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Synthesis of 2,4-Disubstituted Pyrimidines of Possible Biological Interest

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SYNTHESIS OF 2,4- DISUBSTITUTED PYRIMIDINES OF POSSIBLE BIOLOGICAL INTEREST

by

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Under the Direction of Dr. Lucjan Strekowski

ABSTRACT

The synthesis of 2,4-disubstituted pyrimidine derivatives is described. The synthetic route involved the addition reaction of lithiated intermediates, mostly heterocycles, to position 4 of 2-chloropyrimidine to give a dihydropyrimidine intermediate which was oxidized back to a pyrimidine. This was followed by nucleophilic aromatic substitution with various amines of the chlorine in the position 2. A number of compounds were prepared which showed binding towards various serotonin receptors in preliminary biological evaluation.

INDEX WORDS: Organic, organic chemistry, synthesis, synthetic, pyrimidine, 2-chloropyrimidine, lithium, lithiated, heterocycle, heterocyclic, serotonin

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Introduction

The 5-hydroxytryptamine (5-HT) is an important neural transmitter which signals a variety of biological and neurological functions. Recent discoveries and advances in the study of the 5-HT receptor family have opened the area to much further work and review.

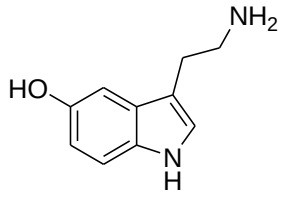


Figure 1. 5-Hydroxytryptamine (serotonin).

The 5-HT_7 receptors are a large family of receptors, ranging from 5-HT_1 to 5-HT_7, named so in order of discovery. The newest member of the 5-HT family, 5-HT_7, was discovered about 10 years ago.

The 5-HT_7 receptor is a G-protein coupled receptor consisting of 2 cystine cross-links and seven transmembrane domains [1]. As with all 5-HT receptors, 5-HT_7 has a high affinity for serotonin, as well as a number of structurally similar compounds, leading to the difficulty of selective 5-HT receptor study.

Four basic types of 5-HT_7 receptors have been identified in rat and human physiology: 5-HT_{7a}, 5-HT_{7b}, 5-HT_{7c}, and 5-HT_{7d}. The difference between these isoforms is the amino acid chain length. In the cases of 5-HT_{7a} and 5-HT_{7b}, the isoforms appear to be legitimately different receptors, though physiological distribution appears fairly uniform. 5-HT_{7c}, found only in rats,

and 5-HT_{7d}, found exclusively in humans, appear to be the result of transcription errors; with both receptors including species-specific exons during transcription. The 5-HT_{7c} and 5-HT_{7d} receptors do not appear to possess any special biological roles [2]. Furthermore, the 5-HT_{7a} and 5-HT_{7b} receptors appear to possess similar binding properties, and differ primarily in their location in the body.

Table 1. The numbers of amino acids in the rat and human 5-HT_7 receptors [2].

	5-HT_{7a}	**5-HT_{7b}**	**5-HT_{7c}**	**5-HT_{7d}**
Human	445	432	-	479
Rat	448	435	470	-

The receptor 5-HT_7 is distributed throughout several areas of the body. This receptor is found primarily in the brain, and to a lesser extent in parts of the digestive tract. Messenger RNA analysis has indicated the greatest presence in the hippocampus, thalamus, and the suprachiasmatic nucleus of the hypothalamus [3]. Lower levels have been found in the ileum, coronary artery, stomach, and colon [2].

A variety of functions have been attributed to the 5-HT_7 receptor. The majority of these biological roles are neurological or regulatory in function and include the learning, sleep cycle interference, thermal regulation, and mood altering effects.

5-HT_7 receptor synthesis has been inhibited in rats using antisense RNA fragments, with the goal of studying receptor effect. The observed result was a decrease in the rat's contextual fear conditioning. This conditioning, resulting from hippocampus activity, allows the rat to interpret environmental factors resulting in a fear response. An end result of the study was to show that 5-HT7 receptors are produced and utilized during times of acute stress [3].

Numerous antidepressants have been demonstrated to exhibit some effect on the 5-HT_7

receptor. This link between 5-HT_7 and depression is further exhibited by the apparent mood-influencing effects and effects on the sleep rhythm. In fact, 5-HT_7 antagonists have been demonstrated to alter rapid eye movement (REM) sleep, resulting in a longer time to achieve REM sleep and a shorter duration of REM sleep [3].

Some other activities of the 5-HT_7 receptor include the 8-hydroxy-2-(di-n-propylamino)-tertraline (8-OH-DPAT) induced hypothermia in guinea pigs and the smooth muscle control. The latter phenomenon creates the potential of 5-HT_7 acting drugs to function as anti-migraine medication [3].

A key difficulty in the study of 5-HT_7 receptors is its strong structural similarity to several of the receptor families, including 5-HT_1 and 5-HT_{2a}. Upon discovery of the 5-HT_7 receptor a review of previously used 5-HT ligands revealed that many of the ligands previously deemed selective in fact exhibited a high affinity for the 5-HT_7 family in addition to the targeted 5-HT receptor. These include the agents methiothepin, 5-carboxamidotryptamine, 8-OH DPAT, and mesulergine [2]. The majority of the 5-HT_7 ligands showed the greatest affinity for the 5-HT_{2a} receptor, followed by several other receptors [1].

$$\text{Receptor} + \text{Inhibitor} \underset{}{\overset{K_i}{\rightleftharpoons}} \text{Receptor-Inhibitor}$$

$$K_i = \frac{[R][I]}{[RI]}$$

$$pK_i = -\log(K_i)$$

Figure 2. A simplified equation for receptor-inhibitor binding and K_i calculation using molar concentrations of the receptor and inhibitor.

As with all inhibitors, the inhibitor affinity for the 5-HT_7 receptor is quantified by study of the equilibrium between the inhibitor-receptor complex and free receptor. The value generally

reported, K_i, is an equilibrium constant (inhibition constant) indicating the ratio of receptor-inhibitor complex against the free receptor.

Inhibitor efficacy is generally regarded to increase as the K_i value grows smaller; as a lower concentration of inhibitor would be required to occupy the same number of receptors.

Reported 5-HT$_7$ Receptor Ligands

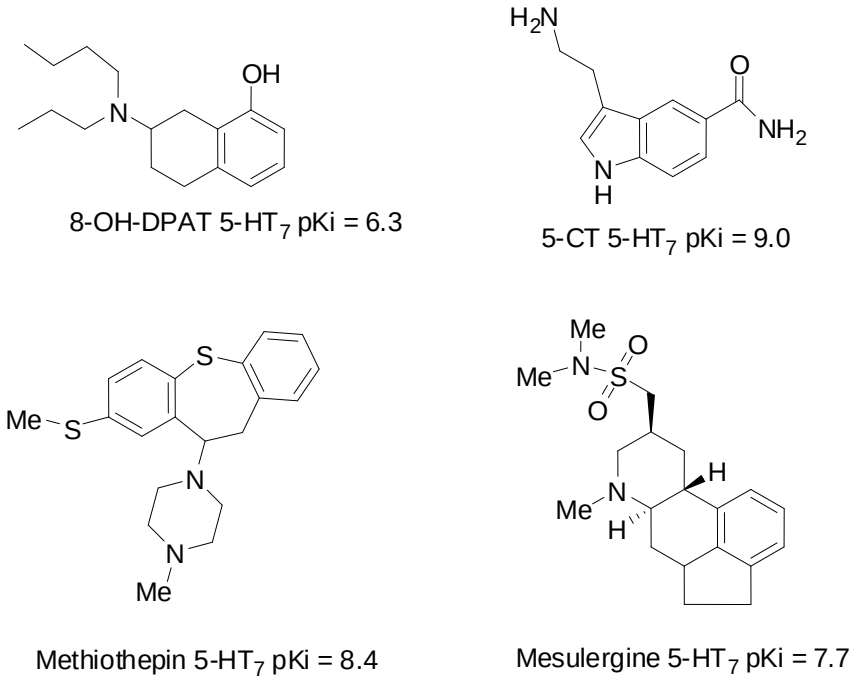


Figure 3. Structures of several 5-HT ligands. These compounds were previously believed to be selective against various other 5-HT receptors, but have since been shown to possess significant 5-HT$_7$ affinity.

Following the initial discovery of the 5-HT$_7$ receptor, numerous pharmaceutical companies rushed into screening studies in an effort to identify selective 5-HT$_7$ ligands. One of the first successes was reported by SmithKline Beecham; they found several active antagonists with a moderate affinity for the 5-HT$_7$ receptor; [2].

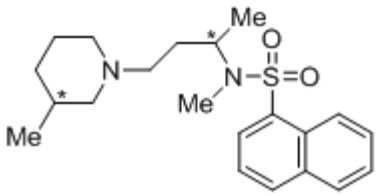


Figure 4. The lead SmithKline Beecham compound for the SB series of 5-HT_7 ligands.

A study of the chiral isomers of the compound give in Figure 4 found that the binding affinity was highest for the RR isomer (pK_i = 6.9). The piperidine chiral center was eliminated via placing the methyl group in position 4, and a variety of aromatic rings were used in place of the initial naphthalene system. Several of these derivatives showed increased activity towards 5-HT_7 receptors. The most selective was, SB-258719, (Figure 5) [2].

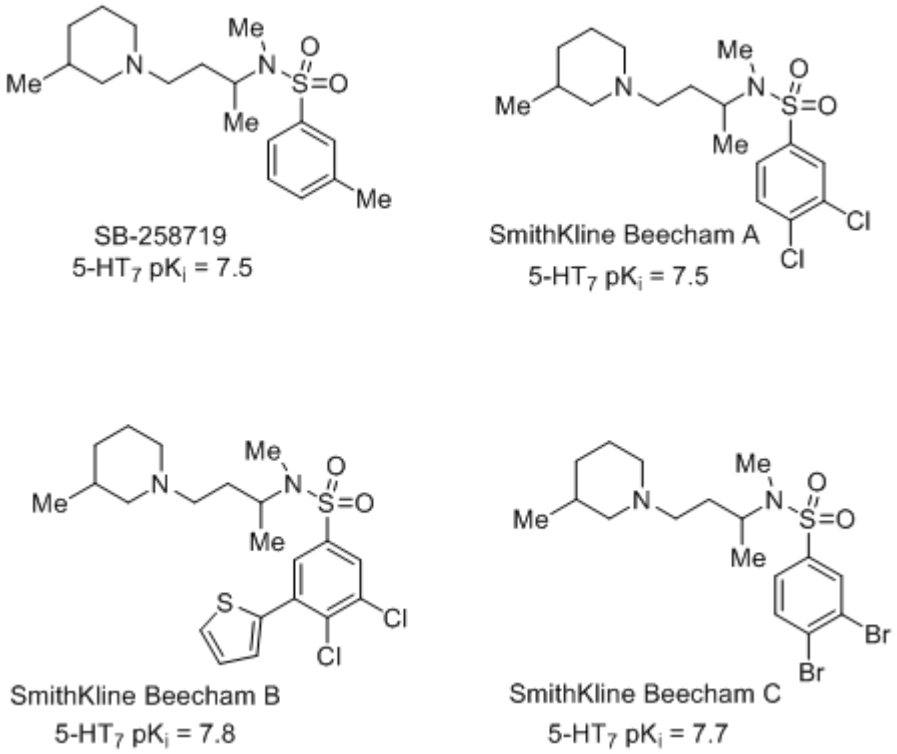


Figure 5. The SmithKline Beecham 5-HT_7 ligand SB-258719 and derivatives.

The next study undertaken was to lock the interconnecting alkyl chain into a heterocyclic

ring. Pyrrolidine derivatives proved more active than the piperidine analogs, and further derivatives of the aromatic substituent yielded several active and selective compounds, including SB-258741 (pK_i = 8.5) and SB-269970 (pK_i = 8.9) [2].

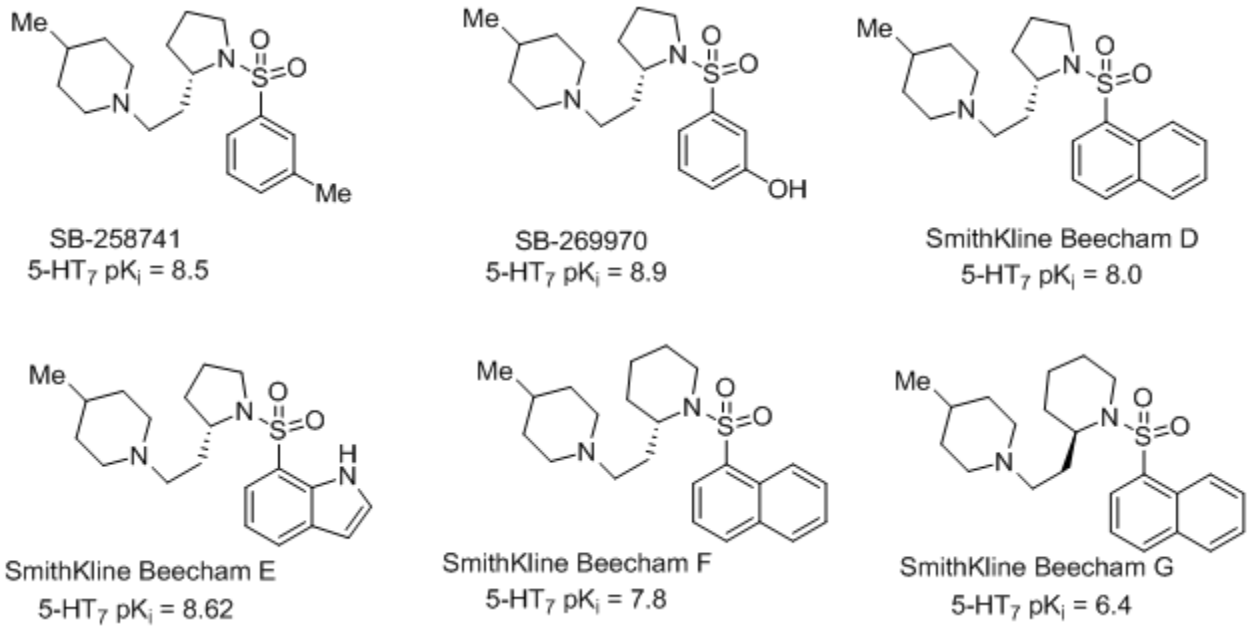


Figure 6. SB-269970, a promising 5-HT_7 ligand, and several similar SmithKline Beecham compounds. This series features a shorter, locked alkyl chain, which improved affinity for the 5-HT_7 receptor.

While SB-269970 exhibited exceptional selectivity and inhibition, the compound was a poor drug candidate, due to its short lifespan *in vivo*, which in turn was attributed to the presence of the phenol group. A large variety of SB-269970 derivatives were tested, largely consisting of modified heterocycles, but results were not encouraging.

A subsequent series of compounds involved replacement the phenol ring of SB-269970 with less polar arenes and the substitution of the position 4 methyl group with a variety of aromatic systems (Figure 7). This series included compound SB-656104, which had a pK_i of 8.70, and bioavailability of 16%; allowing for further study of these compounds as drug candidates.

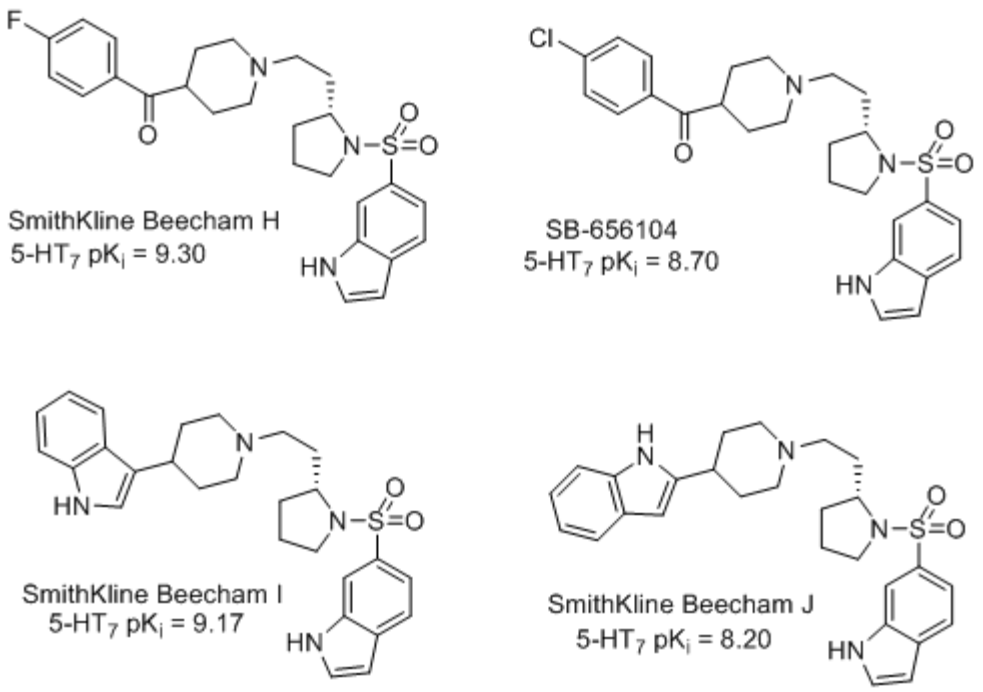


Figure 7. SmithKline Beecham 5-HT$_7$ ligands from the SB series, including SB-656104, which feature aromatic substitutients on the piperidine ring.

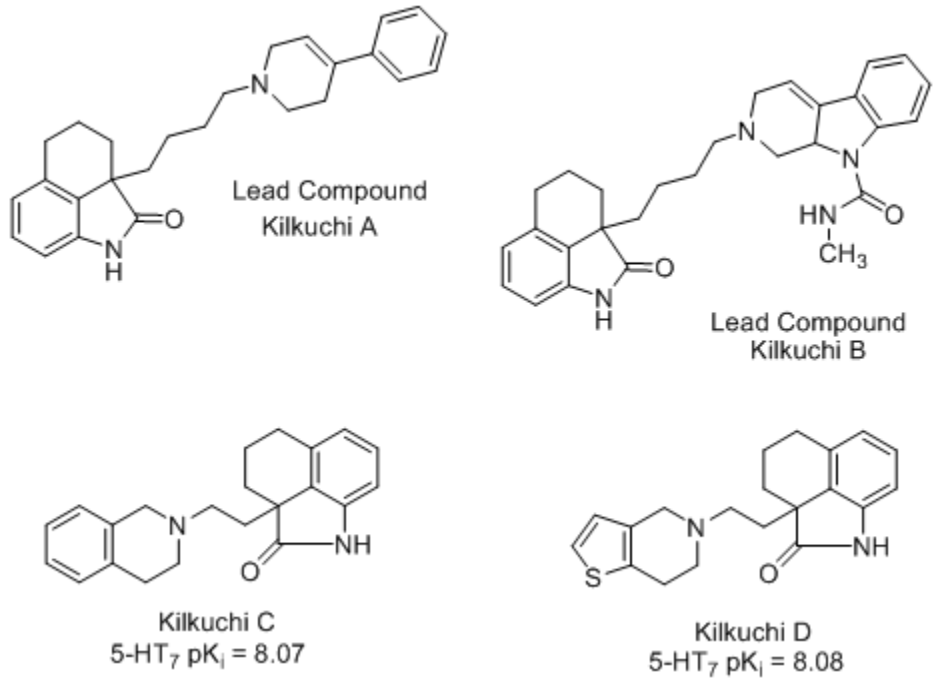


Figure 8. Two lead compounds and derivatives from the 5-HT$_7$ receptor ligands developed by Kilkuchi *et al* [4].

Another group of compounds, developed by Kikuchi *et al*. [4] that have demonstrated

both affinity and selectivity toward the 5-HT_7 receptor are tetrahydropyridoindoles (Figure 8).

Most of this family of compounds exhibited higher 5-HT_7 receptor binding affinities (in the low nanomolar range), but showed little selectivity against other 5-HT receptors. The key factors determined by Kikuchi *et al.* were the interconnecting alkyl chain length, the nitrogen-attached heterocyclic substituent attached to the chain, and the group attached to the secondary/tertiary nitrogen in the main ring.

Studies showed that compounds with a four carbon chain were most selective for 5-HT_7 in the presence of 5–HT_2. Second, the main ring system nitrogen could either remain secondary or the inclusion of an alkyl chain could produce a tertiary system. Brief efforts were made using both methyl and ethyl chains, which yielded a slight decrease in selectivity of the methyl derivative and a significant drop in both affinity and selectivity for the ethyl derivative. These results were attributed to the increased size of the nitrogen-bound group blocking receptor binding.

Lastly, the nitrogen-attached heterocycle was modified. Several bicyclic systems were used, including tetrahydroisoquinoline, imidazopyridine, pyrazolopyridine, thienopyridine, and furopyridine. Of the five bicyclic systems used the isoquinoline compound exhibited the best binding affinity for 5-HT_7, while thienopyridine produced the most selective compound with only a slightly reduced 5-HT_7 affinity.

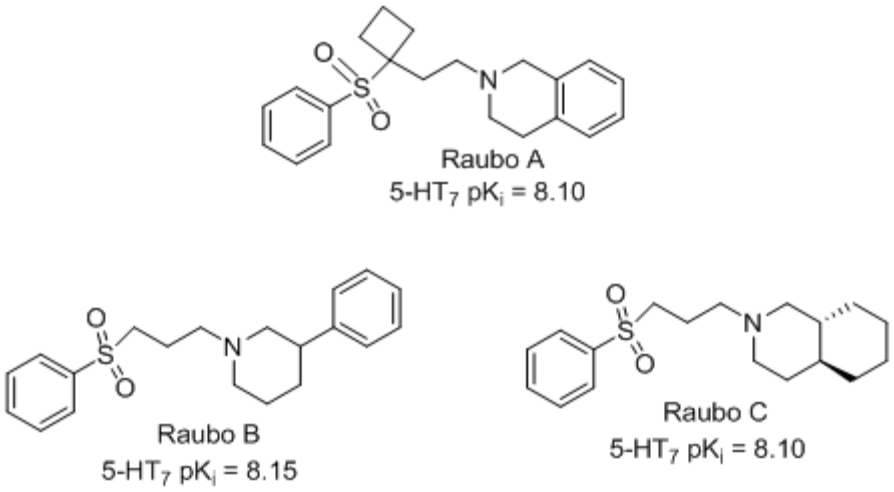


Figure 9. Several of the more active 5-HT_7 receptor ligands developed by Raubo *et al.* [5].

Raubo *et al.* have pursued a class of compounds (Figure 9) that are structurally similar to the SmithKline Beecham series of sulfones [5]. This new series uses a sulfone group between a phenyl ring and a cyclobutane attached to a short alkyl chain with a nitrogen heterocycle on the opposing end, as exemplified by Raubo A. While these compounds exhibited high 5-HT_7 affinity, considerable progress towards selectivity was achieved when the cyclobutane ring was removed from the molecule, leading to a structure considerably closer to the SmithKline Beecham class of ligands.

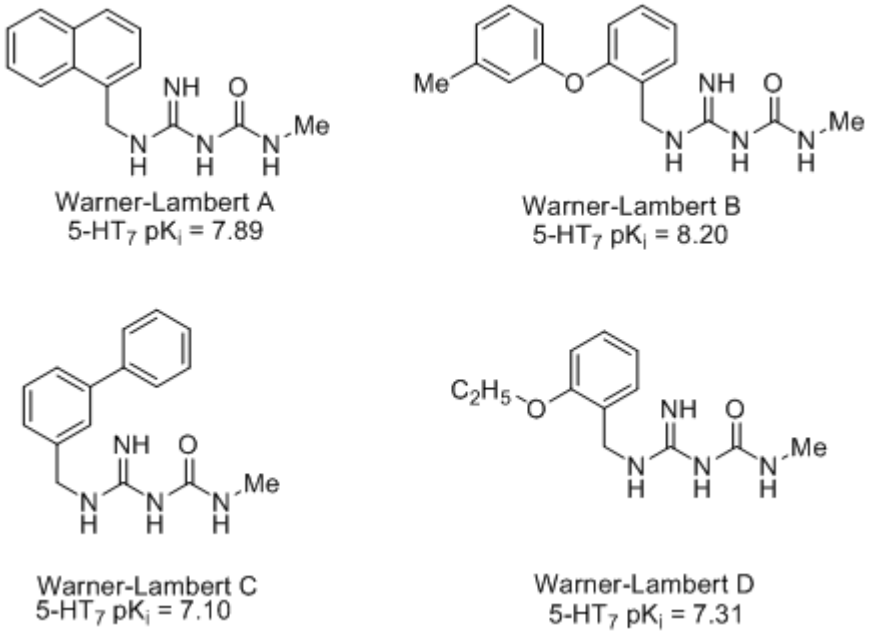


Figure 10. 5-HT_7 receptor ligands developed by Warner-Lambert [2].

Warner-Lambert Company has developed several classes of 5-HT_7 ligands [2]. One group, based on the lead compound (Warner-Lambert A, Figure 10) has shown some promise as a 5-HT_7 ligand. Several derivatives of Warner-Lambert A were studied. The efforts were made to replace the amide group with some other carbonyl. However, these efforts were uniformly unsuccessful, as each derivative possessed lower 5-HT_7 affinity than the initial amide.

Next was a brief effort to alter the substituent on the imine group. However, this too lead to a considerable decrease in 5-HT_7 affinity and was not further pursued. Instead, a new group of derivatives were created by replacing the naphthalene system with a variety of other aromatic systems (Figure 11). Several of these showed improvement in affinity, though selectivity against 5-HT_{2A} was poor.

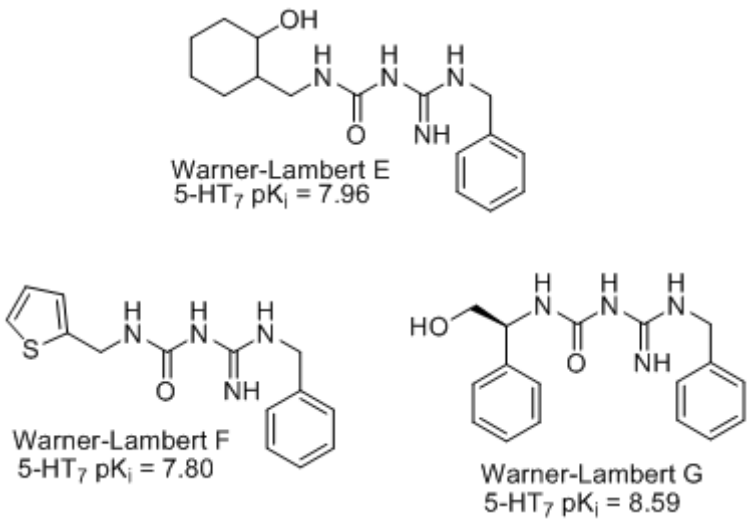


Figure 11. Derivatives of the Warner-Lambert class of compounds with modifications to the amide group.

Returning to the initial naphthalene compound (Warner-Lambert A), a new group of derivatives were prepared by replacement of the amide bound methyl group. Most of the active derivatives contained six-membered rings and were substituted with proton accepting groups. It was speculated that the binding pocket has some space which can readily incorporate large groups as well as form hydrogen bonds [2].

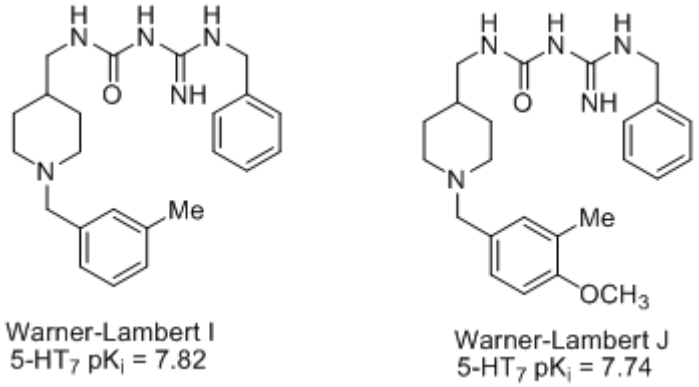


Figure 12. Warner-Lambert compounds modified with piperidine groups.

The next step was the placement of a substituted piperidine ring (attached at position 4)

to the amide group (Figure 12). Various aryl groups were attached to the piperidine nitrogen, though the resulting compounds possessed a greater affinity for the 5-HT_{2A} receptor than for the 5-HT_7.

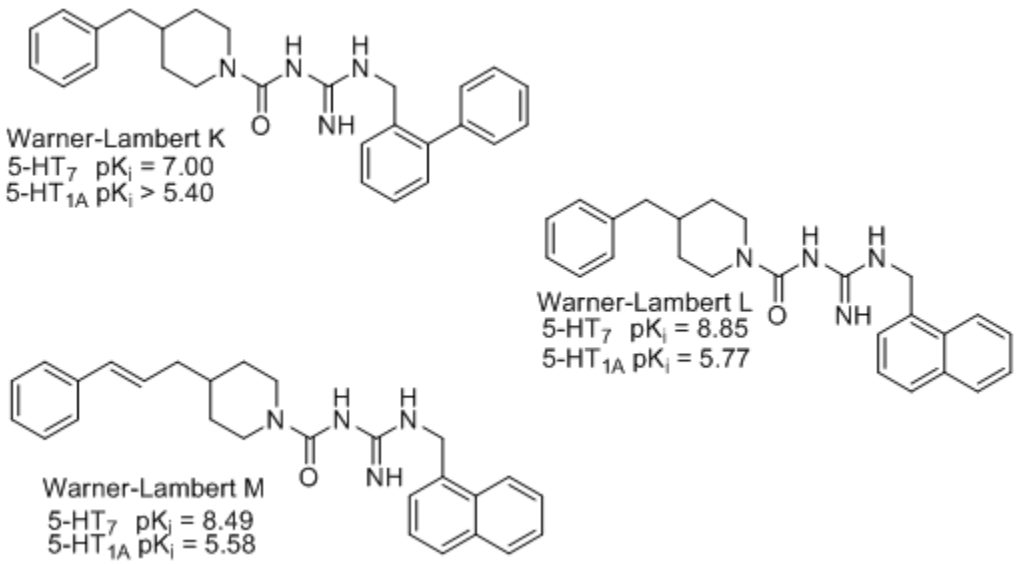


Figure 13. Warner-Lambert compounds which exhibited favorable 5-HT_7 affinity, but also possessed 5-HT_{1A} affinity.

Combination of these factors produced a ligand with considerable 5-HT_7 affinity, but drastically higher 5-HT_{1A} affinity. Efforts were made to change the piperidine to a piperazine, but a significantly larger 5-HT_{1A} affinity remained.

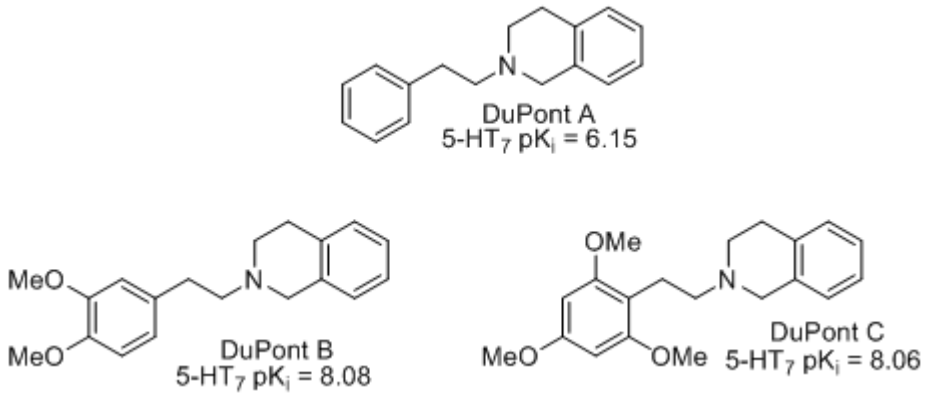


Figure 14. The lead DuPont 5-HT_7 ligand and methoxy derivatives.

A class of tetrahydroquinolines were developed by the DuPont Pharmaceutical Company [2] which showed affinity for the 5-HT_7 receptor, though selectivity was marginal. The initial compounds were synthesized with a variety of aromatic substituents connected to the tetrahydroquinoline via an ethyl chain. It was determined that the inclusion of methoxy groups improved affinity (Figure 14).

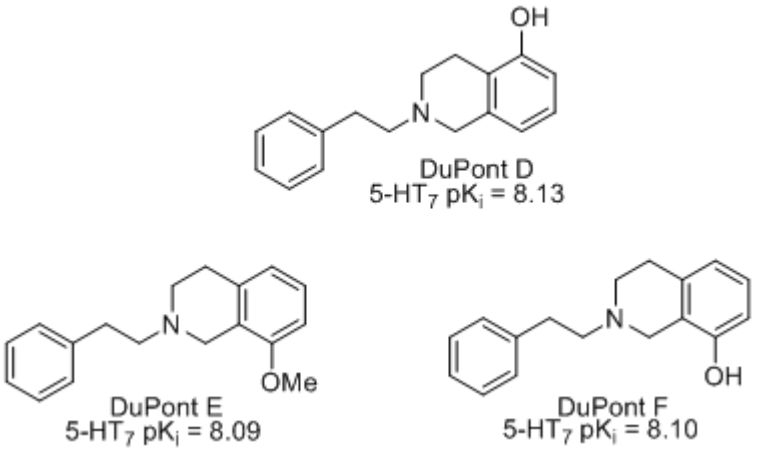


Figure 15. 5-HT_7 ligands developed by DuPont with tetrahydroquinoline substituents.

Using a phenyl ring as the aromatic substituent, a several groups were placed along the tetrahydroquinoline in an effort to further increase 5-HT_7 affinity as show in Figure 15. The more active compound a methoxy group at position 8.

The final compound (Figure 16) was had a decent affinity for the 5-HT_7 receptor, but exhibited poor selectivity against 5-HT_{1D}, 5-HT_{2C}, and 5-HT_6.

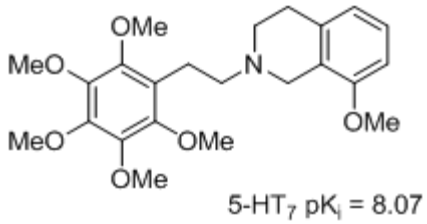


Figure 16. The end DuPont 5-HT_7 ligand.

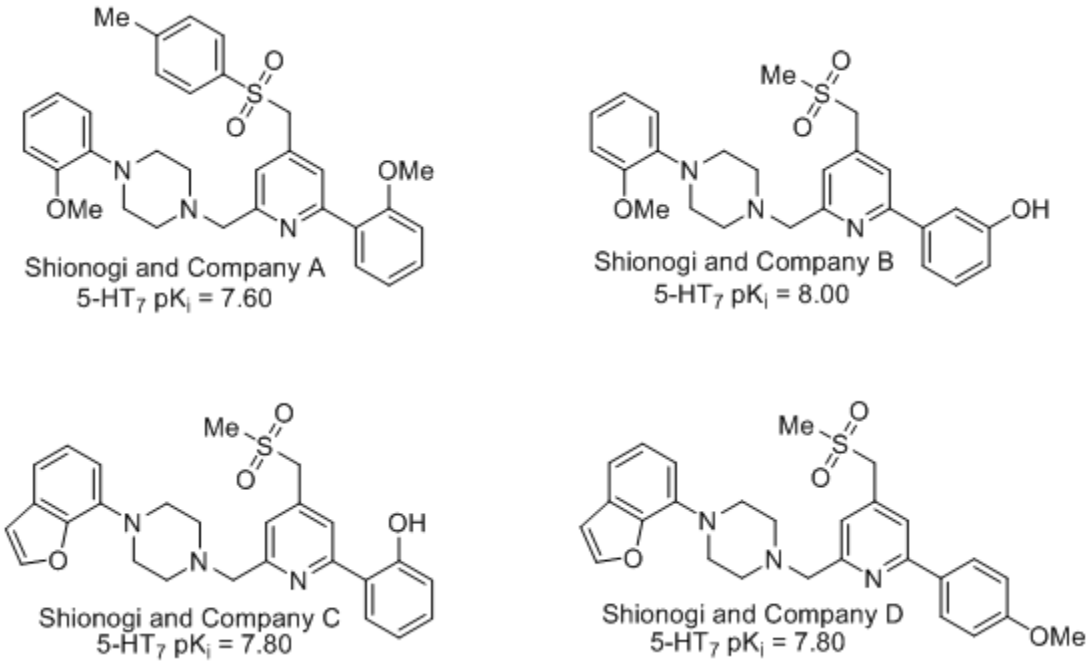


Figure 17. 5-HT_7 ligands developed by Shionogi and Company.

A large class of 5-HT_7 ligands have been developed by the Shionogi and Company [2]. This class consists of a series of 2,4,6 trisubstituted pyridines. The general structure (Figure 17) contains substituted aryl rings at positions 2 and 4 of the pyridine, and a methylene group forming a link between the pyridine and piperazine nitrogens. Further aromatic substitution has been placed on the 4 position of piperazine.

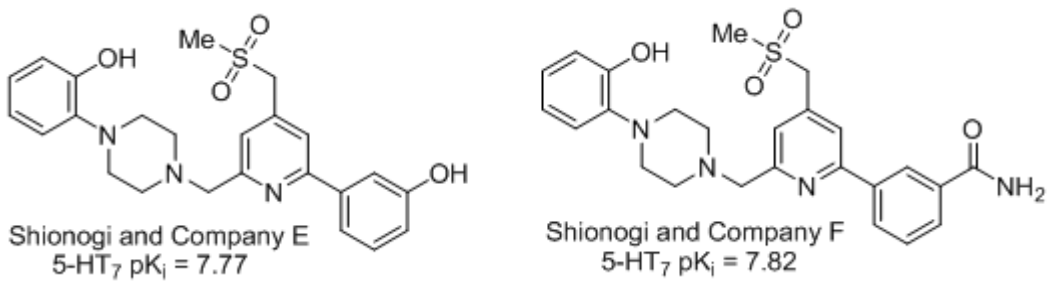


Figure 18. Shionogi and Company 5-HT_7 ligands with position 2 aryl derivatives.

While limited data was provided by Shionogi and Company, a variety of substituted pyridine compounds were reported (Figures 17 & 18). The active compounds contained a pyridine moiety substituted at position 2 with a methoxy or hydroxy group. Little selectivity was observed between ortho and meta substitution, but a notable drop in affinity was seen for para substitution.

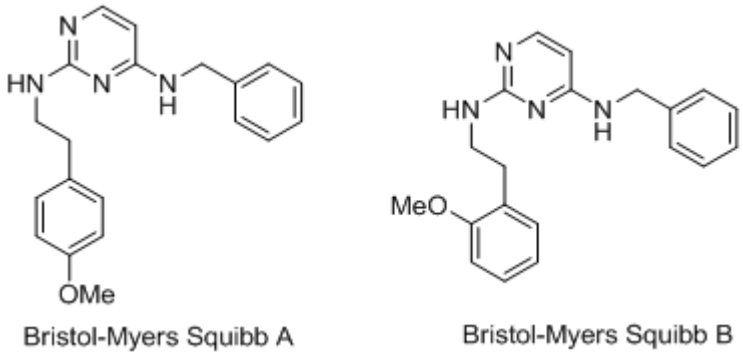


Figure 19. Pyrimidine based 5-HT_7 receptor ligands developed by Bristol-Myers Squibb, possessing an IC_{50} below 50nM.

Bristol-Myers Squibb and Company have reported the development of pyrimidine and triazine based compounds possessing 5-HT_7 receptor activity. While selectivity data was not included, and limited binding data is available; it is known that numerous compounds were developed with an IC_{50} value of under 50nM.

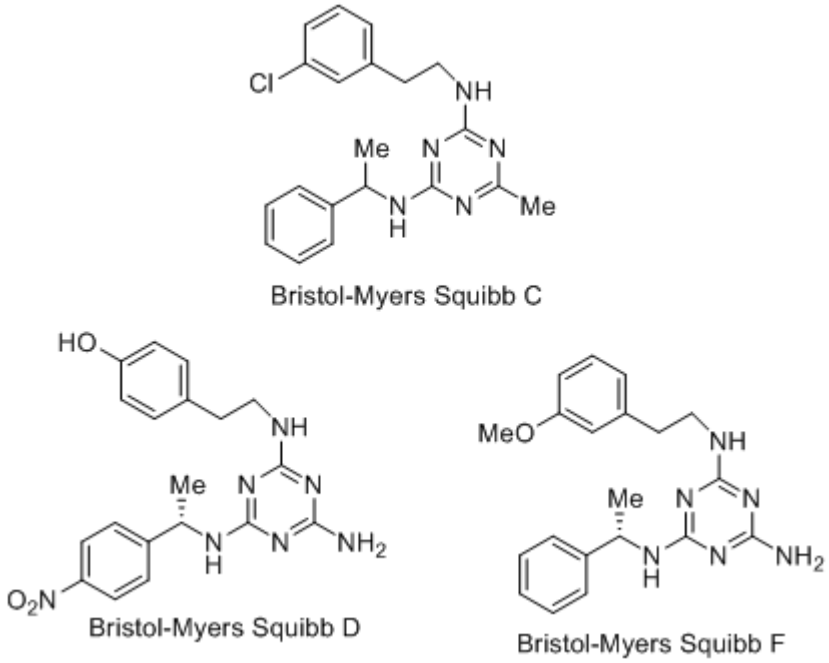


Figure 20. Triazine ring based 5-HT_7 ligands with an IC_{50} below 50nM.

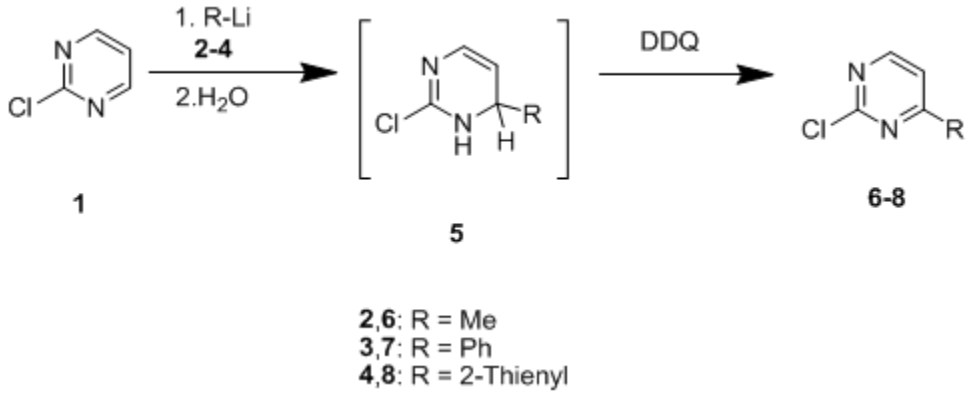
The compounds consisted of 2-4 disubstituted pyrimidines (Figure 19) or 2,4,6-trisubstituted triazines (Figure 20). All the reported substituents were secondary amino groups with short alkyl chains attached to substituted aromatic rings.

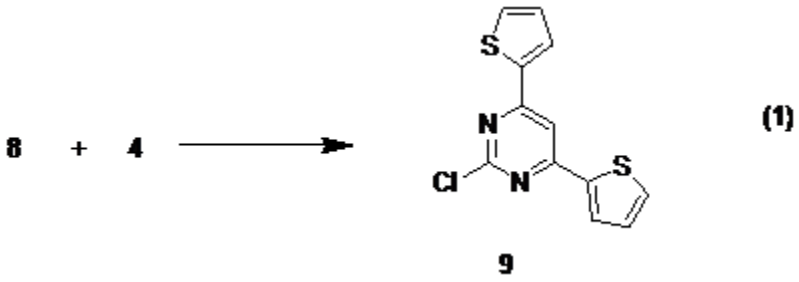
Past Pyrimidine Research

The synthesis of the target pyrimidine compounds was accomplished following a procedure first developed at Georgia State University in 1988, and expanded upon in 1990 [6,7].

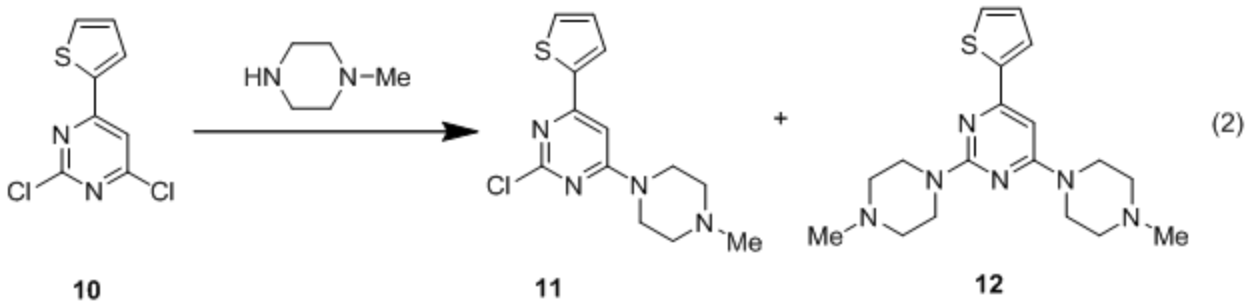
Early work began with the addition of lithiated intermediates to the pyrimidine ring, with the 1,6-dihydropyrimidine intermediate oxidized back to the pyrimidine (Scheme 1). This allowed for additional lithium addition/substitution reactions (Equation 1) to obtain 4,6-disubstituted 2-chloropyrimidines.

Scheme 1





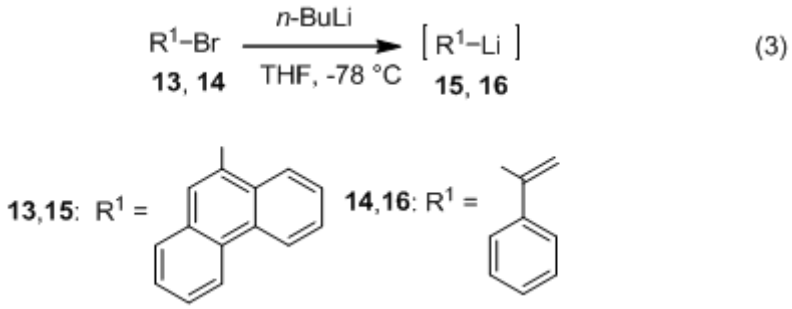
Further study along this line lead to the development of a series of 2,4-disubstiuted and 2,4,6-trisubstituted pyrimidines [9]. Along with the previously established lithium addition/substitution reaction, these compounds were prepared using amines to displace chlorines at positions 2 and 6 (Equation 2). Further study of these compounds indicated favorable pK_i against the serotonin receptor 5-HT_{2A}.



Discussion

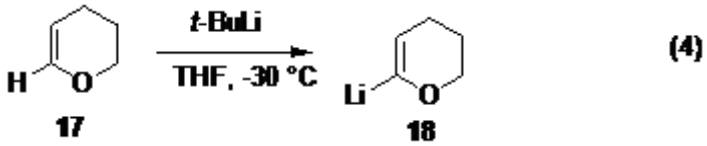
The chemistry described above has been used to synthesize the pyrimidine derivatives in this work. The following text describes chemistry conducted as part of this thesis.

The first step of ligand synthesis was the preparation of the desired organolithium reagent. This was accomplished by either lithium bromine exchange (Equation 3) or lithiation (Equation 4).

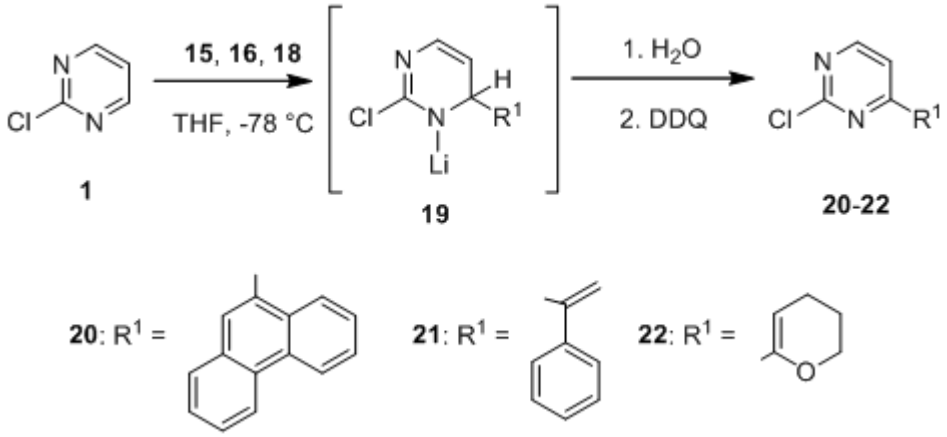


Lithium-bromine exchange was conducted in anhydrous THF under dry nitrogen at low temperature. An excess of the bromine reagent was used to ensure the complete reaction of *n*-butyllithium and prevent the formation of an undesired butylpyrimidine side product.

Lithiation of **17** (Equation 4) was accomplished under mild conditions.



Scheme 2



After the intermediates, **15, 16**, **18**, had been generated, the mixtures were cooled to -78 ˚C and a solution of 2-chloropyrimidine (**1**) in anhydrous THF was introduced dropwise over a period of several minutes. Upon addition, **15**, **16**, & **18** were allowed to react with **1** for 30 min at -78 ˚C, then the temperature was raised to -30 ˚C over 1 h. Any remaining lithium compounds were quenched with water and the mixture was treated with the oxidative reagent DDQ (2,3-dicyano-4,5-dichlorobenzoquinone). Following this procedure, the product **20-22** was extracted with dichloromethane.

Purification of **20**-**22** was accomplished using silica gel chromatography, eluting with a mixture of hexanes and dichloromethane.

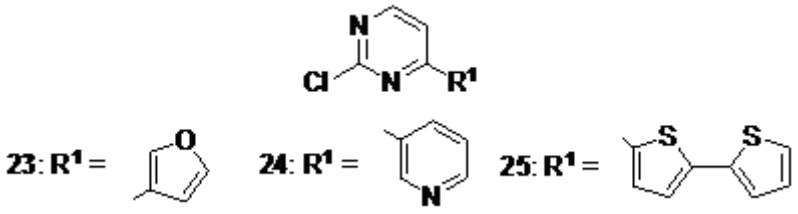
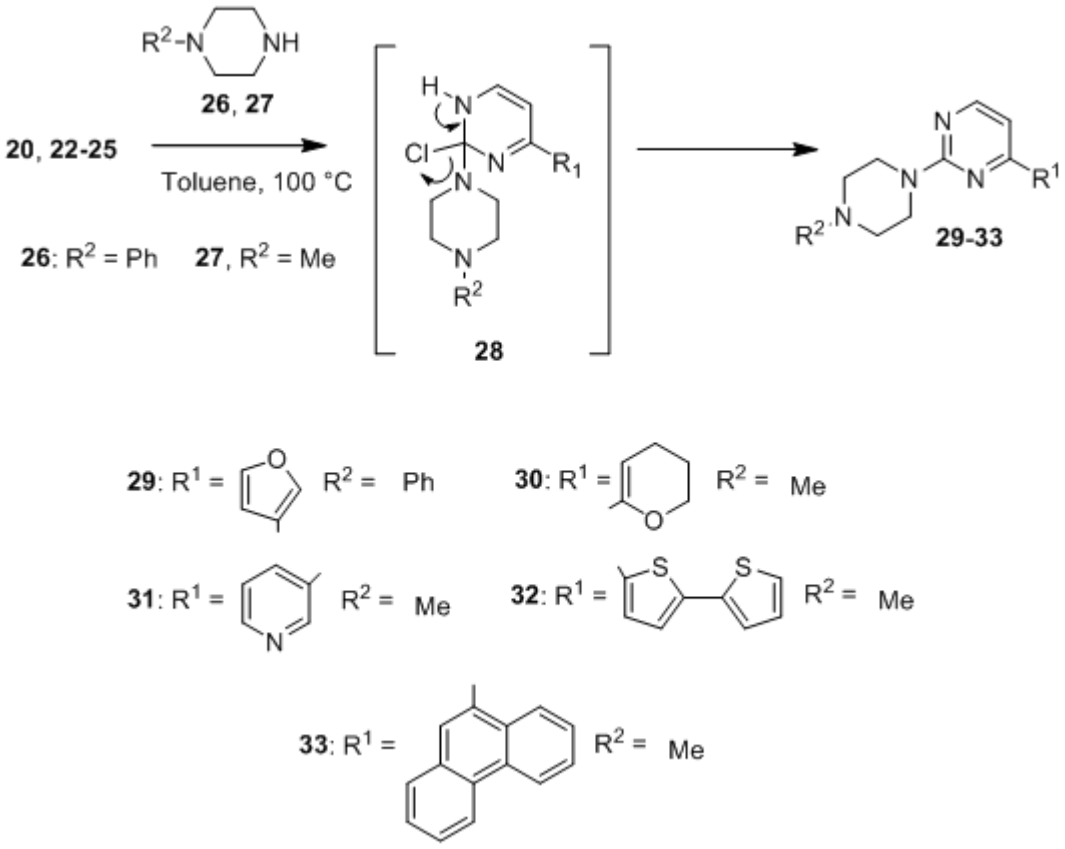


Figure 21. Compounds **23-25** prepared as described in literature [7, 10, 11].

Three additional compounds **23-25** (Figure 21) were obtained following previously established protocol [7, 10, 11].

Scheme 3

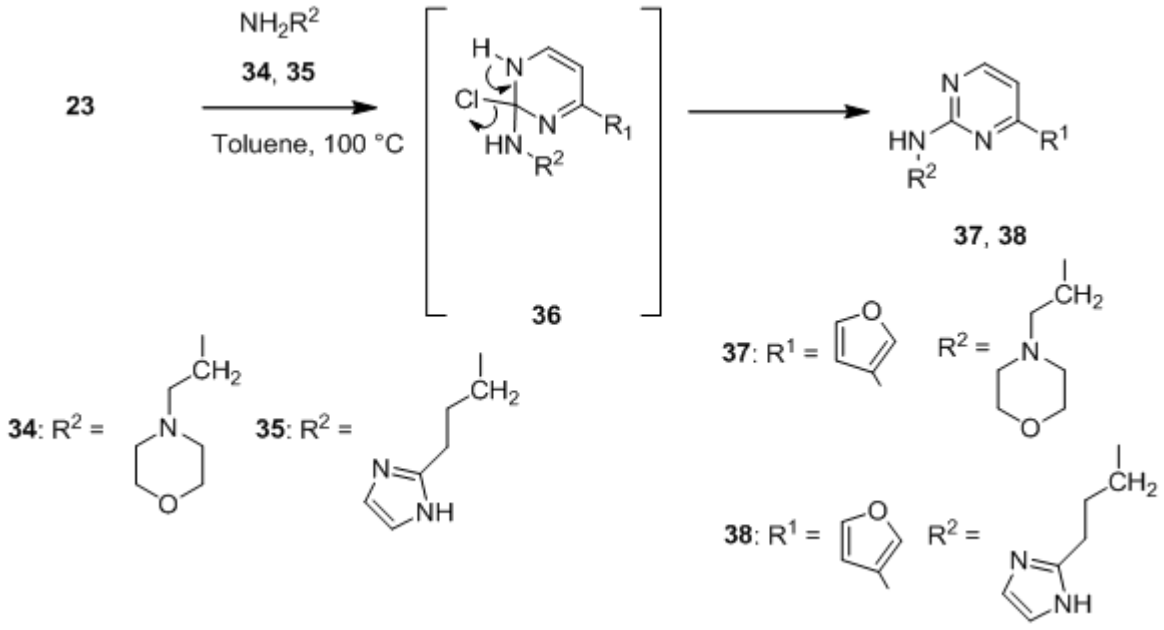


Displacement of the chlorine atom at position 2 of compounds **20-25** was accomplished

by treatment with various piperazines (Schemes 3 and 4). Products **29-33, 37**, & **38** were obtained.

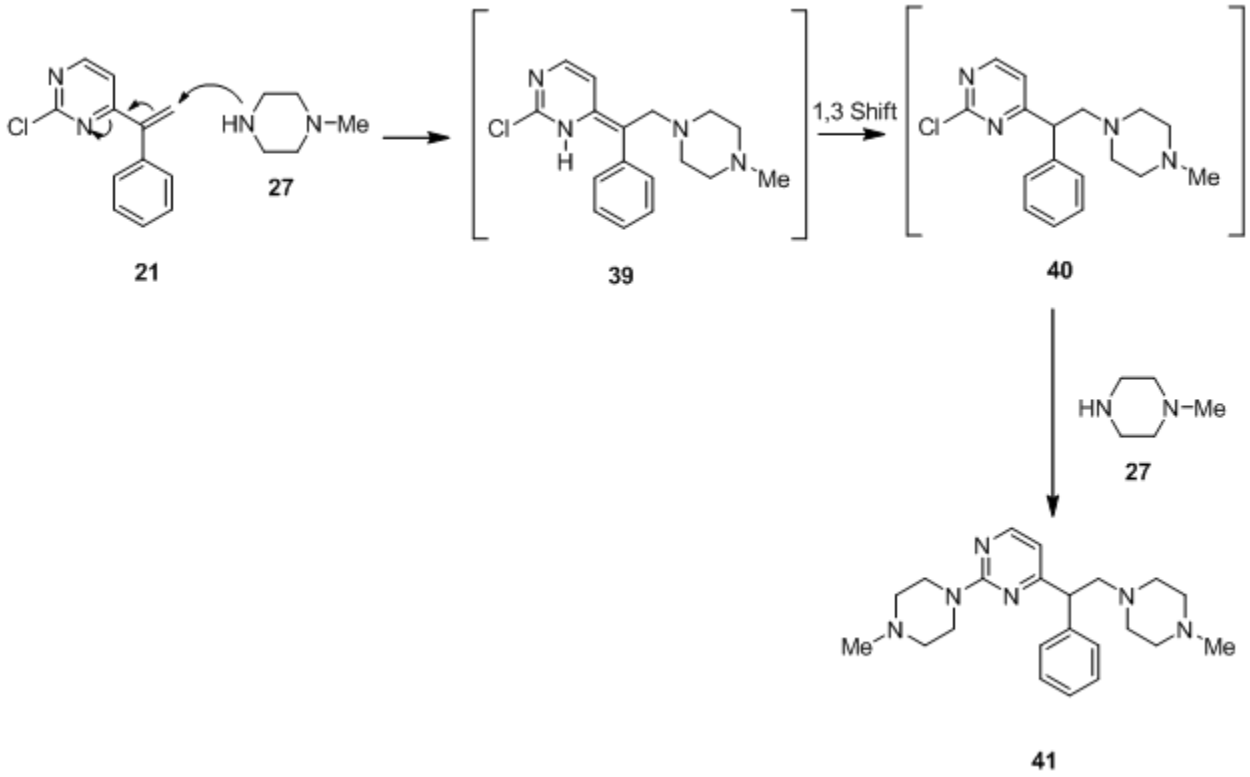
Upon completion of the reaction, the crude product was purified on a chromatotron using silica gel and eluting with a mixture of dichloromethane and methanol

Scheme 4



Structures of the synthesized compounds were verified ^{1}H-NMR spectroscopy and elemental analysis of the hydrobromide or hydrochloride salt. For example, an AB system was observed in the ^{1}H-NMR system for the H5-H6 moiety of the pyrimidine in all compounds. The chemical shifts, approximately 8 ppm for H6 and 6.0-7.5 ppm for H5, are consisted with the literature values. The methylpiperazine moiety was also easily identified by the singlet-triplet-triplet pattern occurring at roughly 2.3 ppm, 2.5 ppm, and 3.9 ppm respectively.

Scheme 5

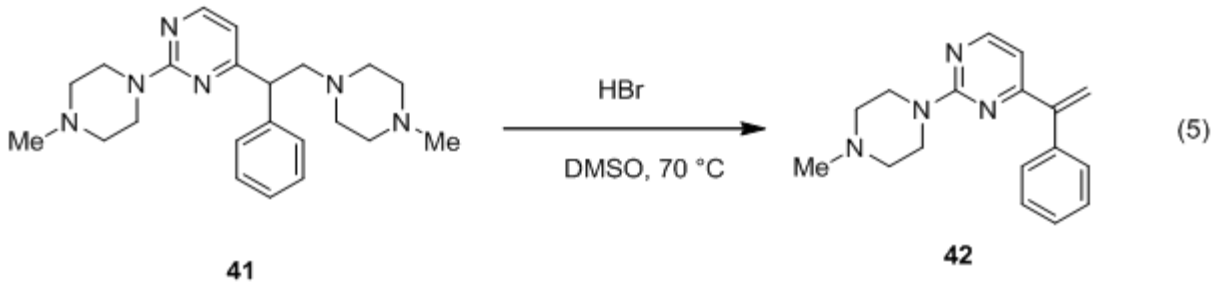


One compound of special interest is compound **21**, which was observed to undergo two independent reactions upon treatment with *N*-methylpiperazine. One reaction is the displacement of the chlorine atom at position 2 of the pyrimidine. The second reaction appears to be a variant of Michael addition, with the involvement of the vinyl substituent at the pyrimidine. The mechanism is suggested in Scheme 5. It should be noted that the alternative reactivity may involve the 1,4-addition first, as shown.

The structural studies on the resulting product **41** involved ^{1}H-NMR spectroscopy and mass spectrometry. The finial structural determination was performed using elemental analysis.

During efforts to record a ^{13}C spectrum of the HBr salt of **41** in DMSO at 70 ˚C the compound underwent elimination of *N*-methylpiperazine, resulting in the complete conversion to the initially expected mono-piperazine product, compound **42** (Equation 5).

This compound was subsequently studied by ^{1}H-NMR spectroscopy, which confirmed both the loss of N-methyl piperazine and the presence of two new vinylic protons. Mass spectrum confirmed the expected molecular weight of 280 g/mol, and the elemental analysis of the carefully prepared hydrochloride salt supported the proposed structure.



41 42 (5)

Biological Activity

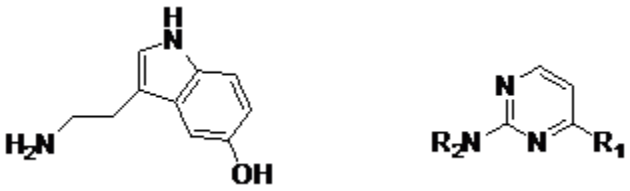


Figure 22. Serotonin and the general structure of the active pyrimidine compounds.

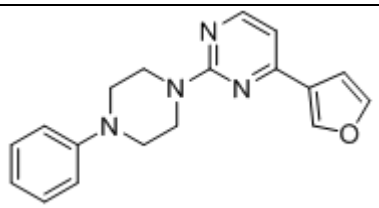
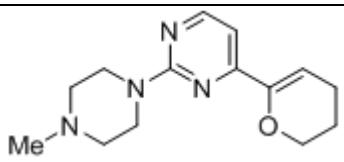
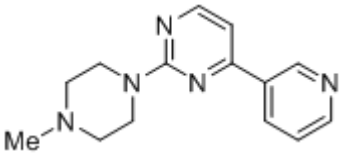
The 5-HT$_7$ active pyrimidines have exhibited a series of general characteristics. Compounds developed by past researchers have proven most active with basic or proton accepting groups in position 4, specifically the 3-furyl group. Along similar lines, piperazine or 4-substituted piperazine has proven virtually essential for a high 5-HT$_7$ affinity. Non-polar groups, specifically short aliphatic chains, have been shown to boost 5-HT$_7$ affinity as well.

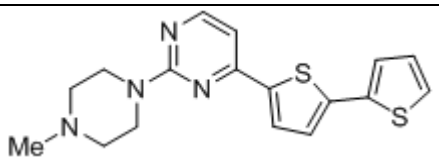
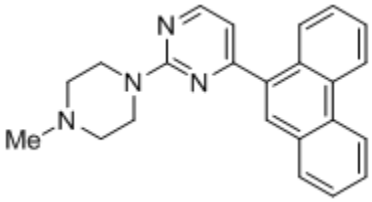
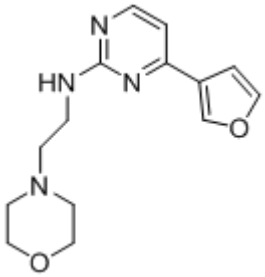
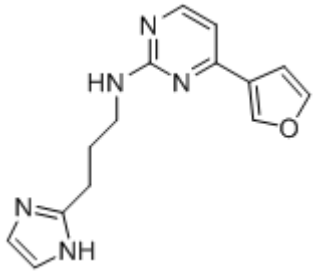
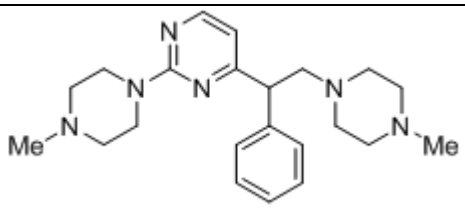
The biological activity of the synthesized compounds **29-33**, **37**, **38**, **40**, & **41** are

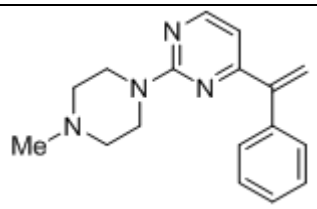
reported in Table 2 as -log K_i or –log K_s (pK_i and pK_s, respectively). K_i is the inhibitive constant and K_s is the estimated inhibitive constant.

The values of pK_i and pK_s both report receptor inhibition, and vary on method and accuracy. Both values were calculated based on the displacement of a radioactive label via the examined receptor; pK_s values consisted of a simpler preliminary test and, as such, are less accurate. The reported pK_i values were determined much more thoroughly, and as such have a greater degree of accuracy.

Table 2. The biological activity of the synthesized ligands **29**-**37** against the 5-HT_{2A} and 5-HT_7 receptor.

Compound	pK_i 5-HT_{2A}	pK_s 5-HT_{2A}	pK_i 5-HT_7	pK_s 5-HT_7
 **29**, $C_{18}H_{18}N_4O \bullet 1.5$ HBr	-	6	-	-
 **30**, $C_{14}H_{20}N_4O \bullet HBr \bullet 1.5\ H_2O$	5.67	-	-	4
 **31**, $C_{14}H_{17}N_5 \bullet 2$ HBr $\bullet 1.5\ H_2O$	-	7	6.12	-

 **32**, $C_{17}H_{18}N_4S_2$ • 1.5 HBr • 2 H_2O	-	4	5.71	-
 **33**, $C_{23}H_{22}N_4$ • 1.5 HBr • 2 H_2O	5.39	-	-	6
 **37**, $C_{14}H_{18}N_4O_2$ • 2 HBr • 0.5 H_2O	5.82	-	-	5
 **38**, $C_{14}H_{15}N_5O$ • 2 HBr • 0.5 H_2O	5.57	-	-	5.89
 **41**, $C_{22}H_{32}N_6$ • 4 HCl • 1 H_2O	-	-	-	-

 **42**, $C_{17}H_{20}N_4 \bullet 3.5\ HBr \bullet 2\ H_2O$	-	-	-	-

Experimental

General

All glassware was dried at 80 °C and cooled under nitrogen. All organolithium reactions were preformed in anhydrous tetrahydrafuran, distilled immediately before usage with benzophenone and sodium. All compounds were transferred using syringes, and all moisture sensitive reactions were preformed under dry nitrogen. All biological activity testing was conducted at the Institute of Pharmacology, the Polish Academy of Sciences.

Generation of Lithium Reagents

Phenanthren-9-yllithium (**15**) and 1-(phenylvinyl)-lithium (**16**) were generated by the bromine-lithium exchange of 9-bromophenanthrene (**13**) and α-bromostyrene (**14**) with *n*-butyllithium (2.5M, 2 mmol) at -78 °C in THF for 30-90 s. (3,4-Dihydro-2*H*-pyran-6-yl)lithium (**18**) was prepared by treatment of 3,4-dihydro-2*H*-pyran (**17**) and *t*-butyllithium at -78 °C; the mixture was allowed to reach 0 °C over 50 min.

Synthesis of 4-Substituted 2-Chloropyrimidines

A solution of 2-chloropyrimidine (2.0 mmol, 229 mg) in THF was added dropwise to solutions of **15, 16**, & **18** over a period of 5 min. The solutions were allowed to react for 30 min at -78 °C, then the temperature was raised to -20 °C over a period of 1 h. Then the mixtures were quenched with water (1 ml) and treated with a solution of DDQ (2.0 mmol, 454 mg) in THF (1 ml). After 15 min, the mixtures were treated with a solution of aqueous NaOH (3M, 18 ml, 6.0 mmol) and products 4-(3,4-dihydro-2*H*-pyran-6-yl)pyrimidine (**20**), 2-chloro-4-(phenanthren-9-yl)pyrimidine (**21**), and 2-chloro- 2-chloro-4-(1-phenylvinyl)pyrimidine (**22**) were extracted with dichloromethane.

Additional compounds 2-chloro-4-(furan-3-yl)pyrimidine (**23**), 2-chloro-4-(pyridin-3-yl)pyrimidine (**24**), and 4-(2,2'-bithiophen-5-yl)-2-chloropyrimidine (**25**) were prepared from 3-bromofuran, 3-bromopyridine, and 2,2'-biothiphene using the previously published literature [7, 10, 11]

All products were purified using a chromatotron with normal phase EMD 60PF_{254} silica gel. The products were eluted using a combination of hexanes/dichloromethane.

Amination

Piperazine derivatives 4-(3-furyl)-2-(4-phenylpiperazino)pyrimidine (**29**), 4-(3,4-dihydro-2*H*-pyran-6-yl)-2-(4-methylpiperazino)pyrimidine (**30**), 2-(4-methylpiperazino)-4-pyridin-3-ylpyrimidine (**31**), 4-(2,2'-bithiophen-5-yl)-2-(4-methylpiperazino)pyrimidine (**32**), 2-(4-methylpiperazino)-4-(9-phenylanthryl)pyrimidine (**33**), 2-(4-methylpiperazinol)-4-(2-(4-

methylpiperazino)-1-phenylethyl)pyrimidine (**41**) were prepared from **20**-**25** (0.6 mmol) and phenylpiperazine or methylpiperazine (3 equivalents, 6 equivalents for **41**) in toluene (3 ml) under reflux for 3 h.

Secondary amine compounds 4-(furan-3-yl)-*N*-(2-morpholinoethyl)pyrimidin-2-amine (**37**) and *N*-(3-(1*H*-imidazol-2-yl)propyl)-4-(furan-3-yl)pyrimidin-2-amine (**38**) were prepared from **23**: **37** (0.60 mmol of **23** with 1.94 mmol of 2-morpholinoethanamine, 16 h, 100 °C) **38** (0.70 mmol of **23** with 2.15 mmol of 3-(1*H*-imidazol-2-yl)propan-1-amine, 16 h, 100 °C).

All products were purified using a chromatotron with normal phase EMD 60PF_{254} silica gel. The products were eluted using a combination of dichloromethane/methanol.

Salt Formation

All salts were formed from products **29**-**33**, **37**, **38**, and **41** by preparing a solution of the individual product in a minimum amount of methanol (0.5-1 ml) and adding a slight excess of hydrobromic acid (48%, 0.30 ml, 1.9 mmol) or hydrochloric acid (12.4M, 0.15 ml, 1.9 mmol). Hydrobromide/hydrochloride salt crystals were formed by precipitation upon addition of Et_2O (5 ml). The resulting salts were dried under vacuum at 80 °C for several hours. The salt of product **42** was produced using a dilute solution HBr (2.1M, 1.5 ml, 0.7 mmol) to avoid disruption of the vinyl group. The salts of **41** and **42** proved too hydroscopic to collect via filtration, and were instead collected by removal of the solvent under vacuum.

2-Chloro-4-(3-furyl)pyrimidine (23) This compound was obtained following the previously described procedure [7].

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.90 (d, *J* = 1.6 Hz, 1H) δ 7.31 (d, *J* = 5.0 Hz, 1H) δ 7.54 (d, *J* = 1.6 Hz, 1H) δ 8.22 (s, 1H) δ 8.57 (d, *J* = 5.0 Hz, 1H); literature ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.90 (d, *J* = 1.6 Hz), δ 7.30 (d, *J* = 5.2 Hz), δ 7.53 (d, *J* = 1.6 Hz) δ 8.21 (s) δ 8.54 (d, *J* = 5.2 Hz).

4-(3-Furyl)-2-(4-phenylpiperazino)pyrimidine hydrobromide (29 • 1.5 HBr) A solution of 2-chloro-4-(3-furyl)pyrimidine (87 mg, 0.48 mmol) was allowed to react under reflux in toluene (1ml) with 1-phenylpiperazine (233 mg, 1.44 mmol) for 3 h at 100 °C. Purification and salt formation were accomplished as described above.

This compound had a mp of 223-225 °C; yield 62%; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.33 (s, 4H), δ 4.00 (s, 4H) δ 6.93 (m, 1H) δ 7.05 (dd, *J* = 1.6, 5.2 Hz, 1H) δ 7.17 (m, 3H) δ 7.29 (t, *J* = 7.2 Hz, 2H) δ 7.84 (d, *J* = 1.6 Hz, 1H) δ 8.41 (d, *J* = 5.6 Hz, 1H) δ 8.56 (s, 1H).

Anal. Calcd. for $C_{18}H_{18}N_4O$ • 1.5 HBr: C, 50.54; H 4.50; N 13.10. Found: C, 50.16; H, 4.30; N, 12.75.

4-(3-Furyl)-N-(2-morpholin-4-ylethyl)pyrimidin-2-amine hydrobromide (37 • 2 HBr • 0.5 H_2O) A solution of 2-chloro-4-(3-furyl)pyrimidine (108 mg, 0.60 mmol) was reacted under reflux in toluene (2 ml) with 4-(2-aminoethyl)morpholine for 16 h. Purification and conversion to a hydrobromide salt were accomplished as described in the general procedure.

This compound had a mp of 143-146 °C; yield 69%; ^{1}H NMR (free base, $CDCl_3$, 400 MHz) δ 2.49 (t, *J* = 4.4 Hz, 5H) δ 2.59 (t, *J* = 6 Hz, 2H) δ 3.55 (q, *J* = 6 Hz, 2H) δ 3.71 (t, *J* = 4.4 Hz, 5H) δ 5.78 (s, 1H) δ 6.66 (d, *J* = 5.2 Hz, 1H) δ 6.85 (m, *J* = 1.8 Hz, 1H) δ 7.48 (d, *J* = 1.8 Hz, 1H) δ 8.07 (s, 1H) δ 8.25 (d, *J* = 5.2, 1H).

Anal. Calcd for $C_{14}H_{18}N_4O_2$ • 2 HBr • 0.5 H_2O: C, 37.77; H, 4.75; N 12.59. Found: C, 37.78; H, 4.76; N, 12.20.

4-(3-Furyl)-*N*-(1*H*-imidazol-2-yl)propyl)pyrimidin-2-amine hydrobromide (38 • HBr • 0.5 H_2O) 2-Chloro-4-(3-furyl)pyrimidine (130 mg, 0.7 mmol) was reacted under reflux in toluene (2 ml) with 3-(1*H*-imidazol-2-yl)propan-1-amine (270 mg, 2.15 mmol) at 100 °C for 17 h. Purification and salt formation were accomplished as described above.

This compound had an mp of 234-236 °C; yield 62%; ^{1}H NMR (free base, $CDCl_3$, D_2O, 400 MHz) δ 2.09 (m, *J* = 6.8 Hz, 2H) δ 3.46 (t, *J* = 6.8 Hz, 2H) δ 4.04 (t, *J* = 6.8 Hz, 2H) δ 6.70 (d, *J* = 5.2 Hz, 1H) δ 6.84 (m, *J* = 2.2 Hz, 1H) δ 6.94 (s, 1H) δ 7.06 (s, 1H) δ 7.49 (m, 2H) δ 8.06 (m, *J* = 2.2 Hz, 1H) δ 8.24 (d, *J* = 5.2 Hz, 1H).

Anal. Calcd. for $C_{14}H_{15}N_5O$ • 2 HBr • 0.5 H_2O: C, 38.30; H 4.12; N, 15.91. Found: C, 38.23; H, 3.93; N, 15.78.

2-Chloro-4-(3,4-dihydro-2*H*-pyran-6-yl)pyrimidine (22)

A solution of 3,4-dihydro-2*H*-pyran (223 mg, 2.65 mmol) in dry THF (1 ml) was cooled to -70 °C under nitrogen and treated dropwise with a solution of *t*-butyllithium (1.6M, 4.62 ml, 2.89 mmol). The temperature of the mixture was raised to 0 °C over 50 min, lowered to -65 °C. A mixture of 2-chloropyrimidine (303 mg, 2.64 mmol) in THF (1 ml) was added dropwise. The temperature was raised to -10 °C over 80 min, and the mixture was worked up and purified according to the general procedure.

This compound was obtained in 17% yield, brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.95 (m, 2H) δ 2.30 (d, *J* = 4.4 Hz, 2H) δ 4.18 (t, *J* = 5.2 Hz, 2H) δ 6.41 (s, 1H) δ 7.14 (d, *J* = 5.2 Hz, 1H)

δ 8.57 (d, *J* = 5.2 Hz, 1H).

4-(3,4-Dihydro-2*H*-pyran-6-yl)-2-(4-methylpiperazino)pyrimidine hydrobromide (30 • 1.25 HBr • 0.5 H_2O)

2-Chloro-4-(3,4-dihydro-2*H*-pyran-6-yl)pyrimidine (92 mg, 0.47 mmol) was allowed to react under reflux with 1-methylpiperazine (139 mg, 1.39 mmol) in toluene (1 ml) at 100 °C for 3h. The resulting solution was purified according to the above procedure.

This compound had a mp of 192-194 °C; yield 80%; ^{1}H NMR (free base, $CDCl_3$, 400 MHz) δ 1.91 (m, 2H) δ 2.25 (d, 4.4 Hz, 2H) δ 2.33 (s, 3H) δ 2.47 (t, *J* = 4.8 Hz, 4H) δ 3.86 (t, *J* = 4.8 Hz, 4H) δ 4.15 (t, *J* = 4.8 Hz, 2H) δ 6.21 (m, 1H) δ 6.74 (d, *J* = 5.2 Hz, 1H) δ 8.32 (d, *J* = 5.2 Hz, 1H).

Anal. Calcd. for $C_{14}H_{20}N_4O$ • 1.25 HBr • 0.5 H_2O: C, 45.39; H, 6.05; N 15.12. Found: C, 45.71; H 6.08; N, 15.27.

2-Chloro-4-(pyridin-3-yl)pyrimidine (24)

This compound was obtained using the previously published procedure [11].

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (dd, *J* = 4.8, 7.6, 1H) δ 7.72 (t, *J* = 4.8, 10 Hz 1H) δ 8.46 (m, 1H) δ 8.73 (d, *J* = 5.2 Hz, 1H) δ 8.79 (s, 1H) δ 9.27 (s, 1H); literature ^{1}H NMR ($CDCl_3$) δ 7.40 (ddd, *J* = 8.1, 4.8, 0.9 Hz, 1H) δ 7.71 (ddd, *J* = 8.4, 0.9 Hz, 1H) δ 7.78 (dd, *J* = 8.4, 2.4 Hz, 1H) δ 8.30 (ddd, *J* = 8.1, 2.1, 2.0 Hz, 1H), δ 8.66-8.68 (m, *J* = 4.8, 2.4, 1.8, 0.9 Hz, 2H) δ 9.18 (dd, *J* = 2.1, 0.9 Hz, 1H).

2-(4-Methylpiperazino)-4-(pyridin-3-yl)pyrimidine hydrobromide (31 • 2 HBr • 1.5 H_2O)

A solution of 2-chloro-4-(pyridin-3-yl)pyrimidine (80 mg, 0.42 mmol) was treated with 1-methylpiperazine (125 mg, 1.25 mmol) in toluene (1 ml) under reflux for 3 h. The reaction was purified as described in the general procedure.

This compound had a mp of 163-165 °C; yield 84%; ^{1}H NMR (DMSO-d_6, 400 MHz,) δ 2.87 (d, *J* = 3.6 Hz, 3H) δ 3.13 MHz (m, 2H) δ 3.37 (m, 2H) δ 3.55 (m, 2H), δ 4.91 (m) δ 7.55 (d, *J* = 5.2 Hz, 1H) δ 7.91 (m, *J* = 5.2 Hz, 1H) δ 8.66 (d, *J* = 5.2 Hz, 1H) δ 8.92 (m, *J* = 5.2 Hz, 2H) δ 9.53 (s, 1H), δ 9.93 (s, 1H).

Anal. Calcd. for $C_{14}H_{17}N_5$ • 1.5 H_2O • 2 HBr: C, 37.86; H 4.99; N, 15.77. Found: C, 38.02; H, 4.46; N, 15.58.

2-Chloro-4(2,2'-bithiophen-5-yl)pyrimidine (25) This compound was obtained following the procedure reported without characterization in published literature [12].

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.07 (m, 1H) δ 7.22 (d, *J* = 4 Hz, 1H) δ 7.32 (t, *J* = 1.2, 4.4 Hz, 2H) δ 7.43 (d, *J* = 5.4 Hz, 1H) δ 7.71 (d, *J* = 4 Hz, 1H) δ 8.52 (d, *J* = 5.4, 1H).

4-(2,2'-Bithiophen-5-yl)-2-(4-methylpiperazino)pyrimidine hydrobromide (32 • 1.5 HBr • 2 H_2O)

2-Chloro-4(2,2'-bithiophen-5-yl)-pyrimidine (103 mg, 0.37 mmol) was allowed to react with 1-methylpiperazine (111 mg, 0.0011 mmol) in toluene (1 ml) for 3 h under reflux. The resulting compound was isolated and converted to a salt using the purification procedure described above.

This compound had a melting point of 187-190 °C; yield 76%; ^{1}H NMR (free base, $CDCl_3$, 400 MHz) δ 2.36 (s, 3H) δ 2.51 (t, *J* = 5.0 Hz, 4H) δ 3.92 (t, *J* = 5.0 Hz, 4H) δ 6.79 (d, *J* = 5.2 Hz,

1H) δ 7.05 (m, *J* = 4.0 Hz, 1H) δ 7.18 (d, *J* = 4 Hz, 1H) δ 7.27 (m, 2H) δ 7.55 (d, *J* = 4 Hz, 1H) δ 8.29 (d, *J* = 5.2 Hz, 1H).

Anal. Calcd. for $C_{17}H_{18}N_4S_2$ • 1.5 HBr • 2 H_2O: C, 40.85; H 4.74; N, 11.21. Found: C, 40.54; H, 4.41; N, 11.04.

2-Chloro-4-(9-phenylanthryl)pyrimidine (20)

A solution of 9-bromoanthracene (400 mg, 1.56 mmol) in THF (2 ml) was treated with butyllithium (2.5 M, 0.6 ml, 1.5 mmol) at -78 °C under dry nitrogen for 30 seconds. A solution of 2-Chloropyrimidine (178 mg, 1.55 mmol) in THF (1 ml) was added dropwise. The reaction was allowed to proceed for 40 minutes, until the temperature reached -30 °C. The work up and purification were preformed as described in the general procedure.

This compound was obtained at a yield 44%; oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (m, *J* = 4.8 Hz, 2H) δ 7.66 (m, 2H) δ 7.88 (m, 2H) δ 8.09 (d, *J* = 8 Hz, 1H) δ 8.66 (m, 2H) δ 8.71 (d, *J* = 8 Hz, 1H).

2-(4-Methylpiperazino)-4-(9-phenylanthryl)pyrimidine hydrobromide (33 • 1.5 HBr • 2 H_2O)

2-Chloro-4-(9-phenylanthryl)pyrimidine (200 mg, 0.69 mmol) was allowed to react with 1-methylpiperazine (207 mg, 2.07 mmol) in toluene (1 ml) under reflux at 100 °C for 3 h. This compound was purified and the salt was formed as described above.

This compound had a mp of 195-198 °C; yield 78%; ^{1}H NMR (free base, $CDCl_3$, 400 MHz) δ 2.32 (s, 3H) δ 2.48 (t, *J* = 10 Hz, 4H) δ 3.95 (t, *J* = 10 Hz, 4H) δ 6.81 (d, *J* = 5.2 Hz, 1H) δ 7.58 (m, 2H) δ 7.65 (m, 2H) δ 7.89 (m, 2H) δ 8.28 (d, *J* = 8.4 Hz, 1H) δ 8.44 (t, *J* = 5.2 Hz, 1H) δ

8.71 (m, *J* = 8.0, 8.4 Hz, 2H).

Anal. Calcd. for $C_{23}H_{22}N_4$ • 1.5 HBr • 2 H_2O: C, 53.97; H 5.42; N, 10.95. Found: C, 54.35; H, 5.04; N, 10.96.

2-Chloro-4-(1-phenylvinyl)pyrimidine (21)

A solution of α-bromostyrene (416 mg, 2.27 mmol) in THF (5 ml) was cooled to -78 °C under dry nitrogen and n-butyllithium (2.5 M, 0.9 ml, 2.25 mmol) was added dropwise over 1min. 2-Chloropyrimidine (227 mg, 2.4 mmol) in THF (1 ml) was introduced drop wise. The solution was allowed to react for 25 min at -78 ˚C, the raised to -40 °C over 40 min. The resulting solution was subject to work-up and purification as described in the general procedure.

This compound was obtained at a yield of 38%; brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75 (d, *J* = 1.2 Hz, 1H) δ 6.45 (d, *J* = 1.2 Hz, 1H) δ 7.09 (d, J = 5.2 Hz, 1H) δ 7.30 (m, 2H) δ 7.38 (m, 3H) δ 8.51 (d, *J* = 5.2 Hz, 1H).

2-(4-Methylpiperazino)-4-(2-(4-methylpiperazino)-1-phenylethyl)pyrimidine hydrochloride (41 • 4 HCl • 1 H_2O)

2-Chloro-4-(1-phenylvinyl)pyrimidine (143 mg, 0.66 mmol) was dissolved in toluene (1 ml) and treated with 1-methylpiperazine (198 mg, 1.98 mmol) for 3 h at 100 °C. The purification and salt formation occurred as described above.

This compound was obtained at a 34% yield; as a thick brown oil; ^{1}H NMR (free base, $CDCl_3$, 400 MHz) δ 2.33 (m, 6H) δ 2.34 (m, 7H) δ 2.50 (m, 9H) δ 2.88 (dd, *J* = 6.0, 6.8 Hz, 1H) δ 3.38 (dd, *J* = 4.8, 8.0 Hz, 1H) δ 3.87 (t, *J* = 5.2 Hz, 4H) δ 4.06 (m, 1H) δ 6.37 (d, *J* = 5.2 Hz, 1H) δ 7.21 (m, 1H) δ 7.27 (m, 2H) δ 7.34 (m, 2H) δ 8.32 (d, *J* = 5.2 Hz, 2H).

Anal. Calcd. for $C_{22}H_{32}N_6$ • 4 HCl • 1 H_2O: C, 48.54; H 7.04; N, 15.44. Found: C, 48.16; H, 7.21; N, 15.17.

2-(4-Methylpiperazino)-4-(1-phenylvinyl)pyrimidine hydrobromide (42 • 3.5 HBr • 2 H_2O)

A sample of 2-(4-Methylpiperazino)-4-(2-(4-methylpiperazino)-1-phenylethyl)pyrimidine hydrobromide was dissolved in DMSO and heated to 70 °C for 40 min. The mixture was cooled to 25 °C and treated with excess sodium carbonate, and the pure product was collected by extraction with dichloromethane.

This compound was a hydroscopic brown oil; yield 99%; ^{1}H NMR (free base, $CDCl_3$, 400 MHz) δ 2.34 (s, 3H) δ 2.46 (m, *J* = 3.0 Hz, 4H) δ 3.90 (m, *J* = 3.0 Hz, 4H) δ 6.70 (m, 1H) δ 7.50 (m, 2H) δ 7.60 (m, 1H) δ 8.08 (m, 2H) δ 8.53 (m, 1H).

Anal. Calcd. for $C_{17}H_{20}N_4$ • 3.5 HBr • 2 H_2O: C, 34.05; H 4.62; N, 9.34. Found: C, 34.30; H, 4.73; N, 8.92.

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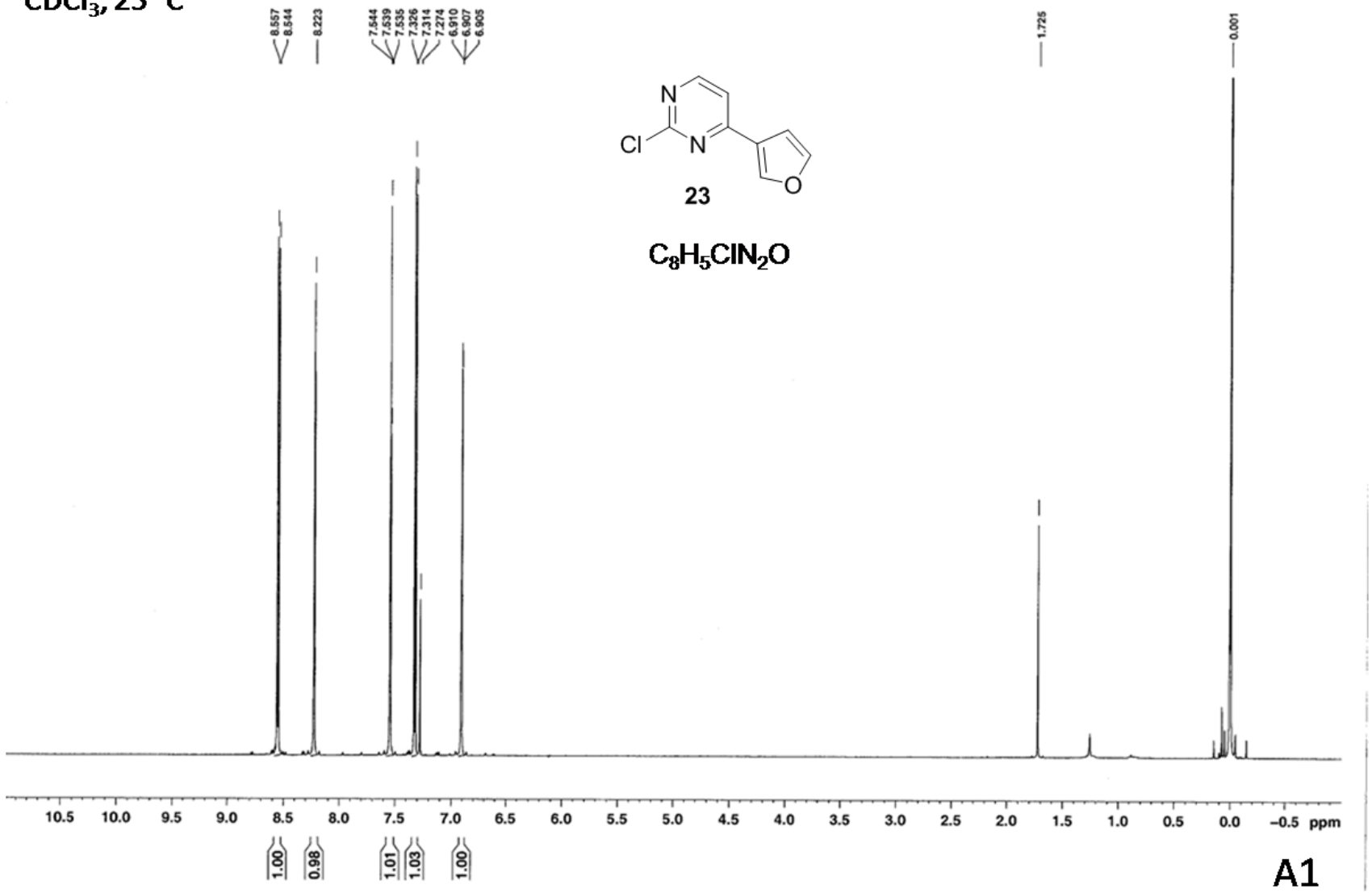
400 MHz

$CDCl_3$, 25 °C



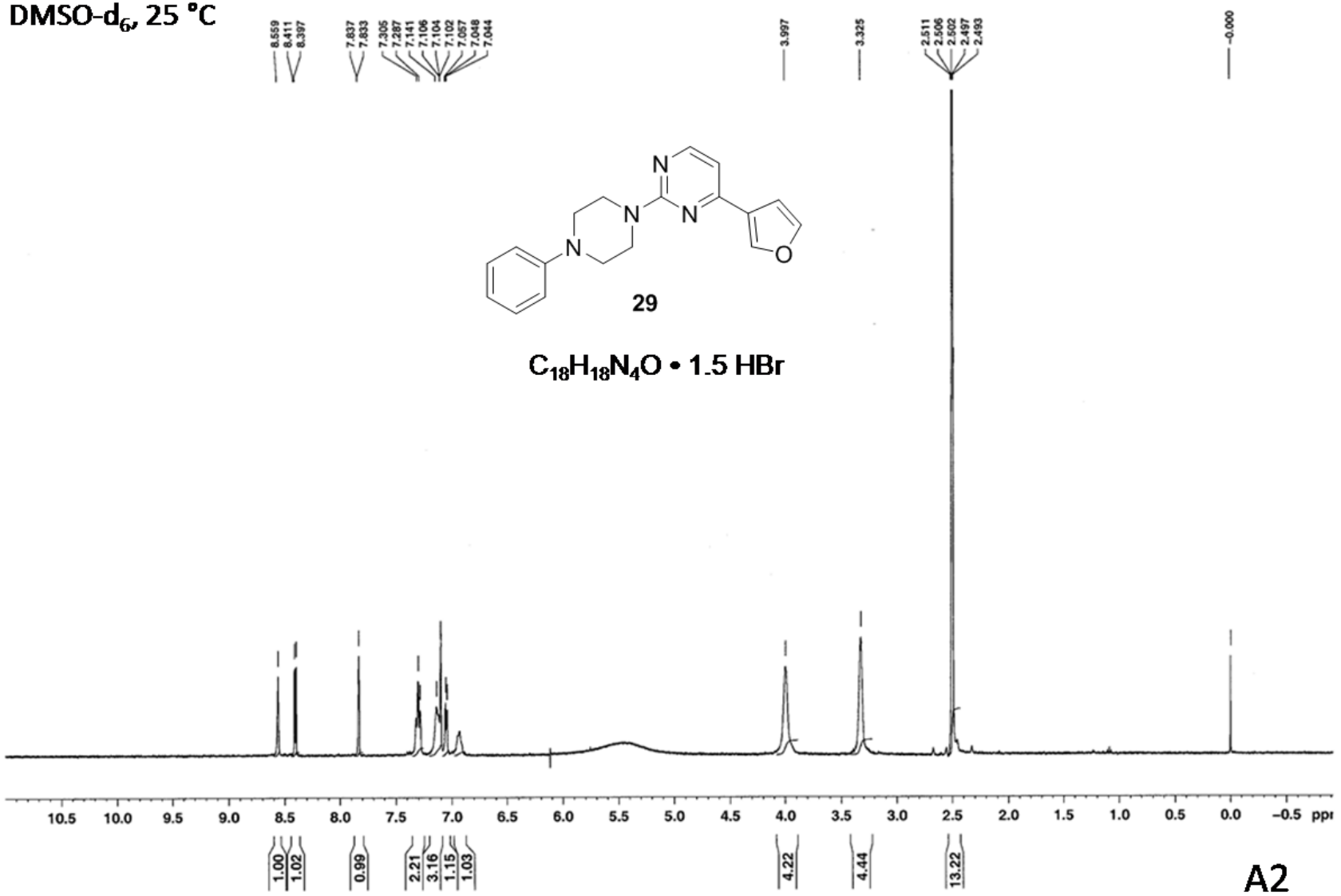
23

$C_8H_5ClN_2O$

A1

400 MHz

DMSO-d_6, 25 °C

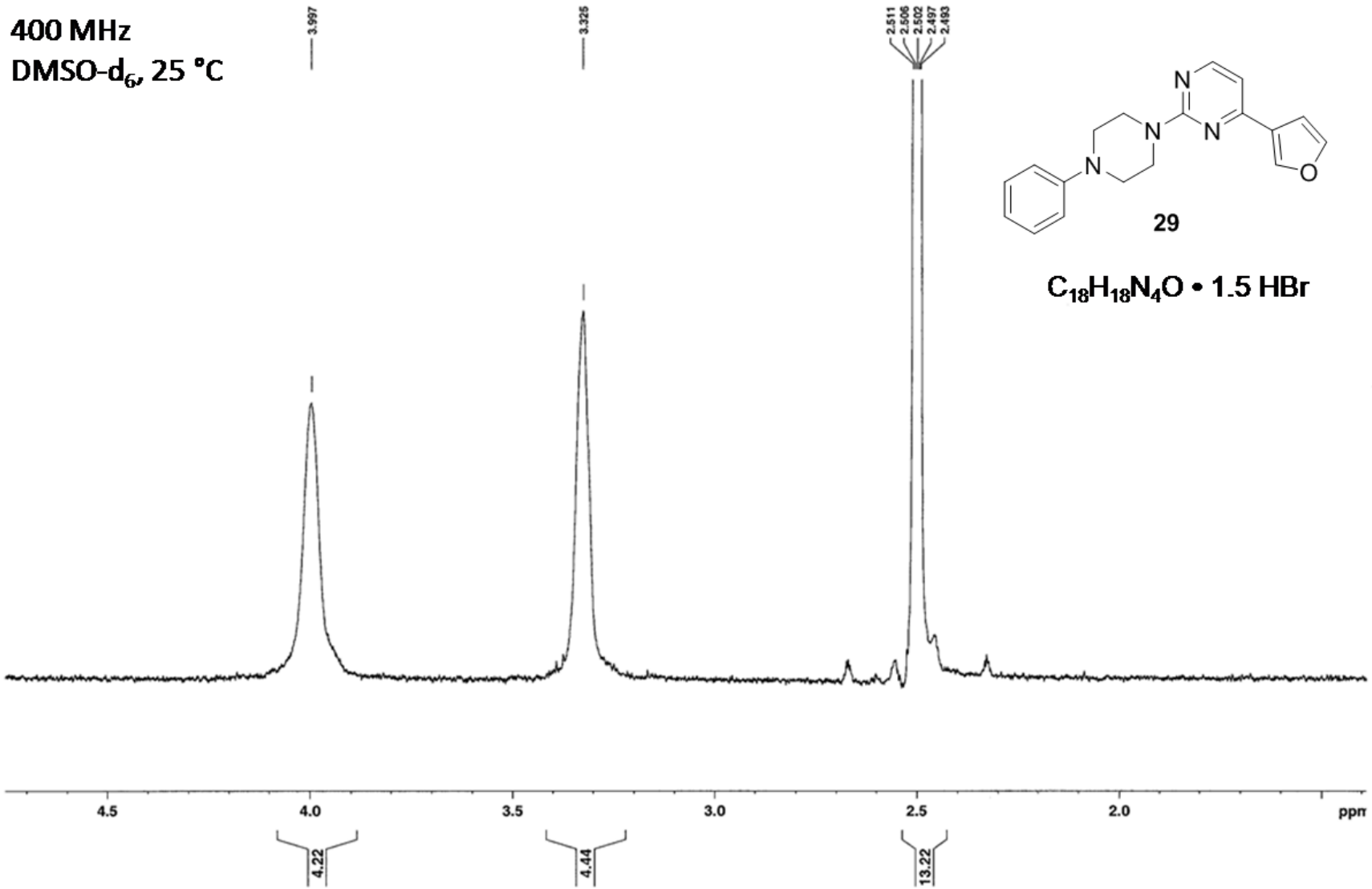


29

$C_{18}H_{18}N_4O \cdot 1.5\ HBr$

A2

400 MHz
DMSO-d_6, 25 °C



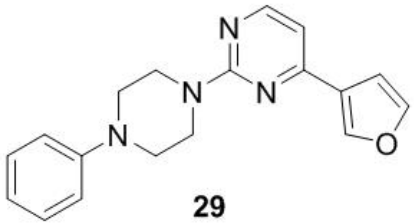
29

$C_{18}H_{18}N_4O \cdot 1.5\ HBr$

A3

400 MHz

DMSO-d_6, 25 °C



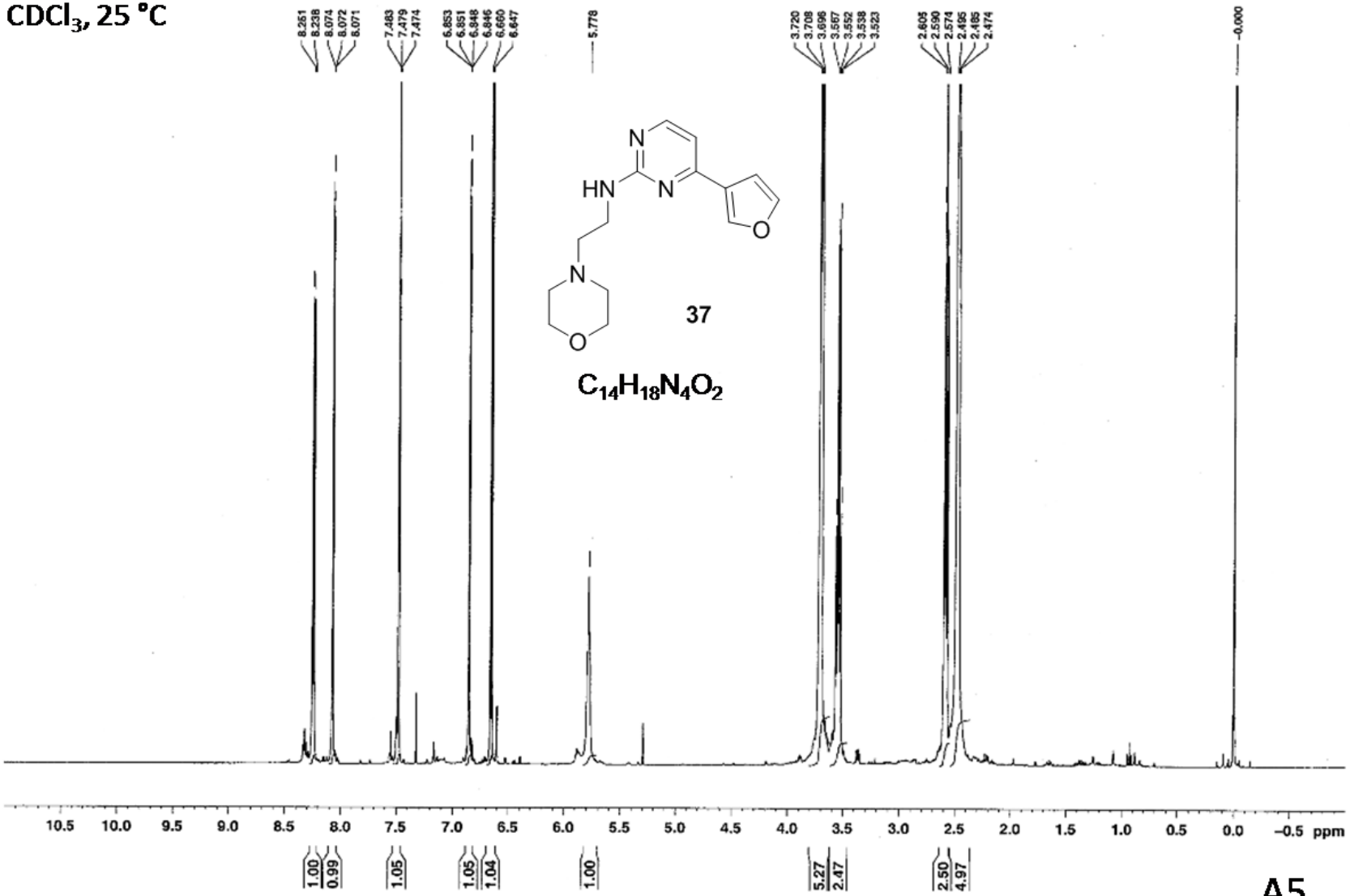
29

$C_{18}H_{18}N_4O \cdot 1.5\ HBr$

A4

400 MHz

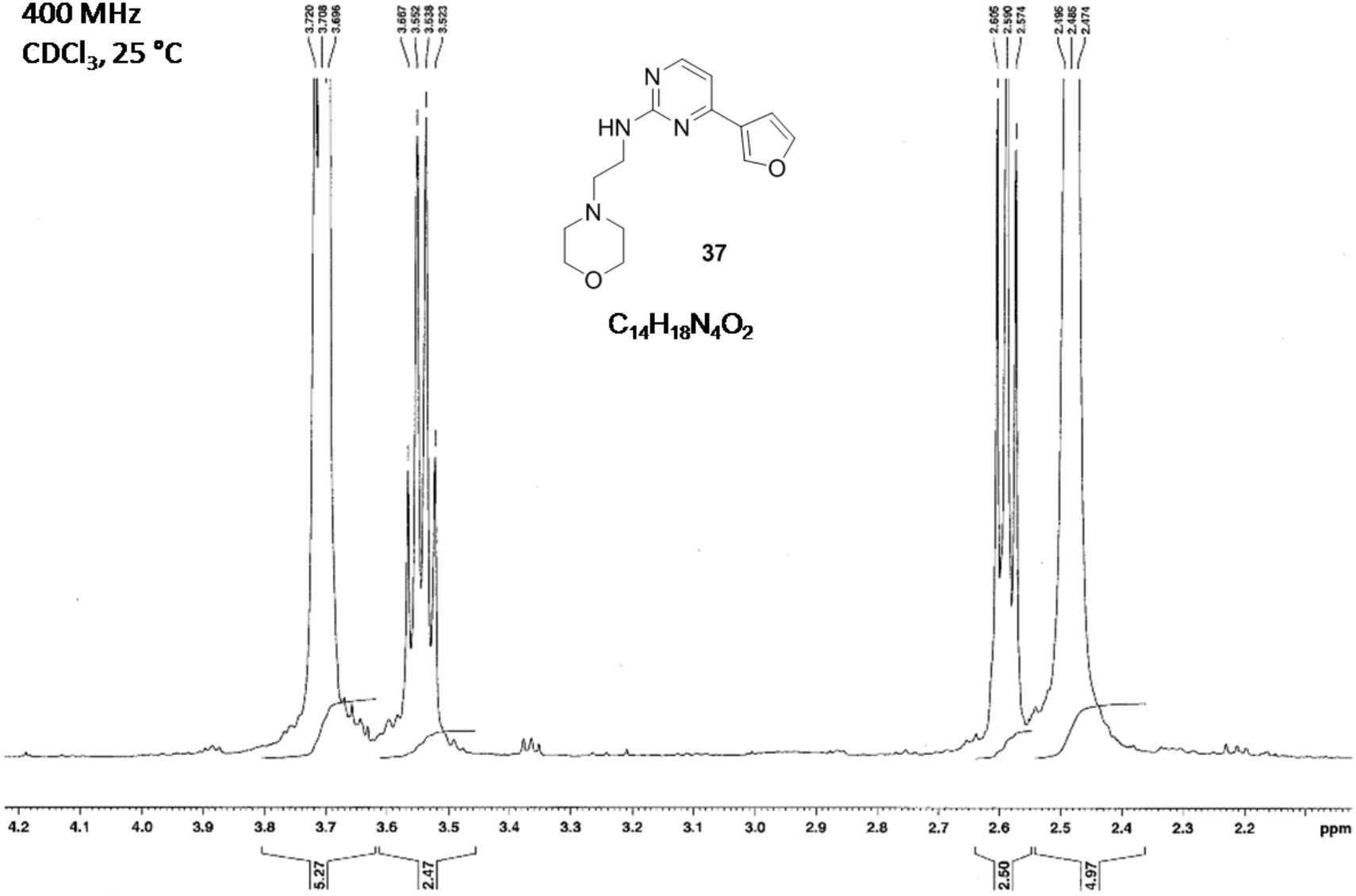
$CDCl_3$, 25 °C



A5

400 MHz

$CDCl_3$, 25 °C



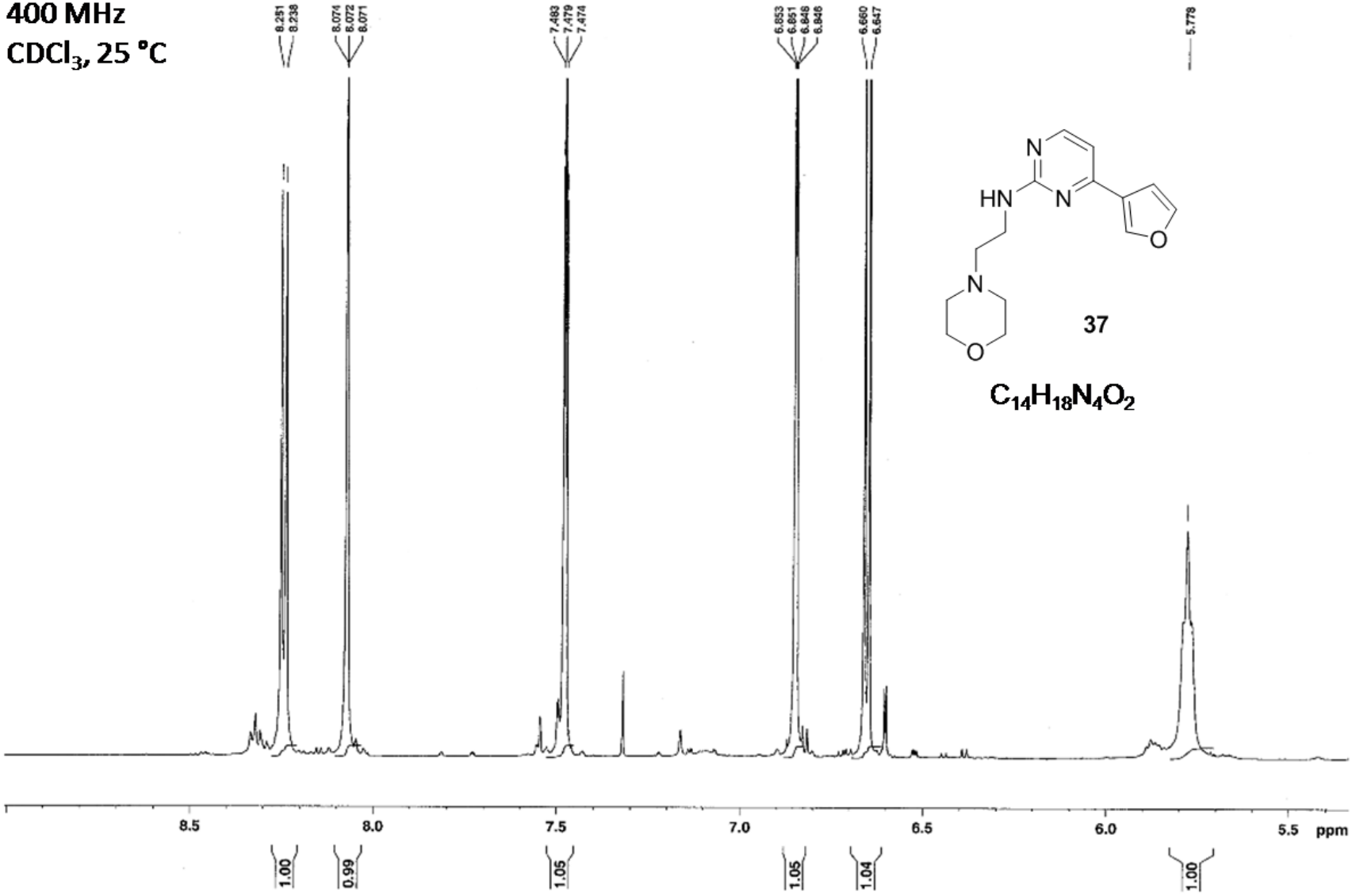
37

$C_{14}H_{18}N_4O_2$

A6

400 MHz

$CDCl_3$, 25 °C



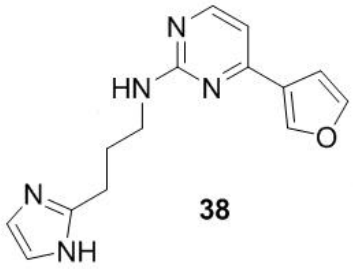
37

$C_{14}H_{18}N_4O_2$

A7

400 MHz

$CDCl_3$, 25 °C



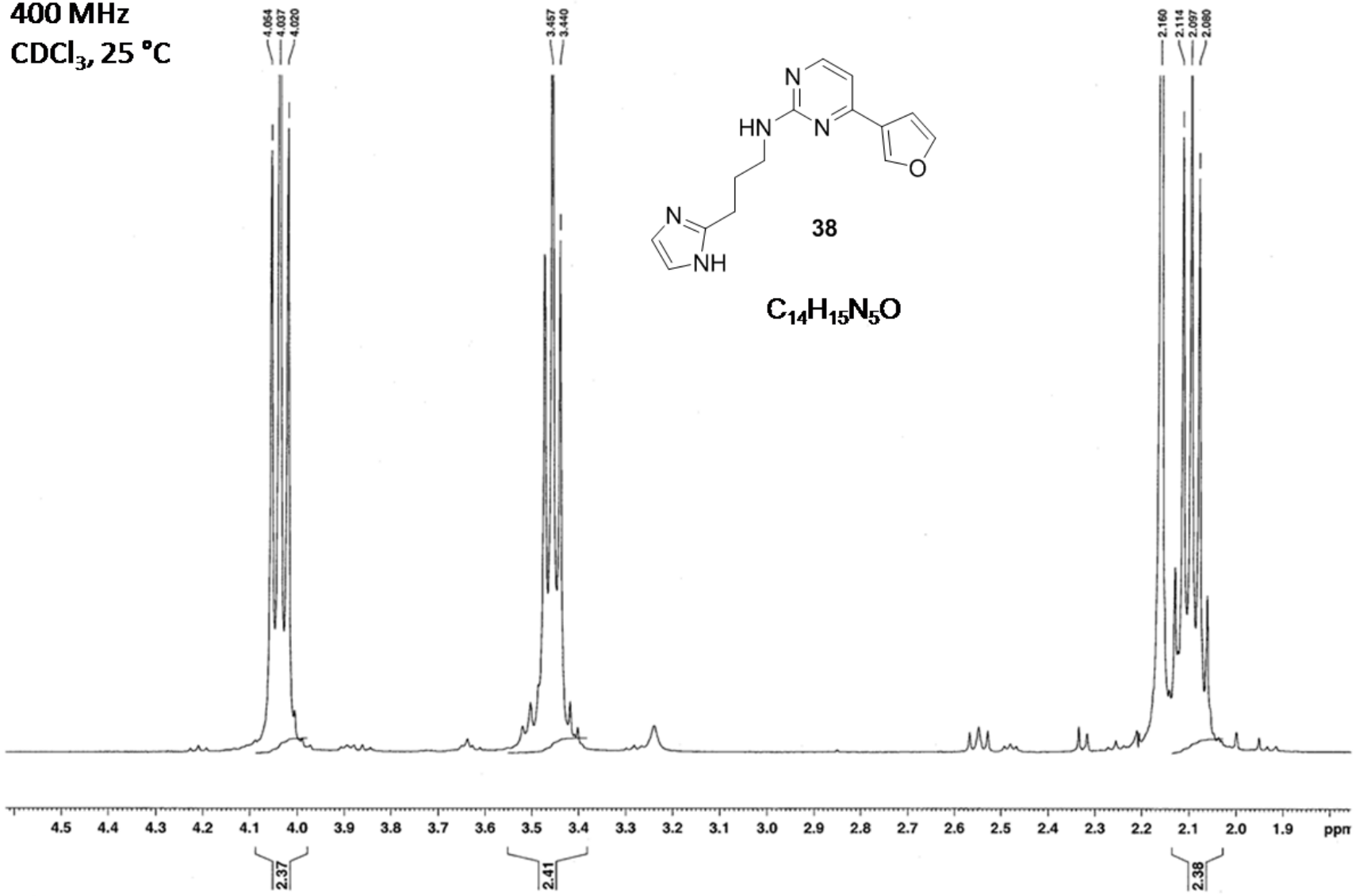
38

$C_{14}H_{15}N_5O$

A8

400 MHz

$CDCl_3$, 25 °C

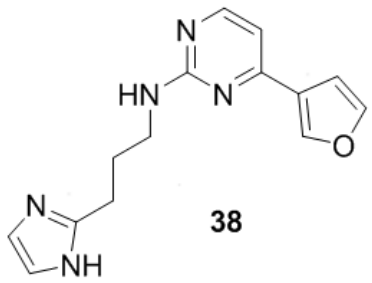


$C_{14}H_{15}N_5O$

A9

400 MHz

$CDCl_3$, 25 °C



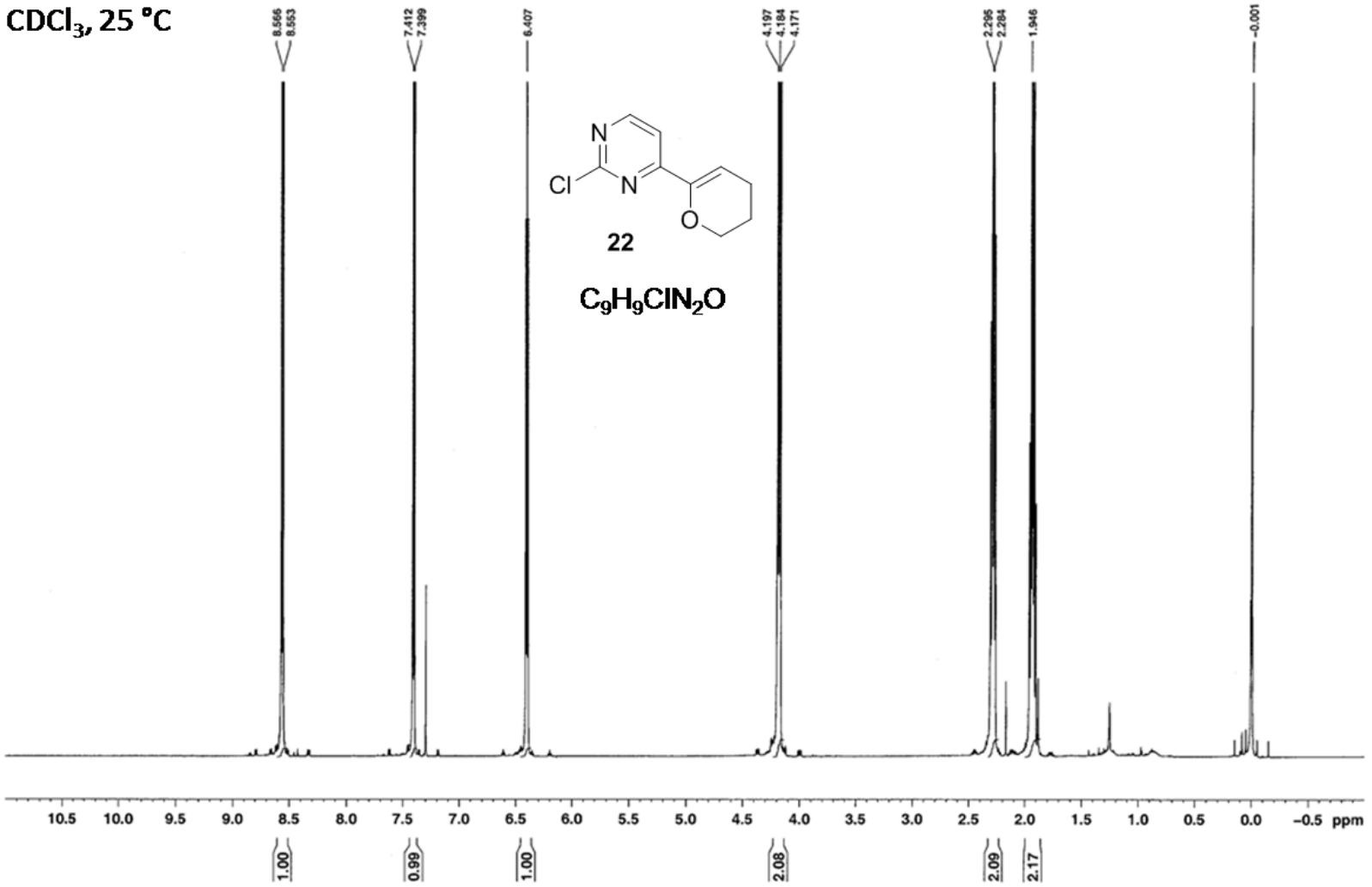
38

$C_{14}H_{15}N_5O$

A10

400 MHz

$CDCl_3$, 25 °C



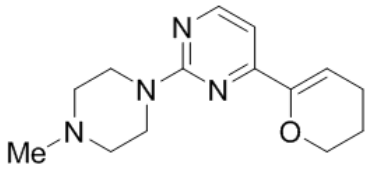
22

$C_9H_9ClN_2O$

A11

400 MHz

$CDCl_3$, 25 °C



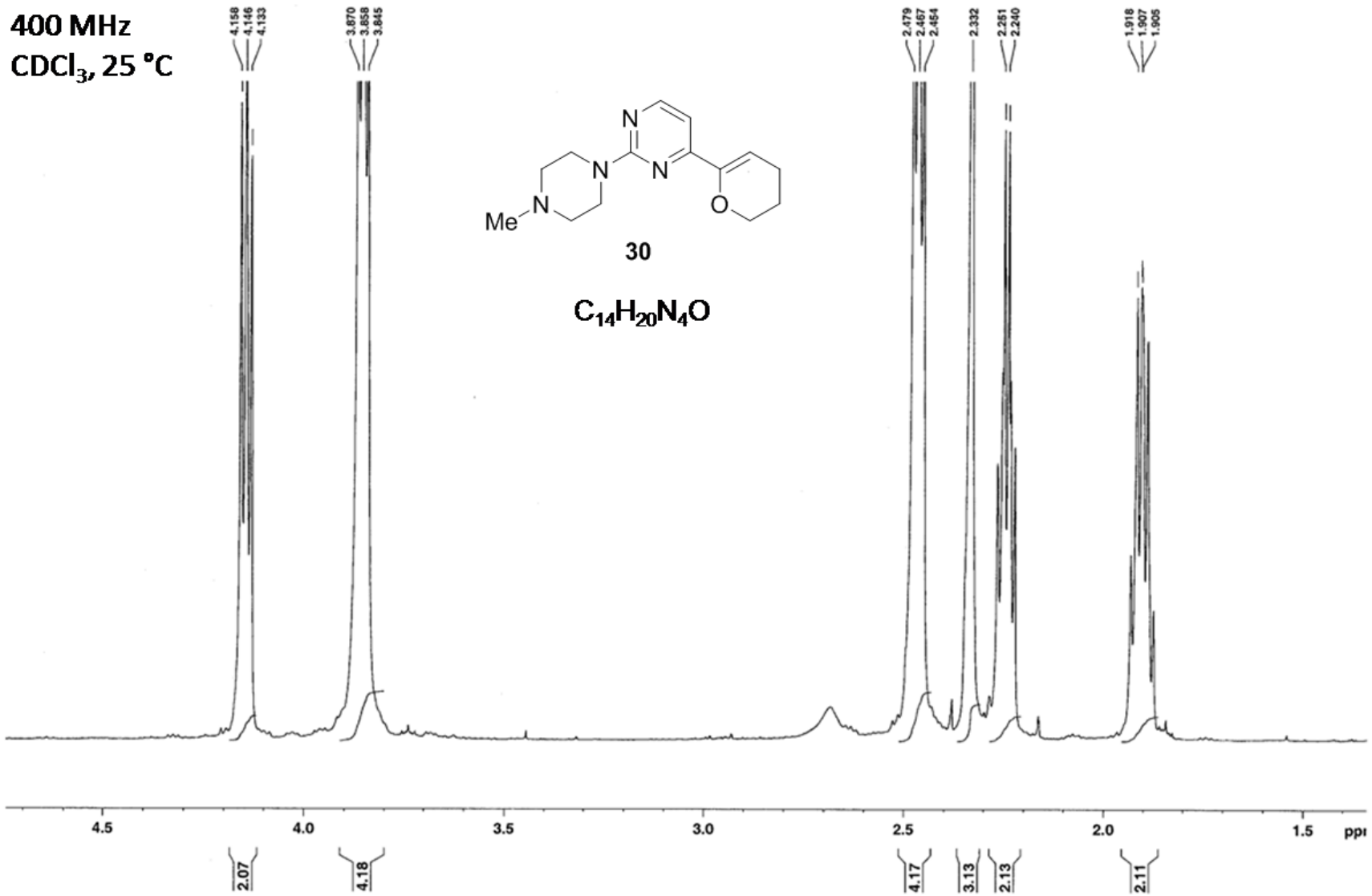
30

$C_{14}H_{20}N_4O$

A12

400 MHz

$CDCl_3$, 25 °C



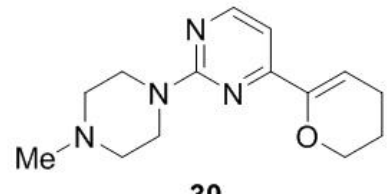
30

$C_{14}H_{20}N_4O$

A13

400 MHz

$CDCl_3$, 25 °C

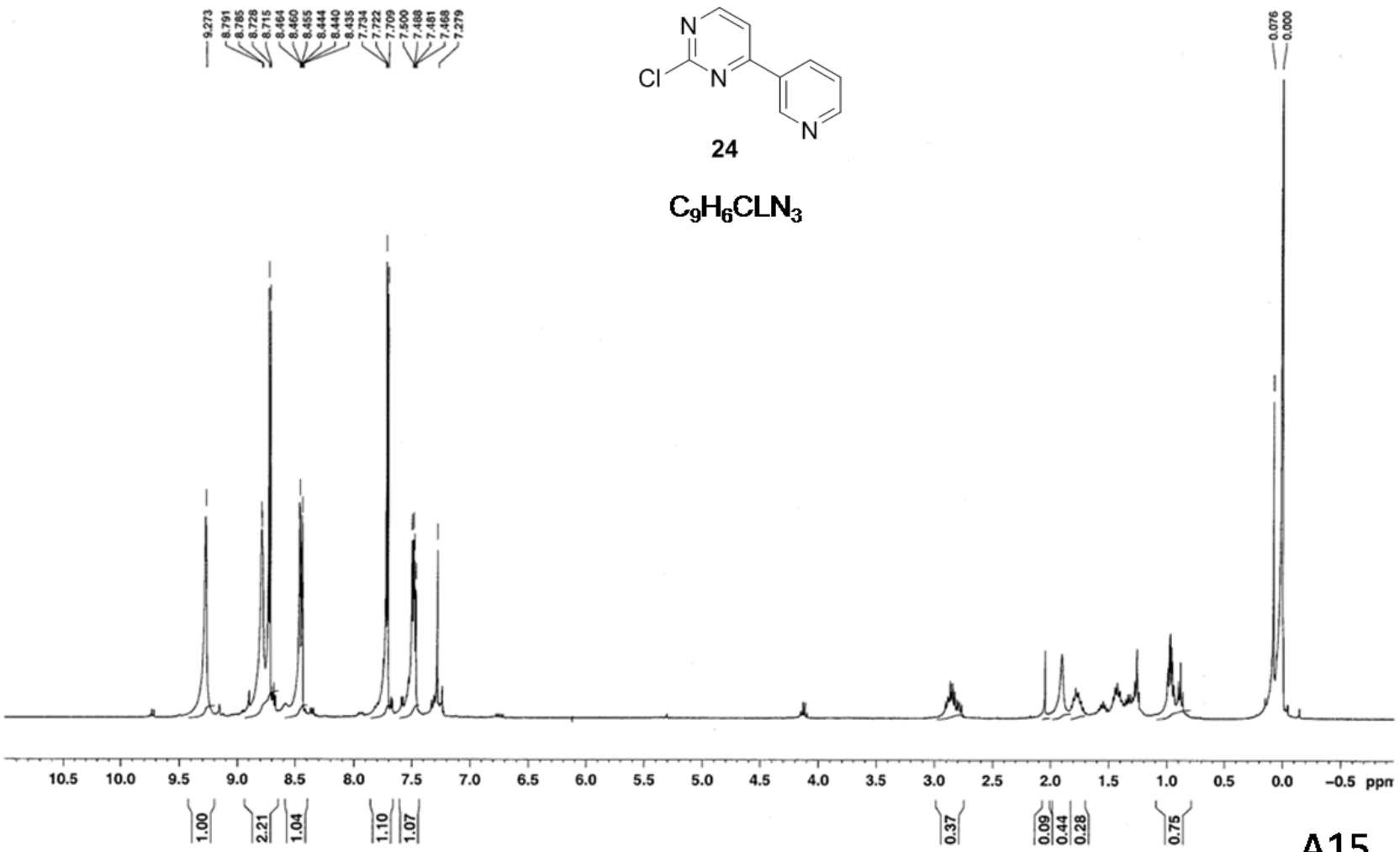


30

$C_{14}H_{20}N_4O$

A14

400 MHz
$CDCl_3$, 25 °C



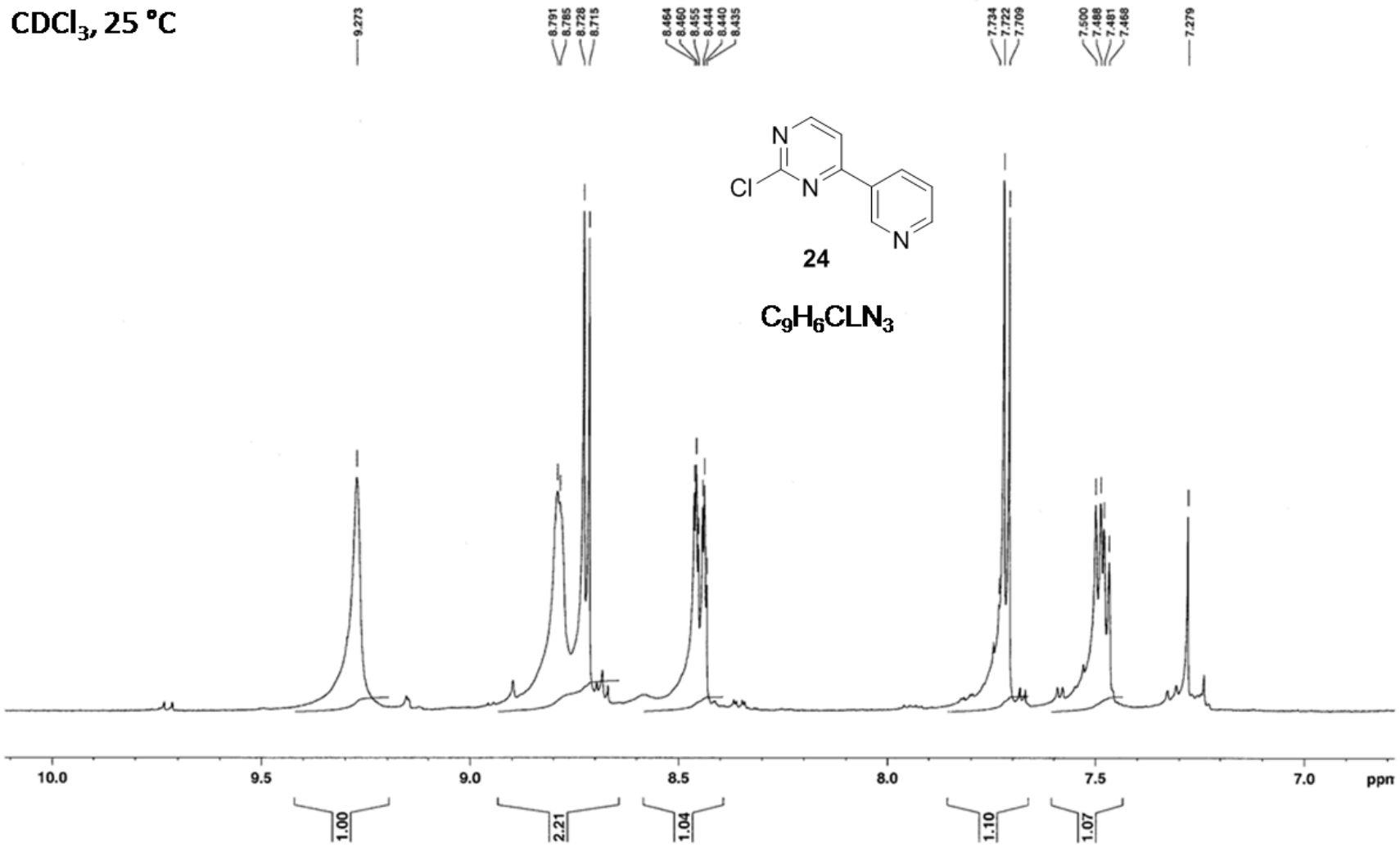
24

$C_9H_6CLN_3$

A15

400 MHz

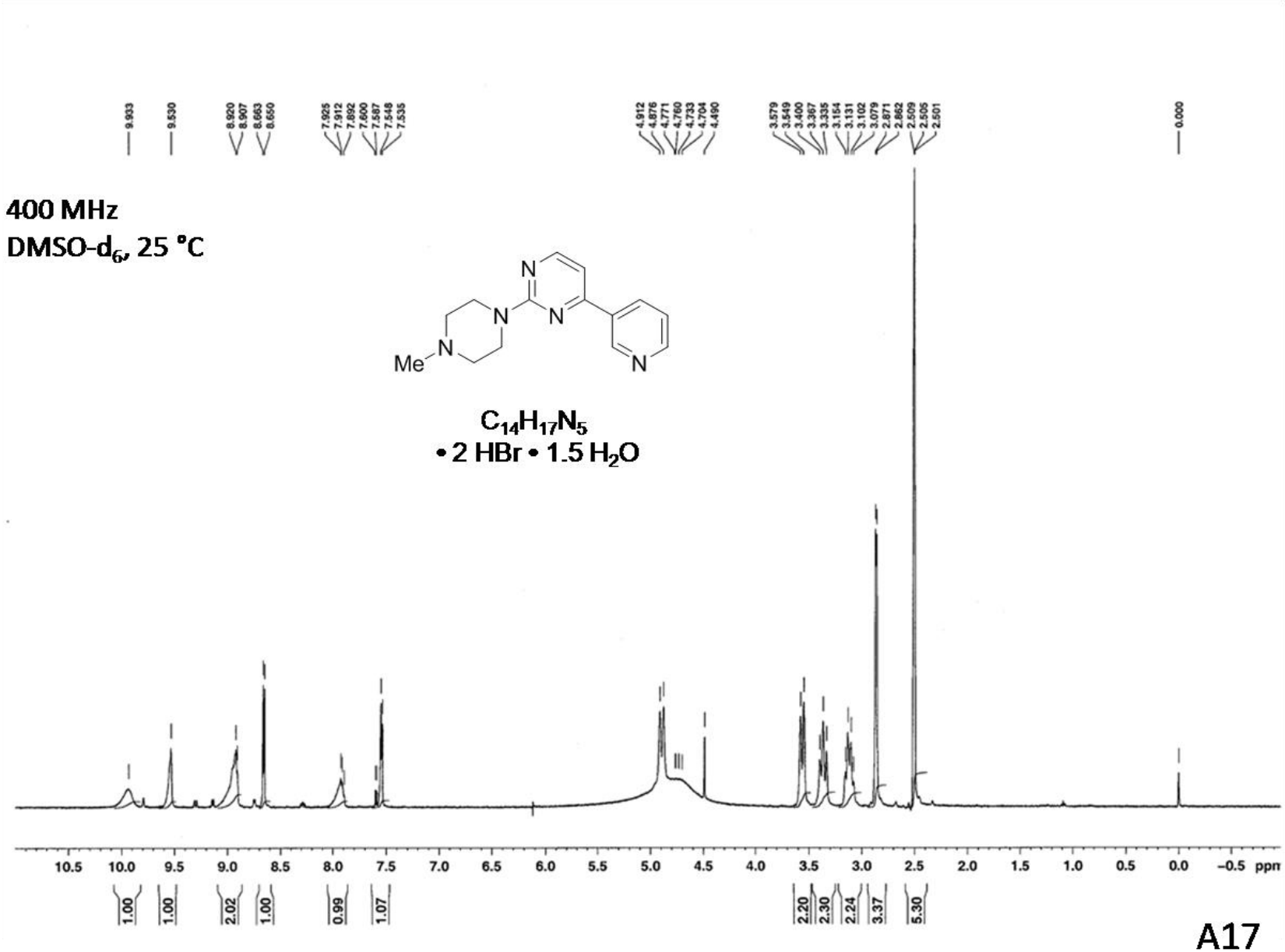
$CDCl_3$, 25 °C



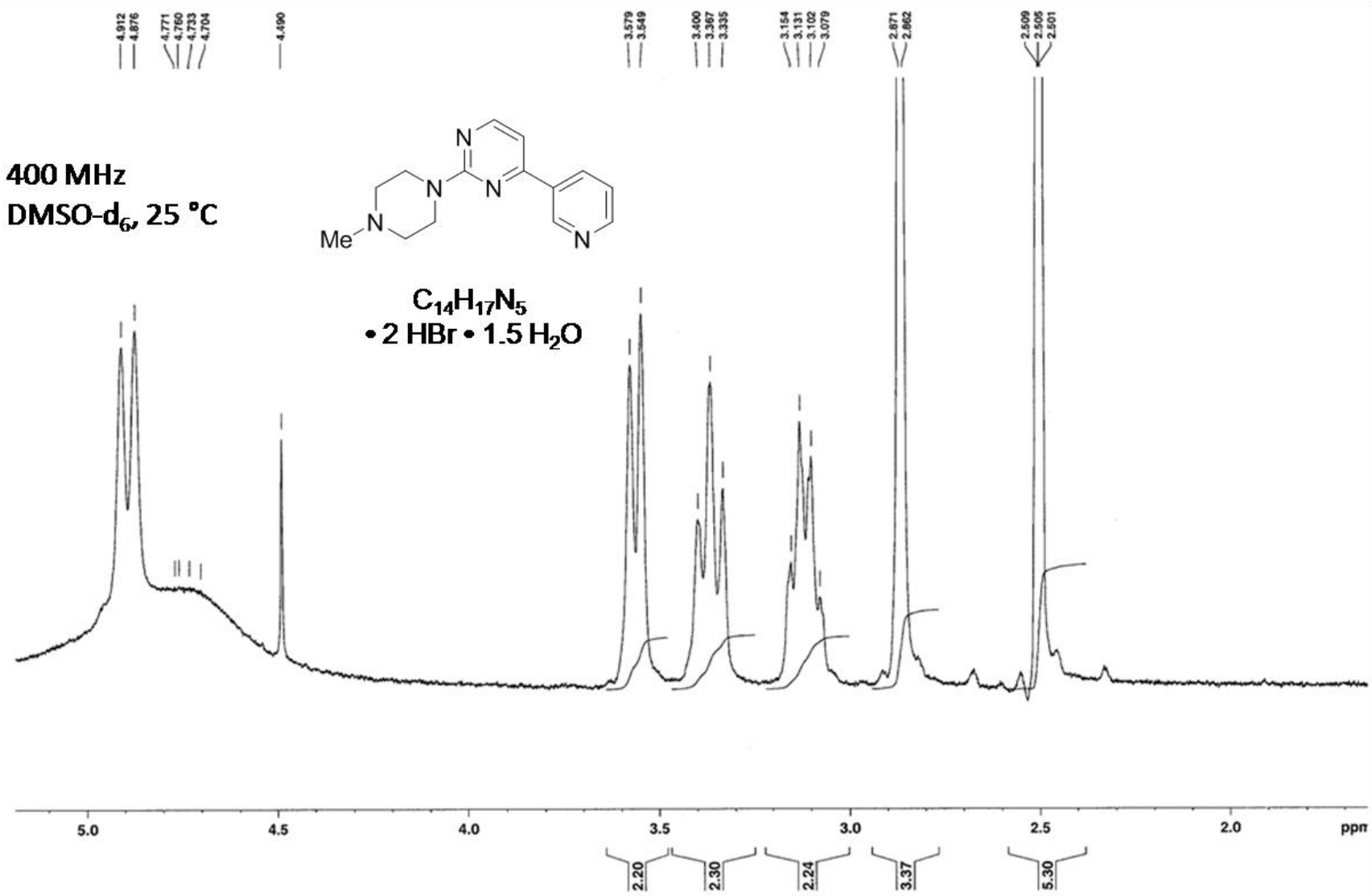
24

$C_9H_6ClN_3$

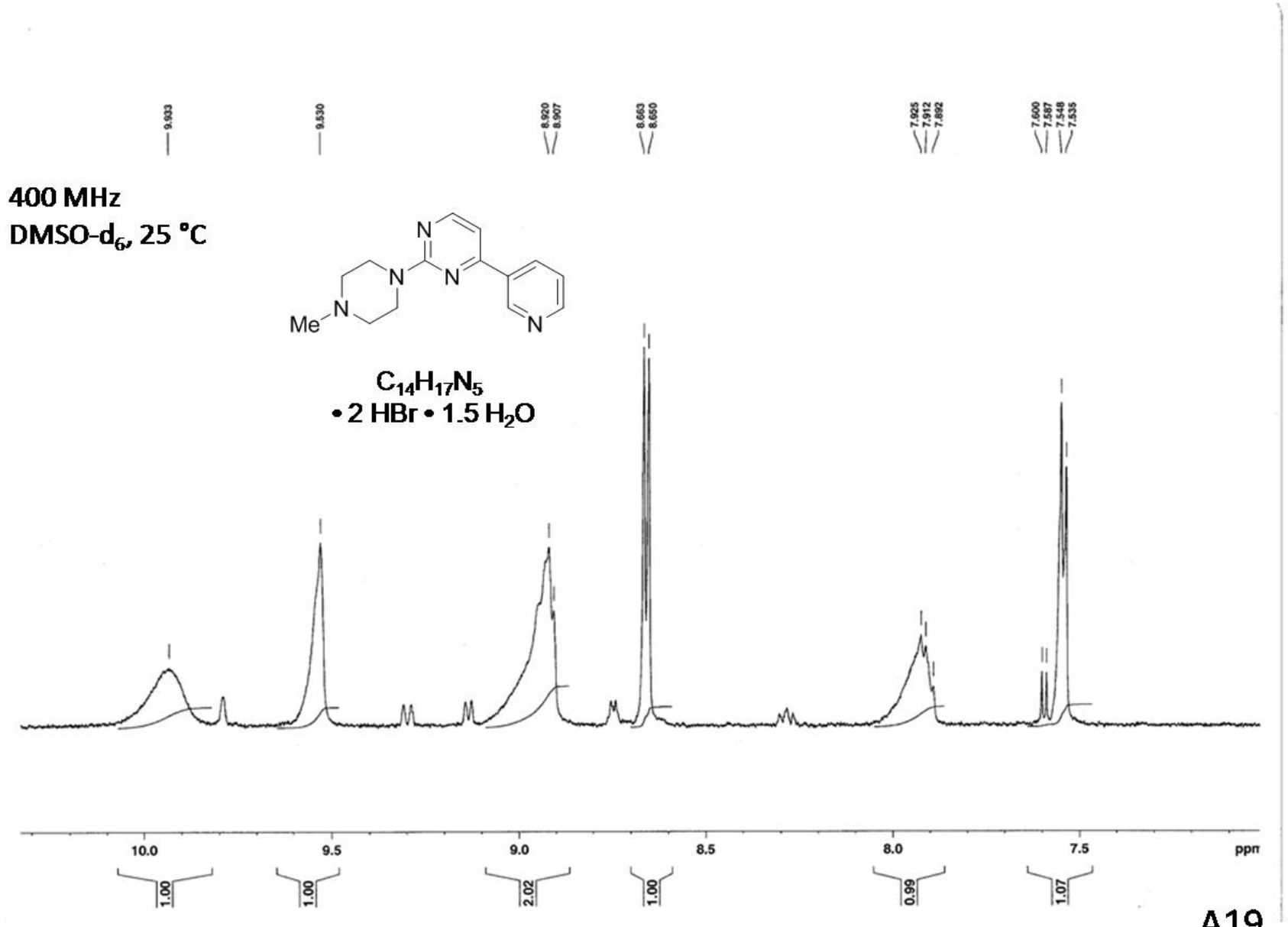
A16


9.933
9.530
8.920
8.907
8.663
8.650
7.925
7.912
7.892
7.600
7.587
7.548
7.535
4.912
4.876
4.771
4.760
4.733
4.704
4.490
3.579
3.549
3.400
3.367
3.335
3.154
3.131
3.102
3.079
2.871
2.862
2.509
2.505
2.501
0.000
400 MHz
DMSO-d6, 25 °C
N
N
N
N
Me
N
C14H17N5
• 2 HBr • 1.5 H2O
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5 ppm
1.00
1.00
2.02
1.00
0.99
1.07
2.20
2.30
2.24
3.37
5.30

A17


4.912
4.876
4.771
4.760
4.733
4.704
4.490
3.579
3.549
3.400
3.367
3.335
3.154
3.131
3.102
3.079
2.871
2.862
2.509
2.505
2.501
400 MHz
DMSO-d6, 25 °C
Me
N
C14H17N5
• 2 HBr • 1.5 H2O
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
2.20
2.30
2.24
3.37
5.30

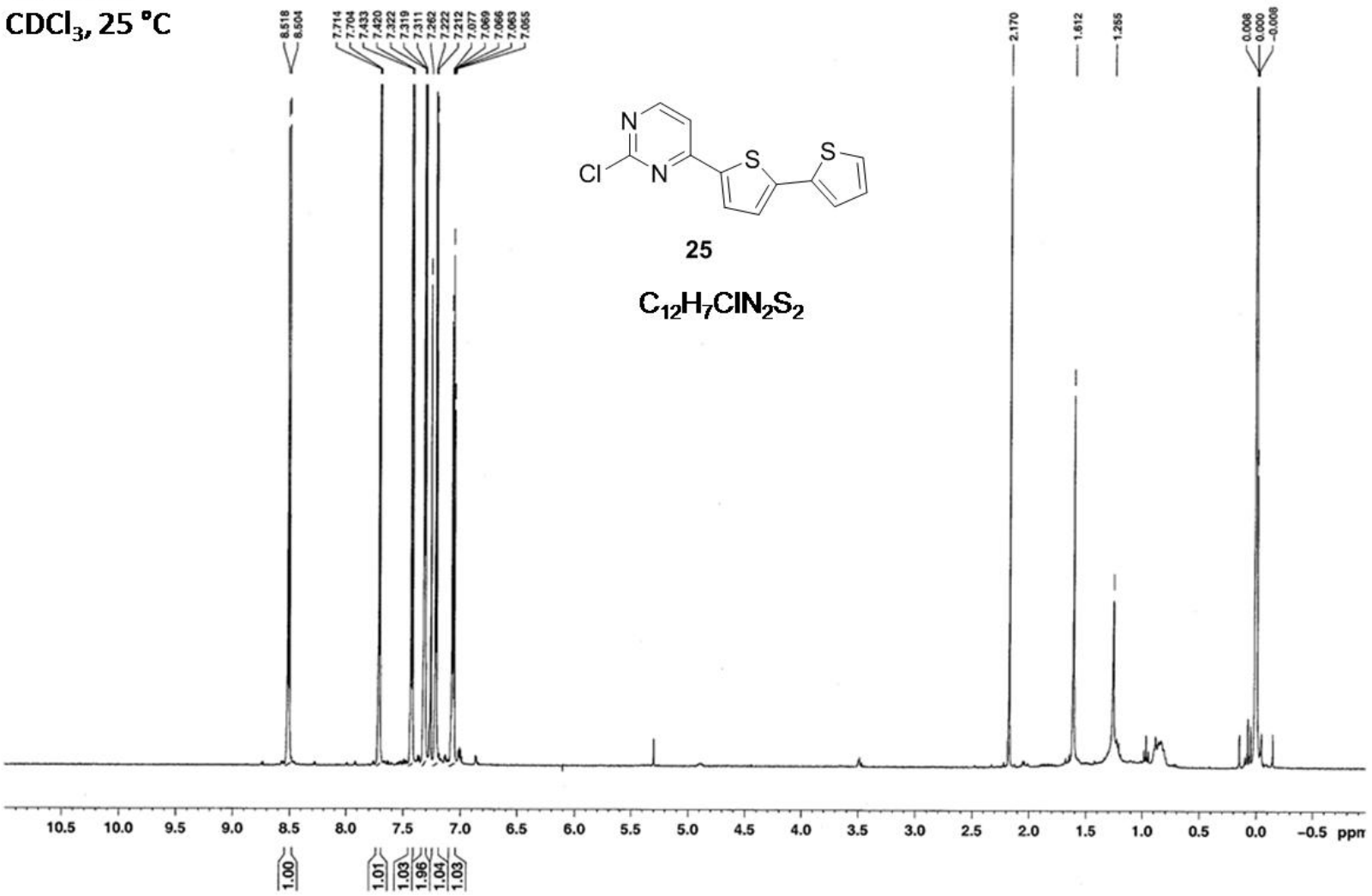
A18


9.933
9.530
8.920
8.907
8.663
8.650
7.925
7.912
7.892
7.600
7.587
7.548
7.535
400 MHz
DMSO-d6, 25 °C
N
N
N
N
Me
N
C14H17N5
• 2 HBr • 1.5 H2O
10.0
9.5
9.0
8.5
8.0
7.5
ppm
1.00
1.00
2.02
1.00
0.99
1.07

A19

400 MHz

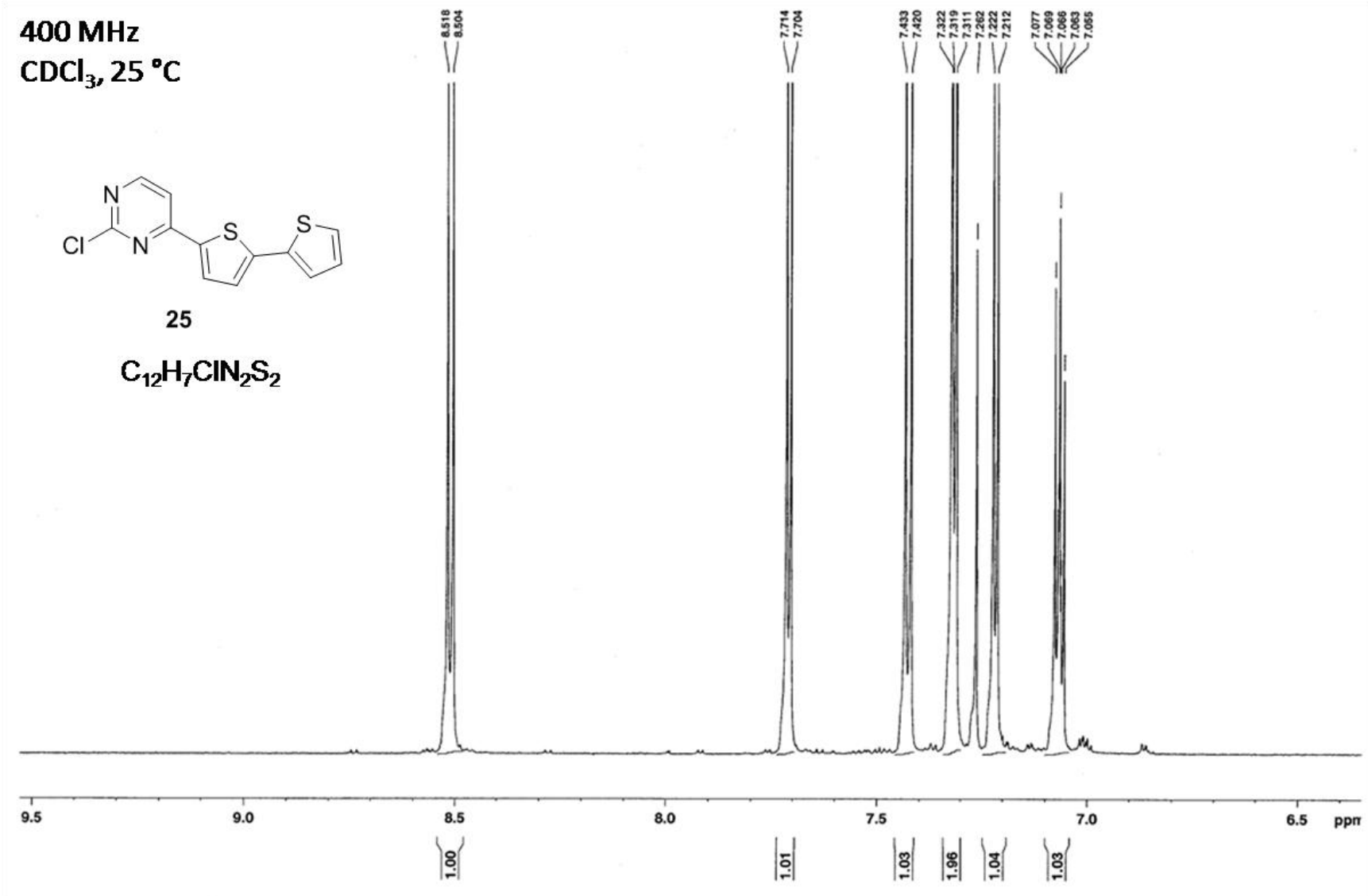
$CDCl_3$, 25 °C



25

$C_{12}H_7ClN_2S_2$

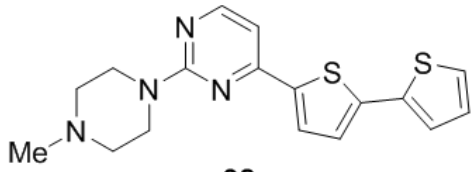
A20


400 MHz
CDCl3, 25 °C
N
Cl
N
S
S
25
C12H7ClN2S2
8.518
8.504
7.714
7.704
7.433
7.420
7.322
7.319
7.311
7.262
7.222
7.212
7.077
7.069
7.066
7.063
7.055
9.5
9.0
8.5
8.0
7.5
7.0
6.5
ppm
1.00
1.01
1.03
1.96
1.04
1.03

A21

400 MHz

$CDCl_3$, 25 °C



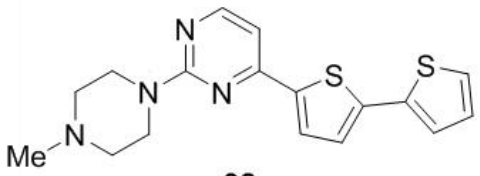
32

$C_{17}H_{18}N_4S_2$

A22

400 MHz

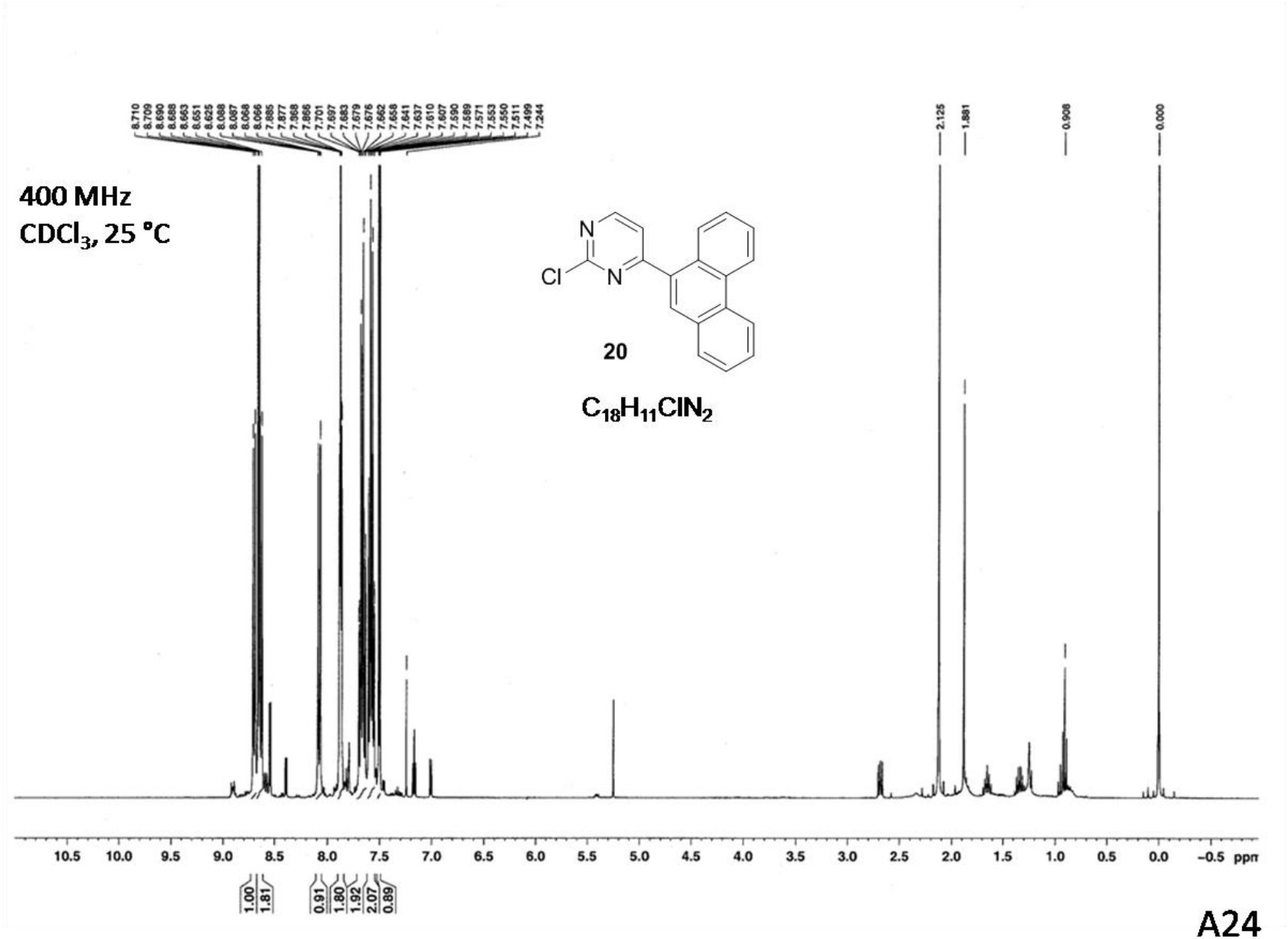
$CDCl_3$, 25 °C



32

$C_{17}H_{18}N_4S_2$

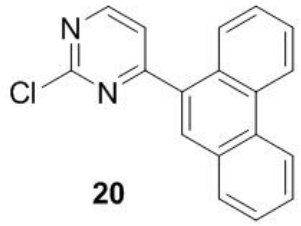
A23


400 MHz
CDCl3, 25 °C
8.710
8.709
8.690
8.688
8.663
8.651
8.625
8.088
8.087
8.068
8.066
7.885
7.877
7.868
7.868
7.701
7.697
7.683
7.679
7.676
7.662
7.658
7.641
7.637
7.610
7.607
7.590
7.589
7.571
7.553
7.550
7.511
7.499
7.244
2.125
1.881
0.908
0.000
N
Cl
N
20
C18H11ClN2
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5 ppm
1.00
1.81
0.91
1.80
1.92
2.07
0.89

A24

400 MHz

$CDCl_3$, 25 °C



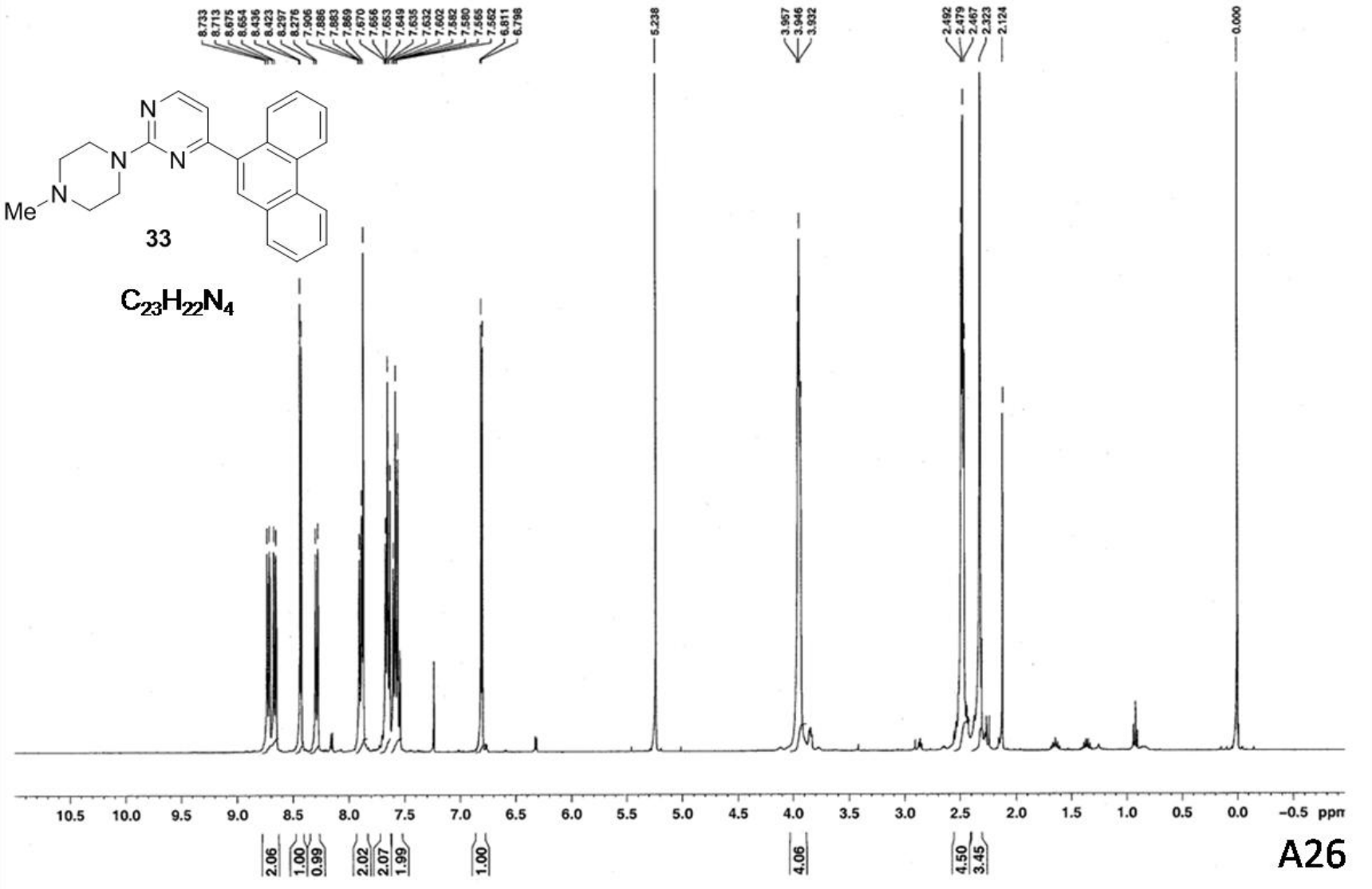
20

$C_{18}H_{11}ClN_2$

A25

400 MHz

$CDCl_3$, 25 °C



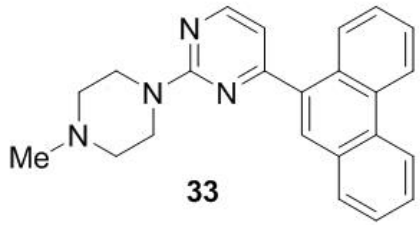
33

$C_{23}H_{22}N_4$

A26

400 MHz

$CDCl_3$, 25 °C



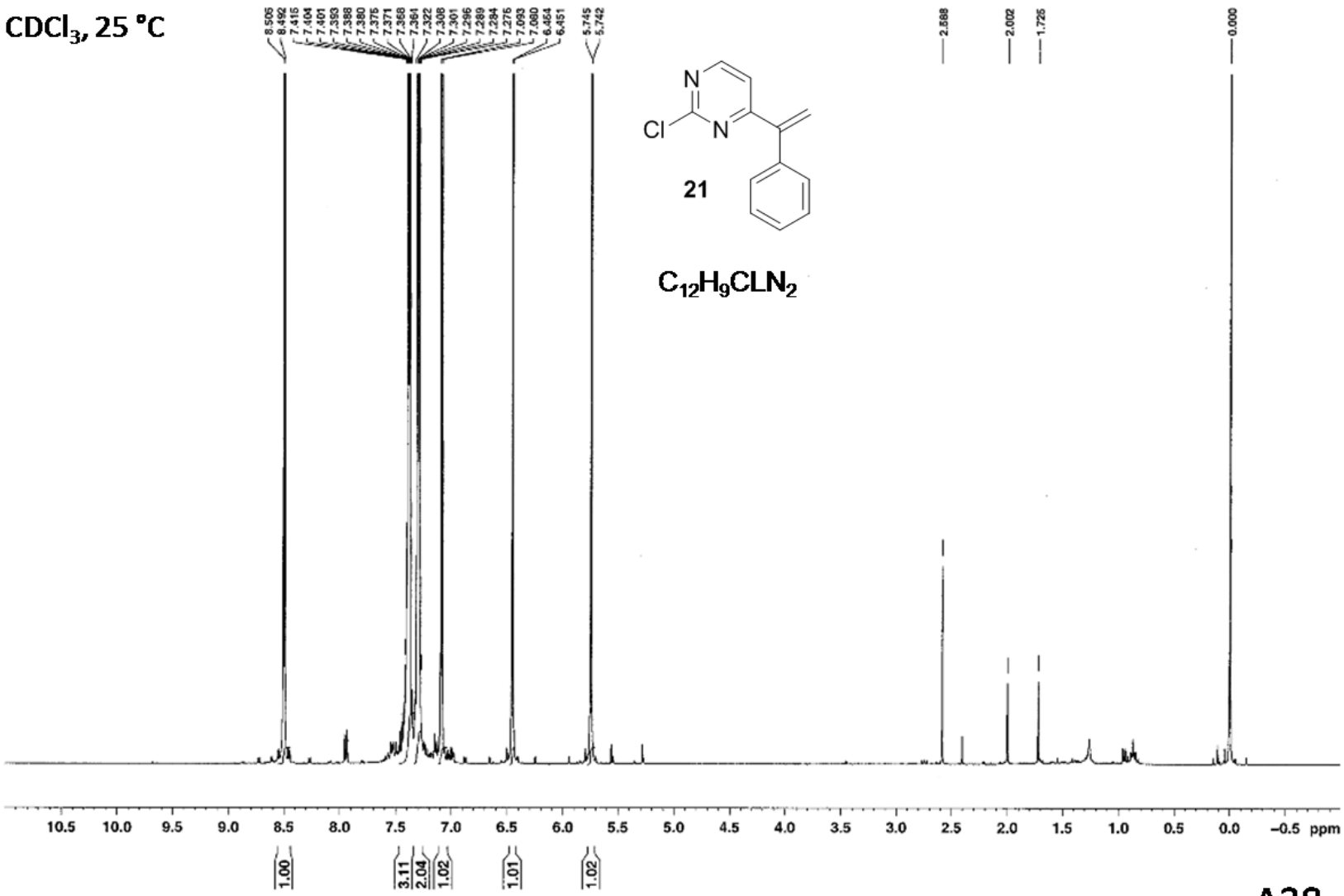
33

$C_{23}H_{22}N_4$

A27

400 MHz

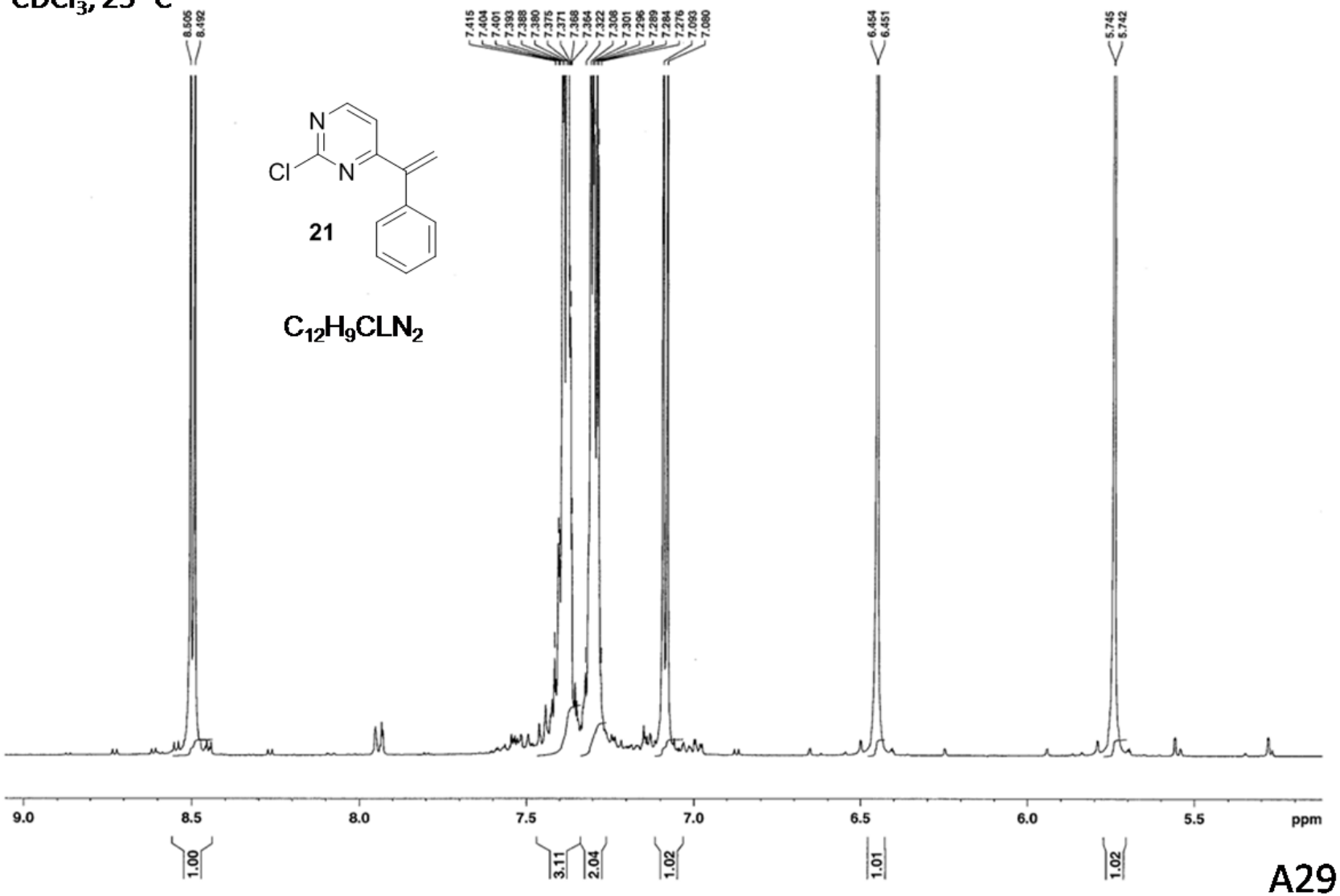
$CDCl_3$, 25 °C



A28

400 MHz

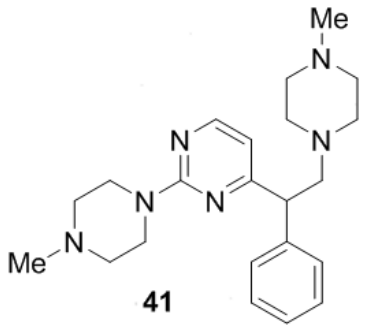
$CDCl_3$, 25 °C



A29

400 MHz

$CDCl_3$, 25 °C



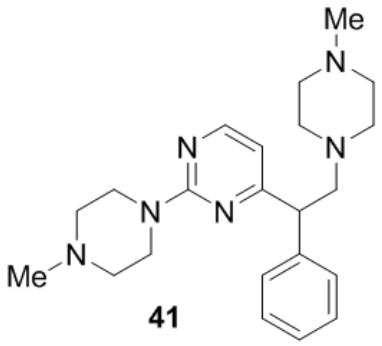
41

$C_{22}H_{32}N_6$

A30

400 MHz

$CDCl_3$, 25 °C



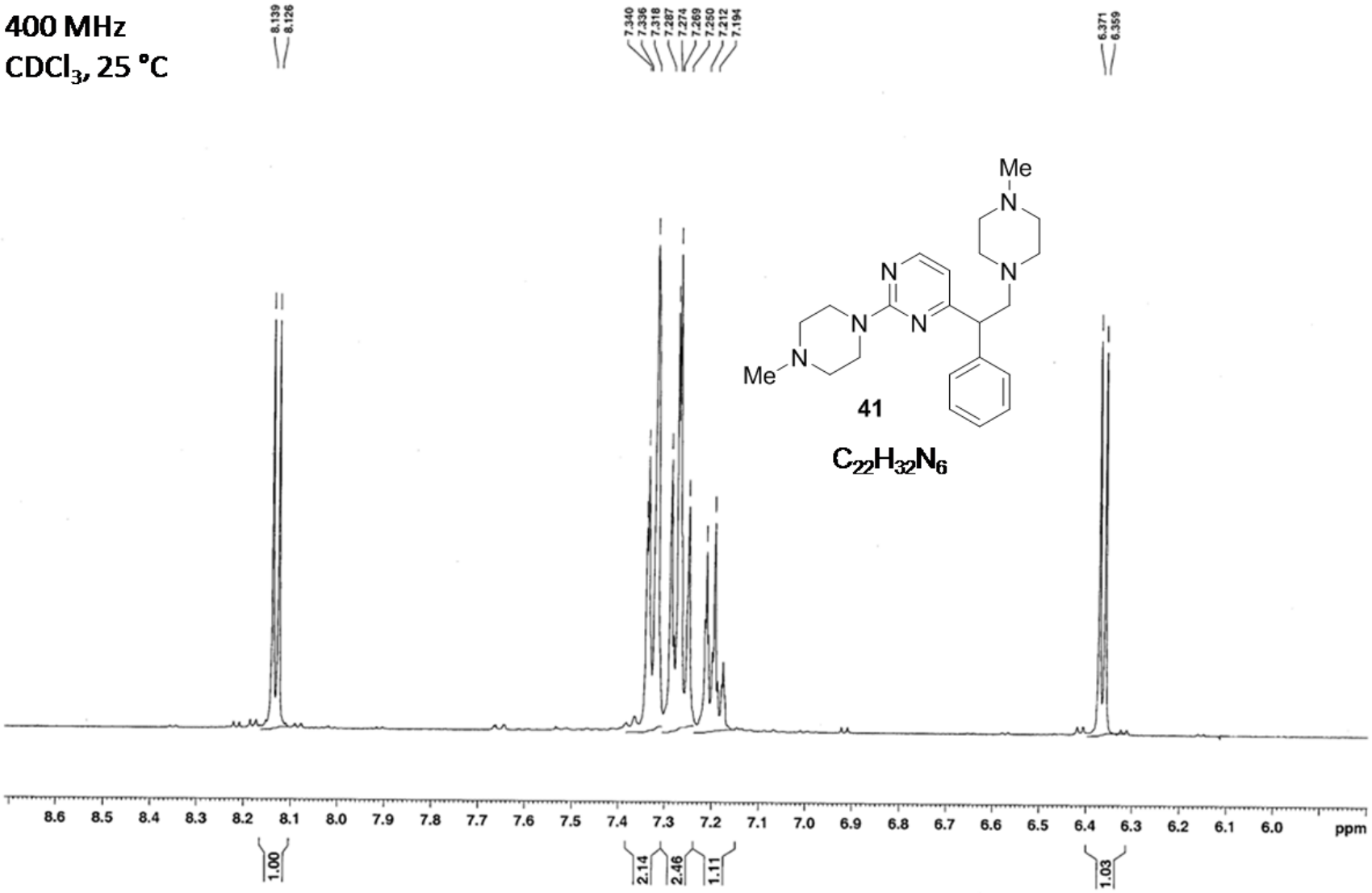
41

$C_{22}H_{32}N_6$

A31

400 MHz

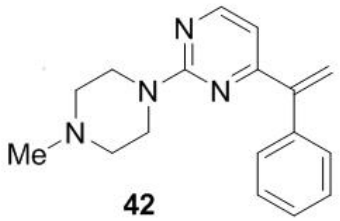
$CDCl_3$, 25 °C



A32

400 MHz

$CDCl_3$, 25 °C



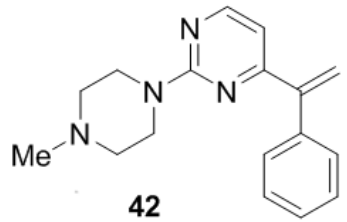
42

$C_{17}H_{20}N_4$

A33

400 MHz

$CDCl_3$, 25 °C



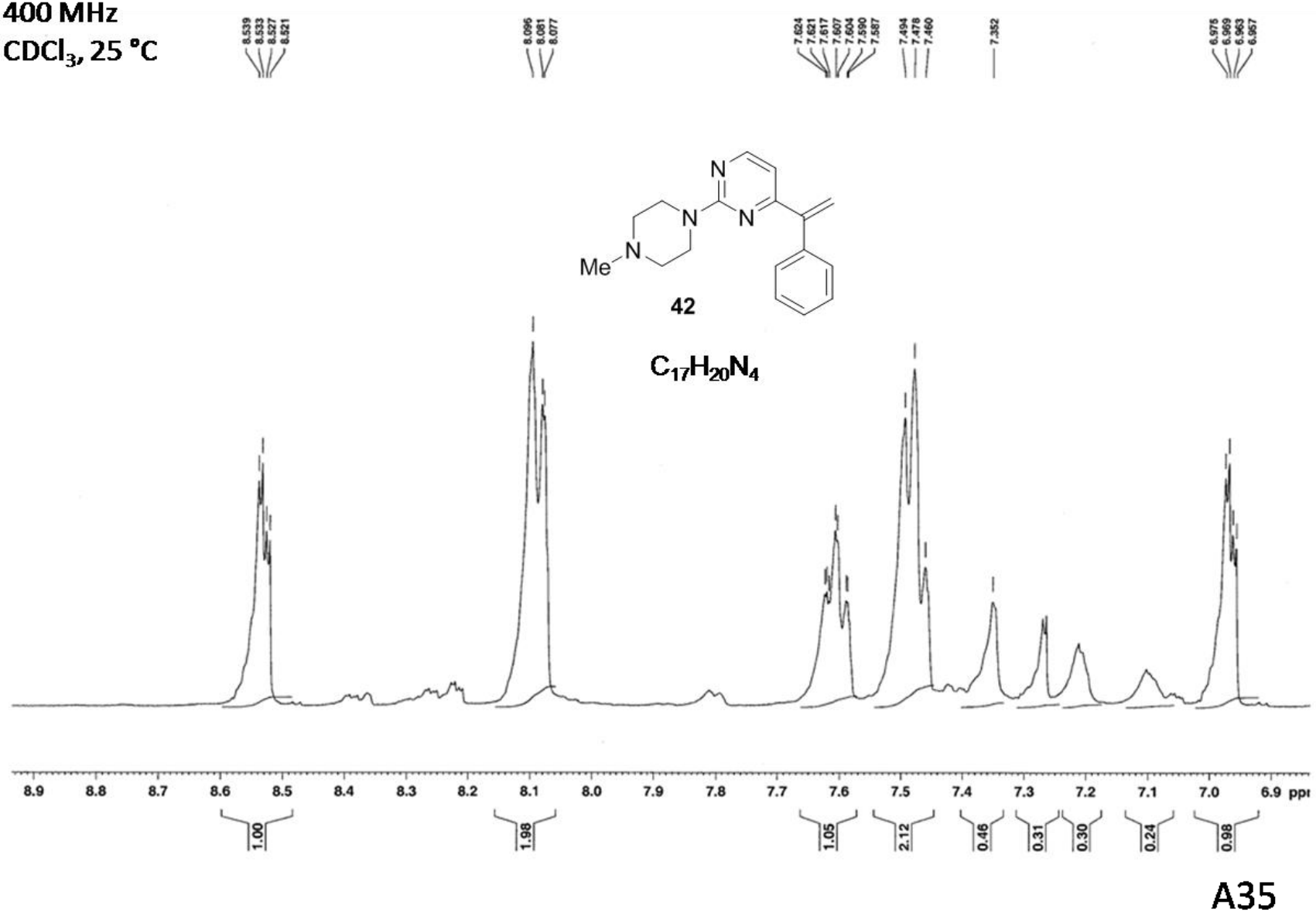
42

$C_{17}H_{20}N_4$

A34

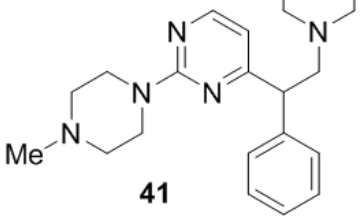
400 MHz

$CDCl_3$, 25 °C



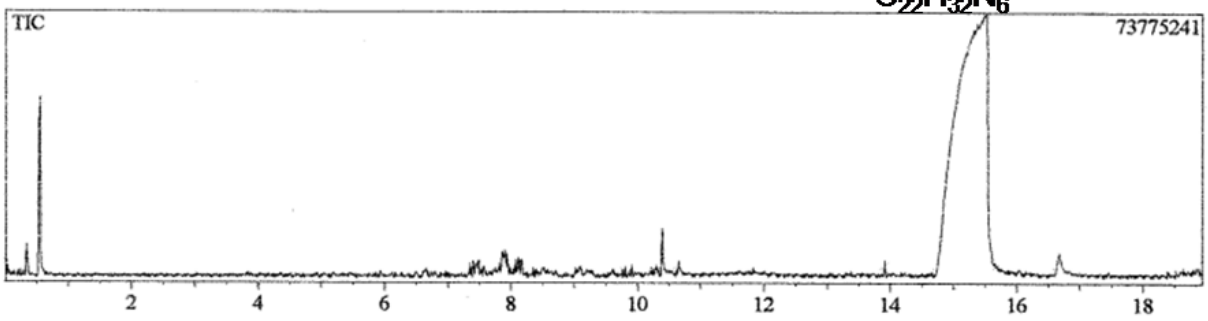
A35

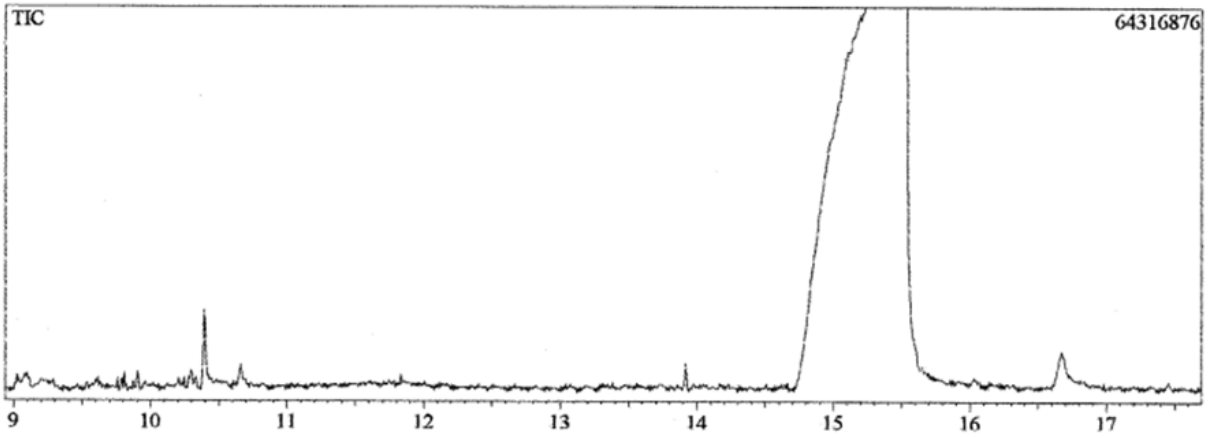
*** CLASS-5000 *** Report No. = 1 Data : SB018.D03 07/07/11 16:51:14
Sample : diadditiondecompb
ID :
Sample Amount : 0
Dilution Factor : 0
Type :
Operator : sam
Method File Name : SAM.MET
Vial No. : 1
Barcode :



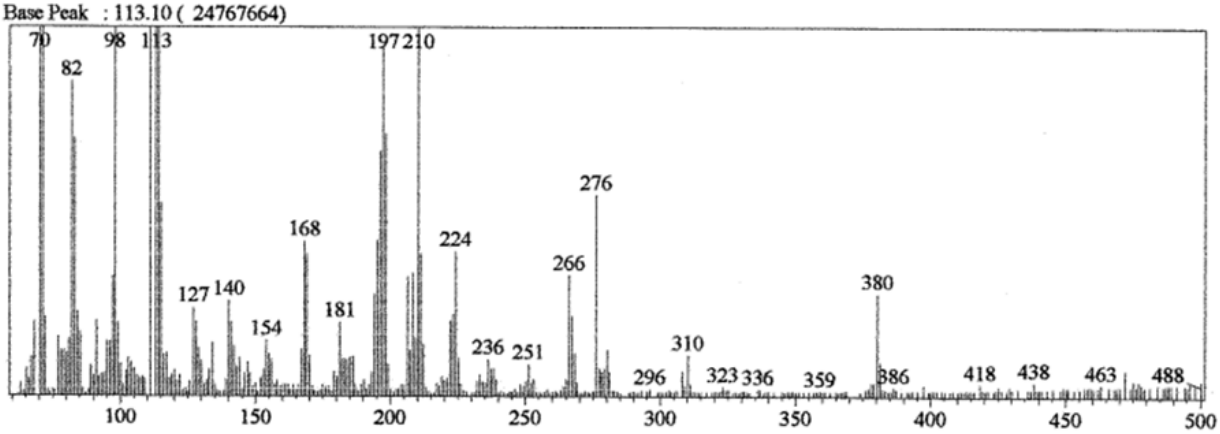
41

$C_{22}H_{32}N_6$



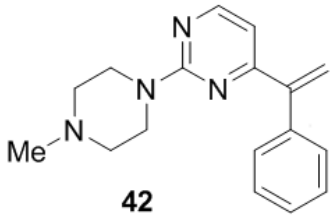


Scan # : 1826
Mass Peak # : 376 Ret. Time : 15.217
Base Peak : 113.10 (24767664)



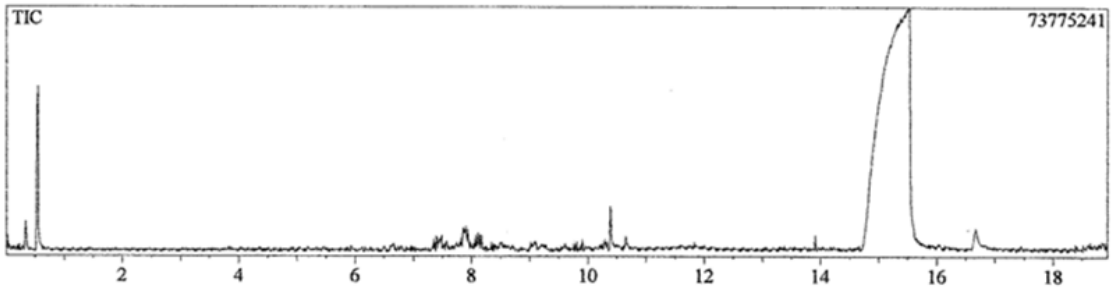
A36

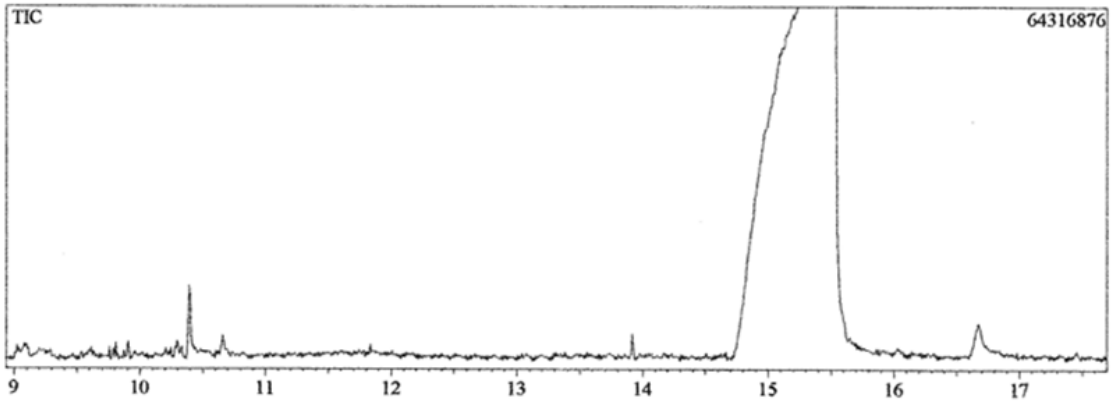
*** CLASS-5000 *** Report No. = 1 Data : SB018.D03 07/07/11 16:51:14
Sample : diadditiondecompb
ID :
Sample Amount : 0
Dilution Factor : 0
Type :
Operator : sam
Method File Name : SAM.MET
Vial No. : 1
Barcode :



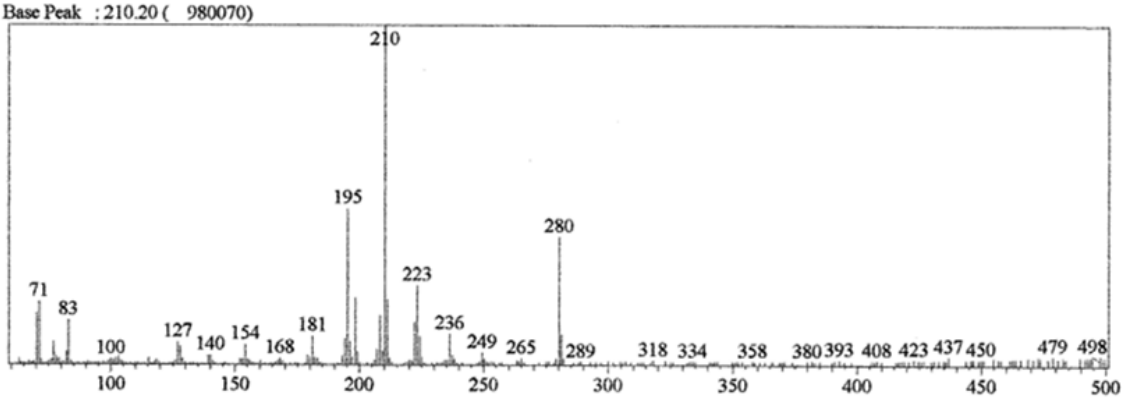
42

$C_{17}H_{20}N_4$





Scan # : 1246
Mass Peak # : 283 Ret. Time : 10.383
Base Peak : 210.20 (980070)



A37