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Synthesis of 2,5-Diaryl-Substituted Thiophenes as Helical Mimetics: Towards the Modulation of Islet Amyloid Polypeptide (IAPP) Amyloid Fibril Formation and Cytotoxicity

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Abstract: A range of 2,5-diarylated thiophenes were synthesised as small molecule mimetics of the α-helix to modulate the amyloidogenesis and cytotoxic effect of islet amyloid polypeptide (IAPP). 3-Substituted thiophene-2-carboxylic acids were used as key intermediates and functionalised by palladium decarboxylative cross-coupling and direct C–H activation successively with overall yields ranging from 23 to 95%. The effect of the ligands on IAPP amyloid fibril formation was evaluated with the thioflavin T (ThT) fluorescence-based assay. Furthermore, the capacity of these compounds to inhibit the cytotoxic effect of IAPP was assessed using β-pancreatic cells.

Introduction

The aberrant assembly of polypeptides into insoluble protein aggregates, including amyloid fibrils, is the hallmark of several diseases, such as Alzheimer's, type II diabetes (DM-2) and systemic amyloidosis.[1] These protein misfolding/aggregation disorders differ by the identity of the protein that misassembles and by the tissue subjected to protein deposition and cellular degeneration.[2] For instance, in patients afflicted by DM-2, the islet amyloid polypeptide (IAPP) deposits in the pancreas, leading to the degeneration of the islets of Langerhans.[3] IAPP is a 37-amino acid C-terminally α-amidated peptide that is co-secreted with insulin by pancreatic β-cells. IAPP is an unusual aggregation-prone peptidic hormone that readily forms amyloid fibrils.[3] The IAPP amyloidogenic process observed in the pancreas is believed to accelerate DM-2 pathogenesis by exacerbating β-cell degeneration and ultimately compromising insulin secretion.[3] When applied to isolated pancreatic β-cells in culture, IAPP is cytotoxic by mechanisms that are still not clearly understood.[4] Over the last two decades, several compounds have been reported to inhibit IAPP aggregation in vitro by interfering with the later stages of fibrillogenesis, that is, through the destabilisation of the ordered cross β-sheet quaternary structure of the amyloid fibrils.[4b,5] However, this mechanism does not prevent the formation of prefibrillar oligomers that were recently recognised as the most cytotoxic proteospecies of the amyloidogenic cascade,[6] suggesting a potential drawback to this approach.

IAPP exhibits a conformational ensemble mainly populated by disordered conformations in its non-aggregated soluble state, although it diverges from an absolute random coil by the presence of local and transient ordered structure.[7] Recent mechanistic studies have suggested that this pro-amyloidogenic peptide undergoes a random coil to α-helix conformational conversion during the initial phase of self-assembly and that the helical intermediates could be on-pathway to amyloid formation.[7,8] According to this model, α-helix formation and self-association of helical segments are linked and accelerate self-assembly,[8] with similar driving forces to those of coiled coil motif formation. Consequently, this accelerated self-assembly generates a high local concentration of the amyloidogenic domain of IAPP (segment 20–29), which has a high propensity to adopt a β-structure, favouring the formation of cross-β-sheet assemblies and en route to amyloid formation. Consistently, IAPP was shown to adopt a helical structure spanning approximately residues 8 to 19 when the peptide was bound to model membranes[9] or glycosaminoglycans (GAGs),[4a] and these interactions accelerate the rate of IAPP amyloid fibril formation.

According to the helical intermediates hypothesis described above, an alternative strategy to control the formation of IAPP amyloid fibrils would be to design molecules that target and stabilise the transient helical segment 8–19 of IAPP, modulating the helix-assembly process. This approach could inhibit the formation of oligomeric and fibrillar aggregates by over-stabilising the helical intermediates, not allowing the propagation of the β-sheet conformation from the 20–29 domain of IAPP. Recent studies using membrane models have shown that, indeed, IAPP can be trapped in a non-amyloid prone helical conformation.[8,9b,10] Alternatively, as reported for lipids and GAGs, helical targeting ligands could potently accelerate the

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self-assembly of IAPP into β-sheet-rich amyloid fibrils by initially shifting the conformational equilibrium towards the α-helix, without overly stabilising the helical motif. Considering that oligomers are the most potent cytotoxic proteospecies,[6c] both pathways will decrease the toxicity induced by the amyloidogenic process of IAPP, either by blocking the formation of prefibrillar assemblies (α-helix over-stabilisation) or by accelerating the structural conversion of oligomers into less cytotoxic amyloid fibrils.

Miranker and Hamilton groups recently developed small molecules targeting the transient helical state of IAPP in order to inhibit lipid-catalysed aggregation.[11] These polycarboxylate ligands were developed on pyridyl, quinoline or peptoid scaffolds and were shown to inhibit lipid-induced IAPP aggregation, but to strongly accelerate IAPP fibrillogenesis in lipid-free conditions. Alternatively, other synthetic templates have been shown to be attractive scaffolds towards interacting/stabilising the α-helical region of proteins.[12] Functionalised terphenyls[13] (compound **1**) represent one such scaffold with a reported application as a mimic of the α-helix side chain of smooth muscle myosin light chain kinase (smMLCK) to disrupt its interaction with calmodulin (CaM; Figure 1 a).[14]

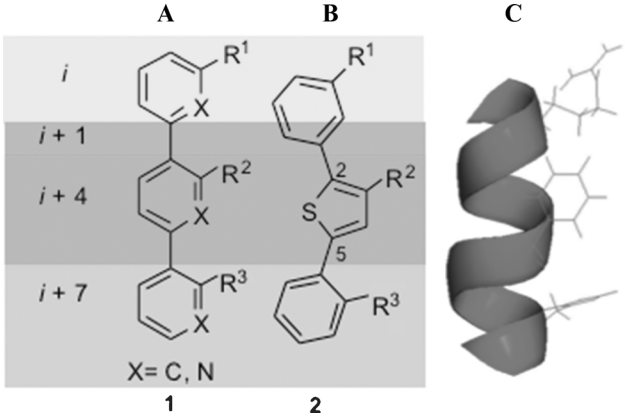


Figure 1. A) 3,2′,2″-Tris-substituted terphenyl template (compound **1**), B) 2,5-diaryl substituted thiophene template (compound **2**), C) ribbon representation of IAPP α-helix (PDB ID: 2KB8).[25]

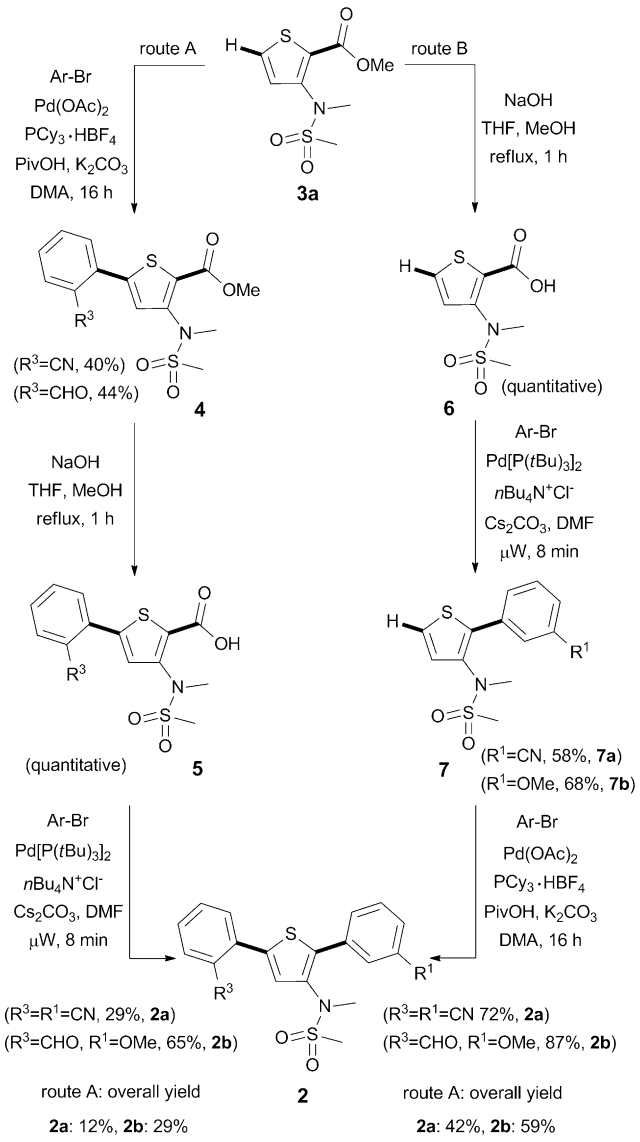
Binding of ligands to the helical motif largely results from the interaction of the ligand with the amino acid side chains projecting on one face of the α-helix and spaced three or four residues away from each other, referred to as *i*, *i*+4 and *i*+7 (Figure 1). In the transient helical conformation of IAPP comprising residues 8–19, residues Arg11, Phe15 and His18 are oriented on one face of the α-helix[9a] and represent the key motif that will be targeted to stabilise the transient α-helix of IAPP (Figure 1 c). As hypothesised from coiled coil motifs formation, the presence of hydrophilic side chains (Arg, His) will provide the specificity of interaction whereas the hydrophobic residue Phe will contribute to the thermodynamic stability of the interaction by hydrophobic core packing.

Relying on the bioisosterism of thiophene and benzene,[15] we have designed a library of compounds related to the terphenyl scaffold. The replacement of benzene with thiophene allows for several significant synthetic advantages. The presence of the heteroatom in thiophene introduces changes in reactivity that allows convenient chemo- and regioselective pathways that are unavailable in the synthesis of terphenyl compounds. Specifically, a five-membered heteroaromatic core scaffold (Figure 1 b, compound **2**) affords a flexible synthetic approach in which substituent modifications can be made in a modular manner while avoiding the long synthetic routes that have been used previously for the synthesis of terphenyls.[14]

The synthesis of diaryl substituted heteroaromatics has been previously accomplished through various palladium catalysed cross-coupling reactions. The predominant strategies involve the utilisation of organometallic precursors and/or result in the formation of symmetrically substituted heteroaromatics.[15b,16] For example, palladium catalysed C–H activation reactions have emerged as attractive methods for the formation of carbon–carbon bonds between heteroarenes and aryl halides without the use of organometallic derivatives.[17] However, the main limitation of C–H functionalisation of 3-substituted thiophenes is the formation of mixed arylated products at the C2 and C5 positions.[18] To avoid this limitation yet still take advantage of a C–H arylation strategy while controlling the regioselectivity of the products, commercially available 3-substituted thiophene 2-carboxylic acids have been used in combination with decarboxylative cross-coupling. Decarboxylative cross-coupling reactions have been developed as a powerful method for the formation of carbon–carbon bonds between aliphatic and aromatic carboxylic acids and aryl or vinyl substrates.[19] Decarboxylative arylation processes circumvent the requirement of organometallic building blocks[20] offering readily available, inexpensive and easy to use coupling partners. In this view, we performed palladium catalysed decarboxylative cross-coupling reaction of thiophene carboxylic acids and various aryl bromides.[18b,21] The combination of both the C–H arylation and decarboxylative cross-coupling reactions allows for a short, modular pathway through which a large library of α-helix mimetic compounds can be readily synthesised. In the current work, the molecules produced by this approach were tested as modulators of the formation of IAPP fibrils as a proof-of-concept. However, the general synthetic route can be used for the preparation of molecules tailored with different side-chain residues to stabilise and/or interact with the α-helix of other proteins for various applications.[22]

Results and Discussion

Two pathways have been envisaged for the preparation of 2,5-diarylated thiophenes (**2**), differing only in the order of the two different coupling reactions (Scheme 1). As illustrated in Scheme 1, route A utilises C5-arylation of the substituted thiophene methyl ester **3 a** resulting in aryl-thiophene intermediate **4** followed by saponification to provide carboxylic acid **5**. Decarboxylative cross-coupling of acid **5** results in the formation of the desired 2,5-diaryl substituted thiophene **2**. Alternatively, initial saponification of ester **3 a** in pathway B provides the thiophene carboxylic acid intermediate **6** that can undergo de-



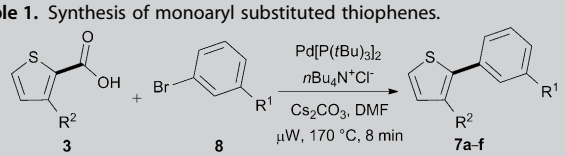
Scheme 1. Comparison of the two synthetic pathways.

carboxylative cross-coupling to afford aryl-thiophene **7**. This is followed by C5-arylation to provide the desired 2,5-diaryl substituted thiophene **2**.

Initially, in order to compare the efficiency of each pathway, both routes were carried out using the same substituted aryl-bromides (2- and 3-bromobenzonitrile). Interestingly, both the C5-arylation and decarboxylative cross-coupling steps in route A resulted in lower yields compared to route B, giving overall yields of 2,5-diaryl substituted thiophene **2a** of 12 and 42% ($R^1=CN$, $R^3=CN$), respectively. In order to examine whether the superior efficiency of route B was general, other functionalised aryl halides were also employed in both pathways. Scheme 1 shows one other example using 2-bromobenzaldehyde and 3-bromoanisole in which, once again, a higher overall yield was observed with route B compared to route A (59 vs. 29%, respectively, $R^1=OMe$, $R^3=CHO$). Route B was therefore chosen for the preparation of the remaining analogues.

The required thiophene carboxylic acids underwent decarboxylative cross-coupling with a variety of aryl-bromides to produce the corresponding arylated thiophenes (Table 1).[18b] The protocol efficiently transforms 3-substituted thiophene carboxylic acid derivatives to a range of 2-aryl-substituted heteroaromatics in moderate to good yields (Table 1). We examined electron-poor and -rich aryl bromides and the results illustrate that both types of substituents are well tolerated in the reaction.

Table 1. Synthesis of monoaryl substituted thiophenes.



Entry	R^2	R^1	Product	Yield[a] [%]
1	*N*-MeMs	CN	**7a**	58
2	*N*-MeMs	OMe	**7b**	68
3	*N*-MeMs	CO_2Et	**7c**	66
4	Me	CN	**7d**	69
5	Me	OMe	**7e**	75
6	Me	CO_2Et	**7f**	61

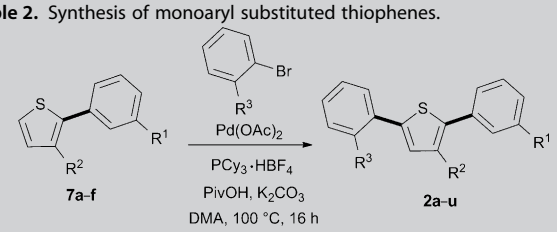
[a] Isolated yields. Condition: thiophene carboxylic acid (2 equiv), aryl bromide (1 equiv), $Pd[P(tBu)_3]_2$ (0.05 equiv), $nBu_4N^+Cl^-$ (1 equiv), Cs_2CO_3 (1.5 equiv), anhydrous DMF, 8 min microwave irradiation at 170 °C.

Fagnou and co-workers have developed C–H activation reaction conditions utilising a wide range of hetroaromatics and aryl bromides.[17q] The products from the decarboxylative cross-coupling reaction were subjected to these C–H activation conditions to effect a regioselective C–H activation at the C5 position of the 2-arylthiophene to generate 2,5-diaryl substituted thiophenes. A range of aryl bromides were utilised and moderate to excellent yields were obtained (Table 2). Moreover, the electron density of the existing substituent aryl group on the thiophene did not affect the yields.

All compounds were initially investigated for their capacity of modulating IAPP amyloid fibril formation by means of the thioflavin T (ThT) fluorescence assay. ThT is a dye that fluoresces upon its binding to protein aggregates with a cross-β-sheet structure, mostly fibrillar in morphology.[23] IAPP amyloidogenesis is a nucleation-dependent polymerisation process that is characterised by a ThT-negative phase (lag-phase; around 6 h), in which the high-energy nucleus is formed, followed by a thermodynamically favourable elongation phase that is characterised by the rapid growth of ThT-positive fibrils (Figure 2A). According to the helical intermediates described above, the random coil→α-helix conformational conversion occurred during the initial stage of the lag phase. Analysis of the aggregation kinetics obtained by ThT fluorescence gave us early mechanistic insights about the effects of these substituted thiophenes on IAPP amyloidogenic pathway.

Among all compounds prepared in the course of this study, compound **2l** (Table 2, entry 16) slowed the formation of ThT-positive aggregates, as observed by the increase of the lag-

Table 2. Synthesis of monoaryl substituted thiophenes.



Entry	R^3	R^2	R^1	Product	Yield[a] [%]
7	CN	Me	OMe	**2c**	23
8	CHO	Me	OMe	**2d**	79
9	CF_3	Me	OMe	**2e**	81
10	CO_2Et	Me	OMe	**2f**	73
11	CO_2Et	Me	CO_2Et	**2g**	94
12	CN	Me	CO_2Et	**2h**	81
13	CF_3	Me	CO_2Et	**2i**	72
14	CHO	Me	CO_2Et	**2j**	65
15	CF_3	Me	CN	**2k**	47
16	CN	Me	CN	**2l**	50
17	H	Me	CN	**2m**	69
18	CHO	*N*-MeMs	OMe	**2b**	87
19	CN	*N*-MeMs	OMe	**2n**	75
20	CF_3	*N*-MeMs	OMe	**2o**	78
21	CO_2Et	*N*-MeMs	CN	**2p**	77
22	CHO	*N*-MeMs	CN	**2q**	64
23	CF_3	*N*-MeMs	CN	**2r**	95
24	CN	*N*-MeMs	CN	**2a**	72
25	CHO	*N*-MeMs	CO_2Et	**2s**	65
26	CF_3	*N*-MeMs	CO_2Et	**2t**	75
27	CN	*N*-MeMs	CO_2Et	**2u**	93

[a] Isolated yields. Condition: heterocyclic thiophene (1 equiv), aryl halide (2 equiv), $Pd(OAc)_2$ (0.05 equiv), $PCy_3{\cdot}HBF_4$ (0.1 equiv), PivOH (0.3 equiv), K_2CO_3 (1.5 equiv), anhydrous DMF, 16 h thermal heating at 100 °C.

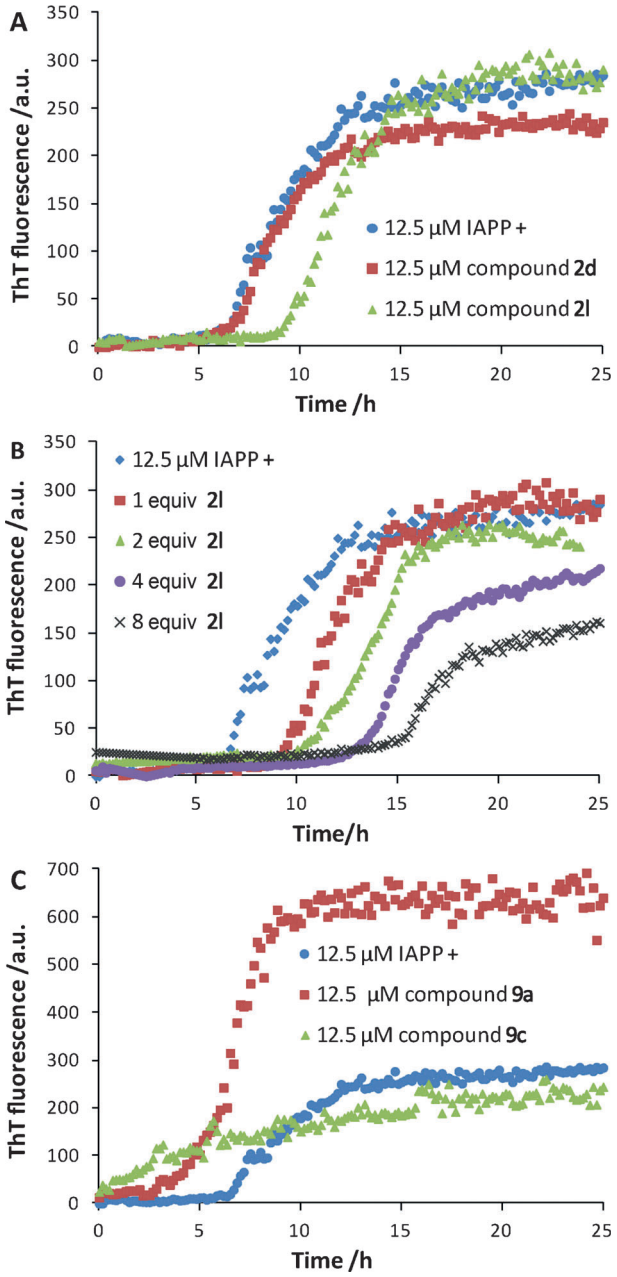


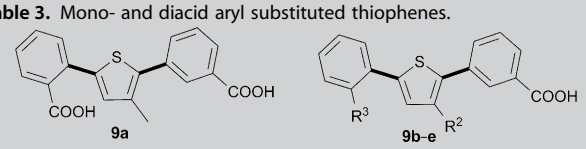
Figure 2. Effects of 2,5-diaryl substituted thiophenes on IAPP kinetics of amyloid fibril formation monitored by ThT fluorescence. IAPP (12.5 μM) was incubated in 20 mM Tris, pH 7.4, at 25 °C without agitation in the absence (A, B and C; ●) or in the presence of 12.5 μM of compound **2d** (A; ■), 12.5 μM compound **2l** (A; ▲), increasing molar equivalent of compound **2l** (B), 12.5 μM of compound **9a** (C; ■) or 12.5 μM compound **9c** (C; ▲). ThT fluorescence (40 μM) was measured every 10 min over the course of 25 h, with excitation at 440 nm and emission at 485 nm.

phase period (Figure 2A) when the compound was used at an equimolar ratio. Moreover, compound **2l** showed concentration-dependence inhibition of the formation of IAPP ThT-positive aggregates, with a lag phase of 15 h at 8 molar equivalents (100 μM; Figure 2B).

At 50 and 100 μM (4 and 8 equivalents, respectively) compound **2l** also decreased the final ThT fluorescence, suggesting that a lower amount of IAPP amyloid fibrils were formed and/or that these aggregates showed a less defined cross-β-sheets quaternary structure. We also varied the concentration of ThT fluorescent dye to confirm that this inhibitory effect was not the result of a displacement of ThT binding to fibrillar aggregates by compound **2l**. Our results showed that in the presence of 10, 40 or 100 μM ThT, the increase of the lag-phase period observed with 12.5 μM of compound **2l** was very similar (data not shown), strongly suggesting that this molecule was, indeed, slowing down the amyloidogenic process. The mechanism by which this 2,5-diaryl substituted thiophene decelerates and partially inhibits IAPP amyloid formation is currently under investigation based on these interesting preliminary results. In contrast, most of the other molecules prepared had little or no effect on the kinetics of IAPP amyloid formation, as represented by compound **2d** (Figure 2A; see the Supporting Information for additional results). Nonetheless, several of these compounds (compounds **2i**, **2j**, **2n**, **2o**, **2p** and **2t**) increased the final ThT fluorescence without affecting the lag phase or the rate of amyloid fibrils formation (see the Supporting Information).

IAPP is a positively charged peptide that displays three positive charges at physiological pH, thus favouring electrostatic interactions with negatively charged molecules. Particularly, we designed several mono- and diacid aryl substituted thiophenes to target one side of the transient IAPP helix that exhibits a hy-

Table 3. Mono- and diacid aryl substituted thiophenes.



Entry	R^3	R^2	Product
28	CN	Me	**9b**
29	CF_3	Me	**9c**
30	CHO	Me	**9d**
31	CF_3	*N*-MeMs	**9e**

drophobic region (Phe15) surrounded by polar and/or charged residues (Arg11 and His18; Table 3).

As suspected, acid(s)-functionalised thiophenes showed profound effects on IAPP amyloidogenesis at a 1:1 molar ratio. Interestingly, monoacid substituted thiophenes with a methyl group at position R^2 (compounds **9b**, **9c** and **9d**) virtually abolished the lag phase without significantly affecting the final ThT fluorescence. This aggregation kinetic suggests that these compounds induce the formation of IAPP aggregates with lower ThT-binding capacities, indicative of non-fibrillar structure (Figure 2C). In sharp contrast, the diacid analogue (compound **9a**) reduced the lag phase and led to a significant increase of the final ThT fluorescence (Figure 2C). This suggests that a larger amount of amyloids was formed in the presence of 1 equivalent of compound **9a** and/or that these amyloid fibrils exhibit a better-defined cross-β-sheet quaternary structure. These possibilities are currently under investigation. To probe if the accelerating effects of the mono- and diacid aryl substituted thiophenes on IAPP amyloidogenesis are simply a result of non-specific charge neutralisation effects, we used benzoic acid as a control compound. The amyloids formation kinetic data obtained in the presence of 12.5 μM (1 equivalent) and 125 μM (10 equivalent) of benzoic acid are very similar to the control (see the Supporting Information). Together, these data indicate that the negative charge(s) on the thiophene scaffold are crucial for the modulating activity and that the nature and/or the position of other substituents also play a key role, suggesting specific interactions. We are currently investigating the mechanisms by which these derivatives modulate the formation of amyloid fibrils.

Subsequently we analysed the cytotoxicity of IAPP species that has been pre-incubated for 20 h in the absence or presence of selected 2,5-diarylthiophene derivatives. We and others have previously reported that IAPP induces death of pancreatic cells when the amyloidogenic peptide is directly added to the cell culture medium.[4,24] In fact, IAPP pre-incubated for 20 h without compounds decreased pancreatic β-cells viability in a concentration-dependant manner (Figure 3A). When IAPP was pre-incubated with 1 molar equivalent of either compound **2d**, **2l** or **9c**, no changes in the proteotoxic effects induced by 50 μM IAPP were observed (Figure 3B). However, pre-incubation of IAPP with the diacid substituted thiophene (compound **9a**) before cell treatment totally abolished the cytotoxic effects of IAPP. This result suggests that

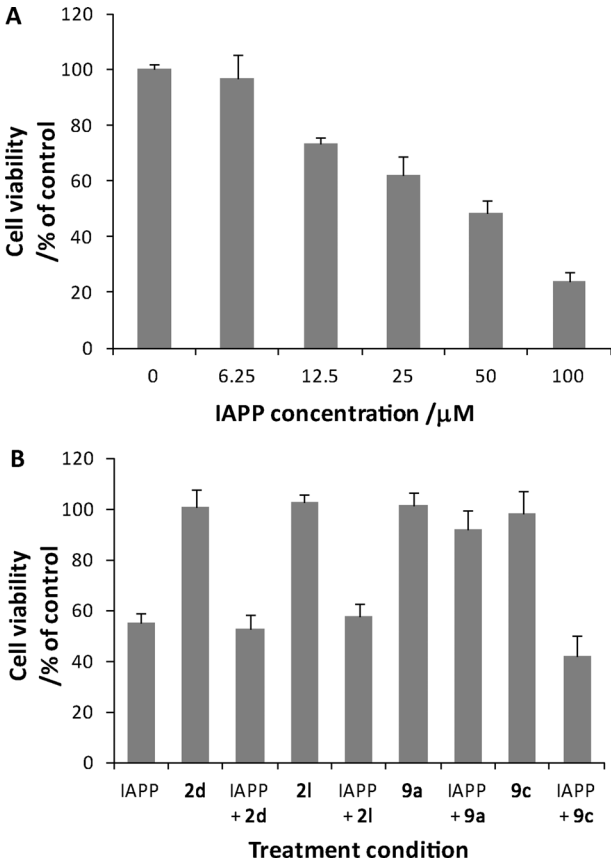


Figure 3. Effects of 2,5-diaryl substituted thiophenes on IAPP-induced toxicity on pancreatic β-cells. A) INS-1 cells were treated with concentrations of IAPP ranging from 0 to 100 μM for 24 h and cell viability was measured by the resazurin reduction assay and compared to cells treated with vehicle only (100% cell viability). B) INS-1 cells were treated with 50 μM IAPP that had been pre-incubated for 20 h in 20 mM Tris, pH 7.4, 25 °C, in the absence or presence of one molar equivalent of the thiophene derivatives. After 24 h incubation, cell viability was measured.

this compound stimulates the formation of poorly toxic IAPP quaternary species, mostly fibrillar, according to the high ThT fluorescence observed (Figure 3B). It is noteworthy that all tested compounds were not toxic on β-pancreatic cells when used at a concentration of 50 μM. In this study, the cytotoxicity assays were performed with IAPP that has been pre-incubated for 20 h without or with compounds, since we wanted to initially evaluate the cytotoxicity of the species (quaternary and/or monomeric) that are present when the ThT fluorescence plateau is reached. We are currently assessing the cytotoxicity of intermediates that are generated during the different amyloidogenic phases (lag, growth and plateau) in the presence of these thiophene derivatives. Although these results are preliminary and biophysical investigations are in progress to delineate the mechanisms by which these molecules interfere with IAPP amyloidogenic process, this study demonstrates that we can modulate not only the kinetics of amyloid fibril formation of an amyloidogenic peptide, but also its cytotoxicity with small molecules that were designed to mimic/target the transient helical motif.

Conclusion

A modular approach has been developed for the synthesis of highly functionalised 2,5-diaryl substituted thiophene scaffolds utilising palladium mediated cross-coupling reactions. The strategy allows us to quickly construct ligands in an efficient manner for screening towards the interaction with and stabilisation of α-helices. In this effort, the ligands were assessed for their capacity to modulate IAPP amyloidogenesis and cytotoxicity on β-pancreatic cells. The preliminary results demonstrated that some of the molecules could act as modulators of IAPP amyloidogenesis by increasing or decreasing the lag-phase period of IAPP amyloid fibril formation. Investigations are in progress to better understand the mechanism by which these molecules interact with IAPP. As several amyloidogenic natively disordered (poly)peptides, including the amyloid-β peptide, calcitonin and α-synuclein, populate helical intermediates during the initial phase of fibril formation, these 2,5-diaryl substituted thiophenes could ultimately lead to the development of novel therapeutics for protein amyloid-related diseases.

Experimental Section

Procedure for decarboxylative cross-coupling

The procedure employed by Forgione and co-workers was used with slight modifications.[18b] In a 2–5 mL, open to air, oven dried microwave vial were added the heterocyclic carboxylic acid (2 equiv), aryl bromide (1 equiv), tetra-*n*-butylammonium chloride (1 equiv), cesium carbonate (1.5 equiv), bis(tri-*tert*-butylphosphine)-palladium(0) (0.05 equiv) and anhydrous DMF (0.1 M of the aryl bromide solution). The vial was capped with a septum and the mixture was pre-stirred for 30 s at 23 °C and submitted to microwave heating at 170 °C for 8 min with stirring and the high absorption setting. The crude mixture was cooled to 23 °C and was filtered over Celite®. The solution was then diluted with EtOAc and the organic layer was washed with a saturated NaCl aqueous solution (3×), saturated $NaHCO_3$ aqueous solution (2×), water (1×), and saturated NaCl aqueous solution (1×). The aqueous phases were combined and extracted with EtOAc. The combined organic phases were dried over sodium sulfate, and after filtration the solvent was evaporated to provide the crude compound.

Procedure for C–H activation

A procedure employed by Fagnou and co-workers was used with slight modifications.[17q] An oven-dried vial equipped with a magnetic stir bar was charged with heterocycle (1 equiv), aryl bromide (2 equiv), $PCy_3{\cdot}HBF_4$ (0.1 equiv), PivOH (0.3 equiv), K_2CO_3 (1.5 equiv), and palladium(II) acetate (0.05 equiv). Anhydrous DMA (0.08 M of the heterocycle solution) was added. Liquid aryl bromides were added after the addition of solvent. The mixture was heated for 16 h at 100 °C. After being cooled to 23 °C, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite. The filtrate was washed with a saturated NaCl aqueous solution (3×), saturated $NaHCO_3$ aqueous solution (2×; unless otherwise stated), water (1×), and saturated NaCl aqueous solution (1×). The aqueous phases were combined and extracted with EtOAc. The combined organic phases were dried over sodium sulfate, and after filtration the solvent was evaporated to provide the crude compound.

Acknowledgements

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Keywords: amyloids · decarboxylative arylation · C–H arylation · peptidomimetics · thiophenes

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