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Synthesis and Spectral Studies of 2-(4-Hydroxyphenyl)-1,2-Dihydro-4H-Benzo[d][1,3]Oxazin-4-One

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Abstract

Benzoxazinone and its derivatives having it fused with other moieties like aromatic ring (Substituted phenyl) or heterocyclic systems (Chromone) were reported to possess many pharmacological activities like anti-inflammatory,antibacterial, analgesic etc. Inspired by this the title compound and some other derivatives of benzoxazinone were synthesised and studied for their spectral properties.

Keywords: Benzoxazinone, anti-inflammatory,analgesic.

Introduction

The study of heterocyclic compounds is a field of interest for scientists for a long time [1].4H-3,1-benzoxazinone derivatives are recognised as an important heterocyclic compound for their numerous biological applications[2].It has been reported that 4H-3,1-Benzoxazinone derivatives possess various pharmaceutical activities like antibacterial, antifungal[3,4], antiphlogistic[5], anticancer[6], antianxiety[7], antiplatelet aggregation activity[8], antidiabetic activity[9], antihypertensive [10]etc.Besides their pharmacological activities benzoxazin derivatives are also considered important because these compounds are not showing any reproductive toxicity, ulcerogenecity, ophthalmotoxicity, ototoxicity etc.[11,12].1,3-Benzoxazin-4-ones are also used in many fields such as research fields,Industries[13] and in clinical work[14].Benzoxazinones are also used as starting material for 4-quinazolone derivatives,that are used in many clinical work[15].Quinazoline-4-(3H)-one derivatives are reported to show many biological activities like anticancer,anti-inflammatory,antiviral,antifungal etc [16,17]. Chromones and their derivatives have also been recognised to be effective compounds to be used as anticancer agent[18,19],anti-inflammatory agent via inhibiting cyclooxygenase[20,21], lipooxygenase[22], diuretic[23,24] ,antibacterial[25] etc. Considering the biological activities of these compounds it was thought useful to synthesize compounds incorporating these systems.

Aim of the Study

Inspired by the wide spectrum of biological activities associated with benzoxazinone and other heterocyclic compounds it was planned to synthesise the title compound and other derivatives which show plenty of activities and to study their structures.

Experimental

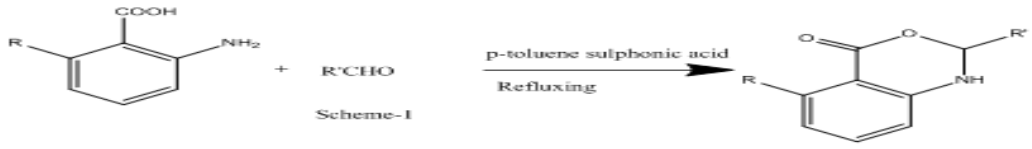
Materials and Methods: All the chemicals were purchased from sigma-aldrich and used without purification. Anthranillic acid used was of analytical grade. It was purified before use by recrytallisation.All the melting points are uncorrected and were taken in open capillaries using sulphuric acid bath.Characterization of synthesised compounds was done with Schimadzu FT-IR Spectrophotometer and Bruker Avance II-400 NMR Spectrometer.Chemical shifts are expressed in ppm units(Delta)downfield from internal tetramethyl silane(TMS) standard. Solvents were purified by using standard procedures. The purity of compounds was checked by TLC, using benzene and ethanol as mobile phase in the ratio of 9:1.Iodine vapours are used as developer.

2-(4-oxo-4H-chromen-3-yl)-1,2-dihydro-4H-benzo[d][1,3]oxazin-4-one(1-a):

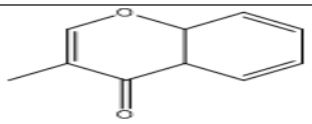
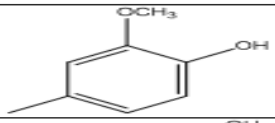
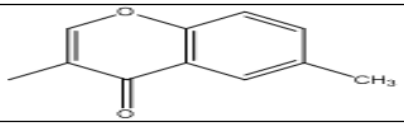
General procedure

To a solution of anthranillic acid(0.6859g; 0.005 mol) dissolved in absolute alcohol , a solution of 3-formyl chromone (0.8709g; 0.005 mol) dissolved in absolute alcohol, was added.p-Toluene sulphonic acid was

then added as catalyst.The reaction mixture was refluxed for 6 hours. The yellow solid separated was filtered, washed with distilled water,dried and then recrystallised from ethanol(scheme-1).The purity of compound was checked by TLC plates using benzene and ethanol in the ratio of 9:1 as mobile phase.Yield= 64% M.P.=206^{0}c,Molecular formula=$C_{17}H_{11}NO4$ requires(%):C=69.62, H=3.78,N=4.78, O=21.82;IRcm^{-1}3344,1690,1614,1325,^{1}H NMR(DMSO, 300 MHz,ppm):δ6.89-6.99(3H,m),7.19(1H,s),7.35(1H,d),7.47(1H,dd),7.58(1H,d),7.73(2H,m),8.03(1H,d),9.09(1H,)



Scheme-I

Compound name	R	R'
1a	H	
1e	I	
1b	H	
1f	I	
1c	H	
1g	I	
1d	H	
1h	I	

2-(4-hydroxy-3-methoxyphenyl)-1,2-dihydro-4H-benzo[d][1,3]oxazin-4-one(1-b):

Anthranillic acid (1.37g; 0.01 mol) and Vanillin (1.52g; 0.01 mol) were reacted according to general procedure for 6 hours.The solid product obtained was worked up as usual . Purity was checked by TLC. Yield= 75%, M.P.=170^{0}c,Molecular formula=$C_{15}H_{13}NO_4$ requires (%):C=66.41,H=4.83,N=5.16;IRcm-^{1} 3344,1690,1325,1HNMR(DMSO,300MHz,ppm):δ3.77 (3H,s),6.80(2H,m),6.89-7.08(3H,m),6.99(1H,d), 7.40(1H,d), 7.73(1H,d), 8.29(1H,s),9.96(1H,s)

2-(4-hydroxyphenyl)-1,2-dihydro-4H-benzo[d][1,3]oxazin-4-one(1-c):

Anthranillic acid (1.37g; 0.01 mol) and 4-hydroxybenzaldehyde (1.37g; 0.01 mol) were reacted according to general procedure.Refluxing was done for 5 hours.The solid obtained was purified.Purity was checked by TLC.

Yield=82%,M.P.=204^{0}c,Molecular formula=$C_{14}H_{11}NO_3$ requires (%):C=69.70%, H=4.60,N=5.81; IR cm^{-1} 3344,1690,1325, ^{1}HNMR (DMSO, 300M Hz, ppm) : δ6.77 (2H,d), 6.82-7.08 (3H,m), 7.31(2H,d), 7.40(1H,d),7.73(1H,d),8.29(1H,s),9.06(1H,s).

2-(6-methyl-4-oxo-4H-chromen-3-yl))-1,2-dihydro-4H-benzo [d] [1,3]oxazin-4-one(1-d):

Anthranillic acid(1.37g; 0.01 mol) and 6-Methyl-3-formylchromone(1.88g; 0.01 mol) were reacted according to general procedure.Refluxing was done for 8 hours.The solid obtained was purified and Purity was checked by TLC. Yield= 78% ,M.P.=192^{0}c,Molecular formula=$C_{18}H_{13}NO_4$ requires(%):C=70.35%, H=4.26,N=4.56; IR cm^{-1} 3344,1690,1325, ^{1}HNMR(DMSO,300MHz,ppm):δ2.46(3H,s),6.89-6.99(3H,m),7.19(1H,s),7.35(1H,d), 7.42 (2H,s),7.61-7.68(2H,m),7.73(1H,d).

5-Iodo-2-(4-oxo-4H-chromen-3-yl)-1,2-dihydro-4H-benzo[d][1,3]oxazin-4-one(1-e):

Iodo anthranillic acid(1.315g; 0.005 mol) and 3-formylchromone (0.8709g; 0.005 mol) were reacted according to general procedure.Refluxing was done for 8 hours.The solid obtained was purified and Purity was checked by TLC. Yield= 78% ,M.P.=192^{0}c,Molecular formula=$C_{17}H_{10}NO_4I$ requires (%):C=48.71%,H=2.40,N=3.34,I=30.27IR-3344, 1690, 1614,1325,^{1}HNMR(DMSO,300MHz,ppm):δ6.48 (1H,s), 6.92 (1H,d), 7.19 (1H,s), 7.23-7.30 (2H,m), 7.45 (1H,s), 7.47 (1H,dd),7.58 (1H,d), 7.74 (1H,dd)8.03 (1H,d).

2-(4-hydroxy-3-methoxyphenyl)-5-iodo-1,2-dihydro-4H-benzo[d][1,3]oxazin-4-one(1-f):

Iodo anthranillic acid(1.315g; 0.005 mol) and vanillin (0.7600g; 0.005 mol) were reacted according to general procedure. Refluxing was done for 8 hours.The solid obtained was purified and Purity was

checked by TLC. Yield = 72%,M.P.=208^{0}c,Molecular formula=$C_{15}H_{12}NO_4$Irequires(%):C=45.36,H=3.05,N= 3.05,I=30.27;IRcm^{-1}3344,1690, 1614,1325,^{1}HNMR(DMSO,300MHz,ppm):δ3.77 (3H,s), 6.80(2H,m),6.92(1H,d),6.99(1H,d), 7.08 (1H,s),7.23-7.30(2H,m),8.29(1H,s),9.99 (1H,d).

2-(4-hydroxyphenyl)-5-iodo-1,2-dihydro-4H-benzo[d][1,3]oxazin-4-one(1-g):

Iodo anthranillic acid(1.315g; 0.005 mol) and 4-hydroxybenzaldehyde (0.60g; 0.005 mol) were reacted according to general procedure for 6 hours.The solid obtained was purified and Purity was checked by TLC. Yield= 82% ,M.P.=206^{0}c,Molecular formula=$C_{14}H_{10}NO_3I$ requires (%): C=45.80%, H=2.75, N=3.82, I=34.75; IRcm $^{-1}$3344,1690,1325,^{1}H NMR (DMSO,300MHz,ppm):δ6.77(2H,d),6.92(1H,d), 7.08 (1H,s),7.23-7.30(4H,m),8.29(1H,s) 9.06 (1H,s).

5-Iodo-2-(6-methyl-4-oxo-4H-chromen-3-yl))-1,2-dihydro-4H-benzo[d][1,3]oxazin-4-one (1-h):

Iodo anthranillic acid (1.315g; 0.005 mol) and 6-methyl-3-formylchromone (0.940g; 0.005 mol) were reacted according to general procedure for 6 hours.The solid obtained was purified and Purity was checked by TLC.Yield=82%, M.P.=190^{0}c, Molecular formula =$C_{18}H_{12}NO_4I$ requires (%): C= 49.91,H=2.79, N=3.23, I=29.29; IRcm $^{-1}$3344, 1690, 1614, 1325,^{1}HNMR(DMSO,300Hz,ppm):δ2.46(3H,s),6.48(1 H,s),6.92(1H,d),7.19(1H,s),7.23-7.30 (2H,m)7.45(2H,s),7.61-7.68(2H,m).

Results and discussion

As the different bifunctional compounds react with formyl group containing aromatic compounds to form benzoxazinone system, anthranillic acid as well as iodo anthranillic acid was refluxed with various formyl group containing compounds, like 3-formyl chromone,6-methyl-3-formyl chromone, vanillin and 4-hydroxy benzaldehyde in presence of p-Toluene sulphonic acid, when compounds 1a to 1h were synthesised.Purity of all the synthesised compounds were first checked by TLC and melting point determination.Then structures were verified by IR and PMR spectral studies.

IR spectrum of compound (1c) a representative compound was not having peak in the region 2750-2850cm^{-1} for formyl group and also in the region 2500cm^{-1} for –COOH group,thus indicating condensation of two compounds. A peak at 3344 cm^{-1} was observed showing presence of N-H stretching. 300MHz PMR spectrum (DMSO) also elucidated structure of compound 1c. It was having seven signals for all the 11 protons present in it. First signal was a singlet at delta 9.06 due to proton of –OH group followed by a singlet at 8.29 due to –NH proton. A multiplet due to C_6-H,C_2-H and C_7-H appeared in the region6.82-7.08.a doublet due to two protons of benzene nucleus appeared at 7.31and other doublet at 6.77.one doublet due to C_5-H of benzoxazine nucleus was at 7.73and other due to C_8-H was at 6.93. The signal due to C_5-H was at higher value than that due to C_8-H of benzoxazine nucleus as deshielding caused by carbonyl group is higher than that caused by –NH group.

Conclusion

The aim of this research work was to synthesize novel derivatives of benzoxazinone, as literature review shows various biological activities of benzoxazinone derivatives .Thus it was planned to synthesize new derivatives of benzoxazinone that may be of medicinal importance.The compounds having benzoxazinone ring are found to show anticancer, anti-inflammatory, antibacterial, antiviral activity etc.The synthesis of such new compounds can always be of great interest for researchers.

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