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Article

Synthesis of 6-(2-Furyl) and 6-(2-Thienyl)-4-trifluoromethylpyrimidinones and pyrimidines from 4-(2-Heteroaryl)-4-methoxy-1,1,1-trifluoro-3-buten-2-ones

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Neste trabalho é apresentada a síntese, em rendimentos razoáveis (50-67%), de novos sistemas biheterocíclicos, duas 6-(2-heteroaril)-4-trifluormetil-2-(1*H*)-pirimidinonas (**2a**,**b**) e uma série de dez 6-(2-heteroaril)-4-trifluormetilpirimidinas (**3a**,**b** - **7a**,**b**) a partir da ciclocondensação de 1,1,1-trifluor-4-(2-heteroaril)-4-metoxi-3-buten-2-onas com uréia e amidinas. As estruturas de todos os compostos foram atribuídas pelos dados de análise elementar, espectrometria de massas e dados de RMN ^{1}H e ^{13}C. Os dados de RMN ^{1}H e ^{13}C são mostrados de maneira sistemática. Também apresentamos os dados de difração de raios-X de um monocristal da 2-amino-6-(tien-2-il)-4-trifluormetilpirimidina (**5b**).

The synthesis of biheterocyclic systems 6-(2-furyl)-pyrimidines and 6-(2-thienyl)-pyrimidines in reasonable yields (50-67%), two 6-(2-heteroaryl)-4-trifluoromethyl-2-(1*H*)-pyrimidinones (**2a**,**b**) and a series of ten 6-(2-heteroaryl)-4-trifluoromethylpyrimidines (**3a**,**b** - **7a**,**b**) from the cyclocondensation of 1,1,1-trifluoro-4-(2-heteroaryl)-4-methoxy-3-buten-2-ones with urea and amidines is reported. Structures of all compounds have been elucidated by elemental analysis, mass spectrometry and ^{1}H, ^{13}C NMR measurements. The ^{1}H and ^{13}C NMR data are systematically reported. The X-ray diffraction data for monocrystal from 2-amino-4-trifluoromethyl-6-(thien-2-yl)-pyrimidine (**5b**) are reported.

Keywords: 4-trifluoromethylpyrimidines, 1,1,1-trifluoro-4-methoxy-3-buten-2-ones, [3 + 3] cyclocondensation

Introduction

Interest in perfluoroalkylated heterocyclic compounds is largely due to the fact that they have enhanced biological activity and can be used as medicinal or agricultural chemicals.[1-8] Among them, fluorinated pyrimidines have been shown to possess high biological activities as bactericides, fungicides, analgesics, antipyretics and anti-inflammatories.[9-15]

Perfluoroalkylated N-containing heterocycles can be obtained by various methods, including the widely used reactions of 1,3-dicarbonyl compounds with bi-nucleophiles. For example, the cyclization of N-C-N blocks (urea, guanidines and amidines) with perfluoroalkyl containing 1,3-bielectrophiles (1,3-diketones, 1,3-ketoesters, 1,3-ketoamides, α,β-enones) is considered the main procedure for the synthesis of perfluoroalkyl substituted pyrimidine derivatives.[15-18]

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Derivatives 2-substituted of the 6-(2-furyl)-4-trifluoromethylpyrimidines and 6-(2-thienyl)-4-trifluoromethylpyrimidines were early synthesized by cyclocondensation respectively of 1-(2-furyl)-4,4,4-trifluorobutane-1,3-dione or 1-(2-thienyl)-4-trifluoro-butane-1,3-dione with amidines $NH_2C(NH)X$ [X = OR, NH_2, SMe], however only few analytical data were reported.[19-23] The patent reports show only melting point as accessible analytical data for these compounds.

The 6-furyl and 6-thienyl derivatives of 2-amino-4-trifluoromethylpyrimidine and 2-hydroxy (or 2-mercapto)-4-trifluoromethylpyrimidine obtained from cyclocon-densation of 1-(2-heteroaryl)-4,4,4-trifluorobutane-1,3-dione and guanidine or urea were applied in effective treatment of cardiorenal disease and in edema.[19] Moreover had demonstrated eficient inhibitory activity in mevalonic acid incorporation during biosynthesis of cholesterol.[20]

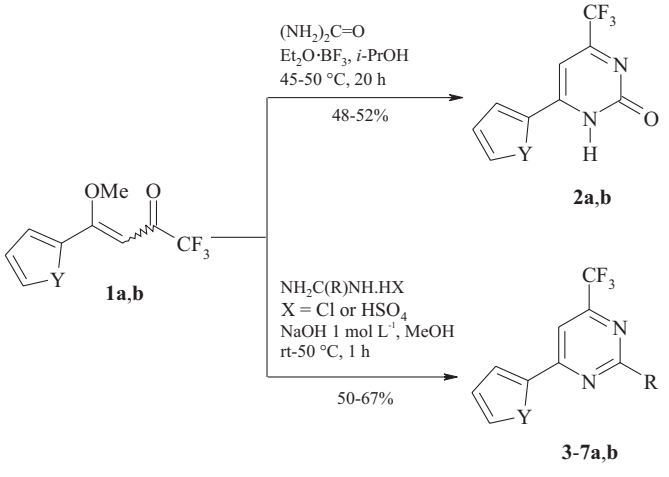
Recently we have reported the synthesis of 4-(2-heteroaryl)-4-methoxy-1,1,1-trifluoro-3-buten-2-ones as building blocks to construct promising trifluoromethyl containing

biheterocyclic systems.[9,24,25] The present work aimed to report efficient procedures for the systematic cyclocondensation of 4-(2-furyl)-4-methoxy-1,1,1-trifluoro-3-buten-2-one (**1a**) and 4-methoxy-4-(2-thienyl)-1,1,1-trifluoro-3-buten-2-one (**1b**) with urea, acetamidine, benzamidine, guanidine, 2-methyl-2-pseudothiourea and 1*H*-pyrazole-1-carboxyamidine for synthesis of the series of biheterocyclic 6-(2-heteroaryl)-4-trifluoromethylpyrimidinones **2** and 6-(2-heteroaryl)-4-trifluoromethylpyrimidines **3**-**5**, **7** and new three ring system 2-(pyrazol-1-yl)-4-trifluoromethyl-6-(2-heteroaryl)pyrimidines **6**.

Results and Discussion

The 4-(2-heteroaryl)-4-methoxy-1,1,1-trifluoromethyl-3-buten-2-ones **1a** and **1b** were prepared using the previously reported procedure.[25] The 6-(2-furyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one **2a** and the 6-(2-thienyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one **2b** were prepared in very low yields (< 10%) from the reaction of **1a** or **1b** with urea in reflux EtOH or, even *i*-PrOH (Scheme 1).[12] Several attempts to improve the yields by refluxing **1a** or **1b** with urea for long periods (2 days) without catalysis were unsuccessful. However, polymeric material was obtained in reactions in MeOH with Brönsted HCl catalysis at room temperature or with Lewis acid BF_3·OEt_2 or Ti(O-*i*Pr)$_4$ catalysis at reflux temperature (>65 °C) for long periods.[15] Our experiments have demostrated that the best medium was anhydrous *i*-PrOH with drops of BF_3·OEt_2 at 50 °C during 20 h, furnishing reasonable yields (50%) for **2a** and **2b**.[12] The ^{1}H NMR spectra have show a single set of signals (see, Experimental) indicating that compounds **2a** and **2b** exist as one of the possible tautomers. The 2(1*H*)pyrimidin-2-one structure was confirmed by characteristic signal from N-H at 12.93-12.95 ppm.

In the search for the optimum cyclocondensations condition for **1a**, **1b** and amidines acetamidine hydrochloride was used as a model amidine. The cyclocondensations in MeOH or *i*PrOH under Brönsted HCl or Lewis BF_3·OEt_2 catalysis were unsuccessful, the reactants were recovered. In contrast to the synthesis of 4-polyfluoroalkylpyrimidines by condensation in refluxing *i*PrOH under Lewis BF_3·OEt_2 catalysis for 4 to 26 h,[12] we have obtained products 6-(2-heteroaryl)-2-methyl-4-trifluoromethyl-pyrimidines **3a** and **3b** in good yields using alkaline medium, reacting acetamidine hydrochloride with a 1 mol L^{-1} KOH aqueous solution and adding to MeOH solution of **1a** or **1b** at room temperature. TLC analyses during reaction period have revealed that the 1,3-dielectrophiles were consumed after 1 hour, furnishing good yields of the pyrimidines **3**. The 6-(2-heteroaryl)-2-phenyl-4-trifluoromethyl-pyrimidines **4a**, **4b**, 2-amino-6-(2-heteroaryl)-4-trifluormethyl-pyrimidines **5a**, **5b**, 6-(2-heteroaryl)-2-(1*H*-pyrazol-1-yl)-4-trifluoro-methylpyrimidines **6a**, **6b** and the 6-(2-heteroaryl)-2-thiomethyl-4-trifluoromethyl-pyrimidines **7a**, **7b** were obtained in similar alkaline medium with the procedure described above. The structure of all compounds was determined from ^{1}H, ^{13}C and mass spectrometry. Based on our previous reports on the chemistry of 6-aryl-4-trifluoromethyl-1*H*-pyrimidin-2-ones and 6-aryl-4-trifluoromethyl-pyrimidines derived from 4-aryl-4-methoxy-1,1,1-trifluoro-3-buten-2-ones, the assignment of each signal in the ^{13}C NMR spectra of compounds **2**-**7** was accurately established.[15,16]



	a	b
Y	O	S

	3a,b	4a,b	5a,b	6a,b	7a,b
R	Me	Ph	NH_2		SMe

Scheme 1. [3 + 3]cyclocondensations.

Table 1. Crystal data[a] and structure refinement for 2-amino-4-trifluoromethyl-6-(2-thienyl)-pirimidine (**5b**)

Crystal data		
Formula	$C_9H_6F_3N_3S$	
Habit	Colorless prisms	
Size / (mm)	0.240 x 0.090 x 0.079	
Symmetry	Monoclinic, $P2_{1/c}$	
Unit cell dimensions / (Å, °)	a = 5.0982(2)	α = 90
	b = 19.4858(7)	β = 95.779(2)
	c = 10.1807(3)	γ = 90
Volume / (Å^3), Z	1006.24(6), 4	
D_c / (g cm^{-3}), F(000)	1.619, 496	
μ / (mm^{-1})	0.339	
θ range for data collection / (º)	3.73 to 28.37	
Index ranges	-6≤h≤6,	
	-26≤k≤26,	
	-13≤l≤13	
Reflections collected	11012	
Independent reflections (R_{int})	2501 (0.0426)	
Completeness to θ	99.4 %	
T_{min}-T_{max}	0.7957-1.0	
Solution	Direct methods SHELXS-97	
Refinement method	Full matrix least-squares on F^2	
Data / restraints / parameters	2501 / 0 / 146	
Goodness-of-fit on F^2	0.947	
Final R indices [I > 2σ(I)]	R1 = 0.0434, wR2 = 0.1209	
R indices, all data	R1 = 0.0790, wR2 = 0.1389	
Largest diff. peak and hole / (e. Å^3)	0.202 and -0.282	

[a]CCDC 286548 contains the supplementary crystallographic data for this paper. These data can be made available free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk or by contacting CCDC.

The ^{1}H and ^{13}C spectra of products showed set of signals attributed to aromatic pyrimidines **3a**, **3b** to **7a**, **7b**. The structure of compound 2-amino-6-(2-thienyl)-4-trifluoromethyl-pyrimidine **5b** was established by X-ray diffraction analysis. The overall view of the molecule is shown in Figure 1. The 6-(2-thienyl)-pyrimidine system is virtually coplanar (the mean deviation of the atoms from the plane is 0.008 Å). The thienyl ring suffers a rotational disorder, atoms S1 and C7 were modeled as exchanged with a minor occupancy fraction refined to 19.6%. The trifluoromethyl group presents a rotational disorder; the three F atoms were refined in a position rotated approximately 45º from their original positions at 5.3% occupancy. Crystal data for **5b** are shown in Table 1.

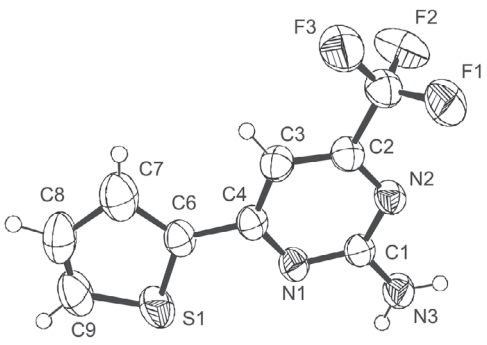


Figure 1. ORTEP Diagram of the X-ray crystal structure of **5b** at a probability level of 50%.

Conclusions

In conclusion, the biheterocyclic systems 6-(2-furyl)- and 6-(2-thienyl)-pyrimidinones and 6-(2-furyl)- and 6-(2-thienyl)-pyrimidines were efficiently obtained by reacting 4-(2-heteroaryl)-4-methoxy-1,1,1-trifluoro-3-buten-2-ones with N-C-N binucleophiles, in reasonable to good yields (50-67%). The best reactional medium for urea cyclocondensation was under BF_3·OEt_2 Lewis acid catalysis. However the cyclocondensations with hydrochoride amidines occurred only in alkaline media with NaOH, pH >15, furnishing good yields of 6-(2-heteroaryl)-pyrimidines.The tricyclic systems 6-(2-furyl)- and 6-(2-thienyl)-2-(1-pyrazolyl)-pyrimidines are new.

Experimental

The synthesis of 4-(2-heteroaryl)-4-methoxy-1,1,1-trifluoro-3-buten-2-one, **1** has been reported elsewhere.[20] Urea, amidines and BF_3·OEt_2 were used as obtained from commercial suppliers. MeOH and *i*-PrOH were purified before using. 1 mol L^{-1} solution of NaOH was prepared by the dissolution of 0.40 g of NaOH in 100 mL of distilled water. Yields listed in Table 2 are of isolated compounds. All melting points were determined on a Reichert Thermovar apparatus and are uncorrected. The ^{1}H and ^{13}C spectra were recorded at 298 K on a Bruker DPX 400 spectrometer (^{1}H at 400.13 MHz, ^{13}C at 100.63 MHz) with digital resolution of ± 0.01 ppm. All the chemical shifts are expressed in ppm, ^{1}H and ^{13}C are reported with respect to internal TMS. 0.1 mol L^{-1} $CDCl_3$ solutions were used except with compounds **2**, 0.1 mol L^{-1} in DMSO-d_6. H-H and C-F coupling constants are in Hz. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, auto-sampler, cross-linked HP-5 capillary column (30 m, 0.32 mm of internal diameter), and helium was used as the carrier. Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University-São Paulo, Brazil). The crystal and molecular structure of **5b** was determined by a single crystal X-ray diffraction study. Data were recorded on a Bruker Kappa Apex II CCD area detector with graphite monochromatized Mo Ka radiation (l 0.71073 Å). The data were processed with SAINT and SADABS. The

structure was solved by direct methods (SHELXS-97)[26] and additional atoms were located in the difference Fourier map and refined on F^2 using the SHELXTL and Wingx packages.[27]

*6-(2-Furyl)[(2-thienyl)]-4-trifluoromethylpyrimidin-2-one (**2a, b**). General Procedure*

Compounds **1a** (3 mmol, 0.67 g) or **1b** (3 mmol, 0.71 g) and urea (3.3 mmol, 0.21 g) were dissolved in 3 mL of anhydrous *i*-PrOH. Then, 3 drops of $BF_3{\cdot}Et_2O$ were added and the mixture was stirred at 50 °C for 20 h. The solvent was partially evaporated and the product crystallized by cooling. The solid was filtered, washed with cold water and recrystallized from MeOH to give **2a** and **2b**, respectively.

*6-(2-Furyl)-4-trifluoromethyl-1H-pyrimidin-2-one, **2a***

Yield 48 %; mp 282-284 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.82 (dd, 1H, *J* 3.5, *J* 1.66, H4'), 7.48 (s, 1H, H5), 7.67 (d, 1H, *J* 3.5, H3'), 8.07 (d, 1H, *J* 1.66, H5'), 12.93 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 157.9 ($^2J_{CF}$ 35), 157.0, 148.5, 147.6, 120.2 (J_{CF} 277), 115.8, 112.9, 100.6; MS (70 eV) *m/z* 230 (M^+, 100), 118 (16), 90 (11), 63 (18). Anal. Calc. for $C_9H_5F_3N_2O_2$: C, 46.97; H, 2.19; N, 12.17. Found: C, 46.87; H, 2.18; N, 12.05.

*6-(2-Thienyl)-4-trifluoromethyl-1H-pyrimidin-2-one, **2b***

Yield 52 %; mp 266-268 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): 7.24 (dd, 1H, *J* 4.8, *J* 3.4, H4'); 7.89 (d, 1H, *J* 4.8, H3'); 7.95 (s, 1H, H5); 8.24 (d, 1H, *J* 3.4, H5'); 12.95 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δ 165.1, 163.5, 156.6 ($^2J_{CF}$ 35), 140.4, 132.6, 130.9, 128.7, 120.2 (J_{CF} 274), 103.5; MS (70 eV) *m/z* 246 (M^+, 100), 227 (10), 134 (30), 69 (17). Anal. Calc. for $C_9H_5F_3N_2SO$: C, 43.91; H, 2.05; N, 11.38. Found: C, 43.59; H, 2.02; N, 11.23.

*6-(2-Furyl)[(2-thienyl)]-4-trifluoromethylpyrimidines (**3-7a, b**). General Procedure*

Acetamidine hydrochloride (3 mmol) was added to an aqueous KOH 1 mol L^{-1} solution (3 mL). The resulting solution was added to a MeOH solution of compounds **1a** (3 mmol, 0.66 g) or **1b** (3 mmol, 0.71 g). The resulting mixture was stirred at room temperature at 50 °C for 1 h. Then MeOH was evaporated and the resulting material was diluted with $CHCl_3$ (50 mL) and washed with water (3 × 20 mL). The organic solution was dried over anhydrous $MgSO_4$ and the solvent was removed, the solid products were recrystallized from hexane, furnishing the pure crystalline products **3a**, **3b**, **5a**, **5b**, **6a** and **6d**. The compounds **7a** and **7b** were oils purified by chromatography column with hexane:chloroform (1:1) as eluent. When the precipitated product was formed, it was filtered, washed with water and dried over $CaCl_2$. The products **4a**, **4b** were obtained pure (GC-MS, ^{1}H NMR).

*6-(2-Furyl)-2-methyl-4-trifluoromethylpyrimidine, **3a***

Yield 48 % (71 %, ref. 28); mp 41-43 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 2.82 (s, 3H, Me); 6.62 (dd, 1H, *J* 3.52 Hz, *J* 1.76 Hz, H4'); 7.38 (d, 1H, *J* 3.52 Hz, H3'); 7.65 (d, 1H, *J* 1.76 Hz, H5'); 7.72 (s, H5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 157.4, 156.1 ($^2J_{CF}$ 35 Hz), 151.0, 145.8, 120.2 (J_{CF} 274), 113.9, 112.8, 107.5 ($^4J_{CF}$ 2.8 Hz), 25.9; (MS (70 eV) *m/z* 228 (M^+, 95), 209 (27), 118 (100), 90 (48), 63 (78). Anal. Calc. for $C_{10}H_7F_3N_2O$: C, 52.64; H, 3.09; N, 12.28. Found: C, 52.82; H, 3.36; N, 12.38.

*2-Methyl-6-(2-thienyl)-4-trifluoromethylpyrimidine, **3b***

Yield 53 %; mp 47-49 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 2.81 (s, 3H, Me); 7.18 (dd, 1H, *J* 5.01, *J* 3.79 Hz, H4'); 7.59 (dd, 1H, *J* 5.01 Hz, *J* 1.04 Hz, H3'); 7.65 (s,1H, H5); 7.84 (dd, 1H, *J* 3.79 Hz, *J* 1.04 Hz, H5'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 161.1, 155.9 ($^2J_{CF}$ 35 Hz), 141.3, 131.5, 128.7, 128.6, 120.2 (J_{CF} 273 Hz), 107.8 ($^4J_{CF}$ 2.8 Hz), 25.9; MS (70 eV) *m/z* 244 (M^+, 100), 225 (13), 134 (72), 69 (21). Anal. Calc. for $C_{10}H_7F_3N_2S$: C, 49.18; H, 2.89; N, 11.47. Found: C, 48.78; H, 2.91; N, 11.41.

*6-(2-Furyl)- 2-phenyl-4-trifluoromethylpyrimidine, **4a***

Yield 61 % (69 %, ref. 29); mp 66-68 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 7.46-7.51 (m, 3H, Ph); 7.47 (d, 1H, *J* 3.3 Hz, H3'); 7.57 (dd, 1H, *J* 3.3 Hz, *J* 1.7 Hz, H4'); 7.63 (d, 1H, *J* 1.7 Hz, H5'); 7.74 (s, 1H, H5); 8.52-8.54 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 157.6, 156.6 ($^2J_{CF}$ 36 Hz), 151.4, 145.8, 136.1, 131.5, 128.6, 128.5, 120.8 (J_{CF} 274 Hz), 113.8, 112.8, 107.9 ($^4J_{CF}$ 2.7 Hz); MS (70 eV) *m/z* 290 (M^+, 96), 271 (16), 118 (100), 90 (52), 63 (75). Anal. Calc. for $C_{15}H_9F_3N_2O$: C, 62.07; H, 3.13; N, 9.65. Found: C, 61.54; H, 3.10; N, 9.38.

*2-Phenyl-6-(2-thienyl)-4-trifluoromethylpyrimidine, **4b***

Yield 67 % (67 %, ref. 28); mp 104-106 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (dd, 1H, *J* 5.0, *J* 3.8 Hz, H4'); 7.48-7.51 (m, 3H, Ph); 7.57 (dd, 1H, *J* 5.0 Hz, *J* 1.05 Hz, H3'); 7.65 (s, 1H, H5); 7.85 (dd, 1H, *J* 3.8 Hz, *J* 1.05 Hz,

H5'); 8.53 - 8.56 (m, 2H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 161.2, 156.4 ($^2J_{CF}$ 36 Hz), 141.8, 136.1, 131.5, 131.4, 128.7, 128.6, 128.5, 120.8 (J_{CF} 274 Hz), 108.2 ($^4J_{CF}$ 2.8 Hz); MS (70 eV) *m/z* 306 (M^+, 100), 287 (5), 134 (73), 69 (8). Anal. Calc. for $C_{15}H_9F_3N_2S$: C, 58.82; H, 2.96; N, 9.15. Found: C, 58.80; H, 3.12; N, 8.72.

2-Amino-6-(2-furyl)-4-trifluoromethylpyrimidine, ***5a***

Yield 50 %; mp 130-132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 5.61 (s, 2H, NH_2); 6.58 (dd, 1H, *J* 3.52 Hz, *J* 1.73 Hz, H4'); 7.23 (dd, 1H, *J* 3.52 Hz, *J* 0.7 Hz, H3'); 7.24 (s, 1H, H5); 7.61 (dd, 1H, *J* 1.73 Hz, *J* 0.7 Hz, H5'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 158.7, 157.2 ($^2J_{CF}$ 35 Hz), 151.1, 145.6, 120.6 (J_{CF} 274 Hz), 113.8, 112.8, 101.2 ($^4J_{CF}$ 2.9 Hz); MS (70 eV) *m/z* 229 (M^+, 100), 118 (35), 90 (24), 63 (37). Anal. Calc. for $C_9H_6F_3N_3O$: C, 47.17; H, 2.64; N, 18.34. Found: C, 48.00; H, 3.20; N, 18.38.

2-Amino-6-(2-thienyl)-4-trifluoromethylpyrimidine, ***5b***

Yield 51 %; mp 141-143 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 5.57 (s, 2H, NH_2); 7.15 (dd, 1H, *J* 5.0 Hz, *J* 3.8 Hz, H4'); 7.19 (s, 1H, H5); 7.54 (dd, 1H, *J* 5.0 Hz, *J* 1.04 Hz, H3'); 7.77 (dd, 1H, *J* 3.8 Hz, *J* 1.04 Hz, H5'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 162.4, 157.0 ($^2J_{CF}$ 35 Hz), 141.5, 130.9, 128.6, 128.4, 120.6 (J_{CF} 274 Hz), 101.4 ($^4J_{CF}$ 2.9 Hz); MS (70 eV) *m/z* 245 (M^+, 100), 226 (10), 204 (45), 134 (59), 69 (28); Anal. Calc. for $C_9H_6F_3N_3S$: C, 44.08; H, 2.47; N, 17.14. Found: C, 44.70; H, 2.65; N, 16.59.

6-(2-Furyl)-2-(1H-pyrazol-1-yl)-4-trifluoromethyl-pyrimidine, ***6a***

Yield 54 %; mp 108-110 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 6.53 (dd, 1H, *J* 2.8 Hz, *J* 1.6 Hz, H4-pyr); 6.64 (dd, 1H, *J* 3.4 Hz, *J* 1.8 Hz, H4'); 7.57 (d, 1H, *J* 3.4 Hz, H3'); 7.69 (d, 1H, *J* 1.6 Hz, H5-pyr); 7.76 (s, 1H, H5); 7.89 (d, 1H, *J* 1.8 Hz, H5'); 8.65 (d, 1H, *J* 2.8 Hz, H3-pyr); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 157.2 ($^2J_{CF}$ 37 Hz), 156.3, 150.4, 146.7, 144.4, 129.8, 120.2 (J_{CF} 274 Hz), 115.6, 113.2, 109.8, 107.6; MS (70 eV) *m/z* 280 (M^+, 100), 261 (8), 213 (75), 118 (8), 90 (8), 63 (14). Anal. Calc. for $C_{12}H_7F_3N_4O$: C, 51.44; H, 2.52; N, 19.99. Found: C, 50.84; H, 2.64; N, 20.09.

2-(1H-Pyrazol-1-yl)-6-(2-thienyl) 4-trifluoromethyl-pyrimidine, ***6b***

Yield 58 %; mp 116-118 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): 6.53 (dd, 1H, *J* 2.8 Hz, *J* 1.58 Hz, H4-pyr); 7.21 (dd, 1H, *J* 4.99 Hz, *J* 3.83 Hz, H4'); 7.65 (dd, 1H, *J* 4.99 Hz, *J* 1.04 Hz, H3'); 7.68 (s, 1H, H5); 7.89 (d, 1H, *J* 1.58 Hz, H3-pyr); 7.95 (dd, 1H, *J* 3.83 Hz, *J* 1.04 Hz, H5'); 8.66 (d, 1H, *J* 2.7 Hz, H5-pyr); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 157.7 ($^2J_{CF}$ 36 Hz), 156.2, 144.5, 140.3, 132.5, 129.9, 129.8, 128.8, 120.2 (J_{CF} 274 Hz), 109.1, 107.9; MS (70 eV) *m/z* 296 (M^+, 100), 287 (8), 229 (82), 134 (15), 69 (9). Anal. Calc. for $C_{12}H_7F_3N_4S$: C, 48.65; H, 2.38; N, 18.91. Found: C, 48.76; H, 2.47; N, 18.90.

6-(2-Furyl)-2-tiomethyl-4-trifluoromethylpyrimidine, ***7a***

Yield 52 %, oil; ^{1}H NMR (400 MHz, $CDCl_3$): 2.61 (s, 3H, SMe); 6.59 (dd, 1H, *J* 3.52 Hz, *J* 1.71 Hz, H4'); 7.36 (dd, 1H, *J* 3.52 Hz, *J* 0.71 Hz, H3'); 7.51 (s, 1H, H5); 7.63 (dd, 1H, *J* 1.71 Hz, *J* 0.71 Hz, H5'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 157.1, 156.0 ($^2J_{CF}$ 36 Hz), 150.7, 146.1, 120.4 (J_{CF} 274 Hz), 114.2, 112.8, 105.3, 13.8; MS (70 eV) *m/z* 260 (M^+, 100), 241 (12), 214 (38), 118 (18), 90 (13), 63 (28). Anal. Calc. for $C_{10}H_7F_3N_2OS$: C, 46.15; H, 2.71; N, 10.76. Found: C, 46.10; H, 2.80; N, 10.78.

6-(2-Thienyl)-2-tiomethyl-4-trifluoromethylpyrimidine, ***7b***

Yield 53 %, oil; ^{1}H NMR (400 MHz, $CDCl_3$): 2.61 (s, 3H, SMe); 7.15 (dd, 1H, *J* 5.0 Hz, *J* 3.9 Hz, H4'); 7.43 (s, 1H, H5); 7.56 (dd, 1H, *J* 5.0 Hz, *J* 1.1 Hz, H3'); 7.80 (dd, 1H, *J* 3.90 Hz, *J* 1.10 Hz, H5'); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 162.7, 155.8 ($^2J_{CF}$ 36 Hz), 140.9, 131.7, 129.1, 128.6, 120.4 (J_{CF} 274 Hz), 105.7, 14.1; MS (70 eV) *m/z* 276 (M^+, 100), 257 (14), 229 (60), 134 (45), 69 (16). Anal. Calc. for $C_{10}H_7F_3N_2S_2$: C, 43.47; H, 2.55; N, 10.14. Found: C, 43.55; H, 2.60; N, 10.20.

Table 2. Bond length (Å) and angles (º) for 2-amino-4-trifluoromethyl-6-(2-thienyl)-pyrimidine (**5b**)

Bond	Length / (Å)	Bonds	Angle / (°)
C1-N3	1.338(2)	N3-C1-N1	117.62(15)
C1-N1	1.346(2)	N3-C1-N2	116.93(15)
C1-N2	1.348(2)	N1-C1-N2	125.45(16)
C2-N2	1.331(2)	N2-C2-C3	124.68(16)
C2-C3	1.365(3)	N2-C2-C10	113.89(16)
C2-C10	1.508(3)	C3-C2-C10	121.40(17)
C3-C4	1.404(3)	C2-C3-C4	115.87(17)
C3-H3	0.9300	C2-C3-H3	122.1
C4-N1	1.328(2)	C4-C3-H3	122.1
C4-C6	1.460(2)	N1-C4-C3	121.50(16)
C6-C7	1.511(3)	N1-C4-C6	116.86(16)
C6-S1	1.681(2)	C3-C4-C6	121.65(17)
C7-C8	1.476(3)	C4-C6-C7	126.76(16)
C7-H7	0.930	C4-C6-S1	119.59(15)
C8-C9	1.330(4)	C7-C6-S1	113.64(12)
C8-H8	0.930	C8-C7-C6	102.90(17)
C9-S1	1.655(3)	C8-C7-H7	128.5
C9-H9	0.930	C6-C7-H7	128.5
C10-F3	1.324(2)	C9-C8-C7	116.2(2)
C10-F2	1.326(2)	C9-C8-H8	121.9
C10-F1	1.328(2)	C7-C8-H8	121.9
N3-H3a	0.860	C8-C9-H9	114.51(18)
N3-H3b	0.860	S1-C9-H9	122.7

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Supplementary Information

Supplementary data ^{1}H, ^{13}C NMR and mass spectra are available free of charge at http://jbcs.sbq.org.br, as PDF file.

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Synthesis of 6-(2-Furyl) and 6-(2-Thienyl)-4-trifluoromethylpyrimidinones and -pyrimidines from 4-(2-Heteroaryl)-4-methoxy-1,1,1-trifluoro-3-buten-2-ones

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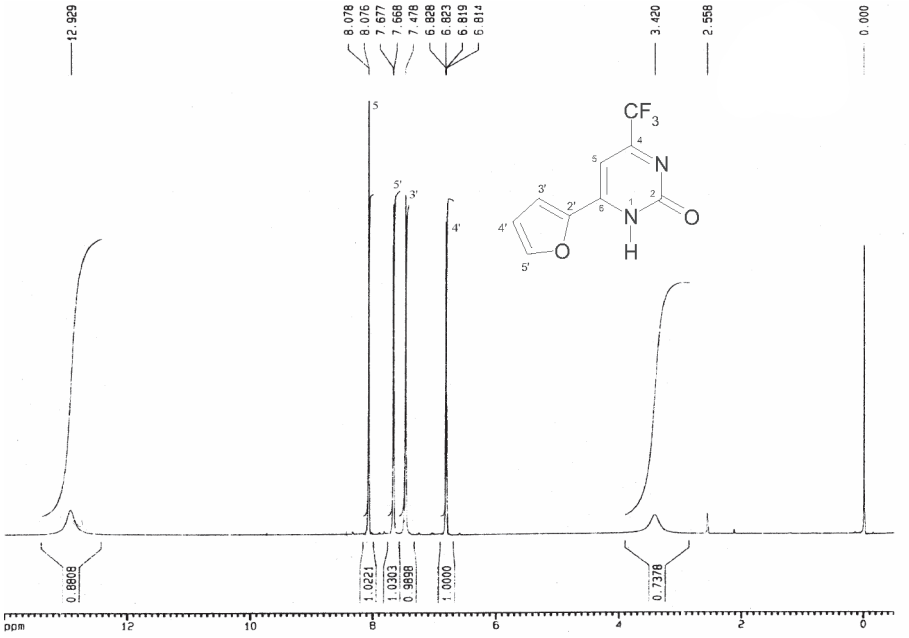

Figure S1. ^{1}H NMR spectrum of the 6-(2-furyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one (**2a**), DMSO-d_6.

*e-mail: alexflores@smail.ufsm.br

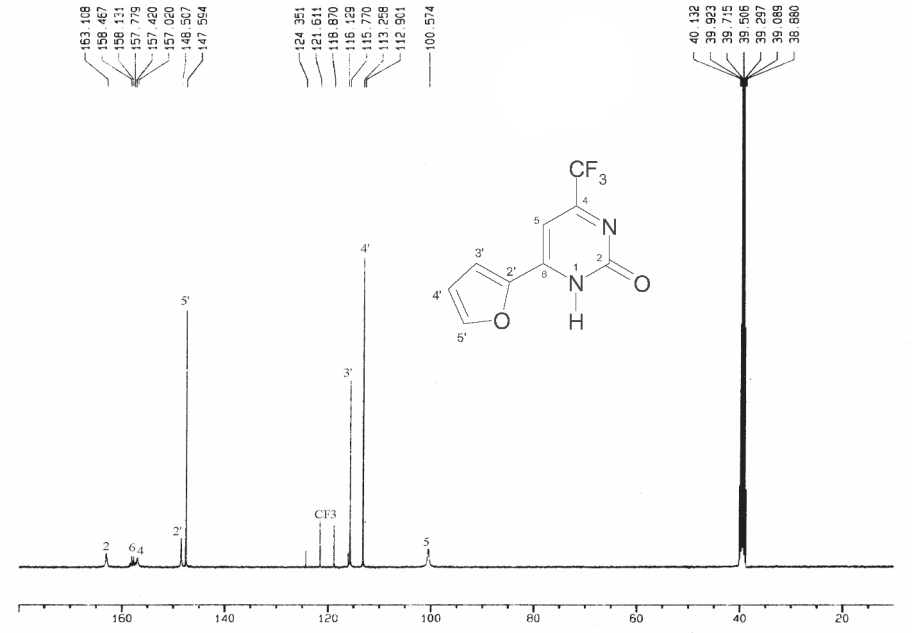

Figure S2. ^{13}C[H] NMR spectrum of the 6-(2-furyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one (**2a**), DMSO-d_6.

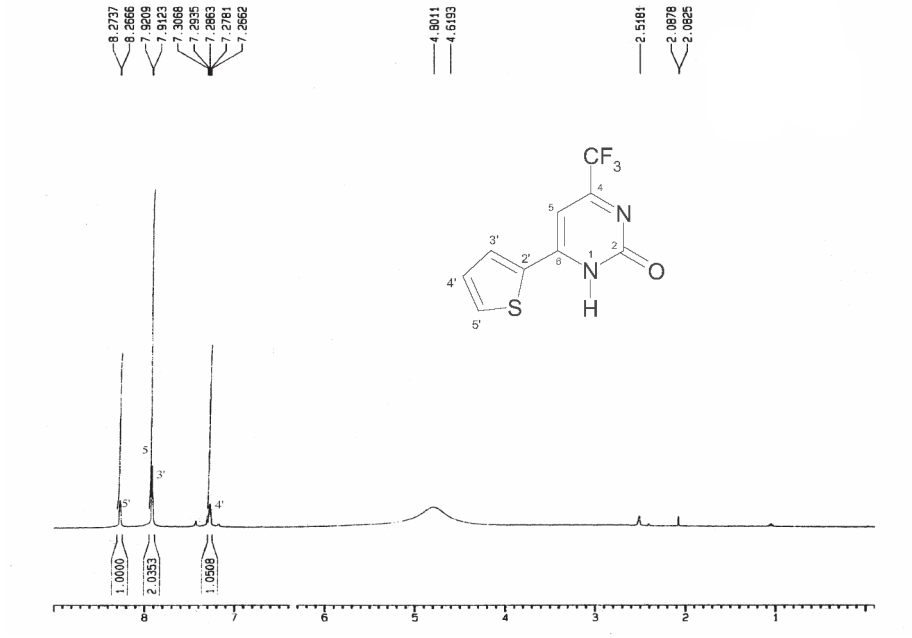

Figure S3. ^{1}H NMR spectrum of the 6-(2-thienyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one (**2b**), DMSO-d_6.

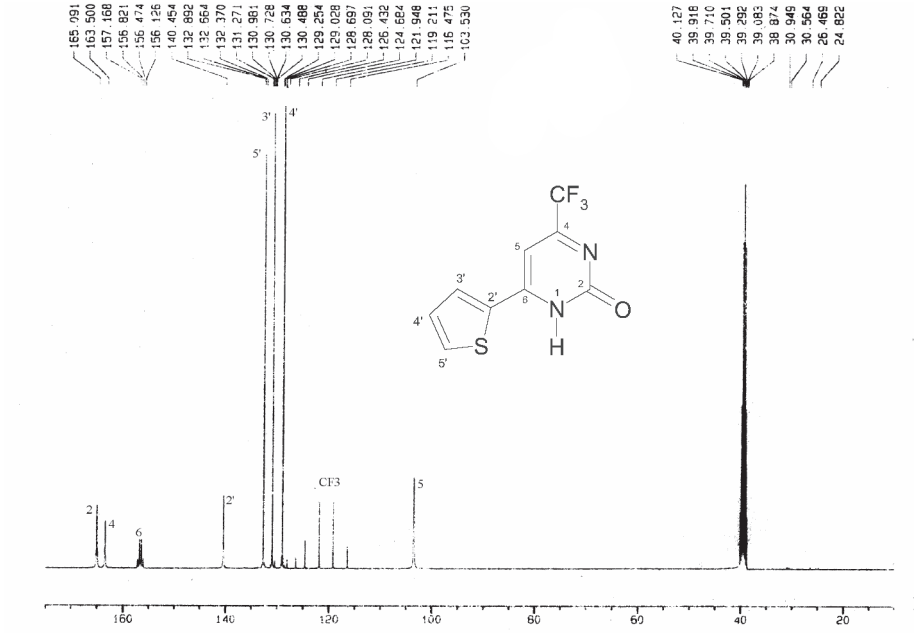

Figure S4. ^{13}C NMR spectrum of the 6-(2-thienyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one (**2b**), DMSO-d_6.

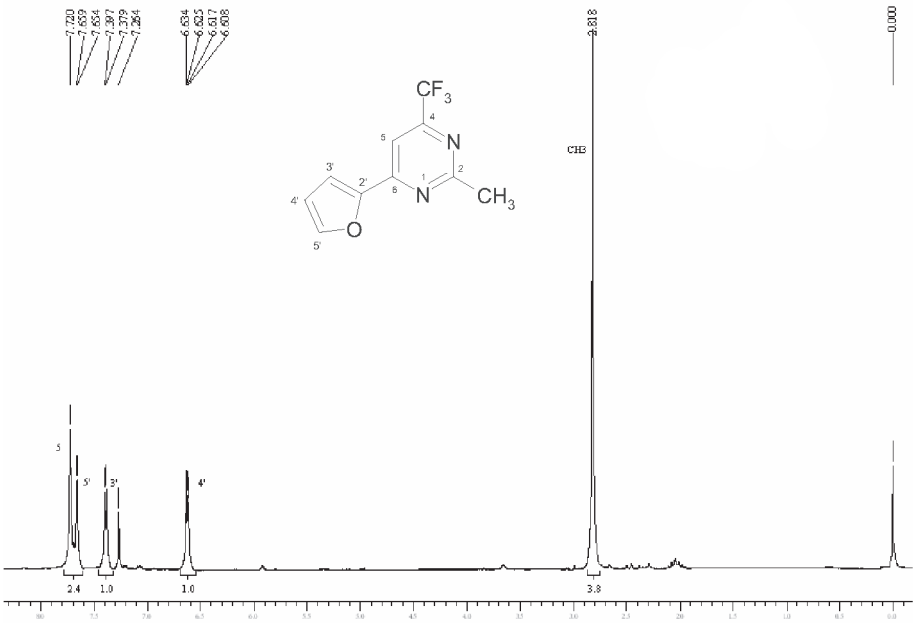

Figura S5. ^{1}H NMR spectrum of the 6-(2-furyl)-2-methyl-4-trifluoromethylpyrimidine (**3a**), $CDCl_3$.

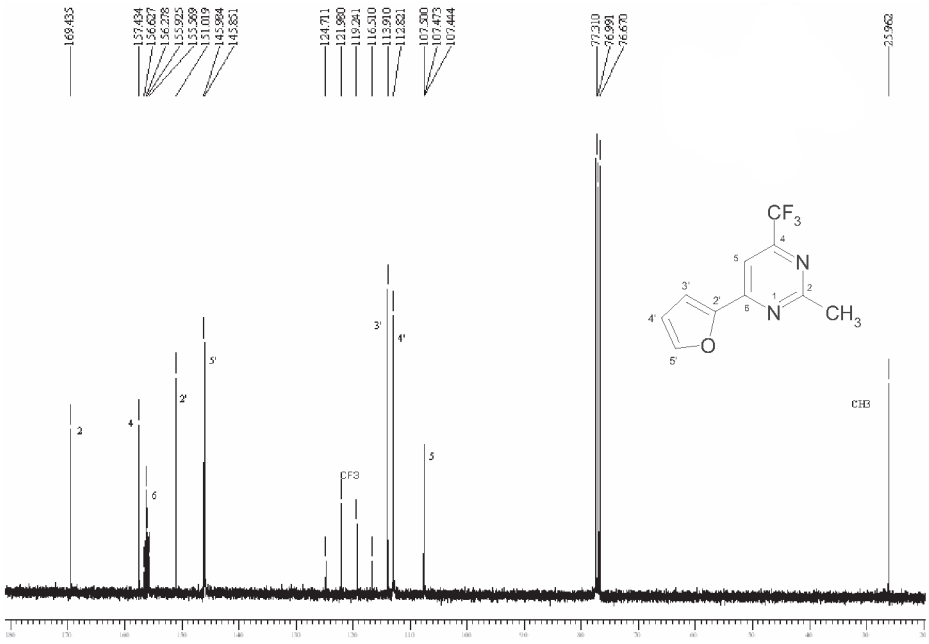

Figure S6. ^{13}C NMR spectrum of the 6-(2-furyl)-2-methyl-4-trifluoromethylpyrimidine (**3a**), $CDCl_3$.

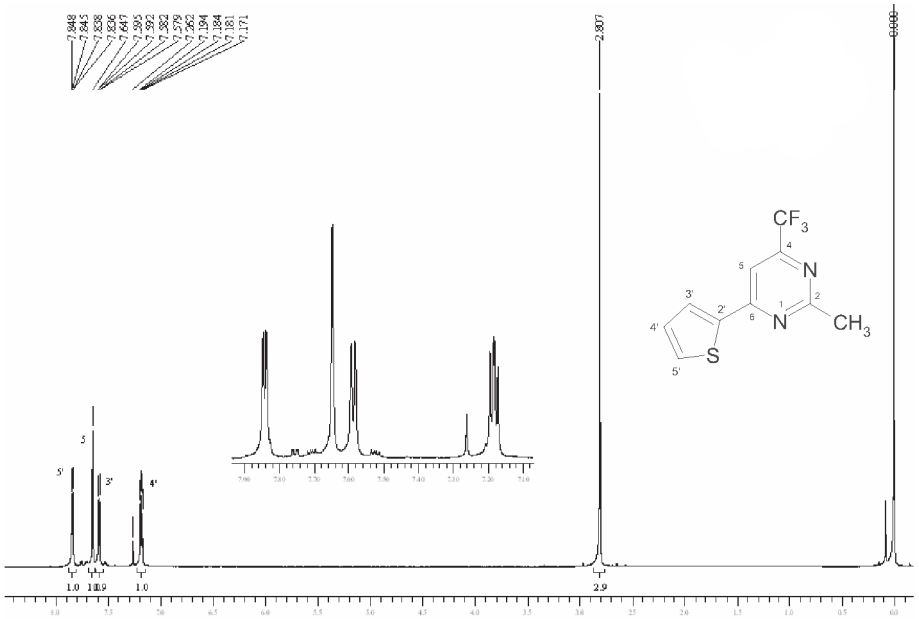

Figure S7. ^{1}H NMR spectrum of the 2-methyl-6-(2-thienyl)-4-trifluoromethylpyrimidine (**3b**), $CDCl_3$.

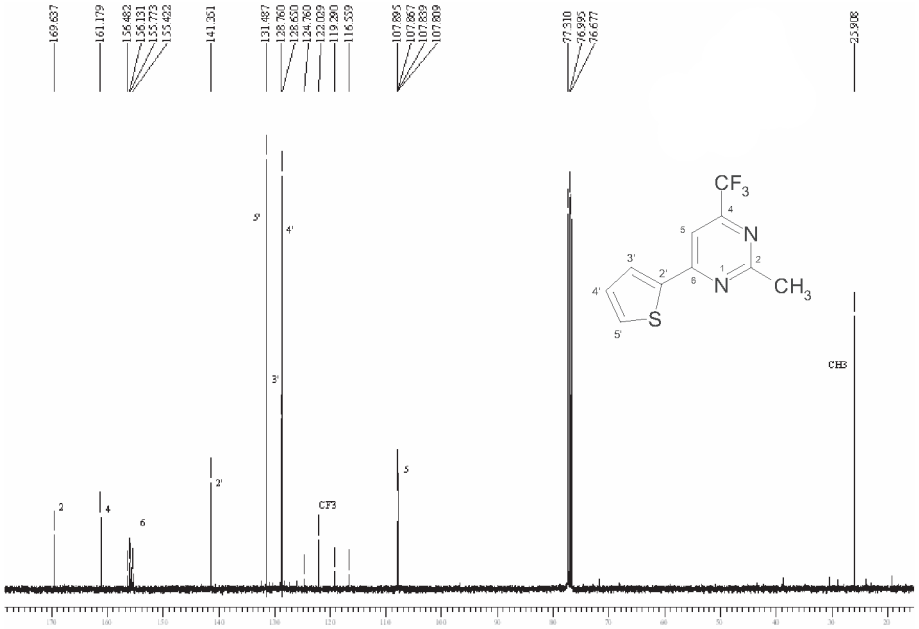

Figure S8. $^{13}C[H]$ NMR spectrum of the 6-(2-thienyl)-2-methyl-4-trifluoromethylpyrimidine **3b**, $CDCl_3$.

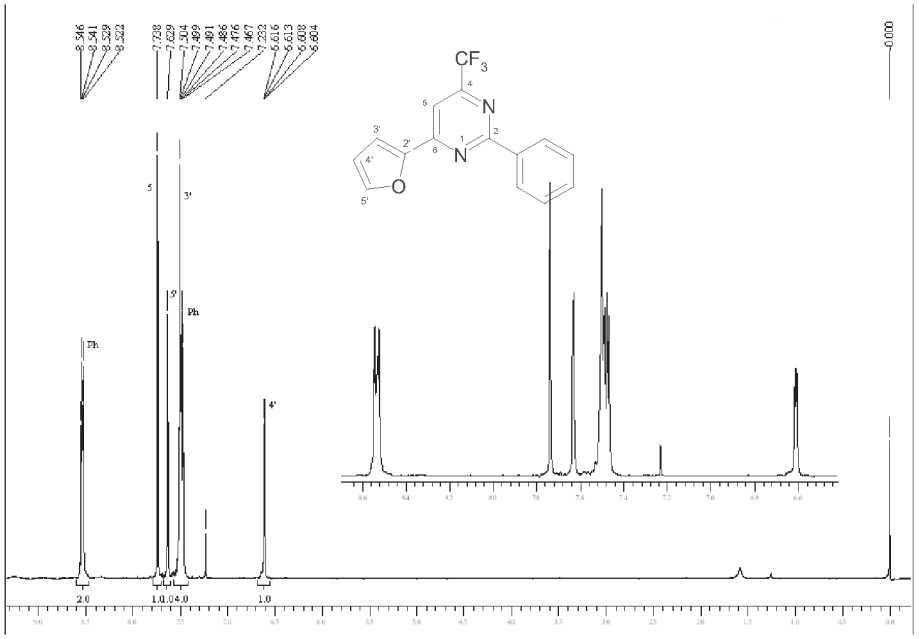

Figure S9. ^{1}H NMR spectrum of the 6-(2-furyl)- 2-phenyl-4-trifluoromethylpyrimidine **4a**, $CDCl_3$.

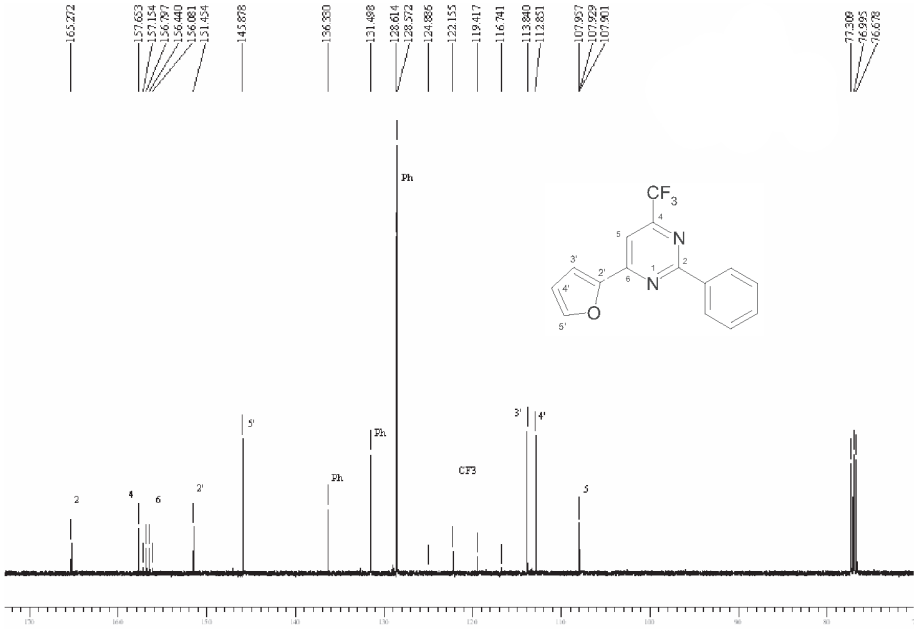

Figure S10. ^{13}C NMR spectrum of the 6-(2-furyl)-2-phenyl-4-trifluoromethylpyrimidine **4a**, $CDCl_3$.

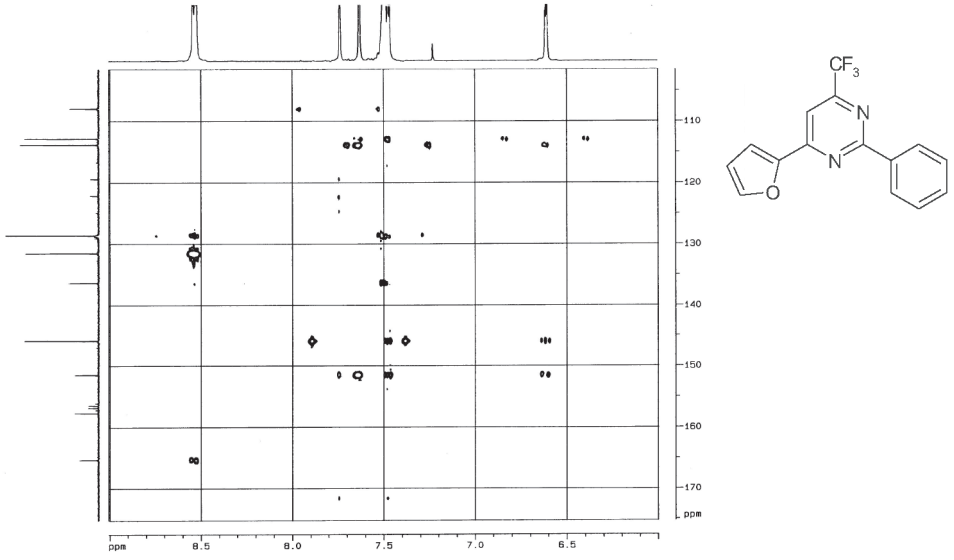

Figure S11. HMBC spectrum of the 6-(2-furyl)-2-phenyl-4-trifluoromethylpyrimidine **3b**, $CDCl_3$.

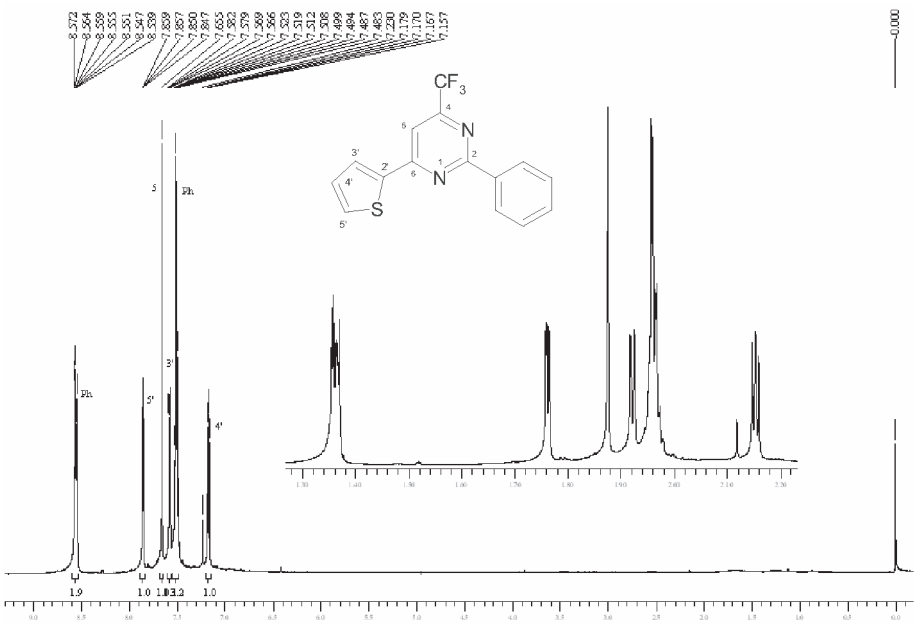

Figure S12. ^{1}H NMR spectrum of the 2-phenyl-6-(2-thienyl)-4-trifluoromethylpyrimidine **4b**, $CDCl_3$.

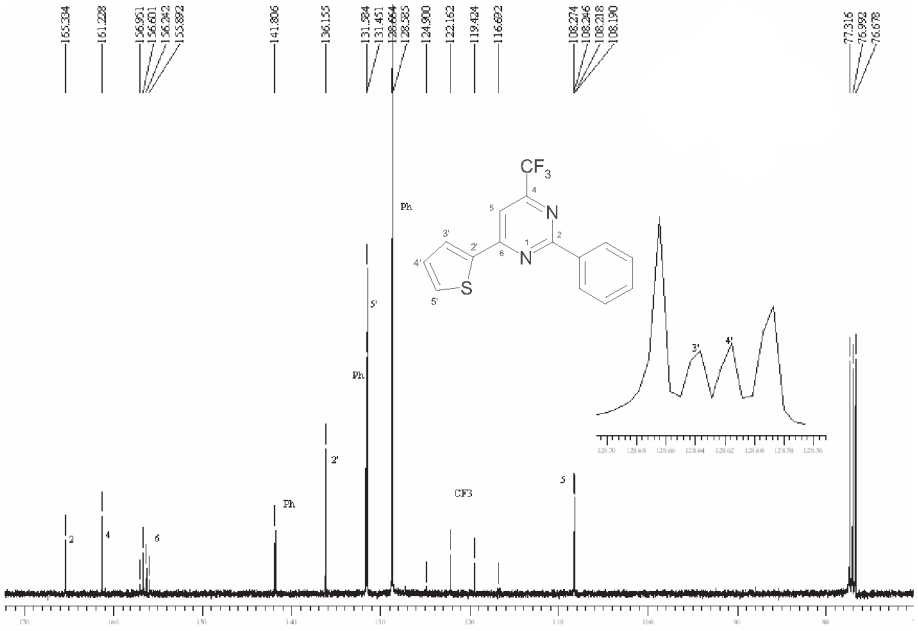

Figure S13. ^{13}C[H] NMR spectrum of the 2-phenyl-6-(2-thienyl)-4-trifluoromethylpyrimidine **4b**, $CDCl_3$.

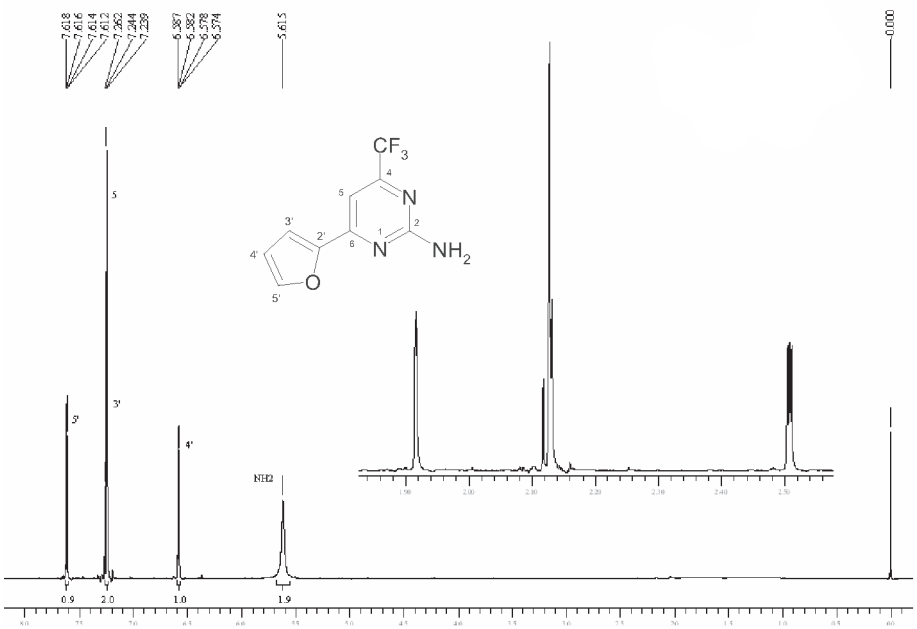

Figure S14. ^{1}H NMR spectrum of the 2-amino-6-(2-furyl)-4-trifluoromethylpyrimidine **5a**, $CDCl_3$.

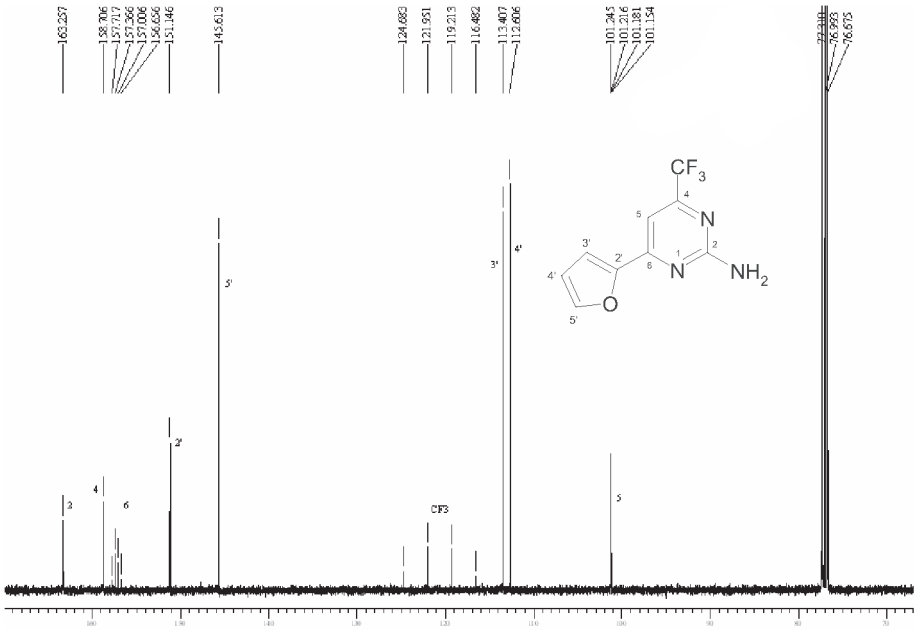

Figure S15. ^{13}C [H] NMR spectrum of the 2-amino-6-(2-furyl)-4-trifluoromethylpyrimidine **5a**, $CDCl_3$.

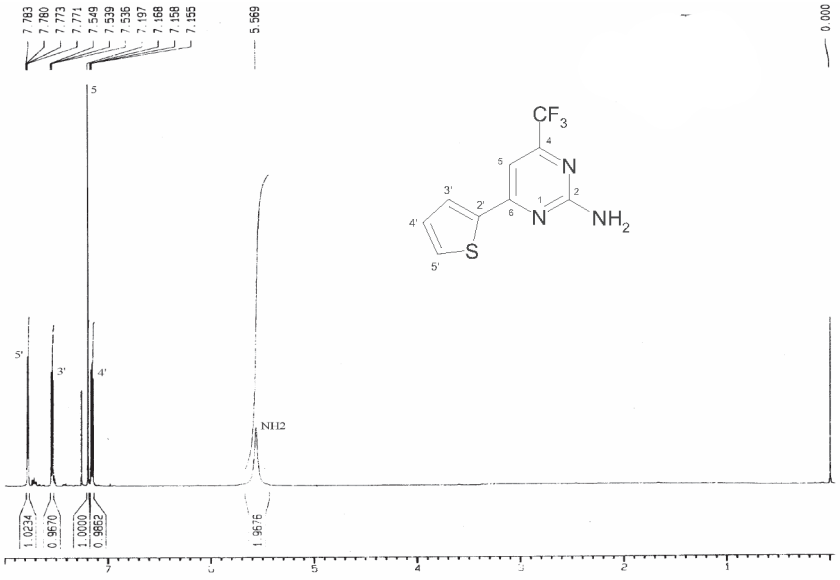

Figure S16. [1]H NMR spectrum of the 2-amino-6-(2-thienyl)-4-trifluoromethylpyrimidine **5b**, $CDCl_3$.

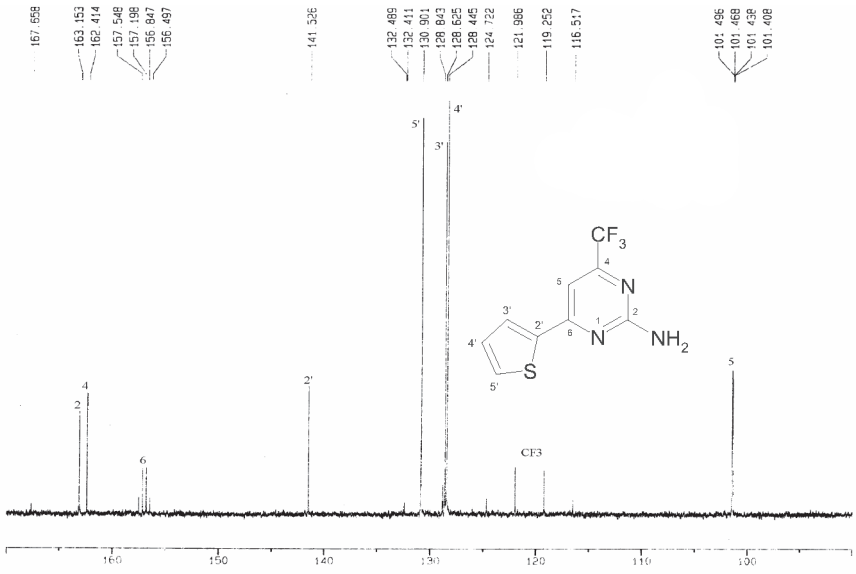

Figure S17. [13]C[H] NMR spectrum of the 2-amino-6-(2-thienyl)-4-trifluoromethylpyrimidine **5b**, $CDCl_3$.

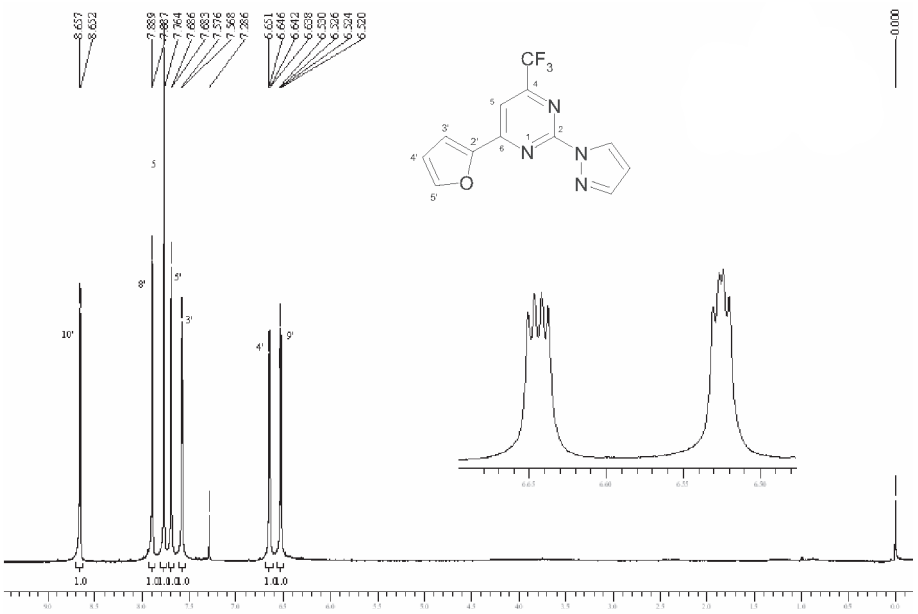

Figure S18. [1]H NMR spectrum of the 6-(2-furyl)-2-(1*H*-pyrazol-1-yl)-4-trifluoromethyl-pyrimidine **6a**, $CDCl_3$.

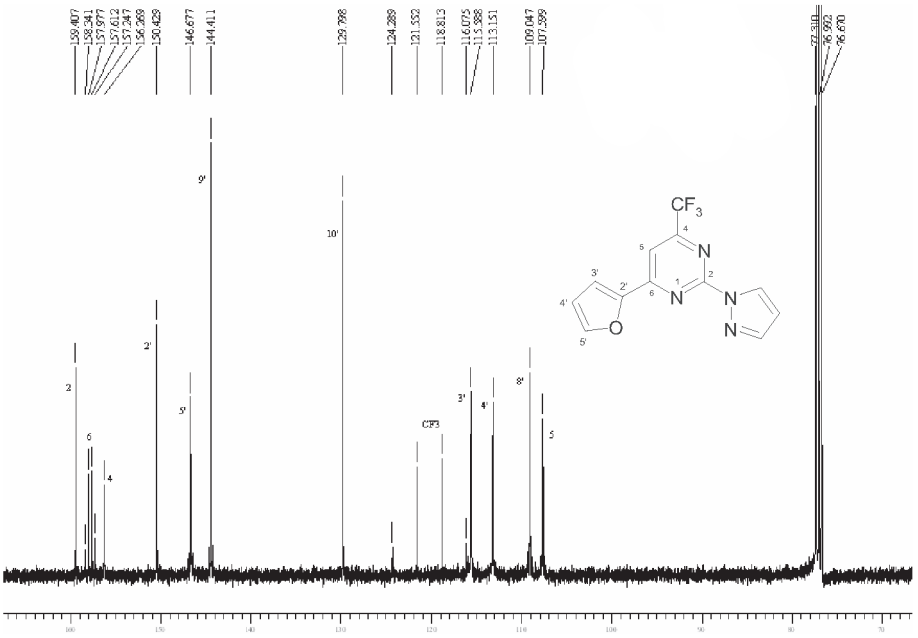

Figure S19. [13]C[H] NMR spectrum of 6-(2-furyl)-2-(1*H*-pyrazol-1-yl)-4-trifluoromethyl-pyrimidine **6a**,$CDCl_3$.

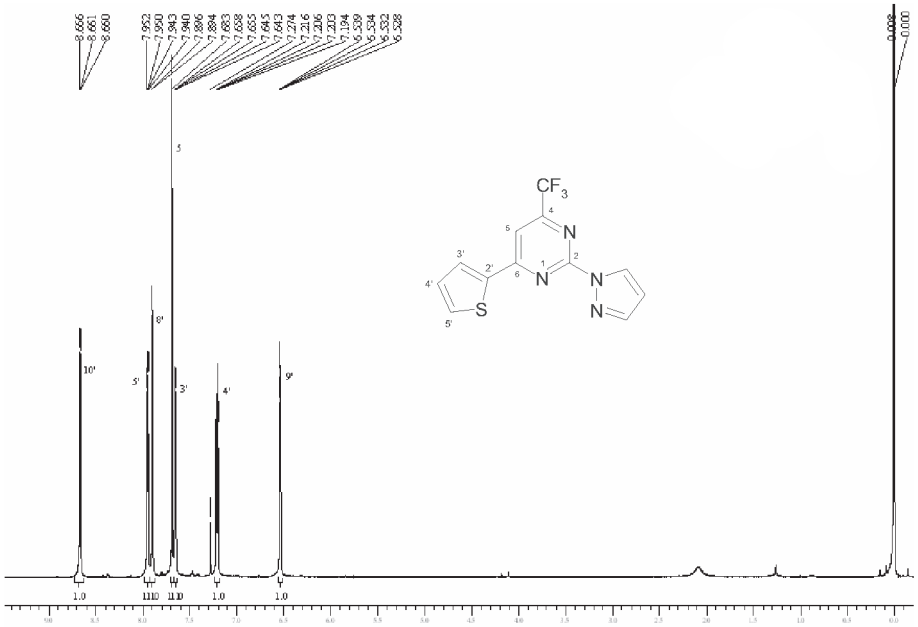

Figure S20. [1]H NMR spectrum of the 2-(1*H*-pyrazol-1-yl)-6-(2-thienyl) 4-trifluoromethylpyrimidine **6b**, $CDCl_3$.

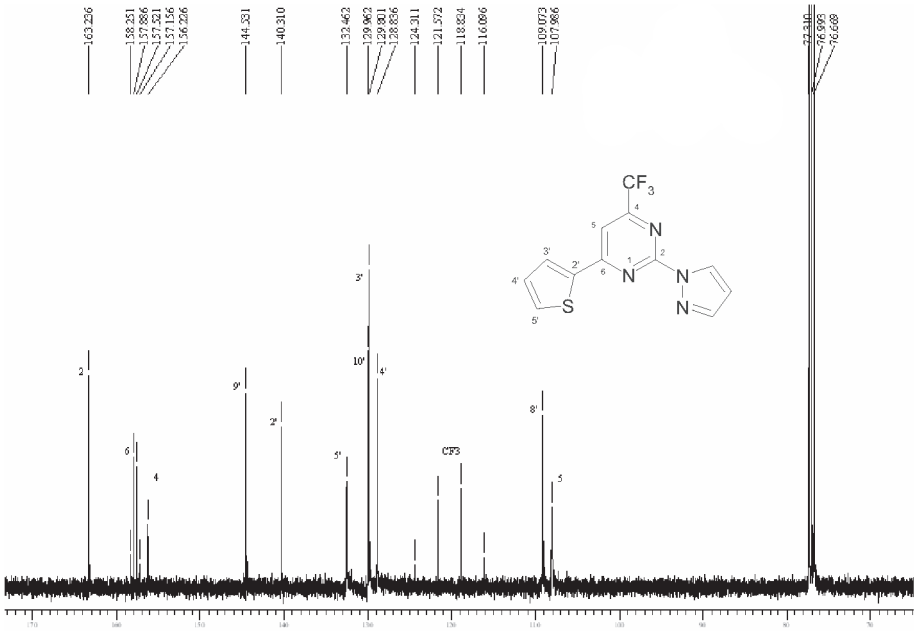

Figure S21. [13]C[H] NMR spectrum of the 2-(1*H*-pyrazol-1-yl)-6-(2-thienyl)-4-trifluoromethylpyrimidine **6b**, $CDCl_3$.

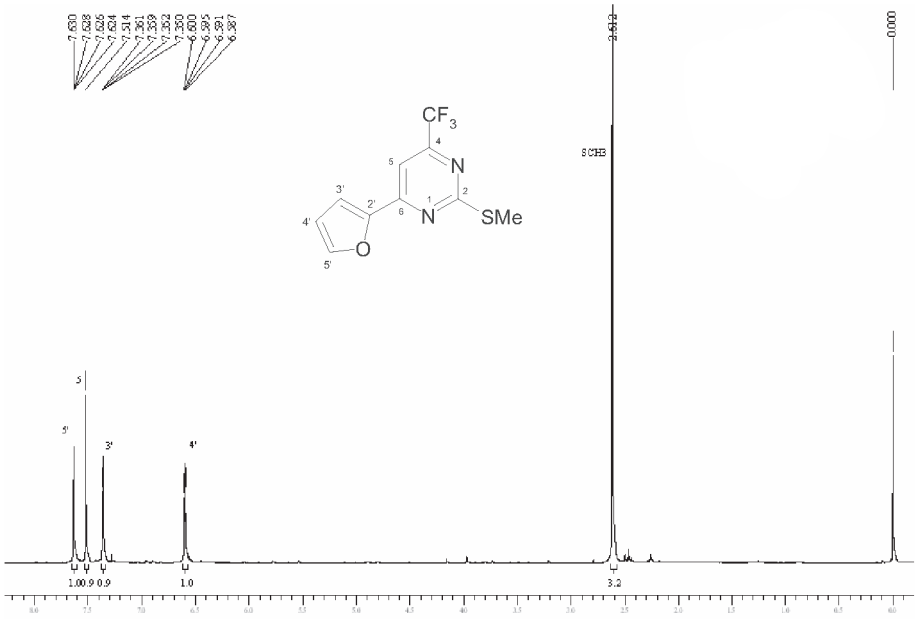

Figure S22. ^{1}H NMR spectrum of the 6-(2-furyl)-2-tiomethyl-4-trifluoromethylpyrimidine **7a**, $CDCl_3$.

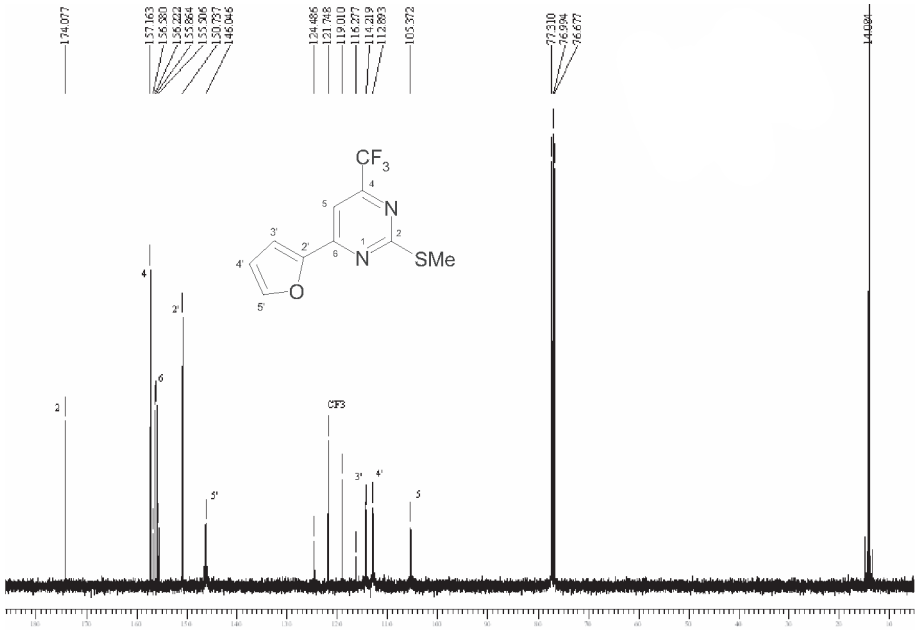

Figure S23. ^{13}C[H] NMR spectrum of the 6-(2-furyl)-2-tiomethyl-4-trifluoromethylpyrimidine **7a**, $CDCl_3$.

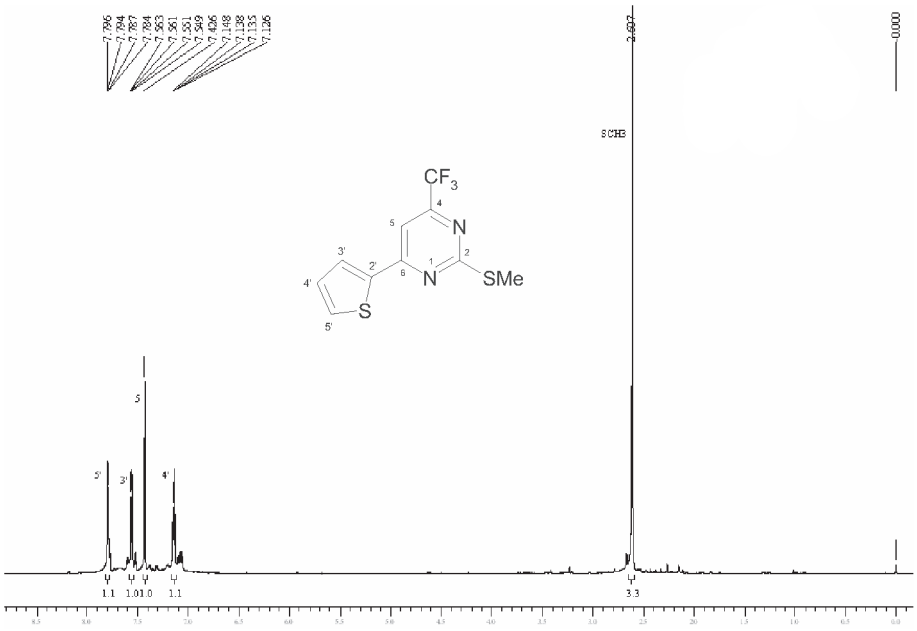

Figure S24. [1]H NMR spectrum of the 6-(2-thienyl)-2-tiomethyl-4-trifluoromethylpyrimidine **7b**, $CDCl_3$.

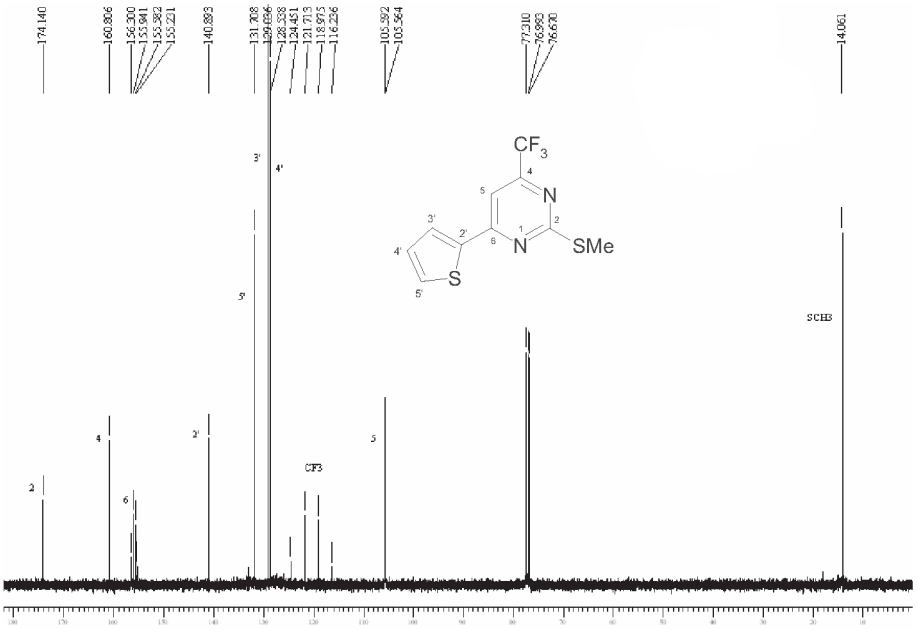

Figure S25. [13]C[H] NMR spectrum of the 6-(2-thienyl)-2-tiomethyl-4-trifluoromethylpyrimidine **7b**, $CDCl_3$.

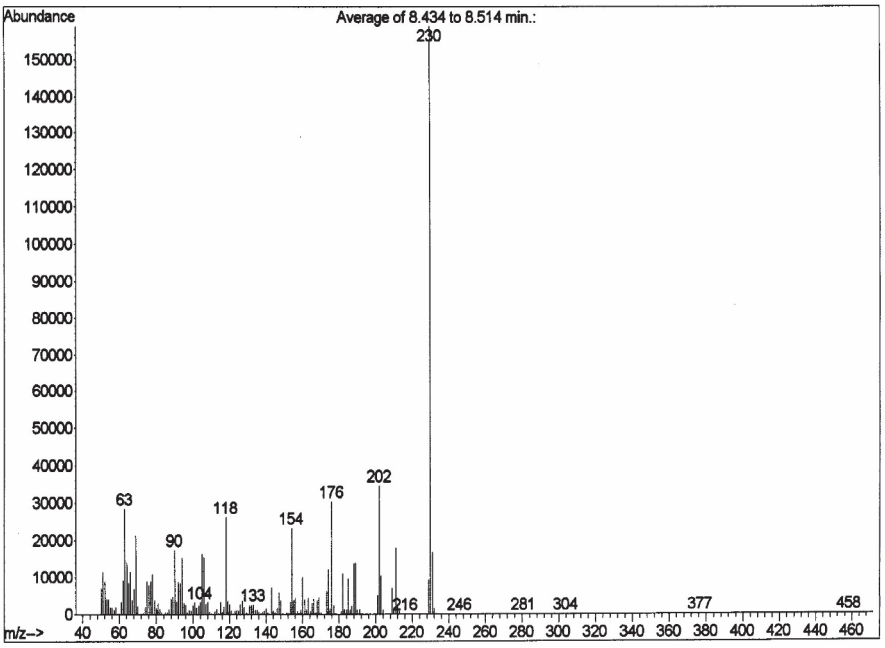

Figure S26. MS of 6-(2-furyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one (**2a**).

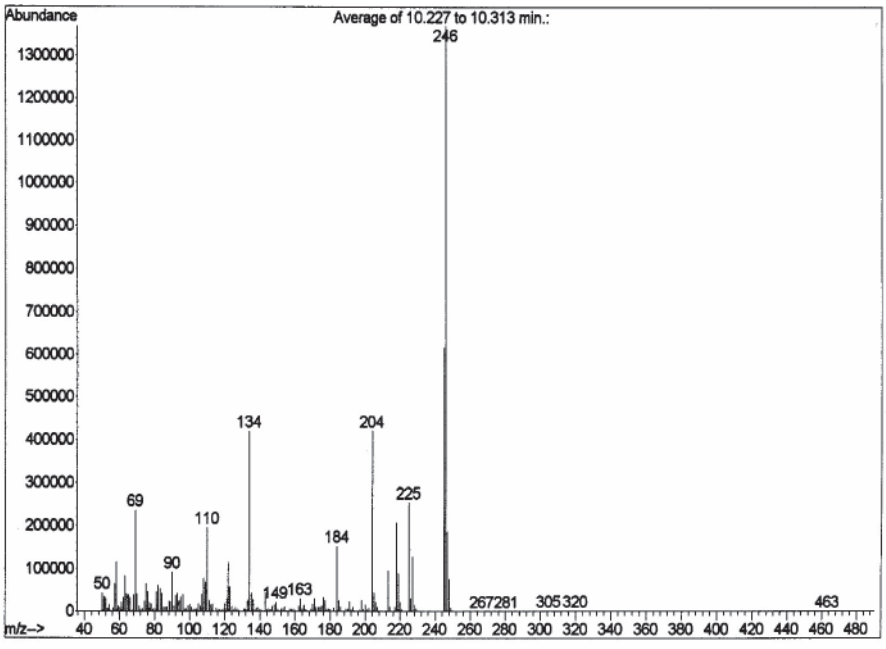

Figure S27. MS of 6-(2-thienyl)-4-trifluoromethyl-1*H*-pyrimidin-2-one (**2b**).

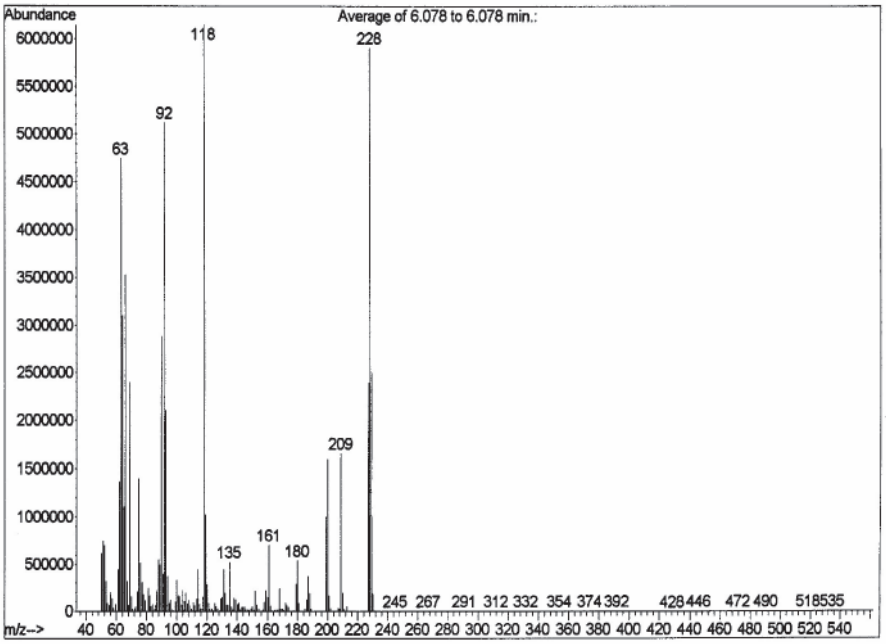

Figure S28. MS of 6-(2-furyl)-2-methyl-4-trifluoromethylpyrimidine (**3a**).

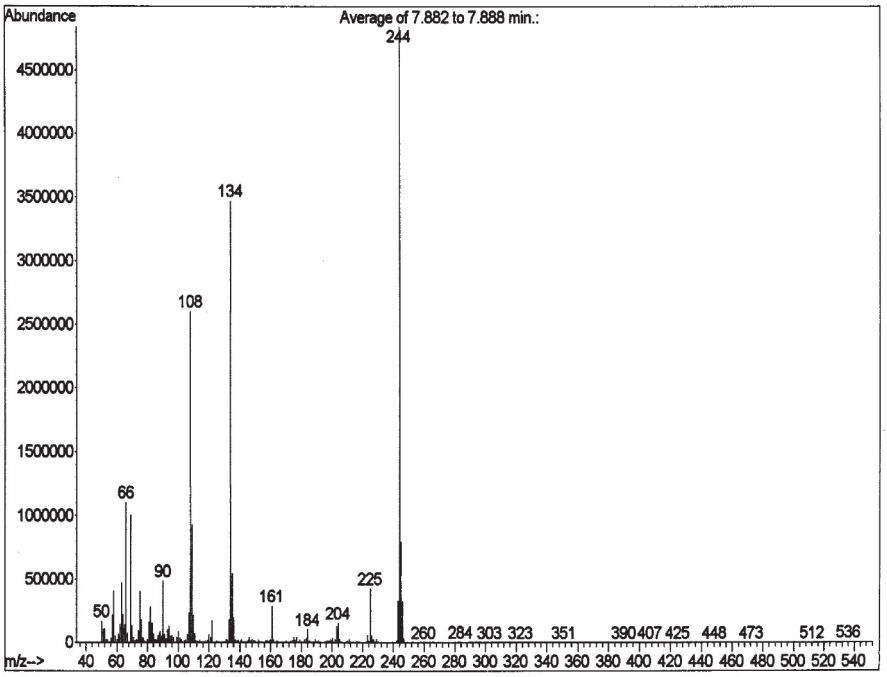

Figure S29. MS of 2-methyl-6-(2-thienyl)-4-trifluoromethylpyrimidine (**3b**).

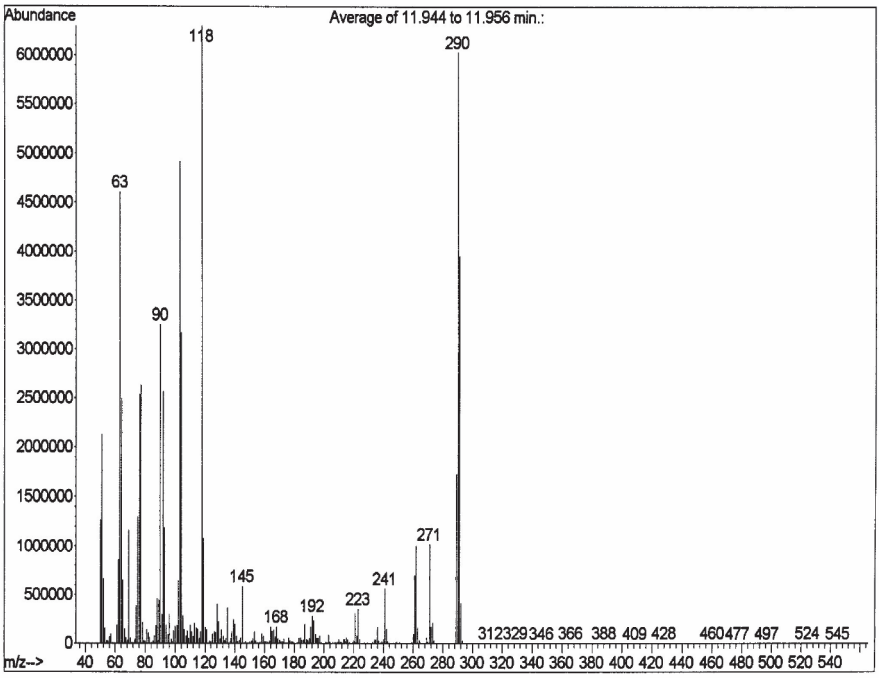

Figure S30. MS of 6-(2-furyl)- 2-phenyl-4-trifluoromethyl-pyrimidine (**4a**).

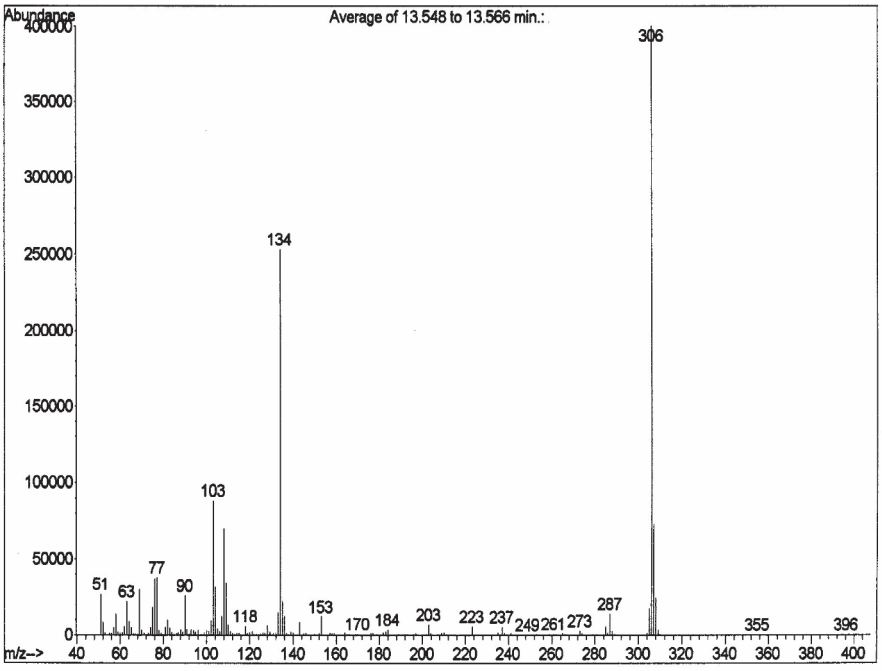

Figure S31. MS of 2-phenyl-6-(2-thienyl)-4-trifluoromethylpyrimidine (**4b**).