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# Novel process for the synthesis of Zaleplon

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**Abstract:**The novel method for synthesis of Zaleplon is described in this novel approach, in which N-[3-[3-(dimethyl amino)-1-oxo-2-propenyl]phenyl] acetamide, dimethyl formamide, sodium hydroxide, tetrabutylammonium bromide, ethylbromide and p- Chloroaniline reacts in sequential manner and forms N-[3-[3-(p-chlorophenylamino)-1-oxo-2-propenyl] phenyl]-N-ethyl acetamide which on treatment with 3-amino -4-cyano pyrazole in hydrochloric acid gives N-[3-(3-Cyano pyrazolo [1, 5-a] Pyrimidin-7-yl) phenyl]-N-ethyl acetamide (Zaleplon).
**Keywords:**N-[3-[3-(dimethyl amino)-1-oxo-2-propenyl]phenyl] acetamide, N-[3-[3-(p-chlorophenylamino)-1-oxo-2-propenyl] phenyl]-N-ethyl acetamide, 3-amino -4-cyano pyrazole, N-[3-(3-Cyano pyrazolo [1, 5-a] Pyrimidin-7-yl) phenyl]-N-ethyl acetamide , Zaleplon).

## Introduction

Zaleplon is a nonbenzodiazepine hypnotic from the pyrazolopyrimidine class.[1] It is one of the few sleep medications which have been found to not cause an increase in road traffic accidents, thus demonstrating a much higher safety profile than many other hypnotics currently in the market.[2] [3] Zaleplon, unlike many other hypnotic drugs, does not interfere with sleep architecture and can be administered for about 5 weeks without the risk of dependence or rebound insomnia upon discontinuation.[4]

Zaleplon is also efficacious in the treatment of middle of the night insomnia without causing residual hangover effects.[5][6] Zaleplon has advantages over benzodiazepines in that it does not disrupt sleep architecture unlike benzodiazepines which whilst inducing sleep actually worsen the quality of it.[7]

Various routes for the synthesis of zaleplon are reported in the literature. Some of the eported routes have drawbacks like poor yield, the product obtained is of inferior quality , the operation involved are not easy to perform on commercial scale.. To overcome these disadvantages, we have developed the novel process for the synthesis of Zaleplon.

Patents US 4626538 and US 5714607 depicts almost same process, which involves the reaction between N-(3-acetylphenyl) ethanamide wth dimethyl formamide dimethylacetal to form N-[3-(3-(dimethylamino)-1-oxo-2-propenyl)]phenyl] acetamide which on acylation with ethyl iodide in presence of sodium hydride gives N—[3-(3-dimethylamino)-1-oxo-2-propenyl] phenyl]-N-ethylacetamide which on condenstion with 3-amino-4-cyano pyrazole in refluxing glacial acetic acid for 8 hours to yield Zaleplon. The operations involved in this process are tedious and reaction takes long time to complete.

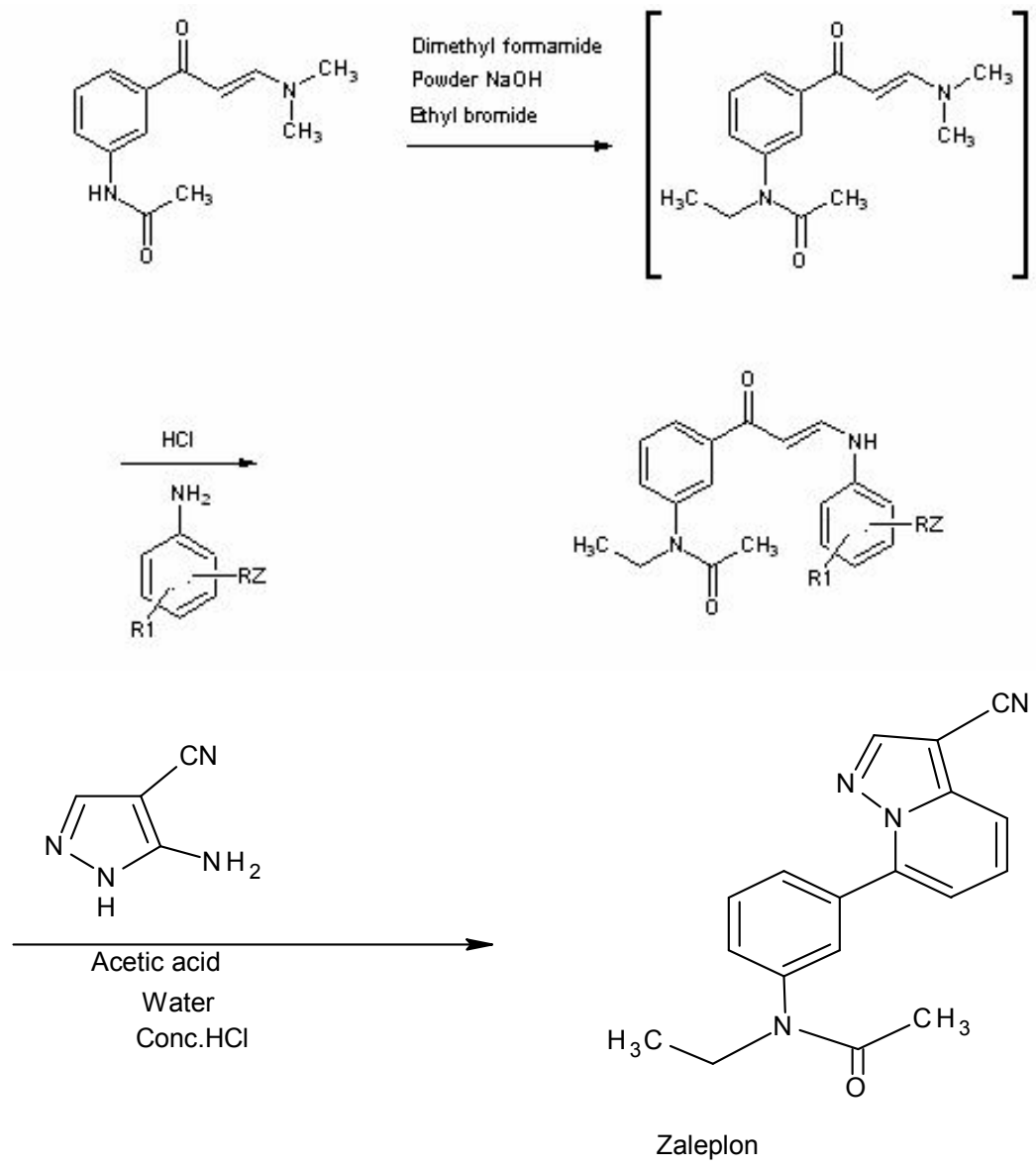
The patent WO 03/068775 $A_1$ reveals process for synthesizing Zaleplon by condensing 3-(N-acetyl-N-ethylamino) β-oxo-phenyl propanol sodium salt with 3-amino-4-cyano pyrazole. The sodium salt was prepared by first treating 3-acetylamino acetophenone with an alkali metal hydroxide, in particular with powdered potassium hydroxide and then with an ethylating reagent, in particular ethyl bromide and the

N-(3-acetylphenyl)-N-ethyl-acetamide which on reaction with formic acid alkyl metal alkanoate in particular in presence of sodium ethanolate. This process comprises use of highly flammable material sodium ethanolate. This process yields the product of low purity.

Thus reported routs have several drawbacks like, tedious process, long reaction time, use of highly flammable chemicals and poor yield and quality and hence not eco-friendly and commercially viable.

## Experiment and Result

The novel method for synthesis of Zaleplon is described in this approach, in which, Solution of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl] acetamide (100 gm, 0.431 mol) in dimethyl formamide (400ml) was stirred at 0-5°C and powdered sodium hydroxide (30 gm, 0.75moles) was then added followed by tetrabutylammonium bromide (1.0 gm). The reaction mixture was stirred at 0-5° for 15 min and then ethylbromide (72.8 gm, 0.668 moles) was added in 1 hr. The reaction mixture was stirred at room temperature for 2 hrs. p- Chloroaniline (66 gm, 0.517 moles) was then added to reaction mixture followed by addition of concentrated hydrochloric acid at 20-25°C to obtain pH of reaction mixture in the range of 3 to 4. The solution was stirred for 3 to 4 hours, chilled to 5-10°C and the crystalline product formed was filtered, washed with water, dried at about 50-60° to yield desried product (130 gm, 88.1%), mp 138° to 140°C.



To a stirred mixture of 3-amino -4-cyano pyrazole (50.6 gm 0.35 mole) and N-[3-[3-(p-chlorophenylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl acetamide (100 gm 0.29 moles) in acetic acid (250 ml) and water (125ml) at room temperature was added to hydrochloric acid (60ml), the solution was stirred for 15 min and then diluted with water (375ml). The solid was washed with water and dried at about 60°C to yield desired product (82 gm, 92%) [N-[3-(3-Cyano pyrazolo [1, 5-a] Pyrimidin-7-yl) phenyl]-N-ethyl acetamide. (Zaleplon)]

**Analytical results and interpretation**

The compound Zaleplon synthesized by above described novel process is interpreted by analytical data given herewith.

M.P.: 187.833°

C,$^{1}$HNMR data: 8.9 (m, 2H), 8.1 (m, 2H), 7.6 (m, 3H), 3.9 (m, 2H), 1.9 (s, 2H), 1.2 (m, 3H),Mass spectra: M+: 306.1/307.1, 226.2, 163.0, 154.1, 123.1.

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