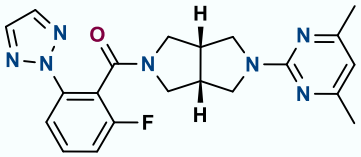
Seltorexant

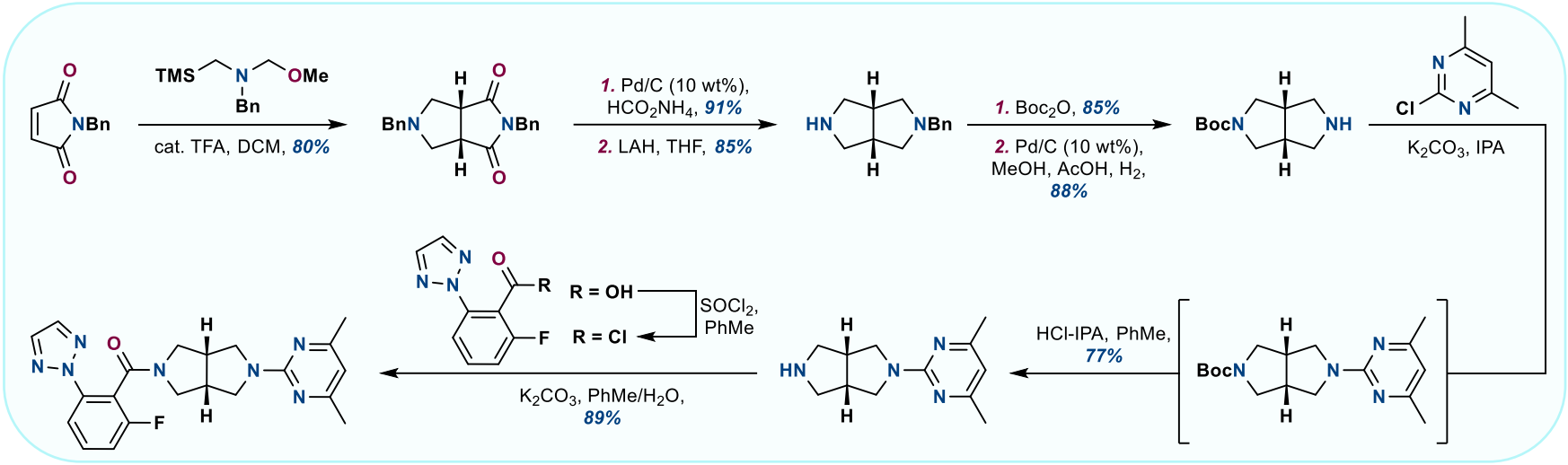
Introduction



Seltorexant

- *Seltorexant, otherwise known as* MIN-202 or JNJ-42847922, was developed by Janssen as am orally available treatment for Major Depressive Disorder (MDD) but has also shown promise as a treatment for insomnia.
- The drug works as a selective orexin-2 (2-SORA) antagonist, a key receptor in the brain which has been linked to the pathophysiology of this MDD.
- As of February 2022, the drug has been in phase III clinical trials for MDD and in phase 2 trials for insomnia.

First Generation Process Route for Early Clinical Studies:



Some Problems with the Route:

1. Four of eight steps are protecting group manipulations for three new bond formations
2. The fourth intermediate depicted was a low-melting solid and has stability issues where boc would come down over time
3. LAH reductions refluxing in THF are a serious safety concern

Notable Strengths of the Route:

1. The [3+2] reaction to build the bicyclic diamine core allowed rapid access to the skeleton and allowed the expensive coupling partner to be brought in late-stage

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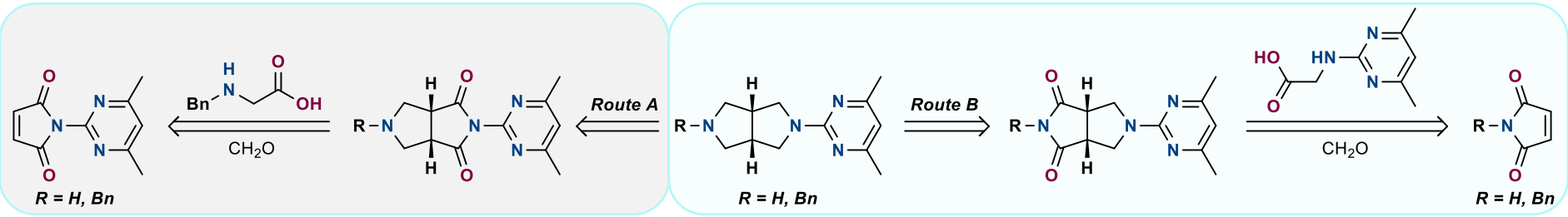
Explored Strategies to Synthesize the Central Fragment

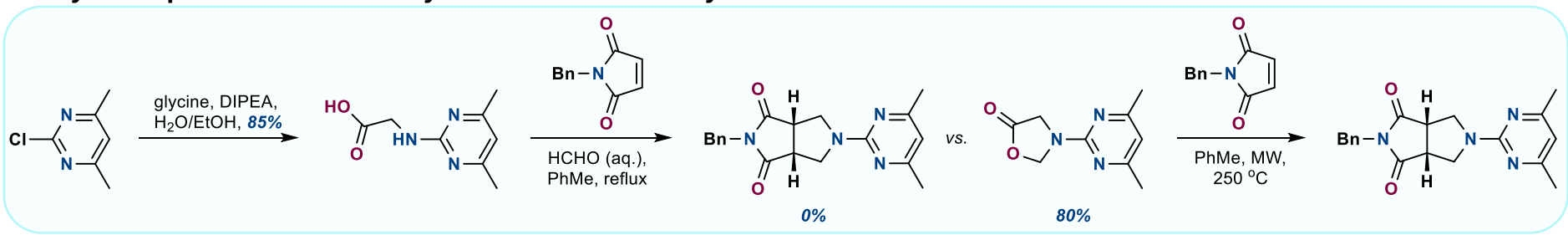


Starting Material Could Not Be Synthesized

Bringing in the pyrimidine early would prevent the need for arduous protecting group manipulation, thus both routes were explored. Route B proved to be the most fruitful

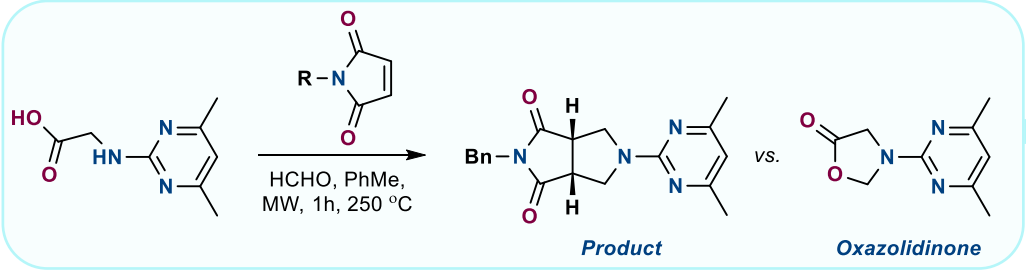
Readily Available

Early Attempts to Afford the Bicyclic Amine with the Pyrimidine Attached



In their efforts to perform the [3+2] cycloaddition, the Janssen team was exclusively isolating the condensation product, without observing any cycloaddition on this substrate. Several additives were screened, however, the oxazolidinone formed was unstable in many polar, protic solvents, and was labile under many acidic or basic conditions. Thus, a thermally induced cycloaddition was explored to overcome the higher activation energy required.

Screening [3+2] Conditions



Entry	Pyrrole-2,5,-dione (equiv.)	HCHO (equiv.)	PhMe (mL/g)	Pdt vs Oxazolidinone (in situ % yield)
1	R = Bn (1.5 equiv.)	1.5	16	Product (81%)
2	R = Bn (1.5 equiv.)	1.5	16	Product (84%)
3	**R = Bn (1.5 equiv.)**	**1.5**	**16**	**Product (91%)**
4	R = Bn (1.5 equiv.)	1.5	12	Product (69%)
5	R = Bn (1.5 equiv.)	1.5	8	Product (58%)
6	R = Bn (1.0 equiv.)	1.0	16	Product (71%)
7	R = H (1.5 equiv.)	1.5	16	Lactone (28%)
8	-	-	16	Lactone (45%)

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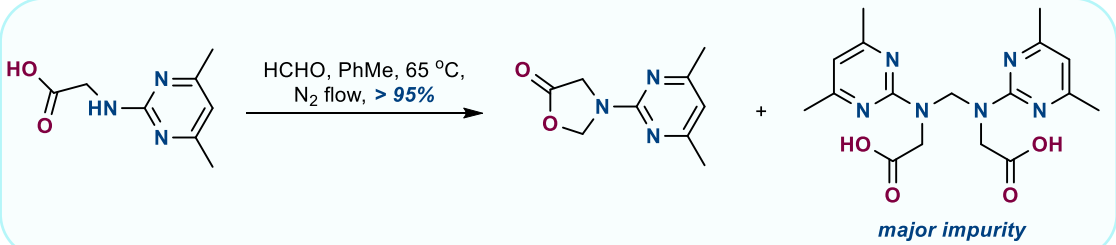
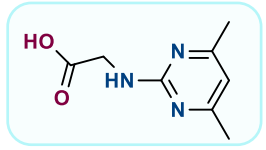
Optimized Conditions to Stepwise Form the Oxazolidinone



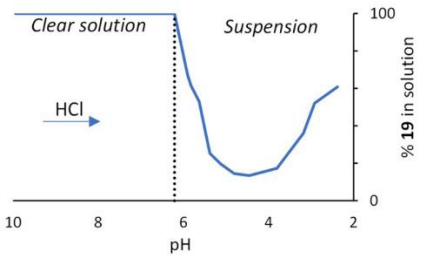
The oxazolidinone was unstable under the demanding thermal conditions due to the presence of water from the paraformaldehyde. To avoid heating excessively while still azeotroping off excess water, nitrogen flow was utilized to this end with excess HCHO.

Highlighting Some Crystallization Efforts

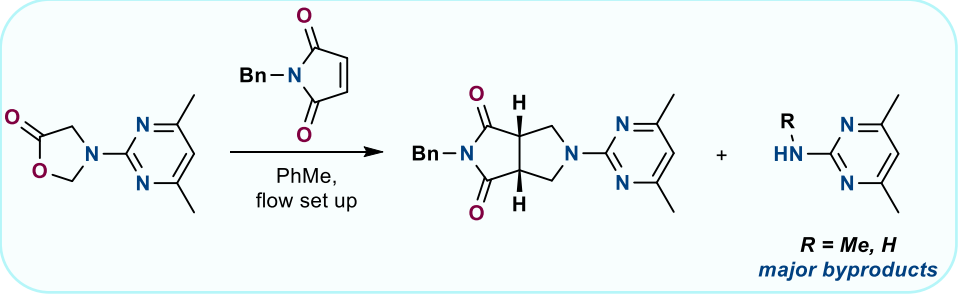


pH	Equiv. HCl	Purity (wt%)	Yield (%)
2.38	5.11	83.7	30.7
4.64	3.69	88.3	80.1
4.82	**3.41**	**97.5**	**85.9**

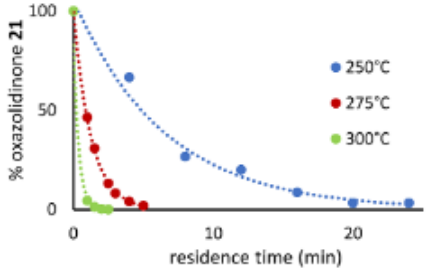
Closely monitoring the pH allowed a clean recrystallization from PhMe



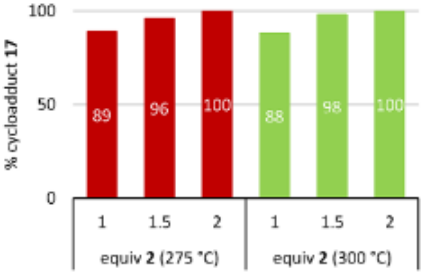
Performing this Transformation Utilizing a Flow Apparatus



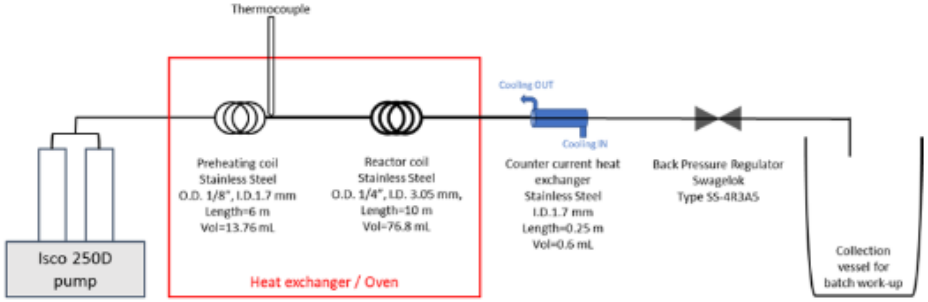
Residence Time at Various Temperatures



Cycloadduct Formation vs Equivalents of pyrrole-2,5-dione



Highlighting Some Crystallization Efforts



Highlighting Some Crystallization Efforts

Entry	Temp. (°C)	Time (min)	Pyrrole-2,5,-dione (equiv.)	Assay Yield (%)	Isolated Yield (%)	Assay of Isolated Pdt. (wt %)
1	275	6	1.25	92.1%	80.7	99.3
2	275	6	1.5	87.1	82.2	100.1
3	300	3.5	1.25	87.9	78.2	100
4	300	3.5	1.5	89.1	73.8	99.5

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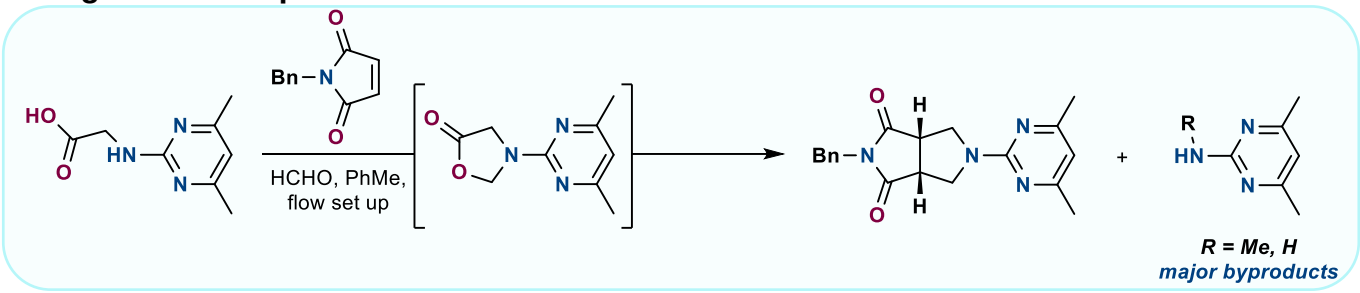
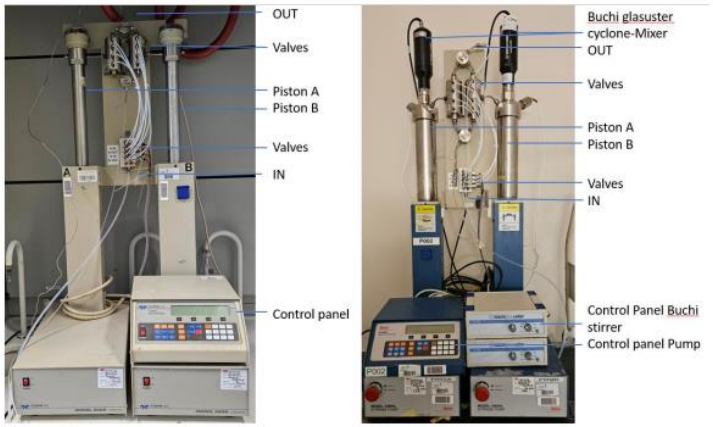
Optimizing the 2-Stage Flow Setup Process



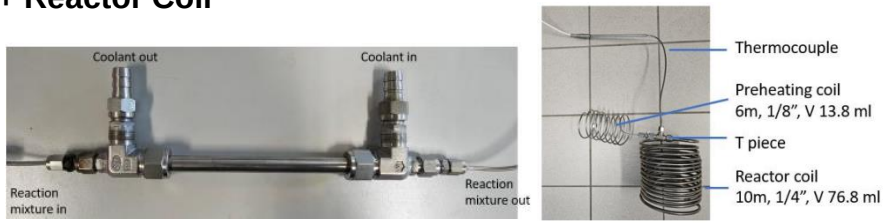
Entry	Temp. A (°C)	Residence Time (min)	Temp. B (°C)	Residence Time (min)	Composition of effluent (mol %) *Lactone : SM : Pdt : byproduct*
1	300	3.5	300	-	0.1 : 0.1 : 57.1 : 19.2
2	200	6	300	2.6	0.1 : 0.1 : 60.8 : 12.6
3	200	4	300	1.7	1 : 0.8 : 50.7 : 11.5
4	180	8	300	3.4	0 : 0: 54.2 : 11.2
5	180	6	300	2.6	0.2 : 0.2 : 54.9 : 15.9
6	180	4	300	1.7	1.1 : 2.9 : 42.0 : 13.9
7	160	8	300	3.4	0 : 0: 62.1 : 8.9
8	160	6	300	2.6	0 : 0 : 62.6 : 6.3
9	160	4	300	1.7	1.1 : 0.8 : 53.3 : 11.4

ISCO 250 D pump and ISCO 1000D pump with overhead magnetic stirring



The Heating Process

The Counter Current Heat Exchanger and Thermocouple + Reactor Coil



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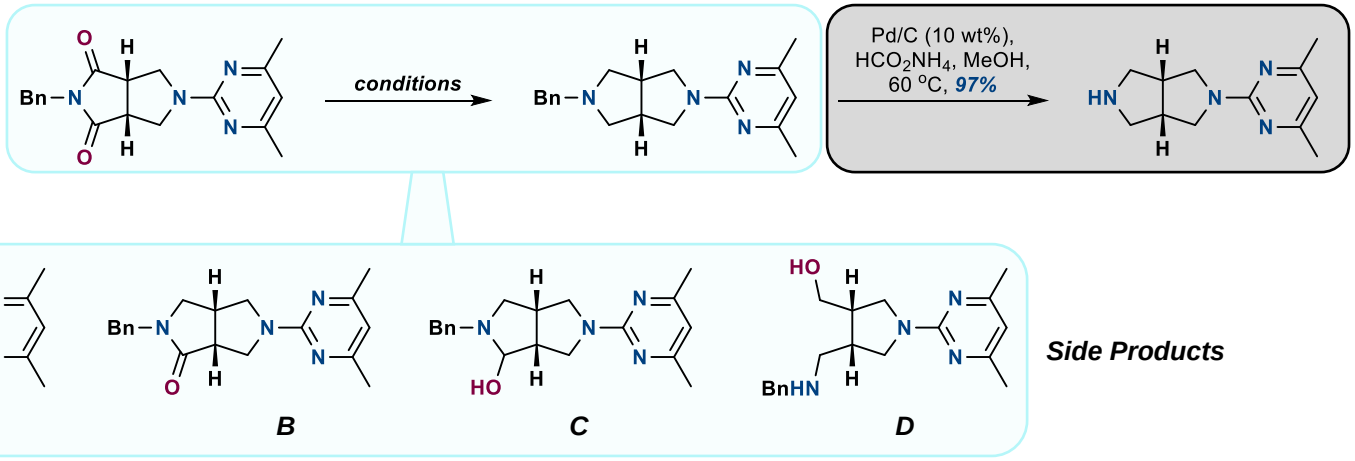
Optimization of the Reduction Protocol and Benzyl Deprotection



Entry	Conditions	Yield %	LC area % SM	LC area % A	LC area % B	LC area % C	LC area % D	LC area % others	LC area % Product
1	Red-Al (2.5 equiv.), PhMe, 60 °C	60	<0.1	1.0	<0.1	2.0	2.8	~1	93.5
2	$B(C_6F_5)_3$ (5 mol%), TMDS (5 equiv.), PhMe, 100 °C	95	<0.1	<0.1	<0.1	<0.1	<0.1	1.1	98.9
3	H_2PtCl_6 (4 mol%), PMHS (6 equiv.), PhMe, 100 °C	75	25.0	<0.1	<0.1	<0.1	<0.1	<0.1	74.8
4	**BH_3·THF (3 equiv.), THF, 10 °C**	**98**	**<0.1**	**<0.1**	**<0.1**	**<0.1**	**<0.1**	**0.8**	**99.0**
5	$NaBH_4$ (2.25 equiv.), BH_3·THF (3 equiv.), THF, 50 °C	91	<0.1	0.2	0.4	0.1	0.2	<0.1	98.9
6	$NaBH_4$ (4.2 equiv.), H_2SO_4 (2.1 equiv.) (3.1 equiv.), THF, 50 °C	82	<0.1	0.8	0.6	0.1	0.5	0.5	97.4

Final Coupling to Form Seltorexant