Abstract of the Thesis

The thesis entitled "**Synthesis and characterization of piperazine containing atypical antipsychotic drug substances and their related compounds**" is divided into five chapters.

The title of the thesis clearly reflects the objective, which is to provide alternate routes for the synthesis of piperazine containing atypical antipsychotic drug substances viz., Quetiapine, Ziprasidone, Aripiprazole, Olanzapine involving the new intermediate compounds along with identification, characterization and synthesis of their related compounds.

CHAPTER-1

This chapter deals (i) an introduction to various types of typical atypical antipsychotic active pharmaceutical ingredients, their individual importance based on pharmacological activity, and comparison among typical and atypical antipsychotic pharmaceutical ingredients; (ii) importance for an alternate synthetic processes for the preparation of active pharmaceutical ingredients to a pharmaceutical industry and reasons for the formation of related compounds (impurities) of an active pharmaceutical ingredient.

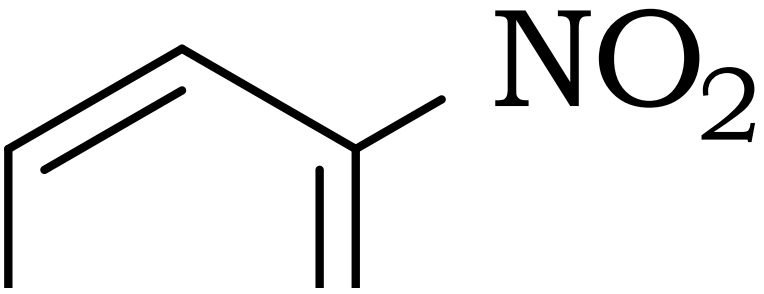
CHAPTER-2

This chapter describes an alternate synthetic pathway for the preparation of Quetiapine (**23**), identification, synthesis and characterization of two process related compounds of Quetiapine. Though there are several synthetic processes are known in the literature for the preparation of Quetiapine, some of these processes involves the use of hazardous, costly raw materials and difficult synthetic processes for the isolation of intermediates and hence become less attractive for the commercial use. Therefore, we have systematically designed a new route to prepare Quetiapine, which is simple, scalable and cost-effective process.

Our proposed new route involves the condensation of two synthons namely, 2-mercapto benzoic acid (**52**) and 1-chloro-2-nitrobenzene (**53**) to get the 2-(2-nitrophenylthio)benzoic acid (**51**). Compound **51** was transformed to amide derivative via acid chloride to get 2-(2-nitrophenylthio)benzamide (**50**). The benzamide derivative was subjected for dehydration with $POCl_3$ to result 2-(2-nitrophenylthio) benzonitrile (**49**). The nitrile compound was reacted with $SnCl_2$ and HCl to get the three member cyclic dibenzo[*b,f*][1,4]thiazepin-11-amine (**38**). Amine **38**, condensed with *N*,*N*-bis(2-chloroethyl)-4-methylbenzenesulfonamide (**54**) to get 11-(4-tosylpiperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (**48**). Compound **48** was further treated with hydrobromic acid in the presence of acetic acid to yield 11-

(piperazin-1-yl)dibenzo[*b,f*][1,4]thiazepine (**31**). Finally compound **31**, condensed with 2-chloroethoxy ethanol to yield desired compound **23** in excellent overall yield (Scheme 1). All these intermediate and final compounds are fully characterized based on their respective spectral data.

Scheme 1:



We have also identified, characterized and synthesized two process related compounds of Quetiapine **55** and **56**, which are generated during the synthetic process. Based on their individual spectral analysis, the following structures were assigned to the identified related compounds.

CHAPTER-3

This chapter mainly focused to overcome the encountered problems during the precedent synthetic pathways and designed three alternate processes to atypical antipsychotic drug substance, Ziprasidone (**24**). As a part of regulatory requirement, one should satisfy with the specified content of related compounds listed in pharmacopoeia; accordingly we have further provided processes to prepare three listed related compounds involving the simple reaction conditions.

The first synthetic approach (Scheme 2) for the preparation of Ziprasidone involves reaction of 3-(1-piperazinyl)-1, 2-benzisothiazole (**62**) with 6-chloro-5-(2-chloroacetyl)indolin-2-one (**60**) under basic conditions to yield 5-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)acetyl)-6-chloroindolin-2-one / keto Ziprasidone (**76**). The resulted keto Ziprasidone was subjected to reduction in the presence of triethyl silane and methane sulfonic acid to afford Ziprasidone (**24**) with good purity and yield. The conversion of keto Ziprasidone to Ziprasidone in a single step is not known in the literature before our attempt.

Scheme 2:

The second pathway (Scheme 3) for the preparation of Ziprasidone utilizes 6-chloro-5-(2-piperazin-1-yl-ethyl)-oxindole (**77**), which is a new intermediate. The synthetic route involves the reaction of 5 - (2-chloro ethyl)–6–chloro oxindole (**61**) with excess moles of piperazine to afford **77**. The compound **77** was condensed with 3-chloro-1,2-benzisothiazole (**78**) to afford the targeted compound Ziprasidone in excellent yield with ICH purity.

Scheme 3:

Our third attempt for the preparation of Ziprasidone involves the reaction of 3-chloro-1, 2-benzisothiazole (**78**) with slight excess molar ratio of bis ethanol amine at an elevated temperature to yield diol

derivative, 2,2'-(benzo[*d*]isothiazol-3-ylazanediyl)diethanol (**81**) and isolated in the form of hydrochloride salt. The diol derivative **81**, was reacted with thionyl chloride to produce dichloro derivative, *N,N*-bis(2-chloroethyl)benzo[*d*]isothiazol-3-amine (**79**) as one of the building blocks for this process. 5 - (2-Chloro ethyl) – 6 – chloro oxindole (**61**) was reacted with pthalimide (**83**) in the presence of potassium carbonate in dimethyl formamide media produced 2-(2-(6-chloro-2-oxoindolin-5-yl)ethyl)isoindoline-1,3-dione (**82**). The resulted pthalimido protected compound was reacted with aqueous monomethylamine to produce another advanced intermediate 5 - (2-amino ethyl) – 6 – chloro oxindole (**80**). The condensation of these advanced synthons produced the targeted compound, Ziprasidone (Scheme 4). The two advanced intermediates **79** and **80** along with their precursors **81** and **82** respectively are new intermediates to prepare compound **24**.

Scheme 4:

This chapter also describes the preparation of three pharmacopoeial impurities, a process related impurity and their characterization by spectral data. The synthesized impurities are 5-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindoline-2,3-dione (**84**), 2-(2-amino-5-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-4-chlorophenyl)acetic acid (**85**), 3-(benzo[*d*]isothiazol-3-yl)-5-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloroindolin-2-one (**86**) and 5-(2-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)ethyl)-6-chloro-3-(propan-2-ylidene)indolin-2-one (**87**).

CHAPTER-4

Chapter-4 deals with new route for the preparation of Aripiprazole (**27**) mainly using Beckmann rearrangement conditions to form carbostyril moiety.

Our attempts involved (Scheme 5) the use of two synthons, 1-(2,3-dichlorophenyl)piperazine (**89**) and 6-hydroxy-2,3-dihydro-1*H*-indene-1-one (**111**) as key starting materials to get 6-(4-(4-(2,3-dichlorophenyl)piperazine-1-yl)butoxy-2,3-dihydro-1*H*-inden-1-one (**110**). The compound **89** was converted to its quaternary salt (**112**) by reaction with 1,4-dichlorobutane (**113**) and was further reacted with **111** to get indanone derivative (**110**). The indanone derivative **110** was converted to its oxime derivative (**109**) and was subjected to Beckmann Rearrangement to yield Aripiprazole (**27**) via the formation of 6-(4-(4-

(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2,3-dihydro-1*H*-inden-1-one O-tosyl oxime (**108**).

Scheme 5:

Two other synthetic approaches (Scheme 6) were also established for the preparation of key intermediate **109**.

Scheme 6:

This chapter also provides the preparation of four related compounds and they are identified as 7-(4-bromo-butoxy)-1*H*-quinolin-2-one (**117**), 7,7'-(butane-1,4-diylbis(oxy))bis(3,4-dihydroquinolin-2(1*H*)-one) (**118**), 7-[4-(7-4-[4-(2,3-dichloro-phenyl)-piperazin-1-yl]-butoxy-3,4-dihydro-quinolin-2-yloxy)-butoxy]-3,4-dihydro-1*H*-quinolin-2-one (**119**) and 6-(4, 3-(hydroxyimino)-2,3-dihydro-1*H*-inden-5-yloxy)butoxy)-2,3-dihydro-1*H*-inden-1-one oxime (**120**).

CHAPTER-5

The present chapter reports the preparation of Olanzapine (**26**) by an alternate method. This chapter also deals with the preparation of four process related compounds and all are fully characterized by their spectral data.

Our synthetic pathway (Scheme 7) used for the preparation of Olanzapine involved the palladium catalyzed coupling of 2-amino-5-methylthiophene-3-carbonitrile (**122**) with 1-bromo-2-iodobenzene (**143**)

in the presence of xantphos ligand and cesium carbonate as base to produce new intermediate, 2-(2-bromophenylamino)-5-methylthiophene-3-carbonitrile (**142**). This intermediate compound **142** was reacted with *N*-methyl piperazine (**125**) in the presence of trimethylaluminium to afford another new intermediate, imine derivative (**141**), which upon subsequent cyclization produced Olanzapine (**26**).

Scheme 7:

This chapter also provides the preparation of four process related compounds. Based on their spectral data, these compounds were identified as 2-Methyl-4-(piperazin-1-yl)-10*H*-benzo[*b*]thieno[2,3-*e*][1,4]diazepine (**130**), 2-Methyl-10*H*-benzo[*b*]thieno[2,3-*e*][1,4]diazepin-4-ol (**144**), Olanzapine *N*-Oxide (**145**) and 1-[Chloromethyl]-1-methyl-4-{2-methyl-10*H*-benzo[*b*]thieno[2,3-*e*][1,4]diazepin-4-yl}piperazin-1-ium chloride (**146**).

In summary, our thesis work describes alternate synthetic processes for the preparation of atypical antipsychotic drugs such as Quetiapine, Ziprasidone, Aripiprazole and Olanzapine. We have also identified, characterized and synthesized the process related compounds of these drugs. Our alternate processes involved new intermediates, different reagents and reaction conditions. These alternate synthetic processes have an advantage to get an early launch opportunity in certain countries where many processes of these drugs were protected through valid patents by innovator companies.