A continuous flow process for the preparation of HIV drug by using of Novel Derivative

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***Abstract*- The synthesis of various pyrimidine derivatives and uses for the preparation HIV drug and it is implementation by continuous-flow process for controlling the side impurity formation to enhance the productivity. Noteworthy, the use of this approach allowed us to rapidly screen a selection of conditions and quickly confirm the viability of preparing the desired pyrimidine derivatives in short reaction times. Yields typically higher than those published earlier using conventional batch or microwave processes were achieved.**

Keywords: **Yield, viability pyrimidine, continuous-flow,HIV Drug.**

INTRODUCTION

Recently, application of the flow technologies for the preparation of fine chemicals, such as natural products or Active Pharmaceutical Ingredients (APIs), has become very popular, especially in academia. Although pharma industry still relies on multipurpose batch or semibatch reactors, it is evident that interest is arising toward continuous flow manufacturing of organic molecules, including highly functionalized and chiral compounds. Continuous flow synthetic methodologies can also be easily combined to other enabling technologies, such as microwave irradiation, supported reagents or catalysts, photochemistry, inductive heating, electrochemistry, new solvent systems, 3D printing, or microreactor technology. This combination could allow the development of fully automated process with an increased efficiency and, in many cases, improved sustainability. It has been also demonstrated that a safer manufacturing of organic intermediates and APIs could be obtained under continuous flow conditions, where some synthetic steps that were not permitted for safety reasons can be performed with minimum risk. In this review we focused our attention only on very recent advances in the continuous flow multistep synthesis of organic molecules which found application as APIs, especially highlighting the contributions described in the literature from 2013 to 2015, including very recent examples not reported in any published review. Without claiming to be complete, we will give a general overview of different approaches, technologies, and synthetic strategies used so far, thus hoping to contribute to minimize the gap between academic research and pharmaceutical manufacturing. A general outlook about a quite young and relatively unexplored field of research, like stereoselective organocatalysis under flow conditions, will be also presented, and most significant examples will be described; our purpose is to illustrate all of the potentialities of continuous flow organocatalysis and offer a starting point to develop new methodologies for the synthesis of chiral drugs. Finally, some considerations on the perspectives and the possible, expected developments in the field are briefly discussed.

Numerous efforts have been made for the synthesis of Rilpivirine derivatives and have been found promising anti-viral activity against both wild-type and mutant viruses. However, numerous steps involved in the synthesis and poor yields, limit the viability of the existing literature reported schemes. In this communication, a cost-effective and efficient protocol for large-scale synthesis of Rilpivirine from 2-(4-Cyanophenylamino)pyrimidin-4-yl-methylbenzenesulfonate (1) which through a facile one step reaction by continuous flow reaction with conversion more than 90-94 % E-isomer and Z-isomer formation is the about 2-4 % .Z-isomer formation about 10-15 % into batch process which is observed less by continuous process.

EXPERIMENTAL SECTION

Preparation of Rilpivirine:

Synthesis of Rilpivirine by using continuous flow in tubular reactor firstly basify the Formula-2 in Dichloromethane and water using ammonia base and dichloromethane layer washed with water and the distilled and taken the residue in Acetonitrile and pump with 5ml/min and similarly the another part add Formula-3 taken in Acetonitrile using pump with flow rate 5ml/min and then heat to 77 to 80 deg C. Pass through the coil reactor with reactor volume 10ml at 65 deg C. with residence time 1.0 min and at the same time adding acetic acid solution pump with flow rate 5 ml/min. to the output of the solution and pass the through tubular reactor with flow rate 2.5 ml/min at 80 deg, with residence time 4.0 min . Collecting the reaction check the absence of Formula-3 by TLC. Collection the reaction mass quench in DMF and water mixture at ambient temperature. Product Precipitated.

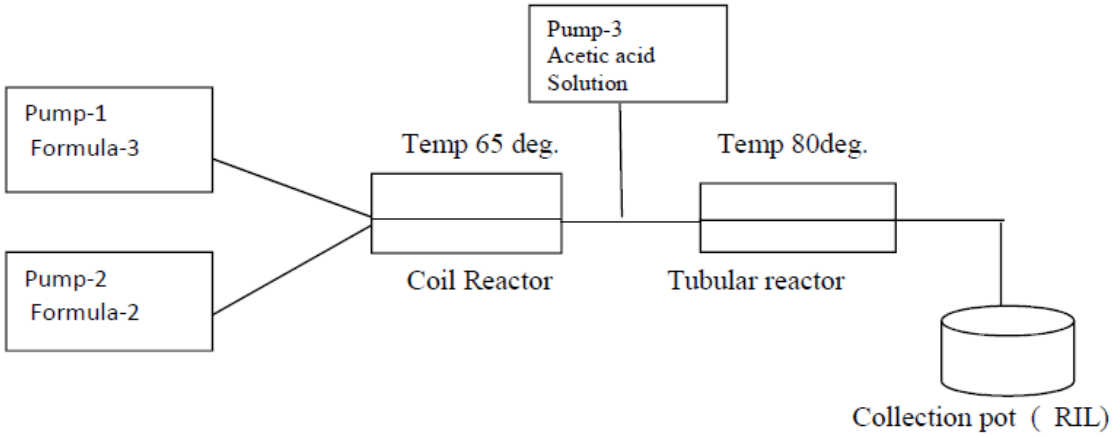
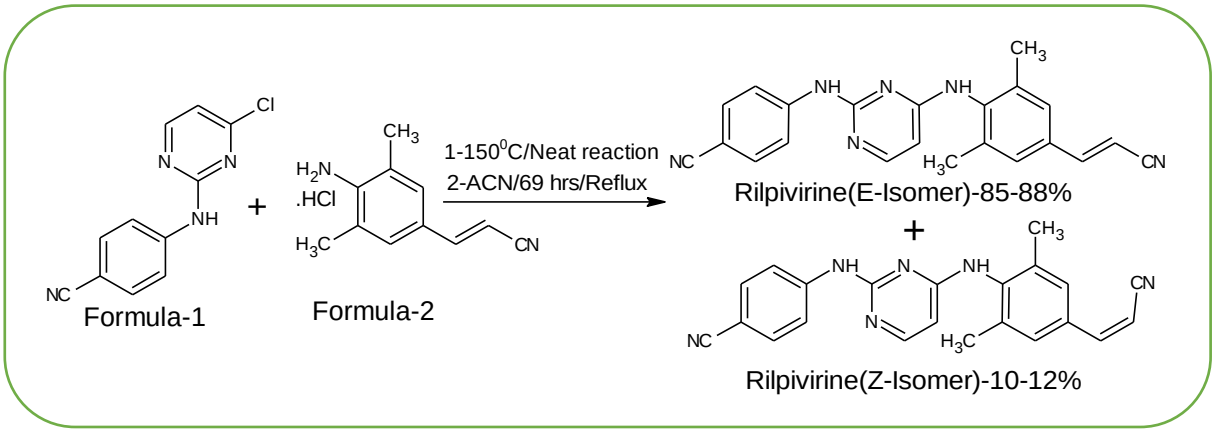


Diagram-1

RESULT AND DISCUSSION

.The '879 patent discloses another process for the preparation of Rilpivirine by condensation of Formula-2 as its hydrochloride salt with Formula-1 in acetonitrile at reflux temperature for 69 hours followed by formation Rilpivirine desired E-isomer about 85-88% and unwanted Z-isomer formation 10-12%.

The process disclosed in the '879 patent is schematically represented as follows:



Scheme: 1-Reported method for synthesis of Rilpivirine

The synthesis of Rilpivirine as discussed in the '879 patent has certain drawbacks as it involves.

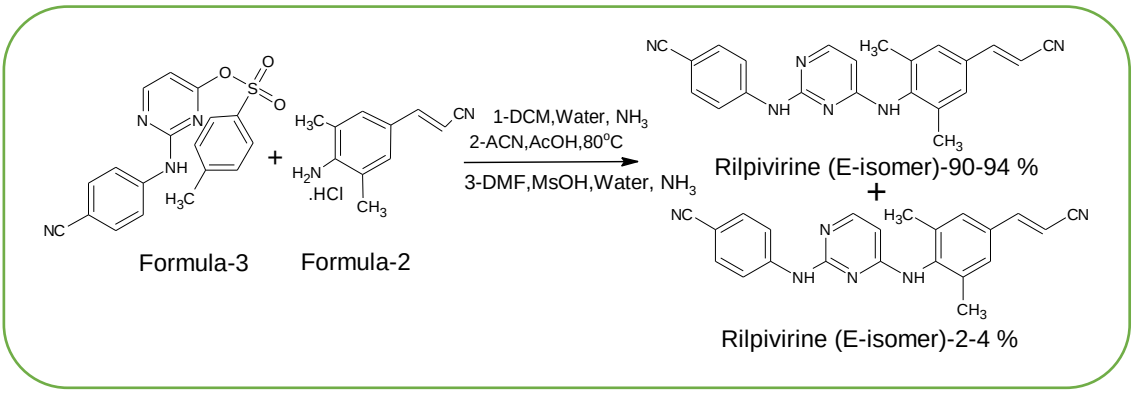
i) As per this patent Z-isomer formation about 10-12% during reaction which is removed by multiple stage purification.

ii) Use of neat reaction conditions extremely at high temperature of about 150°C and involves tedious chromatographic purifications makes the process not viable for large scale manufacturing.

iii) Reaction in presence of acetonitrile at reflux for a period about 69 hours. The prolonged period of reaction maintenance leads to an increase in the manufacturing cycle time and decrease in the product yield and quality.

iv) Isolation of crude rilpivirine hydrochloride at hot conditions such as filtration of crude at temperature 55°C. Solid filtration at high temperature is not viable, particularly on commercial scale operations for producing API's and thus requires utmost care to use.

v) Use of large volumes of solvent for purification of rilpivirine free base, requires high capacity apparatus and thus involves more operational occupancy, which in turn result to an increase in the manufacturing cost, particularly on large scale production of Rilpivirine.



Scheme: 2-Synthetic route for the preparation of Rilpivirine

In the present work, Formula-2 reacted with Novel pyrimidine Derivative Formula-3 by continues process and found the desired Rilpivirine (E-Isomer) about 90-94% and unwanted Z-Isomer formation is about 2-4% due to this yield of the Rilpivirine is increased .

CONCLUSION

In summary, we have described an efficient new approach for the synthesis of Rilpivirine by continuous process with novel derivative 2-(4-Cyanophenylamino)pyrimidin-4-yl-methylbenzenesulfonate benzonitrile (Formula-3) with scope for bulk production.

The main features of this Continuous process include cost-effectiveness and excellent yields of Rilpivirine, which makes this protocol an attractive and valuable alternative to the current methodologies.

ACKNOWLEDGMENTS

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REFERENCES:

1. Gioiello A., Piccinno A., Lozza A.M., Cerra B. The Medicinal Chemistry in the Era of Machines and Automation: Recent Advances in Continuous Flow Technology. *J. Med. Chem.* 2020;**63**:6624–6647. doi: 10.1021/acs.jmedchem.9b01956
2. Cole K.P., Johnson M.D. Continuous flow technology vs. the batch-by-batch approach to produce pharmaceutical compounds. *Expert Rev. Clin. Pharmacol.* 2018;**11**:5–13. doi: 10.1080/17512433.2018.1413936
3. Hughes D.L. Applications of Flow Chemistry in Drug Development: Highlights of Recent Patent Literature. *Org. Process Res. Dev.* 2018;**22**:13–20. doi: 10.1021/acs.oprd.7b00363
4. Linares M.L., López E., Palao E., Alcázar J. *Flow and Microreactor Technology in Medicinal Chemistry.* John Wiley & Sons; New York, NY, USA: 2022. Flow Chemistry Opportunities for Drug Discovery; pp. 67–102. Methods and Principles in Medicinal Chemistry.
5. Feng X-Q, Zeng Z-S, Liang Y-H, et al. Synthesis and biological evaluation of 4-(hydroxyimino) arylmethyl diarylpyrimidine analogues as potential non-nucleoside reverse transcriptase inhibitors against HIV. *Bioorg Med Chem* 2010; 18: 2370–2374
6. Šimon P, Baszczyński O, Šaman D, et al. Novel (2,6-difluorophenyl)(2-(phenylamino)pyrimidin-4-yl)methanones with restricted conformation as potent non-nucleoside reverse transcriptase inhibitors against HIV-1. *Eur J Med Chem* 2016; 122: 185–195.