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### Synthesis of Selective 5-HT<sub>7</sub> Receptor Antagonists

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# SYNTHESIS OF SELECTIVE 5-HT<sub>7</sub> RECEPTOR ANTAGONISTS

by

ADAM J. EHALT

Under the Direction of Dr. Lucjan Strekowski

## ABSTRACT

The 5-HT<sub>7</sub> receptor is the most recent addition to the 5-HT receptor family and has been linked to a variety of physiological and pathophysiological processes. Well established antidepressant pharmaceuticals have recently been found to activate the 5-HT<sub>7</sub> receptor, supporting the role of the 5-HT<sub>7</sub> receptor in the antidepressant mechanism. The synthesis of potent selective 5-HT<sub>7</sub> receptor antagonists could afford a greater understanding of the 5-HT<sub>7</sub> receptor function as well as lead to potential drug candidates.

The synthesis of unfused biheteroaryl derivatives as 5-HT<sub>7</sub> receptor ligands has been described within. These compounds have been tested for biological activity on the 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors. 4-(3'-Furyl)-2-(*N*-substituted-piperazino)pyrimidines were found to be potent 5-

HT<sub>7</sub> receptor ligands. 4-(2'-Furyl)-2-(*N*-substituted-piperazino)pyrimidines have shown high selectivity for the 5-HT<sub>7</sub> receptor over the 5-HT<sub>6</sub> receptor.

INDEX WORDS: Serotonin, 5-HT<sub>7</sub> receptor, Organic, Heterocyclic chemistry, Synthesis, Pyrimidine, Piperazine, Biheteroaryl

SYNTHESIS OF SELECTIVE 5-HT<sub>7</sub> RECEPTOR ANTAGONISTS

by

ADAM J. EHALT

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Masters of Science

in the College of Arts and Sciences

Georgia State University

2011

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2011

# SYNTHESIS OF SELECTIVE 5-HT<sub>7</sub> RECEPTOR ANTAGONISTS

by

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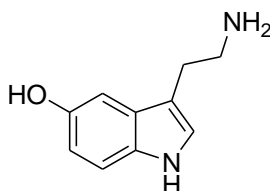
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## 1 INTRODUCTION (LITERATURE REVIEW)

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter responsible for a variety of biological functions in animals.<sup>1</sup> In humans, the effects of 5-HT are achieved through interactions with seven different serotonin receptor families, 5-HT<sub>1-7</sub>.<sup>1</sup>



**Figure 1. 5-Hydroxytryptamine (5-HT, Serotonin)**

In the central nervous system (CNS), many processes are directed by serotonin such as feeding, mood, cognition and memory.<sup>1,2</sup> In the peripheral nervous system (PNS), serotonin regulates cardiovascular and gastrointestinal functioning, smooth muscle contractions, and platelet aggregation.<sup>1,2</sup> Given the many processes governed by serotonin, 5-HT receptors have proven to be successful medicinal targets for the treatment of many physiological disorders.<sup>2,6</sup> Many current therapeutic agents disrupt or modulate activity of 5-HT receptors through various chemical interactions.<sup>2</sup> Each of the seven 5-HT receptor families fills a specific role in achieving the physiological and pathophysiological functions regulated by serotonin.<sup>2,6</sup> Synthesis of a 5-HT ligand with receptor family selectivity could afford more specific and efficient treatment and consequently minimize drug side effects.

Pursuit of a potent ligand that expresses selectivity for a specific 5-HT receptor family would not be modeled after 5-HT because the native ligand 5-HT is inherently non-selective. The molecule must maintain the 5-HT receptor binding pocket specifications but must be chem-

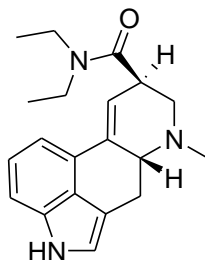
ically distinct to avoid unwanted biological interactions. The 5-HT<sub>7</sub> receptor is the most recently discovered 5-HT receptor and it has generated the interest of medicinal chemists as a potential therapeutic target for the treatment of clinical depression.<sup>6</sup> The development of more potent and selective 5-HT<sub>7</sub> receptor ligands is driven by the potential for the future medicinal applications.

### 1.1 Discovery of Serotonin

5-HT was discovered independently by two American research groups. In the early 1930's Erspamer was investigating the chemical responsible for smooth muscle tissue contractions in rats.<sup>3</sup> Erspamer's investigation led to the successful isolation of 5-HT from the enterochromaffin cells in the gut from which he named it enteramine.<sup>3</sup> Erspamer researched the role of 5-HT on smooth muscle contractions for many years and published volumes of literature under the enteramine title.<sup>3</sup> Aside from being produced in large quantities the enterochromaffin cells in the gut by, 5-HT is stored in considerable quantities on blood platelets to aid in aggregation.<sup>1,2</sup> In 1948, 5-HT was isolated from blood serum by a research group consisting of Page, Rapport, and Green.<sup>1,3</sup> Their search for a chemical component in blood responsible for hypertension would eventually lead to the isolation of 5-HT. The name serotonin was born from the marriage of the two ideas that 5-HT was isolated from blood serum ("ser") and increases tone ("tonin") or constriction in blood vessels.<sup>1,3</sup> Soon it was revealed that enteramine and serotonin were actually the same substance.<sup>1,3</sup> The consolidation of enteramine and serotonin literature combined with the commercial synthesis of 5-HT in 1952 afforded a surge in 5-HT investigation.<sup>1,3</sup>

In 1953, Twarog, a Harvard PhD candidate at the time, published an important discovery under the advisement of Page, co-discoverer of serotonin.<sup>4</sup> Twarog had produced a sensitive bioassay to quantitatively detect serotonin in mammalian tissues using mollusk heart.<sup>4</sup> Mammalian tissues were pulverized and organic tissue extracts were then tested on Twarog's serotonin bioassay. Her bioassay detected 5-HT in many tissues, but most importantly the concentration of 5-HT throughout brain tissue.<sup>4</sup> Twarog's findings opened the door for investigators to probe the role of serotonin in the brain. Research would soon be jump started by an important observation of the structural similarities between 5-HT and a well known psychotropic drug.

Woolley and Shaw were one of the first research groups to realize the connection between the powerful mind altering substance lysergic acid diethylamide (LSD-25, LSD, Figure 2) and 5-HT.<sup>5</sup> At this time it was well known that compounds structurally related to naturally occurring hormones cause disturbances to normal biological function of endogenous ligands.<sup>5</sup> After Hoffman's total synthesis of LSD-25 in 1938, it was clear that LSD-25 and 5-HT shared structural similarities. In fact LSD-25 contains 5-HT as a molecular scaffold.<sup>5</sup> Woolley and Shaw noted that the hallucinogenic affects caused by LSD consumption were strikingly similar to symptoms of mental disorders and soon proposed the cause for mental disturbances to be attributed to serotonin deficiency.<sup>5</sup> Soon after, the discovery that LSD-25 inhibited the function of serotonin provided support for their hypothesis. Research concerning serotonin receptors as drug targets would soon become a very exciting and intriguing area of investigation.<sup>5</sup>



**Figure 2. Lysergic Diethyl Amide (LSD-25, LSD)**

## 1.2 The 5-HT Receptor

The 5-HT receptor has been found widely expressed throughout the CNS and PNS with receptor functions linked to a variety of physiological processes. 5-HT receptor regulation has been linked to developmental, cardiovascular, gastrointestinal, endocrine function, sensory perception, aggression, appetite, sleep, sex, mood, and memory.<sup>1-2, 6</sup> The 5-HT<sub>1-7</sub> receptors belong to a family of proteins called G-protein coupled receptors (GPCRs), with the exception of the ligand-gated ion channel 5-HT<sub>3</sub> receptor.<sup>6</sup> G-protein coupled receptors consist of seven non-polar alpha helices spanning the cell membrane with an *N*-terminus extracellular portion involved with ligand binding and an intracellular carboxy-terminus portion involved with signal communications within the cell.<sup>6, 28-29</sup> Binding occurs when a ligand docks to the extracellular portion of the GCPR, and the ligand is held in place through specific ligand- receptor protein residue interactions.<sup>6</sup> Binding activates a structural change in the receptor protein conformation. This structural change generates a cascade of intracellular events that will ultimately communicate the extracellular transmission and result in the appropriate biological response.<sup>6, 28-29</sup>

Activation of a 5-HT receptor begins with the docking of a molecule to the extracellular binding pocket of the receptor protein. A molecule with affinity towards binding to the receptor active site is called a receptor ligand. Different ligands can activate a receptor and achieve vari-

ous responses, which results in the distinction between receptor agonists, antagonists, and inverse agonists.<sup>6</sup> The term receptor agonist refers to a molecule that has affinity for binding to a receptor and upon docking the ligand mimics the effect of the native ligand, in other words increasing the signal for serotonin function expression. A receptor antagonist, however, refers to a molecule that binds in the receptor active site and inhibits agonist docking and thereby blocking the expression of the native ligand function. There is a third type of receptor ligand which is called an inverse-agonist. An inverse agonist is a ligand that binds in the receptor active site and decreases intracellular signaling, posing the negative effect of a receptor agonist.

The existence of multiple 5-HT receptors has allowed serotonin to achieve such a wide variety of physiological control.<sup>1-2,6</sup> In fact, there are fourteen different subtypes that have been grouped into seven families, 5-HT<sub>1-7</sub> respectively. This classification does not include the multiple receptors arising from alternate gene splicing or the 5-HT receptor mRNA.<sup>1-2</sup> The seven 5-HT receptor families have been extensively investigated for the role each play in the processes regulated by serotonin. This has been aided by the advancement in receptor cloning technologies, gene knock-out mice studies and utilization of potent and selective 5-HT receptor ligands.<sup>6-8</sup> Elucidation of which 5-HT receptor is responsible for specific biological processes would allow for future drug design of selective 5-HT receptor ligands as therapeutic agents.

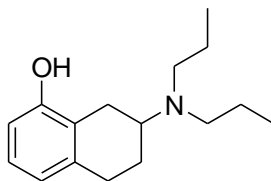
### **1.3 Discovery of the 5-HT<sub>7</sub> Receptor**

The 5-HT<sub>7</sub> receptor (5-HT<sub>7</sub>R) was discovered independently by three research laboratories in 1993, making it the most recent addition to the serotonin receptor subtype family and bringing the grand total of serotonin receptor subtypes to fourteen.<sup>6-8,17</sup> This receptor was discovered by analysis of brain cDNA libraries searching for sequences sharing homology to known



5-HT receptors.<sup>17,22</sup> Studies on the 5-HT<sub>7</sub>R have relied heavily on the use of selective antagonists and 5-HT<sub>7</sub>R knockout mice.<sup>17, 19</sup> Being the most recently discovered, the 5-HT<sub>7</sub> receptor still remains one of the least understood 5-HT receptors.

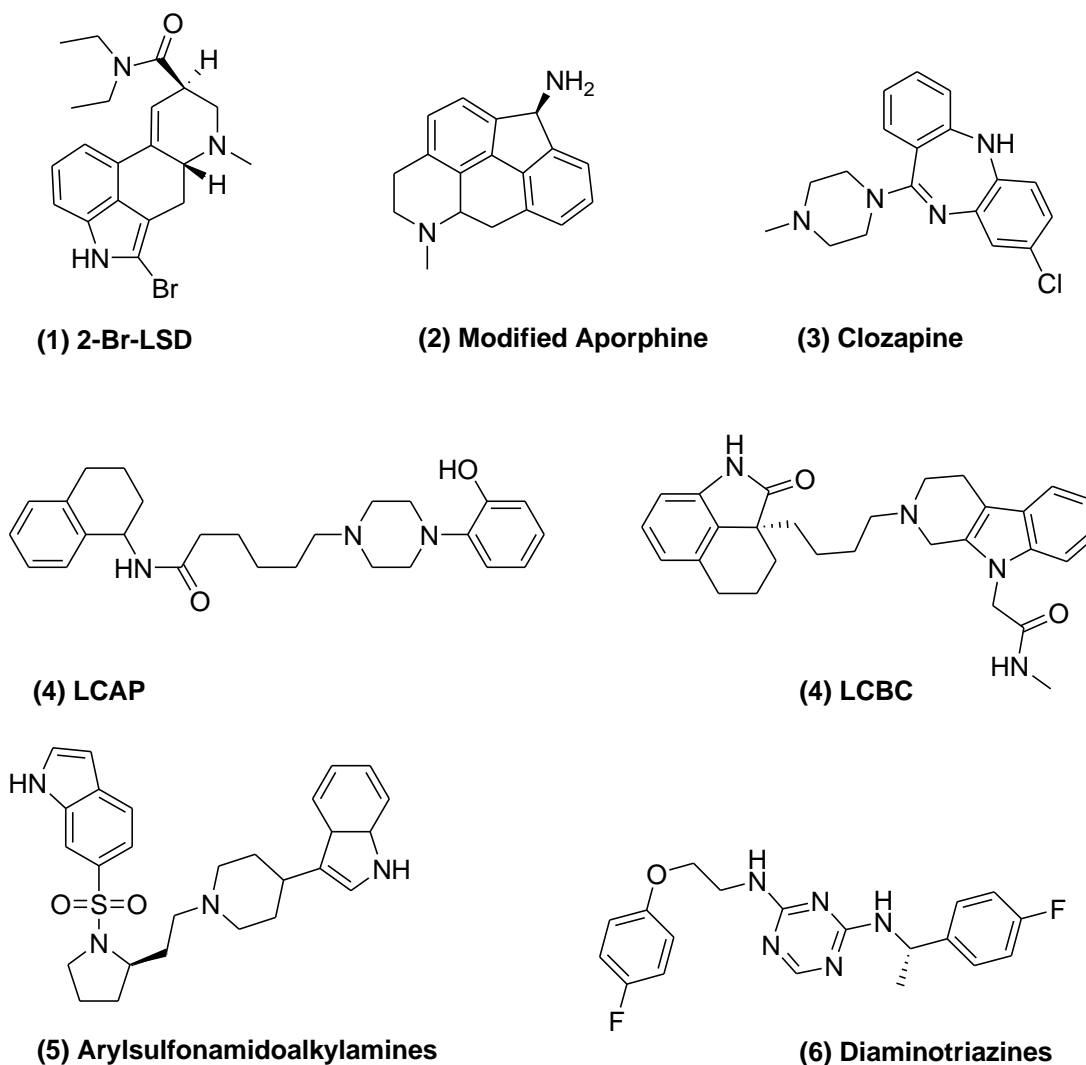
After the discovery of 5-HT<sub>7</sub>, it became apparent that many previously established 5-HT receptor mediated processes may have been interpreted erroneously.<sup>6</sup> One such example is the role of 8-hydroxy-2(di-*n*-propylamino)-tetralin (8-OH-DPAT, Figure 3), which was previously thought to be a selective agonist for the 5-HT<sub>1A</sub> receptor, but has since been discovered to potent agonist activity for the 5-HT<sub>7</sub> receptor.<sup>2,6</sup>



**Figure 3. 8-hydroxy-2(di-*n*-propylamino)-tetralin (8-OH-DPAT)**

In fact, many compounds with structural diversity have been shown to possess affinity for the 5-HT<sub>7</sub> receptor.<sup>2,15</sup> A figure has been compiled below including structural examples of non-selective and selective ligands for the 5-HT<sub>7</sub> receptor.<sup>15</sup>

**Figure 4. Selective and Non-Selective 5-HT<sub>7</sub> Receptor Ligands**



**Figure 4.** Examples from the six general classes of 5-HT<sub>7</sub> receptor antagonists as outlined by Kolaczowski et al. and have been numbered according to each class are shown. (1) ergoline derivatives, (2) aporphine derivatives, (3) tricyclic psychotropic agent derivatives, (4) arylpiperidine, arylpiperazine derivatives [LCAPs] and  $\beta$ -carboline derivatives [LCBCs], (5) arylsulfonamidoalkylamine derivatives, (6) compounds reserved for selective antagonists that are structurally more diverse than the previous five classes.

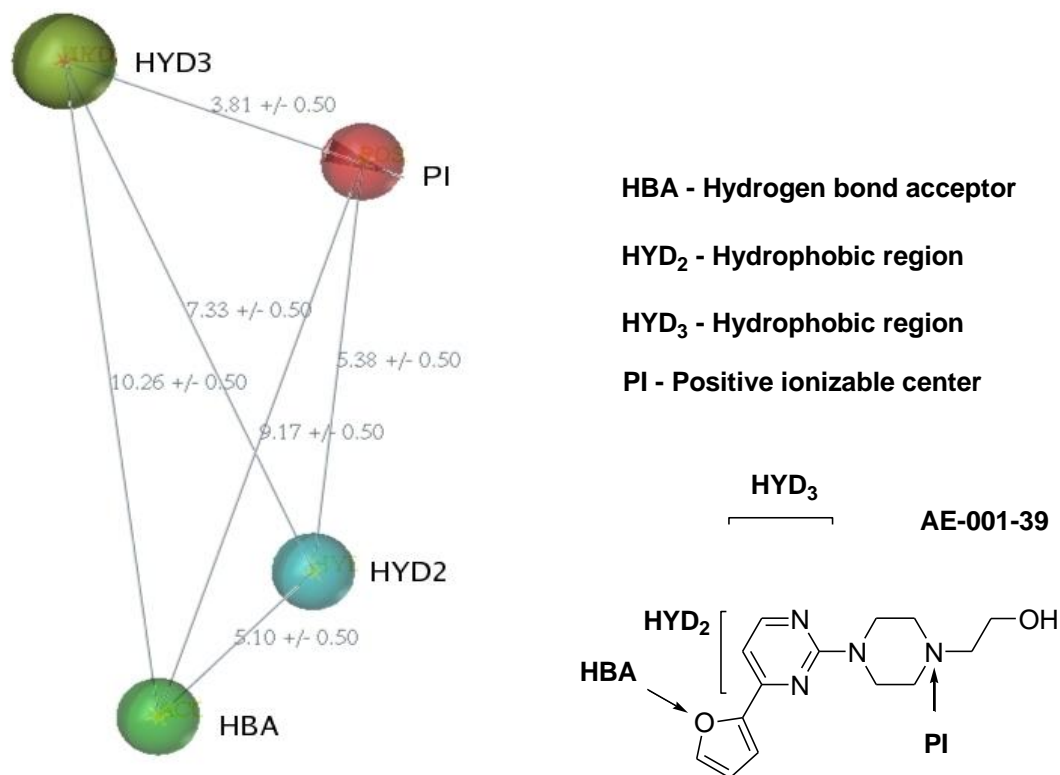
In fact, the 5-HT<sub>7</sub>R antagonists have shown to display a wide variety of structural components.<sup>15</sup> The above figure has been compiled to visualize six classes of 5-HT<sub>7</sub>R antagonists that have been generalized by Kolaczowski et al.: (1) nonselective ergolines, (2) nonselective

aporphines, (3) nonselective tricyclic psychotropic agents, (4) arylpiperidines, arylpiperazines [LCAPs] and  $\beta$ -carbolines [LCBCs], (5) selective arylsulfonamidoalkylamines, (6) and other diverse structure selective antagonists such as diaminotriazines.<sup>15</sup>

A crystal structure for the 5-HT<sub>7</sub>R has not been achieved, making binding pocket 3-D evaluation to rely heavily on molecular modeling using potent ligand binding information. The first pharmacophore model was developed by Lopez-Rodriguez et al in 2000.<sup>30</sup> This receptor pharmacophore was developed to reveal key structural components for 5-HT<sub>7</sub> receptor antagonist binding and employed 30 ligands with structural diversity.<sup>30</sup> The molecular modeling calculations predict the minimum structural requirements for binding include an aromatic ring, a basic nitrogen atom (positive ionizable center, PI) hydrogen bond acceptor (HBA), and a hydrophobic region (HB) 4.9-5.9 Å apart from the basic center.<sup>30</sup> An updated pharmacophore model was published by Lopez-Rodriguez in 2003 using a series of different ligands making minor changes to the structural requirements.<sup>31</sup> In 2006, Kolaczowski et al published a pharmacophore model using selective structurally variant 5-HT<sub>7</sub> ligands and reported an interesting discovery.<sup>15</sup> It has been reported that there may be more than one binding pocket for the 5-HT<sub>7</sub> receptor, which would account for such structural diversity showing such high affinity.<sup>15</sup>

A pharmacophore model recently developed in the Strekowski lab by Jeff Klenc was employed to design more potent and selective 5-HT<sub>7</sub> receptor antagonists.<sup>31</sup> Using available compounds synthesized in the Strekowski lab our pharmacophore model calculations agree with the literature Lopez-Rodriguez pharmacophore model.<sup>30-31</sup>

**Figure 5. Pharmacophore Model for Selective 5-HT<sub>7</sub> Antagonists**



**Figure 5.** The pharmacophore model created by Jeff Klenc in the Streckowski laboratory is shown.<sup>31</sup> Compound **AE-001-39** has been placed side by side with this model to show how this molecule satisfies spatial requirements.

HYD<sub>3</sub> is a predicted hydrophobic pocket that exists inside of the 5-HT<sub>7</sub> binding pocket model. This hydrophobic pocket appears to be less essential for high binding affinity than the HBA and PI. In fact, addition of a butyl group to satisfy this 5-HT<sub>7</sub> model parameter has shown only a slight increase in binding affinity which may be biologically insignificant. In contrast, 5-HT<sub>6</sub> binding affinity increased dramatically for compounds with this hydrophobic addition. A more detailed discussion of compound affinity results can be seen later in the Biological Activity section.

## 1.4 5-HT<sub>7</sub> Receptor Function

In recent studies, evidence reveals that the 5-HT<sub>7</sub> receptor might be a novel target for medicinal chemists for the treatment of various physiological and pathophysiological disorders.<sup>17</sup> The 5-HT<sub>7</sub> receptor has suggested involvement in depression,<sup>6</sup> body thermoregulation,<sup>9</sup> circadian rhythm,<sup>10</sup> learning and memory,<sup>11-12</sup> endocrine and mood regulation,<sup>15</sup> and smooth muscle relaxation in cerebral arteries.<sup>14</sup> These findings indicate that regulation of the 5-HT<sub>7</sub> receptor could be manipulated therapeutically for treatment of such disorders as depression, insomnia, and migraines.<sup>6,10,14</sup> Considering the many processes that could be controlled by inhibiting the 5-HT<sub>7</sub> receptor, is a matter of great importance and opportunity to develop more potent selective 5-HT<sub>7</sub> receptor antagonists for investigation as potential drug candidates.

The 5-HT<sub>7</sub> receptor distribution throughout the brain has been studied using a combination of techniques including knock-out mice and radio-labeled 5-HT subtype receptor antagonists.<sup>15-16</sup> Localization of the 5-HT<sub>7</sub> receptor throughout the brain has stimulated investigation of a potential relationship between this receptor and mental illness.<sup>16, 20</sup> High concentrations of the 5-HT<sub>7</sub> receptor were found in the hypothalamus, thalamus, and hippocampus.<sup>16</sup> These findings support 5-HT<sub>7</sub> receptor involvement in behavior, cognition, and circadian rhythm regulation.<sup>10,16</sup> Depression and schizophrenia are psychiatric disorders that have recently been evaluated the 5-HT<sub>7</sub> receptor as a target for potential treatment.<sup>20</sup> These two disorders have been linked to this receptor using 5-HT<sub>7</sub> receptor KO mice and inhibition studies using selective 5-HT<sub>7</sub> antagonists. The results of both studies show comparable therapeutic profiles to known antipsychotic and antidepressant drugs currently on the market.<sup>18-20</sup>

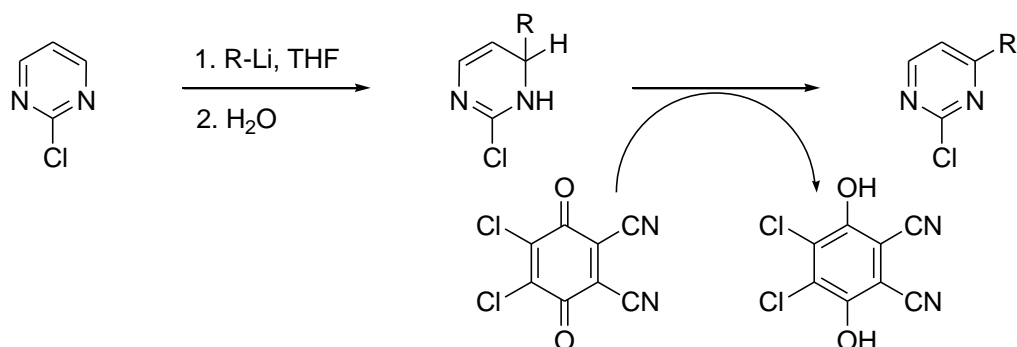
Currently, there is a need for more potent and selective 5-HT<sub>7</sub> receptor antagonists to progress investigation concerning the involvement of this receptor and the aforementioned mental disorders. These potential therapeutic applications emphasize the importance of future investigation and should continue to encourage medicinal chemists to develop more potent selective 5-HT<sub>7</sub> receptor antagonists.

## 2 SYNTHESIS OF UNFUSED BIHETEROARYLS (THIS WORK)

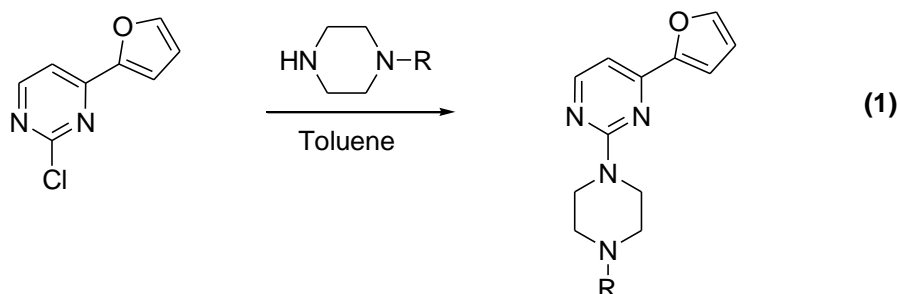
### 2.1 Synthesis of Substituted Pyrimidines

The synthesis of pyrimidines with heteroaryl substituent at position 4 had gone unevaluated until the modifications made by Streckowski *et al.* were published.<sup>23</sup> The earliest work focused on the addition of lithiated species to the pyrimidine ring, which led to the 1, 6-dihydropyrimidine intermediate. This intermediate was oxidized back to pyrimidine with the use of 2,3-dichloro 5,6-dicyanobenzoquinone (DDQ) (Scheme 1).

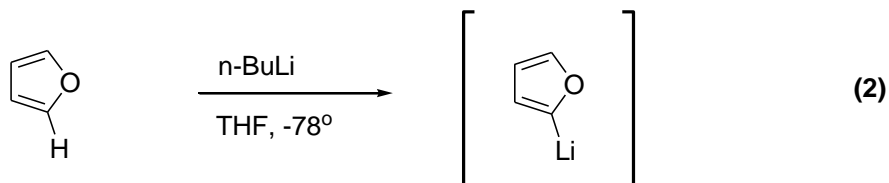
**Scheme 1.**



After the lithium addition/substitution reaction was complete, an amine was used to displace the chlorine at the 2 position, which led to the desired products in moderate yields (Equation 1).

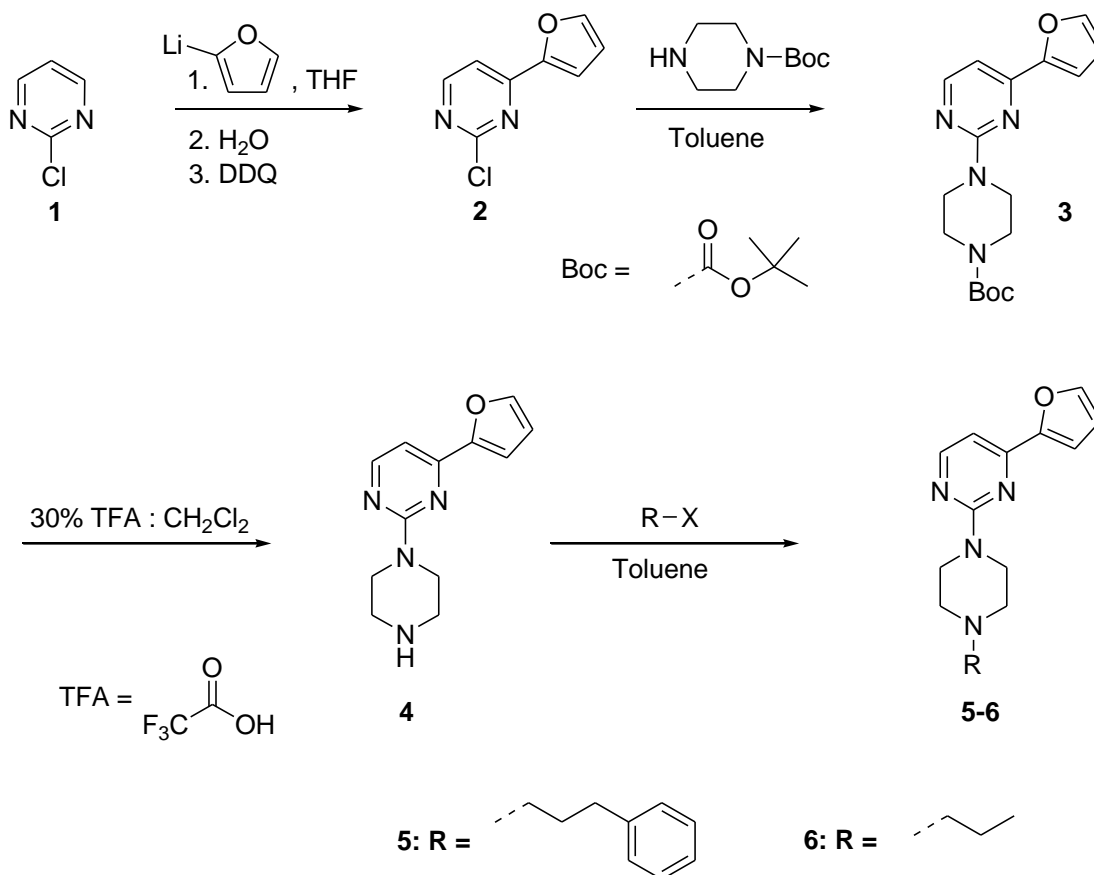


A similar chemistry was used to synthesize the pyrimidine ligands discussed below. 2-Lithiofuran was generated in THF at low temperature by addition of *n*-BuLi to furan. After the lithiation reaction (Equation 2), the corresponding organolithium reagent was used *in situ*.

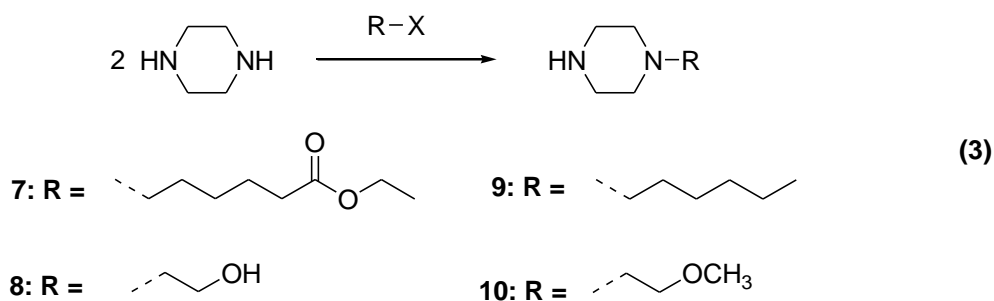


A solution of 2-chloropyrimidine (**1**) in THF was added to the organolithium reagent at -78 °C (Scheme 2). Once the reaction was complete, the mixture was quenched with water/THF (1:1) and the intermediate dihydropyrimidine was rearomatized upon treatment with DDQ to give pyrimidine **2**.

Scheme 2.



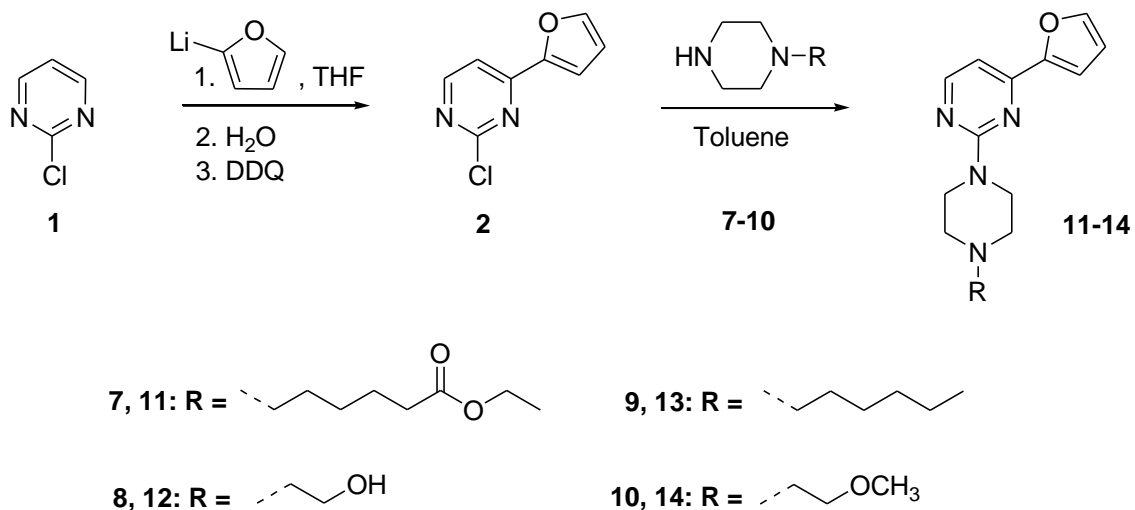
Compounds **5** and **6** were synthesized by treatment of 2-chloropyrimidine **2** with *N*-Boc protected piperazine yielding **3**. Following acidic Boc deprotection the resultant secondary amine **4**, was treated with the corresponding alkyl halide to produce compounds **5** and **6**. Final products **5** and **6** were transformed to the hydrobromide salt and fully characterized.





Compounds **7-10** were synthesized using piperazine and the corresponding alkyl halide in a ratio of 2:1 to prevent dialkylation (Equation 3). The resulting products **7-10** were used in the following reactions without purification (Scheme 3).

**Scheme 3.**



Compounds **11-14** were synthesized using substituted piperazines **7-9** in toluene. Excess of a piperazine was necessary to achieve higher yield for products **11-14**. This direct method seen above in **Scheme 3** was preferred over the Boc-protected method seen in **Scheme 2**. This preference was determined due to less time spent on purification since compounds **7-9** could be used synthetically crude, and for economic factors, as the Boc protecting group added unnecessary expense. Final compounds **11-14** were transformed to the hydrobromide salt and fully characterized.

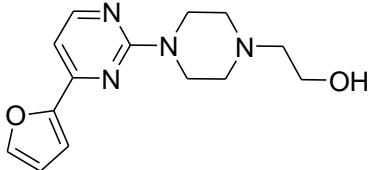
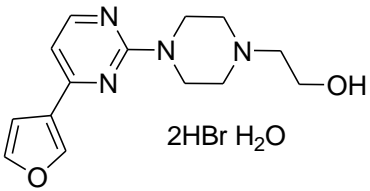
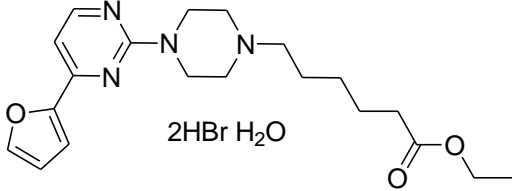
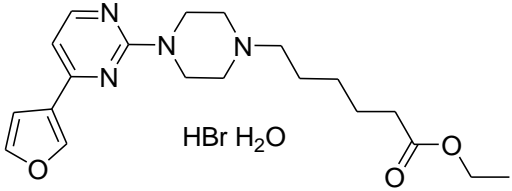
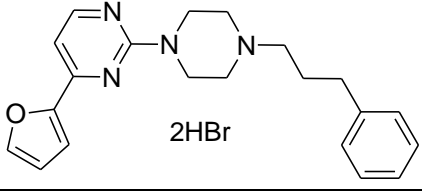
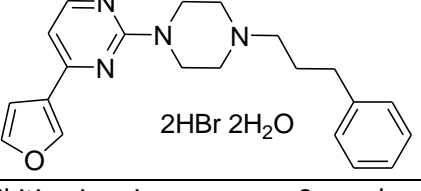
### 3 BIOLOGICAL ACTIVITY

Compounds synthesized in the Streckowski laboratory, including compounds prepared as part of this work, have been recently evaluated by the National Institute of Mental Health. Compounds were selected for binding affinity analysis for the 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors. K<sub>i</sub> determinations were generously provided by the National Institute of Mental Health's Psychoactive Drug Screening Program, Contract # HHSN-271-2008-00025-C (NIMH PDSP). The NIMH PDSP is directed by Bryan L. Roth MD, PhD at the University of North Carolina at Chapel Hill and Project Officer Jamie Driscoll at NIMH, Bethesda MD, USA. These binding studies employ a radio-ligand assay using [<sup>3</sup>H]LSD at a 1 nM concentration with chlorpromazine as a reference in a standard binding buffer following the published procedure.<sup>33-34</sup>

#### 3.1 5-HT<sub>7</sub> and 5-HT<sub>6</sub> Receptor Binding Affinity

Testing for compounds has been performed at the National Institute of Mental Health (NIMH) at the University of North Carolina Chapel Hill. The following table has been populated with binding affinity values for the 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptor. Abbreviations AE denote compounds of this thesis. Derivatives NF (Nilmi Fernando) and SP (Shirish Paranjpe) are included in the following discussion for a comprehensive treatment.

**Table 1.1: Binding Affinity Results for 4-(2'-Furyl) and 4-(3'-Furyl) pyrimidine derivatives**

Compound ID	Structure	5-HT <sub>6</sub> K <sub>i</sub> (nM)	5-HT <sub>7</sub> K <sub>i</sub> (nM)
AE - 001 - 39		N/A*	997.0
SP - 1 - 65	 2HBr H <sub>2</sub> O	342.0	8.5
AE - 001 - 37	 2HBr H <sub>2</sub> O	N/A*	58.0
NTF - 111 - 025	 HBr H <sub>2</sub> O	106.0	0.4
AE - 001 - 69	 2HBr	N/A*	57.0
NTF - 111 - 065A	 2HBr 2H <sub>2</sub> O	70.4	1.6

\*N/A = Less than 50% inhibition in primary assays. Secondary assay not performed.

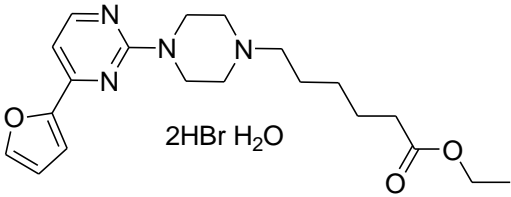
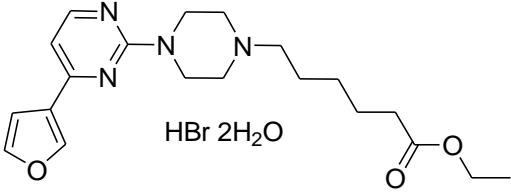
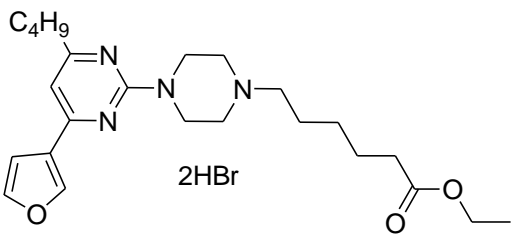
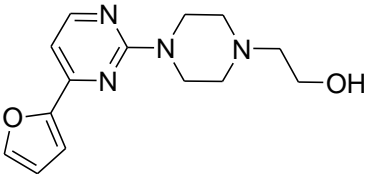
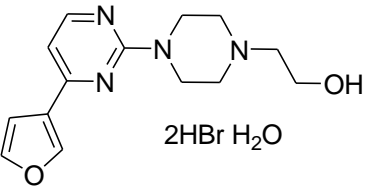
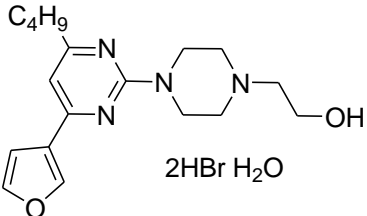
The compounds listed in the table above have been arranged to ease comparison between the K<sub>i</sub> values of three *N'*-substituted piperazines for both 4-(2'-Furyl) and 4-(3'-Furyl) pyrimidine derivatives. The N/A\* corresponds to primary assay binding affinity below the threshold required by the NIMH to proceed with secondary assay testing. Analysis of the data pre-

sented in this table yields a noteworthy difference between the 5-HT<sub>6</sub> receptor binding profile for the 2'- and 3'-Furyl isomers. The 2'-Furyl derivatives, AE-001-37, AE-001-39, and AE-001-69, lack 5-HT<sub>6</sub> affinity. These compounds show high selectivity for the 5-HT<sub>7</sub> receptor over the 5-HT<sub>6</sub> receptor.

The 3'-Furyl isomers, NTF-111-025, SP-1-65, and NTF-111-032, show higher affinity (lower K<sub>i</sub> values) for the 5-HT<sub>7</sub> receptor than the 2'-Furyl isomers. The 3'-Furyl moiety appears to increase affinity towards both the 5-HT<sub>6</sub> receptor and the 5-HT<sub>7</sub> receptor. These results indicate the positioning of the hydrogen bonding acceptor (HBA) plays a critical role in the active site for both 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptors. The positioning of the HBA is essential for binding to the 5-HT<sub>6</sub> receptor, as observed by absence of 5-HT<sub>6</sub> affinity from the 2'-Furyl pyrimidine derivatives. Exploitation of the HBA positioning will likely prove an important feature in future synthesis of compounds expressing receptor selectivity.

Recently in the Streckowski lab, Nilmi Fernando (NTF) and Shirish Paranjpe (SP) have synthesized 2, 4, 6- tri-substituted pyrimidines using the more potent 3'-Furyl derivatives. A table has been presented below comparing two N'-substituted piperazines and the K<sub>i</sub> values for the corresponding di- and tri-substituted pyrimidines.

Table 1.2: Binding Affinity Results for Di- and Tri- Substituted Pyrimidines

Compound ID	Structure	4,6 Pyrimidine Substituents	5-HT <sub>6</sub> K <sub>i</sub> (nM)	5-HT <sub>7</sub> K <sub>i</sub> (nM)
AE-001-37	 2HBr · 2H <sub>2</sub> O	2-furyl, H	N/A*	58.0
NTF-111-025	 HBr · 2H <sub>2</sub> O	3-furyl, H	106.0	0.4
NTF-111-065A	 2HBr	3-furyl, C <sub>4</sub> H <sub>9</sub>	72.0	9.0
AE-001-39		2-furyl, H	N/A*	997.0
SP-1-65	 2HBr · 2H <sub>2</sub> O	3-furyl, H	342.0	8.5
SP-1 -67	 2HBr · 2H <sub>2</sub> O	3-furyl, C <sub>4</sub> H <sub>9</sub>	202.0	7.7

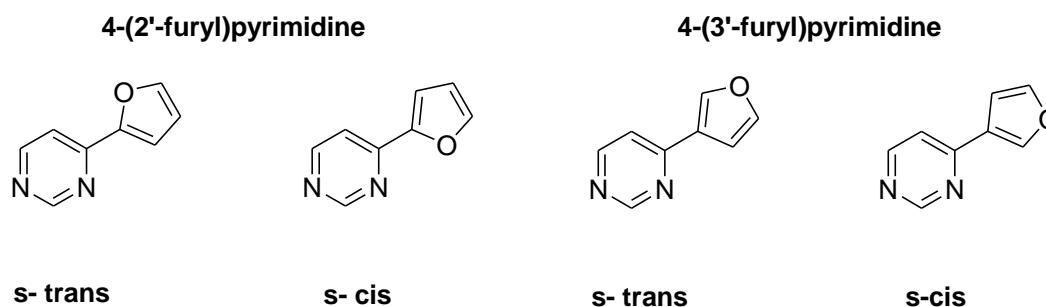
\*N/A = Less than 50% inhibition in primary assays. Secondary assay not performed.

Table 1.2 compares 5-HT<sub>6</sub> and 5-HT<sub>7</sub> K<sub>i</sub> values for two *N'*-substituted piperazines attached to the 2 position on three pyrimidine derivatives. Compounds NTF-111-065A and SP-1-67 are 4-(3'-Furyl) homologues. The addition of the butyl group to the pyrimidine in SP-1-67 adds a flexible hydrophobic character to the compound.

For the two butyl compounds NTF-111-065A and SP-1-67, there is an increase in affinity for the 5-HT<sub>6</sub> receptor. However, the very potent NTF-111-025 loses 5-HT<sub>7</sub>R affinity upon addition of the butyl group as seen in NTF-111-65A, with K<sub>i</sub> values of 0.4 and 9.0 respectively.

For compounds with high affinity for receptor binding, ligand structural geometry must conform to the receptor-bound conformation. Using unfused biheteroaryl compounds has allowed for a modeling advantage by restricted conformation possibilities. The use of rigid molecules for receptor modeling allows less room for conformational ambiguity in the natural receptor-bound conformation. The pyrimidine substituted with a furan is limited to two low energy conformations referred to as *s-cis* and *s-trans* (Figure 6). These low energy conformations occur due to maximal electron delocalization at 0° and 180° torsion angles, or *s-cis* and *s-trans* respectively.

**Figure 6. Cis- and trans- 4-(2'-Furyl) and 4-(3'-Furyl)pyrimidine conformations**



**Figure 6.** Using the unfused biheteroaryl scaffold of furan and pyrimidine limits the low energy structure conformations.

The 2'-Furyl substituent on the pyrimidine has been shown to display a preferred low energy s-trans conformation.<sup>25</sup> Molecular modeling predictions support the 2'-Furyl s-trans conformation preference while the 3'-Furyl derivatives possess slight preference for the s-cis conformation. Only a slight preference is observed for the 3'-Furyl derivatives as the two conformers are spatially similar. These low energy conformation predictions have been supported experimentally by NOESY 2-D NMR spectroscopy.<sup>25-26</sup>

#### 4 CONCLUSION

In recent years, the 5-HT<sub>7</sub> receptor has attracted the interest of medicinal chemists as a therapeutic target for treating many physiological and pathophysiological illnesses. Lacking a crystal structure for this receptor, investigators have relied on modern molecular modeling techniques and potent receptor ligands to attain some insight into the three-dimensional 5-HT<sub>7</sub> receptor binding pocket. A 5-HT<sub>7</sub> pharmacophore model previously developed in the Strekowski lab has provided minimum structural requirements for potent ligand binding and has been used to develop compounds with high 5-HT<sub>7</sub> receptor affinity.

The development of more potent and selective receptor antagonists will help aid in better model calculations and receptor active site understanding. As more selective antagonists are discovered, the availability for research into the true 5-HT<sub>7</sub>R therapeutic potential will be expanded accordingly. Biological results from the recently synthesized set of furylpyrimidine derivatives show minute structural changes have a profound effect on the affinity for the 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptor. Exploitation of the HBA positioning will play a crucial role in producing

more potent and selective 5-HT<sub>7</sub> antagonists as well as other structural and functional modifications to make potent ligands more selective.

## 5 EXPERIMENTAL

### 5.1 General

THF was purified by distillation from sodium benzophenone ketyl under a nitrogen atmosphere. All reagents were purchased from a commercial source and used as received. Glassware was dried in an oven at 120 °C, assembled hot and cooled to room temperature under a continuous nitrogen flow prior to use. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were obtained in CDCl<sub>3</sub> at 27 °C on a Bruker instrument. Elemental analysis was obtained from Atlantic Microlabs, Inc. Melting points are uncorrected. Compound intermediates not sent for biological testing have not been fully characterized. Final products were fully characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectrometry, and elemental analysis.

Radio-ligand binding studies for the 5-HT<sub>7</sub> and 5-HT<sub>6</sub> receptors were performed according to the published procedure by the National Institute of Mental Health.<sup>33,34</sup> These binding studies employ a radio-ligand assay using tritiated [<sup>3</sup>H]LSD at a 1 nM concentration and chlorpromazine as a reference in a standard binding buffer. The “standard binding buffer” was composed of 50 mM Tris HCl, 10 mM MgCl<sub>2</sub>, and 0.1 mM EDTA at pH 7.4. Cell membrane fractions expressing the 5-HT<sub>6</sub> and 5-HT<sub>7</sub> receptor target were used in the 5-HT<sub>6</sub> and 5-HT<sub>7</sub> binding studies respectively. The inhibition constant (IC<sub>50</sub>) value is estimated from the data which is then used to calculate the molecular binding affinity (K<sub>i</sub>) using the Cheng-Prusoff equation:

$$K_i = IC_{50} / (1 + [ligand] / K_D)$$



[Ligand] is the radio-ligand concentration and  $K_D$  is the radio-ligand affinity constant for the target receptor, specifically the 5-HT<sub>6</sub> or 5-HT<sub>7</sub> receptor.<sup>33,34</sup>  $K_i$  is a measure of ligand affinity for a specific receptor. This value is defined as the minimum ligand concentration required for binding to half of the receptor protein population without the presence of a radio-labeled ligand.<sup>33-34</sup>

## 5.2 Lithium Reagents

*n*-Butyllithium (2.5 M in hexanes) was purchased as a commercial reagent. 2-Lithiofuran was generated by treatment of furan with *n*-butyllithium and used immediately<sup>27</sup>.

## 5.3 Synthesis of Pyrimidines

### General procedure for synthesis of 4-(2-furyl)-2-(4-*N*-substituted-piperazino)pyrimidines **5** and **6**

Compounds **5** and **6** were prepared as previously described with slight modifications.<sup>23-</sup>  
<sup>24</sup> A solution of 2-furyllithium (8.7 mmol) in tetrahydrofuran (THF, 5.0 mL) was treated dropwise with 2-chloropyrimidine (1.0 g, 8.7 mmol) in THF (30 mL) at -5 °C under nitrogen atmosphere. The mixture was stirred for 30 min at -5 °C and then quenched with water (5.0 mL) in THF (5.0 mL). After treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ, 1.9 g, 8.7 mmol), the mixture was stirred for 5 min to reach room temperature. The mixture was basified with sodium carbonate (saturated) till pH = 9 and was then extracted with diethyl ether (2 × 30 mL), dried over magnesium sulfate, and concentrated *in vacuo* to provide crude product. The crude product **2** was purified by chromatography eluting with hexanes/diethyl ether (70:30) to provide 2-Chloro-4-(2'-furyl)pyrimidine to be utilized in the next step. A solution of compound **2** and *N*-

Boc-piperazine in toluene was heated to 80 °C for 48 hours, after which the mixture was cooled to room temperature. The reaction mixture was basified with sodium carbonate, extracted with Et<sub>2</sub>O (2 × 20 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The crude residue was purified on a chromatotron with EMD 60PF254 silica gel eluting with dichloromethane/methanol (100:0 for 100 mL, then 95:5 for 250 mL) to provide 4-(2'-furyl)-2-(*N*-Boc-piperazino)pyrimidine. Subsequent de-protection of the Boc group was accomplished by dissolving **3** in 30% trifluoroacetic acid/dichloromethane (3 mL : 7 mL) and stirring the solution under a nitrogen atmosphere. The mixture was basified with sodium carbonate, extracted with Et<sub>2</sub>O (2 × 20 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Complete deprotection was achieved yielding **4** with minimal impurities allowing for progression to the next synthetic step without further purification. A solution of compound 4-(2'-furyl)-2-(piperazino)pyrimidine and the corresponding alkylhalide in toluene was heated to 80 °C for 72 h, after which the mixture was cooled to room temperature. The mixture was basified with sodium carbonate, extracted with EtOAc (2 × 20 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified on a chromatotron with EMD 60PF254 silica gel eluting with dichloromethane/methanol (100:0 for 100 mL, then 95:5 for 250 mL) to afford **5** or **6**.

#### **General procedure for synthesis of 4-(2-furyl)-2-(4-*N*-substituted-piperazino)pyrimidines **11** - **14****

Compounds **11** – **14** were prepared as previously described with slight modifications.<sup>23-24</sup> A mixture of piperazine (58.1 mmol) and K<sub>2</sub>CO<sub>3</sub> (29.0 mmol) in acetonitrile (30 mL), was added a corresponding alkyl halide (29.0 mmol) and heated to reflux overnight. The mixture was allowed to cool to room temperature and then quenched with deionized water and extracted

with EtOAc. Organic extracts were combined, dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The resulting compounds **7 - 10** were considered to be of satisfactory purity and used in the following reactions without further purification. A solution of compound **2** and compounds **7 - 10** in toluene was heated to 80 °C for 48 hours, after which the mixture was cooled to room temperature. The mixture was basified with sodium carbonate, extracted with EtOAc (2 × 20 mL), dried ( $\text{MgSO}_4$ ), filtered and concentrated *in vacuo*. The residue was purified on a chromatotron with EMD 60PF254 silica gel eluting with dichloromethane/methanol (100:0 for 100 mL, then 9:1 for 250 mL) to provide compounds **11 - 14**.

#### 5.4 Hydrobromic Salt Preparation

Formation of the hydrobromide salt was achieved by dissolving compounds **5 - 6**, **11**, and **13 - 14** (0.608 mmol) in MeOH (3 mL) and adding 62% hydrobromic acid (0.608 mmol) drop-wise. After five minutes the reaction flask was diluted with  $\text{Et}_2\text{O}$  (5 mL) to encourage precipitation and the resulting solid was filtered and dried *in vacuo*.

#### 5.5 Compound Characterization

**2-Chloro-4-(2'-furyl)pyrimidine (2, AE-001-35):** This compound was obtained as a white solid in 72 % yield (556 mg); mp 57 - 59 °C;  $^1\text{H}$  NMR:  $\delta$  8.60 (d,  $J$  = 5.2 Hz, 1H), 7.64 (d,  $J$  = 2.3 Hz, 1H), 7.54 (d,  $J$  = 5.2 Hz, 1H), 7.40 (d,  $J$  = 4.1 Hz, 1H), 6.63 (t,  $J$  = 5.2 Hz, 1H);  $^{13}\text{C}$  NMR:  $\delta$  160.6, 158.7, 156.9, 149.34, 145.1, 113.4, 112.0, 112.0

**4-(2'-Furyl)-2-(N-Butoxycarbonyl-piperazino)pyrimidine (3, AE-001-64):** This compound was obtained as a cream colored solid in 69 % yield (750 mg);  $^1\text{H}$  NMR:  $\delta$  8.36 (d,  $J$  = 5.1 Hz, 1H), 7.57 (t,  $J$  = .8 Hz, 1H), 7.18 (d,  $J$  = 2.8 Hz, 1H), 6.90 (d,  $J$  = 5.1 Hz, 1H), 6.56 (d,  $J$  = 1.6 Hz, 1H), 3.88

(t,  $J = 4.9$  Hz, 4H), 3.54 (t,  $J = 4.9$  Hz, 4H), 1.52 (s, 9H);  $^{13}\text{C}$  NMR:  $\delta$  160.6, 157.4, 154.9, 153.9, 151.6, 143.5, 111.2, 110.3, 103.2, 78.9, 42.59, 27.5;

**4-(2'-Furyl)-2-(piperazino)pyrimidine (4, AE-001-67):** This compound was obtained as a brown oil in 91 % yield (978 mg);  $^1\text{H}$  NMR:  $\delta$  8.34 (d,  $J = 5.1$  Hz, 1H), 7.55 (t,  $J = .7$  Hz, 1H), 7.16 (d,  $J = 3.4$  Hz, 1H), 6.86 (d,  $J = 5.1$  Hz, 1H), 6.53 (q,  $J = 2.5$  Hz, 1H), 3.85 (t,  $J = 5.1$  Hz, 4H), 2.95 (t,  $J = 5.1$  Hz, 4H), 1.99 (s, 1H);  $^{13}\text{C}$  NMR:  $\delta$  160.7, 157.3, 154.9, 151.7, 143.4, 111.1, 110.2, 102.9, 45.1, 43.9

**4-(2'-Furyl)-2-(4-(3-phenylpropyl)piperazino)pyrimidine (5, AE-001-69):** This compound was obtained as an amber oil in 62 % yield (88 mg);  $^1\text{H}$  NMR:  $\delta$  8.36 (d,  $J = 5.1$  Hz, 1H), 7.56 (t,  $J = 1.5$  Hz, 1H), 7.34-7.3 (m, 2H), 7.24-7.22 (m, 3H), 7.20-7.18 (m, 1H), 6.88 (d,  $J = 5.0$  Hz, 1H), 6.54 (q,  $J = 5.1$  Hz, 1H), 3.93 (t,  $J = 4.9$  Hz, 4H), 2.69 (q,  $J = 12.1$  Hz, 2H), 2.53 (t,  $J = 4.9$  Hz, 4H), 2.43 (q,  $J = 11.7$  Hz, 2H), 1.91 (m, 2H);  $^{13}\text{C}$  NMR:  $\delta$  160.7, 157.3, 154.9, 151.8, 143.4, 141.1, 127.5, 127.4, 124.8, 111.1, 110.2, 102.9, 57.1, 52.2, 42.8, 32.7, 27.6; Highresolution MS (ESI, positive ion mode): calcd. for  $\text{C}_{21}\text{H}_{25}\text{N}_4\text{O}$  ( $M + 1$ ) $^+$ ,  $m/z$  349.2028, found  $m/z$  349.2039. A hydrobromide salt, mp > 250 °C. Anal Calcd. for  $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O} \cdot 2\text{HBr}$ : C, 49.43; H, 5.14; N, 10.98. Found: C, 49.51; H, 5.36; N, 10.66.

**4-(2'-Furyl)-2-(4-propylpiperazino)pyrimidine (6, AE-001-68):** This compound was obtained as a amber oil in 54 % yield (45 mg);  $^1\text{H}$  NMR:  $\delta$  8.36 (d,  $J = 5.1$  Hz, 1H), 7.56 (q,  $J = 1.3$  Hz, 1H), 7.17 (q,  $J = 2.1$  Hz, 1H), 6.87 (d,  $J = 5.1$  Hz, 1H), 6.55 (q,  $J = 2.6$  Hz, 1H), 3.91 (t,  $J = 5.1$  Hz, 4H), 2.54 (t,  $J = 5.1$  Hz, 4H), 2.37 (m, 2H), 1.59 (m, 2H), 0.95 (t,  $J = 7.4$  Hz, 3H);  $^{13}\text{C}$  NMR:  $\delta$  160.6, 157.3, 154.9, 151.7, 143.4, 111.1, 110.2, 102.9, 59.9, 52.2, 42.7, 19.0, 11.0. A hydrobromide salt, mp >

250 °C. Anal Calcd. for  $C_{15}H_{20}N_4O \cdot 2HBr$ : C, 42.78; H, 5.18; N, 12.55. Found: C, 41.50; H, 5.11; N, 12.90.

**4-(2'-Furyl)-2-(4-ethylhexanoatepiperazino)pyrimidine (11, AE-001-37):** This compound was obtained as a brown oil in 58 % yield (98 mg);  $^1H$  NMR:  $\delta$  8.33 (d,  $J$  = 5.1 Hz, 1H), 7.54 (d,  $J$  = 2.4 Hz, 1H), 7.15 (d,  $J$  = 4.1 Hz, 1H), 6.84 (d,  $J$  = 5.1 Hz, 1H), 6.52 (t,  $J$  = 5.2 Hz, 1H), 4.13 (q,  $J$  = 10.7 Hz, 2H), 3.89 (t,  $J$  = 4.9 Hz, 4H), 2.52 (t,  $J$  = 4.9 Hz, 4H), 2.39 (t,  $J$  = 7.7 Hz, 2H), 2.31 (t,  $J$  = 7.5 Hz, 2H), 1.65 (m, 2H), 1.57 (m, 2H), 1.36 (m, 2H), 1.26 (t,  $J$  = 7.1 Hz, 4H);  $^{13}C$  NMR:  $\delta$  172.7, 160.6, 157.3, 154.9, 151.7, 143.4, 111.1, 110.2, 102.9, 59.2, 57.6, 52.2, 42.6, 33.3, 26.1, 25.5, 23.9, 13.3; Highresolution MS (ESI, positive ion mode): calcd. for  $C_{20}H_{29}N_4O_3$  ( $M + 1$ )<sup>+</sup>,  $m/z$  373.2240, found  $m/z$  273.2224. A hydrobromide salt, mp > 250 °C; Anal Calcd. for  $C_{20}H_{28}N_4O_3 \cdot 2HBr \cdot H_2O$ : C, 43.49; H, 5.84; N, 10.14. Found: C, 43.68; H, 5.84; N, 10.14.

**4-(2'-furyl)-2-(4-ethylhydroxypiperazino)pyrimidine (12, AE-001-39):** This compound was obtained as a pale yellow solid in 86 % yield (240 mg); mp 109-111;  $^1H$  NMR:  $\delta$  8.34 (d,  $J$  = 5.1 Hz, 1H), 7.56 (d,  $J$  = 0.8 Hz, 1H), 7.17 (d,  $J$  = 3.4 Hz, 1H), 6.87 (d,  $J$  = 5.1 Hz, 1H), 6.53–6.54 (m, 1H), 3.91 (t,  $J$  = 4.9 Hz, 4H), 3.69 (t,  $J$  = 5.3 Hz, 2H), 2.87 (s, 1H), 2.59-2.62 (m, 4H);  $^{13}C$  NMR:  $\delta$  160.6, 157.3, 154.9, 151.7, 143.4, 111.1, 110.3, 103.0, 58.6, 56.8, 51.9, 42.7; Highresolution MS (ESI, positive ion mode): calcd. for  $C_{15}H_{20}N_4O$  ( $M + 1$ )<sup>+</sup>,  $m/z$  275.1508, found  $m/z$  275.1497.; Anal Calcd. for  $C_{14}H_{18}N_4O_2$ : C, 61.30; H, 6.61; N, 20.42. Found: C, 61.36; H, 6.78; N, 20.42.

**4-(2'-furyl)-2-(4-hexylpiperazino)pyrimidine (13, AE-001-77):** This compound was obtained as a yellow oil in 58 % yield (150 mg);  $^1H$  NMR:  $\delta$  8.32 (d,  $J$  = 4.8 Hz, 1H), 7.53 (t,  $J$  = 0.8 Hz, 1H), 7.15 (d,  $J$  = 3.4 Hz, 1H), 6.83 (d,  $J$  = 5.1 Hz, 1H), 6.51 (q,  $J$  = 2.6 Hz, 1H), 3.89 (t,  $J$  = 5.1 Hz, 4H), 2.50 (t,  $J$  = 5.1 Hz, 4H), 2.36 (t,  $J$  = 7.8 Hz, 2H), 1.3 (m, 6H), 0.9 (q,  $J$  = 6.8 Hz, 3H);  $^{13}C$  NMR:  $\delta$  160.6,

157.3, 154.8, 151.8, 143.3, 111.0, 110.1, 102.8, 58.0, 52.2, 42.7, 30.8, 26.3, 25.9, 21.6, 13.1;

Highresolution MS (ESI, positive ion mode): calcd. for  $C_{18}H_{27}N_4O$  ( $M + 1$ )<sup>+</sup>,  $m/z$  315.2170, found  $m/z$  315.2185. A hydrobromide salt, mp > 250 °C. Anal Calcd. for  $C_{18}H_{26}N_4O \cdot 2HBr \cdot 1.5H_2O$ : C, 42.96; H, 6.21; N, 11.13. Found: C, 42.99; H, 5.97; N, 11.07.

**4-(2'-furyl)-2-(4-ethylmethoxypiperazino)pyrimidine (14, AE-001-72):** This compound was obtained as a yellow oil in 48 % yield (60 mg); <sup>1</sup>H NMR: δ 8.33 (d,  $J$  = 5.0 Hz, 1H), 7.53 (s, 1H), 7.15 (d,  $J$  = 3.4 Hz, 1H), 6.84 (d,  $J$  = 5.1 Hz, 1H), 6.51 (t,  $J$  = 1.6 Hz, 1H), 3.91 (t,  $J$  = 4.9 Hz, 4H), 3.55 (t,  $J$  = 5.5 Hz, 2H), 3.37 (s, 3H), 2.62 (t,  $J$  = 5.6 Hz, 2H), 2.57 (t,  $J$  = 4.9 Hz, 4H); <sup>13</sup>C NMR: δ 160.6, 157.3, 154.8, 151.7, 143.3, 111.1, 110.1, 102.8, 69.1, 57.9, 57.1, 52.5, 42.5; Highresolution MS (ESI, positive ion mode): calcd. for  $C_{15}H_{21}N_4O_2$  ( $M + 1$ )<sup>+</sup>,  $m/z$  289.1658, found  $m/z$  289.1665. A hydrobromide salt, mp > 250 °C. Anal Calcd. for  $C_{15}H_{21}N_4O_2 \cdot 2HBr$ : C, 40.02; H, 4.93; N, 12.45. Found: C, 40.01; H, 5.01; N, 12.29.

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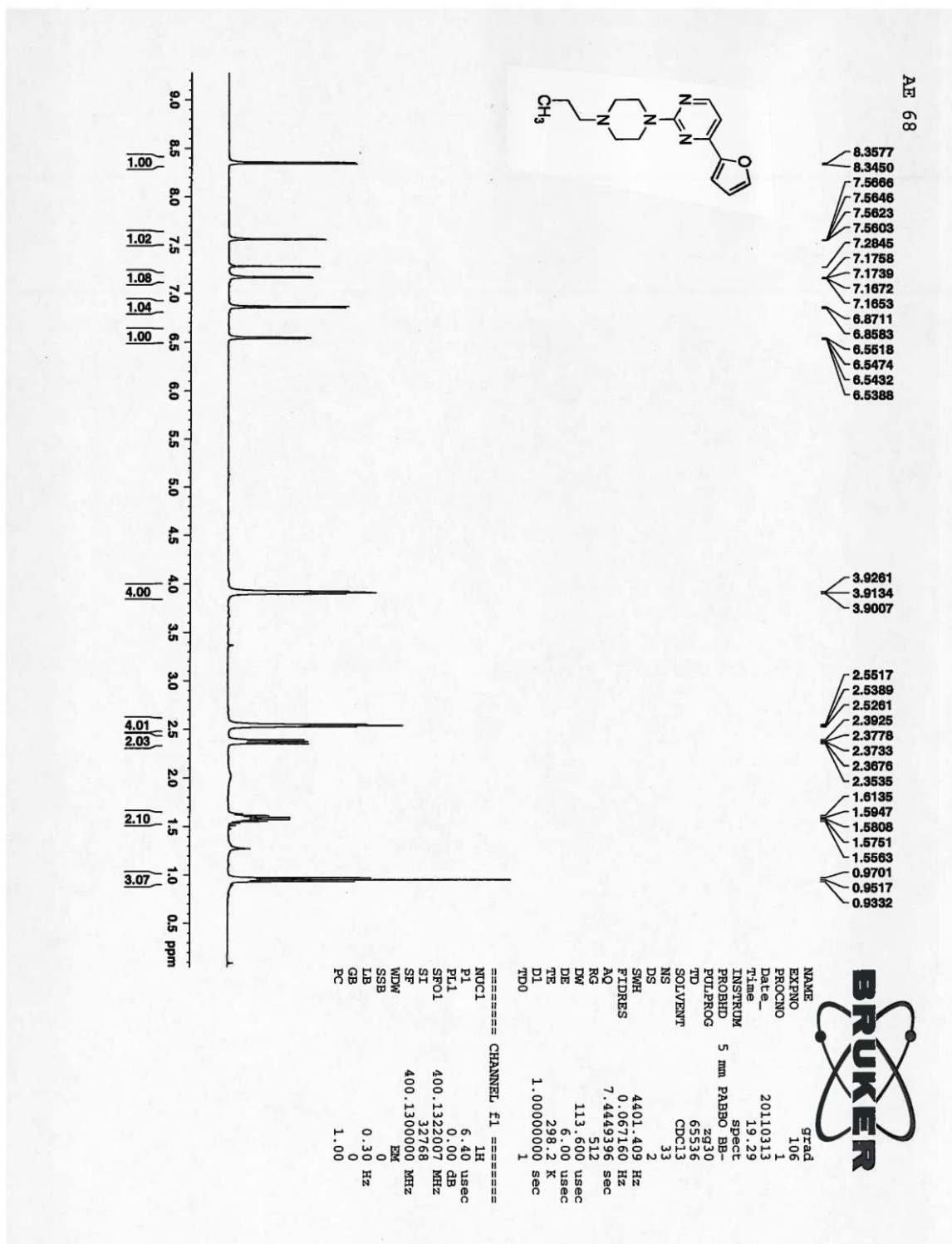
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## 7 SPECTRA



AE 68

160.64  
157.31  
154.88  
151.74  
143.36

111.09  
110.16  
102.87

76.35  
76.04  
75.72

59.85  
52.21  
42.70

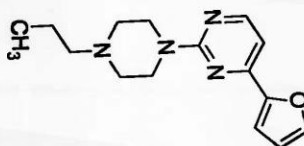
19.02  
10.99



NAME grad  
EXPNO 107  
PROCNO 1  
Date\_ 20110313  
Time\_ 19.37  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 178  
DS 2  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 3251  
DW 20.850 usec  
DE 7.00 usec  
TE 298.2 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

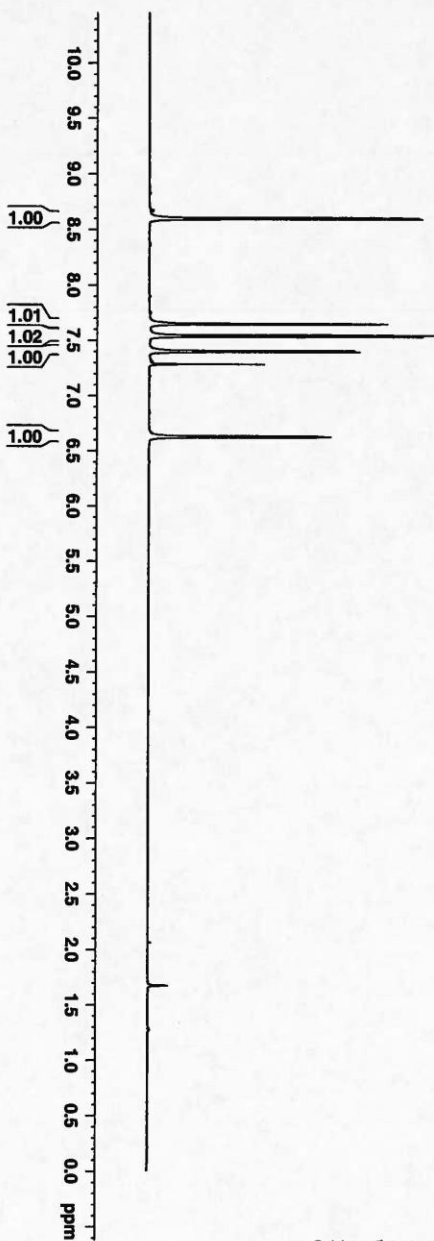
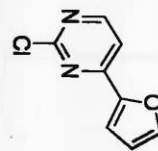
===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40



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

AE 35

8.6043  
8.5912  
7.6522  
7.6503  
7.6479  
7.6464  
7.5463  
7.5333  
7.4056  
7.4042  
7.3968  
7.3953  
7.2839  
6.6325  
6.6281  
6.6236  
6.6193

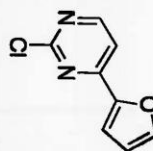


```

NAME      grad
EXPNO     56
PROCNO    1
Date_     20101206
Time      11.08
INSTRUM   5 mm PABBO BB-
PROBHD    spect
PULPROG   zg30
TD         65536
SOLVENT   CDCl3
NS         64
DS         2
SMH        4401.409 Hz
FIDRES     0.067160 Hz
AQ         7.4449396 sec
RG         20.2
DW         113.600 usec
DE         6.00 usec
TE         298.2 K
D1         1.00000000 sec
TD0        1

===== CHANNEL f1 =====
NUC1       1H
P1         6.40 usec
PL1        0.00 dB
SFO1       400.1322007 MHz
SI         32768
SF         400.1300000 MHz
WDW        EM
SSB        0
LB         0.30 Hz
GB         0
PC         1.00
  
```

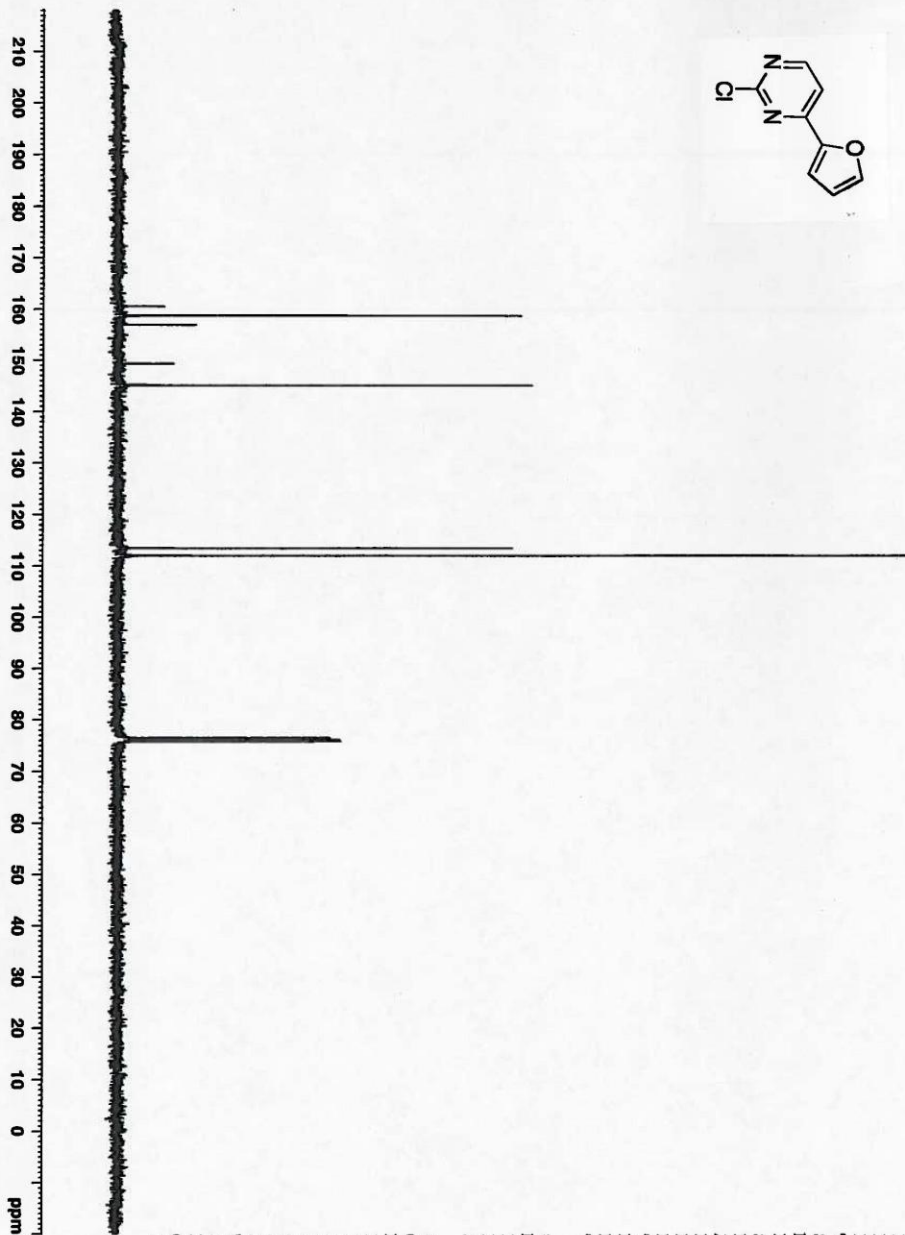
AE 35



160.57  
158.77  
156.93  
149.34  
145.11

113.43  
111.97

76.41  
76.09  
75.78



```

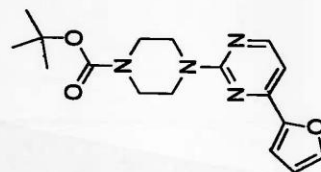
NAME          grad
EXPNO         68
PROCNO        1
Date_         20101211
Time         15.50
INSTRUM       spect
PROBHD        5 mm PABBO BB-
PULPROG       zgpg30
TD            32768
SOLVENT       CDCl3
NS            161
DS            4
SMH           23980.814 Hz
FIDRES        0.731836 Hz
AQ            0.6832628 sec
RG            2048
DW            20.850 usec
DE            7.00 usec
TE            298.2 K
D1            2.0000000 sec
D11           0.0300000 sec
TD0           1

===== CHANNEL f1 =====
NUC1          13C
P1            8.00 usec
PL1           -3.00 dB
SFO1          100.6228298 MHz

===== CHANNEL f2 =====
CPDPRG2       waltz16
NUC2          1H
PCPD2         70.00 usec
PL2           0.00 dB
PL12          10.25 dB
PL13          10.25 dB
SFO2          400.1316005 MHz
SI            32768
SF            100.6128688 MHz
WDW           EM
SSB           0
LB            2.00 Hz
GB            0
PC            1.40
  
```



AE 64



160.61  
157.36  
154.90  
153.88  
151.58  
143.47

111.15  
110.32  
103.24

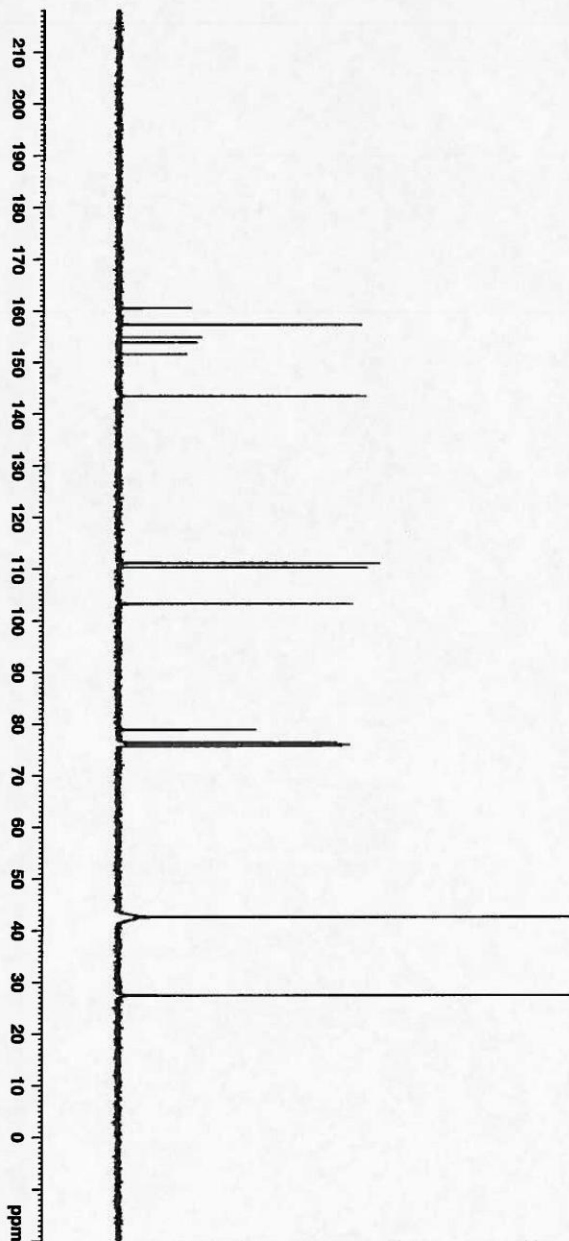
78.91  
76.38  
76.06  
75.75

**BRUKER**

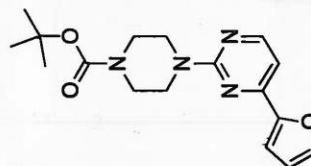
NAME grad  
EXPNO 64  
PROCNO 1  
Date 20101210  
Time 14.11  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 32768  
SOLVENT CDCl3  
NS 323  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.731836 Hz  
AQ 0.6832628 sec  
RG 2048  
DW 20.850 usec  
DE 7.00 usec  
TE 298.2 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

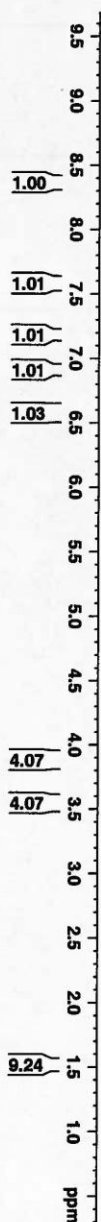
===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40



AE 64

8.3748  
8.36207.5786  
7.5765  
7.2847  
7.1879  
7.1809  
6.9116  
6.8989  
6.5634  
6.55933.8900  
3.8781  
3.8654  
3.5519  
3.5390  
3.5271

1.5176



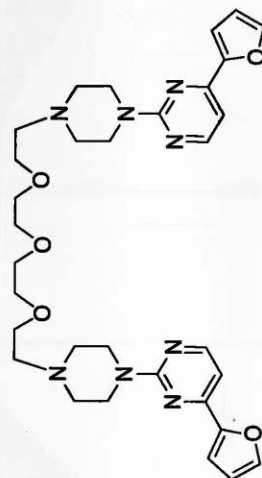
```

NAME          grad
EXPNO         60
PROCNO        1
Date_         20101209
Time          13.43
INSTRUM       spect
PROBHD        5 mm PABBO BB-
PULPROG       zg30
TD            32768
SOLVENT       CDCl3
NS            38
DS            2
SWH           4401.409 Hz
FIDRES        0.134320 Hz
AQ            3.7224948 sec
RG            1625.5
DE            113.600 usec
TE            298.2 K
D1            1.00000000 sec
TD0           1

===== CHANNEL f1 =====
NUC1          1H
P1            6.40 usec
PL1           0.00 dB
SFO1          400.1320007 MHz
SI            32768
SF            400.1300000 MHz
WDW           EM
SSB           0
LB            0.30 Hz
GB            0
PC            1.00

```

AE 49



160.82  
157.31  
154.87  
151.74  
143.35

111.10  
110.16  
102.88

76.34  
76.03  
75.71  
69.67  
69.46  
67.95  
56.95  
52.56  
42.62

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



NAME grad  
EXPNO 108  
PROCNO 1  
Date\_ 20110314  
Time 16.13  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 512  
DS 2  
SMH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 3251  
DM 20.850 usec  
DE 7.00 usec  
TE 298.4 K  
D1 2.0000000 sec  
D11 0.0300000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

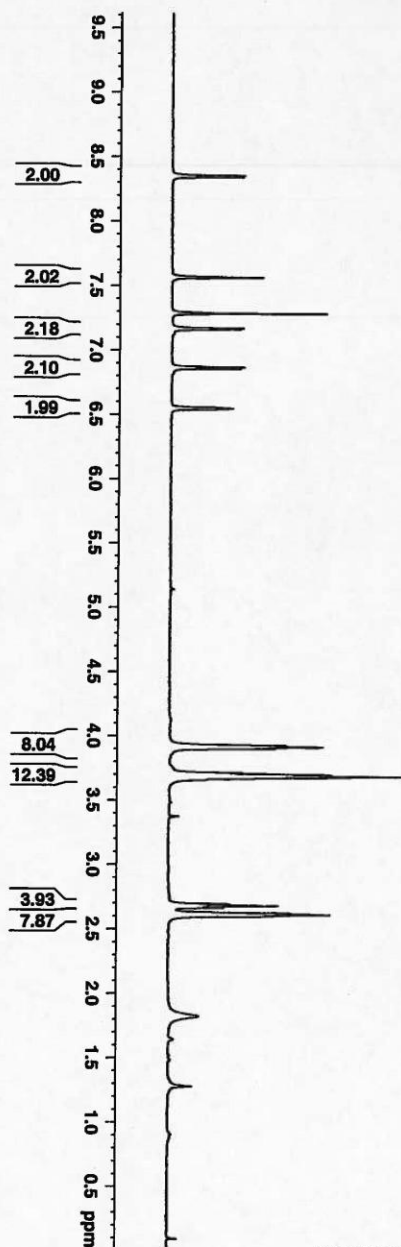
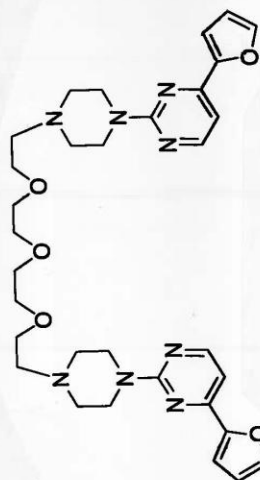
===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40

AE 49

8.3533  
8.34077.5640  
7.2842  
7.1706  
7.1623  
6.8679  
6.8553  
6.5511  
6.5469  
6.54303.9243  
3.9127  
3.9004  
3.7118  
3.6971  
3.6822  
3.6764  
2.6915  
2.6770  
2.6624  
2.6200  
2.6080  
2.5958

1.8197

1.2762

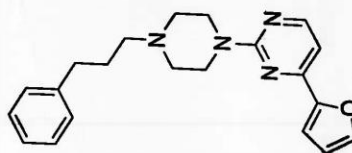


NAME grad  
EXPNO 109  
PROCNO 1  
Date\_ 20110314  
Time 16.42  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 64  
DS 2  
SWH 4401.409 Hz  
FIDRES 0.067160 Hz  
AQ 7.444396 sec  
RG 812.7  
DW 113.600 usec  
DE 6.00 usec  
TE 298.2 K  
D1 1.00000000 sec  
TD0 1

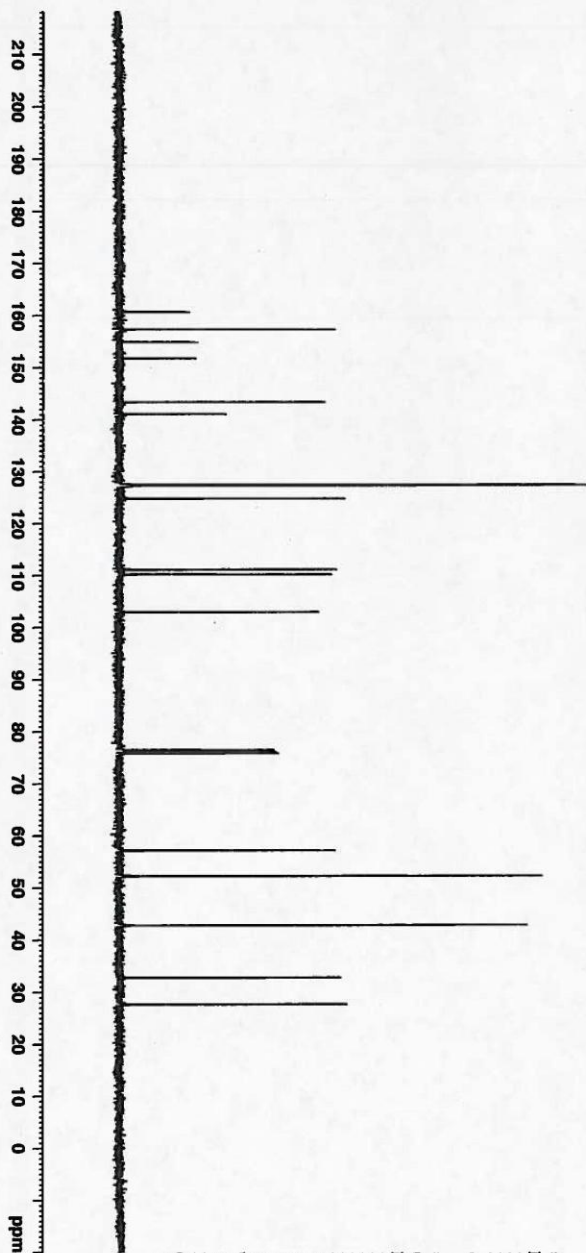
===== CHANNEL f1 =====  
NUC1 1H  
P1 6.40 usec  
PL1 0.00 dB  
SFO1 400.132007 MHz  
SI 32768  
SF 400.130000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



AE 69



160.67
157.33
154.88
151.76
143.38
141.13
127.45
127.37
124.83
111.13
110.20
102.91
76.47
76.15
75.83
57.14
52.20
42.77
32.74
27.62



NAME grad  
EXPNO 103  
PROCNO 1  
Date\_ 20110313  
Time 17.52  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDC13  
NS 45  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 2580.3  
DM 20.850 usec  
DE 7.00 usec  
TE 298.3 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

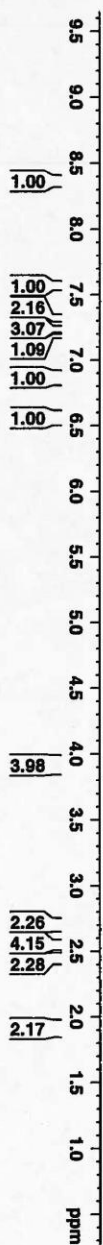
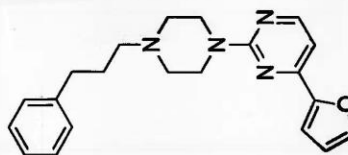
===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDM EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40

AE 69

8.3682  
8.3555  
7.5645  
7.5624  
7.5608  
7.3385  
7.3177  
7.2993  
7.2854  
7.2449  
7.2386  
7.2265  
7.2184  
7.2032  
7.2000  
7.1887  
7.1804  
6.8814  
6.8688  
6.5525  
6.5482  
6.5441  
6.5398

3.9406  
3.9284  
3.9160  
2.7197  
2.7006  
2.6812  
2.6594  
2.5545  
2.5419  
2.5294  
2.4650  
2.4465  
2.4271  
2.4065  
1.9445  
1.9249  
1.9061  
1.8868  
1.8682

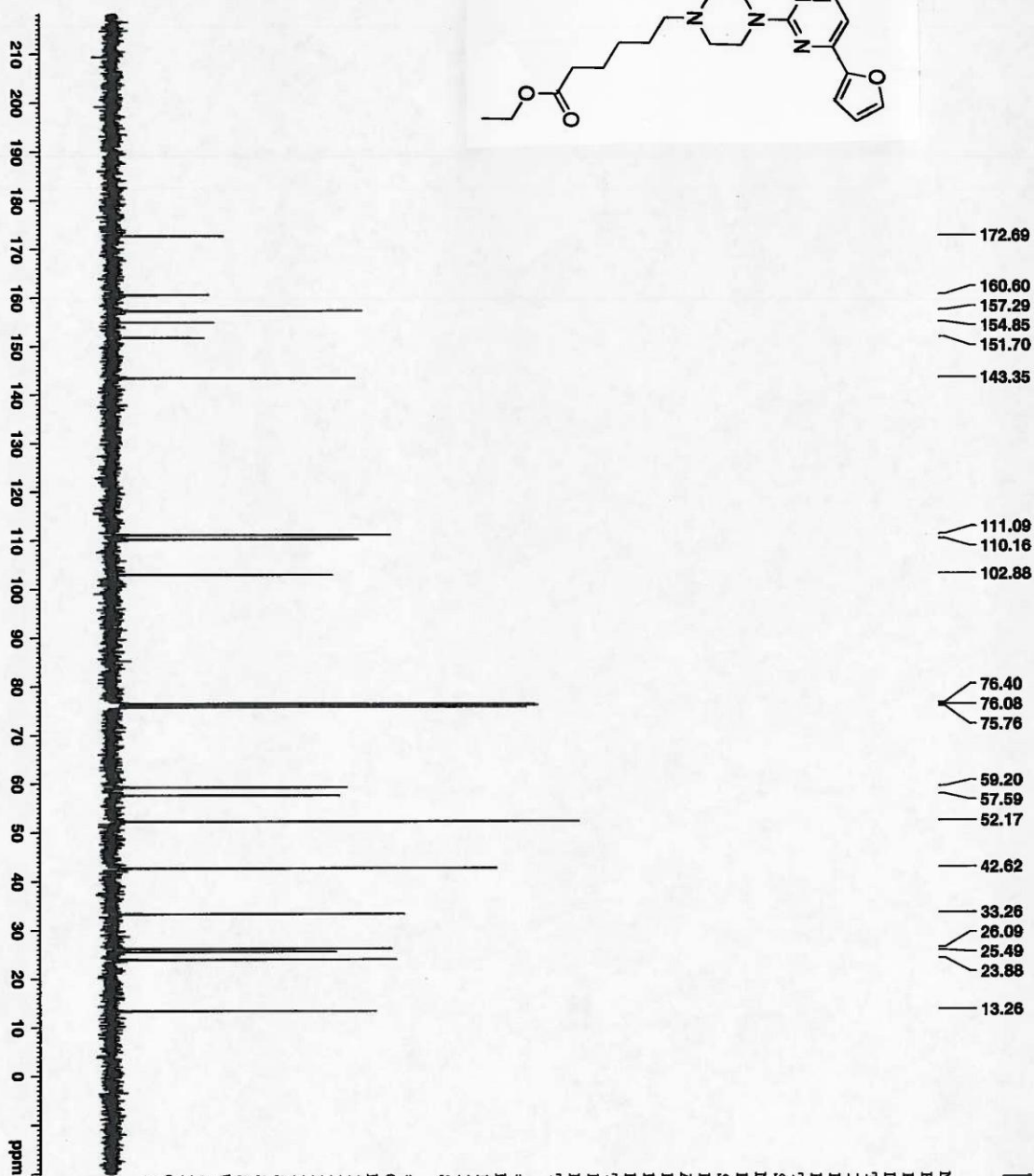
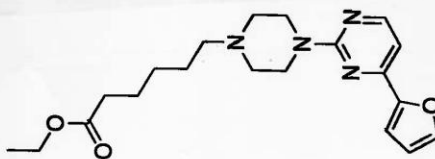


NAME grad  
EXPNO 102  
PROCNO 1  
Date\_ 20110313  
Time\_ 17.34  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 64  
DS 2  
SWH 4401.409 Hz  
FIDRES 0.067160 Hz  
AQ 7.4449396 sec  
RG 90.5  
DW 113.600 usec  
DE 6.00 usec  
TE 298.2 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 6.40 usec  
PL1 0.00 dB  
SFO1 400.1322007 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



AE 37



```

NAME      grad
EXPNO     83
PROCNO    1
Date_     20110209
Time      17.16
INSTRUM   spect
PROBHD    5 mm PABBO BB-
PULPROG   zgpg30
TD        65536
SOLVENT   CDCl3
NS        55
DS        0
SMH       23980.814 Hz
FIDRES    0.365918 Hz
AQ        1.3664756 sec
RG        1290.2
DW        20.850 usec
DE        7.00 usec
TE        298.2 K
D1        2.00000000 sec
D11       0.03000000 sec
TD0       1

===== CHANNEL f1 =====
NUC1      13C
P1        8.00 usec
PL1       -3.00 dB
SFO1      100.6228298 MHz

===== CHANNEL f2 =====
CPDPRG2   waltz16
NUC2      1H
PCPD2     70.00 usec
PL2       0.00 dB
PL12      10.25 dB
PL13      10.25 dB
SFO2      400.1316005 MHz
SI        32768
SF        100.6128688 MHz
WDW        EM
SSB        0
LB        2.00 Hz
GB        0
PC        1.40
  
```

AE 37

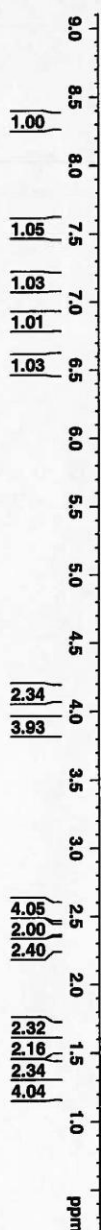
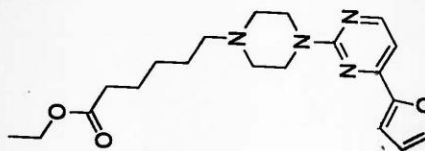
8.3350  
8.3223  
7.5450  
7.5431  
7.5408  
7.5389  
7.2845  
7.1545  
7.1528  
7.1460  
7.1442  
6.8510  
6.8383  
6.5293  
6.5249  
6.5207  
6.5163

4.1525  
4.1347  
4.1168  
4.0990  
3.9029  
3.8906  
3.8785  
2.5290  
2.5166  
2.5041  
2.4065  
2.3876  
2.3681  
2.3289  
2.3103  
2.2914  
1.6827  
1.6635  
1.6443  
1.6255  
1.5836  
1.5641  
1.5451  
1.3843  
1.3660  
1.3523  
1.3459  
1.2713



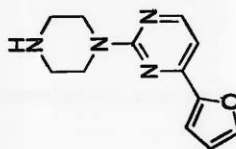
NAME grad  
EXPNO 82  
PROCNO 1  
Date\_ 20110209  
Time 17.05  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 39  
DS 2  
SWH 4401.409 Hz  
FIDRES 0.067160 Hz  
AQ 7.4449396 sec  
RG 228.1  
DW 113.600 usec  
DE 6.00 usec  
TE 298.2 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 6.40 usec  
PL1 0.00 dB  
SFO1 400.1322007 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00





AE 67



160.73  
157.29  
154.85  
151.72  
143.36

111.09  
110.16  
102.86

76.39  
76.07  
75.75

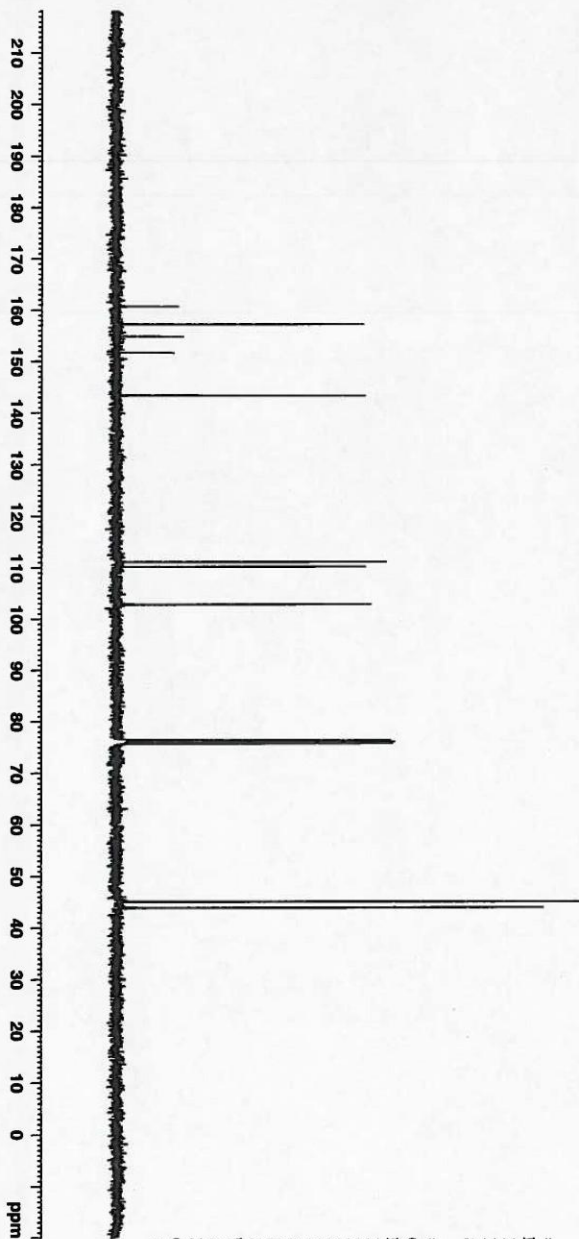
45.05  
43.88



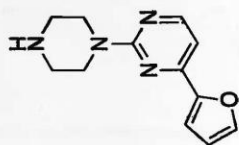
NAME grad  
EXPNO 104  
PROCNO 1  
Date\_ 20110313  
Time 17.58  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
DS 82  
FIDRES 23980.814 Hz  
AQ 0.365918 Hz  
RG 1.3664756 sec  
DE 2580.3  
DW 20.850 usec  
TE 7.00 usec  
D1 298.3 K  
D11 2.00000000 sec  
TD0 0.03000000 sec  
1

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40



AE 67



8.3484  
8.3337

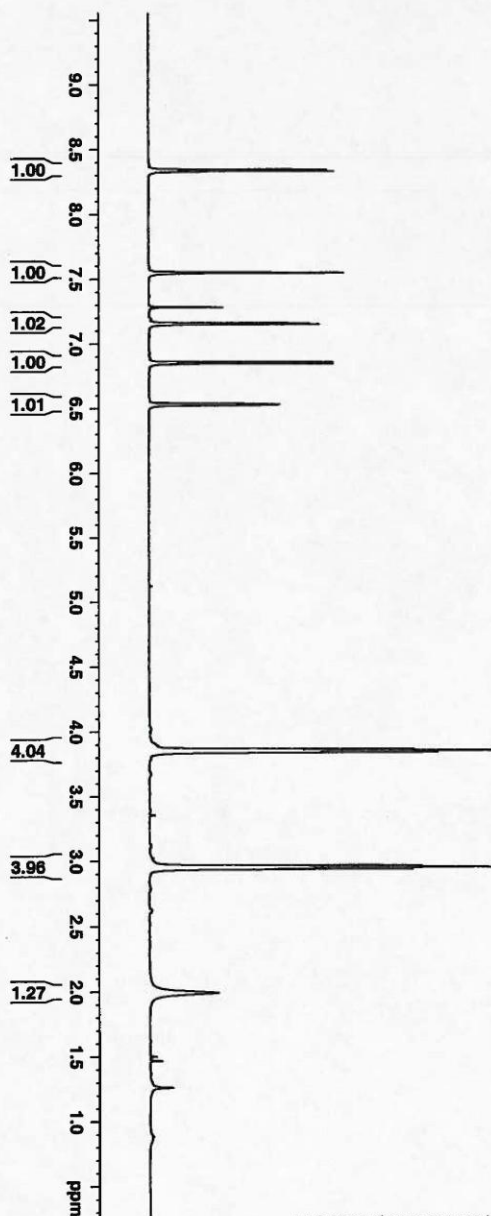
7.5523  
7.5506  
7.5486  
7.2848  
7.1611  
7.1526  
6.8594  
6.8467  
6.5369  
6.5325  
6.5284  
6.5246

3.8648  
3.8522  
3.8395

2.9642  
2.9514  
2.9390

1.9913

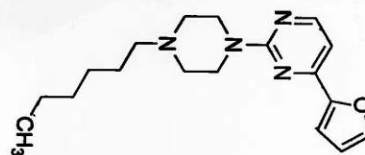
1.2608



NAME grad  
EXPNO 105  
PROCNO 1  
Date\_ 20110313  
Time 18.06  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 11  
DS 2  
SWH 4401.409 Hz  
FIDRES 0.067160 Hz  
AQ 7.4449396 sec  
RG 256  
DW 113.600 usec  
DE 6.00 usec  
TE 298.2 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 6.40 usec  
PL1 0.00 dB  
SFO1 400.1322007 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

AE 77



180.64  
157.27  
154.83  
151.76  
143.29

111.05  
110.10  
102.82

76.41  
76.10  
75.78

57.98  
52.24  
42.72

30.80  
26.30  
25.87  
21.61  
13.06



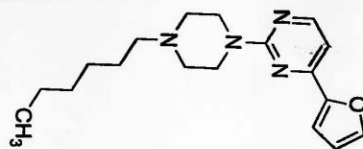
NAME grad  
EXPNO 113  
PROCNO 1  
Date\_ 20110321  
Time 17.23  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 43  
DS 2  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 3649.1  
DW 20.850 usec  
DE 7.00 usec  
TE 301.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40

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

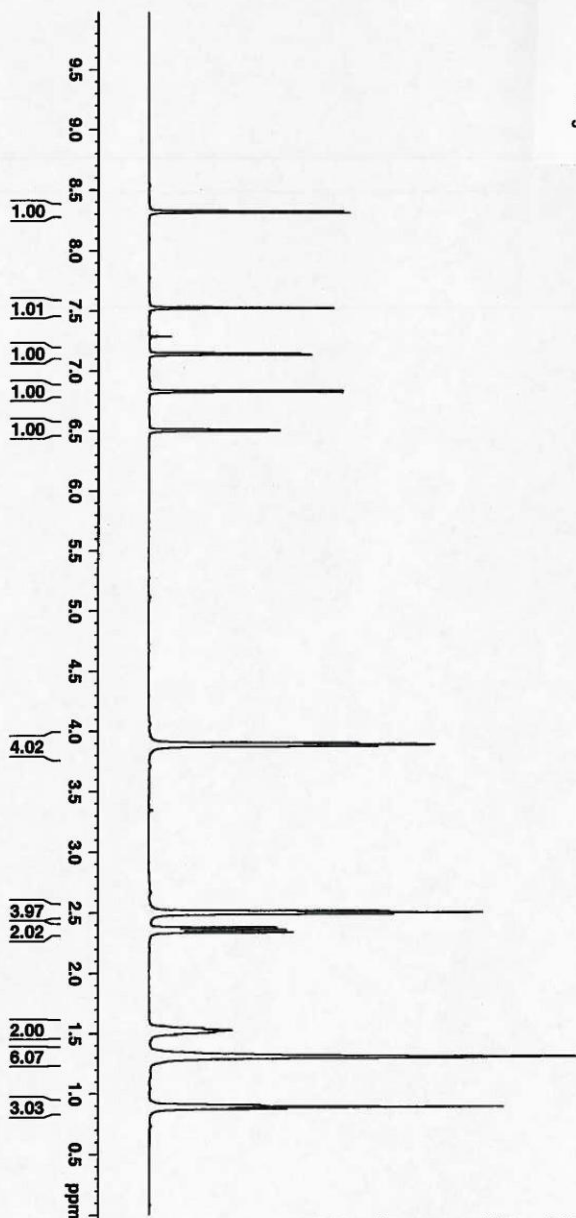
AE 77



8.33  
8.31  
7.53  
7.53  
7.52  
7.29  
7.15  
7.14  
6.84  
6.82  
6.51  
6.51  
6.50  
6.50

3.90  
3.89  
3.87

2.51  
2.50  
2.49  
2.38  
2.36  
2.34  
1.54  
1.52  
1.51  
1.49  
1.30  
0.91  
0.90  
0.89  
0.87



NAME grad  
EXPNO 112  
PROCNO 1  
Date\_ 20110321  
Time\_ 17.15  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 29  
DS 2  
SWH 4401.409 Hz  
FIDRES 0.067160 Hz  
AQ 7.4449396 sec  
RG 28.5  
RG 113.600 usec  
DE 6.00 usec  
TE 300.8 K  
DL 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 6.40 usec  
PL1 0.00 dB  
SFO1 400.132207 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



AE 72

8.3278  
8.3152

7.5336

7.1451

7.1367

6.8409

6.8282

6.5191

6.5149

6.5109

3.9187

3.9067

3.8941

3.5617

3.5479

3.5340

3.3676

2.6323

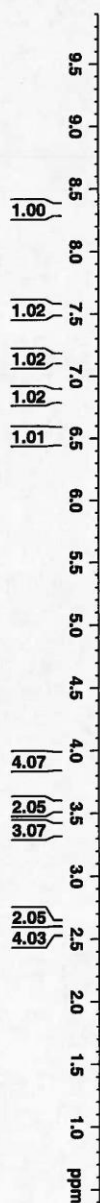
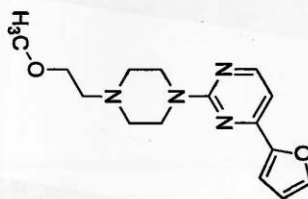
2.6185

2.6045

2.5776

2.5653

2.5527



NAME grad  
EXPNO 110  
PROCNO 1  
Date\_ 20110316  
Time 18.27  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 51  
DS 2  
SWH 4401.409 Hz  
FIDRES 0.067160 Hz  
AQ 7.4449396 sec  
RG 181  
DW 113.600 usec  
DE 6.00 usec  
TE 298.2 K  
D1 1.00000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 1H  
P1 6.40 usec  
PL 0.00 dB  
SFO1 400.1322007 MHz  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

AE 72

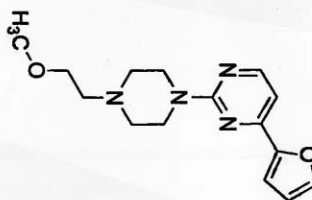
160.60  
157.29  
154.84  
151.72  
143.33

111.08  
110.14  
102.84

76.43  
76.11  
75.79  
69.06

57.94  
57.12  
52.54

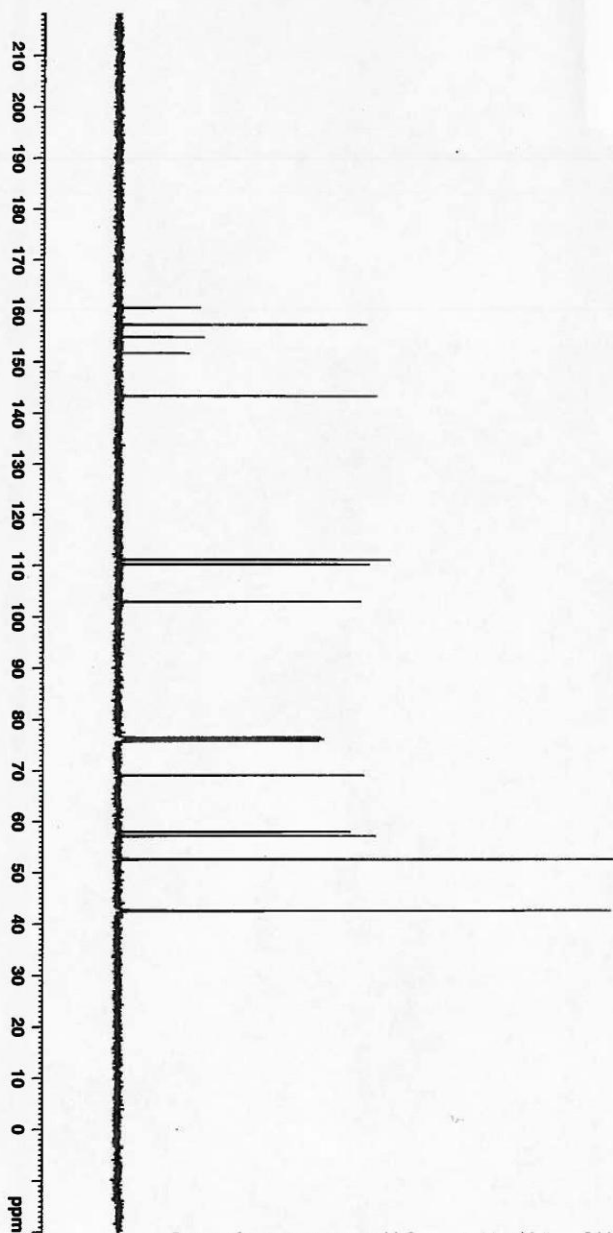
42.54



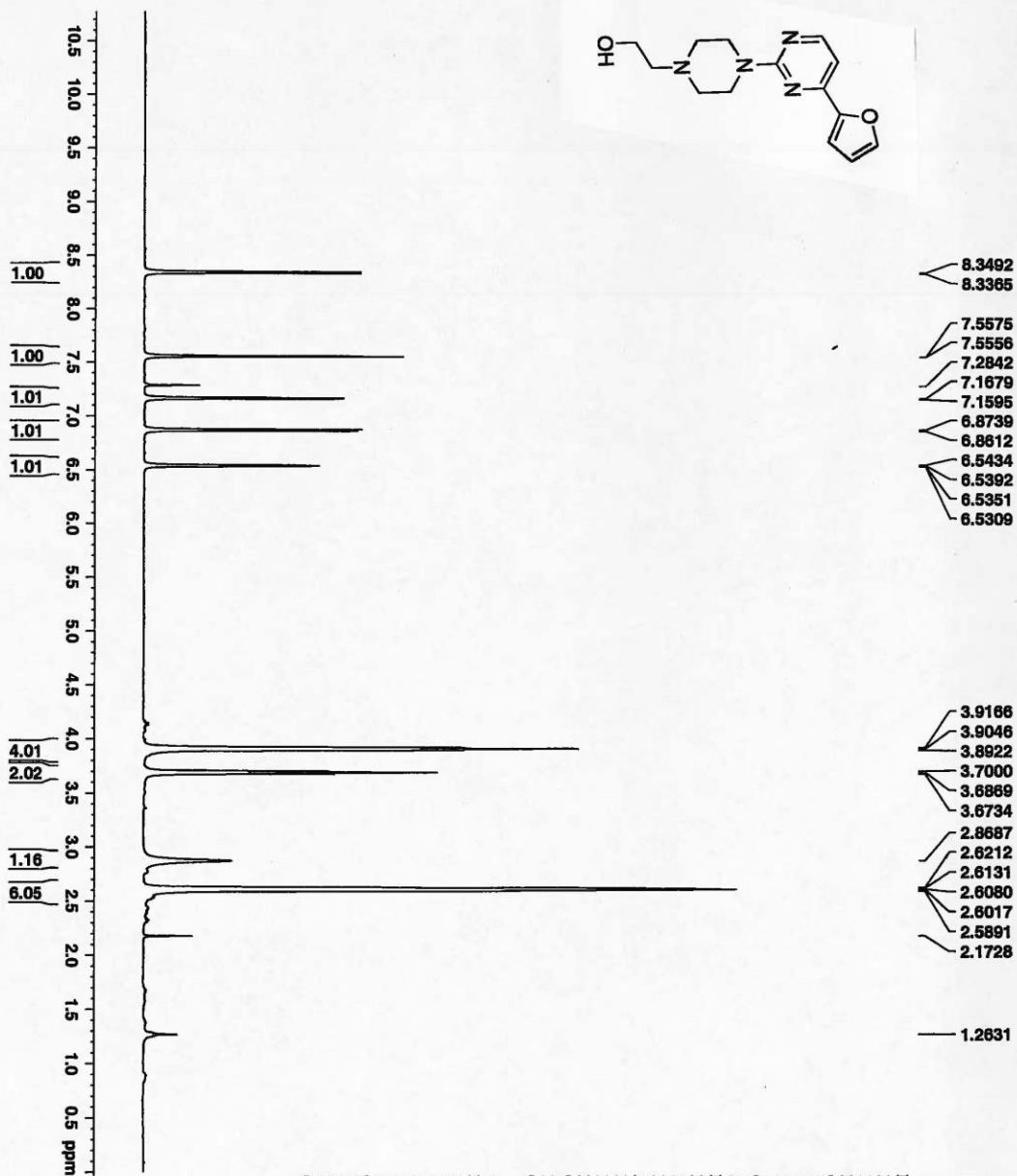
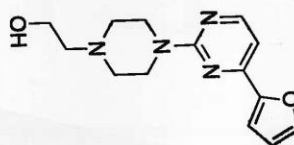
NAME grad  
EXPNO 111  
PROCNO 1  
Date\_ 20110316  
Time 18.38  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 90  
DS 4  
FIDRES 23980.814 Hz  
AQ 0.365918 Hz  
RG 1.3664756 sec  
DW 1625.5  
DE 20.850 usec  
TE 7.00 usec  
D1 298.2 K  
D11 2.00000000 sec  
TD0 0.03000000 sec  
1

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40



AE 39



```

NAME          grad
EXPNO         93
PROCNO        1
Date_         20110222
Time_         9.17
INSTRUM       5 mm PABBO BB-
PROBHD        zg30
PULPROG       65536
TD            CDCl3
SOLVENT       32
NS            2
DS            4401.409 Hz
SWH           0.067160 Hz
FIDRES       7.4449396 sec
AQ           322.5
RG           113.600 usec
DE           6.00 usec
TE           297.7 K
D1           1.00000000 sec
TD0          1

===== CHANNEL f1 =====
NUC1          1H
P1           6.40 usec
PL1          0.00 dB
SFO1         400.1322007 MHz
SI           32768
SF           400.1300000 MHz
WDW          EM
SSB          0
LB           0.30 Hz
GB           0
PC           1.00

```

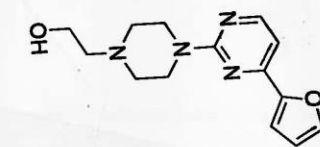
AE 39

160.59  
157.32  
154.89  
151.65  
143.42

111.12  
110.25  
103.04

76.39  
76.08  
75.76

58.56  
56.81  
51.90  
42.73



NAME  
EXPNO 1  
PROCNO 1  
Date\_ 20110222  
Time 9.27  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 32768  
SOLVENT CDCl3  
NS 156  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.731836 Hz  
AQ 0.6832628 sec  
RG 32768  
DW 20.850 usec  
DE 7.00 usec  
TE 298.0 K  
D1 2.00000000 sec  
D11 0.03000000 sec  
TD0 1

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228238 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 0.00 dB  
PL12 10.25 dB  
PL13 10.25 dB  
SFO2 400.1316005 MHz  
SI 32768  
SF 100.6128688 MHz  
WDW EM  
SSB 0  
LB 2.00 Hz  
GB 0  
PC 1.40

