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Synthesis and Anticancer Activity of New Substituted Piperidinones Linked to Pyrimidine, Thiazole, and Triazole Glycoside Derivatives

M. N. M. Yousif [a]*, I. F. Nassar[b], N. M. Yousif[a], H. M. Awad[c], and W. A. El-Sayed[a,d]**

[a] *Photochemistry Department, National Research Centre, Cairo, Egypt*
**e-mail: mahmoud_nabil18@yahoo.com*
[b] *Faculty of Specific Education, Ain Shams University, Cairo, Egypt*
[c] *Tanning Materials and Leather Technology Department, National Research Centre, El-Behouth St, Dokki, Cairo, Egypt*
[d] *Chemistry Department, Faculty of Science, Qassim University, KSA.*
***e-mail: waelshendy@gmail.com*

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Abstract—New piperidinone incorporating pyrimidine, triazine, diazipine, oxatriazine, and thiazole derivatives have been synthesized starting with tetramethylpipridin-4-one. Structures of the newly synthesized compounds are characterized on the basis of spectroscopic and analytical data. The anticancer activity of the prepared compounds has been studied *in vitro* against HCT-116 and MCF-7 human cancer cells using the MTT assay. A number of compounds demonstrates potent activity towards both cell lines with IC_{50} values comparable with doxorubicin.

Keywords: piperidinone, pyrimidine, thiazolopyrimidine, diazipine, oxatriazine, thiazole, anticancer, HCT-116, MCF-7

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INTRODUCTION

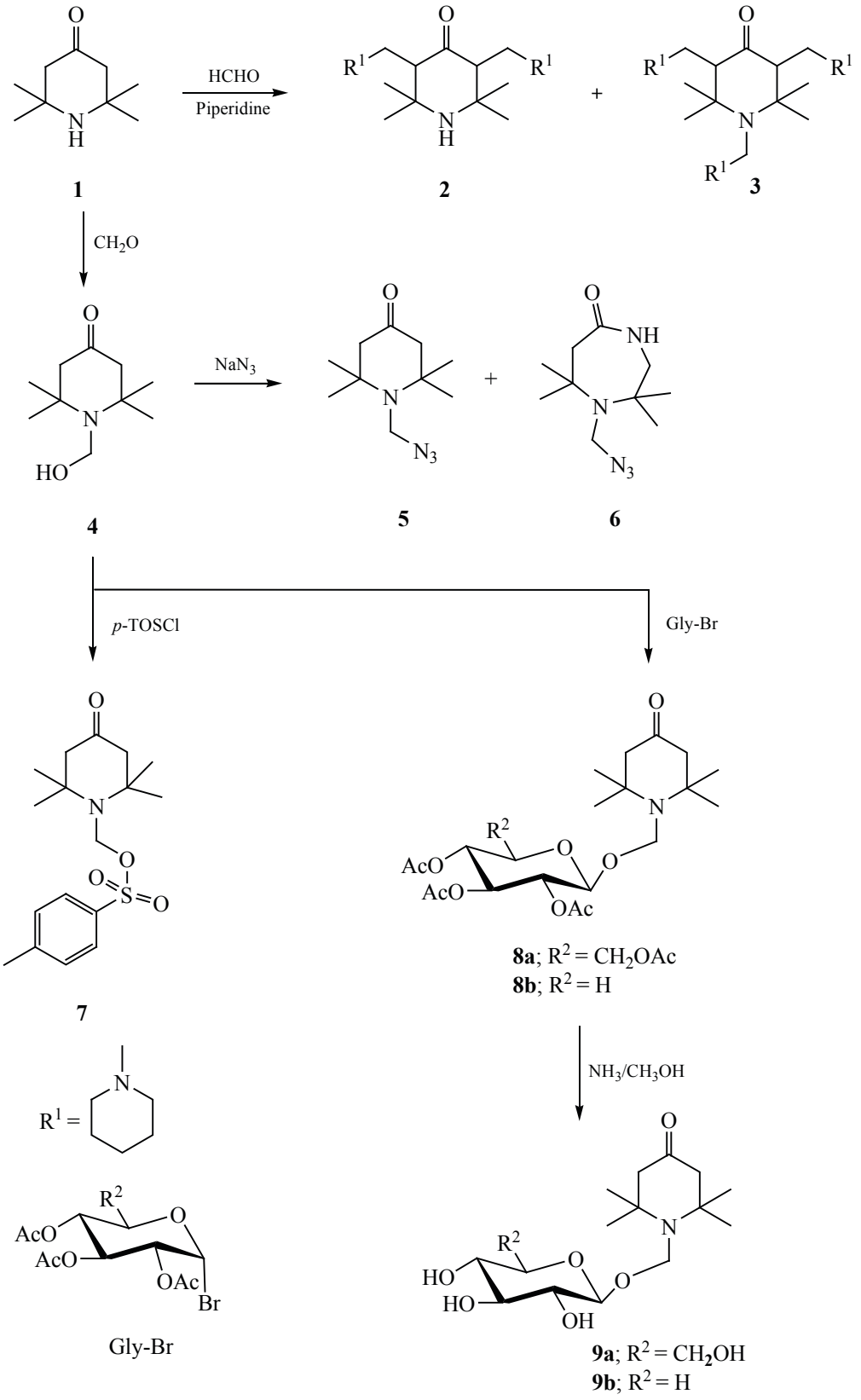
A broad spectrum of compounds containing piperidine ring as an essential part are well known for their analgesic, anti-inflammatory, antidepressant, antipsychotic, antiviral, and antimicrobial activity [1]. Over the recent years, significant effort was directed towards synthesis of simple molecules containing piperidine moiety and characterized by structural similarity to morphine or pethidine but without opoids properties [2].

Interest in chemistry and pharmacology of highly methylated derivatives of pipridinone has been stimulated by the discovery of tetramethylated pipridine as a potent ganglionic blocking agent and its potential in treatment of hypertension [3–6]. Though it has been shown that the activity was not highly specific, but it was associated with a certain degree of shielding of nitrogen atom of a secondary or tertiary amine by nearby substituents. This finding stimulated our effort in design of derivatives of piperidinone linked to a variety of cyclic systems [7–11] that could shield piperidinone nitrogen targeting the enhanced cytotoxic activity. Such compounds and their salts are also used as bases in synthesis [12, 13], in spin labeling method [14, 15], gas treating processes [16], and anticancer [17–19], antioxdidant [20–22], and antimicrobial [23–25] drugs. In the current study we have synthesized novel 2,2,6,6-tetramethylpiperidinone derivatives and tested their activity against two cancer cell lines.

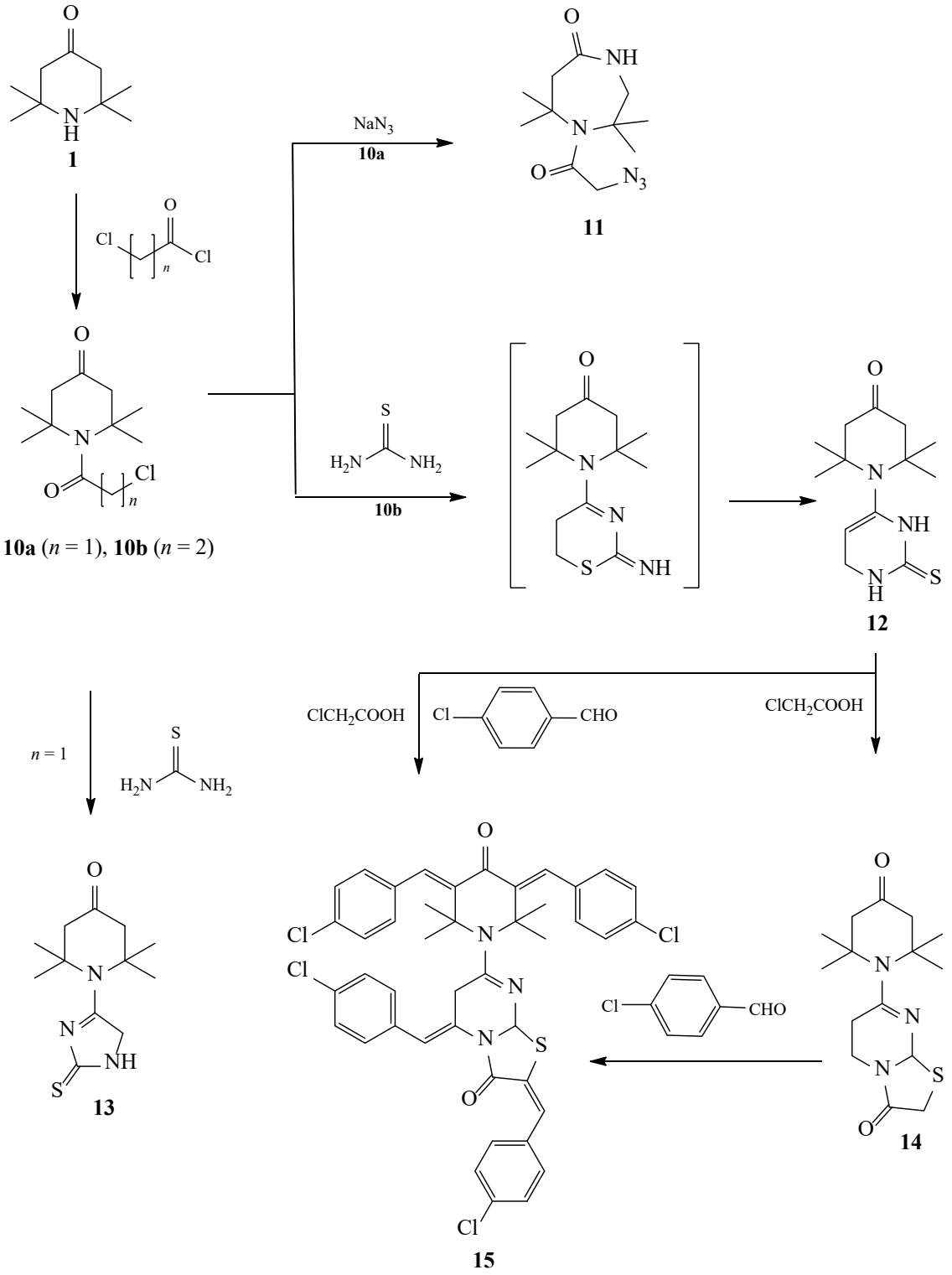
RESULTS AND DISCUSSION

Three active centers of tetramethylpiperidinone derivative **1** allowed it to react with formaldehyde and piperidine (Mannich reaction) affording a mixture of the substituted piperidine **2** with its N^1-substituted analogue **3**. ^{1}H NMR spectrum of compound **3** showed signals of the methylene and piperidinyl protons in addition to disappearance of the corresponding NH signal. In our recent study [26], tetramethylpiperidinone **1** reacted with formaldehyde with formation of hydroxymethyl piperdine derivative **4**. Here compound **4** was reacted with *p*-tolunesulphonyl chloride and sodium azide to give methylbenzenesulfonate **7** and a mixture of azides **5** and **6**, respectively. The diazepanone derivative **6** was produced via the Beckman rearrangement carried out under the reported reaction conditions [27]. IR spectrum of azide **5** and methylbenzenesulfonate **7** did not show the hydroxyl group bands. Also, the hydroxymethyl derivative **4** was reacted with acetobromoglucose and acetobromoxylose with formation of compounds **8a**, **8b**. ^{1}H NMR spectra of the synthesized glycosides demonstrated signals of acetyl

Scheme 1. Synthesis of substituted piperidinone and their *O*-glycosides.

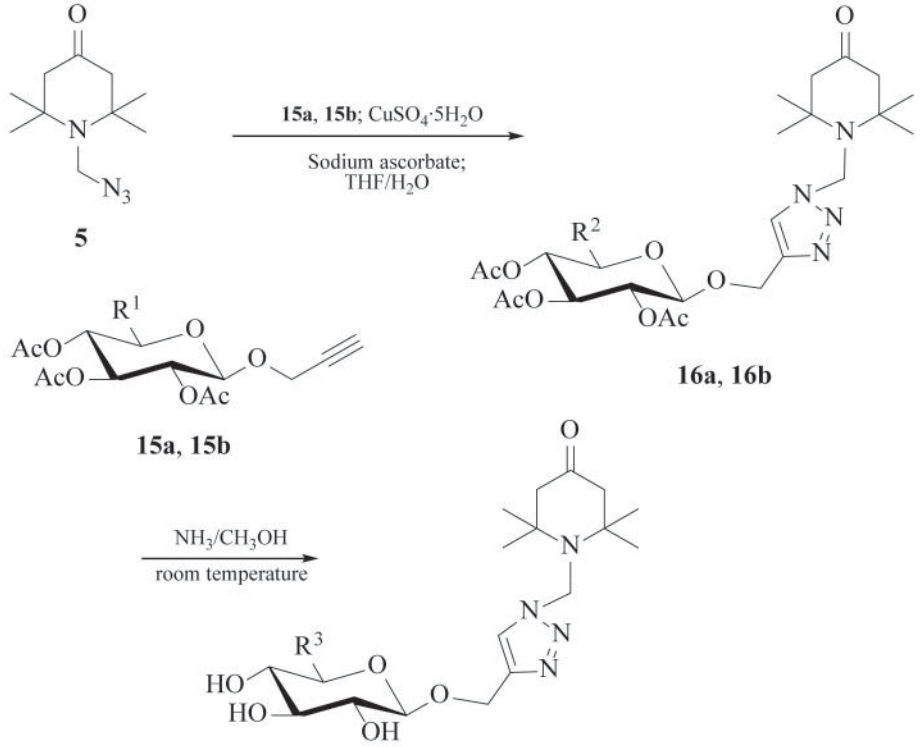


Scheme 2. Synthesis of polysubstituted piperidinone derivatives.



methyl protons in addition to the sugar moiety protons. The coupling constant of the anomeric proton (H^1) indicated the β-configuration of the glycosyl attachment. Deacetylation of compounds **8a**, **8b** was achieved under the action of saturated NH_3–MeOH [28] and afforded free hydroxyl derivatives **9a**, **9b**, respectively.

Scheme 3. Synthesis of 1,2,3-triazole glycosides.



$R^1 = R^2 = R^3 = H$ (**15a**–**17a**), CH_2OH (**15b**–**17b**).

The starting tetramethylpiperidinone **1** was reacted with chloroacetyl chloride and chloropropionyl chloride to give the corresponding *N*-substituted derivatives **10a**, **10b**. Spectral and analytical data accumulated for compounds **10a**, **10b** supported their structures. In IR spectra of compounds **10a**, **10b** a band typical for NH was not recorded. ^{1}H NMR spectrum of compound **10a** demonstrated a signal at 3.59 ppm that corresponded to $C\underline{H_2}Cl$.

Also, the *N*-substituted piperidine derivative **10a** reacted with sodium azide leading to the azidomethyl derivative **11**, formation of which was supported by IR spectrum that showed the bands attributed to the NH and azido groups. Furthermore, the substituted piperidine derivative **10b** reacted with thiourea in alkaline medium to afford the thiopyrimidine derivative **12** (Scheme 2), whereas reaction of compound **10a** with thiourea resulted in formation of the imidazole derivative **13**. Formation of imidazole ring in such reaction was in agreement with the reported earlier mode of heterocyclization [29]. ^{1}H NMR spectrum of compound **12** demonstrated a signal at 3.68 ppm that corresponded to NCH_2. Thiazolopyrimidine derivative **14** was formed in the reaction of compound **12** with chloroacetic acid. Its IR spectrum showed the carbonyl bands and disappearance of the NH band. Four active methylene groups of the thiazolopyrimidine derivative **14** supported its condensation with four moles of *p*-chlorobenzaldhyde with formation of compound **15**. Mass spectrum of compound **15** showed molecular ion peak at *m/z* 799.9 that corresponded to the molecular formula of the assigned structure. Also, compound **15** can be obtained by the reaction of pyrimidine derivative **12** with chloroacetic acid and *p*-chlorobenzaldehyde.

The derivatives of 1,2,3-triazole linked to methoxy glycosides **16a**, **16b** were produced in the reaction of compound **5** with acetylenic sugars possessing the xylopyranosyl and glucopyranosyl moieties, respectively. Acetylated compounds **16a**, **16b** were deacetylated to the corresponding free hydroxyl derivatives **17a**, **17b**, under the action of methanolic ammonia solution and similar reaction conditions [30]. IR spectra of compounds **8a**, **8b** demonstrated disappearance of absorption band of the OH group. In IR spectra of compounds **9a**, **9b** the bands attributed to OH were recorded. ^{1}H NMR spectra of the products **16a**, **16b** exhibited the acetyl-methyl signals

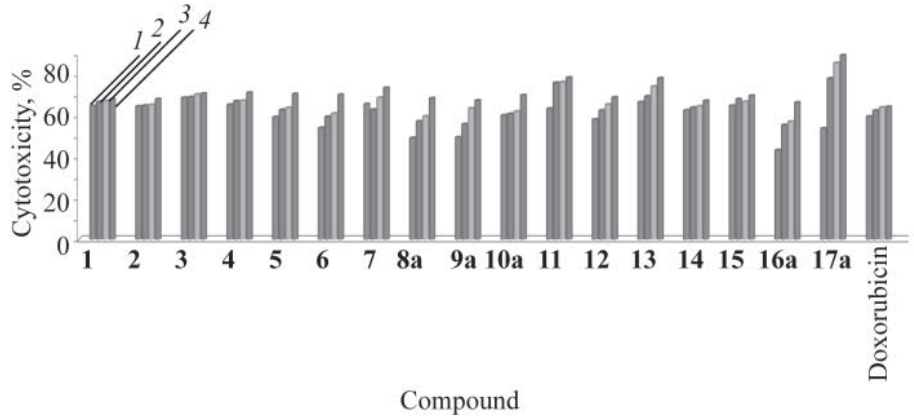


Fig. 1. Dose dependent cytotoxic activity of the synthesized compounds against HCT-116 cancer cells: (*1*) 3.125, (*2*) 6.25, (*3*) 12.5, and (*4*) 25 μM.

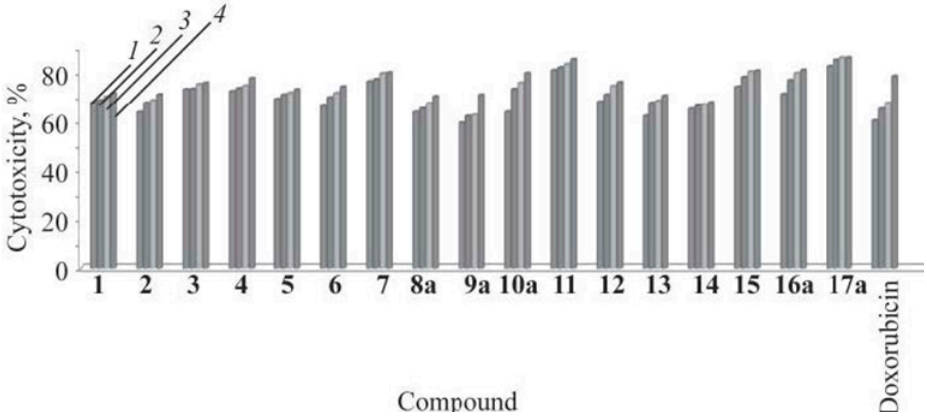


Fig. 2. Dose dependent cytotoxic activity of the synthesized compounds against MCF-7 cancer cells: (*1*) 3.125, (*2*) 6.25, (*3*) 12.5, and (*4*) 25 μM.

and signals of the glycosyl moiety protons. IR spectra of **17a**, **17b** contained the free hydroxyl group band of glycosides (Scheme 3).

Cytotoxicity. The synthesized compounds were tested *in vitro* for their activity against human colorectal carcinoma cells HCT-116 and human breast cancer cells MCF-7 using the MTT assay [31–33] and doxorubicin as a reference. According to the accumulated data all tested compounds suppressed both cancer cells lines in a dose-dependent manner (Figs. 1, 2).

The compounds **8a**, **9a**, and **16a** demonstrated cytotoxic activities toward HCT-116 cell line higher than doxorubicin. The attached sugar moiety or triazolyl-linked xylosyl moiety enhanced cytotoxic activity of these compounds. Furthermore, the azidomethyl derivative **5**, the N^1-alkylated piperdinone **10a** and the pyrimidine-thione derivative **12** showed anticancer activity against HCT-116 cell lines close to that of doxorubicin, proposing that the azido and chloroacetyl groups, and thiopyrimidine moiety initiated cytotoxic activity of the latter compounds.

The activity tests against MCF-7 cell lines revealed that compounds **2**, **8a**, **9a**, **13**, and **14** demonstrated cytotoxic activity higher than doxorubicin. Activity of tetramethylpieridinone **1** was close to that of doxorubicin.

EXPERIMENTAL

TLC was performed using aluminum plates pre-coated with silica gel 60 or 60 F254 (Merck) and visualized by iodine or under UV light (254 nm). Melting points were determined on a Böetius PHMK (VebAnalytik Dresden) apparatus and were uncorrected. IR spectra were recorded (KBr) on a Jasco FT/IR-410 spectrophotometer. NMR spectra were measured on a Varian Gemini 300 and Bruker DRX 400 spectrometers at 25°C using TMS as a reference and $CDCl_3$ and DMSO-d_6 as solvents. Mass spectra were measured on a Varian FINNIGAN MAT 212 spectrometer. Elemental analysis was carried out on

IC_{50} of the synthesized compounds against two cancer cell lines according to the MTT assay

Compound	IC_{50}±SD, μM		Compound	IC_{50}±SD, μM	
	HCT-116	MCF-7		HCT-116	MCF-7
1	7.4 ± 4.9	6.0 ± 2.9	**10a**	9.1 ± 4.3	4.4 ± 2.5
2	7.8 ± 3.7	7.0 ± 2.5	**11**	3.6 ± 1.3	0.5 ± 1.8
3	5.8 ± 4.1	3.8 ± 1.9	**12**	8.8 ± 4.9	4.6 ± 3.2
4	6.8 ± 2.5	3.7 ± 1.3	**13**	4.4 ± 1.9	7.3 ± 3.7
5	8.6 ± 5.2	5.1 ± 3.7	**14**	8.4 ± 3.2	7.8 ± 2.4
6	5.3 ± 4.5	1.2 ± 0.5	**15**	7.0 ± 2.6	1.8 ± 0.4
7	6.7 ± 3.6	1.9 ± 0.3	**16a**	13.0 ± 2.5	2.4 ± 1.1
8a	11.4 ± 4.9	7.6 ± 3.0	**17a**	1.8 ± 5.7	0.4 ± 0.2
9a	11.2 ± 5.1	9.2 ± 3.1	Doxorubicin	9.4 ± 3.9	6.7 ± 2.1

a Perkin Elmer 240 instrument. Anticancer activity tests were performed in the Tanning Materials and Leather Technology Department, National Research Centre.

Synthesis of substituted bis- and tris(piperidine) compounds 2 and 3. Formaldehyde solution (1 mL, 37%) with piperidine (1 mL) was added to a stirred suspension of compound **1** (1.55 g, 10 mmol) in ethanol (30 mL). The mixture was refluxed for 24 h, then volume of the solvent was reduced under vacuum. The precipitated solid was filtered off, dried and recrystallized from toluene/petroleum ether to afford compound **2**. Evaporation of the filtrate to dryness gave compound **3** as a yellowish oil.

2,2,6,6-Tetramethyl-3,5-bis(piperidin-1-ylmethyl) piperidin-4-one (2). Yield 10%, mp 249–250°C. IR spectrum, ν, cm^{-1}: 3340 (NH), 1720 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.54 2s (12H, $4CH_3$), 1.37 m (4H, $2CH_2$), 1.49 m (8H, $4CH_2$), 2.10 t (2H, J = 7.0 Hz, 2CHC=O), 2.40 d.d (2H, J = 7.1 Hz, $H^{a,a'}$), 2.48–2.52 m (8H, $4CH_2$), 2.72 d.d (2H, J = 7.1 Hz, $H^{b,b'}$), 2.74 br.s (1H, NH). MS (*m/z*): 349.5 (M^+, 20%). Found, %: C 72.38; H 11.05; N 11.84. $C_{21}H_{39}N_3O$. Calculated, %: C 72.16; H 11.25; N 12.02.

2,2,6,6-Tetramethyl-1,3,5-tris(piperidin-1-ylmethyl)piperidin-4-one (3). Yield 70%, yellowish oil. IR spectrum, ν, cm^{-1}: 1722 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.15 s, 1.34 s (12H, $4CH_3$), 1.41 m (6H, $3CH_2$), 1.56–1.62 m (12H, $6CH_2$), 2.06 t (2H, J = 7 Hz, 2CHC=O), 2.45–2.53 m (12H, $6CH_2$), 2.70 d.d (2H, J = 7.1 Hz, $H^{a,a'}$), 2.75 d.d (2H, J = 7.1 Hz, $H^{b,b'}$), 3.45 s (2H, NCH_2N). MS (*m/z*): 446.7 (M^+, 15%). Found, %: C 72.33; H 11.17; N 12.70. $C_{27}H_{50}N_4O$. Calculated, %: C 72.59; H 11.28; N 12.54.

Compound **4** was prepared according to the previously reported procedure [26].

Synthesis of compounds 5 and 6. Sodium azide (1.3 g, 20 mmol) was added gradually to a vigorously stirred solution of compound **4** (1.85 g, 10 mmol) in acetic acid (10 mL) containing 3–5 drops of water. The reaction mixture was refluxed for 15 min. Volume of the solvent was reduced under vacuum, and the precipitated solid was filtered off, dried and recrystallized from toluene/pet. ether to afford compounds **5**. Evaporation of the filtrate to dryness gave compound **6** as a yellowish oil.

1-(Azidomethyl)-2,2,6,6-tetramethylpiperidin-4-one (5). Yield 60%. IR spectrum, ν, cm^{-1}: 2104 (N_3), 1722 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 s, 1.24 s (12H, $4CH_3$), 2.24 s, 2.48 s (4H, $2CH_2$), 4.01 br.s (2H, CH_2N). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 20.2, 22.7, 23.7, 26.5, 52.9, 54.6, 59.6, 64.6, 64.3, 210.6. MS (*m/z*): 210.3 (M^+, 20%). Found, %: C 57.03; H 8.49; N 26.81. $C_{10}H_{18}N_4O$. Calculated, %: C 57.12; H 8.63; N 26.64.

1-(Azidomethyl)-2,2,7,7-tetramethyl-1,4-diazepan-5-one (6). Yield 30%, mp 110–111°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 2115 (N_3), 1720 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 s, 1.24 s (12H, $4CH_3$), 2.36 s, 2.49 s, 2.54 3 s (6H, $3CH_2$), 7.82 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm:9.3, 9.4, 22.4, 23.7, 46.5, 52.4, 55.5, 57.3, 62.5, 176.6. MS (*m/z*): 225.4 (M^+,

10%). Found, %: C 53.09; H 8.37; N 31.22. $C_{10}H_{19}N_5O$. Calculated, %: C 53.31; H 8.50; N 31.09.

(2,2,6,6-Tetramethyl-4-oxopiperidin-1-yl)methyl 4-methylbenzenesulfonate (7). To a solution of compound **4** (1.85 g, 10 mmol) in dry pyridine (10 mL) was added *p*-toluene sulfonyl chloride (1.91 g, 10 mmol), and the reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure, and the residue was recrystallized from toluene-pet. ether to afford compounds **7**. Yield 65%, mp 222–223°C. IR spectrum, ν, cm^{-1}: 1725 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 s, 1.29 2 s (12H, $4CH_3$), 2.35 s (3H, CH_3), 2.39 s (4H, $2CH_2$), 4.90 s (2H, CH_2), 7.18 d (2H, *J* = 7.5 Hz, Ar-H), 7.72 d (2H, *J* = 7.5 Hz, Ar-H). MS (*m/z*): 339.4 (M^+, 20%). Found, %: C 60.42; H 7.33; N 4.28. $C_{17}H_{25}NO_4S$. Calculated, %: C 60.15; H 7.42; N 4.13.

Synthesis of compounds 8a, 8b. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide or 2,3,4,6-Tetra-*O*-acetyl-α-D-xylopyranosyl bromide (0.005 mol) dissolved in acetone (15 mL) was added portion-wise to a clear solution of compound **4** (0.005 mol) and KOH (0.28 g, 0.005 mol) in distilled water (2 mL). The reaction mixture was stirred at room temperature till completion according to TLC (petroleum ether–ethyl acetate, 4 : 1 v/v). Evaporation of the solvent afforded an oil which was washed with distilled water (10 mL) and extracted with chloroform. The oil obtained after removal of chloroform was triturated with petroleum ether (bp 40–60°C) (45 mL) upon stirring. The corresponding compounds **8a**, **8b** were obtained after evaporation of petroleum ether.

1-[(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl) oxymethyl]-2,2,6,6-tetramethylpiperidin-4-one (8a). Yellowish oil, yield 47%. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.35, 1.94 2s (12H, $4CH_3$), 1.97 s, 1.99 s, 2.01 s, 2.03 s (12H, $4CH_3CO$), 2.49 s (4H, $2CH_2$), 3.33–3.37 m (1H, $H^{5'}$), 3.88 d.d (1H, *J* = 11.2, *J* = 3.6 Hz, $H^{6''}$), 4.05 d.d (1H, *J* = 11.2, *J* = 3.6 Hz, $H^{6'}$), 4.62 m (1H, $H^{4'}$), 4.88–5.93 m (3H, CH_2, $H^{2'}$), 5.22 d (1H, *J* = 9.6 Hz, $H^{1'}$), 5.29 t (1H, *J* = 8.8 Hz, $H^{3'}$). Found, %: C 55.69; H 7.38; N 3.02. $C_{24}H_{37}NO_{11}$. Calculated, %: C 55.91; H 7.23; N 2.72.

1-[(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)oxymethyl]-2,2,6,6-tetramethylpiperidin-4-one (8b). Oil, yield 52%. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 s, 1.364 s (12H, $4CH_3$), 1.97 s, 1.99 s, 2.02 s (9H, $3CH_3CO$), 2.39 s (4H, $2CH_2$), 3.98 d.d (1H, *J* = 11.2, *J* = 3.6 Hz, $H^{5''}$), 4.11 d.d (1H, *J* = 11.2, *J* = 3.6 Hz, $H^{5'}$), 4.68 m (1H, $H^{4'}$), 4.89–5.95 m (3H, CH_2, $H^{2'}$), 5.24 d (1H, *J* = 9.6 Hz, $H^{1'}$), 5.32 t (1H, *J* = 8.8 Hz, $H^{3'}$). Found, %: C 57.11; H 7.39; N 3.07. $C_{21}H_{33}NO_9$. Calculated, %: C 56.87; H 7.50; N 3.16.

Synthesis of compounds 9a, **9b.** An acetylated nucleoside **8a** or **8b** (5 mmol) was dissolved in dry saturated ammonia solution in methanol (20 mL) and stirred at 0°C for 1 h and then at room temperature upon stirring for 5 h. Removal of the solvent under vacuum gave the corresponding free glycoside **9a** or **9b**.

1-[(β-D-Glucopyranosyl)oxymethyl]-2,2,6,6-tetramethylpiperidin-4-one (9a). Oil, yield 56%. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.21 s, 1.32 s (12H, $4CH_3$), 2.20 s (4H, $2CH_2$), 3.27 m (2H, $H^{6',6''}$), 3.41 m (1H, $H^{5'}$), 3.57 m (2H, $H^{4',3'}$), 4.88–4.95 m (4H, CH_2, $H^{2'}$, OH), 5.18 m (2H, 2OH), 5.27 m (1H, OH), 5.68 d (1H, $H^{1'}$). Found, %: C 55.39; H 8.48; N 4.08. $C_{16}H_{29}NO_7$. Calculated, %: C 55.32; H 8.41; N 4.03.

1-[(β-D-Xylopyranosyl)oxymethyl]-2,2,6,6-tetramethylpiperidin-4-one (9b). Oil, yield 61%. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.14 s, 1.24 s (12H, $4CH_3$), 2.24 s (4H, $2CH_2$), 3.39 m (2H, $H^{5',5''}$), 3.86 m (2H, $H^{4',3'}$), 4.86–4.92 m (4H, CH_2, H^2, OH), 5.20 m (1H, OH), 5.29 m (1H, OH), 5.70 d (1H, $H^{1'}$). Found, %: C 56.59; H 8.42; N 4.29. $C_{15}H_{27}NO_6$. Calculated, %: C 56.77; H 8.58; N 4.41.

Synthesis of compounds 10a, **10b.** Chloroacetyl chloride or chloropropionyl chloride (10 mmol) was added dropwise to a vigorously stirred suspension of compound **1** (1.55 g, 10 mmol) in dry toluene (20 mL), then the reaction mixture was stirred at room temperature for 6 h. The precipitate was filtered off to give the corresponding compound **10a** or **10b**.

1-(2-Chloroacetyl)-2,2,6,6-tetramethylpiperidin-4-one (10a). Yield 90%, mp 235–236°C. IR spectrum, ν, cm^{-1}: 1720 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.21 s, 1.29 s (12H, $4CH_3$), 2.46 s (4H, $2CH_2$), 3.59 s (2H, CH_2Cl). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 27.9 (CH_3), ,47.2 (CN), 50.7, 60.5 (CH_2), 160, 203.3 (CO). MS (*m/z*): 231.72 (M^+, 10%). Found, %: C 56.82; H 7.74; N 5.98. $C_{11}H_{18}ClNO_2$. Calculated, %: C 57.02; H 7.83; N 6.04.

1-(3-Chloropropanoyl)-2,2,6,6-tetramethylpiperidin-4-one (10b). Yield 85%, mp 221–222°C. IR spectrum, ν, cm^{-1}: 1725 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.21 s, 1.42 s (12H, $4CH_3$), 2.64 t (2H, *J* = 7.1 Hz, CH_2), 2.79 s (4H, $2CH_2$), 3.48 t (2H, *J* = 7.1 Hz, CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0, 25, 6,

27.8, 28.0, 36.5, 38.0, 50.7, 60.5, 128.0, 203.3. MS (*m/z*): 245.75 (M^+, 10%). Found, %: C 58.81; H 8.12; N 5.82. $C_{12}H_{20}ClNO_2$. Calculated, %: C 58.65; H 8.20; N 5.70.

1-(2-Azidoacetyl)-2,2,7,7-tetramethyl-1,4-diazepan-5-one (11). Sodium azide (1.3 g, 20 mmol) was added gradually to a vigorously stirred solution of compound **10a** (1.85 g, 10 mmol) in acetic acid (10 mL) containing 3–5 drops of water. The reaction mixture was refluxed for 15 min, then the solvent was evaporated under vacuum, and the residue was recrystallized from methanol to give compound **11**. Yield 65%, mp 80–81°C. IR spectrum, ν, cm^{-1}: 3208 (NH), 2215 (N_3), 1700 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.47 s, 1.50 s (12H, $4CH_3$), 1.52, 2.80 2s (4H, $2CH_2$), 3.32 s (2H, $COCH_2N_3$), 7.50 br.s (1H, NH exchangeable). MS (*m/z*): 253 (M^+, 20%). Found, %: C 52.20; H 7.59; N 27.69. $C_{11}H_{19}N_5O_2$. Calculated, %: C 52.16; H 7.56; N 27.65.

Synthesis of compounds 12 and 13. Compound **10b** or **10a** was added gradually to a solution of thiourea (0.76 g) in ethanol (50 mL) containing KOH (1 g). The reaction mixture was refluxed for 3 h, then cooled down to room temperature and poured onto ice-cold diluted hydrochloric acid. The obtained solid was filtered off, dried and recrystallized form methanol to give the corresponding compound **12** or **13**.

2,2,6,6-Tetramethyl-1-(2-thioxo-1,2,3,6-tetrahydropyrimidin-4-yl)piperidin-4-one (12). Yield 50%, mp 85-86°C. IR spectrum, ν, cm^{-1}: 3220 (NH), 1720 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.20 s, 1.32 s (12H, $4CH_3$), 2.50 s, 2.62 s (4H, $2CH_2$), 3.68 d (2H, J = 6.2 Hz, NCH_2), 6.20 t (1H, J = 6.2 Hz, CH=), 8.9 s, 9.68 s (2H, 2NH exchangeable). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 25.3, 26.0, 26.3, 27.2, 39.5, 49.8, 59.2, 74.3, 116.5, 116.9, 204.4. MS (*m/z*): 267 (M^+, 40%). Found, %: C 58.52; H 7.79; N 15.83. $C_{13}H_{21}N_3OS$. Calculated, %: C 58.40; H 7.92; N 15.72.

2,2,6,6-Tetramethyl-1-(2-thioxo-2,5-dihydro-1*H*-imidazol-4-yl)piperidin-4-one (13). Yield 60%, mp 185-186°C. IR spectrum, ν, cm^{-1}: 3207 (NH), 1720 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 s, 1.34 s (12H, $4CH_3$), 2.15 s, 2.47 s (4H, $2CH_2$), 4.54 s (2H, NCH_2), 8.27 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.0, 26.0, 27.8, 28.0, 36.5, 38.0, 50.7, 60.5, 116.5, 116.9, 128.0, 203.3. MS (*m/z*): 253 (M^+, 10%). Found, %: C 56.94; H 7.68; N 16.63. $C_{12}H_{19}N_3OS$. Calculated, %: C 56.89; H 7.56; N 16.59.

7-(2,2,6,6-Tetramethyl-4-oxopiperidin-1-yl)-6,8a-dihydro-5*H*-thiazolo[3,2-a]pyrimidin-3(2*H*)-one (14). A mixture of compound **12** (2.67 g, 10 mmol) with chloroacetic acid (0.84 g, 10 mmol) and anhydrous sodium acetate (2 g) in acetic acid - acetic anhydride mixture (20 mL, 1 : 1) was refluxed for 3 h, then cooled down to room temperature and poured into ice-cold water. The precipitate was filtered off, dried and crystallized from methanol to give compound **14**. Yield 50%, mp 211–212°C. IR spectrum, ν, cm^{-1}: 1700 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.35 s, 1.44 s (12H, $4CH_3$), 2.18 s (4H, $2CH_2$), 2.19 t (2H, J = 12.4 Hz, CH_2), 2.36 t (2H, J = 12.4 Hz, CH_2), 3.35 s (2H, SCH_2), 4.6 s (1H, CH). MS (*m/z*): 309 (M^+, 10%). Found, %: C 58.11; H 7.58; N 13.35. $C_{15}H_{23}N_3O_2S$. Calculated, %: C 58.23; H 7.49; N 13.58.

7-{3,5-Bis[4-chlorobenzylidene]-2,2,6,6-tetramethyl-4-oxopiperidin-1-yl}-5-[4-chlorobenzylidene]-2-[4-chlorobenzylidene]-6,8a-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-3(2*H*)-one (15). *a*. A mixture of compound **12** (2.67 g, 10 mmol) with chloroacetic acid (0.84 g, 10 mmol), *p*-chlorobenzaldehyde (5.67 g, 40 mmol) and anhydrous sodium acetate (2 g) in acetic acid–acetic anhydride mixture (60 mL; 1 : 1) was refluxed for 3 h, then cooled down to room temperature and poured into ice-cold water. The precipitate was filtered off, dried and crystallized from ethanol to give compound **15**.

b. A mixture of compound **14** (10 mmol) with *p*-chlorobenzaldehyde (5.67 g, 40 mmol) and anhydrous sodium acetate (2 g) in acetic acid/acetic anhydride mixture (30 mL; 1 : 1) was refluxed for 3 h, then cooled down to room temperature and poured into ice-cold water. The precipitate was filtered off, dried and crystallized from ethanol to give compound **15**. Yield 60%, mp 336–337°C. IR spectrum, ν, cm^{-1}: 1700 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.21 s, 2.46 s (12H, $4CH_3$), 3.13 s (2H, CH_2), 4.6 s (1H, CH), 7.61–7.78 m (20H, Ar-H, C*H*=C). MS (*m/z*): 799 (M^+, 10%). Found, %: C 64.37; H 4.52; N 5.18. $C_{43}H_{35}Cl_4N_3O_2S$. Calculated, %: C 64.59; H 4.41; N 5.26.

Synthesis of compounds 16a, **16b.** Sodium ascorbate (0.4 mmol, 0.08 g) and few drops of diisopropylethylamine were added sequentially to a mixture of propargyl glycoside **15a** or **15b** (2 mmol) with azido derivative **5** (2 mmol) in a media of THF–H_2O (2: 1; 15 mL). $CuSO_4 \cdot 5H_2O$ (0.4 mmol, 0.11 g) was then added and the mixture was stirred at 60°C for 6 h (TLC, petroleum ether–EtOAc, 3 : 1). Ethyl acetate (30 mL) was added, and the organic layer was separated, washed with water

and dried. The residue was purified by column chromatography (petroleum ether–EtOAc, 4: 1) to afford the corresponding triazole derivative **16a** or **16b**.

2,2,6,6-Tetramethyl-1-({4-[(2,3,4-tri-*O*-acetyl-β-Dxylopyranosyl)methyl]-1*H*-1,2,3-triazol-1-yl}-methyl)piperidin-4-one (16a). Oil, yield 46%. ^{1}H NMR spectrum (DMSO-d_6), δ ppm: 1.08 s, 1.12 s (12H, 4 CH_3), 1.96 s, 1.98 s, 1.99 s (9H, $3CH_3CO$), 2.65 s (4H, $2CH_2$), 3.93 d.d (1H, *J* = 3.6, 10.8 Hz, H$^{5''}$), 3.98 d.d (1H, *J* = 2.8, 10.8 Hz, H$^{5'}$), 4.52 s (2H, OCH_2), 4.83–4.87 m (1H, *J* = 7 Hz, H$^{4'}$), 5.05 d.d (1H, *J* = 9.6, 8.8 Hz, H$^{2'}$), 5.15 s (2H, NCH_2N), 5.18 d (1H, *J* = 9.6 Hz, H$^{1'}$), 5.28 t (1H, *J* = 8.8, H^3), 7.82 s (1H, triazole-H). Found, %: C 54.82; H 6.79; N 10.74. $C_{24}H_{36}N_4O_9$. Calculated, %: C 54.95; H 6.92; N 10.68.

2,2,6,6-Tetramethyl-1-({4-[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)methyl]-1*H*-1,2,3-triazol-1-yl}-methyl)piperidin-4-one (16b). Oil, yield 51%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.08 s, 1.14 s (12H, $4CH_3$), 1.95 s, 1.97 s, 1.99 s (12H, $4CH_3CO$), 2.68 s (4H, $2CH_2$), 3.55–3.59 m (1H, H$^{5'}$), 3.95 d.d (1H, *J* = 3.6, 10.8 Hz, H$^{6''}$), 4.03 d.d (1H, *J* = 2.8, 10.8 Hz, H$^{6'}$), 4.52 s (2H, OCH_2), 4.85–4.88 m (1H, *J* = 7 Hz, H$^{4'}$), 5.02 d.d (1H, *J* = 9.6, 8.8 Hz, H$^{2'}$), 5.15 s (2H, NCH_2N), 5.20 d (1H, *J* = 9.6 Hz, H$^{1'}$), 5.29 t (1H, *J* = 8.8, H^3), 7.82 s (1H, triazole-H). Found, %: C 54.29; H 6.60; N 9.40. $C_{27}H_{40}N_4O_{11}$. Calculated, %: C 54.35; H 6.76; N 9.39.

Synthesis of deacetylated *N*-glycosides 17a, 17b. An acetylated glycoside **16a**, **16b** (5 mmol) was added to a saturated solution of ammonia in methanol (15 mL) at 0°C and stirred for 20 min, and the mixture was stirred at room temperature for 7 h. After completion of the process (TLC, petroleum ether–hexane, 2 : 1), the solvent was evaporated under reduced pressure at 40°C to give a yellowish residue. Trituration with cold diethyl ether (20 mL) upon stirring afforded a solid which was filtered off, dried and crystallized from ethanol to give the corresponding compound **17a** or **17b**.

2,2,6,6-Tetramethyl-1-({4-[(β-D-xylopyranosyl) methyl]-1*H*-1,2,3-triazol-1-yl}methyl)piperidin-4-one (17a). Yellowish oil, yield 61%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.17, 1.24 2s (12H, $4CH_3$), 2.75 s (4H, $2CH_2CO$), 3.33 m (2H, H$^{5',5''}$), 4.41–4.52 m (2H, H$^{4',3'}$), 4.81 s (2H, OCH_2), 4.89–4.99 m (2H, H$^{2'}$, 2OH), 5.23–5.32 m (3H, NCH_2, OH), 5.35–5.38 m (1H, OH), 5.70 d (1H, *J* = 9.8 Hz, H$^{1'}$), 7.18 s (1H, triazole-H). Found, %: C 54.05; H 7.71; N 13.84. $C_{18}H_{30}N_4O_6$. Calculated, %: C 54.26; H 7.59; N 14.06.

2,2,6,6-Tetramethyl-1-({4-[(β-D-glucopyranosyl)-methyl]-1*H*-1,2,3-triazol-1-yl}methyl)piperidin-4-one (17b). Yellowish oil, 68%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.18 s, 1.24 s (12H, $4CH_3$), 2.74 s (4H, $2CH_2CO$), 3.33 m (2H, H$^{6',6''}$), 3.89 m (1H, H$^{5'}$), 4.43–4.54 m (2H, H$^{4',3'}$), 4.81 s (2H, OCH_2), 4.88–5.02 m (3H, H$^{2'}$, 2OH), 5.21–5.30 m (3H, NCH_2, OH), 5.35–5.37 m (1H, OH), 5.72 d (1H, *J* = 9.8 Hz, H$^{1'}$), 7.18 s (1H, triazole-H). Found, %: C 53.39; H 7.62; N 13.22. $C_{19}H_{32}N_4O_7$. Calculated, %: C 53.26; H 7.53; N 13.08.

Cytotoxic activity. Cell culture of HCT-116 (human colorectal carcinoma) and MCF-7 (human breast adenocarcinoma) cell lines were purchased from the American Type Culture Collection (Rockville, MD) and maintained in DMEM medium which was supplemented with 10% heat-inactivated FBS (fetal bovine serum), 100U/mL penicillin and 100U/mL streptomycin. The cells were grown at 37°C in a humidified atmosphere of 5% CO_2.

MTT cytotoxicity assay. Cytotoxic activity against HCT-116 and MCF-7 human cancer cell lines was estimated using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay, based on the cleavage of tetrazolium salt by mitochondrial dehydrogenases in viable cells [30–33]. Cells were dispensed in a 96 well sterile microplate (5×10^4 cells/well), and a series of different concentrations, in DMSO, of each tested compound or Doxorubicin (positive control) was incubated at 37°C for 48 h in a serum free medium prior to the MTT assay. After incubation, media were carefully removed, 40 μL of MTT (2.5 mg/mL) were added to each well and then incubated for additional 4 h. The purple formazan dye crystals were solubilized by the addition of 200 μL of DMSO. The absorbance was measured at 590 nm on a Spectra Max Paradigm Multi-Mode microplate reader. The relative cell viability was expressed as the mean percent of viable cells compared to the untreated control cells. All experiments were conducted in triplicates and repeated on three different days. All the values were represented as mean ± SD. Values of IC_{50} were determined by SPSS Inc probit analysis (IBM Corp., Armonk, NY, USA).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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