



School of Applied Sciences

WEBINAR REPORT

Department of Chemistry, School of Applied Sciences, REVA University, Bangalore, **organized Virtual webinar entitled "API development: Common Methodologies for Similar API's Synthesis"** on May 25th 2022 from 09:30 AM to 10.30 AM as a part of the knowledge sharing program for the benefit of students.

Resource person:

Dr. Rao Venkataramana Rao Ph. D
DGM-API R&D
CVR Life Sciences, MN-Park/IKP, Shamirpet, Hyderabad
Mobile: 770-292-3131
rao.raman@gmail.com; venkat@cvrls.in

Organizer/s:

**Dr. Madhusudana Reddy M B and
Dr. Nagendra G**
Department of Chemistry, SoAS,
REVA University, Bangalore.

Dr Rao Venkataramana Rao is the Deputy General Manager of CVR Life Sciences. Dr Rao Venkataramana Rao has 21 years of research experience working in various prestigious academic institutions and pharmaceutical industries. Dr Rao Venkataramana Rao has several patents and publications in peer reviewed journals.

Dr. Rao Venkataramana Rao completed his Ph.D from Bangalore University moved to University of Arizona to work with Prof Eugene A Mash for his postdoctoral research. He was then promoted to Research Associate wherein he worked on new coupling reactions with Prof. Dominic V McGrath. After completing his tenure in USA, Dr. Rao Venkataramana Rao moved to India, worked at COSMIC Discoveries, Dr. Reddy's Institute of Life Sciences, Piramal Health Care and Ritvis Labs.

As Deputy General Manager at CVR life sciences, Dr Rao Venkataramana Rao plays a significant role in API design and development. His main research focus is to develop methodologies which can be applied to multiple API synthesis. He has successfully implemented novel methodologies in API synthesis.

Dr. Rao Venkataramana Rao is Scientific advisory member to Journal of Organic Chemistry: Process Development (JOC PD) and International

Journal of Organic Chemistry (IJOC) and also corporate Advisory Member at Dept. of Chemistry, REVA university, Bangalore. He has invited as a resource person to various institutes in India and he delivered invited talks and presented his view on new IPS's structure of synthesis.

Highlights of the talk

- Synthesis of API's on gram scale using literature procedure for polymorph study as well as modified synthetic routes.
Design of synthetic routes and execution of target compounds on CRO model.
- Development and scale up novel and non-infringing processes for drug candidates and demonstration on kilo scale.
- Selection of route for the synthesis of following API's
 - ✓ Eliglustat
 - ✓ Droxidopa synthesis
 - ✓ Jos Barluenga coupling reactions and its applications
 - ✓ Ceretinib
 - ✓ Abiraterone
 - ✓ Olmesartan
 - ✓ Escilatopram
 - ✓ Citalopram
- Cost reduction in the APIs synthesis

The lecture was attended by all PG students, research scholars and faculty of chemistry REVA University and other places. A total of 88 participants attended the live webinar and the feedback given by the participants was appreciated.

We would like to thank, Dr. Rao Venkataramana Rao for delivering the talk and participants, faculty members of chemistry department. We also thank Assistant Director, Department Chemistry, Deputy Director, and management for constant support and encouragement towards academic activities of the school.

Regards,

Dr. Nagendra G,

Associate Professor,

Department of Chemistry, SoAs

REVA University, Bangalore.

Webinar Link : <http://surl.li/cafsv>

School of Applied Science, Department of Chemistry

Organises a Webinar on

API development: Common Methodologies for Similar API's Synthesis



Webinar Link : <http://surl.li/cafsv>

Organizers:

Dr. Madhusudhana Reddy M B and
Dr. Nagendra G
Department of Chemistry, REVA University

Speaker:

Dr. Rao Venkataramana Rao Ph. D
DGM-API R&D CVR Life Sciences
MN-Park/IKP, Shamirpet
Hyderabad, India.

Date : 26th May 2022

Time : 9:30 A. M. to 10:30 A. M.

www.reva.edu.in



Active Pharmaceutical Ingredients (API)
or
Generic APIs

Route of Synthesis (ROS)
selection:

Novel route or prior art

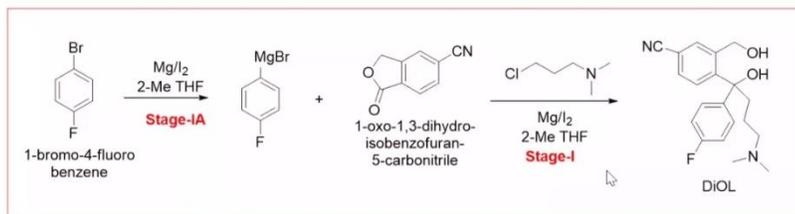
Consider below points for
commercial process

- Raw material availability
- Easy of handling reactions
- Scalability or reproducibility
- No. of steps

Intellectual Property

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Synthetic scheme for Escitalopram and Citalopram:



> Stage-I:

- Reaction was performed in 50gr scale to get the Diol free base compound and isolated 64 - 67% yield.
- HPLC purity observed: **MPP: 99.56% and SMUI: 0.25%..**
- 2-Me THF M.C observed: 0.11% (required M.C is NMT 0.15%)
- 85%-90% of 2-Methyl THF recovered and reused, observed same yield.
- Substantially RMC lower than market price.

Dr. Venkat (Guest) ...

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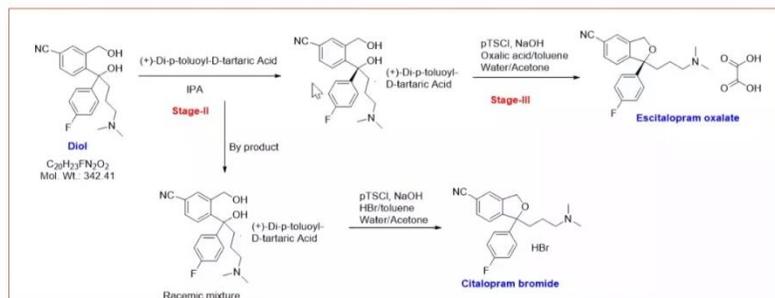


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Synthetic scheme for Escitalopram and Citalopram:



- Both APIs synthesized and scaled up on plant scale

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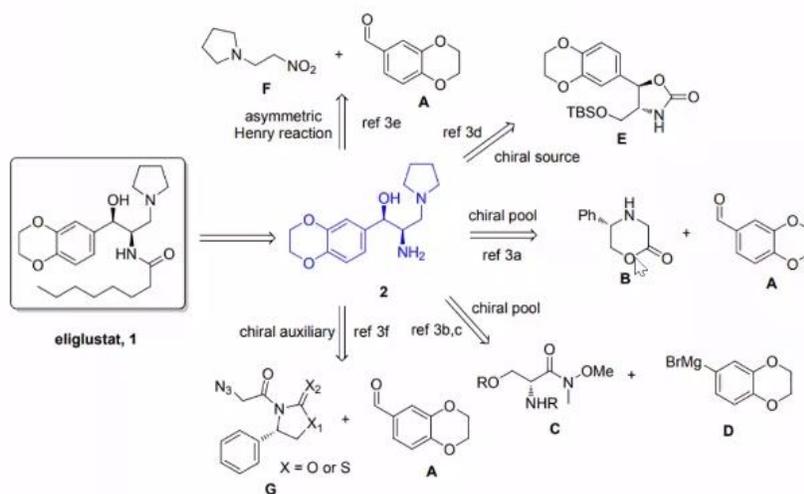
Dr. Venkat (Gue...



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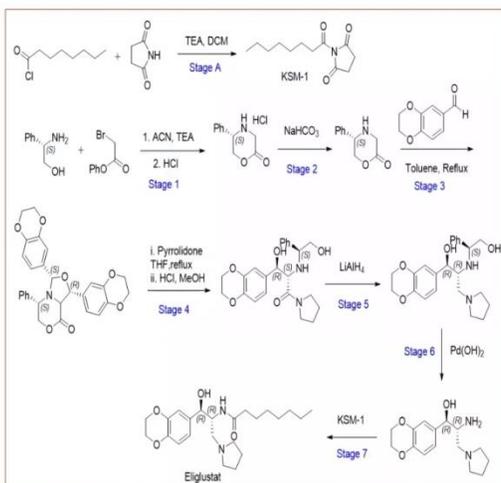
API: Eliglustat Prior art



Ref: *Org. Process Res. Dev.* 2019, 23, 6, 1204

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Eliglustat: Prior art



Demerits:

- Stage 1: 53% yield is reported
- Stage 3: Key step is in low yield ~48% and reaction time 64 h
- Stage 3: Reproducibility is an issue on commercial scale

Dr. Venkat (Guest) Reference: US 7615573 B2, US 2003/0050299 A1 & WO 03/008399 A1

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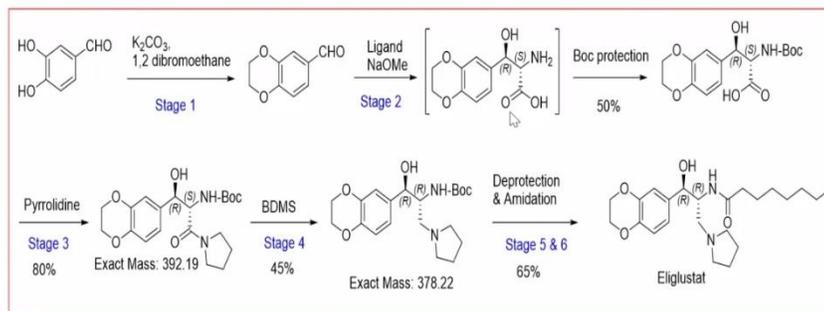


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Route of synthesis



Status:

- Stage 1: Nickel completely removed by using pyrrolidinedithiocarbamate ammonium salt (PDTC)
- Stage 2,3,4 and 6: Characterized by 1H , ^{13}C and Mass spectra.
- **Patent application No.201921011181 (Piramal)**
- Commercial route \$2300 and our route \$ 1130/kg

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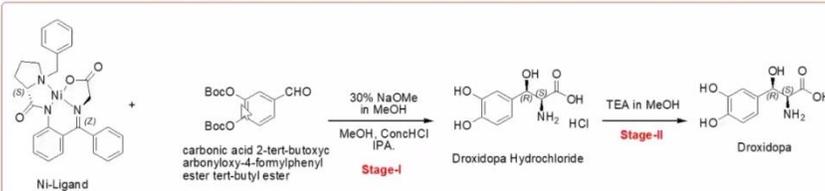


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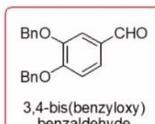
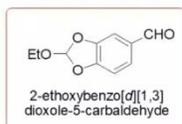
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Droxidopa synthesis



- Patent Application No. 202141038607 (CVR Life Sciences)
- Chiral purity: 100%



Dr. Venkat (Guest) ... 2017/168313 A1

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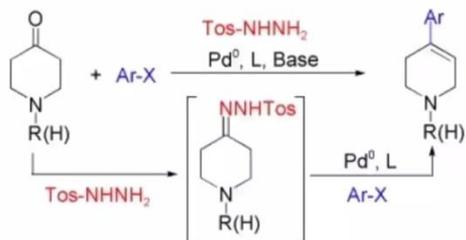


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New technology: Jos Barluenga coupling Part-2

Possible mechanism:



- Very efficient for aromatic and aliphatic "C-C" bond formation
- After completion of the reaction forms as alkene product

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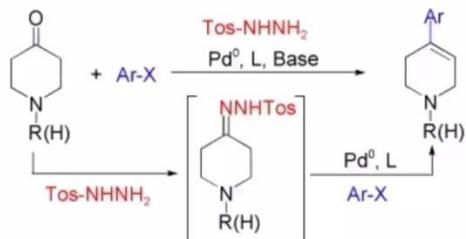


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Dr. Venkat (Guest) ...

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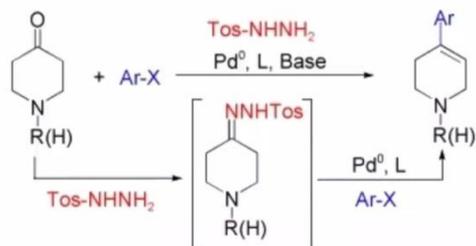


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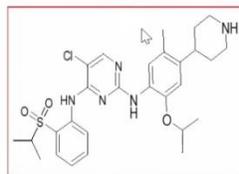
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API: Ceritinib

Inventor: Novartis Pharma

Therapeutic area: Treatment of lung cancer



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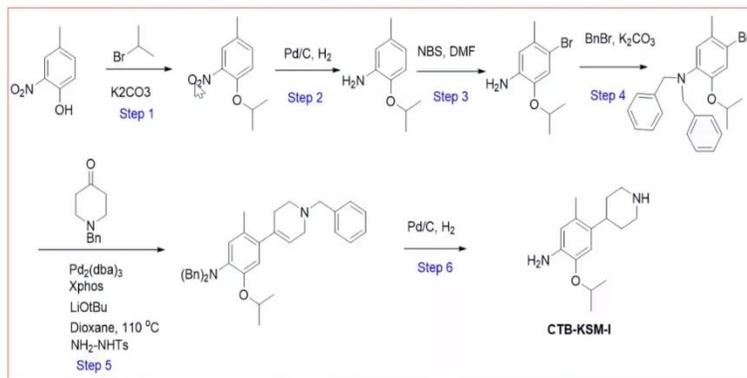
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Jose Barluenga's Approach:



- C-C bond formation gave the 90% yield.
- Four functional groups were reduced in one pot.
- Patent No. WO 2016/199020 A1 (Dr Reddy's)

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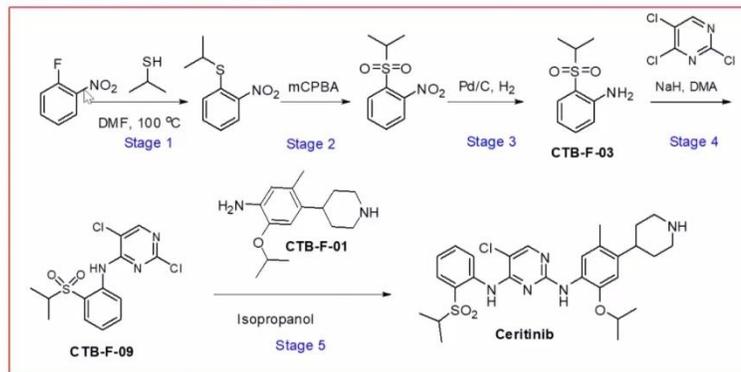


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Synthesis of Ceritinib

Regio-selective transformations :



- Developed a column free procedure for all five stages.

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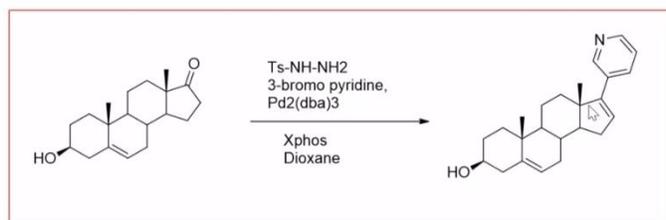
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Barluenga approach: Abiraterone acetate



- Result are not published
- C-C bond found 65% yield

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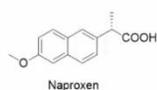
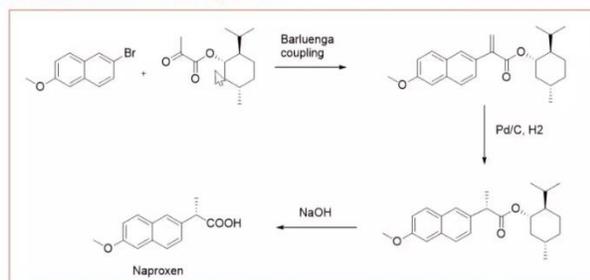
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Naproxen synthesis: Barluenga approach



- Barluenga product is higher yield in stage-1 with menthol pyruvate
- Observed 85:15% of mixture of Naproxen
- Menthol is used as chiral auxiliary for double bond reduction and recovered

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Generic API synthesis

Cost reduction: Using 2-Methyl THF in Grignard reactions Part-3

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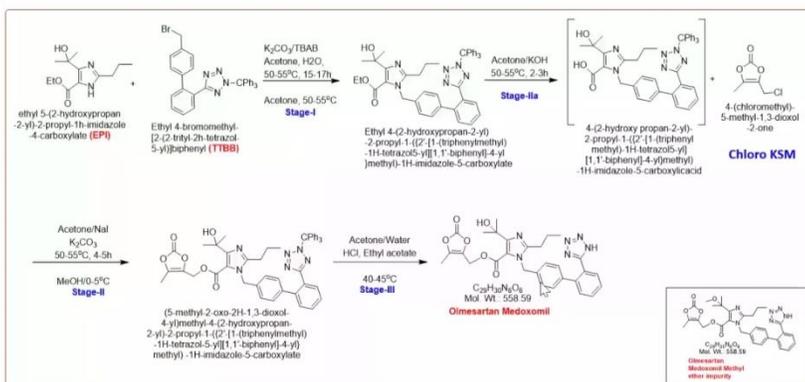


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Synthetic scheme for Olmesartan:



- Observed Methyl ether impurity in final stage around 0.11 to 0.15%
- Investigated all KSMs and identified methyl ether impurity
- TTBB specifications: NLT 94%
- Chloro KSM: NLT 90%
- EPI: Methyl ether impurity limit kept as NMT 0.06%
- Recovered Tri-alcohol in 90%

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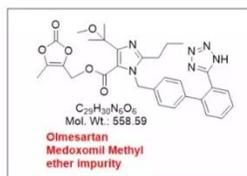


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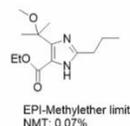
Olmesartan "Methyl" impurity :



Synthesis of EPI:



- THF replaced with 2-Methyl THF
 - 80-90% 2-MethylTHF recovered
 - Cost of commercial EPI around Rs 11000 to 13000
- Dr. Venkat (Guest) OPSS, 2007, 11, 156-159



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API: Escitalopram

➤ Trade name	Cipralext
➤ API Name	Escitalopram and Citalopram
➤ Molecular Formula	
➤ Molecular weight	324.39
➤ Appearance	-
➤ Final Product	-
➤ Biological activity	Antidepressant
➤ Stages	4

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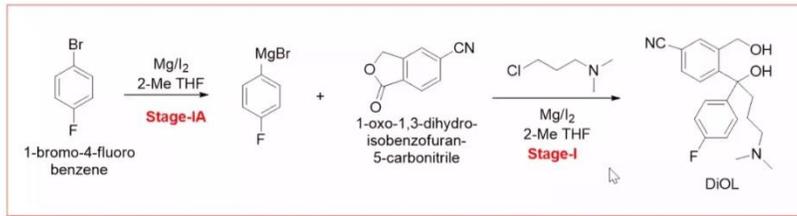


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Synthetic scheme for EScitalopram and Citalopram:



> **Stage-I:**

- > Reaction was performed in 50gr scale to get the Diol free base compound and isolated 64 - 67% yield.
- HPLC purity observed: **MPP: 99.56% and SMUI: 0.25%..**
- > 2-Me THF M.C observed: 0.11% (required M.C is NMT 0.15%)
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