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Improving the Drug Antipyrine: Synthesis of N2-Aryl Analogs Through Oxidation of Dihydroantipyrines

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Synthesis of the Drug Antipyrine Analogs:

Modification of N2-Aryl Analogs through Oxidation of Dihydroantipyrines

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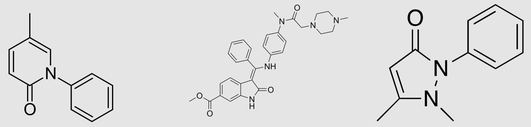
Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal disease characterized by lung remodeling. Antipyrine, a 5-membered pyrazolone ring including two nitrogens and a carbonyl, has been identified as an early-stage alternative lead drug candidate for improved treatment of IPF by collaborators at the Mayo Clinic. Our research group is pursuing synthesis of a library of antipyrine-analogs for improved IPF treatment.



Pirfenidone Nintedanib Antipyrine

Two current drugs (pirfenidone and nintedanib) lacking efficacy are utilized for clinical treatment shown above in comparison to antipyrine. The procedure used to modify existing analogs to add to the drug library are reported. The N2-phenyl group of antipyrine is replaced by more complex aryl groups to alter the electronic characteristics and size of the attachments. Variations in attachment groups allow for potential differences in drug binding to improve antipyrine as an alternative for IPF treatment.

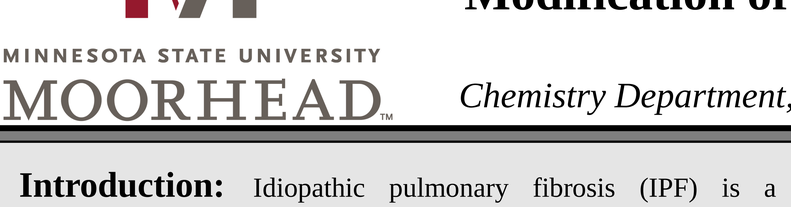


Figure 1: The diagram details the preparation utilized to synthesize the initial substrates used for this project. This process was carried out with CHEM 365 students from 2021, 2022, and 2023.

Analog Types

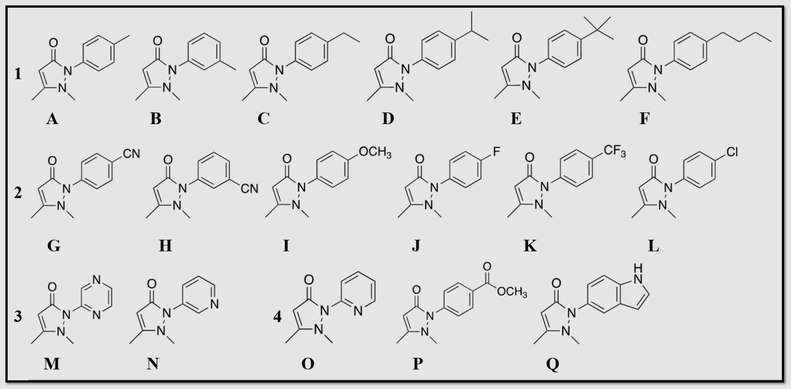


Figure 2: All 14 successful samples and the 3 unsuccessful samples are listed. Sections 1-4 represent different classes of functional groups added as R groups. Section 1 contains nonpolar alkyl additions, 2 contains hydrophilic halide and hydrogen bonding additions, 3 includes variations of the aromatic ring with nitrogen atoms added into the phenyl group, and 4 includes the three unsuccessfully converted analogs.

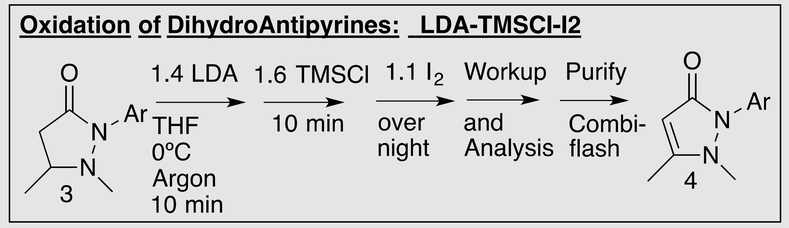


Figure 3: The procedure is represented above including relevant details of reagents, temperatures, mole ratios, and times required.

Table 1: The table includes relevant conversion data, final purity, molecular weight of the products, and the percent yield for all 17 samples tested. The gas chromatography mass spectrometry (GC/MS) machine was used to determine conversion and purity data. * represents unsuccessful trials.

Analog Type	Crude Ratio (P:SM from GC)	Final Purity (%)	Molecular Weight (g/mol)	Percent Yield (%)
A	79:15	100.0	202	63.2
B	92:3	99.2	202	37.0
C	89:5	100.0	216	59.4
D	96:4	98.2	230	40.4
E	96:2	100.0	244	43.7
F	90:6	100.0	244	75.8
G	98:2	100.0	213	60.9
H	91:5	100.0	213	67.9
I	68:30	97.9	218	20.6
J	95:5	94.7	206	49.5
K	96:2	100.0	256	58.2
L	76:15	100.0	222	45.6
M	45:24	98.8	190	3.9
N	68:31	88.9	189	24.5
O*	34:64	X	189	X
P*	4:91	X	246	X
Q*	1:99	X	227	X

Figure 4: The image includes all the successfully converted samples placed together to show differences in final appearance and state of matter of the products.

Figure 5: The picture to the right is purified sample E containing a solid crystal structure.

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Hypothetical Mechanism

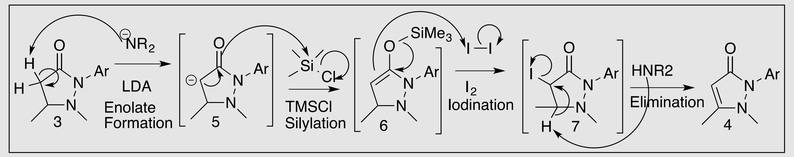
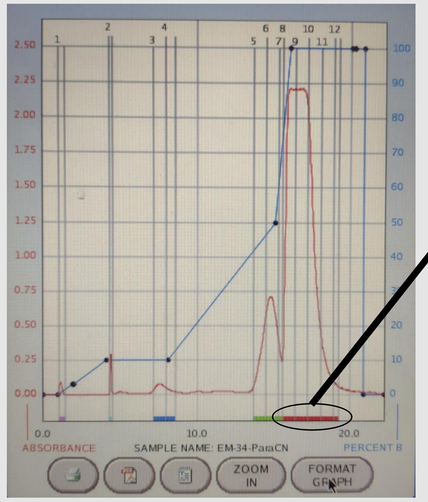


Figure 6: A proposed model for the conversion of antipyrine analogs from starting substrate to final product is shown. Standard arrow pushing mechanisms are illustrated using ChemDraw.



Combiflash

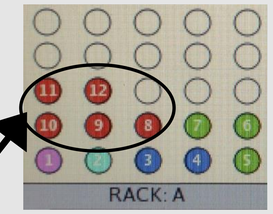


Figure 8: Test tube numbers correspond to the graph to the left where the red colored tubes are the purified desired product which are separated from the green colored starting material.

Figure 7: The images are taken from the combiflash chromatography system used to purify the samples. Sample G is presented in the graph where the red peaks represent different molecules, and the blue line represents the solvent ramp used. The solvent ramp consisted of hexanes (nonpolar) and isopropyl alcohol (polar) which was used to aid in the removal of product from the silica in the column.

Conclusions: The procedure used to modify existing antipyrine analog samples was successful in adding an alkene bond in fourteen of the seventeen attempted samples. Each of the successfully converted samples are novel molecules and were purified to around 90% or greater. This was verified using GC/MS and NMR data. Variations in product conversion success exist based on the nature of the R group attachment. Future considerations include repeating analog trials to see if variations in product conversion were due to chance or are reproducible.

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Unpublished work by prior students: Brent Schulte, Gael Shama, Lola Sibaud, Hawau Abdulsalam, Chem365 students for years 2021, 2022, and 2023.