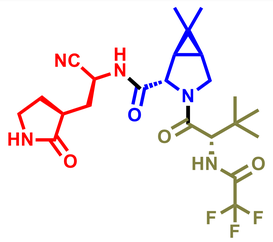
SYNTHESIS OF THE ANTI-COVID THERAPEUTIC NIRMATRELVIR: USING FLOW CHEMISTRY TO ENHANCE EFFICIENCY OF AMIDE TO NITRILE CONVERSION IN A FUNCTIONALLY AND STEREOCHEMICALLY EMBELLISHED ENVIRONMENT

Karuna Veeramani[1], Manish Shinde[1], Bala Chennaiah Darapaneni[2], Vishnuvardhana Vema Reddy Eda[2], Saikat Sen[2], Srinivas Rao Madarapu[3], Rama Mohan Hindupur[3], Srinivas Oruganti *, [1,2]

[1]10X Chemical Process Automation Laboratory; [2]Centre for Process Research and Innovation, Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, Telangana, India; [3]Aurigene Pharmaceutical Services Limited, Bollaram Road, Miyapur, Jaya Prakash Narayan Nagar, Miyapur, Hyderabad 500 049, Telangana, India

ABOUT NIRMATRELVIR (PF-07321332)

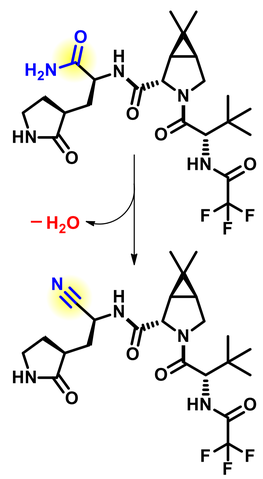


https://commons.wikimedia.org/wiki/File:Paxlovid2022.jpg

- Administered along with Ritonavir as the oral combination therapy Paxlovid
- Developed by Pfizer for the treatment of mild to moderate COVID-19
- Irreversible inhibitor of SARS-CoV-2 viral protease M^{pro}
- Promising *in-vitro* activity against the SARS-CoV-2 variant Omicron
- Undoubtedly one of more complex and synthetically challenging anti-COVID drugs known
- Has six chiral centers, some of which are highly prone towards epimerization
- Synthesis requires a highly orchestrated assembly of three fragments

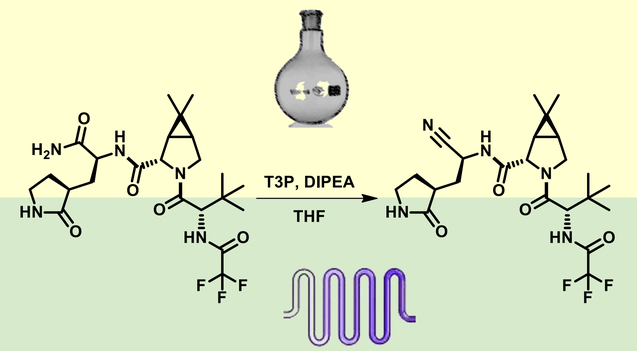
WHY INVESTIGATE ITS SYNTHESIS IN FLOW?

- The end-game in the synthesis of Nirmatrelvir is particularly challenging.
- Involves dehydration of an amide to a nitrile in a functionally and stereochemically embellished environment.
- Employs expensive and difficult to handle reagents such as the Burgess reagent or involves prolonged reaction times which increases the possibility of impurity formation owing to epimerization
- **Objective of our study:** Can flow-based processes offers significant reduction in reaction time without requiring the involvement of reagents which need special handling, storage conditions and are difficult to procure commercially?



END GAME: BATCH VERSUS FLOW

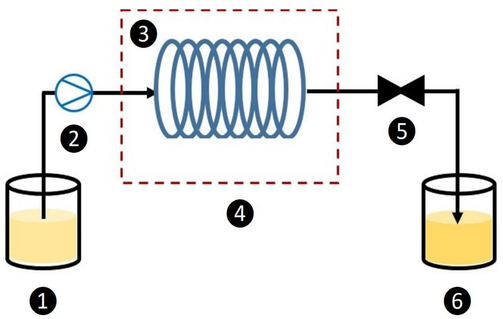
BATCH **reflux, 12-16 h**

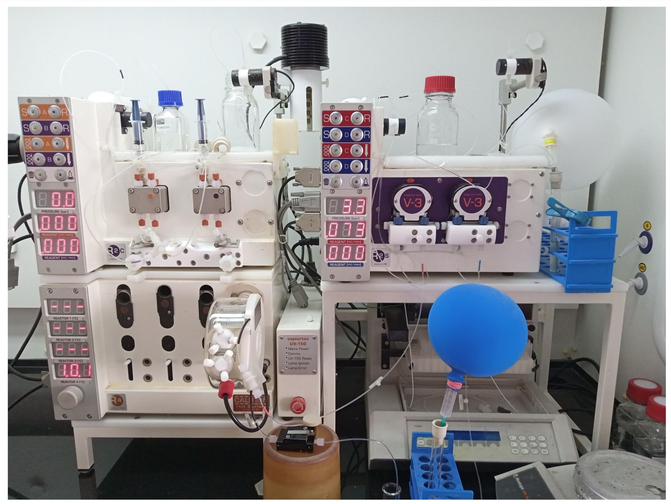


FLOW **100 °C, 30 min**

NIRMATRELVIR SYNTHESIS IN FLOW: EXPERIMENTAL SETUP

1. Inlet – Solution of Amide, DIPEA and T3P in THF
2. Pump; Peristaltic
3. PTFE Coil; Volume 2–10 mL
4. Temperature control; 80 – 110 °C
5. Back Pressure Regulator; 3.0–4.5 bars
6. Outlet – Nirmatrelvir





SUMMARY OF EXPERIMENTAL PARAMETERS AND RESULTS [a]

No.	Temperature (°C)	Residence Time (min)	Moles (eq.) of Reagents		HPLC analysis of output stream (%AUC)		
			DIPEA	T3P	Amide	Product	Σ(Others)
1	80	30	2.5	2	17.11	69.71	13.18
2	100	30	2.5	1.5	13.1	72.42	14.48
3	100	30	2.5	2	0.00	89.31	10.69
4[b]	100	30	2.5	2	1.4	85.69	12.91
5[c]	100	30	2.5	2	2.17	89.82	8.01
6	110	30	2.5	2	0.00	87.38	12.62
7	110	15	2.5	2	24.61	65.18	10.21

[a]All runs were performed in either 2 mL or 10 mL PTFE coils with Vapourtec V-3 peristaltic pumps and variable BPR. Purity of the amide employed as input was typically >85% by HPLC. Yield and purity of the crude Nirmatrelvir, isolated from the output stream, were 60–75% and >90% respectively. Typical results from batch experiments, yield: 65-68%, purity: >90%.

[b]Performed to check process reproducibility

[c]The crude reaction mixture, containing the input amide obtained after reacting (1R,2S,5S)-3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid and (S)-2-amino-3-((S)-2-oxopyrrolidin-3-yl)propanamide in presence of T3P (2 equiv.), DIPEA (2.5 equiv.) and THF, was used directly. The molar equivalents of T3P and DIPEA employed for the dehydration step were estimated based on the moles of the acid employed for amidation.

HIGHLIGHTS OF THE STUDY

- ✓ Significant reduction in reaction time (12-16 h in batch as opposed to 30 min in flow) without impacting the essential quality attributes
- ✓ The flow based process achieves its intended goal without requiring the involvement of reagents which need special handling, storage conditions and are difficult to procure commercially
- ✓ T3P, a reagent which employed to mediate the dehydration step, is well-known for its low toxicity, long shelf-life stability and easy handling
- ✓ The flow-based process does not operate under extreme temperature and pressure regimes

ONGOING EFFORTS & FUTURE PERSPECTIVES

- ✓ Two-stage synthesis (*i.e.* T3P mediated tandem amidation and dehydration) of Nirmatrelvir in flow from (1*R*,2*S*,5*S*)-3-(*tert*-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid and (*S*)-2-amino-3-((*S*)-2-oxopyrrolidin-3-yl)propanamide
- ✓ Demonstration of the above flow processes in pilot-plant and production-level reactors

REFERENCES

- Pfizer Inc., US Patent 11351149 B2, Jun 7, 2022.
- *Science* **2021**, *374*, 1586 –1593

PUBLICATIONS

- Indian Provisional Patent Application, 202241006312
- International PCT Application, PCT/IN2022/050417