SYNTHESIS OF NOVEL ALKYLAMINOHYDROXYPROPOXY COUMARIN DERIVATIVES


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ABSTRACT
Coumarin molecule is used as anticoagulant. Other uses like anti-HIV, anti-tumor, anti-hypertensive, anti-arrhythmia, anti-osteoporosis, pain relief increase research of coumarin derivative. Perkin discovered a synthetic method of coumarin and opened the door in synthetic research. Now a days there are so many methods are used to form coumarin. Warfarin is a well known drug of 4-hydroxy coumarin derivative. It is consider that, propranolol drug act as a lead molecule of β-blocker. Alkylaminohydroxypropoxy side chain is responsible for β-blocking activity in propranolol. Hence synthesis and its characterization of antihypertensive coumarin derivative was our main target.

Keywords: Coumarin, Anticoagulant, antihypertensive agent, Alkylaminohydroxypropoxy.

INTRODUCTION
Coumarin is a widely occurring secondary metabolite that occurs naturally in several plant families and essential oils. Coumarin is an anhydride of o-coumaric acid having white, crystalline lactone, obtainable naturally from several plants, such as tonka bean, lavender, sweet clover grass, apicots, cherries, strawberries, and cinnamon. It is also synthesized from an amino acid, phenylalanine. [1]

Coumarins are a group of important natural compounds, and have been found to have multi-biological activities such as anti-HIV, anti-tumor, anti-hypertensive, anti-arrhythmia, anti-osteoporosis, pain relief, preventing asthma and antisepsis. [2] Natural products like esculetin, fraxetin, daphnetin and other related coumarin derivatives are recognized as inhibitors not only of the lipoxygenase and cyclooxygenase enzymic systems, but also of the neutrophil-dependent superoxide anion generation. Coumarin derivatives also possess anti-inflammatory as well as antioxidant activities. Coumarin possesses immunomodulatory and direct antitumor activity. [3] It has been recommended for treatment of a number of clinical conditions, including high protein oedema and...
brucellosis. Coumarin and some of its derivatives have been tested for treatment of anxiolytic, microcirculation disorders and angiopathic ulcers, and also for treatment of high protein oedemas in animals. \[4\]

Coumarin derivatives are used as therapeutic anticoagulants and as rodenticides by causing fatal haemorrhage. Because the range between efficient therapy and undue hemorrhagic risk may vary greatly from one patient to another, the need for carefully individualized treatment and frequent observations has long been stressed. However, a summary of recent research findings, along with certain principles, may offer possible explanations for responsiveness to make highly efficient lead with fewer side effects to resist both, coagulopathy as well as hypertension. The primary aim of this present work is to study pharmacological and synthetic aspects of the coumarin ring structure especially its combined analogues profile as an anticoagulant and antihypertensive property.

The interesting biological properties of coumarin made these compounds very attractive for organic synthesis. Perkin discovers the synthetic method of coumarin and till today thousands of compounds were synthesized. Other named reactions for coumarin synthesis are Pechmann reaction, Knoevenagel reaction, Wittig reaction, Kostanecki-Robinson reaction and Reformatsky reaction. \[5\] Bose and his colleague discover a new method for synthesis of 4-hydroxy coumarin from substituted phenol. \[6\]

Warfarin is 4-hydroxy coumarin derivative and used as anticoagulant agent. Warfarin mainly acts via inhibition an enzyme vitamin K epoxide reductase that recycles oxidized vitamin K to its reduced form after it has participated in the carboxylation of several blood coagulation proteins, mainly prothrombin and factor VII. \[7\] Propranolol is a lead molecule of non-selective β-blockers. It is a derivative of alkylaminohydroxypropoxy side chain, which is responsible for antihypertensive activity. This side chain also affect pharmacokinetic and pharmacodynamic properties of drugs. \[8\] The main complications of hypertension, i.e. coronary heart disease, ischemic strokes and peripheral vascular disease are usually related to thrombosis. It therefore seems plausible that use of antithrombotic therapy may be of particular benefit in preventing the thrombosis-related complications of elevated blood pressure. \[9\] Therefore our aimed was to synthesize coumarin derivatives which may be use as antihypertensive agent.
RESULT AND DISCUSSION

Synthesis of following compounds was performed. Coumarin moiety plays important role in anticoagulation of blood and sidechain has antihypertensive property. So following compounds are novel series of coumarin derivatives may be used as antihypertensive agent.

![Chemical structure of synthesized compounds]

**TABLE 1: PHYSICAL CHARACTERISTICS DATA OF SYNTHESIZED COMPOUNDS**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Code</th>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>M.F.</th>
<th>M. P. (°C)</th>
<th>Rf * value</th>
<th>% Yield</th>
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<td>60</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>-C(CH_3)_3</td>
<td>C_{16}H_{22}NO_4Cl</td>
<td>212-14</td>
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<td>H</td>
<td>H</td>
<td>-CH_2(CH_2)_2CH_3</td>
<td>C_{16}H_{22}NO_4Cl</td>
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<td>0.33</td>
<td>62</td>
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<td>C_{15}H_{18}NO_4Cl</td>
<td>222-24</td>
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<tr>
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<td>C_{16}H_{20}NO_4Cl</td>
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<td>0.33</td>
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During synthesis many problems were solved by trial and error methods to increase yield. In step one increase the yield by maintain temperature at 65-70 °C. Purification is required in step one, so we tried to purify this products using ethanol: chloroform (9:1) mixture by recrystalisation method. Epoxy derivatives are formed by
using epichlorhydrin in presence of potassium carbonate as a base. At higher temperature sticky products were obtained. Hence this reaction was carried out at 120-125 °C. To get solid product, the epoxy resin was completely separated by using mother solvent i.e. toluene and then dissolved in a minimum quantity of dioxane which was slowly poured in to crushed ice with vigorous stirring and solid epoxy derivative was isolated. Here we have also used benzene in place of toluene but product was not solidified after pour in to crushed ice.

Here epoxy derivative is treated with amine give final product. This reaction was also successful if IPA used as solvent. If solvent or unreacted amine was distilled out then sticky semisolid mass was obtained, so hydrochloric acid salt formation was preferable solution to convert in to solid. This product was hygroscopic and protect from moisture. Synthesized compounds shown in table 1. Here tert-butyl amine gives highest yield among this series.

Synthesized compounds were structurally evaluated using spectroscopic methods like, IR, Mass and NMR techniques. In FTIR analysis, a peak was observed at 1700 cm⁻¹ of carbonyl group, C-O streching of ring skeleton was observed at 1160-1125 cm⁻¹. The N-H streching of secondary amines gives a broad peak between 3350-3300 cm⁻¹. The –OH bending observed at 1380-1310 cm⁻¹. Other frequencies observed due to ring skeleton are around 1600-1450 cm⁻¹ of C=C stretching. Figure 1 show FTIR spectra of BLT2 compounds.
Mass spectra also give structural information of synthesized compound. BLT1 compound was characterized by mass spectra. It shows peak at 311.5 m/z as M-1 and other fragments’ peak at 219, 175 and 161 m/z. Same fragmentation patterns were observed for all synthesized compounds.

NMR spectra was taken and singlet peaks are observed at 1.16 of –CH$_3$ of sidechain, 3.88 of amine, 5.86 of –OH, 4.88 of –CH$_2$ of ring skeleton, while multiplate, triplate and doublet peaks are also observed.
CONCLUSION:
Synthesis and structural characterization of novel derivatives, together with the development of new synthetic methods and increase the yield, will be the useful research in thromoembolism and hypertension conditions. It is a first approach to synthesize alkylaminohydroxypropoxy derivative of coumarin. We conclude that tert-butyl derivative is formed in higher yield which may possess antihypertensive and warfarin like activity.

Figure 3
NMR Spectra of BLT2

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REFERENCES
2. reference required


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