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Methods of synthesis of Pimavanserin: the first drug approved for the treatment of Parkinson's disease psychosis (PDP)

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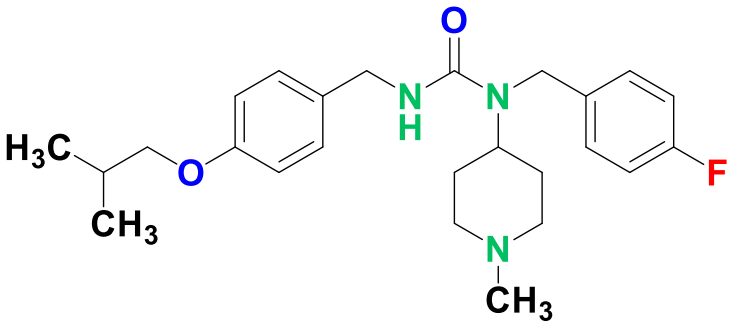
Abstract

Pimavanserin (Nuplazid^{TM}) is the first FDA atypical antipsychotic drug approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). Pimavanserin displays a unique pharmacological profile with nanomolar potency as a 5-HT_{2A} receptor inverse agonist. Due to the importance of Pimavanserin for the field of neurological disorder, numerous reports have appeared in the literature dealing with the synthesis of Pimavanserin. In this article we collect, summarize and discuss the various synthetic strategies and judge their applicability for larger scale drug synthesis.

Pimavanserin (Nuplazid^{TM})



Keywords: Pimavanserin (Nuplazid^{TM}), Parkinsonism, psychosis, 5-HT_{2A} receptor, antipsychotics

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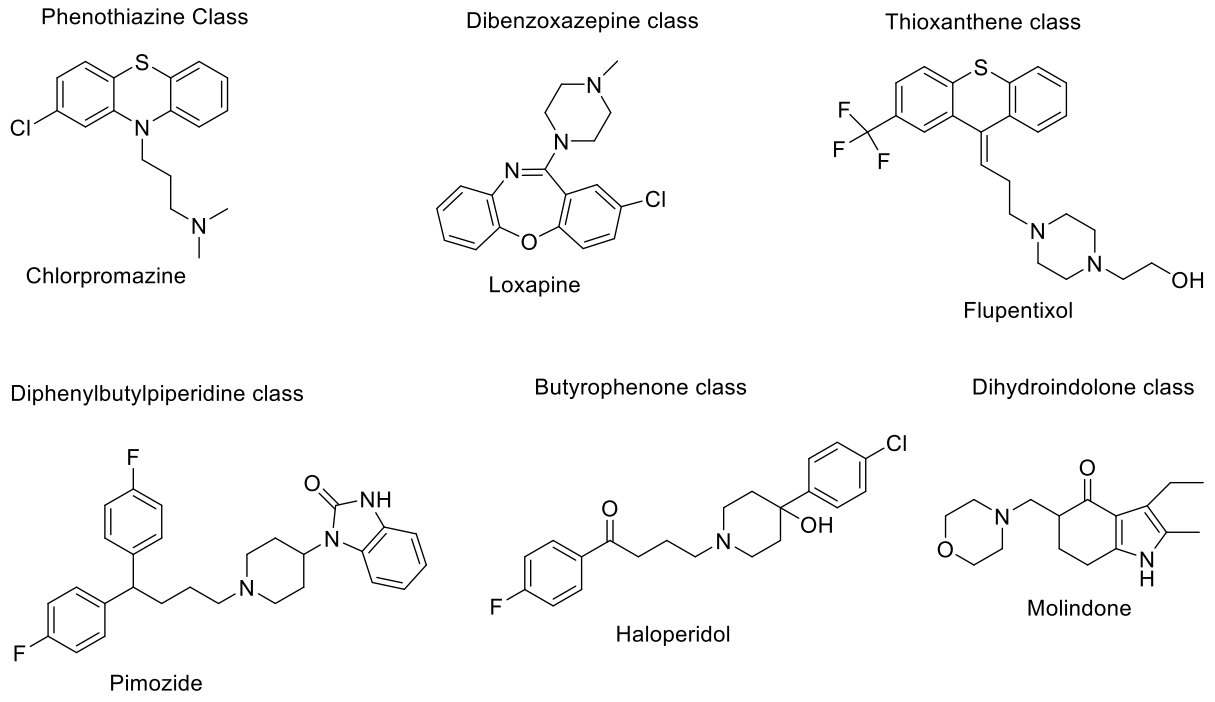
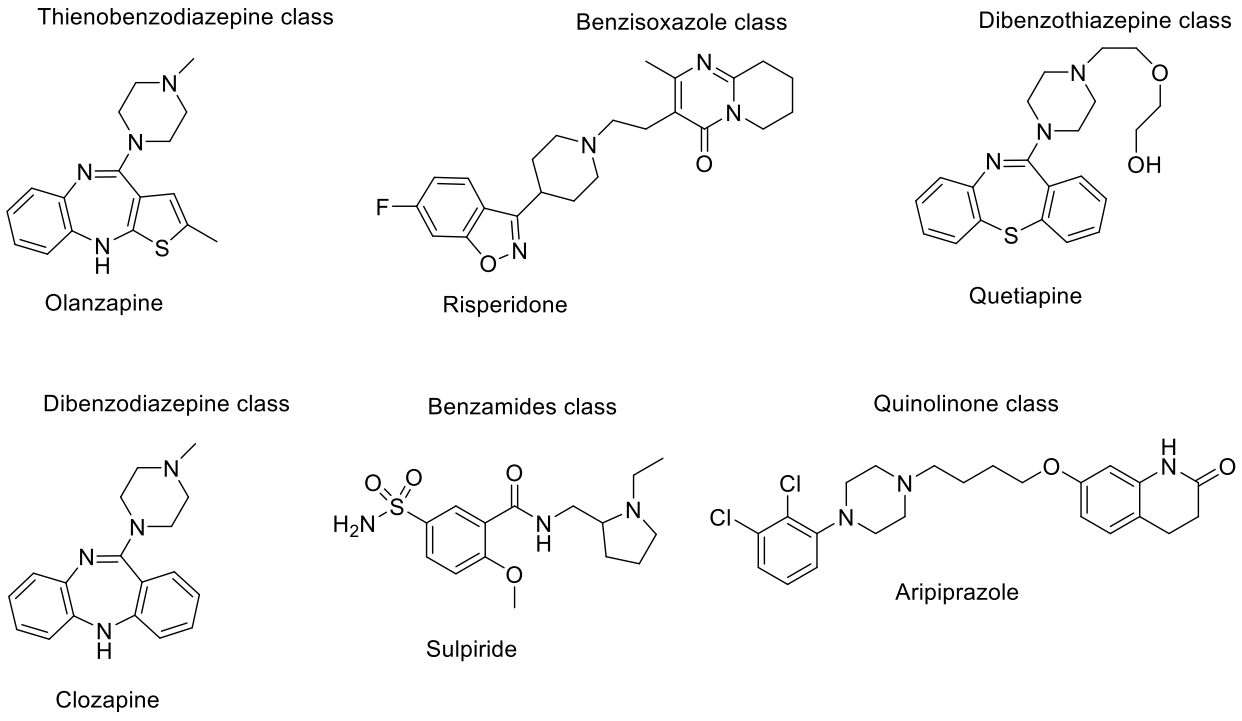
1. Introduction

Parkinson's disease (PD) is a common neurological disorder thought to result from the cellular death of dopamine secreting cells in the substantia nigra.[1] PD is recognized primarily by most people as tremors, limb stiffness, impaired balance, slow movement, muscle rigidity, postural instability, clarity of speech, and less legible handwriting.[2-4] Many PD patients also develop non-motor deficits that are equally disturbing to the well-being of patients and their daily functional activities including autonomic dysfunctions, sensory disturbances and psychosis. The deteriorations associated with Parkinson's disease (PD) are comorbid medical conditions (*e.g*. dementia, depression, sleep disorders, reduced vision), duration of illness and axial rigidity subtype.[5-10] Unfortunately, over the course of the disease the majority of patients are also affected by Parkinson's disease psychosis (PDP), which occurs in up to 60% of individuals.[11] PDP causes them to see, hear, or experience things that are not real (hallucinations),[12,13] or believe things that are not true (delusions).[5]

Psychosis in Parkinson's disease (PD) disturbs the daily functional activities and well-being of patients, places a heavy burden on family members and caregivers, and leads to increased premature placement in nursing homes and long-term care facilities, repeated hospitalizations, and increased morbidity and mortality.[14-16] Therefore, psychotic symptoms in patients with PD require treatment. There are many antipsychotic medications on the market, and they differ in potency in relation to dopaminergic and serotonin receptor types. The first generation or typical antipsychotics[17-19] (Scheme 1) were examined as potential drugs. However, the clinical studies showed the use of typical antipsychotics in patients with PD is complicated due to their ability to block dopaminergic D2 receptors and cause profound dopamine D2 antagonism and drug-induced Parkinsonism symptoms[20] such as dyskinesia which usually accompanied with worsened motor symptoms.[21] Therefore, atypical antipsychotics (AAP); also known as second generation antipsychotics (SGAs) are commonly used.[22] Among these drugs are Olanzapine, Risperidone, Quetiapine and Clozapine (Scheme 2). It is generally accepted that second-generation antipsychotics (SGAs) are safer in patients with PD due to their lower D2 antagonism but they also can cause extrapyramidal side effects, [23,24,21] even in lower rates, in comparison with first-generation antipsychotics (FGAs).[25] Recently Barry *et al*. have published a tutorial review that summarized the synthesis, mode of action, effectiveness and limitations of some of the most clinically used typical and atypical antipsychotics. [26]



Scheme 1. Classes of typical antipsychotics with selected examples.



Scheme 2. Classes of atypical antipsychotics with selected examples.

The treatment of psychosis in PD is therefore a complex task and the choice of atypical antipsychotic is based on patient-specific parameters, potential benefit, and side effects.[27] Accordingly, there is an urgent need to develop novel effective, safer and better-tolerated drugs for improved treatment of PDP.[28] The only antipsychotic with clear evidence regarding efficacy in PD patients is Pimavanserin (Figure 1).

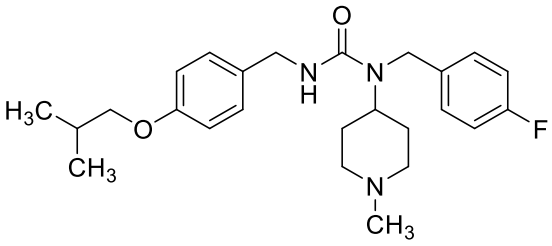


Figure 1. The chemical structure of Pimavanserin.

Pimavanserin (Nuplazid™) is a first medication approved by the FDA for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). It was originally developed by Acadia Pharmaceuticals[29-33] (CAS No. [706779-91-1], April 2016). Pimavanserin is a first-in-class atypical antipsychotic that does not induce clinically significant antagonism of dopaminergic, adrenergic, histaminergic, or muscarinic receptors.[34] Throughout the clinical trial program, Pimavanserin appeared to be safe and well-tolerated, particularly with respect to its lack of deleterious effects on motor function.[29,35] Collective reviews that discuss the pharmacology, pharmacodynamics, pharmacokinetics and clinical trials assessing its efficacy and safety have been reported.[30,36]

Due to the importance of Pimavanserin for the treatment of hallucinations and delusions associated with (PDP), various routes of synthesis of this drug were published in issued patents in late 2004, 2006, 2007, 2009 and 2010.[31-33] As a consequence, to summarize and to discuss the innovative and challenging synthetic strategies of Pimavanserin is crucial. The only article that has described the synthesis methods of Pimavanserin was published in the Chinese language by Gan and Hu.[37] The aim of this review is to describe, discuss, and provide a selection of the most commonly used routes for Pimavanserin synthesis based on many literature sources including patents. Furthermore, from this study, it will be possible to establish or to judge whether novel methods and transformations developed are most frequently employed and which ones are not applicable in large-scale syntheses. We believe that this summary will give an enlightening overview of the chemical methodologies adopted for the synthesis of Pimavanserin as a novel drug candidate for Parkinson's disease psychosis (PDP).

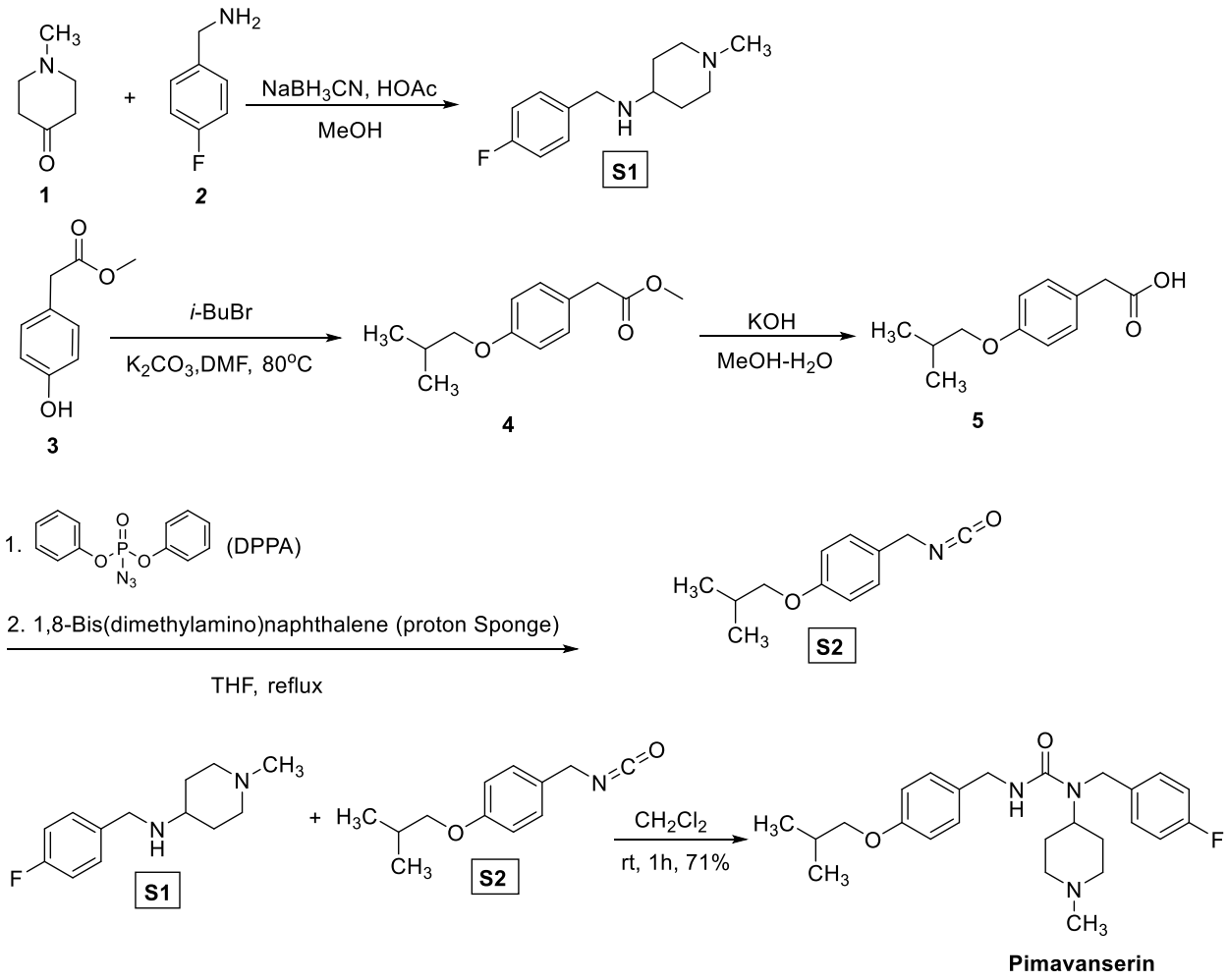
2. Synthesis Methods to Pimavanserin (Nuplazid™)

Pimavanserin, is a member of the class of ureas in which three of the four hydrogens are replaced by 4-fluorobenzyl, 1-methylpiperidin-4-yl, and 4-(isopropyloxy) benzyl groups (Figure 1). The following schemes illustrate the methods used for synthesis of Pimavanserin.

2.1. Method A (Acadia Pharmaceuticals Company, 2004)[32]

Weiner *et al*.[32] devised an efficient production method for the synthesis of Pimavanserin. Their route was improved and developed for the compound's large scale manufacture. The refined process route (Scheme 3) is based on the condensation of readily available *N*-methylpiperidone **1** with *p*-fluorobenzylamine **2** followed by reduction to offer the precursor **S1** quantitatively. Alkylation of commercially available 4-hydroxyphenyl-acetate ester **3** gave compound **4.** Hydrolysis of ester **4** gave the corresponding acid **5**. Heating the carboxylic acid **5** with diphenylphosphoryl azide (DPPA)[38,39] in the presence of base such as 1,8-bis(dimethylamino)-naphthalene[40] produced acyl azides, which thermally underwent the Curtius rearrangement to afford the key

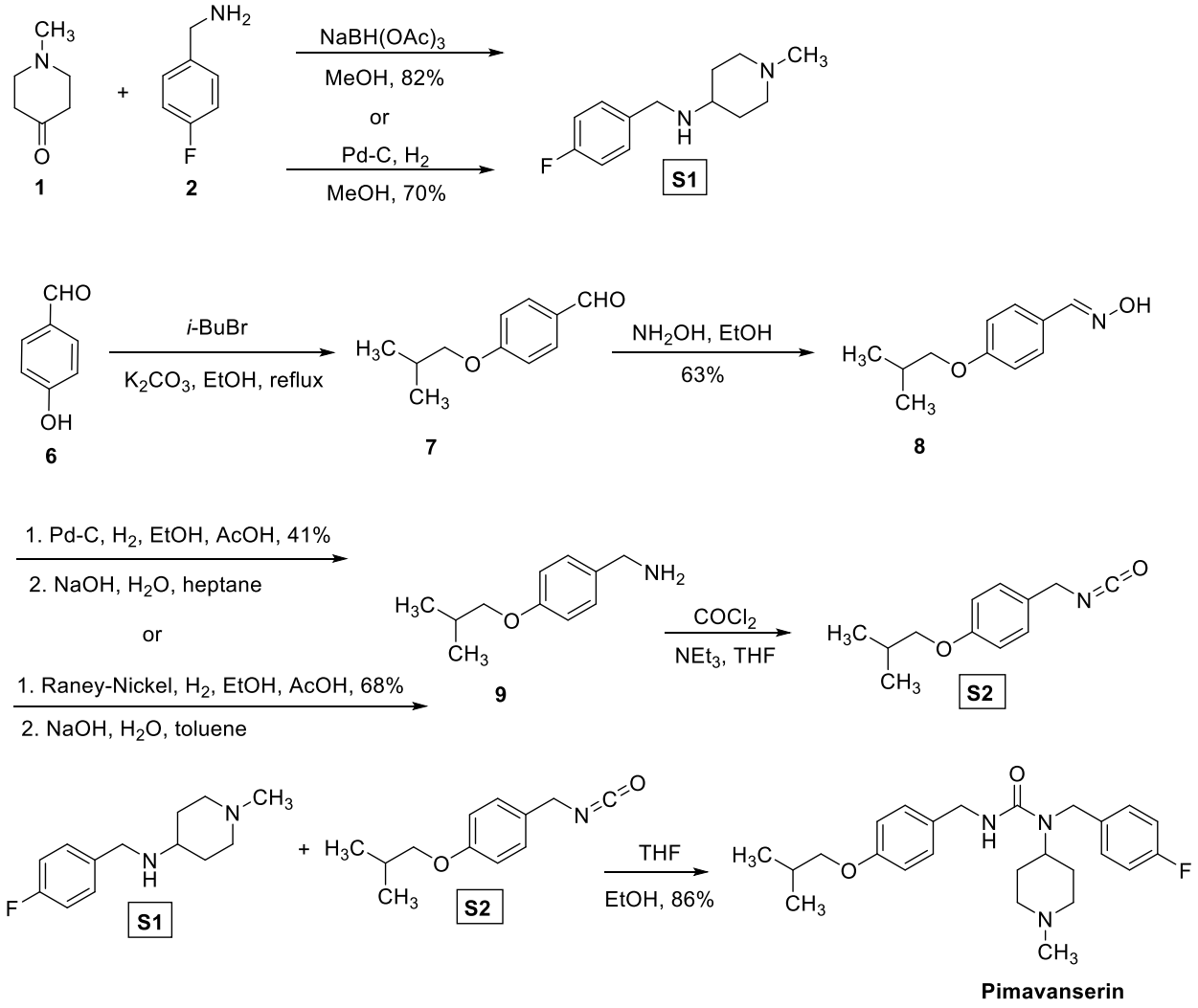
isocyanate **S2**.[41] The isocyanate **S2** thus formed reacts with amine **S1** to furnish the target Pimavanserin (Scheme 3).



Scheme 3

2.2. Method B (Acadia Pharmaceuticals Company, 2006)[33]

Thygesen *et al.*[33] have developed an attractive alternative method for synthesis a wide variety of carbamides and their tartrate salt derivatives including Pimavanserin for large scale manufacture (Scheme 4). Reductive amination between compounds **1** and **2** was accomplished smoothly by using sodium triacetoxyborohydride to generate the key fragment secondary amine **S1**. Treatment of phenol **6** with isobutylbromide in the presence of K_2CO_3 gave the corresponding ether derivative **7**. Subsequent oximation of **7** produced the oxime **8**. Reduction of oxime group and subsequent hydrolysis of ammonium salt formed, yielded the desired primary amine **9**. Treatment of amine **9** with phosgene[42,43] provided the corresponding isocyanate[41] **S2**. Coupling the key synthon **S2** with secondary amine **S1** furnished the target carbamide derivative (Pimavanserin) in high yield. (Scheme 4)



Scheme 4

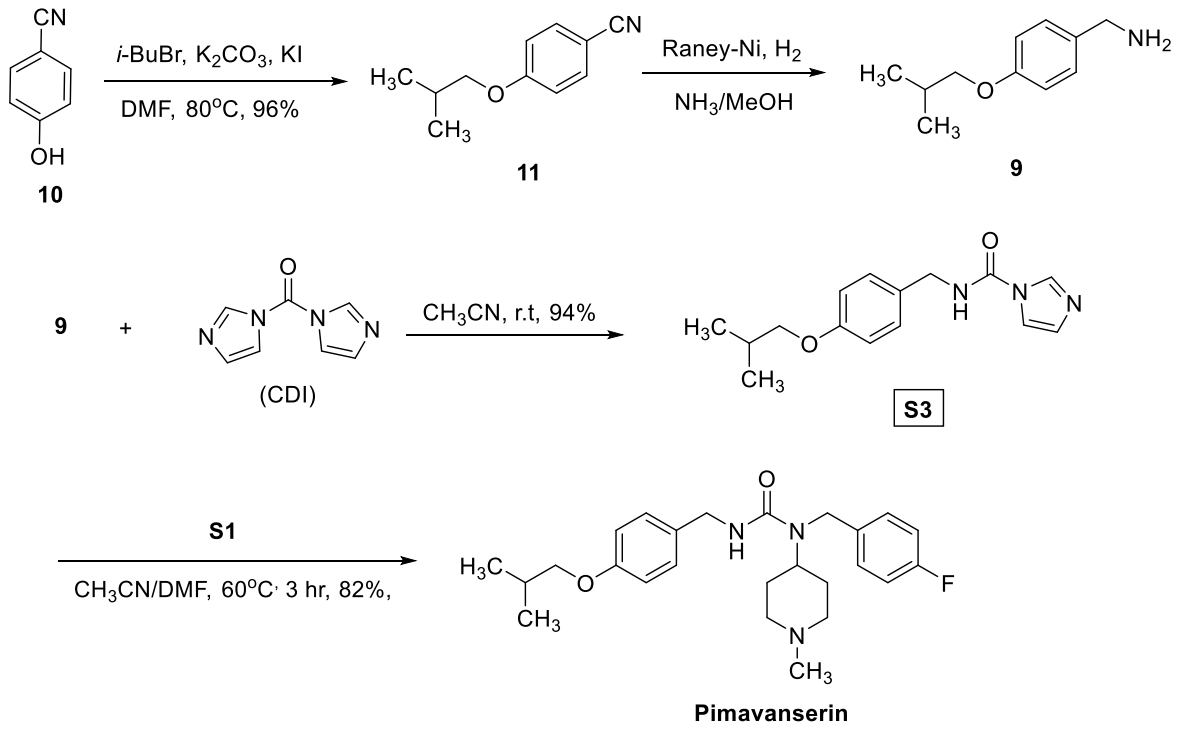
However, both of the above processes for the preparation of Pimavanserin suffer from low process safety, they often utilize hazardous reagents like phosgene[44] or diphenylphosphoryl azide.[45] Accordingly, there was still a need for additional processes allowing the efficient and safe synthesis of Pimavanserin.

In 2016, TEVA Pharmaceutical Industries[46] developed various methods for the production of Pimavanserin. In their patent work it was shown that the highly toxic phosgene and DPPA reagents can be readily substituted by less toxic and less expensive intermediates. The routes of synthesis were based on coupling of readily prepared *N*-(4-fluorobenzyl)-l-methylpiperidin-4-amine **S1** with urea or carbamate derivatives (Scheme 5 and Scheme 6).

2.3. Method C (TEVA Pharmaceutical Industries, 2016)[46]

The first route starts with the readily available 4-cyanophenol **10**. Compound **10** was alkylated with isobutyl bromide in the presence of K_2CO_3 to form the corresponding cyanophenyl ether **11**. Catalytic hydrogenation of cyanophenyl ether **11** with Raney nickel afforded the key intermediate 4-isobutyloxybenzylamine **9**. Coupling of amine **9** with 1,1-carbonyldiimidazole (CDI)[47] in acetonitrile produced the urea synthon **S3**. The urea derivative **S3** was found to be an efficient coupling partner and reaction with *N*-(4-fluorobenzyl)-l-methyl-piperidin-4-amine **S1** in a mixture of CH_3CN and DMF led smoothly to the desired Pimavanserin in an overall

yield of 82%. (Scheme 5) In general, the reaction conditions are convenient for purification, and the reactions proceed with complete conversion. The method is thus convenient for large scale manufacture.

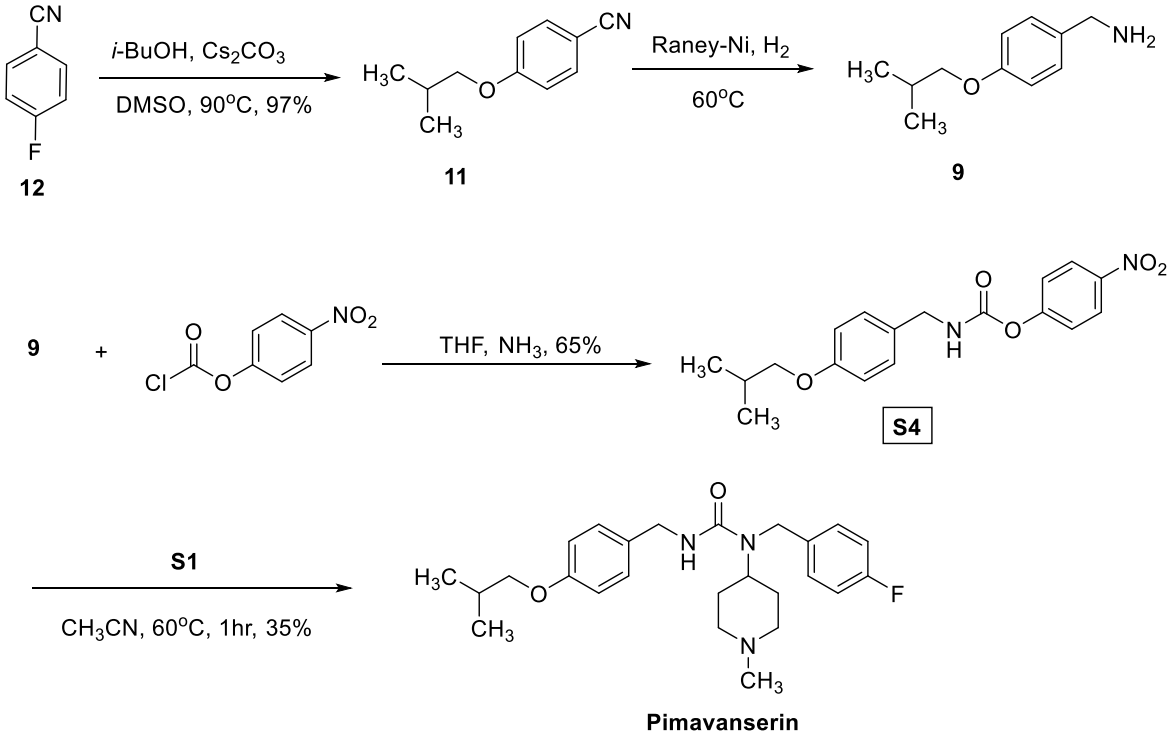


Scheme 5

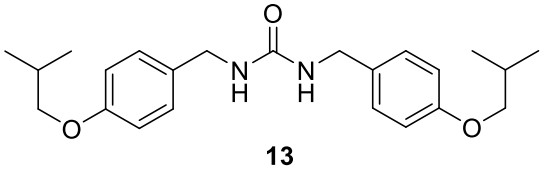
2.4. Method D (TEVA Pharmaceutical Industries, 2016)[46]

A modified approach (Scheme 6) from the same stable involved an alternative synthesis of the isobutyloxybenzonitrile **11** from 4-fluorobenzonitrile **12** and isobutanol, and formation of the urea unit *via* the nitrophenyl carbamate **S4**, giving Pimavanserin, but only in unsatisfactory yield, and furthermore long reaction times were required.[46]

However, the above-mentioned methods (C and D) have disadvantageous features. One particular disadvantage is the formation of l,3-bis-(4-isobutoxybenzyl)urea **13** as a side product. Removal of compound **13** leads to considerable loss from the total weight of crude products.

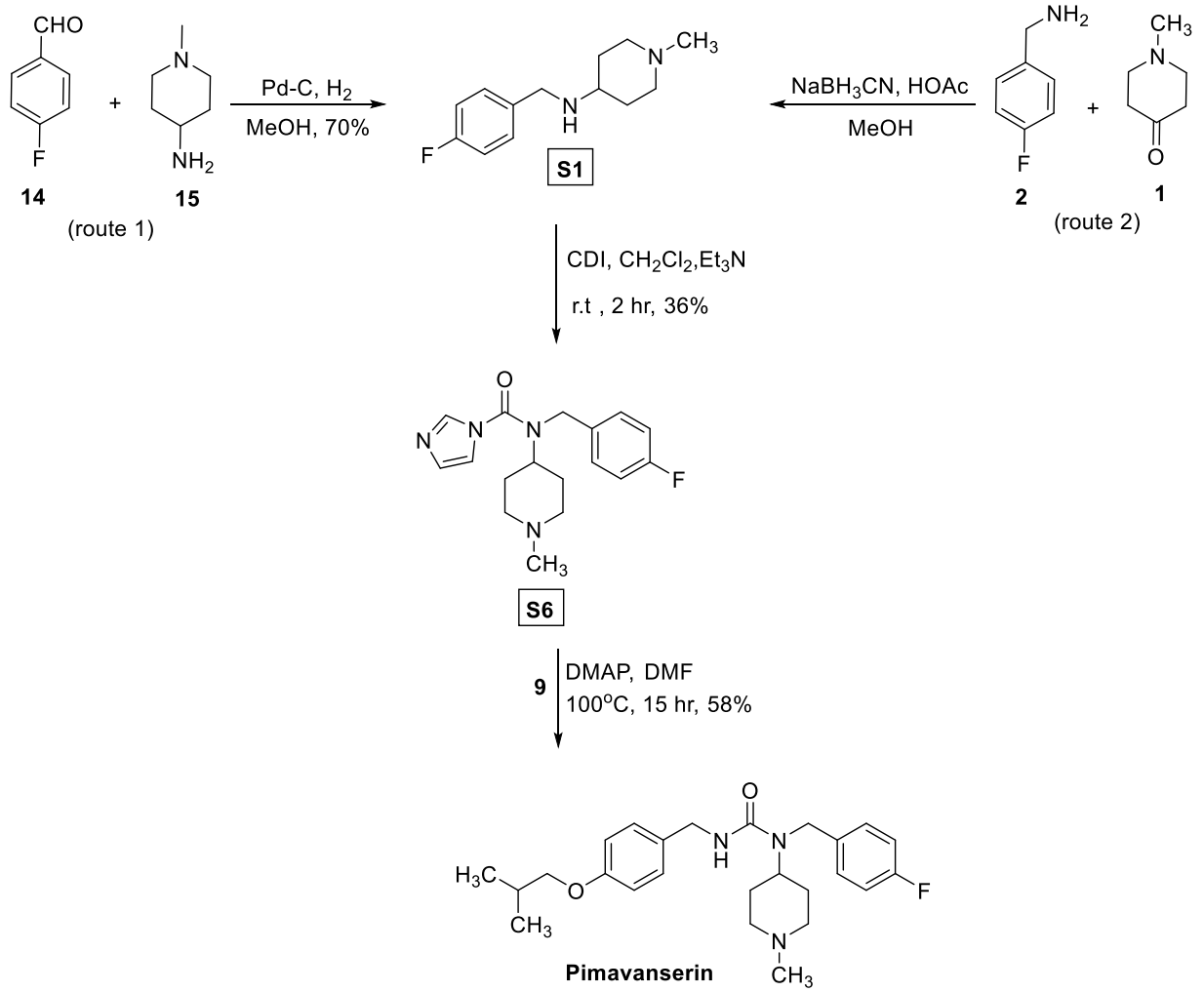


Scheme 6



2.5. Method E. Comparative method

Another possible approach introduced different conditions for the synthesis of Pimavanserin. Initially, the condensation of the readily available *p*-fluorobenzaldehyde **14** with aminopiperidine **15** followed by reduction with Pd/C under hydrogen produced **S1** in one step (route 1). Alternatively, condensation of *N*-methyl-piperidone **1** with *p*-fluorobenzylamine **2** followed by reduction with $NaCNBH_3$ in the presence of acetic acid led to the formation of the same precursor **S1** quantitatively (the second route was described in Method A (Scheme 3). The developed approach was based on the direct coupling of **S1** with 1,1-carbonyldiimidazole (CDI) in presence of Et_3N and CH_2Cl_2 to produce the substituted urea **S6** . The fully elaborated urea component **S6** was then heated with the primary amine **5** in the presence of DMAP and DMF at 100°C to furnish the desired Pimavanserin in good yield (58%) for the final step (Scheme 7). It is noteworthy that the method involves a different approach to Pimavanserin synthesis, but the total yield is very low, also using catalyst with extra heating discourages the use of this approach in comparison with the previous methods.

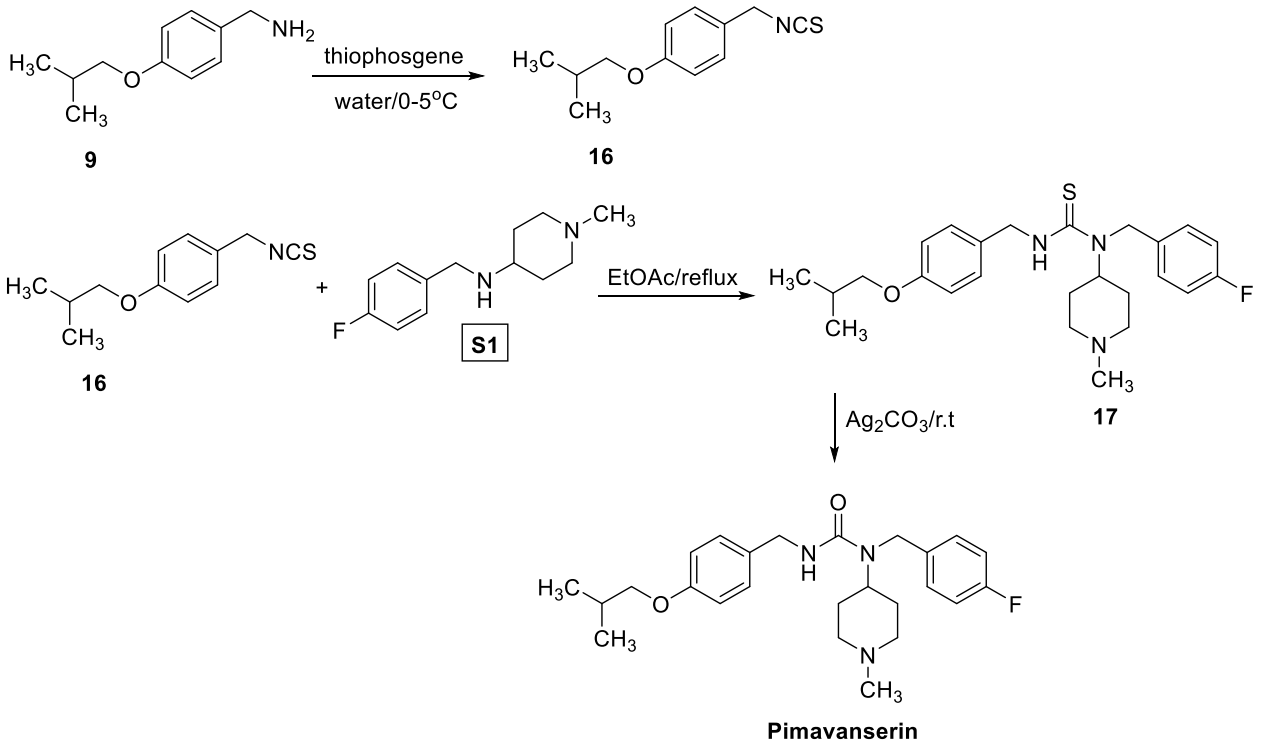


Scheme 7. Coupling of carbamide **S6** derivative with primary amine **9**

2.6. Method F: An environmentally friendly route

A novel and eco-friendly method was developed by Mulakayala *et al*.[48] The synthesis developed from the key starting material 4-isobutyloxybenzylamine **9**. The primary amine **9** was transformed into the corresponding isothiocyanate derivative **16** using thiophosgene in water as the solvent. Coupling of the readily available **S1** intermediate with isothiocyanate **16** produced the thiourea **17**. Compound **17** was desulfurized by silver carbonate to furnish the title compound Pimavanserin. (Scheme 8)

This procedure provides the advantages of easy workup, good yields of products, and use or water as the solvent. No column purification was required for the isolation of the product. However, thiophosgene was used to prepare compound **16** which is considered highly toxic, and the use of silver carbonate, and the formation of silver precipitates as byproducts, tends to the impracticability of the method.



Scheme 8

3. Conclusions

In April 2016, FDA approved Pimavanserin (NuplazidTM) as the first drug indicated for treatment of PDP. Pimavanserin has a unique pharmacological profile with its high and selective affinity for 5-HT_{2A} and 5-HT_{2C} receptors and potent inverse agonist activity at 5-HT_{2A} receptors. The drug has minimal affinity and does not interact with dopaminergic, muscarinic, adrenergic and histaminergic receptor subtypes. Pimavanserin may also be useful for treating psychotic conditions associated with other neurodegenerative diseases and therefore a study in Alzheimer's disease psychosis (ADP) has recently been initiated by ACADIA pharmaceutical company to explore this possibility.[49] Based on the data that collected from different literature resources, a number of observations can be drawn for the syntheses of Pimavanserin,. For example, it is established that the most applicable method used is based on coupling of readily prepared *N*-(4-fluorobenzyl)-l-methylpiperidin-4-amine **S1** with urea derivatives in general. Specifically, CDI reagent is used as powerful coupling agent (Scheme 5). This can be rationalized by considering the efficiency and the safe synthesis routes in comparison with the highly toxic phosgene and DPPA reagents that are used in scheme 3 and 4. Other robust method such as coupling of carbamate derivative to a secondary amine (Scheme 7), appear to be rarely used. The reasons for this might be the low yield product, in addition to the need of catalyst with extra heating. In conclusion, the development and approval of Pimavanserin will encourage the medical arsenal in discovering novel 5-HT_{2A} inverse agonists for improved treatment of psychotic symptoms in psychiatric as specific and neurological disorders as a general. Undoubtedly, many other developed strategies will be discovered in the near future and further applied economic steps will become elaborated in total synthesis of Pimavanserin and various analogs.[50,51] In summary, this article may be helpful to the field of pharmaceutical industry, researchers and scholars working in the field of antipsychotic medicines and health care specialists.

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Author's Biography

Nader Robin Al Bujuq received his BSc (1995) and MSc (2000) degrees from the University of Jordan. He obtained his PhD in Organic Chemistry (2009) from university of Seville, Spain, and European Doctorate research from Stuttgart University. In 2010 he began as an assistant professor of organic chemistry at the Department of Biotechnology and Genetic Engineering at Philadelphia University. In 2015 he moved to work at Taibah University, KSA. His research interests involve design and synthesis of matrix metalloproteinase inhibitors (MMPs).

