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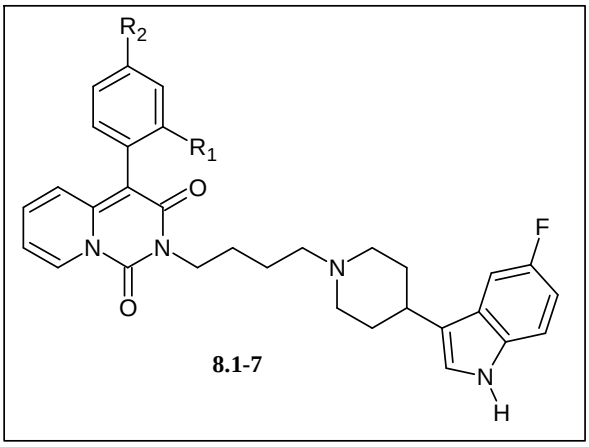

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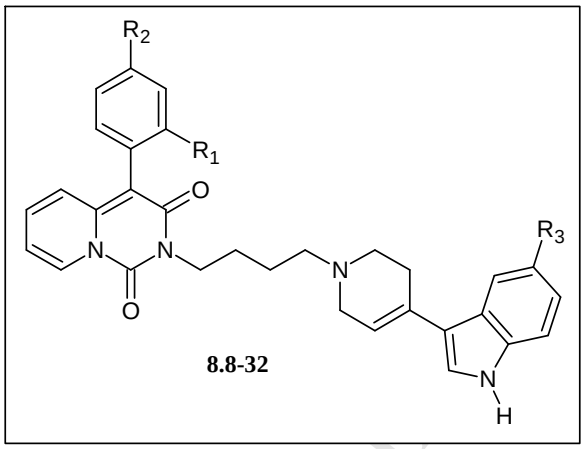

8.8-32

R_1=H, F, Cl, CH_3, OCH_3 R_2= H, F, Cl,CH_3, OCH_3 R_3= F, Br, Cl

Graphical Abstract. The general structure of final compounds.

Novel 4-aryl-pyrido[1,2-*c*]pyrimidines with dual SSRI and 5-HT$_{1A}$ activity. Part 4.

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Abstract

This project describes the synthesis, pharmacological and pharmacodynamic tests on two series of novel derivatives of 2H-pyrido[*1,2-c*]pyrimidine with potential binary binding to 5-HT$_{1A}$ receptors and SSRI+ serotonin transporters. The influence of piperidinyl-indole (**8.1**-**8.7**) and tetrahydropyridinyl-indole (**8.8**-**8.32**) residues and indole 5-position substituents (R_3 = Br, Cl, F) present in the pharmacophore element of ligands on their binding to both molecular targets was tested.

A considerable impact of piperidinyl-indole residue on binding to both targets was confirmed and compounds with a high binding affinity were identified: K_i 5-HT$_{1A}$ = 12.4 nM; K_i SERT = 15.6 nM **8.1**; K_i 5-HT$_{1A}$ = 5.6 nM; K_i SERT = 20.7 nM **8.7**, while the presence of a tetrahydropyridinyl-indole residue was found to reduce the affinity of ligands to 5-HT$_{1A}$R. The presence of chlorine (R_3) in this series resulted in a notable reduction in binding to both targets (5-HT$_{1A}$ and SERT). Selected compounds had their metabolic stability in a first-pass test (human liver microsomes, NADPH) determined *in vitro*, and R_1 and R_2 substituents present on the terminal residue of pyrido[*1,2-c*]pyrimidine were recognized as having an impact on stability.

Keywords: antidepressants, pyrido[1,2-*c*]pyrimidines, dual 5-HT$_{1A}$/SERT activity , ADME

Abbreviations: SERT, 5-HT-T, serotonin transporter; SAR, structure-activity relationship; 5-HT, serotonin; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)tetraline; Ki, inhibitor constant; TMS, tetramethylsilane; NADPH, dihydronicotinamide-adenine dinucleotide phosphate; HRMS, high resolution mass spectrometry; SSRIs, selective serotonin inhibitors; ADME, adsorption-distribution-metabolism-elimination

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1. Introduction

Depression is now the fourth most common disorder in the world and by 2020 it is expected to become the second most common [1]. Disorders in monoaminergic neurotransmission connected to serotonin and noradrenaline play a key role in the pathomechanism of depression. This has been confirmed by the fact that most drugs used in the pharmacotherapy of depression assume the serotoninergic system as their molecular target [2]. The recent introduction of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, escitalopram, paroxetine, sertraline and more is considered a breakthrough in the treatment of depression. They also manifest greater selectivity, which reduces undesirable effects and results in high therapeutic indices [3]. Unfortunately, this group of medications has its shortcomings, as only every third patient reacts to treatment and the latency period extends over 4 to 6 weeks due to slow desensitization of autoreceptors [4]. One hypothesis suggests that the delay in the onset of action is due to a negative feedback control exerted by 5-HT_{1A} autoreceptors on nerve terminal serotonin release [5]. According to this hypothesis, the onset of action is initiated only when this impulse flow is restored following desensitization of 5-HT_{1A} autoreceptors, and a coincident increase in the postsynaptic serotonin level is achieved [6,7].

Research conducted by Artigas [8] and Blier [9] focused on the co-administration of 5-HT_{1A} antagonist (pindolol) and SSRI, which aimed at reducing the latency period. The inconvenience of this research consisted of its lack of antagonist selectivity to 5-HT_{1A} autoreceptors, with a simultaneous antagonism of postsynaptic receptors. A subsequent direction of SSRI+ research pointed to connecting the effects of SSRI with a pre- and postsynaptic agonist that would generate an increase in serotoninergic transmission through acceleration of 5-HT_{1A} autoreceptor desensitization [9,10]. This line of inquiry led to the introduction of vilazodone (Viibryd®) for the treatment of depression [11]. The research described in that work concentrated on the synthesis of novel derivatives of pyrido-pyrimidine

from the SSRI+ group with affinity for 5-HT_{1A} receptors and serotonin transporter (SERT), with piperidinyl-indole and tetrahydropyridinyl-indole residues in their structure. This was expected to increase their degree of affinity for SERT, since those residues are proven to manifest inhibitory activity towards SERT [12-15].

Research directed at discovering ligands with binary binding (5-HT_{1A} and SERT) and appropriate functional activity for 5-HT_{1A} receptors (pre- and postsynaptic agonism) among novel derivatives of pyrido[*1,2-c*]pyrimidine has been carried out in our laboratory for a number of years. It is associated with investigating a new generation of antidepressants from the SSRI+ group. Earlier work in the mentioned research described a series of derivatives of pyrido[*1,2-c*]pyrimidine with 3-(piperidin-4-yl)-1*H*-indole or 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole residues in the pharmacophore element. A series of compounds with a high degree of binding to both molecular targets and a suitable functional profile with 5-HT_{1A} receptor binding (pre- and postsynaptic agonism) was obtained [16-18]. It is worth emphasizing that presynaptic agonism of the 5-HT_{1A} receptor accelerates autoreceptor desensitization, which in turn reduces the latency period. On the other hand, postsynaptic agonism of 5-HT_{1A} receptors can improve neurotransmission in the serotoninergic system [19]. The analysis covered the impact of the degree of hydrogenation of the terminal part of the pyrido[*1,2-c*]pyrimidine structure and the function of benzene ring substituents (*ortho* and *para*) at the 4-position on the binding of ligands to 5-HT_{1A} and SERT [16-18].

Pursuing the research within the SSRI+ group, we have focused on derivatives of 2*H*-pyrido[*1,2-c*]pyrimidine series with binary binding (5-HT_{1A} and SERT) exhibiting agonistic activity (pre- and postsynaptic) to 5-HT_{1A}R. The aim of the research was to determine the impact of substituents (Cl, Br, F) the 5-position (R_3) of the indole present in the pharmacophore portion of each ligand (Fig. 1) on the degree of affinity to both molecular targets. In addition, the impact of piperidinyl and tetrahydropyridinyl residues also present in the pharmacophore element was analysed. Examination of how R_1 and R_2 substituents in the terminal portion of the ligands influences their metabolic stability in a first-pass test with a microsomal fraction from human liver tissue in the presence of NADPH also constituted a part of the project.

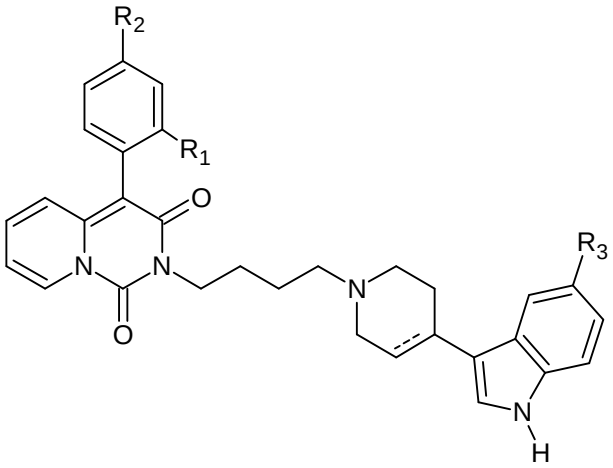


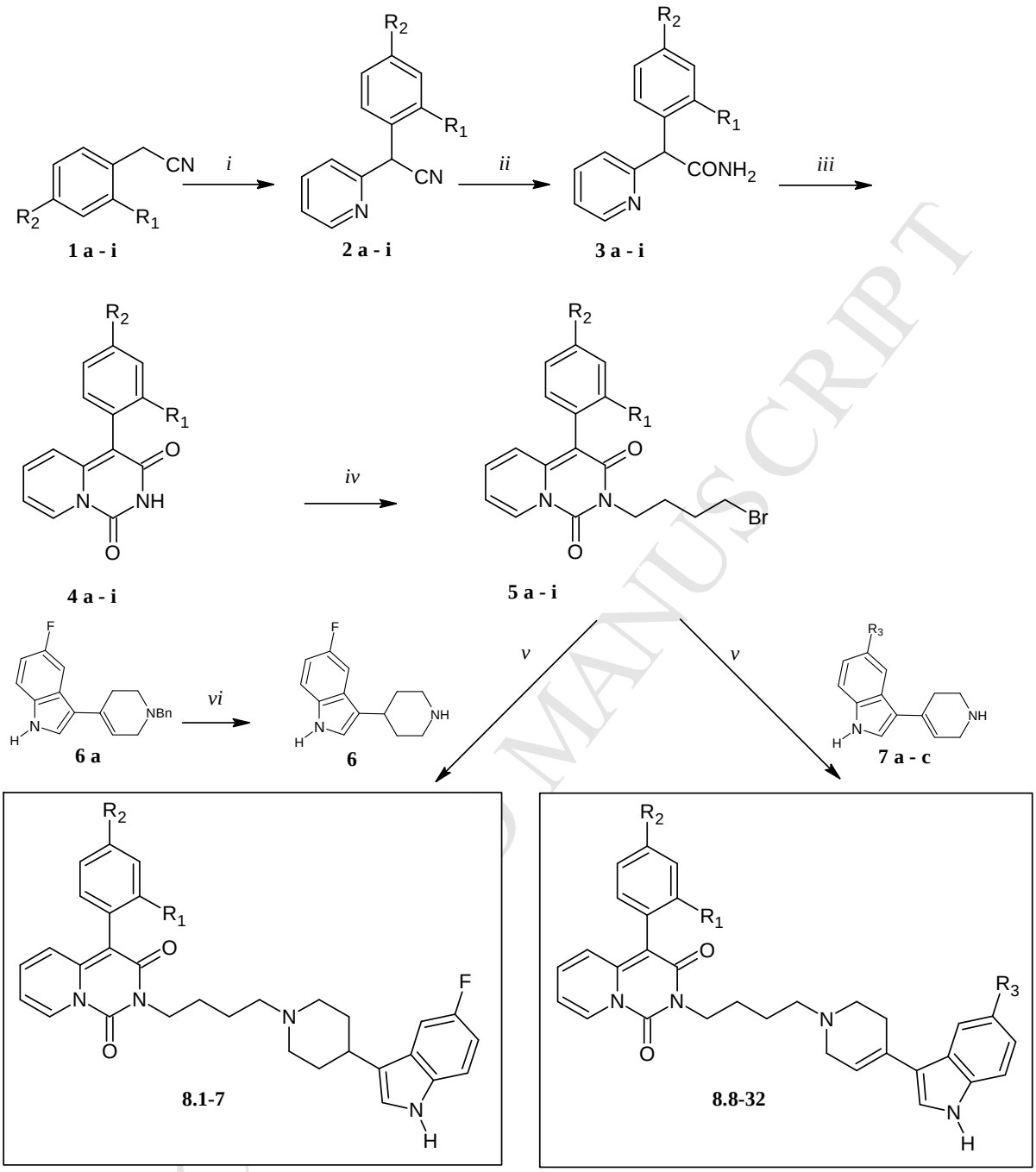
Fig. 1. General structure of pyrido[1,2-*c*]pyrimidines with dual 5-HT_{1A}/SERT activity

2. Results and Discussion

2.1 Chemistry

Final compounds **8.1**-**8.32** were obtained via multi-step synthesis according to Scheme 1. The starting (**2a-i**, **3a-i**, **4a-i**, **5a-i**, **6a**, **6** and **7a-c**) and final compounds (**8.1** - **8.32**) were synthesized according to procedures described in our previous paper [16-18]. All new compounds (**6a** and **8.1-32**) were characterized by physical constants, HRMS, ^{1}H, and ^{13}C NMR spectroscopy.

Scheme 1[a]**.** The synthesis pathways of the investigated compounds.



R_1=H, F, Cl, CH_3, OCH_3 R_2= H, F, Cl,CH_3, OCH_3 R_3= F, Br, Cl

[a] **Reagents and conditions:** (*i*) 2-bromopyridine, KOH, DMSO, Δ; (*ii*) H_2SO_4, CH_3COOH, Δ; (*iii*) diethyl carbonate, EtONa, EtOH abs., Δ; (*iv*) 1,4-dibromobutane, K_2CO_3, acetone, Δ; (*v*) acetionitrile, K_2CO_3, KI, Δ: (*vi*) 10% Pd/C, CH_3OH,

The work resulted in obtaining a number of novel derivatives of *4-aryl*-pyrido[*1,2-c*]pyrimidine with a 5-fluoro-3-(piperidin-4-yl)-1*H*-indole structure in the pharmacophore part and 5-fluoro, 5-chloro and 5-bromo derivatives of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (Scheme 1). The aryl substituent the in 4-*aryl*-pyrido[*1,2-c*]pyrimidine configuration

constituted a benzene ring for compounds **8.1**, **8.8**, **8.17** and **8.25**, whereas in other derivatives the substituents on this ring featured: -F (**8.5, 8.13, 8.21, 8.30**), -Cl (**8.6, 8.14, 8.22**), -OCH_3 (**8.7, 8.16, 8.24, 8.32**), or -CH_3 (**8.15, 8.23, 8.31**) in the *ortho* position, and -F (**8.4, 8.12, 8.20, 8.29**), -Cl (**8.3, 8.11, 8.28**), -OCH_3 (**8.10, 8.19, 8.27**), or -CH_3 (**8.2, 8.9, 8.18, 8.26**) in the *para* position.

2.2 In vitro studies

The test results on the binding of compounds **8.1**-**8.32** to 5-HT_{1A} and 5-HT-T receptors allowed for analyse as to how receptor affinity is influenced by: substituents on the indole portion (-F, -Cl, -Br substituents in the 5-position of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole), the degree of saturation of the pyridine ring of the 3-(piperidin-4-yl)-1*H*-indole structure and *ortho* and *para* position substituents on the aryl ring of pyrido[*1,2-c*]pyrimidine. Binding results for ligands **8.1**-**8.32** to 5-HT_{1A} receptors confirmed very high affinity for compounds **8.7** (K_i = 5.6nM), **8.5** (K_i = 9.2nM), **8.1** (K_i = 12.4nM), **8.4** (K_i = 12.8nM) and **8.6** (K_i = 15.9nM). The degree of affinity for the remaining derivatives ranged from high to average, with K_i values between 23.1 nM and 295.0 nM (in order of increasing K_i : **8.27, 8.30, 8.32, 8.2, 8.25, 8.28, 8.31, 8.22, 8.29, 8.10, 8.3, 8.21, 8.24, 8.20, 8.13, 8.8, 8.17, 8.14, 8.26, 8.9, 8.23, 8.12, 8.16, 8.11, 8.18, 8.19,** and **8.15**; Table 1). Analysis of the impact of indole substituents on binding to 5-HT_{1A} receptors, in turn, indicated that derivatives featuring a fluorine atom at 5-position of the 3-(piperidin-4-yl)-1*H*-indole structure (HHPI) or a bromine atom at 5-position of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (THPI) exhibit either very high or high affinity. The presence of either a fluorine or chlorine atom at the 5-position of the 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (THPI) structure in a derivative was confirmed to cause a drop in the degree of binding to 5-HT_{1A} receptors. A substitution on the aryl ring of pyrido[*1,2-c*]pyrimidine, on the other hand, may be said to cause reduced receptor affinity for derivatives with –CH_3 (**8.2**, **8.9, 8.18, 8.26**) or -Cl (**8.3, 8.11, 8.28**) groups in the *para* position and –CH_3 (**8.15, 8.23, 8.31**) in the *ortho* position in relation to other ligands with analogous HHPI or THPI structures in the pharmacophore element.

The results on binding of the proteins to the serotonin transporter 5-HT-T demonstrated the very high affinity of compounds **8.13** (K_i =3.9 nM), **8.14** (K_i =5.2 nM), **8.12** (K_i =11.3 nM), **8.10** and **8.1** (K_i = 15.6 nM). Affinity values for the remaining compounds ranged from high to poor, i.e. between 19.4 nM and 1.2 μM (in order of increasing K_i : **8.4, 8.7, 8.16, 8.3, 8.5, 8.8, 8.2, 8.9, 8.11, 8.15, 8.6, 8.19, 8.17, 8.27, 8.20, 8.29, 8.18, 8.21, 8.24, 8.23, 8.22, 8.30, 8.25, 8.31, 8.26, 8.28** and **8.32**).

By looking at the effect of indole substituents on binding to the 5-HT-T serotonin transporter protein, it can be stated that ligands featuring a fluorine atom at the 5-position of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (THPI) or 3-(piperidin-4-yl)-1*H*-indole (HHPI) had similarly high affinity, while K_i values for derivatives with a bromine or chlorine atom at the 5-position of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (THPI) ranged from average to high. Substitution on the aryl ring of pyrido[*1*,*2*-*c*]pyrimidine, in turn, resulted in relatively higher affinity for derivatives with -OCH_3 (**8.10, 8.19, 8.27**) or fluorine (**8.4, 8.12, 8.20, 8.29**) in the *para* position. The remaining derivatives showed higher values of K_i.

Table 1 SERT and 5-HT_{1A} receptor binding affinities of 3-(piperidin-4-yl)-1*H*-indole derivatives (HHPI) and 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivatives (THPI).

	R_1	R_2	R_3		K_i 5-HT_{1A} [nM]	K_i SERT [nM]
8.1	H	H	F	HHPI	12.4	15.6
8.2	H	CH_3	F	HHPI	38.5	27.4
8.3	H	Cl	F	HHPI	84.4	25.5
8.4	H	F	F	HHPI	12.8	19.4
8.5	F	H	F	HHPI	9.2	25.7
8.6	Cl	H	F	HHPI	15.9	88.6
8.7	OCH_3	H	F	HHPI	5.6	20.7
8.8	H	H	F	THPI	117.7	27.1
8.9	H	CH_3	F	THPI	153.2	30.3
8.10	H	OCH_3	F	THPI	81.7	15.6
8.11	H	Cl	F	THPI	265.1	58.2
8.12	H	F	F	THPI	219.7	11.3
8.13	F	H	F	THPI	115.5	3.9
8.14	Cl	H	F	THPI	127.3	5.2
8.15	CH_3	H	F	THPI	295.0	58.8
8.16	OCH_3	H	F	THPI	251.5	20.8
8.17	H	H	Cl	THPI	125.8	322.0
8.18	H	CH_3	Cl	THPI	267.1	408.4
8.19	H	OCH_3	Cl	THPI	277.5	311.8
8.20	H	F	Cl	THPI	106.4	329.4
8.21	F	H	Cl	THPI	97.1	435.0
8.22	Cl	H	Cl	THPI	74.4	774.4
8.23	CH_3	H	Cl	THPI	212.5	739.6
8.24	OCH_3	H	Cl	THPI	97.8	717.9
8.25	H	H	Br	THPI	40.1	839.7
8.26	H	CH_3	Br	THPI	144.9	949.4

8.27	H	OCH_3	Br	THPI	23.1	326.5
8.28	H	Cl	Br	THPI	61.6	1000.0
8.29	H	F	Br	THPI	79.1	403.6
8.30	F	H	Br	THPI	32.5	835.8
8.31	CH_3	H	Br	THPI	71.5	879.5
8.32	OCH_3	H	Br	THPI	33.1	1200.0

From our early investigation it appeared that docking of 4-(1-*H*-indol-3-yl)piperidine drivatives to the 5-HT_{1A} receptor is predetermined by basic moiety of the compound and aromatic part interacting with Asp3.32 and Phe6.52 residues in the receptor [17, 18]. In SERT interaction model the Asp fragment was crucial for anchoring protonated nitrogen of fully flexible ligands to the serotonin transporter. The flexibility originates from alkyl spacer of the ligand. For unsubsituted indole ring moieties it is likely the NH group of indole ring can point towards the interior of binding pocket at the 5-HT_{1A} receptor. Here the 5-position of indole ring is substituted with fluorine atom. It is known that the charge distribution around fluorine atom is very similar to that of -OH group, present also naturally in serotonine. Therefore hydrogen bonding is likely to be formed in the smaller binding sub-pocket outlined by transmembrane helices (TMHs) 1-3 and 7. Thus the 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (THPI) or 3-(piperidin-4-yl)-1*H*-indole (HHPI) have high affinity both for 5-HT_{1A} receptor and SERT. The replacement of fluorine atom with bromine or chlorine diminishes significantly possible hydrogen bond formation due to electron charge distribution and steric changes in those derivatives. The phenyl ring in position 4 of the 5,6,7,8-tetrahydro-pyrido[1,2-*c*]pyrimidine moiety can be stacked between Phe3.28 and Tyr2.64 residues. This interaction can be distorted by steric hindrance, e.g. $–OCH_3$ substituent or twisted phenyl ring due to interaction between negative charge distribution around fluorine atom and loin electron pairs of $–OCH_3$ group. Therefore para substituted derivatives are more likely to be bound without additional distortion of yielding higher receptor affinity (**8.10**, **8.19**, **8.27**) and (**8.12**, **8.20**, **8.29**).

In the SERT the pyridopyrimidine moiety is placed to putative low affinity binding site [20, 21]. For ligand docked do far close interaction with $Asp98_{1.45}$ in TMH1 was observed. However, the steric hindrance of $Ph355_{6.53}$ also has to be considered. In addition steric interaction of pyridopyrimidine and $Arg104_{2.52}$ in TMH1 can affect the ligand affinity for SERT moiety. It was established that the presence of the 3-(piperidin-4-yl)-1*H*-indole residue or its 5-methoxy and 5-fluoro derivatives as well as the ortho or para substitution with –

OCH_3/–CH_3 and -F groups in phenyl ring in position 4 of the 5,6,7,8-tetrahydro-pyrido[1,2-c]pyrimidine moiety, are at an advantage with regard to binding affinity. It was also found that the degree of saturation of the 5,6,7,8-tetrahydro-pyrido[1,2-c]pyrimidine system has no influence on the binding activity for both 5-HT_{1A} receptor and SERT compared to unsaturated pyrido[1,2-c]pyrimidine derivatives. The same structural and electronic effects like in 5-HT_{1A} receptor binding are characteristic for SERT protein binding (see Table 1).

2.3 ADME studies

ADME (absorption-distribution-metabolism-elimination) studies are now an integral part of most preclinical projects directed toward obtaining potential drugs possessing not only high activity against a selected molecular target but also desirable pharmacokinetic properties [22, 23].

Drug metabolism is particularly important because biotransformation reactions can cause a decrease or loss of pharmacological activity [24]. For drugs administrated orally, the first-pass effect is a phenomenon of drug metabolism whereby the concentration of a drug is greatly reduced before it reaches the systemic circulation, affecting its efficacy. The liver is the organ responsible for the majority of drug bioconversion, so high throughput methods to study metabolic reactions carried out by liver tissue were developed. The microsome assay, performed *in vitro*, is a standard procedure in metabolic stability testing because it is relatively cheap, easy to handle and involves studying biotransformation against the enzymes most relevant to xenobiotics – cytochromes P450 [25, 26]. *In vitro* incubation of a potential drug in the presence of liver microsomes and NADPH coupled to drug determination by LC-MS techniques ensures sensitive, specific, and reliable results [27, 28].

Metabolic stability

The results of a metabolic stability study in the presence of pooled human liver microsomes and NADPH are shown in Table 2.

Table 2 Metabolic stability of studied compounds.

ID	Unchanged drug at 60 min	HLM $t_{(1/2)}$ [min]
8.8	63.36%	81.97
8.11	50.24%	60.24
8.15	60.52%	75.76
8.16	67.92%	94.34
8.18	64.33%	84.75

8.24	55.65%	67.57
8.25	63.18%	81.97
8.29	51.36%	61.72

About 50–65% of each compound remained unchanged after 60 min of incubation, which in comparison to a similar study focused on arylpiperazine derivatives of Tandon *et al* [29] seems a satisfactorily high value. These experiments revealed only small differences in stability between the studied derivatives but some structure-metabolic stability relationships can still be noted (Fig. 2). The most labile compounds were **8.11** and **8.29**, which both contain hydrogen in the R_1 position and halogens in R_2 and R_3 (Fig. 2).

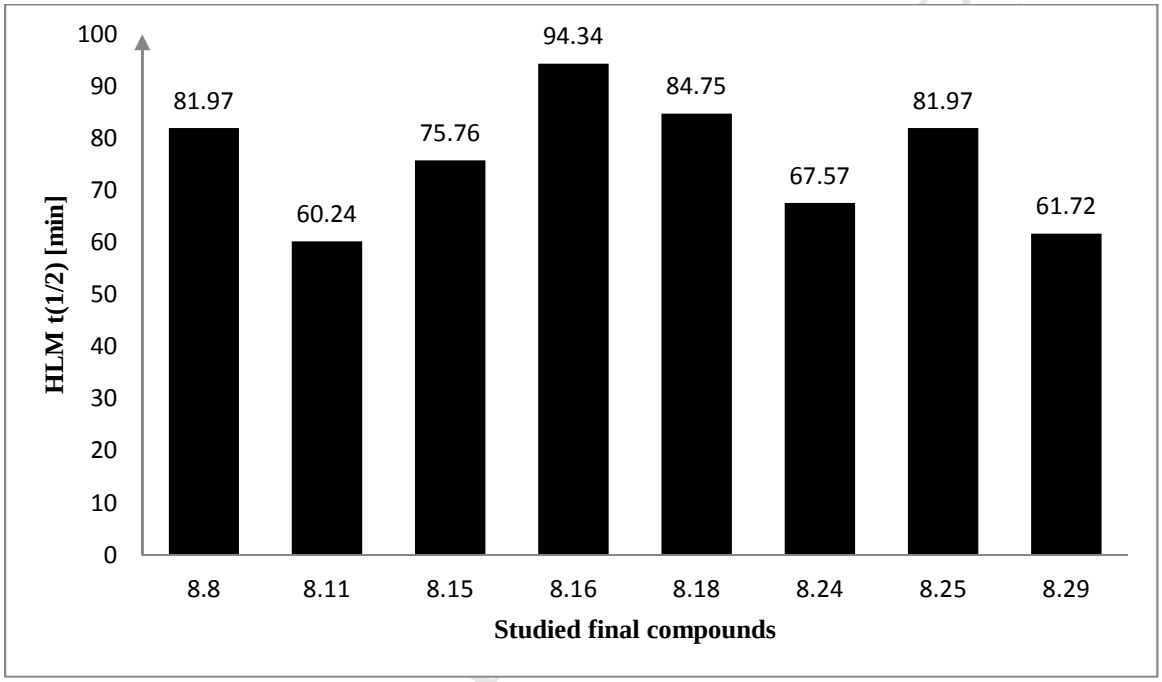


Fig. 2. HLM $t/_{1/2}$ [min] of studied compounds.

The displacement of halogen by hydrogen in R_2 resulted in greater metabolic stability (derivatives **8.8** and **8.25**, respectively). This suggests that the incorporation of chlorine or fluorine in the R_2 position can activate derivatives to some metabolic reactions. On the other hand, the most stable compound, **8.16**, possesses a methoxy- moiety in the R_1 position. Comparing the stability of **8.16** to that of the **8.15** derivative, which contains a methyl substituent instead of a -OCH_3 group, it could be concluded that –OCH_3 possesses stabilizing properties. Nevertheless, stabilizing properties of methoxy moiety are not present in the case of **8.24,** implying a more complex mechanism of metabolic stabilization.

3. Conclusion

By extending the research within the group of 2*H*-pyrido[*1*,*2*-*c*]pyrimidine derivatives, ligands with binary binding to the 5-HT_{1A} receptor and serotonin transporter (SERT), two series, **8.1**-**8.7** and **8.8**-**8.32,** have been obtained. The results of receptor binding tests confirmed that ligands featuring a piperidinyl-indole residue in the pharmacophore element (**8.1**-**8.7**) manifest very high degrees of binding to both molecular targets; compound **8.1** (K_i 5-HT_{1A}=12.4 nM, K_i SERT=15.6 nM) and compound **8.7** (K_i 5-HT_{1A}=5.6 nM, K_i SERT=20.7 nM). The presence of a tetrahydropyridinyl-indole residue (**8.8**-**8.32**) reduces binding to 5-HT_{1A}, while Cl substituents in R_3 reduce binding to both 5-HT_{1A} and SERT. The presence of F in R_3, in turn, results in an increased binding to SERT. *In vitro* tests for metabolic stability in a first-pass test (human liver microsomes, NADPH) run on selected compounds led to the conclusion that R_1 and R_2 substituents present on the pyrido-pyrimidine element of the terminal molecule benefit stability.

4. Experimental protocols

4.1 Chemistry

4.1.1 General remarks

Melting points were determined on an Electrothermal 9100 apparatus with open capillary tubes and are uncorrected. Infrared spectra were recorded on a Shimadzu FT IR-8300 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AVANCE DMX 400WB instrument in $CDCl_3$ (chemical shifts are reported in δ units). Coupling constants (*J*) are in hertz (Hz); the internal reference was TMS. The following abbreviations are used to describe peak patterns when appropriate: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), td (triple doublet), ps (pseudotriplet), 4d (quartet of doublets), m (multiplet), * - peak patterns under DMSO. For the two-dimensional experiments, the pulse sequences, acquisition, and processing parameters were taken from the standard Bruker software library. ESI-HRMS spectra were obtained on a Marimer (PE Biosystems) instrument.

Flash column chromatography was carried out on Merck Silica gel 60 (230–400 mesh ASTM) using the solvent methylene chloride/methanol (99:1, 97:3, 95:5, *v/v*). Thin layer chromatography was run on Merck Silica gel 60 F_{254} plates with a mobile phase of dioxane, toluene, ethanol, and 25% NH_4OH (6.0:3.2:0.5:0.2, *v/v*). Compounds were visualized by UV light (254 nm). Room temperature refers to 20–25°C. The purity (>95%) and homogeneity of the compounds were routinely confirmed by TLC on Merck plates (Kieselgel 60 F254) and ^{1}H NMR spectra.

4.1.2 The starting compounds **2a-i, 3a-i, 4a-i**, **5a-i** were obtained according to procedures described in [16-18,30,31]

4.1.3 Procedure for the synthesis of N-benzyl-5-fluoro-3-(piperidin-4-yl)-1H-indole (**6a**) and *5-fluoro-3-(piperidin-4-yl)-1H-indole* (**6**).

The starting compound **6** can be obtained by two different methods.

First method: metallic sodium (0.2 mol) was slowly added to methanol (100 ml). The mixture was stirred under argon at room temperature until all the sodium had reacted. Next, N-benzyl-4-piperidone (0.1 mol) and 5-fluoro-1*H*-indol (0.05 mol) was added and the reaction mixture was refluxed with stirring for about 24 h. The reaction completion time was determined chromatographically (TLC). The reaction mixture was cooled and poured into 500 ml of water with ice. The crude product was collected and crystallized from ethyl acetate to give compound **6a** (yield: 65.0 %, **m.p.:** 162–163 °C).

HRMS (ESI) calculated for $C_{20}H_{20}FN_2$: 307.1605 $(M+H)^+$ **found** 307.1607.

^{1}H NMR (500 MHz) δ: 2.54 (m, CbH_2), 2.73 (t, CeH_2), 3.23 (pk, CaH_2), 3.67 (s, CH_2), 6.09 (m, CbH), 6.91 (td, $^3J_{H-F}$=9.0, ^{4}J=2.4,C6”H), 7.14 (d, ^{3}J=2.4, C2”H), 7.23 (dd, ^{3}J=8.8, $^4J_{H-F}$=4.6, C7”H), 7.27 (m, C4’H), 7.34 (m, C3’H, C5’H), 7.40 (pd, ^{3}J=7.6, C2’H, C6’H), 7.50 (dd, $^3J_{H-F}$=10.2, ^{4}J=2.4,C4”H), 8.35 (bs, NH).

^{13}C NMR (500 MHz) δ: 29.0 (Cd), 49.9 (Ce), 53.2 (Ca), 62.9 (CH_2), 105.8 (d*, 2J=24.4, C4”), 110.5 (d*, ^{2}J=26.4, C6”), 111.8 (d*, ^{3}J=9.7, C7”), 118.2 (d*, ^{4}J=4.4, C3”), 119.3 (C2”), 123.0 (Cb), 125.5 (d*, ^{3}J=9.7, C3”a), 127.1 (Cc), 128.2 (C2’, C6’), 129.3 (C3’, C5’), 129.5 (C4’), 133.3 (C7”a), 138.3 (C1’), 158.1 (d*, ^{1}J=234.4, C5”).

N-benzyl-5-fluoro-3-(piperidin-4-yl)-1*H*-indole (**6a**) and 0.6 g 10% Pd/C in 300 ml of methanol were hydrogenated with debenzylation under 1 atm at 40°C during 8 h. After filtration of the catalyst and concentration of the filtrate, the crude product was crystallized from ethyl acetate to give compound **6**.

The title compound **6** was isolated as a white powder (yield: 66.1%; **m.p.:** 208–209 °C).

Second method: The starting compound **6** was obtained according to previously described procedures [32].

4.1.4 Preparation of 5-substitued-3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-indole (**7a-c**).

The starting compound **7a-c** was obtained according to procedures described in [12,15,32].

4.1.5 General procedure for the synthesis of 4-aryl-pyrido[1,2-c]pyrimidine-1,3-dione derivatives (**8.1-32**).

Appropriate substrates, i.e. bromobutylpyrido[1,2-*c*]pyrimidine-derivatives **5a-i** (0.0026 mol) and (1,2,3,6-tetrahydro-pyridin-4-yl)-1*H*-indoles **7a-c** (0.0026 mol) or 5-fluoro-3-(piperidin-4-yl)-1H-indole (**6**) as well as K_2CO_3 (0,005 mol), 70 ml of acetonitrile and a catalytic amount of KI was stirred and refluxed for 4–5 h. Reaction time was monitored using TLC. After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The crude residue was purified by crystallization from acetonitrile or by flash chromatography using a mixture of CH_2Cl_2/MeOH (97:3 *v/v*). Proper fractions were identified by TLC and evaporated to dryness to give an analytically pure compound in each case **8.1-32**.

4.1.5.1 2-{4-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-butyl}-4-phenyl-pyrido[1,2-c]pyrimidine-1,3-dione **(8.1)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 62.5% **m.p.** 145 - 147 °C

HRMS (ESI) calculated for $C_{31}H_{32}FN_4O_2$**:** 511.2518 $(M+H)^+$ **found** 511.2518**.**

^{1}H-NMR (500MHz) δ: 1.87 ($C3^xH_2$, q,^{3}J=6.8), 1.98 ($C2^xH_2$,q), 2.09 (CbH_{ax}, CdH_{ax} ,pd), 2.36 (CbH_{eq}, CdH_{eq} , pd), 2.79 ($C4^xH_2$,bps), 3.07 (CaH_{ax}, CeH_{ax}, pt), 2.95 (CcH, pt), 3.48 (CaH_{eq}, CeH_{eq}, bps), 4.21 ($C1^xH_2$, t, ^{3}J=6.8), 6.43 (C7H, m, $^3J_1$=7.6, $^3J_2$=6.3, ^{4}J=1.5), 6.89 (C5H, C6”H, m), 6.94 (C6H, 4d, $^3J_1$=8.3, $^3J_2$=6.3, ^{4}J=1.2), 7.02 (C2”H, ps), 7.17 (C4”H, dd, $^3J_{H-F}$=9.5, ^{4}J=2.4), 7.27-7.33 (C2’H, C6’H, C7”H, m), 7.38 (C4’H, tt, ^{3}J=7.3, ^{4}J=1.5), 7.44 (C3’H, C5’H, tt, ^{3}J=7.1, ^{4}J=1.0), 8.35 (C8H, dt, ^{3}J=7.6, ^{4}J=^{5}J=1.0), 8.54 (NH, bs).

^{13}C-NMR (500MHz) δ: 21.1 ($C3^x$), 24.7 ($C2^x$), 29.7 (Cb, Cd), 31.3 (Cc), 40.9 ($C1^x$), 53.2 ($C4^x$, Ca, Ce), 103.3 (C4”, d* ^{2}J=23.4), 104.6 (C4), 110.4 (C6”, d*, ^{2}J=26.3), 111.1 (C7), 112.2, (C7”, d*, ^{3}J=9.38), 118,2 (C3”), 121.5 (C5), 122.3 (C2”), 126.5 (C3”a, d*, ^{3}J=9.8), 128.0 (C8, C4’), 128.9 (C3’, C5’), 131.3 (C2’, C6’, C7”a), 132.8 (C6), 144.0 (C4a), 148.9 (C1), 157.6 (C5”, d*, ^{1}J=234.4), 157.6 (C5”, d*, ^{1}J=234.4), 160.5 (C3).

4.1.5.2 2-{4-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-butyl}-4-(4-methylphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.2)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol, yield: 73.0% **m.p.** 180 - 181 °C

HRMS (ESI) calculated for $C_{32}H_{34}FN_4O_2$**:** 525.2660 $(M+H)^+$ **found** 525.2650**.**

^{1}HNMR (500 MHz) δ: 1.70 (C3^{x}H$_2$,q), 1.80 (C2^{x}H$_2$,q), 1.90 (CbH$_{ax}$, CdH$_{ax}$,pt), 2.03 (CbH$_{eq}$, CdH$_{eq}$,pd), 2.23 (CaH$_{ax}$,CeH$_{ax}$,pt), 2.39 (C3H, s), 2.56 (C4^{x}H$_2$,t, ^{3}J=7.6), 2.79 (CcH, tt), 3.14 (CaH$_{eq}$,CeH$_{eq}$,pd), 4.20 (C1^{x}H$_2$,t, ^{3}J=7.3), 6.37 (C7H, m), 6.90 (C5H, C6H, C4"H, m), 7.00 (C2"H, d, ^{3}J=2.0), 7.20 (C3'H, C5'H, d, ^{3}J=8.0), 7.25 (C6"H, C7"H, m), 8.07 (NH, bs), 8.32 (C8H, d, ^{3}J=7.6)

^{13}C-NMR (500 MHz) δ: 21.3 (CH3), 23.9 (C3^{x}), 25.4 (C2^{x}), 32.3 (Cb, Cd), 33.1 (Cc), 42.2 (C1^{x}), 54.2 (Ca, Ce), 58.4 (C4^{x}), 103.9 (C4", d*, ^{2}J=23.4), 104.9 (C4), 110.3 (C6", d*, ^{2}J=26.4), 110.6 (C7), 111.8 (C7"a, d*, ^{3}J=9.7), 121.2 (C3"), 121.6 (C5), 121.6 (C2"), 127.0 (C3"a, d*,^{3}J=8.0), 127.9 (C8), 129.5 (C3', C5'), 129.7 (C1'), 131.0 (C2', C6'), 132.2 (C6), 132.8 (C7"a), 137.6 (C4'), 143.5 (C4a), 149.0 (C1), 157.5 (C5", d*,^{1}J=234.4), 160.35 (C1);

4.1.5.3 2-{4-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-butyl}-4-(4-chlorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione (**8.3)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol, yield: 66.0 % **m.p.** 160 - 162 °C

HRMS (ESI) calculated for $C_{31}H_{31}FClN_4O_2$**:** 545.2114 $(M+H)^+$ **found** 545.2135**.**

^{1}HNMR (500 MHz) δ: 1.75 (C3^{x}H$_2$, q), 1.82 (C2^{x}H$_2$, q), 1.97 (CbH$_{ax}$, CdH$_{ax}$, pt), 2.06 (CbH$_{eq}$, CdH$_{eq}$, pd), 2.31 (CaH$_{ax}$, CeH$_{ax}$,pt), 2.63 (C4^{x}H$_2$, t, ^{3}J=7.5), 2.83 (CcH, tt, ^{3}J$_{ax-ax}$=12.0, ^{3}J$_{ax-eq}$ =3.5), 3.20 (CaH$_{ex}$, CeH$_{ex}$, pd), 4.20 (C1^{x}H$_2$, t, ^{3}J=6.5), 6.43 (C7H, m, ^{3}J$_1$=7.5, ^{3}J$_2$=6.5, ^{4}J=1.2), 6.88 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 6.93 (C6"H, td, ^{3}J$_{H-F}$=9.0, ^{4}J=2.5), 6.96 (C6H, dt, ^{3}J$_1$=9.5, ^{3}J$_2$=6.0, ^{4}J=1.0), 7.02 (C2"H, d, ^{3}J=2.0), 7.23-7.30 (C4"H, C7"H, m), 7.42 (C2'H, C6'H, dt, ^{3}J=9.0, ^{4}J=2.0), 8.12 (NH, bs), 8.36 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0)

4.1.5.4 2-{4-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-butyl}-4-(4-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.4)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 75,0% **m.p.** 106-107 °C

HRMS (ESI) calculated for $C_{31}H_{31}F_2N_4O_2$**:** 529,2410 $(M+H)^+$ **found** 529,2427.

^{1}HNMR (500 MHz) : 1.64 (C3^{x}H$_2$, m), 1.79 (CdH$_{ax}$, m), 2.01 (CbH$_{eq}$, CdH$_{eq}$, pd),

2.10 (CaH_{ax}, CeH_{ax}, td), 2.43 ($C4^{x}H_2$, t, ^3J=7.8,), 2.75 (CcH, tt, $^3J_{ax\text{-}ax}$=12.1, $^3J_{ax\text{-}eq}$=3.4,), 3.05 (CaH_{ex}, CeH_{ex}, pb), 4.19 ($C1^{x}H_2$, t, ^3J=7.6), 6.39 (C7H, m, $^3J_1$=7.6, $^3J_2$=6.3, ^4J=1.5), 6.86 (C-5H, dt, ^3J=9.0, ^4J=^5J=1.0), 6.92 (C-6H, C-6”H, m), 6.99 (C2”H, d, ^3J=2.4), 7.13 (C3’H, C5’H, m), 7.22-7.32 (C4”H, C7”H, m), 7.96 (NH, bs), 8.34 (C8H, dt, ^3J=7.3, ^4J=^5J=1.0)

^{13}CNMR (500 MHz) δ: 24.6 ($C3^{x}$), 25.7 ($C2^{x}$), 32.9 (Cb, Cd), 33.5 (Cc), 42.6 ($C1^{x}$), 54.4 (Ca, Ce), 58.8 ($C4^{x}$), 103.8 (C4), 104.0 (C4”, d*,^2J=23.4), 110.2 (C6”, d*, ^2J=25.9), 110.7 (C7), 111.7 (C7’’, d*, ^3J=9.7), 115.8 (C3’, C5’, d*,^2J=21.5), 121.2 (C5), 121.5 (C2”), 121.9 (C3”), 127.1 (C3”a, d*, ^3J=9.8), 128.1 (C8), 128.7 (C1’, d*, ^4J=3.4), 132.9 (C7”a), 133.0 (C2’, C6’, d*, ^3J=7.8), 143.7 (C4a), 148.9 (C1), 157.6 (C-5”, d*,^1J=234.4), 160.2 (C3), 162.3 (C4’, d*, ^1J=247.1)

4.1.5.5 2-{4-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-butyl}-4-(2-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.5)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 56.0% **m.p.** 112 - 113 °C

HRMS (ESI) calculated for $C_{31}H_{31}F_2N_4O_2$**:** 529.2410 $(M+H)^+$ **found** 529.2402**.**

^{1}H NMR (500 MHz) δ: 1.70 ($C3^{x}H_2$, q), 1.81 ($C2^{x}H_2$, m), 1.89 (CaH_{ax}, CeH_{ax}, pt), 2.03 (CbH_{eq}, CdH_{eq}, pd), 2.21 (CaH_{ax}, pt) 2.43 ($C4^{x}H_2$, t, ^3J=7.8), 2.75 (CcH, tt, $^3J_{ax\text{-}ax}$=12.1, $^3J_{ax\text{-}eq}$=3.4,), 3.05 (CaHex, CeHex, pb), 4.19 ($C1^{x}H_2$, t, ^3J=7.6), 6.39 (C7H, m, $^3J_1$=7.6, $^3J_2$=6.3, ^4J=1.5), 6.86 (C5H, dt, ^3J=9.0, ^4J=^5J=1.0), 6.92 (C6H, C6”H, m), 6.99 (C2”H, d, ^3J=2.4), 7.13 (C3’H, C5’H, m), 7.22-7.32 (C4”H, C7”H, m), 7.96 (NH, bs), 8.34 (C8H, dt, ^3J=7.3, ^4J=^5J=1.0)

^{13}C NMR (500 MHz) δ: 24.6 ($C3^{x}$), 25.7 ($C2^{x}$), 32.9 (Cb, Cd), 33.5 (Cc), 42.6 ($C1^{x}$), 54.4 (Ca, Ce), 58.8 ($C4^{x}$), 103.8 (C4), 104.0 (C4”, d*, ^2J=23.4), 110.2 (C6”, d*, ^2J=25.9), 110.7 (C7), 111.7 (C7’’, d*, ^3J=9.7), 115.8 (C3’, C5’, d*,^2J=21.5), 121.2 (C5), 121.5 (C2”), 121.9 (C3”), 127.1 (C3”a, d*, ^3J=9.8), 128.1 (C8), 128.7 (C1’, d*, ^4J=3.4), 132.9 (C7”a), 133.0 (C2’, C6’, d*, ^3J=7.8), 143.7 (C4a), 148.9 (C1), 157.6 (C5”, d*,^1J=234.4), 160.2 (C3), 162.3 (C4’, d*, ^1J=247.1)

4.1.5.6 2-{4-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-butyl}-4-(2-chlorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.6)**

The title compound was isolated as a yellow powder, crystallization from ethanol, yield: 62.0% **m.p.** 140.2 – 143.6 °C

HRMS (ESI) calculated for $C_{31}H_{31}FClN_4O_2$**:** 545.2114 $(M+H)^+$ **found** 545.2135**.**

^{1}HNMR (500MHz) δ: 1.85 ($C3^xH_2$, q), 1.88 ($C2^xH_2$, q), 2.09 (CbH_{ax}, CdH_{ax}, bps), 2.17 (CbH_{eq}, CdH_{eq}, pt), 2.55 ($C4^xH_2$, t), 2.89 (CaH_{ax}, CeH_{ax}, CcH, m), 3.34 (CaH_{eq}, CeH_{eq}, bps), 4.22 ($C1^xH_2$, m), 5.52 (C3'H, m), 6.46 (C7H, m, $^3J_1$=7.3, $^3J_2$=6.1, ^{4}J=1.5), 6.56 (C5H, dt, ^{3}J=9.3, ^{4}J=^{5}J=1.0), 6.92 (C6"H, td, ^{3}J=9.0, ^{4}J=2.4), 7.00 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.3, ^{4}J=1.2), 7.03 (C2"H, d, ^{3}J=2.2), 7.20 (C4"H, dd, $^3J_{H-F}$=9.8, ^{4}J=2.5), 7.24-7.40 (C6'H, C7"H, m), 8.22 (NH, bs), 8.39 (C8H, dt, ^{3}J=7.6, ^{4}J=^{5}J=1.0)

^{13}C NMR (500MHz) δ: 22.0 ($C3^x$), 25.0 ($C2^x$), 30.8 (Cb, Cd), 32.1 (Cc), 36.7 and 53,4 (Ca, Ce), 41.2 ($C1^x$), 57.5 ($C4^x$), 102,0 (C4), 103.6 (C4", d*, ^{2}J=23.4), 110.4, (C6", d*, ^{2}J=26.3), 111.1 (C7), 112.0 (C7", d*, ^{3}J=9.8), 119.6 (C3"), 121.1 (C5), 122.0 (C2"), 126.7 (C3"a, d*, ^{3}J=9.8), 127.5 (C5'), 128.2 (C8), 129.9 (C4'), 130.1 (C3'), 131.8 (C7"a), 132.8 (C1'), 133.5 (C6, C6'), 135.8 (C2'), 144.2 (C4a), 148.9 (C1), 157.7 (C5", d*, ^{1}J=234.9), 159.8 (C3).

4.1.5.7 2-{4-[4-(5-fluoro-1H-indol-3-yl)-piperidin-1-yl]-butyl}-4-(2-methoxyphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.7)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 69.5 % **m.p.** 123 - 126 °C

HRMS (ESI) calculated for $C_{32}H_{34}FN_4O_3$**:** 541.2610 $(M+H)^+$ **found** 541.2631**.**

^{1}H NMR (500MHz) δ: 1.69 ($C3^xH_2$, q), 1.80 ($C2^xH_2$, q), 1.88 (CbH_{ax}, CdH_{ax}, pt), 2.02 (CbH_{eq}, CdH_{eq}, pd), 2.19 ($C4^xH_2$, t), 2.53 (CaH_{ax}, CeH_{ax}, pt), 2.77 (CcH, tt, $^3J_{ax-ax}$=12.0, $^3J_{ax-eq}$=3.4), 3.11 (CaH_{eq}, CeH_{eq}, pd), 3.76 (OCH_3, s), 4.20 ($C1^xH_2$, t, ^{3}J=7.6), 6.36 (C7H, m, $^3J_1$=7.6, $^3J_2$=6.3, ^{4}J=1.5), 6.63 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 6.87 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.3, ^{4}J=1.2), 6.92 (C6"H, td, $^3J_{H-F}$=9.0, ^{4}J=2.4), 7.00 (C3'H, C2"H, m), 7.04 (C5'H, td, ^{3}J=7.3, ^{4}J=1.0), 7.21 (C4"H, dd, $^3J_{H-F}$=7.6, ^{4}J=1.7), 7.23-7.28 (C3'H, C2"H, m), 7.37 (C4'H, 4d, $^3J_1$=8.3, $^3J_2$=7.6, ^{4}J=1.7), 8.03 (NH, bs), 8.32 (C8H, dt, ^{3}J=7.3, ^{4}J=^{5}J=1.2).

^{13}C NMR (500MHz) δ: 24.0 ($C3^x$), 25.5 ($C2^x$), 32.5 (Cb, Cd), 33.2 (Cc), 42.2 ($C1^x$), 54.2 (Ca, Ce), 55.6 (OCH_3), 58.5 ($C4^x$), 101.3 (C4), 103.9 (C4", d*, ^{2}J=23.5), 110.3 (C6", d*, ^{2}J=26.3),

110.5 (C7), 111.4 (C3'), 111.7 (C7", d*, ^{3}J=9.3), 119.0 (C3"), 121.0 (C5'), 121.5 (C1'), 121.6 (C2"), 122.0 (C5), 127.0 (C3"a, d*, ^{3}J=9.2), 127.9 (C8), 129.7 (C4'), 131.9 (C7"a), 132.8 (C6), 133.0 (C6'), 143.7 (C4a), 149.2 (C1), 157.6 (C5", d*, ^{1}J=234.4), 157.9 (C2'), 160.0 (C3).

4.1.5.8 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-phenyl-pyrido[1,2-c]pyrimidine-1,3-dione **(8.8)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 50.67 % **m.p.** 118-119 °C

HRMS (ESI) calculated for $C_{31}H_{30}O_2N_4F$**:** 509.2353 $(M+H)^+$ **found** 509.2363**.**

^{1}H NMR ($CDCl_3$,500 MHz) : 6.85-6.94 (C5H,C6H,C6``H, m), 6.39 (C7H, m, $^{3}J_1$=7.5,$^{3}J_2$=6.0,$^{4}J$=2.0), 8.33 (C8H, d, $^{3}J$=7.5), 7.31 (C2`H,C6`H, dt, $^{3}J$=7.0, $^{4}J$=1.0), 7.39-7.48 (C3`H,C5`H,C4``H, m), 7.35 (C4`H, tt, ^{3}J=7.0), 4.21 ($C1^{x}H_2$, t, ^{3}J=7.0), 1.83 ($C2^{x}H_2$, q, ^{3}J=7.5), 1.76 ($C3^{x}H_2$, q, ^{3}J=7.5), 2.69 ($C4^{x}H_2$, t, ^{3}J=7.5), 3.30 (CaH_2 , bs), 5.95 (CbH, bs), 2.52 (CdH_2 , bs), 2.81 (CeH_2 , t, ^{3}J=5.5), 7.05 (C2``H, d, $^{3}J$=2.0), 7.26 (C7``H, dd, ^{3}J=8.5, $^{4}J_{H-F}$ =4.5), 9.05 (NH, bs)

.

^{13}C NMR ($CDCl_3$, 125MHz) : 149.2 (C1), 160.6 (C3), 105.0 (C4), 144.0 (C4a), 121.7 (C5), 132.8 (C6), 111.1 (C7), 128.1 (C8), 133.0 (C1'), 131.5 (C2', C6'), 129.0 (C3', C5'), 128.2 (C4'), 42.3 ($C1^{x}$), 25.5 ($C2^{x}$), 23.8 ($C3^{x}$), 57.6 ($C4^{x}$), 52.5 (Ca), 116.6 (Cb), 130.0 (Cc), 29.9 (Cd), 50.2 (Ce), 123.9 (C2"), 117.1 (C3", d*), 125.4 (C3"a, d*, ^{3}J=9.8), 105.7 (C4", d*, ^{2}J=24.4), 158.3 (C5", d*, ^{1}J=233.9), 110.6 (C6", d*, ^{2}J=25.9), 112.4 (C7", d*, ^{3}J=9.3), 133.6 (C7"a)

4.1.5.9 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-methylphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.9)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 69.8 % **m.p.** 115-116 °C

HRMS (ESI) calculated for $C_{32}H_{32}O_2N_4F$**:** 523.2509 $(M+H)^+$ **found** 523.2495**.**

^{1}H NMR ($CDCl_3$,500 MHz) : 6.84-6.92 (C5H,C6H,C6``H, m), 6.36 (C7H, m, $^{3}J_1$=7.5,$^{3}J_2$=5.5,^{4}J=2.0), 8.31 (C8H, d, ^{3}J=7.5), 7.23 (C2`H,C6`H,C7"H), 7.18 (C3`H,C5`H , d, ^{3}J=8.5), 4.21 ($C1^{x}H_2$, t, ^{3}J=7.0), 1.82 ($C2^{x}H_2$, q, ^{3}J=7.5), 1.73 ($C3^{x}H_2$, q, ^{3}J=7.0), 2.63

($C4^xH_2$, t, ^3J=7.5), 3.26 (CaH_2 , bs), 5.99 (CbH, bs), 2.45 (CdH_2 , bs), 2.75 (CeH_2 , t, ^3J=5.5), 7.04 (C2``H, s), 7.43 (C4``H, dd, $^3J_{H-F}$=10.5, ^4J=2.0), 2.36 (CH_3, s), 9.06 (NH, bs)

.

^{13}C NMR ($CDCl_3$, 125MHz) : 148.9 (C1), 160.4 (C3), 104.8 (C4), 143.6 (C4a), 121.6 (C5), 132.3 (C6), 110.7 (C7), 127.9 (C8), 131.0 (C1'), 129.5 (C2', C6'), 129.7 (C3', C5'), 137.6 (C4'), 42.2 ($C1^x$), 25.3 ($C2^x$), 23.9 ($C3^x$), 57.6 ($C4^x$), 52.6 (Ca), 117.1 (Cb, C3"), 129.7 (Cc), 29.7 (Cd), 50.0 (Ce), 123.5 (C2"), 125.2 (C3"a, d*, ^3J=9.8), 105.5 (C4", d*, ^2J=23.9), 158.0 (C5", d*, ^1J=233.9), 110.2 (C6", d*, ^2J=26.3), 112.0 (C7", d*, ^3J=10.3), 133.4 (C7"a), 21.3 (CH_3)

4.1.5.10 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-methoxyphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.10)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 67.4 % **m.p.** 111 - 112 °C

HRMS (ESI) calculated for $C_{32}H_{31}O_3N_4FNa$**:** 561.2278 $(M+Na)^+$ **found** 561.2270**.**

^1H NMR (see *supplementary materials*) ($CDCl_3$,500 MHz) : 6.85-6.91 (C5H,C6H,C6``H, m), 6.36 (C7H, m, $^3J_1$=7.5,$^3J_2$=5.0,^4J=2.5), 8.31 (C8H, d, ^3J=7.5), 7.21 (C2`H,C6`H, dt, ^3J=8.5, ^4J=2.0), 6.95 (C3`H,C5`H , dt, ^3J=8.5, ^4J=2.0), 4.21 ($C1^xH_2$, t, ^3J=7.5), 1.82 ($C2^xH_2$, q, ^3J=7.5), 1.71 ($C3^xH_2$, q, ^3J=7.5), 2.60 ($C4^xH_2$, t, ^3J=7.5), 3.23 (CaH_2 , bs), 6.01 (CbH, bs), 2.49 (CdH_2 , bs), 2.73 (CeH_2 , t, ^3J=5.5), 7.06 (C2``H, d, $^3J$=2.0), 7.45 (C4``H, dd, $^3J_{H-F}$=10.5, ^4J=2.5), 7.24 (C7``H, dd, ^3J =8.5, $^4J_{H-F}$=4.5), 3.81 (OCH_3, s), 8.98 (NH, bs)

^{13}C NMR (see *supplementary materials*) ($CDCl_3$, 125MHz) : 148.9 (C1), 160.5 (C3), 104.5 (C4), 143.6 (C4a), 121.6 (C5), 132.2 (C6), 110.7 (C7), 127.9 (C8), 124.8 (C1'), 132.4 (C2', C6'), 114.3 (C3', C5'), 159.2 (C4'), 42.3 ($C1^x$), 25.5 ($C2^x$), 24.2 ($C3^x$), 57.7 ($C4^x$), 52.7 (Ca), 117.7 (Cb), 129.7 (Cc), 28.3 (Cd), 50.1 (Ce), 123.5 (C2"), 117.4 (C3", d*) 125.3 (C3"a, d*, ^3J=9.8), 105.5 (C4", d*, ^2J=24.4), 158.0 (C5", d*, ^1J=233.9), 110.2 (C6", d*, ^2J=26.3), 112.0 (C7", d*, ^3J=9.3), 133.4 (C7"a), 55.3 (OCH_3)

4.1.5.11 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-chlorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione (**8.11)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 71.4 % **m.p.** 124 - 125 °C

HRMS (ESI) calculated for $C_{31}H_{29}O_2N_4FCl$**:** 543.1963 $(M+H)^+$ **found** 543.1964.

^{1}H NMR ($CDCl_3$,500 MHz) : 6.85 (C5H, d, ^{3}J=10.0), 6.94 (C6H, 4d, $^3J_1$=9.5,$^3J_2$=6.0,^{4}J=1.0), 6.40 (C7H, m, $^3J_1$=7.5,$^3J_2$=6.0,^{4}J=1.5), 8.34 (C8H, d, ^{3}J=7.5), 7.39 (C2`H,C6`H, dt, ^{3}J=8.5, ^{4}J=2.0), 7.22-7.28 (C3`H,C5`H,C7``H, m), 4.20 ($C1^xH_2$ ,t, $^3$J=7.5), 1.82 ($C2^xH_2$ , q, $^3$J=7.5), 1.72 ($C3^xH_2$ ,q , $^3$J=7.5), 2.61 ($C4^xH_2$ ,t, $^3$J=7.5), 3.25 ($CaH_2$ , d, $^3$J=0.5), 6.02 (CbH, bs), 2.51 ($CdH_2$ , bs), 2.75 ($CeH_2$ ,t, $^3$J=4.5), 7.08 (C2``H, d, ^{3}J=1.5), 7.45 (C4``H, dd, $^3J_{H-F}$=10.5, $^4$J=2.0), 6.89 (C6``H, td, ^{3}J=9.0, ^{4}J=2.5), 8.86 (NH, bs)

^{13}C NMR ($CDCl_3$, 125MHz) : 148.8 (C1), 160.0 (C3), 103.5 (C4), 143.7 (C4a), 121.0 (C5), 133.0 (C6), 110.9 (C7), 128.1 (C8), 131.3 (C1'), 129.0 (C2', C6'), 132.7 (C3', C5'), 133.7 (C4'), 42.3 ($C1^x$), 25.4 ($C2^x$), 24.1 ($C3^x$), 57.7 ($C4^x$), 52.7 (Ca), 117.7 (Cb), 129.7 (Cd), 50.1 (Ce), 123.4 (C2"), 117.4 (C3", d*) 125.3 (C3"a, d*, ^{3}J=9.8), 105.6 (C4", d*, ^{2}J=23.9), 158.1 (C5", d*, ^{1}J=234.4), 110.3 (C6", d*, ^{2}J=26.3), 112.0 (C7", d*, ^{3}J=9.7), 112.0 (C7``, d*, ^{3}J=9.7), 133.3 (C7"a)

4.1.5.12 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione (**8.12)**

The title compound was isolated as a yellow powder, crystallization from diethyl ether, yield: 61.6 % **m.p.** 115 - 116 °C

HRMS (ESI) calculated for $C_{31}H_{29}O_2N_4F_2$**:** 527.2258 $(M+H)^+$ **found** 527.2245.

^{1}H NMR ($CDCl_3$,500 MHz) : 6.84 (C5H, d, ^{3}J=9.5), 6.92 (C6H, td, ^{3}J=9.0), 6.39 (C7H, t, ^{3}J=6.5), 8.33 (C8H, d, ^{3}J=7.5), 7.27 (C2`H,C6`H,C7``H, m), 7.12 (C3`H,C5`H, m), 4.20 ($C1^xH_2$ ,t, $^3$J=7.5), 1.83 ($C2^xH_2$ , q, $^3$J=7.5), 1.72 ($C3^xH_2$ ,q , $^3$J=7.5), 2.60 ($C4^xH_2$ ,t, $^3$J=7.5), 3.24 ($CaH_2$ , bs), 6.02 (CbH, bs), 2.51 ($CdH_2$ , bs), 2.75 ($CeH_2$ ,t, $^3$J=5.5), 7.10 (C2``H, d, ^{3}J=2.0), 7.45 (C4``H, d, $^3J_{H-F}$=10.0), 6.89 (C6``H, td, ^{3}J=9.0, ^{4}J=2.5), 8.84 (NH, bs)

^{13}C NMR ($CDCl_3$, 125MHz) : 148.9 (C1), 160.2 (C3), 103.7 (C4), 143.8 (C4a), 121.1 (C5), 133.8 (C6), 110.8 (C7), 128.1 (C8), 128.6 (C1', d*,^{4}J=3.4), 133.0 (C2', C6', d*,^{3}J=7.8), 115.8 (C3', C5', d*,^{2}J=21.5), 162.3 (C4', d*,^{1}J=247.0), 42.4 ($C1^x$), 25.4 ($C2^x$), 24.2 ($C3^x$), 57.8 ($C4^x$), 52.8 (Ca), 117.9 (Cb), 129.6 (Cc), 29.7 (Cd), 50.1 (Ce), 123.3 (C2"), 117.5 (C3", d*) 125.3 (C3"a, d*, ^{3}J=9.7), 105.6 (C4", d*, ^{2}J=24.4), 158.0 (C5", d*, ^{1}J=234.0), 110.3 (C6", d*, ^{2}J=26.4), 112.0 (C7", d*, ^{3}J=9.8), 112.0 (C7``, d*, ^{3}J=9.8), 133.3 (C7"a)

4.1.5.13 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione (**8.13)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 45.8 % **m.p.** 122 - 124 °C

HRMS (ESI) calculated for $C_{31}H_{30}F_2N_4O_2$**:** 527.2244 $(M+H)^+$ **found** 527.2258**.**

^{1}H NMR ($CDCl_3$,500 MHz) : 6.73 (C5H, d, ^{3}J=9.0), 6.97 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.0), 6.42 (C7H, m, $^3J_1$=7.0, $^3J_2$=6.5), 8.36 (C8H, dt, ^{3}J=7.5), 7.16 (C3'H, ^{3}J=9.0, ^{4}J=1.0), 7.37 (C4'H, m), 7.22 (C5'H, td, ^{3}J=7.5, ^{4}J=1.5), 7.32 (C6'H, td, ^{3}J=7.5, ^{4}J=2.0), 4.22 ($C1^xH_2$, t, ^{3}J=7.5), 1.83 ($C2^xH_2$, q, ^{3}J=7.5), 1.72 ($C3^xH_2$, q, ^{3}J=7.5), 2.60 ($C4^xH$, t, ^{3}J=7.5), 3.24 (CaH_2 , bs), 6.03 (CbH, bs), 2.53 (CdH_2 , bs), 2.74 (CeH_2 , t, ^{3}J=5.5), 7.13 (C2"H, d, ^{3}J=2.0), 7.46 (C4"H, dd, $^3J_{H-F}$=10.0, ^{4}J=2.5), 6.90 (C6"H, td, ^{3}J=9.0, ^{4}J=2.5), 7.26 (C7"H, dd, ^{3}J=9.0, $^4J_{H-F}$=4.5), 8.91 (NH, bs)

^{13}C NMR ($CDCl_3$, 125MHz) : 149.1 (C1), 159.8 (C3), 98.5 (C4), 144.3 (C4a), 121.7 (C5), 133.3 (C6), 111.0 (C7), 128.3 (C8), 120.5 (C1', d*), 161.1 (C2', d*), 116.2 (C3', d*), 130.3 (C4', d*), 124.6 (C5', d*), 133.6 (C6', d*), 42.5 ($C1^x$), 25.6 ($C2^x$), 24.3 ($C3^x$), 57.9 ($C4^x$), 52.9 (Ca), ~118.3 (Cb), 129.8 (Cc), 28.7 (Cd), 50.3 (Ce), 123.4 (C2"), 117.8 (C3", d*), 125.5 (C3"a, d*), 105.8 (C4", d*), 158.2 (C5", d*), 110.5 (C6", d*), 112.1 (C7", d*), 133.5 (C7"a)

4.1.5.14 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-chlorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.14)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 65.0 % **m.p.** 119 – 120 °C

HRMS (ESI) calculated for $C_{31}H_{29}FClN_4O_2$**:** 543.1963 $(M+H)^+$ **found** 543.1959**.**

^{1}H NMR ($CDCl_3$,500 MHz) : 6.54 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 6.96 (C6H, 4dt, $^3J_1$=9.5, $^3J_2$=7.0), 6.43 (C7H, m, $^3J_1$=9.5, $^3J_2$=7.0), 8.37 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 7.49 (C3'H, m), 7.24-7.34 (C4'H, C5'H, C6'H, m), 4.22 ($C1^xH_2$, t, ^{3}J=7.0), 1.84 ($C2^xH_2$, q, ^{3}J=7.0), 1.72 ($C3^xH_2$, t, ^{3}J=7.0), 2.61 ($C4^xH$, t, ^{3}J=7.5), 3.24 (CaH_2 , d, ^{3}J=2.0), 6.01 (CbH, t), 2.51 (CdH_2 , bs), 2.74 (CeH_2 , t, ^{3}J=6.0), 7.09 (C2"H, d, ^{3}J=2.0), 7.44 (C4"H, dd, $^3J_{H-F}$=10.0, ^{4}J=2.5), 6.88 (C6"H, td, ^{3}J=9.0, ^{4}J=2.5), 7.25 (C7"H, dd, ^{3}J=9.0, $^4J_{H-F}$=4.5), 8.96 (NH, bs)

^{13}C NMR ($CDCl_3$, 125MHz) : 149.2 (C1), 159.8 (C3), 102.4 (C4), 144.2 (C4a), 121.3 (C5), 133.6 (C6), 111.2 (C7), 128.4 (C8), 132.0 (C1'), 136.0 (C2'), 130.2 (C3'), 130.0 (C4'), 127.6 (C5'), 133.5 (C6'), 42.5 ($C1^x$), 25.7 ($C2^x$), 24.2 ($C3^x$), 57.9 ($C4^x$), 52.9 (Ca), 117.9 (Cb), 129.9 (Cc), 28.6 (Cd), 50.3 (Ce), 123.7 (C2"), 117.6 (C3", d*), 125.5 (C3"a, d*), 105.3 (C4"), 158.3 (C5", d*), 110.5 (C6", d*), 112.3 (C7", d*), 133.6 (C7"a)

4.1.5.15 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-methylphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.15)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 63.4 % **m.p.** 116 - 118 °C

HRMS (ESI) calculated for $C_{32}H_{33}FN_4O_2$**:** 523.2517 $(M+H)^+$ **found** 523.2509**.**

^{1}H NMR ($CDCl_3$,500 MHz) : 6.54 (C5H, dt, ^{3}J=9.0, ^{4}J=^{5}J=1.0), 6.88 (C6H, C6"H, m), 6.38 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.0), 8.33 (C8H, dt, ^{3}J=7.0, ^{4}J=^{5}J=1.0), 7.12 (C3'H, dd, ^{3}J=7.0, ^{4}J=1.5), 7.24-7.33 (C4'H, C5'H, C6'H, m), 4.23 ($C1^xH_2$, t, ^{3}J=7.0), 1.84 ($C2^xH_2$, q, ^{3}J=7.5), 1.71 ($C3^xH_2$, m), 2.59 ($C4^xH$, t, ^{3}J=7.5), 3.22 (CaH_2 , d, ^{3}J=2.5), 6.02 (CbH, bs), 2.47 (CdH_2 , bs), 2.71 (CeH_2 , t, ^{3}J=5.5), 7.03 (C2"H, d, ^{3}J=2.5), 7.46 (C4"H, dd, $^3J_{H-F}$=10.5, ^{4}J=2.5), 7.22 (C7"H, dd, ^{3}J=8.5, $^4J_{H-F}$=5.0), 2.14 (CH_3, s), 8.96 (NH, bs)

^{13}C NMR ($CDCl_3$, 125MHz) : 149.2 (C1), 159.9 (C3), 104.1 (C4), 143.7 (C4a), 121.5 (C5), 132.7 (C6), 110.8 (C7), 128.5 (C8), 132.2 (C1'), 138.6 (C2'), 131.7 (C3'), 128.1 (C4'), 126.5 (C5'), 130.7 (C6'), 42.4 ($C1^x$), 25.6 ($C2^x$), 24.3 ($C3^x$), 57.9 ($C4^x$), 53.0 (Ca), 118.1 (Cb), 129.8 (Cc), 28.6 (Cd), 50.2 (Ce), 123.6 (C2"), 117.5 (C3", d*), 125.4 (C3"a, d*), 105.7 (C4"), 158.2 (C5", d*), 110.3 (C6", d*), 112.1 (C7", d*), 133.5 (C7"a), 19.7 (CH_3)

4.1.5.16 2-{4-[4-(5-fluoro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-methoxyphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.16)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 52.4 % **m.p.** 120 - 122 °C

HRMS (ESI) calculated for $C_{32}H_{33}FN_4O_3$**:** 539.2457 $(M+H)^+$ **found** 539.2458**.**

^{1}H NMR ($CDCl_3$,500 MHz) : 6.62 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 6.87 (C6H, C6"H, m), 6.37 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.6), 8.32 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 6.96 (C3'H, d, ^{3}J=8.5), 7.35

(C4'H, 4d, $^{3}J_{1}$=8.5, $^{3}J_{2}$=7.5), 7.02 (C5'H, td, ^{3}J=7.5, ^{4}J=1.0), 7.20 (C6'H, dd, ^{3}J=7.5, ^{4}J=2.0), 4.21 (C1^{x}H$_{2}$, m), 1.83 (C2^{x}H$_{2}$, q, ^{3}J=7.5), 1.73 (C3^{x}H$_{2}$, q, ^{3}J=7.5), 2.63 (C4^{x}H , t, ^{3}J=7.5), 3.26 (CaH$_{2}$, bs), 5.98 (CbH, bs), 2.49 (CdH$_{2}$, bs), 2.75 (CeH$_{2}$, t, ^{3}J=5.0), 7.04 (C2"H, d, ^{3}J=1.0), 7.43 (C4"H, dd, $^{3}J_{H-F}$=10.0, ^{4}J=2.0), 7.24 (C7"H, dd, ^{3}J=8.5, $^{4}J_{H-F}$=5.0), 3.72 (OCH$_{3}$, s), 9.14 (NH, bs)

^{13}C NMR (CDCl$_{3}$, 125MHz) : 149.3 (C1), 160.2 (C3), 101.3 (C4), 143.9 (C4a), 122.1 (C5), 133.1 (C6), 110.8 (C7), 128.0 (C8), 121.5 (C1'), 158.1 (C2'), 111.6 (C3'), 129.9 (C4'), 121.1 (C5'), 132.3 (C6'), 42.3 (C1^{x}), 25.5 (C2^{x}), 24.0 (C3^{x}), 57.7 (C4^{x}), 52.7 (Ca), 117.2 (Cb), 129.9 (Cc), 28.2 (Cd), 50.1 (Ce), 123.8 (C2"), (C3"), 125.4 (C3"a, d*), 105.6 (C4", d*), 158.2 (C5", d*), 110.4 (C6", d*), 112.3 (C7", d*), 133.6 (C7"a), 55.8 (OCH$_{3}$)

4.1.5.17 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-phenyl-pyrido[1,2-c]pyrimidine-1,3-dione **(8.17)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 53.3 % **m.p.** 164 - 166 °C

HRMS (ESI) calculated for $C_{31}H_{30}ClN_4O_2$**:** 525.2057 $(M+H)^+$ **found** 525.2063**.**

^{1}H NMR (see *supplementary materials*) (DMSO ,500 MHz) : 7.76 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 7.11 (C6H, C6"H, m), 6.55 (C7H, m, $^{3}J_{1}$=7.5, $^{3}J_{2}$=5.5, ^{4}J=1.5), 8.29 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 7.28 (C2', C6'H, dt, ^{3}J=7.0, ^{4}J=1.5), 7.44 (C3'H, C5'H, C2"H, m), 7.36 (C4'H, tt, ^{3}J=7.5, ^{4}J=1.5), 4.03 (C1^{x}H$_{2}$, t, ^{3}J=7.0), 1.63 (C2^{x}H$_{2}$, q, ^{3}J=7.0), 1.54 (C3^{x}H$_{2}$, q, ^{3}J=7.0), 2.41 (C4^{x}H , t, ^{3}J=7.0), 3.08 (CaH$_{2}$, d, ^{3}J=3.0), 6.06 (CbH, t), 2.47 (CdH$_{2}$, ps), 2.61 (CeH$_{2}$, t, ^{3}J=6.0), 7.77 (C4"H, d, ^{3}J=2.0), 7.39 (C7"H, d, ^{3}J=8.5), 11.30 (NH, d, ^{3}J=2.0)

^{13}C NMR (see *supplementary materials*) (DMSO , 125MHz) : 148.4 (C1), 159.1 (C3), 103.2 (C4), 143.1 (C4a), 120.3 (C5), 133.3 (C6), 111.0 (C7), 127.2 (C8), 133.5 (C1'), 131.2 (C2', C6'), 128.3 (C3', C5'), 127.9 (C4'), 41.5 (C1^{x}), 25.0 (C2^{x}), 24.0 (C3^{x}), 57.5 (C4^{x}), 52.6 (Ca), 118.3 (Cb), 125.5 (Cc), 28.5 (Cd), 50.0 (Ce), 124.3 (C2"), 115.7 (C3"), 128.9 (C3"a), 119.0 (C4"), 123.8 (C5"), 121.1 (C6"), 113.1 (C7"), 135.3 (C7"a)

4.1.5.18 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-methylphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.18)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 50.2 % **m.p.** 158 - 159 °C

HRMS (ESI) calculated for $C_{32}H_{32}ClN_4O_2$**:** 539.2042 $(M+H)^+$ **found** 539.2088**.**

^{1}H NMR (DMSO ,500 MHz) : 6.76 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 7.09 (C6H, C6"H, m), 6.54 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.5, ^{4}J=1.0), 8.27 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 7.24 (C2', C6'H, dt, ^{3}J=8.0), 7.15 (C3'H, C5'H, dt, ^{3}J=8.0), 4.02 ($C1^xH_2$, t, ^{3}J=7.5), 1.67 ($C2^xH_2$, q, ^{3}J=7.0), 1.53 ($C3^xH_2$, q, ^{3}J=7.0), 2.42 ($C4^xH$, t, ^{3}J=7.5), 3.08 (CaH_2 , d, ^{3}J=2.0), 6.06 (CbH, t), 2.47 (CdH_2 , ps), 2.61 (CeH_2 , t, ^{3}J=5.5), 7.44 (C2"H, d, ^{3}J=3.0), 7.77 (C4"H, d, ^{3}J=2.0), 7.39 (C7"H, d, ^{3}J=8.5), 2.34 (CH_3, s), 11.30 (NH, d, ^{3}J=2.0)

^{13}C NMR (DMSO , 125MHz) : 148.4 (C1), 159.2 (C3), 103.1 (C4), 143.0 (C4a), 120.5 (C5), 133.3 (C6), 111.0 (C7), 127.8 (C8), 130.2 (C1'), 129.0 (C2', C6'), 131.0 (C3', C5'), 136.4 (C4'), 41.5 ($C1^x$), 25.0 ($C2^x$), 24.0 ($C3^x$), 57.4 ($C4^x$), 52.6 (Ca), 118.2 (Cb), 125.5 (Cc), 28.5 (Cd), 50.0 (Ce), 124.3 (C2"), 115.7 (C3"), 129.0 (C3"a), 119.0 (C4"), 123.8 (C5"), 121.1 (C6"), 113.1 (C7"), 135.3 (C7"a), 20.7 (CH_3)

4.1.5.19 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-methoxyphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.19)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 59.4 % **m.p.** 172 - 177 °C

HRMS (ESI) calculated for $C_{32}H_{32}ClN_4O_3$**:** 555.2142 $(M+H)^+$ **found** 555.2177**.**

^{1}H NMR (DMSO ,500 MHz) : 6.77 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 7.09 (C6H, C6"H, m), 6.56 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.5, ^{4}J=1.5), 8.26 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 7.19 (C2', C6'H, dt, ^{3}J=9.0, ^{2}J=2.0), 6.99 (C3'H, C5'H, dt, ^{3}J=9.0, ^{4}J=2.0), 4.02 ($C1^xH_2$, t, ^{3}J=7.0), 1.67 ($C2^xH_2$, q, ^{3}J=7.0), 1.53 ($C3^xH_2$, q, ^{3}J=7.0), 2.41 ($C4^xH$, t, ^{3}J=7.0), 3.08 (CaH_2 , d, ^{3}J=3.0), 6.06 (CbH, t), 2.47 (CdH_2 , ps), 2.60 (CeH_2 , t, ^{3}J=5.5), 7.44 (C2"H, d, ^{3}J=2.5), 7.77 (C4"H, d, ^{3}J=2.0), 7.39 (C7"H, d, ^{3}J=8.5), 3.79 (OCH_3, s), 11.30 (NH, bs)

^{13}C NMR (DMSO , 125MHz) : 148.4 (C1), 159.3 (C3), 103.0 (C4), 143.0 (C4a), 120.5 (C5), 133.2 (C6), 110.9 (C7), 127.8 (C8), 125.1 (C1'), 132.3 (C2', C6'), 113.8 (C3', C5'), 158.4 (C4'), 41.5 ($C1^x$), 24.9 ($C2^x$), 24.0 ($C3^x$), 57.5 ($C4^x$), 52.7 (Ca), 118.3 (Cb), 125.5 (Cc), 28.5 (Cd), 50.0 (Ce), 124.3 (C2"), 115.7 (C3"), 128.9 (C3"a), 119.0 (C4"), 123.8 (C5"), 121.1 (C6"), 113.1 (C7"), 135.3 (C7"a), 55.0 (OCH_3)

4.1.5.20 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.20)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 49.6 % **m.p.** 169 - 173 °C

HRMS (ESI) calculated for $C_{31}H_{29}ClN_4O_2F$**:** 543.1963 $(M+H)^+$ **found** 543.1937**.**

^{1}H NMR (DMSO ,500 MHz) : 6.76 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 7.13 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.5, ^{4}J=1.5), 6.56 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.5, ^{4}J=1.5), 8.30 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 7.31 (C2', C6'H, m), 6.26 (C3'H, C5'H, m), 4.03 ($C1^xH_2$, t, ^{3}J=7.0), 1.68 ($C2^xH_2$, q, ^{3}J=7.0), 1.54 ($C3^xH_2$, q, ^{3}J=7.0), 2.41 ($C4^xH$, t, ^{3}J=7.0), 3.08 (CaH_2 , d, ^{3}J=3.0), 6.06 (CbH, t), 2.47 (CdH_2 , ps), 2.60 (CeH_2 , t, ^{3}J=5.5), 7.44 (C2"H, d, ^{3}J=2.5), 7.77 (C4"H, d, ^{3}J=2.0), 7.10 (C6"H, dd, ^{3}J=9.0, ^{4}J=2.0), 7.38 (C7"H, dd, ^{3}J=9.0,^{5}J=0.5), 11.30 (NH, bs)

^{13}C NMR (DMSO , 125MHz) : 148.3 (C1), 159.2 (C3), 102.1 (C4), 143.3 (C4a), 120.2 (C5), 133.7 (C6), 111.0 (C7), 128.0 (C8), 129.5 (C1', d*, ^{4}J=3.0), 133.3 (C2', C6', d*, ^{3}J=8.0), 115.2 (C3', C5', d*, ^{2}J=21.2), 161.3 (C4', d*, ^{1}J=244.1), 41.6 ($C1^x$), 24.9 ($C2^x$), 24.0 ($C3^x$), 57.5 ($C4^x$), 52.7 (Ca), 118.3 (Cb), 125.5 (Cc), 28.5 (Cd), 50.0 (Ce), 124.3 (C2"), 115.7 (C3"), 128.9 (C3"a), 119.0 (C4"), 123.8 (C5"), 121.1 (C6"), 113.1 (C7"), 135.3 (C7"a)

4.1.5.21 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.21)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 57.5 % **m.p.** 145 - 148 °C

HRMS (ESI) calculated for $C_{31}H_{29}ClN_4O_2F$**:** 543.1963 $(M+H)^+$ **found** 543.1922**.**

^{1}H NMR (see *supplementary materials*) (DMSO ,500 MHz) : 6.61 (C5H, C7H, m), 7.20 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.5, ^{4}J=1.5), 8.33 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 7.29 (C3'H, C5'H, m), 7.45 (C4'H, C2"H, m), 7.32 (C6'H, m), 4.03 ($C1^xH_2$, t, ^{3}J=7.0), 1.69 ($C2^xH_2$, q, ^{3}J=7.0), 1.54 ($C3^xH_2$, q, ^{3}J=7.0), 2.43 ($C4^xH$, t, ^{3}J=7.0), 3.09 (CaH_2 , d, ^{3}J=2.5), 6.06 (CbH, t), 2.48 (CdH_2 , ps), 2.61 (CeH_2 , t, ^{3}J=5.5), 7.78 (C4"H, d, ^{3}J=2.0), 7.10 (C6"H, dd, ^{3}J=8.5, ^{4}J=2.0), 7.39 (C7"H, d, ^{3}J=8.5), 11.30 (NH, bs)

^{13}C NMR (see *supplementary materials*) (DMSO , 125MHz) : 148.3 (C1), 158.6 (C3), 96.6 (C4), 143.6 (C4a), 120.1 (C5), 134.4 (C6), 111.2 (C7), 128.1 (C8), 120.6 (C1', d*, ^{2}J=16.1), 160.4 (C2', d*, ^{1}J=245.1), 115.7 (C3', d*, ^{2}J=22.1), 130.0 (C4', d*, ^{3}J=8.0), 124.4 (C5', d*, ^{4}J=3.4), 133.6 (C6', d*, ^{3}J=3.0) 41.6 (C1^{x}), 24.9 (C2^{x}), 23.9 (C3^{x}), 57.4 (C4^{x}), 52.6 (Ca), 118.2 (Cb), 125.5 (Cc), 28.5 (Cd), 50.0 (Ce), 124.3 (C2"), 115.7 (C3"), 128.9 (C3"a), 119.0 (C4"), 123.8 (C5"), 121.1 (C6"), 113.1 (C7"), 135.3 (C7"a)

4.1.5.22 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-chlorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.22)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 54.0 % **m.p.** 183 - 188 °C

HRMS (ESI) calculated for $C_{31}H_{29}Cl_2N_4O_2$**:** 559.1667 $(M+H)^+$ **found** 559.1695

^{1}H NMR (DMSO ,500 MHz) : 6.44 (C5H, dt, ^{3}J=9.0, ^{4}J=^{5}J=1.0), 7.19 (C6H, 4d, $^{3}J_1$=9.5, $^{3}J_2$=6.0, ^{4}J=1.5), 6.61 (C7H, m, $^{3}J_1$=7.5, $^{3}J_2$=6.0, ^{4}J=1.5), 8.34 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0),), 7.44 (C3'H, C5'H, C2"H, m), 7.59 (C4'H, m), 7.34 (C6'H, m), 4.04 (C1$^{x}H_2$, m), 1.69 (C2$^{x}H_2$, q, ^{3}J=7.0), 1.53 (C3$^{x}H_2$, q, ^{3}J=7.0), 2.42 (C4^{x}H , t, ^{3}J=7.0), 3.08 (CaH_2 , d, ^{3}J=2.5), 6.05 (CbH, t), 2.47 (CdH_2 , ps), 2.60 (CeH_2 , t, ^{3}J=5.5), 7.77 (C4"H, d, ^{3}J=2.0), 7.10 (C6"H, dd, ^{3}J=8.0, ^{4}J=2.0), 7.39 (C7"H, d, ^{3}J=8.5), 11.23 (NH, bs)

^{13}C NMR (DMSO , 125MHz) : 148.4 (C1), 158.4 (C3), 100.7 (C4), 143.3 (C4a), 120.0 (C5), 134.4 (C6), 111.2 (C7), 128.0 (C8), 132.1 (C1'), 134.9 (C2'), 129.7 (C3'), 129.4 (C4'), 127.4 (C5'), 133.7 (C6'), 41.4 (C1^{x}), 24.9 (C2^{x}), 23.9 (C3^{x}), 57.4 (C4^{x}), 52.6 (Ca), 118.3 (Cb), 125.5 (Cc), 28.5 (Cd), 50.0 (Ce), 124.3 (C2"), 115.7 (C3"), 128.9 (C3"a), 119.0 (C4"), 123.8 (C5"), 121.1 (C6"), 113.1 (C7"), 135.3 (C7"a)

4.1.5.23 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-methylphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.23)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 49.0 % **m.p.** 196 - 198 °C

HRMS (ESI) calculated for $C_{32}H_{32}ClN_4O_2$**:** 539.2042 $(M+H)^+$ **found** 539.2081**.**

^{1}H NMR (DMSO ,500 MHz) : 6.42 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 7.19 (C6H, C3'H, C6''H, m), 6.56 (C7H, m, $^{3}J_{1}$=7.5, $^{3}J_{2}$=6.5, ^{4}J=1.5), 8.30 (C8H, dt, ^{3}J=7.5, ^{4}J=^{5}J=1.0), 7.31 (C4'H, C6'H, m), 7,24 (C5'H, m), 4.04 (C1$^{x}H_{2}$, m), 1.69 (C2$^{x}H_{2}$, q, ^{3}J=7.0), 1.53 (C3$^{x}H_{2}$, q, ^{3}J=7.5), 2.42 (C4^{x}H , t, ^{3}J=7.5), 3.08 (CaH_{2} , d, ^{3}J=2.5), 6.06 (CbH, t), 2.47 (CdH_{2} , ps), 2.60 (CeH_{2} , t, ^{3}J=5.5), 7.45 (C2''H, d, ^{3}J=2.5), 7.77 (C4"H, d, ^{3}J=2.0), 7.39 (C7"H, d, ^{3}J=8.5, ^{5}J=0.5), 2.07 (CH_{3}), 11.23 (NH, bs)

^{13}C NMR (DMSO , 125MHz) : 148.5 (C1), 158.7 (C3), 102.4 (C4), 143.0 (C4a), 120.3 (C5), 133.6 (C6), 110.8 (C7), 127.9 (C8), 132.8 (C1'), 138.2 (C2'), 131.6 (C3'), 127.8 (C4'), 125.9 (C5'), 130.0 (C6'), 41.4 (C1^{x}), 24.9 (C2^{x}), 23.9 (C3^{x}), 57.4 (C4^{x}), 52.6 (Ca), 118.3 (Cb), 125.5 (Cc), 28.5 (Cd), 50.0 (Ce), 124.3 (C2"), 115.7 (C3"), 128.9 (C3"a), 119.0 (C4"), 123.8 (C5"), 121.1 (C6"), 113.1 (C7"), 135.3 (C7"a), 19.1 (CH_{3})

4.1.5.24 2-{4-[4-(5-chloro-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-methoxyphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.24)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 52.6 % **m.p.** 128 - 131 °C

HRMS (ESI) calculated for $C_{32}H_{31}ClN_{4}O_{3}H$**:** 555.2142 $(M+H)^{+}$ **found** 555.2172**.**

^{1}H NMR (DMSO ,500 MHz) : 6.43 (C5H, dt, ^{3}J=9.5, ^{4}J=^{5}J=1.0), 6.88 (C6H, 4d, $^{3}J_{1}$=9.0, $^{3}J_{2}$=6.5,^{4}J=1.0), 6.37 (C7H, m, $^{3}J_{1}$=7.5, $^{3}J_{2}$=6.5, ^{4}J=1.5), 8.31 (C8H, dt, ^{3}J=8.5, ^{4}J=^{5}J=1.0), 7.08 (C3'H , dd, ^{3}J=8.5, ^{4}J=2.0), 7,36 (C4'H, td, ^{3}J=8.0, ^{4}J=1.5), 7.03 (C5'H, td, ^{3}J=8.0, ^{4}J=1.0), 7.20 (C6'H, dd, ^{3}J=7.5, ^{4}J=1.5), 4.21 (C1$^{x}H_{2}$, m), 1.83 (C2$^{x}H_{2}$, q, ^{3}J=7.5), 1.72 (C3$^{x}H_{2}$, q, ^{3}J=7.5), 2.61 (C4^{x}H , t, ^{3}J=7.5), 3.24 (CaH_{2} , ps), 6.03 (CbH, t), 2.47 (CdH_{2} , ps), 2.73 (CeH_{2} , t, ^{3}J=5.5), 7.03 (C2''H, d, ^{3}J=1.0), 7.76 (C4"H, d,^{4}J=2.0), 6.97 (C6''H, d, ^{3}J=8.5), 7.24 (C7"H, d, ^{3}J=8.5), 3.73 (OCH_{3} ,s), 9.02 (NH, bs)

^{13}C NMR (DMSO , 125MHz) : 149.1 (C1), 160.1 (C3), 101.2 (C4), 143.8 (C4a), 121.9 (C5), 133.0 (C6), 110.6 (C7), 127.9 (C8), 121.5 (C1'), 158.0 (C2'), 111.5 (C3'), 129.7 (C4'), 121.0 (C5'), 132.1 (C6'), 42.2 (C1^{x}), 25.4 (C2^{x}), 24.0 (C3^{x}), 57.7 (C4^{x}), 52.7 (Ca), 118.1 (Cb), 125.6 (Cc), 28.4 (Cd), 50.1 (Ce), 129.5 (C2"), 117.1 (C3"), 126.1 (C3"a), 120.0 (C4"), 123.0 (C5"), 122.2 (C6"), 112.5 (C7"), 135.2 (C7"a), 55.6 (OCH_{3})

4.1.5.25 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-phenyl-pyrido[1,2-c]pyrimidine-1,3-dione **(8.25)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 67.0 % **m.p.** 200 - 205 °C

HRMS (ESI) calculated for $C_{31}H_{30}N_4O_2Br$**:** 569.1552 $(M+H)^+$ **found** 569.1558**.**

^{1}H NMR ($CDCl_3$,500 MHz) 6.88 (C5H, C6H, m), 6.38 (C7H, m, $^3J_1$=7.5, $^3J_2$=5.0, ^{4}J=2.5), 8.32 (C8H, d, ^{3}J=7.5), 7.30 (C2'H, C6'H, d, ^{3}J=7.5), 7.43 (C3'H, C5'H, t, ^{3}J=7.5), 7.35 (C4'H, t, ^{3}J=7.5), 4.22 ($C1^xH_2$, t, ^{3}J=7.5), 1.83 ($C2^xH_2$, q, ^{3}J=7.5), 1.69 ($C3^xH_2$, q, ^{3}J=7.5), 2.52 ($C4^xH$, t, ^{3}J=7.5), 3.17 (CaH_2 , d, ^{3}J=2.5), 6.08 (CbH, t), 2.40 (CdH_2 , ps), 2.64 (CeH_2 , t, ^{3}J=5.5), 6.97 (C2"H, d, ^{3}J=2.5), 7.96 (C4"H, d, ^{3}J=1.5), 7.21 (C6"H, dd, ^{3}J=8.5, ^{4}J=1.5), 7.17 (C7"H, d, ^{3}J=8.5), 8.97 (NH, bs)

^{13}C NMR ($CDCl_3$, 125 MHz) : 148.9 (C1), 160.2 (C3), 104.8 (C4), 143.6 (C4a), 121.4 (C5), 132.5 (C6), 110.8 (C7), 127.8 (C8), 132.8 (C1'), 131.2 (C2', C6'), 128.8 (C3', C5'), 127.9 (C4'), 42.5 ($C1^x$), 25.5 ($C2^x$), 24.6 ($C3^x$), 58.0 ($C4^x$), 53.2 (Ca), 119.3 (Cb), 126.8 (Cc), 28.9 (Cd), 50.2 (Ce), 122.7 (C2"), 113.1 (C3"), 129.4 (C3"a), 123.1 (C4"), 117.2 (C5"), 124.6 (C6"), 112.7 (C7"), 135.4 (C7"a)

4.1.5.26 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-methylophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.26)**

The title compound was isolated as a orange powder, crystallization from acetonitril, yield: 51.0 %**; m.p.** 296 - 299 °C

HRMS (ESI) calculated for $C_{31}H_{32}N_4O_2NaBr$**:** 605.1528 $(M+Na)^+$ **found** 605.1524**.**

^{1}H NMR ($CDCl_3$,500 MHz) 6.90 (C5H, C6H, m), 6.38 (C7H, m, $^3J_1$=7.5, $^3J_2$=5.0, ^{4}J=2.0), 8.32 (C8H, d, ^{3}J=7.7, ^{4}J=^{5}J=1.0), 7.30 (C2'H, C6'H), 7.23 (C6"H, C7"H, m), 7.19 (C3'H, C5'H, d, ^{3}J=7.0), 4.21 ($C1^xH_2$, t, ^{3}J=7.0), 1.83 ($C2^xH_2$, q), 1.75 ($C3^xH_2$, q), 2.67 ($C4^xH$, t), 3.30 (CaH_2 , ps), 6.02 (CbH, ps), 2.55 (CdH_2 , ps), 2.81 (CeH_2 , ps), 7.05 (C2"H, d, ^{3}J=2.0), 7.90 (C4"H, ps), 8.86 (NH, bs), 2.37 (CH_3)

^{13}C NMR ($CDCl_3$, 125 MHz) : 149.0 (C1), 160.4 (C3), 104.8 (C4), 143.6 (C4a), 121.6 (C5, Cb), 132.3 (C6), 110.7 (C7), 127.9 (C8), 129.7 (C1'), 131.0 (C2', C6'), 129.5 (C3', C5'),

137.6 (C4'), 42.1 ($C1^x$), 25.3 ($C2^x$), 23.9 ($C3^x$), 57.6 ($C4^x$), 52.5 (Ca), 126.7 (Cc), 19.7 (Cd), 50.0 (Ce), 122.8 (C2"), 113.3 (C3"), 129.4 (C3"a), 123.0 (C4"), ~117.0 (C5"), 124.9 (C6"), 112.9 (C7"), 135.4 (C7"a), 21.3 (CH_3)

4.1.5.27. 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-methoxyphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione (**8.27)**

The title compound was isolated as a white powder, crystallization from acetonitril yield: 90.1 % **m.p.** 142-145 °C

HRMS (ESI) calculated for $C_{32}H_{31}N_4O_3NaBr$**:** 621.1477 $(M+Na)^+$ **found** 621.1462**.**

^{1}H NMR ($CDCl_3$, 500 MHz) : 6.87 (C5H, C6H, m), 6.36 (C7H, m, $^3J_1$=11.5, $^3J_2$=7.5, ^{4}J=4.0), 8.30 (C8H, dt, ^{3}J=7.5, $^4J=^5$J=1.0), 7.10-7.22 (C2'H, C6'H, C6"H, C7"H, m), 6.94 (C3'H, C5'H, dt, ^{3}J=8.5, ^{4}J=1.5), 4.22 ($C1^xH_2$, t, ^{3}J=7.5), 1.83 ($C2^xH_2$, q, ^{3}J=7.5), 1.68 ($C3^xH_2$, q, ^{3}J=7.5), 2.52 ($C4^x$H , t, ^{3}J=7.5), 3.16 (CaH_2 , d, ^{3}J=2.0), 6.06 (CbH, t), 2.35 (CdH_2 , ps), 2.62 (CeH_2 , t, ^{3}J=6.0), 6.91 (C2"H, d, ^{3}J=2.0), 7.98 (C4"H, d, ^{3}J=1.5), 3.79 (OCH_3, s), 9.33 (NH, bs)

^{13}C NMR ($CDCl_3$, 125 MHz) : 148.9 (C1), 160.5 (C3), 104.4 (C4), 143.6 (C4a), 121.5 (C5), 132.3 (C6), 110.7 (C7), 127.8 (C8), 124.7 (C1'), 132.3 (C2', C6'), 114.2 (C3', C5'), 159.1 (C4'), 42.5 ($C1^x$), 25.5 ($C2^x$), 24.5 ($C3^x$), 58.0 ($C4^x$), 53.1 (Ca), 119.0 (Cb), 126.8 (Cc), 28.8 (Cd), 50.2 (Ce), 123.0 (C2"), 113.0 (C3"), 129.4 (C3"a), 123.0 (C4"), 116.9 (C5"), 124.5 (C6"), 112.8 (C7"), 135.5 (C7"a), 55.3 (OCH_3)

4.1.5.28 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-chlorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.28)**

The title compound was isolated as a white powder, crystallization from acetonitril, yield: 59.6 % **; m.p.** 220-228 °C

HRMS (ESI) calculated for $C_{31}H_{29}N_4O_2ClBr$**:** 603.1162 $(M+H)^+$ **found** 603.1183**.**

^{1}H NMR ($CDCl_3$, 500 MHz) : 6.87 (C5H, dt, ^{3}J=9.5, $^4J=^5$J=1.0), 6.95 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.5, ^{4}J=1.0), 6.41 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.5, ^{4}J=1.5), 8.35 (C8H, dt, ^{3}J=7.5), 7.40 (C2', C6'H, dt, ^{3}J=8.5, ^{4}J=2.0), 7.20-7.28 (C3'H, C5'H, C6"H, C7"H, m), 4.21 ($C1^xH_2$, t, ^{3}J=7.5), 1.82 ($C2^xH_2$, q), 1.71 ($C3^xH_2$, q), 2.59 ($C4^x$H , t, ^{3}J=7.5), 3.24 (CaH_2 , ps), 6.07 (CbH, ps), 2.52 (CdH_2 , ps), 2.74 (CeH_2 , t, ^{3}J=5.5), 7.07 (C2"H, ps), 7.94 (C4"H, ps), 8.72 (NH, bs)

^{13}C NMR ($CDCl_3$, 125 MHz) : 148.9 (C1), 160.0 (C3), 103.5 (C4), 143.7 (C4a), 121.1 (C5), 133.0 (C6), 110.9 (C7), 128.2 (C8), 131.3 (C1'), 132.7 (C2', C6'), 129.0 (C3', C5'), 133.7 (C4'), 42.4 ($C1^x$), 25.5 ($C2^x$), 24.3 ($C3^x$), 57.8 ($C4^x$), 52.9 (Ca), 119.0 (Cb), 126.8 (Cc), 29.7 (Cd), 50.2 (Ce), 122.6 (C2"), 113.3 (C3"), 129.4 (C3"a), 123.2 (C4"), 117.3 (C5"), 124.9 (C6"), 112.8 (C7"), 135.4 (C7"a)

4.1.5.29 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(4-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.29)**

The title compound was isolated as a yellow powder, crystallization from absolute ethanol yield: 71.0 % **m.p.** 195 - 201 °C

HRMS (ESI) calculated for $C_{31}H_{29}N_4O_2FBr$**:** 587.1458 $(M+H)^+$ **found** 587.1432**.**

^{1}H NMR ($CDCl_3$, 500 MHz) : 6.84 (C5H, dt, ^{3}J=9.5), 6.93 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.0, ^{4}J=1.0), 6.39 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.0, ^{4}J=1.0), 8.33 (C8H, dt, ^{3}J=7.5), 7.25 – 7.30 (C2', C6'H, m), 7.12 (C3'H, C5'H, m), 4.21 ($C1^xH_2$, t, ^{3}J=7.5), 1.82 ($C2^xH_2$, q, ^{3}J=7.5), 1.69 ($C3^xH_2$, q, ^{3}J=7.5), 2.53 ($C4^x$H , t, ^{3}J=7.5), 3.19 (CaH_2 , d, ^{3}J=2.5), 6.10 (CbH, t), 2.46 (CdH_2 , ps), 2.67 (CeH_2 , t, ^{3}J=6.0), 7.04 (C2"H, d, ^{3}J=2.0), 7.97 (C4"H, d, ^{4}J=1.5), 7.23 (C6"H, dd, ^{3}J=9.0, ^{4}J=1.5), 7.19 (C7"H, d, ^{3}J=9.0), 8.67 (NH, bs)

^{13}C NMR ($CDCl_3$, 125 MHz) : 148.9 (C1), 160.2 (C3), 103.7 (C4), 143.7 (C4a), 121.1 (C5), 132.8 (C6), 110.8 (C7), 128.1 (C8), 128.6 (C1', d*, ^{4}J=3.4), 133.0 (C2', C6', d*, ^{3}J=7.8), 115.8 (C3', C5', d*, ^{2}J=21.4), 162.3 (C4', d*, ^{1}J=247.0), 58.0 ($C1^x$), 25.5 ($C2^x$), 24.6 ($C3^x$), 58.0 ($C4^x$), 53.2 (Ca), 119.6 (Cb), 126.9 (Cc), 29.0 (Cd), 50.3 (Ce), 122.5 (C2"), 113.2 (C3"), 129.3 (C3"a), 123.2 (C4"), 117.5 (C5"), 124.8 (C6"), 112.7 (C7"), 135.4 (C7"a)

4.1.5.30 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-fluorophenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.30)**

The title compound was isolated as a white powder, crystallization from absolute alcohol, yield: 61.3 % **; m.p.** 151-157 °C

HRMS (ESI) calculated for $C_{31}H_{29}N_4O_2FBr$**:** 587,1458 $(M+H)^+$ **found** 587,1474

^{1}H NMR (see *supplementary materials*) ($CDCl_3$, 500 MHz) : 6.71 (C5H, dt, ^{3}J=9.5), 6.97 (C6H, C2"H, m), 6.41 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.5, ^{4}J=1.5), 8.34 (C8H, dt, ^{3}J=7.5, ^{4}J=1.0), 7.14 (C3'H, C7"H, m), 7.34 (C4'H, m), 7.19 (C5'H, C6"H, m), 7.28 (C6'H, m), 4.22

($C1^xH_2$, t, ^3J=7.0), 1.83 ($C2^xH_2$, q, ^3J=7.5), 1.69 ($C3^xH_2$, q, ^3J=7.5), 2.52 ($C4^xH$, t, ^3J=7.5), 3.16 (CaH_2 , d, ^3J=2.5), 6.07 (CbH, ps), 2.39 (CdH_2 , ps), 2.63 (CeH_2 , t, ^3J=6.0), 7.95 (C4"H, d, ^3J=1.5), 9.17 (NH, bs)

^{13}C NMR (see *supplementary materials*) ($CDCl_3$, 125 MHz) : 148.9 (C1), 159.7 (C3), 98.3 (C4), 144.1 (C4a), 121.1 (C5), 133.2 (C6), 111.0 (C7), 128.1 (C8), 120.3 (C1', d*, ^2J=16.1), 160.9 (C2', d*, ^1J=247.1), 116.0 (C3', d*, ^2J=22.4), 130.1 (C4', d*, ^3J=8.3), 124.4 (C5', d*, ^4J=3.4), 133.4 (C6', d*, ^3J=2.9), 42.6 ($C1^x$), 25.5 ($C2^x$), 24.5 ($C3^x$), 58.0 ($C4^x$), 53.1 (Ca), 119.2 (Cb), 126.9 (Cc), 28.9 (Cd), 50.2 (Ce), 122.8 (C2"), 113.0 (C3"), 129.4 (C3"a), 123.1 (C4"), 117.1 (C5"), 124.6 (C6"), 112.8 (C7"), 135.4 (C7"a)

4.1.5.31 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-methylphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione (**8.31)**

The title compound was isolated as a yellow crystals, crystallization from absolute alcohol, yield: 84.0 % **; m.p.** 136 - 140 °C

HRMS (ESI) calculated for $C_{32}H_{31}BrN_4O_2Na$**:** 605.1528 $(M+Na)^+$ **found** 605.1535**.**

^1H NMR (CD_2Cl_2 , 500 MHz) : 6.50 (C5H, dt, ^3J=9.5), 6.89 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.5, ^4J=1.5), 6.39 (C7H, m, $^3J_1$=7.5, $^3J_2$=6.0, ^4J=1.5), 8.32 (C8H, dt, ^3J=7.0, ^4J=^5J=1.0), 7.12 (C3'H, d, ^3J =7.0), 7.25 (C4'H, C5'H, C7"H, m), 7.31 (C6'H, C6"H m), 4.19 ($C1^xH_2$, t, ^3J=7.5), 1.80 ($C2^xH_2$, q), 1.66 ($C3^xH_2$, q), 2.52 ($C4^xH$, t, ^3J=7.5), 3.16 (CaH_2 , d, ^3J=3.0), 6.09 (CbH), 2.44 (CdH_2 , ps), 2.66 (CeH_2 , m), 7.09 (C2"H, d, ^3J =2.0), 7.97 (C4"H, d, ^4J=1.5), 2.12 (CH_3, s), 8.96 (NH, bs)

^{13}C NMR ($CDCl_3$, 125 MHz) : 149.6 (C1), 160.1 (C3), 104.3 (C4), 144.1 (C4a), 121.7 (C5), 132.2 (C6), 111.1 (C7), 128.5 (C8), 133.3 (C1'), 139.4 (C2'), 130.9 (C3'), 128.7 (C4'), 126.7 (C5'), 133.2 (C6'), 42.7 ($C1^x$), 26.0 ($C2^x$), 25.0 ($C3^x$), 58.4 ($C4^x$), 53.8 (Ca), 119.9 (Cb), 127.3 (Cc), 29.5 (Cd), 50.7 (Ce), 123.5 (C2", C4"), 113.5 (C3"), 129.8 (C3"a), 117.7 (C5"), 125.1 (C6"), 113.5 (C7"), 136.1 (C7"a), 19.8 (CH_3)

4.1.5.32 2-{4-[4-(5-bromo-1H-indol-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-butyl}-4-(2-methoxyphenyl)-pyrido[1,2-c]pyrimidine-1,3-dione **(8.32)**

The title compound was isolated as a yellow crystals, crystallization from absolute alcohol, yield: 78.0 % **; m.p.** 139 - 141 °C

HRMS (ESI) calculated for $C_{32}H_{32}BrN_4O_3$**:** 599.1658 $(M+H)^+$ **found** 599.1640**.**

^{1}H NMR (CD_2Cl_2 , 500 MHz) : 6.62 (C5H, d, ^{3}J=9.5), 6.87 (C6H, 4d, $^3J_1$=9.5, $^3J_2$=6.5, ^{4}J=1.5), 6.35 (C7H, m, $^3J_1$=8.0, $^3J_2$=6.0, ^{4}J=1.5), 8.31 (C8H, dt, ^{3}J=7.5), 6.96 (C3'H, d, ^{3}J =8.5), 7.35 (C4'H, td, ^{3}J=8.0, ^{4}J=1.5), 7.02 (C5'H, td, ^{3}J=7.0, ^{4}J=1.0), 7.14 – 7.24 (C6'H, C6"H, C7"H, m), 4.22 ($C1^xH_2$, m), 1.83 ($C2^xH_2$, q, ^{3}J=8.0), 1.68 ($C3^xH_2$, q, ^{3}J=8.0), 2.52 ($C4^xH$, t, ^{3}J=8.0), 3.17 (CaH_2 , d, ^{3}J=3.0), 6.08 (CbH, t), 2.44 (CdH_2 , ps), 2.65 (CeH_2 , m), 7.00 (C2"H, d, ^{3}J =2.5), 7.96 (C4"H, d, ^{4}J=1.5), 3.72 (OCH_3, s), 8.87 (NH, bs)

^{13}C NMR ($CDCl_3$, 125 MHz) : 149.1 (C1), 160.1 (C3), 101.2 (C4), 143.7 (C4a), 121.9 (C5), 132.1 (C6), 110.6 (C7), 127.8 (C8), 121.4 (C1'), 157.9 (C2'), 111.4 (C3'), 129.7 (C4'), 120.9 (C5'), 133.0 (C6'), 42.5 ($C1^x$), 25.5 ($C2^x$), 25.6 ($C3^x$), 58.0 ($C4^x$), 53.2 (Ca), 119.2 (Cb), 126.8 (Cc), 28.9 (Cd), 50.2 (Ce), 122.8 (C2"), 113.0 (C3"), 129.4 (C3"a), 123.1 (C4"), 117.1 (C5"), 124.5 (C6"), 112.8 (C7"), 135.5 (C7"a), 55.6 (OCH_3)

4.2 In vitro experiments

All compounds were tested for their affinity towards 5-HT_{1A} and SERT receptors according to procedures described previously with slight modifications [17,18]. Target compounds **8.1** – **8.32** were assessed for in vitro affinity for the 5-HT_{1A} receptor and SERT by radioligand binding assays using [^{3}H] 8-OH-DPAT and [^{3}H]citalopram, respectively, in rat brain tissues.

4.3 Metabolic stability procedure (ADME)

Stock solutions of the studied compounds were made at a concentration of 1 mM in an acetonitrile:water mixture (50:50 v/v). For incubations each compound in solution was diluted to 10 μM with 100 μM NADPH (Sigma-Aldrich, St. Louis, MO, USA) in potassium phosphate buffer (0.1 M, pH 7.4). Incubation was carried out in a water bath at 37 °C and initiated by adding pooled human liver microsomes (HLM) to a final concentration of 0.53 mg/mL (Sigma-Aldrich, St. Louis, MO, USA). Directly after the HLM were added and after 60 min. of incubation, the reaction was ended by adding an equal volume of cold acetonitrile. The samples were immediately centrifuged (10 min. and 10 000 rpm) and the resulting supernatant was kept at -80°C until LC-MS analysis.

LC-MS analysis was performed on an Agilent 1260 system coupled to a SingleQuad 6120 mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). The amount of remaining parent compound was determined accurately using calibration curves (at. 0.1, 0.5. and 1.0 μM

conc.) prepared previously with the same procedure as the biotransformation incubations. A Poroshell C18 EC120 column (3.0 x 100 mm, 2.7 μm, Agilent Technologies, Santa Clara, CA, USA) was used in reverse-phase mode with gradient elution starting with 5% of phase A (0.1% formic acid in water) and 95% phase B (0.1% formic acid in acetonitrile). The amount of phase B was linearly increased to 100% over 30 minutes. The total analysis time was 42 min at 25°C, the flow rate was 0.25 mL/min and the injection volume was 20 μL. The mass spectrometer was equipped with an electrospray ionization source and the ionization mode was positive. A mass analyser was set individually for each derivative to detect pseudomolecular ions [$M+H^+$]. The MSD parameters of the ESI source were as follows: nebulizer pressure 40 psi (N_2), drying gas 10 mL/min (N_2), drying gas temperature 300 °C, capillary voltage 3 kV.

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List of captions:

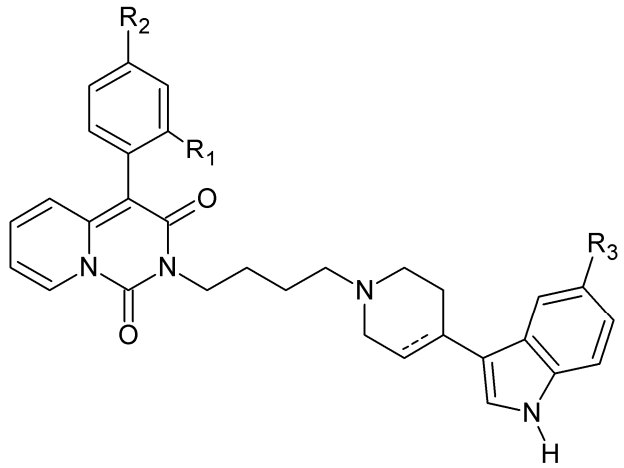
Fig. 1. General structure of pyrido[1,2-*c*]pyrimidines with dual 5-HT_{1A}/SERT activity.

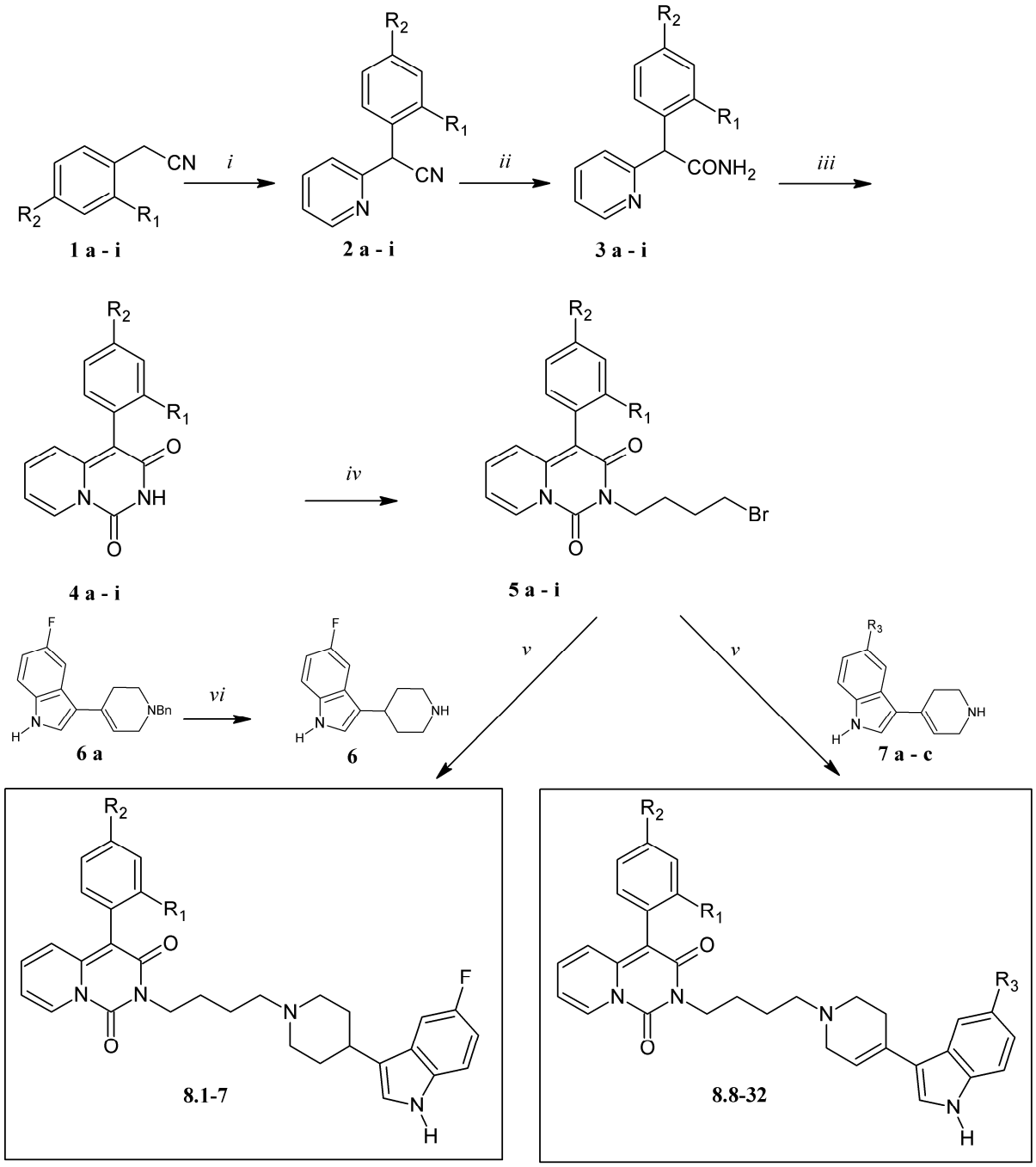
Fig. 2. HLM $t/_{1/2}$ [min] of studied compounds.

Scheme 2[a]. The synthesis pathways of the investigated compounds.

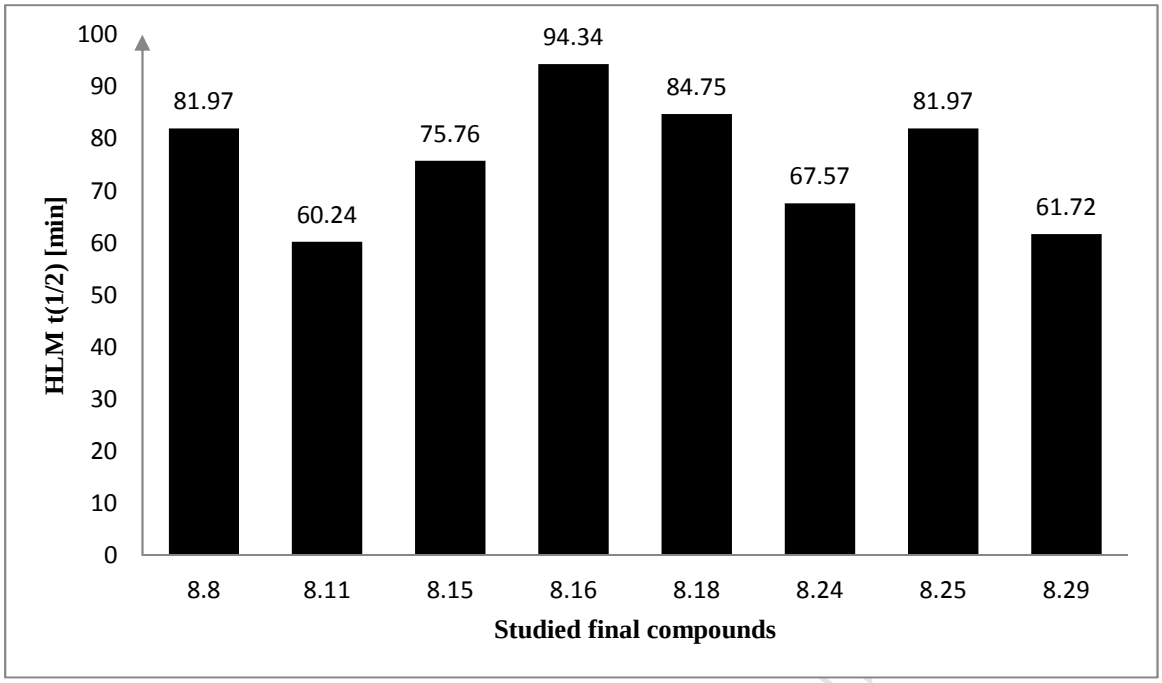
Table 2 SERT and 5-HT_{1A} receptor binding affinities of 3-(piperidin-4-yl)-1*H*-indole derivatives (HHPI) and 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole derivatives (THPI).

Table 2 Metabolic stability of studied compounds.

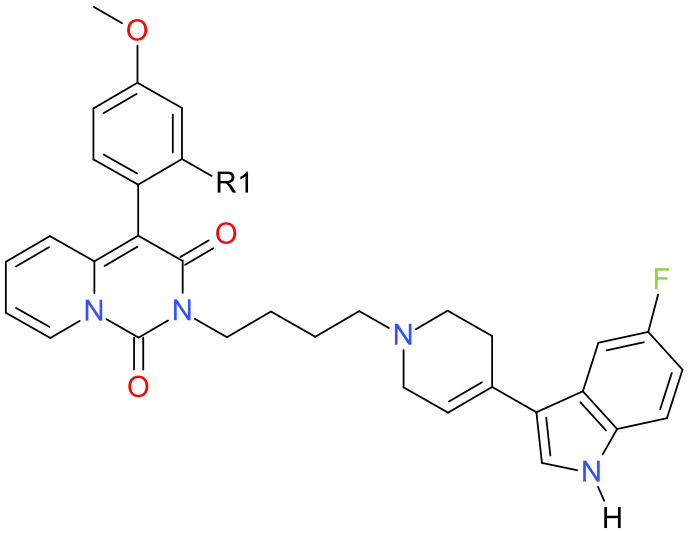




R_1=H, F, Cl, CH_3, OCH_3 R_2= H, F, Cl,CH_3, OCH_3 R_3= F, Br, Cl



- A series of 2H-pyrido[*1,2-c*]pyrimidine derivatives was synthesized.
- The most of tested compounds show dual affinity for 5-HT_{1A} and SERT.
- HHPI series exhibited a high degree of affinity for SERT and 5-HT_{1A}R.
- In vitro tests for metabolic stability in a first-pass test show that R1 and R2 substituents benefit stability.

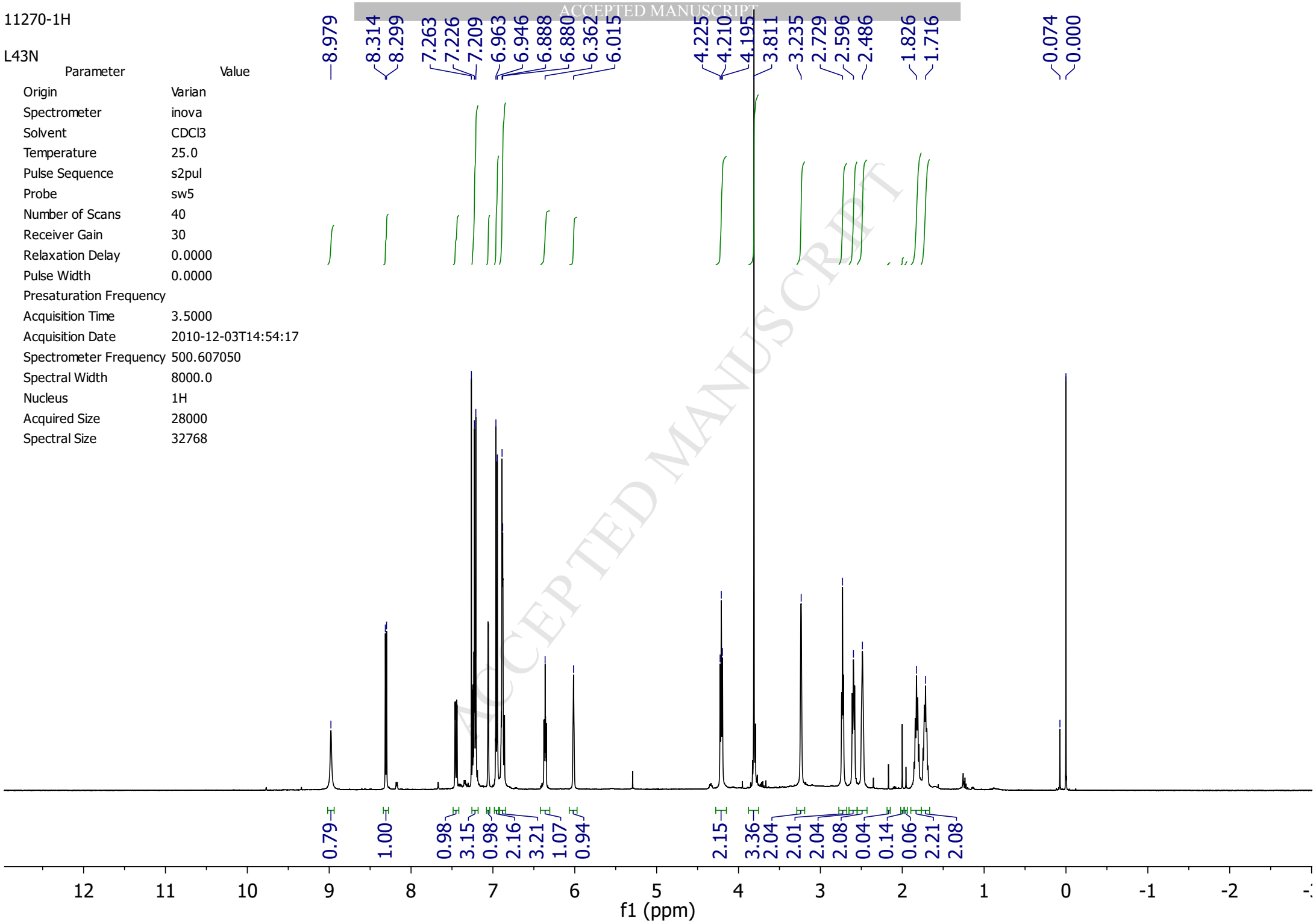


8.10

11270-1H

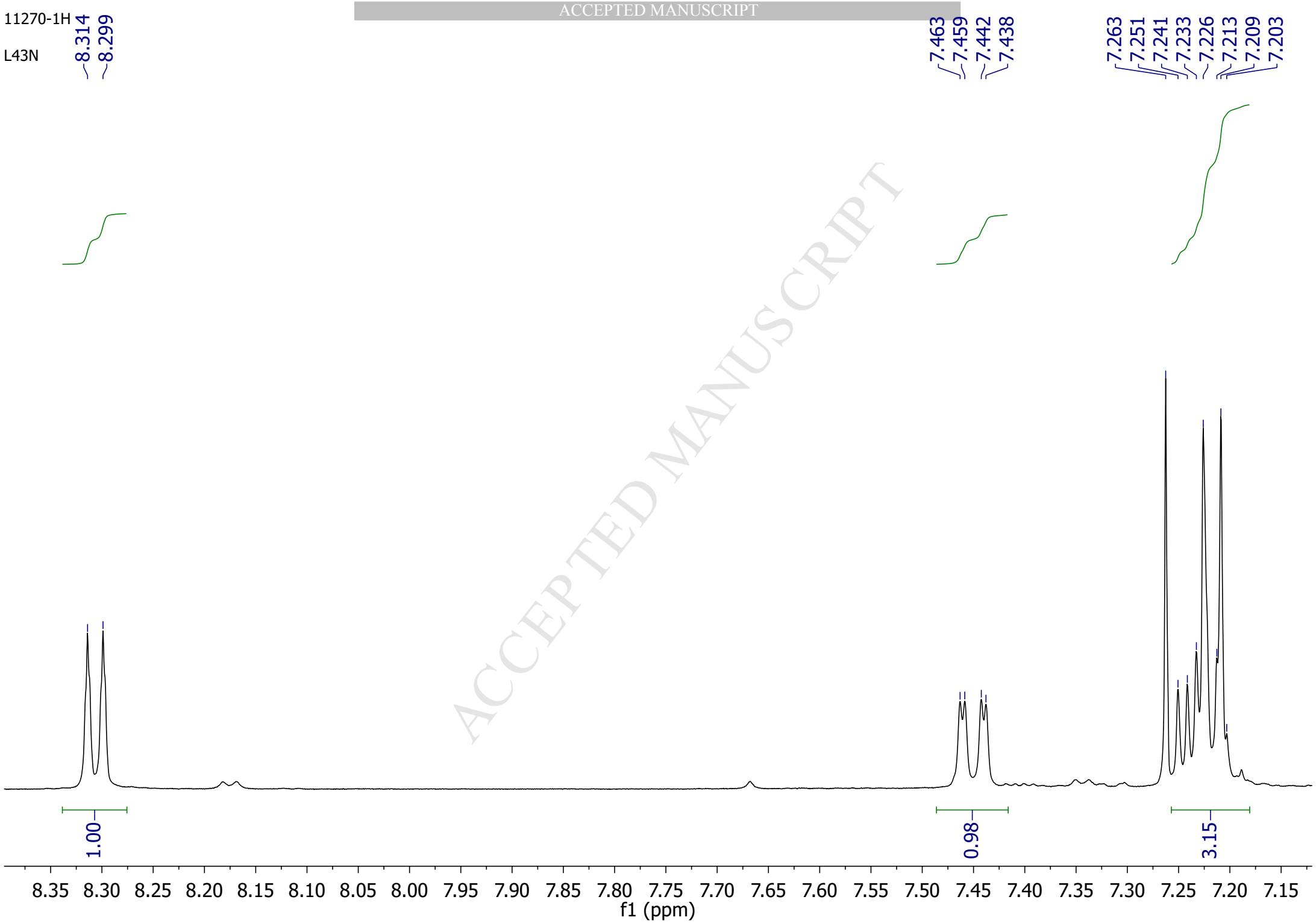
L43N

Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl3
Temperature	25.0
Pulse Sequence	s2pul
Probe	sw5
Number of Scans	40
Receiver Gain	30
Relaxation Delay	0.0000
Pulse Width	0.0000
Presaturation Frequency	
Acquisition Time	3.5000
Acquisition Date	2010-12-03T14:54:17
Spectrometer Frequency	500.607050
Spectral Width	8000.0
Nucleus	1H
Acquired Size	28000
Spectral Size	32768



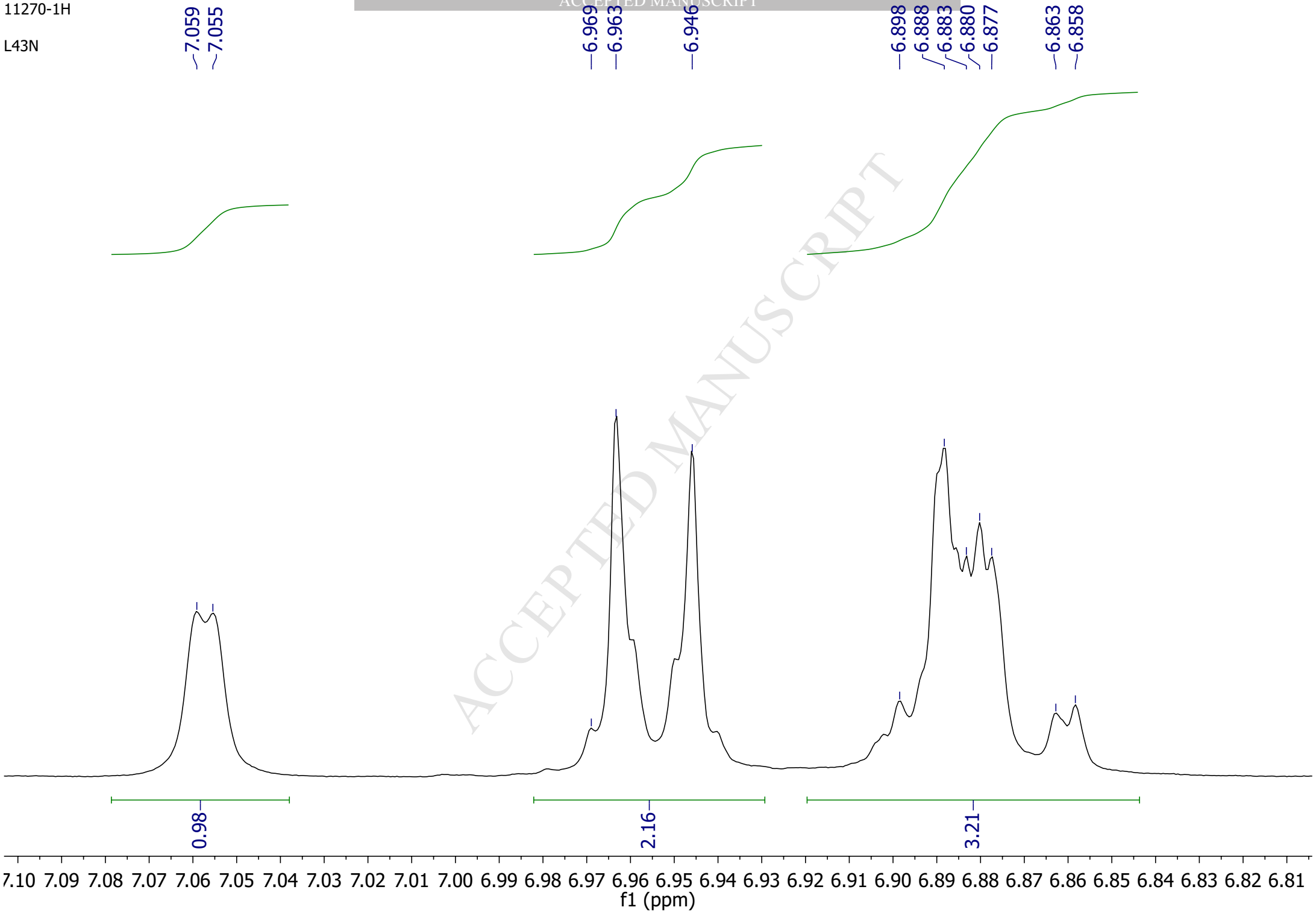
11270-1H

L43N



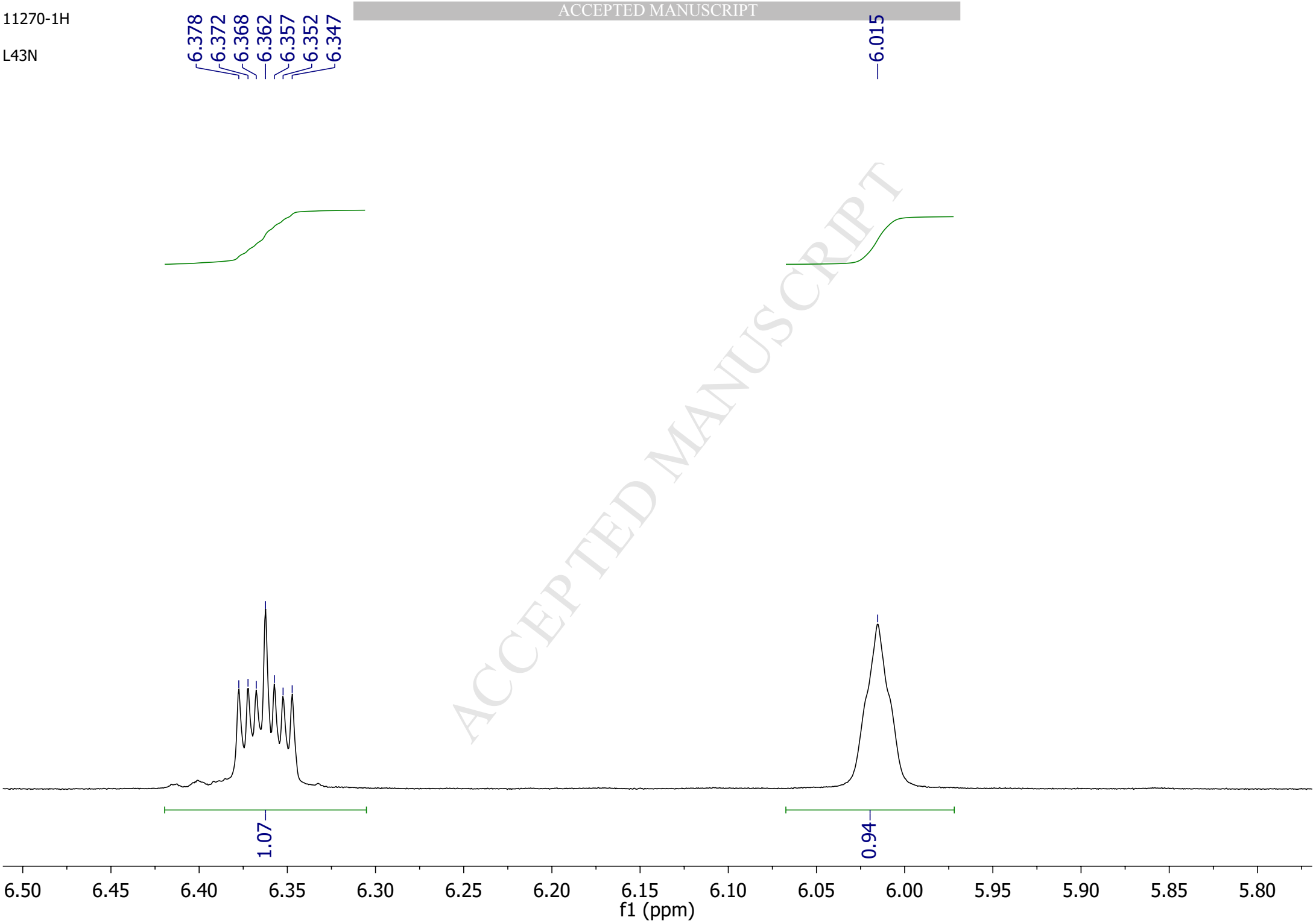
11270-1H

L43N



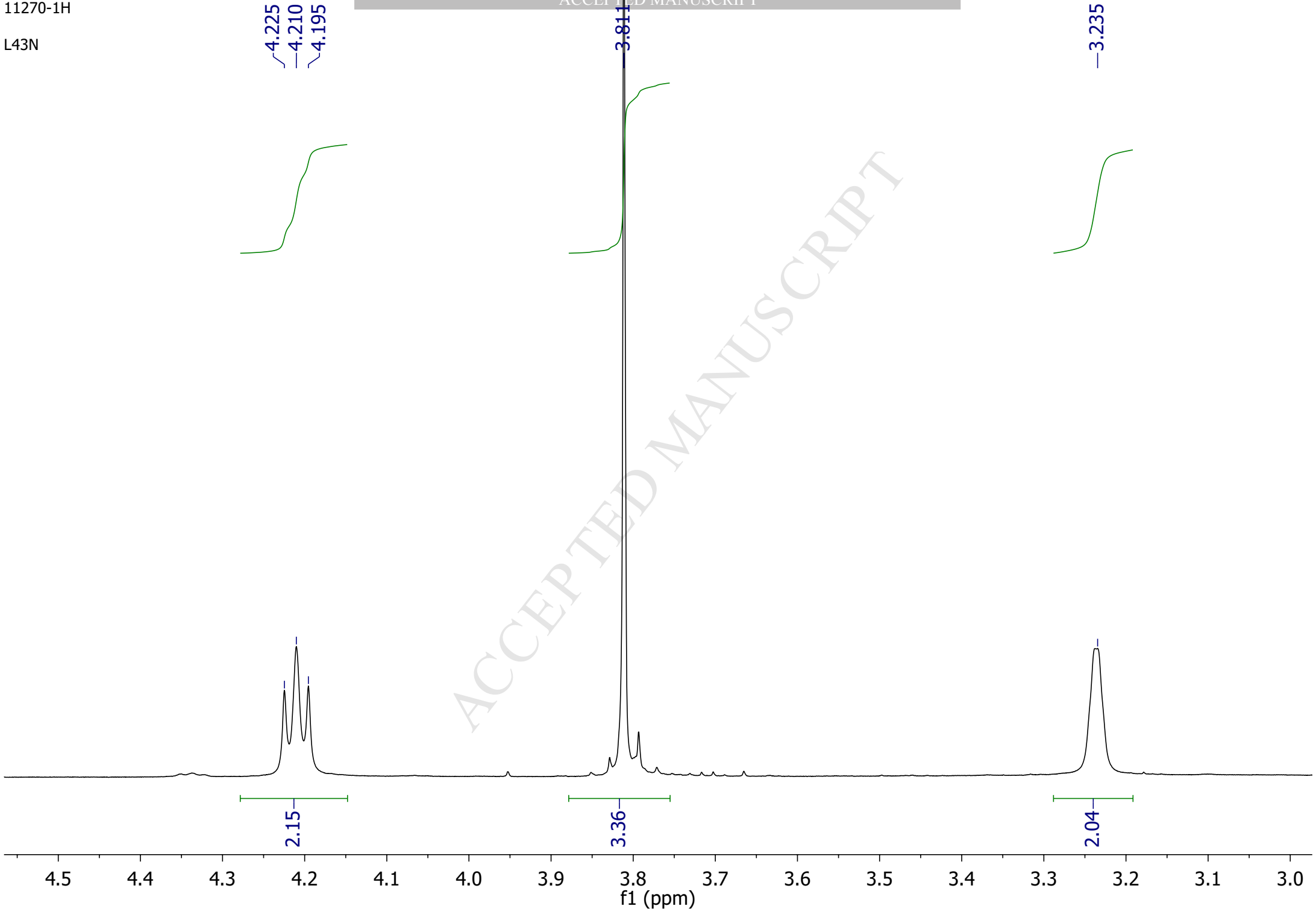
11270-1H

L43N



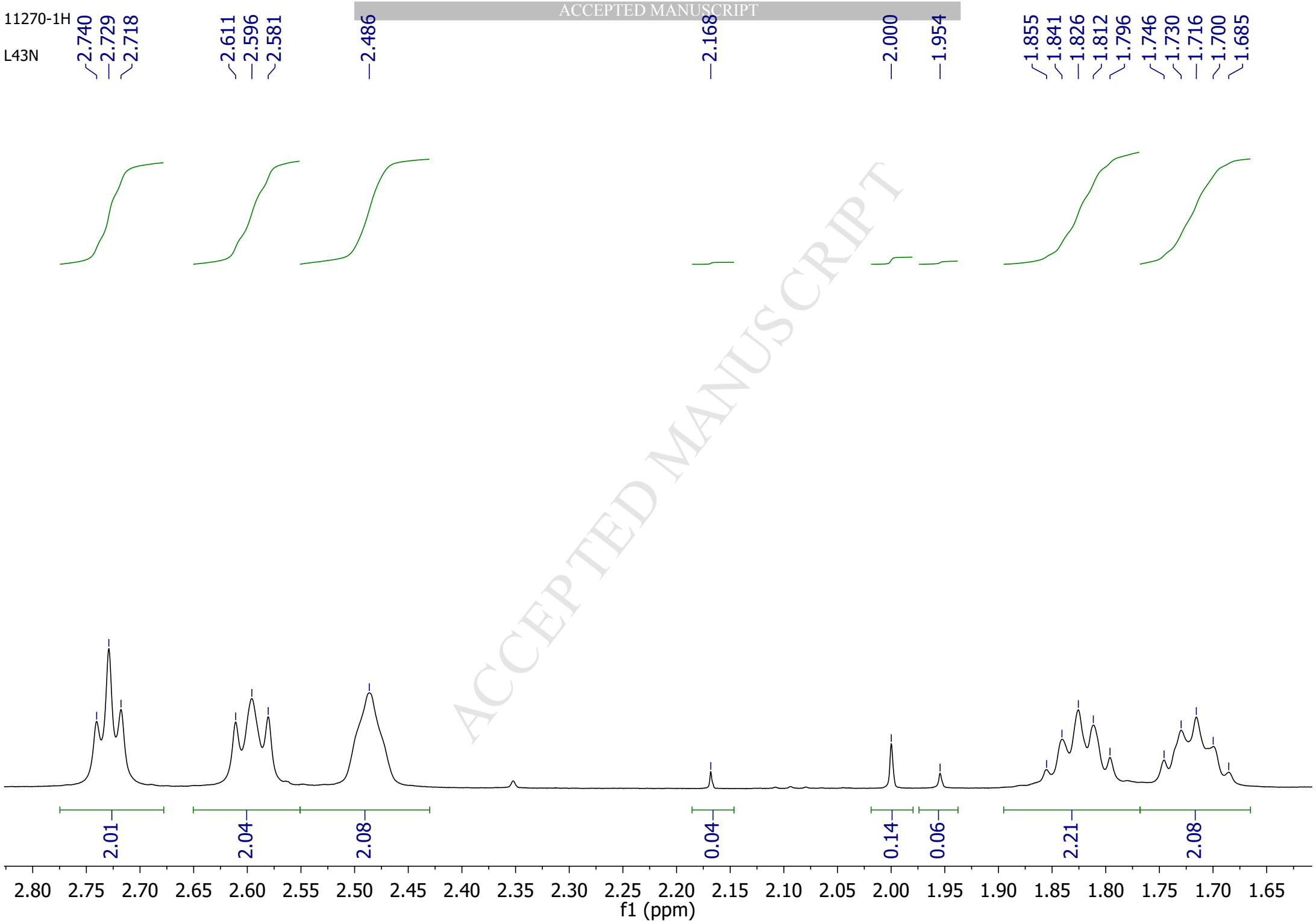
11270-1H

L43N



11270-1H

L43N

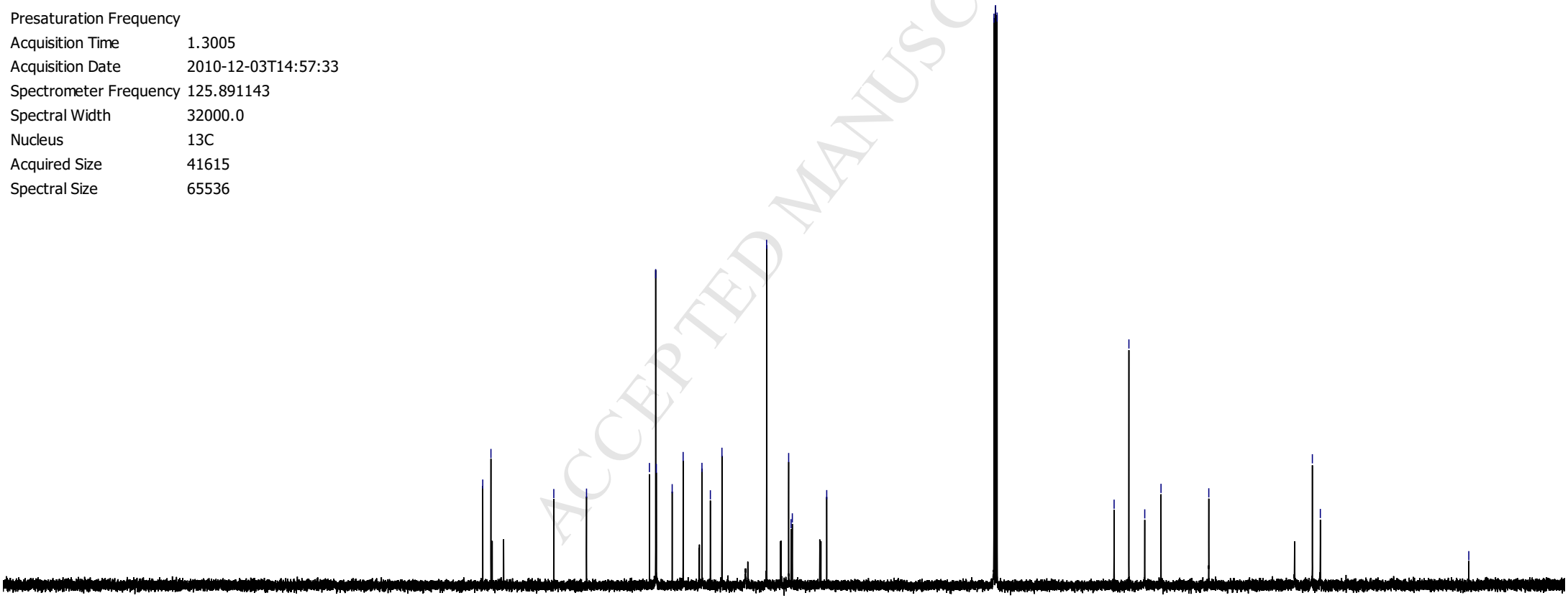


11270-13C

L43N

Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CDCl3
Temperature	25.0
Pulse Sequence	s2pul
Probe	sw5
Number of Scans	616
Receiver Gain	60
Relaxation Delay	1.5000
Pulse Width	0.0000
Presaturation Frequency	
Acquisition Time	1.3005
Acquisition Date	2010-12-03T14:57:33
Spectrometer Frequency	125.891143
Spectral Width	32000.0
Nucleus	13C
Acquired Size	41615
Spectral Size	65536

160.496
159.161
148.931
143.605
133.364
132.347
132.240
129.661
127.879
124.815
123.445
121.563
114.293
110.703
110.313
110.105
104.507
77.284
77.030
76.777
57.729
55.319
52.741
50.094
42.316
25.458
24.159
-0.004



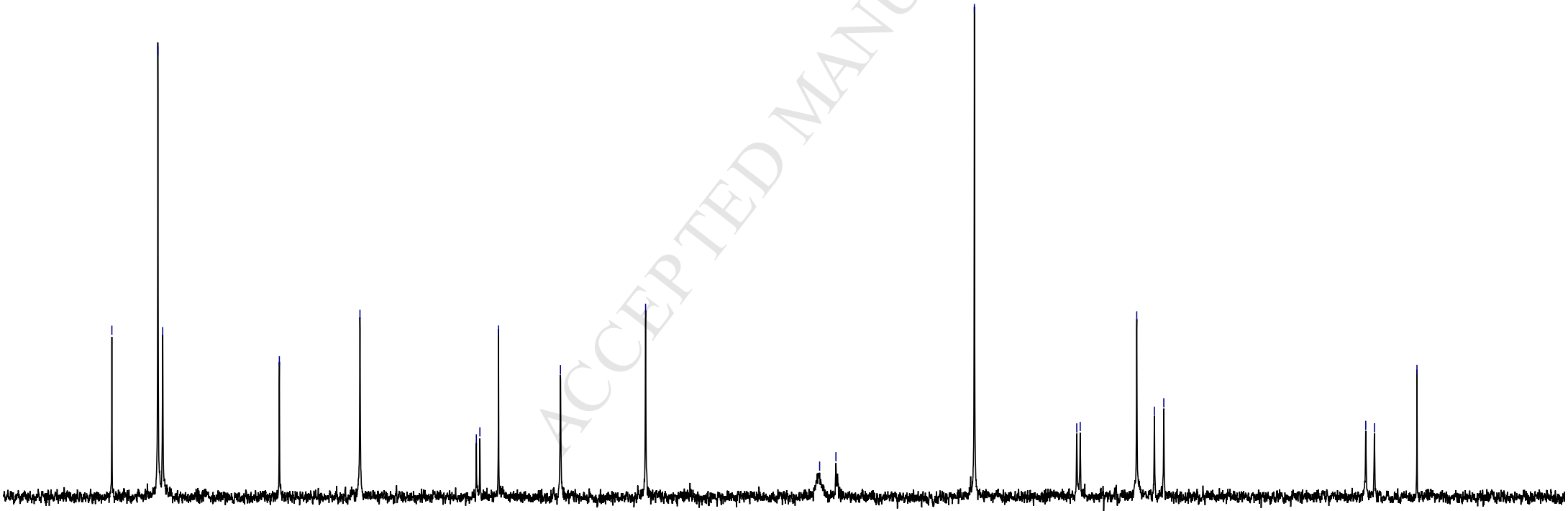
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

11270-13C

L43N

133.364
132.347
132.240
129.661
127.879
125.306
125.227
124.815
123.445
121.563
117.715
117.355
114.293
112.030
111.953
111.433
110.703
110.313
110.105
105.639
105.447
104.507

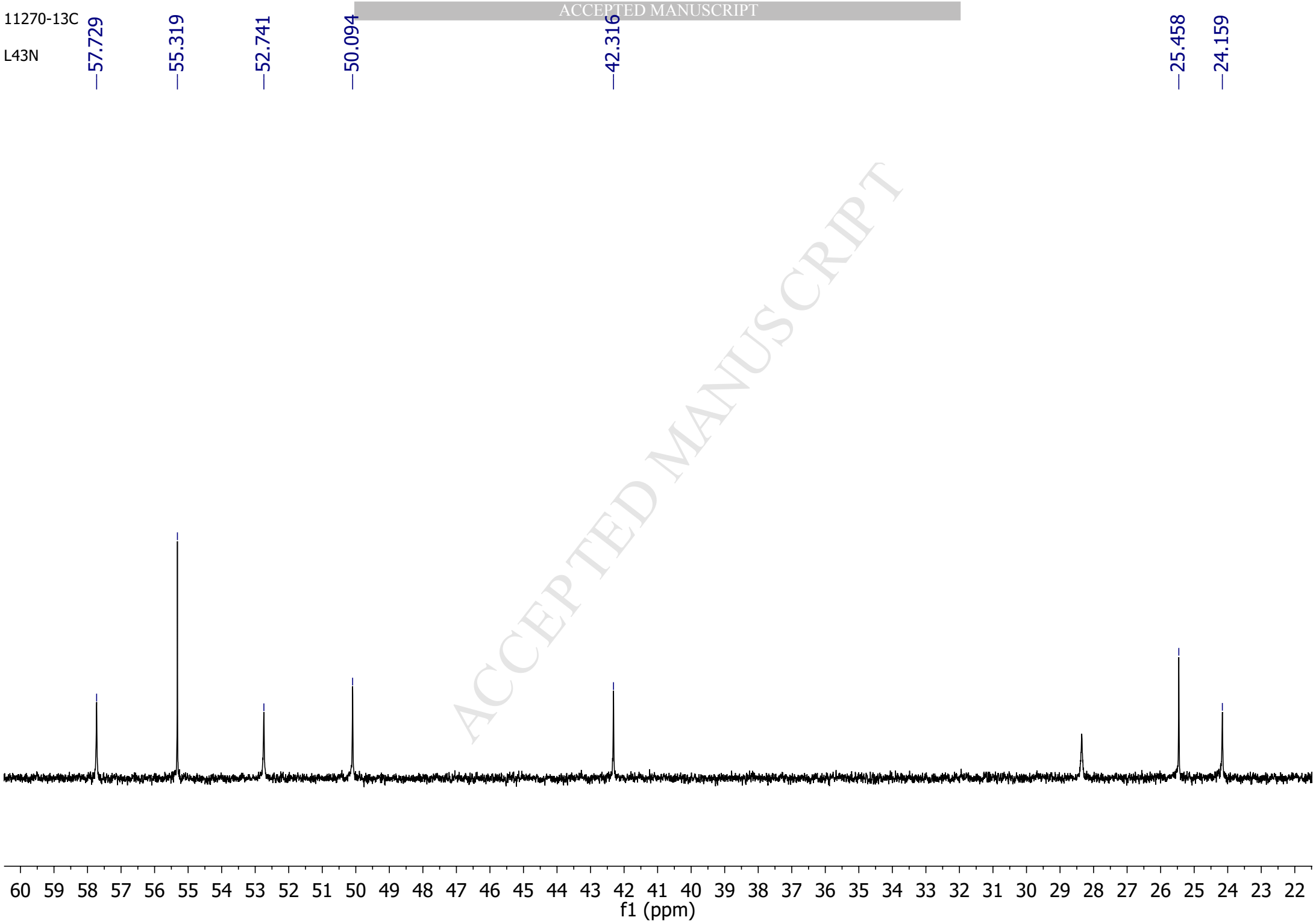


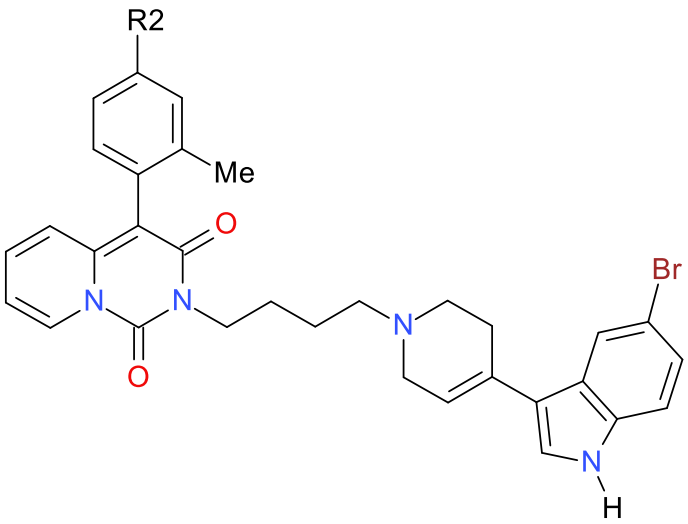
135 134 133 132 131 130 129 128 127 126 125 124 123 122 121 120 119 118 117 116 115 114 113 112 111 110 109 108 107 106 105 104 103 102

f1 (ppm)

11270-13C

L43N



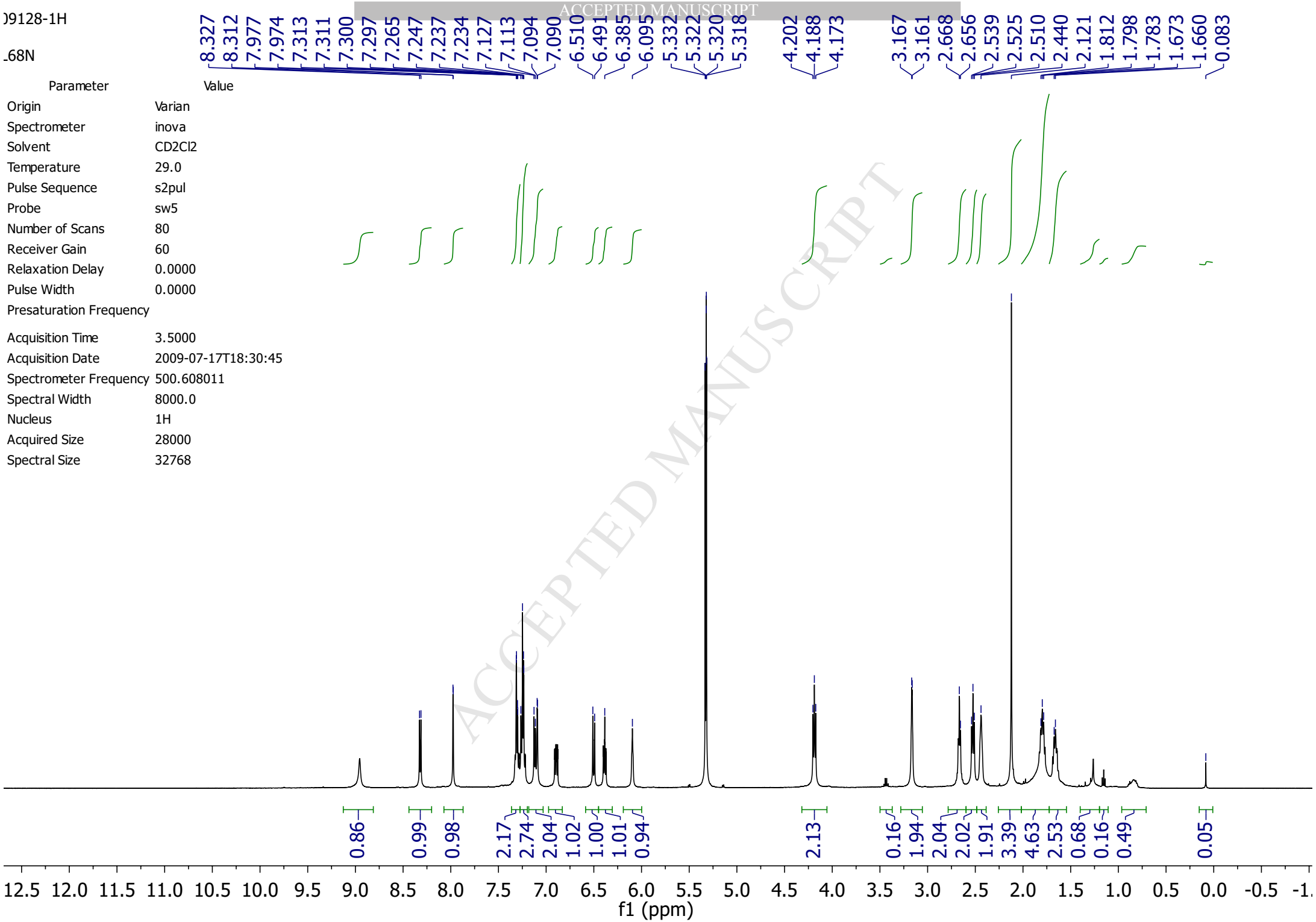


8.31

)9128-1H

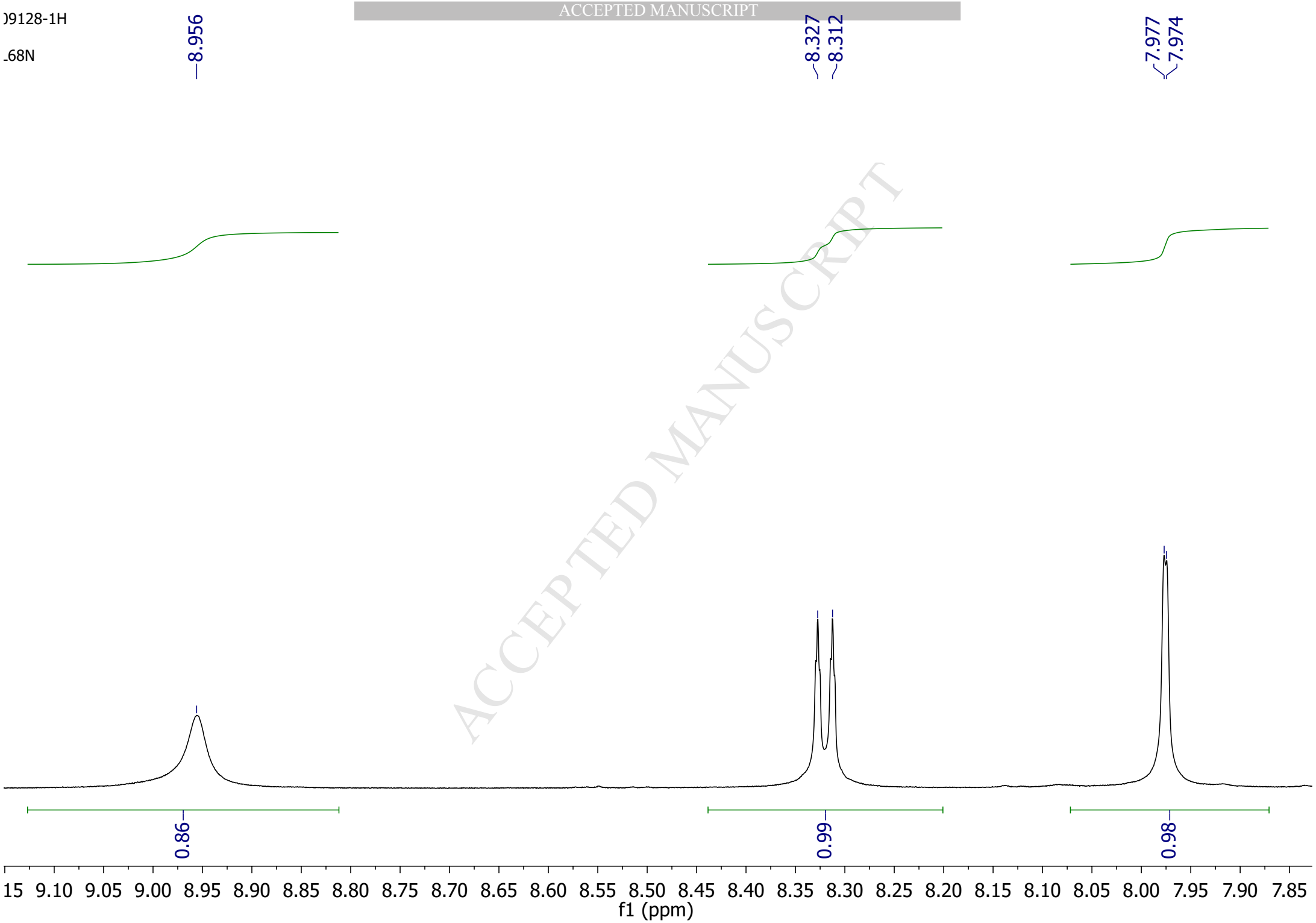
_68N

Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CD2Cl2
Temperature	29.0
Pulse Sequence	s2pul
Probe	sw5
Number of Scans	80
Receiver Gain	60
Relaxation Delay	0.0000
Pulse Width	0.0000
Presaturation Frequency	
Acquisition Time	3.5000
Acquisition Date	2009-07-17T18:30:45
Spectrometer Frequency	500.608011
Spectral Width	8000.0
Nucleus	1H
Acquired Size	28000
Spectral Size	32768



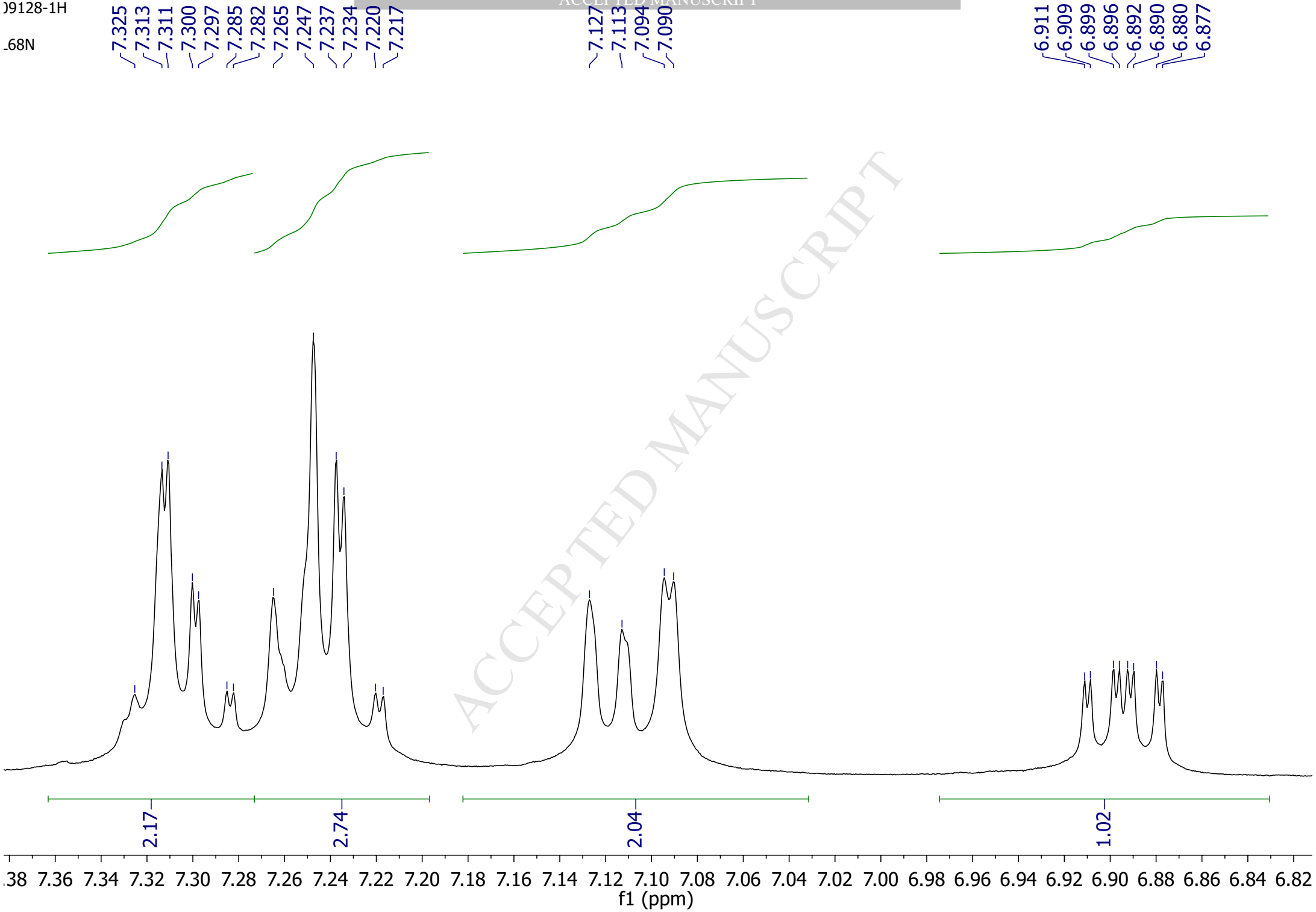
)9128-1H

_68N



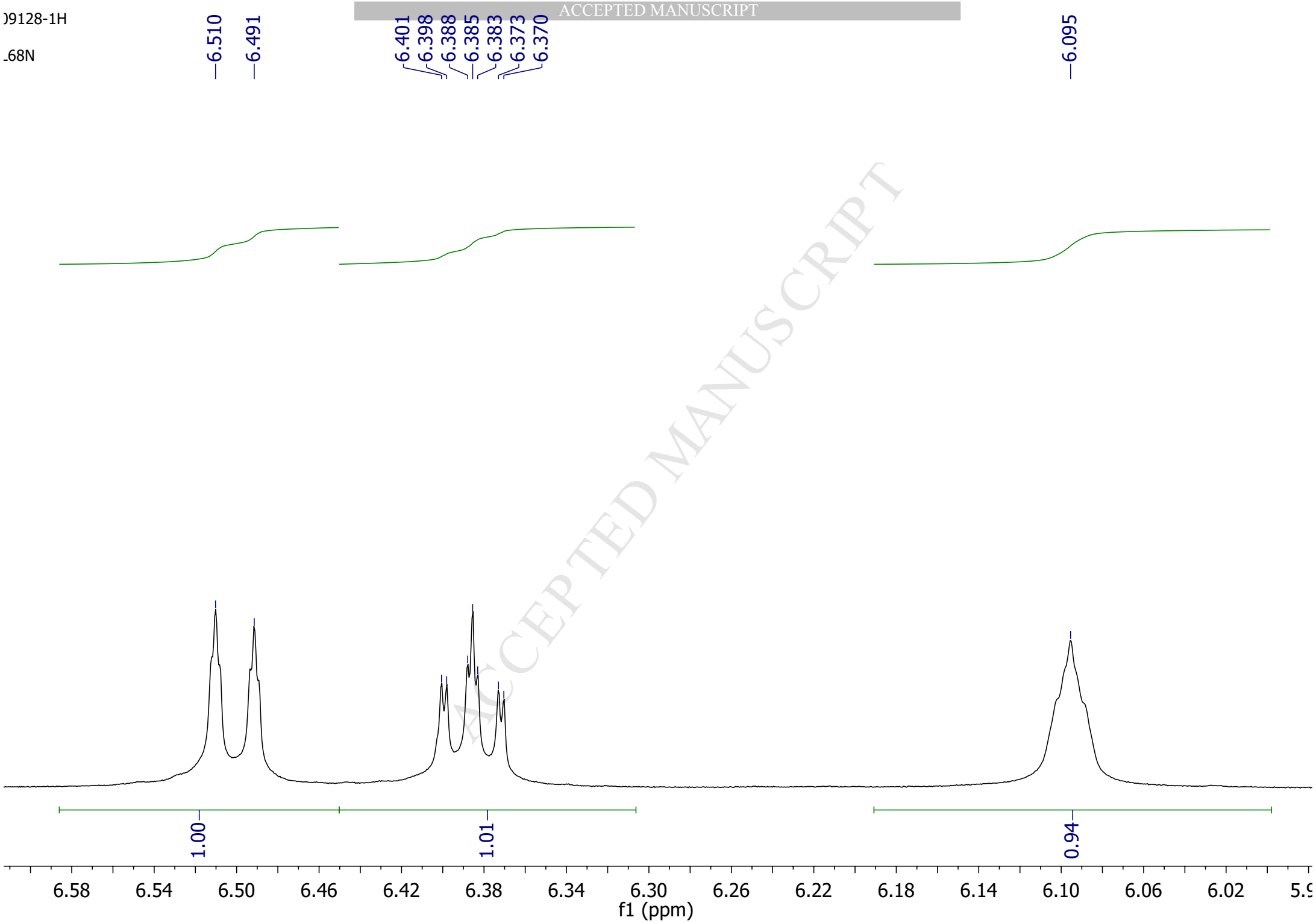
)9128-1H

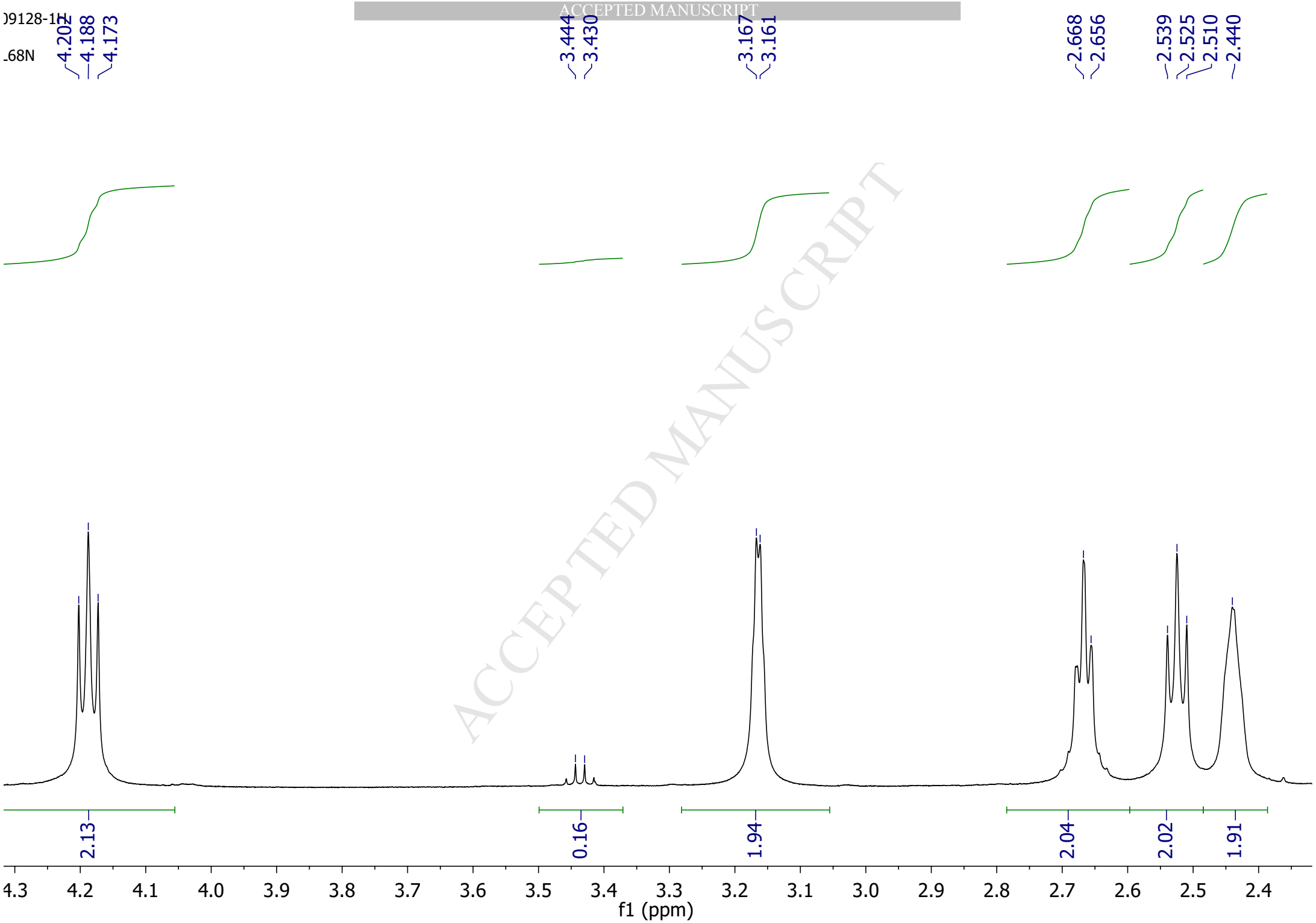
-68N

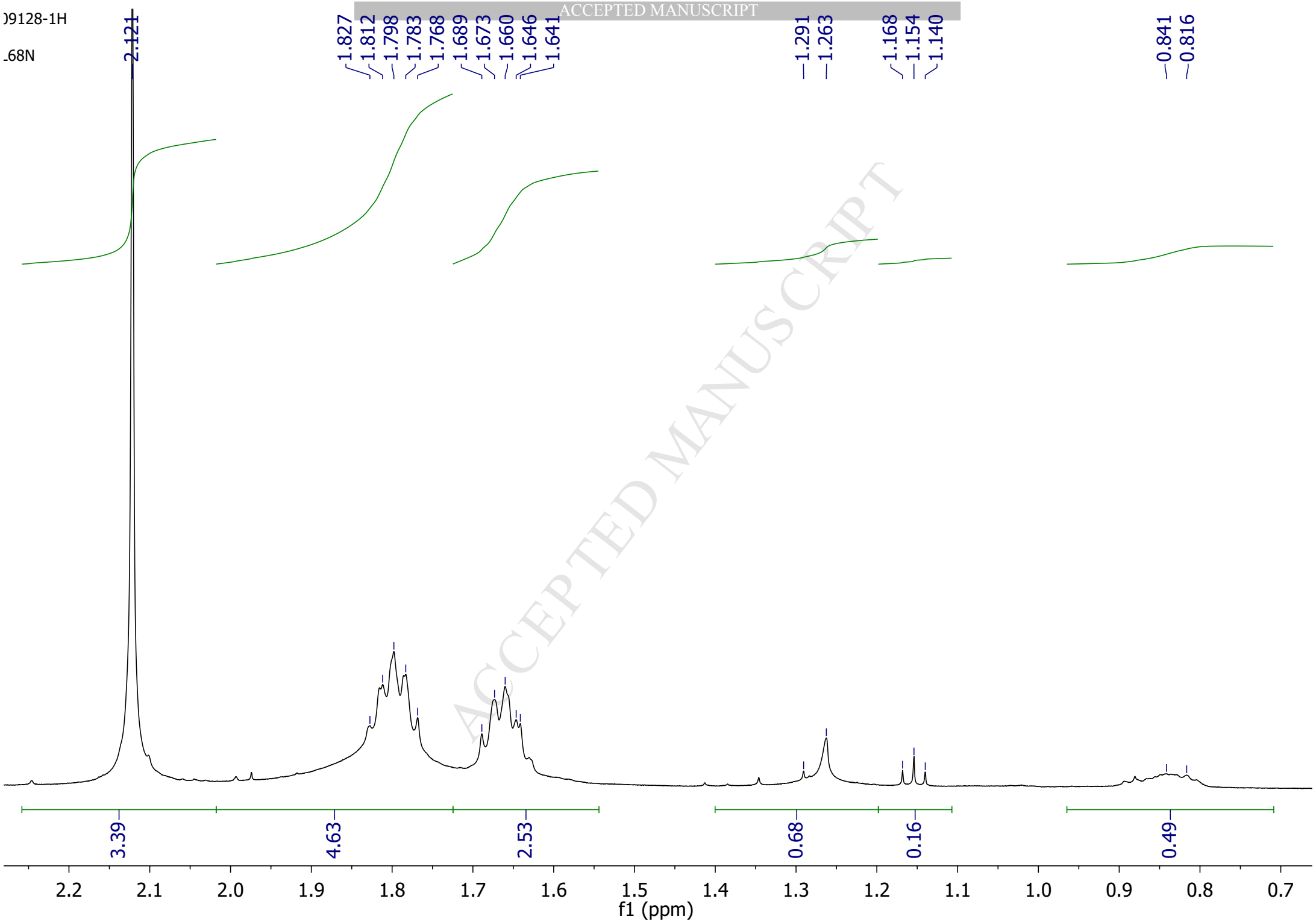


)9128-1H

_68N





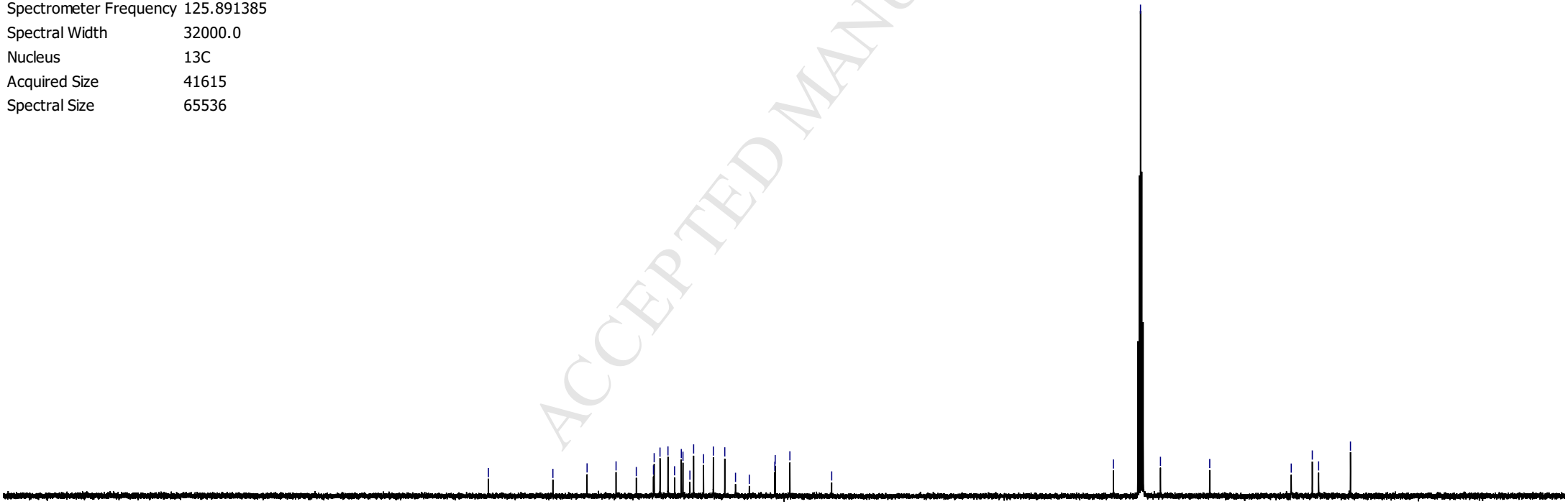


09128-13C

L68N

Parameter	Value
Origin	Varian
Spectrometer	inova
Solvent	CD2Cl2
Temperature	22.0
Pulse Sequence	s2pul
Probe	sw5
Number of Scans	1288
Receiver Gain	60
Relaxation Delay	1.5000
Pulse Width	0.0000
Presaturation Frequency	
Acquisition Time	1.3005
Acquisition Date	2009-07-17T18:51:42
Spectrometer Frequency	125.891385
Spectral Width	32000.0
Nucleus	13C
Acquired Size	41615
Spectral Size	65536

160.139 149.642 144.077 139.359 136.065 133.271 133.155 132.205 130.909 129.835 128.736 128.467 127.339 126.732 125.123 123.524 121.663 119.914 117.672 113.518 113.456 111.066 104.260 58.400 53.996 50.746 42.727 29.460 26.030 25.002 19.818



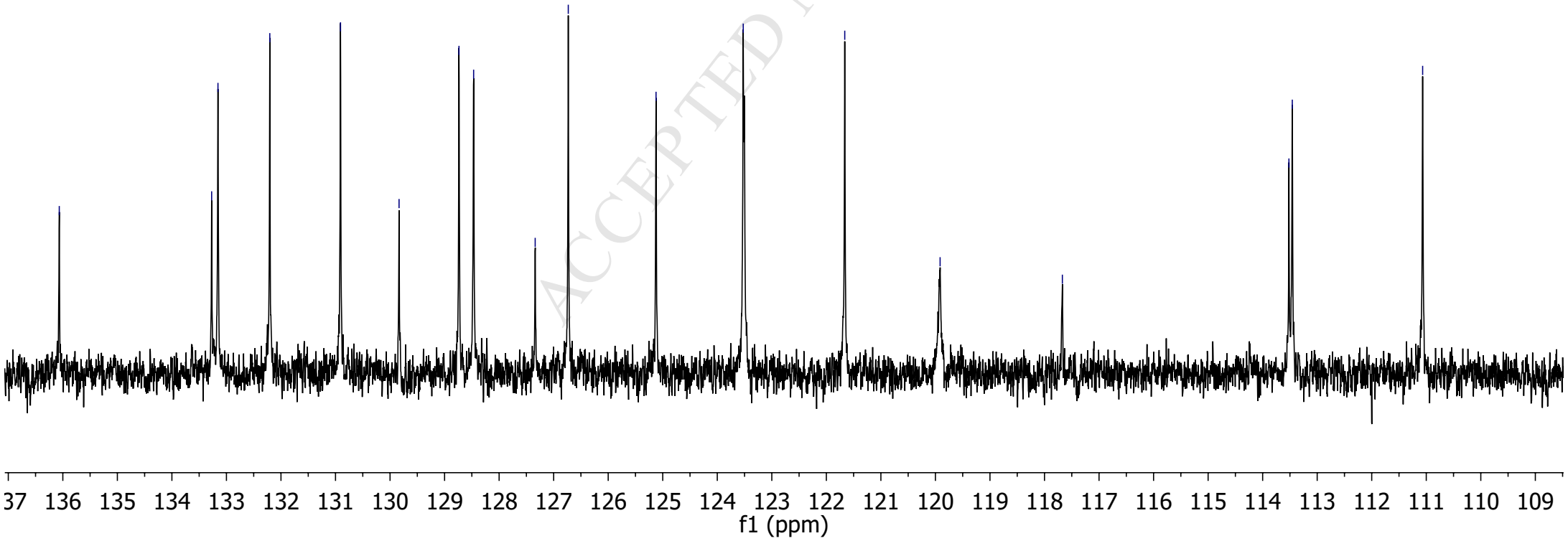
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

09128-13C

L68N

136.061
133.271
133.155
132.205
130.909
129.835
128.736
128.467
127.339
126.732
125.123
123.524
121.663
119.914
117.672
113.518
113.456
111.066



09128-13C

L68N