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Hexafluoroisopropanol as solvent and promotor in the Paal-Knorr synthesis of *N*-substituted diaryl pyrroles

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ABSTRACT

An additive-free synthesis of challenging N-substituted aryl pyrroles from the often poorly soluble corresponding 1,4-diketones by means of the Paal-Knorr pyrrole synthesis is reported, which makes use of the unique properties of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as a solvent and reaction promotor. Our procedure offers simple execution and purification as well as easy scale-up and can be applied in the Paal-Knorr synthesis of a large number of structurally diverse pyrroles including the synthetically challenging tetra- and penta-substituted pyrroles in moderate to excellent yields. HFIP can also be used as solvent in the Paal-Knorr synthesis of furans and thiophenes; however, the solvent effect is more pronounced in synthesis of pyrroles.

1. Introduction

Aryl substituted pyrroles are found in a plethora of natural products and are key structural motifs in many pharmaceuticals, pesticides and fluorescent dyes [1,2]. For instance, Rutecarpine is a non-basic alkaloid with COX-2 inhibitory properties [3]; Lukianol A consists of a 3,4-diaryl substituted pyrrole backbone and has been discussed as an antitumor agent [4]; many structurally diverse pyrroles have been employed as antibacterial, anti-inflammatory or antioxidant agents [5], Chlorfenapyr, a 2-(4-chlorophenyl)-pyrrole, is a widely applied insecticide [6]. Furthermore, aryl-pyrroles have been used in materials science; for instance, in the functionalization of carbon nanotubes [7], or as biomarkers in diagnostics [8]. This list could continue endlessly displaying the vast diversity of applications and, therefore, clearly emphasizing the need of good synthetic access to these chemically valuable compounds.

Pyrroles can be readily obtained via the established Paal-Knorr pyrrole synthesis, which involves the condensation reaction of a 1,4-diketone and a primary amine [9–11]. Usually, the reaction is carried out in polar organic solvents with acid additives (Scheme 1A). However, solvent-free methods [12] or the use of green solvents such as naturally occurring mild organic acids [13], ionic liquids or deep eutectic solvents have been increasingly promoted [14–18]. Recent developments include cascade reaction protocols that provide convenient access to β-functionalized or polycyclic or 1,2-annulated pyrroles [19,20] or the use of chiral acid additives for the atroposelective synthesis of arylpyrroles [21].

During our recent work we have become interested in the 2,5-diphenyl-substituted pyrrole as a central structural motif in the design of potential aggregation inhibitors of the amyotrophic lateral sclerosis (ALS)-related superoxide dismutase 1 (SOD1) [22]. In order to create a library of suitable inhibitor candidates, we envisaged a modular synthesis strategy to access 2,5-diarylpyrroles with varying substituents at the pyrrole nitrogen as well as the phenyl rings. We identified 2,5-bis(4-cyanophenyl)pyrrole (**4**) as a suitable inhibitor precursor, as the nitrile groups can be readily converted into carboxylic acids, esters, amines, amides or aldehydes. Literature known syntheses of N-substituted 2,5-bis(4-cyanophenyl)pyrrole (**4**), which would match our idea of a modular synthesis approach, include palladium-catalyzed CH-activation of N-substituted pyrroles and activated benzonitriles at elevated temperatures [23–26]. However, only few N-substituted pyrroles are commercially available, and, on top of that, expensive. Paal-Knorr pyrrole synthesis starting from the 4,4′-

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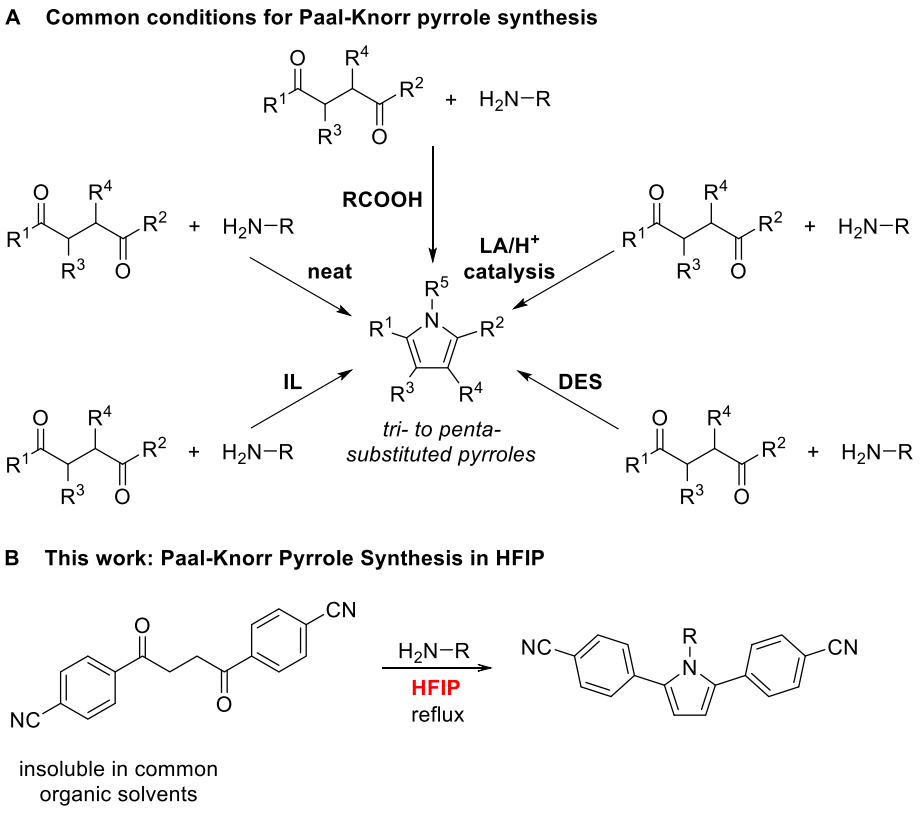


Scheme 1. Synthesis of 2,5-bis(4cyanophenyl) pyrrole (LA: Lewis acid, DES: deep eutectic solvent, IL: ionic liquid).

succinyldibenzonitrile (**1**) and inexpensive commercially available primary amines would allow easy variation of the N-substituent and hence facilitate molecule library synthesis. However, although the Paal-Knorr synthesis is largely established, protocols for the reaction of 1,4-diketones with electron-deficient aromatic substituents are relatively scarce. Taking the few reported examples, the yields are moderate at best, with the exception of a reaction of bis(4-nitrophenyl)butane-1,4-dione with methylamine in acetic acid, which gave excellent 98% yield [27–29].

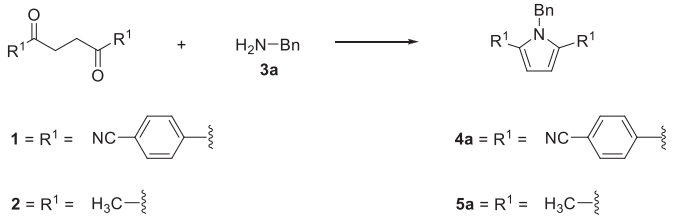
This report centers on the development of a Paal-Knorr pyrrole synthesis protocol using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) as solvent and as sole promotor of the reaction. These conditions are suitable for a broad range of amines and various 1,4-diketones including those with aromatic substituents. Whereas elevated temperatures and long reaction times are required in the conversion of aryl-1,4-diketones, aliphatic 1,4-diketones react instantly. Out of curiosity, we also tested HFIP in the Paal-Knorr synthesis of various furans and thiophenes. Whereas furans could be successfully synthesized upon the addition of catalytic amounts of hydrochloric acid, thiophenes were partly obtained as mixtures of furans and thiophenes using Lawesson's reagent as sulfur source. To reveal the opportunities of the HFIP-promoted Paal-Knorr pyrrole synthesis in the generation of a library of N-substituted 2,5-diarylpyrroles, we end our report with exemplary chemical functionalization of the 2,5-bis(4-cyanophenyl)pyrrole (**4**) core structure.

2. Results and discussion

2.1. HFIP promotes the Paal-Knorr pyrrole synthesis

We started our efforts in the synthesis of 2,5-bis(4-cyanophenyl) pyrrole (**4**) by using N,N-dimethylformamide (DMF) or dimethylsulfoxide (DMSO) and catalytic amounts of p-toluenesulfonic acid (PTSA) in the reaction of 1,4-diketone **1** and benzyl amine (**3a**). Yet, even under reflux conditions, only poor solubility of **1** was observed and, hence, no or little conversion was obtained (Table 1,

Table 1
Optimization of the reaction Conditions.



entry	1/2	3a eq	solvent	cat.	t (h)	T (°C)	yield (%)[a]
1	**1**	5	DMF	PTSA	12	100	0
2	**1**	5	DMSO	PTSA	24	130	12
3	**1**	neat	–	–	96	80	25
4	**1**	2.5	[BmIm]I[b]	PTSA	24	100	0
5	**1**	2.5	CC/U[c]	–	24	80	0
6	**1**	1.5	HFIP	–	48	60	74
7	**2**	1.5	HFIP	–	<0.1	r.t.	99
8	**2**	1.5	H_2O [31]	–	0.5	100	99
9	**2**	1.5	CC/U[c][16]	–	12	80	98
10	**2**	1.5	[BmIm]I[b][15]	–	1	95	98
11	**2**	1.5	None [32]	–	1	100	99

[a] Yields refer to isolated compounds.
[b] [BmIm]I = 1-Butyl-3-methylimidazolium Iodide.
[c] CC/U = 1:1 equimolar mixture of Cholin Chloride and Urea.

entries 1–2). As **1** appeared to be poorly soluble in any common organic solvent, we tried solvent-free conditions (Table 1, entry 3). This led to a slight increase in yield; however, the removal of excess **2a** proved to be difficult. Furthermore, this approach is impractical for expensive or solid amines. Solvent alternatives such as the ionic liquid 1-butyl-3-methylimidazolium iodide [15] (entry 4) or the deep eutectic solvent choline chloride/urea [16] (CC/U, entry 5) were similarly unsuitable as the solubility of **1** was poor and no conversion was observed even at elevated temperatures.

The low solubility of compounds like **1** could be explained by strong aromatic or polar interactions such as hydrogen bonds between the hydroxyl groups of the enol form of **1** and the nitrile groups. Therefore, fluorinated solvents or, more precisely, HFIP should be a suitable alternative due to its very potent hydrogen bonding donor properties, strong ionizing power but low nucleophilicity [30]. Hence, polar interactions such as hydrogen bonds should be disrupted. As HFIP is slightly acidic (pKa = 9.3), it serves as an acid catalyst and solvent at the same time. The low boiling point of 59 °C ensures easy removal at the end of the reaction. When performing the Paal-Knorr synthesis of **1** and **3a** in HFIP at reflux conditions but without any further additives desired **4a** was obtained in 74% yield. However, the reaction was slow and was stopped after two days (entry 6). Since HFIP is relatively expensive, the reaction was carried out at 0.5 M concentration of 1,4-diketone, the maximum concentration, at which **1** was still completely soluble.

As HFIP worked well with aryl-1,4-diketone **1**, we wanted to compare this procedure with literature-reported Paal-Knorr pyrrole synthesis protocols. Therefore, we performed the reaction in HFIP with 2,5-hexanedione (**2**), a commonly used "work horse" in the optimization of Paal-Knorr conditions, and benzyl amine (**3a**, entries 7–11). The reaction with HFIP was completed instantly giving almost quantitative yields of the desired pyrrole **5a** (entry 7). The very same reaction was then carried out under literature known conditions with all procedures giving excellent yields (Table 1, entries 8–11) [15,16,31,32]. In comparison, Paal-Knorr synthesis in HFIP proceeded by far most rapidly.

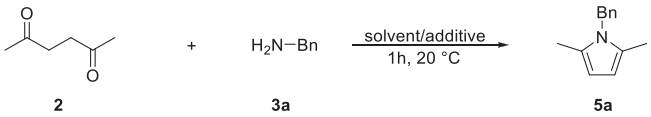
2.2. HFIP can be used as an acid catalyst

As HFIP is relatively expensive compared to more commonly used organic solvents, we have been interested in exploring the possibility of using only catalytic amounts of HFIP in order to accelerate the Paal-Knorr synthesis. This would be useful in case of well-soluble 1,4-diketones and represent an interesting alternative to typical Lewis-acid and Brønstedt-acid additives [9,10]. We chose the conversion of 2,5-hexanedione (**2**) with benzyl amine (**3a**) as our model reaction and initially tested the Paal-Knorr synthesis in various commonly applied organic solvents without HFIP additive (Table 2). Ethanol as protic solvent gave **5a** in the highest yield of 56% after 1h reaction time at room temperature (Table 2, entry 5). When repeating the reaction in ethanol under similar conditions but in the presence of 5-mol% HFIP, the yield had significantly been increased to 82% (Table 2, entry 6) indicating an accelerating effect on the Paal-Knorr synthesis most likely due to the acidic properties of HFIP. However, the reaction proceeds most rapidly in pure HFIP (Table 2, entry 7), and if the unique solubilizing properties of HFIP are required, the catalytic approach are less suitable.

2.3. HFIP-promoted Paal-Knorr pyrrole synthesis is broadly applicable

With the optimized reaction procedure in hand, we started to explore its scope and limitations. Initially, a series of amines (**3**) was reacted with the less reactive diketone **1** as well as the aliphatic 1,4-diketone **2**. Generally, Paal-Knorr synthesis with 4,4′-succinyldibenzonitrile (**1**) was performed under reflux conditions and stopped after two days giving yields of 41–76%, and showing the expected functional-group tolerance (Table 3) [33]. The use of aliphatic amines **3b** to **3f** and diketone **1** resulted in isolated yields of 50–76%. Interestingly, α- and β-branched amines **3f** and **3e** gave higher isolated yields than the sterically less demanding amines **3c** and **3d** (50% and 56%, Table 3, entries 4 and 5). The use of anilines **3g, 3h** and **3i** resulted in lower yields, in general, as they are less nucleophilic. Aniline **3g** gave a respectable isolated yield of 61%. However, Paal-Knorr synthesis of **1** with 4-aminophenol **3h** did not lead to full conversion and, in the case of 4-nitroaniline **3i**, no reaction was observed (Table 3, entries 8 and 9).

Table 2
Optimization of the catalytic activity of HFIP.



2 3a 5a

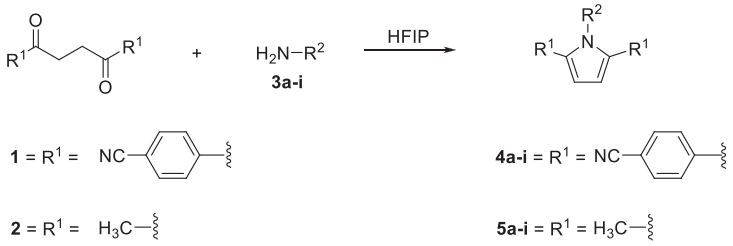
entry	3a eq	solvent	cat.	yield (%)[a]
1	1.5	DCM	–	45
2	1.5	EtOAc	–	41
3	1.5	Et_2O	–	39
4	1.5	Toluene	–	46
5	1.5	EtOH	–	56
6	1.5	EtOH	HFIP (5-mol%)	82
7[b]	1.5	HFIP	–	99

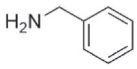
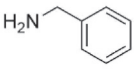
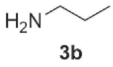
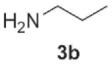
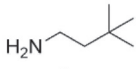
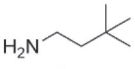
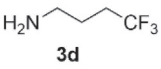
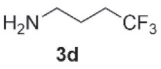
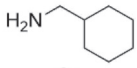
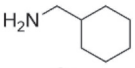
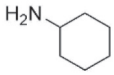
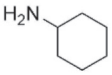
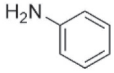
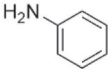
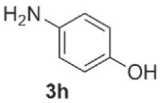
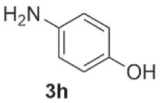
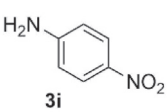
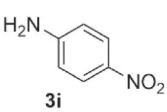
[a] Yields refer to isolated compounds.
[b] Reaction was complete within 5 min.

Paal-Knorr syntheses of the more reactive aliphatic 1,4-diketone **2** were performed at room temperature and completed within few minutes, when aliphatic amines were used. Reactions with alkyl amines **3b** to **3f** (Table 3, entries 11 to 15) gave excellent yields of 94% (**3d**) to almost quantitative 99% (**3b**). The use of less reactive anilines **3g**, **3h** and **3i** still resulted in very good yields of about 90%; however, reflux conditions were required.

Next, we continued our study by applying our reaction conditions to various 1,4-diketones (Table 4) including symmetric aromatic diketones (**6**–**9**, entries 3–6), asymmetric non-branched diketones (**10**–**12**, entries 7–9) and branched diketones (**13**–**16**, entries 10–13). We found that all 1,4-diketones resulted in isolated yields of 62%–82%, whilst a range of functional groups such as thioesters, sulfones, esters and nitro groups were tolerated. Interestingly, and somewhat to our surprise, non-substituted aromatic **6** gave the lowest yields. Aliphatic substituents accelerate the reaction, whereas electron-poor diketones such as **9** (Table 4, entry 6) show slower conversion. The synthesis of tetra- or penta-substituted pyrroles using Paal-Knorr synthesis is generally described as synthetically challenging [34,35]. We found that Paal-Knorr synthesis in HFIP provided poly-substituted **24** to **26** in good to very good yields (Table 4, entries 11–12). We also tested the Paal-Knorr synthesis of diketone **16** with **3a**. **16** is a literature-known precursor of Atorvastatin, one of the most commonly prescribed drugs targeting cardiovascular disease. Atorvastatin can be prepared in large quantities and high purity from **16** by means of a Paal-Knorr synthesis in a toluene/heptane solvent mixture with Pivalic Acid as a catalyst under Dean-Stark-conditions [36]. Hence, we were interested in examining the suitability of our protocol in the Paal-Knorr synthesis of **16** and **3a** as the primary amine. However, no product formation could be observed when carrying out the described reaction and the starting material was reisolated. This was probably due to the low boiling point of HFIP, which did

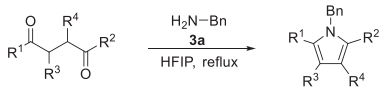
Table 3
Reaction scope of Paal-Knorr-pyrrole synthesis with varying Amines.

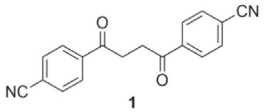
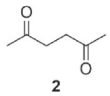
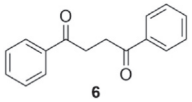
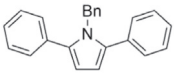
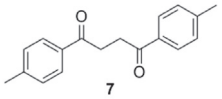
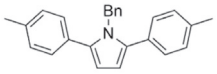
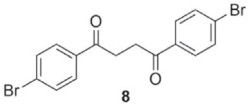
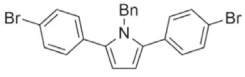
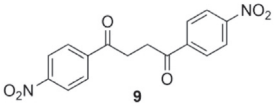
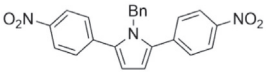
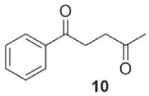
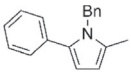
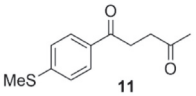
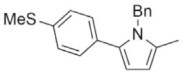
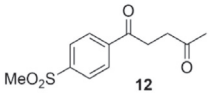
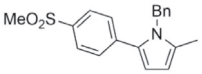
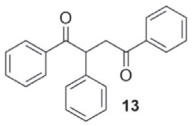
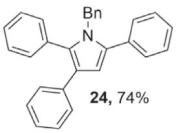
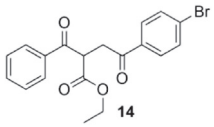
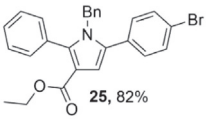
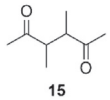
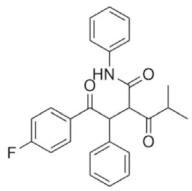
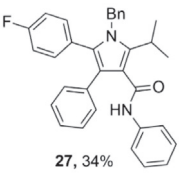


entry	amine	1	t (h)	T	yield[a] (%)	entry	amine	2	t (h)	T	yield[a] (%)
1	 3a	**1**	48	reflux	**4a**, 74	10	 3a	**2**	< 0.1	r.t.	**5a**, 99
2	 3b	**1**	48	reflux	**4b**, 76	11	 3b	**2**	< 0.1	r.t.	**5b**, 99
3	 3c	**1**	48	reflux	**4c**, 56	12	 3c	**2**	< 0.1	r.t.	**5c**, 97
4	 3d	**1**	48	reflux	**4d**, 50	13	 3d	**2**	< 0.1	r.t.	**5d**, 94
5	 3e	**1**	48	reflux	**4e**, 65	14	 3e	**2**	< 0.1	r.t.	**5e**, 98
6	 3f	**1**	48	reflux	**4f**, 76	15	 3f	**2**	< 0.1	r.t.	**5f**, 96
7	 3g	**1**	48	reflux	**4g**, 61	16	 3g	**2**	0.25	reflux	**5g**, 90[c]
8[b]	 3h	**1**	48	reflux	**4h**, 41	17[b]	 3h	**2**	0.25	reflux	**5h**, 88[c]
9	 3i	**1**	48	reflux	**4i**, 0	18	 3i	**2**	0.25	reflux	**5i**, 90[c]

[a] Yields refer to isolated compounds, [b] c(diketone) was 0.25 M

Table 4
Reaction scope of Paal-Knorr-pyrrole synthesis with varying 1,4-Diketones.



entry	diketone	t (h)	T	yield[a]
1	 **1**	48	reflux	 **4a,** 74%
2	 **2**	< 0.1	r.t.	 **5a,** 99%
3[b]	 **6**	48	reflux	 **17,** 62%
4[b]	 **7**	48	reflux	 **18,** 82%
5[b]	 **8**	48	reflux	 **19,** 79%
6[c]	 **9**	48	reflux	 **20,** 66%
7	 **10**	48	reflux	 **21,** 71%
8	 **11**	48	reflux	 **22,** 79%
9	 **12**	48	reflux	 **23,** 78%
10[c]	 **13**	72	reflux	 **24,** 74%
11	 **14**	72	reflux	 **25,** 82%
12	 **15**	< 0.1	r.t.	 **26,** 82%
13	 **16**	72	reflux	 **27,** 34%

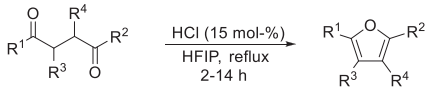
[a] Yields refer to isolated compounds, [b] c(diketone) was 0.25 M, [c] c(diketone) was 0.2 M.

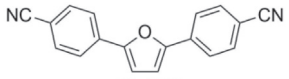
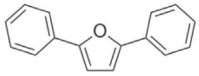
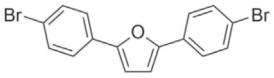
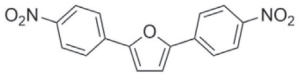
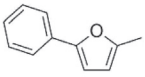
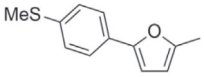
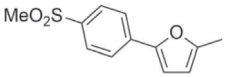
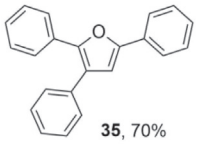
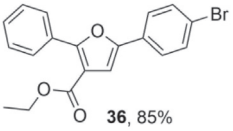
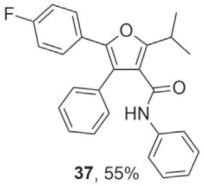
not allow sufficient energy to be added to the reaction to overcome the severe steric hindrance. Nevertheless, the desired product could be obtained in 34% yield when carrying out the reaction in a pressure tube at 90 °C, with all other conditions remaining unchanged (Table 4, entry 13).

2.4. HFIP as solvent in the Paal-Knorr synthesis of furans and thiophenes

The Paal-Knorr-furan synthesis is usually performed under acidic conditions. As HFIP is acidic on its own, we initially tried an acid-additive-free HFIP-promoted protocol using diketones **1** to **15**. However, no conversion was observed even under reflux conditions. Hence, we added catalytic amounts of HCl and obtained the desired furans in good to very good 70–91% yield (Table 5). Even the tetra-substituted furan **37**, using the Atorvastatin precursor **16**, was accessible by this protocol (Table 5, entry 10). This is comparable to previously reported methods, which have usually been performed in organic acids such as acetic acid or corrosive trifluoroacetic acid [37]. In contrast, Paal-Knorr thiophene synthesis

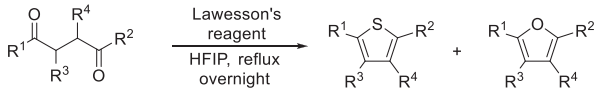
Table 5
Reaction scope of Paal-Knorr-furan synthesis with varying 1,4-Diketones.



entry	diketone	t (h)	yield[a]
1	**1**	2	 **28**, 88%
2[b]	**6**	3	 **29**, 80%
3[b]	**8**	2	 **30**, 91%
4[c]	**9**	2	 **31**, 85%
5	**10**	6	 **32**, 76%
6	**11**	2	 **33**, 87%
7	**12**	4	 **34**, 82%
8[c]	**13**	4	 **35**, 70%
9	**14**	4	 **36**, 85%
10	**16**	14	 **37**, 55%

[a]Yields refer to isolated compounds, [b] c(diketone) was 0.25 M,
[c] c(diketone) was 0.2 M.

Table 6
Reaction scope of Paal-Knorr-thiophene synthesis with varying 1,4-Diketones.



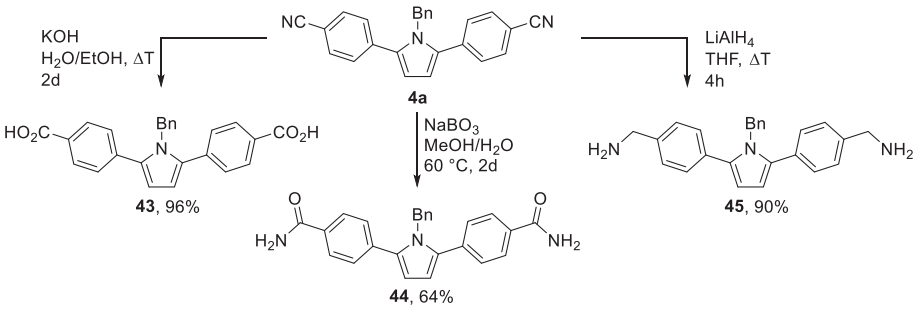
entry	diketone[a]	yield[b]	
1[c]	6	**38**, 56%	**29**, 14%
2	8	**39**, 83%	**30**, not detected
3	9	**40**, 82%	**31**, not detected
4	11	**41**, 73%	**33**, not detected
5	13	**42**, 39%	**35**, 31%

[a] c(diketone) was 0.17 M, [b]Yields refer to isolated compounds except for entry **5** where NMR integrals were used. [c] **38** has been purified by recrystallization giving a yield of 15%.

has proved to be more challenging as the formation of the corresponding furan has found to be a significant side reaction in some cases. We used Lawesson's reagent as a thiol source and refluxed the respective diketone at 0.17 M concentration in HFIP overnight (Table 6). The relatively low concentration was due to the reduced solubility of Lawesson's reagent in HFIP. Whereas diketones **8**, **9** and **11** reacted cleanly and in good yields to the desired thiophenes (Table 6, entries 2–4), diketone **6** and the trisubstituted diketone **13** gave inseparable mixtures of the respective thiophenes **38** and **42** and furans **29** and **35**, respectively (Table 6, entries 1 and 5).

2.5. 2,5-bis(4-Cyanophenyl)pyrrole is a precursor for functionalized aromatic pyrroles

The development of suitable reaction conditions for the Paal-Knorr synthesis with deactivated aromatic 1,4-diketones provided an excellent tool for the modular synthesis of a range of 2,5-diarylpyrroles. As stated in the introduction, we were mainly interested in 2,5-bis(4-cyanophenyl)pyrrole, as this compound can be readily converted into the respective amides, amines, carboxylic acids or aldehydes, which are intended to be explored as potential inhibitors of the aggregation of ALS-related SOD1. To demonstrate the versatility of our approach in the generation of a library of structurally diverse pyrroles, we converted **4a** to the respective dicarboxylic acid **43**, diamide **44** and diamine **45** (Scheme 2). These functionalizations are of special interest as compounds **43** to **45** can participate in electrostatic interactions and hydrogen bonding with our protein of interest SOD1. The conversion of **4a** to the corresponding dicarboxylic acid **43** was performed by basic hydrolysis using potassium hydroxide and succeeded in excellent 96% yield. However, refluxing for three days was required in order to avoid undesired and difficult to separate mixtures of nitriles, amides and carboxylic acids. The diamide **44** was obtained in 64% yield by following a literature reported procedure, which includes



Scheme 2. Functionalization of 2,5-bis(4-cyanophenyl)pyrroles.

equilibration of the nitrile compound (**4a**) with sodium perborate in a methanol-water-mixture for two days at elevated temperatures [38]. Finally, full reduction of **4a** with lithium aluminum hydride gave the diamine **45** in an isolated yield of 90%.

3. Conclusion

In summary, we have presented a new protocol for the well-established Paal-Knorr synthesis, which provides good access to synthetically demanding N-substituted 2,5-diarylpyrroles and higher substituted pyrroles that are interesting compounds for pharmaceutical purposes. Key to synthetic success is the use of HFIP as solvent and, as it is acidic, as catalyst at the same time. Hence, the work-up of the reaction is facilitated as HFIP can easily be removed from the reaction mixture if compared to DMF or DMSO. Our synthetic protocol is broadly applicable, as it was demonstrated by Paal-Knorr synthesis with various primary amines and di- to tetra-substituted 1,4-diketones. The optimized reaction conditions can be applied in gram scale as we have shown in the synthesis of **4a** (Experimental Section). To compare the efficiency of Paal-Knorr synthesis in HFIP with other established methods, we tested aliphatic 2,5-hexanedione **2** as diketone compound and found that the reaction proceeded instantly and at room temperature to give quantitative yields of the desired 2,5-bis(methyl)pyrrole **5a**. However, Paal-Knorr synthesis of 1,4-diaryl-1,4-diketones and electron-poor anilines as well as sterically demanding tetra-substituted 1,4-diketones remains challenging. Additionally, we could show that HFIP can also be applied in Paal-Knorr-furan or -thiophene synthesis; though catalytic amounts of hydrochloric acid have been required to promote the Paal-Knorr synthesis of furans.

Paal-Knorr synthesis is a modular synthesis using 1,4-diketones and primary amines, which are often commercially available and inexpensive. This makes it attractive for the generation of libraries of structurally diverse pyrroles. The successful synthesis of N-substituted 2,5-bis(4-cyanophenyl)-pyrroles has previously been reported, but uses palladium-catalyzed CH-activation of N-substituted pyrroles [23–26], which, compared to primary amines, are less well accessible. In contrast, Paal-Knorr synthesis of 2,5-diarylpyrroles bearing electron-withdrawing functional groups has scarcely been reported. We believe, this was due to the poor solubility of the 1,4-diketone precursors, an issue, which could be solved by using HFIP as solvent. In the last years, fluorinated alcohols such as trifluoroethanol (TFE) and HFIP have experienced increasing use as solvents in organic synthesis [39]. For instance, the positive effects of fluorinated solvents on chemoselectivity, stereoselectivity, yield and functional group tolerance have been reported in the halogenation of BODIPYs, cross-coupling reactions or various other stereoselective reactions [40–44]. Furthermore, a reaction-accelerating effect in several classical syntheses of heterocyclic compounds has been reported [45]. Although HFIP is more expensive than commonly used organic solvents, it is less expensive than many ionic liquids and, hence, could be more often considered as alternative solvent. In our case, the use of HFIP not only improved the solubility of an otherwise more or less insoluble 1,4-diketone and, in this way, expanded the scope of Paal-Knorr synthesis, it also led to fast conversions in the case of aliphatic 1,4-diketones and generally provided good to excellent yields. In the case of well-soluble compounds, we have shown the possibility of using small quantities of HFIP to catalyze the Paal-Knorr synthesis in ethanol. Therefore, we find our Paal-Knorr synthesis in HFIP to be a valuable addition to the literature-known Paal-Knorr synthesis protocols.

4. Experimental Section

4.1. General

1,1,1,3,3,3-Hexafluoroisopropanol was purchased from *ChemPur GmbH* (Karlsruhe, Germany) and used without further purification. Amines were purchased from *ChemPur GmbH* (Karlsruhe, Germany), *Thermo Fischer GmBH* (Kandel, Germany), *TCI Germany GmbH* (Eschborn, Germany) and *Merck* (Darmstadt, Germany) and used without further purification. Yields correspond to isolated compounds unless stated otherwise. Purity is estimated to be >95% based on ^{1}H-NMR spectroscopy. Reactions were monitored by thin layer chromatography (TLC) using standard silica gel pre-coated plates provided by *Merck* (Darmstadt, Germany) and impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or staining with a 2% ethanolic ninhydrin solution or a 3% aqueous solution of potassium permanganate followed by heating. Flash column chromatography was performed on silica gel 60 (230–300 mesh) purchased from *Macherey-Nagel* (Düren, Germany). Reaction work-up and flash chromatography was performed using analytical grade solvents. Analytical grade solvents were purchased from *Th. Geyer GmbH* (Renningen, Germany), *Fisher Scientific GmbH* (Schwerte, Germany) and *Thermo Fischer GmbH* (Kandel, Germany) and used without further purification. ^{1}H- and ^{13}C- NMR spectra were recorded on a *Bruker Avance III 500* spectrometer at 70.49 kG (^{1}H: 300 MHz, ^{13}C: 75 MHz, ^{19}F-NMR: 282 MHz) at 25 °C. The chemical shifts δ are expressed in parts per million (ppm) and referred to the solvent residue proton signals: $CDCl_3$ 7.26 ppm, CD_2Cl_2 5.32 ppm, DMSO-d_6 2.50 ppm, acetone-d_6 2.10 ppm (^{1}H-NMR); $CDCl_3$ 77.2 ppm, CD_2Cl_2 53.8 ppm, DMSO-d_6 39.5 ppm, acetone-d_6 29.8, 206.3 ppm (^{13}C-NMR). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constants in Hz, integration multiplicator. Please note the following clarification for ^{1}H-NMR: In 1,4-disubstituted benzenes the two aromatic proton signals can be assigned to an AA'XX' spin system, which leads to coupling patterns of higher order. For clarity reasons these signals are regarded as doublets and only one coupling constant is given. Infrared spectroscopy was performed on a *JASCO FT/IR-4100* spectrometer; analysis was performed using *JASCO Spectra Manager*. The spectra were recorded in the range of 4000–400 cm^{-1} and absorption bands are given in wave numbers (cm-1). High-resolution mass spectrometry data (HR-MS) were recorded on a *BRUKER microTOF* (ESI) or *JEOL AccuTOF* (EI) device.

4.2. 4,4′-Succinyldibenzonitrile (*1*)

$ZnCl_2$ (5.92 g, 43.4 mmol, 2 equiv), Et_3N (4.6 mL, 32.6 mmol, 1.5 equiv) and absolute ethanol (2.0 mL, 32.6 mmol, 1.5 equiv) were suspended in anhydrous toluene (50 mL) in an atmosphere of argon. The reaction mixture was stirred for 60 min. Then, 4-acetylbenzonitrile (4.73 g, 32.6 mmol, 1.5 equiv) and 4-(2-bromoacetyl)benzonitrile (4.84 g, 21.7 mmol, 1 equiv) were added and the suspension was stirred at room temperature for 7 days. The resulting yellow precipitate was filtered off, dissolved in hot DMF (150 mL, 80 °C) and crystallized by slow addition of methanol (20 mL). After storing at 0 °C for 12 h the crystals were filtered off and dried in air. The product was obtained as a light yellow, microcrystalline powder. 3.75 g, 70% yield. **m.p.**: 261 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 8.16 (d, 4 H, J = 8.61 Hz, 3-H, 3′-H), 8.02 (d, 4 H, J = 8.61 Hz, 4-H, 4′-H), 3.47 (s, 4 H, 7-H, 7′-H); **^{13}C-NMR** could not be measured because the product was not soluble enough in common organic solvents (DCM-d_2, DMSO-d_6, acetone-d_6); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2225, 1680, 1402, 1319, 1304, 1381, 1191, 1172,

1010, 860, 840, 783, 713, 694. **HR-MS** (ESI): *m/z* calculated for $C_{18}H_{12}N_2O_2$+Na^+: 311.0791 $[M+Na]^+$; observed 311.0786.

4.3. 1,4-bis(4-Bromophenyl)butane-1,4-dione (**8**)

$ZnCl_2$ (5.11 g, 37.5 mmol, 2 equiv), Et_3N (4.0 mL, 28.1 mmol, 1.5 equiv) and absolute ethanol (1.72 mL, 28.1 mmol, 1.5 equiv) were suspended in anhydrous toluene (50 mL) in an atmosphere of argon. The reaction mixture was stirred for 60 min. Then, 1-(4-bromophenyl)ethan-1-one (5.56 g, 28.1 mmol, 1.5 equiv) and 2-bromo-1-(4-bromophenyl)ethan-1-one (5.17 g, 17.8 mmol, 1 equiv) were added and the resulting suspension was stirred for 7 days at room temperature. The reaction mixture was washed with 10% H_2SO_4 (50 mL) and a saturated solution of $NaHCO_3$ (50 mL). The aqueous phase was extracted with EtOAc (2 × 50 mL) and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The residue was recrystallized from EtOAc (ca. 100 mL) and the product was obtained as a colorless crystalline solid. 4.98 g, 71% yield. **m.p.**: 289 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 7.95 (d, 4H, J = 8.85 Hz, 2-H, 2′-H), 7.76 (d, 4H, J = 8.85 Hz, 3-H, 3′-H), 3.39 (2, 4H, 6-H, 6′-H); **^{13}C-NMR** could not be measured because the product was not soluble enough in common organic solvents (DCM-d_2, DMSO-d_6, acetone-d_6); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2896, 1667, 1583, 1568, 1482, 1406, 1389, 1279, 1189, 1104, 1071, 977, 742, 783, 760, 658; **HR-MS** (ESI): *m/z* calculated for $C_{16}H_{12}Br_2O_2$+H^+: 394.9277 $[M+H]^+$; observed 394.9289.

4.4. 1,4-bis(4-Nitrophenyl)butane-1,4-dione (**9**)

$ZnCl_2$ (5.62 g, 41.2 mmol, 2 equiv), Et_3N (4.4 mL, 30.9 mmol, 1.5 equiv) and absolute ethanol (1.81 mL, 30.9 mmol, 1.5 equiv) were suspended in anhydrous toluene (50 mL) in an atmosphere of argon. The reaction mixture was stirred for 60 min. Then, 1-(4-nitrophenyl)ethan-1-one (5.00 g, 30.9 mmol, 1.5 equiv) and 2-bromo-1-(4-nitrophenyl)ethan-1-one (5.05 g, 20.6 mmol, 1 equiv) were added and the resulting suspension was stirred for 7 days at room temperature. The precipitated product was isolated by decantation and recrystallized from DMF (ca. 100 mL, 90 °C). The product was obtained as light orange needles. 4.33 g, 64% yield. **m.p.**: 243 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 8.39 (d, 4H, J = 8.88 Hz, 2-H, 2′-H), 8.27 (d, 4H, J = 8.88 Hz, 3-H, 3′-H), 3.54 (s, 4H, 6-H, 6′-H); **^{13}C-NMR** could not be measured because the product was not soluble enough in common organic solvents (DCM-d_2, DMSO-d_6, acetone-d_6); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 1683, 1602, 1517, 1397, 1341, 1317, 1222, 1172, 997, 942, 848, 737, 700, 682; **HR-MS** (EI): *m/z* calculated for $C_{16}H_{12}N_2O_6$: 328.0690 $[M]^+$; observed 328.0688.

4.5. General procedure for the synthesis of tri-to penta-substituted pyrroles

The 1,4-diketone (2 mmol) was dissolved in 4–10 mL of 1,1,1,3,3,3-hexafluoroisopropanol at ambient temperature. The respective amine (3 mmol) was added slowly and the mixture was stirred for the indicated time either at room temperature or under reflux conditions. The reaction mixture was allowed to cool to room temperature and the solvent was removed by means of a rotary evaporator or distilled for reuse. The residue was dissolved in dichloromethane (10 mL) and washed with 4 M HCl (20 mL) to remove excess amine. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The products were mostly pure; however, in some cases column chromatography was necessary using n-hexane/EtOAc as eluents.

4.6. 4,4′-(1-Benzyl-1H-pyrrole-2,5-diyl)dibenzonitrile (**4a**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification, column chromatography (n-hexane/EtOAc 4:1, R_f = 0.40) was performed. Yellow crystals, 338 mg, 74% yield. **Large scale synthesis (10 mmol)**: 72% yield. **m.p.**: 168 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ = 7.58 (d, 4H, J = 6.2 Hz, 8-H, 8′-H), 7.42 (d, 4H, J = 6.2 Hz, 7-H, 7′-H), 7.17–7.12 (m, 3H, 13-H, 13′-H, 15-H), 6.66–6.60 (m, 2H, 14-H, 14′-H), 6.47 (s, 2H, 3-H, 4-H), 5.21 (s, 2H, 11-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ = 137.9 (C-2, C-5), 137.3 (C-6, C-6′), 136.6 (C-12), 132.2 (C-8, C-8′), 128.8 (C-7, C-7′), 128.7 (C-14, C-14′), 127.5 (C-15), 125.5 (C-13, C-13′), 118.7 (C-10, C-10′), 112.1 (C-9, C-9′), 110.6 (C-3, C-4), 49.4 (C-11); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2922, 2221, 1599, 1178, 796, 706; **HR-MS** (ESI): *m/z* calculated for C25H17N3+Na^+: 382.1315 $[M+Na]^+$; observed 382.1314.

4.7. 1-Benzyl-2,5-dimethyl-1H-pyrrole (**5a**)

The reaction mixture was stirred at room temperature for 5 min and worked-up according to the general procedure. Light brown solid, 363 mg, 99% yield. **m.p.**: 48 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.35–7.19 (m, 3H, 10-H, 10′-H, 11-H), 6.91 (d, 2H, J = 8.43 Hz, 9-H, 9′-H), 5.81 (s, 2H, 3-H, 4-H), 5.03 (2, 2H, 7-H), 2.14 (s, 6H, 6-H, 6′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 138.9 (C-8), 128.6 (C-11), 127.7 (C-2, C-5), 126.9 (C-10, C-10′), 125.7 (C-9, C-9′), 105.4 (C-3, C-4), 46.6 (C-7), 12.2 (C-6, C-6′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}): 2918, 1652, 1493, 1408, 1355, 1303, 754, 725, 701, 689; **HR-MS** (ESI): *m/z* calculated for $C_{13}H_{15}N$ + H^+: 186.1277 $[M+H]^+$; observed 186.1275.

4.8. 4,4′-(1-Propyl-1H-pyrrole-2,5-diyl)dibenzonitrile (**4b**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 4:1, R_f = 0.57) was performed. Yellow crystals, 432 mg, 76% yield. **m.p.**: 144 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.72 (d, 4H, J = 6.2 Hz, 8-H, 8′-H), 7.55 (d, 4H, J = 6.2 Hz, 7-H, 7′-H), 6.38 (s, 2H, 3-H, 4-H), 4.06 (7, 2H, J = 7.1 Hz, 11-H), 1.18 (sex, 2H, J = 7.2 Hz, 12-H), 0.43 (t, 3H, J = 7.4 Hz, 13-H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ [ppm] = 138.0 (C-2, C-5), 136.7 (C-6, C-6′), 132.5 (C-8, C-8′), 128.8 (C-7, C-7′), 118.8 (C-10, C-10′), 112.1 (C-9, C-9′), 110.5 (C-3, C-4), 47.5 (C-11), 24.1 (C-12), 10.6 (C-13); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2922, 2358, 2341, 2220, 1600, 834, 777. **HR-MS** (ESI): *m/z* calculated for $C_{21}H_{17}N_3$+H^+: 312.1495 $[M+H]^+$; observed 312.1492.

4.9. 2,5-Dimethyl-1-propyl-1H-pyrrole (**5b**)

The reaction mixture was stirred at room temperature for 5 min and worked-up according to the general procedure. Brown oil, 269 mg, 99% yield. **m.p.**: 192 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 5.68 (s, 2H, 3-H, 4-H), 3.69 (t, 2H, J = 7.5 Hz, 7-H), 2.20 (s, 6 H, 6-H, 6′-H), 1.63 (m, 2 H, J = 7.5 Hz, 8-H), 0.94 (t, 3H, J = 7.5 Hz, 9-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 127.0 (C-2, C-5), 104.9 (C-3, C-4), 45.1 (C-7), 24.3 (C-8), 12.2 (C-6, C-6′), 11.0 (C-9); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2962, 1660, 1518, 1406, 1298, 1018, 892, 742; **HR-MS** (ESI): *m/z* calculated for $C_9H_{15}N$ + H^+ 138.1277 $[M+H]^+$; observed 138.1273.

4.10. 4,4′-(1-(3,3-Dimethylbutyl)-1H-pyrrole-2,5-diyl) dibenzonitrile (**4c**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column

chromatography (n-hexane/EtOAc 4:1, $R_f = 0.73$) was performed. Yellow crystals, 378 mg, 56% yield. **m.p.**: 192 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ [ppm] = 7.73 (d, 4H, J = 6.2 Hz, 8-H, 8′-H), 7.56 (d, 4H, J = 6.2 Hz, 7-H, 7′-H), 6.38 (s, 2H, 3-H, 4-H), 4.07 (t, 2H, J = 7.0 Hz, 11-H), 1.02 (t, 2H, J = 7.0 Hz, 12-H), 0.56 (s, 9H, 14-H, 14′-H, 14″-H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ [ppm] = 137.9 (C-2, C-5), 136.1 (C-6, C-6′), 132.4 (C-8, C-8′), 129.0 (C-7, C-7′), 118.8 (C-10, C-10′), 112.1 (C-9, C-9′), 110.7 (C-3, C-4), 44.0 (C-12), 42.5 (C-11), 29.6 (C-13), 28.7 (C-14); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2959, 2222, 1602, 1491, 1476, 1332, 1268, 1249, 1234, 1178, 1113, 1062, 850, 839, 769, 677; **HR-MS** (ESI): *m/z* calculated for $C_{24}H_{23}N_3$+Na^+: 376.1784 $[M+Na]^+$; observed 376.1785.

4.11. 1-(3,3-Dimethylbutyl)-2,5-dimethyl-1H-pyrrole (**5c**)

The reaction mixture was stirred at room temperature for 5 min and worked-up according to the general procedure. Red-brown solid, 341 mg, 97% yield. **m.p.**: 49 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 5.67 (s, 2H, 3-H, 4-H), 3.74 (m, 2H, J = 4.56 Hz, 7-H), 2.19 (s, 6H, 6-H, 6′-H), 1.46 (m, 2H, J = 4.56 Hz, 8-H), 1.01 (s, 9H, 10-H, 10′-H, 10″-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 126.7 (C-2, C-5), 104.9 (C-3, C-4), 44.5 (C-8), 39.8 (C-7), 29.7 (C-9), 28.9 (C-10, C-10′, C-10″), 12.0 (C-6, C-6′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2954, 1515, 1464, 1442, 1410, 1636, 1296, 1247, 1216, 1179, 1015, 975, 740; **HR-MS** (ESI): *m/z* calculated for $C_{12}H_{21}N$ + H^+: 180.1747 $[M+H]^+$; observed 180.1747.

4.12. 4,4'-(1-(4,4,4-Trifluorobutyl)-1H-pyrrole-2,5-diyl)dibenzonitrile (**4d**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 2:1, $R_f = 0.79$) was performed. Yellow crystals, 338 mg, 50% yield. **m.p.**: 136 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.75 (d, 4H, J = 6.2 Hz, 8-H, 8′-H), 7.58 (d, 4H, J = 6.2 Hz, 7-H, 7′-H), 6.44 (s, 2H, 3-H, 4-H), 4.20 (m, 2H, 11-H), 1.56–1.29 (m, 4H, 12-H, 13-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 137.3 (C-2, C-5), 137.0 (C-6, C-6′), 132.7 (C-8, C-8′), 128.7 (C-7, C-7′), 118.7 (C-10, C-10′), 112.6 (C-9, C-9′), 110.8 (C-3, C-4), 44.5 (C-11), 30.0 (q, C-13), 23.0 (d, C-12); **^{19}F-NMR** (282 MHz): δ = −66.90; **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2224, 1599, 1492, 1250, 1244, 1151, 1019, 1010, 841, 774, 677; **HR-MS** (ESI): *m/z* calculated for $C_{22}H_{16}F_3N_3$+H^+: 380.1369 $[M+H]^+$; observed 380.1364.

4.13. 2,5-Dimethyl-1-(4,4,4-trifluorobutyl)-1H-pyrrole (**5d**)

The reaction mixture was stirred at room temperature for 5 min and worked-up according to the general procedure. Red solid, 386 mg, 94% yield. **m.p.**: 51 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 5.71 (s, 2H, 3-H, 4-H), 3.81 (t, 2H, J = 5.22 Hz, 7-H), 2.20 (s, 6H, 6-H, 6′-H), 2.18–2.03 (m, 2H, 8-H), 1.93–1.81 (m, 2H, 9-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 127.2 (q, C-10), 127.0 (C-2, C-5), 105.5 (C-3, C-4), 42.0 (C-7), 30. 9 (q, C-8), 23.4 (C-8), 12.1 (C-6, C-6′); **^{19}F-NMR** (282 MHz): δ = −66.52; **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2939, 1402, 1380, 1290, 1251, 1135, 1032, 751; **HR-MS** (ESI):. *m/z* calculated for $C_{10}H_{14}F_3N$ + H^+: 206.1151 $[M+H]^+$; observed 206.1151.

4.14. 4,4'-(1-(Cyclohexylmethyl)-1H-pyrrole-2,5-diyl)dibenzonitrile (**4e**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 4:1, $R_f = 0.75$) was performed. Yellow crystals, 436 mg, 65% yield. **m.p.**: 161 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.70 (d, 4H, J = 6.2 Hz, 8-H, 8′-H), 7.53 (d, 4H, J = 6.2 Hz, 7-H, 7′-H), 6.35 (s, 2H, 3-H, 4-H), 3.92 (d, 2H, 11-H), 1.55 (s, 1H, 12-H), 1.41 (m, 2H, 13-H, 13′-H), 1.09–0.73 (m, 6H, 14-H, 14′-H, 15-H), 0.37 (m, 2H, 13-H, 13′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 138.0 (C-2, C-5), 137.3 (C-6, C-6′), 132.4 (C-8, C-8′), 128.6 (C-7, C-7′), 118.8 (C-10, C-10′), 112.0 (C-9, C-9′), 110.4 (C-3, C-4), 52.4 (C-11), 39.4 (C-12), 30.1 (C-13, C-13′), 25.9 (C-15), 25.4 (C-14, C-14′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2922, 2226, 1604, 1490, 1179, 836, 771; **HR-MS** (ESI): *m/z* calculated for $C_{25}H_{23}N_3$+Na^+: 388.1784 $[M+Na]^+$; observed 388.1783.

4.15. 1-(Cyclohexylmethyl)-2,5-dimethyl-1H-pyrrole (**5e**)

The reaction mixture was stirred at room temperature for 10 min and worked-up according to the general procedure. Brown oil, 375 mg, 98% yield. **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 5.68 (s, 2H, 3-H, 4-H), 3.54 (d, 2H, J = 7.14 Hz, 7-H), 2.18 (s, 6H, 6-H, 6′-H), 1.80–1.55 (m, 6H, C-8, C-9, C-9′, C-10, C-10′, C-11), 1.30–1.11 (m, 3H, C-10, C-10′, C-11), 1.06–0.88 (m, 2H, C-9, C-9′); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 127.6 (C-2, C-5), 104.9 (C-3, C-4), 49.8 (C-7), 39.5 (C-8), 31.0 (C-9, C-9′), 26.5 (C-11), 26.0 (C-10, C-10‘), 12.6 (C-6, C-6‘); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2919, 2848, 1511, 1446, 1403, 1353, 1291, 1018, 966, 738; **HR-MS** (ESI): *m/z* calculated for $C_{13}H_{21}N$ + H^+: 192.1747 $[M+H]^+$; observed 192.1747.

4.16. 4,4'-(1-Cyclohexyl-1H-pyrrole-2,5-diyl)dibenzonitrile (**4f**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 4:1, $R_f = 0.61$) was performed. Light yellow solid, 537 mg, 76% yield. **m.p.**: 189 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.72 (d, J = 8.43 Hz, 4H, 8-H, 8'-H), 7.55 (d, 2H J = 8.43 Hz, 7-H, 7′-H), 6.24 (s, 2H, 3-H, 4-H), 3.93 (tt, 1H, J = 3.33 Hz, J = 12.15 Hz, 11-H), 1.85 (d, 2H, J = 12.27 Hz, 12-H, 12′-H), 1.70–1.41 (m, 5H, 12-H, 12′-H, 13-H, 13′-H, 14-H), 1.17–0.99 (m, 2H, (13-H, 13′-H), 0.89–0.69 (m, 1H, 14-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.3 (C-2, C-5), 136.3 (C-6, C-6′), 131.9 (C-8, C-8′), 130.4 (C-7, C-7′), 118.8 (C-10), 111.9 (C-3, C-4), 110.8 (C-9, C-9‘), 59.5 (C-11), 34.6 (C-12, C-12‘), 26.4 (C-13, C-13‘), 25.1 (C-14); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2923, 2857, 2222, 1603, 1489, 1451, 1410, 1397, 1376, 1320, 1265, 1225, 1198, 1177, 1110, 1017, 843, 833, 770, 692; **HR-MS** (EI): *m/z* calculated for $C_{24}H_{21}N_3$: 351.1730 $[M]^+$; observed 351.1730.

4.17. 1-Cyclohexyl-2,5-dimethyl-1H-pyrrole (**5f**)

The reaction mixture was stirred at room temperature for 10 min and worked-up according to the general procedure. Yellow solid, 340 mg, 96% yield. **m.p.**: 56 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 5.64 (s, 2H, 3-H, 4-H), 3.99–3.79 (m, 1H, 7-H), 2.26 (s, 6H, 6-H, 6'-H), 1.98–1.67 (m, 7H, 8-H, 8′-H, 9-H, 9′-H, 10-H), 1.49–1.14 (m, 3H, 9-H, 9′-H, 10-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 127.5 (C-2, C-5), 106.0 (C-3, C-4), 56.3 (C-7), 32.5 (C-8, C-8‘), 26.6 (C-9, C-9‘), 25.6 (C-10), 14.1 (C-6, C-6‘); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2927, 2852, 1654, 1446, 1396, 1344, 1293, 1260, 1215, 1188, 1145, 1057, 1019, 994, 891, 777, 744; **HR-MS** (ESI): *m/z* calculated for $C_{12}H_{19}N$ + H^+: 178.1590 $[M+H]^+$; observed 178.1594.

4.18. 4,4'-(1-Phenyl-1H-pyrrole-2,5-diyl)dibenzonitrile (**4g**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 6:1, $R_f = 0.43$) was performed. Yellow solid, 421 mg, 61% yield. **m.p.**: 192 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.46 (d, 4H, J = 8.52 Hz, 8-H, 8'-H), 7.41–7.30 (m, 3H, 13-

H, 13′-H, 14-H), 7.14 (d, 2H, J = 8.52 Hz, 7-H, 7′-H), 7.06 (d, 2H, J = 7.86 Hz, 12-H, 12′-H), 6.63 (s, 2H, 3-H, 4-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 138.0 (C-2, C-5), 137.1 (C-6, C-6‘), 135.3 (C-11), 131.8 (C-8, C-8‘), 129.4 (C-13, C-13‘), 128.7 (C-12, C-12‘), 128.6 (C-7, C-7‘), 128.4 (C-14), 118.8 (C-10, C-10‘), 112.2 (C-3, C-4), 109.7 (C-9, C-9‘); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2361, 2222, 1599, 1491, 1428, 1346, 1179, 842, 778, 698. **HR-MS** (ESI): *m/z* calculated for $C_{24}H_{15}N_3$+Na^+: 368.1158 [M+Na]$^+$; observed 368.1153.

4.19. 2,5-Dimethyl-1-phenyl-1H-pyrrole (**5g**)

The reaction mixture was stirred at room temperature for 15 min and worked-up according to the general procedure. Yellow solid, 308 mg, 90% yield. **m.p.**: 51 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.51–7.36 (m, 3H, 9-H, 9'-H, 10-H), 7.25–7.16 (m, 2H, 8-H, 8′-H), 5.83 (s, 2H, 3-H, 4-H), 2.00 (s, 6H, 6-H, 6′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.1 (C-7), 128.9 (C-9, C-9′), 128.4 (C-2, C-5), 128.3 (C-10), 127.51 (C-8, C-8′), 105.7 (C-3, C-4), 12.7 (C-6, C-6′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2920, 1596, 1495, 1401, 1318, 1067, 1037, 1006, 772, 746, 716, 684; **HR-MS** (ESI): *m/z* calculated for $C_{12}H_{13}N$ + H^+: 172.1121 [M+H]$^+$; observed 172.1123.

4.20. 4,4'-(1-(4-Hydroxyphenyl)-1H-pyrrole-2,5-diyl) dibenzonitrile (**4h**)

The reaction mixture was refluxed for 2 days in an atmosphere of argon, was protected from sunlight and was worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 3:1, R_f = 0.54) was performed. Yellow solid, 296 mg, 41% yield. **m.p.**: 195 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 9.86 (2, 1H, OH), 7.68 (d, 2H, J = 8.58 Hz, 8-H, 8′-H), 7.23 (d, 2H, J = 8.58 Hz, 7-H, 7′-H), 6.99 (d, 2H, J = 8.70 Hz, 12-H, 12′-H), 6.75–6.73 (m, 4H, 3-H, 4-H, 13-H, 13′-H); **^{13}C-NMR** (75 MHz, DMSO-d_6): δ [ppm] = 157.8 (C-14), 137.4 (C-2, C-5), 135.7 (C-6, C-6′), 132.5 (C-8, C-8′), 130.3 (C-12, C-12′), 129.3 (C-11), 128.7 (C-7, C-7′), 119.3 (C-10, C-10′), 116.5 (C-13, C-13′), 112.6 (C-3, C-4), 109.1 (C-9, C-9′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3335, 2922, 2237, 2222, 1596, 1515, 1259, 1220, 1014, 836, 797, 781, 656; **HR-MS** (ESI): *m/z* calculated for $C_{24}H_{14}N_3O^-$: 360.1142 [M − H]$^-$; observed 360.1133.

4.21. 4-(2,5-Dimethyl-1H-pyrrole-1-yl)phenol (**5h**)

The reaction mixture was refluxed for 15 min and worked-up according to the general procedure. Yellow solid, 329 mg, 88% yield. **m.p.**: 103 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.07 (d, 2H, J = 8.7 Hz, 8-H, 8′-H), 6.91 (d, 2H, J = 8.7 Hz, 9-H, 9′-H), 5.81 (s, 2H, 3-H, 4-H), 5.16 (s, 1H, OH), 1.99 (s, 6H, 6-H, 6′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 155.1 (C-10), 131.9 (C-7), 129.5 (C-8, C-8′), 128.7 (C-2, C-5), 115.6 (C-9, C-9′), 105.3 (C-3, C-4), 12.6 (C-6, C-6′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3242, 1512, 1440, 1408, 1217, 1095, 999, 838, 820, 751; **HR-MS** (ESI): *m/z* calculated for $C_{12}H_{13}NO$ + H^+: 188.1070 [M+H]$^+$; observed 188.1070.

4.22. 2,5-Dimethyl-1-(4-nitrophenyl)-1H-pyrrole (**5i**)

The reaction mixture was refluxed for 15 min and worked-up according to the general procedure. Brown solid, 389 mg, 90% yield. **m.p.**: 143 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 8.33 (d, 2H, J = 6 Hz, 9-H, 9′-H), 7.39 (d, 2H, J = 6 Hz, 8-H, 8′-H), 5.91 (s, 2h; 3-H, 4-H), 2.06 (s, 6H, 6-H, 6′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 128.9 (C-9, C-9′), 128.4 (C-2, C-5), 124.4 (C-8, C-8′), 107.3 (C-3, C-4), 12.8 (C-6, C-6′); **FT-IR (solid): $\tilde{\nu}$ (cm^{-1})** = 1594, 1516, 1490, 1396, 1335, 1223, 1094, 1000, 853, 776, 764, 718, 689; **HR-MS** (ESI): *m/z* calculated for $C_{12}H_{12}N_2O_2$+H^+: 217.0972 [M+H]$^+$; observed 217.0977.

4.23. 1-Benzyl-2,5-diphenyl-1H-pyrrole (**17**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 9:1, R_f = 0.76) was performed. Colorless crystals, 381 mg, 62% yield. **m.p.**: 131 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.42–7.23 (m, 10H, 7-H, 7′-H, 8-H, 8′-H, 9-H, 9′-H), 7.14–7.05 (m, 3H, 13-H, 13′-H, 14-H), 6.63–6.58 (m, 2H, 12-H, 12′-H), 6.35 (s, 2H, 3-H, 4-H), 5.28 (s, 2H, 10-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.2 (C-11), 136.9 (C-2, C-5), 133.7 (C-6, C-6′), 128.9 (C-8, C-8′), 128.3 (C-7, C-7′), 128.2 (C-13, C-13′), 127.0 (C-9, C-9′), 126.7 (C-14), 125.8 (C-12, C-12′), 109.8 (C-3, C-4), 48.6 (C-10); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2357, 1599, 1480, 1448, 1360, 1321, 1024, 752, 731, 699, 663; **HR-MS** (ESI): *m/z* calculated for $C_{23}H_{19}N$ + H^+: 310.1590 [M+H]$^+$; observed 310.1595.

4.24. 1-Benzyl-2,5-di-p-tolyl-1H-pyrrole (**18**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 19:1, R_f = 0.72) was performed. Colorless crystals, 550 mg, 82% yield. **m.p.**: 144 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.25 (d, 4H, J = 8.1 Hz, 7-H, 7′-H), 7.17–7.07 (m, 7H, 8-H, 8′-H, 14-H, 14′-H, 15-H), 6.64–6.60 (m, 2H, 13-H, 13′-H), 6.28 (2, 2H, 3-H, 4-H), 5.24 (s, 2H, 11-H), 2.34 (s, 6H, 10-H, 10′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.5 (C-11), 136.8 (C-2, C-5), 136.5 (C-9, C-9′), 130.8 (C-6, C-6′), 129.0 (C-7, C-7′), 128.8 (C-8, C-8′), 128.2 (C-14, C-14′), 126.7 (C-15), 125.7 (C-13, C-13′), 109.4 (C-3, C-4), 48.4 (C-11), 20.8 (C-10, C-10′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2967, 2357, 2340, 1736, 1436, 1365, 1216; **HR-MS** (ESI): *m/z* calculated for $C_{25}H_{23}N$ + H^+: 338.1903 [M+H]$^+$; observed 338.1902.

4.25. 1-Benzyl-2,5-bis(4-bromophenyl)-1H-pyrrole (**19**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 8:1, R_f = 0.56) was performed. Colorless crystals, 735 mg, 79% yield. **m.p.**: 174 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.46 (d, 4H, J = 8.46 Hz, 7-H, 7′-H), 7.24 (d, 4H, J = 8.46 Hz, 8-H, 8′-H), 7.17–7.08 (m, 3H, 13-H, 13′-H, 14-H), 6.64–6.57 (m, 2H, 12-H, 12′-H), 6.35 (s, 2H, 3-H, 4-H), 5.20 (s, 2H, 10-H); **^{13}C-NMR** (75 MHz, CD2Cl2): δ [ppm] = 138.8 (C-11), 136.0 (C-2, C-5), 132.5 (C-6, C-6′), 131.5 (C-7, C-7′), 130.4 (C-8, C-8‘), 128.4 (C-13, C-13‘), 127.0 (C-14), 125.7 (C-12, C-12‘), 121.0 (C-9, C-9‘), 110.3 (C-3, C-4), 48.7 (C-10); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2962, 2031, 1477, 1409, 1358, 1322, 1259, 1097, 1068, 1008, 820, 776, 762, 715; **HR-MS** (ESI): *m/z* calculated for $C_{23}H_{17}Br_2N$ + H^+: 465.9801 [M+H]$^+$; observed 465.9800.

4.26. 1-Benzyl-2,5-bis(4-nitrophenyl)-1H-pyrrole (**20**)

The reaction mixture was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc 6:1, R_f = 0.43) was performed. Brown solid, 528 mg, 66% yield. **m.p.**: 139 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 8.20 (d, 4H, J = 8.88 Hz, 8-H, 8'-H), 7.56 (d, 4H, J = 8.88 Hz, 7-H, 7′-H), 7.17–7.10 (m, 3H, 13-H, 13′-H, 14-H), 6.67–6.61 (m, 2H, 12-H, 12′-H), 6.59 (s, 2H, 3-H, 4-H), 5.32 (s, 2H, 10-H, the signal overlaps with the solvent residue proton signal); **^{13}C-NMR** (75 MHz, CD2Cl2): δ [ppm] = 146.6 (C-9), 139.3 (C-11), 137.9 (C-6, C-6‘), 137.0 (C-2, C-5), 128.9 (C-7, C-7‘), 128.6 (C-13, C-13‘), 127.4 (C-14), 125.7 (C-10), 123.8 (C-8, C-8‘), 112.9 (C-3, C-4), 49.5 (C-10); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2960, 2921, 2851, 1590, 1508, 1337, 1258, 1012, 792, 750, 697, 678. **HR-MS** (EI): *m/z* calculated for

$C_{23}H_{17}N_3O_4$: 399.1214 $[M]^+$; observed 399.1212.

4.27. 1-Benzyl-2-methyl-5-phenyl-1H-pyrrole (**21**)

The reaction was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (Hexane/EtOAc, 20:1, R_f = 0.46) was performed. Light yellow oil, 175 mg, 71% yield. **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.35–7.19 (m, 9H, 7-H, 7'-H, 8-H, 8'-H, 9-H, 13-H, 13'-H, 14-H), 6.89 (d, 2H, J = 8.19 Hz, 12-H, 12'-H), 6.18 (d, 1H, J = 3.45 Hz, 3-H), 6.01 (dd, 1H, J = 3.45 Hz, J = 0.84 Hz, 4-H), 5.15 (s, 2H, 10-H), 2.14 (s, 3H, 15-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.1 (C-2), 134.4 (C-11), 133.9 (C-6), 130.5 (C-5), 128.6 (C-8), 128.5 (C-9), 128.3 (C-7), 126.9 (C-14), 126.5 (C-12), 125.6 (C-13), 108.0 (C-3), 107.2 (C-4), 47.5 (C-10), 12.3 (C-15); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2914, 1601, 1512, 1495, 1474, 1452, 1444, 1406, 1354, 1310, 1073, 1026, 748, 726, 695, 574, 536, 458; **HR-MS (ESI)**: *m/z* calculated for $C_{18}H_{17}N + H^+$: 248.1434 $[M+H]^+$; observed 248.1437.

4.28. 1-Benzyl-2-methyl-5-(4-(methylthio)phenyl)-1H-pyrrole (**22**)

The reaction was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 20:1, R_f = 0.64) was performed. Off-white solid, 232 mg, 79% yield. **m.p.**: 87.9 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.33–7.14 (m, 7H, C-8, C-13, C-13′, C-14, C-14′, C-15), 6.89 (d, 2H, J = 6.84 Hz, 7-H, 7'-H), 6.16 (d, 1H, J = 3.45 Hz, 3-H), 6.00 (dd, 1H, J = 3.45 Hz, J = 0.78 Hz, 4-H), 5.12 (s, 2H, 11-H), 2.45 (s, 3H, 10-H), 2.13 (s, 3H, 16-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.1 (C-2), 130. 7 (C-5), 130.3 (C-12), 128.8 (C-14), 128.6 (C-7), 126.9 (C-15), 126.4 (C-13), 125.8 (C-8), 125.4 (C-6), 107.9 (C-3), 107.2 (C-4), 47.5 (C-11), 15.5 (C-10), 12.3 (C-16); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2917, 1510, 1496, 1434, 1414, 1356, 1311, 1105, 1029, 818, 760, 727, 694; **HR-MS (ESI)**: *m/z* calculated for $C_{19}H_{19}NS + H^+$: 294.1311 $[M+H]^+$; observed 294.1314.

4.29. 1-Benzyl-2-methyl-5-(4-(methylsulfonyl)phenyl)-1H-pyrrole (**23**)

The reaction was refluxed for 2 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 2:1, R_f = 0.55) was performed. Yellow solid, 254 mg, 78% yield. **m.p.**: 140.4 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.80 (d, 2H, J = 8.31 Hz, 7-H, 7'-H), 7.46 (d, 2H, J = 8.31 Hz, 8-H, 8′-H), 7.35–7.21 (m, 3H, 14-H, 14′-H, 15-H), 6.91 (d, 2H, J = 7.29 Hz, 13-H, 13′-H), 6.36 (d, 1H, J = 3.57 Hz, 3-H), 6.08 (d, 1H, J = 3.57 Hz, 4-H), 5.19 (s, 2H, 11-H), 3.00 (s, 3H, 10-H), 2.17 (s, 3H, 16-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.1 (C-2), 138.5 (C-9), 137.9 (C-6), 132.9 (C-12), 132.5 (C-5), 128.8 (C-14, C-14′), 128.3 (C-8, C-8′), 127.5 (C-78, C-7′), 127.2 (C-15), 125.5 (C-13, C-13′), 110.3 (C-3), 108.1 (C-4), 47.8 (C-11), 44.4 (C-10), 12.3 (C-16); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2922, 1593, 1316, 1302, 1147, 964, 776, 761, 738, 726, 697; **HR-MS (ESI)**: *m/z* calculated for $C_{19}H_{19}NO_2S + H^+$: 326.1209 $[M+H]^+$; observed 326.1211.

4.30. 1-Benzyl-2,3,5-triphenyl-1H-pyrrole (**24**)

The reaction was refluxed for 3 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 10:1, R_f = 0.63) was perfomed. White solid, 285 mg, 74% yield. **m.p.:** 167.5 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] 7.55–7.00 (m, 18H, 7-H, 7′-H, 8-H, 8′-H, 9-H, 11-H, 11′-H, 12-H, 12′-H, 13-H, 15-H, 15′-H, 16-H, 16′-H, 17-H, 21-H, 21′-H, 22-H), 6.66–6.61 (m, 2H, 20-H, 20′-H), 6.57 (s, 1H, 4-H), 5.13 (s, 2H, 18-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.1 (C-2), 136.3 (C-10), 135.6 (C-19), 133.5 (C-6), 133.1 (C-14), 132.4 (C-5), 131.3 (C-8, C-8′), 129.0 (C-12, C-12′), 128.4 (C-16, C-16′), 128.4 (C-7, C-7′), 128.1 (C-15, C-15′), 128.0 (C-21, C-21′), 127.7 (C-9), 127.6 (C-11, C-11′), 127.1 (C-13), 126.7 (C-17), 125.9 (C-20, C-20′), 125.2 (C-22), 123.3 (C-3), 109.6 (C-4), 48.3 (C-18); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 1600, 1450, 1341, 805, 766, 750, 740, 695; **HR-MS (EI)**: *m/z* calculated for $C_{29}H_{23}N$: 385.1830 $[M]^+$; observed 385.1835.

4.31. Ethyl 1-benzyl-5-(4-bromophenyl)-2-phenyl-1H-pyrrole-3-carboxylate (**25**)

The reaction was refluxed for 3 days and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 10:1, R_f = 0.30) was performed. Colorless oil, 377 mg, 82% yield. **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.47 (d, 2H, J = 8.55 Hz, 14-H, 14′-H), 7.40–7.20 (m, 7H, 7-H, 7′-H, 8-H, 8′-H, 9-H, 15-H, 15′-H), 7.19–7.07 (m, 3H, 20-H, 20′-H, 21-H), 6.79 (s, 1H, 4-H), 6.66–6.57 (m, 2H, 19-H, 19′-H), 5.05 (s, 2H, 17-H), 4.10 (q, 2H, J = 7.12 Hz, 11-H), 1.12 (t, 3H, J = 7.12 Hz, 12-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 164.2 (C-10), 140.2 (C-13), 138.0 (C-18), 133.8 (C-6), 132.0 (C-2), 131.7 (C-5), 131.6 (C-14, C-14′), 130.8 (C-7, C-7′, C-8, C-8′), 128.3 (C-20, C-20′), 128.3 (C-9), 127.7 (C-15, C-15′), 127.1 (C-21), 125.7 (C-19, C-19′), 121.7 (C3), 114.4 (C-4), 111.2 (C-16), 59.4 (C-11), 48.5 (C-17), 13.9 (C-12); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 1712, 1474, 1454, 1413, 1267, 1176, 1100, 1073, 1035, 984, 836, 823, 778, 759, 736, 720, 706, 696; **HR-MS (EI)**: *m/z* calculated for $C_{26}H_{22}BrNO_2$: 459.0834 $[M]^+$; observed 459.0830.

4.32. 1-Benzyl-2,3,4,5-tetramethyl-1H-pyrrole (**26**)

The reaction was stirred for 5 min and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 10:1, R_f = 0.85) was performed. Reddish oil, 175 mg, 82% yield. **^{1}H-NMR** (300 MHz,CD_2Cl_2): δ [ppm] = 7.32–7.19 (m, 3H, 9-H, 9′-H, 10-H), 6.88 (d, 2H, J = 6.9 Hz, 8-H, 8′-H), 4.96 (s, 2H, 6-H), 2.03 (s, 6H, 11-H, 11′-H), 1.94 (s, 6H, 12-H, 12′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 139.6 (C-7), 128.5 (C-9, C-9′), 126.7 (C-2, C-5), 125.8 (C-8, C-8′), 122.3 (C-10), 113.0 (C-3, C-4), 46.7 (C-6), 9.5 (C-11, C-11′), 9.2 (C-12, C-12′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2916, 2857, 1643, 1495, 1453, 1393, 1351, 1215, 1190, 1101, 1029, 729, 695; **HR-MS (ESI)**: *m/z* calculated for $C_{15}H_{19}N + H^+$: 214.1590 $[M+H]^+$; observed 214.1589.

4.33. 1-Benzyl-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (**27**)

The reaction mixture was heated for 3 days in a pressure tube at 95 °C. Afterwards, the reaction mixture was diluted with ^{i}PrOH and acetone (1:1, ca. 15 mL) and cooled to 0 °C. The precipitated solid was isolated by filtration, washed with cold water to remove trace solvents, and dried in vacuo to afford the desired product. Yellow crystalline solid, 344 mg, 34% yield. **m.p.**: 219 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.37–6.84 (m, 19, H, 6-H, 6′-H, 7-H, 7′-H, 10-H, 10′-H, 11-H, 11′-H, 12-H, 15-H, 15′-H, 16-H, 16′-H, 17-H, 22-H, 22′-H, 23-H, 23′-H, 24-H), 5.09 (s, 2H, 20-H), 3.24 (sept, 1H, 18-H), 1.36 (d, 6H, J = 6.81 Hz, 19-H, 19′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 160.68 (C-13), 141.31 (C-4), 138.53 (C-9), 138.47 (C-14), 134.83 (C-21), 133.17 (C-7, C-7′), 130.46 (C-11, C-11′), 129.34 (C-1), 128.63 (C-6, C-6′), 128.29 (C-10, C-10′), 128.04 (C-5), 127.20 (C-12), 126.54 (C-17), 125.52 (C-23, C-23′), 123.47 (C-22, C-22′), 121.80 (C-2), 119.46 (C-16, C-16′), 116.12 (C-3), 115.16 (C-24), 114.87 (C-15, C-15′), 47.91 (C-20), 26.63 (C-18), 21.13 (C-19, C-19′); **^{19}F-NMR** (282 MHz, CD_2Cl_2): δ [ppm] = −114.44; **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3403, 2962, 1661, 1595, 1563, 1525, 1496, 1437, 1309, 1242, 1217, 1154, 845, 752, 736, 693: **HR-MS (ESI)**: *m/z* calculated for

$C_{33}H_{29}FN_2O + H^+$: 489.2337 $[M+H]^+$; observed 489.2338.

4.34. General procedure for the synthesis of di-to tetra-substituted furans or thiophenes

The 1,4-diketone (2 mmol) was dissolved in 4–10 mL 1,1,1,3,3,3-hexafluoroisopropanol at ambient temperature. Hydrochloric acid (15 mol-%) for furans or Lawessons's reagent (3.5 mmol) for thiophenes was added slowly and the mixture was stirred for the indicated time under reflux conditions. The reaction mixture was allowed to cool to room temperature and the solvent was removed. The residue was dissolved in an appropriate solvent and the insoluble solids were removed by filtration. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified with an appropriate method (column chromatography or recrystallization).

4.35. 2,5-bis(4-Cyanophenyl)furan (**28**)

The reaction was refluxed for 2 h and worked-up according to the general procedure. For purification the crude product was recrystallized from THF. Yellow solid, 238 mg, 88% yield. **m.p.:** 292.1 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.86 (d, 4H, J = 8.7 Hz, 6-H, 6-H, 6′-H, 6′-H), 7.72 (d, 4H, J = 8.7 Hz, 7-H, 7-H, 7′-H, 7′-H), 6.99 (s, 2H, 2-H, 3-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 152.8 (C-1, C-4), 133.8 (C-5, C-5′), 132.7 (7-C, 7-C, 7′-C, 7′-C), 124.1 (6-C, 6-C, 6′-C, 6′-C), 118.7 (9-C, 9′-C), 110.9 (8-C, 8′-C), 110.7 (2-C, 3-C); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3352, 2222, 1605, 842, 792, 664; **HR-MS (ESI)**: *m/z* calculated for $C_{18}H_{10}N_2O + Na^+$: 293.0685 $[M+Na]^+$; observed 293.0678.

4.36. 2,5-Diphenylfuran (**29**)

The reaction was refluxed for 3 h and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 10:1, R_f = 0.85) was performed. White solid, 176 mg, 80% yield. **m.p.:** 91 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.79 (d, 4H, J = 7.29 Hz, 6-H, 6′-H), 7.45 (t, 4H, J = 7.29 Hz, 7-H, 7′-H), 7.31 (7, 2H, J = 7.29 Hz, 8-H, 8′-H), 6.80 (s, 2H, 2-H, 3-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 155.3 (C-1, C-4), 130.7 (C-5, C-5′), 128.7 (C-7, C-7′), 127.4 (C-8, C-8′), 123.6 (C-6, C-6′), 107.3 (C-2, C-3); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3039, 1610, 1488, 1480, 1260, 1021, 928, 794, 754, 689, 671. **HR-MS (EI)**: *m/z* calculated for $C_{16}H_{12}O$: 220.0888 $[M]^+$; observed 220.0890.

4.37. 2,5-bis(4-Bromophenyl)furan (**30**)

The reaction was refluxed for 2 h and worked-up according to the general procedure. For purification the crude product was recrystallized from THF. Colorless needles, 342 mg, 91% yield. **m.p.:** 205.9 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 7.79 (d, 4H, J = 8.58 Hz, 7-H, 7-H, 7′-H, 7′-H), 7.65 (d, 4H, J = 8.58 Hz, 6-H, 6-H, 6′-H, 6′-H), 7.17 (s, 2H, 2-H, 3-H); **^{13}C-NMR** (75 MHz, DMSO-d_6): δ [ppm] = 152.4 (C-1, C-4), 132.3 (C-6, C-6, C-6′, C-6′), 129.6 (C-5, C-5′), 126.0 (C-7, C-7, C-7′, C-7′), 121.1 (C-8, C-8′), 109.7 (C-2, C-3); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 1471, 1406, 1106, 1072, 1020, 1004, 924, 824, 790, 715, 669; **HR-MS (EI)**: *m/z* calculated for $C_{16}H_{10}Br_2O$: 375.9098 $[M]^+$; observed 375.9104.

4.38. 2,5-bis(4-Nitrophenyl)furan (**31**)

The reaction was refluxed for 2 h and worked-up according to the general procedure. For purification the crude product was recrystallized from THF. Orange solid, 264 mg, 85% yield. **m.p.:** 270.4 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 8.35 (d, 4H, J = 8.85 Hz, 7-H, 7-H, 7′-H, 7′-H), 8.15 (d, 4H, J = 8.85 Hz, 6-H, 6-H, 6′-H, 6′-H), 7.56 (s, 2H, 2-H, 3-H); **^{13}C-NMR** (75 MHz, DMSO-d_6): δ [ppm] = 153.0 (C-1, C-4), 135.7 (C-8, C-8′), 125.1 (C-7, C-7, C-7′, C-7′), 125.0 (C-6, C-6, C-6′, C-6′), 113.6 (C-5, C-5′), 100.0 (C-2, C-3); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3117, 1594, 1504, 1485, 1327, 1287, 1105, 1035, 930, 851, 792, 750, 690; **HR-MS (EI)**: *m/z* calculated for $C_{16}H_{10}N_2O_5$: 310.0584 $[M]^+$; observed 310.0582.

4.39. 2-Methyl-5-phenylfuran (**32**)

The reaction was refluxed for 6 h and worked-up according to the general procedure. For purification column chromatography (n-pentane, R_f = 0.82) was performed. Slightly yellow oil, 128 mg, 81% yield. **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.62 (d, 2H, J = 7.38 Hz, 7-H, 7′-H), 7.36 (t, 2H, J = 7.77 Hz, 8-H, 8′-H), 7.22 (t, 1H, J = 7.95 Hz, 9-H), 6.57 (d, 1H, J = 3.20 Hz, 3-H), 6.08 (d, 1H, J = 3.20 Hz, 2-H), 2.37 (s, 3H, 5-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 152.1 (C-6), 131.1 (C-4), 128.6 (C-8, C-8′), 126.7 (C-9), 123.1 (C-7, C-7′), 107.6 (C-2), 105.9 (C-3), 100.0 (C-1), 13.4 (C-5); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2918, 1667, 1595, 1546, 1488, 1446, 1205, 1065, 1021, 784, 756, 589, 661; **HR-MS (EI)**: *m/z* calculated for $C_{11}H_{10}O$: 158.0732 $[M]^+$; observed 158.0728.

4.40. 2-Methyl-5-(4-(methylthio)phenyl)furan (**33**)

The reaction was refluxed for 2 h and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 10:1, R_f = 0.74) was performed. Yellow solid, 177 mg, 87% yield. **m.p.:** 81.8 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.55 (d, 2H, J = 8.55 Hz, 6-H, 6′-H), 7.24 (d, 2H, J = 8.55 Hz, 5-H, 5′-H), 6.52 (d, 1H, J = 3.18 Hz, 2-H), 6.07 (d, 1H, J = 3.18 Hz, 3-H), 2.49 (s, 3H, 10-H), 2.35 (s, 3H, 9-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 152.0 (C-1), 151. 8 (C-4), 136.9 (C-8), 128.1 (C-5), 126.6 (C-6, C-6′), 123.6 (C-7, C-7′), 107.7 (C-3), 105.6 (C-2), 15.6 (C-9), 13.4 (C-10); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2912, 2402, 1689, 1553, 1492, 1433, 1073, 1020, 974, 793, 771; **HR-MS (EI)**: *m/z* calculated for $C_{12}H_{12}OS$: 204.0609 $[M]^+$; observed 204.0599.

4.41. 2-Methyl-5-(4-(methylsulfonyl)phenyl)furan (**34**)

The reaction was refluxed for 4 h and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 4:1, R_f = 0.74) was performed. White solid, 194 mg, 82% yield. **m.p. (decomposition):** 140 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.89 (d, 2H, J = 8.61 Hz, 6-H, 6′-H), 7.79 (d, 2H, J = 8.61 Hz, 7-H, 7′-H), 6.78 (d, 1H, J = 3.29 Hz, 2-H), 6.15 (dd, 1H, J = 3.29 Hz, J = 0.87 Hz, 3-H), 3.04 (s, 3H, 9-H), 2.39 (s, 3H, 10-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 154.2 (C-5), 150.3 (C-4), 138.0 (C-8), 135.8 (C-1), 127.9 (C-6, C-6′), 123.4 (C-7, C-7′), 109.4 (C-2), 108.4 (C-3), 44.5 (C-9), 13.5 (C-10); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2919, 1590, 1300, 1279, 1143, 1089, 1026, 835, 796, 775; **HR-MS (ESI)**: *m/z* calculated for $C_{12}H_{12}O_3S + H^+$: 237.0580 $[M+H]^+$; observed 237.0582.

4.42. 2,3,5-Triphenylfuran (**35**)

The reaction was refluxed for 4 h and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 20:1, R_f = 0.79) was performed. Colorless crystals, 207 mg, 70% yield. **m.p.**: 95 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.79 (d, 2H, J = 7.71 Hz, 14-H, 14′-H), 7.62 (d, 2H, J = 7.17 Hz, 6-H, 6′-H), 7.51–7.23 (m, 11H, 7-H, 7′H, 8-H, 10-H, 10′-H, 11-H, 11′-H, 12-H, 15-H, 15′-H, 16-H), 6.87 (s, 1H, 2-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 152.5 (C-13), 147.9 (C-1), 134.2 (C-9), 131.1 (C-13), 130.4 (C-5), 128.8 (C-10, C-10′), 128.7 (C-15, C-15′),

128.6 (C-7, C-7′), 127.4 (C-11, C-11′), 127.6 (C-16), 127.6 (C-8), 127.3 (C-12), 126.1 (C-6, C-6′), 124.6 (C-3), 123.7 (C-14, C-14′), 109.5 (C-2); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2922, 2360, 1487, 1143, 950, 804, 766, 753, 687, 568; **HR-MS (EI)**: *m/z* calculated for $C_{22}H_{16}O$: 296.1201 $[M]^+$; observed 296.1202.

4.43. Ethyl 5-(4-bromophenyl)-2-phenylfuran-3-carboxylate (**36**)

The reaction was refluxed for 4 h and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 3:1, R_f = 0.88) was performed. Colorless liquid, 315 mg, 85% yield. **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 8.06 (d, 2H, J = 8.34 Hz, 13-H, 13′-H), 7.64 (d, 2H, J = 8.58 Hz, 6-H, 6′-H), 7.57 (d, 2H, J = 8.58 Hz, 7-H, 7′-H), 7.52–7.39 (m, 3H, 14-H, 14′-H, 15-H), 7.13 (s, 1H, 2-H), 4.31 (q, 2H, J = 7.11 Hz, 10-H), 1.35 (t, 3H, J = 7.11 Hz, 11-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 163.1 (C-9), 156.5 (C-12), 151.3 (C-5), 132.0 (C-7, C-7′), 129.6 (C-1), 129.4 (C-15), 128.8 (C-4), 128.3 (C-13, C-13′), 128.1 (C-14, C-14′), 125.4 (C-6, C-6′), 121.8 (C-8), 116.1 (C-3), 108.5 (C-2), 60.7 (C-10), 14.0 (C-11); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2973, 2360, 1271, 1479, 1267, 1238, 1157, 1094, 1071, 825, 813, 776, 753, 683; **HR-MS (EI)**: *m/z* calculated for $C_{19}H_{16}BrO_3$: 371.0277 $[M]^+$; observed 371.0280**.**

4.44. 5-(4-Fluorophenyl)-2-isopropyl-N,4-diphenylfuran-3-carboxamide (**37**)

The reaction was refluxed for 14 h and worked-up according to the general procedure. For purification column chromatography (n-hexane/EtOAc, 4:1, R_f = 0.62) was performed. Brown solid, 219 mg, 55% yield. **m.p.**: 160 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.38–7.21 (m, 8H, 11-H, 11′-H, 12-H, 15-H, 15′-H, 16-H, 16′-H, 17-H), 7.21–7.12 (m, 2H, 10-H, 10′-H), 6.89 (m, 2H, 6-H, 6′-H), 6.72 (m, 2H, 7-H, 7′-H), 2.43 (sept, 1H, J = 6.78 Hz, 18-H), 1.01 (d, 6H, J = 6.78 Hz, 19-H, 19′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 186.04 (C-4), 168.82 (C-13), 163.38 (C-8), 160.10 (C-1), 135.09 (C-14), 134.79 (C-9), 132.06 (C-6, C-6′), 130.77 (C-11, C-11′), 130.02 (C-15), 128.65 (C-16, C-16′), 128.10 (C-10, C-10′), 127.40 (C-15, C-15′), 127.33 (C-12), 127.10 (C-17), 116.55 (C-2), 114.60 (C-7, C-7′), 105.05 (C-3), 30.88 (C-18), 18.95 (C-19, C-19′); **^{19}F-NMR** (282 MHz, CD_2Cl_2): δ [ppm] = −114.49; **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2965, 1592, 1504, 1489, 1222, 1156, 1074, 845, 740, 704, 687; **HR-MS (ESI)**: *m/z* calculated for $C_{26}H_{22}FNO_2+H^+$: 400.1707 $[M+H]^+$; observed 400.1699.

4.45. 2,5-Diphenylthiophene (**38**)

1,4-Diphenylbutane-1,4-dione (200.2 mg, 0.84 mmol, 1 equiv.) and Lawesson's Reagent (564.5 mg, 1.26 mmol, 3 equiv.) were dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (6 mL) in an atmosphere of argon. The reaction mixture was refluxed for 18 h. The solvent was evaporated and the yellow residue was purified with column chromatography (n-hexane/EtOAc 25:1, R_f = 0.6). The ^{1}H-NMR spectrum revealed a mixture of the product and the corresponding furan in a ratio of 4:1. 139.0 mg, 70% yield. After recrystallization from hexane the product was obtained as white crystals. 29.5 mg, 15% yield. A furan impurification of 2% was detected by ^{1}H-NMR spectroscopy. **m.p.**: 151.7 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.66 (d, 4H, J = 7.26 Hz, 7-H, 7′-H), 7.41 (t, 4H, J = 7.26 Hz, 8-H, 8′-H), 7.37–7.25 (m, 4H, 3-H, 4-H, 9-H, 9′-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 143.5 (C-2, C-5), 134.2 (C-6, C-6′), 128.9 (C-8, C-8′), 127.6 (C-9, C-9′), 125.5 (C-7, C-7′), 124.1 (C-3, C-4); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2158, 1453, 939, 902, 803, 746, 682; **HR-MS (EI)**: *m/z* calculated for $C_{16}H_{12}S$: 236.0660 $[M]^+$; observed 236.0660.

4.46. 2,5-bis(4-Bromophenyl)thiophene (**39**)

1,4-bis(4-Bromo-phenyl)butane-1,4-dione (402.3 mg, 1.0 mmol, 1 equiv.) and Lawesson's Reagent (636.2 mg, 1.5 mmol, 3 equiv.) were dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (6 mL) in an atmosphere of argon. The reaction mixture was refluxed for 18 h. The solvent was evaporated and the yellow residue was purified with column chromatography (n-hexane/EtOAc 25:1, R_f = 0.55). White solid, 328.5 mg 83% yield. **m.p.**: 206.5 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.52 (s, 8H, 7-H, 7′-H, 8-H, 8′-H), 7.32 (s, 2H, 3-H, 4-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 142.59 (C-2, C-5), 133.1 (C-6, C-6′), 132.0 (C-8, C-8′), 127.0 (C-7, C-7′), 124.6 (C-3, C-4), 121.4 (C-9, C-9′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3076, 1446, 1400, 1118, 934, 825, 794; **HR-MS (EI)**: *m/z* calculated for $C_{16}H_{10}Br_2S$: 391.8870 $[M]^+$; observed 391.8867.

4.47. 2,5-bis(4-Nitrophenyl)thiophene (**40**)

1,4-bis(4-Nitrophenyl)-butane-1,4-dione (330 mg, 1.0 mmol, 1 equiv.) and Lawesson's Reagent (622.6 mg, 1.5 mmol, 3 equiv.) were dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (6 mL) in an atmosphere of argon. The reaction mixture was refluxed for 8 h. The solvent was evaporated and the yellow residue was refluxed in saturated sodium carbonate solution (20 mL) for 14 h. The suspension was then extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with saturated sodium carbonate solution (30 mL) and brine (30 mL). After drying over magnesium sulfate and evaporation of the solvent the product was obtained as a highly hygroscopic orange solid. 270 mg, 82% yield. **m.p. (decomposition)**: 257.0 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 8.28 (d, 4H, J = 8.89 Hz, 8-H, 8′-H), 7.83 (d, 4H, J = 8.91 Hz, 7-H, 7′-H), 7.57 (s, 2H, 3-H, 4-H); ^{13}C NMR could not be measured because the product was not soluble in common organic solvents (CD_2Cl_2, DMSO-d_6, acetone-d_6); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 1587, 1506, 1335, 1278, 1107, 846, 796, 746, 682; **HR-MS (EI)**: *m/z* calculated for $C_{16}H_{10}N_2O_4S$: 326.0361 $[M]^+$; observed 326.0358.

4.48. 2-Methyl-5-(4-(methylthio)phenyl)thiophene (**41**)

1-(4-(Methylthio)phenyl)pentane-1,4-dione (223.7 mg, 1.0 mmol, 1 equiv.) and Lawesson's Reagent (638.2 mg, 1.5 mmol, 3 equiv.) were dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (6 mL) in an atmosphere of argon. The reaction mixture was refluxed for 20 h. The solvent was evaporated and the yellow residue was purified with column chromatography (n-hexane/EtOAc 25:1, R_f = 0.65). Light yellow solid, 161.0 mg, 73% yield. **m.p.**: 117.7 °C; **^{1}H-NMR** (300 MHz, CD_2Cl_2): δ [ppm] = 7.47 (d, 2 H, J = 8.37, 7-H, 7′-H), 7.23 (d, 2 H, J = 8.34 Hz, 8-H, 8′-H), 7.09 (d, 2H, J = 3.51 Hz, 4-H), 6.73 (d, 2 H, J = 3.48 Hz, 3-H), 2.49 (s, 6 H, 11-H, 12-H); **^{13}C-NMR** (75 MHz, CD_2Cl_2): δ [ppm] = 141.9 (C-9), 140.0 (C-5), 137.9 (C-2), 132.1 (C-6), 127.3 (C8), 126.8 (C-4), 126.2 (C-7), 123.2 (C-3), 16.2 (C-11), 15.7 (C-12); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 2915, 1497, 1404, 1095, 944, 815, 796; **HR-MS (EI)**: *m/z* calculated for $C_{12}H_{12}S_2$: 220.0380 $[M]^+$; observed 220.0379.

4.49. 2,3,5-Triphenylthiophene (**42**)

1,2,4-Triphenylbutane-1,4-dione (317.2 mg, 1.0 mmol, 1 equiv.) and Lawesson's Reagent (609.4 mg, 1.5 mmol, 3 equiv.) were dissolved in 1,1,1,3,3,3-hexafluoroisopropanol (9 mL) in an atmosphere of argon. The reaction mixture was refluxed for 14 h. The solvent was evaporated and the yellow residue purified with column chromatography (n-hexane/EtOAc 25:1, R_f = 0.7). The ^{1}H-NMR spectrum showed a mixture of the product and the corresponding

furan in a ratio of 1:1. Recrystallization from n-hexane had no effect on the purity. The mixture was obtained as slightly yellow crystals, 300.1 mg, 91% yield. **HR-MS (EI)**: *m/z* calculated for $C_{22}H_{16}S$: 312.0973 $[M]^+$; observed 312.0974.

4.50. 4,4'-(1-Benzyl-1H-pyrrole-2,5-diyl)dibenzoic acid (**43**)

A mixture of 4,4'-(1-benzyl-1H-pyrrole-2,5-diyl)dibenzonitrile (718 mg, 2 mmol, 1 equiv) and KOH (898 mg, 16 mmol, 8 equiv) was refluxed in EtOH/H_2O (15 mL, 2:1) for 3 days. Ethanol was removed under reduced pressure and the resulting suspension was filtered. The filtrate was acidified to pH 2 with concentrated hydrochloric acid. The resulting precipitate was isolated by filtration, washed with cold water and dried under reduced pressure. Light yellow solid, 746 mg, 96% yield. **m.p.**: 273 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 12.91 (s, 2H, CO_2H), 7.92 (d, 4H, J = 8.55 Hz, 8-H, 8′-H), 7.56 (d, 4H J = 8.55 Hz, 7-H, 7′-H), 7.13–7.01 (m, 3H, 14-H, 14′-H, 15-H), 6.56–6.47 (m, 4H, 3-H, 4-H, 13-H, 13′-H), 5.38 (s, 2H, 11-H); **^{13}C-NMR** (75 MHz, DMSO-d_6): δ [ppm] = 167.5 (C-10, C-10′), 138.9 (C-13), 137.4 (C-2, C-5), 137.4 (C-6, C-6′), 130.1 (C-8, C-8‘), 129.5 (C-9, C-9‘), 128.8 (C-14, C-14‘), 128.6 (C-7, C-7‘), 127.4 (C-15), 125.8 (C-13, C-13‘), 112.1 (C-3, C-4), 49.2 (C-11); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3130–2020, 2969, 1698, 1604, 1422, 1278, 915, 866, 776, 701; **HR-MS** (ESI): *m/z* calculated for $C_{25}H_{19}NO_4$+H^+: 398.1387 $[M+H]^+$; observed 398.1385.

4.51. 4,4'-(1-Benzyl-1H-pyrrole-2,5-diyl)dibenzamide (**44**)

A mixture of 4,4'-(1-benzyl-1H-pyrrole-2,5-diyl)dibenzonitrile (718 mg, 2 mmol, 1 equiv) and sodium perborate (1.7 g, 11.1 mmol, 5.5 equiv) was dissolved in MeOH/H_2O (120 mL, 5:1) and equilibrated for 2 days at 60 °C. After cooling to room temperature a crystalline solid was formed and was filtered off along with boric acid and unreacted sodium perborate. The filter cake was washed thoroughly with water to remove water soluble salts and, afterwards, with dichloromethane to remove traces of unreacted starting material. The remaining solid was dissolved in a mixture of THF and Et_2O, washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was obtained as light yellow crystals. 506 mg, 64% yield. **m.p.**: 242 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 7.96 (s, 2H, 11-H, 11'-H), 7.86 (d, 4H, J = 8.31 Hz, 8-H, 8′-H), 7.50 (d, 4H, J = 8.31 Hz, 7-H, 7′-H), 7.35 (s, 2H, 11-H, 11′-H), 7.15–7.04 (m, 3H, 15-H, 15′-H, 16-H), 6.57 (d, 2H, J = 6.45 Hz, 14-H, 14′-H), 6.48 (s, 2H, 3-H, 4-H), 5.37 (s, 2H, 12-H); **^{13}C-NMR** (75 MHz, DMSO-d_6): δ [ppm] = 167.4 (C-10, C-10‘), 138.8 (C-13), 136.9 (C-2, C-5), 135.6 (C-6, C-6‘), 132.5 (C-9, C-9‘), 128.3 (C-15, C-15‘), 127.8 (C-7, C-7‘), 127.8 (C-8, C-8‘), 126.9 (C-16), 125.3 (C-14, C-14‘), 111.1 (C-3, C-4); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3380, 3160, 1650, 1604, 1384, 1328, 853, 766, 710, 673; **HR-MS** (ESI): *m/z* calculated for $C_{25}H_{21}N_3O_2$+H^+: 396.1707 $[M+H]^+$; observed 396.1703.

4.52. ((1-Benzyl-1H-pyrrole-2,5-diyl)bis(4,1-phenylene))-dimethanamine (**45**)

To a suspension of lithiumaluminum hydride (500 mg, 13.2 mmol, 6.6 equiv) in anhydrous THF (50 mL) 4,4'-(1-benzyl-1H-pyrrole-2,5-diyl)dibenzonitrile (718 mg, 2 mmol, 1 equiv) was added and the resulting suspension was refluxed for 3 h in an atmosphere of argon. After cooling to 0 °C, water (2.5 mL) was added slowly and the resulting mixture was stirred for 15 min. Then, a solution of sodium hydroxide (15% water, 2.5 mL) was added slowly to the reaction mixture from which a white solid was precipitated. Sodium sulfate (5 g) was added and the reaction mixture was filtered through Celite. The Celite was washed thoroughly with methyl *tert*-butyl ether. The combined organic phases were evaporated and the resulting yellowish solid was recrystallized from EtOAc. Pale yellow solid, 661 mg, 90% yield. **m.p.**: 152 °C; **^{1}H-NMR** (300 MHz, DMSO-d_6): δ [ppm] = 7.37–7.25 (m, 8H, 7-H, 7'-H, 8-H, 8′-H), 7.18–7.04 (m, 3H, 15-H, 15′-H, 16-H), 6.59 (d, 2H, J = 6.78 Hz, 14-H, 14′-H), 6.30 (s, 2H, 3-H, 4-H), 5.29 (2, 2H, 12-H), 3.69 (s, 4H, 10-H, 10′-H), 2.96 (s br, 4H, 11-H, 11′-H); **^{13}C-NMR** (75 MHz, DMSO-d_6): δ [ppm] = 143.00 (C-9, C-9′), 139.3 (C-13), 136.2 (C-2, C-5), 131.1 (C-6, C-6′), 128.3 (C-15, C-15′), 128.1 (C-8, C-8′), 127.1 (C-7, C-7′), 126.7 (C-16), 125.2 (C-14, C-14′), 109.5 (C-3, C-4), 48.0 (C-12), 45.3 (C-10, C-10′); **FT-IR (solid)**: $\tilde{\nu}$ (cm^{-1}) = 3024, 2849, 1570, 1496, 1438, 1416, 1382, 1360, 1321, 1049, 1016, 968, 819, 769, 729, 694; **HR-MS** (ESI): *m/z* calculated for $C_{25}H_{25}N_3$+H^+: 368.2121 $[M+H]^+$; observed 368.2118.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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