# SYNTHESIS OF 6-[1-(4'-HYDROXYCOUMARIN-3'-YL)-1-PHENYL]PROPIONYL-2H-[1,4]-BENZOXAZIN-3(4H)-ONES

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## Abstract

A series of 6-[1-(4'-Hydroxycoumarin-3'-yl)-1-phenyl]propionyl-2H-[1,4]-benzoxazin-3(4H)-ones(**4**a-l) have been prepared by Michael addition of 4-hydroxycoumarins(**3**a-c) on 1-(2H-3-oxo-[1,4]-benzoxazin-6-yl)-3-arylpropen-1-ones(**2**a-d).

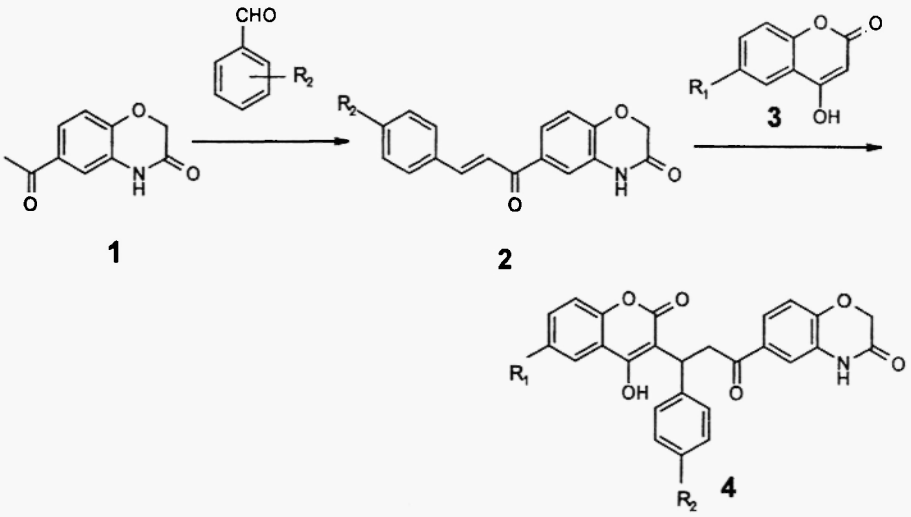
## Introduction

Several 1,4-benzoxazines have been reported to possess diverse types of biological activities. For example, isothiocyanatobenzoxazines possessed excellent anthelmintic activity[1]. Cardiotonic activity was observed for pyridazinyl benzoxazines[2,3]. 2-Hydroxyethylbenzoxazines have been reported as antibacterial agents[4]. Factor Xa is an active enzyme and plays an important role in blood clotting. Recently a number of amidinobenzoxazines have been reported as factor Xa inhibitors leading to anticoagulant activity[5]. Furthermore, a variety of 3-phenethyl-4-hydroxycoumarins such as Warfarin and Acenocoumarol have been reported as anticoagulant agents and are in clinical use[6]. In view of this, and in continuation of our interest in biologically active benzoxazines[7-9], it was planned to synthesize new chemical entities incorporating 4-hydroxycoumarin and benzoxazine moieties.

## Results and Discussion

The required starting materials, 1-benzoxazinyl-3-arylpropen-1-ones(**2**a-d) were prepared by condensation of 6-acetyl-3-oxo-[1,4]-benzoxazine (**1**) with aromatic aldehydes in methanol in presence of sodium at room temperature[10]. Reaction of **2** with various 6-substituted-4-hydroxycoumarins (**3**a-c) in refluxing pyridine gave the title 6-[(coumarinyl)-1-aryl-propionyl]benzoxazinones (**4**a-l) in moderate yields (scheme 1). The structures of compounds **4** were based on their IR and $^1$H NMR spectra. **4** Exhibited typical signals for –C-$CH_2$-CH-Ar system in their $^1$H NMR spectra thus two sets of double doublets for two single protons and a triplet for aromatic methine proton apart from a singlet at δ 4.5 for O-$CH_2$ of benzoxazine ring and a singlet at δ 10.6 for NH proton were observed.

All the compounds reported in Table 1 were based on their correct elemental analyses and Mass spectra of representative compounds.




**Scheme 1**

## Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra was recorded in KBr pellets. $^1$H NMR spectra on a various 200MHz instrument with TMS as internal standard and chemical shifts expressed in δ ppm and Mass spectra on Hewlett Packard Mass spectrometer operating at 70ev.

### Preparation of 1-(3-Oxo-1,4-benzoxazin-6-yl)-3-arylpropen-1-ones 2: General procedure

To a mixture of 6-acetyl-3-oxo-[1,4]-benzoxazine[11] (**1**, 0.01 mole) and a substituted aromatic aldehyde (0.01 mole) in methanol (50 ml) was added sodium (0.02 mol). The reaction mixture was stirred at room temperature until the disappearance of starting materials as monitored by TLC. White crystalline solids were separated during 4-6 hrs. The solids were filtered and washed with cold methanol to give pure **2**.

### General Procedure for the preparation of 4

A mixture of 4-Hydroxycoumarin (**3**, 0.01 mole) and 1-(3-oxo-1,4-benzoxazin-6-yl)-3-arylpropen-1-one (**2**, 0.01 mole) in pyridine (10 ml) was heated to reflux for 4-6 hrs. The progress of the reaction was monitored by TLC. It was poured onto cold water (100 ml), the separated solid was filtered and washed with water (2 x 50 ml). The product was purified by column chromatography using hexane : ethylacetate (1:1) as eluent to give pure **4** as crystalline solids.

**6-[1-(6'-Chloro-4'-hydroxycoumarin-3'-yl)-1-phenyl]propionyl-2H-[1,4]-benzoxazin-3(4H)-one(4a)**

A mixture of 6-chloro-4-hydroxycoumarin(**3**a, 1.96 gm, 0.01 mole) and 1-(3-oxo-1,4-benzoxazin-6-yl)-3-phenylpropen-1-one (**2**a, 0.01 mole, 2.79 gm) in pyridine was heated to reflux for 4-6 hrs. It was worked up according to general procedure described for **4** to give **4**a as crystalline solid. Yield : 2.66 gm (56%); m.p : 223°; IR : 3125 & 1690 $cm^{-1}$; ms (70ev) m/z (%) : 475 ($M^+$, 56%); $^1H$ NMR (DMSO-$d_6$) : δ 3.7 (dd, 1H, $COCH_2$); 4.05 (dd, 1H, $COCH_2$); 4.5 (s, 2H, $OCH_2$); 5.1(t, 1H, ArCH); 6.8-7.9 (m, 12H, ArH & OH); 10.7 (s, 1H, NH). (Found: C, 65.62; H, 3.75; N, 2.14 $C_{26}H_{18}ClNO_6$ requires C, 65.61; H, 3.78; N, 2.10%).

Compounds **4**(b-l) reported in Table 1 were similarly prepared.

Table 1 – Physical data of compounds 4

| Compd* | $R_1$ | $R_2$ | Yield % | M.p °C | Mol. Formula | $^1H$ NMR (δ ppm) DMSO-$d_6$ |
|---|---|---|---|---|---|---|
| 4a | Cl | H | 56 | 223 | $C_{26}H_{18}ClNO_6$ | 3.7(dd,1H,$COCH_2$); 4.05(dd,1H,$COCH_2$); 4.5(s,2H, $OCH_2$); 5.1(t,1H,ArCH); 6.8-7.9(m,12H,ArH&OH); 10.7(s,1H,NH) |
| 4b | Cl | $CH_3$ | 52 | 197 | $C_{27}H_{20}ClNO_6$ | 2.4(s,3H,$ArCH_3$); 3.75(dd,1H,$COCH_2$); 4.05(dd,1H, $COCH_2$); 4.5(s,2H,$OCH_2$); 5.1(t,1H,ArH); 6.8-7.8(m, 11H,ArH&OH); 10.7(s,1H,NH) |
| 4c | Cl | F | 53 | 184 | $C_{26}H_{17}ClFNO_6$ | 3.7(dd,1H,$COCH_2$); 3.95(dd,1H,$COCH_2$); 4.5(s,2H, $OCH_2$); 5.05(t,1H,ArCH); 6.8-7.8(m,11H,ArH&OH); 10.7(s,1H,NH) |
| 4d | Cl | Cl | 57 | 252 | $C_{26}H_{17}Cl_2NO_6$ | 3.7(dd,1H,$COCH_2$); 4.0(dd,1H,$COCH_2$); 4.45(s,2H, $OCH_2$); 5.1(t,1H,ArCH); 6.8-7.8(m,11H,ArH&OH); 10.7(s,1H,NH) |
| 4e | F | H | 54 | 194 | $C_{26}H_{18}FNO_6$ | 3.75(dd,1H,$COCH_2$); 4.05(dd,1H,$COCH_2$); 4.5(s,2H, $OCH_2$); 5.1(t,1H,ArCH); 6.8-7.9(m,12H,ArH&OH); 10.7(s,1H,NH) |
| 4f | F | $CH_3$ | 61 | 224 | $C_{27}H_{20}FNO_6$ | 2.45(s,3H,$ArCH_3$); 3.7(dd,1H,$COCH_2$); 4.1(dd,1H, $COCH_2$); 4.55(s,2H,$OCH_2$); 5.15(t,1H,ArCH); 6.85-7.9(m,11H,ArH&OH); 10.7(s,1H,NH) |
| 4g | F | F | 48 | 175 | $C_{26}H_{17}F_2NO_6$ | 3.75(dd,1H,$COCH_2$); 4.05(dd,1H,$COCH_2$); 4.9(s,2H, $OCH_2$); 5.1(t,1H,ArCH); 6.8-7.8(m,11H,ArH&OH); 10.75(s,1H,NH) |
| 4h | F | Cl | 63 | 181 | $C_{26}H_{17}ClFNO_6$ | 3.7(dd,1H,$COCH_2$); 4.0(dd,1H,$COCH_2$); 4.5(s,2H, $OCH_2$); 5.1(t, 1H, ArCH); 6.8-7.8(m,11H,ArH&OH); 10.6(s,1H,NH) |
| 4i | $CH_3$ | H | 47 | 221 | $C_{27}H_{21}NO_6$ | 2.45(s,3H,$ArCH_3$); 3.75(dd,1H,$COCH_2$); 4.1(dd,1H, $COCH_2$); 4.5(s,2H,$OCH_2$); 5.1(t,1H,ArCH); 6.8-7.8(m,12H,ArH&OH); 10.7(s,1H,NH) |
| 4j | $CH_3$ | $CH_3$ | 49 | 254 | $C_{28}H_{23}NO_6$ | 2.4(s,3H,$ArCH_3$); 2.5(s,3H.$ArCH_3$); 3.7(dd,1H,CO $CH_2$); 4.1(dd,1H,$COCH_2$); 4.5(s,2H,$OCH_2$); 5.1(t,1H, ArCH); 6.8-7.8(m,11H,ArH&OH); 10.75(s,1H,NH) |
| 4k | $CH_3$ | F | 51 | 217 | $C_{27}H_{20}FNO_6$ | 2.4(s,3H,$ArCH_3$); 3.75(dd,1H,$COCH_2$); 4.15(dd,1H, $COCH_2$); 4.55(s,2H,$OCH_2$); 5.1(t,1H,ArCH); 6.8-7.8(m,11H,ArH,OH); 10.65(s,1H,NH) |
| 4l | $CH_3$ | Cl | 55 | 234 | $C_{27}H_{20}ClNO_6$ | 2.45(s,3H,$ArCH_3$); 3.7(dd,1H,$COCH_2$); 4.1(dd,1H, $COCH_2$); 4.5(s,2H,$OCH_2$); 5.1(t,1H,ArCH); 6.85-7.9(m,11H,ArH&OH); 10.7(s,1H,NH) |

* Satisfactory C, H and N analyses were obtained for all the compounds

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**Received on May 9, 2003.**