

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-nicotinitrile

Areef MMH¹, Adel AH, Abdel-Rahman M², Abdel Aleem H² and Magda H Abdellatif^{3*}

¹Chemistry Department, Faculty of Science, Benha University, Egypt

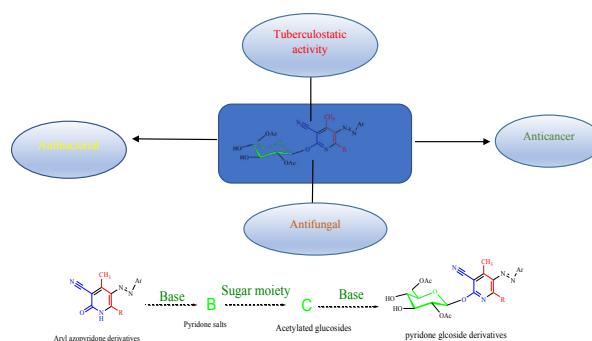
²Chemistry Department, Faculty of Science, Menaufia University, Shebin Elkom, Egypt

³Taif University, Alhawaya, Taif, Saudi Arabia

Abstract

Pyridine derivatives played important roles in the last decade in to approach many and different functionalities, especially as antitumor, antibacterial, anti-fungal, and many of pharmacological activities. Novel compounds of 5-Arylazo-2- [(substituted)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy]-4,6dimethyl nicotine nitrile, (3a-e), generally called (Fluro arylazo pyridine glucosides) were synthesised via green protocol, microwave scheme 3, and the compounds were investigated on the basis of spectroscopic data (FT-IR, 1D, ¹³C), and antibacterial and antifungal studies had been applied.

Graphical Abstract



Keywords: Green chemistry; Green protocol; Pyridines; Fluro compounds; Microwave

Introduction

Pyridine nucleus is one of the most interesting nucleus in organic synthesis. Many uses of pyridines derivatives were investigated in the recent decades especially fluorinated derivatives. One of the recent researches discovered that high tuberculostearic activity of pyridine was observed [1,2].

Also from the amazing character of some pyridine is its high fluorescence activities which was used as molecular sensor of picric acid [3].

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 acquisition of mobile drug resistance genes of microorganisms is a very great resistance and barrier in treating animal and human patients with infectious diseases [4,5]. The importance of the synthesis of novel derivatives of pyridine nucleosides due to their potential use to treat various diseases, such as hepatitis cancer and microbial infections [6-10].

Fluorinated derivatives of pyridines are of high significance in pharmaceutical and medicinal chemistry [11]. Synthesis of poly substituted fluoroarylazopyridone by using green protocol is of great effect in synthetic chemistry and also in pharmaceutical chemistry

[12]. The presence of fluorine atoms in the molecule can change 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 Fluro arylazo pyridine derivatives (1a-e) and their nucleosides (3a-e).

Methodology

Chemistry

General coupling procedures of synthesis of Acetylated -arylazo-2- [(2S, 3S, 4R, 5R)-3, 4, 5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy]-4,6dimethylnicotinonitrile

***Corresponding author:** Abdellatif MH, Deanship of Scientific Research, Taif University, Alhawaya, Taif, Saudi Arabia, Tel: 21974888; E-mail: magdah11uk@hotmail.com

Received October 10, 2017; **Accepted** October 12, 2017; **Published** October 19, 2017

Citation: Areef MMH, Adel AH, Abdel-Rahman M, Abdel Aleem H, Abdellatif MH (2017) 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. Chem Sci J 8: 173. doi: 10.4172/2150-3494.1000173

Copyright: © 2017 Areef MMH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Microwave method: A mixture of 2(1H)-pyridines (1a-e) (10 mmol) and 1'',2'',3'',4'',6''-penta-O-acetyl- α -D-glucopyranose (11 mmol, 4.29 g) where be dissolved in a mixture of methylene chloride/methanol (80/20) then silica gel (200-400 mesh) where be added after that the excess solvent was removed by evaporation. The dried residue was transferred into a 10 mL vial and subjected to microwave irradiation for 2-3 minutes using CEM Microwave system. The product where be purified using column to gain (2a-e).

Conventional method: To a solution of 2(1H)-pyridone (1a-e) (10 mmol) in DMF (10 ml) where be added potassium hydride (4.76 mmol) where be added under nitrogen and the suspension will be stirred at 60°C. After 2 h, the 2, 3, 4, 6-tetra-O-acetyl- α -D-glucopyranosyl bromide (5) (11 mmol, 4.52 g), was added and the solution will be stirred at room temperature for 18 h. The solvent had been evaporated and the residue had been partitioned between CHCl_3 (30 mL) and water (30 mL). The combined organic extracts where be dried on (Na_2SO_4), filtered and evaporated to dryness. The products had been dried and purified using column chromatography to gain the compounds (2a-e) (Schemes 1 and 2).

General procedure for nucleoside deacetylation

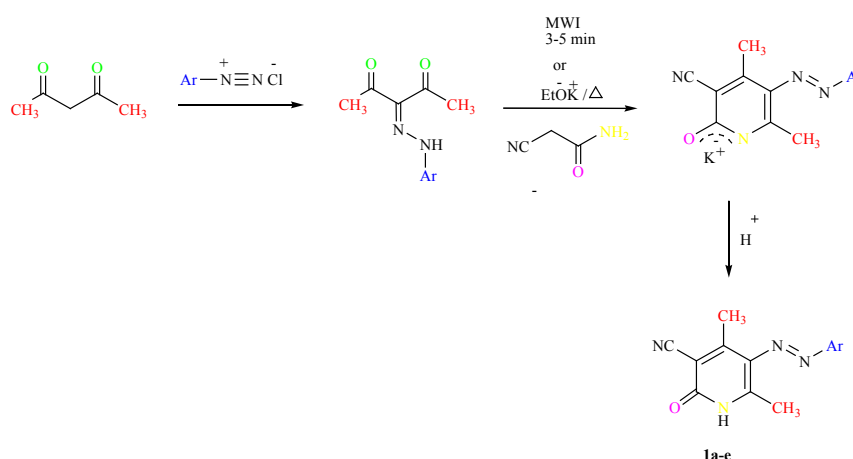
Triethyl amine method: Triethylamine (1.0 mL) had been added

to a solution of glucosides (2a-e). (0.001 mol) in (10 mL MeOH and 3 drops of water). The mixture had been stirred for 18 hours at room temperature. The solvent had been evaporated under reduced pressure and the residue was evaporated with MeOH until triethylamine had removed. The residue was crystallized from appropriate solvent to get compounds (3a-e).

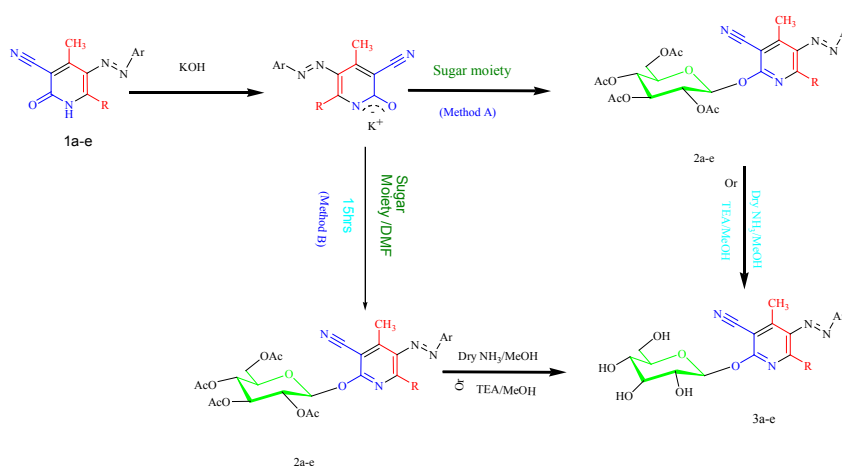
Methanol and dry ammonia: A solution of protected glucosides (0.5 g) in 20 mL of dry methanol at 0°C (2a-e) was subjected to passing of dry ammonia for 30 minutes. The reaction mixture was stirred until it had done and was investigated by TLC (10–12 h). The resultant mixture was concentrated under reduced pressure to afford a crude solid. The products were purified using silica gel chromatography (chloroform: methanol, 20:1), then the products were crystallized from methanol to get the final products (3a-e).

Biology

Novel fluoroazopyridone compounds were tested for their antimicrobial activity and it was determined using a modified Kirby-Bauer disc diffusion method [14]. Briefly, 100 μl of the test bacteria/ fungi were grown in 10 ml of fresh media until they reached a count of approximately 10^8 cells/ml for bacteria or 10^5 cells/ml for fungi [15]. 100 μl of microbial suspension was spread onto agar plates



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



Scheme 2: Synthesis of Pyridone derivatives 2a-e and 3a-e.

corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility by disc diffusion method. The many media available, NCCLS recommends Mueller-Hinton agar due to [16,17]. It results in good batch-to-batch reproducibility. Disc diffusion method for filamentous fungi tested by using approved standard method (M38-A) developed [18] for evaluating the susceptibilities of filamentous fungi to antifungal agents. Disc diffusion method for yeasts developed by using approved standard method (M44-P) [19]. Plates inoculated with filamentous fungi as *Aspergillus flavus* at 25°C for 48 hours; Gram (+) bacteria as *Staphylococcus aureus*, *Bacillus subtilis*; Gram (-) bacteria as *Escherichia coli*, *Pseudomonas aeruginosa* they were incubated at 35-37°C for 24-48 hours and yeast as *Candida albicans* incubated at 30°C for 24-48 hours and, then the diameters of the inhibition zones were measured in millimetres [20]. Standard discs of **Ampicillin** (Antibacterial agent), **Amphotericin B** (Antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 µl of solvent (distilled water, chloroform, DMSO) were used as a negative control. The agar used is Mueller-Hinton agar that is rigorously tested for composition and pH. Further the depth of the agar in the plate is a factor to be considered in the disc diffusion method. This method is well documented and standard zones of inhibition have 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. When a filter paper disc impregnated with a tested chemical is placed on agar the chemical will diffuse from the disc into the agar. This diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area

of chemical infiltration around the disc. If an organism is placed on the agar it will not grow in the area around the disc if it is susceptible to the chemical. This area of no growth around the disc is known as a “**Zone of inhibition**” or “**Clear zone**”. For the disc diffusion, the zone diameters were measured with slipping calipers of the National Committee for Clinical Laboratory Standards. Agar-based methods such as E-test and disk diffusion can be good alternatives because they are simpler and faster than broth-based methods [21-23].

Results and Discussion

Chemistry

General method for green synthesis of arylazo pyridine glucosides had been used [7]. Where Simple, accurate, green procedure where 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 [24,25]. 5-arylazo-2-[(2S,3S,4R, 5R)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yloxy]-4, 6-dimethylnicotinonitrile (3a-e) obtained in high yields by using microwave (MW) irradiation. In this method, a homogenous solid mixture of 2(1H)-pyridones (1a-e) and 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose with silica gel was irradiated in MW for 2-3 minutes. For example, 3-cyano-4,6-Dimethyl-5-arylazo-2(1H)-pyridinones (1a-e) [7] were allowed to be reacted with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide for 2 minutes to give (2a-e) in about 91% yield (Tables 1-11). The same nucleosides, (2a-e) where be gained in good yields by the reaction of the K-salt of pyridnone which was generated in situ, using potassium hydride and an activated sugar moiety [26-28]. 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 (Table 3). Deacetylation of 2a-e were almost done by treatment

Substituted Pyridine	Ar	R
1a		—CH ₃
1b		—CH ₃
1c		—CH ₃
1d		—CH ₃
1e		—CH ₃

Table 1: Substituted Arylazo pyridine glucosides 1a-e.

Samples		Inhibition Zone Diameter					
		Bacterial Species				Fungi	
		G+		G-		Aspergillus flavas	Candida albicans
Bacillus subtilis	Staphylococcus aureus	Escherichia coli	Pseudomonas aeruginosa				
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

Table 2: Antibacterial and antifungal screening of the novel synthesized compounds.

Compound Number	R	Ar	Microwave Method Reaction Time/Yield		Conventional Method Reaction Time/Yield	
			Method A	Method B	Method A	Method B
2a	-CH ₃	C ₇ H ₃ F	2(92)	55(60)	2(92)	48(69)
2b	-CH ₃	C ₆ H ₄ SF ₅	2(90)	58(60)	2(91)	56(63)
2c	-CH ₃	C ₆ H ₅ NF	2(93)	55(60)		
2d	-CH ₃	C ₆ H ₂ Cl ₂ NO				
2e	-CH ₃	C ₁₂ H ₁₁ NF ₄				

Table 3: 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.

No.	R	Ar	Method A	Method B
			Yield %	Yield %
3a	-CH ₃	C ₇ H ₃ F	90	82
3b	-CH ₃	C ₆ H ₄ SF ₅	92	80
3c	-CH ₃	C ₆ H ₅ NF	91	81
3d	-CH ₃	C ₆ H ₂ Cl ₂ NO	92	83
3e	-CH ₃	C ₁₂ H ₁₁ NF ₄	92	80

Table 4: Yield comparison of triethylamine and dry ammonia methods for synthesis of nucleosides 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: Structure formulae for compounds 1a-e and 3a-e.

Compound	Mp. (°C)	Formula (M wt.)	Solvent of Crystallization	Analysis % Calcd. (Found)					
				C	H	N	Cl	F	S
1a	456	C ₁₅ H ₁₀ FN ₅ O ₂ (295.27)	Ethanol/DME	61.01	3.41	23.72		6.43	
1b	240.76	C ₁₄ H ₁₁ F ₅ N ₄ OS 378.32	Ethanol/DME	44.45	2.93	14.81		25.11	8.48
1c	399.66	C ₁₄ H ₁₂ FN ₅ O 285.28	Ethanol/DME	58.94	4.24	24.55		6.66	
1d	487.37	C ₁₄ H ₁₀ Cl ₂ N ₄ O ₂ 337.16	Ethanol/DME	49.87	2.99	16.62	21.03		
1e	363.69	C ₂₀ H ₁₈ F ₄ N ₄ O 406.30	Ethanol/DME	59.11	4.46	13.79		18.7	
3a	794	C ₂₁ H ₂₀ FN ₅ O ₆ 457.41	Ethanol/DME	55.14	4.41	15.31		4.15	
3b	578	C ₂₀ H ₂₁ F ₅ N ₄ O ₆ S (540.5)	Ethanol/DME	44.45	3.92	10.73		17.58	5.93
3c	737	C ₂₀ H ₂₂ FN ₅ O ₆ (472)	Ethanol/DME	53.69	4.96	15.72		4.25	
3d	825	C ₂₀ H ₂₀ Cl ₂ N ₄ O ₇ (499)	Ethanol/DME	48	3.64	16.86			9.65
3e	701	C ₂₆ H ₂₈ F ₄ N ₄ O ₆ (568)	Ethanol/DME	54.93	4.04	11.22	14.3		

Table 6: The Elemental analysis of synthesized compounds.

Compound number	Spectral ¹ H 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	Δ1.77 (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(ε, 3H, CH''', CH''''', CH''''')
3b	Δ1.77(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	Δ1.77(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 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: The Spectral 1H NMR data of the synthesized compounds.

Compound Number	Spectral ¹³ C 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')
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: The Spectral 13C NMR data of the synthesized compounds.

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: LC/ Ms fragmentation of synthesized compounds of scheme 13.

Compound	IR ν cm
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)

Table 10: IR Data for the synthesized compounds scheme 12.

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 where he also used (Table 4).

Biology

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

Microorganism	Gram Reaction	ATCC
<i>Escherichia coli</i>	G	11775
<i>Staphylococcus aureus</i>	G	12600
<i>Candida albicans</i>	Fungus	7102
<i>Aspergillus flavus</i>	Link	

Table 11: The type strain of microorganisms.

worldwide. Genetic mutation and acquisition of mobile drug resistance genes of microorganisms is a very great resistance and barrier in treating animal and human patients with infectious diseases. All investigated compounds show different antibacterial and antifungal activities, these results where be due to the newly derivatives formed from fluoroazo pyridone and their glucosides. The most active compounds were 1a, 3a, 1c, 3c although most of them showed good activity.

Conflict of Interest

The authors declare that there is no conflict.

Author Contributions

Prof. Dr. Mohamed Hemli Areef conducted the plan of work and revised the paper before publishing. Prof. Dr. Adel nassar Abdelrahman directed the synthesis and investigations. Prof. Dr. Abdelaleem Hassan abdelaleem supported us in biological investigation and characterizations. Dr. Magda Abd Ellattif prepared the laboratory and chemicals for synthesis; she collected the material science, made all the investigation and elucidation for all the synthetic compounds using IR, and 1D, finally she wrote the paper and published it. The research work was funded by the researchers work by sharing coasts.

References

- Kibou Z, Cheikh N, Villemin D, Braham NC, Kara BM, et al. (2011) A Simple and Efficient Procedure for a 2-Pyridones Synthesis under Solvent-Free Conditions. *International Journal of Organic Chemistry* 1: 242-249.
- Marina V, Goryaeva G, Burgart YV, Kudyakova YS, Ezhikova MA, et al. (2017) Synthesis of Pyridone Derivatives from 7-Hydroxy-7-polyfluoroalkylhexahydroimidazo[1,2-a] pyridin-5-ones. *Eur J Org Chem*, pp: 3986-3991.
- Abadi AH, Ibrahim TM, Abouzid KM, Lehmann J, Tinsley HN, et al. (2009) Design, synthesis and biological evaluation of novel pyridine derivatives as anticancer agents and phosphodiesterase 3 inhibitors. *Bioorganic & Medicinal Chemistry* 17: 5974-5982.
- Rateb NM, El-Deab HA, Abdou IM (2013) Antimicrobial Evaluation of New Synthesize Pyridine Nucleosides Under Solvent-Free Conditions. *Nucleosides, Nucleotides and Nucleic Acids* 32: 493-509.
- Romeo R, Carnovale C, Salvatore V, Romeo G, Macchi B, et al. (2012) Truncated phosphonated C-1 branched N, O-nucleosides, a new class of antiviral agents. *Bioorg Med Chem* 11: 3652-3657.
- Motaal EAA, El-Gaby MSA, Salem MA (2015) Design, synthesis and anticancer activity of new 3-cyano-2(1H)-pyridone and cyanopyridine-2-(1H)-thione Derivatives. *Oriental Journal of Chemistry* 31: 875-884.
- Abdellattif MH, Maghrabi IA, Areef MMH, ElDeab HA, Mounair SM, et al. (2016) Efficient Microwave-Assisted Solvent-Free Synthesis and Molecular Docking Studies of 2-pyridone derivatives as Anticancer Agents and Evaluation of Cytotoxic Effects. *Journal of Advances in Chemistry*, Vol. 12.
- Abadi AH, Ibrahim TM, Abouzid KM, Lehmann J, Tinsley HN, et al. (2009) Design, synthesis and biological evaluation of novel pyridine derivatives as anticancer agents and phosphodiesterase 3 inhibitors. *Bioorganic and Medicinal Chemistry* 17: 5974-5982.
- Khidre RE, Gogary SRE, Mostafa MS (2017) Design, Synthesis, and Antimicrobial Evaluation of some Novel Pyridine, Coumarin, and Thiazole Derivatives. *J Heterocyclic Chem* 54: 2511.
- Mahmoud MR, El-Azm FSMA, Ali AT, Ali YM (2017) Synthesis and antimicrobial evaluation of some novel dithiolane, thiophene, coumarin, and 2-pyridone derivatives. *Synthetic Communications* 47: 1591-1600.
- Zhou Y, Wang J, Gu Z, Wang S, Zhu W, et al. (2016) Next Generation of Fluorine-Containing Pharmaceuticals, Compounds Currently in Phase II-III Clinical Trials of Major Pharmaceutical Companies: New Structural Trends and Therapeutic Areas. *Chem Rev* 116: 422-518.
- Fujiwara T, O'Hagan O (2014) Successful fluorine-containing herbicide agrochemicals. *J Fluorine Chem* 167: 16-29.
- Purser S, Moore PR, Swallow S, Gouverneur V (2008) Fluorine in medicinal chemistry. *Chem Soc Rev* 37: 320-330.
- Bohm HJ, Banner D, Bendels S, Kansy M, Kuhn B, et al. (2004) Fluorine in Medicinal Chemistry. *Chem Bio Chem* 5: 637-643.
- Hiyama T, Yamamoto H (2000) Biologically Active Organofluorine Compounds. pp: 137-182.
- Tse B (2013) A versatile method to prepare difluorinated primary alcohols and its application to the syntheses of novel acyclic fluorinated nucleosides. *Tetrahedron Letters* 54: 6909-6911.
- Bauer AW, Kirby WM, Sherris C, Turck M (1966) Antibiotic susceptibility testing by a standardized single disk method. *American Journal of Clinical Pathology* 45: 493-496.
- Pfaller MA, Burmeister L, Bartlett MA, Rinaldi MG (1988) Multicenter evaluation of four methods of yeast inoculum preparation. *J Clin Microbiol* 26: 1437-1441.
- Aber RC, Wennersten C, Moellering Jr. RC (1997) Performance antimicrobial susceptibility of Flavobacteria. Vol. 41. National Committee for Clinical Laboratory Standards.
- Wikler MA (1993) National Committee for Clinical Laboratory Standards Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A3. National Committee for Clinical Laboratory Standards, Villanova, PA, USA.
- Wayne PA (2002) Reference Method for Broth Dilution Antifungal Susceptibility Testing of Conidium-Forming Filamentous Fungi: Proposed Standard National Committee for Clinical Laboratory Standards M38-A. NCCLS, Wayne, PA, USA.
- Wayne PA (2003) National Committee for Clinical Laboratory Standards Method for Antifungal Disk Diffusion Susceptibility Testing of Yeast: Proposed Guideline M44-P. NCCLS, Wayne, PA, USA.
- Bauer AW, Kirby WM, Sherris C, Turck M (1966) Antibiotic susceptibility testing by a standardized single disk method. *American Journal of Clinical Pathology* 45: 493-496.
- National Committee for Clinical Laboratory Standards (2003) Method for Antifungal Disk Diffusion Susceptibility Testing of Yeast: Proposed Guideline M44-P. NCCLS, Ashway, PA, USA.
- Liebowitz LD, Ashbee HR, Evans EGV, Chong Y, Mallatova N, et al. (2001) A two-year global evaluation of the susceptibility of *Candida* species to fluconazole by disk diffusion. *Global Antifungal Surveillance Group. Diagn Microbiol Infect Dis* 4: 27-33.
- Matar MJ, Ostrosky-Zeichner L, Paetznick VL, Rodriguez JR, Chen E, et al. (2003) Correlation between E-test, disk diffusion, and microdilution methods for antifungal susceptibility testing of fluconazole and voriconazole. *Antimicrob Agents Chemother* 47: 1647-1651.
- Andrzejawska M, Kanninski J, Kazmierczuk Z (2002) Microwave induced synthesis of ribonucleosides on solid support. *Nucleosides Nucleotides Nucleic Acids* 21: 73-78.
- Pfaller MA, Burmeister L, Bartlett MA, Rinaldi MG (1988) Multicentre evaluation of four methods of yeast inoculum preparation. *J Clin Microbiol* 26: 1437-1441.