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Synthesis of New Tetrazole Derivatives and Their Biological Evaluation[1]

H. A. Soliman[a]*, A. Kalmouch[b], H. M. Awad[c], and N. A. M. Abdel Wahed[d]

[a] *Photochemistry Department, National Research Centre, Dokki, Cairo, 12622 Egypt*
**e-mail: tarek12_2@yahoo.com*

[b] *Peptide Chemistry Department, National Research Centre, Dokki, Cairo, 12622 Egypt*

[c] *Tanning Materials and Leather Technology Department, National Research Centre, Dokki, Cairo, 12622 Egypt*

[d] *Chemistry of Natural and Microbial Products Department, National Research Centre, Dokki, Cairo, 12622 Egypt*

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Abstract—An operationally simple and efficient method of synthesis of novel 1,5-disubstituted tetrazoles with high yields from easily accessible 2-(2-benzamido-3-arylacrylamido)acetate under mild conditions is developed. Anticancer and anti-microbial tests of the new tetrazole derivatives have been carried out.

Keywords: tetrachlorosilane, 1,5-disubstituted tetrazoles, mild conditions, anticancer activity, anti-microbial activity

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INTRODUCTION

Tetrazole derivatives are used as cyclo-oxygenase inhibitors, anti-inflammatory, antiviral, antifungal, hypoglycemic, and anticancer agents [1]. 1,5-Disubstituted tetrazoles (1,5-DSTs) demonstrate activity towards the *cis*-amide bond in peptides because they are isosteres for the *cis*-amide bond in those [2]. Replacement of the *cis*-amide bond by tetrazole ring in peptides enhances their metabolic stability [3]. Cephalosporin and its analogs that are comparable with penicillin structure and activity are known drugs containing 1,5-DST moieties [4, 5].

Many compounds containing 1,5-disubstituted tetrazoles (1,5-DSTs) demonstrate specific biological activity, including anti-tubercular [6], anti-inflammatory [7], antiviral [8], antibiotic [9], and some others [10, 11]. Various methods of synthesis and applications of 1,5-disubstituted tetrazoles have been presented in recent publications [12–16].

Inspired by the above, we have synthesized and characterized different tetrazole-dehydropeptides conjugates and evaluated their anticancer and antimicrobial activity.

RESULTS AND DISCUSSION

In the present study 1,5-disubstituted tetrazole derivatives were synthesized using oxazolone derivatives as the precursors, these upon aminolysis gave the corresponding dehydropeptides. Treatment of the amide bond of dehydropeptide with triazidochlorosilane (TACS) gave the corresponding tetrazole derivatives.

Arylidene derivatives of 2-phenyl-5(4*H*)-oxazolone were synthesized according to the developed earlier method [17], and mixed with amino acid esters hydrochloride in the presence of TEA at room temperature. Accumulation of dehydropeptides started within few minutes. Refluxing of the reaction mixture made the process to complete. The free amino acid ester reacted as a nucleophilic reagent with the carbonyl group of oxazolone cycle, and the ring cleavage took place leading to the corresponding dehydropeptide (Scheme 1).

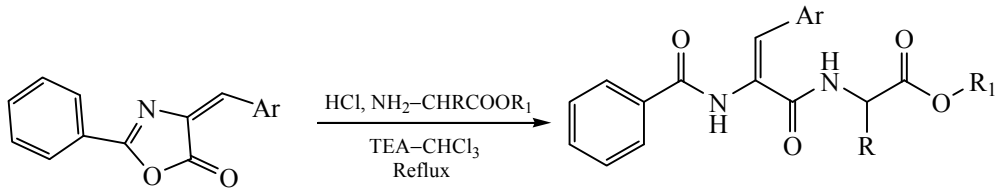
Structures of the compounds **2a–2i** were confirmed by spectral data. IR spectra indicated the presence of two NH groups at ca 3320 and 3218 cm^{-1} and carbonyl groups at ca 1748 and 1658 cm^{-1}. ^1H NMR spectra demonstrated two signals in the range of 8.03–8.90 ppm that disappeared upon D_2O exchange with 2NH groups, and one singlet in the range of 3.9–4.3 attributed to CH_2 of the amino acid [18].

Upon treatment of dehydropeptides **2a–2i** with $SiCl_4/NaN_3$ in acetonitrile for 1.5–3 h, the corresponding new derivatives of 1,5-disubstituted tetrazole **3a–3i** were formed (Scheme 2).

The experimental data indicated high efficiency of the TACS ($SiCl_4/NaN_3$) in the process supporting

[1] The text was submitted by the authors in English.

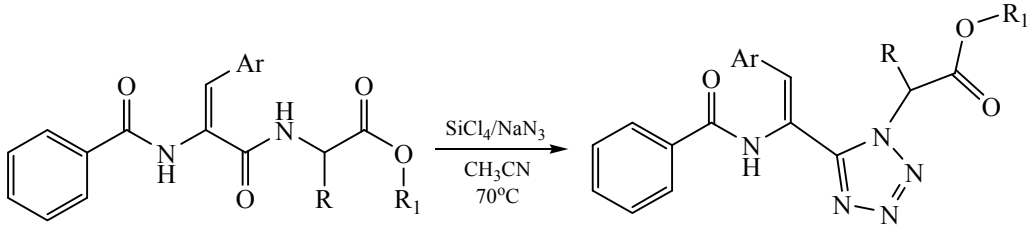
Scheme 1. Synthesis of dehydropeptides **2a–2i.**



1a–1i **2a–2i**

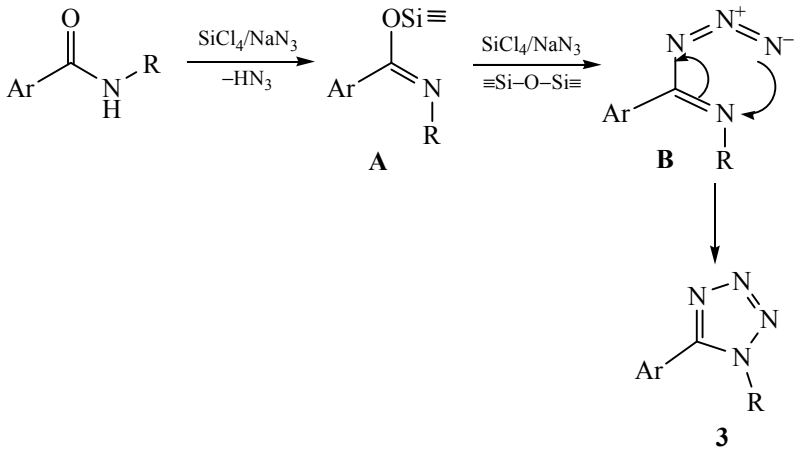
Ar = 4-ClC_6H_4 (**1a, 1h, 1i, 2a, 2h, 2i**), 4-FC_6H_4 (**1b, 2b**), 4-$OMeC_6H_4$ (**1c, 2c**), 3,4-di-$OMeC_6H_3$ (**1d, 2d**), 3,4,5-tri-$OMeC_6H_2$ (**1e, 2e**), 4-$NO_2C_6H_4$ (**1f, 2f**), 2-thionyl (**1g, 2g**); R = H, R_1 = CH_2CH_3 (**2a–2g**), R = H, R_1 = CH_3 (**2h**), R = isopropyl, R_1 = CH_2CH_3 (**2i**).

Scheme 2. Synthesis of 1,5-disubstituted tetrazole derivatives **3a–3i**.



2a–2i **3a–3i**

Scheme 3. A plausible mechanism of formation of 1,5-disubstituted tetrazole.



A **B** **3**

formation of the products with high yield. IR spectra of the synthesized compounds **3a–3i** contained bands at 3295–3225 cm^{-1} for one –NH group, and bands in the ranges of 1759–1740 and 1661–1654 cm^{-1} attributed to two carbonyl groups. ^1H NMR spectra demonstrated a singlet in the range of 8.3-8.9 ppm for NH proton, which disappeared upon exchange with D_2O, and a signal at 6.0–7.0 ppm (CH=).

A plausible mechanism pathway of the reaction (Scheme 3) starts with activation of the carbonyl group by TACS accompanied by losing HN_3 and giving the intermediate **A** which reacts with another mole of TACS to give **B** which rearranges into the product **3**.

The above was supported by the absence of the characteristic bands for one NH group and one carbonyl group at 1626 cm^{-1}. In ^1H NMR spectra signals of an amino acid CH_2 group of **2a–2i** recorded at 4.2 ppm were shifted to 5.3 ppm in the spectra of compounds **3a–3i** under the influence of the neighboring tetrazole ring. An excess of TACS and

Table 1. Experimental data for synthesized derivatives of 1,5-disubstituted tetrazole **3a–3i**

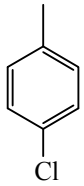
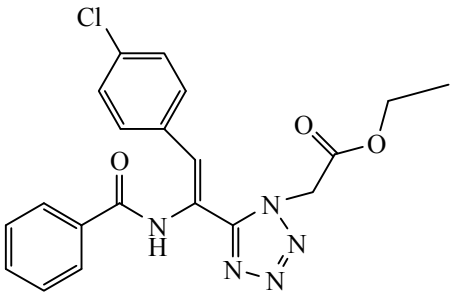
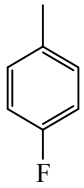
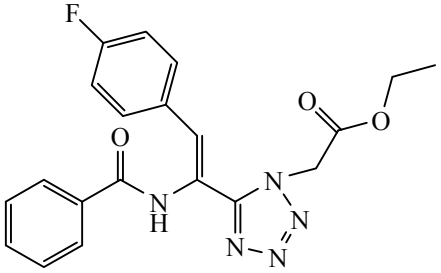
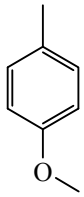
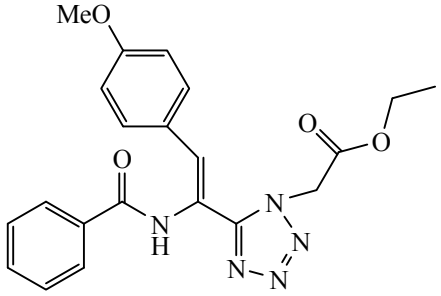
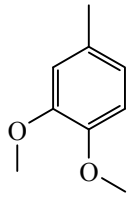
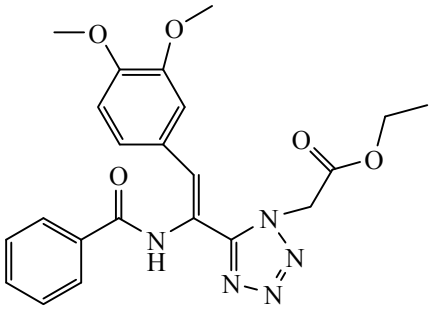
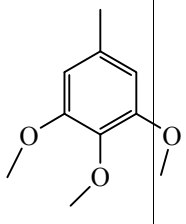
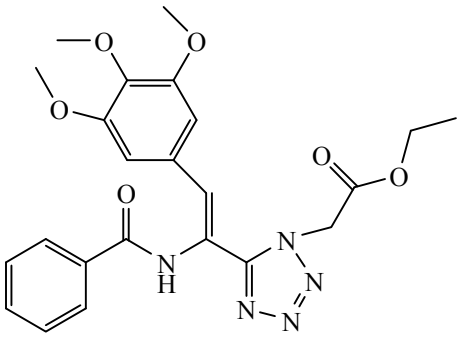
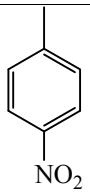
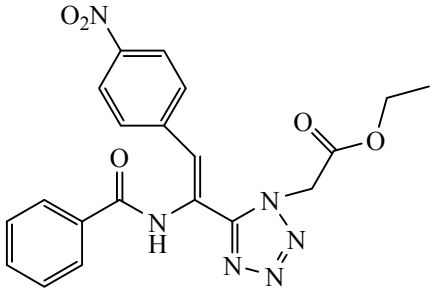
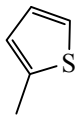
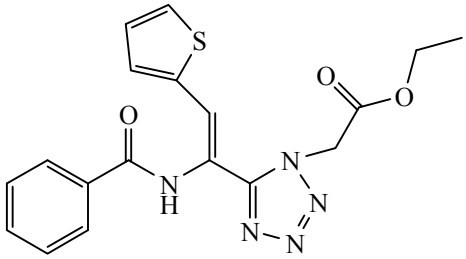
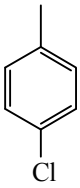
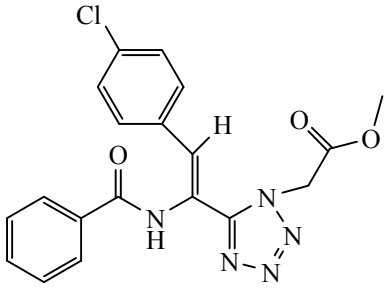
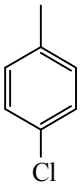
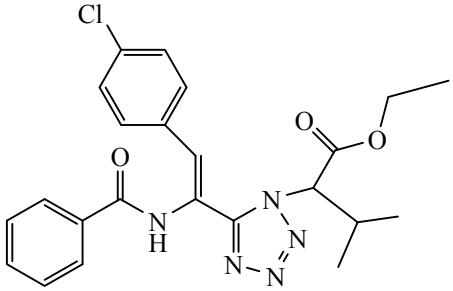
Comp. no.	Ar	Product	Time, h	Yield, %	mp, °C
3a			1.5	95	188
3b			2	80	162
3c			2	93	158
3d			2	92	172
3e			2	95	164

Table 1. (Contd.)

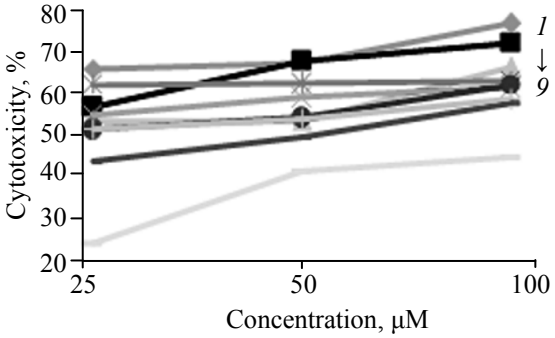
Comp. no.	Ar	Product	Time, h	Yield, %	mp, °C
3f			1.5	90	215
3g			1.5		162
3h			2	88	197
3i			3	80	140

longer reaction time did not improve the results of synthesis.

In vitro anticancer activity. Nine compounds were examined in vitro for their antitumor activity against MCF-7 human breast carcinoma cell line using the MTT assay. The accumulated cytotoxicity data for the compounds were compared against the control, Doxorubicin®. According to the tests the compounds demonstrated cytotoxicity, which was somewhat dose-dependent (see the figure). Five compounds **3a–3c**, **3e**, **3f** demonstrated high anticancer activity (Table 2).

Antimicrobial assay. *Agar diffusion medium.* The synthesized compounds **3a–3i** were assayed in vitro for their antimicrobial activity against the pathogenic microorganisms in DMSO medium. Ciprofloxacin (5 μg/disc) and nystatin (100 units/disc) were used as standards for antibacterial and antifungal activity respectively (Table 3).

According to the tests data, the compounds **3a–3f** demonstrated moderate activity against gram +ve bacteria (*Bacillus subtilis, Staphylococcus aureus*) and gram –ve bacteria (*Pseudomonas aeuroginosa*).



Dose dependence anticancer activity curves for the synthesized compounds **3a–3i** against MCF-7 human cancer cells: (*1–9*) ah1–ah9.

EXPERIMENTAL

The chemicals used in the study, including TMS, were purchased from Sigma-Aldrich.

The determined melting points were uncorrected. IR spectra were recorded for KBr discs on a Mattson FTIR Spectrophotometer 5000. NMR spectra were measured on a Bruker 300 MHz spectrometer in $CDCl_3$. Mass spectra were measured on an Agilent LC-MS spectrometer (pump quarternary 1200 Series, quadruple MSD 6110) equipped with LC column in multimode (ESI+APCI) ion source of MSD. TLC was carried out on Merck silica gel GF254 plates and visualized by UV light at 254 nm and iodine.

General procedure for the synthesis of dehydropeptides (2a–2i). In a round bottom flask, an amino acid ester hydrochloride (1.5 equiv.) was suspended and neutralized by TEA (1.8 equiv.) in chloroform. To a free amino acid ester mixed with chloroform, a chloroform solution of oxazolone was added dropwise. After stirring the mixture for 30 min it was refluxed for 3 h. The solvent was evaporated to dryness and the residue was dissolved in ethyl acetate and washed with 1 N HCl and water. Upon drying the organic layer over anhydrous $MgSO_4$, the solvent was removed under reduced pressure and the residue was treated with ether to obtain the corresponding product as a white powder.

Table 2. IC_{50} values for the compounds **3a–3i** against human breast cancer cells

Compound	IC_{50}, μM
3a	40.2
3b	47.9
3c	44.6
3d	65.3
3e	53.8
3f	53.8
3g	58.7
3h	58.5
3i	84.7
Doxorubicin	18.6

(*E*)-Ethyl 2-[2-benzamido-3-(4-chlorophenyl)acrylamido]acetate (2a). mp 204°C. IR spectrum, ν, cm^{-1}: 3320, 3218, 2973, 1748, 1658. ^1H NMR spectrum, δ, ppm: 8.07 br.s (1H, NH), 8.02 d (*J* = 8.1 Hz, 2H, Ar-H), 7.93 s (1H, NH), 7.70–7.43 m (7H, Ar-H), 6.75 s (1H, =CH), 4.23 s (2H, CH_2), 4.13 q (2H, CH_2), 1.29 t (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 169, 166, 163.5, 133.15, 132.1, 130, 129, 128.7, 127.5, 61, 40.7, 14.10. Found, %: C 32.10; H 4.55; Cl 9.32; N 7.44. $C_{20}H_{19}ClN_2O_4$. Calculated, %: C 62.10; H 4.95; Cl 9.17; N 7.24.

(*E*)-Ethyl 2-[2-benzamido-3-(4-chlorophenyl)acrylamido]-3-methylbutanoate (2i). mp 182°C. IR spectrum, ν, cm^{-1}: 3332, 3225, 2970, 1740, 1658. ^1H NMR spectrum, δ, ppm: 8.03 s (1H, NH), 8.01 d (2H, Ar-H), 8.0 s (1H, NH), 7.70–7.63 m (5H, Ar-H), 7.44 d (2H, Ar-H), 6.77 s (1H, =CH), 4.2 d (1H, CH), 4.21 q (2H, CH_2), 2.2 m (1H), 1.28 t (3H, CH_3), 0.91 d (6H, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 173.2, 166.2, 163.5, 133.5, 132.1, 129, 128.8, 127.5, 115.5, 61.5, 61.2, 30.2, 18.5, 14.10. MS: *m/z*: 428.15 (100.0%), 430.15 (33.0%). Found, %: C 64.61; H 5.38; Cl 8.67; N 6.23. $C_{23}H_{25}ClN_2O_4$. Calculated, %: C 64.41; H 5.88; Cl 8.27; N 6.53.

General procedure for synthesis of tetrazole derivatives (3a–3i). To a mixture of ethyl (or methyl) 2-(2-benzamido-3-arylacrylamido)acetate (5 mmol) with NaN_3 (0.65g, 10 mmol) in 10 mL of acetonitrile TCS (1.2 mL, 10 mmol) was added at ambient temperature then the reaction mixture was warmed up to 50–60°C upon stirring until disappearance of the starting material, according to TLC. The reaction mixture was poured into $NaHCO_3$ aqueous solution and extracted by ethyl acetate. The extracts were dried over $MgSO_4$, concentrated and cooled down to give the corresponding pure product.

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(4-chlorophenyl) vinyl]-1*H*-tetrazol-1-yl}acetate (3a). IR spectrum, ν, cm^{-1}: 3225, 3014, 2993, 1740, 1656. ^1H NMR spectrum, δ, ppm: 8.67 br.s (1H, NH), 7.76 d (*J* = 8.1 Hz, 2H, Ar-H), 7.43–7.33 m (7H, Ar-H), 6.77 s (1H, =CH),

Table 3. In vitro antimicrobial activity of compounds **3a–3i** according to the agar diffusion method[a]

Comp. no.	Inhibition zone diameter, mm				
	gram +ve bacteria		gram –ve bacteria		Fungi
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeuroginosa*	*Candida albicans*
3h	15	14	13	14	11
3i	15	13	13	13	11
3g	15	14	14	14	11
3a	17	16	15	15	12
3e	17	15	14	15	12
3b	18	17	15	16	13
3c	18	16	14	16	13
3d	18	17	16	16	13
3f	18	16	15	16	13

[a] Highly active (+++) = (inhibition zone ≥ 20 mm); moderately active (++) = (inhibition zone 16–19 mm); slightly active (+) = (inhibition zone 10–15 mm).

5.38 s (2H, CH_2), 4.16 q (2H, CH_2), 1.21 t (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 166, 164, 147,133.45, 132, 130, 129, 128.4, 127.5, 61, 47.4, 14.12. Found, %: C 58.53; H 4.21; Cl 8.31; N 16.98. $C_{20}H_{18}ClN_5O_3$. Calculated, %: C 58.33; H 4.41; Cl 8.61; N 17.00.

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(4-florophenyl)vinyl]-1*H*-tetrazol-1-yl}acetate (3b). IR spectrum, ν, cm^{-1}: 3245, 3014, 2983, 1740, 1656. ^{1}H NMR spectrum, δ, ppm: 8.87 br.s (1H, NH), 7.86 d (*J* = 8.1 Hz, 2H, Ar-H), 7.53–7.43 m (7H, Ar-H), 6.97 s (1H, =CH), 5.48 s (2H, CH_2), 4.26 q (2H, CH_2), 1.31 t (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 166, 164,162.2, 147,133.25, 132.1, 130.9, 130.4, 129, 127.6, 117.5,106, 61, 47.4, 14.12. MS: *m/z*: 395.14 (100.0%), 396.14 (23.6%). Found, %: C 60.85; H 4.79; F, 4.61; N 17.51. $C_{20}H_{18}FN_5O_3$. Calculated, %: C 60.75; H 4.59; F, 4.81; N 17.71.

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(4-methoxyphenyl)-vinyl]-1*H*-tetrazol-1-yl}acetate (3c). IR spectrum, ν, cm^{-1}: 3293, 3026, 2962, 1756, 1664. ^{1}H NMR spectrum, δ, ppm: 8,52 s (1H, NH), 7.84 d (2H, ArH), 7.56 –7.46 m (5H, ArH), 6.90 d (2H, Ar-H), 6.81 s (1H, =CH), 5.31 s (2H, CH_2), 4.21 q (2H, CH_2), 3.78 s (3H, OCH_3), 1.06 t (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 166,1 163.9, 160, 146.5, 133.45, 132, 130, 128.9, 127.4, 117.5, 106, 61, 56, 47.4, 14.12. MS: *m/z*: 407.16 (100.0%), 408.16 (24.7%). Found, %: C 61.61; H 5.00; N 17.09. $C_{21}H_{21}N_5O_4$. Calculated, %: C 61.91; H 5.20; N 17.19.

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(3,4-drimethoxy-phenyl)vinyl]-1*H*-tetrazol-1-yl}acetate (3d). IR spectrum, ν, cm^{-1}: 3225, 2969, 1745, 1659. ^{1}H NMR spectrum, δ, ppm: 8.63 s (1H, NH), 8.03 d (2H, ArH), 7.75–7.63 m (3H, ArH), 7.22–7.00 m (3H, ArH), 6.32 s (1H, =CH), 5.11 s (2H, CH_2), 4.11 q (2H, CH_2), 3.83 s (6H, OCH_3), 1.26 t (3H, CH_3). ^{13}C NMR spectrum, δ, pp: 166, 163.8, 149.7, 146.5, 133.2, 132.2, 128.8, 127.5, 117.5, 111.0, 106.0, 61, 60, 56, 47.2, 14.1. MS: *m/z*: 437.17 (100.0%), 438.17 (25.8%). Found, %: C 60.20; H 5.10; N 15.91. $C_{22}H_{23}N_5O_5$. Calculated, %: C 60.40; H 5.30; N 16.01.

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(3,4,5-trimethoxy-phenyl)vinyl]-1*H*-tetrazol-1-yl}acetate (3e). IR spectrum, ν, cm^{-1}: 3295, 3058, 2969, 1755, 1665. ^{1}H NMR spectrum, δ, ppm: 8.53 s (1H, NH),7.85 d (2H, ArH), 7.66–7.55 m (5H, ArH), 6.95 d (2H, Ar-H), 6.82 s (1H, =CH), 5.31 s (2H, CH_2), 4.21 q (2H, CH_2), 3.78 s (6H, OCH_3), 3.72 s (3H, OCH_3), 1.06 t (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 166,1 163.8, 153, 146.5, 133.25, 132.2, 130, 128.8, 127.4, 107.5, 105, 61, 60.5, 56, 47.2, 14.1. MS: *m/z*: 467.18 (100.0%), 468.18 (27.0%). Found, %: C 59.00; H 5.29; N 14.68. $C_{23}H_{25}N_5O_6$. Calculated, %: C 59.09; H 5.39; N 14.98.

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(4-nitrophenyl) vinyl]-1*H*-tetrazol-1-yl}acetate (3f). IR spectrum, ν, cm^{-1}: 3238, 3026, 2990, 1741, 1659. ^{1}H NMR spectrum, δ, ppm: 10.76 s (1H, NH), 8.26 d (2H, ArH), 7.95 d (2H, ArH), 7.66 d (2H, Ar-H), 7.56 t (1H, Ar-H), 7.53 t (2H, Ar-H), 7.18 s (1H, =CH), 5.46 s (2H, CH_2), 4.00 q (2H, CH_2), 1.06 t (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 166, 165.9, 153.72, 147,

140.5, 132.62, 132, 130.42, 128.7, 128.5, 127.97, 123.8, 122.5, 62, 48.7, 13.69. MS: *m/z*: 422.13 (100.0%), 423.14 (22.0%). Found, %: C 56.47; H 4.20; N 19.60; O 18.99. $C_{20}H_{18}ClN_6O_5$. Calculated, %: C 56.87; H 4.30; N 19.90. O 18.94

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(thiophen-2-yl)vinyl]-1*H*-tetrazol-1-yl}acetate (3g). IR spectrum, ν, cm^{-1}: 3295, 3108, 2961, 1750, 1656. ^1H NMR spectrum, δ, ppm: 8.57 s (1H, NH), 8.05 d (*J* = 8.1 Hz, 2H, Ar-H), 7.7–7.63 m (4H, Ar-H), 7.01 d (*J* = 8.1 Hz, 2H, Ar-H), 6.01 s (1H, =CH), 5.48 s (2H, CH_2), 4.16 q (2H, CH_2), 1.30 t (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 166.1, 163.9, 147, 139, 138, 133.2, 132.1, 130.5, 129, 128, 127.6, 106, 61, 47.4, 14.1. MS: *m/z*: 383.11 (100.0%), 384.11 (19.8%). Found, %: C 56.18; H 4.27; N 18.07; S 8.16. $C_{18}H_{17}N_5O_3S$. Calculated, %: C 56.38; H 4.47; N 18.27; S 8.36.

(*Z*)-Methyl 2-{5-[1-benzamido-2-(4-chlorophenyl)-vinyl]-1*H*-tetrazol-1-yl}acetate (3h). IR spectrum, ν, cm^{-1}: 3234, 3064, 2989, 1747, 1650. ^1H NMR spectrum, δ, ppm: 8.55 s (1H, NH), 7.79 d (2H, Ar-H), 7.56 t (1H, Ar-H), 7.47–7.37 m (4H, Ar-H),7.27 d (2H, ArH), 6.81 s (1H, =CH), 5.34 s (2H, CH_2), 3.73 s (3H,OCH_3). ^{13}C NMR spectrum, δ, ppm: 166.1, 163.8, 146.7,133.5, 132.8, 132, 129, 128.6, 127.5, 106, 51.4, 47.1. MS: *m/z*: 397.09 (100.0%), 399.09 (32.4%). Found, %: C 57.16; H 4.00; Cl 8.71; N 17.40. $C_{19}H_{16}ClN_5O_3$. Calculated, %: C 57.36; H 4.05; Cl 8.91; N 17.60.

(*Z*)-Ethyl 2-{5-[1-benzamido-2-(4-chlorophenyl)-vinyl]-1*H*-tetrazol-1-yl}-3-methylbutanoate (3i). IR spectrum, ν, cm^{-1}: 3276, 3055, 2970, 1743, 1658. ^1H NMR spectrum, δ, ppm: 8.67 (s,br, 1H, NH), 8.06 d (2H, Ar-H), 7.73–7.63 m (5H, Ar-H), 7.43 d (2H, Ar-H), 6.27 s (1H, =CH), 4.6 d (1H, CH), 4.21 q (2H, CH_2),2.5 m (1H), 1.29 t (3H, CH_3), 092 d (6H, $2CH_3$); ^{13}C NMR spectrum, δ, ppm:170.2, 164, 146.5,133.15, 132.1, 129, 128.4, 127.5, 72.2, 61.4, 23.2, 17.5, 14.12. *m/z*: 453.16 (100.0%), 455.15 (32.0%). Found, %: C 60.56; H 5.13; Cl 7.81; N 05.43. $C_{23}H_{24}ClN_5O_3$. Calculated, %: C 60.86; H 5.33; Cl 7.81; N 15.43.

Biological activity. *In vitro anticancer activity.* Antitumor activity against the human breast cancer cells was assessed using the 3-[4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay [19–21]. This cancer cell line was purchased from ATCC (Rockville, MD, USA).

The cells were cultured in a 96-well sterile microplate (5×10^4 cells per well) at 37°C in Roswell Park Memorial Institute medium (RPMI-1640) supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 100 U/mL of both penicillin and streptomycin in a 5% CO_2 humidified atmosphere. After 24 h the media were removed and a fresh serum-free media (90 μL/well) were added together with 10 μL of series of compounds or doxorubicin® (positive control) in DMSO for 48 h. Then, media were removed, MTT (40 μL of 2.5 mg/mL) was added to each well and incubated for 4 h. DMSO (200 μL) were added to solubilized the formazan dye crystals (purple color). Using a SpectraMax® Paradigm® Multi-Mode microplate reader, the absorbance was measured at 590 nm. Each experiment was repeated on three different days and conducted in triplicate. The relative cell cytotoxicity was measured according to the following equation:

$$\text{Cytotoxicity} = (1 - A_s/A_b)\times100\%,$$

where A_s is an absorbance of each sample and A_b is an absorbance of the blank. The probit analysis using the SPSS software program (version 20, SPSS Inc., Chicago, IL, USA) was used to determine each IC_{50}.

Antimicrobial assay. Antibacterial activity of the synthesized compounds was tested against *Escherichia coli* NRRL B-210 and *Pseudomonas* NRRL B-23 (gram –ve bacteria), *Bacillus subtilis* NRRL B-543 and *Staphylococcus aureus* NRRL B-313 (gram +ve bacteria) using nutrient agar medium. The antifungal activity of these compounds was also tested against *Candida albicans* NRRL Y-477 using Sabouraud dextrose agar medium [22].

CONCLUSIONS

We have developed a simple protocol for the sustainable synthesis of new derivatives of 1,5-disubstituted tetrazole via the reaction of dehydropeptides with TACS under mild conditions. The dehydropeptides are synthetized by reaction of arylidene derivatives of 2-phenyl-5(4*H*)-oxazolone with amino acid esters hydrochloride in the presence of triethylamine at room temperature. Tests of anticancer and anti-microbial activities of the synthesized tetrazole derivatives indicated moderate to high activity of some products.

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CONFLICT OF INTERESTS

No conflict of interest was declared by the authors.

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