MAOS: A Toolkit to Enhance Capability of Medicinal Chemistry

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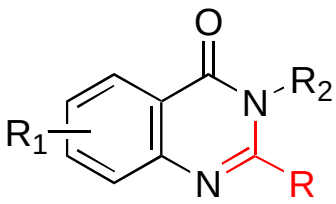
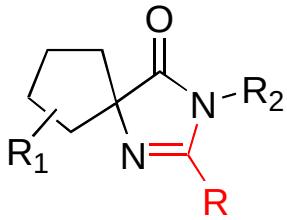
ArQule, Inc.

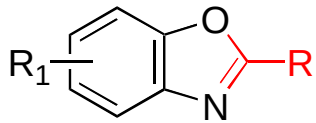
ARQULE®

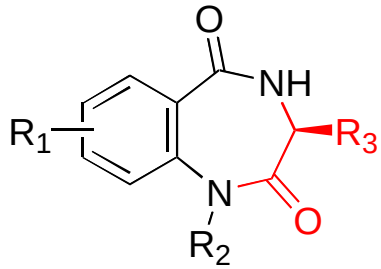
Biotage Users Group Meeting, Boston, May 11, 2006

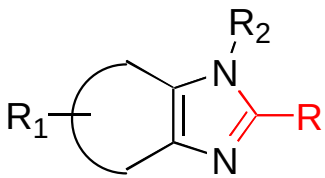
Representatives of Our Toolkits

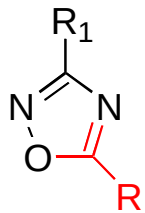


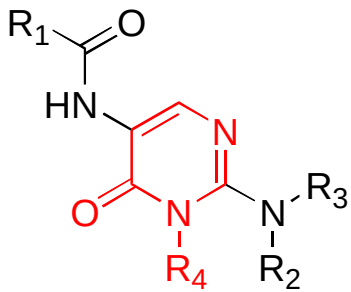


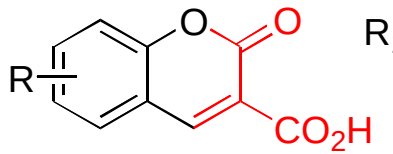


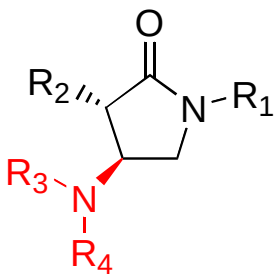


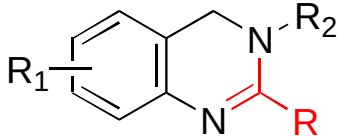


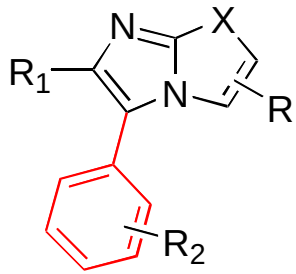


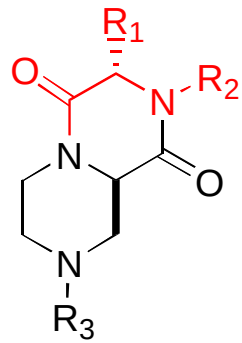








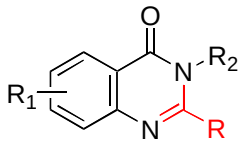




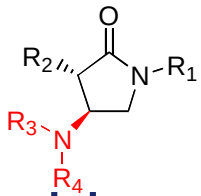
More…

Case Studies

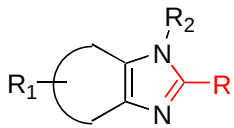
- Case 1: Quinazolinone Natural Products

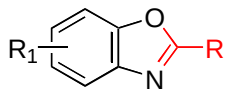


- Case 2: γ-Lactams

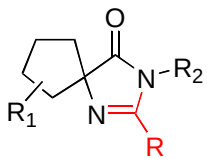


- Case 3: Imidazoles and Benzoxazoles





- Case 4: Spiro Imidazolinones



Acknowledgements

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  - Ping Ye
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  - Jaekyoo Lee
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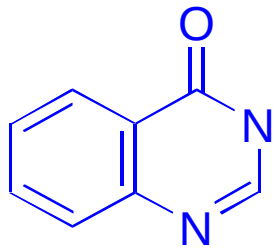
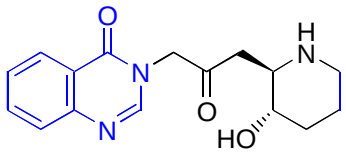
  - Maojun Guo
  - Yousheng Guan
- Analytical
  - Bailin Zhang
  - Djamel Cherrak
  - Grace Bi
  - Many others…
- Biology
  - Chris Wilson
  - Bin Zhang
- Management
  - Carmen Baldino
  - Shi-Chung Ng
  - Daniel Yohannes
  - Libing Yu
  - Michele Harris

Case 1: Quinazolinone Natural Products

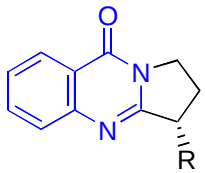


- Rich in Nature
  - ~150 natural products containing this core been isolated
- Validated by Pharmaceutical Industry
  - Numbers of drugs in clinical use

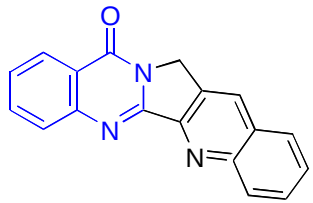
Quinazolinone Natural Products (Examples)



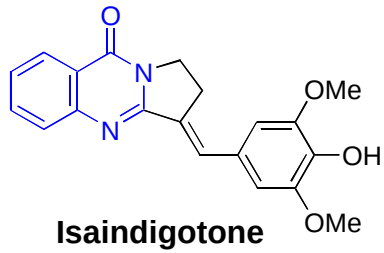
Febrifugine
(Antimalarial)



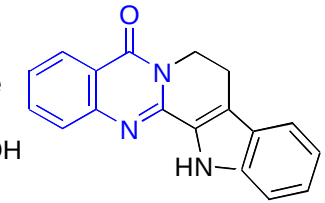
Vasicinones
(Antiinflammatory)
(Antidepressant)



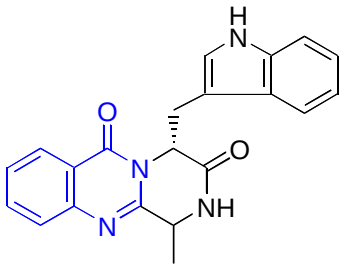
Luotonin
(Topoisomerase I Poison)



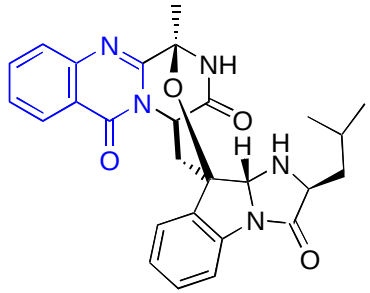
Isaindigotone
(Antiinflammatory)



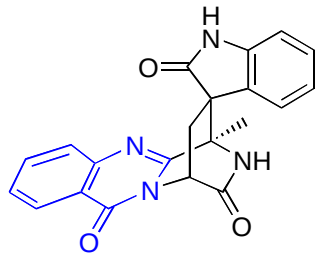
Rutaecarpine
(COX-2 Inhibitor)



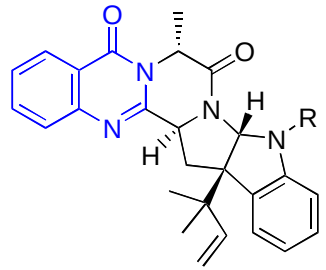
Fumiquinazoline G, F
(Cytotoxic)



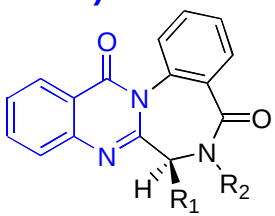
Fumiquinazoline H
(Cytotoxic)



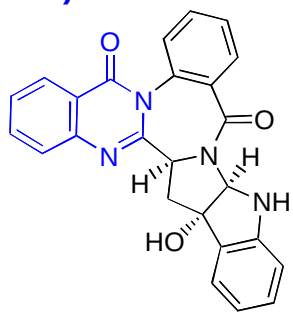
Alantrypinone



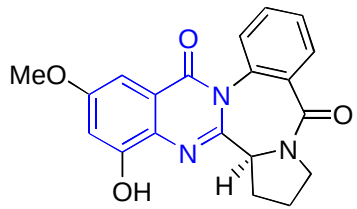
Adeemin, R= H
N-acetylardeemin, R= Ac
(MDR)



Sclerotigenin ($R^1 = R^2 = H$)
Circumdatin F (R^1 = Me, R^2=H)
Asperlicin C (R^1 = 2-CH_2Indole, R^2 = H)
Benzomalvin A (R^1 = Bn, R^2 = Me)



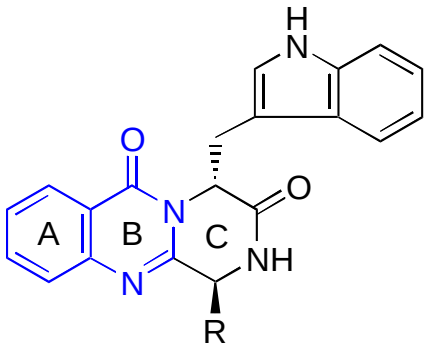
Asperlicin E
(CCK Antagonist)



Circumdatin E
(HCV)

Three Types of Quinazolinone Natural Products

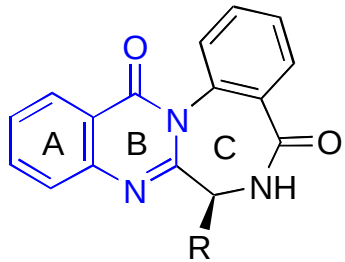
Type 1



Fumiquinazolines

Ping & Katie

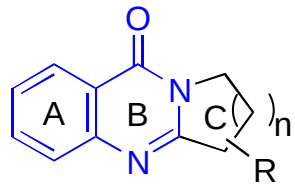
Type 2



Asperlicins

Mira, Yuko, & Jenny

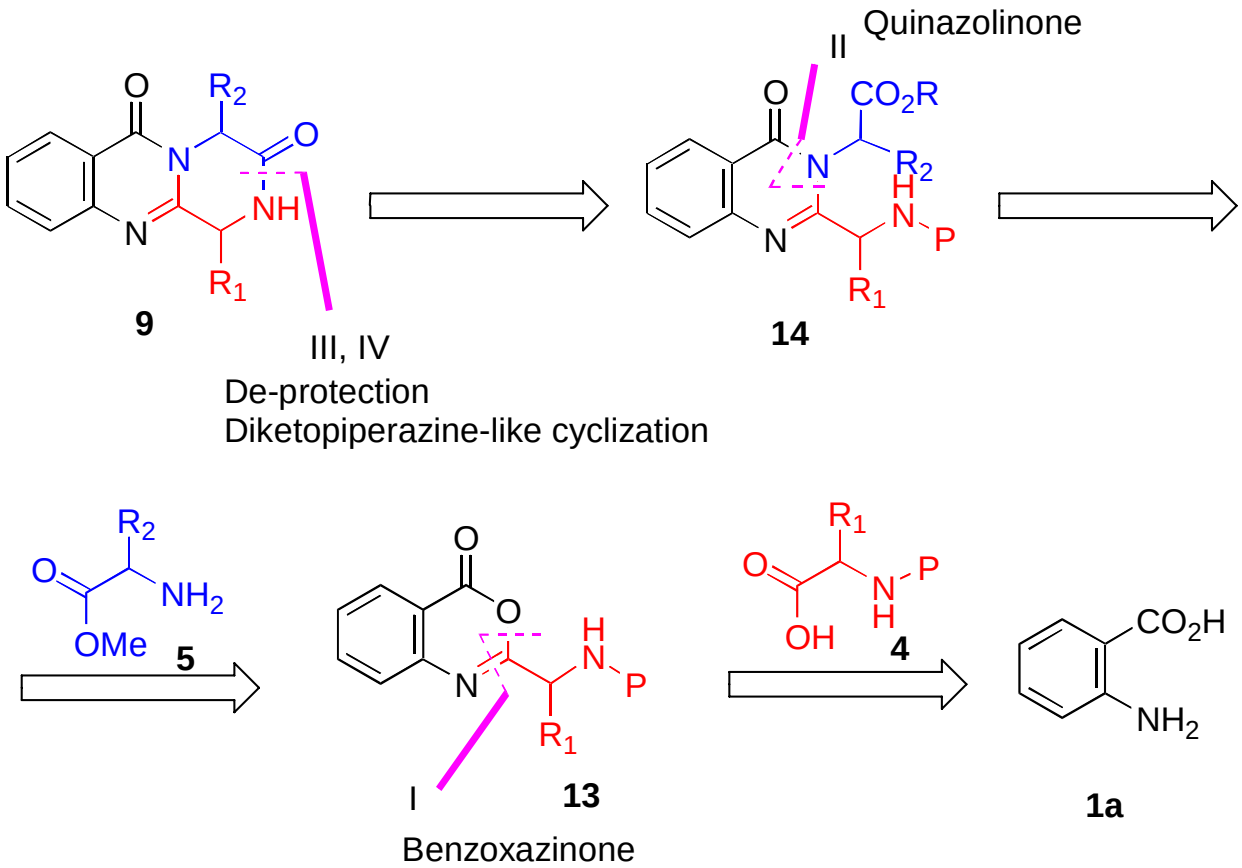
Type 3



Vasicinones

Ping Kevin, & Katie

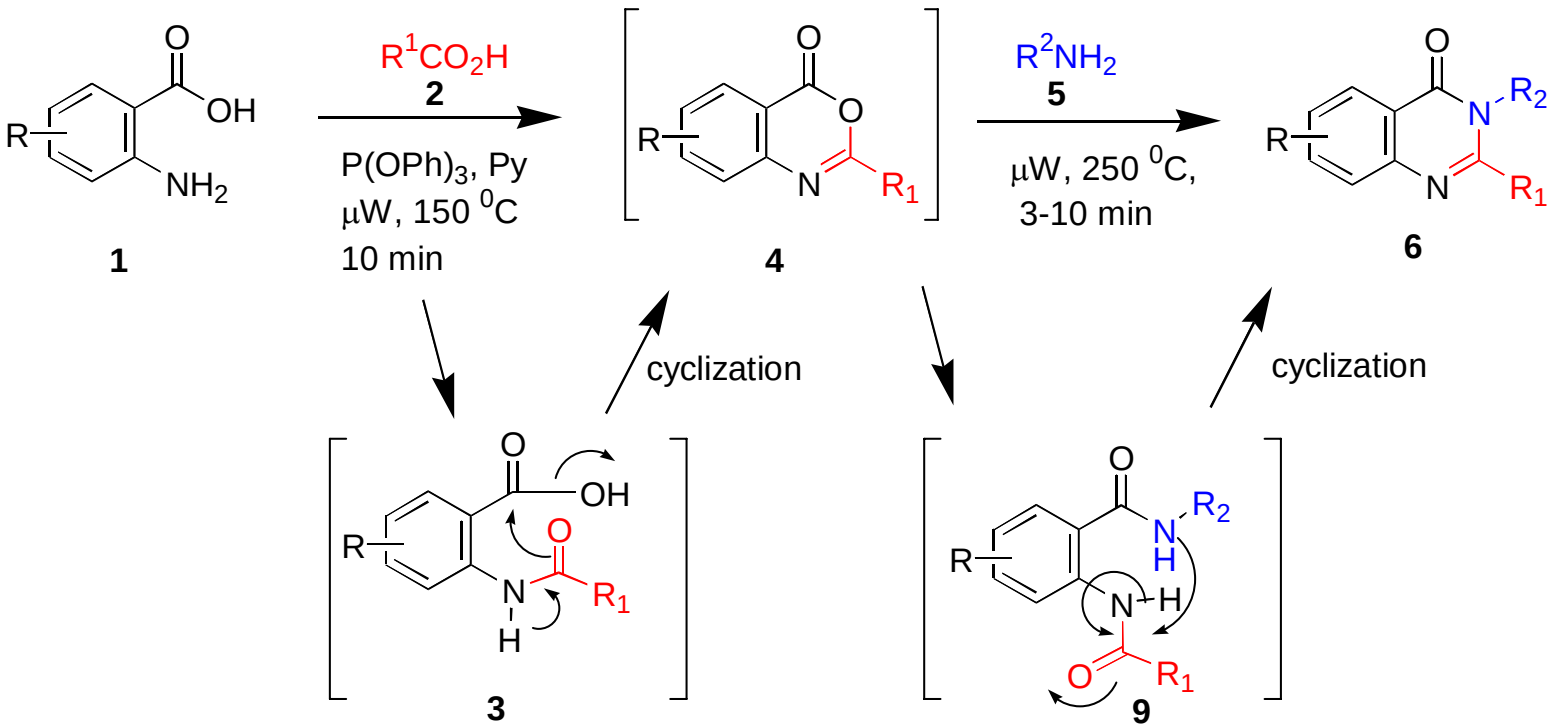
Retro-synthetic Strategy



Methodology Development – A μW Approach

A Novel Method

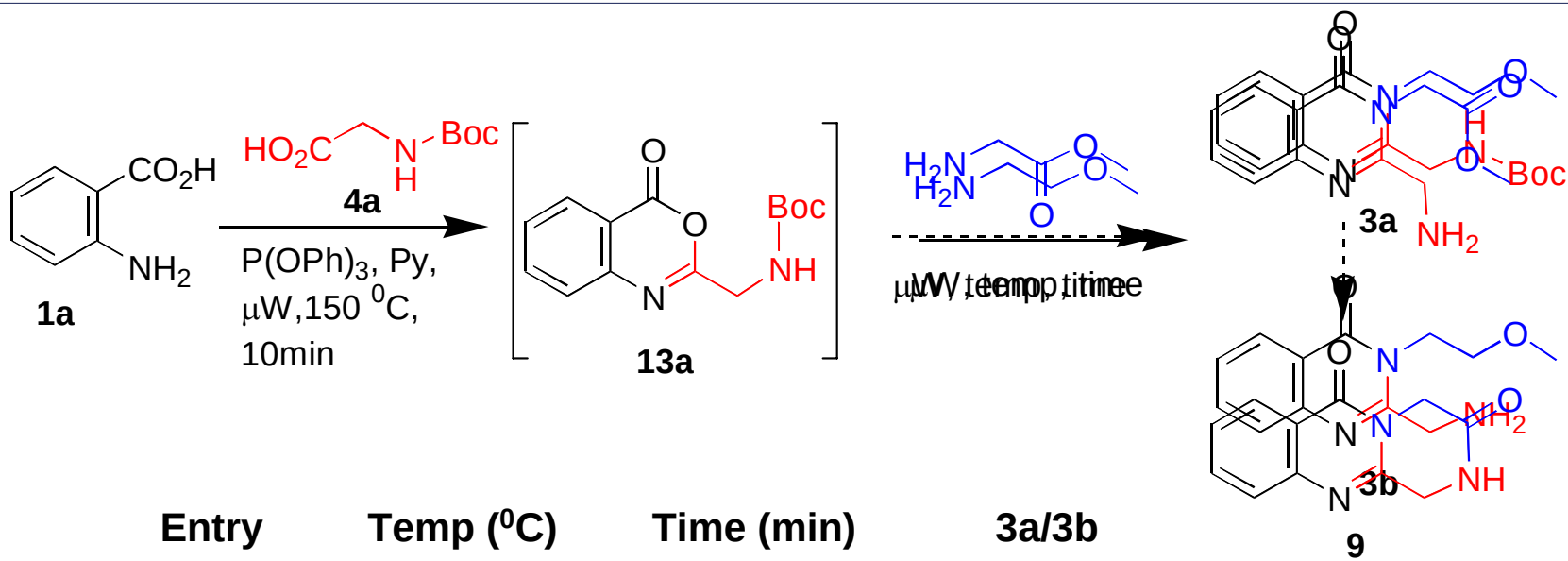
- Microwave technology
- Broad chemistry scope



- One-pot reaction!

Tetrahedron Lett. **2005**, *46*, 1241-1244.

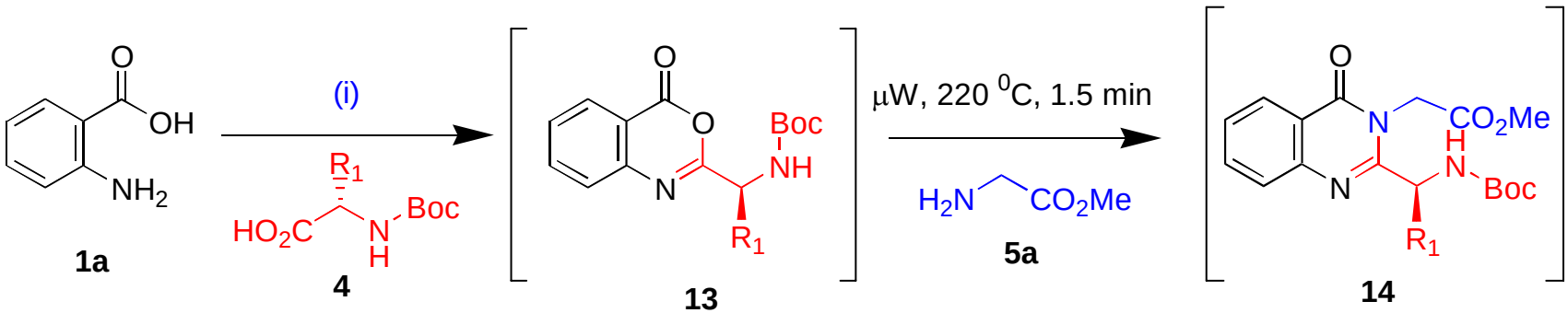
Protecting Group Selection & De-protection

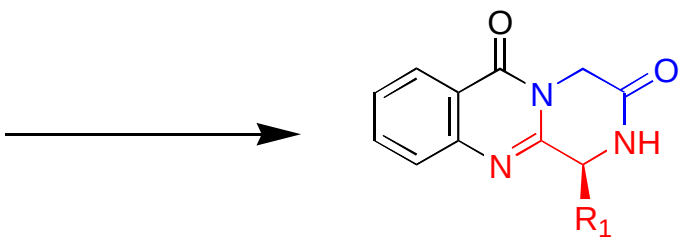


Entry	Temp (^{0}C)	Time (min)	3a/3b
1	180	3	100/0
2	200	3	80/20
3	210	3	10/90
4	220	4	0/100

- Screened Boc, Cbz, Fmoc, Bn
- Boc performed best under the reaction conditions.
- Quinazolinone ring formed at >180 ^{0}C.
- In situ de-Boc at 210 - 220 ^{0}C.

Model Reactions





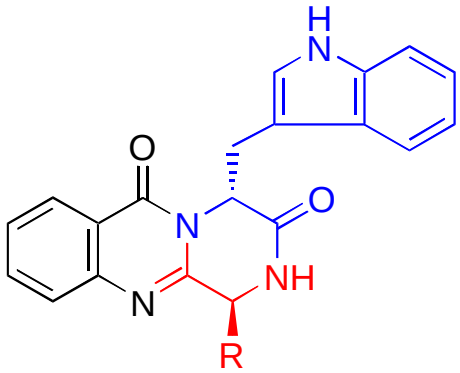
9a, 56%, (R^1 = H)
9b, 62%, (R^1 = Me)

conditions of (i)

R^1 = H
μwave, 150 ^{0}C 10min

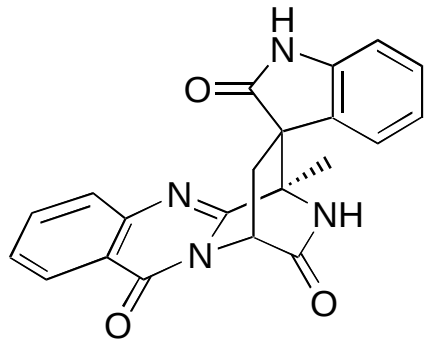
R^1 = Me
conventional heating
55 ^{0}C, 16h

Total Syntheses of Fumiquinazolines



R = H, Glyantrypine, Yield 55%, 70% ee
R = Me, Fumiquinazoline F, Yield 39%, 72% ee
R = *i*-Pr, Fiscalin B, Yield 20%, 50% ee

Formal Total Synthesis



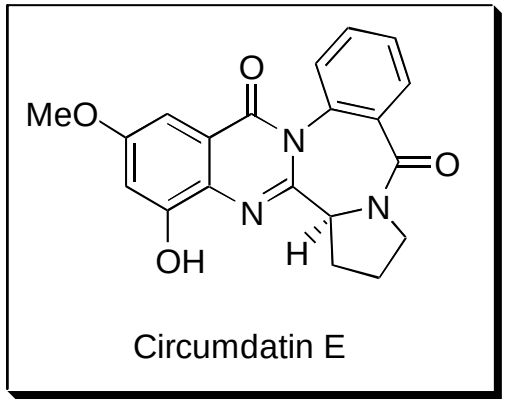
Alantrypinone
5 steps (lit 8 steps)

- Ran into the racemization issue.
- Optimized reaction conditions to get improved ee.
- Obtained enantiomerically pure NPs via re-crystallization or SFC separation.

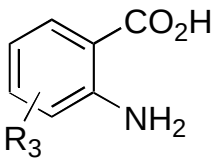
J. Org. Chem. **2005**, *70*, 6339-6345.

Synthesis of Analogs of Circumdatin E

One-pot Sequential Reaction Approach

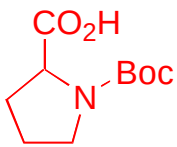


Circumdatin E



1b: R^3 = 4-F
1c: R^3 = 5-Me

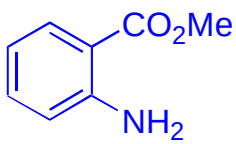
+



2b

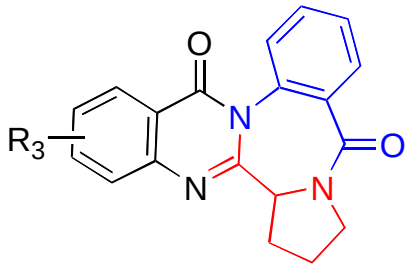
$P(PhO)_3$, Py,
μwave,150 ^{0}C, 10 min

then



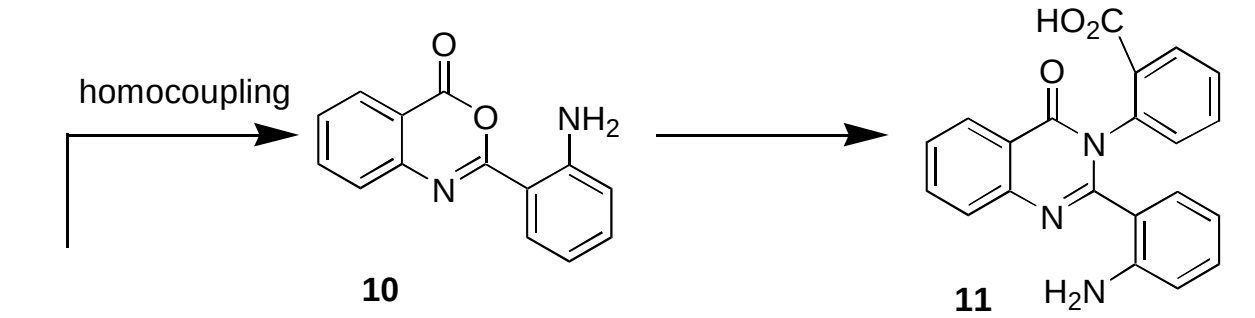
5b

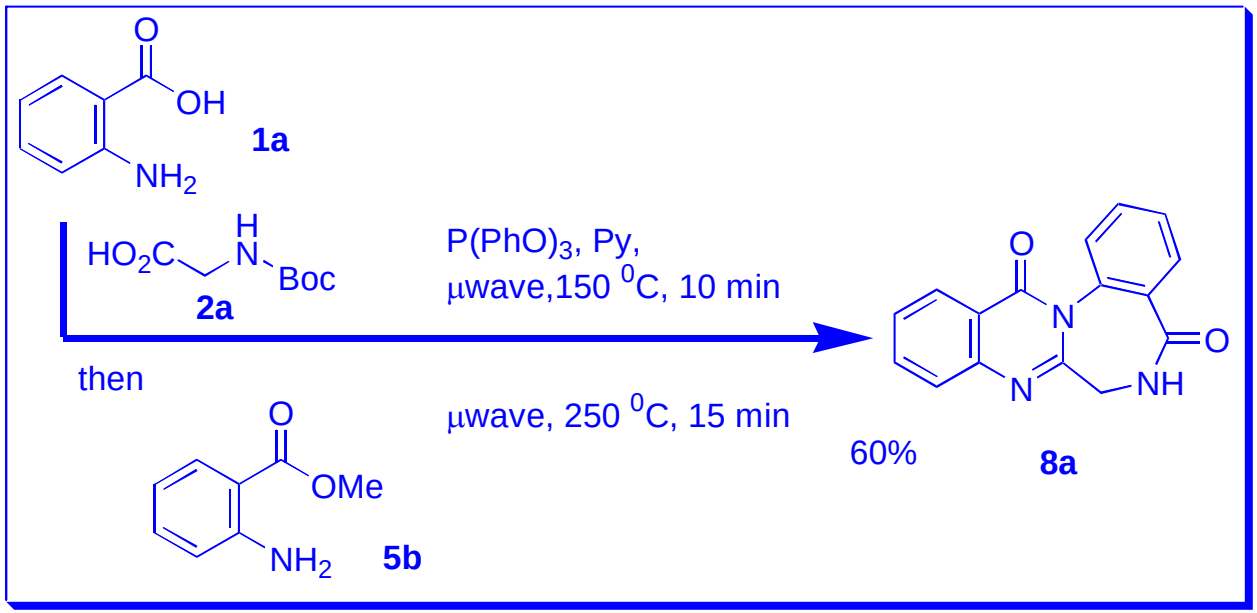
μwave, 250 ^{0}C, 15 min



34%, R^3 = 4-F
28%, R^3 = 5-Me

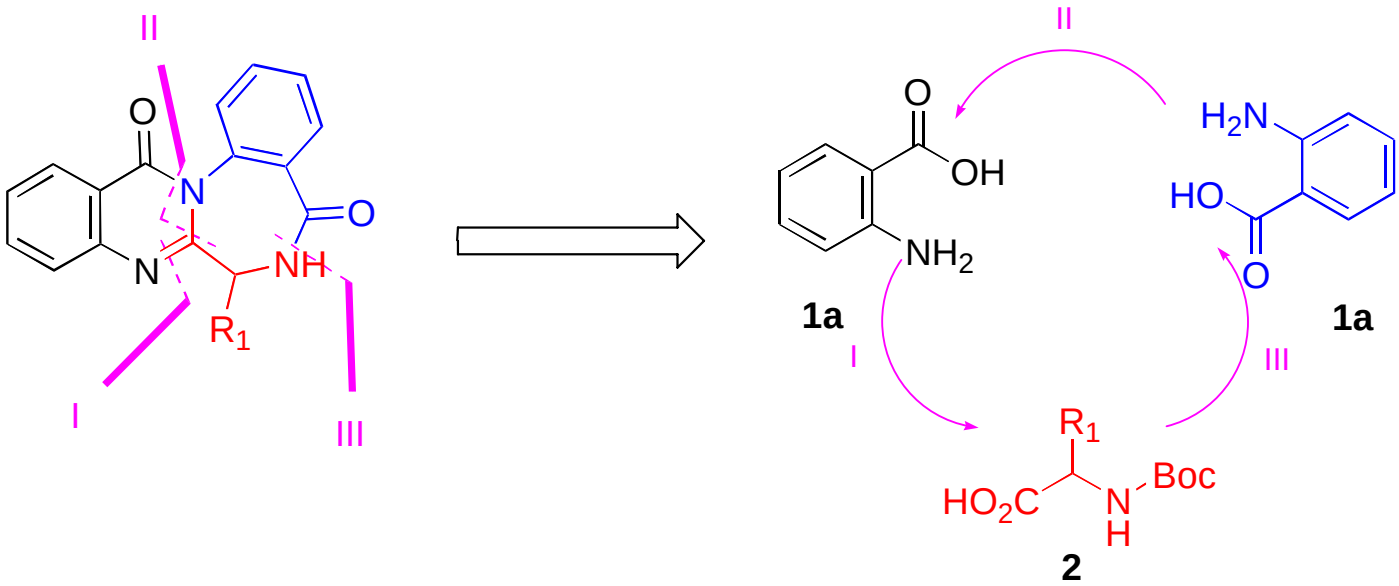
Some Observations

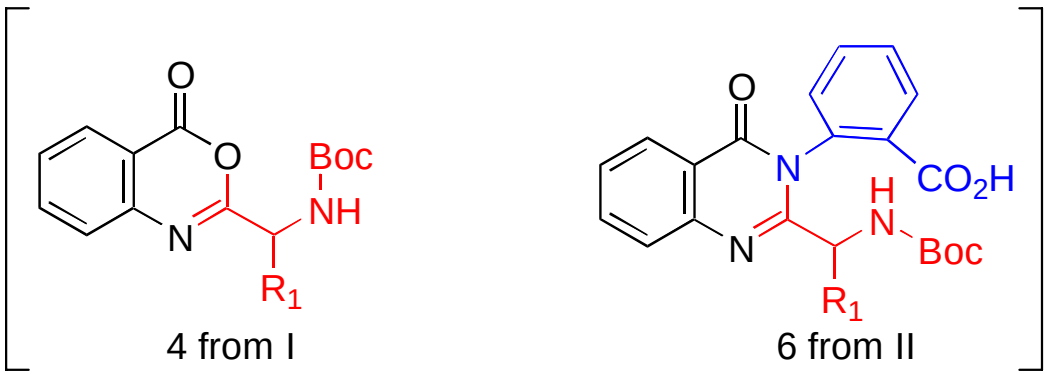




- Only trace amount of **10**, and **11** formed via homo-coupling of **1a**.

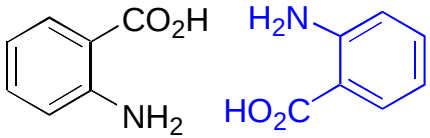
Retrosynthetic Strategy – Domino Approach





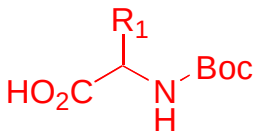
- Domino: The reaction sequence is I, II, then III.

Total Syntheses via Domino Reactions



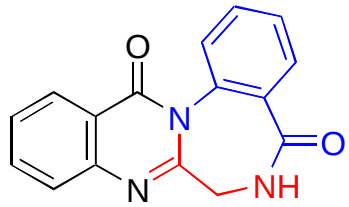
1a

1a

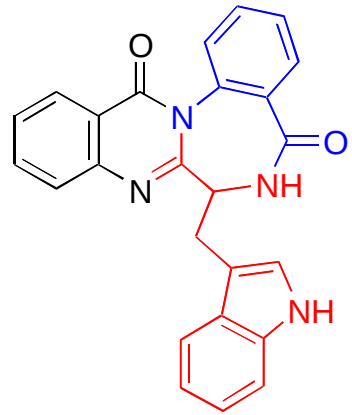


2

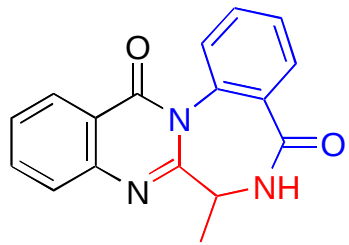
$P(PhO)_3$ (1.2 eq),
Py, μwave,
230 ^{0}C, 20 min



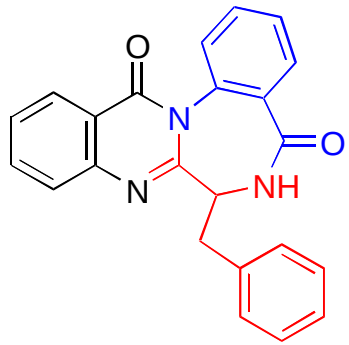
Sclerotigenin (**8a**), 55%
(Anti-insectant)



(±)-Asperlicin C (**14**), 24%
(CCK Antagonist)



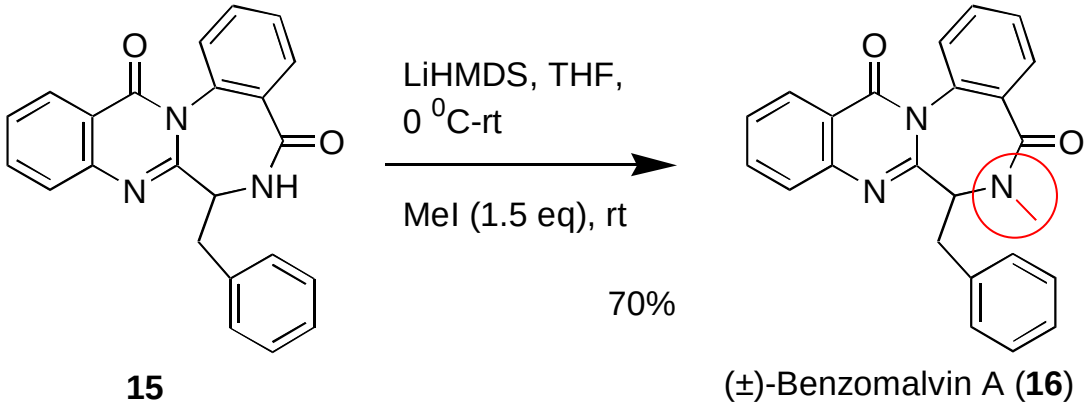
(±)-Circumdatin F (**13**), 32%

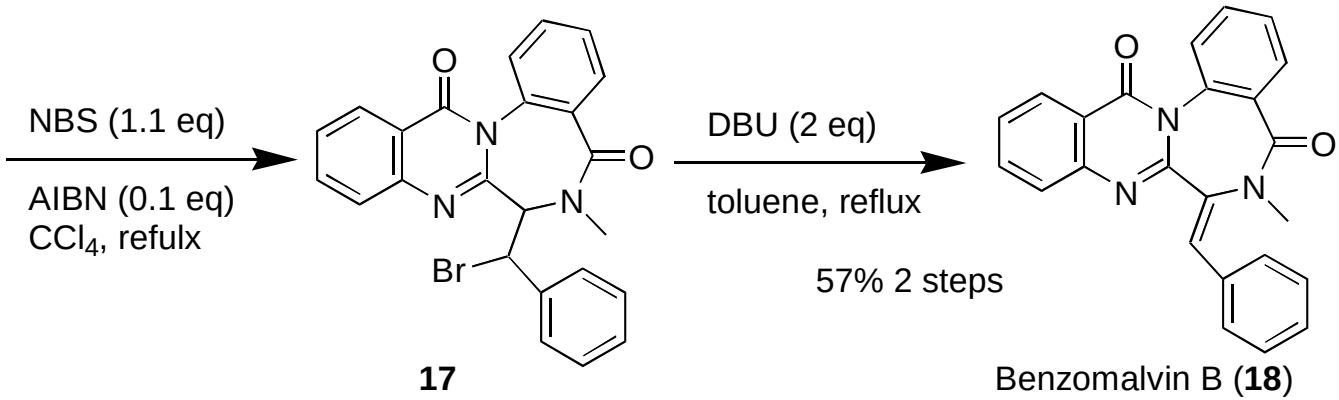


(±)-Demethylbenzomalvin (**15**), 30%

J. Org. Chem. **2005**, *70*, 10488-10493.

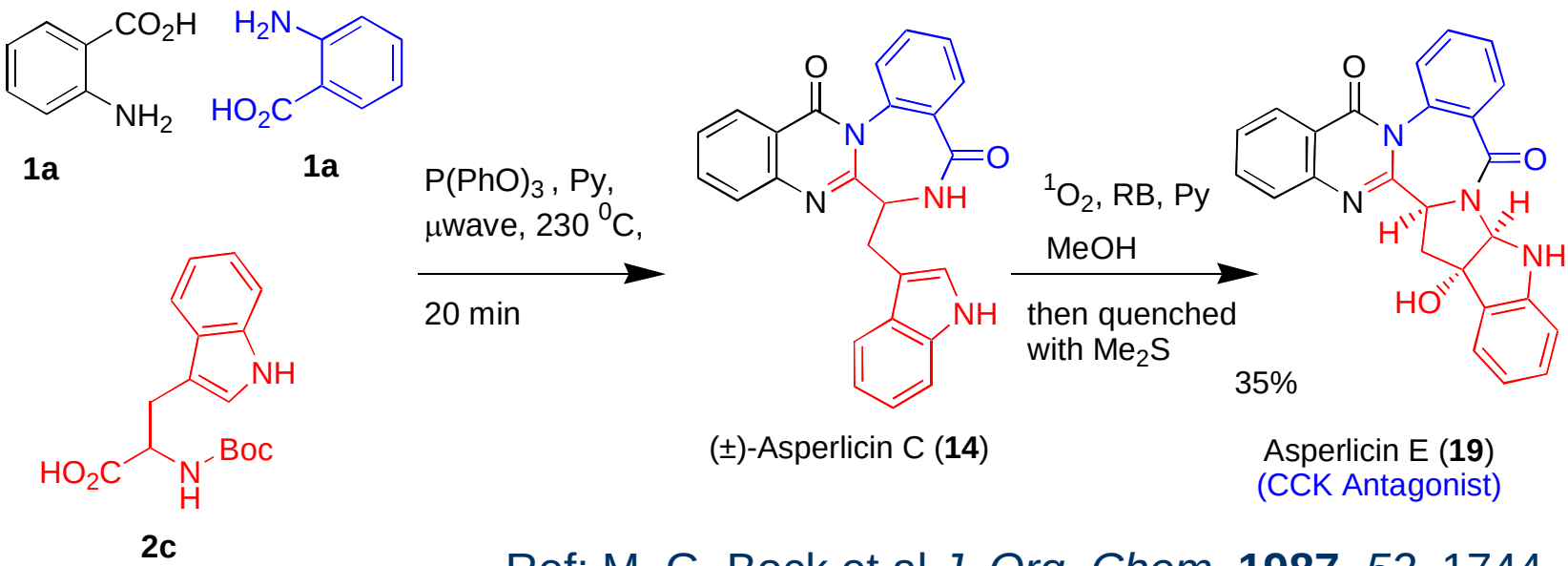
Synthesis of Benzomalvin A and B





- Ref: S. Eguchi et al *Tetrahedron* **1998**, *54*, 7997. (7 steps for **16**; 9 steps for **18**)

Formal Total Synthesis of Asperlicin E

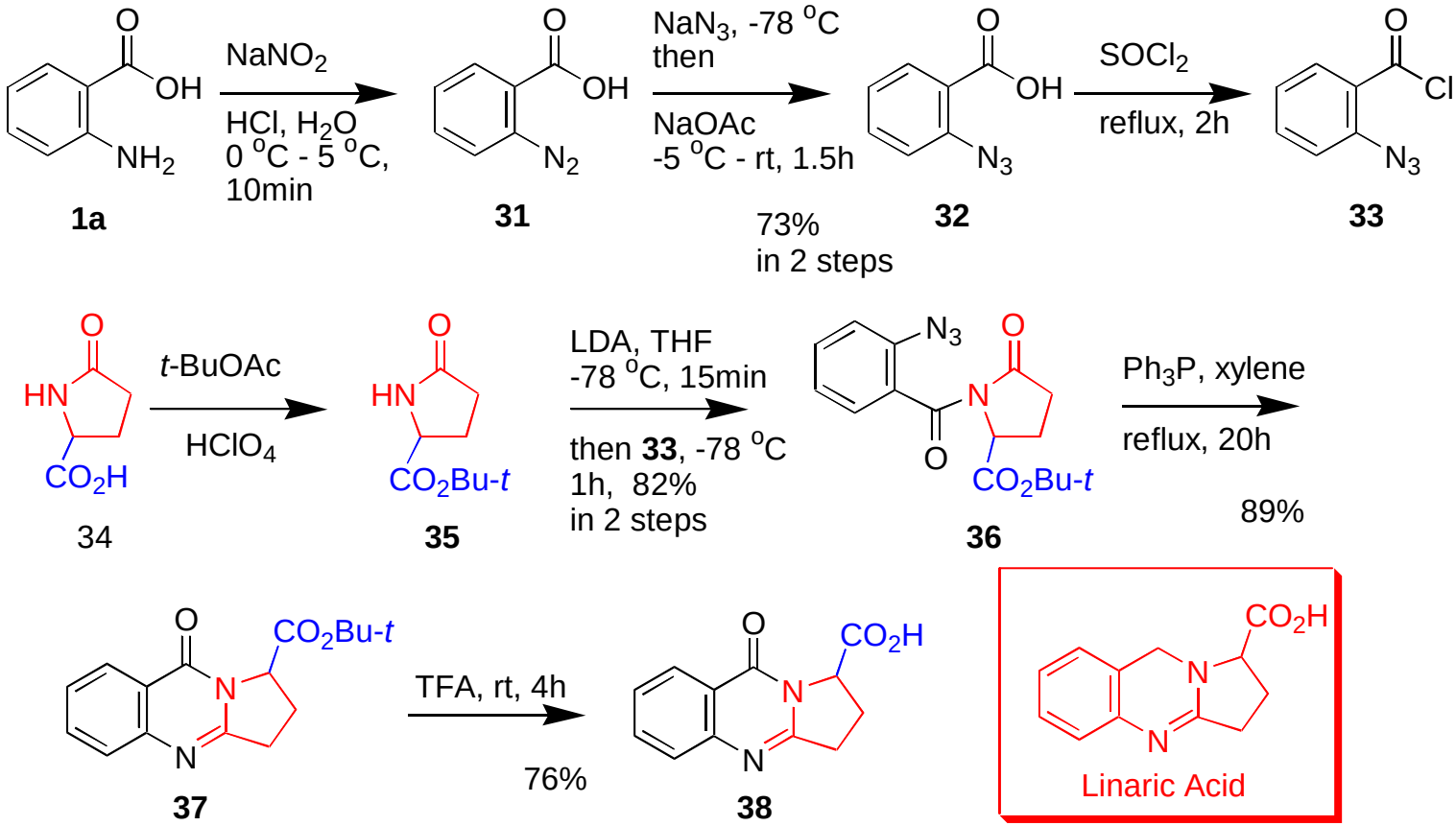


Ref: M. G. Bock et al *J. Org. Chem.* **1987**, *52*, 1744.

(7 steps for **19**)

J. Org. Chem. **2005**, *70*, 10488-10493.

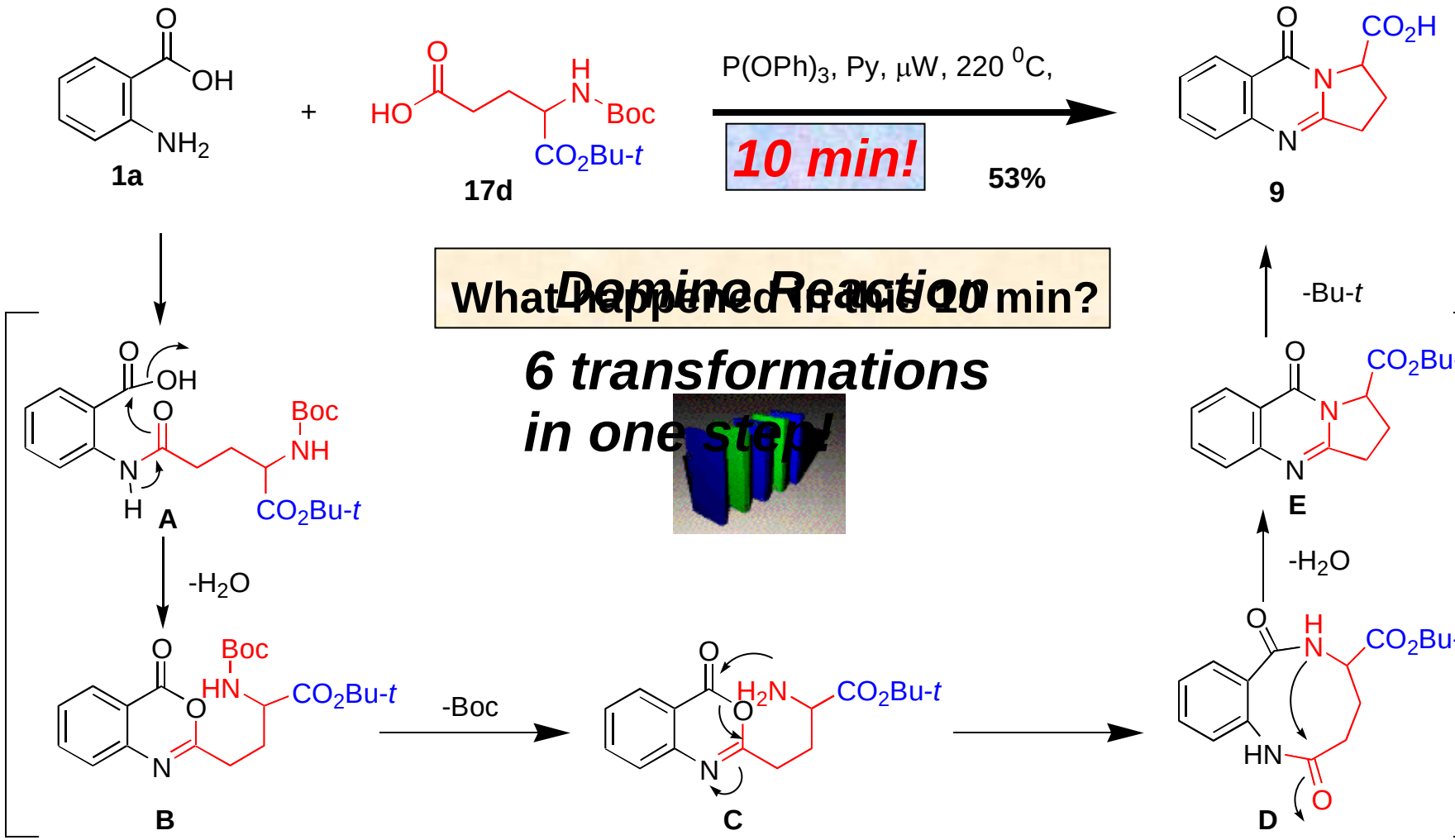
Literature Method for Synthesis of (38)



- 7 steps in days, <40% overall yield.
- Not optimal for the automation.

J.-D. Charrier et al, WO 01/94351.

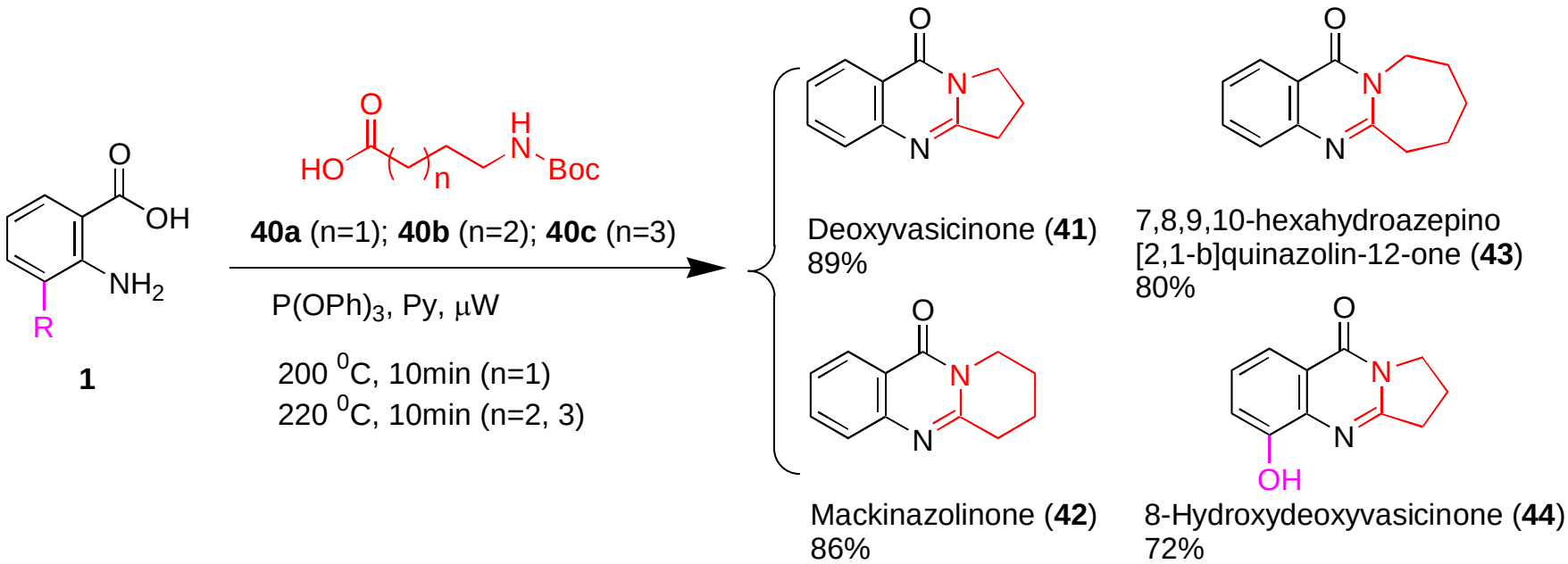
One-Step Synthesis of (9)



Org. Lett. **2005**, *7*, 3363-3366.

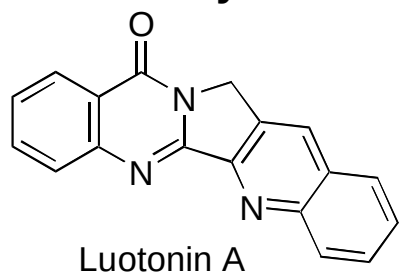
Total Syntheses of Deoxyvasiciones

Intramolecular Domino Reactions



- No protecting group needed on OH.

Formal total synthesis

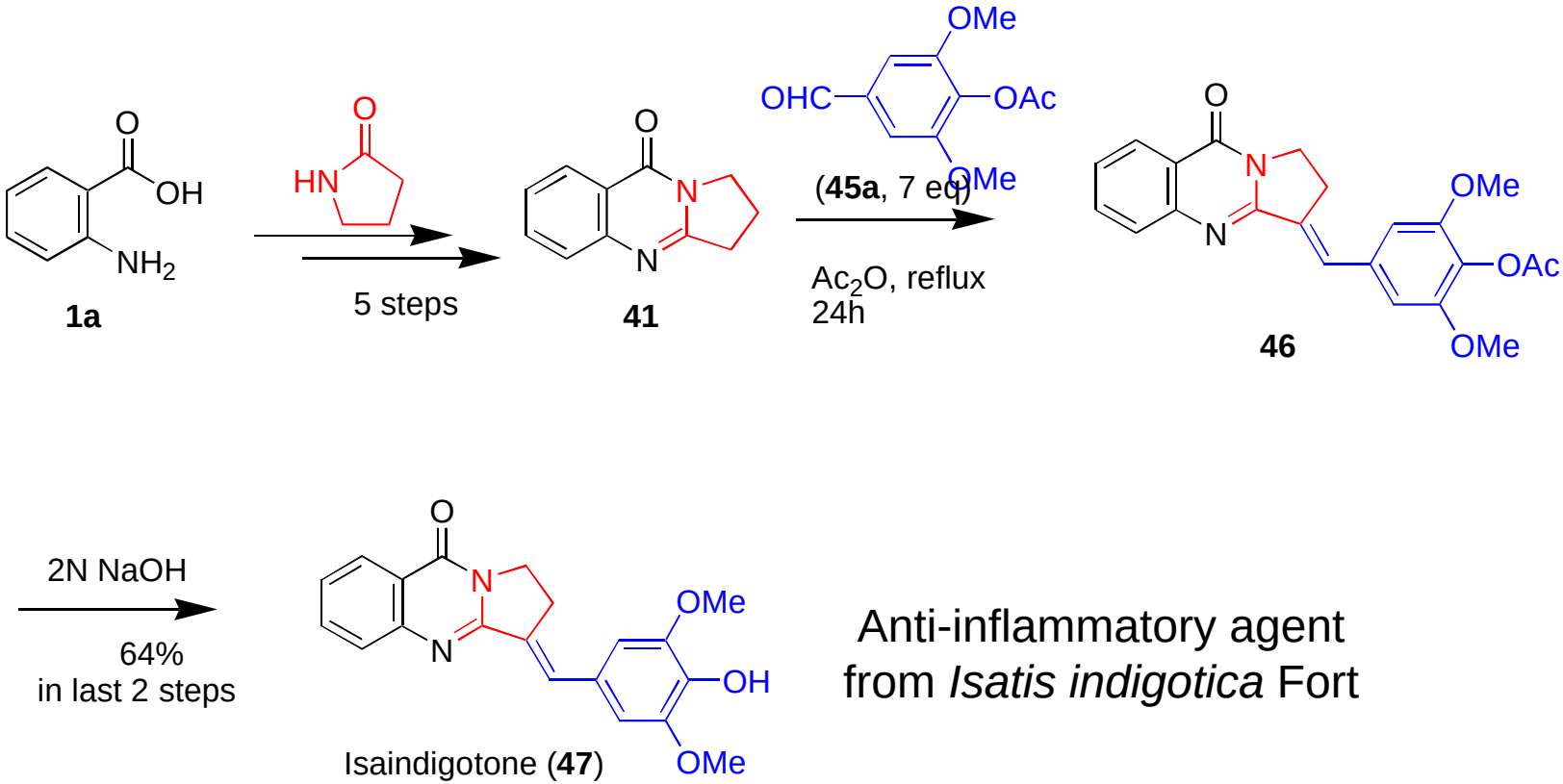


Luotonin A

(Topoisomerase I Inhibitor)

3 Steps (lit 7 steps)

Literature Method for Synthesis of (47)

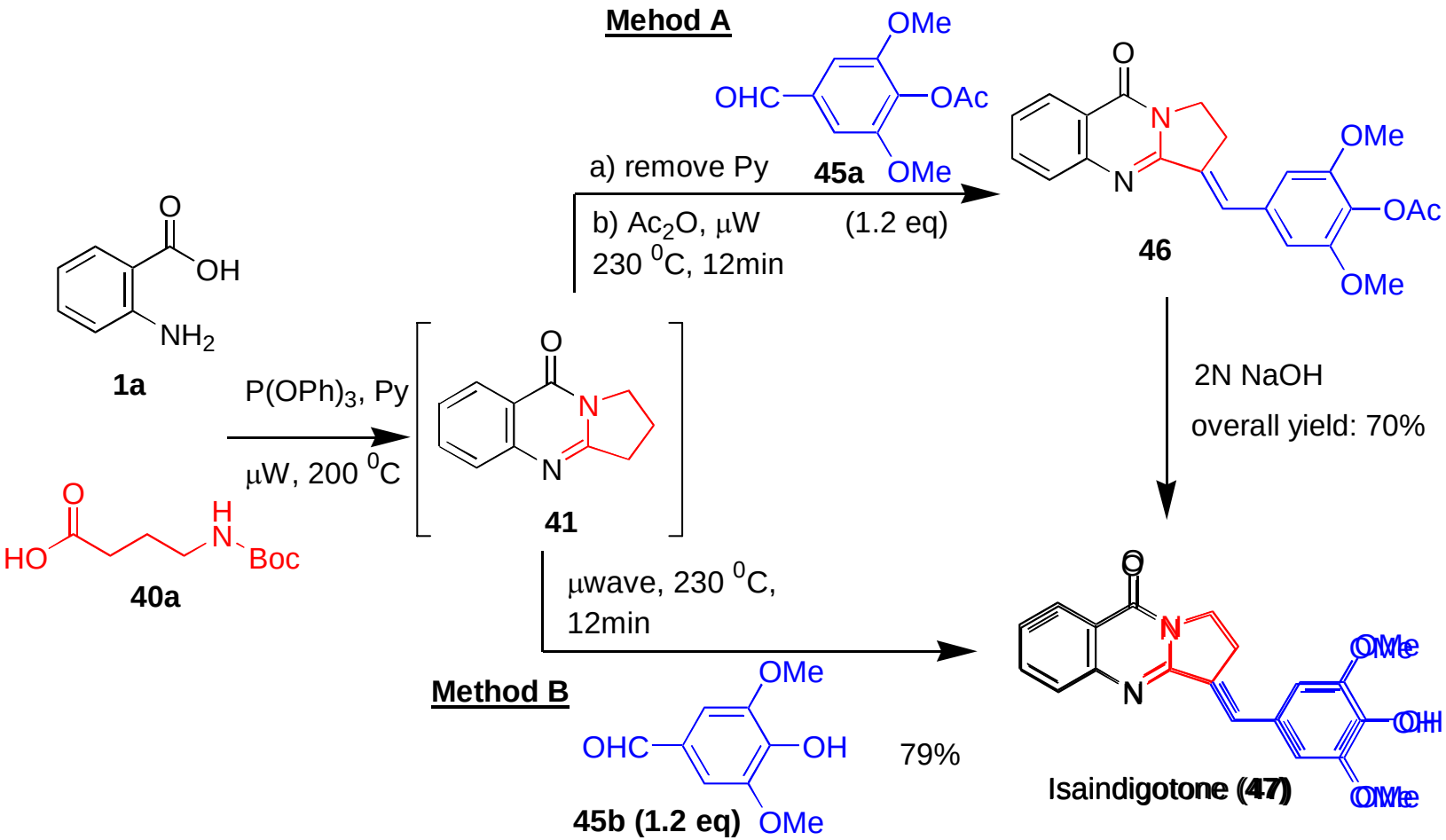


Anti-inflammatory agent
from *Isatis indigotica* Fort

- Eguchi's aza-Wittig approach to **41**.
- 7 liner steps in days.
- Not optimal for the automation.

P. Molina et al *Synthesis* **2000**, 1523.

Total Synthesis of Isaindigotone (47)

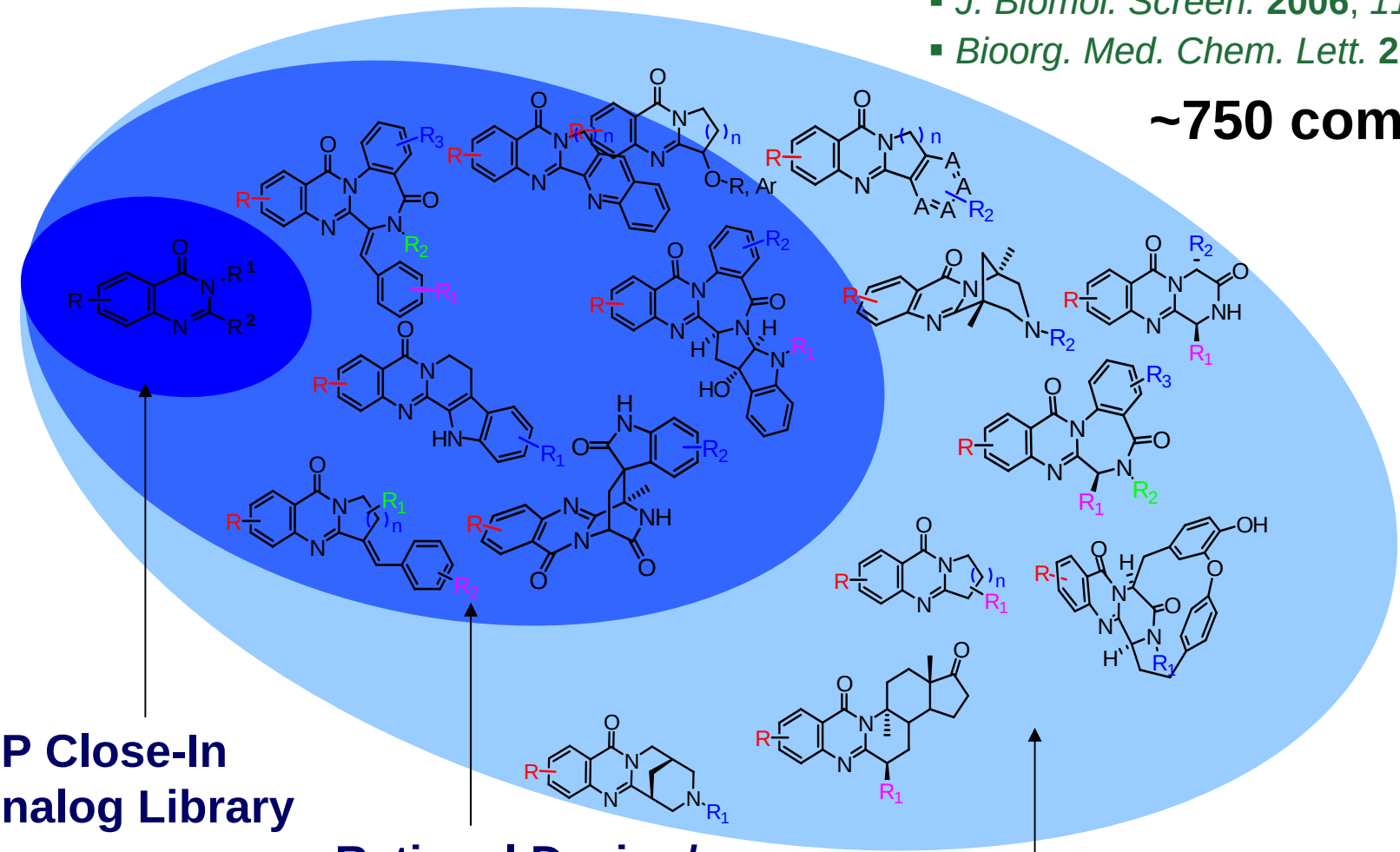


- One-pot Sequential Reaction (Method B)
  - Improved process from literature 7 steps to 2 steps in one-pot.
  - Greatly accelerated library synthesis.

Quinazolinone NP Libraries

- *J. Comb. Chem.* **2006**, *8*, 7.
- *J. Biomol. Screen.* **2006**, *11*, 21.
- *Bioorg. Med. Chem. Lett.* **2006,** *16*, 686.

~750 compounds

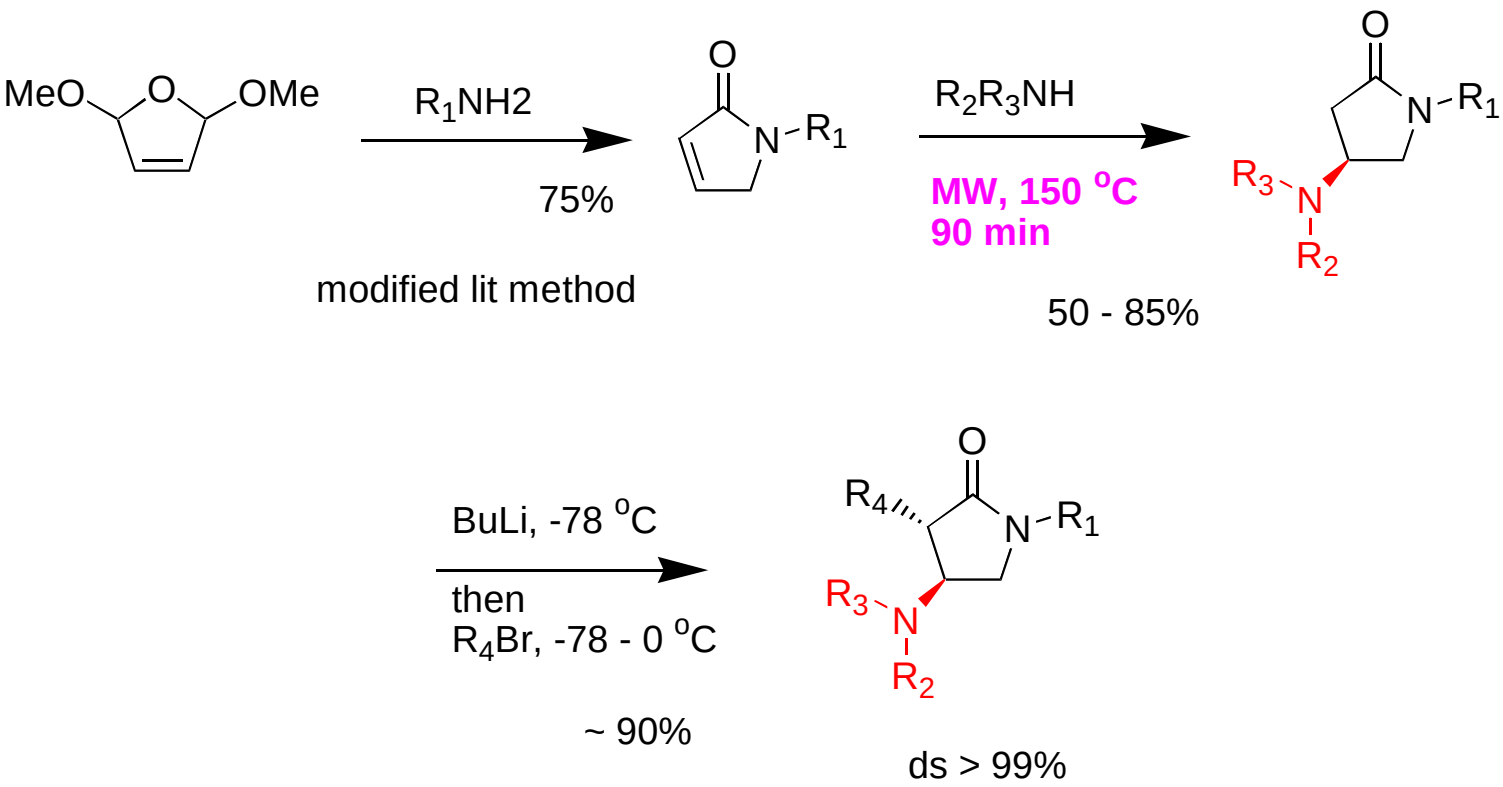


NP Close-In Analog Library

Rational Design/ Hypothesis-Driven Library

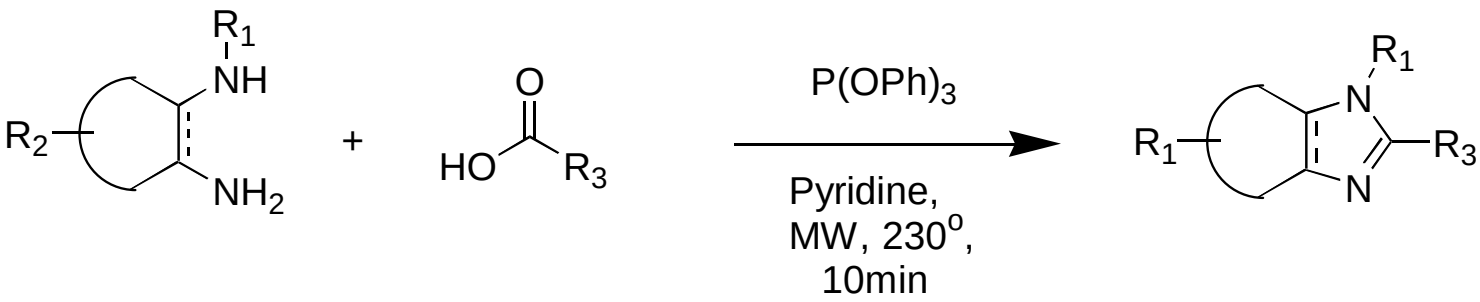
Diversity-Driven Library

Case 2: γ-Lactam - A Potential Kinase Inhibitor

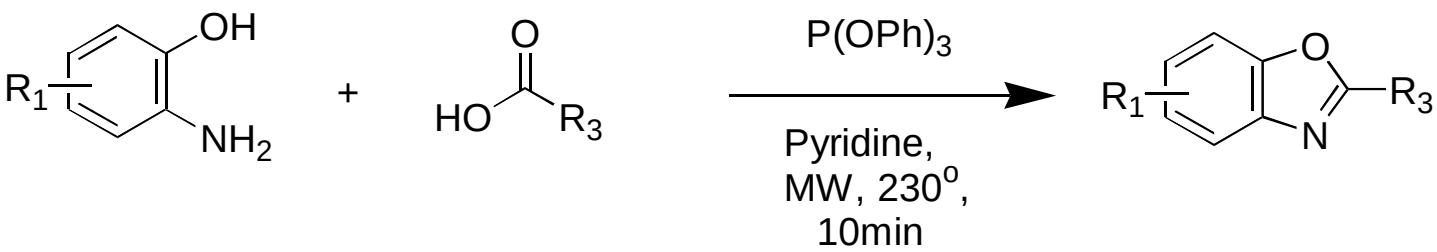


- Low yield (unpractical) when used conventional heating even 3 days!
- MW allowed synthesize the target compounds from concept to library less than 2 weeks.

Case 3: Imidazoles and Benzoxazoles

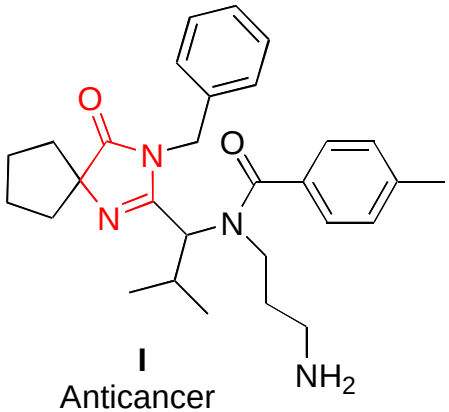


S.-Y. Lin et al *Tetrahedron Lett.* **2006**, *47*, 2883-2886.

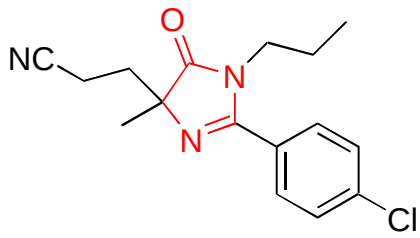


Shou-Yuan & Yuko

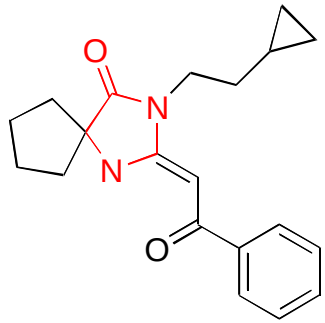
Case 4: Spiro Imidazolinones



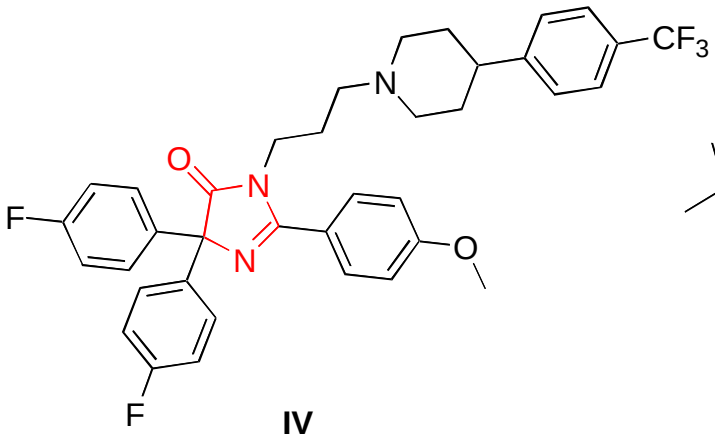
I
Anticancer
Eg5 Inhibitor
Cytokinetics Inc.



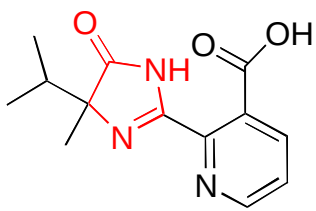
II
Anticancer
Sankyo



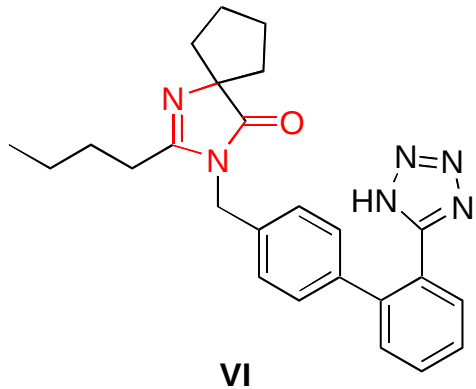
III
Anticancer
Pfizer



IV
Obesity
Bayer



V
Arsenal
Herbicide
American Cynamide Co.

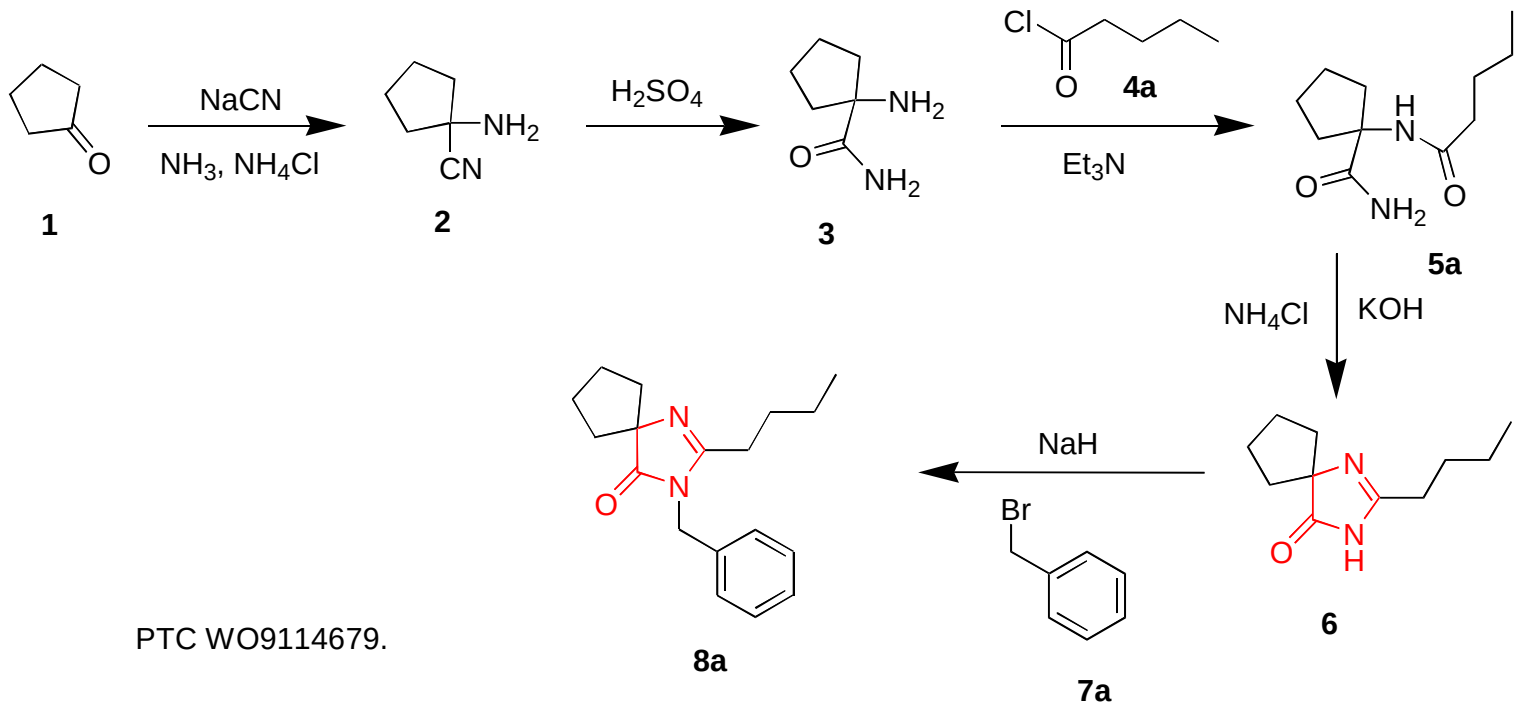


VI
Irbesartan
Cardiovascular
BMS/Sanofi Aventis

Ping & Katie

Literature Precedent I

via Diamides



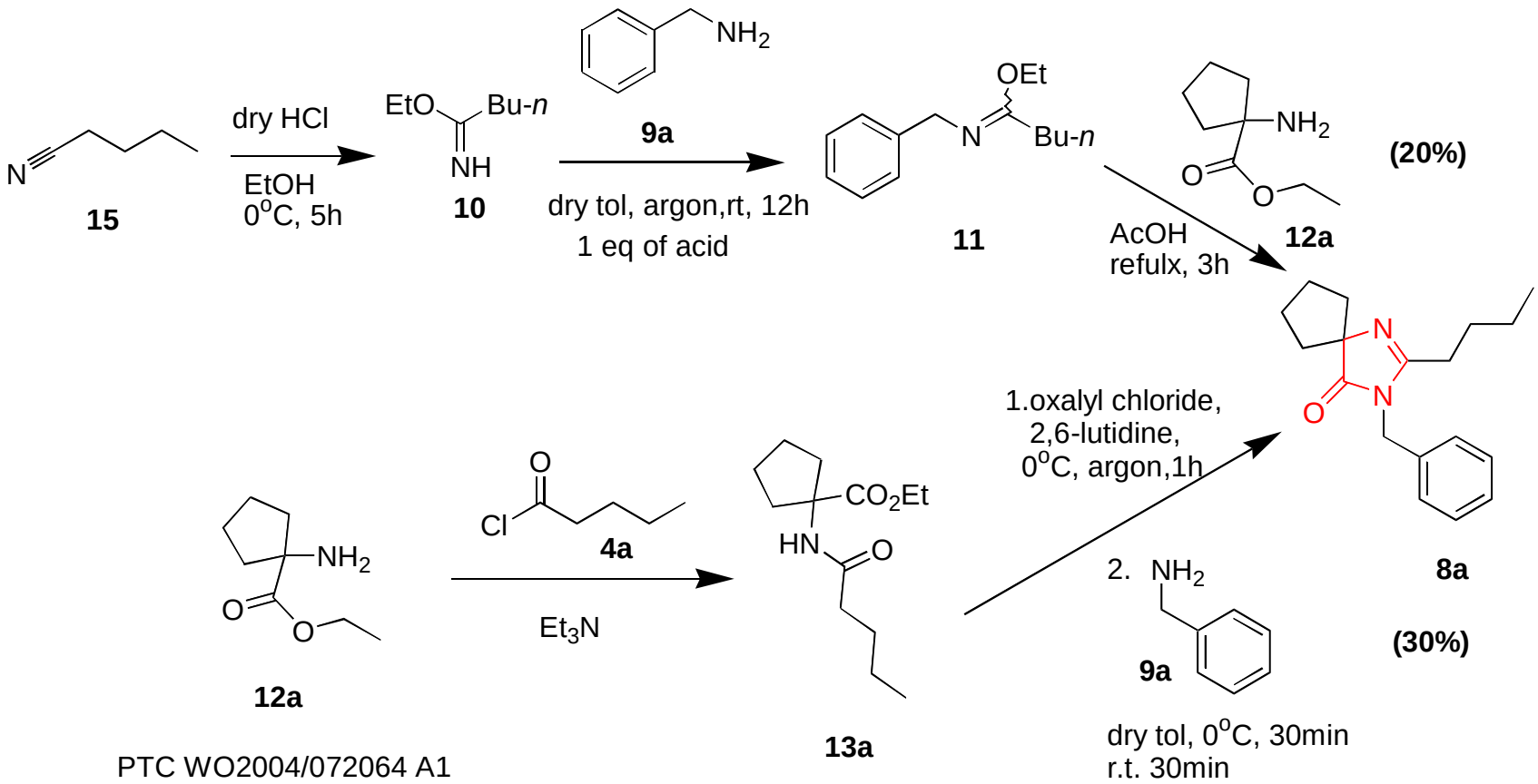
PTC WO9114679.

Drawbacks:

1. 5-step synthesis;
2. Use of hazard reagent NaCN.

Literature Precedent II

via Imidate Esters or Imidoyl Chlorides



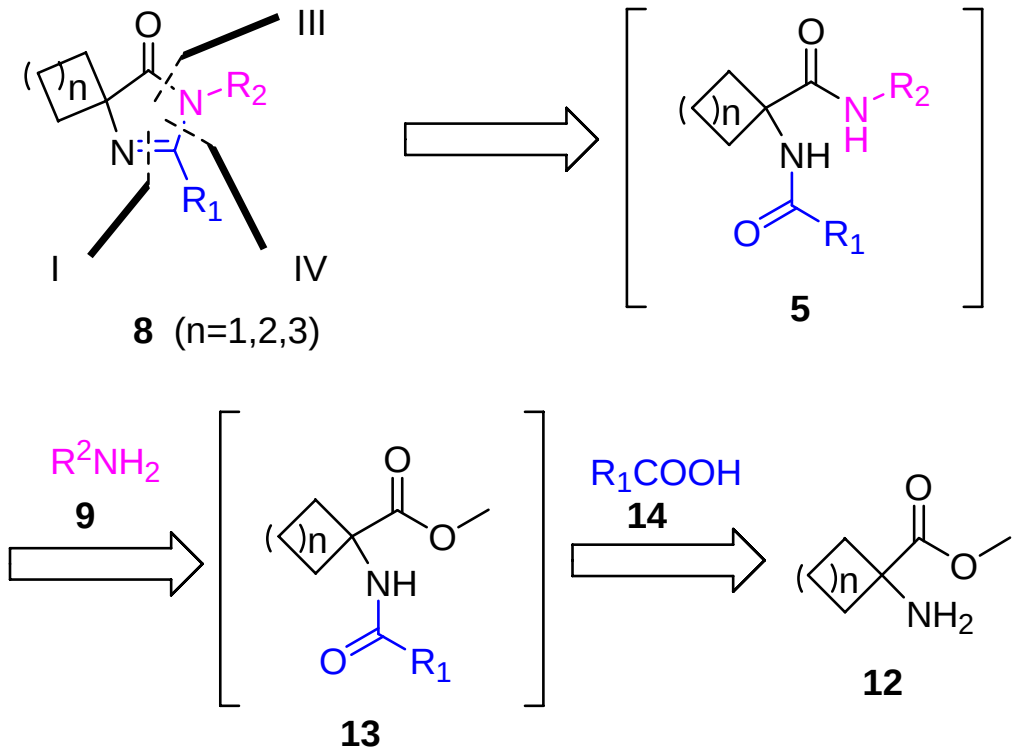
Drawbacks: 1. Un-stability of intermediates;

2. Difficulty of operation;

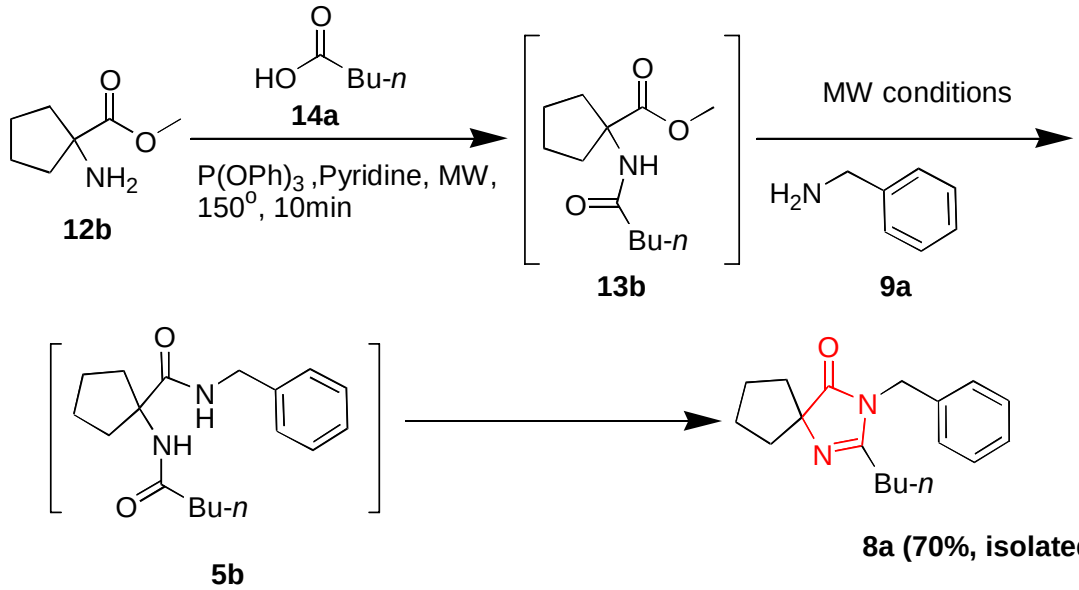
3. Low yields.

Retro-synthetic Strategy - I

1. Three-component one-pot sequential reaction:



Method Development – Strategy I

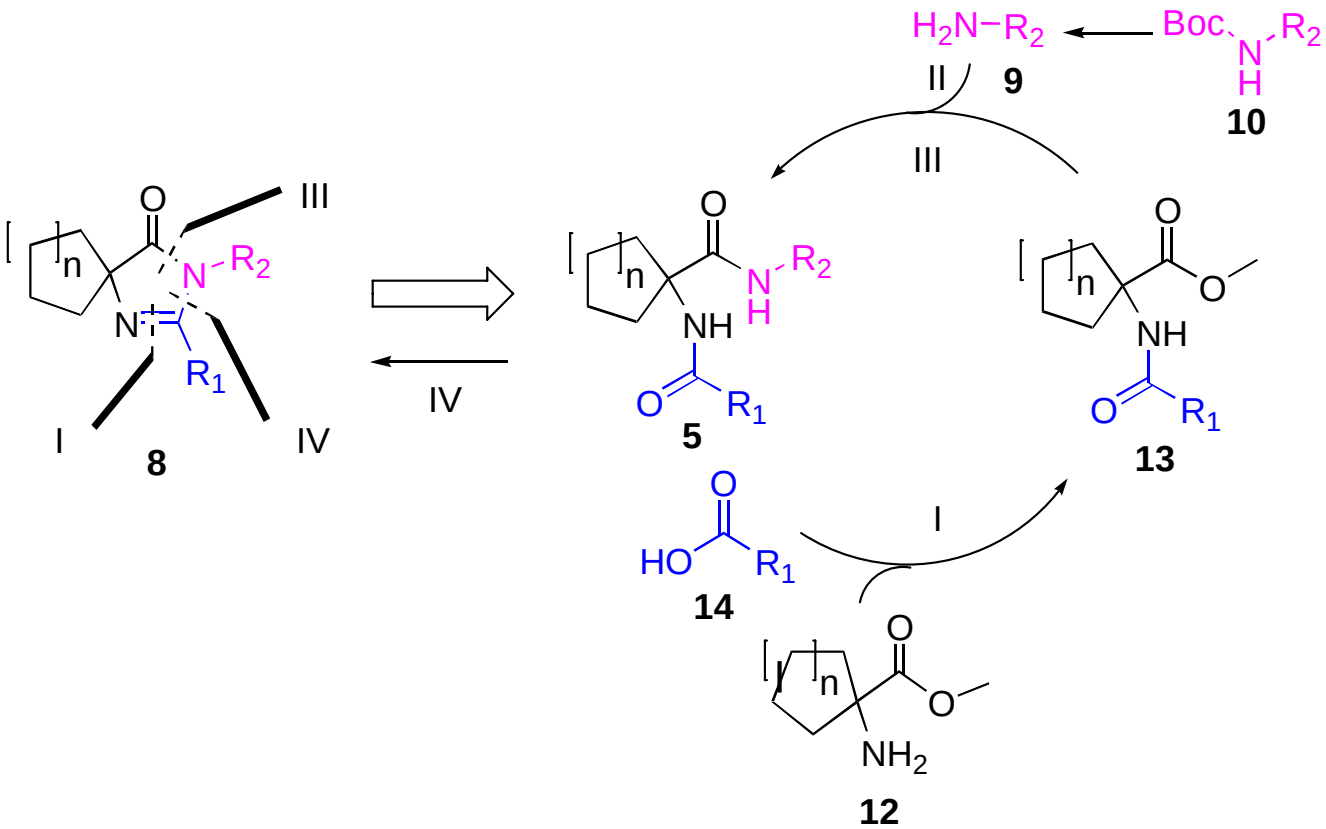


Temp (°C)	Time (min)	13b (%)	5b (%)	8a (%)[a]
200	10	30	30	30
220	10	28	-	62
240	10	2	-	98
250	**10**	**-**	**-**	**100 (70)**

a. Yield determined by HPLC(ELSD) and isolated yield in parentheses.

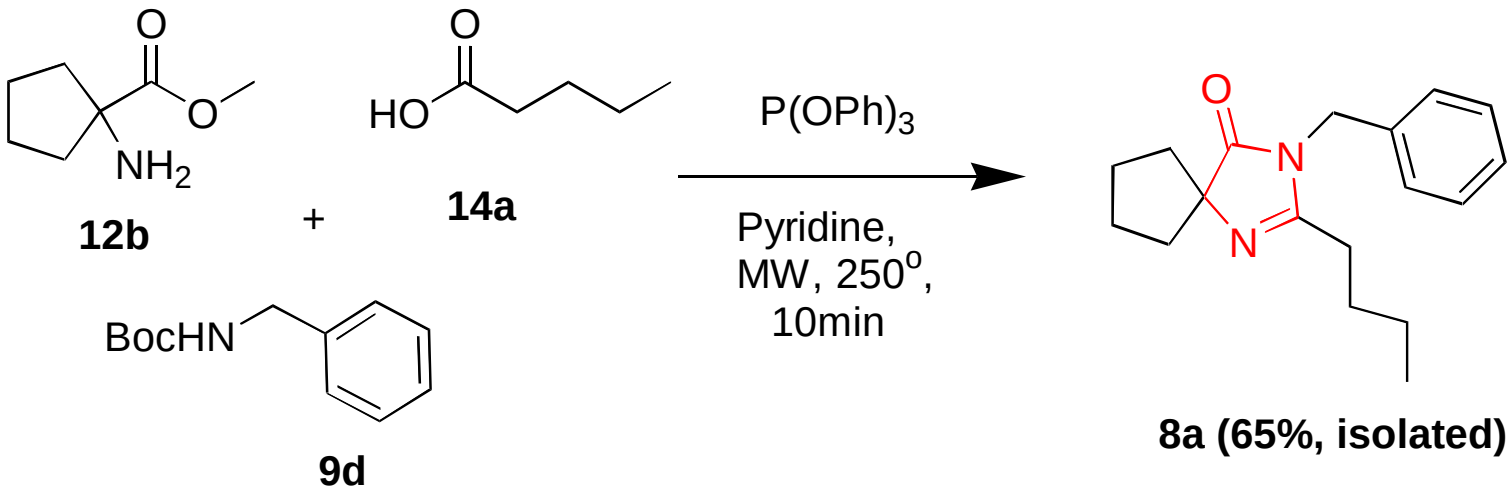
Retro-synthetic Strategy - II

2. Three-component domino reaction



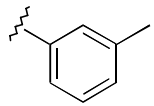
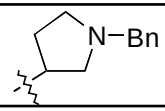
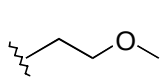
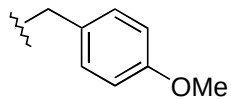
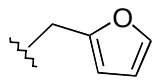
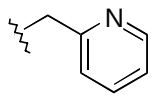
- Simplify operation for library syntheses that needs limited number of amines.

Method Development – Strategy II



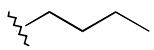
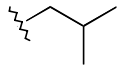
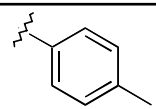
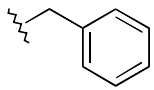
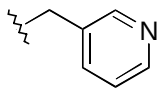
- Feasibility and efficiency of domino reaction.

Chemistry Scope of Amines

Entries	R1R2	R3	R4	Yield(%)[b]
1	cyclopentyl	butyl		98(67)
2	cyclopentyl	butyl		93(78)
3	cyclopentyl	butyl		95(72)
4[a]	cyclopentyl	butyl		97(74)
5	cyclopentyl	butyl		90(51)
6[a]	cyclopentyl	butyl		95(56)

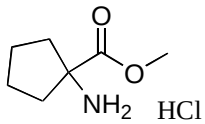
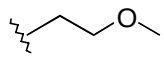
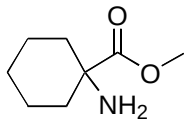
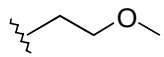
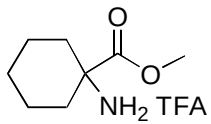
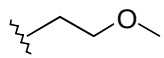
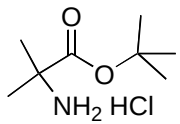
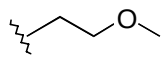
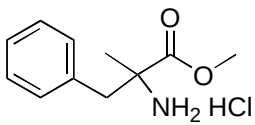
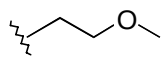
a. Via strategy II domino reaction;
b. Yield determined by HPLC(ELSD) and isolated yield in parentheses.

Chemistry Scope of Acids

Entries	R1R2	R3	R4	Yield(%)[a]
1	cyclopentyl		benzyl	95(70)
2	cyclopentyl		benzyl	90(71)
3	cyclopentyl		benzyl	91(73)
4[b]	cyclopentyl		benzyl	89(69)
5	cyclopentyl		benzyl	95(55)
6	cyclopentyl		benzyl	90(51)

a. Yield determined by HPLC(ELSD) and isolated yield in parentheses;
b. Cyclization step: microwave, 250^{o}, 15 min.

Chemistry Scope of Amino Esters

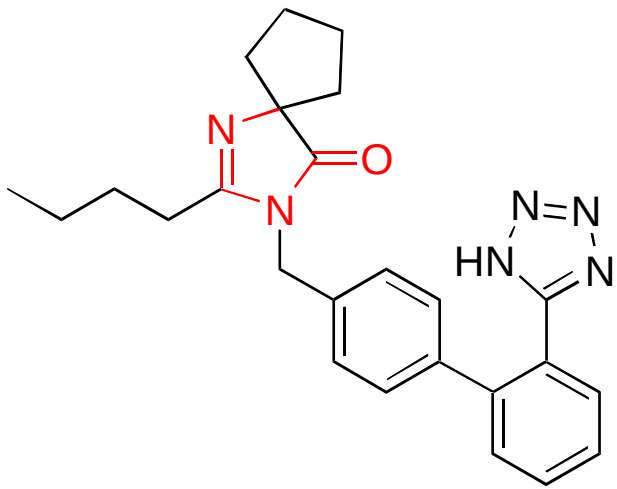
Entries	R1R2	R3	R4	Yield(%)[a]
1		benzyl		92(63)
2[b]		benzyl		82(50)
3[b]		benzyl		95(66)
4		benzyl		82(55)
5		benzyl		95(67)

a. Yield determined by HPLC(ELSD) and isolated yield in parentheses;

b. Cyclization step: MW, 250^{o}C, 15min.

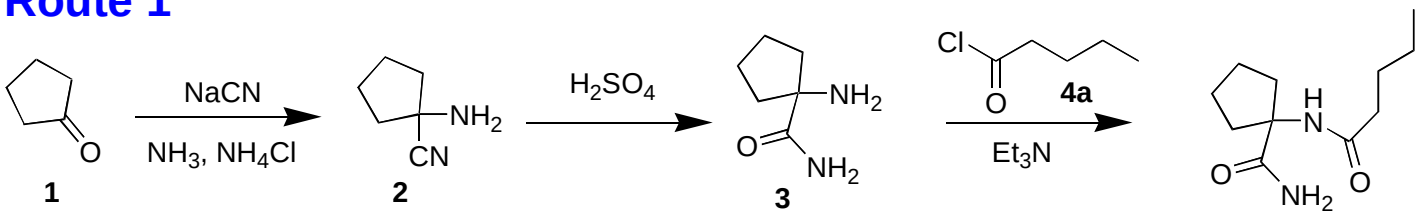
Irbesartan

- Irbesartan (brand name Avapro launched from the alliance between BMS and Sanofi-Aventis) is fastest-growing anti-hypertensive drug and used in the treatment of cardiovascular diseases.

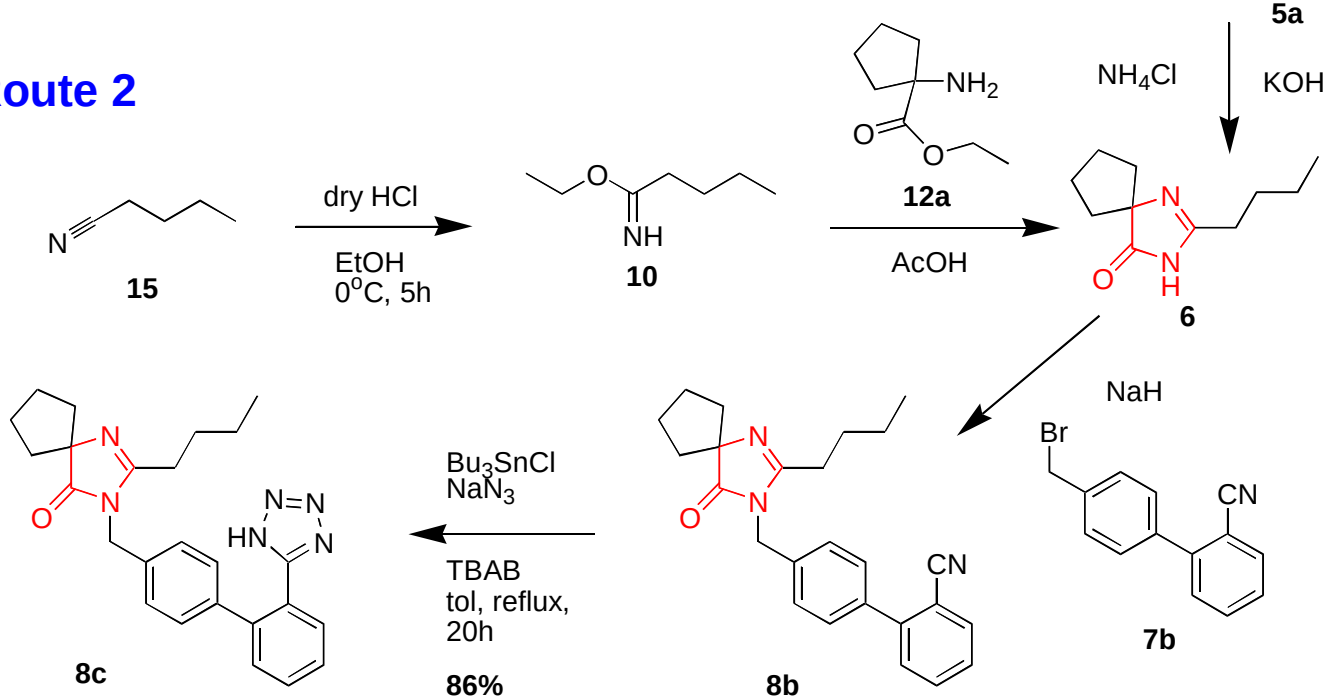


Literature Methods to Irbesartan

Route 1

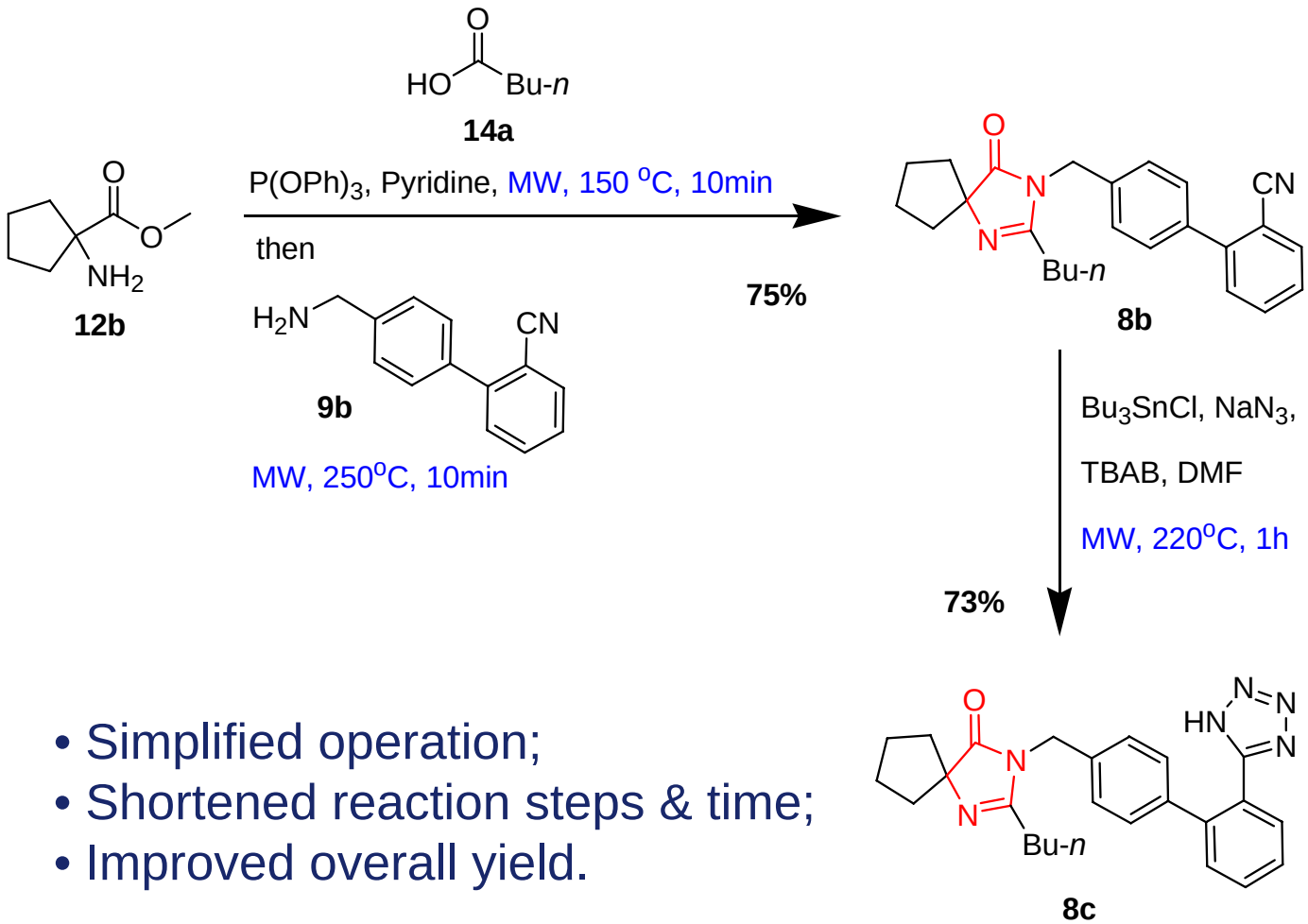


Route 2



PTC WO9114679.

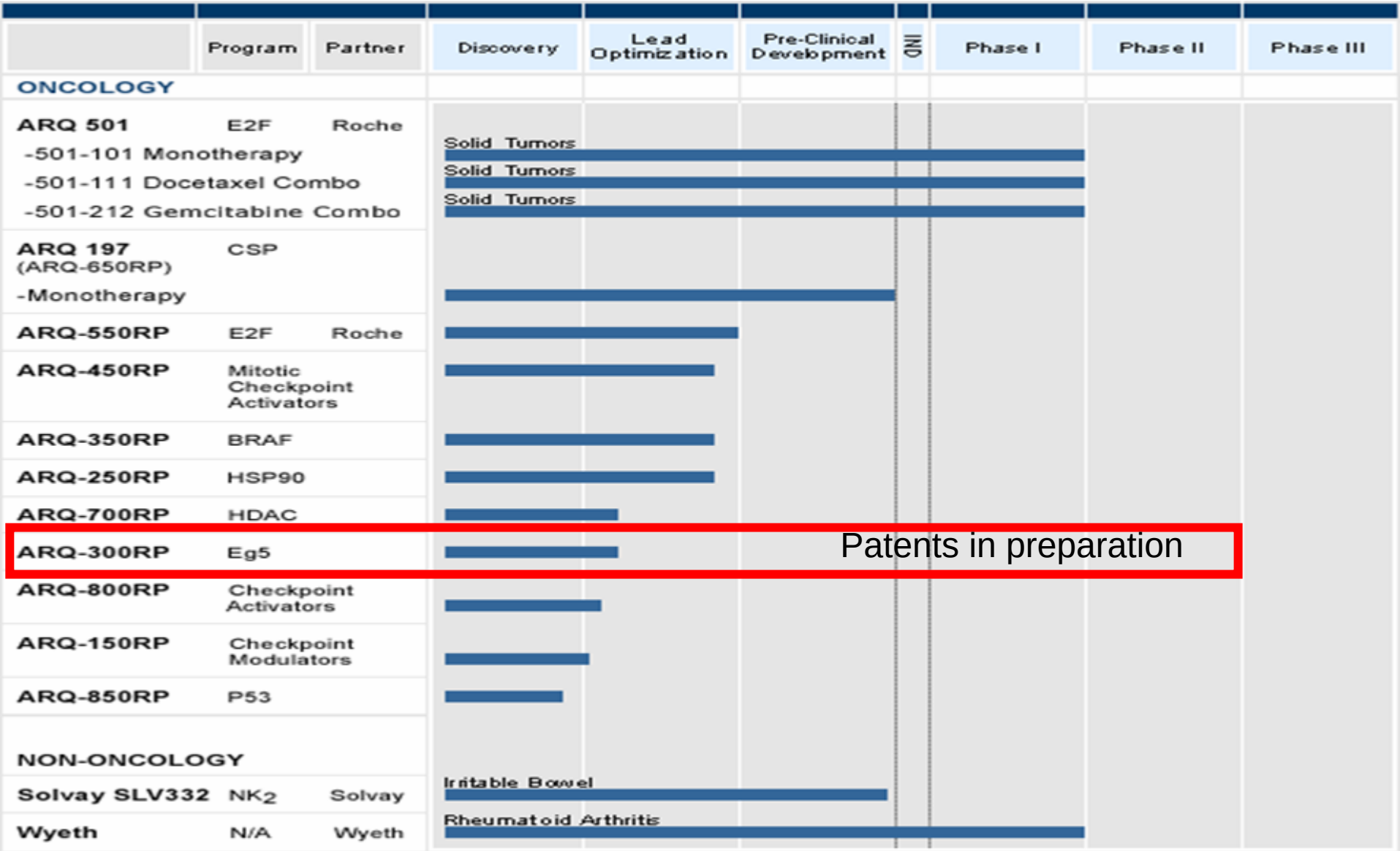
New Method to Irbesartan



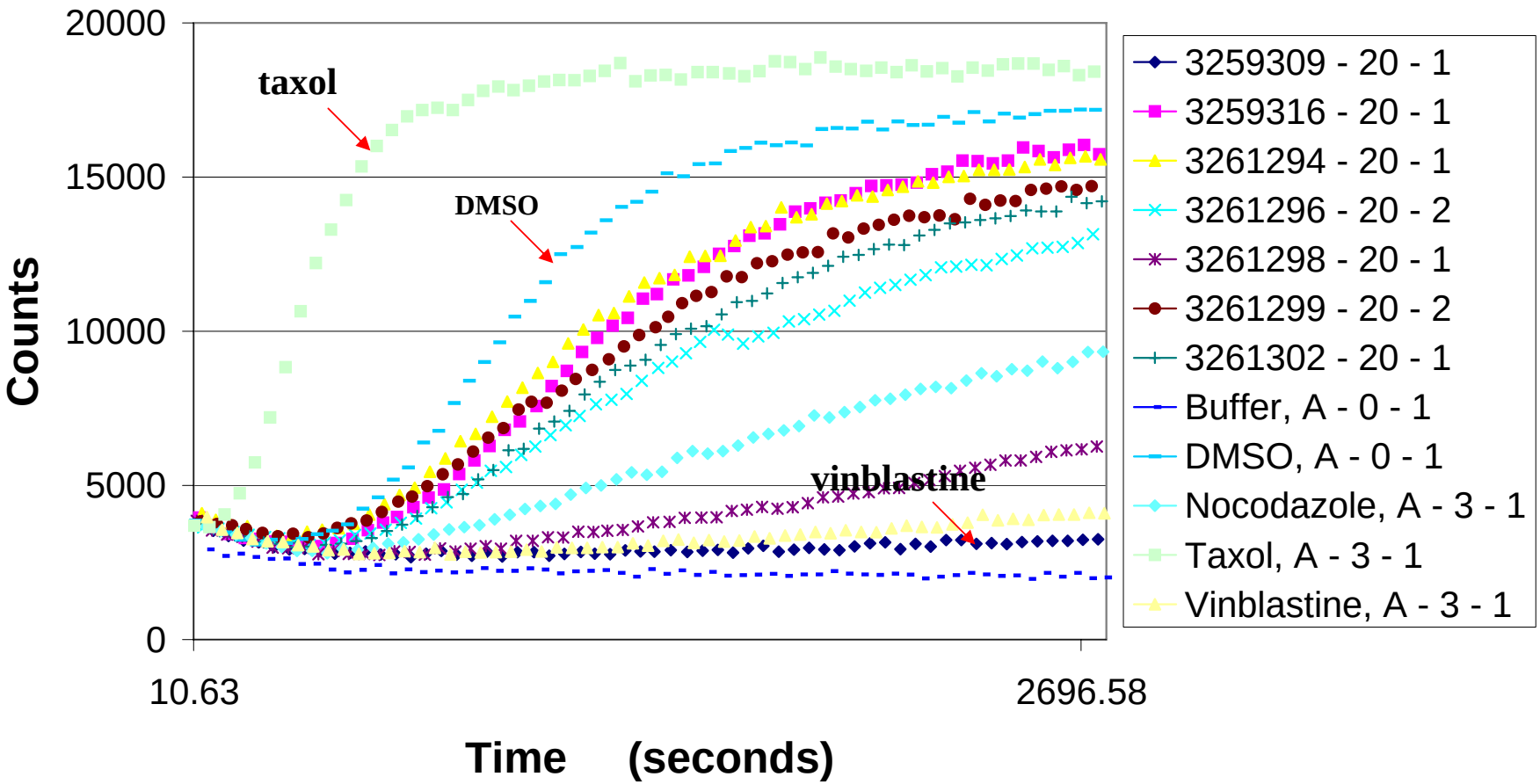
- Simplified operation;
- Shortened reaction steps & time;
- Improved overall yield.

P. Ye et al *J. Org. Chem.* **2006**, *71*, 3137-3140.

Added Values to ArQule's Pipeline



Tubulin Assay with Selected Quinazolinones



- Compound X induced mitotic arrest by inhibiting tubulin polymerization.

Bioorg. Med. Chem. Lett. **2006,** *16*, 686-690.

Summary

- MAOS allows for rapid exploration of different reactions and conditions
- MAOS have been successfully applied to chemical transformations with broad chemistry scope, which are otherwise difficult using conventional means
- MAOS is an useful tool for medicinal chemists

MAOS: A Useful Tool in Medicinal Chemistry

ELSEVIER

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22 March 2006

Dear Professor Liu

TETRAHEDRON LETTERS – Most Requested Articles On ScienceDirect, 2005

I am delighted to inform you that one of your papers has been recognised as a "top-25 most downloaded" article from *Tetrahedron Letters* on ScienceDirect last year.

Microwave-assisted one-pot synthesis of 2,3-disubstituted 3H-quinazolin-4-ones
Tetrahedron Letters 46:8 1241-1244pp 01-Feb-2005
Liu, J.-F.; Lee, J.; Dalton, A.M.; Bi, G.; Yu, L.; Baldino, C.M.; McElory, E.; Brown, M.

To put this achievement into some context:

- *Tetrahedron Letters* was the third most downloaded journal on ScienceDirect during 2005 (from almost 2,500 titles).
- Well over 8,000,000 full text articles were downloaded from Tetrahedron Publications last year alone (nearly 1,000 downloads every hour – throughout the year!).
- Over 4,500 institutes currently take *Tetrahedron Letters* online via ScienceDirect, providing unparalleled worldwide access to the journal's content.
- ScienceDirect is the world's largest electronic collection of science, technology and medicine full text and bibliographic information
- Papers from Tetrahedron Publications have been the #1 and #2 "most requested" articles on CAS, for the last three quarters running*.

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- ~2,500 articles
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