

A Convenient One-pot Synthesis of 2,3-Disubstituted Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones from 2*H*-Thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-diones, Aromatic Aldehydes and Amines

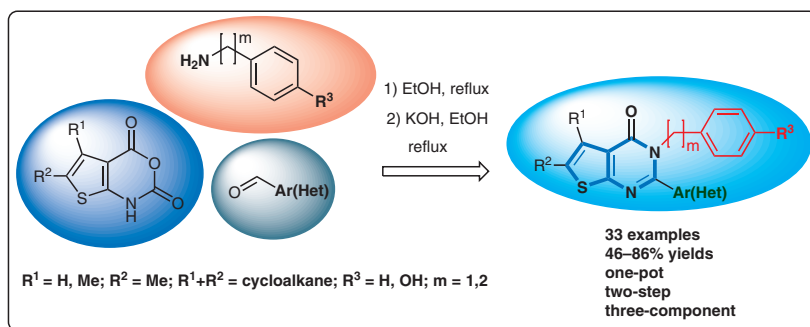
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Abstract An efficient, simple protocol has been established for convenient synthesis of novel 2,3-disubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives in good to high yields through a one-pot, two-step and three-component reaction from 2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-diones, aromatic aldehydes, and amines.

Key words thieno[2,3-*d*]pyrimidin-4(3*H*)-one, one-pot synthesis, intramolecular cyclization, pyrimidinone, quinazolinone

Quinazolinones, especially quinazolin-4(3*H*)-ones (Figure 1) are one of the most important building blocks in medicinal chemistry. Over the past few years, quinazolinones have been applied as prospective drug candidates, demonstrating diverse biological potency, including antimicrobial, anti-inflammatory, antimalarial, antiviral, and anticancer activities.¹ Structurally similar to quinazolinones, thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (Figure 1) also serve as a privileged structure in a variety of drug candidates.² A broad range of thieno[2,3-*d*]pyrimidin-4(3*H*)-ones³ have been identified with properties such as antimicrobial and antibacterial activities,⁴ or as 17β-HSD1 inhibitors,⁵ and zinc-binding MMP-13 inhibitors,⁶ as exemplified by the structures in Figure 1. Therefore, the development of an ef-

ficient protocol towards a simple synthetic pathway for the formation of novel thieno[2,3-*d*]pyrimidin-4(3*H*)-ones is a valid aim in organic synthesis.

Previously reported syntheses of 2,3-disubstituted thieno[2,3-*b*]pyrimidin-4(3*H*)-ones usually required more than two steps starting from 2-aminothiophene-3-carboxylic acid or its ester/carboxamide analogues.^{4,7} Harsh conditions such as POCl₃, P₂O₅ or sodium, or reaction at elevated pressure were necessary for the pyrimidinone ring cyclization.^{8–10} No protocols have yet been reported for the synthesis of 2,3-disubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones in a one-pot reaction.

In the case of quinazolinones, several one-pot protocols using commercially available starting materials, such as anthranilic acid esters, anthranilamide, anthranilonitrile, and isatoic anhydride are reported.^{1a–c,11} For example, Maleki et al. synthesized 2,3-dihydroquinazolin-4(1*H*)-ones from isatoic anhydride, aldehydes and ammonium acetate, using a magnetic silica-based nanocomposite Fe₃O₄/SBA-15 as catalyst.¹² Applying H₃PO₃ as the catalyst, Balalaie et al. investigated a one-pot protocol for the efficient synthesis of spiroquinazolinone derivatives using hydrazides and cyclic ketones.¹³ Isatoic anhydride was also the starting material in the development of potent antiviral agents by Brown et al.¹⁴ We have recently reported a straightforward synthesis of rutaecarpine and its analogues by a fusion reaction using isatoic anhydrides and 4,9-dihydro-3*H*-pyrido[3,4-*b*]in-

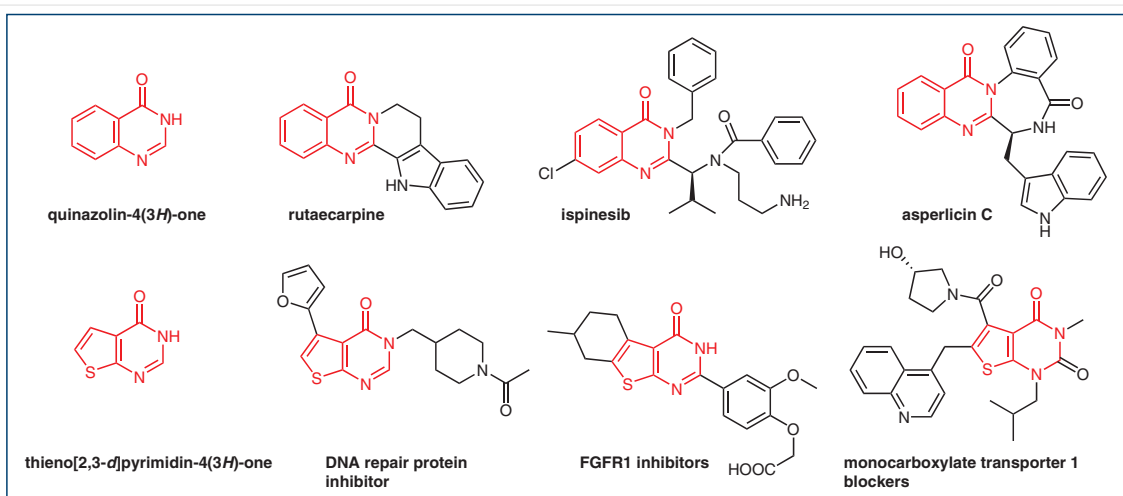


Figure 1 Biologically relevant quinazolin-4(3*H*)-one and thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives

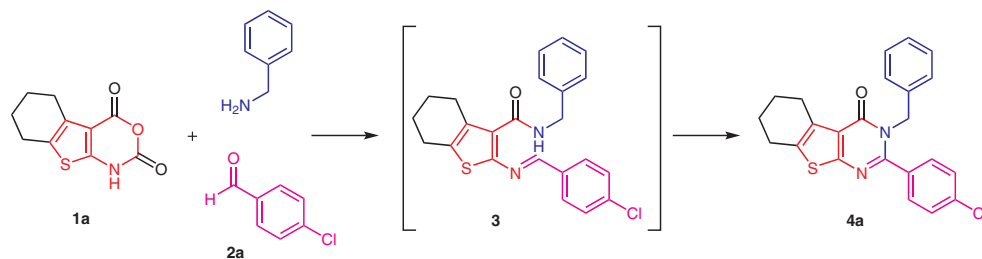
dole.¹⁵ This protocol provided a simple and fast access to large quantities of rutaecarpine and its derivatives, avoiding tedious purification procedures.

Inspired by the general application of isatoic anhydride,¹⁶ we envisaged a very similar compound, 2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione, could be applied to the preparation of thieno-analogues of quinazolineones and enable their biological evaluations. Herein, we present our methodology for the one-pot, two-step, three-component synthesis of 2,3-disubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones.

Initially, we used 5,6,7,8-tetrahydro-2*H*-benzo[4,5]thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione (**1a**; 1.5 mmol), 4-chlorobenzaldehyde (**2a**; 1 mmol), and phenylmethylamine (1.5 mmol) to investigate the reaction conditions (Table 1). Although condensation reactions of isatoic anhydride, alde-

hydes and amines have been reported in the presence of numerous catalysts,¹⁷ and under acidic conditions,¹⁸ application of those protocols to **1a** surprisingly failed to yield the ring-closed target compounds. For example, $\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$ was found to be a reusable catalyst to obtain 2,3-dihydroquinazolin-4(1*H*)-ones.¹⁹ However, when using the same catalyst, no **4a** was formed when **1a** was treated with **2a** and phenylmethylamine and heating the reaction mixture at reflux (Table 1, entry 1). Brønsted acids such as *p*-TsOH and acetic acid also did not promote the fusion reaction. When the three components were heated in ethanol at reflux in the presence of potassium hydroxide (entry 12), the obtained product was confirmed to be ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate, the starting material **1a** having reacted with the ethanol solvent.

Table 1 Optimization of the Conditions for the One-Pot Synthesis of 2,3-Disubstituted Thieno[2,3-*d*]pyrimidin-4(3*H*)-ones **4a**



Entry	Solvent	Additives	Time (h)	Temp (°C)	Yield (%) ^a
1	EtOH	$\text{KAl}(\text{SO}_4)_2 \cdot 12\text{H}_2\text{O}$	20	reflux	– ^b
2	EtOH	<i>p</i> -TsOH	20	reflux	– ^b
3	AcOH	–	20	reflux	– ^b

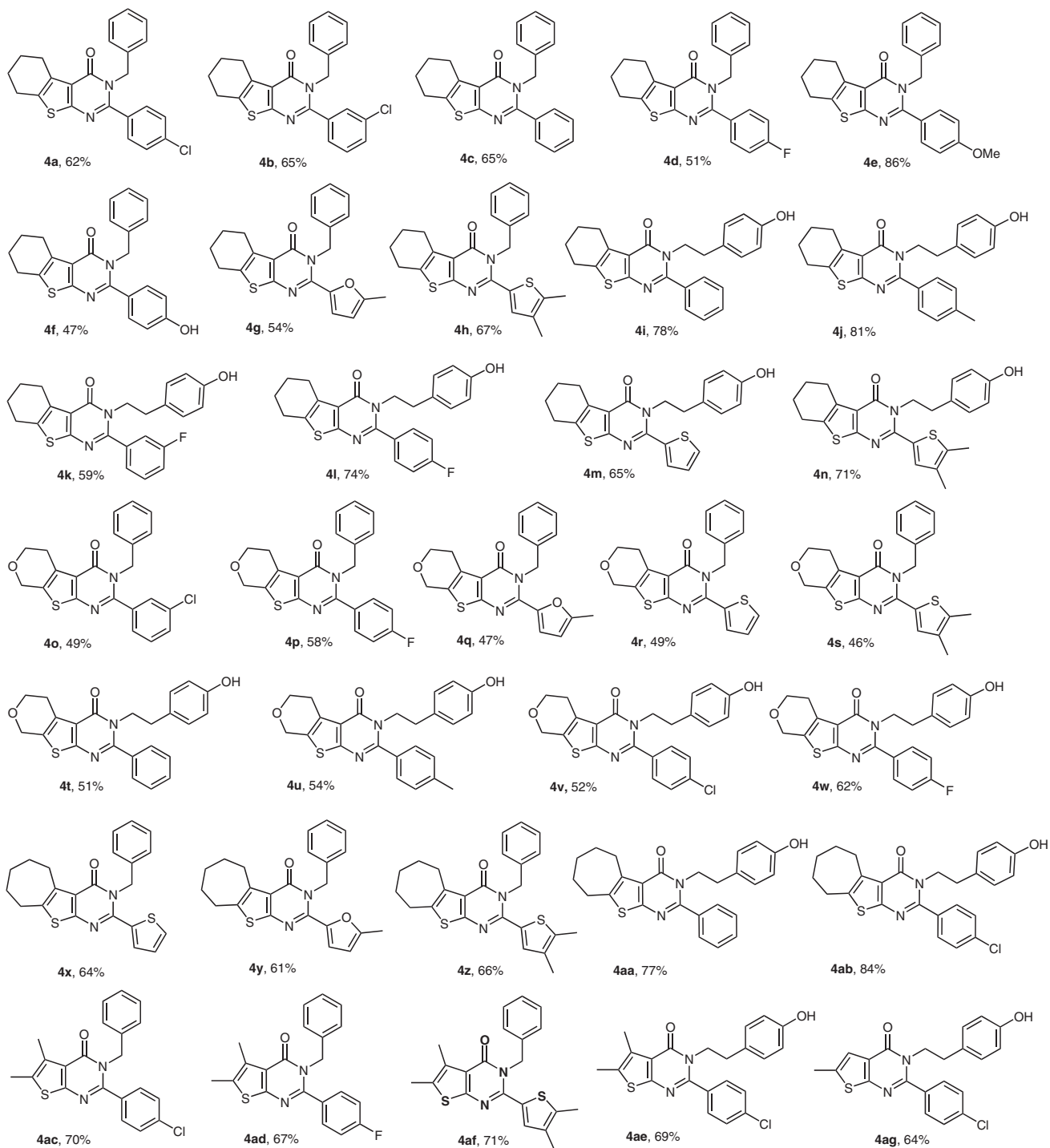
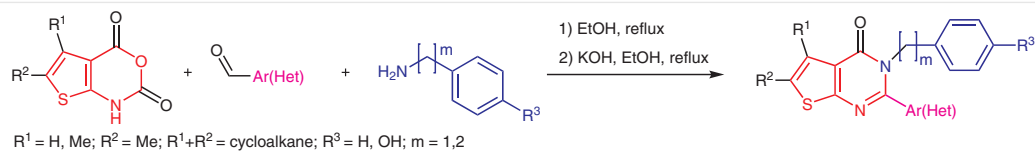
Entry	Solvent	Additives	Time (h)	Temp (°C)	Yield (%) ^a
4	EtOH	K ₂ CO ₃	20 ^c	reflux	32
5	MeOH	K ₂ CO ₃	24 ^c	80	34
6	EtOH	Cs ₂ CO ₃	24	r.t	– ^b
7	EtOH	Cs ₂ CO ₃	2.5 ^c	reflux	51
8	MeOH	Cs ₂ CO ₃	2.5 ^c	80	43
9	MeOH	NaOH	3 ^c	80	48
10	EtOH	Et ₃ N	20 ^c	reflux	– ^b
11	EtOH	<i>N,N</i> -diisopropylamine	20 ^c	reflux	– ^b
12	EtOH	KOH	2	reflux	– ^b
13	EtOH	KOH	2 ^c	reflux	62
14	H ₂ O	KOH	20 ^c	reflux	– ^b
15	MeOH	KOH	2 ^c	80	51
16	DMF	KOH	3 ^c	reflux	46
17	THF	KOH	3 ^c	reflux	– ^b

^a Isolated yield.^b No product obtained.^c The mixture of **1a**, **2a** and phenethylamine was heated at reflux for 12 h before the addition of catalyst.

We then investigated heating the three components in ethanol in the absence of any Brønsted acid or base. Reaction progress was monitored by thin-layer chromatography (TLC) and a yellow spot was detected on TLC plate. Attempts at isolating the yellow compound by chromatography failed. Nevertheless, it could be easily purified by recrystallization from ethanol. After spectroscopic analysis, the yellow compound was confirmed as intermediate **3**. It was proposed that, by an intramolecular cyclization strategy of intermediate **3**, the desired disubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones could be obtained. The protocol was thus modified accordingly. The starting materials **1a**, 4-chlorobenzaldehyde **2a**, and phenethylamine were heated in ethanol for 12 hours to be completely converted into intermediate **3**. Afterwards, potassium carbonate was added to the reaction mixture and heating was continued for 2 h. In this way, the desired target compound **4a** was obtained in 32% yield (Table 1, entry 4). To explore the reaction conditions systematically, different solvents and bases were screened. In general, protic solvents (except water) were tolerated for the reaction, but tetrahydrofuran (aprotic solvent) was detrimental (entry 17). Stronger inorganic bases, such as cesium carbonate, sodium hydroxide, and potassium hydroxide also promoted the formation of the desired product, but organic bases such as trimethylamine and *N,N*-diisopropylamine proved ineffective (entries 10 and 11). The best yields were obtained when the three components were heated in ethanol for 12 hours, followed by additional stir-

ring at reflux in the presence of potassium hydroxide (entry 13). Thus, the overall conversion was achieved in a one-pot, two-step, three-component model.

After determination of optimal reaction conditions, we explored the scope of various substrates in this one-pot protocol for the synthesis of 2,3-disubstituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones (Scheme 1).²⁰ In general, the reaction worked for a range of fused 2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-diones including cyclohexyl-, cycloheptyl-, pyranyl-, and mono or dimethyl-substituted 2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-diones. Aromatic aldehydes such as benzaldehyde or thiophene-2-carbaldehyde were applicable to the reaction. Generally, electron-donating groups on the aldehyde gave improved yields compared with electron-withdrawing groups. For example, the yield of compound **4d** (with fluoro-substitution) was lower for compound **4c**, whereas the yield of **4c** was far lower than that of **4e** (possessing a methoxy-group). A hydroxyl group was compatible with the reaction conditions. Without additional protection, compound **4f** was obtained in 47% yield, although with a lower yield than for compound **4e**. Interestingly, tyramine (with a free hydroxyl group) was a better substrate than benzylamine. This reaction system gave high yields for substrates possessing tetramethylene- and pentamethylene-containing substituents on the thiophene component (compounds **4i**, **4j**, **4aa** and **4ab**), when phenylethylamine was used as the third component.



Scheme 1 One-pot synthesis of 2,3-disubstituted thieno[2-d]pyrimidin-4(3H)-ones

Given that the preparation of the starting ‘anhydride’ compounds did not require any chromatographic purification (see the Supporting Information), the reaction can easily be scaled up to provide larger amounts of target compounds. For example, compound **4m** (1.1 g) was obtained from thiophene-2-carbaldehyde, tyramine 5,6,7,8-tetrahydro-2*H*-benzo[4,5]thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione. All of the synthetic compounds were characterized by ¹H and ¹³C NMR and HRMS analyses. The structure of **4w** was further confirmed by X-ray diffraction analysis, as shown in Figure 2.²¹

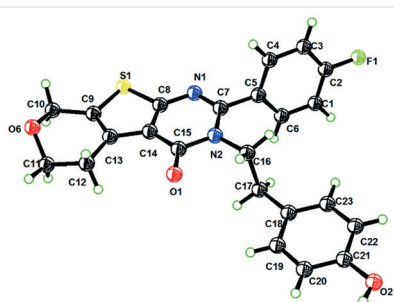


Figure 2 Crystal structure of **4w** (CCDC 1813089)²¹

In conclusion, although dozens of published one-pot procedures using isatoic anhydride as the starting material have been reported for the preparation of substituted quinazolinones, the protocols proved fruitless when applied to 2*H*-thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-diones, to synthesize substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-ones. By changing to the two-step, one-pot and three-component strategy, we have developed an efficient method to synthesize a wide range of 2,3,5,6-substituted thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives in good to high yields (46–86%). This strategy is tolerant of a wide range of aromatic aldehydes and amines, and enables preparation of large quantities of target compounds.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1610157>.

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- (20) **Synthesis of 4a-ag; General Procedure**
A mixture of 2*H*-benzo[4,5]thieno[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione (0.366 mmol, 1.5 equiv), amine (0.366 mmol, 1.5 equiv) and aldehyde (0.244 mmol, 1.0 equiv) in EtOH was heated to reflux for 10–14 h. After TLC indicated that the aldehyde had been completely consumed, KOH (0.488 mmol, 2.0 equiv) was added and the mixture was heated to reflux for a further 6–10 h. Upon completion of the reaction (verified by TLC), the mixture was concentrated under reduced pressure and purified by silica gel chromatography, eluting with petroleum ether/ethyl acetate (10:1–2:1) to obtain the pure product.
3-Benzyl-2-(4-chlorophenyl)-5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4(3*H*)-one (4a): Yield: 62%; white solid; m.p. 157–159 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.35 (d, *J* = 8.1 Hz, 2 H), 7.30–7.19 (m, 4 H), 6.94 (t, *J* = 2.4 Hz, 2 H), 5.23 (s, 2 H), 3.08 (t, *J* = 5.1 Hz, 2 H), 2.81 (t, *J* = 5.6 Hz, 2 H), 2.02–1.82 (m, 4 H); ¹³C NMR (100 MHz, CDCl₃): δ = 161.37 (CON), 158.81, 154.72, 136.68, 136.38, 134.74, 133.46, 132.01, 129.74 (2×CH), 128.92 (2×CH), 128.82 (2×CH), 127.65, 126.80 (2×CH), 121.52, 48.49 (CH₂Ph), 25.78 (CH₂), 25.48 (CH₂), 23.09 (CH₂), 22.42 (CH₂). HRMS: *m/z* [M+H]⁺ calcd for C₂₃H₂₀ClN₂O₃S: 407.09849; found: 407.09697.
- 2-(4-Fluorophenyl)-3-(4-hydroxyphenethyl)-3,5,6,8-tetrahydro-4*H*-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (4w)**: Yield: 62%; white solid; m.p. 247–249 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.23 (s, 1 H), 7.62–7.50 (m, 2 H), 7.42–7.30 (m, 2 H), 6.71–6.55 (m, 4 H), 4.78 (s, 2 H), 4.02–3.88 (m, 4 H), 3.03 (t, *J* = 4.5 Hz, 2 H), 2.69 (t, *J* = 7.6 Hz, 2 H); ¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.80 (CF), 161.34, 161.28, 157.59 (NCO), 155.99 (CPhOH), 155.11, 131.40, 130.83, 130.63/130.54, 129.27 (2×CH), 128.47, 127.76, 120.17, 115.48/115.27, 115.29 (2×CH), 64.36 (CH₂), 63.94 (CH₂), 46.99 (CH₂N), 32.92 (CH₂Ph), 26.02 (CH₂); HRMS: *m/z* [M+H]⁺ calcd for C₂₃H₂₀FN₂O₃S: 423.11787; found: 423.11631.
- (21) CCDC 1813089 contains the supplementary crystallographic data for compound **4w**. The data can be obtained free of charge from www.ccdc.cam.ac.uk/getstructures