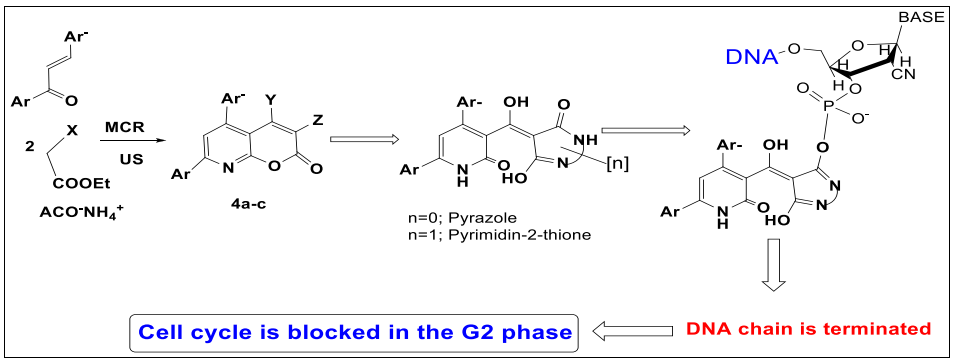
A Facile One-pot Synthesis and Anticancer Evaluation of Interesting Pyrazole and Pyrimidinthione *via* Heterocyclic Interconversion

Sameh A. Rizk* and Safa Shaban

Chemistry Department, Faculty of Science, Ain Shams University, Cairo 11566, Egypt
*E-mail: samehrizk2006@gmail.com; samehrizk@sci.asu.edu.eg

Received November 9, 2018
DOI 10.1002/jhet.3625
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



Design and synthesis of new pyrazole, pyrimidinthione, and triazepinthione derivatives *via* heterocyclic ring opening of azacoumarin were promoted with grinding and ultrasonic reaction conditions. Efficient solventless one-pot synthesis can be well progressed to afford the good yield of new heterocyclic products that were characterized by IR, ^{1}H-NMR, MS, and microanalytical data. Anticancer evaluation for the synthesized compounds exhibited moderate to good cytotoxicity such as pyrazole derivatives **5**, **9**, and **14** that displayed best cytotoxic activities with IC_{50} 8.16 ± 1.1, 7.02 ± 0.6, and 5.12 ± 0.41 µg/mL and 9.28 ± 0.7, 6.45 ± 0.9, and 5.85 ± 0.26 µg/mL for MCF-7 and WI cells, respectively. Pyrimidine derivatives **6**, **11**, and **15** exhibited strong cytotoxicity with IC_{50} 8.9 ± 0.62, 7.16 ± 0.5, and 7.72 ± 0.41 µg/mL against MCF-7.

INTRODUCTION

Many heterocyclic compounds encircling pyridine, pyrazole, and pyrimidine rings are correlated with diverse pharmacological belongings. These classes of heterocyclic compounds have synchronized the cardiovascular system and antimicrobial [1–3], anticancer [4], anticonvulsant [5], antiviral [6–8], anti-human immunodeficiency virus [9], antifungal [10], and anti-leishmanial [11] activities. Pyrano[2,3-*b*]-pyridine (8-azacoumarin) structure is considered a key starting material for many heterocyclic compounds and screening a broad spectrum of biological activity [12]. Also, 8-azacoumarin system is significant because of numerous biological activities associated with this scaffold. Some analogues have been associated with scaffold antitumor *via* stopping the dihydrofolate reductases or tyrosine kinases [13,14], while others are known antiviral agents [15]. This prompted us a specific simple synthesis aiming to construct some new pyridine flattened with pyrazole or pyrimidine thione derivatives in a single molecular framework as a unique key precursor designing new, potent, selective agent appear to be promising for anticancer evaluation.

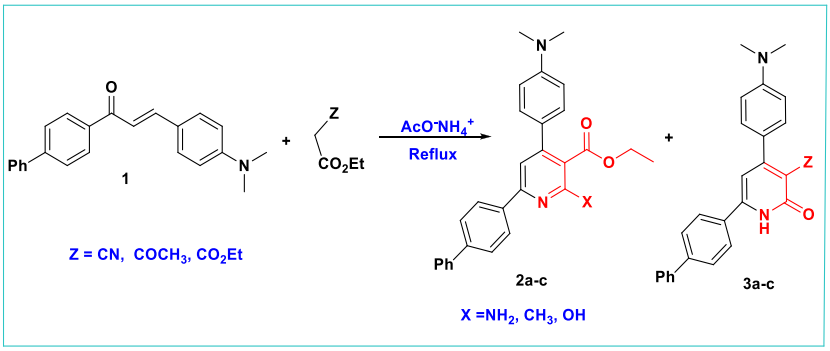
RESULTS AND DISCUSSION

Chemistry. It was previously reported that the thermal and microwave reflux of chalcone **1** with diversity of active methylene, for instance, ethyl cyanoacetate, ethyl acetoacetate, and diethyl malonate with ammonium acetate, produced the pyridine esters **2a–c** and 2-pyridone derivatives **3a–c** in good yield that were outlined in Scheme 1 [16–21].

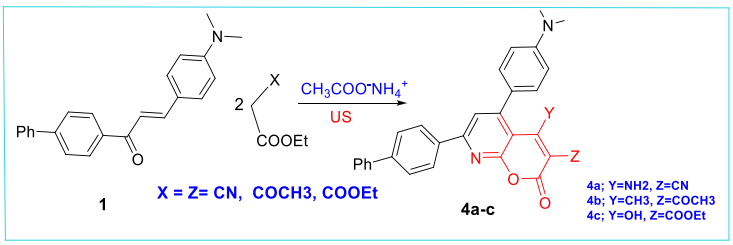
Moreover, the authors reported the reaction of chalcone **1** and ethyl cyanoacetate in the presence of ammonium acetate in a multicomponent reaction (MCR) by mechano-grindstone all together or by sonication using tetrahydrofuran for 25–30 min to afford crude yellow solid products (**4a–c**) (Scheme 2) [22–24].

The IR spectrum of compound **4a** reveals stretching absorption bands at 3434 and 3329 cm^{-1} attributed to asymmetric and symmetric NH_2, respectively, 2223 cm^{-1} for CN group, and 1732 cm^{-1} for C=O group of the coumarin ring that assigned structure to this compound. The ^{1}H-NMR spectrum of compound **4a** shows δ 6.80 ppm corresponding to H3 in pyridine nucleus and broad singlet at δ 5.43 ppm corresponding to the NH_2 protons with the absence of any band at 9.8

Scheme 1. Conventional thermal and microwave promoted the pyridine derivatives **2** and **3**. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 2. Reaction under ultrasonic condition. [Color figure can be viewed at wileyonlinelibrary.com]



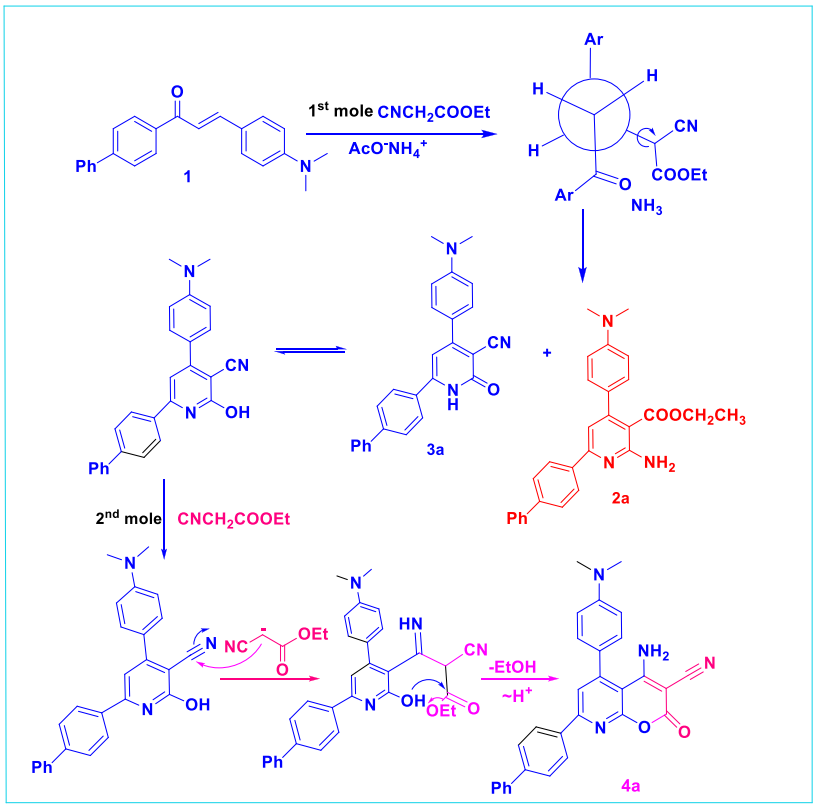
corresponding to NH of pyridine **3** are good evidence in formation of compound **4a**. So the ultrasonic irradiation caused the isomerization of the 2-pyridone **3** to the reactive lactim intermediate, which reacts with another ethyl cyanoacetate affording the pyrano[2,3-*b*]pyridine derivatives **4a–c** as sole products (Scheme 3).

Reaction of azacoumarin **4a** with various nitrogen precursors such as hydrazine hydrate, thiourea, ethylglycinate, and thiosemicarbazide yielded interesting incorporating heterocyclic compounds that have classy anticancer activity. Reaction of cyano azacoumarin **4a** with hydrazine hydrate, thiourea, ethylglycinate, and thiosemicarbazide afforded pyrazole **5**, pyrimidinthione **6**, diazepinone **7**, and triazepinthione **8** derivatives, respectively (Scheme 4). IR spectra will be considered good spectroscopic characterization to investigate the heterocyclic products. The reaction was processed *via* ring opening followed by ring closure and formation of heterocyclic compounds involving geometrical isomerization due to formation of intramolecular hydrogen bond in the heterocyclic products. The IR spectra of compounds **5**, **6**, **7**, and **8** reveal absorption broad bands at 3347–3179 cm^{-1} attributed to NH_2 asymmetric and symmetric stretching frequency and at 1670–1652 cm^{-1} corresponding to stretching frequency of carbonyl of the amide groups in pyridone, pyrazolone, pyrimidone, and triazepinone rings, respectively. The ^{1}H-NMR spectra of compounds **5**, **6**, **7**, and **8** display H3 of pyridone protons at δ 6.80–6.77 ppm, and NH_2 protons are detected at δ 4.22–4.16 ppm for two types of protons of two different amino groups and at δ 9.80 ppm as a singlet corresponding to NH proton.

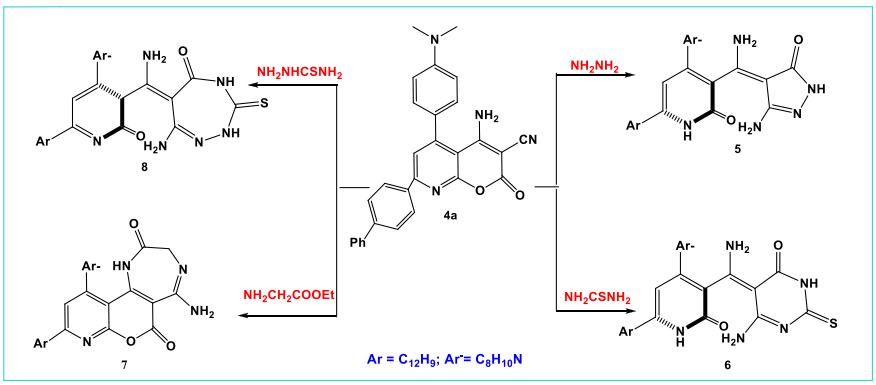
The authors would think that the heterocyclic interconverted compounds **5**, **6**, and **8** become more stable when they dehydrated to afford the 1,8-naphthyridine derivatives *via* intramolecular reaction of the amino group with carbonyl in the pyridone moiety (Scheme 4). The optimization of the heterocyclic compounds is designed as minimized energetic geometrical structures of the synthesized compounds **5**, **6**, and **8** (Fig. 1). The electronic structures of compounds **5**, **6**, and **8** revealed entirely spread over all molecular structure and confirmed these energetic structures of synthesized compounds. Frontier molecular orbitals have the highest occupied molecular orbital and the lowest unoccupied molecular orbital [25–31].

Similarly, reaction of acetylazacoumarin **4b** with hydrazine hydrate, aniline, thiourea, ethylglycinate, and thiosemicarbazide afforded pyrazole **9**, arylidene **10**, pyrimidinthione **11**, ester **12**, and triazepinthione **13**

Scheme 3. The proposal mechanistic equations of the chalcone with ethyl cyanoacetate in the presence of ammonium acetate under ultrasonic reaction conditions. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 4. Reaction of azacoumarin **4a** with different nitrogen nucleophiles under conventional thermal condition. [Color figure can be viewed at wileyonlinelibrary.com]



derivatives, respectively (Scheme 5). IR spectra will be considered good spectroscopic characterization to investigate the heterocyclic products. The reaction was processed *via* ring opening followed by ring closure and formation of heterocyclic compounds involving lactam–lactim dynamic equilibrium due to formation of intramolecular hydrogen bond in the heterocyclic products **9**, **11**, and **13**. The appearance of broad bands at 3347–3179 attributed to NH_2 asymmetric and symmetric peaks and 1668–1652 for carbonyl of amide groups in pyrazole, pyrimidine, and triazepine moieties and devoid any band at 2223 for cyano group in the IR spectra of **9**, **10**, **11**, **12**, and **13** are respectable confirmation for the assigned structures of these compounds. ^{1}H-NMR spectrum of compound **9** exhibits signal at δ 6.80 ppm for pyridine proton and 7.22 ppm for broad singlet for

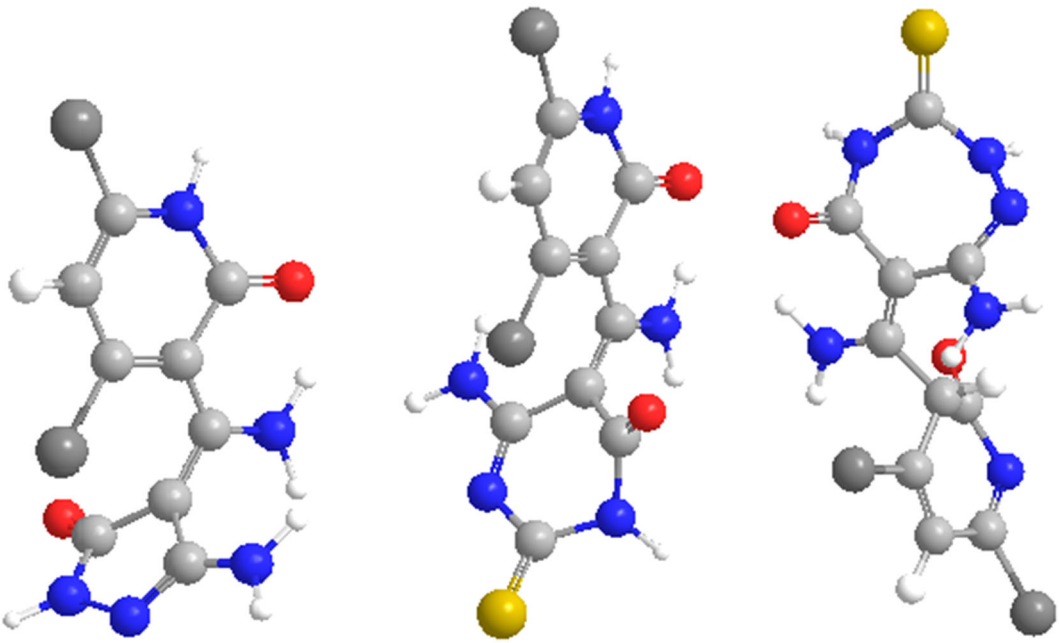
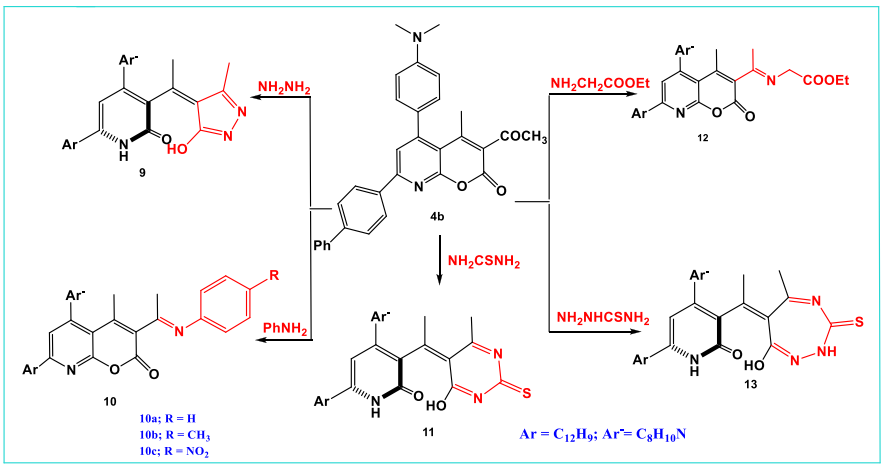


Figure 1. Outline of the optimized structures of compounds **5**, **6**, and **8**. [Color figure can be viewed at wileyonlinelibrary.com]

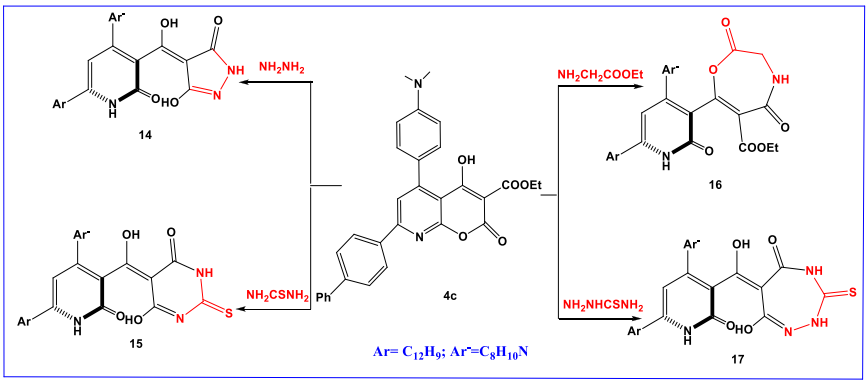
Scheme 5. Reaction of azacoumarin **4b** with different nitrogen nucleophiles under conventional thermal condition. [Color figure can be viewed at wileyonlinelibrary.com]



acidic OH proton and signal at δ 9.80 ppm for singlet NH proton.

Moreover, the behavior of azacoumarin ester **4c** with hydrazine hydrate, thiourea, ethylglycinate, and thiosemicarbazide afforded pyrazole **14**, pyrimidinthione **15**, 1,4-oxazepindione ester **16**, and triazepinthione **17** derivatives, respectively (Scheme 6). IR spectra will be considered good spectroscopic characterization to investigate the heterocyclic products. The reaction was processed *via* ring opening followed by ring closure and formation of heterocyclic compounds involving tautomerization due to formation of intramolecular hydrogen bond in the heterocyclic products **14**, **15**, and **17**. The appearance of broad bands at 3347–3179 attributed to NH_2 asymmetric and symmetric stretching frequency in the IR spectra of **14**, **15**, and **17** confirmed the assigned structure of these compounds. Disappearance of two stretching frequencies of carbonyl of ester and pyrone at 1745 and 1735 cm^{-1} band is due to the absence of the 2CO of ester and lactone groups, and appearance carbonyl of amide group at 1652 cm^{-1} in pyrazole, pyrimidine, and triazepine rings, respectively. ^{1}H-NMR spectrum of compound **15** shows definite singlet bands at δ 6.84, 5.32, 8.12, and 9.82 for pyridine

Scheme 6. Reaction of azacoumarin **4c** with different nitrogen nucleophiles under conventional thermal condition. [Color figure can be viewed at wileyonlinelibrary.com]



proton, the 2OH protons, and NH acidic proton, respectively.

Biological activity. ***Antitumor assay in vitro Ehrlich ascites.*** The authors evaluated the cytotoxicity result (IC_{50}) at 50 µg/mL [29,31,32] of synthesized compounds listed in Table 1 against mammary gland breast MCF-7 and human lung fibroblast WI-38 tumors. Antitumor activity was detected by all synthesized compounds that ranged from very strong to non-cytotoxic. Enhanced the tumor activity MCF-7 and WI cells for pyrazole derivatives **5**, **9**, and **14** at IC_{50} 8.16 ± 1.1, 7.02 ± 0.6, and 5.12 ± 0.41 µg/mL and 9.28 ± 0.7, 6.45 ± 0.9, and 5.85 ± 0.26 µg/mL, respectively. In addition, pyrimidin-2-thione derivatives **6**, **11**, and **15** for MCF-7 and WI cells have better IC_{50} at 8.9 ± 0.62, 7.16 ± 0.5, and 7.72 ± 0.41 µg/mL and 7.8 ± 0.23, 8.48 ± 1.2, and 5.6 ± 0.22 µg/mL, respectively.

Table 1

Cytotoxic activity of some compounds against cancer cell line.

No.	Compound	*In vitro* cytotoxicity IC_{50} (μM)[a]	
		MCF-7	WI-38
1	5-Flourouracil	6.23 ± 0.2	7.65 ± 0.5
2	**1**	36.28 ± 1.7	55.11 ± 1.9
3	**4a**	23.79 ± 1.9	40.36 ± 4.0
4	**4b**	22.37 ± 3.0	38.01 ± 3.2
5	**4c**	20.83 ± 1.3	36.46 ± 2.5
6	**5**	8.16 ± 1.1	9.28 ± 0.7
7	**6**	8.9 ± 0.62	7.8 ± 0.23
8	**7**	38.91 ± 2.8	32.79 ± 2.3
9	**8**	31.85 ± 2.5	59.37 ± 3.9
10	**9**	7.02 ± 0.6	6.45 ± 0.9
11	**10**	18.97 ± 0.9	27.23 ± 1.6
12	**11**	7.16 ± 0.5	8.48 ± 1.2
13	**12**	17.72 ± 4.6	20.42 ± 1.8
14	**13**	19.83 ± 3.2	25.12 ± 2.7
15	**14**	5.12 ± 0.41	5.85 ± 0.26
16	**15**	7.72 ± 0.41	5.60 ± 0.22
17	**16**	19.83 ± 3.2	25.12 ± 2.7
18	**17**	22.12 ± 2.1	38.85 ± 3.6

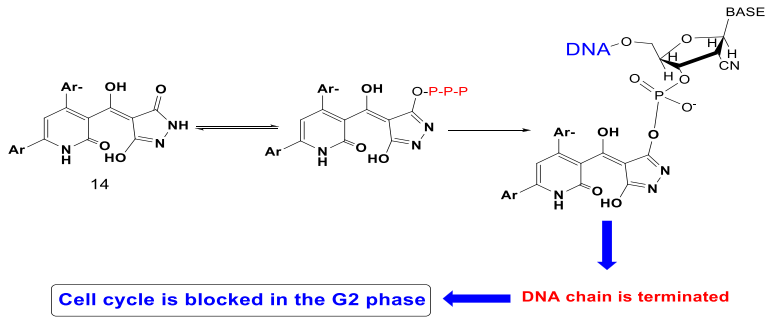
[a]IC_{50} (μM): 1–10 (very strong), 11–20 (strong), 21–50 (moderate activity), 51–100 (weak), and above 100 (non-cytotoxic).

The newly prepared compounds conserved MCF-7 and WI-38 cells and their cytotoxic needful dose controls more than 50% of the cell death. So they showed a variation in inhibition of cell growth with changed their concentration. Compounds **5**, **6**, **9**, **11**, **14**, and **15** exhibited promising activity than compounds **10**, **13**, and **16** toward MCF-7. 8-Azacoumarins **4a**, **4b**, and **4c** displayed moderate IC_{50} against MCF-7 cancer cell line related to DOX.

Structure–activity relationship. Nitrogen bases of DNA (chemical building blocks, adenine, guanine, cytosine, and thymine) were structured from pyrimidine nucleus. The cytotoxicity of pyrimidine toward different cell lines depends on intermolecular hydrogen bond with nucleotides and positive charge on prepared drug compacted with negative charge on the cell wall. Experimental cytotoxicity of the prepared compounds was matching with their structures. Compounds such as **5**, **6**, **9**, **11**, **14**, and **15** exhibited potent activity because of incorporation of the pyrazole, pyrimidin-2-thione, and 1,2,4-triazepinthione to 2-pyridone. OH and NH groups, which may be formed through hydrogen bonding with one of the nucleotides of the DNA and enable the elimination of an oxygen from the phosphate group producing damage to the DNA (Scheme 7) *via* lack of hydroxyl, prohibited repair and control of the tumor cells.

Moreover, the pyrazole derivatives **5**, **9**, and **14** have controlled growth of pieces of tumors through their combination with triphosphate, and extension during replication leads to lesions and disruptions on DNA strands (Scheme 7) [20–32]. The same mechanism occurred in the 2-pyrimidinthione derivatives **6**, **11**, and **15**, same with compounds **5**, **6**, **9**, **11**, **15**, and **16**. Combination of 1,2,4-triazepinthione with sp^2 carbon-

Scheme 7. Mechanism of the antitumor action of compound **14**. [Color figure can be viewed at wileyonlinelibrary.com]



bearing hydrophobic 2-pyridone moiety in compounds **8**, **13**, and **17** would demonstrate cytotoxic activities toward the two surveyed tumor cells.

EXPERIMENTAL

Melting points are uncorrected and measured in open-glass capillaries. FT-IR Shimadzu 8400S Spectrophotometer (New York, NY, USA) in KBr pellets was used to chart IR spectra (υ_{max}, cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were registered on 300 spectrophotometer (Rheinstetten, Germany), 300 and 125 MHz, respectively, in DMSO-d_6 solvents and TMS as internal standard. Shimadzu GCMS-QP-1000 EX mass spectrometer (Shimadzu Corp., Kyoto, Japan) was used to measure the mass spectra *via* EI technique (70 eV). CHN automatic analyzer was used in elemental analyses and measured at Central Security Forces, Cairo, Egypt. Sonication (Toshcon model SW 4 cleaner, 37 kHz, 150 W) achieved the synthesized compounds. Check the purity of synthesized compounds with thin-layer chromatography (TLC). All chemical reagents and solvents were achieved from Alibaba Fine Chemical Company (New Delhi, India) without further purification.

1-([1,1-Biphenyl]-4-yl)-3-(4-(dimethylamino)phenyl)prop-2-en-1-one (1). Grind a mixture of 4-acetylbiphenyl (0.01 mol, 1.96 g), 4-dimethylamino benzaldehyde (0.01 mol, 1.49 g), and 2 g of KOH and mix with a few drops of water for 20 min until the colorless reaction mixture turned light yellow. Then 50 mL of water added to the reaction mixture, the solid that separated was filtered, dried, and crystallized from ethanol as light yellow crystals. Yield 98%, mp 88–90°C. IR (KBr) υ_{max} (cm^{-1}): 1679 (C=O), 1600 (C=C). ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.99 (s, 6H, $-N(CH_3)_2$), 6.8–8.02 (m, 13H, Ar–H; biphenyl and phenyl groups), 7.82 (dd, 1H, H–C=, J = 16.2 Hz), 8.02 (dd, 1H, H–C=, J = 16.2 Hz). ^{13}C-NMR (DMSO): 41.9, 111.3, 121.5, 128.1, 129.4, 130.1, 136.6, 140.9, 145.3, 146.4, 150.5, 188.9. MS *m/z* (% abundance): 327 $[M]^+$ (100%), 329 $[M + 2]^+$ (3.3%). *Anal.* for $C_{23}H_{21}NO$ (327). Cal: C, 84.37; H, 6.46; N, 4.28. Found: C, 84.23; H, 6.24; N, 4.12.

General procedure for synthesis of azacoumarin (pyrano[2,3-*b*]pyridine derivatives 4a–c). ***Method (i).*** Sonicate a mixture of chalcone **1** (1 mmol), ethyl cyanoacetate, ethyl acetoacetate or diethyl malonate (1 mmol), and ammonium acetate (0.04 mol) together in a mortar and then transfer into 10 mL of ethanol in round-bottom flask located in an ultrasonic cleaning bath with E_{max} measured at 30°C. Reaction progress sustained until the reactants disappeared by TLC. Irradiation at 20–25 min afforded yellow solid product, decanted with crushed ice, dried, and recrystallized.

Method (ii). Grind a mixture of chalcone (1 mmol), ethyl cyanoacetate, ethyl acetoacetate or diethylmalonate (1 mmol), and ammonium acetate (0.04 mol) together in an agate mortar and pestle checked by TLC for 25–30 min until the color of reaction mixture turned into yellow, left overnight, and was recrystallized from ethanol.

7-([1,1-Biphenyl]-4-yl)-4-amino-5-(4-(dimethylamino) phenyl)-2-oxo-2*H*-pyrano[2,3-*b*]pyridine-3-carbonitrile (4a). Yield 82%, mp 112–114°C. IR (KBr) υ_{max} (cm^{-1}): 3438, 3329 (asymmetric and symmetric amino group), 2208 (CN group), 1704 (carbonyl group). ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.20 (s, 6H, $-N(CH_3)_2$), 4.34 (s, 2H, NH_2), 6.98–8.32 (m, 14H, Ar–H; biphenyl and phenyl groups and pyridine H_5). ^{13}C-NMR (DMSO): 41.7, 77.6, 104.1, 112.5, 116.1, 127.3, 127.7, 128.2, 129.1, 130.2, 137.6, 139.2, 140.9, 145.7, 146.9, 155.5, 156.3, 164.6, 180.9. MS *m/z* (% abundance): 459 $[M]^+$ (1.2%), 460 $[M + H]^+$ (5.4%). *Anal.* for $C_{29}H_{22}N_4O_2$ (459). Cal: C, 75.97; H, 4.84; N, 12.22. Exp: C, 75.68; H, 4.62; N, 12.14.

4-Methyl-7-([1,1′-biphenyl]-4-yl)-3-acetyl-5-(4-(dimethylamino)phenyl)-2*H*-pyrano[2,3-*b*]pyridin-2-one (4b). Yield 84%, mp 80–82°C. IR (KBr) υ_{max} (cm^{-1}): 3325, 1723, 1678, 1600. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.22 (s, 3H, CH_3CO), 2.38 (s, 3H, CH_3, pyrone C-4), 3.04 (s, 6H, $N(CH_3)_2$), 6.98–8.5 (m, 14H, Ar–H). ^{13}C-

NMR (DMSO): 20.9, 29.7, 41.1, 104.4, 112.4, 122.6, 127.1, 127.7, 128.3, 129.7, 129.9, 137.6, 139.6, 145.8, 146.3, 155.7, 159.2, 159.6, 164.6, 198.5. MS *m/z* (% abundance): 475 $[M]^+$ (11%), 476 $[M + H]^+$ (2.5%). *Anal*. for $C_{31}H_{26}N_2O_3$ (475). Cal: C, 78.46; H, 5.52; N, 5.90. Exp: C, 78.29; H, 5.35; N, 5.72.

Ethyl-4-hydroxy-7-([1,1′-biphenyl]-4-yl)-5-(4-(dimethylamino)phenyl)-2-oxo-2*H*-pyrano[2,3-*b*]pyridine-3-carboxylate (4c). Yield 81%, mp 108–110°C. IR (KBr) υ_{max} (cm^{-1}): 3430, 1726, 1699, 1679, 1591. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.2 (t, 3H, *J* = 8.42, $\underline{CH_3}CH_2$, ester), 2.99 (s, 6H, $-N(CH_3)_2$), 4.12 (q, 2H, *J* = 8.42, $CH_3\underline{CH_2}$, ester), 7.02–8.13 (m, 14H, Ar–H), 13.02 (s, 1H, OH). ^{13}C-NMR (DMSO): 14.7, 41.9, 61.9, 100.1, 104.6, 112.9, 127.4, 128.3, 129.3, 130.1, 137.4, 139.8, 140.7, 145.4, 146.3, 155.6, 159.5, 164.8, 165.1, 172.8. MS *m/z* (% abundance): 507 $[M]^+$ (14%), 508 $[M + H]^+$ (1.9%). *Anal*. for $C_{31}H_{26}N_2O_5$ (507). Cal: C, 73.50; H, 5.17; N, 5.53. Exp: C, 73.62; H, 5.02; N, 5.34.

6-([1,1′-Biphenyl]-4-yl)-3-(amino(3-amino-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)methyl)-4-(4-(dimethylamino)phenyl)pyridin-2(1*H*)-one (5). A mixture of compound **4a** (1 mmol, 4.59 g) and hydrazine hydrate (2 mmol) in boiling EtOH (50 mL) was refluxed for 3 h. After cooling, the separated solid was collected and recrystallized from ethanol to afford white crystals. Yield 88%, mp 254–255°C. IR (KBr) υ_{max} (cm^{-1}): 3442, 1655. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.2 (s, 6H, $-N(CH_3)_2$), 4.52 (s, 2H, NH_2), 6.02 (s, 1H, pyridone C-5), 6.43 (s, 2H, NH_2, pyrazole, C_3), 6.8–7.8 (m, 13H, Ar–H), 12.02 (s, 2H, 2NH, 2 lactam rings). ^{13}C-NMR (DMSO): 41.9, 102.7, 104.9, 111.3, 126.8, 127.3, 129.5, 130.2, 139.9, 140.6, 150.1, 152.1, 160.4, 161.9, 164.8, 174.3. MS *m/z* (% abundance): 491 $[M]^+$ (14%), 492 $[M + H]^+$ (6%). *Anal*. for $C_{29}H_{26}N_6O_2$ (491). Cal: C, 71.00; H, 5.34; N, 17.13. Exp: C, 71.08; H, 5.22; N, 17.24.

4-(4-(Dimethylamino)phenyl)-5-((6-([1,1′-biphenyl]-4-yl)-2-oxo-1,2-dihydropyridin-3-yl)(amino)methylene)-6-amino-2-thioxo-2,5-dihydropyrimidin-4(3*H*)-one (6). A mixture of **4a** (0.01 mol, 4.59 g), thiourea (0.01 mol, 0.76 g), and sodium ethoxide (0.68 g, 0.01 mol) in boiling ethanol (20 mL) was refluxed for 6 h. The reaction mixture was cooled and then poured onto ice (25 g) and neutralized with dil HCl. The solid that separated was filtered and recrystallized from ethanol. Yield 89%, mp 167–169°C. IR (KBr) υ_{max} (cm^{-1}): 3345, 3256, 1659. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.2 (s, 6H, $-N(CH_3)_2$), 4.52 (s, 2H, NH_2, enamine moiety), 6.52 (s, 2H, NH_2, thiopyrimidine C-4), 6.6–7.8 (m, 14H, Ar–H), 11.2 (s, 1H, NH, pyridone moiety), 12.94 (s, 1H, NH, thiopyrimidine moiety). ^{13}C-NMR (DMSO): 41.9, 88.1, 104.9, 111.5, 126.7, 127.6, 129.1, 129.5, 130.2, 134.5, 140.1, 140.9, 150.5, 158.7, 160.3, 161.8, 166.6, 167.8, 185.9. MS *m/z* (% abundance): 535 $[M]^+$ (2.8%), 536 $[M + H]^+$ (4.2%). *Anal*. for $C_{30}H_{26}N_6O_2$ S (535). Cal: C, 67.40; H, 4.90; N, 15.72; S, 6.00. Exp: C, 67.52; H, 4.78; N, 15.59; S, 5.88.

9-([1,1′-Biphenyl]-4-yl)-5-amino-11-(4-(dimethylamino)phenyl)-1,3-dihydro-pyrido[3′,2′:5,6]pyrano[4,3-*e*][1,4]diazepine-2,6-dione (7). Compound **4a** (0.01 mol, 4.59 g) was allowed to react with ethyl glycinate hydrochloride (0.01 mol, 1.39 g) in refluxing pyridine/ethanol (1:10) for 3 h, and the separated solid was filtered off, fractionally crystallized from benzene, and gave yellow crystals. Yield 57%, mp 160–162°C. IR (KBr) υ_{max} (cm^{-1}): 3441, 1640, 1598. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.2 (s, 6H, $-N(CH_3)_2$), 5.58 (s, 2H, CH_2CO, diazepine nucleus), 6.46 (s, 2H, NH_2, diazepin-2-one C-4), 6.98–8.6 (m, 14H, Ar–H), 8.86 (s, 1H, NH, diazepine). ^{13}C-NMR (DMSO): 41.8, 57.3, 93.9, 104.6, 112.4, 123.1, 126.9, 127.3, 127.7, 128.1, 129.1, 130.2, 137.6, 145.9, 146.5, 151.3, 159.2, 164.7, 168.4. MS *m/z* (% abundance): 516 $[M]^+$ (2%), 517 $[M + H]^+$ (2.8%). *Anal*. for $C_{31}H_{25}N_5O_3$ (516). Cal: C, 72.22; H, 4.89; N, 13.58. Exp: C, 72.38; H, 4.76; N, 13.42.

6-(2-((l2-Azanyl)carbonyl)-1-amino-3-(4-(dimethylamino)phenyl)allylidene)-5-amino-3-thioxo-1,2,3,6-tetrahydro-7*H*-1,2,4-triazepin-7-one (8). A mixture of **4a** (1 mmol, 4.59 g) and thiosemicarbazide (1 mmol, 0.91 g) was refluxed in AcOH/MeOH (1:10) for 2 h. The separated solid after cooling was filtered off, dried, and recrystallized from ethanol to afford yellow crystals. Yield 86%, mp 150–152°C. IR (KBr) υ_{max} (cm^{-1}): 3441, 1609. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.1 (s, 6H, $-N(CH_3)_2$), 6.12 (s, 2H, NH_2), 6.53 (s, 1H, CHCO, py), 6.89 (s, 2H, NH_2, diazepin-2-one C-7), 6.88–8.11 (m, 14H, Ar–H), 8. 86 (s, 1H, NHCO, diazepine), 10. 86 (s, 1H, NHCS, diazepine). ^{13}C-NMR (DMSO): 41.9, 49.3, 101.3, 105.3, 111.9, 1277, 128.1, 128.7, 129.5, 140.9, 142.4, 150.2, 160.1, 164, 167.4. MS *m/z* (% abundance): 373 $[M]^+$ (100%), 374 $[M + H]^+$ (2.6%). *Anal*. for $C_{32}H_{27}N_7O_2S$ (573). Cal: C, 67.01; H, 4.71; N, 17.10; S, 5.58. Exp: C, 66.78; H, 4.54; N, 16.81; S, 5.60.

6-([1,1′-Biphenyl]-4-yl)-4-(4-(dimethylamino)phenyl)-3-(1-(3-methyl-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)ethyl)pyridin-2(1*H*)-one (9). A solution of compound **4b** (0.01 mol, 4.75 g) in EtOH (40 mL) and hydrazine hydrate (0.02 mol, 99%) was refluxed for 2 h. After cooling, the separated solid was collected and recrystallized from ethanol as white crystals. Yield 76%, mp 265–266°C. IR (KBr) υ_{max} (cm^{-1}): 3440, 3329, 3197, 1745, 1605. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.3 (s, 3H, CH_3, pyrazolone C-3), 2.6 (s, 3H, CH_3), 3.2 (s, 6H, $-N(CH_3)_2$), 6.2 (s, 1H, pyridone C-5), 6.78–7.98 (m, 13H, Ar–H), 12.54 (s, 2H, 2NH, 2 lactam rings). ^{13}C-NMR (DMSO): 13.7, 23.4, 41.9, 104.6, 105.9, 111.3, 127.6, 129.9, 130.2, 134.5, 139.8, 140.6, 143.9, 150.1, 159.8, 160.1, 161.7, 164.9. MS *m/z* (% abundance): 489 $[M]^+$ (10.5%), 490 $[M + H]^+$ (2.5%). *Anal*. for

$C_{31}H_{28}N_4O_2$ (489). Cal: C, 76.21; H, 5.78; N, 11.47. Found: C, 76.38; H, 5.62; N, 11.26.

7-([1,1′-Biphenyl]-4-yl)-5-(4-(dimethylamino)phenyl)-4-methyl-3-(1-(phenylimino)ethyl)-2*H*-pyrano[2,3-*b*]pyridin-2-one (10a). A solution of compound **4b** (0.01 mol, 4.75 g) in EtOH (50 mL) and aniline (0.01 mol, 0.93 g) was refluxed for 2 h. After cooling, the separated solid was collected and recrystallized from ethanol, as yellow crystals. Yield 89%, mp 114–116°C. IR (KBr) υ_{max} (cm^{-1}): 3444, 1729, 1679. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.11 (s, 3H, CH_3, CH_3–C=N), 2.52 (s, 3H, CH_3, pyrone C-4), 3.2 (s, 6H, $N(CH_3)_2$), 6.96–7.5 (m, 9H, Ar–H, biphenyl moiety), 7.52–8.8 (m, 10H, Ar–H, 2 aryl and pyridine C-5 precursors). ^{13}C-NMR (DMSO): 20.2, 21.8, 41.9, 104.3, 112.1, 119.4, 127.5, 128.3, 129.2, 130.3, 136.1, 137.6, 139.7, 140.1, 146.1, 146.9, 152.3, 155.3, 159.1, 164.6, 175.8. MS *m*/*z* (% abundance): 550 $[M]^+$ (1.2%), 551 $[M + H]^+$ (2.1%). *Anal*. for $C_{37}H_{31}N_3O_2$ (550). Cal: C, 80.85; H, 5.68; N, 7.64. Found: C, 80.98; H, 5.72; N, 7.50.

7-([1,1′-Biphenyl]-4-yl)-5-(4-(dimethylamino)phenyl)-4-methyl-3-(1-(*p*-tolyl-imino)ethyl)-2*H*-pyrano[2,3-*b*]pyridin-2-one (10b). A solution of compound **4b** (0.01 mol, 4.75 g) in EtOH (50 mL) and *p*-toluidine (0.01 mol, 1.07 g) was refluxed for 2 h. After cooling, the separated solid was collected and recrystallized from ethanol as yellow crystals. Yield 92%, mp 108–110°C. IR (KBr) υ_{max} (cm^{-1}): 3444, 1729, 1679. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.98 (s, 3H, CH_3, CH_3–C=N), 2.2 (s, 3H, CH_3), 2.5 (s, 3H, CH_3, pyrone C-4), 3.2 (s, 6H, $N(CH_3)_2$), 6.92–7.3 (m, 8H, Ar–H, 2 phenyl moiety), 7.5–8.8 (m, 10H, Ar–H, biphenyl and pyridine C-5). ^{13}C-NMR (DMSO): 20.2, 21.5, 21.8, 41.9, 104.3, 112.1, 119.4, 127.5, 128.3, 129.2, 130.3, 136.1, 137.6, 139.7, 140.1, 146.1, 146.9, 152.3, 155.3, 159.1, 164.6, 175.8. MS *m*/*z* (% abundance): 564 $[M]^+$ (2.1%), 565 $[M + H]^+$ (2.7%). *Anal*. for $C_{38}H_{33}N_3O_2$ (564). Cal: C, 80.97; H, 5.90; N, 7.45. Found: C, 81.00; H, 5.8; N, 7.33.

7-([1,1′-Biphenyl]-4-yl)-5-(4-(dimethylamino)phenyl)-4-methyl-3-(1-((4-nitrophenyl)imino)ethyl)-2*H*-pyrano[2,3-*b*] pyridin-2-one (10c). A solution of compound **4b** (0.01 mol, 4.75 g) in EtOH (50 mL) and *p*-nitroaniline (0.01 mol, 1.38 g) was refluxed for 4 h. After cooling, the separated solid was collected and recrystallized from ethanol as yellow crystals. Yield 96%, mp 130–132°C. IR (KBr) υ_{max} (cm^{-1}): 3444, 1729, 1679. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.2 (s, 3H, CH_3, CH_3–C=N), 2.6 (s, 3H, CH_3, pyrone C-4), 3.22 (s, 6H, –$N(CH_3)_2$), 6.7–7.9 (m, 8H, Ar–H, 2 phenyl moiety), 7.52–8.7 (m, 10H, Ar–H, biphenyl and pyridine C-5). ^{13}C-NMR (DMSO): 20.2, 21.8, 41.9, 104.3, 112.1, 119.4, 125.1, 127.5, 128.3, 129.2, 130.3, 136.1, 137.6, 139.7, 140.1, 146.1, 146.2, 146.9, 152.3, 155.3, 159.1, 164.6, 175.8. MS *m*/*z* (% abundance): 595 $[M]^+$ (1.8%), 596 $[M + H]^+$ (11.2%). *Anal*. for $C_{37}H_{30}N_4O_4$ (595). Cal: C, 74.73; H, 5.09; N, 9.42. Found: C, 74.82; H, 5.00; N, 9.34.

5-(1-(6-([1,1′-Biphenyl]-4-yl)-4-(4-(dimethylamino)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)ethylidene)-6-methyl-2-thioxo-2,5-dihydropyrimidin-4(3*H*)-one (11). A mixture of **4b** (1 mmol, 4.75 g), thiourea (1 mmol, 0.76 g), and sodium ethoxide (0.7 g, 1 mmol) in ethanol (20 mL) was refluxed for 6 h. The reaction mixture was cooled upon ice (25 g) and neutralized with dil HCl. The separated solid was filtered off and recrystallized from EtOH to afford pyrimidine as orange crystals. Yield 88%, mp 140–142°C. IR (KBr) υ_{max} (cm^{-1}): 3451, 1630. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.02 (s, 3H, CH_3, thiopyrimidine C-4), 2.5 (s, 3H, CH_3, CH_3–C=C–), 3.2 (s, 6H, –$N(CH_3)_2$), 6.22 (s, 1H, pyridine H-5), 6.7–7.8 (m, 13H, Ar–H), 11.32 (s, 1H, NH, pyridone), 13.08 (s, 1H, NH, thiopyrimidine). ^{13}C-NMR (DMSO): 13.7, 20.9, 41.9, 126.3, 127.6, 129.1, 130.2, 130.5, 134.6, 139.9, 140.1, 140.7, 143.4, 150.1, 160.2, 161.3, 164.8, 232.9. MS *m*/*z* (% abundance): 533 $[M]^+$ (1.1%), 534 $[M + H]^+$ (4.2%). *Anal*. for $C_{32}H_{28}N_4O_2S$ (533). Cal: C, 72.16; H, 5.30; N, 10.52; S, 6.02. Found: C, 72.29; H, 5.18; N, 10.36; S, 6.00.

Ethyl((1-(7-([1,1′-biphenyl]-4-yl)-5-(4-(dimethylamino) phenyl)-4-methyl-2-oxo-2*H*-pyrano[2,3-*b*]pyridin-3-yl) ethylidene)amino)acetate (12). A mixture of **4b** (1 mmol, 4.75 g), NH_2CH_2COOEt (1.39 g, 1 mmol), and Py : EtOH (1:10) was refluxed for 3 h. The separated solid was filtered off and crystallized from ethanol as yellow crystals. Yield 62%, mp 214–215°C. IR (KBr) υ_{max} (cm^{-1}): 3451, 1610. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.1 (t, 3H, CH_3, ester), 2.33 (s, 3H, CH_3, coumarin), 2.74 (s, 3H, CH_3 imine), 3.2 (s, 6H, –$N(CH_3)_2$), 3.82 (q, 2H, CH_2, ester), 5.12 (s, 2H, CH_2, imine), 6.78–7.60 (m, 14H, Ar–H). ^{13}C-NMR (DMSO): 14.7, 17.4, 21.9, 41.9, 52.6, 61.7, 112.9, 127.1, 127.8, 128.1, 129.4, 137.7, 139.1, 140.5, 145.1, 146.2, 152.3, 155.6, 159.1, 164.6, 170.7, 177.4. MS *m*/*z* (% abundance): 559 $[M]^+$ (36%), 560 $[M + H]^+$ (6.6%). *Anal*. for $C_{35}H_{33}N_3O_4$ (559). Cal: C, 75.13; H, 5.90; N, 7.51. Found: C, 74.85; H, 5.71; N, 7.32.

6-(1-(6-([1,1′-Biphenyl]-4-yl)-4-(4-(dimethylamino)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)ethylidene)-5-methyl-3-thioxo-1,2,3,6-tetrahydro-7*H*-1,2,4-triazepin-7-one (13). A mixture of **4b** (1 mmol, 4.75 g), $NH_2CSNHNH_2$ (1 mmol, 0.91 g), and AcOH/MeOH (1:10) was refluxed for 2 h and then cooled, and the solid formed was filtered off, dried, and recrystallized from EtOH as reddish brown crystals. Yield 89%, mp 210–212°C. IR (KBr) υ_{max} (cm^{-1}): 3440, 1605. ^{1}H-NMR (DMSO-d_6) δ (ppm): 2.1 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.2 (s, 6H, –$N(CH_3)_2$), 6.3 (s, 1H, pyridine H-5), 6.78–7.60 (m, 13H, Ar–H), 8.9 (s, 1H, NH, lactam of triazepine nucleus), 11.08 (s, 1H, NH, thiolactam of triazepine nucleus), 12.02 (s, 1H, NH, pyridone). ^{13}C-NMR (DMSO): 13.8, 21.7, 41.9, 104.7,

110.9, 111.4, 127.6, 129.1, 134.4, 134.87, 139.89, 140.6, 143.98, 150.1, 155.1, 160.2, 160.94, 164.6, 188.7. MS *m/z* (% abundance): 548 $[M]^+$ (37%), 550 $[M + 2]^+$ (2.6%). *Anal*. for $C_{32}H_{29}N_5O_2$ S (548). Cal: C, 70.18; H, 5.34; N, 12.79; S, 5.85 Found: C, 70.32; H, 5.26; N, 12.65; S, 5.78.

6-([1,1′-Biphenyl]-4-yl)-4-(4-(dimethylamino)phenyl)-3-(hydroxy(3-hydroxy-5-oxo-1,5-dihydro-4*H*-pyrazol-4-ylidene)methyl)pyridin-2(1*H*)-one (14). A solution of compound **4c** (0.01 mol, 5.07 g) in EtOH (50 mL) and hydrazine hydrate (0.02 mol, 99%) was refluxed for 3 h. After cooling, the separated solid was collected and recrystallized from ethanol as white crystals. Yield 88%, mp 290–292°C. IR (KBr) υ_{max} (cm^{-1}): 3443, 3328, 1720, 1670, 1607. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.2 (s, 6H, $-N(CH_3)_2$), 6.22 (s, 1H, pyridine H-5), 6.9–7.88 (m, 13H, Ar–H), 10.02 (s, 1H, OH), 11.82 (s, 2H, 2NH of 2 lactam rings), 12.67 (s, 1H, OH, pyrazol C-3). ^{13}C-NMR (DMSO): 41.9, 104, 111.8, 126.1, 127.3, 127.9, 128.9, 129.9, 130.3, 134.4, 150.1, 150.8, 159.9, 161.2, 174.5, 196.8. MS *m/z* (% abundance): 493 $[M]^+$ (1.8%), 494 $[M + H]^+$ (2.0%). *Anal*. for $C_{29}H_{24}N_4O_4$ (493). Cal: C, 70.72; H, 4.91; N, 11.38. Found: C, 70.84; H, 4.80; N, 11.22.

5-((6-([1,1′-Biphenyl]-4-yl)-4-(4-(dimethylamino)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)(hydroxy)methylene)-6-hydroxy-2-thioxo-2,5-dihydropyrimidin-4(3*H*)-one (15). A mixture of **4c** (1 mmol, 5.07 g), thiourea (1 mmol, 0.76 g), and sodium ethoxide (1 mmol, 0.7 g) in EtOH (4 mL) was grinded for 25–30 min. The reaction mixture was refluxed for 2 h, cooled, and neutralized with dil HCl. The solid was filtered and recrystallized from EtOH as yellow crystals. Yield 83%, mp 158–160°C. IR (KBr) υ_{max} (cm^{-1}): 3442, 1632, 1601. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.2 (s, 6H, $-N(CH_3)_2$), 6.22 (s, 1H, pyridine H-5), 6.9–7.88 (m, 13H, Ar–H), 10.02 (s, 1H, OH, enol moiety), 11.2 (s, 1H, NH, pyridone), 12.82 (s, 1H, OH, thiopyrimidine C-4), 13.02 (s, 1H, NH, thiopyrimidine). ^{13}C-NMR (DMSO): 41.9, 85.2, 104.5, 110.9, 126.7, 127.4, 128.1, 129.6, 130.3, 134.9, 139.9, 140.5, 150.1, 159.8, 160.1, 160.5, 161.1, 166.7, 185.9. MS *m/z* (% abundance): 537 $[M]^+$ (2.1%), 538 $[M + H]^+$ (5.1%). *Anal*. for $C_{30}H_{24}N_4O_4S$ (537). Cal: C, 67.15; H, 4.51; N, 10.44; S, 5.97. Found: C, 67.34; H, 4.42; N, 10.31; S, 6.02.

Ethyl 7-(6-([1,1′-biphenyl]-4-yl)-4-(4-(dimethylamino) phenyl)-2-oxo-1,2-dihydropyridin-3-yl)-2,5-dioxo-2,3,4,5-tetrahydro-1,4-oxazepine-6-carboxylate (16). A mixture of **4c** (1 mmol, 5.07 g), ethyl glycinate (1 mmol, 1.39 g), and Py : EtOH (1:10) was refluxed for 3 h, and the separated solid was filtered off and crystallized from EtOH as yellow crystals. Yield 83%, mp 240–242°C. IR (KBr) υ_{max} (cm^{-1}): 3324, 3265, 1765, 1745, 1690. ^{1}H-NMR (DMSO-d_6) δ (ppm): 1.2 (t, 3H, CH_3, ester), 3.2 (s, 6H, $-N(CH_3)_2$), 3.94 (s, 2H, CH_2CO, oxazepine nucleus), 4.23 (q, 2H, CH_2, ester), 6.03 (s, 1H, pyridone H-5), 6.7–7.68 (m, 13H, Ar–H), 7.98 (s, 1H, NH, oxazepine), 11.02 (s, 1H, NH, pyridone). ^{13}C-NMR (DMSO): 13.9, 41.9, 45.8, 60.8, 102.2, 104.5, 111.9, 126.9, 128.1, 128.9, 129.6, 130.4, 134.5, 139.8, 140.6, 149.8, 159.8, 161.9, 166.9, 168.3, 172.4. MS *m/z* (% abundance): 564 $[M]^+$ (1.8%), 565 $[M + H]^+$ (2.5%). *Anal*. for $C_{33}H_{29}N_3O_6$ (564). Cal: C, 70.33; H, 5.19; N, 7.46. Found: C, 70.46; H, 5.02; N, 7.35.

6-((6-([1,1′-Biphenyl]-4-yl)-4-(4-(dimethylamino)phenyl)-2-oxo-1,2-dihydropyridin-3-yl)(hydroxy)methylene)-7-hydroxy-3-thioxo-2,3,4,6-tetrahydro-5*H*-1,2,4-triazepin-5-one (17). A mixture of **5c** (1 mmol, 5.07 g), $NH_2NHCSNH_2$ (1 mmol, 0.91 g), and AcOH : MeOH (1:10) was grinded for 20 min and then refluxed for 2 h. The separated solid was filtered off, dried, and recrystallized from EtOH to afford brown crystals. Yield 78%, mp 198–200°C. IR (KBr) υ_{max} (cm^{-1}): 3441, 1721, 1635, 1604. ^{1}H-NMR (DMSO-d_6) δ (ppm): 3.2 (s, 6H, $N(CH_3)_2$), 6.2 (s, 1H, pyridine H-5), 6.6–7.62 (m, 13H, ArH), 10.32 (s, 2H, 2OH, 2 hydroxyl groups), 11.2 (s, 1H, NH, pyridone), 12.8 (s, 2H, 2NH, triazepine). ^{13}C-NMR (DMSO): 41.9, 95.1, 105.2, 111.4, 126.2, 127.8, 128.1, 129.4, 129.8, 134.1, 139.8, 140.7, 150.1, 154.8, 161.7, 168.8., 195.9. MS *m/z* (% abundance): 551 $[M]^+$ (1.5%), 552 $[M + H]^+$ (4.5%). *Anal*. for $C_{30}H_{25}N_5O_4S$ (551). Cal: C, 65.32; H, 4.57; N, 12.70; S, 5.81. Found: C, 65.45; H, 4.60; N, 12.62; S, 5.9.

REFERENCES AND NOTES

[1] Patel, N. B.; Agravat, S. N.; Shaikh, F. M. Med Chem Res 2011, 20, 1033.
[2] Patel, N. B.; Agravat, S. N. Chem Heterocycl Compd 2009, 45, 1343.
[3] Tarik, E. S. A. Eur J Med Chem 2009, 44, 4385.
[4] Srivastava, A.; Pandeya, S. N. Int J Cur Pharm Rev Res 2011, 4, 5.
[5] Paronikyan, E. G.; Noravyan, A. S.; Dzhagatspany, I. A.; Nazaryan, I. M.; Paronikyan, R. G. Pharm Chem J 2002, 36, 465.
[6] Bernardino, A. M. R.; De Azevedo, A. R.; Pinheiro, L. C. D.; Borges, J. C.; Carvalho, V. L.; Miranda, M. D.; De Meneses, M. D. F.; Nascimento, M.; Ferreira, D.; Rebello, M. A. Med Chem Res 2007, 16, 352.
[7] De Clercq, E. Curr Opin Microbiol 2005, 8, 552.
[8] Eizuru, Y. Antivir Chem Chemother 2003, 14, 299.
[9] Tucker, T. J.; Sisko, J. T.; Tynebor, R. M.; Williams, T. M.; Felock, P. J.; Flynn, J. A.; Lai, M.; Liang, Y.; McGaughey, G.; Liu, M. J Med Chem 2008, 51, 6503.
[10] Mamolo, M. G.; Zampieri, D.; Falagiani, V.; Vio, L.; Fermeglia, M.; Ferrone, M.; Pricl, S.; Banfi, E.; Scialino, G. ARKIVOC 2004, 5, 231.
[11] Mellol, H.; Echevarria, A.; Bernardino, A. M. R.; Canto-Cavalheiro, M.; Leon, L. L. J Med Chem 2004, 47, 5427.
[12] Gangjee, A.; Adair, A.; Queener, O.; Pneumo, S. F. J Med Chem 1999, 42, 2447.
[13] Geffken, D.; Soliman, R.; Soliman, F. S. G.; Abdel-Khalek, M. M. J Med Chem Res 2011, 20, 408.
[14] Nasr, M. N.; Gineinah, M. M. Arch Pharm 2002, 335, 289.
[15] Katritzky, A. R.; Serdyuk, L.; Chassaing, C.; Toader, D.; Wang, X. J.; Forood, B.; Flatt, B.; Sun, C. C. K J Comb Chem 2000, 2, 182.

[16] Zhuravel, I. O.; Kovalenko, S. M.; Ivachtchenko, A. V.; Balakin, K. V.; Kazmirchuk, V. V. Bioorg Med Chem Lett 2005, 15, 5483.

[17] Trilleras, J.; De La Torre, P.; Pacheco, D. J.; Quiroga, J.; Nogueras, M.; Cobo, J. Lett Org Chem 2011, 8, 652.

[18] Miao, C. B.; Wang, Y. H.; Dong, C. P.; Yang, H. T.; Meng, Q.; Sun, X. Q. Heterocycles 2013, 87, 2599.

[19] Faraji, L.; Arvinnezhad, H.; Alikami, N.; Jadidi, K. Lett Org Chem 2010, 7, 472.

[20] Huang, Z.; Zhao, Q.; Chen, G.; Wang, H.; Lin, W.; Xu, L.; Liu, H.; Wang, J.; Shi, D.; Wang, Y. Molecules 2012, 17, 12704.

[21] Azab, M. E.; Rizk, S. A.; Amr, A. E. Molecules 2015, 20, 18201.

[22] Rizk, S. A.; El-Hashash, M.; El-Badawy, A. J Heterocyclic Chem 2017, 54, 2003.

[23] Rizk, S. A.; El-Sayed, G. A.; El-Hashash, M. J Iranian Chem Soc 2018, 15, 2093.

[24] Shaymma, M. A.; Rizk, S. A.; Khalil, A. Inter Res J Pure Appl Chem 2018, 17, 1.

[25] Rizk, S. A.; El-Hashash, M. J Heterocyclic Chem 2017, 54, 1776.

[26] Rizk, S. A.; Abdelwahab, S. S.; Sallam, H. A. J Heterocyclic Chem 2018, 55, 1604.

[27] Rizk, S. A.; El-Hashash, M.; El-Badawy, A. J Heterocyclic Chem 2018, 55, 2090.

[28] El-Hashash, M. A.; Rizk, S. A.; El-Naggar, A. M.; El-Bana, M. G. J Heterocyclic Chem 2017, 54, 3716.

[29] Elkholy, A. E.; Rizk, S. A.; Rashad, A. M. J Mol Struct 2019, 1175, 788.

[30] Heakal, F. E.; Attia, S. K.; Rizk, S. A.; Abou Essa, M. A.; Elkholy, A. E. J Mol Struct 2017, 1147, 714.

[31] Attia, S. K.; El-Gendy, A. T.; Rizk, S. A. J Mol Struct 2019, 1184, 583.

[32] Al-Abdullah, E. S. Molecules 2011, 16, 3410.