

Supplementary Material

The Dimroth rearrangement as a probable cause for structure misassignments in imidazo[1,2-a]pyrimidines: A ^{15}N -labelling study and an easy method for the determination of regio-chemistry

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Supplementary Tables

Supplementary Table 1

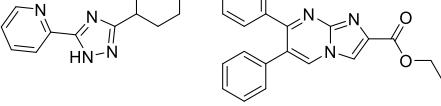
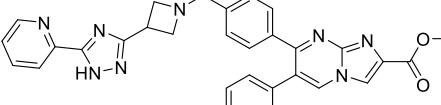
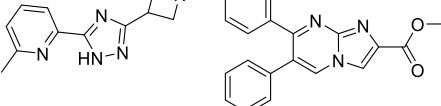
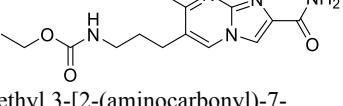
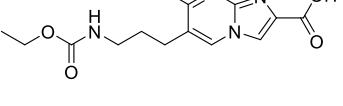
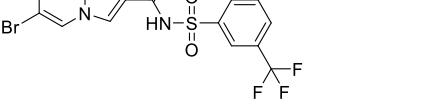
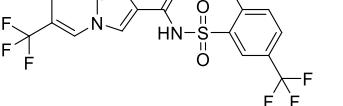
Cpd	Solvent	H-7	H-5	H-3	H-2	C-7	C-5	C-3	C-2
3a	CDCl ₃	8.86	8.58	8.18	-	152.0	130.4	115.8	142.6
	MeOH-d ₄	NS	NS	NS	-	-	-	-	-
	MeCN-d ₃	8.89	8.89	8.09	-	-	-	-	-
	DMSO-d ₆	9.34	9.03	8.27	-	-	-	-	-
5a	CDCl ₃	8.93	9.51	-	8.05	152.3	133.1	116.0	139.0
	MeOH-d ₄	NS	NS	NS	-	-	-	-	-
	MeCN-d ₃	NS	NS	NS	-	-	-	-	-
	DMSO-d ₆	9.07	9.41	-	8.24	-	-	-	-
3b	CDCl ₃	8.79	8.60	8.16	-	150.6	130.6	115.3	144.0
	MeOH-d ₄	NS	NS	NS	-	-	-	-	-
	MeCN-d ₃	NS	NS	NS	-	-	-	-	-
	DMSO-d ₆	9.03	9.41	8.21	-	-	-	-	-
5b	CDCl ₃	8.87	9.74	-	8.16	151.2	133.7	117.0	139.6
	MeOH-d ₄	9.02	9.62	-	8.22	-	-	-	-
	MeCN-d ₃	8.88	9.60	-	8.11	-	-	-	-
	DMSO-d ₆	9.08	9.60	-	8.29	-	-	-	-
3c	CDCl ₃	8.85	8.66	8.18	-	150.9	130.8	115.3	143.8
	MeOH-d ₄	9.01	9.27	8.21	-	-	-	-	-
	MeCN-d ₃	8.89	8.95	8.07	-	-	-	-	-
	DMSO-d ₆	9.07	9.45	8.23	-	-	-	-	-
5c	CDCl ₃	8.92	9.77	-	8.17	151.5	133.9	117.0	139.3
	MeOH-d ₄	9.07	9.65	-	8.23	-	-	-	-
	MeCN-d ₃	8.94	9.64	-	8.12	-	-	-	-
	DMSO-d ₆	9.11	9.63	-	8.28	-	-	-	-
3d	CDCl ₃	8.84	8.58	8.13	-	151.6	130.4	115.1	143.4
	MeOH-d ₄	8.96	9.16	8.18	-	-	-	-	-
	MeCN-d ₃	8.88	8.88	8.04	-	-	-	-	-
	DMSO-d ₆	9.01	9.33	8.22	-	-	-	-	-
5d	CDCl ₃	8.90	9.68	-	8.11	152.0	133.5	116.8	139.0
	MeOH-d ₄	9.09	9.56	-	8.19	-	-	-	-
	MeCN-d ₃	8.91	9.56	-	8.09	-	-	-	-
	DMSO-d ₆	9.06	9.55	-	8.26	-	-	-	-
3e	CDCl ₃	8.84	8.58	8.20	-	151.5	130.4	114.9	143.6
	MeOH-d ₄	NS	NS	NS	-	-	-	-	-
	MeCN-d ₃	NS	NS	NS	-	-	-	-	-
	DMSO-d ₆	9.01	9.34	8.28	-	-	-	-	-
5e	CDCl ₃	8.94	10.06	-	8.24	152.2	133.9	119.8	139.6
	MeOH-d ₄	9.03	9.91	-	8.33	-	-	-	-
	MeCN-d ₃	8.94	9.97	-	8.22	-	-	-	-
	DMSO-d ₆	9.08	9.88	-	8.39	-	-	-	-

NS: not soluble

Supplementary Table 2

Entry	Structure/Name	¹ H-NMR	Reference	Synthesis/Comments
1		¹ H-NMR (300MHz, CDCl ₃): δ (ppm) 9.73 (1H, d, J=2.7Hz), 8.72 (1H, d, J=2.7Hz), 8.43 (1H, s), 4.45 (2H, q, J=7.2Hz), 1.44 (3H, t, J=7.2Hz)	EP1849465	Starting from 5-Br-2-aminopyrimidine with cyclization with ethyl bromopyruvate, followed by hydrolysis * Appears to be an incorrect assignments
2		¹ H-NMR (300MHz, CDCl ₃): δ (ppm) 9.74 (1H, d, J=2.7Hz), 8.94 (1H, d, J=2.7Hz), 8.49 (1H, s), 7.58 (2H, d, J=8.7Hz), 7.52 (2H, d, J=8.7Hz), 4.45 (2H, q, J=7.2Hz), 1.45 (3H, t, J=7.2Hz),	EP1849465	Suzuki on entry 1 * Appears to be an incorrect assignments
3		¹ H-NMR (300MHz, DMSO-d ₆): δ (ppm) 13.50 (1H, brs), 9.68 (1H, d, J=2.7Hz), 9.12 (1H, d, J=2.7Hz), 8.43 (1H, s), 7.85 (2H, d, J=8.7Hz), 7.64 (2H, d, J=8.7Hz).	EP1849465	From hydrolysis of entry 1 * Appears to be an incorrect assignments
4		¹ H NMR (DMSO-d ₆ , 400 MHz): δ (ppm) 9.67 (s, 1H), 8.99 (s, 1H), 8.49 (s, 1H), 5.98 (br s, 2H)	WO2012054233	Starting from 2-amino-5-trifluoromethylpyrimidine with cyclization with bromopyruvic acid * Appears to be an incorrect assignment
5		¹ H NMR (DMSO-d ₆ , 300 MHz): δ (ppm) 9.98 (s, 1H), 9.75-9.76 (d, 1H, J=2.4Hz), 8.97-8.98 (d, 1H, 2.4Hz), 8.70 (s, 1H)	WO201155320	From 2-amino-5-bromopyrimidine with bromomalonaldehyde *Appears to be the correct structure
6		¹ H NMR (DMSO-d ₆ ; 300 MHz): δ (ppm) 9.88 (s, 1H), 8.92 (s, 1H), 8.48 (s, 1H), 8.24 (s, 1H), 7.99 (d, 2H), 7.76 (d, 2H), 4.77 (m, 1H), 4.2 (t, 1H), 3.83 (m, 1H), 3.45 (2H, t), 1.83 (1H, s)	US63621912002	From the 2-amino-5-chloropyrimidine with the respective bromoketone * Appears to be an incorrect assignment
7		¹ H NMR (DMSO-d ₆ , 300 MHz): δ (ppm) 10.84 (s, 1H), 9.85 (d, 1H, J=2.6 Hz), 9.10 (d, 1H, J=2.6 Hz), 8.83 (s, 1H), 8.68 (d, 1H, J=2.0 Hz), 8.36 (d, 1H, J=2.4 Hz), 7.82-7.87 (m, 3H), 7.60-7.65 (m, 3H), 2.61 (s, 3H)	J. Med. Chem., 2011, 54, 2455-2466	From 6-bromo[1,2-a]imidazopyrimidine with a Suzuki and then acetylation *Appears to be the correct assignment
8		¹ H NMR (acetone, 400 MHz): δ (ppm) 9.23-9.49 (m, 1H), 8.65 (d, J=2.5 Hz, 1H), 8.31 (s, 1H), 4.41 (q, J=7.2 Hz, 2H), 2.49 (s, 3H), 1.39 (t, J=7.1 Hz, 3H)	J. Med. Chem., 2011, 54, 7705 - 7712	From 2-amino-5-methylpyrimidine cyclization with (E)-ethyl 3-ethoxyacrylate and NBS.

	Ethyl 6-methylimidazo[1,2- <i>a</i>]pyrimidine-3-carboxylate			*Inconclusive. In addition the next step is a hydrolysis to derive the acid and there is no NMR of the carboxylic acid analogue
9	 N-{trans-3-[{(5-Cyano-6-methylpyridin-2-yl)oxy}-2,2,4,4-tetramethylcyclobutyl]-6-methylimidazo[1,2-a]pyrimidine-3-carboxamide	¹H NMR (DMSO-d₆, 400 MHz): δ (ppm) 9.53 (s, 1H), 8.62 (s, 1H), 8.60 (d, J = 2.5 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 9.3 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 4.78 (s, 1H), 4.11 (d, J = 9.1 Hz, 1H), 2.58 (s, 3H), 2.38 (s, 3H), 1.25 (s, 6H), 1.15 (s, 6H).	<i>J. Med. Chem.</i> , 2011, 54, 7705 - 7712	Amide coupling with the respective carboxylic acid (entry 8) and HBTU and TEA * Appears to be an incorrect assignment
10	 6-Bromo-N-{trans-3-[{(5-cyano-6-methylpyridin-2-yl)oxy}-2,2,4,4-tetramethylcyclobutyl]-6-methylimidazo[1,2-a]pyrimidine-3-carboxamide	¹H NMR (acetonitrile-d₃, 400 MHz): δ (ppm) 9.84 (d, J = 2.5 Hz, 1H), 8.66 (d, J = 2.5 Hz, 1H), 8.40 (s, 1H), 7.86 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 4.75 (s, 1H), 4.11 (d, J = 9.1 Hz, 1H), 2.60 (s, 3H), 1.28 (s, 6H), 1.18 (s, 6H).	<i>J. Med. Chem.</i> , 2011, 54, 7705 - 7712	Same as entry 8. This carboxylic acid was commercially available though *Appears to be the correct assignment
11	 Ethyl 6-fluoroimidazo[1,2- <i>a</i>]pyrimidine-3-carboxylate	¹H NMR (acetonitrile-d₃, 400 MHz): δ (ppm) 9.50 (dd, J = 4.3, 3.0 Hz, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.40 (s, 1H), 4.42 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H)	<i>J. Med. Chem.</i> , 2011, 54, 7705 - 7712	From 2-amino-5-fluoropyrimidine cyclization similar to entry 8 * Appears to be the correct assignment
12	 6-Fluoroimidazo[1,2- <i>a</i>]pyrimidine-3-carboxylic Acid	¹H NMR (DMSO-d₆, 400MHz): δ (ppm) 9.48 (dd, J = 4.3, 3.0 Hz, 1H), 8.89 (d, J = 3.0 Hz, 1H), 8.35 (s, 1H).	<i>J. Med. Chem.</i> , 2011, 54, 7705 - 7712	From hydrolysis of entry 11 * Appears to be the correct assignment
13	 N-((1r,3r)-3-(5-Cyano-6-methylpyridin-2-yloxy)-2,2,4,4-tetramethylcyclobutyl)-6-fluoroimidazo[1,2-a]pyrimidine-3-carboxamide	¹H NMR (acetonitrile-d₃, 400 MHz): δ (ppm) 9.71 (dd, J = 4.5, 3.0 Hz, 1H), 8.70 (d, J = 3.0 Hz, 1H), 8.46 (s, 1H), 7.86 (d, J = 8.6 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H), 6.73 (d, J = 8.8 Hz, 1H), 4.75 (s, 1H), 4.12 (d, J = 9.1 Hz, 1H), 2.60 (s, 3H), 1.28 (s, 6H), 1.13–1.19 (m, 6H).	<i>J. Med. Chem.</i> , 2011, 54, 7705 - 7712	Same as entry 9 * Appears to be the correct assignment

14		Characteristic ^1H NMR (DMSO-d₆, 400 MHz) signals: 9 ppm (s, 1H), 8.4 ppm (s, 1H), 1.4 ppm (t, 3H)	WO200921992	Synthesised from the respective 2-aminopyrimidine with bromopyruvate. * Appears to be an incorrect assignment
15		$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆): δ (ppm) 14.42 (very br, 1H), 9.00 (s, 1H), 8.63 (d, 1H), 8.44 (s, 1H), 8.03 (d, 1H), 7.94 (br., 1H), 7.12-7.52 (m, 10H), 3.89 (s, 3H), 3.50- 3.82 (m, 5H), 3.22-3.39 (m, 2H, under the water signal of the solvent).	WO201091808	Same as entry 13 * Appears to be an incorrect assignment
16		$^1\text{H-NMR}$ (300 MHz, d6-DMSO): δ (ppm) 14.23 (very br., 1H), 9.00 (s, 1H), 8.45 (s, 1H), 7.72-7.88 (m, 2H), 7.15-7.40 (m, 10H), 3.88 (s, 3H), 3.50-3.80 (m, 5H), 3.22-3.39 (m, 2H, under the water signal of the solvent), 2.51 (s, 3H)	WO201091808	Same as entry 13 * Appears to be an incorrect assignment
17		$^1\text{H NMR}$ (500 MHz, CDCl ₃): δ (ppm) 8.95 (d, 2 H, CONH2), 8.22 (s, 1 H, CH), 8.10 (s, 1 H, NCHCN), 5.42 (br s, 1 H, NH), 4.03 (q, 3J = 6 Hz, 2 H, OCH ₂), 3.21 (m, 3J = 6 Hz, 2 H, CH ₂ NH), 2.55 (t, 3J = 6 Hz, 2 H, CCH ₂), 2.44 (s, 3 H, CH ₃), 1.74 (m, 3J = 6 Hz, 2 H, CH ₂), 1.09 (t, 3J = 6 Hz, 3 H, CH ₃ CH ₂).	Synthesis, 2011, 9, 1465 - 1471	From the reaction of a β -enamino Ketone with 1,3- <i>N,N</i> -Bis-nucleophile * Correct regio-isomer. Confirmation with NOESY would be required.
18		$^1\text{H NMR}$ (500 MHz, DMSO-d ₆): d = 11.28 (br s, 1 H, COOH), 8.42 (s, 1 H, CH), 8.28 (s, 1 H, NCHCN), 8.02 (br s, 3 H, NH ³⁺), 3.44 (m, 3J = 6 Hz, 2 H, CH ₂ NH ³⁺), 2.61 (t, 3J = 6 Hz, 2 H, CCH ₂), 2.42 (s, 3 H, CH ₃), 1.80 (m, 3J = 6 Hz, 2 H, CH ₂).	Synthesis, 2011, 9, 1465 - 1471	Same as entry 17 * Correct regio-isomer. Confirmation with NOESY would be required.
19		$^1\text{H NMR}$ (CDCl ₃): δ (ppm) 10.10 (br s, 1H), 8.46 (s, 1H), 8.27 (s, 1H), 7.86 (d, 1H), 7.54 (s, 1H), 7.38 (d, 1H), 7.09 (dd, 1H), 3.91 (s, 3H).	WO201254233	Starting from 2-amino-5-bromopyrimidine, cyclization with bromopyruvic acid and then amide coupling with EDC and DMAP * Appears to be the correct assignment
20		$^1\text{H NMR}$ (MeOH-d ₄): δ (ppm) 9.50 (s, 1H), 8.79 (s, 1H), 8.37-8.41 (m, 2H), 7.73 (d, 1H), 7.63 (d, 1H).	WO201254233	Starting from entry 20 amide coupling with EDC and DMAP * Appears to be an

	N-[[2-chloro-5-(trifluoromethyl)phenyl]sulfonyl]-6-(trifluoromethyl)imidazo[1,2-a]pyrimidine-2-carboxamide			<i>incorrect assignment</i>
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