Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Palladium-Catalyzed Oxidative C-H/C-H Cross-Coupling of Pyrazolo[1,5-*a*]azines with Five-Membered Heteroarenes

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Contents

General Information

Chemicals:

All organic chemicals were obtained from commercial suppliers. $Pd(OAc)_2$, AgOAc was obtained from Chem-Impex and BDH Chemicals Ltd. All solvents were purchased as 100 mL SureSeal bottles from Sigma Aldrich. All reagents and solvents were used as received without repurification.

Characterizations:

1D and 2D NMR was recorded on Bruker 500 MHz spectrometer and chemical shifts are given in parts per million (ppm) relative to residual solvent peaks: 2.50 ppm (^{1}H) and 39.52 ppm (^{13}C) for DMSO-d_6, 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C) for $CDCl_3$. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *J* (Hz) and integration.

HRMS was recorded on Waters LCT mass spectrometer with ESI+ ionization mode.

Analysis:

TLC was performed on pre-cut glass-based silica plate using mixtures of EtOAc + Heptane or EtOAc:EtOH 3:1 + Heptane.

Purification:

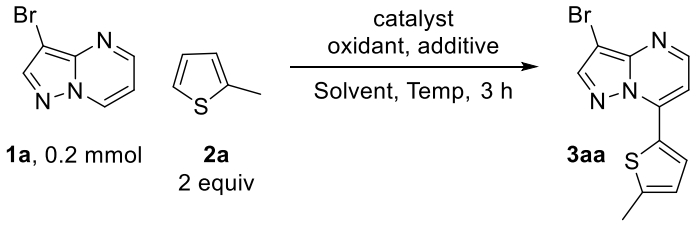
Column chromatography was performed on Biotage Selekt using Biotage Sfär HC D columns and 254 nm as collection wavelength. Gradient condition was given for each compound in the experimental procedure.

Reversed phase preparative HPLC was performed on a Gilson GX-281 chromatography system and 254 nm as collection wavelength. Gradient condition was given for each compound in the experimental procedure.

Reaction Optimization

Procedure:

To a 15 mL screw capped vial was subsequently added 3-bromopyrazolo[1,5-a]pyrimidine **1a** (40 mg, 0.2 mmol, 1 equiv), 2-methylthiophene **2a** (39 mg, 0.4 mmol, 2 equiv), solvent (1 mL, 0.2 M), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), oxidant (0.6 mmol, 3 equiv) and additive (0.2 mmol, 1 equiv). The vial was closed and stirred in a pre-heated aluminum plate at the appropriate temperature for 3 h. After cooling, the reaction mixture was diluted to EtOAc (5 mL), filtered through a filter frit and a Whatman syringe filter (0.45 µm). To the clear filtrate was added 1,3,5-trimethoxybenzene (11.2 mg, 0.66 mmol, 0.34 equiv) and the reaction was concentrated. The crude material was analyzed by ^{1}H NMR in DMSO-d_6. Yield was determined by comparing integration of product peak (8.64 ppm) with the internal standard (6.10 ppm). The results were summarized in the below table.



Entry	Catalyst (mol%)	Oxidant (eq)	Additive (eq)	Solvent	Temp. (°C)	Yield (%)
1	$Pd(OAc)_2$ (10)	Ag_2CO_3 (3)	-	DMSO-d_6	110	45
2	$Pd(OAc)_2$ (10)	Ag_2O (3)	-	DMSO-d_6	110	40
3	$Pd(OAc)_2$ (10)	AgOAc (3)	-	DMSO-d_6	110	55
4	$Pd(OAc)_2$ (10)	AgOAc (3)	-	DMF	110	16
5	$Pd(OAc)_2$ (10)	AgOAc (3)	-	Toluene	110	14
6	$Pd(OAc)_2$ (10)	AgOAc (3)	-	CPME	110	13
7	$Pd(OAc)_2$ (10)	AgOAc (3)	-	1,4-Dioxane	110	13
8	$Pd(OAc)_2$ (10)	AgOAc (3)	-	*tert*-Amylalcohol	110	12
9	$Pd(OAc)_2$ (10)	AgOAc (3)	PivOH (1)	DMSO-d_6	110	65
10	$Pd(OAc)_2$ (10)	AgOAc (3)	PivOH (1)	DMSO-d_6	130	59
11	**$Pd(OAc)_2$ (10)**	**AgOAc (3)**	**PivOH (1)**	**DMSO-d_6**	**90**	**70**
12	$Pd(OAc)_2$ (10)	AgOAc (3)	PivOH (1)	DMSO-d_6	70	60
13	$Pd(OAc)_2$ (10)	AgOAc (3)	AcOH (1)	DMSO-d_6	90	63
14	$Pd(OAc)_2$ (10)	AgOAc (3)	BzOH (1)	DMSO-d_6	90	67
15	$Pd(OAc)_2$ (10)	AgOAc (3)	1-AdCOOH (1)	DMSO-d_6	90	70

16	$Ni(OAc)_2$ (10)	AgOAc (3)	PivOH (1)	DMSO-d_6	90	0
17	$Co(OAc)_2$ (10)	AgOAc (3)	PivOH (1)	DMSO-d_6	90	0
18	-	$Cu(OAc)_2$ (3)	PivOH (1)	DMSO-d_6	90	0
19	-	AgOAc (3)	PivOH (1)	DMSO-d_6	90	0
20	$Pd(OAc)_2$ (10)	-	PivOH (1)	DMSO-d_6	90	0
21	$Pd(OAc)_2$ (5)	AgOAc (3)	PivOH (1)	DMSO-d_6	90	65

Starting materials

Most of the starting materials are commercially available and used as received.

From Fluorochem: **1a**, **1b**, **1e**, **2c**, **2q**, **4a**, **4b**, **4c**, **4e**, **4f**, **4g**.

From Enamine: **1d**, **1g**, **1i**, **2n**, **6**.

From Combi-Blocks: **1f**, **2g**, **2i**, **2p**.

From Chembridge: **1c**.

From Alfa-Aesar: **2b**.

From Sigma-Aldrich: **2d**, **2l**, **2m**, **2r**, **2s**.

From AstaTech: **4d**.

From BLDPharm: **4h**.

From Fluka: **2a**, **2h**.

From Columbia Organic Chemicals: **2o**.

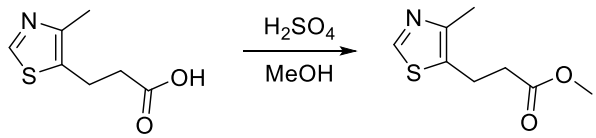
Synthesis of literature-known starting materials

2e was synthesized according to the literature procedure from **2d** and acetic anhydride and ^{1}H NMR was identical to the literature report.[1]

2f was synthesized according to the literature procedure from thiophene-2-carbonyl chloride and dimethyl amine and ^{1}H NMR was identical to the literature report.[2]

2j was synthesized according to the literature procedure from **2i** and acetic anhydride and ^{1}H NMR was identical to the literature report.[3]

2k was synthesized from the corresponding carboxylic acid as described below.



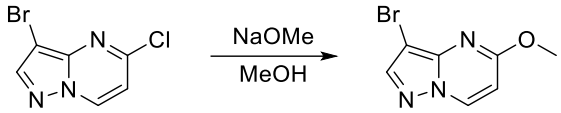
To a solution of 3-(4-methylthiazol-5-yl)propanoic acid (270 mg, 1.58 mmol, obtained from ChemBridge) in MeOH (10 mL) was added H_2SO_4 (6 drops) and the reaction was stirred at 60 °C overnight.

The reaction was concentrated and diluted with EtOAc. The crude material was neutralized to basic pH using NaOH solution and the organic phase was separated, concentrated to afford the desired product.

Yield: 240 mg, 82%, yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 3.69 (s, 3H), 3.10 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.41 (s, 3H). The NMR was identical to the literature report.[4]

Synthesis of literature-unknown starting materials



1h

3-bromo-5-methoxypyrazolo[1,5-*a*]pyrimidine (**1h**)

30 mL vial contaning 3-bromo-5-chloropyrazolo[1,5-*a*]pyrimidine (500 mg, 2.15 mmol, **1f**) in MeOH (10 mL) was treated with sodium methanolate (0.734 mL, 3.23 mmol) and the reaction was stirred at r.t. Reaction completed after 2h.

The reaction was diluted to EtOAc and washed with water and brine. The organic phase was concentrated to afford the desired product.

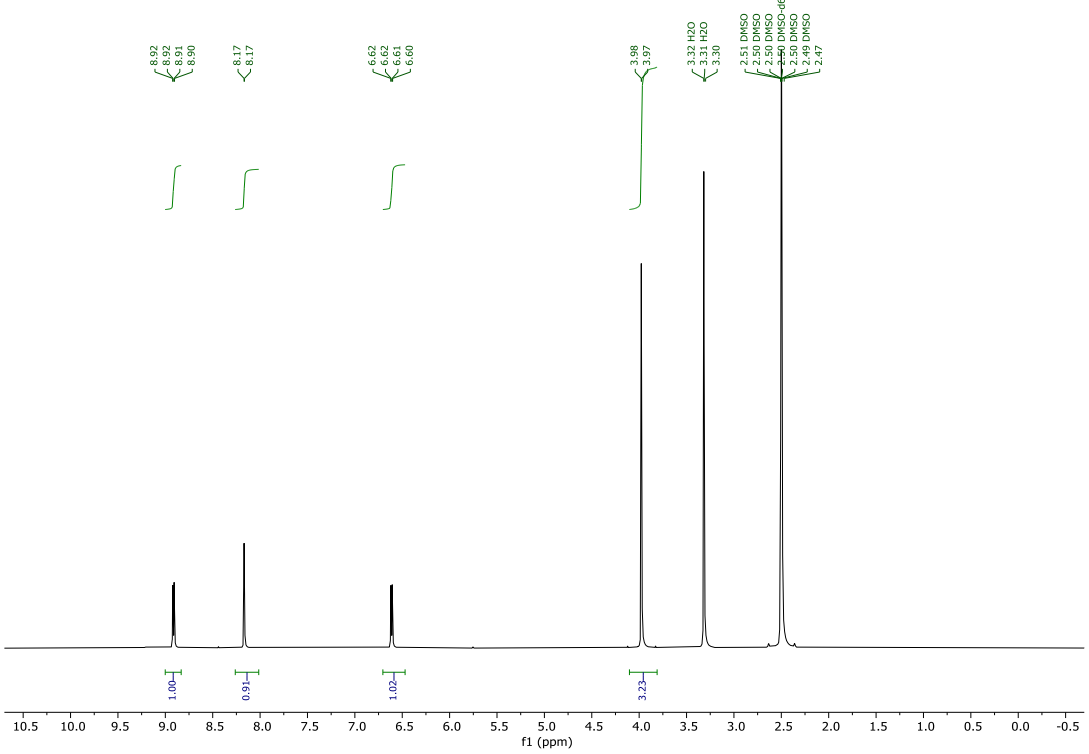
Yield: 491 mg, 86%, light yellow solid.

HRMS: $C_7H_6BrN_3O$ calc.: 227.9772 (M+H), found: 227.9753

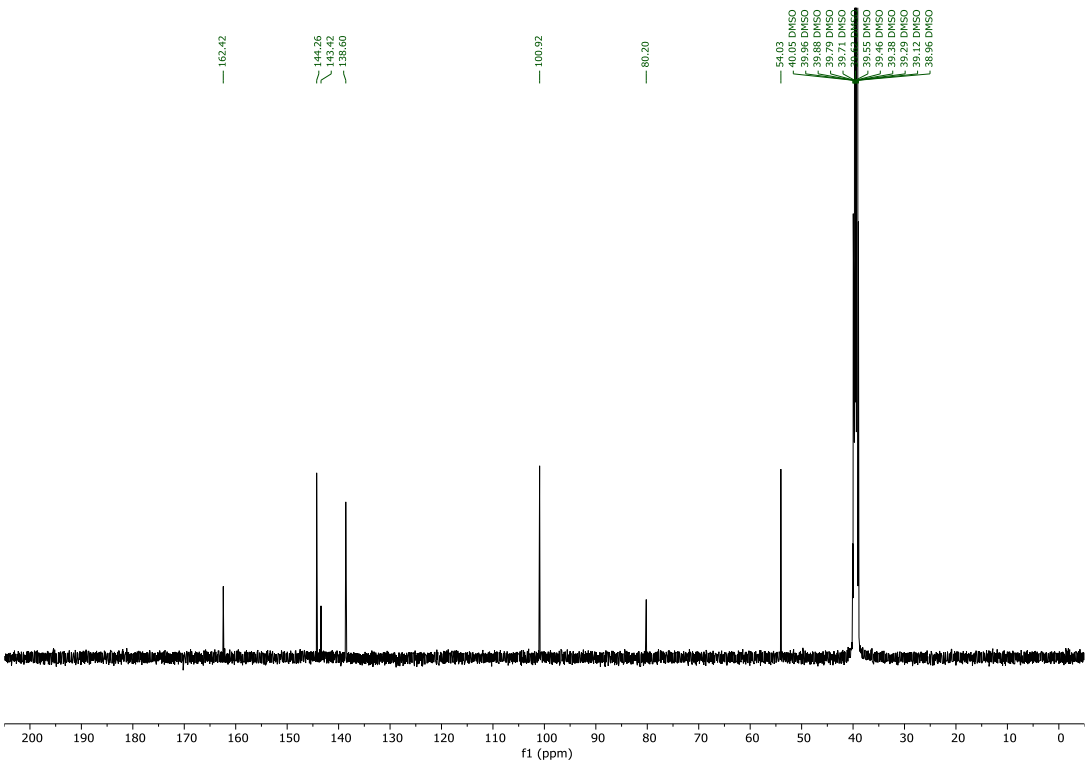
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (dd, J = 7.7, 1.9 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H), 6.61(dd, J = 7.6, 2.0 Hz, 1H), 3.98 (s, 3H).

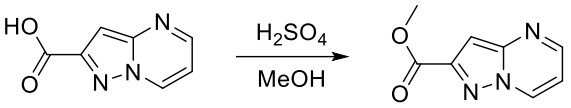
^{13}C NMR (126 MHz, DMSO-d_6) δ 162.4, 144.3, 143.4, 138.6, 100.9, 80.2, 54.0.

^{1}H NMR



^{13}C NMR





1i

methyl 6-bromopyrazolo[1,5-*a*]pyridine-2-carboxylate (**1i**)

A solution of 6-bromopyrazolo[1,5-*a*]pyridine-2-carboxylic acid (200 mg, 0.83 mmol, obtained from Enamine) in MeOH (2 mL) was treated with concentrated H_2SO_4 (2 drops) and the reaction was stirred at 60 °C for 3 h.

The reaction was concentrated and diluted with EtOAc. The crude material was neutralized to basic pH using NaOH solution and the organic phase was separated, concentrated to afford the desired product.

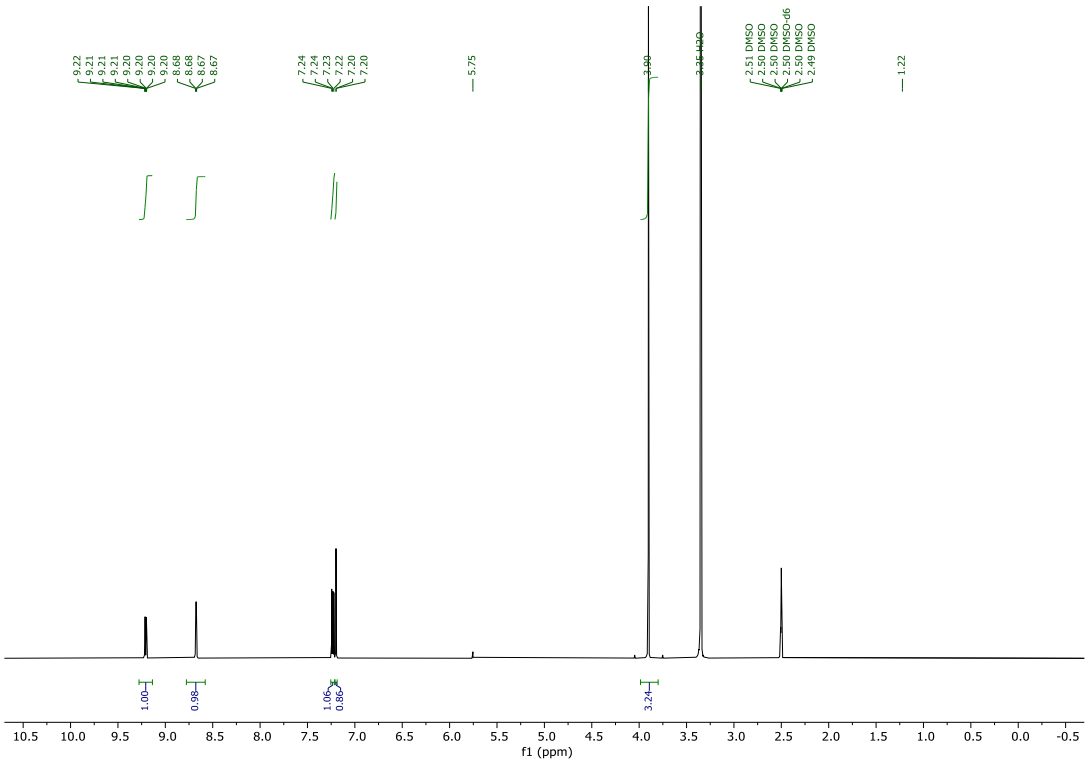
Yield: 50 mg, 23%, light yellow solid.

HRMS: $C_8H_7N_3O_2$ calc.: 178.0616 (M+H), found: 178.0619

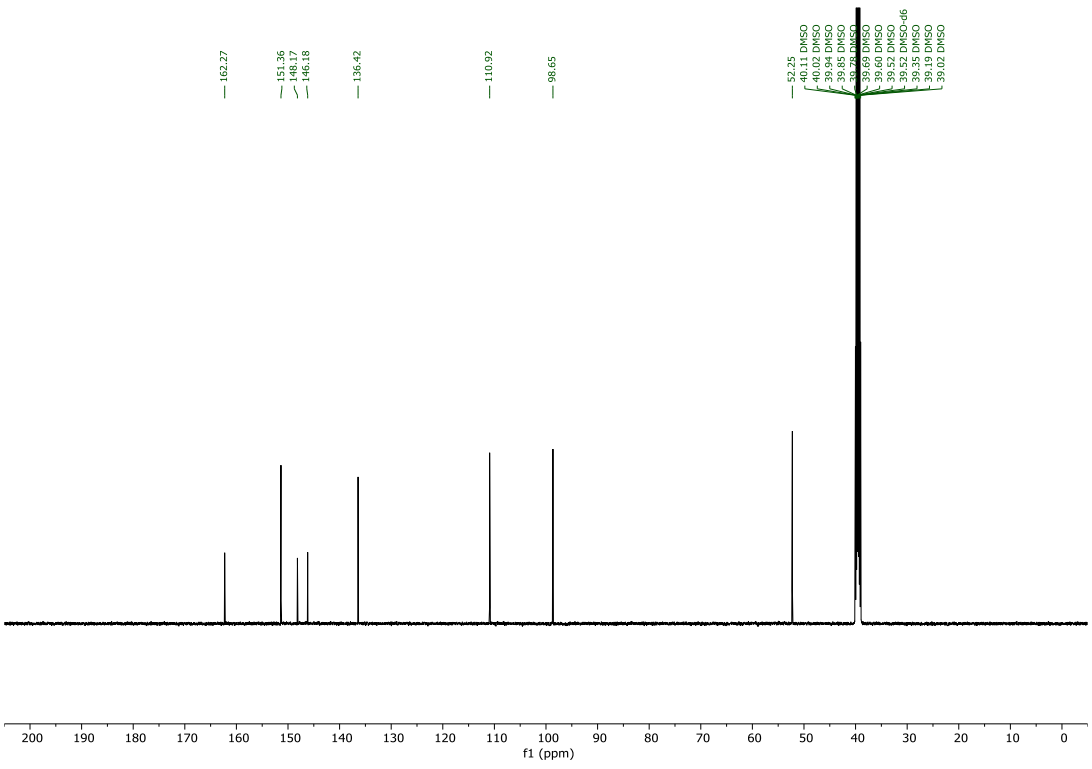
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (ddd, *J* = 7.1, 1.7, 1.0 Hz, 1H), 8.68 (dd, *J* = 4.0, 1.7 Hz, 1H), 7.23 (dd, *J* = 7.1, 4.0 Hz, 1H), 7.20 (d, *J* = 1.0 Hz, 1H), 3.90 (s, 3H).

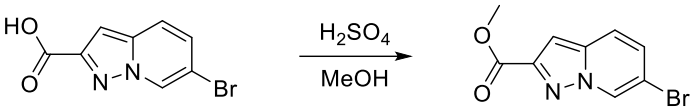
^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 151.4, 148.2, 146.2, 136.4, 110.9, 98.7, 52.3.

^{1}H NMR



^{13}C NMR





4i

methyl 6-bromopyrazolo[1,5-*a*]pyridine-2-carboxylate (**4i**)

A solution of 6-bromopyrazolo[1,5-*a*]pyridine-2-carboxylic acid (200 mg, 0.83 mmol, obtained from Enamine) in MeOH (10 mL) was treated with concentrated H_2SO_4 (1.00 mL) and the reaction was stirred at 65 °C for 3h.

The reaction was concentrated and diluted with EtOAc. The crude material was neutralized to basic pH using NaOH solution and the organic phase was separated, concentrated to afford the desired product.

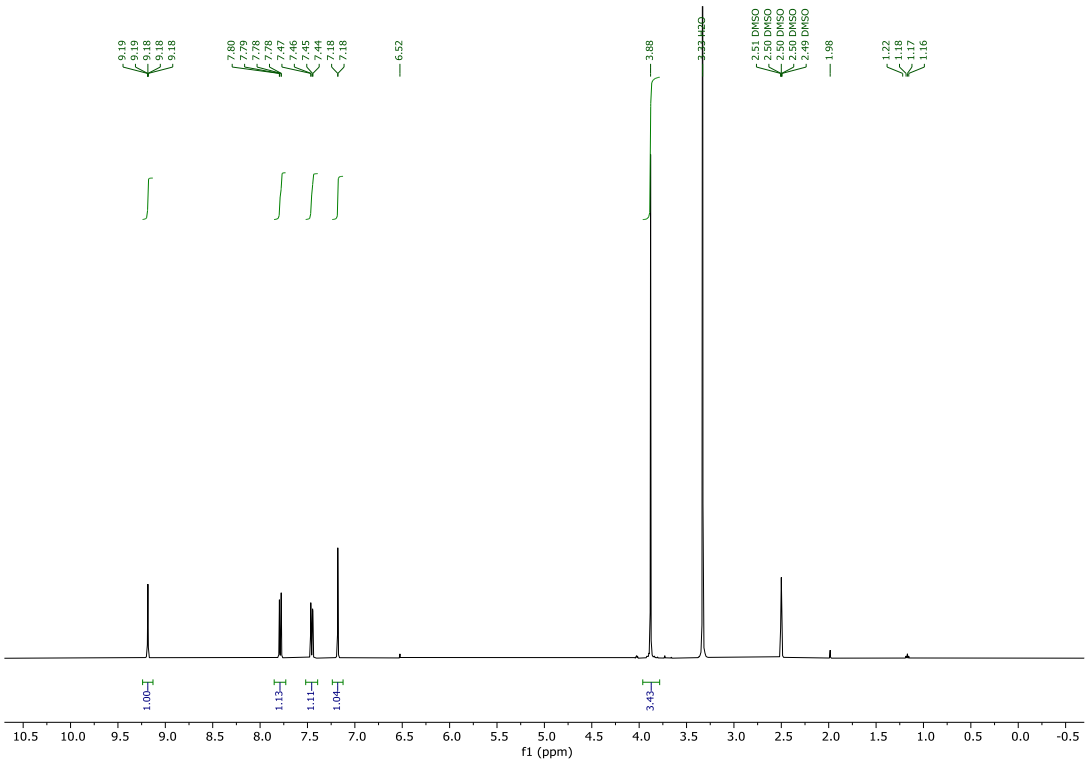
Yield: 160 mg, 76%, white solid.

HRMS: $C_9H_7BrN_2O_2$ calc.: 254.9769, found: 254.9779

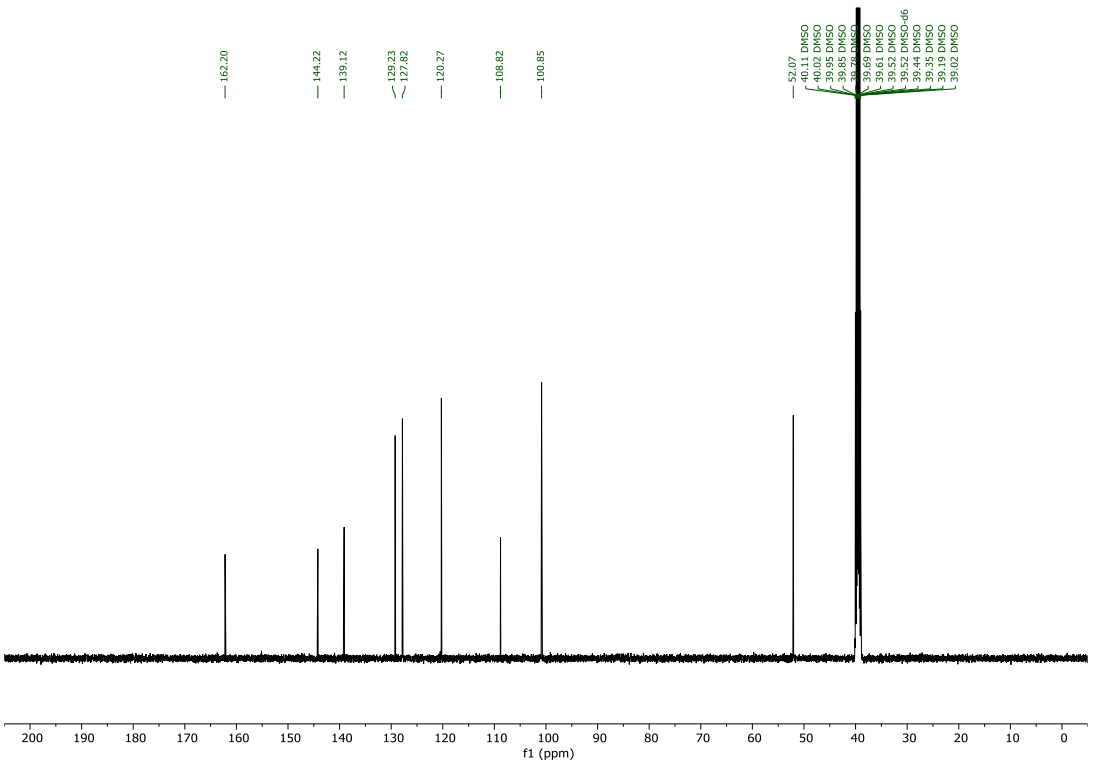
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 – 9.19 (m, 1H), 7.79 (dd, *J* = 9.5, 0.9 Hz, 1H), 7.45 (dd, *J* = 9.4, 1.7 Hz, 1H), 7.18 (d, *J* = 0.9 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 144.2, 139.1, 129.2, 127.8, 120.3, 108.8, 100.9, 52.1.

^{1}H NMR



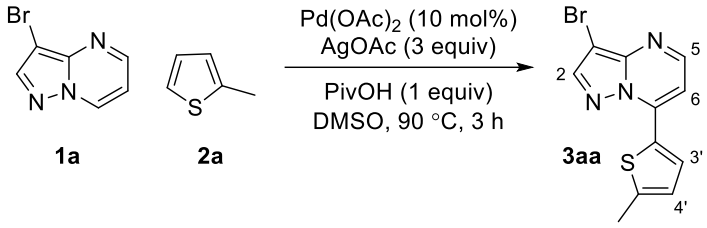
^{13}C NMR



Substrate Scope for pyrazolo[1,5-*a*]pyrimidine and [1,2,4]triazolo[1,5-*a*]pyrimidine (Main text, Scheme 1 and 3)

General procedure 1:

A 15 or 20-mL screw-capped vial was charge with **1** (0.2 mmol), **2** (0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The vial was closed and stirred in a pre-heated aluminum block at 90 °C for 3 h. After cooling, the reaction mixture was diluted to EtOAc (5 mL), filtered through a filter frit and a Whatman syringe filter (0.45 µm). Solvents was removed *in vacuo* (DMSO removal: using Biotage V-10 with Very High Boil mode at 56 °C and 0 mbar, or freeze dryer overnight at < 0.01 mbar) and the crude material was purified as specified.



1a **2a** **3aa**

3-bromo-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3aa**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 40 mg, 67%, yellow solid.

HRMS: $C_{11}H_8BrN_3S$ calc.: 293.9700 (M+H), found: 293.9703

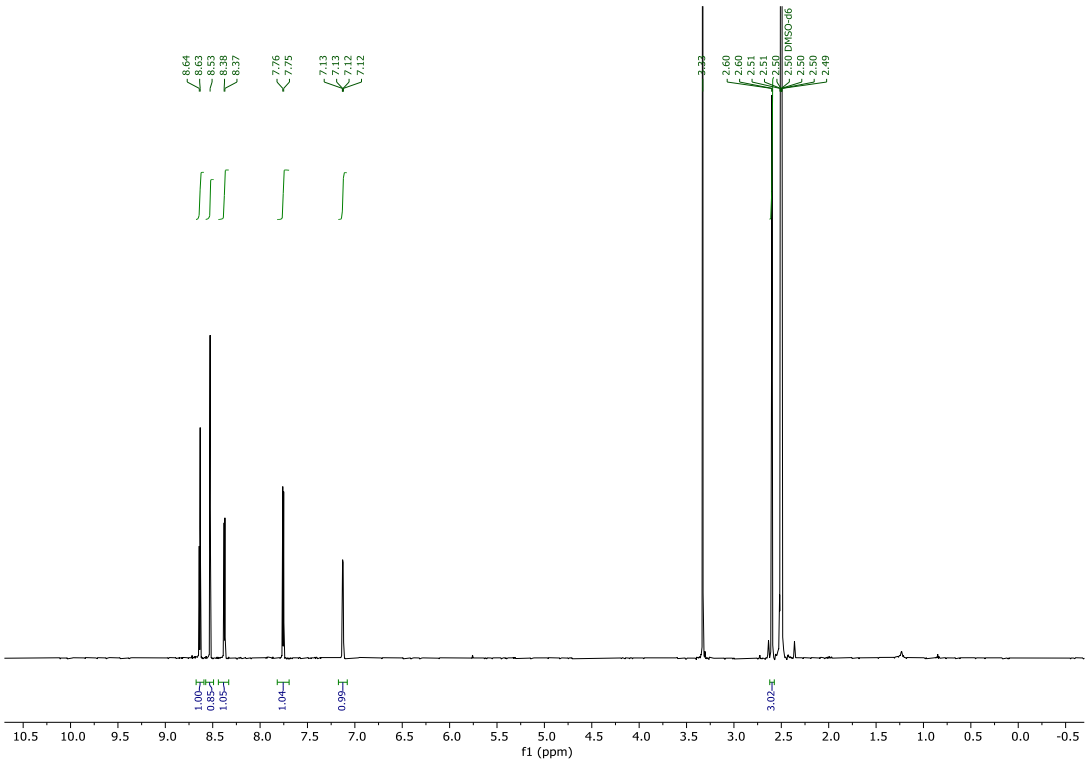
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J* = 4.7 Hz, 1H, H5), 8.53 (s, 1H, H2), 8.38 (d, *J* = 3.9 Hz, 1H, H3'), 7.76 (d, *J* = 4.8 Hz, 1H, H6), 7.13 (dq, *J* = 3.9, 1.0 Hz, 1H, H4'), 2.60 (d, *J* = 1.0 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 150.0, 149.3, 145.8, 143.9, 139.9, 133.0, 126.8, 126.8, 104.1, 83.5, 15.1.

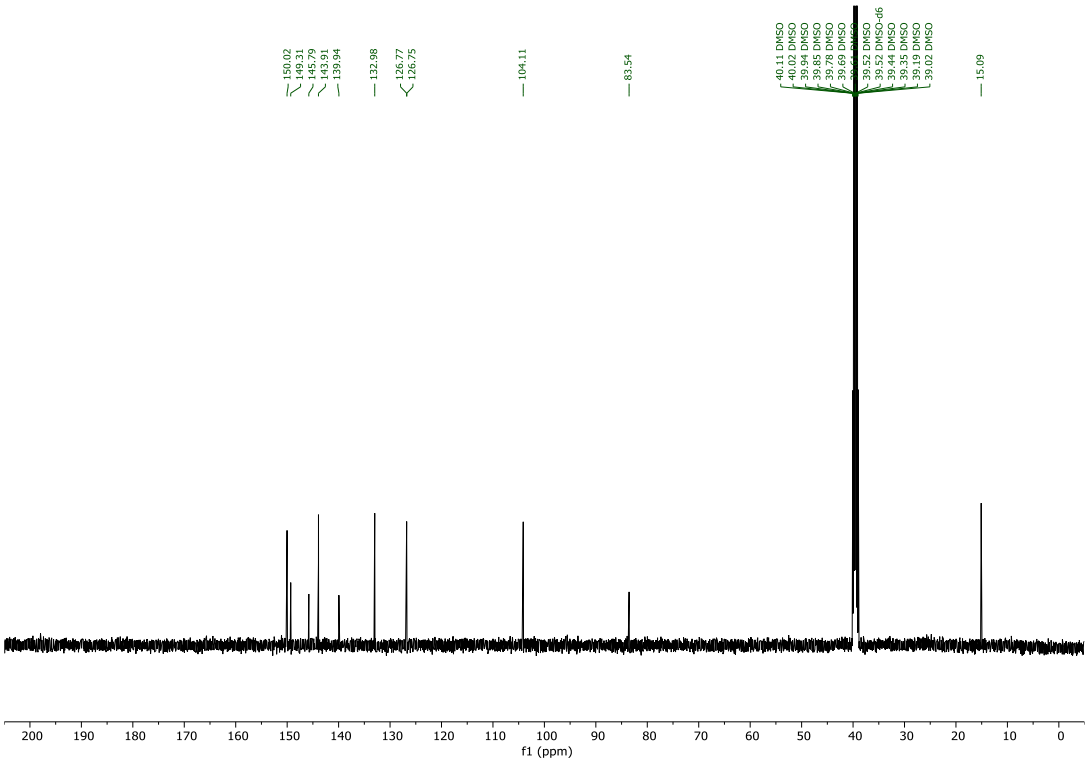
Structure determination:

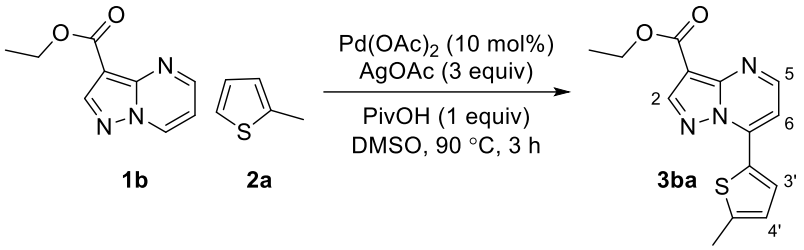
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant *J* = 1.0 Hz.

^{1}H NMR



^{13}C NMR





ethyl 7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3ba**)

Following the general procedure 1 using **1b** (38 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 25% to 100% of EtOAc in heptane over 4 CV as mobile phase.

Yield: 26 mg, 46%, yellow solid.

HRMS: $C_{14}H_{13}N_3O_2S$, calc.: 288.0807 (M+H), found 288.0801

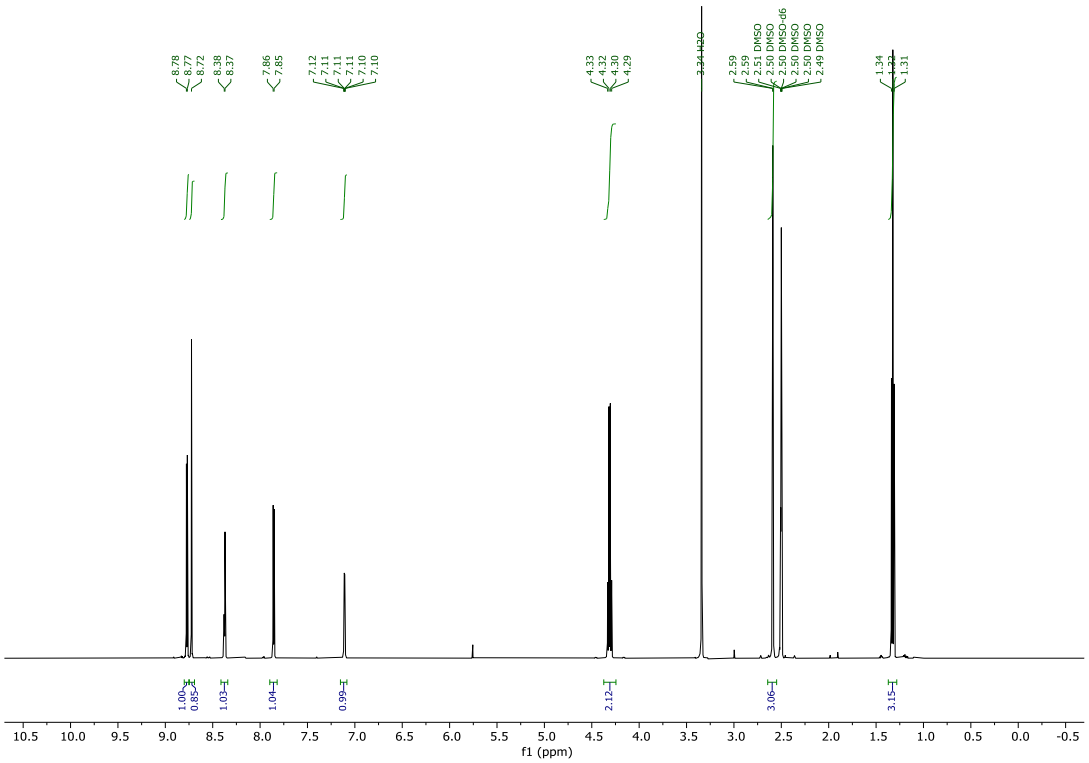
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (d, *J* = 4.8 Hz, 1H, H5), 8.72 (s, 1H, H2), 8.37 (d, *J* = 3.9 Hz, 1H, H3'), 7.86 (d, *J* = 4.8 Hz, 1H, H6), 7.11 (dq, *J* = 3.9, 1.1 Hz, 1H, H4'), 4.31 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.59 (d, *J* = 1.0 Hz, 3H, CH_3), 1.32 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 161.8, 152.0, 150.0, 148.1, 146.7, 140.5, 133.5, 126.9, 126.8, 105.2, 101.7, 59.6, 15.1, 14.5.

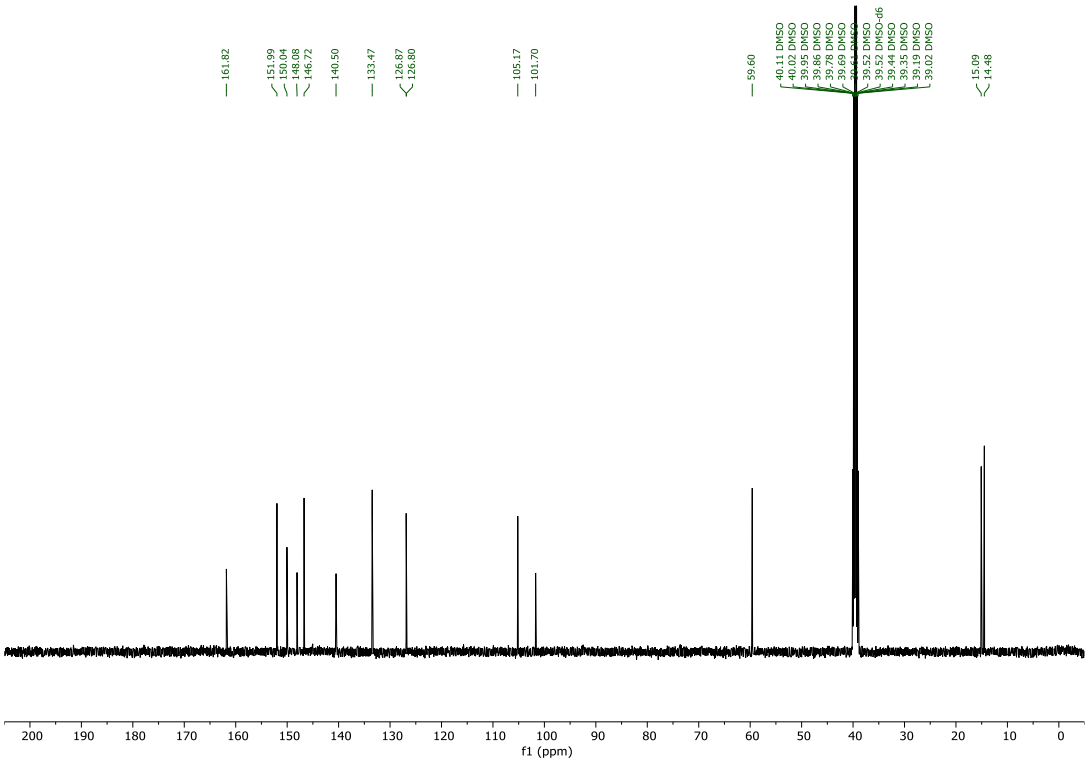
Structure determination:

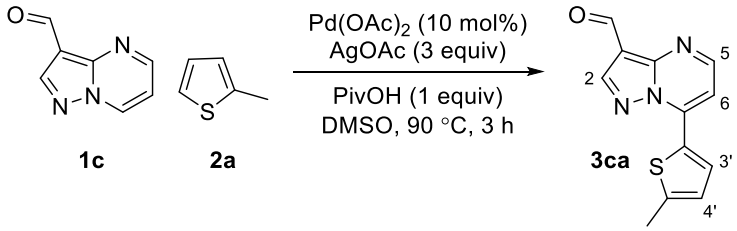
Coupling constant: H5 and H6 have coupling constant *J* = 4.8 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant *J* = 1.0 Hz.

^{1}H NMR



^{13}C NMR





7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carbaldehyde (**3ca**)

Following the general procedure 1 using **1c** (30 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 25% to 100% of EtOAc in heptane over 4 CV as mobile phase.

Yield: 26 mg, 52%, yellow solid.

HRMS: $C_{12}H_9N_3OS$, calc.: 244.0544 (M+H), found 244.0552

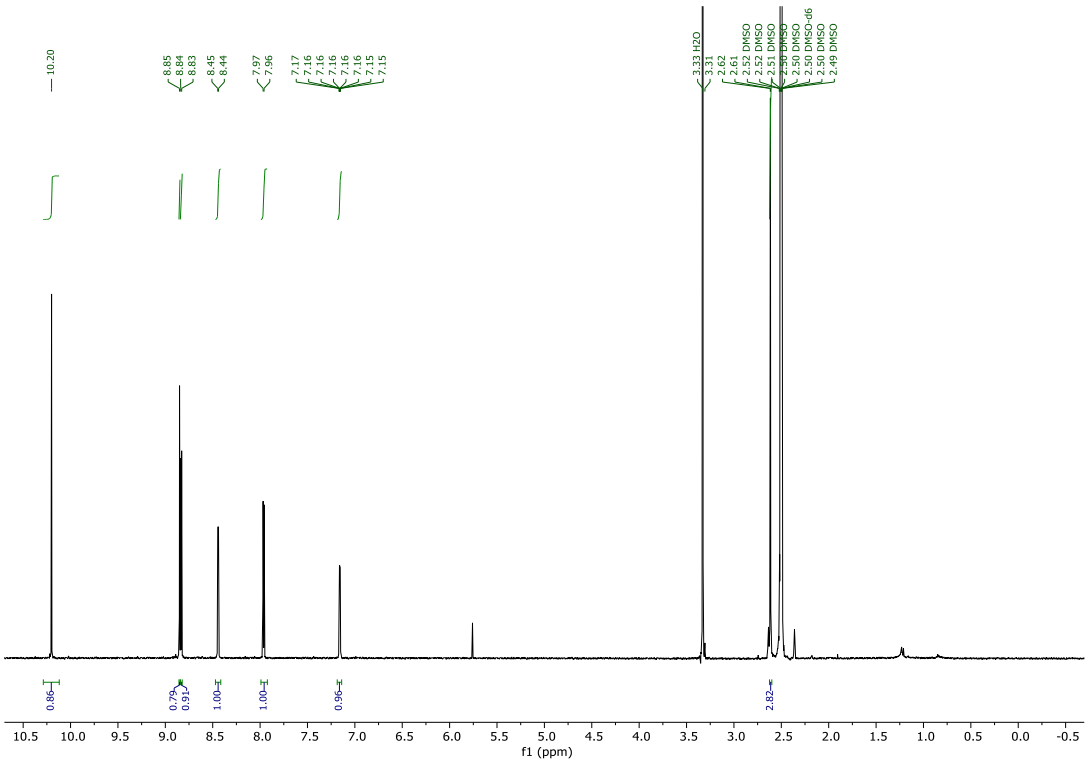
^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (s, 1H, CHO), 8.85 (s, 1H, H2), 8.83 (d, *J* = 4.9 Hz, 1H, H5), 8.44 (d, *J* = 3.9 Hz, 1H, H3'), 7.96 (d, *J* = 5.0 Hz, 1H, H6), 7.16 (dq, *J* = 3.8, 0.9 Hz, 1H, H4'), 2.62 (d, *J* = 1.0 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 182.6, 152.8, 150.6, 149.8, 144.8, 140.9, 133.9, 127.1, 126.6, 111.8, 106.1, 15.2.

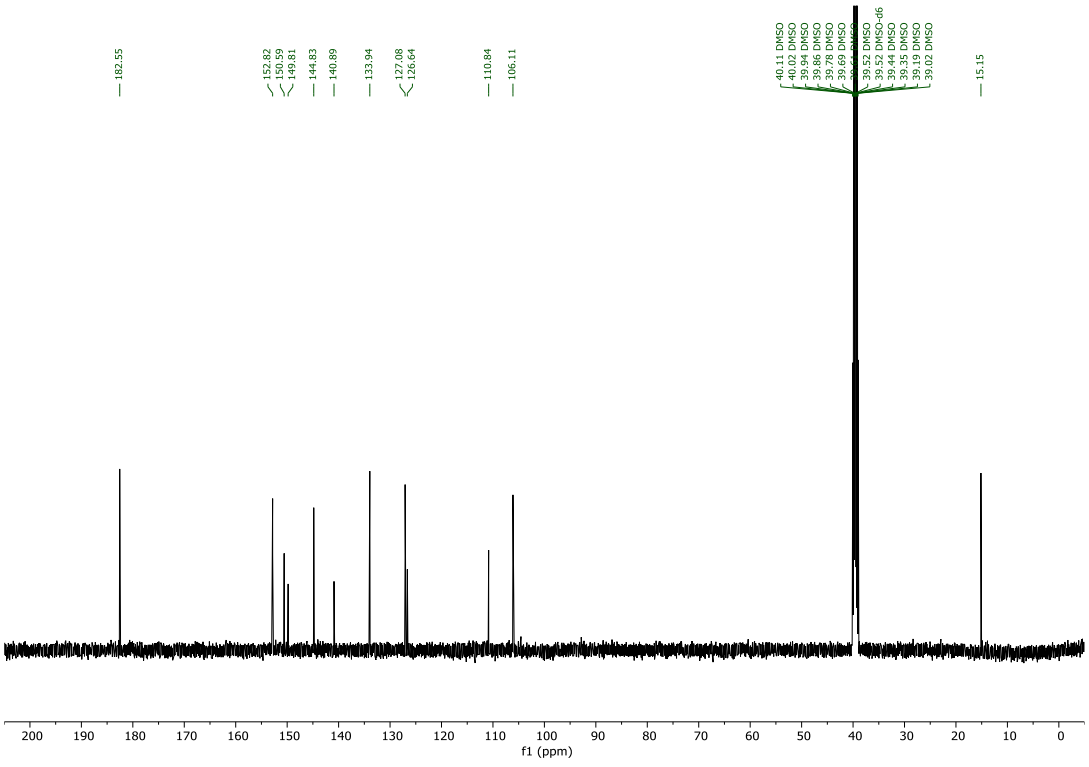
Structure determination:

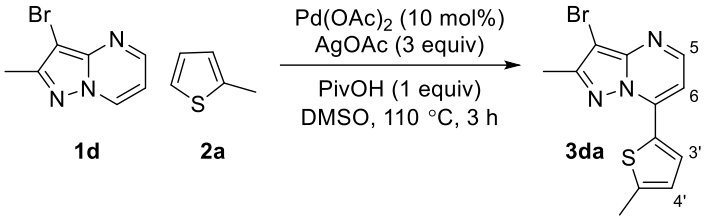
Coupling constant: H5 and H6 have coupling constant *J* = 4.9 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant *J* = 1.0 Hz.

^{1}H NMR



^{13}C NMR





3-bromo-2-methyl-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3da**)

Following general procedure 1 using **1d** (43 mg, 0.2 mmol), **2a** (39 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol) at 110 °C. The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 7% to 60% of EtOAc in heptane over 10 CV as mobile phase and 254 nm as the collecting wavelength.

Yield: 30 mg, 49%, yellow solid.

HRMS: $C_{12}H_{10}BrN_3S$ calc.: 307.9857 (M+H), found: 307.9870

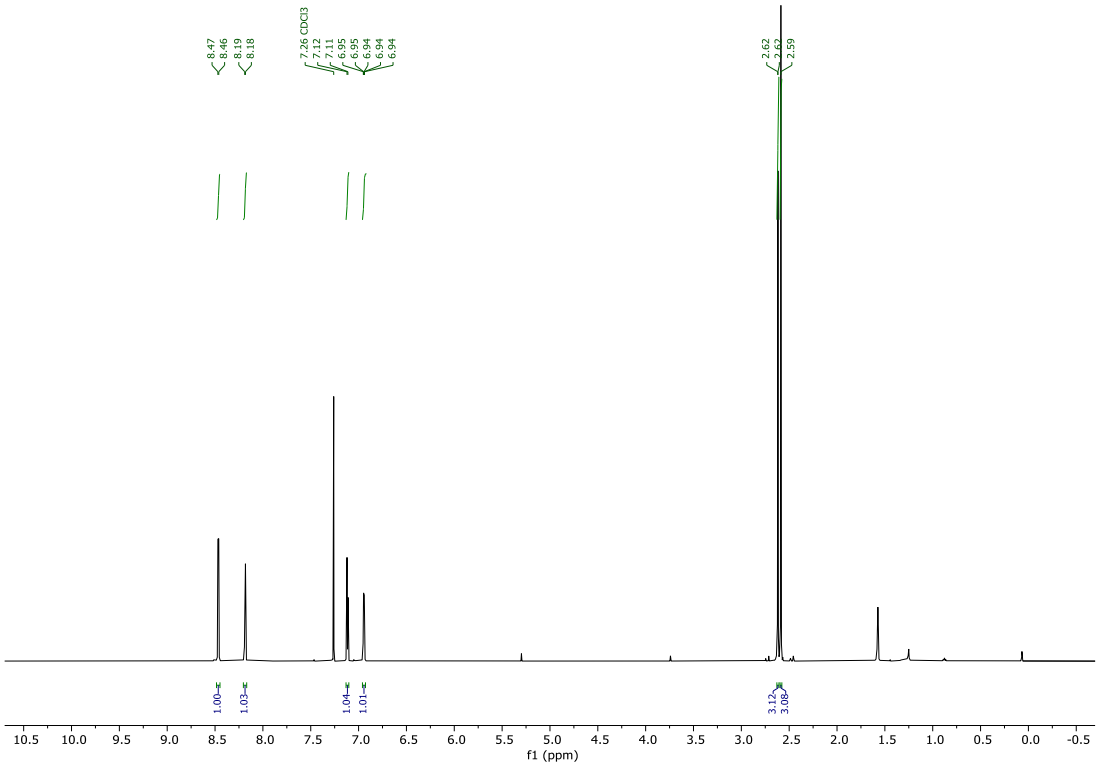
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* = 4.7 Hz, 1H, H5), 8.19 (d, *J* = 3.9 Hz, 1H, H3'), 7.12 (d, *J* = 4.6 Hz, 1H, H6), 6.95 (m, 1H, H4'), 2.62 (d, *J* = 1.0 Hz, 3H, CH_3'), 2.59 (s, 3H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$) δ 153.0, 148.8, 148.3, 146.9, 140.1, 132.5, 128.3, 126.5, 103.3, 84.8, 15.6, 13.5.

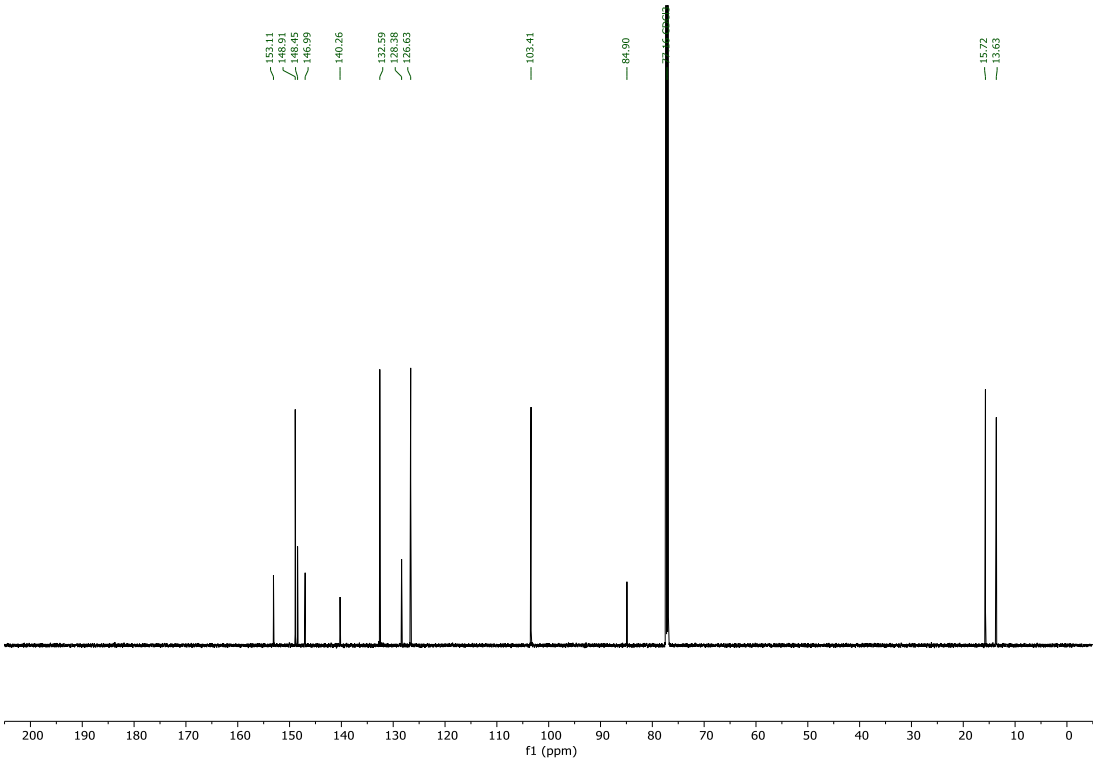
Structure determination:

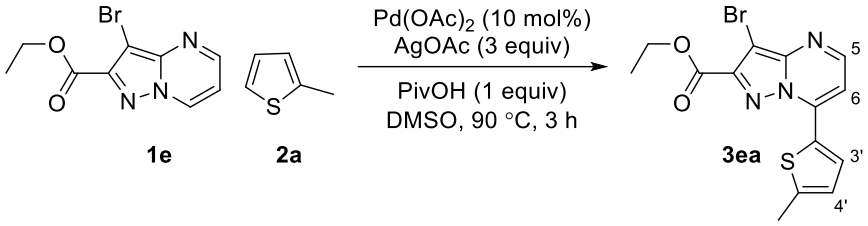
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





ethyl 3-bromo-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxylate (**3ea**)

Following general procedure 1 using **1e** (54 mg, 0.2 mmol), **2a** (39 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase and 254 nm as the collecting wavelength.

Yield: 55 mg, 75%, orange solid.

HRMS: $C_{14}H_{12}BrN_3O_2S$ calc.: 365.9912 (M+H), found: 365.9925

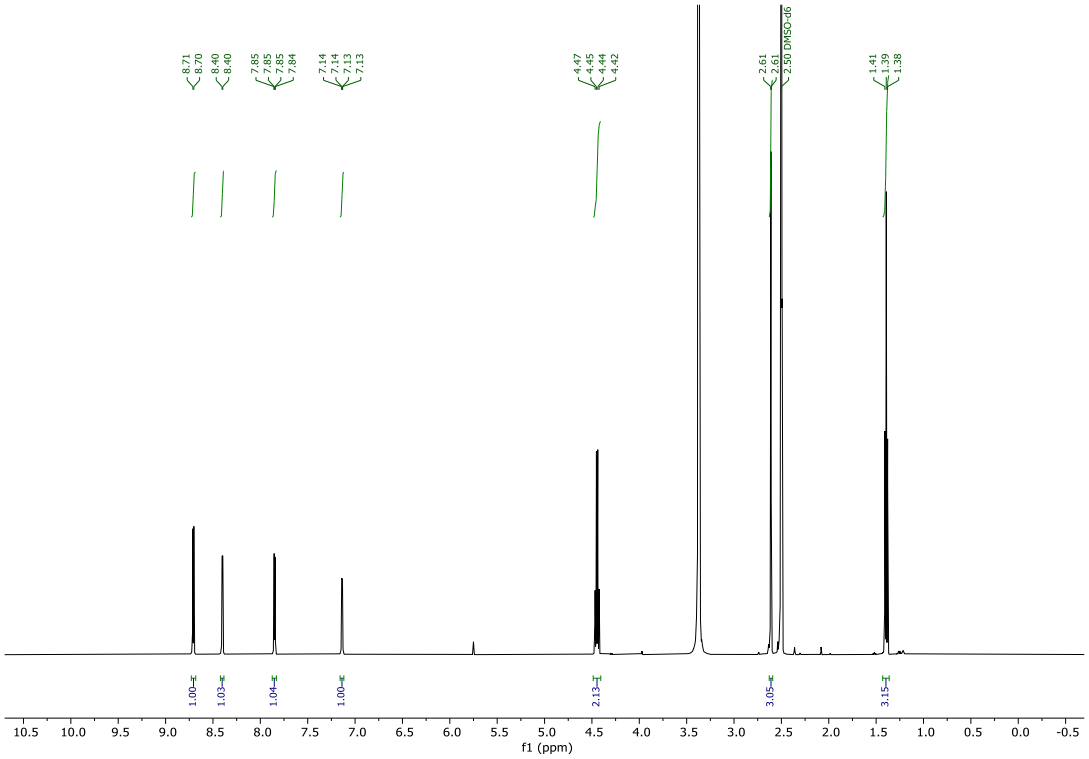
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (d, *J* = 4.7 Hz, 1H, H5), 8.40 (d, *J* = 3.9 Hz, 1H, H3'), 7.85 (dd, *J* = 4.7, 0.9 Hz, 1H, H6), 7.14 (m, 1H, H4'), 4.45 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.61 (d, *J* = 0.9 Hz, 3H, $\underline{CH_3}$), 1.39 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 161.2, 151.5, 150.2, 147.4, 143.0, 140.6, 133.9, 127.5, 126.9, 106.8, 86.8, 61.9, 15.7, 14.6.

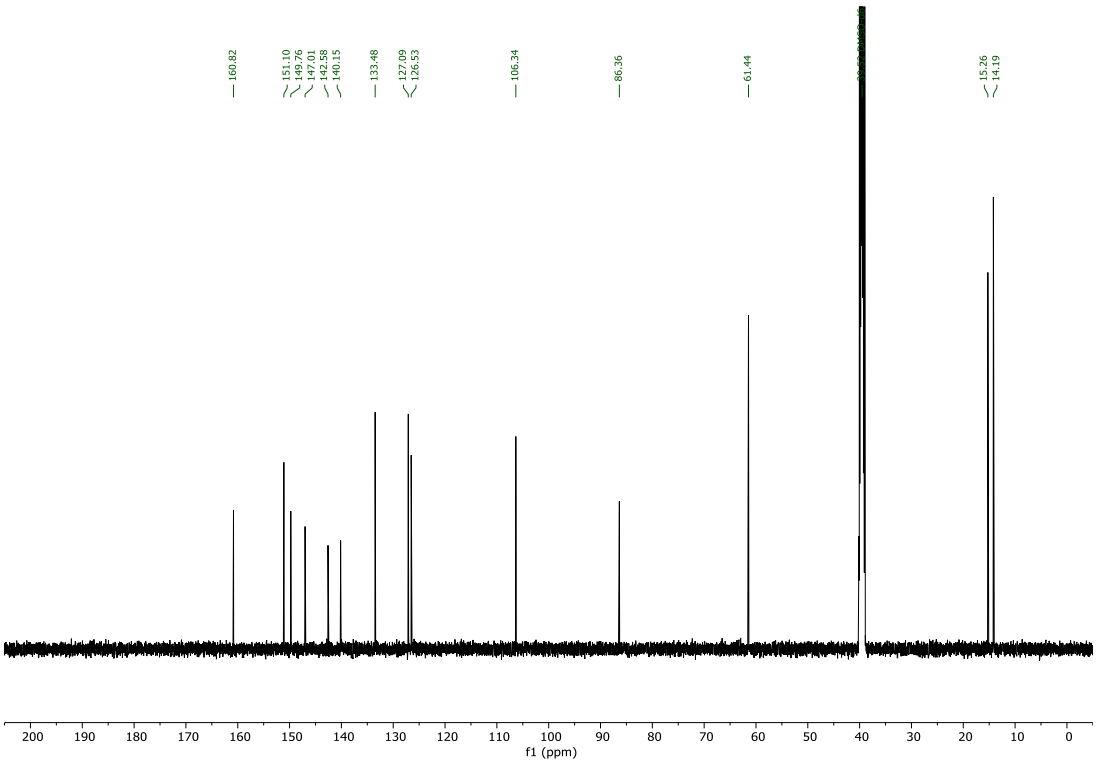
Structure determination:

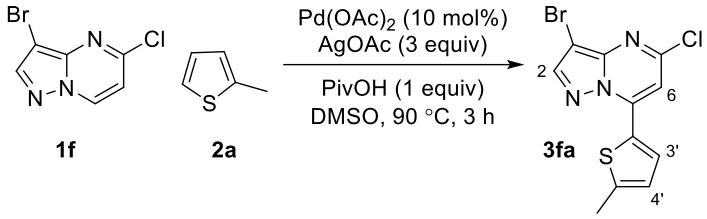
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





3-bromo-5-chloro-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3fa**)

Following the general procedure 1 using **1f** (46 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 7% to 60% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 9 mg, 14%, yellow solid.

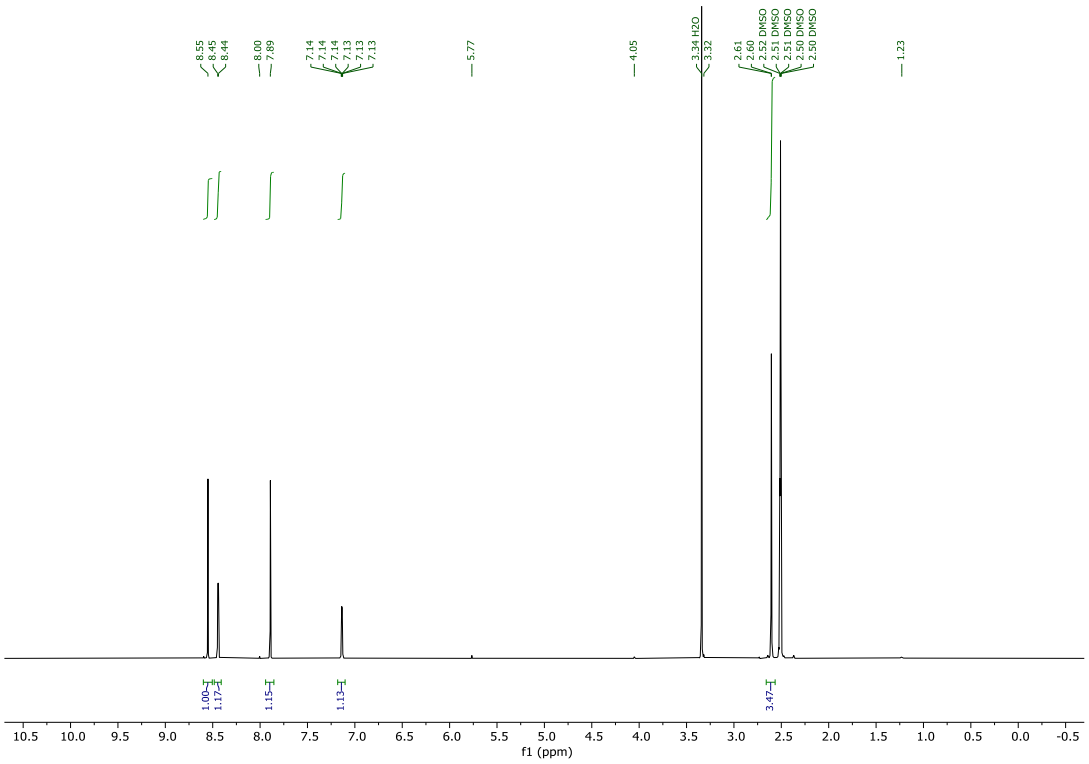
HRMS: $C_{11}H_7BrClN_3S$, calc.: 327.9311 (M+H), found: 327.9312

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 1H, H2), 8.44 (d, J = 4.0 Hz, 1H, H3'), 7.89 (s, 1H, H6), 7.13 (dq, J = 4.0, 1.1 Hz, 1H, H4'), 2.61 (d, J = 1.0 Hz, 3H, CH_3).

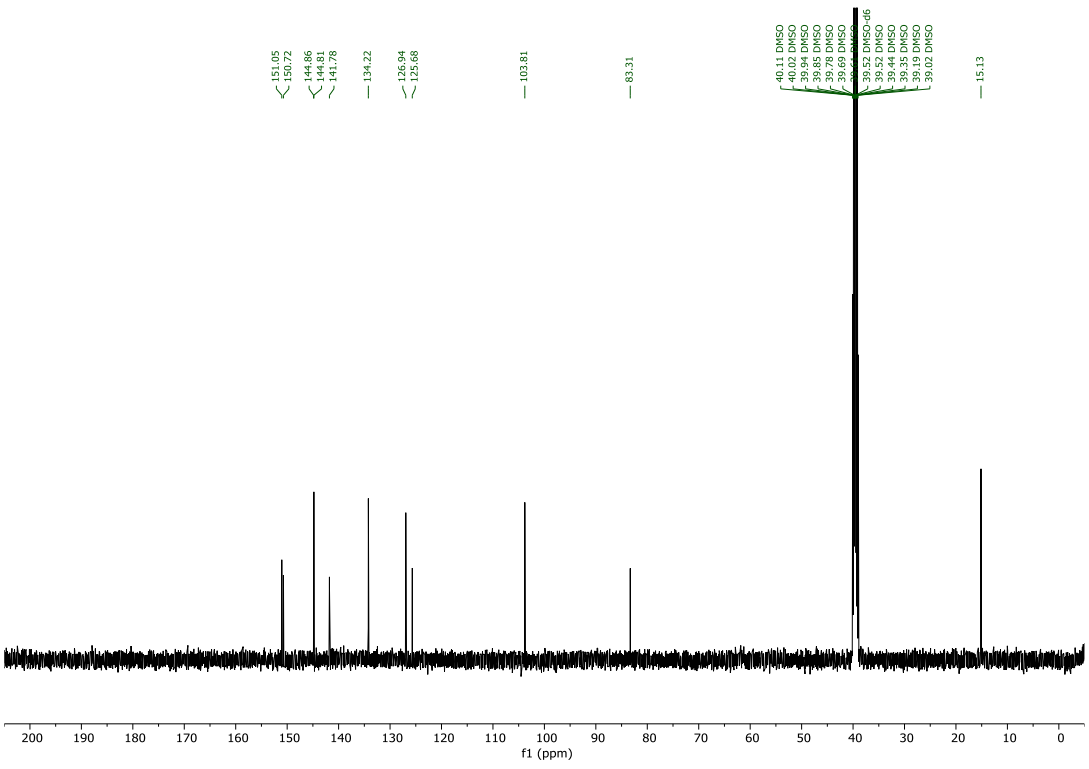
^{13}C NMR (126 MHz, DMSO-d_6) δ 151.1, 150.7, 144.9, 144.8, 141.8, 134.2, 127.0, 125.7, 103.8, 83.3, 15.1.

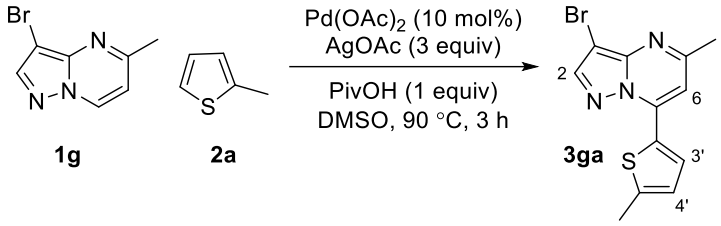
Regioselectivity is analogous to **3aa**.

^{1}H NMR



^{13}C NMR





3-bromo-5-methyl-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3ga**)

Following the general procedure 1 using **1g** (42 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 7% to 60% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 34 mg, 56%, yellow solid.

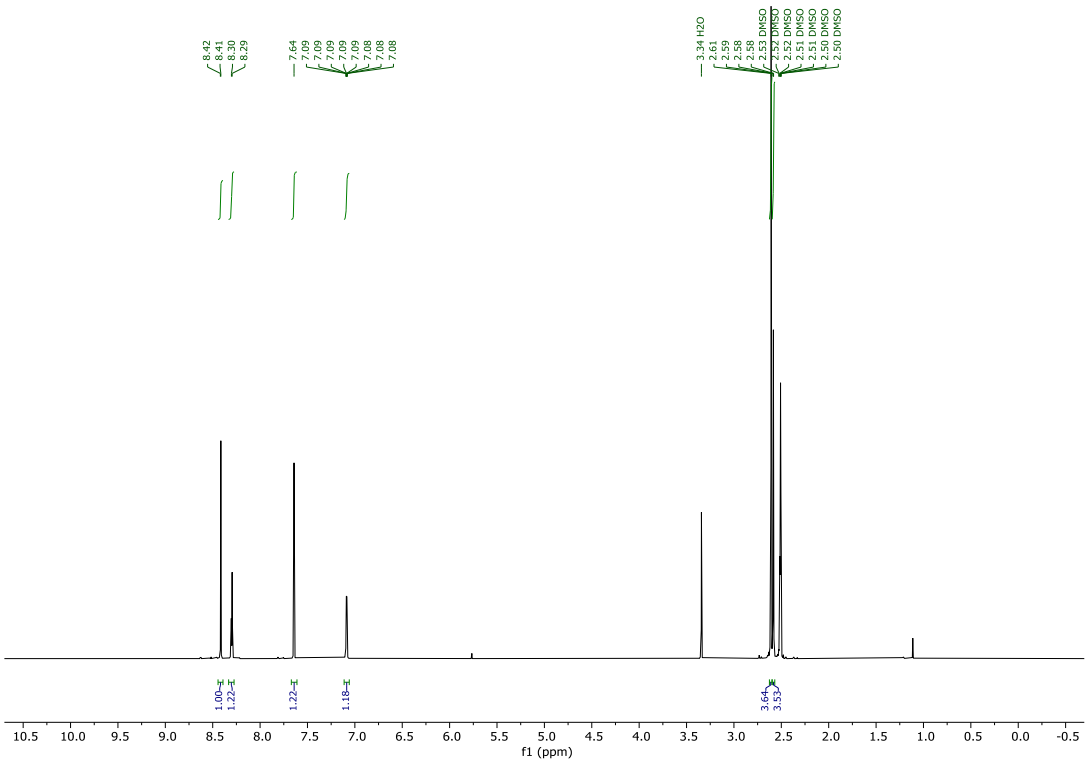
HRMS: $C_{12}H_{10}BrN_3S$, calc.: 307.9857 (M+H), found: 307.9856

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 1H, H2), 8.30 (d, J = 3.8 Hz, 1H, H3'), 7.64 (s, 1H, H6), 7.09 (dq, J = 3.8, 0.9 Hz, 1H, H4'), 2.61 (s, 3H, CH_3), 2.58 (d, J = 1.2 Hz, 3H, CH_3)

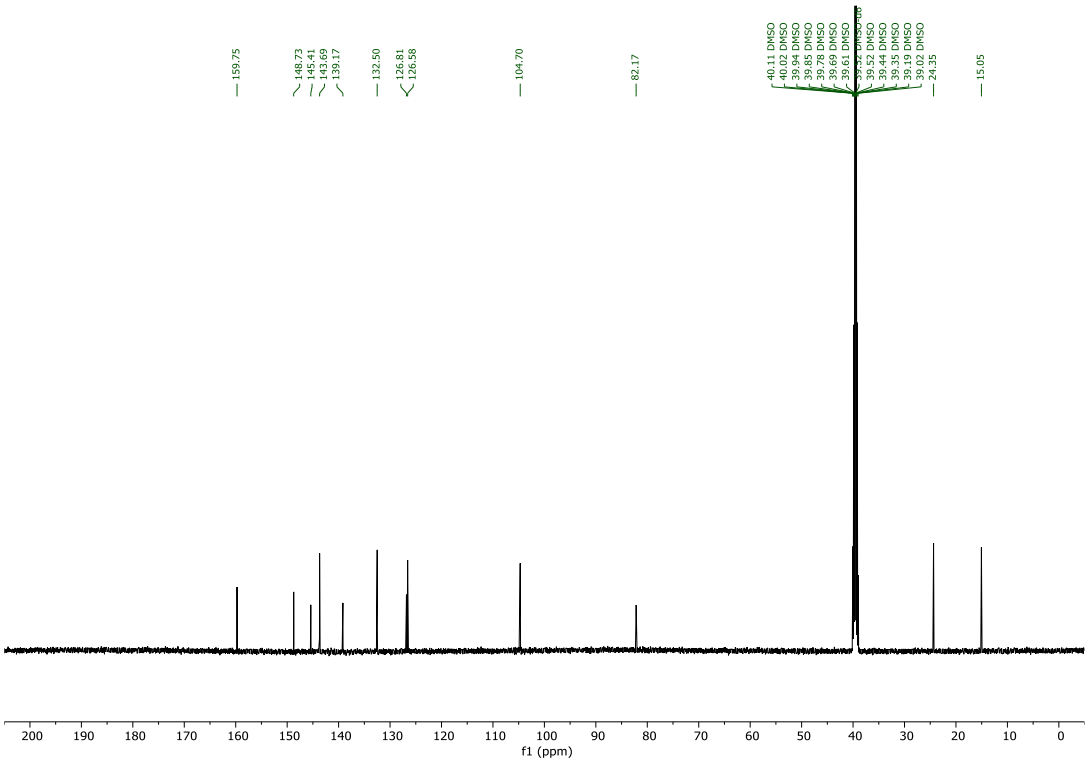
^{13}C NMR (126 MHz, DMSO-d_6) δ 159.7, 148.7, 145.4, 143.7, 139.2, 132.5, 126.8, 126.6, 104.7, 82.2, 24.4, 15.1.

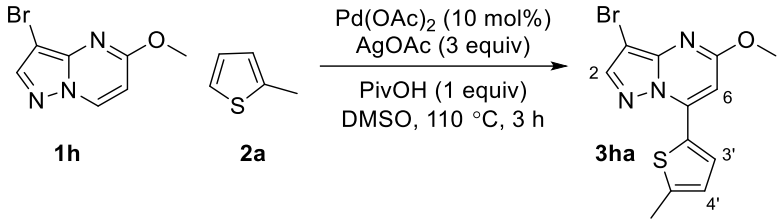
Regioselectivity is analogous to **3aa**.

^{1}H NMR



^{13}C NMR





3-bromo-5-methoxy-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3ha**)

Following the general procedure 1 (temperature increased to 110 °C) using **1h** (46 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 26 mg, 40%, yellow solid.

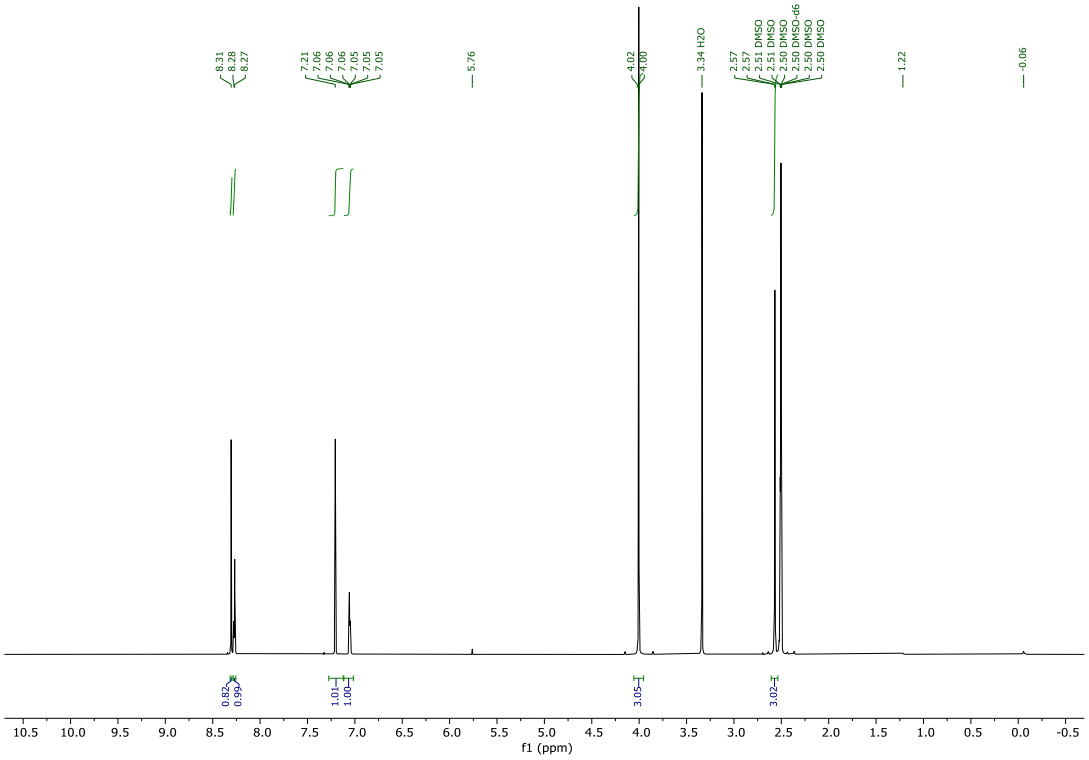
HRMS: $C_{12}H_{10}BrN_3OS$, calc.: 323.9806 (M+H), found: 323.9812

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (s, 1H, H2), 8.27 (d, J = 3.9 Hz, 1H, H3'), 7.21 (s, 1H, H6), 7.05 (dq, J = 3.9, 1.1 Hz, 1H, H4'), 4.00 (s, 3H, OCH_3), 2.57 (d, J = 1.0 Hz, 3H, CH_3).

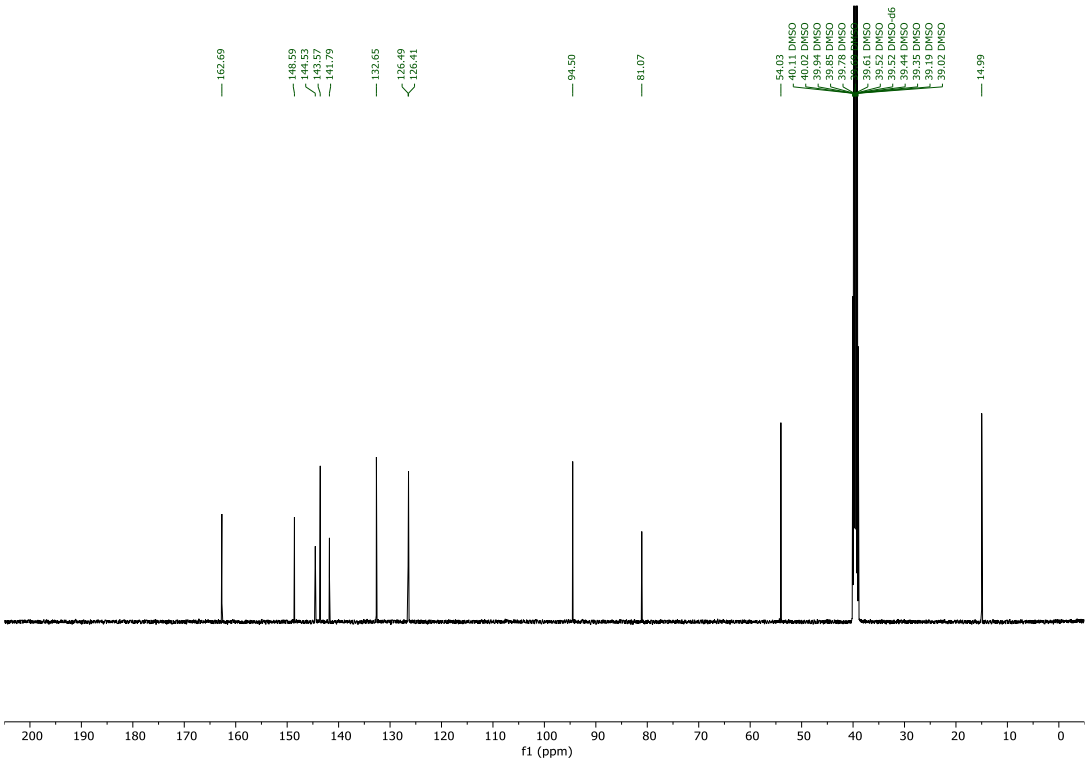
^{13}C NMR (126 MHz, DMSO-d_6) δ 162.7, 148.6, 144.5, 143.6, 141.8, 132.7, 126.5, 126.4, 94.5, 81.1, 54.0, 15.0.

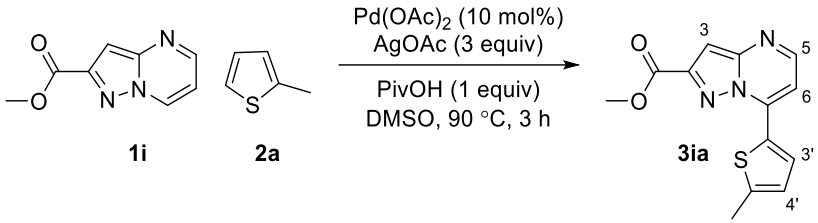
Regioselectivity is analogous to **3aa**.

^{1}H NMR



^{13}C NMR





methyl 7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine-2-carboxylate (**3ia**)

Following the general procedure 1 using **1i** (36 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 4 CV as mobile phase.

Yield: 20 mg, 36%, brown solid.

HRMS: $C_{13}H_{11}N_3O_2S$, calc.: 274.0650 (M+H), found 274.0645

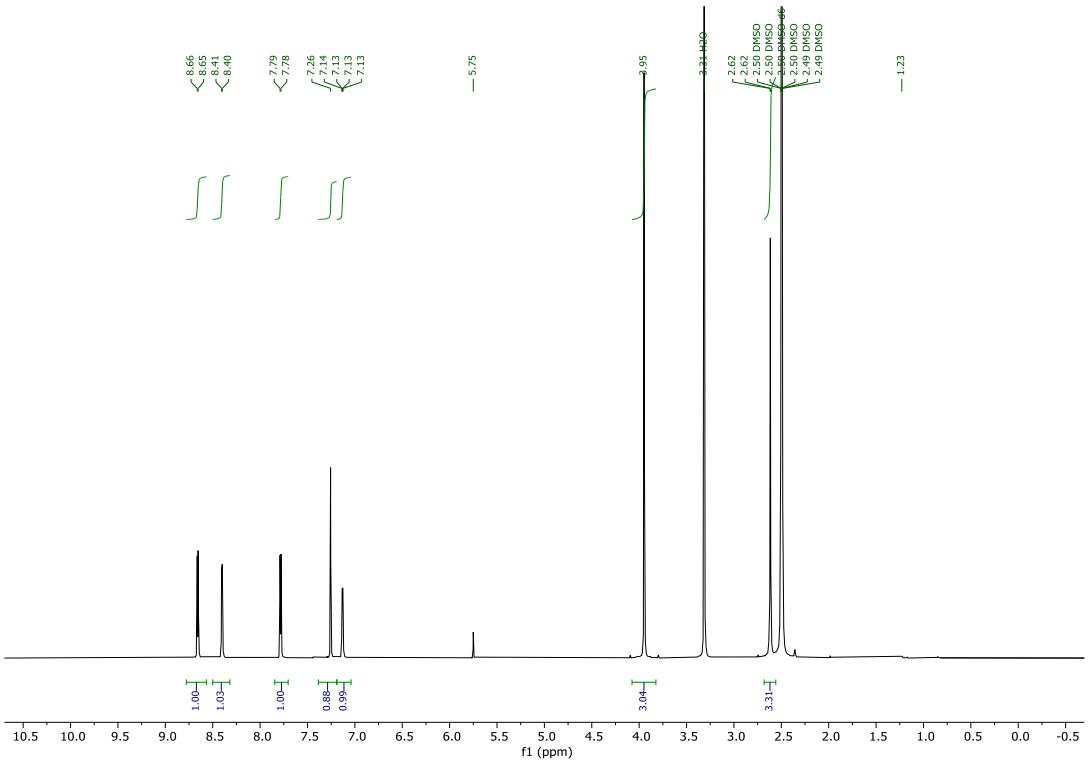
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (d, *J* = 4.7 Hz, 1H, H5), 8.40 (d, *J* = 3.9 Hz, 1H, H3'), 7.78 (d, *J* = 4.7 Hz, 1H, H6), 7.26 (s, 1H, H3), 7.13 (dq, *J* = 4.0, 1.3 Hz, 1H, H4'), 3.95 (s, 3H, OCH_3), 2.62 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 150.2, 149.5, 149.1, 145.8, 139.7, 133.0, 127.1, 126.9, 105.3, 98.9, 52.3, 15.2.

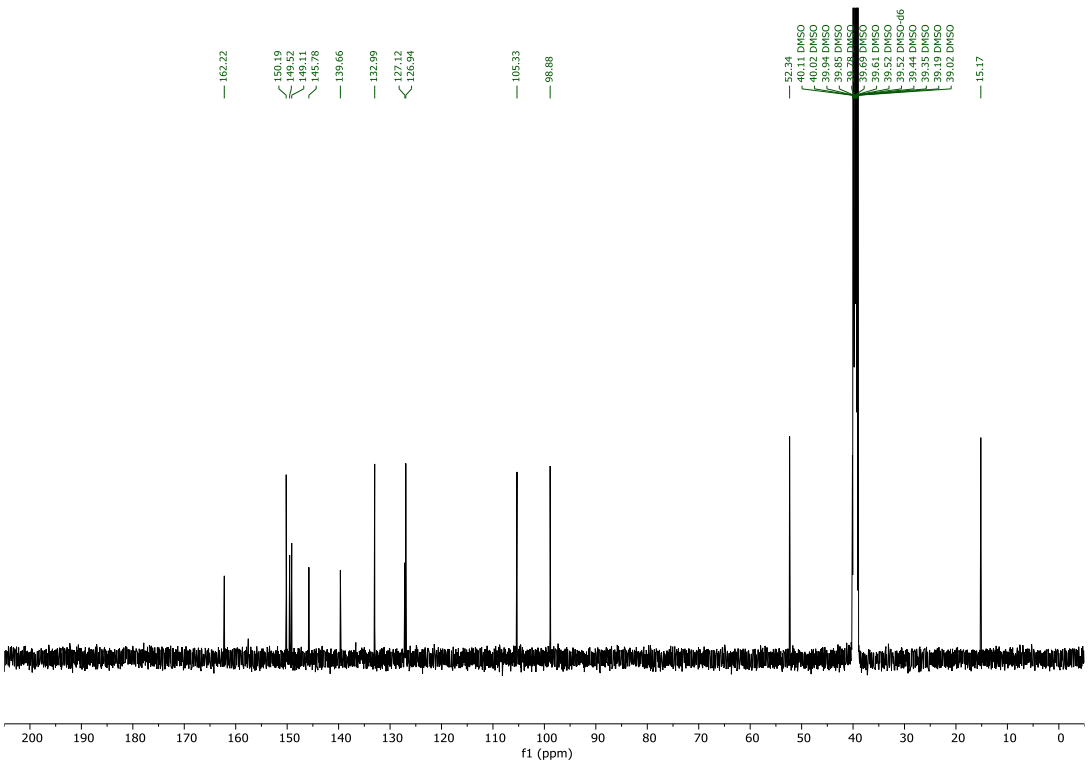
Structure determination:

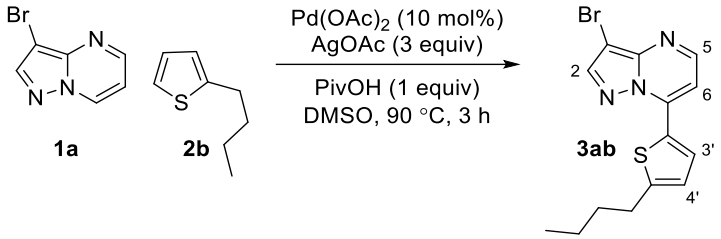
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





3-bromo-7-(5-butylthiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3ab**)

Following general procedure 1 using **1a** (40 mg, 0.2 mmol), **2b** (56 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase and 254 nm as the collecting wavelength.

Yield: 45 mg, 66%, yellow solid.

HRMS: $C_{14}H_{14}BrN_3S$ calc.: 336.0170 (M+H), found: 336.0189

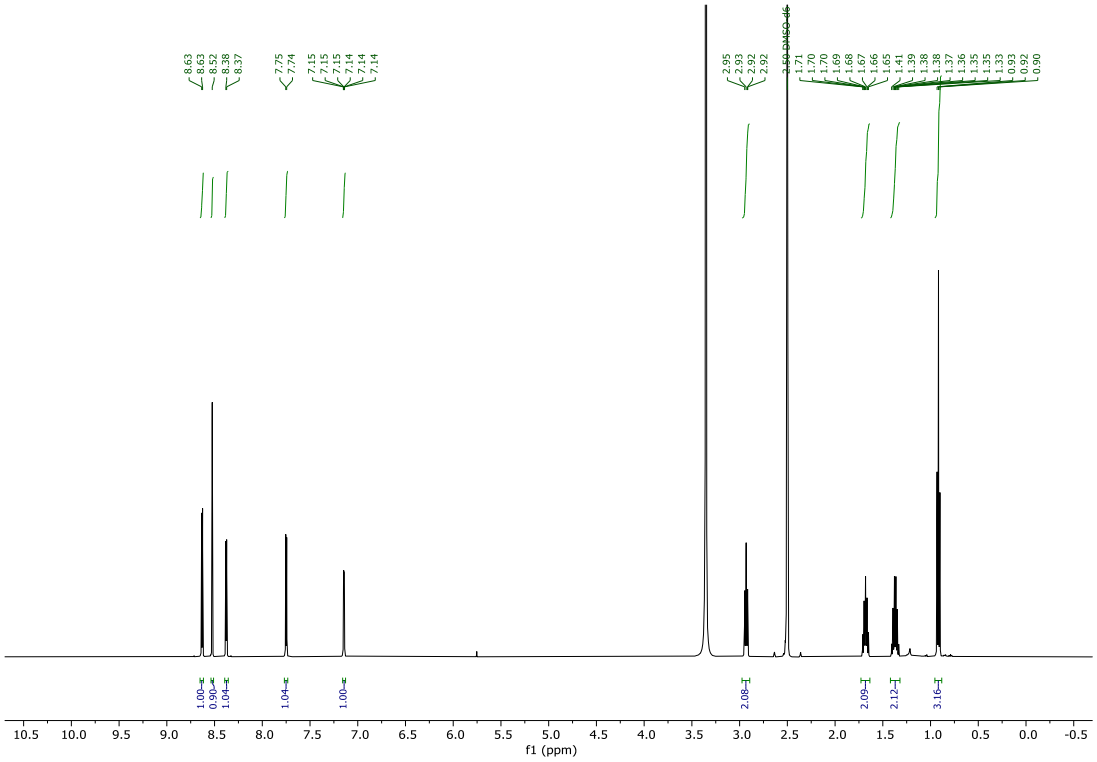
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, *J* = 4.7 Hz, 1H, H5), 8.52 (s, 1H, H2), 8.38 (d, *J* = 4.0 Hz, 1H, H3'), 7.75 (d, *J* = 4.7 Hz, 1H, H6), 7.14 (m, 1H, H4'), 2.93 (t, *J* = 7.4 Hz, 2H, $\underline{CH_2}CH_2CH_2CH_3$), 1.68 (p, *J* = 7.6 Hz, 2H, $CH_2\underline{CH_2}CH_2CH_3$), 1.32 – 1.42 (m, 2H, $CH_2CH_2\underline{CH_2}CH_3$), 0.92 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 155.4, 150.5, 146.3, 144.4, 140.4, 133.3, 127.0, 126.2, 104.6, 84.0, 33.6, 29.6, 22.1, 14.1.

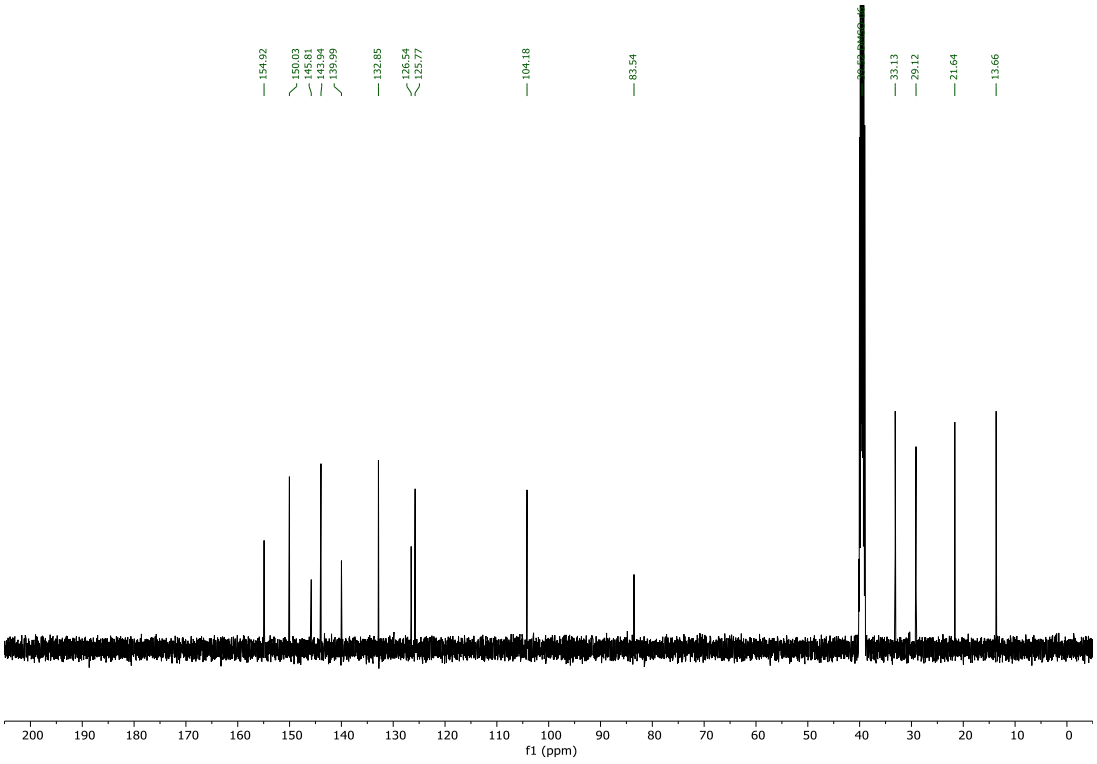
Structure determination:

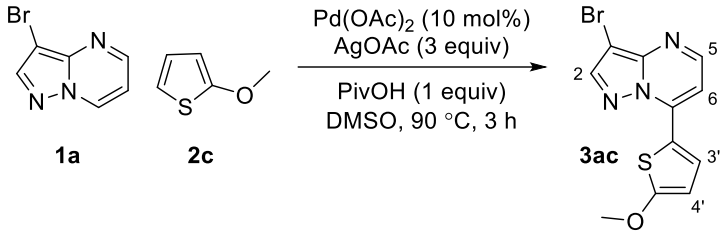
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 4.0 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





3-bromo-7-(5-methoxythiophen-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3ac**)

Following general procedure 1 (temperature increased to 110 °C) using **1a** (40 mg, 0.2 mmol), **2c** (46 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by preparative HPLC on a Kromasil C8 250x20 mm, 10µm, column using a gradient of 25-70% of MeCN in an acid buffer (H_2O/MeCN/FA 95/5/0.2).

Yield: 23 mg, 37%, orange solid.

HRMS: $C_{11}H_8BrN_3OS$ calc.: 309.9650 (M+H), found: 309.9653

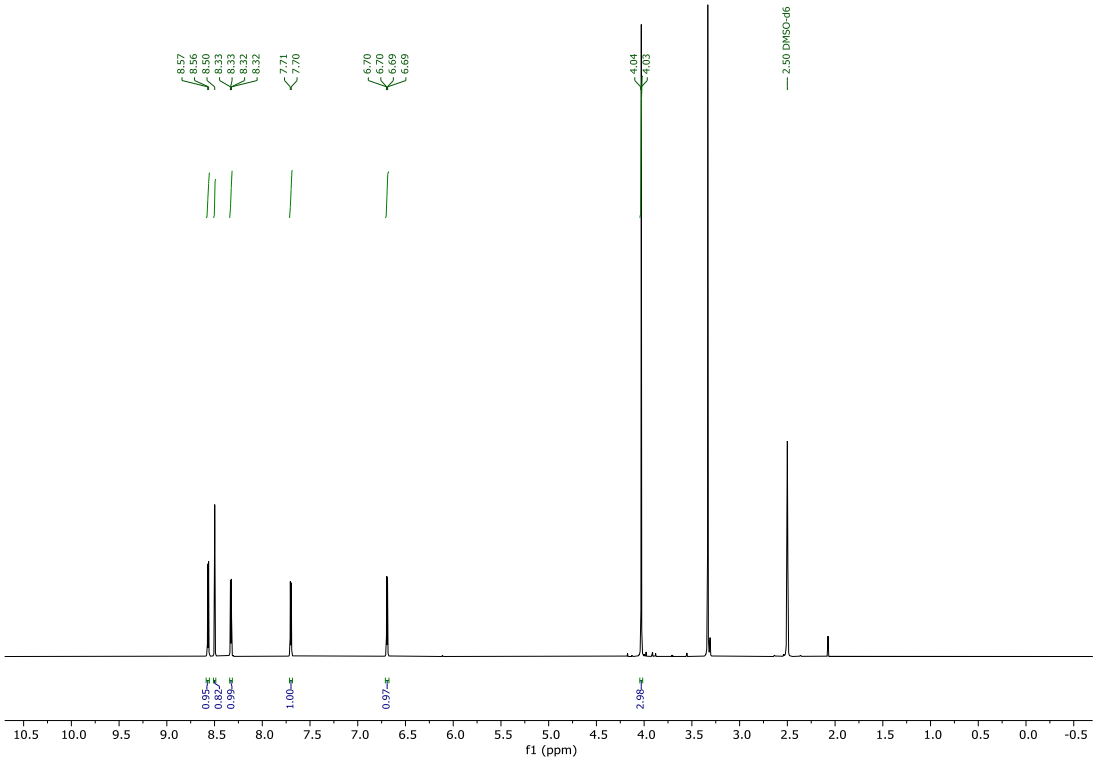
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (d, *J* = 4.8 Hz, 1H, H5), 8.50 (s, 1H, H2), 8.33 (dd, *J* = 4.5, 0.7 Hz, 1H, H3'), 7.70 (d, *J* = 5.1 Hz, 1H, H6), 6.69 (m, 1H, H4'), 4.03 (s, 3H, OCH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 174.0, 149.7, 145.7, 143.8, 140.4, 132.6, 114.1, 106.2, 102.9, 83.2, 60.6.

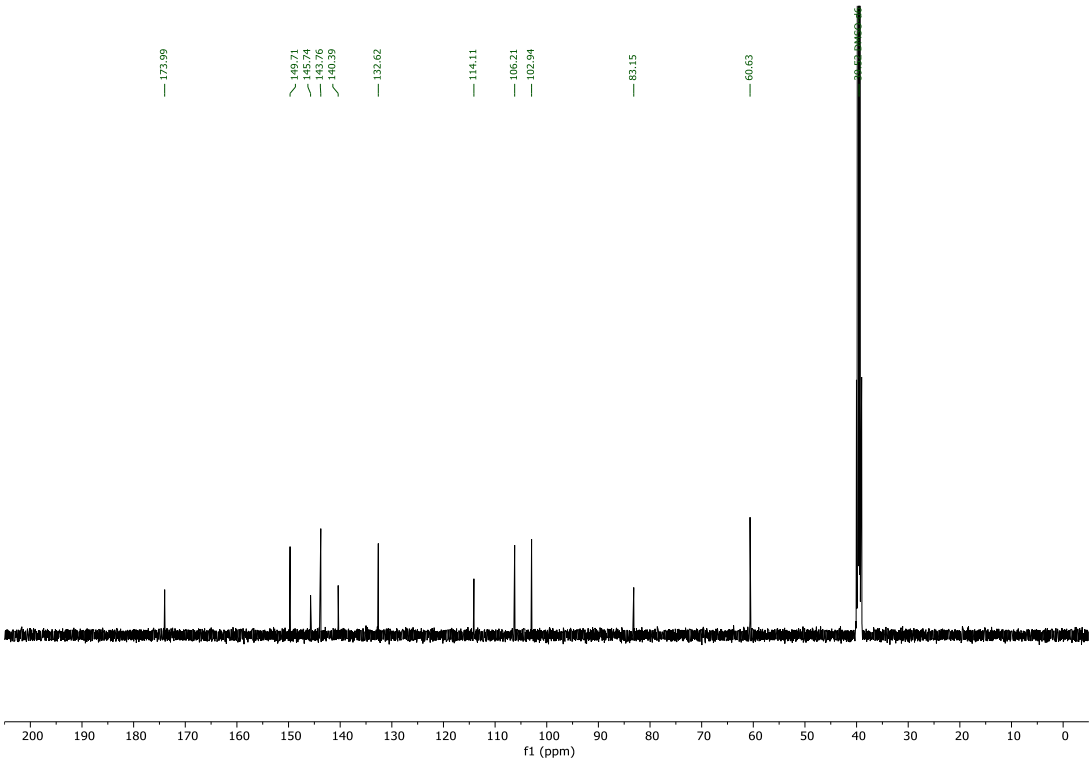
Structure determination:

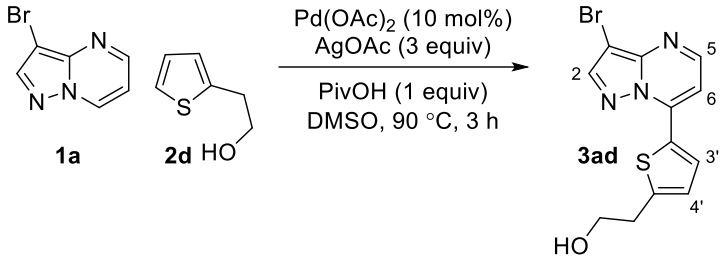
Coupling constant: H5 and H6 have coupling constant *J* = 4.8 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 4.5 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





2-(5-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)thiophen-2-yl)ethan-1-ol (**3ad**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2d** (52 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 18% to 100% of EtOAc in heptane over 6 CV as mobile phase. The fraction containing the product was triturated with small amount of DCM and filtered to afford pure compound.

Yield: 25 mg, 38%, yellow solid.

HRMS: $C_{12}H_{10}BrN_3OS$ calc.: 323.9806 (M+H), found: 323.9816

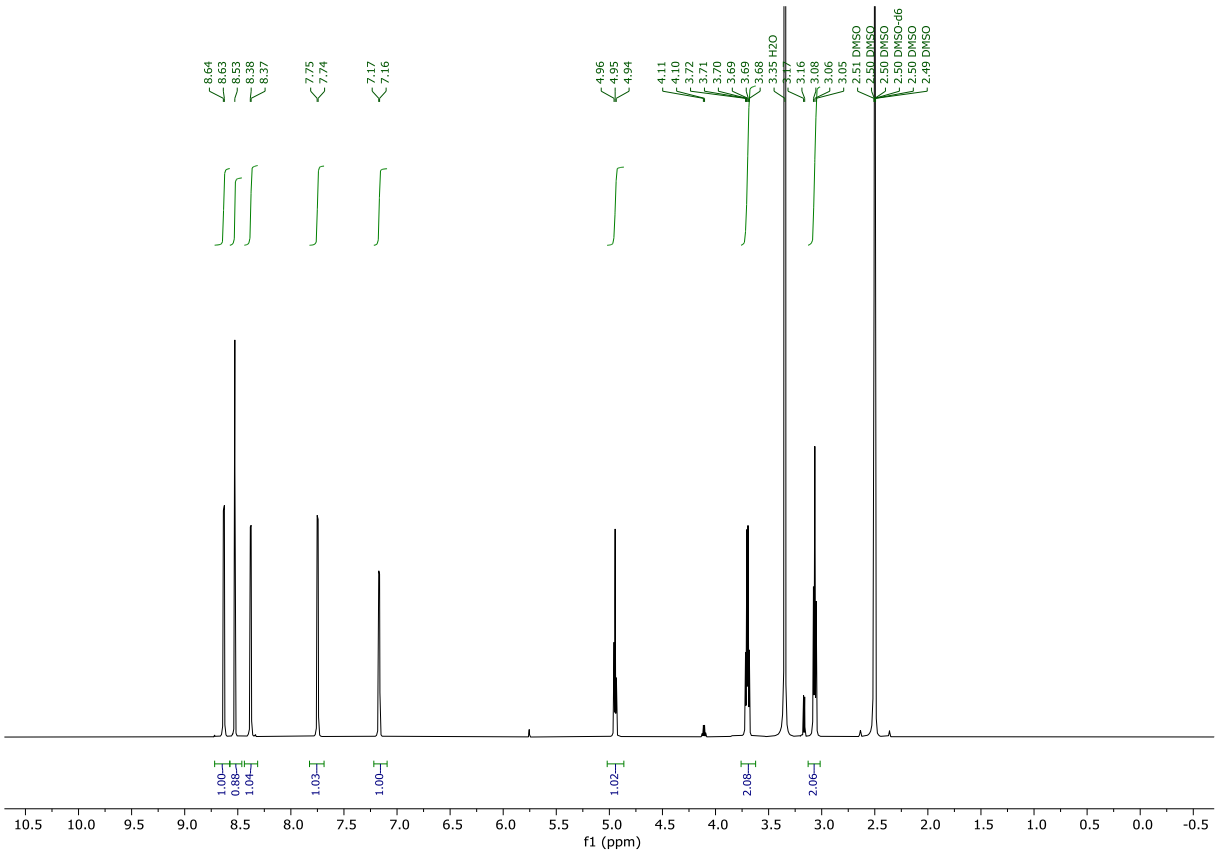
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, *J* = 4.7 Hz, 1H, H5), 8.53 (s, 1H, H2), 8.38 (d, *J* = 3.9 Hz, 1H, H3'), 7.75 (d, *J* = 4.7 Hz, 1H, H6), 7.17 (d, *J* = 3.9 Hz, 1H, H4'), 4.95 (t, *J* = 5.2 Hz, 1H, OH), 3.70 (td, *J* = 6.4, 5.0 Hz, 2H, $CH_2\underline{CH_2}OH$), 3.06 (t, *J* = 6.4 Hz, 2H, $\underline{CH_2}CH_2OH$).

^{13}C NMR (125 MHz, DMSO-d_6) δ 151.9, 150.0, 145.8, 143.9, 140.1, 132.5, 127.1, 126.5, 104.2, 83.5, 61.4, 33.4.

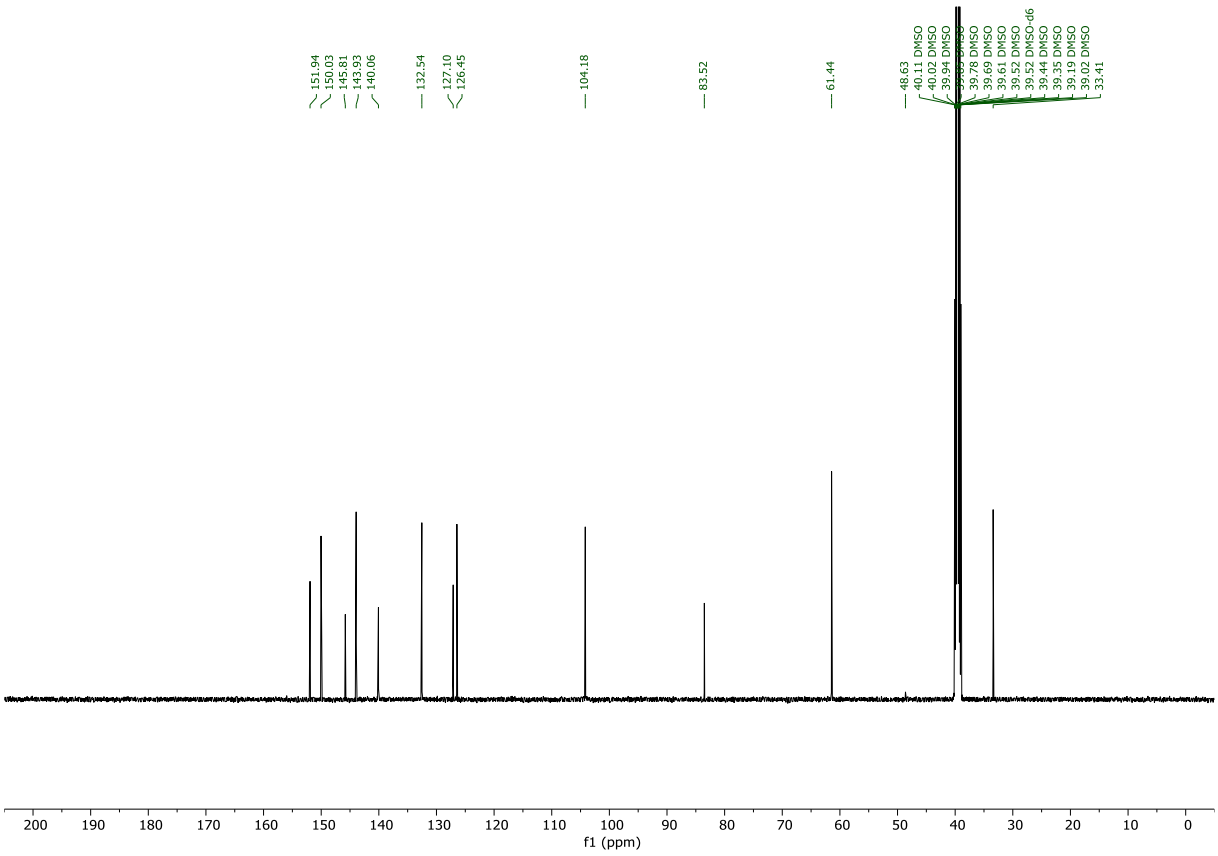
Structure determination:

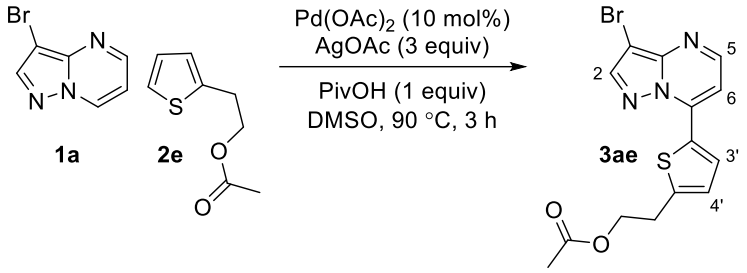
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





2-(5-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)thiophen-2-yl)ethyl acetate (**3ae**)

Following general procedure 1 using **1a** (40 mg, 0.2 mmol), **2e** (69 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by preparative HPLC on a Kromasil C8 250x20 mm, 10µm, column using a gradient of 20-85% of MeCN in an acid buffer (H_2O/MeCN/FA 95/5/0.2).

Yield: 35 mg, 47%, yellow solid.

HRMS: $C_{14}H_{12}BrN_3O_2S$ calc.: 365.9912 (M+H), found: 365.9917

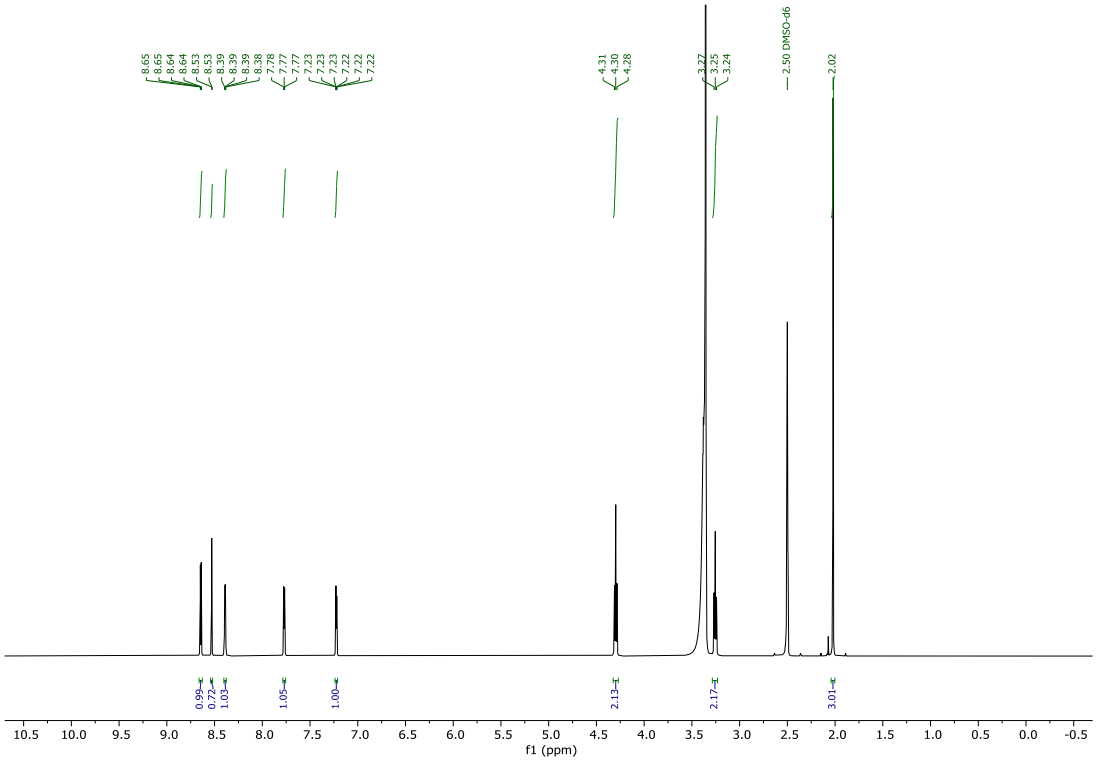
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (d, *J* = 4.7 Hz, 1H, H5), 8.54 (s, 1H, H2), 8.41 (d, *J* = 4.0 Hz, 1H, H3'), 7.79 (d, *J* = 4.7 Hz, 1H, H6), 7.24 (m, 1H, H4'), 4.30 (t, *J* = 6.4 Hz, 2H, $CH_2\underline{CH_2}OAc$), 3.26 (td, *J* = 6.4, 0.8 Hz, 2H, $\underline{CH_2}CH_2OAc$), 2.02 (s, 3H, $\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 170.8, 150.5, 150.3, 146.2, 144.4, 140.3, 133.1, 127.9, 127.3, 104.8, 84.1, 64.2, 29.4, 21.2.

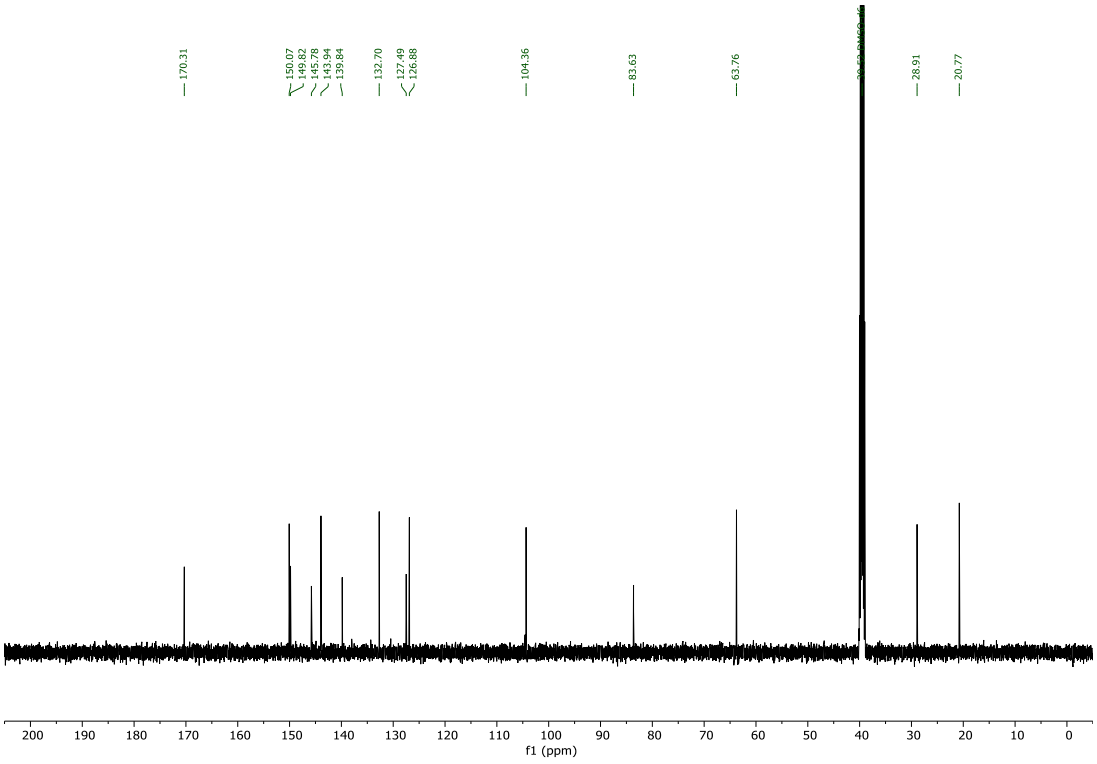
Structure determination:

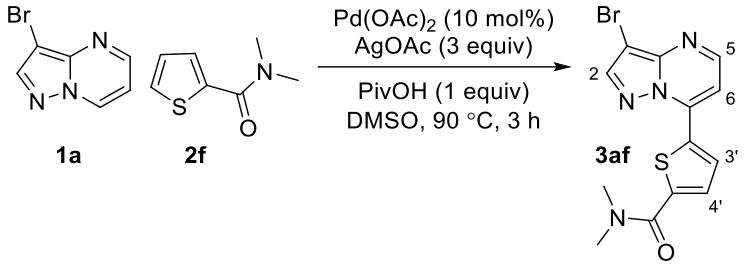
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 4.0 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





5-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-*N*,*N*-dimethylthiophene-2-carboxamide (**3af**)

Following general procedure 1 using **1a** (40 mg, 0.2 mmol), **2f** (62 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by preparative HPLC on a Kromasil C8 250x20 mm, 10µm, column using a gradient of 15-80% of MeCN in an acid buffer (H_2O/MeCN/FA 95/5/0.2).

Yield: 47 mg, 66%, yellow solid.

HRMS: $C_{13}H_{11}BrN_4OS$ calc.: 350.9915 (M+H), found: 350.9911

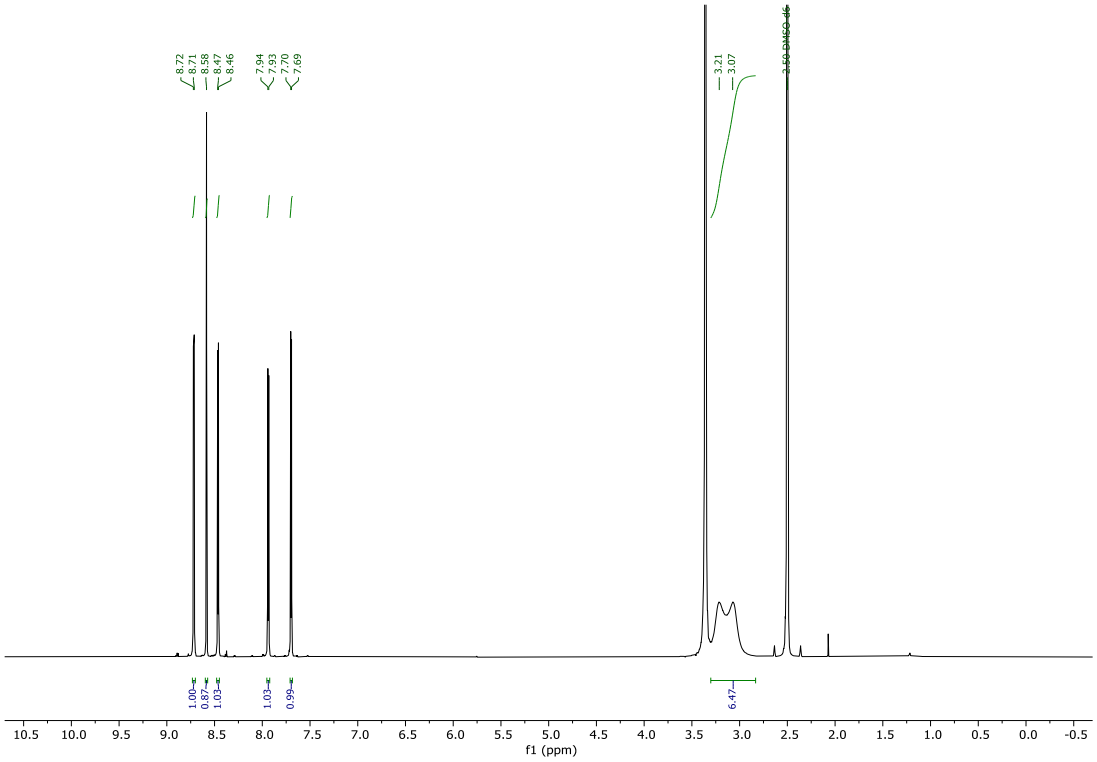
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (d, *J* = 4.7 Hz, 1H, H5), 8.57 (s, 1H, H2), 8.45 (d, *J* = 4.1 Hz, 1H, H3'), 7.92 (d, *J* = 4.7 Hz, 1H, H6), 7.69 (d, *J* = 4.1 Hz, 1H, H4'), 3.14 (br.s, 6H, NMe_2).

^{13}C NMR (126 MHz, DMSO-d_6) δ 163.0, 150.6, 146.1, 145.5, 144.5, 139.6, 132.1, 131.9, 129.6, 105.9, 84.5. (The NMe_2 carbons were not observed)

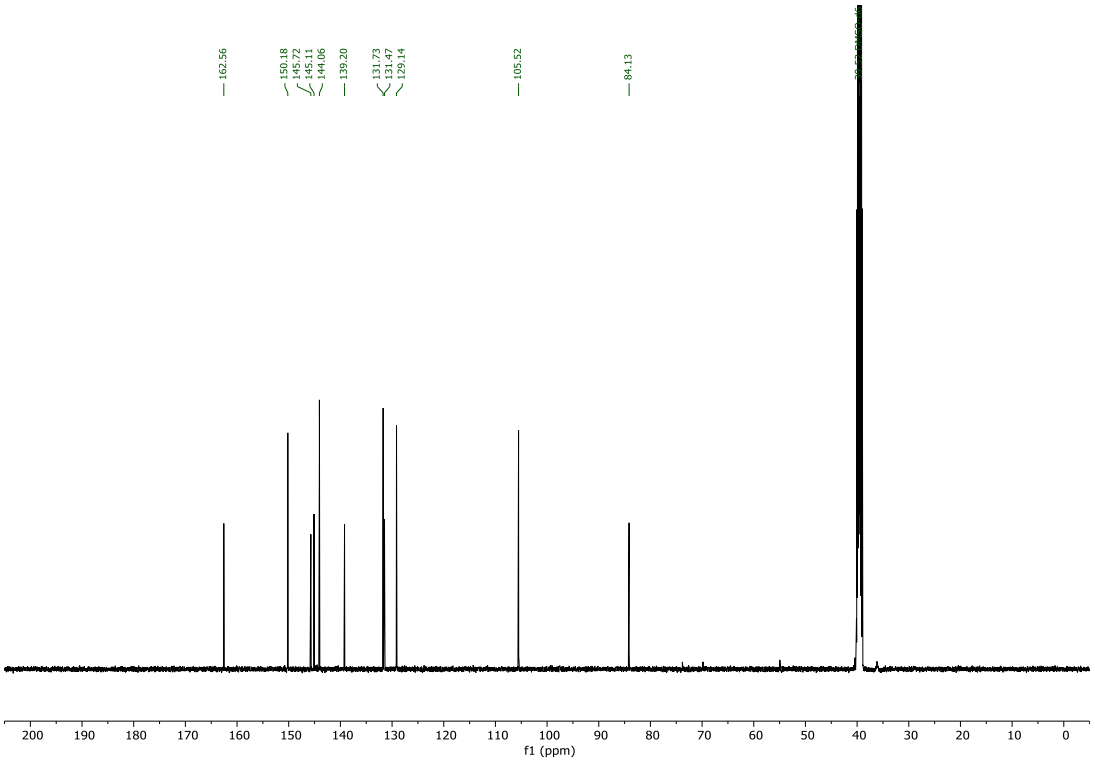
Structure determination:

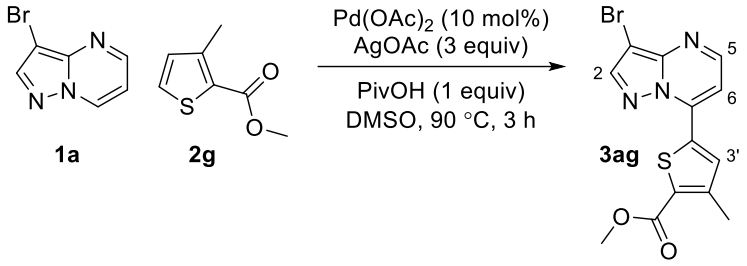
Coupling constant: H5 and H6 have coupling constant *J* = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 4.1 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





methyl 5-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-3-methylthiophene-2-carboxylate (**3ag**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2g** (63 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 25 mg, 35%, yellow solid.

HRMS: $C_{13}H_{10}BrN_3O_2S$ calc.: 351.9755 (M+H), found: 351.9759

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.6, Hz, 1H, H5), 8.27 (s, 1H, H2), 8.05 – 8.06 (m, 1H, H3'), 7.33 (d, *J* = 4.6 Hz, 1H, H6), 3.93 (s, 3H, OCH_3), 2.65 (s, 3H, CH_3).

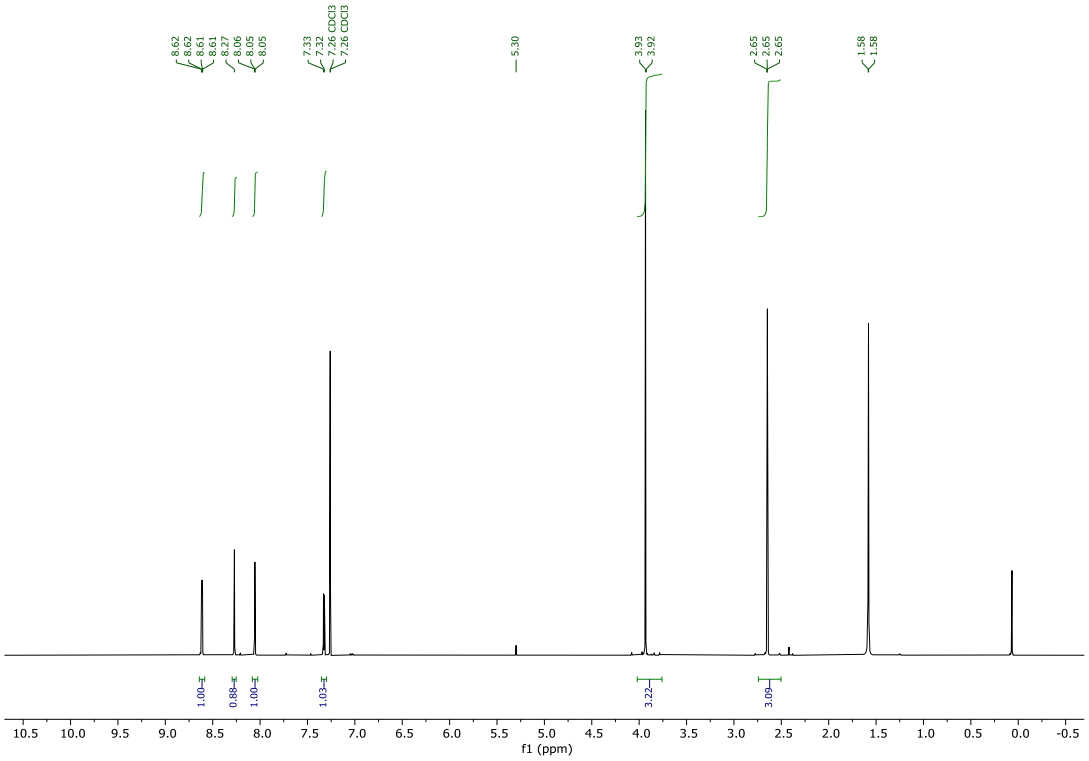
^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 149.1, 146.4, 145.7, 144.3, 139.6, 134.7, 133.0, 132.5, 105.2, 85.4, 52.2, 16.0.

Structure determination:

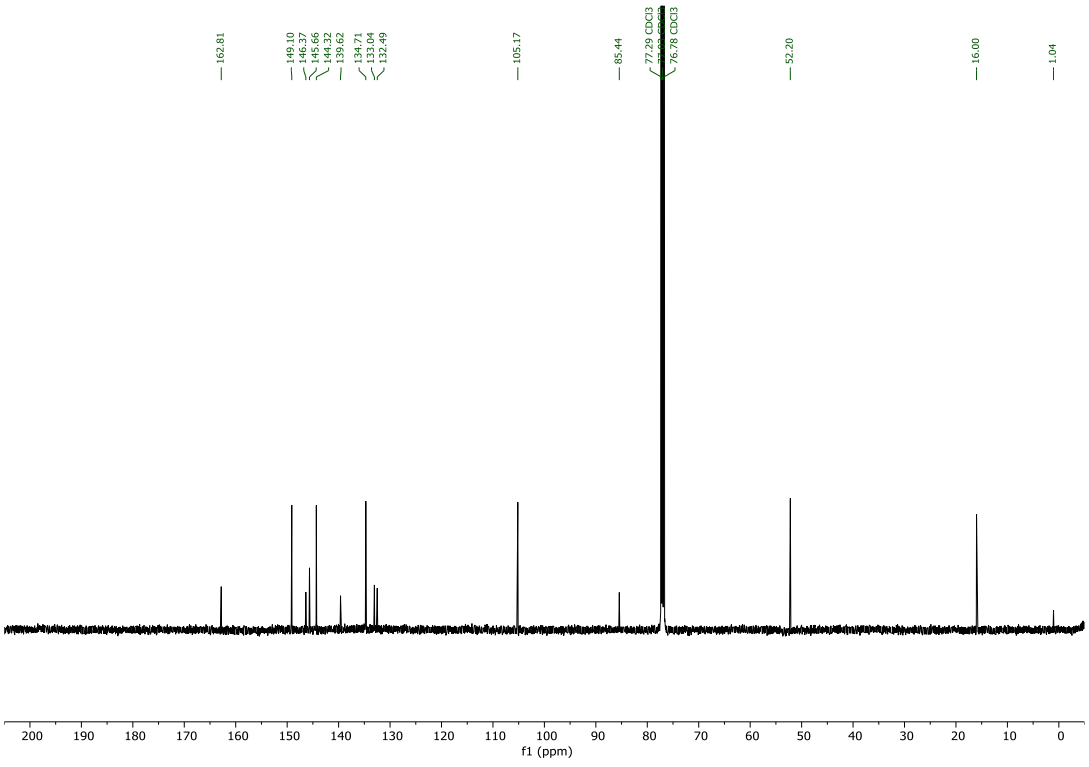
Coupling constant: H5 and H6 have coupling constant *J* = 4.6 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

NOE: H3' has NOE correlation with H6 and CH_3.

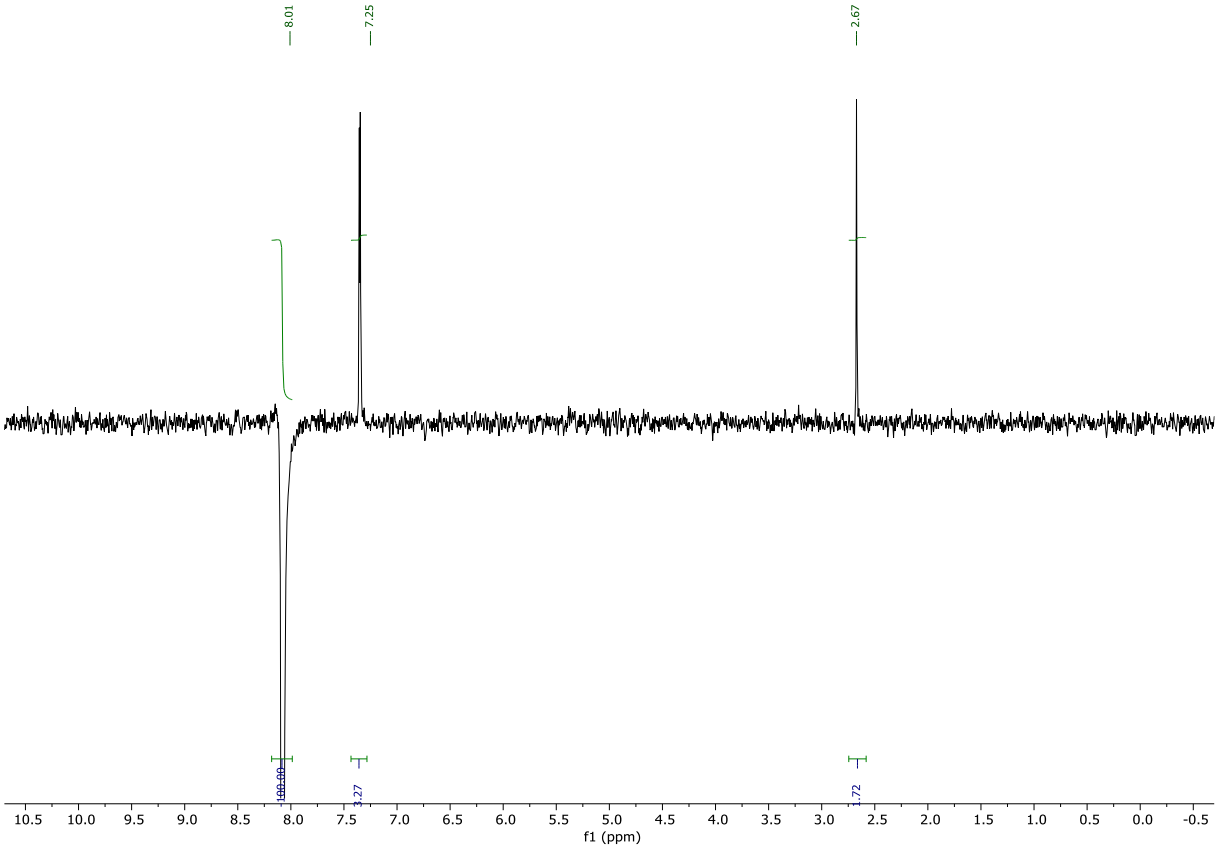
^{1}H NMR

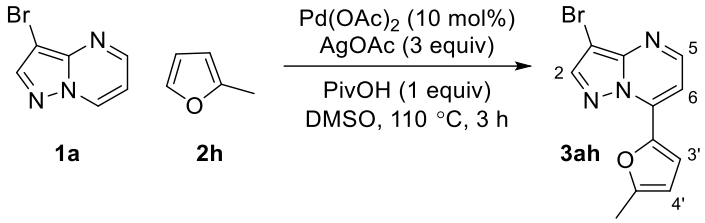


^{13}C NMR



Selective NOE





3-bromo-7-(5-methylfuran-2-yl)pyrazolo[1,5-*a*]pyrimidine (**3ah**)

Following the general procedure 1 (temperature increased to 110 °C) using **1a** (40 mg, 0.2 mmol), **2a** (33 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 7.5 mg, 14%, yellow solid.

HRMS: $C_{11}H_8BrN_3O$ calc.: 277.9929 (M+H), found: 277.9939

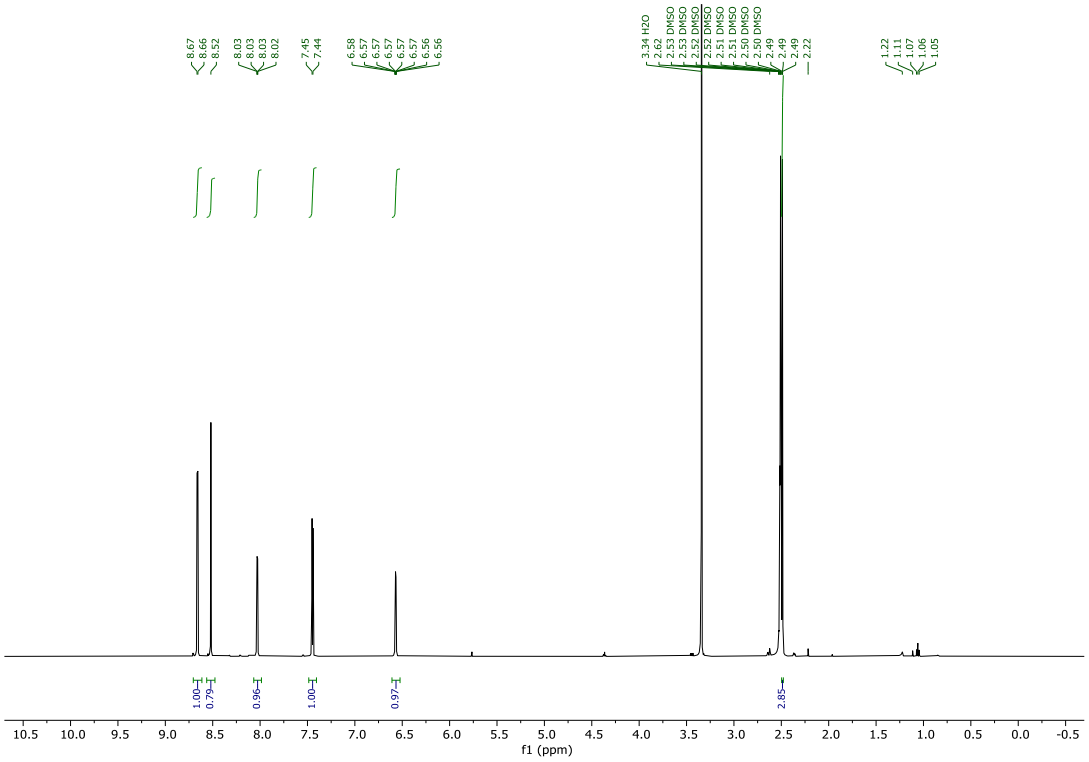
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (d, *J* = 4.6 Hz, 1H, H5), 8.52 (s, 1H, H2), 8.03 (d, *J* = 3.5, 1H, H3'), 7.45 (d, *J* = 4.6 Hz, 1H, H6), 6.57 (dq, *J* = 3.0, 0.9 Hz, 1H, H4'), 2.49 (s, 3H).

^{13}C NMR (126 MHz, DMSO-d_6) δ 157.5, 150.0, 145.6, 144.4, 141.2, 135.3, 121.7, 110.3, 102.8, 83.8, 13.7.

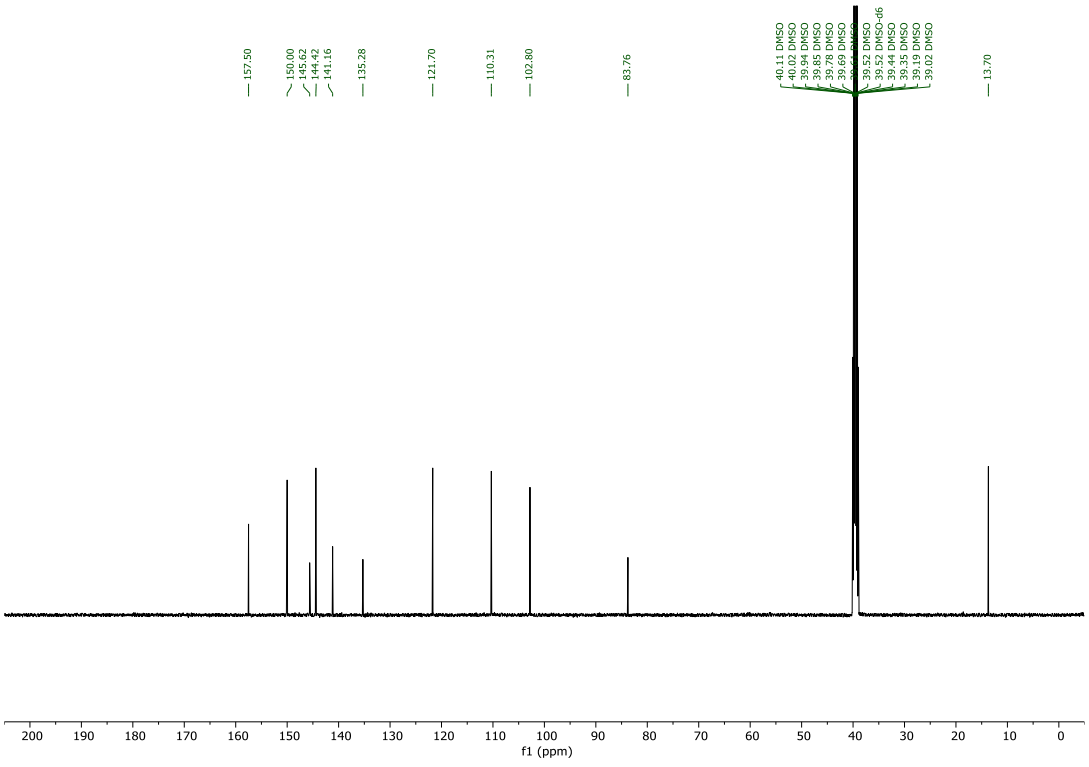
Structure determination:

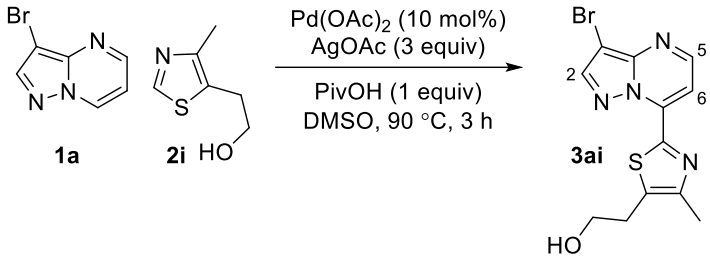
Coupling constant: H5 and H6 have coupling constant *J* = 4.6 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.5 Hz characteristic for C2,C5-substituted furans.

^{1}H NMR



^{13}C NMR





2-(2-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-4-methylthiazol-5-yl)ethan-1-ol (**3ai**)

Following general procedure 1 using **1a** (40 mg, 0.2 mmol), **2i** (57 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by preparative HPLC on a Kromasil C8 250x20 mm, 10µm, column using a gradient of 15-80% of MeCN in an acid buffer (H_2O/MeCN/FA 95/5/0.2).

Yield: 37 mg, 54%, yellow solid.

HRMS: $C_{12}H_{11}BrN_4OS$ calc.: 338.9915 (M+H), found: 338.9935

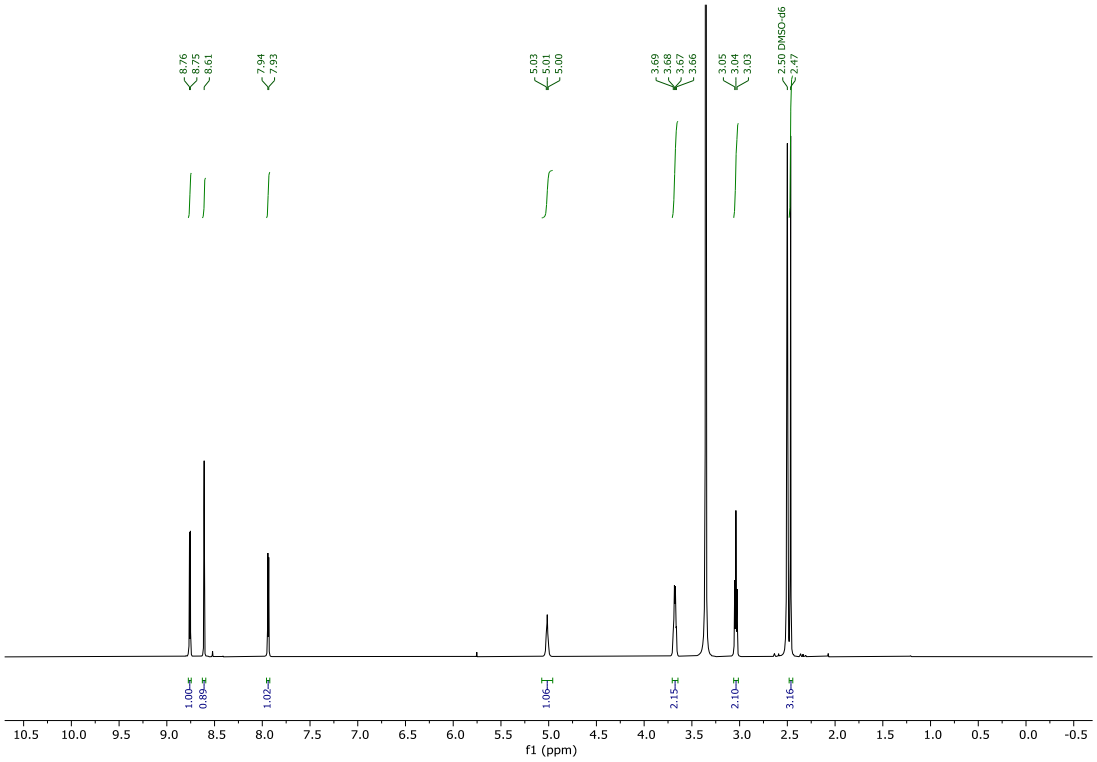
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.76 (d, J = 4.5 Hz, 1H, H5), 8.61 (s, 1H, H2), 7.94 (d, J = 4.5 Hz, 1H, H6), 5.01 (t, J = 4.3 Hz, 1H, $CH_2CH_2\underline{OH}$), 3.68 (q, J = 5.6 Hz, 2H, $CH_2\underline{CH_2}OH$), 3.04 (t, J = 6.1 Hz, 2H, $\underline{CH_2}CH_2OH$), 2.47 (s, 3H, $\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 151.2, 150.8, 148.8, 146.1, 144.6, 139.2, 138.5, 105.4, 84.8, 61.3, 30.2, 15.4.

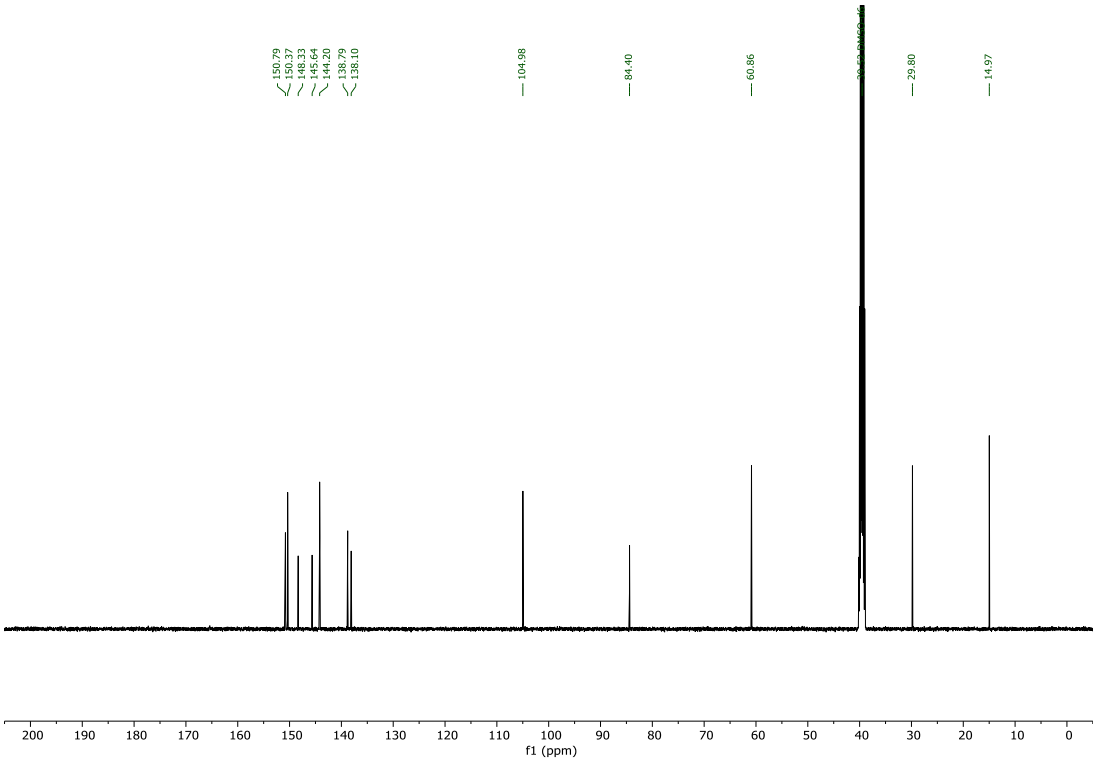
Structure determination:

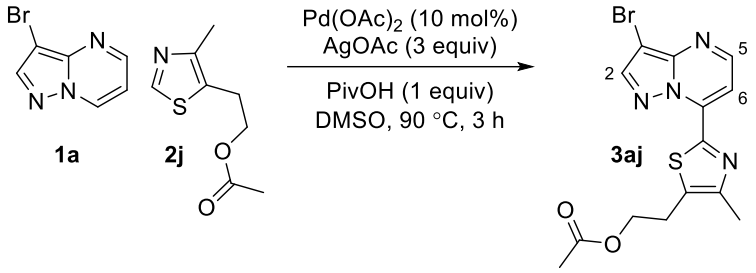
Coupling constant: H5 and H6 have coupling constant J = 4.5 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

^{1}H NMR



^{13}C NMR





2-(2-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-4-methylthiazol-5-yl)ethyl acetate (**3aj**)

Following general procedure 1 using **1a** (40 mg, 0.2 mmol), **2j** (74 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by preparative HPLC on a Kromasil C8 250x20 mm, 10µm, column using a gradient of 15-85% of MeCN in an acid buffer (H_2O/MeCN/FA 95/5/0.2).

Yield: 17 mg, 22%, yellow solid.

HRMS: $C_{14}H_{13}BrN_4O_2S$ calc.: 381.0021 (M+H), found: 381.0030

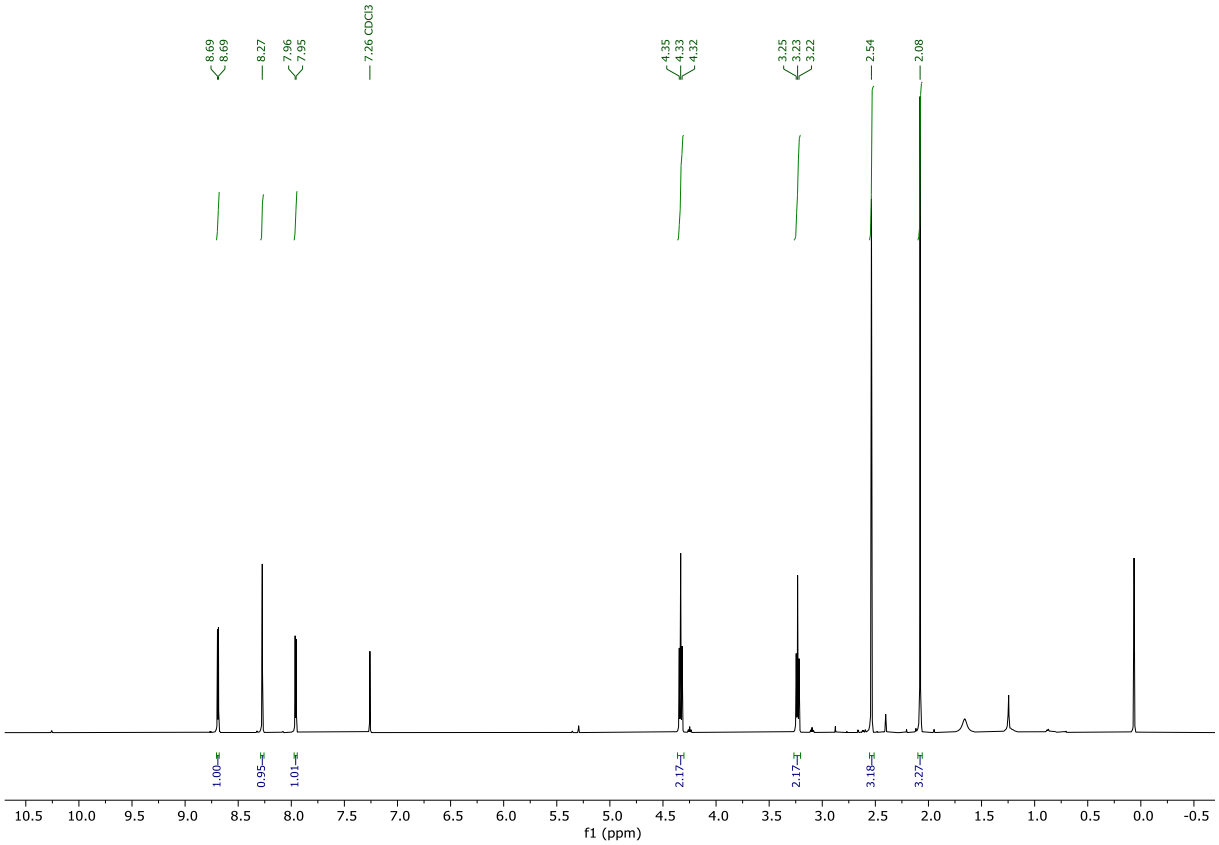
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, *J* = 4.5 Hz, 1H, H5), 8.27 (s, 1H, H2), 7.96 (d, *J* = 4.5 Hz, 1H, H6), 4.33 (t, *J* = 6.6 Hz, 2H, $CH_2\underline{CH_2}OAc$), 3.23 (t, *J* = 6.6 Hz, 2H, $\underline{CH_2}CH_2OAc$), 2.54 (s, 3H, $\underline{CH_3}$), 2.08 (s, 3H, $OCO\underline{CH_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 151.8, 149.6, 149.5, 146.1, 144.1, 138.7, 135.9, 105.1, 85.5, 63.9, 26.2, 20.9, 15.1.

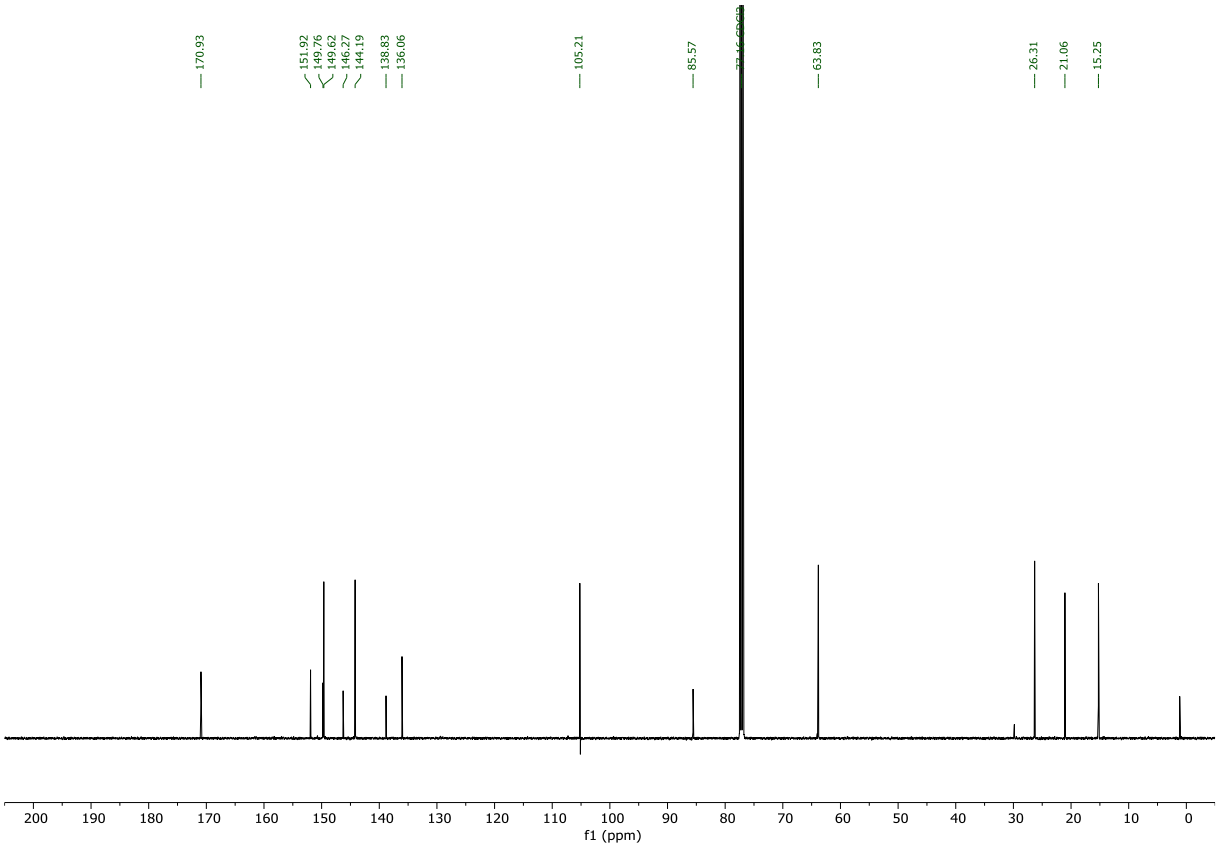
Structure determination:

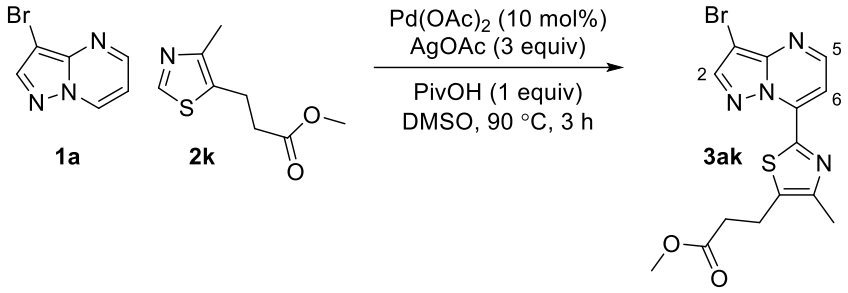
Coupling constant: H5 and H6 have coupling constant *J* = 4.5 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

^{1}H NMR



^{13}C NMR





methyl 3-(2-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-4-methylthiazol-5-yl)propanoate (**3ak**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2k** (75 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 35 mg, 45%, yellow solid.

HRMS: $C_{14}H_{13}BrN_4O_2S$ calc.: 381.0021 (M+H), found: 381.0012

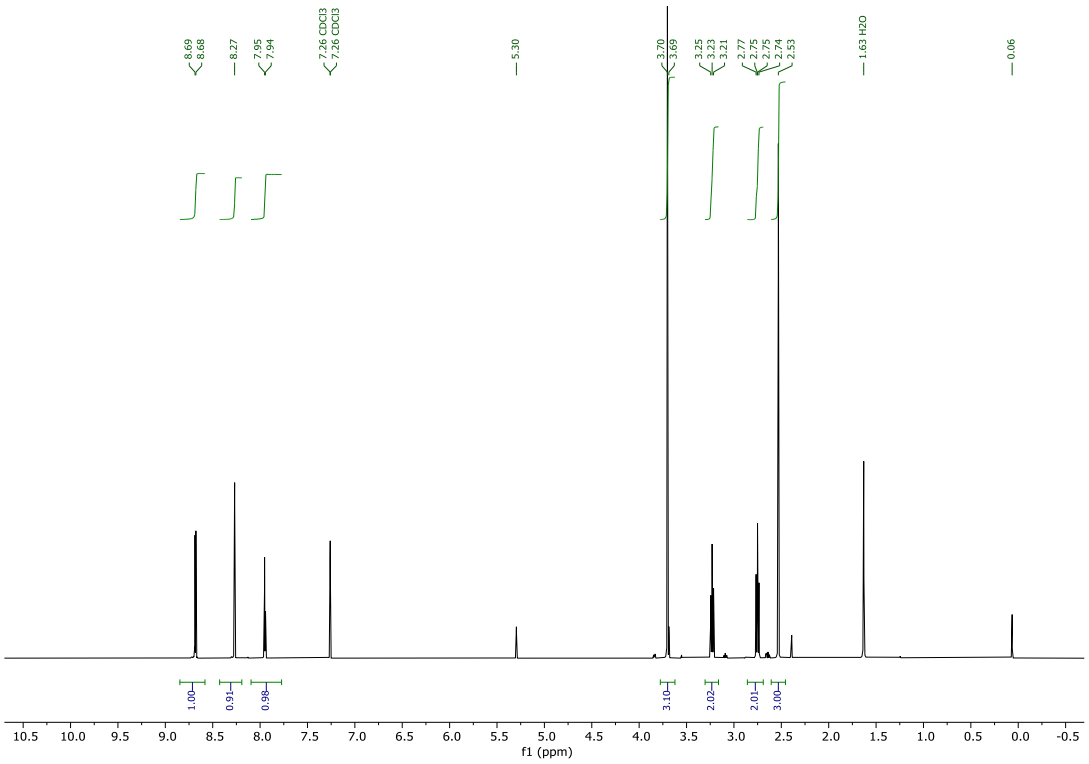
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.5 Hz, 1H, H5), 8.27 (s, 1H, H2), 7.95 (d, *J* = 4.5 Hz, 1H, H6), 3.70 (s, 3H, OCH_3), 3.23 (t, *J* = 7.5 Hz, 2H, CH_2), 2.75 (t, *J* = 7.5 Hz, 2H, CH_2), 2.53 (s, 3H, CH_3).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 151.2, 149.5, 149.2, 146.2, 144.1, 139.0, 105.0, 105.0, 85.4, 52.0, 35.3, 22.0, 15.0.

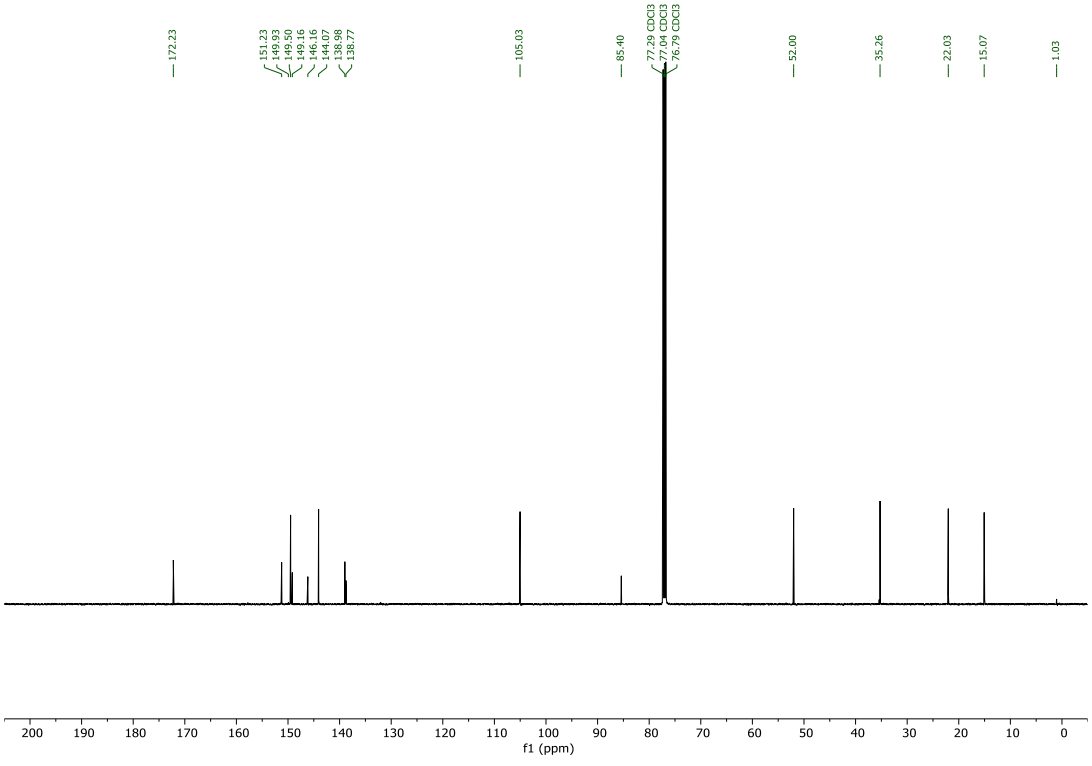
Structure determination:

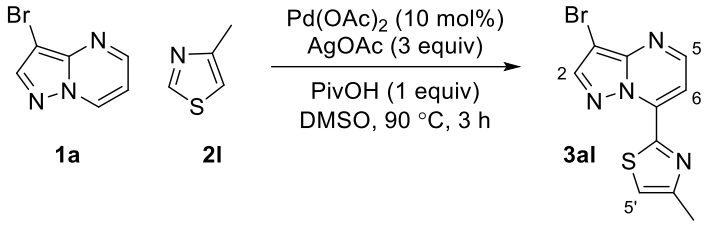
Coupling constant: H5 and H6 have coupling constant *J* = 4.5 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

^{1}H NMR



^{13}C NMR





2-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-4-methylthiazole (**3al**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2l** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 7% to 60% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 25 mg, 42%, yellow solid.

HRMS: $C_{10}H_7BrN_4S$ calc.: 294.9653 (M+H), found: 294.9668

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (d, J = 4.6 Hz, 1H, H5), 8.66 (s, 1H, H2), 8.03 (d, J = 4.5 Hz, 1H, H6), 7.93 – 7.97 (m, 1H, H5'), 2.57 (d, J = 0.8 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 154.1, 152.0, 150.4, 145.6, 144.3, 137.8, 123.3, 105.8, 84.6, 16.8.

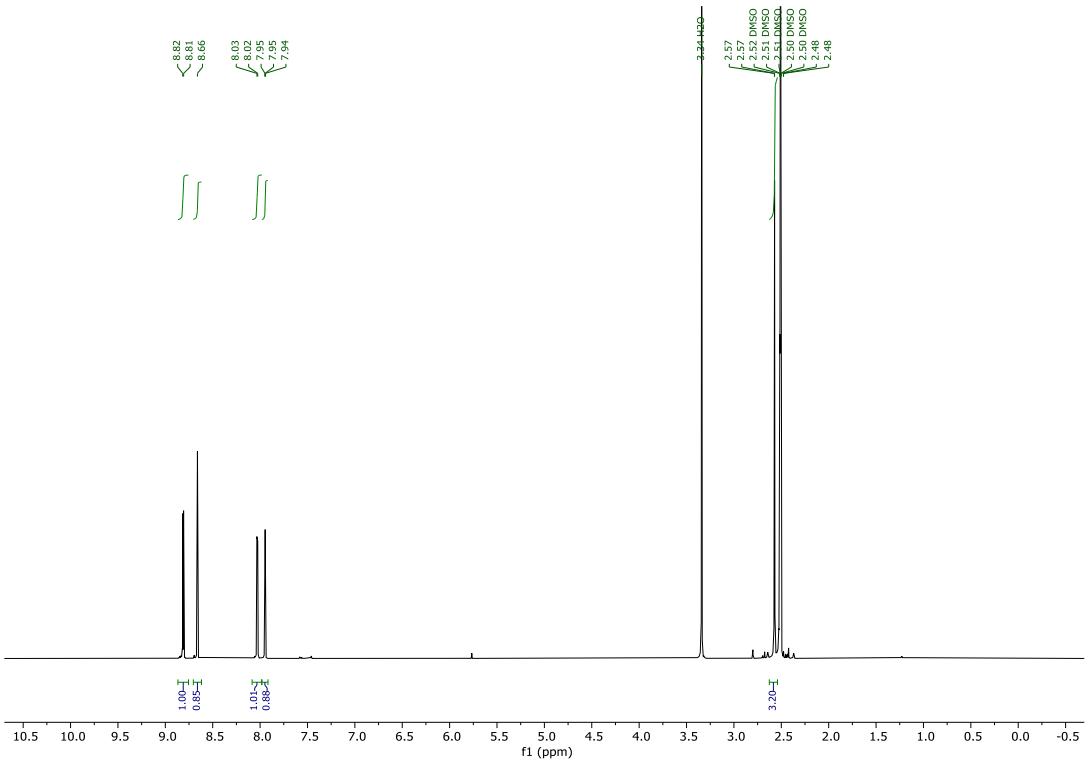
Structure determination:

Coupling constant: H5 and H6 have coupling constant J = 4.6 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

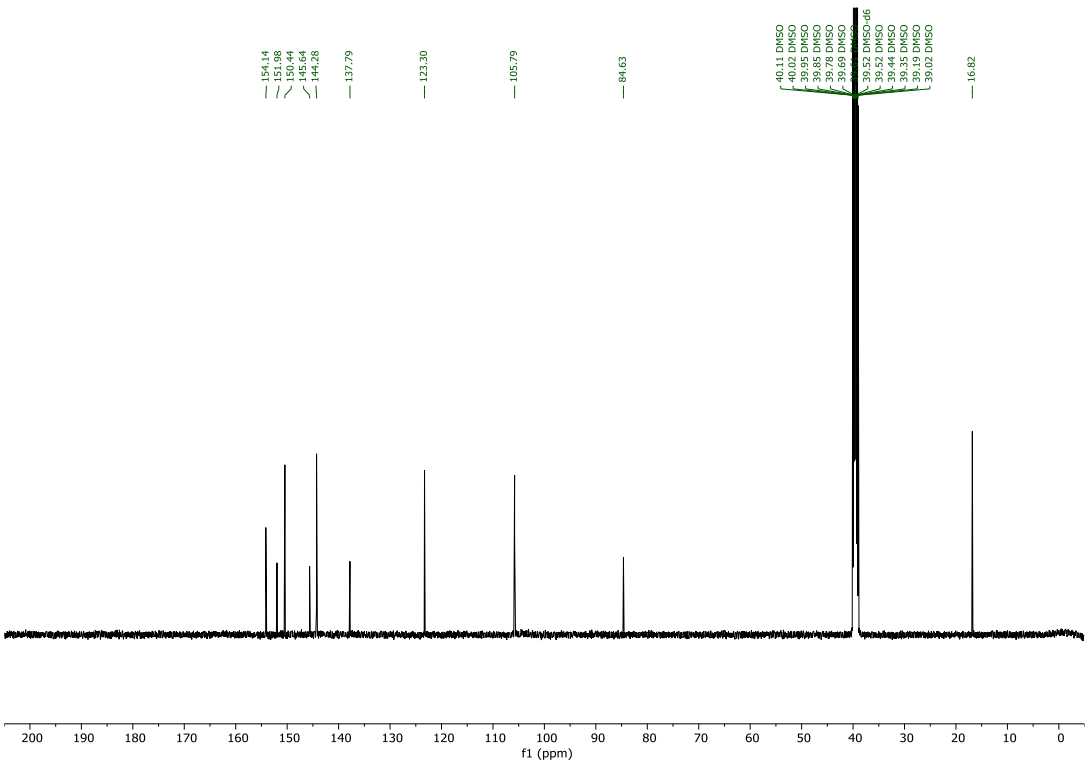
HSQC: C-5' 123.3 ppm, C (CH_3) 16.8 ppm.

HMBC: C/H5' has a correlation with H/C CH_3.

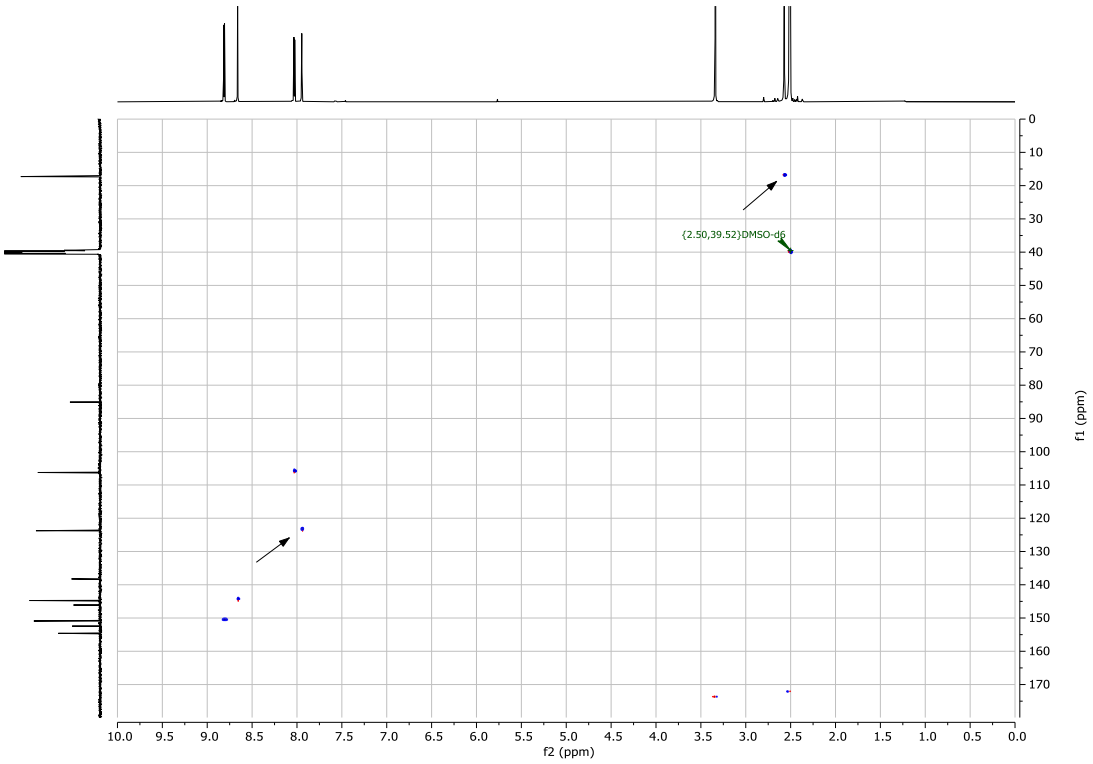
^{1}H NMR



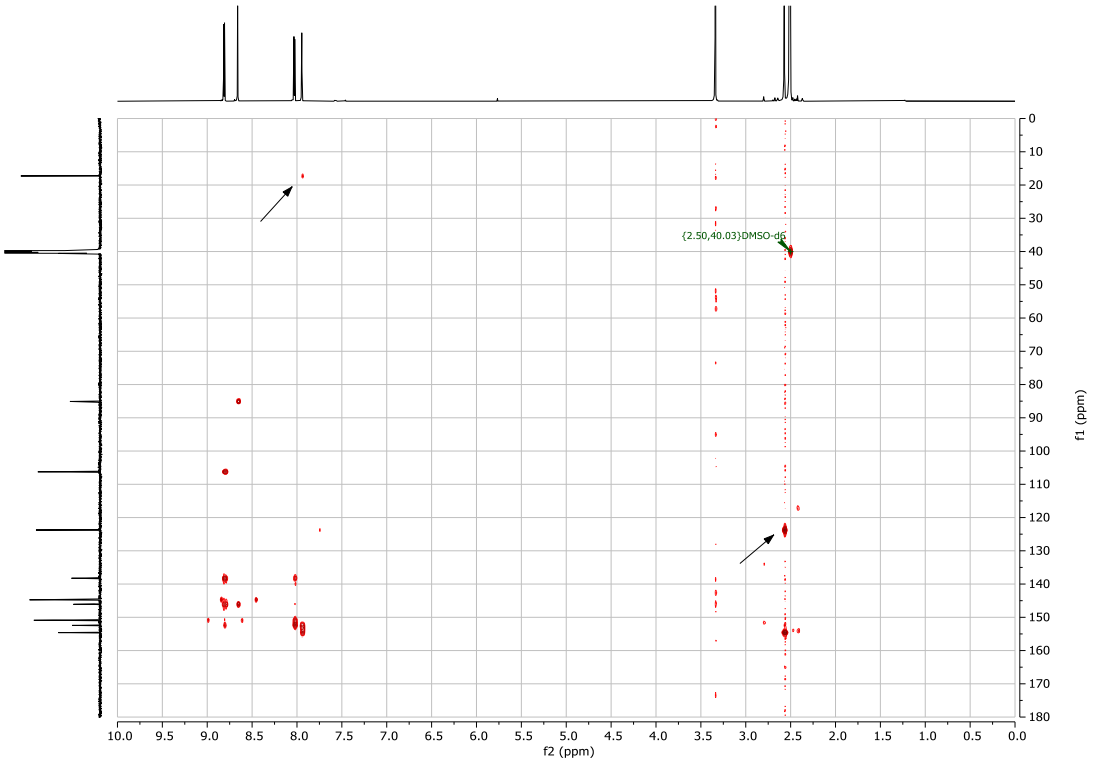
^{13}C NMR

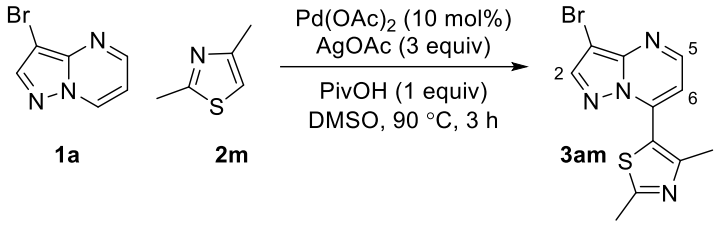


HSQC



HMBC





5-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-2,4-dimethylthiazole (**3am**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2m** (46 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc:EtOH 3:1 in heptane over 10 CV as mobile phase.

Yield: 28 mg, 45%, yellow solid.

HRMS: $C_{11}H_9BrN_4S$ calc.: 308.9810 (M+H), found: 308.9814

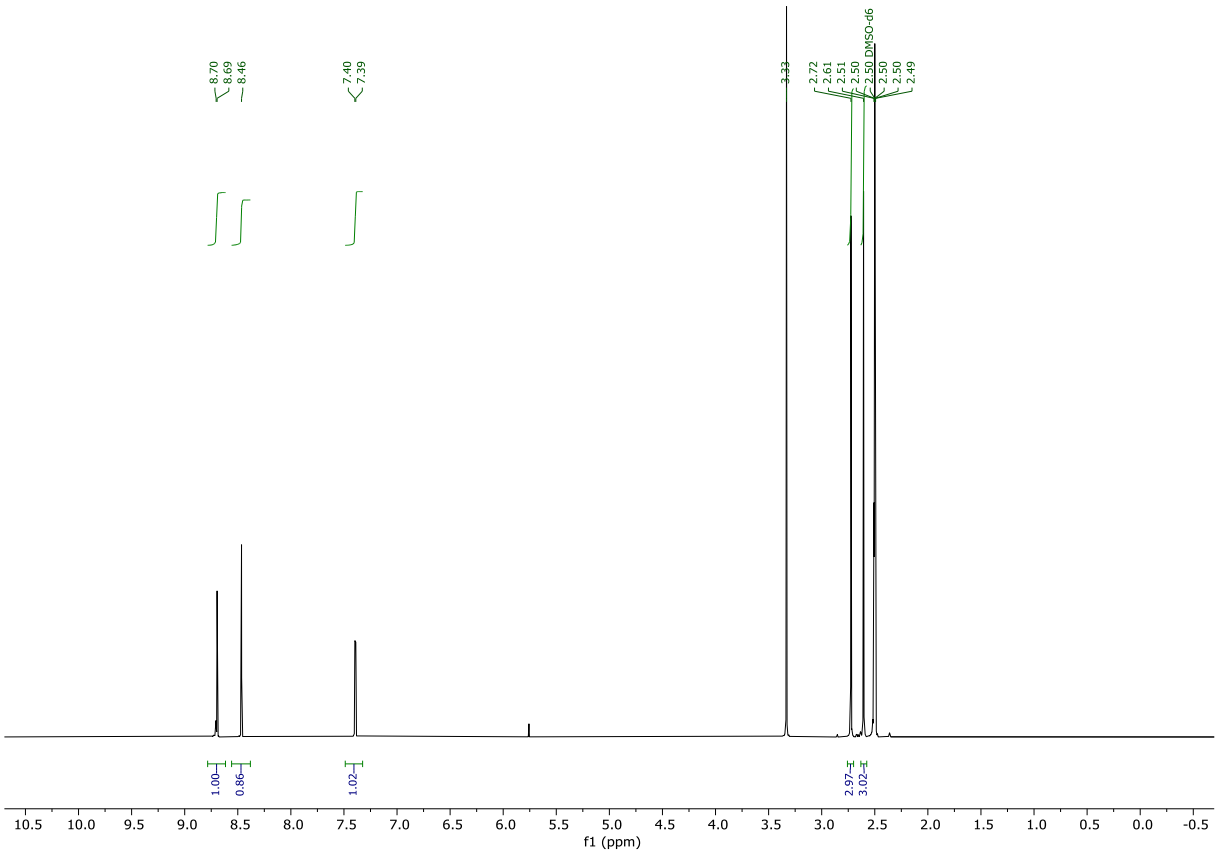
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, J = 4.5 Hz, 1H, H5), 8.47 (s, 1H, H2), 7.39 (d, J = 4.5 Hz, 1H, H6), 2.73 (s, 3H, CH_3), 2.61 (s, 3H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 169.0, 156.1, 150.4, 145.5, 143.7, 139.4, 117.9, 108.9, 84.1, 18.6, 18.0.

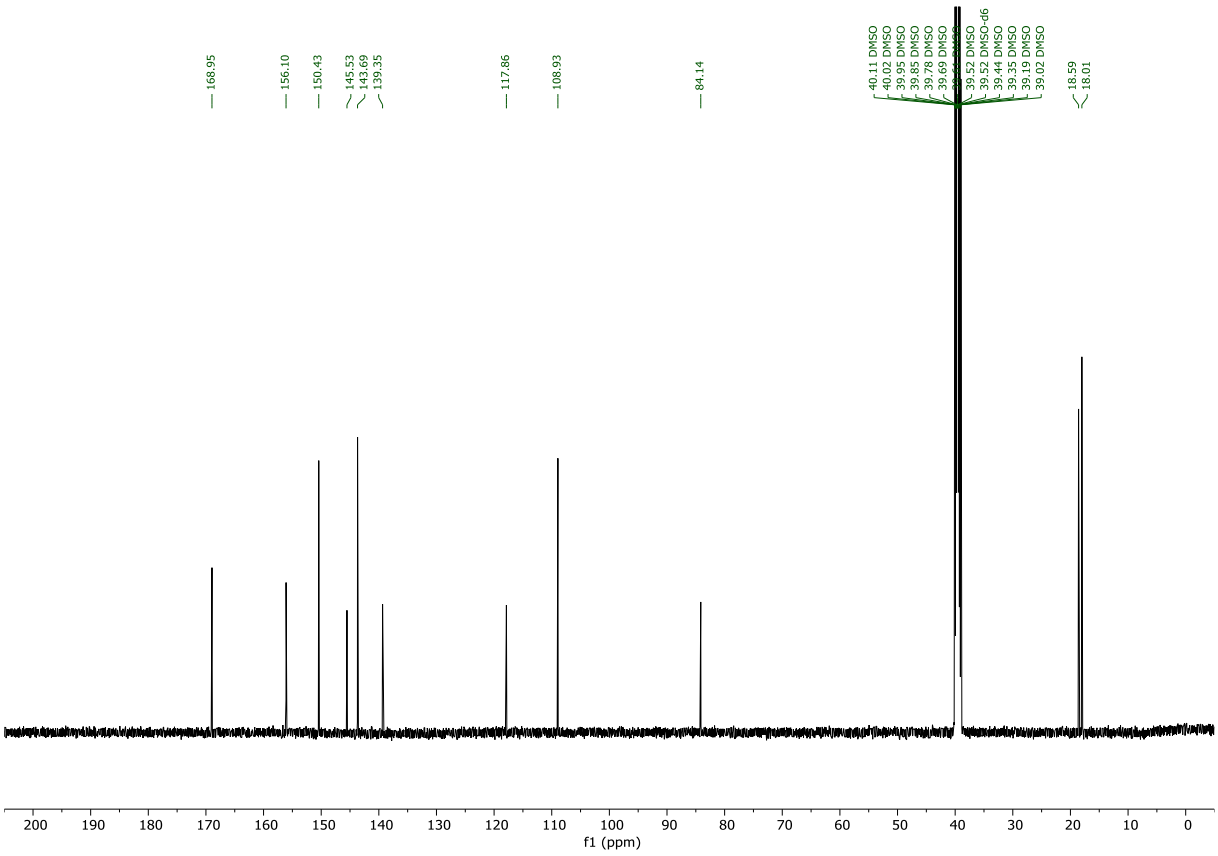
Structure determination:

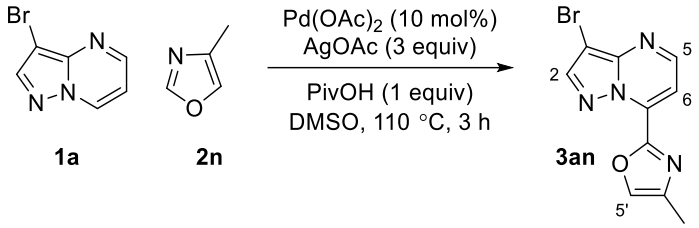
Coupling constant: H5 and H6 have coupling constant J = 4.5 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

^{1}H NMR



^{13}C NMR





2-(3-bromopyrazolo[1,5-*a*]pyrimidin-7-yl)-4-methyloxazole (**3an**)

Following general procedure 1 using **1a** (38 mg, 0.2 mmol), **2n** (33 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol) at 110 °C. The crude material was purified by preparative HPLC on a Kromasil C8 250x20 mm, 10µm, column using a gradient of 25-75% of MeCN in an acid buffer (H_2O/MeCN/FA 95/5/0.2).

Yield: 14 mg, 25%, yellow solid.

HRMS: $C_{10}H_7BrN_4O$ calc.: 278.9881 (M+H), found: 278.9893

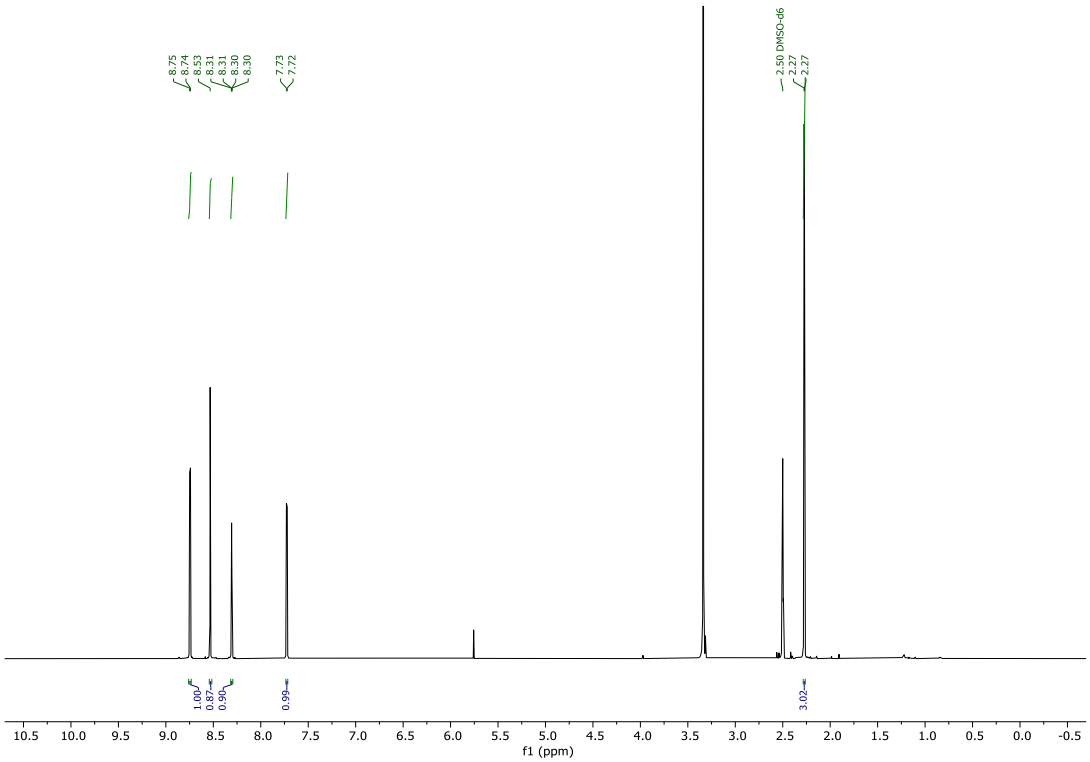
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (d, J = 4.4 Hz, 1H, H5), 8.53 (s, 1H, H2), 8.31 (q, J = 1.1 Hz, 1H, H5'), 7.73 (d, J = 4.4 Hz, 1H, H6), 2.27 (d, J = 1.1 Hz, 3H, CH_3).

^{13}C NMR (126MHz, DMSO-d_6) δ 152.7, 150.7, 146.5, 145.3, 139.4, 139.1, 133.4, 109.2, 85.1, 11.8.

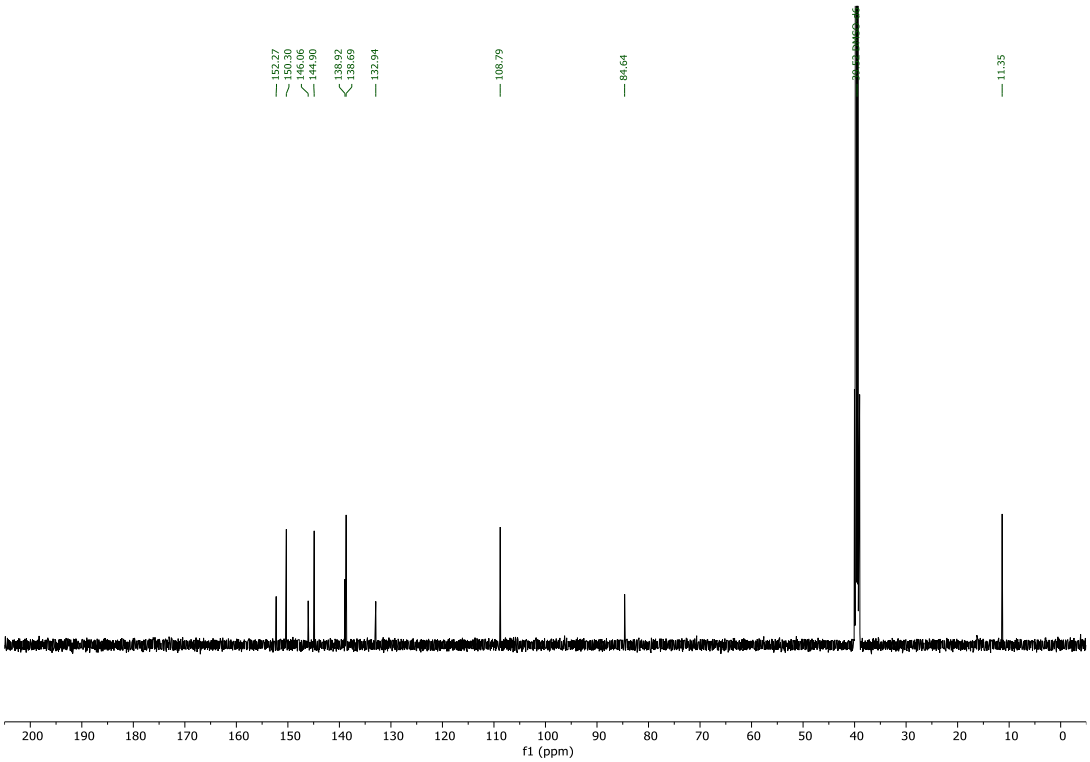
Structure determination:

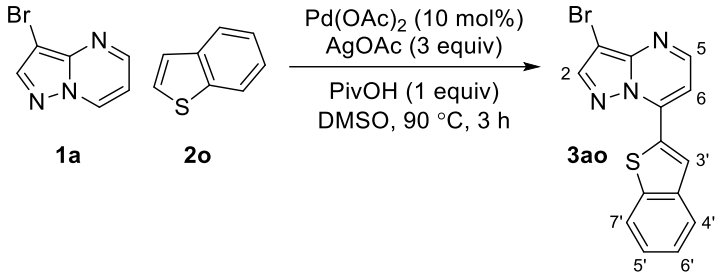
Coupling constant: H5 and H6 have coupling constant J = 4.4 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. Coupling observed between H5' and adjacent CH_3 (1.1 Hz).

^{1}H NMR



^{13}C NMR





7-(benzo[b]thiophen-2-yl)-3-bromopyrazolo[1,5-*a*]pyrimidine (**3ao**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2o** (54 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 7% to 60% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 46 mg, 69%, yellow solid.

HRMS: $C_{14}H_8BrN_3S$ calc.: 329.9700 (M+H), found: 329.9714

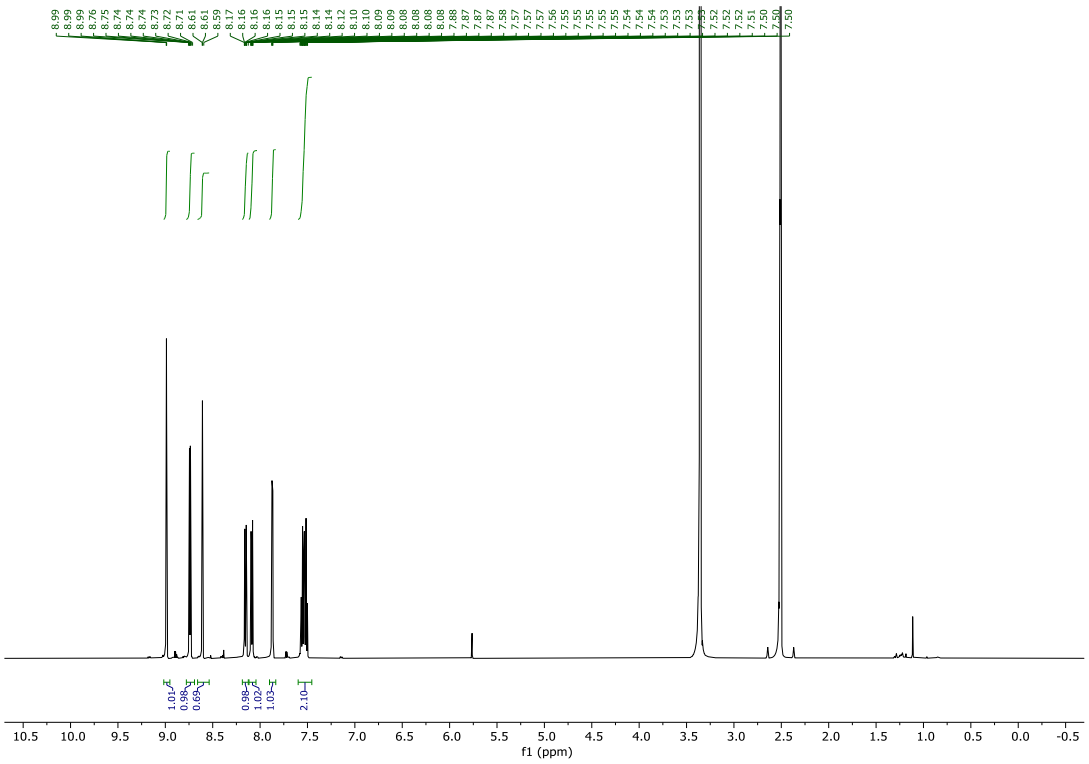
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (d, *J* = 0.8 Hz, 1H, H3'), 8.73 (d, *J* = 4.6 Hz, 1H, H5), 8.60 (s, 1H, H2), 8.12 – 8.18 (m, 1H, H4'), 8.08 (d, *J* = 7.0 Hz, 1H, H7'), 7.87 (d, *J* = 4.6 Hz, 1H, H6), 7.51 – 7.55 (m, 2H, H5' and H6').

^{13}C NMR (126 MHz, DMSO-d_6) δ 150.3, 146.0, 144.2, 141.7, 139.8, 138.3, 130.1, 130.0, 127.0, 125.4, 125.3, 122.6, 106.6, 84.2.

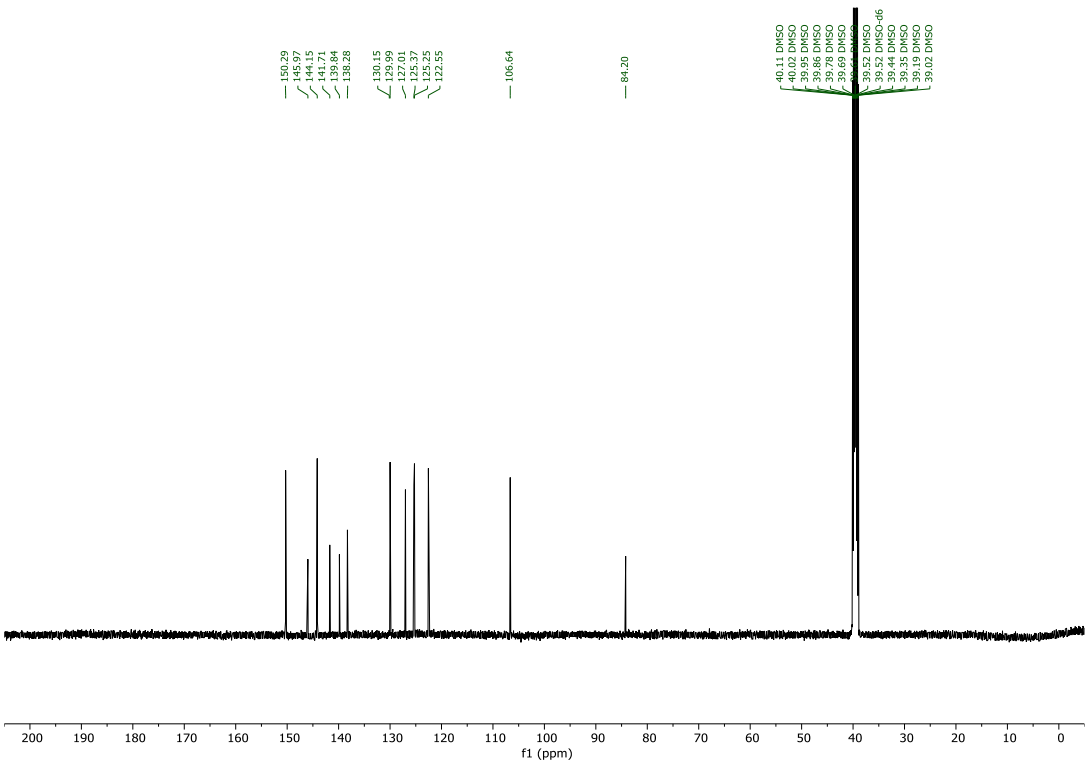
Structure determination:

COSY and coupling constant: H5 and H6 have coupling constant *J* = 4.6 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. NOE: H3' has NOE correlation with H6 and H4'.

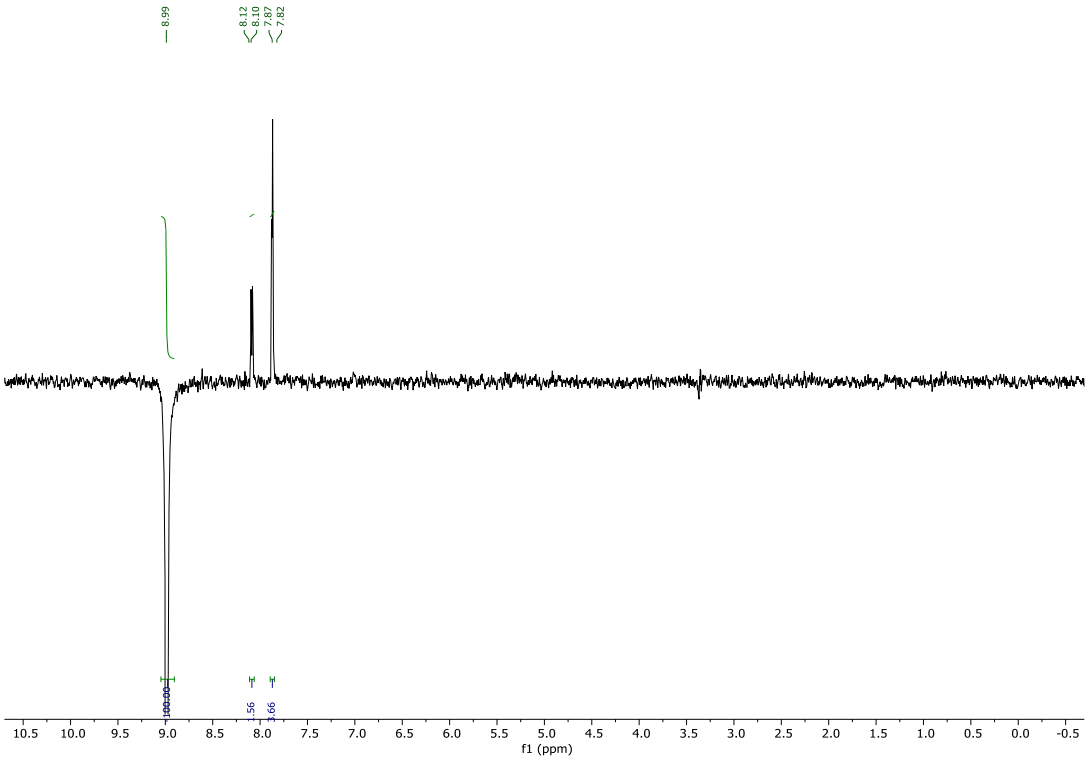
^{1}H NMR

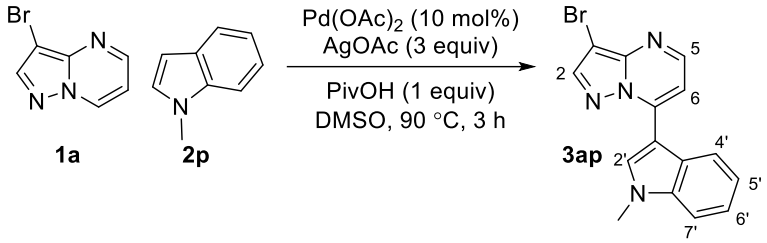


^{13}C NMR



Selective NOE





3-bromo-7-(1-methyl-1Hindol-3-yl)pyrazolo[1,5-*a*]pyrimidine (**3ap**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2p** (53 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 10% to 80% of EtOAc in heptane over 10 CV as mobile phase. Further purification by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 35 to 75% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 16 mg, 24%, yellow solid.

HRMS: $C_{15}H_{11}BrN_4$ calc.: 327.0245 (M+H), found: 327.0251

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.11 (s, 1H, H2'), 8.64 (d, J = 4.7 Hz, 1H, H5), 8.50 (s, 1H, H2), 8.19 (dt, J = 8.0, 1.0 Hz, 1H, H4'), 7.67 – 7.73 (m, 2H, H6 and H7'), 7.33 – 7.42 (m, 2H, H5' and H6'), 4.00 (s, 3H, CH_3).

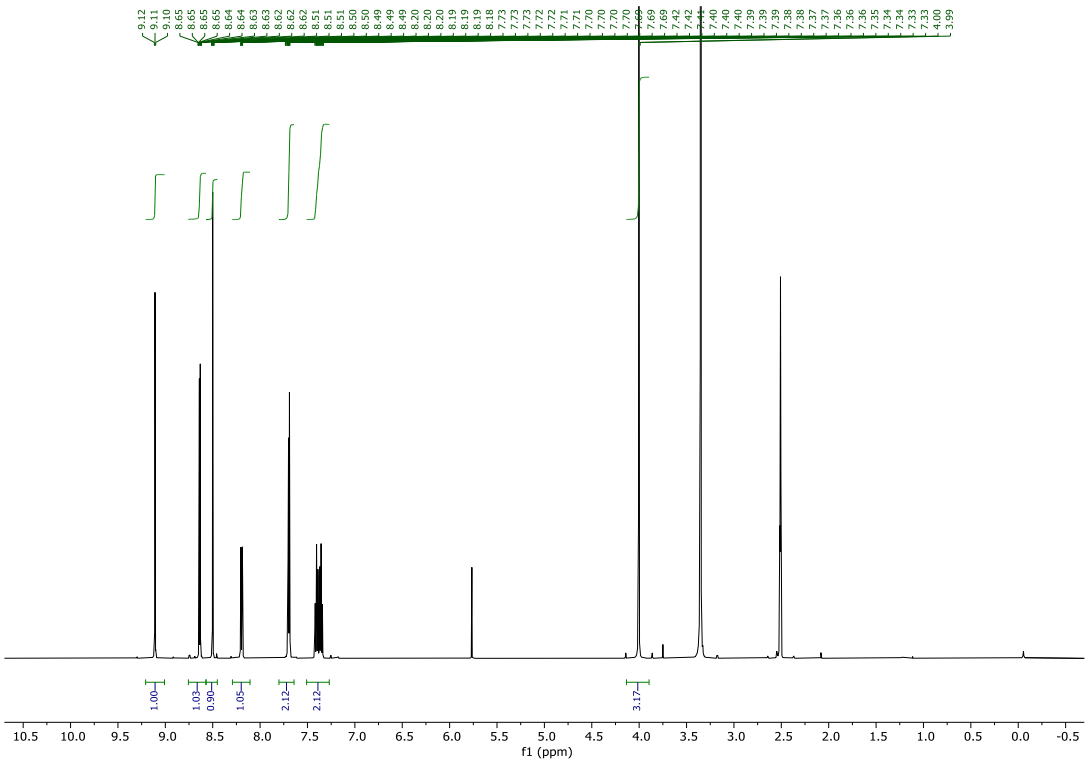
^{13}C NMR (126 MHz, DMSO-d_6) δ 150.1, 146.1, 143.6, 141.6, 137.1, 136.9, 125.3, 123.0, 122.0, 120.2, 111.3, 104.9, 102.7, 83.1, 33.4.

Structure determination:

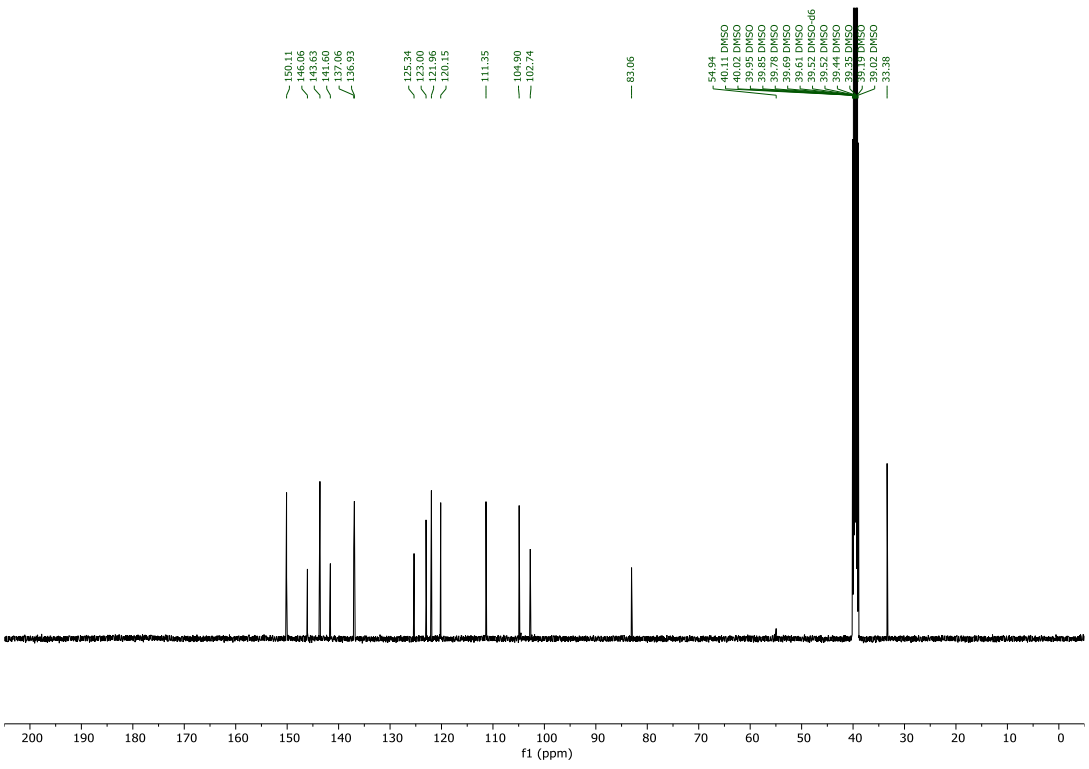
Coupling constant: H5 and H6 have coupling constant J = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

NOE: CH_3 has NOE correlation with H2' and H7'. H4' has NOE correlation with H6 and H5'.

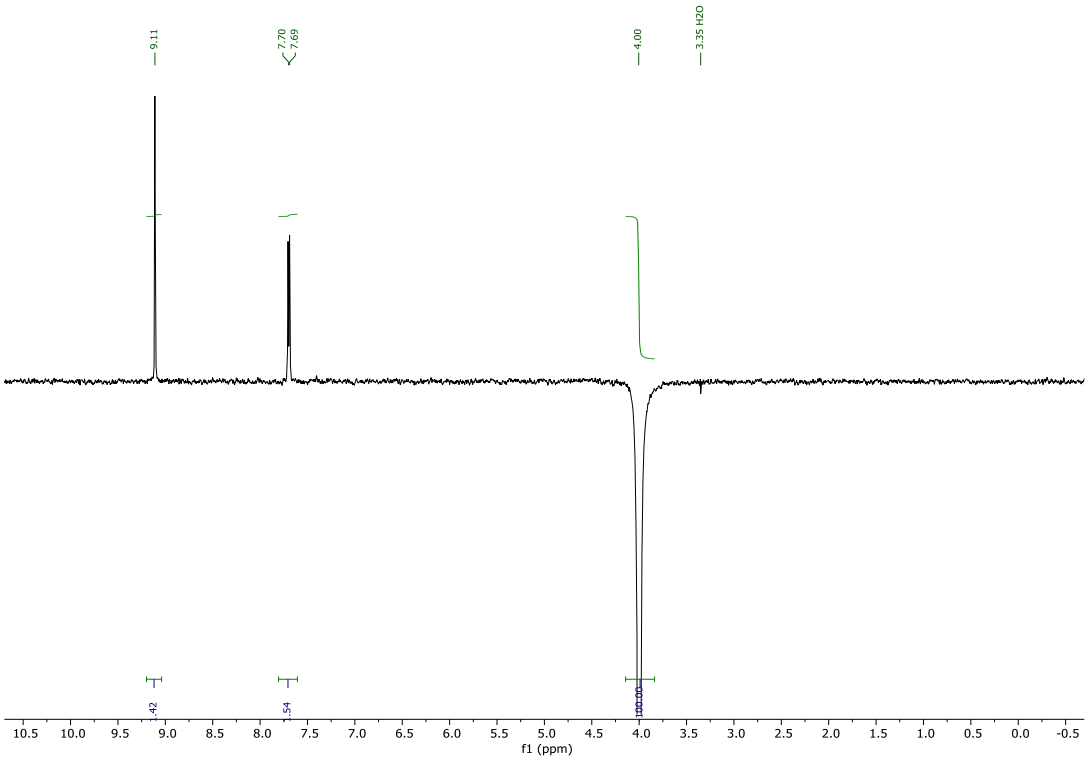
^{1}H NMR

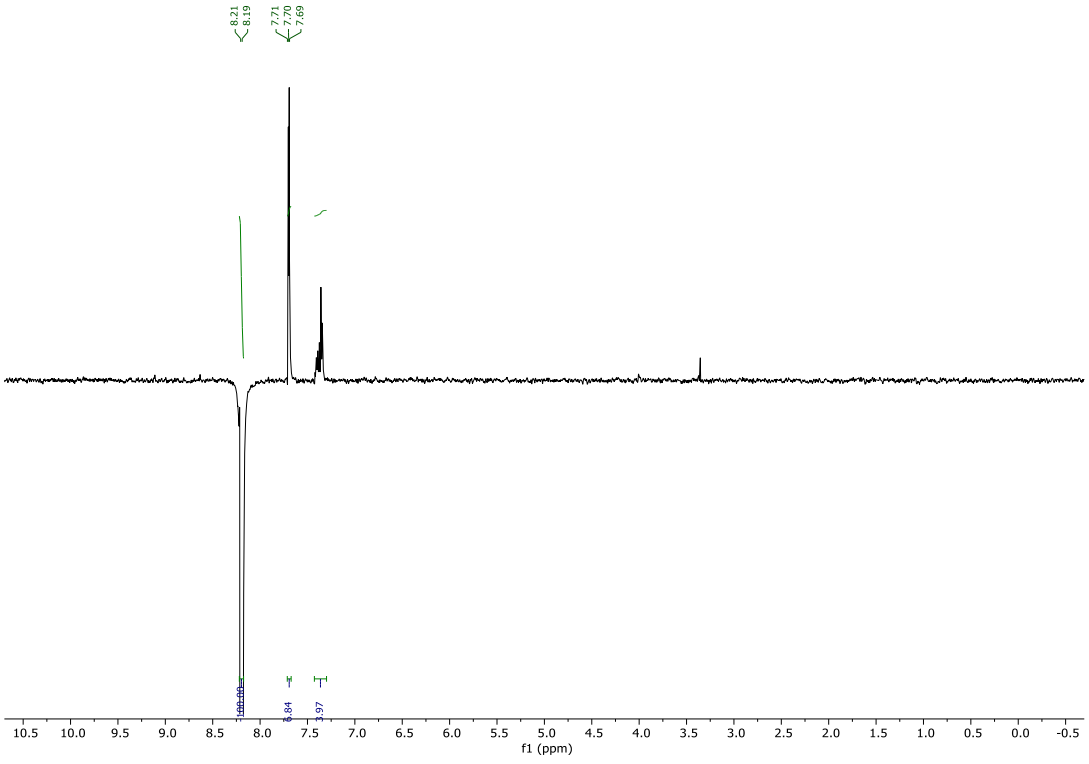


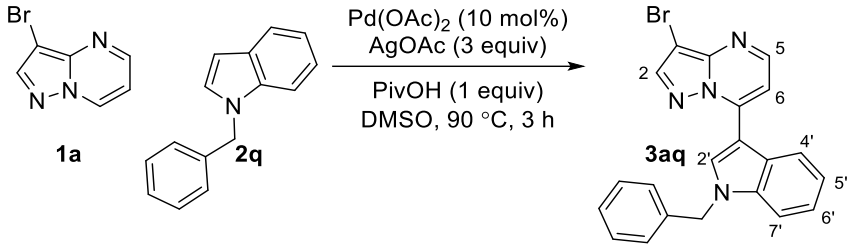
^{13}C NMR



Selective NOE







7-(1-benzyl-1Hindol-3-yl)-3-bromopyrazolo[1,5-*a*]pyrimidine (**3aq**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2q** (84 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 6% to 50% of EtOAc in heptane over 10 CV as mobile phase. Further purification by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 45 to 100% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 35 mg, 43%, yellow solid.

HRMS: $C_{21}H_{15}BrN_4$ calc.: 403.0558 (M+H), found: 403.0573

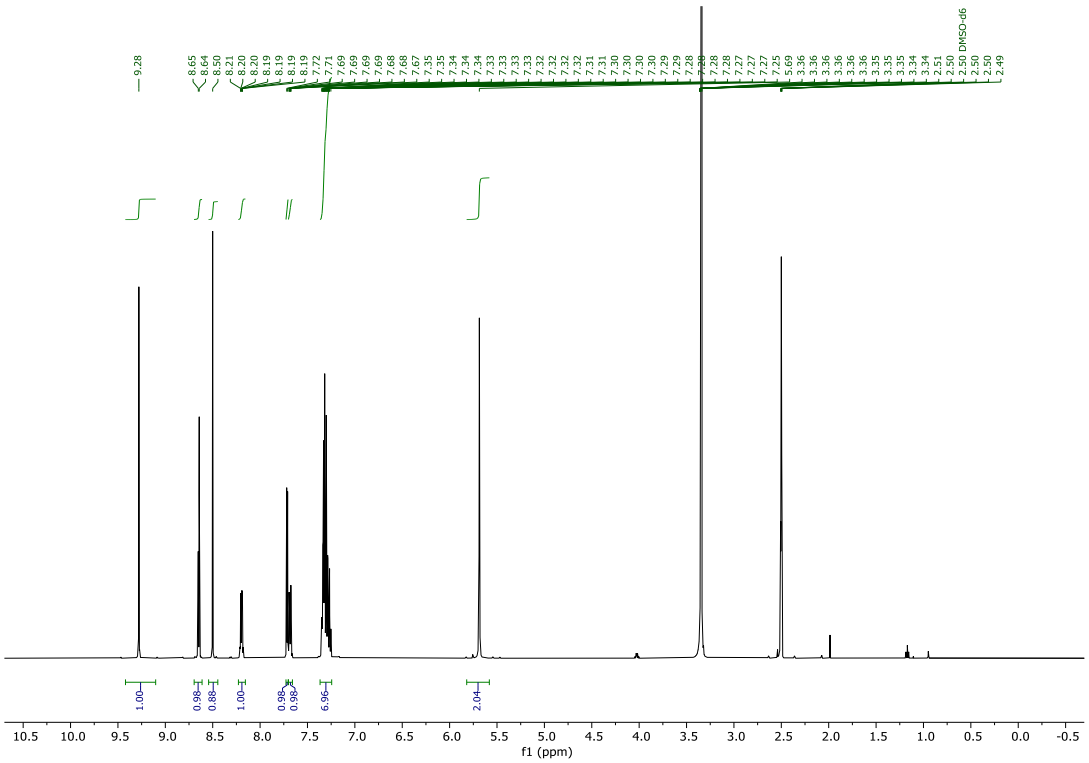
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.28 (s, 1H, H2'), 8.65 (d, J = 4.7 Hz, 1H, H5), 8.50 (s, 1H, H2), 8.16 – 8.23 (m, 1H, H4'), 7.71 (d, J = 4.8 Hz, 1H, H6), 7.66 – 7.70 (m, 1H, H7'), 7.23 – 7.37 (m, 7H, H5' and H6' and C_6H_5), 5.69 (s, 2H, CH_2)

^{13}C NMR (126 MHz, DMSO-d_6) δ 150.2, 146.1, 143.7, 141.5, 137.2, 136.4, 136.3, 128.8, 127.7, 127.2, 125.6, 123.2, 122.0, 120.4, 111.8, 105.2, 103.5, 83.2, 49.7.

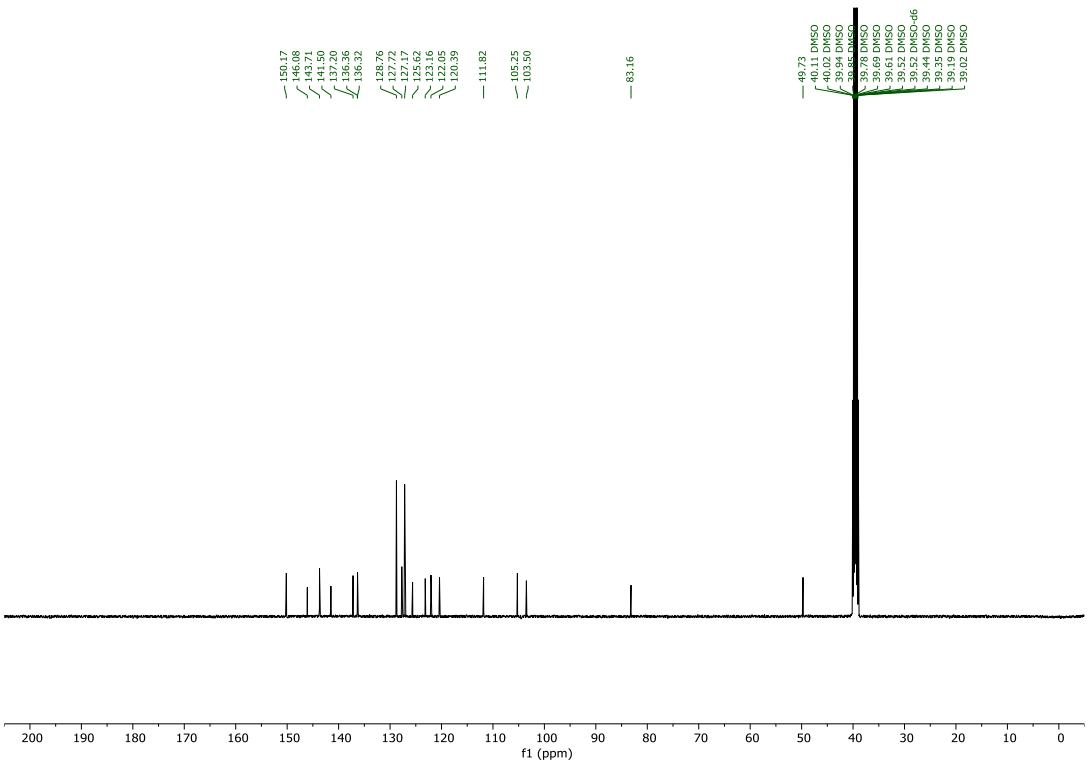
Structure determination:

Coupling constant: H5 and H6 have coupling constant J = 4.7 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines. NOE: CH_2 has NOE correlation with H2', H7' and ortho-H of C_6H_5.

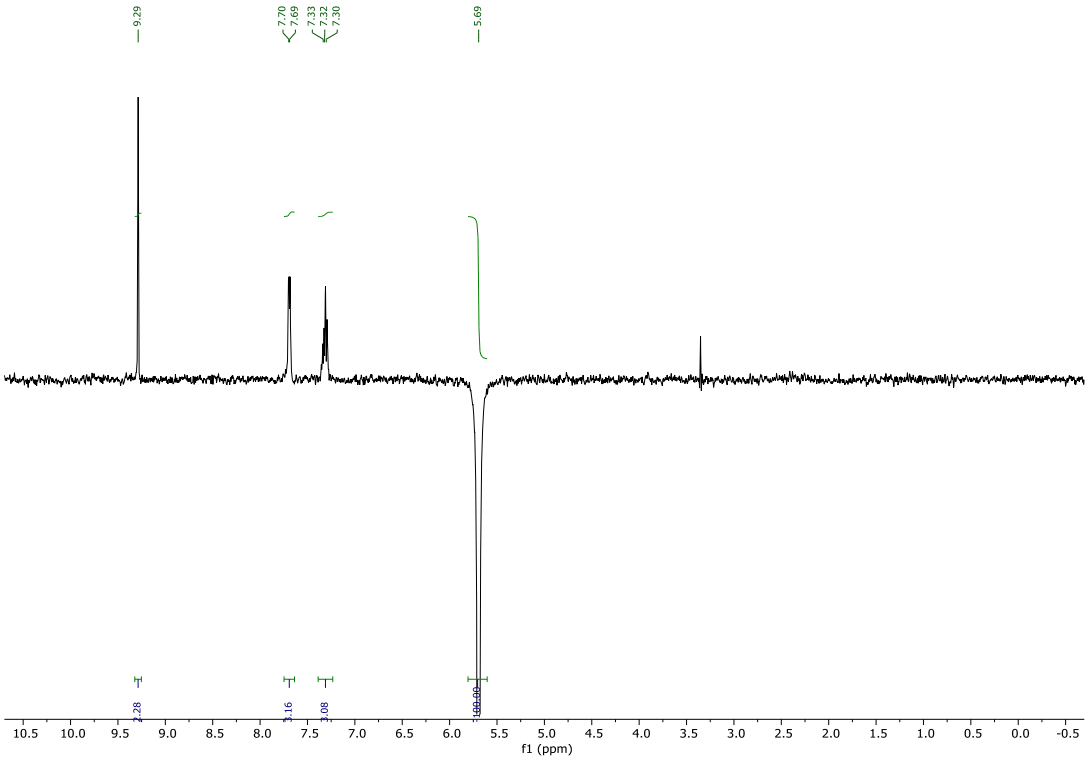
^{1}H NMR

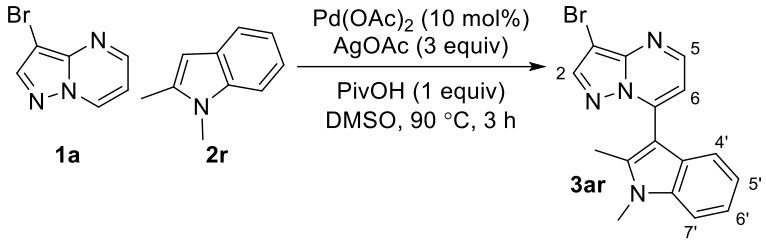


^{13}C NMR



Selective NOE





3-bromo-7-(1,2-dimethyl-1Hindol-3-yl)pyrazolo[1,5-*a*]pyrimidine (**3ar**)

Following the general procedure 1 using **1a** (40 mg, 0.2 mmol), **2r** (59 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 41 mg, 60%, yellow solid.

HRMS: $C_{16}H_{13}BrN_4$ calc.: 341.0402 (M+H), found: 341.0393

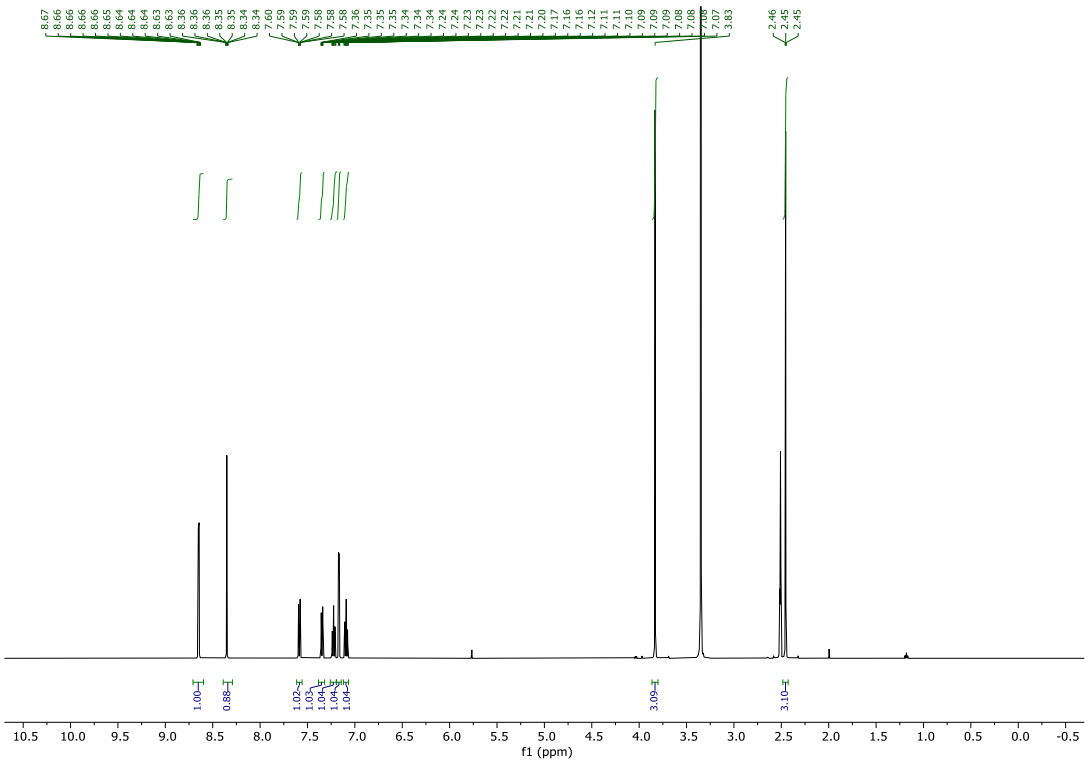
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (d, *J* = 4.3 Hz, 1H, H5), 8.35 (s, 1H, H2), 7.59 (dt, *J* = 8.3, 0.9 Hz, 1H, H7'), 7.35 (dt, *J* = 7.9, 1.0 Hz, 1H, H4'), 7.22 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, H5' or H6'), 7.17 (d, *J* = 4.3 Hz, 1H, H6), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, H5' or H.6'), 3.83 (s, 3H, NCH_3), 2.45 (s, 3H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 150.1, 145.9, 143.6, 143.4, 140.0, 136.7, 125.8, 121.5, 120.3, 119.5, 110.1, 109.8, 102.4, 82.9, 30.0, 12.6.

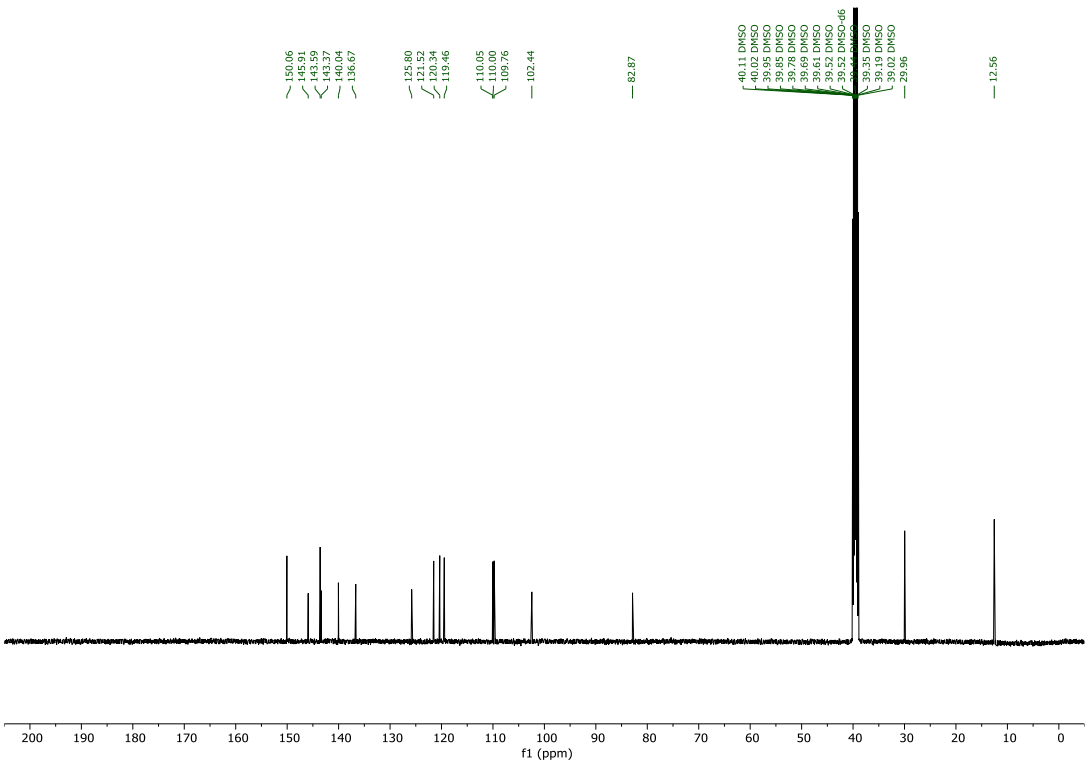
Structure determination:

COSY and coupling constant: H5 and H6 have coupling constant *J* = 4.3 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

^{1}H NMR



^{13}C NMR



3-bromo-7-(imidazo[1,2-*a*]pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine (**3as**)

Following general procedure 1 using **1a** (40 mg, 0.2 mmol), **2s** (47 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). Crude product was purified by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 15 to 75% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 38.8 mg, 62%, light yellow solid.

HRMS: $C_{13}H_8BrN_5$ calc.: 314.0041 (M+H), found: 314.0067

^{1}H NMR(500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.3 Hz, 1H, H5), 8.43 (s, 1H, H2'), 8.21 (s, 1H, H2), 8.17 (ddd, *J* = 6.9, 1.0, 1.0 Hz, 1H, H5'), 7.85 (ddd, *J* = 9.3, 1.0, 1.0 Hz, 1H, H8'), 7.45 (ddd, *J* = 9.0, 6.8, 1.2 Hz, 1H, H7'), 7.15 (d, *J* = 4.3 Hz, 1H, H6), 7.02 (ddd, *J* = 6.9, 6.9, 1.1 Hz, 1H, H6').

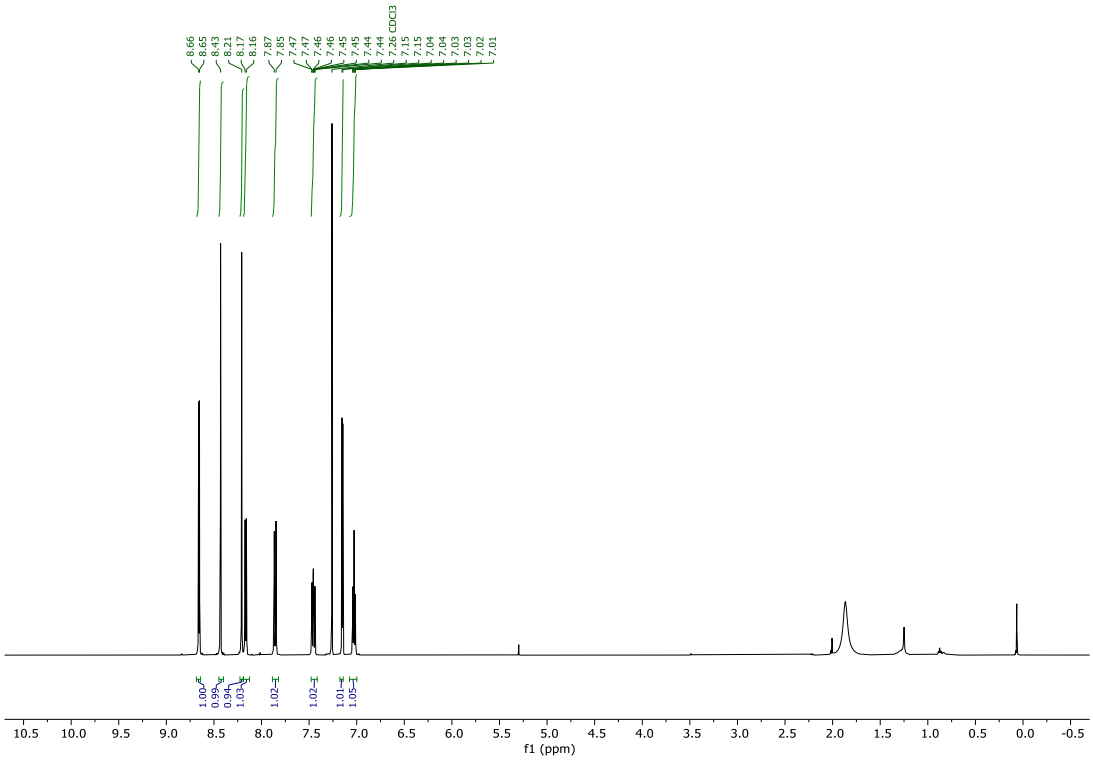
^{13}C NMR(126 MHz, $CDCl_3$) δ 149.6, 148.7, 146.5, 144.9, 139.5, 137.3, 127.6, 127.2, 118.7, 115.7, 113.9, 107.3, 85.6.

Structure determination:

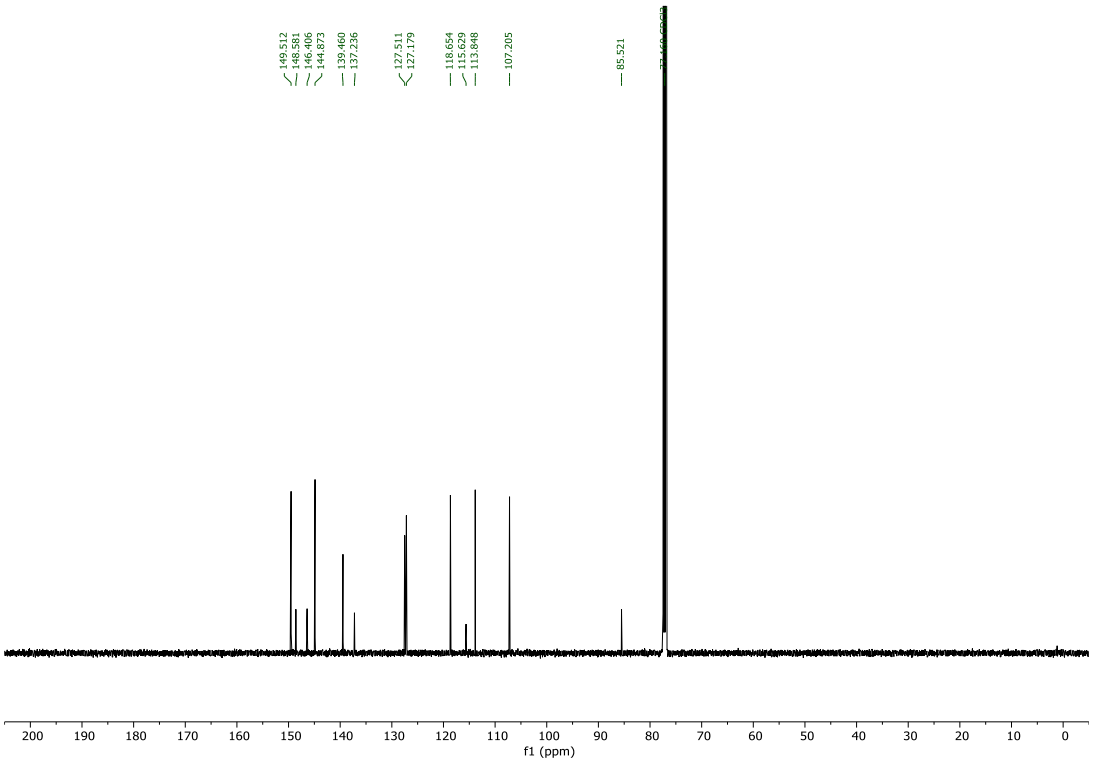
Coupling constant: H5 and H6 have coupling constant *J* = 4.3 Hz characteristic for C7-substituted pyrazolo[1,5-*a*]pyrimidines.

NOE: Correlations observed between H5' to H6 and simultaneous NOE correlations from H6 to H5' and H2'.

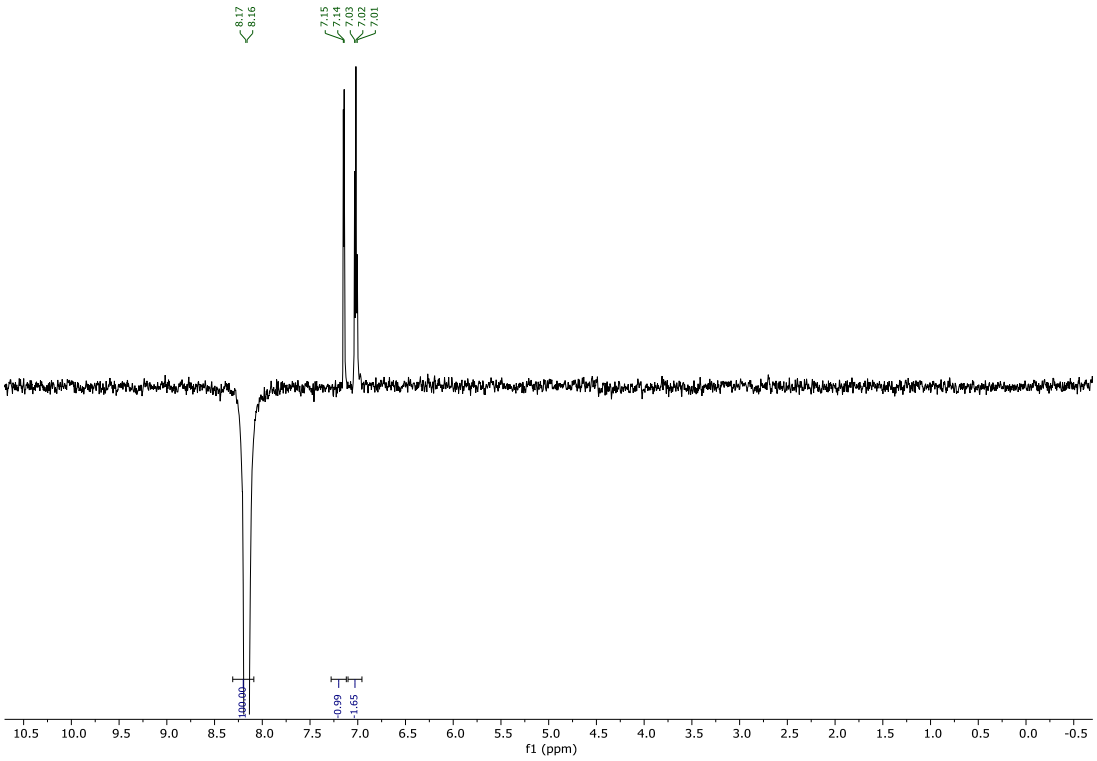
^{1}H NMR



^{13}C NMR



Selective NOE



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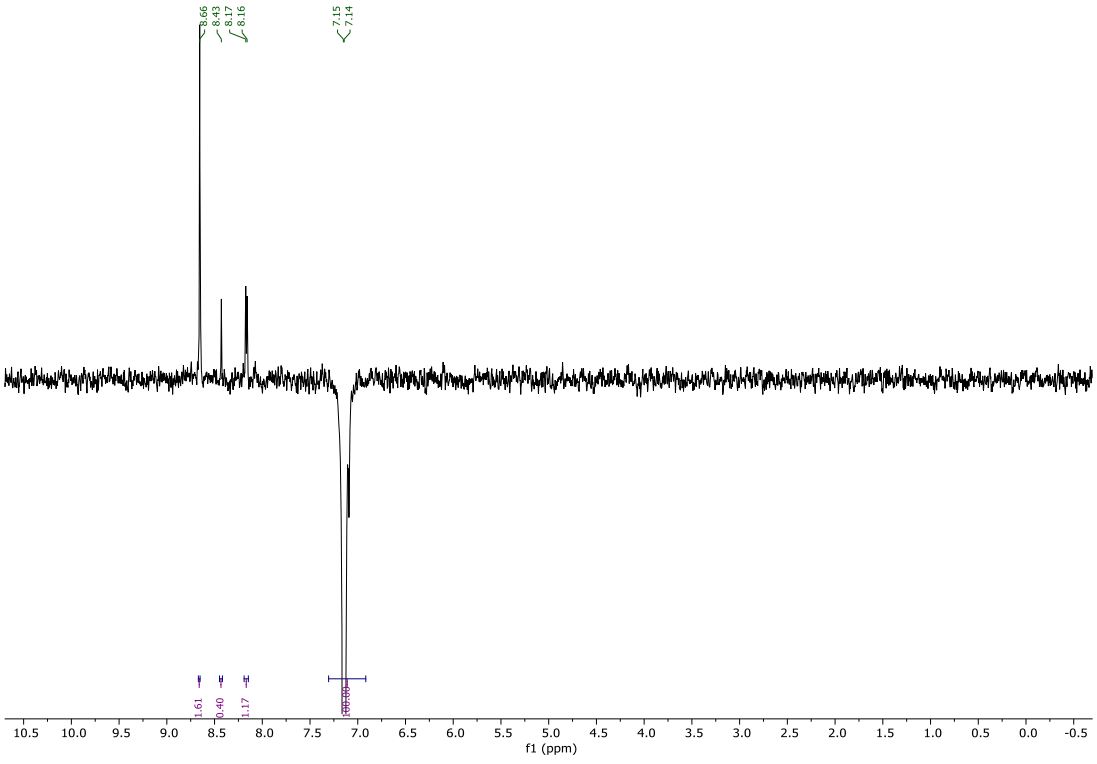
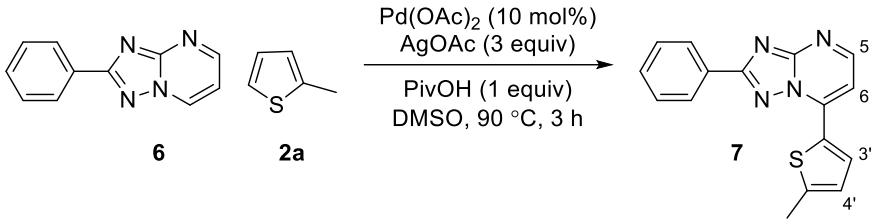




7-(5-methylthiophen-2-yl)-2-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidine (**7**)

Following the general procedure 1 using **6** (39 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (21 mg, 0.2 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 25% to 100% of EtOAc in heptane over 4 CV as mobile phase.

Yield: 16 mg, 28%, yellow solid.

HRMS: $C_{16}H_{12}N_4S$ calc.: 293.0861 (M+H), found: 293.0868

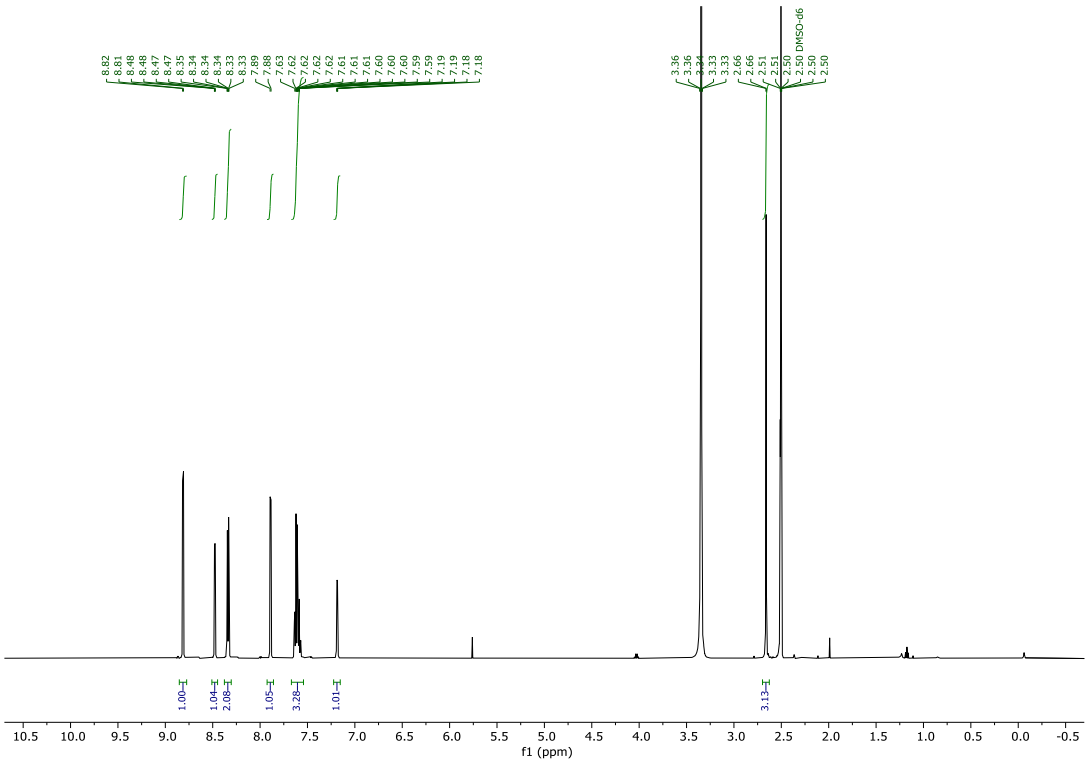
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (d, *J* = 5.0 Hz, 1H, H5), 8.48 (d, *J* = 3.9 Hz, 1H, H3'), 8.31 – 8.37 (m, 2H, C_6H_5), 7.89 (d, *J* = 5.0 Hz, 1H, H6), 7.55 – 7.66 (m, 3H, C_6H_5), 7.19 (dd, *J* = 3.9, 1.1 Hz, 1H, H4'), 2.66 (d, *J* = 1.0 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 164.0, 156.4, 154.0, 150.3, 140.8, 133.7, 130.9, 130.2, 129.1, 127.4, 127.4, 127.0, 105.3, 15.3.

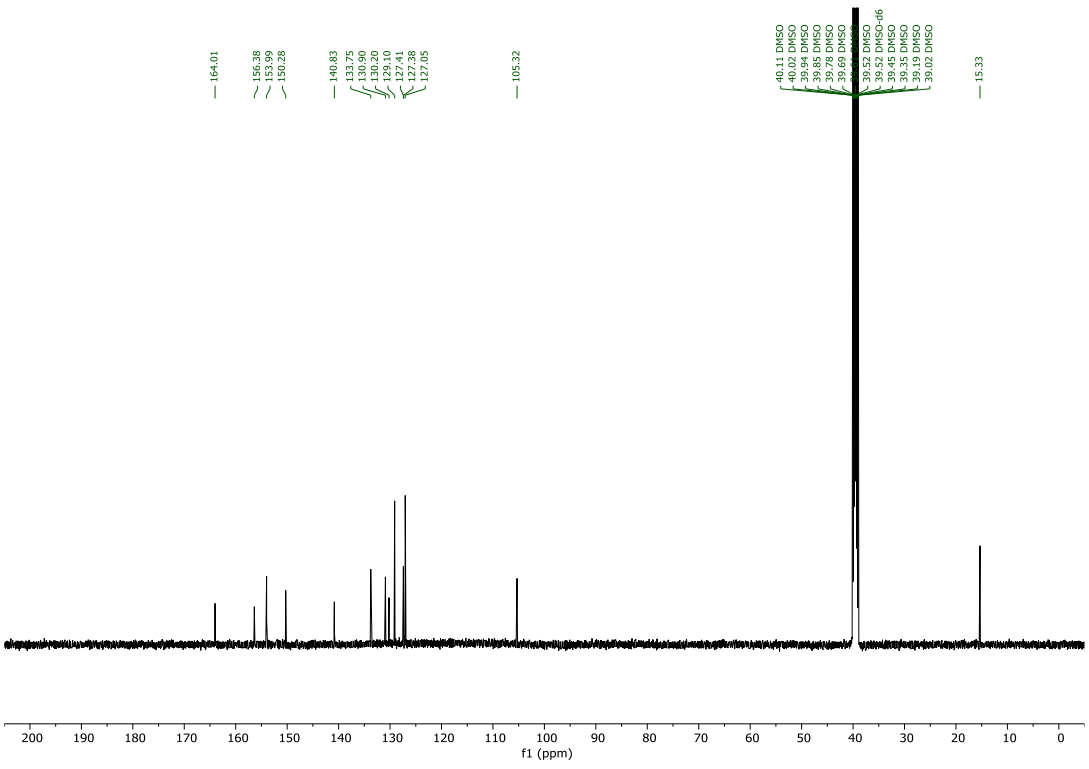
Structure determination:

Coupling constant: H5 and H6 have coupling constant *J* = 5.0 Hz characteristic for C7-substituted [1,2,4]triazolo[1,5-*a*]pyrimidines. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant *J* = 1.0 Hz.

^{1}H NMR



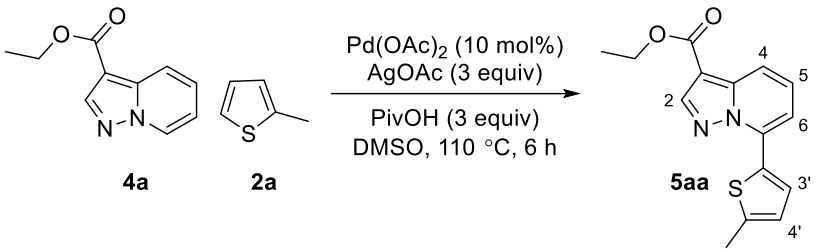
^{13}C NMR



Substrate Scope for pyrazolo[1,5-*a*]pyridine (Main text, Scheme 2)

General procedure 2:

A 15 or 20-mL screw-capped vial was charge with **4** (0.2 mmol), **2** (0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The vial was closed and stirred in a pre-heated aluminum block at 110 °C for 6 h. After cooling, the reaction mixture was diluted to EtOAc (5 mL), filtered through a filter frit and a Whatman syringe filter (0.45 µm). Solvents was removed *in vacuo* (DMSO removal: using Biotage V-10 with Very High Boil mode at 56 °C and 0 mbar, or freeze dryer overnight at < 0.01 mbar) and the crude material was purified as specified.



ethyl 7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5aa**)

Following the general procedure 2 using **4a** (39 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 0% to 30% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 27 mg, 47%, dark brown solid.

HRMS: $C_{15}H_{14}N_2O_2S$ calc.: 287.0854 (M+H), found: 287.0868

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H, H2), 8.11 (d, *J* = 3.8 Hz, 1H, H3'), 8.04 (dd, *J* = 8.6, 1.3 Hz, 1H, H4), 7.77 (dd, *J* = 7.5, 1.3 Hz, 1H, H6), 7.68 (dd, *J* = 8.7, 7.4 Hz, 1H, H5), 7.02 (dd, *J* = 3.8, 1.2 Hz, 1H, H4'), 4.33 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.56 (d, *J* = 1.1 Hz, 3H, CH_3), 1.36 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

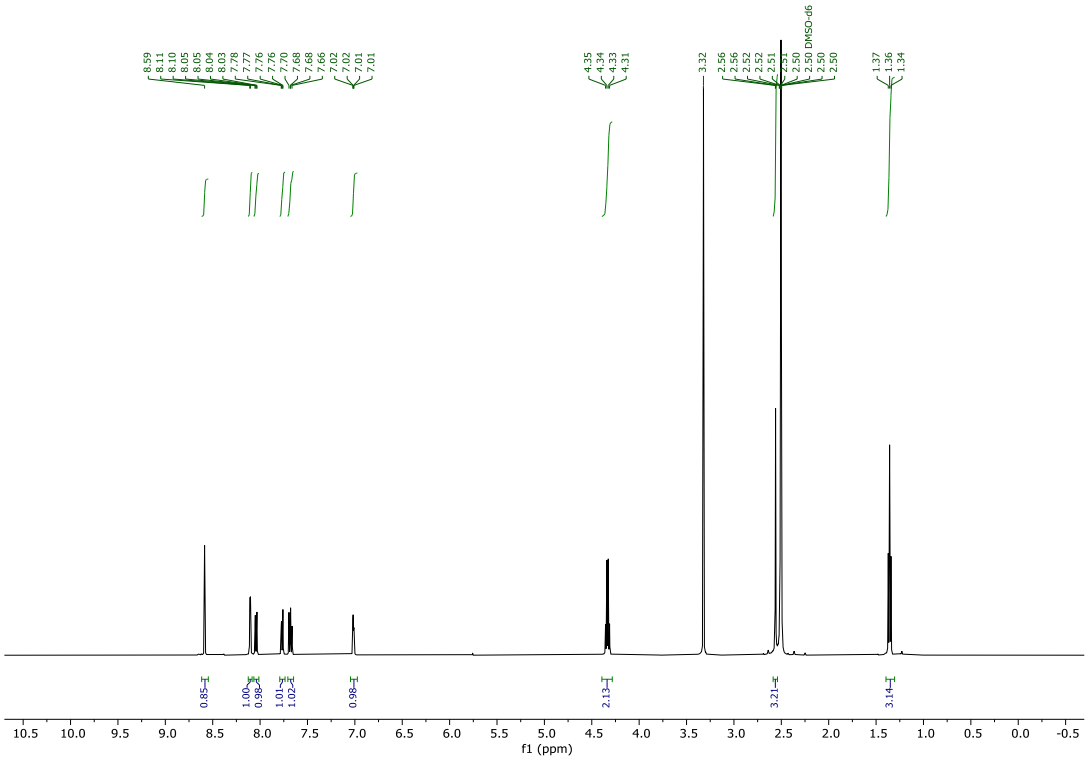
^{13}C NMR (126 MHz, DMSO-d_6) δ 162.6, 144.9, 143.6, 140.9, 134.7, 129.9, 129.4, 128.5, 125.9, 115.5, 111.3, 103.1, 59.7, 14.8, 14.4.

Structure determination:

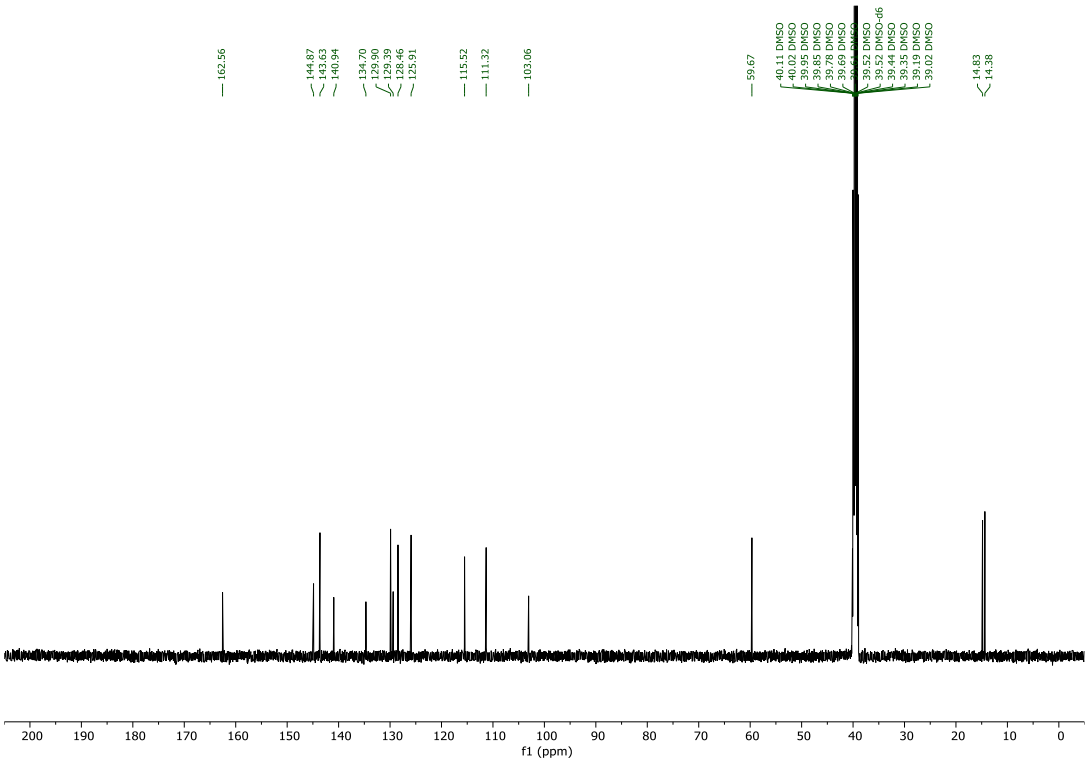
Coupling constant: H5 has large coupling constant with H4 and H6, indicating that reaction did not occur on C-5 or C-6. H3' and H4' have coupling constant *J* = 3.9 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant *J* = 1.0 Hz.

HMBC: H2, H4, H5 have correlation with junction C (140.9 ppm).

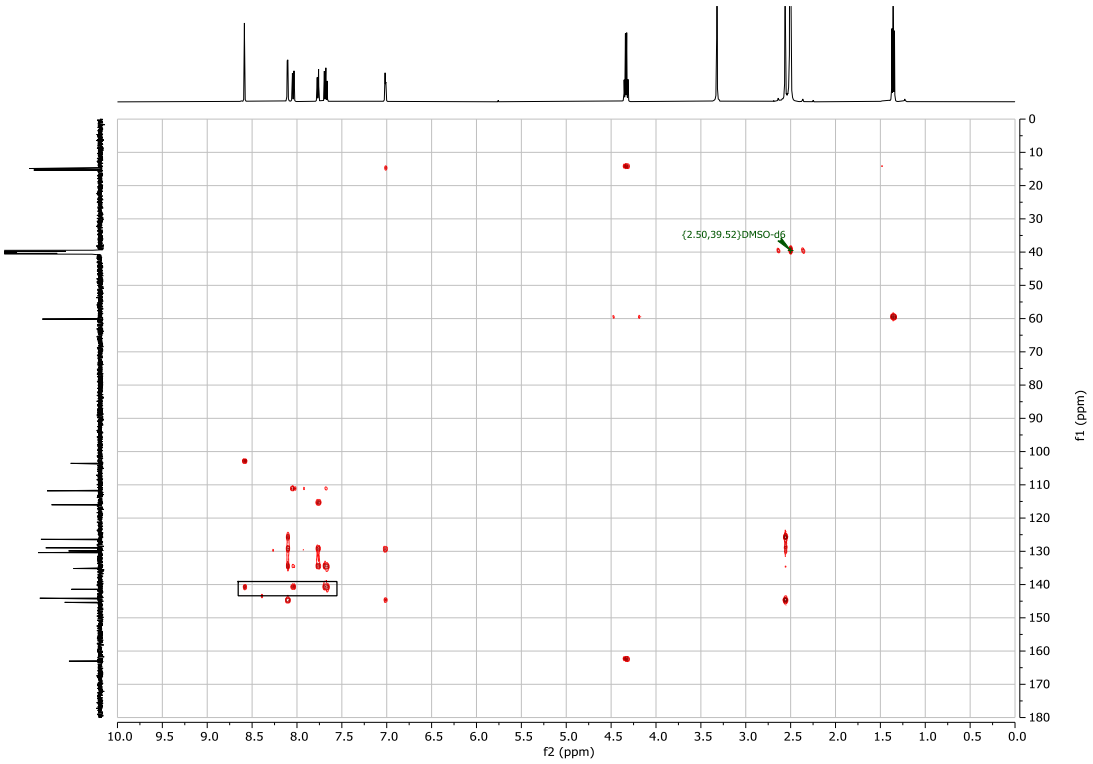
^{1}H NMR

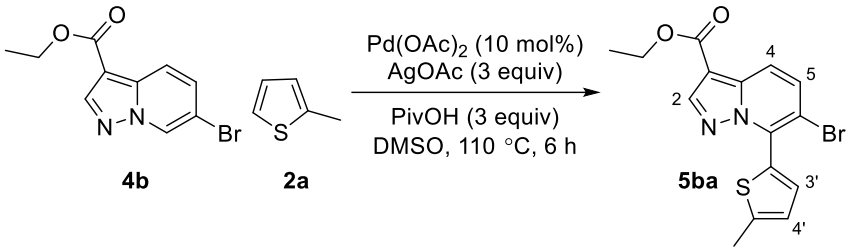


^{13}C NMR



HMBC





ethyl 6-bromo-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5ba**)

Following the general procedure 2 using **4b** (54 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 54 mg, 74%, light gray solid.

HRMS: $C_{15}H_{13}BrN_2O_2S$ calc.: 364.9959 (M+H), found: 364.9973

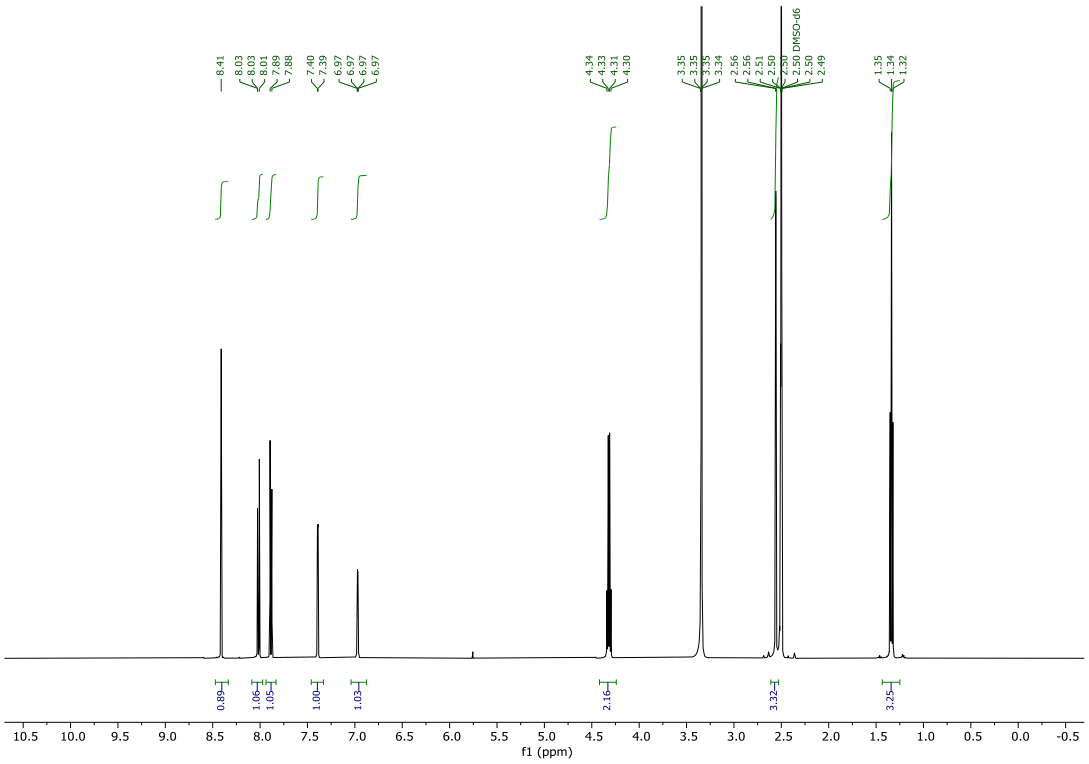
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 1H, H2), 8.02 (d, *J* = 9.4 Hz, 1H, H4 or H5), 7.89 (d, *J* = 9.4 Hz, 1H, H4 or H5), 7.39 (d, *J* = 3.5 Hz, 1H, H3'), 6.97 (dd, *J* = 3.6, 1.1 Hz, 1H, H4'), 4.32 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.56 (d, *J* = 1.1 Hz, 3H, CH_3), 1.34 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 143.9, 143.8, 139.9, 133.9, 132.5, 132.5, 128.0, 125.3, 118.2, 111.0, 104.3, 59.9, 14.9, 14.4.

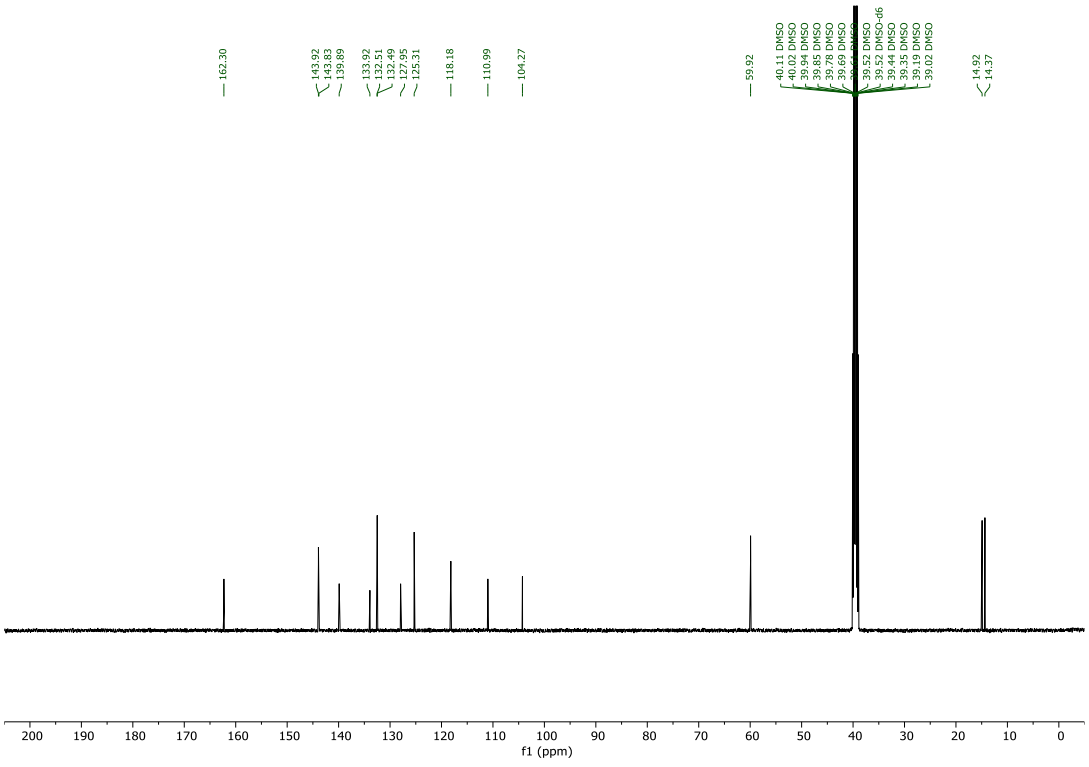
Structure determination:

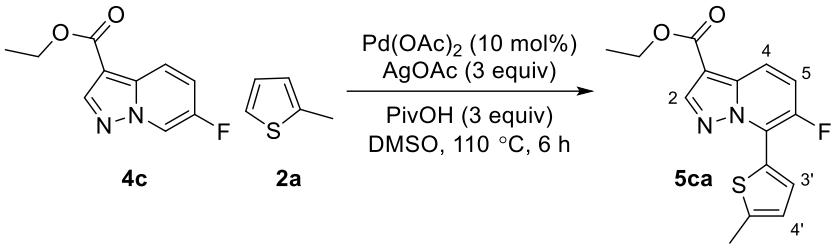
Coupling constant: H4 and H5 have large coupling constant *J* = 9.4 Hz showing they are ortho to each other. H3' and H4' have coupling constant *J* = 3.6 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant *J* = 1.1 Hz.

^{1}H NMR



^{13}C NMR





ethyl 6-fluoro-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5ca**)

Following the general procedure 2 using **4c** (42 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 41 mg, 67%, yellow solid.

HRMS: $C_{15}H_{13}FN_2O_2S$ calc.: 305.0760 (M+H), found: 305.0761

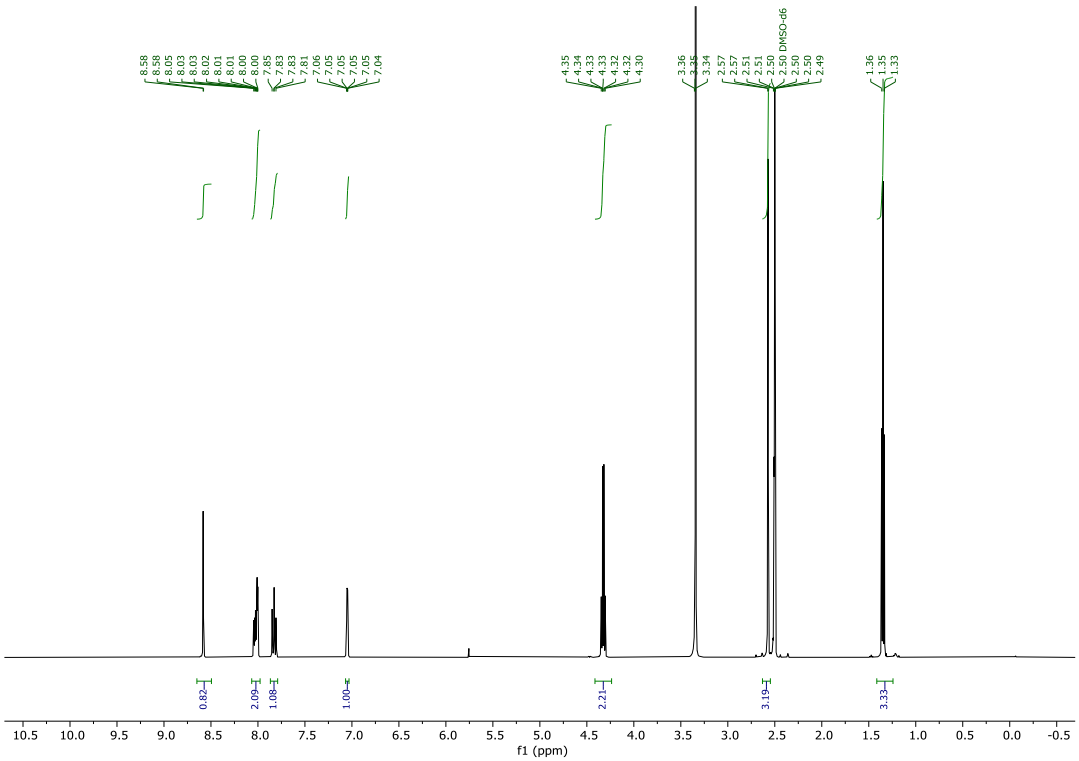
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (d, *J* = 2.1 Hz, 1H, H2), 8.03 (dd, *J* = 9.5, 5.2 Hz, 1H, H4), 8.01 (dd, *J* = 3.9, 1.5 Hz, 1H, H3'), 7.83 (dd, *J* = 11.1, 9.5 Hz, 1H, H5), 7.03 – 7.07 (m, 1H, H4'), 4.33 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.57 (d, *J* = 1.1 Hz, 3H, CH_3), 1.35 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.8, 150.3 (d, *J* = 240.3 Hz), 145.5 (d, *J* = 4.5 Hz), 144.4 (d, *J* = 2.7 Hz), 138.9, 133.1 (d, *J* = 13.6 Hz), 126.3, 124.2 (d, *J* = 6.4 Hz), 124.0 (d, *J* = 26.1 Hz), 120.3 (d, *J* = 26.9 Hz), 115.9 (d, *J* = 9.5 Hz), 104.3, 60.3, 15.1, 14.8.

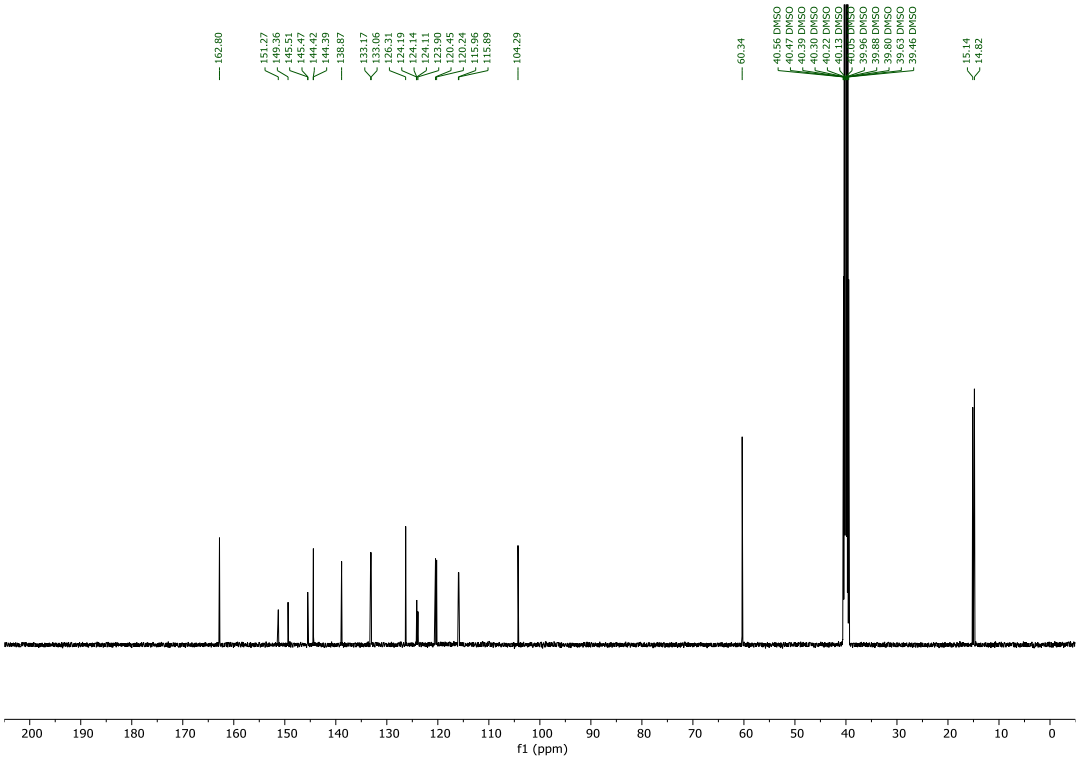
^{19}F NMR (470 MHz, DMSO-d_6) δ -132.17 (TFA as the internal standard)

Regioselectivity is analogous to **5ba**.

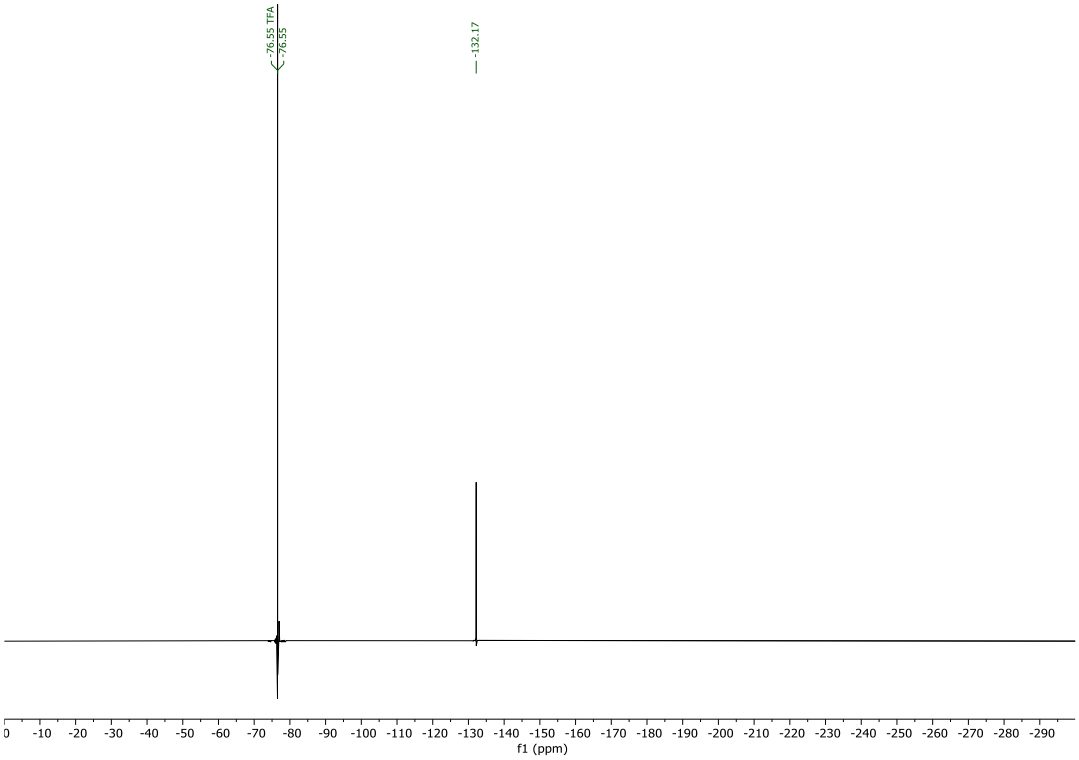
^{1}H NMR

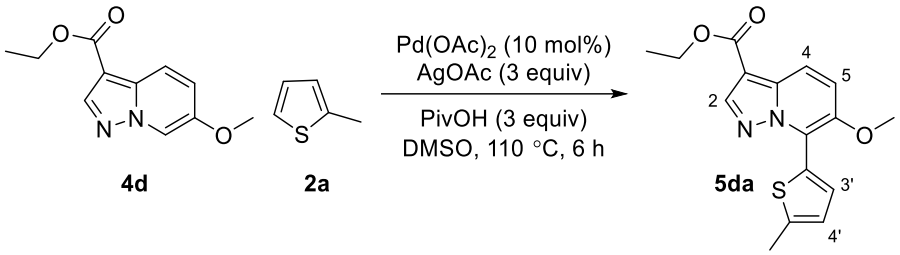


^{13}C NMR



^{19}F NMR


-76.55 TFA
-76.55
-132.17
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240 -250 -260 -270 -280 -290
f1 (ppm)



ethyl 6-methoxy-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5da**)

Following the general procedure 2 using **4d** (44 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 24 mg, 38%, dark brown solid.

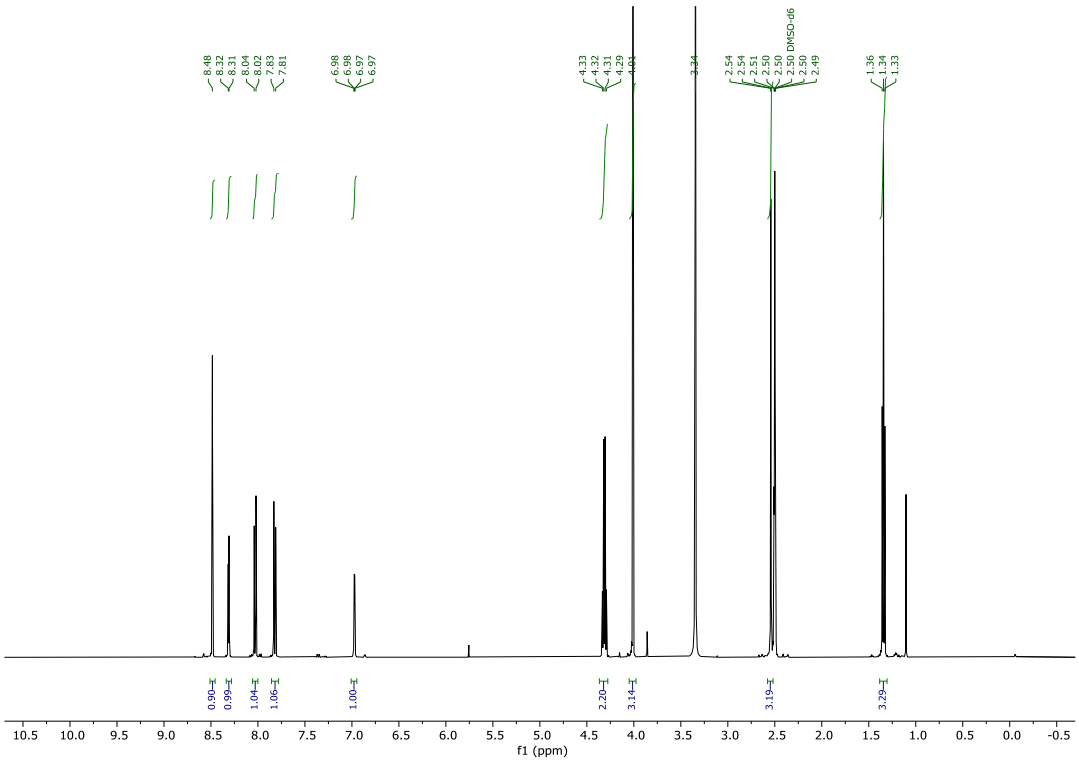
HRMS: $C_{16}H_{16}N_2O_3S$ calc.: 317.0960 (M+H), found: 317.0960

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H, H2), 8.31 (d, *J* = 3.9 Hz, 1H, H3'), 8.03 (d, *J* = 9.6 Hz, 1H, H4), 7.82 (d, *J* = 9.6 Hz, 1H, H5), 6.97 (dd, *J* = 3.9, 1.1 Hz, 1H, H4'), 4.31 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.01 (s, 3H), 2.54 (d, *J* = 1.1 Hz, 3H, CH_3), 1.34 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

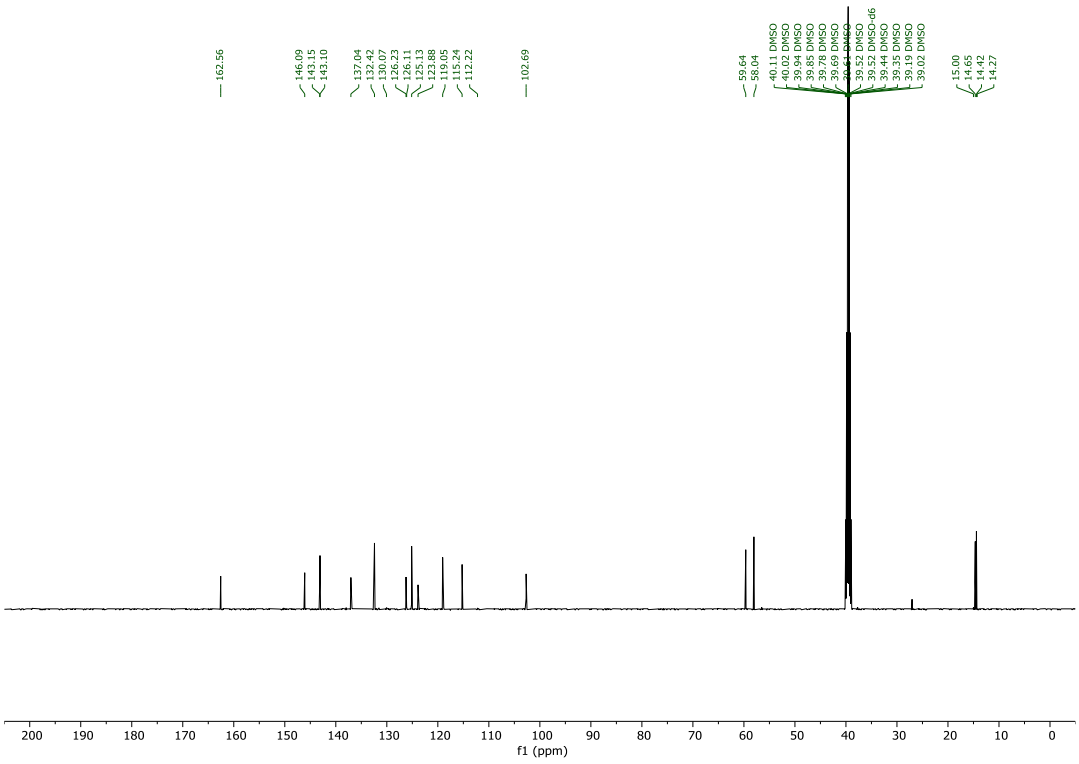
^{13}C NMR (126 MHz, DMSO-d_6) δ 162.6, 146.1, 143.2, 143.1, 137.0, 132.4, 126.2, 125.1, 123.9, 119.1, 115.2, 102.7, 59.6, 58.0, 14.6, 14.4.

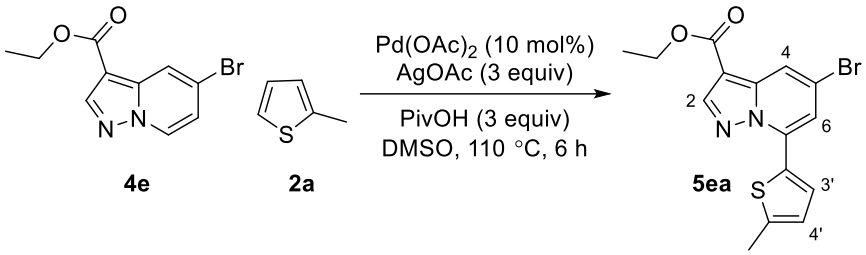
Structure determination is analogous to **5ba**.

^{1}H NMR



^{13}C NMR





ethyl 5-bromo-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5ea**)

Following the general procedure 2 using **4e** (54 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 39 mg, 53%, yellow solid.

HRMS: $C_{15}H_{13}BrN_2O_2S$ calc.: 364.9959 (M+H), found: 364.9970

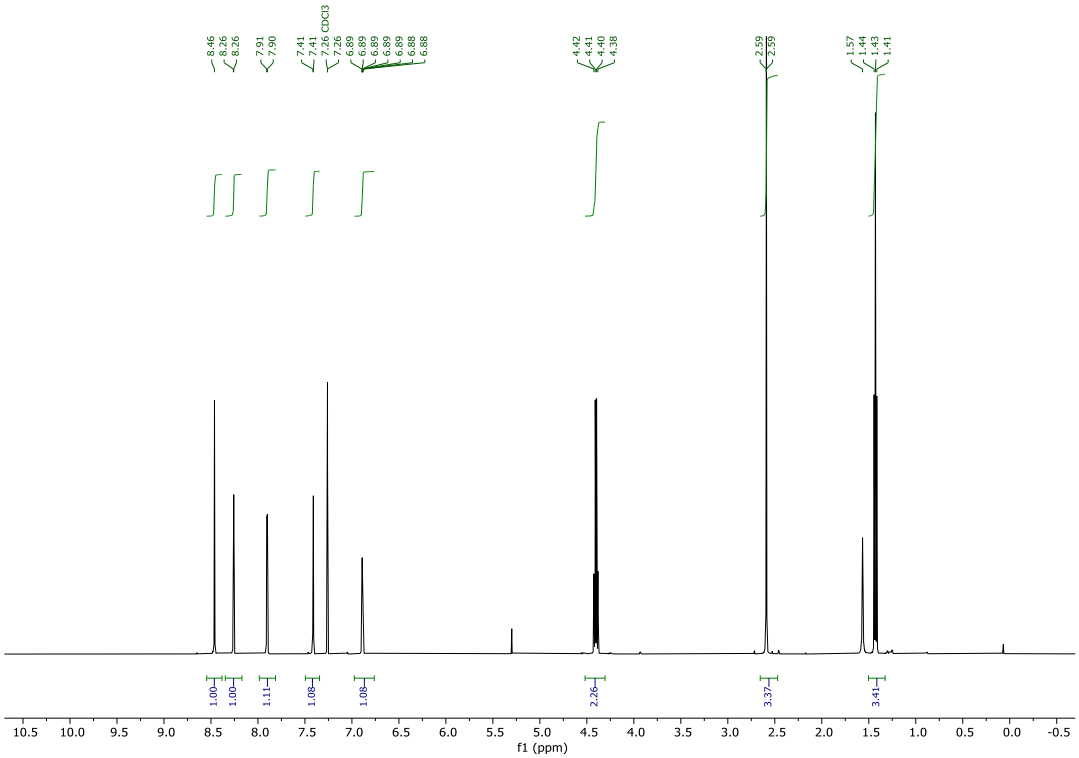
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H, H2), 8.26 (d, *J* = 2.0 Hz, 1H, H4), 7.90 (d, *J* = 3.8 Hz, 1H, H3'), 7.41 (d, *J* = 2.0 Hz, 1H, H6), 6.89 (dt, *J* = 3.8, 1.0 Hz, 1H, H4'), 4.40 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.59 (d, *J* = 1.1 Hz, 3H, CH_3), 1.43 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.3, 145.9, 144.5, 142.2, 136.0, 130.4, 129.2, 125.9, 122.1, 118.3, 114.4, 103.8, 60.3, 15.4, 14.6.

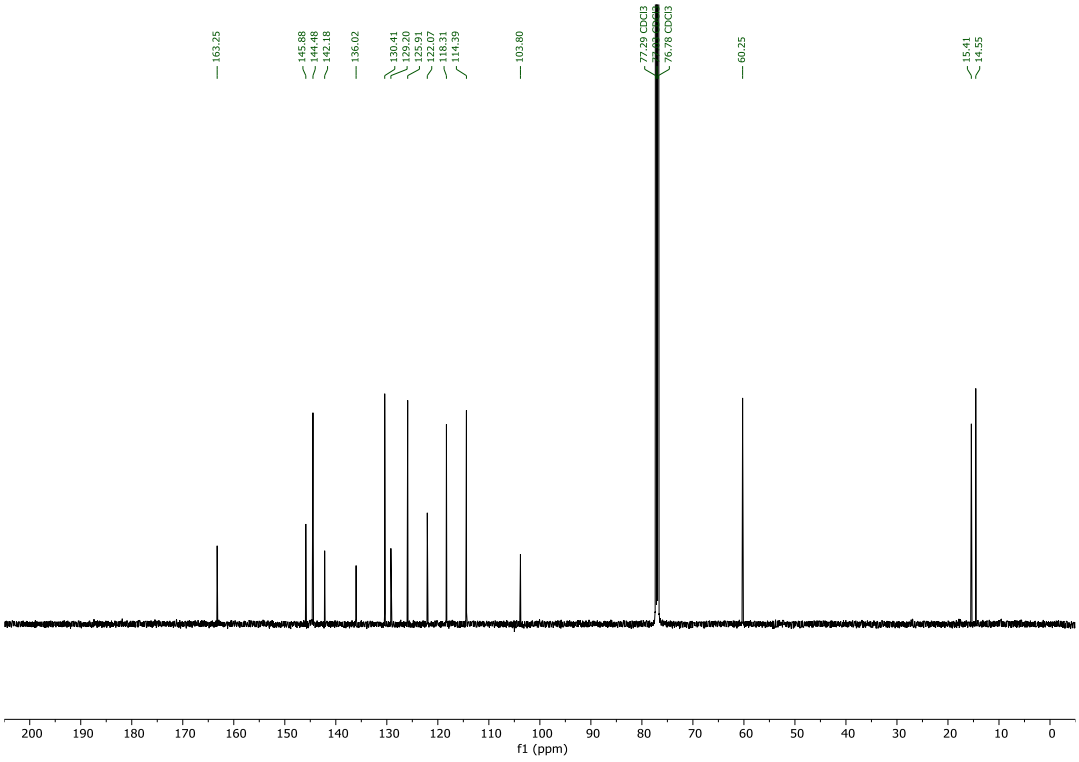
Structure determination:

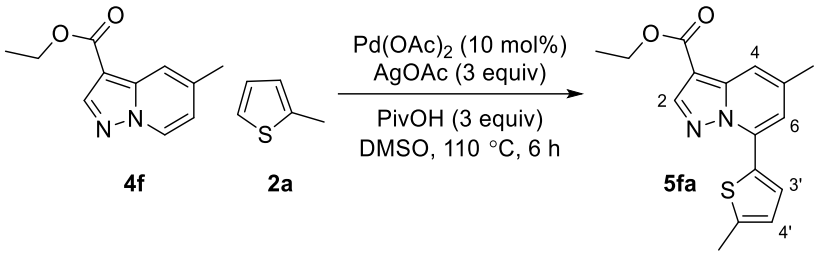
Coupling constant: H4 and H6 have coupling constant *J* = 2 Hz, showing they are meta to each other. H3' and H4' have coupling constant *J* = 3.8 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant *J* = 1.0 Hz.

^{1}H NMR



^{13}C NMR





ethyl 5-methyl-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5fa**)

Following the general procedure 1 using **4f** (41 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase. It was found that the fraction collected contained PivOH (by NMR) and this impurity can be washed out using saturated $NaHCO_3$ solution.

Yield: 18 mg, 30%, brown solid.

HRMS: $C_{16}H_{16}N_2O_2S$ calc.: 301.1011 (M+H), found: 301.1013

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H, H2), 8.06 (d, J = 3.8 Hz, 1H, H3'), 7.78 – 7.82 (m, 1H, H4), 7.61 (d, J = 1.8 Hz, 1H, H6), 6.99 (dt, J = 3.9, 1.1 Hz, 1H, H4'), 4.31 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.54 (d, J = 1.1 Hz, 3H, CH_3), 2.49 (d, J = 1.2 Hz, 3H, CH_3), 1.34 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.7, 144.8, 143.7, 141.0, 139.4, 133.9, 129.8, 129.3, 125.9, 114.4, 113.3, 102.0, 59.6, 21.0, 14.9, 14.4.

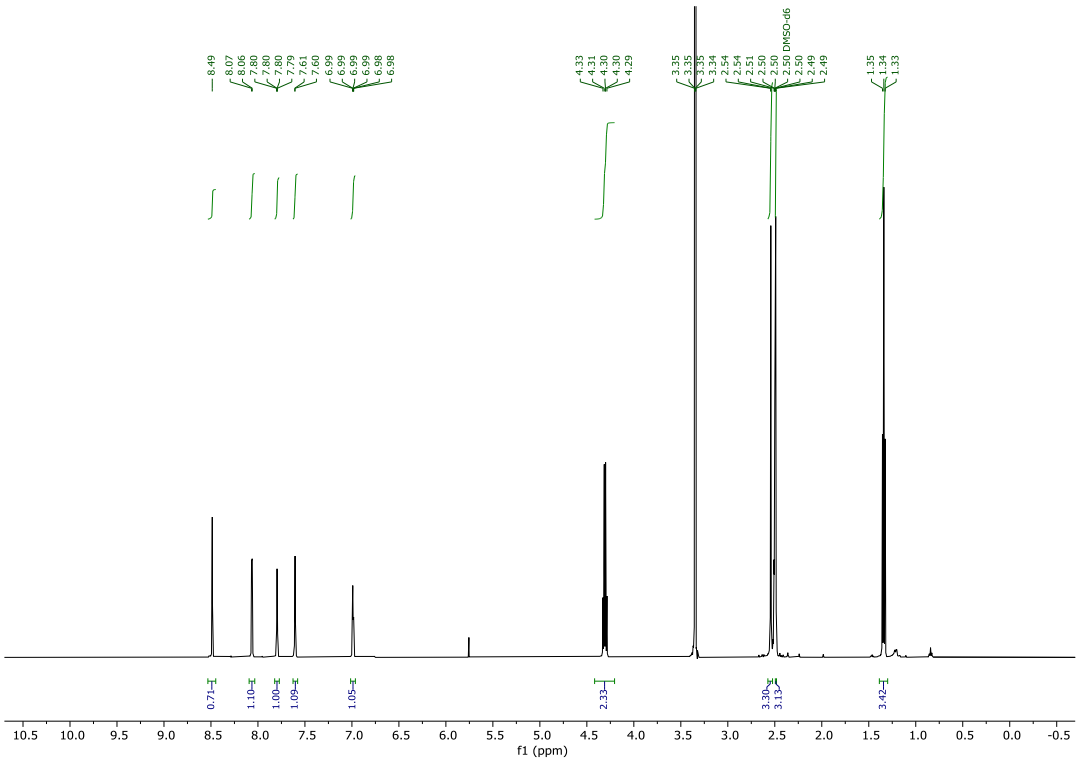
Structure determination:

Coupling constant: H4 and H6 have coupling constant J = 2 Hz, showing they are meta to each other. H3' and H4' have coupling constant J = 3.8 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH_3 have coupling constant J = 1.0 Hz.

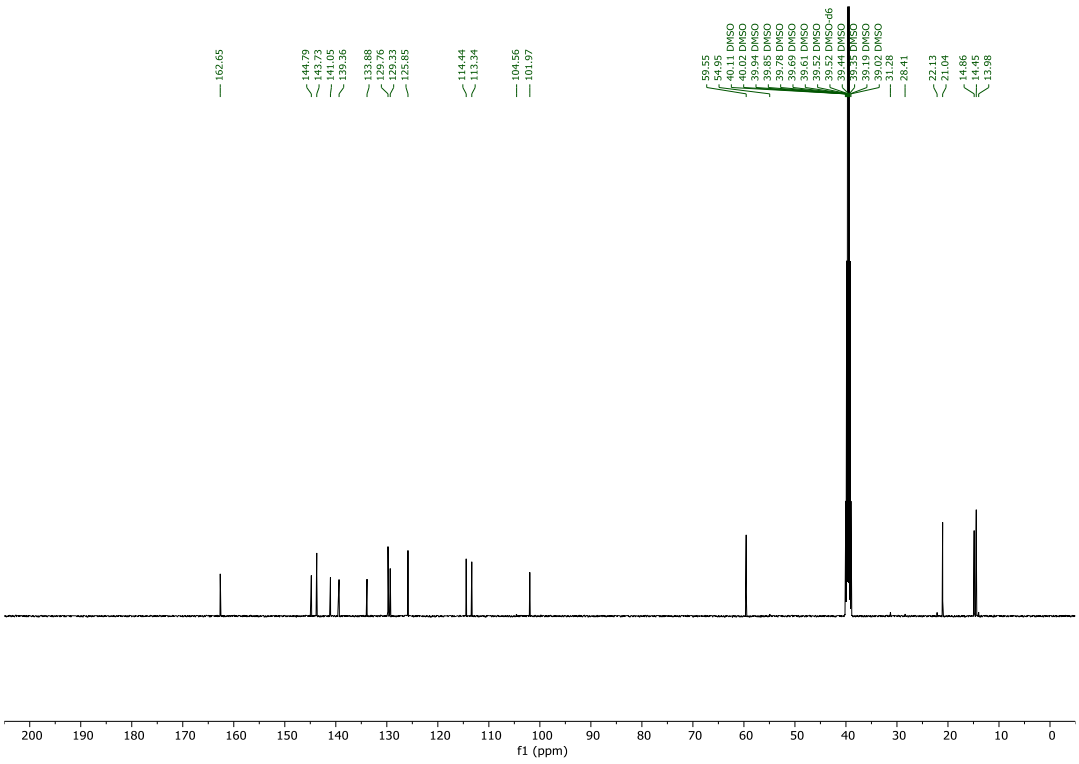
HSQC: C-4 114.4 ppm, C-6 113.3 ppm, C (CH_3) 21.0 ppm.

HMBC: C/H4 and C/H6 have correlation with CH_3.

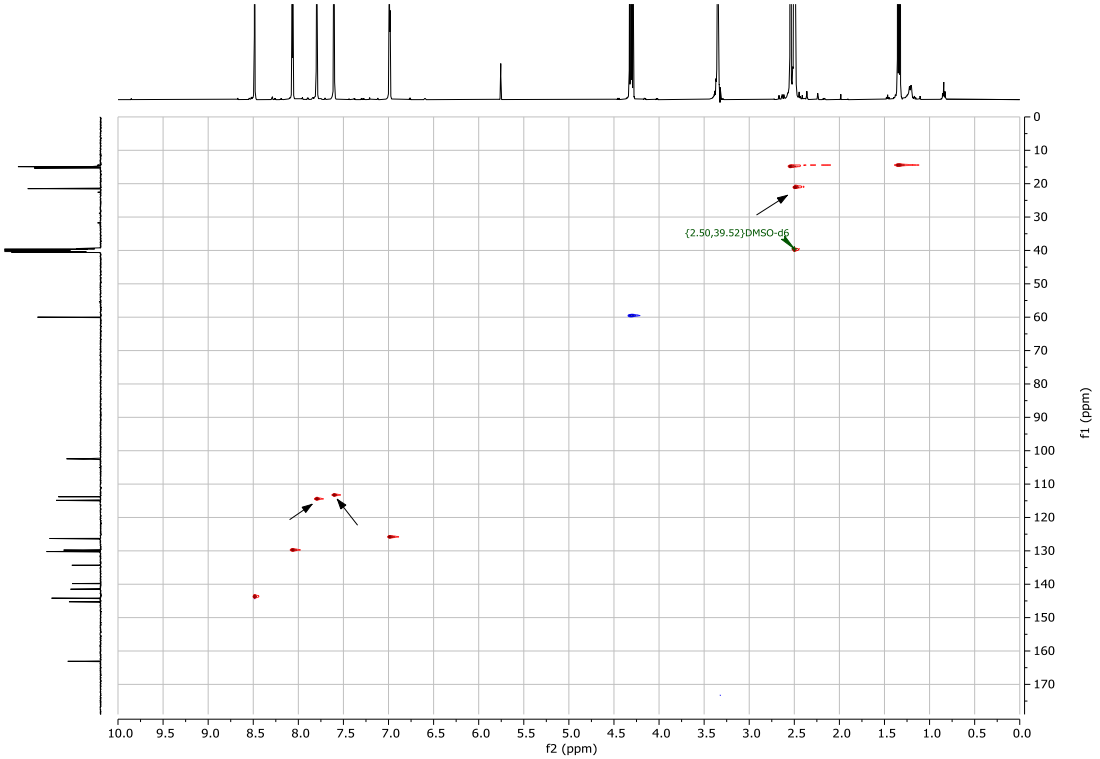
^{1}H NMR



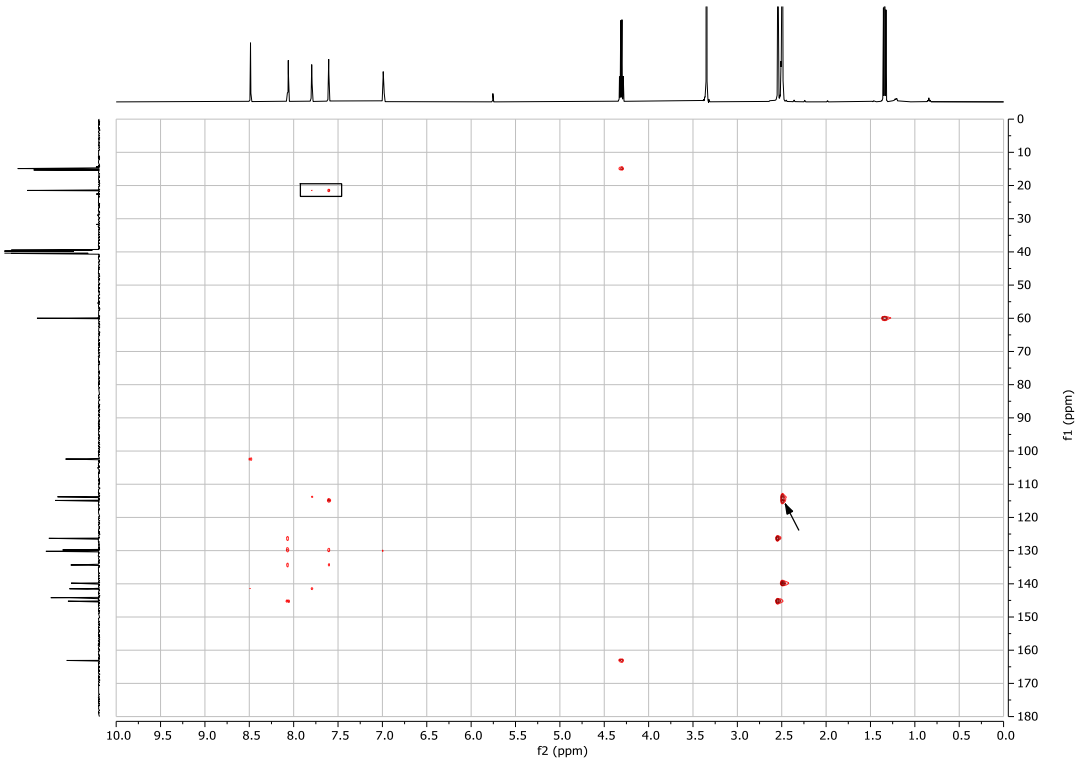
^{13}C NMR

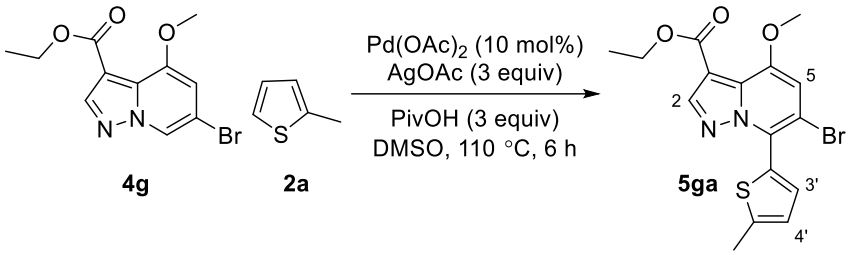


HSQC



HMBC





ethyl 6-bromo-4-methoxy-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5ga**)

Following the general procedure 1 using **4g** (60 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 7% to 60% of EtOAc in heptane over 10 CV as mobile phase. Further purification by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 45 to 85% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 42 mg, 53%, white solid.

HRMS: $C_{16}H_{15}BrN_2O_3S$ calc.: 395.0065 (M+H), found: 395.0066

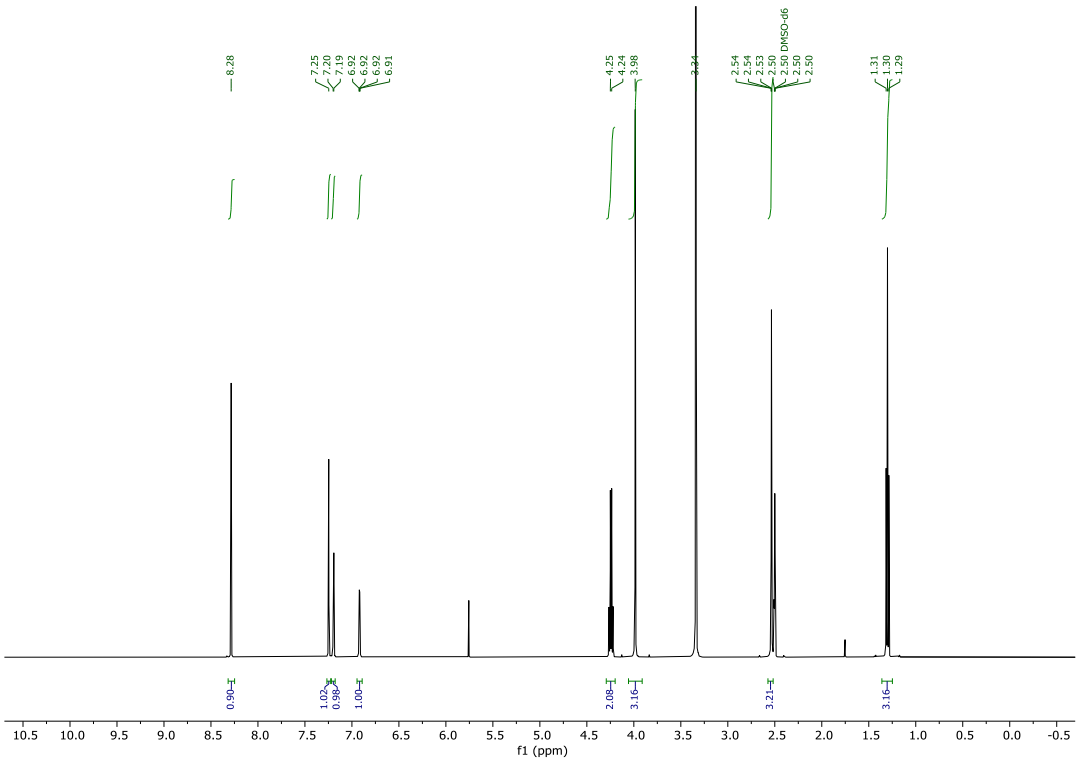
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.28 (s, 1H, H2), 7.25 (s, 1H, H5), 7.20 (d, *J* = 3.5 Hz, 1H, H3'), 6.92 (dd, *J* = 3.5, 1.2 Hz, 1H, H4'), 4.24 (d, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 3.98 (s, 3H, OCH_3), 2.53 (d, *J* = 1.1 Hz, 3H, CH_3), 1.30 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 161.5, 150.3, 144.1, 143.0, 132.6, 131.7, 128.9, 126.3, 125.2, 111.6, 109.7, 106.1, 60.0, 56.7, 15.0, 14.3.

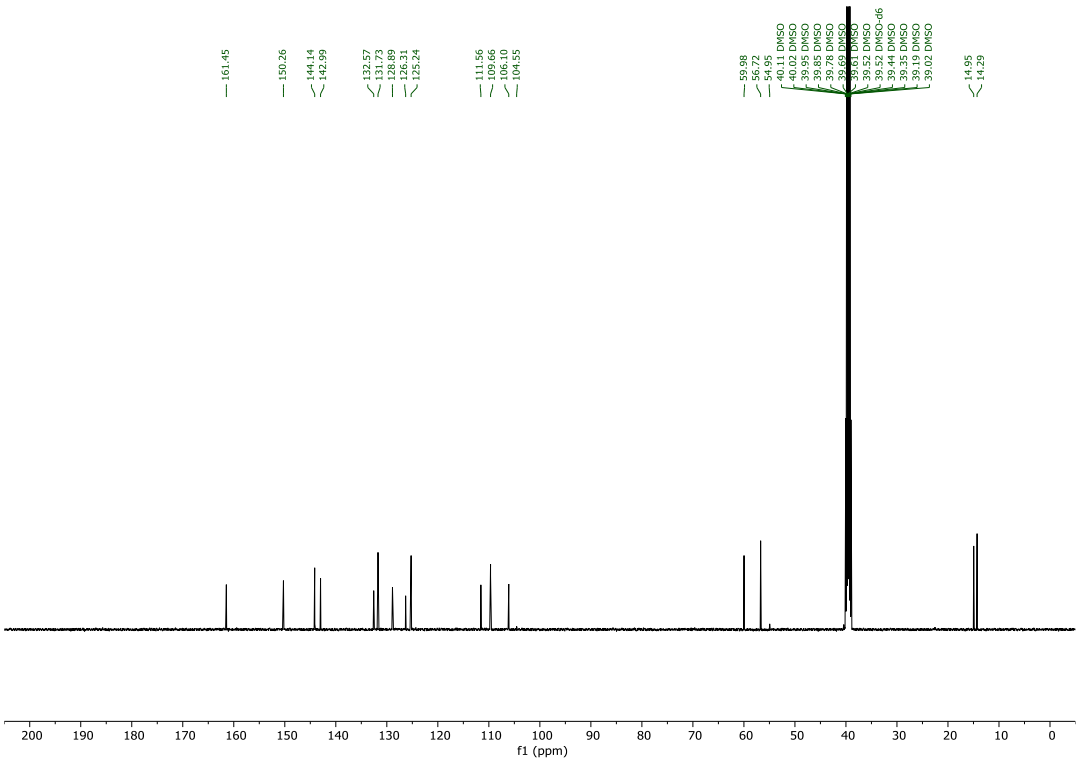
Structure determination:

Coupling constant: H3' and H4' have coupling constant *J* = 3.5 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH3 have coupling constant *J* = 1.1 Hz. NOE: H5 has NOE correlation with OCH_3.

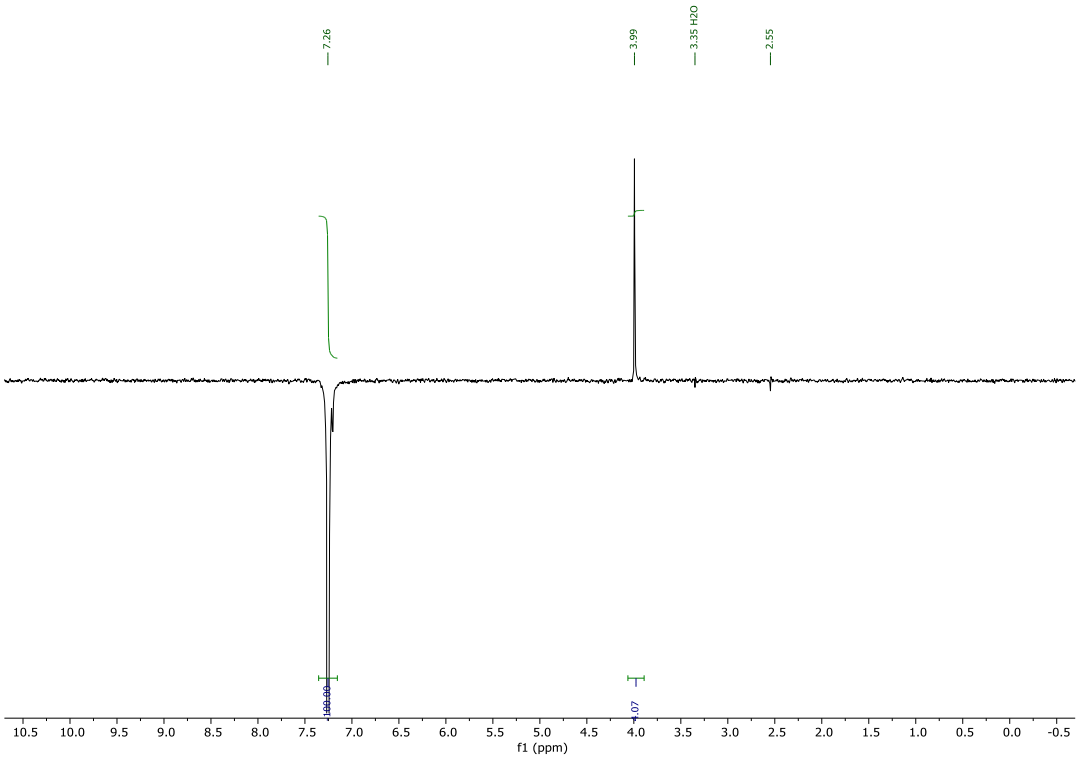
^{1}H NMR

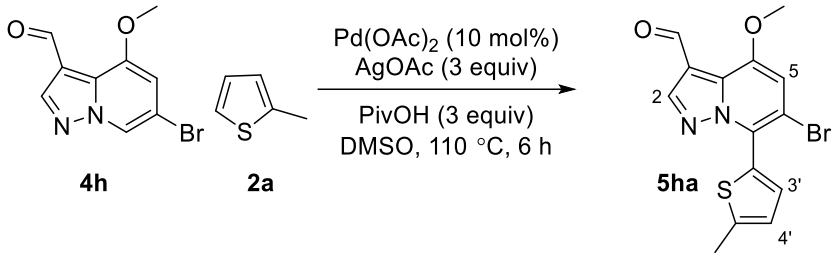


^{13}C NMR



Selective NOE





6-bromo-4-methoxy-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carbaldehyde (**5ha**)

Following general procedure 2 using **1h** (51 mg, 0.2 mmol), **2a** (39 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). Crude product was purified by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 40 to 80% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 42 mg, 59%, yellow solid.

HRMS: $C_{14}H_{11}BrN_2O_2S$ calc.: 350.9803 (M+H), found: 350.9822

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.41 (s, 1H, H2), 7.46 (s, 1H, H5), 7.24 (d, J = 3.5 Hz, 1H, H3'), 6.91 – 6.97 (m, 1H, H4'), 4.11 (s, 3H, -OCH_3), 2.54 (d, J = 0.8 Hz, 3H, CH_3).

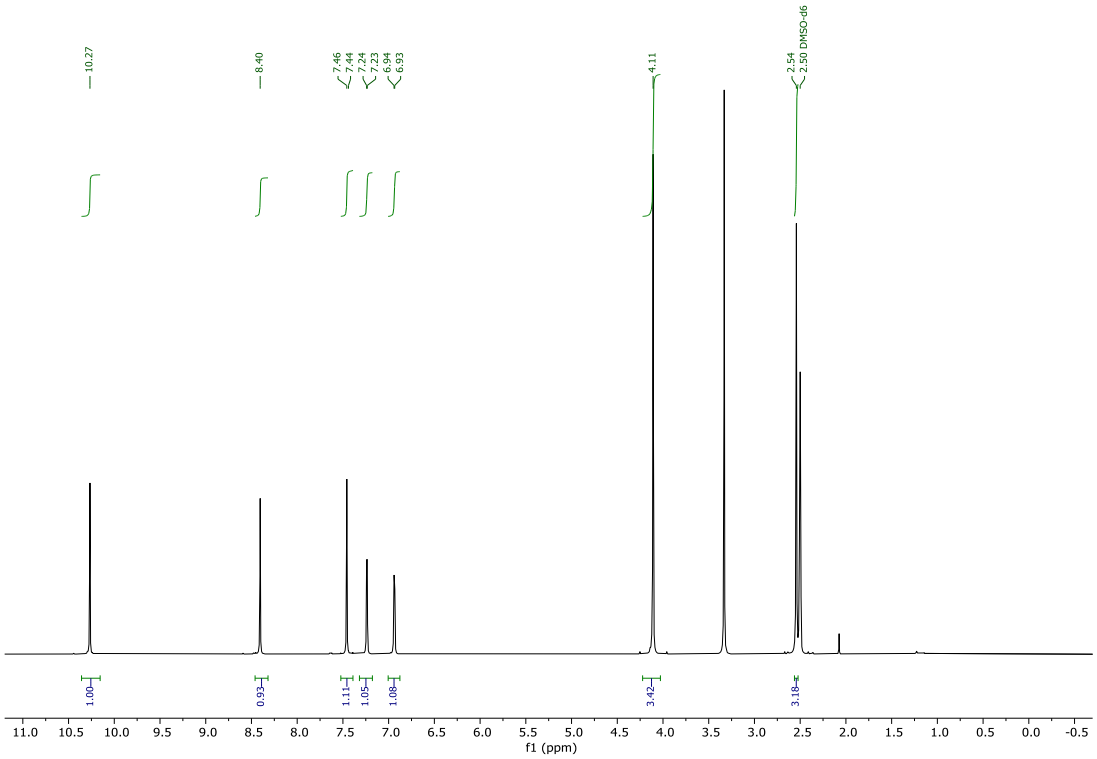
^{13}C NMR (126 MHz, DMSO-d_6) δ 183.9, 150.5, 143.3, 141.3, 134.2, 132.0, 128.3, 126.9, 125.3, 116.0, 111.6, 111.1, 57.4, 14.9.

Structure determination:

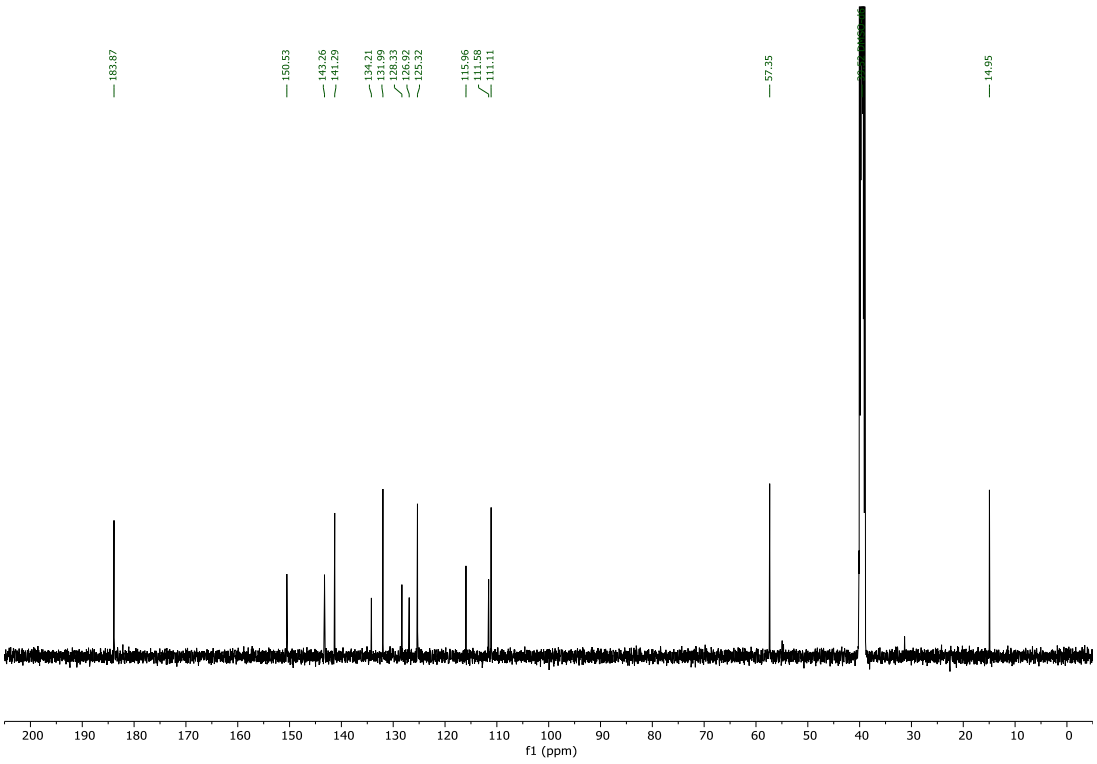
Coupling constant: H3' and H4' have coupling constant J = 3.5 Hz characteristic for C2,C5-substituted thiophenes. Observed coupling J = 0.8 Hz between H4' and adjacent CH_3.

NOE: Correlations observed between H5 and -OCH_3.

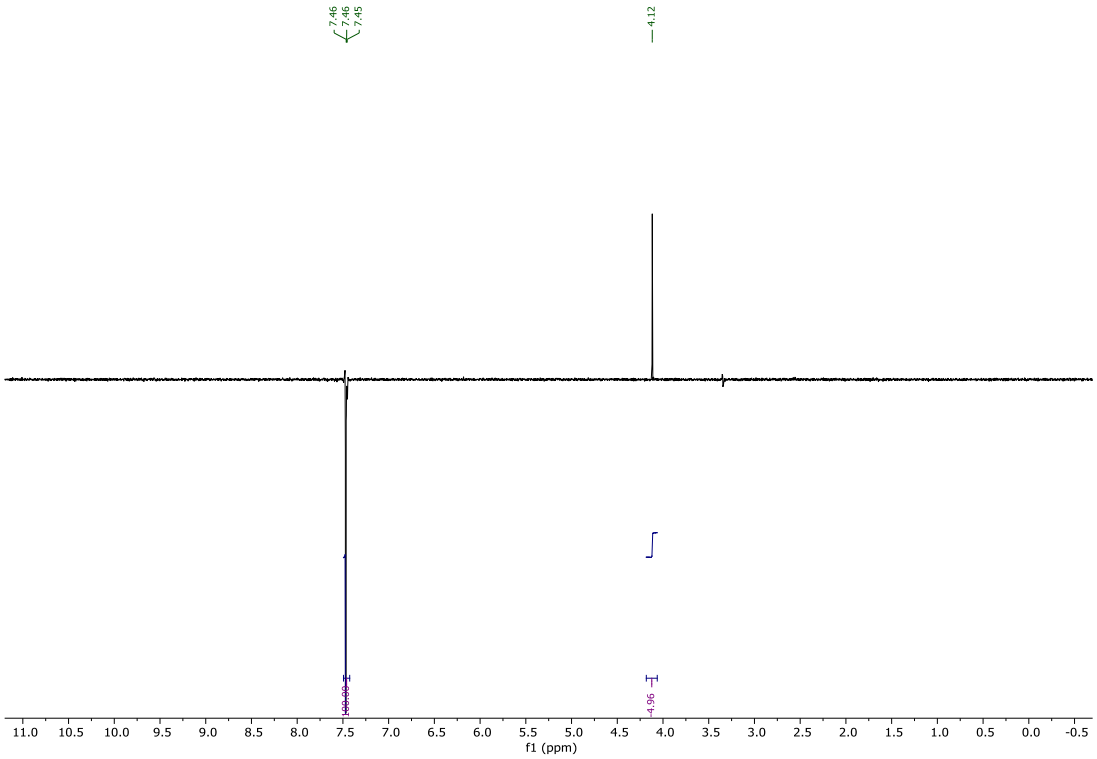
^{1}H NMR

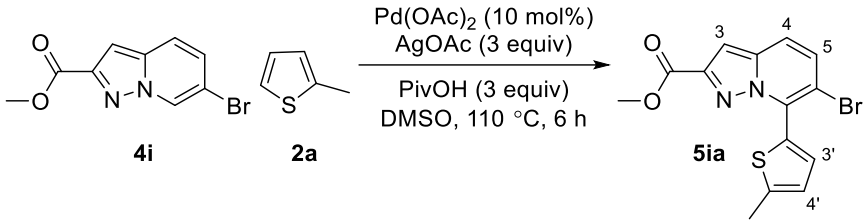


^{13}C NMR



Selective NOE





methyl 6-bromo-7-(5-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-2-carboxylate (**5ia**)

Following the general procedure 2 using **4i** (51 mg, 0.2 mmol), **2a** (40 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 7% to 60% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 51 mg, 73%, light yellow solid.

HRMS: $C_{14}H_{11}BrN_2O_2S$ calc.: 350.9803 (M+H), found: 350.9779

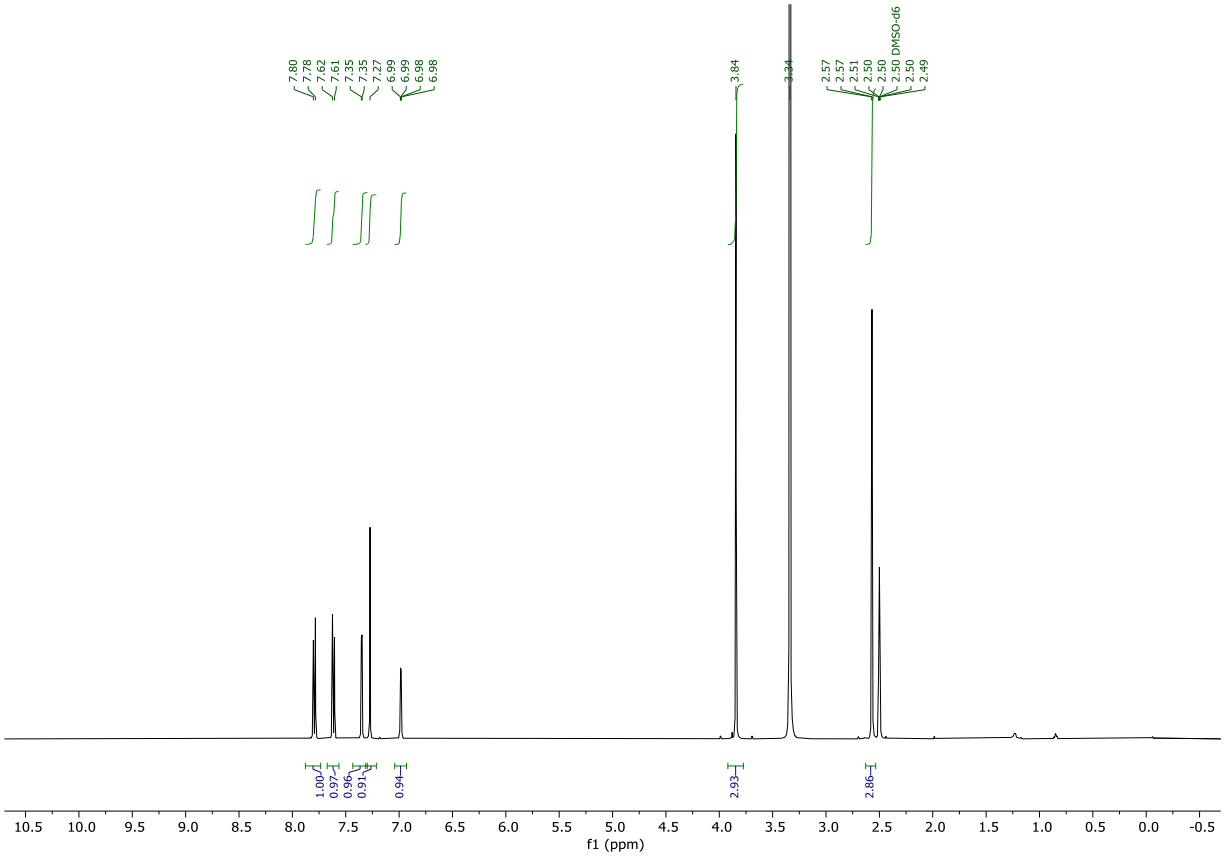
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (d, *J* = 9.4 Hz, 1H, H4), 7.61 (d, *J* = 9.4 Hz, 1H, H5), 7.35 (d, *J* = 3.6 Hz, 1H, H3'), 7.27 (s, 1H, H3), 6.98 (dd, *J* = 3.6, 1.3 Hz, 1H, H4'), 3.84 (s, 3H, OCH_3), 2.57 (d, *J* = 1.1 Hz, 3H, CH_3).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.2, 143.8, 143.4, 140.3, 132.8, 132.1, 128.9, 128.3, 125.5, 119.7, 112.0, 101.8, 52.1, 14.9.

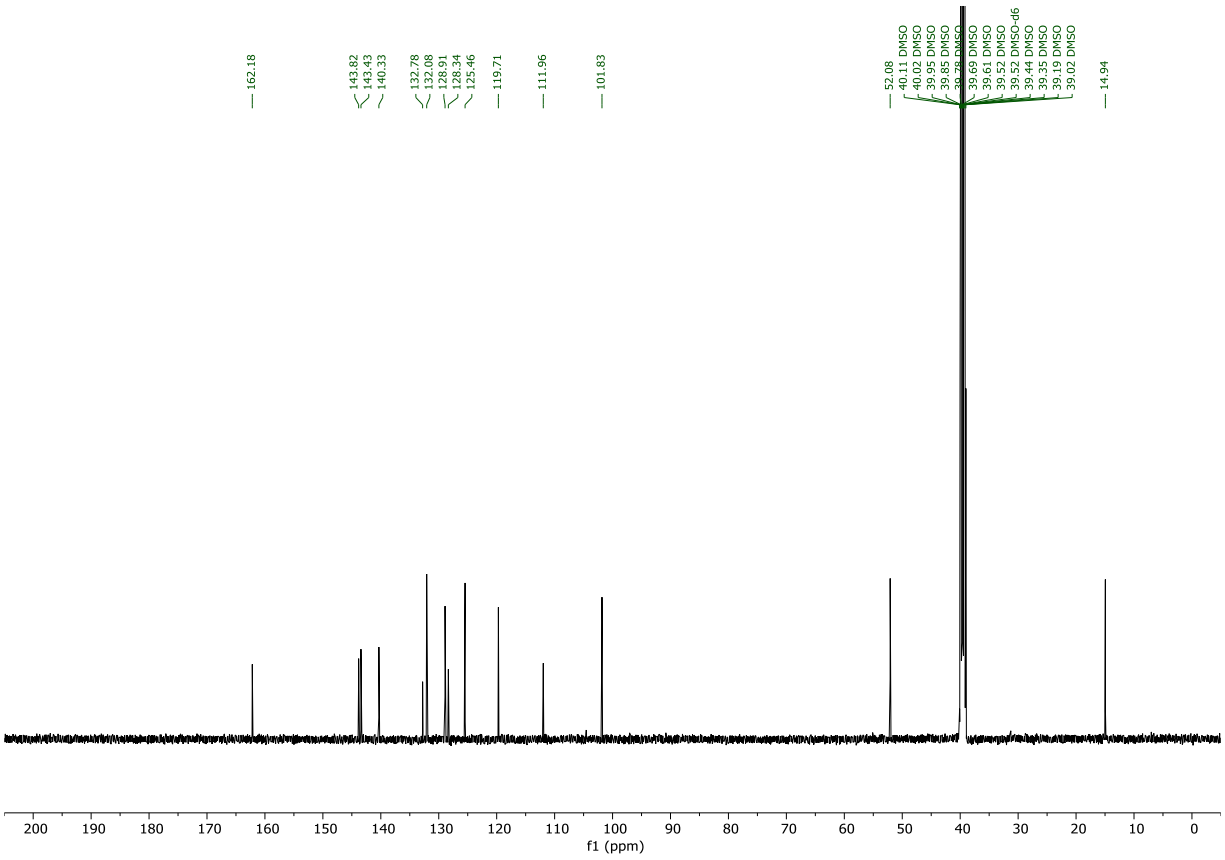
Structure determination:

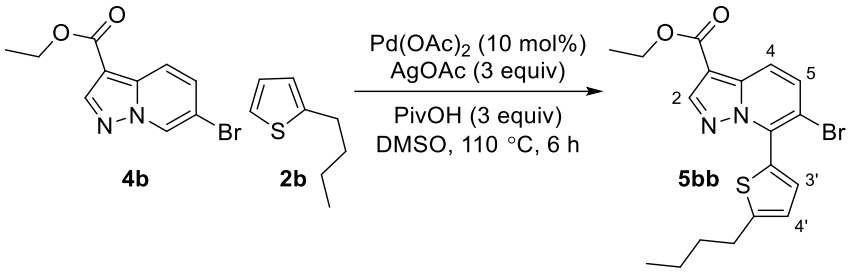
Coupling constant: H4 and H5 have large coupling constant *J* = 9.4 Hz showing they are ortho to each other. H3' and H4' have coupling constant *J* = 3.6 Hz characteristic for C2,C5-substituted thiophenes. H4' and CH3 have coupling constant *J* = 1.1 Hz.

^{1}H NMR



^{13}C NMR





ethyl 6-bromo-7-(5-butylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5bb**)

Following the general procedure 2 using **4b** (54 mg, 0.2 mmol), **2b** (56 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase. It was found that the fraction collected contained PivOH (by NMR) and this impurity can be washed out using saturated $NaHCO_3$ solution.

Yield: 57 mg, 70%, yellow solid.

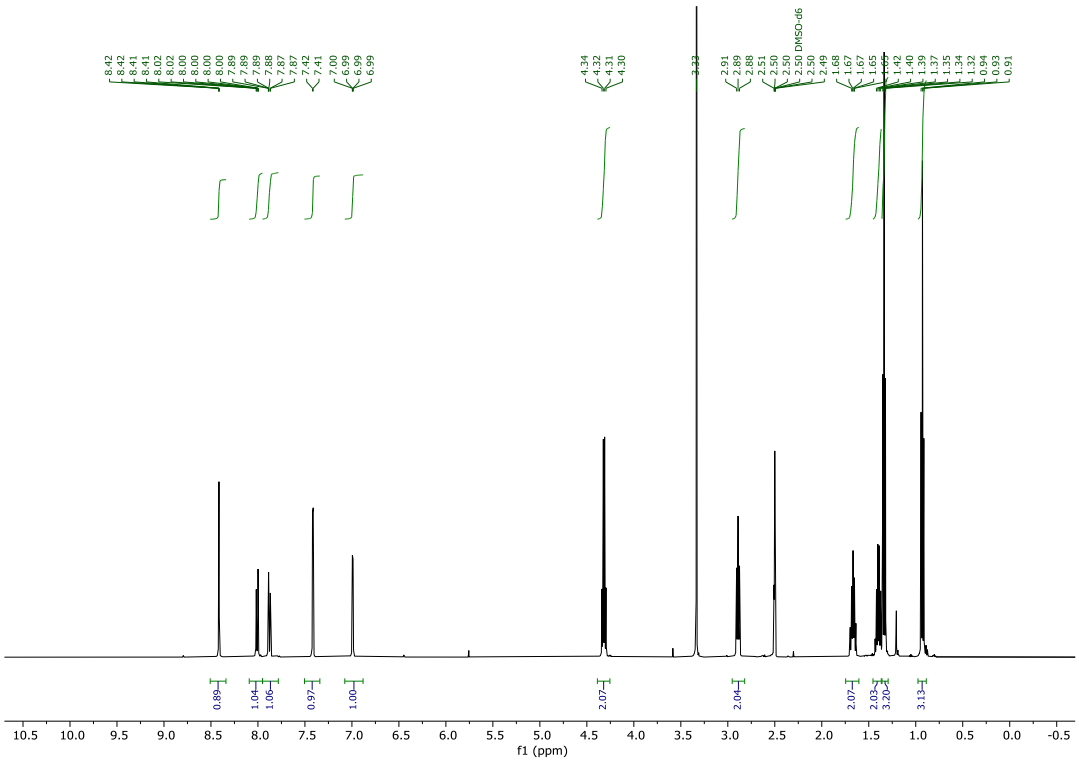
HRMS: $C_{18}H_{19}BrN_2O_2S$ calc.: 407.0429 (M+H), found: 407.0436

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.42 (s, 1H, H2), 7.98 – 8.04 (m, 1H, H4), 7.85 – 7.91 (m, 1H, H5), 7.42 (d, *J* = 3.6 Hz, 1H, H3'), 6.99 (dd, *J* = 3.6, 1.0 Hz, 1H, H4'), 4.32 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.89 (t, *J* = 7.7 Hz, 2H, $\underline{CH_2}CH_2CH_2CH_3$), 1.62 – 1.70 (m, 2H, $CH_2\underline{CH_2}CH_2CH_3$), 1.36 – 1.44 (m, 2H, $CH_2CH_2\underline{CH_2}CH_3$), 1.34 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 0.93 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_2\underline{CH_3}$).

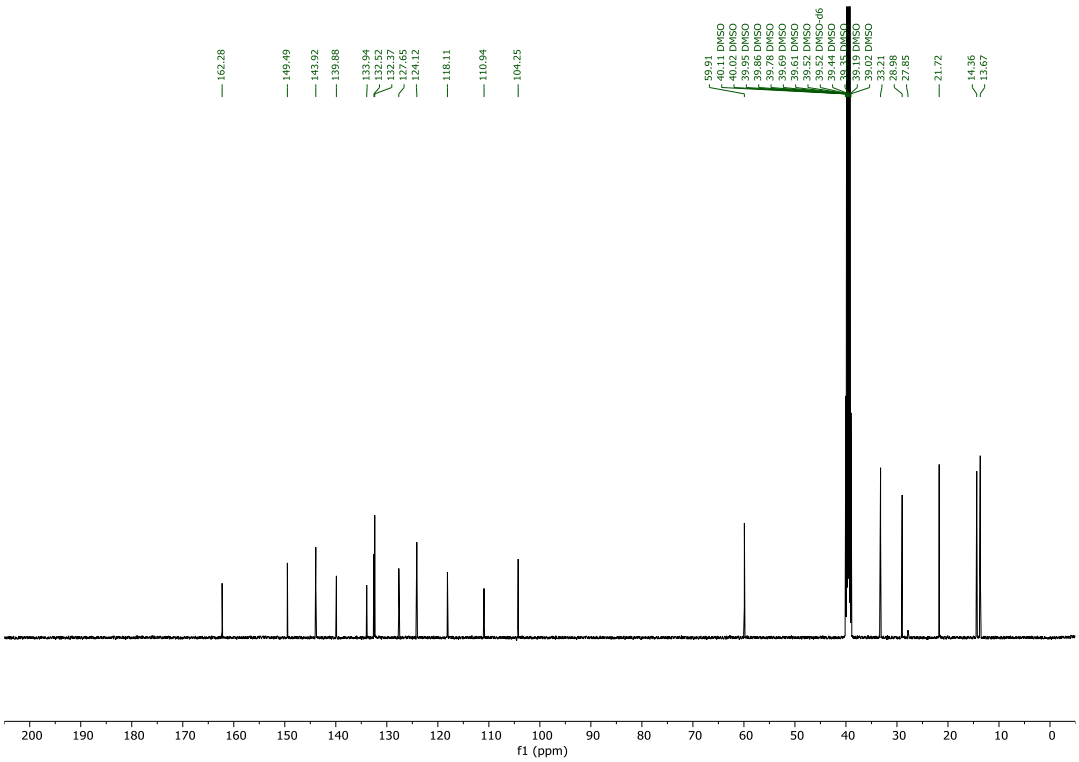
^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 149.5, 143.9, 139.9, 133.9, 132.5, 132.4, 127.6, 124.1, 118.1, 110.9, 104.2, 59.9, 33.2, 29.0, 21.7, 14.4, 13.7.

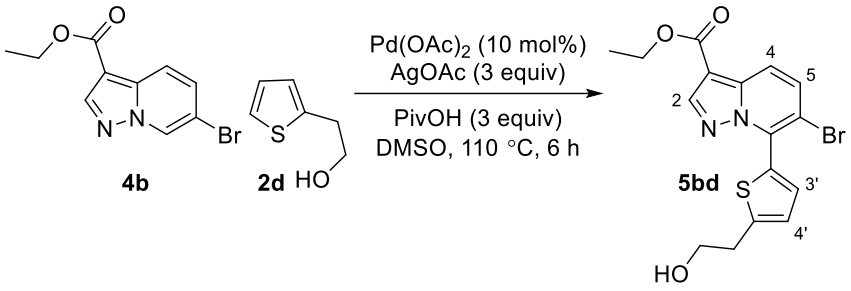
Regioselectivity is analogous to **5ba**.

^{1}H NMR



^{13}C NMR





ethyl 6-bromo-7-(5-(2-hydroxyethyl)thiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5bd**)

Following the general procedure 2 using **4b** (54 mg, 0.2 mmol), **2d** (51 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 12% to 100% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 60 mg, 76%, yellow solid.

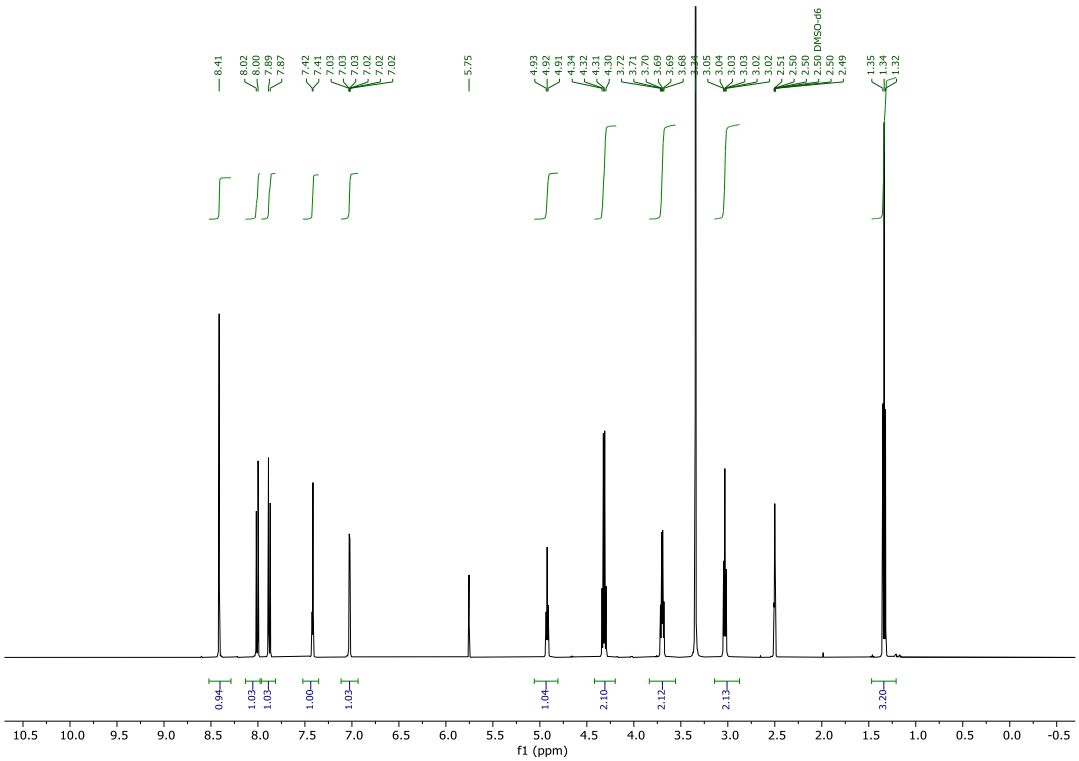
HRMS: $C_{16}H_{15}BrN_2O_3S$ calc.: 395.0065 (M+H), found: 395.0079

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 1H, H2), 8.01 (d, *J* = 9.4 Hz, 1H, H4), 7.88 (d, *J* = 9.4 Hz, 1H, H5), 7.42 (d, *J* = 3.7 Hz, 1H, H3'), 7.03 (dt, *J* = 3.5, 0.9 Hz, 1H, H4'), 4.92 (t, *J* = 5.1 Hz, 1H, OH), 4.32 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 3.70 (td, *J* = 6.5, 5.0 Hz, 2H, $CH_2\underline{CH_2}OH$), 3.03 (td, *J* = 6.5, 0.9 Hz, 2H, $\underline{CH_2}CH_2OH$), 1.34 (t, *J* = 7.1 Hz, 3H, CH_2CH_3).

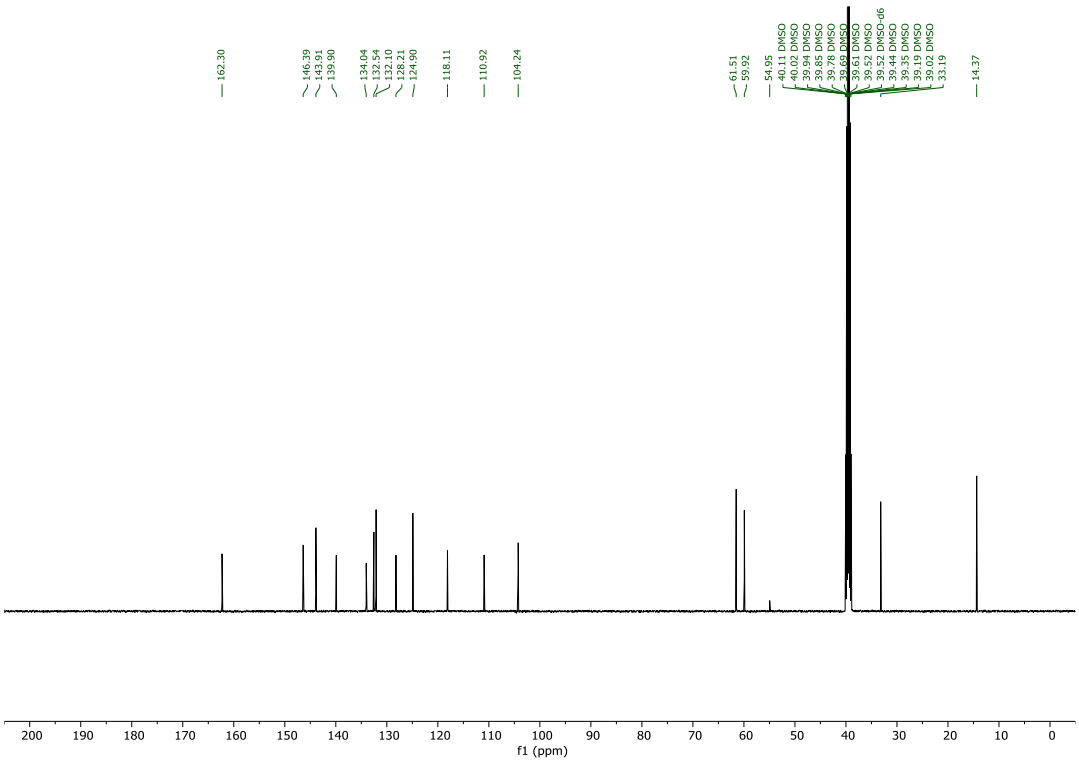
^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 146.4, 143.9, 139.9, 134.0, 132.5, 132.1, 128.2, 124.9, 118.1, 110.9, 104.2, 61.5, 59.9, 33.2, 14.4.

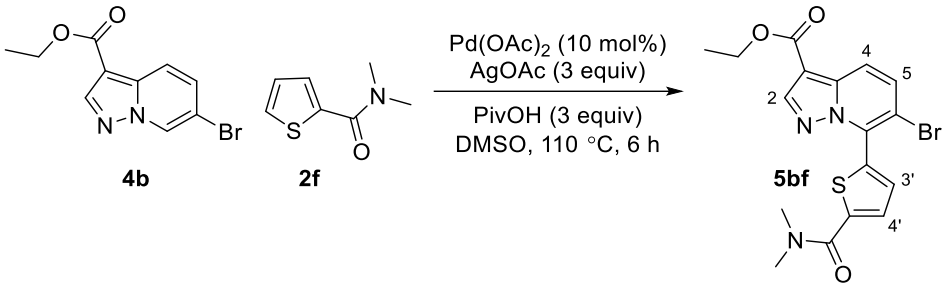
Regioselectivity is analogous to **5ba**.

^{1}H NMR



^{13}C NMR





ethyl 6-bromo-7-(5-(dimethylcarbamoyl)thiophen-2-yl)pyrazolo[1,5-a]pyridine-3-carboxylate (**5bf**)

Following general procedure 2 using **4b** (54 mg, 0.2 mmol), **2f** (62.1 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). Crude product was purified by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 35 to 75% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 49.2 mg, 58%, off-white solid.

HRMS: $C_{17}H_{16}BrN_3O_3S$ calc.: 422.0174 (M+H), found: 422.0194

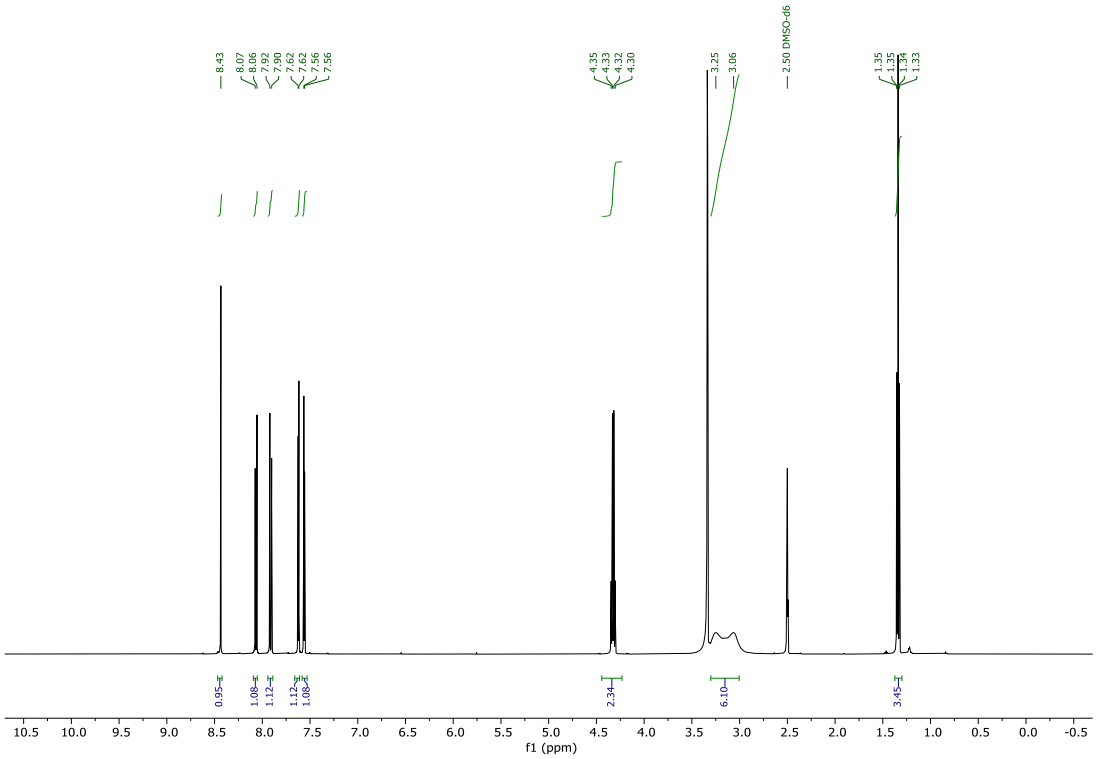
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.06 (d, J = 9.4 Hz, 1H), 7.91 (d, J = 9.4 Hz, 1H), 7.62 (d, J = 3.9 Hz, 1H), 7.56 (d, J = 3.9 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 3.16 (m, 6H), 1.34 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 162.3, 144.0, 141.6, 139.8, 133.5, 132.8, 132.4, 132.1, 128.8, 118.8, 111.5, 104.4, 60.0, 14.4. (The NMe_2 carbons were not observed)

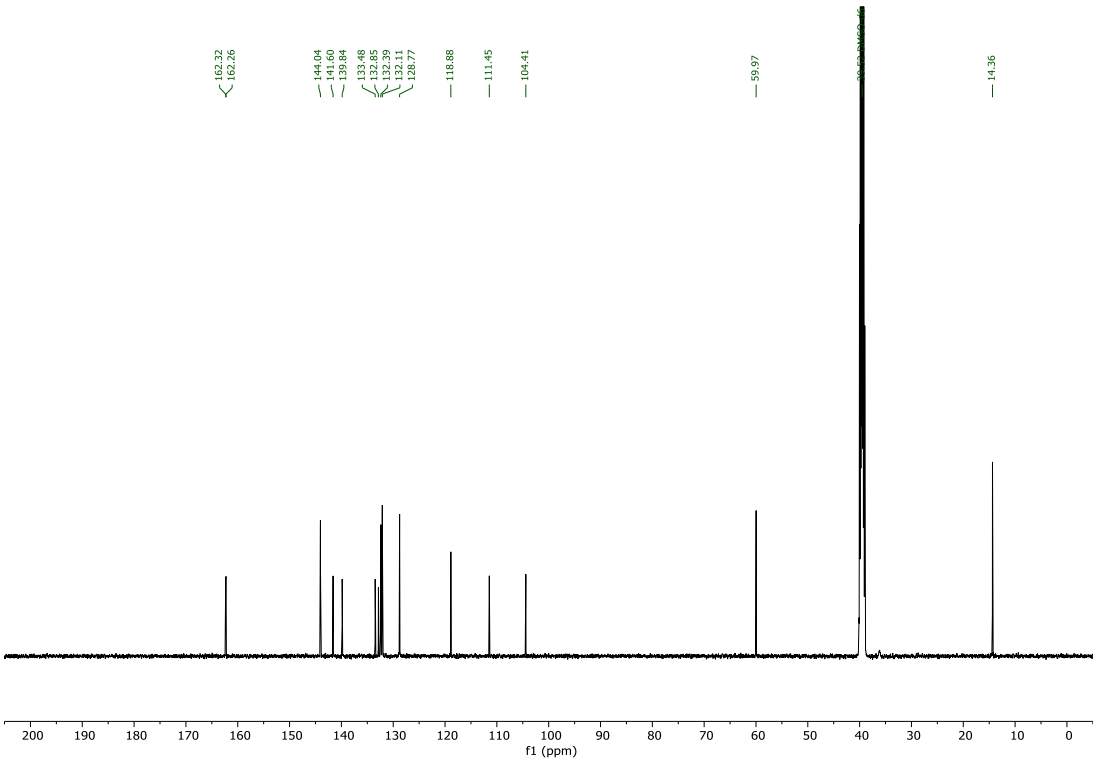
Structure determination:

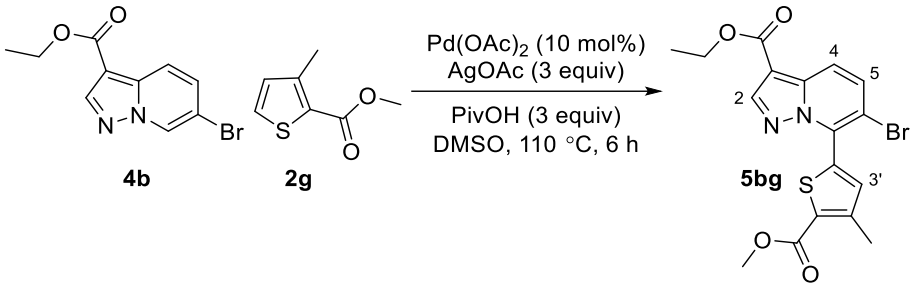
Coupling constant: H4 and H5 have large coupling constant J = 9.4 Hz showing they are ortho to each other. H3' and H4' have coupling constant J = 3.9 Hz characteristic for C2,C5-substituted thiophenes.

^{1}H NMR



^{13}C NMR





ethyl 6-bromo-7-(5-(methoxycarbonyl)-4-methylthiophen-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5bg**)

Following the general procedure 2 using **4b** (54 mg, 0.2 mmol), **2g** (63 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 5% to 40% of EtOAc in heptane over 10 CV as mobile phase. It was found that the fraction collected contained PivOH (by NMR) and this impurity can be washed out using saturated $NaHCO_3$ solution.

Yield: 64 mg, 75%, light yellow solid.

HRMS: $C_{17}H_{15}BrN_2O_4S$ calc.: 423.0014 (M+H), found: 423.0025

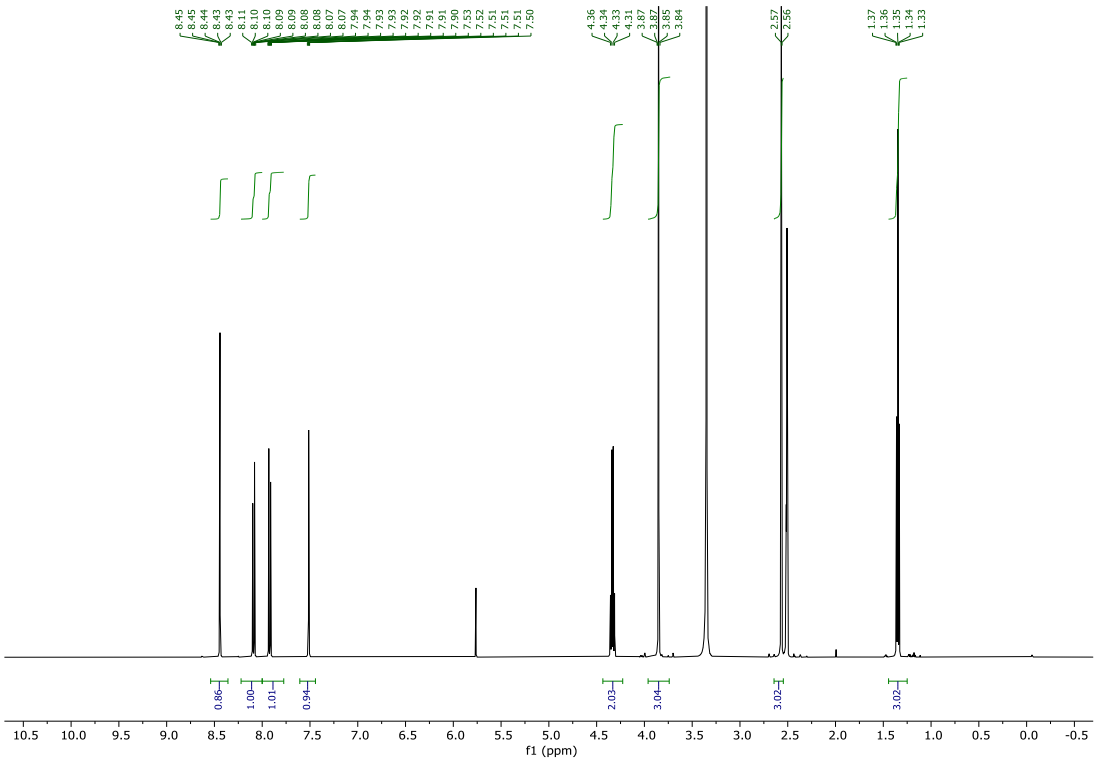
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 (s, 1H, H2), 8.09 (d, J = 9.4 Hz, 1H, H4), 7.92 (d, J = 9.4 Hz, 1H, H5), 7.51 (d, J = 0.6 Hz, 1H, H3'), 4.33 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 3.85 (s, 3H, OCH_3), 2.57 (s, 3H, CH_3), 1.35 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.3, 162.1, 145.2, 144.1, 139.8, 136.2, 134.8, 132.4, 132.3, 128.6, 119.2, 111.5, 104.5, 60.0, 54.9, 15.6, 14.4.

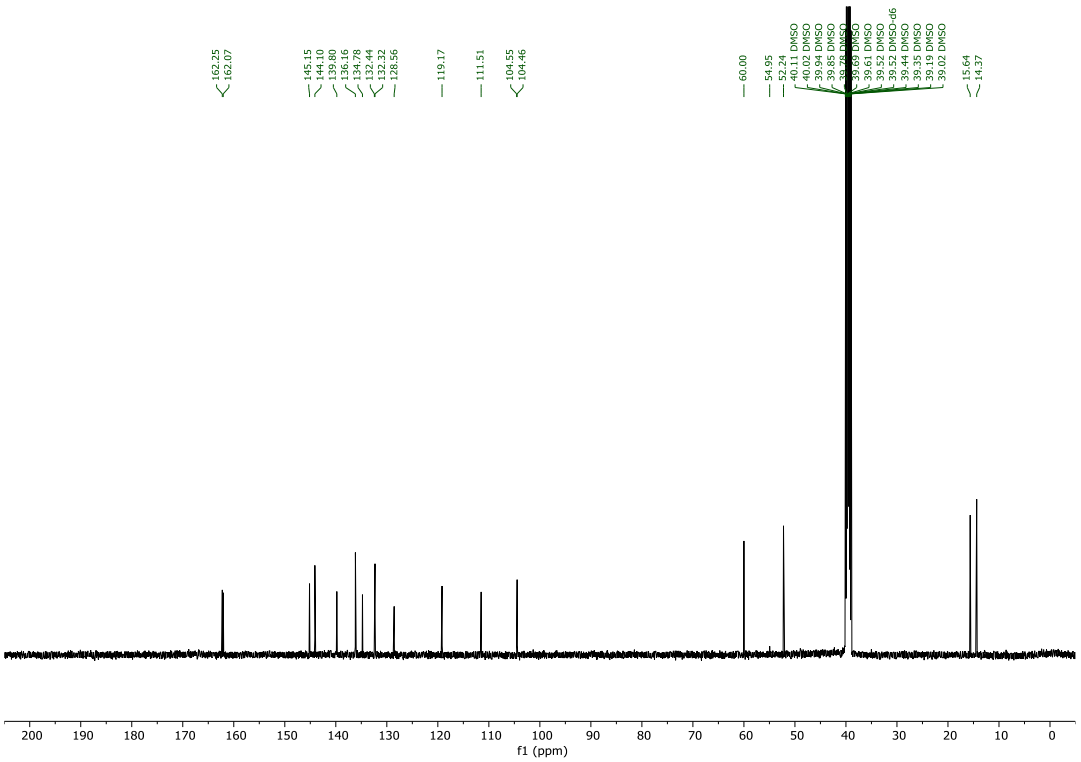
Structure determination:

Coupling constant: H4 and H5 have large coupling constant J = 9.4 Hz showing they are ortho to each other. NOE: H3' has NOE correlation with CH_3.

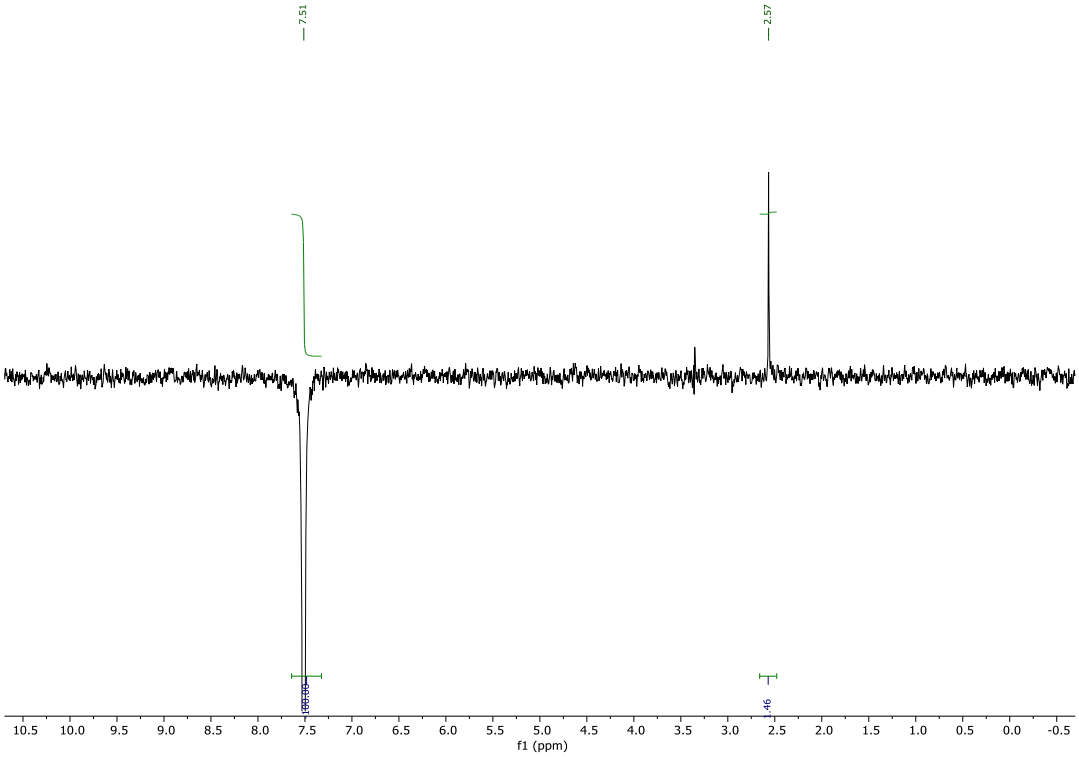
^{1}H NMR

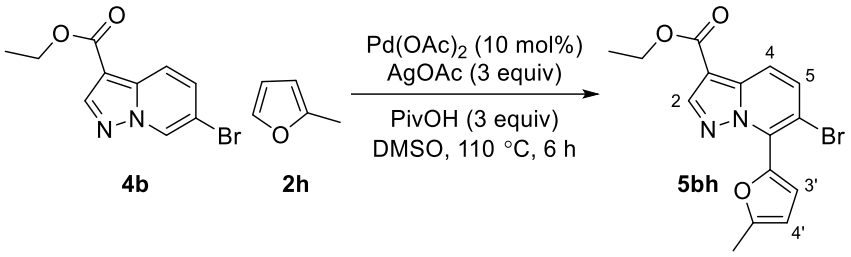


^{13}C NMR



Selective NOE





ethyl 6-bromo-7-(5-methylfuran-2-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5bh**)

Following general procedure 2 using **4b** (54 mg, 0.2 mmol), **2h** (32.8 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 15 to 75% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 16.0 mg, 23%, off-white solid.

HRMS: $C_{15}H_{13}BrN_2O_3$ calc.: 349.0188 (M+H), found: 349.0209

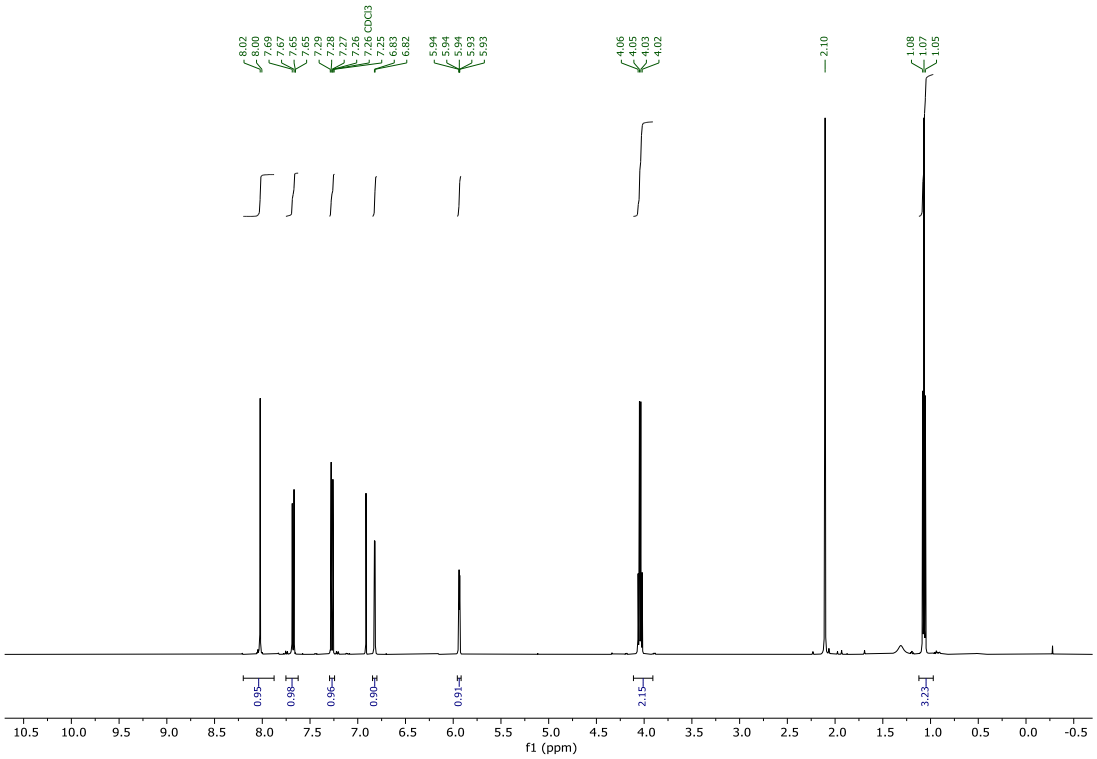
^{1}H NMR (500 MHz, CDCl3) δ 8.37 (s, 1H, H2), 8.02 (d, *J* = 9.4 Hz, 1H, H5), 7.62 (d, *J* = 9.4 Hz, 1H, H4), 7.17 (d, *J* = 3.3 Hz, 1H, H3'), 6.26 – 6.31 (m, 1H, H4'), 4.39 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 2.45 (s, 3H, CH_3), 1.41 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 154.7, 144.7, 141.6, 140.6, 132.5, 131.3, 118.4, 117.9, 109.8, 108.0, 105.1, 60.4, 14.7, 14.1.

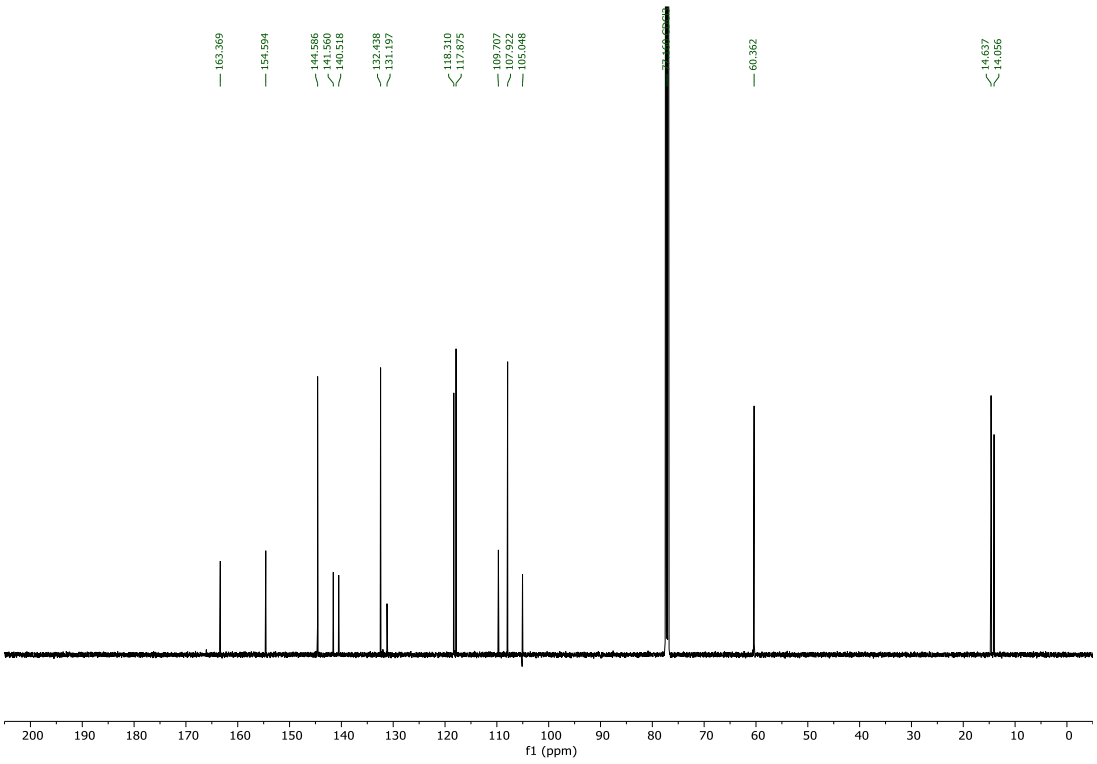
Structure determination:

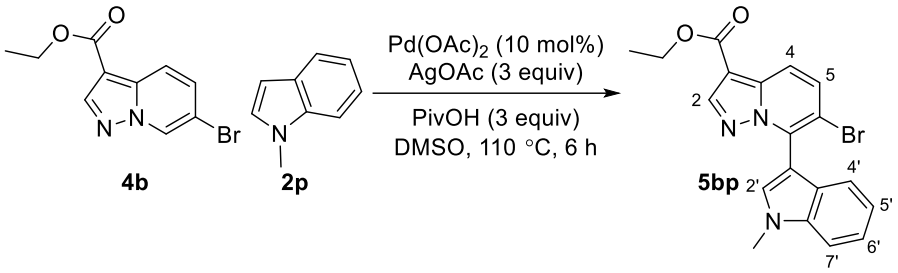
Coupling constant: H4 and H5 have large coupling constant *J* = 9.4 Hz showing they are ortho to each other. H3' and H4' have coupling constant *J* = 3.3 Hz characteristic for C2,C5-substituted furans.

^{1}H NMR



^{13}C NMR





ethyl 6-bromo-7-(1-methyl-1Hindol-3-yl)pyrazolo[1,5-*a*]pyridine-3-carboxylate (**5bp**)

Following the general procedure 2 using **4b** (54 mg, 0.2 mmol), **2p** (53 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by automated flash chromatography on a Biotage Sfär HC D 10 gram column using a gradient from 10% to 80% of EtOAc in heptane over 10 CV as mobile phase.

Yield: 53 mg, 66%, light brown solid.

HRMS: $C_{19}H_{16}BrN_3O_2$ calc.: 398.0504 (M+H), found: 398.0503

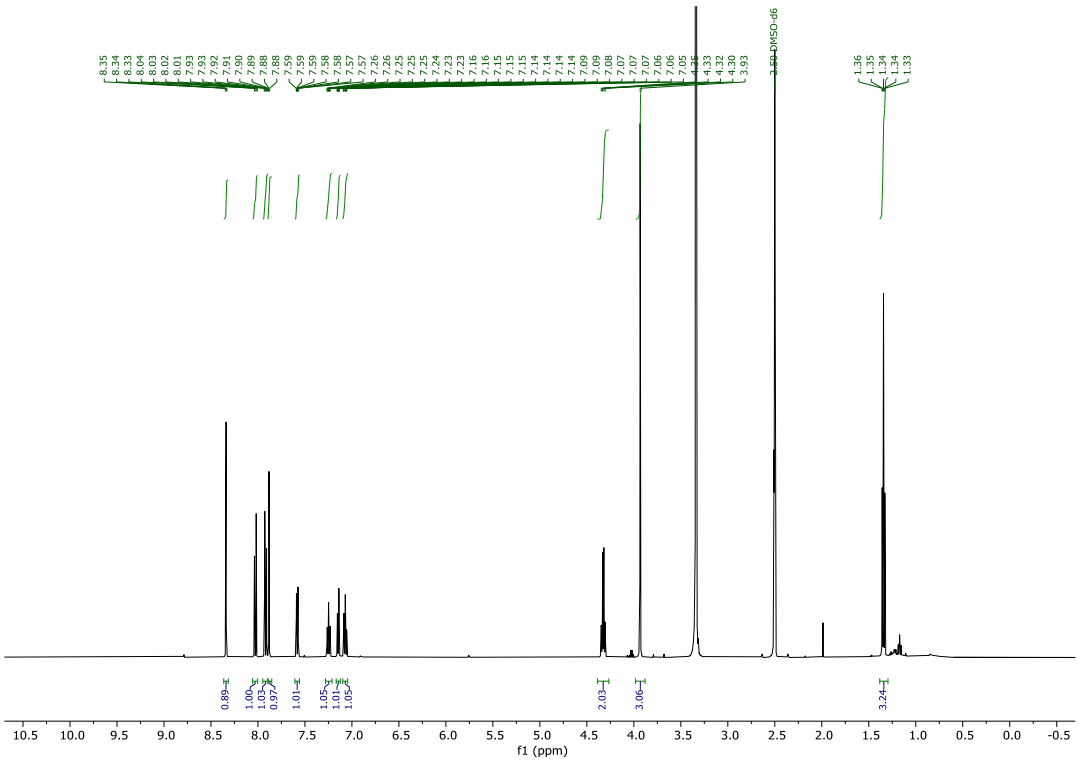
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H, H2), 8.04 (d, *J* = 9.4 Hz, 1H, H4), 7.93 (d, *J* = 9.4 Hz, 1H, H5), 7.89 (s, 1H, H2'), 7.59 (dt, *J* = 8.3, 0.9 Hz, 1H, H7'), 7.26 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, H6'), 7.15 (ddd, *J* = 8.0, 1.2, 0.7 Hz, 1H, H4'), 7.08 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H, H5'), 4.33 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 3.94 (s, 3H, CH_3), 1.35 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.4, 143.9, 140.0, 136.3, 135.7, 132.5, 132.4, 125.9, 121.7, 120.4, 119.9, 117.0, 110.5, 104.8, 104.6, 103.9, 59.8, 32.9, 14.4.

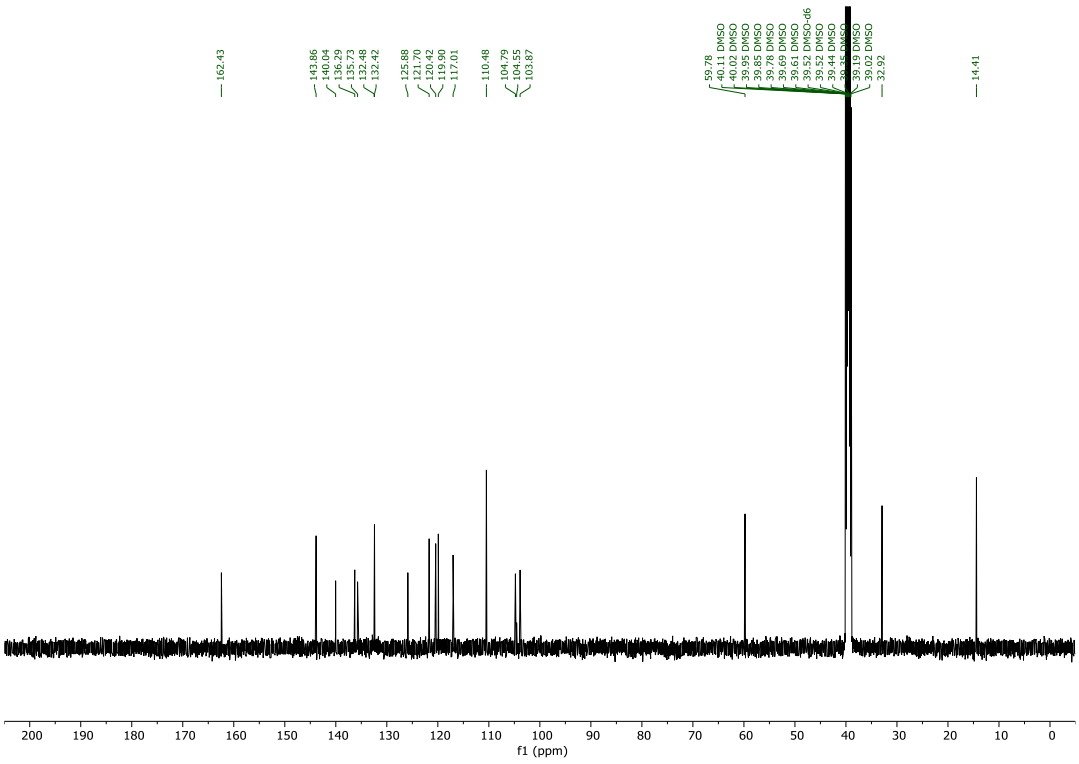
Structure determination:

Coupling constant: H4 and H5 have large coupling constant *J* = 9.4 Hz showing they are ortho to each other. NOE: CH_3 has NOE correlation with H2' and H7'.

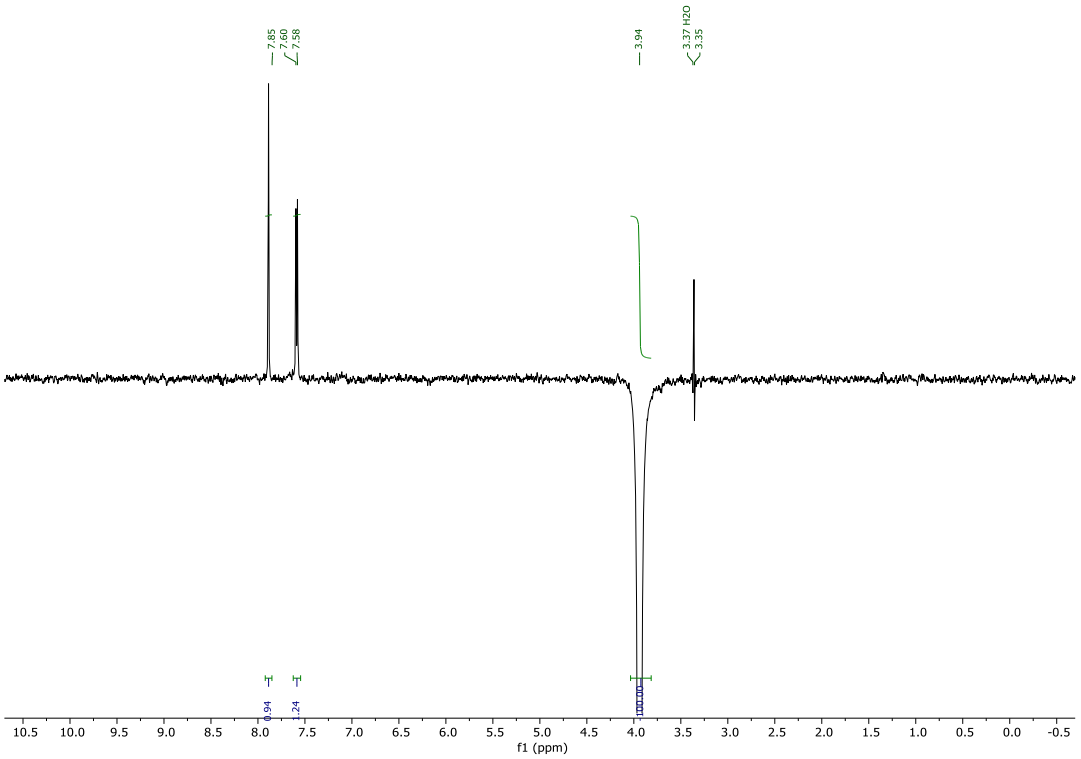
^{1}H NMR

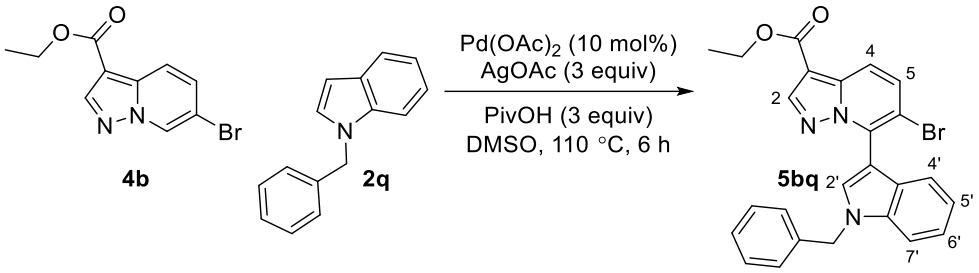


^{13}C NMR



Selective NOE





ethyl 7-(1-benzyl-1Hindol-3-yl)-6-bromopyrazolo[1,5-*a*]pyridine-3-carboxylate (**5bq**)

Following the general procedure 2 using **4b** (54 mg, 0.2 mmol), **2q** (83 mg, 0.4 mmol), DMSO (1 mL), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) and PivOH (63 mg, 0.6 mmol). The crude material was purified by preparative HPLC on an XBridge C18 250x20 mm, 10µm, column using a gradient from 50 to 100% of MeCN in a basic buffer (H_2O/MeCN/NH_4HCO_3 95/5/10 mM).

Yield: 68 mg, 70%, white solid.

HRMS: $C_{25}H_{20}BrN_3O_2$ calc.: 474.0817 (M+H), found: 474.0837

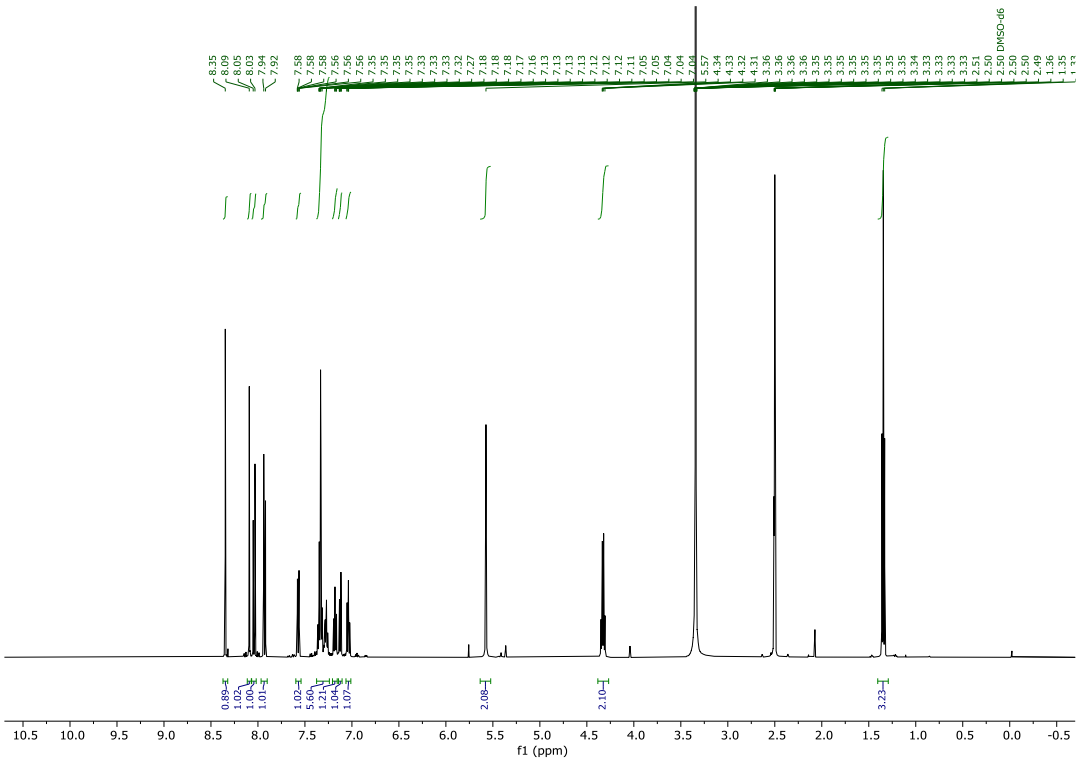
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H, H2), 8.09 (s, 1H, H2'), 8.04 (d, *J* = 9.4 Hz, 1H, H4), 7.93 (d, *J* = 9.3 Hz, 1H, H5), 7.57 (dt, *J* = 8.3, 0.9 Hz, 1H, H7'), 7.23 – 7.4 (m, 5H, C_6H_5), 7.18 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, H6'), 7.12 (ddd, *J* = 8.0, 1.2, 0.7 Hz, 1H, H4'), 7.04 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, H5'), 5.57 (s, 2H, CH_2), 4.33 (q, *J* = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 1.35 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$).

^{13}C NMR (126 MHz, DMSO-d_6) δ 162.4, 143.9, 140.1, 137.7, 135.6, 135.6, 132.4, 132.1, 128.7, 127.6, 127.2, 126.3, 121.8, 120.6, 120.0, 117.1, 111.0, 110.6, 105.5, 103.9, 59.8, 49.5, 14.4.

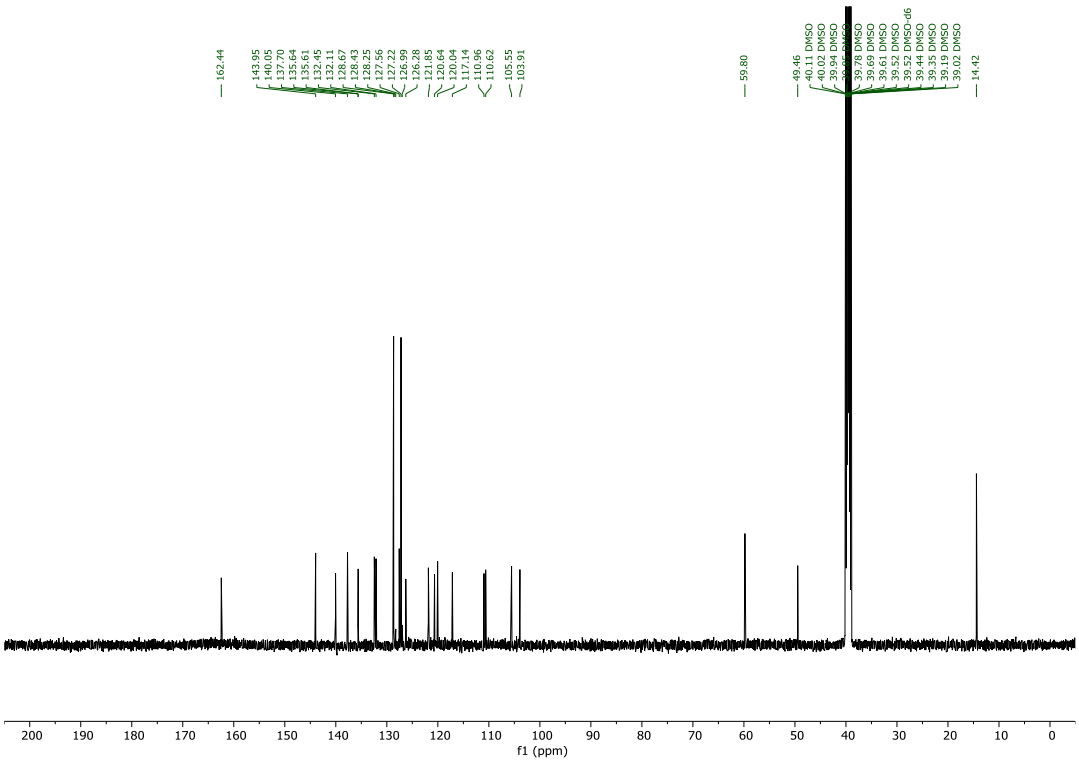
Structure determination:

Coupling constant: H4 and H5 have large coupling constant *J* = 9.4 Hz showing they are ortho to each other. NOE: CH_2 has NOE correlation with H2', H7' and C_6H_5.

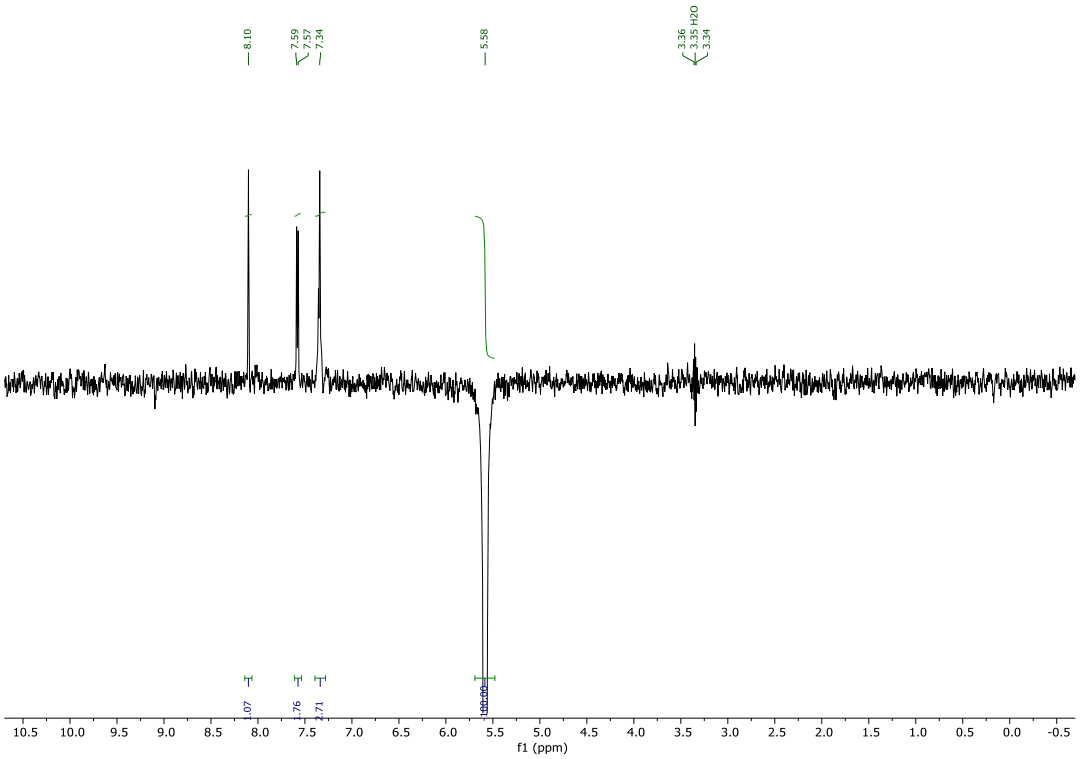
^{1}H NMR



^{13}C NMR



Selective NOE



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