Synthesis and Characterization of New 1,2-Dihydropyridine-3-Carbonitrile Compounds with Study of Expected Biological Activity

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Abstract

New 1,2-dihydropyridine-3-carbonitrile derivative compounds (3,4) were synthesized by cyclization of ketones (compound (1) and compound (2)) with appropriate aldehydes (4-N, N-dimethylaminobenzaldehyde and 4-chloro-2-oxo-2H-chromene-3-carbaldehyde) in presence of ethyl cyano acetate and ammonium acetate. The new synthesized compounds have been characterized using Melting point, FT-IR spectroscopy and ^{1}H-NMR and ^{13}C-NMR spectrum. The evaluation of biological activity of some synthesized compounds (1-4) with different concentration 10 mg mL^{-1}, 1 mg mL^{-1} and 0.1 mg mL^{-1}, against two types of bacteria on gram positive bacterial *Staphylococcus aureus*, *Streptococcus pyogenus* and gram nagetive bacterial *Escherichia coli*, *Klebsiella pneumniae.* [DOI: 10.22401/JNUS.21.2.07]

Keywords**:** 1, 2-Dihydropyridine, 2 H-Chromen-2-Ones.

1.Introduction

2H-chromen-2-one and its derivatives of the most serious O-heterocycles are extensively established at different bioactive natural and synthetic yields [1]. They have been efficient pharmacophores, vastly utilized for the designing and synthesis of novel bioactive compounds [2]. Accordingly, various biological activities like anticoagulation and cardiovascular activities (warfarin) [3] and antimicrobial activities (novobiocin and clorobiocin) [4] have been reported. Antioxidant anti-inflammatory [5], antibacterial – antifungal, anti-HIV, anticoagulant, antitumor, antimicrobial [6,7], Analgesic, anti-pyretic [8]. Pyridine-2(1H)-ones have been believe like serious building blocks at drug discovery as abundant natural yields as well as synthetic compounds having 2-pyridone moiety and possesses a vast kind from biological characteristics. Abundant drugs containing like a skeleton were released into the clinical world and a small further were under clinical trials at e.g., Amrinone [9]. In organization for those, Pyridone and its derivatives move a major role at various biological processes and have large chemical and pharmacological importance [10]. The synthesis of the pyridinone containing heterocyclic systems take an important site at the regality from synthetic organic chemistry, because their therapeutic and pharmacological properties [11]. They have been emerged like integral backbones of over 7000 present drugs [12]. The pyridine nucleus was an integral portion from anticancer and anti-inflammatory agents [13] else. On the anther hand, cyanopyridone and cyanopyridine derivatives have been shown for owns promising antimicrobial [14] and anticancer activities [15]. This investigation demonstrated synthesis of new 1,2-dihydropyridine-3-carbonitrile compounds derived from 7-hydroxy-4-methyl-2H-chromen-2-one with fully characterization, and aiming to further biochemical studies.

2.Experimental

2.1 Synthesis of 4-methyl-7-(2-oxopropoxy)-2H-chromen-2-one (1)

A mixture of 7-hydroxy-4-methyl-2H-chromen-2-one (1.76gm.,0.01 mole), chloroacetone (0.92gm.,0.01 mole) and potassium carbonate (1.38gm.,0.01 mole) in acetone (20 ml.) were refluxed for 6 hrs., the reaction was monitored through TLC (hexane: ethylacetate, 7:3). The reaction mixture has been filtered off, and filtrate was concentrated and allowed to cool. The precipitated was filtered, washed with water and recrystallized from ethanol to give the titled compound [16]. Melting point: 147-149^{0}C, Yields: 80%. The FTIR spectral data showed absorption at (1735cm^{-1}, for υC=O), (1617,1556cm^{-1}, for

υC=C, Ar.), (2915,2845cm^{-1}, for υCH, aliphatic), (1706cm^{-1}, for υC=O, lactone), (3090cm^{-1}, for υAr-H), (1135 cm^{-1}, for υC-O), ^{1}H-NMR spectra data showed signal at (δ=2.0, 3H, s, -CH_3 lactone), (δ=2.8, 3H, s, CO-CH_3), (δ=4.9, 2H, CH_2), (δ=6.1, 1H, s, C=CH of lactone), (δ=6.8-7.6, 3H, m, Ar-H).

2.2 Synthesis of 4-methyl-2-oxo-2H-chromen-7-yl acetate (2)

A solution of 7-hydroxy-4-methyl-2H-chromen-2-one (2.82 gm., 0.016 mole) and acetic anhydride (1.63 ml.,0.016 mole) is refluxed for 1.5hr.,the progress of the reaction was monitored by TLC (hexane: ethylacetate, 7:3, R_f = 0.6).The reaction mixture has been poured at ice-cold water and the separated result has been filtered off and was recrystallized for ethanol. Melting point: 150-151^{0}C, Yields: 91%. The FTIR spectral data showed absorption at (1730cm^{-1}, for υC=O), (1565, 1505cm^{-1}, for υC=C, Ar.), (2938, 2832cm^{-1}, for υCH, aliphatic), (1707cm^{-1}, for υC=O, lactone), (3076cm^{-1}, for υC-H, Ar.), (1133 cm^{-1}, for υC-O).

2.3 General procedure for 1,2-dihydropyridine-3-carbonitrile reaction.

A solution of ketones (0.001 mole) in ethanol (10 ml.), appropriate aldehydes (0.001 mole), ethyl cyanoacetate (0.113g.,0.001 mole), ammonium acetate (0.6g.,0.008 mole) were added [17]. The reaction mixture has been refluxed at 2hrs. The resulting has been filtered off then washed for water, dried and recrystallized from ethanol.

2.4 Synthesis of 4-(4-(dimethylamino) phenyl)-6-((4-methyl-2-oxo-2H-chromen-7-yloxy)methyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3)

Melting point: 103-105d ^{0}C, Yields: 90%. The FTIR spectral data showed absorption at (3220cm^{-1}, for υNH),(3117cm^{-1}, for υC-H, Ar.),(1703cm^{-1}, owing to υC=O Lactone), (1650cm^{-1}, owing to υC=O, amide),(1612cm^{-1}, for υC=N), (1570cm^{-1}, for υC=C, Ar.), (2208 cm^{-1}, for υCN). ^{1}H-NMR spectra data showed signal at 2.4(s,3H owing to CH_3), 3.09(s,6H owing to $N(CH_3)_2$), 4.2(s,2H owing to CH_2), 6.8-8.1 (m,10H owing to (Ar-H,C=CH for lactone ring, C=CH for pyridinone ring and NH). The ^{13}C-NMR spectra data showed signal at 14, 21, 30, 61, 92, 110, 111, 112, 118, 118.7, 119, 120, 131, 132, 133, 134, 153, 154, 154.6, 163, 163.9 and 192.

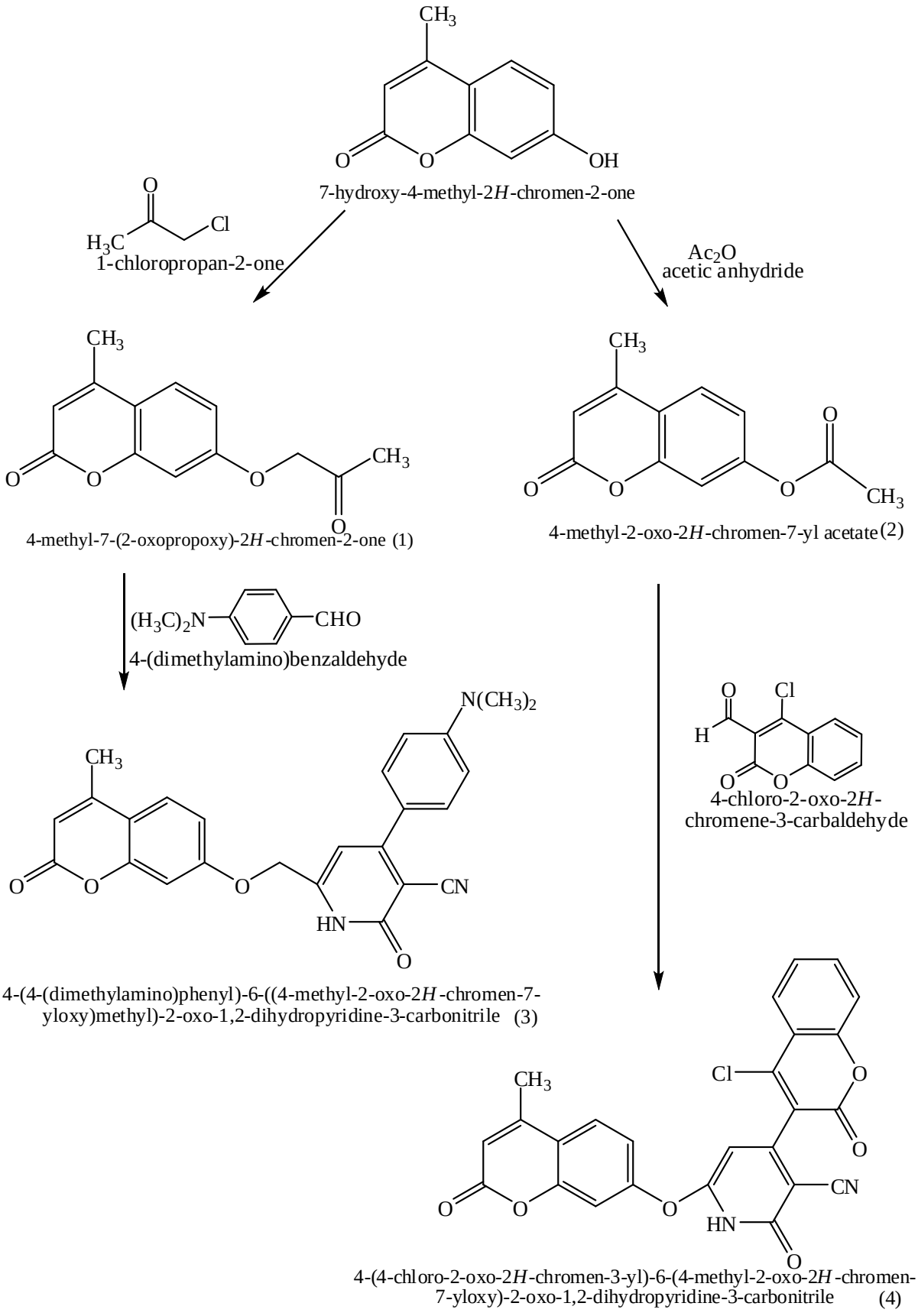
2.5 Synthesis of 4-(4-chloro-2-oxo-2H-chromen-3-yl)-6-(4-methyl-2-oxo-2H-chromen-7-yloxy)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4)

Melting point: up 360^{0}C, Yields: 90%. The FTIR spectral data showed absorption at (3105cm^{-1}, for υNH), (2926cm^{-1}, for υC-H, Ar.), (1739cm^{-1}, owing to υC=O Lactone), (1656cm^{-1}, owing to υC=O, amide),(1618cm^{-1}, for υC=N), (1602cm^{-1}, for υC=C, Ar.), (2220 cm^{-1}, for υCN). ^{1}H-NMR spectra data showed signal at 2.2(s,3H,CH_3), 4.4(s, 1H,-NH for lactame), 6.1 (s,1H,C=CH for pyridinone ring, 6.7(s, 1H,C=CH for lactone ring), 7.4-8.9 (m,7H owing to Ar-H), 10.5 (s, 1H,OH enol). The ^{13}C-NMR spectra data showed signal at 105, 115, 116, 117, 118, 119, 120, 125, 125.5, 135, 138, 147, 148, 150, 153, 154, 158 and 162.

3.Agar Diffusion Assays

By applying the ager plat diffiusion technique [18] some of the synthesized compounds have been screend at vitro to antibacterial activity against *Staphylococcus aureus* and *Streptococcus pyogenus* (Gram +ve bacteria) and *Escherichia coli* and *Klebsiella pneumniae* (Gram-ve bacteria). Intended agar and petridishes have been sterilized through autoclaving to (15 min) by 121^{o}C. The ager plates have been surface injected uniformly for the broth culture from the tested microorganisms. At the solidified medium appropriately spaced away holes have been made all (6 mm) at diameter, have been filled with 100 µl from the prepared compounds.

The synthesized compounds [1], [2], [3] and [4] were dissolved in Dimethylslufoxide (DMSO) in three concentration 10 mg mL^{-1} ,1 mg mL^{-1} and 0.1 mg mL^{-1} . These plates have been incubated by (37^{o}C) to (24 hrs.). The inhibition zones give rises to the various compounds at the bacteria have been examined. For comparison, a standard antibiotic drug, gentamycin, was used as a standard for antimicrobial activity.


7-hydroxy-4-methyl-2H-chromen-2-one
1-chloropropan-2-one
Ac2O
acetic anhydride
4-methyl-7-(2-oxopropoxy)-2H-chromen-2-one (1)
4-methyl-2-oxo-2H-chromen-7-yl acetate (2)
4-(dimethylamino)benzaldehyde
4-chloro-2-oxo-2H-chromene-3-carbaldehyde
4-(4-(dimethylamino)phenyl)-6-((4-methyl-2-oxo-2H-chromen-7-yloxy)methyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3)
4-(4-chloro-2-oxo-2H-chromen-3-yl)-6-(4-methyl-2-oxo-2H-chromen-7-yloxy)-2-oxo-1,2-dihydropyridine-3-carbonitrile (4)

Scheme (1)

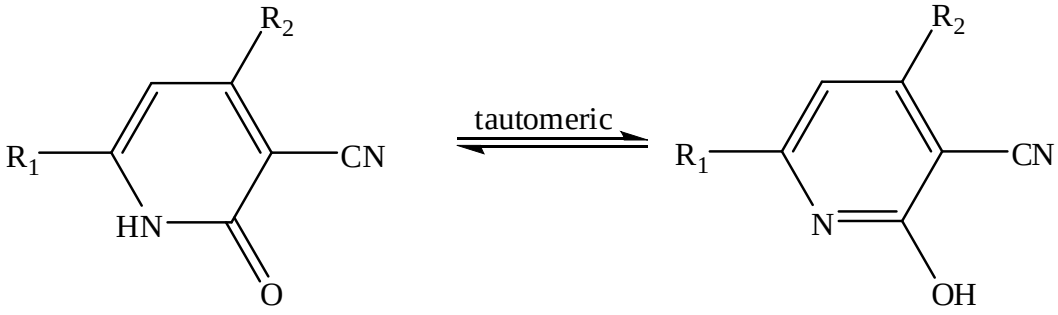
4. Results and Discussion

Compound (1) was prepared by substitution reaction between 7-hydroxy-4-methyl-2H-chromen-2-one with chloroacetone in the presence of acetone as a solvent. FT-IR spectra from Compound (1) showed express absorption bands during (1735) cm^{-1} owing to (C=O) carbonyl group from ketone and the disappeared from absorption band at (3437) cm^{-1} for (OH) group.The characteristic bands of compound (1) are shown in Table (1).

Compound (2) was synthesized through the reaction of 7-hydroxy-4-methyl-2H-chromen-2-one for acetic anhydride to give ester derivative; it was a tetrahedral nucleophilic substitution reaction. The characteristic bands of FTIR spectrum of compound (2) are shown in Table (4). The new 1,2-dihydropyridine-3-carbonitrile compound (3) was synthesized by the reaction of compound (1) with appropriate aldehyde (4-N, N-dimethylaminobenzaldehyde) and ethyl cyanoacetate in presence of ammonium acetate, show in scheme (1). Compound (3) was identified by FT-IR and several from them through ^{1}HNMR and ^{13}C-NMR spectroscopy. The FTIR spectrum of compound (3) shows bands at the frequency of (1650 cm^{-1}) owing to the carbonyl group from amide appears, the NH near (3220) cm^{-1}. And the appearance from absorption band during (2208) cm^{-1} for CN group. The characteristic bands from compound (3) are shown in table (3).

Pyridinones derivatives (4) have been obtained by the reaction of substituted ketone with appropriate aldehyde in the presence of ethyl cyanoacetate and ammonium acetate.

The FTIR spectrum of compound (4) shows bands at the frequency of (1656 cm^{-1}) owing to the carbonyl group from amide appears, the NH near (3105) cm^{-1}. And the appearance from absorption band during (2208) cm^{-1} for CN group. The Characteristic bands from compound (4) are shown in table (3). The ^{1}HNMR spectrum from compound (4) have been showed the following data: 2.2(s, 3H, CH_3), 4.4(s, 1H,O=C-NH), 6.1 (s,1H,C=CH for pyridinone ring, 6.7(s, 1H,C=CH for lactone ring), 7.4 - 8.9 (m,7H owing to Ar-H), 10.5(s, 1H owing to OH enol).



Biological assay

The antibacterial activity of the synthesized compounds (1-4) was evaluated against the bacterial strains *Staphylococcus aureus* and *Streptococcus pyogenus* (Gram +ve bacteria) and *Escherichia coli* and *Klebsiella pneumniae* (Gram -ve bacteria) by the disk diffusion method [19]. Standard drug (Gentamycin) was used at a concentration of 1 mg mL^{-1} for comparisons.

The tested compounds were dissolved in *Dimethylslufoxide (DMSO)* to give a three solution of 10.00 mg mL^{-1}, 1.00 mg mL^{-1} and 0.10 mg mL^{-1}. The inhibition zones have been measured at millimeters during the end from an incubation period from 48 hours during 37°C. *N,N*-dimethylformamide (DMF) have been shown never inhibition zone. Test results have been shown at Table (4).

The data obtained in Table (4) indicate that the starting compound is biologically less active against gram +ve and gram–ve bacteria. The activity from Pyridinones are higher than the activity from the residue from the prepared compounds. The results of the preliminary screening test are listed in Table (4). From the data obtaind in Table (4), it is found that compound (3) has highest activity against *Klebsiella pneumniae (gram–ve bacteria) at solution 10 mg* mL^{-1}, compound (3) is found

to have the highest activity against *Escherichia coli (gram –ve bacteria) at solution1 mg* mL^{-1}. Compound (4) is found to have the highest activity against *Streptococcus pyogenus (Gram +ve bacteria) at solution1 mg* mL^{-1} and compound (4) is found to have the highest activity against *Staphylococcus aureus (Gram +ve bacteria) at solution10 mg* mL^{-1}, while the other solution compounds show either slight or no activity at all.

Table (1)
The FTIR spectrum of compound [1] in scheme (1).

Comp. No.	Characteristic bands of FT-IR spectrum (cm^{-1})					
	υC=O	υC=O Lactone	υC=C Ar.	υC-O-C	υC-H alph.	υC-H Ar.
[1]	1735	1706	1617, 1556	1135	2915, 2845	3090

Table (2)
The FTIR spectrum of compound [2] in scheme (1).

Comp. No.	Characteristic bands of FT-IR spectrum (cm^{-1})					
	υC=O	υC=O Lactone	υC=C ar.	υC-O ester	υC-H alph.	Others
[2]	1730	1707	1505, 1565	1133	2938, 2832	υC-H ar. 3076

Table (3)
Spectral data of compounds [3] and compound [4] in scheme (1).

Comp. No.	Characteristic bands of FT-IR spectrum (cm^{-1})				
	υC=O Lactone	υCN	υC=O amide	υC=C	Others
[3]	1703	2208	1650	1570	υC-H ar. 3117 υC=N 1612 υNH 3220
[4]	1739	2220	1656	1602	υC-H ar. 2926, υC=N 1618, υNH 3105.

Table (4)
Antibacterial activities from several from the synthesized compounds.

Comp. No.	Gram positive						Gram negative					
	S. aureus			*Streptococcus pyogenus*			*E. coli*			*Klebsiella pneumniae*		
	10^{-2}	10^{-3}	10^{-4}	10^{-2}	10^{-3}	10^{-4}	10^{-2}	10^{-3}	10^{-4}	10^{-2}	10^{-3}	10^{-4}
[1]	-	-	-	-	-	-	-	-	-	11	-	-
[2]	-	-	-	-	-	-	-	-	-	-	-	-
[3]	-	-	-	-	-	-	9	11	-	19	15	-
[4]	10	-	-	-	12	-	-	-	-	-	-	-
gentamycin	20	15	10	20	15	10	15	10	-	15	10	-

**** Zone diameter of growth inhibition (mm) after 24 hours, at the concentration 10.00 mg*** mL^{-1}***, 1.00 mg*** mL^{-1} ***and 0.10 mg*** mL^{-1} ***in DMSO.***

5- Conclusions

In this work described the synthesis new 1,2-dihydropyridine-3-carbonitrile compounds derived from 4-methyl-7-(2-oxopropoxy)-2H-chromen-2-one and 4-methyl-2-oxo-2H-chromen-7-yl acetate. The preparation of 1,2-dihydropyridine-3-carbonitrile derivatives, isolation, and characterization of a new compounds. The synthesized compounds were found to have the highest activity against *Klebsiella pneumniae (Grame-ve bacteria) and Streptococcus pyogenus (Gram +ve bacteria).*

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