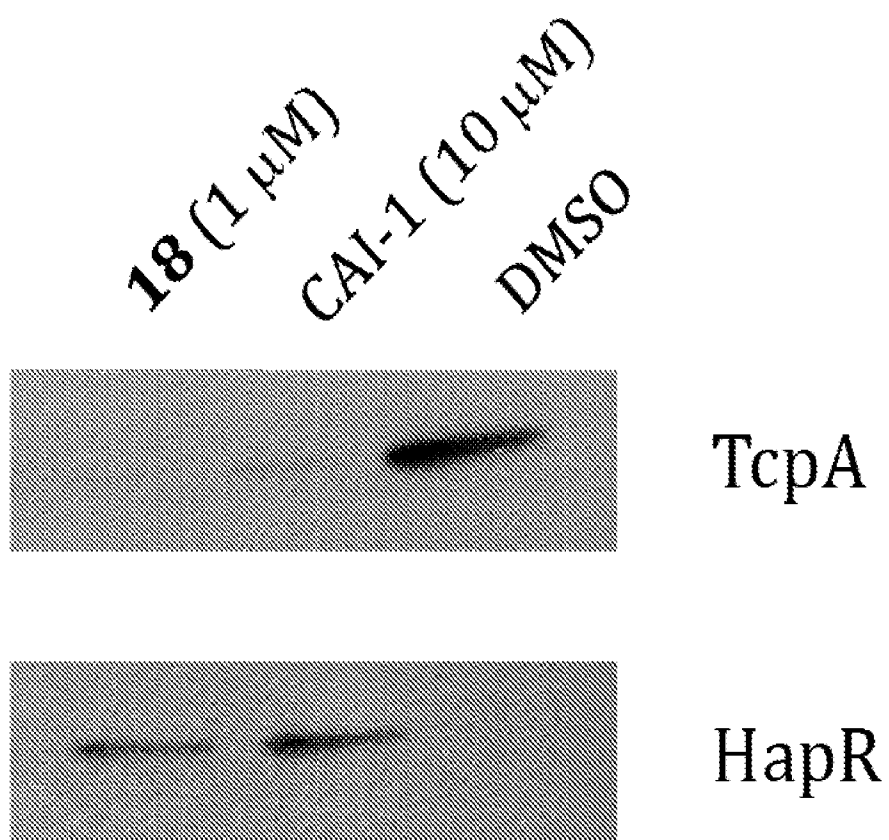


Figure 3.

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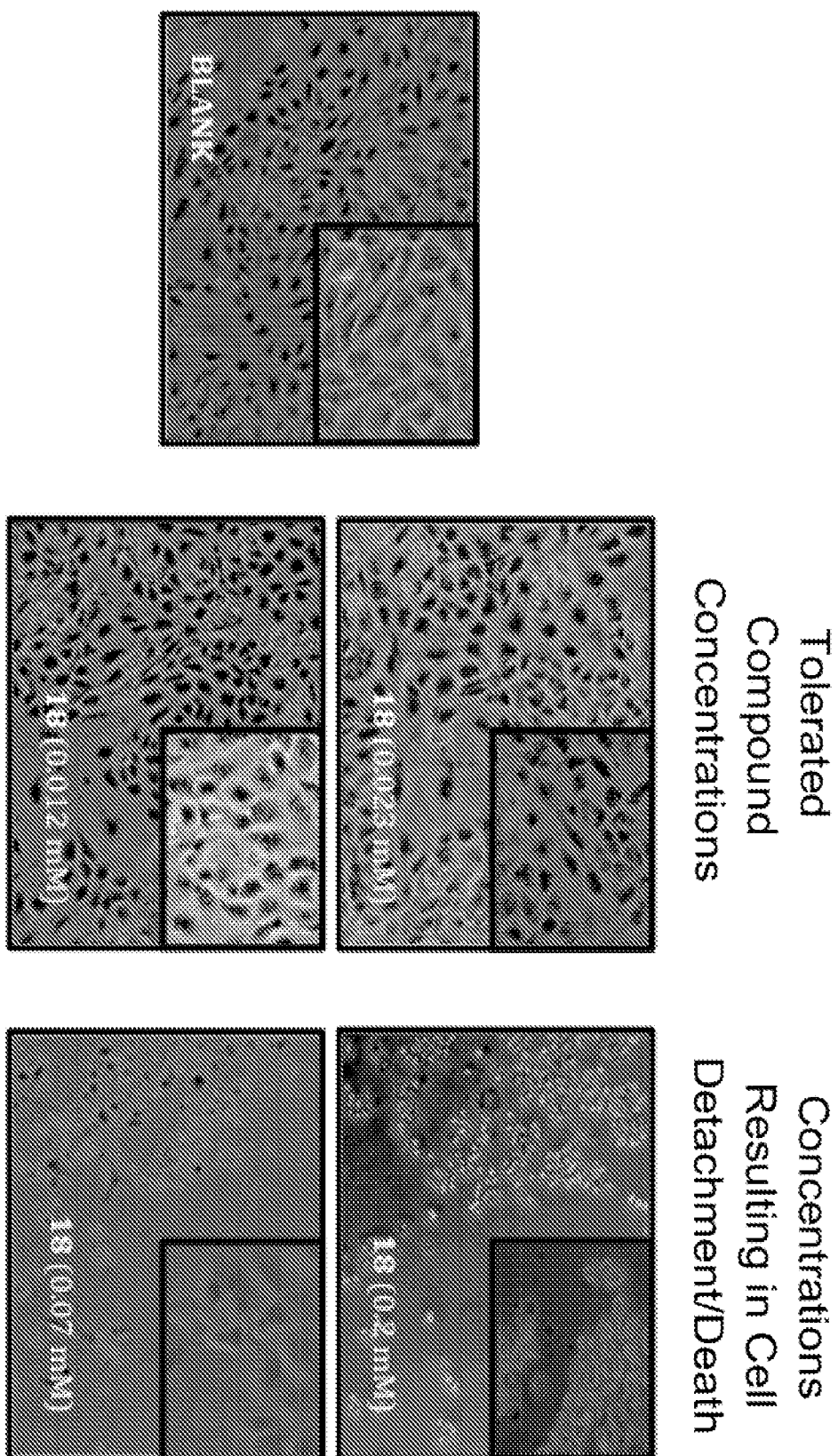


Figure 4

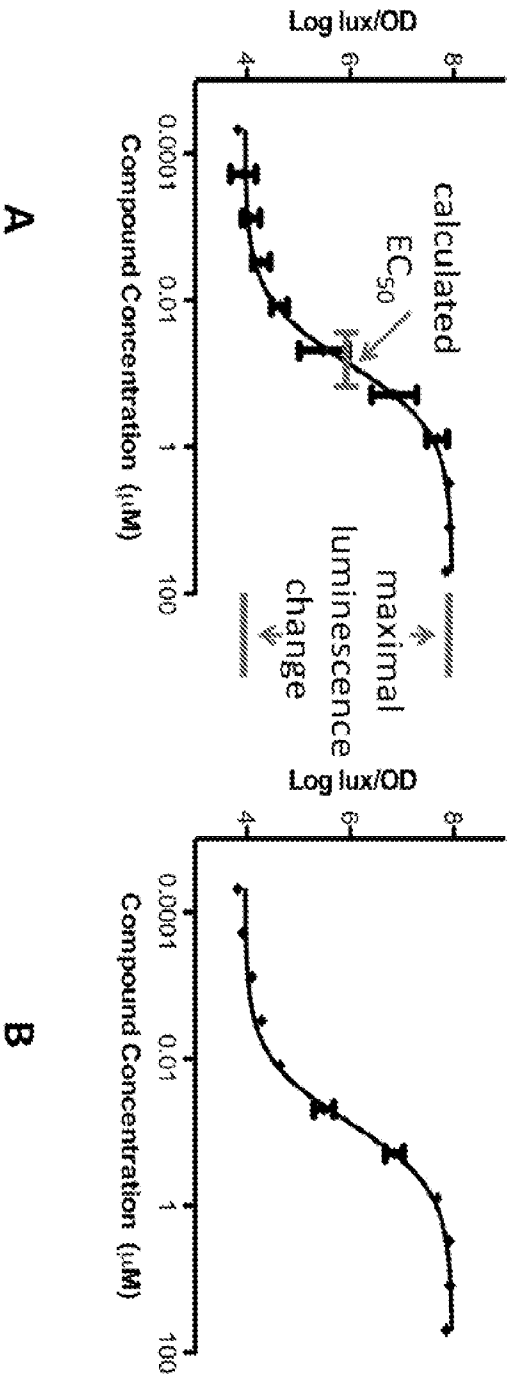
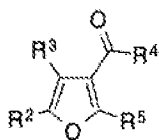
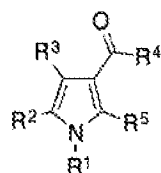


Figure 5

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A.



R¹ = H, alkyl, aryl
 R² = H, alkyl, aryl, halogen (F, Cl, Br, I)
 R³ = H, alkyl, aryl, halogen (F, Cl, Br, I)
 R⁴ = alkyl, aryl
 R⁵ = H, alkyl, aryl, halogen (F, Cl, Br, I)

B.

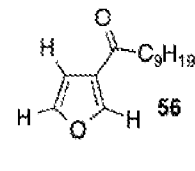
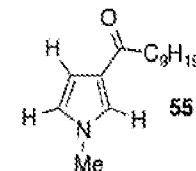
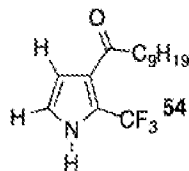
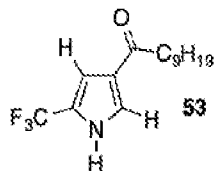
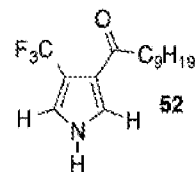
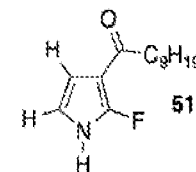
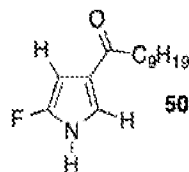
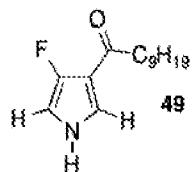
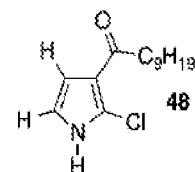
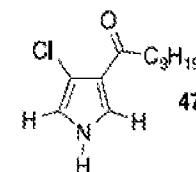
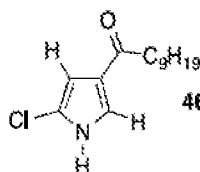
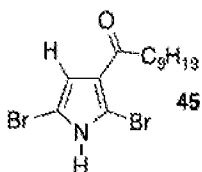
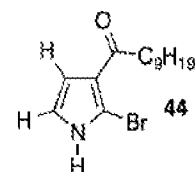
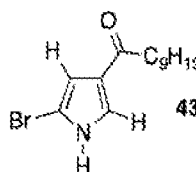
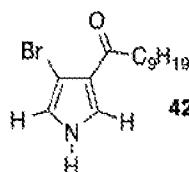
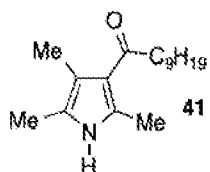
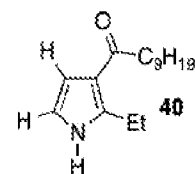
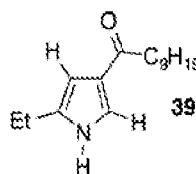
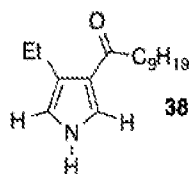
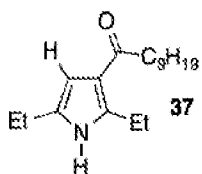
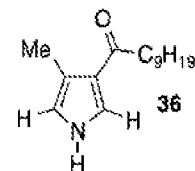
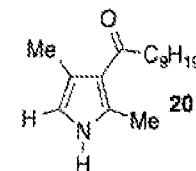
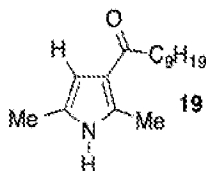
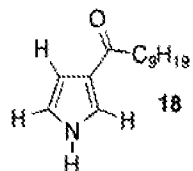


Figure 6

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1. Acylation

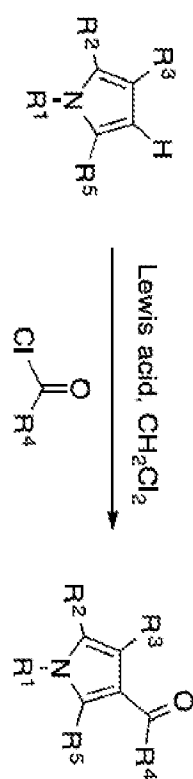
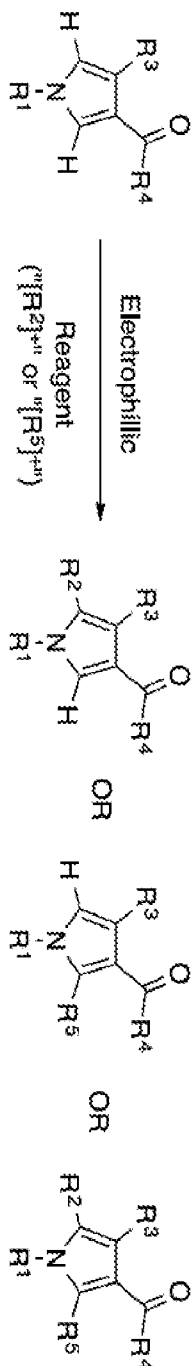
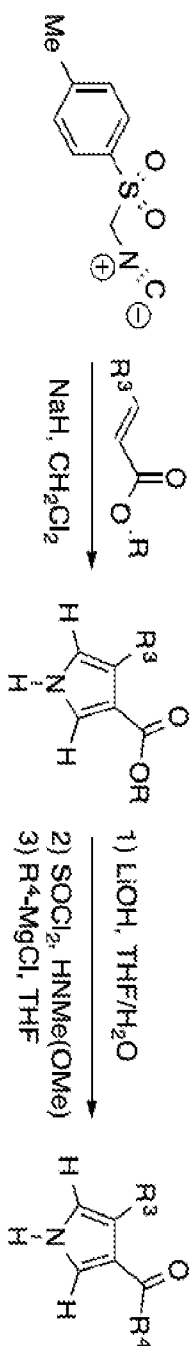


Figure 7

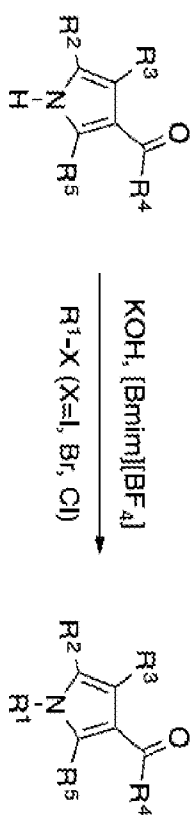
2. Functionalization of 3-Acyl Pyrrole



3. Direct Pyrrole Construction



4. N-Substitution



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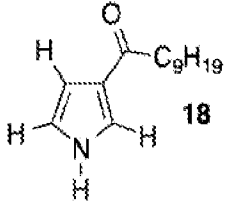
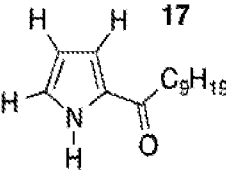
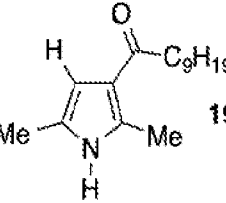
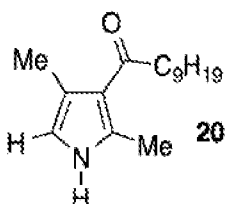
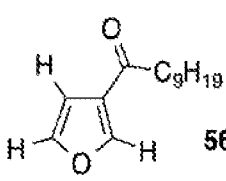
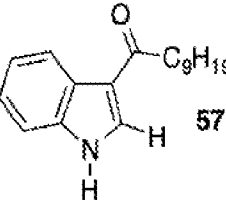
	EC ₅₀ (nM)	% Inhibition
 18	13.3 ^a	91% ^a
 17	5160 ^a	91% ^a
 19	679 ^a	64% ^a
 20	536 ^a	62% ^a
 56	409	82%
 57	>50000	18% ^b

Figure 8

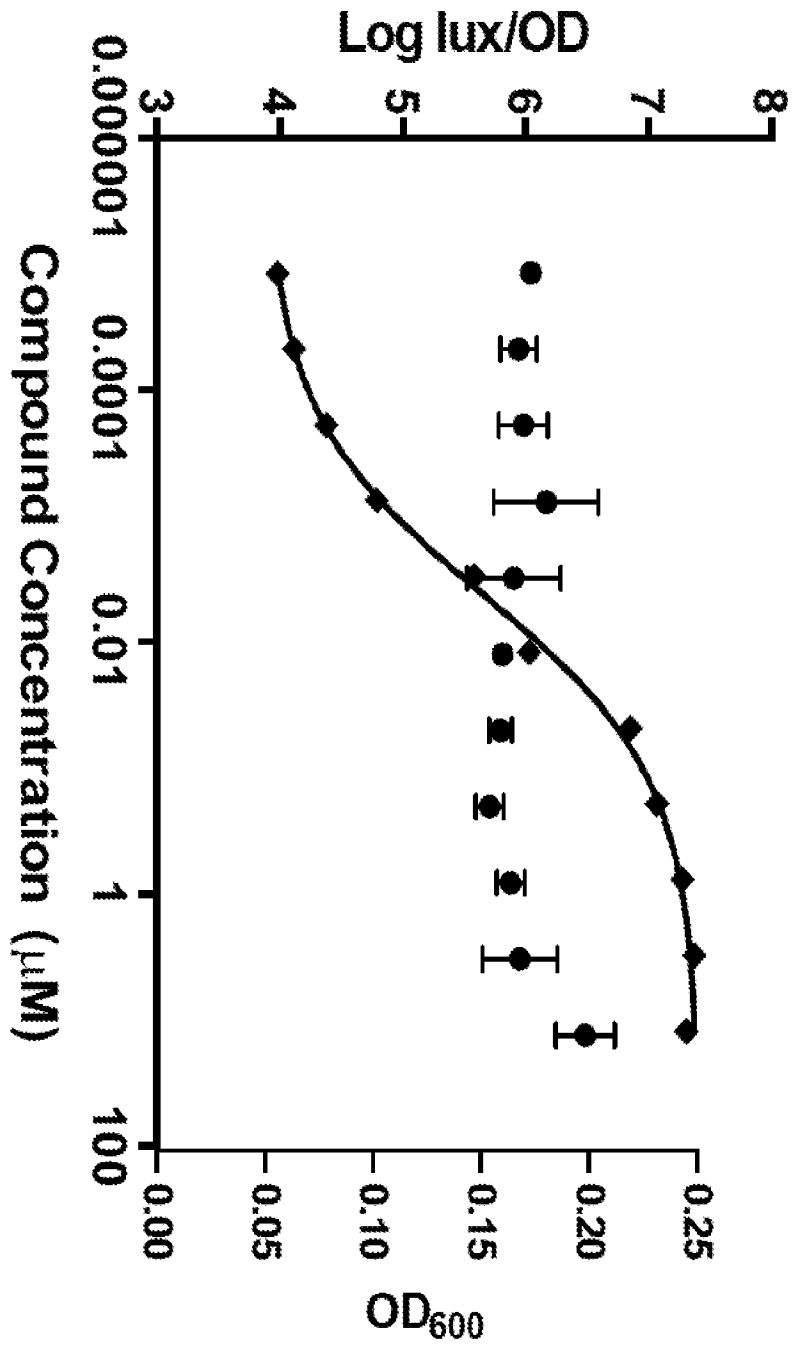


Figure 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/51648

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/40; A61P 31/04; C07D 207/333 (2014.01) CPC - C07D 207/325; C07D 207/333; A61K 31/40 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC(8): A61K 31/40; A61P 31/04; C07D 207/333 (2014.01) CPC: C07D 207/325; C07D 207/333; A61K 31/40 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 514/423; 548/524; 548/517; 548/527; 548/539 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, Google Scholar, PubWEST, SureChem 3-acylpyrrole, 3-decanoyl, 3-octanoyl, 3-dodecanoyl, pyrrole, quorum sensing, antibacterial, bacterial infection, treat, Vibrio cholerae, 1-(1H-pyrrol-3-yl)decan-1-one		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PuBChem-CID 65448370 - Create Date: 24 October 2012 (24.10.2012) pg 1	1, 3
Y		2, 4-16
Y	US 2010/0273890 A1 (BASSLER et al.) 28 October 2010 (28.10.2010) abstract; Fig 13a-13c; para [0006]-[0009]	2, 4-16
Y	US 2012/0322769 A1 (YANG et al.) 20 December 2012 (20.12.2012) para [0007]-[0008], [0171], [0269], [0274], [0301]-[0302], [0326]	2, 4-16
Y	PUBCHEM-CID 682135 - Creat Date: 08 July 2005 (08.07.2005) pg 1, Figure	10
Y	US 6,777,420 B2 (Zhi et al.) 17 August 2004 (17.08.2004) Fig 2A, 3A; col 6, ln 26-37; col 7, ln 6-46; col 9, ln 38-52; col 12, ln 39-44	10
☐ Further documents are listed in the continuation of Box C. ☐		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 31 December 2014 (31.12.2014)		Date of mailing of the international search report 12 JAN 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774