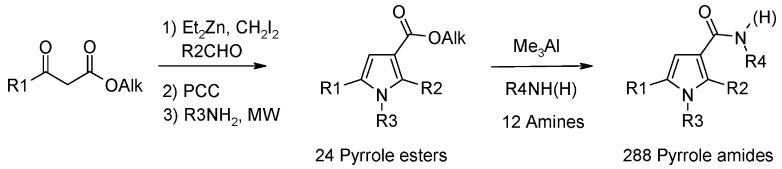
JOURNAL OF combinatorial CHEMISTRY

Article

Solution Phase Synthesis of a Library of Tetrasubstituted Pyrrole Amides

Ivana Bianchi, Roberto Forlani, Giacomo Minetto, Ilaria Peretto, Nickolas Regalia, Maurizio Taddei, and Luca F. Raveglia

J. Comb. Chem., **2006**, 8 (4), 491-499• DOI: 10.1021/cc060008q • Publication Date (Web): 16 May 2006



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 3 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Solution Phase Synthesis of a Library of Tetrasubstituted Pyrrole Amides

Ivana Bianchi, Roberto Forlani, Giacomo Minetto,[§] Ilaria Peretto, Nickolas Regalia, Maurizio Taddei,[§] and Luca F. Raveglia*

NiKem Research, via Zambeletti 25, 20021 Baranzate, Milan, Italy

Received January 25, 2006

An efficient strategy for the solution-phase parallel synthesis of a library of pyrrole-amides is described. Key reactions include functional homologation of β-ketoesters with a set of aldehydes followed by oxidation to produce a series of differently substituted 1,4-dicarbonyl compounds. Rapid cyclization using a microwave-assisted Paal−Knorr reaction provided a set of 24 pyrrole esters that were further functionalized through a trimethylaluminum-mediated aminolysis to obtain a larger library of 288 diverse pyrrole-3-amides. The tetrasubstitution allows a good exploration of the chemical space around the central pyrrole core. The last step was entirely automated with a Bohdan Myriad personal synthesizer.

Introduction

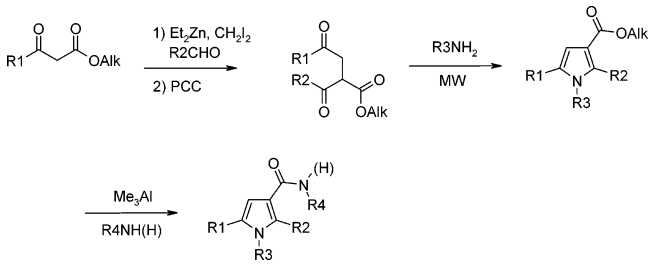
Combinatorial synthesis of small organic molecules carried out both on a solid phase and in solution has become, in recent years, a powerful tool for the rapid identification of novel lead compounds and for the optimization of their biological activity. Among the broad range of templates, heterocyclic molecules represent the most utilized scaffolds for the discovery of novel synthetic drugs.[1] As reported in recent communications, the pyrrole moiety can be found both in natural and synthetic pharmaceutical products.[2] In particular, tetrasubstituted pyrroles have been reported to play an important role as antibacterial, antiviral, anti-inflammatory, and antioxidant agents.[3] For this reason, compounds bearing the pyrrole moiety are of particular interest for the development of a primary, nonfocused, library. Their biological interest notwithstanding, not many combinatorial approaches to pyrrole libraries can be found in the literature.[4]

Paal−Knorr cyclocondensation of 1,4-diketones with amines represents one of the most common approaches to pyrrole synthesis.[2a,5] This strategy has also been utilized for the preparation of pyrrole libraries, both in solution[6] and on the solid phase.[7] In the Paal−Knorr reaction, the 1,4-dicarbonyl compound provides the four carbon atoms with their substituents and the amine provides the pyrrole nitrogen with its substituent. The main limitations preventing extensive use of this method are the harsh conditions required for the cyclization and the low availability of nonsymmetrically substituted 1,4-dicarbonyl compounds. Nevertheless, Minetto and co-workers[8] recently reported straightforward access to pyrrols via Paal−Knorr condensation: 1,4-dicarbonyl compounds are easily prepared by homologation of commercially available β-ketoesters with aldehydes, followed by oxidation, and the following Paal−Knorr cyclization is accelerated under microwave irradiation.

* To whom correspondence should be addressed. E-mail: luca.raveglia@nikemresearch.com.

§ Dipartimeto Farmaco Chimico Tecnologico, Università di Siena, Via A Moro, 53035 Siena, Italy.

Scheme 1. General Scheme for the Synthesis of the Tetra-substituted Pyrrole Amide Library



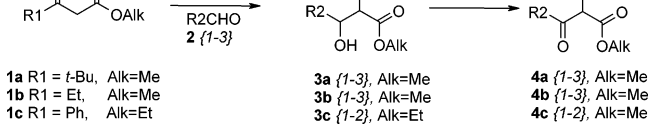
In this article, we report a successful solution-phase strategy for the parallel synthesis of a tetrasubstituted pyrrole amide library. In our approach, the initial array of pyrrole esters was obtained following the report by Minetto, and the final amide library was prepared through a trimethylaluminum-mediated aminolysis. The general synthetic pathway is depicted in Scheme 1.

Results and Discussion

The synthesis of the initial array of 24 tetrasubstituted pyrrole esters was accomplished as reported in Schemes 2 and 3.

The homologation reaction, starting from the commercially available methyl or ethyl β-ketoesters **1a**, **1b**, and **1c** (Scheme 2), was performed using Et_2Zn, CH_2I_2, and aldehydes

Scheme 2. Synthesis of 1,4-diketones[a]



[a] Reagents and conditions: (i) Et_2Zn, CH_2I_2 followed by R2CHO, SiO_2. (ii) PCC, CH_2Cl_2, SiO_2.

2{*1*−*3*} (Figure 1).

10.1021/cc060008q CCC: $33.50
Published on Web 05/16/2006

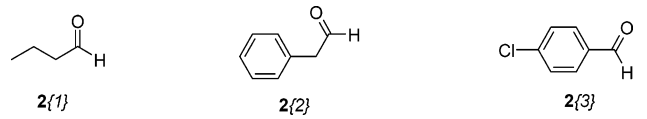
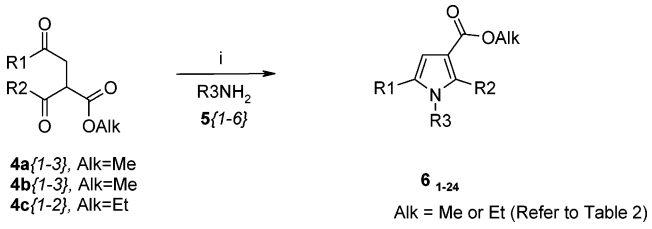


Figure 1. Structure of aldehydes **2**{*1*−*3*} (R2CHO).

Scheme 3. Paal−Knorr Cyclization[a]



[a] Reagents and conditions: (i) $R3NH_2$, AcOH, MW, 170 °C, 12 min, 150 W.

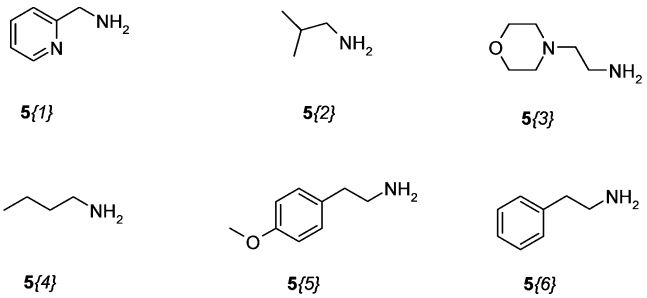


Figure 2. Structure of amines **5**{*1*−*6*}.

Table 1. Yields of 1,4-Dicarbonyl Compounds

	R1	R2	Alk	yield (%)
4a{*1*}	*t*-Bu	*n*-Pr	Me	85
4a{*2*}	*t*-Bu	$PhCH_2$	Me	80
4a{*3*}	*t*-Bu	*p*-Cl−Ph	Me	82
4b{*1*}	Et	*n*-Pr	Me	91
4b{*2*}	Et	$PhCH_2$	Me	90
4b{*3*}	Et	*p*-Cl−Ph	Me	92
4c{*1*}	Ph	*n*-Pr	Et	85
4c{*2*}	Ph	$PhCH_2$	Et	90

The reaction mixture obtained after the addition of the aldehyde was quenched with silica gel, stirred for 30 min, and filtered under vacuum. After removal of the solvent, the crude product was directly submitted to the following oxidative step. The oxidation reaction was accomplished using a solution of freshly prepared pyridinium chlorocromate (PCC)[9] in CH_2Cl_2 at room temperature for 12−24 h. Compounds **4a**{*1*−*3*}, **4b**{*1*−*3*}, and **4c**{*1*−*2*} were isolated as crude products that were used in the following step after a quick filtration on a short pad of silica gel. This procedure yielded pure 1,4-dicarbonyl compounds without aqueous workup, thus avoiding hydrolysis. The yields of the 1,4-dicarbonyl compounds thus obtained are reported in Table 1.

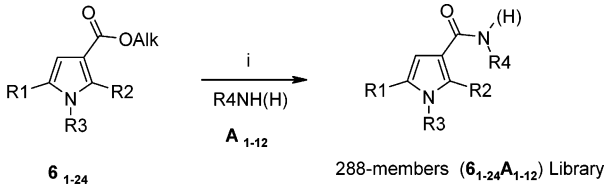
The following Paal−Knorr cyclization of the 1,4-diketoesters was performed in the presence of a set of amines **5**{*1*−*6*} (Figure 2) and acetic acid in a sealed tube under microwave irradiation at 170 °C for 12 min at 150 W (Scheme 3). The workup entailed the addition of a saturated $NaHCO_3$ solution, extraction with ethyl acetate, and flash chromatographic purification.

Table 2. Structures and Yields of the Pyrrole Esters $\mathbf{6}_{1-24}$

	R1	R2	R3	Alk	HPLC purity %[a]	yield (%)
$\mathbf{6}_1$	*t*-Bu	*n*-Pr	pyridin-2-ylmethyl	Me	97.3	84
$\mathbf{6}_2$	*t*-Bu	*n*-Pr	*i*-Bu	Me	96.6	65
$\mathbf{6}_3$	*t*-Bu	*n*-Pr	morpholin-4-ylethyl	Me	99.4	90
$\mathbf{6}_4$	*t*-Bu	$PhCH_2$	pyridin-2-ylmethyl	Me	97.8	77
$\mathbf{6}_5$	*t*-Bu	$PhCH_2$	*i*-Bu	Me	92.9	72
$\mathbf{6}_6$	*t*-Bu	$PhCH_2$	morpholin-4-ylethyl	Me	97.5	75
$\mathbf{6}_7$	*t*-Bu	$PhCH_2$	4-methoxyphenethyl	Me	92.2	97
$\mathbf{6}_8$	*t*-Bu	*p*-Cl−Ph	*i*-Bu	Me	97.0	51
$\mathbf{6}_9$	*t*-Bu	*p*-Cl−Ph	morpholin-4-ylethyl	Me	99.0	49
$\mathbf{6}_{10}$	*t*-Bu	*p*-Cl−Ph	*n*-Bu	Me	98.8	65
$\mathbf{6}_{11}$	Et	*n*-Pr	*i*-Bu	Me	97.0	72
$\mathbf{6}_{12}$	Et	*n*-Pr	morpholin-4-ylethyl	Me	98.4	63
$\mathbf{6}_{13}$	Et	*n*-Pr	phenethyl	Me	98.0	48
$\mathbf{6}_{14}$	Et	$PhCH_2$	*i*-Bu	Me	94.5	60
$\mathbf{6}_{15}$	Et	$PhCH_2$	morpholin-4-ylethyl	Me	96.5	64
$\mathbf{6}_{16}$	Et	$PhCH_2$	4-methoxyphenethyl	Me	97.8	68
$\mathbf{6}_{17}$	Et	*p*-Cl−Ph	pyridin-2-ylmethyl	Me	98.3	61
$\mathbf{6}_{18}$	Et	*p*-Cl−Ph	morpholin-4-ylethyl	Me	93.0	69
$\mathbf{6}_{19}$	Ph	*n*-Pr	*i*-Bu	Et	91.8	69
$\mathbf{6}_{20}$	Ph	*n*-Pr	morpholin-4-ylethyl	Et	98.6	76
$\mathbf{6}_{21}$	Ph	*n*-Pr	phenethyl	Et	90.6	54
$\mathbf{6}_{22}$	Ph	$PhCH_2$	*i*-Bu	Et	95.4	40
$\mathbf{6}_{23}$	Ph	$PhCH_2$	morpholin-4-ylethyl	Et	92.6	47
$\mathbf{6}_{24}$	Ph	$PhCH_2$	phenethyl	Et	94.1	49

[a] HPLC purities are given as area percent (UV) at 254 nm. Conditions are reported in the Experimental Section.

Scheme 4. Weinreb Reaction: Synthesis of the Final Pyrrole Amide Library[a]



Alk = Me or Et (Refer to Table 2)

[a] Reagents and conditions: (i) Me_3Al, R4NH(H), toluene, 16 h, 90 °C.

Not all of the six amines were coupled to all the previously described 1,4-diketoesters, and only some of the possible combinations were selected to synthesize the set of 24 pyrrole esters.

The structures, yields, and purities of the whole pyrrole ester set are reported in Table 2.

The last step of the pyrrole amide library synthesis entailed the trimethylaluminum-mediated direct conversion of pyrrole esters $\mathbf{6}_{1-24}$ (Table 2) into the corresponding amides (Scheme 4) through a Weinreb reaction[10] to avoid any hydrolytic step.

The R4NH(H) amines were selected by an in silico investigation of the diversity and druglikeness of the final compounds with the goal of selecting a set of 12 amines to obtain a 24 × 12 array. A virtual library of 4440 amides was designed from the combination of the previously described 24 pyrrole esters, $\mathbf{6}_{1-24}$, and a set of 185 amines selected from the Available Chemical Directory (ACD).[11] The diversity was determined by first calculating the Cerius[2] combinatorial chemistry default set of molecular descriptors.[12,13] To reduce the influence of highly correlated descriptors, a principal component analysis was conducted on the starting 50 dimensional property space. The cell-based fraction metric was used as selection method for the Monte

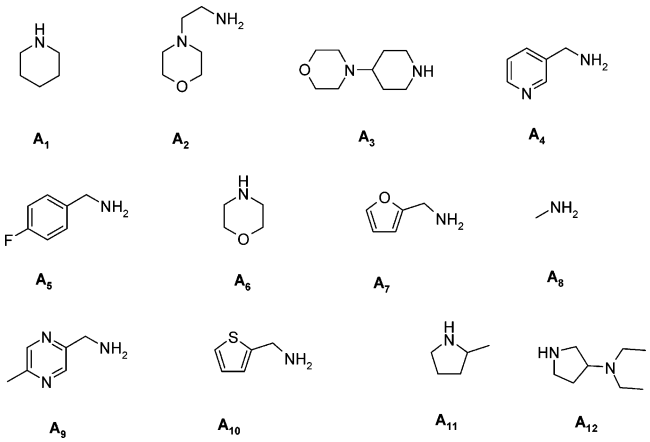


Figure 3. Structure of amines $\mathbf{A_{1-12}}$.

Carlo optimization that was conducted to select the most diverse final compounds: an array-based selection and optimal Lipinski parameters[14] (as an estimate of druglikeness) were imposed. In this way, the set of commercially available amines, $\mathbf{A_{1-12}}$ (Figure 3), was identified.

Different reaction conditions were studied to perform the aminolysis of the esters. The combination of the pyrrole ester $\mathbf{6_{12}}$ with two amines ($\mathbf{A_1}$ and $\mathbf{A_4}$) was explored during the setup to determine yields and purities. The reaction was at first attempted using CH_2Cl_2 as the solvent to simplify the workup. With a standard procedure,[10b] the appropriate amine was initially activated by treatment with an excess of a 2 M solution of trimethylaluminum in hexane (initially 2 equiv) under an inert atmosphere. The mixture was stirred at room temperature in CH_2Cl_2 for 15 min. After activation, a solution of the ester was added at room temperature under an inert atmosphere, and the reaction mixture was heated to reflux overnight. Under these conditions, the reactions did not produce the desired products as shown by LC-MS analysis, which revealed only the presence of unreacted starting material. The use of toluene as the solvent allowed the same reaction to be performed at 90 °C. This simple adjustment resulted in the desired products with both amines being obtained, although, in the case of picolylamine $\mathbf{A_4}$, which is less nucleophilic than piperidine $\mathbf{A_1}$, the conversion was not complete. With the aim of forcing the reaction to completion, the effect of increasing the equivalents of trimethylaluminum was studied. The only drawback to the use of a large excess of the Lewis acid in the reaction was the formation of a white precipitate of aluminum salts during the reaction that made the stirring and, above all, the workup more difficult. We found a reasonable compromise with 5 equiv of trimethylaluminum, obtaining complete conversion with both picolylamine and piperidine without compromising the ease of the workup, essential for its parallelization. The synthesis of the final library was conducted using the automatic Bohdan Myriad personal synthesizer, which offered the additional advantage of maintaining an inert atmosphere during reagent addition, thereby preserving the reactivity of trimethylaluminum. We chose to conduct the library synthesis in 6 runs of 48 simultaneous reactions. In a typical run, the reaction of 4 pyrroles with 12 amines was performed.

With the goal of achieving the final library in the simplest way, the possibility of eliminating the evaporation step was considered. Therefore, the workup was performed with the addition of CH_2Cl_2 and a 2 M solution of NaOH to the reaction to dissolve the aluminum salts. The biphasic mixture thus obtained was consecutively filtered through a phase separator combined with a silica gel cartridge. Thus, it was possible to remove water and purify the compounds eliminating the excess of amine.

According to the procedure described above, it was possible to obtain most of the final products in good to excellent yields and purities without additional chromatographic purification. Generally, we observed that preparative HPLC was required only when the reaction was conducted with amine $\mathbf{A_9}$ as the nucleophile. By applying the aforementioned procedures, we were able to obtain 257 amides out of the planned 288 (89.2% success rate) with an average purity higher than 96% and reaction yields ranging between 40 and 95%. The structures, yields, and purities of a selection of library compounds are reported in Table 3.

The Lipinski profiles of the final library were also calculated and are shown in Figure 4, where they are compared to those of the original virtual library. Lipophilicity was evaluated on the basis of the AlogP98 calculation, as implemented in Cerius[2].[13,15]

As it can be observed from Figure 4, the final library is in good agreement with the Lipinski "Rule of Five", the only issue being the lipophilicity that tends to be on the high side for some of the final compounds. Nevertheless, it can be noted that the applied reagent selection process worked since the average lipophilicity and molecular weight of the final library are much lower than those of the original virtual library.

Conclusion

In conclusion, an efficient synthetic route was developed for the rapid solution-phase combinatorial synthesis of a library of tetrasubstituted pyrrole amides. The tetrasubstitution thus achieved allows a good exploration of the chemical space around the central pyrrole core. The desired products were obtained in medium to high yields and good purities with a simple and parallel workup, making any additional purification superfluous.

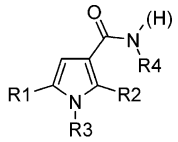
Experimental Section

All reagents were purchased from Sigma-Aldrich (Milan, Italy) and Lancaster (Milan, Italy) in the highest available purity and were used as received. All solvents were purchased from JT Baker and Riedel-de Häen and were used without further purification. The phase separator and silica gel cartridges were purchased from International Sorbent Technology Ltd. (Ystrad Mynach, Hengoed, Mid Glamorgan, U.K.).

LC-MS data were recorded on a Waters ZQ electrospray mass spectrometer equipped with an Alliance HT Waters 2790 separation module and a Waters 996 photodiode array detector using a Luna C18 column (2 × 30 mm, 3 μm).

Method A. Mixture A (95% water, 5% acetonitrile, 0.1% HCOOH)/Mixture B (5% water, 95% acetonitrile, 0.1% HCOOH) were used as eluents as follows: 0−2min, 100% mixture A; 2−5 min, 100−0% mixture A (linear gradient);

Table 3. Characterization of a Selection of Compounds of the Final Amide library



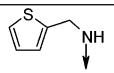
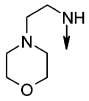
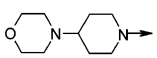
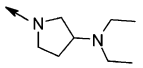
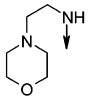
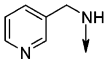
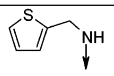
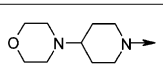
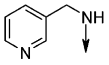
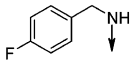
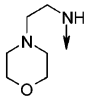
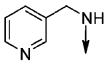
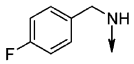
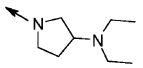
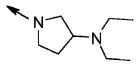
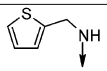
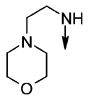
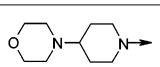
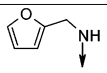
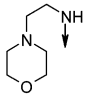
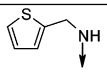
Cpd N.	R1	R2	R3	N(H)R4	LC-MS purity %[a]	Yield %
6$_1$-A$_{10}$	*t*-Bu	*n*-Pr	Pyridin-2-ylmethyl		99	65
6$_3$-A$_2$	*t*-Bu	*n*-Pr	Morpholin-4-ylethyl		99	66
6$_4$-A$_1$	*t*-Bu	CH_2Ph	Pyridin-2-ylmethyl		99.2	90
6$_4$-A$_3$	*t*-Bu	CH_2Ph	Pyridin-2-ylmethyl		99	50
6$_4$-A$_{12}$	*t*-Bu	CH_2Ph	Pyridin-2-ylmethyl		91.6	50
6$_6$-A$_2$	*t*-Bu	CH_2Ph	Morpholin-4-ylethyl		97.7	54
6$_6$-A$_4$	*t*-Bu	CH_2Ph	Morpholin-4-ylethyl		95.5	62
6$_6$-A$_{10}$	*t*-Bu	CH_2Ph	Morpholin-4-ylethyl		99	62
6$_7$-A$_3$	*t*-Bu	CH_2Ph	4-Methoxyphenethyl		99	83
6$_8$-A$_4$	*t*-Bu	*p*-Cl-Ph	*i*-Bu		99	56
6$_{10}$-A$_5$	*t*-Bu	*p*-Cl-Ph	*n*-Bu		99	90
6$_{11}$-A$_2$	Et	*n*-Pr	*i*-Bu		99.2	65
6$_{13}$-A$_1$	Et	*n*-Pr	Phenethyl		99.1	40
6$_{13}$-A$_4$	Et	*n*-Pr	Phenethyl		99	42
6$_{15}$-A$_5$	Et	CH_2Ph	Morpholin-4-ylethyl		99	93
6$_{15}$-A$_{12}$	Et	CH_2Ph	Morpholin-4-ylethyl		99	53
6$_{16}$-A$_8$	Et	CH_2Ph	4-Methoxyphenethyl		89	50

Table 3. (Continued)

$\mathbf{6}_{17}$-$\mathbf{A}_1$	Et	*p*-Cl-Ph	Pyridin-2-ylmethyl		92.3	50
$\mathbf{6}_{17}$-$\mathbf{A}_8$	Et	*p*-Cl-Ph	Pyridin-2-ylmethyl		99.1	50
$\mathbf{6}_{17}$-$\mathbf{A}_{12}$	Et	*p*-Cl-Ph	Pyridin-2-ylmethyl		98.7	36
$\mathbf{6}_{18}$-$\mathbf{A}_8$	Et	*p*-Cl-Ph	Morpholin-4-ylethyl		98.6	77
$\mathbf{6}_{18}$-$\mathbf{A}_{10}$	Et	*p*-Cl-Ph	Morpholin-4-ylethyl		99	85
$\mathbf{6}_{20}$-$\mathbf{A}_2$	Ph	*n*-Pr	Morpholin-4-ylethyl		99.4	69
$\mathbf{6}_{20}$-$\mathbf{A}_8$	Ph	*n*-Pr	Morpholin-4-ylethyl		99.4	90
$\mathbf{6}_{21}$-$\mathbf{A}_3$	Ph	*n*-Pr	Phenethyl		98.7	45
$\mathbf{6}_{21}$-$\mathbf{A}_7$	Ph	*n*-Pr	Phenethyl		99.2	45
$\mathbf{6}_{22}$-$\mathbf{A}_2$	Ph	CH_2Ph	*i*-Bu		98.6	63
$\mathbf{6}_{24}$-$\mathbf{A}_{10}$	Ph	CH_2Ph	Phenethyl		99.6	33

[a] LC-MS purities are given as area percent (UV) at 215 nm. Conditions are reported in the Experimental Section.

5−8 min, 0% mixture A; 8−8.1 min, 0−100% mixture A (stepdown gradient); 8.1−10 min, 100% mixture A.

Method B. Mixture A (95% ammonium acetate 10 mM, 5% acetonitrile)/Mixture B (5% ammonium acetate 10 mM, 95% acetonitrile) were used as eluents as follows: 0−2 min, 100% mixture A; 2−5 min, 100−0% mixture A (linear gradient); 5−9 min, 0% mixture A; 9−9.1 min, 0−100% mixture A (stepdown gradient); 9.1−11 min, 100% mixture A.

The HPLC data were recorded on a Shimadzu VP-5 auto injector equipped with an LC-10 AS separation module and a Shimadzu SPD-M10A diode array detector using a Symmetry C18 column (4.6 × 75 mm, 3 μm). Mixture A (95% water, 5% acetonitrile, 0.05% CF_3COOH)/Mixture B (5% water, 95% acetonitrile, 0.05% CF_3COOH) were used as eluents as follows: 0−0.1 min, 95% mixture A; 0.1−9 min, 95−0% mixture A (linear gradient); 9−12 min, 0% mixture A; 12−12.1 min, 0−95% mixture A (stepdown gradient); 12.1−15 min, 95% mixture A.

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 MHz instrument; chemical shifts were quoted in parts per million and referred to the solvent used. Paal−Knorr cyclizations were performed in a CEM Discover microwave reactor. Weinreb reactions to achieve the final library were performed with a Bohdan Myriad personal synthesizer, which provided the possibility of automating the reagent addition and conducting parallel reactions in inert atmosphere, thus allowing to the preparation of the final library to be faster.

General Procedure for the Synthesis of 1,4-Diketones. Preparation of 2-Butyryl-5,5-dimethyl-4-oxohexanoic Acid Methyl Ester 4a{*1*}. To a solution of diethyl zinc (1 M solution in hexane, 30 mL) in dry dichloromethane (60 mL) cooled at 0 °C, diiodo methane (2.4 mL, 30 mmol) was added dropwise, and the mixture was stirred under an inert atmosphere for 10 min. 4,4-Dimethyl-3-oxo-pentanoic acid methyl ester (1.15 g, 7.3 mmol) was added, and the reaction mixture was stirred for an additional 30 min. Butyraldehyde (0.55 g, 7.68 mmol) was added, and the mixture was stirred for 1 h. Silica gel (20.0 g) was added to the reaction mixture, and the suspension was stirred at room temperature for an additional 30 min. The mixture was filtered under vacuum, and the solvent was evaporated at reduced pressure. The crude product was dissolved in dry dichloromethane, and PCC (3.3 g, 15.3 mmol) was added; the mixture was stirred at room temperature until TLC analysis showed the disappearance of the starting material (hexanes/AcOEt 99:5, R_f = 0.5). The mixture was loaded onto a short plug of silica gel and eluted with dichloromethane. The solvent was evaporated under vacuum to give 1.42 g of the title

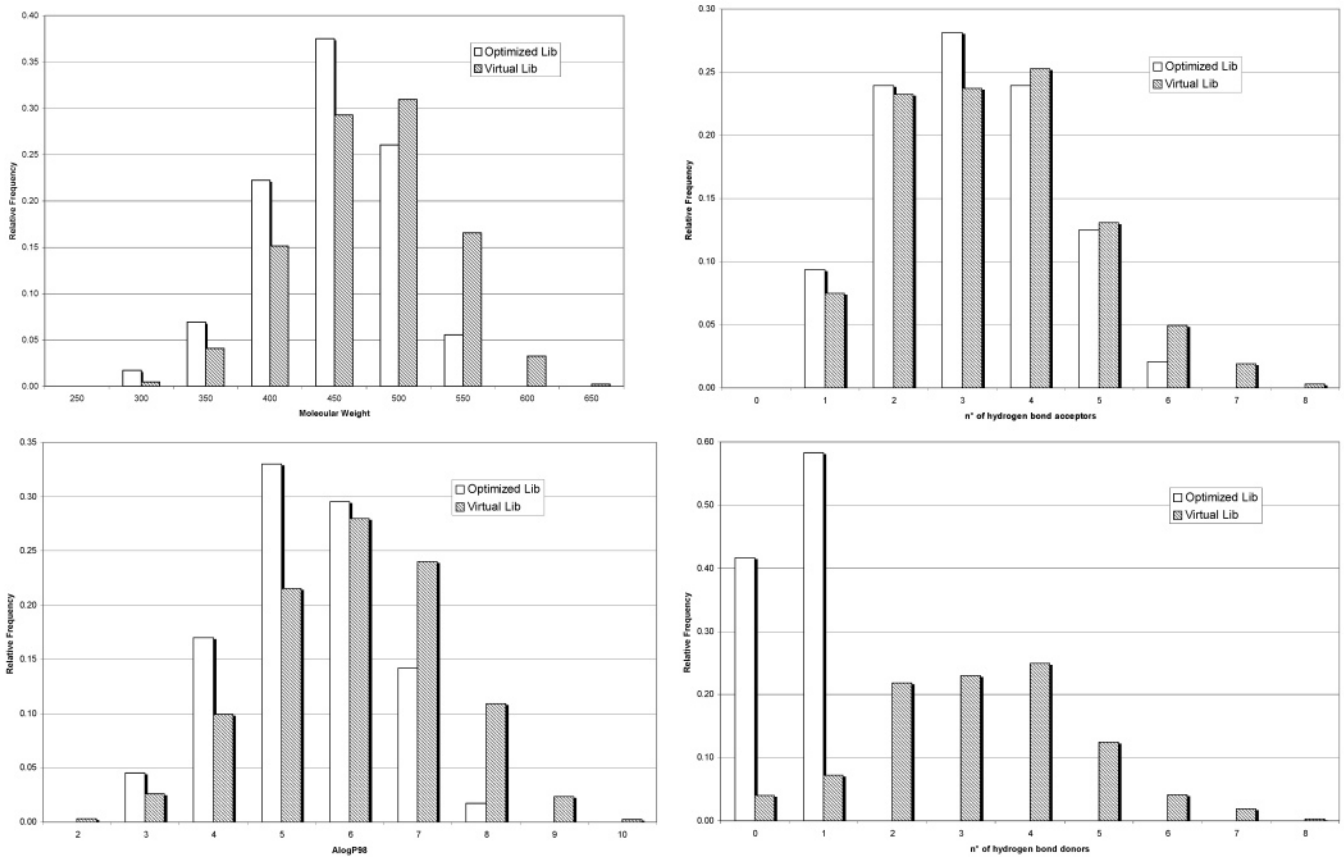


Figure 4. Lipinski profiles of the optimized library compared to the original virtual library.

compound (reaction yield = 85%). Intermediates **4a**{*2*−*3*}, **4b**{*1*−*3*}, and **4c**{*1*−*2*} were prepared via the same procedure.

General Procedure for the Paal−Knorr Reaction. Preparation of 5-*tert*-Butyl-2-propyl-1-pyridin-2-ylmethyl-1*H*-pyrrole-3-carboxylic Acid Methyl Ester 6_1. 2-Butyryl-5,5-dimethyl-4-oxohexanoic acid methyl ester (**4a**{*1*}, 1.5 g, 6.2 mmol) was dissolved in 6 mL of acetic acid. Pyridin-2-ylmethylamine (2.35 g, 21.7 mmol) was added, and the reaction mixture was heated under microwave irradiation (150 W) at 170 °C for 12 min. The reaction mixture was diluted with ethyl acetate (20 mL), and the solvent was washed with a saturated solution of $NaHCO_3$ (3 × 20 mL). The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2 hexanes/AcOEt 9:1); 1.63 g of the pure title compound was isolated (reaction yield = 84%). The purity of $\mathbf{6_1}$ was determined by HPLC (Symmetry column, 97.3%, 254 nm). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.53 (d, J = 5.0 Hz, 1H), 7.73 (ddd, J = 7.9, 7.9, 1.6 Hz, 1H), 7.26 (dd, J = 7.3, 4.7 Hz, 1H), 6.49 (d, J = 7.9 Hz, 1H), 6.25 (s, 1H), 5.39 (s, 2H), 3.68 (s, 3H), 2.62 (m, 2H), 1.30 (m, 2H), 1.19 (s, 9H), 0.78 (t, J = 7.2 Hz, 3H).

Intermediates from $\mathbf{6_2}$ to $\mathbf{6_{24}}$ were prepared following the same procedure. All the intermediates were purified by flash chromatography using hexanes/AcOEt or DCM/MeOH mixtures as eluents.

General Procedure for Weinreb Reaction. Preparation of 5-*tert*-Butyl-2-propyl-1-pyridin-2-ylmethyl-1*H*-pyrrole-3-carboxylic Acid (thiophen-2-ylmethyl)amide 6_1-A_{10}. To a stirred solution of thiophen-2-ylmethylamine (0.03 g, 0.26 mmol) in 1 mL of dry toluene, a 2 M solution of $AlMe_3$ in hexane (1.30 mL, 0.65 mmol) was added at room temperature under an inert atmosphere, and the reaction mixture was allowed to stir at room temperature for 15 min. A solution of 5-*tert*-butyl-2-propyl-1-pyridin-2-ylmethyl-1*H*-pyrrole-3-carboxylic acid methyl ester ($\mathbf{6_1}$, 0.04 g, 0.13 mmol) in dry toluene (2 mL) was added dropwise under an inert atmosphere, and the mixture was heated at 90 °C overnight and then cooled to room temperature. The reaction mixture was diluted with 2 mL of dichloromethane and 2 mL of 2 M NaOH. The crude product was eluted through a phase separator cartridge, and the organic phase was subsequently filtered on a silica gel cartridge to yield the pure final product (33.6 mg, reaction yield = 65%). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.57 (1H, ddd, J = 4.88, 1.73, 0.94 Hz), 7.56 (1H, ddd, J = 7.79, 1.73 Hz), 7.24 (1H, dd, J = 5.35, 1.26 Hz), 7.15 (1H, dd, J = 7.55, 5.03 Hz), 7.04 (1H, dd, J = 3.46, 1.26 Hz), 6.97 (1H, dd, J = 5.35, 3.46 Hz), 6.31 (1H, d, J = 7.87 Hz), 6.07 (1H, s), 6.03 (1H, t, J = 5.82 Hz), 5.39 (2H, s), 4.76 (2H, d, J = 5.66 Hz), 2.70−2.78 (2H, m), 1.44−1.52 (2H, m), 1.23 (9H, s), 0.89 (3H, t, J = 7.24 Hz). LC-MS: m/z 396.5 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

All products belonging to the pyrrole amide library were obtained via the same procedure.

5-*tert*-Butyl-1-(2-morpholin-4-ylethyl)-2-propyl-1*H*-pyrrole-3-carboxylic Acid (2-Morpholin-4-ylethyl)amide (6_3-A_2). ^{1}H NMR (300 MHz, chloroform-*d*): δ 6.33 (1H, br s),

6.03 (1H, br s), 4.09−4.16 (2H, m), 3.71−3.79 (8H, m), 3.46−3.55 (2H, m), 2.88−2.95 (2H, m), 2.50−2.64 (12H, m), 1.59−1.70 (2H, m), 1.38 (9H, s), 1.00 (3H, t, $J = 7.39$ Hz). LC-MS: *m*/*z* 434.6 $[M + H]^+$ (Luna column, method A, 99.0%, 215 nm).

(2-Benzyl-5-*tert*-butyl-1-pyridin-2-ylmethyl-1*H*-pyrrol-3-yl)-piperidin-1-ylmethanone (6_4-A_1). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.51 (1H, ddd, $J = 4.80, 1.81, 0.94$ Hz), 7.47 (1H, td, $J = 7.71, 1.57$ Hz), 7.07−7.18 (4H, m), 7.02 (2H, dd, $J = 8.18, 1.57$ Hz), 6.31 (1H, d, $J = 7.87$ Hz), 6.05 (1H, s), 5.24 (2H, s), 3.89 (2H, s), 3.57−3.63 (4H, m), 1.47−1.71 (6H, m), 1.22 (9H, s). LC-MS: *m*/*z* 416.5 $[M + H]^+$ (Luna column, method B, 99.2%, 215 nm).

(2-Benzyl-5-*tert*-butyl-1-pyridin-2-ylmethyl-1H-pyrrol-3-yl)-(4-morpholin-4-yl-piperidin-1-yl)methanone (6_4-A_3). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.51 (1H, ddd, $J = 4.09, 2.20, 0.94$ Hz), 7.48 (1H, td, $J = 7.79, 1.73$ Hz), 7.05−7.18 (4H, m), 6.98−7.03 (2H, m), 6.32 (1H, d, $J = 7.87$ Hz), 6.05 (1H, s), 5.24 (2H, s), 4.46 (2H, d, $J = 12.27$ Hz), 3.88 (2H, s), 3.68−3.77 (4H, m), 2.77−2.92 (2H, m), 2.50−2.58 (4H, m), 2.43 (1H, t, $J = 11.33$ Hz), 1.86 (2H, d, $J = 11.64$ Hz), 1.33−1.48 (2H, m), 1.22 (9H, s). LC-MS: *m*/*z* 501.6 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

(2-Benzyl-5-*tert*-butyl-1-pyridin-2-ylmethyl-1*H*-pyrrol-3-yl)-(3-diethylaminopyrrolidin-1-yl)methanone (6_4-A_{12}). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.52 (1H, ddd, $J = 4.72, 0.94, 0.79$ Hz), 7.48 (1H, td, $J = 7.79, 1.73$ Hz), 7.02−7.18 (6H, m), 6.29 (1H, d, $J = 7.87$ Hz), 6.18 (1H, s), 5.25 (2H, s), 3.99 (2H, s), 3.84−3.91 (1H, m), 3.74−3.82 (1H, m), 3.49−3.61 (1H, m), 3.36−3.47 (1H, m), 3.17−3.31 (1H, m), 2.58−2.73 (4H, m), 2.06−2.16 (1H, m), 1.77−1.93 (1H, m), 1.22 (9H, s), 1.05 (6H, t, $J = 7.08$ Hz). LC-MS: *m*/*z* 473.6 $[M + H]^+$ (Luna column, method B, 91.6%, 215 nm).

2-Benzyl-5-*tert*-butyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrrole-3-carboxylic Acid (2-Morpholin-4-yl-ethyl)amide (6_6-A_2). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.23 (2H, d, $J = 7.24$ Hz), 7.06−7.18 (3H, m), 6.34 (1H, br s), 6.14 (1H, s), 4.51 (2H, s), 3.94−4.01 (2H, m), 3.65−3.73 (8H, m), 3.48−3.47 (2H, m), 2.43−2.58 (8H, m), 2.35−2.39 (4H, m), 1.37 (9H, s). LC-MS: *m*/*z* 483.6 $[M + H]^+$ (Luna column, method A, 97.7%, 215 nm).

2-Benzyl-5-*tert*-butyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrrole-3-carboxylic Acid (Pyridin-3-ylmethyl)amide (6_6-A_4). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.56 (1H, d, $J = 1.89$ Hz), 8.50 (1H, dd, $J = 5.03, 1.57$ Hz), 7.65 (1H, dt, $J = 7.87, 1.89$ Hz), 7.13−7.25 (4H, m), 7.07 (2H, d, $J = 6.92$ Hz), 6.08 (1H, s), 6.03−6.07 (1H, m), 4.56 (2H, d, $J = 5.98$ Hz), 4.53 (2H, s), 3.98−4.06 (2H, m), 3.64−3.72 (4H, m), 2.44−2.51 (2H, m), 2.36−2.43 (4H, m), 1.36 (9H, s). LC-MS: *m*/*z* 461.6 $[M + H]^+$ (Luna column, method A, 95.5%, 215 nm).

2-Benzyl-5-*tert*-butyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrrole-3-carboxylic Acid (Thiophen-2-ylmethyl)amide (6_6-A_{10}). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.19−7.26 (3H, m), 7.14 (1H, dd, $J = 3.78, 1.26$ Hz), 7.08 (2H, d, $J = 6.92$ Hz), 6.91−7.00 (2H, m), 6.06 (1H, s), 6.01 (1H, t, $J = 5.51$ Hz), 4.72 (2H, d, $J = 5.66$ Hz), 4.54 (2H, s), 3.95−4.02 (2H, m), 3.65−3.70 (4H, m), 2.42−2.50 (2H, m), 2.35−2.41 (4H, m), 1.35 (9H, s). LC-MS: *m*/*z* 466.6 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

{2-Benzyl-5-*tert*-butyl-1-[2-(4-methoxyphenyl)ethyl]-1H-pyrrol-3-yl}-(4-morpholin-4-yl-piperidin-1-yl)methanone (6_7-A_3). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.20−7.27 (2H, m), 7.07−7.17 (3H, m), 7.01 (2H, ddd, $J = 9.05, 2.67, 2.44$ Hz), 6.83 (2H, ddd, $J = 9.12, 2.83, 2.52$ Hz), 5.94 (1H, s), 4.44 (2H, d, $J = 11.33$ Hz), 4.19 (2H, s), 3.92−4.00 (2H, m), 3.78 (3H, s), 3.69−3.75 (4H, m), 2.75−2.87 (4H, m), 2.49−2.57 (4H, m), 2.41 (1H, t, $J = 11.17$ Hz), 1.83 (2H, d, $J = 12.27$ Hz), 1.55−1.73 (2H, m), 1.38 (9H, s). ^{13}C NMR (DMSO-d_6): δ 28.6, 30.5, 31.3, 32.3, 36.7, 46.8, 49.8, 55.5, 61.7, 67, 104.7, 114.5, 116.1, 126.5, 128.3, 128.8, 129.9, 130.3, 133.1, 139.7, 140.4, 158.5, 167.1. LC-MS: *m*/*z* 544.7 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

5-*tert*-Butyl-2-(4-chlorophenyl)-1-isobutyl-1H-pyrrole-3-carboxylic acid (Pyridin-3-ylmethyl)amide (6_8-A_4). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.49 (1H, br s), 8.41 (1H, br s), 7.48 (1H, d, $J = 7.55$ Hz), 7.27−7.37 (4H, m), 7.22 (1H, dd, $J = 7.71, 4.88$ Hz), 6.40 (1H, s), 5.45 (1H, t, $J = 5.66$ Hz), 4.39 (2H, d, $J = 5.98$ Hz), 3.83 (2H, d, $J = 8.18$ Hz), 1.42−1.54 (1H, m), 1.40 (9H, s), 0.61 (6H, d, $J = 6.61$ Hz). LC-MS: *m*/*z* 424.9 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

1-Butyl-5-*tert*-butyl-2-(4-chlorophenyl)-1*H*-pyrrole-3-carboxylic Acid 4-Fluorobenzylamide (6_{10}-A_5). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.33−7.39 (2H, m), 7.27−7.32 (2H, m), 6.98−7.05 (2H, m), 6.90−6.98 (2H, m), 6.39 (1H, s), 5.31 (1H, br. s.), 4.31 (2H, d, $J = 5.35$ Hz), 3.78−3.87 (2H, m), 1.39 (9H, s), 1.24−1.36 (2H, m), 1.06 (2H, dq, $J = 14.87, 7.31$ Hz), 0.69 (3H, t, $J = 7.24$ Hz). ^{13}C NMR (DMSO-d_6): δ 13.5, 19.6, 31.1, 32.3, 33, 41.7, 45.1, 105.2, 115.1, 115.3, 116.6, 128.2, 129.4 (d), 132.3, 132.8, 133.3, 134.9, 136.9 (d), 141, 161.4 (d), 164.4. LC-MS: *m*/*z* 441.9 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

5-Ethyl-1-isobutyl-2-propyl-1*H*-pyrrole-3-carboxylic Acid (2-Morpholin-4-ylethyl)amide (6_{11}-A_2). ^{1}H NMR (300 MHz, chloroform-*d*): δ 5.99 (1H, s), 3.70−3.78 (4H, m), 3.57 (2H, d, $J = 7.87$ Hz), 3.50 (2H, q, $J = 5.87$ Hz), 2.88−2.95 (2H, m), 2.48−2.62 (8H, m), 1.99 (1H, tt, $J = 13.88, 7.20$ Hz), 1.52−1.65 (3H, m), 1.27 (3H, t, $J = 7.55$ Hz), 0.98 (3H, t, $J = 7.39$ Hz), 0.89 (6H, d, $J = 6.61$ Hz). ^{13}C NMR (DMSO-d_6): δ 12.9, 14.4, 19.6, 20.0, 23.8, 27.1, 30.0, 36.1, 49.9, 53.8, 58.4, 66.7, 103.8, 113.9, 133.2, 137.0, 165.4. LC-MS: *m*/*z* 350.5 $[M + H]^+$ (Luna column, method A, 99.2%, 215 nm).

(5-Ethyl-1-phenethyl-2-propyl-1*H*-pyrrol-3-yl)-piperidin-1-ylmethanone (6_{13}-A_1). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.23−7.38 (4H, m), 7.12 (1H, d, $J = 1.57$ Hz), 7.10 (1H, s), 5.83 (1H, t, $J = 0.94$ Hz), 3.91−4.02 (2H, m), 3.54−3.65 (4H, m), 2.86−2.96 (2H, m), 2.58−2.67 (2H, m), 2.49 (2H, dq, $J = 7.45, 0.94$ Hz), 1.63−1.72 (3H, m), 1.51−1.63 (4H, m), 1.23 (3H, t, $J = 7.55$ Hz), 0.92 (3H, t, $J = 7.39$ Hz). ^{13}C NMR (DMSO-d_6): δ 12.9, 14.3, 19.1, 23.7, 24.8, 26.3, 26.7, 37.4, 44.7, 63.3, 103.9, 114.7, 126.9, 128.8, 129.2, 132.8, 133.5, 138.8, 167.5. LC-MS: *m*/*z* 353.5 $[M + H]^+$ (Luna column, method B, 99.1%, 215 nm).

5-Ethyl-1-phenethyl-2-propyl-1*H*-pyrrole-3-carboxylic Acid (Pyridin-3-ylmethyl)amide (6_{13}-A_4). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.60 (1H, s), 8.52 (1H, d, J = 4.72 Hz), 7.71 (1H, d, J = 7.87 Hz), 7.27−7.37 (4H, m), 7.12 (2H, d, J = 6.61 Hz), 6.04 (1H, t, J = 5.66 Hz), 5.95 (1H, s), 4.60 (2H, d, J = 5.98 Hz), 3.94−4.01 (2H, m), 2.92 (4H, ddd, J = 11.17, 8.02, 7.87 Hz), 2.45 (2H, q, J = 7.24 Hz), 1.64 (2H, td, J = 15.26, 7.55 Hz), 1.23 (3H, t, J = 7.39 Hz), 1.00 (3H, t, J = 7.39 Hz). ^{13}C NMR (DMSO-d_6): δ 12.7, 14.4, 19.1, 23.8, 26.8, 37.5, 44.6, 103.7, 113.5, 123.8, 126.9, 128.9, 129.2, 133.1, 135.4, 136.6, 137, 138.7, 148.2, 149.2, 165.5. LC-MS: m/z 376.5 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

2-Benzyl-5-ethyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrrole-3-carboxylic Acid 4-Fluorobenzylamide (6_{15}-A_5). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.26−7.31 (3H, m), 7.22 (2H, d, J = 6.61 Hz), 7.11−7.18 (3H, m), 6.96−7.04 (2H, m), 6.03 (1H, s), 6.00 (1H, br. s.), 4.50−4.55 (4H, m), 3.74−3.83 (2H, m), 3.60−3.69 (3H, m), 2.54 (2H, q, J = 7.24 Hz), 2.27−2.34 (4H, m), 2.19−2.27 (2H, m), 1.26 (3H, t, J = 7.55 Hz). LC-MS: m/z = 450.5 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

[2-Benzyl-5-ethyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrrol-3-yl]-(3-diethylaminopyrrolidin-1-yl)methanone (6_{15}-A_{12}). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.11−7.25 (5H, m), 6.02 (1H, s), 4.28 (2H, s), 3.85 (1H, dd, J = 10.54, 7.08 Hz), 3.70−3.80 (2H, m), 3.61−3.67 (4H, m), 3.54 (1H, td, J = 11.01, 6.92 Hz), 3.38 (1H, t, J = 9.91 Hz), 3.20 (1H, s), 2.58−2.70 (4H, m), 2.53 (2H, q, J = 7.45 Hz), 2.27−2.33 (4H, m), 2.18−2.25 (2H, m), 2.04−2.14 (1H, m), 1.72−1.87 (2H, m), 1.24 (3H, t, J = 7.39 Hz), 1.02 (6H, t, J = 7.08 Hz). LC-MS: m/z 467.6 $[M + H]^+$ (Luna column, method B, 99.0%, 215 nm).

2-Benzyl-5-ethyl-1-[2-(4-methoxyphenyl)ethyl]-1*H*-pyrrole-3-carboxylic Acid Methylamide (6_{16}-A_8). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.22−7.29 (3H, m), 7.12−7.19 (3H, m), 6.86 (2H, ddd, J = 8.89, 2.48 Hz), 6.79 (2H, ddd, J = 9.05, 2.40 Hz), 6.03 (1H, s), 4.41 (2H, s), 3.78 (3H, s), 3.74−3.83 (2H, m), 2.93 (3H, s), 2.51−2.58 (2H, m), 2.46 (2H, dq, J = 7.55, 7.39, 0.94 Hz), 1.25 (3H, t, J = 7.39 Hz). LC-MS: m/z = 377.5 $[M + H]^+$ (Luna column, method B, 89.0%, 215 nm).

[2-(4-Chlorophenyl)-5-ethyl-1-pyridin-2-ylmethyl-1*H*-pyrrol-3-yl]-piperidin-1-ylmethanone (6_{17}-A_1). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.49 (1H, ddd, J = 4.88, 1.73, 0.94 Hz), 7.57 (1H, td, J = 7.71, 1.89 Hz), 7.18−7.30 (6H, m), 7.13 (1H, ddd, J = 7.55, 4.72, 0.94 Hz), 6.53 (1H, d, J = 7.87 Hz), 6.19 (1H, t, J = 0.94 Hz), 5.15 (2H, s), 3.32 (2H, br s), 2.43 (2H, qd, J = 7.45, 0.94 Hz), 1.65 (4H, br s), 1.45 (2H, br s, J = 3.78 Hz), 1.21 (3H, t, J = 7.55 Hz). LC-MS: m/z 408.9 $[M + H]^+$ (Luna column, method B, 92.3%, 215 nm).

2-(4-Chlorophenyl)-5-ethyl-1-pyridin-2-ylmethyl-1H-pyrrole-3-carboxylic Acid Methylamide (6_{17}-A_8). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.48 (1H, ddd, J = 4.88, 1.73, 0.94 Hz), 7.58 (1H, td, J = 7.71, 1.89 Hz), 7.32 (2H, ddd, J = 8.65, 2.36, 2.20 Hz), 7.22 (2H, ddd, J = 8.81, 2.20 Hz), 7.14 (1H, ddd, J = 7.47, 4.96, 0.79 Hz), 6.52 (1H, d, J = 7.87 Hz), 6.46 (1H, t, J = 0.94 Hz), 5.27 (1H, br. s.), 4.99 (2H, s), 2.75 (3H, d, J = 4.72 Hz), 2.43 (2H, qd, J = 7.45, 0.94 Hz), 1.23 (3H, t, J = 7.39 Hz). LC-MS: m/z = 354.8 $[M + H]^+$ (Luna column, method B, 99.1%, 215 nm).

[2-(4-Chlorophenyl)-5-ethyl-1-pyridin-2-ylmethyl-1*H*-pyrrol-3-yl]-(3-diethylaminopyrrolidin-1-yl)methanone (6_{17}-A_{12}). ^{1}H NMR (300 MHz, chloroform-*d*): δ 8.49 (1H, ddd, J = 4.80, 1.65, 0.79 Hz), 7.57 (1H, td, J = 7.71, 1.89 Hz), 7.18−7.29 (4H, m), 7.13 (1H, dd, J = 6.76, 4.88 Hz), 6.51 (1H, d, J = 8.18 Hz), 6.24 (1H, s), 5.13 (2H, s), 2.67−3.90 (5H, m), 2.43 (2H, q), 2.38−2.64 (4H, m), 1.88 (1H, m), 1.52−1.77 (1H, m), 1.22 (3H, t, J = 7.55 Hz), 0.97 (6H, br.s). ^{13}C NMR (DMSO-d_6): δ 12.0, 12.7, 19.5, 43.7, 49.2, 106.0, 120.6, 122.9, 128.8, 131.3, 131.7, 132.8, 136.1, 137.6, 149.7, 157.8, 166.0. LC-MS: m/z 466.0 $[M + H]^+$ (Luna column, method B, 98.7%, 215 nm).

2-(4-Chlorophenyl)-5-ethyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrrole-3-carboxylic Acid Methylamide (6_{18}-A_8). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.44 (2H, ddd, J = 8.65, 2.36, 2.20 Hz), 7.33 (2H, ddd, J = 8.65, 2.36, 2.20 Hz), 6.33 (1H, t, J = 0.94 Hz), 5.22 (1H, d, J = 4.72 Hz), 3.72−3.82 (2H, m), 3.55−3.62 (4H, m), 2.73 (3H, d, J = 4.72 Hz), 2.62 (2H, dq, J = 7.45, 0.94 Hz), 2.28−2.36 (2H, m), 2.19−2.26 (4H, m), 1.32 (3H, t, J = 7.39 Hz). LC-MS: m/z 376.9 $[M + H]^+$ (Luna column, method A, 98.6%, 215 nm).

2-(4-Chlorophenyl)-5-ethyl-1-(2-morpholin-4-ylethyl)-1*H*-pyrrole-3-carboxylic Acid (Thiophen-2-ylmethyl)amide (6_{18}-A_{10}). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.35−7.41 (2H, m), 7.27−7.32 (2H, m), 7.17 (1H, dd, J = 5.03, 1.26 Hz), 6.89 (1H, dd, J = 5.03, 3.46 Hz), 6.78 (1H, dd, J = 3.46, 0.94 Hz), 6.36−6.38 (1H, m), 5.45 (1H, t, J = 5.35 Hz), 4.54 (2H, d, J = 5.66 Hz), 3.79 (2H, t, J = 7.24 Hz), 3.54−3.64 (4H, m), 2.62 (2H, q, J = 7.55 Hz), 2.28−2.37 (2H, m), 2.19−2.28 (4H, m), 1.32 (3H, t, J = 7.39 Hz). ^{13}C NMR (DMSO-d_6): δ 12.7, 19.4, 37.5, 41.2, 53.7, 58.5, 66.5, 104.9, 116.6, 125.0, 125.3, 126.9, 128.2, 132.0, 132.9, 133.3, 133.9, 135.0, 144.0, 164.1. LC-MS: m/z 459.0 $[M + H]^+$ (Luna column, method A, 99.0%, 215 nm).

1-(2-Morpholin-4-ylethyl)-5-phenyl-2-propyl-1*H*-pyrrole-3-carboxylic Acid (2-Morpholin-4-yl-ethyl)amide (6_{20}-A_2). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.32−7.45 (5H, m), 6.40 (1H, br. s.), 6.25 (1H, s), 3.98−4.06 (2H, m), 3.70−3.76 (4H, m), 3.54−3.59 (4H, m), 3.49−3.54 (2H, m), 2.98−3.06 (2H, m), 2.60 (2H, t, J = 5.98 Hz), 2.49−2.57 (4H, m), 2.33−2.41 (2H, m), 2.20−2.25 (4H, m), 1.57−1.77 (2H, m), 1.04 (3H, t, J = 7.39 Hz). LC-MS: m/z 455.6 $[M + H]^+$ (Luna column, method A, 99.4%, 215 nm).

1-(2-Morpholin-4-ylethyl)-5-phenyl-2-propyl-1*H*-pyrrole-3-carboxylic Acid Methylamide (6_{20}-A_8). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.32−7.44 (5H, m), 6.17 (1H, s), 5.67−5.76 (1H, m), 4.04 (2H, t, J = 7.24 Hz), 3.54−3.62 (4H, m), 2.99−3.06 (2H, m), 2.93 (3H, d, J = 5.03 Hz), 2.32−2.41 (2H, m), 2.19−2.28 (4H, m), 1.63−1.76 (2H, m), 1.04 (3H, t, J = 7.39 Hz). ^{13}C NMR (DMSO-d_6): δ 14.5, 23.8, 26.0, 27.1, 41.4, 53.7, 58.9, 66.5, 108.1, 115.3, 127.7, 129.0, 129.3, 132.5, 133.6, 138.5, 165.6. LC-MS: m/z 356.4 $[M + H]^+$ (Luna column, method A, 99.4%, 215 nm).

(4-Morpholin-4-ylpiperidin-1-yl)-(1-phenethyl-5-phenyl-2-propyl-1*H*-pyrrol-3-yl)methanone (6_{21}-A_3). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.31−7.44 (5H, m), 7.12−7.22

(3H, m), 6.86 (2H, dt, $J = 4.72$, 2.36 Hz), 6.10 (1H, s), 4.48 (2H, s), 4.09 (2H, dd, $J = 8.97$, 7.08 Hz), 3.63−3.78 (4H, m), 2.87 (2H, t, $J = 11.64$ Hz), 2.63−2.73 (4H, m), 2.51−2.62 (4H, m), 2.44 (1H, t, $J = 11.01$ Hz), 1.89 (2H, d, $J = 11.33$ Hz), 1.61 (2H, td, $J = 15.10$, 7.55 Hz), 1.38−1.54 (2H, m), 0.97 (3H, t, $J = 7.24$ Hz). ^{13}C NMR (DMSO-d_6): δ 14.3, 23.5, 26.9, 28.7, 37.0, 45.5, 49.8, 61.7, 67.0, 108.4, 115.8, 126.9, 127.7, 128.8, 128.9, 129.0, 129.1, 132.3, 133.6, 135.9, 138.3, 166.9. LC-MS: $m/z = 486.6$ $[M + H]^+$ (Luna column, method B, 98.7%, 215 nm).

1-Phenethyl-5-phenyl-2-propyl-1*H*-pyrrole-3-carboxylic Acid (Furan-2-ylmethyl)amide (6_{21}-A_7). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.30−7.44 (6H, m), 7.16−7.24 (3H, m), 6.85 (2H, dd, $J = 7.24$, 2.20 Hz), 6.29 (2H, ddd, $J = 18.09$, 3.30, 1.26 Hz), 6.22 (1H, s), 6.00 (1H, s), 4.59 (2H, d, $J = 5.03$ Hz), 4.06−4.12 (2H, m), 2.97−3.03 (2H, m), 2.67−2.73 (2H, m), 1.69 (2H, dq, $J = 15.34$, 7.58 Hz), 1.04 (3H, t, $J = 7.39$ Hz). ^{13}C NMR (DMSO-d_6): δ 14.5, 23.7, 27.0, 35.7, 37.2, 45.4, 106.8, 108.4, 110.8, 114.7, 126.9, 127.8, 128.8, 128.9, 129.0, 129.2, 132.4, 133.7, 138.3, 139.0, 142.1, 153.9, 164.9. LC-MS: $m/z = 413.5$ $[M + H]^+$ (Luna column, method B, 99.2%, 215 nm).

2-Benzyl-1-isobutyl-5-phenyl-1*H*-pyrrole-3-carboxylic Acid (2-Morpholin-4-ylethyl)amide (6_{22}-A_2). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.25−7.39 (7H, m), 7.15−7.21 (3H, m), 6.38 (1H, br. s.), 6.32 (1H, s), 4.57 (2H, s), 3.67−3.71 (4H, m), 3.65 (2H, d, $J = 7.87$ Hz), 3.50 (2H, dt, $J = 5.66$ Hz), 2.56 (2H, t, $J = 6.13$ Hz), 2.45−2.51 (4H, m), 1.61 (1H, dq, $J = 13.74$, 6.95 Hz), 0.54 (6H, d, $J = 6.61$ Hz). LC-MS: m/z 492.4446.6 $[M + H]^+$ (Luna column, method B, 98.6%, 215 nm).

2-Benzyl-1-phenethyl-5-phenyl-1*H*-pyrrole-3-carboxylic Acid (Thiophen-2-ylmethyl)amide (6_{24}-A_{10}). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.28−7.42 (7H, m), 7.18−7.25 (4H, m), 7.11−7.17 (3H, m), 6.99−7.03 (1H, m), 6.96 (1H, dd, $J = 5.03$ Hz), 6.63 (2H, dd, $J = 6.61$, 2.83 Hz), 6.30 (1H, s), 6.10 (1H, t, $J = 5.51$ Hz), 4.78 (2H, d, $J = 5.66$ Hz), 4.52 (2H, s), 3.94−4.02 (2H, m), 2.33−2.41 (2H, m). LC-MS: $m/z = 477.6$ $[M + H]^+$ (Luna column, method B, 99.6%, 215 nm).

Acknowledgment. The authors thank Dr. Alberto Cerri, Dr. Sergio Menegon, Dr. Samuele Pedraglio, and Dr. Chiara Bigogno for analytical support and Dr Iain Lingard for careful reading of the manuscript.

Supporting Information Available. ^{1}H NMR spectra of compounds $\mathbf{6_1}$−$\mathbf{6_{24}}$, reported in Table 2, ^{1}H NMR spectra, and LC-MS traces (215 nm) of all compounds reported in Table 3, and ^{13}C NMR spectra of compounds $\mathbf{6_7}$-$\mathbf{A_3}$, $\mathbf{6_{10}}$-$\mathbf{A_5}$, $\mathbf{6_{11}}$-$\mathbf{A_2}$, $\mathbf{6_{13}}$-$\mathbf{A_1}$, $\mathbf{6_{13}}$-$\mathbf{A_4}$, $\mathbf{6_{17}}$-$\mathbf{A_2}$, $\mathbf{6_{18}}$-$\mathbf{A_{10}}$, $\mathbf{6_{20}}$-$\mathbf{A_8}$, $\mathbf{6_{21}}$-$\mathbf{A_3}$, and $\mathbf{6_{21}}$-$\mathbf{A_7}$. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Sperry, J.; Wright, D. *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 723.
(2) (a) Gossauer, A. *Die Chemie der Pyrrole*; Springer-Verlag: Berlin, 1974. (b) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207. (c) Fürstner, A. *Synlett* **1999**, *10*, 1523. (d) Wiley, J. L.; Compton, D. R.; Dai, D.; Lainton, J. A. H.; Phillips, M.; Huffman J. W.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1998**, *285*, 995. (e) Biava, M. *Curr. Med. Chem.* **2002**, *9*, 1859.
(3) (a) Kaiser, D. G.; Glenn, E. M. *J. Pharm. Sci.* **1972**, *61*, 1908. (b) Daisone, G.; Maggio, B.; Schillaci, D. *Pharmazie* **1990**, *45*, 441. (c) Almerico, A. M.; Diana, P.; Barraja, P.; Dattolo, G.; Mingoia, F.; Putzolu, M.; Perra, G.; Milia, C.; Musiu, C.; Marongiu, M. E. *Farmaco* **1997**, *52*, 667. (d) Lehuede, J.; Fauconneau, B.; Barrier, L.; Ourakow, M.; Piriou, A.; Vierfond, J.-M. *Eur. J. Med. Chem.* **1999**, *34*, 991. (e) Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. *Tetrahedron Lett.* **2003**, *44*, 4443. (f) Tejedor, D.; Gonzalez-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390.
(4) (a) Dolle, E. R. *J. Comb. Chem.* **2002**, *4*, 369. (b) Dolle, E. R. *J. Comb. Chem.* **2003**, *5*, 693. (c) Dolle, E. R. *J. Comb. Chem.* **2004**, *6*, 623. (d) Dolle, E. R. *J. Comb. Chem.* **2005**, *7*, 739.
(5) (a) Knorr, L. *Chem. Ber.* **1885**, *18*, 299. (b) Paal, C. *Chem. Ber.* **1885**, *18*, 367. (c) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119.
(6) Hansford, K. A.; Zanzarova, V.; Dorr, A.; Lubell, W. D. *J. Comb. Chem.* **2004**, *6*, 893.
(7) Raghavan, S.; Anuradha, K. *Synlett* **2003**, 711.
(8) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389.
(9) (a) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245. (b) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647. (c) Hunsen, M. *Tetrahedron Lett.* **2005**, *46*, 1651. (d) Agarwal, S.; Tiwari, H. P.; Sharma, J. P. *Tetrahedron* **1990**, *46*, 4417.
(10) (a) Lipton, M. F.; Basha, A.; Weinreb, S. M. In *Organic Syntheses Collection*; Noland, W. E., Ed.; Wiley & Sons Inc.: New York, 1988; Vol. 6, p 492. (b) Basha A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171.
(11) MDL Information Systems Inc., San Leandro, CA.
(12) Brown, R. D.; Hassan, M.; Waldman, M. *J. Mol. Graphics Modell.* **2000**, *18*, 427.
(13) *Cerius*^{2}, version 4.7; Accelrys Inc.: San Diego, CA.
(14) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Delivery Rev.* **1997**, *23*, 3.
(15) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Phys. Chem. A* **1998**, *102*, 3762.

CC060008Q