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Development, Synthesis, Characterization of Triptan and Dihydro Pyridine Heterocycles and Their Applications

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ABSTRACT

Twelve derivatives of Triptan family were identified, process application and their origin in manufacturing process of NSAID drug, were synthesized and characterized. Their structures were verified by synthesis and comparison with the spectral evaluation. Synthesis of dihydro pyridine derivatives, their application and cytotoxic effect is discussed.

Keywords: Etodolac; S-Etodolac; R-Etodolac anti-inflammatory activity; Nonsteroidal anti-inflammatory drugs; Characterization; Amlodipine; Lercanidipine; Nicardipine; Nifedipine

INTRODUCTION

Triptan family Etodolac is used as Nonsteroidal Anti-Inflammatory Drug (NSAID) and it got approval by the USFDA in January 1991. This category drugs are used as painkiller, antipyretic and for inflammation. They are acting for prostaglandins level reduction. Prostaglandin is responsible for pain, fever and tenderness that occur with inflammation. Etodolac blocks the Cyclooxygenase (COX) enzymes which result in decreasing concentrations of prostaglandins and which result in inflammation, pain and fever are reduced gradually.

Research studies were demonstrated activity of etodolac and celecoxib shows selectivity towards inhibition of cyclooxygenase COX-2. Both etodolac and celecoxib can inhibit COX-1 and are known as more selective towards COX-2. Now a days in study r-enantiomer of etodolac shown inhibition of beta-catenin levels in hepatoma cells. Etodolac is approved for the treatment of inflammation and pain caused by osteoarthritis and rheumatoid arthritis.

Intake of etodolac should be avoided by such patients those are having asthma, hives, other allergic reactions with NSAIDs. In addition, it should be avoided by patients having peptic ulcer disease or kidney function, possibly this medication can worsen these conditions. Patients those are undergoing blood thinning medications (anticoagulants), such as warfarin (Coumadin), should take special precautions because it increases the risk of bleeding. Additionally, it is known that etodolac may interact with certain anti-depressant medications, such as sertraline or fluoxetine. Possibly it can increase risks of stroke, heart attack and other cardiovascular conditions. Its usage in children has not been adequately studied. Etodolac is not habit-forming. Before going to surgery intake of NSAID should be discontinued at least 4 days in advance to avoid mild interference with clotting [1-3].

MATERIALS AND METHODS

Triptan derivatives

An equimolar mixture of substituted tryptophol and 1,3-dicarbonyl compound was allowed to stir at 0°C in IPA: Toluene solvent mixture. Catalytic amount of sulfuric acid was added slowly at 0°C in 30 mins. Then ice-cold water and standard extractive workup give corresponding ester compound. Those esters are upon basic hydrolysis gives corresponding acid compounds. Instead of catalytic sulfuric acid one can use IPA. HCl or methanolic HCl to get the same results (Figure 1). Possible origin of compound J, compound L and dimer compound I may be as per reaction Figures as follows:

Synthesis of compound J

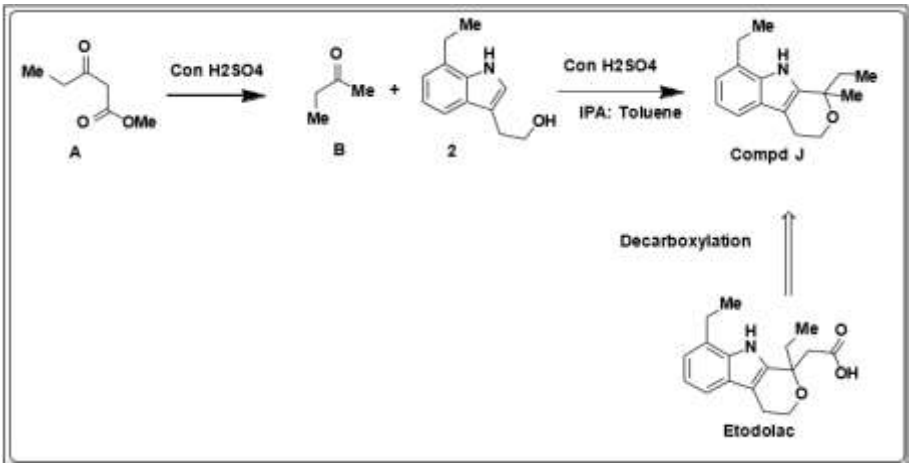

Figure 1: Synthesis of compound 1,8-diethyl-1-methyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indole.

Acid catalyzed decarboxylation of beta keto esters A in corresponding keto compounds B is known to us. From keto compound (B) and corresponding tryptophol (2) to compound J synthesis can be achieved straight forward. Synthesis of compound J from commercially available Etodolac is very difficult as there is no driving force for decarboxylation in API molecule structure. Independently compound J was synthesized using (2.0 g, 0.01 mole) of tryptophol (2), (0.76 g, 0.01 mole) of 2-butanone (B) was stirred in IPA: Toluene (20 mL) at 0°C. To this solution 2 mL conc sulfuric acid was added drop wise and stirred for 30 mins.

Added 50 mL ice cold water and extracted with (50 mL × 3) ethyl acetate, combined organic layer dried over sodium sulfate and evaporated to get crude rection mass, which was purified using flash column chromatography (100-200 mesh silica gel) and Pet ether: Ethyl acetate mobile phase system to get pure white solid compound. Yield=1.4 g, 98% pure. Melting range- 90.8oC, FTIR (cm^{-1}): 3414 (N-H), 2933-2926 (aliphatic), 1462, 1367, 1300 (aliphatic bending), 1076 (asymmetric stretching), 792,752 (aromatic bending),^{1}H NMR ($CDCl_3$): δ 7.41 (s, N-H), 7.29-7.27 (d, 1H), 7.02-6.93 (dd, 2H), 4.01-3.9 (dd, 2H), 2.79-2.72 (m, 3H), 2.68-2.62 (m, 1H), 1.84-1.72 (m, 2H), 1.45 (s, 3H), 1.31-1.26 (t, 3H), Mass: [M+H]=244.1 (Figure 2) [4-6].

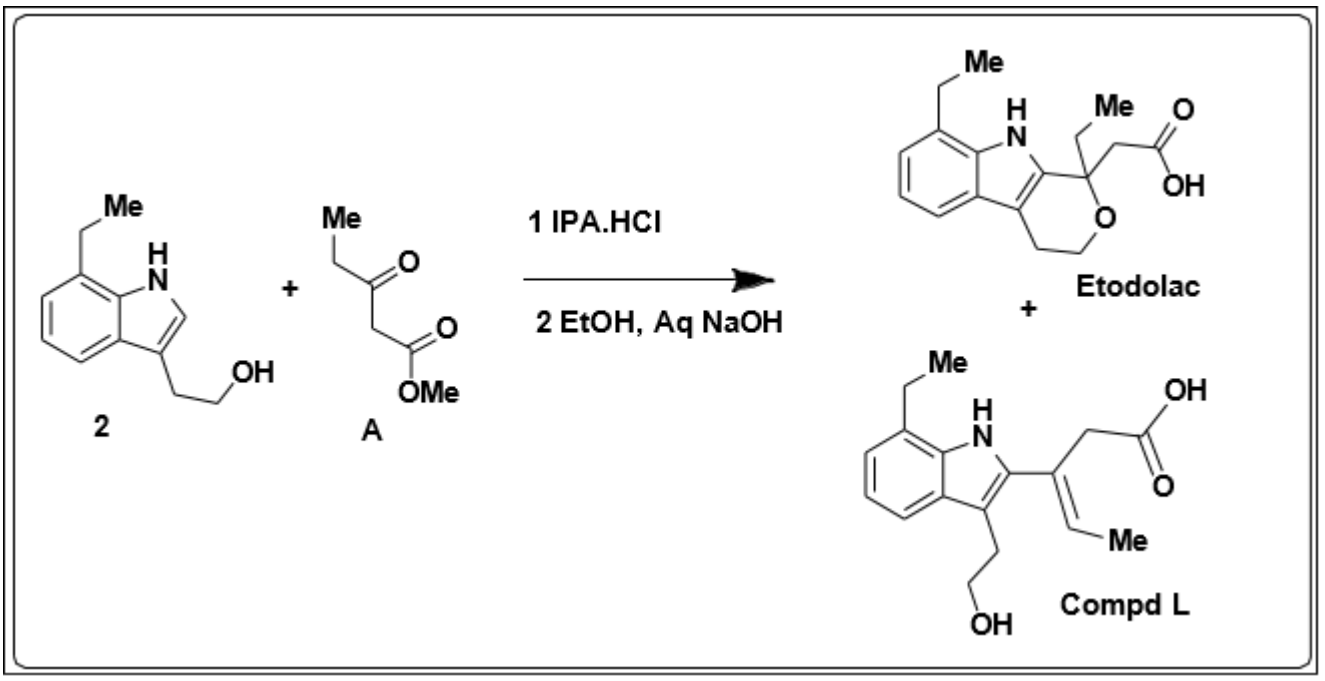

Figure 2: Synthesis of compound L: 3-[7-ethyl-3-(2-hydroxy-ethyl)-1H-indol-2-yl]-pent-3-enoic acid.

An equimolar mixture of (5.0 g, 0.026 mole) tryptophol (2), (3.4 g, 0.026 mole) of keto compound (A) in 50 mL of IPA. HCl was stirred at ambient temperature for 18 hrs. The reaction progress was monitored by TLC or HPLC. After complete conversi on, it was evaporated and 50mL of ethanol was added. The hydrolysis of the reaction is continued in aq NaOH (2.11 g in 5 mL water). The same reaction mixture is stirred for 4-5 hrs.

After complete ester hydrolysis, it is evaporated and made pH acidic using dilute hydrochloric acid. Standard extractive procedure gave mixture of API and compound L. Above crude reaction mass is purified using flash chromatography (100-200 mesh silica gel, pet ether: ethyl acetate) to get pure compound L. Yield=0.4 g, 95% pure. Melting range-146.8°C, FTIR (cm^{-1}): 3377 (N-H, O-H, -COOH), 2933-2926 (aliphatic C-H), 1678(-COOH), 1462, 1367, 1300 (aliphatic bending), 1076 (asymmetric stretching), 792,752 (aromatic bending), ^{1}H NMR (DMSO-d6): δ 12.2 (bs, 1H), 10.5 (s, 1H), 7.32-7.26 (dd, 1H), 6.95-6.84 (m, 2H), 6.0 (m, 1H), 4.75 (s, 1H), 3.6 (t, 5H), 2.8 (m, 5H), 1.8 (d, 3H), 1.2 (t, 5H). Mass: [M+H]+=288.4.

Compound L is an intermediate in the process. One can conclude it is formed during API synthesis and before Michael addition step. Possible origin of compound I in process is as Figure below (Figure 3) [7-9].

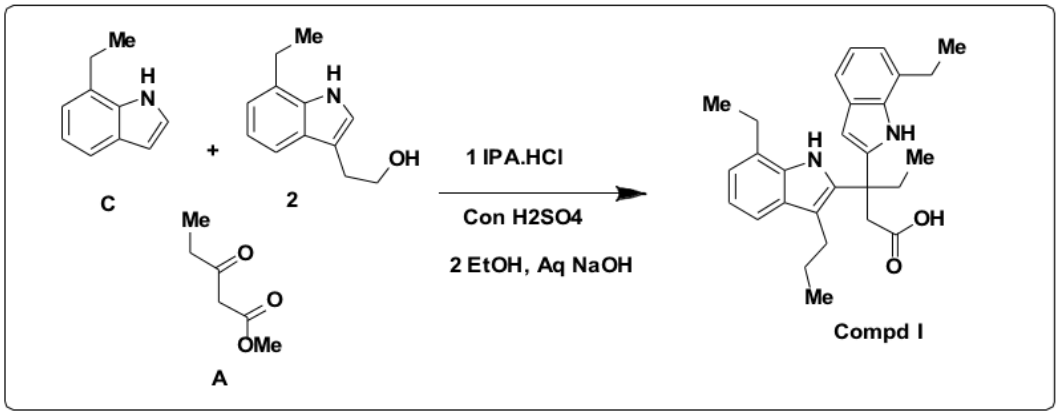

Figure 3: Synthesis of compound I: 3-[7ethyl-3-(2-hydroxy-ethyl)-1H-indol-2-yl]-3-(7-ethyl-1H-indol-3-yl)-pentanoic.

Synthesis of compound I independently by using an equimolar mixture of commercially available (0.7 g, 0.005 mole) 7-ethyl indole (C), (1.0 g, 0.005 mole) of tryptophol (2) and (0.7 g, 0.005 mole) of keto compound (A) was stirred in 10mL IPA: Toluene (1:1) at 0°C. To this mixture catalytic amount of Conc. H_2SO_4 was added (Figures 4 and 5).

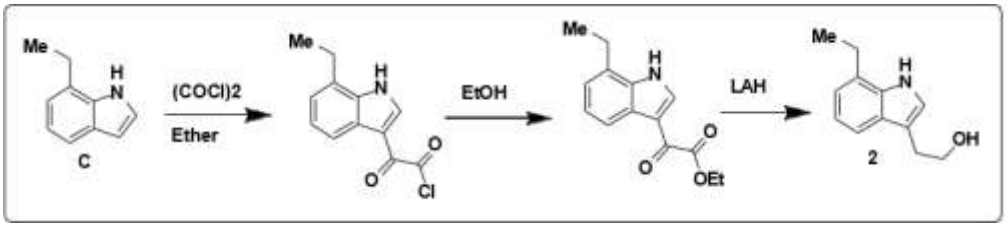

Figure 4: Compound H (R1= $-CH_2-CH_3$).

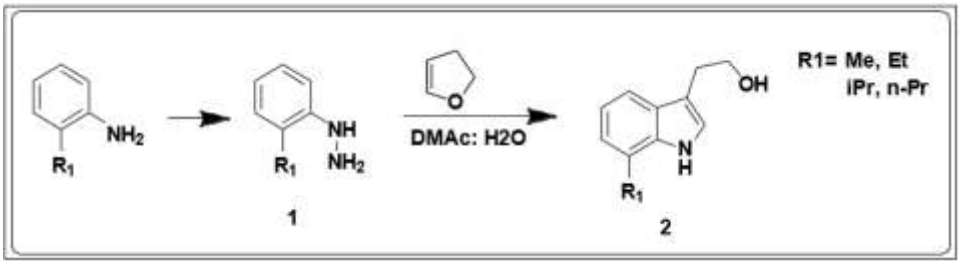

Figure 5: Reaction scheme for key intermediate compound 2

RESULTS AND DISCUSSION

Representative procedure

Step- I: Synthesis of (2-Isopropyl-phenyl)-hydrazine4: To a stirred solution of conc. hydrochloric acid (36%, 40 mL) and 2-isopropyl aniline (8 g, 59.2 mol). A solution of sodium nitrite (4.2 g, 60.9 mol) in 20 mL of water was added dropwise in 1 hr. After an additional 15 min 30.0 g of stannous chloride ($2H_2O$) in 30 mL of hydrochloric acid added gradually (2 hr). The same reaction continued for an additional 1 hr and solid was filtered and dried. It was made basic using 50% aq. sodium hydroxide and extracted in ether. The combined ether layer was dried over sodium sulphate and evaporated to get tan solid (Yield=7.7 g, 86.3%). It was stirred in methanolic HCl or IPA HCl and evaporated to get (2-Isopropyl-phenyl)-hydrazine hydrochloride compound. Similarly, other R1= $-CH_3$, $-CH_2-CH_3$ and $-CH_2-CH_2-CH_3$ hydrazine hydrochlorides are prepared.

Step II: Synthesis of 2-(7-isopropyl-1H-indol-3-yl)-ethanol3: In a stirred solution of above compound (2-isopropyl-phenyl)-hydrazine hydrochloride (4.0 g, 0.02 mole), 100mL DMAc: H_2O (1:1) and 2 mL concentrated sulfuric acid heated at 90°C. Then added (1.5 g, 0.02 mole) 2,3-dihydrofuran drop wise at 90°C. Around 3-4 hr will require for completion of reaction. It was monitored by TLC [10-12].

After completion of the reaction, it was cooled to room temperature and was made pH basic using aqueous sodium bicarbonate and it was extracted with ethyl acetate (50 mL × 3). Separated organic layer was washed with brine and dried over sodium sulphate. After solvent evaporation got title compound 2-(7-isopropyl-1H-indol-3yl)-ethanol (2.0 g, 65%). Similarly, other R1=$-CH_3$, $-CH_2-CH_3$ and $-CH_2-CH_2-CH_3$ compounds are prepared. The origin of compound H is a tryptophol and it is processing related intermediate. It is carried forwarded in trace amount from step I of condensation with keto compound.

Melting range: 51.1°C, FTIR (cm^{-1}): 3404-3257(N-H, O-H), 2933-2926 (aliphatic C-H), 1462, 1367, 1300 (aliphatic bending), 1076 (asymmetric stretching), 792,752 (aromatic bending),1HNMR ($CDCl_3$): δ 8.0 (bs, N-H), 7.41 (d, 1H), 6.9-7.1 (dd, 3H), 3.8-3.9 (m, 2H), 2.95-3.0 (t, 2H), 2.9-2.75 (dd, 2H), 1.5 (t, 1H), 1.25-1.30 (t, 3H). Mass: [M+H]+=190.4.

The rest eight compounds are formed from either tryptophol (2) and keto compounds containing those corresponding substituted starting materials in traces amounts [13-15].

Identification of origin and synthesis of triptan derivatives

As per reported in literature chem comm. 47(39),11143-11145,2011 and Chemische Berichte 118(10),4073-85,1985, synthesis of keto compound (A) involves 2-butanone may contaminate corresponding carbonyl compounds are responsible for the formation of compound C, compound F and compound G or corresponding alkyl halide is contaminated in ethyl iodide which upon Grignard reaction leads formation of corresponding keto compounds and compound C, compound F and compound G (Figure 6).

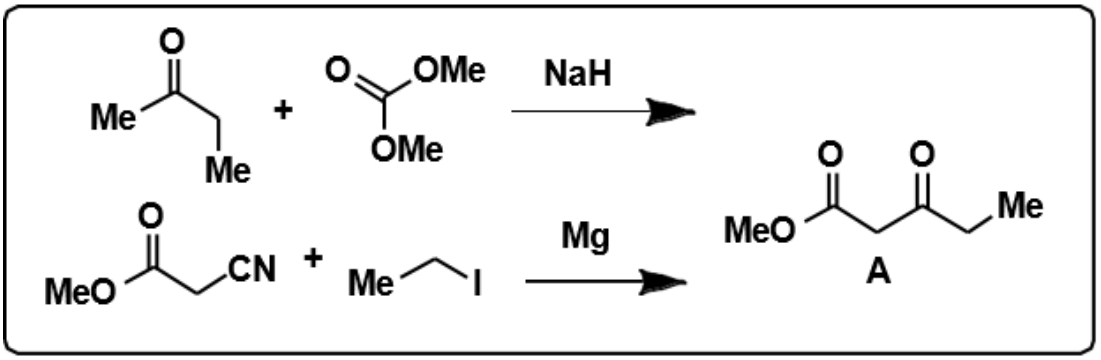

Figure 6: Reaction scheme for compound A.

And tryptophol is responsible for the formation of compounds A, B, D and E. They may be formed due to the presence of corresponding amines in the starting material 2-ethyl aniline, which may carry forwarded to corresponding impurities (Figures 7 and 8, Table 1).

General synthetic scheme for triptan derivatives

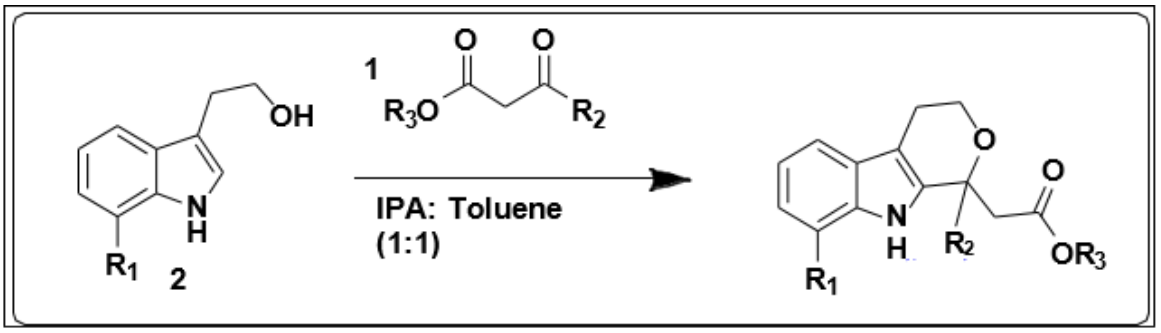

Figure 7: General synthetic scheme for triptan derivatives.

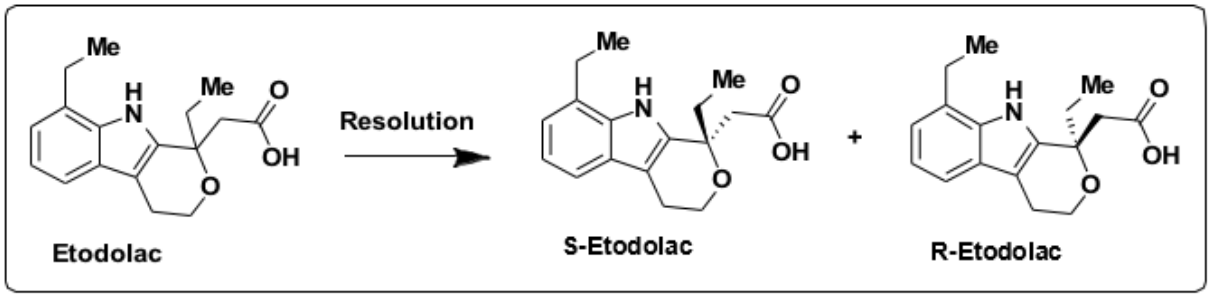

Figure 8: General synthetic scheme for triptan derivatives.

Table 1: Yield and labeling of etodolac derivatives.

S. No	R1	R2	R3	Yield (%)	Compounds
1	H	$-CH_2CH_3$	H	80	A
2	0	$-CH_2CH_3$	H	75	B
3	$-CH_2CH_3$	0	H	84	C
4	$-CH(CH_3)_2$	0	H	73	D
5	$-CH_2CH_2CH_3$	$-CH_2CH_3$	H	83	E
6	$-CH_2CH_3$	$-CH(CH_3)_2$	H	52	F
7	$-CH_2CH_3$	$-CH_2CH_2CH_3$	H	52	G
9	$-CH_2CH_3$	0	0	30	K

Representative procedure

In the mixture of corresponding tryptophol compound 1 in toluene (10 vol) and corresponding keto compound 2 in IPA (10 vol) at 0°C catalytic amount of concentrated sulfuric acid (~0.01equi.) was added. It was monitored by TLC/HPLC after every 30 mins time interval. After completion of the reaction, 100 vol ice cold water was added into it and pH was made basic using aqueous sodium bicarbonate. The aqueous mixture was extracted with ethyl acetate, combined organic layer was separated, dried over sodium sulphate and solvent was evaporated to get corresponding ester compounds. Above ester compounds are purified using flash column (100-200 mesh silica gel) and petroleum ether: ethyl acetate solvent system. Esters are characterized by mass and FTIR. These esters are hydrolyzed in standard base catalyzed conditions and standard extractive workup to get corresponding pure acid compounds from A to G. In the case of compound K ester obtained after purification step as a final compound. This objective is further explored in ecofriendly solvent free acid silica and microwave condition. But for market regulatory requirement API synthesis route preferred for their preparation [16].

Spectral interpretation

Compound A: (1-ethyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indol1-yl)-acetic acid: White solid. Yield: 80% (1.5 g, 96% pure). IR (cm^{-1}) 3377 (N-H), 2974 (aliphatic), 1708 (Acid-C=O), 1467,1373 (aliphatic bending), 1236 (asymmetric stretching), 748 (aromatic bending).^{1}H NMR ($CDCl_3$): δ 8.63 (s, N- H), 7.5 (d, 1H), 7.3 - 7.0 (dd, 3H), 4.2 - 3.9 (m, 2H), 2.95 (dd, 2H), 2.8 (m, 2H), 2.1 (q, 2H), 0.75 (t, 3H). MS: m/z 258.4[M+H]. Melting point = 98.4°C.

Compound B: (1-ethyl-8-methyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indol-1-yl)-acetic acid: White solids. Yield: 75% (2.1 g, 96%). IR (cm^{-1}) 3358 (N-H), 2954,2866 (aliphatic), 1750 (Acid-C=O), 1348-1352, 1320, 1217 (aliphatic bending), 775 (bending). 1H NMR (DMSO-d6): δ 8.7 (s,1H), 7.4 - 6.95 (m, 3H), 3.9 (m, 4H), 2.9 (bs, 2H), 2.85-2.75 (m, 2H), 2.8 (m, 2H), 2.1 (q, 2H), 0.75(t, 3H). MS: m/z 295 [M-H]-. Melting point =127°C.

Compound C: 1(-ethyl-1,3,9-tetrahydro-pyrano[3,4-b] indol-1yl)-acetic acid: White solid. Yield**:** 84% (0.7 g, 95%). IR (cm^{-1}) 3315 (N-H), 2968 (aliphatic), 1735 (Acid-C=O), 1413 (aliphatic bending), 1201-1033 (asymmetric stretching), 750 (bending). ^{1}H NMR (DMSO-d6): δ 8.6 (s, 1H, N-H), 7.2 (dd, 1H), 7.02-6.9 (dd, 2H), 4.1 (m, 2H), 3.0 (s, 2H), 2.8-2.7 (m, 4H), 1.7 (s, 3H), 1.3 (t, 3H). MS: m/z 274.5 [M+H]. Melting point=161.7°C.

Compound D: (1-ethyl-8-isopropyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indol-1yl)-acetic acid: Off white solid. Yield: 73% (0.45 g, 98%). IR (cm^{-1}) 3419 (-COOH O-H), 2968-2926 (aliphatic), 1712 (acid -C=O, 1462, 1367, 1300 (aliphatic bending), 1197 (asymmetric stretching), 792,752 (bending). ^{1}H NMR ($CDCl_3$): δ 8.6 (s, 1H), 7.3 (d, 1H), 7.0 (dt, 2H), 4.0 (m, 2H), 3.1 (p, 1H), 3.0 (d, 1H), 2.7 (q, 1H), 2.1 (q, 1H), 1.9 (q, 1H), 1.3 (dd, 6H), 0.8 (t, 3H). MS: m/z 302.4 [M+H]. Melting point=161.9°C.

Compound E: (1-ethyl-8-propyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indol-1yl)-acetic acid yellow liquid. Yield: 83% (0.8 g, 90%), IR (cm^{-1}) 3358 (N-H), 2962, 2931,2872 (aliphatic), 1708 (Acid C=O), 1454, 1305 (aliphatic bending), 1195 (asymmetric stretching), 781,744 (bending). ^{1}H NMR (CDCl3): δ 8.6 (s,1H), 7.3 (d, 1H), 7.0 (dd, 1H), 6.9 (d, 1H), 4.0 (q, 2H), 3.4 (q, 2H), 3.0 (d, 2H), 2.7 (q, 2H), 2.5 (t, 2H), 2.0 (m, 2H), 1.6 (t, 2H), 1.1 (t, 3H), 0.9 (t, 4H), 0.8 (t, 3H). MS: m/z 302.5 [M+H], 324.4 [M+Na].

Compound F: (8-ethyl-1-isopropyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indol-1yl)-acetic acid: Yellow solid. Yield: 52% (1.5 gg, 96%). IR (cm^{-1}): 3414 (N-H), 2972-2866 (aliphatic), 1689 (Acid -C=O), 1438, 1230 (aliphatic bending), 1072 (asymmetric stretching), 748 (aromatic), ^{1}H NMR ($CDCl_3$): δ 8.52 (s, 1H), 7.32 (dd, 1H), 7.1 - 6.9 (dd, 2H), 4.1-3.9 (m, 2H), 2.8 (t, 3H), 2.8 (m, 4H), 2.5 (m, 1H), 1.25 (t, 3H), 1.0 (d, 3H), 0.9 (d, 3H). MS: m/z 302.5 [M+H]. Melting point = 105.8°C.

Compound G: (8-ethyl-1-propyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indol-1yl)-acetic acid: Yellow solid. Yield: 52% (1.5 g, 96%). IR (cm^{-1}): 3342 (NH), 2962-2866 (aliphatic), 1708 (Acid-C=O), 1452, 1130 (aliphatic bending), 1072 (asymmetric stretching), 744 (aromatic bending), ^{1}H NMR ($CDCl_3$): δ 8.52 (s, 1H), 7.3 (dd, 1H), 7.0 - 6.9 (dd, 2H), 4.2-3.8 (m, 2H), 3.1 (q, 2H), 2.8 (m, 4H), 2.5 (m, 1H), 1.3 (t, 3H), 1.0 (d, 3H), 0.8 (d, 3H). MS: m/z 302.5 [M+H]. Melting point=80.3°C.

Compound K: (1,8-diethyl-1,3,4,9-tetrahydro-pyrano[3,4-b] indol-1yl)-acetic acid methyl ester: White solid compound. Yield: 30% (0.7 g, 85%). IR (cm^{-1}) 3305 (N-H), 2954-2866 (aliphatic), 1645 (acid -C=O), 1585, 1537, 1440 (aliphatic bending), 1292-1236 (asymmetric stretching), 758,750 (aromatic bending), ^{1}H NMR (DMSO-d6): δ 9.0 (s, 1H), 7.3 (dd, 1H), 7.01-6.9 (dd, 2H), 4.0 - 3.85 (m, 2H), 2.85-2.75 (m, 2H), 2.7 (t, 6H), 2.0 (t, 1H), 1.9 (m, 1H), 1.3 (t, 3H), 0.8 (t, 3H).
MS: m/z 302.4 [M+H], 324 [M+Na]. Melting point = 129.5°C.

Chiral seperation of r- etodolac and s-etodolac

In a suitable round bottom flask place 50 g (0.1740 moles) of racemic etodolac API, 21.17 g (0.1746 moles) of (S)-(-)-α-methylbenzylamine in 250 ml of acetone were stirred. It continued at room temperature for the next 2 hr. Collect obtained salt by filtration in Buchner funnel. Transfer it in a suitable conical flask and dissolve in water. Adjust the pH 1-2 of the solution using 10% dilute HCl solution and reflux it at 100°C for 30 mins. The reaction mass was allowed to cool at room temperature and filter to obtain pure R-Etodolac product.

White solid compound. Yield: 30% (15 g, 98%). IR (cm^{-1}) 3350 (N-H), 2944-2856 (aliphatic), 1737 (Acid -C=O), 1580, 1532 (aliphatic bending), 758,750 (Aromatic bending), 1H NMR (DMSO-d6): δ 8.6 (s, 1H), 7.3 - 6.9 (dd, 3H), 1.3 (t, 3H), 0.8 (t, 3H). MS: m/z 288.2 [M+H]. Melting point=140.1°C.

Similar procedure is repeated for S-Etodolac using (R)- (-)-α-methylbenzylamine.

White solid compound. Yield: 30% (15g, 98%). IR (cm^{-1}) 3350 (N-H), 2944-2856 (aliphatic), 1737 (Acid -C=O), 1580, 1532 (aliphatic bending), 758,750 (aromatic bending), ^{1}H NMR (DMSO-d6): δ 8.6 (s, 1H), 7.3-6.9 (dd, 3H), 1.3 (t, 3H), 0.8 (t, 3H). MS: m/z 288.2 [M+H]. Melting point=136.5°C (Figures 9 and 10) (Table 2).

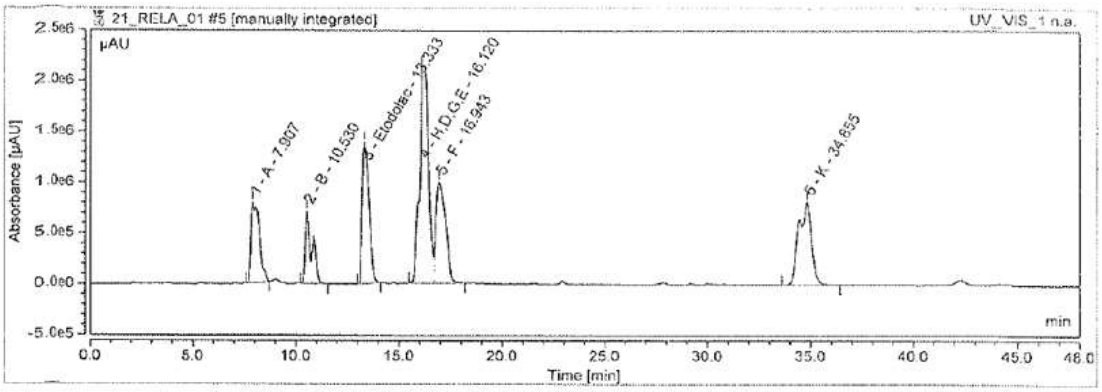

Figure 9: HPLC chromatograph of mixture of all etodolac derivatives.

General synthetic reaction scheme for oxidation of calcium channel blockers

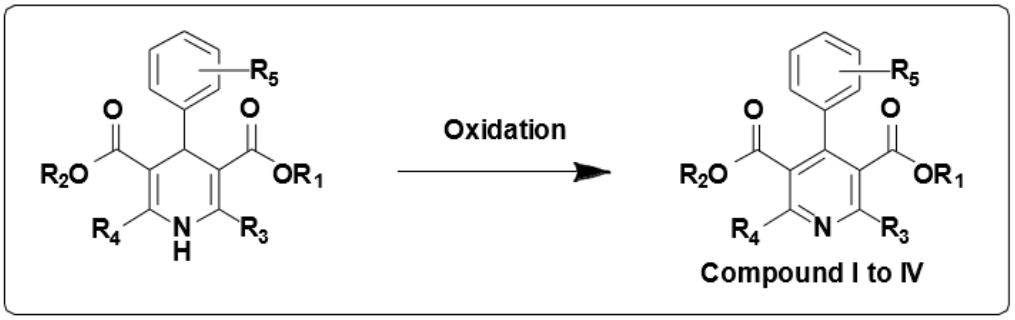

Figure 10: General synthetic scheme for oxidation of calcium channel blockers.

Table 2: Details about compound I to IV.

Drug	R1	R2	R3	R4	R5
Amlodipine	Me	Et	Me	$O(CH_2)2NH_2$	o-Cl
Lercanidipine	$Ph_2C(CH_2)2N(Me)CH_2C(Me)_2$	Me	Me	Me	m-NO_2
Nicardipine	$(CH_2)_2NMeBn$	Me	Me	Me	m-NO_2
Nifedipine	Me	Me	Me	Me	o-NO_2

General experimental procedures

To a stirred solution of free base of commercially available dipine family drug (Amlodipine, Lercanidipine, Nicardipine, Nifedipine) in (20 vol: 5 vol) dichloromethane: Acetic acid, aq solution of CrO_3 (2 mol eq) at cooled condition was added at same temperature. The oxidative completion of the reaction was observed by either TLC or HPLC. Here DCM: MeOH mobile phase system is used. After complete conversion of it, the aqueous workup was done and solvent was evaporated to get crude pyridine derivative of corresponding drug.
The product was enriched using flash and DCM: MeOH mobile phase to get corresponding molecule oxidized derivative which is further used for characterization and tox study.
Innovatively above oxidation work can be explored in solvent free cupper complexes in future. Above synthesized pyridine derivatives also developed with CuO oxidation in presence of THF as solvent and room temperature condition. Aqueous workup followed by flash column chromatography gives pure oxidized derivatives which is considered for further cytotoxic study [17].

Dehydro amlodipine compound I: (3-ethyl-5-methyl-2-((2-aminoethoxy) methyl)-4-(2-chlrophenyl)-6-methylpyridine-3,5-dicarboxylate liquid compound. Yield: 70% (0.3 g, 92%). IR (cm^{-1}) 2954-2827 (Aliphatic -H), 1728 (ester), 1234 (asymmetric stretching), 758,750 (aromatic bending), ^{1}H NMR (DMSO-d6): δ 7.42 (dd, 1H), 7.32 (dd, 1H), 7.27 (dd, 1H), 7.19 (dd, 1H), 4.8 (q, 2H), 4.0 (s, 2H), 3.59 - 3.54 (m, 5H), 2.8 (t, 2H), 2.6 (s, 3H), 0.9 (t, 3H). MS: m/z 406.9 [MH]+.
Dehydro nicardipines compound II: 2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid methyl-2-[methyl(phenylmethyl)amino] ethyl ester liquid compound. Yield: 65% (0.4 g, 94%). IR (cm^{-1}) 2904-2837 (Aliphatic - H), 1732 (ester), 1223 (C-O-C Asymmetric stretching), 734,690 (aromatic bending). ^{1}H NMR (DMSO-d6): δ 8.1-8.3 (dd, 2H), 7.7-7.4 (m, 7H), 4.5 (s, 2H), 4.2 (s, 2H), 3.59 (s, 2H), 3.4 (s, 1H), 2.9 (d, 3H), 2.5 (s, 2H), 1.4 (s, 6H). MS: m/z 477.9 [MH]+.
Dehydro lercanidipine compound III: 2,6-dimethyl-4-(3-nitro-phenyl) pyrdine-3,5-dicarboxylic acid-2[N-(3,3-diphenyl-propyl)-N-methylamino]-1,1-dimethyl ethylmethyl-5-methyl ester Liquid compound. Yield: 65% (0.4 g, 94%). IR (cm^{-1}) 2945 (Aliphatic -H), 1728 (ester), 1530, 1350 (asymmetric stretching), 736,700 (aromatic bending),^{1}H NMR (DMSO-d6): δ 8.37-8.34 (dd, 2H), 7.7 (d, 2H), 7.2 (s, 10H), 4.0 (m, 2H), 3.8 (s, 4H), 3.1 (dd, 6H), 2.8 (s, 4H), 2.7 (s, 2H), 1.4 (s, 6H). MS: m/z 609.8 [MH]+.
Dehydro nifedipine compound IV: 2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyrdinedicarboxylic acid yellow solid. Yield: 88% (1g, 96%). IR(cm^{-1}) 1722 (diester), 1525, 1236 (asymmetric stretching), 702, 656 (aromatic bending), ^{1}H NMR (DMSO-d6): δ 8.37-8.34 (dd, 2H), 7.7 (d, 2H), 7.2 (s, 10H),

4.0 (m, 2H), 3.8 (s, 4H), 3.1 (s, 6H), 2.8 (s, 4H), 2.7 (s, 2H), 1.4 (s, 6H). MS: m/z 345.8 [M+H].
Melting range: 105.9°C.
The above 3 dehydro derivatives (except dehydro nifedipine) are liquid in nature and those can be converted into their solid hydrochloride salt form to increase their bioavailability using IPA: HCl or ethereal HCl.

Experimental

Here commercial solvents have been used for purification and reaction purposes. Thin-Layer Chromatography (TLC) visualization done in standard lab instruments was run on silica gel 60 F254 precoated plates. FT-IR analysis is done by using Perkin Elmer ATR spectrometer. TMS is used as internal standard for ^{1}H NMR spectra. DMSO-d_6 and $CDCl_3$ solvents are used. Mass analysis of the samples was analyzed using a direct mass analyzer system. Acute cytotoxicity is measured with Trypan Blue Dye Exclusion method and MTT assay standard technique is used for some synthesized derivatives (Figures 11 and.12)

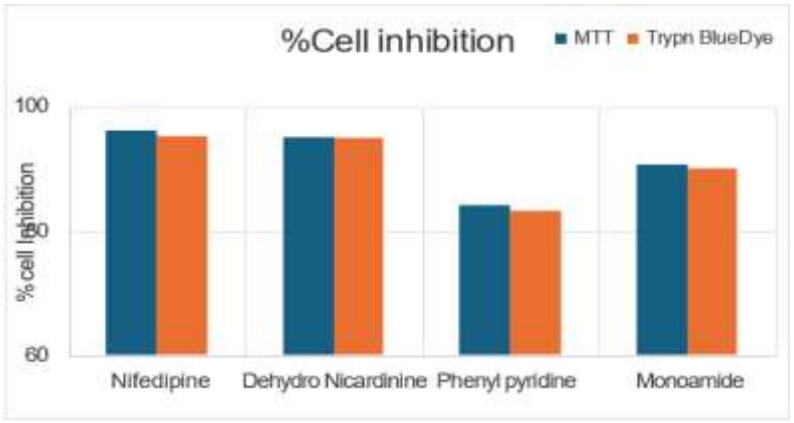

Figure 11: % Cell inhibition of nifedipine dihydro pyridine derivatives.

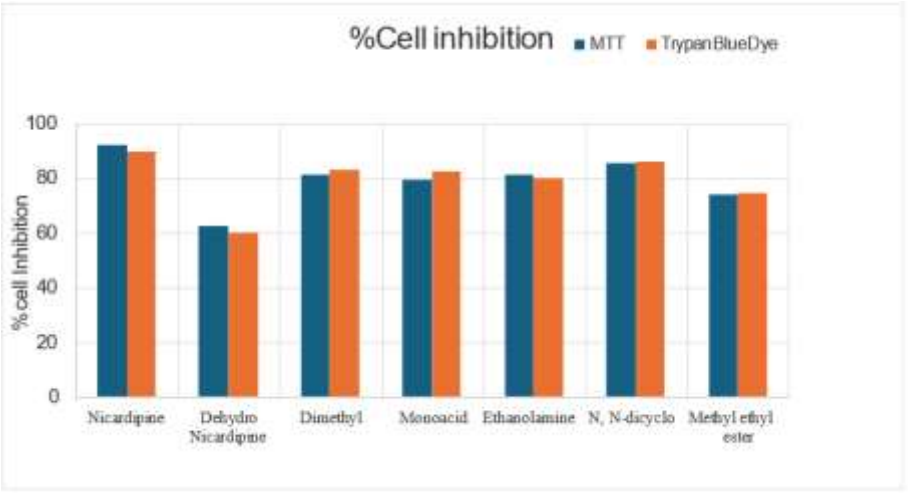

Figure 12: % Cell inhibition of nicardipine dihydro pyridine derivatives.

CONCLUSION

Triptan derivatives were synthesized, characterized and identified their origin in synthesis process. Cytotoxic study of drug and its stability at different conditions is an important aspect need to evaluate at each step of the drug. During its storage potential side products are forming and their unusual behavior with patient may lead serous effects. Oxidative degradation side products are mainly forming during storage and hence here their importance discussed.

AUTHOR CONTRIBUTIONS

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