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Original Article

Simple, convergent synthesis of the pyrazole linked pyridine derivatives: Micro-wave, sonication and conventional methods

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ABSTRACT

The re-emergence of antimicrobial infections which are resistant to conventional drug therapy has demonstrated the need for alternative chemotherapy. The preparation of skeleton is an important in the novel drug development. Herein, the skeleton is developed based on anti-ulcerative drugs. A convergent synthesis, approached to simplify the synthesis and succeeded to prepare novel pyrazole-pyridine linked derivatives **(SLN1–SLN10)**. Finally, coupled both pyrazole and pyridine derivatives by approaching micro-wave, Sonication and conventional techniques. The efficient technology identified as Sonication technique basically time and yield.

1. Introduction

For therapeutic purposes, a drug substance with well-known chemical structure is used for developing more efficient drugs. The basic idea to prepare more analogues compounds that related drug candidates with efficient technologies. Organic molecules owe their biological activity to a variety of structural features. Sometimes a set of activities is associated with the structural backbone of a molecule.

The anti ulcer drugs, **Omeprazole (a)**, is a proton pump inhibitor (PPIs) and inhibits the action of hydrogen/potassium adenosine triphosphatase (H+/K+ATPase) in parietal cells.[1–5] **Lansoprazole (b)** is an antiulcer agent and proton pump inhibitor.[4,5]

Pantoprazole (c) suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H+,K+)-ATPase enzyme system at the secretary surface of the gastric parietal cell.[6,7] **Rabeprazole (d)** is also demonstrated efficacy in healing and symptom relief of gastric and duodenal ulcers.[2,8,9] **Ilaprazole (e)** is a proton pump inhibitor (PPI) used in the treatment of dyspepsia, peptic ulcer disease (PUD), and duodenal ulcer Fig. 1.[10]

The art has endeavoured to synthesize a variety of piperazine derivatives. Among the piperzine derivatives available as anti-ulcer drugs, 1-[2-(orthochloro-robenzydryloxy)ethyl]-4-(ortho-methylbenzyl)piperzine well known.[11,12] The selection of well-known skeleton, strategic synthetic approach, technologies applied for reactions. The maximum anti-

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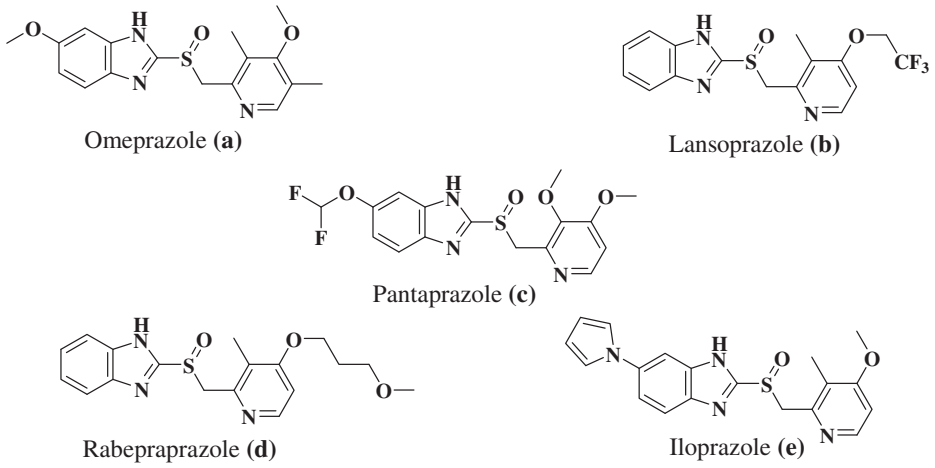

Fig. 1 – Several anti-ulcer drugs in the market.

ulcerative drugs are prazoles. The prazoles skeleton considered for development of novel moieties into literature. The idea to incorporate the piperazine with pyridine derivatives of prazoles considered to design new skeleton (Fig. 2).

A strategy of convergent synthesis, that aims to improve the efficiency of multi-step chemical synthesis, most often in organic synthesis. In linear synthesis the overall yield quickly drops with each reaction step. Here in, the synthesis of two tiles derivatives and coupled considered easy and found excellent literature for easy synthesis of both ends approached convergent than linear.

The reliable technology useful for reaching target is very important to reach target very simple and cost effective. The second technology is the way of reaction conditions are using, for getting lesser reaction timings and high yield. The N-alkylation step differentiated via Micro Wave, Sonication and Conventional method.

The microwave mediated organic reactions[13] take place more rapidly, safely, and in an environmentally friendly manner, with high yields. Very little solvent and even the use of water as a solvent is a big advantage of microwave chemistry. Recently, microwave,[14] and ultrasonication[15] assisted synthesis in organic chemistry is quickly growing. Many organic reactions proceed much faster with higher yields under microwave irradiation compared to conventional heating. It has long been know that molecules undergo excitation with electromagnetic radiation is a technique for microwave synthesis.[16] Ultra-Sonication reactions enhances the reaction rates up to a million times, believed to be due small cavities (100 microns) which implode, creating tremendous heat and pressure, shock waves, and particular accelerations.

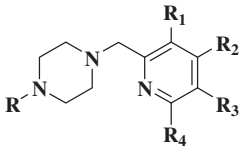

Fig. 2 – Designed skeleton.

2. Results and discussion

2.1. *Chemistry*

In continuation of our research interest was to synthesize a series of new pyrazole linked pyridine derivatives **(SLN1–SLN10)** to re-emergence antiulcer activity. Our study focussed the synthesis and rest of the activity studies is under progress. (Scheme 1).

In the synthesis of **Int-1,** we have used some earlier patented work.[17] The cyclised ester **(3)** was prepared by Cyclisation of ethyl di bromopropionate **(1)** with pyrocatechol **(2)** in anhy. acetone. The cyclised ester (3) hydrolysed using NaOH in ethanol and water to afford acid **(4)**.[18] The acid **(4)** converted to acid chloride **(5)** using oxallyl chloride and further coupled with piperzine in present of sodium acetate and further followed pH adjustments to afford **Int-1** according to (Scheme 2).

The compound 2,3-Dichlorophenylpiperazine (2,3-DCPP) **(Int-2)** well known intermediate in the synthesis of aripiprazole and one of its metabolites.[19,20] This is prepared by cyclisation of 2,3-dichloro aniline (7) with dichloro ethyl amine (8) using aq.HCl to afford (2,3-DCPP) (Int-2) according to (Scheme 3).

The choro **(9)** and **(10)** using $POCl_3$ as a chlorinating reagent to afford choro compound **(10) and (15)**. The further traditional approach for the synthesis[21] of **(Int-3)** to **(Int-7)** as shown in Scheme 4.

The conversion of nitro compounds **(9)** and **(14)** to corresponding conversation of choro compounds **(10), (15)** and **(26)** into **(11), (16), (19), (22),** and **(27)** using appropriate alcohols, the methylation of compound **(25)** using DMS to afford methylated compound **(26).** The further conversion of compounds, **(11), (16), (19), (22), (24)** & **(29)** to acetate using acetic anhydride to afford compounds, **(12), (17), (20), (23),** and **(28).** These all these compounds further hydrolysed NaOH to offered **(13), (18), (21)** and **(27)**. Finally chlorinated all these compounds using $SOCl_2$ under similar reaction condition to afford **(Int-3)** to **(Int-7)** according to Scheme 4.[21,22]

The Novel targets **(SLN1–SLN10)** were synthesized by simple coupling using different technologies (microwave, ultra-sonication and normal conventional method). Basically,