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A Facile Route to Functionalized Cyclopenta[*b*]thiophenones Based on the Structure of the Selective COX-2 Inhibitor Flosulide

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Summary. The synthesis of three thiophene analogues of Flosulide – a potent and selective inhibitor of cyclooxygenase subtype 2 (COX-2) – is described. Utilizing combined *Friedel-Crafts* acylation and alkylation of 2-chlorothiophene, simplified procedures were developed to obtain cyclopenta[*b*]-thiophenones as key products which were further derivatized by nitration, nucleophilic aromatic substitution, reduction, and mesylation.

Keywords. COX-2 Inhibitor; Cyclopenta[*b*]thiophene; Aminothiophene.

Ein einfacher Weg zu funktionalisierten Cyclopenta[*b*]thiophenonen basierend auf der Struktur des selektiven COX-2-Hemmers Flosulid

Zusammenfassung. Die Synthese dreier Thiophenanaloga von Flosulid – ein potenter und selektiver Hemmer der Cyclooxygenase vom Subtyp 2 (COX-2) – wird beschrieben. Durch Anwendung kombinierter *Friedel-Crafts*-Acylierung und -Alkylierung von 2-Chlorthiophen wurden vereinfachte Verfahren zur Herstellung von Cyclopenta[*b*]thiophenen als Schlüsselsubstanzen entwickelt, welche weiter durch Nitrierung, nucleophile aromatische Substitution, Reduktion und Mesylierung derivatisiert wurden.

Introduction

Selective COX-2 inhibitors are expected to be potent antiinflammatory agents without ulcerous side effects which are typical for classic nonsteroidal antiinflammatory drugs (NSAIDs) [1, 2]. An important subset of these compounds is represented by N-arylmethanesulfonamides based on the structures of **CPG28237** and **CPG28238** (Flosulide) [3].

Whereas substituent positions, sulfonamide acidity, and the 1-oxo group turned out to be essential [4], the bioisosteric exchange of benzene by thiophene was a

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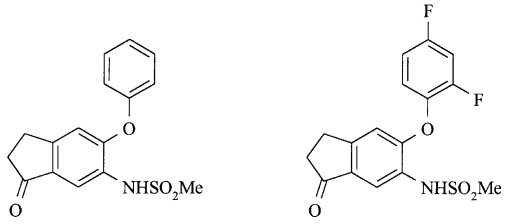


CPG28237 **CPG28238**

Fig. 1. Selective COX-2 inhibitors based on N-arylmethanesulfonamides

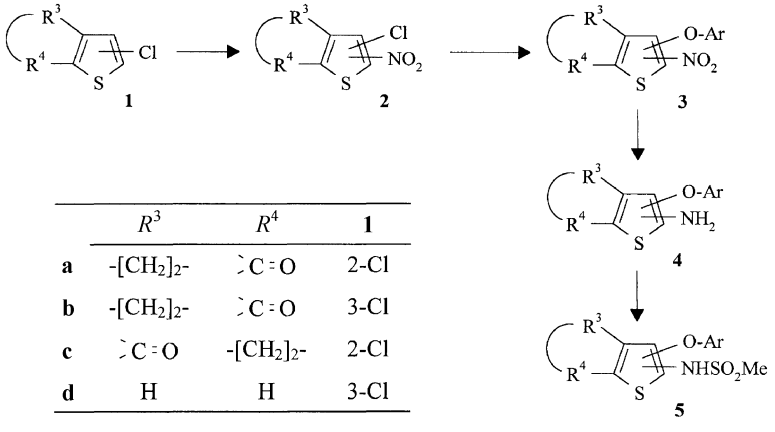
5a: $R^1 = MeSO_2NH$, $R^2 = 2,4\text{-}F_2C_6H_3O$ **5c**: $R^1 = MeSO_2NH$, $R^2 = PhO$
5b: $R^1 = 2,4\text{-}F_2C_6H_3O$, $R^2 = MeSO_2NH$

Fig. 2. Thiophene analogues of Flosulide

hopeful way to improve physiological effects. This method has been demonstrated in several examples by our group, among them the sedativum Brotizolam (® Lendormin) [5] derived from valium and the analgesic Tenoxicam (® Tilcotil) [6] derived from Piroxicam (® Felden). From the possible isomers we were especially interested in the synthesis of compounds **5a–c**.

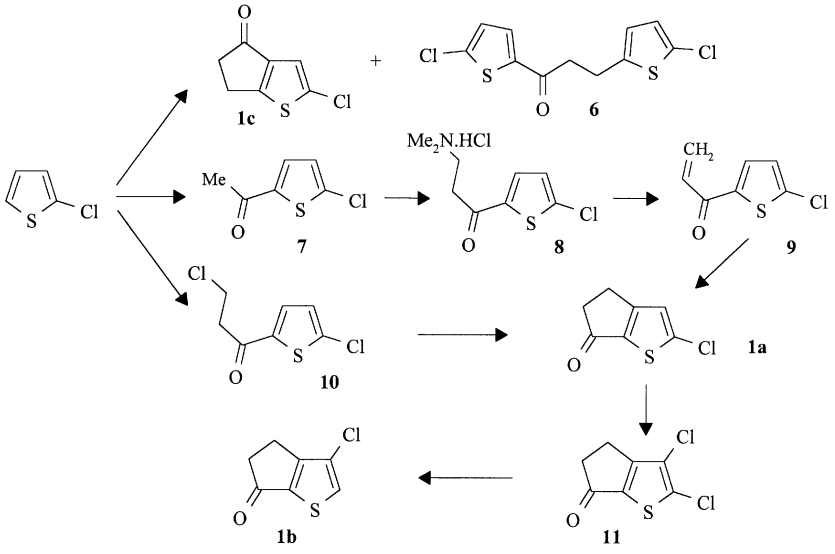
Results and Discussion

Substituents were introduced through *o*-chloro-nitro-thiophenes by nucleophilic aromatic substitution with sodium phenolate, reduction of the nitro group, and mesylation (Scheme 1), similarly demonstrated on the benzene analogue [7].



	R^3	R^4	1
a	-$[CH_2]_2$-	>C=O	2-Cl
b	-$[CH_2]_2$-	>C=O	3-Cl
c	>C=O	-$[CH_2]_2$-	2-Cl
d	H	H	3-Cl

Scheme 1. Introduction of substituents starting from chlorothiophenes **1**



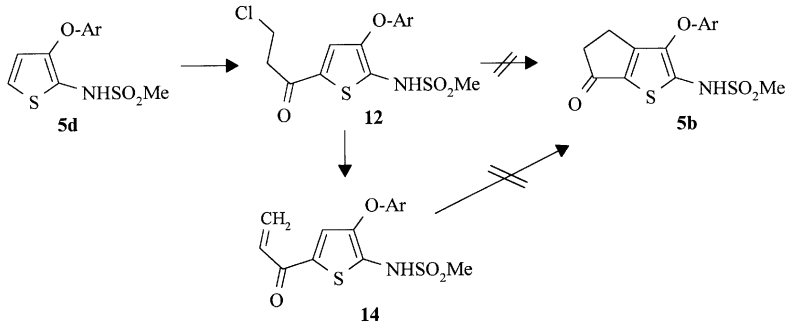
Scheme 2. Synthesis of cyclopenta[*b*]thiophenones by combined *Friedel-Crafts* acylation and alkylation

The synthesis of the only known chlorocyclopenta[*b*]thiophenone **1c** involves 5 steps: chloromethylation of 2-chlorothiophene, alkylation with diethyl malonate, hydrolysis, decarboxylation, and *Friedel-Crafts* cyclization [8].

As a substantial simplification we developed a method employing combined *Friedel-Crafts* acylation and alkylation (Scheme 2). Starting from 2-chlorothiophene and acrylic acid, we directly obtained isomer **1c** by action of polyphosphoric acid. These findings contrast with the results from the analogous reaction with methacrylic acid where the corresponding 6-one-derivative was obtained [9]. Instead we detected the formation of large amounts of ketone **6**, obviously formed by intermolecular acylation of the primary alkylation product with a second equivalent of 2-chlorothiophene, resulting in a yield of only 9% **1c**.

To obtain the vinyl ketone **9** we applied selective acylation with acetic acid anhydride and *o*-phosphoric acid to 2-chlorothiophene in position 5 [10] with subsequent *Mannich* reaction resulting in the dimethylamine hydrochloride **8** [11] in good yields. Elimination by steam distillation, however, led to a remarkable degree of polymerization, yielding only 30 to 59% of vinyl ketone **9**. Although the final cyclization could be accomplished by polyphosphoric acid as well as by conc. sulfuric acid, the overall yield was only about 10%.

To shorten this procedure, we again used combined *Friedel-Crafts* acylation and alkylation of 2-chlorothiophene with 3-chloropropanoyl chloride, analogously demonstrated in synthesis of indanone derivatives [12]. The first step, the acylation, was selectivity achieved in chloroform with aluminum chloride as catalyst in 80% yield. Subsequent experiments on cyclization with conc. sulfuric acid pointed out that application of ketone **10** as its complex with aluminum chloride clearly increased the reactivity with respect to *Friedel-Crafts* alkylation: When this complex was produced from the isolated compound **10** and aluminum chloride in chloroform, the yield of the annelated product **1a** rose from 5–10% to 21%



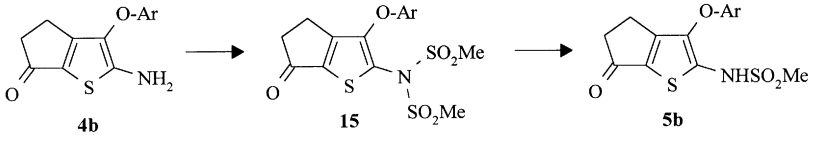
Scheme 3. Attempts for subsequent annelation; Ar = 2,4-$F_2C_6H_3$

compared to cyclization of the free compound. As a consequence, the crude complex isolated from *Friedel-Crafts* acylation of 2-chlorothiophene was cyclized without preceding aqueous workup. Although the overall yield of 13% was somewhat lower than from the two-step procedure, this finally represents the most efficient way. Isomer **1b** was derived by chlorination with chlorine and aluminum chloride as catalyst in position 3 and selective reduction with zinc in acetic acid in position 2 in high yields.

Subsequently, we aimed at an improvement of the yield of the annelation step, this time starting from the already substituted thiophene **5d** (Scheme 3). However, at the stage of the *Friedel-Crafts* acylation with 3-chloropropanoyl chloride, a maximum yield of only 38% of **12** was obtained using 1.4 equivalents of aluminum chloride as catalyst. This was explained by competing reactions at the sulfonamide nitrogen atom. Nevertheless, subsequent cyclization could neither be achieved with sulfuric acid or polyphosphoric acid nor on the aluminum chloride complex of compound **12** with sulfuric acid. Even the alternate way *via* the unstable vinyl ketone **14** produced by elimination of HCl from **12** with potassium acetate led exclusively to decomposition upon cyclization with polyphosphoric acid. Similar examples are known from other 2-acryloylthiophenes [9] and acryloylbenzenes [12].

After nitration of chlorothiophenes **1** by usual methods (Scheme 1), nucleophilic aromatic substitution with phenol or difluorophenol was carried out with potassium carbonate in acetone and in dimethylformamide for the less reactive isomer **2d**. Substitution of isomer **2b** was only satisfactory when applying 3.2 equivalents difluorophenol and 3.0 equivalents potassium carbonate in a 1.4:1 mixture of ether and tetrahydrofuran.

The resulting compounds **3** were reduced by hydrogen/*Raney* nickel (W2) to the amines **4** in good yields. Due to the low stability of the non-annelated derivative **4d**, the reaction time was considerably reduced by raising the reaction temperature to 50°C, and the crude amine solution was directly applied for the next step.



Scheme 4. Methanesulfonylation *via* dimesylation; Ar = 2,4-$F_2C_6H_3$

Amines **4a**, **4c**, and **4d** were mono-mesylated in pyridine with methanesulfonyl chloride, whereas for amine **4b** only application of triethylamine in tetrahydrofuran or, with an even higher overall yield, dimesylation and subsequent mono-cleavage with sodium methoxide (Scheme 4) was successful.

Experimental

Melting points were measured on a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 200 FS NMR spectrometer (200.13 MHz) or on a JOEL FX 90Q NMR spectrometer (88.55 MHz) in $CDCl_3$ (internal standard: *TMS*, $\delta = 0.00$ ppm) or *DMSO*-d_6 (2.50 ppm ref. to internal *TMS*). Abbreviations: *DIPE* = diisopropyl ether, *MTBE* = methyl-*t*-butyl ether, Ph = phenyl, Th = thiophene, *CT* = cyclopenta[*b*]thiophene. Elemental analyses agreed satisfactorily with the calculated values.

2-Chloro-4,5-dihydro-6H-cyclopenta[b] thiophen-6-one (**1a**, C_7H_5ClOS)

320 g (2.40 mol) $AlCl_3$ were added to a mixture of 190 g (1.60 mol) 2-chlorothiophene and 244 g (1.92 mol) 3-chloropropanoyl chloride in 1.5 l abs. $CHCl_3$ at 0°C within 1 h and stirred for 2 h at room temperature. The solvent was distilled off and the residue taken up in 2 l conc. H_2SO_4 and heated for 2 h at 90°C. The mixture was poured into 6 l ice water, filtered over hyflo, and extracted with ether. The organic layers were washed with water, 2 *N* NaOH, and again water, dried over Na_2SO_4, filtered, and evaporated. Recrystallization of the crude product from *DIPE* yielded 34.5 g **1a** (12%) as colourless crystals.

M.p.: 78–79°C (ether); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 6.96 (s, 1H, *CT*-H3), 3.04–2.98 (m, 2H, *CT*-H5), 2.90–2.81 (m, 2H, *CT*-H4) ppm.

3-Chloro-4,5-dihydro-6H-cyclopenta[b]thiophen-6-one (**1b**, C_7H_5ClOS)

A mixture of 64.0 g (310 mmol) **11**, 41.6 g (620 mmol) zinc, 67 ml acetic acid, and 222 ml water was heated at reflux for 4 h. The mixture was diluted with 300 ml 2 *N* HCl, extracted with CH_2Cl_2, and the organic layer was washed with sat. $NaHCO_3$ solution and dried over Na_2SO_4, filtered, and evaporated. Recrystallization of the crude product from *DIPE* yield 48.9 g **1b** (92%) as colourless crystals.

M.p.: 83–85°C (*DIPE*); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.66 (s, 1H, *CT*-H2), 3.02–2.91 (m, 4H, *CT*-H4,5) ppm.

2-Chloro-5,6-dihydro-4H-cyclopenta[b]thiophen-4-one (**1c**, C_7H_5ClOS)

A solution of 20.0 g (169 mmol) 2-chlorothiophene and 14.6 g (203 mmol) acrylic acid in 20 ml dichloromethane was added to 800 g *PPA* at 60°C within 2 h and stirred for 1 h. The mixture was poured into 1 l ice water, diluted with 500 ml ether, filtered over hyflo, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and sat. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and evaporated. The residue was distilled at 65–80°C/ 0.04 mbar and recrystallised from *MTBE*, yielding 2.54 g **1c** (9%) as colourless crystals.

M.p.: 100–101°C (*MTBE*); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.01 (s, 1H, *CT*-H3), 3.21–3.11 (m, 2H, *CT*-H5), 2.93–2.81 (m, 2H, *CT*-H4) ppm.

2-Chloro-4,5-dihydro-3-nitro-6H-cyclopenta[b]thiophen-6-one (**2a**, $C_7H_4ClNO_3S$)

A cold solution of 8.4 g (133 mmol) fuming HNO_3 in 150 ml conc. H_2SO_4 was added to 20.0 g (116 mmol) **1a** in 150 ml conc. H_2SO_4 at 0°C and stirred for 3 h. The mixture was poured into 1 l ice

water, filtered, and the residue was triturated with water. Recrystallization from 150 ml ethanol yielded 20.0 g **2a** (80%) as yellow crystals.

M.p.: 127–128°C (ethanol); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 3.43–3.30 (m, 2H, *CT*-H5), 2.99–2.87 (m, 2H, *CT*-H4) ppm.

3-Chloro-4,5-dihydro-2-nitro-6H-cyclopenta[b]thiophen-6-one (**2b**, $C_7H_4ClNO_3S$)

Applying the same procedure as for **2a** and a reaction time of 5 h at −30°C, 43.0 g (249 mmol) **1b** gave 39.8 g **2b** (64%) as yellow crystals.

M.p.: 139°C (ethanol); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 3.10–3.04 (m, 2H, *CT*-H5), 2.98–2.91 (m, 2H, *CT*-H4) ppm.

2-Chloro-5,6-dihydro-3-nitro-4H-cyclopenta[b]thiophen-4-one (**2c**, $C_7H_4ClNO_3S$)

Applying the same procedure as for **2a** and a reaction time of 1 h 2.75 g (16 mmol) **1c** gave 3.03 g **2c** (87%) as beige crystals.

M.p.: 125–126°C (ethanol); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 3.28–3.15 (m, 2H, *CT*-H5), 3.08–2.95 (m, 2H, *CT*-H6) ppm.

2-(2,4-Difluorophenoxy)-4,5-dihydro-3-nitro-6H-cyclopenta[b]thiophen-6-one (**3a**, $C_{13}H_7F_2NO_4S$)

To a mixture of 17.8 g (82 mmol) **2a** and 22.9 g (176 mmol) 2,4-difluorophenol in 700 ml abs. acetone, 22.6 g (164 mmol) K_2CO_3 were added at 5°C stirred for 2 h warmed up to 25°C, and stirred for further 4 h. The mixture was filtered over hyflo, the solvent replaced by dichloromethane, and washed with 1 *N* NaOH solution and water. The organic layer was dried over Na_2SO_4, filtered, evaporated, and the crude product was recrystallized from ethanol yielding 12.8 g **3a** (50%) as colourless crystals.

M.p.: 160–161°C (ethanol); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.31–6.99 (m, 3H, Ph-H3,5,6), 3.44–3.33 (m, 2H, *CT*-H5), 2.87–2.77 (m, 2H, *CT*-H4) ppm.

3-(2,4-Difluorophenoxy)-4,5-dihydro-2-nitro-6H-cyclopenta[b]thiophen-6-one (**3b**, $C_{13}H_7F_2NO_4S$)

A suspension of 11.9 g (54.6 mmol) **2b**, 22.7 g (175 mmol) 2,4-difluorophenol, and 22.7 g (164 mmol) dry K_2CO_3 in 70 ml abs. ether and 50 ml abs. *THF* was heated at reflux for 4 h. The mixture was filtered over hyflo, the filtrate evaporated and the residue filtered over 100 g silica gel with ethyl acetate, dried over Na_2SO_4, filtered, and evaporated. The crude product was triturated with 50 ml ether and recrystallized from ethyl acetate yielding 5.08 g **3b** (30%) as yellow crystals.

M.p.: 188–189°C (ethyl acetate); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.32–7.19 (m, 1H, Ph-H6), 7.08–6.88 (m, 2H, Ph-H3,5), 2.82–2.74 (m, 2H, *CT*-H5), 2.50–2.42 (m, 2H, *CT*-H4) ppm.

5,6-Dihydro-3-nitro-2-phenoxy-4H-cyclopenta[b]thiophen-4-one (**3c**, $C_{13}H_9NO_4S$)

Applying the same procedure as for **3a** and a reaction time of 5 h at reflux, 2.00 g (9.20 mmol) **2c** and 3.00 g (32.2 mmol) phenol gave 1.05 g **3c** (42%) as colourless crystals.

M.p.: 179–181°C (ethanol); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.47–7.16 (m, 5H, Ph-H2-6), 3.11–3.04 (m, 2H, *CT*-H5), 2.95–2.88 (m, 2H, *CT*-H6) ppm.

3-(2,4-Difluorophenoxy)-2-nitro-thiophene (**3d**, $C_{10}H_5F_2NO_3S$)

A mixture of 24.8 (152 mmol) 3-chloro-2-nitro-thiophene, 39.0 g (300 mmol) 2,4-difluorophenol, and 45.6 g (330 mmol) K_2CO_3 in 250 ml abs. *DMF* was stirred at 100°C for 1 h. The mixture was

poured into water, acidified with 2 *N* HCl to $pH = 5$, and extracted with CH_2Cl_2. The combined organic layers were washed with 2 *N* NaOH, dried over Na_2SO_4, filtered, evaporated, and the crude product was recrystallized from CH_2Cl_2 yielding 35.0 g **3d** (90%) as colourless crystals.

M.p.: 105°C (EtOH); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.39 (d, 1H, Th-H5, $^3J_{H,H} = 6.0$ Hz), 7.18–7.28 (m, 1H, Ph-H3), 6.83–7.04 (m, 2H, Ph-H5,6), 6.48 (d, 1H, Th-H4, $^3J_{H,H} = 6.0$ Hz) ppm.

3-Amino-2-(2,4-difluorophenoxy)-4,5-dihydro-6H-cyclopenta[b]thiophen-6-one (**4a**, $C_{13}H_9F_2NO_2S$)

11.7 g (38 mmol) **3a** in 300 ml abs. methanol were hydrogenated with 11 g *Raney* nickel(W2) at 70 psi in a *Parr* apparatus. The suspension was filtered over hyflo, and the solvent was distilled off. Recrystallization of the crude product (9.7 g) from ethyl acetat gave 7.4 g **4a** (70%) as pale green crystals.

M.p.: 177–178°C (ethyl acetate); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.26–6.84 (m, 3H, Ph-H3,5,6), 3.51 (br s, 2H, NH_2), 2.96–2.85 (m, 4H, *CT*-H4, 5) ppm.

2-Amino-3-(2,4-difluorophenoxy)-4,5-dihydro-6H-cyclopenta[b]thiophen-6-one (**4b**, $C_{13}H_9F_2NO_2S$)

5.00 g (16.1 mmol) **3b** in 150 ml methanol were hydrogenated with 5.0 g *Raney* nickel (W2) at 70 psi in a *Parr* apparatus. The suspension was filtered over hyflo, dried over Na_2SO_4, and the crude product was purified by chromatography (KG 60, *PE*:*EE* = 1:1) yielding 2.91 g **4b** (65%) as colourless crystals.

M.p.: 153–156°C (SC); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 6.98–6.72 (m, 3H, Ph-H3,5,6), 4.87 (s, 2H, -NH_2), 2.78–2.68 (m, 2H, *CT*-H5), 2.63–2.55 (m, 2H, *CT*-H4) ppm.

3-Amino-5,6-dihydro-2-phenoxy-4H-cyclopenta[b]thiophen-4-one (**4c**, $C_{13}H_{11}NO_2S$)

1.00 g (3.60 mmol) **3c** in 40 ml abs. methanol were hydrogenated with 1 g *Raney* nickel (W2) at 70 psi in a *Parr* apparatus. The suspension was filtered over hyflo, the solvent distilled off, and the crude product recrystallized from ethanol yielding 0.38 g **4c** (43%) as colourless crystals.

M.p.: 148–151°C (ethyl acetate); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.34–6.97 (m, 5H, Ph-H2-6), 3.96 (br, s, 2H, NH_2), 3.17–3.07 (m, 2H, *CT*-H5), 2.87–2.76 (m, 2H, *CT*-H6) ppm.

3-(2,4-Difluorophenoxy)-2-thiopheneamine (**4d**, $C_{10}H_7F_2NOS$)

5.00 g (19.4 mmol) **3d** in 200 ml methanol were hydrogenated with 5.0 g *Raney* nickel (W2) at 50°C/70 psi in a *Parr* apparatus. The suspension was filtered over hyflo, concentrated to 15 ml, and used immediately for sulfonylation without further purification.

^{1}H NMR (200 MHz, δ, $CDCl_3$): 6.98–6.69 (m, 5H, Ph-H3,5,6, NH_2), 6.56 (d, 1H, Th-H5, $^3J_{H,H} =$ 6.2 Hz), 6.48 (d, 1H, Th-H4, $^3J_{H,H} = 6.2$ Hz)

N-(2-(2,4-Difluorophenoxy)-5,6-dihydro-6-oxo-4H-cyclopenta[b]thiophen-3-yl)-methanesulfonamide (**5a**, $C_{14}H_{11}F_2NO_4S_2$)

A solution of 7.4 g (26 mmol) **4a** in 100 ml abs. pyridine was treated dropwise with 3.9 g (34 mmol) methanesulfonyl chloride in 10 ml abs. pyridine at −10°C and stirred for 90 min. The solvent was distilled off and the residue taken up in water and extracted with ethyl acetate. The organic layer was washed with 2 *N* HCl and water, dried over Na_2SO_4, filtered, evaporated, and the crude product was recrystallized from ethanol yielding 6.0 g **5a** (60%) as colourless crystals.

M.p.: 173–175°C(ethanol); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.32–6.88 (m, 3H, Ph-H3,5,6), 6.33 (s, 1H, NH), 3.20–3.08 (m, 2H, *CT*-H5), 3.13 (s, 3H, CH_3), 2.85–2.73 (m, 2H, *CT*-H6) ppm.

N-(3-(2,4-Difluorophenoxy)-5,6-dihydro-6-oxo-4H-cyclopenta[b]thiophen-2-yl) methanesulfonamide (**5b**, $C_{14}H_{11}F_2NO_4S_2$)

A solution of 550 mg (1.26 mmol) **15** in 6 ml abs. methanol was stirred at 0 °C with 135 mg (2.52 mmol) sodium methoxide for 20 min. The mixture was poured into 2 *N* HCl and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, evaporated, and the crude product was recrystallized from acetonitrile yielding 390 mg **5b** (86%) as colourless crystals.

M.p.: 160–162°C (acetonitrile); ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 7.53–7.40 (m, 1H, Ph-H6), 7.25–7.11 (m, 1H, Ph-H3), 7.10–6.99 (m, 1H, Ph-H5), 3.58–3.27 (br, s, 1H, NH), 3.11 (s, 3H; CH_3), 2.75–2.64 (m, 2H, *CT*-H5), 2.53–2.46 (m, 2H, *CT*-H4) ppm.

N-(5,6-Dihydro-4-oxo-2-phenoxy-4H-cyclopenta[b]thiophen-3-yl)methanesulfonamide (**5c**, $C_{14}H_{13}NO_4S_2$)

Applying the same procedure as for **5a** using 200 mg (0.80 mmol) **4c** and a reaction time of 10 min at 0°C gave 200 mg **5c** (77%) as colourless crystals.

M.p.: 170–171°C (ethanol); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.49–7.06 (m, 5H, Ph-H2-6), 6.52 (br s, 1H, NH), 3.23 (s, 3H, CH_3), 3.23–3.09 (m, 2H, *CT*-H5), 2.92–2.79 (m, 2H, *CT*-H4) ppm.

N-(3-(2,4-Difluorophenoxy)-2-thienyl)methansulfonamide (**5d**, $C_{11}H_9F_2NO_3S_2$)

Applying the same procedure as for **5a** using the crude solution of amine **4d** and a reaction time of 90 min at −40°C gave **5d** (33% overall yield **3d**→**5d**) as colourless crystals.

M.p.: 68°C (*DIPE*); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.07 (d, 1H, Th-H5, $^3J_{H,H} = 6.7$ Hz), 7.03–6.78 (m, 3H, Ph-H3,5,6), 6.56 (d, 1H,Th-H4, $^3J_{H,H} = 6.7$ Hz), 6.43 (s, 1H, NH), 3.12 (s, 3H, CH_3) ppm.

1,3-(Bis-(5-chloro-2-thienyl))-propan-1-one (**6**, $C_{11}H_8Cl_2OS_2$)

A solution of 5.00 g (42 mmol) 2-chlorothiophene and 3.65 g (50 mmol) acrylic acid in 5 ml abs. CH_2Cl_2 was slowly dropped on 210 g polyphosphoric acid with stirring. The mixture was hydrolyzed with 100 ml ice water, extracted with ether, and the combined organic layers were washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography (silica gel KG 60, *PE*:*EE* = 7:1) yielding 1.35 g **6** (22%) as colourless crystals.

M.p.: 55–56°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.47 (d, 1H, ThA-H3, $^3J_{H,H} = 3.9$ Hz), 6.94 (d, 1H, ThA-H4, $^3J_{H,H} = 3.9$ Hz), 6.69 (d, 1H, ThB-H3, $^3J_{H,H} = 3.9$ Hz), 6.59 (d, 1H, ThB-H4, $^3J_{H,H} = 4.1$ Hz), 3.15 (s, 4H, -CH_2-CH_2-) ppm.

1-(5-Chloro-2-thienyl)-propen-1-one (**9**, C_7H_5ClOS)

A mixture of 4.00 g (15.7 mmol) 1-(5-chloro-2-thienyl)-3-dimethylaminopropan-1-one hydrochloride [11] and 20 ml water was steam distilled, the product extracted with ethyl acetate, dried over Na_2SO_4, and the solvent was distilled off yielding 1.6 g **9** (59%) as an oil.

$n_D^{20} = 1.6255$; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.55 (d, 1H, Th-H3, $^3J_{H,H} = 4.1$ Hz), 6.98 (d, 1H, Th-H4, $^3J_{H,H} = 4.1$ Hz), A_2B-System CH=CH_2: 7.00, 6.47, 5.89 ($^2J_{gem} = 17$ Hz, $^3J_{trans} = 10$ Hz, $^3J_{cis} = 2$ Hz); $C_7H_5ClOS \cdot 0.25\ H_2O$ (177.13); calcd.: C 47.5, H 3.1; found: C 47.5, H 3.1.

3-Chloro-1-(5-chloro-2-thienyl)propan-1-one (**10**, $C_7H_6Cl_2OS$)

33.7 g (253 mmol) $AlCl_3$ were added to a solution of 20.0 g (169 mmol) 2-chlorothiophene and 25.7 g (202 mmol) 3-chloropropanoyl chloride in 200 ml abs. chloroform at 10 °C in small portions, stirred for 1 h and, after raising the temperature to 25°C, for 4 h. The mixture was poured into 300 ml ice water containing 5 ml conc. HCl, stirred for 15 min, and extracted with CH_2Cl_2. The organic layers were washed with water, dried over Na_2SO_4, filtered, evaporated, and the crude product was recrystallized from methanol yielding 28.4 g **10** (80%) as colourless crystals.

M.p.: 22–24°C (methanol); ^{1}H NMR (90 MHz, δ, $CDCl_3$): 7.52 (d, 1H, Th-H3, $^3J_{H,H} = 4.1$ Hz), 6.98 (d, 1H, Th-H4, $^3J_{H,H} = 4.1$ Hz), 3.88 (t, 2H, Cl-CH_2, $^3J_{H,H} = 7.1$ Hz), 3.33 (d, 2H, CO-CH_2, $^3J_{H,H} = 7.1$ Hz) ppm.

2,3-Dichloro-4,5-dihydro-6H-cyclopenta[b]thiophen-6-one (**11**, $C_7H_4Cl_2OS$)

To a suspension of 101 g (760 mmol) $AlCl_3$ in 150 ml abs. $CHCl_3$, a solution of 61.0 g (350 mmol) **1a** in 150 ml abs. $CHCl_3$ was slowly added at 0°C, followed by 32.3 g (0.46 mmol) Cl_2 in 290 g abs. $CHCl_3$, and stirred for 1 h at 0°C and for 2 h at room temperature. The mixture was poured on ice water, the organic layer washed with 2 *N* HCl and the aqueous solutions were extracted with $CHCl_3$. The combined organic layers were dried over Na_2SO_4, filtered, evaporated, and the crude product was recrystallized from *DIPE* yielding 64.3 g **11** (88%) as pale yellow crystals.

M.p.: 60–61°C (*DIPE*); ^{1}H NMR (200 MHz, δ, $CDCl_3$) 3.02–2.96 (m, 2H, *CT*-H5), 2.92–2.86 (m, 2H, *CT*-H4) ppm.

N-(5-(3-Chloro-1-oxo-propyl)-3-(2,4-difluorophenoxy)-2-thienyl)methanesulfonamide (**12**, $C_{14}H_{12}ClF_2NO_4S_2$)

To a suspension of 720 mg (5.39 mmol) $AlCl_3$ in 8 ml abs. $CHCl_3$ at 0°C, 520 mg (4.13 mmol) 3-chloropropanoyl chlorid were slowly added, followed by 1.20 g (3.93 mmol) **5d** in 8 ml abs. $CHCl_3$, and stirred for 2 h at 60°C. The mixture was poured into 2 *N* HCl, extracted with ethyl acetate, the organic layer washed with 2 *N* HCl, dried over Na_2SO_4, filtered, evaporated, and the crude product was purified by chromatography (100 g silica gel KG 60, CH_2Cl_2: *EE* = 10:1) and subsequent recrystallization from *MTBE* yielding 580 mg **12** (37%) as colourless crystals.

M.p.: 115–117°C (*MTBE*); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.16 (s, 1H, Th-H4), 7.11–6.82 (m, 4H, Ph-H3,5,6, NH), 3.83 (t, 2H, CH_2-Cl, $^3J_{H,CH_2} = 6.8$ Hz), 3.21 (t, 2H, CH_2-C=O, $^3J_{H,CH_2} = 6.8$ Hz, 3.14 (s, 3H, CH_3) ppm.

N-(3-(2,4-Difluorophenoxy)-5,6-dihydro-6-oxo-4H-cyclopenta[b]thiophene-2-yl)-N-(methylsulfonyl)methanesulfonamide (**15**, $C_{15}H_{13}F_2NO_6S_3$)

A solution of 500 mg (1.78 mmol) amine **5b** and 360 mg (3.56 mmol) triethylamine in 5 ml abs. *THF* was treated with 410 mg (3.56 mmol) methanesulfonyl chloride at −30°C and stirred for 2 h. The mixture was poured into 2 *N* HCl, extracted with ethyl acetate, the organic layer washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4, filtered, evaporated, and the crude product was recrystallised from acetonitrile yielding 590 mg **15** (72%) as colourless crystals.

M.p.: 178°C (acetonitrile); ^{1}H NMR (200 MHz, δ, $CDCl_3$): 7.30–7.17 (m, 1H, Ph-H3), 7.04–6.80 (m, 2H, Ph-H5, 6), 3.49 (s, 6H, CH_3), 2.75–2.66 (m, 2H, *CT*-H5), 2.47–2.39 (m, 2H, *CT*-H4) ppm.

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