Supporting Information

***Org. Commun*. 10:1 (2017) 114-121**

An optimized and very detailed, grams scale synthesis of CTEP, through a complete characterization of all the isolated and purified intermediates

Silvana Alfei* and Irum Baig

Dipartimento di Farmacia (DIFAR), Università di Genova, Viale Cembrano,4 16147, Genova, Italia

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* Corresponding author: E-mail*:* **alfei@difar.unige.it***;* Phone: (+) 39 0103532296; Fax: (+) 39 0103532684

S.1. General Procedures

Melting points, determined on a Leica Galen III hot stage apparatus, are uncorrected. FTIR spectra were recorded as films or KBr pellets on a Perkin Elmer System 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance DPX 300 Spectrometer at 300 and 75.5 MHz respectively using $CDCl_3$ or DMSO-d_6 as solvents and tetramethylsilane (TMS) as internal reference and assigned through DEPT135 experiments. Coupling constant values were given in Hertz (Hz). Fully decoupled ^{13}C NMR spectra are reported. Chemical shifts were reported in δ (ppm, parts per million) units relative to the internal standard TMS (δ = 0.00 ppm) and the splitting patterns were described as follows: s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet) and brs (broad singlet). Elemental analyses were performed by an EA1110 Analyzer Fisons Instruments (Milan, Italy) and were within 0.4% of theoretical values. Piridinium, *p*-toluenesulfonate (PPTS) was prepared according to known procedure.[18,19] All the reagents and solvents were purchased from Aldrich. The solvents were dried and distilled according to standard procedures. Petroleum ether refers to the fraction with boiling point 40-60 °C. Silica gel is Merck Silica gel (0.040-0.063 mm).

S.2. Synthesis and characterization of compounds 7-11

*2.2.1 Ethyl (E,Z)-(2-hydroxyimino)-3-oxobutanoate (**7**):* To a precooled (0-5 °C) stirred solution of 3-oxobutyric acid ethyl ester (**6**) (5.15 g, 0.040 mol) and acetic acid (5.30 g, 5 mL, 0.088 mol, 2.19 equiv.) a solution of sodium nitrite (3.04 g, 0.044 mol, 1.1 equiv.) in 5.8 mL of water was added dropwise.
The initially yellow mixture was stirred for 1 hour at room temperature becoming soon orange and then hydrolyzed with water (25 mL). The acidic waters were extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were washed with water (2 x 15 mL) and with $NaHCO_3$ sat. then dried on Na_2SO_4 for the night. After removing of the organic solvent under reduced pressure **7** was obtained (6.39 g, 0.040 mol).

Yellowish oil, yield (mixture of *E/Z* isomers 12.3/1), 100% (lit.: 92%).[14] ^{1}H NMR (300 MHz, $CDCl_3$, ppm), (major compound): δ = 10.25 (brs, 1H, OH), 4.39 (q, *J* = 7.1 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 1.35 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$, ppm), (mixture of *E/Z* isomers): δ = 197.90 (*Z*) and 194.44 (*E*) (C=O of ketone), 162.04 (*E*) and 160.94 (*Z*) (C=O of ester), 151.15 (*E*) and 149.87 (*Z*) (C=NOH), 62.79 (*Z*) and 62.57 (*E*) (CH_2O), 30.30 (*Z*) and 25.33 (*E*) (CH_3C=O), 14.09 (*Z*) and 13.99 (*E*) (CH_3). IR (Neat, cm^{-1}), (mixture of *E/Z* isomers): 3347 (OH), 1744 and 1728 (C=O of ester), 1699 and 1687 (C=O of ketone), 1627 (C=N of oxime). Anal. Cald. for $C_6H_9NO_4$ (Mw 159.14): C, 45.28; H, 5.70; N, 8.80; Found: C, 44.95; H, 6.10; N, 9.02.

*2.2.2 Ethyl (E,Z)-(2-hydroxyimino)-(E,Z)-3-(4-trifluoromethoxyphenylimino)butanoate (**8**):* To a stirred solution of **7** (5.4 g, 0.034 mol) in dry toluene (35 mL), 4-trifluoromethoxyaniline (6.02 g, 0.034 mol, 4.6 mL, 1.00 equiv.) and PPTS[18,19] (0.4272 g, 0.0017 mol, 0.05 equiv.) were added and the resulting suspension was heated at 75 ° C. Immediately a solution is obtained which was stirred for 7 hours at 75 ° C under reduced pressure removing the separated water with a Dean-Stark-Trap.
The light brown solution, which when cooled already showed some crystals, was evaporated under reduced pressure and the crude product was obtained as light brown solid. It was crystallized with $CHCl_3$/*n*-pentane obtaining **8** (8.6 g; 0.027 mmol).

Off-white solid, yield (mixture of four geometric isomers), 80%; m.p. 101-104 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm), (major compound at equilibrium): δ = 12.66 (s, 1H, OH), 7.31 and 6.92 (m, 4H, CH= of phenyl), 4.27 (q, *J* = 7.1 Hz, 2H, CH_2), 2.02 (s, 3H, CH_3), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm): δ = 163.01 (C=NPh), 162.78 (C=O), 152.85 (C=NOH), 148.21 (C-OCF_3 of phenyl), 144.83 (C-N of phenyl), 121.82 (CH= of phenyl), 120.97 (CH= of phenyl), 118.45 (CF_3), 60.90 (CH_2), 15.05 (CH_3C=N), 13.97 (CH_3CH_2). IR (KBr, cm^{-1}): 3407 (OH), 3108 and 3001 (phenyl), 1709 (C=O of ester), 1656 (C=N of imine), 1627 (C=NOH of oxime). Anal. Cald. for $C_{13}H_{13}N_2O_4F_3$ (Mw 318.25): C, 49.06; H, 4.12; N, 8.80; Found: C, 49.04; H, 4.22; N, 8.65.

*2.2.3 2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1H-imidazole-4-carboxylic acid ethyl ester (**9**):* To the imines mixture **8** (10.8 g, 0.034 mol) dissolved in dry toluene (34 mL), triethylorthoacetate (19.3 g, 21.8 mL, 0.119 mol, 3.5 equiv.), *p*-toluensulphonic acid (0.13 g, 0.68 mmol, 0.02 equiv.) and Pd/C 10% (0.800 g) were added.
The suspension was stirred under H_2 at 1.5 bar for 5 hours at r.t. At the end of the reaction, catalyst was filtered on silica gel which was washed with dry toluene (25 mL). The isolation of **9** was made according to two different procedures.

Procedure a.[12] The yellow solution was extracted with 1 N HCl until transparent waters; then these acidic waters were neutralized with 2 N NaOH (pH = 7), extracted with dichloromethane (4 x 25 mL) and dried on Na_2SO_4. After removal of the solvent under reduced pressure the crude product was obtained as a light brown solid which was treated with petroleum ether instead of *n*-eptane,[12] to obtain **9** (7.84 g, 0.024 mmol).

Procedure b. In another preparation from **8** (1.73 g, 5.44 mmol) the yellow solution was directly evaporated at reduced pressure obtaining a yellow oil which when cool crystallized. This crude product was treated with petroleum ether to obtain **9** (1.13 g, 3.44 mmol).

Procedure a.[12] Off-white crystals, yield, 71% (lit.: 44%);[12] m.p. 142-144 °C. *Procedure b*. White crystals, yield, 63% (lit.: 44%);[12] m.p. 145-146 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 7.38-7.25 (m, 4H, CH= of phenyl), 4.37 (q, *J* = 7.1 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.40 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$, ppm): δ = 163.21 (C=O of ester), 149.92 (C-OCF_3 of phenyl), 144.99, 136.76, 133.58 (C of imidazole), 129.21 (CH= of phenyl), 127.19 (C-N of phenyl), 122.33 (CH= of phenyl), 122.09 and 118.67 (CF_3, $^1J_{CF}$ = 256 Hz), 60.56 (CH_2O), 14.54 (CH_3C), 13.65 (CH_3C), 10.83 (CH_3CH_2). IR (KBr, cm^{-1}): 3114 and 3059 (aromatics), 1709 (C=O of ester). Anal. Cald. for $C_{15}H_{15}N_2O_3F_3$ (Mw 328.29): C, 54.88; H, 4.61; N, 8.54; Found: C, 54.80; H, 4.62; N, 8.80.

*2.2.4 2-(2-Chloropyridin-4-yl)-1-[2,5-dimethyl-1-(4-trifluoromthoxyphenyl)- 1H-imidazol-4-yl]ethanone (**10**):* To a precooled (0-5°C) solution of 0.5 M potassium bis(trimethylsilyl)amide (KHMDS) (10.5 g, 0.0483 mol, 2.1 equiv.) in dry toluene (100 mL) a solution of **9** (7.57 g, 0.023 mol, 1 equiv.) and 2-chloro-4-methylpyridine (2.96 g, 0.023 mol, 1.01 equiv.) in dry toluene (115 mL) were dripped. The orange suspension was stirred at 0-5°C for 1 hour then added with 2.9 eq. of AcOH (3.99 g, 0.0665 mol, 3.8 mL) and H_2O (90 mL) and neutralized with acetic acid (q.b at pH = 7). The aqueous phase was separated and the organic phase was washed with water (105 mL).
The combined waters were extracted with ethyl acetate (140 mL) and the combined organic phases were dried over anhydrous $MgSO_4$ overnight. After removal of the solvent under reduced pressure the crude product was obtained as a pale orange oil which crystallized on standing. The crystals so obtained were treated with *n*-pentane with stirring to get **10** (7.7 g, 0.019 mol).

Pale yellow solid, yield: 83% (lit.: 92% on the crude dark brown oil);[12] m.p. 112 °C. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 8.31 (d, J_o = 5.0 Hz, 1H, CH= of pyridine), 7.44-7.24 [m, 6H, (4CH= of phenyl + 2CH= of pyridine)], 4.35 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.26 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$, ppm): δ = 192.49 (C=O of ketone), 151.51 (C-OCF_3 of phenyl), 149.87 (C of pyridine), 149.35 (CH= of pyridine), 147.99 (C of pyridine), 144.21 (C of imidazole), 137.01 (C of imidazole), 135.02 (C of phenyl), 133.57 (C of imidazole), 129.05 (CH= of phenyl), 125.73 (CH= of pyridine), 124.20 (CH= of pyridine), 122.34 (CH= of phenyl), 122.08 and 118.65 (CF_3, $^1J_{CF}$ = 259 Hz), 44.72 (CH_2), 13.87 (CH_3), 11.16 (CH_3). IR (KBr, cm^{-1}): 3072 (aromatics), 1671 (C=O of ketone). Anal. Cald. for $C_{19}H_{15}N_3O_2F_3Cl$ (Mw 409.79): C, 55.68; H, 3.69; N, 10.26; Found: C, 55.67; H, 3.62; N, 10.57.

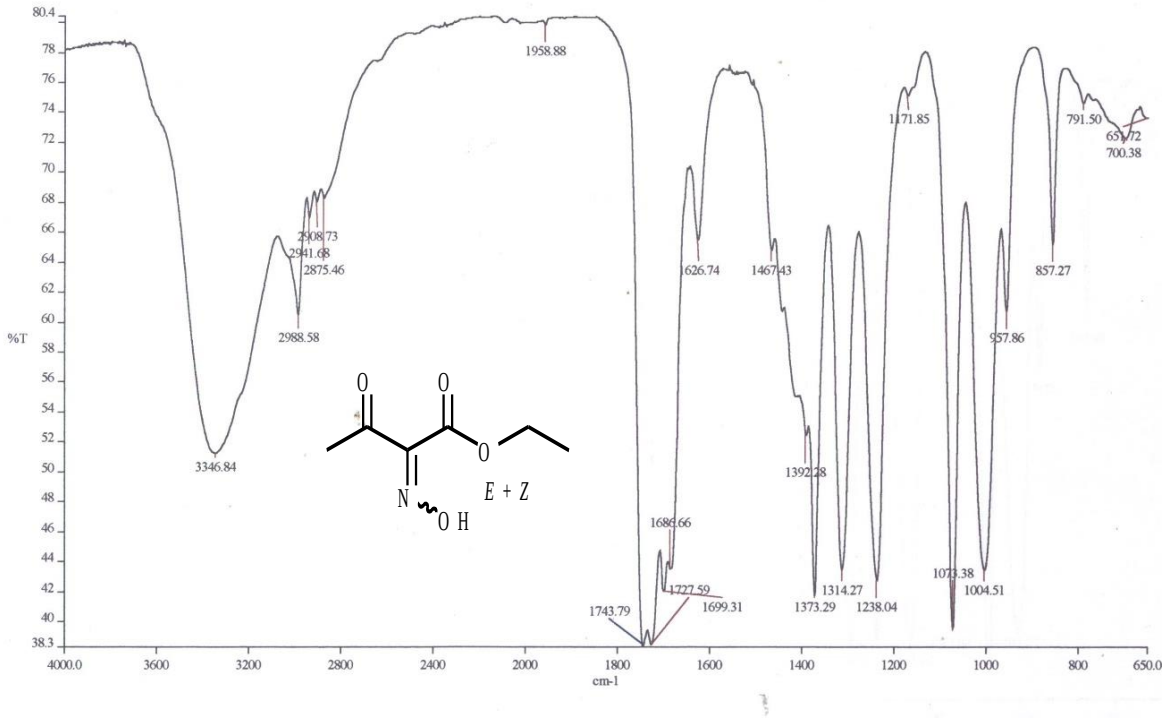
*2.2.5 3-Chloro-2-(2-chloropyridin-4-yl)-3-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1H-imidazol-4-yl]propenal (**11**):* 2-(2-Chloropyridin-4-yl)-1-[2,5-dimethyl-1-(4-trifluoromthoxyphenyl)-1*H*-imidazol-4-yl]ethanone (**10**) from the preceding step (7.9 g, 0.019 mol) was dissolved in dry dichloromethane (58 mL) and added dropwise to a precooled (0-5 °C) suspension of (chloromethylene)dimethyliminium chloride (6.2 g, 0.048 mol, 2.5 equiv.) in dry dichloromethane (35 mL). The reaction mixture was stirred at 0-5 °C for 1 hour, then diluted with water (100 mL).
At reduced pressure ~110 mL of dichloromethane were removed obtaining a suspension which was filtered, the residue mass was washed with water and then dissolved in dry dichloromethane. The mixture H_2O/dichloromethane (pH = 1) was neutralized with 4 N NaOH (15 mL). After separation of the organic phase, the aqueous layer was extracted with dry dichloromethane (q.b at colorless extracts) and the combined organic phases were washed with water. The organic solvent was dried on $MgSO_4$ overnight then evaporated at reduced pressure to get crude **11** as an orange oil which crystallized on standing. It was treated with petroleum ether under stirring obtaining **11** (8.67 g, 0.019 mol).

Strong yellow solid, yield: 100 % (lit.: 83% on the crude dark brown oil);[12] m.p. 136-138 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ = 9.85 (brs, 1H, CH of aldehyde), 8.45 (d, J_o = 4.8 Hz, 1H, CH= of pyridine), 7.48-7.29 [m, 6H, (4CH= of phenyl + 2 CH= of pyridine)], 2.30 (brs, 3H, CH_3), 2.16 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$, ppm): δ = 188.64 (C=O of aldehyde), 151.54 (C-OCF_3 of phenyl), 150.13 (C of pyridine), 149.62 (CH= of pyridine), 148.99 (C of pyridine), 146.17 (C of imidazole), 145.21 (C of imidazole), 136.79 (C of phenyl), 133.60 (C of imidazole), 131.54 (C=C), 129.38 (C=C), 129.14 (CH= of phenyl), 125.59-125.45 (CH= of pyridine), 123.85-123.71 (CH= of pyridine) , 122.47 (CH= of phenyl), 122.06 and 118.63 (CF_3, $^1J_{CF}$ = 259 Hz), 13.79 (CH_3), 11.23 (CH_3). IR (KBr, cm^{-1}): 3113, 3069,3038 and 3003 (aromatics), 1671 (C=O of aldehyde). Anal. Cald. for $C_{20}H_{14}N_3O_2F_3Cl_2$ (Mw 456.25): C, 52.65; H, 3.09; N, 7.01; Found: C, 52.86; H, 3.22; N, 7.35.

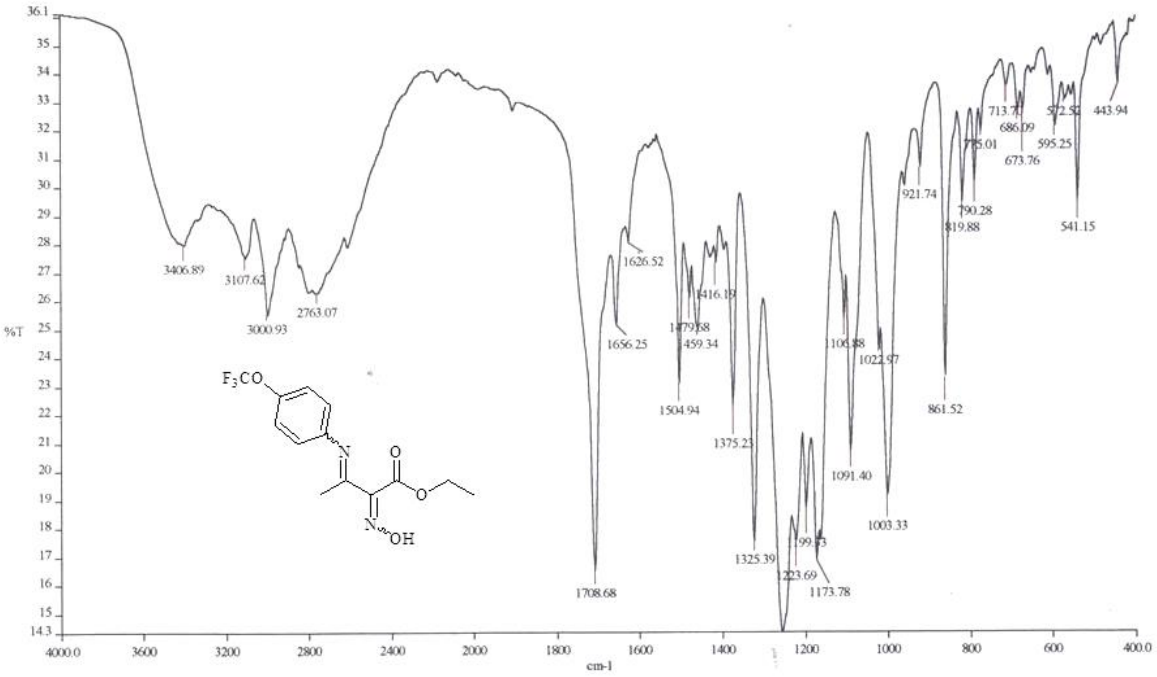
*2.3. Synthesis and characterization of 2-Chloro-4-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1H-imidazol-4-ylethynyl] pyridine (**5**):* A solution of 3-Chloro-2-(2-chloropyridin-4-yl)-3-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-yl]propenal (**11**) (9.19 g, 0.020 mol) in dry tetrahydrofuran (110 mL) was added dropwise to a precooled (-10 to -15 °C) suspension of potassium *tert*-butoxide (4.9 g, 0.044 mol, 2.2 equiv.) in dry tetrahydrofuran (60 mL). The light brown reaction mixture was stirred at 0-5 °C for 1 hour, then quenched at 0-5 °C with 1 N HCl (100 mL). Volatiles were evaporated under reduced pressure (40 °C) and the suspension which arose was filtered. This compound, the HCl salt of **5**, was washed with water (60 mL). This material was taken up in dichloromethane (q.b. to dissolve the mass) and treated with 1 N $NaHCO_3$ solution (107 mL, pH = 7-8).
The aqueous layer was separated and extracted with dichloromethane until colorless extracts. The organic phases were washed with water (100 mL), dried on $MgSO_4$ overnight and then evaporated at reduced pressure to get crude **5** as a dark solid which was crystallized from DCM/*n*-pentane obtaining **5** (4.95 g, 0.013 mol).

Off-white or pale yellow solid, yield, 63%, overall yield 27% (lit.: 27%, overall yield 9%);[12] m.p. 119-120 °C. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ = 8.42 (d, J_o = 5.1 Hz, 1H, CH= of pyridine), 7.67-7.50 [m, 5H, (4 CH= of phenyl + 1 CH= of pyridine)], 7.49 (d, J_m = 1.36 Hz 1H, CH= of pyridine), 2.34 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.15 (s, 3H, CH_3). ^{13}C NMR (75.5 MHz, DMSO-d_6, ppm): δ = 150.66 (C-OCF_3 of phenyl), 150.02 (CH= of pyridine), 148.43 (C of pyridine), 144.86 (C-N of phenyl), 136.11 (C of imidazole), 134.31 (C of imidazole), 134.10 (C of imidazole), 129.59 (CH= of phenyl), 124.59 (CH= of pyridine), 123.95 (CH= of pyridine), 122.24 (CH= of phenyl), 121.66 and 118.25 (CF_3, $^1J_{CF}$ = 257 Hz), 117.92 (C of pyridine), 90.96 (C of alkine), 87.41 (C of alkine), 13.48 (CH_3), 10.09 (CH_3). IR (KBr, cm^{-1}): 3060 (aromatics), 2211 (alkine). Anal. Cald. for $C_{19}H_{13}ClF_3N_3O$ (Mw 391.77): C, 58.25; H, 3.34; N, 10.73; Found: C, 58.40; H, 3.39; N, 10.99.

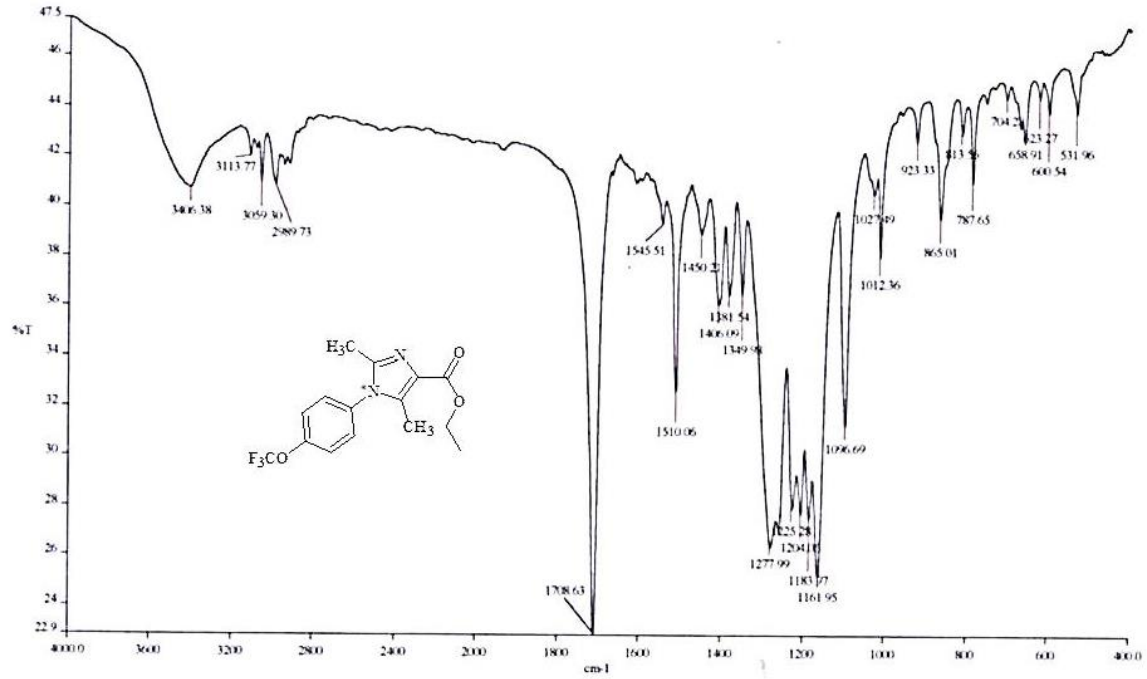
S.3. IR spectra of compounds 7-11 and 5 (CTEP)



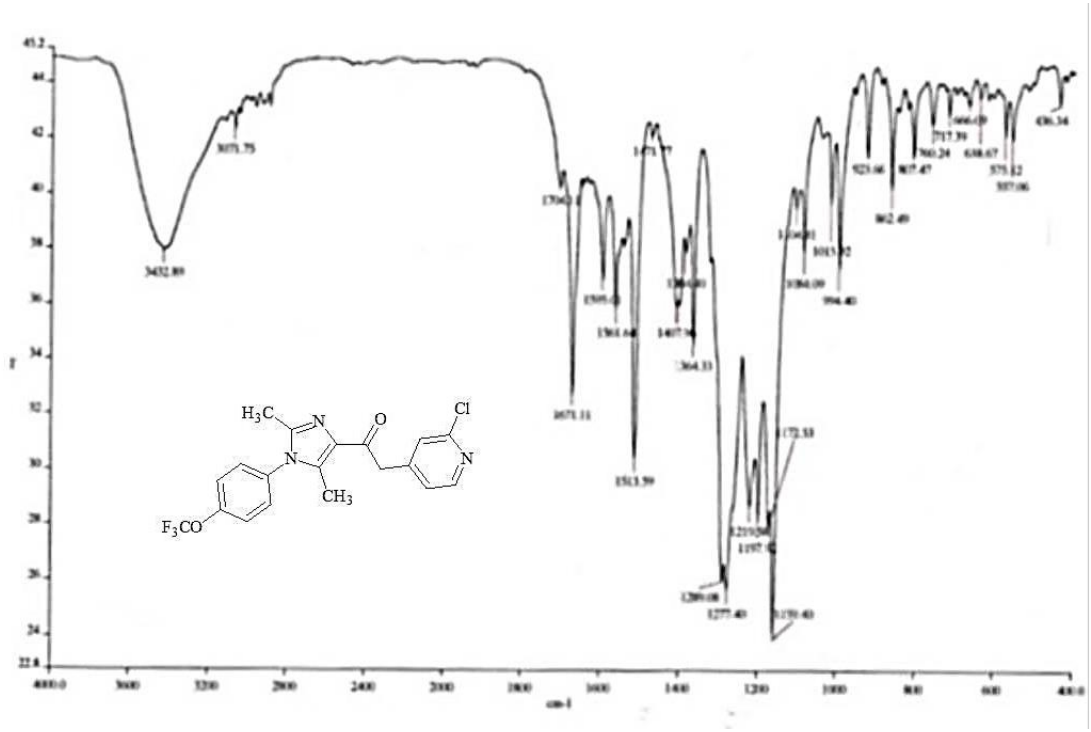
IR spectrum of Ethyl (*E*,*Z*)-(2-hydroxyimino)-3-oxobutanoate (**7**) (Neat, cm^{-1})



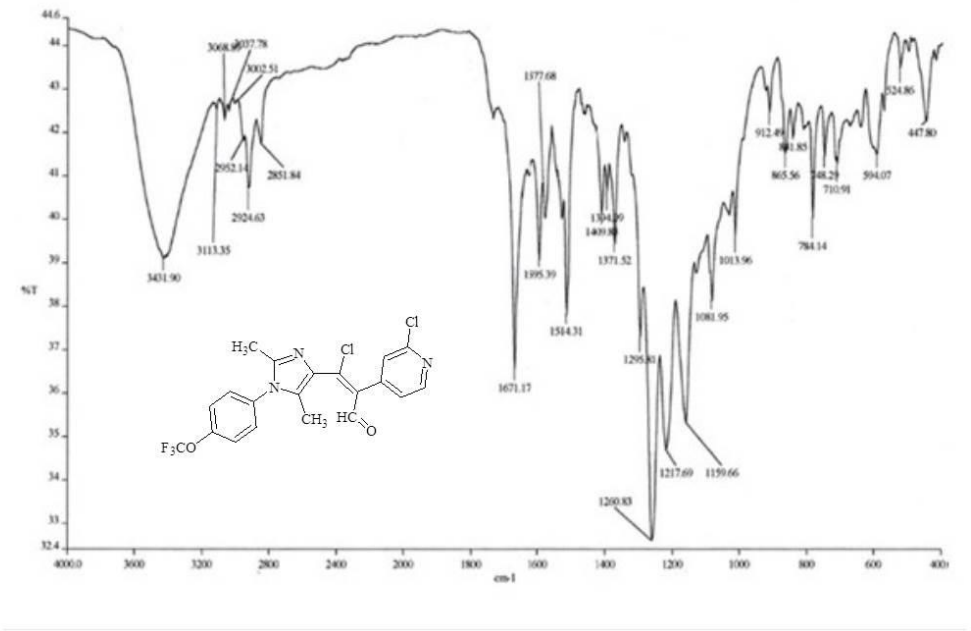
IR spectrum of Ethyl (*E,Z*)-(2-hydroxyimino)-(*E,Z*)-3-(4trifluoromethoxyphenylimino)butanoate (**8)** (KBr, cm^{-1})



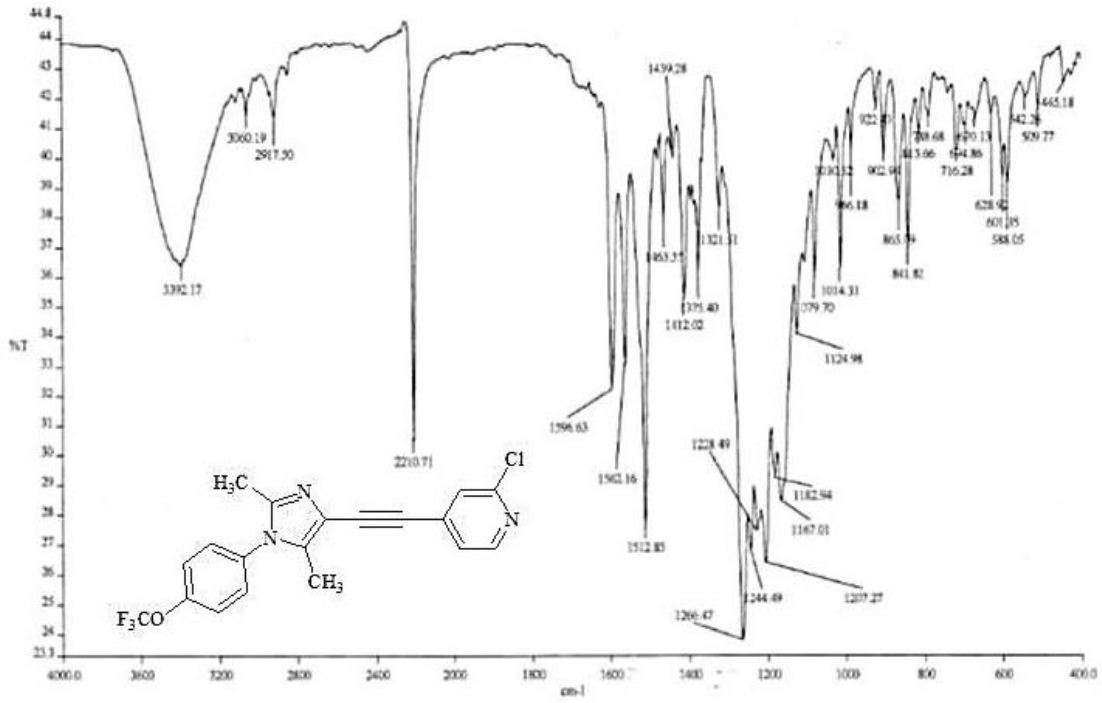
IR spectrum of 2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazole-4-carboxylic acid ethyl ester (**9**) (KBr, cm^{-1})



IR spectrum of 2-(2-Chloropyridin-4-yl)-1-[2,5-dimethyl-1-(4-trifluoromthoxyphenyl)-1*H*-imidazol-4-yl]ethanone (**10**) IR (KBr, cm^{-1})

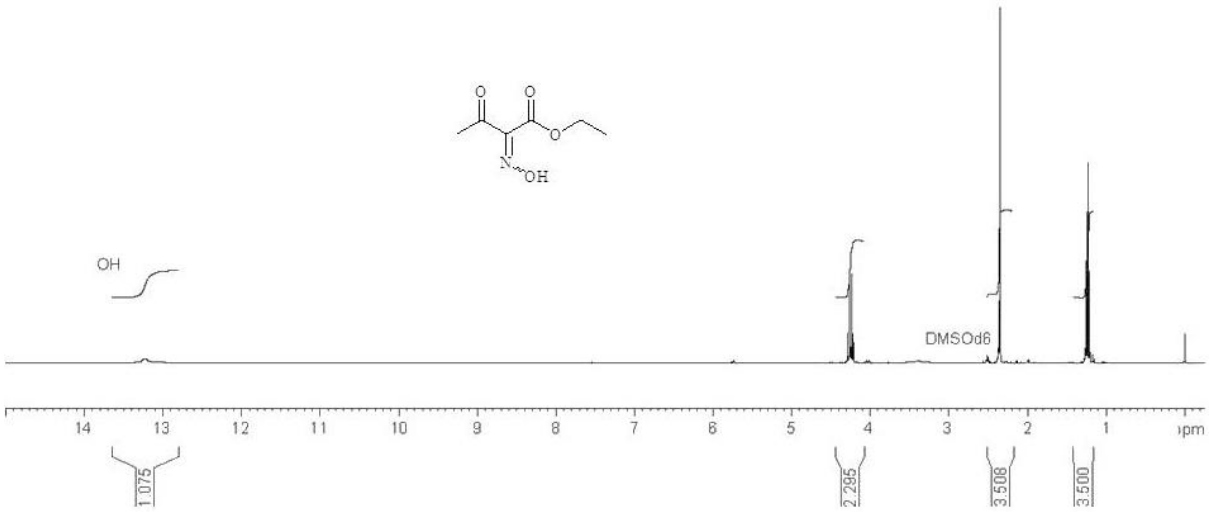


IR spectrum of 3-Chloro-2-(2-chloropyridin-4-yl)-3-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-yl]propenal (**11**) (KBr, cm^{-1})

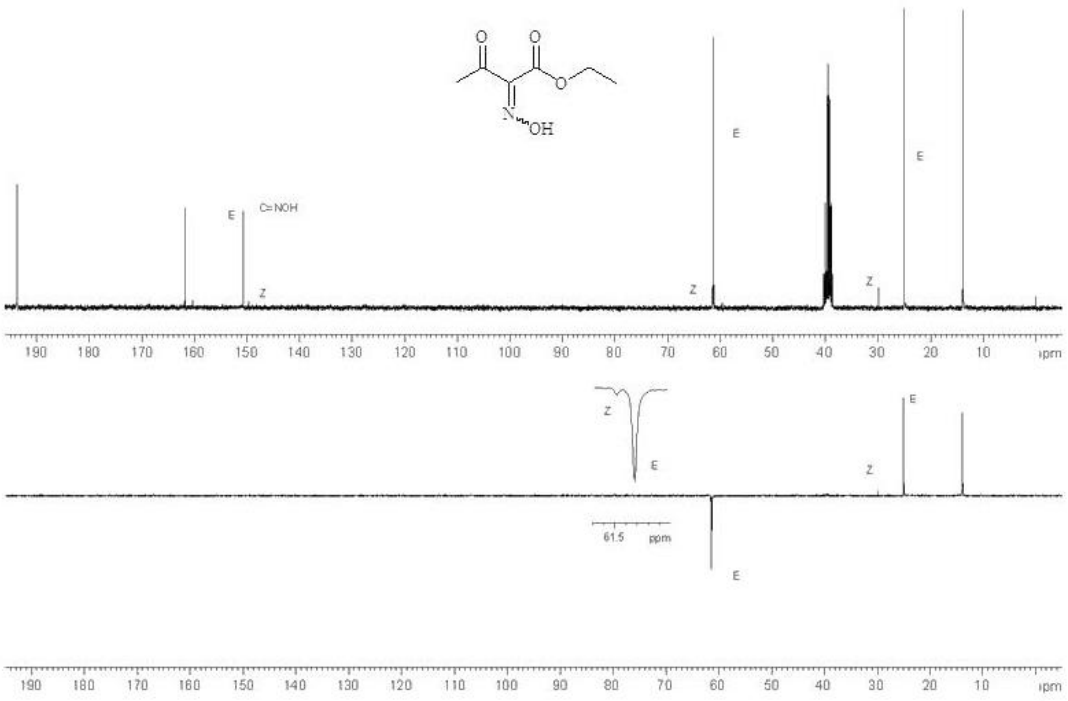


IR spectrum of 2-Chloro-4-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-ylethynyl]pyridine (**5**) (KBr, cm^{-1})

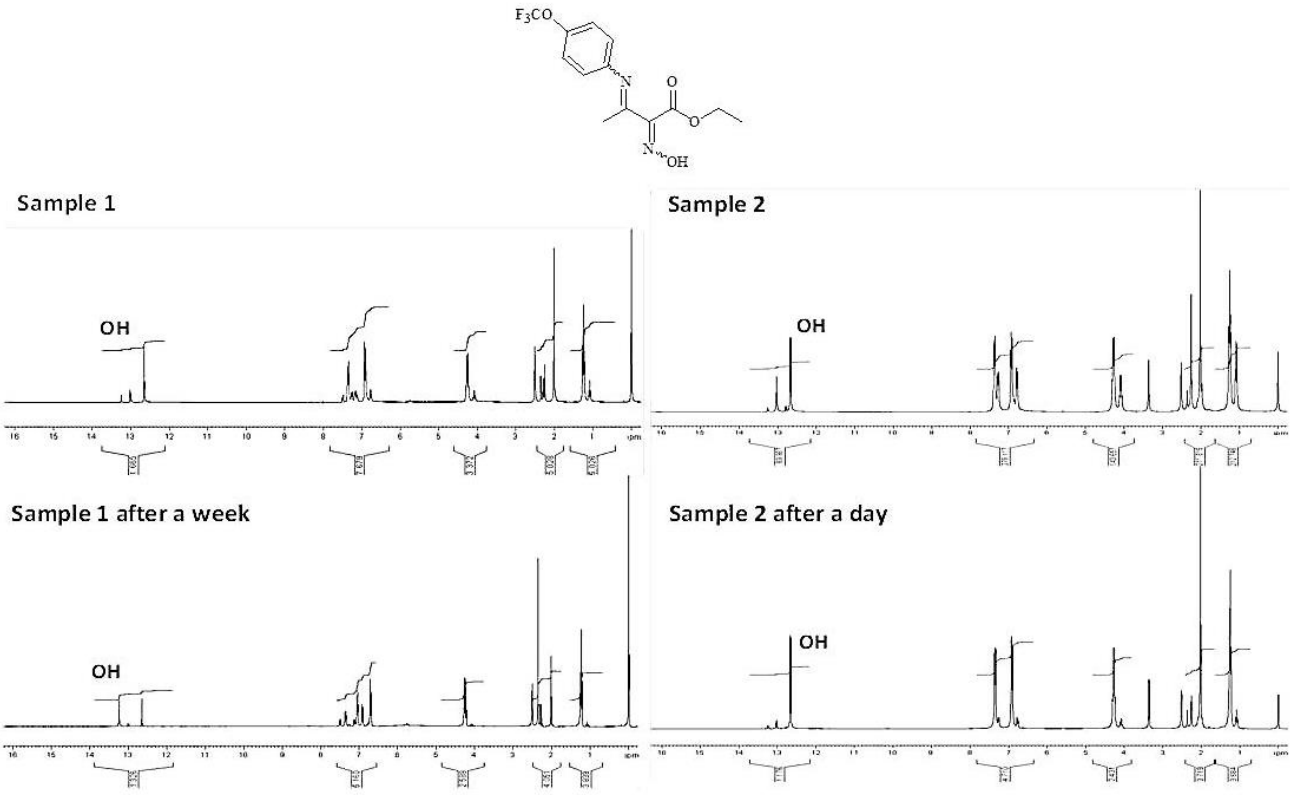
S.4. ^{1}H NMR and ^{13}C NMR spectra of compounds 7-11 and 5 (CTEP)



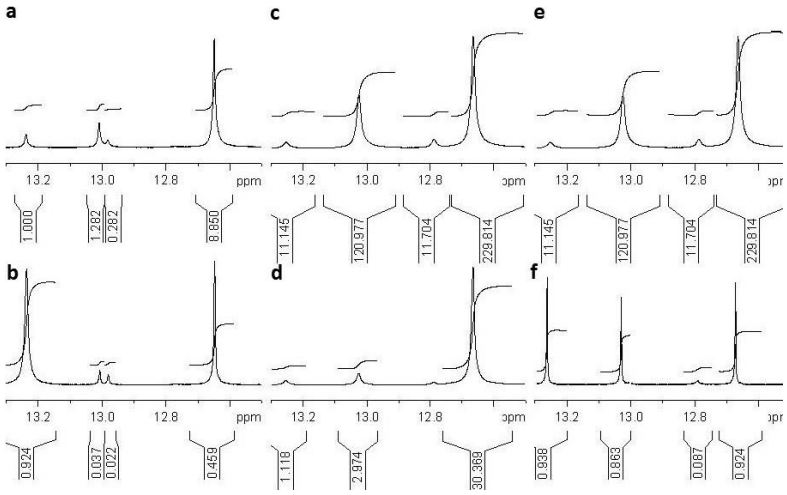
^{1}H NMR of Ethyl (*E*,*Z*)-(2-hydroxyimino)-3-oxobutanoate (**7**) (300 MHz, DMSO-d_6)



^{13}C NMR and DEPT135 of Ethyl (*E*,*Z*)-(2-hydroxyimino)-3-oxobutanoate (**7**) (75.5 MHz, DMSO-d_6)

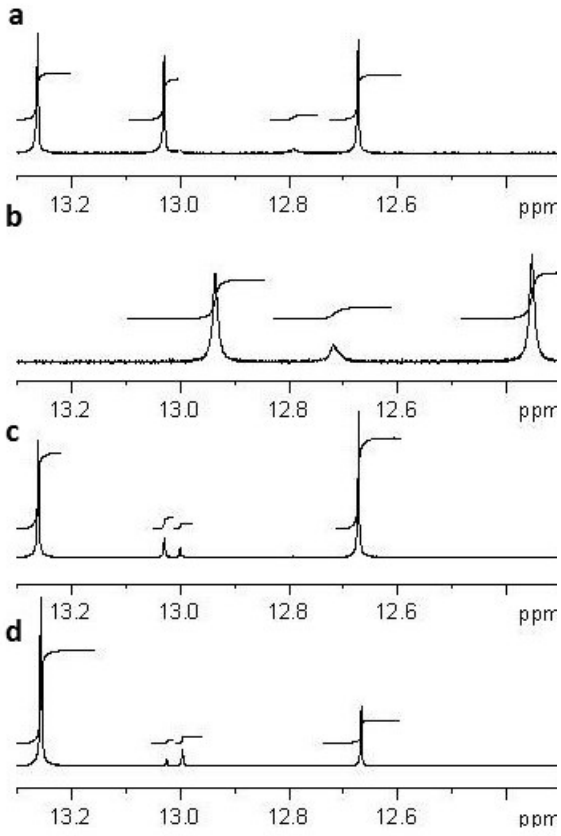


^{1}H NMR of Ethyl (*E*,*Z*)-(2-hydroxyimino)-(*E*,*Z*)-3-(4-trifluoromethoxyphenylimino)butanoate (**8**) (300 MHz, DMSO-d_6)



δ_{OH} (ppm)	Abundance (%) of the different peaks in the various batches over time				
	#1		#2		
	fresh	1 week	fresh	1 day	5 months
12.65	77.7	**31.9**	61.4	88.3	32.8
12.79	0	0	3.3	0	3.0
12.98	2.5	1.5	0	0	0
13.01	11.1	2.6	32.0	8.4	30.7
13.24	8.9	**64.0**	3.0	3.2	33.5

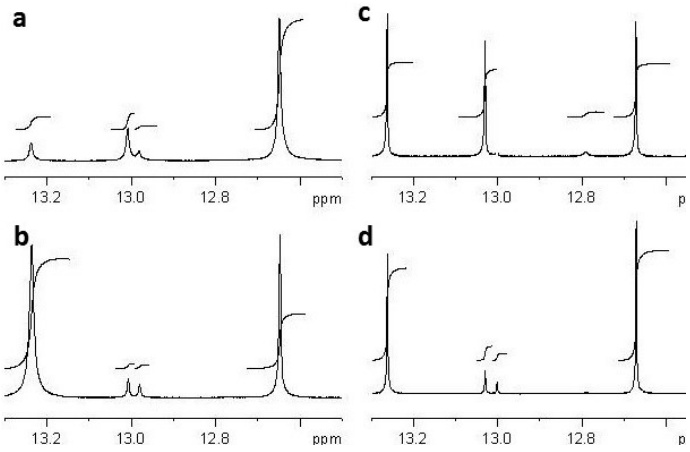
^{1}H NMR (DMSO-d_6) spectrum of **8** acquired at r.t. (peaks of the OH group): (a) batch #1 freshly prepared, (b) batch #1 after a week at r.t., (c, e) batch #2 freshly prepared, (d) batch #2 after a day at r.t., (f) batch #2 after 5 months at r.t.. and related Table of abundance (%)



δ_{OH} (ppm)	Abundance (%) of the different peaks in batch #2 with heating up and over time			
	acquisition at r.t	acquisition at 75°C	acquisition at r.t.[a]	acquisition at r.t.[b]
12.35	0	**47.9**	0	0
12.67	32.8	0	**49.1**	**18.2**
12.72	0	11.1	0	0
12.79	3.0	0	0	0
12.94	0	**40.9**	0	0
12.98	0	0	3.0	5.2
13.03	30.7	0	6.4	2.2
13.26	33.5	0	**41.5**	**74.3**

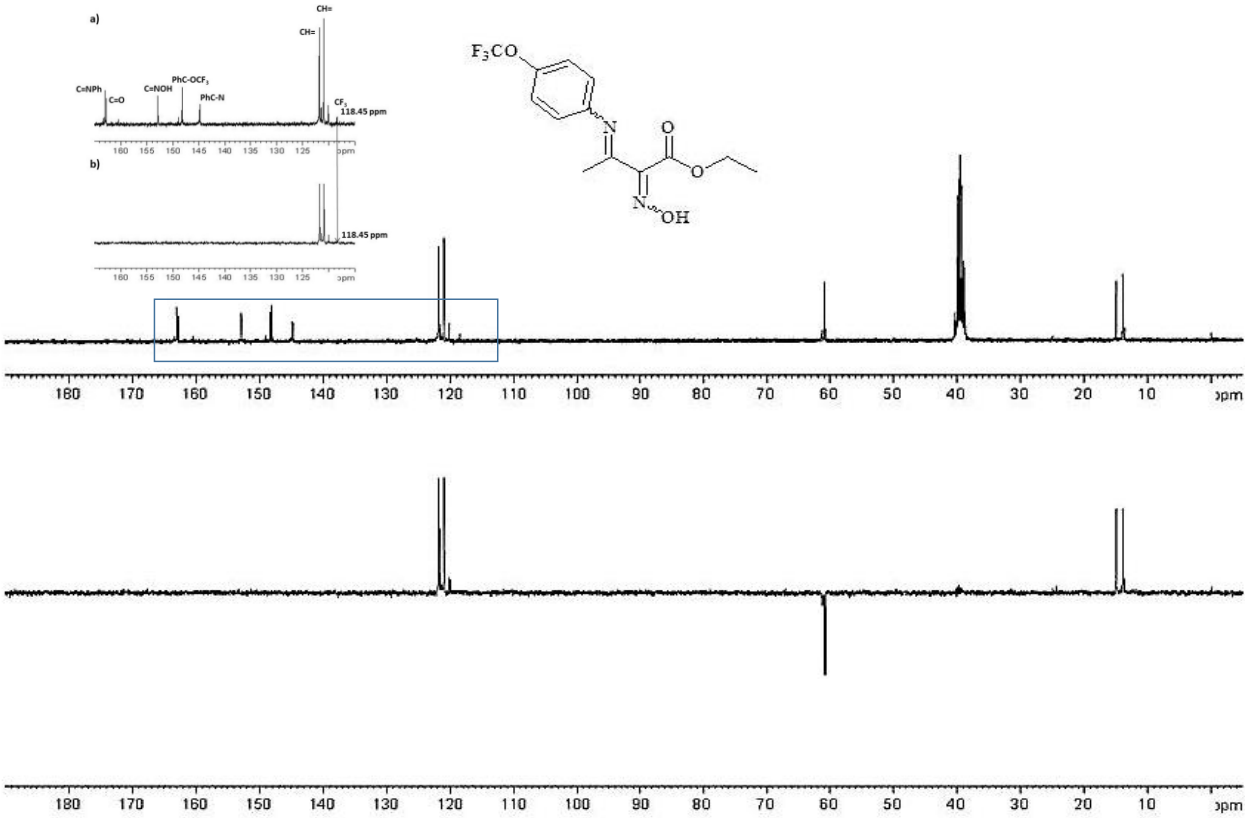
[a] after heating up for few minutes at 75°C and then cooling;
[b] after heating up at 75°C for 24 h and then cooling

^{1}H-NMR (DMSO-d_6) spectrum of **8** [batch #2 after 5 months at r.t. (peaks of the OH group)]: (a) acquired at r.t., (b) acquired at 75°C (c) acquired at r.t. after heating up and then cooling (d) acquired at r.t after heating up at 75°C for 24 h and then cooling and related Table of abundance (%).

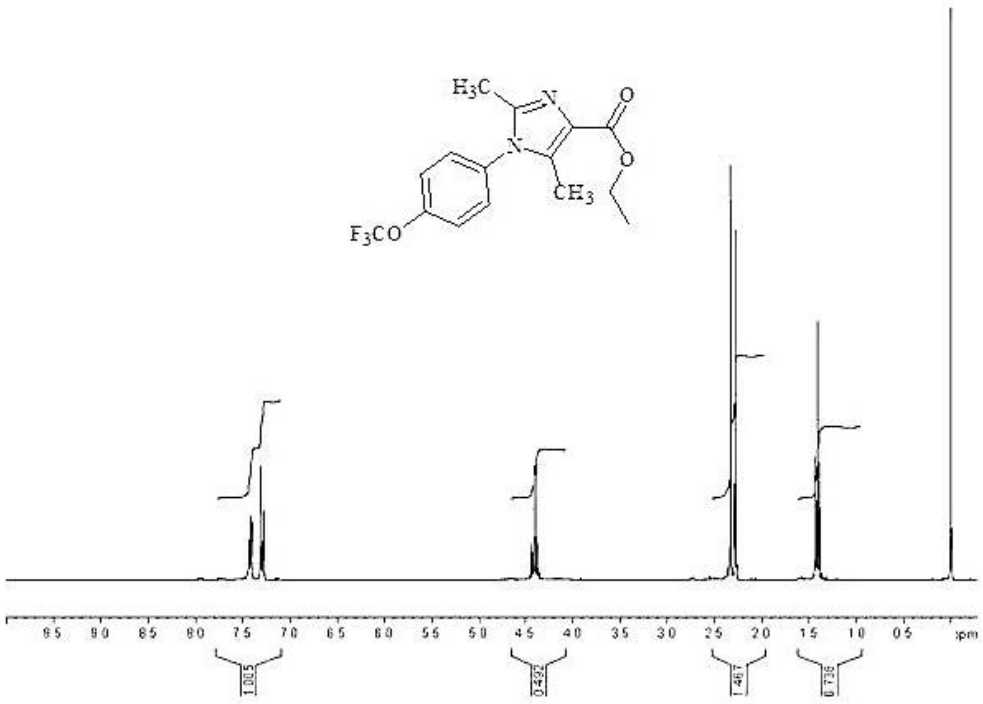


δ_{OH} (ppm)	Abundance (%) of the different peaks in the various batches over time and by heating			
	#1		#2	
	fresh	1 week r.t.	5 months r.t.	heated at 75°C
12.65	77.7	**31.9**	32.8	**49.1**
12.98	2.5	**1.5**	0	**3.0**
13.01	11.1	**2.6**	30.7	**6.4**
13.24	8.9	**64.0**	33.5	**41.5**

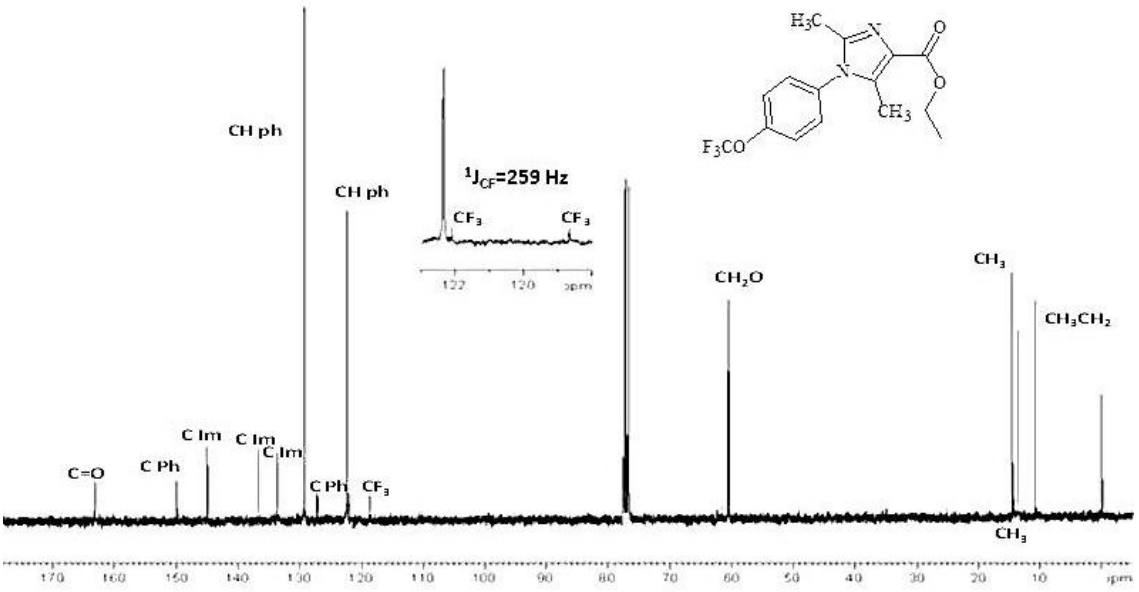
^{1}H-NMR (DMSO-d_6) spectrum of **8** acquired at r.t. (peaks of the OH group): (a) batch #1 freshly prepared, (b) batch #1 after a week at r.t., (c) batch #2 after 5 months at r.t., (d) batch #2 after briefly heating up at 75°C and then cooling and related Table of abundance (%)



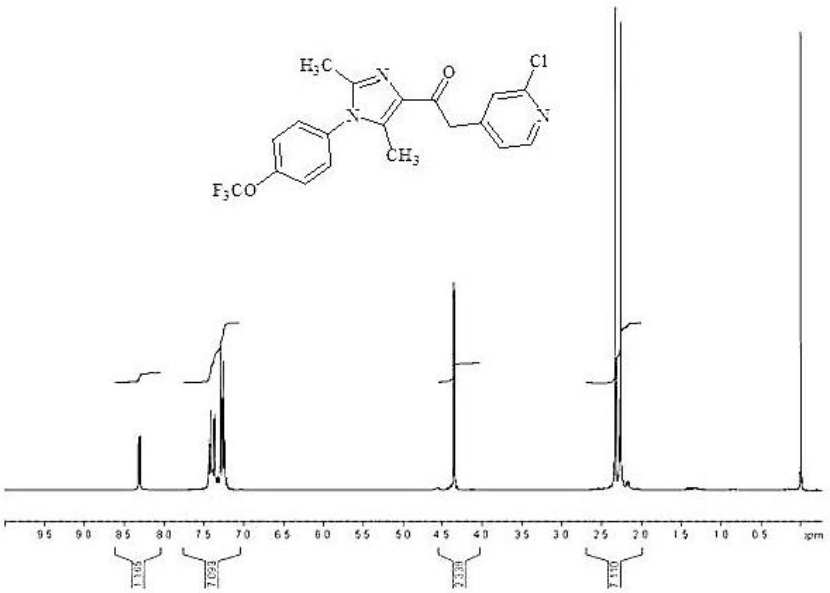
^{13}C NMR and DEPT135 of Ethyl (*E*,*Z*)-(2-hydroxyimino)-(*E*,*Z*)-3-(4-trifluoromethoxyphenylimino)butanoate (**8**) (75.5 MHz, DMSO-d_6)



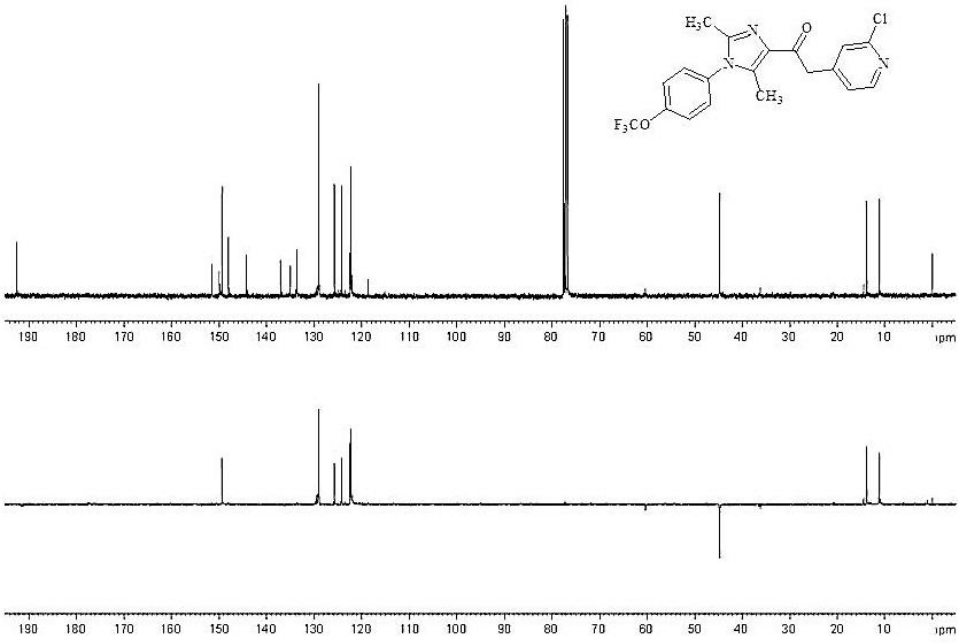
^{1}H NMR of 2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazole-4-carboxylic acid ethyl ester (**9**) (300 MHz, $CDCl_3$)



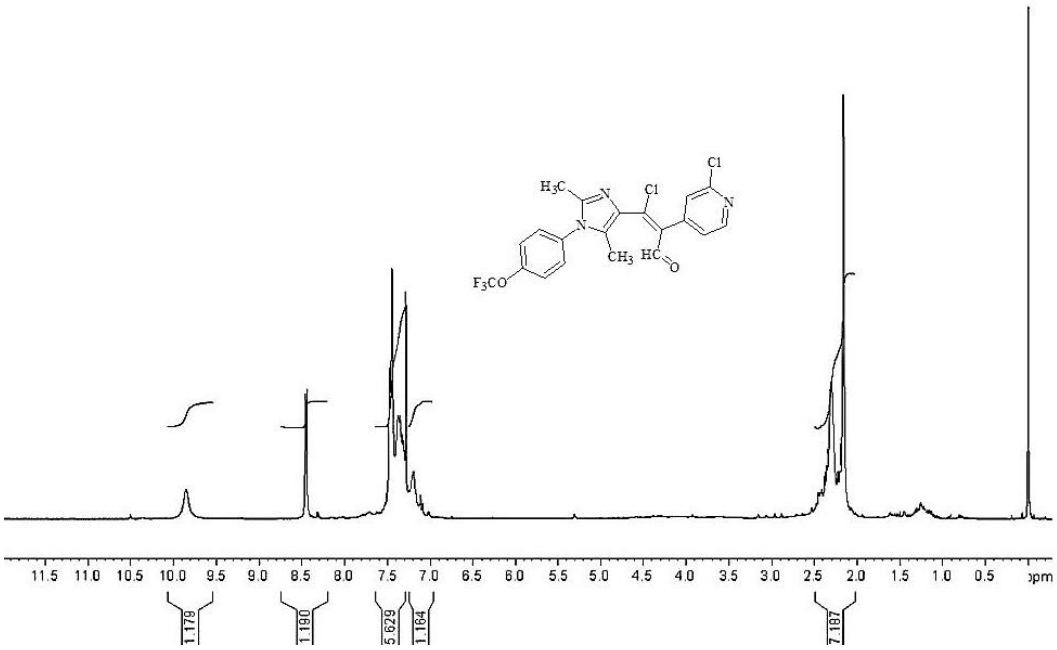
^{13}C NMR of 2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazole-4-carboxylic acid ethyl ester (**9**) (75.5 MHz, $CDCl_3$)



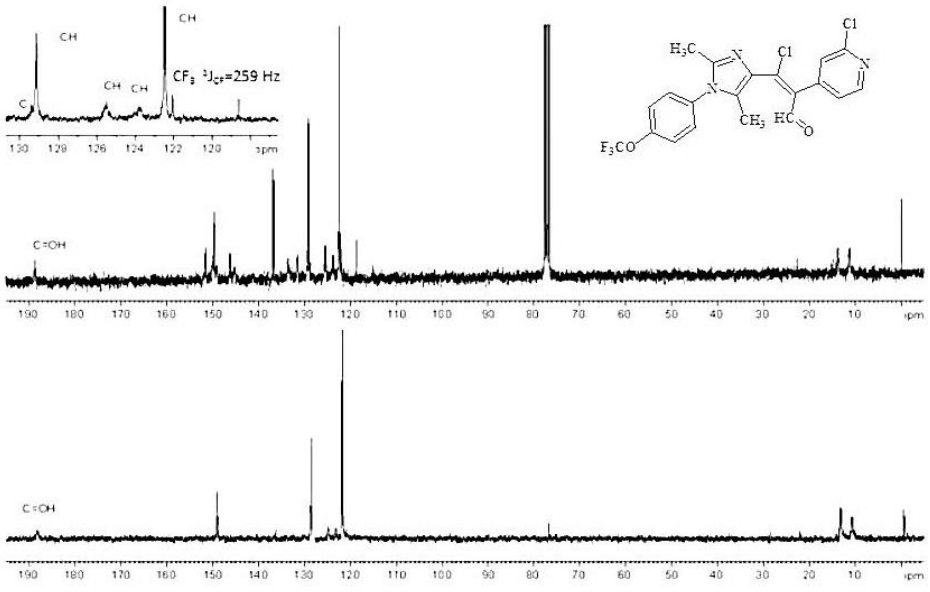
^{1}H NMR of 2-(2-Chloropyridin-4-yl)-1-[2,5-dimethyl-1-(4-trifluoromthoxyphenyl)-1*H*-imidazol-4-yl]ethanone (**10**) (300 MHz, $CDCl_3$)



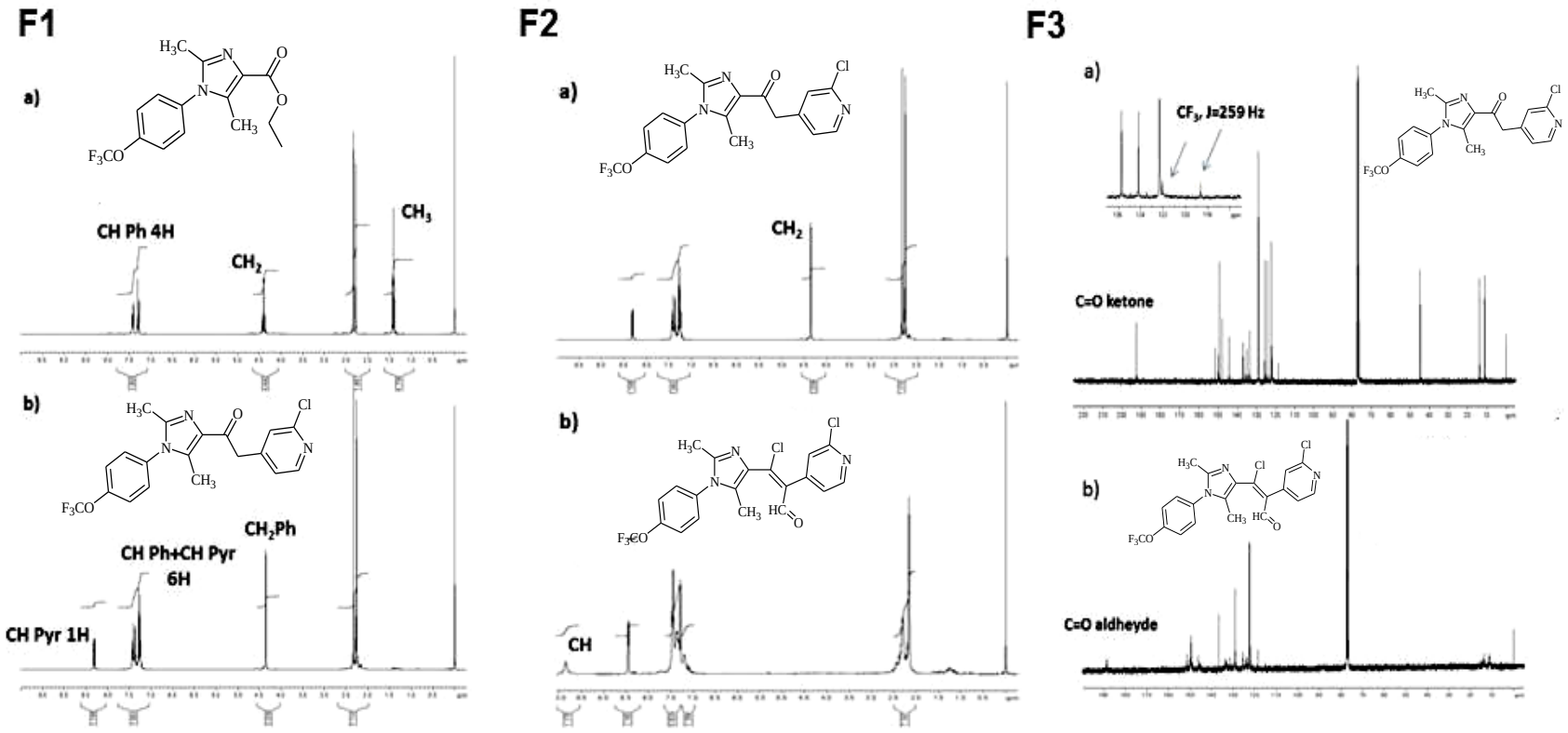
^{13}C NMR and DEPT135 of 2-(2-Chloropyridin-4-yl)-1-[2,5-dimethyl-1-(4-trifluoromthoxyphenyl)-1*H*-imidazol-4-yl]ethanone (**10**) (75.5 MHz, $CDCl_3$)



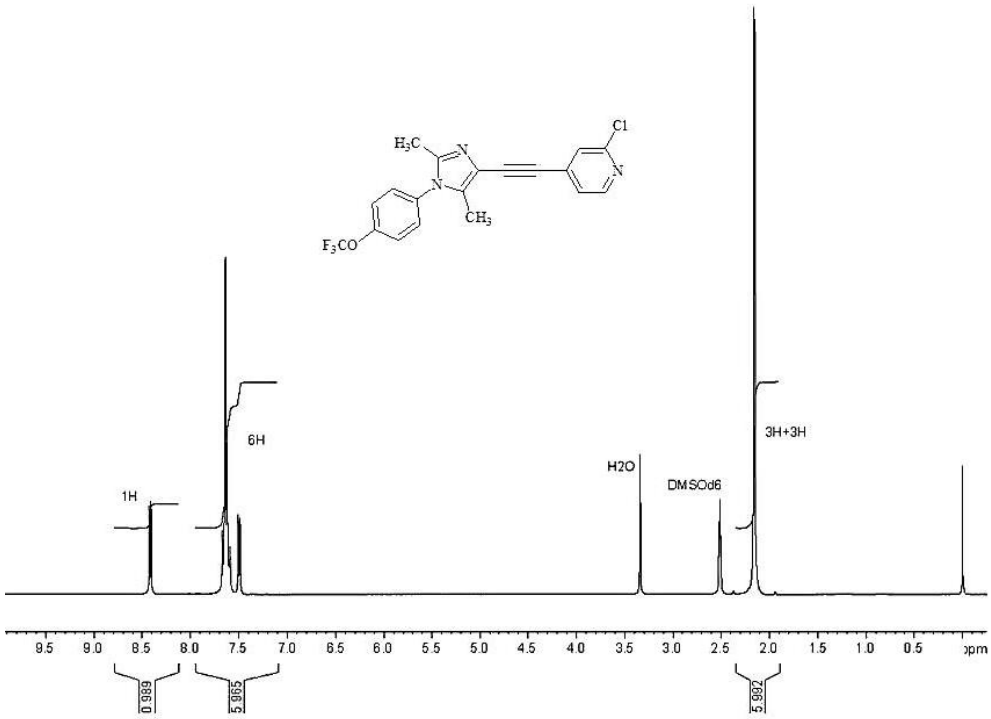
^{1}H NMR of 3-Chloro-2-(2-chloropyridin-4-yl)-3-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-yl]propenal (**11**) (300 MHz, $CDCl_3$)



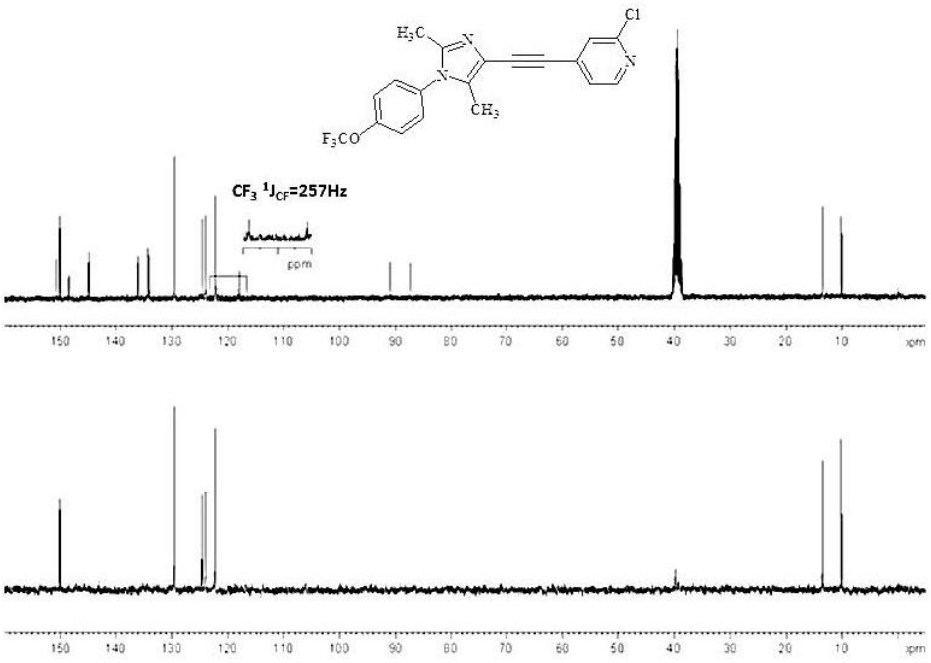
^{13}C NMR and DEPT135 of 3-Chloro-2-(2-chloropyridin-4-yl)-3-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-yl]propenal (**11**) (75.5 MHz, $CDCl_3$)



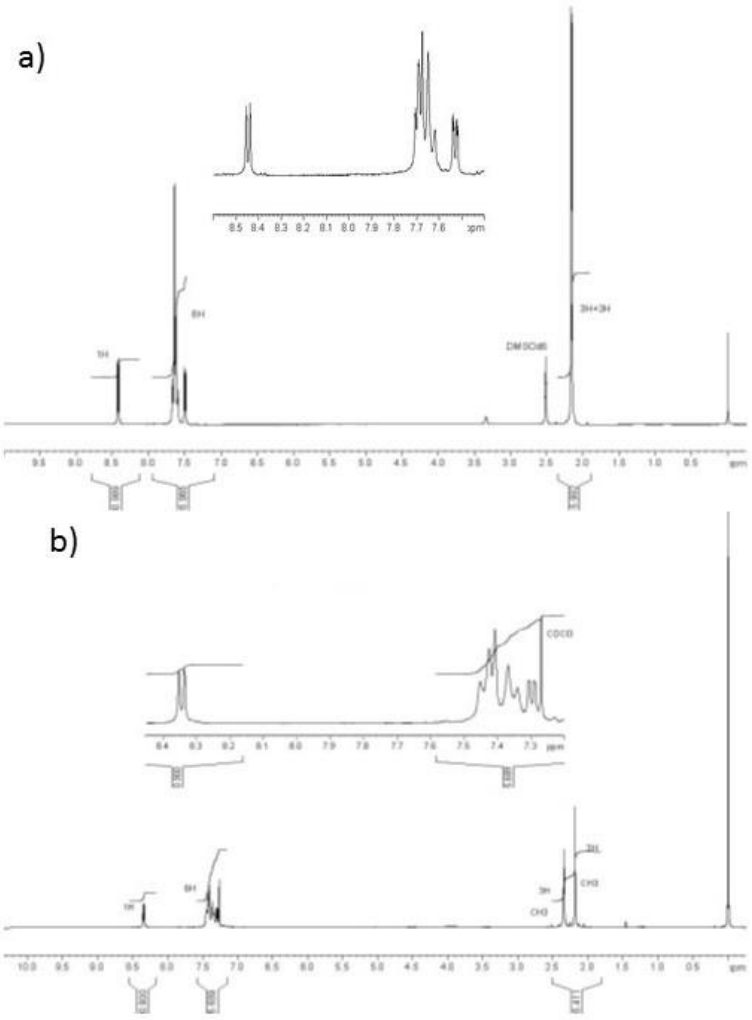
Comparison beteween NMR spectra of compounds **9**, **10** and **11**: **F1.** ^{1}H NMR of **9** (**a**) and of **10** (**b**), (300 MHz, $CDCl_3$); **F2.** ^{1}H NMR of **10** (**a**) and of **11** (**b**), (300 MHz, $CDCl_3$); **F3.** ^{13}C NMR of **10** (**a**) and of **11** (**b**), (75.5 MHz, $CDCl_3$)



^{1}H NMR of 2-Chloro-4-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-ylethynyl]pyridine (**5**) (300 MHz, DMSO-d_6)



^{13}C NMR and DEPT135 of 2-Chloro-4-[2,5-dimethyl-1-(4-trifluoromethoxyphenyl)-1*H*-imidazol-4-ylethynyl]pyridine (**5**) (75.5 MHz, DMSO-d_6)



Comparison between ^{1}H NMR di **5** in DMSO-d_6 (a) and in $CDCl_3$ (b)

S5. Percentage variation of geometric isomers of 8 in varius batches over time and/or with heating up deducted from ^{1}H NMR (300 MHz, DMSO-d_6) spectra

Table S1. Percentages of geometric isomers of **8** in varius batches over time (spectra acquired at r.t.)

Compound 8	Geometric Isomer 1	Geometric Isomer 2	Geometric Isomer 3	Geometric Isomer 4
Sample A	8.9 %	11.1 %	2.5 %	77.7 %
Sample A[a]	**64.0 %**	2.6 %	1.5 %	**31.9 %**
Sample B	3.0 %	32.3 %	3.3 %	62.4 %
Sample B[b]	3.2 %	8.4 %	0.0 %	88.3 %
Sample B[c]	**33.5 %**	**30.7 %**	3.0 %	**32.8 %**

[a]After a week at r.t.; [b]after a day at r.t.; [c]after five months at r.t.

Table S2. Percentages of geometric isomers of **8** with heating up (spectra acquired at r.t. and at 75°C)

Terms of acquisition of ^{1}H NMR spectra for Sample B[a]	Geometric Isomer 1	Geometric Isomer 2	Geometric Isomer 3	Geometric Isomer 4
r.t.	33.5 %	30.7 %	3.0 %	32.8 %
75°C	**40.9 %**	11.1 %		**47.9 %**
r.t.[b]	**41.5 %**	6.4 %	3.0 %	**49.1 %**
r.t. after long heating up[c]	**74.3 %**	2.2 %	5.3 %	**18.2 %**

[a]Kept for five months at r.t.; [b]after heating up at 75°C and then cooling; [c]75°C for 24 h and then cooling.

Table S3. Percentages of geometric isomers of **8** in varius batches over time and with heating up (spectra acquired at r.t.)

Compound 8	Geometric Isomer 1	Geometric Isomer 2	Geometric Isomer 3	Geometric Isomer 4
Sample A[a]	8.9%	11.1%	2.5%	77.7%
Sample A[b]	**64%**	**2.6%**	**1.5%**	**31.9%**
Sample B[c]	33.5%	30.7%	3.0%	32.8%
Sample B[c,d]	**41.5%**	**6.4%**	**3.0%**	**49.1%**

[a]Freshly prepared; [b]after a week; [c]after five mouths at r.t.; [d]heated up for short time and then cooled

S6. Chemical and physical properties of compounds 7-11 and 5 (CTEP)

Table S4. Formulas, MW, physical state, melting point and elemental analysis results of the reported compounds

Compounds	Formula	MW	Physical state	m.p.	Required (%)	Founded (%)	Error (%)
7	$C_6H_9NO_4$	159.14	Yellowish oil	Oil	C 45.28 H 5.7 N 8.8	C 44.95 H 6.10 N 9.02	C - 0.33 H + 0.4 N + 0.22
8	$C_{13}H_{13}F_3N_2O_4$	318.25	Off-white solid	101-104 °C	C 49.06 H 4.12 N 8.8	C 49.04 H 4.22 N 8.65	C - 0.02 H + 0.1 N - 0.15
9	$C_{15}H_{15}F_3N_2O_3$	328.29	Off-white crystals[a] White crystals[b]	142-144 °C[a] 145-146 °C[b]	C 54.88 H 4.61 N 8.54	C 54.80 H 4.62 N 8.80	C - 0.08 H + 0.01 N + 0.26
10	$C_{19}H_{15}ClF_3N_3O_2$	409.79	Yellowish solid	112 °C	C 55.68 H 3.69 N 10.26	C 55.67 H 3.62 N 10.57	C - 0.01 H - 0.07 N + 0.31
11	$C_{20}H_{14}Cl_2F_3N_3O_2$	456.25	Strong yellow solid	136-138 °C (dec)	C 52.65 H 3.09 N 7.01	C 52.86 H 3.22 N 7.35	C + 0.21 H + 0.13 N + 0.34
5 CTEP	$C_{19}H_{13}ClF_3N_3O$	391.77	Off-white solid	119-120 °C	C 58.25 H 3.34 N 10.73	C 58.40 H 3.39 N 10.99	C + 0.15 H + 0.05 N + 0.26

[a]Obtained with *Procedure a;*[12] [b]Obtained with *Procedure b*