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RESEARCH ARTICLE

AN EFFICIENT REDUCTION PROCESS AT KEY INTERMEDIATE STAGES IN DABIGATRAN, DOMPERIDONE AND OLANZAPINE API'S

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ABSTRACT

Objective: The present paper describes the simple and efficient protocol for the reduction of key intermediates in three API's like Dabigatran, Domperidone and Olanzapine using Iron metal with Ammonium formate as main reagents with suitable solvent system. In Dabigatran and Domperidone the conversions are nitro to amine and in Olanzapine nitrile reduction followed by cyclization.

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INTRODUCTION

Dabigatran is used to help prevent strokes or serious blood clots in people who have atrial fibrillation (a condition in which the heart beats irregularly, increasing the chance of clots forming in the body and possibly causing strokes) without heart valve disease (Pollack *et al*., 2015; Eikelboom, 2013; Stangier *et al*., 2015). Domperidone is an effective anti-emetic (medicine used to prevent vomiting and nausea). It increases the intestinal movements and facilitates emptying of the bowel (Reddymasu *et al*., 2007; Simard *et al*., 2008) and Olanzapine is an antipsychotic medication that affects chemicals in the brain. Olanzapine is used to treat the symptoms of psychotic conditions such as schizophrenia and bipolar disorder (manic depression) in adults and children who are at least 13 years old (Reddymasu *et al., 2007;* Leucht *et al*., 2013). These three are important API's in respective therapeutic areas, because of more consumption in market; continuous production optimization is requiredin different academic and industrial areas. We have optimized excellent processes especially in reduction stage in mentioned API's. In previous reduction conditions Raney-Ni metal catalyst and stannous chloride were used but they are too cost, having lot of safety issues, recovery is high risk, not cost effective and industrially not viable.

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To avoid these problems we have optimized new and safe conversion method, reagents are Iron and Ammonium formate with suitable solvent system.

Scheme:

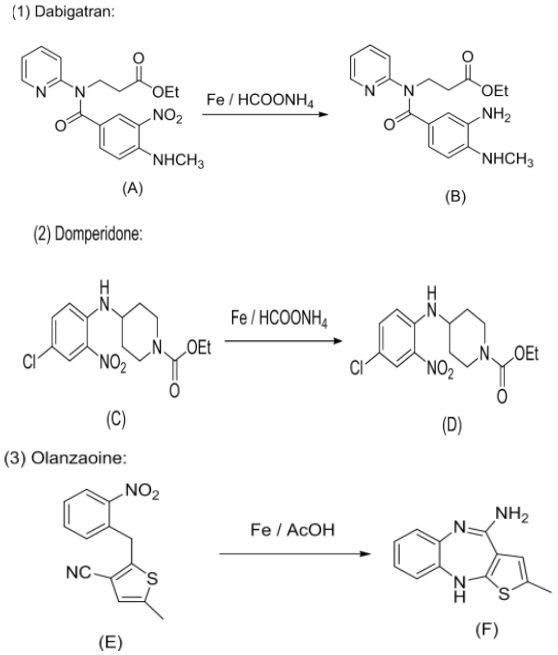
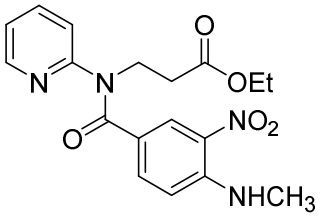
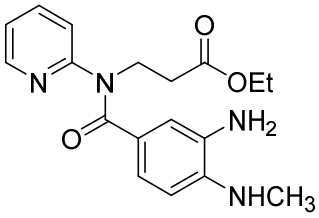
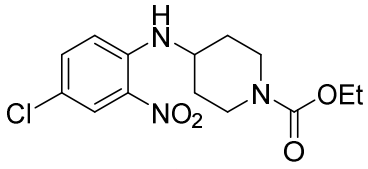
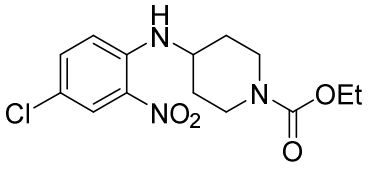
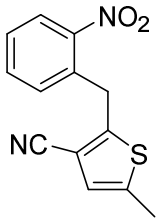
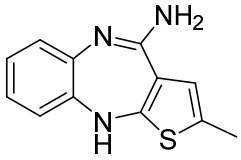


Table. All experimental details explained in below

S No	API	Intermediate	After Reduction	Previous Condition	Optimized Condition
1	Dabigatran	 (A)	 (B)	Raney-Ni / H_2 (gas) / Ethyl acetate / 60°C / 20hr	Iron Powder /Ammonium Formate / Toluene : EtOH :Water / 80-90°C / 3hr
2	Domperidone	 (C)	 (D)	Raney-Ni / H_2 (gas) / Toluene / 80°C / 36hr	Iron Powder /Ammonium Formate / Toluene : EtOH :Water / 90-100°C / 3hr
3	Olanzapine	 (E)	 (F)	$SnCl_2$. HCl / Ethyl acetate / Reflux	Iron Powder / Acetic acid : EtOH : Water / Reflux / 5hr

EXPERIMENTAL

Thin layer chromatography was run on silica gel-G and visualization was done using UV light or iodine. IR spectra were recorded by Perkin-Elmer 1000 instrument in KBr pellets. ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-D6 solvent using trimethylsilane as the internal standard by the 300MHz spectrometer. By Jeol-JMS D-300 spectrometer, mass spectra were recorded. Starting materials which were used in this chapter were prepared in-house, characterized and used as such.

RESULTS AND DISCUSSION

Compound (A) and (C) reacts with Ammonium formate in the presence of Iron metal using Toluene, Ethanol and water a solvent system at 60-80°C around 2-3Hrs gave title products (B) and (D), In case (E) to (F) conversion required Iron water as main reagent with acetic acid, ethanol waster mixture as solvent system at reflux condition around 5hr gave the desired product. Obtained reduced products quality compared with standard samples which are already available in-house.

Conclusion

We developed a versatile and useful reduction condition at key intermediate stage in Dabigatran, Domperidone and Olanzapine API's. These optimized novel processes are fast reaction conversion, easy work up and handling the reagents, minimum time cycle and cost effective.

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