Facile Palladium-Catalyzed Synthesis of 3-Arylpyrazolo-[1,5-*a*]pyrimidines

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Abstract: An efficient palladium-catalyzed synthesis of 3-arylpyrazolo[1,5-*a*]pyrimidines has been investigated. The key step in the synthesis is a Suzuki biaryl coupling of 3-bromo-2,5-dimethyl-7-aminopyrazolo[1,5-*a*]pyrimidines with arylboronic acids to provide 3-arylpyrazolo[1,5-*a*]pyrimidines in moderate to good yield. The synthetic utility of this methodology has been demonstrated by a concise and convergent synthesis of R121920, a potent $CRHR_1$ antagonist recently undergoing clinical evaluations.

Keywords: biaryl coupling; palladium catalysis; pyrazolo[1,5-*a*]pyrimidines; Suzuki coupling

Introduction

Development of novel methods for biaryl coupling has attracted considerable attention from chemists because of the ubiquitous presence of the biaryl moiety in a wide variety of organic compounds of current interest such as natural products, advanced materials, liquid crystals and more importantly used as ligand molecular probes for biological processes.[1–3] To date, commonly used catalytic methods such as Kharasch,[4] Negishi,[5] Stille,[6] and Suzuki[7,8] reactions are available in the literature for the construction of biaryl molecules. Among these the Stille and Suzuki reactions are considered to be versatile due to the mild reaction conditions and extreme tolerance to a wide variety of functional groups. The toxicity of organotin compounds coupled with the difficulty in removing tin impurities makes the Stille reaction less preferable to the Suzuki reaction. Even though biaryl couplings utilizing Stille and Suzuki reactions are well documented in the literature, very few examples are available for the synthesis of heterocyclic biaryl compounds.[9–11] In this article, we present a facile palladium-catalyzed strategy for the synthesis of 3-arylpyrazolo[1,5-*a*]pyrimidines involving the Suzuki reaction as the key step.

As a part of our ongoing research program for drug development as well as the synthesis of target-specific molecular probes for the *in vivo* imaging of biological processes, we are interested in studying the structure-activity relationship (SAR) of 3-arylpyrazolo[1,5-*a*]pyrimidine derivatives. Arylpyrazolo[1,5-*a*]pyrimidines are known for their potent utility as analgesics, benzodiazepine receptor antagonists, angiotensin II receptor antagonists, angiogenesis inhibitors, anti-inflammatory agents, neuropeptide Y (NPY1) receptor antagonists, COX-2 selective inhibitors and corticotropin-releasing hormone receptor type 1 ($CRHR_1$) antagonists (Figure 1).[12–19]

Most of the reported syntheses of 3-arylpyrazolo[1,5-*a*]-pyrimidines start with suitably functionalized arylacetonitriles and follow a step-by-step route to form the corresponding 5-aminopyrazole derivatives. Further condensation of the 5-aminopyrazole derivatives with the respective 1,3-diketones, imines, nitriles, or esters followed by functional group manipulations give the desired 3-arylpyrazolo[1,5-*a*]pyrimidines.[20–22] The potential of this strategy is limited due to the multistep synthetic route and the limited availability of functionalized arylacetonitriles, which impose severe restric-

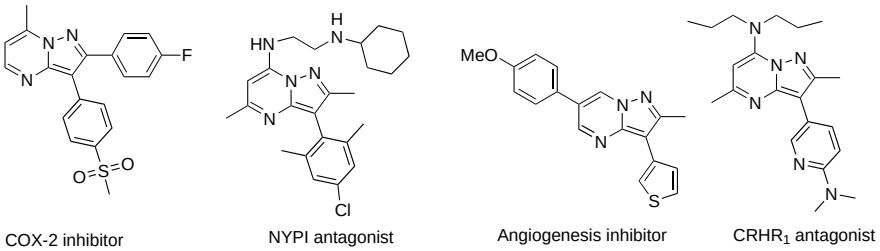

Figure 1. Examples of biologically active 3-arylpyrazolo[1,5-*a*]pyrimidines.

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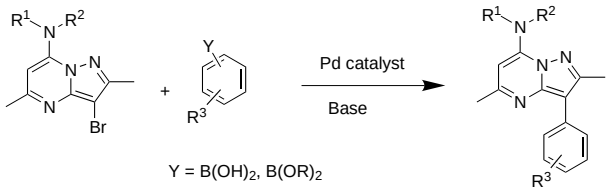
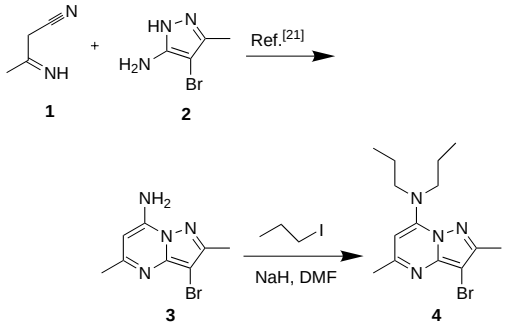


Scheme 1. Synthesis of 3-arylpyrazolo[1,5-*a*]pyrimidines.



Scheme 2. Synthesis of 3-bromo-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine.

tions on the substituents that can be placed on the 3-aryl group. Therefore, we have sought to develop a convergent strategy for the synthesis of 3-arylpyrazolo[1,5-*a*]-pyrimidines by utilizing a Suzuki cross-coupling of the common intermediate 3-bromo-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (**4**) with various arylboronic acids/esters as the key step (Scheme 1). Since arylboronic acids are commercially available, or can be easily prepared from the corresponding bromides,[23] this methodology would offer a higher degree of flexibility on the functional groups that can be present on the 3-aryl moiety, thereby providing a better understanding of the SAR of the target compounds.

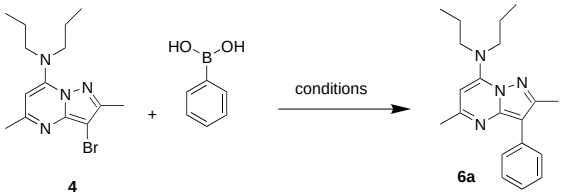
Results and Discussion

3-Bromo-7-amino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidine (**3**) was synthesized by the condensation of 3-iminobutyronitrile (**1**) and 3-amino-4-bromo-5-methylpyrazole (**2**) using a reported procedure.[24] Subsequent synthesis of the key intermediate, 3-bromo-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (**4**) for Suzuki coupling was achieved by the dipropylation of **3** using *n*-propyl iodide in the presence of NaH in *N,N*-dimethylformamide (Scheme 2).

Suzuki reaction of the heteroaryl bromide **4** with phenylboronic acid was then attempted under several conditions using various palladium catalysts and bases (Table 1).

$Pd(OAc)_2$ and Pd/PPh_3 failed to promote the biaryl coupling, whereas $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were successful in effecting the desired coupling. The bases used for the coupling also played a critical role in the reaction. For example, potassium carbonate did not afford much product, probably because it is not basic enough to pursue the reaction. On the other hand, harsh conditions

Table 1. Optimization of the Suzuki coupling of 3-bromo-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidines with phenylboronic acid under various conditions.



S. No.	Base	Solvent system	Catalyst	Yield of the product [%][a]
1	K_2CO_3	EtOH-H_2O	$Pd(OAc)_2$	–[b]
2	K_2CO_3	EtOH-H_2O	Pd/Ph_3P	–[b]
3	K_2CO_3	EtOH-H_2O	$Pd(PPh_3)_4$	18
4	NaOH	EtOH-H_2O	$Pd(PPh_3)_4$	38
5	NaOH	DME-H_2O	$Pd(PPh_3)_4$	42
6	NaOH	DME-H_2O	$PdCl_2(PPh_3)_2$	50
7	NaOH	DME-H_2O	$Pd_2(dba)_3$	45
8	NaOH	PEG 400-H_2O	$Pd_2(dba)_3$	40
9	NaOH	PEG 400-H_2O	$Pd_2(dba)_3$	20[c]
10	KOH	1,4-dioxane-H_2O	$PdCl_2(PPh_3)_2$	21

[a] Yields represent the isolated yields of the products after column chromatography and are based on the aryl bromide **4**.
[b] Only starting materials were recovered under these conditions.
[c] The reaction was carried out under microwave irradiation for one minute (3×20 s exposure), temperature = 110 °C.

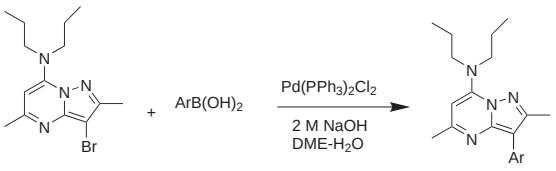
provided by refluxing potassium hydroxide resulted in low yield of the coupling product, presumably due to the extensive cleavage of the heterocyclic ring. Also, in general high boiling polar solvents were found to improve the yield of the Suzuki coupling. The best result was obtained by using dichlorobis(triphenylphosphine)palladium [$PdCl_2(PPh_3)_2$] as the catalyst in the presence of 3 equivalents of 2 M NaOH in DME-H_2O. Thus, for example, arylpyrazolopyrimidine **6** was isolated in 50% yield when **4** was coupled with phenylboronic acid. After optimizing the reaction conditions with phenylboronic acid and **4**, we set out to explore the coupling methodology for the synthesis of various substituted 3-arylpyrazolo[1,5-*a*]pyrimidines. Under identical conditions, Suzuki coupling of **4** with 4-fluorophenylboronic acid, 4-trifluoromethylboronic acid and 4-acetylphenylboronic acid provided the corresponding 3-arylpyrazolo[1,5-*a*]pyrimidine derivatives in moderate yields (Table 2). Similarly, the coupling of **4** with a heteroarylboronic acid such as 3-benzo[*b*]thiopheneboronic acid proceeded uneventfully in good yields. However, the attempted coupling of naphthaleneboronic acid proceeded in low yield and the product **6j** was obtained as an inseparable mixture along with the bromide **4** (Table 2). The yield (20%) of **6j** was assigned from the ratio of ^{1}H NMR integrations of C6-H protons of pyrazolo[1,5-*a*]pyrimidine rings. The C6-H protons of **6j** appear at $\delta = 5.82$ and that of precursor aryl bromide **4** appears at $\delta = 5.78$.

Next, we focused our attention on demonstrating the utility of this methodology by developing a concise synthetic route to R121920 (**6f**), a potent $CRHR_1$ receptor antagonist presently under clinical evaluation.[25] The requisite 6-dimethylamino-3-pyridylboronic acid was prepared by lithiation of the corresponding bromide using *n*-BuLi at $-78\,^\circ$C followed by boronylation with B(O-*i*-Pr)$_3$. However, the difficulty in isolation, purification and handling of this boronic acid prompted us to attempt the coupling with the corresponding neopentyl boronate ester which could be easily prepared in good yield by quenching the reaction mixture at $-40\,^\circ$C with neopentyl glycol. Gratifyingly, Suzuki coupling of **4** with the boronate ester proceeded smoothly to provide the desired product **6f** in 41% yield (Table 2). The compatibility of the air-stable boronate esters in the coupling reaction opens up the possibility for the introduction of sensitive functional groups into the 3-aryl moiety of the pyrazolo[1,5-*a*]pyrimidines.

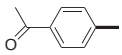
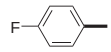
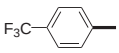
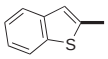
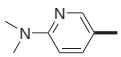
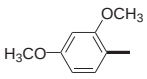
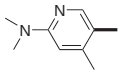
Our rigorous efforts to couple 7-aminopyrazolopyrimidine (**3**) with phenylboronic acid did not afford the desired product and the coupling proceeded in poor yield in the case of the corresponding mono-Boc-protected derivative of **3**. Instead, a considerable amount of the starting halides were recovered in these reactions.

Similarly, our attempt to couple 2-methylphenylboronic acid and 2,4,-dimethoxyphenylboronic acid with **4** also failed to give the desired pyrazolo[1,5-*a*]pyrimidines. Instead, hydrodeboronation of the boronate ester, recovery of **4** (70%) along with the formation of 3-hydroxy-2,5,-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]-pyrimidine (20%) was the major reaction pathway observed under the standard reaction conditions. Addition of one equivalent of the phase transfer catalyst tetrabutylammonium bromide, which is known to reduce the extent of hydrodeboronation,[26] did not have any significant effect on the course of the reaction.

Table 2. Suzuki coupling of 3-bromo-2,5-dimethyl-7-dipropylaminopyrazolo[1,5-*a*]pyrimidine (**4**) with various arylboronic acids.



4 **5a - j** **6a - j**

S. No.	Aryl group (Ar)	Product	Yield [%][a]
1		**6a**	50[b]
2		**6b**	44
3		**6c**	48
4		**6d**	39
5		**6e**	55
6		**6f**	41[c]
7		**6g**	–
8		**6h**	–
9		**6i**	–
10		**6j**	20[d]

[a] Unless otherwise stated, the yields represent the isolated yields of the products after column chromatography and are based on the aryl bromide **4**.

[b] Both phenylboronic acid and the corresponding neopentyl boronate ester gave the product **6a** in comparable yield.

[c] The Suzuki coupling was conveniently carried out using the neopentyl boronate ester of 6-dimethylamino-3-pyridylboronic acid.

[d] The product was obtained as an inseparable mixture and the yield is based on the ^{1}H NMR spectrum.

Similarly, our efforts with the coupling of **5i** and **4** for the synthesis of R121919 (**6i**), a potent $CRHR_1$ antagonist did not yield the desired product. The failure of these reactions reveals that sterically demanding substituents on the *ortho*-position of the boronic acid are not well tolerated. These results are summarized in Table 2.

Conclusions

A versatile method for the convergent synthesis of 3-arylpyrazolo[1,5-*a*]pyrimidines utilizing Suzuki coupling as a key step is unraveled in the present work. The scope of this work is demonstrated by the concise synthesis of R121920 (**6f**), a potent $CRHR_1$ receptor antagonist. However, sterically demanding substituents in the *ortho*-position of the boronic acids are not well tolerated in these reactions. Since 3-arylpyrazolo[1,5-*a*]-pyrimidines are the structural skeletons of a variety of biologically active molecules, this methodology can be used as a novel tool for the synthesis and SAR studies of target compounds for various pharmaceutical applications.

Experimental Section

General

Melting points were determined on a Fisher melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker PPX 300 and 400 MHz spectrometers. ^{19}F NMR spectra were recorded on a Bruker PPX 282.5 MHz spectrometer. Spectra are recorded in $CDCl_3$ and chemical shifts are reported in ppm relative to TMS for ^{1}H and $CFCl_3$ for ^{19}F as internal standards. The mass spectra were recorded on JKS-HX 11UHF/HX110 HF Tandem Mass Spectrometer in the FAB+mode. The HPLC analyses were performed using a Waters 1525 HPLC system (column: Phenomenex, Prodigy ODS 4.6 × 250 mm, 5 μm). Flash column chromatography was performed on silica gel (Fisher 200–400 mesh) using the solvent system indicated.

Typical Procedure for the Synthesis of Arylboronate Esters: 5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-*N*,*N*-dimethylpyridine-2-amine (5f)

A solution of the aryl bromide (825 mg, 4.104 mmol) in THF under argon was treated with *n*-BuLi (1.97 mL, 4.925 mmol, 1.2) dropwise at −78 °C and allowed to stir for 20 min. Triisopropyl borate (1.9 mL, 8.208 mmol) was rapidly added to this solution and the reaction mixture was further stirred for 2 h; maintaining the temperature at −78 °C. The temperature was then gradually allowed to reach −40 °C and finely powdered neopentyl glycol (427 mg, 4.104 mmol) was added. The solution was then warmed to room temperature and stirred for further 12 h. The reaction mixture was then quenched with water, the organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was concentrated and column chromatographed (70:30 hexane: EtOAc) to give **5f** as a colorless solid; yield: 65%; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, 1 H, *J* = 1.1 Hz, Ar-H), 7.78 (dd, 1 H, *J* = 1.9, 8.5 Hz, Ar-H), 6.46 (d, 1 H, *J* = 8.6 Hz, Ar-H), 3.72 (s, 4 H, 2 × OCH_2), 3.11 (s, 6 H, 2 × NCH_3), 1.02 (s, 6 H, 2 × CH_3).

Typical Procedure for the Suzuki Coupling: 3-[6-(Dimethylamino)pyridin-3-yl]-2,5-dimethyl-*N*,*N*-dipropylpyrazolo[1,5-*a*]pyrimidine-7-amine (6f)

A suspension of the aryl bromide **4** (174 mg, 0.535 mmol), arylboronate ester **5f** (150 mg, 0.643 mmol) and $PdCl_2(PPh_3)_2$ (37 mg, 10 mol %) in 1,2-dimethoxyethane (2 mL) was thoroughly deaerated and stirred under argon. Deionized water (200 μL) and aqueous NaOH (550 μL, 2 M) were added to the reaction mixture and heated at 100 °C for 5 h. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, passed through a short pad of celite, concentrated and column chromatographed (90:10 hexane:EtOAc) to give the desired product as a pale yellow solid in 41% yield. HPLC analysis of the compound was performed by eluting with CH_3CN: H_2O: Et_3N 85:15:0.3 (R_T = 9.59 minutes). **6f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.48 (d, 1H, *J* = 2.3 Hz, Ar-H), 7.91 (dd, 1H, *J* = 2.3, 8.8 Hz, Ar-H), 6.65 (d, 1H, *J* = 8.8 Hz, Ar-H), 5.79 (s, 1H, C6-H), 3.70 (t, 4 H, *J* = 7.7 Hz, 2 × NCH_2), 3.12 [s, 6 H, $N(CH_3)_2$], 2.54 (s, 3 H, Ar-CH_3), 2.45 (s, 3 H, Ar-CH_3), 1.70 (m, 4 H, 2 × CH_2), 0.94 (t, 6 H, *J* = 7.4 Hz, 2 × CH_3); HRMS: calcd. for $C_{21}H_{31}N_6$ (MH^+): 367.2610; found: 367.2599; mp 102 °C.

General Experimental Procedure for Table 1

A suspension of the aryl bromide **4** (81 mg, 0.25 mmol, 1 equiv.), phenyl boronic acid (37 mg, 0.3 mmol, 1.2 equiv.) and the palladium catalyst (18 mg, 10 mol %) in the given organic solvent (1 mL) was thoroughly deaerated and stirred under argon. Deionized water (100 μL) and aqueous base (3 equiv, 2 M) were added to the reaction mixture and heated at reflux for 3–5 h. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, passed through a short pad of celite, concentrated and column chromatographed to give **6**.

General Procedure for Table 2

A suspension of the aryl bromide **4** (0.5 mmol, 1 equiv.), aryl boronic acid **5a–j** (1.2 equiv.) and $PdCl_2(PPh_3)_2$ (37 mg, 10 mol %) in 1,2-dimethoxyethane (2 mL) was thoroughly deaerated and stirred under argon. Deionized water (200 μL) and aqueous NaOH (3 equiv, 2 M) were added to the reaction mixture and heated at 100 °C for 3–5 h. The reaction mixture was diluted with EtOAc, dried over $MgSO_4$, passed through a short pad of celite, concentrated and column chromatographed to give the desired product.

Products

2,5-Dimethyl-3-phenyl-*N*,*N*-dipropylpyrazolo[1,5-*a*]pyrimidine-7-amine (6a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (m,

2H, Ar-H), 7.42 (m, 2H, Ar-H), 7.25 (m, 1H, Ar-H), 5.81 (s, 1H, C6-H), 3.71 (t, 4H, $J = 7.7$ Hz, $2 \times NCH_2$), 2.57 (s, 3H, Ar-CH_3), 2.47 (s, 3H, Ar-CH_3), 1.71 (m, 4H, $2 \times CH_2$), 0.93 (t, 6H, $J = 7.4$ Hz, $2 \times CH_3$); HRMS: calcd. for $C_{20}H_{27}N_4$ (MH^+): 323.2236; found: 323.2219; mp 61 °C.

1-[4-(7-Dipropylamino-2,5-dimethylpyrazolo[1,5-*a*]pyrimidin-3-yl)phenyl]ethanone (6b): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.02$ (dd, 2H, $J = 1.8$, 6.6 Hz, Ar-H), 7.92 (dd, 2H, $J = 1.8$, 6.7 Hz, Ar-H), 5.85 (s, 1H, C6-H), 3.73 (t, 4H, $J = 7.8$ Hz, $2 \times NCH_2$), 2.63 (s, 3H, CO-CH_3), 2.62 (s, 3H, Ar-CH_3), 2.50 (s, 3H, Ar-CH_3), 1.73 (m, 4H, $2 \times CH_2$), 0.97 (t, 6H, $J = 7.4$ Hz, $2 \times CH_3$); HRMS calcd. for $C_{22}H_{28}N_4O$ (MH^+): 365.2341; found: 365.2342; mp 104 °C.

3-(4-Fluorophenyl)-2,5-dimethyl-*N,N*-dipropylpyrazolo[1,5-*a*]pyrimidine-7-amine (6c): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (dd, 2H, $J = 8.7$, 5.4 Hz, Ar-H), 7.04 (t, 2H, $J = 9.0$ Hz, Ar-H), 5.74 (s, 1H, C6-H), 3.63 (t, 4H, $J = 7.4$ Hz, $2 \times NCH_2$), 2.46 (s, 3H, Ar-CH_3), 2.39 (s, 3H, Ar-CH_3), 1.64 (sextet, 4H, $J = 7.5$ Hz, $2 \times CH_2$), 0.87 (t, 6H, $J = 7.5$ Hz, $2 \times CH_3$); ^{19}F NMR (282.35 MHz, $CDCl_3$): $\delta = -116.59$; HRMS: calcd. for $C_{20}H_{26}N_4F$ (MH^+): 341.2142; found: 341.2158.

2,5-Dimethyl-*N,N*-dipropyl-3-(4-trifluoromethylphenyl)-pyrazolo[1,5-*a*]pyrimidine-7-amine (6d): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, 2H, $J = 8.0$ Hz, Ar-H), 7.66 (d, 2H, $J = 8.1$ Hz, Ar-H), 5.84 (s, 1H, C6-H), 3.73 (t, 4H, $J = 7.7$ Hz, $2 \times NCH_2$), 2.59 (s, 3H, Ar-CH_3), 2.49 (s, 3H, Ar-CH_3), 1.74 (m, 4H, $2 \times CH_2$), 0.97 (t, 6H, $J = 7.4$ Hz, $2 \times CH_3$); ^{19}F NMR (282.35 MHz, $CDCl_3$): $\delta = -61.32$; HRMS: calcd. for $C_{21}H_{25}F_3N_4O$: 390.2031; found: 390.2030; mp 130 °C.

3-(1-Benzothien-2-yl)-2,5-dimethyl-*N,N*-dipropylpyrazolo[1,5-*a*]pyrimidine-7-amine (6e): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.83$ (d, 1H, $J = 8.3$ Hz, Ar-H), 7.76 (d, 1H, $J = 8.5$ Hz, Ar-H), 7.74 (s, 1H, Ar-H), 7.32 (dt, 1H, $J = 1.1$, 7.9 Hz, Ar-H), 7.22 (dd, 1H, $J = 1.1$, 8.2 Hz, Ar-H), 5.85 (s, 1H, C6-H), 3.73 (t, 4H, $J = 7.6$ Hz, $2 \times NCH_2$), 2.73 (s, 3H, Ar-CH_3), 2.57 (s, 3H, Ar-CH_3), 1.75 (m, 4H, $2 \times CH_2$), 0.97 (t, 6H, $J = 7.4$ Hz, $2 \times CH_3$); HRMS: calcd. for $C_{22}H_{26}N_4S$: 378.1878; found: 378.1895; mp 142 °C.

Acknowledgements

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