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Key Intermediates: A Simple and Highly Selective Synthesis of 5-*Amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* for Applications in the Crop Protection

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Abstract

A series of six pyrazoles was synthesized by Michael-type addition reaction. The molecules 5-*amino*-1-*aryl*-1H-*pyrazole*-4-*carbonitrile* (3a-f) were synthesized from (ethoxymethylene)malononitrile (1) and fluorinated and non-fluorinated aryl hydrazines (2a-f) using ethanol and fluorinated ethanol as solvents at reflux. An excellent regio-selectivity was found when pyrazole derivatives were formed as an exclusive product. No other regioisomer or uncyclised hydrazide was observed. Their structures were confirmed by spectroscopy data (^{1}H, ^{13}C, ^{19}F, COSY (correlation spectroscopy), HSQC (heteronuclear single-quantum correlation spectroscopy) and HMBC (heteronuclear multiple-bond correlation spectroscopy); MS (mass-spectrometry). The yields ranged from good to excellent (47% - 93%) under mild reaction conditions. It would indicate a high selectivity in the one-step work procedure. These products (3a-f) and derivatives have a potential academic and industrial use as key intermediates, in special, for application in crop protection.

Keywords

Aryl Pyrazole, Aryl Hydrazine, Amino Pyrazole, 5-Amino-1-aryl-1*H*-pyrazole-4-carbonitriles

1. Introduction

Heterocyclic compounds containing nitrogen have played a major role in modern pesticide industry; it has been

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reported that more than 85% of pesticides with high activity and low toxicity contain nitrogen heterocyclic compounds [1]. Pyrazoles are important heterocyclic compounds. They are also useful synthons and building blocks for many heterocyclic products and can act as a binucleophile [2] with a broad spectrum of remarkable biological activities. Many derivatives containing pyrazole nucleus have been commercialized as herbicides, insecticides, and fungicides for plant protection [3].

Several compounds of this type can be directly applied as pest-control agents, in particular as acaricides and nematicides [4]-[6], whereas others can be used for the treatment of bacterial, inflammatory diseases and some cancers [4]. As they have proven to be useful intermediates for the preparation of new biological materials, the synthesis and applications of alkyl and aryl pyrazoles have been widely studied in the past few years [7]-[9].

Pyrazole compounds prepared by chemists and biologists have gained widespread attention as they have become fairly accessible and show diverse properties [10]-[12]. These compounds, whose structure include pyrazole rings, have been used as herbicides to inhibit germination in some weeds and as fungicides agents, because combined with zymoproteins, they can activate the apoptosis proteins and cause the fungi to die [13] [14].

As a pharmacophore, the 1-alkyl or aryl-1H-pyrazole unit has been patented and widely reported in previous studies [6]. It is used for several drugs, such as the herbicides by Pyraflufen-ethyl (Japan, Idametsu), Nipyraclofen (Bayer CropScience), and JV485 (Monsanto Bayer). Some representative examples are used in comercial products, such as Tebufenpyrad, an acaricide [15], and Ethiprole [16] (Bayer CropScience), for lepidopterans insects.

Experiments on aryl pyrazole insecticides began in 1985 [17] [18] and led to the development of Regent® (BASF), a Fipronil-based insecticide widely used [12] [16] [19]. Fipronil is the first phenyl pyrazole insecticide introduced in the market [20]. This aryl pyrazole is highly effective against a significant range of economically important insect pests, and it has become a cornerstone in insect control programs in both non-crop and crop pest control situations in many areas of the world [21]. This and other pyrazole derivatives have reached development status as crop insecticides (**Figure 1**).

In previous papers, our group reported the synthesis of a series of fluorinated pyrazole-5-carboxamide derivatives structurally related to the commercial acaricide Tebufenpyrad (**Figure 1**), in ethanol and fluorinated alcohols as solvents. Specifically, the use of trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) as solvents confirmed the influence of the fluorinated alcohols on the regioselectivity of the reaction [6]. With these precedents, it was decided to explore the reaction between (ethoxymethylene)malononitrile (**1**) and fluorinated and non-fluorinated aryl hydrazines (**2a-f**) to produce a series of 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* to find compounds with high regioselectivity and without the presence of isomers in order to develop new pyrazole derivatives with potential use in crop protection.

2. Experimental Section

2.1. General Methods

All the reagents were commercially available and used as received from the supplier. The solvents were analyt-

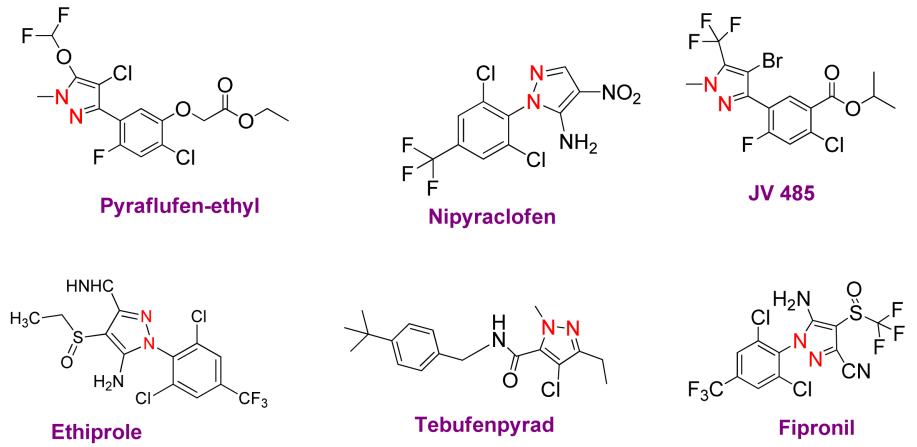


Figure 1. Structure of 1-alkyl and 1-aryl-1*H*-pyrazole derivatives used as agrochemicals.

iccal-grade and were purified according to standard methods. The purity and chemical structure of the synthesized compounds were checked by TLC, CG, UPLC-MS, HRMS (in case **2b** and **2e**), NMR spectra, and melting point.

Analytical TLC was performed on a Merck precoated TLC plate (Silica Gel 60 F_{254}). Gas chromathographic (GC) analyses were performed on a DANI Master GC chromatograph equipped with a 5% diphenyl, 95% dimethylpolysiloxane, low bleed capillary column (30 m × 0.53 mm, 0.5 μm film thickness) and a flame ionization detector. Column Chromatography was performed on silica gel (70 - 230 mesh ASTM). High-purity grade, pore size 60 Å. Isolated and authentic compounds were used as internal standards to perform quantitative GC analyses. Ultra performance liquid chromatography and mass-spectrometry (UPLC-MS) analyses were performed on a H-CLASS SQD2 Detector (Waters). HRMS were obtained on a Bruker micro QTOF-Q11 mass spectrometer equipped with an electrospray ionization (ESI). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz). ^{19}F NMR (300 MHz), COSY (Correlation spectroscopy), HSQC (heteronuclear single-quantum correlation spectroscopy) and HMBC (heteronuclear multiple-bond correlation spectroscopy) experiments were recorded on a Bruker Avance 300 spectrometer in $CDCl_3$ using TMS as internal standard. Coupling constants are given in Hz and chemical shifts are reported in δ values in ppm. Data are reported as follows: chemical shift, multiplicity (s = singlet, s br = broad singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. Melting points (Mp) were recorded on a Büchi b-540 micro melting point apparatus and were uncorrected.

2.2. General Procedure for the Synthesis of 5-*Amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* (3a-f)

To a solution of aryl hydrazine (**2a-f**) [phenylhydrazine **2a**, 4-fluorophenylhydrazine hydrochloride **2b**, (perfluorophenyl)hydrazine **2c**, 4-(trifluoromethyl)phenylhydrazine **2d**, [2,6-dichloro-4-(trifluoromethyl)phenyl] hydrazine **2e**, and 4-methoxyphenylhydrazine hydrochloride **2f**]; *i.e*., (1.2 mmol) in absolute ethanol (or trifluoroethanol) (2 mL) with stirring, (ethoxymethylene)malononitrile **(1)** was added slowly. Once the addition was complete, the solution was carefully brought to reflux keeping nitrogen atmosphere.

The reaction mixture was refluxed for 4 hours except for **3a** (0.5 hours). The reaction crude was purified by column chromatography on silica gel adsorption with a hexane/ethyl acetate gradient mixture as eluants. The above mentioned general procedure gave **3a-f** in 84%, 47%, 63%, 67%, 47%, and 68% yields, respectively. Once purified, the pyrazole was characterized by NMR (^{1}H, ^{13}C, ^{19}F, COSY, HSQC and HMBC).

For aryl hydrazines hydrochlorides **2b, 2f** (1.2 mmol), a previous step of neutralization with Et_3N (1.0 mmol) at 0˚C in ethanol (2 mL) was needed. Then, (ethoxymethylene)malononitrile **(1)** was added as described in the methodology above. In this case, the reaction crude was diluted with ethyl acetate (50 mL) and washed with water (30 mL). The organic phase obtained was dried over Na_2SO_4, filtered, and the organic solvent was evaporated under reduced pressure. The workup and purification of the crude product was identical with that described above.

2.3. The Physical Data of the Synthesized Products Are as Follows

a) 5-*Amino*-1-*phenyl*-1*H*-*pyrazole*-4-*carbonitrile* (3a)

Compound **3a** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (5:1 → 3:1) and was isolated as white crystals (84%); Mp = 138.5˚C - 139.6˚C (140.0˚C - 140.5˚C) [22]; ^{1}H NMR [300 MHz ($CDCl_3$)] δ = 4.81 (s br, 2H, NH_2); 7.40 - 7.55 (m, 5H, CH); 7.57 (s, 1H, CH); ^{13}C NMR [75 MHz]: δ = 75.6 (C); 114.1 (C); 124.1 (CH); 128.8 (CH); 129.8 (CH); 136.9 (C); 141.2 (CH); 150.0 (C).

b) 5-*Amino*-1-(4-*fluorophenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (3b)

Compound **3b** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (6:1 → 4:1) and was isolated as white powder (47 %); Mp = 178.5˚C - 179.8˚C (177.0˚C - 178.0˚C) [23]; ^{1}H NMR [300 MHz ($CDCl_3$)] δ = 4.61 (s br, 2H, NH_2); 7.19 - 7.26 (m, 2H, CH); 7.47 - 7.51 (m, 2H, CH); 7.63 (s, 1H, CH); ^{19}F NMR [300 MHz] δ = −110.96 (s, 1F)^{13}C NMR [75 MHz]: δ = 76.1(C); 113.8 (C); 116.8 - 117.1 (CH, ^{1}J = 23.09 Hz); 126.4 - 126.5 (CH, ^{2}J = 9.50 Hz); 132.9 (C); 141.3 (CH); 149.8 (C); 160.7 and 164,0 (C, ^{2}J = 250.34 Hz).

c) 5-*Amino*-1-(*perfluorophenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (3c)

Compound **3c** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (7:1 → 5:1) and was isolated as a white solid (63 %); Mp = 135.4˚C - 136.4˚C; ^{1}H NMR [300 MHz ($CDCl_3$)] δ = 4.69 (s br, 2H, NH2); 7.73 (s, 1H, CH); ^{19}F NMR [300 MHz] δ = −158.95 (t, 2F); −148.58 (t, 1F); −143.24 (d, 2F).^{13}C NMR [75 MHz]: δ = 76.4(C); 113.1 (C); 143.4 (CH); 152.1 (C). It was not possible to assign the other carbons corresponding to this molecule. ^{1}H-^{1}H COSY NMR (300 MHz, $CDCl_3$) δ_H/δ_H 7.76/7.76, 4.72/4.72. ^{1}H-^{13}C HSQC NMR (300 MHz, $CDCl_3$) δ_H/δ_C 7.75/143.4.^{1}H-^{13}C HMBC NMR δ_H/δ_C 7.76/76.4, 7.76/112.1, 7.76/152.1. HRMS (ESI^-): Anal.Calcd. for $C_{10}H_3F_5N_4^-$: 273.0194; found: 273.0206.

d) 5-*Amino*-1-(4-(*trifluoromethyl*)*phenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (3d)

Compound **3d** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (6:1 → 4:1) and was isolated as yellow solid (67 %); Mp = 156.9˚C - 158.3˚C (170.0˚C - 171.0˚C) [22]; ^{1}H NMR [300 MHz ($CDCl_3$)] δ = 4.73 (s br, 2H, NH_2); 7.67 (d, ^{1}J = 8.91, 3H, CH); 7.78 (d, ^{2}J = 8.36, 2H, CH);. ^{19}F NMR [300 MHz] δ = −62.30 (s, 3F) ^{13}C NMR [75 MHz]: δ = 77.2 (C); 113.6 (C); 121.6 - 125.2(q, ^{1}J = 272.58Hz, CF_3; it was not possible to assign the other half of this quartet); 123.9 (CH); 127.2 (CH); 130.4 - 130.8 (q,^{2}J=32.0Hz); 140.0(C); 141.9 (C); 150.0(C).

e) 5-*Amino*-1-(2,6-*dichloro*-4-(*trifluoromethyl*)*phenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (3e)

Compound **3e** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (6:1 → 3:1) and was isolated as white solid (47%); Mp = 163.5˚C - 164.8˚C; ^{1}H NMR [300 MHz ($CDCl_3$)] δ = 4.70 (s br, 2H, NH_2); 7.72 (s, 1H, CH); 7.77 (s, 2H, CH). ^{19}F NMR [300 MHz] δ = −63.22 (s, 2F).^{13}C NMR [75 MHz]: δ = 75.4 (C); 113.4 (C); (116.5, 120.1, 123.7, 127.3, q, ^{1}J = 273.58Hz -CF_3); 126.2 (CH); (133.8, 134.2, 134.7, 134.9,q, ^{2}J = 34.59Hz-CF_3); 136.7(C); 142.9 (CH); 151.4(C). ^{1}H-^{1}H COSY NMR (300 MHz, $CDCl_3$) δ_H/δ_H 7.77/7.77, 7.72/7.72, 4.69/4.69. ^{1}H-^{13}C HSQC NMR (300 MHz, $CDCl_3$) δ_H/δ_C 7.77/126.2, 7.72/142.9.^{1}H-^{13}C HMBC NMR δ_H/δ_C 7.77/75.4, 7.77/134.7, 7.77/136.7. HRMS (ESI^+): Anal. Calcd. for $C_{11}H_5Cl_2F_3N_4Na^+$: 342.9736.; found: 342.9731.

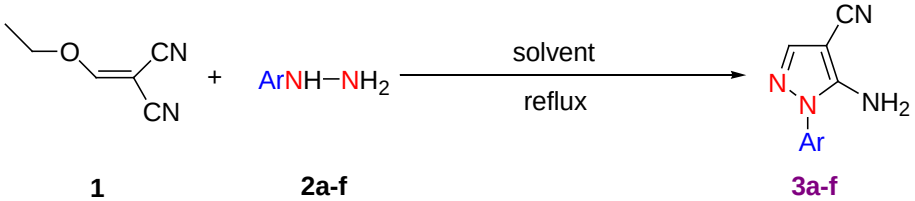
f) 5-*Amino*-1-(4-*methoxyphenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (3f)

Compound **3f** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (6:1 → 3:1) and was isolated as a dark yellow powder (68%); Mp = 148.4˚C - 148.8˚C (144.9˚C - 145.9˚C) [24] [25]; ^{1}H NMR [300 MHz ($CDCl_3$)] δ = 3.86 (s, 3H, CH_3); 4.61(s br, 2H, NH_2); 7.00 - 7.03 (d, ^{1}J = 8.39Hz, 2H, CH); 7.37 - 7.40 (d, ^{2}J = 9.18 Hz, 2H, CH); 7.60 (s, 1H, CH); ^{13}C NMR [75 MHz]: δ = 75.5(C); 114.2(C); 115.0 (CH); 126.1(CH); 129.5(C); 140.9 (CH); 149.9 (C); 159.9 (C).

3. Results and Discussion

3.1. Design and Synthesis of 5-Amino-1-aryl-1H-pyrazole-4-carbonitriles (3a-f)

It is known that (ethoxymethylene)malononitrile can undergo not only 1,3-dipolar cycloadditions but also nucleophilic addition with hydrazines to selectively produce aminopyrazoles or hydrazides [22]-[25]. The additions of fluorinated and non-fluorinated aryl hydrazine (**2a-f**) to (ethoxymethylene)malononitrile (**1**) in solvent at reflux resulted in the cyclized product 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* (**3a-f**) as an exclusive product. Supplementary, the 3-amino regioisomer or uncyclised hydrazide was not observed. Different substituted aryl hydrazines were utilized in this work to obtain the cyclized pyrazoles in a one-step reaction with high regioselectivity. The synthetic route is shown in **Scheme 1**.



Scheme 1. Synthesis of 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* (3a-f).**3a** Ar = C_6H_5; **3b** Ar = 4-F-C_6H_4; **3c** Ar = C_6F_5; **3d** Ar = 4-CF_3-C_6H_5; **3e** Ar = 2,6-Cl_2-4-CF_3-C_6H_2; **3f** Ar = 4-CH_3O-C_6H_4.

3.2. Selection of the Solvent

Initially, it was showen the effectiveness of TFE as a solvent in the preparation of 5-*amino*-1-*phenyl*-1*H*-*pyrazole*-4-*carbonitrile* **3a**. (Ethoxymethylene)malononitrile **1** was treated with phenylhydrazine **2a** at reflux in various solvents (TFE, EtOH, MeOH and THF) (**Table 1**, entries 1-4). As it is clear from this table, the highest yields of the desired pyrazole were obtained with TFE and ethanol as solvents (**Table 1**, entries 1 and 2). The reaction in an aprotic solvent, such as THF (**Table 1**, entry 3), occured quite slowly after 30 min and a low yield of the product was obtained. When methanol was used as a protic solvent (**Table 1**, entry 4) the yield of the product increased but the reaction did not improve as significantly as when EtOH or TFE were used.

In order to show the generalities of this reaction, different substituted pyrazoles were synthesized using a variety of aryl hydrazines in TFE as a solvent, chosen for its great yield in the first assays (**Table 2**). The substituted aryl hydrazines reacted smoothly under the same reaction conditions to give of moderate to low yield of the desired pyrazoles (**Table 2**, entries 2 - 5). The highest yield was achieved for **3a** in TFE after 30 min (**Table 2**, entry 1), butit was not possible to reproduce this performance for the other aryl hydrazines employed.

The low to moderate yields obtained from TFE in the synthesis of different aryl pyrazoles were compared with the results obtained from the synthesis carried out under the same reaction conditions with EtOH as a solvent (**Table 3**). It was then decided to continue the synthesis with EtOH as a solvent, as it showed yields ranging from good to excellent. Besides, EtOH is cheaper than TFE, is commercially available, and it is also eco-friendly because it is obtained from a renewable source.

3.3. Synthesis of Aryl Pyrazoles

The synthesis of the compounds **3a-f** was accomplished in a one-step reaction. Yields ranged from good to excellent (46% - 93%), though no attempt was made to optimize the conditions for each reaction.

A detailed study of different aryl hidrazines was performed toward the formation of aryl pyrazole derivatives (**Table 3**, entries 1-6). To study the influence of stereo and electronic effects between the hydrazines **2a-f** and the substrate **1** toward the formation of **3a-f**, fluorinated and non-fluorinated phenyl groups were chosen as Ar substituents. At the same time, the fully unsubstituted hydrazine ring, phenylhydrazine **2a**, was also considered as the model substrate to identify the method of choice for the synthesis of aryl pyrazoles.

It was found that the yield is high (93%) when there are no substituents in the hydrazine ring **3a**, (**Table 3**, entry 1). The yield is low when there are some substituents in hydrazines which contain electron-withdrawing groups such as 4-fluorophenyl (**2b**), pentafluorophenyl (**2c**), 4-trifluoromethylphenyl (**2d**), 2,6-dichloro-4-trifluoromethylphenyl (**2e**) or electron-donating groups such as 4-methoxyphenyl (**2f**) (**Table 3**, entries 2-6).

Table 1. Effects of different solvents on the synthesis of 5-*amino*-1-*phenyl*-*1H*-*pyrazole*-4-*carbonitrile* 3a.

Entry	Solvents[a]	Time (h)	Product	Yields[b] (%)
1	TFE	0.5	**3a**	(100)[c]
2	EtOH	0.5	**3a**	84 (93)[c]
3	THF	0.5	**3a**	(33)[c]
4	MeOH	0.5	**3a**	(60)[c]

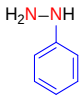
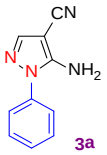
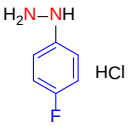
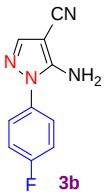
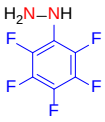
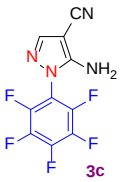
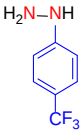
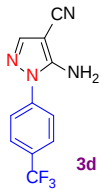
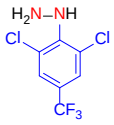
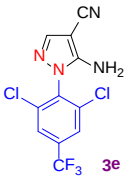
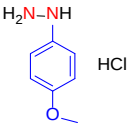
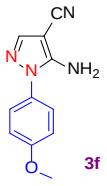
a. TFE: Trifluoroethanol; EtOH: Ethanol; THF: Tetrahydrofuran; MeOH: Methanol.b. Isolated yields.c. Quantified by GC (internal standard method).

Table 2. Synthesis of 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* (3a-f) in TFE.

Entry	Time (h)	Products	Yields[a] (%)
1	0.5	**3a**	(100)[b]
2	4	**3b**	29 (30)[b]
3	4	**3c**	(20)[b]
4	4	**3d**	28 (30)[b]
5	4	**3f**	46 (43)[b]

a. Isolated yields.b. Quantified by GC (internal standard method).

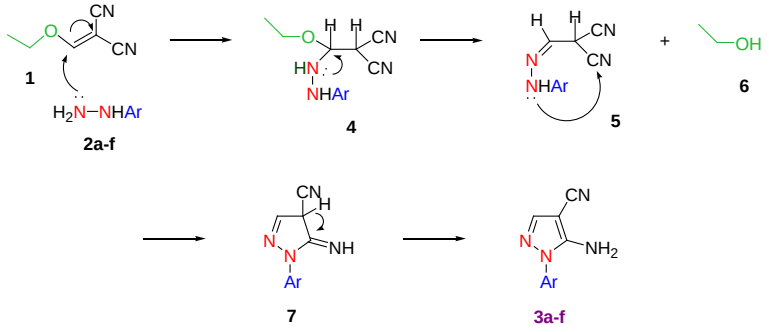
Table 3. Synthesis of 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitrile* (3a-f) in ethanol as a solvent.

Entry	Ar	Products[a]	Time (h)	Yields[b] (%)		
				Found	Reported	Ref.
1	 **2a**	 **3a**	0.5	84 (93)[c]	69	[22]
2	 **2b**	 **3b**	4	(66)[c]	97	[23]
3	 **2c**	 **3c**	4	63 (65)[c]		[26]
4	 **2d**	 **3d**	4	67 (80)[c]	71	[22]
5	 **2e**	 **3e**	4	47 (46)[c]		[17]
6	 **2f**	 **3f**	4	68	69	[25]

a. All the products were characterized by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, COSY, HSQC, HMBC and MS spectral data. b. Isolated yields. c. Quantified by GC (internal standard method).

3.4. Mechanism of the Reaction and Selectivity in the Addition

After reviewing the literature, a plausible mechanism for the formation of the 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* (**3a-f**) may be explained by the initial Michael type addition [22]. First, the most nucleophilic amino group is added selectively to the *β*-carbon of **1,** resulting in the intermediate hydrazide **4**. The latter, by elimination, and rearranges to give alkylidene hydrazide **5** and ethanol **6** as a leaving group. The intermediate **5** undergoes intramolecular cycloaddition by the nucleophilic attack of the second amine on the nitrile carbon and gives the pyrazole imine **7**. This, consequent upon aromatization leads to the 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* (**3a-f)**, as depicted in **Scheme 2**.



Scheme 2. A plausible mechanism for the formation of 3a-f.

4. Conclusion

This study has clearly demonstrated that 5-*amino*-1-*aryl*-1*H*-*pyrazole*-4-*carbonitriles* can be synthesized and used as predecessors—key intermediates—of a wide variety of heterocycles for academic interest and agrochemical applications. We have shown that it is possible to synthesize a series of six pyrazoles by a one-step reaction involving the refluxing of the reactants in ethanol as the most suitable solvent. A plausible mechanism was proposed to explain the regioselectivity observed for the reaction. In general, the yields of pyrazoles obtained under the experimental conditions with aromatic hydrazines and (ethoxymethylene)malononitrile ranged from good to excellent, with a simple and efficient methodology. The aryl pyrazoles **3a-f** were obtained and characterized by NMR and MS spectroscopy. It is worth mentioning that the functional groups (*i.e.* cyano, amine and fluor) in the pyrazole moiety could have interesting applications in the crop protection. Currently, we are working with these key intermediaries to the development of new agrochemicals.

Acknowledgements

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Supplementary Information

Experimental Section

1) General

All the reagents were commercially available and used as received from the supplier. The solvents were analytical-grade and were purified according to standard methods. The purity and chemical structure of the synthesized compounds were checked by TLC, CG, UPLC-MS, HRMS (in case **2b** and **2e**), NMR spectra, and melting point.

Analytical TLC was performed on a Merck precoated TLC plate (Silica Gel 60 F254). Gas chromathographic (GC) analyses were performed on a DANI Master GC chromatograph equipped with a 5% diphenyl, 95% dimethylpolysiloxane, low bleed capillary column (30 m × 0.53 mm, 0.5 µm film thickness) and a flame ionization detector. Column Chromatography was performed on silica gel (70 - 230 mesh ASTM). High-purity grade, pore size 60 Å. Isolated and authentic compounds were used as internal standards to perform quantitative GC analyses. Ultra performance liquid chromatography and mass-spectrometry (UPLC-MS) analyses were performed on a H-CLASS SQD2 Detector (Waters). HRMS were obtained on a Bruker micro QTOF-Q11 mass spectrometer equipped with an electrospray ionization (ESI). ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz). ^{19}F NMR (300 MHz), COSY, HSQC and HMBC experiments were recorded on a Bruker Avance 300 spectrometer in CDCl3 using TMS as internal standard. Coupling constants are given in Hz and chemical shifts are reported in δ values in ppm. Data are reported as follows: chemical shift, multiplicity (s = singlet, s br = broad singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. Melting points were recorded on a Büchi b-540 micro melting point apparatus and were uncorrected.

2) General Procedure for the Synthesis of 5-amino-1-aryl-1H-pyrazole-4-carbonitriles (3af)

To a solution of aryl hydrazine (**2a-f**) [phenylhydrazine **2a**, 4-fluorophenylhydrazine hydrochloride **2b**, (perfluorophenyl)hydrazine **2c**, 4-(trifluoromethyl)phenylhydrazine **2d**, [2,6-dichloro-4-(trifluoromethyl) phenyl] hydrazine **2e**, and 4-methoxyphenylhydrazine hydrochloride **2f**]; *i.e.*, (1.2 mmol) in absolute ethanol (or trifleoroethanol) (2 ml) with stirring, (ethoxymethylene)malononitrile **(1)** was added slowly. Once the addition was complete, the solution was carefully brought to reflux keeping nitrogen atmosphere.

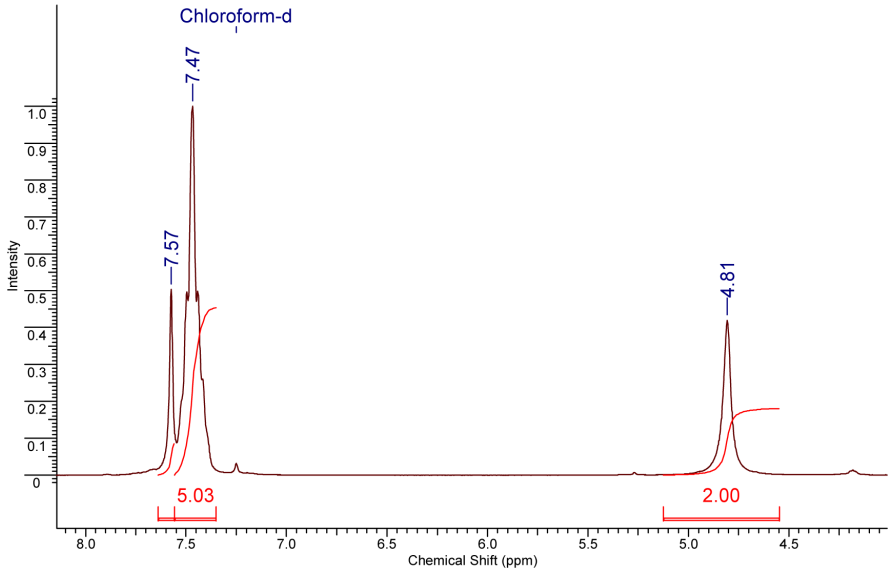
The reaction mixture was refluxed for 4 hours except for **3a** (0.5 hours). The reaction crude was purified by column chromatography on silica gel adsorption with a hexane/ethyl acetate gradient mixture as eluants. The above mentioned general procedure gave **3a-f** in 84%, 47%, 63%, 67%, 47%, and 68% yields, respectively. Once purified, the pyrazole was characterized by NMR (^{1}H, ^{13}C, ^{19}F, COSY, HSQC and HMBC).

For aryl hydrazines hydrochlorides **2b, 2f** (1.2 mmol), a previous step of neutralization with Et3N (1.0 mmol) at 0˚C in ethanol (2 ml) was needed. Then, (ethoxymethylene)malononitrile **(1)** was added as described in the methodology above. In this case, the reaction crude was diluted with ethyl acetate (50 ml) and washed with water (30 ml). The organic phase obtained was dried over Na_2SO_4, filtered, and the organic solvent was evaporated under reduced pressure. The workup and purification of the crude product was identical with that described above.

3) Characterization of Products

5-*amino*-1-*phenyl*-1*H*-*pyrazole*-4-*carbonitrile* (**3a**): Compound **3a** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (5:1 → 3:1) and was isolated as white crystals. (84%); M.p. 138.5˚C - 139.6˚C (140.0˚C - 140.5˚C) [24]; ^{1}H NMR [300 MHz (CDCl3)] δ = 4.81 (s br, 2H, NH2); 7.40 - 7.55 (m, 5H, CH); 7.57 (s, 1H, CH); ^{13}C NMR [75 MHz]: δ = 75.6 (C); 114.1 (C); 124.1 (CH); 128.8 (CH); 129.8 (CH); 136.9 (C); 141.2 (CH); 150.0 (C)). MS m/z (%): Calc. 184.07; found: 185.0 [M^{+} + 1].

^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC and MS Spectra: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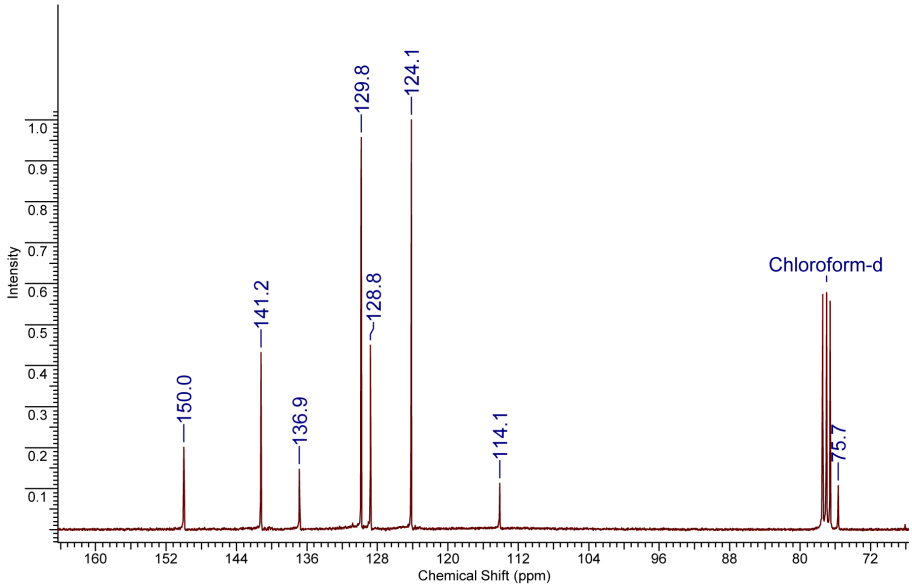
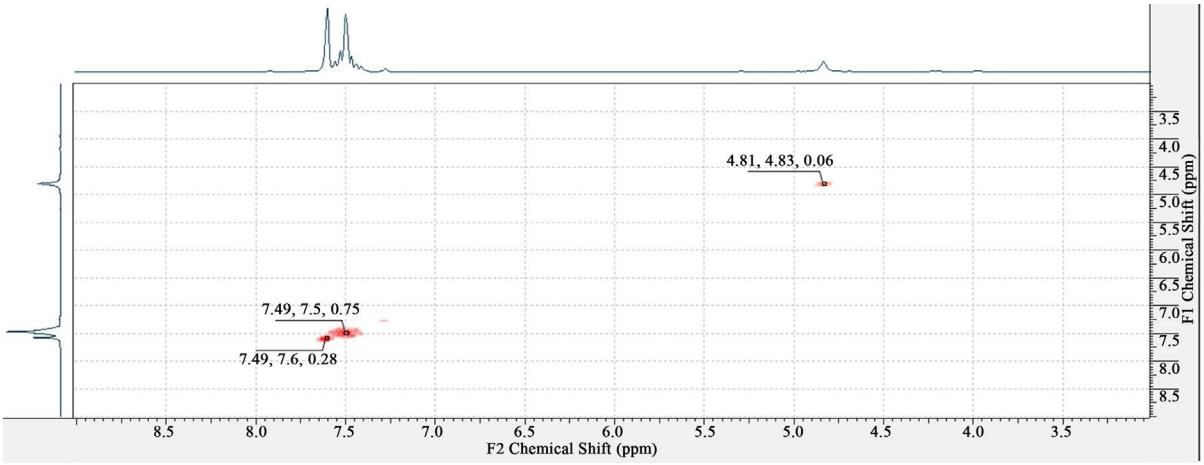
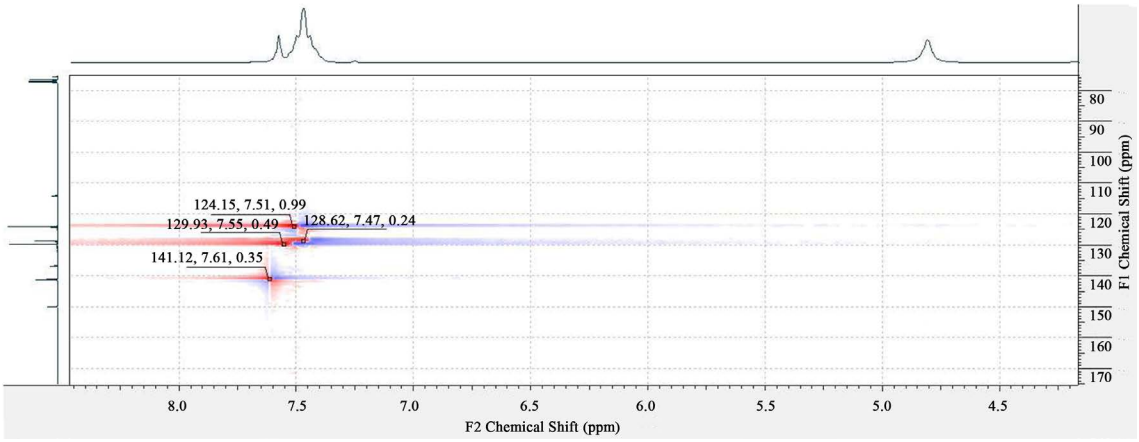
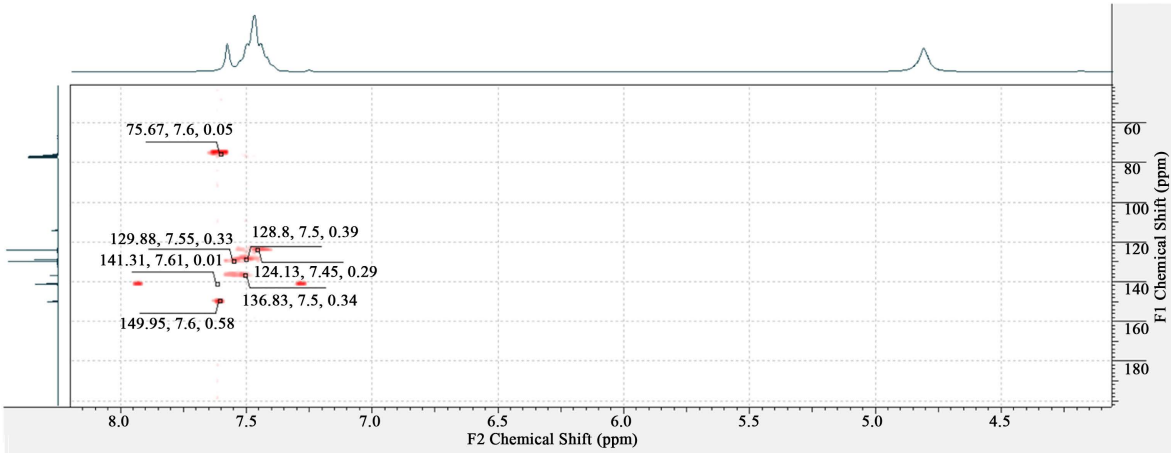
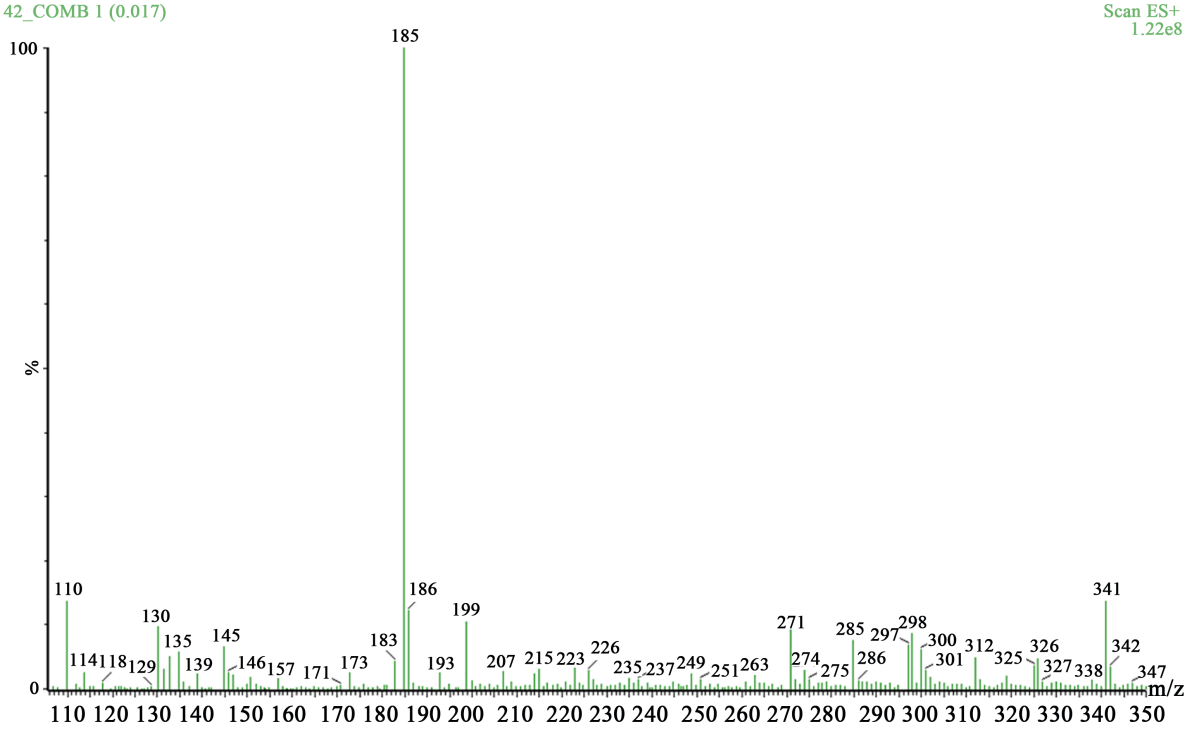
7.47
7.57
4.81
5.03
2.00
Intensity
Chemical Shift (ppm)


129.8
124.1
141.2
128.8
Chloroform-d
150.0
136.9
114.1
75.7
Intensity
Chemical Shift (ppm)


4.81, 4.83, 0.06
7.49, 7.5, 0.75
7.49, 7.6, 0.28
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

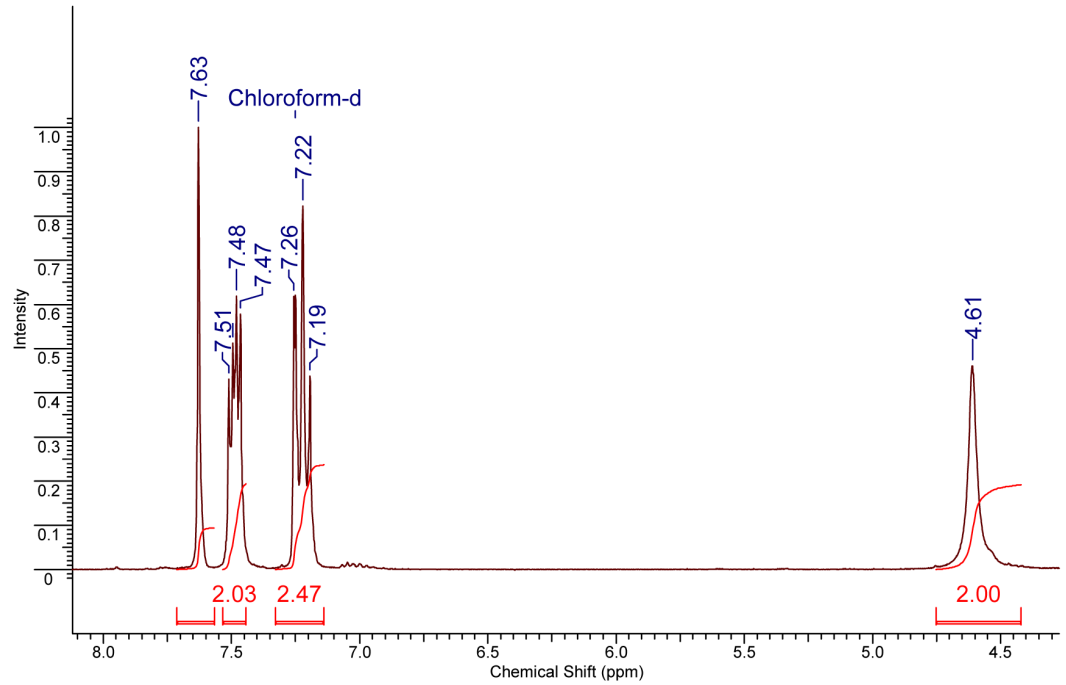

124.15, 7.51, 0.99
129.93, 7.55, 0.49
128.62, 7.47, 0.24
141.12, 7.61, 0.35
F1 Chemical Shift (ppm)
F2 Chemical Shift (ppm)

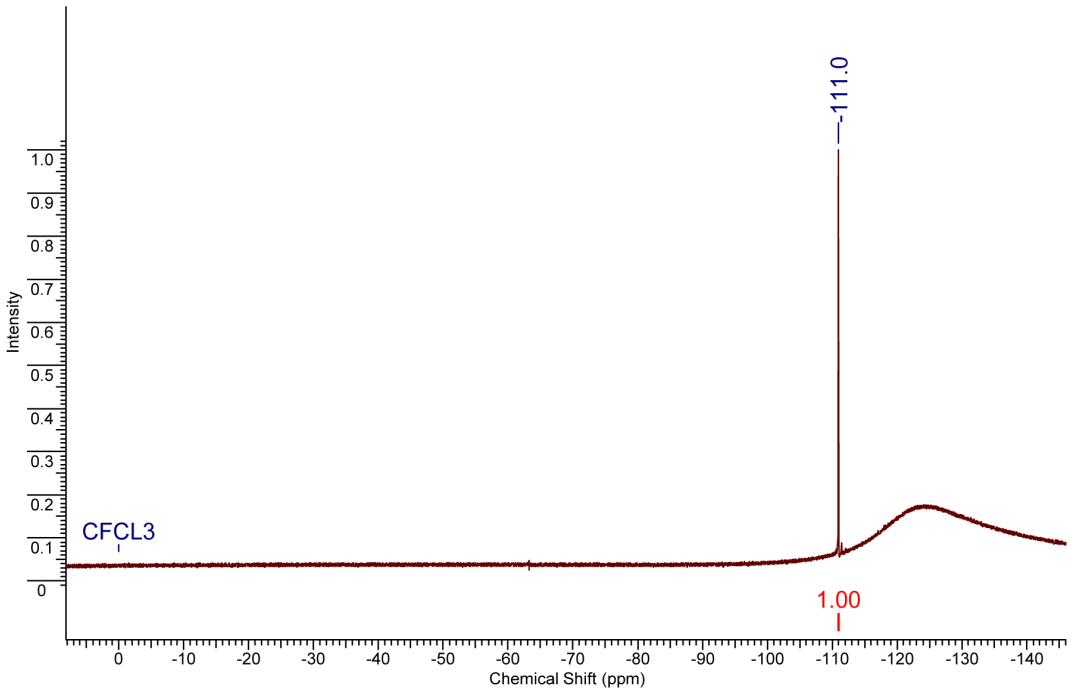

75.67, 7.6, 0.05
129.88, 7.55, 0.33
128.8, 7.5, 0.39
141.31, 7.61, 0.01
124.13, 7.45, 0.29
136.83, 7.5, 0.34
149.95, 7.6, 0.58
F1 Chemical Shift (ppm)
F2 Chemical Shift (ppm)

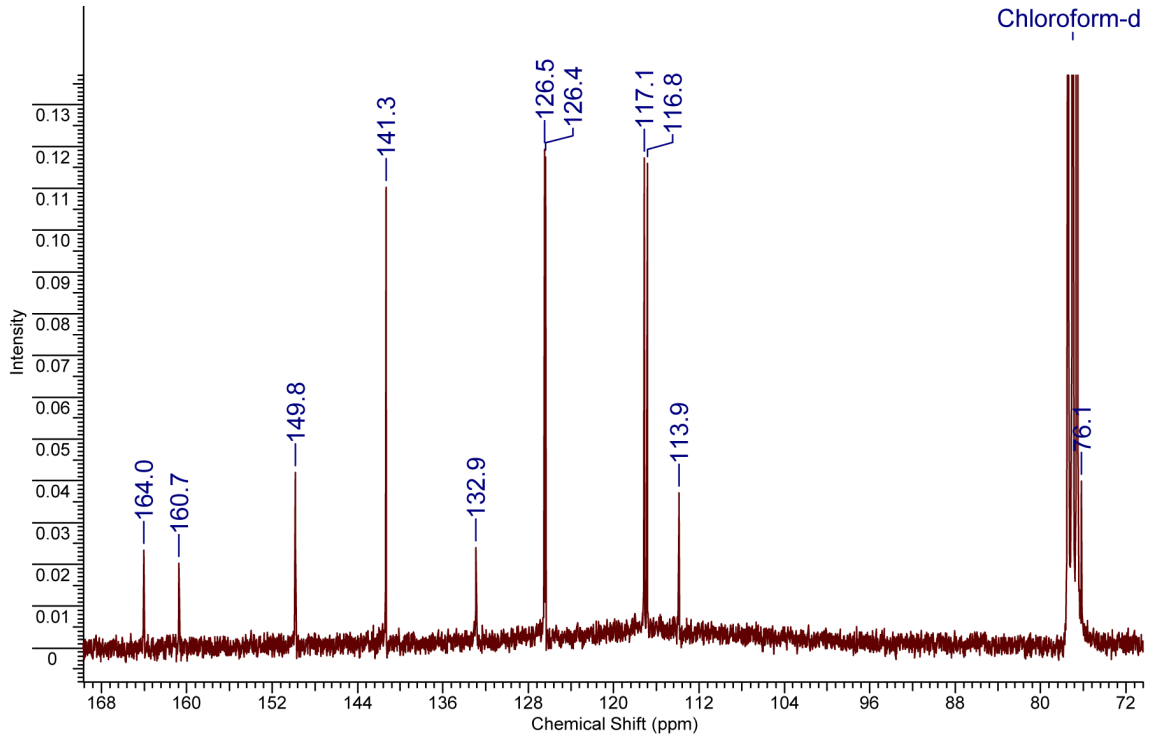

42_COMB 1 (0.017)
Scan ES+
1.22e8
%
m/z

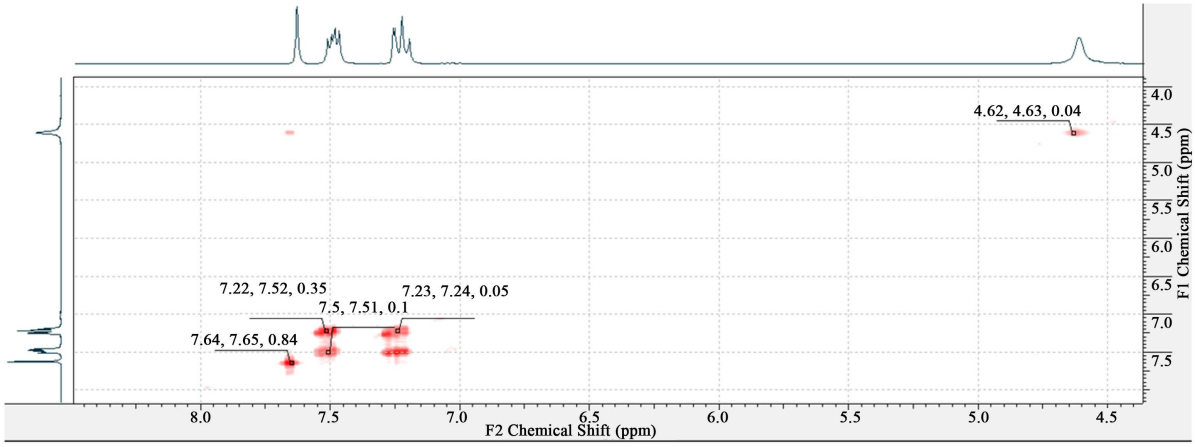
5-*amino*-1-(4-*fluorophenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (**3b**): Compound **3b** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane /ethyl acetate gradient (6:1 → 4:1) and was isolated as white powder. (47%); M.p. 178.5˚C - 179.8˚C (177.0˚C - 178.0˚C) [24]; ^{1}H RMN [300 MHz (CDCl3)] δ = 4.61 (s br, 2H, NH2); 7.19 - 7.26 (m, 2H, CH); 7.47 - 7.51 (m, 2H, CH); 7.63 (s, 1H, CH); ^{19}F RMN [300 MHz] δ = −110.96 (s, 1F) ^{13}C NMR [75 MHz]: δ = 76.1(C); 113.8 (C); 116.8 - 117.1 (CH, ^{1}J = 23.09 Hz); 126.4 - 126.5 (CH, ^{2}J = 9.50 Hz); 132.9 (C); 141.3 (CH); 149.8 (C); 160.7 and 164,0 (C, ^{2}J = 250.34 Hz). MS m/z (%): Calc. 202.6; found: 203. 0 [M^{+} + 1].

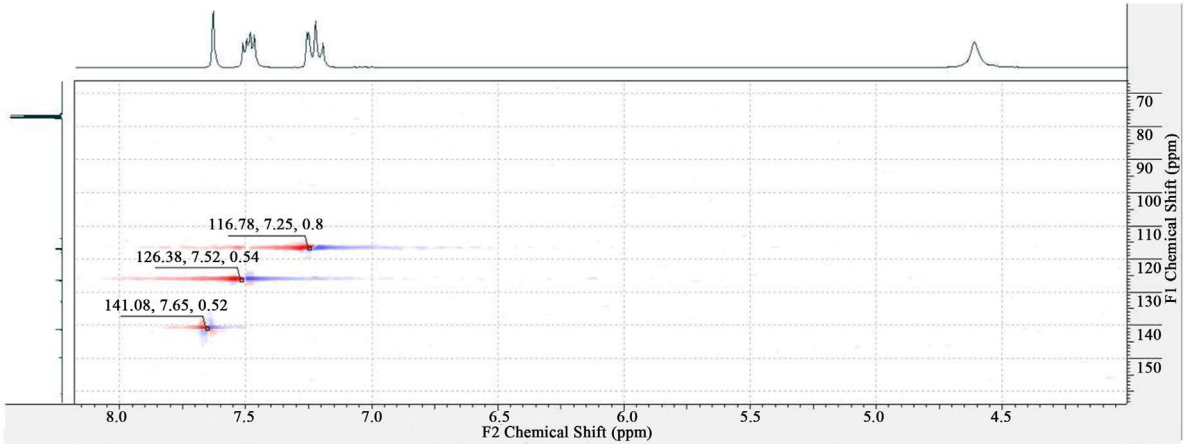
^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC and MS Spectra:






Chloroform-d
Intensity
164.0
160.7
149.8
141.3
132.9
126.5
126.4
117.1
116.8
113.9
76.1
Chemical Shift (ppm)


4.62, 4.63, 0.04
7.22, 7.52, 0.35
7.23, 7.24, 0.05
7.5, 7.51, 0.1
7.64, 7.65, 0.84
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)


116.78, 7.25, 0.8
126.38, 7.52, 0.54
141.08, 7.65, 0.52
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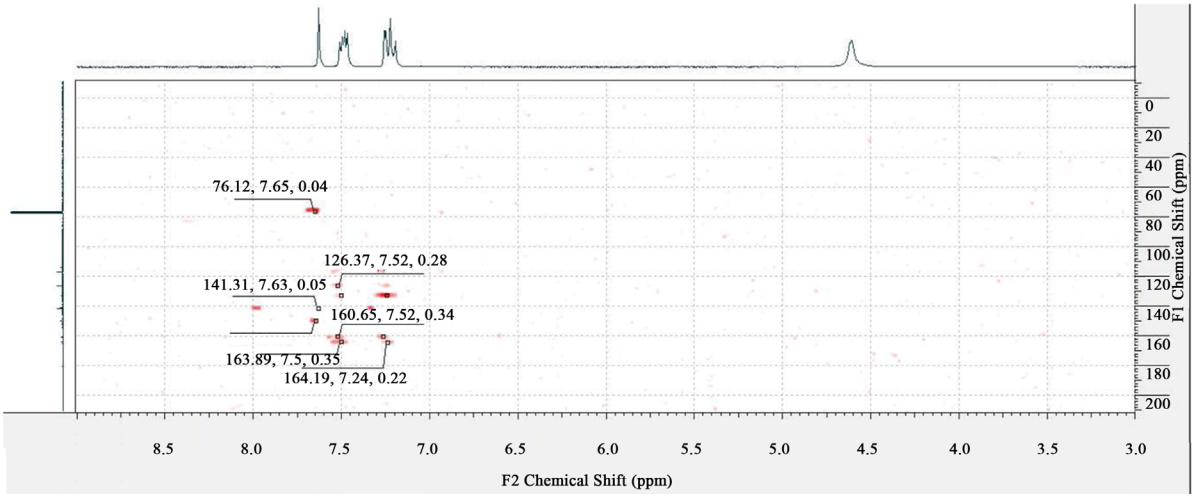
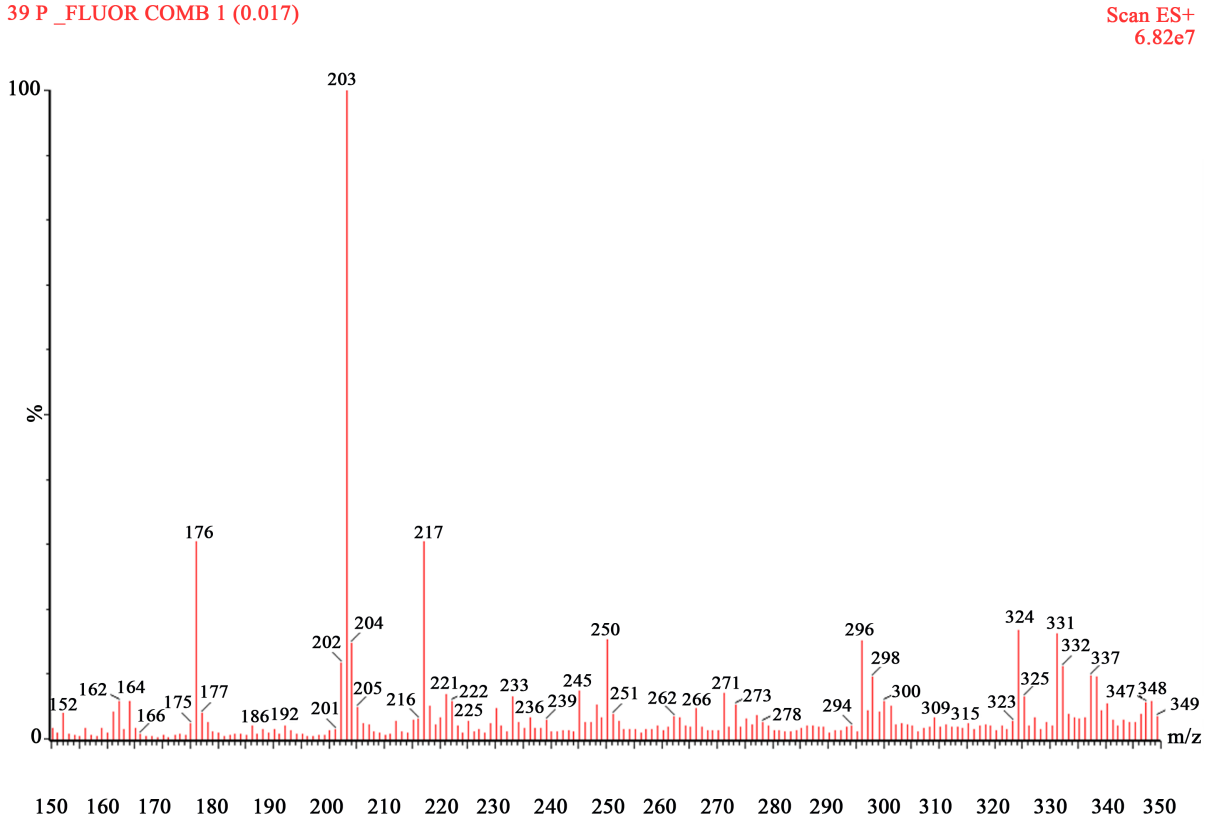
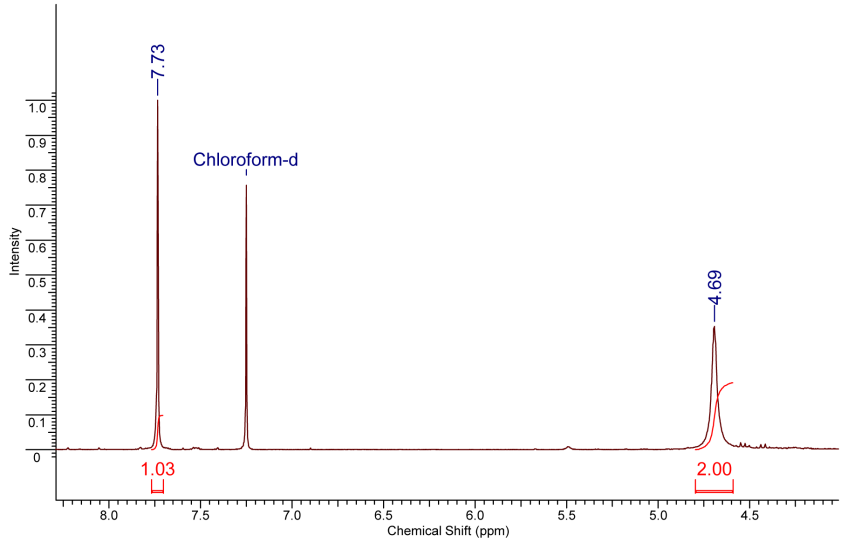
F1 Chemical Shift (ppm)

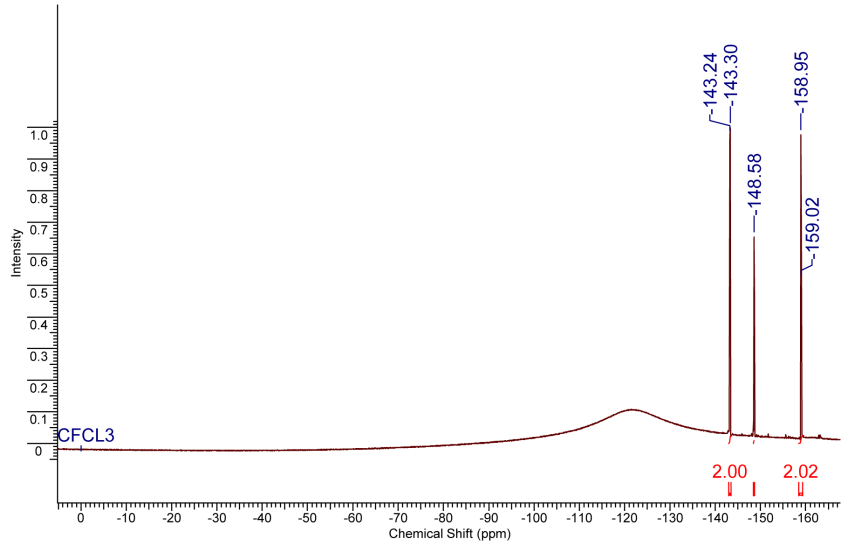


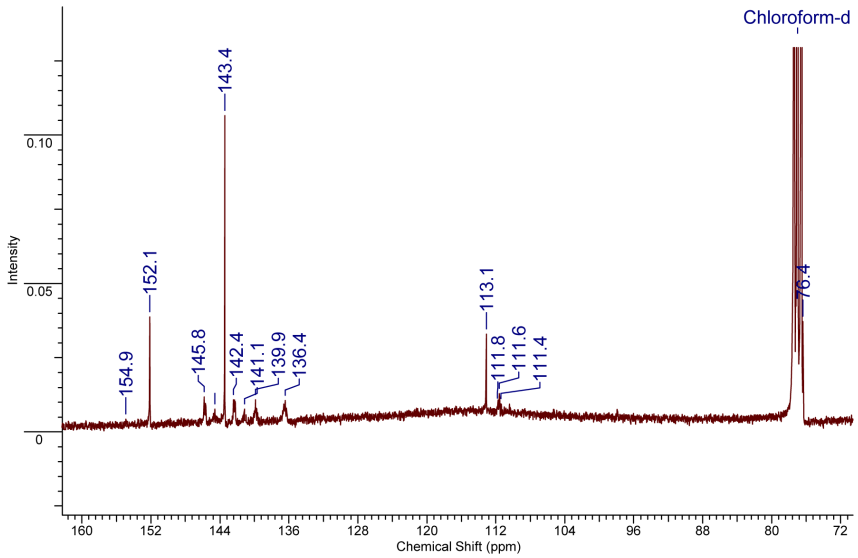


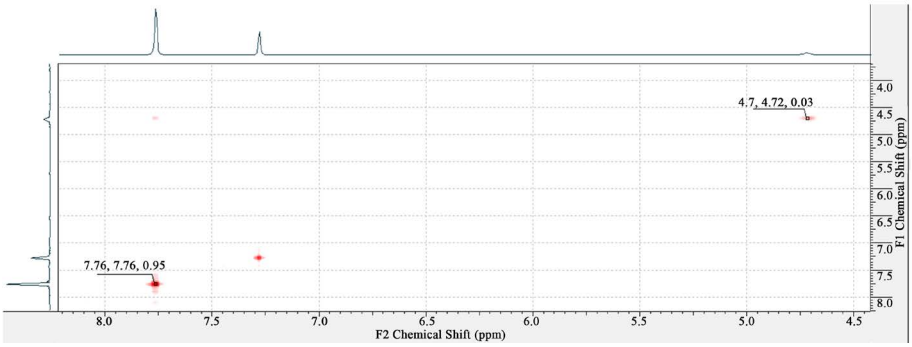
5-*amino*-1-(*perfluorophenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (**3c**): Compound **3c** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (7:1 → 5:1) and was isolated as white solid. (63 %); M.p. 135.4˚C - 136.4˚C; ^{1}H RMN [300 MHz (CDCl3)] δ = 4.69 (s br, 2H, NH2); 7.73 (s, 1H, CH); ^{19}F RMN [300 MHz] δ = −158.95 (t, 2F); −148.58 (t, 1F); −143.24 (d, 2F). ^{13}C NMR [75 MHz]: δ = 76.4(C); 113.1 (C); 143.4 (CH); 152.1 (C). It was not possible to assign the other carbons corresponding to this molecule. ^{1}H-^{1}H COSY NMR (300 MHz, CDCl3) δH/δH 7.76/7.76, 4.72/4.72. ^{1}H-^{13}C HSQC NMR (300 MHz, CDCl3) δH/δC 7.75/143.4. ^{1}H-^{13}C HMBC NMR δH/δC 7.76/76.4, 7.76/112.1, 7.76/152.1. HRMS (ESI^{-}): Anal.Calcd. for C10H3F5N4^{-}: 273.0194; found: 273.0206.

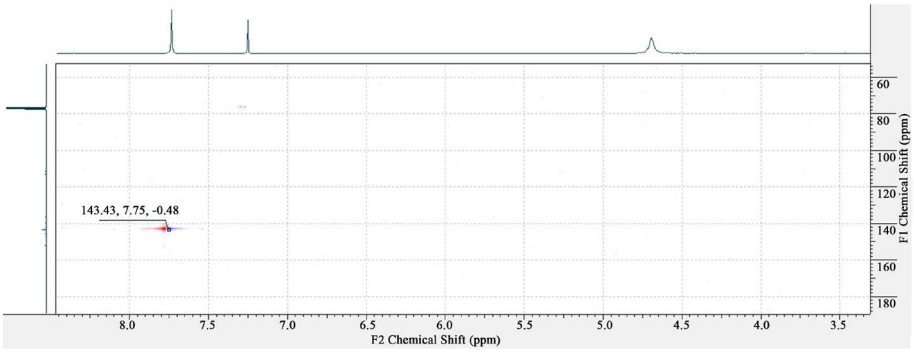
^{1}H NMR, ^{19}F, ^{13}C NMR, COSY, HSQC, HMBC and HRMS Spectra:

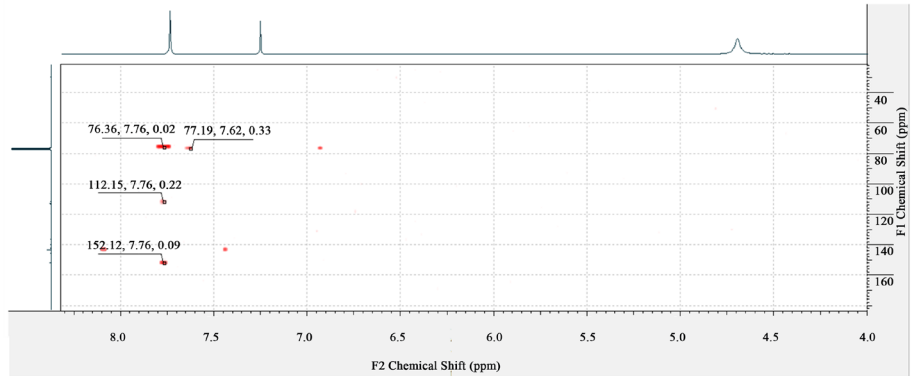

7.73
Chloroform-d
4.69
Intensity
1.03
2.00
Chemical Shift (ppm)

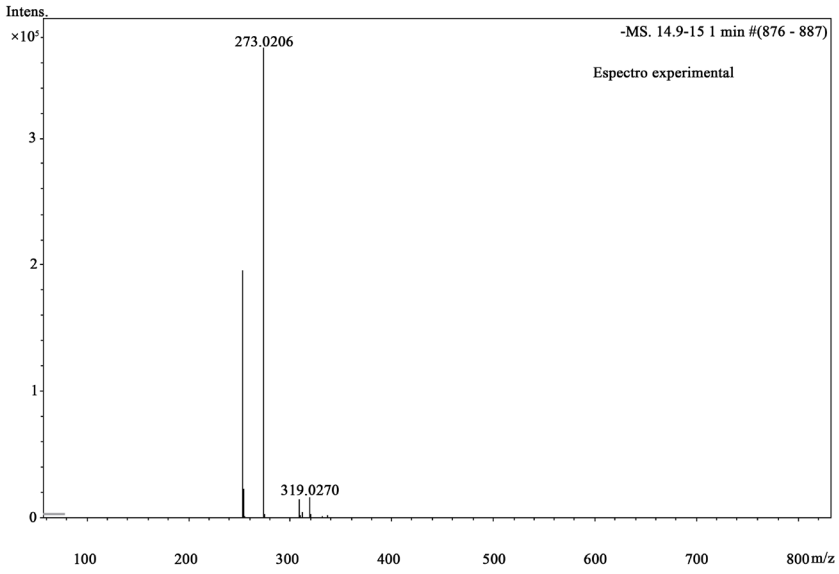

143.24
143.30
158.95
148.58
159.02
Intensity
CFCL3
2.00
2.02
Chemical Shift (ppm)


Chloroform-d
143.4
152.1
154.9
145.8
142.4
141.1
139.9
136.4
113.1
111.8
111.6
111.4
76.4
Intensity
Chemical Shift (ppm)


4.7, 4.72, 0.03
7.76, 7.76, 0.95
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

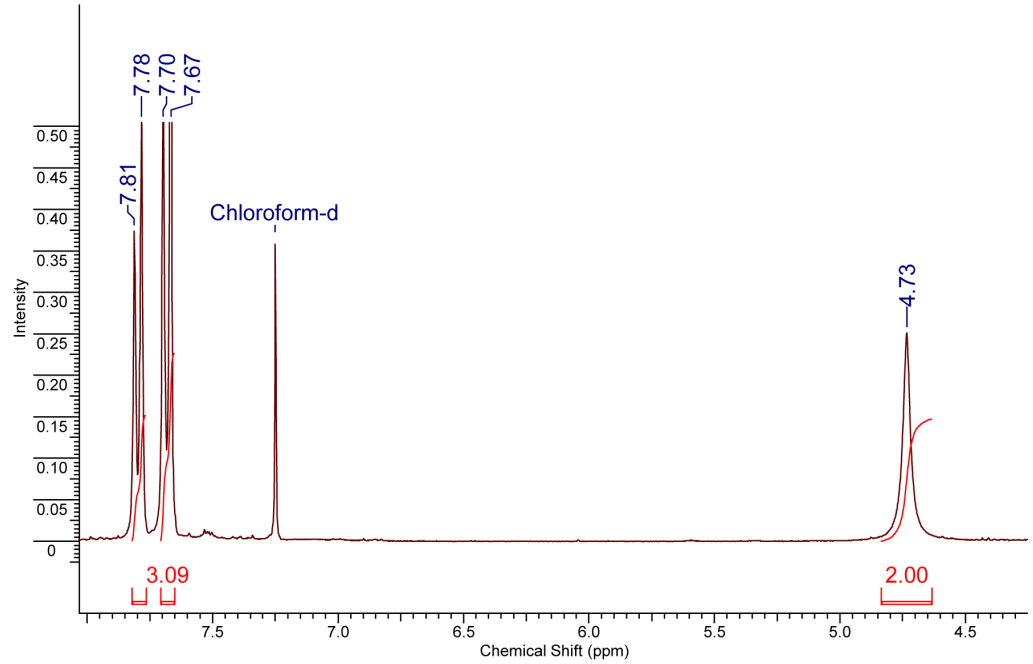

143.43, 7.75, -0.48
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

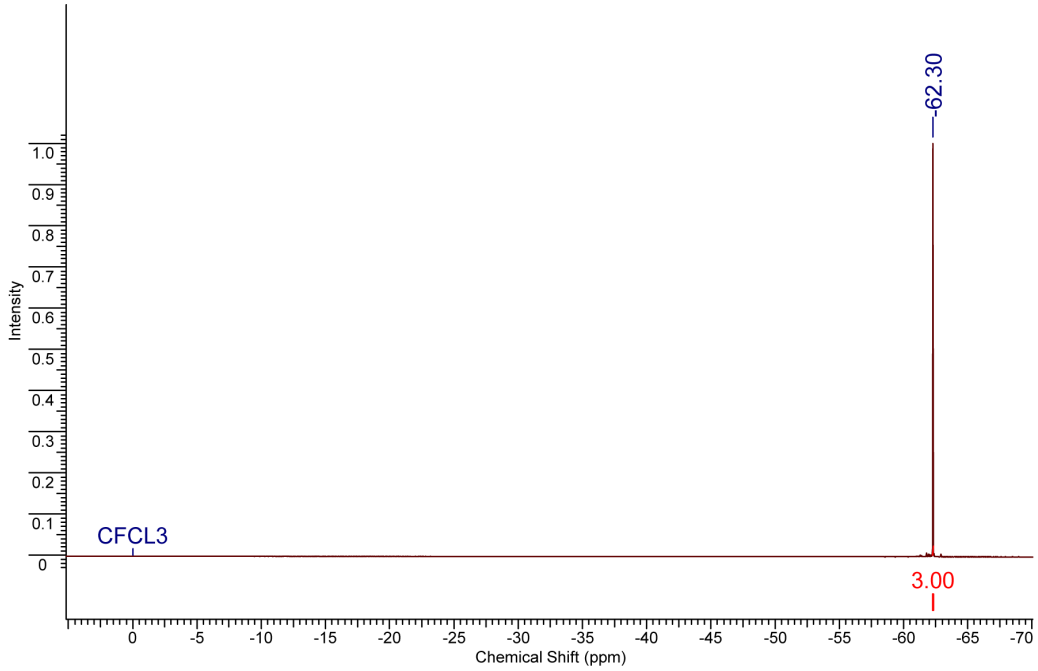

76.36, 7.76, 0.02
77.19, 7.62, 0.33
112.15, 7.76, 0.22
152.12, 7.76, 0.09
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

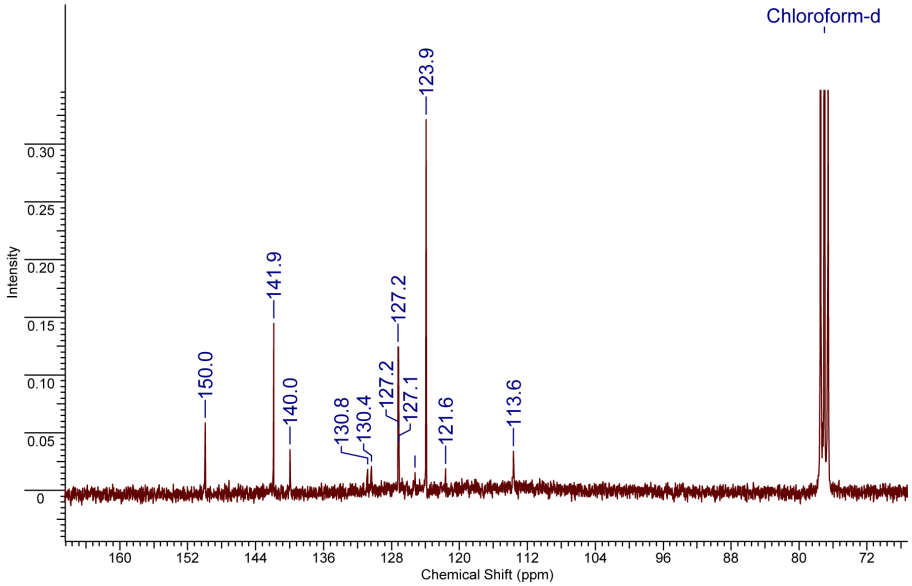

Intens.
×10⁵
-MS. 14.9-15 1 min #(876 - 887)
Espectro experimental
273.0206
319.0270
m/z

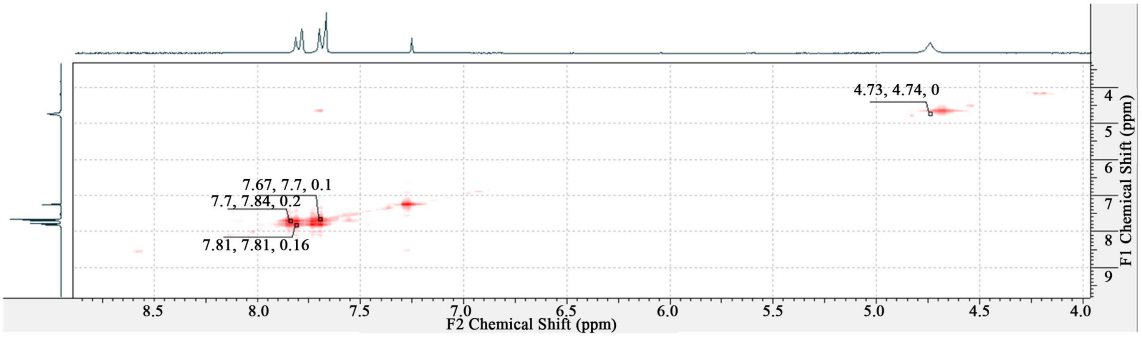
5-*amino*-1-(4-(*trifluoromethyl*)*phenyl*)-1*H-pyrazole*-4-*carbonitrile* (**3d**): Compound **3d** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (6:1 → 4:1) and was isolated as yellow solid. (67%); M.p. 156.9˚C - 158.3˚C (170.0˚C - 171.0˚C) [25]; ^{1}H RMN [300 MHz (CDCl3)] δ = 4.73 (s br, 2H, NH2); 7.67 (d, ^{1}J = 8.91, 3H, CH); 7.78 (d, ^{2}J = 8.36, 2H, CH). ^{19}F RMN [300 MHz] δ = −62.30 (s, 3F); ^{13}C NMR [75 MHz]: δ = 77.2 (C); 113.6 (C); 121.6 - 125.2(q, ^{1}J = 272.58 Hz, CF_3; it was not possible to assign the other half of this quartet); 123.9 (CH); 127.2 (CH); 130.4 - 130.8 (q, ^{2}J = 32.0 Hz); 140.0 (C); 141.9 (C); 150.0 (C). MS m/z (%): Calc. 252.0; found: 253. 0 [M^{+} + 1].

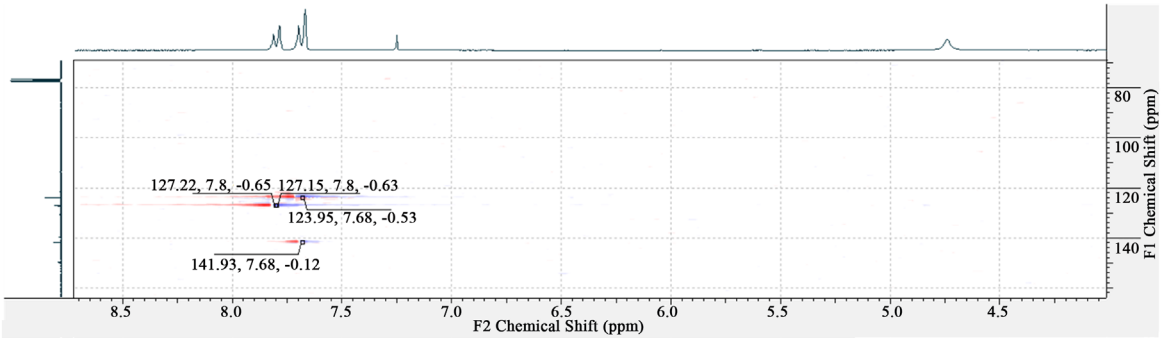
^{1}H NMR, ^{19}F, ^{13}C NMR, COSY, HSQC, HMBC and MS:

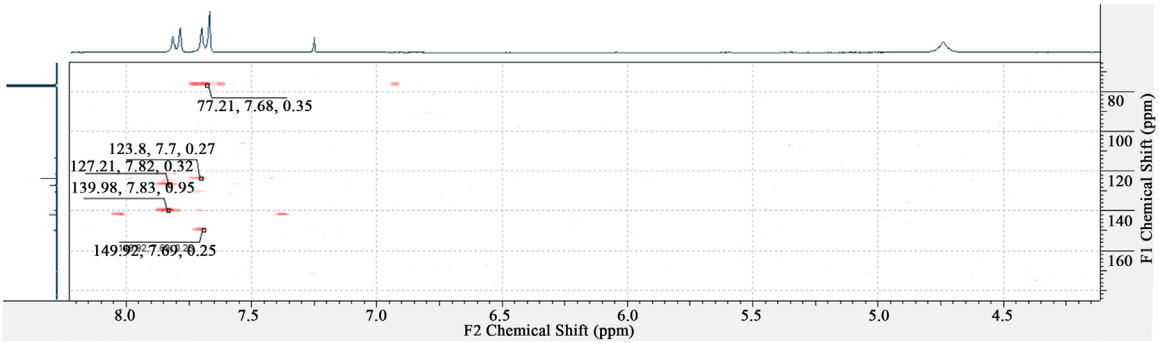


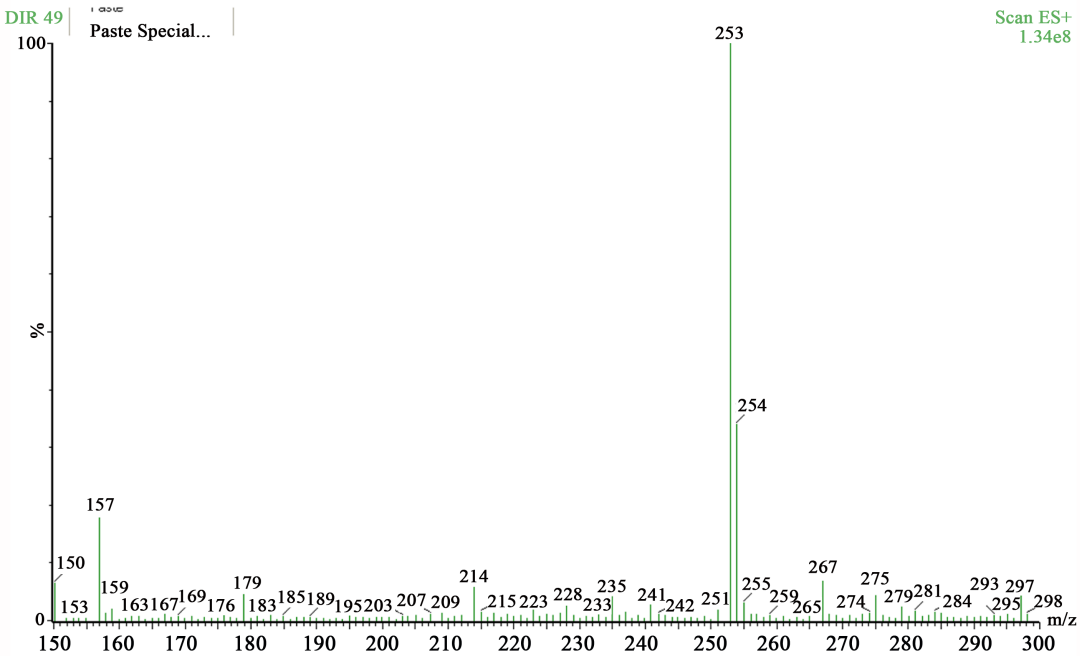



Chloroform-d
123.9
141.9
127.2
150.0
140.0
130.8
130.4
127.2
127.1
121.6
113.6
Intensity
Chemical Shift (ppm)


4.73, 4.74, 0
7.67, 7.7, 0.1
7.7, 7.84, 0.2
7.81, 7.81, 0.16
F1 Chemical Shift (ppm)
F2 Chemical Shift (ppm)

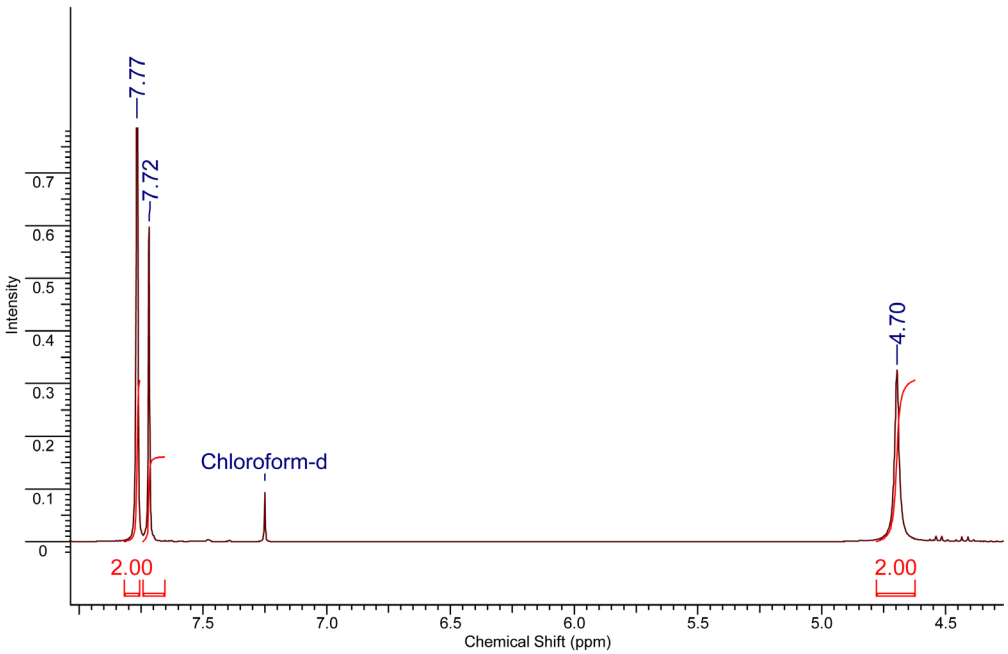

127.22, 7.8, -0.65
127.15, 7.8, -0.63
123.95, 7.68, -0.53
141.93, 7.68, -0.12
F1 Chemical Shift (ppm)
F2 Chemical Shift (ppm)

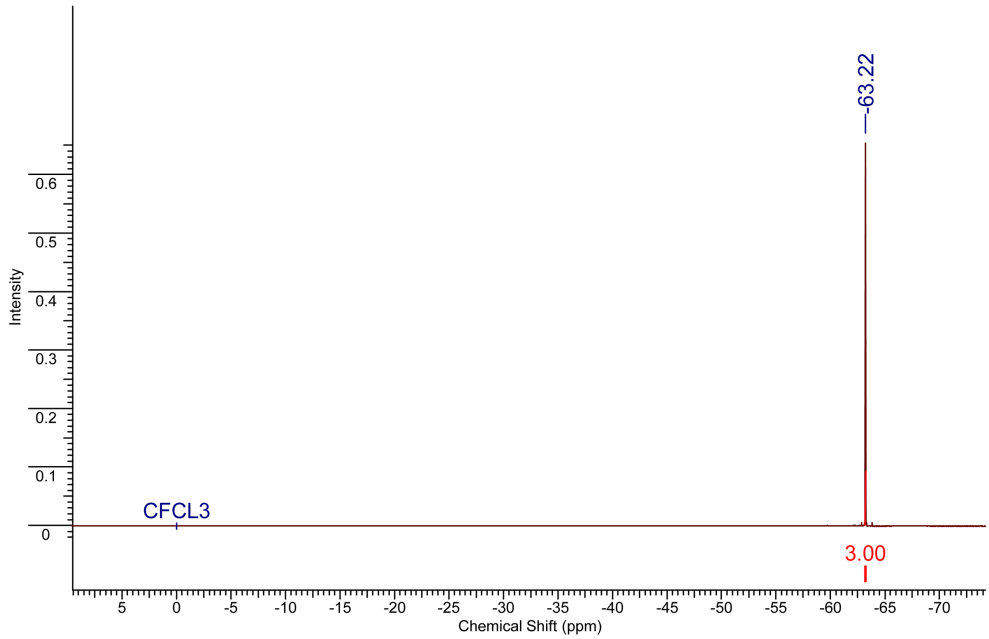

77.21, 7.68, 0.35
123.8, 7.7, 0.27
127.21, 7.82, 0.32
139.98, 7.83, 0.95
F1 Chemical Shift (ppm)
F2 Chemical Shift (ppm)

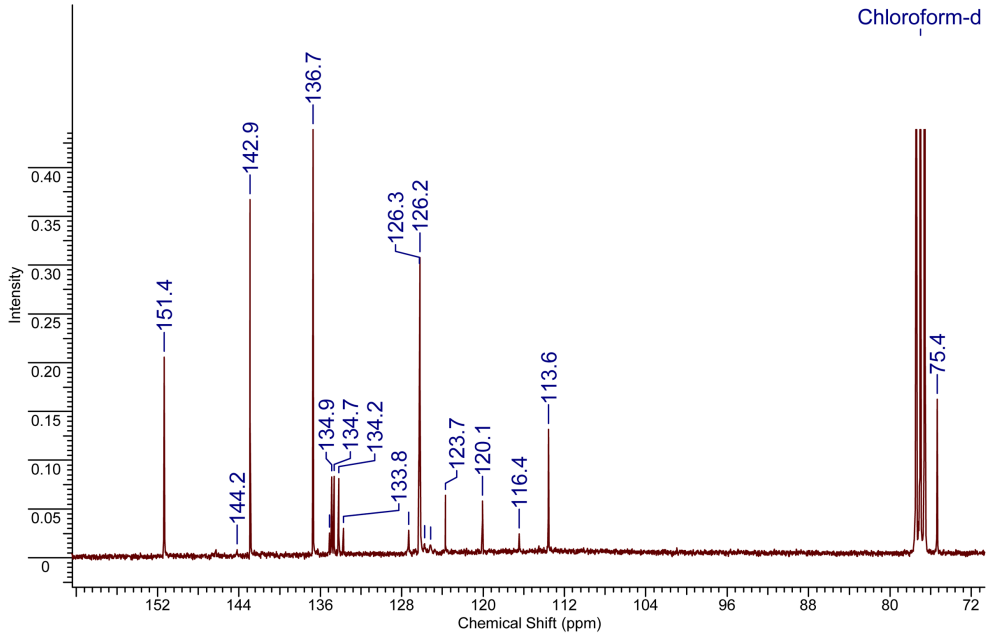


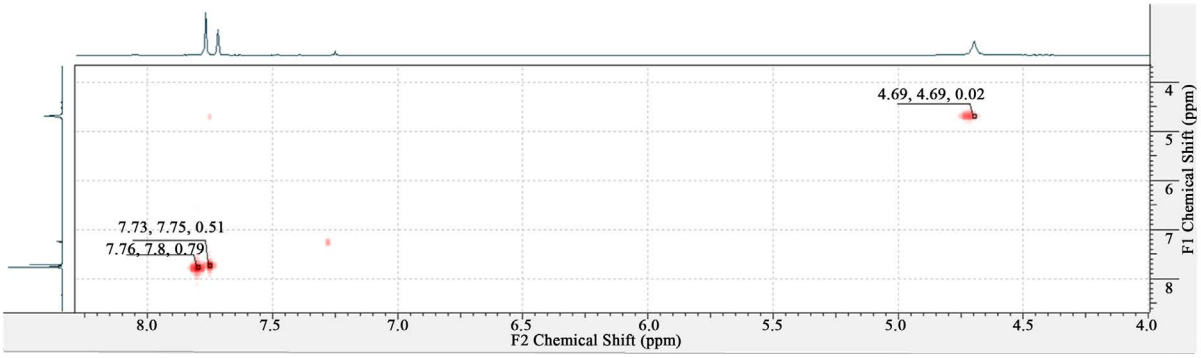
5-*amino*-1-(2,6-*dichloro*-4-(*trifluoromethyl*)*phenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (**3e**): Compound **3e** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane /ethyl acetate gradient (6:1 → 3:1) and was isolated as white solid. (47%); M.p. 163.5˚C - 164.8˚C; ^{1}H RMN [300 MHz ($CDCl_3$)] δ = 4.70 (s br, 2H, NH_2); 7.72 (s, 1H, CH); 7.77 (s, 2H, CH). ^{19}F RMN [300 MHz] δ = −63.22 (s, 2F). ^{13}C NMR [75 MHz]: δ = 75.4 (C); 113.4 (C); (116.5, 120.1, 123.7, 127.3, q, ^{1}J = 273.58 Hz - CF3); 126.2 (CH); (133.8, 134.2, 134.7, 134.9, q, ^{2}J = 34.59 Hz - CF3); 136.7(C); 142.9 (CH); 151.4(C). ^{1}H-^{1}H COSY NMR (300 MHz, $CDCl_3$) δH/δH 7.77/7.77, 7.72/7.72, 4.69/4.69. ^{1}H-^{13}C HSQC NMR (300 MHz, CDCl3) δH/δC 7.77/126.2, 7.72/142.9. ^{1}H-^{13}C HMBC NMR δH/δC 7.77/75.4, 7.77/134.7, 7.77/136.7. HRMS (ESI^{+}): Anal. Calcd. for $C11H_5C_{l2}F_3N_4Na^{+}$: 342.9736; found: 342.9731.

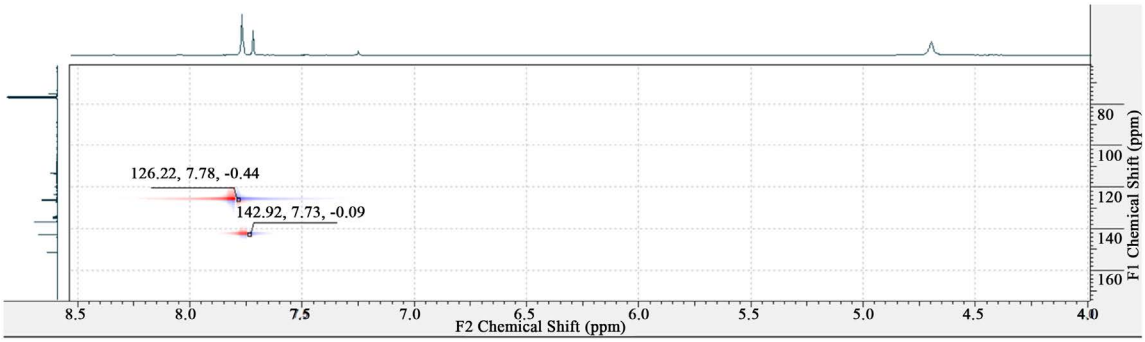
^{1}H NMR, ^{19}F, ^{13}C NMR, COSY, HSQC, HMBC and HRMS Spectra:

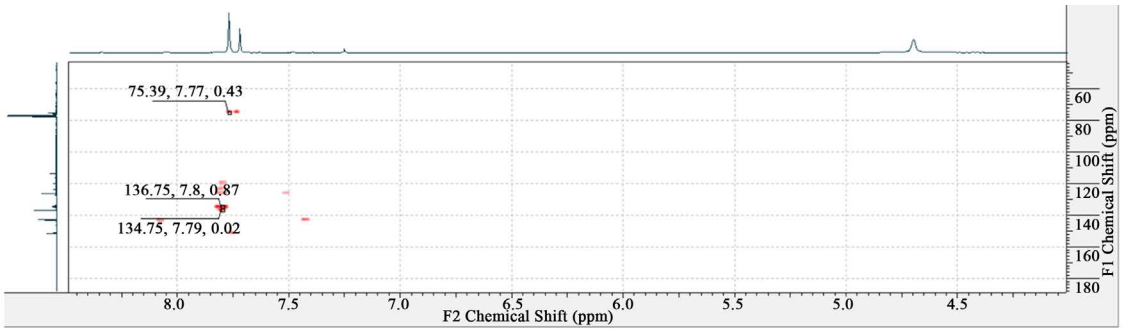


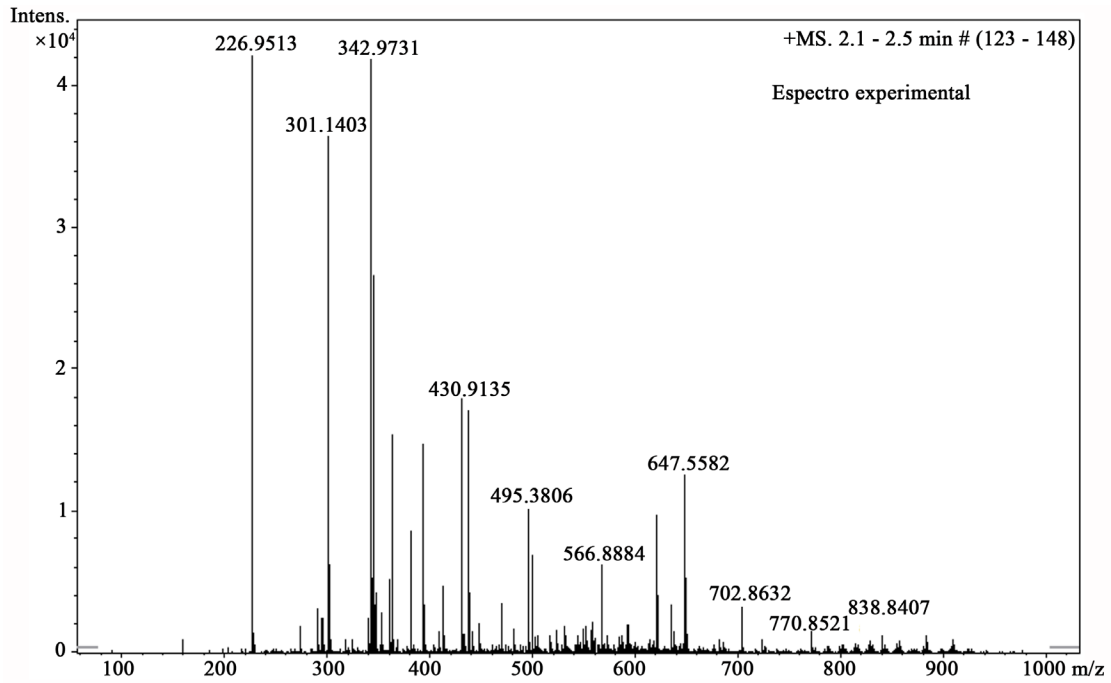

-63.22
Intensity
CFCL3
3.00
Chemical Shift (ppm)


Chloroform-d
136.7
142.9
151.4
126.3
126.2
134.9
134.7
134.2
133.8
123.7
120.1
116.4
113.6
144.2
75.4
Intensity
Chemical Shift (ppm)


4.69, 4.69, 0.02
7.73, 7.75, 0.51
7.76, 7.8, 0.79
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

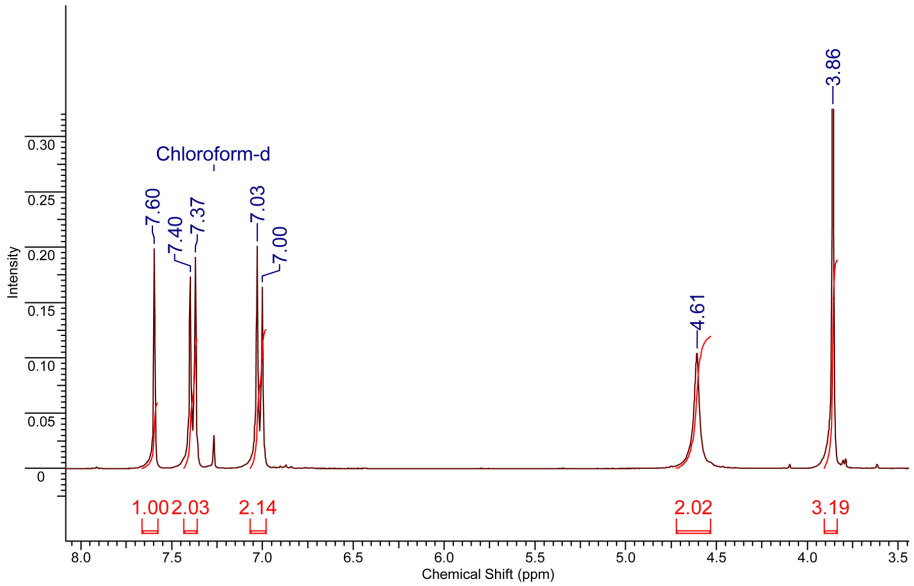


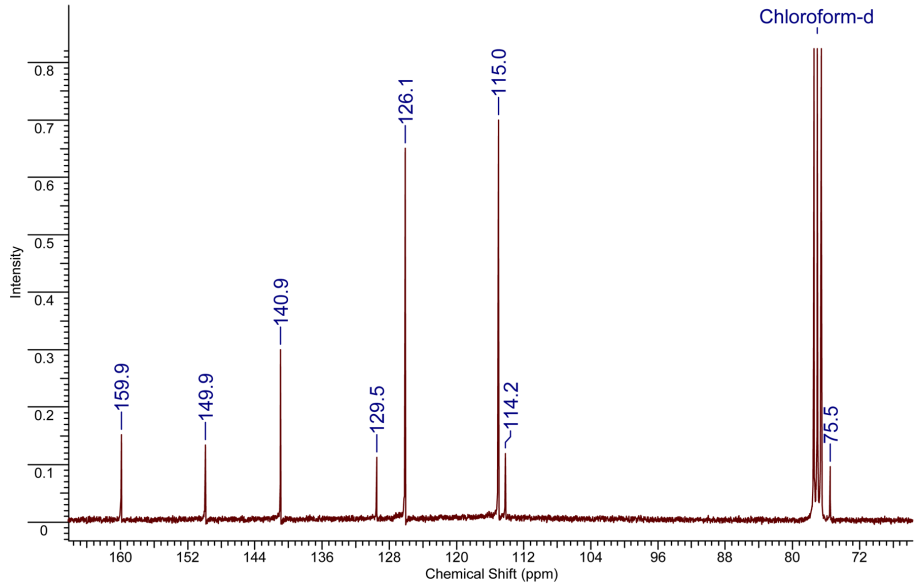


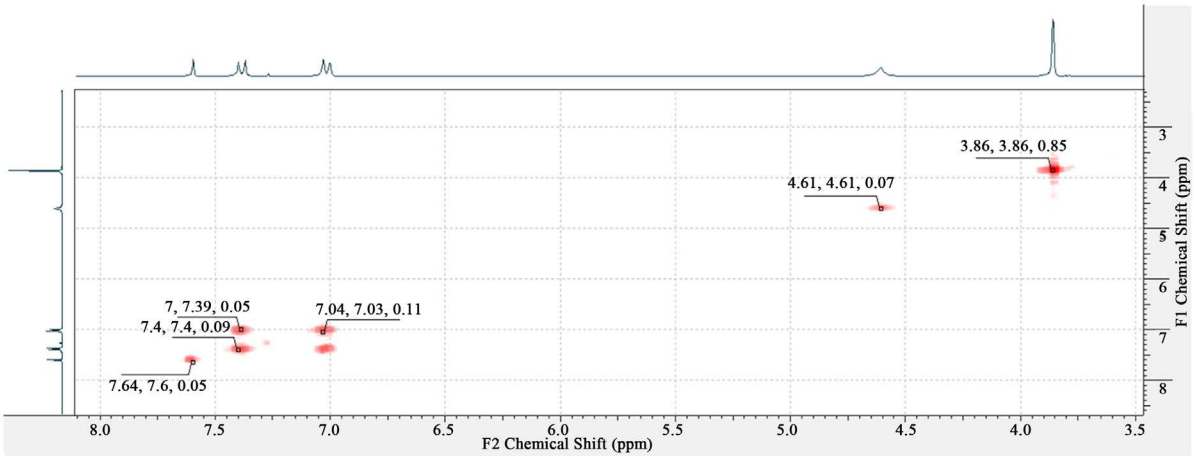


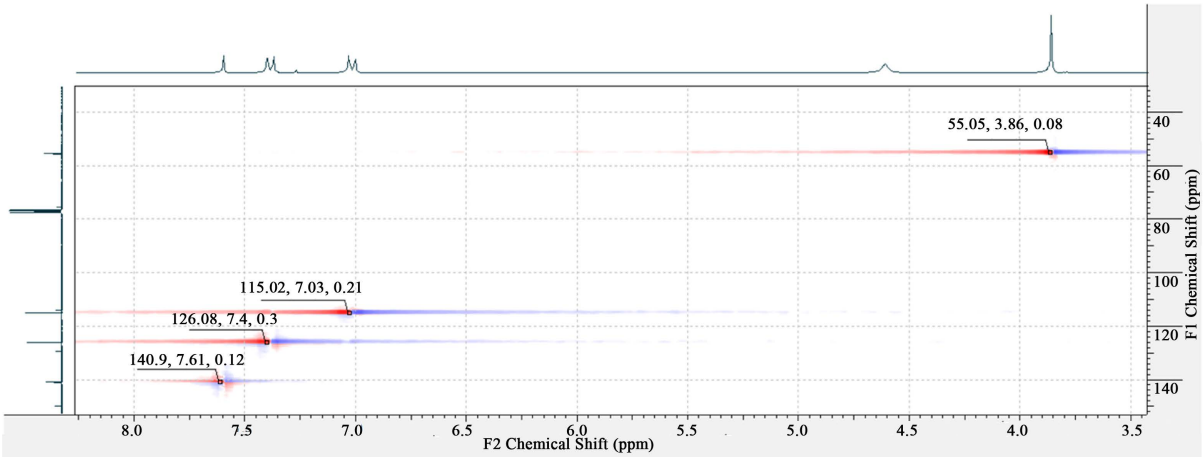
5-*amino*-1-(4-*methoxyphenyl*)-1*H*-*pyrazole*-4-*carbonitrile* (**3f**): Compound **3f** was obtained according to the general procedure. The product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate gradient (6:1 → 3:1) and was isolated as dark yellow poder. (68%); M.p. 148.4˚C - 148.8˚C (144.9˚C - 145.9˚C) [24]; ^{1}H RMN [300 MHz ($CDCl_3$)] δ = 3.86 (s, 3H, CH_3); 4.61(s br, 2H, NH_2); 7.00 - 7.03 (d, ^{1}J = 8.39 Hz, 2H, CH); 7.37 - 7.40 (d, ^{2}J = 9.18Hz, 2H, CH); 7.60 (s, 1H, CH); ^{13}C NMR [75 MHz]: δ = 75.5(C); 114.2(C); 115.0 (CH); 126.1(CH); 129.5(C); 140.9 (CH); 149.9 (C); 159.9 (C). MS m/z (%): Calc. 214.08; found: 215.0 [M^{+}+ 1].

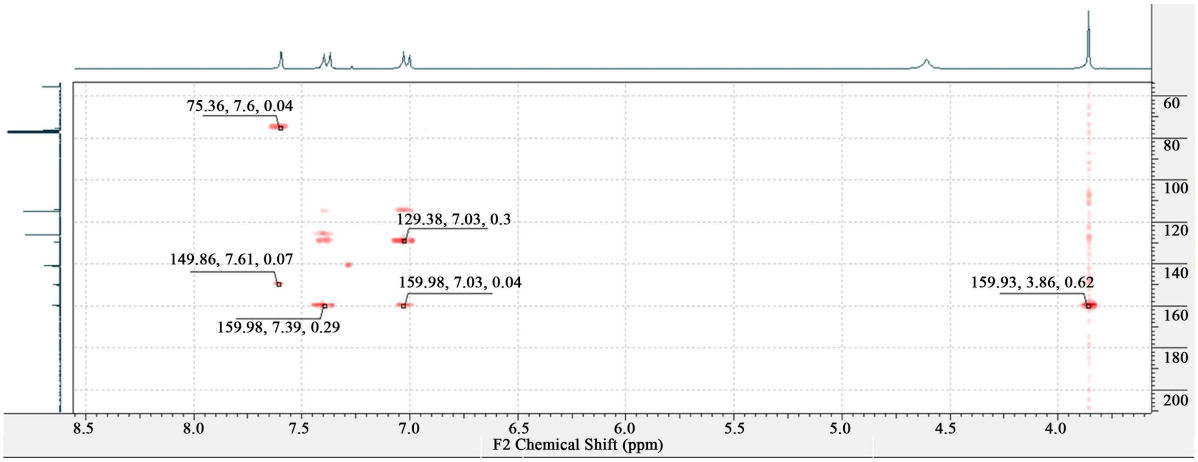
^{1}H NMR, ^{13}C NMR, COSY, HSQC, HMBC and MS Spectra:

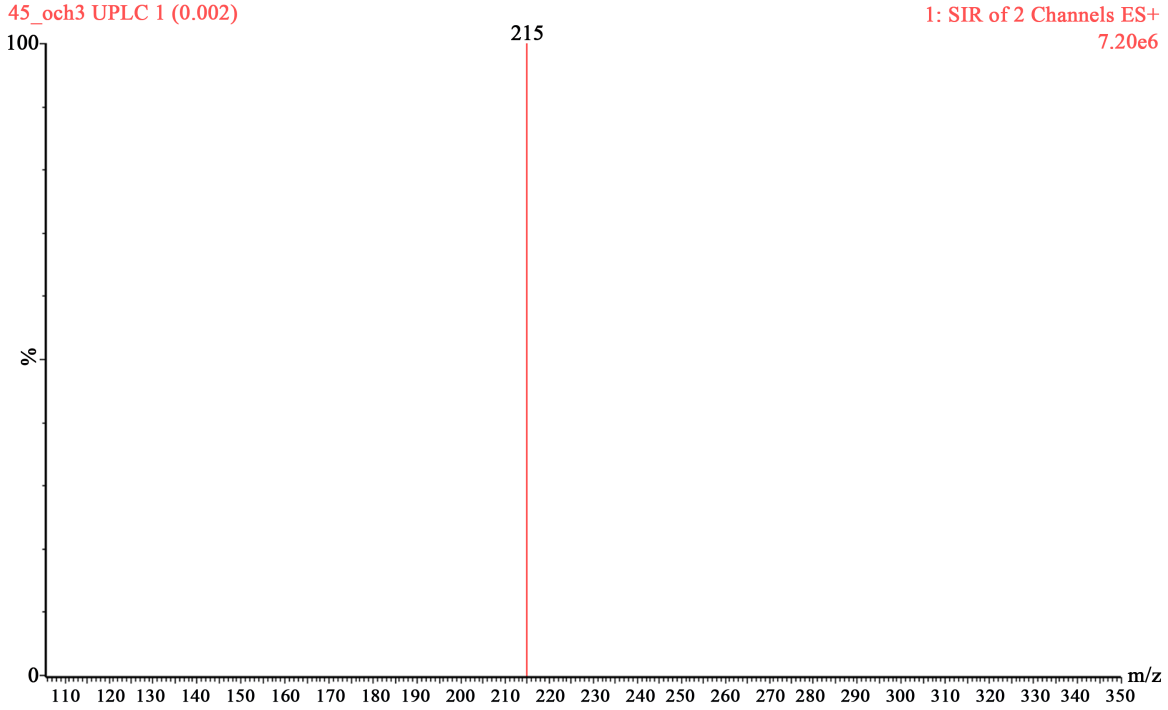

Chloroform-d
7.60
7.40
7.37
7.03
7.00
4.61
3.86
Intensity
1.00
2.03
2.14
2.02
3.19
Chemical Shift (ppm)


Chloroform-d
159.9
149.9
140.9
129.5
126.1
115.0
114.2
75.5
Intensity
Chemical Shift (ppm)


3.86, 3.86, 0.85
4.61, 4.61, 0.07
7, 7.39, 0.05
7.4, 7.4, 0.09
7.04, 7.03, 0.11
7.64, 7.6, 0.05
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)


55.05, 3.86, 0.08
115.02, 7.03, 0.21
126.08, 7.4, 0.3
140.9, 7.61, 0.12
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)


75.36, 7.6, 0.04
129.38, 7.03, 0.3
149.86, 7.61, 0.07
159.98, 7.03, 0.04
159.98, 7.39, 0.29
159.93, 3.86, 0.62
F2 Chemical Shift (ppm)


45_och3 UPLC 1 (0.002)
1: SIR of 2 Channels ES+
7.20e6
215
100
%
0
m/z