Potential Celecoxib analogue precursors derived via Aldol condensation

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ABSTRACT

Various indanone compounds, 1-indanone and 1,3-indanedione specifically, have the potential to undergo Aldol condensations to form precursors to compounds structurally similar to the Non-Steroidal Anti-Inflammatory Drug (NSAID) CELEBREX (celecoxib). A series of potential analogous precursors in the form of alpha-beta unsaturated ketones have been developed. The conversion of these precursors into pyrazoline compounds was attempted. After oxidation of the pyrazoline compounds, they could potentially have biological activity by acting through CycloOxygense-2 (COX-2) in the same manner to CELEBREX.

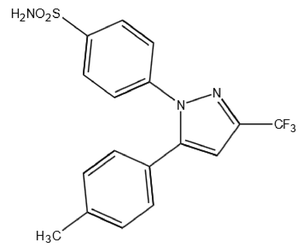
INTRODUCTION

The broader objective of this research was to produce equally viable or better performing analogs for the prescription drug CELEBREX. CELEBREX is in the NSAID class of medications, which are used to inhibit CycloOXygenase-2 (COX-2), a promoter of inflammation. CELEBREX is unique as it does not inhibit COX-1 as other NSAIDs do. COX-1 prevents the stomach from producing enough of a mucus coating to protect it from its digestive acids when traditional NSAIDs bind to it; this can lead to ulcers in long term use. Celecoxib is selective for COX-2 due to steric hindrance. Celecoxib's relatively large structure fits into the pocket in the channel for COX-2. COX-1 does not have this pocket in its channel, therefore, celecoxib cannot bind. This is due to the two enzymes being isoforms, which means that their channels share the same chemical structure, but differ in spatial orientation. Specifically, there is a conformational difference in one specific amino acid that creates the pocket in COX-2.

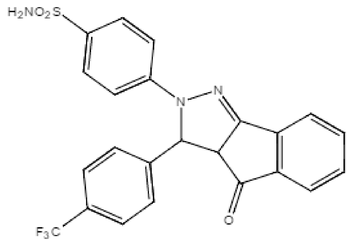
DISCUSSION

There has been modest success with these procedures in regard to percent yields, as they ranged between single digits to mid-eighties. When analyzing the *Gamma* compounds with Nuclear Magnetic Imaging (NMR), a reaction was deemed successful if, at minimum, robust aromatic peaks were present between six and eight ppm, and if the peaks for the aldehyde functional group (10-11 ppm) and hydrogen peaks for the carbon directly between the two carbonyls (~3.25 ppm) had disappeared. The criterion for infrared (IR) analysis of these compounds included rightward shift in the carbonyl region (around 1700 wavenumbers) due to increased conjugation of the product. Several compounds were deemed to have potential, but required further investigation. A few of the 1,3-indanedione compounds managed to produce desired results when reflux as added or when they were stirred for a longer period of time. Indanone compounds seemed to perform better when stirred for longer or adding a drying step over night after the vacuum filtration.

COMPOUNDS

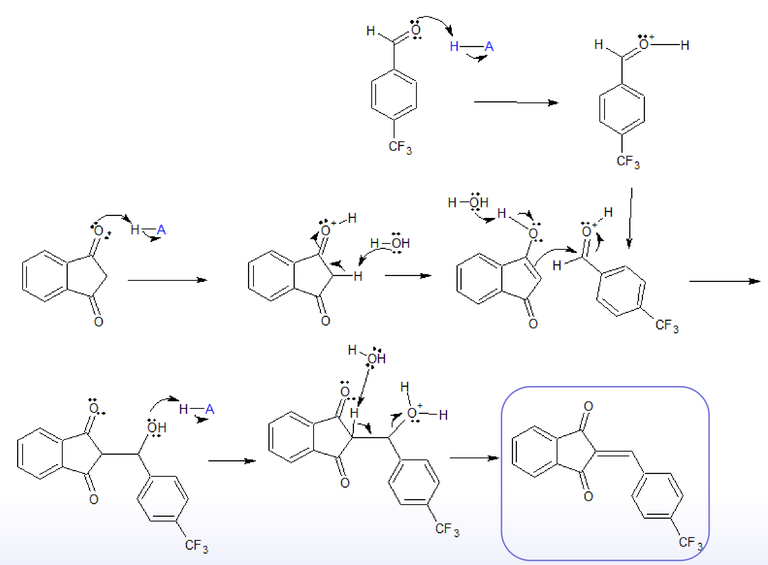


4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide
(CELEBREX)



4-(4-oxo-3-(4-(trifluoromethyl)phenyl)-3a,4-dihydroindeno[1,2-c]pyrazol-2(3H)-yl)benzenesulfonamide
(*Delta 1*)

POSSIBLE REACTION MECHANISM



Reactions mechanism for acid catalyzed Aldol condensation for with 1,3-indanedione and (4-(trifluoromethyl)-benzaldehyde to produce 2-(4-(trifluoromethyl)benzylidene)-1H-indene-1,3(2H)-dione
(*Gamma 1*)

NMR RESULTS

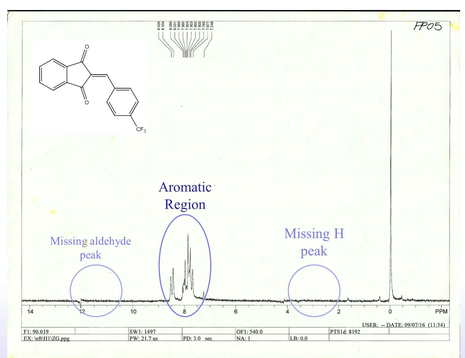
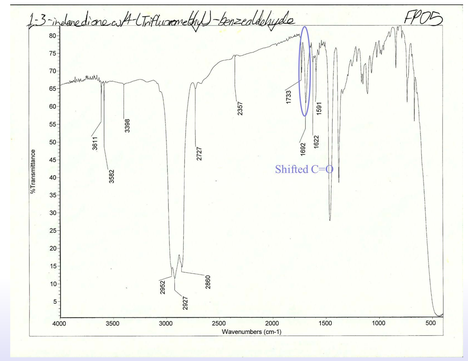


Table 1: Experimental versus Literature NMR Data for *Gamma* 1

Literature Values	Experimental Values
(d) 8.52	(d)8.48
(m) 8.08-8.02	(m)8.066-7.966
(s) 7.90	(s) 7.924
(m) 7.89-7.83	(m) 7.903-7.8
(d) 7.76	(d)7.721

IR RESULTS



MATERIALS & METHODS

Generation of *Gamma* Compounds

Acid Catalyzed Aldol Condensations

Combined 5.0 mmol equivalent 1,3-indanedione, 0.03 mol equivalent of L-proline, 1.1 mol equivalent benzaldehyde and 20 mL methanol with stir bar into a 50 mL round bottom flask. The reaction was stirred for ~6 days. The resulting mixture was vacuum filtered and washed with methanol.

Base Catalyzed Aldol Condensations

Combined 20.0 mmol equivalent 1-indanone, 20.0 equivalent benzaldehyde, and ~20 mL ethanol into 50 mL round bottom flask and stirred. 1M NaOH was added drop wise until a cream colored, semisolid precipitate formed. The mixture was cooled in an ice bath for 30 minutes. The resulting mixture was vacuum filtered and washed with cold methanol.

Generation of *Delta* Compounds

Forming an Imine to Produce a Ring Closure

Added 16 mmol equivalent *Gamma* compound, 17.6 mmol equivalent 4-SAPH.HCl, and ~8-9 mL ethanol to 25 mL round bottom flask. The mixture was refluxed for 4 hours with stirring. After cooling to room temperature, the mixture was vacuum filtered.

REFERENCES

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2. Lee, C.-J., *et al.* "Direct B-acylation of 2-Arylidene-1,3-indandiones with acyl chlorides catalyzed by organophosphanes." *Chemical Communications* **2014**, *50* (40), 5304-5406.
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