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Green Synthesis of Novel 5-Arylazo-2-[(2S, 3S, 4R, 5R)-3, 4, 5-Trihydroxy-6-(Hydroxymethyl) Tetrahydro-2H-Pyran-2-Yloxy]-4, 6-Dimethyl 3-Nicotinonitrile

Magda H. Abdellattif[1*], Mohamed Mohamed Helmy Arief[2], Adel A. H. Abdel-Rahman[3], Abdel-Aleem H. Abdel Aleem[3], Abdel Moneam Farag Eissa[2]

[1]Deanship of Scientific Research, Taif University, Alhawaya, Taif, KSA
[2]Chemistry Department, Faculty of Science, Benha University, Benha, Egypt
[3]Chemistry Department, Faculty of Science, Menaufia University, Shebin Elkom, Egypt
Email: mmharief@gmail.com, adelnassar63@science-mnf.eg, aleem@science-mnf.eg, m.hasan@tu.edu.sa, *magdah11uk@hotmail.com, amf_eissa@yahoo.com

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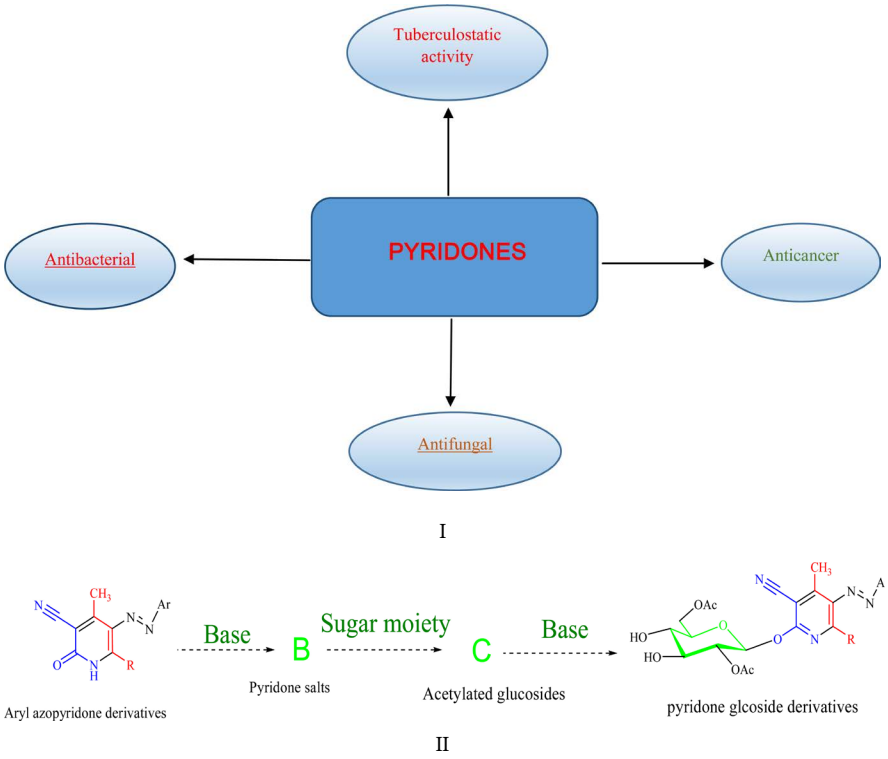
Abstract

Introduction: Pyridone derivatives played important roles in the last decade to approach many and different functionalities, especially as anti-tumor, antibacterial, anti-fungal, and many of pharmacological activities. **Methodology**: Novel compounds of 5-Arylazo-2-[(substituted)-3, 4, 5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy]-4, 6-dimethyl-nicotinonitrile, (3a-e), generally called (fluroarylazopyridine glucosides) were synthesised via green protocol, microwave. **Results**: The compounds were investigated by (IR, ^{1}HNMR, ^{13}CNMR and mass spectrometry). Where some of pharmacological activities like antibacterial and antifungal studies had been investigated and characterized. It was found that 3a-d had characterized by high activities as antibacterial and antifungal. Where microwave synthetic methods were more efficient, gave higher products quantity, and more saving for time requirement and for using of much more solvents.

Keywords

Green Chemistry, Green Protocol, Pyridones, Fluroazo Compounds, Microwave

Graphical Abstract



1. Introduction

Pyridine nucleus is one of the most interesting nucleus in organic synthesis. Many uses of pyridones derivatives were investigated in the recent decades especially fluorinated derivatives. One of the recent researches discovered that high tuberculostatic activity of pyridone was observed [1].

Also the amazing character of some pyridone is its high fluorescence activities which were used as molecular sensor of picric acid [2].

It has been of great importance in the exploring of some novel antimicrobial compounds in veterinary as well as human medicine worldwide.

Genetic mutation and propagation of drug resistance genes of microorganisms are a very great factor that being as a strong barrier in treating the infectious diseases for animal and human patients [3] [4].

The importance of the synthesis of novel derivatives of pyridone nucleosides is due to their strong affinity to treat many diseases, for example hepatitis, cancer and many of microbial infections [5] [6] [7] [8] [9].

Fluorinated derivatives of pyridones are of high significance in pharmaceutical and medicinal chemistry [10] [11]. Synthesis of poly substituted fluroarylazopyridone by using green protocol is of great effect in synthetic chemistry and also in pharmaceutical chemistry [12]. Actually in the molecule which contains fluorine atoms became of high change in its lipophilicity, which also affect and

change the rate of transportation through lipid membranes [13].

Achievement of green and sustainable chemistry protocol instead of classical methods synthetic chemistry nowadays is of high interest, especially in synthesis of some novel substituted fluro pyridone derivatives (1a-e) and their nucleosides (3a-e).

2. Results and Discussion

a) Chemistry

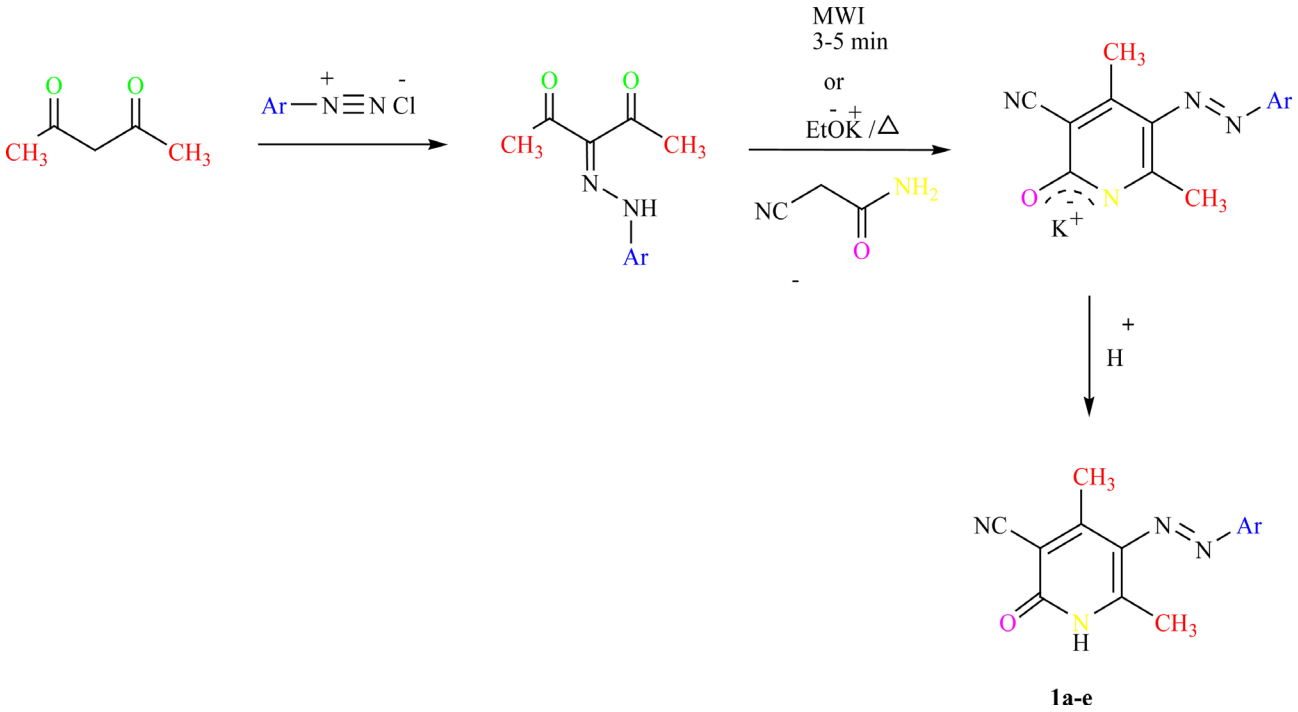
General technique for green formation of arylazo pyridone glucosides had been used [14] [15].

Scheme 1. Represents the general method for synthesis of pyridine derivatives 1(a-e) where, Scheme 2. Represents the general method for synthesis of pyridine derivatives 2(a-e) and 3(a-e).

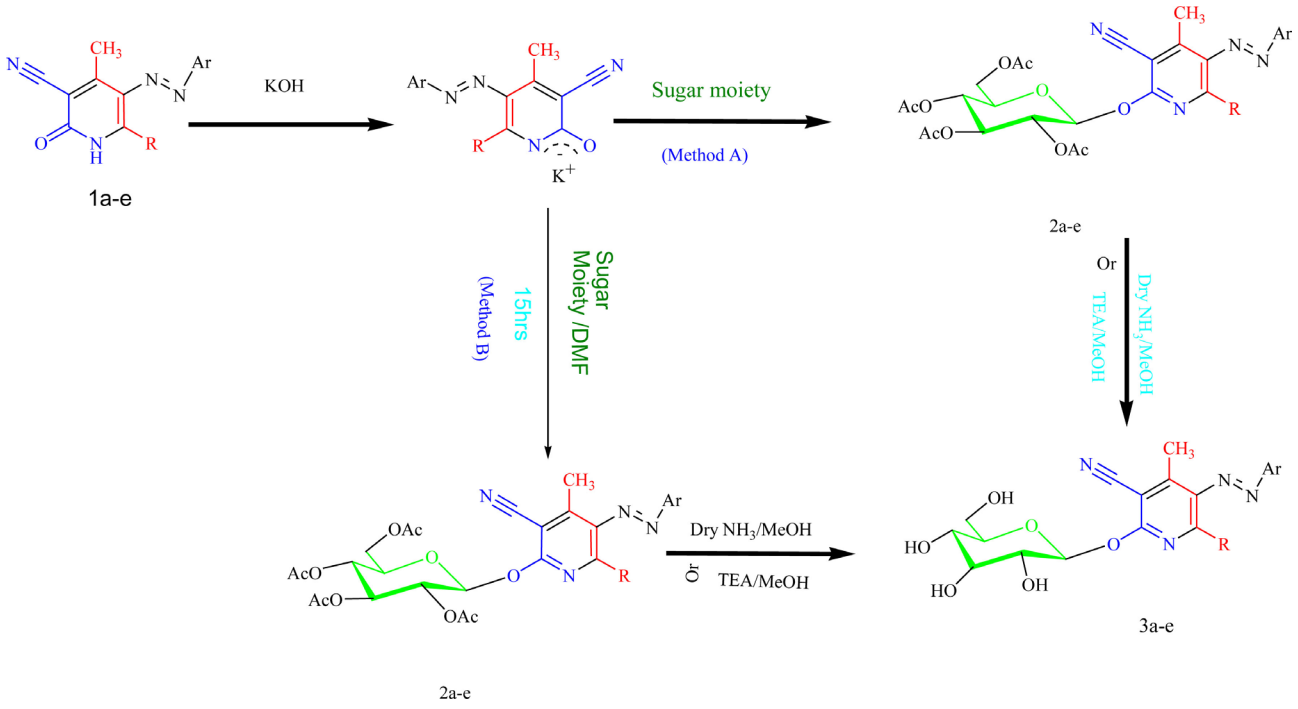
Where Simple, accurate, green procedure were be used in synthesis of 5-arylazo-2-[(2S, 3S, 4R, 5R)-3, 4, 5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy]-4, 6-dimethylnicotinonitrile [16] [17] [18] [19].

5-arylazo-2-[(2S, 3S, 4R, 5R)-3, 4, 5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy]-4, 6-dimethylnicotinonitrile (3a-e) had been got in very good yields where microwave irradiation had been used.

In this method, a homogenous solid mixture of 2(1H)-pyridones (1a-e) and acetyled-*α*-D-glucopyranose derivatives with silica gel was irradiated in MW for 2-3 minutes. For example, 3-cyano-4, 6-Dimethyl-5-arylazo-2(1*H*)-pyridinones (1a-e) [14] [15] were allowed to be reacted with acetylaed-*α*-D-glucopyranosyl bromide derivative for 2 minutes to give (2a-e) in about 91% yield.



Scheme 1. Synthesis of Pyridone derivatives 1a-e.



Scheme 2. Synthesis of Pyridone derivatives 2a-e & 3a-e.

The same nucleosides, (2a-e) were be gained in very high yields by the reaction of the K-salt of pyridnone which was generated in situ, using potassium hydride and an activated sugar moiety. The K-salt of 3-cyano-4, 6-dimethyl-5-arylazo-2(1H)-pyridinones (1a-e) were allowed to react with *α*-bromoglucose in DMF for 15 hours to give (2a-e) in average 73% yield.

Deacetylation of 2a-e were almost done by treatment of alkali and although anhydrous media is useful to reduce the amount of alkali but catalytic reaction may be applied. But in fact a mixture of Triethylamine in MeOH and water be used in deacetylation or a mixture of methanol and dry ammonia were be also used.

Table 1 which illustrated the structure of the substituents of Compound 1 (a-e), where One could notice the difference between microwave method and conventional method in time of synthesis and the yield percentage of the product from Table 2. Also it had been noticed the difference between triethyl amine method and methanol and dry ammonia method in the yield percentage of the product as represented in Table 3.

The final structures of the expected compounds had been also represented in Table 4. Where the elemental analysis of the synthetic compounds had been illustrated in Table 5. Also ^{1}HNMR, ^{13}CNMR, Ms-LC, and IR studies had been illustrated at Tables 6-9, respectively.

b) Biology

It has been of great importance in the exploring of some novel antimicrobial compounds in veterinary as well as human medicine worldwide. Genetic mutation and propagation of drug resistance genes of microorganisms are a very

Table 1. Substituted Arylazopyridine glucosides 1a-e.

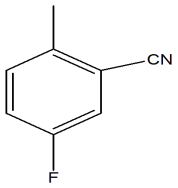
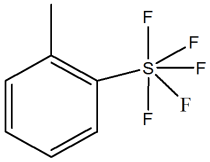
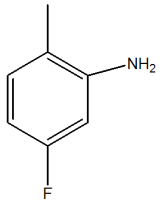
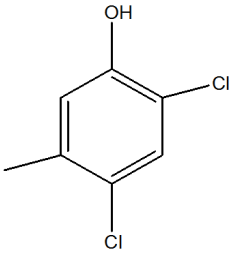
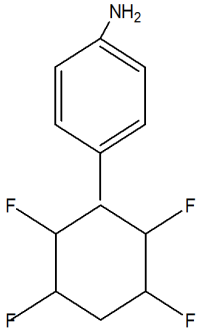
Substituted pyridone	Ar	R^2
1a		**—CH_3**
1b		**—CH_3**
1c		**—CH_3**
1d		**-CH_3**
1e		**-CH_3**

Table 2. Comparison between conventional methods and microwave methods for the Synthesis of Acetylated 5-arylazo-2-[(2S, 3S, 4R, 5R)-3, 4, 5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy]-4, 6-dimethyl 3-nicotinonitrile.

Compound number	R	Ar	Microwave method		Conventional	
			time	yield	time	yield
2a	—CH_3	C_7H_3F	2	92	55	60
2b	—CH_3	$C_6H_4SF_5$	2	94	48	69
2c	—CH_3	C_6H_5NF	2	90	58	60
2d	-CH_3	$C_6H_2Cl_2NO$	2	91	56	63
2e	-CH_3	$C_{12}H_{11}NF_4$	2	93	55	60

Table 3. Yeild % percentage comparison of trimethylamine and dry ammonia methods for novel of nucleosides 3a-e.

Compound number	R =	Ar =	Method A	Method B
3a	—CH_3	C_7H_3F	90	82
3b	—CH_3	$C_6H_4SF_5$	92	80
3c	—CH_3	C_6H_5NF	91	81
3d	-CH_3	$C_6H_2Cl_2NO$	92	83
3e	-CH_3	$C_{12}H_{11}NF_4$	92	80

Table 4. Structure formulae for compounds 1a-e & 3a-e.

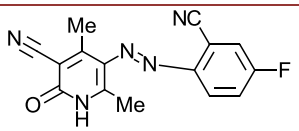
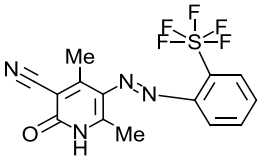
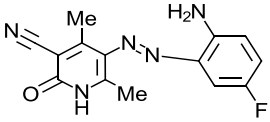
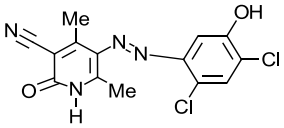
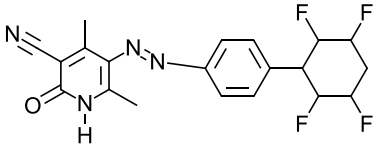
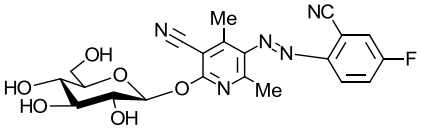
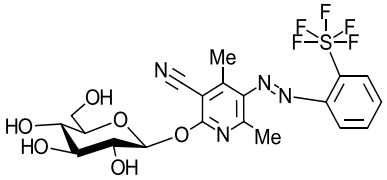
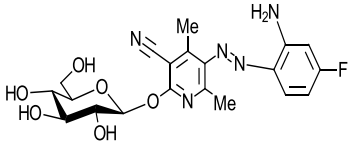
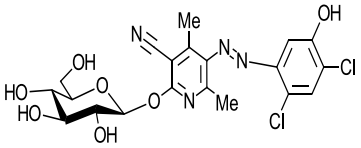
Compound number	Compound name	Compound structure
1a	5-[(E)-2-Cyano-4-fluorophenylazo]-4,6-dimethyl-2-oxo-1H-pyridine-3-carbonitrile	
1b	5-[(E)-o-(Pentafluorothio)phenylazo]-4,6-dimethyl-2-oxo-1H-pyridine-3-carbonitrile	
1c	5-[(E)-2-Amino-5-fluorophenylazo]-4,6-dimethyl-2-oxo-1H-pyridine-3-carbonitrile	
1d	5-[(E)-2,4-Dichloro-5-hydroxyphenylazo]-4,6-dimethyl-2-oxo-1H-pyridine-3-carbonitrile	
1e	5-[(E)-p-(2,3,5,6-Tetrafluorocyclohexyl)phenylazo]-4,6-dimethyl-2-oxo-1H-pyridine-3-carbonitrile	
3a	5-[(E)-2-Cyano-4-fluorophenylazo]-2-[(2S,3S,4R,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy]-4,6-dimethylnicotinonitrile	
3c	5-[(E)-o-(Pentafluorothio)phenylazo]-2-[(2S,3S,4R,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy]-4,6-dimethylnicotinonitrile	
3d	5-[(E)-2-Amino-4-fluorophenylazo]-2-[(2S,3S,4R,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy]-4,6-dimethylnicotinonitrile	
3e	5-[(E)-2,4-Dichloro-5-hydroxyphenylazo]-2-[(2S,3S,4R,5R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yloxy]-4,6-dimethylnicotinonitrile	

Table 5. The Elemental analysis of synthesized compounds.

Compd.	Mp. (˚C)	Formula (Mwt)	Solvent of crystallization	Analysis % Calcd. (Found)					
				C	H	N	Cl	F	S
1a	456	$C_{15}H_{10}FN_5O$	Ethanol/DME	61.01	3.41	23.72		6.43	
1b	240.76	$C_{14}H_{11}F_5N_4OS$	Ethanol/DME	44.45	2.93	14.81		25.11	8.48
1c	399.66	$C_{14}H_{12}FN_5O$	Ethanol/DME	58.94	4.24	24.55		6.66	
1d	487.37	$C_{14}H_{10}Cl_2N_4O_2$	Ethanol/DME	49.87	2.99	16.62	21.03		
1e	363.69	$C_{20}H_{18}F_4N_4O$	Ethanol/DME	59.11	4.46	13.79		18.7	
3a	794	$C_{21}H_{20}FN_5O_6$	Ethanol/DME	55.14	4.41	15.31		4.15	
3b	578	$C_{20}H_{21}F_5N_4O_6S$	Ethanol/DME	44.45	3.92	10.73		17.58	5.93
3c	737	$C_{20}H_{22}FN_5O_6$	Ethanol/DME	53.69	4.96	15.72		4.25	
3d	825	$C_{20}H_{20}Cl_2N_4O_7$	Ethanol/DME	48	3.64	16.86			9.65
3e	701	$C_{26}H_{28}F_4N_4O_6$	Ethanol/DME	54.93	4..04	11.22	14.3		

Table 6. ^{1}H NMR spectrum data of the novel compounds.

Compound number	Spectral1H NMR data
1a	δ1.77 (s, CH_3, 3H), 1.7 (s, CH_3, 3H), 7.5 (q, 3H, Ar-H)
1b	δ1.77 (s, CH_3, 3H), 1.7 (s, CH_3, 3H,), 7.2 - 7.5 (m, 4H, Ar-H)
1c	δ1.9 (s, CH_3, 3H), 1.77 (s, CH_3, 3H), 6.9 (q, 3H, Ar-H),
1d	δ1.9 (s, CH_3, 3H), 1.77 (s, CH_3, 3H), 7.4 (d, 2H, Ar-H)
1e	Δ 1.77 (s, CH_3, 3H), 1.7 (s, CH_3, 3H), 2.3 (m, CH_2, 2H), 5.4 (m, CH, 4H), 3.98 (m, H, CH), 8.9 (s, H, Ar-H)
3a	δ(s, CH_3, 3H), 1.7 (s, CH_3, 3H), 7.5 (m, 3H, Ar-H), 3.4 (d, 2H, -CH_2”””), 6.9 (d, 1H, -CH’), 2.4 (m, H, OH), 4.4 (m, 3H, CH’”, CH””, CH””)
3b	Δ 1.77 (s, CH_3, 3H), 1.7 (s, CH_3, 3H), 7.5 (m, 4H, Ar-H), 3.4 (d, 2H, -CH_2”””), 6.9 (d, 1H, -CH’), 2.4 (m, H, OH), 4.4 (m, 3H, CH’”, CH””, CH””)
3c	Δ 1.77 (s, CH_3, 3H), 1.7 (s, CH_3, 3H), 7.5 (m, 4H, Ar-H), 3.4 (d, 2H, -CH_2”””), 6.1 (d, 1H, -CH’), 3.4 (m, 4H, 4OH, 2H, NH_2), 4.4 (m, 3H, CH’”, CH””, CH””)
3d	δ1.77 (s, CH_3, 3H), 1.7 (s, CH_3, 3H), 6.7-7.5 (d, d, 2H, Ar-OH), 2.9 (m, H, 5OH), 6.1 (d, 1H, -CH’), 3.37 - 4.4 (m, 3H, CH’”, CH””, CH””)
3e	δ1.77 (s, CH_3, 3H), 1.7 (s, CH_3, 3H), 7.5 (q, 3H, Ar-H), 7.2 (s, 2H, -CH_2”””), 6.9 (d, 1H, -CH”), 2.4 (m, H, OH), 4.4 (q, 4H, CH’, CH’”, CH””, CH””)

Table 7. ^{13}C NMR spectrum data of the novel compounds.

Compound number	Spectral 13C NMR data
1a	δ, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 184 (s, C2, -C-O), 163 (s, C4,), 108 (s, C5, Ar-), 165 (s, C6, Ar-), 111 (s, C1’, Ar’), 119 (s, C3’, Ar’), 114 (s, C2’, Ar’), 118 (C, CN’) 164 (s, C4’, Ar’), 119 (s, C5’, Ar’), 130 (s, C6’, Ar’),
1b	δ, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 180 (s, C2, -C-O), 157 (s, C4,), 105 (s, C5, Ar-), 164 (s, C6, Ar-), 128 (s, C1’, Ar’), 130 (s, C3’, Ar’), 128 (s, C2’, Ar’) 124 (s, C4’, Ar’), 154 (s, C5’, Ar’), 128 (s, C6’, Ar’),
1c	δ, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 184 (s, C2, -C-O), 157 (s, C4,), 108 (s, C5, Ar-), 165 (s, C6, Ar-), 111 (s, C1’, Ar’), 103 (s, C3’, Ar’), 148 (s, C2’, Ar’) 164 (s, C4’, Ar’), 106 (s, C5’, Ar’), 131 (s, C6’, Ar’),

Continued

1d	*δ*, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 184 (s, C2, -C-O), 157 (s, C4,), 105 (s, C5, Ar-), 164 (s, C6, Ar-), 128 (s, C1', Ar'), 130 (s, C3', Ar'), 128 (s, C2', Ar') 124 (s, C4', Ar'), 154 (s, C5', Ar'), 118 (s, C6', Ar').
1e	*δ*, 19 (s, C, CH_3), 118 (s, C, CN), 153 (s, C, -C=O), 117 (s, C3, Ar-), 157 (s, C4, Ar-), 115 (s, C5, Ar-), 163 (s, C6, Ar-), 128 (s, C1', Ar'), 130 (s, C3', C5', Ar'), 128 (s, C2', C6', Ar') 124 (dd, C4', Ar'), 31 (m, C1'''), 92 (m, C2''', C6''') , 85 (m, C3''', C5''') 27 (C4''')
3a	*δ*, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 184 (s, C2, -C-O), 163 (s, C4,), 108 (s, C5, Ar-), 165 (s, C6, Ar-), 111 (s, C1', Ar'), 119 (s, C3', Ar'), 114 (s, C2', Ar'), 118 (C, CN') 164 (s, C4', Ar'), 119 (s, C5', Ar'), 130 (s, C6', Ar'), 131 (s, C1''), 67 (s, C2''), 67 (s, C3''), 67 (s, C4''), 81 (s, C5''), 60 (s, C6''),
3b	*δ*, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 180 (s, C2, -C-O), 157 (s, C4,), 105 (s, C5, Ar-), 164 (s, C6, Ar-), 128 (s, C1', Ar'), 130 (s, C3', Ar'), 128 (s, C2', Ar') 124 (s, C4', Ar'), 154 (s, C5', Ar'), 128 (s, C6', Ar'), 131 (s, C1''), 67 (s, C2''), 67 (s, C3''), 67 (s, C4''), 81 (s, C5''), 60 (s, C6''),
3c	*δ*, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 184 (s, C2, -C-O), 157 (s, C4,), 108 (s, C5, Ar-), 165 (s, C6, Ar-), 111 (s, C1', Ar'), 103 (s, C3', Ar'), 148 (s, C2', Ar') 164 (s, C4', Ar'), 106 (s, C5', Ar'), 131 (s, C6', Ar'), 131 (s, C1''), 67 (s, C2''), 67 (s, C3''), 67 (s, C4''), 81 (s, C5''), 60 (s, C6''),
3d	*δ*, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 184 (s, C2, -C-O), 157 (s, C4,), 105 (s, C5, Ar-), 164 (s, C6, Ar-), 128 (s, C1', Ar'), 130 (s, C3', Ar'), 128 (s, C2', Ar') 124 (s, C4', Ar'), 154 (s, C5', Ar'), 118 (s, C6', Ar'), 131 (s, C1''), 67 (s, C2''), 67 (s, C3''), 67 (s, C4''), 81 (s, C5''), 60 (s, C6''),
3e	*δ*, 19 (s, C, CH_3), 81 (s, C3, Ar), 118 (s, C, CN), 184 (s, C2, -C-O), 157 (s, C4,), 105 (s, C5, Ar-), 164 (s, C6, Ar-), 128 (s, C1', Ar'), 130 (s, C3', C5', Ar'), 128 (s, C2', C6', Ar') 124 (dd, C4', Ar'), 131 (s, C1''), 67 (s, C2''), 67 (s, C3''), 67 (s, C4''), 81 (s, C5''), 60 (s, C6''), 31 (m, C1'''), 92 (m, C2''', C6''') , 85 (m, C3''', C5''') 27 (C4''')

Table 8. LC/Ms Fragmentation spectrum data of synthesized compounds of Scheme 13.

Compound	m/z	Abundance%
1a	295.27	98
1b	378.32	99
1c	285.28	97
1d	337.16	99
1e	406	99
3a	457.41	96
3b	540.5	98
3c	472	97
3d	498	98
3e	568	99

Table 9. IR spectrum data for the synthesized compounds Scheme 12.

Compound	IR υ cm^{-1}
1a	3123 (NH), 2220 (CN), 1646 (CO)
1b	3226 (NH), 2215 (CN), 1717 (CO).
1c	3300, 3400 (NH_2); 1645 (C=O) 3195 (NH), 2223 (CN)
1d	3300 (OH), 2230 (CN), 1690 (CO), 3500 (NH)
1e	3200 (OH), 1640 (CO), 3300 (NH), 2250 (CN)
3a	3300, 3400 (NH_2); 1645 (C=O) 3195 (NH), 2223 (CN)
3b	3100 (NH), 1650 (CO), 2228 (CN)
3c	3195 (NH), 2223 (CN), 1645 (C=O)
3d	3300 (OH); 1680 (C=O); 2224 (CN); 3455 (NH)
3e	3300 (NH), 2225 (CN), 1650 (C=O)

great factor that being as a strong barrier in treating the infectious diseases for animal and human patients.

All investigated compounds show different antibacterial and antifungal activities, these results were be due to the newly derivatives formed from fluroazo pyridone and their glucosides.

The most active compounds were 1a, 3a, 1c, 3c although most of them showed good activity.

One could notice that Table 10, represented the antibacterial and the anti-fungal effects of the new synthetic compounds. Where Table 11 represented the strain of organism.

3. Methodolgy

3.1. Chemistry

3.1.1. General Coupling Procedures of Synthesis of Acetylated-Arylazo-2-[(2S, 3S, 4R, 5R)-3, 4, 5-Trihydroxy-6-(Hydroxymethyl) Tetrahydro-2H-Pyran-2-Yloxy]-4,6 Dimethylnicotinonitrile

Microwave synthesis will be performed using CEM Microwave system. Melting

Table 10. Virtual screening for *in vitro* Antibacterial and antifungal of the novel fluroarylazopyridin-2-one derivatives.

Samples		Inhibition zone diameter					
		Bacterial species				Fungi	
		Gram positive		Gram negative			
		Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus flavas*	*Candida albicans*
	control DMSO	0.0	0.0	0.0	0.0	0.0	0.0
Standard	Ampicillin Antibacterial agent	26	21	25	26	---	---
	Amphotericin Antifungal agent	-----	----	----	----	16	19
	0	21	17	17	15	12	12
	1a	14	13	12	13	11	11
	3a	16	16	14	14	11	11
	1b	10	12	12	13	0.0	0.0
	3b	15	13	14	13	0.0	0.0
	1c	11	11	11	11	0.0	0.0
	3c	19	29	20	22	0	0
	1d	12	13	12	14	0.0	0.0
	3d	17	27	17	23	0.0	0.0
	1e	0.0	0.0	0.0	9	0.0	0.0

Table 11. The type strain of microorganisms.

Microorganism	Gram Reaction	ATCC
Escherichia coli	G^-	11,775
Staphylococcus aureus	G^+	12,600
Candida albicans	Fungus	7102
Aspergillus flavus	*Link*	

points will be determined on (Pyrex capillary) Gallenkamp apparatus. Infrared spectra will be recorded with a Thermo Nicolet Nexus 470 FT-IR spectrometer in the range 4000 - 400 cm^{-1} using potassium bromide disks. ^{1}H-NMR spectra, ^{13}C-NMR spectra will be obtained on Varian Gemini 400 and 200 MHz FT NMR spectrometer in $CDCl_3$ and DMSO-d_6; chemical shifts will be recorded in δ (ppm) units, relative to Me_4Si as an internal standard. The mass spectra will be recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Thin-layer chromatography (TLC) will be carried out on pre-coated Merck silica gel F_{254} plates. Column chromatography will be performed on a Merck silica gel. The reagents will be purchased from Aldrich and used without further purification.

a) Green Microwave method

A solution of 2(1*H*)-pyridones (1a-e) (10 mmol) and acetylated-α-D-glucopyranose derivatives (11 mmol, 4.29 g) had been prepared by dissolving in methylene chloride/methanol (80/20) then silica gel (200 - 400 mesh) mixture. Then the excess solvent had been subjected to vaporization to be removed. The dried residue had been transferred into a vial and subjected to microwave irradiation for 2 - 3 minutes using CEM Microwave system. The product will be purified using column to gain (2a-e).

b) Conventional method

A solution of 2(1*H*)-pyridone (1a-e) (10 mmol) in DMF (15 ml) had been mixed with potassium hydride (4.76 mmol) under nitrogen they had been stirred at 60˚C. After 2 h, the acetylated glucopyranosyl bromide (5) (15 mmol,), had been added and the solution had been stirred at normal temperature for 15 h. The solvent had been evaporated and reminder prepared material had been partitioned between $CHCl_3$ (30 mL) and water (30 mL). Mixed organic extracts had been dried on (Na_2SO_4), filtered and vaporized until complete dryness. The crude synthetic compounds had been dried and purified using column chromatography to gain the compounds (2a-e).

3.1.2. General Procedure for Nucleoside Deacetylation

a) Triethyl amine method

Triethylamine (1.0 ml) had been mixed with glucosides solution of (2a-e). (1 m mol) in (10 ml methanol and few drops of water). The mixture had been stirred for 15 hours at normal. Reduced pressure had been applied for the vaporization and the residue was evaporated with methanol until triethylamine had removed. The synthetic compounds had been crystallized using suitable solvents to get compounds (3a-e).

b) Methanol and dry ammonia

Dry methanol (20 ml) solution of protected glucosides (0.5 g) of at 0˚C (2a-e) had been treated by dry ammonia for 25 minutes. The reaction mixture had been stirred till it had done and finally had been investigated by TLC. Reduced pressure had been applied to get the resultant products concentrated till crude solid had been reached. A solution (chloroform: methanol, 20:1), and silica gel chro-

matography had been applied to the products for purification. Methanol had been applied for crystallization to gain (3a-e).

3.2. Biology

A method of Kirby-Bauer had been used for the determination of antimicrobial activity for novel fluroazopyridone compounds [20].

This had been carried out using special concentration of the test bacteria/fungi and had been grown up in a certain concentration of fresh media and then left it to grow up to 10^8 cells/mL for bacteria 10^5 cells/mL for fungi [21].

Onto agar plates a concentration of 100 µl of bacterial of fungal suspension had been spread according to the broth for their maintenance. Each isolated colony for any organism used had played a pathological effect on primary and tested. Utility of disc diffusion method that many media were available, NCCLS [22] gave a recommendation of using Mueller-Hinton agar because of [23] [24] their reproducibility in good batch-to-batch.

An approved standard method (M38-A) disc diffusion method which had been applied to filamentous fungi tested [24] [25] [26] to evaluate the pathological activity of filamentous fungi to antifungal agents. Using an approved standard method (M44-P) had been used for disc diffusion method for yeasts developed by [25]. *Aspergillus flavus* used as an example of *fungi* had been incubated at 25˚C for 48 hours. *Staphylococcus aureus, Bacillus subtilis* used as an example of Gram positive bacteria, where *Escherichia coli*, *Pseudomonas aeuroginosa* used as an example of Gram negative bacteria, both had been incubated at 35˚C - 37˚C for 24 - 48 hours.

Where; Candida *albicans* used as yeast had been incubated at 30˚C for 24 - 48 hours.

The inhibition zones diameter had been measured in millimetres [20].

A positive control for microbial activity had been served by standard discs of Ampicillin (Antibacterial agent), Amphotericin B (Antifungal agent). A negative control had been achieved by immersing of filter discs in 10 µl of solvent (distilled water, chloroform, DMSO). Meuller-Hinton agar was used for tested the composition and pH.

In addition a factor had been considered in the disc diffusion method was the depth of the agar in the plate. This method was a very known one and well documented and standard zones of inhibition had been determined for susceptible and resistant values. Blank paper disks (Schleicher & Schuell, Spain) with a diameter of 8.0 mm were impregnated 10 µl of tested concentration of the stock solutions. An impregnated filter paper disc with a tested chemical had been put on agar and the novel chemical compound had been diffused from the disc into the agar. By this diffusion the chemical compound had been transferred in the agar only around the disc. The size of the area of chemical infiltration around the disc had been determined by the chemical compound solubility and its molecular size. Bacteria organism had not been grown up when placed in the agar

which contains the chemical compounds under investigation. This area of no growth around the disc had been named as a "Zone of inhibition" or "Clear zone". The diffusion, the zone diameters were measured with the National Committee for Clinical Laboratory Standards. Good alternatives methods had been characterized such as E-test and disk diffusion and they were simpler and faster techniques [26].

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