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Scope and Applicability of an Expedient Synthesis Leading to Polysubstituted 3-(Carboxyphenyl)pyrroles

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Abstract: A convenient three-step route toward a functionalized pyrrole building block for novel anti-inflammatory agents is reported. In contrast to previous strategies, the present approach focuses on inexpensive starting materials and application on a multigram scale. A high degree of functional diversity is demonstrated in various derivatives, and the scope and limitations of this route are discussed. Complementary to the described tetrasubstituted pyrroles, a novel ring-closure protocol based on the Feist–Benary condensation affords trisubstituted analogues.

Keywords: chalkones, Feist–Benary condensation, Paal–Knorr cyclization, pyrrole synthesis, Stetter reaction

3-(p-Carboxyphenyl)pyrroles have been identified in a target-driven drug discovery project to be suitable lipophilic anchors for the development of novel anti-inflammatory agents. In particular, compound **1a** (Fig. 1) served as a structural template for a focused derivatization program.

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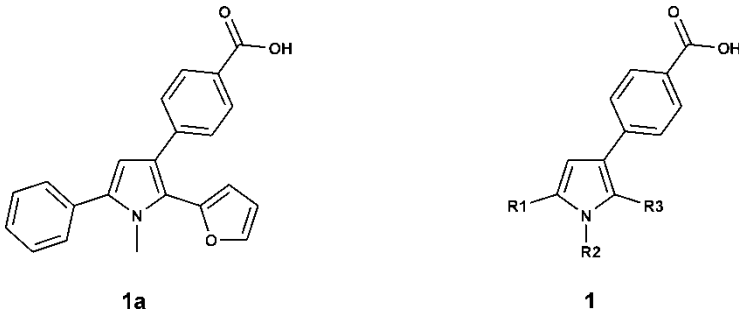
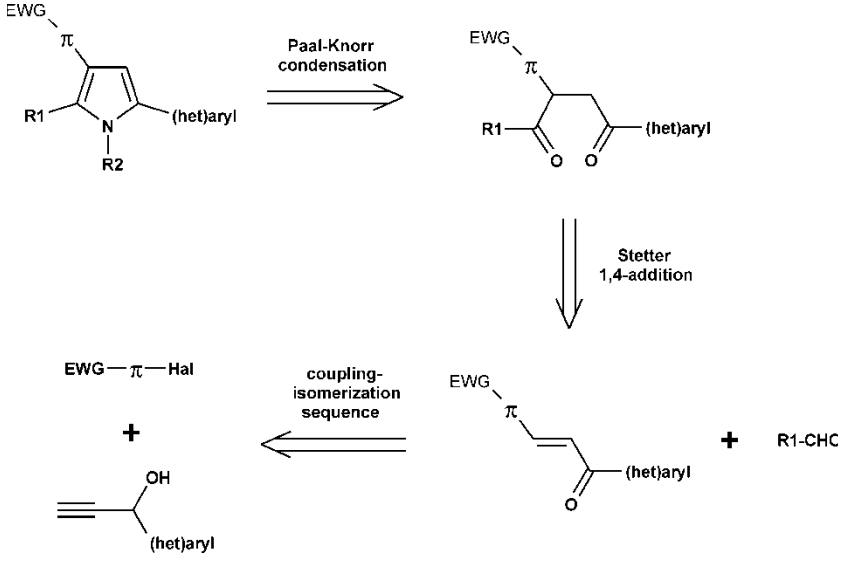


1a **1**

Figure 1. Tetra-substituted 3-(carboxyphenyl)pyrroles.

We therefore sought a robust procedure to synthesize structural analogues of **1a**, keeping the benzoic acid moiety constant and varying the 1,2,5-subsitution pattern on the pyrrole core **1** (Fig. 1).

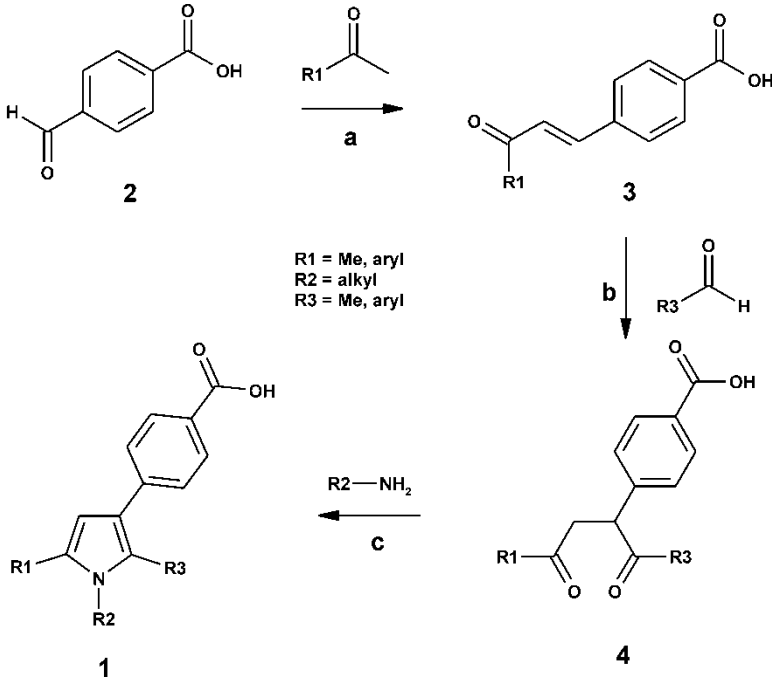
Most strategies for the synthesis of substituted pyrroles involve ring formation, either from 1,4-dicarbonyl compounds and primary amines (Paal–Knorr condensation)[1] or from condensation of α-aminocarbonyl derivatives with activated α-methylene ketones.[2] Although a few reports describe interesting routes to 2,3,5-triaryl-substituted pyrroles,[3a–c] Braun et al.[4a,b] reported a powerful coupling–isomerization–Stetter–Paal–Knorr multicomponent sequence, based on the Sonogashira coupling of (hetero)aryl-propynols with electron-deficient (hetero)aryl halides in the first step (Scheme 1).



Scheme 1. Reported multicomponent synthesis of tetrasubstituted pyrroles.[4a]

Unfortunately, only few adequately substituted propargyl alcohols are commercially available, and their preparation requires additional synthetic steps. For our purposes, we decided to replace the Sonogashira reaction with a simple aldol-type condensation, which was also amenable to bulk intermediate upscaling. Scheme 2 demonstrates that the synthesis of chalkones **3** and subsequent Stetter 1,4-addition of a carboxaldehyde effectively provide 1,4-diketones, which could undergo Paal–Knorr condensation. Importantly, none of the three steps require protection of the carboxyl moiety, as a basic environment ensures its deprotonated form.

In the first step, it was essential that the synthesis of chalkones **3** worked well for all substrates, irrespective of the electronic nature of the corresponding acetophenone. Thus, under basic aqueous conditions (2N NaOH/EtOH)[5a,b] with subsequent acidic workup (to effect both liberation of the carboxylate and elimination of the hydroxyl group to the saturated system), electron-deficient aromatic ketones (e.g., 4-fluoroacetophenone, Table 1, entry b) as well as electron-rich ones (e.g., 4-methoxyacetophenone, entry c) gave chalkones in yields similar to unsubstituted acetophenone (entry a). Because of the insoluble character of the benzoic acid moiety, all



Scheme 2. Three-step synthesis of 3-(carboxyphenyl)pyrroles: Reagents and typical conditions: a) 2 N NaOH, EtOH, rt, 4 h; b) K_2CO_3, triethylamine, 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride, EtOH, reflux, 8 h; c) EtOH, reflux, 3h.

Table 1. Substitution pattern and yields for the three-step synthesis of pyrroles 1

				Yield (%)			
Entry	R1	R2	R3	Step 1	Step 2	Step 3	Total
a	Phenyl	Methyl	2-Furyl	77	95	63	46
b	4-Fluorophenyl	Methyl	2-Furyl	75	86	90	58
c	4-Methoxyphenyl	Methyl	2-Furyl	85	85[a]	64	46
d	4-Cyanophenyl	Methyl	2-Furyl	77	85[a]	51	33
e	4-tBuNHSO$_2$-phenyl	Methyl	2-Furyl	64	85[a]	79	43
f	4-(N-BOC) aminophenyl	Methyl	2-Furyl	56	79	58	26
g	Methyl	Methyl	2-Furyl	36	59	32	7
h	4-Pyridyl	Methyl	2-Furyl	32	85[a]	96	26
i	Phenyl	2-Phenylethyl	2-Furyl	77	95	73[b]	53
j	Phenyl	2-(Dimethylamino) ethyl	2-Furyl	77	95	73[b]	53
k	Phenyl	2-(1-Morpholin-yl) ethyl	2-Furyl	77	95	70[b]	51
l	Phenyl	2-Phenylethyl	Methyl	77	50	30[b]	12
m	Phenyl	2-Methoxyethyl	Methyl	77	50	39[b]	15

[a]Not purified by chromatography. Yield estimated by TLC.
[b]Cyclization by microwave irradiation (5 min, 180°C).

compounds could be isolated by filtration after acidic workup. The scope of this reaction is not limited to substituted acetophenones but can also be applied to heteroaryl ketones. However, 4-acetylpyridine (entry h) gave poorer yields (32%), as the workup was more pH sensitive because of the added basic functionality. Acetone (R1 = Me, entry g) was prone to double condensation under the chosen reaction conditions but sufficient amounts of the corresponding unsaturated methyl ketone (36% yield) could be obtained.

Stetter 1,4-addition[6] of furfural (R3 = 2-furyl) to various chalkones **3** usually gave good yields of 1,4-diketones **4** in the presence of two different bases after several hours of heating in ethanolic solution (1 equivalent of K_2CO_3 was used to deprotonate the acid and 1 equivalent of triethylamine was later added to promote the reaction). In some cases, crude products were purified by flash chromatography; others were judged sufficiently pure by thin-layer chromatography (TLC) to continue the synthesis without purification (as indicated in Table 1). The catalyst responsible for an Umpolung of furfural was carefully chosen; toxic cyanides were not considered an option, as it was intended to scale up the synthesis for development purposes, and alkali cyanides are inappropriate for the Umpolung of aliphatic aldehydes because of their high basicity.[6] The more recently reported thiazolium catalysts worked

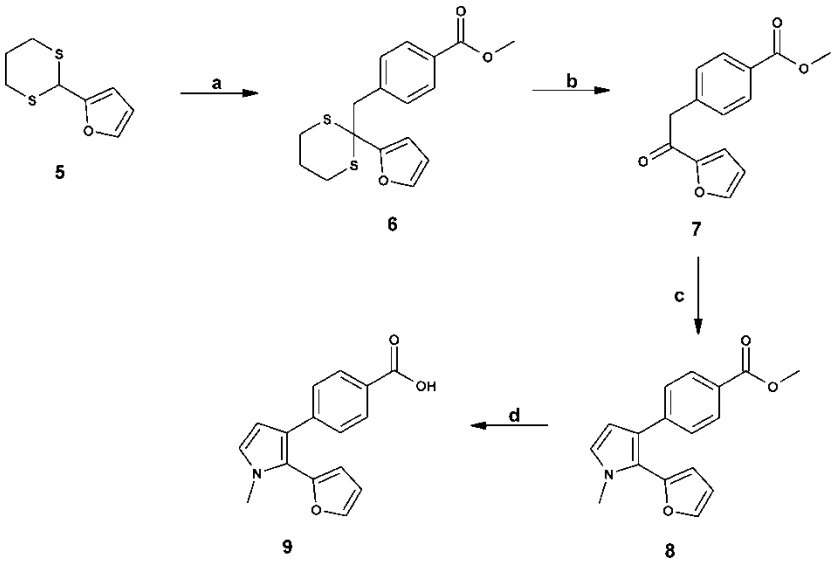
nicely in our hands, and we opted for the commercially available 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride[6] (CAS 4568-71-2). Employment of this catalyst was also applicable to aliphatic aldehydes, as exemplified by acetaldehyde (entries l and m) where yields dropped notably to 50%, presumably because of autocondensation.

Paal–Knorr cyclization of 1,4-diketones **4** was conveniently achieved by treatment with excess primary amine and acetic acid at elevated temperatures.[7] In the simple case of R2 = Me, it was sufficient to react **4** in an ethanolic solution of methylamine under reflux. In the case of bulkier and functionalized amines, higher temperatures and/or extended reaction periods were required to promote cyclization. Up to a scale of approx. 1 g, this could be achieved by microwave irradiation[8] in a closed vessel, whereas larger batches had to be carried out in pressurized autoclave systems. For instance, the N-(2-methoxy)ethyl substituent was once introduced in 46 h under reflux in EtOH and once by microwave irradiation in an Emrys Optimizer™ (5 min, 180°C, entry m). In most cases, acidification upon completion of the reaction afforded the crystalline products **1** in yields of 50–95% (after purification), except for R1 or R3 = methyl (entries l and m) where yields were only 30–40%, hinting at lower activation of the corresponding 1,4-diketones toward nucleophilic attack by the primary amine.

Importantly, the described route is tolerant of many functional groups that were introduced with the ketone scaffold R1 [e.g., halogen, methoxy, cyano, BOC-protected amine, and N-(t-butyl)sulfonamide]. Not surprisingly, unprotected amines, free carboxylic acids, ketones or aldehydes were not compatible with the synthesis. Table 1 summarizes selected scaffolds that have been investigated in our series.

The synthesis of analogous, five-unsubstituted pyrroles (R1 = H) was accomplished by a different route (Scheme 3), as unsaturated aldehydes are not suitable substrates for Stetter reactions. Thus, the dithioacetal of furfural (**5**)[9] was benzylated to **6**[10] and deprotected in good yields. Interestingly, the only suitable reagent for dethioacetalization was found to be mercury acetate,[11] whereas less hazardous reagents such as Clayfen,[12] CAN,[13] or DMSO/HCl[14] proved to be inefficient. The obtained 2-oxoethylbenzoate **7** was then transformed into the desired N-methyl pyrrole **8** by applying a modified Feist–Benary condensation[15] with 1,2-dibromoethylacetate[16] and methylamine. This conversion represents, to the best of our knowledge, the first such condensation performed on benzyl ketones rather than β-ketoesters where the 1,3-dicarbonyl system activates the CH_2 group. Thus, the phenyl ring proved to be sufficient to promote cyclization. These findings nicely complement previous reports of benzyl ketones cyclizing with chloroacetamides to give pyrrolin-2-ones.[17] Finally, ester hydrolysis yielded carboxylic acid **9**.

In summary, we have been able to devise an expedient three-step route toward 3-(p-carboxyphenyl)pyrroles with a high degree of functional diversity, as demonstrated by a variety of substituents in position 5. This



Scheme 3. Synthesis of 5-unsubstituted pyrroles. Reagents: a) n-BuLi, methyl 4-(bromomethyl)benzoate, TMEDA, THF, $-78^{\circ}C$, 25 h; b) $Hg(OAc)_2$, H_2O/acetonitrile, rt, 30 min; c) 1,2-dibromoethyl acetate, methylamine (THF solution), EtOH, rt, 48 h; d) LiOH, THF/H_2O/MeOH, $50^{\circ}C$, 2 h.

route is suitable for large-scale production of the target molecules. To obtain the five-unsubstituted analogues, we developed a novel synthetic approach based on a modified Feist–Benary condensation of a benzyl ketone. The scope of the latter reaction will be studied, and results shall be reported in due course.

EXPERIMENTAL

Starting materials were purchased from Aldrich or Fluka. All reactions were monitored by TLC using silica-gel F254 plates (Merck), detected by UV light. Flash chromatography was carried out on silica gel 60 (40–63 μM, Merck) or with prepacked Biotage™ cartridges with the indicated solvent system. Melting points were measured on a Büchi melting-point apparatus B-545 and are uncorrected. ^{1}HNMR spectra were recorded at 400 MHz on a Bruker FT-NMR spectrometer as ppm downfield from tetramethylsilane with multiplicity, number of protons, and coupling constants. The following abbreviations are used to indicate spin multiplicities: s (singlet), bs (broad signal), d (doublet), t (triplet), and m (multiplet). Mass spectra were recorded on a Finnigan AQA spectrometer, applying electrospray ionization (ESI).

General Procedure for the Synthesis of Tetrasubstituted Pyrroles 1a–m

Aqueous NaOH 2N, (66 mmol) was added to a stirred slurry of the desired ketone (33 mmol) and 4-carboxybenzaldehyde **(2)** (33 mmol) in EtOH (120 ml). The obtained mixture was stirred at ambient temperature for 4 h, acidified with 1 N HCl, and filtered. The filter cake was triturated with hot EtOH. After cooling, the solid material was collected and dried to give chalkone **3**. To a slurry of **3** (3.49 mmol) in anhydrous EtOH (20 mL), subsequently Na_2CO_3 (3.49 mmol), freshly distilled carboxaldehyde (4.19 mmol), 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride (0.690 mmol), and triethylamine (3.49 mmol) were added under argon. The mixture was stirred at reflux temperature for 6 h. After cooling, the mixture was partitioned between 1 N HCl and EtOAc. After exhaustive extraction of the aqueous layer, the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to give crude diketone **4**. A solution of this material (2.35 mmol) in EtOH (10 mL) was treated with primary amine (11.8 mmol) and—in the case of amines other than methylamine—acetic acid (7 mmol). The mixture was heated to reflux for 3 h or irradiated in an Emrys Optimizer^{TM} for 5 min at 180 °C. After cooling, the mixture was partitioned between 1 N HCl and EtOAc. After exhaustive extraction of the aqueous layer, the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was recrystallized from, or triturated with, EtOAc.

Data

4-(2-Furan-2-yl-1-methyl-5-phenyl-1H-pyrrol-3-yl)benzoic acid (1a): mp = 212°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99 (d, 2H, 8.7 Hz), 7.56 (dd, 1H, J = 1.9 Hz, 0.8 Hz), 7.43–7.39 (m, 4H9, 7.34–7.39 (m, 1H), 7.36 (d, 2H, J = 8.7 Hz), 6.51 (s, 1H), 6.50 (dd, 1H, J = 3.3 Hz, 1.9 Hz), 6.41 (dd, 1H, J = 3.3 Hz, 0.8 Hz), 3.56 (s, 3H). MS (ESI): m/z = 344 [MH +].

4-[5-(4-Fluorophenyl)-2-furan-2-yl-1-methyl-1H-pyrrol-3-yl]benzoic acid (1b): mp = 211°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.98 (d, 2H, J = 8.6 Hz); 7.53 (dd, 1H, J = 1.9 Hz, 0.8 Hz); 7.45 (dd, 2H, J = 8.8 Hz, 5.3 Hz); 7.36 (d, 2H, J = 6.8 Hz); 7.14 (t, 2H, J = 8.6 Hz); 6.50 (dd, 1H, J = 3.3 Hz, 1.9 Hz); 6.47 (s, 1H); 6.40 (dd, 1H, J = 3.3 Hz, 0.8 Hz), 3.51 (s, 3H). MS (ESI): m/z = 362 [MH +].

4-[2-Furan-2-yl-5-(4-methoxyphenyl)-1-methyl-1H-pyrrol-3-yl] benzoic acid (1c): mp = 239°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.82 (dd, 1H, J = 1.9 Hz, 0.8 Hz); 7.81 (d, 2H, J = 7.9 Hz); 7.46 (d, 2H, J = 7.1 Hz); 7.28 (d, 2H, J = 7.9 Hz); 7.03 (t, 2H, J = 7.1 Hz); 6.64 (dd, 1H, J = 3.3 Hz, 1.9 Hz); 6.61 (dd, 1H, J = 3.3 Hz, 0.8 Hz); 6.52 (s, 1H); 3.79 (s, 3H); 3.44 (s, 3H). MS (ESI): m/z = 374 [MH +].

4-[5-(4-Cyanophenyl)-2-furan-2-yl-1-methyl-1H-pyrrol-3-yl]benzoic acid (1d): mp = 225 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.92 (d, 2H, J = 8.4 Hz); 7.83 (dd, 1H, J = 1.9 Hz, 0.8 Hz); 7.81 (d, 2H, J = 7.8 Hz); 7.77 (d, 2H, J = 7.8 Hz); 7.28 (d, 2H, J = 8.4 Hz); 6.82 (s, 1H); 6.68–6.64 (m, 2H); 3.53 (s, 3H). MS (ESI): m/z = 369 [MH +].

4-[5-(4-tert-(Butylsulfamoyl)phenyl)-2-furan-2-yl-1-methyl-1H-pyrrol-3-yl]benzoic acid (1e): mp = 229°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.89 (d, 2H, J = 8.4 Hz); 7.82 (s, 1H); 7.81 (d, 2H, J = 8.4 Hz); 7.74 (d, 2H, J = 8.4 Hz); 7.57 (s, 1H); 7.29 (d, 2H, J = 8.4 Hz); 6.76 (s, 1H); 6.67–6.64 (m, 2H); 3.53 (s, 3H); 1.12 (s, 9H). MS (ESI): m/z = 479 [MH +].

4-[5-(4-tert-(Butoxycarbonylamino)phenyl)-2-furan-2-yl-1-methyl-1H-pyrrol-3-yl]-benzoic acid (1f): mp = 195°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99 (d, 2H, J = 8.5 Hz); 7.56 (dd, 1H, J = 1.9 Hz, 0.8 Hz); 7.46 (d, 2H, J = 8.5 Hz); 7.41 (d, 2H, J = 8.5 Hz); 7.35 (d, 2H, J = 8.5 Hz); 6.63 (s, 1H); 6.50 (dd, 1H, J = 3.3 Hz, 1.9 Hz); 6.47 (s, 1H); 6.40 (dd, 1H, J = 3.3 Hz, 0.8 Hz); 3.53 (s, 3H); 1.55 (s, 9H). MS (ESI): m/z = 459 [MH +].

4-(2-Furan-2-yl-1,5-dimethyl-1H-pyrrol-3-yl)benzoic acid (1 g): mp = 223°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.76 (dd, 1H, J = 1.9 Hz, 0.8 Hz); 7.74 (d, 2H, J = 8.5 Hz); 7.17 (d, 2H, J = 8.5 Hz); 6.61 (dd, 1H, J = 3.3 Hz, 1.9 Hz); 6.52 (dd, 1H, J = 3.3 Hz, 0.8 Hz); 6.22 (s, 1H); 3.35 (s, 3H); 2.26 (s, 3H). MS (ESI): m/z = 282 [MH +].

4-(2-Furan-2-yl-1-methyl-5-pyridin-4-yl-1H-pyrrol-3-yl)benzoic acid (1 h): mp = 228°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.62 (dd, 2H, J = 6.2 Hz, 1.6 Hz); 7.83 (dd, 1H, J = 1.9 Hz, 0.8 Hz); 7.81 (d, 2H, J = 8.5 Hz); 7.57 (d, 2H, J = 6.2 Hz); 7.28 (dd, 2H, J = 8.5 Hz); 6.88 (s, 1H); 6.69–6.65 (m, 2H); 3.57 (s, 3H). MS (ESI): m/z = 345 [MH +].

4-(2-Furan-2-yl-1-phenethyl-5-phenyl-1H-pyrrol-3-yl)benzoic acid (1i): mp = 210°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.99 (d, 2H, J = 8.6 Hz), 7.61 (dd, 1H, J =1.9 Hz, 0.7 Hz), 7.37–7.46 (m, 4H), 7.36 (d, 2H, J = 8.6 Hz), 7.13–7.17 (m, 3H), 6.77 (m, 2H), 6.53 (dd, 1H, J = 3.3 Hz, 1.9 Hz), 6.48 (s, 1H), 6.34 (dd, 1H, J = 3.3 Hz, 0.7 Hz), 4.13 (t, 2H, J = 8 Hz), 2.68 (t, 2H, J = 8 Hz). MS (ESI): m/z = 434 [MH +].

4-[1-(2-(Dimethylamino)ethyl)-2-furan-2-yl-5-phenyl-1H-pyrrol-3-yl] benzoic acid (1j): mp = 189°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.90 (d, 2H, J = 8.3 Hz), 7.54 (m, 1H), 7.41–7.49 (m, 4H), 7.37 (m, 1H), 7.29 (d, 2H, J = 8.3 Hz), 6.48 (s, 1H), 6.45 (dd, 1H, J = 3.2 Hz, 1.8 Hz), 6.42 (d, 1H, J = 3.2 Hz), 4.19 (t, 2H, J = 7.9 Hz), 2.46 (t, 2H, J = 7.9 Hz), 2.12 (s, 6H). MS (ESI): m/z = 401 [MH +].

4-[2-Furan-2-yl-1-(2-morpholin-4-yl-ethyl)-5-phenyl-1H-pyrrol-3-yl]benzoic acid (1 k): mp = 219°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 7.78 (d, 2H, J = 8.4 Hz), 7.45 (m, 1H), 7.29–7.37 (m, 4H), 7.18–7.27 (m, 1H), 7.16 (d, 2H, J = 8.4 Hz), 6.38 (dd, 1H, J = 3.2 Hz, 1.9 Hz), 6.33 (s, 1H), 6.29 (d, 1H, J = 3.2 Hz), 3.95 (t, 2H, J = 7.3 Hz), 3.39 (m, 4H), 2.20 (t, 2H, J = 7.3 Hz), 2.20 (m, 4H). MS (ESI): m/z = 443 [MH +].

4-(2-Methyl-1-phenethyl-5-phenyl-1H-pyrrol-3-yl)benzoic acid (1l): mp = 179°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.12 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz), 7.35–7.45 (m, 5H), 7.20–7.24 (m, 3H), 6.93 (m, 2H), 6.27 (s, 1H), 4.16 (t, 2H, J = 7.7 Hz), 2.81 (t, 2H, J = 7.7 Hz), 2.36 (s, 3H). MS (ESI): m/z = 382 [MH +].

4-[1-(2-Methoxyethyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl]benzoic acid (1 m): mp = 154°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 8.11 (d, 2H, J = 8.4 Hz), 7.53 (d, 2H, J = 8.4 Hz), 7.40–7.46 (m, 4H), 7.32–7.36 (m, 1H), 6.36 (s, 1H), 4.15 (t, 2H, J = 6.4 Hz), 3.48 (t, 2H, J = 6.4 Hz), 3.24 (s, 3H), 2.50 (s, 3H). MS (ESI): m/z = 336 [MH +].

Methyl 4-(2-Furan-2-yl-[1,3]dithian-2-ylmethyl)benzoate (6)

To a solution of 2-[1,3]dithian-2-yl-furan **(5)**[9] (18.2 g, 97.7 mmol) in anhydrous THF (400 mL) at −78°C, TMEDA (113 g, 972 mmol) and n-BuLi (1.6M in hexane, 61 mL, 97.7 mmol) were added subsequently via dropping funnel. The mixture was stirred at that temperature for 60 min. A solution of methyl 4-(bromomethyl)-benzoate (22.4 g, 97.7 mmol) in anhydrous THF (100 mL) was added slowly, and the mixture was allowed to reach ambient temperature. Stirring was continued for 20 h. The mixture was carefully quenched with aq. NH_4Cl, stirred for another 30 min, and extracted with EtOAc. The combined extracts were washed with 1 N HCl, aq. $NaHCO_3$, and brine; dried (Na_2SO_4); and evaporated. The crude product was purified by flash chromatography (SiO_2, cyclohexane/EtOAc 10:1) to give **6**, mp = 84°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.72 (td, 2H, J = 8.3 Hz, 1.8 Hz); 7.68 (dd, 1H, J = 1.8 Hz, 0.8 Hz); 6.91 (d, 2H, J = 8.3 Hz); 6.38 (dd, 1H, J = 3.3 Hz, 1.8 Hz); 6.27 (dd, 1H, J = 3.3 Hz, 0.8 Hz); 3.79 (s, 3H); 3.42 (s, 2H); 2.87–2.77 (m, 2H); 2.75–2.64 (m, 2H); 2.00–1.91 (m, 1H); 1.82–1.68 (m, 1H). MS (ESI): m/z = 334 (M + H).

Methyl 4-(2-Furan-2-yl-2-oxoethyl)benzoate (7)

To a solution of **6** (6.00 g, 17.9 mmol) in 80% aq. acetonitrile (60 mL), $Hg(OAc)_2$ (14.3 g, 7.26 mmol) was added. After stirring at ambient temperature for 30 min, the mixture was filtered through celite and rinsed with Et_2O.

The filtrate was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was passed through a plug of silica gel (toluene/EtOAc 20:1) to give 2.92 g (66%) of **7** as a yellow oil of sufficient purity for the following step. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.02 (d, 1H, J = 1.7 Hz); 7.90 (d, 2H, J = 8.3 Hz); 7.62 (d, 1H, J = 3.3 Hz); 7.42 (d, 2H, J = 8.3 Hz); 6.74 (dd, 1H, J = 3.3 Hz, 1.7 Hz); 4.28 (s, 2H); 3.82 (s, 3H). MS (ESI): m/z = 245 (M + H).

4-(2-Furan-2-yl-1-methyl-1H-pyrrol-3-yl)benzoic Acid (9)

To a solution of **7** (3.24 g, 13.2 mmol) in anhydrous THF (20 mL), methylamine (33% in EtOH, 16.5 mL, 132 mmol) was added. The resulting solution was stirred for 30 min at ambient temperature under argon. 1,2-Dibromoethyl acetate[16] (3.26 g, 13.2 mmol) in anhydrous THF (5 mL) was added. After 24 h, another 16.5 mL of methylamine solution was added, and the mixture was stirred until no more starting material was detected by TLC (SiO_2, cyclohexane/EtOAc 1:1, R_f (product) = 0.65). The mixture was then partitioned between 1 N HCl and EtOAc. After exhaustive extraction of the aqueous layer, the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (SiO_2, cyclohexane/EtOAc 3:1) to give 2.54 g (68%) of methyl ester **8**. LiOH (8.5 mg, 0.355 mmol) was added to a solution of **8** (20 mg, 0.071 mmol) in THF/MeOH/H_2O (3:1:1, 1 mL). After stirring at 60°C for 2 h, the mixture was acidified with 1 N HCl and extracted with EtOAc. The combined extracts were dried (Na_2SO_4) and evaporated to give 19 mg (quant.) of **9**, mp = 187°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.8 (bs, 1H); 7.86–7.67 (m, 3H); 7.20 (d, 2H, J = 8.2 Hz); 6.98 (d, 1H, J = 2.4 Hz); 6.60 (s, 1H); 6.56 (d, 2H, J = 2.9 Hz); 6.42 (d, 1H, J = 2.4 Hz); 3.53 (s, 3H). MS (ESI): m/z = 268 (M + H).

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