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Novel acyclonucleoside analog bearing a 1,2,4-triazole–Schiff base: Synthesis, characterization and analytical studies using square wave-adsorptive stripping voltammetry and HPLC

Ali F. Alghamdi [a,*], Nadjet Rezki [a,b]

[a] *Department of Chemistry, Faculty of Science, Taibah University, Al-Madinah Al-Munawarah 30002, Saudi Arabia*
[b] *Department of Chemistry, Faculty of Sciences, University of Sciences and Technology Mohamed Boudiaf Laboratoire de Chimie and Electrochimie des Complexes Metalliques (LCECM) USTO-MB, P.O. Box 1505, El M'nouar, Oran, Algeria*

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Abstract

New acyclonucleoside analogs tethered by a 1,2,4-triazole scaffold were synthesized through the condensation of 4-amino-5-(2-phenyleth-1-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**2**) with benzaldehyde followed by the alkylation of the resulting Schiff base (**3**)with 2-bromoethanol, 3-chloropropanol and/or 3-chloropropan-1,2-diol. Voltammetric studies were carried out for the analysis of 1×10^{-6} mol L^{-1} of the newly synthesized acyclonucleoside analogs (**4–6**) using square wave-adsorptive stripping voltammetry (SW-AdSV). The sharp voltammetric peak and high reduction current were recorded using a Britton–Robinson B–R pH 10 buffer at $E_p = -1250$ mV on the hanging mercury drop surface (HMDE) and Ag/AgCl reference electrode. Several experimental conditions were studied, such as the supporting electrolytes, the pH, and the accumulation time, as well as the potential, the scan rate, the frequency and the step potential for 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (**6**). The analytical performance of the voltammetric technique was investigated through the analysis of the calibration curve, the detection limit, the recovery and the stability. The voltammetric analytical applications were evaluated by the recovery of compound (**6**) in the urine and plasma samples. The HPLC technique was also applied for the separation of compound (**6**) from interference using a C-18 (5 μm) column with UV detection at 254 nm.

Keywords: Acyclonucleoside analog; 1,2,4-Triazoles; Schiff bases; Square wave voltammetry; Adsorptive stripping voltammetry; HPLC; Biological fluids

1. Introduction

During the last several years, the 1,2,4-triazole nucleus has emerged as one of the most attractive azoles in medicinal chemistry, exhibiting anticancer, anti-inflammatory, analgesic and anticonvulsant activities [1–4]. Moreover, the incorporation of an azomethine Schiff base linkage into a 1,2,4-triazole scaffold resulted in the formation of several therapeutically active

* Corresponding author.
E-mail address: alifh2006@hotmail.com (A.F. Alghamdi).
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compounds, which may significantly potentiate antimicrobial activities [5–7]. On the other hand, heterocycles carrying hydroxylated acyclic side chains such as acyclovir (ACV), ganciclovir (GCV), penciclovir (PCV), and (*S*)-9-(2,3-dihydroxypropyl) adenine are important classes of acyclonucleosides endowed with significant antiviral activity [8–11].

Consequently, the synthesis of heterocycles incorporating open chain carbohydrate residues was the subject of extensive research articles that focused on modification of the heterocyclic base and/or the acyclic side chain [12–15].

Recently, considerable attention has been devoted to the application of electrochemical analysis in analytical chemistry owing to these methods' high sensitivity, accuracy and low cost instrumentations. The most common methods are voltammetry techniques, which have been extensively used in the pharmaceutical industry, the metal industry, complexation chemistry, biological samples and environmental applications. The most widespread voltammetric techniques are polarography, square wave voltammetry, cyclic voltammetry and stripping techniques [16–22]. On the other hand, HPLC has gained much attention as a powerful, accurate and regularly used analytical technique in environmental, industrial and biological analyses [23–30].

During the continuation of our search on the synthesis of acyclonucleoside analogs [31–33], a new series of acyclonucleoside analogs bearing a 1,2,4-triazole Schiff base moiety were synthesized with the intention to explore their voltammetric behavior using square wave-adsorptive stripping voltammetry.

2. Results and discussion

2.1. Chemistry

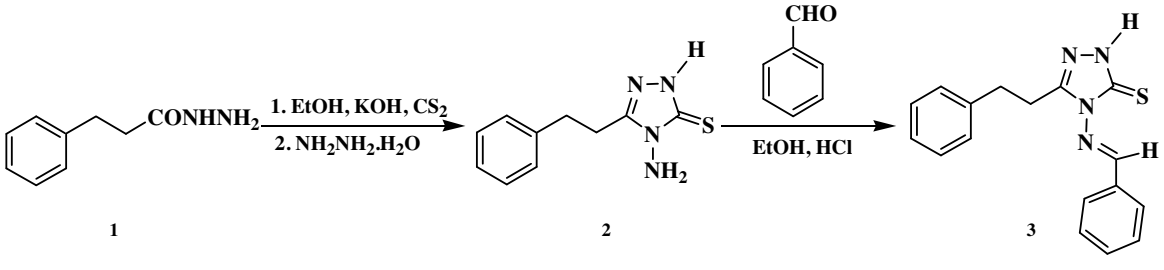
The synthetic methodology employed for the preparation of the precursor 4-amino-5-(2-phenyleth-1-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**2**) required multistep reactions as outlined in Scheme 1. Thus, the treatment of 3-phenylpropanoic acid hydrazide with carbon disulfide in ethanolic potassium hydroxide solution, at 0 °C for 16 h, afforded the corresponding potassium dithiocarbazate salt, which upon refluxing with hydrazine hydrate for 4 h yielded the corresponding aminotriazole (**2**) in 90% yield. The synthesized triazole was identical to that previously prepared in 63% yield by the fusion of 3-phenylethanoic acid with thiocarbohydrazide for 20–25 min [34]. The multistep synthesis strategy adopted in the present work has been widely reported in literature for the preparation of several 4-amino-1,2,4-triazole-2-thione derivatives in higher yield [35,36], although the strategy required a longer time and several steps compared to the one pot synthesis of similar derivatives *via* the reaction of the appropriate carboxylic acid with thiocarbohydrazide [37,38].

The formation of triazole (**2**) was confirmed by spectroscopic data. Its IR spectrum revealed the presence of the characteristic absorption bands for the triazole ring at 3275–3348 cm^{-1} (N–H, NH_2), 1605 cm^{-1} (C=N) and 1295 cm^{-1} (C=S). In the ^1H NMR spectrum, the appearance of two characteristic singlets at δ_H 5.67 and 14.33 ppm, corresponding to NH_2 and NH protons, confirmed the predominance of the thione form.

Conversely, thermal condensation of aminotriazole (**2**) with benzaldehyde in refluxing ethanol in the presence of a catalytic amount of hydrochloric acid provided the corresponding Schiff base (**3**) in 92% yield (Scheme 2).

The ^1H NMR spectrum of Schiff base (**3**) confirmed the absence of the singlet corresponding to the NH_2 group and the presence of a distinctive singlet at δ_H 9.74 attributed to the azomethine proton. The ^{13}C NMR analysis also supported the formation of Schiff base (**3**) in the thione form, through the appearance of two characteristic signals at δ_C 163.04 and 165.48 ppm belonging to the C=N and C=S groups, respectively.

Base catalyzed alkylation (NaOEt) of Schiff base (**3**) with bromoethanol, chlorobutanol and/or 3-chloropropane-1,2-diol, in refluxing ethanol for 6 h, afforded the desired acyclonucleoside analogs (**4–6**) in 84–88%



Scheme 1. Synthesis of Schiff base **3**.

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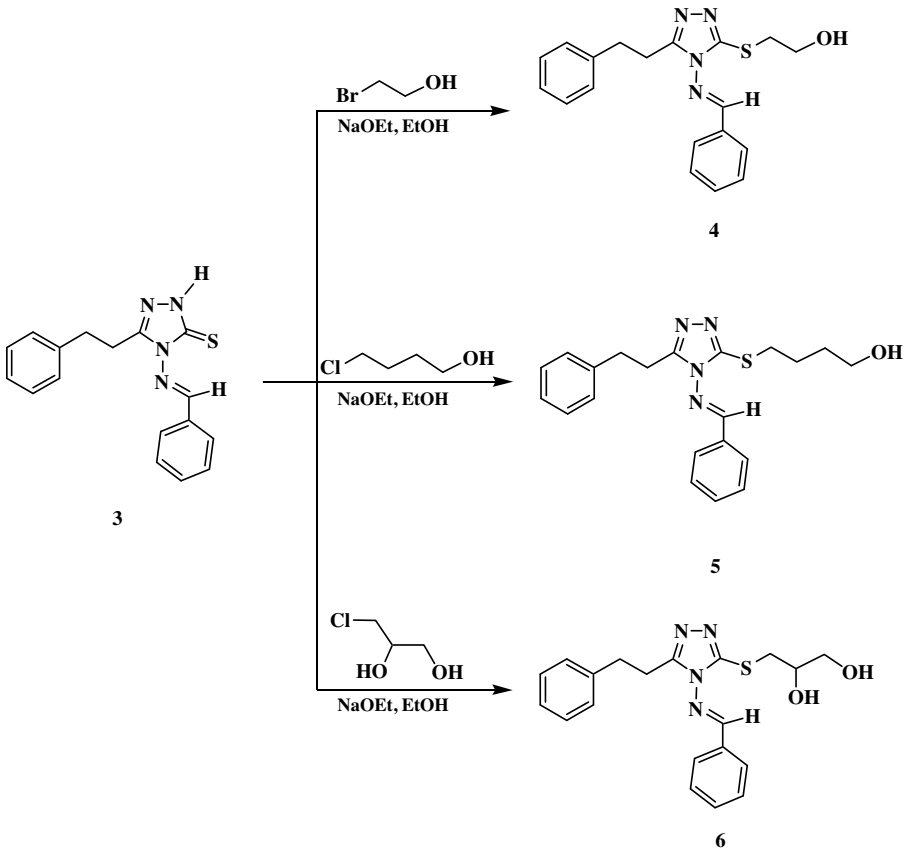

Scheme 2. Synthesis of acyclonucleoside analogs **4–6**.

yield. The structural assignments of the acyclonucleoside analogs (**4–6**) were established on the basis of their IR, ^{1}H NMR and ^{13}C NMR spectral data. In the ^{1}H NMR spectra of compounds (**4**) and (**5**), the SCH_2 protons appeared as triplets at δ_H 3.24–3.32 ppm and integrated for two protons. The OH proton attached to the ethyl side-chain in compound (**4**) appeared as a triplet at δ_H 5.04 ppm ($J = 4.4$ Hz) while the OH proton bonded to the butyl side chain in compound (**5**) resonated as a broad singlet at δ_H 4.62 ppm. In addition, the ^{1}H NMR spectrum of compound (**6**) showed two exchangeable proton signals at δ_H 4.70 and 4.99 ppm integrating for two and are characteristic of the two hydroxyl groups of the glycerol side chain.

2.2. Voltammetric results

A solution of 1×10^{-6} mol L^{-1} of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (**6**) was analyzed by SW-AdSV using different analytical parameters, yielded a cathodic voltammogram at $E_p = -1250$ mV in B–R buffer pH 10, 60 s accumulation time, −0.6 V accumulation potential, 300 mV s^{-1} scan rate, 10 Hz, 250 mV step potential, 0.6 mm^2 drop size and 2600 rpm stirrer rate. The resulted cathodic current was suggested by electrochemical reduction of the exocyclic azomethine group (–N=CH–) as illustrated in Scheme 3.

The voltammetric studies were conducted on a 1×10^{-6} mol L^{-1} sample of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (**6**) using some analytical parameters as summarized in Table 1 and illustrated in Figs. 1–4. These parameters were studied to achieve a high current (sensitivity) and a sharp voltammetric peak. In general, the voltammetric current reached the highest value by use B–R supporting electrolyte, pH 10, 60 s acc time, −0.6 V acc potential, 300 mV s^{-1} scan rate, 10 Hz frequency, 250 mV step potential, 0.6 mm^2 drop size and 2600 rpm stirrer.

2.2.1. Voltammograms under optimum conditions

The analytical studies revealed that the selected parameters recorded high reduction current for all synthesized compounds as summarized in Table 1, and the square wave-adsorptive stripping, cyclic and

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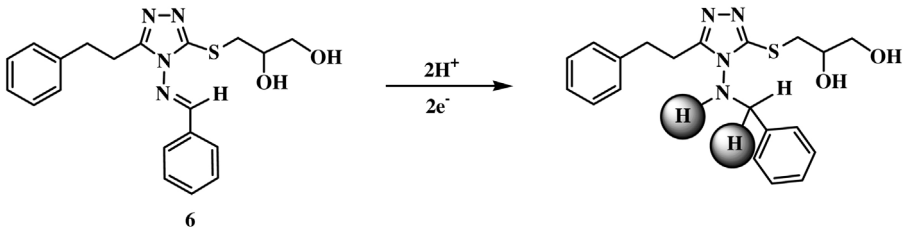

6

Scheme 3. Proposed reduction mechanism of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (**6**).

Table 1
Results of the optimum analytical conditions of compound **6** by SW-AdSV.

Parameters no.	Analytical parameters	Measurements number	Analytical range and parameters	Optimum parameter
1	Supporting electrolytes	7	B–R (pH3, pH7, pH10) Acetate, Phosphate, Carbonate and Ammonia	B–R pH10
2	pH	8	pH 7.5–11	pH 10
3	E_{acc} (V)	9	−0.8 to +0.4	E_{acc} −0.6 V
4	t_{acc} (s)	7	0.0–180	t_{acc} 60 s
5	Scan rate (mV s^{-1})	9	50–500	300 mV s^{-1}
6	Frequency (Hz)	6	5–30	10 Hz
7	Step potential (mV)	16	10–350	250 mV
8	Drop size (mm^2)	4	0.15–0.6	0.6 mm^2
9	Stirrer (rpm)	6	0.0–3000	2600 rpm

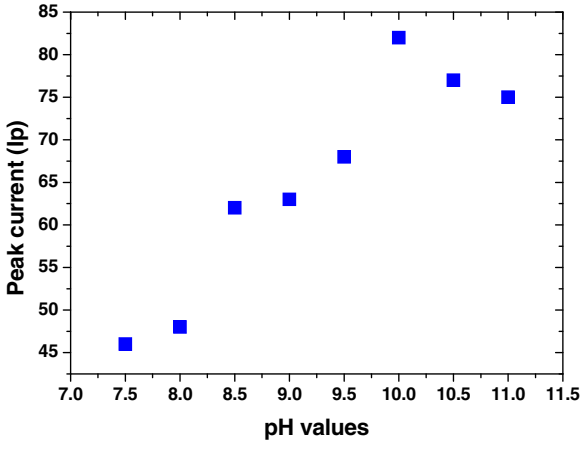

Fig. 1. Effect of pH on electrochemical signal of 1×10^{-6} mol L^{-1} of compound **6** at B–R over the pH range 7.5–11.

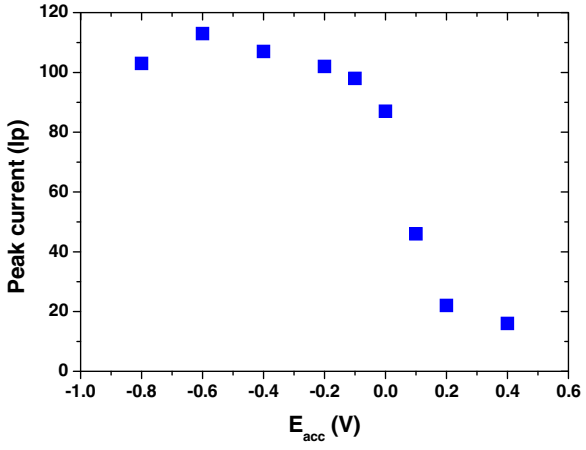

Fig. 2. Effect of acc potential (E_{acc}) on voltammetric signal of 1×10^{-6} mol L^{-1} of compound **6** at B–R and pH 10 over the E_{acc} range −0.8 to +0.4 V.

multi-cyclic voltammograms were illustrated in Figs. 5–7 over the potential range from −0.5 to −1.5 V. Cyclic voltammetry confirmed that the analyzed compound did not show any irreversible characteristic nature. Multi-cyclic voltammetry of fifth cathodic sweeps for 1×10^{-6} mol L^{-1} of compound **6** at 100 mV s^{-1} scan rate is shown in Fig. 7, which confirmed that the HMDE surface was saturated by the analyte from the first sweep; thereafter, the reduction currents were sharply decreased.

On other hand, SW-AdSV was also investigated for the determination of acyclonucleoside analogs (**4**) and (**5**) compared to compound (**6**) under optimum parameters (Figs. 8 and 9). The analytical results revealed that compounds (**4**) and (**5**) gave high current (I_p) = 1550 nA at E_p = −1100 mV for each one; compared to that displayed by compound (**6**) (I_p) = 788 nA at E_p = −1150 mV. This finding may presumably be due to the higher inductive effect resulting from the

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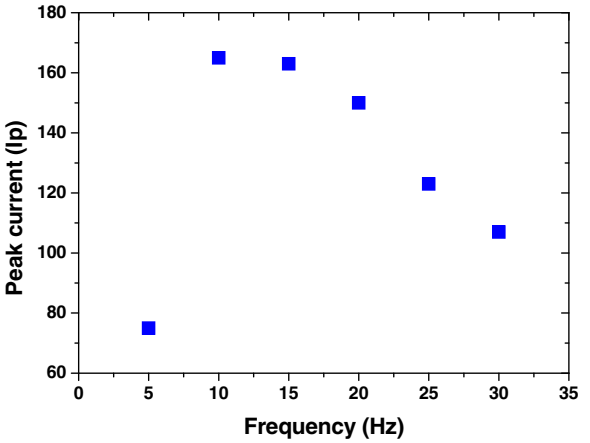

Fig. 3. Effect of frequency (Hz) on voltammetric signal of 1×10^{-6} mol L^{-1} of compound **6** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc} and 300 mV s^{-1} over the range 5–30 Hz.

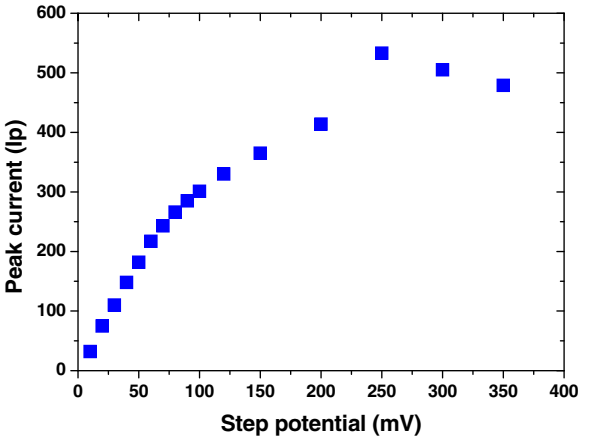

Fig. 4. Effect of step potential (mV) on voltammetric signal of 1×10^{-6} mol L^{-1} of compound **6** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc}, 300 mV s^{-1} and 10 Hz over the range 10–350 mV.

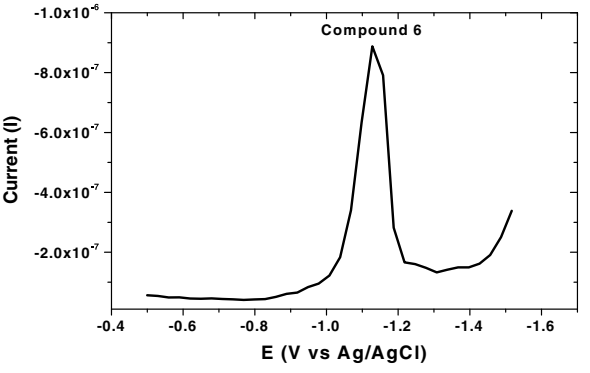

Fig. 5. SW-AdSV voltammogram of 1×10^{-6} mol L^{-1} of compound **6** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc}, 300 mV s^{-1}, 10 Hz, 250 mV step potential and 0.6 mm^2 over the potential range from −0.5 to −1.5 V.

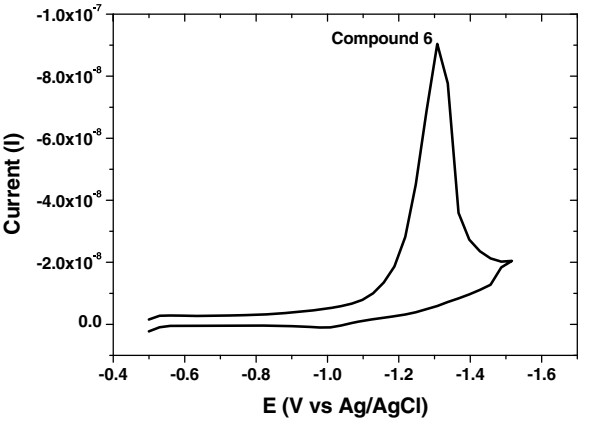

Fig. 6. Cyclic Voltammogram of 1×10^{-6} mol L^{-1} of compound **6** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc}, 300 mV s^{-1}, 10 Hz, 250 mV step potential and 0.6 mm^2 over the potential range from −0.5 to −1.5 V.

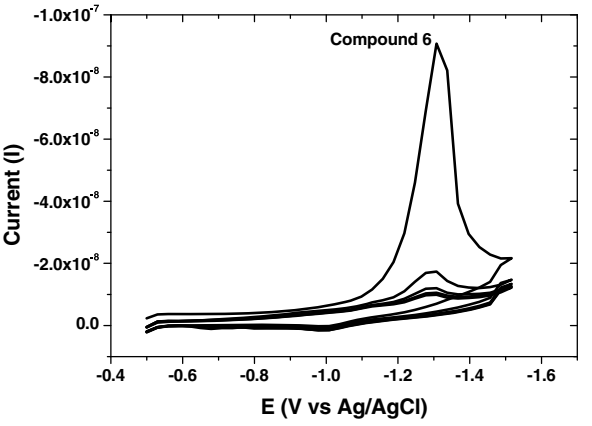

Fig. 7. Multi-Cyclic Voltammogram of 1×10^{-6} mol L^{-1} of compound **6** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc}, 300 mV s^{-1}, 10 Hz, 250 mV step potential and 0.6 mm^2 over the potential range from −0.5 to −1.5 V.

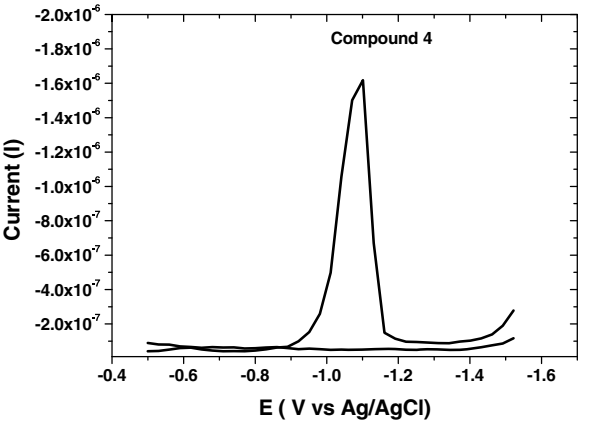

Fig. 8. SW-AdSV of 1×10^{-6} mol L^{-1} of compound **4** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc}, 300 mV s^{-1}, 10 Hz, 250 mV step potential and 0.6 mm^2 over the potential range from −0.5 to −1.5 V.

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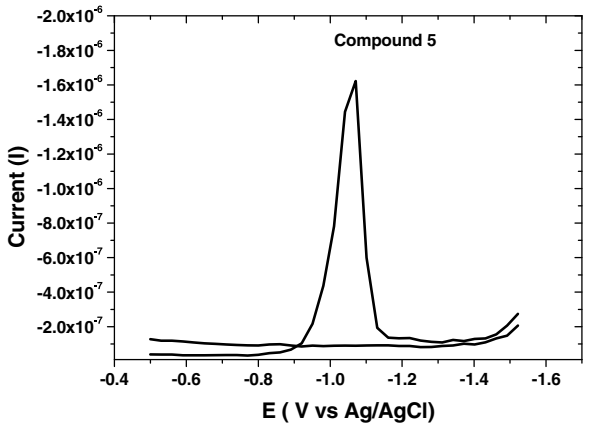

Fig. 9. SW-AdSV of 1×10^{-6} mol L^{-1} of compound **5** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc}, 300 mV s^{-1}, 10 Hz, 250 mV step potential and 0.6 mm^2 over the potential range from −0.5 to −1.5 V.

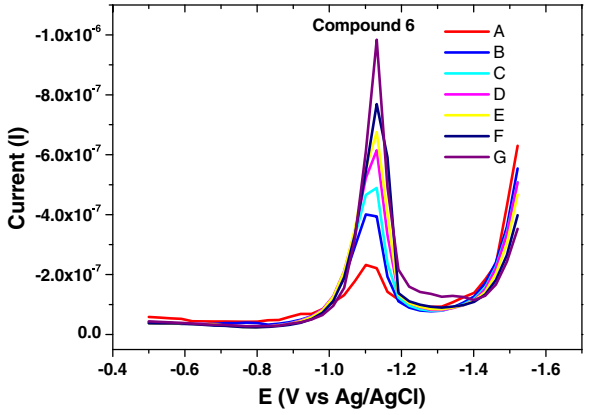

Fig. 10. SW-AdSV of compound **6** at B–R, pH 10, −0.6 V E_{acc}, 60 s t_{acc}, 300 mV s^{-1}, 10 Hz, 250 mV step potential and 0.6 mm^2 ($A = 1 \times 10^{-7}$, $B = 3 \times 10^{-7}$, $C = 5 \times 10^{-7}$, $D = 8 \times 10^{-7}$, $E = 1.2 \times 10^{-6}$, $F = 1.6 \times 10^{-6}$, $G = 2 \times 10^{-6}$ mol L^{-1}) over the potential range from −0.5 to −1.5 V.

presence of the two electron withdrawing hydroxyl groups in compound (**6**).

2.3. Analytical performance characteristics

Several analytical characteristics were investigated for the evaluation of the proposed SW-AdSV technique under the optimum conditions, such as calibration curve, recovery, stability and reproducibility.

2.3.1. Calibration curve

Under the optimum conditions, a linear relationship between the SW-AdSV peak current and compound (**6**) concentrations was observed (Fig. 10) over the range 1×10^{-7} to 2×10^{-6} mol L^{-1}. The calibration curve was calculated using the following least square equations:

$$I_p(\text{nA}) = 3.5 \times 10^8 C + 208.8 \quad r = 0.98, \quad n = 7$$

where I_p, Reduction current in nano-amperes; C, concentration of compound **6** in mol L^{-1}; r, correlation coefficient; n, measurements number.

According to the calibration curve, the detection limit of SW-AdSV for compound (**6**) determination was calculated to be 3.4×10^{-9} mol L^{-1}.

2.3.2. Recovery, stability and reproducibility

The precision and accuracy of the adopted SW-AdSV method was evaluated by the study of the recovery of 2.0×10^{-7} mol L^{-1}, stability and reproducibility of 1.0×10^{-6} mol L^{-1} of compound (**6**), and yielded the 104% ± 1.0 recovery value. The cathodic current was almost stable for 80 min and 0.4% relative standard deviation (RSD %) was observed for eight measurements of the analyte.

2.4. Determination of compound **6** in spiked human biological samples

A 2.0×10^{-6} mol L^{-1} solution of compound **6** was pipetted into centrifuge tubes containing 0.5 mL of biological samples (human urine and plasma), and the centrifuging of the biological sample was run for 3 min. Into the centrifuge tube, 1.0 mL of $ZnSO_4 \cdot 7H_2O$, 0.1 mL of NaOH and 1.0 mL of MeOH were added to the biological samples, and the mixture was centrifuged for 8 min at 4000 rpm. The solution was subsequently filtered using 0.45-μm filter papers, and a 0.5-mL volume of the liquid was transferred into the electrochemical cell and diluted to 10 mL with B–R buffer pH 10. The centrifuging operation was used for removing the interfering substances [39]. The developed SW-AdSV was applied for the recovery of 2.0×10^{-6} mol L^{-1} of compound **6** in urine and plasma samples, which yielded 95.2% ± 1.1 and 90% ± 1.0, respectively.

2.5. Analytical results of HPLC

The HPLC technique was also investigated for the determination of the chemical behavior of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (**6**) in a mixture of methanol, acetonitrile and water mobile phase (70:20:10, v/v/v%) with UV detector at 254 nm and 1.0 mL/min flow rate. The HPLC signal for compound **6** was observed at 6.0×10^{-4} mol L^{-1} with 3.7 min as retention time (408 Abs) (Fig. 11).

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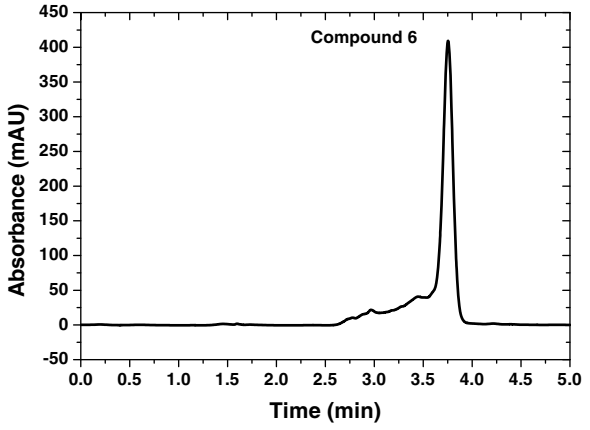

Fig. 11. HPLC signal of 6.0×10^{-4} mol L^{-1} of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (**6**).

3. Experimental

3.1. General methods

The melting points were determined on a Melt-temp apparatus and are uncorrected. TLC was performed on Merck silica gel 60 F254, and the spots were visualized by UV light absorption. The IR spectra were measured using potassium bromide pellets on a Perkin-Elmer 1430 series FT-IR spectrometer. ^{1}H NMR spectra were recorded on an Advance Bruker NMR spectrometer at 400 MHz, and the ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using TMS as the internal standard. Elemental analyses were performed using a GmbH-Vario EL III Element Analyzer (Germany).

3.2. Synthesis and characterization of 4-amino-5-(2-phenyleth-1-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (2)

Carbon disulfide (15 mmol) was added dropwise to a stirred solution of acid hydrazide **1** (10 mmol) in absolute ethanol (30 mL) containing potassium hydroxide (15 mmol) at 0 °C. Stirring was continued for 16 h at room temperature, and then the solution was diluted with diethyl ether. The resulting potassium dithiocarbazinate salt was filtered, washed with diethyl ether and was used without further purification since it was moisture-sensitive.

A mixture of the potassium dithiocarbazinate salt (10 mmol), hydrazine hydrate (20 mmol) and water (10 mL) was heated under reflux for 4 h. After cooling, it was diluted with water, and then acidified with aqueous hydrochloric acid. The crude triazole thus obtained was filtered and recrystallized from ethanol to give compound **2** in 90% yield, m.p. 229–230 °C, Lit mp: 227.9 °C [34]. IR (υ, cm^{-1}): 3275–3348 (NH, NH_2), 3081 (Ar–H), 2913 (Ar–H), 1605 (C=N), 1295 (C=S). ^{1}H NMR: δ_H 3.00 (t, 2H, 6.0 Hz, CH_2), 3.15 (t, 2H, 6.0 Hz, CH_2), 5.67 (s, 2H, NH_2), 7.30–7.58 (m, 5H, Ar–H), 14.33 (s, 1H, NH triazole) ppm. ^{13}C NMR: δ_C 31.12 (CH_2), 35.46 (CH_2), 115.78, 123.60, 127.82, 129.21, 132.56, 134.89, 161.84, 164.87 (Ar–C, C=N, C=S) ppm. Anal. Calc. for $C_{10}H_{12}N_4S$: C 54.52, H 5.49, N 25.43. Found: C 54.63, H 5.41, N 25.29.

3.3. Synthesis and characterization of 4-benzylideneamino-5-(2-phenyleth-1-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (3)

A mixture of triazole **2** (10 mmol) and benzaldehyde (10 mmol) was refluxed in ethanol (25 mL) containing HCl (0.5 mL) for 4 h. The solid thus formed on cooling was recrystallized from ethanol to give Schiff base **3** in 92% yield, mp: 180–181 °C. IR (υ, cm^{-1}): 3325 (NH), 3068 (Ar–H), 2936 (Ar–H), 1612 (C=N), 1290 (C=S). ^{1}H NMR: δ_H 3.02 (t, 2H, 6.0 Hz, CH_2), 3.16 (t, 2H, 6.0 Hz, CH_2), 7.27–7.75 (m, 10H, Ar–H), 9.74 (s, 1H, H–C=N), 14.29 (s, 1H, NH triazole). ^{13}C NMR: δ_C 31.35 (CH_2), 36.12 (CH_2), 114.49, 116.14, 123.71, 126.50, 127.65, 129.44, 131.76, 132.24, 133.65, 140.14, 161.69, 163.04, 165.48 (Ar–C, C=N, C=S). Anal. Calc. for $C_{17}H_{16}N_4S$: C 66.21, H 5.23, N 18.17. Found: C 66.17, H 5.37, N 18.24.

3.4. General procedure for the synthesis of acyclonucleoside analogs 4–6

To a solution of compound **3** (1 mmol) in an ethanolic solution of sodium ethoxide, prepared from sodium metal (0.023 g) in ethanol (15 mL), the appropriate hydroxyl alkylating agent (1.1 mmol) was added with stirring and later heated under reflux for 6 h. The reaction mixture was concentrated, cooled, diluted with water and left overnight. The precipitate formed was filtered, washed with water, and recrystallized from ethanol to yield acyclonucleoside analogs **4–6**.

3.4.1. Characterization of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2-hydroxyeth-1-yl)thio]-1,2,4-triazole (4)

This compound was obtained in 88% yield, m.p. 252–253 °C. IR (υ, cm^{-1}): 3368 (OH), 3042 (Ar–H), 2918 (Ar–H), 1602 (C=N). ^{1}H NMR: δ 3.02 (t, 2H, 6.0 Hz, CH_2), 3.13 (t, 2H, 6.0 Hz, CH_2), 3.25 (t, 2H, J = 4.4 Hz, SCH_2), 3.76–3.81 (m, 2H, CH_2O), 5.04 (t,

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1H, $J = 4.4$ Hz, D_2O exchangeable, OH), 7.31–7.70 (m, 10H, Ar–H), 9.71 (s, 1H, H–C=N) ppm. ^{13}C NMR: δ 31.62 (CH_2), 35.40 (CH_2), 42.54 (SCH_2), 61.21 (OCH_2), 114.78, 116.80, 124.45, 126.23, 127.93, 129.79, 131.23, 132.78, 133.83, 140.46, 162.11, 163.42 (Ar–C, C=N) ppm. Anal. Calc. for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90. Found: C 64.59; H 5.91; N 15.67.

3.4.2. Characterization of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(4-hydroxybut-1-yl)thio]-1,2,4-triazole (5)

This compound was obtained in 84% yield, m.p. 215–216 °C. IR (υ, cm^{-1}): 3346 (NH), 3022 (Ar–H), 2914 (Ar–H), 1611 (C=N). ^1H NMR: δ 1.86–1.97 (m, 4H, CH_2CH_2), 3.01 (t, 2H, 6.0 Hz, CH_2), 3.14 (t, 2H, 6.0 Hz, CH_2), 3.32 (t, 2H, $J = 4.4$ Hz, SCH_2), 3.69 (t, 2H, $J = 4.4$ Hz, CH_2O), 4.62 (bs, 1H, D_2O exchangeable, OH), 7.29–7.70 (m, 10H, Ar–H), 9.70 (s, 1H, H–C=N) ppm. ^{13}C NMR: δ_C 28.70 (CH_2), 29.53 (CH_2), 31.23 (CH_2), 35.64 (CH_2), 41.10 (SCH_2), 60.43 (OCH_2), 114.90, 116.62, 123.41, 126.62, 127.89, 130.32, 131.14, 132.54, 133.83, 140.70, 161.34, 163.56 (Ar–C, C=N) ppm. Anal. Calc. for $C_{21}H_{24}N_4OS$: C, 66.29; H, 6.36; N, 14.72. Found: C, 66.43; H, 6.58; N, 14.84.

3.4.3. Characterization of 4-benzylideneamino-5-(2-phenyleth-1-yl)-3-[(2,3-dihydroxyprop-1-yl)thio]-1,2,4-triazole (6)

This compound was obtained in 87% yield, m.p. 268–269 °C. IR (υ, cm^{-1}): 3325 (NH), 3068 (Ar–H), 2936 (Ar–H), 1612 (C=N), 1290 (C=S). ^1H NMR: δ_H 3.03 (t, 2H, 6.0 Hz, CH_2), 3.18 (t, 2H, 6.0 Hz, CH_2), 3.24 (dd, 1H, $J = 4.4$ Hz, $J = 12.8$ Hz, SCH_2), 3.30–3.39 (m, 3H, SCH_2, CH_2O), 3.57–3.64 (m, 1H, CHO), 4.70 (bs, 1H, D_2O exchangeable, OH), 4.99 (bs, 1H, D_2O exchangeable, OH), 7.22–7.70 (m, 10H, Ar–H), 9.76 (s, 1H, H–C=N) ppm. ^{13}C NMR: δ_C 31.45 (CH_2), 35.82 (CH_2), 39.61 (SCH_2), 64.49 (CH_2O), 69.18 (CHO), 114.77, 116.46, 123.62, 126.90, 127.42, 129.08, 131.71, 132.42, 133.48, 140.57, 161.71, 163.46 (Ar–C, C=N) ppm. Anal. Calc. for $C_{20}H_{22}N_4O_2S$: C, 62.80; H, 5.80; N, 14.65. Found: C, 63.09; H, 5.69; N, 14.35.

3.5. Voltammetric measurements

The voltammetric measurements were usually were carried out using a 797 VA (Metrohm) controlled by VA computrace 2.0 control software at room temperature. The voltammetric technique was applied by conventional three electrodes system: hanging mercury drop electrode (HMDE), Ag/AgCl reference electrode and platinum auxiliary electrode. The pH values were recorded using a Hanna instrument pH 211. The analyte solution was initially purged with nitrogen gas for 100 s with stirring. In order to obtain voltammograms of the analyte under optimum conditions, 10 mL of supporting electrolyte was injected in dry and clean electrochemical cell, followed by the addition of the analyzed sample. The reduction scanning was applied over the potential range from −0.5 to −1.5 V for 60 s with stirring of the analyzed solution and 300 mV s^{-1} scan rate.

3.6. HPLC measurements

High-performance liquid chromatography technique was used for the analysis of novel triazole acyclonucleoside analogs using Ultimate 3000, Thermo Scientific Dionex with UV–vis detector, auto sampler, 0.01 mL manual loop injector and 5 μm C-18 column. For injection of triazole samples, micropipette 0.01–1.00 mL was used.

4. Conclusions

The condensation of 4-amino-5-(2-phenyleth-1-yl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione (**2**) with benzaldehyde in acidic media afforded the corresponding Schiff base (**3**) which, upon alkylation with hydroxyalkylating agents, furnished new acyclonucleoside analogs (**4–6**) in excellent yields.

In this study, efficient, accurate and fast square wave-adsorptive stripping voltammetric (SW-AdSV) as well as HPLC techniques have been successfully adopted for the determination of the newly synthesized triazolic acyclonucleoside analogs.

The described techniques were demonstrated to be convenient for the determination of all synthesized acyclonucleoside analogs and exhibited high sensitivity and specificity. The accuracy and precision of the presented methods were checked on the optimized parameters that divulged a dynamic linear concentration ranges with a low limit of detection over a wide range of concentrations. The accuracy and selectivity of the developed methods were demonstrated by recovery studies.

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