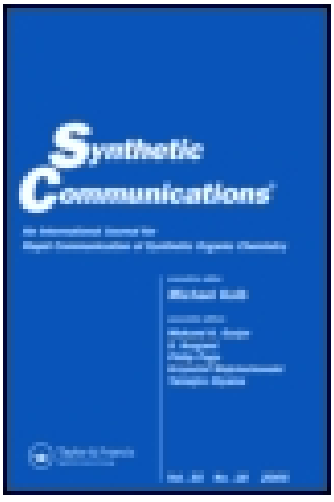

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Regioselective Synthesis of Highly Aryl-Substituted Pyrrole Carboxylates as Useful Medicinal Chemistry Leads

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Regioselective Synthesis of Highly Aryl-Substituted Pyrrole Carboxylates as Useful Medicinal Chemistry Leads

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Abstract: The regioselective syntheses of two pharmaceutically relevant pyrrole scaffolds are described. A synthetic route for the preparation of differentially substituted pyrrole-3,4-dicarboxylates is presented and exemplified. This route circumvents some of the problems and limitations associated with previous butynedioic diester condensations and 1,3-dipolar cycloaddition reactions. A route to the related 4,5-diarylpyrrole-2-carboxylic acid scaffold is also presented. Both routes allow for the regiocontrolled preparation of highly substituted pyrrole pharmacophore cores.

Keywords: condensation, heterocycles, hydrazides, ketones, pyrroles

INTRODUCTION

Pharmaceutically relevant molecules tend to fall into classes based on privileged core structures. The bis-aryl substituted five-membered heterocycle template is observed in many recently approved pharmaceuticals. One subset of this template is the biologically active bis-aryl pyrrole series. The most well-known example is atorvastatin calcium (Fig. 1).

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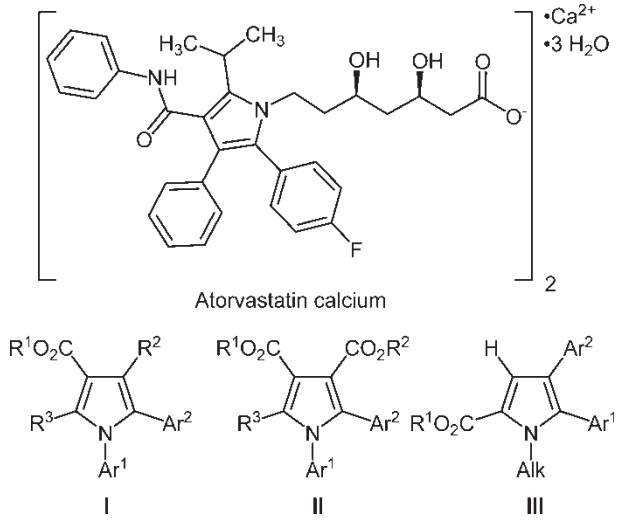
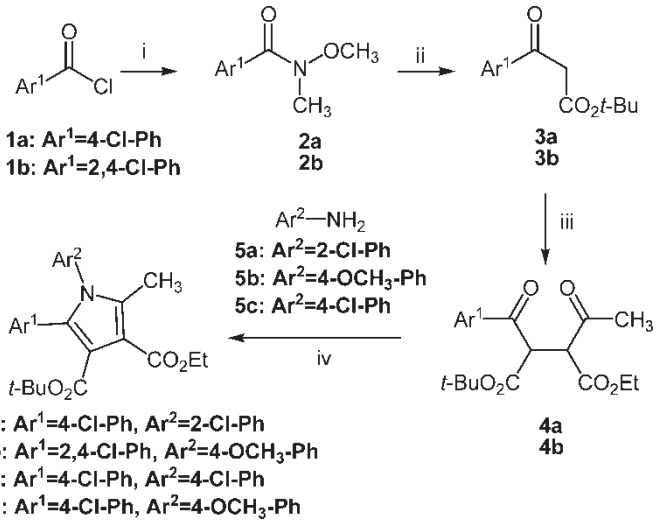


Figure 1. Bis-aryl pyrroles.

Although many examples of scaffold **I** have been prepared by Paal–Knorr[1] synthesis in the literature, scaffolds **II** and **III** are much less common. Most literature syntheses of pyrrole-3,4-dicarboxylates (**II**) are based on the condensation of a 2-phenylsulfonylaziridine with a butynedioic diester[2] or other 1,3-dipolar cycloadditions to a substituted alkyne.[3] These earlier routes possess the inherent disadvantage of poor regiocontrol in preparing unsymmetrical diester products. The only literature preparation of scaffold **III** is based on aryl couplings with bromopyrroles.[4] As part of a drug discovery program, a regioselective route to unsymmetrical dicarboxylate scaffold **II** and also a novel route to 4,5-diarylpyrrole-2-carboxylic acid scaffold **III** were developed. These routes provide regiocontrolled methodology to pharmaceutically interesting cores with multiple points of derivatization.

RESULTS AND DISCUSSION

The preparation of scaffold of type **II** was initiated with the intention of preparing regiocontrolled, pentasubstituted pyrrole products. Ethyl and *tert*-butyl esters were chosen based on their complementary hydrolysis procedures. This selective deprotection approach allowed further regiocontrolled carboxylate derivatization at each site. Commercially available acid chlorides **1a** and **1b** were used to prepare the respective Weinreb[5] amides **2a**[6] and **2b**[7] in $\geq$95% yield (Scheme 1).



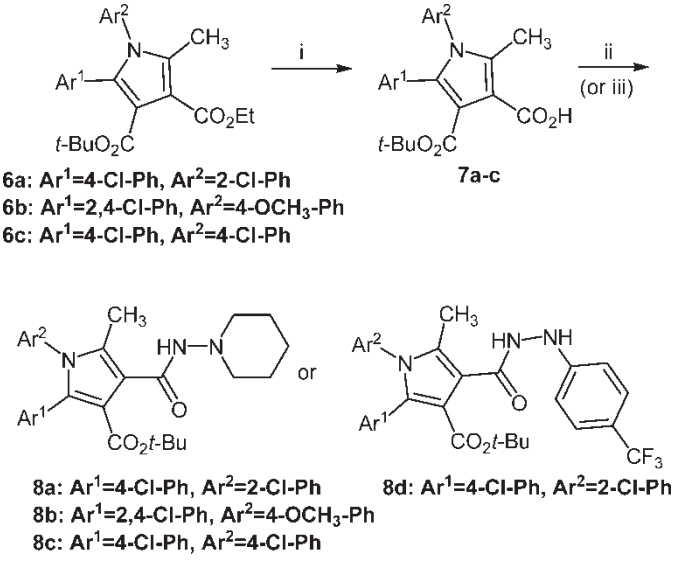
Scheme 1. (i) HCl • NH(OMe)Me, pyridine, CH_2Cl_2; (ii) *t*-BuOAc, LDA, THF, −78°C; (iii) NaOEt, EtOH, then ethyl 2-bromoacetoacetate; (iv) EtOH, AcOH.

2a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, $J = 8.7$ Hz, 2H), 7.38 (d, $J = 8.7$ Hz, 2H), 3.54 (s, 3H), 3.36 (s, 3H); ESI MS m/z 200 $[C_9H_{10}ClNO_2 + H]^+$. Our data were in good agreement with those provided in Ref. 6.

2b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, $J = 8.7$ Hz, 2H), 7.38 (d, $J = 8.7$ Hz, 2H), 3.54 (s, 3H), 3.36 (s, 3H); ESI MS m/z 234 $[C_9H_9Cl_2NO_2 + H]^+$. Our data were in good agreement with those provided in Ref. 7.

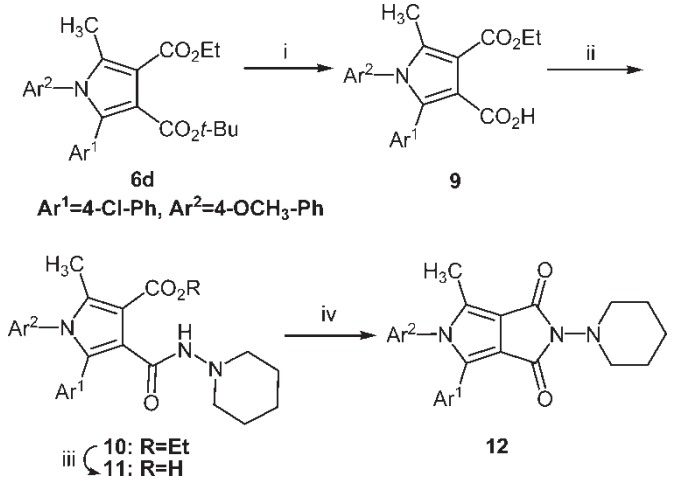
Condensation of the *N,O*-dimethylhydroxyamides with the enolate of *tert*-butyl acetate gave esters **3a** and **3b** in 100% and 89% yields, respectively. The key step in the synthesis was the condensation of the β-ketoesters with an α-haloketone.[8] Deprotonation of **3a** and **3b** with sodium ethoxide in ethanol followed by treatment of each with ethyl 2-bromoacetoacetate gave highly functionalized, key intermediates **4a** and **4b** in 19% and 25% yields, respectively. Paal–Knorr cyclizations of **4a** or **4b** with anilines **5a–c** in refluxing acetic acid and ethanol gave pyrroles **6a–d** in yields ranging from 20–77%. To demonstrate their selective deprotection potential, compounds **6a–c** were first hydrolyzed to their corresponding acids (**7a–c**) in good yields (75–98%) using sodium hydroxide in aqueous ethanol (Scheme 2).

Four traditional amide couplings were performed on this system using benzotriazo-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent)[9] to give hydrazides **8a–d** in yields ranging from 45 to 69%. Alternatively, ester **6d** was treated with trifluoroacetic acid to selectively deprotect the *t*-butyl ester in the presence of the ethyl ester to give carboxylic acid **9** quantitatively (Scheme 3). Coupling of acid **9** with 1-aminopiperidine



Scheme 2. (i) NaOH, H_2O/EtOH, reflux; (ii) BOP reagent, Et_3N, 1-aminopiperidine, CH_2Cl_2; (iii) BOP reagent, Et_3N, 4-trifluoromethylphenyl hydrazine, CH_2Cl_2.

gave the alternatively substituted derivative **10** in 56% yield. The utility of this route was further demonstrated through the preparation of pyrrolosuccinimide **12**. Ester **10** was hydrolyzed under basic conditions to give acid **11** in 87% yield. The cyclization of **11** to form ring-fused **12** in 65% yield was used to



Scheme 3. (i) CF_3COOH, CH_2Cl_2; (ii) BOP reagent, Et_3N, 1-aminopiperidine, CH_2Cl_2; (iii) NaOH, H_2O/EtOH, reflux; (iv) BOP reagent, Et_3N, CH_2Cl_2.

confirm the structure of intermediate **11**. The formation of acid **11** also fully exemplified the ability to selectively deprotect and derivatize the differentiated esters in either order.

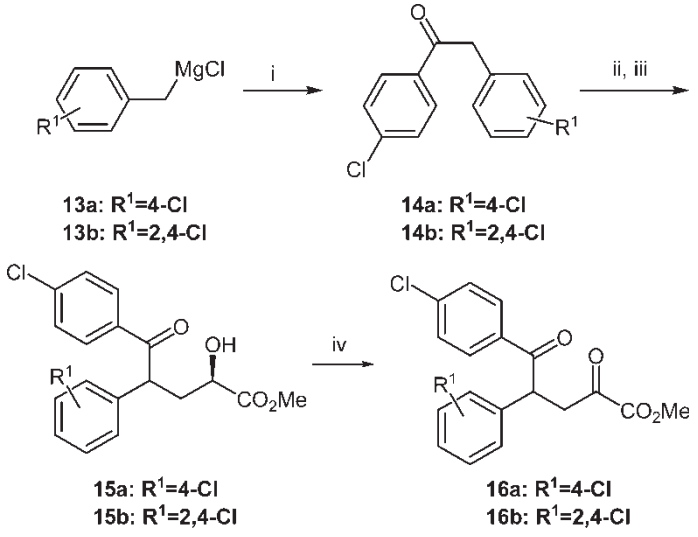
The preparation of scaffold **III** began with the preparation of ketones **14a** and **14b** in 57% and 59% yield respectively.

Data for 14a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, $J = 6.9$ Hz, 1.5 Hz, 2H), 7.43 (dd, $J = 7.2$ Hz, 1.8 Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 2H), 4.23 (s, 2H).

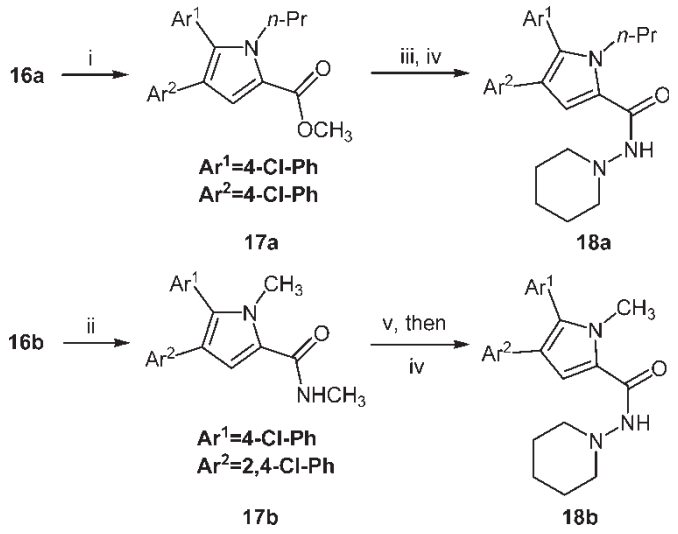
Data for 14b: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, $J = 6.6$ Hz, 1.8 Hz, 2H), 7.40–7.50 (m, 3H), 7.15–7.25 (m, 2H), 4.37 (s, 2H). Our data were in good agreement with those provided in Ref. 10.

This was achieved through the addition of Grignard reagents **13a** and **13b** to previously prepared Weinreb amide **2a** (Scheme 4). The ketones were deprotonated and condensed with methyl glycidate ester to give alcohols **15a** and **15b** in 34% and 47% yield, respectively. Dess–Martin periodinane oxidation[11] of the alcohols provided the key precursors 1,4-diketoesters **16a** and **16b** for the pyrrole-forming cyclization.

Esters **16a** and **16b** were condensed with *n*-propylamine and methylamine respectively (Scheme 5). Condensation of **16a** with *n*-propylamine in refluxing acetic acid and ethanol gave **17a** in 61% yield from **15a**. Hydrolysis of **17a** with sodium hydroxide in aqueous ethanol gave the acid intermediate in 73% yield. The acid was immediately coupled with BOP reagent and 1-aminopiperidine to give amide **18a** in 59% yield. The volatility of methylamine solutions required the condensation of diketone **16b** be performed in a



Scheme 4. (i) **2a**, ether; (ii) (a) NaH, THF, 0°C, (b) methyl-(*R*)-glycidate; (iii) Dess–Martin periodinane, CH_2Cl_2.



Scheme 5. (i) *n*-propylamine, CH_3CO_2H, EtOH, reflux; (ii) methylamine, CH_3CO_2H, EtOH, sealed tube; (iii) NaOH, EtOH, H_2O, reflux; (iv) BOP, 1-aminopiperidine, Et_3N, CH_2Cl_2; (v) KOH, 18-crown-6, ethylene glycol, reflux.

sealed tube. In addition to forming the pyrrole, the excess of highly nucleophilic methylamine displaced the methyl ester simultaneously under the condensation conditions to give methyl amide **17b** in 75% yield. The methyl amide of **17b** proved difficult to hydrolyze; however, treatment of **17b** with potassium hydroxide and 18-crown-6 at high temperature in ethylene glycol afforded the acid intermediate in 95% yield. Coupling of the crude acid and 1-aminopiperidine with BOP reagent furnished pyrrole **18b** in 26% yield.

In summary, we have exemplified the preparation of two highly functionalized, medicinally interesting pyrrole scaffolds. The scaffolds can be quickly prepared from commercially available starting materials. The products from these pyrrole syntheses provide sites for further derivatization via the differentially protected esters of scaffold **II** or the single methyl ester of scaffold **III**. These synthetic routes complement the currently available literature methods for the preparation of highly substituted pyrrole scaffolds.

EXPERIMENTAL

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. All reactions were performed using oven-dried glassware under an atmosphere of nitrogen unless otherwise indicated. Proton and carbon nuclear magnetic resonance spectra were obtained on a Bruker AV 300 spectrometer at 300 MHz for proton or on a Bruker AV 500

spectrometer at 500 MHz for proton. Spectra are given in parts per million (δ), and coupling constants, J, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton spectra, and the solvent peak was used as the reference peak for carbon spectra. Melting points were obtained in open capillary tubes and are uncorrected. Mass spectra were obtained on a Finnigan LCQ Duo LCMS ion trap electrospray ionization (ESI) mass spectrometer. HPLC analyses were obtained using a Symmetry C18 column (250 × 4.6 mm, Waters) with UV detection at 254 nm using gradient elution (10% to 100% acetonitrile in water containing 0.1% TFA over 30 min, then hold for 5 min).

General Procedure for the Preparation of Compounds 3a and b

A solution of lithium diisopropylamide (LDA) was prepared at −10°C by the addition of 1.6 M *n*-BuLi in hexanes (1.0 eq) to diisopropylamine (1.0 eq) in THF followed by warming to room temperature. The solution of LDA was cooled to −78°C, and *tert*-butyl acetate (1.0 eq) was added to it dropwise. After 15 min, a solution of compound **2** (0.8 eq) in THF was slowly added to it. The solution was stirred for an hour at −78°C and then allowed to warm to room temperature over 3 h. The solution was acidified with aqueous 1 N HCl solution and extracted into ether. The organic layer was dried ($MgSO_4$) and concentrated to afford the crude product, which was used directly in the next step.

Data

3-(4-Chlorophenyl)-3-oxo-propionic acid *tert*-butyl ester (3a). (6.8 g, ∼100%); ^{1}H NMR (300 MHz, $CDCl_3$) (keto form only) δ 7.88 (d, $J = 8.7$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 3.87 (s, 2H), 1.43 (s, 9H); ESI MS m/z 198 $[C_{13}H_{15}ClO_3 - C_4H_9 + H]^+$.

3-(2,4-Dichlorophenyl)-3-oxo-propionic acid *tert*-butyl ester (3b). (5.5 g, 89%); ^{1}H NMR (300 MHz, $CDCl_3$) (keto form only) δ 7.88 (d, $J = 8.7$ Hz, 2H), 7.45 (d, $J = 8.7$ Hz, 2H), 3.87 (s, 2H), 1.43 (s, 9H); ESI MS m/z 233 $[C_{13}H_{14}Cl_2O_3 - C_4H_9 + H]^+$.

General Procedure for the Preparation of Compounds 4a and b (General Method A)

A solution of β-keto ester **3a** and **b** (1.0 eq) in ethanol was treated with a solution of sodium ethoxide in ethanol (1.2 eq). After 10 min, this solution was added to a solution of ethyl 2-bromoacetoacetate (1.1 eq) in 1:1

ethanol/toluene. The resulting solution was stirred at room temperature for 7 h. The solution was quenched by adding 0.5 N HCl solution and extracted into EtOAc. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford product **4a** and **b**.

Data

2-Acetyl-3-(4-chlorobenzoyl)-succinic acid 4-*tert*-butyl ester 1-ethyl ester (4a): (1.4 g, 19%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–8.06 (m, 2H), 7.26–7.48 (m, 2H), 5.21 (d, $J = 6.8$ Hz, 0.5 H), 5.11 (d, $J = 6.6$ Hz, 0.5H), 4.70 (d, $J = 5.7$ Hz, 0.5H), 4.68 (d, $J = 5.7$ Hz, 0.5H), 4.25 (q, $J = 2.7$ Hz, 1H), 4.07 (q, $J = 3.6$ Hz, 1H), 2.50 (s, 1.5H), 2.38 (s, 1.5H), 1.32 (s, 4.5H), 1.26 (s, 4.5H), 1.13 (t, $J = 4.5$ Hz, 3H); ESI MS m/z 327 $[C_{19}H_{23}ClO_6 - C_4H_9 + H]^+$.

2-Acetyl-3-(2,4-dichlorobenzoyl)-succinic acid 4-*tert*-butyl ester 1-ethyl ester (4b): (2.62 g, 25%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02–8.07 (m, 2H), 7.45–7.49 (m, 2H), 5.22 (d, $J = 11.1$ Hz, 0.5H), 5.12 (d, $J = 11.1$ Hz, 0.5 H), 4.70 (d, $J = 6.0$ Hz, 0.5H), 4.67 (d, $J = 6.0$ Hz, 0.5H), 4.25 (q, $J = 7.2$ Hz, 1H), 4.07 (q, $J = 7.2$ Hz, 1H), 2.50 (s, 1.5H), 2.38 (s, 1.5H), 1.32 (s, 4.5H), 1.30 (s, 4.5H), 1.10 (t, $J = 7.2$ Hz, 3H); ESI MS m/z 327 $[C_{19}H_{23}ClO_6 - C_4H_9 + H]^+$.

General Procedure for the Preparation of Compounds 6a–d (General Method B)

A solution of compound **4a** and **b** (1.0 eq), substituted aniline **5a–c** (1.6 eq), and acetic acid (1.0 eq) in ethanol was heated at reflux for 24 h. After cooling, the reaction was quenched by the addition of a saturated aqueous $NaHCO_3$ solution and extracted into EtOAc. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the product **6a–d**.

Data

1-(2-Chlorophenyl)-2-(4-chlorophenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-ethyl ester (6a): (0.5 g, 36%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.50 (m, 8H), 4.34 (d, $J = 7.2$ Hz, 2H), 2.22 (s, 3H), 1.37 (s, 9H); ESI MS m/z 418 $[C_{25}H_{25}Cl_2NO_4 - C_4H_9 + H]^+$.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-ethyl ester (6b): (0.12 g, 20%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70–7.40 (m, 7H), 4.34 (d, $J = 7.2$ Hz, 2H), 3.78

(s, 3H), 2.04 (s, 3H), 1.36 (t, $J = 7.2$ Hz, 3H), 1.28 (s, 9H); ESI MS m/z 504 $[C_{26}H_{27}Cl_2NO_5 + H]^+$.

1,2-Bis-(4-chlorophenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-ethyl ester (6c): (0.53 g, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, $J = 8.7$ Hz, 2H), 7.18 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 8.5$ Hz, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 4.33 (q, $J = 7.2$ Hz, 2H), 2.28 (s, 3H), 1.38 (s, 9H), 1.36 (t, $J = 6.9$ Hz, 3H); ESI MS m/z 418 $[(C_{25}H_{25}Cl_2NO_4 - C_4H_9) + H]^+$.

2-(4-Chlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 3-*tert*-butyl ester 4-ethyl ester (6d): (1.55 g, 48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, $J = 8.5$ Hz, 2H), 7.06 (d, $J = 8.5$ Hz, 2H), 6.93 (d, $J = 8.9$ Hz, 2H), 6.84 (d, $J = 8.9$ Hz, 2H), 4.33 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 3H), 2.27 (s, 3H), 1.38 (s, 9H), 1.33 (t, $J = 7.2$ Hz, 3H); ESI MS m/z 414 $[C_{26}H_{28}ClNO_5 - C_4H_9 + H]^+$.

General Procedure for the Preparation of Compounds 7a–c (General Method C)

A solution of compound **6a–c** (1.0 eq) in ethanol was combined with a 1.0 M solution of NaOH (3 eq). The resulting solution was heated at reflux for 6 h, poured into ice-cold aqueous 0.5 N HCl solution, and extracted into EtOAc. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to afford product **7a–c**.

Data

1-(2-Chlorophenyl)-2-(4-chlorophenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 3-*tert*-butyl ester (7a): (0.40 g, 75%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.20–7.52 (m, 8H), 2.29 (s, 3H), 1.24 (s, 9H); ESI MS m/z 446 $[C_{23}H_{21}Cl_2NO_4 + H]^+$.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 3-*tert*-butyl ester (7b): (0.13 g, 98%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.20–7.52 (m, 8H), 2.29 (s, 3H), 1.24 (s, 9H); ESI MS m/z 446 $[C_{24}H_{23}Cl_2NO_5 + H]^+$.

1,2-Bis-(4-chlorophenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 3-*tert*-butyl ester (7c): (0.44 g, 88%); ^{1}H NMR (300 MHz, CD_3OD) δ 7.39 (d, $J = 7.2$ Hz, 2H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.10–7.20 (m, 4H), 2.35 (s, 3H), 1.25 (s, 9H); ESI MS m/z 387 $[C_{23}H_{17}Cl_2NO_4 - C_4H_9 + H]^+$.

General Procedure for the Preparation of Hydrazides 8a–d (General Method D)

This procedure illustrates the general methods for the preparation of hydrazides **8a–d**, **10**, **12**, **18a**, and **18b**. A solution of acid **7a–c** (1.0 eq) in CH_2Cl_2 at 0°C under N_2 was treated with triethylamine (2.5 eq), BOP reagent (1.2 eq), and 1-aminopiperidine (1.2 eq for targets **8a–c**) or 4-trifluoromethylphenyl hydrazine (1.2 eq for target **8d**). The resulting solution was stirred at room temperature for 18 h and then diluted with water. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford product **8a–d**.

Data

1-(2-Chlorophenyl)-2-(4-chlorophenyl)-5-methyl-4-(piperidin-1-ylcarbamoyl)-1*H*-pyrrole-3-carboxylic acid *tert*-butyl ester (8a): (0.15 g, 69%); mp 225–226°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.50 (m, 8H), 2.84–2.87 (m, 4H), 2.10 (s, 3H), 1.70–1.76 (m, 4H), 1.45–1.50 (m, 2H), 1.22 (s, 9H); ESI MS m/z 528 $[C_{28}H_{31}Cl_2N_3O_3 + H]^+$; HPLC 96.0% (AUC), $t_R = 19.3$ min.

2-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)-5-methyl-4-(piperidin-1-ylcarbamoyl)-1*H*-pyrrole-3-carboxylic acid *tert*-butyl ester (8b): (0.11 g, 45%); mp 188–189°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, $J = 1.7$ Hz, 1H), 7.18–7.20 (m, 2H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 3.75 (s, 3H), 2.84–2.88 (m, 4H), 2.16 (s, 3H), 1.72–1.76 (m, 4H), 1.40–1.60 (m, 2H), 1.18 (s, 9H); ESI MS m/z 558 $[C_{29}H_{33}Cl_2N_3O_4 + H]^+$; HPLC >99% (AUC), $t_R = 19.4$ min.

1,2-Bis-(4-chlorophenyl)-5-methyl-4-(piperidin-1-ylcarbamoyl)-1*H*-pyrrole-3-carboxylic acid *tert*-butyl ester (8c): (0.29 g, 55%); mp 271–272°C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.36 (d, $J = 8.6$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.09–7.15 (m, 4H), 2.83–2.85 (m, 4H), 2.15 (s, 3H), 1.70–1.76 (m, 4H), 1.45–1.50 (m, 2H), 1.23 (s, 9H); ESI MS m/z 528 $[C_{28}H_{31}Cl_2N_3O_3 + H]^+$; HPLC 97.5% (AUC), $t_R = 19.9$ min.

1-(2-Chlorophenyl)-2-(4-chlorophenyl)-5-methyl-4-[*N*′-(4-trifluoromethylphenyl)-hydrazinocarbonyl]-1-*H*-pyrrole-3-carboxylic acid *tert*-butyl ester (8d): (0.14 g, 65%); mp 169–170°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.50 (m, 10H), 7.03 (d, $J = 8.4$ Hz, 2H), 2.18 (s, 3H), 1.23 (s, 9H); ESI MS m/z 604 $[C_{30}H_{26}Cl_2F_3N_3O_3 + H]^+$; HPLC > 99% (AUC), $t_R = 31.5$ min.

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-5-methyl-1*H*-pyrrole-3,4-dicarboxylic acid 4-ethyl ester (9). A solution of compound **8d** (0.40 g, 0.85 mmol) in CH_2Cl_2 (1.0 mL) was treated with trifluoroacetic acid (0.6 mL) and stirred at room temperature for 3 h. The solution was concentrated under reduced pressure, and the resulting residue was co-evaporated from ether to afford acid **9** (0.35 g, 100%) as a brown solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.29 (d, $J = 6.6$ Hz, 2H), 7.15–7.20 (m, 4H), 6.93 (d, $J = 6.6$ Hz, 2H), 4.20 (q, $J = 7.0$ Hz, 2H), 3.75 (s, 3H), 2.17 (s, 3H), 1.25 (t, $J = 7.2$ Hz, 3H); ESI MS m/z 414 $[C_{22}H_{20}ClNO_5 + H]^+$.

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-2-methyl-4-(piperidn-1-ylcarbamoyl)-1*H*-pyrrole-3-carboxylic acid ethyl ester (10). Compound **9** (0.25 g, 0.60 mmol) was treated with 1-aminopiperidine using general method D to afford **10**: (0.17 g, 56%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08–7.12 (m, 4H), 6.85–6.91 (m, 4H), 4.33 (q, $J = 7.2$ Hz, 2H), 3.80 (s, 3H), 2.60–2.70 (m, 4H), 2.05 (s, 3H), 1.60–1.65 (m, 4H), 1.30–1.40 (m, 2H), 1.26 (t, $J = 7.2$ Hz, 3H); ESI MS m/z 496 $[C_{27}H_{30}ClN_3O_4 + H]^+$.

5-(4-Chlorophenyl)-1-(4-methoxyphenyl)-2-methyl-4-(piperidin-1-ylcarbamoyl)-1*H*-pyrrole-3-carboxylic acid (11). A solution of compound **10** (0.17 g, 0.33 mmol) in ethanol (2 mL) was combined with a 1.0 M solution of NaOH (2 mL, 2.0 mmol). The resulting solution was heated at reflux for 18 h, poured into ice-cold, aqueous 1 N HCl, and extracted into EtOAc. The organic layer was separated, dried ($MgSO_4$), and concentrated to afford acid **11** (0.14 g, 87%) as a yellow powder; ^{1}H NMR (300 MHz, CD_3OD) δ 7.22 (d, $J = 8.5$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 7.08 (d, $J = 8.9$, 2H), 6.93 (d, $J = 8.9$ Hz, 2H), 3.80 (s, 3H), 3.30–3.40 (m, 4H), 2.36 (s, 3H), 1.80–1.90 (m, 4H), 1.50–1.70 (m, 2H); ESI MS m/z 468 $[C_{25}H_{26}ClN_3O_4 + H]^+$.

4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-6-methyl-2-piperidin-1-yl-5*H*-pyrrole[3,4-*c*]pyrrole-1,3-dione (12). Acid **11** (0.11 g, 0.24 mmol) was treated according to general method D without the additional of a hydrazine to afford compound **12** (0.07 g, 65%) as a white powder. Mp 237–239°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, $J = 8.6$ Hz, 2H), 7.18 (d, $J = 8.5$ Hz, 2H), 7.08 (d, $J = 8.7$ Hz, 2H), 6.95 (d, $J = 8.7$ Hz, 2H), 3.86 (s, 3H), 3.32–3.36 (m, 4H), 2.25 (s, 3H), 1.70–1.74 (m, 4H), 1.45–1.50 (m, 2H); ESI MS m/z 450 $[C_{25}H_{24}ClN_3O_3 + H]^+$; HPLC > 99% (AUC), $t_R = 27.2$ min.

General Procedure for the Preparation of Compounds 15a and b (General Method E)

A solution of ketone **14a** and **b** (1.0 eq) in THF was treated with washed 60% NaH dispersion in oil (1.0 eq). After 15 min a solution of methyl (2*R*)-

glycidate (1.0 eq) was added, and the resulting solution was stirred at room temperature for 18 h. The reaction was quenched through the addition of saturated aqueous NH_4Cl solution and extracted into diethyl ether. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford ester **15a** and **b**.

Data

4,5-Bis-(4-chlorophenyl)-2-hydroxy-5-oxo-pentanoic acid methyl ester (15a): (1.41 g, 34%); ^{1}H NMR (mixture of diasteroisomers) (300 MHz, $CDCl_3$) δ 7.10–7.90 (m, 8H), 4.80–5.00 (m, 2H), 4.20–4.30 (m, 1H), 3.80–3.90 (m, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 2.80–3.00 (m, 2H), 2.10–2.40 (m, 2H); ESI MS m/z 349 $[C_{18}H_{15}Cl_3O_4 - OH + H]^+$.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-2-hydroxy-5-oxo-pentanoic acid methyl ester (15b): (3.61 g, 47%); ^{1}H NMR (mixture of diasteroisomers) (300 MHz, $CDCl_3$) δ 7.90 (d, $J = 1.7$ Hz, 1H), 7.87 (d, $J = 1.7$ Hz, 1H), 7.35–7.45 (m, 3H), 7.10–7.20 (m, 2H), 5.30–5.40 (m, 1H), 4.20–4.30 (m, 0.5H), 4.00–4.10 (m, 0.5H), 3.78 (s, 1.5H), 3.71 (s, 1.5H), 2.82 (dd, $J = 24$ Hz, 5.5 Hz, 1H), 2.70–2.80 (m, 0.5H), 2.40–2.50 (m, 0.5H), 2.20-2.30 (m, 0.5H), 1.85–1.95 (m, 0.5H); ESI MS m/z 383 $[C_{18}H_{15}Cl_3O_4 - OH + H]^+$.

General Procedure for the Preparation of Compounds 16a and b (General Method F)

A solution of alcohol **15a** and **b** (1.0 eq) was taken up in CH_2Cl_2 containing Dess–Martin periodinane (1.0 eq), and the resulting solution was stirred at room temperature for 3 h. The solution was diluted with CH_2Cl_2 and washed successively with aqueous $Na_2S_2O_3$ solution and aqueous $NaHCO_3$ solution. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to give diketones **16a** and **b**, which were used without further purification.

Data

4,5-Bis-(4-chlorophenyl)-2,5-dioxo-pentanoic acid methyl ester (16a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.40 (m, 8H), 5.00 (m, 1H), 3.80–4.00 (m, 4H), 3.00–3.20 (m, 1H).

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-2,5-dioxo-pentanoic acid methyl ester (16b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–8.20 (m, 7H), 4.47 (dd,

$J = 10.5$ Hz, 3.3 Hz, 1H), 3.90 (s, 3H), 3.80–3.90 (m, 1H), 3.02 (dd, $J = 18.6$ Hz, 3.3 Hz, 1H).

4,5-Bis-(4-chlorophenyl)-1-propyl-1*H*-pyrrole-2-carboxylic acid methyl ester (17a). A solution of ketone **16a** (1.4 g, 3.8 mmol) and *n*-propyl amine (0.50 mL, 6.1 mmol) in ethanol (10 mL) and acetic acid (5 mL) was heated at 50°C for 20 h. The solution was cooled to room temperature and concentrated to half its volume under reduced pressure. The concentrate was diluted with EtOAc and washed with water followed by saturated aqueous $NaHCO_3$. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was then purified by flash column chromatography (silica gel, 9:1 hexanes/EtOAc) to afford **17a** (0.91 g, 61% over two steps); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, $J = 6.6$ Hz, 2H), 7.10–7.30 (m, 5H), 7.00 (dd, $J = 6.3$ Hz, 2.0 Hz, 2H), 4.15 (t, $J = 7.5$ Hz, 2H), 3.87(s, 3H), 1.55–1.65 (m, 2H), 0.74 (t, $J = 7.5$ Hz, 3H), ESI MS m/z 388 $[C_{21}H_{19}Cl_2NO_2 + H]^+$.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid methylamide (17b). Solutions of diketone **16b** (2.20 g, 5.7 mmol) in EtOH (5 mL), methylamine in EtOH (20 mL, 33 wt.%), and neat acetic acid (10 mL) were charged into a sealed tube. The reaction mixture was heated at 100°C for 14 h and then cooled to room temperature. The solution was concentrated under reduced pressure, and the residue was diluted with EtOAc. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 4:1 hexanes/ethyl acetate) to give **17b** (1.67 g, 75%); mp 166–167°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, $J = 2.1$ Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 7.03 (dd, $J = 8.3$ Hz, 2.1 Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 6.68 (s, 1H), 6.02 (d, $J = 3.1$ Hz, 1H), 3.84 (s, 3H), 2.97 (d, $J = 4.5$ Hz, 3H); ESI MS m/z 393 $[C_{19}H_{15}Cl_3N_2O + H]^+$; HPLC 97.0% (AUC), $t_R = 25.8$ min.

4,5-Bis-(4-chlorophenyl)-1-propyl-1*H*-pyrrole-2-carboxylic acid piperidin-1-ylamide (18a). A solution of compound **17a** (0.90 g, 2.3 mmol) in EtOH (15 mL) was combined with aqueous 1.0 N NaOH (8 mL, 8 mmol). The resulting mixture was heated at reflux for 28 h, poured into ice-cold aqueous 1 N HCl, and extracted into EtOAc. The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure to afford the corresponding acid (0.79 g, 73%) as a light brown solid. The crude acid was treated by general method D to afford hydrazide **18a** (0.56 g, 59%) as a white powder; mp 195–196°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, $J = 1.9$ Hz, 1H), 7.00–7.10 (m, 2H), 6.90–6.95 (m, 2H), 6.70–6.80 (m, 3H), 5.53 (s, 1H), 4.16 (t, $J = 7.5$ Hz, 2H), 2.80–3.00 (m, 4H), 1.74–1.80 (m, 4H), 1.50–1.60 (m, 2H), 0.71 (t, $J = 7.5$ Hz, 3H); ESI MS m/z 456 $[C_{25}H_{27}Cl_2N_3O + H]^+$; HPLC 99.0% (AUC), $t_R = 24.7$ min.

5-(4-Chlorophenyl)-4-(2,4-dichlorophenyl)-1-methyl-1*H*-pyrrole-2-carboxylic acid piperidin-1-ylamide (18b). Amide **17b** (0.040 g, 0.10 mmol) in ethylene glycol (1.0 mL) was treated with KOH (0.030 g, 0.53 mmol) and 18-crown-6 (0.10 g, 0.38 mmol). The resulting mixture was heated at reflux for 6 h, cooled to room temperature, and diluted with EtOAc. The organic layer was separated, washed with aqueous 1 N HCl, dried ($MgSO_4$), and concentrated under reduced pressure to afford the corresponding acid (0.050 g, 95%). The crude acid was treated by general method D to afford hydrazide **18b** (0.040 g, 26%) as a white powder; mp 208–210°C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.40 (d, $J = 2.1$ Hz, 1H), 7.35 (d, $J = 8.6$ Hz, 2H), 7.16 (d, $J = 8.6$ Hz, 3H), 7.07 (d, $J = 8.3$ Hz, 1H), 6.87 (s, 1H), 3.77 (s, 3H), 2.80–2.90 (m, 4H), 1.70–1.80 (m, 4H), 1. 40–1.50 (m, 2H); ESI MS m/z 462 $[C_{23}H_{22}Cl_3N_3O + H]^+$; HPLC 96.2% (AUC), $t_R = 19.9$ min.

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