Available online at **www.joac.info**

ISSN: 2278-1862

Journal of Applicable Chemistry

2015, 4 (2): 461-466

(International Peer Reviewed Journal)

Synthesis, Characterization And Biological Activity Studies Of Substituted 2-Amino-3-Ethoxycarbonyl-5-Oxo-4-(Substituted Phenyl) -4H, 5H–Pyrano-[3, 2-c]-Chromene

Vishal P. Narodia, Milan S. Vadodaria*, Kartik D. Ladva, Govind V. Vagadiya

*Department of Chemistry, Shree M. & N. Virani Science College, Yogidham Gurukul, Rajkot – 360005, Gujarat, **INDIA**

Email: msvadodaria@vsc.edu.in

Accepted on 20th March 2015

ABSTRACT

Catalytic reaction of 5,8-Dimethyl-4-hydroxycoumarin (0.01mol) and α-cyano- cinnamate in solution state gives good yield of Substituted 2-Amino-3-ethoxycarbonyl-5-oxo-4-(substituted phenyl)-4H, 5H-pyrano-[3, 2-c]-chromene. The structures of new compounds were confirmed on the basis of UV, IR, NMR and Mass spectral studies.

Keywords: Catalyst piperidine, 5,8-Dimethyl-4-hydroxycoumarin, α-cyano cinnamate, substituted 2-Amino-3-ethoxycarbonyl-5-oxo-4-(substitutedphenyl)-4H,5H-pyrano-[3,2-c]-chromene,spectral confirmation.

INTRODUCTION

Natural and synthetic coumarins containing 3:4 fused ring systems are known to exhibit various physiological properties [1-3]. Coumarin has anti-tumor activity [4] and anti-fungal properties [5]. Cyclocoumarol [6] and dicoumarol are one of the most active anticoagulant. It is also used in the treatment of asthma [7], lymphedema [8] and reported antioxidant [9].

In view of the interesting biological properties of above mentioned fused tricyclic system, it was very pertinent to study the chemistry and synthesis of such systems and to prepare few series of such congeners. Hence several new heterocycles were prepared as per reaction scheme mentioned for further synthetic study.

MATERIALS AND METHODS

Preparation of 5, 8-dimethyl-4-hydroxycoumarin: It was prepared according to method of Shah and coworkers [10, 11].

Preparation of 2-Amino-8, 10-dimethyl-3-ethoxycarbonyl-5-oxo-4-(4-hydroxy-3-methoxy- phenyl)-4H, 5H-pyrano-[3, 2-c]-chromene [12]: 5,8-Dimethyl-4-hydroxycoumarin (0.01mol) and α-cyano cinna mate (0.01 mol), absolute ethanol (30 mL) and catalytic amount of piperidine (0.1 mL) was taken in round

bottom flask, refluxed in water bath for 5-6 h. The reaction mixture was cooled and the product was colle cted by filtration. The crude product was recrystalised from N, N-dimethylformamide (DMF); Yield, 70 %, m.p. 210ºC. Similarly, other ethyl-2-amino-4-(substituted phenyl)-5-oxo-4H-5H-pyrano-[3,2-c]-chromene-3-carboxylate were also prepared.

RESULTS AND DISCUSSION

The constitution of newly synthesized compounds was supported by UV, IR, NMR and Mass spectra study. The details are as under.

Ultra Violet spectral study: The UV spectra of newly synthesized compounds were taken on ELICO SL 159 UV-VIS spectrophotometer. The UV spectra were taken in DMF and also in other acidic and alkaline conditions. The bathochromic as well as hypsochromic shifts are recorded. The UV spectral trend and changes in electronic transfer band (ET bands) are mentioned in table 1. It is observed that in most of the cases λ_{max} values were observed at 271,274,277,280,283, 298,307,316,319 and 322nm. The other ET bands appeared at 214,229,235, 238, 253,292,313and 349 nm. As UV spectra of compounds are taken in acidic and basic medium, a considerable shift changes in λ_{max} values and also changes in ET bands were observed.

Table 1 : Physical data of substituted 2-Amino-3-ethoxy carbonyl-5-oxo-4(substituted phenyl)-4H, 5H–pyrano-[3, 2-c]-chromene.

Code	R_1	R_2	R_3	R_4	R	Molecular Formula	Molecular Weight gm/mol	M.P. (ºC)	Elemental Analysis		
									C	H	N
VAM-1	CH_3	H	CH_3	H	4-Hydroxy-3-methoxy phenyl	$C_{24}H_{23}NO_7$	437	210	65.99 (65.90)	5.33 (5.30)	3.22 (3.20)
VAM-2	CH_3	H	CH_3	H	3-Bromo phenyl	$C_{23}H_{20}BrNO_5$	470	200	58.70 (58.74)	4.30 (4.29)	2.95 (2.98)
VAM-3	H	CH_3	H	H	3-Bromo phenyl	$C_{22}H_{18}BrNO_5$	456	220	57.97 (57.91)	3.95 (3.98)	3.00 (3.07)
VAM-4	H	H	H	CH_3	4-Hydroxy-3-methoxy phenyl	$C_{23}H_{21}NO_7$	423	210	65.30 (65.24)	5.03 (5.00)	3.30 (3.31)
VAM-5	H	CH_3	H	H	4-Hydroxy-3-methoxy phenyl	$C_{23}H_{21}NO_7$	423	220	65.20 (65.24)	5.02 (5.00)	3.33 (3.31)
VAM-6	H	H	-Benzo-		3-Bromo phenyl	$C_{25}H_{18}BrNO_5$	492	210	60.95 (60.99)	3.71 (3.69)	2.80 (2.85)
VAM-7	CH_3	H	CH_3	H	3-Nitro phenyl	$C_{23}H_{20}N_2O_7$	436	244	63.32 (63.30)	4.67 (4.62)	6.40 (6.42)
VAM-8	H	H	H	CH_3	3-Nitro phenyl	$C_{22}H_{18}N_2O_7$	422	250	62.55 (62.56)	4.35 (4.30)	6.69 (6.63)
VAM-9	H	CH_3	H	H	3-Nitro phenyl	$C_{22}H_{18}N_2O_7$	422	242	62.59 (62.56)	4.39 (4.30)	6.67 (6.63)
VAM-10	H	H	H	H	3-Nitro phenyl	$C_{21}H_{16}N_2O_7$	408	222	61.75 (61.77)	3.91 (3.95)	6.85 (6.86)
VAM-11	H	H	H	H	3-Bromo phenyl	$C_{21}H_{16}BrNO_5$	442	225	57.04 (57.03)	3.60 (3.65)	3.10 (3.17)
VAM-12	H	H	H	H	4-Hydroxy-3-methoxy phenyl	$C_{22}H_{19}NO_7$	409	190	65.52 (65.54)	4.61 (4.68)	3.44 (3.42)
VAM-13	H	H	-Benzo-		3-Nitro phenyl	$C_{25}H_{18}N_2O_7$	458	240	65.57 (65.50)	3.99 (3.96)	6.15 (6.11)

VAM-14	H	H	-Benzo-	4-Hydroxy-3-methoxy phenyl	$C_{26}H_{21}NO_7$	459	202	67.95 (67.97)	4.67 (4.61)	3.00 (3.05)
VAM-15	-Benzo-	H	H	3-Nitro phenyl	$C_{25}H_{18}N_2O_7$	458	225	65.55 (65.50)	3.92 (3.96)	6.13 (6.11)
VAM-16	-Benzo-		H	H	3-Bromo phenyl	$C_{25}H_{18}BrNO_5$	492	227	60.91 (60.99)	3.62 (3.69)	2.87 (2.85)
VAM-17	-Benzo-		H	H	4-Hydroxy-3-methoxy phenyl	$C_{26}H_{21}NO_7$	459	230	67.95 (67.97)	4.65 (4.61)	3.01 (3.05)
VAM-18	CH_3	H	H	CH_3	3-Nitro phenyl	$C_{23}H_{20}N_2O_7$	436	> 300	63.33 (63.30)	4.66 (4.62)	6.44 (6.42)
VAM-19	CH_3	H	H	CH_3	3-Bromo phenyl	$C_{23}H_{20}BrNO_5$	470	> 300	58.75 (58.74)	4.36 (4.29)	2.90 (2.98)
VAM-20	CH_3	H	H	CH_3	4-Hydroxy-3-methoxy phenyl	$C_{24}H_{23}NO_7$	437	> 300	65.93 (65.90)	5.32 (5.30)	3.23 (3.20)
VAM-21	H	H	CH_3	CH_3	3-Nitro phenyl	$C_{23}H_{20}N_2O_7$	436	287	63.35 (63.30)	4.63 (4.62)	6.40 (6.42)
VAM-22	H	H	CH_3	CH_3	3-Bromo phenyl	$C_{23}H_{20}BrNO_5$	470	262	58.70 (58.74)	4.30 (4.29)	2.99 (2.98)
VAM-23	H	H	CH_3	CH_3	4-Hydroxy-3-methoxy phenyl	$C_{24}H_{23}NO_7$	437	258	65.97 (65.90)	5.35 (5.30)	3.27 (3.20)
VAM-24	H	Cl	CH_3	H	3-Nitro phenyl	$C_{22}H_{17}ClN_2O_7$	456.5	285	57.90 (57.80)	3.77 (3.72)	6.10 (6.13)
VAM-25	H	H	H	CH_3	3-Bromo phenyl	$C_{22}H_{18}BrNO_5$	456	230	57.95 (57.91)	3.92 (3.98)	3.01 (3.07)

→ Values in parenthesis denote the calculated percentage of composition.

Infra-Red (IR) spectral study: The infrared spectra were recorded on SHIMADZU FT IR-8400 spectrophotometer by KBr pellet method. The IR (KBr) spectra of all carboxylate compounds showed band in the range of 3300-3550 cm^{-1} due to amine stretching frequency of free amino group. Most of ketones gave carbonyl stretching vibration in the region of 1700-1740cm^{-1}, esteric ketones gave stretching vibration band observed at around 1685 cm^{-1}, C-N stretching band showed band in between 1280-1350 cm^{-1}, while ether linkage (C-O-C) appeared at region of 1060-1100 cm^{-1}. The aromatic out of plane bending region showed bands in the range of 1430 to 1530 cm^{-1}.C-Br gave stretching band at 700-750 cm^{-1}.

Nuclear Magnetic Resonance (^{1}H NMR) spectral study: The ^{1}H NMR spectra of newly synthesized compounds were taken in BRUKER AC 300 MHz FT NMR spectrometer using $CDCl_3$+DMSO-d_6 as a solvent and TMS as internal standard. In the compound VAM-6, the amino protons were observed at 8.1 δ ppm. In case of ethyl (-CH_2-CH_3) protons were observed at δ value 3.95. The aromatic protons were observed between 7.20 to 8.24 δ ppm.

Mass spectral study: Mass spectra were recorded on JEOL SX-120/DX-6000 spectrometer. All the newly synthesized compounds gave typical molecular ion peak according to their molecular weight.

Spectral characterization:

UV spectral study: The λ-max and other values shown below in Neutral (N); Acidic (A); Alkaline (B) medium. All spectra are taken in DMF. The λ values are shown in nm and Extinction Coefficient (ε) values are shown in brackets.

Code	λ_1 (ε)	λ_2 (ε)	λ_3 (ε)
VAM-1 (N)	238 (0.342)	**283 (2.285)**	313 (2.218)
VAM-1 (A)	229 (0.263)	**277 (2.237)**	316 (2.218)
VAM-1 (B)	235 (0.301)	253 (0.301)	**307 (2.033)**
VAM-2 (N)	214 (0.491) 244 (0.234)	**298 (2.245)**	-
VAM-2 (A)	235 (0.342)	292 (2.420) **298 (2.441)**	-
VAM-2 (B)	214 (0.512) 235 (0.342)	-	**319 (1.817)**
VAM-5 (N)	214 (0.523) 235 (0.263)	280 (2.439)	**322 (2.464)**
VAM-5 (A)	235 (0.301)	**280 (2.440)**	316 (2.425)
VAM-5 (B)	214 (0.523) 235 (0.263)	274 (2.260)	**316 (2.484)**
VAM-6 (N)	244 (0.234)	**271 (1.852)**	349 (1.533)
VAM-6 (A)	214 (0.477) 244 (0.234)	271 (1.559)	**319 (1.874)**
VAM-6 (B)	214 (0.435) 244 (0.263)	**274 (1.835)**	349 (1.277)

→ Dark value indicates λ_{max} of compound in different media.

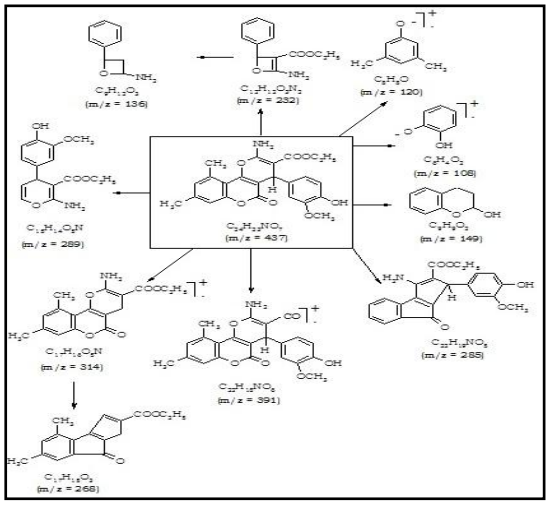
Spectral Study of 2-Amino-7, 8-benzo-3-ethoxycarbonyl-5-oxo-4-(3-bromo phenyl)-4H, 5H-pyrano-[3, 2-c]-chromene (VAM-6)

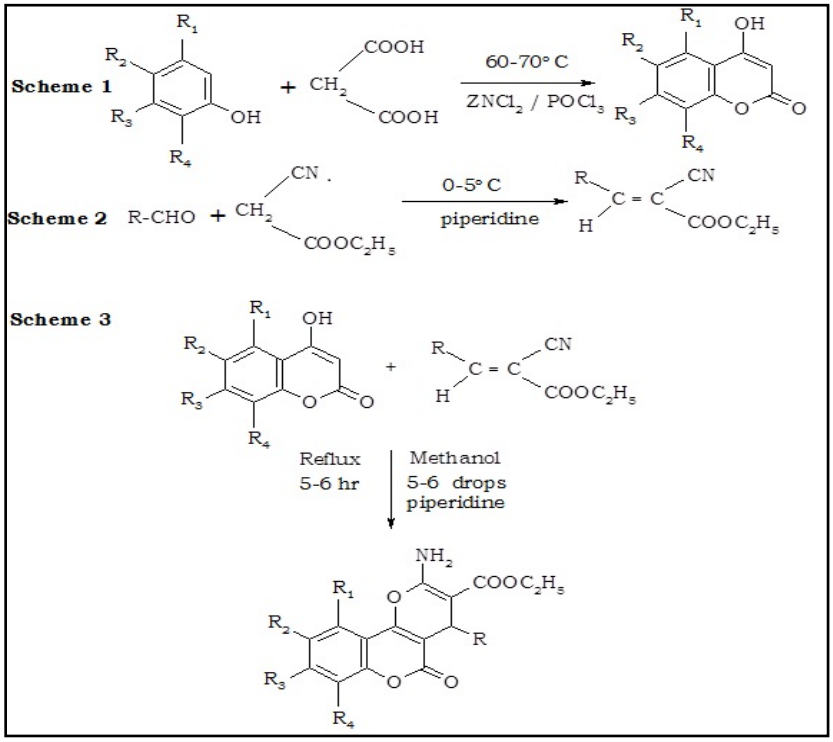
IR (KBr) cm^{-1}: 3436.9 (N-H); 1704.9 (C=O); 1689.5 (Esteric C=O); 1253.6 (C-N); 1519.8, 1461.9, 1420.0 (C-H, o.o.p); 740.6 (C-Br); 1087.9 (Ester C-O-C).

^{1}H NMR (300 MHz ($CDCl_3$ + DMSO-d_6)); δ ppm :1.14 (t, 3H, CH_3); 3.95 (q, 2H, CH_2- CH_3); 4.75 (s, 2H, CH); 7.20 (t, 1H, Ar-H); 7.26 (d, 1H, Ar-H); 7.35 (d, 1H, Ar-H); 7.45 (s, 1H, Ar-H); 7.54 (d, 1H, Ar-H); 7.66 (t, 1H, Ar-H); 7.78 (t, 1H, Ar-H); 8.0 (d,1H, Ar-H); 8.1 (S, 2H, NH_2); 8.24 (S, 1H, Ar-H).

Mass(FAB): M. Wt. = 491 gm/ mol; [m/e (%)]; (M+1) **492 (39.73**); 460 (6.66); 446 (38.66); 391 (71.33); 379 (5.33); 336 (58.11); 307 (60.19); 289 (41.33); 232 (69.33); 214 (10.66); 167 (7.99); **154 (100);** 136 (82.66); 120 (13.20); 107 (24.66).

Possible mass fragmentation of 2-Amino-8, 10-dimethyl-3-ethoxycarbonyl-5-oxo-4-(4-hydroxy-3-methoxyphenyl)-4H, 5H-pyrano-[3, 2-c]-chromene (VAM-1)





Reaction scheme

Where R_1, R_2, R_3, R_4 = H, CH_3, Benzo, Cl, etc, R = 3-bromo phenyl, 3-nitro phenyl,4-hydroxy-3-methoxy phenyl.

APPLICATIONS

Antimicrobial profile: Table-2 shows the comparative antimicrobial study of 10 compounds from this chapter. It was found that VAM-18 has shown promising activity against fungi Candida albicans ATCC 10231.

Table 2 : Antimicrobial profile of ethyl-2-amino-5-oxo-4-(substituted phenyl)-4H, 5H-pyrano-[3,2-c]-chromenes.

Code	R_1	R_2	R_3	R_4	R	Antimicrobial Activity						
						Antibacterial		Antifungal				
						Staph. Aureus 209-p	E.coli ESS 2231	Aspergillus fumigants	Candida albicans	Candida albicans ATCC 10231	Candida kruse i G03	Candida glabrata H05
VAM-1	CH_3	H	CH_3	H	4-Hydroxy-3-methoxy phenyl	-	-	-	-	-	-	-
VAM-2	CH_3	H	CH_3	H	3-Bromo phenyl	-	-	-	-	-	-	-
VAM-6	H	H	-Benzo-		3-Bromo phenyl	-		-	-	-	-	-
VAM-8	H	H	H	CH_3	3-nitro phenyl	-	-	-	9h	-	-	-
VAM-9	H	CH_3	H	H	3-nitro phenyl	-	-	-	11h	-	-	-
VAM-18	CH_3	H	H	CH_3	3-nitro phenyl	-	-	-	12h	12	-	-
VAM-19	CH_3	H	H	CH_3	3-Bromo phenyl	-	-	-	-	-	-	-
VAM-21	H	H	CH_3	CH_3	3-nitro phenyl	-	-	-	-	-	-	-
VAM-24	H	Cl	CH_3	H	3-nitro phenyl	-	-	-	-	-	-	-
VAM-25	H	H	H	CH_3	3-Bromo phenyl	-	-	-	-	-	-	-

CONCLUSIONS

The structural characterization was done well with the various analytical and spectral support to the newly synthesized Pyranochromenes. The present investigation was carried out as the coumarins, cyclocoumarol and dicoumarol are proved most active pharmacaological moieties. The selected compounds were screened for their antimicrobial activity and 30% were active antifungal compounds.

ACKNOWLEDGEMENT

Authors are thankful to University Grants Commission, New Delhi, India, for the financial support.

REFERENCES

[1] T.O.Soinae, *J. Pharm. Sci***, 1964,** 53, 231.
[2] S.Sethna, *Proc. of 56th Science Congress Pt. II.*, **1969,** 85.
[3] D.Malleshwar, V.Sundaramurthy, *Synthesis*, **1982**, 337-432.
[4] http://www.ncbi.nlm.nih.gov/pubmed/9583093
[5] http://www.ncbi.nlm.nih.gov/pubmed/18386483
[6] R.S. Overmann, *J. Boi. Chem***, 1980,** 153, 5.
[7] H.Liu, Extraction and Isolation of Compounds from Herbal Medicines. In: Willow, J. and H. Liu (Eds.) *Traditional Herbal Medicine Research Methods*, John Wiley and Sons, Inc. **2011**.
[8] N.Farinola, N. Piller, *Lymphatic Research and Biology*, **2005,** 3(2), 81–86.
[9] T.T. Phuong, M.H. Tran, M.N.Tran, T.H. Do, S.M. Byung, J.K. Seung, S.K. Tae, S.C. Jae, H.B. Ki, *Phytotherapy Research*, **2010,** 24(1), 101–106.
[10] V.R.Shah, J.L. Bose, R.C.Shah, *J. Org. Chem*, **1960,** 25, 677.
[11] A.Shah, N. Bhatt, R. Raval, V.M. Thakor, *Curr. Science*, **1984**, 84**,** 1293.
[12] K.Shrihari, V. Sundaramurthy, *Proc. Ind. Acad. Sci*., **1980,** 89, 405.