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Synthesis and Antibacterial Activity Study of *N*-Substituted Acetamide Derivatives of 4-Hydroxy-2-oxo-*2H*-Chromene

*Aziz-ur-Rehman, S. Rasool, M.A.Abbasi,S.Z. Siddiqui, A. Riaz, A. Tahir, H.M.A. Asif, [1]I. Ahmad
*Department of Chemistry, Government College University, Lahore, Pakistan
[1]Department of Pharmacy, TheIslamia University of Bahawalpur, Bahawalpur, Pakistan
E-mail: *azizryk@yahoo.com, rehman@gcu.edu.pk

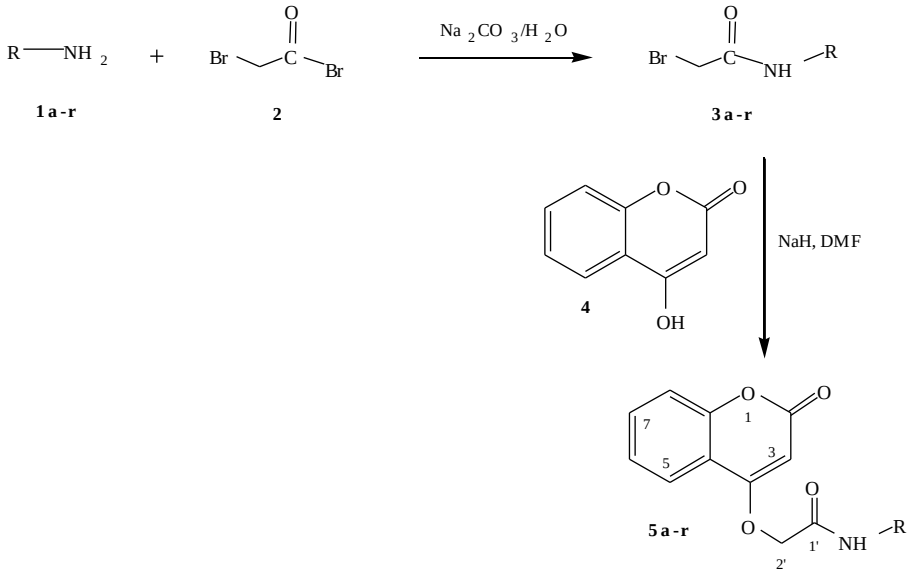
ABSTRACT
The heterocyclic coumarin derivatives are well known for their biological potential.Thepresented work demonstrates the evaluation of some *N*-substituted acetamoyl derivatives of4-hydroxy-2-oxo-*2H*-chromene (**4**)against certain strains of gram bacteria. First,*N*-substituted-2-bromoacetamide, **3a-r**, were synthesized by the reaction of aralkyl/aryl amines, **1a-r**, with 2-bromoacetyl bromide (**2**) in an aqueous medium under definite pH control.In the second step, the resulted electrophiles, **3a-r**, were made to react **4**in a polar aprotic solvent using a weak base as an activator to synthesize the final *N*-substituted-2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetamide, **5a-r**. The synthesis of compounds,**5a-r**, was corroborated by TLC initially and spectral data of IR,[1]H-NMR and EIMS finally. The MIC results of antibacterial activity rendered these molecules valuable inhibitors of all the bacterial strains taken into account.

Keywords: 4-Hydroxy-2-oxo-*2H*-chromene, acetamides, antibacterial activity, spectral analysis.

1. INTRODUCTION
Coumarins, a group of naturally occurring heterocylic compounds, have been isolated from different plants including Tonka bean etc.These molecules possess the fused benzene and α-pyrone rings[1-4].The compounds derived from coumarins are known to exhibit noticeable biological activities such as antibacterial, anti-malarial, anticoagulant,anti-tubercular, anticancer,antioxidant, antiviral, anti-HIV, anti-inflammatory etc[5-11]. These molecules have also been employed bythe ancient Egypt as medicine[12]. A large number of such type of moleculesalso have their application in the field ofagriculture[12,13].The acetamoyl functionality is also noted to be present in bioactive important compounds used as drugs. Molecules bearing this moiety are known to possess anticonvulsant, anti-inflammatory, antioxidant, anticancer, anti-arthritic, antifungal and anti-bacterial activities[14-20].

A series of molecules bearing both coumarin and acetamoyl moieties were synthesized with an aim to evaluate the pharmacological significance of these molecules. Owing to biological activities of ether derivatives of coumarin[7,9,21], we extended our last work on*O*-substituted derivatives[22].The pharmacological evaluation of these compounds was performed against the different bacterial strains of gram-bacteria and their MIC results depicted them as valuable for drug designing.

2. RESULTS AND DISCUSSION
The *N*-substituted-2-[(2-oxo-2*H*-chromen-4-yl)oxy]acetamide, (**5a-r**) were synthesized to inaugurate new biological active compounds according to the protocol given in Scheme 1. The detailed procedures along with necessary conditions are elaborated in experimental section.



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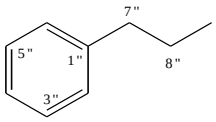
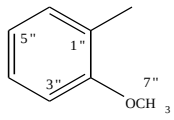
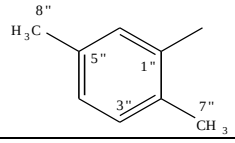
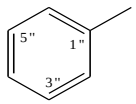
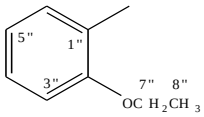
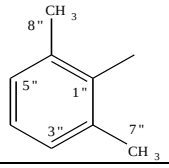
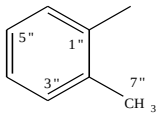
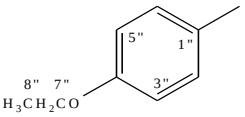
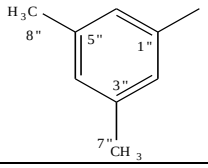
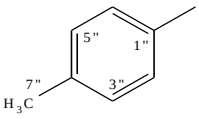
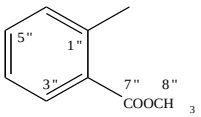
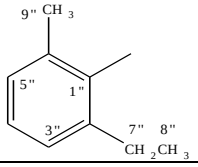
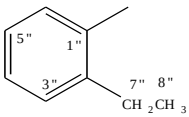
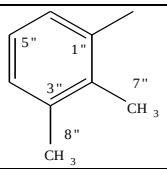
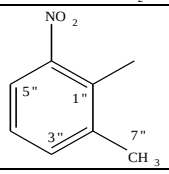
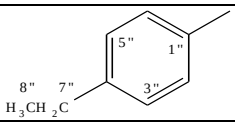
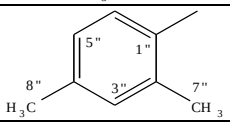
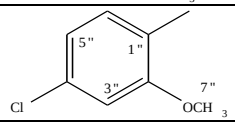
Comp.	-R	Comp.	-R	Comp.	-R
5a		**5g**		**5m**	
5b		**5h**		**5n**	
5c		**5i**		**5o**	
5d		**5j**		**5p**	
5e		**5k**		**5q**	
5f		**5l**		**5r**	

Scheme 1: Synthesis of *N*-Substituted-2-[(2-oxo-*2H*-chromen-4-yl)oxy]acetamide (**5a-r**)

2.1 *Chemistry*

Structures of all the synthesized molecules (**5a-r**)were elucidated by IR, ^{1}H-NMR and EIMS spectral data given in experimental section. One of the listed compounds has been explicated by spectral data.

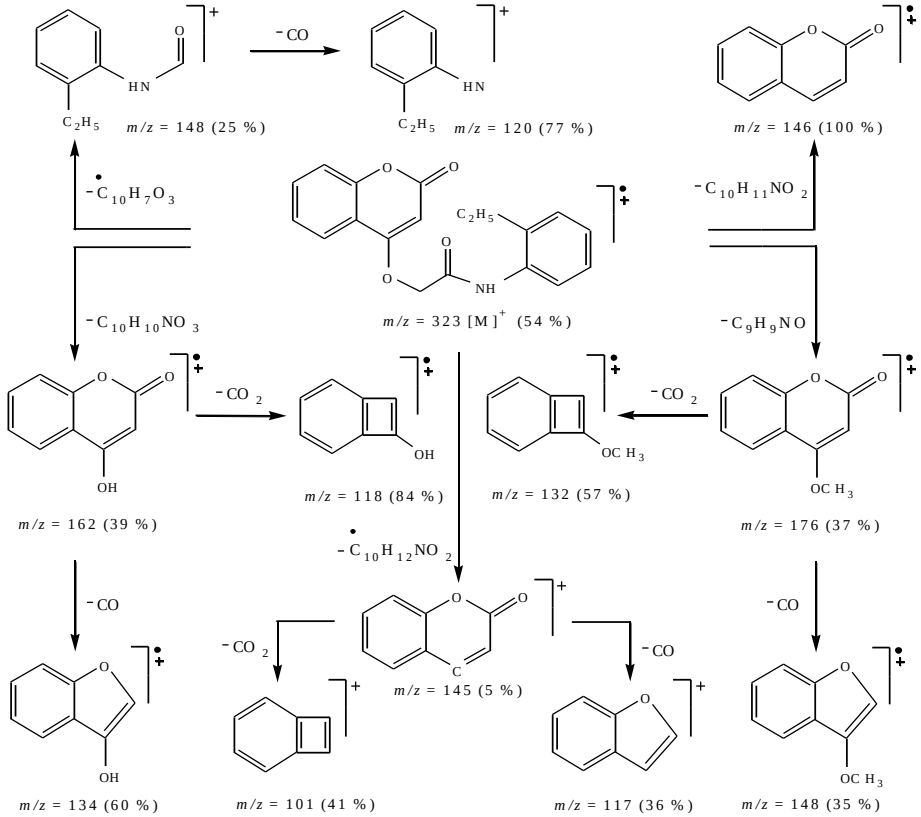


Fig.1: Mass Fragmentation pattern of *N*-(2-Ethylphenyl)-2-[(2-oxo-*2H*-chromen-4-yl)oxy]acetamide (**5e**)

The compound **5e** was filtered as light grey amorphous solid and noted to have 82% yield and 108-110^{o}Cmelting point. Its molecular formula, $C_{19}H_{17}NO_4$, was erected through molecular ion peak along with other fragments in EIMS spectrum and by counting the protons with the help of integration curve in ^{1}H-NMR spectrum. The suggested fragmentation pattern of this molecule is given in Figure 1. The absorption bands supporting the coumarin, amide and ether functionalities appeared at 3439 (N-H), 3073 (Ar C-H), 1736 (ester C=O), 1679 (amide C=O), 1601 (Ar C=C) and 1154 (C-O) in IR spectrum. In proton NMR spectrum, five signals with single proton integration,as one singlet, two doublets and two triplets,resonated at δ7.83 (d, J = 8.0 Hz, 1H, H-5), 7.62 (t, J = 8.0 Hz, 1H, H-7), 7.38 (d, J = 8.0 Hz, 1H, H-8), 7.34 (t, J = 8.0 Hz, 1H, H-6) and 5.80 (s, 1H, H-3) for the five protons of 2-oxo-*2H*-chromen-4-yl moiety. The *N*-substituted 2-ethylphenyl ring appeared at δ 7.94 (d, J = 8.0 Hz, 1H, H-6"), 7.29-7.22 (m, 2H, H-4" & H-5") and 7.18 (d, J = 7.6 Hz, 1H, H-3") in aromatic section for phenyl ring and δ 2.63 (q, J = 7.6 Hz, 2H, H-7") and 1.22 (t, J = 7.6 Hz, 3H, CH_3-8") in aliphatic section for ethyl group. The linkage of these two moieties, that is, 2-oxo-*2H*-chromen-4-yl and *N*-(2-ethylphenyl)-2-ylacetamidewas corroborated through the singlet present at δ 4.81 (s, 2H, H-2') with an integration of two protons of methylene group. The above discussion thoroughly supported the suggested structure of **5e**, named as *N*-(2-Ethylphenyl)-2-[(2-oxo-*2H*-chromen-4-yl)oxy]acetamide.

2.2 *Antibacterial (in vitro) activity*

The antibacterial activity of the synthesized molecules is elaborated in Table 1 and Table 2 as %age inhibition and MIC values, taking ciprofloxacin as reference drug.All the synthesized molecules exhibited valuable MIC values except **5d** and **5g**, remained inactive against certain strains.*S. typhi* and *B. subtilis* were inhibited by all the molecules, but more efficiently against former, and a few molecules remained inactive against the remaining strains. Against *S. typhi*, the whole series of compounds was excellent inhibitor except **5d** which remained moderate inhibitor.*E. coli* was also excellently inhibited by all the molecules but relativelya little low by **5o** and not at all by **5d**. Moderate inhibition was presented against *P. aeruginosa* by all the molecules except **5d** and **5g**, the inactive ones. This strain was best inhibited by only two molecules, **5p** with MIC of 9.86±0.12 µg/mLand **5q** with MIC of 9.52±0.51 µg/mL with respect to that of ciprofloxacin, 7.14±0.18µg/mL, the reference standard. Against *S. aureus*, comparatively less number of molecules remained excellent inhibitors. The molecules **5l-o** and **5r** remained moderate inhibitors but **5d** and **5g**were inactive at all. Among all the synthesized molecules, the compounds **5p** and **5q** were the best inhibitors against all the bacterial strains taken into account. The most probably their best activity might be attributed to the diortho-substituted phenyl ring attached to the nitrogen of acetamoyl group in addition to all other functionalities present in the molecule.

Table 1: The %age inhibition for antibacterial activity

Compound	Percentage Inhibition (%)				
	Gram negative bacteria			Gram positive bacteria	
	S. typhi	***E.coli***	***P.aeruginosa***	***B. subtilis***	***S. aureus***
5a	75.56±0.61	83.55±0.32	66.20±0.60	79.20±0.30	68.35±0.35
5b	75.11±0.52	75.50±0.47	60.90±0.67	70.85±0.76	67.80±0.41
5c	75.56±0.19	74.50±0.40	58.65±0.05	68.00±0.12	65.35±0.95
5d	51.00±0.78	46.26±0.05	36.95±0.95	59.70±0.52	45.25±0.90
5e	80.67±0.22	81.20±0.70	62.65±0.48	73.40±0.10	66.35±0.62
5f	74.55±0.36	74.30±0.60	58.78±0.70	62.25±0.55	65.15±0.57
5g	70.50±0.28	72.60±0.74	44.90±0.80	57.00±0.50	47.80±0.31
5h	75.28±0.39	69.30±0.20	55.70±0.63	67.70±0.30	65.65±0.55
5i	76.83±0.94	78.75±0.25	60.65±1.05	73.10±0.65	65.35±0.65
5j	71.89±0.22	73.10±0.40	61.80±0.30	65.05±0.75	68.20±0.80
5k	78.72±0.17	84.50±0.20	64.40±0.80	76.90±0.80	67.85±0.45
5l	72.61±0.34	66.95±0.75	57.40±0.70	71.65±1.02	51.60±0.90
5m	74.17±0.61	75.50±0.50	55.60±0.40	66.05±0.15	56.95±0.25
5n	64.50±0.50	83.50±0.20	58.00±0.27	67.50±0.21	61.15±0.63
5o	71.39±1.00	61.25±0.35	61.05±0.05	65.90±0.30	60.85±0.15
5p	82.28±0.50	79.10±1.00	69.35±0.35	73.00±0.90	65.00±0.20
5q	82.84±0.33	75.95±0.75	70.05±0.42	70.55±0.25	70.65±0.25
5r	70.50±0.35	73.25±0.55	57.50±0.61	64.20±0.01	62.50±0.71
Ciprofloxacin	**91.05±0.68**	**92.32±0.42**	**92.50±0.34**	**92.02±053**	**91.44±0.64**

3. CONCLUSION

The given scheme of reactions was carried out to synthesize some new molecules bearing multiple functionalities including coumarin and acetamide with an aim to elucidate their antibacterial potential. The synthesis was also followed by structural characterization of synthesized molecules. The resulting molecules executed excellent

inhibition against all the five bacterial strains taken into account. The molecules, **5p** and **5q** were the most active ones among the whole series of molecules owing to the presence of diortho-substituted phenyl ring, that is, 2-ethyl-6-methylphenyl and 2-methyl-6-nitrophenyl rings respectively. Such type of molecules should be further synthesized and considered for drug discovery pathway so that these might be applicable as drug molecules to cure certain diseases caused by these bacterial strains.

Table 2: The MIC values for antibacterial activity

Compound	MIC (µg/mL)				
	Gram negative bacteria			Gram positive bacteria	
	S. typhi	***E.coli***	***P.aeruginosa***	***B. subtilis***	***S. aureus***
5a	9.10±0.76	8.97±0.60	10.48±0.33	8.76±0.50	9.83±0.90
5b	9.23±0.67	9.20±0.56	13.86±0.16	9.43±0.35	9.89±0.56
5c	9.29±0.70	9.38±0.17	16.96±0.47	10.11±0.73	10.13±0.64
5d	19.56±0.33	-	-	14.31±0.49	-
5e	8.78±0.49	8.78±0.50	12.74±0.11	9.46±0.49	10.42±0.50
5f	9.45±0.10	9.27±0.15	16.24±0.90	10.44±0.21	10.57±0.38
5g	9.80±0.11	9.34±0.07	-	16.37±0.15	-
5h	9.60±0.01	10.05±0.11	17.52±0.95	10.71±0.19	10.63±0.10
5i	9.27±0.51	9.11±0.57	15.39±0.67	9.24±0.33	10.36±0.12
5j	9.92±0.41	9.63±0.31	14.75±0.72	10.58±0.11	9.75±0.19
5k	9.11±0.34	8.34±0.10	10.89±0.16	8.87±0.13	10.14±0.90
5l	9.78±0.50	10.22±0.64	15.36±0.66	9.78±0.67	19.80±0.13
5m	9.57±0.84	9.12±0.72	17.85±0.23	10.65±0.54	16.78±0.44
5n	10.98±0.16	8.86±0.50	16.55±0.49	10.23±0.76	13.69±0.58
5o	9.89±0.80	12.96±0.30	14.74±0.12	10.42±0.18	14.80±0.33
5p	8.66±0.57	8.76±0.58	9.86±0.12	9.25±0.78	10.26±0.44
5q	8.13±0.45	8.90±0.12	9.52±0.51	9.65±0.04	9.78±0.47
5r	10.02±0.51	9.49±0.12	16.89±0.38	10.86±0.27	12.36±0.12
Ciprofloxacin	**7.45±0.58**	**7.16±0.58**	**7.14±0.18**	**7.29±0.90**	**7.80±0.19**

NOTE: Minimum inhibitory concentration (MIC) was measured with suitable dilutions (5-30 µg/well) and results were calculated using EZ-Fit Perrella Scientific Inc. Amherst USA software.

4. MATERIALS AND METHODS

4.1 *General*

4-Hydroxy-2-oxo-*2H*-chromene (Merck),2-bromoacetyl bromide (Alfa Aesar) and aralkyl/arylamines (Merck, Riedel-de Haen, Aldrich and Alfa Aesar)were used without further purificationand the solvents were of analytical grade. Thin layer chromatography (TLC) was run using*n*-$C_6H_{14}$and EtOAc as solvent system. The TLC plates were purchased through local supplierand were visualized *via* UV at 254 nm. The absorption bands in I.R. spectra were captured using Jasco-320-A spectrophotometer by pellet method (KBr). The proton NMR spectra were recorded using Bruker spectrometers in $CDCl_3$ at 400 MHz.The EIMS spectra were recorded using JMS-HX-110 spectrometer. Melting points were accountedin open capillary tube using Griffin-George apparatus.

4.2 *General procedure for the synthesis of N-substituted-2-bromoacetamide (3a-r)*

Aralkyl/aryl amines (**1a-r**,5.0 mmol) weresuspended in 15 mL distilled water in a 125 mL iodine flask and aqueous Na_2CO_3 (12%) solution (5 mL) was added.After stirring for 5-10 minutes, 2-bromoacetyl bromide (**2**,5.0 mmol) was added by parts to the reaction flask on continuous vigorous shaking for about 1.0 hour. The pH was maintained at 8-10strictly for the reaction to progress. The solid precipitates were filtered off from the medium and washed by distilled water.

4.3*General procedure for the synthesis of N-substituted-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5a-r)*

4-Hydroxy-2-oxo-*2H*-chromene (**4**,0.3mmol) was homogeneously mixed with DMF (13 mL) in a 50 mL round bottom flask. The activator, NaH (0.3mmol) was added and the mixture was continuously stirred for 0.75 hour. After then*N*-substituted-2-bromoacetamide (**3a-r**,0.3 mmol) were added and further stirring was continued for 4-6 hours. The frequently performed TLC monitored the reaction till completion. Ten times distilled water (130 mL) was added to the mixture in a separate 250 mL beaker on gentle shaking.After aging for 0.25 hour, solid products were recovered through filtration, washed by distilled water, dried and stored for further use.

4.4 *Antibacterialactivity assay*

The sterilized 96-wells microplates were used to assess the antibacterial potential and also under sterilespecified condition. The basic consideration in this method was the change in absorbance which in turn relates to the microbial growth in log phase and microbial cell number[23,24].

4.5 *Statistical analysis*

The results were concludedafterthree-fold calculations, analyzed by ME 2010 andpresented as mean ± SEM.

4.6 *Characterization of the synthesized compounds (5a-r)*

4.6.1 *N-(2-Phenylethyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5a)*

Light yellow amorphous solid; Yield: 82%; M.P.: 128-130 ^{o}C; HR-MS: $[M]^{+}$323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243);IR (KBr, υ_{max}, cm^{-1}): 3448 (N-H), 3077 (Ar C-H), 1736 (ester C=O), 1665 (amide C=O), 1601 (Ar C=C), 1173 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.83 (s, 1H, CON-H), 7.93 (d, *J* = 8.4 Hz, 1H, H-5), 7.63 (t, *J* = 8.4 Hz, 1H, H-7), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.34 (t, *J* = 8.0 Hz, 1H, H-6), 7.17-7.11 (m, 5H, H-2" to H-6"), 5.78 (s, 1H, H-3), 4.79 (s, 2H, H-2'), 3.42 (t,*J* = 7.2 Hz,2H, H-8"), 2.69 (t,*J* = 7.2 Hz,2H, H-7"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (51%), 176 (38%), 162 (40%), 148 (56%), 146 (BP, 100%), 145 (9%), 134 (52%), 132 (59%), 120 (76%), 118 (83%), 117 (38%), 101 (41%).

4.6.2 *N-Phenyl-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5b)*

White amorphous solid; Yield: 74%; M.P.: 116-118 ^{o}C; HR-MS: $[M]^{+}$295.0844 (Calcd. For $C_{17}H_{13}NO_4$; 295.0913); IR (KBr, υ_{max}, cm^{-1}): 3447 (N-H), 3052 (Ar C-H), 1734 (ester C=O), 1678 (amide C=O), 1604 (Ar C=C), 1139 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.89 (s, 1H, CON-H), 7.93 (d, *J* = 8.4 Hz, 1H, H-5), 7.64 (t, *J* = 8.0 Hz, 1H, H-7), 7.56 (d, *J* = 8.4 Hz, 2H, H-2" &H-6"), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.35 (t, *J* = 8.4 Hz, 2H, H-3" &H-5"), 7.32 (t, *J* = 8.4 Hz, 1H, H-6), 7.18 (t, *J* = 8.0 Hz, 1H, H-4"),5.77 (s, 1H, H-3), 4.76 (s, 2H, H-2'); EIMS (*m/z*): 295 $[M]^{\bullet+}$ (55%), 176 (37%), 162 (41%), 148 (39%), 146 (BP, 100%), 145 (5%), 134 (59%), 132 (57%), 120 (24%), 118 (80%), 117 (36%), 101 (44%), 92 (73%).

4.6.3 *N-(2-Methylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5c)*

Light grey amorphous solid; Yield: 77%; M.P.: 132-134 ^{o}C; HR-MS: $[M]^{+}$309.1004 (Calcd. for $C_{18}H_{15}NO_4$; 309.1043); IR (KBr, υ_{max}, cm^{-1}): 3429 (N-H), 3053 (Ar C-H), 1738 (ester C=O), 1673 (amide C=O), 1603 (Ar C=C), 1153 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.75 (s, 1H, CON-H), 7.93 (d, *J* = 8.0 Hz, 1H, H-5), 7.72 (d, *J* = 8.4 Hz, 1H, H-6"), 7.64 (t, *J* = 8.0 Hz, 1H, H-7), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.36 (t, *J* = 8.0 Hz, 1H, H-6), 7.16 (d, *J* = 8.4 Hz, 1H, H-3"), 7.11 (t, *J* = 8.0 Hz, 1H, H-5"), 7.08 (t, *J* = 8.0 Hz, 1H, H-4"), 5.73 (s, 1H, H-3), 4.76 (s, 2H, H-2'), 2.26 (s, 3H, CH_3-7"); EIMS (*m/z*): 309 $[M]^{\bullet+}$ (58%), 176 (36%), 162 (48%), 148 (32%), 146 (BP, 100%), 145 (6%), 134 (78%), 132 (58%), 118 (89%), 117 (36%), 106 (74%), 101 (45%).

4.6.4 *N-(4-Methylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5d)*

White amorphous solid; Yield: 79%; M.P.: 138-140 ^{o}C; HR-MS: $[M]^{+}$ 309.1004 (Calcd. for $C_{18}H_{15}NO_4$; 309.1043); IR (KBr, υ_{max}, cm^{-1}): 3434 (N-H), 3057 (Ar C-H), 1739 (ester C=O), 1675 (amide C=O), 1607 (Ar C=C), 1155 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.67 (s, 1H, CON-H), 7.91 (d, *J* = 8.4 Hz, 1H, H-5), 7.63 (t, *J* = 8.0 Hz, 1H, H-7), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.36 (t, *J* = 8.0 Hz, 1H, H-6), 7.34 (d, *J* = 8.4 Hz, 2H, H-2" & H-6"), 7.15 (d, *J* = 8.0 Hz, 2H, H-3" & H-5"), 5.78 (s, 1H, H-3), 4.77 (s, 2H, H-2'), 2.27 (s, 3H, CH_3-7"); EIMS (*m/z*): 309 $[M]^{\bullet+}$ (56%), 176 (37%), 162 (49%), 148 (36%), 146 (BP, 100%), 145 (8%), 134 (75%), 132 (59%), 118 (85%), 117 (31%), 106 (77%), 101 (44%).

4.6.5 *N-(2-Ethylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5e)*

Light grey amorphous solid; Yield: 82%; M.P.: 108-110 ^{o}C; HR-MS: $[M]^{+}$ 323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243); IR (KBr, υ_{max}, cm^{-1}): 3439 (N-H), 3073 (Ar C-H), 1736 (ester C=O), 1679 (amide C=O), 1601 (Ar C=C), 1154 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm):8.91 (s, 1H, CON-H), 7.94 (d, *J* = 8.0 Hz, 1H, H-6"), 7.83 (d, *J* = 8.0 Hz, 1H, H-5), 7.62 (t, *J* = 8.0 Hz, 1H, H-7), 7.38 (d, *J* = 8.0 Hz, 1H, H-8), 7.34 (t, *J* = 8.0 Hz, 1H, H-6), 7.29-7.22 (m, 2H, H-4" & H-5"), 7.18 (d, *J* = 7.6 Hz, 1H, H-3"), 5.80 (s, 1H, H-3), 4.81 (s, 2H, H-2'), 2.63 (q, *J* = 7.6 Hz, 2H, H-7"), 1.22 (t, *J* = 7.6 Hz, 3H, CH_3-8"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (54%), 176 (37%), 162 (39%), 148 (60%), 146 (BP, 100%), 145 (5%), 134 (60%), 132 (57%), 120 (77%), 118 (84%), 117 (36%), 101 (41%).

4.6.6 *N-(4-Ethylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5f)*

Light grey amorphous solid; Yield: 79%; M.P.: 192-194 ^{o}C; HR-MS: $[M]^{+}$ 323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243); IR (KBr, υ_{max}, cm^{-1}): 3432 (N-H), 3075 (Ar C-H), 1736 (ester C=O), 1674 (amide C=O), 1606 (Ar C=C), 1156 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.52 (s, 1H, CON-H), 7.92 (d, *J* = 8.0 Hz, 1H, H-5), 7.61 (t, *J* = 8.0 Hz, 1H, H-7), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.34 (t, *J* = 8.4 Hz, 1H, H-6), 7.09 (d, *J* = 8.0 Hz, 2H, H-2" & H-6"),

6.94 (d, *J* = 8.4 Hz, 2H, H-3" & H-5"), 5.77 (s, 1H, H-3), 4.79 (s, 2H, H-2'), 2.57 (q, *J* = 7.6 Hz, 2H, H-7"), 1.11 (t, *J* = 7.6 Hz, 3H, CH_3-8"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (58%), 176 (39%), 162 (34%), 148 (66%), 146 (BP, 100%), 145 (8%), 134 (64%), 132 (56%), 120 (76%), 118 (83%), 117 (32%), 101 (46%).

4.6.7 ***N-(2-Methoxyphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5g)***

Cream white amorphous solid; Yield: 85%; M.P.: 214-216 °C; HR-MS: $[M]^+$325.0954 (Calcd. for $C_{18}H_{15}NO_5$; 325.0983);IR (KBr, υ_{max}, cm^{-1}): 3438 (N-H), 3074 (Ar C-H), 1735 (ester C=O), 1665 (amide C=O), 1606 (Ar C=C), 1159 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.59 (s, 1H, CON-H), 8.13 (d, *J* = 8.0 Hz, 1H, H-6"), 7.92 (d, *J* = 8.4 Hz, 1H, H-5), 7.64 (t, *J* = 8.4 Hz, 1H, H-7), 7.38 (d, *J* = 8.4 Hz, 1H, H-8), 7.36 (t, *J* = 8.4 Hz, 1H, H-6), 7.08 (t, *J* = 8.0 Hz, 1H, H-5"), 6.93 (t, *J* = 8.4 Hz, 1H, H-4"), 6.84 (d, *J* = 8.4 Hz, 1H, H-3"), 5.76 (s, 1H, H-3), 4.77 (s, 2H, H-2'), 3.86 (s, 3H, CH_3-7"); EIMS (*m/z*): 325 $[M]^{\bullet+}$ (52%), 176 (37%), 162 (45%), 150 (26%), 148 (34%), 146 (BP, 100%), 145 (6%), 134 (54%), 132 (55%), 122 (69%), 118 (84%), 117 (35%), 101 (46%).

4.6.8 ***N-(2-Ethoxyphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5h)***

Light grey amorphous solid; Yield: 73%; M.P.: 198-200 °C; HR-MS: $[M]^+$339.1104 (Calcd. for $C_{19}H_{17}NO_5$; 339.1137);IR (KBr, υ_{max}, cm^{-1}): 3456 (N-H), 3053 (Ar C-H), 1736 (ester C=O), 1665 (amide C=O), 1606 (Ar C=C), 1156 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.56 (s, 1H, CON-H),7.92 (d, *J* = 8.4 Hz, 1H, H-5), 7.63 (t, *J* = 8.0 Hz, 1H, H-7), 7.43 (dd, *J* = 8.0, 2.0 Hz, 1H, H-6"), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.34 (t, *J* = 8.4 Hz, 1H, H-6), 7.11 (dt, *J* = 8.0, 2.0 Hz, 1H, H-4"), 6.83 (dt, *J* = 8.0, 2.4 Hz, 1H, H-5"), 6.74 (dd, *J* = 8.0, 2.4 Hz, 1H, H-3"), 5.76 (s, 1H, H-3), 4.79 (s, 2H, H-2'), 3.79 (q, *J* = 7.6 Hz, 2H, H-7"), 1.19 (t, *J* = 7.6 Hz, 3H, CH_3-8"); EIMS (*m/z*): 339 $[M]^{\bullet+}$ (53%), 176 (34%), 164 (26%), 162 (44%), 148 (37%), 146 (BP, 100%), 145 (8%), 136 (73%), 134 (52%), 132 (55%), 118 (81%), 117 (37%), 101 (43%).

4.6.9 ***N-(4-Ethoxyphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5i)***

Pink amorphous solid; Yield: 80%; M.P.: 194-196 °C; HR-MS: $[M]^+$ 339.1104 (Calcd. for $C_{19}H_{17}NO_5$; 339.1137); IR (KBr, υ_{max}, cm^{-1}): 3439 (N-H), 3071 (Ar C-H), 1732 (ester C=O), 1678 (amide C=O), 1604 (Ar C=C), 1152 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm):8.61 (s, 1H, CON-H), 7.93 (d, *J* = 8.0 Hz, 1H, H-5), 7.63 (t, *J* = 8.0 Hz, 1H, H-7), 7.37 (d, *J* = 8.4 Hz, 1H, H-8), 7.34 (t, *J* = 8.4 Hz, 1H, H-6), 6.93 (d, *J* = 8.0 Hz, 2H, H-2" & H-6"), 6.76 (d, *J* = 8.4 Hz, 2H, H-3" & H-5"), 5.78 (s, 1H, H-3), 4.74 (s, 2H, H-2'), 3.92 (q, *J* = 7.6 Hz, 2H, H-7"), 1.27 (t, *J* = 7.6 Hz, 3H, CH_3-8"); EIMS (*m/z*): 339 $[M]^{\bullet+}$ (51%), 176 (36%), 164 (28%), 162 (48%), 148 (34%), 146 (BP, 100%), 145 (7%), 136 (76%), 134 (58%), 132 (59%), 118 (88%), 117 (36%), 101 (47%).

4.6.10 ***N-(2-Methoxycarbonylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide(5j)***

White amorphous solid; Yield: 77%; M.P.: 186-188 °C; HR-MS: $[M]^+$ 353.0894 (Calcd. for $C_{19}H_{15}NO_6$; 353.0903); IR (KBr, υ_{max}, cm^{-1}): 3429 (N-H), 3051 (Ar C-H), 1737 (ester C=O), 1675 (amide C=O), 1601 (Ar C=C), 1152 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.91 (s, 1H, CON-H), 8.64 (d, *J* = 8.0 Hz, 1H, H-6"), 8.06 (d, *J* = 8.0 Hz, 1H, H-3"), 7.91 (d, *J* = 8.4 Hz, 1H, H-5), 7.63 (t, *J* = 8.4 Hz, 1H, H-7), 7.53 (t, *J* = 8.0 Hz, 1H, H-5"), 7.43 (d, *J* = 8.0 Hz, 1H, H-8), 7.35 (t, *J* = 8.0 Hz, 1H, H-6), 7.15 (t, *J* = 8.0 Hz, 1H, H-4"), 5.74 (s, 1H, H-3), 4.75 (s, 2H, H-2'), 3.87 (s, 3H, CH_3-8"); EIMS (*m/z*): 353 $[M]^{\bullet+}$ (54%), 178 (22%), 176 (35%), 162 (40%), 150 (71%), 148 (32%), 146 (BP, 100%), 145 (8%), 134 (50%), 132 (56%), 118 (82%), 117 (31%), 101 (47%).

4.6.11 ***N-(2,3-Dimethylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5k)***

White amorphous solid; Yield: 74%; M.P.: 126-128 °C; HR-MS: $[M]^+$ 323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243); IR (KBr, υ_{max}, cm^{-1}): 3448 (N-H), 3059 (Ar C-H), 1735 (ester C=O), 1664 (amide C=O), 1598 (Ar C=C), 1149 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.69 (s, 1H, CON-H), 7.92 (d, *J* = 8.4 Hz, 1H, H-5), 7.63 (t, *J* = 8.0 Hz, 1H, H-7), 7.53 (d, *J* = 8.4 Hz,1H, H-6"), 7.37 (d, *J* = 8.0 Hz, 1H, H-8), 7.33 (t, *J* = 8.4 Hz, 1H, H-6), 7.17 (t, *J* = 8.4 Hz, 1H, H-5"), 7.07 (d, *J* = 8.4 Hz, 1H, H-4"), 5.74 (s, 1H, H-3), 4.77 (s, 2H, H-2'), 2.34 (s, 3H, CH_3-7"), 2.12 (s, 3H, CH_3-8"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (51%), 176 (35%), 162 (47%), 148 (64%), 146 (BP, 100%), 145 (8%), 134 (53%), 132 (51%), 120 (75%), 118 (82%), 117 (36%), 101 (49%).

4.6.12 ***N-(2,4-Dimethylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5l)***

Cream white amorphous solid; Yield: 81%; M.P.: 132-134 °C; HR-MS: $[M]^+$ 323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243); IR (KBr, υ_{max}, cm^{-1}): 3437 (N-H), 3078 (Ar C-H), 1732 (ester C=O), 1677 (amide C=O), 1606 (Ar C=C), 1168 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.73 (s, 1H, CON-H), 7.92 (d, *J* = 8.0 Hz, 1H, H-5), 7.74 (d, *J* = 8.0 Hz, 1H, H-6"), 7.61 (t, *J* = 8.0 Hz, 1H, H-7), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.36 (t, *J* = 8.0 Hz, 1H, H-6), 7.09 (d, *J* = 8.0 Hz, 1H, H-5"), 6.94 (s, 1H, H-3"), 5.79 (s, 1H, H-3), 4.78 (s, 2H, H-2'), 2.27 (s, 3H, CH_3-7"), 2.22 (s, 3H, CH_3-8"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (54%), 176 (36%), 162 (41%), 148 (63%), 146 (BP, 100%), 145 (6%), 134 (57%), 132 (59%), 120 (71%), 118 (84%), 117 (38%), 101 (41%).

4.6.13 ***N-(2,5-Dimethylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5m)***
White amorphous solid; Yield: 74%; M.P.: 128-130 ^{o}C; HR-MS: $[M]^{+}$ 323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243); IR (KBr, υ_{max}, cm^{-1}): 3439 (N-H), 3061 (Ar C-H), 1737 (ester C=O), 1676 (amide C=O), 1604 (Ar C=C), 1162 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.79 (s, 1H, CON-H), 7.93 (d, *J* = 8.4 Hz, 1H, H-5), 7.64 (t, *J* = 8.0 Hz, 1H, H-7), 7.40 (d, *J* = 8.0 Hz, 1H, H-8), 7.36 (t, *J* = 8.4 Hz, 1H, H-6), 7.19 (s, 1H, H-6"), 7.06 (d, *J* = 8.0 Hz, 1H, H-3"), 6.92 (d, *J* = 8.0 Hz, 1H, H-4"), 5.77 (s, 1H, H-3), 4.74 (s, 2H, H-2'), 2.34 (s, 3H, CH_3-7"), 2.14 (s, 3H, CH_3-8"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (53%), 176 (36%), 162 (42%), 148 (61%), 146 (BP, 100%), 145 (5%), 134 (54%), 132 (53%), 120 (71%), 118 (87%), 117 (33%), 101 (42%).

4.6.14 ***N-(2,6-Dimethylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5n)***
White amorphous solid; Yield: 71%; M.P.: 122-124 ^{o}C; HR-MS: $[M]^{+}$ 323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243); IR (KBr, υ_{max}, cm^{-1}): 3453 (N-H), 3059 (Ar C-H), 1736 (ester C=O), 1678 (amide C=O), 1601 (Ar C=C), 1162 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.78 (s, 1H, CON-H), 7.93 (d, *J* = 8.4 Hz, 1H, H-5), 7.64 (t, *J* = 8.4 Hz, 1H, H-7), 7.39 (d, *J* = 8.0 Hz, 1H, H-8), 7.34 (t, *J* = 8.0 Hz, 1H, H-6), 7.15-7.08 (m, 3H, H-3" to H-5"), 5.73 (s, 1H, H-3), 4.78 (s, 2H, H-2'), 2.23 (s, 6H, CH_3-7" & CH_3-8"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (57%), 176 (38%), 162 (43%), 148 (66%), 146 (BP, 100%), 145 (9%), 134 (54%), 132 (53%), 120 (76%), 118 (85%), 117 (39%), 101 (43%).

4.6.15 ***N-(3,5-Dimethylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5o)***
White amorphous solid; Yield: 83%; M.P.: 130-132 ^{o}C; HR-MS: $[M]^{+}$ 323.1154 (Calcd. for $C_{19}H_{17}NO_4$; 323.1243); IR (KBr, υ_{max}, cm^{-1}): 3438 (N-H), 3051 (Ar C-H), 1733 (ester C=O), 1679 (amide C=O), 1602 (Ar C=C), 1162 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.23 (s, 1H, CON-H), 7.92 (d, *J* = 8.0 Hz, 1H, H-5), 7.63 (t, *J* = 8.0 Hz, 1H, H-7), 7.37 (d, *J* = 8.0 Hz, 1H, H-8), 7.34 (t, *J* = 7.6 Hz, 1H, H-6), 7.19 (s, 2H, H-2" & H-6"), 6.93 (s, 1H, H-4"), 5.76 (s, 1H, H-3), 4.77 (s, 2H, H-2'), 2.26 (s, 6H, CH_3-7" & CH_3-8"); EIMS (*m/z*): 323 $[M]^{\bullet+}$ (50%), 176 (32%), 162 (49%), 148 (68%), 146 (BP, 100%), 145 (9%), 134 (54%), 132 (56%), 120 (79%), 118 (83%), 117 (37%), 101 (45%).

4.6.16 ***N-(2-Ethyl-6-methylphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5p)***
White amorphous solid; Yield: 78%; M.P.: 158-160 ^{o}C; HR-MS: $[M]^{+}$337.1316 (Calcd. for $C_{20}H_{19}NO_4$; 337.1368); IR (KBr, υ_{max}, cm^{-1}): 3446 (N-H), 3057 (Ar C-H), 1738 (ester C=O), 1675 (amide C=O), 1604 (Ar C=C), 1165 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.62 (s, 1H, CON-H), 7.93 (d, *J* = 8.0 Hz, 1H, H-5), 7.64 (t, *J* = 8.0 Hz, 1H, H-7), 7.37 (d, *J* = 8.4 Hz, 1H, H-8), 7.34 (t, *J* = 8.0 Hz, 1H, H-6), 7.18-7.09 (m, 3H, H-3" to H-5"), 5.77 (s, 1H, H-3), 4.73 (s, 2H, H-2'), 2.44 (q, *J* =7.6 Hz, 2H, H-7"), 1.98 (s, 3H, CH_3-9"), 1.03 (t, *J* =7.6 Hz, 3H, CH_3-8"); EIMS (*m/z*): 337 $[M]^{\bullet+}$ (56%), 176 (36%), 162 (69%), 148 (32%), 146 (BP, 100%), 145 (6%), 134 (96%), 132 (55%), 118 (83%), 117 (36%), 101 (44%).

4.6.17 ***N-(2-Methyl-6-nitrophenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5q)***
Light yellow amorphous solid; Yield: 81%; M.P.: 200-202 ^{o}C; HR-MS: $[M]^{+}$354.0859 (Calcd. for $C_{18}H_{14}N_2O_6$; 354.0878); IR (KBr, υ_{max}, cm^{-1}): 3449 (N-H), 3055 (Ar C-H), 1735 (ester C=O), 1671 (amide C=O), 1607 (Ar C=C), 1167 (C-O); ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm): 8.72 (s, 1H, CON-H),7.97 (d, *J* = 8.0 Hz, 1H, H-5"), 7.92 (d, *J* = 8.0 Hz, 1H, H-5), 7.63 (t, *J* = 8.0 Hz, 1H, H-7), 7.38 (d, *J* = 8.0 Hz, 1H, H-8), 7.35 (t, *J* = 8.0 Hz, 1H, H-6), 7.32 (d, *J* = 8.4 Hz, 1H, H-3"), 6.56 (t, *J* = 8.4 Hz, 1H, H-4"), 5.73 (s, 1H, H-3), 4.79 (s, 2H, H-2'), 2.25 (s, 3H, CH_3-7"); EIMS (*m/z*): 354 $[M]^{\bullet+}$ (56%), 179 (23%), 176 (35%), 162 (47%), 151 (73%), 148 (37%), 146 (BP, 100%), 145 (5%), 134 (58%), 132 (54%), 118 (87%), 117 (38%), 101 (43%).

4.6.18 ***N-(5-Chloro-2-methoxyphenyl)-2-[(2-oxo-2H-chromen-4-yl)oxy]acetamide (5r)***
Grey amorphous solid; Yield: 87%; M.P.: 232-234 ^{o}C; HR-MS: $[M]^{+}$359.0367 (Calcd. for $C_{18}H_{14}ClNO_5$; 359.0392);IR (KBr, υ_{max}, cm^{-1}): 3468 (N-H), 3073 (Ar C-H), 1731 (ester C=O), 1679 (amide C=O), 1593 (Ar C=C), 1168 (C-O), 703 ; ^{1}H-NMR (400 MHz, $CHCl_3$-d_1, δ, ppm):8.90 (s, 1H, CON-H), 8.37 (d, *J* = 2.4 Hz, 1H, H-6"), 7.91 (d, *J* = 8.0 Hz, 1H, H-5), 7.62 (t, *J* = 8.0 Hz, 1H, H-7), 7.38 (d, *J* = 8.4 Hz, 1H, H-8), 7.35 (t, *J* = 7.6 Hz, 1H, H-6), 7.03 (dd, *J* = 8.8, 2.4 Hz, 1H, H-4"), 6.79 (d, *J* = 8.8 Hz, 1H, H-3"), 5.75 (s, 1H, H-3), 4.75 (s, 2H, H-2'), 3.90 (s, 3H, CH_3-7"); EIMS (*m/z*): 359 $[M]^{\bullet+}$ (57%), 184 (27%), 176 (33%), 162 (43%), 156 (71%), 148 (36%), 146 (BP, 100%), 145 (7%), 134 (56%), 132 (53%), 118 (86%), 117 (32%), 101 (48%).

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