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Antibacterial activity of coumarine derivatives synthesized from 4-amino-7-chloro-2-oxo-2H-chromen -3-carbaldehyde and comparison with standard drug

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ABSTRACT

In present paper , we report the organic syntheses of three compounds from 4-Amino-7-chloro -2-oxo-2H –chromen -3-carbaldehyde and describe the results of antibacterial activity of purified compounds.7-Chloro-4-[(2-hydroxy-benzylidene)-amino]-2-oxo-2H-chromen-3-carbaldehyde(1a).4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxy-phenylamino)-2-oxo-2H-chromen-3-carbaldehyde (2a) ,([4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxyl-phenylamino)-2-oxo-chromen-3-ylmethylene]-amino)-acetic acid (3a),have been synthesized and characterized using melting points , IR spectra , 1H-NMR and 13C-NMR spectra. The antibacterial activity of synthesized compounds and streptomycin and cefalexine at concentractions of 2mg/ml, 3mg/ml and 5mg/ml , have been evaluated against three strains of bacterial culture; Staphylococcus aureus, E.coli and Bacillus cereus. The compounds show bacteriostatic and bactericidal activity.

Keywords: Coumarine derivatives , antibacterial activity ,IR,1H-NM,13C-NMR, Streptomycine.

INTRODUCTION

Starting from 4-Amino-7-chloro -2-oxo-2H –chromen -3-carbaldehyde (a); derivatives (1a,2a,3a) are synthesized.Coumarin derivatives are large group of heterocyclic with oxygen as heteroatom.Coumarin is a chemical compound (specifically , a benzo-α-

pyrone) found in many plants notably in high concentration in the tonka bean (Dipteryx odorata), vanilla grass (Anthoxanthum odoratum) , woodruff (Galium odoratum) , mullein (Verbascum spp), and sweet grass (Hierochloe odorata).Coumarine and their derivatives have shown varius biological activities. Their fame has come mainly from their antithrombic, antiinflammatory, vasodilatory , and antiviral activities. Other several coumarin derivatives have antimicrobial properties 9 (Z.M.Nofal ;M.El-Zahar; and S.Abd El Karim), with reflux and condensation we have synthesize some new coumarin derivatives and to investigate their antibacterial activity against Staphylococcus aureus, E.coli and Bacillus cereus.The antibacterial activity of synthesized compounds is compared with antibacterial activity of Cefalexine and Streptomycine.

EXPERIMENTAL SECTION

Experimental Chemistry

7-Chloro-4-[(2-hydroxy-benzylidene)-amino]-2-oxo-2H-chromen-3-carbaldehyde (1a), 4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxy-phenylamino)-2-oxo-2H-chromen-3-carbaldehyde (2a) , ([4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxyl-phenylamino)-2-oxo-chromen-3-ylmethylene]-amino)-acetic acid (3a) are synthesized.

Measurement

The identification of derivatives 4-hydroxy-chromen-2-one (1a,2a,3a) , is made by using melting point , IR , 1H NMR , 13C NMR spectra and elemental analysis. Melting point was determinated on a Electrothermal apparatus (Fisher Scientific 2555) in a open capillary tube and are uncorrected.Infrared spectra were recorded in cm-1 for KBr pellts on a FT-IR Shimadzu 8400S spectrophotometer with resolution 4 cm-1 . 1H NMR spectra were recorded on a Bruker UNITY plus-500 ‘NMR 1’ spectrometer using DMSO-d6 as the solvent and TMS as the internal references standard (σ = 0,00 ppm).Chemical shifts are expressed in δ ppm.Mass spectra were taken on a LKB 9000 mass spectrometer. Element analysze was performed on a Perikin-Elmer 240 BCHN analyzer.The purity of the compounds (synthesized) was routinely checked by TLC using Merck Kieselgel-60 (F-254) and benzene,toluene,glacial acetic acid (80:10:10)as mobile phase. The spots were exposed in iodine vapour for visualization.

Preparation of 7-Chloro-4-[(2-hydroxy-benzylidene)-amino]-2-oxo-2H-chromen-3-carbaldehyde (1a)

For this synthesis is used as substrat in a 100 ml flask mixed 5 g 4-amino-7-chloro-2-oxo-2H-chromen-3-carbaldehyde , 10ml Dioxane , 0.5ml Et3N

The mixture was refluxed at 100 oC for 5h. The obtained crystals yellow are filtred and rinsed with ethanol and dried at room temperature.Recrystallization form absolute ethanol gave a yellow product of 80% yield, melting point 327 oC.

(Scheme.1)

Preparation of 4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxy-phenylamino)-2-oxo-2H-chromen-3-carbaldehyde (2a)

In a 100 ml flask were mixed 4g 7-Chloro-4-[(2-hydroxy-benzylidene)-amino]-2-oxo-2H-chromen-3-carbaldehyde with 10ml Ethanol , 3g amino fenole .The mixture was refluxed at 90 oC for ca. 6h .

Theobtained red crystals are filtred and dried at room temperature . Recrystallization form C2H5OH gave red crystals product of 70 % yield,meltingpoint, 399 oC.

(Scheme 2) .

Preparation of ([4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxyl-phenylamino)-2-oxo-chromen-3-ylmethylene]-amino)-acetic acid (3a)

In a 100 ml flask were mixed 3g of 4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxy-phenylamino)-2-oxo-2H-chromen-3-carbaldehyde ,with 10 ml Ethanol.The mixture was refluxed at 100 oC in water bath for ca. 8 h .The flask was placed in an ice bath for 1h until yellow crystalline precipitate was formed.After filtration the product was recrystallized from C2H5OH .The recrystallizacion gave a red product at 70% yield, melting.point;459 oC.

(Scheme 3).

Table-1 Analytical data

Compd m.p M.F Elemental analysis. Calculatet :Found (calc) % C H N O Cl

1a 327 oC C17H10ClNO4 62.30 62.28 3.08 3.00 4.27 4.20 19.53 19.50 10.8 10.7

2a 399 oC C23H16N2O5 69.00 68.5 4.03 4.00 7 6.95 19.98 19.98

3a 459 oC C25H21N3O6 63.35 63.30 4.61 4.58 9.15 9.12 20.89 20.87

Antibacterial activity

The purified synthesized compounds (1a,2a,3a) was subjected to test in vitro its antibacterial activity against three bacterial cultures ; Staphylococcus aureus,E.Coli and B.cereus. Antibacterial activity of compounds was investigated applying the Kirby-Bayer method or disc method (d=5.5 mm max. capacity 10 µg)

Table 2 Antibacterial activity- Staphylococcus aureus

Inhibition zone (mm)

Compound 2mg/ml 3mg /ml 5mg/ml

1a 11 15 17

2a 12 16 19

3a 13 16 20

Cephalexine 8 8 8

Streptomycine 20 20 20

Table 3 Antibacterial activity – E.Coli Inhibition zone (mm)

Compound 2mg/ml 3mg /ml 5mg/ml

1a 7 12 16

2a 8 14 18

3a 9 18 17

Cephalexine 8 8 8

Streptomycine 20 20 20

Table 4 Antibacterial activity – Bacillus cereus Inhibition zone (mm)

Compound 2mg/ml 3mg /ml 5mg/ml

1a 7 12 17

2a 8 13 18

3a 11 17 19

Cephalexine 9 9 9

Streptomycine 20 20 20

RESULTS AND DISCUSSION

By reacting equimolar amounts of 4-Amino-7-chloro -2-oxo-2H –chromen -3-carbaldehyde and correspomding reagents (according scheme 1) under reflux reaction condictions product 1a is synthesized in 80 % yield.

By reacting equimolar amounts 7-Chloro-4-[(2-hydroxy-benzylidene)-amino]-2-oxo-2H-chromen-3-carbaldehyde and corresponding reagents (according scheme 2) under reflux reaction condictions product 2a is synthesized in 70 % yield.

By reacting equimolar amounts of 4-[(2-Hydroxy-benzylidene)-amino]-7-(4-hydroxy-phenylamino)-2-oxo-2H-chromen-3-carbaldehyde and corresponding reagents (according scheme 3) under reflux reaction condictions product 3a is synthesized in 80% yield.

The structure of 4-Amino-7-chloro -2-oxo-2H –chromen -3-carbaldehyde derivatives (1a,2a,3a) were determined fromtheir IR, 1H NMR , 13C NMR spectar and their melting points as follows.

For (1a); IR bands (KBr,cm-1) 3850-2400cm-1 (OH) , NH ; 2910 cm-1 (C-HO stretch.), 1720 cm-1 (C=O) , 1600 (C=C stretch.) , 750 cm-1 (C-H bend.) 600 cm-1 (C-Cl stretch.)

1H NMR (DMSO-d6) δppm ;9.68 ppm s(H,CHO) , 7.21-7.53 t(H,aromatic) , 5.18 s (H,OH) 4.0

13 C NMR (DMSO) δppm ; 166.9ppm (C-Cl), 162ppm (C,COO) ; 152ppm (C,C-O) ; 133.4 (C,C-Cl); 121.7 , 125.6 , 128.0 (3C-aromatic)

For (2a) IR bands (KBr,cm -1) 3400cm-1(OH) 3200 cm-1 (N-H stretch.) , 3000 cm-1 (C-H stretch.), 3200 cm 1 (N-H stretch.), 2730cm1 (C-H stretch.) , 1725cm1 (C=O stretch.),1600cm1(C=C stretch.) , 1050cm1(C-O stretch), 750cm1(C-H bend.)

1H NMR (DMSO-d6) δppm 6.37 , 6.39 , 7.41 t(3H aromatic) 5.0(H,OH), 4.0 d(H,NH), 5.0ppm (H,OH), 4.0ppm s(NH)

13C NMR (DMSO)δppm181ppm(C,C-NH),178ppm(C,CHO),162ppm (C,COO),151ppm (C,C-O), 105,109 ,116,127ppm (4C aromatic)

For (3a) IR bands (KBr,cm -1) 3280 cm-1 (O-H stretch.),3180cm-1(NH stretch.), 3000cm-1(C-H stretch.),2400cm-1(O-H carbocylic),1760cm-1(C=O stretch.),1650cm-1(C=N stretch),1710cm-1(C=O),1020cm-1(C-O),750cm-1(C-H bend.)

1H NMR (DMSO-d6) δppm 7.4 ,6.5,6.4 (3H aromatic), 5.0 (H.OH) , 4.0 s(H,NH) , 3.53ppm t(CH2), 2.65ppm t(3H,CH3N) , 11.40-155 ppm t(4H,2CH2)

13CNMR (DMSO) δppm 176.0ppm (C,COOH), 167.ppm (C,C-NH), 162.0 (C,C=O), 151.7ppm(C,C-O), 127,109,105ppm (3C aromatic), 51.6(C,C-N), 46.6(C,C-N) , 62.7(C,C-OH), 30.6,27.8ppm (C,CH2)

CONCLUSION

From the results the followin conclusion were drawn:The study provides the first evidence that compounds (1a,2a,3a) obviously inhibit the growth of S.auerus , E.coli and B.cereus.

The compounds (1a,2a,3a) compared with the antibacterial activity of Streptomycine in S.aureus ,E.coli and B.cereus.

This study provided the first evidence that these compounds 1a,2a,3a showed a significant antibacterial effect against S.aureus,E.coli and B.Cereus.

The chemical structures of synthesizen compounds were determined according to extensive NMR experiments and published data.

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