Synthesis and Anticancer Evaluation of New Thiazole and Thiadiazole Derivatives Bearing Acetanilide Moiety

Ali El-Rayyesa, Ehab Abdel-Latifb,*, Ahbarah M. Solimanc, and Ali Saeedbd

a Chemistry Department, Faculty of Science, Northern Border University, Arar, 1321 Saudi Arabia
b Department of Chemistry, Faculty of Science, Mansoura University, Mansoura, 35516 Egypt
c Department of Chemistry, Faculty of Science, Omar Al-Mukhtar University, 919 Libya
d Department of Chemistry, Faculty of Science, Sa’adah University, Sa’adah, 71333 Yemen
*e-mail: ehabattia00@gmx.net

Received July 20, 2022; revised July 30, 2022; accepted August 2, 2022

Abstract—New thiazole and thiadiazole derivatives bound to the acetanilide moiety were synthesized and evaluated for their cytotoxic activity. The precursor N-(4-acetamidophenyl)-N'-phenylthiourea (2) was cyclocondensed with ethyl bromoacetate to afford a mixture of the two isomers, 2-(4-acetamidophenylimino)-3-phenylthiazolidin-4-one (3a, 23%) and 3-(4-acetamidophenyl)-2-phenyliminothiazolidin-4-one (3b, 71%). The Knoevenagel reaction of 3b with various aromatic aldehydes afforded 5-arylidene-2-phenyliminothiazolidin-4-one derivatives 5a–5e. Intramolecular cyclization of thiourea scaffold 2 with chloroacetone and/or phenacyl chloride gave the conforming thiazole derivatives 6a and 6b. A new series of thiadiazole derivatives 9a–9c and 11a–11c was synthesized by the reaction of N-(4-acetamidophenyl)-N'-phenylthiourea (2) with selected derivatives of hydrazonoyl halide in ethanol and triethylamine. The structures of the synthesized thiazole and thiadiazole compounds were elucidated by their compatible spectral data. The cytotoxic activity of the synthesized thiazole and thiadiazole derivatives was screened against four human cancer cell lines and showed promising results. Thiazolidin-4-one compound 5d showed the strongest cytotoxic effects on hepatocellular carcinoma (IC50 = 8.80 ± 0.31 μg/mL), mammary gland breast cancer (IC50 = 7.22 ± 0.65 μg/mL) and colorectal carcinoma (IC50 = 9.35 ± 0.61 μg/mL) cell lines.

Keywords: arylthiourea, thiazolidin-4-ones, hydrazonoyl halides, thiadiazoles, cytotoxicity

DOI: 10.1134/S1070363222100267

INTRODUCTION

Thiourea derivatives are important synthons in the synthesis of biologically active heterocyclic compounds that have a wide range of biological applications [1]. In particular, the most significant thiourea derivatives demonstrated antiviral [2], cytotoxic potential [3], antibacterial and antifungal [4] and anticancer activities [5]. 4-Thiazolidinone derivatives have also attracted continuing interest due to their valuable biological activities [6-8] such as anti-inflammatory [9], antimicrobial [10], antidiabetic and antiviral [11, 12], anti-tuberculostatic [13], anti-malarial [14], COX-2 inhibitor activities [15], anti-HIV [16], anti-oxidant [17], Anti-urease Agents [18] and anti-cancer [19, 20]. A number of thiazolidinone-based compounds with various substituents surrounding the core nucleus are being investigated as potential anticancer agents (Fig. 1) [21, 22]. While, thiazole scaffold have medical claims such as bacteriostatic, antibiotics [23], anti-inflammatory [24], analgesics [25, 26], and anti-HIV [27]. Some of these thiazole-containing compounds have been transferred into clinical trials and cancer therapy—Dasatinib and Dabrafenib (Fig. 1) [28, 29].

In addition, 1,3,4-thiadiazoles exhibit a wide range of biological activities, including antimicrobial [30, 31], antitumor [32–34], antioxidant [35], antidepressant [36], antibacterial [37], antifungal [38], anticonvulsant [39], anti-inflammatory [40], against covid-19 [41], and antiproliferative activities [42], as well as the treatment of Alzheimer disease [43, 44]. 2-(4-Fluorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (5) (Fig. 1) inhibited tumor cell proliferation derived from nervous system cancers (medulloblastoma/medulloblastoma, glioma, and rhabdosarcoma) and peripheral cancers (lung and colon carcinoma). The thiadiazole derivatives
and 6 (Fig. 1) are not toxic to normal cells [45, 46]. The present research article reported on the efficient synthesis of some new highly functionalized thiazole and 1,3,4-thiadiazole derivatives utilizing \(N\)-(4-acetamido-phenyl)-\(N'\)-phenylthiourea as a key starting synthon, and an evaluation of their cytotoxicity against HepG2, MCF-7, HTC-116, and PC-3 cell lines.

**RESULTS AND DISCUSSION**

Reaction of 4-aminoacetanilide (1) with phenyl isothiocyanate furnished the key start \(N\)-(4-acetamido-phenyl)-\(N'\)-phenylthiourea (2) [47]. The regioselective reaction of 1,3-diarylthiourea derivative 2 with ethyl bromoacetate proceeded in ethanol containing fused CH\(_3\)COONa (0.5 g) to afford two isomeric thiazolidin-4-ones 3a and 3b (Scheme 1). The comparable electronic nature of the thiourea nitrogen atoms appears to dominate the outcome of the cyclization reaction and an almost 1:3 mixture of the two 2-iminothiazolidine-4-ones 3a and 3b is obtained, the ratio was determined from the \(^1\)H NMR spectrum. The cyclization’s regioselectivity is influenced not only by the reaction conditions and the \(\delta\)-halocarbonyl derivative used, but also by the nature of the thiourea intermediate’s two substituents. The regioselective reaction of unsymmetrical thiourea with alpha-haloesters is dependent on the \(pK_a\)'s of the amines. The regioselective product 2-imino-4-thiazolidinone is formed when an amine is attached to a thiourea with a lower \(pK_a\) as part of the imino component and another amine with a higher \(pK_a\) contributes to the other heterocyclic nitrogen.

When unsymmetrical thiourea 2 having a phenyl and a \(p\)-acetamidophenyl groups reacted with ethyl bromoacetate, a mixture of two isomers acetamidophenylimino 3a and phenylimino 3b (with a ratio of 1 : 3) has been obtained. The measured \(pK_a\) of aniline...
that, the singlet for one proton at δ 9.89 ppm indicated the acetamido group (CONH). The $^{13}$C NMR spectrum displayed the carbon signal of the methylene group (thiazolidine-4-one ring) at δ 37.18 ppm. Also, the carbon signals of carbonyl groups were observed at δ 169.05 (C=O, amide) and δ 172.88 ppm (C=O, thiazolidinone ring) respectively.

In an attempt to prepare the pyranothiazole derivatives 4, the thiazolidin-4-one derivative 3b was heated with 2-(4-methylbenzylidene)malononitrile in ethanol and piperidine. Unfortunately the reaction did not furnish our targeting pyranothiazole derivatives 4 while the 5-arylidenethiazolidin-4-one scaffolds 5 are isolated as a sole product in each case (Scheme 2). Compounds 5 were also obtained directly by refluxing the 2-phenyliminothiazolidin-4-one derivative 3b with various substituted benzaldehydes (4-toulaldehyde, 4-anisaldehyde, 2,5-dimethoxybenzaldehyde, 4-nitrobenzaldehyde and/or 3-(4-chlorophenyl)-4-formyl-1-phenyl-1H-pyrazole) in acetic acid containing sodium and p-acetamidoaniline are 4.63 and 5.46, respectively. Thus, the amine with the lower pK$_a$ contributes to the imino component, while the other amine attached to the thiourea with the higher pK$_a$ contributes to the other heterocyclic nitrogen in the 2-imino-4-thiazolidinone skeleton (3b). Fortunately, the 3-(4-acetamidophenyl)-2-phenyliminothiazolidin-4-one (3b) was isolated from its isomeric 2-(4-acetamidophenylimino)-3-phenylthiazolidin-4-one (3a) by recrystallization of the regioselective mixture from ethyl alcohol. The proposed structure of the isolated product 3b was assessed by spectral and analytical data. The IR spectrum of 3b identified absorptions at 3295 and 1728 cm$^{-1}$ due to the presence of N–H and thiazolidinone (C=O) functions, respectively. The $^1$H NMR spectrum displayed a singlet at δ 2.01 ppm for the methyl group and a singlet at δ 4.15 ppm for the methylene group of the thiazolidinone ring. The upfielded chemical shift of the AA'BB' system of the isolated isomer 3b at δ 6.79 ppm refers to the ortho-aromatic protons of phenylimino-moieties. In addition to that, the singlet for one proton at δ 9.89 ppm indicated the acetamido group (CONH). The $^{13}$C NMR spectrum displayed the carbon signal of the methylene group (thiazolidine-4-one ring) at δ 37.18 ppm. Also, the carbon signals of carbonyl groups were observed at δ 169.05 (C=O, amide) and δ 172.88 ppm (C=O, thiazolidinone ring) respectively.

In an attempt to prepare the pyranothiazole derivatives 4, the thiazolidin-4-one derivative 3b was heated with 2-(4-methylbenzylidene)malononitrile in ethanol and piperidine. Unfortunately the reaction did not furnish our targeting pyranothiazole derivatives 4 while the 5-arylidenethiazolidin-4-one scaffolds 5 are isolated as a sole product in each case (Scheme 2). Compounds 5 were also obtained directly by refluxing the 2-phenyliminothiazolidin-4-one derivative 3b with various substituted benzaldehydes (4-toulaldehyde, 4-anisaldehyde, 2,5-dimethoxybenzaldehyde, 4-nitrobenzaldehyde and/or 3-(4-chlorophenyl)-4-formyl-1-phenyl-1H-pyrazole) in acetic acid containing sodium.
Scheme 2. Synthesis of 5-arylidene-2-phenyliminothiazolidin-4-one derivatives 5a–5e.

acetate (Scheme 2). The IR of thiazolidine-4-one 5b identified absorptions at 3308 cm⁻¹ (N–H), 1714 and 1660 cm⁻¹ (two carbonyl groups). Whereas, ¹H NMR spectrum displayed singlet signals at δ 2.06 and 3.79 ppm for the protons of methyl (CH₃) and methoxy (OCH₃) groups. The two singlet signals for the methine (CH= C) and N–H protons are observed at δ 7.76 and 10.11 ppm. The ¹H NMR of the synthesized compounds 5a–5e clearly shows the disappearance of thiazole methylene group and detection of CH=C. The ¹³C NMR spectrum demonstrated carbon signals at δ 24.39 (CH₃) and 55.47 ppm (OCH₃). The signal at δ 143.07 ppm identified the carbon of thiazole-C5. The signal of imine group (C=N) was resonated at δ 160.60 ppm. Furthermore, the carbon signals at δ 163.61 and 168.23 ppm indicated...
the carbonyl groups (C=O, amide), and (C=O, ring), respectively.

Furthermore, the reaction of diaryl thiourea derivative 2 with α-halogenated reagents (chloroacetone and/or phenacyl chloride) in boiling ethanol and triethylamine furnished the conforming thiazole compounds 6a and 6b. The reaction starts via nucleophilic substitution of the chlorine atom from α-chloroketone to yield the alkylated intermediate A, which underwent intramolecular nucleophilic addition of N–H function to the carbonyl group. The produced intermediate B undergoes elimination of water molecule to the targeting thiazole derivative 6a and 6b (Scheme 3). The IR spectrum of 6a indicated absorptions at 3240 and 1669 cm⁻¹ for the N–H and C=O functions, respectively. The ¹H NMR spectrum showed singlet signals for two methyl protons at δ 1.89 and 2.09 ppm, a singlet for the proton of thiazole-C₅ at δ 6.95 ppm, and a singlet for the proton of N–H function at δ 9.17 ppm. The aromatic protons are observed in the region from δ 7.07 to 7.43 ppm. The ¹³C NMR spectrum of 6a exhibited carbon signals at δ 16.90 (CH₃) and 24.55 ppm (CH₃). The carbon signal of thiazole-C5 was resonated at δ 95.82 ppm. Furthermore, the carbon signal of carbonyl group was resonated at δ 169.70 ppm (C=O, amide group).

Heating the diaryl thiourea derivative 2 in ethanol and triethylamine with the 2-oxo-N-arylpropanehydrazonoyl chlorides 7a–7c produced the conforming 5-acetylthiadiazole derivatives 9a–9c rather than the thiazole-based skeleton 8a–8c (Scheme 4). The reaction was initiated by nucleophilic substitution of the chlorine atom from the hydrazonoyl chloride derivative 7 to yield the alkylated intermediate C1. This intermediate C1 failed to tautomerize into the intermediate C2, and the loss of a water molecule resulted in the formation of the assumed arylazothiazoles 8. However, the sulfide intermediate C1 favors the nucleophilic addition of the N–H function (from the hydrazone moiety) to the C=N
group to constitute the intermediate D, which undergoes elimination of the aniline molecule and furnishes the corresponding 5-acetyl-1,3,4-thiadiazoles 9a–9c (Scheme 4). Thiadiazole compound 9b showed the characteristic IR absorptions at 3290, 1665, 1657 cm\(^{-1}\) due to N–H and two carbonyl (C=O) groups. The \(^1\)H NMR spectrum exhibited singlet signals for the protons of three methyl groups at δ 2.03, 2.38 and 2.45 ppm, a multiplet for eight aromatic protons in the region δ 6.70–7.53 ppm and a singlet for the proton of the N–H function at δ 10.12 ppm. The \(^13\)C NMR spectrum displayed carbon signals at δ 23.81 (CH\(_3\)), 24.52 (CH\(_3\)) and 26.12 ppm (CH\(_3\)). The aromatic carbon atoms were indicated by the signals at δ 114.51, 114.83, 122.62, 124.77, 128.65, 129.34, 131.25, and 133.70 ppm. Furthermore, the carbon signals at δ 158.17 and 162.94 ppm indicated the signals of carbonyl groups (C=O, amide group) and (C=O, acetyl group), respectively.

Furthermore, the reactivity of the N-(4-acetamido-phenyl)-N′-phenylthiourea (2) with various ethyl 2-chloro-2-(2-phenylhydrazono)acetates 10a–10c was also conducted. The reaction proceeds by refluxing the reactants in ethanol containing triethylamine to afford the respective 5-ethoxycarbonyl-1,3,4-thiadiazole derivatives 11a–11c (Scheme 5). 1,3,4-Thiadiazoles 11a–11c were formed through nucleophilic substitution of the chlorine atom (from hydrazonoyl chlorides 10a-c) to yield the alkylated intermediate E, which undergoes intramolecular cyclization of the N–H group (hydrazone moiety) on the carbon activated of the imino group (C=N). The formed intermediate F rapidly loses an aniline molecule, yielding the corresponding 1,3,4-thiadiazoles 11a–11c. The structures of thiadiazole products 11a–11c were established based on their analytical and spectral data. The thiadiazole compound 11a showed the characteristic infrared absorptions at 3365 for the N–H stretching and at 1737 and 1657 cm\(^{-1}\) due to the two carbonyl (C=O) groups. The \(^1\)H NMR spectrum of 11a displayed triplet and quartet signals that resonated at δ 1.18 and 4.20 ppm due to the protons of the ethyl group, and a singlet for the protons of the methyl group (CH\(_3\)CO) at δ 2.07 ppm. The aromatic protons are observed as multiplet signals at δ 6.82–7.65 ppm. The proton of the N–H group was identified as a singlet at δ 10.11 ppm. The \(^13\)C NMR spectrum of 11a showed carbon signals at δ 14.34 (CH\(_3\)), 23.55 (CH\(_3\)) and 61.50 ppm (OCH\(_2\)). The aromatic carbon atoms are identified by the carbon signals at δ 114.93, 121.62, 123.85, 125.51, 129.06, 129.87, 133.44, and 139.29 ppm. The signals at δ 144.57 and 150.23 ppm indicated the carbon atoms of the thiadiazole ring. Moreover, the signals of carbonyl groups were
In vitro antitumor activity. Cancer is recognized as the most serious disease in the world, with severity and lethality caused by inconsistency in cell growth and proliferation [48, 49]. Chemotherapy is the most fundamental and important approach in cancer treatment, employing a wide range of natural and synthetic compounds to destroy cancer cells [50]. The inability of the current chemotherapeutic system to distinguish between normal and cancerous cells has been its main drawback [51]. As a result, the major challenge for medicinal chemists has been the development of safe and effective chemotherapeutic agents. The current study aims to look into the anticancer activity of chemically synthesized thiazolidine-4-one, thiazole, and 1,3,4-thiadiazole derivatives against four human cancer cell lines: HepG2 (hepatocellular carcinoma), MCF-7 (mammary gland breast cancer), HTC-116 (colorectal carcinoma) and PC-3 (human prostate cancer carcinoma).

The effects of thiazole and thiadiazole compounds 3b, 5a–5e, 6a, 6b, 9a–9c, and 11a–11c on the viability of these cell lines were studied by applying the MTT assay [52, 53] using 5-fluorouracil (5-FU) as a reference drug. The results (Table 1) showed that the majority of the prepared compounds had moderate to strong cytotoxicity effects on the cancer cell lines tested. 5-(4-Nitrobenzylidene)thiazolidin-4-one compound 5d displayed the highest cytotoxicity on two cancer cell lines HepG2 (IC$_{50}$ 8.80 ± 0.31 μg/mL) and MCF-7 (IC$_{50}$ 7.22 ± 0.65 μg/mL), their IC$_{50}$ values are close to the standard anticancer drug 5-fluorouracil. In addition, it showed strong cytotoxic effects among the other two cancer cell lines HTC-116 (IC$_{50}$ 9.35 ± 0.61 μg/mL) and PC-3 (IC$_{50}$ 12.57 ± 1.09 μg/mL). Furthermore, 2-phenylimino-thiazolidin-4-one derivatives 5b, 5c, and 5e showed equipotent anticancer activity against all cell lines with IC$_{50}$ values ranging from 11.80 to 19.07 μg/mL. In contrast, the investigated thiadiazole derivatives 9a–9c and 11a–11c showed considering activity against breast cancer cell lines as indicated by the MCF-7 profile (Table 1). Thiadiazole compounds 9c and 11c, in particular, demonstrated the most pronounced activity against the MCF-7 cell line when compared to 5-fluorouracil, with IC$_{50}$ values of 17.32 and 15.64 μg/mL, respectively.

The structure-activity relationship gave a clear picture of the activity of these title compounds. The addition of a substituent on the benzylidene moiety that is linked to the thiazolidine-4-one ring affects anticancer acidity. The presence of an electron-donating methoxy group observed at δ 162.80 (amide group) and 169.78 ppm (ester group).

In vitro antitumor activity. Cancer is recognized as the most serious disease in the world, with severity and lethality caused by inconsistency in cell growth and proliferation [48, 49]. Chemotherapy is the most fundamental and important approach in cancer treatment, employing a wide range of natural and synthetic compounds to destroy cancer cells [50]. The inability of the current chemotherapeutic system to distinguish between normal and cancerous cells has been its main drawback [51]. As a result, the major challenge for medicinal chemists has been the development of safe and effective chemotherapeutic agents. The current study aims to look into the anticancer activity of chemically synthesized thiazolidine-4-one, thiazole, and 1,3,4-thiadiazole derivatives against four human cancer cell lines: HepG2 (hepatocellular carcinoma), MCF-7 (mammary gland breast cancer), HTC-116 (colorectal carcinoma) and PC-3 (human prostate cancer carcinoma).

The effects of thiazole and thiadiazole compounds 3b, 5a–5e, 6a, 6b, 9a–9c, and 11a–11c on the viability of these cell lines were studied by applying the MTT assay [52, 53] using 5-fluorouracil (5-FU) as a reference drug. The results (Table 1) showed that the majority of the prepared compounds had moderate to strong cytotoxicity effects on the cancer cell lines tested. 5-(4-Nitrobenzylidene)thiazolidin-4-one compound 5d displayed the highest cytotoxicity on two cancer cell lines HepG2 (IC$_{50}$ 8.80 ± 0.31 μg/mL) and MCF-7 (IC$_{50}$ 7.22 ± 0.65 μg/mL), their IC$_{50}$ values are close to the standard anticancer drug 5-fluorouracil. In addition, it showed strong cytotoxic effects among the other two cancer cell lines HTC-116 (IC$_{50}$ 9.35 ± 0.61 μg/mL) and PC-3 (IC$_{50}$ 12.57 ± 1.09 μg/mL). Furthermore, 2-phenylimino-thiazolidin-4-one derivatives 5b, 5c, and 5e showed equipotent anticancer activity against all cell lines with IC$_{50}$ values ranging from 11.80 to 19.07 μg/mL. In contrast, the investigated thiadiazole derivatives 9a–9c and 11a–11c showed considering activity against breast cancer cell lines as indicated by the MCF-7 profile (Table 1). Thiadiazole compounds 9c and 11c, in particular, demonstrated the most pronounced activity against the MCF-7 cell line when compared to 5-fluorouracil, with IC$_{50}$ values of 17.32 and 15.64 μg/mL, respectively.

The structure-activity relationship gave a clear picture of the activity of these title compounds. The addition of a substituent on the benzylidene moiety that is linked to the thiazolidine-4-one ring affects anticancer acidity. The presence of an electron-donating methoxy group

---

### Table 1. In vitro cytotoxic activity of the synthesized thiazole and thiadiazole compounds

| Compound | HepG2 ($\mu$g/mL) | MCF-7 ($\mu$g/mL) | HCT-116 ($\mu$g/mL) | PC-3 ($\mu$g/mL) |
|----------|-------------------|-------------------|---------------------|-----------------|
| 5-FU     | 7.91 ± 0.28       | 5.52 ± 0.21       | 5.23 ± 0.14         | 8.03 ± 0.25     |
| 3b       | 39.82 ± 1.35      | 37.54 ± 2.17      | 39.12 ± 1.32        | 59.09 ± 1.98    |
| 5a       | 29.50 ± 0.87      | 28.08 ± 1.30      | 31.84 ± 1.85        | 33.24 ± 1.69    |
| 5b       | 13.55 ± 1.60      | 14.69 ± 1.38      | 17.25 ± 1.07        | 16.15 ± 1.11    |
| 5c       | 12.71 ± 1.57      | 13.78 ± 1.31      | 16.90 ± 1.39        | 19.07 ± 1.96    |
| 5d       | 8.80 ± 0.31       | 7.22 ± 0.65       | 9.35 ± 0.61         | 12.57 ± 1.09    |
| 5e       | 13.34 ± 0.93      | 11.80 ± 0.90      | 15.07 ± 1.24        | 17.3 ± 1.27     |
| 6a       | 65.36 ± 2.94      | 75.24 ± 2.87      | 66.43 ± 2.31        | 71.71 ± 2.32    |
| 6b       | 63.03 ± 3.31      | 77.46 ± 3.22      | 68.96 ± 3.63        | 72.50 ± 3.26    |
| 9a       | 53.09 ± 2.20      | 37.47 ± 1.20      | 50.92 ± 2.66        | 52.43 ± 2.67    |
| 9b       | 62.34 ± 3.98      | 25.40 ± 1.24      | 55.49 ± 2.35        | 71.31 ± 3.33    |
| 9c       | 34.30 ± 1.82      | 15.64 ± 1.18      | 28.50 ± 1.41        | 27.50 ± 1.64    |
| 11a      | 73.07 ± 2.39      | 31.45 ± 2.05      | 80.94 ± 3.60        | 82.31 ± 2.69    |
| 11b      | 41.88 ± 1.31      | 27.50 ± 1.83      | 43.22 ± 1.35        | 47.96 ± 1.90    |
| 11c      | 31.66 ± 2.08      | 17.32 ± 1.25      | 32.87 ± 2.48        | 37.29 ± 2.61    |

*IC$_{50}$, µg/mL: 1–10 (very strong), 11–20 (strong), 21–50 (moderate), and 51–100 (weak). Values represent means ± SD of triplicates.*
Experimental

Gallenkamp electric apparatus is used to measure the melting points. Infrared spectra (IR) were recorded on a Thermo Scientific Nicolet iS10 FTIR spectrometer. The 1H NMR and 13C NMR spectra were recorded on a Bruker AV 400 MHz using DMSO-d6 as a solvent. The mass analyses were obtained by a Kratos MS equipment (EI mode at 70 eV). C, H, and N analyses were determined on Perkin-Elmer 2400 analyzer.

Preparation of N-(4-acetamidophenyl)-N′-phenylthiourea (2). Phenyl isothiocyanate (1.20 g, 10 mmol) was added to a hot stirred suspension of 4-aminobenzaldehyde (1.50 g, 10 mmol) in hot ethanol (20 mL). The mixture was refluxed for 10–15 min. The precipitated product was filtered and dried to afford the thiourea derivative 2. Gray crystals, yield 84%, mp 212–213°C, lit. mp 213°C [47].

Synthesis of 3-(4-acetamidophenyl)-2-phenylimino-thiazolidin-4-one (3b). A suspension of diaryl thiourea (1.71 g, 6 mmol), ethyl bromoacetate (0.99 g, 6 mmol), and fused sodium acetate (0.5 g) were added to a hot stirred suspension of 4-aminoacetanilide (1.50 g, 10 mmol) in hot ethanol (20 mL). The mixture was refluxed for 3 h. The solid that formed was collected, dried, and then subjected to recrystallization from 50 mL ice-cold water. The precipitate that formed was picked up by filtration and then subjected to recrystallization by heating in ethyl alcohol. Yellow crystals, yield 74%, mp 278–280°C. IR spectrum, ν, cm⁻¹: 3306 (N–H), 1715 (C=O), 1661 (C=O), 1632 (C=N). 1H NMR spectrum, δ, ppm: 2.05 s (3H, CH3), 2.34 s (3H, CH3), 6.92 d (2H, J = 8.40 Hz, HAr), 7.33 d (2H, J = 8.40 Hz, HAr), 7.47–7.59 m (9H, HAr), 7.77 s (1H, CH=C), 9.96 (s, 1H, CONH). 13C NMR spectrum, δ, ppm: 20.13, 24.35, 119.81 (2C), 119.87 (2C), 120.12, 121.36 (2C), 128.47 (2C), 129.08, 129.53 (2C), 129.95 (2C), 130.41, 130.63, 136.32, 139.52, 140.23, 142.97, 152.40, 163.74, 168.08. Found, %: C 70.12; H 4.98; N 9.90. C25H19N3O2S. Calculated, %: C 70.24; H 4.95; N 9.83. MS: m/z: 427 [M⁺].

SYNTHESIS AND ANTICANCER EVALUATION OF NEW THIAZOLE-2-phenylimino-thiazolidin-4-one (3a). Yellow crystals, yield 70%, mp 284–285°C. IR spectrum, ν, cm⁻¹: 3308 (N–H), 1714 (C=O), 1660 (C=O), 1632 (C=N). 1H NMR spectrum, δ, ppm: 2.06 s (3H, CH3), 3.79 s (3H, OCH3), 6.91 d (2H, J = 8.80 Hz, HAr), 7.08 d (2H, J = 8.80 Hz, HAr), 7.52–7.55 m (7H, HAr), 7.60 d (2H, J = 8.40 Hz, HAr), 7.76 s (1H, CH=C), 10.11 (s, 1H, CONH). 13C NMR spectrum, δ, ppm: 24.39, 55.47, 114.91 (2C), 117.94, 118.88 (2C), 120.01 (2C), 122.30 (2C), 125.73, 129.04 (2C), 129.79, 130.24, 132.15 (2C), 135.86, 138.66, 143.17, 152.58, 161.09, 163.61, 167.83. Found, %: C 67.86; H 4.82; N 9.55. C25H19N3O2S. Calculated, %: C 67.70; H 4.77; N 9.47. MS: m/z: 443 [M⁺].

SYNTHESIS AND ANTICANCER EVALUATION OF NEW THIAZOLE-2-phenylimino-thiazolidin-4-one (3b). A suspension of diaryl thiourea (1.71 g, 6 mmol), ethyl bromoacetate (0.99 g, 6 mmol), and fused sodium acetate (0.5 g) were added to a hot stirred suspension of 4-aminoacetanilide (1.50 g, 10 mmol) in hot ethanol (20 mL). The mixture was refluxed for 3 h. The solid that formed was collected, dried, and then subjected to recrystallization from 50 mL ice-cold water. The precipitate that formed was picked up by filtration and then subjected to recrystallization by heating in ethyl alcohol. Yellow crystals, yield 70%, mp 284–285°C. IR spectrum, ν, cm⁻¹: 3308 (N–H), 1714 (C=O), 1660 (C=O), 1632 (C=N). 1H NMR spectrum, δ, ppm: 2.06 s (3H, CH3), 3.79 s (3H, OCH3), 6.91 d (2H, J = 8.80 Hz, HAr), 7.08 d (2H, J = 8.80 Hz, HAr), 7.52–7.55 m (7H, HAr), 7.60 d (2H, J = 8.40 Hz, HAr), 7.76 s (1H, CH=C), 10.11 (s, 1H, CONH). 13C NMR spectrum, δ, ppm: 24.39, 55.47, 114.91 (2C), 117.94, 118.88 (2C), 120.01 (2C), 122.30 (2C), 125.73, 129.04 (2C), 129.79, 130.24, 132.15 (2C), 135.86, 138.66, 143.17, 152.58, 161.09, 163.61, 167.83. Found, %: C 67.86; H 4.82; N 9.55. C25H19N3O2S. Calculated, %: C 67.70; H 4.77; N 9.47. MS: m/z: 443 [M⁺].
C_{26}H_{23}N_{3}O_{4}S. Calculated, %: C 65.94; H 4.90; N 8.87. MS: \textit{m/z}: 473 \, [M^+]^*.

3-(4-Acetamidothiophenyl)-5-(4-nitrobenzylidene)-2-phenylimino-thiazolid-4-one (5d). Yellow crystals, yield 82%, mp 260–262°C. IR spectrum, ν, cm\(^{-1}\): 3322 (N–H), 1171, 1646 (C=O). \(^1\)H NMR spectrum, δ, ppm: 2.09 s (3H, CH\(_3\)), 6.92 d (2H, J = 8.40 Hz, H\(_{24}\)), 6.98 d (2H, J = 8.00 Hz, H\(_{25}\)), 7.20–7.80 m (7H, H\(_{22}\)), 7.93 s (1H, CH=CH), 8.31 d (2H, J = 8.4 Hz, H\(_{24}\)), 10.29 (s, 1H, CONH). \(^13\)C NMR spectrum, δ, ppm: 132.36, 134.44, 137.05, 139.53, 143.18, 149.87, 164.50, 164.80, 165.70, 166.71, 168.24. Found, %: C 62.71; H 3.90; N 12.32. C\(_{2140}\)H\(_{17}\)N\(_{3}\)O\(_{4}\). Calculated, %: C 62.87; H 3.96; N 12.22. MS: \textit{m/z}: 458 \, [M^+]^*.

Preparation of 3-(4-acetamidothiophenyl)-2-phenylimino-thiazole 6a and 6b. In a 50 mL RBF, aryl thiourea derivative 2 (1.42 g, 5 mmol) and each of the α-chloroketone (5 mmol) (chloroacetone and/or phenacyl chloride) were refluxed for 3 h in 25 mL of ethanol (HPLC), and 0.2 mL of triethylamine for 4–6 h. The precipitate that formed was isolated by filtration and recrystallized from EtOH/DMF mixture to yield the triazolyl thiadiazole compounds 9a–9c and 11a–11c, respectively.

N-(4-(4-Acetyl-1,3,4-thiadiazol-2(3H)-ylidene)amino)phenyl)acetamide (9a). Yellow powder, yield 77%, mp 248–250°C. IR spectrum, ν, cm\(^{-1}\): 3320 (N–H), 1670, 1654 (C=O). \(^1\)H NMR spectrum, δ, ppm: 2.15 s (3H, CH\(_3\)), 2.43 s (3H, CH\(_3\)), 2.45 s (3H, CH\(_3\)), 6.77 d (2H, J = 7.90 Hz, H\(_{22}\)), 7.12 d (2H, J = 8.40 Hz, H\(_{24}\)), 7.35–7.58 m (5H, H\(_{23}\)), 10.3 s (1H, CONH). \(^13\)C NMR spectrum, δ, ppm: 23.63, 25.12, 114.43, 114.92 (2C), 123.53 (2C), 125.30, 128.91 (2C), 129.65 (2C), 133.46, 134.72, 141.90, 150.76, 164.80, 165.03, 168.56. Found, %: C 66.28; H 4.15; N 11.93. C\(_{2140}\)H\(_{17}\)N\(_{3}\)O\(_{4}\). Calculated, %: C 66.85; H 4.30; N 11.93. MS: \textit{m/z}: 589 \, [M^+]^*.

N-(4-(4-Acetyl-1,3,4-thiadiazol-2(3H)-ylidene)amino)phenyl)acetamide (9b). Yellow powder, yield 74%, mp 238–240°C. IR spectrum, ν, cm\(^{-1}\): 3290 (N–H), 1665, 1657 (C=O). \(^1\)H NMR spectrum, δ, ppm: 2.03 s (3H, CH\(_3\)), 2.38 s (3H, CH\(_3\)), 2.45 s (3H, CH\(_3\)), 6.70 d (2H, J = 8.00 Hz, H\(_{22}\)), 6.91 d (2H, J = 7.60 Hz, H\(_{24}\)), 7.38–7.53 m (4H, H\(_{24}\)), 10.12 s (1H, CONH). \(^13\)C NMR spectrum, δ, ppm: 23.81, 24.52, 26.12, 114.51, 114.83 (2C), 122.62 (2C), 124.77, 128.65 (2C), 129.34 (2C), 131.25, 133.70, 143.93, 147.35, 158.87, 162.94. Found, %: C 62.41; H 5.03; N 15.38. C\(_{19}\)H\(_{15}\)N\(_{3}\)O\(_{2}\). Calculated, %: C 62.28; H 4.95; N 15.29. MS: \textit{m/z}: 366 \, [M^+]^*.
N-(4-((5-Acetyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)amino)phenyl)-acetamide (9c).

Yellow powder, yield 69%, mp 259–270°C. IR spectrum, ν, cm⁻¹: 3370 (N–H), 1671, 1648 (C=O). ¹H NMR spectrum, δ, ppm: 2.07 s (3H, CH₃), 2.46 s (3H, CH₃), 6.79 d (2H, J = 8.80 Hz, Hₐ), 7.23 d (2H, J = 8.80 Hz, Hₐ), 7.55–7.78 m (4H, Hₐ), 10.15 (s, 1H, NH). ¹³C NMR spectrum, δ, ppm: 23.94, 26.33, 114.11, 115.30 (2C), 8.80 Hz, H. Brown powder, yield 74%, mp 266–268°C. IR spectrum, ν, cm⁻¹: 3365 (N–H), 1737, 1657 (C=O).

Ethyl 5-((4-acetamidophenyl)imino)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (11a).

Brown powder, yield 70%, mp 284–286°C. IR spectrum, ν, cm⁻¹: 3369 (N–H), 1739, 1665 (C=O). ¹H NMR spectrum, δ, ppm: 1.27 s (3H, CH₃), 2.09 s (3H, CH₃), 2.39 s (3H, CH₃), 4.18 s (2H, OCH₂), 6.93 d (2H, J = 8.80 Hz, Hₐ), 7.38 d (2H, J = 8.90 Hz, Hₐ), 7.56–7.78 m (4H, Hₐ), 10.01 s (1H, NH). ¹³C NMR spectrum, δ, ppm: 14.92, 24.35, 61.82, 114.30 (2C), 122.34 (2C), 123.66, 125.81, 129.10 (2C), 132.24, 139.15, 144.64, 152.61, 162.77, 169.85. Found, %: C 54.56; H 4.18; N 13.35. C18H17ClN3O3S. Calculated, %: C 54.74; H 4.11; N 13.44. MS: m/z: 416 [M]+.

**Cytotoxicity assay.** Using the MTT assay, the above-mentioned cell line was used to determine the inhibitory effects of the thiazole and thiadiazole compounds on cell growth [52,53]. This colorimetric test relies on mitochondrial succinate dehydrogenase in practical cells to convert the yellow 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) to a purple formazan derivative. Hep2 was cultivated in RPMI-1640 medium containing 10% fetal bovine serum. At 37°C in a 5% CO₂ incubator, anti-toxins included 100 units/mL penicillin and 100 μg/mL streptomycin. The cell line was seeded in a 96-well plate at a density of 1 × 10⁴ cells/well [54] for 48 h at 37°C in a 5 percent CO₂ environment. The cells were incubated for 24 h after being treated with different concentrations of compounds. Following 24 h of medication treatment, 20 μL of 5 mg/mL MTT solution was added and incubated for 4 h. To dissolve the purple formazan formed, 100 μL of dimethyl sulfoxide (DMSO) is added to each well. The colorimetric test is measured and recorded at 570 nm absorbance using a plate reader (EXL 800) from the United States. The relative cell viability was calculated as (A570 of treated samples/ A570 of untreated samples) × 100.

**CONCLUSIONS**

Treatment of 2-iminothiazolidine-4-one compound 3b with some aromatic aldehydes affords 5-arylidene-2-phenyliminothiazolidin-4-one derivatives 5a–5e. Thiazole derivatives 6a and 6b were synthesized upon cyclizing N-(4-acetamidophenyl)-N'-phenylthiourea (2) with chloroacetone and/or phenacyl chloride. A new series of 5-substitutedthiadiazole scaffolds, 9a–9c and 11a–11c were synthesized via intramolecular cyclization of thiourea derivative 2 with the appropriate hydrazonoyl halides 7a–c and 10a–c in ethanol containing an amount of triethylamine. The synthesized thiazole and thiadiazole compounds exhibited moderate to strong cytotoxic effects on four human cancer cell lines (HepG2, MCF-7, HTC-116, and PC-3). The best activity was obtained with compound 5d against hepatocellular carcinoma (IC₅₀ 8.80 ± 0.31 μg/mL), mammary gland breast cancer (IC₅₀ 7.22 ± 0.31 μg/mL), and colorectal carcinoma (IC₅₀ 9.35 ± 0.61 μg/mL) cell lines compared with the reference drug (5-fluorouracil).
ACKNOWLEDGMENTS

The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number “IF_2020_NBU_234.”

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Khasawneh, M.A., AlKaabi, A., Samadi, A., Antony, P., Vijayan, R., Al-Keridis, L.A., Saadeh, H.A., and Abutah, N., Arab. J. Chem., 2022, vol. 15, no. 7, p. 103905. https://doi.org/10.1016/j.arabjc.2022.103905

2. Kondo, H., Koshizuka, T., Majima, R., Takahashi, K., Ishioka, K., Suzutani, K., and Inoue, N., Antivir. Res., 2021, vol. 196, p. 105207. https://doi.org/10.1016/j.antiviral.2021.105207

3. Ray, U., John, F., Pooppadi, S., George, J., Sma, S., and Raghavan, S.C., J. Heterocycl. Chem., 2021, vol. 58, no. 1, p. 40. https://doi.org/10.1002/jhet.4145

4. Abbas, S.Y., El-Sief, M.A.M.Sh., Basyouni, W.M., Fakhr, I.M.I., and El-Gammal, E.W., Eur. J. Med. Chem., 2013, vol. 64, p. 111. https://doi.org/10.1016/j.ejmech.2013.04.002

5. Al-Harbi, R.A., El-Sharief, M.A.S., and Abbas, S.Y., Bioorg. Chem., 2019, vol. 90, p. 103088. https://doi.org/10.1016/j.bioorg.2019.103088

6. Nirwan, S., Chahal, V., and Kakkar, R., J. Heterocycl. Chem., 2019, vol. 56, no. 4, p. 1239. https://doi.org/10.1002/jhet.3514

7. Abdellatif, K.R., Abdelgawad, M.A., Elshemy, H.A., and Alsayed, S.S., Bioorg. Chem., 2016, vol. 64, p. 1. https://doi.org/10.1016/j.bioorg.2015.11.001

8. Aqlan, F.M., Al-Bogami, A.S., Alqahtani, N.F., Wani, M.Y., and Khan, S.A., J. Mol. Struct., 2022, vol. 1250, no. 2, p. 131771. https://doi.org/10.1016/j.molstruc.2021.131771

9. Chulovska, Z., Chaban, T., Drapak, I., Matiychuk, V., Chaban, I., and Nektagaev, I., Biointerface Res. Appl. Chem., 2021, vol. 11, no. 1, p. 8009. https://doi.org/10.33263/BRIAC111.80098017

10. Mandal, M.K., Ghosh, S., Naesens, L., RajBhat, H., and Singh, U.P., Bioorg. Chem., 2021, vol. 114, p. 105153. https://doi.org/10.1016/j.bioorg.2021.105153

11. Gummidi, L., Kerru, N., Ebenezer, O., Awolade, P., Sanni, O., Islam, Md. S., and Singh, P., Bioorg. Chem., 2021, vol. 115, p. 105210. https://doi.org/10.1016/j.bioorg.2021.105210

12. Vaarla, K., Vishwapathi, V., Vermeire, K., Vedula, R.R., and Kulkarni, C.V., J. Mol. Struct., 2022, vol. 1249, p. 131662. https://doi.org/10.1016/j.molstruc.2021.131662

13. Trotsko, N., Eur. J. Med. Chem., 2021, vol. 215, p. 113266. https://doi.org/10.1016/j.ejmech.2021.113266

14. Jain, S., Kumar, A., and Saini, D., Exp. Parasitol., 2018, vol. 185, p. 107. https://doi.org/10.1016/j.exppara.2018.01.015

15. Omar, Y.M., Abdel-Moty, S.G., and Abu-Allah, H.H.M., Bioorg. Chem., 2020, vol. 97, p. 103657. https://doi.org/10.1016/j.bioorg.2020.103657

16. Bielenica, A., Szulczyk, D., Olejarz, W., Maddedu, S., Giliberti, G., Materek, I.B., Koziol, A.E., and Struga, M., Biomed. Pharmacother., 2017, vol. 94, p. 804. https://doi.org/10.1016/j.biopha.2017.07.152

17. Djukica, M., Fresatidoub, M., Xenikakisb, I., Geronicakib, A., Angelovac, V.T., Savicd, V., Pasica, M., Krilovicab, B., Djukice, D., Gobeljicab, Pavlicab, M., Djuricab, A., Stanojevicd, I., Vojvodicf, D., and Sasogf, L., Chem. Biol. Interact., 2018, vol. 286, p. 119. https://doi.org/10.1016/j.cbi.2018.03.013

18. Rahim, F., Zaman, K., Ullah, H., Taha, M., Wadooda, A., Javed, M.T., Rehman, W., Ashraf, M., Uddin, R., Uddin, I., Asg, H., Khan A.A., and Khan, K.M., Bioorg. Chem., 2015, vol. 63, p. 123. https://doi.org/10.1016/j.biocbi.2015.10.005

19. Abumelha, H.M.A., and Saeed, A., J. Heterocycl. Chem., 2020, vol. 57, p. 1816. https://doi.org/10.1002/jhet.3906

20. Kryshchyshyn-Dylevych, A., Radko, L., Feniuk, N., Garazd, M., Kashchak, N., Posyniak, A., Niemczuk, K., Stoika, R., Lesyk, R., Bioorg. Chem., 2021, vol. 50, no.15, p. 116453. https://doi.org/10.1016/j.bmc.2021.116453

21. Appalanaidu, K., Kotcherlakota, R., Dadmal, T.L., Bollu, V.S., Kumbe, R.M., and Patra, C.R., Bioorg. Med. Chem. Lett., 2016, vol. 26, p. 5361. https://doi.org/10.1016/j.bmcl.2016.08.013
SYNTHESIS AND ANTICANCER EVALUATION OF NEW THIAZOLE

2143

22. Kumar, K.S.S., Hanumappa, A., Vetrivel, M., Hegde, M., Girish, Y.R., Byregowda, T.R., Rao, S., Raghavan, S.C., and Rangappa, K.S., *Bioorg. Med. Chem. Lett.*, 2015, vol. 25, p. 3616. https://doi.org/10.1016/j.bmcl.2015.06.069

23. Makkhot, Y.N., Khaleed, J.M.A., Alharbi, N.S.H.A., Mohammed, F.A.N., Almekhlafi, F.A., Abutaha, N.M., Kheder, N., Asiri, Y.I., Bin Muhsinah, A., and Alsaryari, A., *Polycycl. Aromat. Compd.*, 2022. https://doi.org/10.1080/10406638.2021.1984952

24. Modrić, M., Božičević, M., Faraho, I., Bosnar, M., and Škorić, I., *J. Mol. Struct.*, 2021, vol. 1239, p. 130526. https://doi.org/10.1016/j.molstruc.2021.130526

25. Kumara, G. and Singh, N.P., *Bioorg. Chem.*, 2021, vol. 107, p. 104608. https://doi.org/10.1016/j.bioorg.2020.104608

26. Pember, S.O., Mejia, G.L., Price, T.J., and Pasteris, R.J., *Bioorg. Med. Chem. Lett.*, 2016, vol. 26, p. 2965. https://doi.org/10.1016/j.bmcl.2016.02.061

27. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

28. Sabt, A., Abdelrahman, M.T., Abdelraof, M., and Rashdan, H.R.M., *ChemistrySelect*, 2022, vol. 7, no. 17, p. e202200691. https://doi.org/10.1002/slct.202200691

29. Luszczki, J.J., Karpinski, M., Matysiaik, J., and Niewiadomy, A., *Pharmacol. Rep.*, 2015, vol. 67, no. 3, p. 588. https://doi.org/10.1016/j.pharep.2014.12.008

30. Rashdan, H.R.M., Abdelmonsef, A.H., Abou-Krish, M.M., and Yousef, T.A., *Bioorg. Med. Chem. Lett.*, 2022, vol. 32, no. 6, p. 108557. https://doi.org/10.1016/j.bmcl.2022.108557

31. Shehadi, I.A., Abdelrahman, M.T., Abdelraof, M., and Rashdan, H.R.M., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

32. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

33. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

34. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

35. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

36. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

37. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

38. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

39. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

40. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

41. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

42. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

43. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

44. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

45. Rashdan, H.R.M., Shehadi, I.A., Abdelrahman, M.T., and Hemdan, B.A., *Molecules*, 2021, vol. 26, no. 16, p. 4817. https://doi.org/10.3390/molecules26164817

RUSSIAN JOURNAL OF GENERAL CHEMISTRY Vol. 92 No. 10 2022
46. Matysiak, J. and Opolski, A., *Bioorg. Med. Chem.*, 2006, vol. 14, p. 4483.
   https://doi.org/10.1016/j.bmc.2006.02.027
47. Tiwari, S.S. and Swaroop, A., *J. Indian Chem. Soc.*, 1961, vol. 38, p. 245.
48. Lagergren, P., Schandl, A., Aaronson, N.K., Adami, H.O.,
   Lorenzo, F., Denis, L., Faithfull, S., Liu, L., Meunier, F.,
   and Ulrich, C., *Mol. Oncol.*, 2018, vol. 13, no. 3, p. 624.
   https://doi.org/10.1002/1878-0261.12428
49. Bhat, M., Poojary, B., Kalal, B.S., Swamy, P.M.G.,
   Kabilan, S., Kumar, V., Shruthi, N., Anand, S.A.A., and
   Pai, V.R., *Future Med. Chem.* 2018, vol. 10, no. 9, p. 1017.
   https://doi.org/10.4155/fmc-2017-0191
50. Beretta, G.L., Cassinelli, G., Pennati, M., Zuco, V., and
   Gatti, L., *Eur. J. Med. Chem.*, 2017, vol. 142, p. 271.
   https://doi.org/10.1016/j.ejmech.2017.07.062
51. Zwick, E., Bange, J. and Ullrich, A., *Endocr. Relat. Cancer*, 2001, vol. 8, p. 161.
52. Mosmann, T., *J. Immunol. Methods*. 1983, vol. 65, p. 55.
   https://doi.org/10.1016/0022-1759(83)90303-4
53. Denizot, F., and Lang, R., *J. Immunol. Methods*, 1986, vol. 89, p. 271.
   https://doi.org/10.1016/0022-1759(86)90368-6
54. Weichselbaum, R.R., Mauceri, H.J., Hanna, N.N.,
   Beckett, M.A., Gorski, D.H., Staba, M.-J., Stellato, K.A.,
   Bigelow, K., Heimann, R., Gately, S., Dhanabal, M.,
   Soff, G.A., Sukhatme, V.P., and Kufe, D.W., *Nature*,
   1998, vol. 394, p. 287.
   https://doi.org/10.1038/28412