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## Synthesis of Substituted Pyrimidines and Pyridines as Ligands to the 5-HT<sub>7</sub> Receptor

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# SYNTHESIS OF SUBSTITUTED PYRIMIDINES AND PYRIDINES AS LIGANDS TO THE 5-HT<sub>7</sub> RECEPTOR

by

AVA L. BLAKE

Under the Direction of Dr. Lucjan Strekowski

## ABSTRACT

Of the seven existing classes of serotonin receptors, the 5-HT<sub>7</sub> receptors (5-HT<sub>7</sub>Rs) are the most recently discovered. Abundance of 5-HT<sub>7</sub> in the central nervous system is suggestive of the receptor's role in several physiological and pathophysiological functions. Existing research has afforded a number of compounds exhibiting specific affinity to the receptor. These selective ligands can provide structural information about the receptor and can serve as the foundation for pharmacological profiling. This thesis describes the synthesis of substituted pyrimidines and pyridines for affinity to the 5-HT<sub>7</sub> receptor. Organometallic species are the cornerstone for several of the synthetic pathways.

INDEX WORDS: Serotonin 5-HT, 5-HT<sub>7</sub> receptor, Pharmacophore model, Pyrimidines, Pyridines, Synthesis, Conjugate addition, Vinyl, Heterocycle, Organometallic, Palladium catalysis

SYNTHESIS OF SUBSTITUTED PYRIMIDINES AND PYRIDINES AS LIGANDS TO THE  
5-HT<sub>7</sub> RECEPTOR

by

AVA L. BLAKE

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

2010

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2010

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5-HT<sub>7</sub> RECEPTOR

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College of Arts and Sciences

Georgia State University

May 2010

## **DEDICATION**

This thesis is dedicated to my parents, my inspiration and my support, Mr. and Mrs. Harry and Eulalee Blake. All thanks be to God the Most High.

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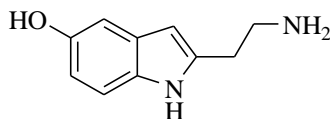
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## 1 INTRODUCTION

Since the isolation of 5-hydroxytryptamine (5-HT) or serotonin (Figure 1) more than fifty years ago, countless biological assays have affirmed its influence throughout the human anatomy.<sup>1</sup> The biogenic amine is associated with an array of physiological processes including glucose metabolism in the liver and cardio valvular operations as well as those of the central nervous system.<sup>2,1</sup> Studies have implicated cerebral serotonin in the regulation of sleep, mood, thermoregulation, feeding, pain-perception, learning, memory, and arousal.<sup>3,4</sup> Its functions are accomplished through the activation of a large family of specific receptors. Of the seven classifications of these receptors, the 5-HT<sub>7</sub> subtype is the most recently unearthed and its function the most unclear. For thorough understanding of the 5-HT<sub>7</sub> receptor, the development of highly selective ligands is imperative to determining its biological significance.



**1**

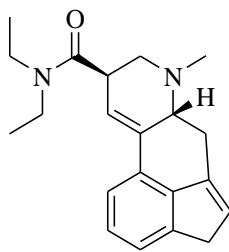
5-hydroxytryptamine (5-HT)

### 1.1 Overview of Serotonin

Once known as enteramine, serotonin was first detected within the cells of rodent intestine where it regulates smooth muscle contractions.<sup>4</sup> Although discovered in nonneural tissues, 5-HT is significantly distributed throughout the central nervous system (CNS) of vertebrates and invertebrates alike. In humans, serotonin-containing neurons are situated primarily within the

raphe nuclei of the midbrain.<sup>4,5</sup> From each nucleus, serotonergic neurons project to multiple regions of the CNS including the forebrain, brainstem, cerebellum and spinal cord.<sup>5,6</sup> The two-step biosynthetic pathway of serotonin features a sequential hydroxylation and decarboxylation of the amino acid tryptophan.<sup>4</sup> Once packed into vesicles, 5-HT is released into the synapse. A transmembrane protein, the 5-HT transporter (5-HTT or SERT) modulates neurotransmission by removing 5-HT from the synaptic cleft for either reuptake into synaptic vesicles for re-release or metabolic degradation by monoamine oxidase A (MAO-A).<sup>6</sup>

The structural semblance of 5-HT with the hallucinogenic agent (+)-lysergic acid diethylamide (**2**, LSD), discovered shortly before, suggested the association of serotonin with the mechanism of psychoactive substances. Moreover, this 5-HT might be linked to psychological disorders. Intensive studies have since implicated dysregulation of the 5-HT system in the onset of a number of CNS disorders.<sup>6</sup>



**2**

Lysergic acid diethylamide (LSD)

These studies focused upon the direct and indirect assays of neurotransmitter function; the treatment efficacy of agents affecting 5-HT function; and, the manipulation of the availability of 5-HT by removing tryptophan.<sup>6</sup> Accordingly, therapeutic agents affecting the 5-HT system have gained wide use in the treatment of CNS disorders.<sup>4,6,7</sup> Selective serotonin reuptake inhibitors (SSRIs) competitively bind to serotonin transporters, thereby hindering the reuptake of the neurotransmitter.<sup>8</sup> SSRIs, such as the tricyclic fluoxetine (Prozac) or the atypical sertraline (Zoloft),

are widely employed as pharmacological treatments for depression and other illnesses including anxiety, schizophrenia, and panic disorders. Monoamine oxidase inhibitors (MAOIs) also induce an elevated amount of serotonin in the synapse and thus reduce neurotransmitter activity. MAOIs likewise elicit an antidepressant response and have long been employed in pharmacological depression therapies.<sup>6,7</sup>

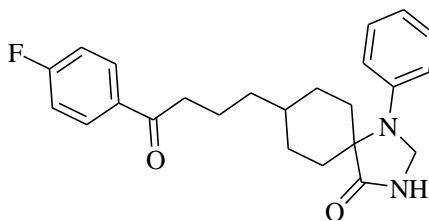
## 1.2 Receptors to Serotonin (5-HT)

The physiological and pathological influence of serotonin is attributed to the neurotransmitter's activation of at least fourteen distinct receptors. These receptors are categorized based on structure (amino acid sequence homology), operation (pharmacology), and signal transduction pathways into seven families 5-HT<sub>1</sub> through 5-HT<sub>7</sub>.<sup>9</sup> The receptors belong to the superfamily of G protein coupled receptors (GPCRs), with the exception of the 5-HT<sub>3</sub> receptor class. Subdivided into 5-HT<sub>3A</sub> and 5-HT<sub>3B</sub>, these receptors are ligand-gated ion channels.<sup>8</sup>

Representing a large family of transmembrane proteins, GPCRs modulate the transmission of extracellular chemical signals. Associated with guanosine triphosphate (GTP), they modulate signal transduction pathways, such as that of cyclic adenosine monophosphate (cAMP), eliciting cellular responses.<sup>10</sup> The 5-HT GPCRs are comprised of seven trans-membrane (TM) helices that form an anticlockwise helix bundle. These GPCR feature a single amine bound to an aromatic ring by a two carbon chain and include all 5-HT receptors, except 5-HT<sub>3</sub> subtype as noted. GPCR signal transmission is effected through the rearrangement of the trans-membrane domains to expose the G-protein binding site at the interior. This rearrangement may occur spontaneously or proceed from small molecule or peptide binding in the interior of the transmembrane bundle.<sup>9</sup> Accordingly, these receptors have been the target of binding studies to

evaluate physiological influence. Ligand-receptor binding assays are performed to provide structural and functional information for potential pharmacological use.

The earliest identified receptors, 5-HT<sub>1</sub> and 5-HT<sub>2</sub>, emerged out of radioligand assays on 5-HT and the structurally comparable LSD **2**. The results suggested that serotonin and the hallucinogen functioned via the same receptor. So began the development of selective 5-HT antagonists as radioligands for studying serotonergic receptors. It was found that a tritiated analog of spiperone **3**, a dopamine ligand, demonstrated affinity for non-dopaminergic sites at which tritiated 5-HT also displayed affinity. Subsequent assays concluded that [<sup>3</sup>H]spiperone and [<sup>3</sup>H]5-HT labeled two distinctive binding sites, later termed 5-HT<sub>1</sub> and 5-HT<sub>2</sub>. Shortly thereafter, 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>2</sub>, and 5-HT<sub>3</sub> receptors were identified.<sup>8</sup> Receptor classifications and molecular cloning experiments expanded the family to include more subtype populations, the 5-HT<sub>4</sub> receptor, and the higher end receptors 5-HT<sub>5</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> of the late 1980s and the 1990s.<sup>8</sup>



**3**

Spiperone

### 1.3 The 5-HT<sub>7</sub> Receptor

First cloned in 1993, the 5-HT<sub>7</sub> receptor family has been positively identified in a number of species including guinea pig, mouse, rat, pig, and human.<sup>12</sup> Most recently, the receptor has been cloned from members of the arthropoda and the nematoda phyla.

As a member of the GPCR family, the 5-HT<sub>7</sub> receptor is positively coupled to adenylate cyclase and activates extracellular signal-regulated kinase (ERK). It has recently been estab-



lished that the 5-HT<sub>7</sub> receptor is also coupled to a G<sub>12</sub>-protein through which it activates small GTPases.<sup>13,14</sup> Nonetheless, the 5-HT<sub>7</sub> receptors demonstrate a low overall amino acid homology (~40%) with the other G-protein coupled serotonergic receptors.<sup>9</sup>

Alternative splicing of the receptor mRNA has resulted in four isoforms in rat and human tissues, i.e., 5-HT<sub>7(a), (b), (c)</sub> in rats and 5-HT<sub>7(a), (b), (d)</sub> in humans.<sup>13</sup> The isoforms, differing only in length and amino acid composition at the carboxyl terminal, exhibit a high degree of interspecies amino acid homology (~95%).<sup>9,13</sup> These isoforms also demonstrate comparable pharmacological attributes, signal transduction pathways, and tissue distributions.<sup>13</sup> For the human variants, the gene encoding 5-HT<sub>7</sub> is located on chromosome 10q23.3-q24.4 with the most abundant isoform 5-HT<sub>7(a)</sub> consisting of 445 amino acids.

In situ hybridization and ligand binding approaches indicate the localization of 5-HT<sub>7</sub> throughout the peripheral and central nervous systems.<sup>15</sup> In the periphery, 5-HT<sub>7</sub> is found in the gastrointestinal tract, in skull blood vessels, and in vascular smooth muscle, as well as in the spleen, kidney, and within certain optic tissues.<sup>13</sup> Messenger RNA distribution confirms that cerebral 5-HT<sub>7</sub> is abundant in the hippocampus, thalamus, hypothalamus, and cerebral cortex.<sup>16</sup> In the hypothalamus, the receptor is isolated in the suprachiasmatic area, a region associated with circadian rhythm regulation.<sup>17</sup> This widespread distribution suggests the participation of 5-HT<sub>7</sub> in an array of physiological processes.

#### 1.4 Ligands to the 5-HT<sub>7</sub> Receptor

The 5-HT<sub>7</sub> receptor is characterized by high affinity for 5-HT (**1**), 5-carboxytryptamine (5-CT), 5-methoxytryptamine (5-MeOT), and methiothepin as well as a moderate affinity for 8-OH-DPAT (Figure 1).<sup>15</sup>

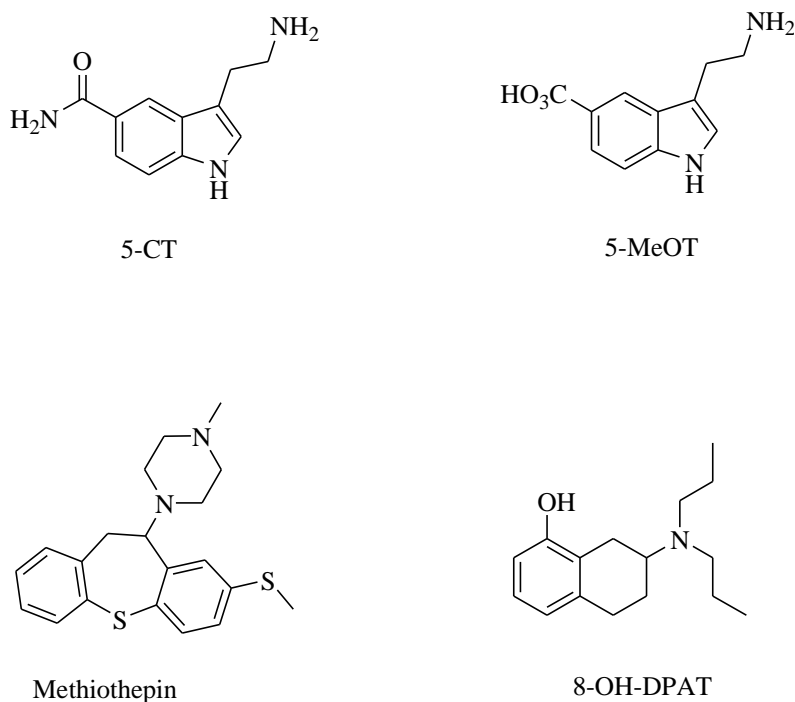


Figure 1. 5-CT, 5-MeOT, methiothepin, and 8-OH-DPAT bind to the 5-HT<sub>7</sub> receptor

In the years following the positive characterization of the 5-HT<sub>7</sub> receptors, binding assays afforded a number of non-selective ligands demonstrating high receptor affinity. These agents typically behave as antagonists blocking the activity of the endogenous ligand 5-HT as well as other agonists. Agonist binding at the 5-HT<sub>7</sub> receptor increases intracellular levels of cAMP.<sup>18</sup> Pittalá *et al.* describe several of these non-selective ligands and their classes: ergolines (including 2-Br-LSD and mesulergine), piperidine derivatives (including ritanserin, risperidone, and spiperone **2**), and aporphine derivatives (including R(3)-aporphine) as shown in Figure 2.<sup>15</sup>

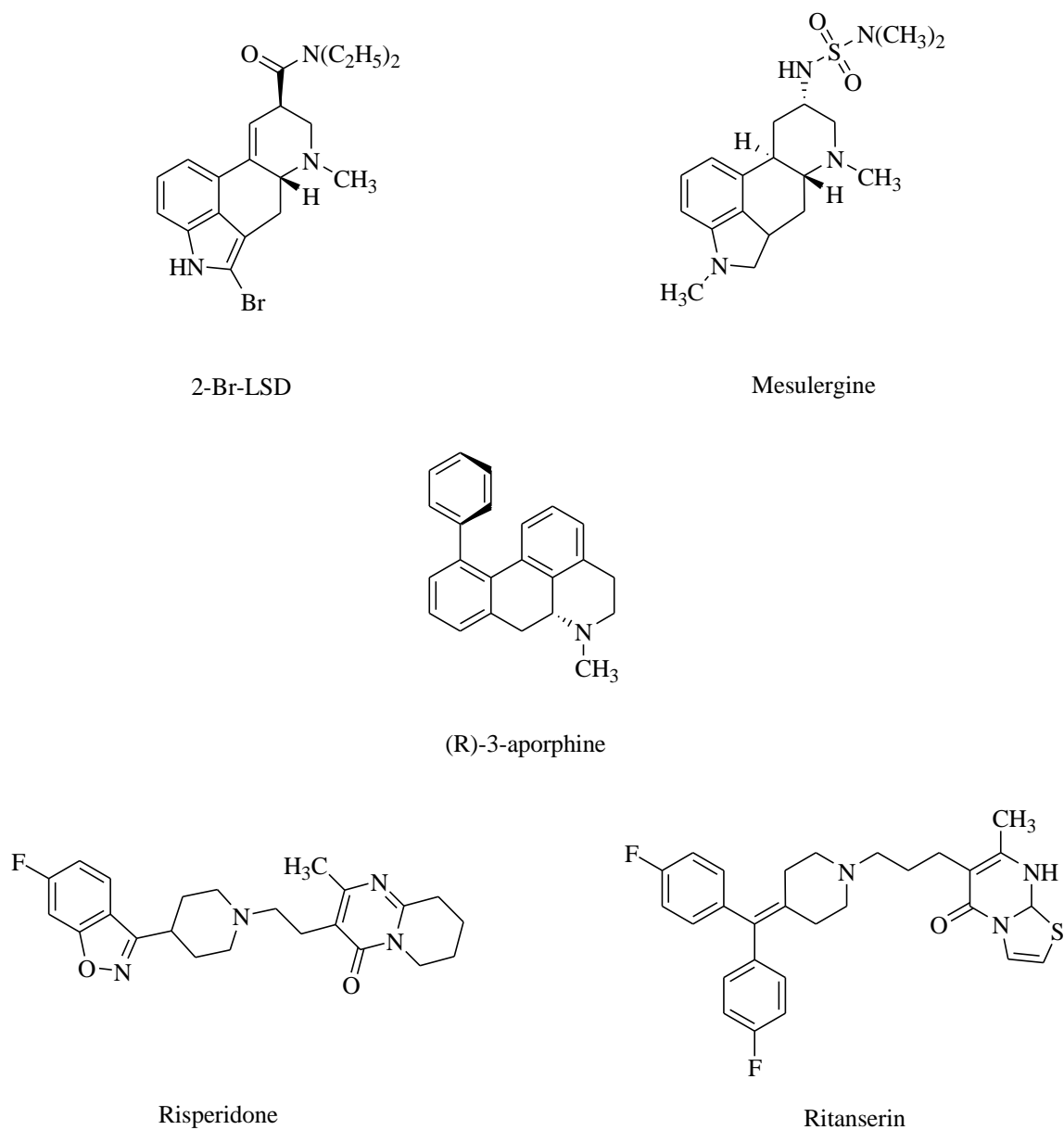


Figure 2. Several non-selective 5-HT<sub>7</sub> ligands<sup>15</sup>

A number of psychoactive drugs have also demonstrated non-selective affinity to the 5-HT<sub>7</sub> receptor.<sup>13</sup> These agents include the antipsychotic cyclic analogues clozapine, mianserin, and maprotiline, as well as a number of phenothiazines (including chlorpromazine) and thioxanthenes (including chlorprothixene), Figure 3.<sup>13,15</sup>

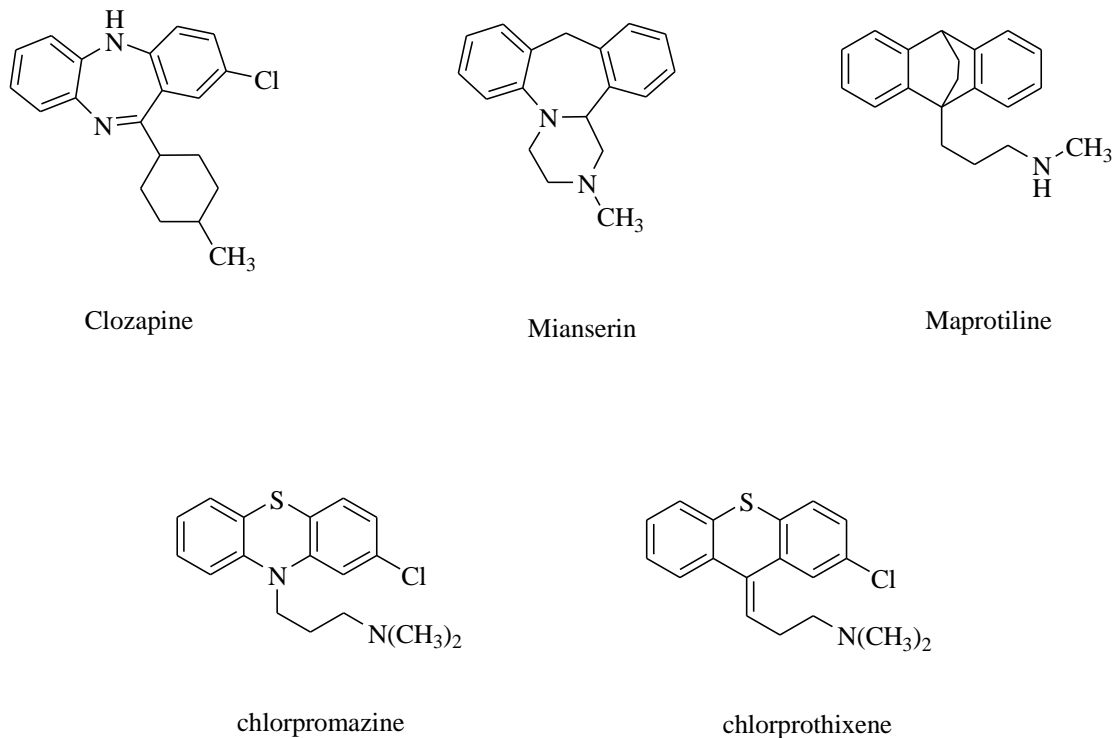


Figure 3. Psychoactive agents demonstrating non-selective 5-HT<sub>7</sub> receptor affinity<sup>13,15</sup>

The widespread distribution of 5-HT<sub>7</sub> and the diverse array of agents exhibiting receptor affinity suggest a wealth of physiological functions for the receptor. Efforts to elucidate the physiology of the 5-HT<sub>7</sub> receptor rely upon the development of selective antagonists and agonists. Within the last two decades, a number of selective ligands to the 5-HT<sub>7</sub> receptor have been developed and are representative of a diverse group of chemical compound classes.

In the early 1990s, a highthroughput screening (HTS) of the SmithKline Beecham compound bank against the human cloned 5-HT<sub>7</sub> receptor provided **3** as a four-component diastereomeric mixture (Figure 4). Subsequent structural modifications and a series of structure-activity-relationship (SAR) studies on the compound resulted in the reporting of the first selec-

tive 5-HT<sub>7</sub> antagonists. Members of the arylsulfonamide class, SB-258719 (**4**, pK<sub>i</sub> = 7.5) and its pyrrolidine derivatives SB-269970 (**5**, pK<sub>i</sub> = 8.9) and SB-258741 (pK<sub>i</sub> = 8.5) demonstrated modest 5-HT<sub>7</sub> affinity as well as at least 100-fold selectivity over other serotonergic receptors. Subsequent analogues include SB-656104 (**6**, pK<sub>i</sub> = 8.7) and SB-691673 (**7**, pK<sub>i</sub> = 8.65).<sup>15,19</sup> Originally deemed antagonists, recent biological assays have reported some level of inverse agonist activity for the three early arylsulfonamide ligands. Inverse agonists bind to the receptor and decrease cAMP activation; SB-258719, is closest to a neutral antagonist, SB-258741 is a partial inverse agonist, and SB-269970 is a full inverse agonist at recombinant 5-HT<sub>7</sub>.<sup>20</sup>

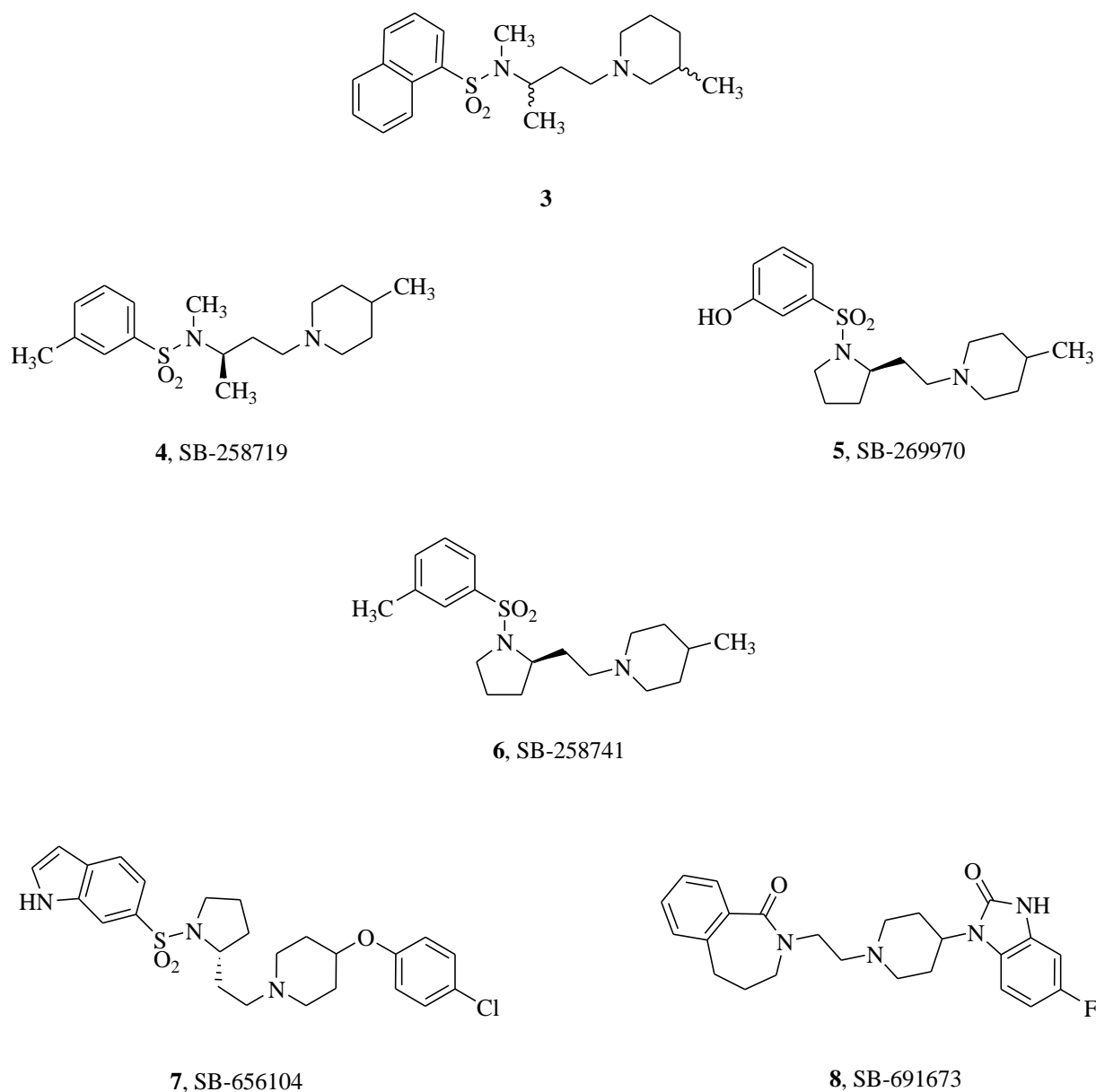


Figure 4. Selective 5-HT<sub>7</sub> receptor ligands of the arylsulfonamide class<sup>15,19</sup>

Another major class of 5-HT<sub>7</sub> ligands consists of the tetrahydrobenzindoles first reported in 1999.<sup>21</sup> Kikuchi and coworkers under Meiji Seika Kaisha, Ltd., identified DR-4004 (**8**, pK<sub>i</sub> = 8.67) as a potent 5-HT<sub>7</sub> antagonist (Figure 5).<sup>21</sup> The (2-methoxyphenyl)piperazinyl derivatives

published in a later paper provided **9** ( $\text{pK}_i = 8.29$ ), an antagonist demonstrating affinity at the 5-HT<sub>7</sub> receptor.<sup>13</sup> Subsequent SAR studies expanded the class to include a number of fused-ring analogues. These compounds, DR-4446 (**10**,  $\text{pK}_i = 8.01$ ), DR-4365 (**11**,  $\text{pK}_i = 8.45$ ), and DR-4485 (**12**,  $\text{pK}_i = 8.14$ ), demonstrate significant affinity for the 5-HT<sub>7</sub> receptor over other relevant serotonergic receptors like 5-HT<sub>2</sub>. The halogenated derivative DR-4485 exhibits superior oral bioavailability.<sup>15</sup>

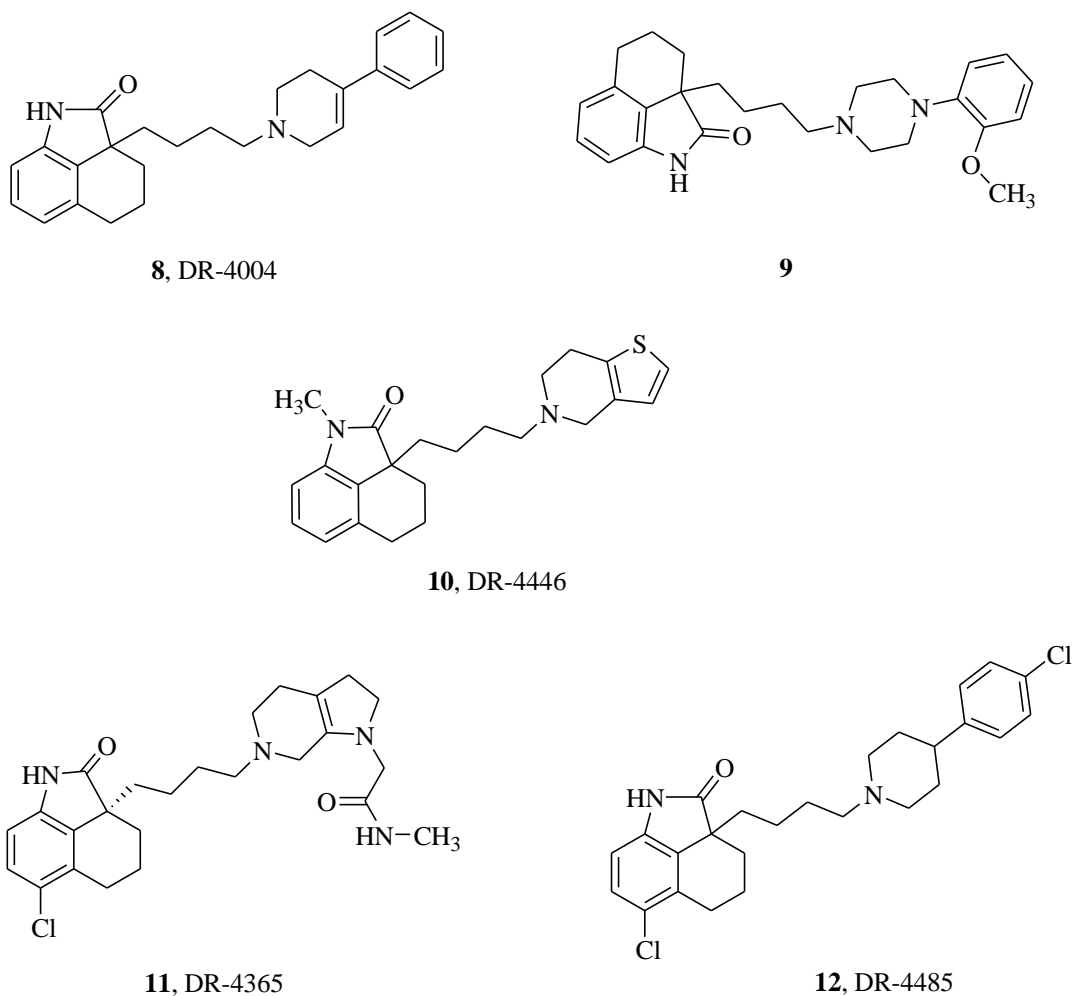
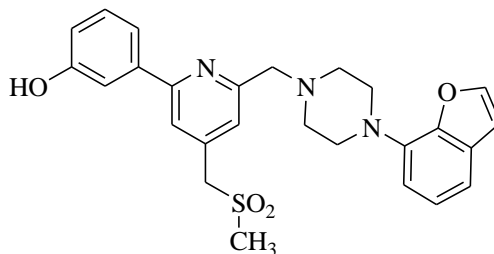
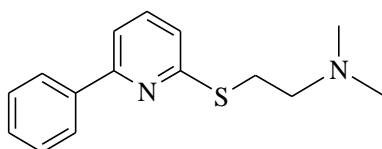


Figure 5. The tetrahydrobenzindoles class of serotonin receptors

Patents filed in 1999 and 2000 contributed to pyridines and piperazines as emergent classes of 5-HT<sub>7</sub> receptor ligands. With the identification of **13**, pK<sub>i</sub> = 9.2 Shinogi *et al.* were first to report a pyridine derivative demonstrating agonist activity at 5-HT<sub>7</sub> receptors.<sup>15</sup> Parikh and coworkers at Pfizer Inc. introduced a series of 4-(pyridin-2-yl)piperazine derivatives as 5-HT<sub>7</sub> agonists.<sup>22</sup>

**13**

Developed from a series of thiazoles and thiopyridines under Merck in 2004, compound **14** (pK<sub>i</sub> = 9.22) exhibits high affinity and selectivity over other 5-HT receptors.<sup>23</sup>

**14**

Also during 2004, Leopoldo *et al.* focused research efforts upon the influence of the 1-arylpiperazine moieties in 5-HT<sub>7</sub> ligands developed by Kikuchi and Parikh among others. These efforts afforded a series of high affinity 5-HT<sub>7</sub> receptor ligands based on *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-4-aryl-1-piperazinealkylamide structures.<sup>24</sup> Structural modifications, including variations in alkyl chain length and aromatic substitution linked to the N-1 piperazine ring, provided several high affinity compounds. From these 1-(2-methoxyphenyl)piperazine derivatives, namely **14** (pK<sub>i</sub> = 7.94), compounds **15** (pK<sub>i</sub> = 8.38) and **16** (pK<sub>i</sub> = 9.66) were devel-



oped and are presented in Figure 6. The hydroxy-substituted **14** (**LP-44**) is a potent 5-HT<sub>7</sub> receptor putative agonist with selectivity over 5-HT<sub>1a</sub> and 5-HT<sub>2a</sub> receptors; **16** is a selective antagonist.<sup>24</sup>

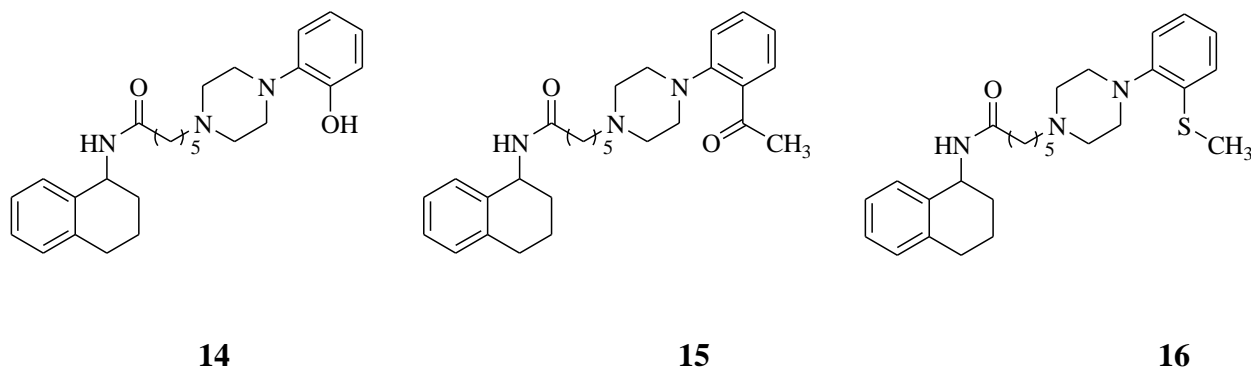
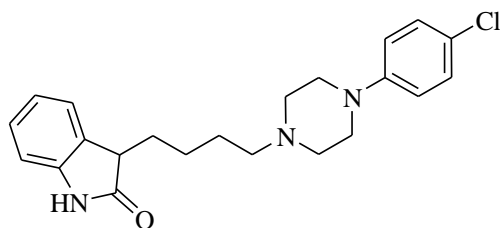
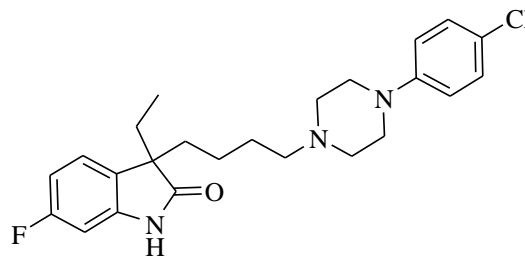
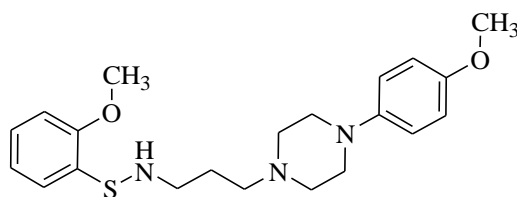


Figure 6. 1-(2-methoxyphenyl)piperazine derivatives demonstrating agonist to antagonist activities at the 5-HT<sub>7</sub> receptor.<sup>24</sup>

Related to tetrahydrobenzindole family of 5-HT<sub>7</sub> receptors are the structurally similar oxindole derivatives reported in 2008.<sup>25</sup> The compounds feature an oxindole scaffold and long-chain arylpiperazine. The oxindole structure is less rigid than the tetrahydrobenzindole skeleton resulting in decreased lipophilicity; this decrease is hoped to increase bioavailability for potential pharmacological use. Several of these compounds demonstrated high affinity and proved to be highly potent antagonists. Representatives of the series are **17** (pK<sub>i</sub> = 8.15) and **18** (pK<sub>i</sub> = 9.10).<sup>25</sup>

**17****18**

Yoon and coworkers report a series of 1-arylpiperazines developed as sulfonamide analogs. Piperazine derivatives based on the structure of SB-269970 were designed and evaluated against the human recombinant 5-HT<sub>7</sub> serotonin receptor in 2008. Of the series, 4-methoxy-*N*-[3[(4-substituted phenyl)piperazino]propyl]benzene sulfonamide **19** (IC<sub>50</sub> = 37) demonstrates good activity and good selectivity over 5-HT<sub>1a</sub>, 5-HT<sub>2a</sub>, 5-HT<sub>2c</sub>, and 5-HT<sub>6</sub> receptors.<sup>26</sup>

**19**

The development of diaminotriazine, diaminopyridine, and diaminopyrimidine 5-HT<sub>7</sub> ligands prompted an investigation into the effect of nitrogen atom position and frequency on affinity. In 2004, researchers at Bristol-Myers Squibb Pharmaceuticals reported a series of amino-triazines and aminopyridines exhibiting selective antagonist activity at the 5-HT<sub>7</sub> receptor.<sup>27</sup> The studies on the amino-azines led these researchers to examine receptor affinity with heteroaryl compounds of various nitrogen atom frequencies and positions. Variation in the position of the

nitrogen in the ring significantly altered 5-HT<sub>7</sub> binding affinity. A series of diaminopyridines, diaminopyrimidines, and diaminotriazines demonstrating selective 5-HT<sub>7</sub> receptor affinity were afforded. Representative compounds are **21** (pK<sub>i</sub> = 8.4) and **22** (pK<sub>i</sub> = 8.7) as shown in Figure 7.<sup>28</sup>

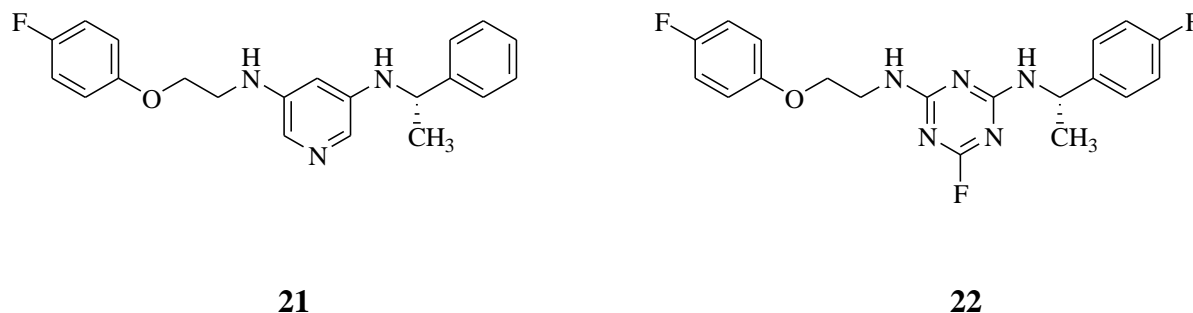


Figure 7. Diaminopyridine and diaminotriazine compounds demonstrating selective activity to the 5-HT<sub>7</sub> receptor.<sup>28</sup>

While piperazines and sulfonamides make up a large class of selective ligands to the 5-HT<sub>7</sub> receptor, receptor ligands come from an array of chemical families. As research into novel selective ligands has continued, diversity among the chemical classes exhibiting selective affinity has likewise expanded. Many compounds of the aporphine family function as selective ligands to several of the serotonergic receptors. A 5-HT<sub>7</sub> selective aporphine derivative was developed from modifications performed on R-(3)-aporphine (Figure 3). These modifications focused on altering the substitution pattern in C11 of the phenyl ring; several different ortho substituents were introduced. These derivatizations provided the highly selective and potent atropisomeric biaryl aporphine derivatives **23** (pK<sub>i</sub> = 8.42) and **24** (pK<sub>i</sub> = 7.42) shown in Figure 8.<sup>29</sup> The aporphines functioned as antagonists and inhibited 5-HT stimulation of cAMP.<sup>29</sup>

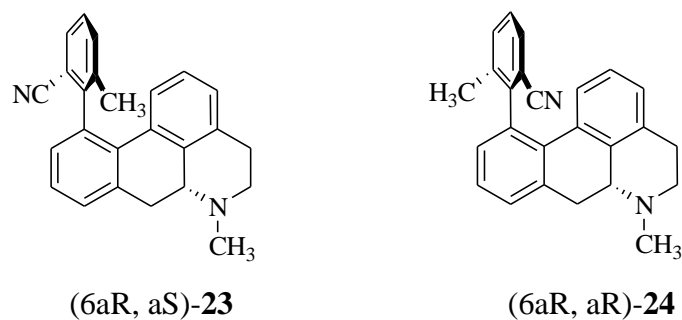


Figure 8. Aporphine derivatives demonstrating affinity to the 5-HT<sub>7</sub> receptor.<sup>29</sup>

Holmberg and coworkers reported the selectivity of a series of 8-substituted-3-aminochromans (3,4-dihydro-2*H*-1-benzopyrans) and 2-aminotetralins in 2004 and 2005. Binding to 5-HT<sub>7</sub> of these structures was found to be stereospecific; (S)-tetralin and (R)-chromans are the favored enantiomers.<sup>30</sup> The reported ligands exhibit activity at the 5-HT<sub>7</sub> receptor ranging from antagonist to full agonist. A few of the compounds demonstrate high selectivity over other receptors. Derived from the series is a putative selective receptor agonist, **25**, AS-19, Figure 9.<sup>31</sup>

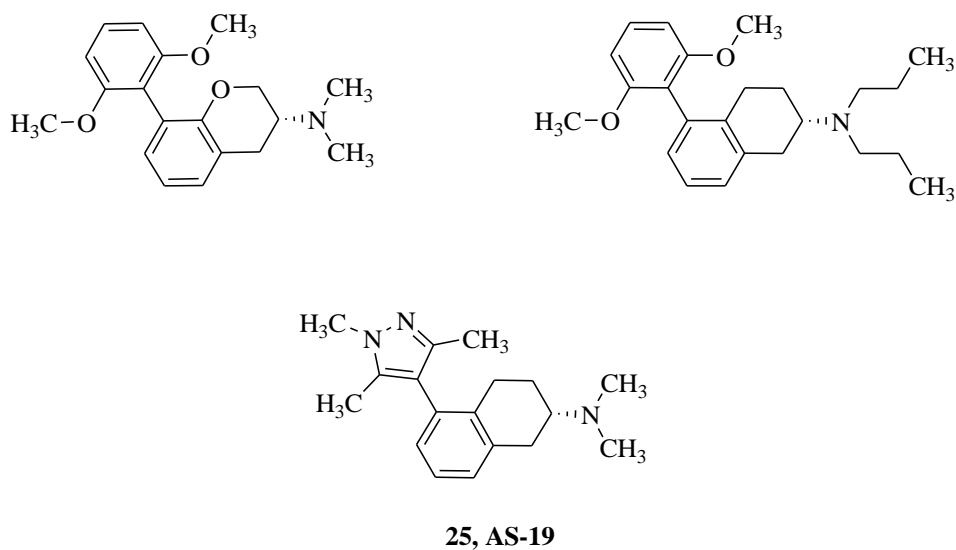


Figure 9. Aminochroman and aminotetralin derivatives.<sup>30, 15</sup>

Several reports and filed patents have also featured the synthesis of quinolines, pyrrolidnes, and aminoalkyl sulfones as selective, high affinity 5-HT<sub>7</sub> receptor ligands. More recent papers and patents have included benzimidazolone as well as other quinoline and piperazine derivatives.<sup>32,33</sup> A selection of these compounds is presented in Figure 10 with their respective pK<sub>i</sub> values.

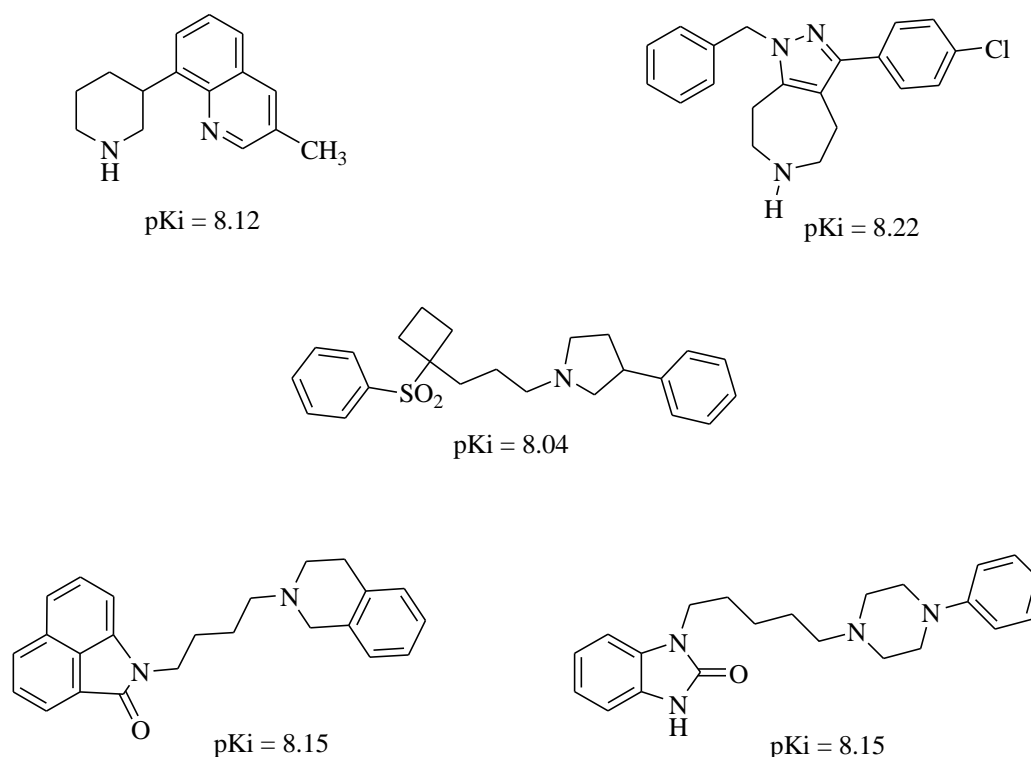


Figure 10. Several compounds displaying 5-HT<sub>7</sub> receptor selectivity and affinity.

### 1.5 The 5-HT<sub>7</sub> Receptor and Physiological Processes

The affinity of 5-HT<sub>7</sub> for several psychoactive agents coupled to its cerebral localization has generated substantial research into the role of the receptor in neurological disorders such as depression and anxiety. Indeed, during the past decade the receptor has been associated with a number of physiological processes within the central nervous system as well as in the periphery. Pharmacological agents and/or knockout mice (in which functional 5-HT<sub>7</sub> receptors are absent) are used in animal behavioral models devised to simulate human disorders.<sup>5</sup> Deviant behaviors are indicative of a neurological disorder. Multiple behavioral assays have indicated an anti-

anxiety effect for SB-269970, the selective ligand originally classified as a 5-HT<sub>7</sub> selective antagonist.<sup>3,5,15</sup>

Early on, these behavioral models also revealed the significance of 5-HT<sub>7</sub> in the suprachiasmatic nucleus (SCN), a brain region associated with the circadian biological clock, sleep, and mood. Pharmacological profiling, again with SB-269970, confirmed that the 5-HT<sub>7</sub> receptor mediates 8-OH-DPAT-induced phase resetting within the SCN. Phase-setting tempers the sleep pattern according to periods of day and night. The antidepressant-like activity, altered sleep patterns, and light/dark immobility observed in these studies highlight the effect of 5-HT<sub>7</sub> on the SCN.<sup>15</sup>

In behavioral models used in the assessment of antidepressants, 5-HT<sub>7</sub> receptor blockage or receptor gene inactivation produces antidepressant behavior. Concurrent administration of SB-269970 with antidepressants has elicited antidepressant activity in several behavioral tests.<sup>3,5</sup> Fittingly, it has been suggested that the affinity of various antidepressants (presented in Figure 4) for the 5-HT<sub>7</sub> receptor is the driving force behind their physiological function.<sup>5</sup> The high affinities of clozapine and risperidone (Figure 4) for the receptor established the link between 5-HT<sub>7</sub> and schizophrenia shortly after the introduction of the 5-HT<sub>7</sub> receptor class. More recently, the atypical antipsychotics and established antidepressants, amisulpride and aripiprazole have demonstrated high affinity for the 5-HT<sub>7</sub> receptor.<sup>15,34</sup>

Several other physiological operations are associated, to an extent, with the 5-HT<sub>7</sub> receptor. Obsessive compulsive disorder (OCD), epilepsy, migraine, thermoregulation, and certain cognitive functions have also been linked to the receptor.<sup>24</sup> For OCD, typified by obsessive thoughts and repetitive or specific behavior, treatment is often a selective serotonin reuptake inhibitors (SSRI) antidepressant. Interestingly, behavioral model testing has shown that 5-

HT<sub>7</sub>receptor antagonism using SB-269970, or through receptor gene inactivation, decreases the occurrence of compulsive behavior.<sup>5</sup> The elevated abundance of 5-HT<sub>7</sub> in the thalamus has been suggestive of a role of the 5-HT<sub>7</sub> receptor in epilepsy, a neurological disorder that induces sudden seizures. It was found that the selective 5-HT<sub>7</sub> antagonist SB-269970 reduced unprompted epileptic activity in rats.<sup>23, 25</sup> Cranial vasodilation, associated with migraines, is regulated by serotonin which in turn is regulated by 5-HT<sub>7</sub> among the other 5-HT receptors. Nonetheless, as was observed with antidepressants, several anti-migraine drugs exhibit moderate to high affinity at the 5-HT<sub>7</sub> receptor.<sup>34</sup> Gargaglioni and coworkers established the relationship between 5-HT<sub>7</sub> and thermoregulation using SB-269970. The 5-HT<sub>7</sub> receptor was shown to regulate hypothermia occurring from reduced oxygen content.<sup>15</sup> Cifariello et al. at the University of L'Aquila in Italy report the influence of 5-HT<sub>7</sub> receptor in learning and memory. Administration of SB-269970 to lab mice improved memory in multiple behavioral tests.<sup>3</sup>

Motor activity of the gastrointestinal tract and bladder function have also both been associated with the receptor. Stimulation of neuronal 5-HT<sub>7</sub> receptors produced muscle relaxation in pig small intestine. Subsequent research has sought to elucidate the influence of 5-HT<sub>7</sub> in gastrointestinal disorders such as irritable bowel syndrome. The 5-HT<sub>7</sub> receptor has recently been linked to an excitatory physiological role in the control of bladder function. Selective ligand SB-269970 increased bladder pressure and volume, ultimately eliminating the impulse to urinate.<sup>15</sup>

## 1.6 The Pharmacophore Model

The multitude of chemical families that contribute to the library of selective 5-HT<sub>7</sub> receptor ligands thwarts immediate recognition of the structural aspects that promote ligand-receptor interaction. Identification of these structural features is essential to uncovering the tertiary structure of the receptor. Furthermore, at present there is no X-ray crystallography structure



available for the 5-HT<sub>7</sub> receptor. A computer generated 3-dimensional pharmacophore model highlighting these structural aspects can be used to predict affinity among structurally similar compounds; to facilitate the design and synthesis of novel ligands; and to fully assess the physiological functions of the receptor. Ultimately these efforts will advance the clinical applications associated with the 5-HT<sub>7</sub> receptor.

Lopez-Rodriguez established the first pharmacophoric hypothesis for 5-HT<sub>7</sub> receptor antagonism in 2000.<sup>35</sup> These early efforts provided a minimal list of the structural requirements for 5-HT<sub>7</sub> receptor nonselective antagonism: an aromatic ring, a basic nitrogen atom (positive charged center, PI), a H-bonding acceptor group (HBA), and a hydrophobic region (HYD) at 4.9 – 5.9 Å apart from the basic nitrogen center.

Later in 2004, the same group reported an optimization and validation of their former model to incorporate the several new selective 5-HT<sub>7</sub> receptor antagonists that had since been developed. Using a series naphtholactam and naphthosultam derivatives, the researchers formulated an updated model and revised the essential structural requirements.<sup>15,36</sup> According to the revised model, a basic nitrogen atom (positive charged center, PI), a H-bonding acceptor group (HBA), and three hydrophobic regions (HYD) at the distances presented in Figure 11 below are necessary.<sup>36</sup>

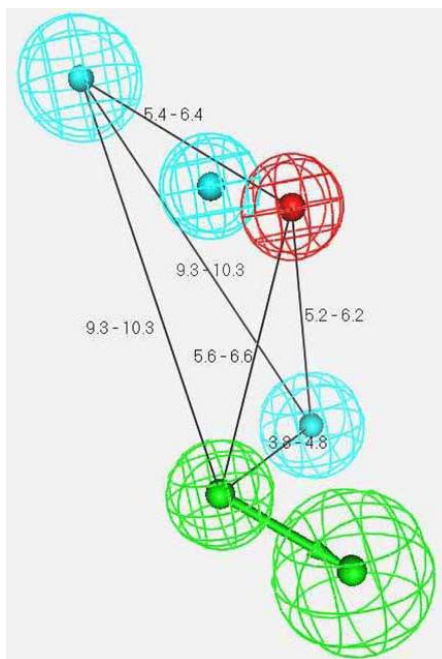
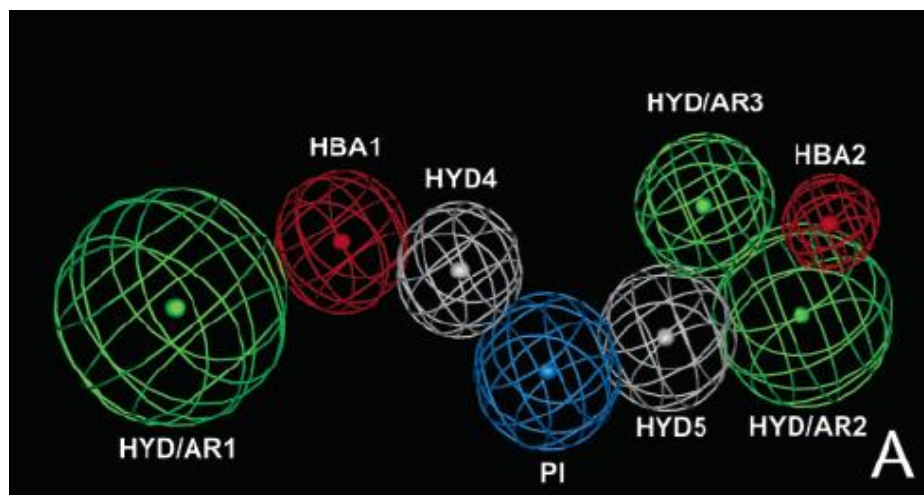


Figure 11. A revised molecular model of 5-HT<sub>7</sub> antagonism (blue, HYD; red, PI ; green, HBA)<sup>36</sup>

A conformational analysis of the selected ligands bound at the transmembrane domain of the 5-HT<sub>7</sub> receptor was performed. This afforded a pharmacophoric model in which the most favorable (high affinity) naphtholactam or naphthosultam compounds featured a spacer of an optimal chain length.<sup>36</sup> The 3D model revealed how the ligands bind to the amino acid residues of the transmembrane binding site of the 5-HT<sub>7</sub>. According to the model, the HBA feature of the ligand interacts with the hydroxyl groups of serine and threonine; the HYD1 feature binds phenylalanine via aromatic interaction, the PI moiety forms an ionic bond or salt bridge with an aspartic acid residue; and the HYD3 region interacts with aromatic residues phenylalanine and tyrosine of the binding site via  $\pi$ - $\pi$  interaction.<sup>36</sup>

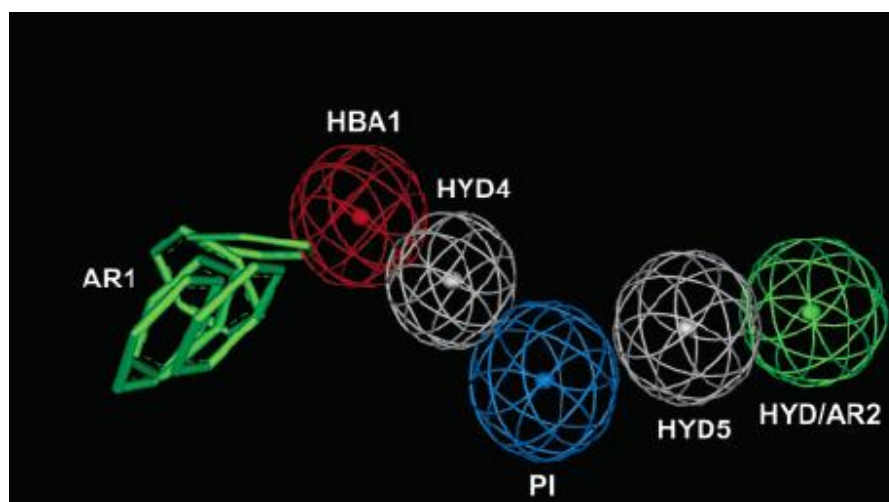
Kolaczkowski and Bojarski et al. also report two novel 5-HT<sub>7</sub> antagonism pharmacophores based on direct ligand-receptor interaction of thirty-one receptor antagonists.<sup>40</sup> The two

proposed models describe the structural features required for affinity and those required for selectivity. The affinity model, formulated using nonselective ligands, outlines six structural features of the ligand structure that promote general ligand-receptor interaction: a PI, three hydrophobic/aromatic regions (HYD/AR1-3), and two hydrogen bond acceptors (HBA1 and HBA2). Affinity to 5-HT<sub>7</sub> receptor requires at least three of these components aligned in a specific spatial arrangement. According to the selectivity pharmacophore, only three features are essential for selective affinity. A PI and AR1 at 6.9 -7.7 Å apart are required. They propose that the AR1 must be specifically aligned to promote an aromatic  $\pi$ - $\pi$  stacking with phenylalanine or an ion- $\pi$  interaction with arginine in the binding site. Figure 12 presents a summary of the essential structural features for affinity and selectivity and the respective distances between each moiety.<sup>15,40</sup>



	PI	HYD/AR1	HYD/AR2	HYD/AR3
<b>HYD/AR1</b>	6.9 – 9.4			
<b>HYD/AR2</b>	4.3 – 7.8	11.1 – 14.4		
<b>HYD/AR3</b>	3.7 – 6.1	8.75	4.1 – 4.8	
<b>HBA1</b>	3.7 – 5.1	3.7 – 3.8	8.3 – 10.1	6.9
<b>HBA2</b>	5.1 – 6.9	14.2	2.8 – 3.7	2.8 – 3.7

(a)



	PI	HYD/AR1	HYD/AR2
<b>HYD/AR1</b>	6.9 – 7.7		
<b>HYD/AR2</b>	4.3 – 7.0	11.1 – 13.2	
<b>HBA1</b>	3.7 – 5.1	3.7 – 3.8	8.3 -10.1

(b)

Figure 12. Pharmacophore model for affinity (a) and for selectivity (b) with the respective distances (Å) as proposed by Kolaczowski et al.<sup>40</sup>

Our research group has also developed a 3-D pharmacophore model for 5-HT<sub>7</sub> receptor antagonism. The generation of a 3-D computational model of the TM domain complexed with ligands of interest was achieved with SYBYL v8.1. A series of substituted pyrimidine compounds were prepared and assessed for inhibition of a radioligand at the 5-HT<sub>2a</sub> and the 5-HT<sub>7</sub> receptors. According to the 3-D QSAR studies, the essential structural features are : a PI, a HBA, and two HYD regions. Figure 13 depicts the hypothesized model and a representative compound, synthesized in our lab, which bears the essential structural aspects.

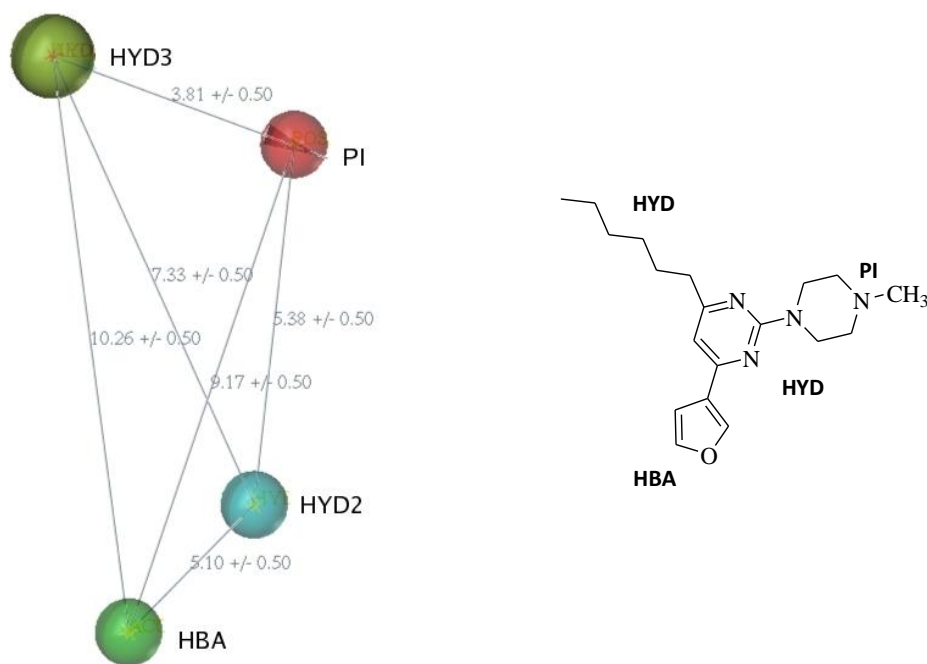
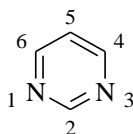


Figure 13. Our pharmacophore model and a representative compound labeled accordingly

## 1.7 Overview of Pyrimidines and Pyridines

Pyrimidines and pyridines have contributed to the diverse library of compounds demonstrating selective affinity to the 5-HT<sub>7</sub> receptor. Novel diaminopyrimidines, diaminopyridines, and thiopyridines have been described. Ligands synthesized in this thesis feature pyrimidine and pyridine moieties combined with piperazines, a prominent group among the compounds brandishing selective affinity to the 5-HT<sub>7</sub> receptor. Specifically, these substituted pyrimidines and pyridines will contribute to the class of arylpiperazines, a major category of selective 5-HT<sub>7</sub> receptor ligands. Preparation of novel, structurally diverse pyrimidine and pyridine analogs requires a consideration of the structural features that govern their chemical reactivity.



**Pyrimidine**

Pyrimidine is a prominent member of the diazine family of heterocyclics. It is found throughout nature as a component of nucleic acids, nucleotides and corresponding nucleosides. Purines, comprised of fused pyrimidine and imidazole rings, are essential components of DNA and RNA. The aromatic heterocycle is also widespread among pharmaceutical agents. Oxygenated pyrimidines, or, barbituric acid derivatives, are commonly employed as therapeutic sedatives and antidepressants; several sulfa drugs including antibacterials, antihypertensives, and antifolates feature a pyrimidine moiety.<sup>44</sup> First isolated in 1899, the heterocycle has been extensively studied affording a wealth of information regarding its physical and chemical attributes.<sup>45</sup>

In pyrimidine, each of the four  $sp^2$  hybridized carbon atoms features a p orbital perpendicular to the plane of the ring and each p orbital contains one pi electron. The nitrogen atoms are likewise  $sp^2$  hybridized each containing one  $\pi$  electron in their p orbitals for a total of six  $\pi$  electrons. The lone pair electrons do not contribute to the aromatic  $\pi$  electron sextet.<sup>45</sup>

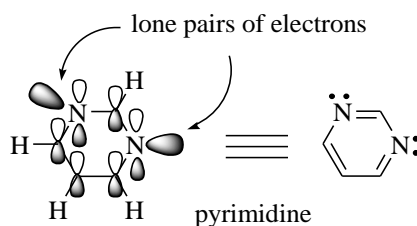


Figure 14. Orbital image of pyrimidine featuring lone pair electrons.<sup>45</sup>

These unshared electrons at the two nitrogen atoms contribute to the low basicity of pyrimidine ( $pK_a = 1.3$ ) compared to pyridine ( $pK_a = 5.2$ ), bearing a single imine nitrogen atom. The electronegative nitrogen atoms induce polarization in the sigma bond framework. The resultant increase in electron deficiency at the 2, 4, and 6 positions makes these carbon atoms more susceptible to nucleophilic attack. This nucleophilic attack is especially feasible when a displaceable halide is a substituent.<sup>46</sup> For halo-diazines in which the halide is alpha or gamma to a nitrogen, nucleophilic displacements become even more facile. The 2- and 4- halo-pyrimidines are particularly reactive because the anionic intermediates receive direct mesomeric stabilization from both imine nitrogen atoms, figure 15.<sup>45</sup>

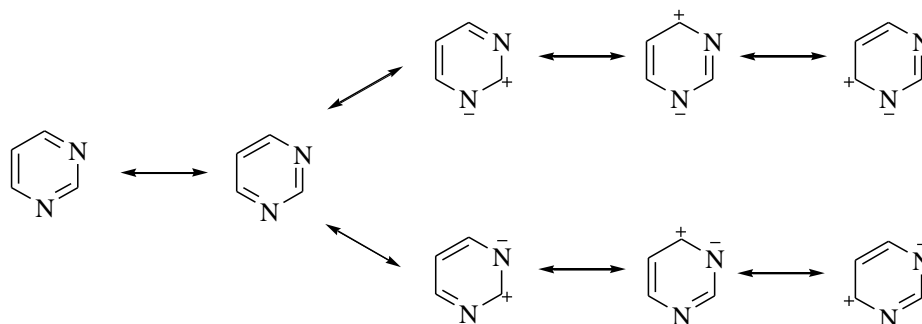
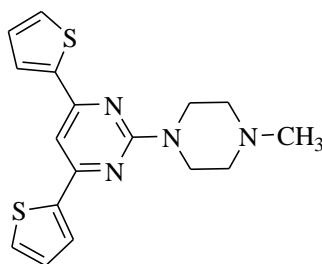


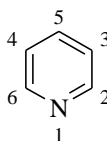
Figure 15. Mesomeric structures of pyrimidine. The positions 2,4, and 6 bear the positive charge.<sup>45</sup>

These structural aspects are the foundation of the chemistry that drive the development of pyrimidine compounds of biological interest. Pyrimidine compounds have been explored for use as histamine and adenosine receptor antagonists as well as among several other biological receptors and modulators.<sup>47,48</sup> As previously described, several diaminopyrimidines have been synthesized for selective affinity at the 5-HT<sub>7</sub> receptor. Foregoing research efforts of our group have provided a series of substituted pyrimidines exhibiting affinity to the 5-HT<sub>2a</sub> receptor. Functionalization of the pyrimidine ring was achieved using organolithium reagents to supply aryl substituents at the positions 2 and 4 as well as a methylpiperazine moiety at position 6. Heteroaryl substituents at positions 2 and 4 afforded the most efficacious ligands within the series. A potent representative of these compounds is **28** (pK<sub>i</sub> 5-HT<sub>2a</sub> = 8.1).<sup>49</sup>





This work has been translated into the present investigations focusing upon the development of substituted pyrimidine ligands for the 5-HT<sub>7</sub> receptor. The synthesis of the compounds we present incorporates a vinyl moiety that enables further derivatization and subsequent addition of methylpiperazine at the 2-position.



### Pyridine

Pyridine is a ubiquitous chemical compound. The aromatic, monocyclic azine is utilized as a reagent or as a polar aprotic solvent. It is salient in a number of biological systems and industrial applications. Naturally occurring pyridines include the nicotinamides, a component of the vitamin B group.<sup>46,47</sup> Pyridines are precursors to various pharmaceuticals, adhesives, agricultural chemicals, and synthetic pigments.<sup>46</sup>

The aromatic nitrogen heterocycle is closely related to benzene as it differs only by the replacement of one –CH unit with N. The five carbon atoms are sp<sup>2</sup> hybridized as is the nitrogen atom forming a delocalized  $\pi$  system extending as a closed loop above and below the plane of the ring. The carbon-nitrogen bonds are slightly shorter than C-C bonds owing to the increased electronegativity of the nitrogen atom. Consequently, the aromatic system is slightly distorted as electron density is concentrated at the N atom. The nitrogen lone pair is not involved in the aromatic  $\pi$  electron system and instead contributes to the basicity of pyridine (pK<sub>a</sub> = 5.2).

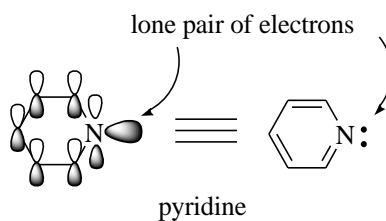


Figure 16. Orbital diagram of pyridine

Polarized mesomeric contributors in which nitrogen is negatively charged illustrate the electron deficiency at positions 2, 4, and 6 of the ring, Figure 17. These positions are the crux of the chemistry of pyridines.<sup>45</sup>

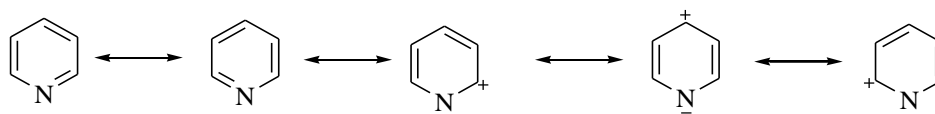


Figure 17. Resonance contributors to pyridine structures.<sup>45</sup>

As with the pyrimidines, these structural and electronic characteristics govern the chemical reactivity of pyridine. Several patents have described the synthesis of pyridines as selective 5-HT<sub>7</sub> receptor agonists and antagonists.<sup>50,51</sup> A recent report features the preparation of a series of 4,6-disubstituted 2-(4-methyl-1-piperazinyl) pyridines demonstrating selective affinity for the 5-HT<sub>7</sub> receptor over the 5-HT<sub>1a</sub> and 5-HT<sub>2a</sub> receptors. Several of these analogs feature a heteroaryl substituents. The synthetic pathway features ring formation via [3 + 3] annulation, a benzotriazole-assisted Katritzky methodology.<sup>52,53</sup> Our research also focuses upon the addition of a methyl piperazine substituent and heteroaryl groups to the pyridine ring. However, we outline

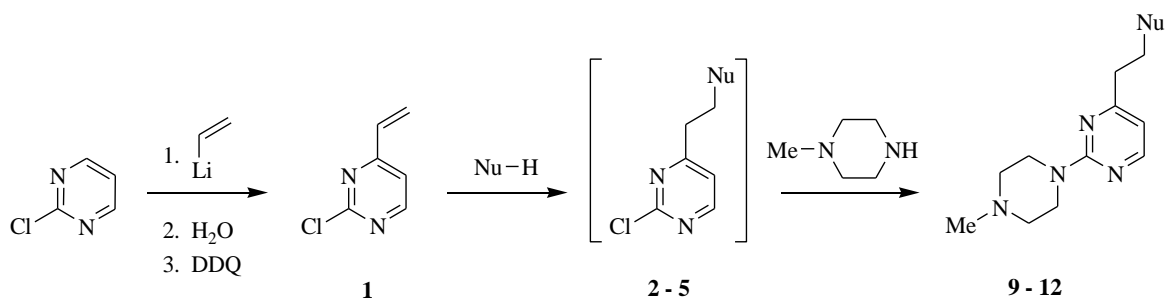
methods incorporating direct C – C and C – N atom coupling on the pyridine ring via Suzuki coupling and Buchwald-Hartwig amination.

## 2 RESULTS AND DISCUSSION

### 2.1 Synthesis of Substituted Pyrimidines

As described, a number of ligands to the 5-HT<sub>7</sub> receptor featuring a pyrimidinyl moiety have been reported. It is with this in mind that several functionalized pyrimidines have been derived from the starting compound 2-chloropyrimidine.

#### 2.1.1 From 2-Chloropyrimidine



#	Nu - H
2, 9	H <sub>2</sub> N-Et
3, 10	H <sub>2</sub> N-Bu <sup>t</sup>
4, 11	H <sub>2</sub> N-Bu <sup>n</sup>
5, 12	

Scheme 1.

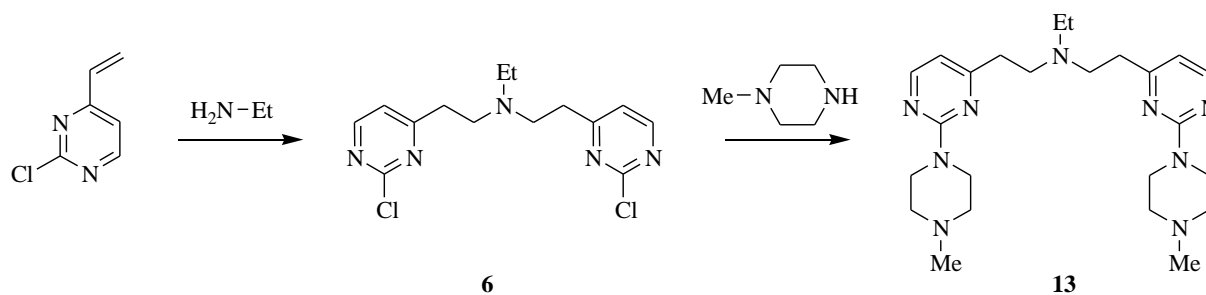
The reaction of a vinylolithium reagent with 2-chloropyrimidine at the C4=N3 bond is an efficient method for the addition of a vinyl moiety at position 4.<sup>54</sup> In situ generated vinylolithium from the reaction of tetravinyltin with the tert-butyllithium reagent as reported by Streckowski et al. Rearomatization of the resultant dihydro intermediate using the powerful oxidizing agent 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is also reported and afforded **1**, 2-chloro-4-vinylpyrimidine in Scheme 1.<sup>55</sup>

#### 2.1.2 Nucleophilic Conjugate Addition

The treatment of 2-chloro-4-vinylpyrimidine **1** with various nucleophiles in equimolar amount provided the 1,4 conjugate addition product, compounds **2** - **5**. Nuclear magnetic resonance NMR analysis affirms that compounds **2** - **5** exhibit the characteristic pyrimidine doublet which represents the unsubstituted 5- and 6- position hydrogens of the aromatic ring with a coupling constant of approximately 5 Hz. These compounds also bear two triplet peaks which correspond to the methylene hydrogens obtained in the conjugate addition product. The addition of ethylamine yielded the single addition compound **2**. Triplet and quartet peak signals corresponding to the methyl and methylene hydrogens, respectively, of the ethylamine group are also apparent at 1.10 and 2.69 ppm. Resonance analysis of compound **3** features the characteristic pyrimidine peaks at 7.21 and 8.50 ppm as well as a singlet signal at 1.09 ppm corresponding to the hydrogens of the tert-butyl amine group. Compound **4**, the structural isomer of **3**, displays the characteristic NMR signal pattern of a butyl group: a triplet far peak downfield (0.91 ppm) corresponding to the three shielded methyl hydrogens; multiplet peak signals at 1.33 and 1.46 ppm representing the interior methylene groups; and a triplet further downfield 2.64 ppm for the

methylene group nearest the electronegative N atom of the butyl moiety. Analysis of the NMR spectrum of **5** indicates the presence of pyrimidine as its characteristic peaks are apparent at 7.20 and 7.49 ppm with a coupling constant of 5 Hz. The  $-\text{CH}_2-$  hydrogens are represented by the triplet peaks at 2.83 and 2.98 ppm. The phenyl group hydrogens correspond to the multiplet signals, integrating to five hydrogens, evident at 6.85, 6.93, and 7.20 ppm. The spectrum also features distinctive methyl piperazine signals; two triplet peaks at 2.68 and 3.20 corresponding to the four piperazinyl hydrogens.

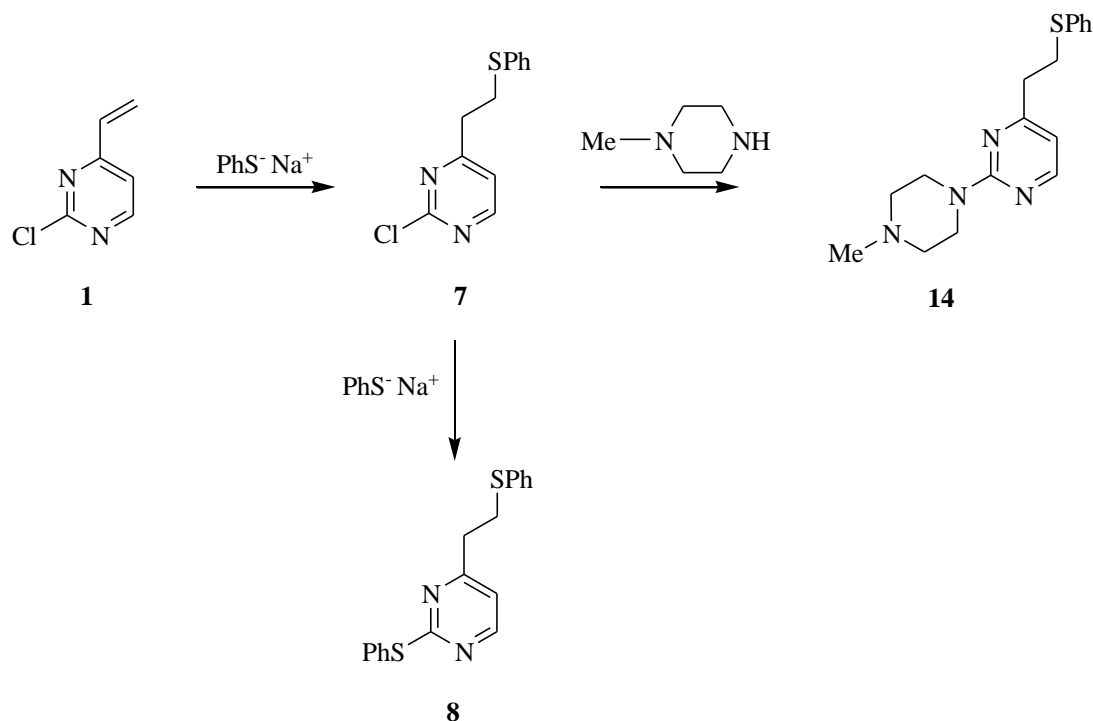
The addition of ethylamine to **2** in 0.55 equivalents afforded a conjugate addition dimer product **6** as the major product obtained as shown in Scheme 2. Characteristic pyrimidinyl proton peak signals are apparent in the NMR spectrum of **6**. At 2.88 ppm, the doublet of triplet signals correspond to the eight methylene hydrogens forming the bridge between the two pyrimidine rings. Triplet and quartet peak signals corresponding to the  $-\text{CH}_3$  and  $-\text{CH}_2-$  hydrogens, respectively, of the ethylamine group are also apparent at 1.00 and 2.58 ppm.



Scheme 2.

For the addition of amine nucleophiles, conjugate addition across the vinyl group was preferred over substitution at the chlorine atom. The major product obtained from the addition of benzenethiolate, however, favored displacement at the 2-chloro position (18 % yield) and di-

addition with replacement of the chlorine atom as well as addition across the vinyl moiety as shown in Scheme 3. Compound **7** is a minor product and the diaddition compound **8** is preferred. This occurrence is attributed to the increased nucleophilicity of the larger, more basic sulfur atom.



Scheme 3.

Nucleophilic displacement of chloride in the 4-substituted 2-chloropyrimidines by treatment with excess 1-methylpiperazine provides compounds **9 – 12** (Scheme 1). The *N*-methylpiperazine nucleophile displaces the chloride atom via an addition elimination reaction as shown in Figure 18. Delocalization of negative charge over the 1- and 3- position electronegative N atoms supports the displacement of the 2-position chlorine atom by the nitrogen nucleophile. The anionic intermediates are stabilized by both nitrogen atoms as shown in the mesomeric isomers which promote substitution of the halogen atom.

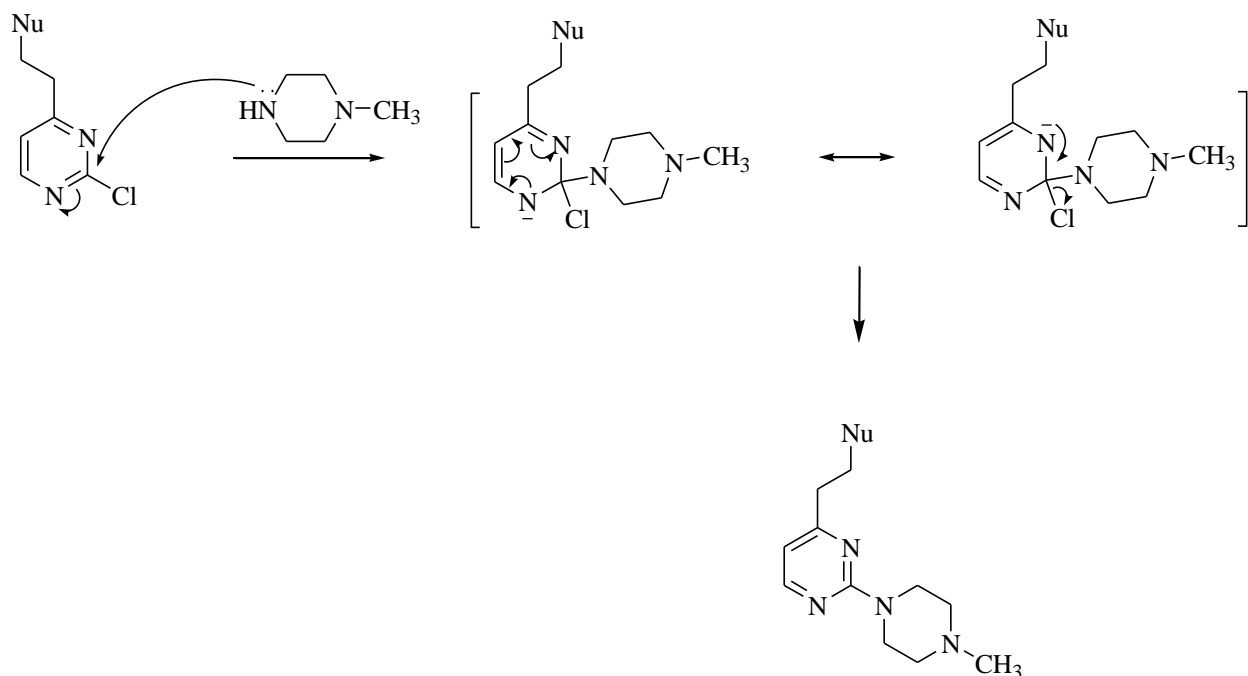


Figure 18. Proposed mechanism for the addition-elimination of the chlorine atom by N-methylpiperazine.

The NMR spectra of compounds **9-12** retain the signal pattern of their corresponding 2-chloro intermediate compounds **2-5**, slightly shifted; however, they now also feature the characteristic methylpiperazine peaks; a singlet signal representing the three methyl hydrogens and two triplet peaks corresponding to the hydrogens of the four methylene group of the piperazine ring.

## 2.2 Synthesis of Substituted Pyridines

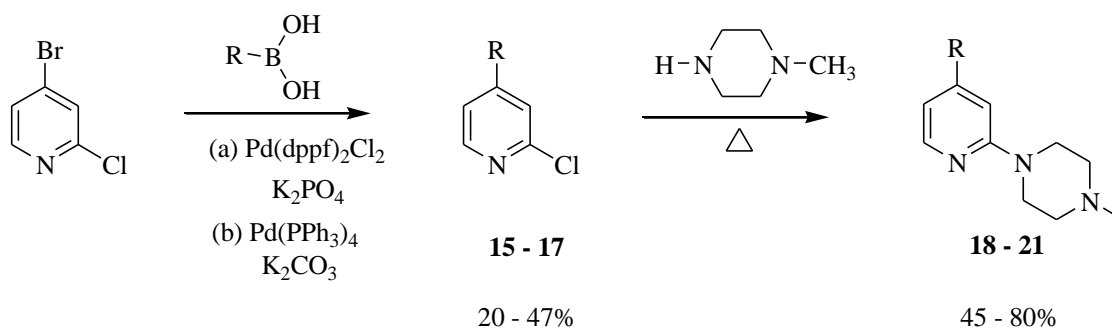
Several compounds demonstrating selective affinity to the 5-HT<sub>7</sub> receptor feature a pyridine moiety. Foregoing research has expanded the class of 5-HT<sub>7</sub> receptor ligands to include novel thiopyridines, aminopyridines, and arylpyridines as have been described..<sup>15, 22, 27</sup> The synthesis of disubstituted pyridine compounds presented in this thesis has been achieved with methods incorporating organometallic catalysis.

### 2.2.1 Suzuki Coupling to Bromopyridine via Palladium Catalysis

In 1981, the continued research of Suzuki and Miyaura efforts afforded an efficient methodology for the synthesis of biaryl compounds through the palladium catalyzed cross-coupling of aryl boronic acids with aryl halides.<sup>56</sup> In what has become known as the Suzuki cross-coupling reaction, palladium facilitates the carbon-carbon coupling between organoboron compounds and organic halides or triflates.<sup>56</sup> This method of coupling is both stereo- and regioselective and provides an efficient means for the synthesis of biaryl compounds.

Addition to 4-bromo-2-chloropyridine was achieved via Suzuki coupling. The reaction of the nitrogen heterocycle with a heteroarylboronic acid in the presence of strong base yielded the substituted products **15-18** as shown in Scheme 4. Attack at the 4-bromo position was favored over that at the 2-chloro position. This occurrence is attributed to the larger size and decreased basicity of the bromine atom.





#	R
15, 18	
16, 19	
17, 20	
21	

Scheme 4.

NMR spectroscopic analysis of compound **15** featured several peaks within the aromatic region. A doublet at 8.40 ppm with a coupling constant of 5.2 Hz corresponded to the 3-position H atom of the pyridine ring. The multiplet peak signals apparent at 7.40 and 7.45 ppm represent the protons of the 5- and 6-positions of the pyridine ring overlapped with protons of the . These hydrogen atoms experience significant coupling and thus exhibit multiple signals. <sup>1</sup>HNMR spectra of compounds **16** and **17** bear similar peak signal patterns thus confirming addition of the heteroaryl group.

The reaction of the 4-bromo-2-chloropyridine with the Pd(0) species formed a Pd(II)-halide-aryl complex in the oxidative addition step as shown in Figure 19.<sup>57</sup> In the ancillary metalthesis stage, the bromide anion of the Pd(II) complex is exchanged for the basic anion. During transmetallation, the in situ generated tetravalent borate complex readily exchanges the aryl group for the anion of the Pd(II)-aryl-anion complex. The bis-aryl Pd(II) complex undergoes reductive elimination and the Pd(0) catalyst is regenerated with the formation of a new carbon-carbon bond between the pyridine ring and the heteroaryl affording compounds **15 - 17**.

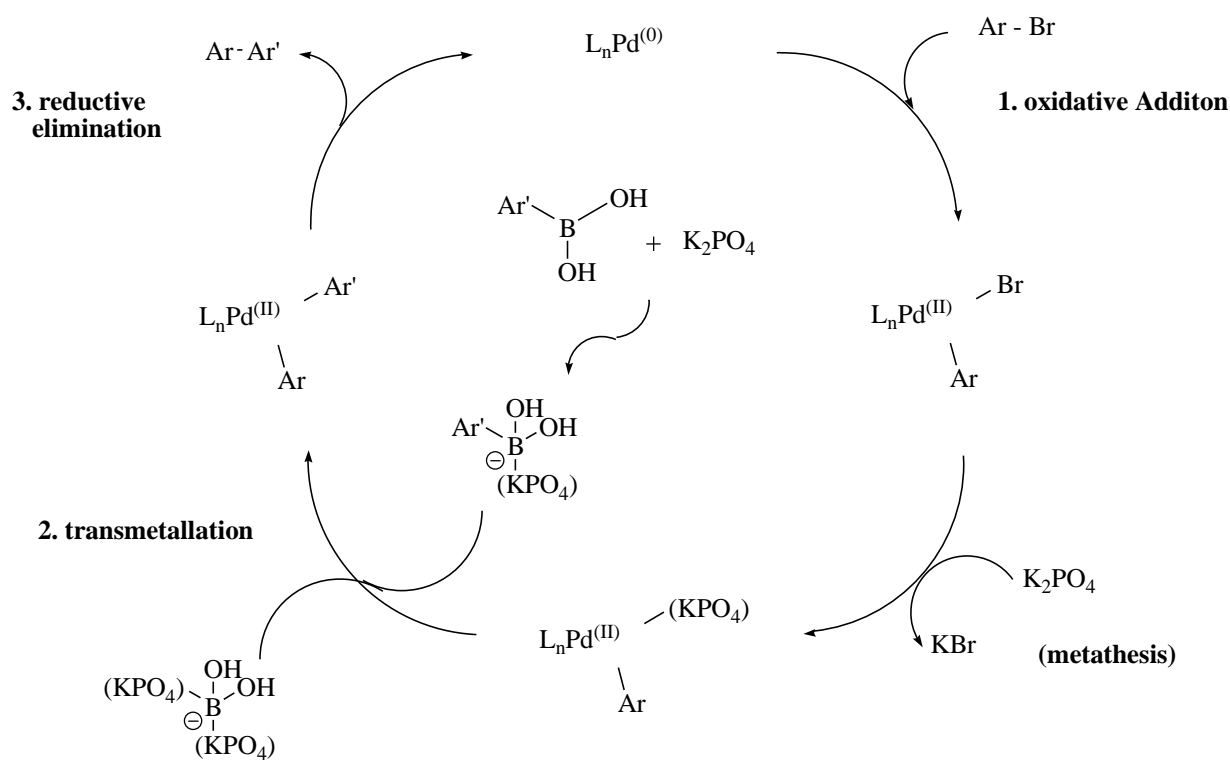
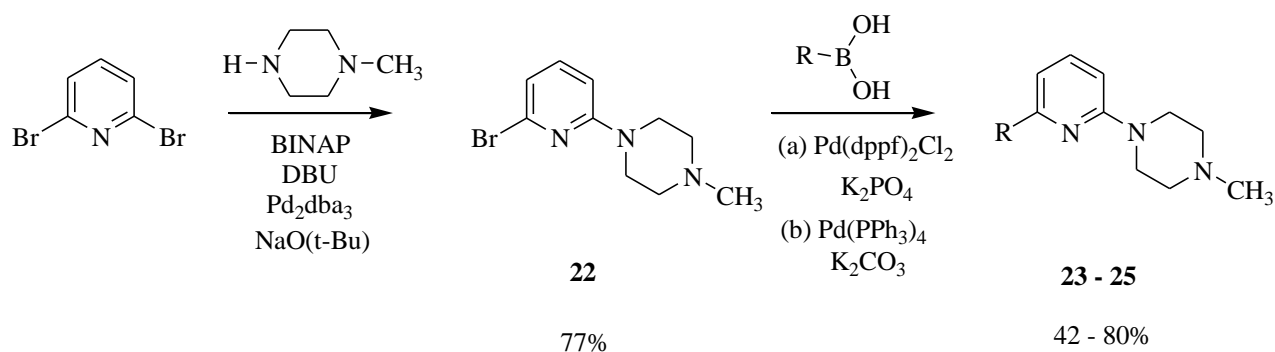


Figure 19. The mechanism of the Suzuki cross-coupling reaction of 4bromo-2-chloropyridine and an arylboronic acid.<sup>56</sup>

Heating of compounds **15** – **17** in neat methylpiperazine afforded compounds **18** – **21** in appreciable yields. Resonance analysis of these compounds feature the respective heteroaryl and pyridine peaks of compounds **15** – **17**. Peak signals corresponding methyl piperazine peaks, however, are also apparent in these spectra confirming displacement of the 2-position chlorine atom by the nitrogen nucleophile *N*-methylpiperazine.

### 2.2.2 Amination of Di-bromopyridine via Palladium Catalysis

Established methods for the formation of a C – N bond typically feature harsh reaction conditions, difficult copper reagents, toxic organostannanes, non-regiospecificity in product, or low synthetic yield.<sup>57,58</sup> In 1995, Buchwald and Hartwig independently reported the transition metal catalyzed hetero cross-coupling between aryl halides and amines under basic conditions.<sup>59</sup> The Buchwald-Hartwig reaction has provided an efficient means for the addition of *N*-methylpiperazine to position 2 of 2,6-dibromopyridine as shown in Scheme 5.



#	R
23	
24	
25	

Scheme 5.

A proposed mechanism for the catalytic cycle of the amination of 2,6-dibromopyridine is presented in Figure 20. The reaction of BINAP with the palladium catalyst  $\text{Pd}_2(\text{dba})_3$  forms a complex which undergoes oxidative addition to form a BINAP–Pd-halopyridine complex. This complex can coordinate directly to the *N*-methylpiperazine prior a deprotonation /transmetallation step in which the halide is transferred to the metal cation of the base sodium tert-butoxide providing the BINAP-Pd(II)-aryl-amino complex. Alternatively, metathesis may succeed oxidative addition and the halide is exchanged for the basic anion generating the BI-NAP-Pd(II)-aryl-anion complex. The methylpiperazine is coordinated in the transmetallation step affording the BINAP-Pd(II)-aryl-amino complex. The resulting complex undergoes reduc-

tive elimination regenerating the original BINAP-Pd(0) complex and affording the desired aryl-amino compound **22**.<sup>59</sup>

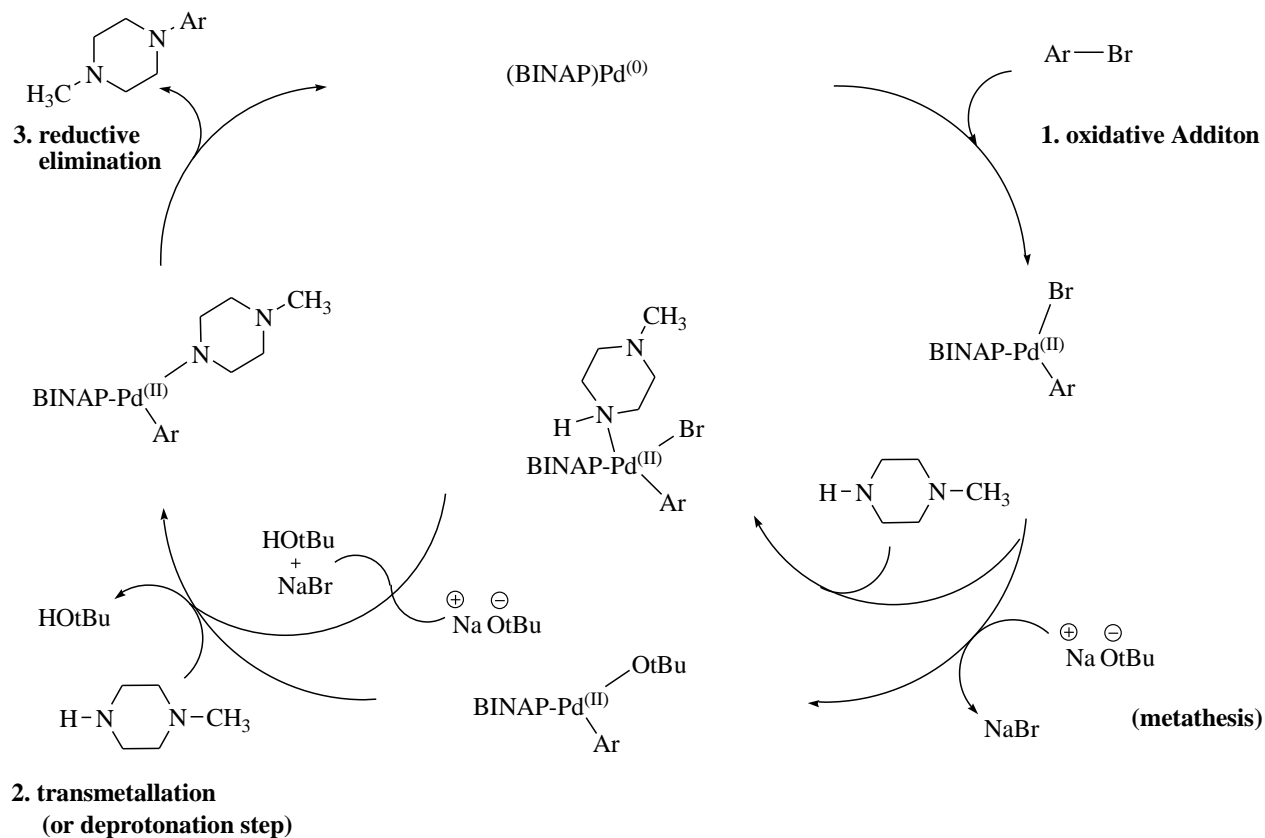


Figure 20. A proposed mechanism for the Buchwald-Hartwig amination of 2,6-dibromopyridine.

The palladium catalyst in the presence of strong base BINAP facilitated the addition of 1-methylpiperazine to 2,6-dibromopyridine for **22** as shown in Scheme 5. It is proposed that BINAP prevented the generation of the catalytically inert bis-amino-Pd(II).<sup>59</sup>

Proton NMR spectroscopic analysis of **23** featured distinctive pyridine peak signals at 6.36, 6.56, and 7.11 ppm. The characteristic peaks corresponding to *N*-methylpiperazine are also

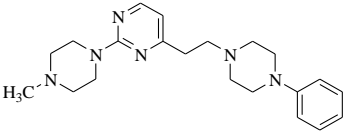
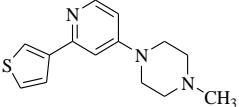
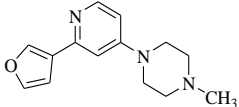
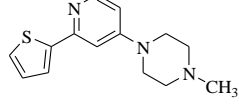
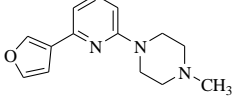
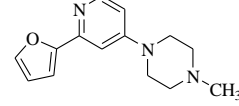
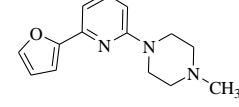
apparent. The singlet at 2.16 ppm corresponds to the three protons of the methyl group. Coupling exhibited among the hydrogens of the methylene groups of the pyridine ring is demonstrated by the two triplet peak signals at 2.30 and 3.37 ppm.

Compounds **23** – **25** were then prepared under the conditions outlined for Suzuki coupling above using **22** as the halopyridine reagent. These compounds retained the pattern of the NMR signals of the starting compound **22**. The NMR spectra now also features the signals indicative of their respective heteroaryl moieties, peak signals within the aromatic region 6.0 – 8.0 ppm.

### 2.3 Biological activity of Substituted Pyrimidines and Pyridines

Biological affinities to the 5-HT<sub>7</sub> receptor for selected purified pyrimidines and pyridines were obtained. Several of the synthesized disubstituted pyrimidines were too hygroscopic to form hydrobromic acid salts for biological testing. Salts for pyrimidine (**12**) and pyridine (**18** – **21** and **23** -**25**) compounds were shipped to collaborative researchers at the Institute of Pharmacology of the Polish Academy of Sciences. Values were also determined for binding to the 5-HT<sub>2</sub> and 5-HT<sub>6</sub> receptors as they are structurally and physiologically comparable. Results are presented in Table 1.1

**Table 1.1 Biological Activities**

<b>Compound</b>	<b>K<sub>i</sub> 5-HT<sub>2A</sub> (nM)</b>	<b>K<sub>i</sub> 5-HT<sub>7</sub> (nM)</b>	<b>K<sub>i</sub> 5-HT<sub>6</sub> (nM)</b>
	561	757	24820
	89	79	203
	41	17	417
	150	396	785
	163	11	982
	328	307	2803
	1936	1135	3405

Compounds **19** and **24** demonstrate the highest affinity and selectivity to the 5-HT<sub>7</sub> receptor over 5-HT<sub>2</sub> and 5-HT<sub>6</sub> receptors. It is proposed that the position of the heteroaryl substituent, the heteroatom, and the position of the heteroatom in the ring have affected the efficacy of binding. The 3-furyl moiety of the 2,4-disubstituted (**19**, K<sub>i</sub> = 17 nM, pK<sub>i</sub> = 7.77) and the 2,6-disubstituted (**24**, K<sub>i</sub> = 11 nM, pK<sub>i</sub> = 7.96) pyridines demonstrate highest affinity among the compounds tested. It is likely that the heteroaryl moiety of these substituted pyridines would correspond to the hydrophobic (HYD) or aromatic (AR) group as proposed in several of the pharmacophoric models, in particular, that presented by Bojarski. The identity of the heteroatom (i.e., oxygen vs. sulfur) and the position (i.e., 2- vs. 3-) can affect interaction at the binding site. The 3-furyl group of **19** and **24** HYD/AR may engage in the strongest interaction with the aromatic phenyl groups of the phenylalanine and tyrosine of the binding site.<sup>38,39</sup>

### 3 EXPERIMENTAL

#### 3.1 Synthesis of 2,4-Disubstituted Pyrimidines

**4-vinyl-2chloropyrimidine (1).** A solution of tetravinyl tin (1.29 ml, 7.1 mmol) in THF (2 ml) was stirred under nitrogen atmosphere. The temperature of the solution was lowered to -78 °C and 3.54 ml (6.0 mmol) of tert-butyllithium was added. After 10 min, white precipitate had formed and 0.75 g (5.3 mmol) of 2-chloropyrimidine was added dropwise. The temperature was allowed to reach -30 °C and the vessel removed from the nitrogen atmosphere. The temperature was decreased to -78 °C. To quench the reaction, a mixture of deionized water (5 ml) and THF (5 ml) was added. Following the water mixture, one molar equivalent of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone DDQ (1.23 g) dissolved in THF was added. Aqueous NaOH (0.3 g) was then added until the mixture became basic. The mixture was extracted with 20 ml hexanes:THF (2 x



20 ml, 1:1). The extract was dried with magnesium sulfate, filtered, and then concentrated under reduced pressure. The residual oil was purified by chromatograph on silica gel using a mobile phase of hexanes: dichloromethane (3:1); yield 0.390 g (2.78 mmol, 52 %) of **1**. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 5.79 (dd, *J* = 12.6 Hz, 0.8 Hz, 1H, -CH), 6.51 (dd, *J* = 17.2 Hz, 0.8 Hz, 1H, -CH), 6.68 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H, -CH), 7.2 (d, *J* = 5.2 Hz, 1H, -CH), 8.84 (d, *J* = 5.2 Hz, 1H, -CH). <sup>13</sup>CNMR (CDCl<sub>3</sub>): δ 165.5, 161.6, 159.9, 133.9, 125.3, 116.5. High-resolution MS (ESI, positive ion mode): calcd. for C<sub>6</sub>H<sub>5</sub>ClN<sub>2</sub> (M + 1)<sup>+</sup>, *m/z* 141.0218; found *m/z* 141.0220.<sup>48</sup>

**2-(2-Chloropyrimidin-4-yl)-N-ethylethanamine (2).** Ethylamine (0.08 ml, 0.99 mmol) was added to a solution of **1** (0.20 g, 1.00 mmol) in 2 ml of toluene. The mixture was stirred for 48 h, monitored with TLC at 24 h intervals. Deionized water (2 ml) was added to quench the reaction. Aqueous Na<sub>2</sub>CO<sub>3</sub> (0.30 g in 1 ml water) was then added. The resulting solution was extracted with hexanes: THF (2 x 20 ml, 1:1) and dried over magnesium sulfate. The pale yellow oil was purified by chromatography on silica gel eluting with hexanes and then hexanes/ ethyl acetate (4 : 3) followed by 1:1 dichloromethane/methanol) to yield 0.055 g (0.30 mmol, 30%) of **2**. <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 1.10 (t, *J* = 3.2 Hz, 3H, -CH<sub>3</sub>), 1.91 (s, 1H, -NH), 2.69 (q, *J* = 3.2 Hz, 2H, -CH<sub>2</sub>-), 2.95 (t, *J* = 6.8 Hz, 2H, -CH<sub>2</sub>-), 3.04 (t, *J* = 6.8 Hz, 2H, -CH<sub>2</sub>-), 7.17 (d, *J* = 5.2 Hz, 1H, -CH), 8.49 (d, *J* = 5.2 Hz, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): δ 172.6, 161.3, 159.1, 119.3, 47.7, 43.9, 37.8, 151. *High resolution ms* (ESI, positive ion mode): calcd. for C<sub>8</sub>H<sub>13</sub>N<sub>3</sub>Cl (M + 1)<sup>+</sup>, *m/z* 186.0798; found *m/z* 186.0798.

### General Procedure for 3,4

Nucleophiles (1.40 mmol) were added to **1** (1.40 mmol) stirring in 1 ml toluene. The mixture was then stirred overnight at room temperature. A TLC analysis indicated the absence of **1**. Wa-

ter (5 ml) was added and the solution was extracted with ether (2 x 20 ml). The organic layers were collected, dried over magnesium sulfate, and concentrated under reduced pressure.

***N*-(2-(2-Chloropyrimidin-4-yl)ethyl)-2-methylpropan-2-amine (3).**

The pale yellow oil was purified by chromatography on silica gel eluting with dichloromethane to yield 0.082 g of **3** (0.38 mmol, 38%). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 1.09 (s, 9H, -C(CH<sub>3</sub>)<sub>3</sub>), 2.91 (t, *J* = 6.0 Hz, 2H, -CH<sub>2</sub>-), 2.97 (t, *J* = 6.0 Hz, 2H, -CH<sub>2</sub>-), 7.21 (d, *J* = 4.8 Hz, 1H, -CH), 8.50 (d, *J* = 4.8 Hz, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): δ 173.0, 161.3, 159.0, 119.4, 50.5, 41.1, 39.0, 29.0. *High resolution ms* (ESI, negative ion mode): calcd. for C<sub>10</sub>H<sub>15</sub>N<sub>3</sub>Cl (M - H)<sup>-</sup>, *m/z* 212.0955; found *m/z* 212.0947.

***N*-(2-(2-Chloropyrimidin-4-yl)ethyl)butan-1-amine (4).** The yellow oil was purified by chromatography dichloromethane followed by dichloromethane/ ethyl acetate/ methanol (4: 3: 1) to yield **4** (0.14 g, 0.64 mmol, 46 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 0.91 (t, *J* = 7.2 Hz, 3H, -CH<sub>3</sub>), 1.33 (m, 2H, -CH<sub>2</sub>-), 1.46 (m, H, -CH<sub>2</sub>), 2.64 (t, *J* = 7.2 Hz, 2H, -CH<sub>2</sub>-), 2.95 (t, *J* = 6.4 Hz, 2H, -CH<sub>2</sub>-), 3.03 (t, *J* = 6.4 Hz, 2H, -CH<sub>2</sub>-), 7.17 (d, *J* = 5 Hz, 1H, -CH), 8.50 (d, *J* = 5 Hz, 1H, -CH). *High resolution ms* (ESI, negative ion mode): calcd. for C<sub>10</sub>H<sub>15</sub>N<sub>3</sub>Cl (M - H)<sup>-</sup>, *m/z* 212.0955; found *m/z* 212.0933.

**2-Chloro-4-(2-(4-phenylpiperazino)ethyl)pyrimidine (5).** *N*-Phenylpiperazine (0.275 g, 1.96 mmol) was added to a solution of **1** (0.3 ml, 1.96 mmol) in 2 ml toluene. The mixture was heated under reflux for refluxed 2 h. The mixture was then quenched with a solution of sodium carbonate in 5 ml water. The mixture was allowed to reach room temperature before extraction with ether (2 x 20 ml). The organic layers were collected, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residual yellow oil was purified by chromatography eluting with hexanes/ethyl acetate (4: 1) then hexanes/ ethyl acetate/ ethanol (8: 6: 1) to

yield 0.13 g of **6** (0.43 mmol, 22 %).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.68 (t,  $J$  = 4.8 Hz, 4H, - $\text{CH}_2$ -), 2.83 (t,  $J$  = 6.6 Hz, 2H, - $\text{CH}_2$ -), 2.98 (t,  $J$  = 6.6 Hz, 2H, - $\text{CH}_2$ -), 3.20 (t,  $J$  = 4.8 Hz, 4H, - $\text{CH}_2$ ), 6.85 (m, 1H, -CH), 6.93 (m, 2H, -CH), 7.20 (d,  $J$  = 6 Hz, 1H, -CH), 7.26 (m, 2H, -CH), 8.49 (d,  $J$  = 6 Hz, 1H, -CH).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.8, 161.2, 159.1, 151.2, 129.1, 119.8, 119.3, 116.1, 56.7, 53.0, 49.1, 35.1.

***N,N*-Bis-[2-(2-chloro-pyrimidin-4-yl)ethylamine (6).** Ethylamine (0.08 ml, 0.99 mmol) was added to a solution of **1** (0.25 g, 1.79 mmol) in 2 ml of toluene. The mixture was stirred for 48 h, monitored with TLC at 24 h intervals. Deionized water (2 ml) was added to quench the reaction. Aqueous  $\text{Na}_2\text{CO}_3$  (0.30 g in 1 ml water) was then added. The resulting solution was extracted with hexanes: THF (2 x 20 ml, 1:1) and dried over magnesium sulfate. The solution was concentrated under reduced pressure and purified by chromatography on silica gel eluting with hexanes:/iethyl ether/methanol (4:1:1) to yield 0.085 g (0.26 mmol, 26%) of **12**.  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.0 (t,  $J$  = 7.2 Hz, 3H, - $\text{CH}_3$ ), 1.62 (br s, 1H, -NH), 2.58 (q,  $J$  = 7.2 Hz, 2H, - $\text{CH}_2$ -), 2.88 (dt,  $J$  = 23.6 Hz, 6.0 Hz, 2H, - $\text{CH}_2$ -), 7.03 (d,  $J$  = 5.2 Hz, 1H, -CH), 8.44 (d,  $J$  = 5.2 Hz, 1H, -CH).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.1, 161.2, 158.9, 119.4, 51.9, 47.0, 35.4, 11.7. *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_{21}\text{H}_{31}\text{N}_6$  ( $M + 1$ ) $^+$ ,  $m/z$  367.2610; found  $m/z$  367.2609.

**2-Chloro-4-(2-(phenylthio)ethyl)pyrimidine (7).** Sodium benzenethiolate (0.135 g, 1.00 mmol) was added to **1** (0.140 g, 1.00 mmol) stirring in 1 ml of toluene. The mixture was refluxed 6 hrs before quenching with 5 ml water. Ether was added and the mixture partitioned between ether and water (2 x 10 ml). The organic layers were collected, dried over magnesium sulfate, and concentrated under reduced pressure. The residual yellow oil was purified with hexanes/dichloromethane (100 : 0 and then 9:1) to yield 0.090 g of **9** (0.02 mmol, 3 %).  $^1\text{H}$ NMR

(400 MHz,  $\text{CDCl}_3$ ):  $\delta$  3.08 (t,  $J = 7$  Hz, 2H,  $-\text{CH}_2-$ ), 3.36 (t,  $J = 7$  Hz, 2H,  $-\text{CH}_2-$ ), 7.12 (d,  $J = 5$  Hz, 1H,  $-\text{CH}$ ), 7.32 (m, 5H,  $-\text{Ar}$ ), 8.51 (d,  $J = 5$  Hz, 1H,  $-\text{CH}$ ).  $^{13}\text{CNMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.8, 159.2, 135.1, 130.1, 129.1, 126.7, 119.4, 37.1, 32.1.

**2-(Phenylthio)-4-(2-(phenylthio)ethyl)pyrimidine (8).** A solution of sodium benzenethiolate (0.135 g, 1.00 mmol, in 1 ml anhydrous tetrahydrofuran) was added to **1** stirring in 1 ml of toluene. The mixture was heated under reflux for 6 h before quenching with 5 ml water and extracted with ether/water (2 x 40 ml). The organic layers were collected, dried over magnesium sulfate, and concentrated under reduced pressure. The residual yellow oil was purified by chromatography eluting with hexanes/dichloromethane (100 : 0) to yield 0.03 g **11** (0.09 mmol, 9 %).  $^1\text{HNMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.95 (t,  $J = 7.4$  Hz, 2H,  $-\text{CH}_2-$ ), 3.23 (t,  $J = 7.4$  Hz, 2H,  $-\text{CH}_2-$ ), 6.35 (d,  $J = 5$  Hz, 1H,  $-\text{CH}$ ), 7.19 (m, 1H,  $-\text{CH}$ ), 7.29 (m, 1H,  $-\text{CH}$ ), 7.37 (m, 1H,  $-\text{CH}$ ), 8.18 (d,  $J = 5$  Hz, 1H,  $-\text{CH}$ ).  $^{13}\text{CNMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.4, 168.6, 157.4, 135.5, 135.3, 129.7, 129.5, 129.1, 129.1, 129.0, 126.3, 116.6, 38.8, 36.8. *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_{17}\text{H}_{18}\text{S}_2\text{N}_2$  ( $M + 1$ ) $^+$ ,  $m/z$  325.0833; found  $m/z$  325.0829.

### General procedure for 9 - 14

Neat N-methylpiperazine (1.30 mmol) was added to the 2-chloro-4-vinylpyrimidine compound **2** – **5** (0.65 mmol) stirring in 1 ml toluene. The mixture was heated under reflux for 3 h after which time a TLC analysis indicated the absence of the starting material, compounds **2** - **5**. The mixture was then quenched with water (5 ml). The mixture was allowed to reach room temperature before extraction with ether (2 x 20 ml). The organic phases were collected, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a yellow oil.

**N-ethyl-2-(2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)ethanamine (9).** This compound was obtained according to the general procedure above. The yellow oil obtained was purified with

dichloromethane/methanol (100: 0, then 1:1) to yield 0.021 g of **7** (0.08 mmol, 30 %).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.11 (t,  $J = 7.2$  Hz, 3H,  $-\text{CH}_3$ ), 2.34 (s, 3H,  $-\text{CH}_3$ ), 2.46 (t,  $J = 5$  Hz, 2 H,  $-\text{CH}_2-$ ), 2.68 (q,  $J = 6.8$  Hz, 2H,  $-\text{CH}_2-$ ), 2.79 (t,  $J = 6.6$  Hz, 2H,  $-\text{CH}_2-$ ), 2.98 (t,  $J = 6.6$  Hz, 2H,  $-\text{CH}_2-$ ), 3.87 (t,  $J = 5$  Hz, 2H,  $-\text{CH}_2-$ ), 6.38 (d,  $J = 4.8$  Hz, 1H,  $-\text{CH}$ ), 8.19 (d,  $J = 4.8$  Hz, 1H,  $-\text{CH}$ ).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  166.8, 161.0, 158.8, 111.2, 52.6, 44.5, 42.8, 42.63, 41.0, 33.2. *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_{13}\text{H}_{24}\text{N}_5$  ( $M + 1$ ) $^+$ ,  $m/z$  250.2032; found  $m/z$  250.2024.

**Synthesis of 2-methyl-N-(2-(2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)ethyl)propan-2-amine (10).** This compound was obtained according to the general procedure above. The yellow oil was purified with a mobile phase of dichloromethane: ethyl acetate: methanol (8: 6: 3) to yield 0.05 g **8** (0.17 mmol, 31 %).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.11 (s, 9H,  $-\text{C}(\text{CH}_3)_3$ ), 2.35 (s, 3H,  $-\text{CH}_3$ ), 2.48 (t,  $J = 4.8$  Hz, 3H,  $-\text{CH}_2-$ ), 2.77 (t,  $J = 6.8$  Hz, 2H,  $-\text{CH}_2-$ ), 2.96 (t,  $J = 6.8$  Hz, 2H,  $-\text{CH}_2-$ ), 3.86 (t,  $J = 4.8$  Hz, 2H,  $-\text{CH}_2-$ ), 6.41 (d,  $J = 5$  Hz, 2H,  $-\text{CH}_2-$ ), 8.20 (d,  $J = 5$  Hz, 2H,  $-\text{CH}_2-$ ).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.5, 161.7, 157.4, 109.4, 55.0, 50.3, 46.3, 43.7, 40.9, 34.9, 38.5, 29.0. *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_{15}\text{H}_{28}\text{N}_5$  ( $M + 1$ ) $^+$ ,  $m/z$  278.2345; found  $m/z$  278.2345.

**N-(2-(2-(4-Methylpiperazino)pyrimidin-4-yl)ethyl)butan-1-amine (11).** The yellow oil was purified by chromatography with an eluent of dichloromethane/ethyl acetate/methanol (4: 3: 1) to yield 0.054 g of **7** (0.19 mmol, 30%).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.92 (t,  $J = 7.2$  Hz, 3H,  $-\text{CH}_3$ ), 1.34 (m, 2H,  $-\text{CH}_2-$ ), 1.46 (m, 2H,  $-\text{CH}_2-$ ), 1.82 (br s, 1H,  $-\text{NH}$ ), 2.34 (s, 3H,  $-\text{CH}_3$ ), 2.47 (t,  $J = 5$  Hz, 4H,  $-\text{CH}_2-$ ), 2.63 (t,  $J = 7.2$  Hz, 2H,  $-\text{CH}_2-$ ), 2.77 (t,  $J = 6.6$  Hz, 2H,  $-\text{CH}_2-$ ), 2.98 (t,  $J = 6.6$  Hz, 2H,  $-\text{CH}_2-$ ), 3.84 (t,  $J = 5$  Hz, 4H,  $-\text{CH}_2-$ ), 6.39 (d,  $J = 5$  Hz, 1H,  $-\text{CH}$ ), 8.19 (d,  $J = 5$  Hz,

1H, -CH).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.4, 161.7, 157.4, 109.3, 55.0, 52.6, 49.5, 48.2, 46.3, 43.6, 37.7, 35.4, 32.3, 20.6, 14.0. *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_{15}\text{H}_{28}\text{N}_5$  ( $M + 1$ )<sup>+</sup>,  $m/z$  278.2345; found  $m/z$  278.2340.

**2-(4-Methylpiperazin-1-yl)-4-(2-(4-phenylpiperazino)ethylpyrimidine (12).** The yellow oil was purified by chromatography eluting with dichloromethane/ethyl acetate/methanol (4: 3: 1) to yield 0.065 g **8** (0.18 mmol, 35 %).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.34 (t,  $I = 6$  Hz, 3H, -CH<sub>2</sub>-), 2.48 (t,  $J = 4.8$  Hz, 4H, -CH<sub>2</sub>-), 2.70 (t,  $J = 4.8$  Hz, 4H, -CH<sub>2</sub>-), 2.81(m, 4H, -CH<sub>2</sub>-), 3.23 (t,  $J = 4.8$  Hz, 4H, -CH<sub>2</sub>-), 3.85 (t,  $J = 4.8$  Hz, 4H, -CH<sub>2</sub>-), 6.42 (d,  $J = 4.8$  Hz, 1H, -CH), 6.86 (m, 1H, -CH), 6.95 (m, 1H, -CH), 7.27 (m, 1H, -CH), 8.20 (d,  $J = 4.8$  Hz, 1H, -CH). *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_{21}\text{H}_{31}\text{N}_6$  ( $M + 1$ )<sup>+</sup>,  $m/z$  367.2610; found  $m/z$  367.2609. A hydrobromide salt was prepared according to general procedure above. *Anal.* calcd. For  $\text{C}_{21}\text{H}_{34}\text{N}_6 \cdot 3\text{HBr} \cdot 0.5\text{H}_2\text{O}$ : C, 40.80; H, 5.54; N, 13.59; found C, 40.65; H, 5.96; N, 13.56.

***N,N*-Bis-[2-(2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)ethylamine (13).**

*N*-Methylpiperazine (0.12 ml, 1.11 mmol) was added to a solution of **2** (0.12 g, 0.37 mmol) in 1 ml toluene. The mixture was refluxed for 1 h and monitored with TLC analysis until the absence of **2** was apparent. Water (5 ml) was added and the mixture extracted with hexanes/diethyl ether (2 x 20 ml, 1:1). The organic layers were collected, dried over magnesium sulfate, and concentrated under reduced pressure. The pale yellow oil was purified by chromatography on silica gel with a mobile phase of dichloromethane/methanol (1:1) to yield 0.045 g of **13** (0.10 mmol, 28%).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.07 (t,  $J = 7.2$  Hz, 3H, -CH<sub>3</sub>), 2.35 (s, 3H, -CH<sub>3</sub>), 2.48 (t,  $J = 5.0$  Hz, 2H, -CH<sub>2</sub>-), 2.73 (m, 4H, -CH<sub>2</sub>-), 2.91 (m, 4H, -CH<sub>2</sub>-), 3.86 (t,  $J = 5.0$  Hz, 2H, -CH<sub>2</sub>-), 6.37 (d,  $J = 4.8$  Hz, 2H, -CH), 8.18 (d,  $J = 4.8$  Hz, 2H, -CH).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.8,

162.0, 157.2, 109.4, 55.0, 52.0, 47.4, 46.3, 43.7, 35.4, 12.2. *High resolution ms* (ESI, positive ion mode): calcd. for  $C_{24}H_{40}N_9$  ( $M + 1$ )<sup>+</sup>,  $m/z$  454.3407; found  $m/z$  454.3405.

**2-(4-Methylpiperazino)-4-(2-(phenylthio)ethyl)pyrimidine (14).** The yellow oil was purified by chromatography eluent with dichloromethane/methanol (100: 0, then 20: 1) to yield 0.014 g **10** (0.04 mmol, 63 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): 2.35 (s, 3H, -CH<sub>3</sub>), 2.47 (t,  $J$  = 5 Hz, 4H, -CH<sub>2</sub>-), 2.88 (t,  $J$  = 7 Hz, 2H, -CH<sub>2</sub>-), 3.31 (t,  $J$  = 7 Hz, 2H, -CH<sub>2</sub>-), 3.85 (t,  $J$  = 5 Hz, 4H, -CH<sub>2</sub>-), 6.35 (d,  $J$  = 4.8 Hz, 2H, -CH<sub>2</sub>-), 7.19 (m, 1H, -CH), 7.27 (m, 2H, -CH), 7.37 (d,  $J$  = 3.8 Hz, 2H, -CH), 8.18 (d,  $J$  = 4.8 Hz, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): 177.7, 168.5, 157.6, 129.4, 128.9, 128.9, 126.1, 109.2, 55.0, 46.2, 43.6, 37.3, 31.8. *High resolution ms* (ESI, positive ion mode): calcd. for  $C_{17}H_{23}N_4S$  ( $M + 1$ )<sup>+</sup>,  $m/z$  315.1643; found  $m/z$  315.1648.

## 3.2 Synthesis of Disubstituted Pyridines

All reaction employed a palladium bidentate catalyst. The catalyst aided in substitution of the pyridine compounds.

### 3.2.1 Preparation of 2,4-Disubstituted Pyridines

**2-Chloro-4-(3-thienyl)pyridine (15).** A solution of 4-bromo-2-chloro-pyridine (0.15 ml, 1.35 mmol) and thiophene-3-boronic acid (0.09 g, 0.683 mmol) in 5 ml of 1,4 dioxane under nitrogen atmosphere was treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)<sub>2</sub>Cl<sub>2</sub>, 0.02 g, 0.02 mmol) and potassium phosphate dibasic (0.28 g, 1.64 mmol). The mixture was heated under reflux for 48 h. The vessel was removed from the heat source and its temperature allowed to reach room temperature. The mixture was vacuum filtered through 0.5 cm of Celite ® and washed with ether (10 ml). The filtrate was concentrated under reduced pressure.<sup>8</sup> Purification of the yellow-brown oil was achieved by chromatography with an eluent

of hexanes on silica gel to yield 0.034 g of **15** (0.27 mmol, 20 %).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40 (m, 2H, -CH), 7.45 (m, 1H, -CH), 7.52 (s, 1H, -CH), 7.70 (m, 1H, -CH), 8.40 (d,  $J = 5.2$  Hz, 1H, -CH).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.4, 150.1, 145.7, 138.2, 127.5, 125.6, 124.1, 121.1, 119.7. *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_9\text{H}_6\text{ClNS}$  ( $M + 1$ ) $^+$ ,  $m/z$  195.9988; found  $m/z$  195.9979.

**2-Chloro-4-(3-furyl)pyridine (16).** Furan-3-boronic acid (0.38 g, 3.38 mmol),  $\text{Pd}(\text{dppf})_2\text{Cl}_2$  (0.09 g, 0.11 mmol), and potassium phosphate dibasic (1.18 g, 6.75 mmol) were added to a solution of 4-bromo-2-chloro-pyridine (0.25 ml, 2.25 mmol) in 5 ml dioxane under a nitrogen atmosphere. The mixture was heated under reflux for 72 h before removal from the heat source and the temperature allowed to reach room temperature. The mixture was filtered through 0.5 cm Celite ® and washed with ether (10 ml). The filtrate was concentrated under reduced pressure.<sup>9</sup> The yellow oil obtained was purified by chromatography with hexanes to yield 0.099 g of **16** (0.54 mmol, 24 %).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.69 (d,  $J = 0.6$  Hz, 1H, -CH), 7.25 (d,  $J = 2.6$  Hz, 1H, -CH), 7.34 (s, 1H, -CH), 7.50 (d,  $J = 0.6$  Hz, 1H, -CH), 7.86 (s, 1H, -CH), 8.31 (d,  $J = 2.6$  Hz).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  152.3, 150.1, 114.7, 143.4, 140.9, 123.3, 120.6, 119.1, 108.2. *High resolution ms* (ESI, positive ion mode): calcd. for  $\text{C}_9\text{H}_6\text{ClNO}$  ( $M + 1$ ) $^+$ ,  $m/z$  180.0216; found  $m/z$  180.0224.

**2-Chloro-4-(2-thienyl)pyridine (17).** Thiophene-2-boronic acid (0.43 g, 3.38 mmol), tetrakis(triphenylphosphine) palladium  $\text{Pd}(\text{PPh}_3)_4$  (0.20 g, 0.18 mmol), and potassium carbonate (0.93 g, 6.75 mmol) were added to 4-bromo-2-chloropyridine (0.25 ml, 2.25 mmol) stirring in 6 ml dioxane under a nitrogen atmosphere. The mixture was heated to reflux for 96 h. After removal of the reaction vessel from the heat source, the temperature was allowed to reach room temperature before filtration through 0.5 cm Celite ®. The filtrate was concentrated under reduced



pressure.<sup>9</sup> The yellow oil was purified with hexanes to yield 0.214 g of **17** (1.09 mmol, 49 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 7.08 (m, 1H, -CH), 7.32 (m, 1H, -CH), 7.41 (m, 1H, -CH), 7.44 (m, 2H, -CH), 8.29 (d, *J* = 2.6 Hz, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): 152.4, 150.1, 144.4, 140.0, 128.6, 128.1, 126.2, 120.1, 118.8. *High resolution ms* (ESI, positive ion mode): calcd. for C<sub>9</sub>H<sub>7</sub>NSCl (M + 1)<sup>+</sup>, m/z 195.9988; found m/z 195.9989.

**1-Methyl-4-(4-(3-thienyl)pyridin-2-yl)piperazine (18).** A stirring mixture of 1-methylpiperazine (1 ml) and **15** (0.08 g, 0.38 mmol) was heated to 200 °C overnight in a sealed tube. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting brown oil was purified with a mobile phase of dichloromethane: methanol (8 : 1) to yield 0.079 g **18** (0.31 mmol, 80 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 2.34 (s, 3H, -CH<sub>3</sub>), 2.53 (t, *J* = 5.0 Hz, 2H, -CH<sub>2</sub>-), 3.61 (t, *J* = 5.0 Hz, 2H, -CH<sub>2</sub>-), 6.82 (m, 2H, -CH), 7.29 (m, 2H, -CH), 7.56 (s, 1H, -CH), 8.19 (m, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): δ 160.2, 148.5, 144.3, 140.7, 126.6, 126.0, 122.4, 111.5, 104.1, 54.9, 46.2, 45.3. *High resolution ms* (ESI, positive ion mode): calcd. for C<sub>14</sub>H<sub>17</sub>N<sub>3</sub>S (M + 1)<sup>+</sup>, m/z 260.1221 found m/z 260.1223.

**1-(4-(3-Furyl)pyridine-2-yl)-4-methylpiperazine (19).** A stirring mixture of 1-methylpiperazine (1 ml) and **16** (0.08 g, 0.43 mmol) was heated to 200 °C overnight in a sealed tube. The mixture was removed from the heat source and allowed to reach room temperature. Ether (20 ml) was added and the solution concentrated under reduced pressure. The brown oil was purified with by chromatography eluting with dichloromethane/methanol (95 : 5) to yield 0.075 g of **19** (0.30 mmol, 71 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 2.34 (s, 3H, -CH<sub>3</sub>), 2.53 (t, *J* = 5.0 Hz, 2H, -CH<sub>2</sub>-), 3.60 (t, *J* = 5.0 Hz, 2H, -CH<sub>2</sub>-), 6.72 (m, 3H, -CH), 7.49 (m, 1H, -CH), 7.81 (s, 1H, -CH), 8.16 (m, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): δ 160.1, 148.35, 144.0, 141.4,

140.0, 125.2, 110.9, 108.5, 103.5, 54.87, 46.1, 45.2. *Anal.* calcd. For  $C_{14}H_{17}N_3O \cdot 2HBr$ : C, 41.51; H, 4.73; N, 10.37; found C, 41.04; H, 4.39; N, 11.07.

**1-Methyl-4-(4-(2-thienyl)pyridin-2-yl)piperazine (20).** A mixture of 1-methylpiperazine (1 ml) and **17** (0.11 g, 0.56 mmol) was stirred overnight at 200 °C in a sealed tube. The mixture was removed from the heat source and allowed to reach room temperature. Ether (20 ml) was added and the solution concentrated under reduced pressure. The residual brown oil was purified by chromatography eluting with hexanes: dichloromethane (9: 1) to yield 0.064 g of **20** (0.25 mmol, 45 %).  $^1H$ NMR (400 MHz,  $CDCl_3$ ):  $\delta$  2.36 (s, 3H, -CH<sub>3</sub>), 2.55 (t,  $J$  = 5.0 Hz, 2H, -CH<sub>2</sub>-), 3.62 (t,  $J$  = 5.0 Hz, 2H, -CH<sub>2</sub>-), 6.83 (s, 1H, -CH), 6.86 (d,  $J$  = 5.2 Hz, 1H, -CH), 7.11 (dd,  $J$  = 4.0 Hz,  $J$  = 4.8 Hz, 1H, -CH), 7.36 (d,  $J$  = 4.4 Hz, 1H, -CH), 7.44 (d,  $J$  = 2.8 Hz, 1H, -CH), 8.18 (d,  $J$  = 5.2 Hz, 1H, -CH).  $^{13}C$ NMR (400 MHz,  $CDCl_3$ ):  $\delta$  160.1148.5, 142.8, 142.5, 128.1, 126.3, 124.8, 110.7, 103.2, 54.9, 46.2, 45.3. A hydrobromide salt was prepared according to general procedure above. *Anal.* calcd. For  $C_{14}H_{17}N_3S \cdot 2HBr, 0.5H_2O$ : C, 39.09; H, 4.69; N, 9.77; found C, 39.46; H, 4.80; N, 9.34.

**1-(4-(2-Furyl)pyridin-2-yl)-4-methylpiperazine (21).** (a) Furan-2-boronic acid (0.30 g, 2.7 mmol),  $Pd(PPh_3)_4$  (0.15 g, 0.18 mmol), and potassium carbonate (0.933 g, 6.75 mmol) were added to a solution of 4-bromo-2-chloro-pyridine (0.25 ml, 2.25 mmol) in 5 ml dioxane under a nitrogen atmosphere. The mixture was heated under reflux for 72 h before removal from the heat source and the temperature allowed to reach room temperature. The mixture was filtered through 0.5 cm Celite ® and washed with ether (10 ml). The filtrate was concentrated under reduced pressure. The yellow oil obtained was sufficiently purified by chromatography with hexanes to yield 0.29 g of the chloro intermediate, 2-chloro-4-(2-furyl)pyridine (1.61 mmol, 72 %).  $^1H$ NMR (400 MHz,  $CDCl_3$ ):  $\delta$  6.43 (m, 1H, -CH), 6.78 (dd,  $J$  = 3.4 Hz,  $J$  = 0.6 Hz, 1H, -CH),

7.28 (dd,  $J = 5.4$  Hz,  $J = 1.4$  Hz, 1H, -CH), 7.40 (dd,  $J = 1.8$  Hz,  $J = 0.6$  Hz, 1H, -CH), 7.44 (dd,  $J = 1.8$  Hz,  $J = 0.6$  Hz, 1H, -CH), 8.22 (dd,  $J = 5.4$  Hz,  $J = 0.6$  Hz, 1H, -CH). *High resolution ms* (ESI, positive ion mode): calcd. for  $C_{10}H_7ClO$  ( $M + 1$ )<sup>+</sup>,  $m/z$  180.0216; found  $m/z$  180.0328. **(b)** A mixture of 1-methylpiperazine (1 ml) and 2-chloro-4-(2-furyl)pyridine (0.26 g, 1.69 mmol) was stirred overnight at 200 °C in a sealed tube. The reaction was removed from the heat source and allowed to reach room temperature. Ether (20 ml) was added and the solution concentrated under reduced pressure. The residual brown oil was purified by chromatography eluting with dichloromethane/ethanol (100: 1) to yield 0.309 g of **21** (1.27 mmol, 76 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  2.35 (s, 3H, -CH<sub>3</sub>), 2.54 (t,  $J = 5.0$  Hz, 2H, -CH<sub>2</sub>-), 3.62 (t,  $J = 5.0$  Hz, 2H, -CH<sub>2</sub>-), 6.49 (q,  $J = 1.6$  Hz, 1H, -CH), 6.78 (m, 1H, -CH), 6.86 (dd,  $J = 1.2$  Hz,  $J = 5.2$  Hz, 1H, -CH), 6.39 (s, 1H, -CH), 7.49 (m, 1H, -CH), 8.17 (dd,  $J = 0.4$  Hz, 5.2 Hz, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  160.1, 152.3, 148.3, 143.1, 138.8, 111.9, 108.4, 107.9, 100.9, 54.9, 46.2, 45.2. *High resolution ms* (ESI, positive ion mode): calcd. for  $C_{14}H_{18}N_3O$  ( $M + 1$ )<sup>+</sup>,  $m/z$  244.1450; found  $m/z$  244.1459. A hydrobromide salt was prepared according to general procedure above. *Anal.* calcd. For  $C_{14}H_{17}N_3O \cdot 2HBr$ : C, 41.51; H, 4.73; N, 10.37; found C, 41.24; H, 4.78; N, 10.51.

### 3.2.2 Preparation of 2,6-Disubstituted Pyridines

**1-(6-Bromopyridin-2-yl)-4-methylpiperazine (22).** A mixture of 2,6-dibromo-pyrimidine (1.00 g, 4.22 mmol) and 1-methylpiperazine (0.16 ml, 1.41 mmol) was stirred in 5 ml dry toluene. The solution was treated with tert-butoxide (0.01 g, 0.14 mmol), tris(debenzylideneacetone)dipalladium(0) Pd<sub>2</sub>dba<sub>3</sub> (0.01 g, 0.01 mmol), (±)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene BINAP (0.03 g, 0.04 mmol), and 1,8-Diazabicyclo[5.4.0]undec-7-ene DBU (0.51 ml, 3.44 mmol). The mixture was heated in a sealed

tube for 48 h. The vessel was removed from heat and the mixture partitioned between ethyl acetate and water. The aqueous phase was extracted with ethyl acetate (2 x 20 ml). The organic layers were collected and washed with 1.6 M hydrochloric acid (20 ml). An equivalent volume of sodium hydroxide (20 ml) was added to the acidic solution. Solid sodium bicarbonate was added until the solution became basic, approximately pH 8 as measured with pH paper. The solution was back extracted with ethyl acetate (25 ml) and the organic layers obtained were washed with brine.<sup>10</sup> Concentrated under reduced pressure, the organic layers contained the crude product **23** (0.277 g, 1.09 mmol, 77 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 2.16 (s, 3H, -CH<sub>3</sub>), 2.30 (t, *J* = 4.4 Hz, 2H, -CH<sub>2</sub>-), 3.37 (t, *J* = 4.4 Hz, 2H, -CH<sub>2</sub>-), 6.36 (d, *J* = 4.0 Hz, 1H, -CH), 6.56 (d, *J* = 4.0 Hz, 1H, -CH), 7.11 (m, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): 160.1, 152.3, 148.3, 143.1, 138.8, 111.9, 108.4, 107.9, 100.9, 54.9, 46.2, 45.2. *High resolution ms* (ESI, positive ion mode): calcd. for C<sub>10</sub>H<sub>14</sub>N<sub>3</sub> (M + 1)<sup>+</sup>, *m/z* 256.0449; found *m/z* 256.0444.

**1-Methyl-4-(6-(3-thienyl)pyridine-2-yl)piperazine (23).** Thiophene-3-boronic acid (0.20 g, 1.54 mmol), Pd(dppf)<sub>2</sub>Cl<sub>2</sub> (0.03 g, 0.04 mmol), potassium phosphate dibasic (0.47 g, 2.69 mmol) were combined with **22** (0.14 g, 0.54 mmol) in 5 ml of 1,4 dioxane under nitrogen gas. The reaction was heated under reflux for 72 h before removal from the heat source. The mixture reached room temperature, after which time the mixture was filtered through 0.5 cm Celite ® and washed with ether (20 ml). The filtrate was concentrated under reduced pressure. The resulting brown oil was purified by chromatography with dichloromethane/methanol (50:1) to yield 0.059 g of **23** (0.23 mmol, 42 %). <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>): δ 2.35 (s, 3H, -CH<sub>3</sub>), 2.53 (t, *J* = 5.0 Hz, 2H, -CH<sub>2</sub>-), 3.64 (t, *J* = 5.0 Hz, 2H, -CH<sub>2</sub>-), 6.54 (d, *J* = 4.0 Hz, 1H, -CH), 6.97 (d, *J* = 4.0 Hz, 1H, -CH), 7.33 (m, 1H, -CH), 7.49 (t, 4 Hz, 1H, -CH), 7.63 (m, 1H, -CH), 7.86 (m, 1H, -CH). <sup>13</sup>CNMR (400 MHz, CDCl<sub>3</sub>): δ 159.0, 154.4, 143.0, 138.2, 126.4, 125.7, 123.0, 109.7, 105.2,

55.0, 46.3, 45.1. *Anal.* calcd. For  $C_{14}H_{17}N_3S \cdot 2HBr \cdot H_2O$ : C, 39.09; H, 4.69; N, 9.77; found C, 39.11; H, 4.79; N, 9.90.

**1-(6-(3-Furyl)pyridine-2-yl)-4-methylpiperazine (24).** Furan-3-boronic acid (0.06 g, 0.53 mmol),  $Pd(dppf)_2Cl_2$  (0.01 g, 0.01 mmol), and potassium phosphate dibasic (0.16 g, 0.92 mmol) were added to **22** (0.07 g, 0.26 mmol) stirring in 5 ml of 1,4 dioxane under nitrogen pressure. The mixture was heated to reflux for 96 h. The reaction vessel was removed from the heat source and allowed to reach room temperature before filtration through 0.5 cm of Celite ®. The filtrate was concentrated under reduced pressure and purified by chromatography eluting with hexanes to yield 0.050 g of **25** (0.21 mmol, 80 %).  $^1H$ NMR (400 MHz,  $CDCl_3$ ):  $\delta$  2.37 (s, 3H, -CH<sub>3</sub>), 2.57 (t,  $J$  = 5.0 Hz, 2H, -CH<sub>2</sub>-), 3.64 (t,  $J$  = 5.0 Hz, 2H, -CH<sub>2</sub>-), 6.54 (m, 1H, -CH), 6.85 (m, 1H, -CH), 7.30 (m, 1H, -CH), 7.49 (m, 1H, -CH), 7.99 (s, 1H, -CH).  $^{13}C$ NMR (400 MHz,  $CDCl_3$ ):  $\delta$  159.1, 149.75, 143.4, 141.1, 138.0,  $\delta$  127.7, 109.5, 108.8, 105.0, 55.0, 54.9, 46.3, 45.5, 45.0. *High resolution ms* (ESI, positive ion mode): calcd. for  $C_{14}H_{18}N_3O$  ( $M + 1$ )<sup>+</sup>,  $m/z$  244.1461; found  $m/z$  244.1450. *Anal.* calcd. For  $C_{14}H_{17}N_3O \cdot 2HBr \cdot 2H_2O$ : C, 38.12; H, 5.25; N, 9.52; found C, 38.23; H, 5.33; N, 9.72.

**1-(6-(2-Furyl)pyridin-2-yl)-4-methylpiperazine (25).** Furan-3-boronic acid (0.03 g, 0.27 mmol) and  $Pd(PPh_3)_4$  (0.02 g, 0.01 mmol) were added to **22** stirring in dimethylformamide (4 ml). Potassium carbonate (0.13 g, 0.96 mmol) dissolved in 1 ml water was added and the reaction mixture refluxed 72 h. The reaction vessel was removed from the heat source and allowed to reach room temperature before filtration through 0.5 cm Celite ®. The yellow filtrate was partitioned between ethyl acetate and water (2 x 20 ml). The organic layers were combined, dried over magnesium, and filtered. The filtrate was then concentrated under reduced pressure. The brown oil was purified by chromatography eluting with dichloromethane/ethanol (26: 1) to yield

0.025 g of **26** (0.102 mmol, 38 %).  $^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.34 (s, 3H, -CH<sub>3</sub>), 2.52 (t,  $J$  = 5.0 Hz, 4H, -CH<sub>2</sub>-), 3.61 (t,  $J$  = 5.0 Hz, 4H, -CH<sub>2</sub>-), 6.57 (d,  $J$  = 3.6 Hz, 1H, -CH), 6.77 (d,  $J$  = 3.6 Hz, 1H, -CH), 6.85 (d,  $J$  = 5.2 Hz, 1H, -CH), 6.92 (s, 1H, -CH), 7.48 (d,  $J$  = 1.6 Hz, 1H, -CH), 8.17 (d,  $J$  = 5.2 Hz, 1H, -CH).  $^{13}\text{C}$ NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  160.1, 152.3, 148.3, 143.1, 138.8, 111.9, 108.4, 107.9, 100.9, 54.9, 46.2, 45.2. *Anal. calcd.* For  $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O} \cdot 2\text{HBr} \cdot 2\text{H}_2\text{O}$ : C, 38.29; H, 4.82; N, 9.57; found C, 37.94; H, 5.02; N, 9.54.

### 3.3 Preparation of Hydrobromic Salts

All salts were prepared using 48% 9N HBr solution in 0.9:1 molar ratio with the free base compounds of interest.

## 4 CONCLUSIONS

Addition at the vinyl moiety of 2-chloropyrimidine has been achieved with various nucleophiles. For stronger nucleophiles, substitution occurs preferentially at the chloro position rather than addition across the vinyl group. Addition of a heteroaryl compound to the 4-bromo-2-chloropyridine ring is achieved via Suzuki coupling. Substitution of the chlorine atom with 1-methylpiperazine is achieved under high heating conditions. Mono-substitution at bromine of 2,6-dibromopyridine was accomplished through the use of a divalent palladium catalyst.

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## **6 APPENDICES**

### **Appendix Spectra**

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6.727  
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6.710  
6.687  
6.684  
6.575  
6.573  
6.532  
6.529  
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5.817  
5.793  
5.318  
5.315

1.671  
1.161

0.014  
0.011



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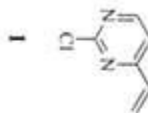
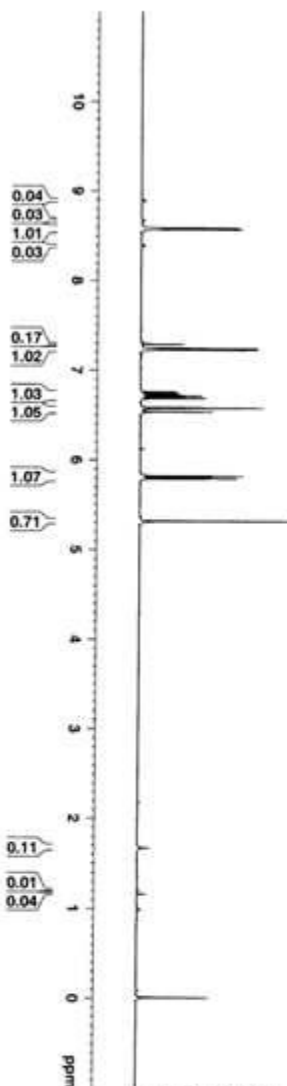
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RG 287.4

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DE 7.00 usec  
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RECPRST 0.0000000 sec  
MCPRK 0.0150000 sec

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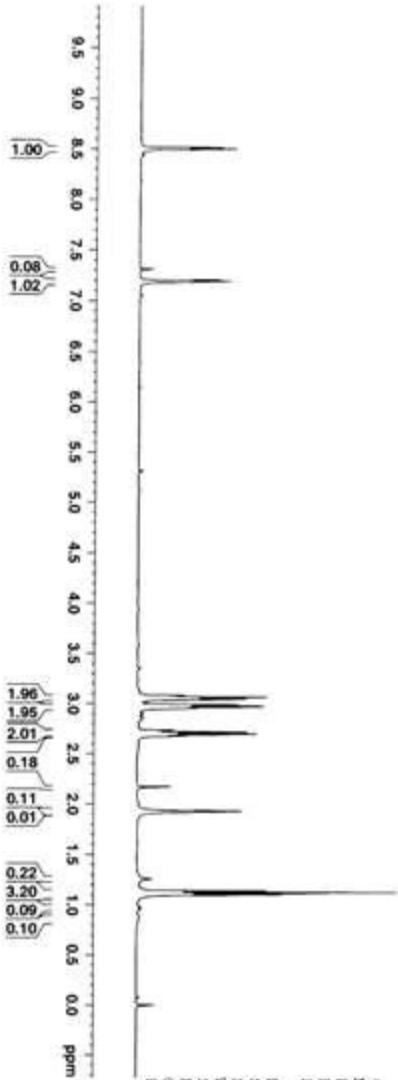
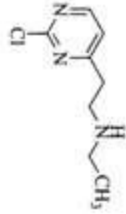
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DS 2  
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FIDRES 0.126314 Hz  
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MCREX 0.01500000 sec

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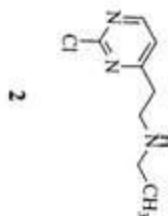
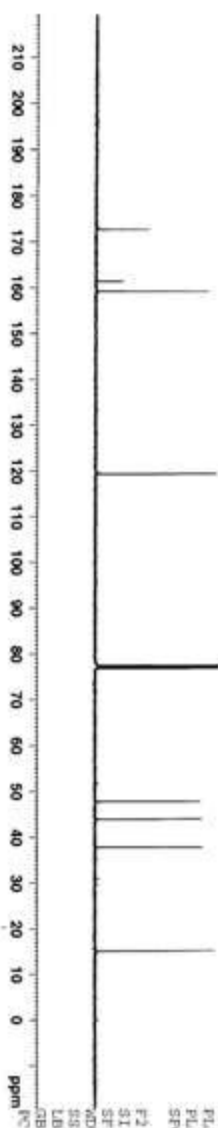
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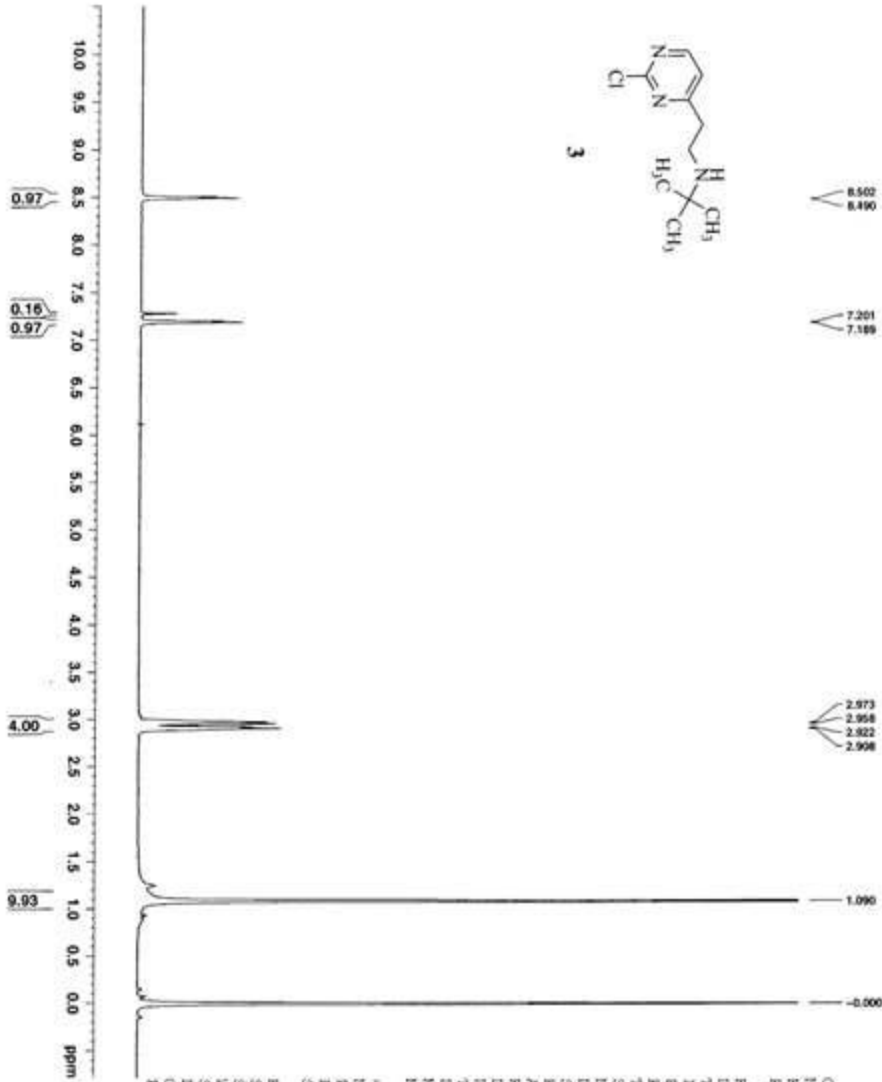
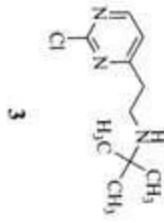
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No title



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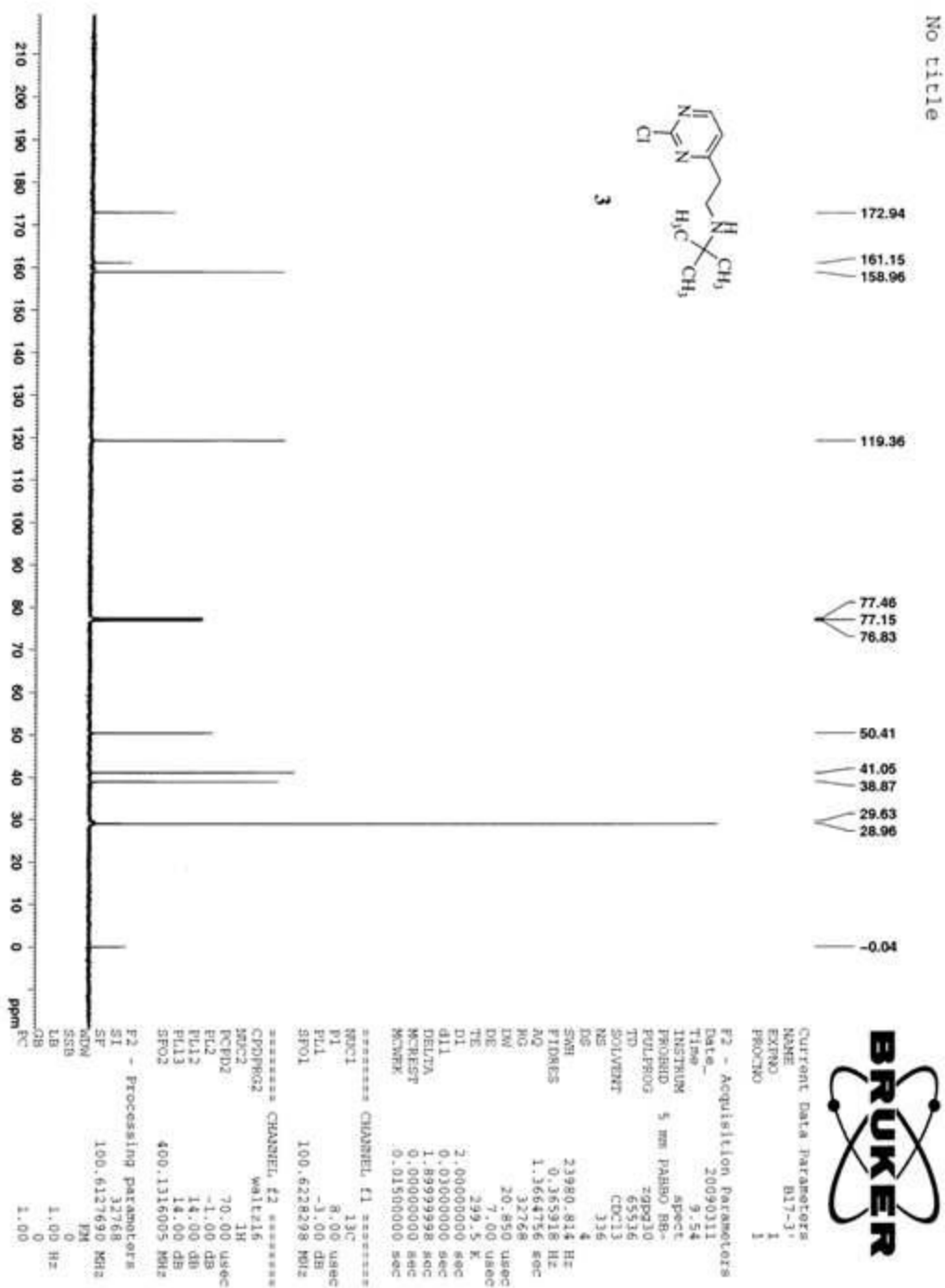
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No title

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DI 1.00000000 sec

MCPEST 0.00000000 sec

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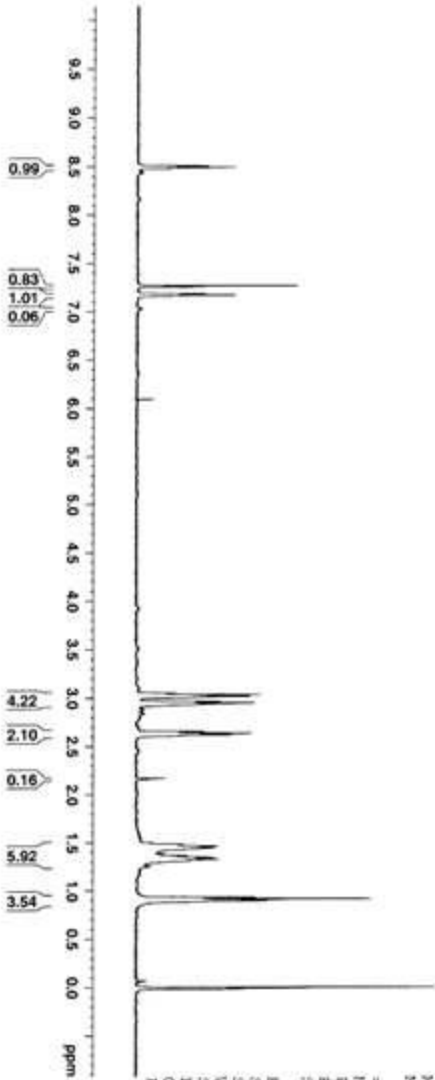
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DE 7.00 usec  
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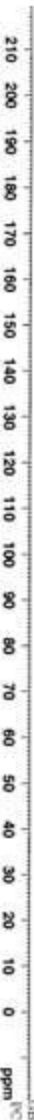
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PL12 14.00 dB  
PL13 14.00 dB  
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GB 0  
PC 1.40





No title

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77.35  
77.03  
76.72  
51.87  
47.04  
35.43  
11.70



Current Data Parameters  
NAME B07-S-Cl3  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters

Date\_ 20090310  
Time 17.06  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 512  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 2608  
EX 20.850 usec  
DE 7.00 usec  
TE 301.3 K  
D1 2.0000000 sec  
d11 0.0100000 sec  
DELTA 1.8999998 sec  
PCREST 0.0000000 sec  
MCNPR 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.628298 MHz

===== CHANNEL f2 =====  
CROSSPO2  
WALTZ16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 dB  
PL12 14.00 dB  
PL13 14.00 dB  
SFO2 400.1316095 MHz

F2 - Processing Parameters  
SI 32768  
SF 100.612590 MHz  
WDW EM  
SSB 0  
LB 1.00 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



No title



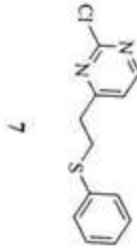
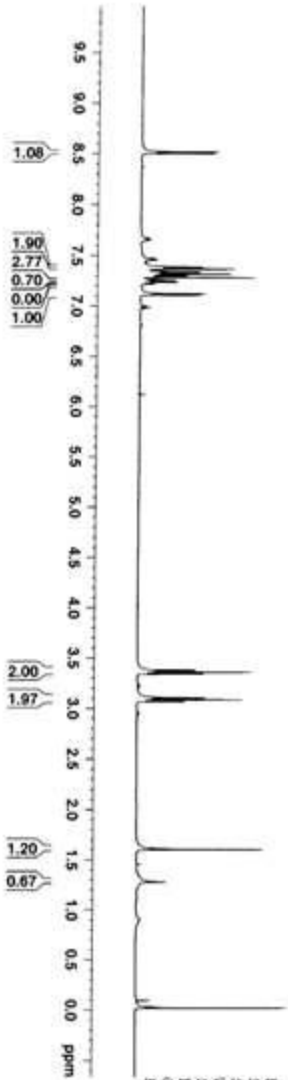
Current Data Parameters  
NAME B26-S  
EXPNO 1  
PROCNO 1

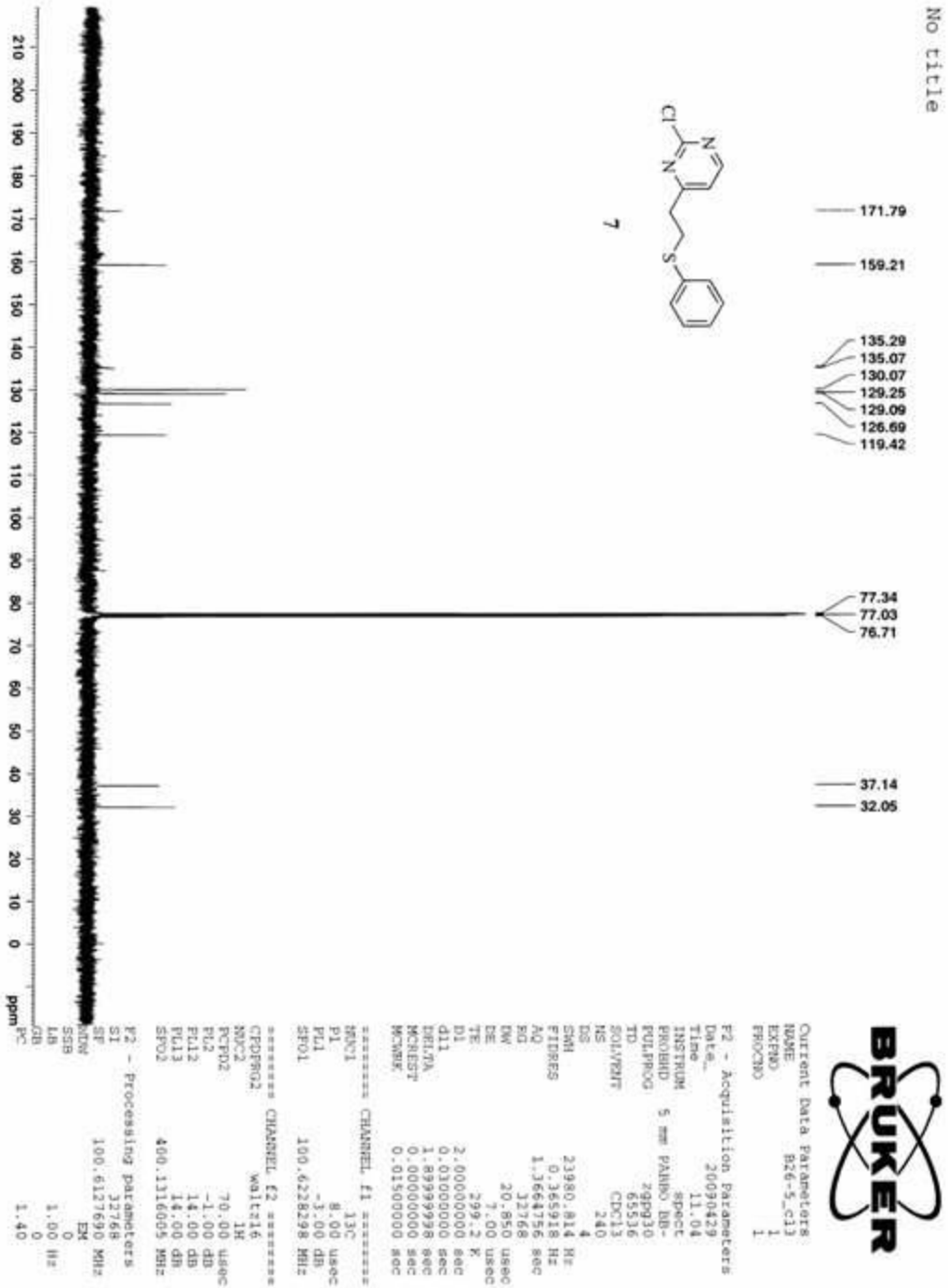
F2 - Acquisition Parameters

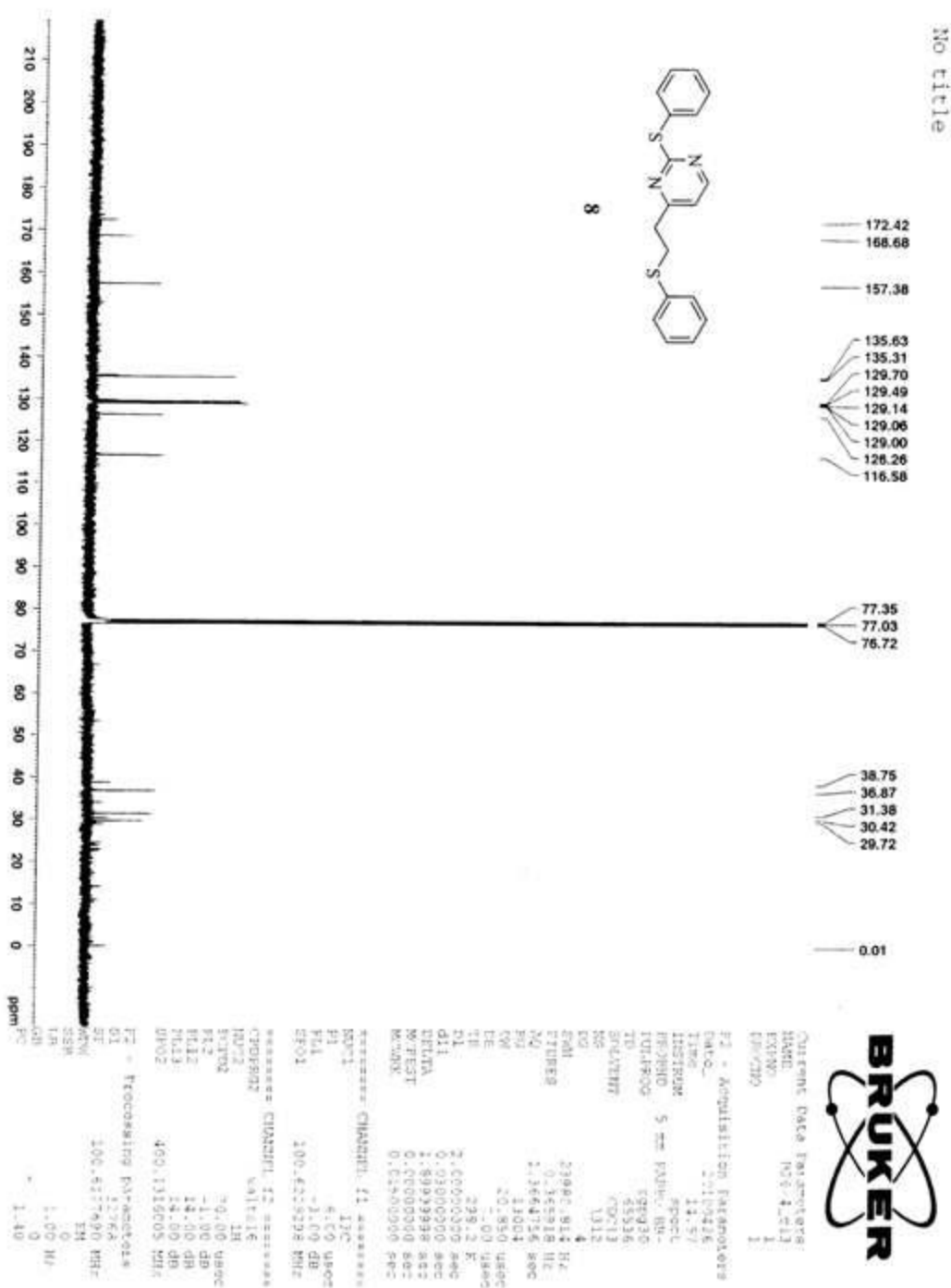
Date\_ 20090429  
Time 10.43  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584293 sec  
RG 362  
DE 60.400 usec  
TE 298.7 K  
DI 1.00000000 sec  
MCREST 0.00000000 sec  
MCWPR 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.80 usec  
PL 0.00 dB  
SFO1 400.1324710 MHz

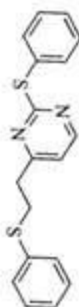
F2 - Processing parameters  
SI 32768  
SF 400.130000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



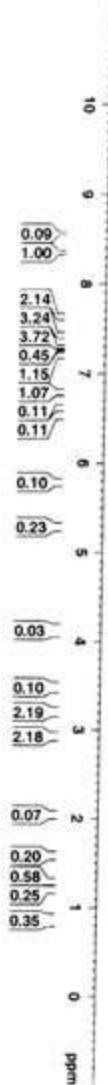




No title



8



Current Data Parameters  
NAME: 826-4(2)  
EXPNO: 1  
PROCNO: 1

F2 - Acquisition Parameters  
Date\_: 20090518  
Time: 11.34  
INSTRUM: spect  
PROBHD: 5 mm PABBO BB-  
PULPROG: zg30  
TD: 65536  
SOLVENT: CDCl<sub>3</sub>  
NS: 16  
DS: 2  
SWH: 8379.146 Hz  
FIDRES: 0.12614 Hz  
AQ: 1.945421 sec  
RG: 203.2  
DE: 60.400 usec  
TE: 298.2 K  
DI: 1.00000000 sec  
MCHEST: 0.00000000 sec  
MCHP2: 0.01000000 sec

===== CHANNEL f1 =====  
NUC1: 1H  
P1: 12.80 usec  
PL1: 0.00 dB  
SFO1: 400.134720 MHz

F2 - Processing parameters  
SI: 32768  
SF: 400.136104 MHz  
WDW: EM  
SSB: 0  
LB: 0.30 Hz  
GB: 0  
PC: 1.00



No title

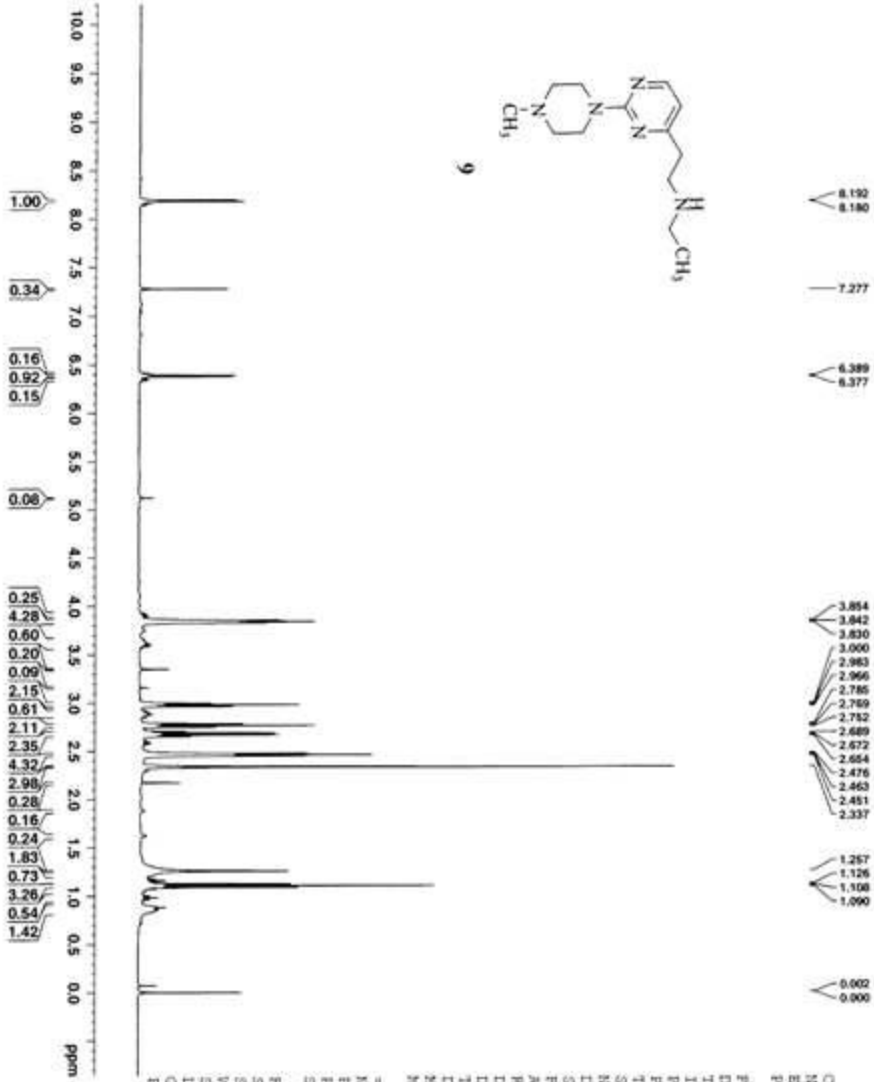


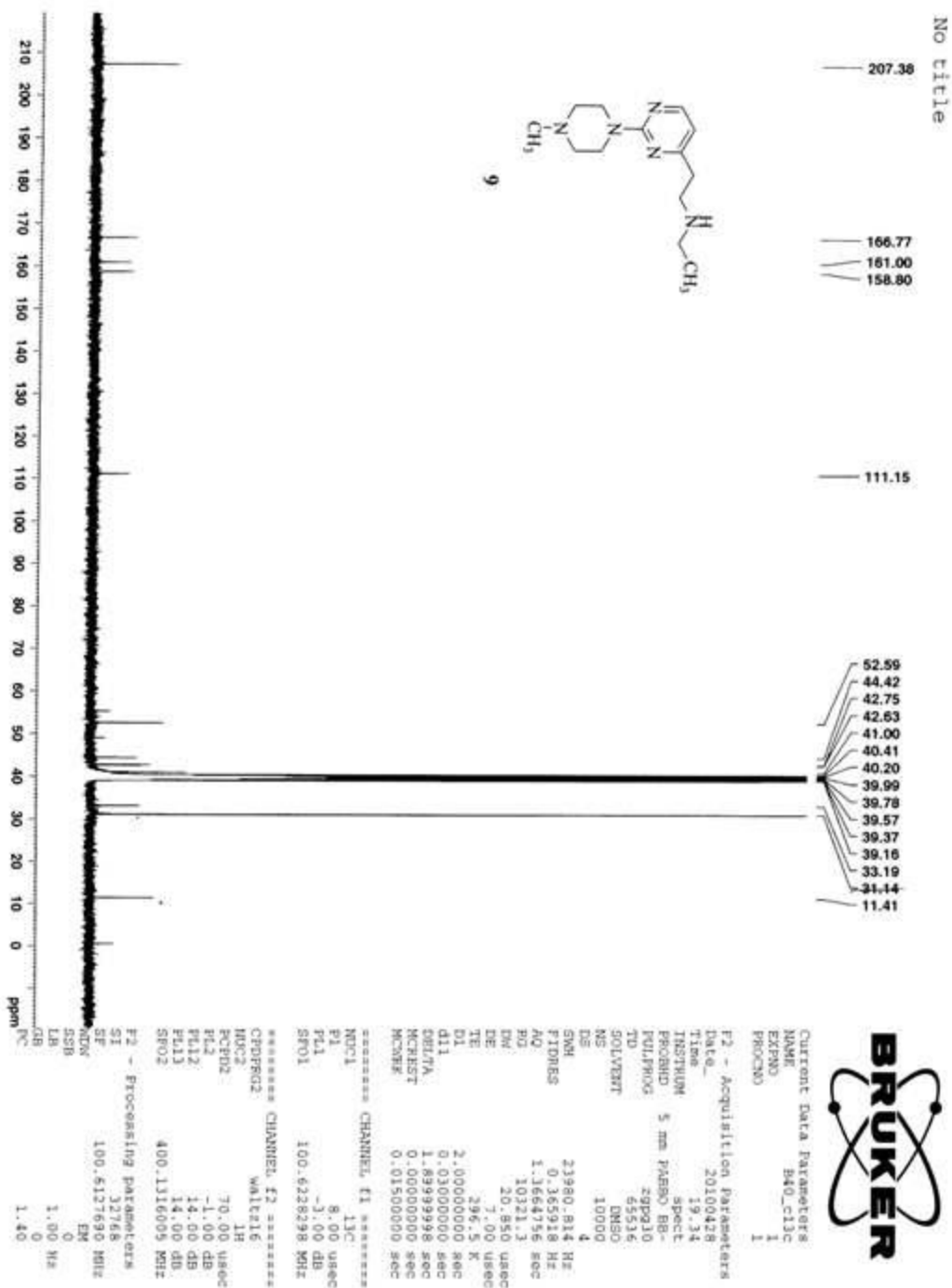
Current Data Parameters  
NAME: B40-5  
EXPNO: 1  
PROCNO: 1

F2 - Acquisition Parameters  
Date\_: 20090505  
Time: 12.05

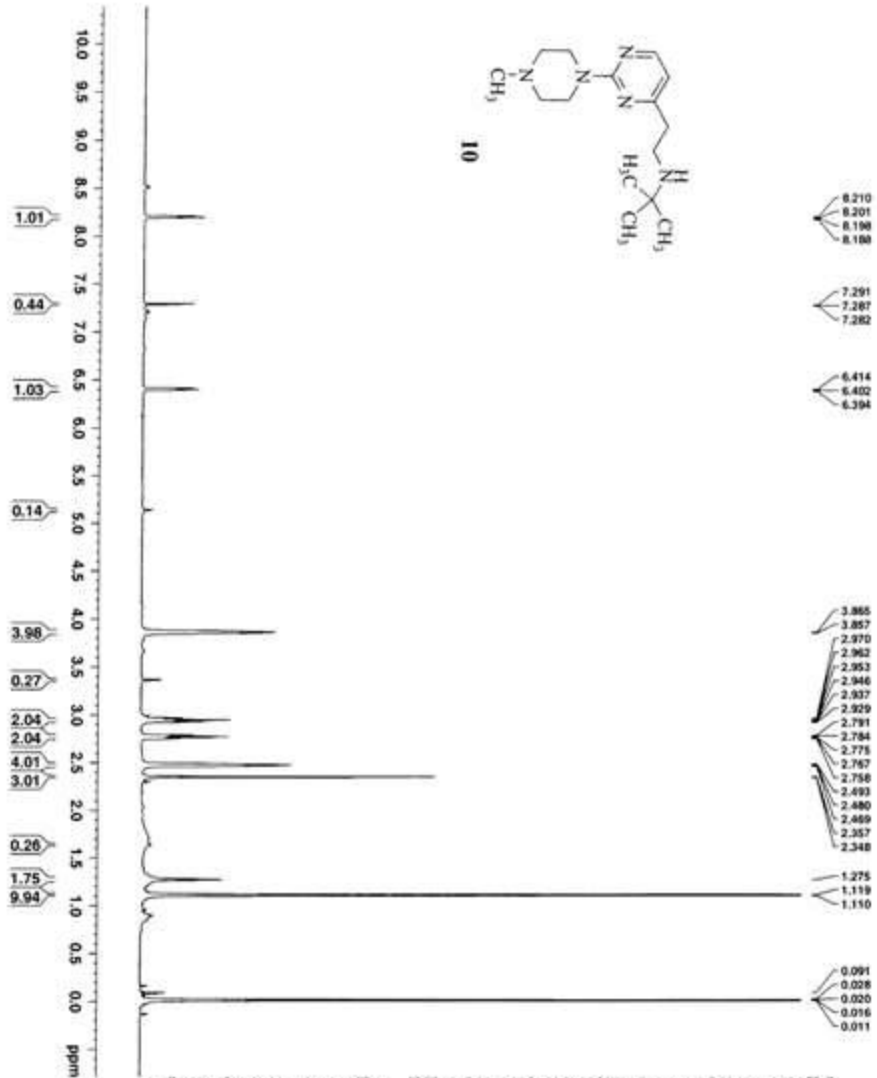
INSTRUM: spect  
PROBHD: 5 mm PABBO BB-  
PULPROG: zg30  
TD: 65536  
SOLVENT: CDCl3  
NS: 16  
DS: 2  
SWH: 8378.146 Hz  
FIDRES: 0.12614 Hz  
AQ: 3.9584243 sec  
RG: 128  
TM: 60.400 usec  
DE: 7.00 usec  
TE: 298.2 K  
D1: 1.00000000 sec  
MCREST: 0.00000000 sec  
MCMX: 0.01500000 sec

===== CHANNEL f1 =====  
NUC1: 1H  
P1: 12.80 usec  
PL1: 0.00 dB  
SFO1: 400.132410 MHz  
F2 - Processing Parameters  
SI: 32768  
SF: 400.130053 MHz  
WDW: EM  
SSB: 0  
LB: 0.30 Hz  
GB: 0  
PC: 1.00





No title



Current Data Parameters  
NAME: B19-2  
EXPNO: 1  
PROCNO: 1

F2 - Acquisition Parameters  
Date\_ : 20090317  
Time : 15:41

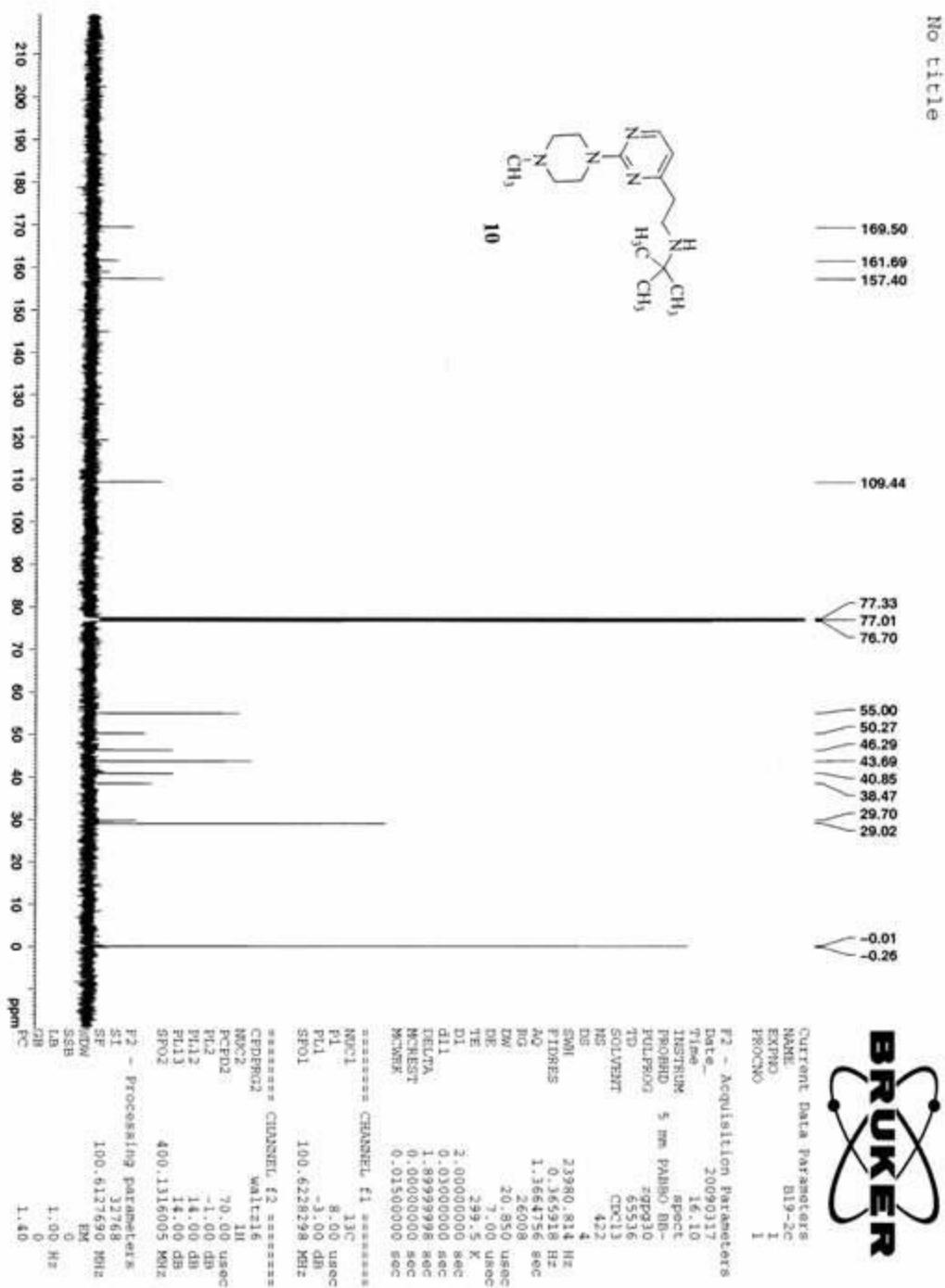
INSTRUM : spect  
PROBHD : 5 mm PABBO BB-  
PULPROG : zg30  
TD : 65536  
SOLVENT : CDCl3  
NS : 16  
DS : 2

SWH : 8278.146 Hz  
FIDRES : 0.126214 Hz  
AQ : 3.9584243 sec  
RG : 128

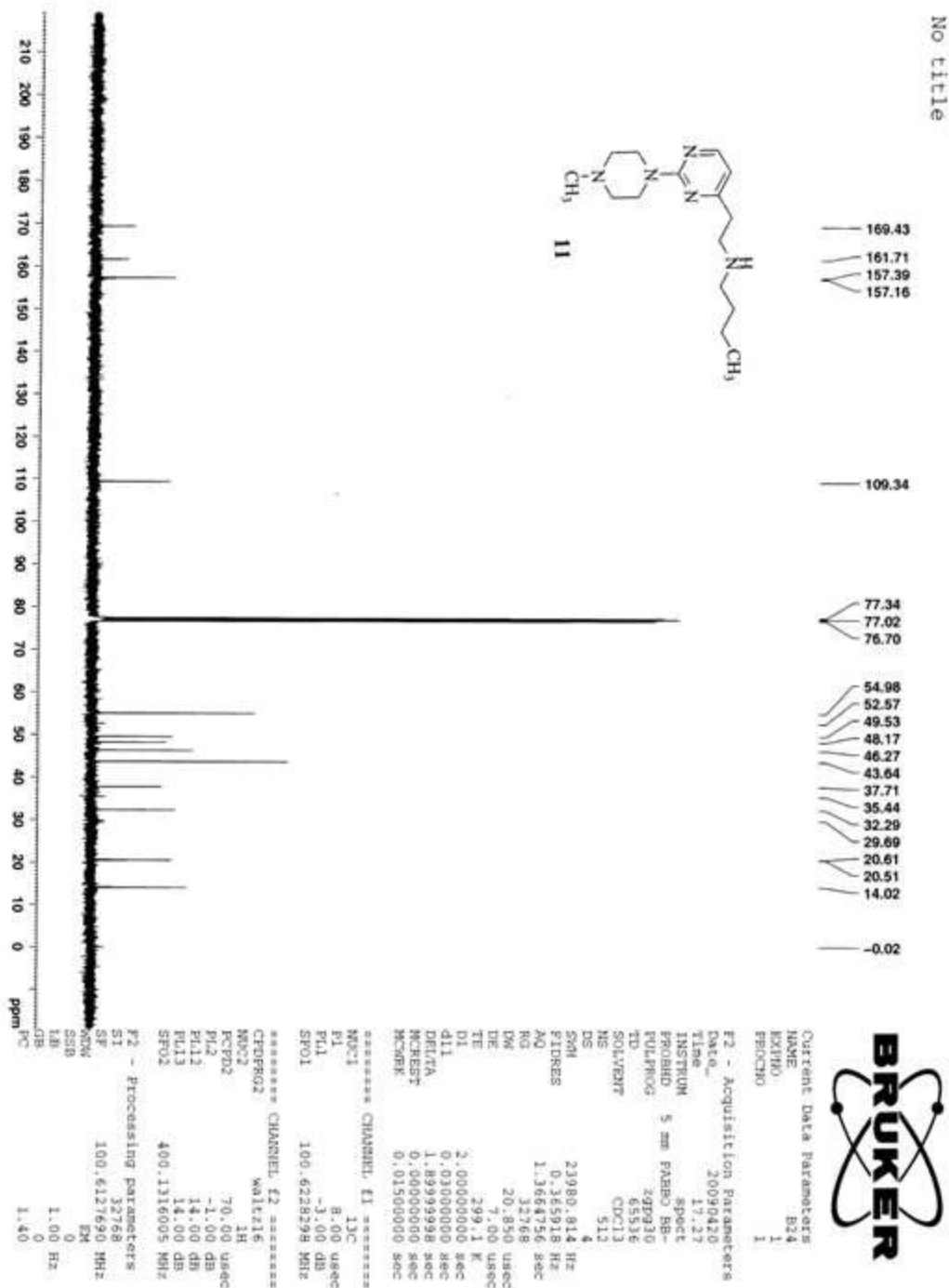
DE : 60.400 usec  
TE : 298.9 K  
D1 : 1.00000000 sec  
MCREST : 0.00000000 sec  
M-PRK : 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 : 1H  
P1 : 12.80 usec  
PL1 : 0.00 dB  
SFO1 : 400.1324710 MHz

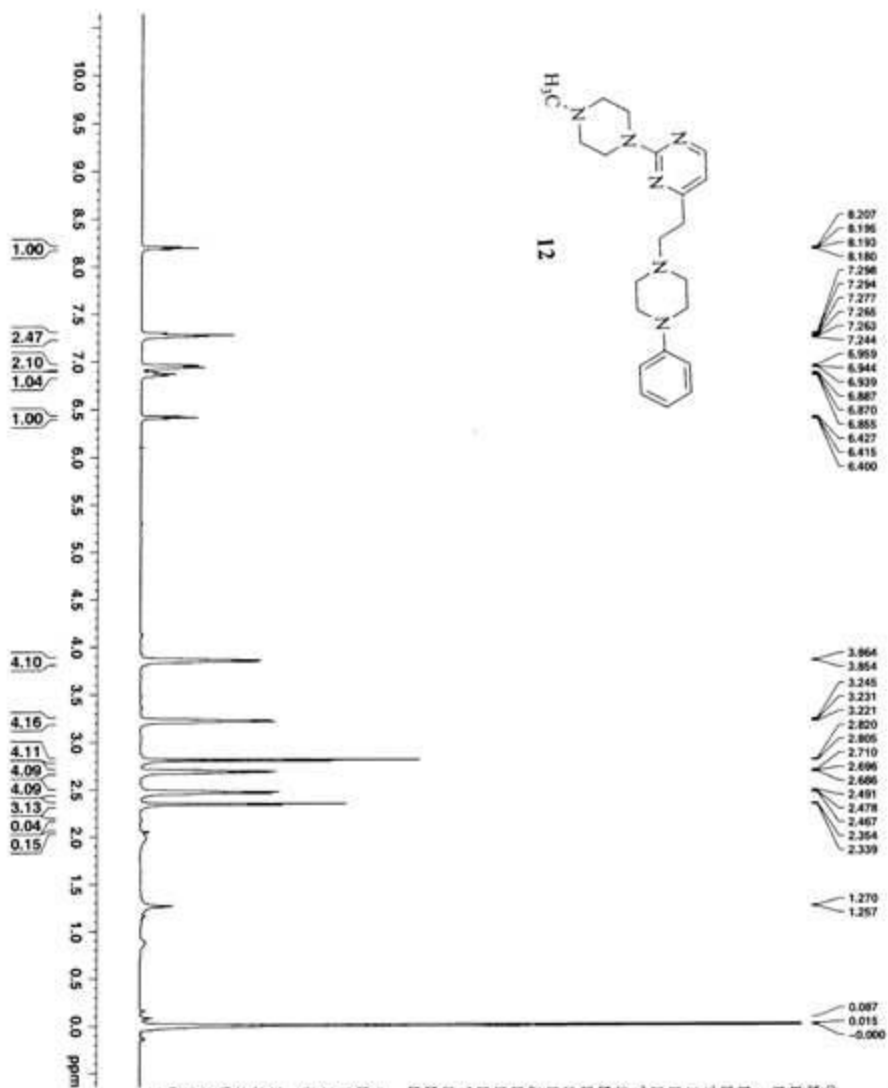
F2 - Processing parameters  
SI : 12768  
SF : 400.1300000 MHz  
WDW : EM  
SSB : 0  
LB : 0.30 Hz  
GB : 0  
PC : 1.00







No title



Current Data Parameters  
NAME B18-2  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090311  
Time 17.12

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9588241 sec  
RG 90.5  
PD 60.400 usec  
DE 7.00 usec  
TE 298.7 K  
D1 1.00000000 sec  
MCREST 0.00000000 sec  
MCBRK 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.1300073 MHz  
WDW EX  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

No title



Current Data Parameters  
NAME R39-2  
EXPNO 1  
PROCNO 1

## F2 - Acquisition Parameters

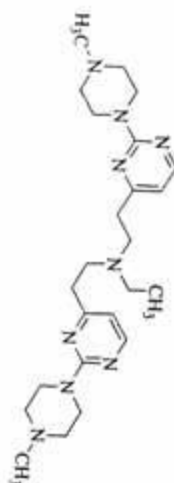
Date\_ 20090502  
Time 16.53  
INSTRUM spect  
PROBHD 5 mm PABO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 228.1  
IN 60.400 usec  
DE 7.00 usec  
TE 298.7 K  
D1 1.00000000 sec  
MCREST 0.00000000 sec  
MCPRK 0.01500000 sec

## ===== CHANNEL f1 =====

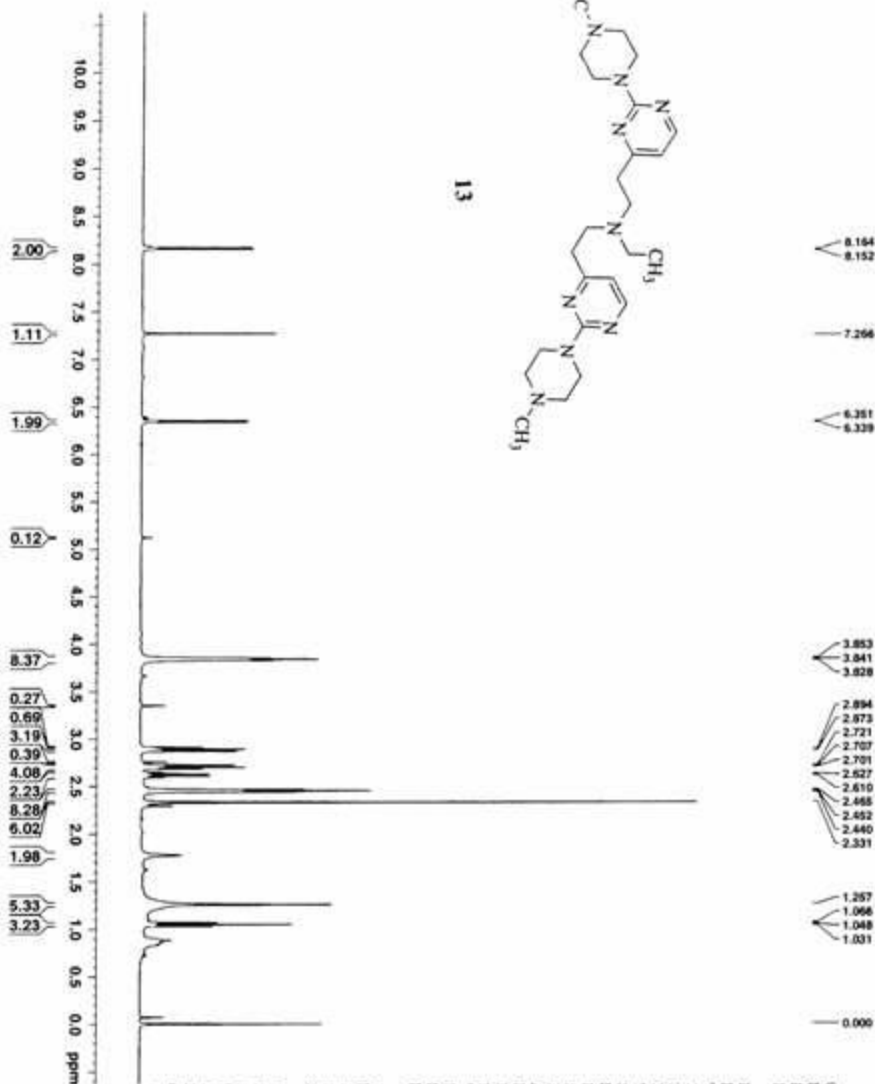
MUCL 1M  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

## F2 - Processing parameters

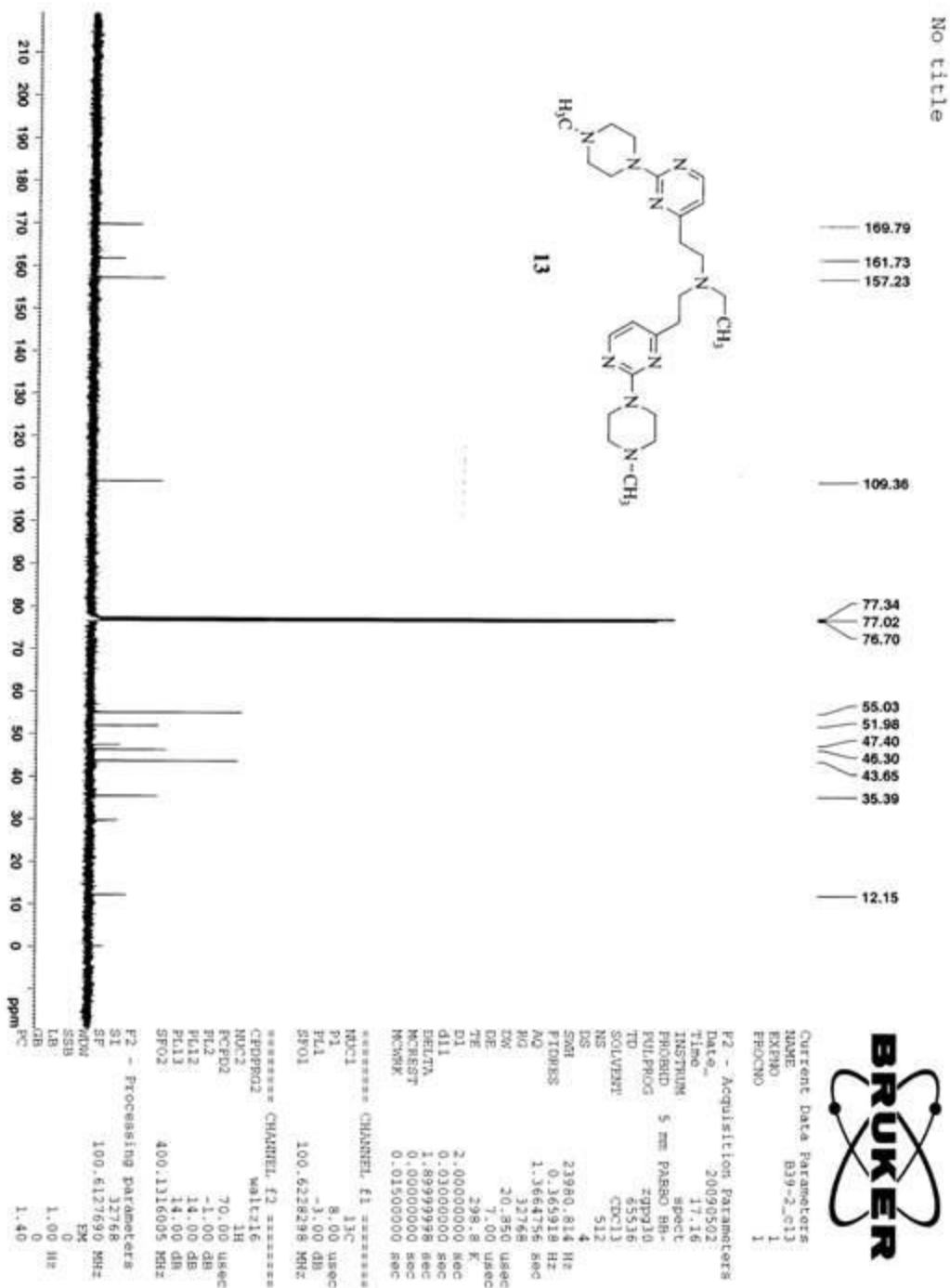
SI 32768  
SF 400.130073 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



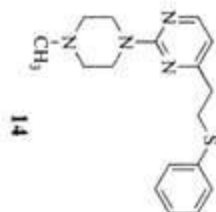
13







No title



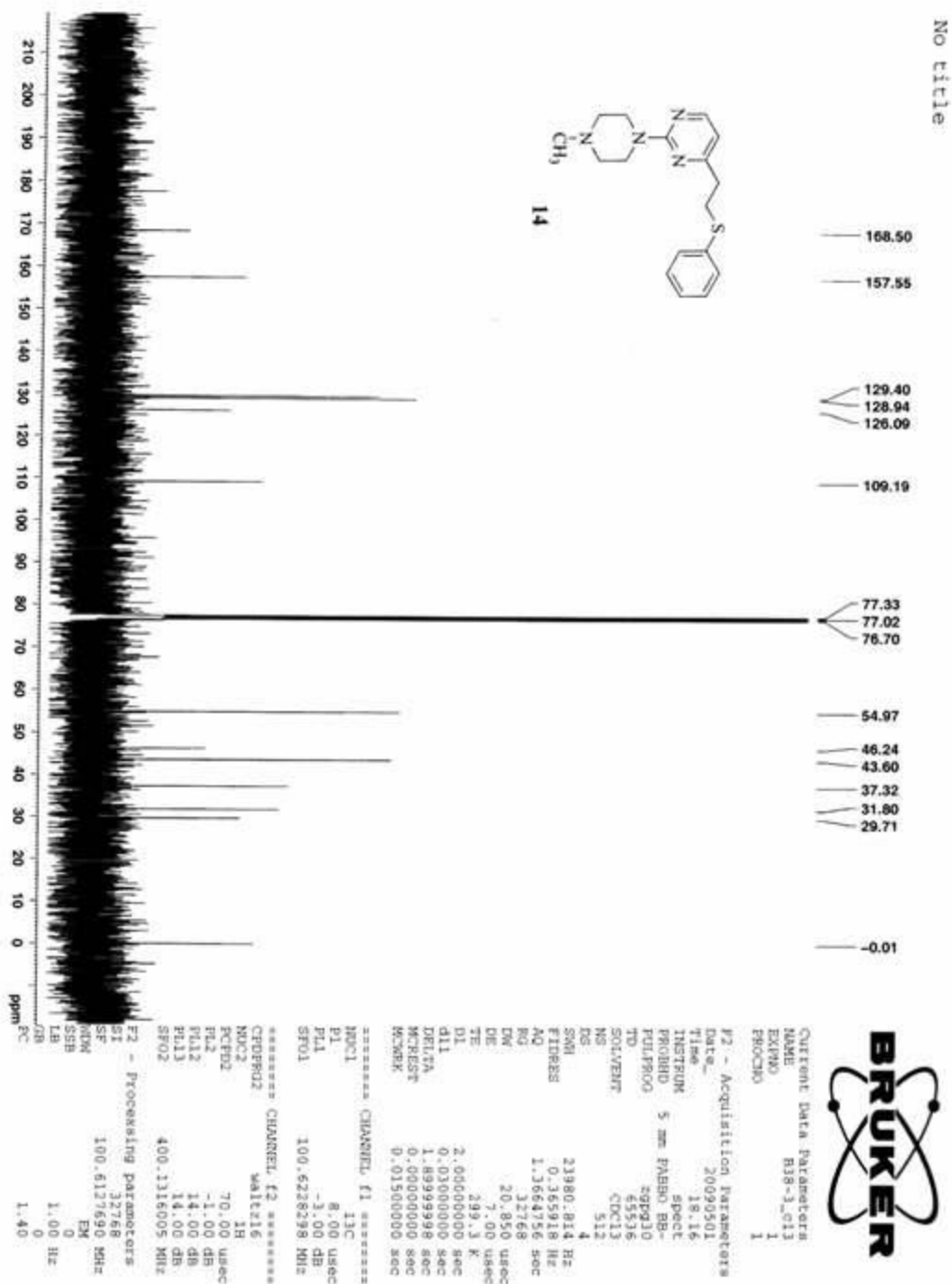
Current Data Parameters  
NAME B18-3  
EXNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090501  
Time 17.43

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.12614 Hz  
AQ 3.958423 sec  
RG 382  
DE 60.400 usec  
TE 298.9 K  
D1 1.00000000 sec  
MCREST 0.00000000 sec  
MCMRG 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.130093 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



No title



5.293

1.823

1.252

0.000



Current Data Parameters  
NAME B1-4  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090526  
Time\_ 10.44

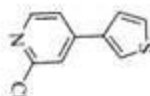
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2

SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.9584243 sec  
RG 143.7

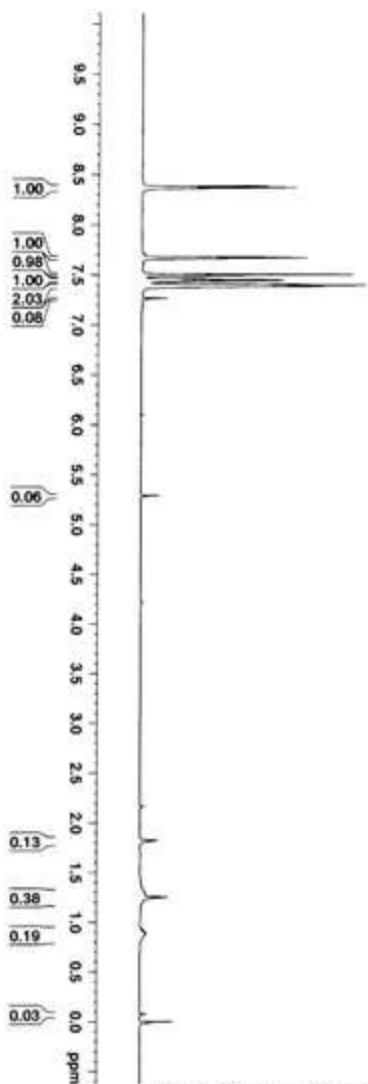
DE 60.400 usec  
TE 297.3 K  
D1 1.00000000 sec  
MCREG 0.00000000 sec  
MCNRM 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.130086 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



15



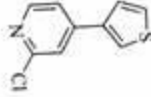
No title

152.36  
150.13  
145.73  
138.18  
127.50  
125.59  
124.05  
121.13  
119.66

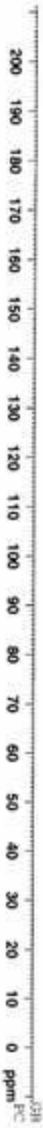
77.34  
77.02  
76.70



0.00



15



Current Data Parameters  
NAME R41-4-cl3  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090604  
Time\_ 13.15

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 447  
DS 4

SWH 23980.814 Hz  
FIDRES 0.165918 Hz  
AQ 1.1664756 sec  
RG 32768

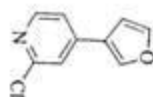
EW 20.850 usec  
DE 7.00 usec  
TE 298.1 K  
D1 3.00000000 sec  
d11 0.03000000 sec  
DELTA 1.88999998 sec  
MCREST 0.00000000 sec  
MCNTRK 0.01500000 sec

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

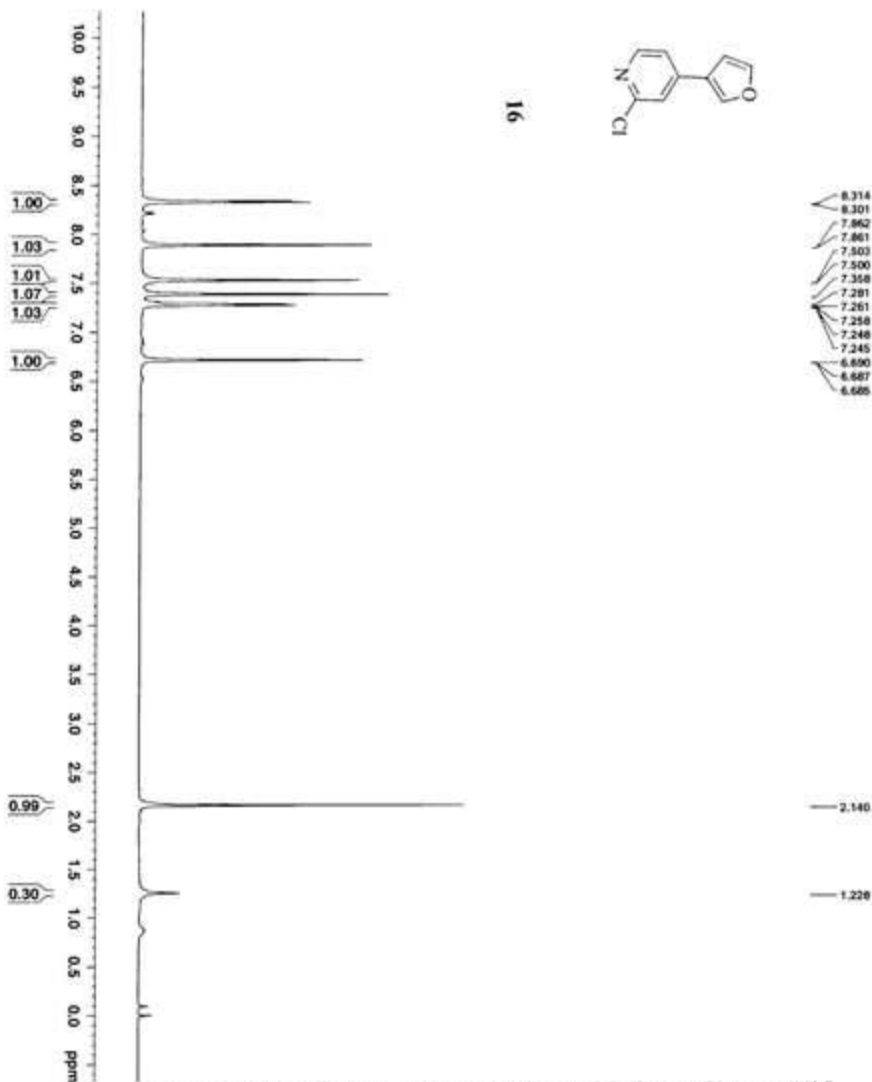
===== CHANNEL f2 =====  
CROSSPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 dB  
PL12 14.00 dB  
PL13 14.00 dB  
SFO2 400.1316005 MHz

F2 - Processing parameters  
SI 32768  
SF 100.6127690 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

No title



16



```
Current Data Parameters
NAME          B49-4
EXPMO         1
PROCNO        1
```



```

P3 - Acquisition Parameters
Date_ 20090618
Time 18:24

```

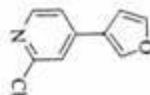
INSTRUM	spec
PROBHD	5 mm PABBO BR-
PULPROG	2930
TD	65536
SOLVENT	CDCl <sub>3</sub>
MS	CDCl <sub>3</sub>

LOS	678.146 Hz	
SAN	0.146314 Hz	
FIGURES	3.95424 sec	
AO		65
RG		
DF	60.400 msec	
DE	7.00 msec	
TE	297.6 K	
DI	1.00000000 sec	
MCNEST	0.00000000 sec	
MCNRK	0.01500000 sec	

```
===== CHANNEL #1 =====
MOC1      1M
P1         12.80 usec
PL1        0.00 db
SFO1       400.1324710 MHz
```

P2 - Processing parameters	
SI	32768
SP	400.1300000 MHz
MDM	Hz
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

No title



16

152.30  
150.06  
144.67  
143.14  
140.87

123.34  
120.58  
119.12

108.15

77.35  
77.04  
76.72



Current Data Parameters  
NAME 849\_c13  
EXPTD 1  
PROCNO 1

F2 - Acquisition Parameters

Date\_ 20090622  
Time 13.16  
INSTRUM spect  
PROBHD 5 mm PABBO BH-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 65  
DS 4

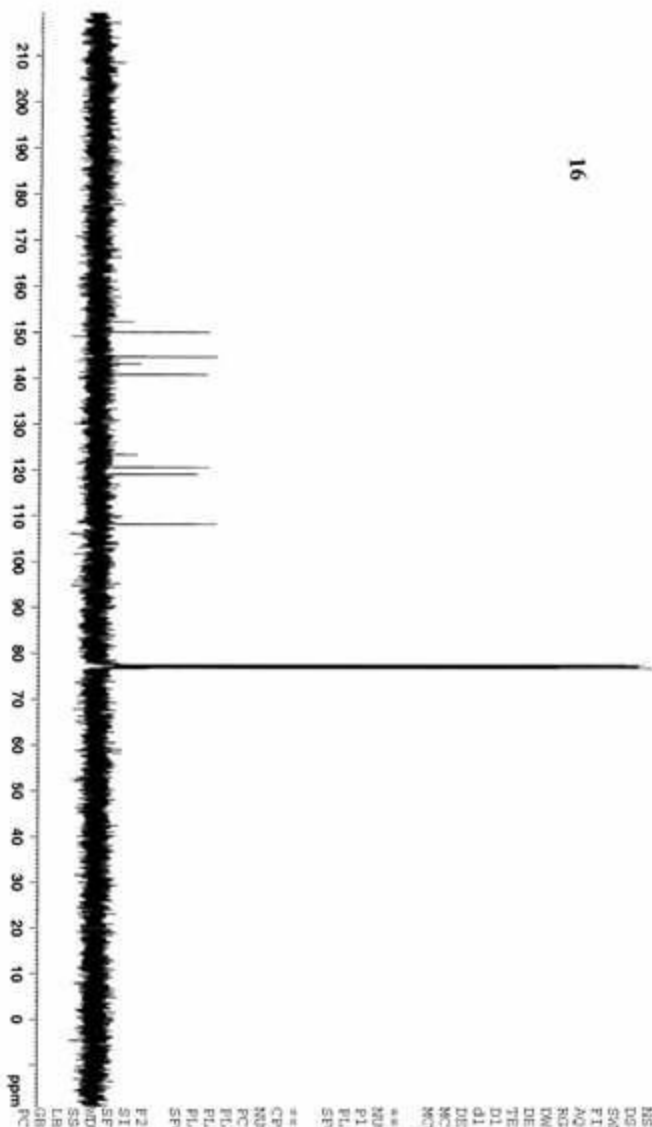
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 32768  
RW 20.850 usec  
DE 7.00 usec  
TE 297.8 K

DL 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
MCREST 0.00000000 sec  
MCRMK 0.01500000 sec

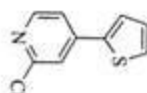
\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228298 MHz

\*\*\*\*\* CHANNEL f2 \*\*\*\*\*  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 dB  
PL12 14.00 dB  
PL13 14.00 dB  
SFO2 400.1316005 MHz

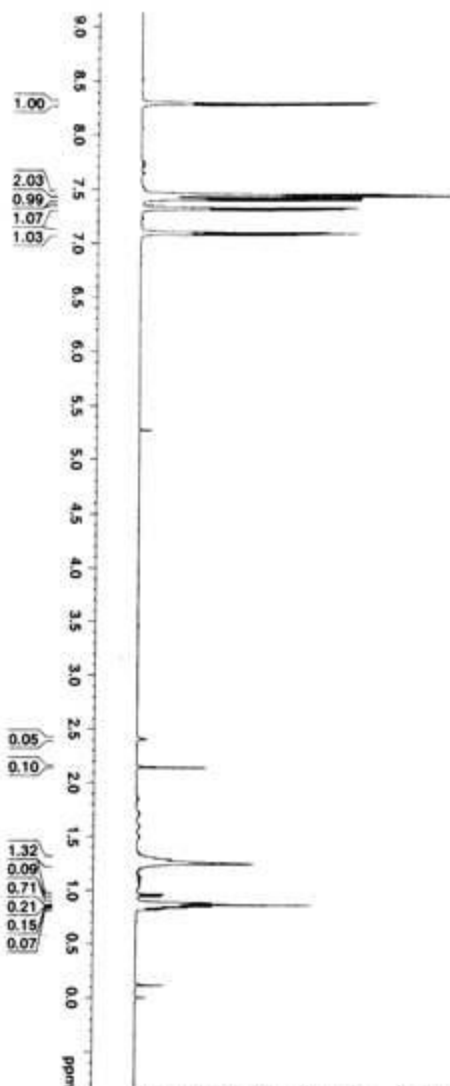
F2 - Processing parameters  
SI 32768  
SF 100.6127690 MHz  
RG 65536  
SFO 400.1316005 MHz  
LB 0  
GB 0  
PC 1.40



No title



17



Current Data Parameters  
NAME B92-4/5  
EXTRNO 1  
PROCNO 1

P2 - Acquisition Parameters  
Date\_ 20090708  
Time 11.41  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
FIDRES 0.12614 Hz  
AQ 3.958421 sec  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.12614 Hz  
AQ 3.958421 sec  
RG 328.5  
IN 60.400 usec  
DE 7.00 usec  
TE 297.5 K  
D1 1.00000000 sec  
MCREST 0.00000000 sec  
MCMRK 0.01500000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

P2 - Processing Parameters  
SI 32  
SF 400.1299912 MHz  
WDW EM  
SSB 0  
LB 0.20 Hz  
GB 0  
PC 1.00





No title

152.39  
150.13  
144.41  
139.65  
128.63  
128.12  
126.23  
120.05  
118.75



Current Data Parameters  
NAME RS2\_c13b1  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20100428

Time 9.11

INSTRUM spect

PROBHD 5 mm PABO BB-

PULPROG zgpg30

TD 65536

SOLVENT CCl3

NS 127

DS 4

SWH 23980.814 Hz

FIDRES 0.365918 Hz

AQ 1.3664756 sec

RG 32768

IN 20.850 usec

DE 7.00 usec

TE 296.9 K

DI 2.0000000 sec

d11 0.0300000 sec

DELTA 1.8999998 sec

MCREST 0.0000000 sec

MCRM 0.0150000 sec

===== 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 -1.00 dB

PL12 14.00 dB

PL13 14.00 dB

SFO2 400.1316005 MHz

F2 - Processing Parameters

SI 32768

SF 100.6127690 MHz

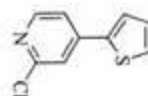
WDW EM

SSB 0

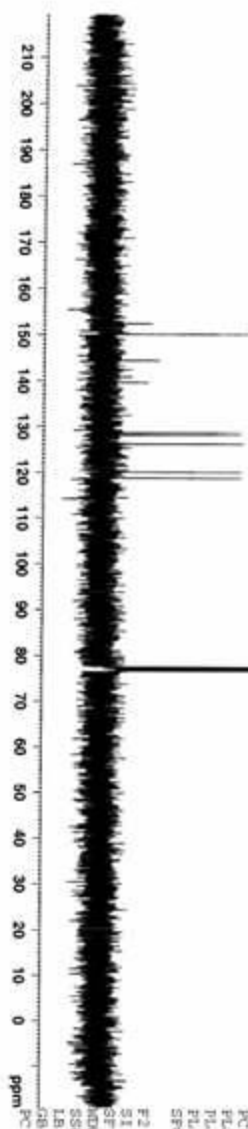
LB 1.00 Hz

GB 0

PC 1.40



17



No title

8.198  
8.186  
8.003  
7.963  
7.377  
7.290  
6.832  
6.817  
5.274  
3.619  
3.608  
3.596  
3.555  
3.370  
3.357  
3.346  
2.701  
2.544  
2.532  
2.520  
2.291  
2.278  
2.242  
2.206  
1.256  
0.001



Current Data Parameters  
NAME B48-1  
EXNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090618  
Time\_ 11.38

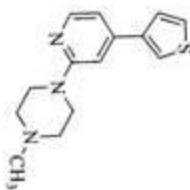
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2

SWH 6278.146 Hz  
FIDRES 0.12614 Hz  
AQ 3.9584243 sec  
RG 45.1

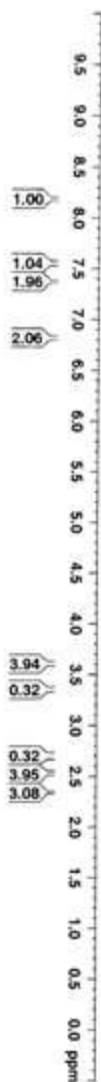
DE 60.400 usec  
TE 297.7 K  
DI 1.00000000 sec  
MCREST 0.00000000 sec  
MTRK 0.01500000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.1299995 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

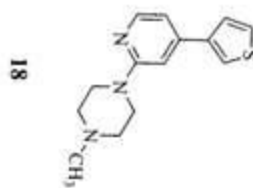


18



No title

160.22  
148.45  
144.31  
140.74  
126.59  
125.99  
122.44  
111.52  
104.14  
77.46  
77.15  
76.83  
54.93  
46.23  
45.32



Current Data Parameters  
NAME B48\_C13  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090622  
Time 12:57

INSTRUM spect  
PROBHD 5 mm PABBO BR-

PULPROG zgpg30  
TD 65536

SOLVENT CDCl3  
NS 180

DS 4  
SWH 23980.814 Hz

FIDRES 0.365918 Hz  
AQ 1.3664756 sec

RG 20642.5  
RW 20.850 usec

DE 7.00 usec  
TE 297.9 K

DI 2.00000000 sec  
d11 0.01000000 sec

DELTA 1.89999998 sec  
WREST 0.00000000 sec

MCPRK 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec

P2 -1.00 dB  
SFO1 100.6228298 MHz

===== CHANNEL f2 =====  
CPOPRG2 waltz16  
NUC2 1H

PWPRG2 70.00 usec  
PL2 -1.00 dB

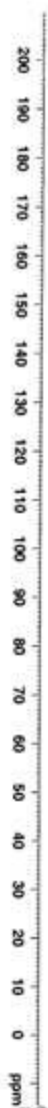
PL12 14.00 dB  
PL13 14.00 dB

SFO2 400.1316005 MHz

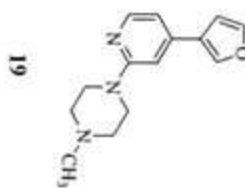
F2 - Processing parameters  
SI 32768

SF 100.6127690 MHz  
RG 0

AW 0  
SGB 0  
GB 0  
PC 1.40



No title



8.167  
8.155  
8.007  
7.809  
7.489  
7.485  
7.306

5.285

3.609  
3.597  
3.584  
3.562  
3.480  
3.462  
3.442  
3.382  
3.370  
3.367  
2.818  
2.547  
2.535  
2.522  
2.423  
2.390  
2.377  
2.343  
2.301  
2.155  
1.257  
1.220  
1.202  
1.186

0.086  
0.000



Current Data Parameters  
NAME BSI-1  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090624  
Time 13:07

INSTRUM spect  
PROBHD 5 mm PABBO RH-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2

SNH 8278.146 Hz  
FIDRES 0.12614 Hz  
AQ 3.9584241 sec  
RG 40.2

DE 60.400 usec  
TE 297.7 K  
D1 1.00000000 sec  
MCREST 0.00000000 sec  
MCPX 0.01500000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*

NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

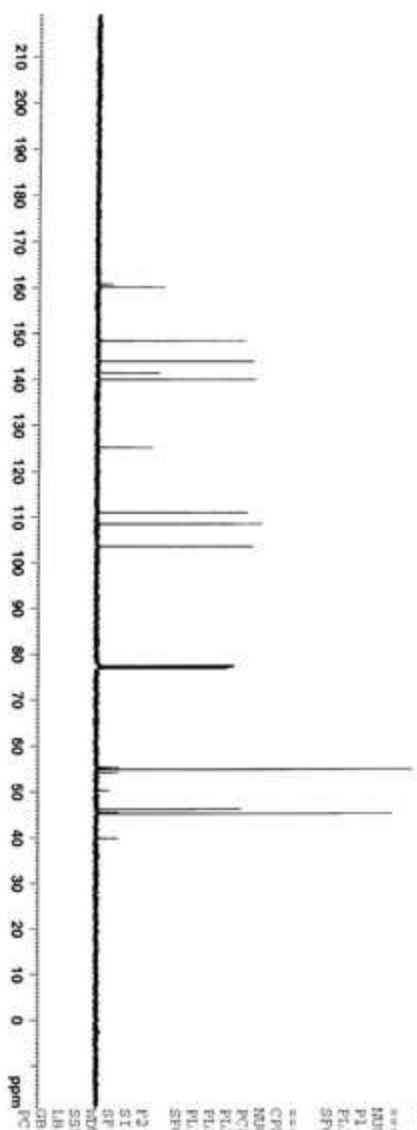
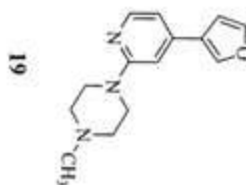
F2 - Processing parameters

SI 32768  
SF 400.1299317 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



No title

160.75  
160.12  
148.35  
143.95  
141.37  
139.97  
125.17  
110.94  
108.46  
103.51  
77.45  
77.14  
76.82  
55.33  
54.87  
54.16  
48.16  
46.08  
45.47  
45.23  
39.80



Current Data Parameters  
NAME BSI-1-Cl1  
EXPO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090624  
Time 13.27

INSTRUM spect

PROBHD 5 mm PABBO BH-

PULPROG zgpg30

TD 65536

SOLVENT CDCl3

NS 106

DS 4

SWH 23980.814 Hz

FIDRES 0.365918 Hz

AQ 1.3664756 sec

RG 32768

WD 20.850 usec

DE 7.00 usec

TE 298.3 K

DL 2.00000000 sec

dll 0.03000000 sec

DELTA 1.89999998 sec

MCREST 0.00000000 sec

MCYRK 0.01500000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*

NUC1 13C

P1 8.00 usec

PL -1.00 dB

SFO1 100.628298 MHz

\*\*\*\*\* CHANNEL f2 \*\*\*\*\*

CPDPRG2 waltz16

NUC2 1H

PCPD2 70.00 usec

PL2 -1.00 dB

PL12 14.00 dB

PL13 14.00 dB

SFO2 400.1316005 MHz

F2 - Processing Parameters

SI 32768

SF 100.6137690 MHz

WDW EM

SGB 0

LH 1.00 Hz

GB 0

1.40

No title

8.188  
8.176  
7.440  
7.433  
7.366  
7.355  
7.285  
7.116  
7.106  
7.104  
7.094  
6.867  
6.854  
6.829

5.296

3.636  
3.624  
3.612  
3.470  
3.362

2.563  
2.550  
2.538  
2.362  
2.301  
2.193

1.267

0.012



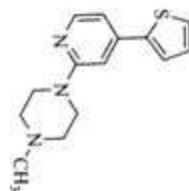
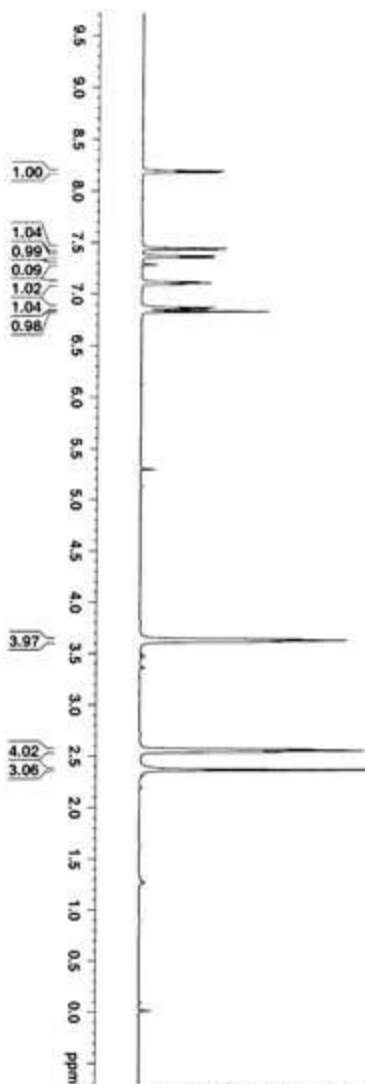
Current Data Parameters  
NAME B67  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090828  
Time 18.34

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2  
SWH 8278.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.958423 sec  
RG 80.6  
EQ 60.400 usec  
DE 7.00 usec  
TE 297.8 K  
D1 1.00000000 sec  
MCREST 0.00000000 sec  
MCWRR 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



No title

160.14  
148.52  
142.84  
142.50  
128.12  
126.31  
124.76  
110.65  
103.23  
77.41  
77.09  
76.77  
54.93  
46.24  
45.27



Current Data Parameters  
NAME B67\_c13  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters

Date\_ 20090831  
Time 11.56  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 160  
DS 4  
SFO 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.3664756 sec  
RG 26008  
FW 20.850 usec  
DE 7.00 usec  
TE 397.9 K  
D1 3.00000000 sec  
d11 0.03000000 sec  
DELTA 1.80999998 sec  
MCHEST 0.00000000 sec  
MCHFR 0.01500000 sec

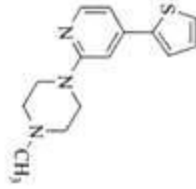
\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 13C  
P1 8.00 usec  
PL1 -1.00 db  
SFO1 100.628298 MHz

\*\*\*\*\* CHANNEL f2 \*\*\*\*\*  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 db  
PL12 14.00 db  
PL13 14.00 db  
SFO2 400.1316005 MHz

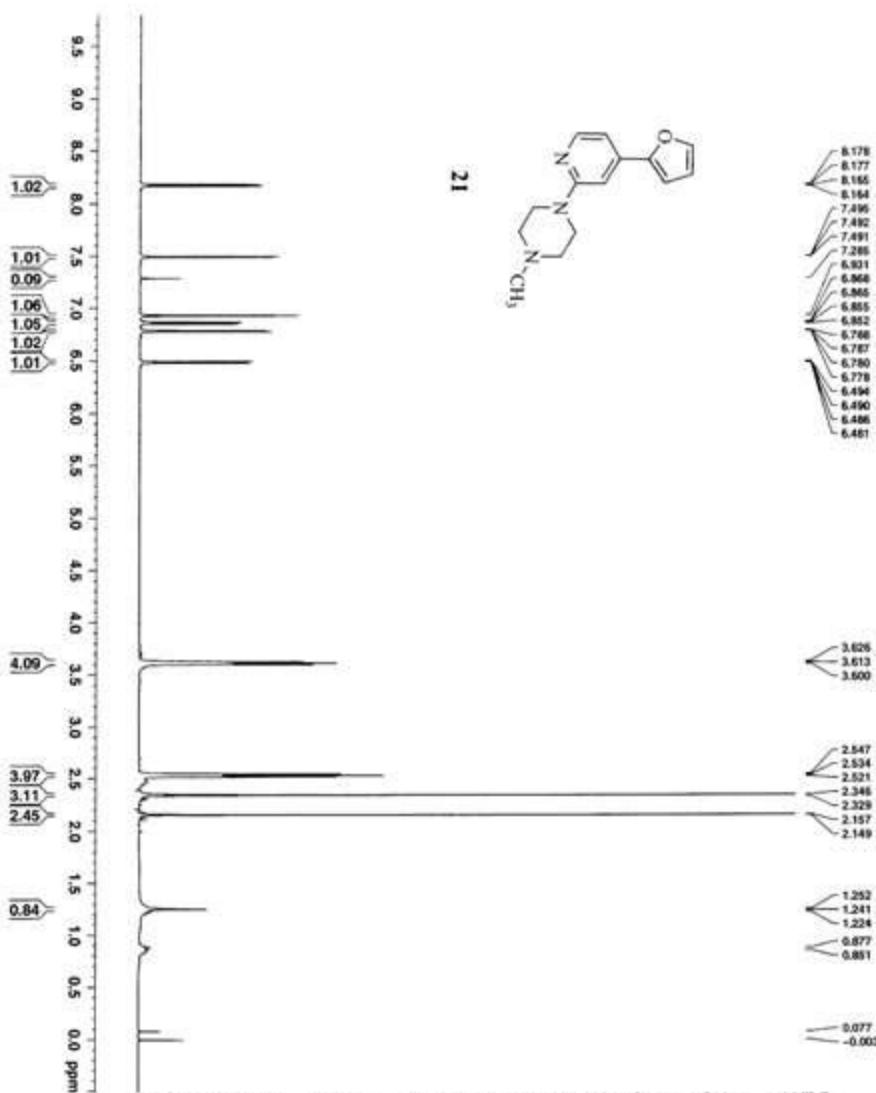
F2 - Processing parameters  
SI 32768  
SF 100.6127690 MHz  
RG 0  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.00

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

20



No title



Current Data Parameters	
NAME	B72-5
EXPNO	1
PROCNO	1

P2 - Acquisition Parameters  
Date\_ 20091022

INSTRUM	Spec
PRODUCED	PRODUCED

PULPRICG	Eg30
----------	------

SOLVENT	CDCl <sub>3</sub>
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
13	13
14	14
15	15
16	16
17	17
18	18
19	19
20	20
21	21
22	22
23	23
24	24
25	25
26	26
27	27
28	28
29	29
30	30
31	31
32	32
33	33
34	34
35	35
36	36
37	37
38	38
39	39
40	40
41	41
42	42
43	43
44	44
45	45
46	46
47	47
48	48
49	49
50	50
51	51
52	52
53	53
54	54
55	55
56	56
57	57
58	58
59	59
60	60
61	61
62	62
63	63
64	64
65	65
66	66
67	67
68	68
69	69
70	70
71	71
72	72
73	73
74	74
75	75
76	76
77	77
78	78
79	79
80	80
81	81
82	82
83	83
84	84
85	85
86	86
87	87
88	88
89	89
90	90
91	91
92	92
93	93
94	94
95	95
96	96
97	97
98	98
99	99
100	100

522

0-126314

3,7504675  
65  
65

2008	60,500
2007	7,000

716	295.9
717	1.00000000

MCNREST	0.0000000000
MCNREST	0.0100000000

**Figure 4**

NUC1 1M

PLI 0.00

[illegible]

	Accounting	Paid
67		32768

DATE \_\_\_\_\_  
WITH \_\_\_\_\_  
FROM \_\_\_\_\_

2.75	0
2.75	0.30
2.75	0

男 女

1

1



No title

160.08  
152.27  
148.32  
143.12  
138.84  
  
111.87  
108.42  
107.90  
100.91  
  
77.43  
77.11  
76.79  
  
54.92  
46.23  
45.24  
  
29.70



Current Data Parameters  
NAME 872.c13  
EXNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20091023  
Time 11.45

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 434  
DS 4

SWH 23980.814 Hz  
FIDRES 0.165918 Hz  
AQ 1.1664756 sec  
RG 13004  
IN 20.850 usec  
DE 7.00 usec  
TE 296.2 K

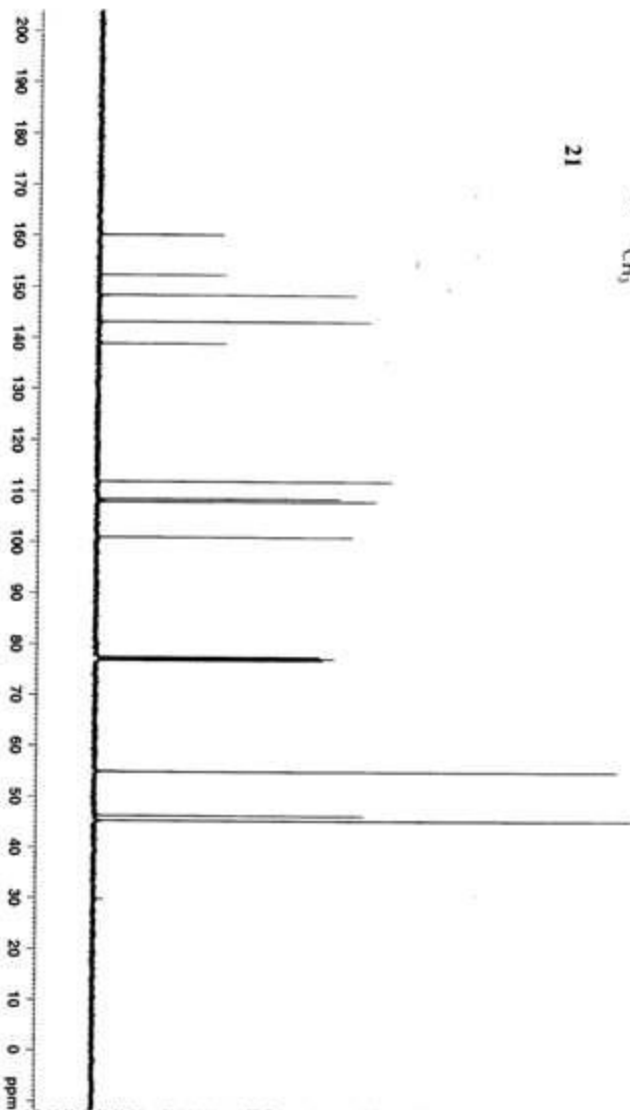
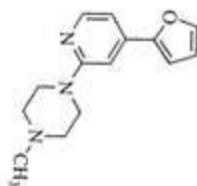
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
MCREST 0.00000000 sec  
MCWPR 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -1.00 dB  
SFO1 100.628298 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 dB  
PL12 14.00 dB  
PL13 14.00 dB  
SFO2 400.1316005 MHz

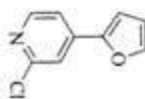
F2 - Processing Parameters  
SI 32768  
SF 100.6127690 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.00

21



No title

8.234  
8.233  
8.221  
8.219  
7.447  
7.446  
7.443  
7.441  
7.404  
7.403  
7.401  
7.399  
7.287  
7.284  
7.274  
7.270  
6.787  
6.785  
6.778  
6.777  
6.434  
6.430  
6.426  
6.421



Current Data Parameters  
NAME S71-4  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20091013  
Time\_ 12.19

INSTRUM spect  
PROBHD 5 mm BBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2

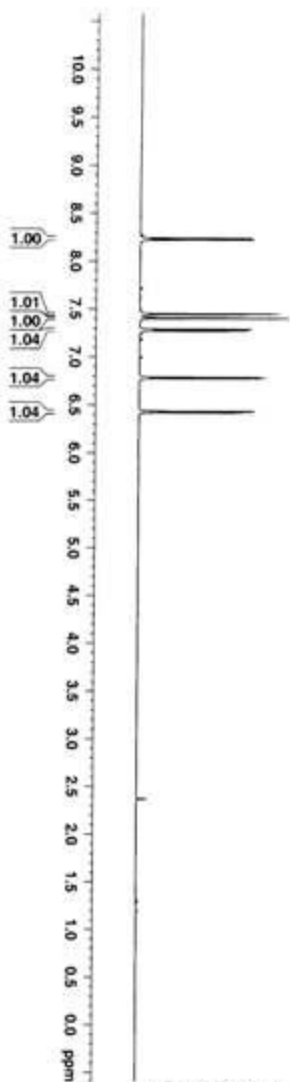
SWH 8378.146 Hz  
FIDRES 0.126314 Hz  
AQ 3.958423 sec  
RG 28.5

TM 60.400 usec  
DE 7.00 usec  
TE 313.2 K  
D1 1.00000000 sec  
MCHEST 0.00000000 sec  
MCPRK 0.01500000 sec

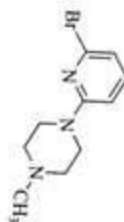
\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing Parameters

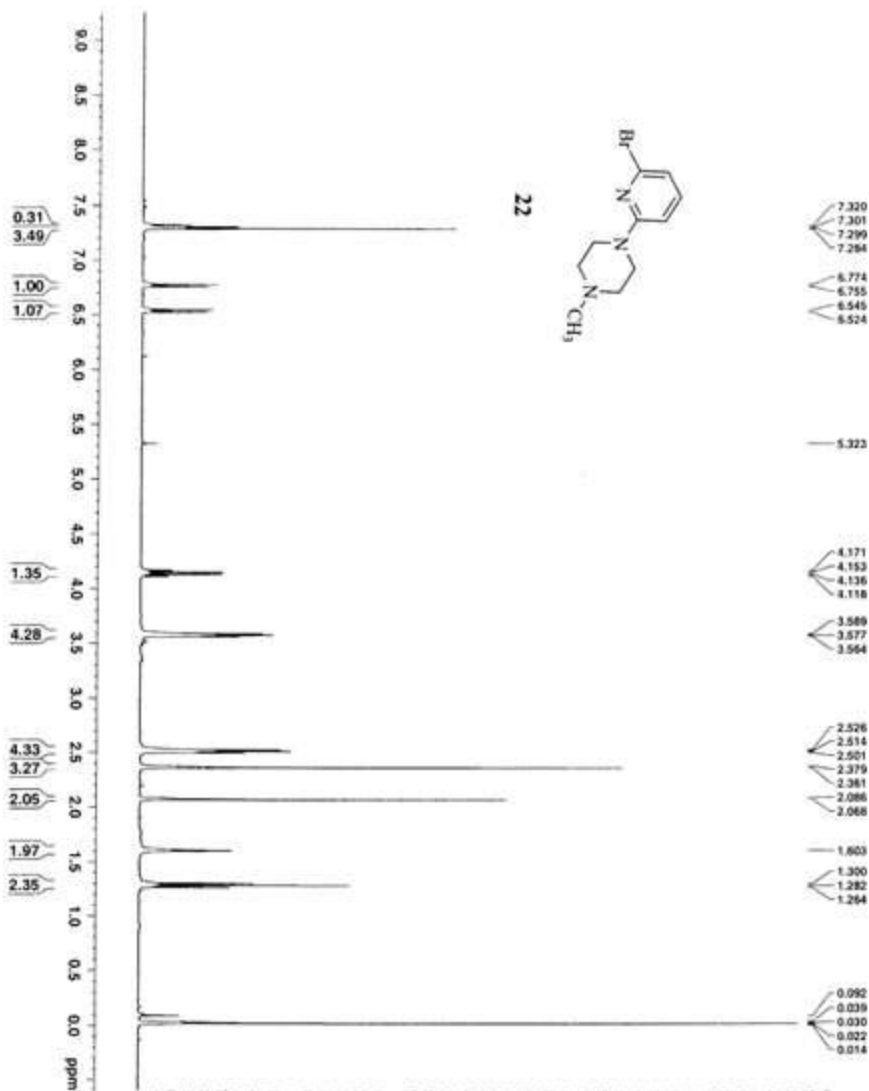
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00



No title



22



Current Data Parameters  
NAME B74\_crude  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20100129  
Time 10.36

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 32  
DS 2

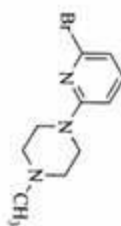
SWH 8278.145 Hz  
FIDRES 0.12614 Hz  
AQ 3.958423 sec  
RG 645.1  
DE 60.400 usec  
TE 297.3 K

D1 1.00000000 sec  
MCREST 0.00000000 sec  
MCPRK 0.01500000 sec

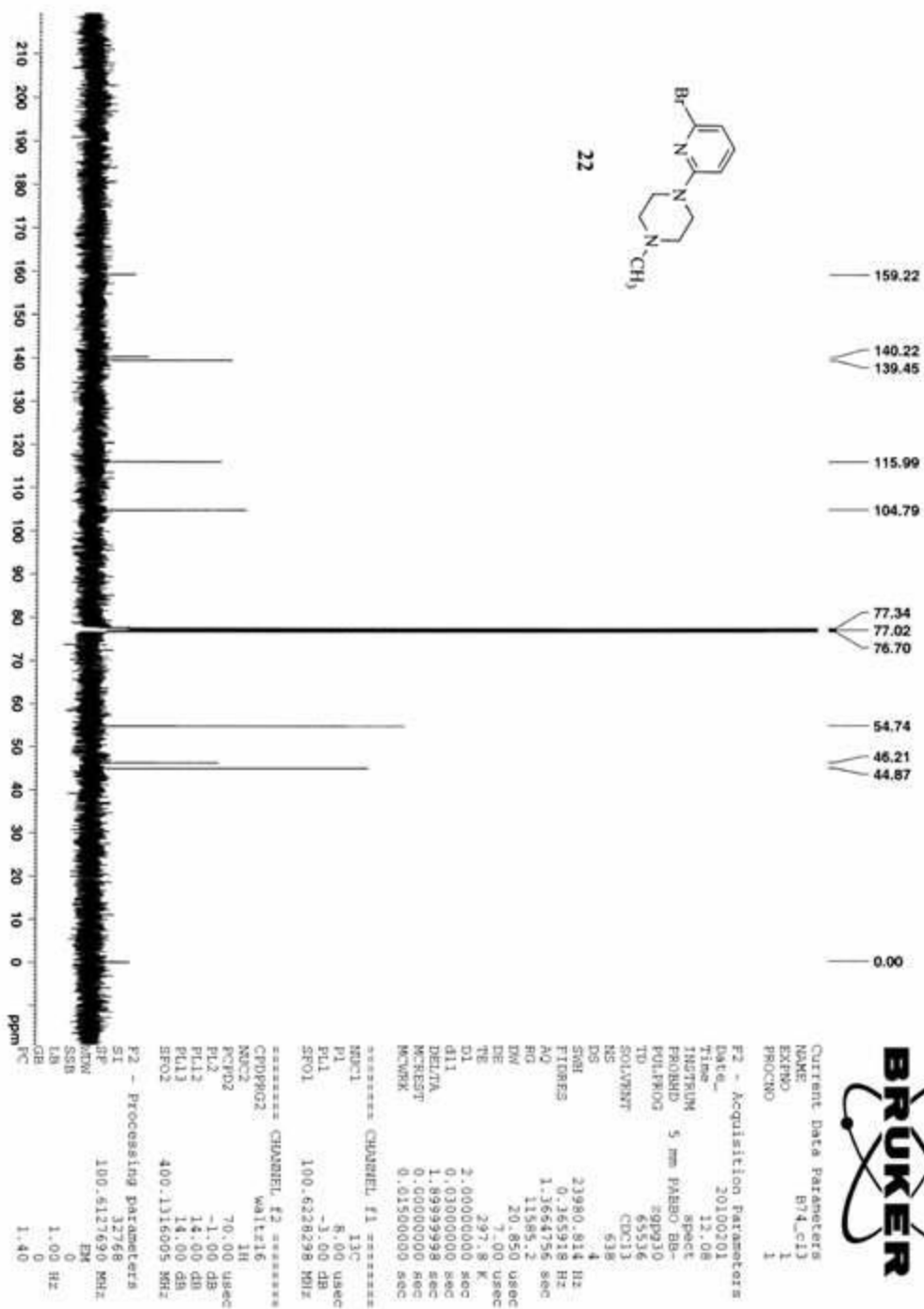
\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 1H  
P1 12.80 usec  
PL 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.30 Hz  
GB 0  
PC 1.00

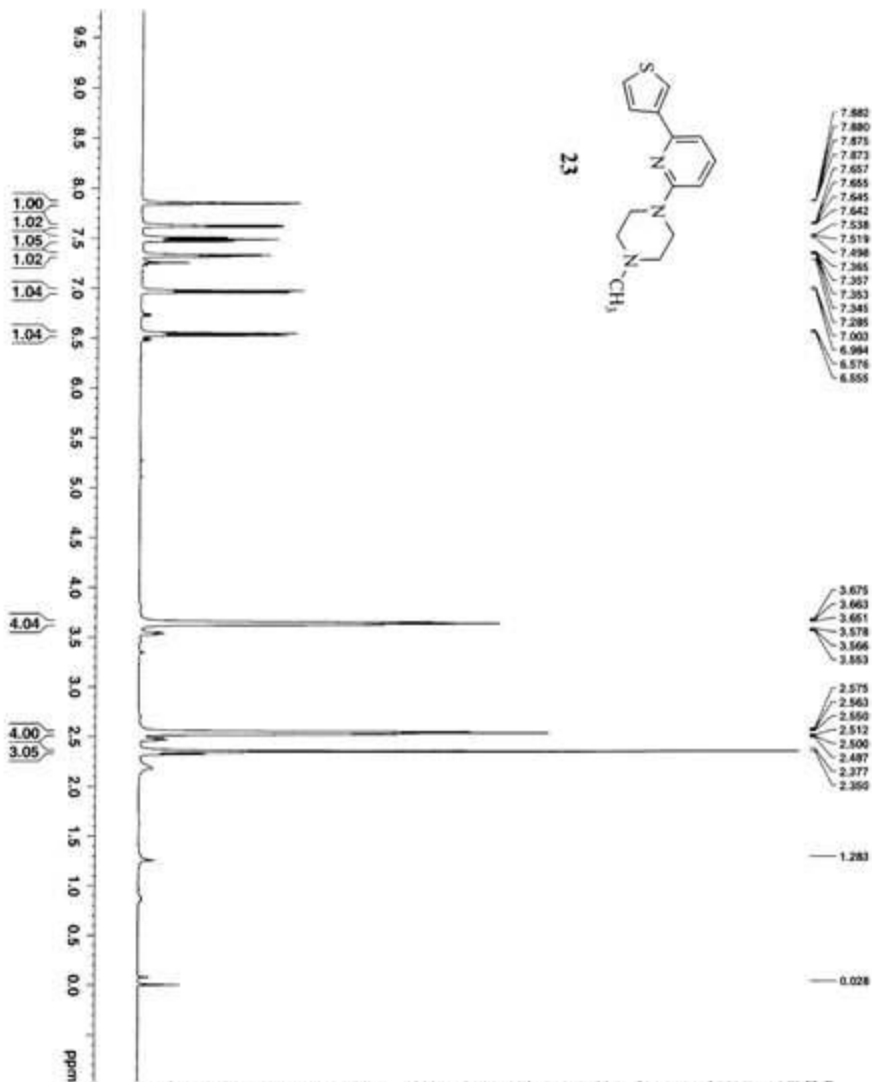
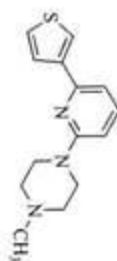
No title



22



No title



Current Data Parameters  
NAME B47  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090618  
Time 12.19

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2

SNR 8278.146 Hz  
FIDRES 0.12614 Hz  
AQ 3.958423 sec  
RG 80.6  
DE 60.400 usec  
TE 297.6 K

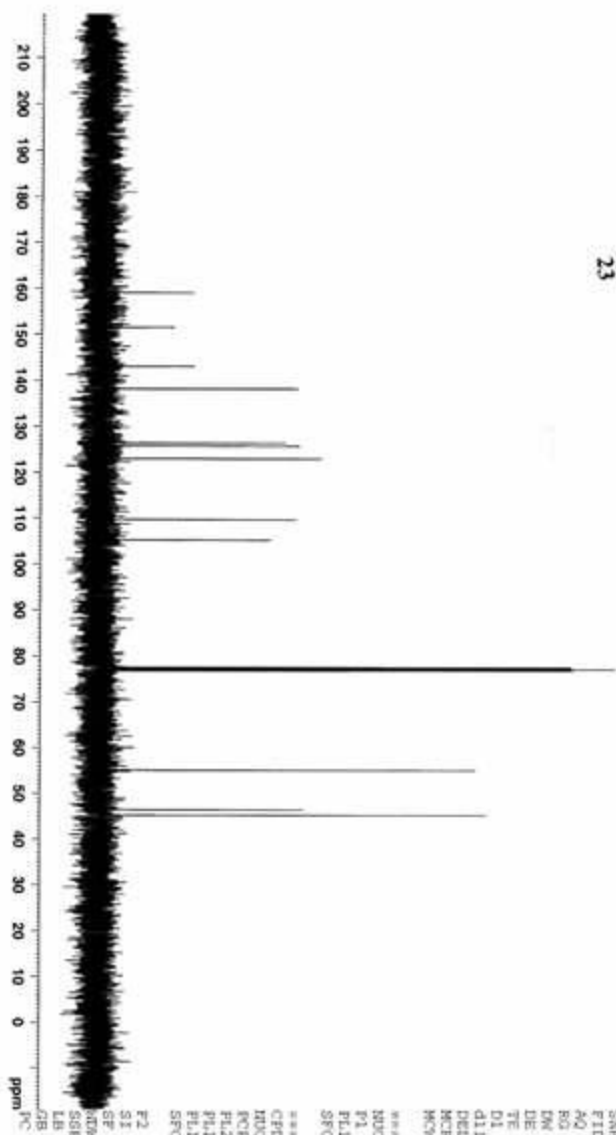
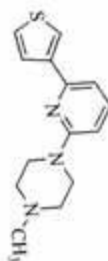
D1 1.00000000 sec  
DCREST 0.00000000 sec  
MCWRR 0.01500000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing parameters  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.10 Hz  
GB 0  
PC 1.00

No title

159.03  
151.47  
143.02  
138.16  
126.37  
125.71  
122.97  
109.65  
105.18  
77.41  
77.10  
76.78  
54.99  
46.30  
45.09



Current Data Parameters  
NAME B47\_c13  
EXNO 1  
PROCNO 1

F2 - Acquisition Parameters

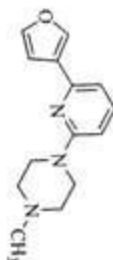
Date\_ 20090623  
Time 10.51  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
FIDRES 0.36518 Hz  
AQ 1.3564756 sec  
RG 32768  
IN 20.850 usec  
DE 7.00 usec  
TE 297.8 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
MCREST 0.00000000 sec  
MCNRF 0.01500000 sec

\*\*\*\*\* CHANNEL f1 \*\*\*\*\*  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.628258 MHz

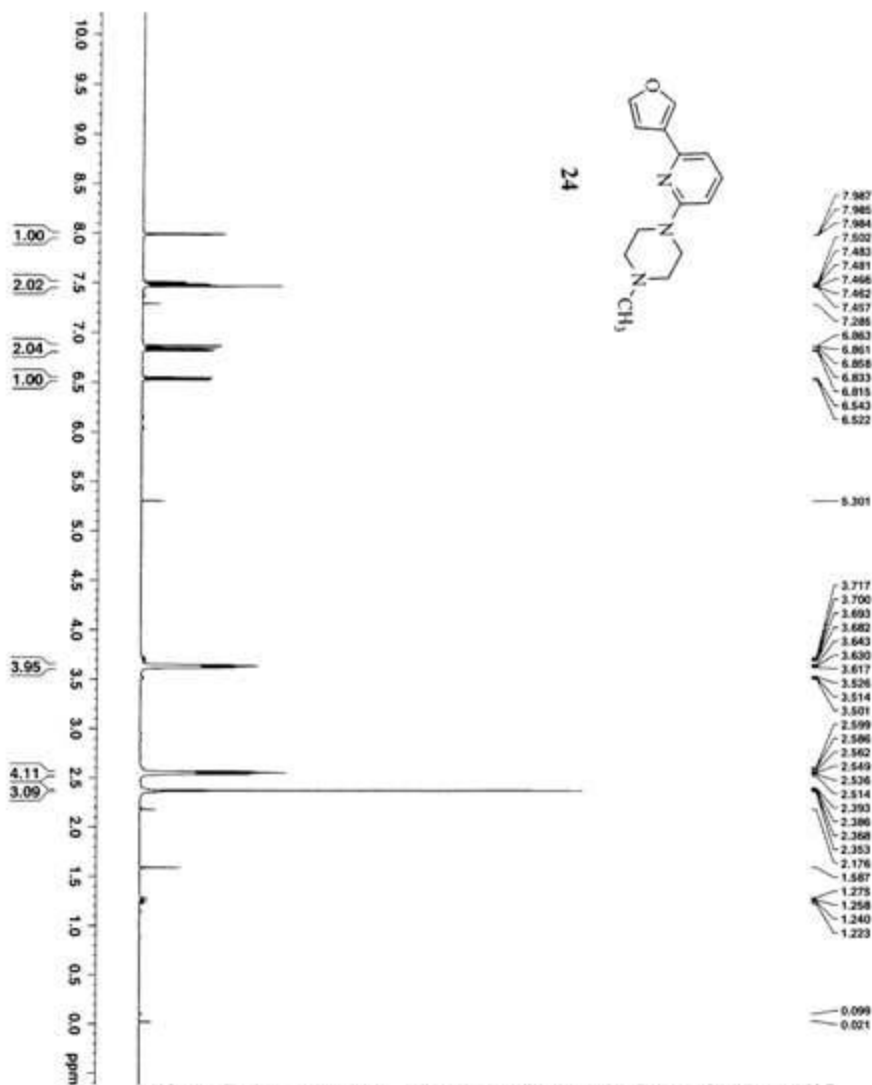
\*\*\*\*\* CHANNEL f2 \*\*\*\*\*  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 dB  
PL12 14.00 dB  
PL13 14.00 dB  
SFO2 400.316005 MHz

F2 - Processing parameters  
SI 32768  
SF 100.6127890 MHz  
BN 8K  
GB 0  
PC 1.00 Hz  
LB 0  
GB 1.40

No title



24

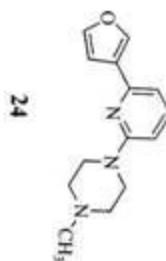


Current Data Parameters  
NAME: B68-5  
EXPNO: 1  
PROCNO: 1

F2 - Acquisition Parameters  
Date\_: 20090929  
Time: 13.41  
INSTRUM: spect  
PROBHD: 5 mm PABBO BB-  
PULPROG: zg30  
TD: 65536  
SOLVENT: CDCl3  
NS: 1  
DS: 2  
SWH: 8278.146 Hz  
FIDRES: 0.13614 Hz  
AQ: 3.9584213 sec  
RG: 71.8  
RW: 60.400 usec  
DE: 7.00 usec  
TE: 296.5 K  
D1: 1.00000000 sec  
MCREST: 0.00000000 sec  
MCPRK: 0.01500000 sec

===== CHANNEL f1 =====  
NUC1: 1H  
P1: 12.80 usec  
PL1: 0.00 dB  
SFO1: 400.1324710 MHz  
F2 - Processing parameters  
SI: 32768  
SF: 400.1300000 MHz  
WDW: EM  
SSB: 0  
LB: 0.30 Hz  
GB: 0  
PC: 1.00

No title



159.08
149.75
143.40
141.08
138.00
127.67
109.47
108.79
105.03
77.41
77.09
76.77
54.96
54.89
46.28
45.47
45.04
28.90



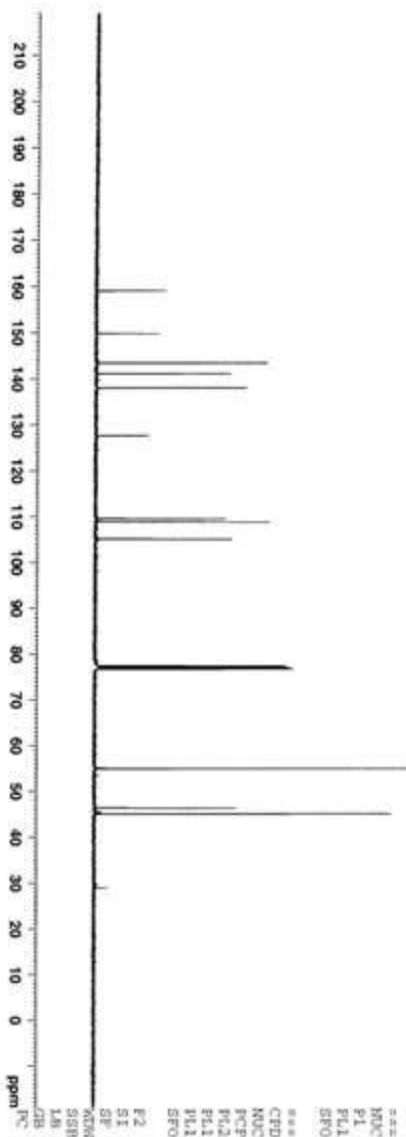
Current Data Parameters  
NAME R68-5\_c13  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20090929  
Time 13:51  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
FIDRES 0.3213  
SOLVENT CDCl3  
NS 512  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.16518 Hz  
AQ 1.3664756 sec  
RG 19390.4  
IN 20.850 usec  
DE 7.00 usec  
TE 298.6 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
MCREST 0.00000000 sec  
MCRR 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.6228998 MHz

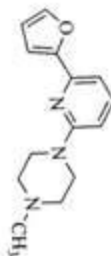
===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 dB  
PL12 14.00 dB  
PL13 14.00 dB  
SFO2 400.1316005 MHz

F2 - Processing parameters  
SI 32768  
SF 100.6127690 MHz  
RG 65536  
WDW EM  
SSB 0  
GB 0  
PC 1.00 Hz  
SC 0  
PR 1.00

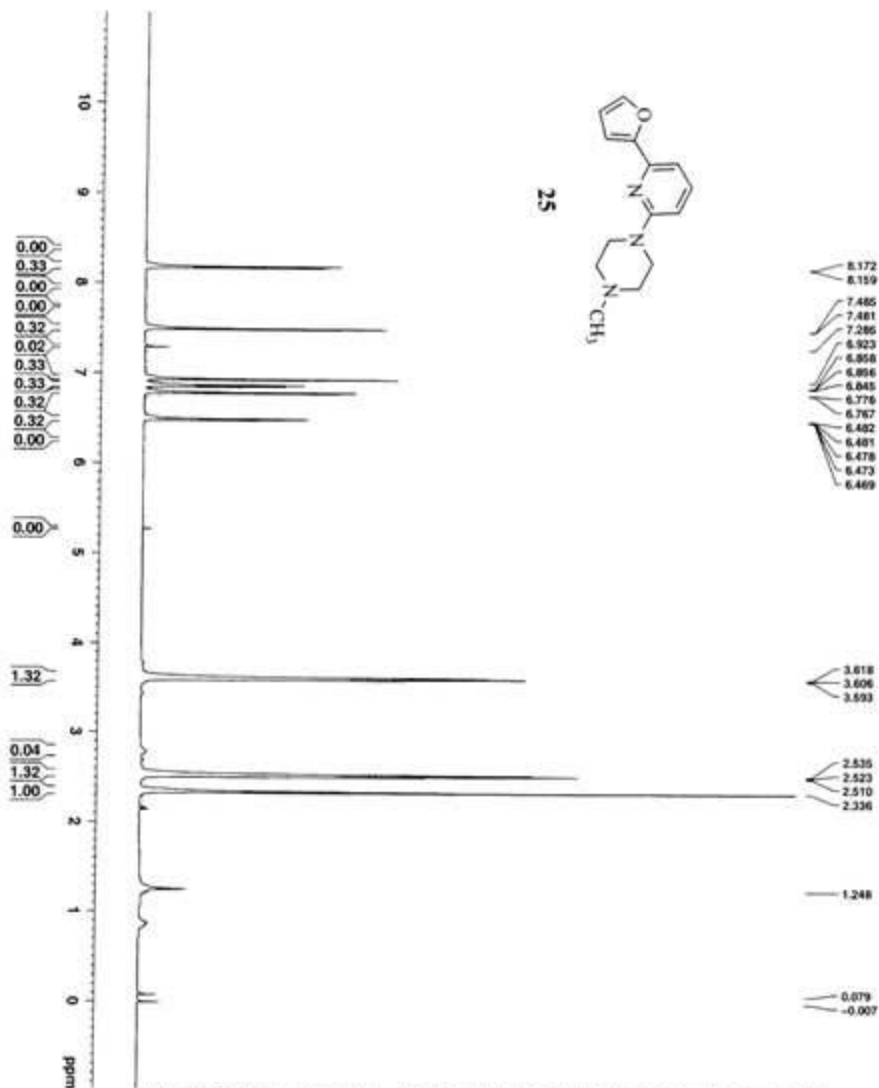




No title



25



Current Data Parameters  
NAME H73-4  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters  
Date\_ 20091103  
Time 12.56

INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zg30  
TD 65536  
SOLVENT CDCl3  
NS 16  
DS 2

SWH 8278.146 Hz  
FIDRES 0.12614 Hz  
AQ 3.958423 sec  
RG 45.3  
WDW 60.400 usec  
SSB 0

TE 300.2 K  
D1 1.00000000 sec  
MCPRST 0.00000000 sec  
MCWEX 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 1H  
P1 12.80 usec  
PL1 0.00 dB  
SFO1 400.1324710 MHz

F2 - Processing Parameters  
SI 32768  
SF 400.1300000 MHz  
WDW EM  
SSB 0  
LB 0.10 Hz  
GB 0  
PC 1.00

No title

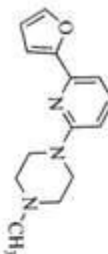
160.07  
152.27  
148.32  
143.11  
138.83

111.87  
108.41  
107.90  
100.90

77.44  
77.13  
76.81

54.93  
46.24  
45.24

29.70



25



Current Data Parameters  
NAME R1-4.c1  
EXPNO 1  
PROCNO 1

F2 - Acquisition Parameters

Date\_ 20091103  
Time 13.17  
INSTRUM spect  
PROBHD 5 mm PABBO BB-  
PULPROG zgpg30  
TD 65536  
SOLVENT CDCl3  
NS 122  
DS 4  
SWH 23980.814 Hz  
FIDRES 0.365918 Hz  
AQ 1.366456 sec  
RG 32768  
IN 20.850 usec  
DE 7.00 usec  
TE 295.9 K  
D1 2.00000000 sec  
d11 0.03000000 sec  
DELTA 1.89999998 sec  
MCREST 0.00000000 sec  
MCMRG 0.01500000 sec

===== CHANNEL f1 =====  
NUC1 13C  
P1 8.00 usec  
PL1 -3.00 dB  
SFO1 100.628958 MHz

===== CHANNEL f2 =====  
CPDPRG2 waltz16  
NUC2 1H  
PCPD2 70.00 usec  
PL2 -1.00 dB  
PL12 14.00 dB  
PL13 14.00 dB  
SFO2 400.116005 MHz

F2 - Processing parameters  
SI 32768  
SF 100.6127690 MHz  
WDW EM  
SSB 0  
LB 1.00 Hz  
GB 0  
PC 1.40

