Synthesis of Retigabine Analogs & Enamide Oxidation towards Stemona Alkaloids

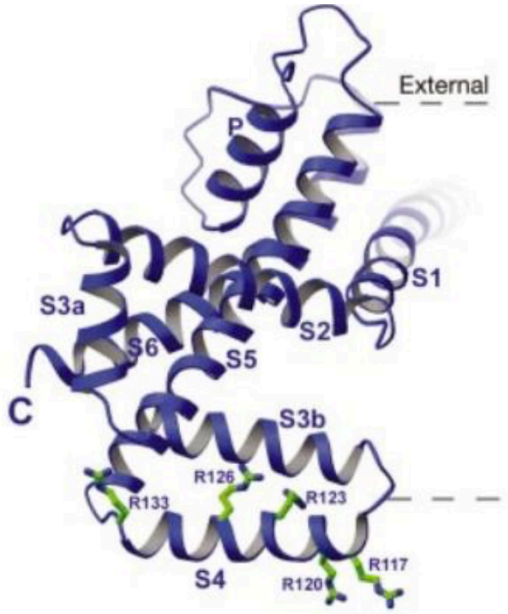
Ruiting Liu
Wipf Group
02/25/2017

Contents

- Retigabine analogs
  - Introduction to Retigabine and structrual modification
  - Synthesis of Retigabine analogs and biological results
- Enamide Oxidation towards Stemona alkaloids
  - Introduction to stemona alkaloids
  - Previous work
  - Proposal of enamide as common intermediate
  - Model study of tricyclic enamide
  - Synthesis of tricyclic enamide and the results of oxidation

Potassium Ion Channel

- Potassium ion channel are membrane proteins that allow rapid and selective flow of K+ ions across the cell membrane, and thus generate electrical signals in cells.
- Voltage-gated K+ channels (Kv channels), open and close upon changes in the transmembrane potential.



Structure of KvAP Voltage-Gated Potassium Ion Channel α-Subunit

Nature **2003**, 423 (6935), 33-41

KCNQ Channel

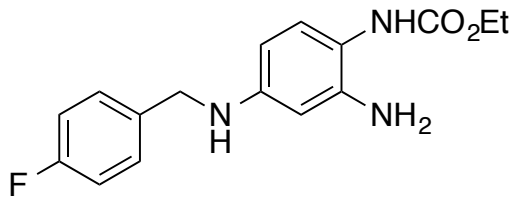
- KCNQ genes encode members of the Kv7 family of K+ channel subunits
- The KCNQ family comprises of five subunits (KCNQ1-5).
- In the nervous system, Kv7.2 to Kv7.5 form the α-subunits of the low-threshold voltage-gated potassium channel
- Most channels are comprised of Kv7.2 and Kv7.3 heteromeric or Kv7.2 homomeric subunits

Pharmacology & therapeutics 90(1): 1-19.
Neuron 53(5): 663-675

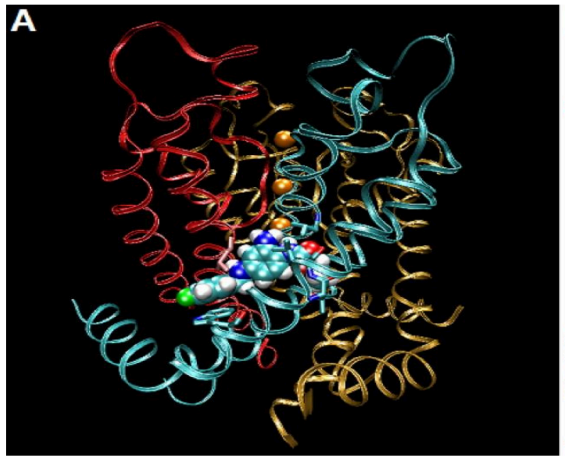
4

Retigabine

- Retigabine is the first potassium channel opener approved by FDA in 2011 for the treatment of partial-onset seizures.
- Recent reports have highlighted retigabine effectiveness in treatment of tinnitus



Retigabine

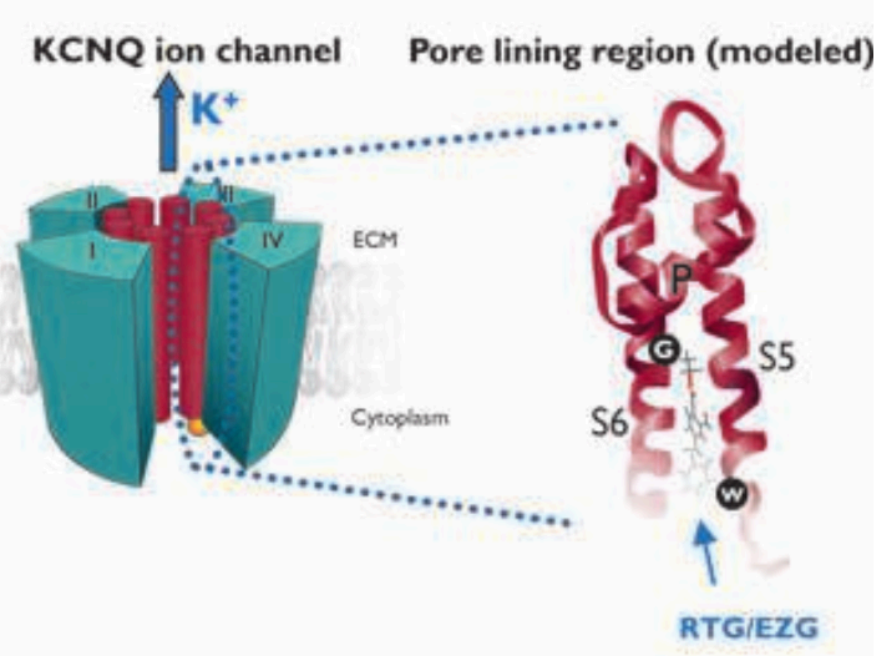


Three-Dimensional Model of Retigabine Docked to the Active Site of a Kv7.3 Domain

Mol. Pharmacol. **2009**, 75 (2), 272-280

Proc. Natl Acad. Sci. USA 110, 9980–9985 (2013).

- Activates all KCNQ2-5 channels
- Retigabine open these channels at more hyperpolarized potentials



Retigabine (RTG)/Ezogabine (EZG) at KCNQ2–5 channels

Epilepsia, 53(3):412–424, 2012

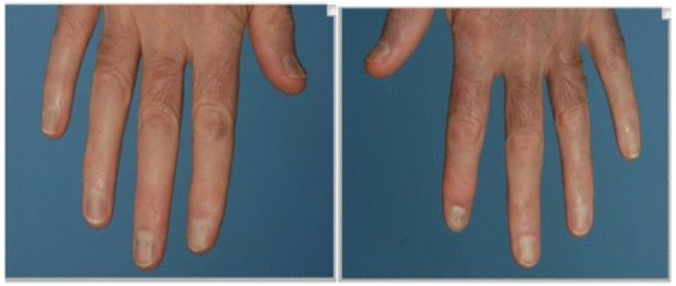
Adverse Effect of Retigabine

- Recent data showed severe side effects associated with retigabine, including urinary retention, blue skin discoloration and retinal abnormalities
- Non specific among KCNQ2-5
- KCNQ4 and KCNQ5 are not involved in the pathology of hyperexcitability-related disorders.
- KCNQ4 is the primary potassium channel in the smooth muscle of the bladder, where it regulates contractility

Expert opinion on drug discovery 8(11): 1429-1437

Adverse Effect of Retigabine

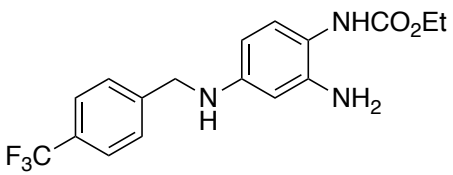
- Recent studies in rats have implicated pigmented dimerization products of retigabine in producing the discolouration



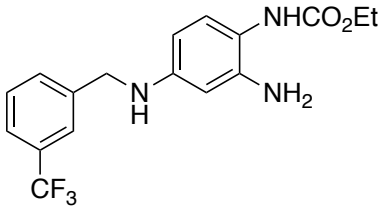
Purple/blue discolouration of the *left* and *right* nail beds of the hands

Epilepsy Curr, 15 (S1) (2015), pp. 339–340
BMC Oral Health. 2015; 15: 122.

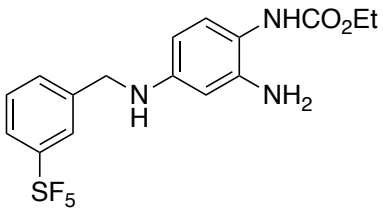
Previous Modification of Retigabine



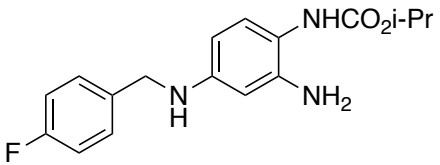
EC_{50} = 0.91 μM



EC_{50} = 0.74 μM

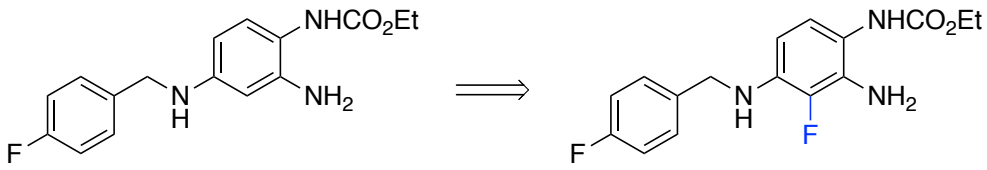


EC_{50} = 1.34 μM



EC_{50} = 1.48 μM

Table 1: KCNQ2/3 Current Shift EC50 of NR's Retigabine Analogs

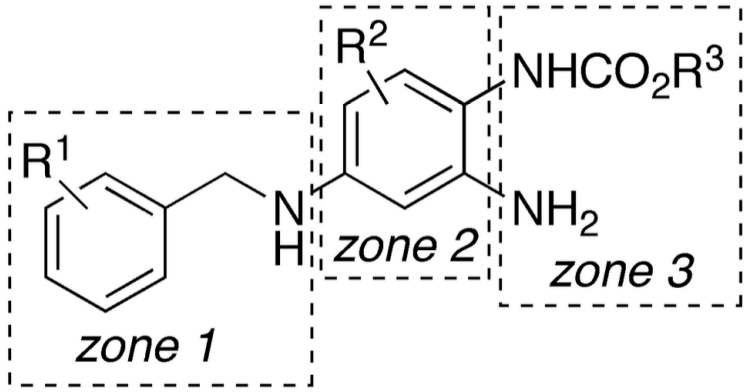


Retigabine
Ec_{50} = 3.3 μM

SF0034
Ec_{50} = 0.6 μM

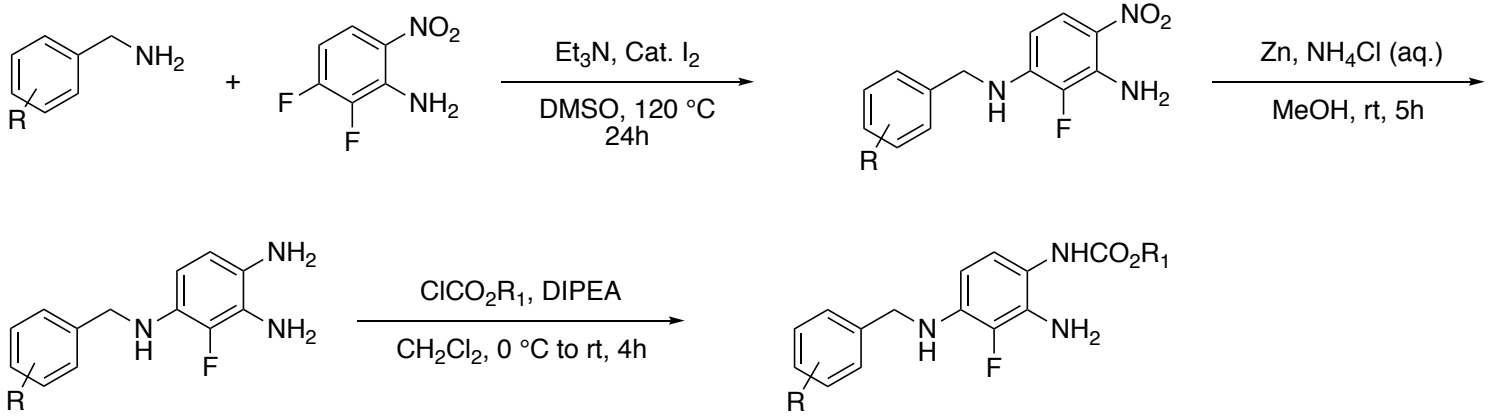
Mole Pharm, 2016, 89 (6) 667-677

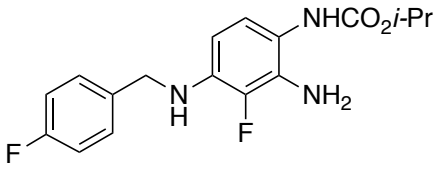
Selective KCNQ2/3 channel activators



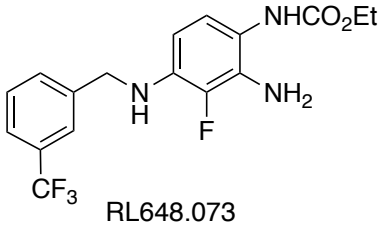
- Zone 1: incorporating a heteroaromatic group to probe the structure-activity relationship of retigabine
- Zone 2: introducing fluorine that might be responsible for the selectivity
- Zone 3: different carbamates to investigate steric relevance

Synthesis

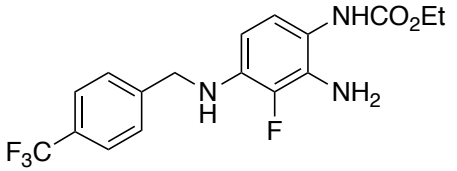




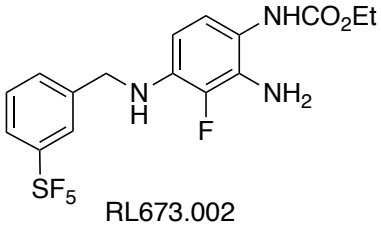
RL648.086
36%



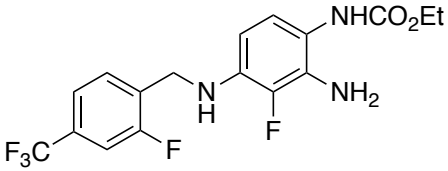
RL648.073
59%



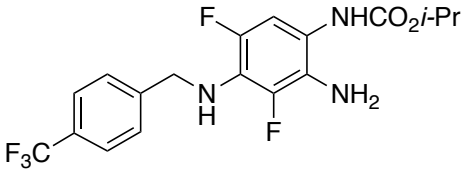
RL648.081
45%



RL673.002
30%

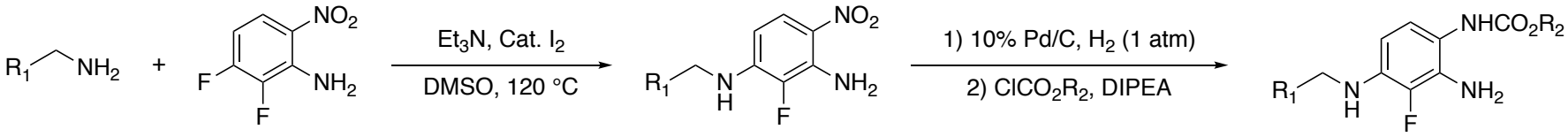


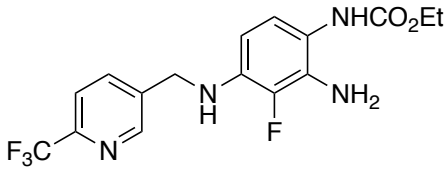
RL702.018
26%



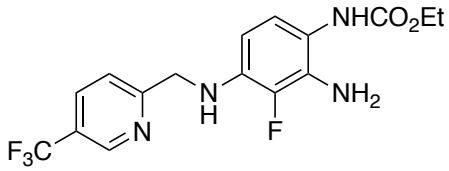
RL719.71
33%

Synthesis

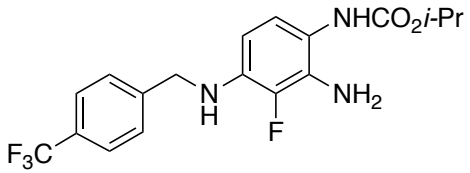




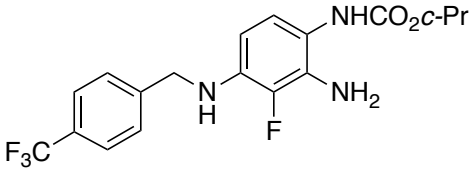
RL702.24
46%



RL702.31
32%

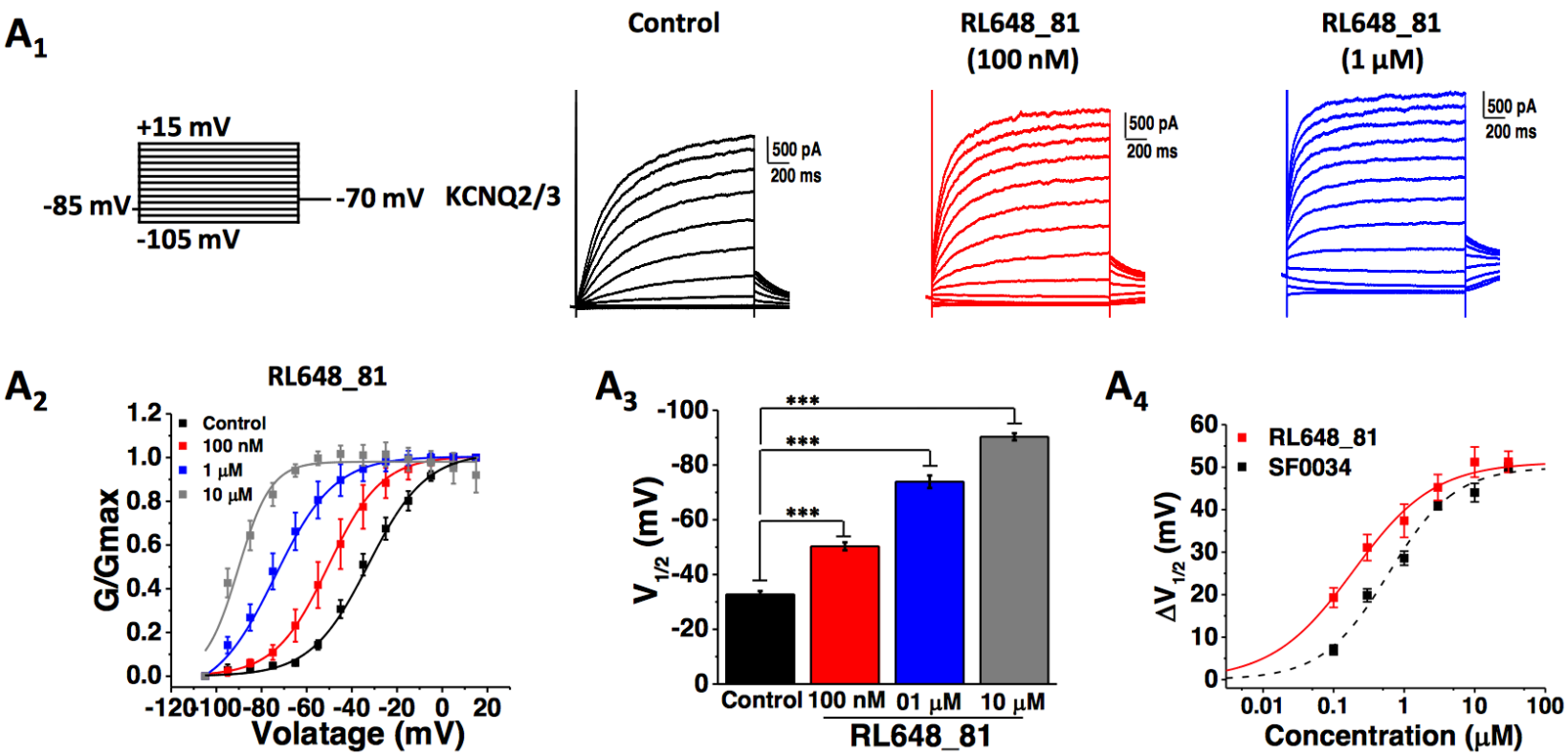


RL702.032
52%



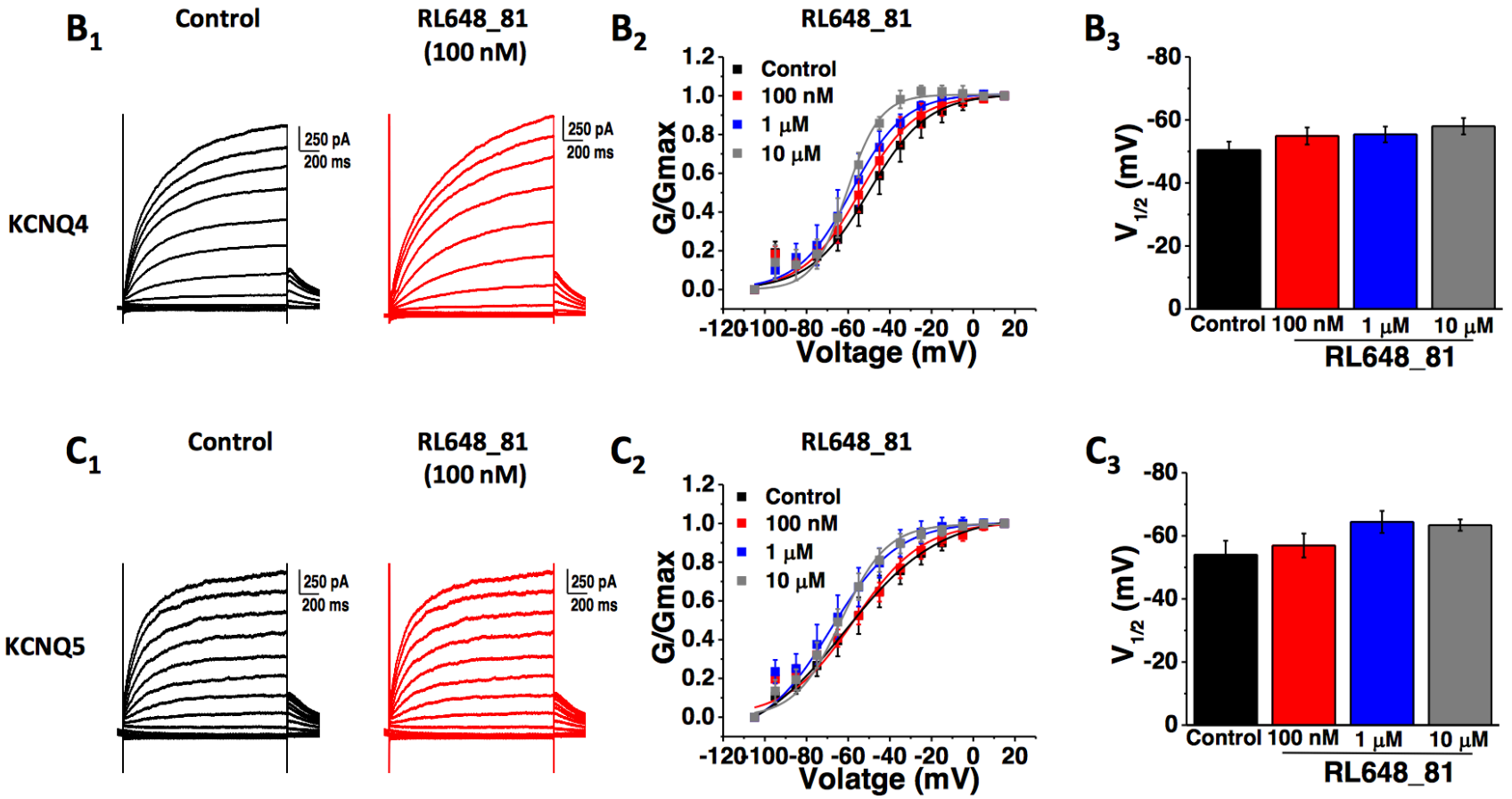
RL702.56
33%

Results



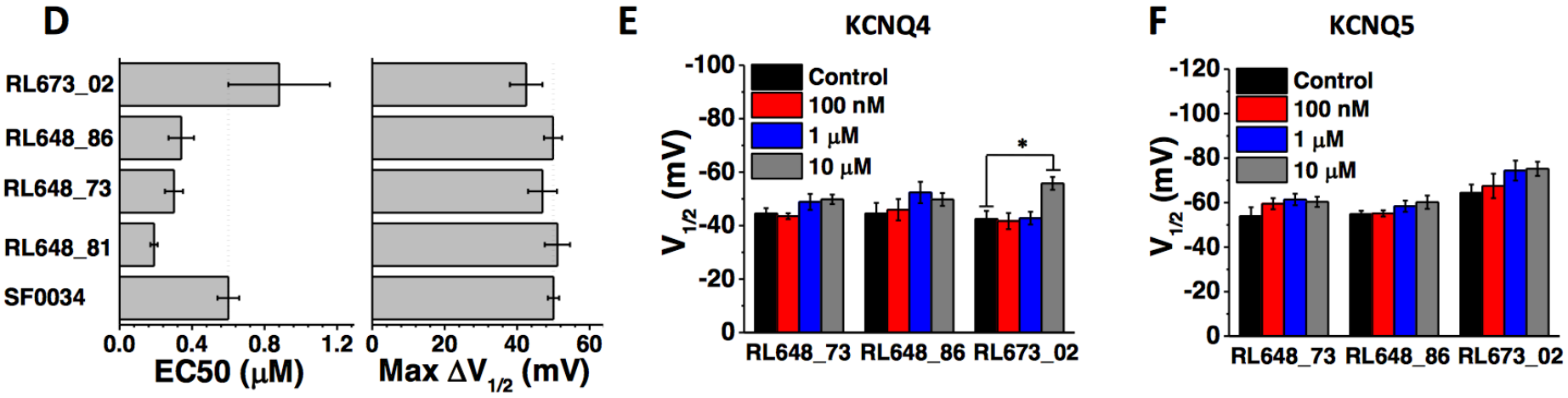
RL648_81 (EC_{50} 0.19 ± 0.02 μM, n=4-11; red)
SF0034 (EC_{50} 0.60 ± 0.06 μM, n=5-21; black)

Mol Pharm, 2016, 89 (6) 667-677



RL648_81 does not activate either KCNQ4 or KCNQ5

Results



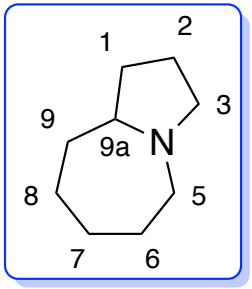
EC50 and maximal V1/2 values

Half activation (V1/2) of KCNQ4 currents calculated from normalized G-V Boltzmann curves in presence of 100 nM, 1 μM and 10 μM of RL648_73, RL648_86 and RL673_02

Conclusion

- Synthesized a series of retigabine analog
- RL648_81 is 15 times more potent than retigabine, selective towards KCNQ2/3 channel

Stemona Alkaloids

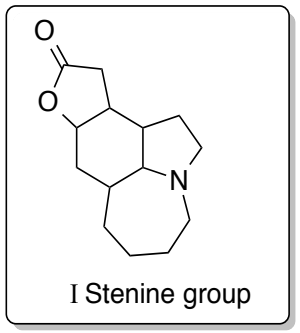


- Over 139 members were isolated from the Stemonaceae plant family, mostly featuring a pyrrolo [1,2-a] azepine

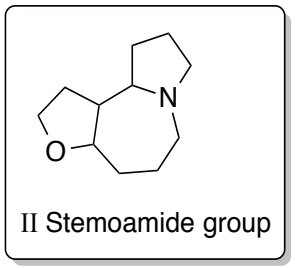
- The roots of those plants are claimed to have antituberculosis, antibacterial, antifungal and antihelmintic properties in traditional chinese medicine

Nat. Prod. Rep., **2010**, 1908

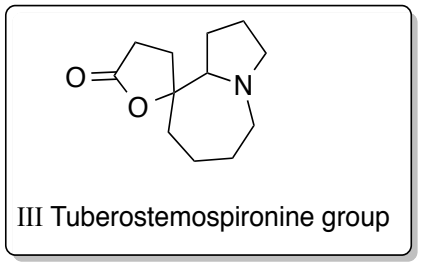
Structural Diversity and Classification



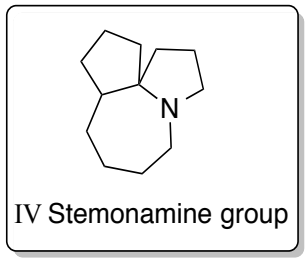
I Stenine group



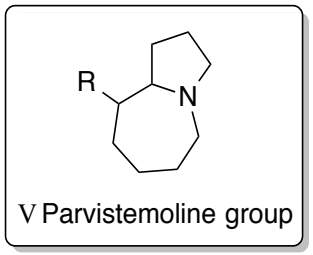
II Stemoamide group



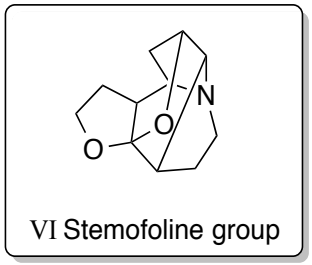
III Tuberostemospironine group



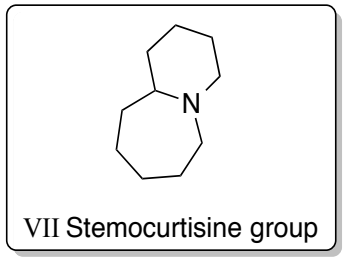
IV Stemonamine group



V Parvistemoline group

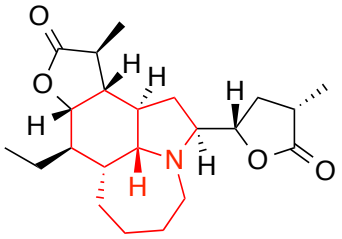


VI Stemofoline group

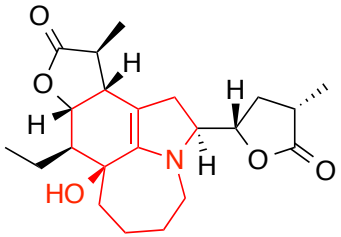


VII Stemocurtisine group

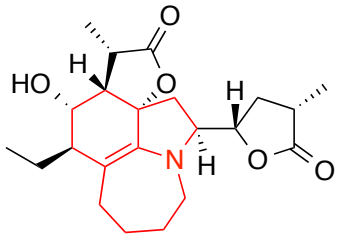
Structures of Interest



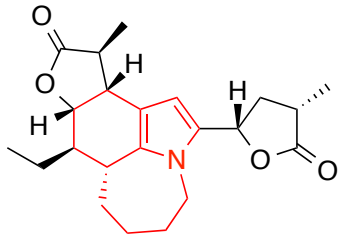
(-)-Tuberostemonine



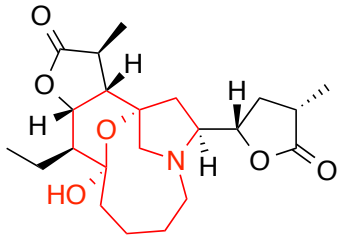
Tuberostemonol



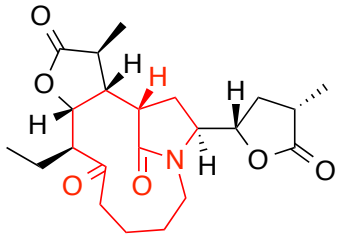
Oxotuberostemonine



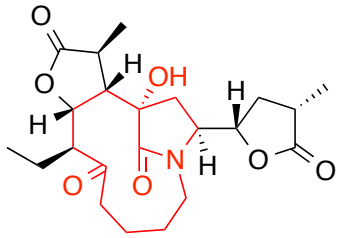
Didehydrotuberostemonine



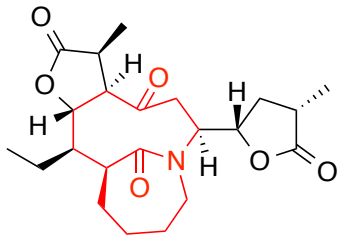
Sessifoliamide G



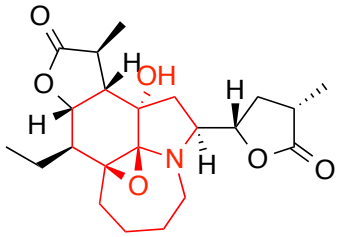
Sessifoliamide E



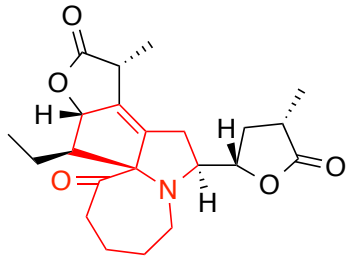
Tuberostemoline



Tuberostemonone

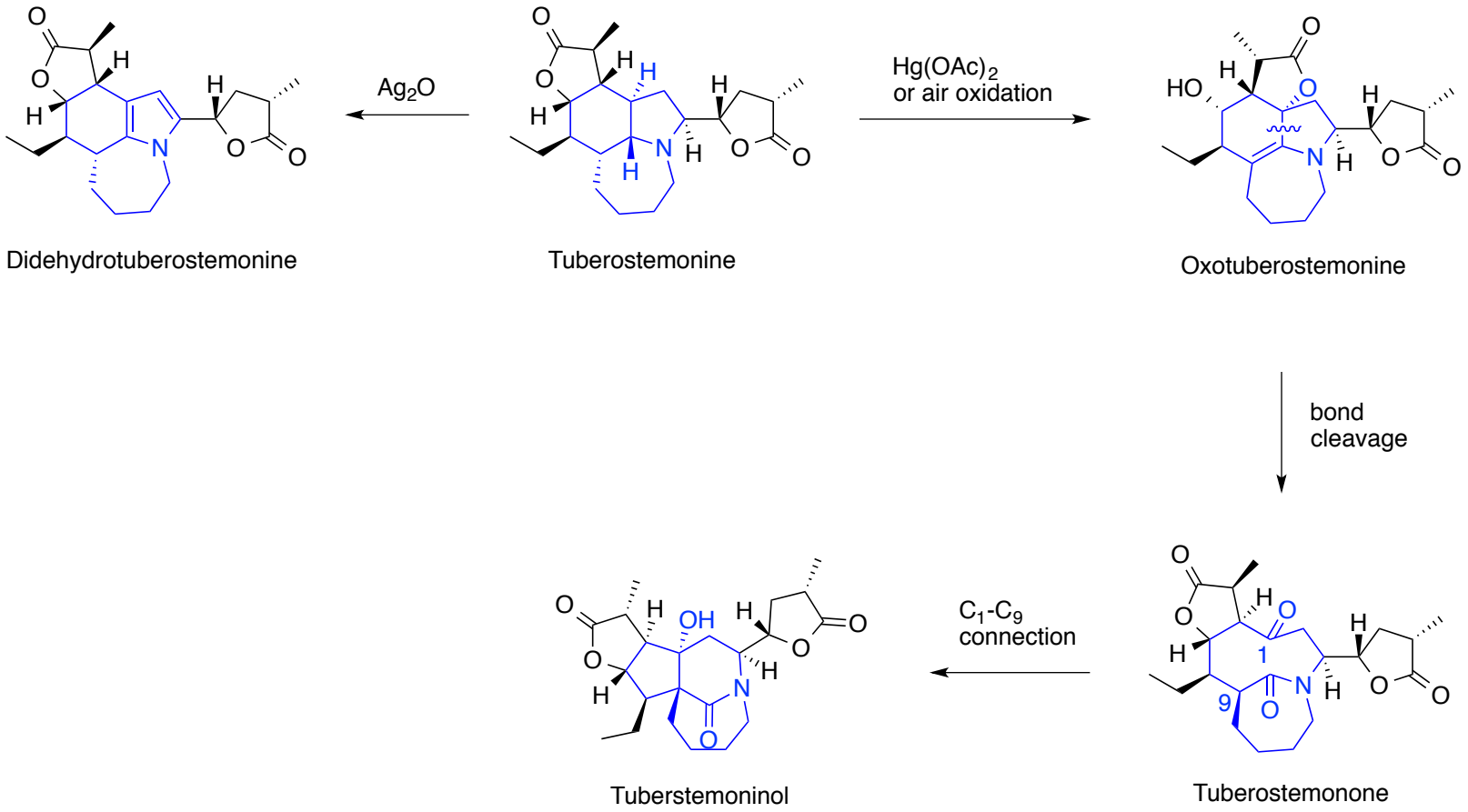


Epoxy-tuberostemonol



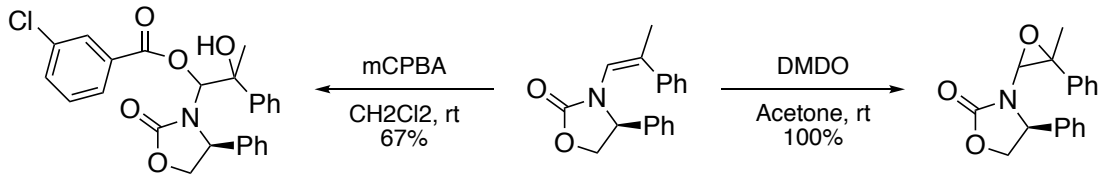
Neotuberostemoenone

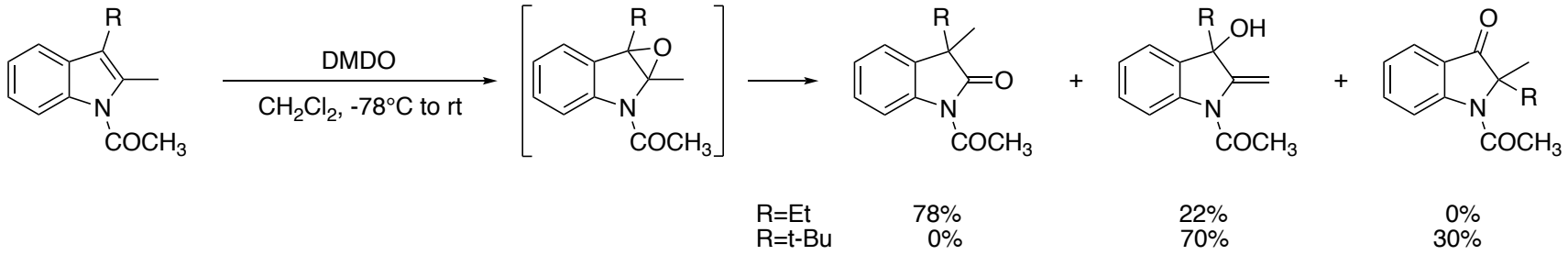
Proposed Biogenetic Relationship



Can. J. Chem. **1962**, 40, 455
J. Nat. Prod. **1992**, *55*, 571

Previous Studies of Indole/Enecarbamates Oxidation





R=Et	78%	22%	0%
R=t-Bu	0%	70%	30%

J. Org. Chem. **2004**, 1704
J. Am. Chem. Soc., **1993**, 8867

Acknowledgement

- Professor Peter Wipf
- Wipf group members (Past and present)
- Dr. Steve Geib
- Dr. Thanos Tzounopoulos