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Graphical Abstract

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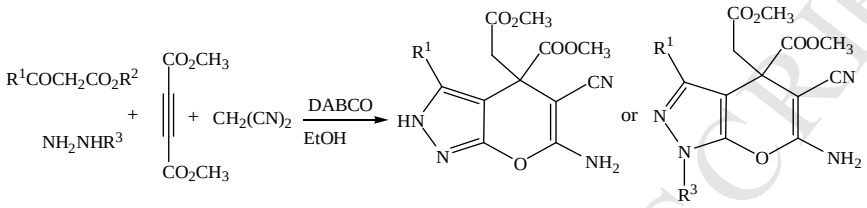

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Convenient DABCO-catalyzed one-pot synthesis of multi-substituted pyrano[2,3-c]pyrazole dicarboxylates

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ABSTRACT

We developed an efficient and simple one-pot synthesis of functionalized multi-substituted 2,4-dihydro-pyrano[2,3-c]pyrazole dicarboxylates from β-ketoesters, hydrazine, dimethyl acetylene dicarboxylate and malononitrile in EtOH. This four-component one-pot reaction carried out in the presence of DABCO catalyst showed advantages over a one-pot three-component method in its simple procedure, high yield and low toxicity.

1. Introduction

Pyrazole and pyran are both cyclic structural units found in many different natural and synthetic products that exhibit a wide range of biological activities.[1] Pyran-containing compounds exhibit analgesic, anticoagulant and anticancer effects.[2] *4H*-Chromenes contain skeletons similar to pyran. They are widespread in nature and are pharmacologically potent, being employed as drugs, pigments and in cosmetics.[3] Many types of bioactive drugs with broad medicinal and agrochemical applications contain both pyran and pyrazole rings,[4] and both structures are present in pyran[2,3-c]pyrazole and its derivatives, which exhibit various biological activities and pharmacological properties.[5] Therefore, much research has focused on the synthesis and bioactivities of compounds containing these structural units.

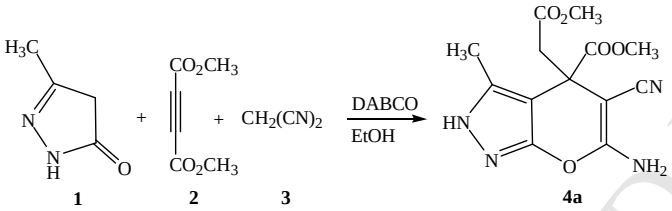
One-pot, multicomponent reactions (MCRs) constitute a powerful class of synthetic methods owing to their short reaction times, high efficiencies and unique selectivities.[6] They can form several chemical bonds simultaneously.[7] The carbon-carbon triple bond is one of the most important structural units in the formation of different rings via its reaction with different active substances. Acetylenedicarboxylate has recently been extensively used in the one-pot formation of various heterocyclic systems.[8] The pharmaceutical and biological importance of multi-substituted dihydropyrano[2,3-c]pyrazoles has led to the investigation of many synthetic approaches.[9] The triple carbon-carbon bond can undertake various active roles in organic reactions for the facile and efficient production of various heterocyles.[10] For example, the reaction of alkynes with O-acetyl- or O-benzoyl-substituted anilines yields the corresponding quinolines.[11] Highly functionalized 1,4-pyranonaphthoquinone has been prepared from the reaction of aniline, diethylacetoacetylene, hydroxyl-naphthalene-1,4-dione and an aldehyde under microwave irradiation without the use of a solvent or catalyst.[12] An atom-economic method for the one-pot synthesis of substituted 4*H*-chromene, *4H*-pyran and oxepine derivatives has been developed using a reaction involving three components: 1,3-diketones, diethyl acetylenedicarboxylate and malononitrile.[13] Multicomponent domino reactions in aqueous media catalyzed by L-proline have recently been developed for the synthesis of functionalized 4*H*-pyrano[2,3-c]pyrazoles.[14] Variations of, or an increase in the number of the various functional groups in the pyran or pyrazole ring may modify the biological properties of the resulting compounds.

Pyrazol-5-one, malononitrile, β-ketoesters and hydrazine are important intermediates that are widely used in the synthesis of functionalized and novel organic compounds.[15] Many recent studies have reported the one-pot synthesis of pyrano[2,3-c]pyrazoles in the presence of different catalysts.[16] Acetylene dicarboxylate has been little used in the synthesis of novel bioactive compounds, but it is considered here in the important task of developing a direct, convenient, economic and efficient

multicomponent one-pot method for the synthesis of novel pyrano[2,3-c]pyrazole compounds.

2. Results and discussion

To establish the optimal reaction conditions for the synthesis of multi-substituted pyrano[2,3-c]pyrazol dicarboxylates, our initial experiments were focused on a one-pot reaction involving pyrazol-5-one, malononitrile and dimethyl acetylene-dicarboxylate. For a low risk and eco-friendly process, both EtOH and water are used as the preferred solvents for all of the optimization experiments. All of the reactions were performed via heating at 50 ºC for the appropriate time period. Compound **4a** was obtained in low to moderate yields in the presence of DBU, DDC, KOH, CH_3COONa, HOAc, L-proline or piperidine as the catalyst. Interestingly, **4a** was obtained in a high yield using DABCO (20 % mol) as a catalyst in EtOH rather than in water (Table 1). The yield decreased when the reaction proceeded at room temperature or over 50 ºC. According to experimental results, the protocol described in Scheme 1 is applicable to a different type of pyrazole-5-ones. The detailed experimental results obtained with this three-component one-pot reaction were listed in Table **2**. Based on these results, a reaction stirring in EtOH with 20 % mol DABCO catalyst was selected as the optimal condition for the three-component synthesis of other compounds.



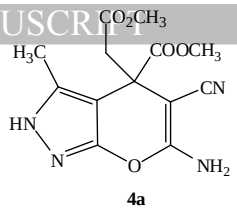
1 **2** **3** **4a**

Scheme 1. Three-component one-pot reaction for the synthesis of compound **4a**.

Table 1. Optimization of reaction conditions involving catalyst and solvent screening for the synthesis of **4a**.

Entry	catalyst (20 mol %)	solvent	t (h)	yield of **4a** (%)	
				A [a]	**B** [b]
1	Piperidine	EtOH	2 h	50	60
2	Pyrrolidine	EtOH	2 h	45	30
3	KOH	EtOH	2 h	20	25
4	CH_3COONa	EtOH	2 h	25	30
5	L-proline	EtOH	2 h	65	70
6	DBU	EtOH	2 h	35	45
7	DDC	EtOH	2 h	20	25
8	DABCO	CH_2Cl_2	1 h	35	45
9	DABCO	MeCN	1 h	50	65
10	DABCO	MeOH	1 h	65	72
11	DABCO	H_2O	1 h	50	55
12	DABCO	EtOH	1 h	80	88

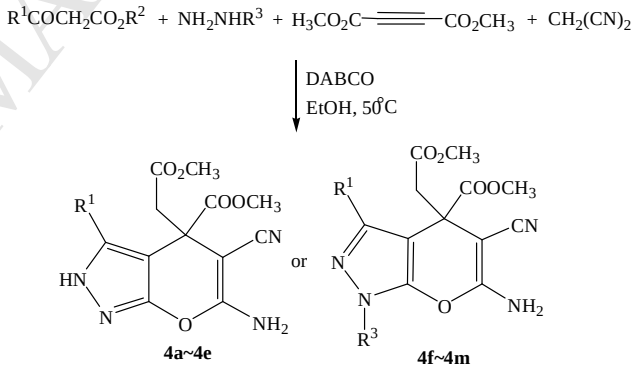
[a] Isolated yields for the three-component one-pot reaction.
[b] Isolated yields for the four-component one-pot reaction.



4a

Fig. 1 Structure of compound **4a.**

In comparison to the three-component one-pot reaction, for the four-component reaction, four reactants, including β-ketoesters, hydrazine, dimethyl acetylenedicarboxylate and malononitrile underwent a reaction to yield the target compound without preparing pyrazol-5-one. Similar to the above optimization, the catalysts, solvents and temperature used in the four-component reaction for the synthesis of compound **4a** were also investigated to optimize the reaction conditions (Table 1). It is important to note that when the reaction was carried out in EtOH using DABCO as the catalyst, the yield of product **4a** reached 88 %. However, the yield of compound **4a** decreased when the reaction was attempted in water using the same catalyst. In addition, some by-products mixed with **4a** were formed when water or EtOH was used as the solvent at room temperature or under refluxing conditions in the presence of the DABCO catalyst.



4a~4e **4f~4m**

Scheme 2. Four-component one-pot reaction for the synthesis of compounds **4a-m**.

Next, all of the compounds were prepared via the four-component one-pot reaction due to the short reaction time, simple procedure and atom efficiency of this method. Although the four-component reaction appears simple and convenient, the product was not formed when the four reactants were mixed together, despite using a similar method to the three-component one-pot reaction. Therefore, the dropwise addition of a mixture of acetylene diacetate and malononitrile into a mixture of methyl/ethyl acetoacetate and hydrazine in ethanol under stirring and heating at 50 ºC to produce the final product in high yield.

After having established the optimal reaction conditions, the effect of the type of β-ketoesters and hydrazine was examined. The reaction yield and reaction time indicated that hydrazine hydrate increased the reaction rate more than phenyl hydrazine or substituted phenyl hydrazine (Table 2). While phenyl hydrazine or substituted phenyl hydrazine participate in the reaction, the completion of the reaction required more time, and the yield of product decreased. The results listed in Table 2 also

indicated that 3-oxo aliphatic acid methyl ester afforded slightly higher yields compared to methyl benzoyl acetate. Methyl β-ketoesters resulted in slightly higher yields than that of ethyl β-ketoesters (not shown). The results obtained in the three- and four-component reactions were summarized in Table 2.

Table 2. One-pot synthesis of dihydropyrano[2,3-c]pyrazoles.

Entry	Product	R^1	R^2	R^3	% yield[b] A[a] / B[b]
1	**4a**	Me	Me	H	85 / 90
2	**4b**	Et	Me	H	80 / 85
3	**4c**	n-Pro	Me	H	83 / 88
4	**4d**	iso-Pro	Me	H	85 / 92
5	**4e**	Ph	Me	H	75 / 82
6	**4f**	Me	Me	Me	82 / 87
7	**4g**	Me	Me	Ph	80 / 85
8	**4h**	Et	Me	Ph	76 / 83
9	**4i**	n-Pro	Me	Ph	80 / 85
10	**4j**	iso-Pro	Me	Ph	82 / 88
11	**4k**	Ph	Me	Ph	78 / 82
12	**4l**	Me	Me	*o*-ClPh	70 / 80
13	**4m**	Me	Me	*p*-ClPh	75 / 80

[a] Isolated yields for the three-component one-pot reaction.
[b] Isolated yields for the four-component one-pot reaction.

The structures of **4a~4m** were confirmed by ^{1}H NMR, ^{13}C NMR, MS and IR spectroscopy. The detailed data and associated spectra were provided in the supporting information. The structure of representative compound **4a** was precisely determined by single crystal X-ray analysis (**Fig. 2**). (See the supporting information for more details).

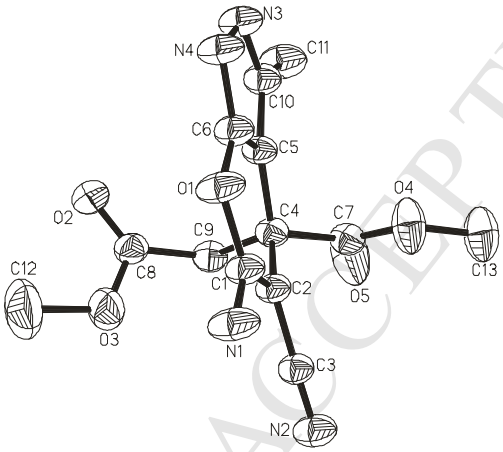
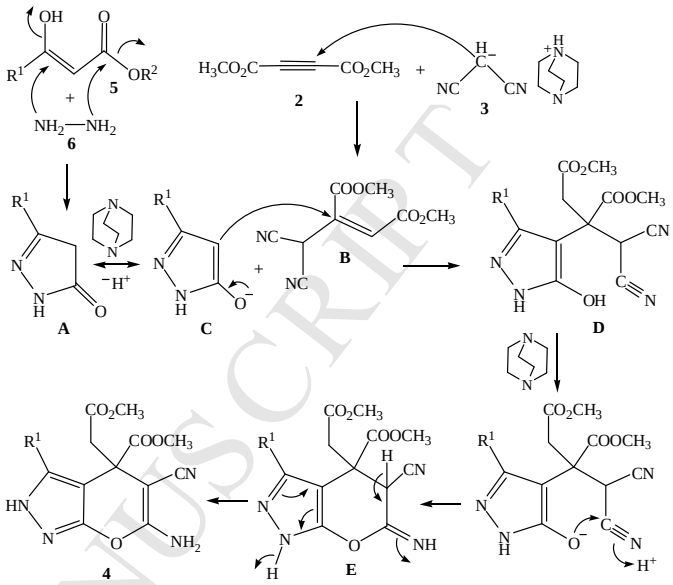


Figure 2. ORTEP diagram for the molecular structure of compound **4a**.

A detailed reaction mechanism catalyzed by DABCO for the formation of pyrano[2,3-c]pyrazole dicarboxylate were shown in Scheme 3. The role of DABCO might just simply be serving as an effective general base. Initially, spontaneous condensation of methyl β-ketoesters with the hydrazine formed pyrazole-5-one, and the Michael addition of malononitrile to dimethyl acetylene dicarboxylate led to the formation of intermediate B, respectively. Then, the Michael addition of intermediate C to intermediate B resulted in an intermediate D in the presence of DABCO. Next, the intramolecular nucleophilic attack of the oxygen to one of the nitrile group afforded intermediate E. Finally, subsequent isomerization occurred in the pyran and pyrazole rings produced the final compound **4**.



Scheme 3. Proposed reaction mechanism for the DABCO catalyzed one-pot synthesis of multi-substituted pyrano[2,3-c]pyrazole dicarboxylates.

Conclusion

We report a novel and convenient one-pot synthesis of multi-substituted pyrano[2,3-c]pyrazole dicarboxlate derivatives using three-component and four-component reactions. The four-component reactions proceeded smoothly and resulted in good to excellent yields. Our one-pot method offers several advantages, including short reaction time, simple experimental procedure and no toxic byproducts. The products are interesting nitrogen and oxygen heterocyclic molecules containing two carboxyl groups.

4. Experimental

4.1. General information

All of the solvents were purified and dried prior to use. The chemicals used in this study were analytical grade and purchased from TCI, Alfa and Acros. The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker INOVA–400 NMR instrument at 400 MHz and 100 MHz using TMS as an internal standard and DMSO-d_6 as the solvent. The chemical shifts were given in parts per million (d scale), and the coupling constants were given in Hertz. Infrared (IR) spectra were recorded on a BRUKER–EQUINOX55 spectrophotometer using KBr pellets. ESI-MS spectra and HRMS data were obtained using a TOF-MS spectrometer.

4.2 General procedure for the three-component one-pot synthesis of multi-substituted pyrano[2,3-c] pyrazole dicarboxylates (4)

DABCO (20 % mmol) was added to a mixture of pyrazol-5-one (2 mmol), dimethyl acetylenedicarboxylate (2 mmol) and malononitrile (2 mmol) in 10 mL of EtOH. The reaction mixture was heated at 50 ºC for 30–60 min. After the reaction was completed, the mixture was cooled to room temperature. After 5 mL of water was added, the resulting clear solution was maintained at room temperature for one additional day resulting in the precipitation of large quantities of crystals. White or colorless crystals were obtained via filtration with successive washing with water and ethyl acetate. The pure product was obtained by recrystallization in 80 % EtOH.

4.3 General procedure for the four-component one-pot synthesis of multi-substituted pyrano[2,3-c] pyrazole dicarboxylates (4)

An EtOH (5 mL) solution containing dimethyl acetylenedicarboxylate (2 mmol), malononitrile (2 mmol) and DABCO (20 % mmol) was added dropwise within 5 min to a stirred mixture of ethyl acetoacetate (2 mmol) and hydrazine (2 mmol) in EtOH (5 mL) at room temperature. Then, the reaction mixture was stirred at 50 ºC for 30–60 min. After completion of the reaction, a white or colorless crystal was obtained using a method similar to one mentioned above.

4.3.1. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-4-carboxylate (**4a**). White crystals, mp: 212–214 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 12.25 (s, 1H, NH), 7.08 (s, 2H, NH_2), 3.65 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.06 (d, 1H, *J*=15.2 Hz, CH_{2a}), 2.91 (d, 1H, *J*=15.2 Hz, CH_{2b}), 2.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.0, 169.2, 161.7, 154.5, 135.8, 119.0, 94.2, 55.8, 52.8, 51.2, 43.4, 10.3. IR (KBr) *v*: 3322, 3173 (brs, NH, NH_2), 2958 (C-H), 2196 (C≡N), 1733 (COO), 1662, 1601, 1497, 1409 (C=C, C=N), 1252, 1155, 1073, 1022 (C-O, C-N), 717, 580 (N-H) cm^{-1}; ESI-MS *m/z*: 307 $[M+H]^+$, 247, 233; HRMS (ESI) calcd for $C_{13}H_{15}N_4O_5$ $[M+H]^+$ 307.0964, found 307.0995.

4.3.2. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-ethyl-2,4-dihydropyrano[2,3-c] pyrazole-4-carboxylate (**4b**). White crystals; mp: 232–234 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 12.27 (s, 1H, NH), 7.09 (s, 2H, NH_2), 3.64 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.05 (d, 1H, *J*=15.2 Hz, CH_{2a}), 2.91 (d, 1H, *J*=15.2 Hz, CH_{2b}), 2.49 (q, 2H, CH_2), 1.09(t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.3 (C_1), 169.2, 161.7, 154.4, 141.1, 119.0, 93.5, 55.8, 52.8, 51.1, 43.5, 17.9, 12.5; IR (KBr) ν: 3321, 3280, 3169 (brs, NH, NH_2), 2955 (C-H), 2196 (C≡N), 1732 (COO), 1662, 1598, 1498, 1410 (C=C, C=N), 1249, 1155, 1020 (C-O, C-N), 727, 585 (N-H) cm^{-1}; ESI-MS *m/z*: 321 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}N_4O_5$ $[M+H]^+$ 321.1120, found 321.1146.

4.3.3. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-propyl-2,4-dihydropyrano[2,3-c] pyrazole-4-carboxylate (**4c**). White crystals; mp: 237–239 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 12.25(s, 1H, NH), 7.09(s, 2H, NH_2), 3.63(s, 3H, OCH_3), 3.43(s, 3H, OCH_3), 3.04(d, 1H, *J*=15.2 Hz, CH_{2a}), 2.45(m, 2H, CH_2), 2.91(d, 1H, *J*=15.2 Hz, CH_{2b}), 1.51 (m, 2H, CH_2), 0.85(t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.4 (C_1), 169.2, 161.7, 154.4, 139.6, 119.0, 93.9, 55.8, 52.8, 51.1, 43.4, 26.4, 20.9, 13.4; IR (KBr) ν: 3321, 3173 (brs, NH_2), 2954 (C-H), 2195 (C≡N), 1730 (COO), 1720 (COO), 1661, 1595, 1495, 1408 (C=C, C=N), 1246, 1156, 1070, 1016 (C-O, C-N), 722, 580 (N-H) cm^{-1}; ESI-MS *m/z*: 335 $[M+H]^+$, 275, 261; HRMS (ESI) calcd for $C_{15}H_{19}N_4O_5$ $[M+H]^+$ 335.1277, found 335.1353.

4.3.4. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-isopropyl-2,4-dihydro-2,4-dihydro pyrano[2,3-c] pyrazole- 4-carboxylate (**4d**). White crystals; mp: 218–220 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 12.30 (s, 1H, NH), 7.09 (s, 2H, NH_2), 3.64 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.04 (d, 1H, *J*=15.2 Hz, CH_{2a}), 2.90 (d, 1H, J=15.2 Hz, CH_{2b}), 2.87 (m, 1H, *J*=6.8 Hz, CH), 1.19 (d, 3H, *J*=6.8 Hz, CH_3), 1.09 (d, 3H, *J*=6.8 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.5, 169.2, 161.7, 154.0, 145.4, 119.0, 92.6, 55.9, 52.8, 51.1, 43.6, 24.9, 21.7, 21.3; IR (KBr) *v*: 3351, 3172 (brs, NH_2), 2980, 2954 (C-H), 2195 (C≡N), 1731 (COO), 1662, 1602, 1495, 1408 (C=C, C=N), 1241, 1154, 1137, 1016 (C-O, C-N), 697, 629 (N-H) cm^{-1}; ESI-MS *m/z*: 335 $[M+H]^+$, 275, 261. HRMS (ESI) calcd for $C_{15}H_{19}N_4O_5$ $[M+H]^+$ 335.1277, found 335.1327.

4.3.5. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-4-carboxylate (**4e**). White crystals; mp: 212–214 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 12.82 (s, 1H, NH), 7.50–7.25 (m, 5H, C_6H_5), 7.24 (s, 2H, NH_2), 3.64 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 2.88 (d, 1H, J=15.2 Hz, CH_{2a}), 2.59 (d, 1H, J=15.2 Hz, CH_{2b}); ^{13}C NMR (100 MHz, DMSO-d_6): 172.6, 169.0, 161.6, 154.9, 139.0, 129.2, 128.7, 127.9, 118.5, 95.3, 55.7, 52.9, 51.1, 43.4; IR (KBr) *v*: 3306, 3183 (brs, NH, NH_2), 2955 (C-H), 2193 (C≡N), 1731 (COO), 1641, 1599, 1500, 1407 (C=C, C=N), 1241, 1156, 1031 (C-O, C-N), 768, 688, 636 (C_6H_5) cm^{-1}; ESI-MS *m/z*: 369 $[M+H]^+$, 309, 295. HRMS (ESI) calcd for $C_{18}H_{17}N_4O_4$ $[M+H]^+$ 369.1121, found 369.1143.

4.3.6. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1,3-dimethyl-4H-pyrano[2,3-c] pyrazole-4-carboxylate (**4f**). White crystals; mp: 152–154 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.31 (s, 2H, NH_2), 3.65 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.44 (s, 3H, CH_3), 3.05–2.91 (dd, 2H, *J*=15.2 Hz, CH_2), 2.01 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.8, 169.2, 160.5, 144.3, 142.0, 118.1, 92.8, 56.7, 52.8, 51.2, 44.2, 33.3, 12.9; IR (KBr) ν: 3403, 3325, 3218 (brs, NH_2), 2956 (C-H), 2199 (C≡N), 1736 (COO), 1663, 1561, 1437, 1403 (C=C, C=N), 1240, 1010 (C-O, C-N) cm^{-1}; ESI-MS *m/z*: 321 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}N_4O_5$ $[M+H]^+$ 321.1120, found 321.1155.

4.3.7. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-methyl-4H-pyrano[2,3-c] pyrazole-4-carboxylate (**4g**). White crystal; mp: 192–194 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.75–7.34 (m, 5H, C_6H_5), 7.49 (s, 2H, NH_2), 3.71(s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.12–2.98 (dd, *J*=15.6 Hz, CH_3), 2.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.5, 169.3, 160.4, 144.6, 144.0, 137.1, 129.3, 126.4, 119.9, 118.1, 95.5, 56.5, 55.9, 53.0, 51.3, 43.9, 18.5, 13.1; IR (KBr) ν: 3440, 3337, 3226 (brs, NH_2), 2952 (C-H), 2193 (C≡N), 1737 (COO), 1702 (COO), 1646, 1521, 1444, 1395 (C=C, C=N), 1233, 1007 (C-O, C-N), 756, 696 cm^{-1}; ESI-MS *m/z*: 383 $[M+H]^+$, 405 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_4O_5$ $[M+H]^+$ 383.1254, found 383.1277.

4.3.8. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-ethyl-4H-pyrano[2,3-c]pyrazole-4-carboxylate (**4h**). White crystals; mp: 148–150 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.77–7.34 (m, 5H, C_6H_5), 7.49 (s, 2H, NH_2), 3.70 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.10 (d, 1H, *J*=15.6 Hz, CH_{2a}), 2.98 (d, 1H, *J*=15.6 Hz, CH_{2b}), 2.50 (m, 2H, CH_2), 1.17 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.8, 169.3, 160.4, 149.2, 144.0, 137.2, 129.3, 126.4, 119.9, 118.1, 94.9, 56.6, 53.1, 51.3, 43.9, 40.0, 38.8, 20.3, 11.7; IR (KBr) *v*: 3439, 3341, 3231 (brs,

NH_2), 2978, 2957 (C-H), 2195 (C≡N), 1739 (COO), 1707 (COO), 1648, 1578, 1519, 1440, 1398 (C=C, C=N), 1249, 1135, 1069, 1013 (C-O, C-N), 763, 691 cm^{-1}. ESI-MS *m/z*: 397 $[M+H]^+$. HRMS (ESI) calcd for $C_{20}H_{21}N_4O_5$ $[M+H]^+$ 397.1434, found 397.1477.

4.3.9. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-propyl-4H-pyrano[2,3-c] pyrazole- 4-carboxylate (**4i**). White crystals; mp: 156–158 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.33–7.78 (m, 5H, C_6H_5), 7.51 (s, 2H, NH_2), 3.69 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.10 (d, 1H, *J*=15.6 Hz, CH_{2a}), 2.99 (d, 1H, *J*=15.6 Hz, CH_{2b}), 2.48 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 0.93 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.8 (C1), 169.2, 160.4, 148.0, 143.9, 137.5, 129.3, 126.4, 119.9, 118.1, 95.16, 56.6, 53.01, 51.3, 43.9, 28.9, 20.4, 13.7; IR (KBr) ν: 3490, 3356, 3194 (brs, NH_2), 2957 (C-H), 2194 (C≡N), 1727 (2COO), 1658, 1596, 1520, 1454, 1396 (C=C, C=N), 1246, 1006 (C-O, C-N), 745, 684 cm^{-1}; ESI-MS *m/z*: 411 $[M+H]^+$. HRMS (ESI) calcd for $C_{21}H_{23}N_4O_5$ $[M+H]^+$ 411.1590, found 411.1566.

4.3.10. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-isopropyl-4H-pyrano[2,3-c]pyrazole-4-carboxylate (**4j**). White crystals; mp: 182–184 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.51 (s, 2H, NH_2), 7.34–7.76 (m, 5H, C_6H_5), 3.70 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.10 (d, *J*=15.2 Hz, CH_{2a}), 2.98 (d, *J*=15.2 Hz, CH_{2b}), 2.80 (m, 1H, *J*=6.8 Hz, CH), 1.24 (d, 3H, *J*=6.8 Hz), 1.12 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 172.0 (C_1), 169.2, 160.3, 153.5, 143.5, 137.1, 129.3, 126.4, 120.0, 118.1, 94.2, 56.7, 53.0, 51.3, 44.0, 26.6, 22.2, 21.7; IR (KBr) ν: 3388, 3318, 3209 (brs, NH_2), 2971 (C-H), 2200 (C≡N), 1748 (COO), 1725 (COO), 1663, 1598, 1520, 1456, 1396 (C=C, C=N), 1228, 1166, 1091, 1000 (C-O, C-N), 754, 691 cm^{-1}; ESI-MS *m/z*: 411 $[M+H]^+$. HRMS (ESI) calcd for $C_{21}H_{23}N_4O_5$ $[M+H]^+$ 411.1590, found 411.1559.

4.3.11. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1,3-diphenyl-4H-pyrano[2,3-c] pyrazole-4-carboxylate (**4k**). White crystals; mp: 220–224 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.36–7.87 (m, 10H, $2C_6H_5$), 7.64 (s, 2H, NH_2), 3.70 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 2.97 (d, 1H, *J*=15.6 Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 172.0, 169.0, 160.3, 147.4, 144.5, 136.9, 132.5, 129.5, 128.7, 128.5, 127.7, 127.0, 120.4, 117.7, 95.9, 56.6, 53.1, 51.2, 44.0; IR (KBr) *v*: 3401, 3323, 3210 (brs, NH2), 2954 (C-H), 2200 (C≡N), 1736 (COO), 1657, 1596, 1520, 1454, 1401 (C=C, C=N), 1240, 1074, 997 (C-O, C-N), 755, 688 cm^{-1}; ESI-MS *m/z*: 445 $[M+H]^+$. HRMS (ESI) calcd for $C_{24}H_{21}N_4O_5$ $[M+H]^+$ 445.1590, found 445.1528.

4.3.12. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-(o-chlorophenyl)-3-propyl-2,4-dihydropyrano[2,3-c]pyrazole- 4-carboxylate (4 l). White crystals, mp: 188–190 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.70–7.52 (m, 4H, *o*-Cl-C_6H_4), 7.30 (s, 2H, NH_2), 3.72 (s, 3H, CH_3), 3.46 (s, 3H, OCH_3), 3.13 (d, 1H, *J*=15.6 Hz, CH_{2a}), 2.96 (d, 1H, *J*=15.6 Hz, CH_{2b}), 2.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.6 (C_1), 169.2, 160.4, 145.2, 145.1, 133.7, 131.2, 130.7, 130.2, 129.7, 128.2, 118.2, 93.9, 56.7, 53.0, 51.3, 44.3, 13.1; IR (KBr) *v*: 3449, 3315, 3172 (brs, NH_2), 2198 (C≡N), 1736 (COO), 1664, 1582, 1538, 1436, 1399 (C=C, C=N), 1241, 1138, 1092, 1018 (C-O, C-N) cm^{-1}; ESI-MS *m/z*: 417 $[M+H]^+$. HRMS (ESI) calcd for $C_{19}H_{18}N_4O_5$ $[M+H]^+$ 417.0887, found 417.0890.

4.3.13. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-(p-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-4-carboxylate (**4m**). White crystals; mp: 208–210 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): 7.80 (d, 2H, *J*=9.2 Hz, *p*-Cl-C_6H_4), 7.54 (d, 2H, *J*=9.2 Hz, *p*-Cl-C_6H_4), 7.52 (s, 2H, NH_2), 3.70 (s, 3H, CH_3), 3.46 (s, 3H, OCH_3), 3.12 (d, 1H, *J*=15.6 Hz, CH_{2a}), 2.98 (d, 1H, *J*=15.6 Hz, CH_{2b}), 2.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.4 (C_1), 169.2, 160.3, 145.1, 144.1, 135.9, 130.5, 129.2, 121.2, 118.0, 95.7, 56.5, 53.1, 51.3, 43.9, 13.1; IR (KBr) *v*: 3411, 3329, 3229 (brs, NH_2), 2955 (C-H), 2196 (C≡N), 1722 (COO), 1659, 1591, 1523, 1393 (C=C, C=N), 1237, 1161, 1092, 1025 (C-O, C-N) cm^{-1}; ESI-MS *m/z*: 417 $[M+H]^+$. HRMS (ESI) calcd for $C_{19}H_{18}N_4O_5$ $[M+H]^+$ 417.0887, found 417.0967.

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.

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Supporting Information

Convenient DABCO-catalyzed one-pot synthesis of multi-substituted pyrano[2,3-c]pyrazole dicarboxylates

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1. General information

All of the solvents were purified and dried prior to use. The chemicals used in this study were analytical grade and purchased from TCI, Alfa and Acros. The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker INOVA–400 NMR instrument at 400 MHz and 100 MHz using TMS as an internal standard and DMSO-d_6 as the solvent. The chemical shifts were given in parts per million (d scale), and the coupling constants were given in Hertz. Infrared (IR) spectra were recorded on a BRUKER–EQUINOX55 spectrophotometer using KBr pellets. ESI-MS spectra and HRMS data were obtained using a TOF-MS spectrometer.

2. General procedure for the preparation of compounds 4a-4m

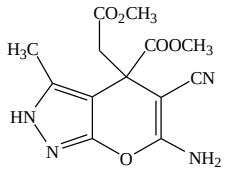
(1) General procedure for the three-component one-pot synthesis of multisubstituted pyrano[2,3-c] pyrazole dicarboxylates (4)

DABCO (20 % mmol) was added to a mixture of pyrazol-5-one (2 mmol), dimethyl acetylenedicarboxylate (2 mmol) and malononitrile (2 mmol) in 10 mL of EtOH. The reaction mixture was heated at 50 ℃ for 30–60 min. After the reaction was completed, the mixture was cooled to room temperature. After 5 mL of water was added, the resulting clear solution was maintained at room temperature for one additional day resulting in the precipitation of large quantities of crystals. White or colorless crystals were obtained via filtration with successive washing with water and ethyl acetate. The pure product was obtained by recrystallization in 80 % EtOH.

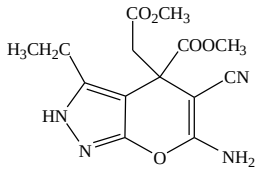
(2) General procedure for the four-component one-pot synthesis of multisubstituted pyrano[2,3-c] pyrazole dicarboxylates (4)

An EtOH (5 mL) solution containing dimethyl acetylenedicarboxylate (2 mmol), malononitrile (2 mmol) and DABCO (20 % mmol) was added dropwise within 5 min to a stirred mixture of ethyl acetoacetate (2 mmol) and hydrazine (2 mmol) in EtOH (5 mL) at room temperature. Then, the reaction mixture was stirred at 50 ℃ for 30–60 min. After completion of the reaction, a white or colorless crystal was obtained using a method similar to one mentioned above.

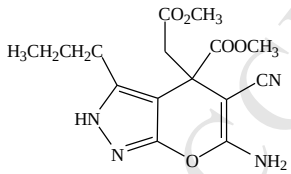
3. Physical and spectroscopic data for compounds 4a-4m



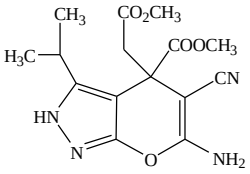
4.3.1. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-4-carboxylate (**4a**). White crystals, mp: 212–214 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 12.25 (s, 1H, NH), 7.08 (s, 2H, NH_2), 3.65 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 3.06 (d, 1H, J=15.2 Hz, CH_{2a}), 2.91 (d, 1H, J=15.2 Hz, CH_{2b}), 2.12 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.0, 169.2, 161.7, 154.5, 135.8, 119.0, 94.2, 55.8, 52.8, 51.2, 43.4, 10.3. IR (KBr) v: 3322, 3173 (brs, NH, NH_2), 2958 (C-H), 2196 (C≡N), 1733 (COO), 1662, 1601, 1497, 1409 (C=C, C=N), 1252, 1155, 1073, 1022 (C-O, C-N), 717, 580 (N-H) cm^{-1}; ESI-MS *m/z*: 307 $[M+H]^+$, 247, 233; HRMS (ESI) calcd for $C_{13}H_{15}N_4O_5$ $[M+H]^+$ 307.0964, found 307.0995.



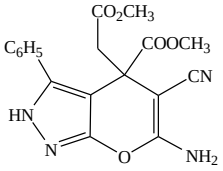
4.3.2. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-ethyl-2,4-dihydropyrano[2,3-c] pyrazole-4- carboxylate (**4b**). White crystals; mp: 232–234 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 12.27 (s, 1H, NH), 7.09 (s, 2H, NH_2), 3.64 (s, 3H, OCH_3), 3.43 (s, 3H, OCH_3), 3.05 (d, 1H, J=15.2 Hz, CH_{2a}), 2.91 (d, 1H, J=15.2 Hz, CH_{2b}), 2.49 (q, 2H, CH_2), 1.09(t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.3 (C_1), 169.2, 161.7, 154.4, 141.1, 119.0, 93.5, 55.8, 52.8, 51.1, 43.5, 17.9, 12.5; IR (KBr) ν: 3321, 3280, 3169 (brs, NH, NH_2), 2955 (C-H), 2196 (C≡N), 1732 (COO), 1662, 1598, 1498, 1410 (C=C, C=N), 1249, 1155, 1020 (C-O, C-N), 727, 585 (N-H) cm^{-1}; ESI-MS *m/z*: 321 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}N_4O_5$ $[M+H]^+$ 321.1120, found 321.1146.



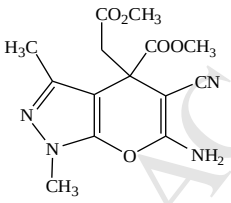
4.3.3. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-propyl-2,4-dihydropyrano[2,3-c] pyrazole-4-carboxylate (**4c**). White crystals; mp: 237–239 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 12.25(s, 1H, NH), 7.09(s, 2H, NH_2), 3.63(s, 3H, OCH_3), 3.43(s, 3H, OCH_3), 3.04(d, 1H, J=15.2 Hz, CH_{2a}), 2.45(m, 2H, CH_2), 2.91(d, 1H, J=15.2 Hz, CH_{2b}), 1.51 (m, 2H, CH_2), 0.85(t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.4 (C_1), 169.2, 161.7, 154.4, 139.6, 119.0, 93.9, 55.8, 52.8, 51.1, 43.4, 26.4, 20.9, 13.4; IR (KBr) ν: 3321, 3173 (brs, NH_2), 2954 (C-H), 2195 (C≡N), 1730 (COO), 1720 (COO), 1661, 1595, 1495, 1408 (C=C, C=N), 1246, 1156, 1070, 1016 (C-O, C-N), 722, 580 (N-H) cm^{-1}; ESI-MS *m/z*: 335 $[M+H]^+$, 275, 261; HRMS (ESI) calcd for $C_{15}H_{19}N_4O_5$ $[M+H]^+$ 335.1277, found 335.1353.



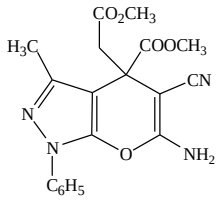
4.3.4. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-isopropyl-2,4-dihydro-2,4-dihydro pyrano [2,3-c]pyrazole-4-carboxylate (**4d**). White crystals; mp: 218–220 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 12.30 (s, 1H, NH), 7.09 (s, 2H, NH_2), 3.64 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.04 (d, 1H, *J*=15.2 Hz, CH_{2a}), 2.90 (d, 1H, J=15.2 Hz, CH_{2b}), 2.87 (m, 1H, *J*=6.8 Hz, CH), 1.19 (d, 3H, *J*=6.8 Hz, CH_3), 1.09 (d, 3H, *J*=6.8 Hz, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 172.5, 169.2, 161.7, 154.0, 145.4, 119.0, 92.6, 55.9, 52.8, 51.1, 43.6, 24.9, 21.7, 21.3; IR (KBr) *v*: 3351, 3172 (brs, NH_2), 2980, 2954 (C-H), 2195 (C≡N), 1731 (COO), 1662, 1602, 1495, 1408 (C=C, C=N), 1241, 1154, 1137, 1016 (C-O, C-N), 697, 629 (N-H) cm^{-1}; ESI-MS *m/z*: 335 $[M+H]^+$, 275, 261. HRMS (ESI) calcd for $C_{15}H_{19}N_4O_5$ $[M+H]^+$ 335.1277, found 335.1327.



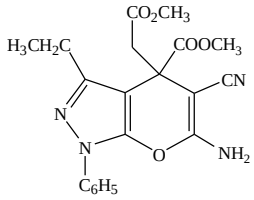
4.3.5. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-3-phenyl-2,4-dihydropyrano[2,3-c] pyrazole-4-carboxylate (**4e**). White crystals; mp: 212–214 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 12.82 (s, 1H, NH), 7.50–7.25 (m, 5H, C_6H_5), 7.24 (s, 2H, NH_2), 3.64 (s, 3H, OCH_3), 3.36 (s, 3H, OCH_3), 2.88 (d, 1H, J=15.2 Hz, CH_{2a}), 2.59 (d, 1H, J=15.2 Hz, CH_{2b}); ^{13}C NMR (100 MHz, DMSO-d_6): 172.6, 169.0, 161.6, 154.9, 139.0, 129.2, 128.7, 127.9, 118.5, 95.3, 55.7, 52.9, 51.1, 43.4; IR (KBr) *v*: 3306, 3183 (brs, NH, NH_2), 2955 (C-H), 2193 (C≡N), 1731 (COO), 1641, 1599, 1500, 1407 (C=C, C=N), 1241, 1156, 1031 (C-O, C-N), 768, 688, 636 (C_6H_5) cm^{-1}; ESI-MS *m/z*: 369 $[M+H]^+$, 309, 295. HRMS (ESI) calcd for $C_{18}H_{17}N_4O_4$ $[M+H]^+$ 369.1121, found 369.1143.



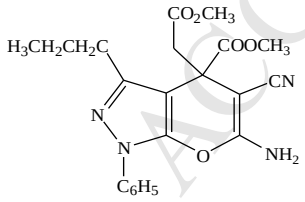
4.3.6. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1,3-dimethyl-4H-pyrano[2,3-c] pyrazole-4-carboxylate (**4f**). White crystals; mp: 152–154 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 7.31 (s, 2H, NH_2), 3.65 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.44 (s, 3H, CH_3), 3.05–2.91 (dd, 2H, *J*=15.2 Hz, CH_2), 2.01 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.8, 169.2, 160.5, 144.3, 142.0, 118.1, 92.8, 56.7, 52.8, 51.2, 44.2, 33.3, 12.9; IR (KBr) v: 3403, 3325, 3218 (brs, NH_2), 2956 (C-H), 2199 (C≡N), 1736 (COO), 1663, 1561, 1437, 1403 (C=C, C=N), 1240, 1010 (C-O, C-N) cm^{-1}; ESI-MS *m/z*: 321 $[M+H]^+$; HRMS (ESI) calcd for $C_{14}H_{16}N_4O_5$ $[M+H]^+$ 321.1120, found 321.1155.



4.3.7. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-methyl-4H-pyrano[2,3-c] pyrazole- 4-carboxylate (**4g**). White crystal; mp: 192–194 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 7.75–7.34 (m, 5H, C_6H_5), 7.49 (s, 2H, NH_2), 3.71(s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.12–2.98 (dd, J=15.6 Hz, CH_3), 2.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.5, 169.3, 160.4, 144.6, 144.0, 137.1, 129.3, 126.4, 119.9, 118.1, 95.5, 56.5, 55.9, 53.0, 51.3, 43.9, 18.5, 13.1; IR (KBr) ν: 3440, 3337, 3226 (brs, NH_2), 2952 (C-H), 2193 (C≡N), 1737 (COO), 1702 (COO), 1646, 1521, 1444, 1395 (C=C, C=N), 1233, 1007 (C-O, C-N), 756, 696 cm^{-1}; ESI-MS *m/z*: 383 $[M+H]^+$, 405 $[M+Na]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_4O_5$ $[M+H]^+$ 383.1254, found 383.1277.

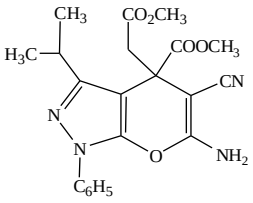


4.3.8. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-ethyl-4H-pyrano[2,3-c] pyrazole-4-carboxylate (**4h**). White crystals; mp: 148–150 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 7.77–7.34 (m, 5H, C_6H_5), 7.49 (s, 2H, NH_2), 3.70 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.10 (d, 1H, J=15.6 Hz, CH_{2a}), 2.98 (d, 1H, J=15.6 Hz, CH_{2b}), 2.50 (m, 2H, CH_2), 1.17 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.8, 169.3, 160.4, 149.2, 144.0, 137.2, 129.3, 126.4, 119.9, 118.1, 94.9, 56.6, 53.1, 51.3, 43.9, 40.0, 38.8, 20.3, 11.7; IR (KBr) *v*: 3439, 3341, 3231 (brs, NH_2), 2978, 2957 (C-H), 2195 (C≡N), 1739 (COO), 1707 (COO), 1648, 1578, 1519, 1440, 1398 (C=C, C=N), 1249, 1135, 1069, 1013 (C-O, C-N), 763, 691 cm^{-1}. ESI-MS *m/z*: 397 $[M+H]^+$. HRMS (ESI) calcd for $C_{20}H_{21}N_4O_5$ $[M+H]^+$ 397.1434, found 397.1477.

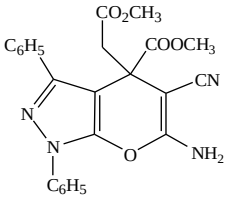


4.3.9. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-propyl-4H-pyrano[2,3-c] pyrazole- 4-carboxylate (**4i**). White crystals; mp: 156–158 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 7.33–7.78 (m, 5H, C_6H_5), 7.51 (s, 2H, NH_2), 3.69 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 3.10 (d, 1H, J=15.6 Hz, CH_{2a}), 2.99 (d, 1H, J=15.6 Hz, CH_{2b}), 2.48 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 0.93 (t, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.8 (C1), 169.2, 160.4, 148.0, 143.9, 137.5, 129.3, 126.4, 119.9, 118.1, 95.16, 56.6, 53.01, 51.3, 43.9, 28.9, 20.4, 13.7; IR (KBr) ν: 3490, 3356, 3194 (brs, NH_2),

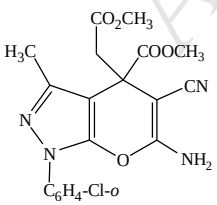
2957 (C-H), 2194 (C≡N), 1727 (2COO), 1658, 1596, 1520, 1454, 1396 (C=C, C=N), 1246, 1006 (C-O, C-N), 745, 684 cm^{-1}; ESI-MS *m/z*: 411 $[M+H]^+$. HRMS (ESI) calcd for $C_{21}H_{23}N_4O_5$ $[M+H]^+$ 411.1590, found 411.1566.



4.3.10. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-phenyl-3-isopropyl-4H-pyrano[2,3-c] pyrazole-4-carboxylate (**4j**). White crystals; mp: 182–184 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 7.51 (s, 2H, NH_2), 7.34–7.76 (m, 5H, C_6H_5), 3.70 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3), 3.10 (d, *J*=15.2 Hz, CH_{2a}), 2.98 (d, *J*=15.2 Hz, CH_{2b}), 2.80 (m, 1H, *J*=6.8 Hz, CH), 1.24 (d, 3H, *J*=6.8 Hz), 1.12 (d, 3H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 172.0 (C_1), 169.2, 160.3, 153.5, 143.5, 137.1, 129.3, 126.4, 120.0, 118.1, 94.2, 56.7, 53.0, 51.3, 44.0, 26.6, 22.2, 21.7; IR (KBr) *v*: 3388, 3318, 3209 (brs, NH_2), 2971 (C-H), 2200 (C≡N), 1748 (COO), 1725 (COO), 1663, 1598, 1520, 1456, 1396 (C=C, C=N), 1228, 1166, 1091, 1000 (C-O, C-N), 754, 691 cm^{-1}; ESI-MS *m/z*: 411 $[M+H]^+$. HRMS (ESI) calcd for $C_{21}H_{23}N_4O_5$ $[M+H]^+$ 411.1590, found 411.1559.

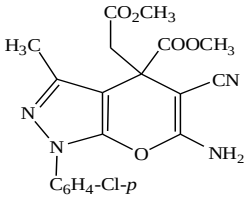


4.3.11. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1,3-diphenyl-4H-pyrano[2,3-c] pyrazole- 4-carboxylate (**4k**). White crystals; mp: 220–224 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 7.36–7.87 (m, 10H, $2C_6H_5$), 7.64 (s, 2H, NH_2), 3.70 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 2.97 (d, 1H, *J*=15.6 Hz, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): 172.0, 169.0, 160.3, 147.4, 144.5, 136.9, 132.5, 129.5, 128.7, 128.5, 127.7, 127.0, 120.4, 117.7, 95.9, 56.6, 53.1, 51.2, 44.0; IR (KBr) *v*: 3401, 3323, 3210 (brs, NH2), 2954 (C-H), 2200 (C≡N), 1736 (COO), 1657, 1596, 1520, 1454, 1401 (C=C, C=N), 1240, 1074, 997 (C-O, C-N), 755, 688 cm^{-1}; ESI-MS *m/z*: 445 $[M+H]^+$. HRMS (ESI) calcd for $C_{24}H_{21}N_4O_5$ $[M+H]^+$ 445.1590, found 445.1528.



4.3.12. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-(o-chlorophenyl)-3-propyl-2,4-dihydropyrano[2,3-c]pyrazole-4-carboxylate (4 l). White crystals, mp: 188–190 ℃. ^{1}H NMR (400 MHz, DMSO-d_6): 7.70–7.52 (m, 4H, *o*-Cl-C_6H_4), 7.30 (s, 2H, NH_2), 3.72 (s, 3H, CH_3), 3.46 (s, 3H,

OCH_3), 3.13 (d, 1H, *J*=15.6 Hz, CH_{2a}), 2.96 (d, 1H, *J*=15.6 Hz, CH_{2b}), 2.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.6 (C_1), 169.2, 160.4, 145.2, 145.1, 133.7, 131.2, 130.7, 130.2, 129.7, 128.2, 118.2, 93.9, 56.7, 53.0, 51.3, 44.3, 13.1; IR (KBr) *v*: 3449, 3315, 3172 (brs, NH_2), 2198 (C≡N), 1736 (COO), 1664, 1582, 1538, 1436, 1399 (C=C, C=N), 1241, 1138, 1092, 1018 (C-O, C-N) cm^{-1}; ESI-MS *m/z*: 417 $[M+H]^+$. HRMS (ESI) calcd for $C_{19}H_{18}N_4O_5$ $[M+H]^+$ 417.0887, found 417.0890.



4.3.13. Methyl 6-amino-5-cyano-4-(methoxycarbonylmethyl)-1-(p-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-4-carboxylate (**4m**). White crystals; mp: 208–210 ℃. ^1H NMR (400 MHz, DMSO-d_6): 7.80 (d, 2H, *J*=9.2 Hz, *p*-Cl-C_6H_4), 7.54 (d, 2H, *J*=9.2 Hz, *p*-Cl-C_6H_4), 7.52 (s, 2H, NH_2), 3.70 (s, 3H, CH_3), 3.46 (s, 3H, OCH_3), 3.12 (d, 1H, *J*=15.6 Hz, CH_{2a}), 2.98 (d, 1H, *J*=15.6 Hz, CH_{2b}), 2.14 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): 171.4 (C_1), 169.2, 160.3, 145.1, 144.1, 135.9, 130.5, 129.2, 121.2, 118.0, 95.7, 56.5, 53.1, 51.3, 43.9, 13.1; IR (KBr) *v*: 3411, 3329, 3229 (brs, NH_2), 2955 (C-H), 2196 (C≡N), 1722 (COO), 1659, 1591, 1523, 1393 (C=C, C=N), 1237, 1161, 1092, 1025 (C-O, C-N) cm^{-1}; ESI-MS *m/z*: 417 $[M+H]^+$. HRMS (ESI) calcd for $C_{19}H_{18}N_4O_5$ $[M+H]^+$ 417.0887, found 417.0967.

4. ^{1}H NMR, ^{13}C NMR, IR and MS spectra of compounds 4a-4m

```
xinjiang daxue varian inova-400 1H-4N
zainaipuguli-zai-5-169-abulajiang
in DMSO

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file           exp  spin             20
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at             3.744 alfa          6.600
np             52412       FLAGS
fb              4000 il                n
bs                16 in                n
d1             3.000 dp                y
nt                20 hs               nn
ct                20       PROCESSING
   TRANSMITTER         fn        not used
tn                H1       DISPLAY
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tof            400.0 wp           5673.6
tpwr              59 rfl          1090.9
pw             5.000 rfp             0
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dn               C13 lp            -13.2
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dmm                c sc                0
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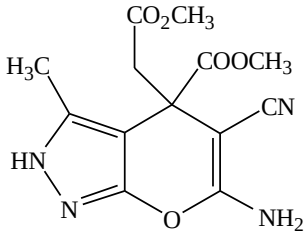
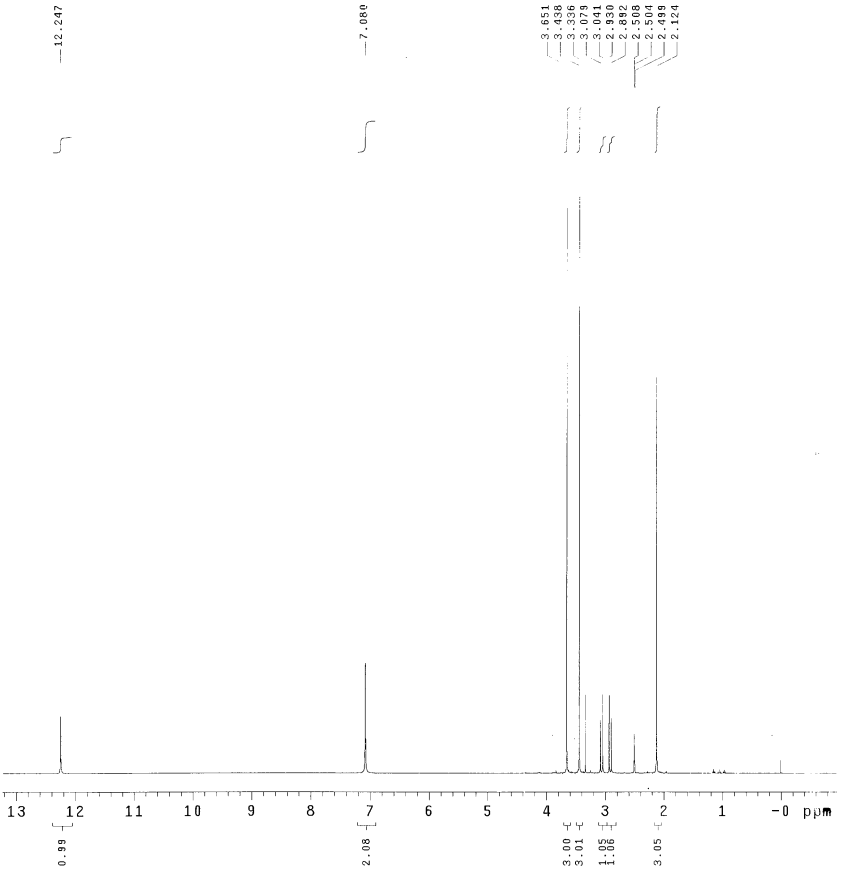


4a

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zainaipuguli-zai-5-169-abulajiang
in DMSO

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at             1.199 alfa         20.000
np             59968       FLAGS
fb             14000 il                n
bs                16 in                n
d1             3.000 dp                y
nt                800 hs               nn
ct                800       PROCESSING
   TRANSMITTER         lb            1.00
tn               C13  fn        not used
sfrq         100.525       DISPLAY
tof           1500.0 sp           -1567.1
tpwr              56 wp           24999.2
pw             5.000 rfl           1567.8
     DECOUPLER       rfp              0
dn                H1 rp             -15.3
dof            400.0 lp            -254.7
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dmf            13400 vs              237
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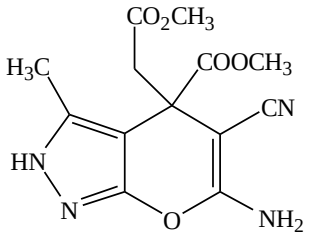
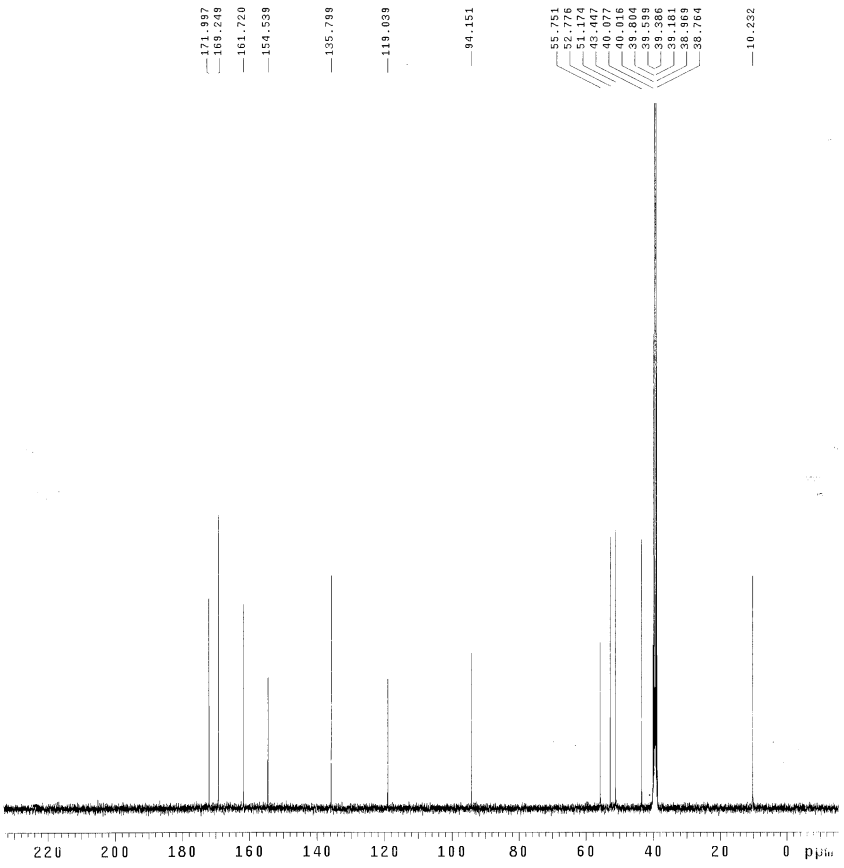
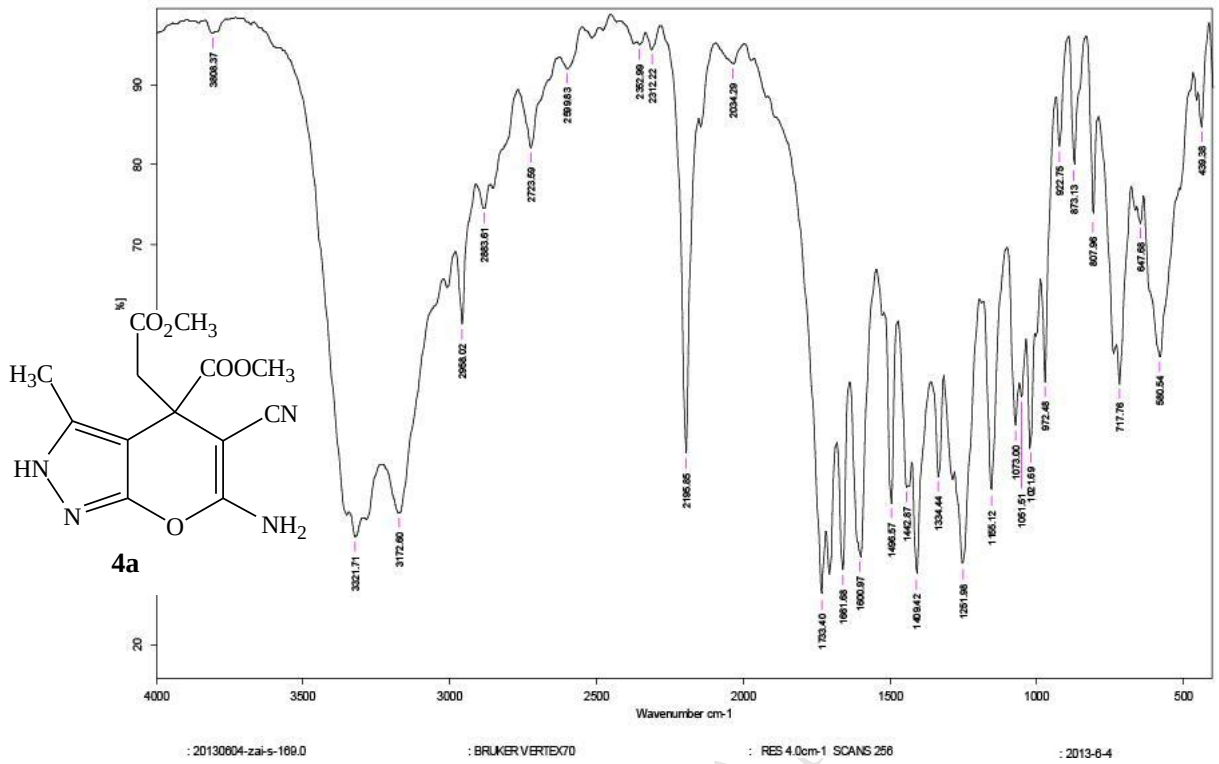


4a

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439.38
: 20130604-zai-s-169.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4

CO2CH3
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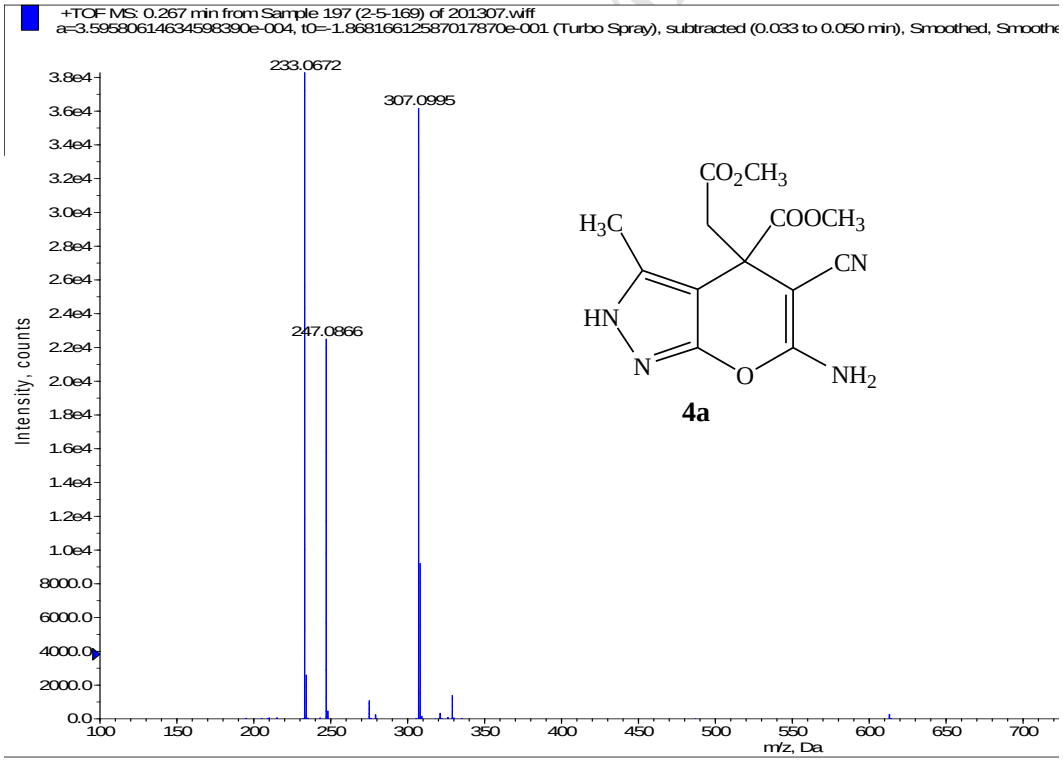
N
O
NH2

4a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Intensity, counts
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3.6e4
3.4e4
3.2e4
3.0e4
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2.6e4
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2.0e4
1.8e4
1.6e4
1.4e4
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1.0e4
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400
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500
550
600
650
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CO2CH3
H3C
COOCH3
CN
HN
N
O
NH2

4a

```
xinjiang daxue varian inova-400 1H-4N
zai-5-168-abulajiang in DMSO

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solvent       DMSO  gain             30
file           exp  spin             20
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at           3.744  alfa          6.600
np           52412        FLAGS
fb            4000  il                n
bs              16  in                n
d1           3.000  dp                y
nt              20  hs               nn
ct              20      PROCESSING
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tn              H1       DISPLAY
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tof          800.0  wp           5752.2
tpwr            59  rfl           691.5
pw           5.000  rfp             0
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dn              C13  lp            -14.1
dof               0       PLOT
dm              nnn  wc             180
dmm               c  sc               0
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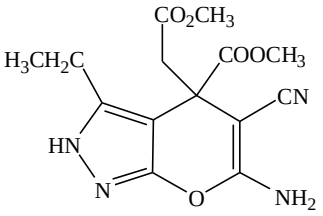
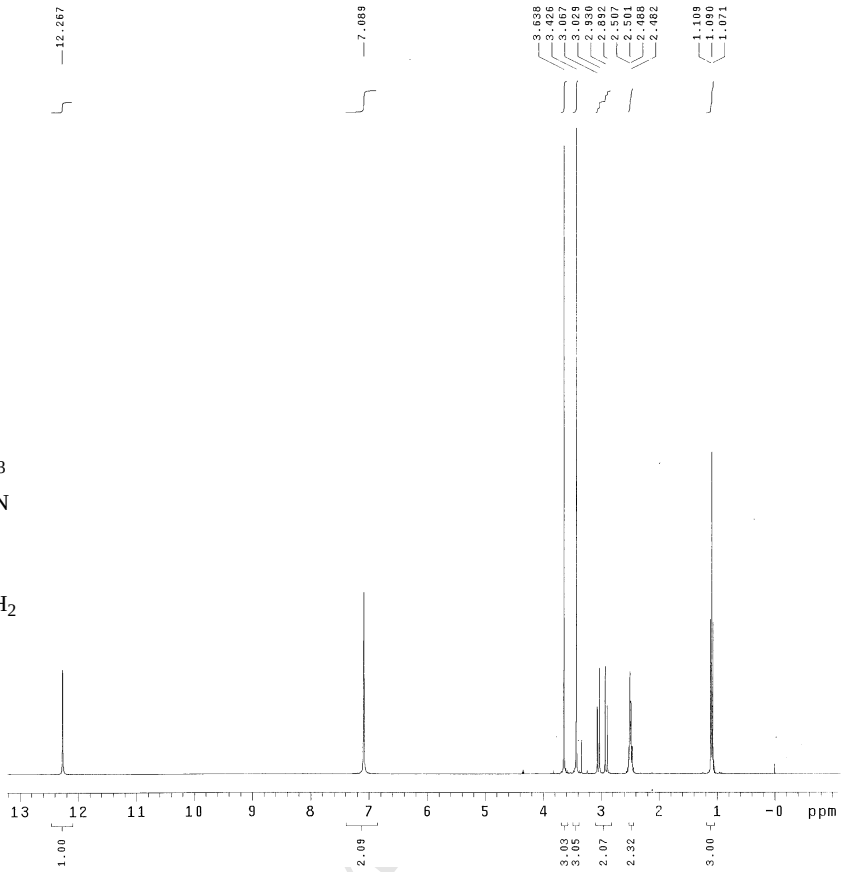
dmf           20056  th               9
                     nm    ph
```



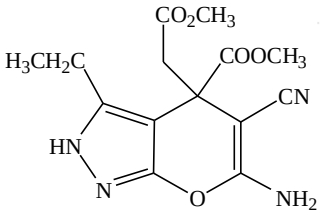
4b



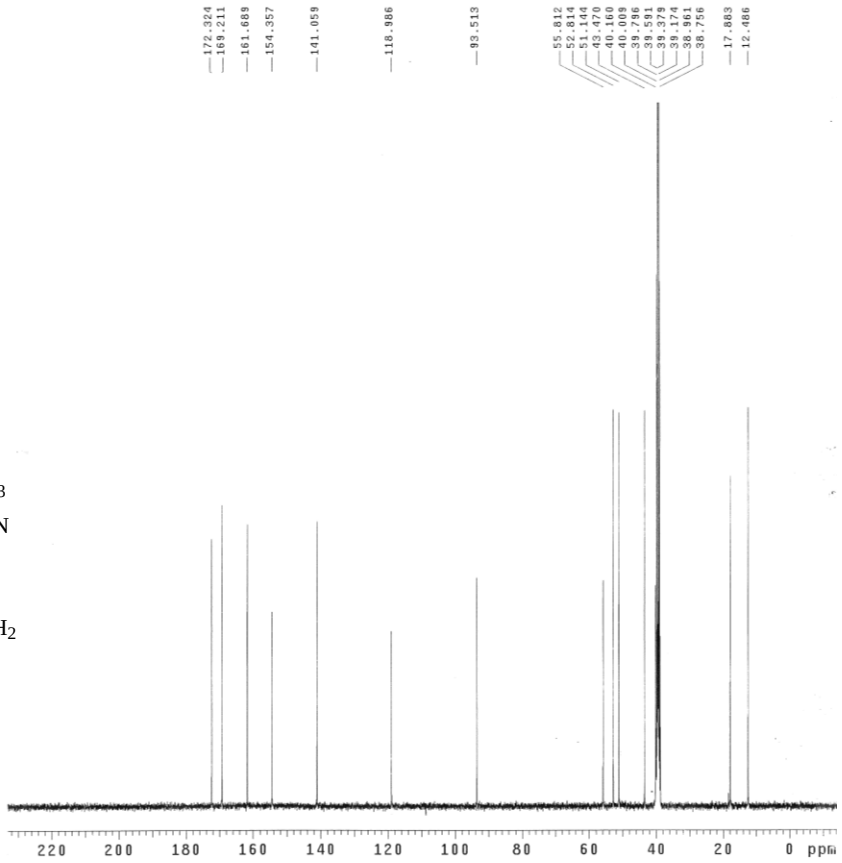

```
xinjiang daxue varian inova-400 13C-4N
zainaipuguli-zai-5-168-abulajiang
in DMSO

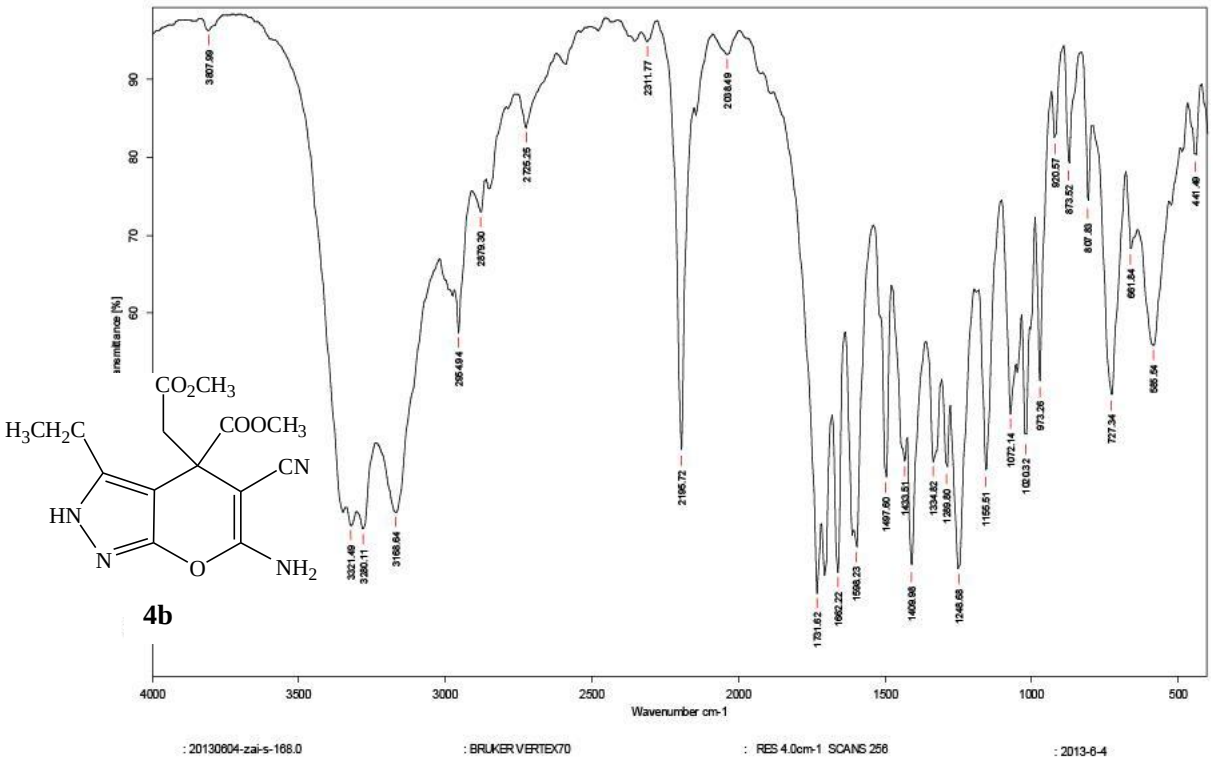
exp2  s2pul

      SAMPLE                SPECIAL
date   May 28 2013  temp       not used
solvent       DMSO  gain             50
file           exp  spin             20
   ACQUISITION      hst           0.008
sw          25000.0  pw90         10.800
at            1.199  alfa         20.000
np            59968        FLAGS
fb            14000  il                n
bs               16  in                n
d1            3.000  dp                y
nt             2000  hs               nn
ct             2000      PROCESSING
   TRANSMITTER      lb             1.00
tn              C13  fn        not used
sfrq        100.525       DISPLAY
tof          1500.0  sp            -1567.1
tpwr             56  wp           24999.2
pw           5.000  rfl           1567.8
   DECOUPLER        rfp             0
dn                H1  rp            -21.6
dof            400.0  lp            -261.4
dm               yyy       PLOT
dmm                w  wc             180
dpwr              42  sc               0
dmf            13400  vs             263
                      th              12
                      nm    ph
```



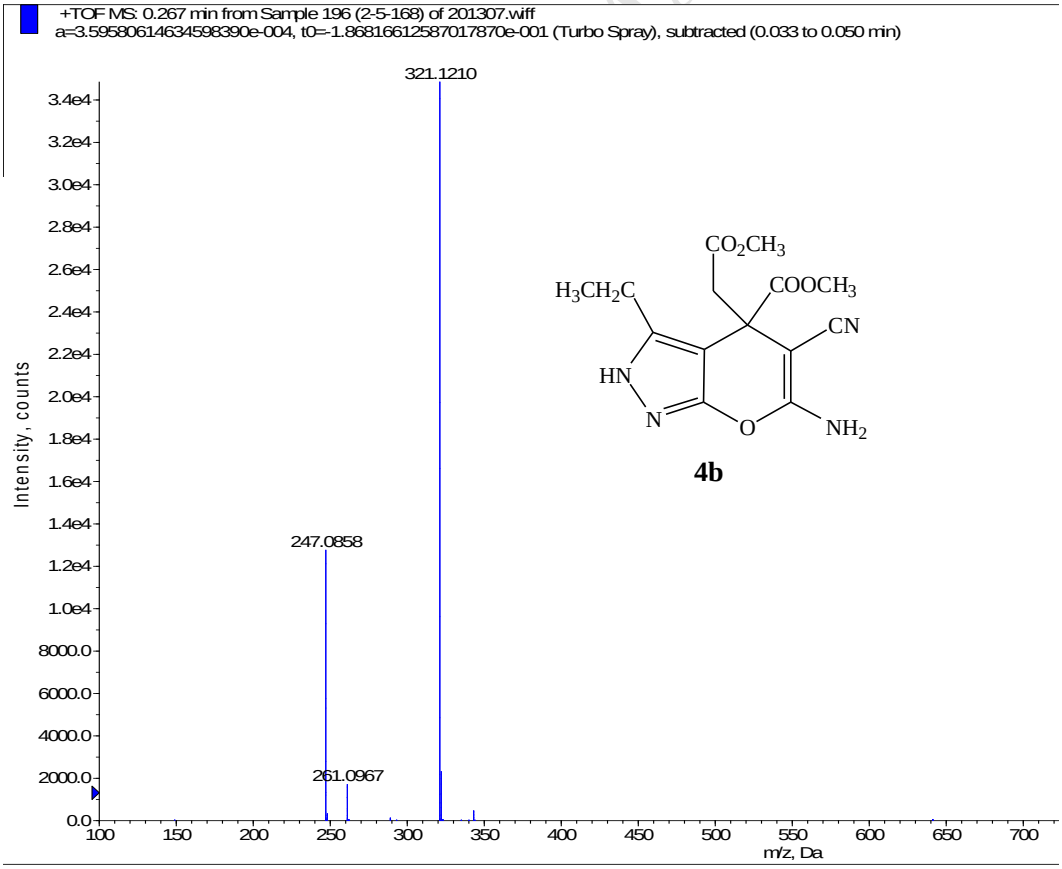
4b




3807.99
3321.48
3280.11
3168.64
2954.94
2879.30
2725.25
2311.77
2195.72
2036.49
1731.62
1662.22
1598.23
1497.60
1433.51
1408.98
1334.82
1289.80
1246.68
1155.61
1072.14
1020.32
973.26
920.57
873.52
807.83
727.34
661.84
588.54
441.49
90
80
70
60
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
: 20130604-zai-s-168.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4

CO2CH3
H3CH2C
COOCH3
CN
HN
N
O
NH2

4b


+TOF MS: 0.267 min from Sample 196 (2-5-168) of 201307.wiff
a=3.59580614634598390e-004, t0=-1.86816612587017870e-001 (Turbo Spray), subtracted (0.033 to 0.050 min)
321.1210
247.0858
261.0967
Intensity, counts
3.4e4
3.2e4
3.0e4
2.8e4
2.6e4
2.4e4
2.2e4
2.0e4
1.8e4
1.6e4
1.4e4
1.2e4
1.0e4
8000.0
6000.0
4000.0
2000.0
0.0
100
150
200
250
300
350
400
450
500
550
600
650
700
m/z, Da

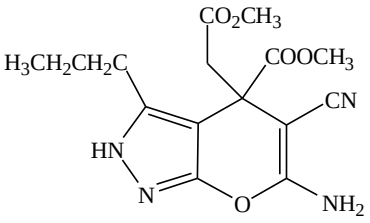
CO2CH3
H3CH2C
COOCH3
CN
HN
N
O
NH2

4b

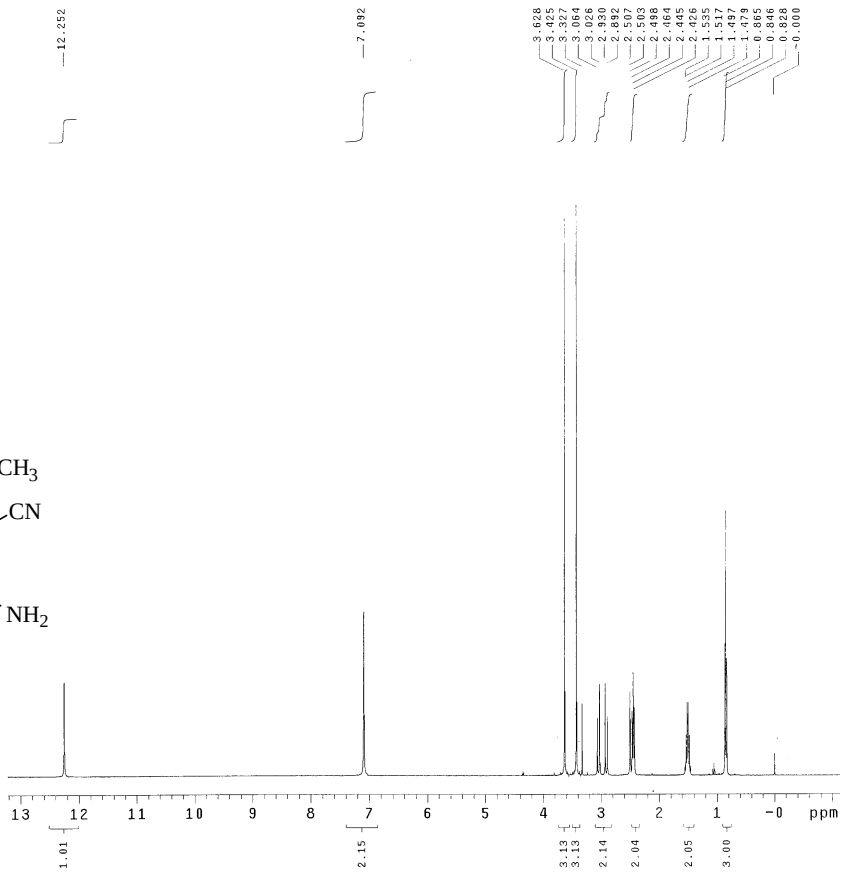
```
xinjiang daxue varian inova-400 1H-4N
zai-5-167-abulajiang in DMSO

exp1  s2pul

      SAMPLE              SPECIAL
date   May 20 2013  temp       not used
solvent       DMSO  gain             30
file           exp  spin             20
    ACQUISITION      hst           0.008
sw          6999.7  pw90         10.800
at           3.744  alfa          6.600
np           52412       FLAGS
fb            4000  il                n
bs              16  in                n
d1           3.000  dp                y
nt              20  hs               nn
ct              20      PROCESSING
    TRANSMITTER      fn       not used
tn               H1      DISPLAY
sfrq        399.742  sp          -477.9
tof           800.0  wp          5763.5
tpwr             59  rfl          691.5
pw            5.000  rfp              0
    DECOUPLER        rp           -83.6
dn               C13  lp           -14.1
dof                0        PLOT
dm               nnn  wc             180
dmm                c  sc               0
dpwr              45  vs             122
dmf            20056  th               4
                      nm    ph
```



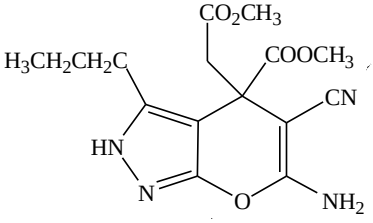
4c



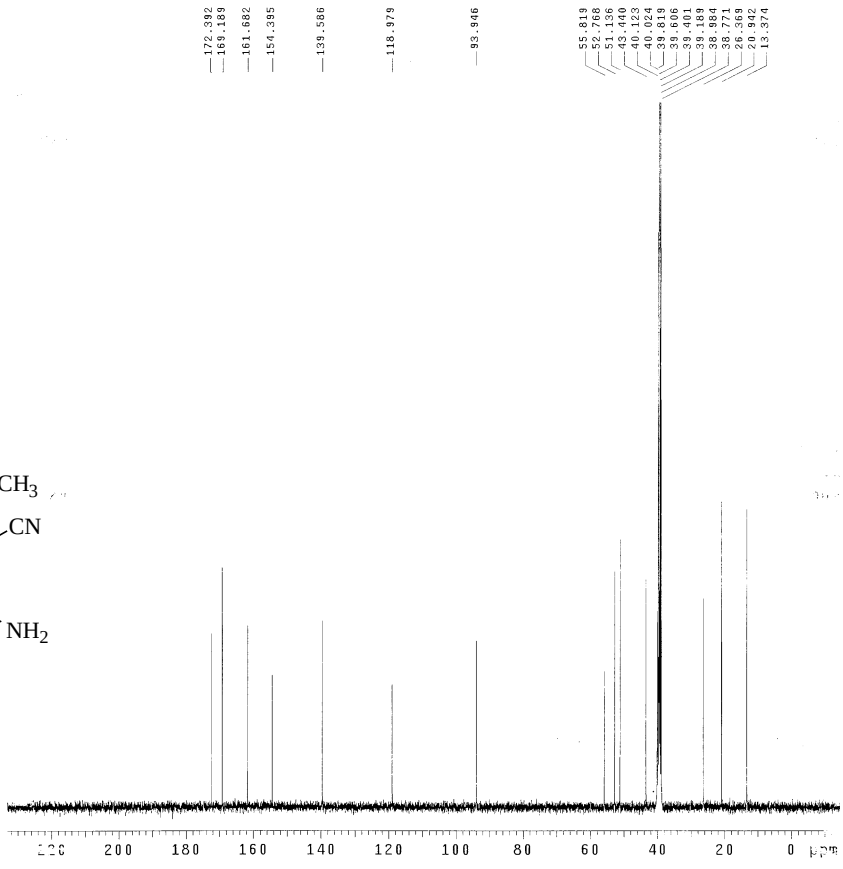

```
xinjiang daxue varian inova-400 13C-4N
zainaipugulI-zai-5-167-abulajiang
in DMSO

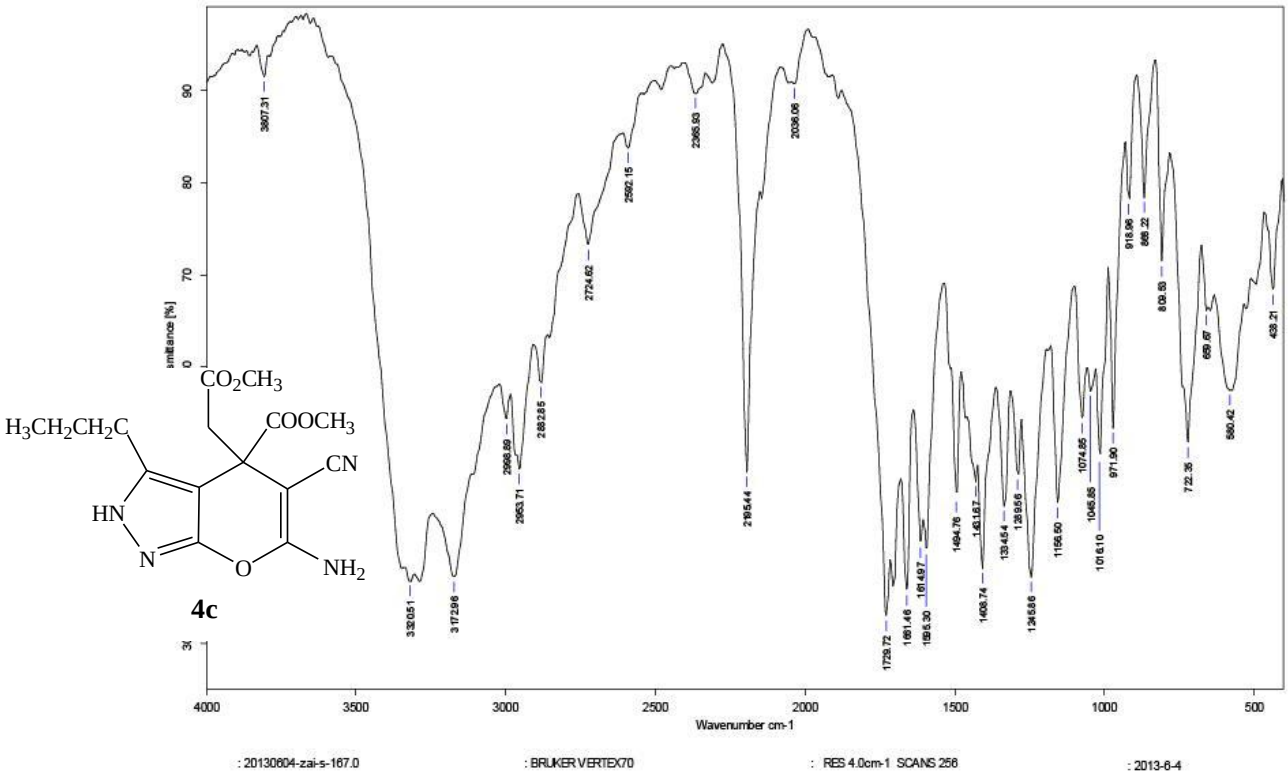
exp2  s2pul

      SAMPLE              SPECIAL
date   May 28 2013  temp       not used
solvent       DMSO  gain             50
file           exp  spin             20
    ACQUISITION      hst           0.008
sw          25000.0  pw90         10.800
at            1.199  alfa         20.000
np            59968       FLAGS
fb            14000  il                n
bs               16  in                n
d1            3.000  dp                y
nt             1000  hs               nn
ct             1000      PROCESSING
    TRANSMITTER      lb             1.00
tn               C13  fn       not used
sfrq        100.525       DISPLAY
tof          1500.0  sp          -1567.1
tpwr             56  wp          24999.2
pw            5.000  rfl          1567.8
    DECOUPLER        rfp              0
dn               H1  rp            -27.9
dof           400.0  lp           -261.4
dm              yyy        PLOT
dmm               w  wc             180
dpwr             42  sc               0
dmf           13400  vs             284
                      th              12
                      nm    ph
```



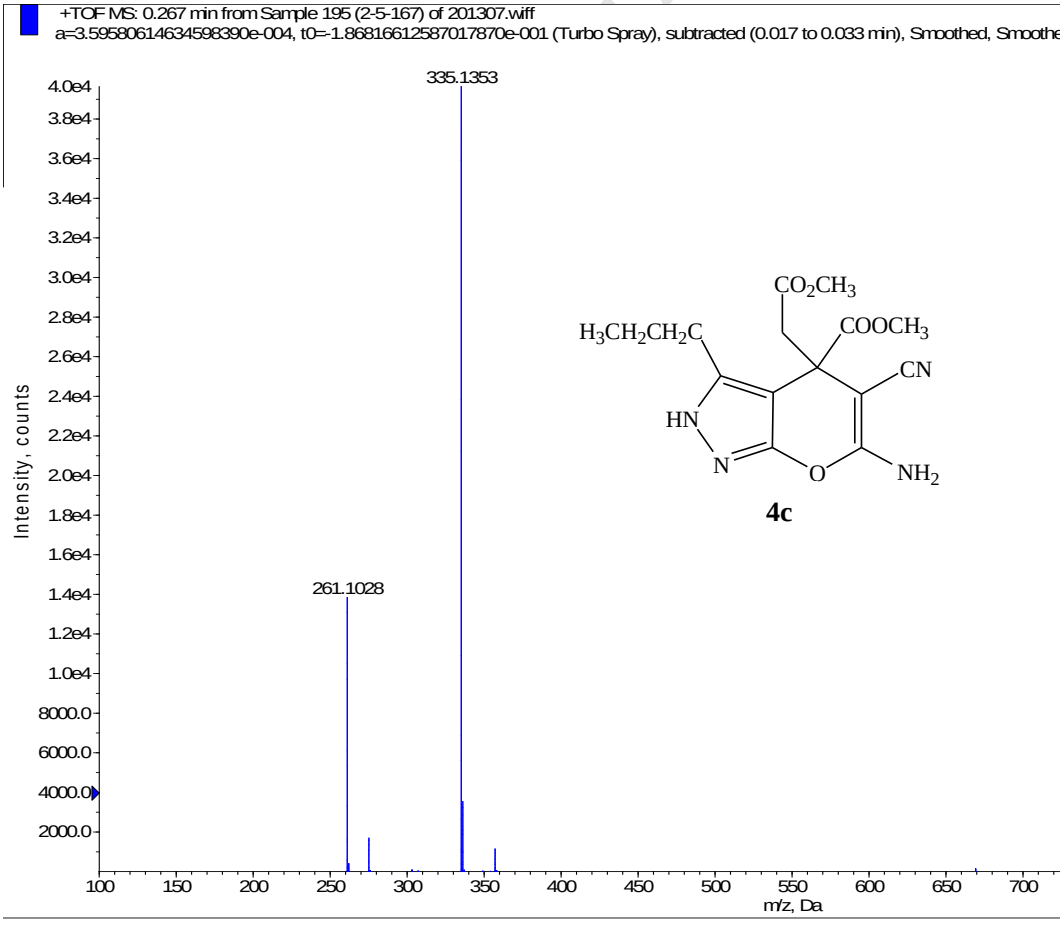
4c




3607.31
2965.93
2592.15
2038.06
2774.62
2908.88
2953.71
2882.85
3320.51
3172.96
2195.44
1729.72
1661.46
1615.30
1494.76
1408.74
1334.54
1285.56
1156.50
1074.85
1045.85
1016.10
971.90
918.96
868.22
809.53
722.35
659.67
560.42
439.21
Transmittance [%]
Wavenumber cm-1
: 20130604-zai-s-167.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4

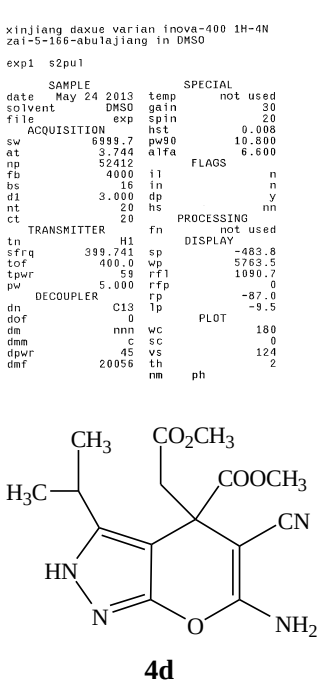
CO2CH3
H3CH2CH2C
COOCH3
CN
HN
N
O
NH2

4c


+TOF MS: 0.267 min from Sample 195 (2-5-167) of 201307.wiff
a=3.59580614634598390e-004, t0=-1.86816612587017870e-001 (Turbo Spray), subtracted (0.017 to 0.033 min), Smoothed, Smoothe
335.1353
261.1028
Intensity, counts
m/z, Da

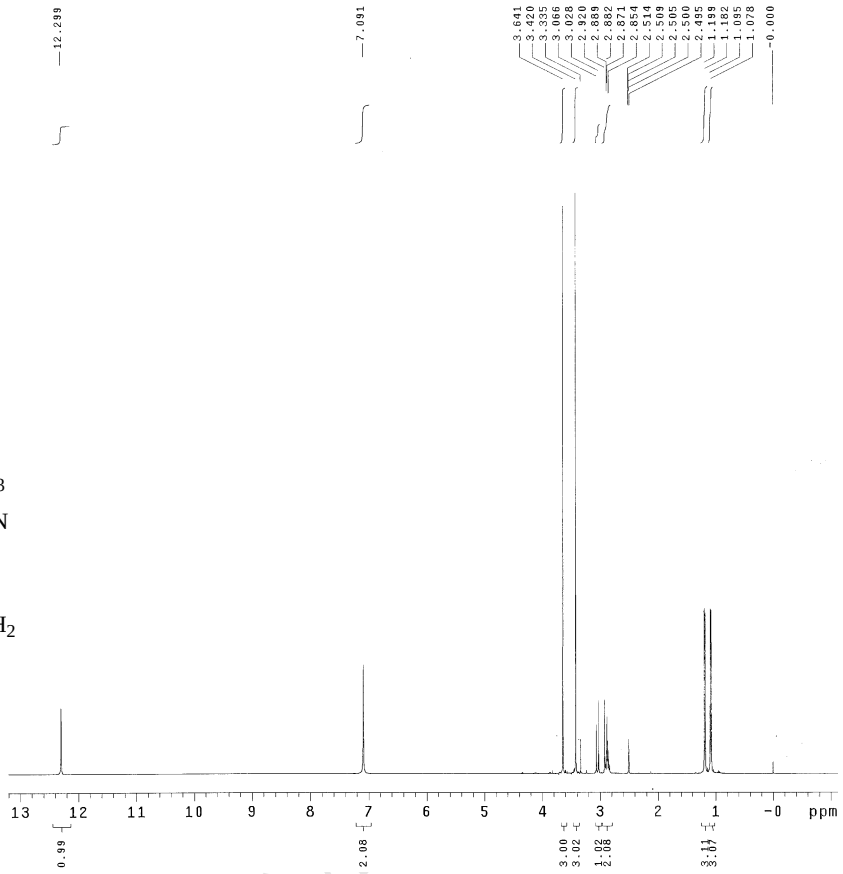
CO2CH3
H3CH2CH2C
COOCH3
CN
HN
N
O
NH2

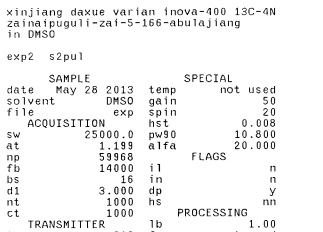
4c

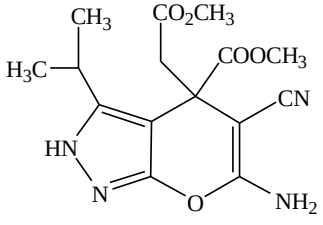

xinjiang daxue varian inova-400 1H-4N
zai-5-166-abulajiang in DMSO
exp1 s2pul
SAMPLE
date May 24 2013
solvent DMSO
file exp
ACQUISITION
sw 6999.7
at 3.744
np 52412
fb 4000
bs 16
d1 3.000
nt 20
ct 20
TRANSMITTER
tn H1
sfrq 399.741
tof 400.0
tpwr 59
pw 5.000
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 45
dmf 20056
SPECIAL
temp not used
gain 30
spin 20
hst 0.008
pw90 10.800
alfa 6.600
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -483.8
wp 5763.5
rfl 1090.7
rfp 0
rp -87.6
lp -9.5
PLOT
wc 180
sc 0
vs 124
th 2
nm ph

CH3
CO2CH3
H3C
COOCH3
CN
HN
N
O
NH2

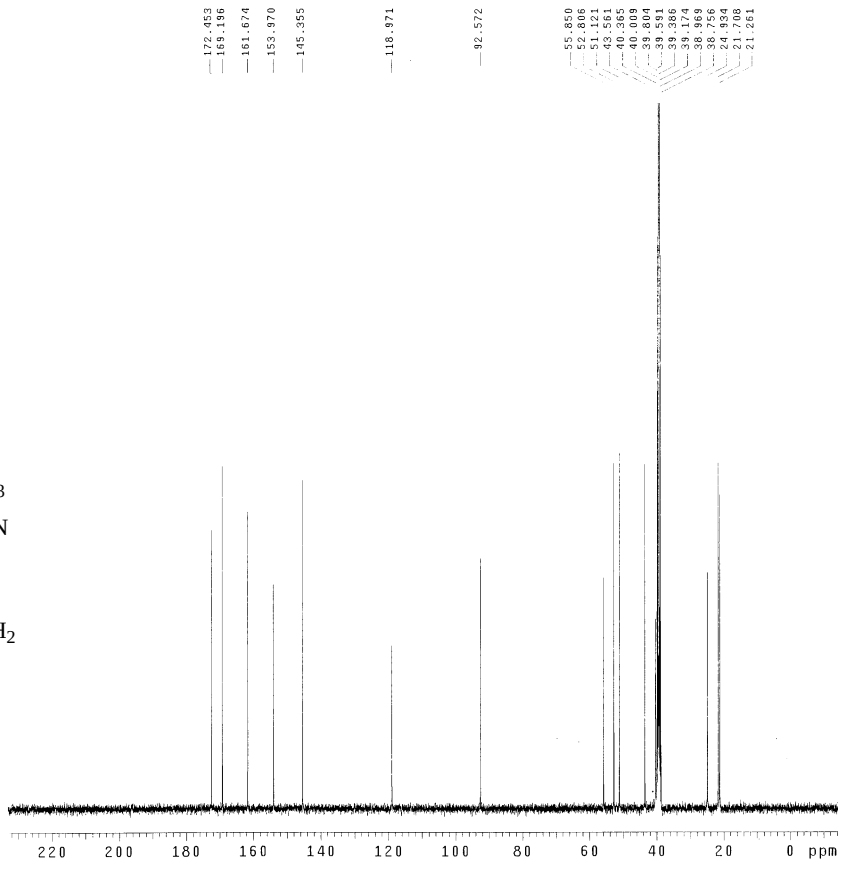
4d

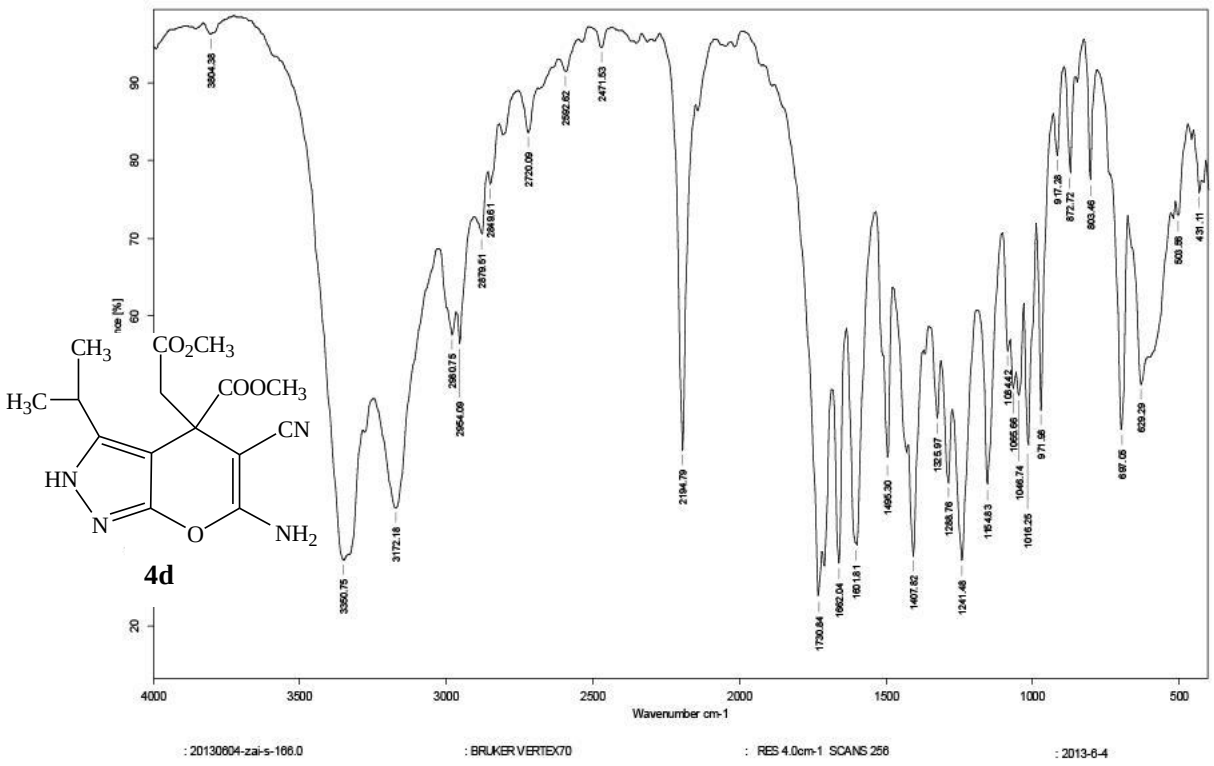

12.239
7.091
3.641
3.420
3.335
3.066
3.028
2.920
2.889
2.882
2.871
2.654
2.514
2.508
2.505
2.500
2.495
1.199
1.182
1.095
1.078
0.000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.99
2.08
3.00
3.02
1.02
2.08
3.11
3.07


xinjiang daxue varian inova-400 13C-4N
zainaipugull-zai-5-166-abulajiang
in DMSO
exp2 s2pul
SAMPLE
date May 28 2013
solvent DMSO
file exp
ACQUISITION
sw 25000.0
at 1.199
np 59968
fb 14000
bs 16
d1 3.000
nt 1000
ct 1000
TRANSMITTER
tn C13
sfrq 100.525
tof 1500.0
tpwr 56
pw 5.000
DECOUPLER
dn H1
dof 400.0
dm yyy
dmm w
dpwr 42
dmf 13400
SPECIAL
temp not used
gain 50
spin 20
hst 0.008
pw90 10.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1567.1
wp 24998.2
rfl 1567.8
rfp 0
rp -8.5
lp -261.4
PLOT
wc 180
sc 0
vs 280
th 12
nm ph


CH3
CO2CH3
H3C
COOCH3
CN
HN
N
O
NH2

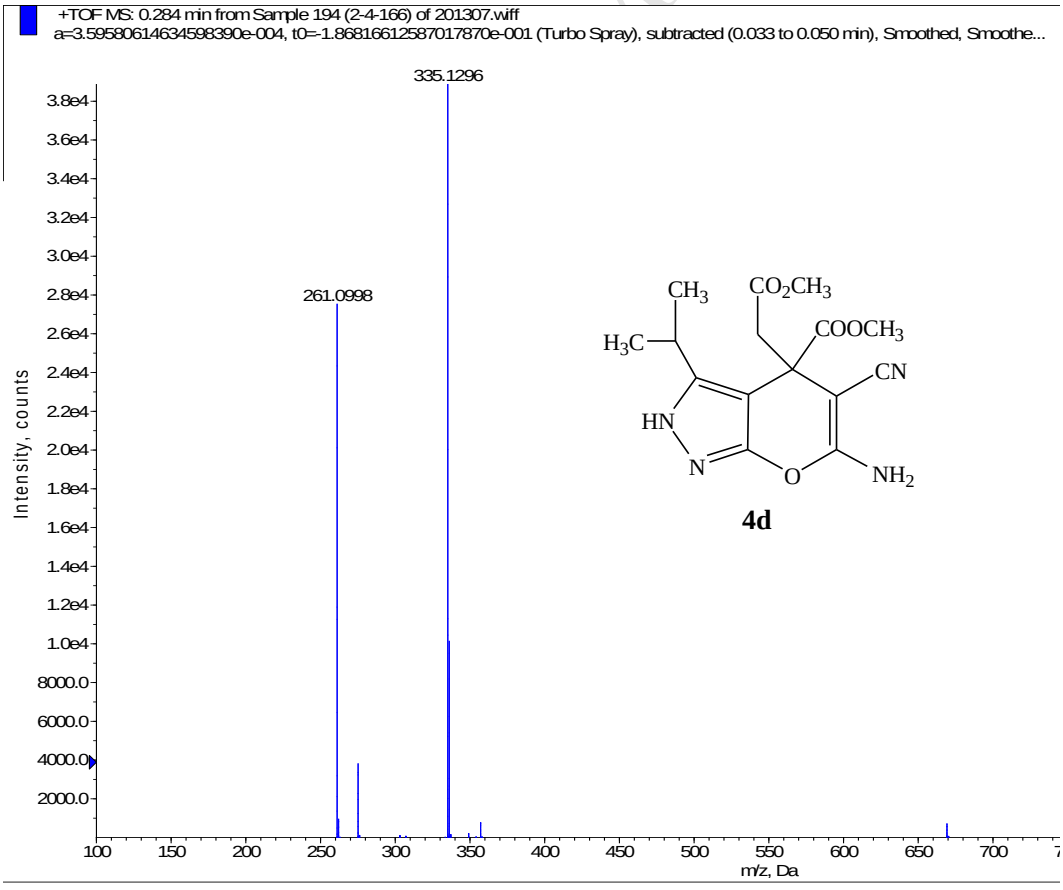
4d


172.453
169.196
161.674
153.970
145.355
118.971
92.572
55.850
52.806
51.121
43.561
40.365
40.009
39.804
39.591
39.386
39.174
38.969
38.756
24.934
21.708
21.261
220 200 180 160 140 120 100 80 60 40 20 0 ppm


3604.38
3350.75
3172.18
2954.09
2880.75
2870.51
2784.61
2720.09
2592.62
2471.83
2194.79
1730.84
1662.04
1601.61
1496.30
1407.62
1355.97
1288.76
1241.48
1154.83
1095.66
1046.74
1016.25
971.88
917.28
872.72
803.46
697.05
629.29
503.86
431.11
Wavenumber cm-1
: 20130604-zai-s-166.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4

CH3
CO2CH3
H3C
COOCH3
CN
HN
N
O
NH2

4d


+TOF MS: 0.284 min from Sample 194 (2-4-166) of 201307.wiff
a=3.59580614634598390e-004, t0=-1.86816612587017870e-001 (Turbo Spray), subtracted (0.033 to 0.050 min), Smoothed, Smoothe...
335.1296
261.0998
Intensity, counts
m/z, Da

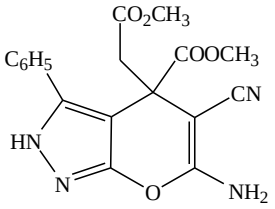
CH3
CO2CH3
H3C
COOCH3
CN
HN
N
O
NH2

4d

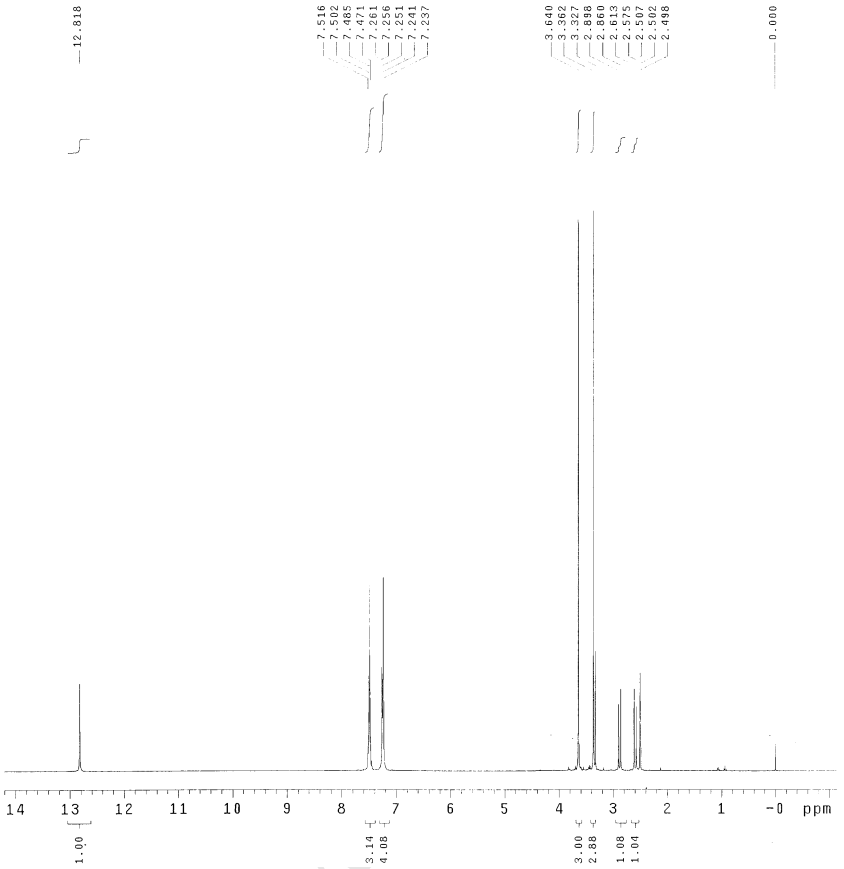
```
xinjiang daxue varian inova-400 1H-4N
zainaipuguli-zai-6-192-abulajiang
in DMSO

exp1  s2pul

      SAMPLE              SPECIAL
date   Jun 14 2013  temp       not used
solvent       DMSO  gain             30
file           exp  spin             20
   ACQUISITION      hst           0.008
sw          6999.7  pw90         10.800
at           3.744  alfa          6.600
np           52412        FLAGS
fb            4000  il                n
bs              16  in                n
d1           3.000  dp                y
nt              40  hs               nn
ct              40       PROCESSING
   TRANSMITTER      fn       not used
tn              H1        DISPLAY
sfrq       399.742  sp          -456.3
tof          800.0  wp          6132.9
tpwr            59  rfl          692.8
pw           5.000  rfp             0
   DECOUPLER        rp          -83.7
dn              C13  lp          -11.1
dof               0       PLOT
dm              nnn  wc             180
dmm               c  sc               0
dpwr             45  vs             120
dmf           20056  th               4
                     nm    ph
```



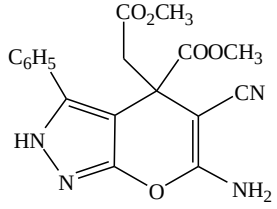
4e



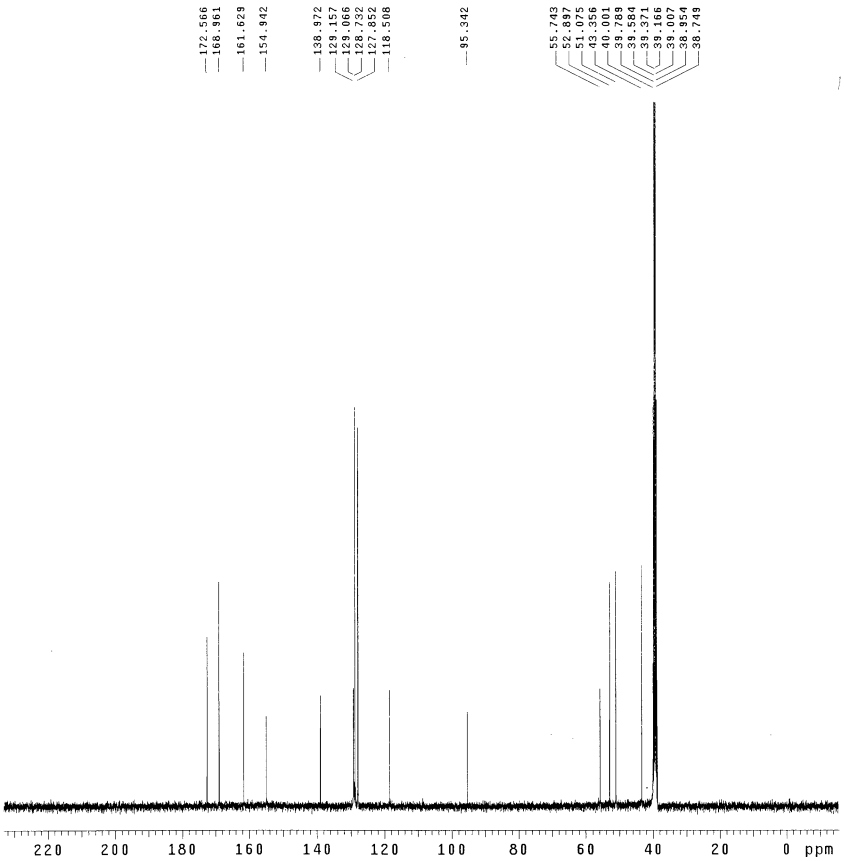

```
xinjiang daxue varian inova-400 13C-4N
zainaipuguli-zai-6-192-abulajiang
in DMSO

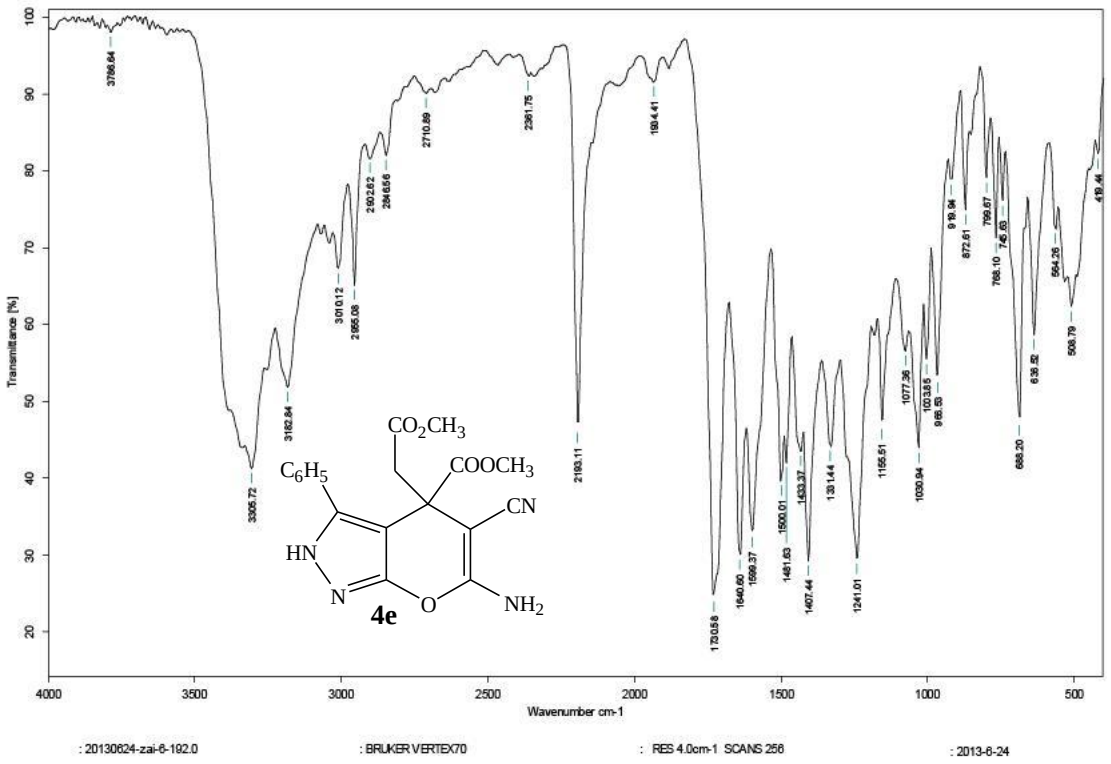
exp2  s2pul

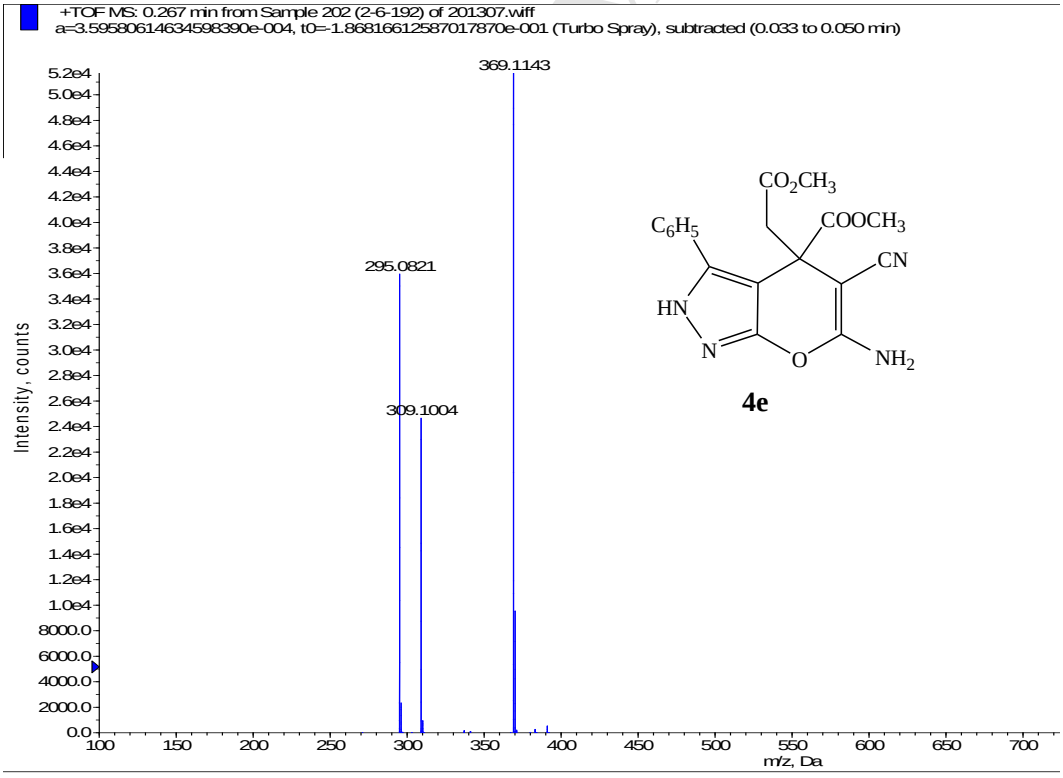
      SAMPLE              SPECIAL
date   Jul 18 2013  temp       not used
solvent       DMSO  gain             50
file           exp  spin             20
   ACQUISITION      hst           0.008
sw          25000.0  pw90         10.800
at            1.199  alfa         20.000
np            59968        FLAGS
fb            14000  il                n
bs               16  in                n
d1            3.000  dp                y
nt              600  hs               nn
ct              600       PROCESSING
   TRANSMITTER      lb            1.00
tn              C13  fn       not used
sfrq       100.525        DISPLAY
tof          1500.0  sp          -1567.1
tpwr             56  wp          24999.2
pw           5.000  rfl          1567.8
   DECOUPLER        rfp             0
dn               H1  rp           -59.2
dof           400.0  lp          -266.7
dm              yyy       PLOT
dmm               w  wc             180
dpwr             42  sc               0
dmf           13400  vs             201
                     th              14
                     nm    ph
```

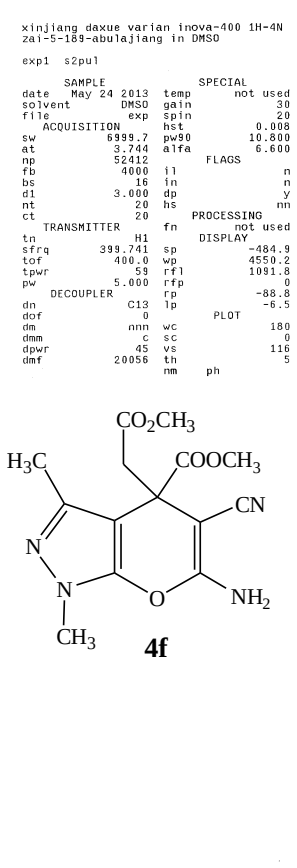


4e



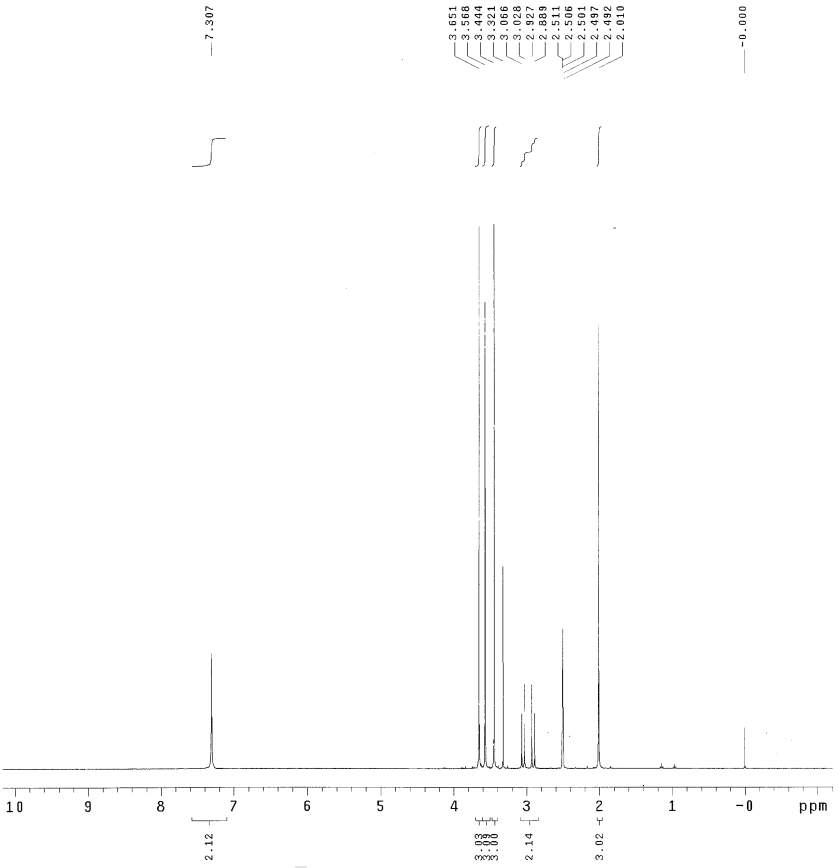

Transmittance [%]
Wavenumber cm-1
3766.64
3305.72
3162.84
3010.12
2955.08
2923.62
2846.56
2710.89
2361.75
2193.11
1994.41
1730.58
1640.60
1599.37
1500.01
1481.63
1453.37
1407.44
1331.44
1241.01
1165.51
1077.36
1030.94
1003.85
965.50
918.94
872.61
799.57
768.10
745.03
688.20
638.82
564.26
508.79
419.44
4e
: 20130624-zai-6-192.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-24

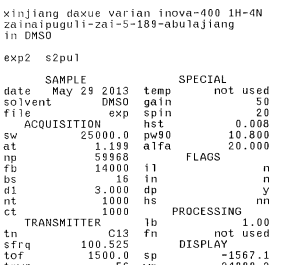

+TOF MS: 0.267 min from Sample 202 (2-6-192) of 201307.wiff
a=3.59580614634598390e-004, t0=-1.86816612587017870e-001 (Turbo Spray), subtracted (0.033 to 0.050 min)
Intensity, counts
m/z, Da
369.1143
295.0821
309.1004
4e

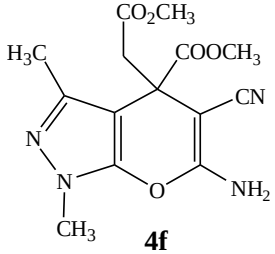

xinjiang daxue varian inova-400 1H-4N
zai-5-189-abulajiang in DMSO
exp1 s2pul
SAMPLE
date May 24 2013
solvent DMSO
file exp
ACQUISITION
sw 6999.7
at 3.744
np 52412
fb 4000
bs 16
d1 3.000
nt 20
ct 20
TRANSMITTER
tn H1
sfrq 399.741
tof 400.0
tpwr 59
pw 5.000
DECOUPLER
dn C13
dof 0
dm nnn
dmm c
dpwr 45
dmf 20056
SPECIAL
temp not used
gain 30
spin 20
hst 0.008
pw90 10.800
alfa 6.600
FLAGS
il n
in n
dp y
hs nn
PROCESSING
fn not used
DISPLAY
sp -484.9
wp 4550.2
rfl 1091.8
rfp 0
rp -88.8
lp -6.5
PLOT
wc 180
sc 0
vs 116
th 5
nm ph

CO2CH3
H3C
COOCH3
CN
N
N
O
NH2
CH3

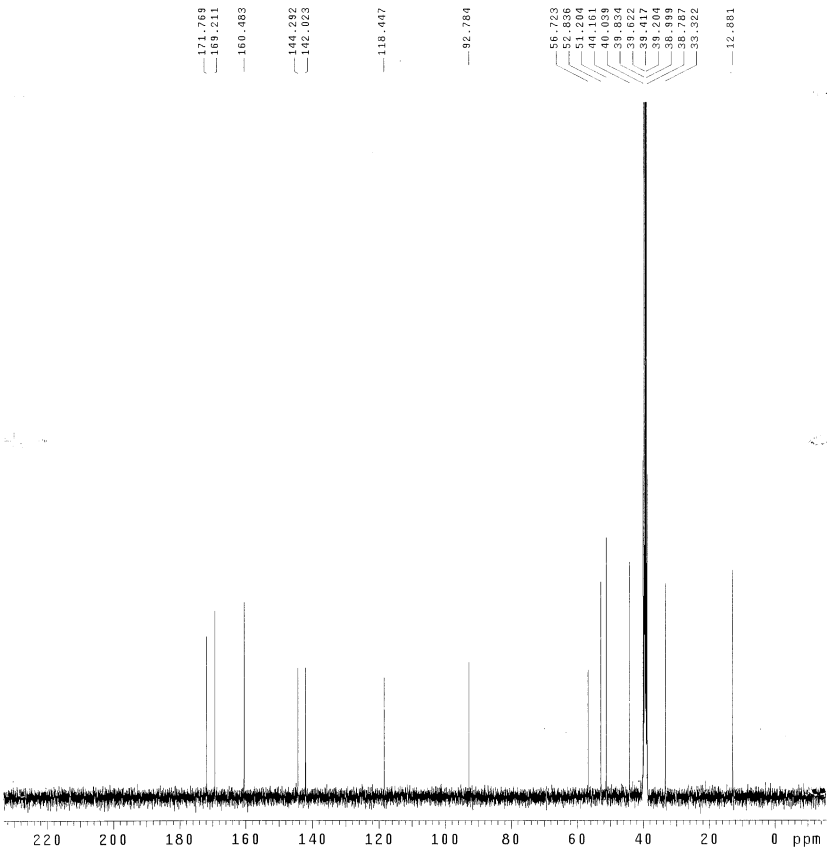
4f


7.307
3.651
3.568
3.444
3.321
3.066
3.028
2.927
2.888
2.511
2.506
2.501
2.497
2.492
2.010
-0.000
10 9 8 7 6 5 4 3 2 1 -0 ppm
2.12
3.03
3.00
2.14
3.02


xinjiang daxue varian inova-400 1H-4N
zainaipuguli-zai-5-189-abulajiang
in DMSO
exp2 s2pul
SAMPLE
date May 29 2013
solvent DMSO
file exp
ACQUISITION
sw 25000.0
at 1.199
np 59968
fb 14000
bs 16
d1 3.000
nt 1000
ct 1000
TRANSMITTER
tn C13
sfrq 100.525
tof 1500.0
tpwr 56
pw 5.000
DECOUPLER
dn H1
dof 400.0
dm yyy
dmm w
dpwr 42
dmf 13400
SPECIAL
temp not used
gain 50
spin 20
hst 0.008
pw90 10.800
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -1567.1
wp 24999.2
rfl 1567.8
rfp 0
rp -6.2
lp -241.1
PLOT
wc 180
sc 0
vs 498
th 9
nm ph


CO2CH3
H3C
COOCH3
CN
N
N
O
NH2
CH3

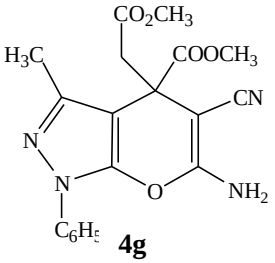
4f


171.769
169.211
160.483
144.292
142.023
118.447
92.784
56.723
52.836
51.204
44.161
40.039
39.834
39.622
39.417
39.204
38.999
38.787
33.322
12.881
220 200 180 160 140 120 100 80 60 40 20 0 ppm

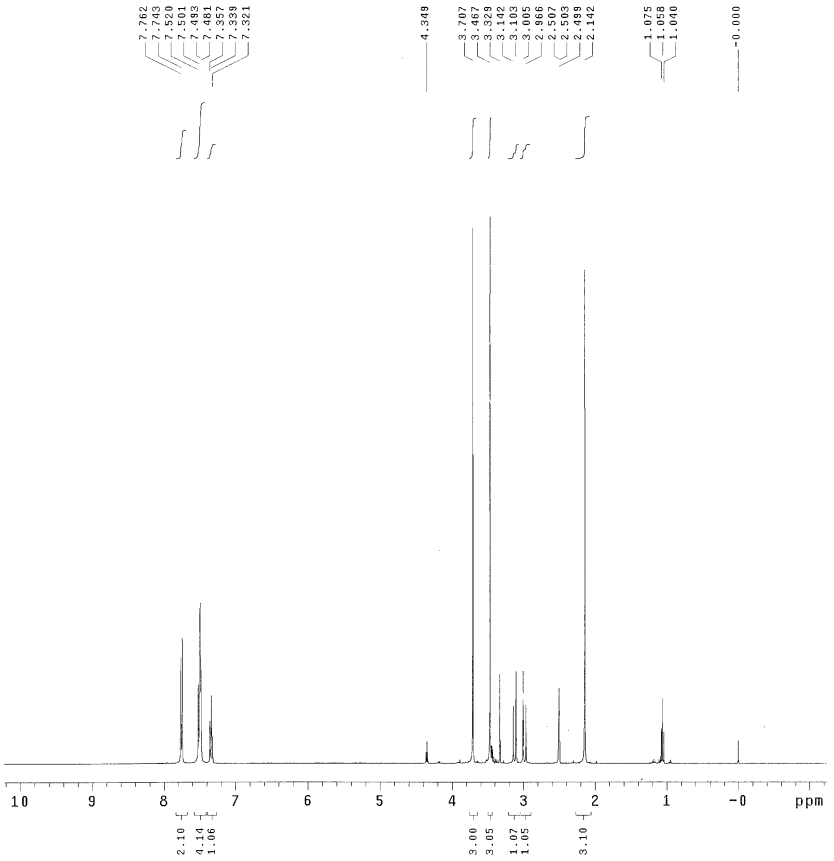
```
xinjiang daxue varian inova-400 1H-4N
zainaipuhguli-1-zai-4-160-abulajiang
in DMSO

exp1  s2pul

      SAMPLE            SPECIAL
date   May  2 2013  temp       not used
solvent       DMSO  gain             30
file           exp  spin             20
   ACQUISITION      hst           0.008
sw          6999.7  pw90          10.800
at           3.744  alfa           6.600
np           52412       FLAGS
fb            4000  il                n
bs              16  in                n
d1           3.000  dp                y
nt              40  hs               nn
ct              40      PROCESSING
   TRANSMITTER      fn         not used
tn              H1      DISPLAY
sfrq       399.741  sp            -506.9
tof          400.0  wp            4595.1
tpwr            59  rfl           1091.1
pw           5.000  rfp              0
   DECOUPLER        rp            -116.4
dn              C13  lp             -14.5
dof               0        PLOT
dm              nnn  wc              180
dmm               c  sc                0
dpwr             45  vs              118
dmf           20056  th                4
                     nm    ph
```



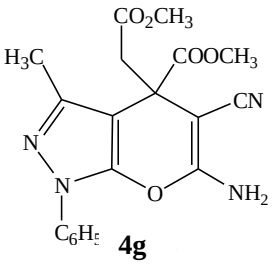
4g



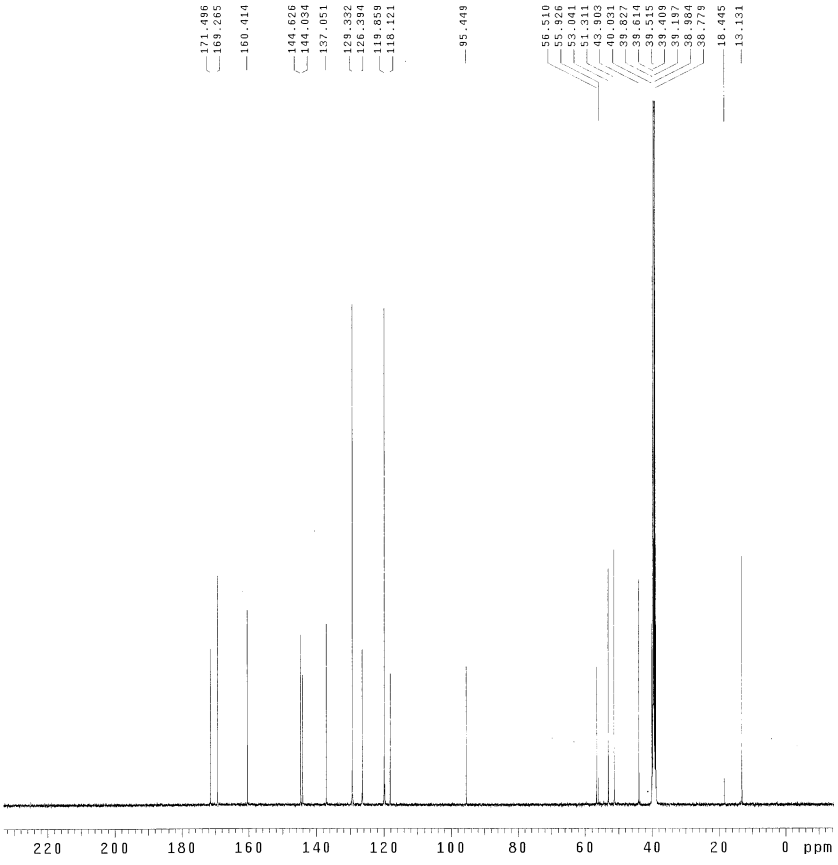

```
xinjiang daxue varian inova-400 13C-4N
zainaipuguli-zai-5-160-abulajiang
in DMSO

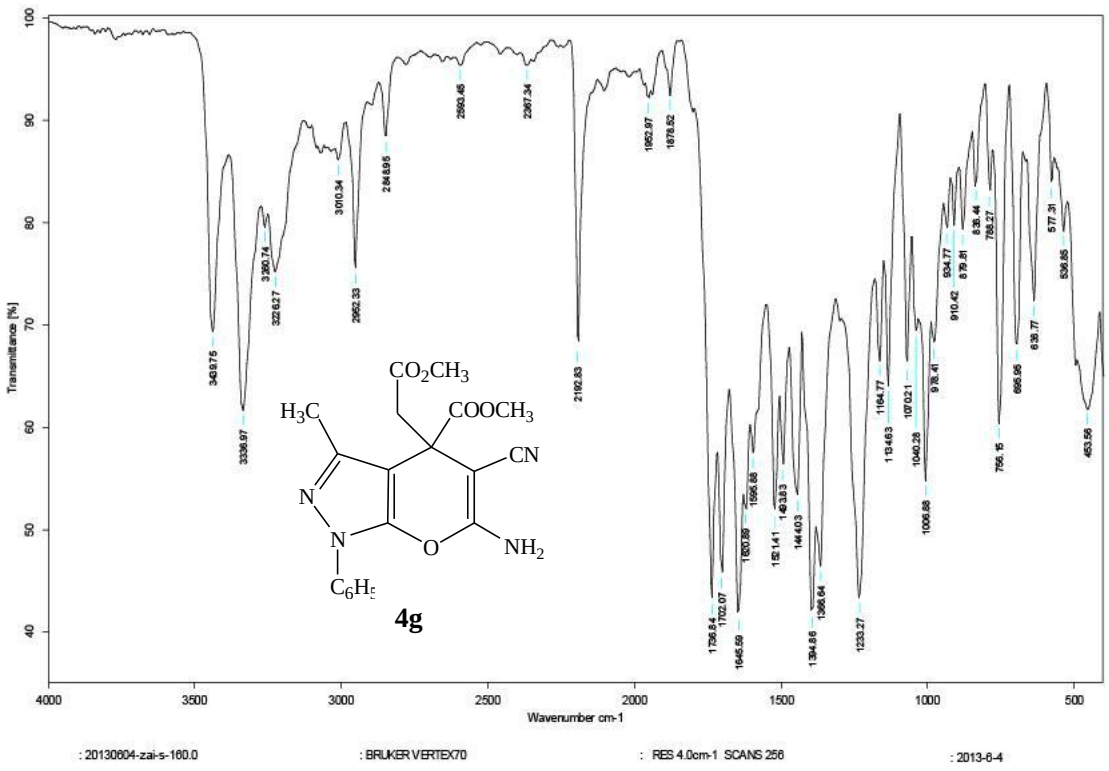
exp2  s2pul

      SAMPLE            SPECIAL
date   May 28 2013  temp       not used
solvent       DMSO  gain             50
file           exp  spin             20
   ACQUISITION      hst           0.008
sw         25000.0  pw90          10.800
at           1.199  alfa          20.000
np           59968       FLAGS
fb           14000  il                n
bs              16  in                n
d1           3.000  dp                y
nt            8800  hs               nn
ct            8800      PROCESSING
   TRANSMITTER      lb            1.00
tn              C13  fn         not used
sfrq       100.525      DISPLAY
tof          1500.0  sp          -1567.1
tpwr            56  wp           24999.2
pw           5.000  rfl           1567.8
   DECOUPLER        rfp              0
dn              H1  rp             -40.4
dof           400.0  lp            -261.4
dm              yyy       PLOT
dmm               w  wc              180
dpwr             42  sc                0
dmf           13400  vs              269
                     th                4
                     nm    ph
```

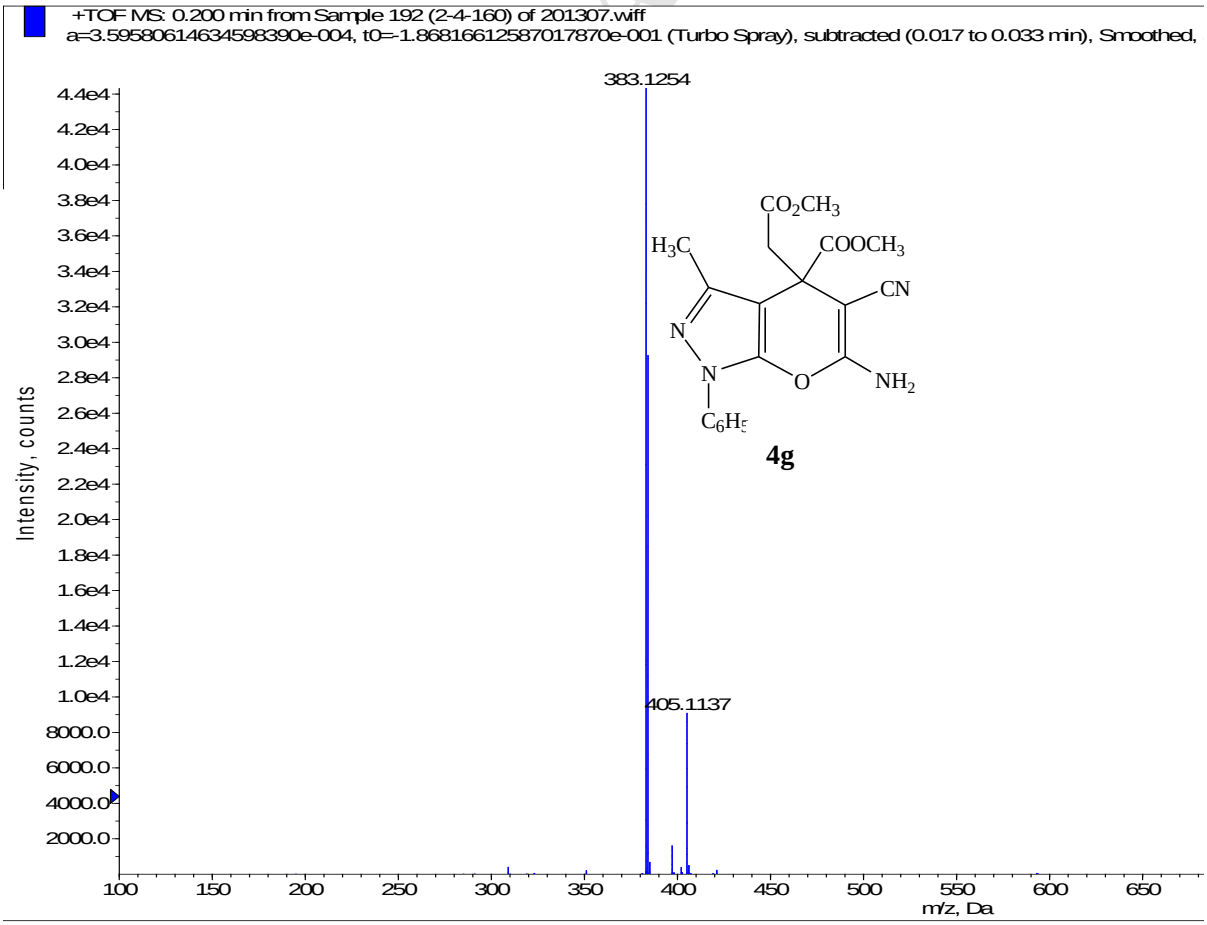


4g




Transmittance [%]
Wavenumber cm-1
: 20130604-zai-s-160.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4
CO_2CH_3
H_3C
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5

4g

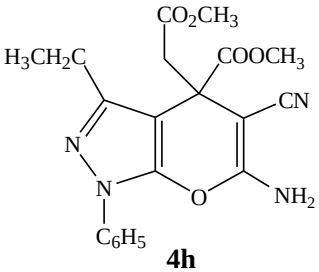

+TOF MS: 0.200 min from Sample 192 (2-4-160) of 201307.wiff
a=3.595806146345983 90e-004, t0=-1.8681661258701787 0e-001 (Turbo Spray), subtracted (0.017 to 0.033 min), Smoothed,
383.1254
405.1137
Intensity, counts
m/z, Da
CO_2CH_3
H_3C
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5

4g

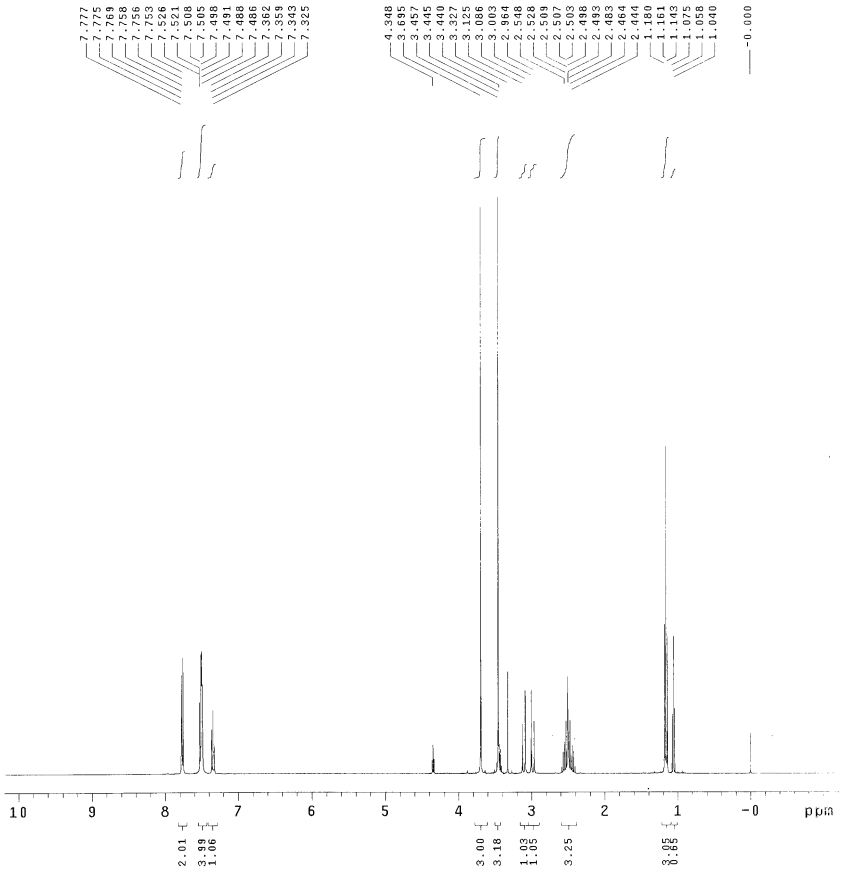
```
xinjiang daxue varian inova-400 1H-4N
zai-5-174-abulajiang in DMSO

exp1  s2pul

      SAMPLE                SPECIAL
date    May 24 2013  temp       not used
solvent        DMSO  gain             30
file            exp  spin             20
   ACQUISITION       hst           0.008
sw           6999.7  pw90         10.800
at            3.744  alfa          6.600
np            52412       FLAGS
fb             4000  il                n
bs               16  in                n
d1            3.000  dp                y
nt               20  hs               nn
ct               20       PROCESSING
   TRANSMITTER       fn       not used
tn               H1       DISPLAY
sfrq       399.741  sp           -484.5
tof          400.0  wp           4561.3
tpwr            59  rfl          1091.4
pw           5.000  rfp             0
    DECOUPLER       rp           -85.1
dn              C13  lp           -15.7
dof               0        PLOT
dm              nnn  wc            180
dmm               c  sc              0
dpwr             45  vs            123
dmf           20056  th              5
                     nm    ph
```



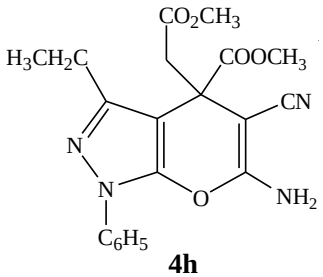
4h



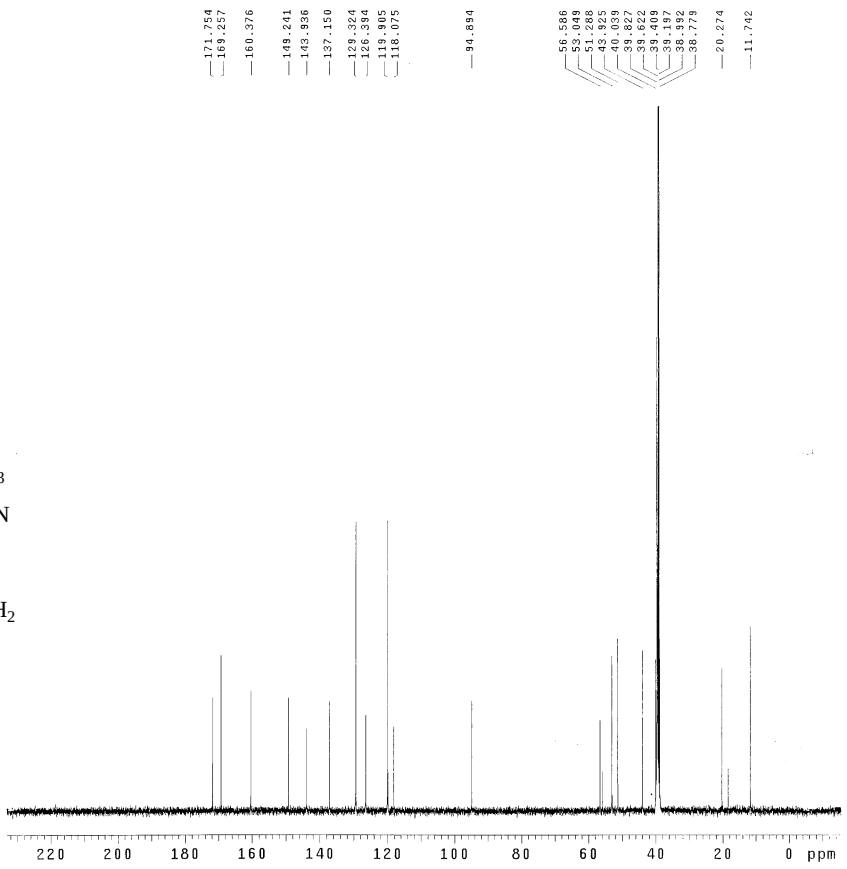

```
xinjiang daxue varian inova-400 13C-4N
zainaipuguli-zai-5-174-abulajiang
in DMSO

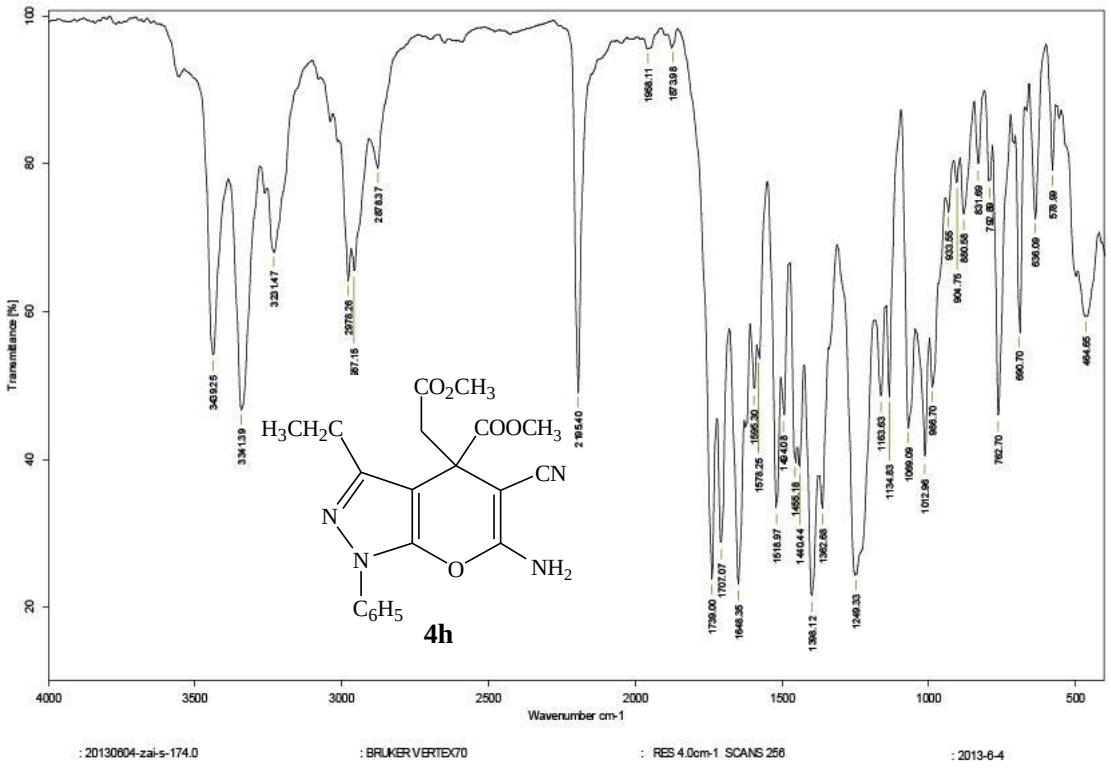
exp2  s2pul

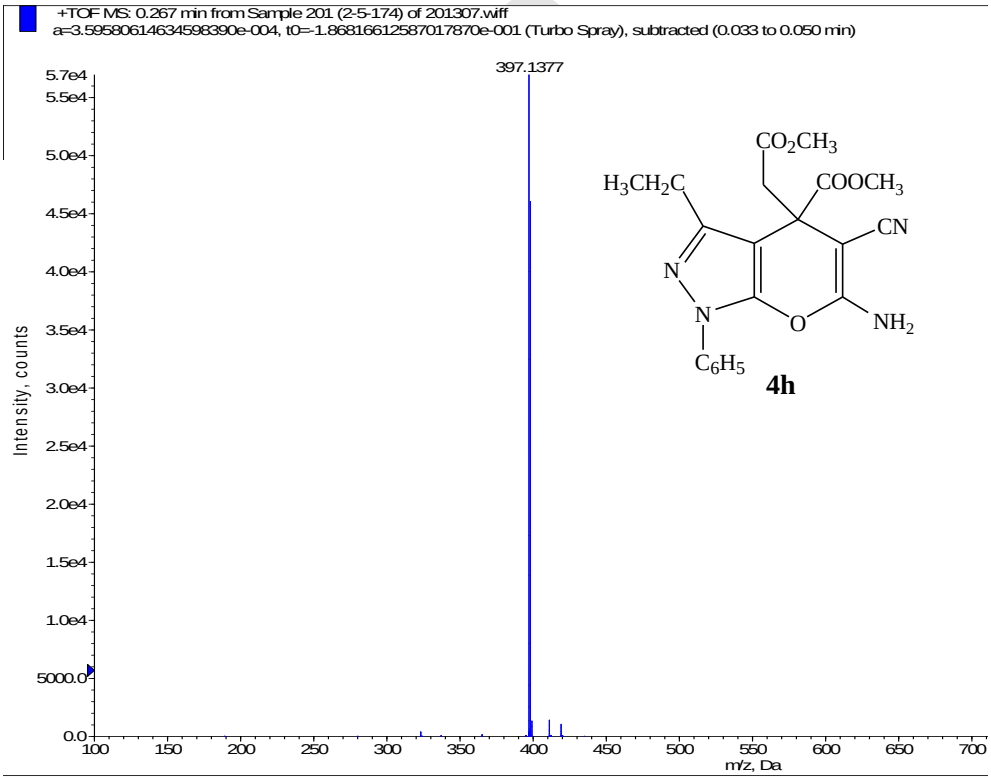
      SAMPLE                SPECIAL
date    May 29 2013  temp       not used
solvent        DMSO  gain             50
file            exp  spin             20
   ACQUISITION       hst           0.008
sw          25000.0  pw90         10.800
at            1.199  alfa         20.000
np            59968       FLAGS
fb            14000  il                n
bs               16  in                n
d1            3.000  dp                y
nt             1000  hs               nn
ct             1000       PROCESSING
   TRANSMITTER       lb            1.00
tn              C13  fn       not used
sfrq       100.525       DISPLAY
tof          1500.0  sp           -1567.1
tpwr             58  wp           24999.2
pw           5.000  rfl           1567.8
    DECOUPLER       rfp             0
dn               H1  rp            -6.5
dof           400.0  lp           -254.7
dm              yyy        PLOT
dmm               w  wc            180
dpwr             42  sc              0
dmf           13400  vs            237
                     th             12
                     nm    ph
```



4h



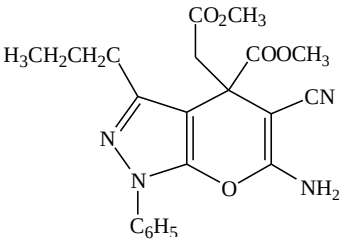

Transmittance [%]
Wavenumber cm-1
: 20130604-zai-s-174.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4
CO_2CH_3
H_3CH_2C
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5
4h


+TOF MS: 0.267 min from Sample 201 (2-5-174) of 201307.wiff
a=3.5958061463459839 0e-004, t0=-1.8681661258701787 0e-001 (Turbo Spray), subtracted (0.033 to 0.050 min)
397.1377
Intensity, counts
m/z, Da
CO_2CH_3
H_3CH_2C
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5
4h

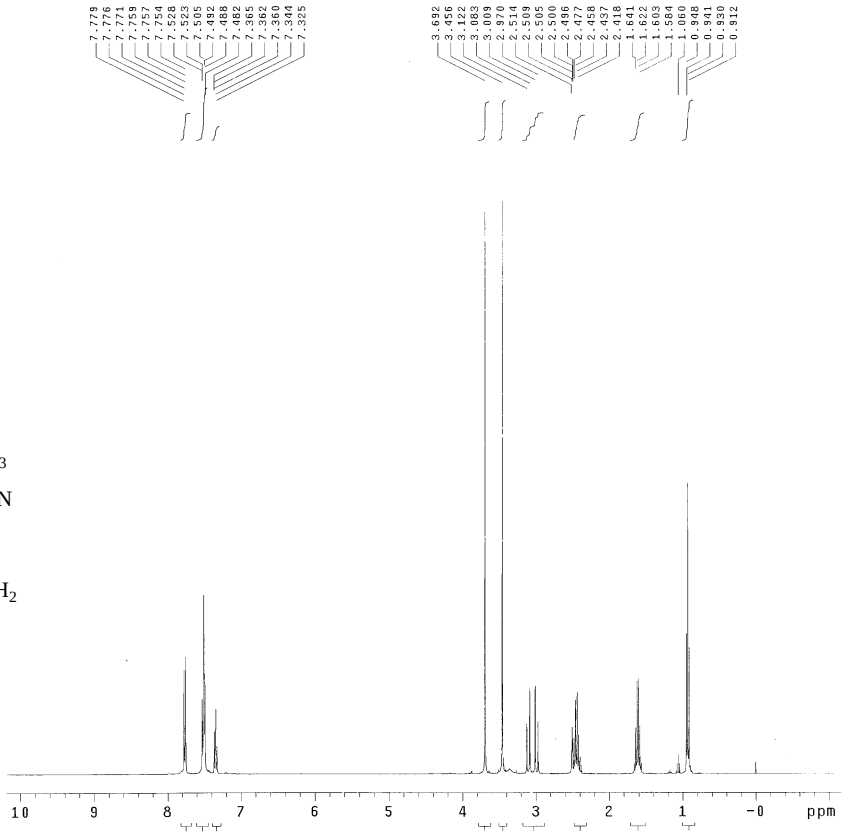
```
xinjiang daxue varian inova-400 1H-4N
zai-5-173-abulajiang in DMSO

exp1  s2pul

      SAMPLE              SPECIAL
date    May 20 2013  temp       not used
solvent        DMSO  gain             30
file            exp  spin             20
   ACQUISITION       hst           0.008
sw           6999.7  pw90         10.800
at            3.744  alfa          6.600
np            52412        FLAGS
fb             4000  il                n
bs               16  in                n
d1            3.000  dp                y
nt               40  hs               nn
ct               40      PROCESSING
   TRANSMITTER       fn       not used
tn               H1      DISPLAY
sfrq       399.742  sp           -465.9
tof          800.0  wp           4538.9
tpwr            59  rfl           690.6
pw           5.000  rfp              0
    DECOUPLER       rp            -80.7
dn              C13  lp            -14.1
dof               0       PLOT
dm              nnn  wc              180
dmm               c  sc                0
dpwr             45  vs              122
dmf           20056  th                4
                     nm    ph
```



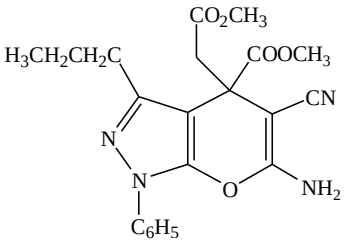
4i



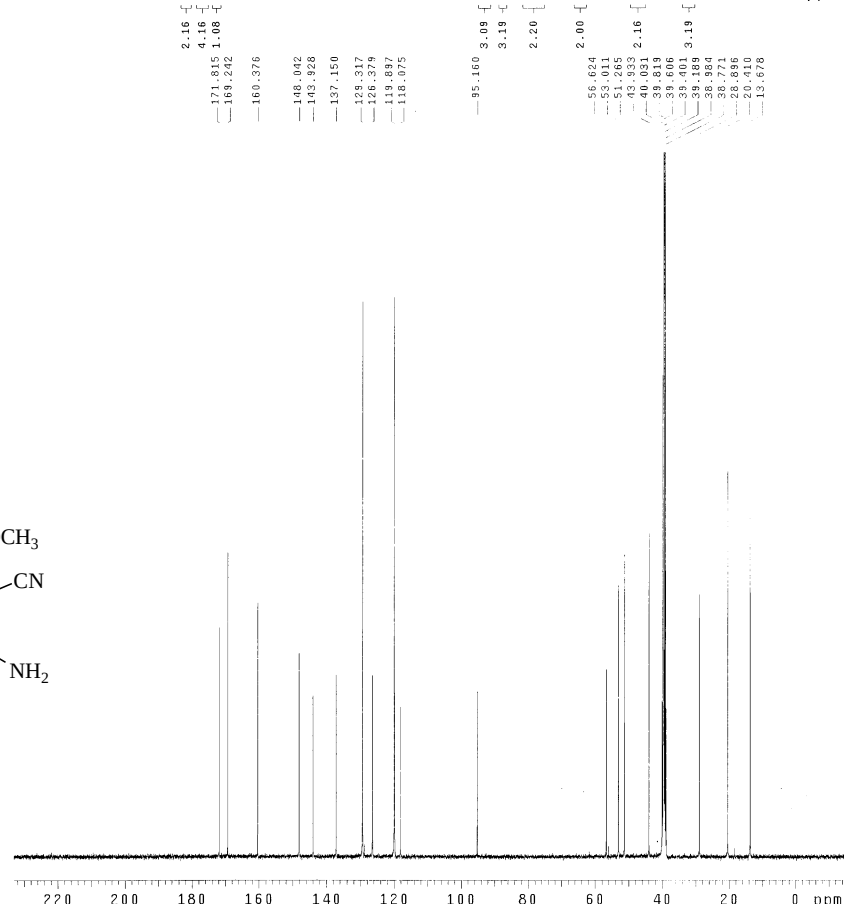

```
xinjiang daxue varian inova-400 13C-4N
zainaipuguli-zai-5-173-abulajiang
in DMSO

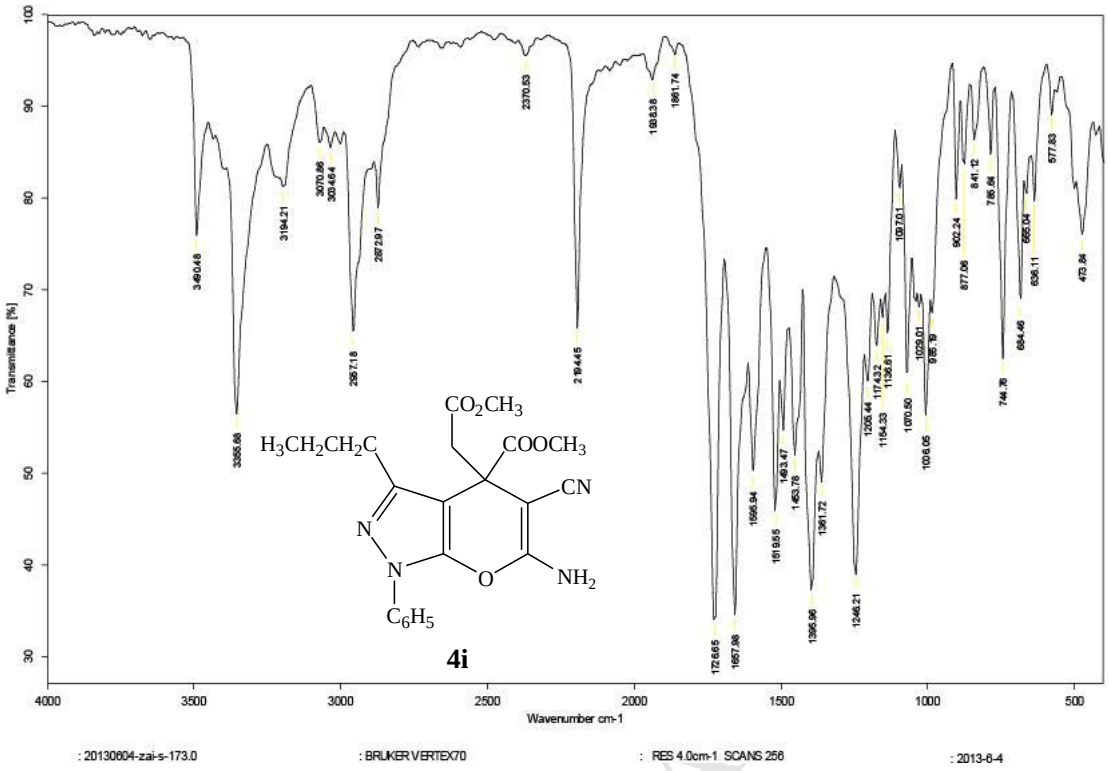
exp2  s2pul

      SAMPLE              SPECIAL
date    May 29 2013  temp       not used
solvent        DMSO  gain             50
file            exp  spin             20
   ACQUISITION       hst           0.008
sw          25000.0  pw90         10.800
at            1.199  alfa         20.000
np            59968        FLAGS
fb            14000  il                n
bs               16  in                n
d1            3.000  dp                y
nt             3000  hs               nn
ct             3000      PROCESSING
   TRANSMITTER       lb             1.00
tn              C13  fn       not used
sfrq       100.525       DISPLAY
tof          1500.0  sp           -1567.1
tpwr             56  wp           24999.2
pw           5.000  rfl           1567.8
    DECOUPLER       rfp              0
dn               H1  rp            -16.7
dof           400.0  lp            -254.7
dm              yyy       PLOT
dmm               w  wc              180
dpwr             42  sc                0
dmf           13400  vs              237
                     th               12
                     nm    ph
```

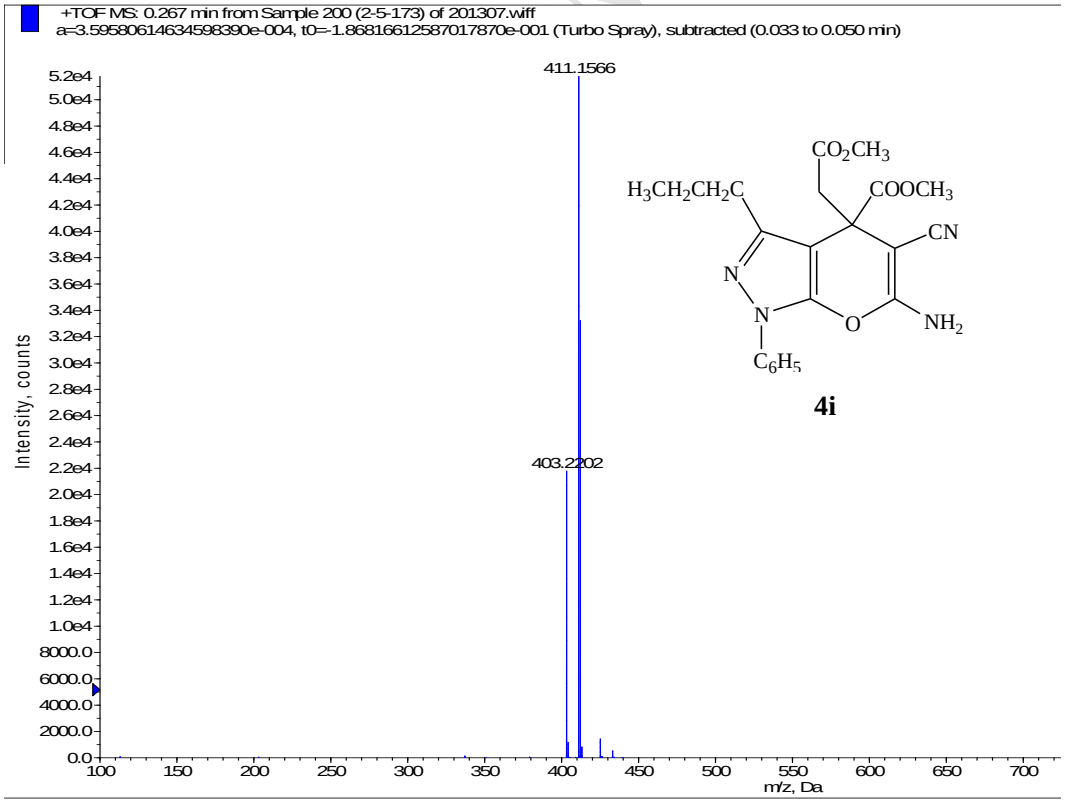


4i




Transmittance [%]
Wavenumber cm-1
: 20130604-zai-s-173.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4
CO_2CH_3
$H_3CH_2CH_2C$
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5

4i

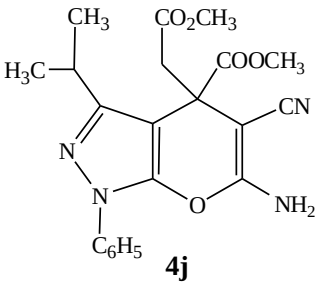

+TOF MS: 0.267 min from Sample 200 (2-5-173) of 201307.wiff
a=3.59580614634598390e-004, t0=-1.86816612587017870e-001 (Turbo Spray), subtracted (0.033 to 0.050 min)
411.1566
403.2202
Intensity, counts
m/z, Da
CO_2CH_3
$H_3CH_2CH_2C$
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5

4i

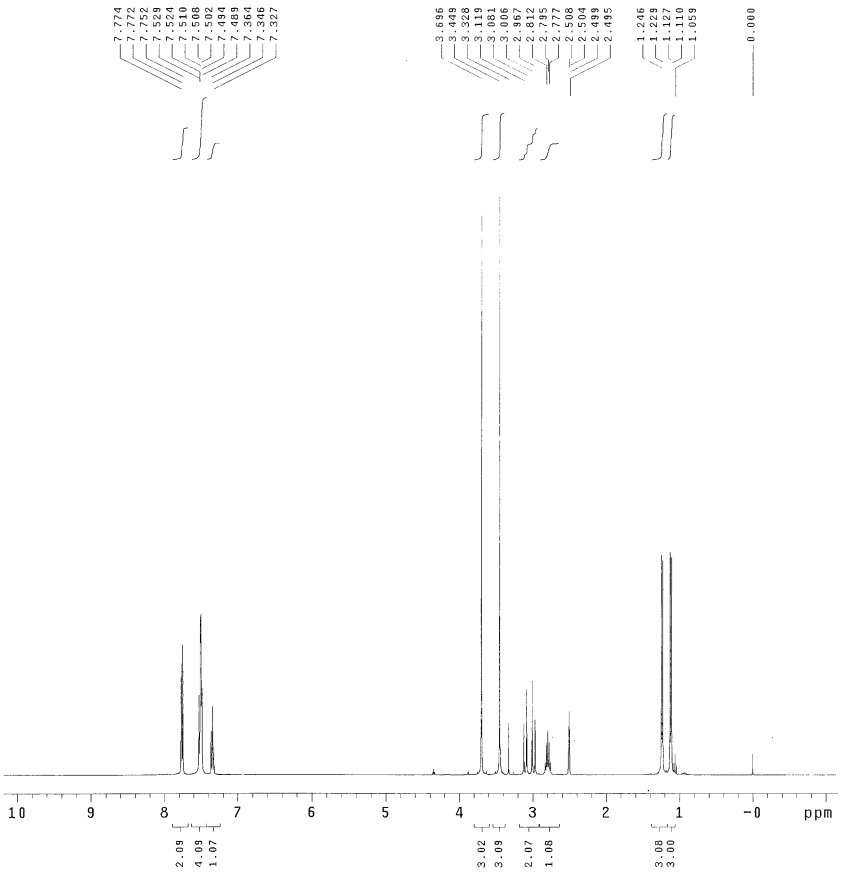
```
xinjiang daxue varian inova-400 1H-4N
zai-5-172-abulajiang in DMSO

exp1  s2pul

      SAMPLE                SPECIAL
date    May 20 2013  temp        not used
solvent        DMSO  gain              30
file            exp  spin              20
   ACQUISITION       hst            0.008
sw           6999.7  pw90          10.800
at            3.744  alfa           6.600
np            52412        FLAGS
fb             4000  il                n
bs               16  in                n
d1            3.000  dp                y
nt               40  hs               nn
ct               40      PROCESSING
   TRANSMITTER       fn        not used
tn               H1        DISPLAY
sfrq       399.742  sp            -466.1
tof          800.0  wp            4538.9
tpwr            59  rfl            690.8
pw           5.000  rfp               0
    DECOUPLER       rp            -84.3
dn              C13  lp            -10.6
dof               0        PLOT
dm              nnn  wc              180
dmm               c  sc                0
dpwr             45  vs              123
dmf           20056  th                4
                     nm    ph
```



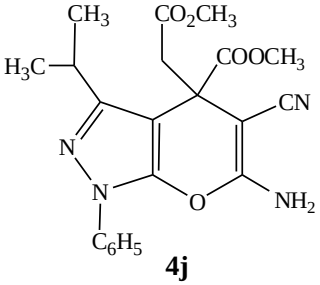
4j



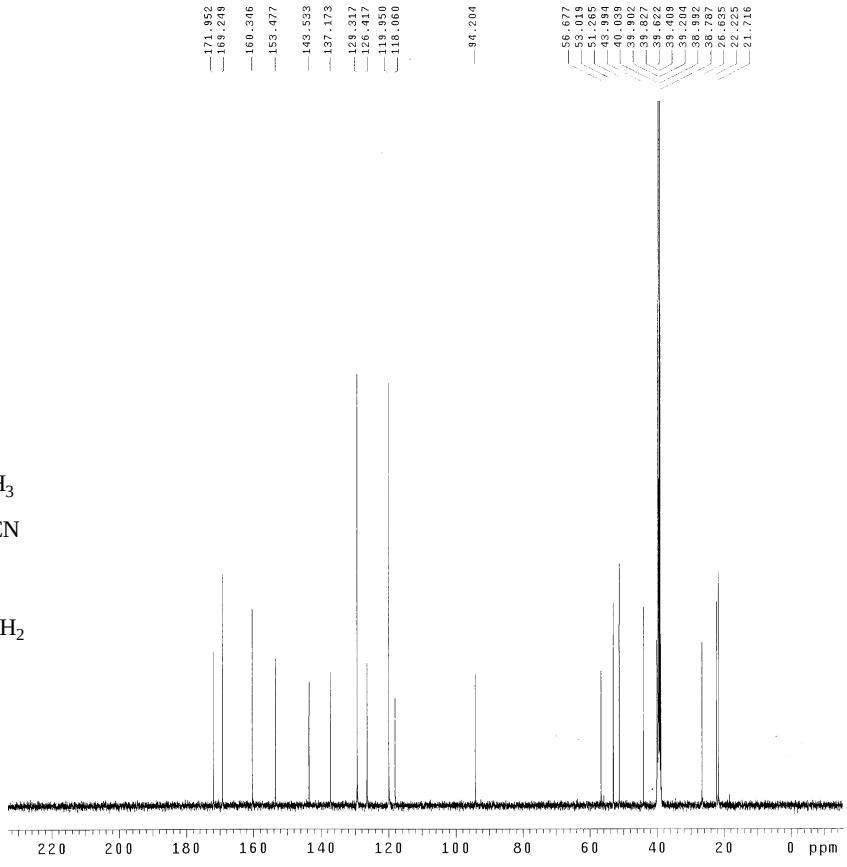

```
xinjiang daxue varian inova-400 13C-4N
zainaipugull-zai-5-172-abulajiang
in DMSO

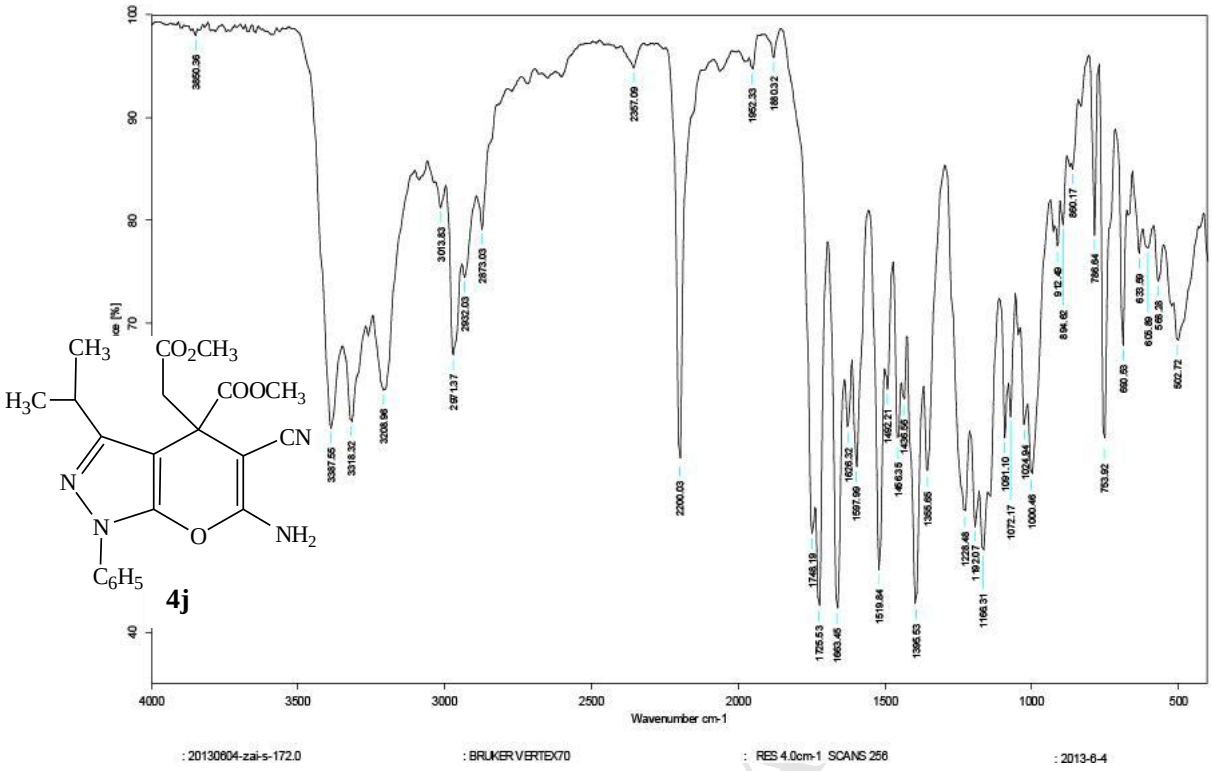
exp2  s2pul

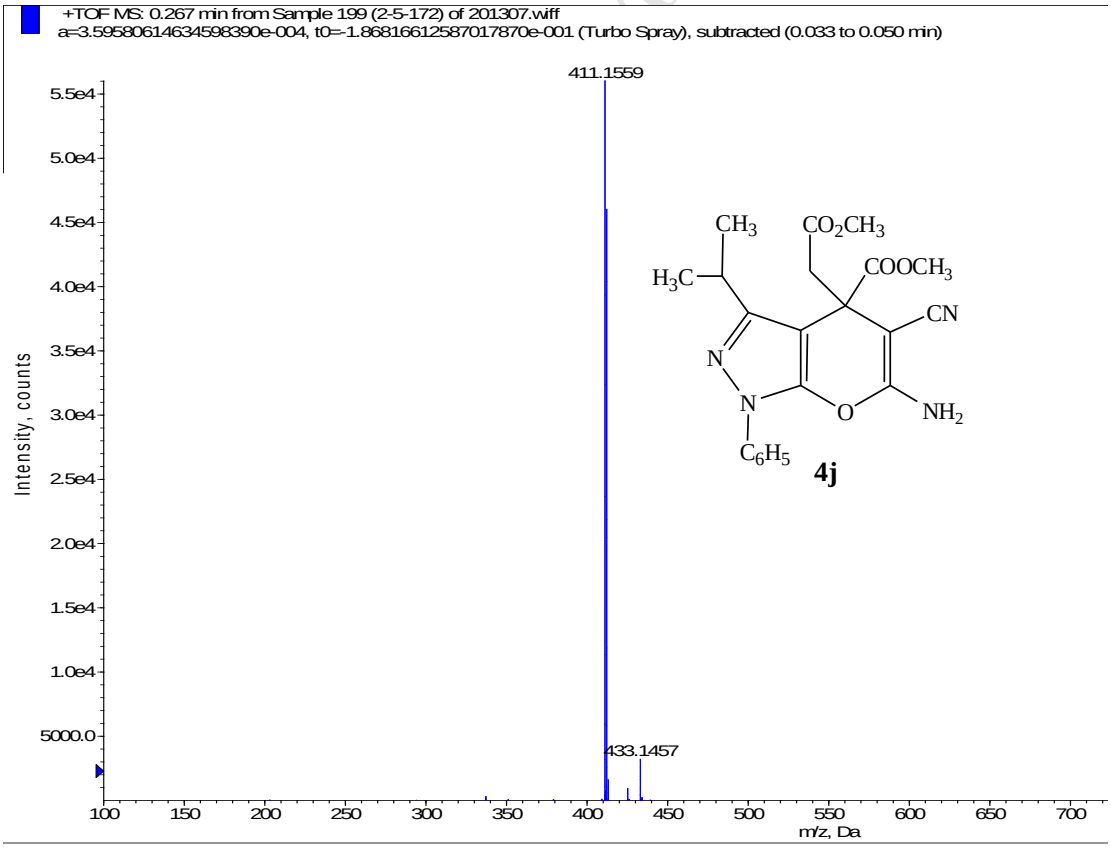
      SAMPLE                SPECIAL
date    May 28 2013  temp        not used
solvent        DMSO  gain              50
file            exp  spin              20
   ACQUISITION       hst            0.008
sw          25000.0  pw90          10.800
at            1.199  alfa          20.000
np            59968        FLAGS
fb            14000  il                n
bs               16  in                n
d1            3.000  dp                y
nt             1300  hs               nn
ct             1300      PROCESSING
   TRANSMITTER       lb             1.00
tn              C13  fn        not used
sfrq       100.525        DISPLAY
tof         1500.0  sp            -1567.1
tpwr            56  wp           24999.2
pw           5.000  rfl           1567.8
    DECOUPLER       rfp               0
dn               H1  rp             -33.0
dof           400.0  lp            -272.6
dm              yyy        PLOT
dmm               w  wc              180
dpwr             42  sc                0
dmf           13400  vs              251
                     th               12
                     nm    ph
```



4j



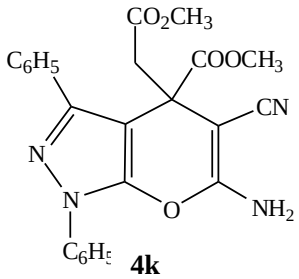

Wavenumber cm-1
: 20130604-zai-s-172.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4
4j


+TOF MS: 0.267 min from Sample 199 (2-5-172) of 201307.wiff
a=3.59580614634598390e-004, t0=-1.86816612587017870e-001 (Turbo Spray), subtracted (0.033 to 0.050 min)
411.1559
433.1457
Intensity, counts
m/z, Da
4j

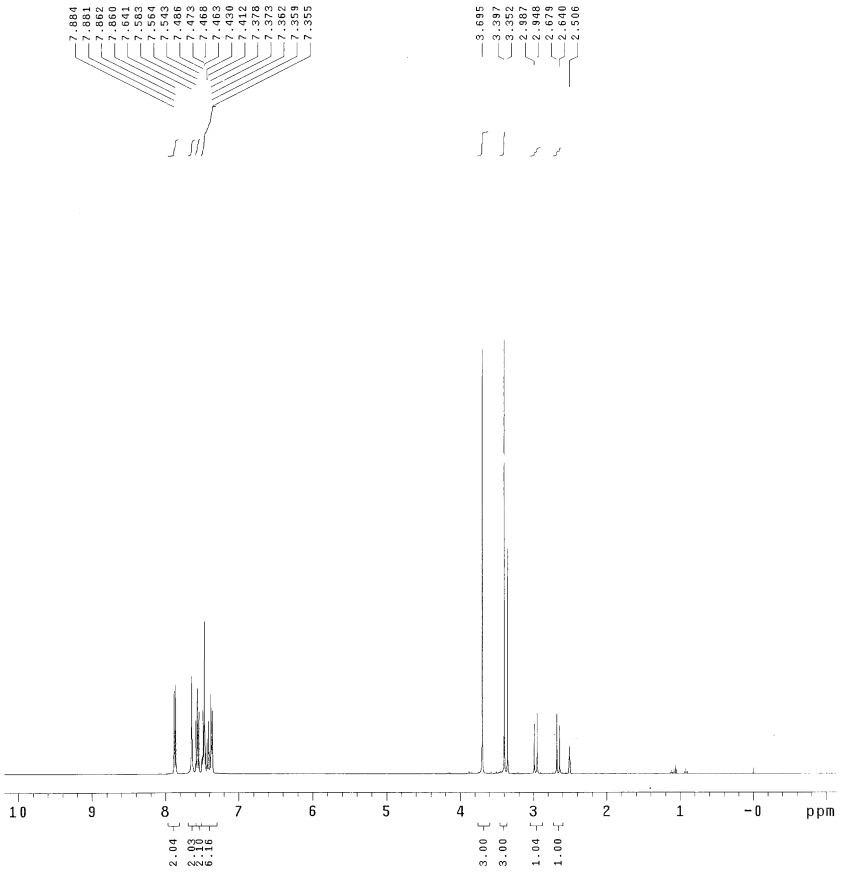
```
xinjiang daxue varian inova-400 1H-4N
zai-5-171-abulajiang in DMSO

exp1  s2pul

      SAMPLE              SPECIAL
date   May 20 2013  temp       not used
solvent       DMSO  gain             30
file           exp  spin             20
   ACQUISITION      hst           0.008
sw          6999.7  pw90         10.800
at           3.744  alfa          6.600
np           52412       FLAGS
fb            4000  il                n
bs              16  in                n
d1           3.000  dp                y
nt              40  hs               nn
ct              40      PROCESSING
   TRANSMITTER      fn        not used
tn               H1      DISPLAY
sfrq       399.742  sp           -476.4
tof          800.0  wp          4550.2
tpwr            59  rfl          690.0
pw           5.000  rfp             0
   DECOUPLER        rp           -79.6
dn              C13  lp           -16.5
dof               0      PLOT
dm              nnn  wc              180
dmm               c  sc                0
dpwr             45  vs               92
dmf           20056  th                6
                     nm    ph
```



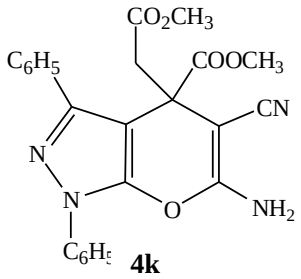
4k



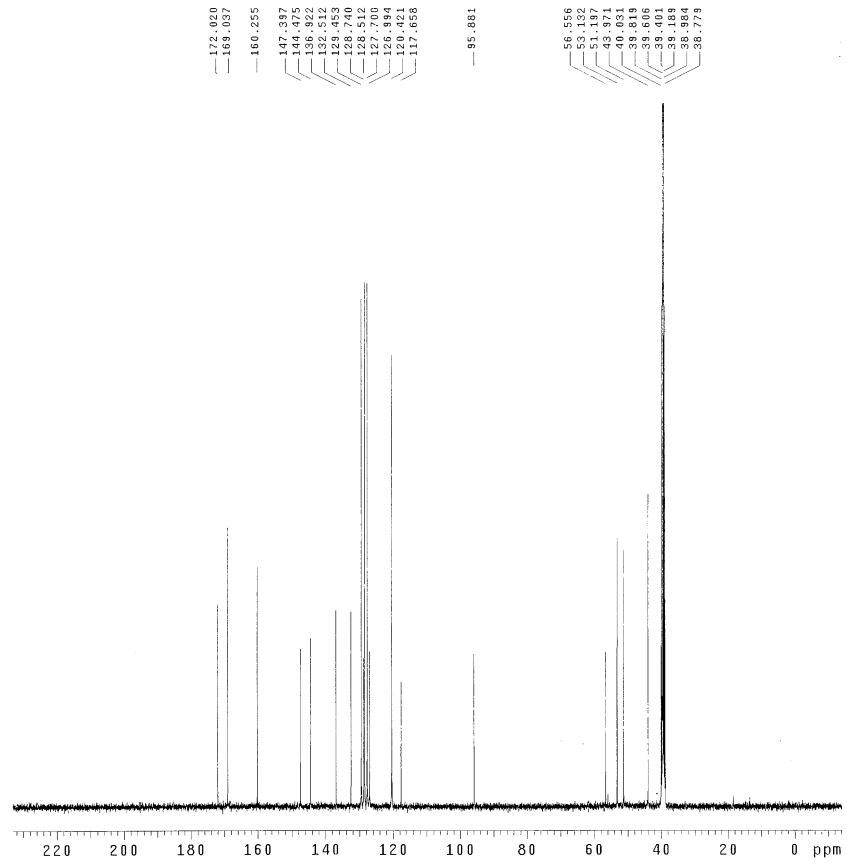

```
xinjiang daxue varian inova-400 13C-4N
zainaipugull-zai-5-171-abulajiang
in DMSO

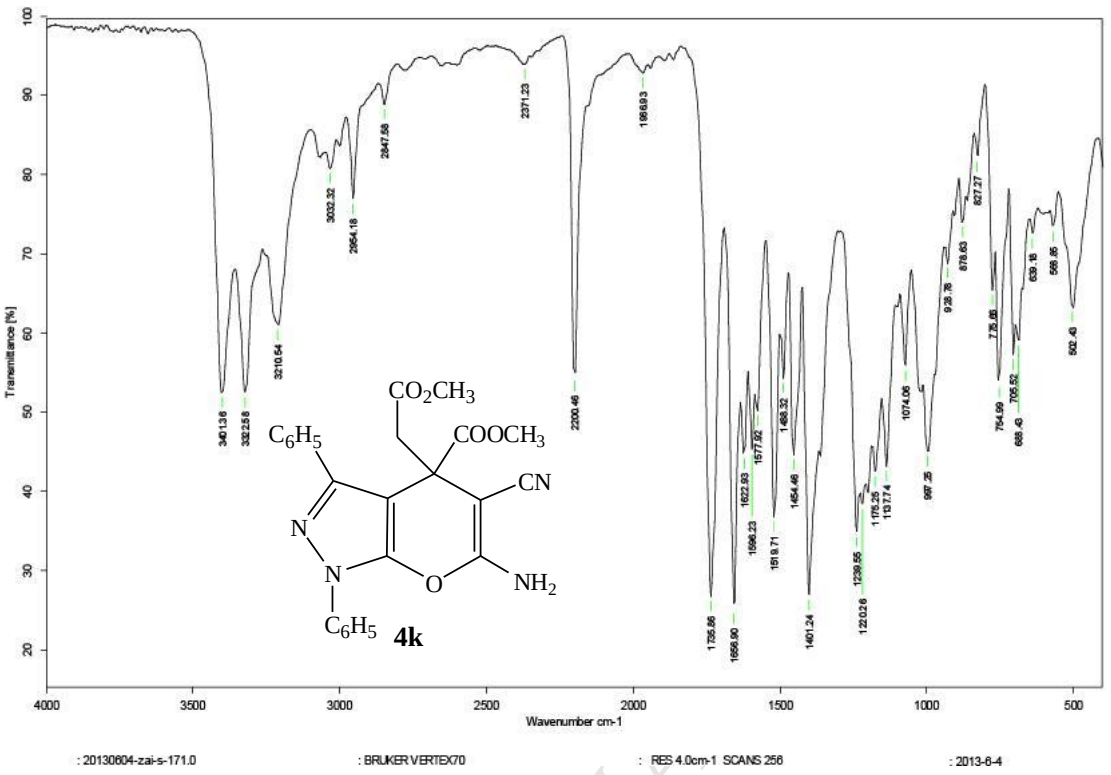
exp2  s2pul

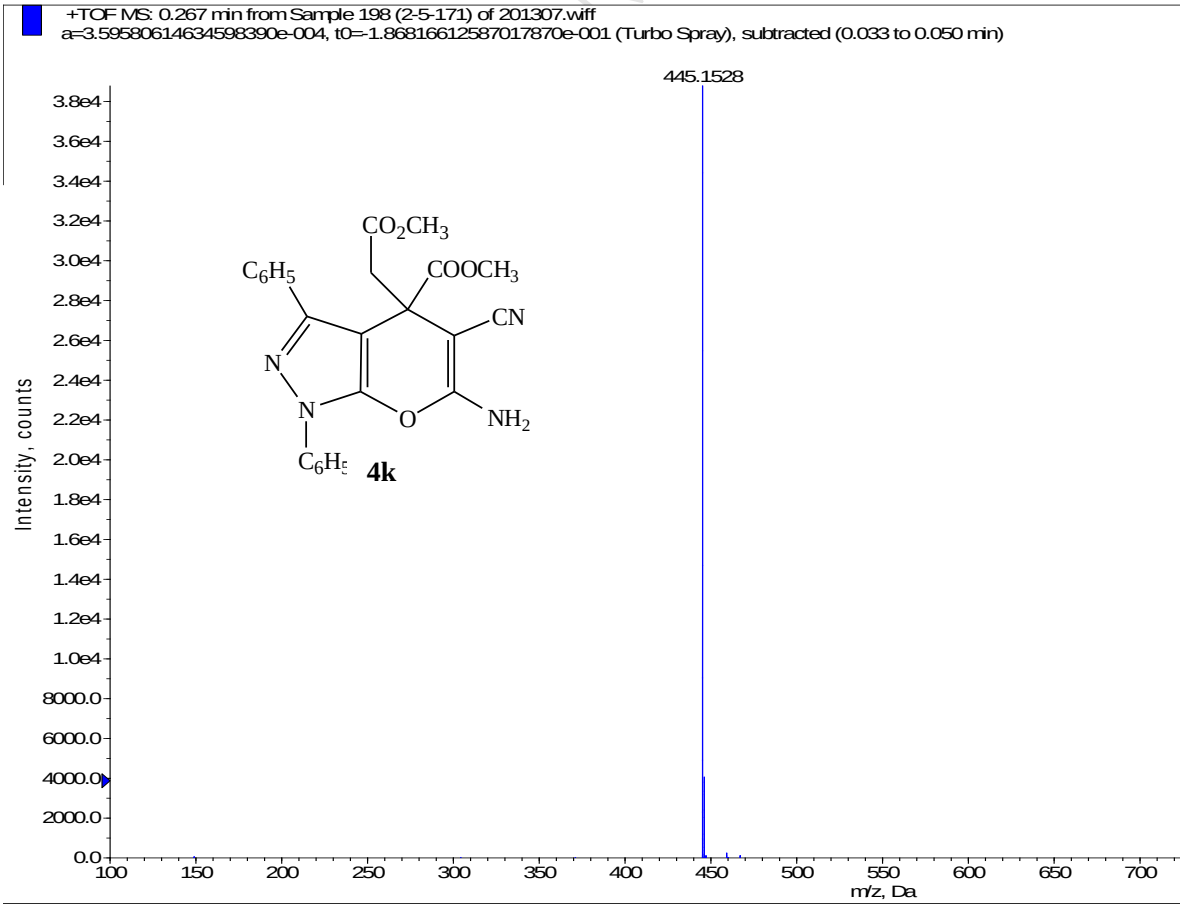
      SAMPLE              SPECIAL
date   May 28 2013  temp       not used
solvent       DMSO  gain             50
file           exp  spin             20
   ACQUISITION      hst           0.008
sw         25000.0  pw90         10.800
at           1.199  alfa         20.000
np           59968       FLAGS
fb           14000  il                n
bs              16  in                n
d1           3.000  dp                y
nt            1400  hs               nn
ct            1400      PROCESSING
   TRANSMITTER      lb            1.00
tn              C13  fn        not used
sfrq       100.525      DISPLAY
tof         1500.0  sp           -1567.1
tpwr            56  wp          24999.2
pw           5.000  rfl          1567.8
   DECOUPLER        rfp             0
dn               H1  rp            -11.5
dof           400.0  lp           -262.6
dm              yyy      PLOT
dmm               w  wc              180
dpwr             42  sc                0
dmf           13400  vs              251
                     th               12
                     nm    ph
```



4k



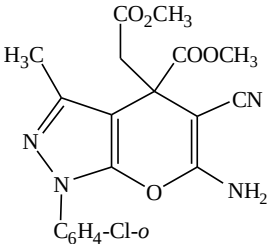

Transmittance [%]
Wavenumber cm-1
: 20130604-zai-s-171.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-4
CO_2CH_3
C_6H_5
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5
4k


+TOF MS: 0.267 min from Sample 198 (2-5-171) of 201307.wiff
a=3.5958061463459839 0e-004, t0=-1.8681661258701787 0e-001 (Turbo Spray), subtracted (0.033 to 0.050 min)
445.1528
Intensity, counts
m/z, Da
CO_2CH_3
C_6H_5
$COOCH_3$
CN
N
N
O
NH_2
C_6H_5
4k

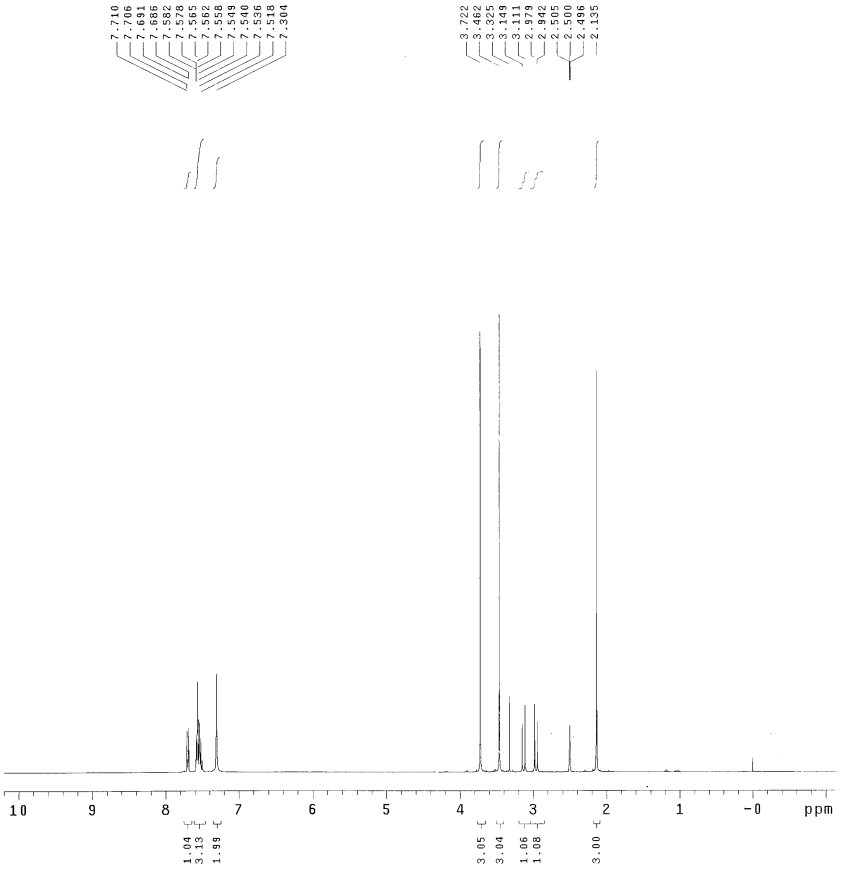
```
xinjiang daxue varian inova-400 1H-4N
zainaipuguli-zai-6-193-abulajiang
in DMSO

exp1  s2pul

      SAMPLE                SPECIAL
date   Jun 14 2013  temp        not used
solvent       DMSO  gain              30
file           exp  spin              20
   ACQUISITION      hst            0.008
sw          6999.7  pw90          10.800
at           3.744  alfa           6.600
np           52412       FLAGS
fb            4000  il                n
bs              16  in                n
d1           3.000  dp                y
nt              20  hs               nn
ct              20      PROCESSING
   TRANSMITTER      fn        not used
tn              H1      DISPLAY
sfrq       399.742  sp            -468.5
tof          800.0  wp            4546.2
tpwr            59  rfl            693.6
pw           3.000  rfp               0
   DECOUPLER        rp            -80.9
dn              C13  lp            -11.1
dof               0       PLOT
dm              nnn  wc              180
dmm               c  sc                0
dpwr             45  vs               97
dmf           20056  th                4
                     nm    ph
```



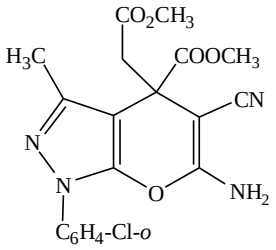
4l



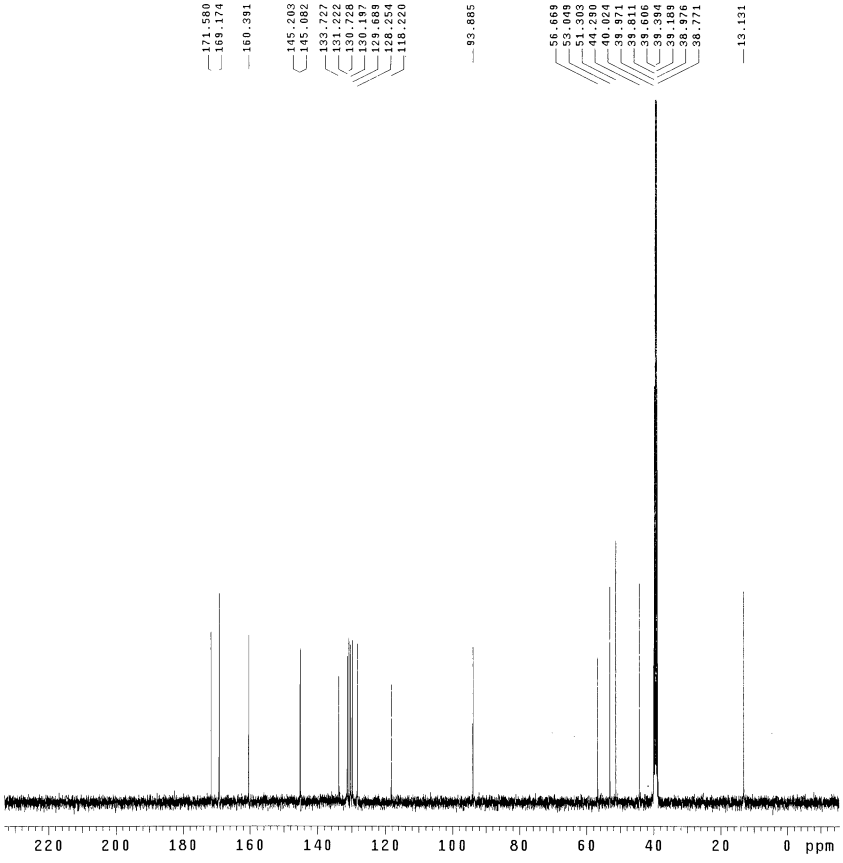

```
xinjiang daxue varian inova-400 13C-4N
zainaipuguli-zai-6-193-abulajiang
in DMSO

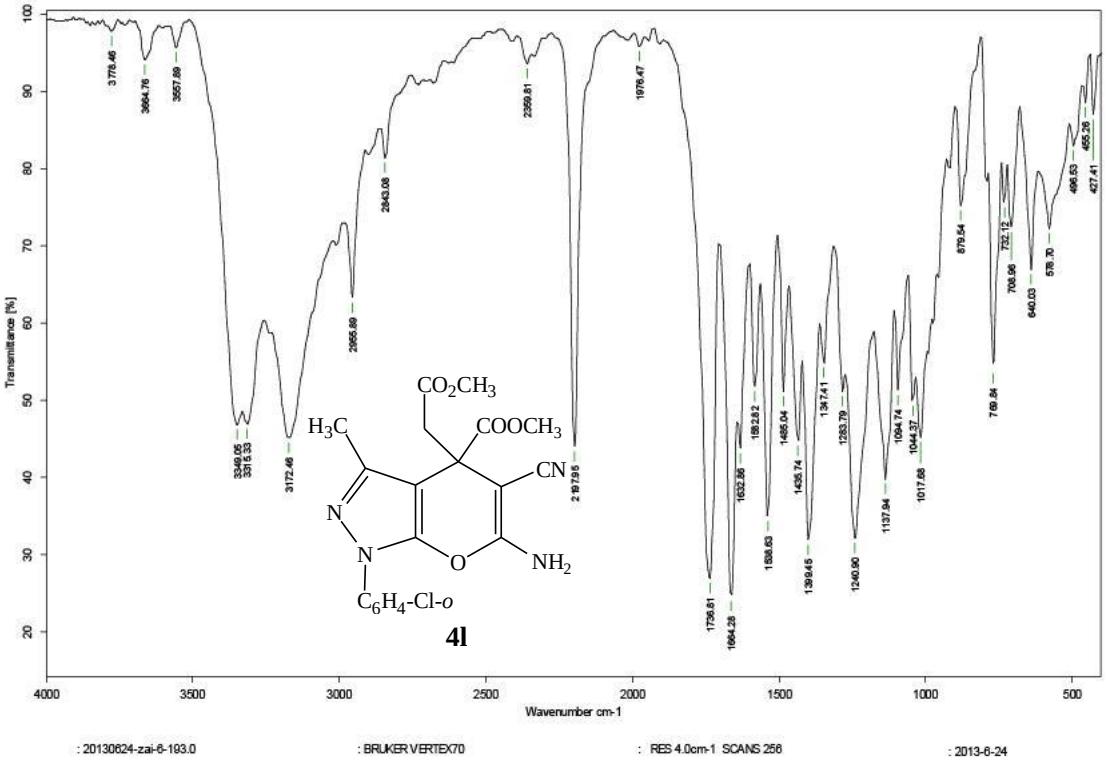
exp2  s2pul

      SAMPLE                SPECIAL
date   Jul 18 2013  temp        not used
solvent       DMSO  gain              50
file           exp  spin              20
   ACQUISITION      hst            0.008
sw         25000.0  pw90          10.800
at           1.195  alfa          20.000
np           59968       FLAGS
fb           14000  il                n
bs              16  in                n
d1           3.000  dp                y
nt             300  hs               nn
ct             300      PROCESSING
   TRANSMITTER      lb             1.00
tn              C13  fn        not used
sfrq       100.525      DISPLAY
tof         1500.0  sp            -1567.1
tpwr            56  wp            24999.2
pw           5.000  rfl            1567.8
   DECOUPLER        rfp               0
dn              H1  rp              -46.8
dof          400.0  lp            -242.0
dm             yyy       PLOT
dmm              w  wc              180
dpwr            42  sc                0
dmf          13400  vs              208
                    th               14
                    nm    ph
```

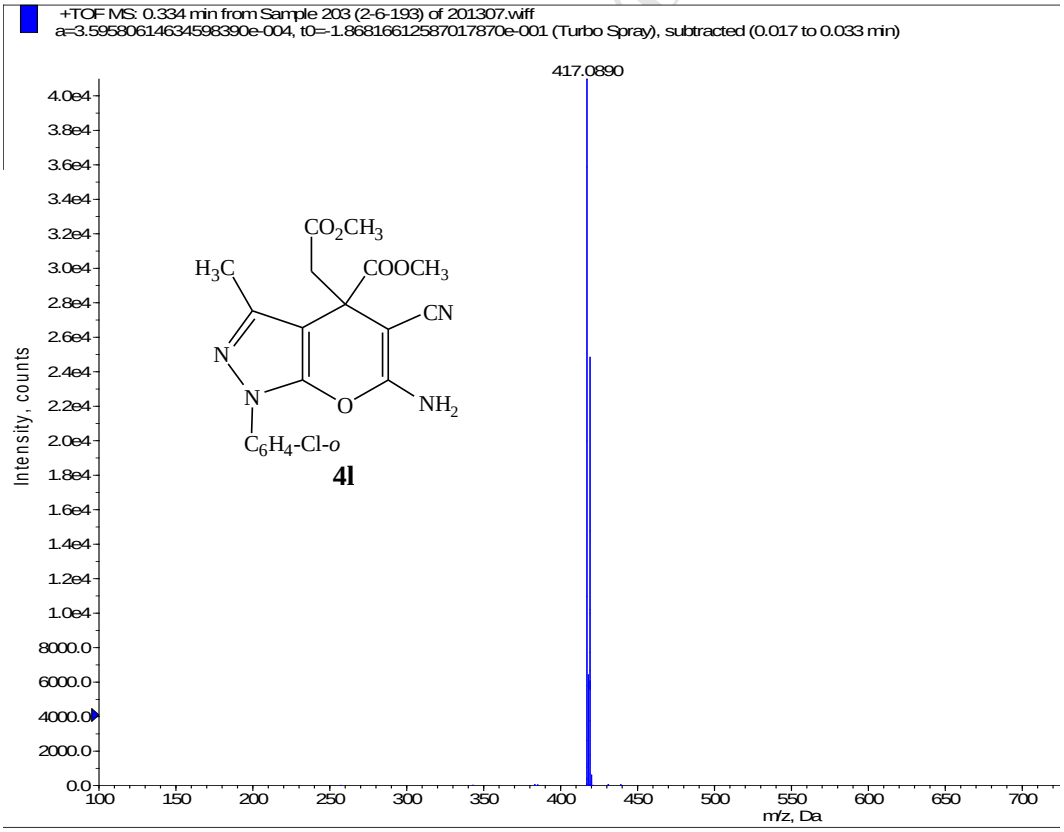


4l




Transmittance [%]
Wavenumber cm-1
: 20130624-zai-6-193.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-6-24
CO_2CH_3
H_3C
$COOCH_3$
CN
N
N
O
NH_2
C_6H_4-Cl-*o*

4l

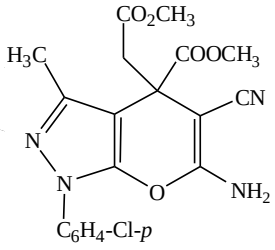

+TOF MS: 0.334 min from Sample 203 (2-6-193) of 201307.wiff
a=3.59580614634598390e-004, t0=-1.86816612587017870e-001 (Turbo Spray), subtracted (0.017 to 0.033 min)
417.0890
Intensity, counts
m/z, Da
CO_2CH_3
H_3C
$COOCH_3$
CN
N
N
O
NH_2
C_6H_4-Cl-*o*

4l

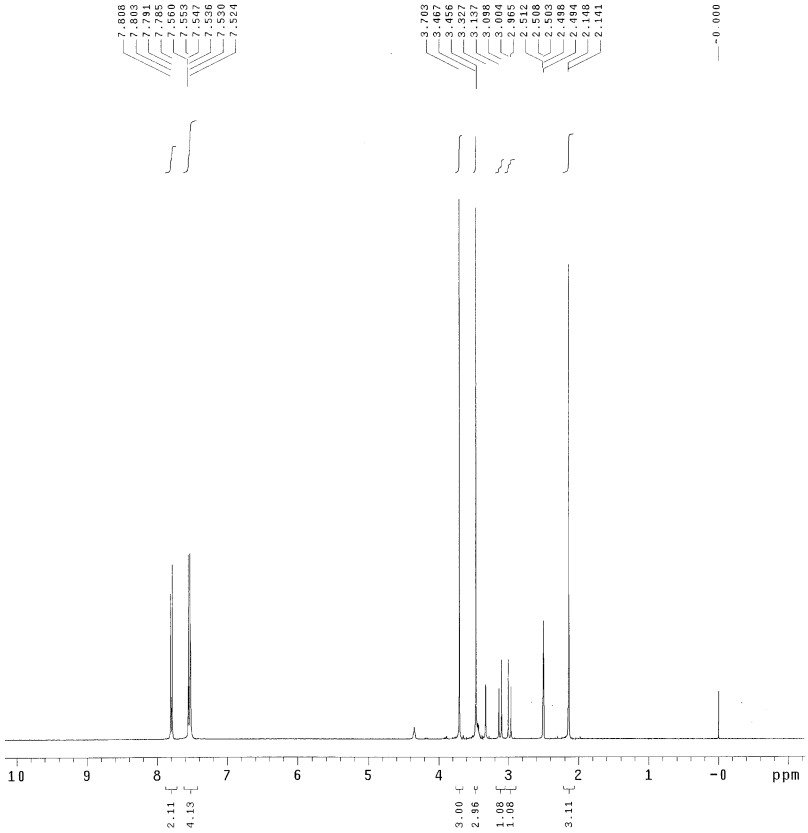
```
xinjiang daxue varian inova-400 1H-4N
zainaipuhguli-2-zai-4-161-abulajiang
in DMSO

exp1  s2pul

      SAMPLE              SPECIAL
date   May  2 2013  temp       not used
solvent       DMSO  gain             30
file           exp  spin             20
   ACQUISITION      hst           0.008
sw          6998.7  pw90         10.800
at           3.744  alfa          6.600
np           52412       FLAGS
fb            4000  il                n
bs              16  in                n
di           3.000  dp                y
nt              20  hs               nn
ct              20      PROCESSING
   TRANSMITTER       fn       not used
tn              H1       DISPLAY
sfrq       399.741  sp            -495.6
tof          400.0  wp           4561.3
tpwr            59  rfl          1091.1
pw           5.000  rfp             0
   DECOUPLER        rp           -115.5
dn              C13  lp            -15.3
dof               0       PLOT
dm              nnn  wc             180
dmm               c  sc               0
dpwr             45  vs             120
dmf           20056  th               4
                     nm    ph
```



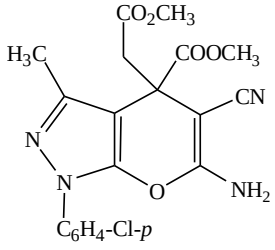
4m



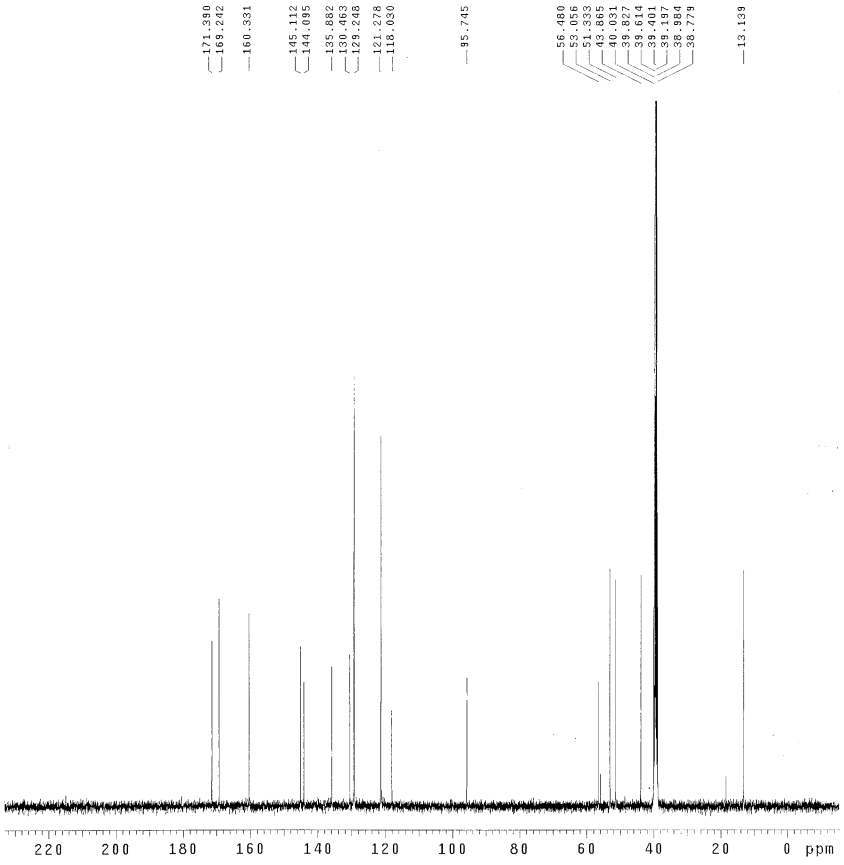

```
xinjiang daxue varian inova-400 13C-4N
zainaipuguli-zai-5-161-abulajiang
in DMSO

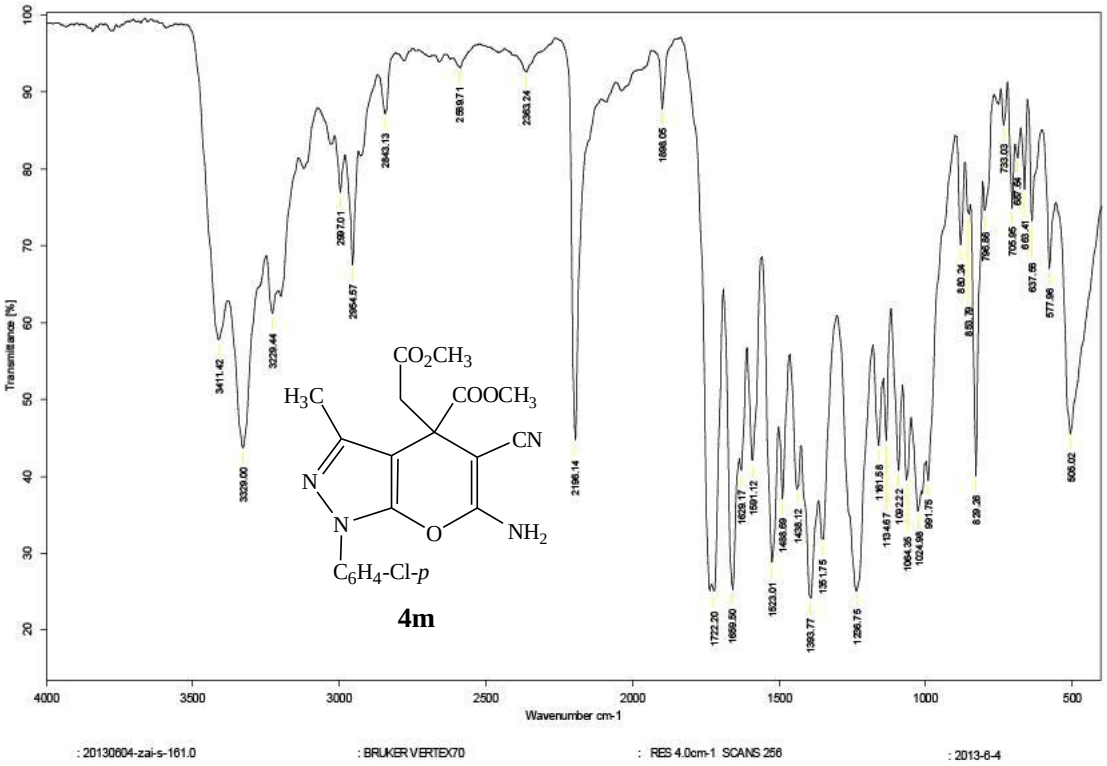
exp2  s2pul

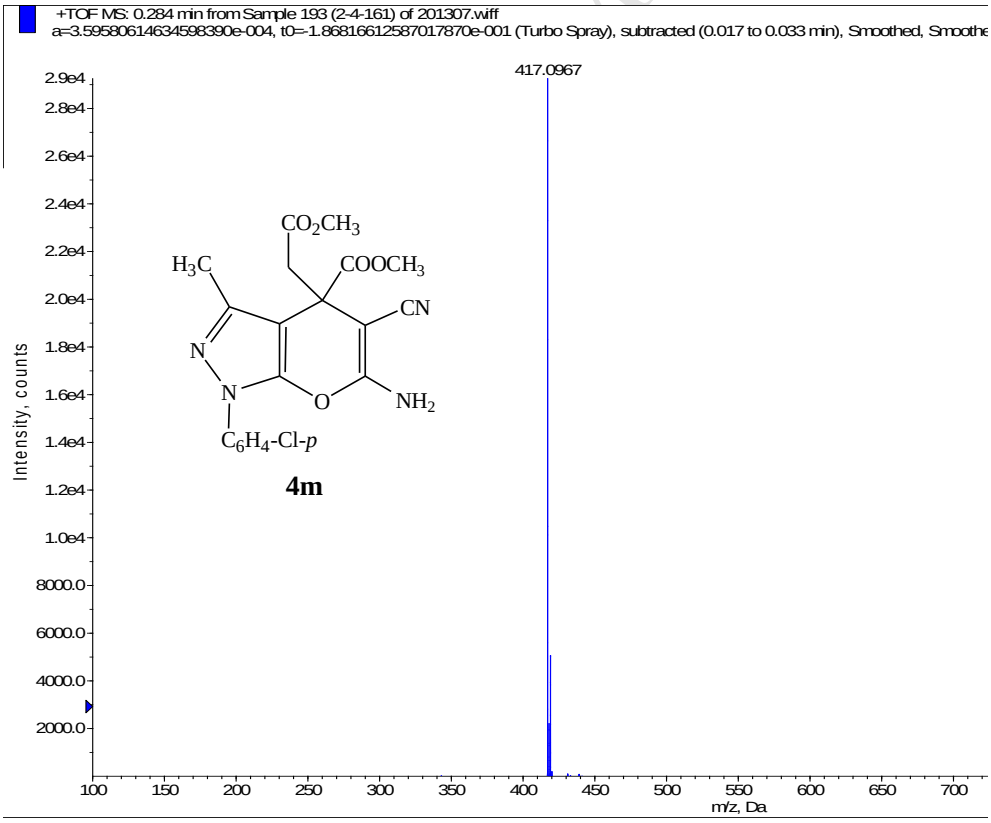
      SAMPLE              SPECIAL
date   May 28 2013  temp       not used
solvent       DMSO  gain             50
file           exp  spin             20
   ACQUISITION      hst           0.008
sw          25000.0  pw90         10.800
at            1.199  alfa         20.000
np            59968       FLAGS
fb            14000  il                n
bs               16  in                n
d1            3.000  dp                y
nt             1000  hs               nn
ct             1000      PROCESSING
   TRANSMITTER       lb            1.00
tn              C13  fn       not used
sfrq       100.525       DISPLAY
tof          1500.0  sp           -1567.1
tpwr             56  wp           24999.2
pw            5.000  rfl          1567.8
   DECOUPLER        rfp              0
dn               H1  rp             -36.3
dof           400.0  lp            -261.4
dm              yyy       PLOT
dmm               w  wc             180
dpwr             42  sc               0
dmf           13400  vs             256
                     th              12
                     nm    ph
```



4m




Transmittance [%]
Wavenumber cm-1
3411.42
3329.00
3229.44
2957.01
2924.57
2843.13
2158.71
2363.24
2196.14
1868.05
1722.20
1659.50
1623.17
1591.12
1523.01
1463.89
1438.12
1393.77
1351.75
1238.75
1161.56
1134.67
1092.22
1064.26
1024.98
991.75
850.24
829.26
796.86
733.03
705.95
687.54
663.41
637.55
577.96
508.02
: 20130604-zai-s-161.0
: BRUKER VERTEX70
: RES 4.0cm-1 SCANS 256
: 2013-8-4


+TOF MS: 0.284 min from Sample 193 (2-4-161) of 201307.wiff
a=3.5958061463459839e-004, t0=-1.8681661258701787e-001 (Turbo Spray), subtracted (0.017 to 0.033 min), Smoothed, Smoothe
417.0967
Intensity, counts
m/z, Da

4m

5. X-ray crystallographic data data for compound 4a.

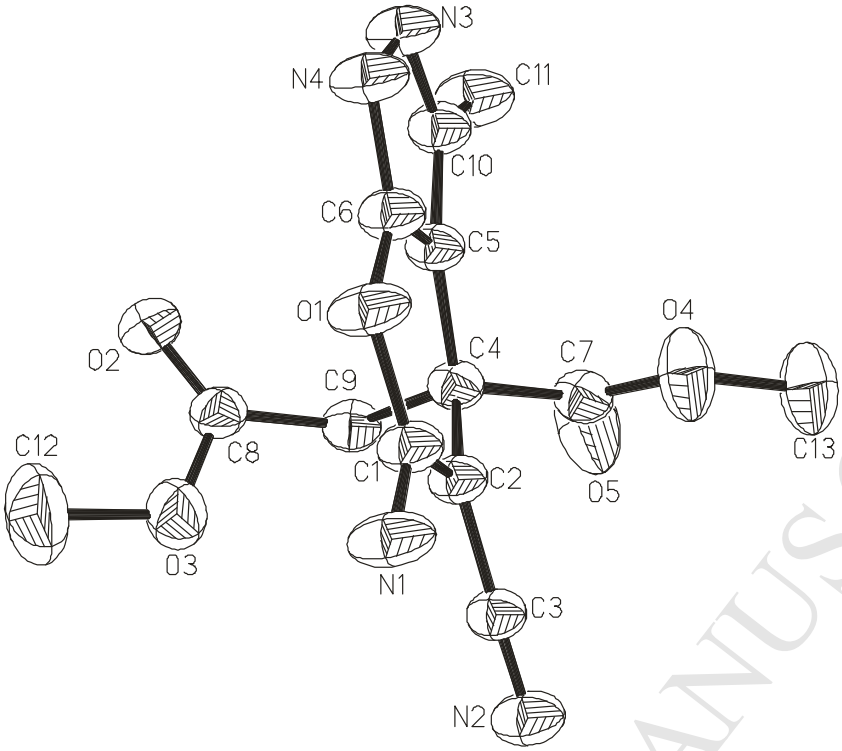


Figure 1. ORTAP diagram of compound **4a**

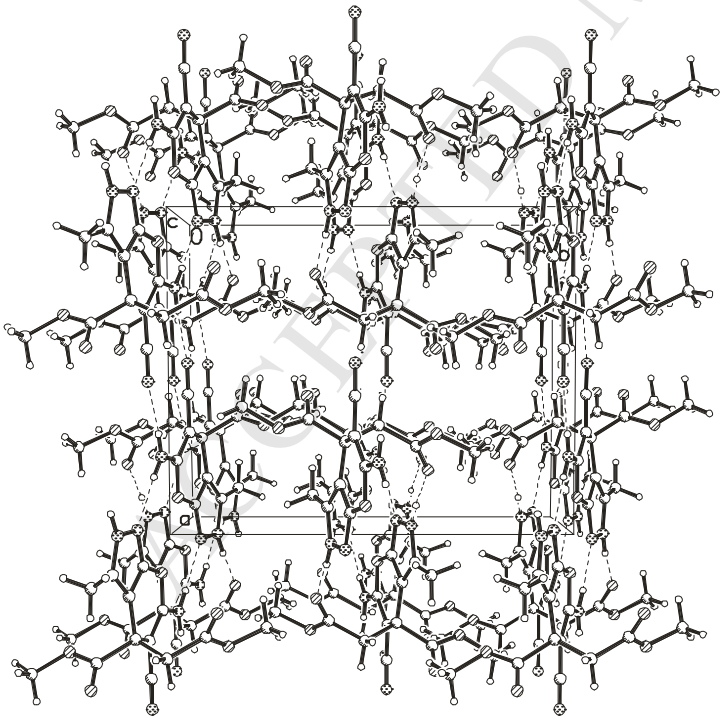


Figure 2. Packing diagram of compound **4a**

Table 1. Crystal data and structure refinement for A.

Identification code	a
Empirical formula	C13 H14 N4 O5
Formula weight	306.28
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 11.4834(17) A alpha = 90 deg.
	b = 14.134(3) A beta = 97.363(4) deg.
	c = 9.8205(15) A gamma = 90 deg.
Volume	1580.8(4) A^3
Z, Calculated density	4, 1.287 Mg/m^3
Absorption coefficient	0.101 mm^-1
F(000)	640
Crystal size	0.79 x 0.65 x 0.26 mm
Theta range for data collection	3.26 to 27.47 deg.
Limiting indices	-14<=h<=14, -18<=k<=18, -12<=l<=12
Reflections collected / unique	13236 / 3585 [R(int) = 0.0358]
Completeness to theta = 27.47	99.1 %
Absorption correction	Empirical
Max. and min. transmission	0.9607 and 0.9281
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3585 / 0 / 204
Goodness-of-fit on F^2	1.006
Final R indices [I>2sigma(I)]	R1 = 0.0771, wR2 = 0.2307
R indices (all data)	R1 = 0.1227, wR2 = 0.3179
Extinction coefficient	0.077(15)
Largest diff. peak and hole	0.377 and -0.343 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for A. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	1108(2)	-149(2)	1038(2)	68(1)
C(3)	4310(2)	-387(2)	1675(3)	51(1)
N(4)	-284(2)	-630(2)	2406(3)	67(1)
C(1)	2272(2)	-143(2)	893(3)	54(1)
N(1)	2423(2)	164(2)	-353(3)	70(1)
N(2)	5277(2)	-387(2)	1552(3)	72(1)
N(3)	-199(2)	-995(2)	3707(3)	66(1)
O(2)	2016(2)	1382(2)	4720(3)	93(1)
C(2)	3121(2)	-409(2)	1916(3)	49(1)
C(4)	2914(2)	-633(2)	3400(3)	51(1)
C(5)	1621(2)	-770(2)	3370(3)	50(1)
C(6)	827(2)	-508(2)	2246(3)	57(1)
C(7)	3585(2)	-1532(2)	3866(3)	59(1)
C(8)	2769(3)	1082(2)	4113(3)	60(1)
C(9)	3391(2)	173(2)	4390(3)	57(1)
O(3)	3158(3)	1565(2)	3113(3)	91(1)
O(4)	3335(3)	-2244(2)	3057(3)	96(1)
O(5)	4277(3)	-1579(2)	4870(4)	131(2)
C(10)	915(2)	-1084(2)	4315(3)	59(1)
C(11)	1197(3)	-1469(3)	5715(4)	89(1)
C(13)	3967(4)	-3127(3)	3389(5)	110(2)
C(12)	2625(6)	2475(4)	2770(7)	149(2)

Table 3. Bond lengths [A] and angles [deg] for A.

O(1)-C(1)	1.363(3)
O(1)-C(6)	1.366(3)
C(3)-N(2)	1.132(3)
C(3)-C(2)	1.416(3)
N(4)-C(6)	1.317(3)
N(4)-N(3)	1.370(4)
C(1)-N(1)	1.331(4)
C(1)-C(2)	1.360(4)
N(1)-H(1A)	0.8600
N(1)-H(1B)	0.8600
N(3)-C(10)	1.346(4)
N(3)-H(3A)	1.01(4)
O(2)-C(8)	1.189(4)
C(2)-C(4)	1.539(4)
C(4)-C(5)	1.494(3)
C(4)-C(7)	1.526(4)
C(4)-C(9)	1.550(4)
C(5)-C(10)	1.381(4)
C(5)-C(6)	1.389(4)
C(7)-O(5)	1.187(4)
C(7)-O(4)	1.291(4)
C(8)-O(3)	1.320(4)
C(8)-C(9)	1.479(4)
C(9)-H(9A)	0.9700
C(9)-H(9B)	0.9700
O(3)-C(12)	1.445(5)
O(4)-C(13)	1.460(4)
C(10)-C(11)	1.476(5)
C(11)-H(11A)	0.9600
C(11)-H(11B)	0.9600
C(11)-H(11C)	0.9600
C(13)-H(13A)	0.9600
C(13)-H(13B)	0.9600
C(13)-H(13C)	0.9600
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600
C(1)-O(1)-C(6)	115.9(2)
N(2)-C(3)-C(2)	176.3(3)
C(6)-N(4)-N(3)	101.9(2)
N(1)-C(1)-C(2)	127.1(2)

N(1)-C(1)-O(1)	110.1(2)
C(2)-C(1)-O(1)	122.7(2)
C(1)-N(1)-H(1A)	120.0
C(1)-N(1)-H(1B)	120.0
H(1A)-N(1)-H(1B)	120.0
C(10)-N(3)-N(4)	113.5(2)
C(10)-N(3)-H(3A)	120(2)
N(4)-N(3)-H(3A)	126(2)
C(1)-C(2)-C(3)	119.0(2)
C(1)-C(2)-C(4)	125.0(2)
C(3)-C(2)-C(4)	115.6(2)
C(5)-C(4)-C(7)	111.1(2)
C(5)-C(4)-C(2)	106.4(2)
C(7)-C(4)-C(2)	108.8(2)
C(5)-C(4)-C(9)	112.2(2)
C(7)-C(4)-C(9)	107.4(2)
C(2)-C(4)-C(9)	110.9(2)
C(10)-C(5)-C(6)	103.8(2)
C(10)-C(5)-C(4)	134.1(3)
C(6)-C(5)-C(4)	122.0(2)
N(4)-C(6)-O(1)	119.5(3)
N(4)-C(6)-C(5)	114.7(3)
O(1)-C(6)-C(5)	125.9(2)
O(5)-C(7)-O(4)	122.7(3)
O(5)-C(7)-C(4)	123.6(3)
O(4)-C(7)-C(4)	113.6(3)
O(2)-C(8)-O(3)	121.7(3)
O(2)-C(8)-C(9)	125.6(3)
O(3)-C(8)-C(9)	112.6(3)
C(8)-C(9)-C(4)	113.5(2)
C(8)-C(9)-H(9A)	108.9
C(4)-C(9)-H(9A)	108.9
C(8)-C(9)-H(9B)	108.9
C(4)-C(9)-H(9B)	108.9
H(9A)-C(9)-H(9B)	107.7
C(8)-O(3)-C(12)	117.4(3)
C(7)-O(4)-C(13)	117.7(3)
N(3)-C(10)-C(5)	106.2(3)
N(3)-C(10)-C(11)	122.0(3)
C(5)-C(10)-C(11)	131.8(3)
C(10)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11C)	109.5

H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
O(4)-C(13)-H(13A)	109.5
O(4)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
O(4)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
O(3)-C(12)-H(12A)	109.5
O(3)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
O(3)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for A. The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	34(1)	108(2)	61(1)	28(1)	4(1)	7(1)
C(3)	40(1)	61(2)	53(2)	7(1)	3(1)	1(1)
N(4)	38(1)	99(2)	64(2)	16(1)	6(1)	-3(1)
C(1)	35(1)	68(2)	58(2)	9(1)	4(1)	1(1)
N(1)	39(1)	111(2)	60(2)	29(1)	6(1)	6(1)
N(2)	44(1)	94(2)	77(2)	13(1)	8(1)	1(1)
N(3)	42(1)	94(2)	62(2)	13(1)	6(1)	-3(1)
O(2)	83(2)	80(2)	126(2)	-7(2)	52(2)	2(1)
C(2)	35(1)	59(2)	52(2)	8(1)	4(1)	1(1)
C(4)	36(1)	58(2)	56(2)	9(1)	-2(1)	1(1)
C(5)	36(1)	61(2)	53(2)	7(1)	0(1)	-4(1)
C(6)	40(1)	72(2)	59(2)	11(1)	4(1)	-2(1)
C(7)	46(2)	65(2)	64(2)	13(1)	-3(1)	0(1)
C(8)	50(2)	63(2)	67(2)	-10(1)	9(2)	-7(1)
C(9)	47(2)	68(2)	53(2)	1(1)	-3(1)	-4(1)
O(3)	121(2)	69(2)	89(2)	16(1)	41(2)	15(1)
O(4)	119(2)	62(2)	93(2)	-5(1)	-35(2)	24(1)
O(5)	143(3)	78(2)	145(3)	10(2)	-83(2)	18(2)
C(10)	49(2)	71(2)	57(2)	9(1)	3(1)	-2(1)
C(11)	72(2)	126(3)	72(2)	34(2)	15(2)	1(2)
C(13)	137(4)	63(2)	122(4)	6(2)	-10(3)	30(2)
C(12)	218(7)	82(3)	155(5)	40(3)	58(5)	46(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for A.

	x	y	z	U(eq)
H(1A)	3120	211	-581	84
H(1B)	1825	316	-930	84
H(9A)	3325	-20	5325	68
H(9B)	4217	265	4316	68
H(11A)	2033	-1478	5962	134
H(11B)	895	-2101	5744	134
H(11C)	846	-1078	6351	134
H(13A)	3694	-3599	2721	164
H(13B)	3829	-3337	4284	164
H(13C)	4792	-3025	3380	164
H(12A)	2978	2753	2031	223
H(12B)	2744	2882	3558	223
H(12C)	1798	2394	2494	223
H(3A)	-880(30)	-1110(30)	4250(40)	86(11)

Table 6. Torsion angles [deg] for A.

C(6)-O(1)-C(1)-N(1)	175.9(3)
C(6)-O(1)-C(1)-C(2)	-4.8(4)
C(6)-N(4)-N(3)-C(10)	0.5(4)
N(1)-C(1)-C(2)-C(3)	-1.3(5)
O(1)-C(1)-C(2)-C(3)	179.6(3)
N(1)-C(1)-C(2)-C(4)	171.5(3)
O(1)-C(1)-C(2)-C(4)	-7.7(5)
N(2)-C(3)-C(2)-C(1)	-180(100)
N(2)-C(3)-C(2)-C(4)	7(5)
C(1)-C(2)-C(4)-C(5)	15.8(4)
C(3)-C(2)-C(4)-C(5)	-171.2(2)
C(1)-C(2)-C(4)-C(7)	135.5(3)
C(3)-C(2)-C(4)-C(7)	-51.5(3)
C(1)-C(2)-C(4)-C(9)	-106.5(3)
C(3)-C(2)-C(4)-C(9)	66.5(3)
C(7)-C(4)-C(5)-C(10)	53.1(4)
C(2)-C(4)-C(5)-C(10)	171.3(3)
C(9)-C(4)-C(5)-C(10)	-67.2(4)

C(7)-C(4)-C(5)-C(6)	-131.5(3)
C(2)-C(4)-C(5)-C(6)	-13.2(4)
C(9)-C(4)-C(5)-C(6)	108.2(3)
N(3)-N(4)-C(6)-O(1)	179.8(3)
N(3)-N(4)-C(6)-C(5)	-0.3(4)
C(1)-O(1)-C(6)-N(4)	-172.9(3)
C(1)-O(1)-C(6)-C(5)	7.1(4)
C(10)-C(5)-C(6)-N(4)	0.0(4)
C(4)-C(5)-C(6)-N(4)	-176.7(3)
C(10)-C(5)-C(6)-O(1)	179.9(3)
C(4)-C(5)-C(6)-O(1)	3.3(5)
C(5)-C(4)-C(7)-O(5)	-118.3(4)
C(2)-C(4)-C(7)-O(5)	124.9(4)
C(9)-C(4)-C(7)-O(5)	4.7(4)
C(5)-C(4)-C(7)-O(4)	62.2(3)
C(2)-C(4)-C(7)-O(4)	-54.6(3)
C(9)-C(4)-C(7)-O(4)	-174.7(3)
O(2)-C(8)-C(9)-C(4)	99.4(4)
O(3)-C(8)-C(9)-C(4)	-82.2(3)
C(5)-C(4)-C(9)-C(8)	-54.1(3)
C(7)-C(4)-C(9)-C(8)	-176.5(2)
C(2)-C(4)-C(9)-C(8)	64.7(3)
O(2)-C(8)-O(3)-C(12)	-0.6(6)
C(9)-C(8)-O(3)-C(12)	-179.0(4)
O(5)-C(7)-O(4)-C(13)	-1.8(6)
C(4)-C(7)-O(4)-C(13)	177.7(3)
N(4)-N(3)-C(10)-C(5)	-0.6(4)
N(4)-N(3)-C(10)-C(11)	-179.6(3)
C(6)-C(5)-C(10)-N(3)	0.4(3)
C(4)-C(5)-C(10)-N(3)	176.3(3)
C(6)-C(5)-C(10)-C(11)	179.3(4)
C(4)-C(5)-C(10)-C(11)	-4.7(6)

Table 7. Hydrogen bonds for A [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...N(2)#1	0.86	2.19	3.043(3)	169.1
N(1)-H(1B)...N(4)#2	0.86	2.18	3.043(4)	177.3
N(3)-H(3A)...O(2)#3	1.01(4)	1.79(4)	2.804(4)	176(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z #2 -x,-y,-z #3 -x,-y,-z+1