Synthesis of 3-Methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one: How To Avoid O-Acylation

ARTICLE *in* JOURNAL OF CHEMICAL EDUCATION · FEBRUARY 2015

Impact Factor: 1.11 · DOI: 10.1021/ed5000636

2 AUTHORS:

Vanya Kurteva
Bulgarian Academy of Sciences
68 PUBLICATIONS **329** CITATIONS
SEE PROFILE

Maria Atanassova
University of Chemical Technology and Met…
68 PUBLICATIONS **292** CITATIONS
SEE PROFILE

Supporting Information

Synthesis of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one. How to avoid O-acylation.

Vanya B. Kurteva[†,*] and Maria A. Petrova [‡]

[†]Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, Acad. G. Bonchev street, Block 9, BG 1113, Sofia, Bulgaria

[‡]University of Chemical Technology and Metallurgy, Department of General and Inorganic Chemistry, 8 Kliment Ohridski blvd.1756 Sofia, Bulgaria

*E-mail: vkurteva@orgchm.bas.bg

Table of Contents

1. List of reagents and lab equipment

1.1. List of reagents

1.1.1. For synthesis

3-Methyl-1-phenyl-2-pyrazolin-5-one, >98 %, CAS number 89-25-8, Merck-Schuchardt

p-Toluoyl chloride, >98 %, CAS number 874-60-2, Fluka

Calcium hydroxide, >96 %, CAS number 1305-62-0, Sigma-Aldrich

1,4-Dioxane, >99.8 %, CAS number 123-91-1, LabScan

Hydrochloric acid, 36 %, CAS number 7647-01-0, Valerus

1.1.2. For recrystallization and analyses

Methanol, >99.9 %, CAS number 67-56-1, LabScan

Acetone, >99.8 %, CAS number 67-64-1, LabScan

Heptane, >99 %, CAS number 142-82-5, LabScan

Ethanol, >99.9 %, CAS number 64-17-5, LabScan

Dichloromethane, >99.8 %, CAS number 75-09-2, LabScan

Chloroform-D, 99.90 %, CAS number 865-49-6, Deutero GmbH

1.2. List of lab equipment

1.2.1. For the first step; synthesis of acyl pyrazolone

Two-neck round-bottomed flask, 250 ml

Magnetic stirrer

Super power magnetic stir bar

Heating mantle

Water condenser

Protecting tube, containing silica gel with moisture indicator (blue)

Dropping funnel, 10 ml

Beaker, 400 ml

Cylinders

1.2.2. For the second step; work-up, recrystallization and analysis

Buechner funnel

Filter paper

Filtering flask

Adapter for filter funnels
Round-bottomed flasks
Cylinders
Filter funnels
Adapter for filter funnels
Silica gel thin-layer chromatography (TLC) plates
TLC developing chamber
TLC glass capillaries
UV lamp, 254 nm
Automated melting point system
Capillary tubes for melting point determination
NMR tubes

1.2.3. For protection

Well ventilated hood
Laboratory coats
Safety glasses
Protective gloves

2. Safety and Hazards

The starting 3-methyl-1-phenyl-2-pyrazolin-5-one possesses acute oral toxicity and irritates skin and eyes. Calcium hydroxide can cause severe skin irritation, chemical burns, blindness, or lung damage. p-Toluoyl chloride is a lachrymator and causes skin and eyes corrosion and burns. Dioxane is a carcinogenic flammable liquid, which is irritating to the eyes and respiratory tract. Exposure may cause damage to the central nervous system, liver and kidneys. Hydrochloric acid is a toxic compound, which has a corrosive effect on human tissue, with the potential to damage respiratory organs, eyes, skin, and intestines irreversibly. The solvents used for TLC and recrystallization, dichloromethane, methanol, ethanol, heptane and acetone, are flammable liquids. Dichloromethane causes skin and eye irritation and possesses carcinogenicity. Methanol is acute toxic if swallowed, in contact with skin or if inhaled. Acetone causes serious eye irritation and may cause drowsiness or dizziness. Heptane causes skin irritation and may be fatal if swallowed and enters airways. It is very toxic to aquatic life

with long lasting effects. Deuterated chloroform is a suspected carcinogen and should be handled with care. Unprotected exposure to these chemicals has to be limited. Avoid breathing solvents' vapors and release reagents to the environment.

The hazards of acyl pyrazolones are not known and the students have to handle them with extreme care.

Safety glasses, gloves, and laboratory coat were all worn during these exercises. Both syntheses and recrystallizations were carried out by using safety heaters with temperature controllers. All exercises, including NMR tube's preparations, were handled in a well-ventilated hood. All wastes were disposed appropriately.

3. Student Handout: Lab procedure

3.1. Objectives

- ✓ Synthesis of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one
- ✓ Recrystallization from different solvents and product analysis
- ✓ NMR spectra of acyl pyrazolones and O-acylated compounds

3.2. General

The students performed selective C-acylation of 3-methyl-1-phenyl-2-pyrazolin-5-one by using p-toluoyl chloride as acylating agent in the presence of calcium hydroxide. The product was purified by recrystallization and its chromatographic and physical parameters were determined. To the best of our knowledge, similar experiments were not achieved by students. The protocol is appropriate for student's exercises due to several practical features:

- ✓ Fast conversion – all synthetic work can be performed in less than 6 h
- ✓ Simple manipulation – do not need special precautions
- ✓ No tedious work-up – simple recrystallization and filtration
- ✓ Applicable for other heterocyclic systems

The signals in the NMR spectra of a series of acyl pyrazolones were assigned and compared with those of the corresponding O-acylated compound.

3.3. Experimental protocols

3.3.1. Synthesis of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one

All reagents were purchased from Merck, Aldrich and Fluka and were used without any further purification. LabScan HPLC grade solvents were used as a reaction media and for recrystallization. LabScan 1,4-dioxane was analytical grade with water content max. 0.05 %. Fluka silica gel/TLC-cards 60778 with fluorescent indicator 254 nm were used for TLC chromatography. The melting point was determined in a capillary tube on SRS MPA100 OptiMelt (Sunnyvale, CA, USA) automated melting point system.

The *typical reaction procedure* is as follows: The starting 3-methyl-1-phenyl-1H-pyrazol-5-one (8.7 g, 50 mmol) was placed in a 2-neck round-bottom boiling flask and was dissolved in dry dioxane (60 ml) under gentle heating. $Ca(OH)_2$ (7.4 g, 100 mmol) was added and the mixture was stirred at room temperature for 0.5 h. 4-Methylbenzoyl chloride (6.5 ml, 50 mmol) was then added and the mixture was refluxed with stirring for 1 h. The reaction mixture was cooled to room temperature and poured into 10 % aq. HCl (250 ml). The solid phase formed was filtered off, washed with water, dried on air, and recrystallized from methanol/acetone.

The synthetic part is divided in two sessions:

Laboratory session 1; synthesis of the crude product

Total – 6 h.

1. Build the necessary equipment in a well-ventilated hood: a 250 ml two-neck round bottom flask, condenser with moisture stopper (glass tube with calcium chloride or silica gel with moisture indicator), high turbulence magnetic stir bar, magnetic stirrer, and heating mantle.
2. Insert 3-methyl-1-phenyl-2-pyrazolin-5-one and dioxane and heat gently till full dissolution.

Steps 1 and 2 need 0.5 h overall.

3. Add $Ca(OH)_2$ and reflux 0.5 h under vigorous stirring.
4. Cool to 0^oC with an ice-bath and add the p-toluoyl chloride dropwise *via* a dropping funnel.
5. Reflux the reaction mixture for 1.5 h.

Steps 4 and 5 need 2.5 h overall.

6. Cool the reaction mixture to room temperature.
7. Add the reaction mixture to 10 % aq. HCl under vigorous stirring.

Steps 6 and 7 need 0.5 h overall.

8. After 1.5 h separate the residue formed by filtration and wash with water and then with ethanol.
9. Place the crude product on a filter paper and leave to become air dried in desiccator.

Steps 8 and 9 need 2 h overall.

Optional: When keep the acidic mixture at room temperature overnight before filtration, the calcium complex is fully destroyed and the yield is slightly increased. The prolongation is 4 h and 0.5 h for filtration in the next day.

Laboratory session 2; recrystallization and analyses

Total 4-5 h per day.

1. Recrystallize the crude product from methanol-acetone.
2. Analyze the crude product by TLC on silica gel.
3. Prepare a sample for NMR and send for recording spectra.
4. Filter the crystals and dry in air.
5. Recrystallize the pure product from diffident solvents and solvent systems.
6. Filter the crystals and dry in air.
7. Analyze pure compounds by TLC and melting point.

3.3.2. NMR spectra of acyl pyrazolones and O-acylated compounds

The NMR spectra were recorded on a Bruker Avance II+ 600 spectrometer (Rheinstetten, Germany) at 25^{o}C as chloroform-d solutions; the chemical shifts were quoted in ppm in δ-values against tetramethylsilane (TMS) as an internal standard and the coupling constants were calculated in Hz. The assignment of the signals was confirmed by applying 2D techniques. The spectra were recorded as $3x10^{-2}$ M solutions in order to avoid transmolecular interactions in NOESY experiments. The spectra were processed with Topspin 2.1 program.

It is very important for second-year undergraduate students to acquire basic knowledge in the interpretation of NMR spectra and in the application of the method for structure determination. At the end of these exercises they managed to analyze the spectra of the crude products, which is much more complicated than the analyses of pure compounds.

General laboratory sequence

1. Analyze the proton spectrum: integral intensities, multiplicity of the signals, characteristic chemical shifts, coupling constants.
2. Analyze the cross peaks in ^{1}H-^{1}H 2D experiment COSY to receive information about the neighboring groups.
3. Analyze the cross peaks in ^{1}H-^{1}H 2D experiment NOESY to receive information about steric remoteness of the protons.
4. Analyze carbon spectrum and DEPT experiment.
5. Analyze the cross peaks in ^{1}H-^{13}C 2D experiment HSQC to recognize which proton with which carbon is directly connected.

6. Analyze the cross peaks in ^{1}H-^{13}C 2D experiment HMBS to assign the signals of quaternary carbons.

7. Build the whole picture and describe the full spectra.

Laboratory session 3; 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one

Duration: flexible.

1. Assign the signals in the spectra.

2. Determine the tautomeric state of the product in chloroform-d.

Laboratory session 4; series of acyl pyrazolones

Duration: flexible.

1. Assign the signals in the spectra of 3-methyl-4-(4-flourobenzoyl)-1-phenyl-pyrazol-5-one.

2. Assign the signals in the spectra of 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one.

3. Assign the signals in the spectra of 3-methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one.

4. Analyze the influence of the type and place of the substituent on the signals pattern and chemical shift.

Laboratory session 5; O-acylated compounds

Duration: flexible.

1. Assign the signals in the spectra of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-methylbenzoate.

2. Assign the signals in the spectra of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-fluorobenzoate.

3. Compare the spectra with those of the corresponding C-acylated products.

4. Analyze the spectra of the crude reaction products.

4. Instructor's notes

Several acyl derivatives were preliminary obtained by the teachers, namely 4-(4-methylbenzoyl)-, 4-(4-fluorobenzoyl)-, 4-(4-phenylbenzoyl)-, and 4-(3-methylbenzoyl)-3-methyl-1-phenyl-1H-pyrazol-5-ones, in order to choose the most appropriate for the students experiments example. The O-acylated products with 4-methylbenzoyl and 4-fluorobenzoyl chloride were also prepared to demonstrate the difference in the NMR spectra of C-acylated and O-acylated compounds.

The notes for instructors are the following:

Note 1. It is important to protect the reaction mixture from moisture to avoid acyl chloride hydrolysis. Use anhydrous dioxane; water content below 0.05 %.

Note 2. Grind pyrazolone before addition of 1,4-dioxane to accelerate the dissolution.

Note 3. It is important to dissolve fully the starting pyrazolone before addition of calcium hydroxide.

Note 4. Use calcium hydroxyde in 2 equivalents to trap the liberated hydrogen chloride and keep the reaction media basic.

Note 5. It is necessary to use high turbulence magnetic stir bar to afford the efficient complex formation because calcium hydroxide forms very heavy residue, which cannot be stirred with common bars.

Note 6. The addition of acyl chloride to the mixture can generate heat. Be very careful and add the reagent dropwise under cooling.

Note 7. Observe the color of the reaction mixture. It changes from yellow to orange.

Note 8. Stir vigorously during the addition of the reaction mixture to hydrochloric acid in order to avoid lumps formation. The latter hindered the decomposition of the complex and can result in a decrease of the product yield. If the lumps are formed, they have to be grinded.

Note 9. Keep the acidic mixture at room temperature as long as possible before filtration to achieve complete complex decomposition.

Note 10. Wash carefully the residue to dissolve fully $CaCl_2$ and eventually traces of $Ca(OH)_2$.

Note 11. Wash further with small portions of ethanol to eliminate the dark brown colored impurities.

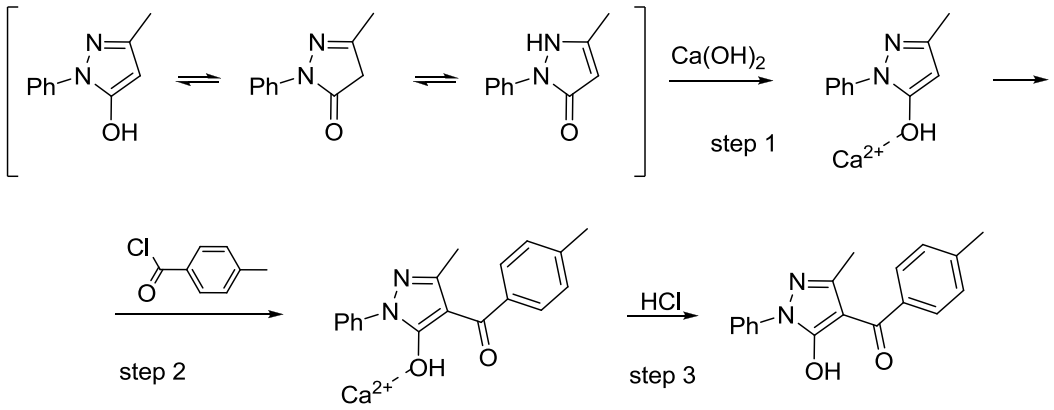
Note 12. Crucial elements in the assignment of signals in NMR spectra:

- ✓ ^{1}H Spectrum – characteristic pattern: two singlets in strong field for C*H*$_3$ groups; aromatic area: two doublets with integrals of 2 for the protons of aromatic acyl substituent, doublet for 2 protons for ortho, doublet of doublets for 2 protons for meta and doublet of doublets for 1 proton for para-phenyl; broad singlet for hydroxyl proton in low field.
- ✓ ^{1}H-^{1}H NOESY interaction of methyl from the aromatic substituent - explicitly distinguishing both methyl groups and the aromatic protons of the acyl group.
- ✓ ^{1}H-^{1}H COSY experiment – recognition of the neighboring protons.
- ✓ ^{13}C Spectrum – characteristic pattern: two *C*H$_3$ groups in strong field; aromatic area: two double intensive signals for aryl group carbons, two double intensive signals for ortho and meta phenyl carbons, one signal for para-phenyl; quaternary carbons: 7 signals, two of them in low field (*C*=O and *C*-OH).
- ✓ DEPT experiment – recognition of *C*H from quaternary carbons.
- ✓ ^{1}H-^{13}C HSQC interaction – direct connection between protons and carbons.
- ✓ ^{1}H-^{13}C HMBC experiment – recognition of quaternary carbons: C*H*-2 and C*H*-6 with C_q-4 and C*H*-3 and C*H*-5 with C_q-1 in Ar group, C*H*-2 and C*H*-6 with *C*=O, C*H*-3 and C*H*-5

with C_q-1 in N-Ph, CH_3 of pyrazolone with C_q-3 and C_q-4, no interactions of C_q-5 of pyrazolone ring in low field.

5. Student's results

The eight second-year undergraduate students performed 4 experiments in couples to obtain selectively 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one *via* a protocol described above (Scheme S1).



Scheme S1. Synthesis of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

Two experiments were carried out as one-day procedure, i.e. with 1.5 h prolongation of step 3, and two as two-days. The yields of the crude products and pure compounds after first recrystallization from methanol-acetone are summarized on Table S1.

Table S1. Synthesis of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one*.

Run	Duration of step 3	Crude product, yield	Recrystallized product, yield
1	1.5 h	12.72 g, 87 %	10.53 g, 72 %
2	1.5 h	12.86 g, 88 %	10.38 g, 71 %
3	15 h	13.30 g, 91 %	10.82 g, 74 %
4	15 h	13.16 g, 92 %	10.96 g, 75 %

*Theoretical yield: 14.62 g, 50 mmol scale.

The crude product was analyzed by TLC on silica gel. The mobile phase was varied and was found that 5 % methanol in dichloromethane, i.e. MeOH:CH_2Cl_2 5:95, lead to best separation. Two slight impurities were detected, more polar and less polar in respect to the target compound. The following R_f-values were measured:

Product: R_f 0.55 (MeOH:CH_2Cl_2 5:95)

Non-polar impurity: R_f 0.89 (MeOH:CH_2Cl_2 5:95)

Polar impurity R_f 0.43 (MeOH:CH_2Cl_2 5:95)

Picture S1. TLC of the crude product in different concentrations.

The pure compounds were submitted to second recrystallization. Each student performed 3 individual experiments starting from 500 mg pure 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one. Several solvents and solvent systems were applied, namely: heptane, acetone, methanol, ethanol, methanol-water, ethanol-water. It was found that heptane causes serious loose of product, while all other solvents led to excellent yields.

Two different types of crystals were obtained, yellow needles from heptane and colorless plates from acetone, while alcohols and alcohol-water mixtures grew white powder. The melting points of the crystal phases were measured on the automatic melting point system. Each student measured the melting point of each crystal phase, i.e. 6 measurements each. The results are listed on Table S2. As seen, the crystals from heptane and acetone gave clear and sharp melting points, while the powders from the rest of the solvents and solvent systems showed broad intervals, which is an indication for non-homogeneity.

Table S2. Results from the recrystallization from different solvents.

Solvent	Experiments	Crystal type	Yield	m. p.*
heptane	2	yellow needles	195-225 mg, 39-45 %	102-103^{o}C
acetone	6	colorless plates	368-398 mg, 74-80 %	126-127^{o}C
methanol	4	white powder	432-453 mg, 86-90 %	129-135^{o}C
ethanol	4	white powder	412-429 mg, 82-86 %	130-136^{o}C
methanol-water	4	white powder	457-479 mg, 91-96 %	132-138^{o}C
ethanol-water	4	white powder	464-476 mg, 93-95 %	133-137^{o}C

*The most reproducible values from 8 students' measurements.

NMR spectroscopy exercises

The students worked individually and assigned all signals in proton and carbon spectra of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one in chloroform-d by analysing 1D and 2D experiments:

NMR ($CDCl_3$) ^{1}H 2.146 (s, 3H, C*H*$_3$-3), 2.457 (s, 3H, C*H*$_3$ Ar), 7.306 (tt, 1H, J_{34} 7.5, J_{24} 1.1, C*H*-4 Ph), 7.320 (dd, 2H, J_{23} 8.2, J_{35} 0.6, C*H*-3 and C*H*-5 Ar), 7.473 (ddd, 2H, J_{23} 8.5, J_{34} 7.5, J_{35} 2.0, C*H*-3 and C*H*-5 Ph), 7.568 (dt, 2H, J_{23} 8.1, J_{26} 1.8, C*H*-2 and C*H*-6 Ar), 7.880 (ddd, 2H, J_{23} 8.6, J_{26} 1.9, J_{24} 1.1, C*H*-2 and C*H*-6 Ph), 9.874 (bs, 1H, O*H*); ^{13}C 16.02 (*C*H$_3$-3), 21.68 (*C*H$_3$ Ar), 103.53 (C_{quat}-4 Pyr), 120.73 (*C*H-2 and *C*H-6 Ph), 126.62 (*C*H-4 Ph), 128.17 (*C*H-2 and *C*H-6 Ar), 129.08 (*C*H-3 and *C*H-5 Ph or *C*H-3 and *C*H-5 Ar), 129.13 (*C*H-3 and *C*H-5 Ph or *C*H-3 and *C*H-5 Ar), 134.64 (C_{quat}-1 Ar), 137.27 (C_{quat}-1 Ph), 142.69 (C_{quat}-4 Ar), 147.91 (C_{quat}-3 Pyr), 161.81 (C_{quat}-5 Pyr), 191.63 (*C*=O); COSY cross peaks 7.306/7.473, 7.320/7.568, 7.473/7.880; NOESY cross peaks 2.146/7.568, 2.457/7.320, 7.306/7.473, 7.320/7.568, 7.473/7.880; HSQC cross peaks 2.146/16.02, 2.457/21.68, 7.306/126.62, 7.320/129.08 or 129.13, 7.473/129.08 or 129.13, 7.568/128.17, 7.880/120.73; HMBC cross peaks 2.146/103.53, 2.146/147.91, 2.457/129.08 or 129.13, 2.457/142.69, 7.306/120.73, 7.320/21.68, 7.320/129.08 or 129.13, 7.320/134.64, 7.473/120.73 (weak), 7.473/129.08 or 129.13, 7.473/137.27, 7.568/128.17, 7.568/142.69, 7.568/191.63, 7.880/120.73, 7.880/126.62, 7.880/137.27 (weak).

As a second step, the students interpreted the spectra of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one. In these exercises they clearly understood the influence of the type of the aromatic substituent on the chemical shift of the closed nuclei. They also learn how to recognize and measure the coupling constants with fluorine. The full assignment of the spectra is the following:

NMR ($CDCl_3$) ^{1}H 2.127 (s, 3H, C*H*$_3$), 7.202 (ddd, 2H, J_{23} 8.7, J_{3F} 8.6, J_{35} 1.9, C*H*-3 and C*H*-5 Ar), 7.314 (td, 1H, J_{34} 7.4, J_{24} 1.0, C*H*-4 Ph), 7.472 (ddd, 2H, J_{23} 7.6, J_{34} 7.4, J_{35} 1.8, C*H*-3 and C*H*-5 Ph), 7.679 (ddd, 2H, J_{23} 8.7, J_{2F} 5.3, J_{26} 2.1, C*H*-2 and C*H*-6 Ar), 7.869 (ddd, 2H, J_{23} 7.6, J_{26} 1.9, J_{24} 1.1, C*H*-2 and C*H*-6 Ph), 10.190 (bs, 1H, O*H*); ^{13}C 15.97 (*C*H$_3$), 103.45 (C_{quat}-3 Pyr), 115.71 (d, J_{3F} 22.0, *C*H-3 and *C*H-5 Ar), 120.87 (*C*H-2 and *C*H-6 Ph), 126.86 (*C*H-4 Ph), 129.19 (*C*H-3 and *C*H-5 Ph), 130.48 (d, J_{2F} 9.0, *C*H-2 and *C*H-6 Ar), 133.95 (d, J_{1F} 3.1, C_{quat}-1 Ar), 137.14 (C_{quat}-1 Ph), 147.69 (C_{quat}-4 Pyr), 161.18 (C_{quat}-5 Pyr), 164.95 (d, J_{4F} 253.4, C_{quat}-4 Ar), 191.01 (*C*=O); COSY cross peaks 7.202/7.679, 7.314/7.472, 7.472/7.869; HSQC cross peaks 2.127/15.97, 7.202/115.71, 7.314/126.86, 7.472/129.19, 7.679/130.48, 7.869/120.87; HMBC cross peaks 2.127/103.45, 2.127/147.69, 7.202/115.71, 7.202/133.95, 7.202/164.95,

7.314/120.87, 7.314/129.19 (weak), 7.472/120.87 (weak), 7.472/129.19, 7.472/137.14, 7.679/130.48, 7.679/164.95, 7.679/191.01, 7.869/120.87, 7.869/126.86, 7.869/137.14 (weak).

Two more acyl pyrazolone spectra were analyzed, 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one and 3-methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one. The first example was very useful for teaching as shows second order spectra in the aromatic area. The second compound demonstrated the influence of the position of the substituent on the signals pattern, multiplicity and chemical shift.

At the end, the spectra of two esters, the corresponding unacceptable O-acylated compounds, obtained by the teachers, were studied. Based on the results, the spectra of the crude reaction mixtures were analyzed and was found that no O-acylation was achieved during the synthesis.

6. Pictures

During the course, the students documented all steps of their education. Some were inserted in the regular lab protocols and in the final report as well.

Selected pictures are given bellow:

Picture S2. Mixture of 3-methyl-1-phenyl-1H-pyrazol-5-one and $Ca(OH)_2$ before (left) and after (right) heating.

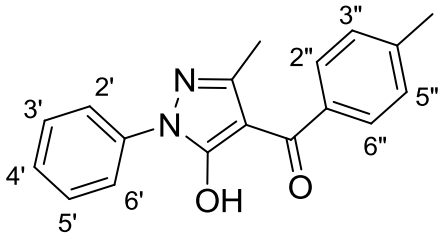
Picture S3. Reaction mixture before (left) and after (right) addition of p-toluoyl chloride.

Picture S4. Crude 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

Picture S5. Crystals of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one grown from acetone (left) and heptane (right) before (up) and after (down) filtration.

Picture S6. Bruker Avance II+ 600 spectrometer.

7. NMR spectra



7.1. 3-Methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one:

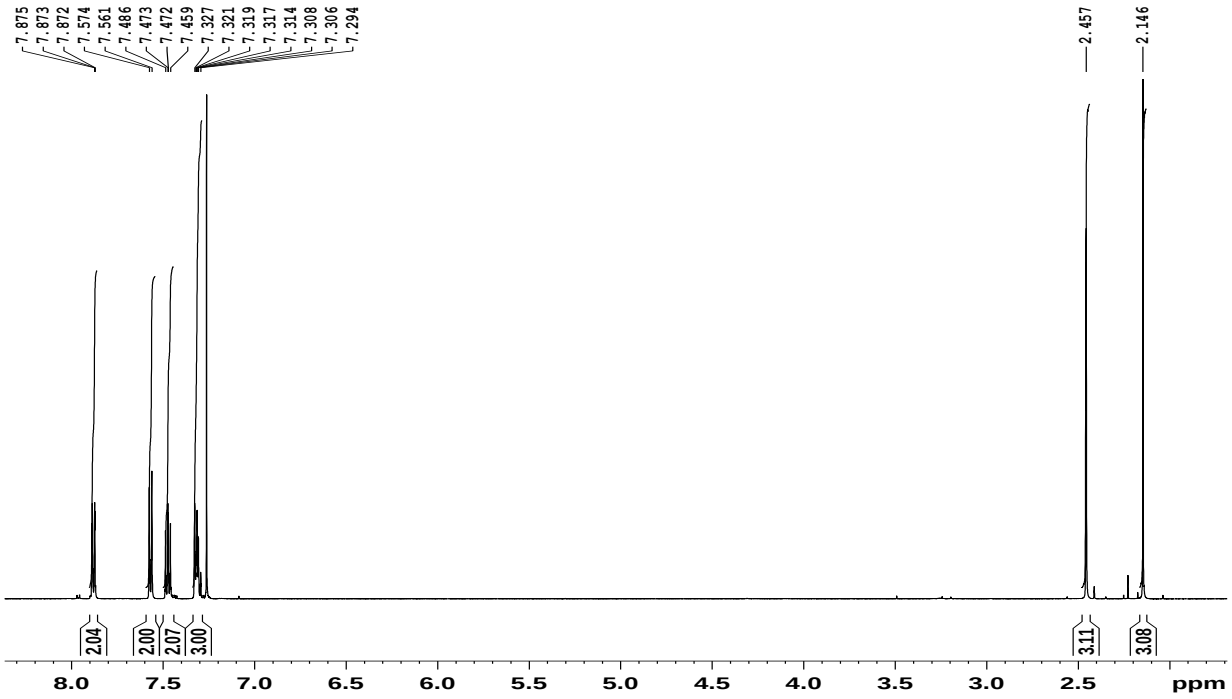


Figure S1. ^{1}H spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

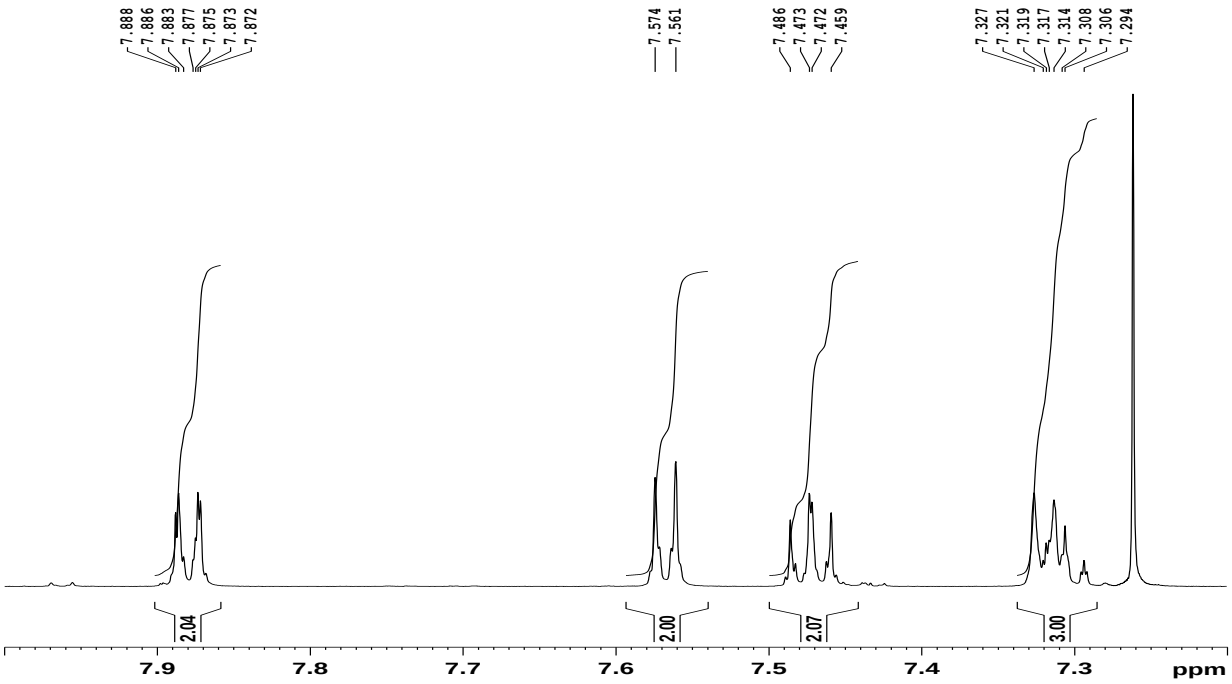


Figure S2. The aromatic area of ^{1}H spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

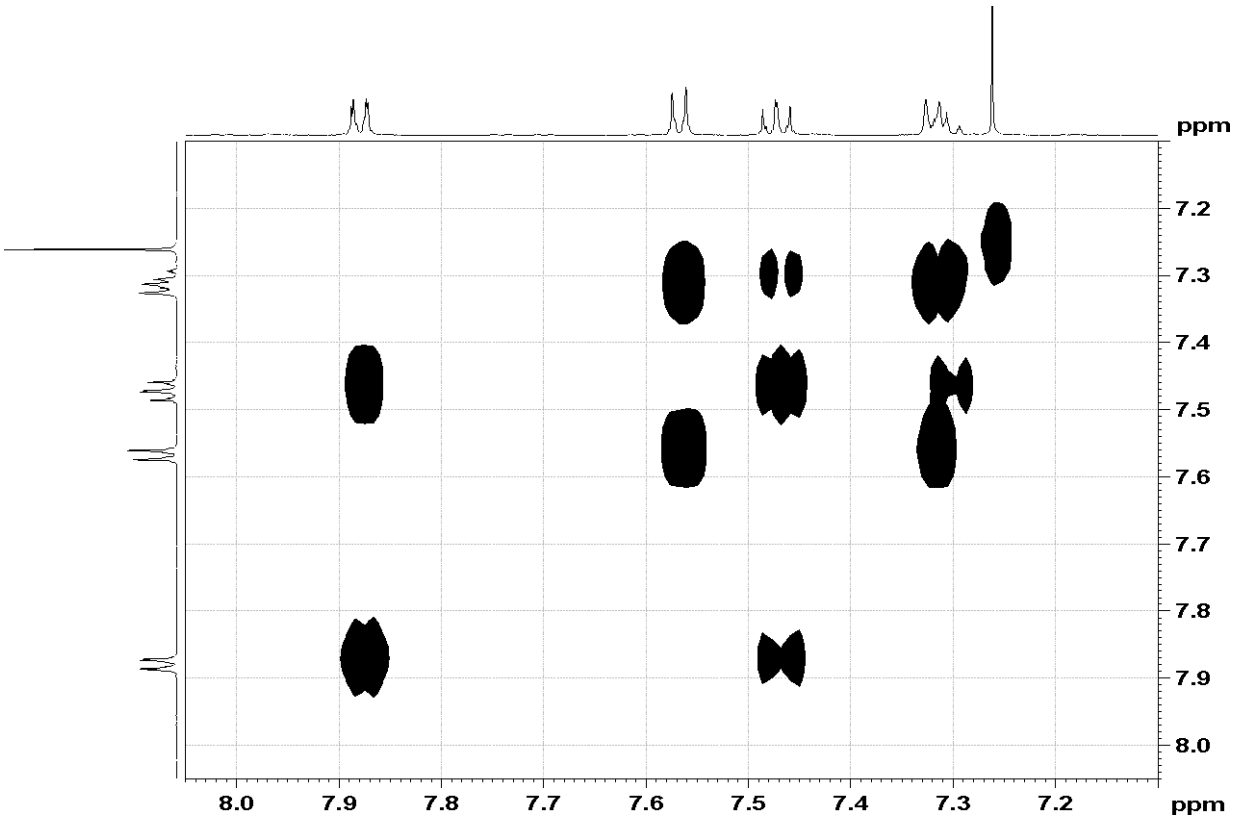


Figure S3. ^{1}H-^{1}H COSY spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

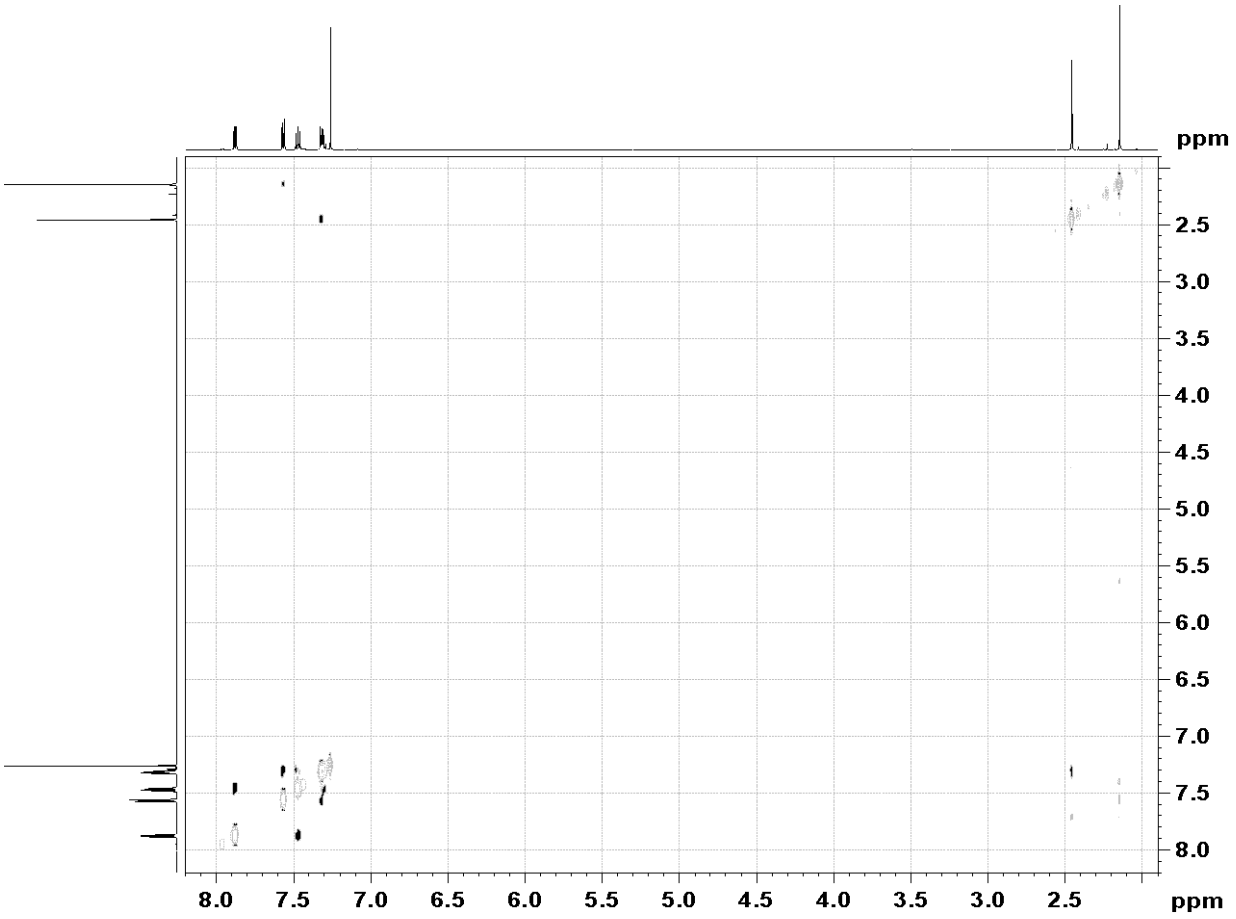


Figure S4. ^{1}H-^{1}H NOESY spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

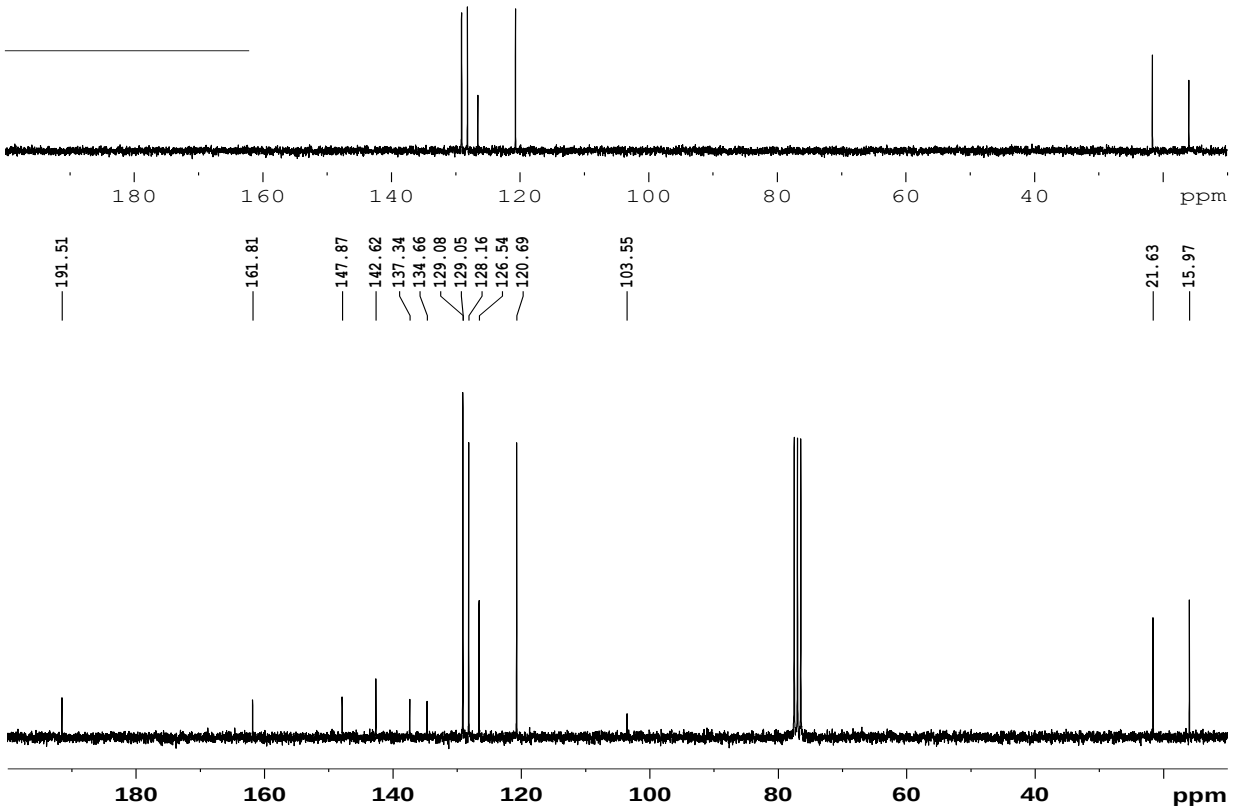


Figure S5. ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

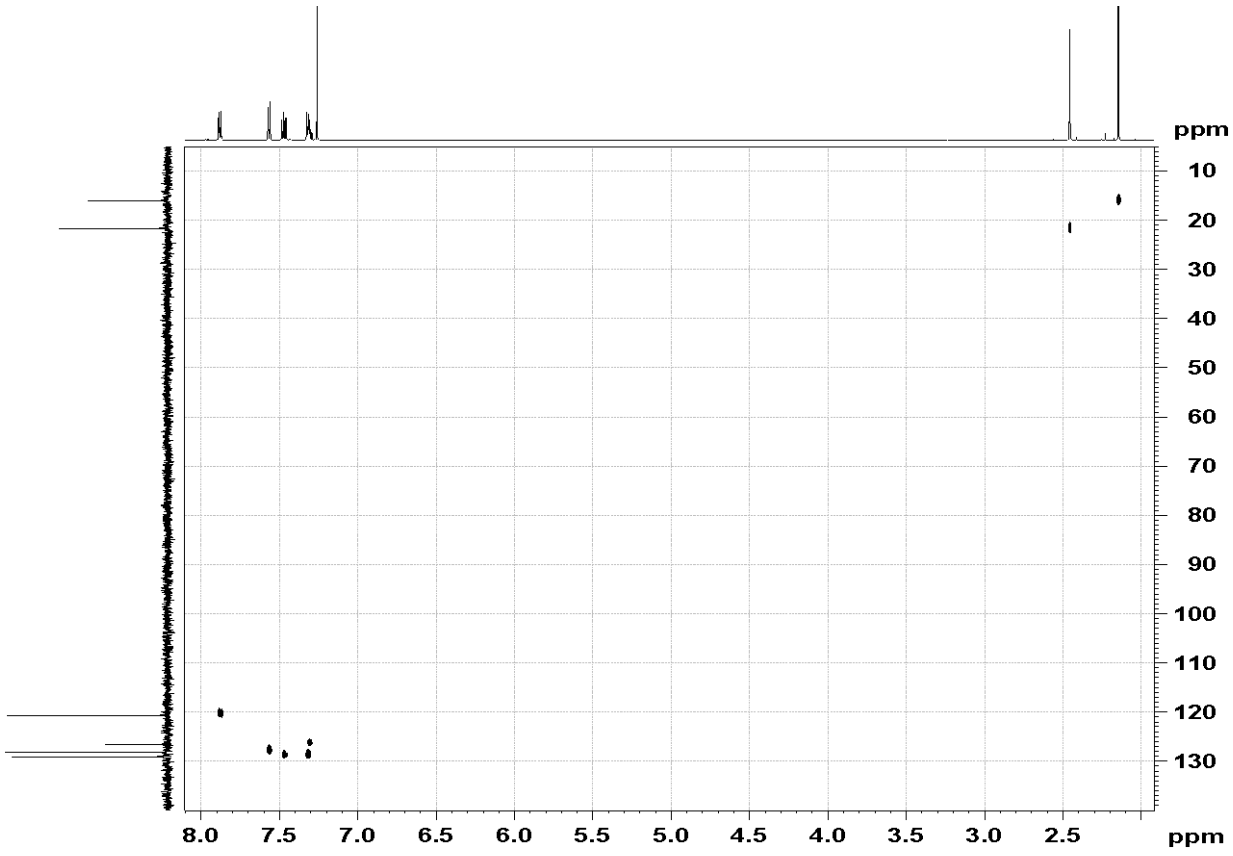


Figure S6. ^{1}H-^{13}C HSQC spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

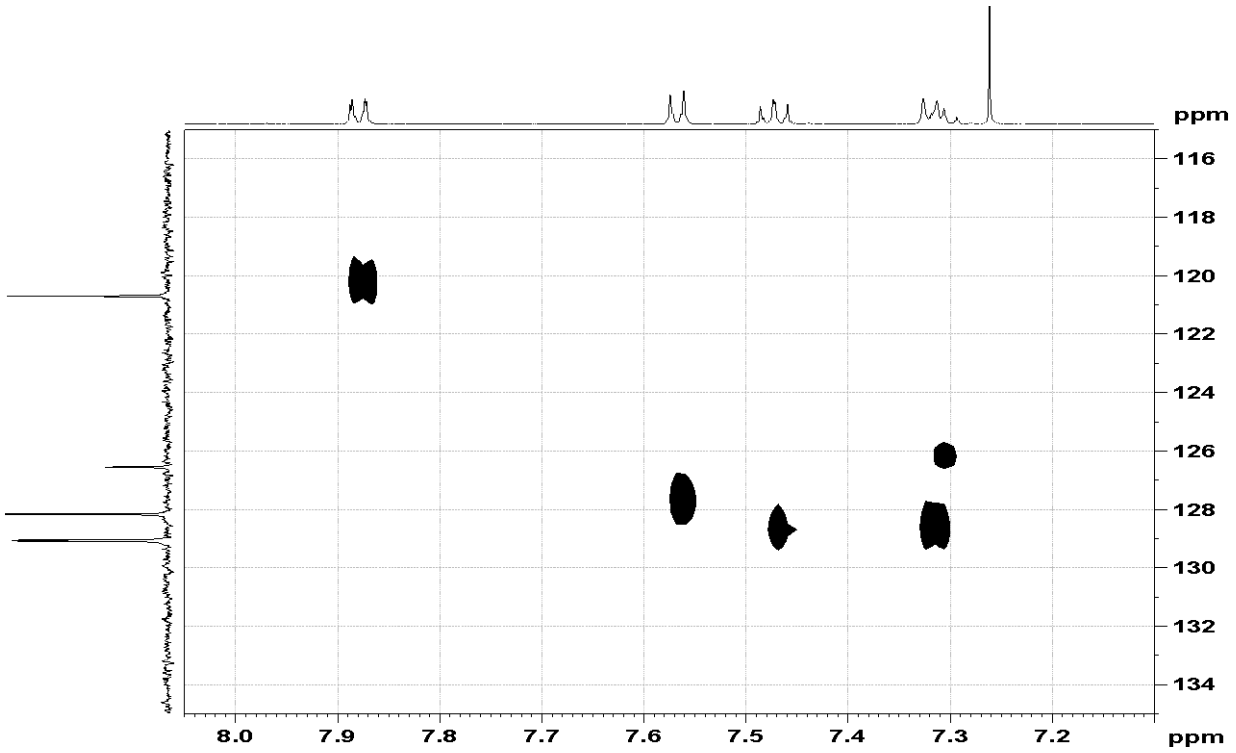


Figure S7. The aromatic area of ^{1}H-^{13}C HSQC spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

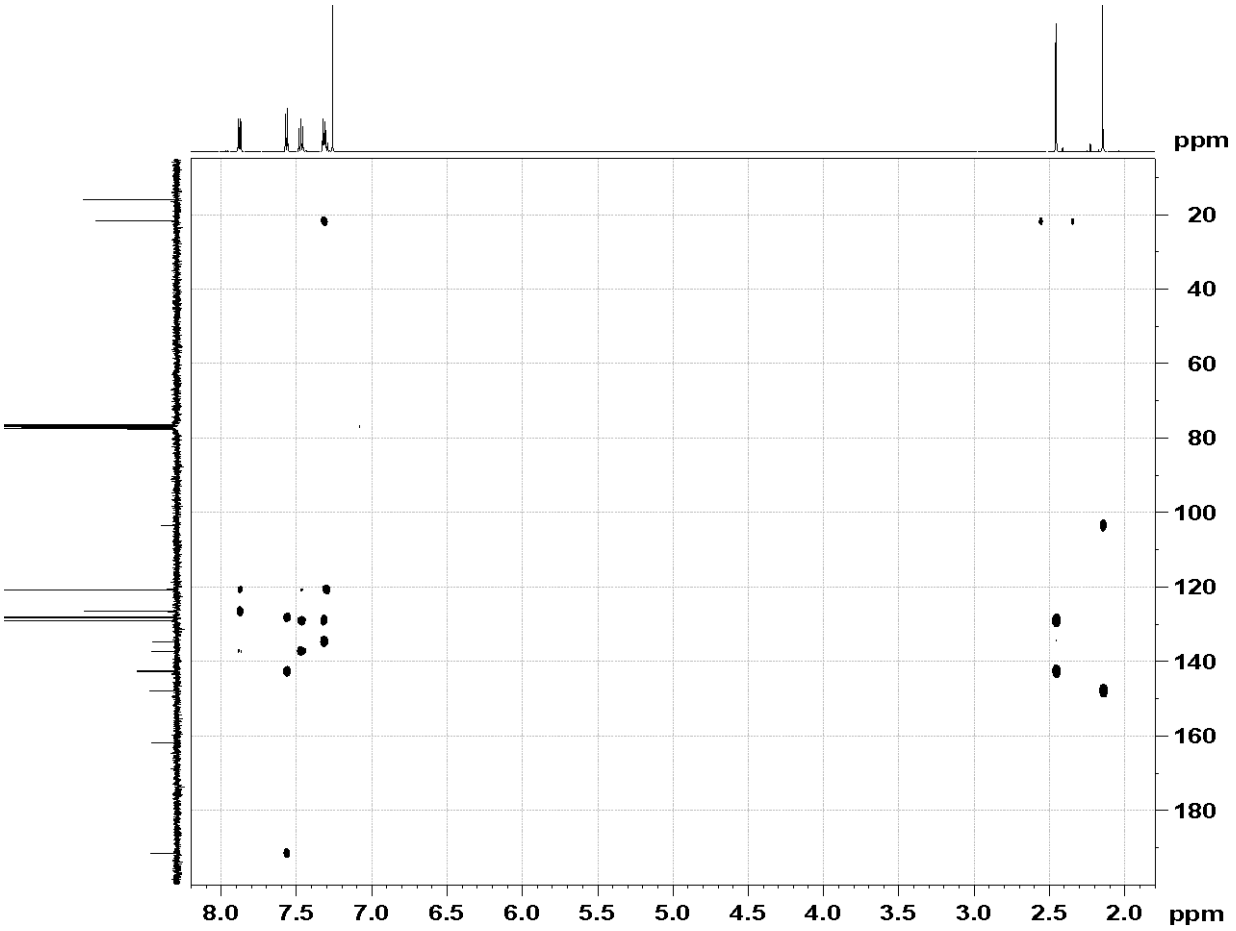


Figure S8. ^{1}H-^{13}C HMBC spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

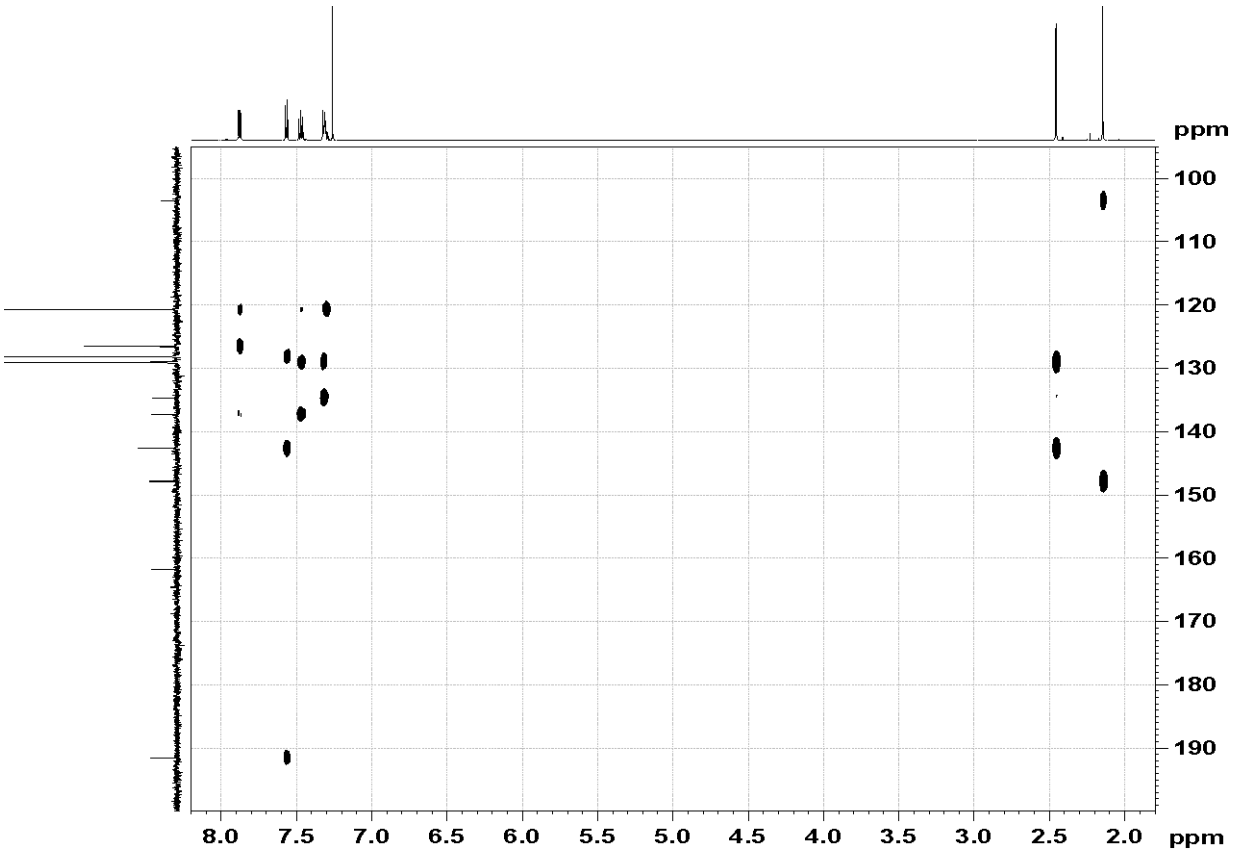


Figure S9. Partial ^{1}H-^{13}C HMBC spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.

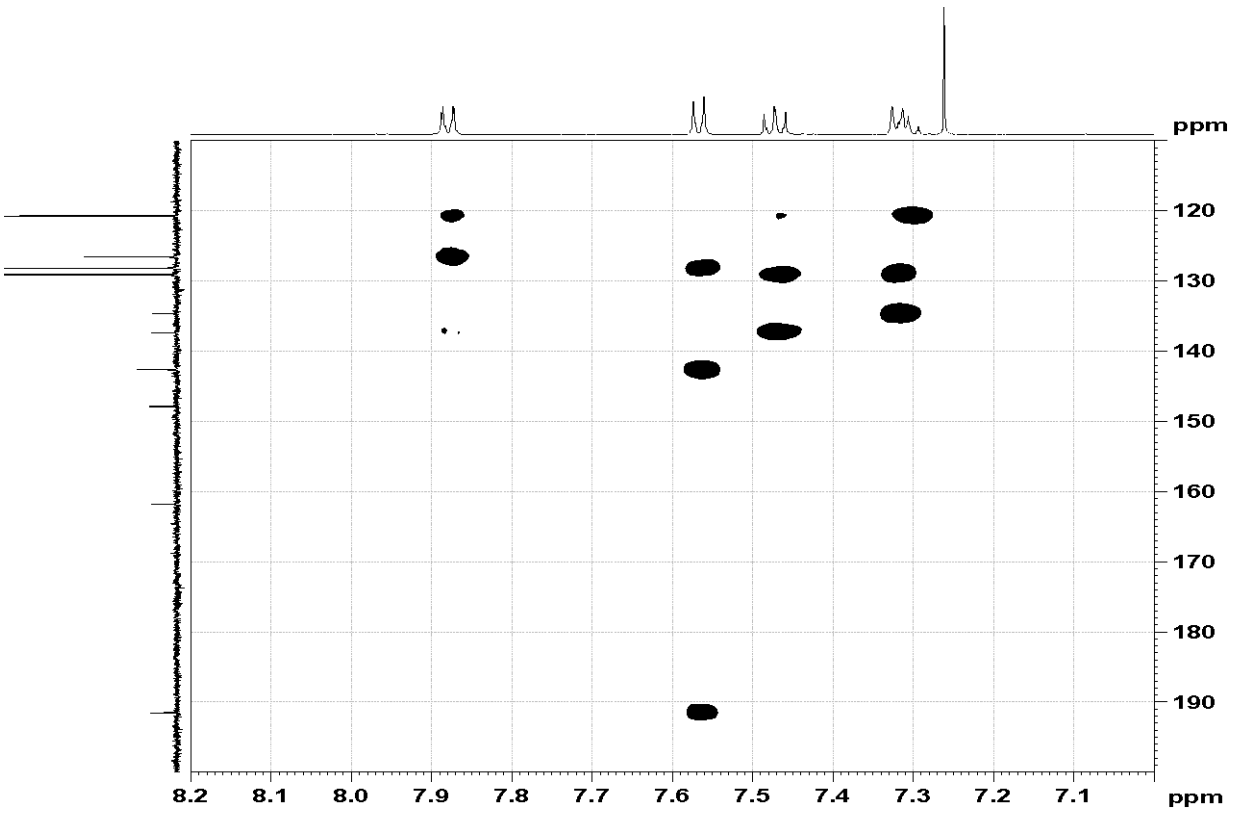
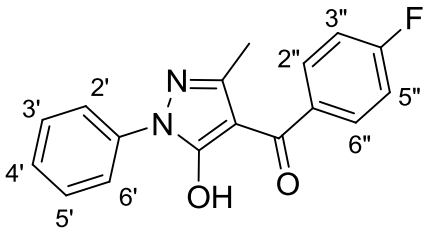


Figure S10. The aromatic area of ^{1}H-^{13}C HMBC spectrum of 3-methyl-4-(4-methylbenzoyl)-1-phenyl-pyrazol-5-one.



7.2. 4-(4-Fluorobenzoyl)-3-methyl-1-phenyl-pyrazol-5-one:

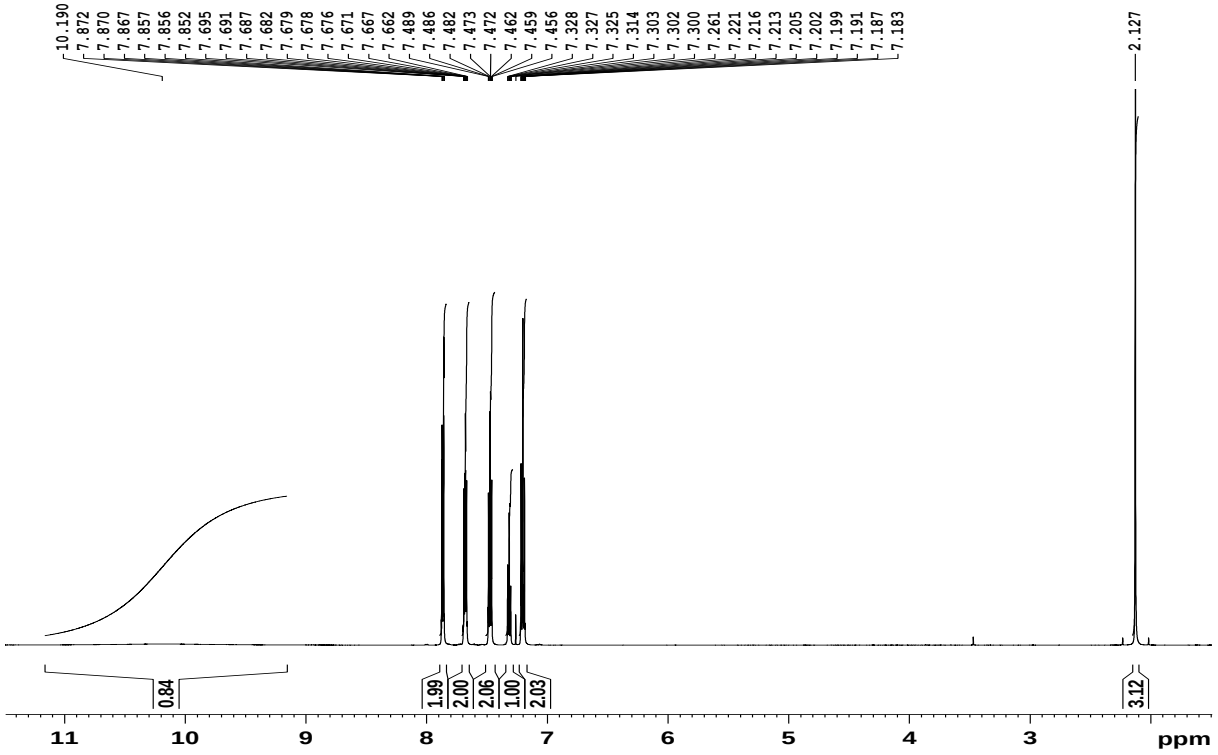


Figure S11. ^{1}H spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

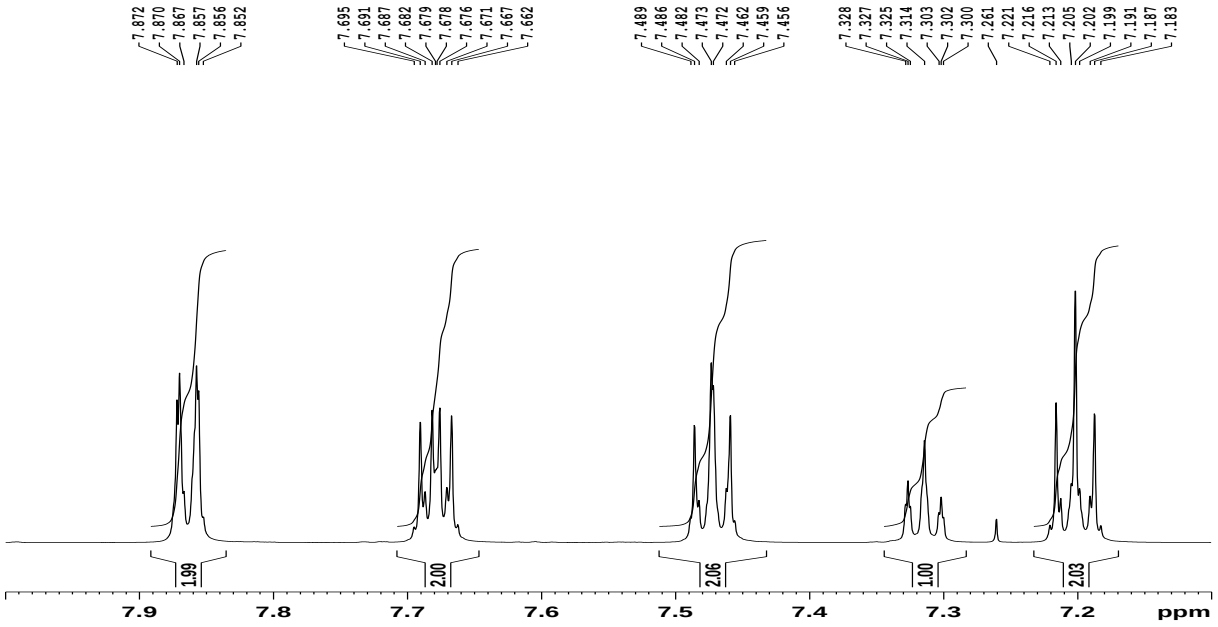


Figure S12. The aromatic area of ^{1}H spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

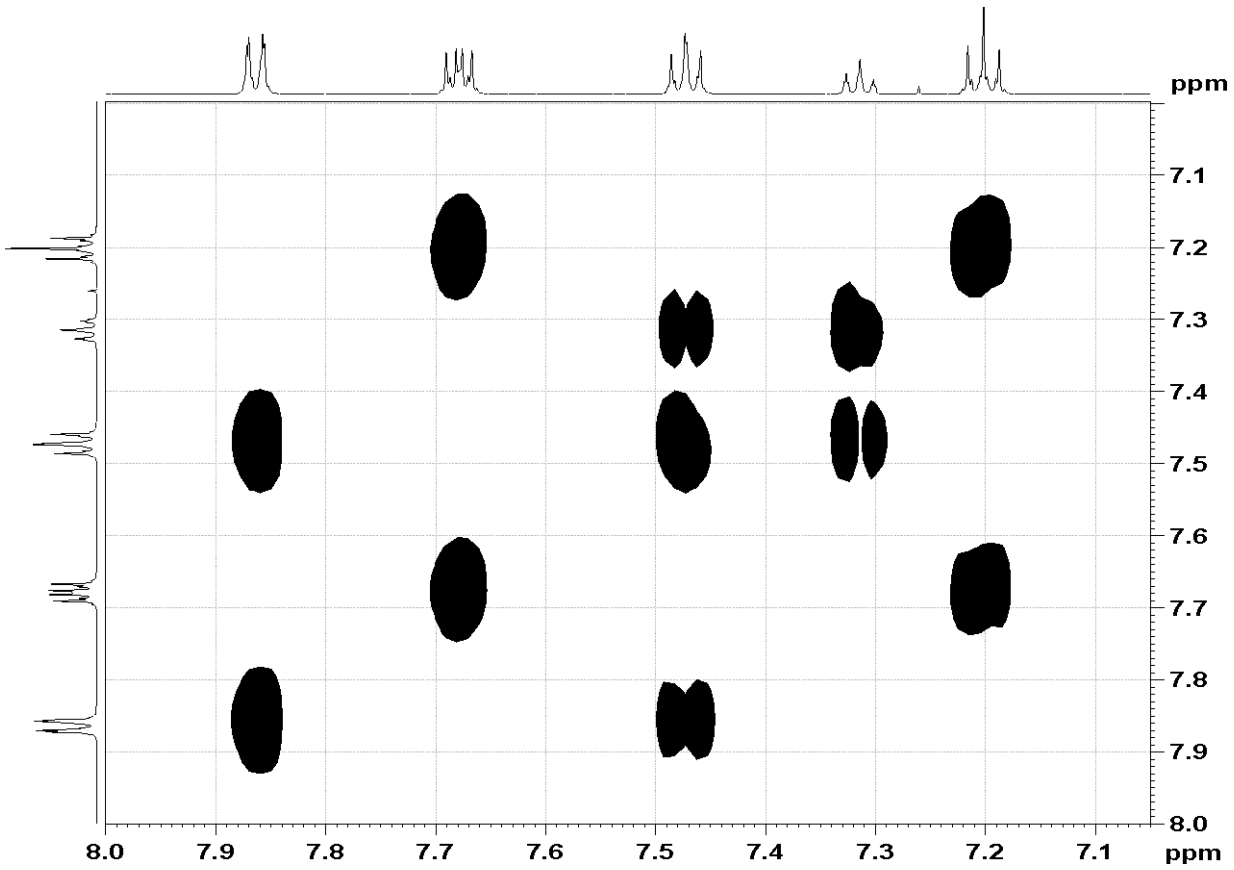


Figure S13. ^{1}H-^{1}H COSY spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

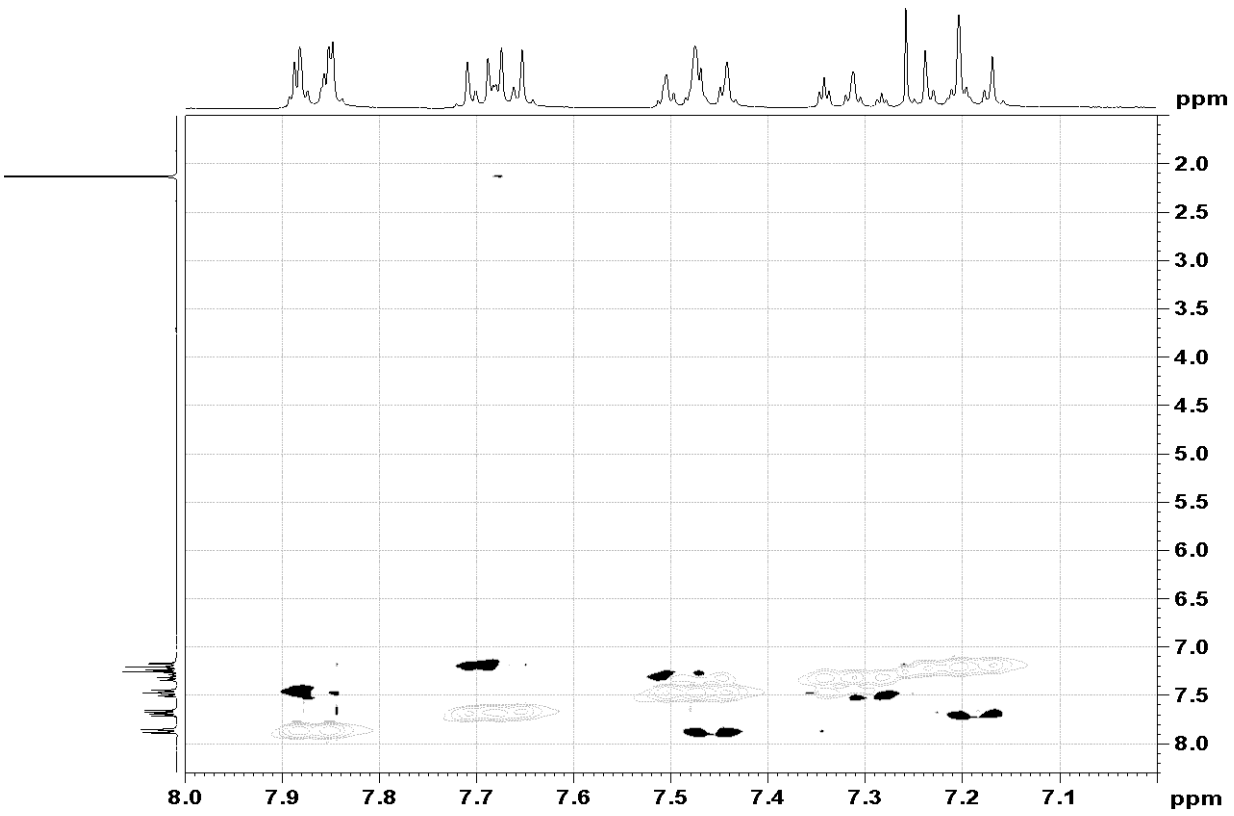


Figure S14. ^{1}H-^{1}H NOESY spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

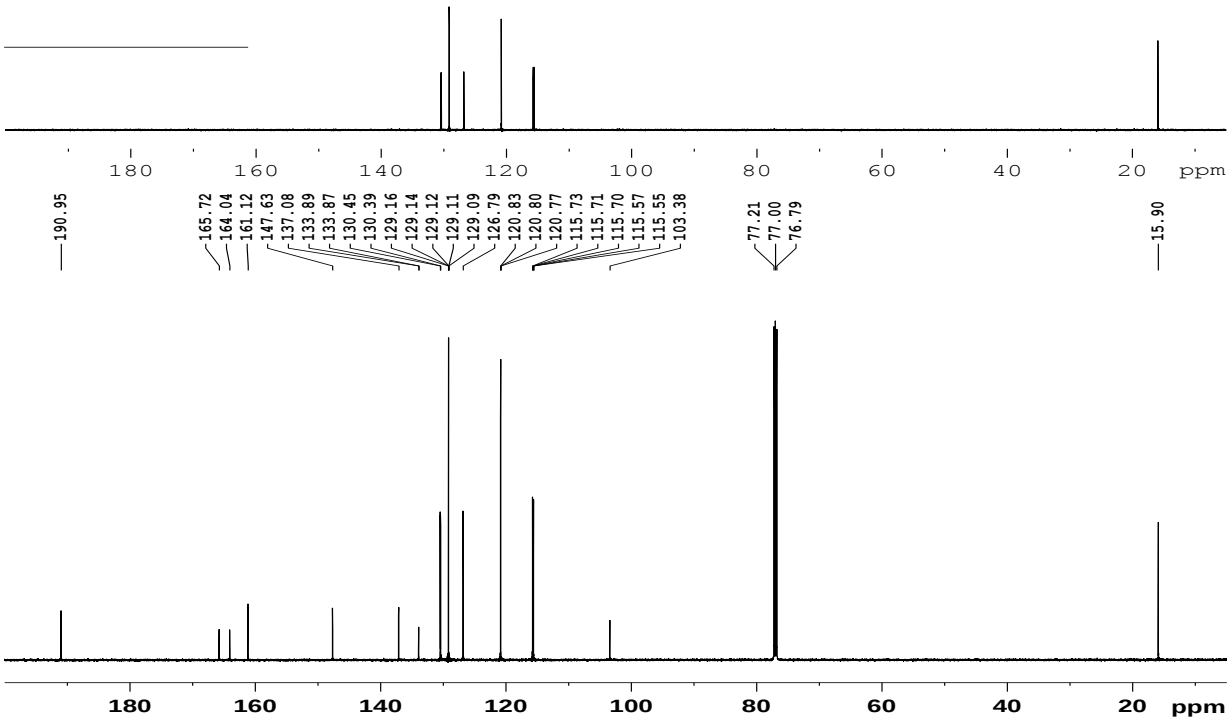


Figure S15. ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

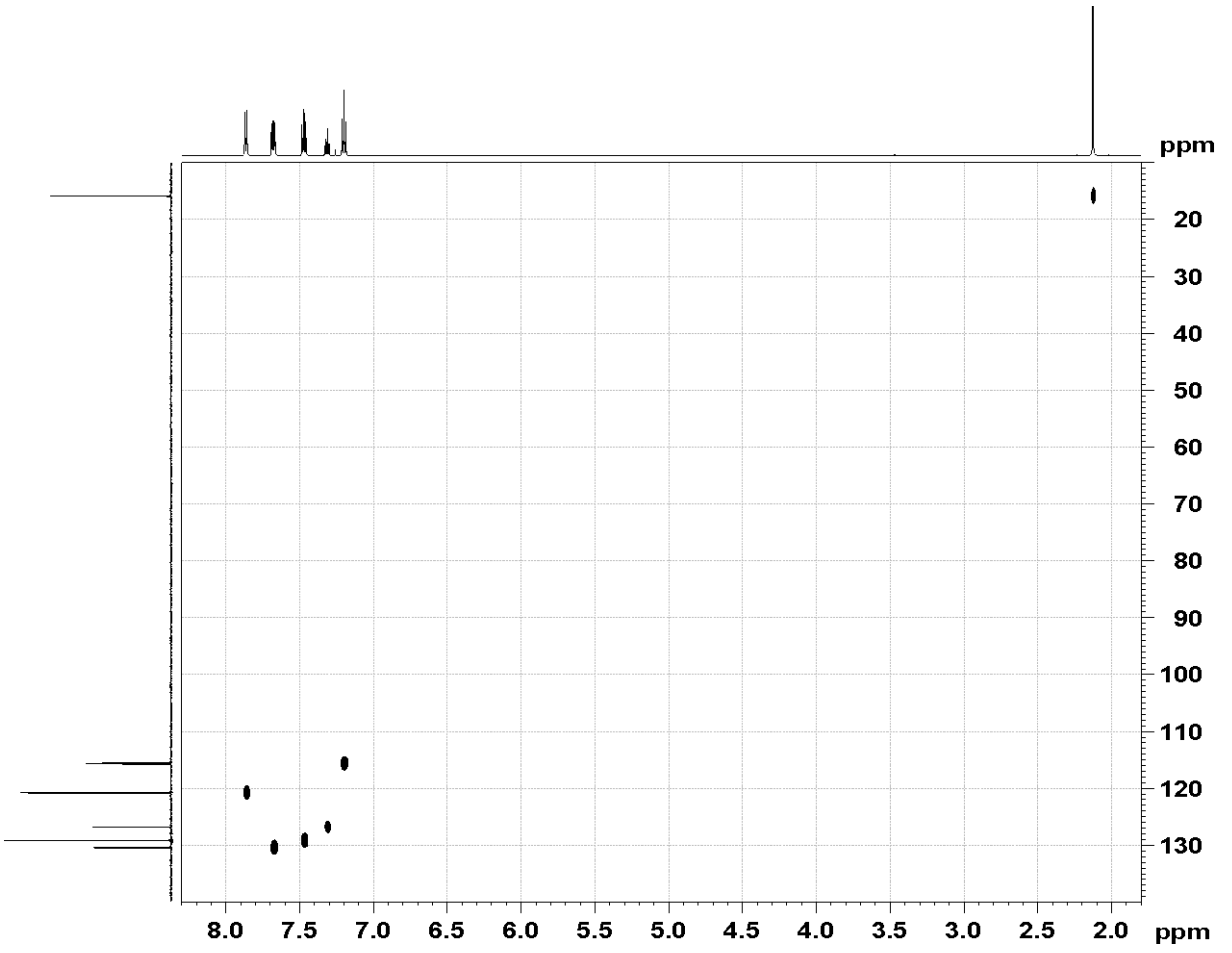


Figure S16. ^{1}H-^{13}C HSQC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

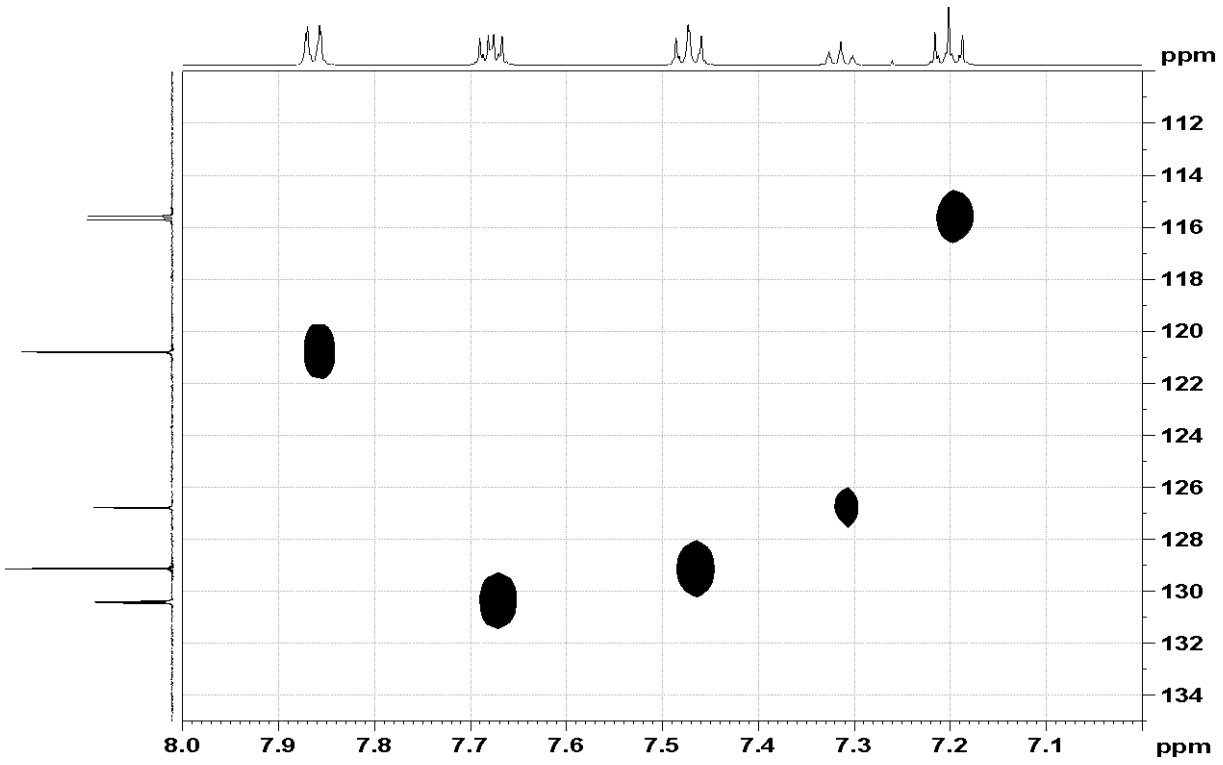


Figure S17. The aromatic area of ^{1}H-^{13}C HSQC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

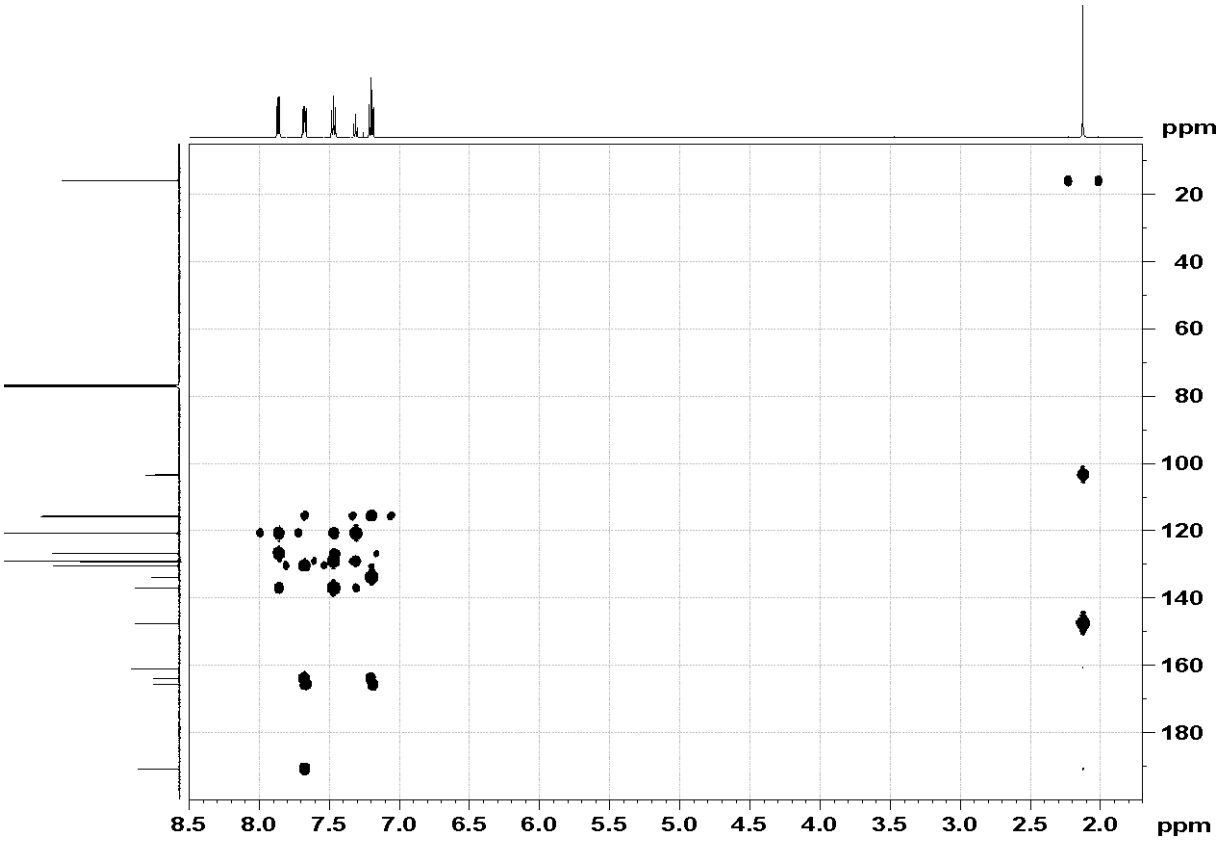


Figure S18. ^{1}H-^{13}C HMBC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

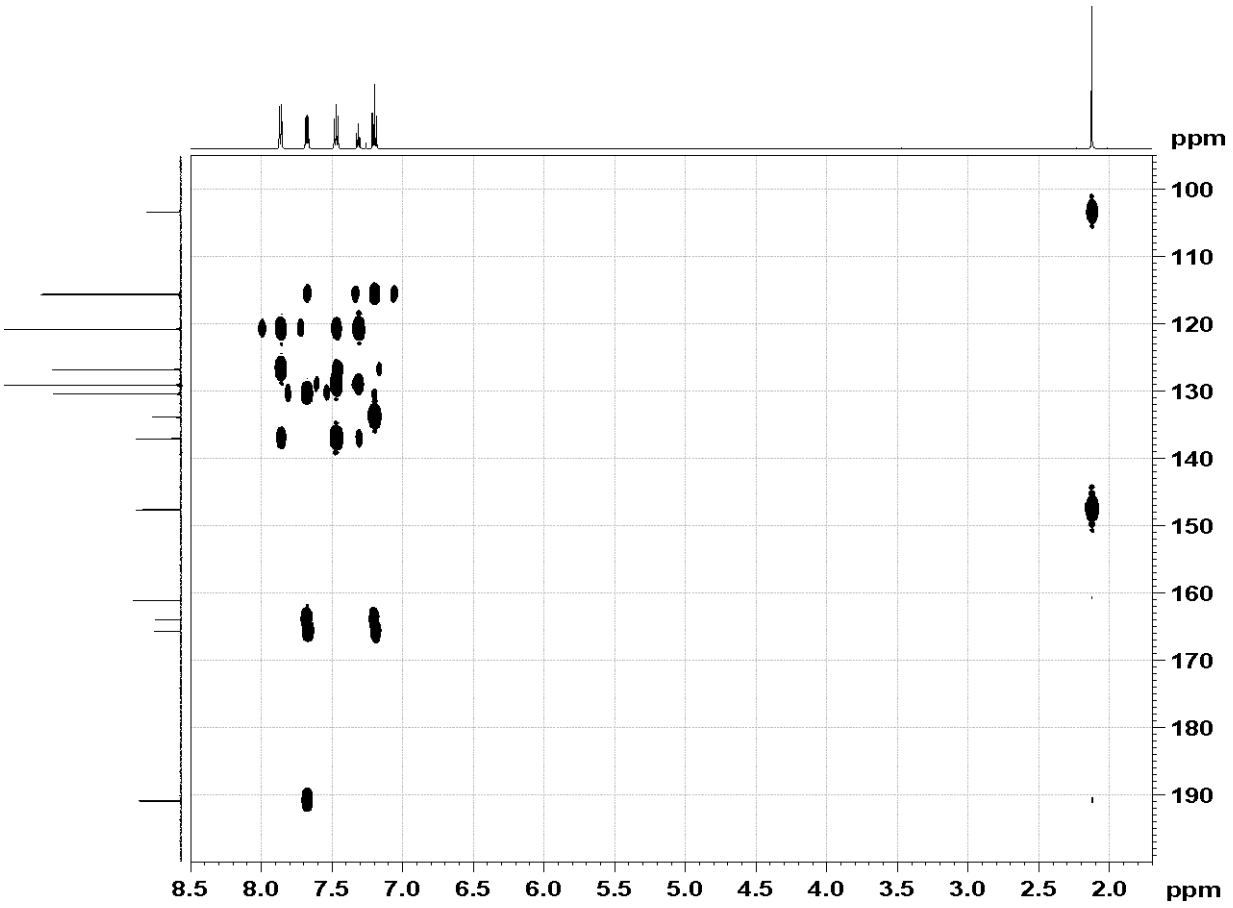


Figure S19. Partial ^{1}H-^{13}C HMBC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.

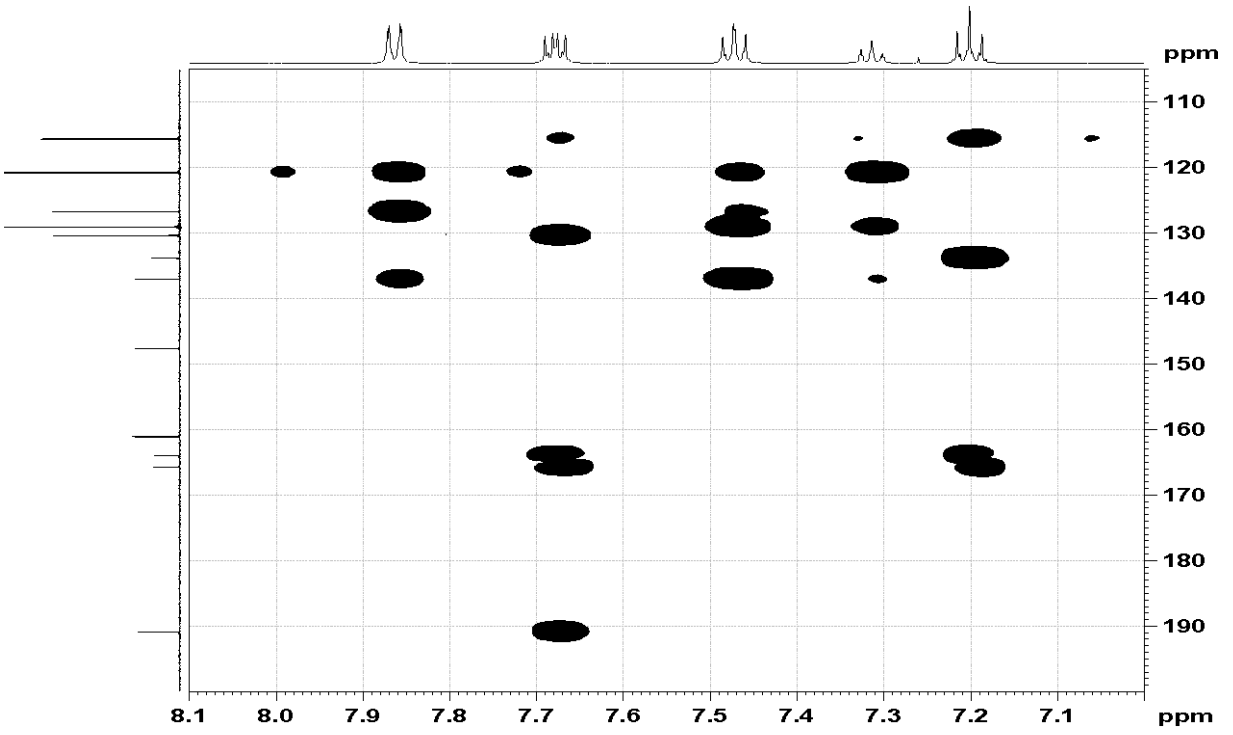
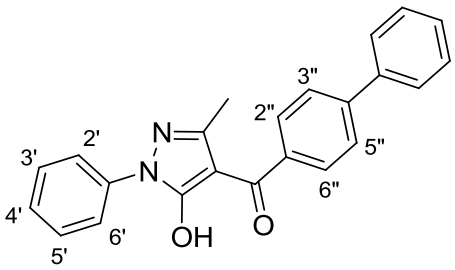


Figure S20. The aromatic area of ^{1}H-^{13}C HMBC spectrum of 3-methyl-4-(4-fluorobenzoyl)-1-phenyl-pyrazol-5-one.



7.3. ***3-Methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one***

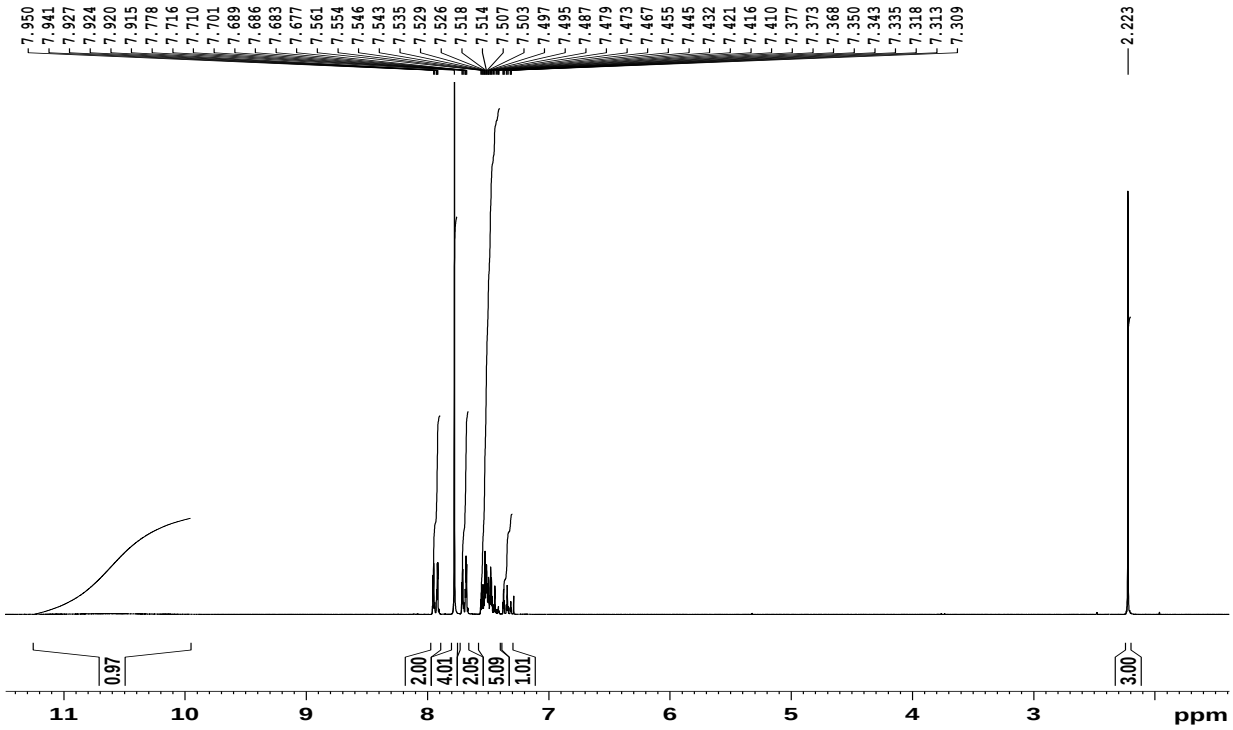


Figure S21. ^{1}H spectrum of 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one.

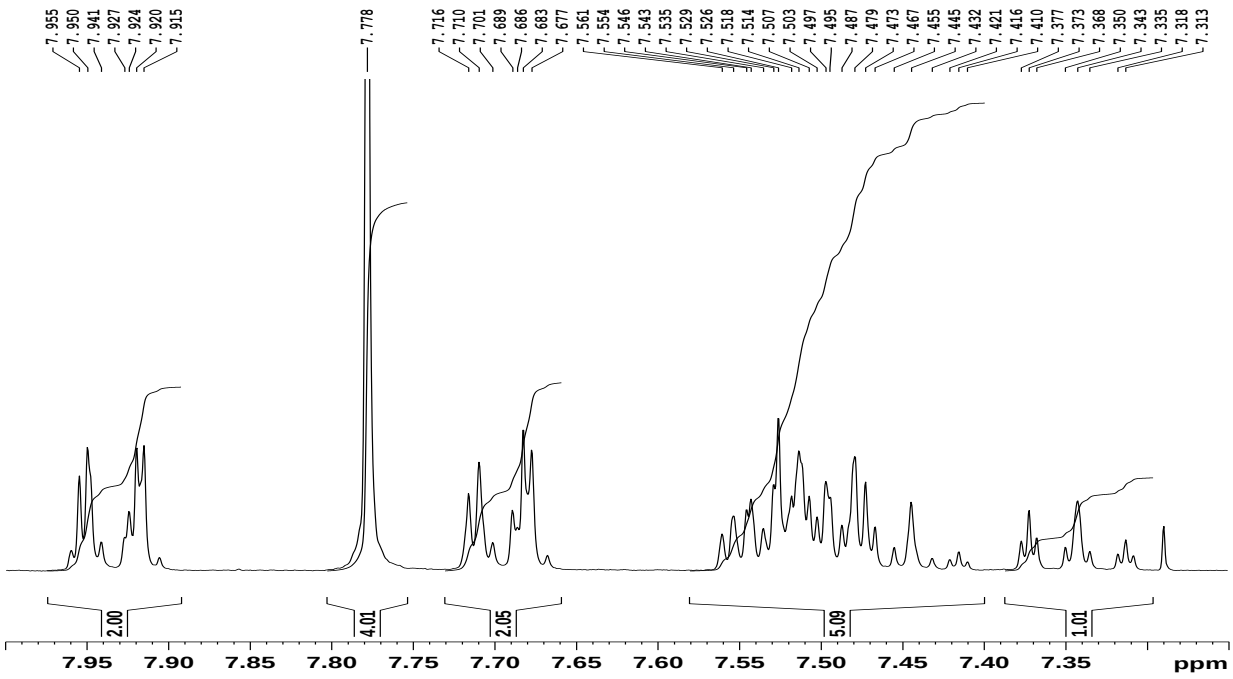


Figure S22. The aromatic area of ^{1}H spectrum of 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one.

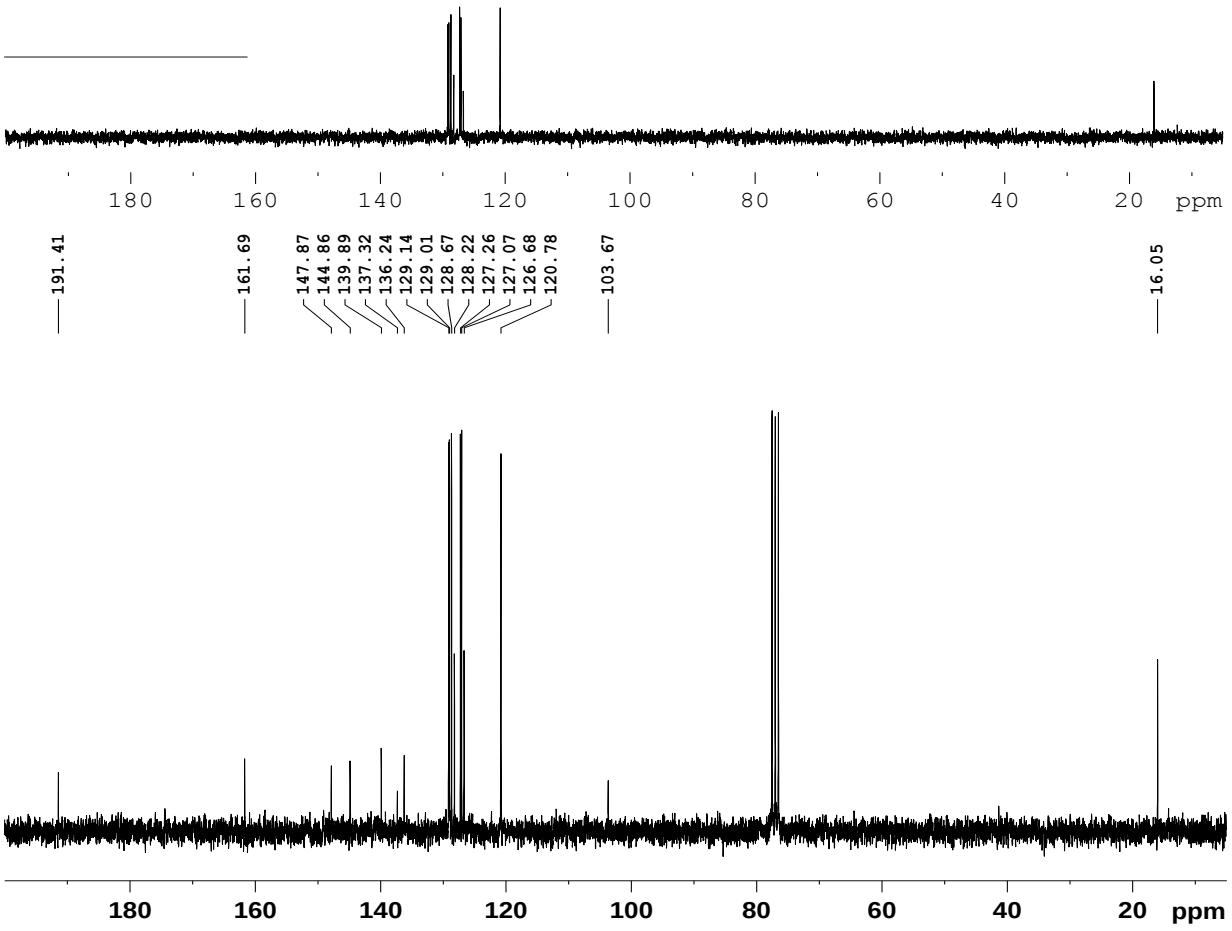


Figure S23. ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one.

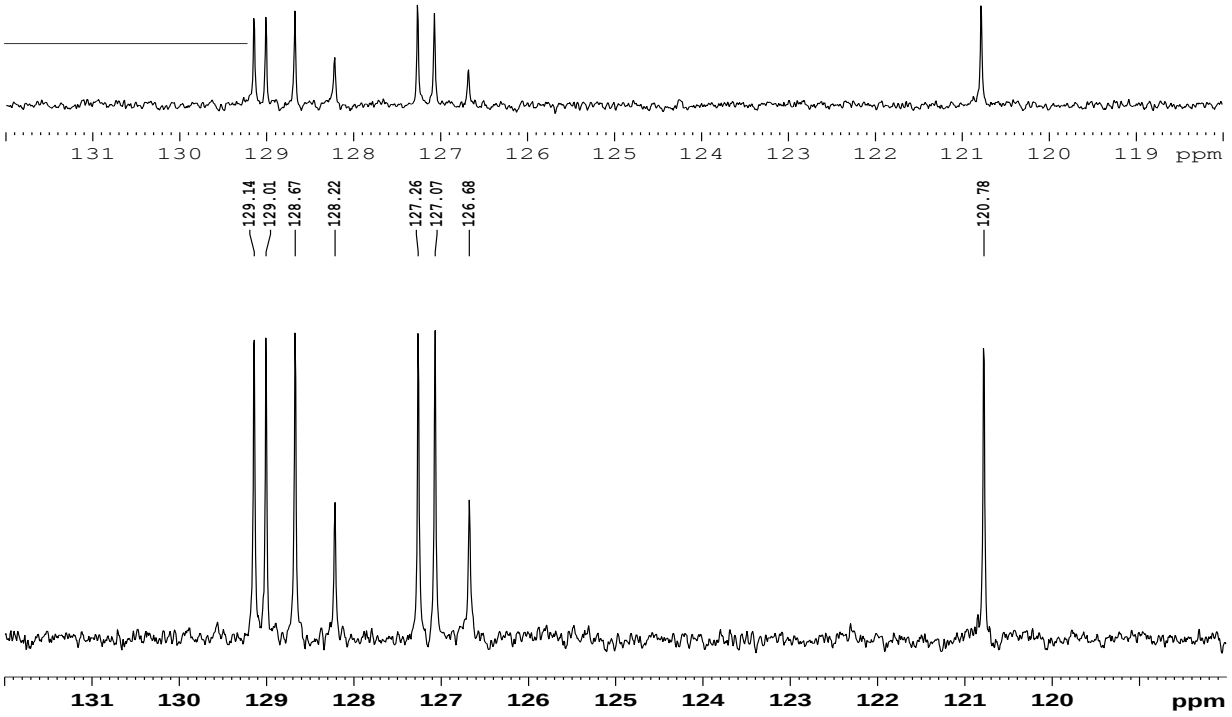
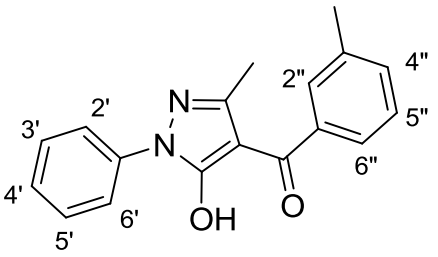


Figure S24. The aromatic area of ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-4-(4-phenylbenzoyl)-1-phenyl-pyrazol-5-one.



7.4. ***3-Methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one***

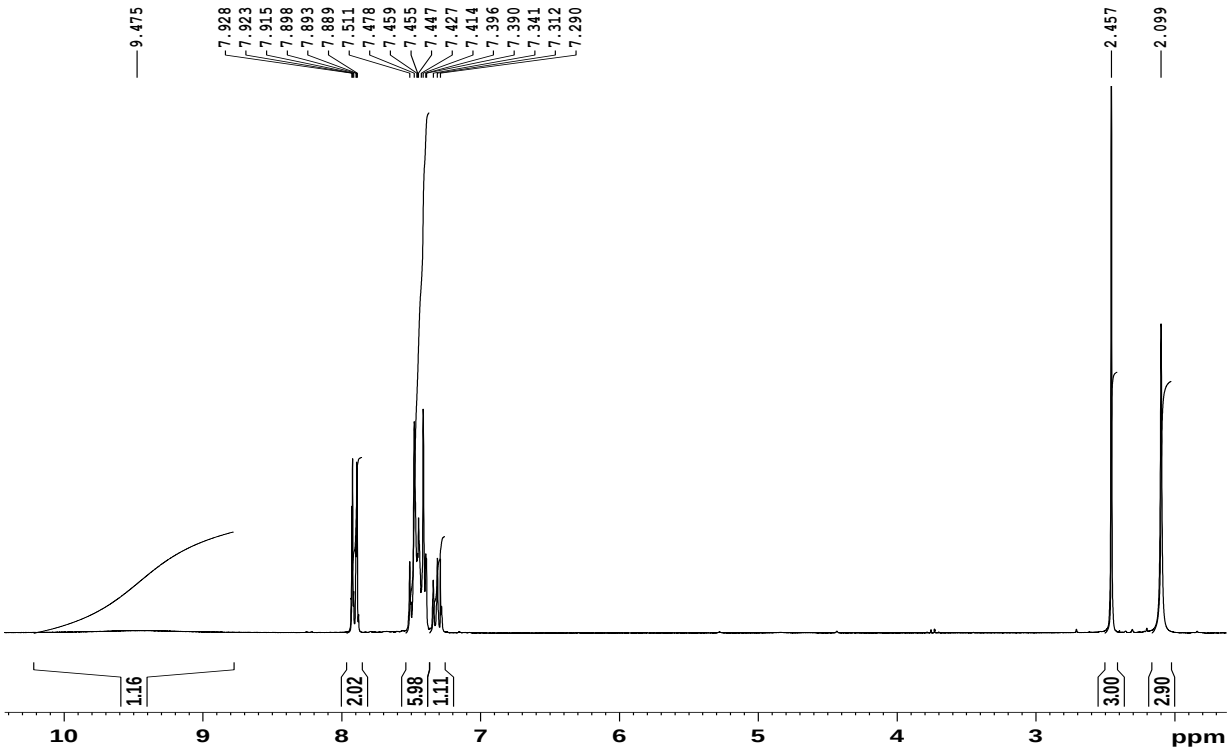


Figure S25. ^{1}H spectrum of 3-methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one.

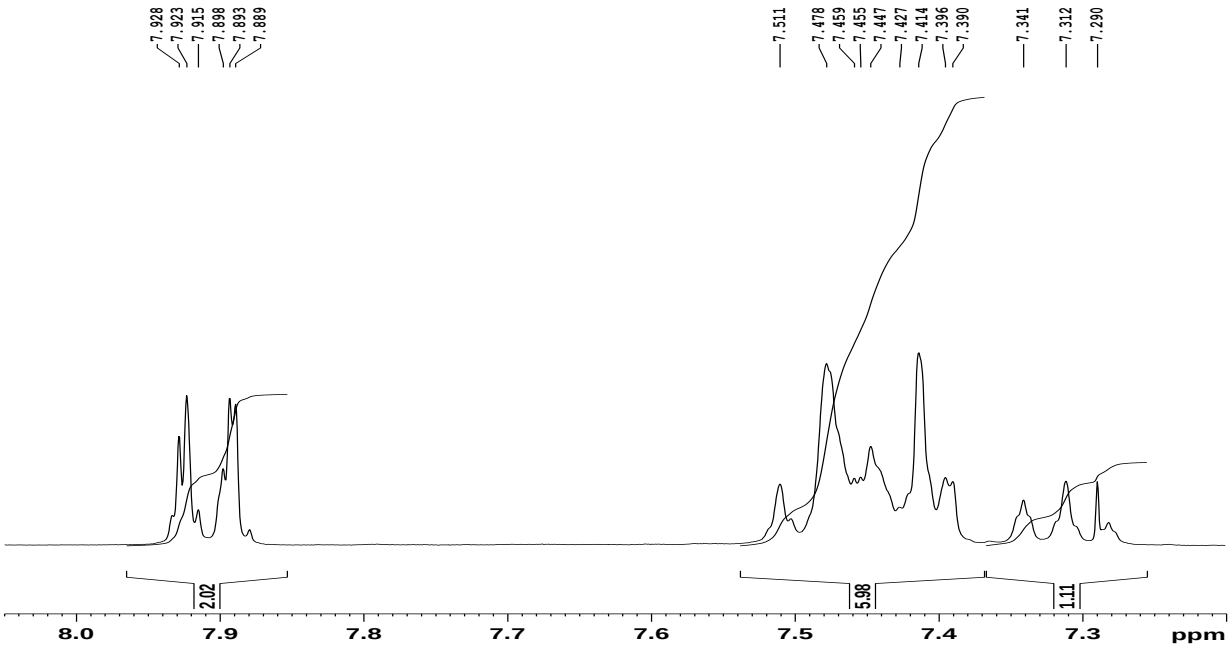


Figure S26. The aromatic area of ^{1}H spectrum of 3-methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one.

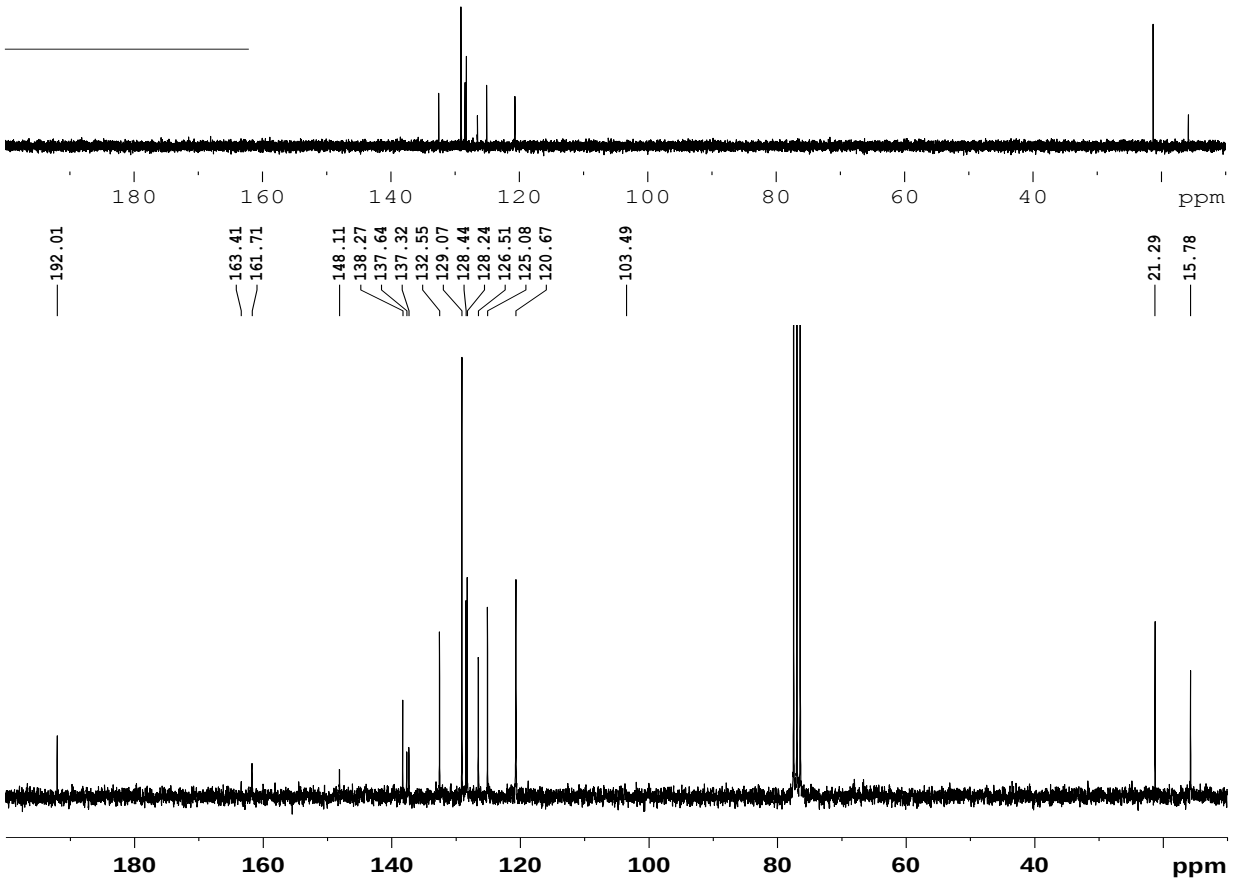


Figure S27. ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one.

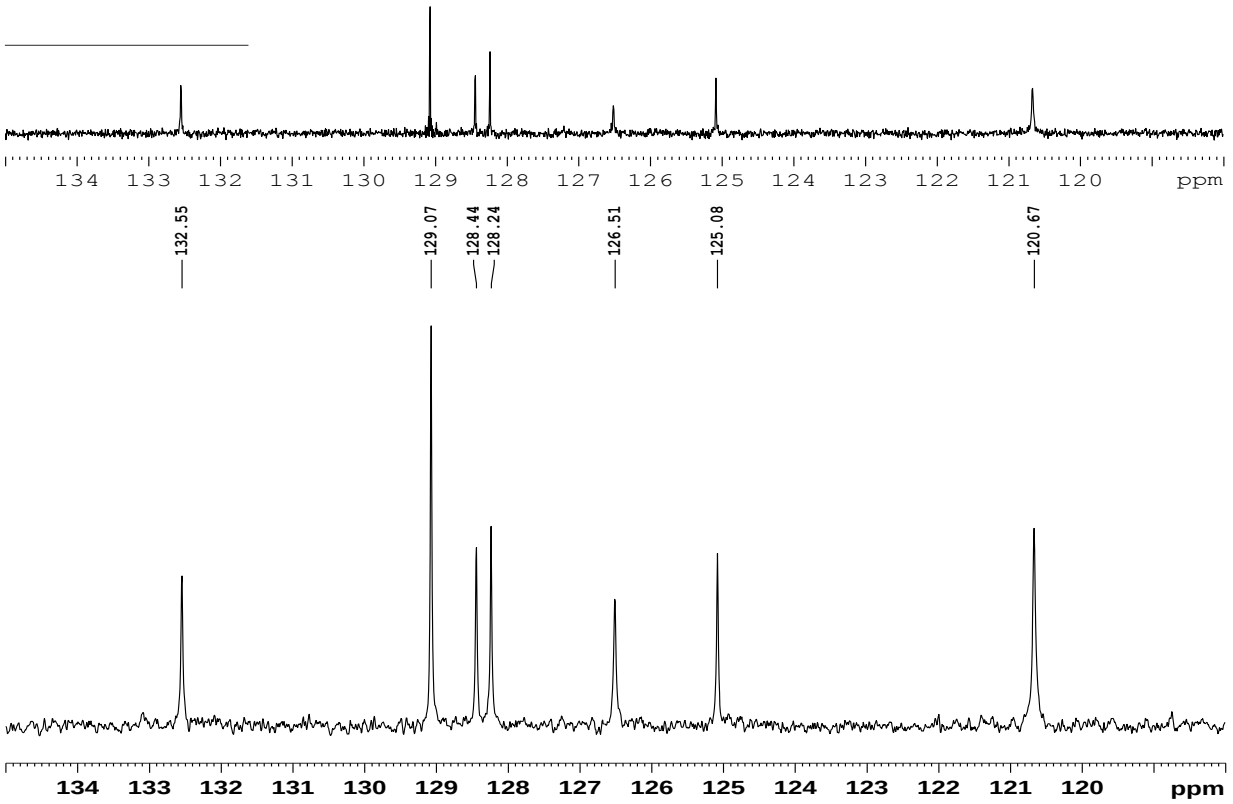
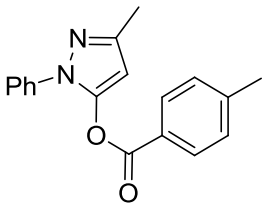


Figure S28. The aromatic area of ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-4-(3-methylbenzoyl)-1-phenyl-pyrazol-5-one.



7.5. 3-Methyl-1-phenyl-1H-pyrazol-5-yl 4-methylbenzoate

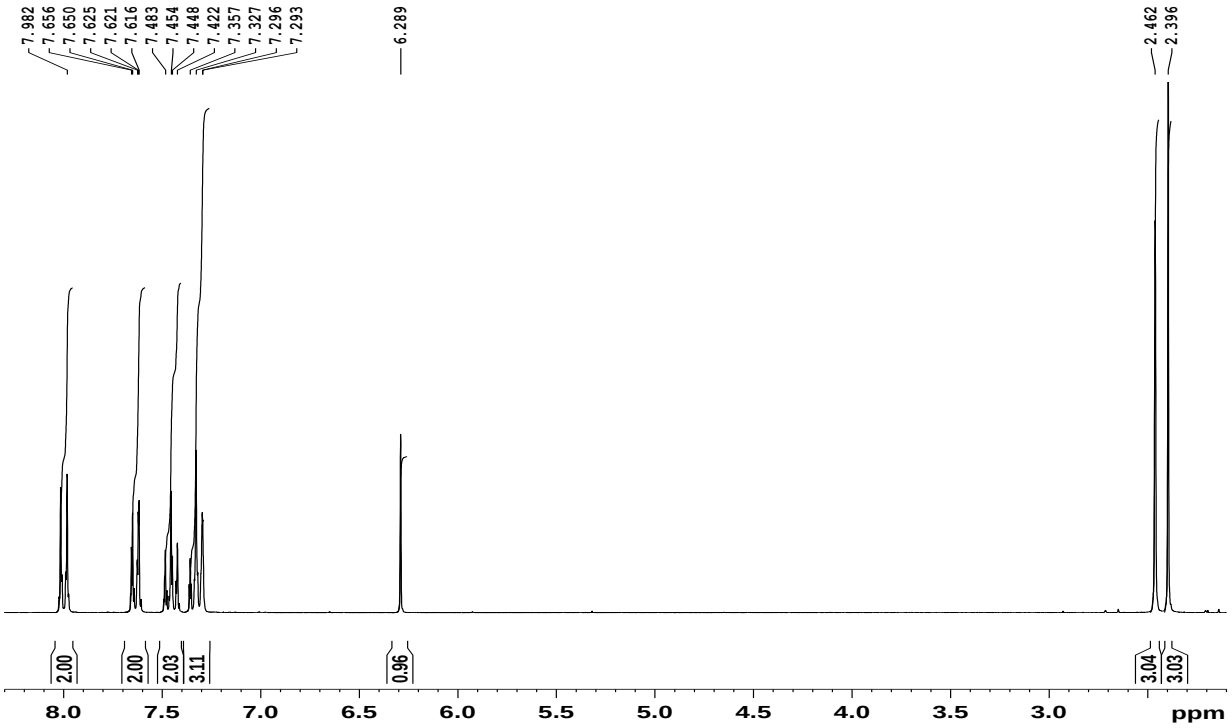


Figure S29. ^{1}H spectrum of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-methylbenzoate.

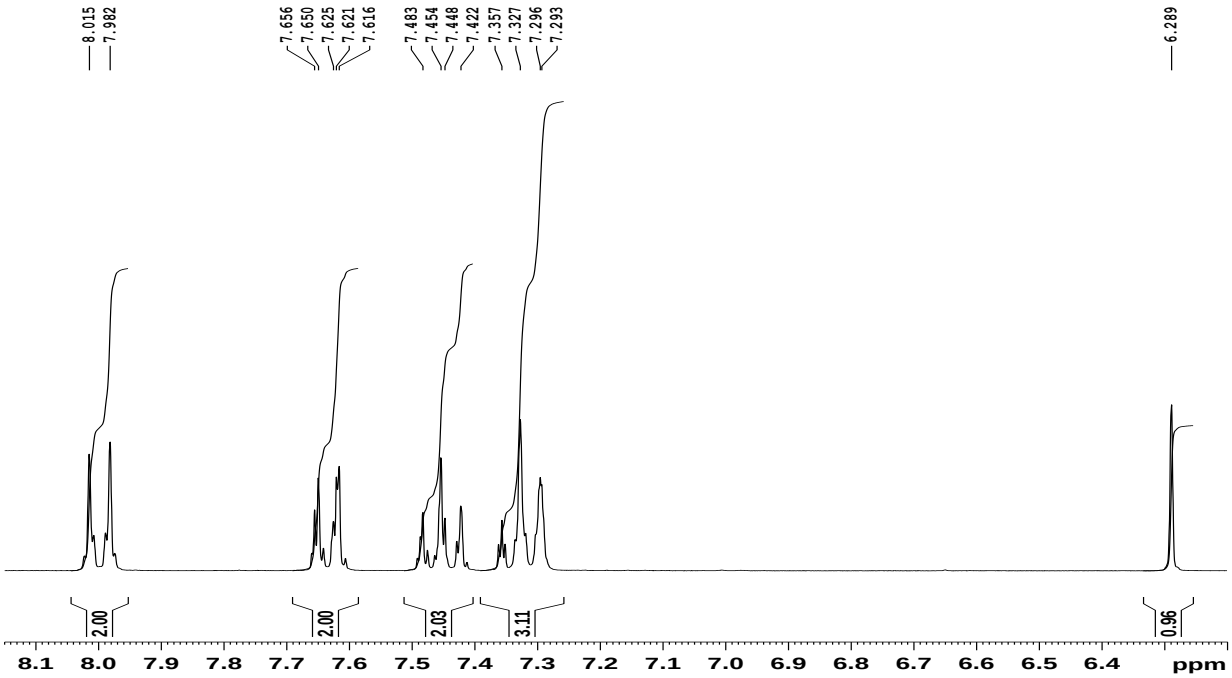


Figure S30. The aromatic area of ^{1}H spectrum of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-methylbenzoate.

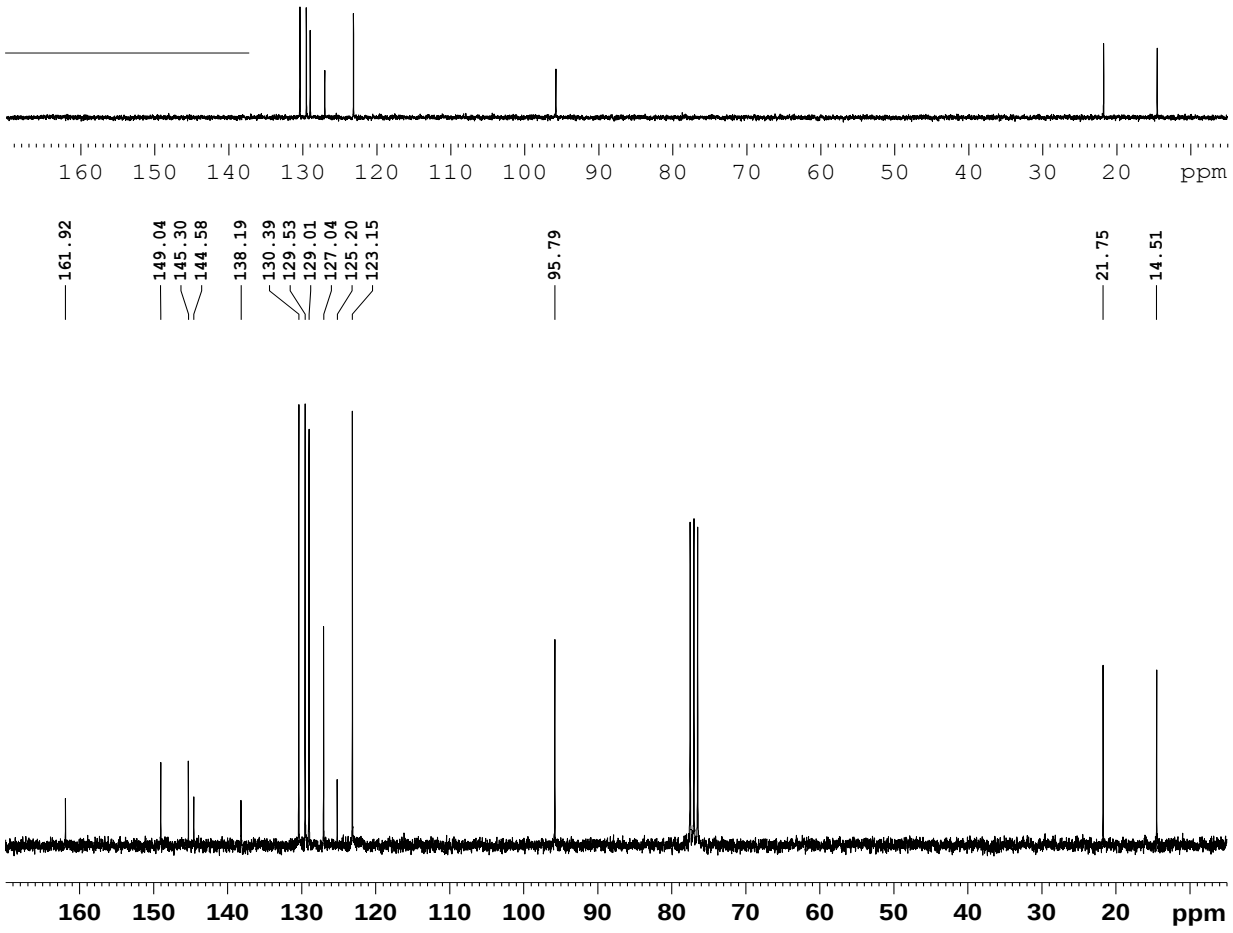


Figure S31. ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-methylbenzoate.

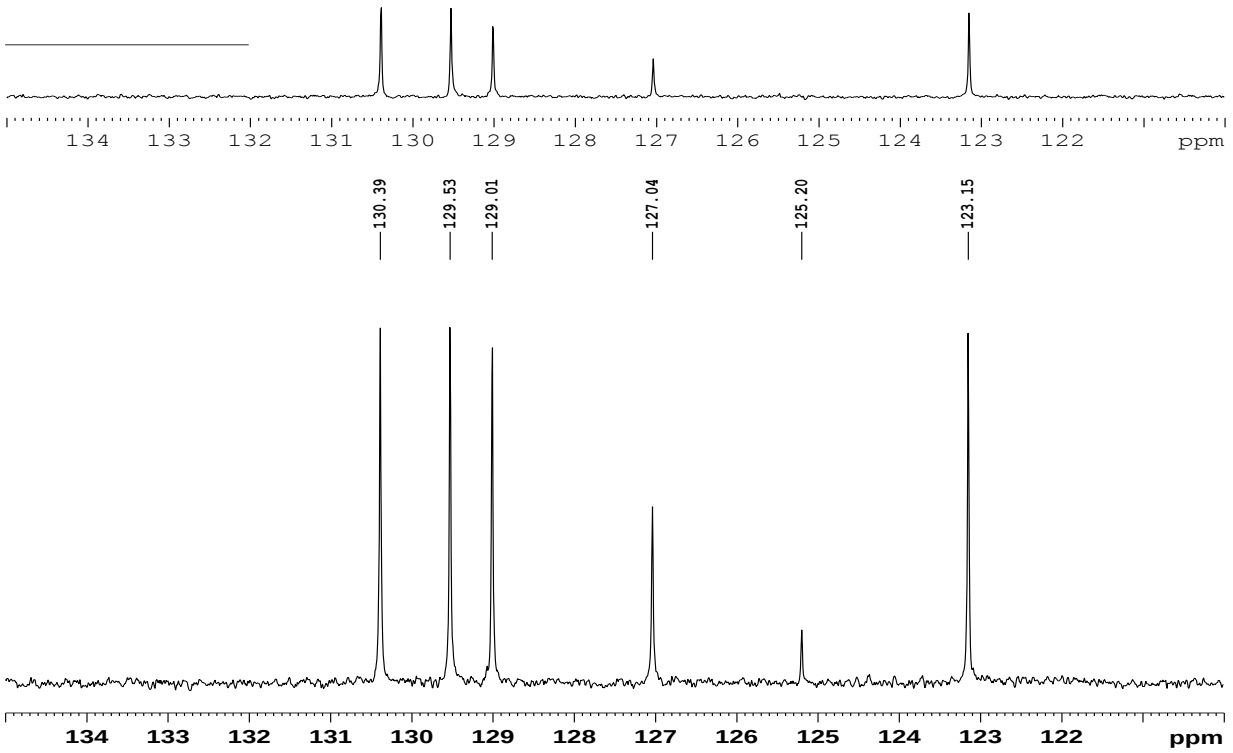
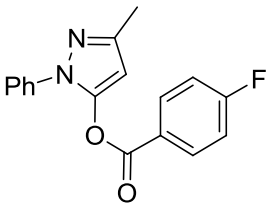


Figure S32. The aromatic area of ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-methylbenzoate.



7.6. 3-Methyl-1-phenyl-1H-pyrazol-5-yl 4-fluorobenzoate

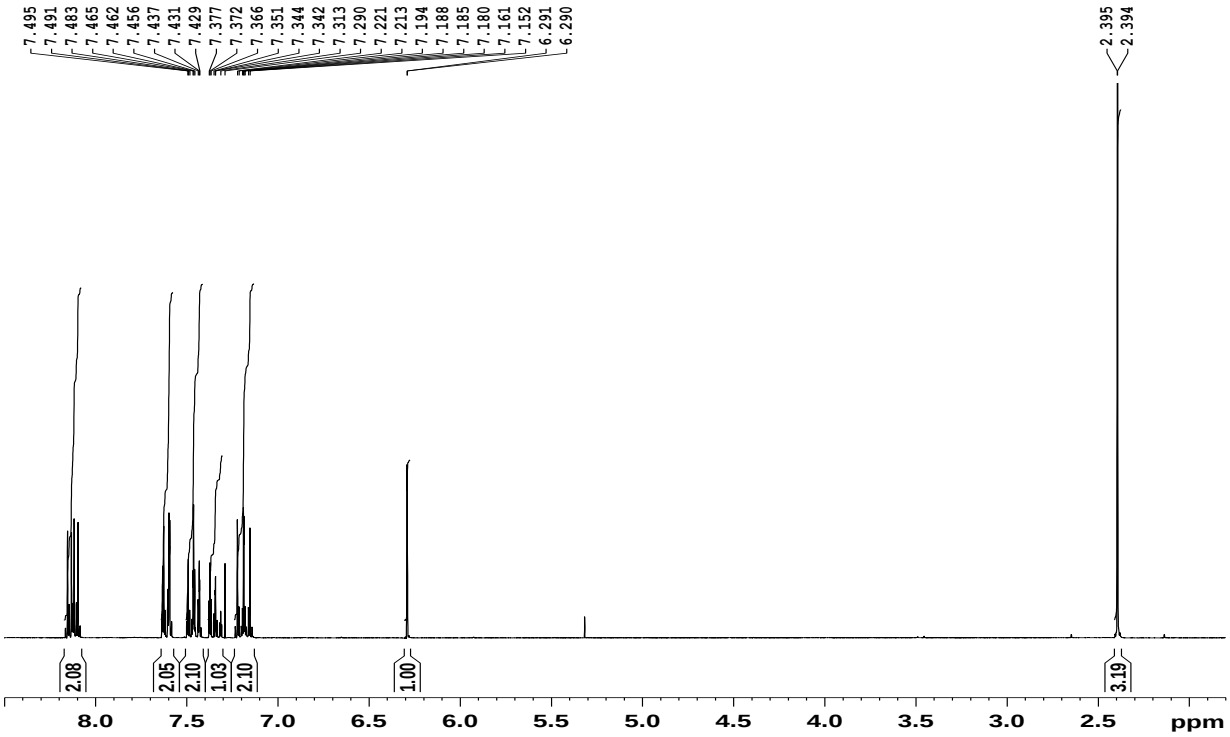


Figure S33. ^{1}H spectrum of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-fluorobenzoate.

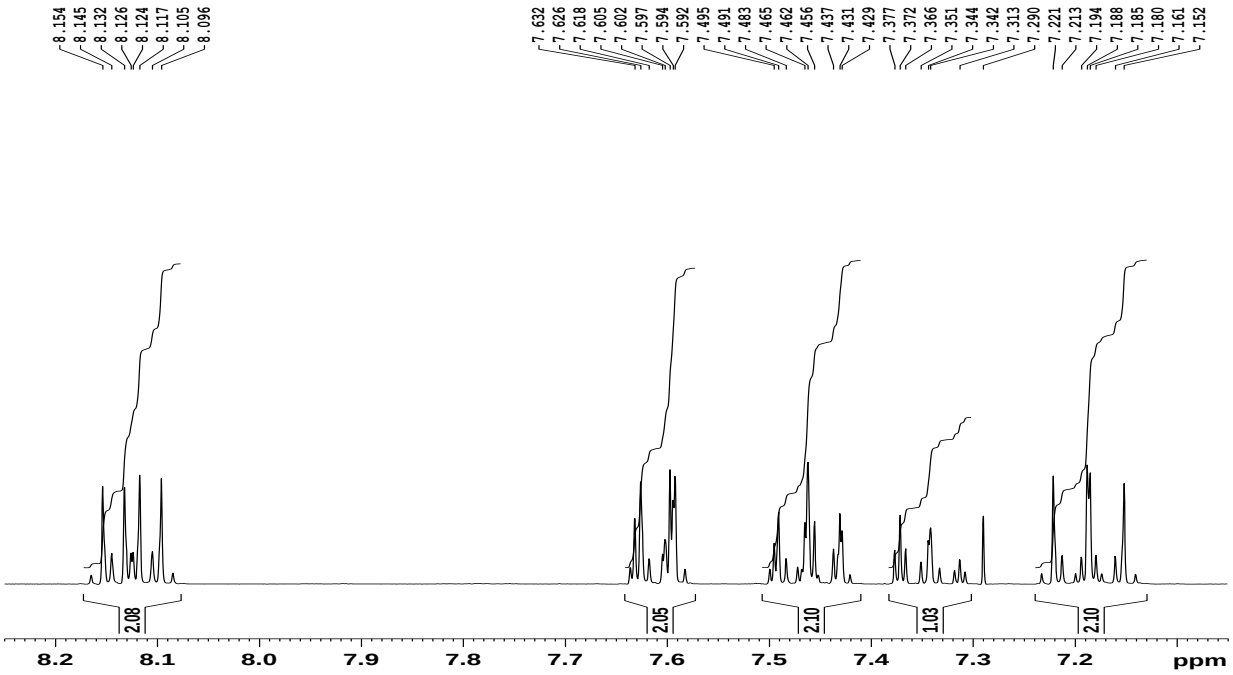


Figure S34. The aromatic area of ^{1}H spectrum of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-fluorobenzoate.

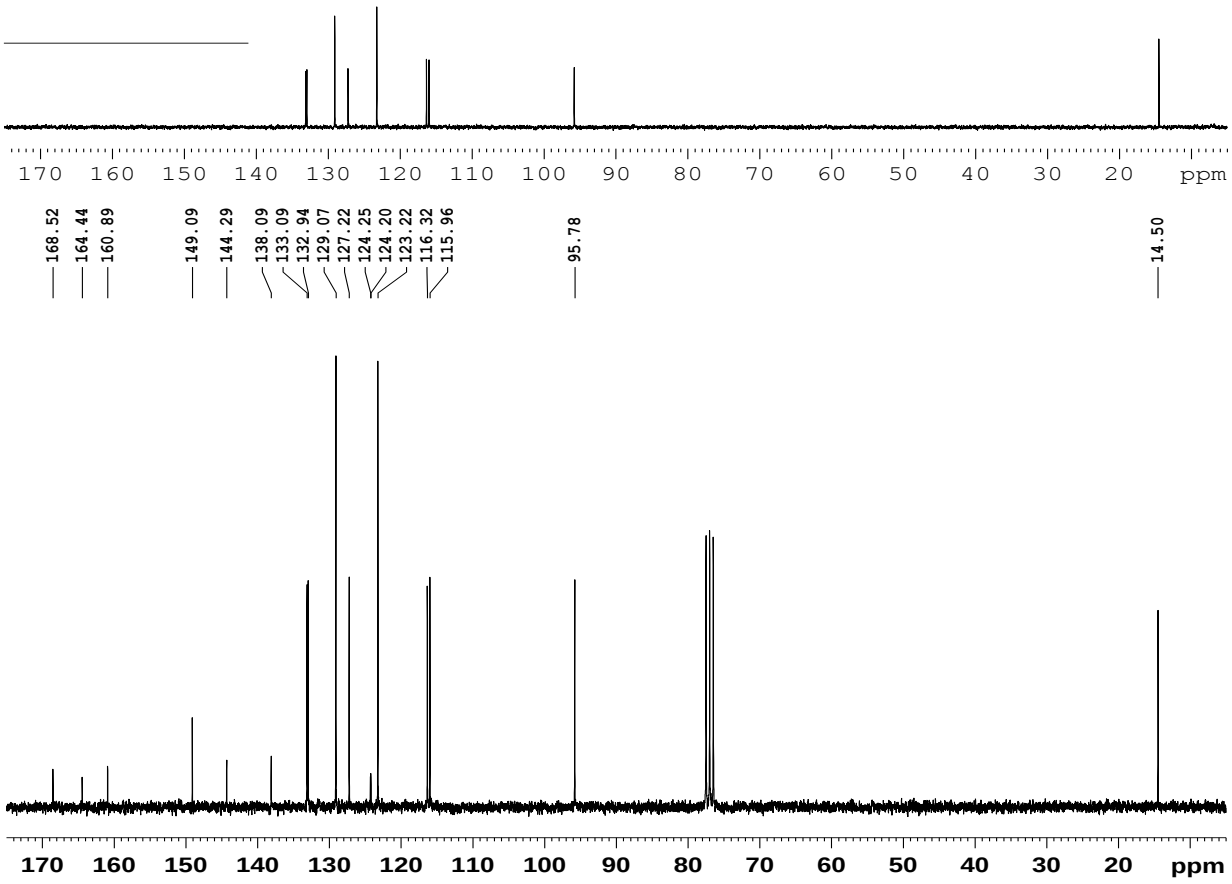


Figure S35. ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-fluorobenzoate.

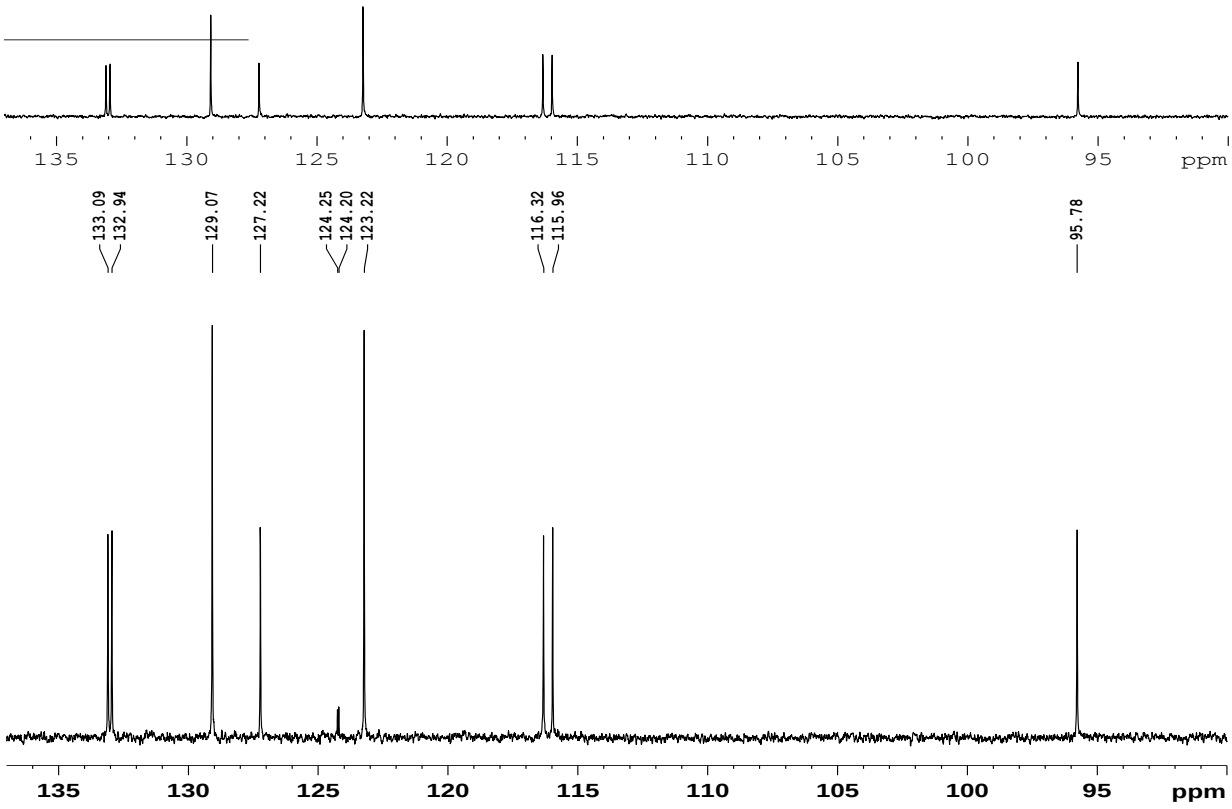


Figure S36. The aromatic area of ^{13}C spectrum (down) and DEPT experiment (up) of 3-methyl-1-phenyl-1H-pyrazol-5-yl 4-fluorobenzoate.