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Synthesis, Reactions, and Antimicrobial Activity of *N*-Hydroxy-triacetonamine Derivatives

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SIMPLE and one step method for preparation of *N*-hydroxy-2,2,6,6-tetramethyl-4-piperidone is reported. *N*-Hydroxy-2,2,6,6-tetramethyl-4-piperidone **(1)** reacts with formaldehyde, formaldehyde and piperidine to afford compounds **(3)** and **(4)** respectively. Compound **(1)** reacts with sodium azide and α-bromosugar to afford corresponding products. Compound **(1)** reacts with 2-(4-chlorobenzylidene)malononitrile to afford 1,6-napthyridine derivative **(9)**. *N*-Hydroxy-2,2,6,6-tetramethyl-4-piperidone (**1**) reacts with *p*-chlorobenzaldehyde and cyanoacetamide to produce 1,6-napthyridine derivative **(10a)**. *N*-Hydroxy derivative (**1**) reacts also with *p*-chlorobenzaldehyde and ethylcyanoacetate to afford 1,6-napthyridine **(10b)**. Antimicrobial screening of some of the synthesized compounds has been performed.

Keywords: 2,2,6,6-Tetramethyl-4-piperidone, triacetonamine, *N*-hydroxy-triacetonamine, formaldehyde.

Introduction

Preparation of 2,2,6,6-teramethyl-piperidin-4-one (triacetonamine) still attract researchers all over the world because of its importance and various applications[1-3]. 2,2,6,6-Tetramethyl-piperidine derivatives have different biological effects. 2,2,6,6- Tetramethyl- piperidine derivatives have anticancer, analgesic, antipyretic and anticholinergic effects[4,5]. Also, 2,2,6,6-tetramethyl-piperidin-4-one have hypotensive and vasodilator activity as demonstrated by intravital microcirculation method[6]. 3,5-Bis(4-(dimethylamino) benzylidene)-2,2,6,6-tetramethylpiperidin-4-one (**I**), and 8-(4chlorobenzylidene)-4-(4-chlorophenyl)-5,5,7,7-tetramethyl-3,4,5,6,7,8-hexahydropyrido[4,3-*d*]pyrimidine-2(1*H*)-thione **(II)** have more anticancer activity against breast cancer cell lines than reference drug used in the study (Fig. 1) [22]. 7-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-4,4,6,6-tetramethyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*] pyridine-2-carbothioamide **(III)** and *N*-(7-(2-Chlorobenzylidene)-3-(2-chlorophenyl)-4,4,6,6-tetramethyl-3,3a,4,5,6,7-hexahydro-2*H*-pyrazolo[4,3-*c*]pyridine-2carbonothioyl)acetamide **(IV)** show high antitumor activity against hepatocellular carcinoma HepG2 cell lines[7].

1-Hydroxy-2,2,6,6-tetramethylpiperidin-4-one derivatives are used as antioxidants[8-10], contrast agents [11,12], spin probes [13-15], spin labels [16,17], hindered amine light stabilizers[18], nitroxide mediated redical polymerization agents[19,20].

Preperation of 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one (*N*-hydroxy-triacetonamine) starting from 2,2,6,6- tetramethylpiperidin-4-one was done through two steps (Scheme 1)[21]. The methods of preparation of 1-hydroxy-2,2,6,6-tetramethylpiperidin-4-one (*N*-hydroxy-triacetonamine) which is mentioned in the literature are difficult and expensive, so we will report simple and one step method for its

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preparation (Scheme 1)[21].

Also, reactions of *N*-hydroxytriacetonamine with various organic reagents will be reported.

Results and Discussion

2,2,6,6-Tetramethyl-4-piperidone contains different functions groups which could be used to react with various organic reagents. Active methylene adjacent to carbonyl group was used to prepare different chalcones which further react with different organic reagents[22]. In this article, we will prepare *N*-hydoxy derivative of triactonamine which will be the starting material. Although the oxygen of hydroxyl group linked to nitrogen in *N*-hydroxy-2,2,6,6-tetramethyl-4-piperidone **(2)** which is good electronegative atom, the oxygen atom of hydroxyl group is still a nucleophile which can react with different electrophiles.

2,2,6,6-Tetramethyl-4-piperidone (**1)** reacts with hydrogen peroxide in potassium hydroxide to afford *N*-hydroxy-2,2,6,6-tetramethyl-4-piperidone (**2)** (Scheme 1). *N*-Hydroxy-2,2,6,6-tetramethyl-4-piperidone (**2)** reacts with formaldehyde to give compound **(3)** which reacts with piperidine to affords compound **(4**) (Scheme 2). Compound (**4)** can be prepared directly by reacting *N*-hydroxy-2,2,6,6-tetramethyl-4-piperidone (**2)** with formaldehyde and piperidine (Scheme 2). Spectral data (IR, MS, ^{1}H NMR) are in agreement with the assigned structure of compounds **(2)**, **(3)** and **(4)**. The mass spectrum of compound (**2)** shows molecular ion peak at m/z 171. The ^{1}H NMR spectrum of compound **(3)** show characteristic signal at δ4.8 corresponding to OCH_2O. The IR spectrum of compound **(4)**

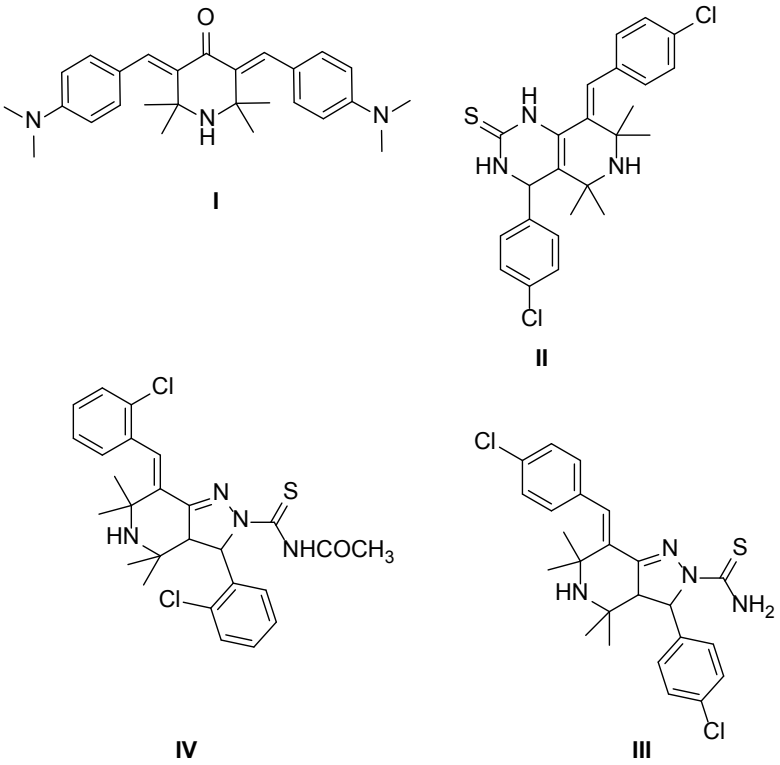
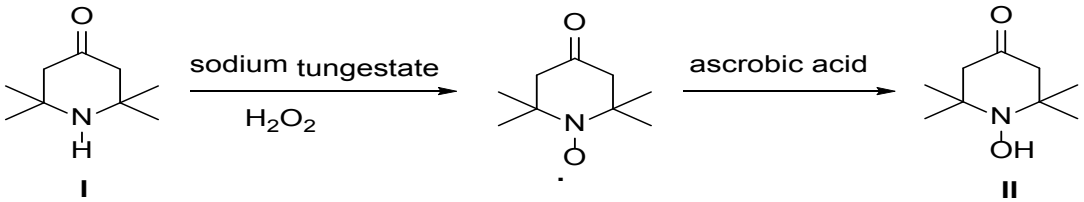
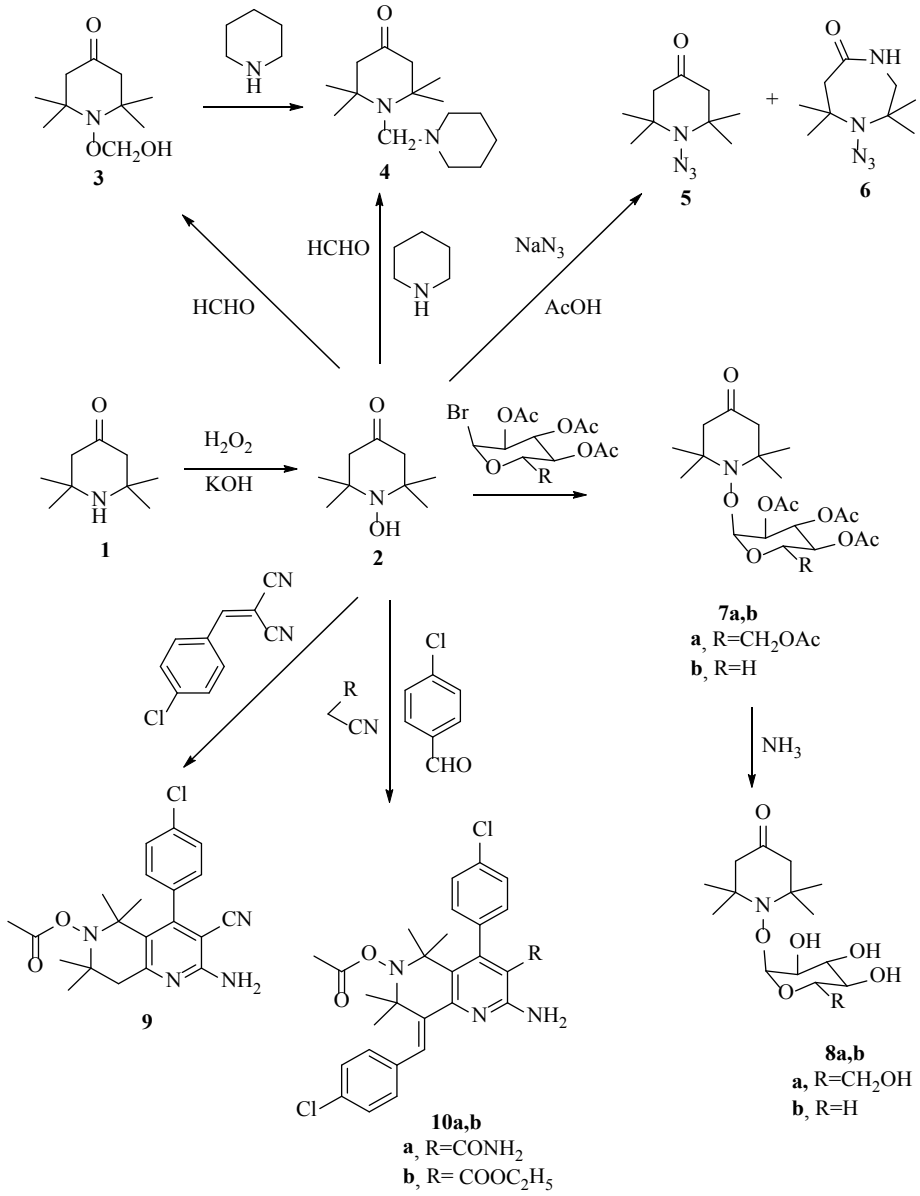


Fig. 1.



Scheme 1



Scheme 2

shows disappearance of absorption band for hydroxyl group.

N-Hydroxy-2,2,6,6-tetramethyl-4-piperidone **(2)** reacts with sodium azide to afford 1-azido-2,2,6,6-tetramethylpiperidin-4-one **(5)** and 1-azido-2,2,7-trimethyl-1,4-diazepan-5-one **(6)**. Although separation of compound **(6)** was done accidently, but it is expected. Ring expansion of piperidine derivative while reaction with sodium azide is reported[23]. The Infrared spectrum of compounds **(5)** and **(6)** show characteristic absorption band for azide group. Also, the IR spectrum of compound **(6)** show absorption band for carbonyl group of amide. The ^{1}H NMR of compound **(6)** shows signal for CH_2N at δ 4.00.

N-Hydroxy-2,2,6,6-tetramethyl-4-piperidone **(2)** reacts with α-bromoacetoglucose and α-bromoacetoxylose to afford 2-(acetoxymethyl)-6-((2,2,6,6-tetramethyl-4-oxopiperidin-1-yl)oxy) tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(7a)** and 2-((2,2,6,6-tetramethy-4-oxopiperidin-1-yl) oxy)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate **(7b)** respectively. Deacetylation of compounds **(7a,b)** were accomplished by ammonia solution to afford 2,2,6,6-tetramethyl-1-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)

piperidin-4-one **(8a)** and 2,2,6,6-tetramethyl-1-((3,4,5-trihydroxytetrahydro-2*H*-pyran-2-yl) oxy) piperidin-4-one **(8b)**. The structures of compounds **(7a,b)** and **(8a,b)** were elucidated from ^{1}H NMR, IR, and mass spectral data.The IR of compounds **(7a,b)** show disappearance of absorption band for hydroxyl group and appearance of absorption band for carbonyl group of an ester. The ^{1}H NMR of compound **(7a)** shows signal at δ2.30 corresponding to CH_3CO.The IR spectra of compounds **(8a,b)** show appearance of absorption band for hydroxyl group which indicate deacetylation of compounds (**7a,b)**. *N*-Hydroxy-2,2,6,6-tetramethyl-4-piperidone (**2)** reacts with 2-(4-chlorobenzylidene)malononitrile to give 2-amino-4-(4-chlorophenyl)-3-cyano-5,5,7,7-tetramethyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl acetate **(9)**. Also, *N*-hydroxy-2,2,6,6-tetramethyl-4-piperidone **(2)** reacts with *p*-chlorobenzaldehyde and cyanoacetamide to afford 2-amino-3-carbamoyl-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,5,7,7-tetramethyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl acetate **(10a**). In addition, *N*-hydroxy-2,2,6,6-tetramethy-4-piperidone (**2)** reacts with *p*-chlorobenzaldehyde and ethylcyanoacetate to produce ethyl-6-acetoxy-2-amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate (**10b)**. The spectral data of compounds **(9)**, and **(10a,b)** are compatible with the proposed structure. The IR spectrum of compound **(9**) shows absorption band for cyano group at 2201 cm^{-1}.The ^{1}H NMR spectrum of compound **(9**) shows signal for aromatic protons at 7.25 and 7.68.The ^{13}C NMR of compound (**9)** shows signals for SP^2 carbon. The IR spectrum of compound **(10a)** show absorption band for carbonyl group of amide at 1644 cm^{-1}. The ^{1}H NMR of compounds **(10a,b)** show signals at δ 4.73 and 5.99 corresponding to hydrogen linked to SP^2 carbon.

Antimicrobial activity

The antimicrobial activity of new compounds was done according to reported procedure[24]. Antimicrobial screening of some of the synthesized compounds is summarized in the following table (Table 1). Most of tested compounds show moderate activity against reference drug. Compound (**5)** shows highest antibacterial activity against reference drug cefotaxime. Also, compound **(10a**) shows highest antifungal activity against reference drug nystatin.

TABLE 1. Antimicrobial activities of some prepared compounds (diameter of inhibition zones in mm.).

Compound No.	Gram positive bacteria		Gram negative bacteria		Fungi
	B. subtilis	*B. cereus*	*P. aeruginosa*	*E. coli*	*Aspergillusniger*
2	10	20	20	18	10
3	12	25	12	13	14
4	14	21	15	14	19
5	50	10	16	11	15
9	10	4	14	15	20
10a	16	9	21	10	26
Cefotaxime	26	28	30	29	-
Nystatin	-	-	-	-	20

Experimental

All melting points are uncorrected and measured using Electro-thermal IA 9100 apparatus (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). ^{1}H NMR was determined on a Jeol-Ex-400 NMR spectrometer (Jeol, Tokyo, Japan) and chemical shifts were expressed as part per million; ppm (δ values) against TMS as internal standard. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA). Microanalyses were operated using Mario El Mentar apparatus and satisfactory results were within the accepted range (±0.30) of the calculated values. Follow up the reactions and checking the purity of the compounds was made by TLC on silica gel-protected aluminium sheets (Type 60 F254, Merck). Mass spectra, and elemental analysis were done in Microanalytical Centre in Faculty of Science, Cairo University. ^{1}H &^{13}C NMR, IR spectra, and antimicrobial activity were done in National Research Centre, Cairo, Egypt. All used chemicals were of reagent grade and were used as supplied directly unless otherwise stated.

1-Hydroxy-2,2,6,6-tetramethylpiperidin-4-one (2)

Triacetonamine **1** (1.55 g, 0.01 mol.) was dissolved in 20 ml methanol. This solution was added to 20 ml acetone containing KOH solution (1g. KOH in 5 ml H_2O). Then, we add 5 ml H_2O_2 (36 %) dropwise with stirring at room temperature. The reaction mixture is heated at 70 °C with stirring for 2 hours. The reaction mixture is evaporated under reduced pressure. The solid residue crystallized from water to give compound **2** in 71 % yield (m.p. 88-90 °C). IR (KBr, cm^{-1}) ν: 3490 (OH), 1709 (C=O). MS, m/z (%) 171 (M+, 90%), 140 (M+-OH, 34%). ^{1}HNMR ($CDCl_3$) δppm: 1.15 (s, 6H, $2CH_3$), 1.17 (s, 6H, 2 CH_3), 2.17 (s, 4H, 2 CH_2), 7.25 (brs, 1H, OH). Anal. calcd. For $C_9H_{17}NO_2$ (171.24): C, 63.13; H, 10.01; N, 8.18. Found: C, 63.09; H, 9.94; N, 8.03.

1-(Hydroxymethoxy)-2,2,6,6-tetramethylpiperidin-4-one (3)

A mixture of compound **2** (0.01 mole), and formaldehyde (0.01 mole) is heated under reflux with stirring in 50 ml absolute ethanol for 1 hour. The reaction mixture is evaporated under reduced pressure to give solid residue. The solid is recrystallized from ethanol to afford compound **3** (yield 62 %, m.p. 105-107 °C). IR (KBr, cm^{-1}) ν: 3440 (OH), 1714 (C=O). MS, m/z (%) 201 (M+, 90%), 184 (M+-OH, 34%). ^{1}HNMR ($CDCl_3$) δppm: 1.13 (s, 6H, 2 CH_3), 1.17 (s, 6H, 2 CH_3), 2.20 (s, 4H, 2 CH_2), 4.8 (s, 2H, CH_2), 6.15 (brs, 1H, OH). Anal.calcd. For $C_{10}H_{19}NO_3$ (201.27): C, 59.68; H, 9.52; N, 6.96. Found: C, 59.59; H, 9.48; N, 6.88.

2,2,6,6-Tetramethyl-1-(piperidin-1-ylmethoxy) piperidin-4-one (4)

Method A

A mixture of compound **3** (0.01 mole), piperidine (0.01 mole) is refluxed in 50 mL absolute ethanol under TLC control. The reaction mixture is evaporated under reduced pressure. The residue collected crystallized from ethanol to give compound **4** (yield 61 %). IR (KBr, cm^{-1}) ν: 1709 (C=O). MS, m/z (%) 268 (M+, 46%). ^{1}HNMR ($CDCl_3$) δppm: 1.13 (s, 6H, 2 CH_3), 1.17 (s, 6H, 2 CH_3), 1.45 (m, 6H, $3CH_2$), 1.80 (s, 4H, 2 CH_2), 2.43 (t, 4H, *J*=7.1 Hz, CH_2N), 5.30 (s, 2H, OCH_2N). Anal.calcd. For $C_{15}H_{28}N_2O_2$ (268.40): C, 67.13; H, 10.52; N, 10.44. Found: C, 67.21; H, 10.60; N, 10.52.

Method B

A mixture of compound **2** (0.01 mole), and formaldehyde (0.01 mole), piperidine (0.01 mole) are heated under reflux with stirring in 50 ml absolute ethanol under TLC control. The reaction mixture is evaporated under reduced pressure to give solid residue. The solid is recrystallized from ethanol to afford compound **4** (yield 69 %, m.p. 95-97 °C).

Preparation of compounds(5) and (6)

Compound **2** (0.01 mole) is refluxed with sodium azide (0.01 mole) in 5 mL acetic acid and 4 drops of water for 15 minutes. The precipitate formed is filtered, dried and crystallized from benzene to afford compound **5**. The filterate is evaporated under reduced pressure to produce compound **6**.

1-Azido-2,2,6,6-tetramethylpiperidin-4-one (5)

Yield 73%, m.p. 220-222 °C, brown powder. IR (KBr, cm^{-1}) ν: 2125 (N_3), 1722 (C=O). MS, m/z (%) 196 (M+, 36%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.36 (s, 6H, 2 CH_3), 1.57 (s, 6H, 2 CH_3), 1.92 (s, 4H, 2 CH_2). ^{13}C NMR ($CDCl_3$) δ ppm: 29.3 ($4CH_3$), 53.5 (2C), 54.1 ($2CH_2$), 173.9 (C=O). Anal.calcd. For $C_9H_{16}N_4O$ (196.25): C, 55.08; H, 8.22; N, 28.55. Found: C, 55.12; H, 8.28; N, 28.60.

1-Azido-2,2,7-trimethyl-1,4-diazepan-5-one(6)

Yield 10 %, m.p.190-192 °C, brown powder. IR (KBr, cm^{-1}) ν: 3300 (NH), 2130 (N_3), 1693 (C=O). MS, m/z (%) 211 (M+, 70%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.16 (s, 6H, 2 CH_3), 1.41 (s, 6H, 2 CH_3), 2.14 (s, 2H, CH_2), 4.00 (s, 2H, CH_2N), 5.01 (brs, 1H, NH). ^{13}C NMR ($CDCl_3$) δ ppm: 22.1, 25.0, 28.6, 32.8 ($4CH_3$), 47.0, 53.5 (2C), 56.3, 57.7 (CH_2), 173.9 (C=O). Anal.calcd. For $C_9H_{17}N_5O$ (211.27): C, 51.17; H, 8.11; N, 33.15. Found: C, 51.20; H, 8.18; N, 33.20.

General method for preparation of compounds(7a,b)

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 2-hydroxytetrahydro-2H-pyran-3,4,5-triyl triacetate (0.005 mole) dissolved in acetone (15 mL) was added portion-wise to a clear solution of compound **2** (0.005 mole) and potassium hydroxide (0.28g, 0.005 mole) in distilled water (2 ml). The reaction mixture was stirred at room temperature until reaction was judged complete by TLC(pet. ether/ethyl acetate, 4:1 v/v). Evaporation of the solventafforded a residue which was washed with distilled water (10 mL) followed by extraction with chloroform. The obtained residue after removal of chloroform was triturated with petroleum ether (b.p. 40-60 °C) (45 mL) with stirring. The solid product was filtered, dried and recrystallized from ethanol to produce compound **7a,b**.

2-(Acetoxymethyl)-6-((2,2,6,6-tetramethyl-4-oxopiperidin-1-yl)oxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate(7a)

IR (KBr, cm^{-1}) ν: 1709 (C=O), 1742 (C=O). MS, m/z (%) 501 (M+, 31%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.23 (s, 6H, 2 CH_3), 1.47 (s, 6H, 2 CH_3), 2.21 (s, 4H, 2CH_2), 2.30 (s, 12H, 4 CH_3), 4.73 (t, 3H, *J*=7 Hz, CHO), 5.30 (d, 2H, *J* =7 Hz, CH_2), 5.80 (d, 2H, *J*=7 Hz, CH_2). Anal.calcd. For $C_{23}H_{35}NO_{11}$ (501.35): C, 55.08; H, 7.03; N, 2.79. Found: C, 55.11; H, 7.09; N, 2.82.

2-((2,2,6,6-tetramethyl-4-oxopiperidin-1-yl)oxy) tetrahydro-2H-pyran-3,4,5-triyl triacetate(7b)

IR (KBr, cm^{-1}) ν: 1721 (C=O), 1737 (C=O). MS, m/z (%) 429 (M+, 12%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.23 (s, 6H, 2 CH_3), 1.29 (s, 6H, 2 CH_3), 2.10 (s, 4H, 2CH_2), 2.20 (s, 9H, 3 CH_3), 3.83 (t, 2H, *J*=7 Hz, CHO), 5.34 (q, 1H, *J*=7 Hz, CH), 5.54 (d, 2H, *J*=7 Hz, CH_2), 5.74 (d, 2H, *J*=7 Hz, CH). Anal.calcd. For $C_{20}H_{31}NO_9$ (429.47): C, 55.93; H, 7.28; N, 3.26. Found: C, 56.01; H, 7.32; N, 3.31.

General method for preparation of compounds (8a,b)

The acetylated glycosides **7a,b** (5 mmol) was dissolved in dry saturated methanolic ammonia solution (20 mL) and stirred at 0 °C for 1 h, then stirring was persisted at r.t. for 5 h. Removal of the solvent under vacuum at 40 °C gave a solid residue, which was recrystallized from ethanol to give the corresponding free glycoside 8a,b.

2,2,6,6-tetramethyl-1-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy) piperidin-4-one(8a)

IR (KBr, cm^{-1}) ν: 3350 (OH), 1739 (C=O). MS, m/z (%) 333 (M+, 16%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.35 (s, 6H, 2 CH_3), 1.61 (s, 6H, 2 CH_3), 2.35 (s, 4H, 2CH_2), 3.61 (t, 3H, *J*=7 Hz, 3 CH), 3.71 (q, 1H, *J*=7 Hz, CH), 3.80 (d, 2H, *J*=7 Hz, CH_2), 4.80 (d, 2H, *J*=7 Hz, OCH_2O), 6.21 (brs, 4H, OH). Anal.calcd. For $C_{15}H_{27}NO_7$ (333.38): C, 54.04; H, 8.16; N, 4.20. Found: C, 54.10; H, 8.19; N, 4.29.

2,2,6,6-tetramethyl-1-((3,4,5-trihydroxytetrahydro-2H-pyran-2-yl)oxy)piperidin-4-one(8b)

IR (KBr, cm^{-1}) ν: 3410 (OH), 1742 (C=O). MS, m/z (%) 303 (M+, 12%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.41 (s, 6H, 2 CH_3), 1.52 (s, 6H, 2 CH_3), 2.25 (s, 4H, 2CH_2), 3.70 (t, 2H, *J*=7 Hz, 2 CH), 3.78 (q, 1H, *J*=7 Hz, CH), 3.91 (d, 2H, *J*=7 Hz, CH_2), 5.21 (d, 1H, *J*=7 Hz, OCHO), 7.1 (brs, 3H, 3OH). Anal.calcd. For $C_{14}H_{25}NO_6$ (303.36): C, 55.43; H, 8.31; N, 4.62. Found: C, 55.49; H, 8.37; N, 4.68.

2-Amino-4-(4-chlorophenyl)-3-cyano-5,5,7,7-tetramethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl acetate(9)

Compound **2**(0.01 mole) is heated under reflux for 4 hours with 2-(4-chlorobenzylidene) malononitrile (0.01 mole) in ammoniumacetate (1 g.) and acetic acid (10 mL). The reaction mixture is poured into water. The solid precipitate is filtered, dried, crystalized from ethanol/ water mixture (5:1). Yield 71 %, m.p. 180-182°C, brown powder. IR (KBr, cm^{-1}) ν: 3364 (NH_2), 2201 (CN),1759 (C=O). MS, m/z (%) 398 (M+, 23%).^{1}H NMR ($CDCl_3$) δ ppm: 1.24 (s, 6H, 2 CH_3), 1.35 (s, 6H, 2 CH_3), 2.03 (s, 2H, CH_2), 2.44 (s, 3H, CH_3), 5.41 (brs, 2H, NH_2), 7.25 (d, 2H, *J*=7.5 Hz, Ar),7.68 (d, 2H, *J*=7.5 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ ppm: 1.0, 1.7, 24.8, 29.7, 30.9, 113.7 (CN), 128.6, 128.9, 129.0, 129.1, 129.1, 129.2, 129.4, 135.0, 136.0 (Ar-C), 153.8 (C=O). Anal.calcd. For $C_{21}H_{23}ClN_4O_2$ (398.89): C, 63.23; H, 5.81; N, 14.05. Found: C, 63.30; H, 5.88; N, 14.09.

2-Amino-3-carbamoyl-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,5,7,7-tetramethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl acetate(10a)

Compound **2** (0.01 mole) is heated under reflux for 4 hours with *p*-chlorobenzaldehyde (0.02 mole) and cyanoacetamide (0.01 mole) in ammonium acetate (1 g.) and acetic acid (10 mL). The reaction mixture is poured into water. The precipitate formed is filtered, dried, crystalized from ethanol. Yield 63 %, m.p. 235-237°C, dark brown powder. IR (KBr, cm^{-1}) ν: 3425 (NH_2), 1644 (C=O). MS, m/z (%) 539 (M+, 10%).^{1}H NMR ($CDCl_3$) δ ppm: 1.18 (s, 6H, 2 CH_3), 1.71 (s, 6H, 2 CH_3), 2.46 (s, 3H, CH_3), 4.73 (s, 1H, =CH), 6.79 (d, 4H, *J*=7.5 Hz, Ar), 7.55 (d, 4H, *J*=7.5 Hz, Ar), 7.79 (brs, 2H, NH_2), 12.72 (brs, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ ppm: 10.3 (4CH_3), 20.3, 40.2, 45.5 (C), 116.4 (CH=), 116.4, 120.6, 128.3, 128.7, 128.9, 129.1, 129.2, 129.8 (Ar), 165.3, 161.9 (2 C=O). Anal.calcd. For $C_{28}H_{28}Cl_2N_4O_3$ (539.46): C, 62.34; H, 5.23; N, 10.39. Found: C, 62.39; H, 5.28; N, 10.42.

Ethyl-6-acetoxy-2-amino-8-(4-chlorobenzylidene)-4-(4-chlorophenyl)-5,5,7,7-tetramethyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carboxylate (10b)

Compound **2** (0.01 mole) is heated under reflux for 4 hours with *p*-chlorobenzaldehyde (0.02 mole) and ethylcyanoacetate (0.01 mole) in ammonium acetate (1 g.) and acetic acid (10 mL). The reaction mixture is poured into water. The

precipitate formed is filtered, dried, crystalized from ethanol/water (5:1). Yield 51 %, m.p. 210-212°C, pale yellow powder. IR (KBr, cm^{-1}) ν: 3452 (NH_2), 1737 (C=O). MS, m/z (%) 568 (M+, 7%). ^{1}H NMR ($CDCl_3$) δ ppm: 1.20 (s, 6H, 2 CH_3), 1.69 (s, 6H, 2 CH_3), 1.75 (t, 3H, *J*=8 Hz, CH_3), 2.04 (s, 3H, CH_3), 3.78 (q, 2H, *J*=8 Hz, OCH_2),5.99 (s, 1H, =CH), 7.25 (d, 4H, *J*=7.5 Hz, Ar), 7.37 (d, 4H, *J*=7.5 Hz, Ar), 7.48 (brs, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ ppm: 13.4, 13.5, 45.3, 50.2, 50.8, 57.8, 58.7, 61.5, 62.6, 99.8, 128.1, 128.9, 129.01, 129.04, 129.1, 129.2, 129.6, 129.7 (Ar-C), 166.0, 166.3 (2 C=O). Anal.calcd. For $C_{30}H_{31}Cl_2N_3O_4$ (568.50): C, 63.38; H, 5.50; N, 7.39. Found: C, 63.42; H, 5.56; N, 7.42.

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تحضير، التفاعلات، و الفاعليه ضد الميكروبات لمشتقات ان-هيدروكسي-ترایاسیتونامین

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تم تحضير ان-هيدروكسي-ترایاسیتونامین ١ في خطوه واحده و بسيطه. ان-هيدروكسي-ترایاسیتونامین ١ يتفاعل مع العديد من الكواشف العضويه. ان-هيدروكسي-ترایاسیتونامین ١ يتفاعل مع الفورمالدهايد و الفورمالدهايد و البيبريدين لتحضير مركبات ٣ و ٤. ان-هيدروكسي-ترایاسیتونامین ١ يتفاعل مع ازيد الصوديوم و الفا بروموشوجر لكي يكون المركبات المقابله. ان-هيدروكسي-ترایاسیتونامین ١ يتفاعل مع مشتق من المالونونيتريل لكي يكون مشتق من ١،٦-نفثريدين ٩. ان-هيدروكسي-ترایاسیتونامین ١ يتفاعل ايضا مع بارا كلوروبنزالدهايد و سيانواسيتاميد لكي يكون مشتق من ١،٦ نفثريدين ١٠a. ان-هيدروكسي-ترایاسیتونامین ١ يتفاعل ايضا مع بارا كلوروبنزالدهايد وايثيل سيانو اسيتات لكي يكون مشتق من ١،٦ نفثريدين ١٠b.الفاعليه ضد الميكروبات لبعض المركبات المحضره تم قياسها.