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Synthesis and fluorescence activity of some new benzocoumarin amino acid derivative

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ABSTRACT

A series of new benzocoumarin amino acid and glycosidic derivatives were synthesized with the aim of evaluating their fluroscence activity. The newly synthesized glycosidic derivatives were prepared using sugar trichloroacitamidate derivatives. The structures of the new compounds were confirmed by ^{1}H-NMR spectrometry. Out of the fourteen tested compounds, four derivatives exhibited very high emission maxima at 440 nm which are benzo[5,6]coumarine-3-carboxyl L-hydroxyproline methyl ester 3, benzo[5,6]coumarine-3-carboxyl DL-phenylalanine methyl ester 4a, benzo[5,6]coumarine-3-carboxyl DL-threonine methyl ester 4c and benzo[5,6] coumarine-3-carboxyl *O*-(2:3,5:6-di-*O*-isopropylidene-α-D-mannofuranosyl) L-serine methyl ester 5c. Accorrding to these previous results these compounds con be subjected for further studies to be used as laser dyes or fluorescent probes.

Keywords: Amino acids, Benzocoumarin, Fluorescence activity.

INTRODUCTION

Coumarin compounds have widespread usage in many applications. Several fluorescent organic chromophores derived from coumarins have been used as fluorescent brighteners, laser dyes and organic nonlinear optical materials (Amit, R. J. 2009); coumarins constitute the largest class of laser dyes in the ‘blue-green’ region (Jones, G., 1985). Due to their inherent photochemical characteristics, reasonable stability, good solubility and relative ease of synthesis coumarin derivatives have been extensively investigated for electronic and photonic applications such as charge-transfer agents, solar energy collectors and nonlinear optical materials (Christie, R., M., *et al*., 2000). They are widely used as fluorescent labels and pigments, as fluorescent probes for physiological and enzymatic measurements, as signaling units in sensors and in sophisticated photo physical systems. Coumarin chromophores exhibit intense fluorescence on substitution of various functional groups at different positions (Sanghi, S., *et al.*, 1995) and appropriatlely substituted coumarins find application as fluorescent dyes for synthetic fibers and as light fluorescent pigments, which impart vivid brilliance to paints and printing inks (Voedisch R. W. 1973).

MATERIAL AND METHODS

Materials and reagents

The boiling point range of the petroleum ether used was 40-60 ^{o}C. Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} plastic plates (E. Merck, layer thickness 0.2 mm) in the following solvent systems, S_1: petroleum ether/ethyl acetate (3 : 1); S_2: petroleum ether/ethyl acetate (1 : 1); S_3: petroleum ether/ethyl acetate (1 : 2); S_4: methanol/chloroform (1:10), S_5: n-hexane/ethyl acetate (15:1). The spots on thin layer plates were detected by UV lamp. Melting points were determined on a Buchi 510 melting-point apparatus and the values are uncorrected. ^{1}H NMR spectra were measured on Bruker (300 MHz) and TMS was used as internal standard and Mass spectra were measured on a GC-MSQP 1000EX Schimadzu at microanalytical laboratory, Cairo University, Cairo, Egypt.

Chemical Method

Benzo[5,6]coumarine-3-carboxyl β-alanine methyl ester (2)

Yellow crystals (0.95 g, 67%), R_f = 0.49(S_2), m.p. 170 ^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.68 (s, 1H, CH pyranone ring), 9.18-9.22 (brs, 1H, NH), 8.51-7.50 (m, 6H, ArH), 8.14-7.50 (m, 5H, ArH) , 3.81-3.77 (m, 2H, $NHCH_2$), 3.75 (s, 3H, OCH_3), 2.73-2.69 (m, 2H, CH_2CO). m/z 325.

Benzo[5,6]coumarine-3-carboxyl L-hydroxy proline methyl ester (3)

White crystals (1.0 g, 63%), R_f = 0.16 (S_3), m.p. 190^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.92 (s, 1H, CH pyranone ring), 8.30 (d, 1H, *J* = 8.7 Hz, ArH), 8.08 (d, 1H, *J* = 9.0 Hz, ArH), 7.95 (d, 1H, *J* = 7.8 Hz, ArH), 7.75-7.58 (m, 2H, ArH), 7.50 (d, 1H, *J* = 9, ArH), 4.89 (t, *J* = 8.1 Hz, 1H, NCH), 4.45-4.57 (brs, 1H, OH), 3.83 (s, 3H, OCH_3), 3.87-3.82 (m, 1H, OCH), 3.68 (d, *J* = 11.7 Hz, NCH_2), 2.54-2.13 (m, 2H, CH_2). m/z 367

Benzo[5,6]coumarine-3-carboxyl DL-phenyl alanine methyl ester (4a).

Faint yellow crystals (1.4 g, 80%), R_f = 0.39(S_1), m.p. 94 ^{o}C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.62 (s, 1H, CH pyranone ring), 9.30 (d, 1H, *J* = 7.2 Hz, NH), 8.41 (d, 1H, *J* = 8.4 Hz, ArH), 8.12 (d, 1H, *J* = 9.0 Hz, ArH), 7.95 (d, 1H, *J* = 8.1 Hz, ArH), 7.75-7.64 (m, 2H, ArH), 7.51 (d, 1H, *J* = 9.0 Hz, ArH), 7.32-7.25 (m, 5H, ArH), 5.04-5.02 (m, 1H, NCH), 3.77 (s, 3H, OCH_3), 3.29-3.21 (m, 2H, CH_2-ph).

Benzo[5,6]coumarine-3-carboxyl L-methionine methyl ester (4b)

Brown crystals (1.09 g, 65%), R_f = 0. 35(S_1), m.p. 118-121 ^{o}C . ^{1}H-NMR (300 MHz,$CDCl_3$): δ = 9.68 (s, 1H, CH pyranone ring), 9.36 (d, 1H, NH), 8.44 (d ,1H, *J* = 8.4 Hz, ArH), 8.15 (d, 1H, *J* = 9.0 Hz, ArH), 7.94-7.64 (m, 3H, ArH), 7.54 (d, 1H, *J* = 9.0 Hz, ArH), 5.10-4.91 (m, 1H, NCH), 3.81 (s, 3H, OCH_3), 3.01-3.04 (m, 2H, SCH_2), 2.64-2.61 (m, 2H, CH_2), 2.16 (s, 3H, SCH_3). m/z 385

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Benzo[5,6]coumarine-3-carboxyl DL-threonine methyl ester (4c)

Brown crystals (1.06 g, 68%), R_f = 0.39 (S_2), m.p. 158°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.62 (s, 1H, CH pyranone ring), 9.54 (d, 1H, *J* = 8.1 Hz, NH), 8.39 (d, 1H, *J* = 8.4 Hz ,ArH), 8.10 (d, 1H, *J* = 9.0 Hz, ArH), 7.93 (d, 1H, *J* = 8.1 Hz, ArH) , 7.77-7.58 (m, 2H, ArH), 7.49 (d, 1H, *J* = 9.0 Hz, ArH), 4.85-4.81 (m, 1H, NCH), 4.51-4.46 (m, 1H, OCH), 3.83 (s, 3H, OCH_3), 2.6-2.8 (brs, 1H, OH), 1.35-1.23 (m, 3H, CH_3). m/z 355

Benzo[5,6]coumarine-3-carboxyl L-serine methyl ester (4d)

Yellow crystals (1.05 g, 70%), R_f = 0.23(S_2), m.p. 120°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.68 (s, 1H, CH pyranone ring), 9.68-9.66 (m, 2H, NH, CH pyranone), 8.44 (d, 1H, *J* = 8.4 Hz, ArH) , 8.15 (d, 1H, *J* = 9.0 Hz, ArH) , 7.96 (m, 1H, *J* = 7.8 Hz, ArH), 7.80-7.75 (m, 1H, ArH), 7.67-7.62 (m, 1H, ArH), 7.54 (d, 1H, *J* = 9.0 Hz, ArH), 4.94-4.89 (m, 1H, NCH), 4.13-4.11 (m, 2H, OCH_2), 3.86 (s, 3H, OCH_3). m/z 341

Benzo[5,6]coumarine-3-carboxyl L-tyrosiene methyl ester (4e)

Yellowish brown (1.09 g, 60%), R_f =0.44(S_2), m.p. 122-125°C. ^{1}H-NMR (300 MHz,$CDCl_3$): δ = 9.59 (s, 1H, CH pyranone ring), 9.31 (d, 1H, *J* = 7.8 Hz, NH), 8.37 (d, 1H, *J* = 8.4 Hz, ArH), 8.09 (d, 1H, *J* = 9.0 Hz ,ArH), 7.92 (d ,1H, *J* = 7.8 Hz ,ArH), 7.74 (d, 1H, *J* = 8.4 Hz, ArH), 7.64 (d, 1H, *J* = 7.2 Hz, ArH), 7.48 (d, 1H, *J* = 9.0 Hz, ArH), 7.14-7.11 (m, 2H , ArH), 6.82-6.79 (m, 2H, ArH), 5.01-5.00 (m, 1H, NCH), 3.77 (s, 3H, OCH_3), 3.23-3.08 (m, 2H, CH_2-ph). m/z 417

Benzo[5,6]coumarine-3-carboxyl O-(2:3,5:6-di-O-isopropylidene-α-D-mannof-uranosyl) L-hydroxyproline methyl ester (5a)

Yellow crystals (0.76 g, 28%), R_f = 0.27(S_2), m.p. 110°C. ^{1}H-NMR (300 MHz,$CDCl_3$): δ = 8.85 (s, 1H, CH pyranone ring), 8.25 (d, 1H, *J* = 8.4 Hz, ArH), 8.05(d, 1H, *J* = 9.0 Hz, ArH), 7.92 (d, 1H, *J* = 8.4 Hz, ArH), 7.70-7.56 (m , 2H, ArH), 7.45 (d, 1H, *J* = 9.0 Hz, ArH), 5.27 (s, 1H, H-1), 4.76-4.70 (m, 2H, NCH, H-3), 4.54 (d, *J* = 6.0 Hz, 1H, H-2), 4.41-4.39 (m, 1H, H-5), 4.06-3.98 (m, 4H, NCH, H-6, H-6'), 3.67 (s, 3H, OCH_3), 2.50-2.2 (m, 3H, HOCH, CH_2), 1.43, 1.37, 1.35, 1.30 (4s, 12H, $4CH_3$).

Benzo[5,6]coumarine-3-carboxyl O-(2:3,5:6-di-O-isopropylidene-α-D-manno-furanosyl) DL-threonine methyl ester (5b)

Yellow crystals (0.65 g, 25%), R_f=0.24(S_4), m.p. 194°C. ^{1}H-MNR (300 MHz, $CDCl_3$): δ= 9.68 (s, 1H, CH pyranone ring), 9.45 (d, 1H, *J* = 8.1 Hz, NH), 8.45 (d, 1H, *J* = 8.4 Hz, ArH), 8.15 (d, 1H, *J* = 9.0, ArH), 7.97 (d, 1H, *J* = 8.4, ArH), 7.79-7.52 (m, 3H, ArH), 5.13 (s, 1H, H-1), 4.92-4.83 (m, 2H, NHCH, H-3), 4.66 (d, 1H, *J* = 6.0 Hz, H-2), 4.50-4.47 (m, 1H, H-5), 4.24-4.05 (m, 2H, H-5, H-6), 3.89-3.73 (m, 4H, H-6, OCH_3), 1.48, 1.42, 1.39, 1.32 (4s, 12H, $4CH_3$), 0.95 (s, 3H, CH3).

Benzo[5,6]coumarine-3-carboxyl O-(2:3,5:6-di-O-isopropylidene-α-D-manno-furanosyl) L-serine methyl ester (5c)

White crystals (0.76 g, 30%), R_f =0.42(S_2), m.p. 128-131°C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 9.68 (s, 1H, CH pyranone ring), 9.45-9.42 (m, 1H, NH), 8.46 (d, 1H, *J* = 6.6 Hz, ArH) , (d, 1H, *J* = 9.3 Hz, ArH), 7.94 (d, 1H, *J* = 6.6 Hz, ArH), 7.78-7.64 (m, 2H, ArH), 7.49 (d, 1H, *J* = 9.3 Hz, ArH), 5.01 (s, 1H ,H-1), 4.99 (m, 1H, NHCH), 4.96-4.85 (m, 1H, H-3) ,4.66 (d, 1H, *J* = 6.0 Hz, H-2), 4.40-4.25 (m, 1H, H-4), 4.04-3.94 (m, 5H, H-5, H-6, H-6', CH_2O), 3.82 (s, 3H, OCH_3), 1.45, 1.40, 1.32, 1.30 (4s, 12H, $4CH_3$). m/z 583

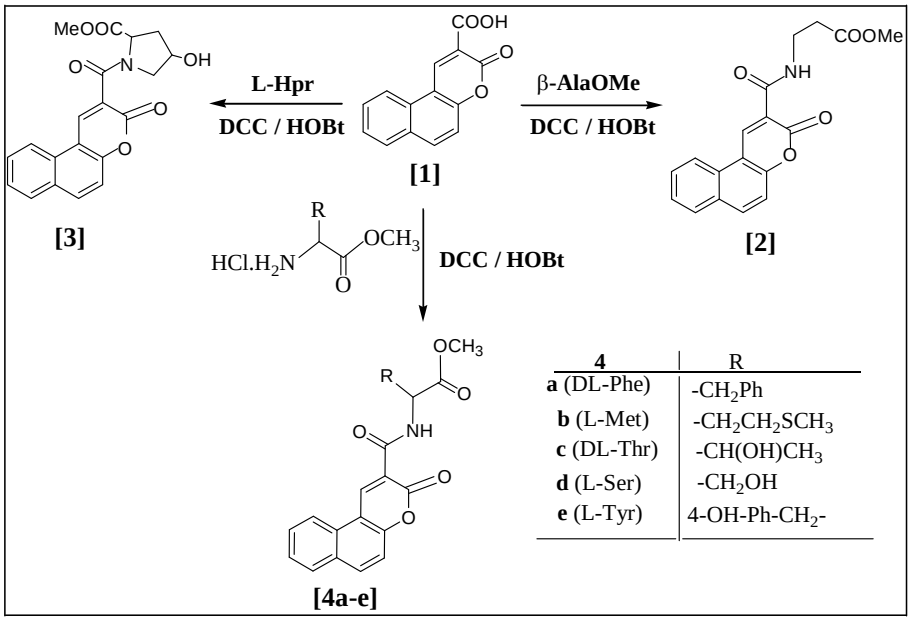
Fluroscence Study

The uv/vis absorption and fluorescence measurements were conducted at room temperature and allowed to stand for 10 min with concentration $1x10^{-5}$ $molL^{-1}$. A Shimadzu-UV Probe Version 2.33 UV-Visible automatic recording spectrophotometer with 1 cm quartz cell was used for the absorbance measurements. A JASCO-FP6300 spectrofluorometer with 1 cm quartz cell was used for the excitation and emission measurements.

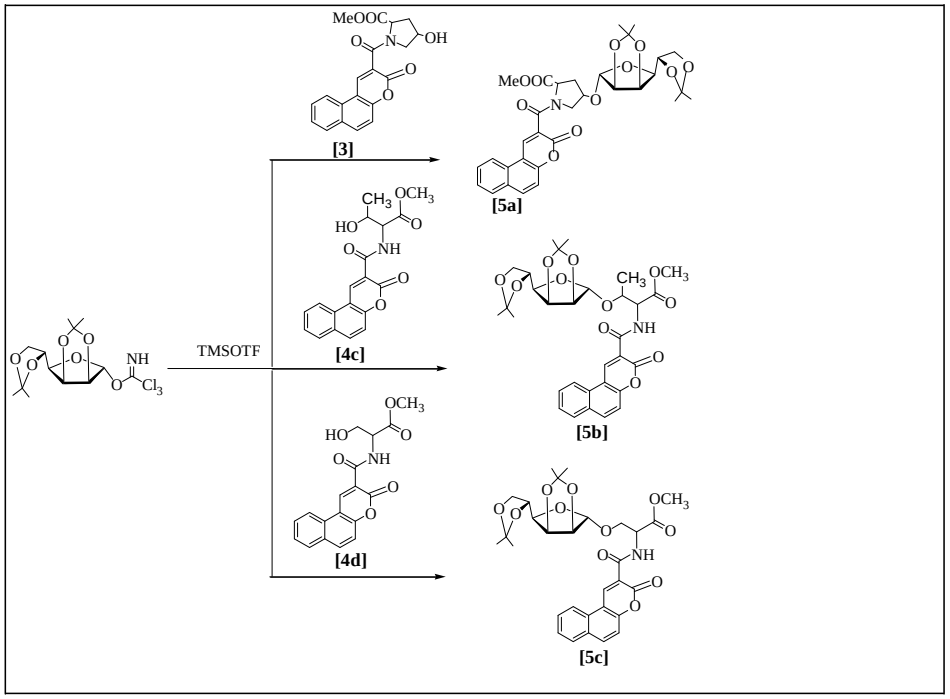
RESULTS AND DISSCUSION

Chemistry

In the present study, the compounds 2, 3 and 4a-e were prepared as discussed in the literature through the DCCI coupling method Scheme 1, some of these synthesized derivatives were further subjected to glycosilation using two carbohydrates to yield compounds 5a, 5b and 5c Scheme (2). The synthesis of the manno benzo[5,6] coumarine-3-carboxy amino acid esters 5a, b and c by glycosilation of 3, 4c and 4d as an alcohol acceptor precursor, with *O*-(2:3,5:6-di-*O*-isopropylidene-α-Dmannofuranose)trichloroacetamidate as donor precursor in the presence of catalytic amount of trimethylsilyltrifluoro methane sulfonate (TMSOTf) as Lewis acid to afford the α-anomeric forms 5a, b and c in 25 %, 30 % and 28 % yield, respectively. The chemical structure of the amino acid glycosidic derivatives 5a, 5b, 5c and 6 were confirmed by ^{1}H-NMR. The ^{1}H-NMR exhibit the following common data: Signals of the protons of CH of the pyranone ring appeared in the range 9.68-8.84 ppm, signals of the protons of CONH groups of the peptide bonds appeared in the range 9.45-8.25 ppm except for L-hydroxyproline methyl ester derivative, multiplet signals between 8.46-7.45 ppm are of the six aromatic protons, singlet signal from 3.84 to 3.67 ppm for the three protons of OCH_3 of the ester groups, in addition to signals characteristic for the amino acid side chain and carbohydrates moiety (see Experimental part).



Scheme 1: Synthesis of different benzocoumarin amino acid derivatives.



Scheme (2): Glycosilation of some benzocoumarin amino acid derivatives with α- isopropylidene-α-mannofuranosyl trichloroacetamidate derivative.

UV-Vis spectra at different solvent

The studies of absorption spectra of coumarin derivatives were performed in ethanol, methanol, benzene, ether and acetonitrile solvents at a concentration $1x10^{-5}$ $molL^{-1}$. The absorption spectrum of coumarin derivatives in ethanol shows a maximum absorption bands at 225 nm and 260 nm due to n-π* (Bakier, E., and M. S. A. Abdel-Mottaleb, 2005) and absorption around 370 nm due to the π-π* transition (Rodembusch F. S., *et al.*, 2007). The shape of absorption spectra of all the compounds is very similar to each other. The connection of amino acids moiety may increase π-conjugation. The general observation is that there is little influence on the absorption spectrum shift values with increasing solvent polarity. Effect of different solvents on UV-vis spectra for coumarin derivatives is shown in Figures (1-5).

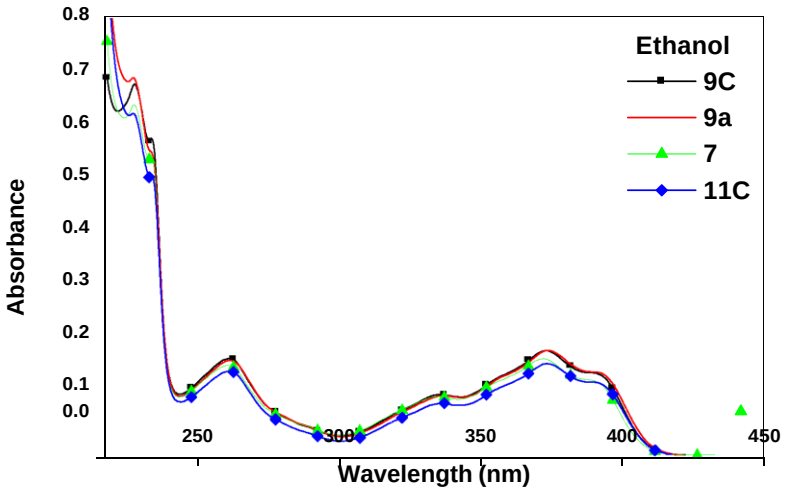


Figure (1): UV-Vis spectra for 1 x10^{-5} molL^{-1} of coumarin derivatives in ethanol.

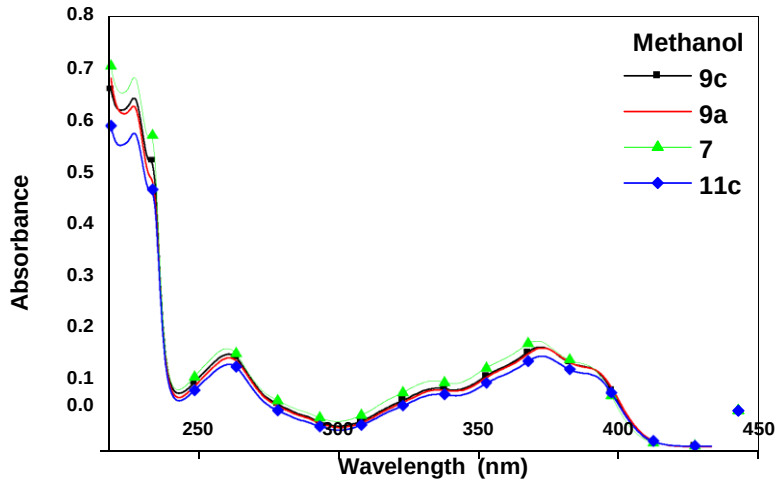


Figure (2): UV-Vis spectra for 1 x10^{-5} molL^{-1} of coumarin derivatives in Methanol.

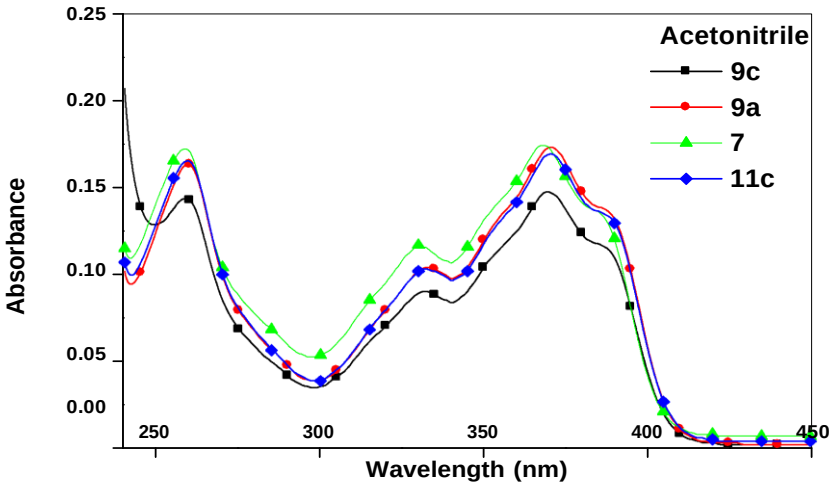


Figure (3): UV-Vis spectra for 1 x10^{-5} molL^{-1} of coumarin derivatives in acetonitrile.

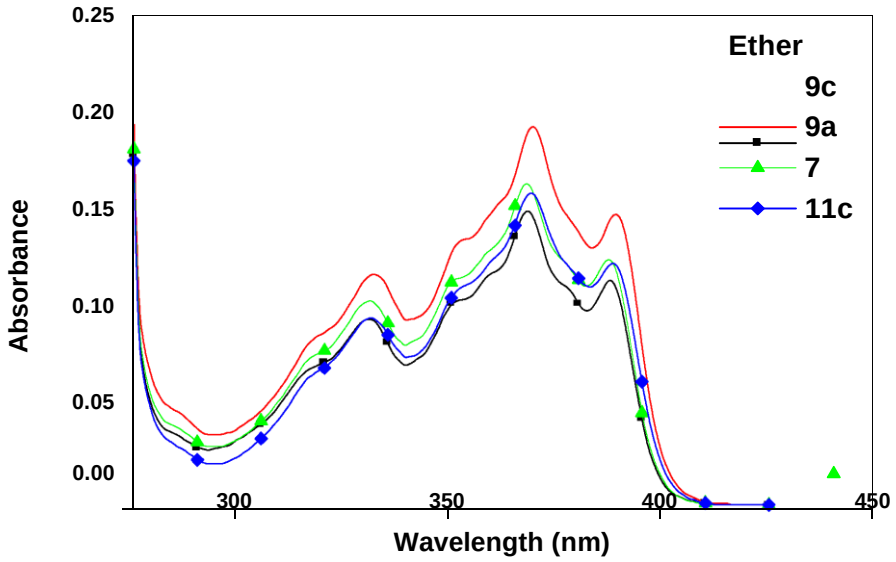


Figure (4): UV-Vis spectra for 1 x10^{-5} molL^{-1} of coumarin derivatives in ether.

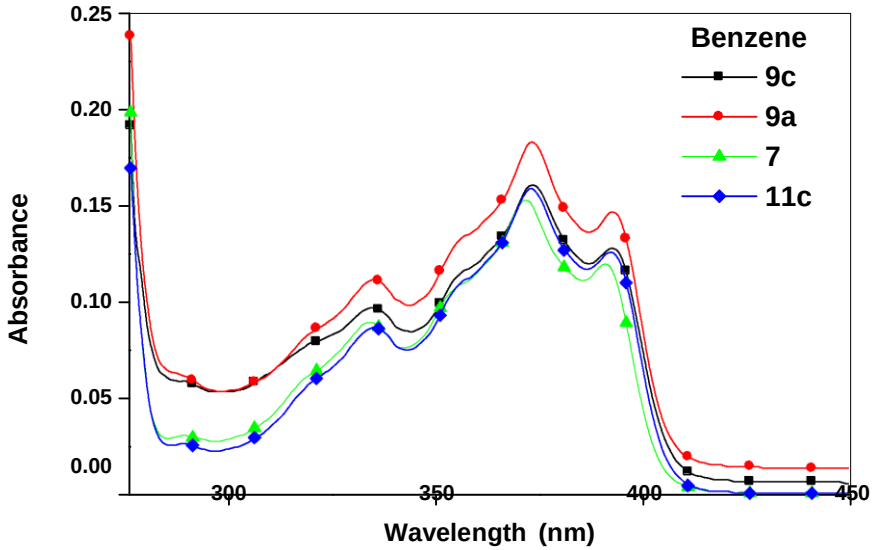


Figure (5): UV-Vis spectra for 1 x10^{-5} molL^{-1} of coumarin derivatives in benzene.

Fluorescence spectra at different solvent

Coumarins derivatives have many advantages including high fluorescence quantum yield, large Stokes shift, excellent light stability, and less toxicity. Therefore coumarins have been widely used in the fields of biology, medicine, perfumes, cosmetics, and fluorescent dyes. By far coumarin derivatives have been used as fluorescent probes of pH, for detection of nitric oxide, nitroxide, and hydrogen peroxide. Moreover, coumarin derivatives have served as good chemosensors of anions including cyanide, fluoride, pyrophosphate, acetate, benzoate, and dihydrogenphosphate as well as various metal ions comprised of Hg(II), Cu(II), Zn(II), -Ni(II), Ca(II), Pb(II), Mg(II), Fe(III), Al(III), Cr(III), and Ag(I). Several systems containing coumarin exhibited simultaneous sensitivity toward two or more different metal ions, e.g. Ca(II) and Mg(II), Ni(II) and Co(II), Cu(II) and Hg(II), Na(I) and K(I), Cu(II) and Ni(II), Hg(II) and Ag(I), Cu(II)/Ni(II)/Cd(II), Zn(II)/Cd(II)/Pb(II), or Ni(II)/Pd(II)/Ag(I). The excitation and emission maxima of the coumarin derivatives can be found at 370 and 440 nm, respectively (Fig. 6-10). The studies of fluorescence of coumarin derivatives were performed in ethanol, methanol, benzene, ether and acetonitrile solvents at a concentration 1x10^{-5} molL^{-1}.

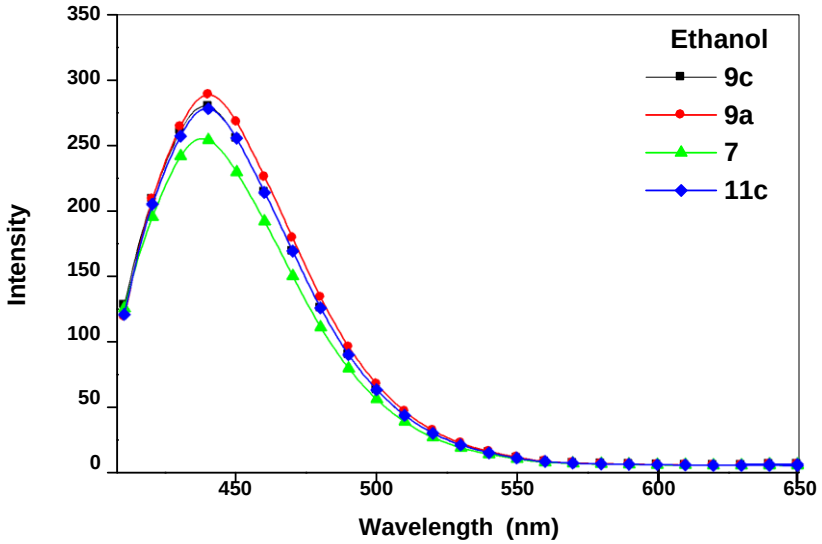


Figure (6): Fluorescence spectra for $1x10^{-5}$ $molL^{-1}$ coumarin derivatives in ethanol.

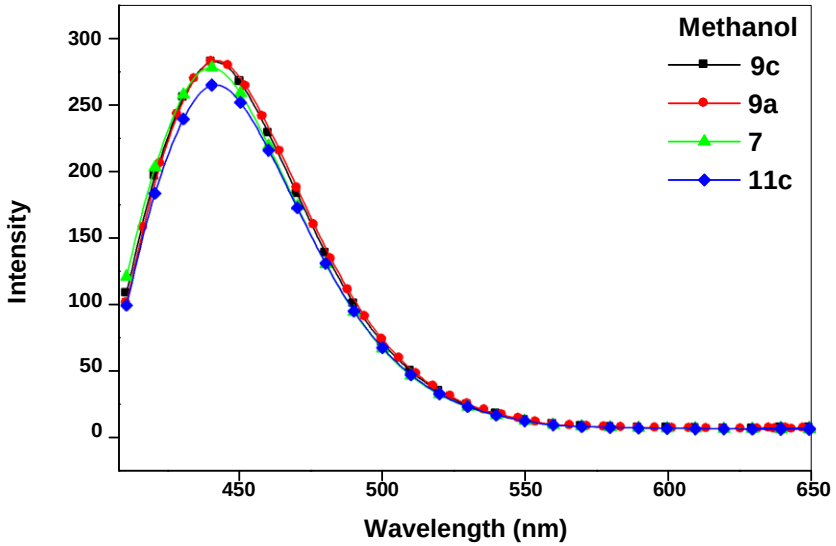


Figure (7): Fluorescence spectra for $1x10^{-5}$ $molL^{-1}$ coumarin derivatives in methanol.

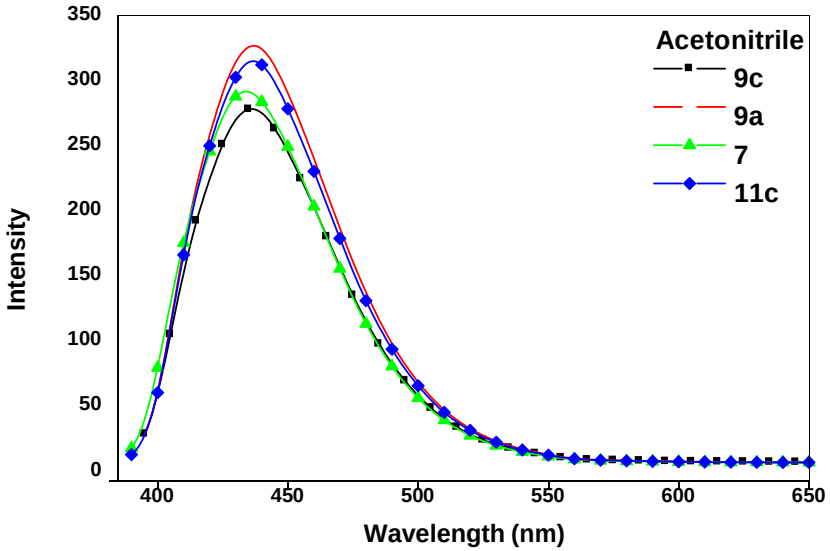


Figure (8): Fluorescence spectra for $1x10^{-5}$ $molL^{-1}$ coumarin derivatives in acetonitrile.

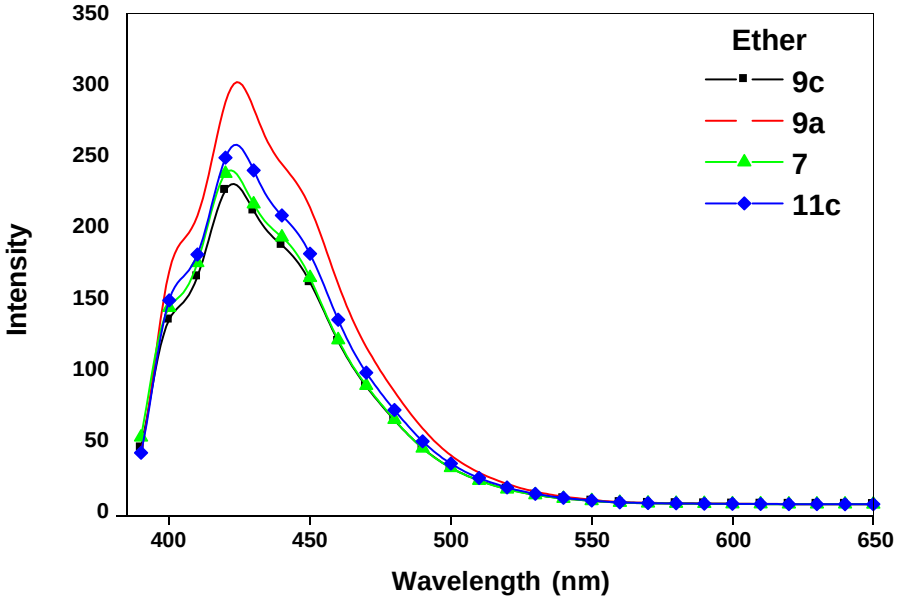


Figure (9): Fluorescence spectra for $1x10^{-5}$ $molL^{-1}$ coumarin derivatives in ether.

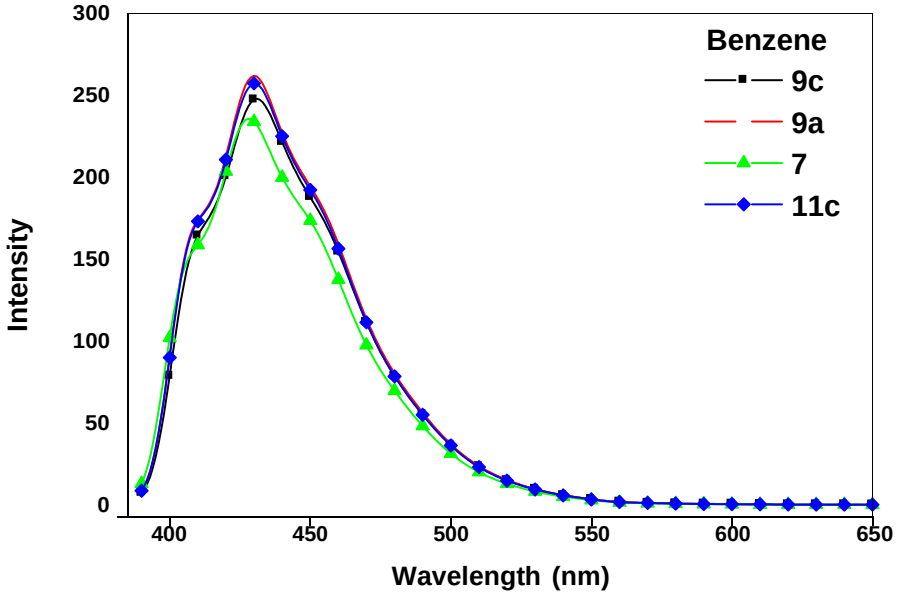


Figure (10): Fluorescence spectra for $1x10^{-5}$ $molL^{-1}$ coumarin derivatives in benzene.

CONCLUSION

The article afforded an easy and facile method for preparation of benzo[5,6]coumarin-3-carboxyl amino acid glycosidic derivatives coupling in addition to studying the fluorescence activity to all synthesized compounds. Four compounds (3, 4a, 4c and 5c) showed high fluorescence and thus can be used in the synthesis of laser dyes or probes.

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تخليق و دراسة النشاط الفلوروسينى لبعض مشتقتات الكومارين

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الملخص العربى

لقد تم تخليق و دراسة النشاط الفلوروسينى لبعض المركبات المشتقه من الكومارينات لما تتميز به الكومارينات من نشاط فلوروسينى. ولقد وجد ان هناك أربعة مركبات (٣، ٤أ، ٤ج و ٥ج) لها نشاط فلوروسينى عالى ومن ثم يمكن استخدامهم فى الكثير من الصناعات الهامه.