Synthesis of Selective 5-HT6 and 5-HT7 Receptor Antagonists

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SYNTHESIS OF SELECTIVE 5-HT_6 and 5-HT_7 RECEPTOR ANTAGONISTS

by

ELIZABETH A. RAUX

Under the Direction of Dr. Lucjan Strekowski

ABSTRACT
The development of novel selective 5-HT_6 and 5-HT_7 receptor antagonists is an ever-growing area of interest among medicinal chemists. The potential of developing a therapeutic agent useful as an antipsychotic or antidepressant, as well as the possibility to develop a drug for Alzheimer’s disease and obesity has led to an increase in synthesis of possible lead compounds. The synthesis of unfused biheteroaryl derivatives is described within. The derivatives have been evaluated for binding affinity at 5-HT_2A, 5-HT_6 and 5-HT_7 receptors.

The most potent 5-HT_6 receptor antagonists include a benzene ring, a hydrophobic group and a protonated nitrogen atom. The most potent and selective compound synthesized is 1-[3-butyl-5-
(thienyl)phenyl]-4-methylpiperazine. The binding site of the 5-HT\textsubscript{7} receptor is similar to that of the 5-HT\textsubscript{6} receptor and the most selective and potent 5-HT\textsubscript{7} receptor antagonist also contains a protonated nitrogen atom and a hydrophobic group. The difference in selectivity between the 5-HT\textsubscript{6} and 5-HT\textsubscript{7} receptor antagonists is the aromatic ring. The most potent 5-HT\textsubscript{7} receptor antagonist synthesized contains a pyridine ring instead of benzene, as in the 5-HT\textsubscript{6} receptor antagonist. The most potent and selective 5-HT\textsubscript{7} receptor antagonist is 1-{[4-(3-furyl)-6-methylpyridin-2-yl]-4-methylpiperazine. The need to increase selectivity for both 5-HT\textsubscript{6} and 5-HT\textsubscript{7} receptors has led to the synthesis of flexible-chain linked derivatives and the results are described within.

INDEX WORDS: Serotonin, 5-HT\textsubscript{7}, 5-HT\textsubscript{6}, organic, heterocyclic chemistry, synthesis, benzene, quinazoline, pyridine, pyrimidine, biheteroaryl
SYNTHESIS OF SELECTIVE 5-HT_{6} and 5-HT_{7} RECEPTOR ANTAGONISTS

by

ELIZABETH A. RAUX

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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by

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1 INTRODUCTION

1.1 Background on Serotonin

Serotonin (5-hydroxytryptamine; 5-HT) was discovered over 60 years ago and continues to generate interest as one of the most attractive and successful targets for medicinal chemists. Serotonin is an abundant mammalian neurotransmitter involved in numerous central nervous system and peripheral processes. Page was the first to successfully isolate serotonin from blood serum, after which Rapport was able to identify the compound as 5-hydroxytryptamine (Figure 1).¹ A second line of inquiry stemmed from the histological studies of the cells present in the lining of the gastrointestinal tract. Erspamer successfully isolated a substance that he called ‘enteramine’ in 1930, which he later discovered was identical to 5-hydroxytryptamine.²

![Figure 1. 5-Hydroxytryptamine (Serotonin, 5-HT)](image)

Over two decades later Twarog and Page discovered the presence of serotonin in the mammalian brain, which led to the discovery of serotonergic neurons and a surge in research of serotonin as a therapeutic target.² Serotonin is an abundant neurotransmitter which elicits its effects by interacting with a variety of membrane bound receptors. To date there have been 14 serotonin receptor subtypes classified, which are grouped into 7 families (5-HT₁ to 5-HT₇).¹⁻⁶
1.2 Background on 5-HT$_7$ Receptor

The most recently discovered receptor 5-HT$_7$ was isolated simultaneously in 1993 by seven different research groups and has since been identified in rat, mouse, guinea pig, human and porcine.$^{4,6}$ The 5-HT$_7$ receptor was identified as a G-protein coupled receptor, having seven transmembrane domains. It is positively coupled to adenylyl cyclase activity through the activation of the Gs proteins.$^{4,8}$ The exact structure of the G-protein coupled receptor is still unknown due to the inability to grow crystals suitable for x-ray crystallography studies.$^7$

Alternative splicing of the 5-HT$_7$ receptor gene was reported to generate different isoforms: 5-HT$_7$(A), (B), (C) in rat and 5-HT$_7$(A), (B), (D) in human, that differ only in their amino acid composition and their carboxyl terminal tail. Alternative splicing is a process by which the exons of the RNA produced by transcription of a gene are reconnected in multiple ways during RNA splicing. The resulting different mRNA may be translated into different protein isoforms thus, a single gene may code for multiple proteins. The most abundant isoform in humans is 5-HT$_7$A receptor, which consists of 445 amino acids with a long carboxy terminus. The functions of the splice variants however do not differ greatly from each other.

There are many examples of potent 5-HT$_7$ receptor ligands that act as both agonists and antagonists. An agonist is a chemical that binds to a receptor and triggers a response. An agonist often mimics the action of a naturally occurring substance; in this case serotonin. An antagonist is a chemical that binds to the receptor and elicits a reduced response or blocks the response.

The 5-HT$_7$ receptors are defined by their high affinity for 5-HT, 5-carboxamidotryptamine (5-CT), methiothepin, and 5-methoxytryptamine. They also show a low affinity for pindolol, sumatriptan, and busprione, which are all agonists of 5-HT$_{1A}$ (Figure 2).$^8$ The greatest abundance
of 5-HT₇ receptor is found in the brain (thalamus, hypothalamus, limbic, and cortical regions), but these receptors are also found in the periphery (spleen, kidney, heart, coronary artery, and gastrointestinal tract). 5-HT₇ receptors have been associated with the control of circadian rhythms, sleep, depression, migraine, memory, and schizophrenia. Because of the implications in effecting depression, 5-HT₇ has become an attractive target for drug discovery and the identification of possible antidepressant therapeutic agents.

![Figure 2. Compounds Known to Interact with Serotonin Receptors.](image)

Amisulpride (Figure 3), which is an approved drug in Italy for the treatment of schizophrenia has recently been reevaluated to determine the target of the drug more accurately. It was believed that amisulpride targeted the dopamine receptors; D₂ and D₃, which allow for dopaminergic modulation. After testing, however, it was discovered that amisulpride is a high potency competitive antagonist for the human 5-HT₇A receptor. The study was conducted on wild-type and 5-HT₇ knockout mice where the knockout mice did not respond to amisulpride in either the forced
swim test or the tail suspension test. Based on these results it can be inferred that the 5-HT\textsubscript{7A} receptor is responsible for the antidepressant actions of amisulpride and therefore is a promising target for future therapeutic agents targeting antidepressant therapy.\textsuperscript{9}

![Figure 3. Amisulpride](image)

The development of a selective 5-HT\textsubscript{7} antagonist has been challenging since the tertiary structure of the membrane G-protein coupled receptor is still unknown. Because of this, many molecular modeling techniques have been used in order to develop a reasonable pharmacophore model. 3D-QSAR studies were performed in our laboratory at GSU in order to gain a better understanding of the 5-HT\textsubscript{7} receptor binding site. These QSAR studies were based on 10 structures synthesized in our lab that showed the highest affinity for the 5-HT\textsubscript{7} receptor. It was possible to develop a pharmacophore model that displays 4 distinct features needed for selective binding: a H-bonding acceptor group (HBA), two hydrophobic regions (HYD2/HYD3), and a protonated nitrogen atom (PI, positive ion) (Figure 4). An example of one of the compounds synthesized in our laboratory is shown below and the appropriate regions are labeled. This compound has all four of the required binding areas present and leads to a tight binding in the binding site and fits the pharmacophore model proposed.
This pharmacophore model is very similar to previous models that have been developed, with one inconsistency present. The distance calculated based on the current set of ligands between the protonated nitrogen atom and the hydrogen bond acceptor is calculated to be 8.7 – 9.7 Å. The distance reported in previously published work is between 5.6 – 6.7 Å (Figure 5). This discrepancy in data may be due to the use of more flexible ligands in the previous studies, which would lead to an inaccurate fit into the binding site, and result in a shorter distance.
Combining the pharmacophore model proposed from our compounds with the knowledge that the binding site is located along the transmembrane helix it is possible to develop ligands that are highly selective for the 5-HT$_7$ receptor. The central binding point for the ligand is a central asparagine amino acid. Also present is a $\pi$-$\pi$ interaction of the aromatic ring with that of phenylalanine in the binding pocket, or an ion-$\pi$ interaction with arginine. The development of a pharmacophore model has allowed a more organized design for 5-HT$_7$ antagonists.

There are two classes of 5-HT$_7$ receptor antagonists, non-selective antagonists and selective antagonists. Non-selective antagonists are broken into five classes: ergolines, antipsychotic tricylic analogues, piperidine derivatives, aporphine derivatives, and phenylpiperazines. Ergolines, such as 2-Br-LSD, are effective at treating migraine, hypotension, postpartum hemorrhage and Parkinson’s disease (Figure 6). Antipsychotic tricylic analogues such as clozapine can be
effective at treating schizophrenia, although it is assumed that both D₂ and 5-HT₂A help to play a role in the antidepressant activity of clozapine (Figure 6).\textsuperscript{11} Piperidine derivatives, such as spiperone act as both a 5-HT₂ antagonist and show an affinity for the 5-HT₇ receptor (Figure 6).\textsuperscript{11} Aporphine derivatives, which were just recently developed by Johansson \textit{et al.} have appeared to show moderate selectivity over 5-HT₁A and dopamine D₂A receptors (Figure 6).\textsuperscript{11} The last class of non-selective antagonist is that of the phenylpiperazines, such as 1-(\textit{m}-chlorophenyl)piperazine (\textit{m}CPP), which are known as the classic serotonin antagonists. However they show low affinity and poor selectivity for the 5-HT₇ binding site (Figure 6).\textsuperscript{11}

The development of a selective 5-HT₇ receptor antagonist is a somewhat more complicated matter. Numerous studies have been done to gain insight into the structure of the 5-HT₇ receptor for a more accurate development of therapeutic agents. There have been several 5-HT₇ antagonists synthesized and tested, but it is still a challenge to develop a highly selective ligand for this

\textbf{Figure 6. Structures of Non-selective 5-HT₇ Receptor Antagonists.}
receptor because there are many similarities between the binding of 5-HT$_{1A}$, 5-HT$_{2A}$ and 5-HT$_7$ receptors. High-throughput screening was performed in 1998 by SmithKline Beecham (now GlaxoSmithKline) which led to the discovery of the first selective 5-HT$_7$ antagonist, SB-258719 (Figure 7).\footnote{11} This compound was selective for 5-HT$_7$, but there was a need to increase the affinity for the 5-HT$_7$ receptor. The discovery of SB-258719 provided for an onset in the development of selective 5-HT$_7$ drugs. After modifications were made on this compound, SB-269970 was discovered to have high affinity and selectivity for the 5-HT$_7$ receptor (Figure 7). After \textit{in vivo} studies however it was revealed that this compound had a high blood clearance because of the phenol hydroxyl group present in the molecule. GlaxoSmithKline (GSK) has more recently developed compounds that are related to SB-269770 replacing of the phenol group with various heterocyles, and replacing the methylpiperidine ring with aromatic substituents. GSK discovered that the overall affinity for 5-HT$_7$ was reduced with the addition of the heterocyles, although SB-656104 was discovered to have a decent affinity for the 5-HT$_7$ receptor and showed promising results \textit{in vivo}. The discovery of a selective 5-HT$_7$ receptor ligand and the development of a pharmacophore model have helped make the design of a novel 5-HT$_7$ antagonist much simpler and the activity more predictable.

![Chemical Structures](image)

\textit{Figure 7. Selective 5-HT$_7$ Receptor Antagonists.}
There have been two patents filed that incorporate some of the structures that have been synthesized by our laboratory. The first patent which has been filed contains four compounds that have been synthesized in the Strekowski laboratory; however the field of invention for the patent is not for 5-HT\textsubscript{7} receptors, but instead for that of H\textsubscript{4} histamine receptor. The H\textsubscript{4} histamine receptor is another G-coupled protein receptor, however it has different functionality than that of the serotonin 5-HT\textsubscript{7} receptor.\textsuperscript{12} The results of antagonistic activity at the H\textsubscript{4} receptor show that the compounds synthesized below have a good affinity for both the H\textsubscript{4} receptor and the 5-HT\textsubscript{7} receptor. This evidence shows how difficult it is to predict and synthesize a selective 5-HT\textsubscript{7} antagonist.

\textbf{Table 1. Binding Affinity for Unfused Biheteroaryls.}\textsuperscript{a}

<table>
<thead>
<tr>
<th>ID No.</th>
<th>R</th>
<th>H\textsubscript{4} Binding K\textsubscript{i} (nM)</th>
<th>5-HT\textsubscript{7} Binding K\textsubscript{i} (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>3-thienyl</td>
<td>37</td>
<td>79</td>
</tr>
<tr>
<td>27</td>
<td>2-furyl</td>
<td>87</td>
<td>307</td>
</tr>
<tr>
<td>28</td>
<td>3-furyl</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>51</td>
<td>2-thienyl</td>
<td>90</td>
<td>396</td>
</tr>
</tbody>
</table>

\textsuperscript{a}H\textsubscript{4} data taken from ref 12.

Also, it has been found that clozapine (Figure 6), which was previously mentioned as a nonselective antagonist for 5-HT\textsubscript{7} is an agonist of the H\textsubscript{4} receptor.\textsuperscript{13} The interaction with the H\textsubscript{4} receptor could be anticipated by looking at the similarity in structure of histamine and serotonin
(Figure 8). Both molecules have an ethylamine chain off of a nitrogen containing heterocycle. When considering binding in the receptor site, there must be a hydrogen bond acceptor and some sort of hydrophobic interaction in each pocket at around the same distance from each other. This phenomenon would explain why similar compounds could interact with both binding sites to illicit a response. The similarity between the two receptors however adds another difficulty in developing a selective 5-HT\textsubscript{7} antagonist with a receptor that doesn’t function in the same manner, yet has a slight affinity for compounds that act as potent 5-HT\textsubscript{7} antagonists.

![Figure 8. Serotonin and Histamine.](image)

A second patent was recently filed based on 5-HT\textsubscript{7} receptor antagonists with pyridine scaffolds.\textsuperscript{14} Although the synthesis of the molecules is different; there is one structure that is very similar to those that were synthesized in Strekowski’s laboratory. This compound has a high affinity for 5-HT\textsubscript{7} and a slight selectivity over 5-HT\textsubscript{2A} (Table 2). Comparing compounds described in the patent\textsuperscript{14} (Table 2) with those synthesized in our laboratory (Table 3) it is found that similar compounds in our lab have a slightly higher affinity and selectivity over the best compound listed in the patent (Table 3).
Table 2. Selectivity of 4(3-Thienyl)pyridines Synthesized by Bojarski et al.\textsuperscript{14}

<table>
<thead>
<tr>
<th>Structure</th>
<th>5-HT$_{2a}$ $K_i$ (nM)</th>
<th>5-HT$_7$ $K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 3" /></td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>
Table 3. Selectivity of Unfused Biheteroaryls Synthesized at GSU.

<table>
<thead>
<tr>
<th>Structure</th>
<th>5-HT(2A) (K_i) (nM)</th>
<th>5-HT(7) (K_i) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>115</td>
<td>117</td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>445</td>
<td>139</td>
</tr>
</tbody>
</table>

The activity is increased with the simple replacement of the 3-thienyl group with that of the 3-furyl group, which can be explained because oxygen is a better hydrogen bonding acceptor group than sulfur, which leads to better binding in the active site and an increase in activity.

Previously synthesized compounds in our lab have had a high affinity for the 5-HT\(7\) receptor, but a low selectivity in the presence of the 5-HT\(2A\) receptor. In order to increase the selectivity it was important to take into consideration the binding pocket once again. Since the derivatives we synthesized were small molecules that would fit in many different binding pockets it was essential to expand the size of our molecule to increase the selectivity. A previously published pharmacophore model suggests that there is an additional hydrophobic binding site located in between the PI and HYD3, and also another hydrogen bond acceptor located next to the first that was identified in our studies (Figure 5).\(^{15}\)
Based on the additional hydrophobic site in this model it is apparent that there is a hydrophobic site in the binding pocket that would help increase the selectivity of the antagonist for the 5-HT\textsubscript{7} receptor. Previously published work shows that the addition of linker connecting the aromatic region with the protonated nitrogen atom leads to an increase in selectivity for the 5-HT\textsubscript{7} receptor.\textsuperscript{5,15-20} All of the previously published work attached a linker ranging from 3 – 5 carbons in length connecting the heteroaryl portion to another aromatic portion (Table 4).

**Table 4. Selective 5-HT\textsubscript{7} Antagonists.**

<table>
<thead>
<tr>
<th>Structure</th>
<th>5-HT\textsubscript{7} $K_i$ (nM)</th>
<th>5-HT\textsubscript{2A} $K_i$ (nM)</th>
<th>5-HT\textsubscript{1A} $K_i$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td>37</td>
<td>5168</td>
<td>----</td>
</tr>
<tr>
<td>Ref 5.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
<td>0.38</td>
<td>------</td>
<td>11</td>
</tr>
<tr>
<td>Ref 19.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
<td>7±2</td>
<td>------</td>
<td>219±11</td>
</tr>
<tr>
<td>Ref 15.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
By adding a 3 – 5 carbon chain linker, the selectivity for 5-HT\textsubscript{7} was increased significantly, as is evident in the table above. This also helps provide a better pharmacophore model, since it is apparent that there is another small pocket for the binding of the other aromatic side chain present. The addition of both a spacer and a second aromatic moiety leads to a large increase in selectivity for the 5-HT\textsubscript{7} receptor. Based on that principle we synthesized a number of similar compounds and submitted them for biological activity. These new dimeric compounds are discussed in section 2.5.

### 1.3 Background on 5-HT\textsubscript{6} Receptor

Monsma \textit{et al.}\textsuperscript{21} and Ruat \textit{et al.} simultaneously isolated the first cDNA coding for a 5-HT\textsubscript{6} receptor from rat striatum in 1993.\textsuperscript{22} Three years later in 1996 the human 5-HT\textsubscript{6} receptor was cloned by Kohen \textit{et al.} as a gene codifying a polypeptide chain of 440 amino acids, which is positively coupled to the adenylyl cyclase cascade via the G\textsubscript{s} protein.\textsuperscript{23} The 5-HT\textsubscript{6} receptor, like the 5-HT\textsubscript{7} receptor is a G-protein coupled receptor which corresponds to a seven-transmembrane spanning protein.\textsuperscript{22,23} The 5-HT\textsubscript{6} receptor is mostly located in the central nervous system, however low levels have been detected in the stomach and adrenal glands.\textsuperscript{21} Within the brain the highest concentration is in the striatum (caudate nucleus) and low to moderate levels are found in the
nucleus accumbens, hippocampus, hypothalamus, amygdala, cerebellum and olfactory tubercle.\textsuperscript{21-25} Since 5-HT\textsubscript{6} is mostly located in the central nervous system, it was suggested that a selective 5-HT\textsubscript{6} ligand would have very few peripheral side effects. The 5-HT\textsubscript{6} receptor initially showed high affinity to numerous potent antipsychotic and antidepressant drugs, however there were contradictory results about the effect of the drugs on 5-HT\textsubscript{6}. The first paper that discussed nonselective 5-HT\textsubscript{6} receptor ligands discovered that tricyclic antipsychotic agents and some antidepressants bound to the 5-HT\textsubscript{6} receptor with high affinity.\textsuperscript{6} Examples include thioridazine, thioxanthene chlorprothixene, amoxapine and loxapine which bound with K\textsubscript{i} values ranging from 3 – 15 nM (Figure 9). However not all antipsychotics showed high affinity for 5-HT\textsubscript{6}. Spiperone and haloperidol showed a much lower affinity with K\textsubscript{i} values of 1595 nM and >5000 nM, respectively (Figure 9).\textsuperscript{6} The discovery that 5-HT\textsubscript{6} might play a role in psychoses led to a surge in research, however in order to truly determine the function of the 5-HT\textsubscript{6} receptor, a selective ligand had to be developed.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Nonselective 5-HT\textsubscript{6} Receptor Antagonists.}
\end{figure}
In 1998 the first selective 5-HT\textsubscript{6} receptor ligand was reported, which prompted others to quickly publish their work. Sleight \textit{et al.}\textsuperscript{26} indentified the bisaryl sulfonamides (Figure 10) as very selective 5-HT\textsubscript{6} antagonists. Shortly thereafter MS-245 and 4-bromo-\textit{N}-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)benzenesulfonamide were published (Figure 10).\textsuperscript{27} Although the discoveries were separate the sulfonamide moiety is present in all agents. The main reason for the similarity between the results of different research groups was that most of the lead compounds were found after high-throughput screening. After testing the sulfonamides the major problem was discovered to be low CNS penetration. This opened the door for nonsulfonamide derivatives as well.

![Figure 10. 5-HT\textsubscript{6} Antagonists.](Image)

The first nonsulfonamide discovered as a potent selective 5-HT\textsubscript{6} receptor antagonist was 5-methoxy-2-phenyl-\textit{N},\textit{N}-dimethyltryptamine (PMDT) (Figure 10).\textsuperscript{6} Testing was performed using
the newly developed selective 5-HT$_6$ derivatives to develop a better understanding of the role of the 5-HT$_6$ receptor. Some of the selective 5-HT$_6$ ligands were tested in patients with mental disorders and the results were inconclusive because not all of the patients reacted to the 5-HT$_6$ receptor ligands that were used. A role for 5-HT$_6$ receptors in mental disorders could not be firmly established, but is still being pursued.

The 5-HT$_6$ receptor function has also been associated with cholinergic neurotransmission, which prompted interest into the possible implication of the receptor in cognitive impairment (learning and memory) related to neurological diseases such as Alzheimer’s disease. Also, recently it has been shown that selective 5-HT$_6$ ligands are able to reduce food intake, which could lead to a treatment for obesity, which is an ever increasing global disease that so far is an unmet clinical need. Right now there are a number of compounds that have entered clinical trials for the treatment of Alzheimer’s disease, schizophrenia and obesity (Figure 11). There are currently, however no marketed 5-HT$_6$ receptor ligands as therapeutic agents and the synthesis of new potentially useful derivates continues to be of great interest and importance.
In hopes of making the development of more selective 5-HT$_6$ receptor ligands simpler, it is important to have a better understanding of the binding pocket. Since the 5-HT$_6$ receptor like the 5-HT$_7$ receptor is a G-protein coupled receptor it is not possible to make a crystal structure, and so a pharmacophore model was developed based on known 5-HT$_6$ receptor antagonists. Known 5-HT$_6$ antagonists (45) were used to develop a 3D pharmacophore model using HypoGen from the Catalyst software. It was determined from the pharmacophore model that the structural features needed for an antagonist to bind were a protonated nitrogen atom, which can interact with Asp, a hydrogen bond acceptor group which interact with Ser and Asn, a hydrophobic site interacting in a hydrophobic pocket and an aromatic ring hydrophobic site which interacts with Phe (Figure 12).
Figure 12. 3D Pharmacophore model for 5-HT₆ receptor. The HYD and PI features are drawn as globes, whereas HBA and AR features are shown as two globes because of the directional nature of these chemical functions.²⁸

A second pharmacophore model has recently been proposed using HipHop which is also part of the Catalyst software.²⁴ The difference between the two programs is that HipHop uses a much narrower scope and only looks as highly active compounds, whereas HypoGen looks at a large range of activities and has a larger number of compounds in the study. The following observations can be made by comparing the pharmacophore models below (Figure 13): The main difference is the presence of the “H1” hydrophobic center in the HipHop model. Also evident are the distances between the hydrophobic, aromatic ring centers and the positive ammonium group. Overall, however, the configuration is compatible between the two models.²⁴ The hydrophobic region (H1) is not essential for activity, however when this region is added to the pharmacophore model it generated an 83% hit rate of known 5-HT₆ antagonists where as the HypoGen model only recorded a 25% hit rate. The HipHop model therefore would be a better model to use in order to conduct
high-throughput screening in hopes of generating a lead compound for the development of a selective 5-HT\(_6\) receptor ligand.

![Figure 13. Comparison between (a) the best HipHop pharmacophore model and (b) the HypoGen model.\(^{24}\) (Cyan: hydrophobic groups; green: hydrogen bond acceptor; orange: aromatic ring; red: positive ionizable group)](image)

The 5-HT\(_6\) receptor is one of the more recently discovered serotonin receptors so the development of novel 5-HT\(_6\) receptor ligands with better pharmacokinetic and pharmacodynamic properties is still needed. Since a pharmacophore model and various selective 5-HT\(_6\) antagonists have been identified there is more attention being paid to the function of the 5-HT\(_6\) receptors. Now that there are newer 5-HT\(_6\) antagonists with better blood brain barrier penetration, it will be interesting to see what therapeutic potential is identified.
2 SYNTHESIS OF UNFUSED BIHETEROARYLS

2.1 Synthesis of Substituted Pyrimidines

The synthesis of pyrimidines with heteroaryl substituent at position 4 had gone unevaluated until the modifications made by Strekowski et al. were published.\textsuperscript{29-31} The earliest work focused on the addition of lithiated species to the pyrimidine ring, which led to the 1,6-dihydropyrimidine intermediate. This intermediate was oxidized back to pyrimidine with the use of 2,3-dichloro 5,6-dicyanobenzoquinone (DDQ) (Scheme 1).

Scheme 1.

This newly developed synthesis made it possible to then add another lithiated species to the pyrimidine ring, leading to 4,6-disubstituted pyrimidine. This procedure was later used to synthesize a number of 2,4,6-trisubstituted pyrimidines.\textsuperscript{30-31} After the lithium addition/substitution reaction was complete, an amine was used to displace the chlorine at the 2 position, which led to the desired products (Equation 1).
A similar chemistry was used to synthesize the pyrimidine ligands discussed below. The organolithium reagents, 3-lithiothiophene and 2-lithiofuran were generated in THF at low temperature by addition of \( n\text{-BuLi} \) to 3-bromothiophene and furan respectively.\(^{31} \) After the lithium halogen exchange reaction (Equation 2), the corresponding organolithium reagent was used \textit{in situ}. A solution of 2-chloropyrimidine (1) in THF was added to the organolithium reagent at -78 °C (Scheme 2). Once the reaction was complete, the reaction mixture was quenched with water/THF (1:1) and the intermediate dihydropyrimidine was rearomatized upon treatment with DDQ to give pyrimidines 2 and 3.

\[
\begin{align*}
\text{SBr} & \xrightarrow{\text{n-BuLi, THF, -78°C}} \text{SLi} \\
\end{align*}
\] (2)

Addition of a ethyllithium or \( n\)-butyllithium to 2 and 3 followed by treatment with DDQ furnished 4,6-disubstituted pyrimidines 4 – 6 (Scheme 2). Crude products were purified on a chromatotron eluting with hexanes and ether.

The final compounds 7 – 9 were synthesized by treatment of 2-chloropyrimidines 4 – 6 with \( N\)-methylpiperazine.
Scheme 2.

The preparation and use of 2-chloro-4-vinylpyrimidine (10) is shown in Scheme 3. Thus, vinyl lithium reagent was generated by the addition of tert-butyllithium dropwise to a solution of tetravinyltin in THF at -70 °C. The mixture was stirred for 15 min at -70 °C before use. Upon the generation of the lithium reagent, a solution of 2-chloropyrimidine (1) in THF was added at -78 °C and the mixture was allowed to warm to -40 °C over 1 h (Scheme 3). Once the reaction was complete, the mixture was quenched with water, and the intermediate dihydropyrimidine was oxidized with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). The crude mixture was treated with an aqueous solution of sodium hydroxide in order to solubilize the hydroquinone which was
removed with the water extraction. Purification of the 2-chloro-4-vinylpyrimidine (10) was done using silica gel chromatography eluting with a mixture of hexanes and ether.

**Scheme 3.**

As shown in Scheme 3, 2-chloro-4-vinylpyrimidine (10) undergoes a 1,4-conjugate nucleophilic addition across the vinyl group to give 11 – 14. The reaction was conducted in toluene. The mixture was stirred for 2 h at 90 °C, after which time the mixture was basified with aqueous sodium carbonate and extracted with ether to generate the crude products 11 – 14. The crude products were used to synthesize the final products 15 – 18. The 2-chloro substituent in 11 – 14 was displaced with N-methylpiperazine in toluene at 80 °C overnight. The mixture was basified with aqueous sodium carbonate and extracted with ether. Purification of 15 – 18 was done on a chromatotron eluting with a mixture of hexanes and ether.

The conjugate addition reaction is useful to expand the chain length and add various groups to the ring that otherwise would be difficult. Simple amines undergo addition readily as do small alkoxide ions. Addition of phenoxide was also attempted, but, surprisingly, there was no reaction.
The successful addition of ethanethiolate ion to the vinyl group of 10 should be noted. The highest yield (61%) was observed with the addition of benzylamine, which is a primary amine and is highly nucleophilic. Dimethylamine is also a good nucleophile for this addition reaction, but the yield (27%) is lower.

Scheme 4.

1,4-Conjugate addition was also performed using Grignard reagents in the presence of copper iodide (Scheme 4). To a solution of copper iodide in THF was added methylmagnesium bromide or phenylmagnesium bromide at -50 °C. The mixture was stirred for 10 min, after which a mixture of 2-chloro-4-vinylpyrimidine in THF was added dropwise. The mixture was stirred to -40 °C for 2 h, and quenched with aqueous ammonium chloride to give the corresponding product 21 or 22. Purification was done on a chromatotron eluting with hexanes and ether. The addition reaction was unsuccessful in the absence of copper iodide.

The reaction was attempted with a catalytic amount of copper iodide first, however, the yields were low (32%). Under optimized conditions the ratio of RMgBr:CuI is 2:1. The overall yield for this reaction was thus increased to 70%. The increase in yield is likely a result of the favored 1,4-conjugate addition upon addition of copper as well as the catalytic effect of copper on the reaction rate. When copper is not present the Grignard reagent does not react. Structures 21
and 22 are consistent with their $^1$H NMR, $^{13}$C NMR and high resolution mass spectra. It is apparent from the absorption pattern for the propyl group on the $^1$H NMR that the addition of methylmagnesium bromide results in the selective addition of the methyl group to the vinyl moiety of compound 21.$^{37}$

Additional evidence for selective nucleophilic addition to the vinyl group over chloride displacement is shown in Figure 14. The intermediate product shown was synthesized in our laboratory by Ava Blake and resulted from the treatment of 10 with 0.55 equivalents of ethylamine. The intermediate product, 2-(2-chloropyrimidin-4-yl)-N-(2-(2-chloropyrimidin-4-yl)ethyl)-N-ethylethanamine was the major product isolated confirming the rate of conjugate addition to the vinyl group is faster than the displacement of the chloride.$^{37}$

![Figure 14. 2-(2-Chloropyrimidin-4-yl)-N-(2-(2-chloropyrimidin-4-yl)ethyl)-N-ethylethanamine.](image)

2.2 Synthesis of Substituted Quinazolines

The synthesis of quinazoline derivatives has been evaluated previously for the use as selective 5-HT$_7$ receptor ligands, however a very different approach was taken.$^{38}$ The quinazoline scaffold was used in order to develop novel receptor ligands and also confirm that the previously discussed 1,4-conjugate nucleophilic addition reaction is not restricted to the pyrimidine scaffold.
A similar procedure that was used for the reaction above on pyrimidine was utilized for the addition of a vinyl group to the 4-position of quinazoline with slight modifications. The vinyllithium addition was first attempted on commercially available quinazoline following the same procedure that was used for addition to the pyrimidine scaffold (Equation 3).

\[
\begin{align*}
\text{N} & \quad \text{N} \\
1 & \quad \text{Sn} \\
3 & \quad \text{B} \\
2 & \quad \text{D} \\
4 & \quad \text{Q} \\
\end{align*}
\]

\[\text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad 1 \quad \text{Sn} \quad \text{t-BuLi}, \text{THF} \quad 2 \quad \text{DDQ} \quad X \quad (3)\]

The vinyllithium reagent was generated by the addition of \textit{tert}-butyllithium dropwise to a solution of tetravinyltin in THF at $-70^\circ C$. The reaction mixture was stirred for 5 min at $-70^\circ C$ before use. Vinyllithium was then added to a solution of quinazoline in THF at $-78^\circ C$ and the mixture was allowed to warm to $-60^\circ C$ over 1 h (Equation 3). Then, the mixture was quenched with water, and treated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Upon workup the desired 4-vinylquinazoline product was not found. In order to determine whether the addition of the vinyllithium was not working or if the oxidation was the problem the presumed dihydroquinazoline derivative was isolated by extracting with ether. Purification was done on a chromatotron eluting with hexanes, ether and methanol. The result was the isolation of the dihydroquinazoline derivative, which was confirmed by $^1$H NMR. The absorption of the NH peak was evident at 2.99 ppm, which confirms the dihydroquinazoline product. Once the product was isolated it became apparent that the problem was the oxidation step. A previously published method using the milder oxidizing agent potassium ferricyanide was carried out (Scheme 5). To a mixture of potassium ferricyanide in aqueous saturated potassium hydroxide was added a mixture
of dihydroquinazoline in benzene. The reaction mixture was stirred vigorously at room temperature for 1 h. The benzene layer was extracted to give pure 4-vinylquinazoline.

**Scheme 5.**

After establishing a plausible synthetic route to 4-vinylquinazoline, the synthesis of a more complex quinazoline was attempted. Thus, 2,4-dichloroquinazoline was prepared as previously described with slight modifications to improve the yield (Scheme 6). The chlorination of substrate 23 (Scheme 6) was accomplished by the addition of phosphorous oxychloride in N,N-dimethylaniline in the presence of a catalytic amount of N,N-dimethylformamide. The mixture was heated for 6 h, after which it was poured over ice, and the resulting solid was filtered. The crude solid was recrystallized with isopropanol to produce pure 2,4-dichloroquinazoline (24).

The selective reduction of 2,4-dichloroquinazoline (24) to 2-chloroquinazoline (25) was attempted using a previously published procedure. A two-phase mixture of 24 in dichloromethane was covered with a solution of aqueous saturated brine which contained 9% ammonium hydroxide. The mixture was treated with powdered zinc and heated under reflux. After workup, the product was isolated in a low yield (3%). Different conditions were tried for the selective reduction in order to optimize the yield. The experiments are described as follows.

Bis(triphenylphosphine)palladium(II) dichloride and tributylphosphine were added to a mixture of 24 in dry THF. Tributyltin hydride was added and the mixture was stirred at room temperature
for 5 h (Equation 4). The mixture was concentrated and purification was done on a chromatotron eluting with hexanes and ether. 2-Chloroquinazoline was isolated in 17% yield, however residual tin remained in the product, which could not be removed. For this reason the previously used biphasic system was re-examined with slight modifications to improve yield.

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{N} \\
\text{Cl}
\end{array}
\xrightarrow{(PPh_3)_2PdCl_2, Bu_3P, Bu_3SnH, THF}
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{Cl}
\end{array}
\]

(4)

The zinc that was previously used in this reaction had oxidized and was the most likely explanation for the low yield previously obtained in the selective reduction reaction. In order to increase the yield, zinc had to be activated. Powdered zinc was washed with hydrochloric acid (2%), filtered and washed again with HCl (2%), and then water, ethanol, and finally ether, and dried under reduced pressure to furnish activated zinc metal. The reaction was repeated as specified above to give pure 2-chloroquinazoline (25) in 54% yield. This improved yield allowed for the synthesis of 25 to be scaled up and the addition of the vinyllithium reagent to be attempted.
Scheme 6.

The conditions mentioned above for the addition of the vinyl group to quinazoline were used to synthesize 2-chloro-4-vinylquinazoline (26) in 68% yield (Scheme 6). Thus, 2-chloro-4-vinylquinazoline (26) underwent a selective 1,4-conjugate nucleophilic addition across the vinyl group when equimolar amounts of nucleophile and vinylquinazoline were used. The crude
products then underwent a chloride displacement with \(N\)-methylpiperazine to provide products 27 – 34 in 23 – 50% yield. The conjugate addition reaction was selective over the chloride displacement reaction, however in all cases there was some addition/displacement product isolated after purification. The ratio as shown in \(^1\)H NMR was 5:1. The selectivity of the vinyl addition was generally decent, but the purification of the products proved to be challenging. In order to exclusively produce the addition/displacement product three equivalents of nucleophile and one equivalent of 2-chloro-4-vinylquinazoline were used and products 35 and 36 were produced (Scheme 6).

In order to improve the yield of the 1,4-conjugate nucleophilic addition reactions, the chloride displacement reaction with \(N\)-methylpiperazine was carried out before the vinyl lithium reagent was added to quinazoline ring (Scheme 7). The same conditions and procedures were used for the reaction sequence below; the only difference is the order of the reaction sequence which led to an increase in yield and simplified purification. Also, in this case the nucleophile can be added in excess because there is no possibility for the double reaction. This reaction sequence resulted in increased yields of the overall synthesis to 50 – 63%. Although there is selectivity in the conjugate addition reaction over the chloride displacement reaction the overall process in synthesizing derivatives was easier through this route because a large amount of the intermediate 2-(4-methylpiperazino)-4-vinylquinazoline (38) could be synthesized and only one step was needed to synthesize final products.

Selectivity for nucleophilic conjugate addition to the vinyl group can be confirmed by comparing the identical products isolated from the two separate schemes. The products that are isolated are confirmed by \(^1\)H NMR, \(^{13}\)C and high-resolution mass spectrometry. The higher yields
for the products in Scheme 7 can be explained by the simplification in purification that results from fewer side products (Table 5).

**Scheme 7.**

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<tbody>
<tr>
<td>27</td>
<td>NMe₂</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>HN-Bu”</td>
<td>32</td>
<td>OMe</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>NHCH₂Ph</td>
<td>33</td>
<td>SEt</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>N–Me</td>
<td>34</td>
<td>SPh</td>
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</tr>
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Table 5. Yields from Scheme 6 and Scheme 7.

<table>
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<tr>
<th>Compound #</th>
<th>Yield (Scheme 6)</th>
<th>Yield (Scheme 7)</th>
</tr>
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<tbody>
<tr>
<td>27</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>28</td>
<td>31%</td>
<td>55%</td>
</tr>
<tr>
<td>29</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td>30</td>
<td>40%</td>
<td>53%</td>
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<tr>
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<td>35%</td>
<td>54%</td>
</tr>
<tr>
<td>34</td>
<td>50%</td>
<td>63%</td>
</tr>
</tbody>
</table>

The synthesis of 4-(3-furyl)-2-(4-methylpiperazino)quinazoline (40) is given in Scheme 8. The organolithium reagent, 3-lithiofuran, was generated in THF at low temperature by addition of n-BuLi to 3-bromofuran as previously described (Equation 2). The organolithium reagent was used in situ for the reaction with 2-chloroquinazoline (25) in THF at -78 °C (Scheme 8). Once the reaction was complete as shown by TLC analysis, the reaction mixture was quenched with water/THF (1:1) and the intermediate dihydroquinazoline was rearomatized upon the addition of DDQ. Purification was done on a chromatotron eluting with hexanes and ethyl acetate to provide 2-chloro-4-(furan-3-yl)quinazoline (39). A simple chloride displacement was done to provide the final product 40 in 69% yield. The oxidation with DDQ was successful, which was surprising, but could be because the vinyl moiety used previously is more reactive than the furan ring. DDQ could have resulted in side reactions with the vinyl group that would not be possible with the furan ring, allowing in this case a successful rearomatization.
Quinazoline derivatives were also synthesized starting from 2,4-dichloroquinazoline through a chloride displacement reaction that was accomplished the same as previously discussed (Scheme 9). This reaction led to a mixture of mono (41) and disubstituted (42) products in 31% and 18% yield respectively. The mono-substituted product underwent a second chloride displacement with N-phenylpiperazine to provide 43 in 27% yield. It is known that 2,4-dichloroquinazoline reacts regioselectively at the 4-position in a variety of reactions; the difference in reactivity was utilized in order to selectively give the desired compound 41. The difference in reactivity can be explained by the stabilizing influence of the resonance forms of 4-chloroquinazoline over those of 2-chloroquinazoline (Figure 15).
Scheme 9.

Figure 15. Resonance Structures of 4-Chloroquinazoline and 2-Chloroquinazoline.
2.3 Synthesis of Substituted Benzenes

Coupling reactions are one of the most commonly used methods to form new carbon-carbon bonds with a benzene ring.\textsuperscript{43,45-48} Palladium cross-coupling reactions are used widely by medicinal chemists to synthesize the desired products.\textsuperscript{43}

The first step in the synthesis of 2,4-disubstituted and 2,4,6-trisubstituted benzenes was accomplished through a Buchwald-Hartwig amination. This reaction was first reported in the mid-1980’s and couples amines to aryl halides in the presence of palladium or nickel catalysts.\textsuperscript{43} This reaction was first used in academic settings for the use in natural product total synthesis, and in industry for the preparation of materials on a kilogram scale.\textsuperscript{44} The general mechanism for this reaction is well understood and follows a palladium catalytic cycle (Figure 16). Although this procedure was developed a number of years ago it was still necessary to test various conditions in order to develop a method that would lead to monoaddition to the dibromo-substituted benzene ring.
Figure 16. Palladium Catalytic Cycle for Buchwald-Hartwig Amination.

The starting material, 1,3-dibromo-5-butybenzene (46) is not commercially available, but can be synthesized easily (Scheme 10). \(^4\) N-Bromosuccinimide dissolved in N,N-dimethylformamide was added to a solution of 4-butylniline in N,N-dimethylformamide at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 3 h, and concentrated. The crude residue was purified using a plug of silica gel eluting with hexanes and concentrated to provide a 2,6-dibromo-4-butybenzamine (45, Scheme 10). The Sandmeyer reaction was used to synthesize 1,3-dibromo-5-butybenzene (46). 2,6-Dibromo-4-butybenzeneamine in ethanol and sulfuric acid were combined and heated to 75 °C. Sodium nitrite was added in small portions and the mixture was allowed to stir at 75 °C for 2 h. Ice water was added and the reaction was extracted with dichloromethane and concentrated. The crude residue was purified on a chromatotron eluting with hexanes. Thus, 1,3-dibromo-5-butybenzene (46) was generated in a 50% overall yield. After the synthesis of 46, a palladium-cross coupling reaction could be attempted and the conditions could be optimized.
Scheme 10.

The first set of conditions included 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) as the ligand, tris(dibenzylideneacetone)dipalladium(0) (Pd$_2$dba$_3$) as the palladium catalyst and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base and sodium tert-butoxide to help initiate the reaction (Scheme 11). These conditions were used to synthesize 50 giving a low yield of 27% (Scheme 11). 1,3-dibromobenzene (47) was combined with BINAP, Pd$_2$dba$_3$ and DBU and N-methylpiperazine in toluene. The mixture was heated to 60 °C and sodium tert-butoxide (few crystals) was added. The mixture was refluxed overnight. After workup the crude product was provided. Since the yield (27%) was not decent, new conditions were tried.
Scheme 11.

<table>
<thead>
<tr>
<th>#</th>
<th>R</th>
<th>R'</th>
<th>#</th>
<th>R</th>
<th>R'</th>
</tr>
</thead>
<tbody>
<tr>
<td>46,49</td>
<td>n-Bu</td>
<td>-----</td>
<td>57</td>
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</tr>
<tr>
<td>47,50</td>
<td>H</td>
<td>-----</td>
<td>58</td>
<td>Me</td>
<td></td>
</tr>
<tr>
<td>48,51</td>
<td>Me</td>
<td>-----</td>
<td>59</td>
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<td></td>
<td>65</td>
<td>Me</td>
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The catalyst and ligand were kept constant however DBU was no longer used. Instead, only sodium tert-butoxide was used as a base. All of the reagents were combined in a round bottom flask and the mixture was heated under reflux overnight. The mixture was filtered over Celite, and concentrated to provide a crude residue. The residue was purified on a chromatotron to improve the yield to 54%. The yield could be improved further by changing either the catalyst of ligand to determine which conditions are the best for this reaction sequence, but it was not necessary for this synthesis because enough intermediate was synthesized easily for this two step synthesis.
The second step of this reaction sequence is a Suzuki coupling reaction. Also, in this instance it was important to try different conditions to find one that worked well. A Suzuki reaction involves the coupling of an aryl boronic acid and an aryl halide to form a new carbon-carbon bond.

The first method used a mixture of 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex and potassium phosphate in 1,4-dioxane (Scheme 11). A mixture of boronic acid, 50, 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex and potassium phosphate were combined in 1,4-dioxane. The reaction stirred at 100 °C over 7 days, after which it was filtered and extracted with dichloromethane. The crude residues were purified on a chromatotron eluting with hexanes and ether to give 52 – 58. The reaction time was too long for this method to be useful and new conditions were needed.

A mixture of 3-thienylboronic acid, 1-(3-bromophenyl)-4-methylpiperazine (50), tetrakis(triphenylphosphine)palladium and potassium carbonate in 1,4-dioxane and water were combined and the mixture was stirred at 100 °C for 5 days. The mixture was filtered through Celite and concentrated. The mixture was purified on chromatotron eluting with hexanes, ether and methanol to provide 61 in 23% yield. The solubility of the reagents seemed to be poor, so a new solvent was needed to further increase the yield.

The third set of conditions tried were similar to the second tried only instead of using 1,4-dioxane as a solvent, N,N-dimethylformamide was used and the reaction was carried out in a sealed tube in hopes of decreasing the reaction time necessary for the reaction to go to completion. The same protocol was followed as stated above. A mixture of boronic acid, 1-(3-bromophenyl)-4-methylpiperazine (50), tetrakis(triphenylphosphine)palladium and potassium carbonate in N,N-dimethylformamide and water were combined in a sealed tube and the mixture was stirred at 80 °C
The mixture was filtered, dichloromethane and water were added, and the organic layer was washed with water in order to remove DMF. The crude products were purified on a chromatotron eluting with hexanes, ether and methanol to provide pure products in 12 – 76% yield. The low yields were seen when coupling 2-substituted boronic acids and the highest yields were seen when coupling 3-substituted boronic acids.

Both the Buchwald-Hartwig and the Suzuki reaction are well known reactions in which the conditions can be further optimized for individual derivatives if needed by altering ligand, catalyst, base or solvent.

The previously optimized protocols for each reaction were used in the next synthesis of 1,4-didubstituted benzenes (Scheme 12). The Buchwald-Hartwig reaction was used to couple 1,4-dibromobenzene with N-methylpiperazine in 46% yield. Then the coupling of 67 with aryl boronic acids under the conditions used above provides the final products 68 – 69.

1-(3,5-Di(3-furyl)phenyl)-4-methylpiperazine (72) was also synthesized following the similar coupling procedures. The only difference in the synthesis is that 2.5 equivalents of 3-furanboronic acid was used to 1.0 equivalent of 71. The final product 72 was isolated in 4% yield.
Compound 72 was synthesized to ensure that work previously published in our lab based on 5-HT$_{2A}$ was correct and that a symmetrical compound would not have a good affinity for 5-HT$_{7}$ receptor.$^{29}$

**Scheme 13.**

The benzene compound 74 was prepared in a similar manner. However, instead of using N-methylpiperazine, N-benzylpiperazine was utilized. Compound 74 was synthesized by a Suzuki coupling of 73 with 3-furanboronic acid (Scheme 14).

**Scheme 14.**

The preparation of benzene derivatives was important to determine if a nitrogen was essential in the ring system for there to be activity in the 5-HT receptor binding site.
2.4 Synthesis of Substituted Pyridines

Pyridine is one of the most commonly used heterocyclic compounds for both agrochemicals and pharmaceuticals. It has previously been noted that pyridine is a good scaffold for the synthesis of 5-HT\textsubscript{7} receptor antagonists. The synthesis of the previously synthesized pyridines was done in a cyclization reaction, and was limited in the substituents that could be used. The synthesis that was used in our lab started with a ring system already intact and coupling reactions were conducted in order to add various substituents. The synthesis of substituted pyridines is similar to the synthesis of the previously discussed benzene derivatives. It is slightly more challenging however to construct the pyridine ring system so that coupling reactions can be completed.

The synthesis begins with 4-hydroxy-6-methyl-2\textsubscript{H}-pyran-2-one (75) by treatment with ammonium hydroxide in ethanol at 130 °C for 24 h (Scheme 15). The mixture is then concentrated to dryness to provide 76 in >99% yield. This reaction is very useful for converting a pyranone to a pyridinone.

The next step is a bromination reaction with phosphorous tribromide. Compound 76 is combined with 1.3 equivalents phosphorous tribromide in a sealed tube at 190 °C for 5 h. The mixture is poured over ice-water and allowed to stand overnight at room temperature. The solution is extracted with dichloromethane and concentrated to provide 2,4-dibromo-6-methylpyridine (77) in 9% yield. Since the yield was low, bromination was attempted by treatment of 76 with phosphorous oxybromide (Scheme 15).

4-Hydroxy-6-methylpyridin-2(1\textsubscript{H})-one (76) was combined with toluene and 4.0 equivalents of phosphorous oxybromide was added to the solution. The mixture was heated under reflux for 5 h,
then poured over ice-water and basified with aqueous saturated sodium hydroxide. The aqueous layer was extracted with ethyl acetate and concentrated. This procedure resulted in a mixture of starting material and product based on $^1$H NMR. Although the yield for the reaction with phosphorous tribromide was low, it worked and resulted in clean product without the need of purification, so it was utilized in the synthesis of the pyridine substituted derivatives.

Scheme 15.

The next two steps in the synthesis are identical to those that were used in the synthesis of the benzene derivatives. First, a Buchwald-Hartwig amination reaction is done with $N$-methylpiperazine and 2,4-dibromo-6-methylpyridine (77). $N$-Methylpiperazine, 77, BINAP, sodium tert-butoxide, Pd$_2$dba$_3$, and toluene are combined in a sealed tube and the mixture was stirred at 80 °C overnight. The mixture was filtered through celite, washed with ethyl acetate and concentrated to provide crude 1-(4-bromo-6-methylpyridin-2-yl)-4-methylpiperazine (78). The
residue was purified on a chromatotron eluting with hexanes, ether and methanol to provide 78 in 8% yield (Scheme 15). This yield is extremely low, but enough starting material was generated after this reaction to complete the synthesis so optimization of these conditions was not necessary. If this synthesis needed to be repeated however different conditions would have to be looked at.

The last step in the synthesis of substituted pyridine rings in a Suzuki coupling reaction. A mixture of 1-(4-bromo-6-methylpyridin-2-yl)-4-methylpiperazine (78), a boronic acid, Pd(PPh3)4, potassium carbonate, DMF and water in a sealed tube was heated at 90 °C overnight. The mixture was filtered through Celite™, washed with ethyl acetate and concentrated. The residue was purified on a chromatotron eluting with hexanes, ether and methanol to provide 79 - 81 in 4-31% yield (Scheme 15).

The next set of compounds synthesized is similar to the discussed pyridines. The difference is that the methyl group is in the 4-position instead of the 2-position. Commercially available 4-methylpyridine-2,6-diol (82) undergoes bromination with phosphorous tribromide to prepare 2,6-dibromo-4-methylpyridine (83) in 16% yield (Scheme 16). 1-(6-Bromo-4-methylpyridin-2-yl)-4-methylpiperazine (84) is synthesized under the previously discussed Buchwald-Hartwig conditions in 26% yield. Lastly, compounds 85 – 87 are prepared through a Suzuki coupling reaction in 16 – 32% yield.
2.5 Synthesis of Flexible-Chain Linked Derivatives

Starting from previously reported 5-HT7 receptor agonists and antagonists we synthesized a series of compounds intending to increase the selectivity for the 5-HT7 receptor. There have been very few selective 5-HT7 antagonists synthesized.4, 5, 15, 17, 19, 56 Table 4 shows the most selective 5-HT7 antagonists. The few that have been the most selective over the other 5-HT receptors all contain a hydrophobic chain linked to a separate aromatic compound containing a hydrogen bond acceptor group.15 We synthesized a series of compounds by joining benzene and pyridine derivative previously synthesized in our lab, with parts of known selective 5-HT7 antagonists previously synthesized.15, 18, 57 The three linkers that were chosen were done so based on ease of
synthesis and the expected affinity to the binding pocket. We chose 1-(4-bromobutyl)indolin-2-one, 4-bromobutyl phenylsulfone, and 6-bromo-N-(4-cyanobenzyl)hexanamide.\textsuperscript{15,18,57}

1-Boc-piperazine (88) was synthesized as a starting material for use in the procedures to follow.\textsuperscript{58} Piperazine in dichloromethane was cooled to 0 °C, treated with di-\textit{tert}-butyl dicarbonate dissolved in dichloromethane and the mixture was stirred at 0 °C for 2 h and then warmed to room temperature for 24 h. The precipitate was filtered, dissolved in water, and the aqueous solution was basified with potassium carbonate, extracted with ether and concentrated to give 1-Boc-piperazine 88 (Equation 5).

\begin{equation}
\text{piperazine} \quad \xrightarrow{\text{BocO, DCM, 0 °C - rt}} \quad 88
\end{equation}

3,5-Dibromotoluene (48) or 2,6-dibromopyridine (89) were combined with 1-Boc-piperazine (88), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, tris(dibenzylideneacetone)dipalladium(0) and sodium \textit{tert}-butoxide in toluene in a sealed tube and heated to 90 °C overnight. The mixture was filtered over Celite\textsuperscript{TM}, washed with EtOAc and concentrated to prepare compounds 90 and 91 (Scheme 17).

Compounds 90 and 91 then undergo a Suzuki coupling with 3-furanboronic acid through the same procedure discussed previously for synthesis of benzene derivatives. A mixture of 3-furanboronic acid, 90 and 91, tetrakis(triphenylphosphine)palladium and potassium carbonate in N,N-dimethylformamide and water were combined in a sealed tube and stirred at 80 °C overnight. The mixture was filtered through Celite\textsuperscript{TM} and washed with ethyl acetate. The filtrate was washed with water and concentrated. The crude residue was purified on a chromatotron eluting with hexanes and ether to provide 92 and 93 (Scheme 17).
Products 92 and 93 were deprotected using trifluoroacetic acid in dichloromethane. The mixture was stirred for 1 h at room temperature, after which the mixture was concentrated to give 94 and 95 (Scheme 17).

Scheme 17.

4-Bromo-2-chloropyridine (96) was combined with 3-furanboronic acid, tetrakis(triphenylphosphine)palladium and potassium carbonate in N,N-dimethylformamide and water in a sealed tube and the mixture was stirred at 90 °C overnight. The mixture was filtered through Celite™ and washed with ethyl acetate. The filtrate was washed with water and concentrated. The crude residue was purified on a chromatotron eluting with hexanes and ether to provide 2-chloro-4-(furan-3-yl)pyridine (97) (Scheme 18).
Excess 1-Boc-piperazine (88) was added to a solution of 2-chloro-4-(furan-3-yl)pyridine (97) in toluene and the mixture stirred overnight at 90 °C. The mixture was concentrated to prepare compound 98 (Scheme 18).

Deprotection of the amino group was accomplished by reacting 98 in dichloromethane with trifluoroacetic acid. The mixture was concentrated, basified with aqueous saturated sodium bicarbonate and extracted with dichloromethane to prepare a crude residue. The residue was purified on a chromatotron eluting with hexanes, ether and methanol to provide 1-[4-(3-furyl)pyridin-2-yl]piperazine (99, Scheme 18).

Scheme 18.

The piperazine function of compounds 94, 95 and 99 was alkylated with various alkyl halide derivatives that were synthesized by Jeffrey Klenc by known synthetic procedures.\textsuperscript{15,18,57} Compounds 94, 95 and 99 were dissolved in acetonitrile, and the appropriate bromoalkyl derivative was added, followed by the addition of triethylamine. The mixture was stirred at 60 °C overnight.\textsuperscript{15} The mixture was then concentrated and dissolved in dichloromethane. The solution
was washed with water and then concentrated. The crude residue was purified on a chromatotron eluting with hexanes, ether and methanol to prepare compounds 100 – 108 in 15 – 44 % yield (Scheme 19).

**Scheme 19.**

Compounds 100 – 102 were synthesized based on previously described literature. The cyanobenzyl hexamide derivative that was described with the best affinity and selectivity (Figure 17) was modified based on previously synthesized compounds which showed good affinity from our studies. Previously reported data showed that five methylene units separating the amide
moiety and the piperazine ring were preferred over other chain lengths.\textsuperscript{18} It was also discovered that the position and the nature of the substituent on the phenyl ring linked to the piperazine ring was critical; shifting the substituent from the 2-position to the 3- or 4- position resulted in loss of affinity. The piperazine moieties used in our studies have substituents at the 4-position, however we are also adding a nitrogen to the phenyl substituent in the form of 2,4- and 2,6-substituted pyridine rings. The effect of the pyridine ring is thus far unknown, however compounds have been sent to our collaborator for evaluation of binding affinity.

![Figure 17. Most Selective N-(4-cyanobenzyl)hexamide Derivative.\textsuperscript{15}](image)

Compounds 103 – 105 were also synthesized based on previously published work.\textsuperscript{57} Aminoalkyl phenyl sulfones were discovered to be possible 5-HT\textsubscript{7} receptor antagonists through molecular modeling studies which showed an overlap with SB-269970 (Figure 18), which as discussed previously is a known 5-HT\textsubscript{7} antagonist. The gem-dimethyl sulfone was coupled with various piperazine and piperadine molecules to generate a small library of compounds, in which the most selective is shown in Figure 16. Testing showed that this compound had an excellent selectivity (> 100 fold) over the other receptors tested. It was also revealed that substitution at the 3-position of the amine moiety showed attenuation of functional activity without a decrease in selectivity. The compounds synthesized in our lab are substituted at the 4-position. Such
compounds were not described in this paper, so the affinity and selectivity of our compounds is yet unknown.

![Figure 18. Sulfone With Highest Affinity and Selectivity.](image)

The synthesis of compounds 106 – 108 was also based on the previously published work. The published paper described a series of oxindole derivatives in order to develop a pharmacophore model which was based on highly selective 5-HT₇ receptor antagonists. This study led to the development of a pharmacophore model that can be used for high throughput screening in order to generate a lead target for drug synthesis. The most potent derivative (Figure 19) had a high selectivity and affinity. It was shown that by extending the alkyl chain to five methylene groups, the selectivity for 5-HT₇ over 5-HT₁₅ was decreased leading to the use of a 4 carbon chain linker, which resulted in increased selectivity for the 5-HT₇ receptor. Using a monocyclic ring structure, such as in Figure 18 rather than a bicyclic system in Figure 19 leads to poor affinity for 5-HT₁₅ which is preferred.

![Figure 19. Most Potent Oxindole Derivative.](image)
3 BIOLOGICAL ACTIVITY

The compounds that were prepared as described above were submitted for biological testing against the 5-HT$_{2A}$, 5-HT$_{7}$ and 5-HT$_{6}$ receptors, and the results are shown in Table 6. The biological assays were conducted by Bojarski et al. at the Institute of Pharmacology, Polish Academy of Sciences and were performed as previously described.$^{59,60}$

Table 6. Structure and binding data for 5-HT$_{2A}$, 5-HT$_{6}$ and 5-HT$_{7}$ antagonists.

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3.1 5-HT\textsubscript{7} and 5-HT\textsubscript{6} Selective Ligands

The studies in our laboratory previously focused on 5-HT\textsubscript{1A} and 5-HT\textsubscript{2A} receptors; however, the discovery of the 5-HT\textsubscript{7} receptor led to the interest in this area as well.

Previous structure-activity relationship analysis was performed for the 5-HT\textsubscript{2A} receptor ligands and it was indicated that pyrimidines containing 2-thienyl and 3-furyl groups have the highest affinity for the 5-HT\textsubscript{2A} receptor.\textsuperscript{60} The pyrimidine compounds synthesized were however not
selective for the 5-HT$_{2A}$ receptor, but also had a high affinity to the 5-HT$_7$ receptor. Based on these findings it was necessary to determine if the rigidity of the furan ring was indeed what allowed for such high affinity to both the 5-HT$_{2A}$ and 5-HT$_7$ receptors. Compound 17 (Table 6) was synthesized in order to test these findings and the data shows that when the rigidity of the furan ring is taken away so is the affinity for the receptors. When compound 17 is compared with the affinity of compound 8 it is apparent that the rigidity of the furan ring increases the affinity by ten fold over that of the flexible ether in compound 17.

Also, compounds 7 – 9 were synthesized to complete the set that had previously been synthesized in our lab. Compound 9 showed high affinity for both the 5-HT$_{2A}$ receptor and 5-HT$_7$ receptor, however there was no selectivity.

A series of quinazoline derivatives was tested as well, all which show poor affinity for the 5-HT$_{2A}$, 5-HT$_6$ and 5-HT$_7$ receptors. Only compound 36 appears to show affinity for 5-HT$_7$ and it also shows 100 fold selectivity over the other two receptors tested. Compound 36 is much bulkier than the others synthesized and contains two phenyl-piperazine groups. These groups could interact with the two different hydrophobic binding areas better than the rest that were synthesized. Most of the other species that were tested are aliphatic chains containing a heteroatom which if not placed in the right part of the binding pocket could lead to repulsion and poor affinity.

Benzene derivatives were then synthesized to determine whether a nitrogen containing heterocycle was needed for the ligand to retain affinity for the binding pocket. The biological data shows that the benzene ligands still have affinity for the receptor. By looking at the biological data it is evident that when a hydrogen or methyl group is present on the scaffold (52, 57) there is a higher affinity for the 5-HT$_7$ receptor than for the 5-HT$_6$ receptor. However when the methyl group is extended to a butyl group (61 – 63), the selectivity for the 5-HT$_6$ receptor is 100 fold
greater than for 5-HT$_{2A}$ or 5-HT$_{7}$. These are important starting points for the development of a highly selective 5-HT$_{6}$ or 5-HT$_{7}$ receptor antagonist.

The pyridines that were tested showed high affinity for all three receptors tested, therefore they are not selective ligands.

Testing was also done on the flexible-chain linked derivatives in hopes of increasing selectivity.

4 CONCLUSION

Since the discovery of serotonin (5-HT) over 60 years ago the search for therapeutic agents targeting the HT receptors has been ever-growing. The discovery of 5-HT$_{7}$ receptor in 1993 led to a surge in research to determine the function of the receptor. Once this receptor was determined to be associated with sleep, depression, migraine, memory and schizophrenia the development of a therapeutic agent targeting one of these areas was underway. The 5-HT$_{6}$ receptor was discovered directly before the 5-HT$_{7}$ receptor however less is known about the 5-HT$_{6}$ receptor. The 5-HT$_{6}$ receptor has been associated with Alzheimer’s disease, obesity, and psychosis. The discovery of a drug that selectively targets the 5-HT$_{6}$ receptor could result in a breakthrough in research and the first real treatment for Alzheimer’s disease.

The synthesis of numerous scaffolds based on the many pharmacophore models available for both the 5-HT$_{6}$ and 5-HT$_{7}$ receptors has led to the development of some novel highly selective compounds. The synthesis of numerous potential receptor ligands has led to a better understanding of what it necessary to develop a selective 5-HT$_{7}$ or 5-HT$_{6}$ receptor antagonist.
Our laboratory has synthesized hundreds of pyrimidines compounds for testing against 5-HT\textsubscript{2A}, 5-HT\textsubscript{1A} and 5-HT\textsubscript{7} receptors. The result was the development of new chemistry through the addition of a lithiated species to the pyrimidine ring followed by oxidation with DDQ\textsuperscript{29-31}. The extension to that work was the addition of vinyllithium to the pyrimidine ring. 2-Chloro-4-vinylpyrimidine (10) then underwent 1,4-conjugate addition in order to yield another variety of compounds for testing. Quinazoline derivatives were then tested to see if this chemistry could be duplicated.

Benzenes and pyridines were next derivatized because of recently published patents that showed high selectivity for 5-HT\textsubscript{7} with pyridine. Benzene was looked at because it was questioned whether a nitrogen was necessary in the aromatic ring to retain affinity. The biological activity shows that nitrogen is not necessary, however without nitrogen there is a high selectivity for 5-HT\textsubscript{6} over 5-HT\textsubscript{7}.

Lastly, the synthesis of flexible-chain linked derivatives will help to determine whether a longer and therefore more complex structure is necessary for increase selectivity for the 5-HT\textsubscript{7} and 5-HT\textsubscript{6} receptors.

4.1 Future Work

The search for a selective 5-HT\textsubscript{7} receptor antagonist continues to be a major area of interest among medicinal chemists. There are numerous pharmacophore models that have been proposed and based on those it appears there are six key interactions that are necessary to have high affinity and selectivity: two H-bonding acceptor groups (green), three hydrophobic regions (blue), and a protonated nitrogen (red) (Figure 5).
There is a hydrophobic site in the binding pocket that could help increase the selectivity of the antagonist for the 5-HT7 receptor. Previously published work shows that the addition of a flexible-chain linked aromatic region leads to an increase in selectivity for the 5-HT7 receptor.5,15-20 All of the previously published work attached a linker ranging from 3-5 carbons in length connecting the heteroarene portion to another aromatic portion (Table 4).

By adding a 3 – 5 carbon chain linker, the selectivity for 5-HT7 was increased significantly, as is evident from Table 4. The spacer has not been modified in order to explore the possibilities of the binding in the hydrophobic region. It would be informative to make derivatives with cyclopropane to cyclohexane rings installed in the linker (Figure 20). Also in order to increase the solubility in plasma which needs to be taken into account, the use of a polyethylene glycol linker could be attempted. It would be useful to determine how nonpolar the linker has to be or if there are amino acids present that could interact with the oxygen present in the polyethylene glycol moiety (Figure 20). This has yet to be explored and could lead to interactions that would lead to a more selective 5-HT7 antagonist.
Figure 20. Examples for Future Synthesis.

Also modifying the previously synthesized compounds in our lab with the addition of long alkyl chains with the addition of simple amines or thiols should be investigated also (Figure 21).

Figure 21. Alkyl Chain Derivatives for Future Work.
5 EXPERIMENTAL

5.1 General

THF was purified by distillation from sodium benzophenone ketyl under a nitrogen atmosphere. All reagents were purchased from a commercial source and used as received. Glassware was dried in an oven at 120 °C, assembled hot and cooled to room temperature under a continuous nitrogen flow prior to use. Hydrobromide salts of the piperazine products were obtained by using the general procedure, and the salts were crystallized from methanol. In several cases it was necessary to dilute the methanolic solution with ether to induce crystallization. GC/MS spectra were obtained on a Shimadzu GC-17A gas chromatotron coupled to a Shimadzu QP-5000 mass spectrometer at 70 eV. NMR data were obtained in CDCl$_3$ at 27 °C on a Bruker instrument (400 MHz) and elemental analysis was obtained on a Perkin Elmer 2400 Series II CHN analyzer. Melting points are uncorrected. Intermediates that were not sent for analysis of biological activity were not fully characterized. Final products were fully characterized by $^1$H NMR, $^{13}$C NMR, accurate mass, and elemental analysis. Radioligand binding studies for the 5-HT$_{2A}$, 5-HT$_7$ and 5-HT$_6$ receptors were performed according to the published procedure.  

5.2 Lithium Reagents

$n$-Butyllithium (2.5 M in hexanes) and tert-butyllithium (1.7 M in pentane) were commercial reagents. 3-Lithiothiophene was generated by lithium halogen exchange reaction between 3-bromothiophene and $n$-butyllithium. A solution of the corresponding bromo derivative (12.5 mmol) in anhydrous THF (15 mL) was cooled to -70 °C and treated dropwise with $n$-butyllithium (6.3 mL, 12.6 mmol) for 5 min. The mixture was stirred at -70 °C for 30 min before treatment with 2-chloropyrimidine. 2-Lithiofuran was generated by lithiation of furan. Vinylithium was
generated by the reaction of tetravinyltin with tert-butyllithium as previously described.\textsuperscript{60-63} A solution of tetravinyltin (0.7 mL, 3.2 mmol) in tetrahydrofuran (5.0 mL), was treated dropwise with tert-butyllithium (7.4 mL, 12.6 mmol) at -78 °C for 5 min, and the mixture was stirred for an additional 15 min at -78 °C before use.

5.3 Synthesis of Pyrimidines

General procedure for synthesis of 4,6-substituted 2-(4-methylpiperazino)pyrimidines 7 – 9. Compounds 7 – 9 were prepared as previously described with slight modifications.\textsuperscript{30,61} A solution of 2-furyllithium or 3-thienyllithium (8.7 mmol) in THF (5.0 mL) was treated dropwise with 2-chloropyrimidine (1.0 g, 8.7 mmol) in tetrahydrofuran (30 mL) at -5 °C under nitrogen atmosphere. The mixture was stirred for 30 min at -5 °C, then quenched with water (5.0 mL) in tetrahydrofuran (5.0 mL). After treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ, 1.9 g, 8.7 mmol), the reaction solution stirred for 5 min to reach room temperature. The solution was basified with sodium carbonate (saturated) till pH = 9 and was then extracted with diethyl ether (2 × 30 mL), dried over magnesium sulfate, and concentrated in vacuo to provide a crude residue. The crude residue was purified by chromatography eluting with hexanes/diethyl ether (80:20) to provide 2 and 3 which were utilized in the next step. A solution of either ethyllithium or n-butyllithium (1.2 mmol) was added dropwise to a solution of 2 or 3 (1.1 mmol) in tetrahydrofuran (3.0 mL) at -78 °C. The reaction solution stirred for 5 min, then quenched with water (1.0 mL) in tetrahydrofuran (1.0 mL) and allowed to warm to room temperature. After treatment with 2,3-dichloro-5,6-dicyanoquinone (DDQ, 1.1 g, 8.7 mmol), the reaction solution was allowed to stir for 5 min to reach room temperature. The solution was basified with sodium carbonate (saturated) till
pH = 9 and was then extracted with diethyl ether (2 × 20 mL), dried over magnesium sulfate, and concentrated *in vacuo* to provide crude residue. The crude residue was purified by chromatography eluting with hexanes/diethyl ether (80:20) to provide 4 – 6 which were utilized for the reaction with *N*-methylpiperazine. A solution of compound 4 – 6 (179 mg, 0.75 mmol) and *N*-methylpiperazine (0.25 mL, 2.26 mmol) in toluene (3.0 mL) was heated to 80 °C overnight, after which the mixture was cooled to room temperature. The reaction mixture was basified with sodium carbonate, extracted with Et₂O (2 × 15 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. The crude residue was purified on a chromatotron with EMD 60PF₂⁵₄ silica gel eluting with dichloromethane/methanol (100:0 for 100 mL, then 9:1 for 250 mL) to provide 7 – 9.

*2-Chloro-4-(2-furyl)pyrimidine (2, EAR-II-56)*: This compound was obtained as a white solid in 56 % yield (884 mg), mp 57 – 59 °C. ¹H NMR (CDCl₃, 400 MHz): δ 8.56 (d, *J* = 4.8 Hz, 1H), 7.63 (s, 1H), 7.52 (d, *J* = 5.2 Hz, 1H), 7.38 (d, *J* = 3.6 Hz, 1H), 6.61 (t, *J* = 1.6 Hz, 1H); ¹³C NMR (CDCl₃, 400 MHz): δ 161.8, 159.9, 158.1, 150.6, 146.3, 114.6, 113.2, 113.1; High-resolution ms (ESI, positive ion mode): calcd. for C₈H₅ClN₂O (M + 1)⁺, *m/z* 181.0162; Found *m/z* 181.0169. Anal Calcd. for C₈H₆ClN₂O: C, 53.21; H, 2.79; N, 15.51. Found: C, 53.61; H, 2.26; N, 15.48.

*2-Chloro-4-(3-thienyl)pyrimidine (3, EAR-II-66(5))*: This compound was obtained as a white solid 14% yield (123 mg), mp 58 – 60 °C. ¹H NMR (CDCl₃, 400 MHz): δ 8.59 (d, *J* = 5.2 Hz, 1H), 8.22–8.21 (m, 1H), 7.69 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 7.47 (d, *J* = 5.4 Hz, 1H), 7.45–7.43 (m, 1H). Anal Calcd. for C₈H₅ClN₂S: C, 47.90; H, 2.26; N, 13.24. Found: C, 48.20; H, 2.56; N, 12.98.

*2-Chloro-4-ethyl-6-(2-furyl)pyrimidine (4, EAR-II-60)*. This compound was obtained as a white solid in 55% yield (96 mg), mp 28 – 30 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.61 (s, 1H), 7.40 (s,
1H), 7.35 (d, J = 3.6 Hz, 1H), 6.59–6.58 (m, 1H), 2.81 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H); 13C NMR (CDCl₃, 400 MHz): δ 175.9, 161.2, 157.8, 150.7, 145.6, 115.6, 112.8, 110.77, 30.9, 12.7; High-resolution ms (ESI, positive ion mode): calcd. for C₁₀H₉ClN₂O (M + 1)⁺, m/z 209.0476; Found m/z 209.0482.

4-Butyl-2-chloro-6-(2-furyl)pyrimidine (5, EAR-II-58). This compound was obtained as a white solid in 73% yield, (190 mg); mp 30 – 33 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.63 (s, 1H), 7.40 (s, 1H), 7.36 (d, J = 3.6 Hz, 1H), 6.61–6.60 (m, 1H), 2.79 (t, J = 8.0 Hz, 2H), 1.80–1.72 (m, 2H), 1.48–1.39 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 175.2, 157.8, 150.9, 145.8, 113.0, 111.9, 93.5, 37.8, 31.1, 22.6, 14.0; High-resolution ms (ESI, positive ion mode): calcd. for C₁₂H₁₃ClN₂O (M + 1)⁺, m/z 237.0795; Found m/z 237.0795.

4-Butyl-2-chloro-6-(3-thienyl)pyrimidine (6, EAR-II-67). This compound was obtained as a clear colorless oil in 76% yield (53 mg). ¹H NMR (CDCl₃, 400 MHz): δ 8.18–8.17 (m, 1H), 7.67 (dd, J = 5.2 Hz, 1.2 Hz, 1H), 7.43–7.41 (m, 1H), 7.30 (s, 1H), 2.77 (t, J = 8.0 Hz, 2H), 1.78–1.71 (m, 2H), 1.46–1.37 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H).

4-Ethyl-6-(2-furyl)-2-(4-methylpiperazino)pyrimidine (7, EAR-II-62). This compound was obtained as a clear colorless oil in 61% yield (63 mg). ¹H NMR (CDCl₃, 400 MHz): δ 7.52 (s, 1H), 7.12 (d, J = 3.2 Hz, 1H), 6.77 (s, 1H), 6.51–6.50 (m, 1H), 3.91 (t, J = 4.8 Hz, 4H), 2.64 (q, J = 7.4 Hz, 2H), 2.48 (t, J = 4.8 Hz, 4H), 2.34 (s, 3H), 1.27 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 173.2, 162.0, 155.8, 153.3, 144.1, 112.1, 110.8, 102.4, 55.3, 46.5, 43.8, 31.4, 12.7; High-resolution ms (ESI, positive ion mode): calcd. for C₁₅H₂₀N₄O (M + 1)⁺, m/z 273.1725; Found m/z
A hydrobromide salt, mp > 250 °C; Anal Calcd. for C_{15}H_{20}N_{4}O•2HBr: C, 41.50; H, 5.11; N, 12.70. Found: C, 41.79; H, 4.87; N, 12.28.

4-Butyl-6-(furyl)-2-(4-methylpiperazino)pyrimidine (8, EAR-II-59(2)). This compound was obtained as clear colorless oil in 78% yield (178 mg). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.52 (s, 1H), 7.11 (d, \(J = 3.2\) Hz, 1H), 6.75 (s, 1H), 6.52–6.50 (m, 1H), 3.90 (t, \(J = 4.6\) Hz, 4H), 2.60 (t, \(J = 7.4\) Hz, 2H), 2.48 (t, \(J = 4.6\) Hz, 4H), 2.35 (s, 3H), 1.74–1.66 (m, 2H), 1.42–1.37 (m, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 172.4, 162.1, 155.8, 153.4, 144.1, 112.2, 110.8, 103.1, 55.3, 46.5, 43.9, 38.1, 30.8, 22.7, 14.2; High-resolution ms (ESI, positive ion mode): calcd. for C\(_{17}\)H\(_{24}\)N\(_4\)O \(\left(\text{M} + 1\right)^+\), \(m/z\) 301.2026; Found \(m/z\) 301.2028. A hydrobromide salt, mp 183–185 °C; Anal Calcd. for C\(_{17}\)H\(_{24}\)N\(_4\)O•HBr: C, 53.55; H, 6.61; N, 14.10. Found: C, 53.34; H, 6.60; N, 14.69.

4-Butyl-2-(4-methylpiperazino)-6-(thiophen-3-yl)pyrimidine (9, EAR-II-69(2)). This compound was obtained as a white solid in 11% yield (6.3 mg), mp 33 – 35 °C. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.00 (bs, 1H), 7.63 (d, \(J = 5.2\) Hz, 1H), 7.36–7.34 (m, 1H), 6.67 (s, 1H), 3.93 (bs, 4H), 2.60 (t, \(J = 7.4\) Hz, 2H), 2.49 (t, \(J = 4.8\) Hz, 4H), 2.35 (s, 3H), 1.74–1.66 (m, 2H), 1.43–1.37 (m, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 172.3, 159.9, 141.7, 126.4, 126.2, 125.6, 104.9, 91.2, 55.3, 46.5, 43.9, 38.1, 30.9, 22.7, 14.2; High-resolution ms (ESI, positive ion mode): calcd. for C\(_{17}\)H\(_{24}\)N\(_4\)S \(\left(\text{M} + 1\right)^+\), \(m/z\) 317.1800; Found \(m/z\) 317.1800. Anal Calcd. for C\(_{17}\)H\(_{24}\)N\(_4\)S, H\(_2\)O: C, 64.81; H, 7.74; N, 16.30. Found: C, 64.41; H, 7.83; N, 16.70.

2-Chloro-4-vinylpyrimidine (10, EAR-I-137). This compound was synthesized according to previously published work.\(^{34}\) The \(^1\)H NMR spectrum of 10 [(CDCl\(_3\)] \(\delta\) 8.57 (d, \(J = 5.0\) Hz, 1H),
7.22 (d, $J = 5.0$ Hz, 1H), 6.70 (m, 1H), 6.52 (m, 1H), 5.80 (m, 1H) was virtually identical with that reported in literature for the compound obtained by an independent route.\textsuperscript{47} \textsuperscript{13}C NMR (CDCl$_3$): δ 165.5, 161.6, 159.9, 133.9, 125.3, 116.5; \textit{High-resolution ms} (ESI, positive ion mode): calcd. for $C_6H_5ClN_2 (M + 1)^+$, $m/z$ 141.0218; found $m/z$ 141.0220.

**General procedure for the synthesis of 15 -18.** To a mixture of 2-chloro-4-vinylpyrimidine (0.115 g, 1.0 mmol) in toluene (5.0 mL) was added the corresponding nucleophile (dimethylamine, benzylamine, methoxide or ethane thiolate) (0.14 g, 1.0 mmol). The mixture was stirred at room temperature overnight or at 90 °C for 2 h, then cooled to room temperature, basified with sodium carbonate and extracted with ethyl ether (2 × 15 mL). The organic extracts were combined, dried over magnesium sulfate, and concentrated \textit{in vacuo} to provide crude 2-chloro-4-substituted pyrimidine derivatives 11 – 14, that without further purification were used for the reaction with $N$-methylpiperazine. Thus, a solution of crude compounds 11 – 14 and $N$-methylpiperazine (0.14 mL, 1.2 mmol) in toluene (4.0 mL) was heated to 80 °C until a TLC analysis on silica gel eluting with hexanes/ethyl ether (80:20) showed the absence of 11 – 14 (several hours). The solution was cooled to room temperature, basified with sodium carbonate and extracted with ethyl ether (2 × 15 mL). The organic extracts were combined, dried over magnesium sulfate, and concentrated \textit{in vacuo} to provide crude compounds 15 – 18. The crude products were purified on a chromatotron with normal phase EMD 60PF$_{254}$ silica gel eluting with hexanes/ethyl ether/methanol (80:15:5) to give 15 – 18.

**2-(2-Chloropyrimidin-4-yl)-$N,N$-dimethylethanamine (11, EAR-I-47(2)).** This compound was obtained as a light yellow oil in 27% yield. Product decomposed when put on silica gel for
purification. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.52 (d, $J = 5.2$ Hz, 1H), 7.21 (d, $J = 5.2$ Hz, 1H), 2.95 (t, $J = 7.2$ Hz, 2H), 2.75 (t, $J = 7.6$ Hz, 2H), 2.34 (s, 6H).

$N,N$-Dimethyl-2(2-(4-methylpiperazino)pyrimidin-4-yl)ethanamine (15, EAR-I-53(2)). This compound was obtained as a brown oil in 55% yield; $^1$H NMR (CDCl$_3$): δ 8.20 (d, $J = 4.8$ Hz, 1H), 6.41 (d, $J = 4.8$ Hz, 1H), 3.86 (t, $J = 5.2$ Hz, 4H), 2.77–2.74 (m, 2H), 2.71–2.69 (m, 2H), 2.48 (t, $J = 5.2$ Hz, 4H), 2.35 (s, 3H), 2.31 (s, 6H); $^{13}$C NMR (CDCl$_3$): δ 169.2, 161.7, 157.4, 109.4, 57.9, 54.9, 46.2, 45.2, 43.6, 35.7. High-resolution MS (ESI, positive ion mode): calcd. for C$_{13}$H$_{23}$N$_5$ (M$^+$ + 1), m/z 250.2007; found m/z 250.2032.

$N$-Benzyl-2(2-chloropyrimidin-4-yl)ethanamine (12, EAR-I-35(4)). This compound was obtained as a light yellow oil in 61% yield (268 mg). $^1$H NMR (CDCl$_3$): δ 8.51 (d, $J = 5.2$ Hz, 1H), 7.34–7.27 (m, 5H), 7.17 (d, $J = 4.8$ Hz, 1H), 3.83 (s, 2H), 3.09 (d, $J = 6.8$ Hz, 2H), 3.09 (t, $J = 7.6$ Hz, 2H).

$N$-Benzyl-2(2-(4-methylpiperazino)pyrimidin-4-yl)ethanamine hydrobromide (16, EAR-I-40). This salt was obtained in 62% yield; mp 110–112 °C; $^1$H NMR (DMSO-$d_6$): δ 10.0 (bs, 1H), 8.96 (bs, 1H), 8.37 (d, $J = 4.8$ Hz, 1H), 7.58–7.55 (m, 2H), 7.49–7.42 (m, 3H), 6.73 (d, $J = 5.4$ Hz, 1H), 4.68 (d, $J = 14.4$ Hz, 2H), 4.24 (t, $J = 5.4$ Hz, 2H), 3.55–3.50 (m, 2H), 3.39–3.29 (m, 4H), 3.06 (t, $J = 7.6$ Hz, 4H), 2.86 (bs, 3H); $^{13}$C NMR (CDCl$_3$): δ 169.0, 161.6, 157.6, 129.1, 128.5, 128.3, 127.3, 109.4, 54.9, 53.6, 47.4, 46.2, 43.6, 36.8; MS (ESI) m/z 312 (M$^+$ + H). Anal. Calcd for C$_{18}$H$_{25}$N$_5$•4HBr•H$_2$O: C, 33.10; H, 4.78; N, 10.72. Found: C, 33.43; H, 5.10; N, 10.66.
2-Chloro-4-(2-methoxyethyl)pyrimidine (13, EAR-I-39). This compound was obtained as a light yellow oil in 58% yield (63 mg). $^1$H NMR (CDCl$_3$): $\delta$ 8.53 (d, $J = 4.8$ Hz, 1H), 7.23 (d, $J = 5.2$ Hz, 1H), 3.79 (t, $J = 6.4$ Hz, 2H), 3.36 (s, 3H), 3.03 (t, $J = 6.0$ Hz, 2H).

4-(2-Methoxyethyl)-2-4-methylpiperazino)pyrimidine (17, EAR-I-55). The free base was obtained as an oil in 55% yield; $^1$H NMR for the free base (CDCl$_3$): $\delta$ 8.22 (d, $J = 5.0$ Hz, 1H), 6.44 (d, $J = 5.0$ Hz, 1H), 3.87 (t, $J = 5.0$ Hz, 4H), 3.77 (t, $J = 6.8$ Hz, 2H), 3.37 (s, 3H), 2.85 (t, $J = 6.8$ Hz, 2H), 2.48 (t, $J = 4.8$ Hz, 4H), 2.36 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 168.1, 161.7, 157.4, 109.4, 70.9, 58.7, 55.0, 46.2, 43.6, 38.0. High-resolution MS for the free base (ESI, positive ion mode): calcd. for C$_{12}$H$_{20}$N$_4$O (M$^+$+ 1), m/z 237.1705; found m/z 237.1715. The hydrobromide salt was obtained as a brown solid; mp 114–116 °C. Anal. calcd for: C$_{12}$H$_{20}$N$_4$O•3HBr: C, 30.09; H, 4.24; N, 11.70. Found: C, 29.86; H, 4.34; N, 12.12.

2-Chloro-4-(2-(ethylthio)ethyl)pyrimidine (14, EAR-I-32(3)). This compound was obtained as a light yellow oil in 20% yield (69 mg). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.53 (d, $J = 4.8$ Hz, 1H), 7.16 (d, $J = 4.8$ Hz, 1H), 3.07 (t, $J = 6.6$ Hz, 2H), 2.96 (t, $J = 6.6$ Hz, 2H), 2.58 (q, $J = 7.4$ Hz, 2H), 1.27 (t, $J = 7.4$ Hz, 3H).

4-(2-(Ethylthio)ethyl)-2-(4-methylpiperazino)pyrimidine (18, EAR-I-46(1)). This compound was obtained as an oil in 25% yield; $^1$H NMR (CDCl$_3$): $\delta$ 8.22 (d, $J = 5.0$ Hz, 1H), 6.41 (d, $J = 5.0$ Hz, 1H), 3.87 (t, $J = 4.8$ Hz, 4H), 2.92–2.90 (m, 2H), 2.88–2.86 (m, 2H), 2.60 (q, $J = 7.4$ Hz, 2H), 2.49 (t, $J = 4.8$ Hz, 4H), 2.36 (s, 3H), 1.29 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 168.9, 161.7, 157.4, 109.1, 55.0, 46.2, 43.6, 38.0, 29.8, 26.0, 14.7. High-resolution MS (ESI, positive ion mode): calcd. for C$_{13}$H$_{22}$N$_4$S (M$^+$+ 1), m/z 267.1632; found m/z 267.1643.
General procedure for the synthesis of 21 and 22. To a solution of copper iodide (0.03 g, 0.18 mmol) in tetrahydrofuran (2.0 mL) was added Grignard reagent (3.0 M in hexanes, 0.32 mL, 0.96 mmol) at -50 °C. The mixture was stirred for 10 min, after which compound 10 (100 mg, 0.71 mmol) in tetrahydrofuran (4.0 mL) was added dropwise. The mixture was stirred to -40 °C over 2 h, quenched with saturated aqueous NH₄Cl. The mixture was extracted with ethyl acetate (2 × 15 mL); the organic layers were combined, dried over magnesium sulfate, and concentrated on a rotary evaporator to provide crude 19 and 20. Without further purification, 19 and 20 were used for the reaction with N-methylpiperazine. Thus, a solution of crude 19 and 20 and N-methylpiperazine (0.04 mL, 0.33 mmol) in toluene (3.0 mL) was heated to 120 °C until TLC analysis showed the absence of 19 and 20 (several hours). The mixture was cooled to room temperature, basified with sodium carbonate, and extracted with diethyl ether (2 × 10 mL). The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo. The residues were purified on a chromatotron with EMD 60PF₂₅₄ silica gel eluting with hexanes/ethyl ether/methanol (80:15:5) to provide 21 and 22.

2-Chloro-4-propylpyrimidine (19, EAR-I-126). This compound was obtained as a light yellow oil in 55% yield (28 mg). ¹H NMR (CDCl₃, 400 MHz): δ 8.51 (d, J = 5.2 Hz, 1H), 7.13 (d, J = 5.2 Hz, 1H), 2.75 (t, J = 7.6 Hz, 2H), 1.81–1.74 (m, 2H), 1.00 (t, J = 7.6 Hz, 3H).

2-(4-Methylpiperazino)-4-propylpyrimidine (21, EAR-I-128). This compound was obtained as an oil in 56% yield; ¹H NMR (CDCl₃): δ 8.22 (d, J = 5.2 Hz, 1H), 6.46 (d, J = 5.2 Hz, 1H), 4.67 (d, J = 14.0 Hz, 2H), 3.96 (t, J = 14.0 Hz, 2H), 3.36–3.25 (m, 7H), 2.56 (t, J = 7.6 Hz, 2H), 1.75–1.70 (m, 2H), 0.97 (t, J = 7.6 Hz, 3H); ¹³C NMR (CDCl₃): δ 170.2, 160.3, 157.3, 110.0, 65.8, 60.5,
2-Chloro-4-phenethylpyrimidine (20, EAR-I-86(2)). This compound was obtained as a light yellow oil in 32% yield (125 mg). $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.47 (d, $J = 4.8$ Hz, 1H), 7.32–7.28 (m, 2H), 7.23–7.10 m, 3H), 7.02 (d, $J = 4.8$ Hz, 1H), 3.07 (t, $J = 9.2$ Hz, 4H).

2-(4-Methylpiperazino)-4-phenethylpyrimidine (22, EAR-I-87). This compound was obtained as an oil in 77% yield; $^1$H NMR (CDCl$_3$): $\delta$ 8.19 (d, $J = 5.0$ Hz, 1H), 7.31 (t, $J = 7.2$ Hz, 2H), 7.23–7.21 (m, 3H), 6.35 (d, $J = 5.0$ Hz, 1H), 3.88 (t, $J = 4.8$ Hz, 4H), 3.04 (q, $J = 7.2$ Hz, 2H), 2.90 (q, $J = 7.2$ Hz, 2H), 2.49 (t, $J = 4.8$ Hz, 4H), 2.37 (s, 3H); $^{13}$C NMR (CDCl$_3$): $\delta$ 170.0, 161.7, 157.3, 141.4, 128.4, 128.3, 125.9, 109.0, 55.0, 46.3, 43.6, 39.4, 34.2. High-resolution MS (ESI, positive ion mode): calcd. for C$_{17}$H$_22$N$_4$ (M$^+$ + 1), m/z 283.1931; found m/z 283.1923.

5.4 Synthesis of Quinazolines

2,4-Dichloroquinazoline (24, EAR-II-45): 2,4-dichloroquinazoline was prepared as previously described$^{40}$ with slight modifications to improve the yield. Benzoylurea (5.0 g, 30.8 mmol), phosphorus oxychloride (14.9 mL, 163.4 mmol), N,N-dimethylaniline (1.6 mL, 12.3 mmol) and N,N-dimethylformamide (2 drops) were combined in a round bottom flask under nitrogen atmosphere. The mixture was heated to 120° C for 6 h, after which the reaction was cooled to room temperature, and poured over ice. The mixture was filtered, washed with water (300 mL) and dried under reduced pressure at room temperature overnight. The pink solid was crystallized with i-PrOH (50 mL) to provide 2,4-dichloroquinazoline (24, 2.95 g, 48%) as an off-white solid, mp 64–66 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.31 (d, $J = 8.4$ Hz, 1H), 8.03 (t, $J = 4.4$ Hz, 2H),
7.79–7.75 (m, 1H); $^{13}$C NMR (DMSO- $d_6$, 400 MHz) $\delta$ 162.8, 150.3, 140.8, 134.9, 126.9, 122.3, 115.3, 114.3.

**2-Chloroquinazoline (25, EAR-I-138):** 2-Chloroquinazoline was prepared as previously described.\(^{40}\) 2,4-Dichloroquinazoline (24, 1.0 g, 5.00 mmol) was combined with CH$_2$Cl$_2$ (20 mL) in a round bottom flask. A solution of 9% NH$_3$ in a saturated aqueous solution of NaCl (20 mL) was added to the mixture followed by activated Zn (dust, 32 mesh) (980 mg, 15.0 mmol). The mixture was vigorously stirred for 5 h at 40° C under nitrogen atmosphere. The mixture was then cooled to room temperature and filtered through Celite washing with CH$_2$Cl$_2$ (20 mL). The organic layer was washed with aqueous hydrochloric acid (1.0 N, 20 mL), dried (Na$_2$SO$_4$), filtered and concentrated *in vacuo*. The solid was purified on a chromatotron with EMD 60PF$_{254}$ silica gel eluting with hexanes/ethyl acetate (4:1 for 100 mL, then 1:1 for 100 mL) to provide 2-chloroquinazoline (25, 443 mg, 54%) as a yellow solid. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 9.33 (s, 1H), 8.04–7.97 (m, 3H), 7.74–7.70 (m, 1H).

**2-Chloro-4-vinylquinazoline (26, EAR-II-9).** 2-Chloro-4-vinylquinazoline was prepared according to Babbitt.\(^{39}\) tert-Butyllithium (3.70 mL, 6.30 mmol) was added to a solution of tetravinyltin (0.84 mL, 4.62 mmol) in tetrahydrofuran (10.0 mL) at -78 °C. The reaction mixture was stirred for 5 min at -78 °C until a cloudy white suspension formed, after which a solution of 2-chloroquinazoline (25, 960 mg, 4.20 mmol) in tetrahydrofuran (7.0 mL) was added dropwise. The mixture was allowed to warm to -60 °C slowly over 1 h, after which the reaction was quenched dropwise with a mixture of water (2.0 mL) and tetrahydrofuran (2.0 mL). The mixture was allowed to warm to room temperature, then basified with aqueous sodium carbonate until the pH = 9, extracted with Et$_2$O (2 × 30 mL), dried (MgSO$_4$), filtered and concentrated *in vacuo* to provide
a crude yellow solid of 2-chloro-4-vinyl-3,4-dihydroquinazoline (85 mg, 0.44 mmol). A solution of this product dissolved in benzene (2.0 mL) was added to a solution of potassium hydroxide (0.079 g, 1.41 mmol), potassium ferricyanide (III) (0.350 g, 1.05 mmol) in water (0.50 mL) under nitrogen atmosphere at room temperature. The mixture was stirred vigorously for 5 h, after which benzene (20 mL) and water (20 mL) were added and the organic layer was extracted, dried (MgSO$_4$), filtered and concentrated in vacuo to provide **2-chloro-4-vinylquinazoline (26, 57 mg, 68%)** as a off-white solid; mp 65 – 67 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.21 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 4.8$ Hz, 1H), 7.94 (t, $J = 7.2$ Hz, 1H), 7.68 (t, $J = 5.6$ Hz, 1H), 7.59–7.52 (m, 1H), 6.97 (dd, $J = 9.2$, 1.6 Hz, 1H), 6.02 (dd, $J = 9.2$, 1.6 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 165.5, 157.8, 153.2, 135.0, 129.2, 128.4, 128.2, 128.1, 124.6, 121.4. High-resolution ms (ESI, positive ion mode): calcd. for C$_{10}$H$_7$ClN$_2$ (M$^+$ + 1), m/z 190.0379; found m/z 190.0376. Anal. Calcd. for C$_{10}$H$_7$ClN$_2$: C, 63.01; H, 3.70; N, 14.70. Found: C, 62.64; H, 3.55; N, 15.00.

**General procedure for the synthesis of 4-substituted-2-(4-methylpiperazino)quinazolines 27 – 34.** To a mixture of 2-chloro-4-vinylquinazoline (26, 0.15g, 0.78 mmol) in toluene (3.0 mL) was added the corresponding nucleophile (0.12 g, 0.78 mmol). The mixture was stirred at 90 °C for 2 h. The mixture was cooled to room temperature, basified with sodium carbonate and extracted with ethyl ether (2 × 15 mL). The organic extracts were combined, dried over magnesium sulfate, and concentrated in vacuo to provide crude 4-substituted 2-chloroquinazolines that without further purification were used for the reaction with N-methylpiperazine. Thus, solutions of crude compounds and N-methylpiperazine (0.30 mL, 2.7 mmol) in toluene (3.0 mL) were heated to 80 °C until a TLC analysis on silica gel eluting with hexanes/ethyl ether/methanol (80:15:5) showed the absence of intermediates (several hours). The solution was cooled to room temperature,
basified with sodium carbonate, and extracted with ethyl ether (2 × 15 mL). The organic extracts were combined, dried over magnesium sulfate, and concentrated in vacuo to provide crude compounds 27 – 34. The crude products were purified by chromatotron with EMD 60PF254 silica gel eluting with hexanes/ethyl ether/methanol (50:40:10) to give 27 – 34.

N,N-Dimethyl-2-[2-(4-methylpiperazino)quinazolin-4-yl]ethanamine (27, EAR-II-27). The free base was obtained as a yellow oil in 27% yield; ¹H NMR for the free base (CDCl₃): δ 7.86 (d, J = 8.0 Hz, 1H), 7.60–7.57 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H), 3.99 (t, J = 5.0 Hz, 4H), 3.29 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 8.0 Hz, 2H), 2.51 (t, J = 5.0 Hz, 4H), 2.36 (s, 6H), 2.35 (s, 3H); ¹³C NMR for the free base (CDCl₃): δ 170.1, 158.4, 152.3, 133.3, 126.4, 124.6, 122.1, 118.6, 57.6, 55.1, 46.3, 45.5, 43.8, 32.4. High-resolution MS (ESI, positive ion mode): calcd. for C₁₇H₂₅N₅ (M⁺ + 1), m/z 300.2175; found m/z 300.2188. A hydrobromide salt: mp 100 – 106 °C (dec.). Anal. Calcd. for C₁₇H₂₅N₅•3.5HBr•H₂O: C, 34.00; H, 5.12; N, 11.66. Found: C, 33.74; H, 5.40; N, 11.26.

N-[2-(2-(4-Methylpiperazino)quinazolin-4-yl)ethyl]butanamine (28, EAR-II-37(2)). The free base was obtained as a brown oil in 31% yield; ¹H NMR for the free base (CDCl₃): δ 7.83 (d, J = 8.0 Hz, 1H), 7.62–7.53 (m, 2H), 7.14 (d, J = 8.0 Hz, 1H), 3.96 (s, 4H), 3.49 (t, J = 6.6 Hz, 2H), 3.30 (t, J = 6.6 Hz, 2H), 2.81 (t, J = 7.2 Hz, 2H), 2.51 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H), 1.64–1.59 (m, 3H), 1.40–1.32 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ¹³C NMR for the free base (CDCl₃): δ 169.1, 158.3, 152.5, 133.8, 126.6, 124.7, 122.6, 118.6, 55.2, 49.3, 46.8, 46.4, 44.1, 32.5, 31.2, 20.6, 14.0; High-resolution MS (ESI, positive ion mode): calcd. for C₁₉H₂₉N₅ (M⁺ + 1), m/z 328.2503; found m/z 328.2501. A hydrobromide salt: mp 153 – 155 °C. Anal. Calcd. for C₁₉H₂₉N₅•3HBr•3H₂O: C, 36.04; H, 6.21; N, 11.06. Found: C, 35.89; H, 6.00; N, 11.28.
N-Benzyl-2-[2-(4-methylpiperazino)quinazolin-4-yl]ethanamine (29, EAR-II-57). The free base was obtained as a yellow oil in 50% yield; $^1$H NMR for the free base (CDCl$_3$): $\delta$ 7.84 (d, $J = 8.0$ Hz, 1H), 7.64–7.56 (m, 2H), 7.33 (d, $J = 4.4$ Hz, 4H), 7.28–7.25 (m, 1H), 7.18 (t, $J = 8.0$ Hz, 1H), 3.96 (d, $J = 4.6$ Hz, 4H), 3.88 (s, 2H), 3.38 (t, $J = 6.2$ Hz, 2H), 3.22 (t, $J = 6.2$ Hz, 2H), 2.49 (t, $J = 4.6$ Hz, 4H), 2.36 (s, 3H), 2.26 (bs, 1H); $^{13}$C NMR for the free base (CDCl$_3$): $\delta$ 170.1, 158.4, 152.4, 140.2, 133.6, 128.6, 128.3, 127.2, 126.5, 124.7, 122.4, 118.8, 55.2, 54.2, 46.7, 46.4, 44.0, 33.7. *High-resolution MS* (ESI, positive ion mode): calcd. for C$_{22}$H$_{27}$N$_5$ (M$^+$ + 1), m/z 362.2354; found m/z 362.2345. A hydrobromide salt: mp 160–162 °C. Anal. Calcd. for C$_{22}$H$_{27}$N$_5$•3HBr: C, 43.73; H, 5.00; N, 11.59. Found: C, 43.88; H, 5.48; N, 11.39.

2-(4-Methylpiperazin-1-yl)-4-[2-(4-methylpiperazino)]quinazoline (30, EAR-I-139). This compound was obtained as a brown solid in 40% yield; mp 72–74 °C; $^1$H NMR (CDCl$_3$): $\delta$ 7.88 (d, $J = 7.6$ Hz, 1H), 7.63–7.57 (m, 2H), 7.22–7.18 (m, 1H), 4.00 (t, $J = 8.0$ Hz, 4H), 3.37–3.32 (m, 2H), 2.98–2.94 (m, 2H), 2.66 (bs, 4H), 2.52 (t, $J = 4.8$ Hz, 8H), 2.37 (s, 3H), 2.33 (s, 3H); Anal. Calcd. for C$_{20}$H$_{30}$N$_6$: C, 67.76; H, 8.53; N, 23.71. Found: C, 67.93; H, 8.84; N, 23.96.

2-(4-Methylpiperazin-1-yl)-4-[2-(4-phenylpiperazino)ethyl]quinazoline (31, EAR-II-20). The free base was obtained as a brown oil in 23% yield; $^1$H NMR for the free base (CDCl$_3$): $\delta$ 7.90 (d, $J = 8.0$ Hz, 1H), 7.66–7.58 (m, 2H), 7.31–7.27 (m, 2H), 7.21 (t, $J = 8.0$ Hz, 1H), 6.97 (d, $J = 8.0$ Hz, 2H), 6.88 (t, $J = 7.2$ Hz, 1H), 4.03 (s, 4H), 3.39 (t, $J = 7.8$ Hz, 2H), 3.27 (t, $J = 4.8$ Hz, 4H), 3.02 (t, $J = 7.8$ Hz, 2H), 2.79 (t, $J = 4.8$ Hz, 4H), 2.55 (t, $J = 6.0$ Hz, 4H), 2.39 (s, 3H); $^{13}$C NMR for the free base (CDCl$_3$): $\delta$ 170.2, 159.3, 152.5, 151.4, 133.6, 129.3, 126.7, 124.8, 122.5, 119.9, 118.8, 116.3, 56.6, 55.2, 53.4, 49.3, 46.3, 43.9, 31.9. *High-resolution MS* (ESI, positive ion mode): calcd. for C$_{25}$H$_{32}$N$_6$ (M$^+$ + 1), m/z 417.2751; found m/z 417.2767. A hydrobromide salt:
mp 190 – 194 °C (dec.). Anal. Calcd. for C_{25}H_{32}N_{6}•4HBr•2H_{2}O: C, 38.68; H, 5.19; N, 10.83. Found: C, 38.78; H, 5.51; N, 10.46.

4-(2-Methoxyethyl)-2-(4-methylpiperazino)quinazoline (32, EAR-II-24). This compound was obtained as a yellow solid in 27% yield; mp 35–37 °C; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.86 (d, \(J = 8.0\) Hz, 1H), 7.61–7.55 (m, 2H), 7.18 (t, \(J = 8.0\) Hz, 1H), 3.99 (t, \(J = 4.8\) Hz, 4H), 3.94 (t, \(J = 7.2\) Hz, 2H), 3.41–3.38 (m, 5H), 2.51 (t, \(J = 4.8\) Hz, 4H), 2.35 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 168.9, 158.4, 152.3, 133.4, 126.4, 124.7, 122.2, 118.8, 70.5, 58.8, 55.1, 46.3, 43.8, 34.1. High-resolution MS (ESI, positive ion mode): calcd. for C\(_{16}\)H\(_{22}\)N\(_4\)O (M\(^+\) + 1), m/z 287.1874; Found m/z 287.1872. Anal. Calcd. for C\(_{16}\)H\(_{22}\)N\(_4\)O: C, 67.11; H, 7.74; N, 19.56. Found: C, 67.33; H, 8.05; N, 19.22.

4-(2-(Ethylthio)ethyl)-2-(4-methylpiperazino)quinazoline (33, EAR-II-26). This compound was obtained as a yellow solid in 35% yield; mp 38–40 °C; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.83 (d, \(J = 8.0\) Hz, 1H), 7.63–7.55 (m, 2H), 7.18 (t, \(J = 7.0\) Hz, 1H), 4.00 (t, \(J = 4.8\) Hz, 4H), 3.41 (t, \(J = 7.0\) Hz, 2H), 3.07 (t, \(J = 8.0\) Hz, 2H), 2.63 (q, \(J = 7.0\) Hz, 2H), 2.51 (t, \(J = 4.8\) Hz, 4H), 2.36 (s, 3H), 1.30 (t, \(J = 8.0\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 169.8, 158.6, 152.5, 133.6, 126.6, 124.6, 122.4, 118.6, 55.3, 46.5, 44.0, 34.6, 29.3, 26.4, 15.0. High-resolution MS (ESI, positive ion mode): calcd. for C\(_{17}\)H\(_{24}\)N\(_4\)S (M\(^+\) + 1), m/z 317.1789; Found m/z 317.1800; Anal. Calcd. for C\(_{17}\)H\(_{24}\)N\(_4\)S: C, 64.52; H, 7.64; N, 17.70. Found: C, 64.71; H, 7.81; N, 17.30.

2-(4-Methylpiperazino)-4-[2-(phenylthio)ethyl]quinazoline (34, EAR-II-41(3)). This compound was obtained as a yellow oil in 50% yield; \(^1\)H NMR for the free base (CDCl\(_3\)): \(\delta\) 7.71 (d, \(J = 8.4\) Hz, 1H), 7.62–7.54 (m, 2H), 7.40 (d, \(J = 7.6\) Hz, 2H), 7.30 (t, \(J = 7.6\) Hz, 2H), 7.21 (d, \(J = 7.2\) Hz, 1H), 7.14 (t, \(J = 6.8\) Hz, 1H), 4.00 (s, 4H), 3.51–3.43 (m, 4H), 2.52 (t, \(J = 5.2\) Hz, 4H), 2.37 (s, 3H); \(^{13}\)C NMR for the free base (CDCl\(_3\)): \(\delta\) 169.4, 158.5, 152.5, 136.4, 133.7, 129.6,
129.2, 126.6, 126.4, 124.5, 122.4, 118.6, 55.3, 46.4, 44.0, 33.9, 31.2. High-resolution ms (ESI, positive ion mode): calcd. for C_{21}H_{24}N_{4}S (M^+ + 1), m/z 365.1791; Found m/z 365.1800. A hydrobromide salt: mp 135 – 137 °C. Anal. Calcd. for C_{21}H_{24}N_{4}S•2HBr•H_{2}O: C, 46.34; H, 5.18; N, 10.28. Found: C, 46.14; H, 5.18; N, 9.88.

**N-Benzyl-4-[2-(benzylamino)ethyl]quinazolin-2-amine (35, EAR-I-165(2)).** Benzylamine (0.09 mL, 0.86 mmol) was added to a mixture of 2-chloro-4-vinylquinazoline (26, 165 mg, 0.86 mmol) in toluene (3.0 mL). The mixture was stirred at 60 °C overnight, after which it was cooled to room temperature. The mixture was basified with sodium carbonate, extracted with Et_{2}O (2 × 15 mL), dried (MgSO_{4}), filtered and concentrated to a brown oil. The crude oil was purified by chromatotron with normal phase EMD 60PF_{254} silica gel eluting with hexanes/ethyl ether/methanol (4:1:0 for 100 mL, then 4:1:1 for 300 mL) to provide **N-benzyl-4-[2-(benzylamino)ethyl]quinazolin-2-amine (35, 100 mg, 32%)** as an off-white solid; mp 36 – 38 °C.

\(^1\text{H NMR (CDCl}_3, 400 MHz): \delta 7.72 (d, J = 8.0 Hz, 1H), 7.60–7.52 (m, 2H), 7.42 (d, J = 7.4 Hz, 2H), 7.36–7.20 (m, 8H), 7.14 (t, J = 7.4 Hz, 1H), 4.72 (d, J = 5.6 Hz, 2H), 3.88 (s, 2H), 3.30 (t, J = 6.4 Hz, 2H), 3.11 (t, J = 6.4 Hz, 2H); \(^{13}\text{C NMR for the free base (CDCl}_3): \delta 158.5, 152.0, 139.4, 133.6, 128.5, 127.9, 127.4, 127.2, 126.4, 124.6, 122.4, 119.1, 53.3, 46.0, 45.5, 29.7. High-resolution ms (ESI, positive ion mode): calcd. for C_{24}H_{23}N_{4} (M + 1)^+, m/z 367.1939; found m/z 367.1923.

**2-(4-Phenylpiperazin-1-yl)-4-[2-(4-phenylpiperazin-1-yl)ethyl]quinazoline (36, EAR-II-17(1)).** N-Phenylpiperazine (0.11 mL, 0.78 mmol) was added to mixture of 2-chloro-4-vinylquinazoline (26, 150 mg, 0.78 mmol) in toluene (3.0 mL) under N\(_2\). The mixture was heated to 80 °C for 1 hr, and then cooled to room temperature. The mixture was basified with sodium hydroxide, extracted
with Et₂O (2 × 15 mL), and the extract was dried (MgSO₄), filtered and concentrated. The crude oil was purified by chromatotron with EMD 60PF₂₅₄ silica gel eluting with hexane/ethyl ether/methanol (4:1:0 for 100 mL, then 4:1:1 for 200 mL) to provide **2-(4-phenylpiperazin-1-yl)-4-[2-(4-phenylpiperazino)ethyl]quinazoline** as the top baseline spot (36, 38 mg, 10%) as a white solid; mp 90–92 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.95 (d, J = 10.8 Hz, 1H), 7.68–7.61 (m, 2H), 7.34–7.22 (m, 5H), 7.03 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.93–6.87 (m, 2H), 4.16 (t, J = 4.8 Hz, 4H), 3.42 (t, J = 8.0 Hz, 2H), 3.34–3.28 (m, 8H), 3.04 (t, J = 8.0 Hz, 2H), 2.80 (s, 4H); ¹³C NMR (CDCl₃, 400 MHz): δ 152.3, 151.5, 133.6, 129.2 (2 signals), 129.1, 128.3, 128.9, 126.5, 124.7, 122.4, 120.1, 118.5, 116.5 (2 signals), 116.2, 53.2, 53.0, 49.5, 49.0, 43.9, 29.7. High-resolution ms (ESI, positive ion mode): calcd. for C₃₀H₃₄N₆ (M + 1)⁺, m/z 479.2933; found m/z 479.2923.

**2-(4-Methylpiperazin-1-yl)quinazoline (37, EAR-II-12):** 1-Methylpiperazine (0.800 mL, 7.2 mmol) was added to a solution of 2-chloroquinazoline (25, 400 mg, 2.4 mmol) in toluene (4.0 mL). The mixture was heated to 90 °C for 2 hrs, after which the mixture was cooled to room temperature. The mixture was basified with sodium carbonate, extracted with Et₂O (2 × 20 mL), and the extract was dried (MgSO₄), filtered and concentrated. The crude oil was purified by chromatotron with normal phase EMD 60PF₂₅₄ silica gel eluting with hexanes/ethyl ether/methanol (4:1:0 for 100, then 1:1:1 for 200 mL) to provide **2-(4-methylpiperazin-1-yl)quinazoline (37, 310 mg, 57%)** as an off-white solid; mp 80–82 °C; ¹H NMR (CDCl₃, 400 MHz): δ 8.99 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 4.00 (t, J = 5.0 Hz, 4H), 2.52 (t, J = 5.0 Hz, 4H), 2.36 (s, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 161.4, 159.2, 152.3, 134.0,
127.3, 125.6, 122.4, 119.3, 55.1, 46.2, 44.0; **High-resolution ms** (ESI, positive ion mode): calcd. for C_{13}H_{17}N_{4} (M^+ + 1), m/z 229.1451; found m/z 229.1453.

**2-(4-Methylpiperazino)-4-vinylquinazoline (38, EAR-II-54).** tert-Butyllithium (3.6 mL, 6.1 mmol) was added dropwise to a solution of tetravinyltin (0.82 mL, 4.51 mmol) in tetrahydrofuran (10 mL) at -78 °C. A mixture of 2-(4-methylpiperazino)quinazoline (37, 0.93 g, 4.1 mmol) in tetrahydrofuran (5.0 mL) was added dropwise and the mixture was warmed to -60 °C. The mixture was quenched with water:tetrahydrofuran (1:1), basified with saturated aqueous sodium hydroxide till pH = 9, then extracted with ether (2 × 20 mL). The extract was dried (MgSO_{4}), filtered and concentrated to provide 2-(4-methylpiperazino)-4-vinyl-3,4-dihydroquinazoline (450 mg, 45%) which was taken on without purification. 2-(4-Methylpiperazino)-4-vinyl-3,4-dihydroquinazoline (438 mg, 1.7 mmol) dissolved in benzene (11.0 mL) was added to a solution of potassium hydroxide (0.306 g, 5.46 mmol), and potassium ferricyanide (III) (1.3 g, 4.08 mmol) in water (2.5 mL) under nitrogen atmosphere at room temperature. The mixture was stirred vigorously for 5 h, after which benzene (20 mL) and water (20 mL) were added and the organic layer was extracted with Et_{2}O (2 × 15 mL), dried (MgSO_{4}), filtered and concentrated to provide 2-(4-methylpiperazino)-4-vinylquinazoline (38, 0.31 g, 71 %) as a yellow solid; mp 140 – 142 °C. $^{1}$H NMR (CDCl_{3}, 400 MHz): δ 7.93 (d, J = 8.4 Hz, 1H), 7.63–7.57 (m, 2H), 7.46 (q, J = 8.4 Hz, 1H), 7.21–7.17 (m, 1H), 6.71 (dd, J = 8.4, 2.4 Hz, 1H), 5.77 (dd, J = 5.2, 2.0 Hz, 1H), 4.03 (t, J = 4.8 Hz, 4H), 2.52 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H); $^{13}$C NMR (CDCl_{3}, 400 MHz): δ 162.8, 158.8, 153.8, 133.7, 130.9, 126.5, 124.6, 124.5, 122.5, 117.9, 55.4, 46.5, 44.1; **High-resolution ms** (ESI, positive ion mode): calcd. for C_{15}H_{18}N_{4} (M + 1)^{+}, m/z 255.1615; Found m/z 255.1616.
2-Chloro-4-(3-furyl)quinazoline (39, EAR-I-131(2)): 3-Bromofuran (0.08 mL, 0.91 mmol) was added to THF (2.0 mL) at -78 °C in a round bottom under nitrogen atmosphere. n-Butyllithium (0.36 mL, 0.91 mmol, 2.5M in hexanes) was added to the solution and the mixture was warmed to -60 °C. The mixture was then recooled to -78 °C and 2-chloroquinazoline (25, 150 mg, 0.91 mmol) dissolved in THF (1.0 mL) was added dropwise to form a dark brown mixture. The mixture was allowed to warm to -60 °C and stirred for 90 min. The mixture was quenched with H₂O (1.0 mL) and 2,3-dichloro-5,6-dicyanoquinone (DDQ, 200 mg, 0.91 mmol) was added. The mixture was allowed to warm to room temperature, extracted with hexanes/THF (1:1, 2 × 20 mL), and the extract was dried (MgSO₄), filtered and concentrated in vacuo to a yellow solid. The solid was purified on a chromatotron with EMD 60PF₂₅₄ silica gel eluting with hexanes/ethyl acetate (3:1 for 300 mL) to provide 2-chloro-4-(3-furyl)quinazoline (39, 44 mg, 22%) as a yellow solid, mp 70 – 72 °C. ¹H NMR (CDCl₃, 400 MHz): δ 8.54 (d, J = 8.0 Hz, 1H), 8.22 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.97–7.94 (m, 1H), 7.74–7.66 (m, 2H), 7.11 (s, 1H).

4-(3-furyl)-2-(4-methylpiperazino)quinazoline (40, EAR-I-132): 1-Methylpiperazine (0.06 mL, 0.57 mmol) was added to a solution of 2-chloro-4-(3-furyl)quinazoline (39, 44 mg, 0.19 mmol) in toluene (1.0 mL). The mixture was heated to 70 °C overnight, then cooled to room temperature, basified with potassium carbonate and extracted with EtOAc (2 × 20 mL). The extract was dried (Na₂SO₄), filtered and concentrated in vacuo to a yellow-orange oil. The oil was purified on a chromatotron with EMD 60PF₂₅₄ silica gel eluting with hexanes/ethyl ether (4:1 for 100 mL, then 1:1 for 100 mL) to provide 4-(3-furyl)-2-(4-methylpiperazino)quinazoline (40, 38 mg, 69%) as a yellow solid, mp = 67 – 69 °C. ¹H NMR (CDCl₃, 400 MHz): δ 8.08 (m, 2H), 7.67–7.64 (m, 2H), 7.61–7.60 (m, 1H), 7.24–7.20 (m, 1H), 7.02 (s, 1H), 4.05 (t, J = 5.0 Hz, 4H), 2.55 (t, J = 5.0 Hz,
4H), 2.38 (s, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 161.3, 158.7, 153.5, 144.1, 143.3, 133.5, 126.5, 126.0, 124.5, 122.4, 117.8, 111.4, 55.2, 46.3, 43.9. MS (ESI) $m/z$ 294 (M$^+$). Anal Calcd. for C$_{17}$H$_{18}$N$_4$O: C, 69.37; H, 6.16; N, 19.03. Found: C, 69.21; H, 6.16; N, 18.83.

2-Chloro-4-(4-methylpiperazino)quinazoline (41, EAR-II-40(1)) and 2,4-bis(4-methylpiperazino)quinazoline (42, EAR-II-40(2)): 1-Methylpiperazine (0.14 mL, 1.25 mmol) was added to a solution of 2,4-dichloroquinazoline (250 mg, 1.25 mmol) in toluene (4.0 mL) under nitrogen atmosphere. The mixture was stirred at 70 °C, then cooled to room temperature, basified with sodium carbonate and extracted with Et$_2$O (2 × 20 mL). The extract was dried (MgSO$_4$), filtered and concentrated in vacuo. The crude residue was purified on a chromatotron with EMD 60PF$_{254}$ silica gel eluting with dichloromethane/methanol (100:0 for 100 mL, then 9:1 for 250 mL) to provide 2-chloro-4-(4-methylpiperazino)quinazoline (41, 103 mg, 31%) as a colorless oil. Also isolated was 2,4-bis(4-methylpiperazino)quinazoline (42, 60 mg, 18%) as a colorless oil.

2-Chloro-4-(4-methylpiperazino)quinazoline (41, EAR-II-40(1)). $^1$H NMR (CDCl$_3$): δ 7.85 (d, $J = 8.4$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.71 (t, $J = 8.0$ Hz, 1H), 7.42 (t, $J = 8.0$ Hz, 1H), 3.90 (t, $J = 4.6$ Hz, 4H), 2.60 (t, $J = 4.6$ Hz, 4H), 2.37 (s, 3H). $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 165.4, 156.5, 153.5, 133.4, 128.1, 125.4, 125.3, 114.8, 54.9, 49.7, 46.2.

2,4-Bis(4-methylpiperazino)quinazoline (42, EAR-II-40(2)). $^1$H NMR (CDCl$_3$): δ 7.67 (d, $J = 8.4$ Hz, 1H), 7.51 (m, 2H), 7.07–7.03 (m, 1H), 3.93 (bs, 4H), 3.70 (t, $J = 4.6$ Hz, 4H), 2.61 (t, $J = 4.6$ Hz, 4H), 2.51 (t, $J = 4.6$ Hz, 4H), 2.37 (d, $J = 7.2$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 165.8, 158.4, 154.6, 132.6, 126.4, 125.3, 120.8, 112.2, 55.3, 55.1, 49.9, 46.4, 46.4, 44.1; High-resolution ms (ESI, positive ion mode): calcd. for C$_{18}$H$_{27}$N$_6$ (M + 1)$^+$, $m/z$ 327.2282; Found $m/z$
327.2297. A hydrobromide salt, mp 108–112 °C dec. *Anal* Calcd. for C₁₈H₂₆N₆·2HBr: C, 44.28; H, 5.78; N, 17.21. Found: C, 44.60; H, 5.73; N, 17.42.

4-(4-Methylpiperazino)-2-(4-phenylpiperazino)quinazoline (43, EAR-II-43(4)). *N*-Phenylpiperazine (0.17 mL, 1.14 mmol) was added to a solution of 2-chloro-4-(4-methylpiperazino)quinazoline (100 mg, 0.38 mmol) in toluene (3.0 mL) under nitrogen atmosphere. The mixture was stirred at 80 °C overnight, then cooled to room temperature, basified with sodium carbonate and extracted with Et₂O (2 × 30 mL). The extract was dried (MgSO₄), filtered and concentrated in vacuo. The crude residue was purified on a chromatotron with normal phase EMD 60PF₂₅₄ silica gel eluting with dichloromethane/methanol (100:0 for 100 mL, then 9:1 for 250 mL, and finally 7:1 for 100 mL) to provide 4-(4-methylpiperazino)-2-(4-phenylpiperazino)quinazoline (43, 40 mg, 27%) as an off-white solid, mp 48 – 50 °C. ¹H NMR (CDCl₃): δ 7.69 (d, J = 8.0 Hz, 1H), 7.54–7.52 (m, 2H), 7.31–7.25 (m, 2H), 7.09–7.05 (m, 1H), 6.99 (d, J = 8.0 Hz, 2H), 6.88 (t, J = 7.2 Hz, 1H), 4.06 (t, J = 5.2 Hz, 4H), 3.72 (t, J = 4.6 Hz, 4H), 3.27 (t, J = 5.2 Hz, 4H), 2.65 (t, J = 4.6 Hz, 4H), 2.38 (s, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 165.9, 158.5, 154.5, 151.7, 132.6, 129.4, 126.4, 125.3, 120.9, 120.2, 116.4, 112.3, 55.1, 49.9, 49.8, 46.4, 44.2; *High-resolution ms* (ESI, positive ion mode): calcd. for C₂₃H₂₉N₆ (M + 1)⁺, m/z 389.2457; Found m/z 389.2454.

5.5 Synthesis of Benzenes

2,6-Dibromo-4-butylaniline hydrobromide (45, EAR-II-106(2)). *N*-Bromosuccinimide (14.0 g, 79.1 mmol) dissolved in N,N,-dimethylformamide (40 mL) was added to a solution of 4-butylaniline (44, 5.0 mL, 31.6 mmol) in N,N,-dimethylformamide (40 mL) at 0 °C dropwise. The mixture was stirred at 0 °C for 3 h, and concentrated to dryness in vacuo. The crude residue was purified by
through a plug of silica gel (2.0 g), eluting with hexanes (4.0 L) and concentrated to provide 2,6-dibromo-4-butylbenzenamine as a red solid in 49% yield (4.73 g). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.19 (s, 2H), 4.39 (bs, 2H), 2.45 (t, \(J = 7.6\) Hz, 2H), 1.55–1.50 (m, 2H), 1.34–1.25 (m, 2H), 0.91 (t, \(J = 7.6\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 139.8, 134.7, 131.7, 108.9, 34.3, 33.7, 22.3, 14.1; High-resolution ms (ESI, positive ion mode): calcd. for C\(_{10}\)H\(_{13}\)Br\(_2\)N (M + 1)\(^+\), \(m/z\) 305.9493; Found \(m/z\) 305.9492.

1,3-Dibromo-5-butylbenzene (46, EAR-II-110(3)). 2,6-Dibromo-4-butylbenzenamine (45, 4.7 g, 15.3 mmol), ethanol (94 mL) and sulfuric acid (5.8 mL) were combined in a round bottom flask and heated to 75 °C. Sodium nitrite (3.1 g, 45.9 mmol) was added in small portions and the mixture was stirred at 75 °C for 2 h, then cooled in an ice bath, and treated with ice-H\(_2\)O (40 mL). The mixture was extracted with CH\(_2\)Cl\(_2\) (2 \(\times\) 150 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. The crude residue was purified on a chromatotron with EMD 60PF\(_{254}\) silica gel eluting with hexanes (100% for 200 mL) to provide 1,3-dibromo-5-butylbenzene (46, 2.3 g) as a clear yellow oil in 50 % yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.47 (s, 1H), 7.25 (s, 2H), 2.54 (t, \(J = 7.4\) Hz, 2H), 1.60–1.52 (m, 2H), 1.38–1.29 (m, 2H), 0.92 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 147.0, 133.2, 131.4 (2 signals), 130.5, 122.8, 35.2, 33.3, 22.4, 14.0.

1-(3-Bromophenyl)-4-methylpiperazine (50, EAR-II-84). (Method A) 1,3-Dibromobenzene (47, 5.0 g, 21.1 mmol), N-methylpiperazine (0.77 mL, 6.96 mmol), and toluene (20 mL) were stirred in a round bottom flask under nitrogen atmosphere for 5 min. 2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl (BINAP, 0.13 g, 0.21 mmol) and tris(dibenzylideneacetone)dipalladium(0) (Pd\(_{2}\)dba\(_3\), 0.05 g, 0.06 mmol) were added quickly and the flask was refilled with nitrogen, after which 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.6 mL, 17.5 mmol) was added via syringe. The
mixture was warmed to 60 °C before treatment with sodium tert-butoxide (0.01 g, 0.05 mmol) in one portion. The mixture was then heated to 110 °C overnight, then cooled and partitioned between EtOAc (40 mL) and water (40 mL). The aqueous layer was extracted with EtOAc (40 mL). The organic layers were combined and washed with 1.6 M HCl (2 × 25 mL). The aqueous acidic layer containing product was basified with a 1M NaOH solution (50 mL), and then solid sodium bicarbonate was added to pH = 8.5, and the mixture was extracted with EtOAc (2 × 40 mL). The organic layers were washed with brine (25 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to provide 50. This compound was obtained as a brown oil in 27% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.09 (t, $J = 8.0$ Hz, 1H), 7.03 (s, 1H), 6.94 (d, $J = 8.0$ Hz, 1H), 6.82 (dd, $J = 8.0$, 2.0 Hz, 1H), 3.20 (t, $J = 4.8$ Hz, 4H), 2.55 (4.8 Hz, 4H), 2.34 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 152.6, 130.5, 123.4, 122.3, 118.8, 114.5, 55.1, 48.8, 46.3; High-resolution ms (ESI, positive ion mode): calcd. for C$_{11}$H$_{15}$BrN$_2$ (M + 1)$^+$, m/z 255.0497; Found m/z 255.0493.

Compounds 49 & 51. (Method B). Compounds 46 or 48 (1.0 g, 3.4 mmol), N-methylpiperazine (0.37 mL, 3.4 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.15 g, 0.25 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.15 g, 0.17 mmol) and sodium tert-butoxide (0.39 g, 4.08 mmol) in toluene (6.0 mL) were combined in a sealed tube and the mixture was heated to 80 °C overnight. The mixture was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted and washed with EtOAc (10 mL), and the organic layers were combined and washed with a 1.6 M HCl solution (2 × 5 mL). The aqueous acidic layer containing product was then basified with a 1M NaOH solution (10 mL), and solid sodium bicarbonate was added to pH = 8.5 before extraction with EtOAc (2 × 15 mL). The organic layers were washed
with brine (10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to provide 49 and 51.

1-(3-Bromophenyl)-4-methylpiperazine (49, EAR-II-122). This compound was obtained as a clear yellow oil in 28% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 6.85 (t, $J = 2.0$ Hz, 1H), 6.80 (s, 1H), 6.64 (s, 1H), 3.19 (t, $J = 5.2$ Hz, 4H), 2.56–2.49 (m, 6H), 2.34 (s, 3H), 1.58–1.54 (m, 2H), 1.37–1.31 (m, 2H), 0.91 (t, $J = 7.6$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 152.3, 145.5, 122.9, 122.4, 116.0, 114.7, 55.0, 48.7, 46.1, 35.8, 33.4, 22.3, 13.9; High-resolution ms (ESI, positive ion mode): calcd. for C$_{15}$H$_{13}$BrN$_2$ (M + 1)$^+$, m/z 311.1123; Found m/z 311.1133.

1-(3-Bromo-5-methylphenyl)-4-methylpiperazine (51, EAR-II-85). This compound was obtained as a brown oil in 54% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 6.84 (s, 1H), 6.80 (s, 1H), 6.63 (s, 1H), 3.19 (t, $J = 4.8$ Hz, 4H), 2.54 (t, $J = 4.8$ Hz, 4H), 2.34 (s, 3H), 2.27 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 152.5, 140.6, 131.1, 123.2, 116.1, 115.4, 55.2, 48.9, 46.3, 21.7; High-resolution ms (ESI, positive ion mode): calcd. for C$_{12}$H$_{17}$BrN$_2$ (M + 1)$^+$, m/z 269.0653; Found m/z 269.0653.

**General Procedure for synthesis of compounds 52 – 58. (Method A).** A mixture of a boronic acid (3-furanboronic acid, 3-thiopheneboronic acid, 2-furanboronic acid, and 2-thiopheneboronic acid) (0.112 g, 0.88 mmol), 50 or 51 (0.150 g, 0.59 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.02 g, 0.05 mmol), and potassium phosphate (0.221 g, 1.04 mmol) in 1,4-dioxane (6.0 mL) was degassed with nitrogen and the mixture was stirred at 100 °C over 7 days. The mixture was cooled to room temperature, filtered through Celite™, washed with Et$_2$O (20 mL), and concentrated to provide crude residues 52 – 58. These
products were purified by chromatography eluting with hexanes/diethyl ether (80:20) to give 52 – 58.

1-[3-(3-Furyl)phenyl]-4-methylpiperazine (52, EAR-II-86(2)). This compound was obtained as a yellow oil in 28% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.70 (s, 1H), 7.46 (s, 1H), 7.26 (t, $J = 5.6$ Hz, 1H), 7.03 (s, 1H), 6.99 (d, $J = 7.6$ Hz, 1H), 6.85 (dd, $J = 8.4$, 1.6 Hz, 1H), 6.68 (s, 1H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 151.9, 143.6, 138.7, 133.5, 129.7, 127.1, 117.8, 115.0, 113.9, 109.2, 55.3, 49.3, 46.3; High-resolution mass spectra (ESI, positive ion mode): calcd. for C$_{13}$H$_{18}$N$_2$O (M + 1)$^+$, m/z 243.1497; Found m/z 243.1492. A hydrobromide salt: a white solid, mp 215 – 217 °C. Anal Calcd. for C$_{15}$H$_{18}$N$_2$O•2HBr: C, 44.58; H, 4.99; N, 6.93. Found: C, 44.31; H, 4.99; N, 6.52.

1-Methyl-4-[3-(3-thienyl)phenyl]piperazine (53, EAR-II-81(2)). This compound was obtained as a clear colorless oil in 22% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.42 (t, $J = 2.0$ Hz, 1H), 7.36 (d, $J = 2.0$ Hz, 2H), 7.29 (t, $J = 8.0$ Hz, 1H), 7.14 (s, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 6.87 (dd, $J = 8.0$, 2.0 Hz, 1H), 3.27 (t, $J = 4.8$ Hz, 4H), 2.62 (t, $J = 4.8$ Hz, 4H), 2.38 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 151.8, 143.1, 137.0, 129.7, 126.7, 126.2, 120.5, 118.5, 115.2, 114.6, 55.3, 49.3, 46.3; High-resolution mass spectra (ESI, positive ion mode): calcd. for C$_{15}$H$_{18}$N$_2$S (M + 1)$^+$, m/z 259.1269; Found m/z 259.1269. A hydrobromide salt: a white solid, mp 200 – 205 °C dec. Anal Calcd. for C$_{15}$H$_{18}$N$_2$S•3HBr: C, 35.95; H, 4.22; N, 5.66. Found: C, 35.97; H, 4.19; N, 5.66.

1-Methyl-4-[3-(2-thienyl)phenyl]piperazine (54, EAR-II-87(3)). This compound was obtained as a clear colorless oil in 21% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.29–7.24 (m, 3H), 7.15 (s, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 7.06 (t, $J = 4.4$ Hz, 1H), 6.86 (dd, $J = 8.4$, 2.0 Hz, 1H), 3.26 (t, $J = 4.8$ Hz, 4H), 2.59 (t, $J = 4.8$ Hz, 4H), 2.36 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 151.7, 144.9,
135.2, 129.6, 127.8, 124.6, 123.0, 117.7, 115.2, 113.8, 55.1, 49.0, 46.1; High-resolution ms (ESI, positive ion mode): calcd. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}S (M + 1)^+, m/z 259.1269; Found m/z 259.1279. A hydrobromide salt: a white solid, mp >250 °C. Anal Calcd. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}S\textsubscript{•}2HBr: C, 42.87; H, 4.80; N, 6.67. Found: C, 42.45; H, 4.78; N, 6.65.

1-[3-(2-Furyl)phenyl]-4-methylpiperazine (55, EAR-II-105(2)). This compound was obtained as a clear colorless oil in 24% yield. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 7.44 (s, 1H), 7.28–7.25 (m, 2H), 7.16 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.62 (d, J = 3.2 Hz, 1H), 6.45 (s, 1H), 3.27 (t, J = 4.6 Hz, 4H), 2.60 (t, J = 4.6 Hz, 4H), 2.36 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz): δ 154.5, 151.7, 142.0, 131.8, 129.6, 115.7, 115.4, 111.7, 111.5, 105.1, 55.3, 49.2, 46.3; High-resolution ms (ESI, positive ion mode): calcd. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O (M + 1)^+, m/z 243.1497; Found m/z 243.1487. A hydrobromide salt: a white solid, mp 240 – 242 °C. Anal Calcd. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O\textsubscript{•}2HBr, 0.5 H\textsubscript{2}O: C, 43.61; H, 5.12; N, 6.78. Found: C, 43.24; H, 5.12; N, 7.15.

1-[3-(3-Furyl)-5-methylphenyl]-4-methylpiperazine (56, EAR-II-88(2)). This compound was obtained as a clear colorless oil in 23% yield. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 7.68 (s, 1H), 7.44 (s, 1H), 6.85 (s, 1H), 6.82 (s, 1H), 6.67 (s, 2H), 3.23 (t, J = 4.8 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.34 (d, J = 8.8 Hz, 6H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz): δ 151.7, 143.4, 139.2, 138.5, 133.1, 126.9, 118.6, 115.7, 111.1, 109.1, 55.1, 49.2, 46.1, 21.7; High-resolution ms (ESI, positive ion mode): calcd. for C\textsubscript{16}H\textsubscript{20}N\textsubscript{2}O (M + 1)^+, m/z 257.1654; Found m/z 257.1657. A hydrobromide salt: a white solid, mp 230 – 232 °C. Anal Calcd. for C\textsubscript{16}H\textsubscript{20}N\textsubscript{2}O\textsubscript{•}2HBr: C, 45.96; H, 5.30; N, 6.70. Found: C, 46.30; H, 5.28; N, 6.34.
1-Methyl-4-[3-methyl-5-(3-thienyl)phenyl]piperazine (57, EAR-II-98(2)). This compound was obtained as a clear colorless oil in 20% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.40 (s, 1H), 7.35 (s, 2H), 6.95 (s, 1H), 6.92 (s, 1H), 6.70 (s, 1H), 3.25 (t, $J = 4.8$ Hz, 4H), 2.61 (t, $J = 4.8$ Hz, 4H), 2.35 (d, $J = 5.2$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 151.9, 143.1, 139.3, 136.9, 126.8, 126.0, 120.3, 119.4, 116.0, 111.9, 55.3, 49.3, 46.2, 22.0; High-resolution ms (ESI, positive ion mode): calcd. for C$_{16}$H$_{20}$N$_2$S (M + 1)$^+$, m/z 273.1425; Found m/z 273.1432. A hydrobromide salt: a white solid, mp 245 – 247 °C. Anal Calcd. for C$_{16}$H$_{20}$N$_2$S•1.5HBr, 2H$_2$O: C, 44.89; H, 4.85; N, 6.03. Found: C, 44.71; H, 5.23; N, 6.42.

1-Methyl-4-[3-methyl-5-(2-thienyl)phenyl]piperazine (58, EAR-II-103 (2)). This compound was obtained as a clear colorless oil in 25% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.26 (t, $J = 8.0$ Hz, 2H), 7.05 (t, $J = 3.6$ Hz, 1H), 6.97 (d, $J = 9.6$ Hz, 2H), 6.69 (1H), 3.26 (t, $J = 4.8$ Hz, 4H), 2.62 (t, $J = 4.8$ Hz, 4H), 2.35 (d, $J = 12$ Hz, 6H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 151.7, 145.0, 139.3, 135.1, 127.8, 124.4, 123.0, 118.7, 116.2, 111.1, 55.1, 49.1, 46.1, 21.7; High-resolution ms (ESI, positive ion mode): calcd. for C$_{16}$H$_{20}$N$_2$S (M + 1)$^+$, m/z 273.1425; Found m/z 273.1434. A hydrobromide salt: a white solid, mp >250 °C. Anal Calcd. for C$_{16}$H$_{20}$N$_2$S•2HBr, 0.5 H$_2$O: C, 43.36; H, 5.23; N, 6.23. Found: C, 43.47; H, 5.15; N, 6.71.

1-(3-Butyl-5-(3-thienyl)phenyl)-4-methylpiperazine (61, EAR-II-126 (2)). (Method B). A mixture of 3-thienylboronic acid (0.09 g, 0.77 mmol), 1-(3-bromophenyl)-4-methylpiperazine (0.17 g, 0.51 mmol), tetrakis(triphenylphosphine)palladium (0.04 g, 0.04 mmol), potassium carbonate (0.21 g, 1.53 mmol) in 1,4-dioxane (5.0 mL) and water (0.3 mL) was degassed with N$_2$ gas and the reaction was stirred at 100 °C overnight. The mixture was cooled to room temperature
and filtered through Celite™, washed with Et₂O (20 mL), and evaporated to provide crude residue 61. The crude residue was purified by chromatography eluting with hexanes/diethyl ether (80:20) to give 61. This compound was obtained as a clear colorless oil in 23% yield. 

\[ \text{\textsuperscript{1}H NMR (CDCl}_3, 400 MHz): \delta 7.40 (t, J = 2.4 Hz, 1H), 7.35 (s, 2H), 6.96 (s, 1H), 6.92 (s, 1H), 6.71 (s, 1H), 3.26 (t, J = 4.8 Hz, 4H), 2.62–2.58 (m, 6H), 2.36 (s, 3H), 1.66–1.58 (m, 2H), 1.43–1.35 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H); \text{\textsuperscript{13}C NMR (CDCl}_3, 400 MHz): \delta 151.9, 144.5, 143.3, 136.8, 126.9, 126.0, 120.3, 118.9, 115.6, 112.1, 55.4, 49.5, 46.3, 36.3, 33.9, 22.7, 14.2; \text{High-resolution ms (ESI, positive ion mode): calcd. for C}_{19}H_{26}N_2S (M + 1)^+, m/z 315.1895; Found m/z 315.1910. \text{A hydrobromide salt: a white solid, mp 215 – 217 °C. \text{Anal Calcd. for C}_{19}H_{26}N_2S\cdot2HBr: C, 47.91; H, 5.93; N, 5.88. Found: C, 47.50; H, 6.19; N, 6.20.}

\section*{General Procedure for Substitution of bromide with boronic acids (59 – 60 & 62 – 65).} (Method C). Compounds 59 – 60 & 62 – 65 were synthesized as previously described with slight modifications.\textsuperscript{47} A mixture of a selected boronic acid (0.20 g, 1.8 mmol), 49 or 50 (0.32 g, 1.2 mmol), tetrakis(triphenylphosphine)palladium (0.10 g, 0.09 mmol), and potassium carbonate (0.497 g, 3.6 mmol) in dimethylformamide (5.0 mL) and water (0.5 mL) were combined in a sealed tube, degassed with N₂ gas and allowed to stir at 90 °C overnight. The mixture was cooled to room temperature and filtered through Celite™, washed with ethyl acetate (20 mL), and evaporated to provide crude residues 59 – 60 & 62 – 65. The crude residues were purified by chromatography eluting with hexanes/diethyl ether (80:20) to give 59 – 60 & 62 – 65.

\textbf{1-(3-Furan-2-yl)-5-methylphenyl)-4-methylpiperazine (59, EAR-II-135(2)).} This compound was obtained as a clear colorless oil in 12% yield. 
\[ \text{\textsuperscript{1}H NMR (CDCl}_3, 400 MHz): \delta 7.46 (s, 1H), 7.09 (s, 1H), 7.03 (s, 1H), 6.69 (s, 1H), 6.63 (d, J = 3.6 Hz, 1H), 6.47 (dd, J = 2.0, 3.2 Hz, 1H), \]
3.31 (t, J = 5.0 Hz, 4H), 2.67 (t, J = 5.0 Hz, 4H), 2.42 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ154.4, 151.4, 141.7, 139.1, 131.5, 116.6, 116.2, 111.5, 108.9, 104.8, 54.9, 48.9, 45.8, 21.8; *High-resolution ms* (ESI, positive ion mode): calcd. for C$_{16}$H$_{20}$N$_2$O (M + 1)$^+$, m/z 257.1654; Found m/z 257.1651. A hydrobromide salt: a white solid, mp 245 – 249 °C. *Anal Calcd.* for C$_{16}$H$_{20}$N$_2$O•2HBr: C, 45.96; H, 5.30; N, 6.70. Found: C, 45.64; H, 5.26; N, 6.81.

**1-[3-Butyl-5-(3-furyl)phenyl]-4-methylpiperazine (60, EAR-II-129).** This compound was obtained as a clear colorless oil in 70% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.69 (s, 1H), 7.43 (t, J = 1.6 Hz, 1H), 6.85 (s, 1H), 6.82 (s, 1H), 6.67 (d, J = 6.8 Hz, 2H), 3.23 (t, J = 5.2 Hz, 4H), 2.58–2.56 (m, 6H), 2.34 (s, 3H), 1.65–1.57 (m, 2H), 1.40–1.34 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 151.8, 144.4, 143.4, 138.5, 133.1, 127.1, 118.1, 115.4, 111.3, 109.2, 55.3, 49.4, 46.2, 36.2, 33.8, 22.6, 14.1; *High-resolution ms* (ESI, positive ion mode): calcd. for C$_{19}$H$_{26}$N$_2$O (M + 1)$^+$, m/z 299.2123; Found m/z 299.2136. A hydrobromide salt: a white solid, mp 215 – 219 °C. *Anal Calcd.* for C$_{19}$H$_{26}$N$_2$O•2HBr, 0.5 H$_2$O: C, 48.63; H, 6.23; N, 5.97. Found: C, 48.55; H, 6.14; N, 6.20.

**1-[3-Butyl-5-(2-thienyl)phenyl]-4-methylpiperazine (62, EAR-II-136(2)).** This compound was obtained as a clear colorless oil in 24% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.27–7.23 (m, 2H), 7.06–7.04 (m, 1H), 6.97 (t, J = 2.0 Hz, 1H), 6.94 (s, 1H), 6.70 (s, 1H), 3.25 (t, J = 5.2 Hz, 4H), 2.60–2.57 (m, 6H), 2.6 (s, 3H), 1.64–1.58 (m, 2H), 1.40–1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 151.9, 145.4, 144.6, 135.2, 127.9, 124.6, 123.1, 118.3, 115.9, 111.5, 55.3, 49.4, 46.3, 36.2, 33.8, 22.7, 14.2; *High-resolution ms* (ESI, positive ion mode): calcd. for C$_{19}$H$_{26}$N$_2$O (M + 1)$^+$, m/z 315.1895; Found m/z 315.1885. A hydrobromide salt: a white solid,
mp 234 – 236 °C. Anal Calcd. for C_{19}H_{26}N_{2}S•1.5HBr: C, 52.36; H, 6.36; N, 6.43. Found: C, 52.01; H, 6.40; N, 6.50.

1-[3-Butyl-5-(2-furyl)phenyl]-4-methylpiperazine (63, EAR-II-134). This compound was obtained as a clear colorless oil in 76% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.44 (s, 1H), 7.07 (s, 1H), 7.01 (s, 1H), 6.68 (s, 1H), 6.61 (d, $J = 3.2$ Hz, 1H), 6.45 (q, $J = 3.2$ Hz, 1H), 3.26 (t, $J = 4.8$ Hz, 4H), 2.59 (t, $J = 5.6$ Hz, 6H), 2.36 (s, 3H), 1.65–1.58 (m, 2H), 1.40–1.34 (m, 2H), 0.93 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 154.7, 151.7, 144.4, 141.9, 131.7, 116.1, 116.0, 111.7, 109.2, 105.0, 55.3, 49.3, 46.2, 36.3, 33.8, 22.6, 14.2; High-resolution ms (ESI, positive ion mode): calcd. for C$_{19}$H$_{26}$N$_2$O (M + 1)$^+$, m/z 299.2123; Found m/z 299.2124. A hydrobromide salt: a white solid, mp 180 – 182 °C. Anal Calcd. for C$_{19}$H$_{26}$N$_2$O•HBr: C, 60.16; H, 7.17; N, 7.38. Found: C, 60.37; H, 7.15; N, 7.54.

1-Methyl-4-(5-methylbiphenyl-3-yl)piperazine (64, EAR-II-173). This compound was obtained as a white solid in 25% yield, mp 30 – 32 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.57–7.54 (m, 2H), 7.42–7.38 (m, 2H), 7.34–7.31 (m, 1H), 6.94 (s, 1H), 6.90 (s, 1H), 6.75 (s, 1H), 3.26 (t, $J = 4.8$ Hz, 4H), 2.59 (t, $J = 4.8$ Hz, 4H), 2.37 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 151.9, 142.4, 142.1, 139.3, 128.8, 127.4, 127.3, 120.0, 116.0, 112.6, 55.4, 49.4, 46.3, 22.0; High-resolution ms (ESI, positive ion mode): calcd. for C$_{18}$H$_{22}$N$_2$ (M + 1)$^+$, m/z 267.1861; Found m/z 267.1870. Anal Calcd. for C$_{18}$H$_{22}$N$_2$: C, 81.16; H,8.32 ; N, 10.52. Found: C, 81.15; H, 8.52; N, 10.30.

1-Methyl-4-[3-methyl-5-(5-methyl-2-thienyl)phenyl]piperazine (65, EAR-II-175(6)). This compound was obtained brown oil in 15% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.06 (d, $J = 3.2$
Hz, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 6.69 (dd, $J = 3.6, 1.2$ Hz, 1H), 6.65 (s, 1H), 3.23 (t, $J = 5.2$ Hz, 4H), 2.58 (t, $J = 4.8$ Hz, 4H), 2.49 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H). A hydrobromide salt: a white solid, mp 238 – 240 °C. Anal Calcd. for C$_{17}$H$_{22}$N$_2$S•1.5HBr.H$_2$O: C, 47.95; H, 6.04; N, 6.58. Found: C, 47.84; H, 5.89; N, 6.65.

**1-(4-Bromophenyl)-4-methylpiperazine (67, EAR-II-148).** 1,4-Dibromobenzene (1.0 g, 4.2 mmol), N-methylpiperazine (0.46 mL, 4.2 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, 0.20 g, 0.31 mmol), tris(dibenzyldieneacetone)dipalladium(0) (0.19 g, 0.21 mmol) and sodium tert-butoxide (0.48 g, 5.04 mmol) in toluene (6.0 mL) were combined in a sealed tube and heated to 80 °C overnight. The mixture was partitioned between EtOAc (10 mL) and water (10 mL). The aqueous layer was extracted and washed with EtOAc (10 mL), and the organic layers were combined and washed with 1.6 M HCl (2 × 5 mL). The aqueous acidic layer containing product was then basified with an aqueous 1M NaOH solution to pH = 8.5 before an extraction with EtOAc (2 × 15 mL). The organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to provide 1-(4-bromophenyl)-4-methylpiperazine (499 mg, 47%) as a brown oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.33 (d, $J = 10.4$ Hz, 2H), 6.79 (d, $J = 10.4$ Hz, 2H), 3.17 (t, $J = 4.8$ Hz, 4H), 2.56 (t, $J = 4.8$ Hz, 4H), 2.35 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 150.2, 131.8, 117.6, 111.8, 54.9, 48.9, 46.1.

**General Procedure for Synthesis of 1,4-Substituted Benzenes 68 – 69.** A mixture of a boronic acid (3-thiopheneboronic acid or 2-furanboronic acid) (0.14 g, 1.17 mmol), 1-(4-bromophenyl)-4-methylpiperazine (65, 0.20 g, 0.78 mmol), tetrakis(triphenylphosphine)palladium (0.07 g, 0.06 mmol), and potassium carbonate (0.32 g, 2.34 mmol) in dimethylformamide (5.0 mL) and water (0.4 mL) were combined in a sealed tube, degassed with N$_2$ gas and allowed to stir at 90 °C
overnight. The mixture was cooled to room temperature and filtered through Celite\textsuperscript{TM}, washed with ethyl acetate (20 mL), and evaporated to provide crude residues. The crude residues were purified on a chromatotron with EMD 60PF\textsubscript{254} silica gel eluting with hexanes/diethyl ether (80:20) to provide pure 68 and 69.

1-Methyl-4-(4-(3-thienyl)phenyl)piperazine (68, EAR-II-140(4)). This compound was obtained as a white solid in 16% yield, mp = 207 – 208 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 7.50 (d, J = 8.8 Hz, 2H), 7.34–7.32 (m, 3H), 6.95 (d, J = 8.8 Hz, 2H), 3.204 (t, J = 4.8 Hz, 4H), 2.59 (t, J = 4.8 Hz, 4H), 2.36 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz): δ 150.5, 142.4, 127.6, 127.4, 126.3, 126.1, 118.6, 116.2, 55.3, 49.1, 46.3; High-resolution ms (ESI, positive ion mode): calcd. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}S (M + 1\textsuperscript{+}), m/z 259.1269; Found m/z 259.1274. Anal Calcd. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}: C, 69.73; H, 7.02; N, 10.84. Found: C, 69.29; H, 7.13; N, 10.74.

1-(4-(2-Furyl)phenyl)-4-methylpiperazine (69, EAR-II-149). This compound was obtained as a white solid in 29% yield, mp 151 – 154 °C. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): δ 7.60 (d, J = 13.2 Hz, 2H), 7.43 (s, 1H), 6.96 (d, J = 13.2 Hz, 2H), 6.51 (d, J = 4.8 Hz, 1H), 6.50–6.44 (m, 1H), 3.27 (t, J = 4.8 Hz, 4H), 2.61 (t, J = 4.8 Hz, 4H), 2.38 (s, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 400 MHz): δ 155.2, 150.3, 141.1, 124.8, 122.7, 115.8, 111.5, 102.9, 54.9, 48.6, 46.0; Anal Calcd. for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.08; H, 7.47; N, 11.81.

1-(3,5-Dibromophenyl)-4-methylpiperazine (71, EAR-II-169). 1,3,5-Tribromobenzene (1.0 g, 3.1 mmol), N-methylpiperazine (0.34 mL, 3.1 mmol), 2,2‘-bis(diphenylphosphino)-1,1’-binaphthyl (BINAP, 0.14 g, 0.23 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.14 g, 0.15 mmol) and sodium tert-butoxide (0.36 g, 3.72 mmol) in toluene (12.0 mL) were combined in a sealed tube and heated to 80 °C overnight. The mixture was partitioned between EtOAc (10 mL) and water (10
mL). The aqueous layer was extracted and washed with EtOAc (10 mL), and the organic layers were combined and washed with 1.6 M HCl (2 × 5 mL). The aqueous acidic layer containing product was then basified with an aqueous solution of 1M NaOH to pH = 8.5 before an extraction with EtOAc (2 × 15 mL). The organic layers were washed with brine (10 mL), dried over magnesium sulfate, filtered and concentrated in vacuo to provide 1-(3,5-dibromophenyl)-4-methylpiperazine (71, 557 mg, 56%) as a brown oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.08 (t, $J=1.6$ Hz, 1H), 6.93 (d, $J=1.6$ Hz, 2H), 3.20 (t, $J=5.0$ Hz, 4H), 2.54 (t, $J=5.0$ Hz, 2H, 3.25 (s, 3H).

1-(3,5-Di(3-furyl)phenyl)4-methylpiperazine (72, EAR-II-171(2)). A mixture of 3-furanboronic acid (0.60 g, 4.99 mmol), 1-(3,5-dibromophenyl)-4-methylpiperazine (69, 0.56 g, 1.66 mmol), tetrakis(triphenylphosphine)palladium (0.19 g, 0.16 mmol), and potassium carbonate (0.69 g, 4.99 mmol) in dimethylformamide (12.0 mL) and water (1.0 mL) were combined in a sealed tube, degassed with nitrogen and allowed to stir at 90 °C overnight. The mixture was cooled to room temperature and filtered through Celite™, washed with ethyl acetate (20 mL), and evaporated to provide crude residues. The crude residues were purified on a chromatotron with EMD $60\text{PF}_{254}$ silica gel eluting with hexanes/diethyl ether (80:20 over 100 mL, the 80:15(with 5% methanol) to provide 1-(3,5-di(3-furyl)phenyl)4-methylpiperazine (72, 23.0 mg, 4%) as a white solid, mp = 57 – 59 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.71 (s, 2H), 7.46 (t, $J=2.0$ Hz, 2H), 7.08 (s, 1H), 6.93 (d, $J=1.2$ Hz, 2H), 6.68 (t, $J=1.6$ Hz, 2H), 3.27 (t, $J=4.8$ Hz, 4H), 2.59 (t, $J=4.8$ Hz, 4H), 2.35 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 152.3, 143.7, 138.8, 133.9, 126.9, 115.8, 112.8, 109.2, 55.2, 49.3, 46.3; High-resolution ms (ESI, positive ion mode): calcd. for C$_{19}$H$_{20}$N$_2$O$_2$ (M + 1)$^+$, $m/z$ 309.1603; Found $m/z$ 309.1611. Anal Calcd. for C$_{19}$H$_{20}$N$_2$O$_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.90; H, 6.85; N, 8.80.
1-Benzyl-4-(3-bromo-5-methylphenyl)piperazine (73, EAR-II-177(2)). 3,5-Dibromotoluene (5.0 g, 20.0 mmol), benzylpiperazine (1.7 mL, 10.0 mmol), 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, 0.46 g, 0.75 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.45 g, 0.50 mmol) and sodium tert-butoxide (1.72 g, 18.0 mmol) in toluene (20.0 mL) were combined in a sealed tube and heated to 80 °C overnight. The mixture was filtered over Ceilite, washed with EtOAc (20 mL) and concentrated in vacuo to provide 1-benzyl-4-(3-bromo-5-methylphenyl)piperazine (2.6 g, 76%) as a brown oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.35 (s, 2H), 7.33 (d, $J = 2.8$ Hz, 2H), 7.31–7.27 (m, 1H), 6.83 (s, 1H), 6.79 (s, 1H), 6.62 (s, 1H), 3.55 (s, 2H), 3.17 (t, $J = 4.8$ Hz, 4H), 2.57 (t, $J = 4.8$ Hz, 4H), 2.26 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): δ 152.6, 140.6, 138.1, 131.1, 129.3, 128.5, 127.3, 123.1, 116.0, 115.4, 63.2, 53.1, 48.9, 21.7; High-resolution ms (ESI, positive ion mode): calcd. for C$_{18}$H$_{21}$BrN$_2$ (M + 1)$^+$, m/z 345.0966; Found m/z 345.0976.

1-Benzyl-4-[3-(3-furyl)-5-methylphenyl]piperazine (74, EAR-II-178). A mixture of a 3-furanboronic acid (0.08 g, 0.72 mmol), 1-benzyl-4-(3-bromo-5-methylphenyl)piperazine (71, 0.16 g, 0.47 mmol), tetrakis(triphenylphosphine)palladium (0.04 g, 0.03 mmol), and potassium carbonate (0.19 g, 1.41 mmol) in dimethylformamide (4.0 mL) and water (0.4 mL) were combined in a sealed tube, degassed with nitrogen gas and allowed to stir at 80 °C overnight. The mixture was cooled to room temperature and filtered through CeliteTM, washed with ethyl acetate (20 mL), and evaporated to provide crude residues. The crude residues were purified on a chromatotron with EMD 60PF$_{254}$ silica gel eluting with hexanes/diethyl ether (80:20 for 250 mL) to provide 1-benzyl-4-(3-(3-furyl)-5-methylphenyl) (74, 51.7 mg, 33%) as a clear colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.73 (t, $J = 1.6$ Hz, 1H), 7.49 (t, $J = 1.6$ Hz, 1H), 7.43–7.37 (m, 4H), 7.34–
7.28 (m, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 6.71 (q, \(J = 1.6\) Hz, 2H), 3.63 (s, 2H), 3.27 (t, \(J = 4\) Hz), 2.67 (t, \(J = 4\) Hz), 2.38 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 152.1, 143.5, 139.3, 138.6, 138.1, 133.2, 129.3, 128.4, 127.3, 127.1, 118.7, 115.9, 111.2, 109.2, 63.2, 53.3, 49.5, 21.9; \textit{High-resolution ms} (ESI, positive ion mode): calcd. for C\(_{22}\)H\(_{24}\)N\(_2\)O (M + 1), \(m/z\) 333.1967; Found \(m/z\) 333.1952. A hydrobromide salt: a white solid, mp 220 – 224 °C dec. \textit{Anal} Calcd. for C\(_{22}\)H\(_{24}\)N\(_2\)O: C, 53.46; H, 5.30; N, 5.67. Found: C, 54.43; H, 5.51; N, 5.51.

5.6 Synthesis of Pyridines

\textbf{4-Hydroxy-6-methylpyridin-2(1H)-one (76, EAR-II-130).} Ammonium hydroxide (11.3 mL) was added to a mixture of 4-hydroxy-6-methyl-2\(H\)-pyran-2-one (75, 11.3 g, 89.6 mmol) in ethanol (28.2 mL). The mixture was stirred at 130 °C overnight, then cooled to room temperature and concentrated \textit{in vacuo} to yield 4-hydroxy-6-methylpyridin-2(1H)-one (76, 11.0 g, >99%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 5.59 (d, \(J = 2.4\) Hz, 1H), 5.33 (d, \(J = 2.4\) Hz, 1H), 3.43 (bs, 1H), 2.07 (s, 3H).

\textbf{2,4-Dibromo-6-methylpyridine (77, EAR-II-133).} 4-Hydroxy-6-methylpyridin-2(1H)-one (76, 2.0 g, 16.1 mmol) was combined with phosphorous tribromide (5.6 g, 20.9 mmol) in a sealed tube and the mixture was heated at 190 °C for 5 h. The mixture was poured over ice and allowed to warm to room temperature overnight. Extracted mixture with dichloromethane (3 × 300 mL), dried (MgSO\(_4\)), filtered and concentrated \textit{in vacuo} to provide 2,4-dibromo-6-methylpyridine (75, 2.0 g, 9%). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.52 (d, \(J = 1.2\) Hz, 1H), 7.31 (d, \(J = 1.2\) Hz, 1H), 2.55 (s, 3H).
1-(4-Bromo-6-methylpyridin-2-yl)-4-methylpiperazine (78, EAR-II-145). 2,4-Dibromo-6-methylpyridine (77, 2.67 g, 10.6 mmol), N-methylpiperazine (1.1 mL, 10.6 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, 0.49 g, 0.79 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.48 g, 0.53 mmol) and sodium tert-butoxide (1.2 g, 12.7 mmol) in toluene (50.0 mL) were combined in a sealed tube and heated to 80 °C overnight. The mixture was filtered over Celite, washed with EtOAc (20 mL) and concentrated in vacuo to provide 1-(4-bromo-6-methylpyridin-2-yl)-4-methylpiperazine (78, 0.22 g, 8%) as a brown oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 6.64 (s, 1H), 6.59 (s, 1H), 3.54 (t, $J$ = 4.8 Hz, 4H), 2.49 (t, $J$ = 4.8 Hz, 4H), 2.35 (s, 3H), 2.33 (s, 3H).

General Procedure for Synthesis of Compounds 79 – 81. A mixture of a boronic acid (3-furanboronic acid, 2-furanboronic acid or 3-thiopheneboronic acid) (0.03 g, 0.55 mmol), 1-(4-bromo-6-methylpyridin-2-yl)-4-methylpiperazine (78, 0.10 g, 0.37 mmol), tetrakis(triphenylphosphine)palladium (0.03 g, 0.03 mmol), and potassium carbonate (0.17 g, 1.1 mmol) in dimethylformamide (4.0 mL) and water (0.3 mL) were combined in a sealed tube, degassed with nitrogen and stirred at 90 °C overnight. The mixture was cooled to room temperature and filtered through Celite™, washed with ethyl acetate (20 mL). The filtrate was washed with water (3 × 25 mL) and brine (20 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to provide crude residue. The crude residue was purified on a chromatotron with EMD 60PF$_{254}$ silica gel eluting with hexanes/diethyl ether (80:20 over 200 mL, 1:1 over 150 mL, and finally 1:1 (with 5% methanol) for 200 mL) to provide pure 79 – 81.

1-(4-(3-Furyl)-6-methylpyridin-2-yl)-4-methylpiperazine (79, EAR-II-157(2)). This compound was obtained as a clear colorless oil in 31% yield. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.79 (s, 1H),
7.48 (s, 1H), 6.69 (s, 1H), 6.62 (s, 1H), 6.51 (s, 1H), 3.60 (t, $J = 4.8$ Hz, 4H), 2.55 (t, $J = 4.8$ Hz, 4H), 2.42 (s, 3H), 2.36 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 157.5, 144.0, 141.8, 140.0, 128.7, 125.6, 110.5, 108.8, 100.6, 55.1, 46.4, 45.5, 24.8; High-resolution ms (ESI, positive ion mode): calcd. for C$_{15}$H$_{19}$N$_2$O (M + 1)$^+$, m/z 258.1606; Found m/z 258.1598. A hydrobromide salt: a white solid, mp 150 – 152 °C. Anal Calcd. for C$_{15}$H$_{19}$N$_3$O•HBr, 0.5H$_2$O: C, 51.88; H, 6.10; N, 12.10. Found: C, 51.90; H, 6.50; N, 12.06.

1-Methyl-4-(6-methyl-4-(2-thienyl)pyridine-2-yl)piperazine (80, EAR-II-158(8)). This compound was obtained as a clear colorless oil in 4% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.41 (d, $J = 3.2$ Hz, 1H), 7.34 (d, $J = 4.8$ Hz, 1H), 7.09 (t, $J = 3.6$ Hz, 1H), 6.74 (s, 1H), 6.63 (s, 1H), 3.61 (t, $J = 4.8$ Hz, 4H), 2.55 (t, $J = 4.8$ Hz, 4H), 2.43 (s, 3H), 2.36 (s, 3H). A hydrobromide salt: a white solid, mp 132 – 134 °C. Anal Calcd. for C$_{15}$H$_{19}$N$_3$S•HBr: C, 50.85; H, 5.69; N, 11.86. Found: C, 51.10; H, 5.69; N, 11.53.

1-(4-(2-Furyl)-6-methylpyridin-2-yl)-4-methylpiperazine (81, EAR-II-166(8)). This compound was obtained as a clear colorless oil in 7.2% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.47 (t, $J = 1.2$ Hz, 1H), 6.75 (t, $J = 1.6$ Hz, 2H), 6.72 (s, 1H), 6.47 (q, $J = 3.2$ Hz, 1H), 3.62 (t, $J = 4.8$ Hz, 4H), 2.54 (t, $J = 4.8$ Hz, 4H), 2.41 (s, 3H), 2.35 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 159.9, 157.5, 152.8, 143.0, 139.4, 111.9, 108.0, 107.7, 98.2, 55.0, 46.2, 45.3, 24.8; High-resolution ms (ESI, positive ion mode): calcd. for C$_{15}$H$_{19}$N$_3$O (M + 1)$^+$, m/z 258.1606; Found m/z 258.1628. A hydrobromide salt: a white solid, mp 148 – 150 °C. Anal Calcd. for C$_{15}$H$_{19}$N$_3$O•HBr, H$_2$O: C, 50.57; H, 6.22; N, 11.79. Found: C, 50.41; H, 6.42; N, 11.39.

2,6-Dibromo-4-methylpyridine (83, EAR-II-179). A Mixture of 4-methylpyridine-2,6-diol (82, 5.0 g, 39.9 mmol) and phosphorous tribromide (4.9 mL, 51.9 mmol) in a sealed tube was heated at
190 °C overnight. The mixture was poured over ice and allowed to warm to room temperature, then extracted with dichloromethane (3 × 300 mL), dried (MgSO₄), filtered and concentrated in vacuo to provide 2,6-dibromo-4-methylpyridine (83, 1.65 g, 16%). ^1^H NMR (CDCl₃, 400 MHz): δ 57.60 (s, 2H), 2.30 (s, 3H).

1-(6-Bromo-4-methylpyridin-2-yl)-4-methylpiperazine (84, EAR-II-184). A mixture of 2,6-dibromo-4-methylpyridine (83, 1.36 g, 5.4 mmol), N-methylpiperazine (0.60 mL, 5.4 mmol), 2,2’-bis(diphenylphosphino)-1,1’-binaphthyl (BINAP, 0.25 g, 0.40 mmol), tris(dibenzyldieneacetone)dipalladium(0) (0.25 g, 0.27 mmol) and sodium tert-butoxide (0.62 g, 6.5 mmol) in toluene (15.0 mL) was heated to 80 °C in a sealed tube overnight. The mixture was filtered over Celite, washed with EtOAc (20 mL) and concentrated in vacuo to provide 1-(6-bromo-4-methylpyridin-2-yl)-4-methylpiperazine (84, 0.37 g, 26%) as a brown oil. The crude product was purified on a chromatotron with EMD 60PF₂₅₄ silica gel eluting with hexanes/diethyl ether (80:20 over 200 mL, 1:1 over 150 mL, and finally 1:1 (with 5% methanol) for 200 mL) to provide pure 84. ^1^H NMR (CDCl₃, 400 MHz): δ 6.61 (s, 1H), 6.32 (s, 1H), 3.54 (t, J = 4.8 Hz, 4H), 2.49 (t, J = 4.8 Hz, 4H), 2.33 (s, 3H), 2.21 (s, 3H).

General Procedure for the Synthesis of Compounds 85 – 87. A mixture of a boronic acid (3-furanboronic acid, 3-thipheneboronic acid, or 2-thiopheneboronic acid) (0.11 g, 1.02 mmol), 1-(6-bromo-4-methylpyridin-2-yl)-4-methylpiperazine (84, 0.11 g, 0.68 mmol), tetrakis(triphenylphosphine)palladium (0.07 g, 0.05 mmol), potassium carbonate (0.28 g, 2.04 mmol) in dimethylformamide (4.0 mL) and water (0.5 mL) in a sealed tube was degassed with nitrogen and stirred at 85 °C overnight. The mixture was cooled to room temperature and filtered through Celite™, washed with ethyl acetate (20 mL). The filtrate was washed with water (3 × 25
mL) and brine (20 mL), dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified on a chromatotron with EMD 60PF₂₅₄ silica gel eluting with hexanes/diethyl ether (80:20 over 200 mL, 1:1 over 150 mL, and finally 1:1 (with 5% methanol) for 200 mL) to provide pure 85 – 87.

1-(6-(2-Furyl)-4-methylpyridin-2-yl)-4-methylpiperazine (85, EAR-III-2(2)). This compound was obtained as a clear colorless solid in 16% yield, mp 150 – 152 °C. ¹H NMR (CDCl₃, 400 MHz): δ 7.95 (q, J = 1.6 Hz, 1H), 7.43 (t, J = 2.0 Hz, 1H), 6.83 (q, J = 1.6 Hz, 1H), 6.67 (s, 1H), 6.35 (s, 1H), 3.60 (t, J = 4.8 Hz, 4H), 2.53 (t, J = 4.8 Hz, 4H), 2.35 (s, 3H), 2.28 (s, 3H); High-resolution ms (ESI, positive ion mode): calcd. for C₁₅H₁₉N₂O (M + 1)⁺, m/z 258.1606; Found m/z 258.1608. Anal Calcd. for C₁₅H₁₉N₃O•2HBr, H₂O: C, 41.21; H, 5.30; N, 9.61. Found: C, 40.86; H, 5.23; N, 9.76.

1-Methyl-4-(4-methyl-6-(3-thienyl)pyridine-2-yl)piperazine (86, EAR-III-1). This compound was obtained as a clear colorless oil in 32% yield (60 mg). ¹H NMR (CDCl₃, 400 MHz): δ 7.83 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 4.8 Hz, 1H), 7.32 (t, J = 4.8 Hz, 1H), 6.83 (s, 1H), 6.38 (s, 1H), 3.62 (t, J = 4.8 Hz, 4H), 2.53 (t, J = 4.8 Hz, 4H), 2.34 (s, 3H), 2.29 (s, 3H); ¹³C NMR (CDCl₃, 400 MHz): δ 159.4, 151.2, 148.9, 143.0, 126.4, 125.5, 122.8, 111.2, 105.7, 55.0, 46.3, 45.2, 21.5; High-resolution ms (ESI, positive ion mode): calcd. for C₁₅H₁₉N₃S (M + 1)⁺, m/z 274.1378; Found m/z 274.1385. A hydrobromide salt: a white solid, mp 132 – 134 °C. Anal Calcd. for C₁₅H₁₉N₃S•HBr, 1.5H₂O: C, 47.25; H, 6.08; N, 11.02. Found: C, 47.44; H, 6.04; N, 11.27.

1-Methyl-4-(4-methyl-6-(2-thienyl)pyridine-2-yl)piperazine (87, EAR-II-183). This compound was obtained as a clear colorless oil in 25% yield. ¹H NMR (CDCl₃, 400 MHz): δ 7.50 (dd, J = 3.6, 0.8 Hz, 1H), 7.30 (dd, J = 5.2, 1.2 Hz, 1H), 7.06–7.04 (m, 1H), 6.86 (s, 1H), 6.34 (s, 1H), 3.61
(t, J = 4.8 Hz, 4H), 2.53 (t, J = 4.8 Hz, 4H), 2.34 (s, 3H), 2.28 (s, 3H); 13C NMR (CDCl₃, 400 MHz): δ 159.0, 150.2, 148.9, 146.2, 127.6, 126.5, 123.6, 109.5, 105.7, 54.9, 46.2, 45.0, 21.5;

High-resolution ms (ESI, positive ion mode): calcd. for C₁₅H₁₉N₃S (M + 1)⁺, m/z 274.1378; Found m/z 274.1398. A hydrobromide salt: a yellow solid, mp 148 – 150 °C. Anal Calcd. for C₁₅H₁₉N₃S•2HBr, H₂O: C, 39.75; H, 5.11; N, 9.27. Found: C, 39.42; H, 5.03; N, 9.60.

5.7 Synthesis of Flexible-Chain Linked Derivatives

**tert-Butyl piperazine-1-carboxylate (88, EAR-III-3(2)).** Di-tert-butyl dicarbonate (13.8 mL, 58.0 mmol) in dichloromethane (50 mL) was added to a solution of piperazine (10.0 g, 116.0 mmol) in dichloromethane (160 mL) at 0 °C. The mixture was stirred for 2 h, warmed to room temperature and stirred overnight. A white precipitate was filtered, and dissolved in saturated aqueous potassium carbonate, extracted with ether (2 × 40 mL) and concentrated to provide tert-butyl-piperazine-1-carboxylate (88) as a white solid in 50% yield. ¹H NMR (CDCl₃, 400 MHz): δ 3.38 (t, J = 4.8 Hz, 4H), 2.80 (t, J = 4.8 Hz, 4H), 1.71 (s, 1H), 1.46 (s, 9H).

**Synthesis of compounds 90 & 91.** 3,5-Dibromotoluene (48, 1.0 g, 4.0 mmol) or 2,6-dibromopyridine (89, 1.0 g, 4.2 mmol) was combined with 1-Boc-piperazine (0.74 g, 4.0 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, 0.18 g, 0.30 mmol), tris(dibenzyldieneacetone)dipalladium(0) (0.18 g, 0.20 mmol) and sodium tert-butoxide (0.46 g, 4.8 mmol) in toluene (10.0 mL). The mixture was stirred in a sealed tube and heated to 90 °C overnight. The mixture was filtered over Ceilite, washed with EtOAc (20 mL) and concentrated in vacuo to provide crude residues of 90 or 91. The residues were purified on a chromatotron with EMD 60PF₂₅₄ silica gel eluting with hexanes/diethyl ether (80:20 over 200 mL, 1:1 over 150 mL, and finally 1:1 (with 5% methanol) for 200 mL) to provide pure 90 or 91.
**tert-Butyl 4-(3-bromo-5-methylphenyl)piperazine-1-carboxylate (90, EAR-III-4).** This compound was obtained as brown oil in 55% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 6.83 (s, 2H), 6.63 (s, 1H), 3.55 (t, \(J = 5.0\) Hz, 4H), 3.11 (t, \(J = 5.0\) Hz, 4H), 2.27 (s, 3H), 1.48 (s, 9H).

**tert-Butyl 4-(6-bromopyridine-2-yl)piperazine-1-carboxylate (91, EAR-III-7(3)).** This compound was obtained as brown oil in 17% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.31 (t, \(J = 7.6\) Hz, 1H), 6.77 (d, \(J = 7.6\) Hz, 1H), 6.51 (d, \(J = 8.4\) Hz, 1H), 3.52 (s, 8H), 1.48 (s, 9H).

**General procedure for Suzuki coupling to prepare 92 & 93.** A mixture of 3-furanboronic acid (0.36 g, 3.2 mmol), \(\text{90 or 91 (0.76 g, 2.2 mmol), tetrakis(triphenylphosphine)palladium (0.19 g, 0.17 mmol), and potassium carbonate (0.89 g, 6.45 mmol) in } N,N\text{-dimethylformamide (15.0 mL) and water (1.5 mL) in a sealed tube was degassed with nitrogen and stirred at 80 °C overnight. The mixture was cooled to room temperature and filtered through Celite™, washed with ethyl acetate (20 mL). The filtrate was washed with water (3 × 25 mL) and brine (20 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo to provide crude residue 92 or 93. The crude residue was purified on a chromatotron with EMD 60PF\(_{254}\) silica gel eluting with hexanes/ether (80:20 over 200 mL) to provide 92 or 93.

**tert-Butyl 4-[3-(3-furyl)--5-methylphenyl]piperazine-1-carboxylate (92, EAR-III-5).** This compound was obtained as yellow oil in 45% yield. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.69 (s, 1H), 7.45 (s, 1H), 6.85 (s, 2H), 6.67 (s, 2H), 3.59 (t, \(J = 4.8\) Hz, 4H), 3.15 (t, \(J = 4.8\) Hz, 4H), 2.34 (s, 3H), 1.48 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 400 MHz): \(\delta\) 154.9, 152.0, 143.6, 139.5, 138.7, 133.4, 126.9, 119.4, 116.5, 111.8, 109.2, 80.1, 49.8, 28.6, 21.9; High-resolution ms (ESI, positive ion mode): calcd. for C\(_{20}\)H\(_{26}\)N\(_2\)O\(_3\) (M + 1), \(m/z\) 343.2022; Found \(m/z\) 343.2024.
**tert-Butyl 4-[6-(3-furyl)pyridine-2-yl]piperazine-1-carboxylate (93, EAR-III-14).** This compound was obtained as clear colorless oil in 37% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.96 (q, $J$ = 1.6 Hz, 1H), 7.49 (t, $J$ = 7.6 Hz, 1H), 7.45 (t, $J$ = 1.6 Hz, 1H), 6.84–6.83 (m, 1H), 6.82 (s, 1H), 6.52 (d, $J$ = 8.4 Hz, 1H), 3.57 (s, 8H), 1.49 (s, 9H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 159.0, 155.0, 150.0, 143.6, 141.3, 138.3, 130.5, 127.7, 109.9, 108.9, 105.4, 80.1, 45.2, 28.6; *High-resolution ms* (ESI, positive ion mode): calcd. for C$_{18}$H$_{23}$N$_3$O$_3$ (M + 1)$^+$, m/z 330.1818; Found m/z 330.1804.

**General procedure for the deprotection of Boc protected piperazine to provide 94 and 95.** 1-Trifluoroacetic acid (1.0 mL) was added to a solution of tert-butyl-4-[3-(3-furyl)-5-methylphenyl]piperazine-1-carboxylate (92, 0.32 g, 0.96 mmol) or tert-butyl 4-[6-(3-furyl)pyridine-2-yl]piperazine-1-carboxylate (93) in dichloromethane (5.0 mL). The reaction mixture was stirred for one hour, and then concentrated *in vacuo*. A solution of cold saturated sodium bicarbonate was added slowly to the residue to the pH = 9. The aqueous layer was washed with dichloromethane (2 × 15 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide 94 or 95.

**1-[3-(3-Furyl)-5-methylphenyl]piperazine (94, EAR-III-9).** This compound was obtained as brown oil in 56% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.68 (s, 1H), 7.43 (t, $J$ = 1.2 Hz, 1H), 6.83 (s, 2H), 6.66 (s, 2H), 3.72 (bs, 1H), 3.18 (t, $J$ = 4.8 Hz, 4H), 3.05 (t, $J$ = 4.8 Hz, 4H), 2.32 (s, 3H); $^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta$ 152.2, 143.5, 139.3, 138.6, 133.2, 126.9, 119.0, 116.0, 111.3, 109.1, 50.2, 45.8, 21.8; *High-resolution ms* (ESI, positive ion mode): calcd. for C$_{15}$H$_{19}$N$_2$O (M + 1)$^+$, m/z 243.1497; Found m/z 243.1501.
1-[6-(2-Furyl)pyridine-2-yl]piperazine (95, EAR-III-17). This compound was obtained as clear colorless oil in 70% yield. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.95 (s, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.44 (t, $J = 2.0$ Hz, 1H), 7.24 (bs, 1H), 6.86–6.82 (m, 2H), 6.50 (d, $J = 8.4$ Hz, 1H), 3.72 (t, $J = 4.8$ Hz, 4H), 3.15 (t, $J = 4.8$ Hz, 4H).

2-Chloro-4-(3-furyl)pyridine (97, EAR-III-6). A mixture of 3-furanboronic acid (1.30 g, 12.3 mmol), 4-bromo-2-chloropyridine (96, 2.0 g, 10.3 mmol), tetrakis(triphenylphosphine)palladium (0.95 g, 0.82 mmol), and potassium carbonate (4.2 g, 30.9 mmol) in $N,N$-dimethylformamide (25.0 mL) and water (3.0 mL) in a sealed tube was degassed with nitrogen and stirred at 90 °C overnight. The mixture was cooled to room temperature and filtered through Celite™, washed with ethyl acetate (20 mL). The filtrate was washed with water (3 × 25 mL) and brine (20 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to provide crude residue 97. The crude product was purified on a chromatotron with EMD 60PF$_{254}$ silica gel eluting with hexanes/ether (80:20 over 300 mL) to provide 2-chloro-4-(3-furyl)pyridine (97, 0.568 g, 31%) as a white solid, mp 98 – 100 °C. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 8.35 (d, $J = 5.2$ Hz, 1H), 7.89 (s, 1H), 7.53 (s, 1H), 7.40 (s, 1H), 7.29 (dd, $J = 5.2$, 1.2 Hz, 1H), 6.72 (s, 1H).

1-(4-(3-Furyl)pyridin-2-yl)piperazine (99, EAR-III-15). Boc-piperazine (88, 0.91 g, 4.8 mmol) was added to 2-chloro-4-(3-furyl)pyridine (97, 0.44 g, 2.44 mmol) in toluene (7.0 mL) in a sealed tube. The mixture was stirred at 125 °C for three days, then concentrated, and the crude residue (98) was used in the next step without purification. Trifluoroacetic acid (1.0 mL) was added to a mixture of tert-butyl 4-(4-(3-furyl)pyridin-2-yl)piperazine-1-carboxylate (98, 0.34 g, 1.0 mmol) in dichloromethane (5.0 mL). The mixture was stirred at room temperature for one hour, after which the mixture was concentrated in vacuo. A solution of cold saturated sodium bicarbonate was
added slowly to the residue to the pH = 9. The aqueous layer was washed with dichloromethane (2 × 15 mL), dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified on a chromatotron with EMD 60PF254 silica gel eluting with hexanes/ether (80:20 over 250 mL) to provide 1-(4-(furan-3-yl)pyridin-2-yl)piperazine (99, 0.17 g, 73% yield) as a brown solid; mp 100 – 102 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.18 (d, $J = 5.2$ Hz, 1H), 7.82 (s, 1H), 7.51 (t, $J = 5.2$ Hz, 1H), 6.76 (dd, $J = 5.2$, 1.2 Hz, 1H), 6.72–6.71 (m, 2H), 3.62 (t, $J = 5.2$ Hz, 4H), 4.11 (bs, 1H), 3.07 (t, $J = 5.2$ Hz, 4H).

**General procedure for the synthesis of compounds 100 – 108.** Triethylamine (0.02 mL, 0.21 mmol) was added to a mixture of 94, 95 or 99 (0.035 g, 0.14 mmol), the alkylbromide (6-bromo-N-(4-cyanobenzyl)hexanamide, (5-bromo-2-methylpentan-2-ylsulfonyl)benzene or 1-(4-bromobutyl)indolin-2-one (0.21 mmol) in acetonitrile (4.0 mL). The mixture was stirred at 60 °C overnight, and then concentrated. The residue was dissolved in dichloromethane (15 mL), and the solution was washed with water (2 × 15 mL), dried (MgSO$_4$), filtered and concentrated. The residue was purified on a chromatotron with EMD 60PF254 silica gel eluting with hexanes/ether/methanol (80:20 over 300 mL, then 50:50 (w/5% methanol) to provide 100 – 108.

**N-(4-Cyanobenzyl)-6-[4-(3-(3-furyl)-5-methylphenyl)piperazine-1-yl)hexanamide (100, EAR-III-10).** The free base was obtained as a white solid in 15% yield; mp 116 – 118 °C; $^1$H NMR (CDCl$_3$): δ 7.68 (s, 1H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.45 (t, $J = 1.6$ Hz, 1H), 7.37 (s, 1H), 7.35 (s, 1H), 6.83 (d, $J = 5.6$ Hz, 2H), 6.66 (s, 2H), 6.05 (bs, 1H), 3.22 (t, $J = 4.6$ Hz, 4H), 2.61 (t, $J = 4.6$ Hz, 4H), 2.41 (t, $J = 7.2$ Hz, 2H), 2.33 (s, 3H), 2.59 (t, $J = 7.6$ Hz, 2H), 1.74–1.67 (m, 2H), 1.61–1.53 (m, 2H), 1.41–1.36 (m, 2H); $^{13}$C NMR (CDCl$_3$): δ 173.2, 151.9, 144.3, 143.6, 139.4, 138.6, 133.2, 132.6, 128.3, 127.0, 118.9, 118.8, 115.8, 111.3, 111.1, 109.2, 58.5, 53.4, 49.3, 43.1, 36.5,
27.2, 26.6, 25.6, 21.9; High-resolution MS (ESI, positive ion mode): calcd. for C_{29}H_{36}N_{4}O_{2} (M^{+} + 1), m/z 471.2760; found m/z 471.2774. Anal. Calcd. for C_{29}H_{36}N_{4}O_{2}: C, 74.01; H, 7.28; N, 11.91. Found: C, 73.69; H, 7.20; N, 11.98.

N-(4-Cyanobenzyl)-6-[4-(3-(furyl)pyridin-2-yl)piperazin-1-yl]hexanamide (101, EAR-III-19). The free base was obtained as a yellow oil in 44% yield; $^1$H NMR for the free base (CDCl$_3$): δ 7.95 (s, 1H), 7.60 (d, $J$ = 6.8 Hz, 2H), 7.48 (t, $J$ = 7.2 Hz, 1H), 7.45 (t, $J$ = 5.2 Hz, 1H), 7.38 (d, $J$ = 8.4 Hz, 2H), 6.84–6.82 (m, 2H), 6.51 (d, $J$ = 8.4 Hz, 1H), 6.11 (bs, 1H), 4.49 (d, $J$ = 6.4 Hz, 2H), 3.66 (t, $J$ = 4.6 Hz, 4H), 2.66 (t, $J$ = 4.6 Hz, 4H), 2.48 (t, $J$ = 7.4 Hz, 2H), 2.27 (t, $J$ = 7.4 Hz, 2H), 1.76–1.68 (m, 2H), 1.67–1.61 (m, 2H), 1.45–1.38 (m, 2H); $^{13}$C NMR for free base (CDCl$_3$): δ 173.2, 159.1, 150.0, 144.3, 143.6, 141.3, 138.2, 132.6, 128.4, 127.8, 118.9, 111.4, 109.8, 108.9, 105.2, 58.6, 53.1, 46.0, 45.0, 43.2, 36.5, 27.1, 25.6; High-resolution MS (ESI, positive ion mode): calcd. for C$_{27}$H$_{31}$N$_{5}$O$_{2}$ (M$^+$ + 1), m/z 458.2556; found m/z 458.2552. A hydrobromide salt, brown wax, mp 35–37 °C. Anal. Calcd. for C$_{27}$H$_{31}$N$_{5}$O$_{2}$•2HBr•H$_2$O: C, 50.88; H, 5.53; N, 10.99. Found: C, 51.03; H, 5.50; N, 11.11.

N-(4-Cyanobenzyl)-6-(4-(3-(furyl)pyridin-2-yl)piperazin-1-yl)hexanamide (102, EAR-III-16). The free base was obtained as a white solid in 38% yield; mp 103–105 °C; $^1$H NMR (CDCl$_3$): δ 8.17 (d, $J$ = 5.2 Hz, 1H), 7.81 (s, 1H), 7.61 (dd, $J$ = 6.4, 1.6 Hz, 2H), 7.49 (t, $J$ = 1.6 Hz, 1H), 7.37 (d, $J$ = 8.0 Hz, 2H), 6.74 (dd, $J$ = 5.2, 1.2 Hz, 1H), 6.70 (s, 2H), 6.05 (bs, 1H), 4.49 (t, $J$ = 6.0 Hz, 2H), 3.58 (t, $J$ = 4.8 Hz, 4H), 2.56 (t, $J$ = 4.8 Hz, 4H), 2.40 (t, $J$ = 7.4 Hz, 2H), 2.26 (t, $J$ = 7.4 Hz, 2H), 1.75–1.67 (m, 2H), 1.61–1.53 (m, 2H), 1.43 (m, 1.34 (m, 2H); $^{13}$C NMR (CDCl$_3$): δ 173.0, 160.1, 148.4, 144.1, 141.4, 140.0, 132.4, 128.2, 125.1, 118.7, 111.2, 111.0,
108.4, 103.4, 58.4, 53.0, 45.2, 43.0, 36.4, 27.1, 26.4, 25.4; Anal. Calcd. for C$_{27}$H$_{31}$N$_5$O$_2$: C, 70.87; H, 6.83; N, 15.31. Found: C, 71.12; H, 6.99; N, 15.65.

1-(3-(3-Furyl)-5-methylphenyl-4-(phenylsulfonyl)pentyl)piperazine (103, EAR-III-13). The free base was obtained as a yellow oil in 40% yield; $^1$H NMR for the free base (CDCl$_3$): δ 7.88 (dd, $J = 7.6$, 1.6 Hz, 2H), 7.68 (s, 1H), 7.65 (t, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.6$ Hz, 2H), 7.45 (t, $J = 1.6$ Hz, 1H), 6.83 (d, $J = 7.2$ Hz, 2H), 6.66 (s, 2H), 3.21 (t, $J = 4.8$ Hz, 4H), 2.59 (t, $J = 4.8$ Hz, 4H), 2.38 (t, $J = 7.6$ Hz, 2H), 2.33 (s, 3H), 1.77–1.73 (m, 2H), 1.67–1.57 (m, 2H), 1.31 (s, 6H); $^{13}$C NMR for free base (CDCl$_3$): δ 160.3, 151.9, 143.6, 139.4, 138.6, 135.7, 133.7, 133.2, 130.7, 128.9, 127.1, 118.8, 115.9, 111.2, 109.3, 63.0, 58.8, 53.5, 49.4, 33.0, 21.9, 21.7, 21.1; High-resolution MS (ESI, positive ion mode): calcd. for C$_{27}$H$_{34}$N$_2$O$_3$S (M$^+$ + 1), $m/z$ 467.2368; found $m/z$ 467.2384. A hydrobromide salt; mp 200 – 203 °C dec. Anal. Calcd. for C$_{27}$H$_{34}$N$_2$O$_3$S •2HBr,H$_2$O: C, 50.16; H, 5.92; N, 4.33. Found: C, 50.45; H, 5.88; N, 4.61.

1-[6-(3-Furyl)pyridin-2-yl)-4-(4-methyl-4-(phenylsulfonyl)pentyl)piperazine (104, EAR-III-20). The free base was obtained as a clear colorless oil in 31% yield; $^1$H NMR for the free base (CDCl$_3$): δ 7.95 (s, 1H), 7.88 (d, $J = 7.6$ Hz, 2H), 7.65–7.63 (m, 1H), 7.55 (t, $J = 8.0$ Hz, 2H), 7.45 (t, $J = 1.8$ Hz, 1H), 7.44 (s, 1H), 6.83 (dd, $J = 8.0$, 1.8 Hz, 2H), 6.51 (d, $J = 8.4$ Hz, 1H), 3.59 (t, $J = 4.8$ Hz, 4H), 2.55 (t, $J = 4.8$ Hz, 4H), 2.38 (t, $J = 7.2$ Hz, 2H), 1.77–1.73 (m, 2H), 1.63–1.61 (m, 2H), 1.31 (s, 6H); $^{13}$C NMR for free base (CDCl$_3$): δ 159.2, 149.9, 143.6, 141.2, 138.2, 135.7, 133.7, 130.7, 128.9, 127.8, 109.7, 108.9, 105.2, 105.0, 63.0, 58.9, 53.2, 45.2, 33.0, 21.1, 21.0; A hydrobromide salt; 230 – 232 °C. Anal. Calcd. for C$_{25}$H$_{31}$N$_3$O$_3$S •2HBr,H$_2$O: C, 47.70; H, 5.50; N, 6.40. Found: C, 47.40; H, 5.57; N, 6.63.
1-[4-(3-Furyl)pyridin-2-yl]-4-(4-methyl-4-(phenylsulfonyl)pentyl)piperazine (105, EAR-III-18). The free base was obtained as a clear colorless oil in 21% yield; $^1$H NMR for the free base (CDCl$_3$): $\delta$ 8.17 (d, $J = 5.2$ Hz, 1H), 7.89 (s, 1H), 7.87 (d, $J = 1.2$ Hz, 1H), 7.65 (t, $J = 7.4$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 2H), 7.49 (t, $J = 1.2$ Hz, 1H), 6.74 (dd, $J = 5.2$, 1.2 Hz, 1H), 6.70 (s, 2H), 3.57 (t, $J = 4.8$ Hz, 4H), 2.55 (t, $J = 4.8$ Hz, 4H), 2.38 (t, $J = 7.4$ Hz, 2H), 1.81–1.73 (m, 2H), 1.63–1.56 (m, 2H), 1.31 (s, 6H); $^{13}$C NMR for free base (CDCl$_3$): $\delta$ 160.3, 154.4, 148.6, 144.1, 141.5, 140.1, 135.7, 133.7, 130.7, 128.9, 125.4, 111.1, 108.6, 103.6, 63.0, 58.9, 53.3, 45.4, 32.9, 21.7, 21.0; High-resolution MS (ESI, positive ion mode): calcd. for C$_{27}$H$_{31}$N$_3$O$_3$S (M$^+$ + 1), m/z 454.2164; found m/z 454.2172. A hydrobromide salt; mp 180–184 °C (dec). Anal. Calcd. for C$_{27}$H$_{31}$N$_3$O$_3$S•2HBr,H$_2$O: C, 47.40; H, 5.57; N, 6.63. Found: C, 47.02; H, 5.39; N, 6.88.

1-[4-(4-(3-Furyl)-5-methylphenyl)piperazin-1-yl)butyl]indolin-2-one (106, EAR-III-21). The free base was obtained as a white solid in 33% yield; mp 110–113 °C dec; $^1$H NMR (CDCl$_3$): $\delta$ 7.68 (s, 1H), 7.44 (t, $J = 1.6$ Hz, 1H), 7.25 (t, $J = 8.0$ Hz, 2H), 7.02 (t, $J = 7.6$ Hz, 1H), 6.85 (t, $J = 8.0$ Hz, 1H), 6.82 (d, $J = 8.0$ Hz, 2H), 6.66 (s, 2H), 3.75 (t, $J = 7.2$ Hz, 2H), 3.52 (s, 2H), 3.21 (t, $J = 4.8$ Hz, 4H), 2.59 (t, $J = 4.8$ Hz, 4H), 2.33 (s, 3H), 1.78–1.72 (m, 2H), 1.65–1.59 (m, 2H); High-resolution MS (ESI, positive ion mode): calcd. for C$_{27}$H$_{31}$N$_3$O$_2$ (M$^+$ + 1), m/z 430.2495; found m/z 430.2504. A hydrobromide salt. Anal. Calcd. for C$_{27}$H$_{31}$N$_3$O$_2$•2HBr: C, 54.84; H, 5.62; N, 7.11. Found: C, 55.03; H, 5.61; N, 7.32.

1-[4-(4-(6-(3-Furyl)pyridin-2-yl)piperazin-1-yl)butyl]indolin-2-one (107, EAR-III-23). The free base was obtained as a brown oil in 20% yield; mp 242–244 °C; $^1$H NMR (CDCl$_3$): $\delta$ 7.96 (s, 1H), 7.48–7.43 (m, 2H), 7.26 (t, $J = 7.2$ Hz, 2H), 7.02 (t, $J = 7.6$ Hz, 1H), 6.87–6.79 (m, 3H), 6.50 (d, $J = 8.4$ Hz, 1H), 3.75 (t, $J = 6.8$ Hz, 2H), 3.59 (t, $J = 4.8$ Hz, 4H), 3.52 (s, 2H), 2.55 (t, $J =
4.8 Hz, 4H), 2.43 (t, $J = 7.2$ Hz, 2H), 1.78–1.71 (m, 2H), 1.65–1.60 (m, 2H); 

*High-resolution MS* (ESI, positive ion mode): calcd. for C$_{25}$H$_{28}$N$_4$O$_2$ (M$^+$ + 1), $m/z$ 417.2291; found $m/z$ 417.2288. A hydrobromide salt. *Anal.* Calcd. for C$_{25}$H$_{28}$N$_4$O$_2$$\cdot$2HBr, H$_2$O: C, 50.53; H, 5.41; N, 9.39. Found: C, 49.96; H, 5.52; N, 9.02.

1-[4-(4-(3-Furyl)pyridin-2-yl)piperazin-1-yl)butyl]indolin-2-one (108, EAR-III-22(2)). The free base was obtained as a white solid in 42% yield; mp 99–101 °C; $^1$H NMR (CDCl$_3$): δ 8.19 (d, $J = 5.2$ Hz, 1H), 7.83 (t, $J = 1.2$ Hz, 1H), 7.51 (t, $J = 1.6$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 2H), 7.04 (t, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 7.6$ Hz, 1H), 6.74 (dd, $J = 5.2$, 1.2 Hz, 1H), 6.72 (s, 2H), 3.77 (t, $J = 7.2$ Hz, 2H), 3.60 (t, $J = 4.8$ Hz, 4H), 3.54 (s, 2H), 2.58 (t, $J = 4.8$ Hz, 4H), 2.45 (t, $J = 7.2$ Hz, 2H), 1.80–1.73 (m, 2H), 1.68–1.60 (m, 2H); $^{13}$C NMR (CDCl$_3$): δ 175.2, 160.3, 148.6, 144.7, 144.1, 141.5, 140.1, 128.0, 125.4, 124.8, 124.6, 122.3, 111.1, 108.7, 108.5, 103.6, 58.1, 53.2, 45.4, 39.9, 36.0, 25.4, 24.3; *High-resolution MS* (ESI, positive ion mode): calcd. for C$_{25}$H$_{28}$N$_4$O$_2$ (M$^+$ + 1), $m/z$ 417.2291; found $m/z$ 417.2289; *Anal.* Calcd. for C$_{25}$H$_{28}$N$_4$O$_2$, 2H$_2$O: C, 66.35; H, 7.13; N, 12.38. Found: C, 66.32; H, 6.95; N, 12.41.
6 REFERENCES

(1) Whitaker-Azmitia, P.M. Neuropsychopharmacology. 1999, 21, No. 2S.
(9) Abbas, A.I.; Hedlund, P.B.; Huang, X.; Tran, T.B.; Meltzer, Y.; Roth, B.L. Psychopharmacology. 2009, 205, 119-128.
(14) Bojarski, A. “New 4,6-disubstituted 2-(4-methylpiperazin-1-yl)pyridine derivatives, a process for their preparation, pharmaceutical composition containing these compounds, their use, a method for modulating monoaminergic receptor activity and monoaminergic receptor modulating agent.” Patent pending, EU 10382/09, 2009.
(47) Drysdale, Martin James; Dymock, Brian William; Finch, Harry; Webb, Paul; Mcdonald, Edward; James, Karen Elizabeth; Cheung, Kwai Ming; Mathews, Thomas Peter. PCT Int. Appl. (2004), WO 2004072051 A1 20040826, 55–56.
(54) Fallahpour, R. Synthesis. 2000, 12, 1665-1667.


7 **SPECTRA**
Current Data Parameters
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PROCNO  1

F2 - Acquisition Parameters
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TDC  65536
SOLVENT  D2O
NS  47
DS  4
GSH  23986.834 Hz
FIDRES  0.395998 Hz
AQ  1.365756 sec
F2  50000
IM  20.850 usec
TE  7.00 usec
T1  298.9 K
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T1M  0.00000000 sec
T1MREST  0.00000000 sec
T1MRK  0.00000000 sec

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PL2  -3.00 dB
SF01  100.6224298 MHz

---------- CHANNEL f2 ----------
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PCP02  1m
PCP02  80.000 usec
PL12  126.000 mm
PL12  15.10 mm
SF02  499.1118000 kHz

F2 - Processing parameters
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LB  1.90 Hz
GR  0
FC  1.40
145
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EPRID: 1
PROCID: 1

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FULLPROD: 2g/mol
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DD: 2
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FIDRES: 0.48314 Hz
AQ: 5.6589683 sec
BG: 256
DW: 89.480 usec
DE: 7.06 usec
TE: 296.6 K
DI: 1.00000000 sec
MCATEST: 6.00000000 sec
MCWORK: 5.00000000 sec

CHANNEL 11
MC1: 12.80 usec
PL1: 0.00 dB
SR01: 460.1324008 MHz

P2 - Processing parameters
SI: 32768
SF: 460.1300000 MHz
LOG: 0
SB: 0.30 Hz
PC: 1.000