Accepted Manuscript

Synthesis of thiazole derivatives bearing an incorporated Z-5-aminopent-3-enoic acid fragment

Alexander G. Zavozin, Nikolai V. Ignat'ev, Michael Schulte, Sergei G. Zlotin

PII: S0040-4020(13)01001-6

DOI: 10.1016/j.tet.2013.06.060

Reference: TET 24536

To appear in: *Tetrahedron*

Received Date: 13 April 2013

Revised Date: 7 June 2013

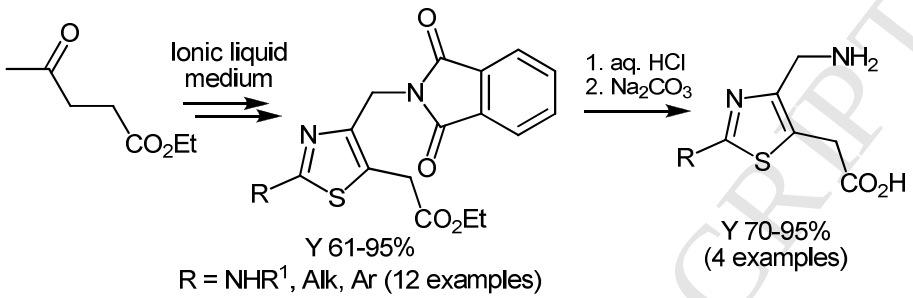
Accepted Date: 17 June 2013

Please cite this article as: Zavozin AG, Ignat'ev NV, Schulte M, Zlotin SG, Synthesis of thiazole derivatives bearing an incorporated Z-5-aminopent-3-enoic acid fragment, *Tetrahedron* (2013), doi: 10.1016/j.tet.2013.06.060.

Graphical Abstract

Synthesis of thiazole derivatives bearing an incorporated Z-5-aminopent-3-enoic acid fragment

Alexander G. Zavozin, Nikolai V. Ignat'ev, Michael Schulte, Sergei G. Zlotin*



Synthesis of thiazole derivatives bearing an incorporated Z-5-aminopent-3-enoic acid fragment

Alexander G. Zavozin[a], Nikolai V. Ignat'ev[b], Michael Schulte[b], Sergei G. Zlotin[a,] *

[a] N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., Moscow 119991, Russia

[b] Merck KGaA, PC-RL, Frankfurter Strasse 250, D-64293 Darmstadt, Germany

* Corresponding author: Tel.: +7(499)1371353, Fax: +7(499)1355328, E-mail: zlotin@ioc.ac.ru

Abstract: Novel compounds bearing a joint thiazole and a Z-5-aminopent-3-enoic acid fragments have been synthesized from readily accessible 5-bromolevulinic esters through a sequence of nucleophilic substitution, bromination, Hantzsch-type heterocyclization and Gabriel-like deprotection reactions. A majority of these reactions proceed in ionic liquid media that enhances their efficiency and selectivity in comparison to the corresponding reactions in conventional organic solvents. The compounds have a significant pharmaceutical potential.

Key words: Thiazole derivatives, Z-5-aminopent-3-enoic acid, levulinic acid, Hantzsch reaction, bromination reaction, ionic liquids.

1. Introduction

5-Aminopentanoic acid is an analog of γ-aminobutanoic acid (GABA), which plays a key role in mammalians nervous system functioning.[1] It interacts with $GABA_A$-receptor as a moderately active agonist[2] and targets at the RDL (resistance to dieldrin) receptor.[3] Z-5-Aminopent-3-enoic acid acts also as a $GABA_A$-receptor agonist, being more active than 5-aminopentanoic acid.[4]

Thiazole derivatives have found broad applications in drug design for inflammation,[5] hypertension,[6] treatment of bacterial[7] and HIV infections[8] and some other diseases.[9] Among them, aminothiazoles are known as ligands for estrogen receptors[10] and adenosine receptor antagonists.[11] It can be expected that functionalized compounds of the structure **1**, in which the thiazole moiety is incorporated into the Z-5-aminopent-3-enoic acid fragment (Figure 1), would be capable to interact with different types of receptors responsible for the most essential functions of living systems. This approach can be used to develop novel multi-target remedies. To our best knowledge, the compounds described by general formula **1** have not been reported so far.

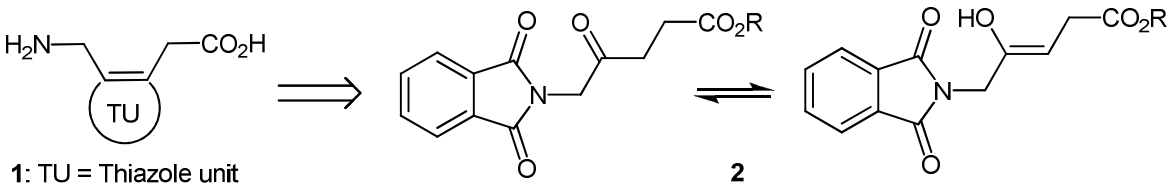
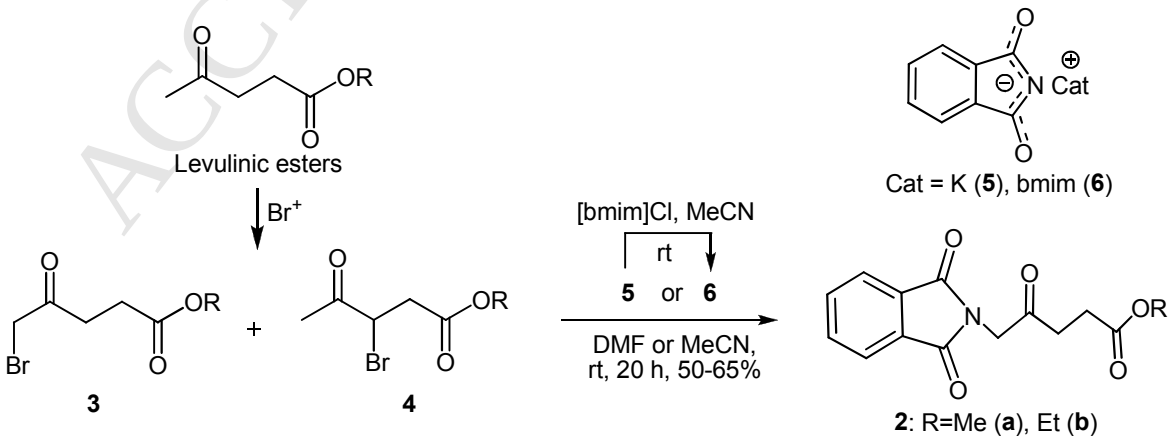


Figure 1. Target molecules **1** and key precursors **2**.

2. Results and discussion

5-Phthalimido-4-oxopentanoic (levulinic) esters **2** bearing protected amino and carboxylic groups along with the carbonyl group between carbon atoms C3 and C4 were chosen as key precursors (Figure 1). It is worth mentioning that 5-phthalimido-levulinic acid **2** (R = H) itself exhibits hypolipidemic activity and reduces serum triglyceride and cholesterol levels in CF_1 mice.[12]

γ-Ketoesters **2** (R = Alk) are commonly synthesized by nucleophilic substitution of the bromine atom in 5-bromolevulinic esters **3** with potassium phthalimide **5** (Scheme 1).[13a-d] However, it is hard to obtain pure terminal bromides **3**; bromination of levulinic esters usually affords a mixture of isomers **3** and **4** in varied ratios.[13d, 14-16] To simplify the experimental procedure and to skip the separation of isomers **3** and **4** we decided to use a mixture of bromides **3** and **4** (3:1, prepared by the known protocol[13d]) directly in the reactions with potassium phthalimide **5**. We expected that less hindered terminal bromides **3** would react with **5** at higher rates than isomeric bromides **4**. Indeed, the reaction of bromides **3**/**4** mixture (R = Me or Et) with imide **5** proceeds regioselectively resulting in the formation preferably of 5-phthalimido-4-oxoesters **2a** or **2b**. Compounds **2a,b** can be easily isolated from unreacted 3-bromolevulinates **4a,b** due to different solubility in diethyl ether. Pure phthalimide ketoesters **2a** or **2b** were obtained in 50% yield (Scheme 1).

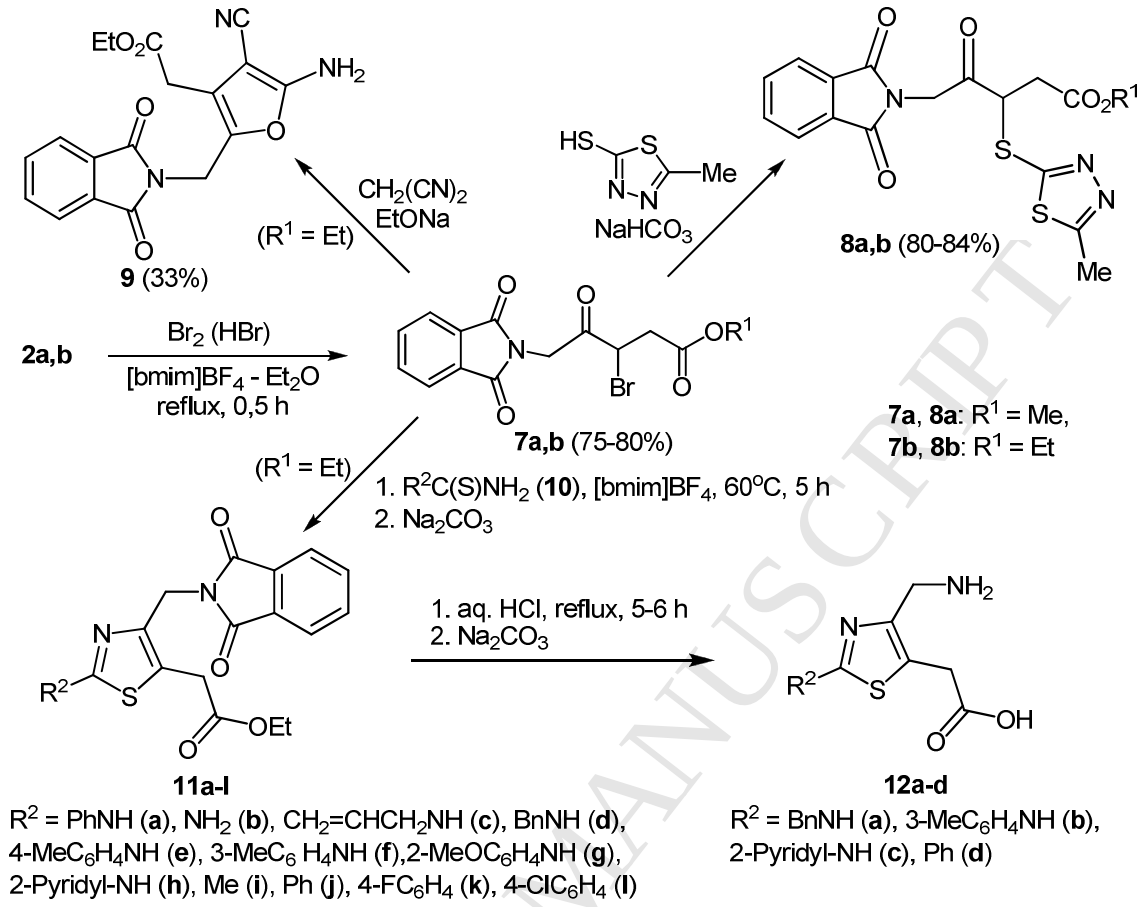


Scheme 1. Synthesis of 5-(phthalimido)levulinates **2a,b**.

Furthermore, we improved the yields of products **2a** and **2b** up to 65% by using reagent **6** with 1-butyl-3-methylimidazolim (bmim) cation instead of potassium phthalimide **5**. The so far unknown salt **6,** which is a congener of an ionic liquid (IL),[17] was prepared by an ion exchange reaction between **5** and [bmim]Cl in anhydrous MeCN at ambient temperature. The reaction appeared to be reversible, regardless of the **5** / [bmim]Cl ratio (1 : 1 or 2 : 1), the product **6** contains chloride originated from the salt [bmim]Cl. That was confirmed by microanalysis (Cl: 3.00 %) and ^{1}H NMR data (integral intensity of the signals is less than it should be for four aromatic protons). The presence of chloride in reagent **6** does not hinder the reaction with compounds **3**. However it should be taken into account in order to calculate correctly the required quantity of the reagents. Unlike potassium phthalimide **5**, the compound **6** is readily soluble in MeCN or DMF, that is beneficial for the reaction (Scheme 1) providing better yields of phthalimide derivatives **2a** or **2b**.

The reaction of compounds **2a** and **2b** with bromine afforded 3-bromoderivatives **7a** and **7b** correspondingly. The best results were obtained in the [bmim]BF_4 – Et_2O (2 : 3, v/v) solvent system in the presence of a catalytic amount of HBr. Under these conditions the reaction time could be significantly reduced (40 h in Et_2O versus 0.5 h in the [bmim]BF_4 – Et_2O system). Furthermore, the ionic liquid [bmim]BF_4 can be easily recovered and reused in the same reaction without a reduction in yield (Scheme 2). Surprisingly, the bromination of ketoesters **2a** and **2b** did not occur in pure ionic liquid [bmim]BF_4 without the addition of Et_2O. Further research is required to find out the reason for this unexpected result.

We found that bromine atom in bromoketones **7a**,**b** could be easily substituted with various nucleophiles. Sulfides **8a** and **8b** were obtained in 80-84% yields in reactions of the compounds **7a** or **7b** with 5-methyl-1,3,4-thiadiazole-2-thiol. Intereaction of **7b** with malononitrile proceeds as a domino-reaction which includes nucleophilic substitution and intramolecular cyclization resulting in the formation of furan derivative **9** in moderate yield of 33% (Scheme 2).



Scheme 2. Synthesis and reactions of 3-bromo-4-keto-5-(phthalimido)valeric esters **7a,b**.

By means of its reaction with thiourea **10a-h** or thioamide **10i-l** derivatives, bromoketone **7b** was converted into the corresponding thiazoles **11a-l** (the Hantzsch reaction). To optimize the reaction conditions we studied a model reaction of bromoketone **7b** with phenylthiourea (**10a**) in conventional organic solvents and in ionic liquid [bmim][BF_4] (Table 1). The reaction did not proceed by refluxing in EtOH for 5 h (Entry 1). However, the reaction in acetone (56 ^oC, 5 h) afforded the desired thiazole derivative **11a** in 85% yield (Entry 2). A further improvement in the yield of **11a** (92%) was achieved in the IL medium (60 ^oC, 5 h) (Entry 3). Various thiourea derivatives **10b-h** were involved in the reaction with bromoketone **7b** in these conditions (Entries 4-10). The corresponding thiazoles **11b-h** were obtained in high yields (Entries 4-10). Moreover, thioacetamide (**10i**) and thiobenzamides **10j-l** are also reactive enough to be involved in this reaction. Though a longer reaction time (12-15 h) was needed to reach reasonable yields of alkyl- or aryl substituted isothiazoles **10j-l** (Entries 11-14). The IL can be regenerated and reused in the reaction between compounds **7b** and **10g**. Moreover, the yield of product **11g** in the second run was in 5% higher than in the first cycle, probably due to the presence of a minor quantity of dissolved **11g** in the recovered IL from the previous run. The synthesis of thiazoles

from ordinary α-bromoketones and thiourea derivatives in the ionic liquid medium have been recently reported.[9a] However the reported protocol does not describe a treatment step essential for product isolation. To our best knowledge, α-halogen ketones bearing other functional groups have not been employed so far in the reactions with thiourea or thioamide derivatives in ionic liquids.

Table 1. Synthesis of 2-R^2-5-ethoxycarbonylmethyl-4-phtalimidomethylthiazoles **11** [a]

Entry	Product **11**	R^2	Yield, % (cycle)	Mp, °C
1 [b]	**a**	PhNH	0	-
2 [c]	**a**	PhNH	85	144-146
3	**a**	PhNH	92	144-146
4	**b**	NH_2	86	182-184
5	**c**	AllylNH	89	94-95
6	**d**	BnNH	87	119
7	**e**	4-MeC_6H_4NH	80	135-136
8	**f**	3-MeC_6H_4NH	95	144-145
9	**g**	2-$MeOC_6H_4NH$	76 (1), 81(2)	135-136
10	**h**	2-Pyridyl-NH	82	161-163
11 [d]	**i**	Me	61	116-118
12 [e]	**j**	Ph	76	132-134
13 [e]	**k**	4-FC_6H_4	72	124-125
14 [e]	**l**	4-ClC_6H_4	70	137-138

[a] Unless other conditions are pointed out, the reaction with **7b** (0.30 g, 0.82 mmol) was carried out with in $[bmim]BF_4$ (1-2 mL) at 60 °C for 5 h. [b] The reaction was carried out by refluxing in EtOH. [c] The reaction was carried out by refluxing in acetone. [d] The reaction was carried out for 15 h. [e] The reaction was carried out for 12 h.

Phthalimido esters **11d,f,h,j** were hydrolyzed to the target 2-(4-aminomethyl-thiazol-5-yl) acetic acid derivatives **12a-d** by a modified Gabriel protocol. Deprotection of the esters **11d,f,h,j** was achieved by refluxing in aqueous HCl. The generated amino acid hydrochlorides **12·HCl** were converted to the corresponding amino acids **12a-d** by treatment with Na_2CO_3 The amino acids (**12)** are crystalline high-melting point compounds insoluble in most organic solvents. The

structures and purity of the compounds **12** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy and HRMS spectrometry data.

3. Conclusion

In summary, we have synthesized the previously unknown thiazole derivatives **12** bearing the Z-5-aminopent-3-enoic acid structural fragment. The synthesis includes substitution of bromine atom in 5-bromolevulinic esters **3** by means of the reaction with potassium or 1-butyl-3-methylimidasolium phthalimides. The regioselective reaction of 2-phthalimido-4-oxoesters **2** with bromine followed by a Hantzsch-type substitution/heterocyclization domino reaction sequence leads to the formation of the thiazole derivatives **11**. The synthesis of the amino acids **12** was performed via a Gabriel-like deprotection of heterocycles **11**. All reactions within this protocol, with the exception of the last one, efficiently proceed in ionic liquid media. That resulted in improved product yield and selectivity in comparison to the reactions in conventional organic solvents. We believe that prepared thiazole derivatives **12** and their analogs may be useful precursors in the development of novel multi-target remedies for various therapies.

4. Experimental

4.1. General

The IR spectra (KBr pellets) were recorded on a Bruker ALPHA-T spectrometer. Thin layer chromatography was performed on TLC Silica gel 60 F_{254} (Merck) plates, visualization by I_2 or UV. The NMR spectra were recorded on a Bruker AM 300 (^{1}H 300.13; ^{13}C 75.47 MHz) spectrometer. The chemical shifts are reported in ppm relative to tetramethylsilane. The mass spectra were recorded on a Kratos MS-30 (UK) electron ionization spectrometer (EI = 70 eV). The high resolution mass spectra (HRMS) were measured on a Bruker micrOTOF II Electrospray Ionization (ESI) mass spectrometer. The measurements were done in a positive ion mode (interface capillary voltage: 4500 V) or in a negative ion mode (3200 V); mass range from *m/z* 50 to *m/z* 3000 Da; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). A syringe was used to inject a solution of the examined compound in acetonitrile, methanol, or water (flow rate 3 µL/min). Nitrogen was applied as a dry carrier; interface temperature was set at 180^{o}C. Melting points were measured on a Boetius heating table. For microanalyses a EURO Vector-3000 analyzer was used. The solvents were pre-purified. The research-grade reagents were used as supplied by Merck.

4.2. General procedure for the synthesis of alkyl 5-phthalimido-levulinates 2a and 2b

Method A. Potassium phthalimide **5 (**1.15 g, 6.21 mmol) was slowly added (10-15 min) to a stirred solution of isomeric bromides **3** and **4** (6:4) (10.0 mmol) in dry DMF (8 mL) cooled with ice-bath. The reaction mixture was kept stirred at ambient temperature for 20 h. Then water (50 mL) was added to the mixture. The precipitate was filtered off, washed successively with water (10 mL) and dried on air. The solid was dissolved in chloroform (10 mL), the insoluble fraction (phthalimide) was filtered off and the filtrate was rotary-evaporated. The residue was subjected to flash chromatography (silica gel, 66% benzene/EtOAc) to afford 5-phthalimido-levulinates **2a** or **2b**.

Method B. A solution of the mixture **6** / [bmim]Cl (3 : 1) (2.80 g) in MeCN (10 mL) was dropwise added to a stirred solution of isomeric bromides **3** and **4** (6:4) (10.0 mmol) in MeCN (10 mL) cooled with ice-bath. The reaction mixture was kept stirred at ambient temperature for 20 h. The solvent was evaporated under reduced pressure (10 Torr) and water (50 mL) was added to the residue. Products **2a** or **2b** were isolated as described above.

*4.2.1. Methyl 5-(1,3-dioxoisoindolin-2-yl)-4-oxopentanoate (**2a**)* (0.83 g, 50%) (Method A) or (1.00 g, 60%) (Method B) as a white solid, m.p. 94-95 ^{o}C (n-hexane/EtOAc) (lit.[13a] m.p. 97 ^{o}C); R_f (75% benzene/EtOAc) 0.52; δ_H ($CDCl_3$) 7.90-7.70 (4H, m), 4.56 (2H, s), 3.69 (3H, s), 2.86 (3H, t, *J* 6.60 Hz), 2.66 (2H, t *J* 6.60 Hz).

*4.2.2. Ethyl 5-(1,3-dioxoisoindolin-2-yl)-4-oxopentanoate (**2b**)* (0.90 g, 52%) (Method A) or (1.13 g, 65%) (Method B) as a white solid, m.p. 81-82 ^{o}C (n-hexane/EtOAc) (lit.[13b] m.p. 74-75 ^{o}C); R_f (75% benzene/EtOAc) 0.63; δ_H ($CDCl_3$) 7.90-7.70 (4H, m), 4.55 (2H, s), 4.12 (2H, q *J* 7.34 Hz), 2.85 (2H, t *J* 6.60 Hz), 2.65 (2H, t *J* 6.60 Hz), 1.26 (3H, t *J* 7.70 Hz). The ^{1}H NMR characteristics of **2a** and **2b** are in agreement with reported data.[18,19]

4.3. Preparation of the [bmim]phthalimide (6) – [bmim]Cl (3:1) mixed salts system

Potassium phthalimide **5** (4.45 g, 24.0 mmol) was slowly added to a stirred solution of [bmim]Cl (4.20 g, 24.0 mmol) in dry MeCN (20 mL) at RT. The reaction mixture was stirred for 12 h at ambient temperature. The colorless precipitate was filtered off and washed with MeCN (5 mL). The filtrate was evaporated at 60 ^{o}C under reduced pressure (10 torr) to afford the [bmim]phthalimide (**6**) – [bmim]Cl (3 : 1) mixed salts system (6.25 g, 91 %) as an yellow oil; δ_H (DMSO-d_6) 9.42 (1H, s), 7.83 (1H, s), 7.75 (1H, s), 7.42-7.30 (3H, m, Ph), 4.18 (2H, t, *J* 7.2 Hz), 3.88 (3H, s), 1.75 (2H, quintet, *J* 7.2 Hz), 1.24 (2H, sextet, *J* 7.2 Hz), 0.88 (3H, t, *J* 7.2 Hz); δ_C (DMSO-d_6) 185.1, 139.2, 137.0, 130.2 (2C), 123.5, 122.2, 119.4 (2C), 48.4, 35.6, 31.4, 18.7,

13.1; HRMS: MH^+- Pht, found: 139.1236. $C_8H_{15}N_2$ requires 139.1230. The same mixed salt was obtained in the experiment where potassium phthalimide **5** (4.45 g, 24.0 mmol) was used in double excess to [bmim]Cl (2.10 g, 12.0 mmol). The product (mixed salt) was used in further experiments without purification.

4.4. General procedure for the synthesis of alkyl 3-bromo-5-phthalimido-levulinates 7a and 7b

Bromine (0.11 mL, 2.20 mmol) was added to a stirred suspension of alkyl 5-phthalimido-levulinates **2a** or **2b** (2.0 mmol), $[bmim]BF_4$ (2.0 g) in Et_2O (2 mL) with 2 drops of HBr. The reaction mixture was refluxed for 30 min (without Et_2O the reaction did not proceed), cooled down to RT and extracted with diethyl ether (3×20 mL). The combined extracts were washed successively with aqueous $NaHCO_3$ (15 mL), H_2O (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure (10 torr). The residue was triturated with n-hexane (20 mL), the precipitate was filtered and dried on air to afford alkyl 3-bromo-5-phthalimido-levulinates **7a** or **7b**.

*4.4.1. Methyl 3-bromo-5-(1,3-dioxoisoindolin-2-yl)-4-oxopentanoate (**7a**)* (0.53 g, 75%) as a colourless crystals, m.p. 120-121 °C; [Found: C, 47.34; H, 3.41; Br, 22.58; N, 3.90. $C_{14}H_{12}BrNO_5$ (354.16) requires C, 47.48; H, 3.42; Br, 22.56; N, 3.95%]; R_f (75% benzene/EtOAc) 0.70; ν_{max} 1774, 1738, 1721, 1415, 725 (CHBr) cm^{-1}; δ_H ($CDCl_3$) 7.88-7.72 (4H, m), 5.08 (1H, d, *J* 17.9 Hz, H_b5), 4.82 (1H, t, *J* 7.3 Hz, 3H), 4.68 (1H, d, *J* 17.9 Hz, H_a5), 3.73 (3H, s), 3.34 (1H, dd, *J* 17.3, 8.1 Hz, H_b2), 3.00 (1H, dd, *J* 17.3, 6.2 Hz, H_a2); δ_C ($CDCl_3$) 195.8, 169.9, 167.4, 134.3 (2C), 132.1, 123.7 (2C), 52.4, 44.3, 41.8, 38.2; HRMS: MNa^+, found 375.9794. $C_{14}H_{12}BrNO_5$ requires 375.9791.

*4.4.2. Ethyl 3-bromo-5-(1,3-dioxoisoindolin-2-yl)-4-oxopentanoate (**7b**)* (0.59 g, 80%) as a colourless crystals, m.p. 97-99 °C; [Found: C, 49.19; H, 3.75; Br, 21.74; N, 3.82. $C_{15}H_{14}BrNO_5$ (368.18) requires C, 48.93; H, 3.83; Br, 21.70; N, 3.80%]; R_f (75% benzene/EtOAc) 0.74; ν_{max} 1777, 1720, 1419, 716 (CHBr) cm^{-1}; δ_H ($CDCl_3$) 7.88-7.72 (4H, m), 5.08 (1H, d, *J* 17.9 Hz, H_b5), 4.82 (1H, t, *J* 7.3 Hz, H3), 4.70 (1H, d, *J* 17.9 Hz, H_a5), 4.18 (2H, q, *J* 7.0 Hz, OCH_2), 3.34 (1H, dd, *J* 17.3, 8.1 Hz, H_b2), 3.00 (1H, dd, *J* 17.3, 6.2 Hz, H_a2), 1.26 (3H, t *J* 7.3 Hz, Me); δ_C ($CDCl_3$) 195.7, 169.4, 167.4, 134.3 (2C), 132.1, 123.7 (2C), 61.5, 44.3, 41.9, 38.5, 14.1; HRMS: MH^+, found 368.0125, MNa^+, found 389.9939. $C_{15}H_{14}BrNO_5$ requires 368.0128 and 389.9948.

4.4.3. Recycling procedure. To ionic liquid remained after extraction of the reaction mixture with Et_2O a fresh portions of **2b** (0.58 g, 2.0 mmol), Et_2O (2 mL), HBr (2 drops) and Br_2 (0.11 mL, 2.2 mmol) were added and the reaction was re-performed as described above to afford (0.64 g, 87%) of bromoketone **7b**.

4.5. General procedure for the synthesis of sulfides 8a and 8b

A mixture of alkyl 3-bromo-5-phthalimido-levulinate **7a** or **7b** (1.0 mmol), 5-methyl-1,3,4-thiadiazole-2-thiol (0.13 g, 1.0 mmol), $NaHCO_3$ (0.21 g, 2.5 mmol) and acetone (10 mL) was stirred at RT for 48 h (TLC control). The solvent was evaporated *in vacuo* and water (30 mL) was added to the residue. The precipitate was filtered and washed successively with water (5 mL) and n-hexane (5 mL) to afford corresponding sulfide **8a** or **8b**.

*4.5.1. Methyl 5-(1,3-dioxoisoindolin-2-yl)-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)-4-oxopentanoate (**8a**)* (0.32 g, 80%) as a light-brown powder, m.p. 140-141 ^oC (n-hexane/EtOAc); [Found: C, 50.27; H, 3.58; N, 10.35; S, 15.64. $C_{17}H_{15}N_3O_5S_2$ (405.45) requires C, 50.36; H, 3.73; N, 10.36; S, 15.82%]; R_f (66% benzene/EtOAc) 0.33; ν_{max} 2956, 1776, 1721, 1405, 728 cm^{-1}; δ_H ($CDCl_3$) 7.86-7.70 (4H, m), 5.11 (1H, t, *J* 4.7 Hz, H3), 5.05 (1H, d, *J* 17.9 Hz, H_b5), 4.82 (1H, d, *J* 17.9 Hz, H_a5), 3.73 (3H, s), 3.20 (1H, dd, *J* 17.4, 8.1 Hz, H_b2), 3.04 (1H, dd, *J* 17.4, 6.6 Hz, H_a2), 2.74 (3H, s); δ_C ($CDCl_3$) 197.2, 169.9, 166.8, 166.4, 133.6 (2C), 131.6, 123.1 (2C), 51.8, 46.8, 44.8, 34.9, 15.3; HRMS: MH^+, found 406.0529, MNa^+, found: 428.0347. $C_{17}H_{15}N_3O_5S_2$ requires 406.0526 and 428.0345.

*4.5.2. Ethyl 5-(1,3-dioxoisoindolin-2-yl)-3-(5-methyl-1,3,4-thiadiazol-2-ylthio)-4-oxopentanoate (**8b**)* (0.35 g, 84%) as a light-yellow powder, m.p. 117-119 ^oC (n-hexane/EtOAc); [Found: C, 51.62; H, 4.20; N, 10.03; S, 15.28. $C_{18}H_{17}N_3O_5S_2$ (419.48) requires C, 51.54; H, 4.08; N, 10.02; S, 15.29%]; R_f (66% benzene/EtOAc) 0.42; ν_{max} 2993, 1776, 1725, 1414, 732 cm^{-1}; δ_H ($CDCl_3$) 7.84-7.68 (4H, m), 5.09 (1H, t, *J* 4.8 Hz, H3), 5.04 (1H, d, *J* 18.1 Hz, H_b5), 4.79 (1H, d, *J* 18.1 Hz, H_a5), 4.15 (2H, q, *J* 7.1 Hz), 3.16 (1H, dd, *J* 17.4, 8.3 Hz, H_b2), 3.01 (1H, dd, *J* 17.4, 5.3 Hz, H_a2), 2.73 (1H, s), 1.24 (3H, t, *J* 7.1 Hz); δ_C ($CDCl_3$) 197.7, 170.0, 167.4, 167.0, 161.8, 134.1 (2C), 132.1, 123.6 (2C), 61.5, 47.4, 45.4, 35.7, 15.8, 14.1; HRMS: MH^+, found 420.0672, MNa^+, found: 442.0497. $C_{18}H_{17}N_3O_5S_2$ requires 420.0682 and 442.0502.

4.6. Synthesis of ethyl 2-(5-amino-4-cyano-2-((1,3-dioxoisoindolin-2-yl)methyl)fur-3-yl)acetate (9)

Dicyanomethane (0.046 g, 0.70 mmol) and **7a** (0.25 g, 0.68 mmol) were slowly added to a stirred solution of Na (0.016 g) in abs. EtOH (1 mL) at RT. The resulting suspension was stirred at 90 ^{o}C for 2.5 h, cooled to ambient temperature, diluted with water (30 mL) and extracted with EtOAc (3 x 15 ml). Combined extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (10 Torr). The residue was purified by column chromatography (silica gel, 66% benzene/EtOAc) to afford compound **9** (0.08 g, 33%) as a colourless crystals, m.p. 181-183 ^{o}C; R_f (75% benzene/EtOAc) 0.30; ν_{max} 3356 (NH_2), 2217 (CN), 1776, 1724, 1657 (NH_2) cm^{-1}; δ_H($CDCl_3$) 7.88-7.72 (4H, m), 4.90 (2H, s, NH_2), 4.70 (2H, s), 4.20 (2H, q, *J* 7.0 Hz), 3.66 (2H, s), 1.30 (3H, t, *J* 7.0 Hz); δ_C($CDCl_3$/DMSO-d_6) 169.3, 166.9, 162.6, 135.6, 133.8 (2C), 131.4, 122.8 (2C), 116.6, 114.7, 60.6, 31.4, 29.3, 13.6; HRMS: MH^+, found 354.1081, MNa^+, found: 376.0902. $C_{18}H_{15}N_3O_5$ requires 354.1084 and 376.0904.

4.7. General procedure for the synthesis of thiazole derivatives 11

A mixture of ethyl 3-bromo-5-phthalimidolevulinate **7b** (0.30 g, 0.82 mmol) and thiourea or thioamide **10** (0.82 mmol) in [bmim]BF_4 (1-2 mL) was stirred at 60 °C for the time given in the Table 1. After the reaction completion (TLC monitoring), the reaction mixture was diluted with Na_2CO_3 20% aqueous solution (20 mL). Precipitated products **11a-c,e,g,i-l** were filtered and washed successively with water (2×5 mL) and cold Et_2O (2 mL) and crystallized from $CHCl_3$/n-hexane or EtOAc/n-hexane solvent mixture. Oily products **11d,f,h** were extracted with EtOAc (3×10 mL), the combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, 75% benzene/EtOAc) to afford thiazoles **11** (**d,f,h**).

For recovering of ionic liquid the basic aqueous solution of [bmim]BF_4 was evaporated to a half of the volume and extracted with CH_2Cl_2 (3×6 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure (10 Torr). The remaining IL was dried at 80 °C for 0.5 h (10 Torr) and could be further reused in the reactions described above.

*4.7.1. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-(phenylamino)thiazol-5-yl) acetate (**11a**)* as a light-yellow crystals, m.p. 144-146 °C ($CHCl_3$/hexane); [Found: C, 62.74; H, 4.58; N, 9.93; S, 7.73. $C_{22}H_{19}N_3O_4S$ (421.45) requires C, 62.69; H, 4.54; N, 9.97; S, 7.61%]; R_f (75% benzene/EtOAc) 0.68; ν_{max} 3308, 1769, 1733, 1708, 1528, 1395, 1187, 747, 713 cm^{-1}; δ_H ($CDCl_3$) 7.85-7.68 (4H, m), 7.40-7.20 (5H, m), 7.00 (1H, t, *J* 6.8 Hz), 4.77 (2H, s), 4.18 (2H, q, *J*

7.1 Hz), 3.96 (2H, s), 1.28 (t, 3H, *J* 7.1 Hz); δ_C ($CDCl_3$) 170.3, 167.9, 163.5, 142.5, 140.0, 134.0 (2C), 132.3, 129.4 (2C), 123.4 (2C), 123.2, 118.3 (2C), 115.3, 61.5, 35.1, 31.8, 14.2.

*4.7.2. Ethyl 2-(2-Amino-4-(1,3-dioxoisoindolin-2-yl)methylthiazol-5yl) acetate (**11b**)* as a light-yellow crystals, m.p. 182-184 °C; [Found: C, 55.41; H, 4.29; N, 11.89; S, 9.08. $C_{16}H_{15}N_3O_4S$ (345.36) requires C, 55.64; H, 4.38; N, 12.17; S, 9.28%]; R_f (25% benzene/EtOAc) 0.46; ν_{max} 3410 (NH_2), 1766, 1729, 1710, 1633, 1531, 1395, 1180, 717 cm^{-1}; δ_H (DMSO-d_6) 7.95-7.75 (4H, m) 6.81 (2H, s, NH_2), 4.51 (2H, s), 4.08 (2H, q, *J* 6.8 Hz), 3.80 (2H, s), 1.18 (3H, t, *J* 6.8 Hz); δ_C (DMSO-d_6) 170.1, 167.2, 166.7 (2C), 142.6, 134.4 (2C), 131.5 (2C), 123.0 (2C), 112.1, 60.4, 35.0, 30.9, 13.9.

*4.7.3. Ethyl 2-(2-allylamino-4-((1,3-dioxoisoindolin-2-yl)methyl)thiazol-5-yl) acetate (**11c**)*. as a colourless crystals, m.p. 94-95 °C ($CHCl_3$/n-hexane); [Found: C, 59.28; H, 5.10; N, 11.21; S, 8.19. $C_{19}H_{19}N_3O_4S$ (385.42) requires C, 59.21; H, 4.97; N, 10.90; S, 8.32%]; R_f (75% benzene/EtOAc) 0.40; ν_{max} 3313, 2982, 1767, 1740, 1711, 1545, 1403, 1336, 1193, 1173, 716 cm^{-1}; δ_H ($CDCl_3$) 7.85-7.68 (4H, m), 5.93-5.78 (1H, m, CH), 5.25 (1H, d, *J* 17.0 Hz, NH), 5.14 (2H, d, *J* 9.8 Hz, CH_2=CH), 4.68 (2H, s), 4.15 (2H, q, *J* 7.2 Hz), 3.91 (2H, s), 3.78 (2H, t, *J* 6.8 Hz, CH_2NH), 1.27 (3H, t, *J* 7.2 Hz); δ_C ($CDCl_3$) 170.5, 168.0 (2C), 167.8, 143.6, 133.8 (2C), 133.6, 132.3 (2C), 123.3 (2C), 117.2, 114.6, 61.2, 48.2, 35.4, 31.9, 14.2.

*4.7.4. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-((phenylmethyl)amino)thiazol-5-yl) acetate (**11d**)* as a colourless crystals, m.p. 119 °C (n-hexane/EtOAc); [Found: C, 63.42; H, 4.83; N, 9.63; S, 7.30. $C_{23}H_{21}N_3O_4S$ (435.48) requires C, 63.43; H, 4.86; N, 9.65; S, 7.36.%]; R_f (75% benzene/EtOAc) 0.58; ν_{max} 3215 (NH), 1772, 1716, 1578, 1395, 1202, 714 cm^{-1}; δ_H ($CDCl_3$) 7.92-7.68 (4H, m), 7.40-7.20 (5H, m), 5.38 (1H, br s), 4.72 (2H, s), 4.35 (2H, d, *J* 6.4 Hz), 4.18 (2H, q, *J* 6.8 Hz), 3.90 (2H, s), 1.25 (3H, t, *J* 6.8 Hz); δ_C ($CDCl_3$) 170.6, 167.9, 162.5, 143.7, 137.6, 133.8 (2C), 132.3, 128.6 (2C), 127.8, 127.7 (2C), 123.3 (2C), 114.6, 61.3, 49.8, 35.4, 31.9, 14.2.

*4.7.5. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-((4-methylphenyl)amino)thiazol-5-yl) acetate (**11e**)* as a light-yellow crystals, m.p. 135-136 °C ($CHCl_3$/n-hexane); [Found: C, 63.46; H, 4.82; N, 9.70; S, 7.38. $C_{23}H_{21}N_3O_4S$ (435.48) requires C, 63.43; H, 4.86; N, 9.65; S, 7,36%]; R_f (75% benzene/EtOAc) 0.66; ν_{max} 3359, 1770, 1732, 1710, 1530, 1393, 1188, 713 cm^{-1}; δ_H ($CDCl_3$) 7.88-7.66 (4H, m), 7.14-7.02 (5H, m), 4.75 (2H, s), 4.18 (2H, q, *J* 5.9 Hz), 3.92 (2H, s),

2.28 (3H, s), 1.27 (3H, t, *J* 6.6 Hz); δ_C ($CDCl_3$) 170.4, 167.9, 163.9, 143.4, 137.8, 133.9 (2C), 132.8, 132.3, 129.9 (2C), 123.3 (2C), 118.8 (2C), 115.0, 61.4, 35.3, 31.8, 20.8, 14.2.

*4.7.6. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-((3-methylphenyl)amino)thiazol-5-yl) acetate (**11f**)* as a light-yellow crystals, m.p. 144-145 °C ($CHCl_3$/n-hexane); [Found: C, 63.40; H, 4.80; N, 9.63; S, 7.31. $C_{23}H_{21}N_3O_4S$ (435.48) requires C, 63.43; H, 4.86; N, 9.65; S, 7.36%]; R_f (75% benzene/EtOAc) 0.62; ν_{max} 3344, 1769, 1737, 1710, 1525, 1393, 1182, 713 cm^{-1}; δ_H ($CDCl_3$) 7.85-7.66 (4H, m), 7.15 (2H, t, *J* 6.8 Hz), 7.04 (1H, s), 6.98 (1H, d, *J* 7.6 Hz), 6.80 (1H, d, *J* 7.2 Hz), 4.76 (2H, s), 4.18 (2H, q *J* 7.0 Hz), 3.94 (2H, s), 2.29 (3H, s), 1.28 (3H, t, *J* 7.0 Hz); δ_C ($CDCl_3$) 170.4, 167.9, 163.2, 143.4, 140.2, 139.4, 133.9 (2C), 132.3, 129.2, 123.8, 123.4 (2C), 118.8, 115.3, 115.2, 61.4, 35.4, 31.8, 21.5, 14.2; HRMS: MH^+, found 436.1319. $C_{23}H_{21}N_3O_4S$ requires 436.1326.

*4.7.7. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-((2-methoxyphenyl)amino)thiazol-5-yl) acetate (**11g**)* as a colourless crystals, m.p. 135-136 °C (n-hexane/EtOAc); [Found: C, 61.29; H, 4.51; N, 9.31; S, 7.15. $C_{23}H_{21}N_3O_5S$ (451.48) requires C, 61.18; H, 4.69; N, 9.31; S, 7.10%]; R_f (75% benzene/EtOAc) 0.69; ν_{max} 3335, 1772, 1720, 1542, 1392, 1248, 711 cm^{-1}; δ_H ($CDCl_3$) 7.90-7.60 (6H, m), 6.98-6.78 (3H, m), 4.80 (2H, s), 4.20 (2H, q, *J* 7.0 Hz), 3.95 (2H, s), 3.80 (3H, s), 1.25 (3H, t, *J* 7.0 Hz); δ_C ($CDCl_3$) 170.4, 167.9, 162.2, 147.5, 143.5, 133.9 (2C), 132.4, 129.9, 123.4 (2C), 121.9, 121.1, 116.2, 115.4, 110.2, 61.4, 55.7, 35.4, 31.9, 14.2.

*4.7.8. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-(2-pyridinylamino)thiazol-5-yl) acetate (**11h**)* as a light-yellow crystals, m.p. 161-163 °C; [Found: C, 59.65; H, 4.21; N, 13.32; S, 7.65. $C_{21}H_{18}N_4O_4S$ (422.44) requires C, 59.70; H, 4.29; N, 13.26; S, 7.59%]; R_f (75% benzene/EtOAc) 0.51; ν_{max} 3296, 1769, 1734, 1711, 1532, 1480 (2-Pyridyl), 1395, 1194, 768, 714 cm^{-1}; δ_H ($CDCl_3$) 8.35-8.20 (2H, br d, *J* 4.1 Hz), 7.85-7.67 (4H, m), 7.52 (1H, t, *J* 7.1 Hz), 6.82 (1H, t, *J* 6.0 Hz), 6.68 (1H, d, *J* 8.3 Hz), 4.80 (2H, s), 4.18 (2H, q, *J* 7.1 Hz), 3.96 (2H, s), 1.25 (3H, t, *J* 7.1 Hz); δ_C ($CDCl_3$) 170.6, 168.0, 158.5, 151.3, 146.9, 142.0, 137.7, 133.9 (2C), 132.3, 123.3 (2C), 118.5, 116.3, 110.2, 61.3, 35.4, 31.7, 14.2; HRMS: MH^+, found 423.1144. $C_{21}H_{18}N_4O_4S$ requires 423.1122.

*4.7.9. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-methylthiazol-5-yl) acetate (**11i**)* as a colourless crystals, m.p. 116-118 °C; [Found: C, 58.97; H, 4.69; N, 8.27; S, 9.58. $C_{17}H_{16}N_2O_4S$ (344.38) requires C, 59.29; H, 4.68; N, 8.14; S, 9.31%] R_f (75% benzene/EtOAc) 0.53; ν_{max} 2953 (CH_3 ring), 1766, 1734, 1708, 1394, 1186, 718 cm^{-1}; δ_H ($CDCl_3$) 7.86-7.70 (4H, m), 4.88 (2H, s),

4.20 (2H, q, *J* 6.8 Hz), 4.04 (2H, s), 2.60 (3H, s), 1.26 (3H, t, *J* 6.8 Hz); δ_C ($CDCl_3$) 170.0, 167.8, 164.7, 147.2, 133.9 (2C), 132.2, 126.7, 123.4 (2C), 61.4, 35.3, 31.9, 19.2, 14.1; HRMS: MH^+, found 345.0902. $C_{17}H_{16}N_2O_4S$ requires 345.0904.

*4.7.10. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-phenylthiazol-5-yl) acetate (**11j**)* as a colourless crystals, m.p. 132-134 °C ($CHCl_3$/n-hexane); [Found: C, 64.91; H, 4.38; N, 6.88; S, 7.95. $C_{22}H_{18}N_2O_4S$ (406.45) requires C, 65.01; H, 4.46; N, 6.89; S, 7.89%]; R_f (85% n-hexane/EtOAc) 0.48; ν_{max} 1778, 1770, 1720, 1392, 1190, 716 cm^{-1}; δ_H ($CDCl_3$) 7.95-7.64 (6H, m), 7.45-7.30 (3H, m), 4.96 (2H, s), 4.20 (2H, q, *J* 6.8 Hz), 4.10 (2H, s), 1.27 (3H, t, *J* 6.8 Hz); δ_C ($CDCl_3$) 169.9, 167.9, 166.4, 148.7, 134.0 (2C), 133.4, 132.3, 129.9, 128.8 (2C), 127.1, 126.4 (2C), 123.4 (2C), 61.6, 35.6, 32.1, 14.2; HRMS: MH^+, found 407.1060. $C_{22}H_{18}N_2O_4S$ requires 407.1060.

*4.7.11. Ethyl 2-(4-((1,3-dioxoisoindolin-2-yl)methyl)-2-(4-fluorophenyl)thiazol-5-yl) acetate (**11k**)* as a colourless crystals, m.p. 124-125 °C (n-hexane/EtOAc); R_f (85% n-hexane/EtOAc) 0.50; ν_{max} 1769, 1731, 1716, 1395, 1189, 718 cm^{-1}; δ_H ($CDCl_3$) 7.91-7.66 (6H, m), 7.10-7.00 (2H, m), 4.95 (2H, s), 4.20 (2H, q, *J* 7.0 Hz), 4.10 (2H, s), 1.28 (t, 3H, *J* 7.0 Hz); δ_C ($CDCl_3$) 169.9, 167.9, 165.4 (1C, d, $J_{C,F}$ 18.1 Hz), 162.2, 148.7, 134.0 (2C), 132.3, 129.8, 128.3 (1C, d, $J_{C,F}$ 8.3 Hz), 127.2, 123.4 (2C), 115.8 (1C, d, $J_{C,F}$ 22.6 Hz), 61.7, 35.5, 32.1, 14.2; HRMS: MH^+, found 425.0964. $C_{22}H_{17}FN_2O_4S$ requires 425.0966.

*4.7.12. Ethyl 2-(2-(4-chlorophenyl)-4-((1,3-dioxoisoindolin-2-yl)metyl)thiazol-5-yl) acetate (**11l**)* as a colourless crystals, m.p. 137-138 °C ($CHCl_3$/n-hexane); R_f (85% n-hexane/EtOAc) 0.52; ν_{max} 1768, 1733, 1716, 1396, 1194, 717 cm^{-1}; δ_H ($CDCl_3$) 7.95-7.65 (6H, m), 7.40-7.28 (2H, m), 4.96 (2H, s), 4.22 (2H, q, *J* 6.8 Hz), 4.12 (2H, s), 1.30 (3H, t, *J* 6.8 Hz); δ_C ($CDCl_3$) 169.9, 167.9, 164.4, 148.9, 135.9, 134.0 (2C), 132.3, 132.0, 129.0 (2C), 127.7 (2C), 127.5, 123.5 (2C), 61.7, 35.6, 32.2, 14.2; HRMS: MH^+, found 441.0663. $C_{22}H_{17}ClN_2O_4S$ requires 441.0670.

4.8. General procedure for the synthesis of amino acids 12

A mixture of compound **11** (0.69 mmol) in 12% HCl (6 mL) was refluxed for 6 h and cooled to ambient temperature. A solid mixture of hydrochloride **12**·HCl and phthalic acid was filtered off and washed with cold water (2 × 5 mL). The aqueous Na_2CO_3 was added to combined mother liquid to adjust pH 7.0. The precipitate was filtered and washed successively with water (5 mL) and acetone (5 mL) to afford crude amino acid **12**. The latter (0.10 g) was suspended in water

(10 mL), the suspension was treated with Na_2CO_3 and pH value was adjust to 7.0 by the addition of AcOH. The precipitate was filtered and washed successively with water (5 mL) and acetone (5 mL) to afford corresponding amino acid **12**.

*4.8.1. 2-(4-Aminomethyl-2-((phenylmethyl)amino)thiazol-5-yl) acetic acid (**12a**)* (0.17 g, 89%) as a colourless crystals, m.p. 220-225 °C (dec.); ν_{max} 3410-2170, 1655, 1554, 1369, 1279, 757, 702 cm^{-1}; δ_H (DMSO-d_6/CF_3CO_2H 2.5/1) 10.36 (1H, br s), 8.28-8.10 (3H, m), 7.40-7.20 (5H, m), 4.52 (2H, s), 3.98 (2H, s), 3.81 (2H, s); δ_C (DMSO-d_6/CF_3CO_2H 2.5/1) 171.9, 168.8, 136.4, 131.1, 129.6 (2C), 128.9, 128.6 (2C), 119.2, 49.9, 34.4, 31.7; MS 259 [M-H_2O] for $C_{13}H_{15}N_3O_2S$; HRMS: MH^+, calcd: 278.0958; found: 278.0952.

*4.8.2. 2-(4-Aminomethyl-2-((3-methylphenyl)amino)thiazol-5-yl) acetic acid (**12b**)* (0.18 g, 95%) as a colourless crystals, m.p. 210-212 °C (dec) (H_2O); ν_{max} 3500-2300, 1687, 1623, 1576, 1553, 699, 681 cm^{-1}; δ_H (DMSO-d_6) 10.20 (1H, s), 8.70-8.20 (2H, br s), 7.60 (1H, s), 7.40 (1H, s), 7.18 (1H, s), 6.72 (1H, s), 3.90 (2H, s), 3.72 (2H, s), 2.26 (3H, s); MS 259 [M-H_2O] for $C_{13}H_{15}N_3O_2S$; HRMS: MH^+, calcd: 278.0958; found: 278.0952.

*4.8.3. 2-(4-Aminomethyl-2-((2-pyridyl)amino)thiazol-5-yl) acetic acid (**12c**)* (0.14 g, 75%) as a light-yellow crystals, m.p.>300 °C (dec) (MeOH/H_2O); ν_{max} 3500-2400, 1616, 1603, 1543, 1413, 1375, 1091, 765, 686 cm^{-1}; δ_H (DMSO-d_6/CF_3CO_2H) 8.41-8,25 (4H, m), 8.12 (1H, t, *J* 7.3 Hz), 7.40-7.20 (2H, m), 4.12-4.00 (2H, m), 3.86 (2H, s); MS 246 [M-H_2O] for $C_{11}H_{12}N_4O_2S$; HRMS: MH^+, calcd: 265.0754; found: 265.0760.

*4.8.4. 2-(4-Aminomethyl-2-phenylthiazol-5-yl)acetic acid (**12d**)* (0.12 g, 70%) as a colourless crystals, m.p. 210-213 °C (dec) (H_2O); ν_{max} 3500-2400, 1622, 1555, 1378, 1368, 758, 689 cm^{-1}; δ_H (DMSO-d_6/CF_3CO_2H) 8.38-8.11 (3H, br s), 7.98-7.80 (2H, br s), 7.50-7.30 (3H, br s), 4.12 (2H, s), 3.95 (2H, s); δ_C (DMSO-d_6/CF_3CO_2H) 171.7, 166.6, 147.1, 133.5, 130.9, 129.8, 129.7 (2C), 126.6 (2C), 37.2, 31.8; HRMS: MH^+, calcd for $C_{12}H_{12}N_2O_2S$: 249.0692; found: 249.0698.

Acknowledgements

This work was supported by Merck KGaA, Darmstadt, Germany.

Supplementary data

Supplementary data for this paper can be found in the online version at doi:XXX

References and notes

1. (a) *Goodman and Gilman's the Pharmacological Basis of Therapeutics.* (Eds J. G. Hardman, L. E. Limbird, A. G. Gilman). (New York: McGraw-Hill, 2001); (b) *Basic Neurochemistry: Molecular, Cellular and Medical Aspects* (Eds G. J. Siegel, R. W. Alberts, S. Brady, D. Price). (Boston, MA: Academic Press, Elsevier, 2006).
2. Kerr, D.I.B.; Ong, J. *Br. J. Pharmacol*., **1984**, *83*, 169-174.
3. McGonigle, I.; Lummis, S.C.R. *Biochemistry*, **2010**, *49*, 2897-2902.
4. Allan, R.D.; Dickenson, H.W.; Johnston, G.A.R.; Kazlauskas, R.;Tran, H.W. *Austr. J. Chem*., **1985**, *38*, 1651-1656.
5. Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719-1728.
6. Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doherty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Batley, B. L.; Painchaud, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olson, S. C. J. *J. Med. Chem*. **1992**, *35*, 2562-2572.
7. Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett*. **1994**, *4*, 1601-1606.
8. Bell, F. W.; Cantrell, A. S.; Hoegberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Sahlberg, C.; Ternansky, R. J.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929-4936.
9. (a) Potevar, T. M.; Ingale S.A.; Srinivasan, K. V. *Tetrahedron*, **2007**,*63*, 11066-11069.; (b) Aoyama, T.; Murata, S.; Arai, I.; Araki, N.; Takido, T.; Suzuki, Y.; Kodomari, M. *Tetrahedron*, **2006**, *62***,** 3201-3213.(c) Pumpor, K.; Windeisen, E.; Burger, K. *J. Heterocyclic Chem.*,**2003**, *40*, 435-442.
10. Fink, B.A.; Mortensen, D.S.; Stauffer, S.R.; Aron, Z.D.; Katzenellenbogen, J.A. *Chem. Biol*. **1999**, *6*, 205-219.
11. Van Muijlwijk-Koezen, J.E.; Timmerman, H.; Vollinga, R.C.; Von Drabbe Kunzel, J.F.; De Groote, M.; Visser, S.; Ijzerman, A.P. *J. Med. Chem*. **2001**, *44*, 749-762.
12. Chapman, Jr., J.M.; Cocolas, G.H.; Hall, I.H. *J. Med. Chem*., **1983**, *26*, 243-246.
13. (a) Pichat, L.; Hucleux, M.; Herbert, M. *Bull. Soc. Chim. France*, 1956, 1750-1751; (b) Rykowski, Z.; Burak, K.; Chabudzinski, Z. *Roczniki Chemii*, 1977, *51*, 1675-1678; (c) Zavyalov, S.I.; Zavozin, A.G. *Russ. Chem. Bull.* **1987**, *36*, 1663-1666; (d) Zavyalov, S.I.; Kravchenko, N.E.; Ezhova, G.I.; Kulikova, L.B.; Zavozin, A.G.; Dorofeeva, O.V. *Pharm. Chem. J*. **2007**, *41*, 105-108.
14. Zavozin, A.G.; Kravchenko, N.E.; Ignat'ev, N.V.; Zlotin, S.G. *Tetrahedron Letters*, **2010**, *51*, 545-547.
15. MacDonald, S.F. *Can. J. Chem.*,**1974**, *52*, 3257-3258.
16. Sorg, A.; Siegel, K.;Bruckner, R. *Chem. Eur. J*.,**2005**, *11*, 1610-1624.
17. (a) *Ionic Liquids in Synthesis*, 2nd ed., (eds. P. Wasserscheid, T. Welton), Wiley-VCH, Weinheim, Germany, **2008**. (b) Zlotin, S.G.; Makhova, N.N. *Mendeleev Commun*., **2010**, *20* (2), 63-71; (c) Zlotin, S.G. Makhova, N.N. *Russ. Chem. Rev*., **2010**, *79* (7) 543–583.
18. Wang, J.; Scott, A.I. *Tetrahedron Let*., **1997**, *38*, 739-740.

19. Iida, K.; Tokiwa, S.; Ishii, T.; Kajiwara, M. *J. Label. Compd. Radiopharm*., **2002**, *45*, 569-576.

Supporting Information

Synthesis of thiazole derivatives bearing incorporated Z-5-aminopent-3-enoic acid fragment

Alexander G. Zavozin[a], Nikolai V. Ignat'ev[b], Michael Schulte[b], Sergei G. Zlotin[a]

[a] N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., Moscow 119991, Russia

[b] Merck KGaA, PC-RL, Frankfurter Strasse 250, D-64293 Darmstadt, Germany

^{1}H NMR, ^{13}C NMR and mass spectra of synthesized compounds

Figure 1. ^{1}H NMR spectra of **2a**

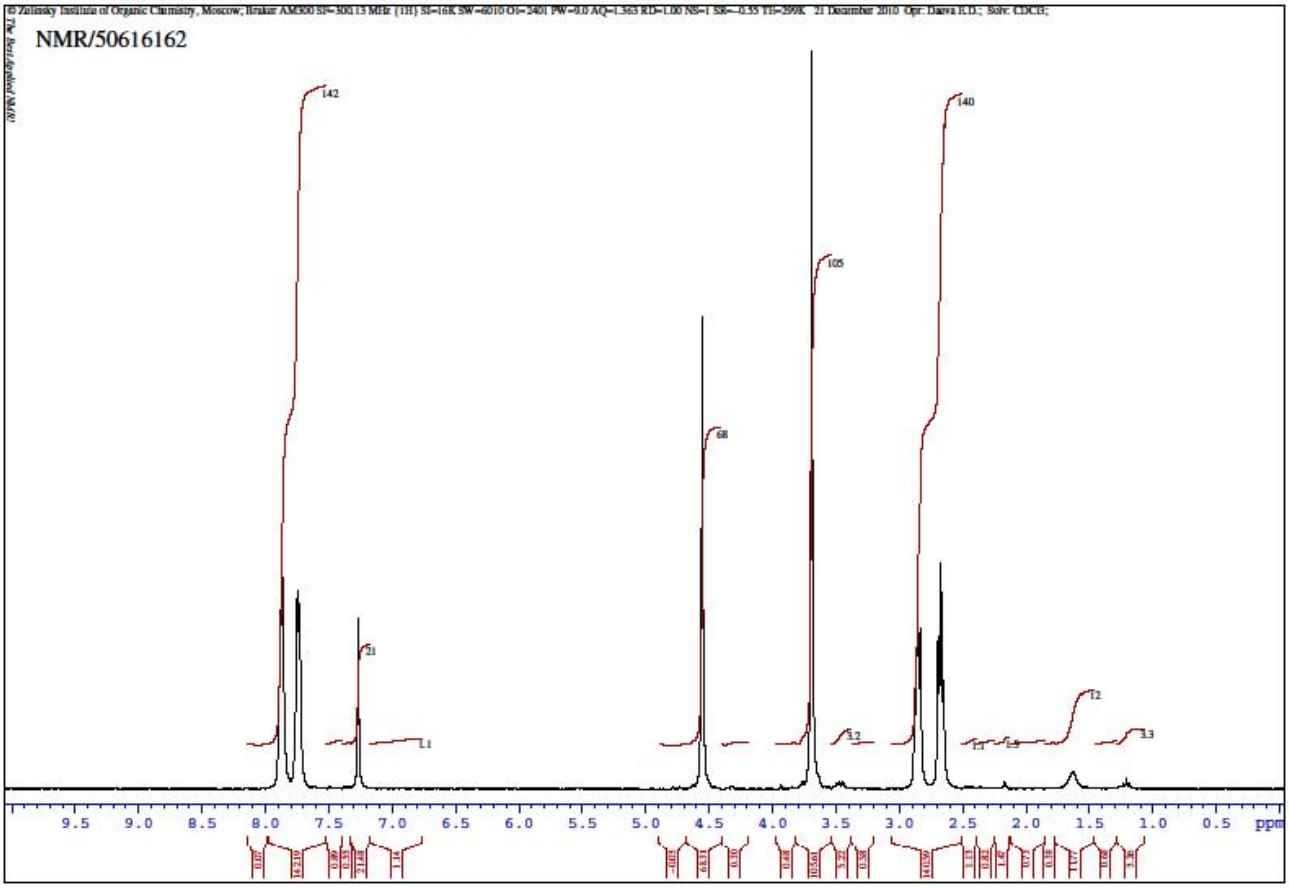


Figure 2. ^{1}H NMR spectra of **2b**

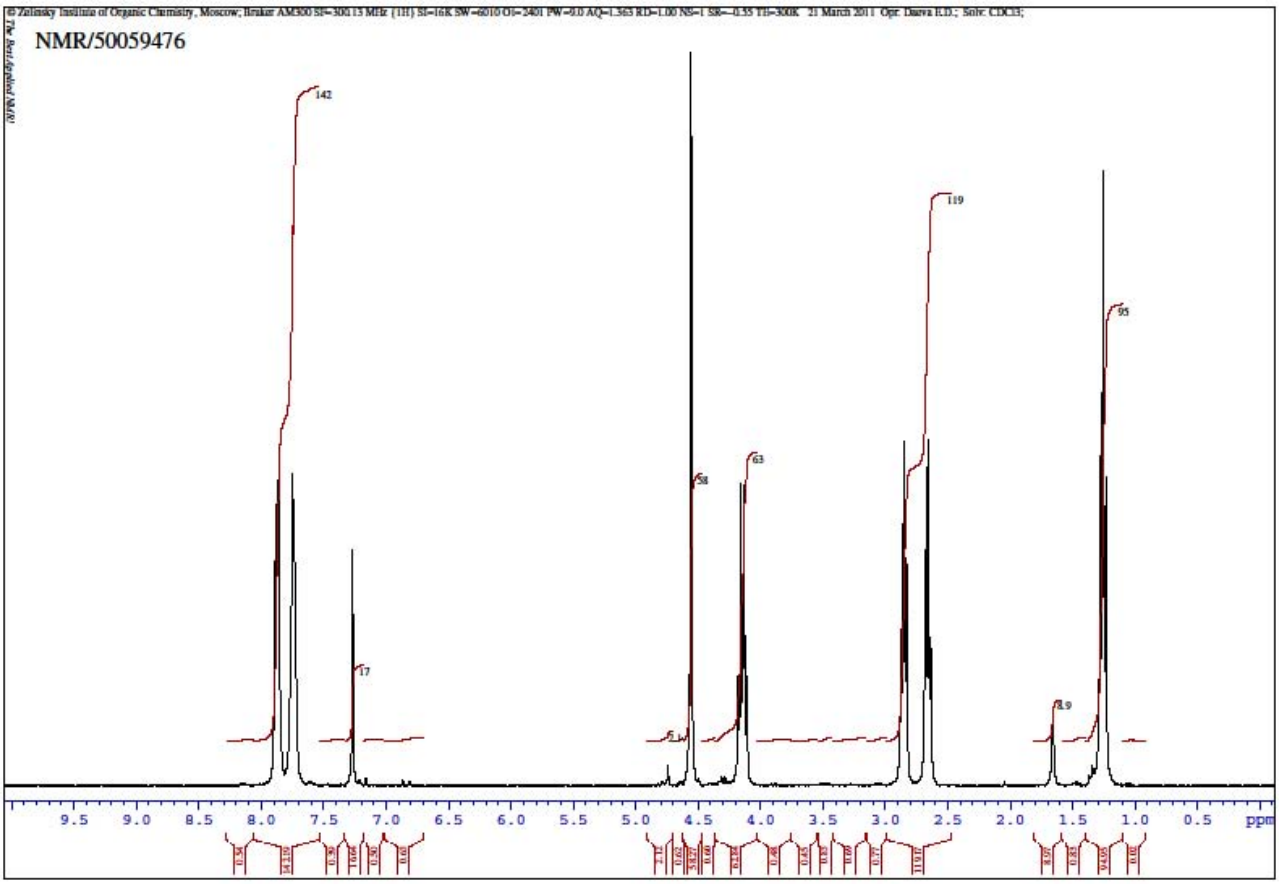


Figure 3. ^{1}H NMR spectra of salt **6**

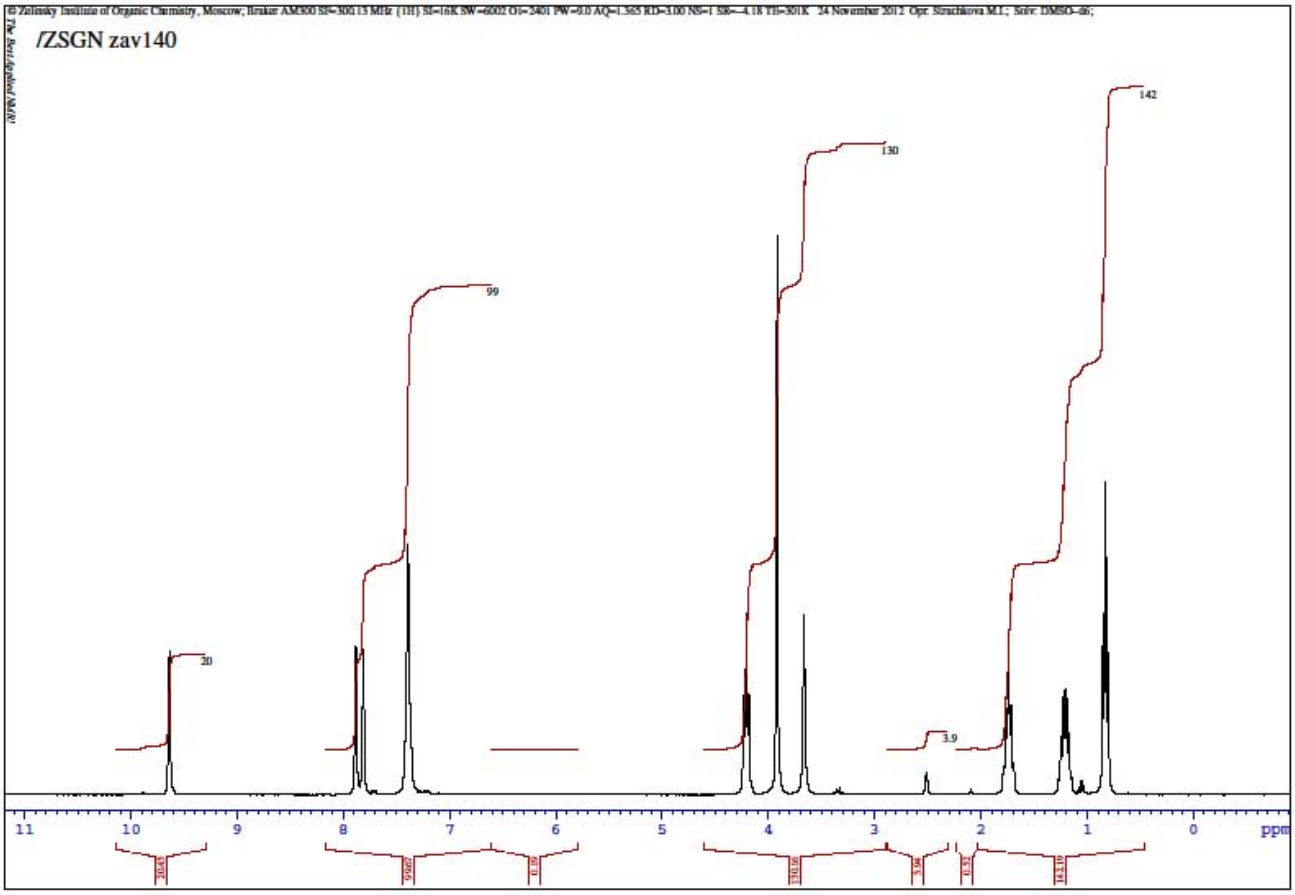


Figure 4. ^{13}C NMR spectra of salt **6**

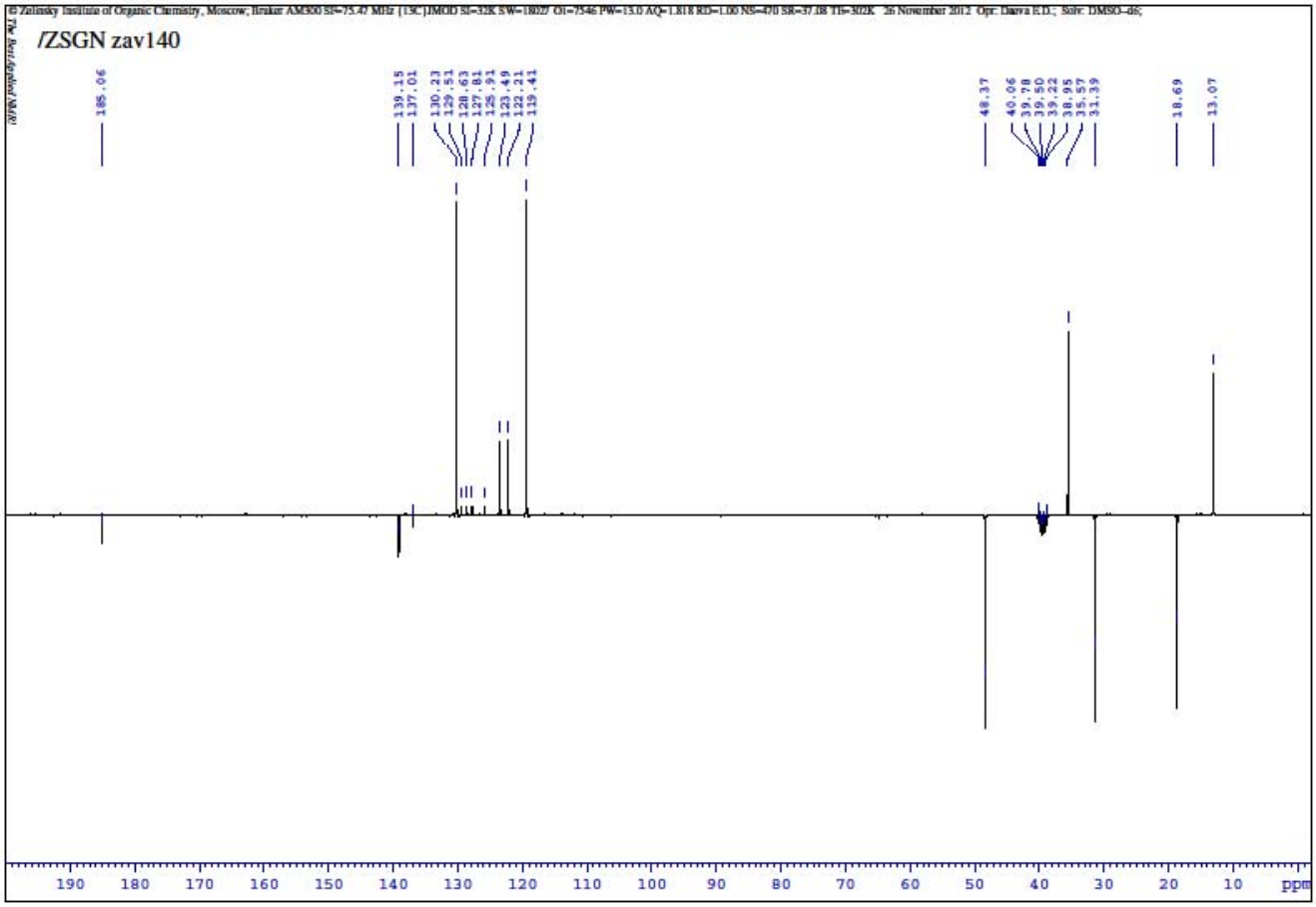


Figure 5. ^{1}H NMR spectra of **7a**

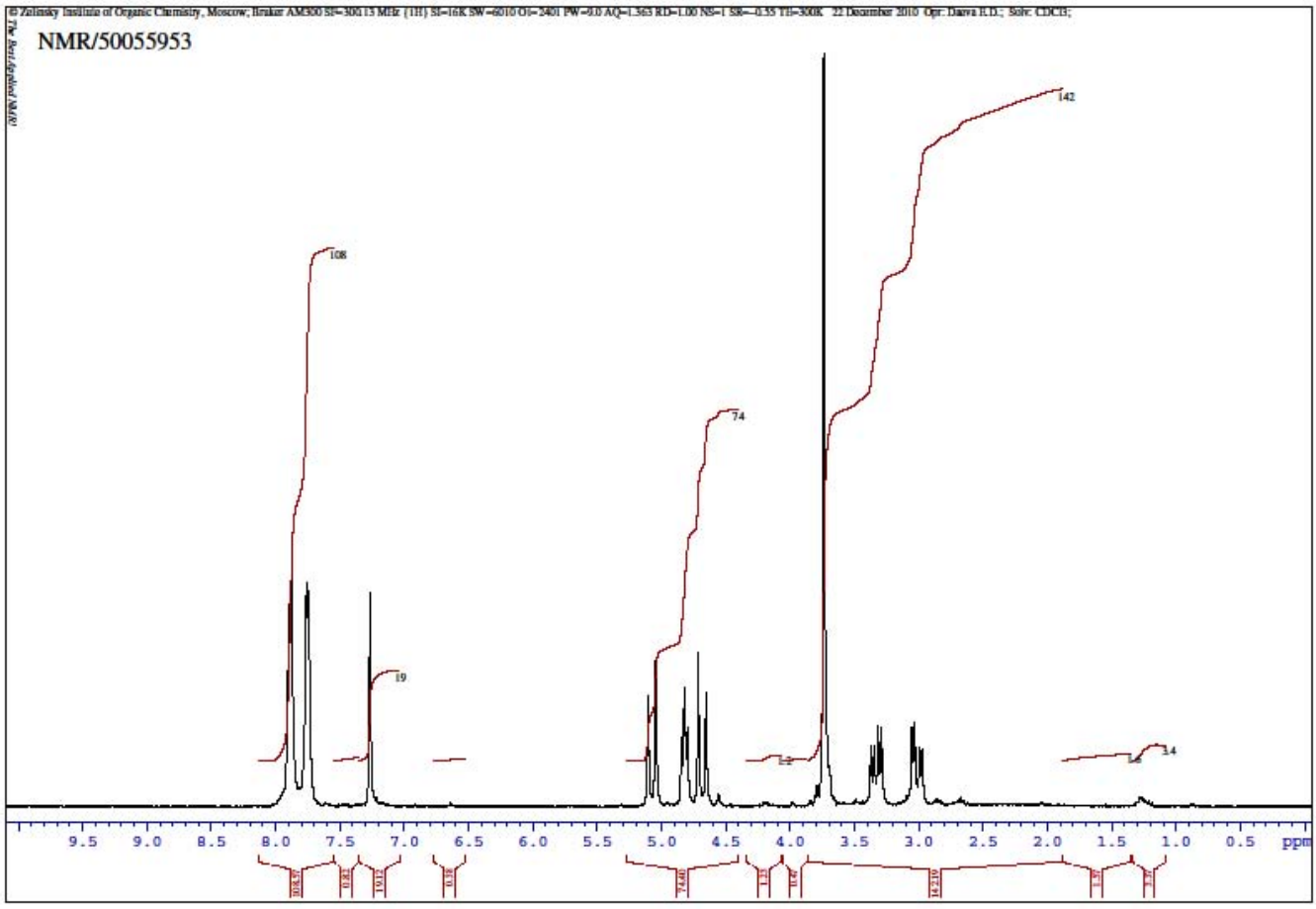


Figure 6. ^{13}C NMR spectra of **7a**

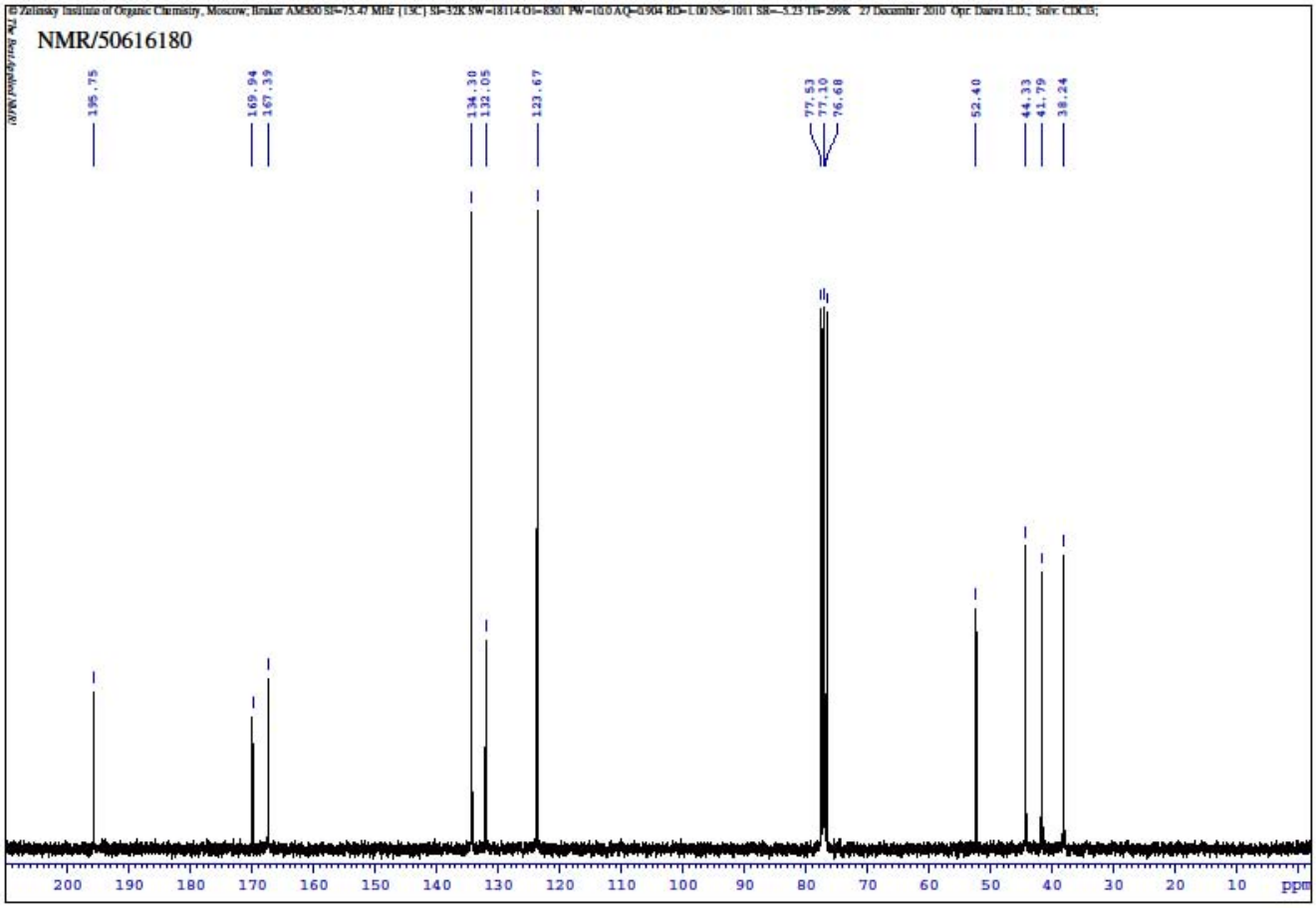


Figure 7. ^{1}H NMR spectra of **7b**

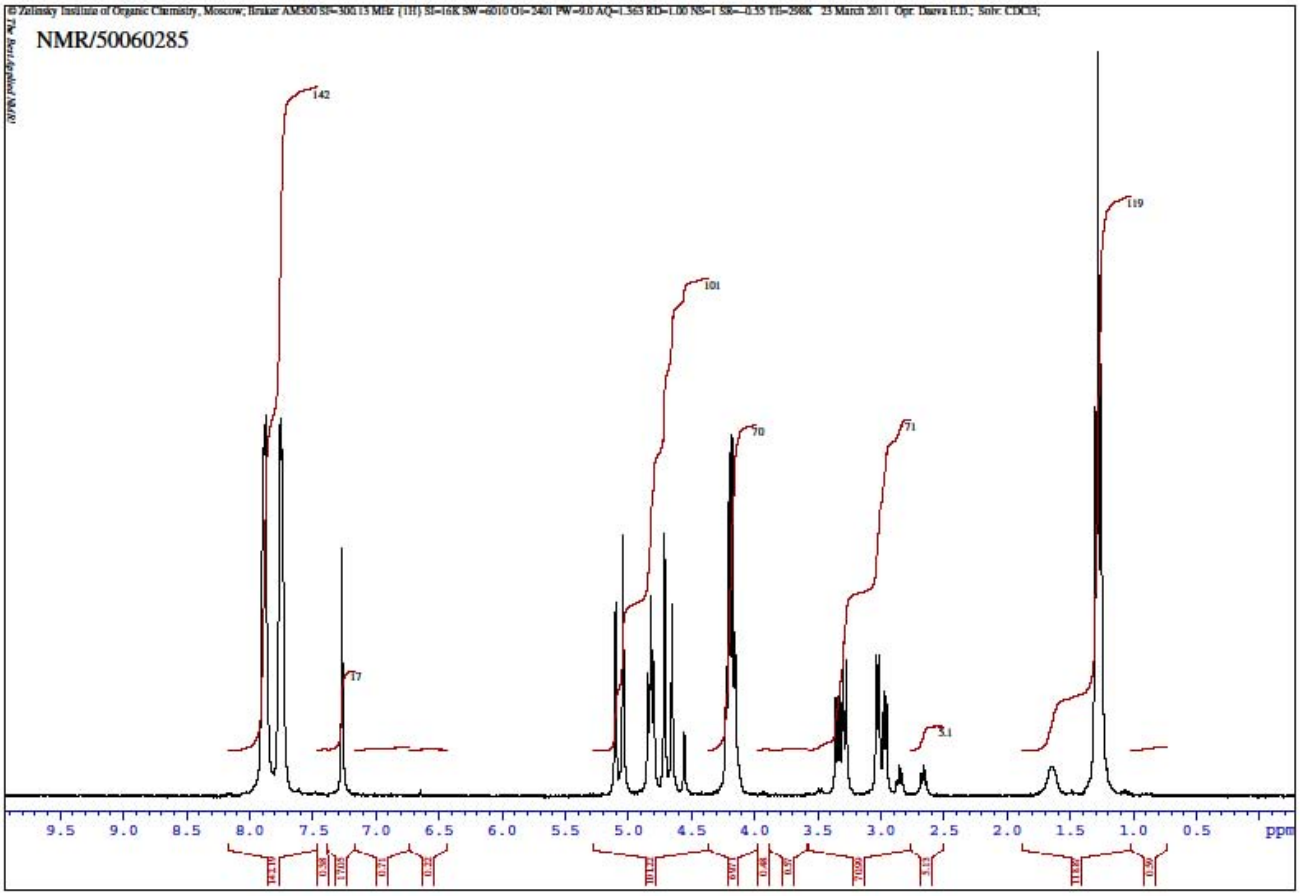


Figure 8. ^{13}C NMR spectra of **7b**

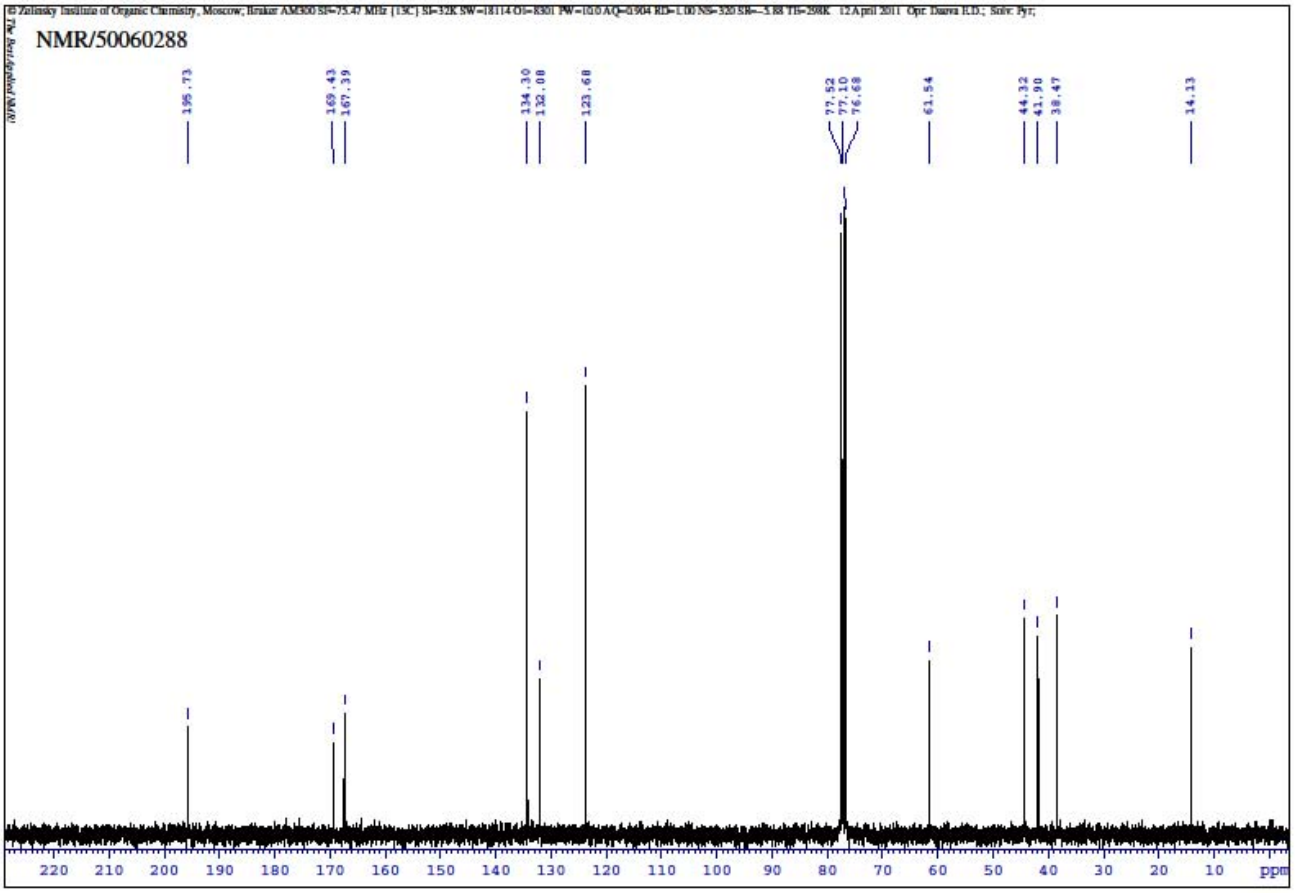


Figure 9. ^{1}H NMR spectra of **8a**

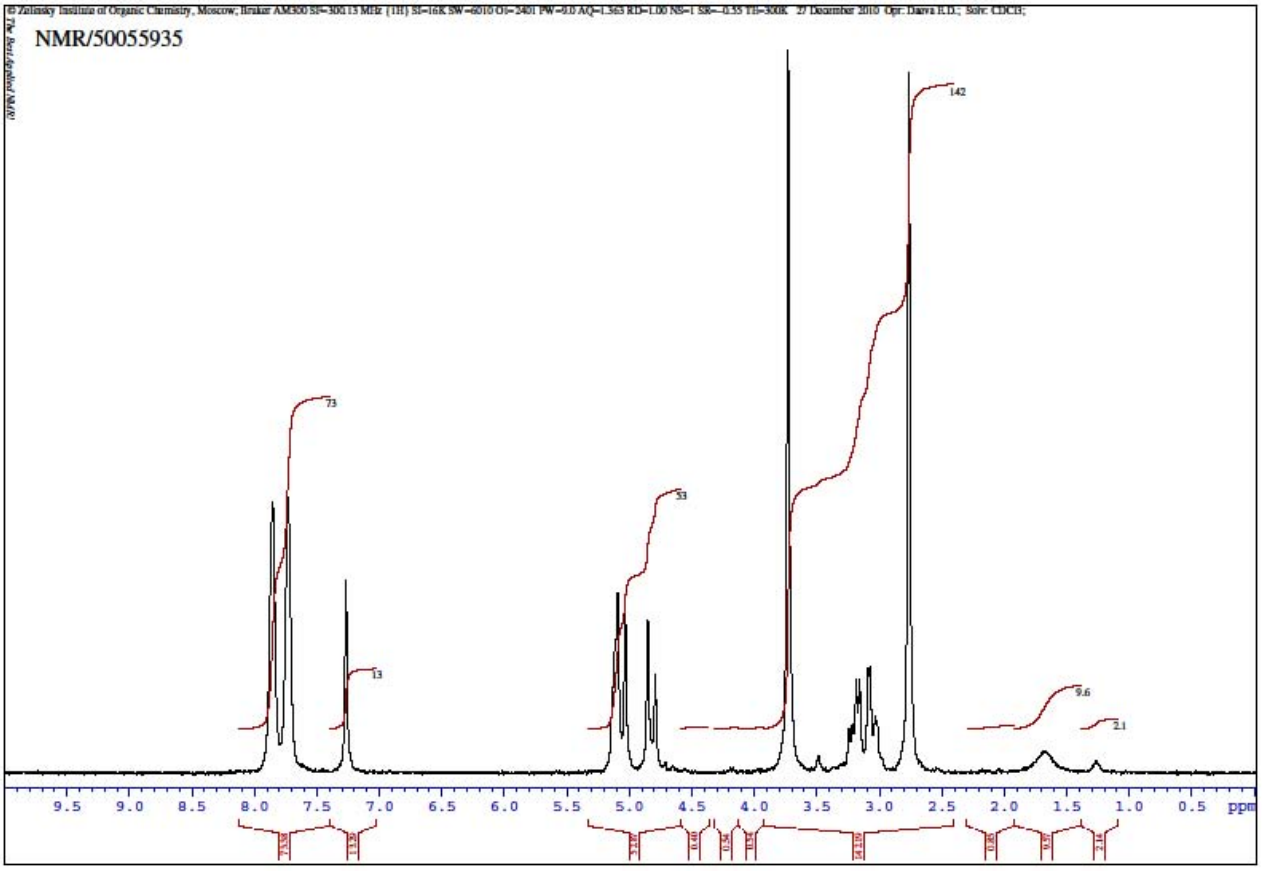


Figure 10 ^{13}C NMR spectra of **8a**

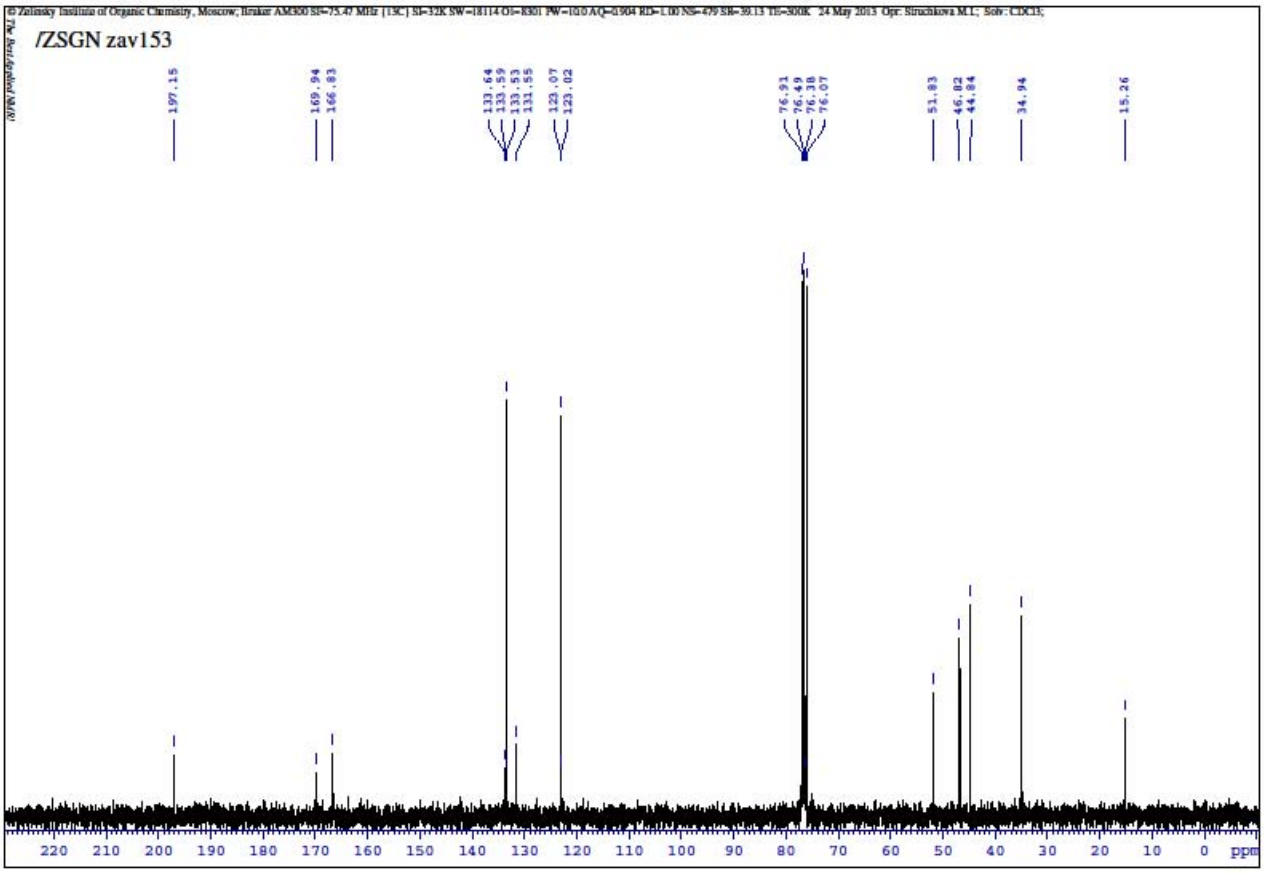


Figure 11. ^{1}H NMR spectra of **8b**

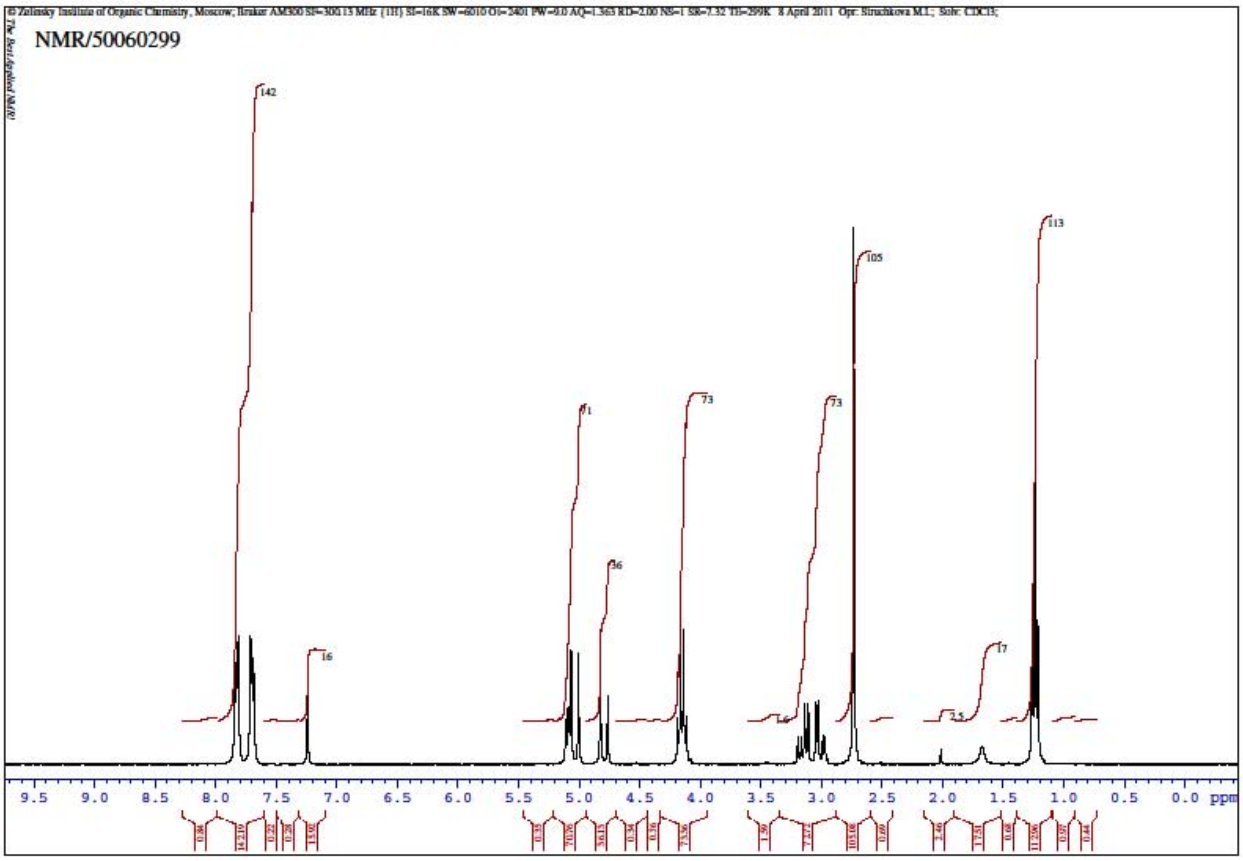


Figure 12. ^{13}C NMR spectra of **8b**

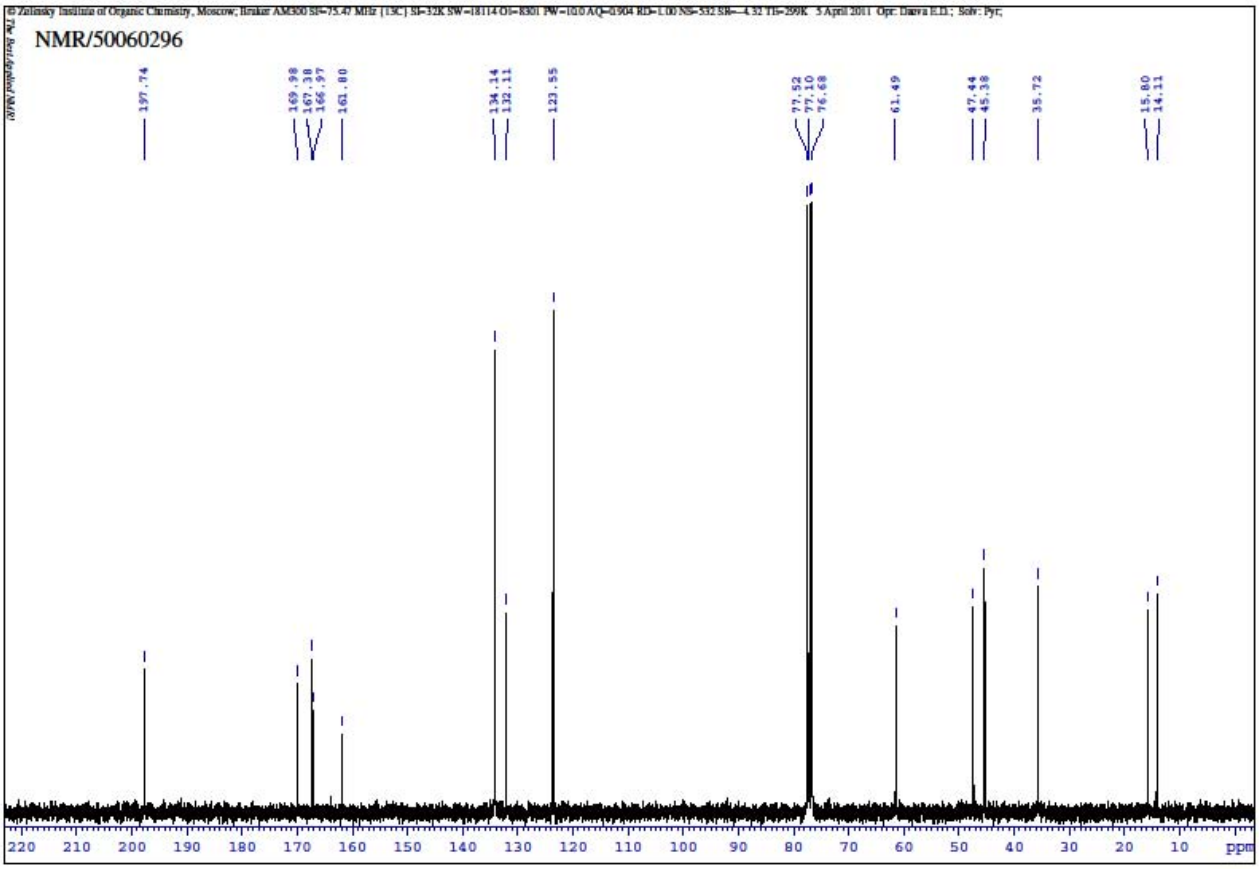


Figure 13. ^{1}H NMR spectra of **9**

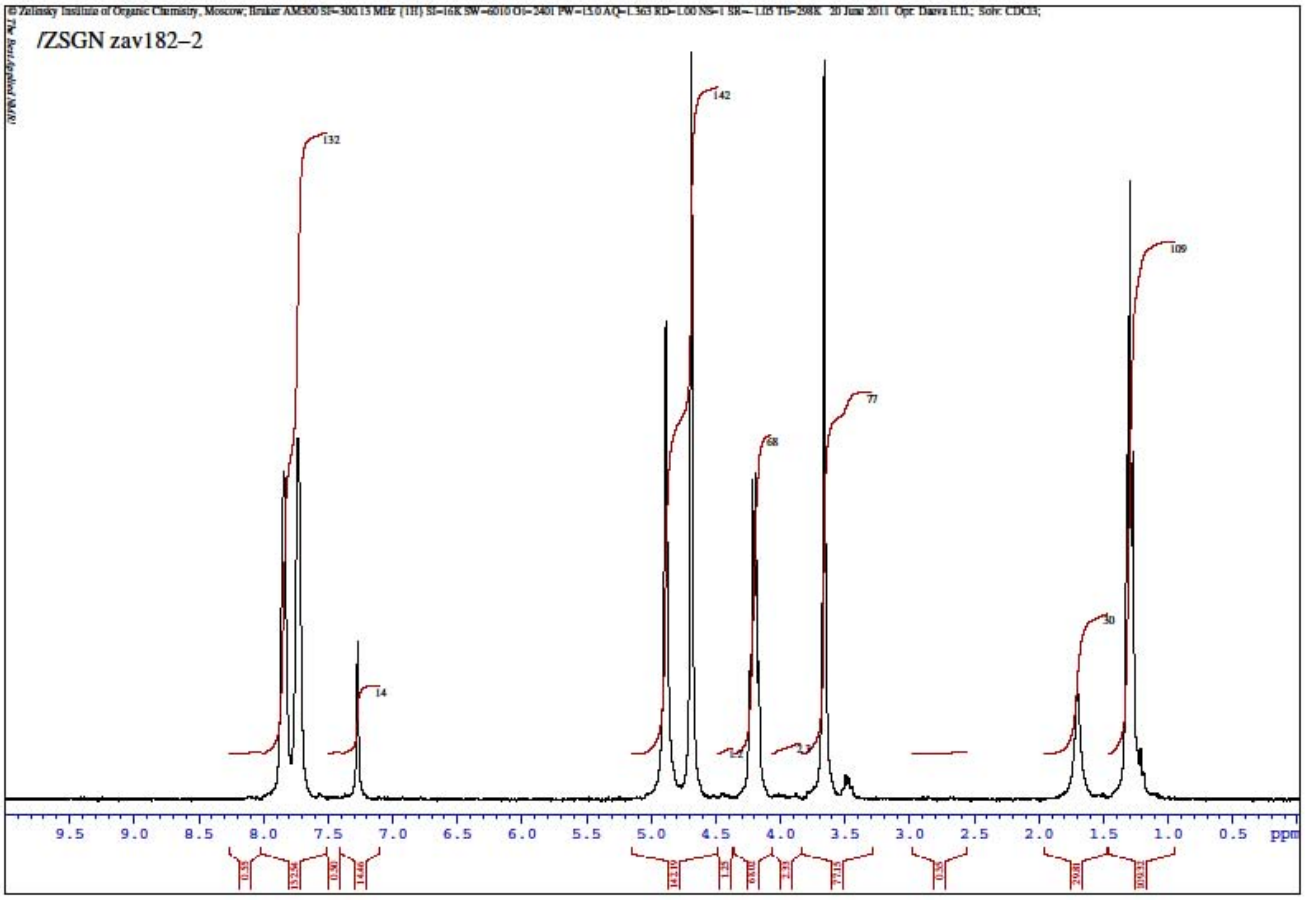


Figure 14. ^{13}C NMR spectra of **9**

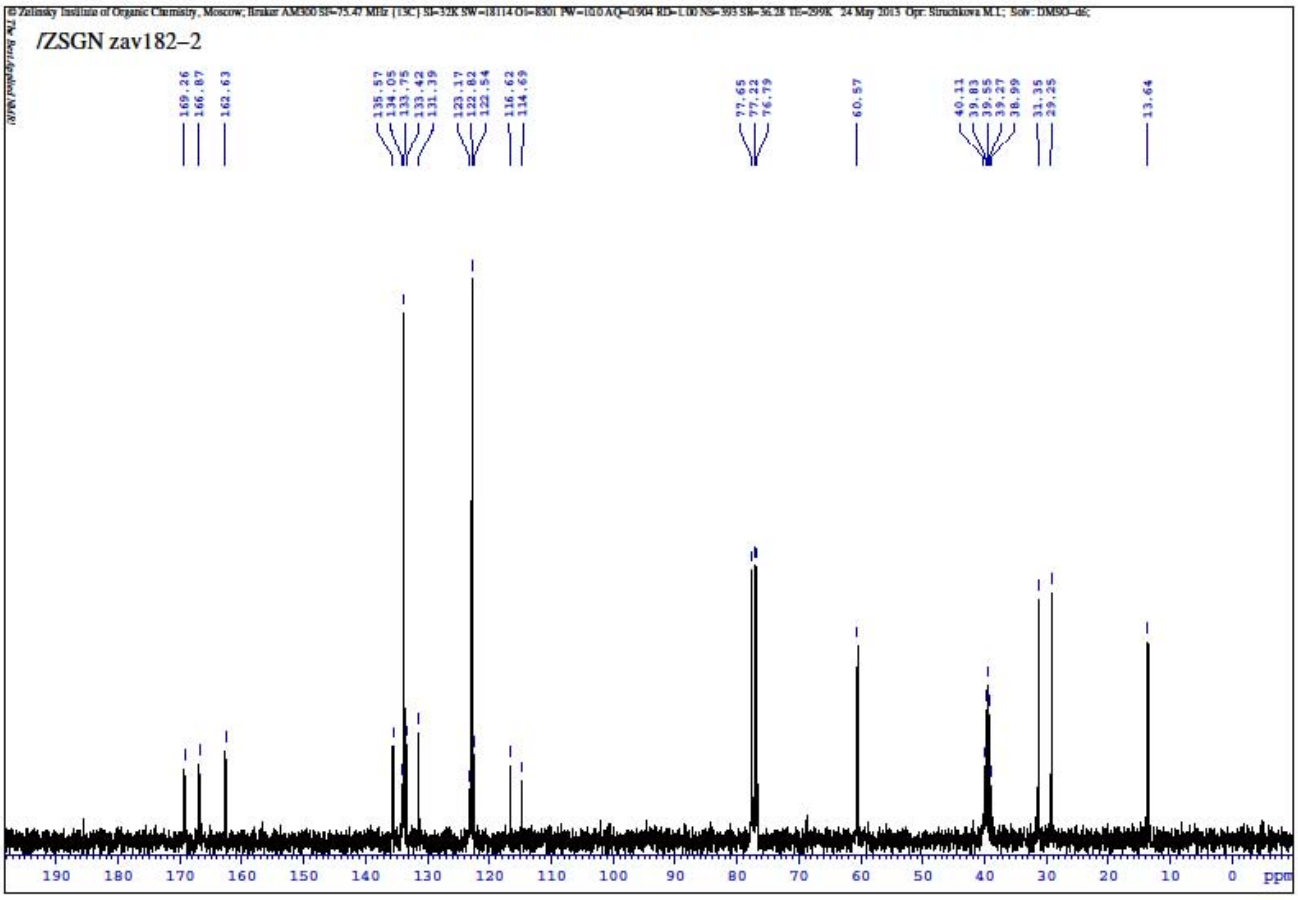


Figure 15. ^{1}H NMR spectra of **11a**

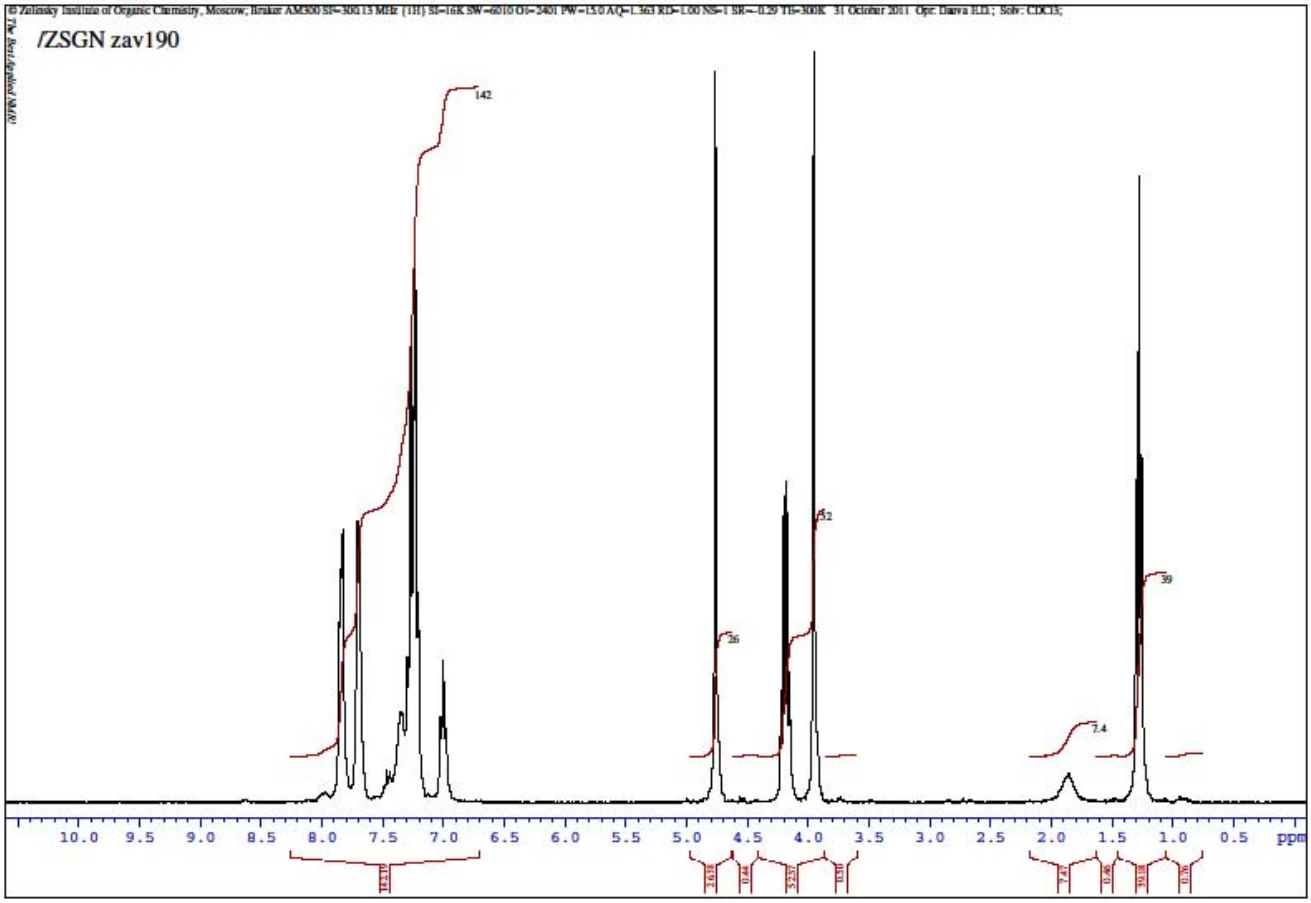


Figure 16. ^{13}C NMR spectra of **11a**

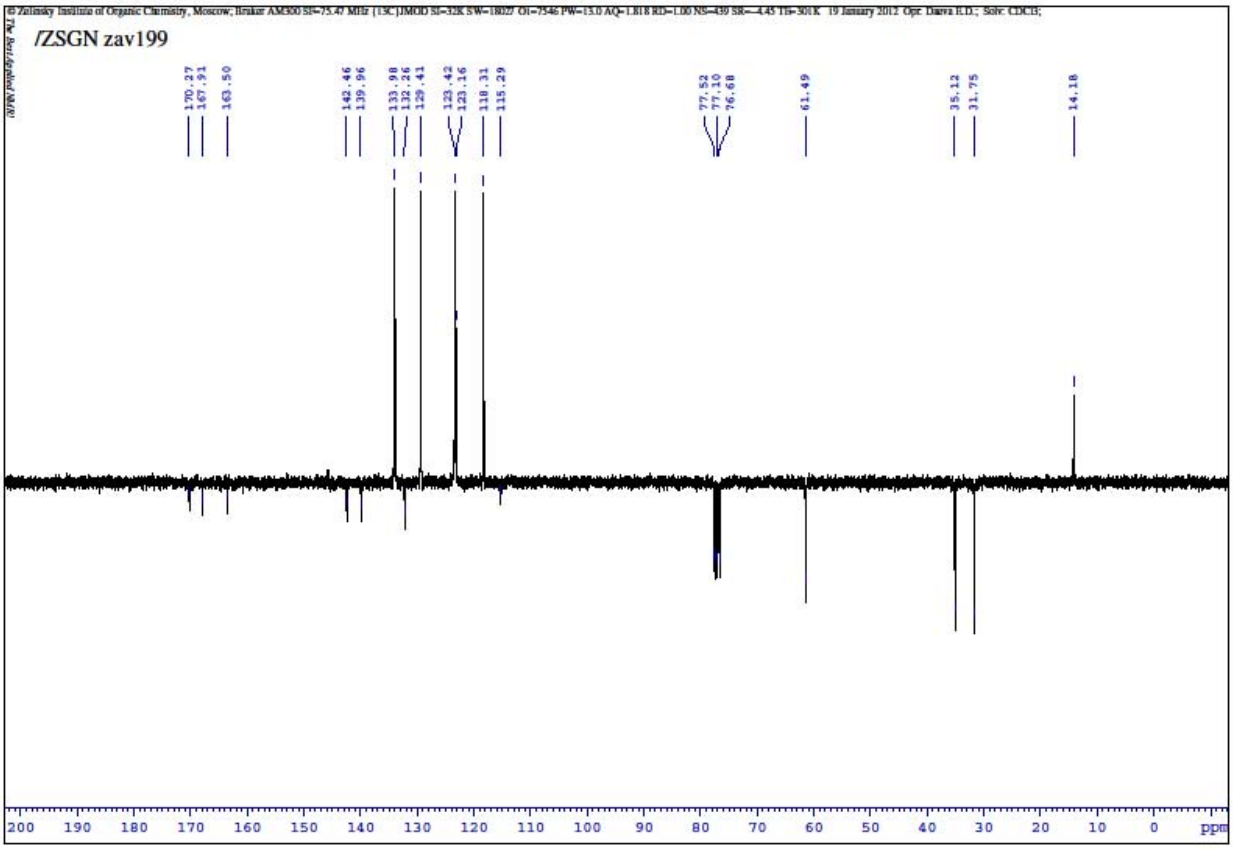


Figure 17. ^{1}H NMR spectra of **11b**

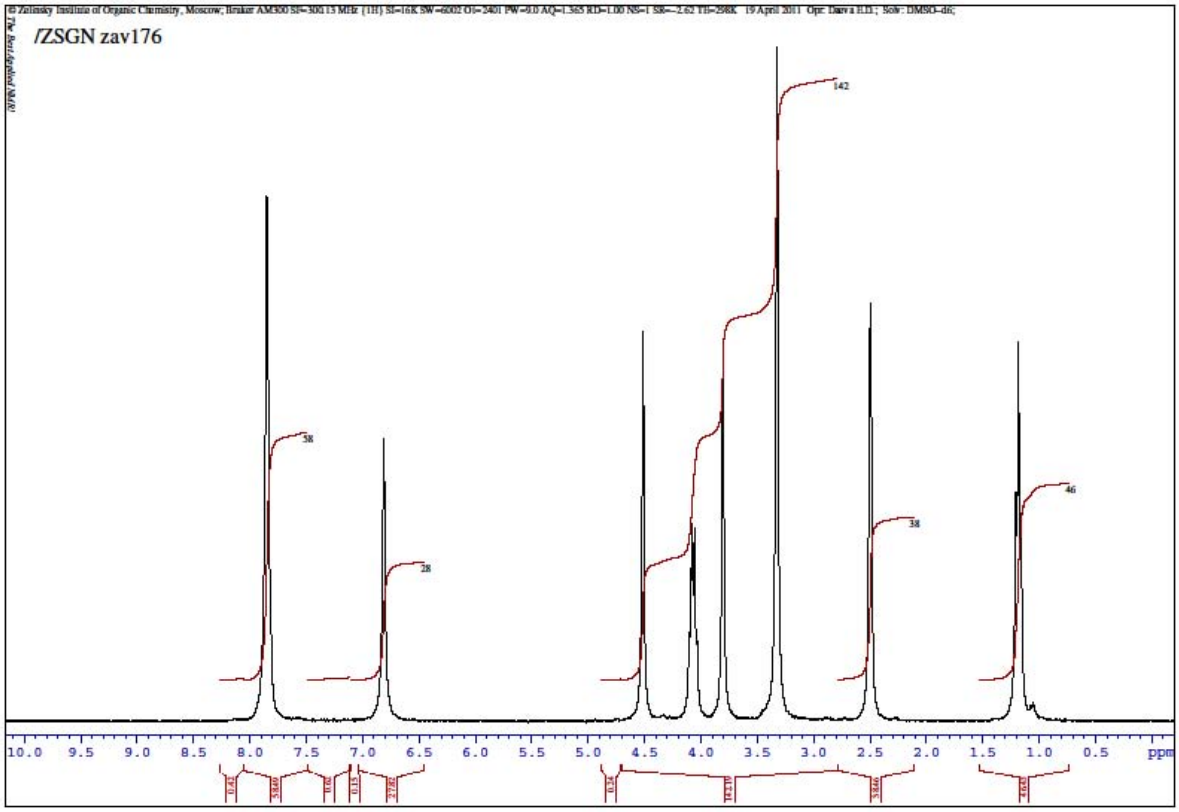


Figure 18. ^{13}C NMR spectra of **11b**

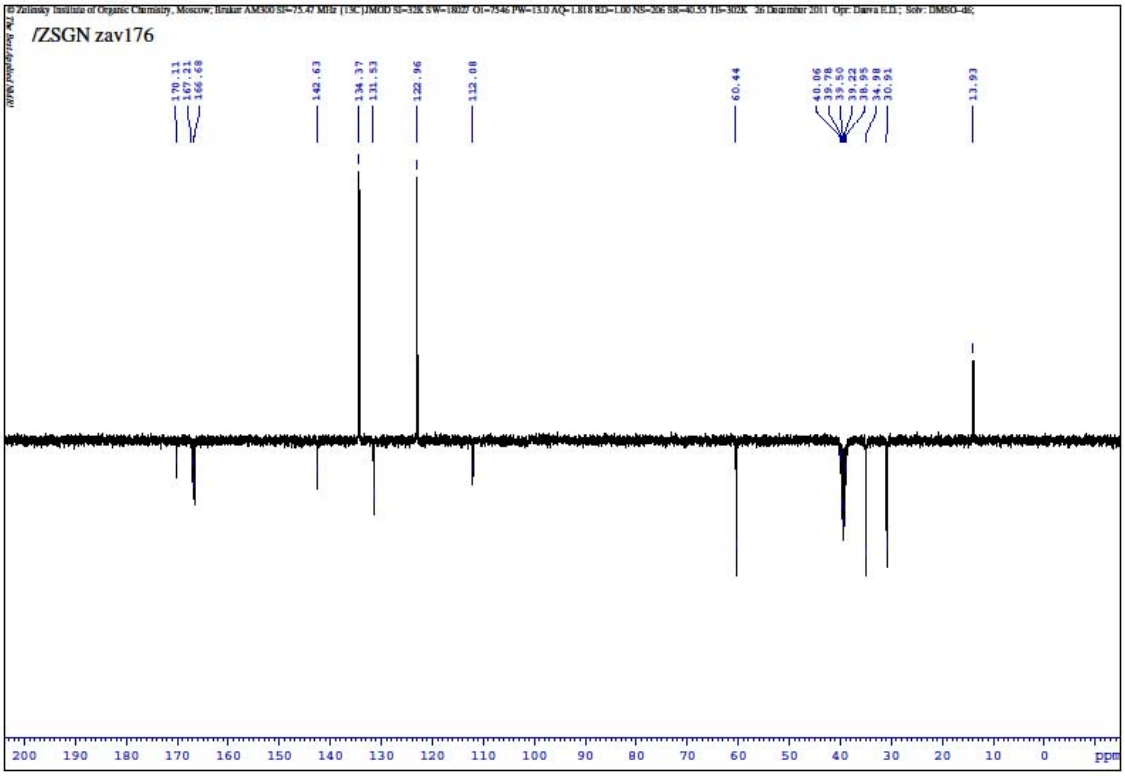


Figure 19. ^{1}H NMR spectra of **11c**

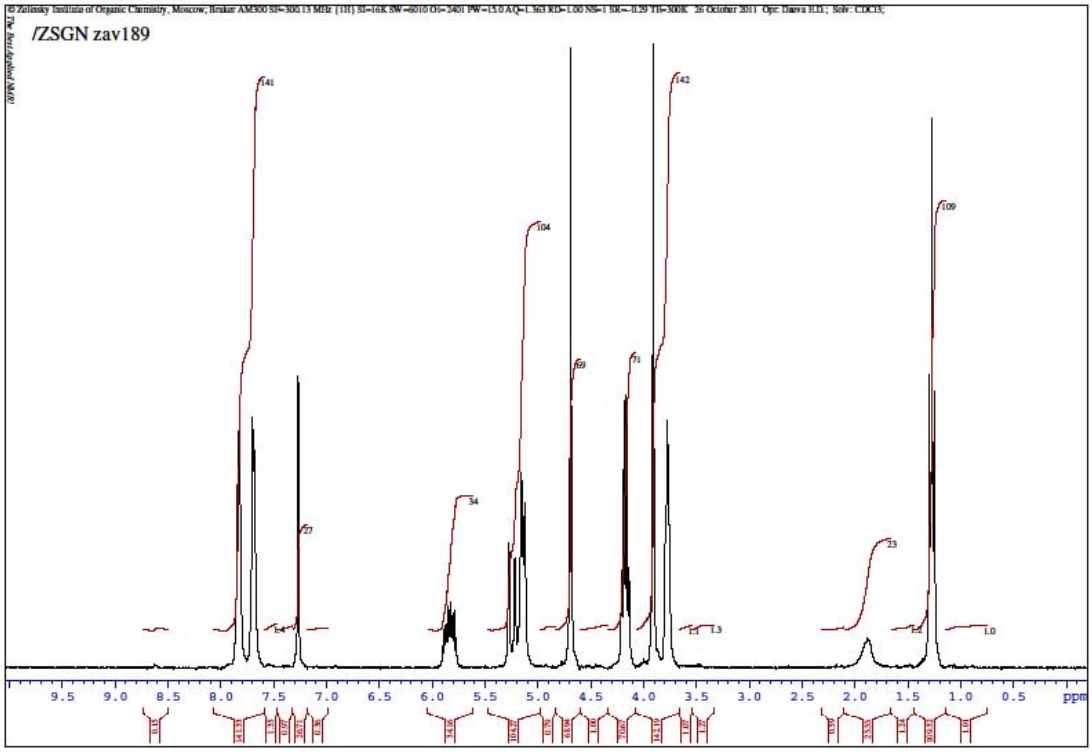


Figure 20. ^{13}C NMR spectra of **11c**

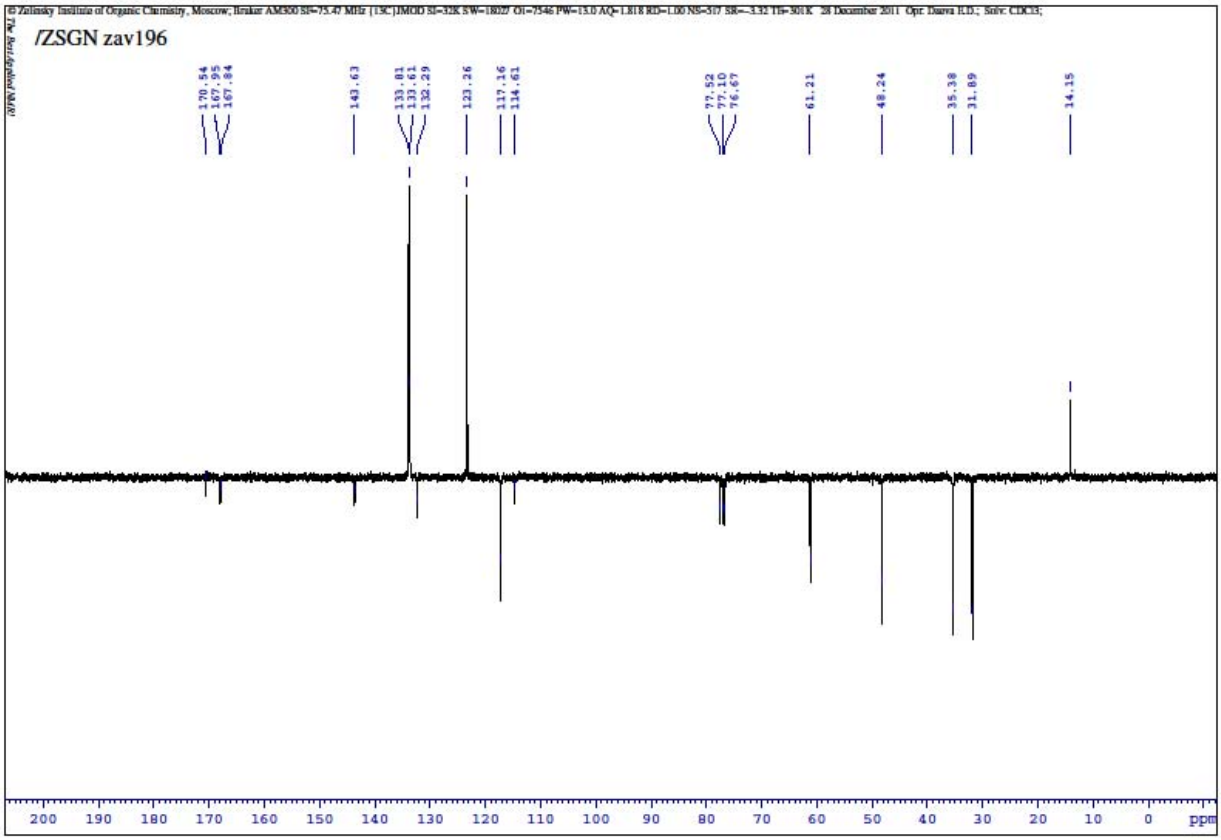


Figure 21 ^{1}H NMR spectra of **11d**

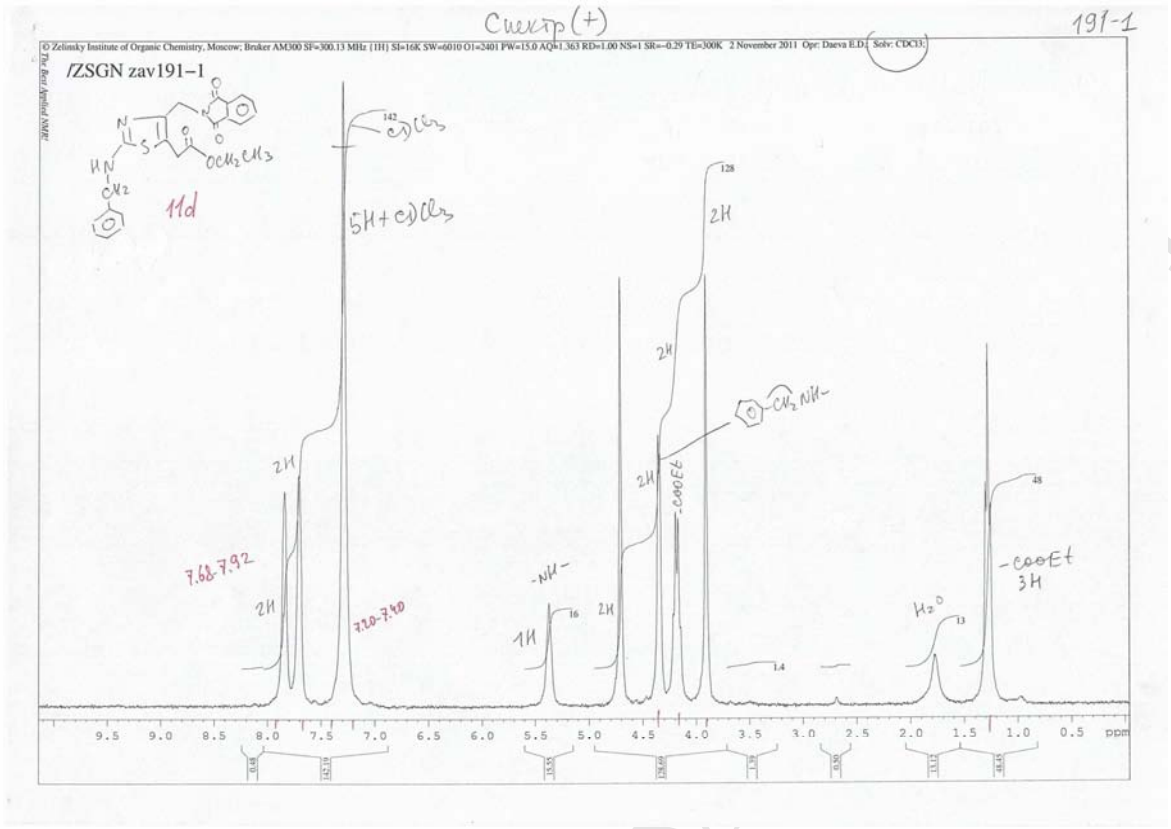


Figure 22 ^{13}C NMR spectra of **11d**

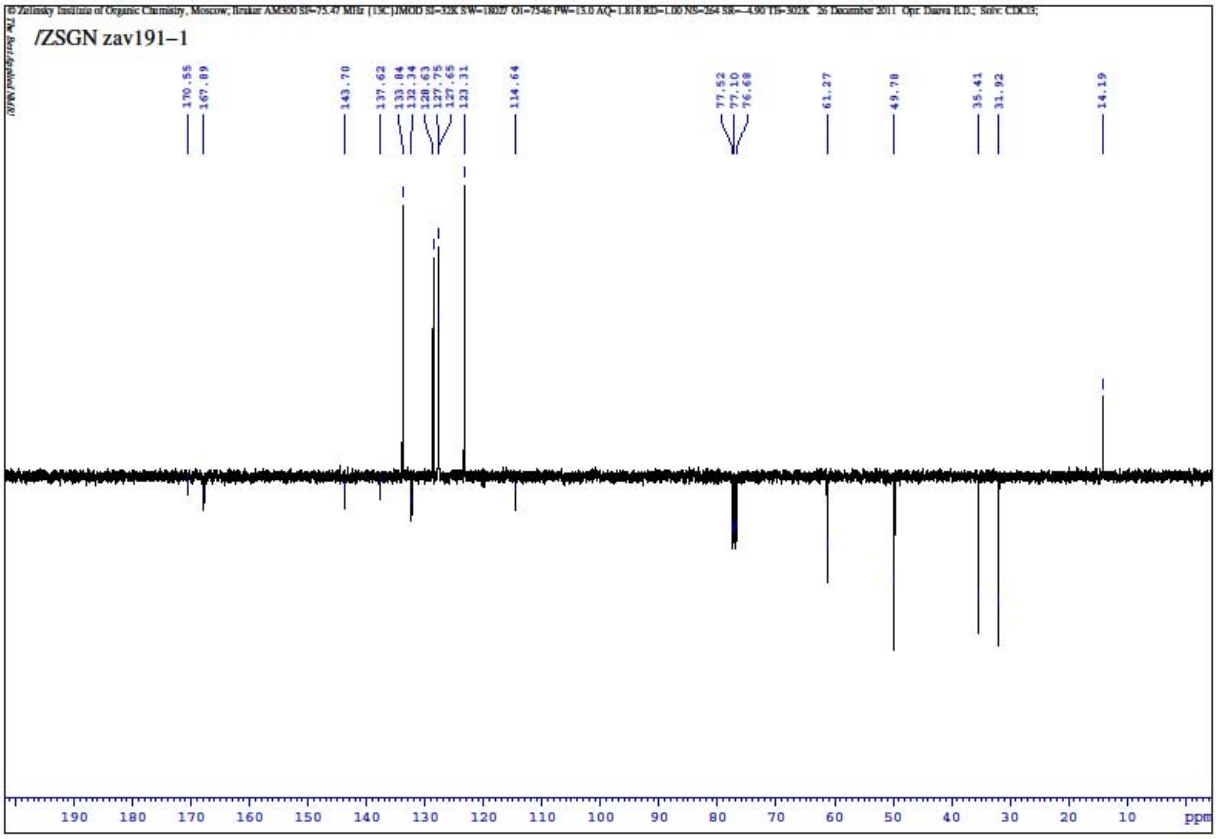


Figure 23 ^{1}H NMR spectra of **11e**

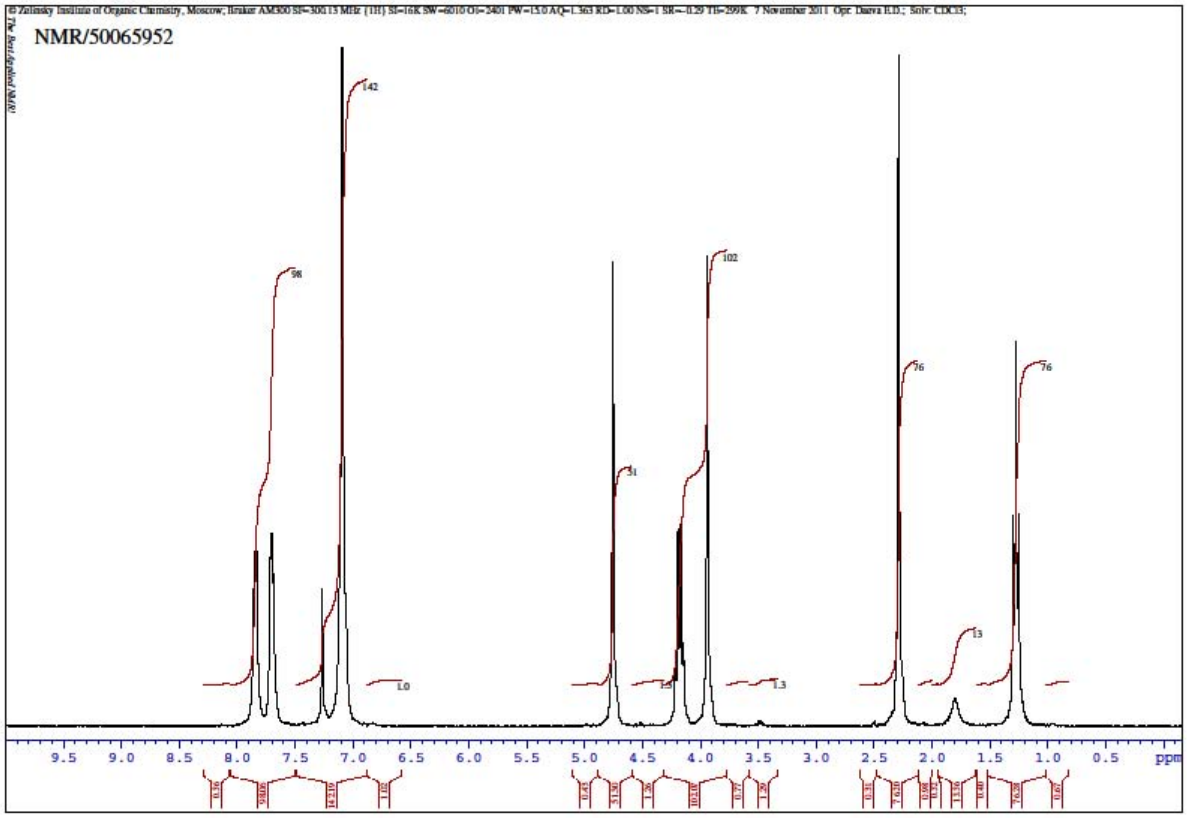


Figure 24 ^{13}C NMR spectra of **11e**

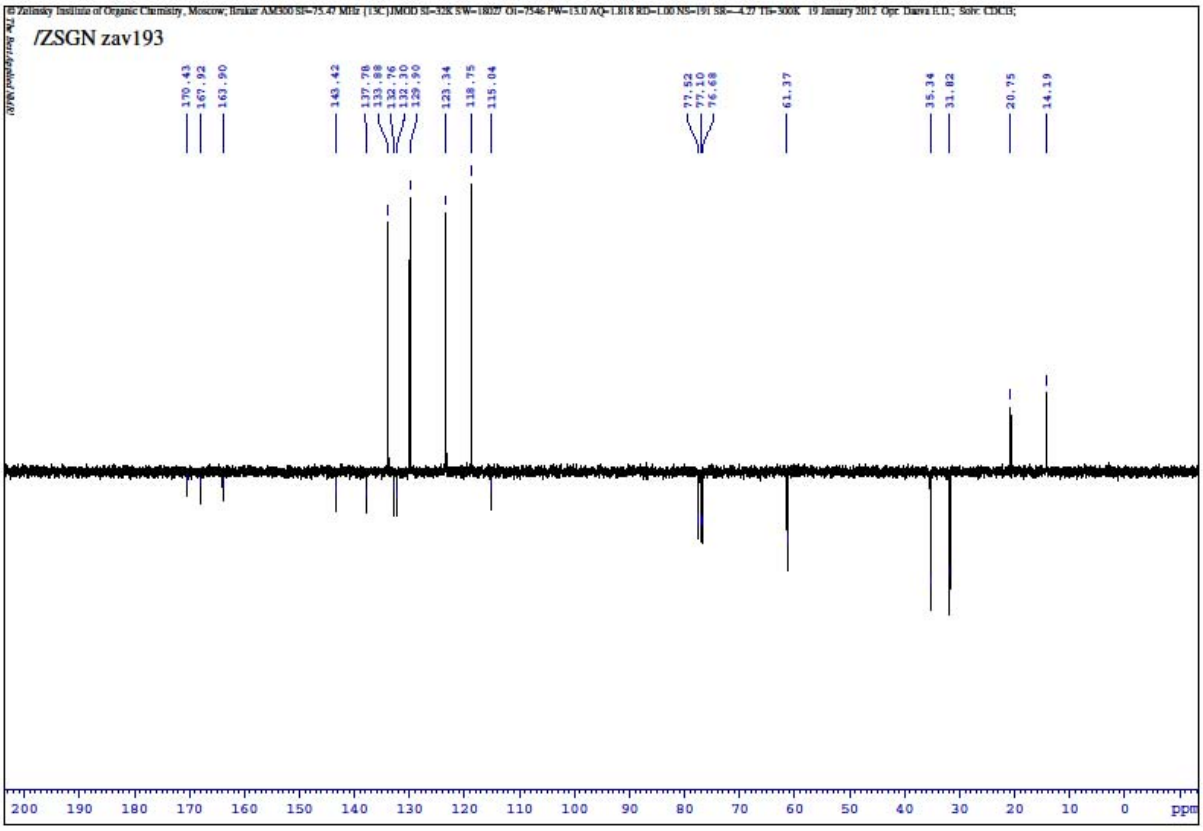


Figure 25 ^{1}H NMR spectra of **11f**

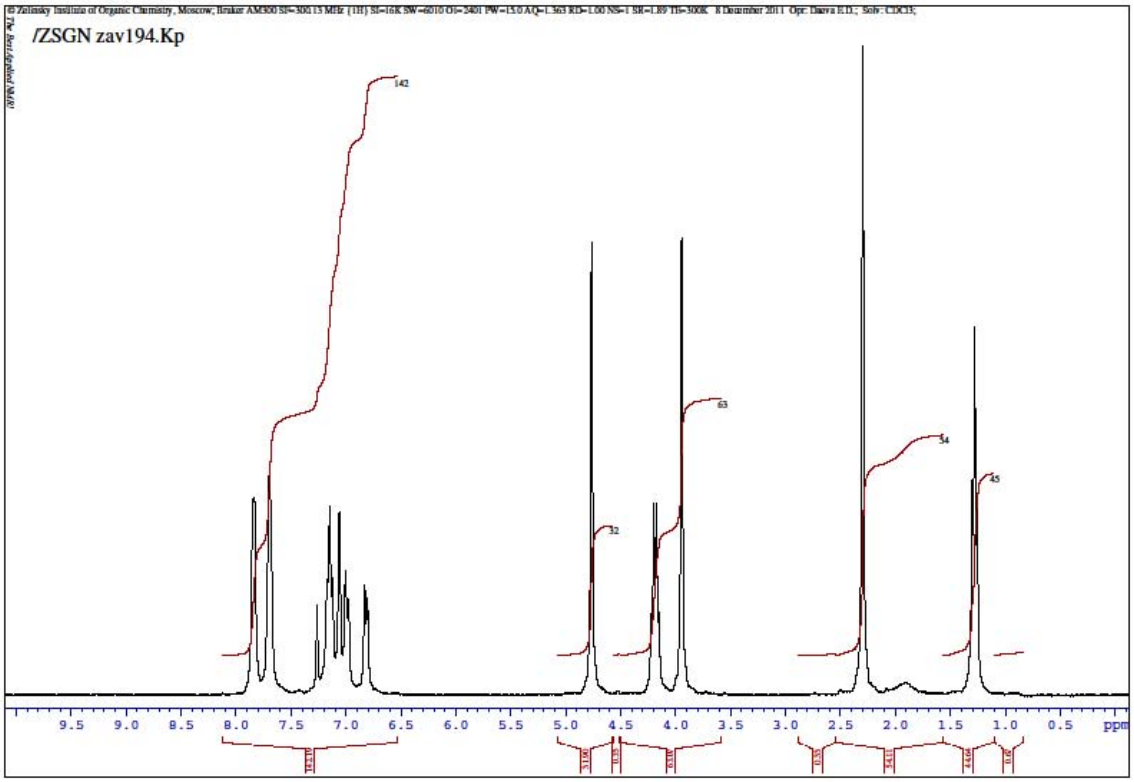


Figure 26 ^{13}C NMR spectra of **11f**

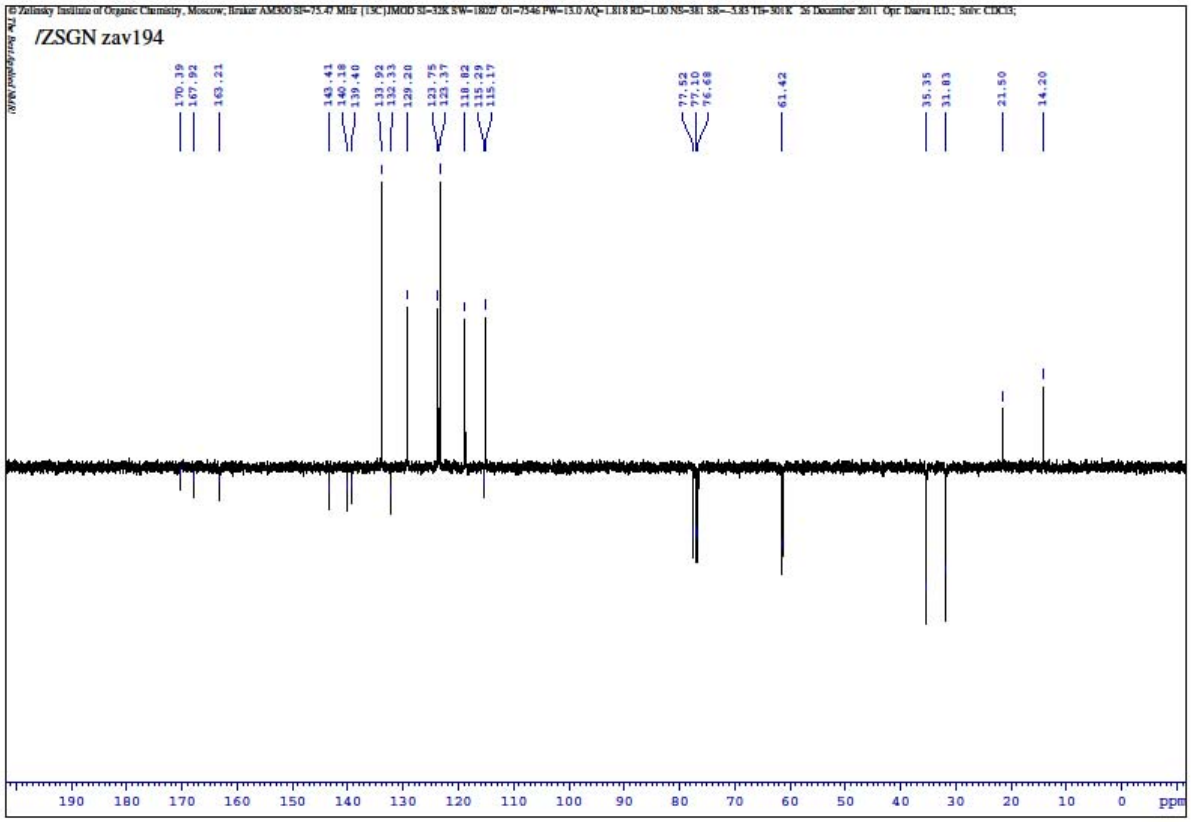


Figure 27 ^{1}H NMR spectra of **11g**

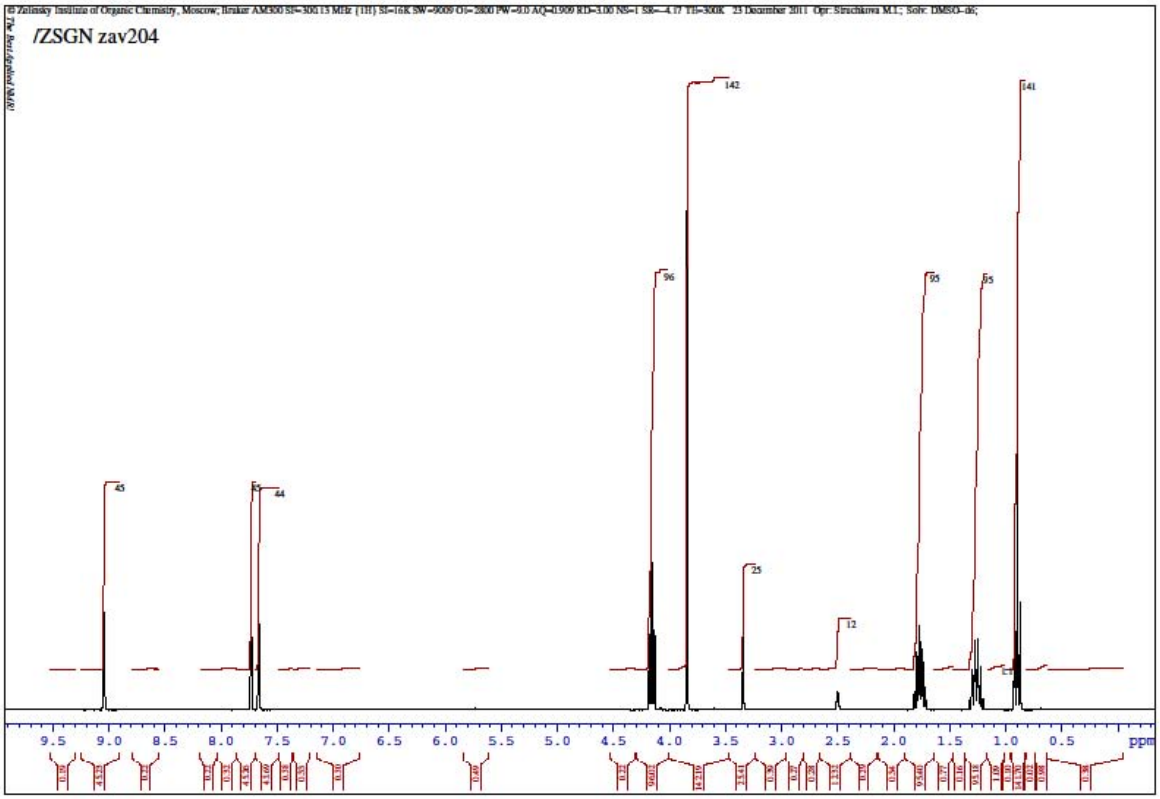


Figure 28 ^{13}C NMR spectra of **11g**

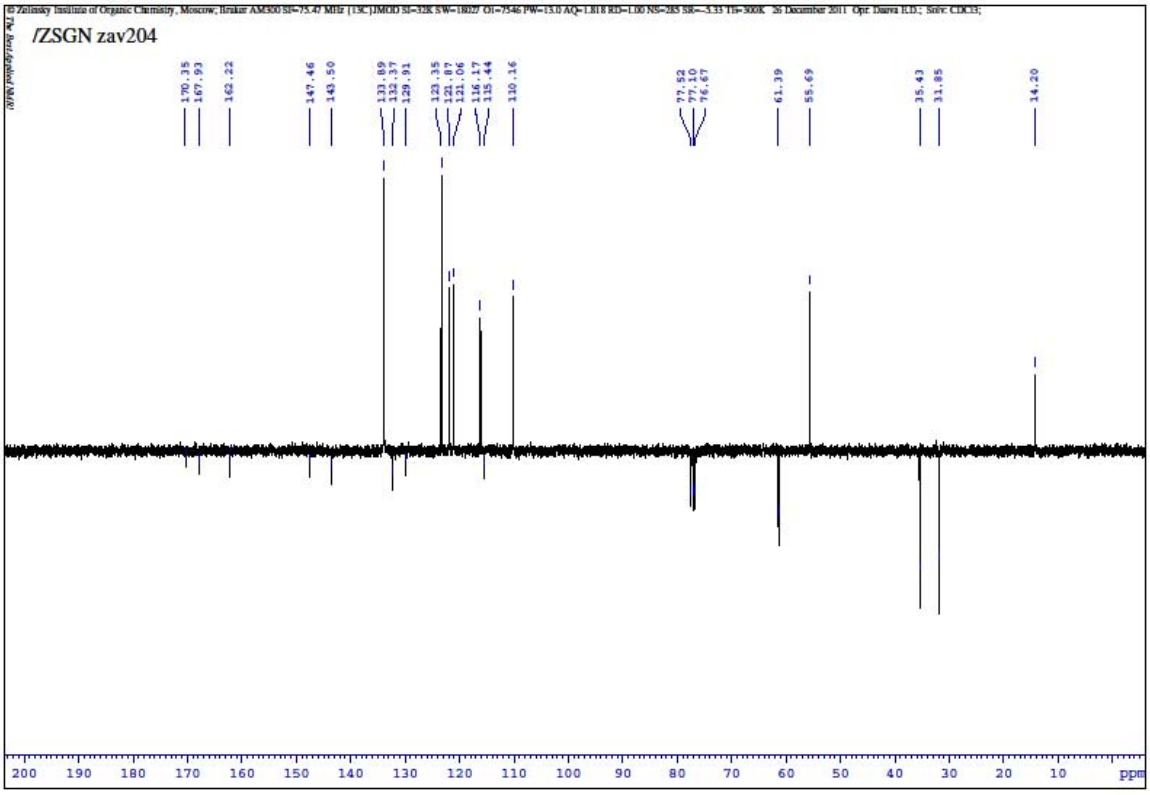


Figure 29 ^{1}H NMR spectra of **11h**

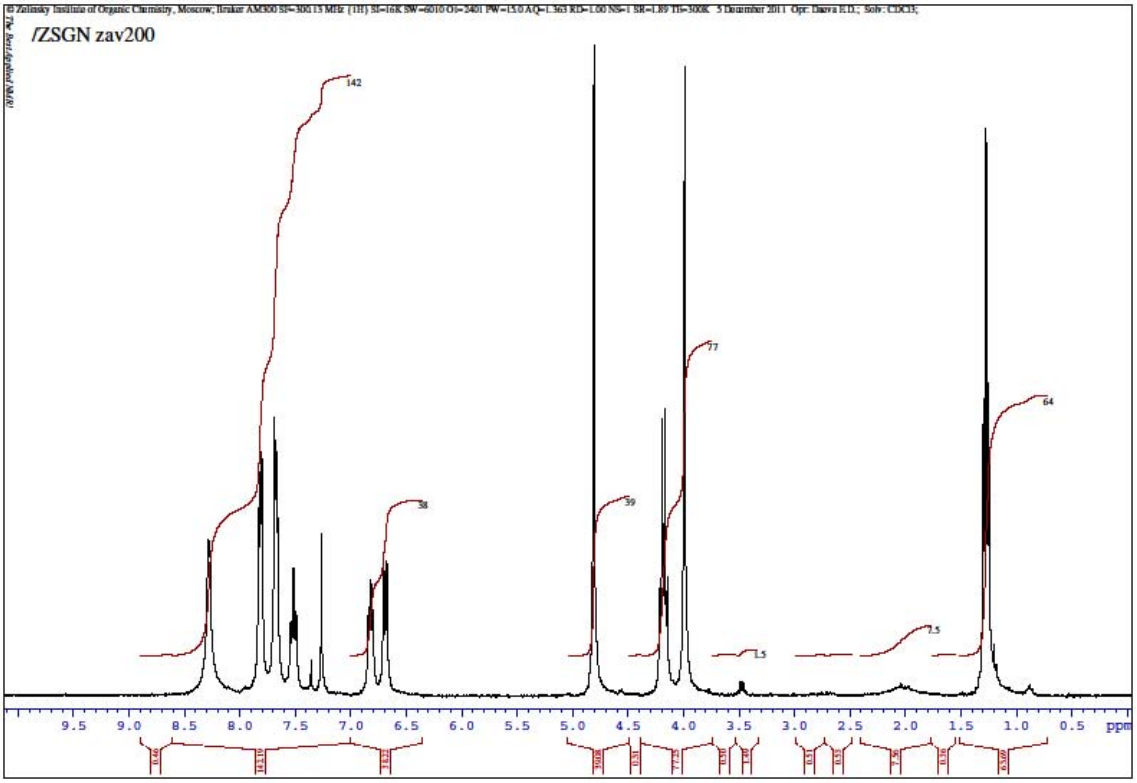


Figure 30 ^{13}C NMR spectra of **11h**

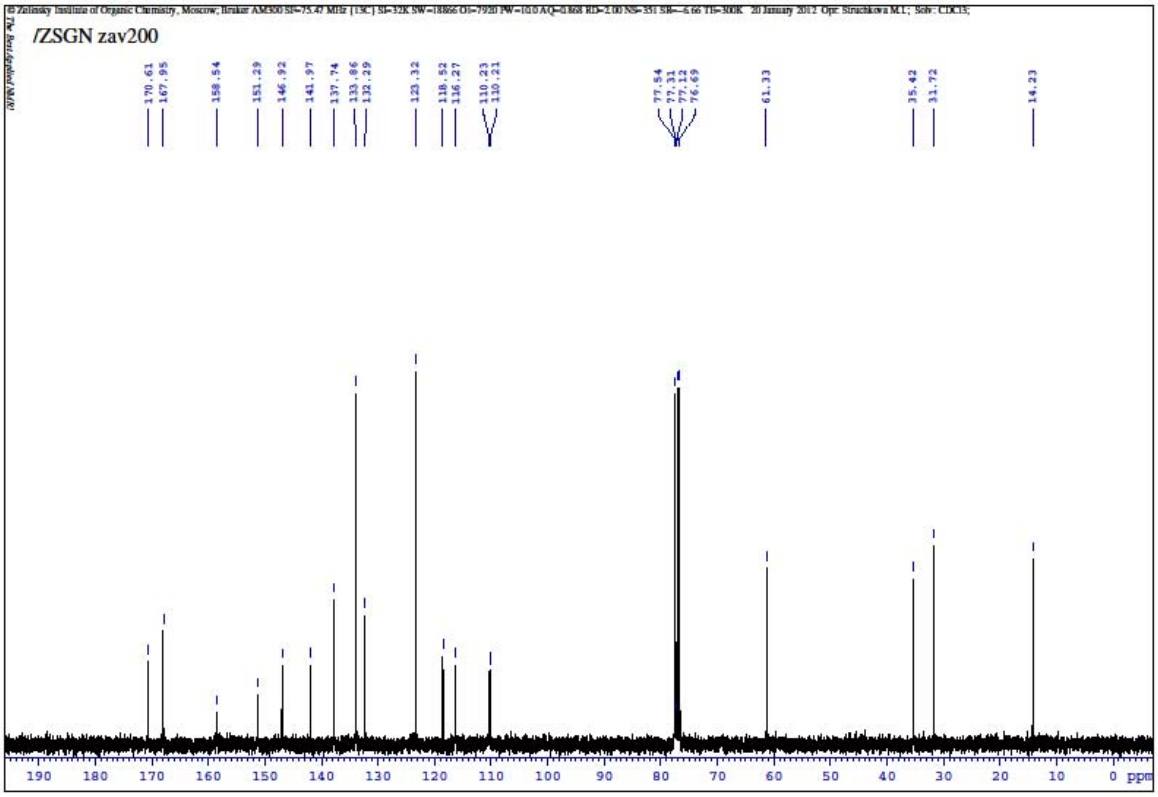


Figure 31 ^{1}H NMR spectra of **11i**

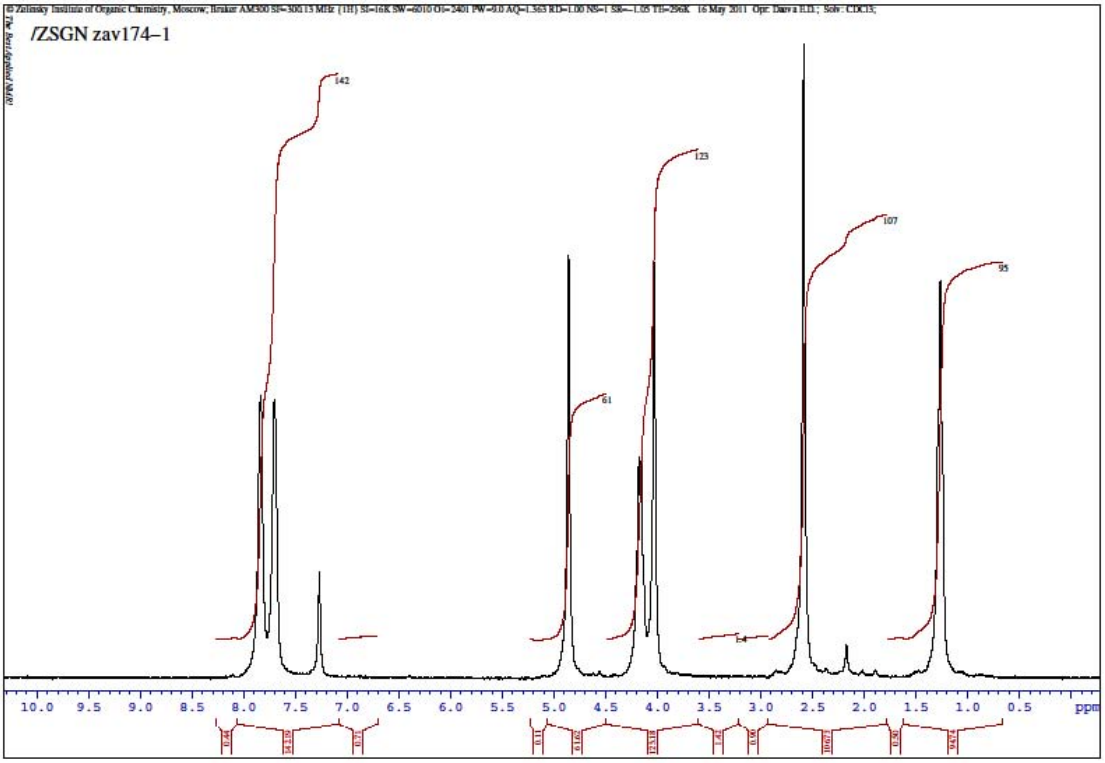


Figure 32 ^{13}C NMR spectra of **11i**

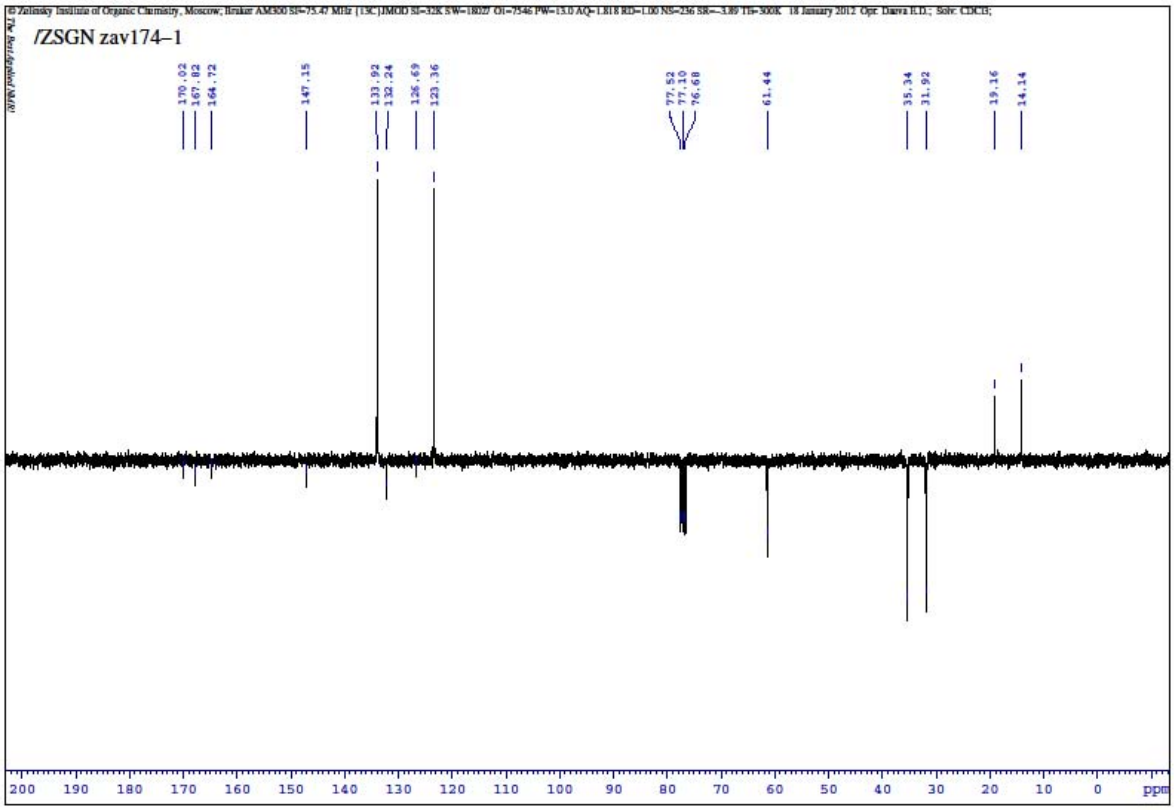


Figure 33 ^{1}H NMR spectra of **11j**

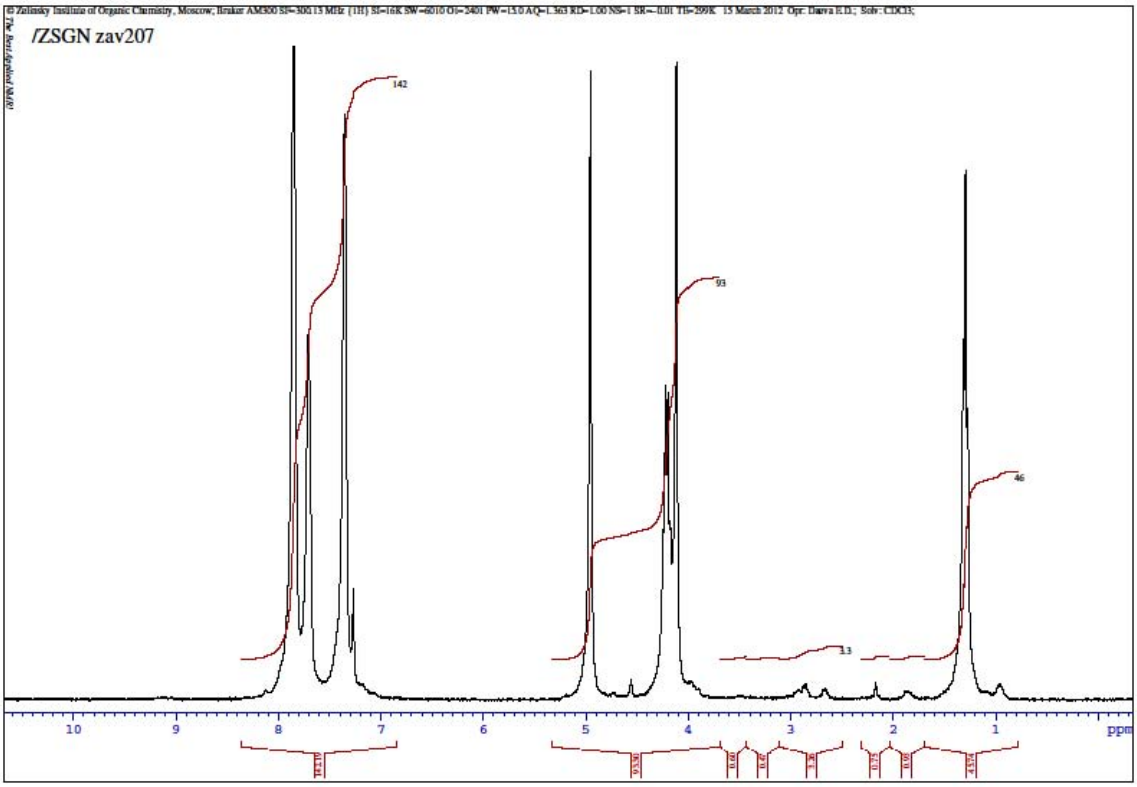


Figure 34 ^{13}C NMR spectra of **11j**

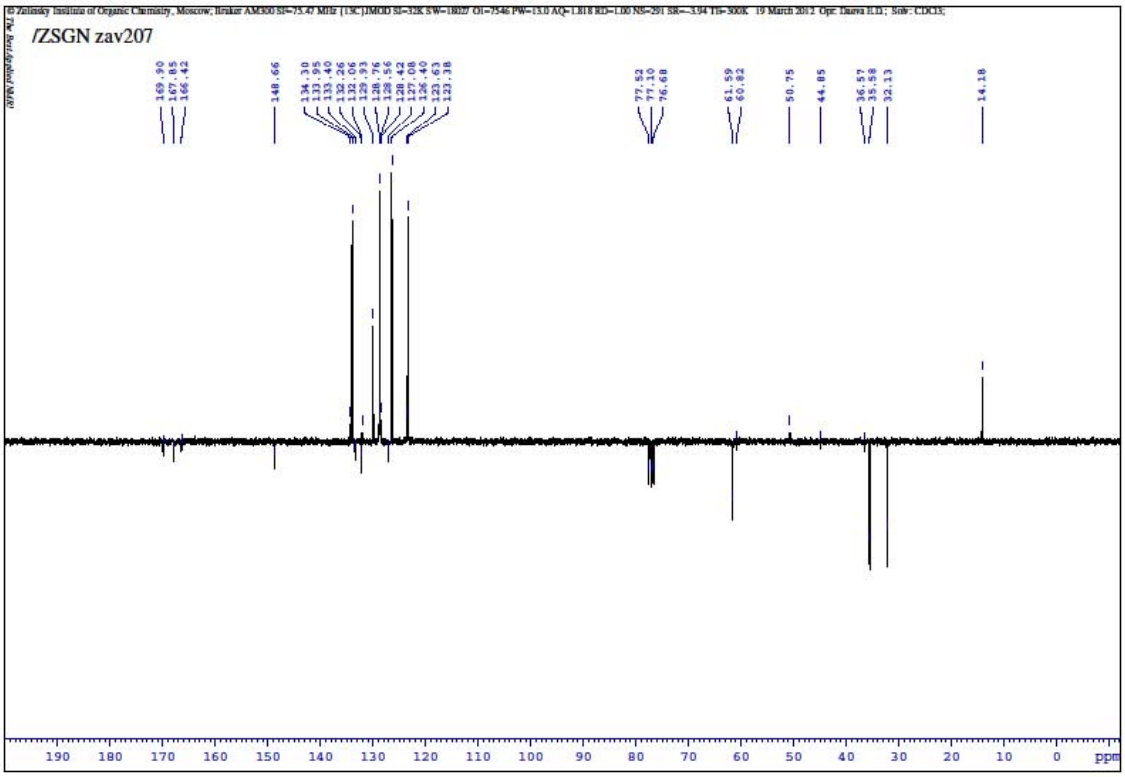


Figure 35 ^{1}H NMR spectra of **11k**

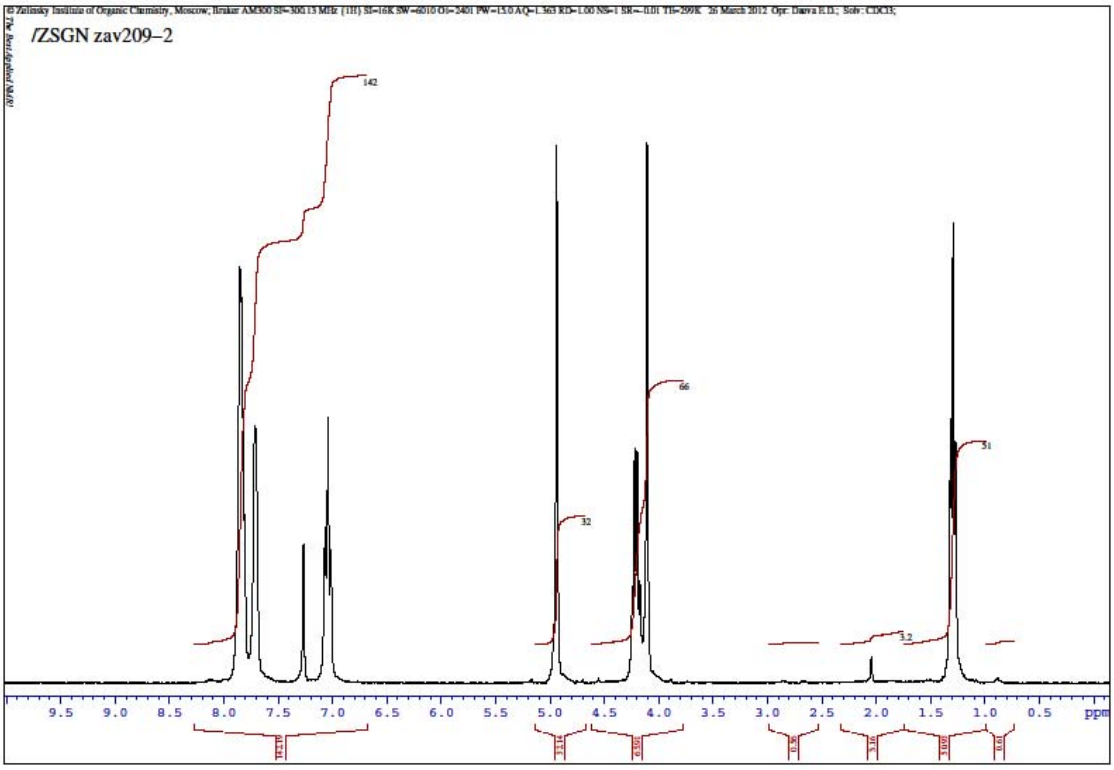


Figure 36 ^{13}C NMR spectra of **11k**

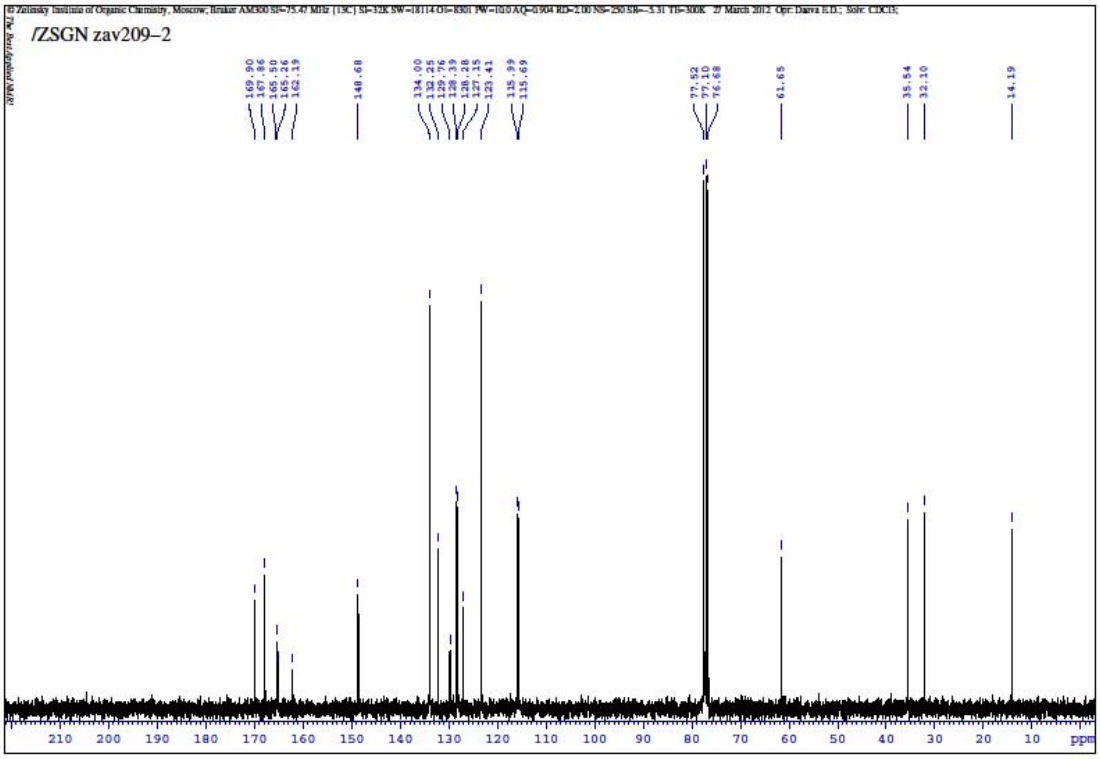


Figure 37 ^{1}H NMR spectra of **11l**

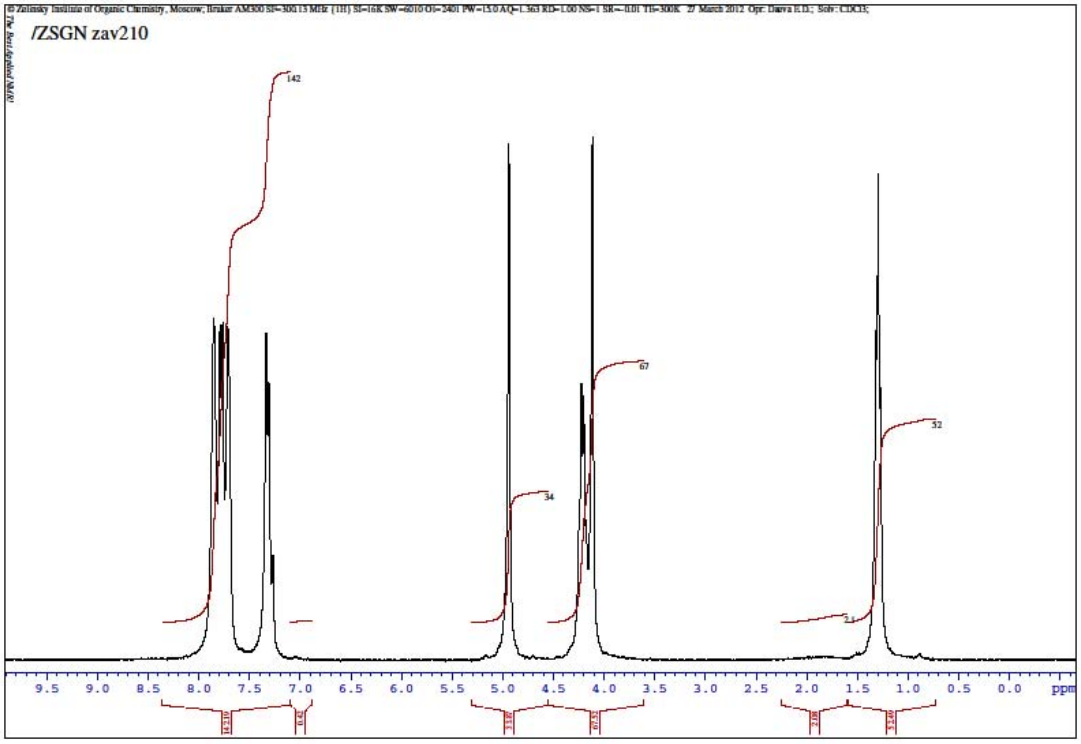


Figure 38 ^{13}C NMR spectra of **11l**

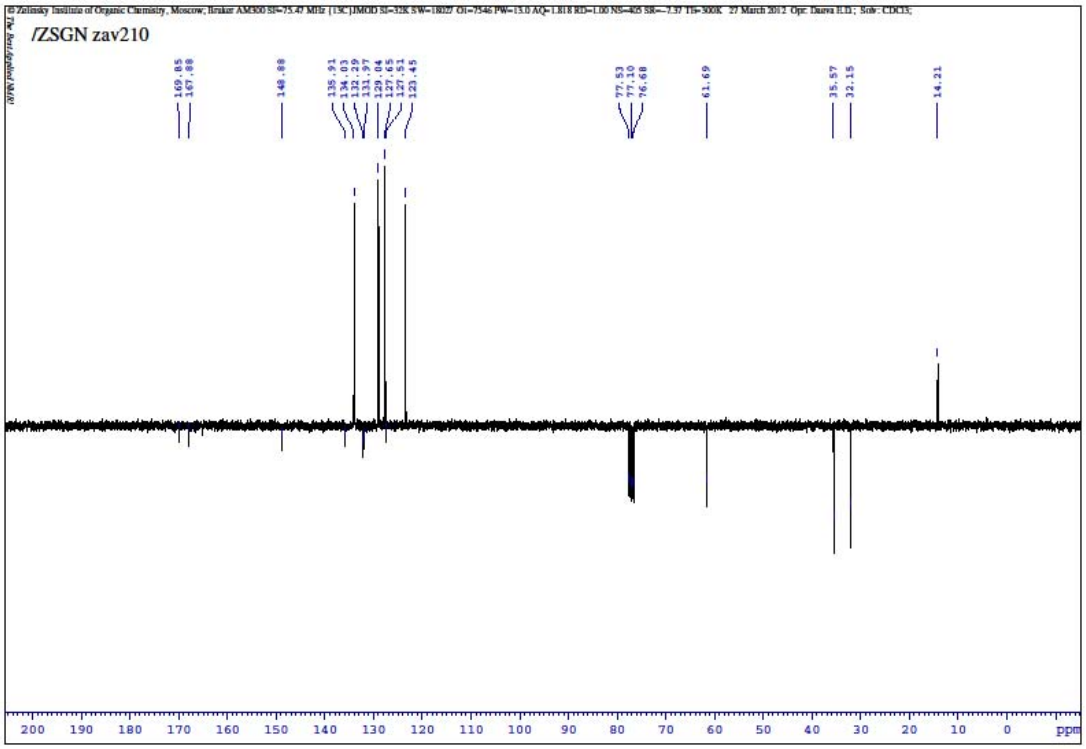
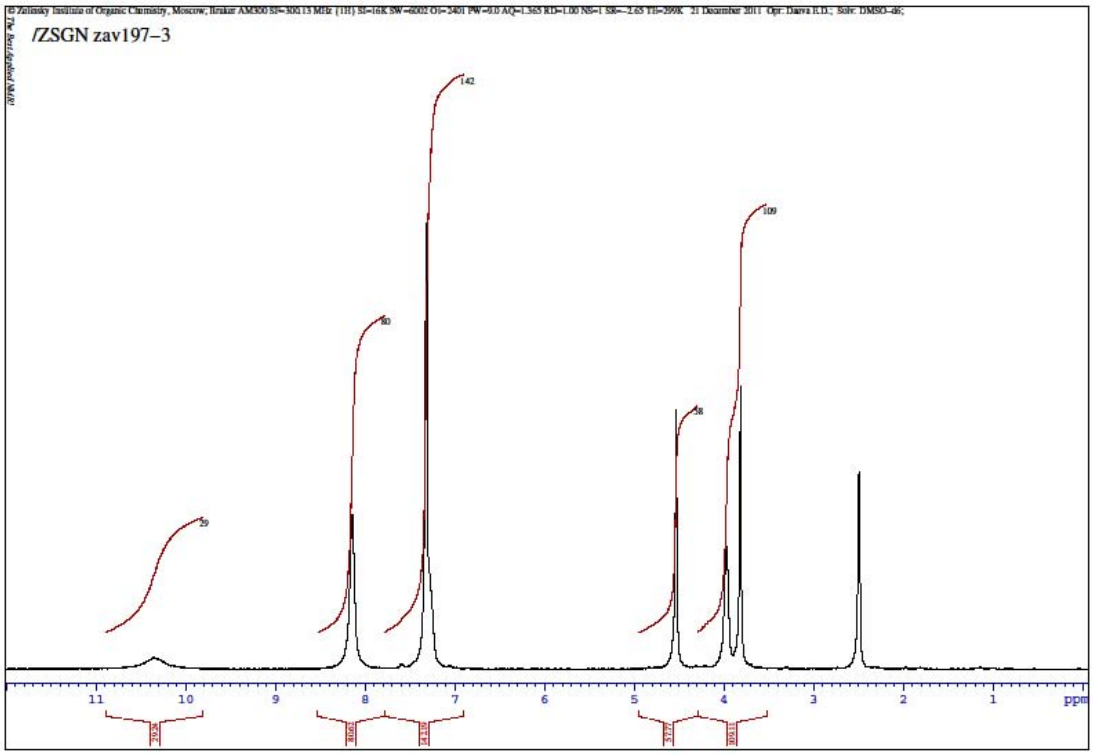


Figure 39 ^{1}H NMR spectra of aminoacid **12a**



v

Figure 40 ^{13}C NMR spectra of aminoacid **12a**

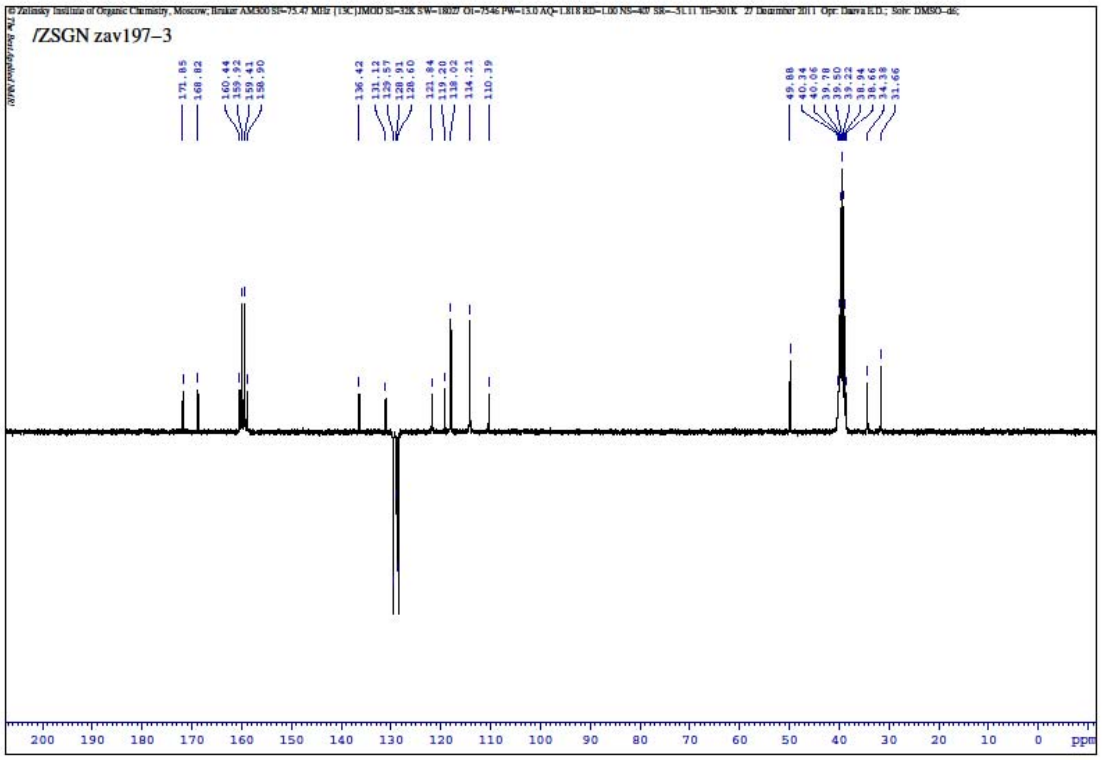


Figure 41. ^{1}H NMR spectra of **12b**

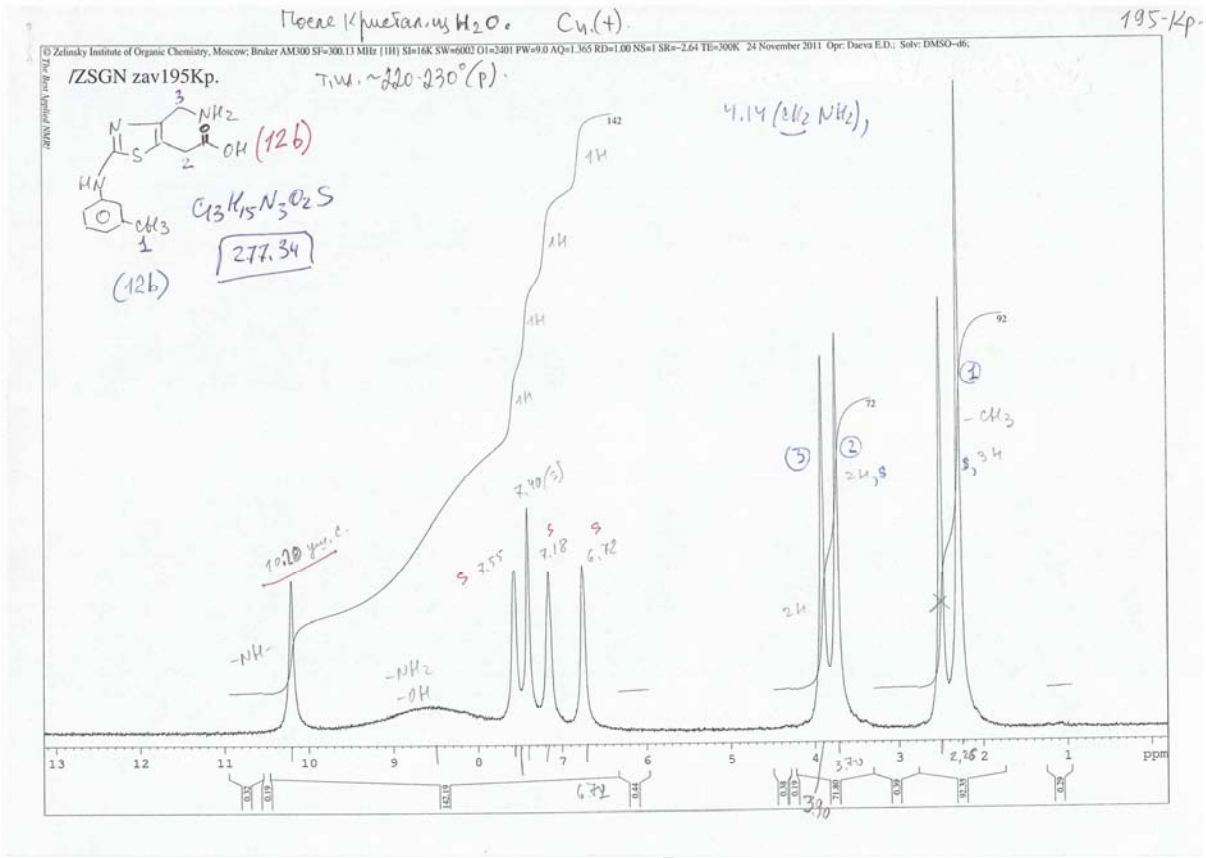


Figure 42. MS spectra of **12b**

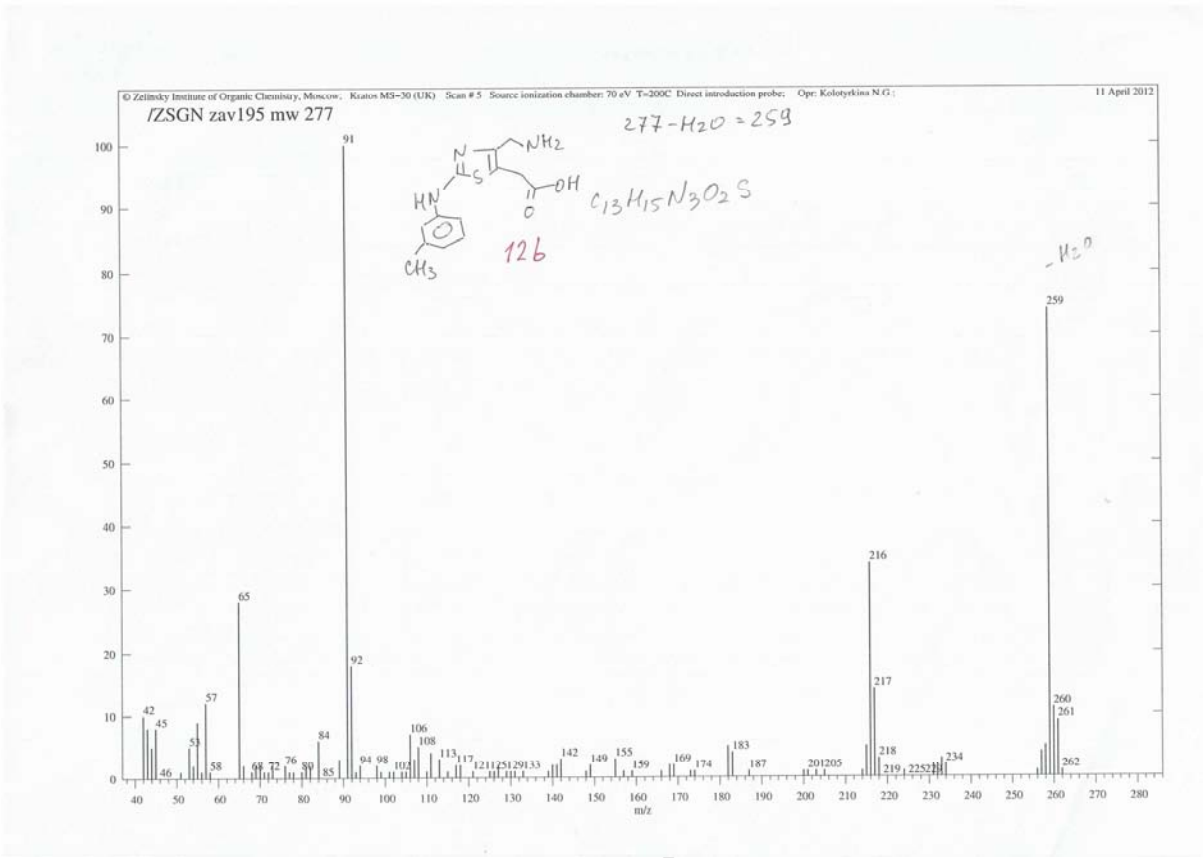


Figure 43 MS spectra of aminoacid **12c**

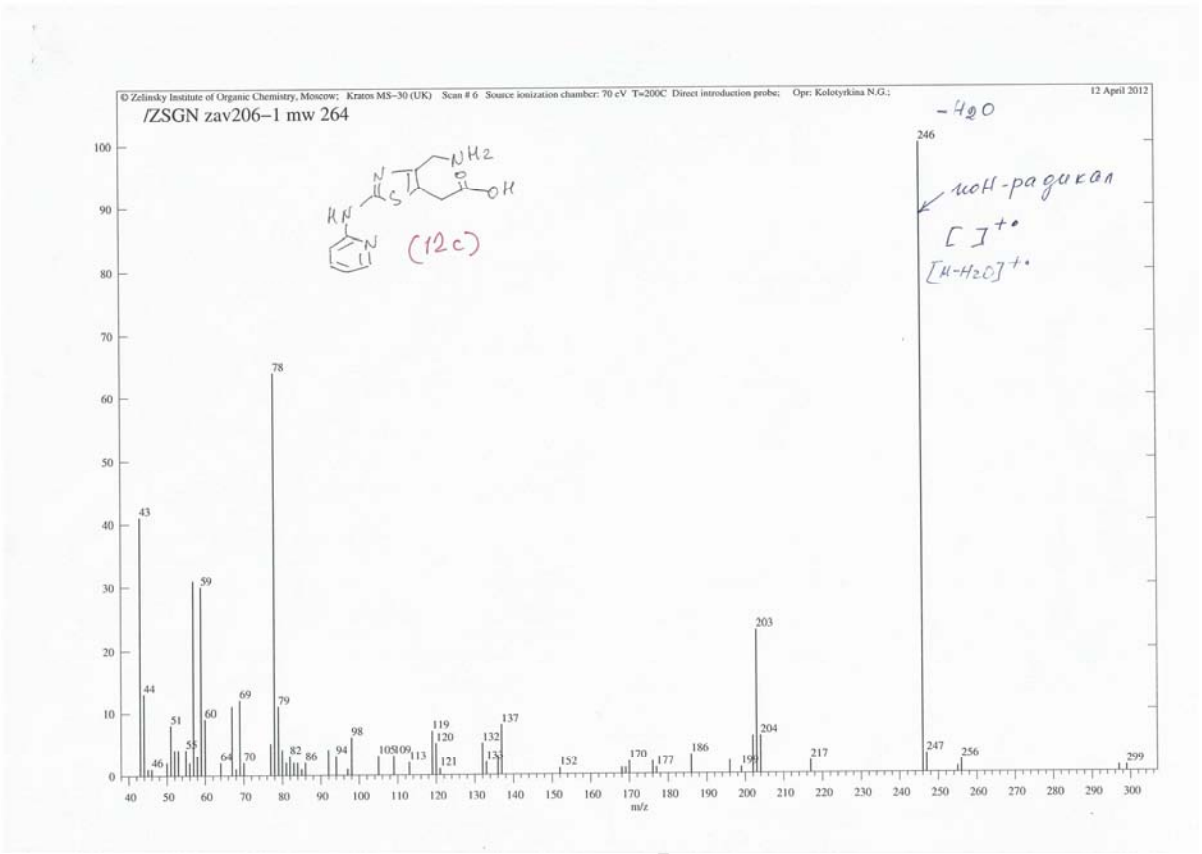


Figure 44. ^{1}H NMR spectra of **12c**

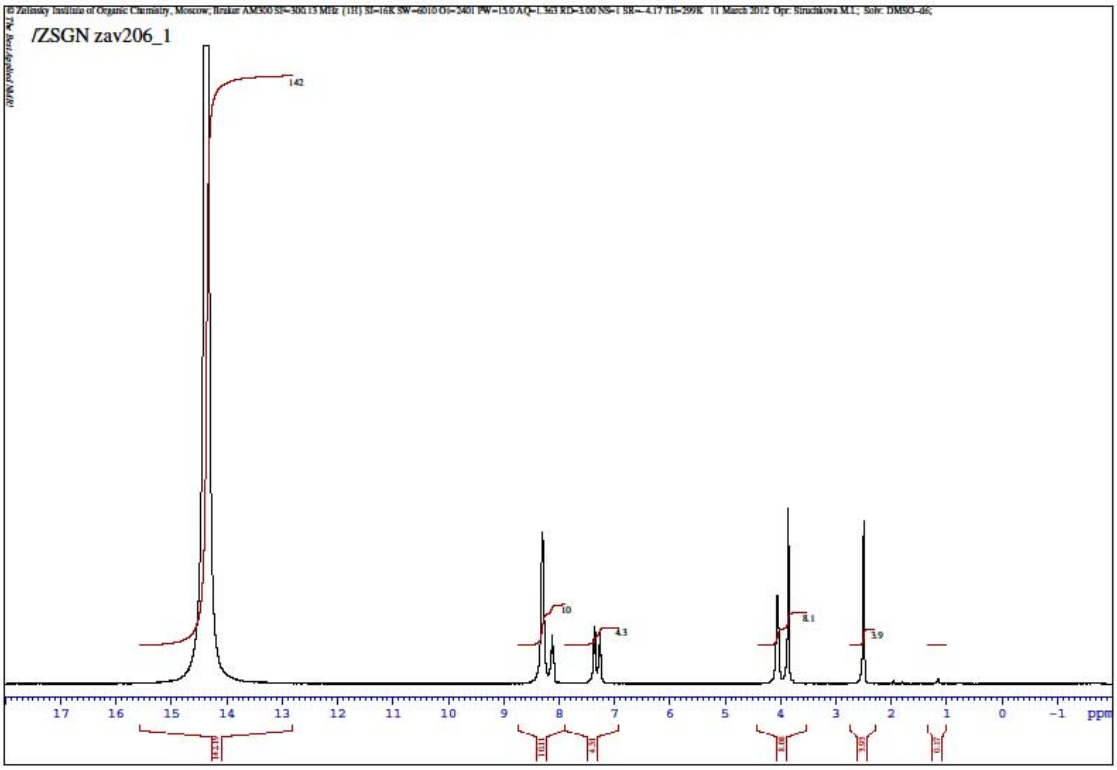


Figure 45 ^{13}C NMR spectra of **12d**

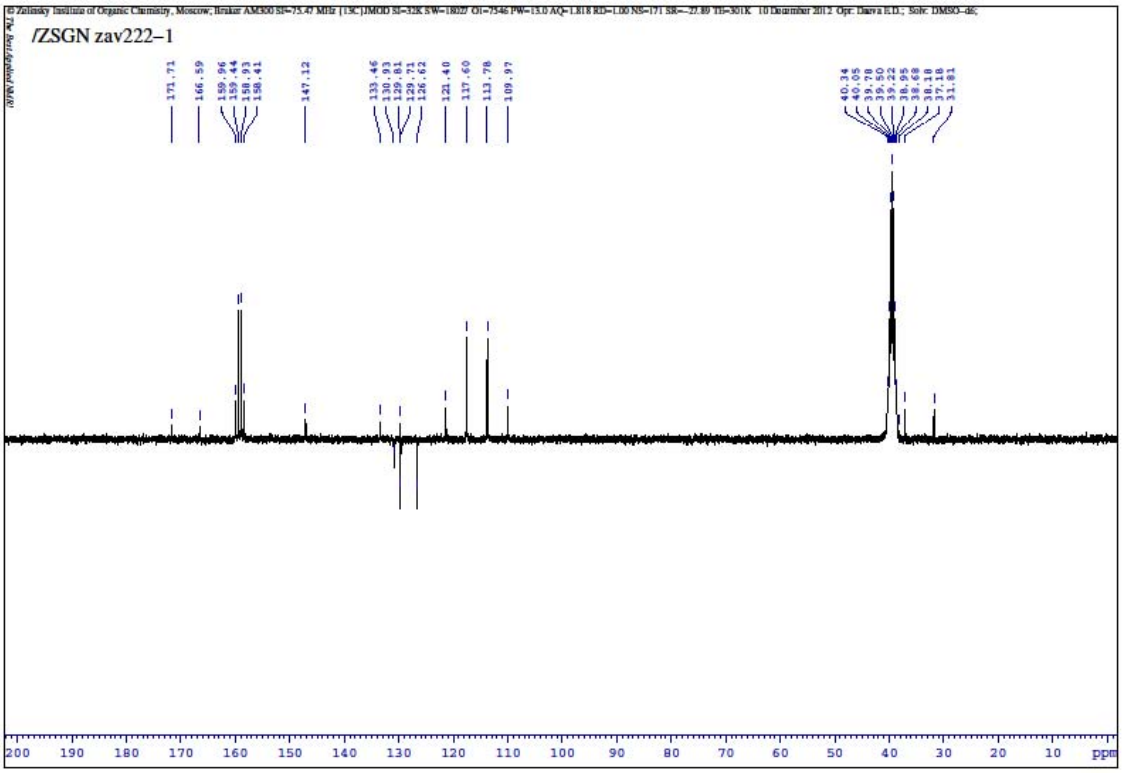
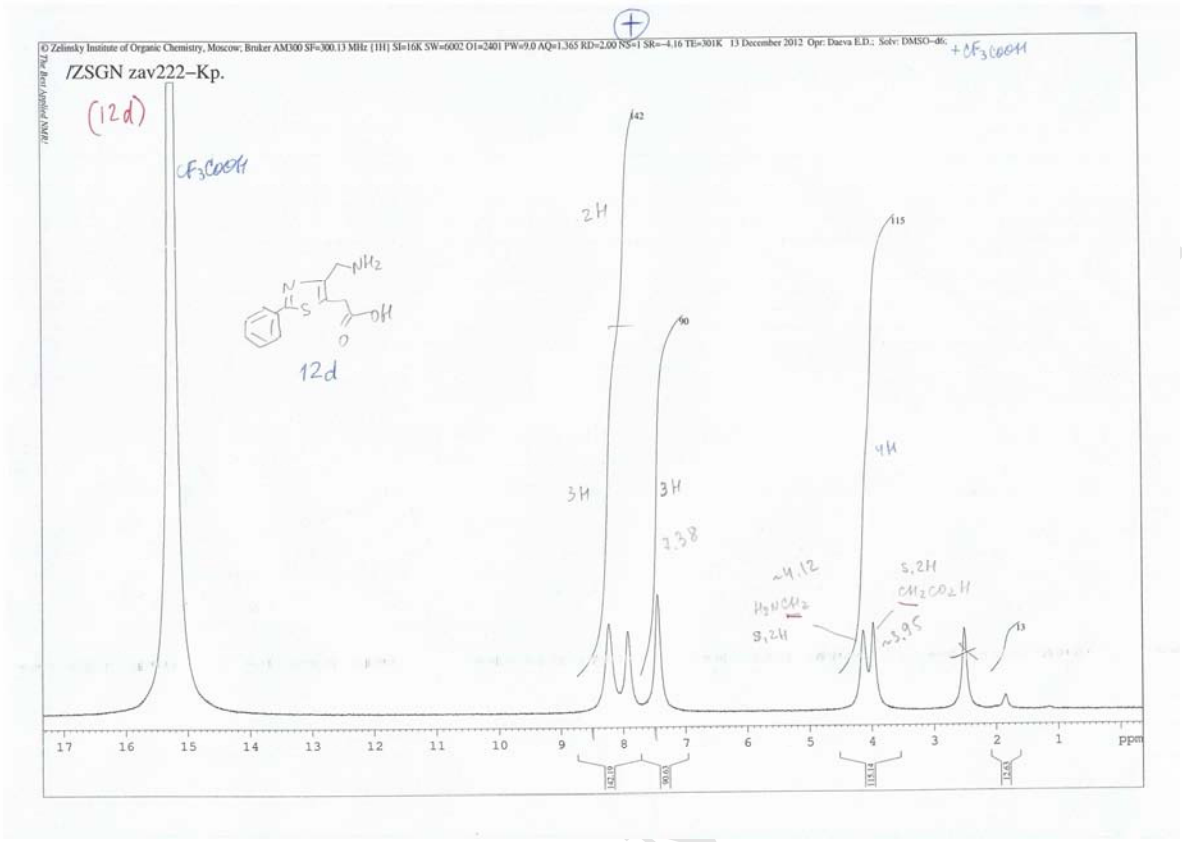
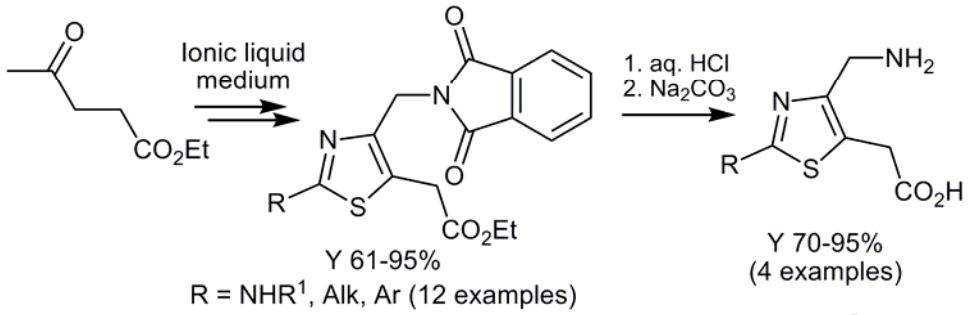


Figure 46. ^{1}H NMR spectra of **12d**



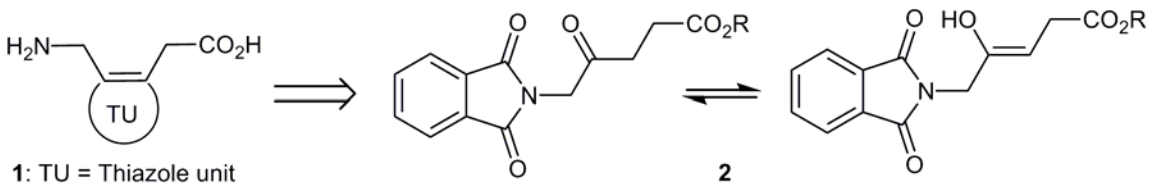
Synthesis of thiazole derivatives bearing an incorporated Z-5-aminopent-3-enoic acid fragment

Alexander G. Zavozin, Nikolai V. Ignat'ev, Michael Schulte, Sergei G. Zlotin*



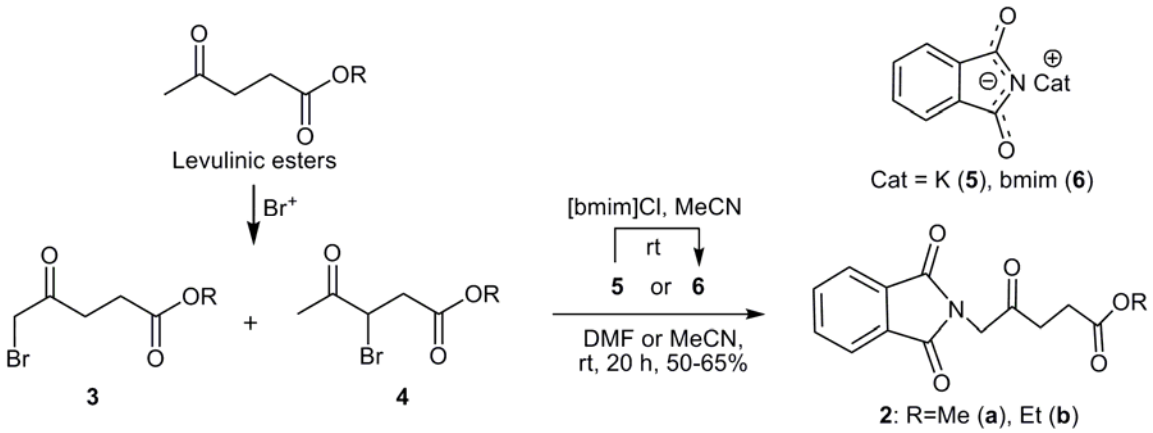
Y 61-95%
R = NHR[1], Alk, Ar (12 examples)

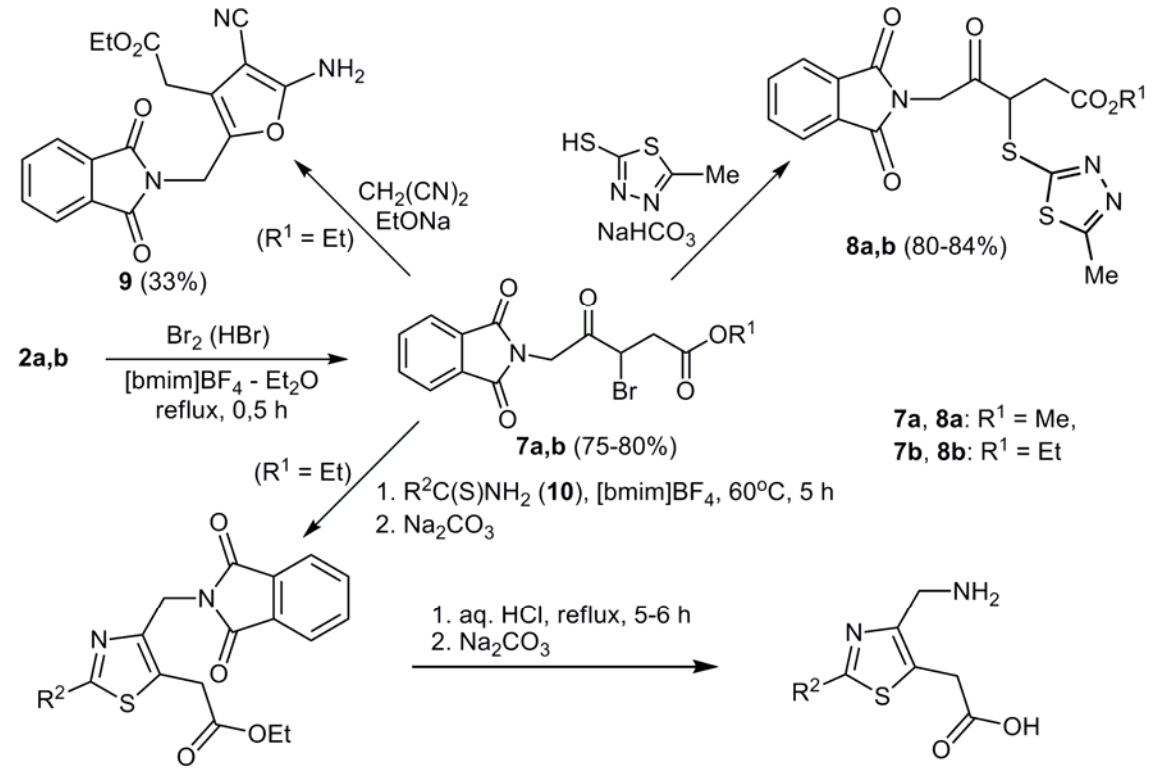
Y 70-95%
(4 examples)



1: TU = Thiazole unit

2





R^2 = PhNH (**a**), NH_2 (**b**), CH_2=CHCH_2NH (**c**), BnNH (**d**), 4-MeC_6H_4NH (**e**), 3-MeC_6 H_4NH (**f**),2-MeOC_6H_4NH (**g**), 2-Pyridyl-NH (**h**), Me (**i**), Ph (**j**), 4-FC_6H_4 (**k**), 4-ClC_6H_4 (**l**)

R^2 = BnNH (**a**), 3-MeC_6H_4NH (**b**), 2-Pyridyl-NH (**c**), Ph (**d**)