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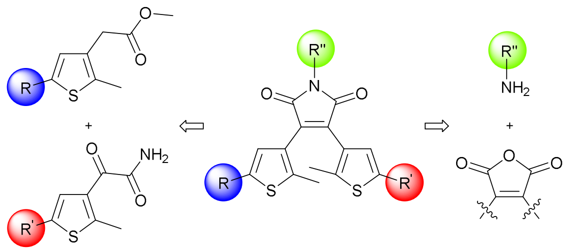

Synthetic routes for the functionalization of photochromic dithienylmaleimides at three different positions are reported.

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ARTICLE

Functionalization of Photochromic Dithienylmaleimides

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Photochromic dithienylmaleimides are well known molecular switches, but for applications the suitable functionalization of the photochromic scaffold is required. We report here synthetic routes to dithienylmaleimides, which are functionalized at three different positions: at each of the thiophene moieties and the maleimide nitrogen. A Perkin-type condensation of two thiophene precursors is used as the key step to assemble the maleimide core, which allows the synthesis of non-symmetrically substituted dithienylmaleimides, such as photochromic amino acids. A different approach to the maleimide core is provided by the reaction of a dithienylmaleic anhydride with amines or hydrazides leading to maleimide protected dithienylmaleimides and photochromic labeled natural amino acids. The photochromic properties of the new photoswitches were investigated showing reversible photochromism in polar organic solvents.

Introduction

Photochromism has attracted large attention in material science[1] and as a tool in molecular biology.[2] A variety of applications are found in molecular optoelectronics[3] and optical data storage.[4-6] In the field of life sciences, molecular switches were used to control enzyme activity,[7-10] Watson-Crick base pairing,[11-13] the regulation of neuronal activity by photochromic ligands for ion channels and receptors,[14-20] antibiotic effects[21, 22] and even the agility of a living organism[23] by light. This broad applicability is one of the reasons why photopharmacology has evolved into a vibrant field of research.[24] Various photochromic molecules, like azobenzenes,[25] spiropyrans,[26] spirooxazines,[26] fulgides[27] and diarylethenes[28, 29] have been developed. All these photoswitches can be reversible toggled between two isomers using light. The well investigated dithienylethenes (DTEs), including dithienylmaleimides, are characterized by a nearly quantitative photochemical conversion between the photoisomers, which are often thermally stable. Irradiation with light of a specific wavelength switches the DTEs between their open and closed photoisomers, which differ in conformational flexibility and electronic conjugation (Figure 1).

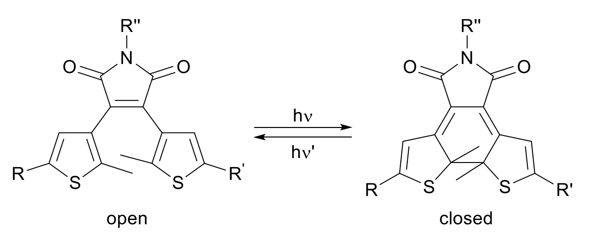


Figure 1. Reversible photochemical isomerization of a dithienylmaleimide between the open and closed photoisomer by irradiation with light of different wavelength.

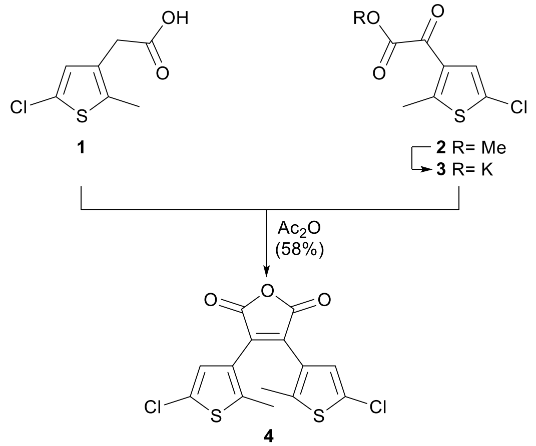
Many DTEs show high fatigue resistance.[28] Despite their outstanding photophysical properties the synthesis of DTEs, in particular of non-symmetric derivatives, is laborious.[13, 30] Different synthetic routes for the preparation of dithienylmaleimides were established. Starting from 3,4-dibromomaleimides and 3,4-diiodomaleimides, respectively, both thiophene moieties can be attached by palladium catalyzed Suzuki coupling.[31-33] However, only nitrogen protected maleimides can be used and the synthesis of non-symmetric compounds is challenging. Another route uses the reaction of a dithienylmaleic anhydride with amines to the corresponding maleimide.[34-36] The synthesis of diarylmaleimides by intramolecular Perkin condensation of two independently prepared precursors gives selective access to non-symmetric diarylmaleimides.[10, 37, 38] Compared to diarylperfluorocyclopentenes and diarylcyclopentenes, diarylmaleimides are more hydrophilic and better water soluble, which is valuable for applications in biology and pharmacy. The absorption maxima of diarylmaleimides are shifted to higher wavelengths and thus the photoisomerization can be induced by light with lower energy reducing potential cell damage.[28] Moreover, the biocompatibility of diarylmaleimides is known from bisindolylmaleimides, for instance arcyriarubins and arcyriaflavins with antibiotic activities, several other potent protein kinase and sirtuin inhibitors.[10, 39-43] However, a better synthetic access to functionalized photochromic dithienylmaleimides is desirable in order to extend their applications. Herein we discuss the synthesis of functionalized dithienylmaleimides substituted on each thiophene moiety and the maleimide nitrogen atom.

Results and discussion

Synthesis

Functionalization of the maleimide nitrogen atom

The transformation of diarylmaleic anhydrides into their corresponding diarylmaleimides provides an easy access to compounds with a functionalized maleimide nitrogen atom.[28] Complex functionalities or protecting groups can be introduced at the maleimide nitrogen by reaction with amines or hydrazides. We used the adapted synthetic approach of Scandola *et. al*.[36] for the synthesis of anhydride **4** as precursor (Scheme 1).

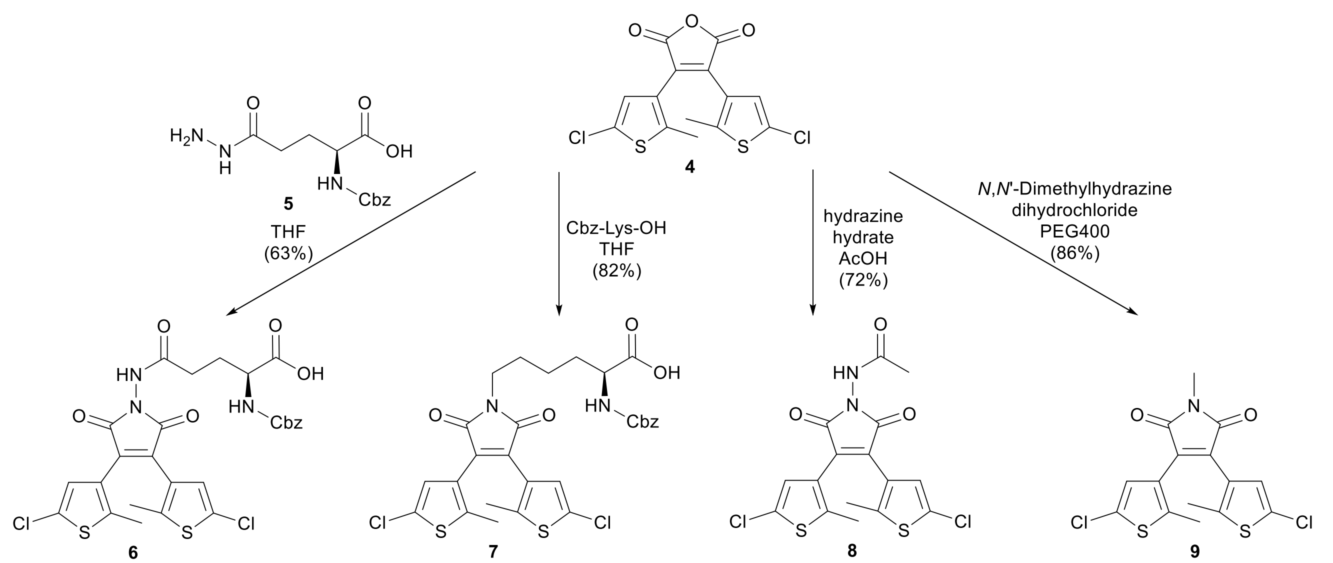


Scheme 1. Synthesis of dithienylmaleic anhydride **4**.

Methyl ester **2** was converted to its potassium salt **3** and condensed in a Perkin reaction with carboxylic acid **1** yielding the photochromic maleic anhydride **4**. The anhydride moiety allows the subsequent functionalization with hydrazides or amines (Scheme 2). Therefore maleic anhydride **4** was treated with α-Cbz protected L-glutamic acid γ-hydrazide[44] (**5**) and α-Cbz protected L-lysine to give amino acids **6** and **7** with a photochromic dithienylmaleimide on each sidechain. Photochromic tripeptides forming hydrogels with different aggregation modes mainly depending on the switch moiety were recently reported.[45] The reaction of hydrazine hydrate in acetic acid as solvent and 1,2-dimethylhydrazine dihydrochloride, respectively, with maleic anhydride **4** afforded the maleimide nitrogen protected dithienylmaleimides **8** and **9** in good yields (Scheme 2). Remarkably, the formation of any maleic hydrazide or other tautomers was not observed. The protected maleimides **8** and **9** could be used for further functionalizations on the thiophene moieties by palladium-catalyzed cross coupling reactions or other reactions using the reactivity of the heteroaryl chlorides.

Functionalization as photochromic amino acid

Recently, DTE-based non-natural amino acids were synthesized and successfully introduced into small peptides.[46] However, their water-solubility is limited due to the diaryl perfluorocyclopentene core and therefore we developed a more polar dithienylmaleimide amino acid. Compounds **13a** and **13b** were prepared by a Perkin condensation[10, 37, 38] of the thiophene precursors **10** and **11** bearing a protected primary amino or carboxyl group, respectively (Scheme 3). The Alloc group was chosen as a suitable protection for the amine as it is stable during the synthesis of compound **12**. Diester thiophene **11** provides in 4-position the carboxylic ester giving the maleimide core in the Perkin condensation. The ester in 2-position will serve as carboxylate of the amino acid. Both carboxylic acids were protected as methyl ester. Alloc group and methyl ester of **12** were cleaved simultaneously with boron tribromide giving amino acid **13a** in 47% yield, accompanied by 20% of the Alloc amino acid **13b** as byproduct. A selective non-hydrolytic deprotection of the methyl ester of **12** is possible in low yield using lithium iodide in a polar aprotic solvent.[47, 48] A large excess of lithium iodide and reflux were necessary to achieve conversion; several solvents were tested with best yields in acetone (see ESI, Table S1). Standard basic hydrolytic conditions for the deprotection of the methyl ester afforded the deprotected maleic anhydride (see ESI, Scheme S2). The synthesis of thiophene **10** is depicted in Scheme 4. Bromination[49] of 2-methyl thiophene (**14**) and subsequent Rosenmund-von Braun reaction[50] giving nitrile **16** were performed according to literature procedures.



Scheme 2. Synthesis of the functionalized photochromic dithienylmaleimides **6** - **9** starting from maleic anhydride **4**.

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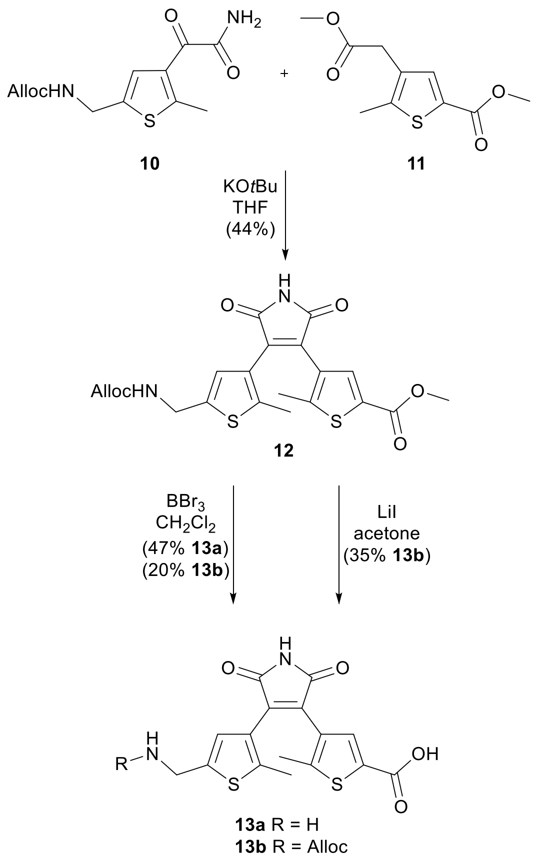
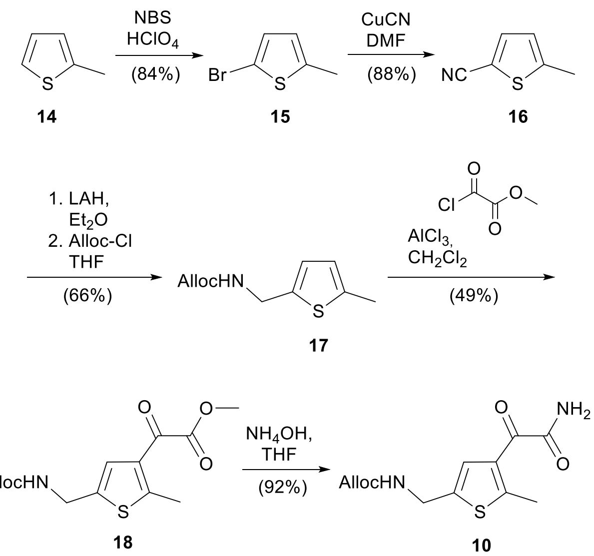


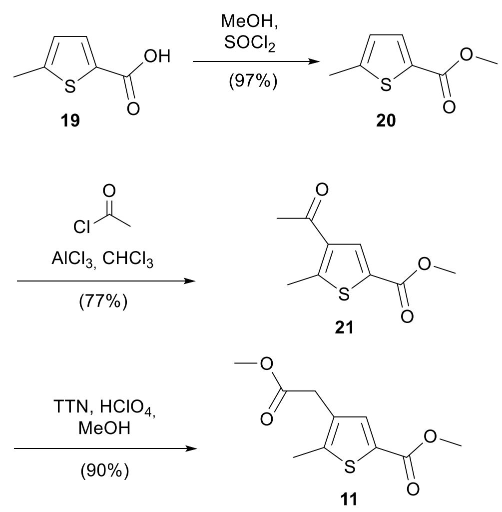
Scheme 3. Perkin condensation of thiophenes **10** and **11** yielding dithienylmaleimide **12** and after deprotection **13a** and **13b**.

The reduction of nitrile **16** with lithium aluminum hydride followed by immediate protection with allyl chloroformate afforded carbamate **17** in good yield. Using Fmoc chloride instead led to the respective Fmoc derivative in lower yields and caused the formation of side products in the subsequent Friedel-Crafts acylation. The yield of glyoxylester **18** in the Friedel-Crafts acylation depends critically on the sequence of the reagent addition. Best results were obtained by mixing **17** and methyl chlorooxoacetate before adding aluminum chloride in small portions. Quenching the reaction with saturated sodium hydrogen carbonate solution avoids the addition of hydrochloric acid to the allyl double bond. Aminolysis with aqueous ammonia converted the glyoxylester **18** in high yield into compound **10**. The overall yield for **10** after six steps is 22%.

Thiophene **11** was prepared by esterification[51] of methyl thiophene acid **19** in the presence of thionyl chloride followed by Friedel-Crafts acylation and finally a thallium trinitrate (TTN) mediated oxidative rearrangement[52] (Scheme 5). All intermediates were isolated in good to excellent yields with an overall yield of 68% for three steps. Initial moderate yields for the Friedel-Crafts acylation of around 40% significantly increased to 77% after rigorous removal of stabilizers from the solvent chloroform.



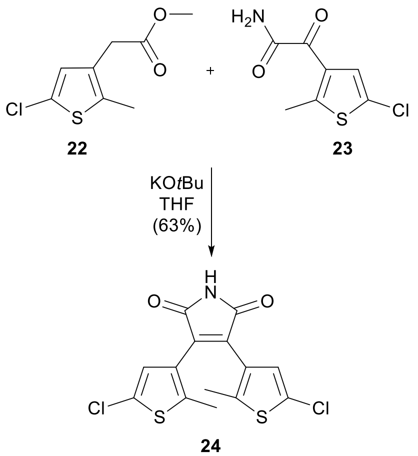
Scheme 4. Synthesis of thiophene **10**.



Scheme 5. Synthesis of thiophene **11**.

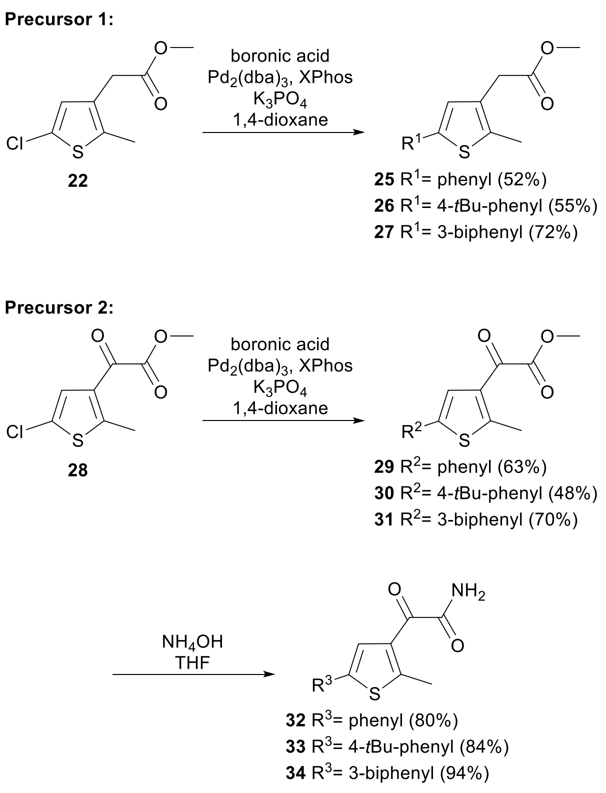
Functionalization by Suzuki coupling

Dithienylmaleimides are conveniently synthesized by the Perkin-type condensation. The reaction of two precursors yields the maleimide core without the need for protection of the maleimide nitrogen. Scheme 6 shows the intramolecular Perkin condensation of the two chlorosubstituted precursors **22** and **23**. Both precursors can be differently functionalized by Suzuki coupling before used in the Perkin condensation yielding non-symmetric dithienylmaleimides.



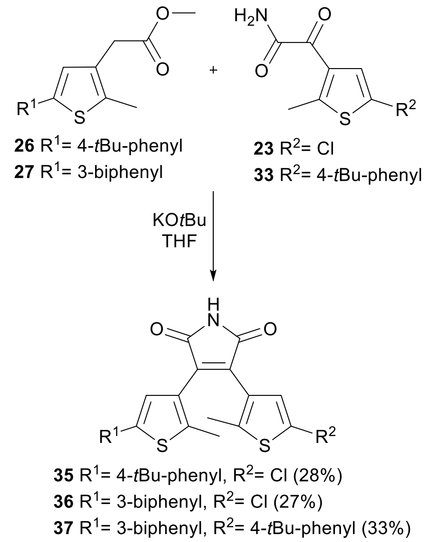
Scheme 6. Perkin condensation of **22** and **23** yielding dithienylmaleimide **24**.

Recently, we described the synthesis of symmetric diarylmaleimides, with thiophene moieties functionalized by palladium-catalysis prior to the condensation reaction.[10] Based on this strategy we prepared a small series of non-symmetric diarylmaleimides (Scheme 7).



Scheme 7. Synthesis of functionalized precursors **25 - 27** and **32 - 34**.

The Perkin condensation to the maleimide core was performed under basic conditions combining the different thiophenes. Scheme 8 summarizes the synthesis of the non-symmetric photoswitches **35 - 37**.



Scheme 8. Synthesis of non-symmetric substituted dithienylethenes **35** - **37** by Perkin condensation.

Photochromic properties

The dithienylmaleimide core structure can be toggled reversibly between a ring-open and ring-closed photoisomer (Figure 1). The photochemical properties of photochromic compounds **4**, **6 - 9**, **12**, **13a**, **13b**, **24** and **35 - 37** were investigated by UV-Vis spectroscopy. Despite of reports that diarylmaleimides are not able to undergo photoisomerization in polar solvents due to a twisted intramolecular charge transfer (TICT),[53-55] we could observe reversible photoisomerization of the dithienylmaleimides **6 - 9**, **12**, **13a**, **13b**, **24** and **35 - 37** in methanol or dimethylsulfoxide, respectively. Figure 2 shows the changes of the UV-Vis spectra of compound **12** upon irradiation with light of 312 nm (Herolab, 6 W).

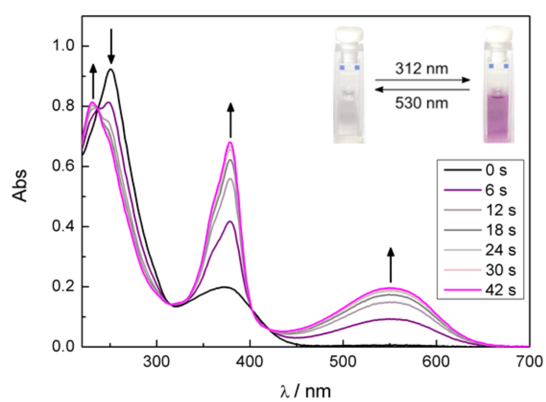


Figure 2. Changes of the UV-Vis absorption spectra of dithienylmaleimide amino acid **12** (50 µM in MeOH) upon light irradiation with 312 nm; arrows indicate the changes of the absorption maxima over 42 s irradiation in periods of 6 s (Herolab, 6 W); the cuvettes show the color of the solution before and after irradiation.

Upon irradiating a methanol solution of the ring-open form of compound **12** with UV light (312 nm), the absorption band at 250 nm immediately decreases. Simultaneously, new absorption maxima at 232 nm, 378 nm and 550 nm arise (Figure 2) causing the color change of the sample from slightly yellow to purple. The isosbestic points indicate a clean conversion between two components. Compared to typical DTE-cyclopentenes the absorption maxima are red shifted. The photostationary state was reached after 42 s of irradiation (Herolab, 312 nm, 6 W) and the open form can be regained by irradiation with visible light (> 420 nm) for 5 min. The photoswitchable amino acid **12** is stable over at least seven closing/opening cycles (Figure 3).

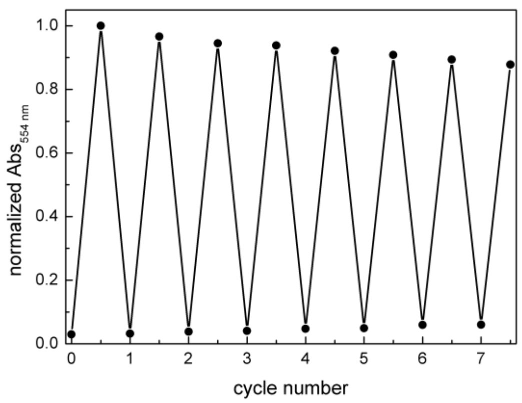


Figure 3. Cycle performance of the dithienylmaleimide amino acid **12** (50 µM in MeOH). Changes in absorption at 554 nm were measured during alternate irradiation with light of 312 nm for 60 s (Herolab, 6 W) and 530 nm(CREE-XP green, 700 mA) for 5 min.

The absorption maxima and their corresponding extinction coefficients for the open and closed form of all synthesized photochromic compounds are summarized in Table 1. Interestingly, the long wavelength absorption maximum of compound **13a** is blue shifted to 537 nm compared to photoswitches **12** and **13b**, which may indicate an interaction of the Alloc group with the dithienylmaleimide core. In contrast the selective removal of the methyl ester has almost no influence on the photochromic properties. In comparison to bischloro dithienylmaleimide **24** the functionalized maleimides **35** - **37** show a bathochromic shift in their absorption maxima of the closed photoisomer. The enlarged π-system of the substituted thiophenes can explain this shift to higher wavelengths.

Conclusions

In summary, we have prepared several photochromic dithienylmaleimides. Maleimide nitrogen atom functionalized derivatives were obtained by the reaction of dithienylmaleic anhydride with different hydrazides and amines. Using a Perkin-type condensation non-symmetric dithienylmaleimides were synthesized including a photochromic amino acid and dithienylmaleimides with different aromatic substituents on each thiophene moiety. Reversible photoisomerization in dimethylsulfoxide and methanol was observed for all synthesized photochromic compounds.

Table 1. UV-Vis spectroscopic data of the open and closed (PSS) form of the synthesized photochromic compounds.[a]

Compound	Solvent	Conc. [µM]	λ_{max} open (ε)	λ_{max} closed (ε)
4	MeOH	100	242 (26.0), 298 (9.5)	359 (16.0), 523 (3.7)
6	DMSO	50	387 (4.6)	359 (17.4), 510 (3.2)
7	DMSO	50	381 (5.0)	355 (20.8), 500(4.1)
8	DMSO	50	386 (6.0)	359 (22.7), 508 (4.3)
9	DMSO	50	380 (3.3)	351 (12.9), 498 (2.7)
12	MeOH	50	250 (18.5)	232 (16.2), 378 (13.6), 550 (3.9)
13a	MeOH	50	252 (13.0)	231 (11.3), 375 (10.0), 537 (2.7)
13b	MeOH	50	250 (14.3)	232 (12.6), 378 (10.3), 549 (2.8)
24	MeOH	50	240 (20.2), 370 (4.5)	234 (20.6), 352 (13.8), 497 (2.5)
35	MeOH	100	264 (18.5), 292 (17.1)	369 (9.7), 543 (3.0)
36	MeOH	100	255 (28.8), 291[b] (14.3)	369 (10.1), 540 (3.7)
37	MeOH	100	262 (26.1), 297 (20.7)	391 (11.5), 586 (5.7)

[a] UV-Vis spectroscopic data are reported for solutions at 25 °C and reported in nm (λ_{max}) and 10^3 cm^{-1} M^{-1} (ε). The PSS were obtained by irradiation of solutions of the open isomer with light of 312 nm (Herolab, 6 W). [b] Shoulder.

Experimental section

General information: Commercial reagents and starting materials were purchased from Acros Organics, Alpha-Aesar, Fluka, Sigma Aldrich or VWR and used without further purification. Solvents were used in p.a. quality and dried according to common procedures, if necessary. To purify the chloroform for Friedel-Crafts acylations, it was washed with sulfuric acid (1 M), dried over calcium chloride, filtered through silica, subsequently refluxed with phosphorus pentoxide (5 – 10 g/L) and distilled under nitrogen atmosphere. Compounds **1**[10], **2**[10], **5**[44], **15**[49], **16**[50], **20**[51], **22**[10], **25**[10], **28**[10], **29**[10] and **32**[10] were prepared according to previously reported procedures. Flash column chromatography was performed on a Biotage Isolera One automated flash purification system with UV/Vis detector using Sigma Aldrich MN silica gel 60 M (40-63 µm, 230-400 mesh) for normal phase or pre-packed Biotage SNAP cartridges (KP-C18-HS) for reversed phase chromatography. Reaction monitoring *via* TLC was performed on alumina plates coated with silica gel (Merck silica gel 60 F_{254}, 0.2 mm). Melting points were determined using a Stanford Research Systems OptiMelt MPA 100. NMR spectra were recorded on a Bruker Avance 300 (^{1}H 300.13 MHz, ^{13}C 75.48 MHz), Bruker Avance 400 (^{1}H 400.13 MHz, ^{13}C 100.61 MHz) or Avance III 600 (^{1}H 600.25 MHz, ^{13}C 150.95 MHz) instrument. The spectra are referenced against the NMR-solvent, chemical shifts are reported in ppm and coupling constants J are given in Hz. Resonance multiplicity is abbreviated as: s (singlet), d (doublet), t (triplet), m (multiplet) and b (broad). Carbon NMR signals are reported with (+) for primary/tertiary, (−) for secondary and (q) for quaternary carbons. The assignment resulted from DEPT, HSQC and HMBC experiments. Mass spectra were recorded on a Finnigan MAT95 (EI-MS), Agilent Q-TOF 6540 UHD (ESI-MS, APCI-MS), Finnigan MAT SSQ 710 A (EI-MS, CI-MS) or ThermoQuest Finnigan TSQ 7000 (ES-MS, APCI-MS) spectrometer. UV/Vis absorption spectroscopy was performed using a Varian Cary BIO 50 UV/Vis/NIR spectrometer. IR-spectra were recorded with a Specac Golden Gate Diamond Single Reflection ATR System in a Bio-Rad FT-IR-Spectrometer Excalibur FTS 3000 and peak positions are reported in wavenumbers (cm^{-1}). Standard hand-held lamps were used for visualizing TLC plates and to carry out the ring-closure reactions at 312 nm (Herolab, 312 nm, 6 W). The ring-opening reactions were performed with the light of a 200 W tungsten light bulb which was passed through a 420 nm cut-off filter to eliminate higher energy light or the light of a green LED (CREE-XP green, 530 nm, 700 mA). The power of the light is given based on the specifications supplied by the company when the lamps were purchased. A light detector was not used to measure the intensity during the irradiation experiments.

3,4-Bis(5-chloro-2-methylthiophen-3-yl)furan-2,5-dione (4): To obtain the potassium salt **3**, the ester **2** was dissolved in EtOH (2.5 mL/mmol) and KOH (1.0 eq) was added. After stirring overnight the solvent was removed and the salt **3** was used without further purification. A mixture of the acid **1** (984 mg, 5.16 mmol), the potassium salt **3** (1.25 g, 5.16 mmol) and acetic anhydride (15 mL) was heated to 120 °C for 5 h. The reaction was cooled to room temperature and quenched by adding water (20 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by automated flash column chromatography (PE/CH_2Cl_2, 30% - 60% CH_2Cl_2) to yield the maleic anhydride **4** (1.07 g, 58%) as gray solid. R_f: 0.45 (PE/CH_2Cl_2: 1/1); m.p.: 205 °C; IR (neat) ν_{max}: 3108, 2922, 1843, 1766, 1629, 1539, 1460, 1252, 1047, 1177, 990, 919; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.94 (s, 6H, thiophene-CH_3), 7.03 (s, 2H, thiophene-H); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 14.1 (+), 125.2 (q), 125.3 (q), 127.2 (+), 134.5 (q), 141.4 (q), 164.5 (q); HRMS (ESI): calcd. for $C_{14}H_9Cl_2O_3S_2$ $(M+H)^+$ 358.9365; found 358.9362.

***N*²-((Benzyloxy)carbonyl)-*N*⁵-(3,4-bis(5-chloro-2-methylthiophen-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-*L*-glutamine (6):** Maleic anhydride **4** (40 mg, 0.11 mmol) was added to a solution of acid hydrazide **5** (30 mg, 0.10 mmol) in THF (1 mL) in a crimp top vial. After heating to 85 °C for 16 h the reaction was quenched with 1 M aqueous HCl solution (1 mL) and water (1 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by automated reversed phase flash column chromatography (MeCN/H_2O with 0.05% TFA, 10% - 95% MeCN) yielded compound **6** (40 mg, 63%) as orange solid. R_f: 0.01 (EtOAc); m.p.: 103 °C; IR (neat) ν_{max}: 3250, 2924, 1789, 1727, 1522, 1462, 1434, 1215, 1175, 990; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.74 – 1.88 (m, 1H, CO-(CH_2)$_2$-CH), 1.94 (s, 6H, thiophene-CH_3), 2.00 – 2.10 (m, 1H, CO-(CH_2)$_2$-CH), 2.38 – 2.48 (m, 2H, CO-(CH_2)$_2$-CH), 4.03 (dt, J = 9.0, 4.8 Hz, 1H, CH_2-CH-NH), 5.05 (s, 2H, O-CH_2-Ph), 7.03 (s, 2H, thiophene-H), 7.31 – 7.40 (m, 5H, Ph-H), 7.68 (d, J = 8.0 Hz, 1H, CH-NH-CO), 10.63 (s, 1H, N-NH-CO), 12.70 (bs, 1H, COOH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 14.2 (+), 26.1 (−), 29.1 (−), 53.1 (+), 65.4 (−), 125.0 (q), 125.8 (q), 127.6 (+), 127.6 (+), 127.7 (+), 128.3 (+), 131.2 (q), 136.8 (q), 140.6 (q), 156.1 (q), 166.9 (q), 170.8 (q), 173.4 (q); HRMS (ESI): calcd. for $C_{27}H_{24}Cl_2N_3O_7S_2$ $(M+H)^+$ 636.0427; found 636.0428.

(S)-2-(((Benzyloxy)carbonyl)amino)-6-(3,4-bis(5-chloro-2-methylthiophen-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoic acid (7): Triethylamine (131 µL, 0.95 mmol) was added to a suspension of maleic anhydride **4** (97 mg, 0.27 mmol) and Cbz-Lys-OH (83 mg, 0.30 mmol) in THF (5 mL) in a crimp top vial. After heating to 85 °C for 16 h the reaction was quenched with 1 M aqueous HCl solution (3 mL) and water (3 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by automated reversed phase flash column chromatography (MeCN/H_2O with 0.05% TFA, 50% - 100% MeCN) yielded compound **7** (138 mg, 82%) as orange solid. R_f: 0.09 (PE/EtOAc: 1/1); m.p.: 88 °C; IR (neat) ν_{max}: 3351, 3095, 2932, 2870, 1698, 1526, 1438, 1404, 1211, 989; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.29 – 1.43 (m, 2H, CH_2-(CH_2)$_3$-CH), 1.51 – 1.65 (m, 3H, CH_2-(CH_2)$_3$-CH), 1.67 – 1.79 (m, 1H, CH_2-(CH_2)$_3$-CH), 1.91 (s, 6H, thiophene-CH_3), 3.49 (t, J = 7.1 Hz, 2H, N-CH_2-(CH_2)$_3$), 3.93 (dt, J = 7.9, 4.6 Hz, 1H, NH-CH-CH_2), 5.02 (s, 2H, O-CH_2-Ph), 7.00 (s, 2H, thiophene-H), 7.28 - 7.37 (m, 5H, Ph-H), 7.57 (d, J = 8.0 Hz, 1H, CO-NH-CH), 12.55 (s, 1H, COOH); ^{13}C-NMR (101 MHz, DMSO-d_6): δ = 14.1 (+), 22.8 (−), 27.4 (−), 30.2 (−), 37.7 (−), 53.5 (+), 65.3 (−), 124.6 (q), 126.4 (q), 127.6 (+), 127.7 (+), 127.7 (+), 128.2 (+), 132.3 (q), 136.9 (q), 139.8 (q), 169.6 (q), 173.8 (q); HRMS (ESI): calcd. for $C_{28}H_{27}Cl_2N_2O_6S_2$ $(M+H)^+$ 621.0682; found 621.0684.

***N*-(3,4-Bis(5-chloro-2-methylthiophen-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)acetamide (8):** Hydrazine hydrate (39 µL, 0.81 mmol) was added to a solution of maleic anhydride **4** (97 mg, 0.27 mmol) in acetic acid (3.5 mL). The reaction mixture was heated to 100 °C for 20 h and then water (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Purification by automated flash column chromatography (PE/EtOAc, 15% - 50% EtOAc) yielded compound **8** (81 mg, 72%) as orange solid. R_f: 0.23 (PE/EtOAc: 2/1); m.p.: 131 °C; IR (neat) ν_{max}: 3328, 3088, 2924, 2359, 1717, 1702, 1510, 1429, 1255, 1193, 988; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 1.95 (s, 6H, thiophene-CH_3), 2.03 (s, 3H, CO-CH_3), 7.01 (s, 2H, thiophene-H), 10.58 (s, 1H, NH); ^{13}C-NMR (101 MHz, DMSO-d_6): δ = 14.2 (+), 20.0 (+), 125.0 (q), 125.8 (q), 127.6 (+), 131.3 (q), 140.6 (q), 166.9 (q), 168.5(q); HRMS (ESI): calcd. for $C_{16}H_{13}Cl_2N_2O_3S_2$ $(M+H)^+$ 414.9739; found 414.9741.

3,4-bis(5-chloro-2-methylthiophen-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (9): Maleic anhydride **4** (54 mg, 0.15 mmol) and 1,2-dimethylhydrazine dihydrochloride (60 mg, 0.45 mmol) were heated to 160 °C for 12 h in PEG400 (2 mL) in a crimp top vial. Then water (15 mL) was added and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by automated flash column chromatography (PE/EtOAc, 3% - 10% EtOAc) yielded compound **9** (48 mg, 86%) as orange foam. R*f*: 0.32 (PE/EtOAc: 19/1); IR (neat) ν_{max}: 3098, 2924, 2851, 1765, 1697, 1435, 1386, 1250, 1174, 980; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.93 (s, 6H, thiophene-C*H*$_3$), 3.13 (s, 3H, N-C*H*$_3$), 6.89 (s, 2H, thiophene-*H*); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 14.9 (+), 24.4 (+), 126.0 (q), 127.2 (+), 127.2 (q), 132.7 (q), 140.2 (q), 170.2 (q); HRMS (ESI): calcd. for $C_{15}H_{12}Cl_2NO_2S_2$ $(M+H)^+$ 373.9649; found 373.9652.

Allyl ((4-(2-amino-2-oxoacetyl)-5-methylthiophen-2-yl)methyl) carbamate (10): To a solution of oxoacetate **18** (282 mg, 0.95 mmol) in THF (5 mL) was added a NH_4OH solution (32% in H_2O) (1.18 mL, 9.50 mmol) at 0 °C. The reaction was stirred for 90 min at room temperature and then quenched with water (5 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Compound **10** (253 mg, 94%) was obtained as yellow solid and used without further purification. R*f*: 0.21 (PE/EtOAc: 1/1); m.p.: 108 °C; IR (neat) ν_{max}: 3402, 3301, 3167, 2962, 1750, 1686, 1649, 1535, 1460, 1254, 1047, 796; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.70 (s, 3H, thiophene-C*H*$_3$), 4.44 (d, *J* = 6.1 Hz, 2H, thiophene-C*H*$_2$NH), 4.59 (d, *J* = 5.1 Hz, 2H, CH$_2$=CHC*H*$_2$O), 5.21 (dd, *J* = 10.4, 0.5 Hz, 1H, C*H*$_2$=CHCH$_2$), 5.24 – 5.43 (m, 2H, C*H*$_2$=CHCH$_2$ and N*H*), 5.90 (ddt, *J* = 16.2, 10.7, 5.5 Hz, 1H, CH$_2$=C*H*CH$_2$), 6.05 (bs, 1H, N*H*$_2$), 7.06 (bs, 1H, N*H*$_2$), 7.86 (s, 1H, thiophene-*H*); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 16.7 (+), 39.8 (−), 65.9 (−), 117.9 (−), 129.0 (+), 130.8 (q), 132.7 (+), 137.0 (q), 155.7 (q), 156.1 (q), 164.4 (q), 182.1 (q); HRMS (ESI): calcd. for $C_{12}H_{18}N_3O_4S$ $(M+NH_4)^+$ 300.1013; found 300.1012.

Methyl 4-(2-methoxy-2-oxoethyl)-5-methylthiophene-2-carboxylate (11): Thallium trinitrate (850 mg, 1.91 mmol) and 70% $HClO_4$ (0.30 mL) were added to a suspension of **21** (316 mg, 1.59 mmol) in MeOH (10 mL) at room temperature. After stirring for 24 h the mixture was concentrated under vacuum and diluted with water (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and purification of the crude product by automated flash column chromatography (PE/EtOAc, 3% - 15% EtOAc) yielded compound **11** (331 mg, 91%) as colorless oil. R*f*: 0.34 (PE/EtOAc: 5/1); IR (neat) ν_{max}: 2997, 2953, 2845, 1736, 1704, 1535, 1457, 1392, 1331, 1291, 1250, 1194, 1132, 1063, 1006, 927, 874, 785, 751; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H, thiophene-C*H*$_3$), 3.54 (s, 2H, thiophene-C*H*$_2$C(O)OCH$_3$), 3.69 (s, 3H, thiophene-CH$_2$C(O)OC*H*$_3$), 3.84 (s, 3H, C(O)OC*H*$_3$), 7.60 (s, 1H, thiophene-*H*); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 13.9 (+), 33.9 (−), 52.1 (+), 52.3 (+), 129.2 (q), 130.8 (q), 135.7 (+), 144.1 (q), 162.7 (q), 171.0 (q); HRMS (APCI): calcd. for $C_{10}H_{12}O_4S$ $(M+H)^+$ 229.0529; found 229.0531.

Methyl 4-(4-(5-((((allyloxy)carbonyl)amino)methyl)-2-methyl-thiophen-3-yl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)-5-methylthiophene-2-carboxylate (12): KO*t*Bu (1 M in THF, 0.88 mL, 0.88 mmol) was added to a solution of glyoxylamide **10** (206 mg, 0.73 mmol) in anhydrous THF (5 mL) at 0 °C under nitrogen atmosphere. After stirring for 90 min at 0 °C, diester **11** (200 mg, 0.88 mmol) in THF (2 mL) was added at 0 °C and stirred for 3 d at room temperature. Then the reaction was quenched with 1 M aqueous HCl solution (3 mL) and diluted with EtOAc (10 mL). The organic phase was washed with water (2 x 10 mL), brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and purification of the crude product by automated flash column chromatography (PE/EtOAc, 25% - 50% EtOAc) yielded **12** (148 mg, 44%) as yellow foam. R*f*: 0.20 (PE/EtOAc: 2/1); IR (neat) ν_{max}: 3289, 3070, 2952, 1703, 1540, 1458, 1339, 1248, 994, 909, 727; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.90 (s, 3H, thiophene-C*H*$_3$); 1.98 (s, 3H, thiophene-C*H*$_3$), 3.87 (s, 1H, OC*H*$_3$), 4.45 (d, *J* = 6.0 Hz, 2H, thiophene-C*H*$_2$NH), 4.60 (d, *J* = 4.9 Hz, 2H, CH$_2$=CHC*H*$_2$O), 5.13 – 5.27 (m, 2H, C*H*$_2$=CHCH$_2$ and CH$_2$N*H*CO), 5.31 (dd, *J* = 17.2, 1.2 Hz, 1H, C*H*$_2$=CHCH$_2$), 5.92 (ddt, *J* = 16.2, 10.8, 5.5 Hz, 1H, CH$_2$=C*H*CH$_2$), 6.90 (s, 1H, thiophene-*H*), 7.74 (s, 1H, thiophene-*H*), 8.03 (bs, 1H, CON*H*CO); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 15.0 (+), 15.3 (+), 39.9 (−), 52.3 (+), 65.9 (−), 117.9 (−), 125.8 (q), 126.7 (+), 127.5 (q), 130.9 (q), 132.7 (+), 134.8 (q), 134.9 (+), 139.4 (q), 142.1 (q), 148.6 (q), 156.0 (q), 162.1 (q), 170.0 (q), 170.2 (q); HRMS (ESI): calcd. for $C_{21}H_{21}N_2O_6S_2$ $(M+H)^+$ 461.0838; found 461.0836.

4-(4-(5-(Aminomethyl)-2-methylthiophen-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-5-methylthiophene-2-carboxylic acid (13a) and 4-(4-(5-((((Allyloxy)carbonyl)amino)methyl)-2-methylthiophen-3-yl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)-5-methylthiophene-2-carboxylic acid (13b): A solution of BBr_3 (1 M in CH_2Cl_2, 2.0 mL, 2.00 mmol) was added to a solution of compound **12** (92 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (6 mL) in a crimp top vial. The mixture was heated to 40 °C for 5 h. Then water (4 mL) was added *via* syringe and the suspension was stirred at 40 °C for additional 30 min. After cooling to room temperature the solvent was removed at the rotary evaporator. Purification by automated reversed phase flash column chromatography (MeCN/H_2O with 0.05% TFA, 3% - 100% MeCN) yielded compound **13a** (34 mg, 47%) as yellow solid and compound **13b** (18 mg, 20%) as yellow solid.

Analytical data of 13a: R*f*: 0.02 (PE/EtOAc: 1/1); m.p.: 173 °C; IR (neat) ν_{max}: 3008, 2924, 1766, 1712, 1681, 1545, 1463, 1344, 1188, 1137, 1001, 839, 799, 756, 723; ^{1}H-NMR (600 MHz, MeOD): δ = 2.00 (s, 3H, thiophene-C*H*$_3$), 2.08 (s, 3H, thiophene-C*H*$_3$), 4.27 (s, 2H, thiophene-C*H*$_2$NH), 7.18 (s, 1H, thiophene-*H*), 7.64 (s, 1H, thiophene-*H*); ^{13}C-NMR (151 MHz, MeOD): δ = 14.7 (+), 15.3 (+), 38.5 (−), 128.5 (q), 129.3 (q), 132.2 (+), 132.8 (q), 133.1 (q), 135.0 (q), 135.7 (q), 136.3 (+), 144.6 (q), 149.7 (q), 164.6 (q), 172.4 (q), 172.6 (q); HRMS (ESI): calcd. for $C_{16}H_{15}N_2O_4S_2$ $(M+H)^+$ 363.0469; found 363.0468.

Analytical data of 13b: R*f*: 0.04 (PE/EtOAc: 1/1); m.p.: 94 °C; IR (neat) ν_{max}: 2926, 1981, 1769, 1709, 1544, 1459, 1344, 1246, 1185, 1150, 1049, 991, 849, 762; ^{1}H-NMR (300 MHz, CD_3CN): δ = 1.93 (s, 3H, thiophene-C*H*$_3$), 1.97 (s, 3H, thiophene-C*H*$_3$), 4.33 (d, *J* = 6.3 Hz, 2H, thiophene-C*H*$_2$NH), 4.52 (d, *J* = 5.3 Hz, 2H, CH$_2$=CHC*H*$_2$O), 5.18 (dd, *J* = 10.5, 1.4 Hz, 1H, C*H*$_2$=CHCH$_2$), 5.27 (dd, *J* = 17.3, 1.6 Hz, 1H, C*H*$_2$=CHCH$_2$), 5.74 – 6.05 (m, 1H, CH$_2$=C*H*CH$_2$), 6.14 (bs, 1H, CH$_2$N*H*CO), 6.79 (s, 1H, thiophene-*H*), 7.60 (s, 1H, thiophene-*H*), 8.80 (bs, 1H, COO*H*); ^{13}C-NMR (75 MHz, CD_3CN): δ = 14.8 (+), 15.2 (+), 40.1 (−), 66.0 (−), 117.5 (−), 127.2 (q), 127.4 (+), 129.1 (q), 131.4 (q), 134.1 (q), 134.4 (+), 136.2 (+), 136.2 (q), 141.2 (q), 141.8 (q), 149.6 (q), 157.1 (q), 162.9 (q), 171.6 (q), 171.7 (q); HRMS (ESI): calcd. for $C_{20}H_{18}N_2O_6S_2$ $(M+H)^+$ 447.0679; found 447.0676.

Alternative procedure to obtain 13b: Compound **12** (40 mg, 0.09 mmol) was dissolved in acetone (10 mL) and LiI (350 mg, 2.60 mmol) was added. The mixture was heated to 100 °C overnight. After cooling to room temperature it was quenched with 1 M aqueous HCl solution (5 mL) and diluted with CH_2Cl_2 (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed at the rotary evaporator. Automated reversed phase flash column chromatography (MeCN/H_2O with 0.05% TFA, 3% - 100% MeCN) yielded compound **13b** (14 mg, 35%) as yellow solid.

Allyl ((5-methylthiophen-2-yl)methyl)carbamate (17): LAH (2.78 g, 73.2 mmol) was added in portions to a solution of nitrile **16** (3.01 g, 24.4 mmol) in anhydrous Et_2O (250 mL) at 0 °C under nitrogen atmosphere. After stirring for 4 h at room temperature the reaction was quenched with water (80 mL) and saturated aqueous $NaHCO_3$ solution (50 mL) at 0 °C. The suspension was filtered and the aqueous phase was extracted with Et_2O (3 x 80 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. Then the residue was dissolved in anhydrous THF (100 mL) and pyridine (2.47 mL, 30.50 mmol) was added at 0 °C. Within 1 h allyl chloroformate (4.02 mL, 37.82 mmol) in anhydrous THF (5 mL) was dropped to the solution *via* a syringe pump at 0 °C. After stirring for 14 h at room temperature the reaction was quenched cautiously with water (50 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification of the crude product by automated flash column chromatography (PE/EtOAc, 8% - 15% EtOAc) yielded **17** (3.40 g, 66%) as yellow oil. R_f: 0.20 (PE/EtOAc: 9/1); IR (neat) ν_{max}: 3335, 3073, 2922, 1695, 1514, 1426, 1236, 982, 799; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H, thiophene-CH_3), 4.44 (d, J = 5.7 Hz, 2H, thiophene-CH_2NH), 4.61 (d, J = 5.3 Hz, 2H, CH_2=CHCH_2O), 5.05 (bs, 1H, NH), 5.25 (dd, J = 10.4, 0.3 Hz, 1H, CH_2=CHCH$_2$), 5.30 (dd, J = 17.1, 1.2 Hz, 1H, CH_2=CHCH$_2$), 5.92 (ddt, J = 16.4, 10.8, 5.7 Hz, 1H, CH_2=CHCH$_2$), 6.57 (dd, J = 3.1, 1.0 Hz, 1H, 4-thiophene-H), 6.74 (d, J = 3.1 Hz, 1H, 3-thiophene-H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 15.4 (+), 40.1 (−), 65.7 (−), 117.8 (−), 124.8 (+), 125.7 (+), 132.8 (+), 138.8 (q), 139.9 (q), 155.9 (q); HRMS (ESI): calcd. for $C_{10}H_{14}NO_2S$ $(M+H)^+$ 212.0740; found 212.0740.

Methyl 2-(5-((((allyloxy)carbonyl)amino)methyl)-2-methylthiophen-3-yl)-2-oxoacetate (18): Carbamate **17** (169 mg, 0.80 mmol) and methyl chlorooxoacetate (81 µL, 0.88 mmol) were dissolved in anhydrous CH_2Cl_2 (6 mL) under nitrogen atmosphere. Then aluminum chloride (427 mg, 3.20 mmol) was added in portions at 0 °C and the suspension was stirred for 20 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (1 mL) at 0 °C and diluted with water (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by automated flash column chromatography (PE/EtOAc, 15% - 40% EtOAc) to obtain **18** (117 mg, 49%) as brown oil. R_f: 0.22 (PE/EtOAc: 3/1); IR (neat) ν_{max}: 3395, 2954, 1726, 1670, 1517, 1434, 1242, 1200, 1112, 984, 757; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.70 (s, 3H, thiophene-CH_3) 3.91 (s, 3H, OCH_3), 4.42 (d, J = 6.1 Hz, 2H, thiophene-CH_2NH), 4.58 (d, J = 5.3 Hz, 2H, CH_2=CHCH_2O), 5.16 – 5.34 (m, 3H, CH_2=CHCH$_2$ and NH), 5.90 (ddt, J = 16.3, 10.8, 5.6 Hz, 1H, CH_2=CHCH$_2$), 7.32 (s, 1H, thiophene-H); ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 16.3 (+), 39.7 (−), 52.8 (+), 65.9 (−), 118.0 (−), 127.5 (+), 131.0 (q), 132.6 (+), 138.0 (q), 154.8 (q), 156.1 (q), 164.0 (q), 180.0 (q); HRMS (ESI): calcd. for $C_{13}H_{16}NO_5S$ $(M+H)^+$ 298.0744; found 298.0744.

Methyl 4-acetyl-5-methylthiophene-2-carboxylate (21): Thiophene **20** (800 mg, 5.12 mmol) and acetyl chloride (550 µL, 7.68 mmol) were dissolved in purified anhydrous $CHCl_3$ (10 mL) under nitrogen atmosphere. After cooling to 0 °C aluminum chloride (2.05 g, 15.4 mmol) was added in small portions. The yellow suspension was heated to 45 °C overnight upon turning bright red, then the reaction was quenched with ice/water and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by automated flash column chromatography (PE/EtOAc, 5% - 25% EtOAc) and compound **21** (781 mg, 77%) was obtained as colorless solid. R_f: 0.41 (PE/EtOAc: 3/1); m.p.: 84 °C; IR (neat) ν_{max}: 3007, 2957, 1717, 1678, 1539, 1457, 1439, 1254, 1233, 1074, 1021, 745; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.52 (s, 3H, thiophene-CH_3), 2.76 (s, 3H, acetyl-CH_3), 3.88 (s, 3H, OCH_3), 8.03 (s, 1H, thiophene-H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 16.8 (+), 29.6 (+), 52.3 (+),128.5 (q), 135.0 (+), 136.3 (q), 155.8 (q), 162.0 (q), 193.7 (q); HRMS (APCI): calcd. for $C_9H_{10}O_3S$ $(M+H)^+$ 199.0423; found 199.0424.

General procedure A: Suzuki coupling. To a suspension of $Pd_2(dba)_3$ (5 mol%), XPhos (10 mol%), the appropriate boronic acid (1.5 eq) and K_3PO_4 (1.5 eq) in 1,4-dioxane (0.5 M) the appropriate ester (1.0 eq) was added. The resulting mixture was heated to 100 °C and stirred overnight. After cooling to room temperature the reaction mixture was diluted with EtOAc and the organic phase was washed two times with water. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

General procedure B: Aminolysis. An NH_4OH solution (25% in H_2O) (10.0 eq) was added to a solution of the appropriate oxoacetate (1.0 eq) in THF (0.3 M) at 0 °C. The reaction was stirred for 1 h at room temperature and then quenched with water. The aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

General procedure C: Perkin condensation. KO*t*Bu (1 M in THF) (1.2 eq) was added to a solution of the appropriate amide (1.0 eq) in THF (0.2 M) at 0 °C. After 90 min stirring at 0 °C the appropriate ester (1.0 eq) was added at 0 °C and stirred overnight at room temperature. The reaction was quenched with 1 M HCl and diluted with EtOAc. The organic phase was washed three times with water and one time with brine. The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure.

2-(5-Chloro-2-methylthiophen-3-yl)-2-oxoacetamide (23): Compound **23** was prepared from **28** (800 mg, 3.66 mmol) according to general procedure B. The amide **23** (640 mg, 85%) was obtained as light yellow solid and used without further purification. m.p.: 183 °C; IR (neat) ν_{max}: 3446, 3252, 1996, 1670, 1618, 1296, 1221, 1153; ^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ = 2.64 (s, 3H, thiophene-C*H*$_3$), 7.49 (s, 1H, thiophene-*H*), 7.94 (bs, 1H, N*H*), 8.25 (bs, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$): δ = 15.2 (+), 123.9 (q), 128.4 (+), 131.4 (q), 150.9 (q), 166.1 (q), 184.2 (q); HRMS (ESI): calcd. for $C_7H_{10}ClN_2O_2S$ $(M+NH_4)^+$ 221.0146; found 221.0144.

3,4-Bis(5-chloro-2-methylthiophen-3-yl)-1*H*-pyrrole-2,5-dione (24): Compound **24** was prepared from amide **23** (600 mg, 2.95 mmol) and ester **22** (720 mg, 3.54 mmol) according to general procedure C. Purification by automated flash column chromatography (heptane/EtOAc: 5/1) yielded **24** (660 mg, 63%) as orange solid. R*f*: 0.18 (heptane/EtOAc: 5/1); m.p.: 237 °C; IR (neat) ν_{max}: 3381, 2939, 2818, 1653, 1437, 1002; ^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ = 1.87 (s, 6H, thiophene-C*H*$_3$), 6.97 (s, 2H, thiophene-*H*), 11.25 (bs, 1H, N*H*); ^{13}C-NMR (101 MHz, DMSO-*d*$_6$): δ = 14.6 (+), 125.0 (q), 127.0 (q), 128.4 (+), 133.6 (q), 140.0 (q), 171.4 (q); HRMS (ESI): calcd. for $C_{14}H_{10}Cl_2NO_2S_2$ $(M+H)^+$ 357.9525; found 357.9523.

Methyl 2-(5-(4-(*tert*-butyl)phenyl)-2-methylthiophen-3-yl)acetate (26): Compound **26** was prepared from **22** (200 mg, 0.98 mmol) according to general procedure A. Purification by automated flash column chromatography (PE/EtOAc, 0% - 25% EtOAc) yielded **26** (163 mg, 55%) as yellow liquid. R*f*: 0.63 (PE/EtOAc: 5/1); IR (neat) ν_{max}: 2961, 1736, 1609, 1520, 1435, 1364, 1239, 1018, 825; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9H, *t*Bu), 2.41 (s, 3H, thiophene-C*H*$_3$), 3.55 (s, 2H, thiophene-C*H*$_2$C(O)OCH$_3$), 3.71 (s, 3H, thiophene-CH$_2$C(O)OC*H*$_3$), 7.08 (s, 1H, thiophene-*H*), 7.32-7.40 (m, 2H, Ph), 7.43-7.52 (m, 2H, Ph); ^{13}C-NMR (75 MHz, $CDCl_3$): δ =13.3 (+), 31.3 (+) 34.1 (−), 34.6 (q), 52.1 (+), 124.7 (+), 125.2 (+), 125.7 (+), 130.1 (q), 131.6 (q), 134.8 (q), 140.1 (q), 150.2 (q), 171.6 (q); HRMS (ESI): calcd. for $C_{18}H_{23}O_2S$ $(M+H)^+$ 303.1413; found 303.1418.

Methyl 2-(5-([1,1'-biphenyl]-3-yl)-2-methylthiophen-3-yl)acetate (27): Compound **27** was prepared from **22** (500 mg, 2.44 mmol) according to general procedure A. Purification by automated flash column chromatography (PE/EtOAc, 0% - 15% EtOAc) yielded **27** (569 mg, 72%) as yellow liquid. R*f*: 0.50 (PE/EtOAc: 5/1); IR (neat) ν_{max}: 1707, 1597, 1449, 1262, 1174, 755, 696; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 3H, thiophene-C*H*$_3$), 3.58 (s, 2H, thiophene-C*H*$_2$C(O)OCH$_3$), 3.72 (s, 3H, thiophene-CH$_2$C(O)OC*H*$_3$), 7.19 (s, 1H, thiophene-*H*), 7.37-7.45 (m, 3H, Ph), 7.46-7.54 (m, 3H, Ph), 7.59-7.66 (m, 2H, Ph), 7.74-7.76 (m, 1H, Ph); ^{13}C-NMR (75 MHz, $CDCl_3$): δ =2.44 (s, 3H, thiophene-C*H*$_3$), 3.58 (s, 2H, thiophene-C*H*$_2$C(O)OCH$_3$), 3.72 (s, 3H, thiophene-CH$_2$C(O)OC*H*$_3$), 7.19 (s, 1H, thiophene-*H*), 7.37-7.42 (m, 1H, Ph), 7.43-7.47 (m, 3H, Ph), 7.48-7.54 (m, 2H, Ph), 7.60-7.65 (m, 2H, Ph), 7.74-7.76 (m, 1H, Ph); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 13.3 (+), 34.1 (−), 52.1 (+), 124.3 (+), 124.4 (+), 125.3 (+), 126.0 (+), 127.2 (+), 127.5 (+), 128.8 (+), 129.2 (+), 130.3 (q), 134.8 (q), 135.5 (q), 139.9 (q), 140.9 (q), 141.9 (q), 171.5 (q); HRMS (EI): calcd. for $C_{20}H_{18}O_2S$ $(M^{+\bullet})$ 322.1028; found 322.1032.

Methyl 2-(5-(4-(*tert*-butyl)phenyl)-2-methylthiophen-3-yl)-2-oxoacetate (30): Compound **30** was prepared from **28** (500 mg, 2.29 mmol) according to general procedure A. Purification by automated flash column chromatography (PE/EtOAc, 0% - 15% EtOAc) yielded **30** (350 mg, 48%) as dark yellow liquid. R*f*: 0.67 (PE/EtOAc: 5/1); IR (neat) ν_{max}: 2961, 2866, 1732, 1676, 1456, 1191, 1127, 993, 753; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9H, *t*Bu), 2.78 (s, 3H, thiophene-C*H*$_3$), 3.96 (s, 3H, thiophene-CH$_2$C(O)OC*H*$_3$), 7.39-7.44 (m, 2H, Ph), 7.46-7.51 (m, 2H, Ph), 7.63 (s, 1H, thiophene-*H*); ^{13}C-NMR (75 MHz, $CDCl_3$): δ =16.3 (+), 31.3 (+) 34.7 (q), 52.8 (+), 124.2 (+), 125.6 (+), 126.0 (+), 130.3 (q), 132.2 (q), 140.5 (q), 151.3 (q), 153.5 (q), 164.1 (q), 180.2 (q); HRMS (EI): calcd. for $C_{18}H_{20}O_3S$ $(M^{+\bullet})$ 316.1133; found 316.1139.

Methyl 2-(5-([1,1'-biphenyl]-3-yl)-2-methylthiophen-3-yl)-2-oxoacetate (31): Compound **31** was prepared from **28** (500 mg, 2.29 mmol) according to general procedure A. Purification by automated flash column chromatography (PE/EtOAc, 0% - 15% EtOAc) yielded **31** (537 mg, 70%) as yellow oil. R*f*: 0.40 (PE/EtOAc: 5/1); IR (neat) ν_{max}: 3028, 1724, 1668, 1598, 1464, 1197, 1132, 1000, 748, 695; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.81 (s, 3H, thiophene-C*H*$_3$), 3.98 (s, 3H, thiophene-CH$_2$C(O)OC*H*$_3$), 7.36-7.43 (m, 1H, Ph), 7.45-7.49 (m, 2H, Ph), 7.50-7.57 (m, 3H, Ph), 7.60-7.65 (m, 2H, 4-H, Ph), 7.73-7.76 (m, 2H, Ph, thiophene-*H*); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 16.4 (+), 52.9 (+), 124.6 (+), 124.7 (+), 124.8 (+), 126.9 (+), 127.2 (+), 127.7 (+), 128.9 (+), 129.5 (+), 132.3 (q), 133.5 (q), 140.2 (q), 140.6 (q), 142.2 (q), 154.0 (q), 164.0 (q), 180.1 (q); HRMS (ESI): calcd. for $C_{20}H_{15}O_2S$ $(M+H^+) - (H_2O)$ 319.0787; found 319.0787.

2-(5-(4-(*tert*-Butyl)phenyl)-2-methylthiophen-3-yl)-2-oxoacetamide (33): Compound **33** was prepared from **30** (312 mg, 0.99 mmol) according to general procedure B. The amide **33** (250 mg, 84%) was obtained as light yellow solid and used without further purification. m.p.: 202 °C; IR (neat) ν_{max}: 3395, 2955, 1712, 1651, 1454, 1191, 575; ^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ = 1.29 (s, 9H, *t*Bu), 2.71 (s, 3H, thiophene-C*H*$_3$), 7.36-7.48 (m, 2H, Ph), 7.51-7.59 (m, 2H, Ph), 7.74 (s, 1H, thiophene-*H*), 7.91 (s, 1H, N*H*), 8.26 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$): δ = 15.4 (+), 30.9 (+), 34.3 (q), 124.4 (+), 125.0 (+), 126.0 (+), 129.7 (q), 133.0 (q), 138.9 (q), 150.5 (q), 150.6 (q), 167.0 (q), 185.5 (q); HRMS (ESI): calcd. for $C_{17}H_{20}NO_2S$ $(M+H^+)$ 303.1240; found 303.1240.

2-(5-([1,1'-Biphenyl]-3-yl)-2-methylthiophen-3-yl)-2-oxoacetamide (34): Compound **34** was prepared from **31** (250 mg, 0.74 mmol) according to general procedure B. The amide **34** (224 mg, 94%) was obtained as light yellow solid and used without further purification. m.p.: 151 °C; IR (neat) ν_{max}: 3393, 3302, 3184, 1721, 1652, 1597, 1456, 1352, 1196, 747, 689,. 608; ^{1}H-NMR (300 MHz, DMSO-*d*$_6$): δ = 2.73 (s, 3H, thiophene-C*H*$_3$), 7.39-7.44 (m, 1H, Ph), 7.47-7.56 (m, 3H, Ph), 7.58-7.66 (m, 2H, Ph), 7.71-7.75 (m, 2H, Ph), 7.83-7.85 (m, 1H, N*H*), 7.93 (bs, 2H, Ph, thiophene-*H*), 8.28 (bs, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$): δ = 15.4 (+), 123.4 (+), 124.4 (+), 125.5 (+), 126.4 (+), 126.8 (+), 127.7 (+), 128.9 (+), 129.9 (+), 133.1 (q), 133.2 (q), 138.7 (q), 139.5 (q), 141.1 (q), 151.1 (q), 166.9 (q), 185.6 (q); HRMS (ESI): calcd. for $C_{19}H_{16}NO_2S$ $(M+H^+)$ 322.0896; found 322.0893.

3-(5-(4-(*tert*-Butyl)phenyl)-2-methylthiophen-3-yl)-4-(5-chloro-2-methylthiophen-3-yl)-1H-pyrrole-2,5-dione (35): Compound **35** was prepared from amide **23** (100 mg, 0.49 mmol) and ester **26** (178 mg, 0.59 mmol) according to general procedure C. Purification by automated flash column chromatography (PE/EtOAc, 0% - 25% EtOAc) yielded **35** (62 mg, 28%) as dark green solid. R_f: 0.47 (PE/EtOAc: 5/1); m.p.: 145 °C; IR (neat) ν_{max}: 3055, 2961, 1707, 1459, 1338, 1181, 1018, 987, 825; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.28 (s, 9H, *t*Bu), 1.88 (s, 3H, thiophene-C*H*$_3$), 1.99 (s, 3H, thiophene-C*H*$_3$), 7.02 (s, 1H, thiophene-*H*), 7.28 (s, 1H, thiophene-*H*), 7.40-7.49 (m, 4H, Ph), 11.27 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 14.0 (+), 14.2 (+), 30.9 (+), 34.2 (q), 124.0 (+), 124.3 (q), 124.7 (+), 125.9 (+), 126.7 (q), 127.8 (q), 127.9 (+), 130.2 (q), 132.7 (q), 134.1 (q), 139.3 (q), 139.5 (q), 139.8 (q), 150.3 (q), 171.0 (q), 171.1 (q); HRMS (ESI): calcd. for $C_{24}H_{26}ClN_2O_2S_2$ $(M+NH_4)^+$ 473.1119; found 473.1116.

3-(5-([1,1'-biphenyl]-3-yl)-2-methylthiophen-3-yl)-4-(5-chloro-2-methylthiophen-3-yl)-1H-pyrrole-2,5-dione (36): Compound **36** was prepared from amide **23** (100 mg, 0.49 mmol) and ester **27** (160 mg, 0.49 mmol) according to general procedure C. Purification by automated flash column chromatography (PE/EtOAc, 0% - 25% EtOAc) yielded **36** (63 mg, 27%) as dark red solid. R_f: 0.16 (PE/EtOAc: 5/1); m.p.: 137 °C; IR (neat) ν_{max}: 2736, 1705, 1338, 1022, 1006 756, 700; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.91 (s, 3H, thiophene-C*H*$_3$), 2.01 (s, 3H, thiophene-C*H*$_3$), 7.03 (s, 1H, thiophene-*H*), 7.37-7.44 (m, 1H, Ph), 7.46-7.56 (m, 5H, thiophene-*H*, Ph), 7.58-7.63 (m, 1H, Ph), 7.69-7.75 (m, 2H, Ph), 7.77-7.79 (m, 1H, Ph), 11.30 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 14.1 (+), 14.2 (+), 123.2 (+), 124.1 (+), 124.3 (q), 125.1 (+), 126.1 (+), 126.6 (q), 126.7 (+), 127.7 (+), 127.9 (+), 128.0 (q), 128.9 (+), 129.8 (+), 132.8 (q), 133.6 (q), 134.0 (q), 139.4 (q), 139.5 (q), 139.6 (q), 140.2 (q), 141.1 (q), 171.0 (q), 171.1 (q); HRMS (ESI): calcd. for $C_{26}H_{22}ClN_2O_2S_2$ $(M+NH_4)^+$ 493.0806; found 493.0804.

3-(5-([1,1'-Biphenyl]-3-yl)-2-methylthiophen-3-yl)-4-(5-(4-(tert-butyl)phenyl)-2-methylthiophen-3-yl)-1H-pyrrole-2,5-dione (37): Compound **37** was prepared from amide **33** (260 mg, 0.86 mmol) and ester **27** (277 mg, 0.86 mmol) according to general procedure C. Purification by automated flash column chromatography (PE/EtOAc, 0% - 15% EtOAc) yielded **37** (155 mg, 33%) as purple solid. R_f: 0.13 (PE/EtOAc: 5/1); m.p.: 145 °C; IR (neat) ν_{max}: 2921, 2851, 1707, 1334, 831, 756; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.27 (s, 9H, *t*Bu), 2.02 (s, 6H, thiophene-C*H*$_3$, thiophene-C*H*$_3$), 7.31 (s, 1H, thiophene-*H*), 7.38-7.43 (m, 3H, Ph), 7.44-7.50 (m, 5H, thiophene-*H*, Ph), 7.50-7.52 (m, 1H, Ph), 7.54-7.56 (m, 1H, Ph), 7.58-7.61 (m, 1H, Ph), 7.68-7.71 (m, 2H, Ph), 7.76-7.78 (m, 1H, Ph), 11.27 (s, 1H, N*H*); ^{13}C-NMR (75 MHz, DMSO-d_6): δ = 14.3 (+), 31.0 (+), 34.3 (q), 123.2 (+), 124.1 (+), 124.2 (+), 124.8 (+), 125.4 (+), 126.0 (+), 126.1 (+), 126.8 (+), 127.7 (+), 128.2 (q), 128.3 (q), 128.9 (+), 129.9 (+), 130.3 (q), 133.7 (q), 133.9 (q), 134.0 (q), 139.4 (q), 139.5 (q), 139.6 (q), 139.8 (q), 140.1 (q), 141.1 (q), 150.3 (q), 171.6 (q), 171.7 (q); HR-MS (ESI): calcd. for $C_{36}H_{32}NO_2S_2$ $(M+H)^+$ 576.1879; found 576.1875.

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Notes and references

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1. J. Zhang, Q. Zou and H. Tian, *Adv. Mater.*, 2013, **25**, 378-399.
2. W. Szymański, J. M. Beierle, H. A. V. Kistemaker, W. A. Velema and B. L. Feringa, *Chem. Rev.*, 2013, **113**, 6114-6178.
3. D. Gust, J. Andreasson, U. Pischel, T. A. Moore and A. L. Moore, *Chem. Commun.*, 2012, **48**, 1947-1957.
4. S. Kawata and Y. Kawata, *Chem. Rev.*, 2000, **100**, 1777-1788.
5. C. C. Corredor, Z. L. Huang and K. D. Belfield, *Adv. Mater.*, 2006, **18**, 2910-2914.
6. V. A. Barachevsky, M. M. Krayushkin, V. V. Kyiko and E. P. Grebennikov, *Phys. Status Solidi C*, 2011, **8**, 2841-2845.
7. D. Vomasta, C. Högner, N. R. Branda and B. König, *Angew. Chem. Int. Ed.*, 2008, **47**, 7644-7647.
8. D. Vomasta, A. Innocenti, B. König and C. T. Supuran, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1283-1286.
9. B. Reisinger, N. Kuzmanovic, P. Löffler, R. Merkl, B. König and R. Sterner, *Angew. Chem. Int. Ed.*, 2014, **53**, 595-598.
10. C. Falenczyk, M. Schiedel, B. Karaman, T. Rumpf, N. Kuzmanovic, M. Grøtli, W. Sippl, M. Jung and B. König, *Chem. Sci.*, 2014, **5**, 4794-4799.
11. M. Singer and A. Jäschke, *J. Am. Chem. Soc.*, 2010, **132**, 8372-8377.
12. S. Barrois and H.-A. Wagenknecht, *Beilstein J. Org. Chem.*, 2012, **8**, 905-914.
13. H. Cahová and A. Jäschke, *Angew. Chem. Int. Ed.*, 2013, **52**, 3186-3190.
14. M. R. Banghart, A. Mourot, D. L. Fortin, J. Z. Yao, R. H. Kramer and D. Trauner, *Angew. Chem. Int. Ed.*, 2009, **48**, 9097-9101.
15. T. Fehrentz, M. Schönberger and D. Trauner, *Angew. Chem. Int. Ed.*, 2011, **50**, 12156-12182.
16. I. Tochitsky, M. R. Banghart, A. Mourot, J. Z. Yao, B. Gaub, R. H. Kramer and D. Trauner, *Nat. Chem.*, 2012, **4**, 105-111.
17. A. Mourot, T. Fehrentz, Y. Le Feuvre, C. M. Smith, C. Herold, D. Dalkara, F. Nagy, D. Trauner and R. H. Kramer, *Nat. Methods*, 2012, **9**, 396-402.
18. M. Schönberger and D. Trauner, *Angew. Chem. Int. Ed.*, 2014, **53**, 3264-3267.
19. M. Schönberger, M. Althaus, M. Fronius, W. Clauss and D. Trauner, *Nat. Chem.*, 2014, **6**, 712-719.
20. I. Tochitsky, A. Polosukhina, Vadim E. Degtyar, N. Gallerani, Caleb M. Smith, A. Friedman, Russell N. Van Gelder, D. Trauner, D. Kaufer and Richard H. Kramer, *Neuron*, 2014, **81**, 800-813.
21. W. A. Velema, J. P. van der Berg, M. J. Hansen, W. Szymanski, A. J. M. Driessen and B. L. Feringa, *Nat. Chem.*, 2013, **5**, 924-928.

22. O. Babii, S. Afonin, M. Berditsch, S. Reiβer, P. K. Mykhailiuk, V. S. Kubyshkin, T. Steinbrecher, A. S. Ulrich and I. V. Komarov, *Angew. Chem. Int. Ed.*, 2014, **53**, 3392-3395.
23. U. Al-Atar, R. Fernandes, B. Johnsen, D. Baillie and N. R. Branda, *J. Am. Chem. Soc.*, 2009, **131**, 15966-15967.
24. W. A. Velema, W. Szymanski and B. L. Feringa, *J. Am. Chem. Soc.*, 2014, **136**, 2178-2191.
25. H. M. D. Bandara and S. C. Burdette, *Chem. Soc. Rev.*, 2012, **41**, 1809-1825.
26. G. Berkovic, V. Krongauz and V. Weiss, *Chem. Rev.*, 2000, **100**, 1741-1754.
27. Y. Yokoyama, *Chem. Rev.*, 2000, **100**, 1717-1740.
28. M. Irie, *Chem. Rev.*, 2000, **100**, 1685-1716.
29. H. Tian and S. Yang, *Chem. Soc. Rev.*, 2004, **33**, 85-97.
30. P. Raster, S. Weiss, G. Hilt and B. König, *Synthesis*, 2011, **2011**, 905-908.
31. M. Dubernet, V. Caubert, J. Guillard and M.-C. Viaud-Massuard, *Tetrahedron*, 2005, **61**, 4585-4593.
32. S. V. Shorunov, M. M. Krayushkin, F. M. Stoyanovich and M. Irie, *Russ. J. Org. Chem.*, 2006, **42**, 1490-1497.
33. A. El Yahyaoui, G. Félix, A. Heynderickx, C. Moustrou and A. Samat, *Tetrahedron*, 2007, **63**, 9482-9487.
34. M. M. Krayushkin, V. Z. Shirinyan, L. I. Belen'kii, A. A. Shimkin, A. Y. Martynkin and B. M. Uzhinov, *Russ. J. Org. Chem.*, 2002, **38**, 1335-1338.
35. M. Ohsumi, T. Fukaminato and M. Irie, *Chem. Commun.*, 2005, 3921-3923.
36. M. T. Indelli, S. Carli, M. Ghirotti, C. Chiorboli, M. Ravaglia, M. Garavelli and F. Scandola, *J. Am. Chem. Soc.*, 2008, **130**, 7286-7299.
37. M. M. Faul, L. L. Winneroski and C. A. Krumrich, *J. Org. Chem.*, 1998, **63**, 6053-6058.
38. M. M. Faul, L. L. Winneroski and C. A. Krumrich, *Tetrahedron Lett.*, 1999, **40**, 1109-1112.
39. W. Steglich, *Pure & Appl. Chem.*, 1989, **81**, 281-288.
40. T. Tamaoki and H. Nakano, *Nat. Biotechnol.*, 1990, **8**, 732-735.
41. P. D. Davis, C. H. Hill, G. Lawton, J. S. Nixon, S. E. Wilkinson, S. A. Hurst, E. Keech and S. E. Turner, *J. Med. Chem.*, 1992, **35**, 177-184.
42. D. A. E. Cross, A. A. Culbert, K. A. Chalmers, L. Facci, S. D. Skaper and A. D. Reith, *J. Neurochem.*, 2001, **77**, 94-102.
43. L. Meijer, M. Flajolet and P. Greengard, *Trends Pharmacol. Sci.*, 2004, **25**, 471-480.
44. E. Khalifa, J. H. Bieri and M. Viscontini, *Helv. Chim. Acta*, 1973, **56**, 2911-2919.
45. J. T. van Herpt, M. C. A. Stuart, W. R. Browne and B. L. Feringa, *Chem. Eur. J.*, 2014, **20**, 3077-3083.
46. K. Fujimoto, T. Maruyama, Y. Okada, T. Itou and M. Inouye, *Tetrahedron*, 2013, **69**, 6170-6175.
47. K. Fuji, T. Kawabata and E. Fujita, *Chem. Pharm. Bull.*, 1980, **28**, 3662-3664.
48. J. W. Fisher and K. L. Trinkle, *Tetrahedron Lett.*, 1994, **35**, 2505-2508.
49. Y. Goldberg and H. Alper, *J. Org. Chem.*, 1993, **58**, 3072-3075.
50. *US Pat.*, WO0214349 (A2), 2002.
51. *US Pat.*, WO2013025424 (A1), 2013.
52. A. McKillop, B. P. Swann and E. C. Taylor, *J. Am. Chem. Soc.*, 1973, **95**, 3340-3343.
53. T. Yamaguchi and M. Irie, *Chem. Lett.*, 2004, **33**, 1398-1399.
54. T. Yamaguchi, K. Uchida and M. Irie, *J. Am. Chem. Soc.*, 1997, **119**, 6066-6071.
55. M. Irie and K. Sayo, *J. Phys. Chem.*, 1992, **96**, 7671-7674.