Synthesis of Novel Isochromen-1-one analogues of Etodolac

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Synthesis of Novel Isochromen-1-one analogues of Etodolac

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Abstract. In the present work, anti-inflammatory drug based novel isochromen-1-one, their thio and *N*-methylated analogues were synthesized from the etodolac bulk drug, **1**. All the synthesized compounds were purified and successfully characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. All the derivatives procured are with remarkable yields from 67-72%.

1. Introduction

Isochromen-1-ones are important heterocyclic compounds found in some variety of plant species [1] and also synthesized more nowadays. These compounds exhibits therapeutic properties including anti-inflammatory [2], immunomodulatory action [3], anti-allergic [4], antifungal [5-6], cytotoxic [7-8], antimicrobial activity [9], and antimalarial effect [10]. Isochromen-1-one analogues are useful synthetic intermediates of heterocyclic compounds including isoquinolines, isochromones and pyridones [11]. Some of the isochromen-1-one derivatives have been shown to be useful in inhibition of antigen-antibody reactions and play a vital role in the treatment of diseases associated with allergic or immunological reactions [12]. A large number of 3-phenyl isochromen-1-one and 3-substituted phenyl-3,4-dihydroisocoumarin-1-one have been tested for various pharmacological activities including anti-inflammatory and anti-allergic activities and proved to be useful in the treatment of asthma [13. In addition to this they also showed anti-inflammatory activity and can be used to treat and control emphysema [14].

Inflammation due to release of chemicals from tissues, migrating cells and so on leads to inflammatory diseases and may results in neurodegenerative disease or may develop into cancer. Present medication used as anti-inflammatory agents have the risk of myocardial and other serious coronary heart diseases for chronic uses. Though numerous active anti-inflammatory drugs were in market, it is still a inspiring job for the scientist to develop more active and less noxious drugs [15]. Etodolac is an anti-inflammatory drug used in the diagnosis and cure of numerous musculoskeletal complaints, arthritis, inflammations and dental aches. It also performs bacteriostatic activity by inhibiting bacterial DNA synthesis. Clinical trials estimated the analgesic prospective of Etodolac in oral surgery, acute musculoskeletal injury and episiotomy. It has principle mechanism of action by inhibiting arachidonic acid signaling pathway by means of an effect on cyclooxygenase enzyme.

Isochromen-1-ones were effectively synthesized by palladium catalyzed reactions, electrophilic aromatic substitutions and cyclization of 2-allyl- and alkenyl benzoic acid. Tajudeen *et al*., have reported in synthesis of 3-substituted isochromen-1-ones from homophthalic acid and ester [16]. We, Napoleon *et al*., have reported the synthesis, antioxidant and *in vitro* anti-inflammatory

activity of drug based isochromen-1-ones and their thio analogues derived from ketoprofen [17]. In continuation of our interest in synthesis and biological activities of isocoumarins, we report the synthesis of isochromen-1-one analogues of etodolac.

2. Methodology

2.1. Materials

This study was conducted in two steps namely the synthesis and characterization of synthesized analogues of Etodolac. The chemicals and reagents were acquired from Sigma–Aldrich (India) and SD-Fine (India) and utilized without further purification. The materials which needed for this study are etodolac, thionyl chloride, homophthalic acid, lawesson's reagent, methyl iodide and solvents such as tetra hydro furan, toluene and petroleum ether: ethyl acetate as mobile base for TLC and column chromatography. Thin layer chromatography (TLC) was performed on preparative plates of silica gel. Visualization was made with iodine chamber. Column chromatography was performed by using silica gel (100-200 mesh). NMR spectra were recorded on a Bruker Advance II-300 MHz spectro meter using TMS as internal standard (chemical shifts δ in ppm).

2.2: General procedure for the synthesis of 3-((1,8-diethyl-1,3,4,9-tetrahydropyrano [3,4-b]indo l-1-yl)methyl) - 1H- isochromen-1-one, **3**

To the mixture of Etodolac (6 mmol, 1.8 g) in 10ml of THF was added thionyl chloride (7mmol, 3.5ml) and refluxed for 1 hour to afforded (1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl) acetyl chloride (**2).** The completion of reaction was observed by the halt of SO_2 gas. The removal of surplus thionyl chloride was passed out by distillation under reduced pressure. Further a base trap was connected in order to neutralize the excess vapour evolved.

A mixture of Homophthalic acid, **2a,** 2mmol, 0.36 g) and 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetyl chloride, **2** (in-situ) was heated to 200 ºC under oil bath for about the time period of 4 h. Then the reaction mixture was cooled to room temperature and then diluted with ethyl acetate, aqueous solution of sodium carbonate was added to remove the unreacted homophthalic acid. Separated the organic layer and dried with anhydrous sodium sulphate, then concentrated and chromatographed on silica gel using n-hexane as eluent to afford compound **3** as a brown colour solid. The structure of the purified compound **3** was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

2.3: General procedure for the synthesis of 3-((1, 8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b] indol-1-yl) methyl)-1-H-isochromene-1-thione, **4**

A mixture of compound (**3**) (2 mmol, 0.574 g) and Lawesson's reagent (1 mmol, 0.402g) was added and refluxed at 110 ºC in the presence of toluene (10 ml) as a solvent for 1 h. The progress of the reaction was checked by TLC via petroleum ether: ethyl acetate as mobile base. After completion of reaction, reaction mass stripped off to remove toluene and the residue was cleansed by column chromatography through petroleum ether: ethyl acetate as a solvent system. The structure of the purified compound, **4** was confirmed by ^{13}C NMR.

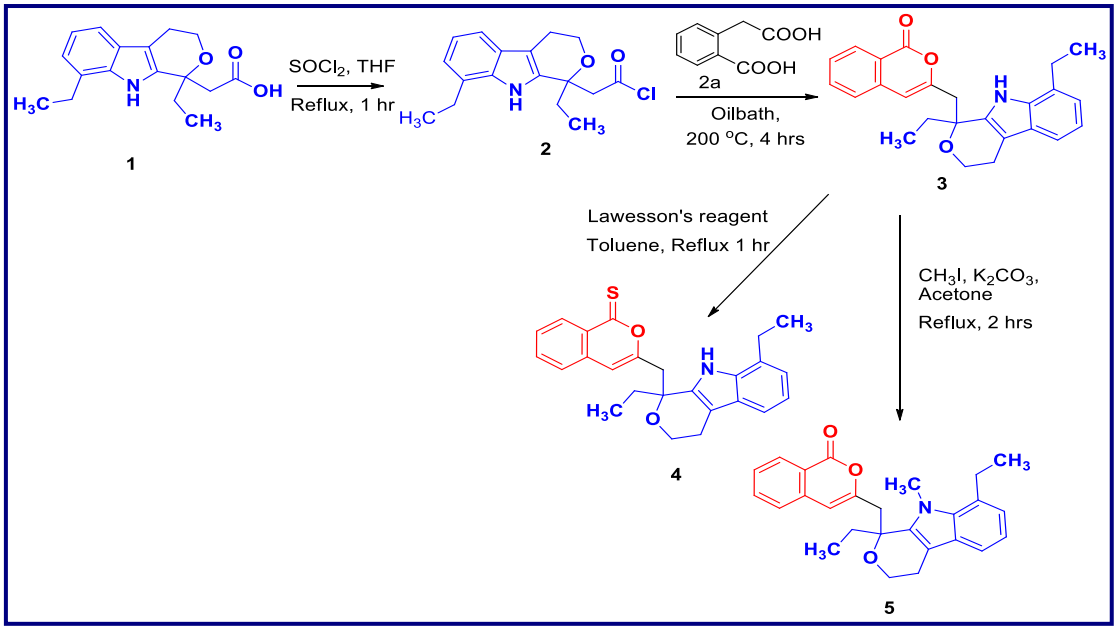
2.4: General procedure for the synthesis of 3-((1,8-diethyl-1,3,4,9-tetrahydro-9-methyl pyrano [3,4-b]indol-1-yl) methyl)-1H-isochromen-1-one, **5**

A mixture of acetone (20 ml), CH_3I (3 mmol, 0.420 g) and potassium carbonate (4 mmol, 0.560 g) was refluxed for 1 hour, then compound **3** (2 mmol, 0.574 g) was added and the reaction mixture was refluxed for additional 1 h. After the completion of reaction, acetone was stripped of over rota

evaporator and crude was diluted with ethyl acetate and water. The separated organic layer was concentrated and obtained crude was purified by column chromatography to afford compound **5** which was confirmed by ^{1}H NMR, ^{13}C NMR and Mass analysis.

3. Results and Discussion

3.1 Scheme. Synthesis of isochromen-1-one, isochromen-1-thione and their *N*-methyl etodolac analogues.



3.2 Synthesis

The isochromen-1-ones, and their thio, *N*-methyl analogues viz., **3**, **4** and **5** were synthesized successfully from etodolac. The compound **3** synthesized was confirmed by using ^{1}H NMR and mass spectra. ^{1}H NMR revealed that it has 25 protons in that 9 are aromatic with triplets for each three protons at δ 1.18 and δ 0.89 ppm endorsing two methyl groups. The peak at δ 6.10 ppm is the characteristic peak of C_4-proton of the isochromen-1-ones ring (supplementary Fig. 3). All the remaining 9 protons are due to aromatic and NH protons which appeared in the region of δ 7.83-6.50 ppm. ^{13}C NMR spectrum shows with 25 carbons in which the carbonyl group of isocoumarin showed a peak at 162.81 ppm (supplementary Fig. 4). The mass spectrum further confirms the compound **3** by the ionization of molecular peak ion (M+1) at m/z 388.2 (supplementary Fig. 2). In ^{13}C NMR, the lactum carbonyl group peak of isochromen-1-one appeared at δ 162.81ppm.

The compound **4** was obtained from compound **3** through an isosteric substitution of oxygen to sulphur in isochromen-1-one ring for thionation using lawesson's reagent. The thio-analogue with same proton count showed similar ^{1}HNMR spectra however in the ^{13}C NMR spectra, thio carbonyl group appeared at 187.70 ppm (supplementary Fig.5) which confirmed for thionation (supplementary Fig.5). The compound **5** was then obtained by *N*-methylation of compound **3** using CH_3I and K_2CO_3 in acetone under reflux for 2 hr. The compound **5** is confirmed through ^{1}H NMR spectra showing appearance of methyl protons and disappearance of NH proton, similarly additional carbon peaks in ^{13}C NMR spectra (26 carbons) revealed the methylation on nitrogen (supplementary Fig. 8), and the mass spectra further confirmed the molecular peak ion at 402.07 (M+1) (supplementary Fig. 6). In the ^{1}H NMR spectrum, compound **5** showed a singlet and two triplets respectively for each three protons

at δ3.66 (*N*-CH_3), δ1.18, 0.91 for the three methyl groups. The value of δ 5.95 ppm is the significant characteristic peak of C_4-proton present in the isochromen-1-one ring (supplementary Fig. 7) and remaining 8 aromatic protons were showed at δ of 8.31-5.95 ppm. In ^{13}C NMR, the isochromen-1-one of carbonyl peak appeared at δ 162.81 and the methyl carbon showed at δ 35.94.

3.3 Optimization of reaction condition

In the synthesis of Isocoumarins, conversion of acid to acid chloride was key step. Unfortunately, the desired yield was not obtained when etodolac was treated with thionyl chloride without solvent at room temperature. So in order to optimize the reaction conditions various solvents were used for optimizing the yield. Percentage yield of 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetyl chloride, **2** obtained are shown in table **1**. When pyridine as catalytic amount (5drops) with THF as solvent used was afforded 88.9% yield. However, the conversion of acid to acid chloride in the presence of pyridine requires 2 hours of reflux and further more pyridine is highly toxic, it was not chosen. Better yield was obtained when THF was used as a solvent and the reaction mixture containing etodolac and thionyl chloride was refluxed for 1 hour. The percentage yield of 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetyl chloride, **2** under different solvent conditions were given in Table **1.**

Table: 1 Optimization of reaction condition for the synthesis of key intermediate 2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)acetyl chloride, **2**

Entry	Solvents	Time (hr)	Temp. (ºC)	Yield (%)
1	No solvent	24	30	51.4
2	DMF	26	30	82.2
3	THF	36	30	85.0
4	No solvent	3	50	78.3
5	DMF	2	50	82.8
6	THF	1	50	85.9
7	Pyridine (catalytic amount)	26	30	85.6
8	Pyridine (catalytic amount)	2	50	88.4

Reaction condition: Etodolac **1**, (6 mmol, 1.8gm), Thionylchloride, (7 mmol, 3.5ml), Solvent (10 mL), Yield of 1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl) acetyl chloride, **2**.

3.4 Analytical data

3-((1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)methyl)-1H-isochrom en-1-one. **3;** Yield; 72.5 %; Brown in color; mp; 145-148˚C. $C_{25}H_{25}NO_3$; FT IR (KBr, cm^{-1}): 1715.37 (C=O stretch), 3362.28 (N-H stretch), 2961.16 (aromatic C-H stretch), 1172.51 (C-O stretch). ^{1}H NMR (300MHz, $CDCl_3$): *δ* (ppm) 7.83-7.73 (d, *J* =3.0Hz, 2H), 7.41 (s,1H), 7.26-7.28 (d, *J* =6.0Hz, 1H), 7.09-7.07 (d, *J* =6.0Hz, 4H), 6.91 (s,1H), 6.52 (s,1H), 4.36-4.33 (d, *J* =9.0Hz, 2H), 3.98 (s, 1H), 3.50 (s,1H), 2.75-2.71 (t, *J* =12.0Hz, 3H), 2.28 (s, 1H), 1.91 (s, 1H), 1.18 (s, 3H), 0.91 (s,3H). ^{13}C NMR (100MHz, $CDCl_3$): 7.63, 13.41, 23.21, 26.99, 29.63, 53.20, 62.21, 78.92, 113.16, 115.96, 118.02, 119.80, 121.23, 122.04, 125.66, 127.49, 128.01, 128.99, 130.02, 131.74, 134.18, 134.72, 138.32, 153.58 and 162.81ppm): MASS, m/z: 388.2.

3-((1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indol-1-yl)methyl)-1-H-isochromene-1-thione, ***4;*** Yield; 67.6 %; Reddish brown in color; mp; 193-196 ºC; $C_{25}H_{25}NO_2S$. Mol. Wt: 403.5, ^{1}H NMR (300MHz, $CDCl_3$): *δ* (ppm) ^{1}H NMR (300MHz, $CDCl_3$): *δ* (ppm) 7.83-7.73 (d, *J* =3.0Hz, 2H), 7.41

(s,1H), 7.26-7.28 (d, *J* =6.0Hz, 1H), 7.09-7.07 (d, *J* =6.0Hz, 4H), 6.91 (s,1H), 6.52 (s,1H), 4.36-4.33 (d, *J* =9.0Hz, 2H), 3.98 (s, 1H), 3.50 (s,1H), 2.75-2.71 (t, *J* =12.0Hz, 3H), 2.28 (s, 1H), 1.91 (s, 1H), 1.18 (s, 3H), 0.91 (s,3H). ^{13}CNMR (100MHz, $CDCl_3$): 25 peaks δ: 187.70, 138.32, 132.96, 132.74, 131.74, 129.78, 129.07, 128.01, 127.37, 125.66, 122.25, 121.23, 119.80, 118.35, 118.02, 113.16, 79.76, 62.19, 53.25, 29.63, 26.80, 23.21, 13.41 and 7.68ppm):

3-((1,8-diethyl-1,3,4,9-tetrahydro-9-methylpyrano[3,4-b]indol-1-yl)methyl)-1H-isochromen-1-one, **5:** Yield; 70.4 % ; Light brown, mp; 160-163ºC; $C_{26}H_{27}NO_3$ ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31-8.29 (d, *J* =6.0Hz, 1H), 7.75-7.72 (t, *J* =9.0Hz, 1H), 7.52 (s,1H), 7.43-7.39 (t, *J* =12.0Hz 1H), 7.12 (s,1H), 6.95-6.93 (d, *J* =6.0Hz, 1H), 5.95 (s, 1H), 4.38-4.34 (t, *J* =12.0Hz, 1H), 3.68-3.66 (d, *J* = 6.0Hz, 2H), 3.41-3.38 (d, *J* =9.0Hz, 2H), 2.75-2.71 (t, *J* =12.0Hz, 4H), 2.33 (s, 2H), 2.02 (m, 3H), 1.19-1.17 (t, *J* =9.0Hz, 3H), 0.92(s, 3H); ^{13}C NMR (100MHz, $CDCl_3$ δ ppm): 162.81, 153.56, 137.91, 134.72, 134.18, 131.96, 130.02, 129.24, 128.99, 128.60, 127.48, 124.24, 122.99, 122.04, 119.23, 115.96, 115.92, 82.43, 62.18, 52.99, 35.94, 30.42, 28.09, 24.51, 13.48, 7.61ppm. Mass m/z: 402.07(M+1).

4. Conclusion

In summary, we have developed a productive and novel synthesis of isochromen-1-one, their thio and methyl analogues were made from an anti-inflammatory drug etodolac by the modification of carboxylic group of etodolac with better yields.

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