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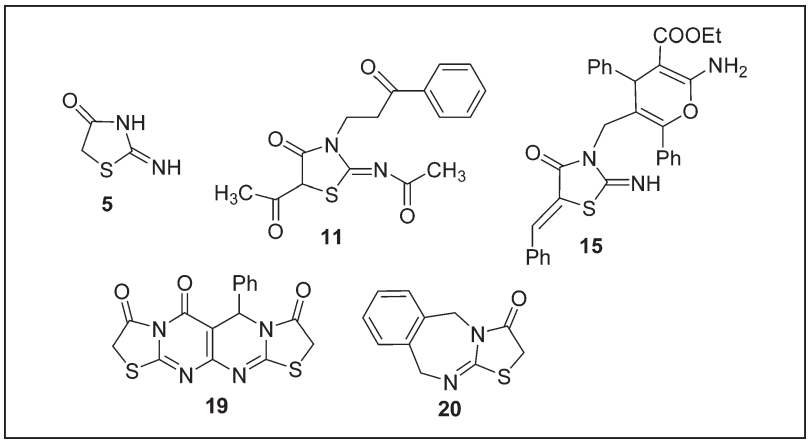

Annulations of 2-imino-4-thiazolidinone (**5**) *via* cycloaddition followed by cyclocondensation reaction with 1,3-diphenylpropenone (**6**), benzylidenemalonate, and 1,2-bis(chloromethyl)benzene gave **7**, **19** and **20**, respectively. Reaction of **5** with suitable electrophiles (Mannich bases of arylalkanone), 1,4-dichlorobenzene (diarylmethylation), and formylation afforded **8/9**, **21/22**, and **23**, respectively.

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INTRODUCTION

The structural and therapeutic diversity coupled with commercial viability of small heterocyclic molecules have fascinated organic and medicinal chemists. In recent years, 4-thiazolidinones are one of the most extensively investigated classes of compounds. The thiazolidinone ring system has been widely used in the investigation of pharmacologically active heterocyclic compounds [1–4], perhaps most notably as a common structural motif in the Rosiglitazone class of PPAR-8 agonists **1** [5]. In contrast, the isosteric 2-imino-4-thiazolidinone and its tautomeric 2-amino-4-thiazolidinone have been less investigated in the medicinal chemistry field, although potent anti-inflammatory Darbufelone (**2**) [6] and antiviral activities [7] have been found. They are less common, despite the clear opportunity to introduce an additional handle for chemical diversity and thus enable exploration of unmapped regions of a thiazolidinone-based pharmacophore (region B) **3**. One reason might be the lack of efficient synthetic methods to prepare iminothiazolidinones, in particular with distinct substitution patterns on each of the nitrogen atoms. The amidine moiety is found in a wide range of biologically active molecules, including various serine protease inhibitors [8] and antiprotozoal agents [9].

Furthermore, the diamidines exhibit broad spectrum of antimicrobial activity [10]. In light of the pharmaceutical importance of several fused bicyclic ring systems, the most important are those containing a nitrogen ring-junction, where a nitrogen is common to two rings [11,12], such as levamisole (imidazo[2,1-*b*]thiazole) (**4**) [12]. So, the objective of this work was directed to annulate 2-imino-4-thiazolidinone (**5**) *via* cycloaddition followed by cyclo-condensation reaction, as a part of our continuing interest in the synthesis of biologically active molecules [13–17].

RESULTS AND DISCUSSION

The 2-iminothiazolidin-4-one (**5**) has three active centers the amido group (N_3H—CO), imino group (=N_6H), and the active methylene group ($C_5H_aH_b$).

The molecular parameters and the electronic structure of 2-iminothiazolidin-4-one (**5**) indicate that the nucleophilicity is decreasing in the following order amido group (—NH—CO) > imino group (=NH) > active methylene (—CH_2—). The reaction between amidine moiety as a bifunctional nucleophile with different reagents to produce bridgehead nitrogen heterocycles of

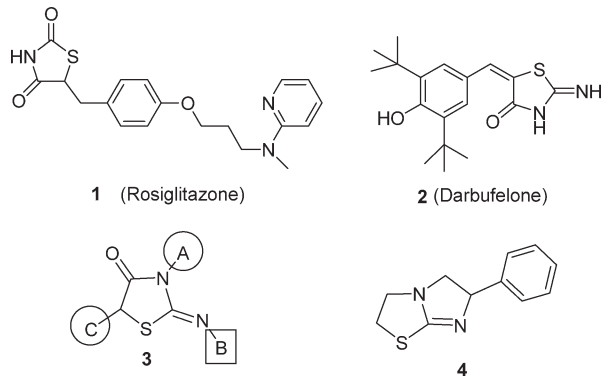


Figure 1. Thiazole derivatives reported to have pharmacological activities.

expected pharmacological activities, pursued us to synthesize thiazolopyrimidines which were recently prepared as patent in the literatures because of their interesting biological and pharmaceutical activities [18–20].

The influence of substituents at positions 6 and 7 as well as the substitution pattern of the two phenyl rings in the positions 2 and 5 on activity is also reported [21]. Therefore, this study provides a suitable method for the selective synthesis of thiazolo[3,2-*a*]pyrimidinone derivative **7** through the reaction of 2-imino-4-thiazolidinone (**5**) with benzalacetophenone (**6**) in ethanol in presence of triethylamine *via* cycloaddition followed by cyclocondensation reaction. Its constitution was supported by elemental analysis, IR, ^{1}H-NMR, and MS spectra.

Another route for synthesis of 5-arylthiazolo[3,2-*a*]pyrimidine *via* condensation of compound **5** with suitable electrophiles is a straightforward and often used approach. The substitution pattern of the annulated pyrimidine ring formed is determined in these reactions by the structure of the biselectorophile. Accordingly, Mannich bases of arylalkanone are used to afford **8** and **9**, which characterized by their spectroscopic properties (IR, ^{1}H-NMR, and MS) and elemental analysis. Intramolecular cyclization of compound **8** to **10** between secondary amine and carbonyl group was unsuccessful. However, *N*-(5-acetyl-4-oxo-3-(3-oxo-3-phenylpropyl)thiazolidin-2-ylidene)acetamide (**11**) was obtained instead of the anticipated thiazolo[3,2-*a*]pyrimidinone **10**. Its structure was ascertained by elemental analysis, IR, ^{1}H-NMR, and mass spectra. Several arylidene derivatives

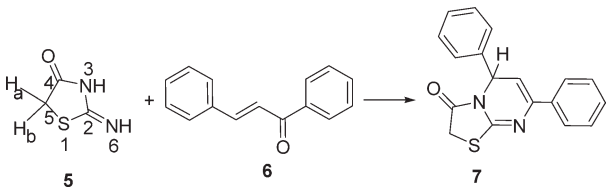


Figure 2. Synthesis of thiazolo[3,2-*a*]pyrimidinone derivative **7**.

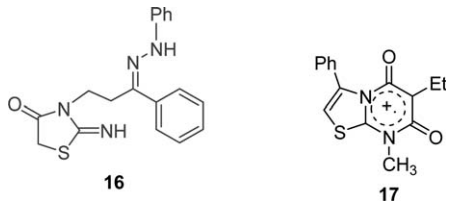


Figure 3. Structures of hydrazone derivative **16** and meso-ionic 6-ethyl-3-phenylthiazolo[3,2-*a*]pyrmidine-5,7-dione (**17**).

have bacteriostatic and strong fungistatic action [13]. Therefore, Claisen-Schmidt condensation of **8** with two moles of 4-methoxybenzaldehyde in ethanol catalyzed by few drops of acetic acid gave a single isomer of the arylidene **12**. Its structure was elucidated by IR, ^{1}H-NMR, and mass spectra. Furthermore, it was decided to prepare binary pyran attached 2-(methyl)imino-1,3-thiazolidin-4-one aiming to improve their biological potency, because pyrans individually or in combination with heterocycles possess significant biological properties [21a]. Accordingly, the reaction of 2-imino-4-thiazolidinone (**5**) with two moles of activated cyano olefin such as ethyl 2-cyano-3-phenylacrylate (**13**) catalyzed by triethylamine afforded compound **15**. The structure of **15** is based on analytical and spectroscopic features. A plausible mechanism for the formation of pyran derivative **15** probably involves an acyclic Michael adduct as intermediate **14** which cyclizes *via* the addition of enolic hydroxyl group to the cyano group [21b]. It is accompanied with rearrangement at C-5 in the thiazole ring.

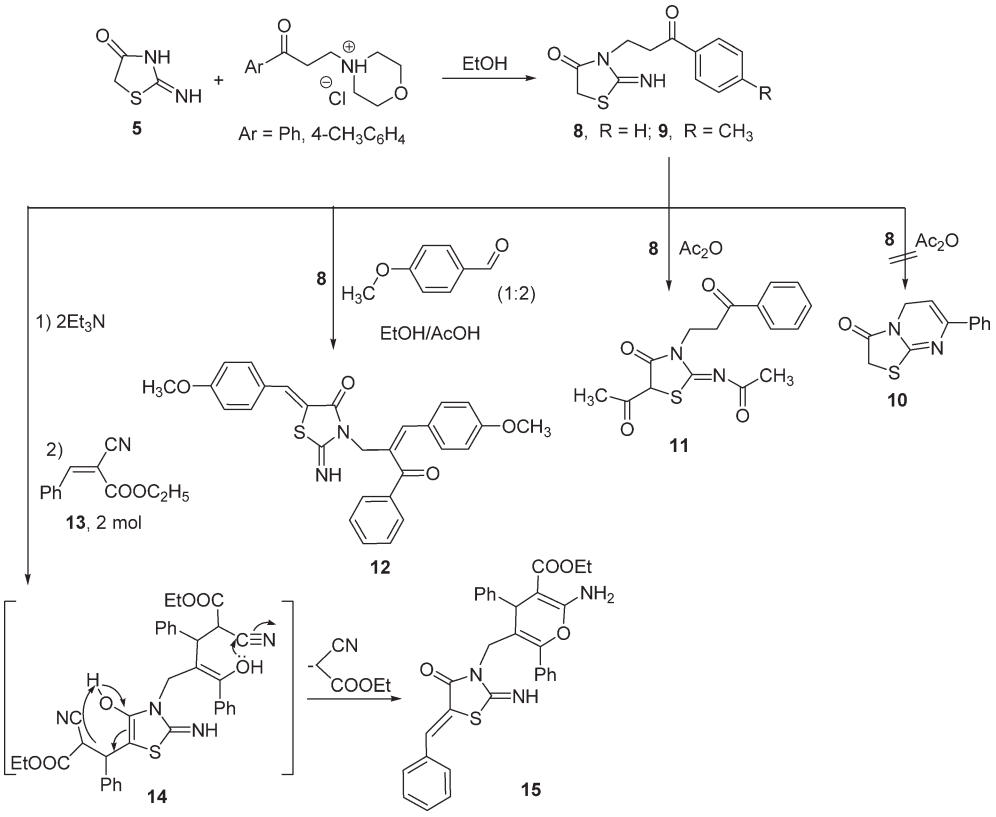
The geometry of compound **12** was established by the quantum mechanical calculations using the PM3 semiempirical molecular orbital method. The (*Z,Z*) configuration was found to have the lower total energy (−6569.7 k cal/mol), (*E,Z)* configuration have −6568.3 k cal/mol, and the higher energy for (*E,E*) configuration (−6565 k cal/mol) in (*Z*)-3-((*Z*)-2-benzoyl-3-(4-methoxyphenyl)allyl)-2-imino-5-(4-methoxybenzylidene) thiazolidin-4-one (**12**).

Table 1

The important quantum chemical parameters for the effective atoms and bonds in compound **5**, as obtained from PM3 semiempirical MO calculations.

Atom	Atomic charge	Bond	Bond length	Bond order
N_6	−0.077	N_6—H(N_6)	0.9882 Å	0.958
N_3	−0.021	N_3—H(N_3)	0.9968 Å	0.943
C_5	−0.222	C_5—H(C_5)a	0.1060 Å	0.962
		C_5—H(C_5)b	0.1057 Å	0.963
H(N_6)	+0.082			
H(N_3)	+0.105			
H(C_5)a	+0.118			
H(C_5)b	+0.117			

Scheme 1. Synthesis and reactions of 2-imino-3-(3-oxo-3-phenylpropyl)thiazolidin-4-one (**8**).

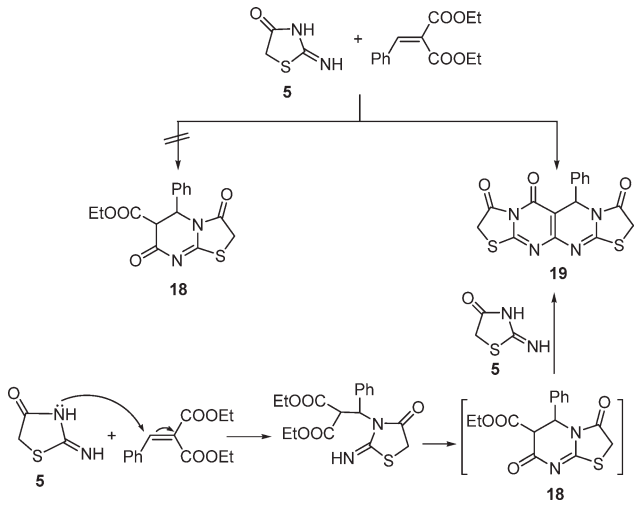


Finally, formation of hydrazone derivative **16** was achieved by treatment of **8** with phenylhydrazine in alcohol catalyzed by of few drops of acetic acid. However, Glennon [22] synthesized meso-ionic 6-ethyl-3-phenylthiazolo[3,2-*a*]pyrmidine-5,7-dione (**17**) by thermal condensation of 2-methylamino-4-phenylthiazole with *bis*(2,4,6-trichlorophenyl)ethyl-malonate.

There is an interest for introduction of a substituent at C-5 of pyrimidine moiety because biological activity enhancement of the products formed [23–25]. Therefore, this prompted us to prepare ethyl 3,7-dioxo-5-phenyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylate (**18**) through the cyclocondensation of **5** with benzylidenemalonate which is formed *in situ* was unsuccessful. However, the *bis* fused thiazolo[3,2-*a*]pyrimidine **19** was isolated as angular compound instead of **18**. Compatible analytical and spectroscopic evidences were gained for structure of **19**.

Furthermore, the interesting Psychopharmacological activity of benzodiazepine [26,27] enthused us to synthesize the 5,10-dihydrobenzo[*e*]thiazolo[3,2-*a*][1,3]diazepin-3(2*H*)-one (**20**). Compound **20** has been obtained through cyclocondensation of **5** with 1,2-*bis*(chloromethyl)benzene [28]. Formulation of structure **20** was based on elemental analysis, IR, ^{1}H-NMR, and MS spectra. An attempted diarylmethylation of **5** with 1-chloro-4-(chloromethyl)benzene in the presence of K_2CO_3/acetone in molar ratio (1:2) gave a mixture of **21** and **22**, which isolated by column chromatography using ethyl acetate/petroleum ether (60–80°C) (1:4) as eluent for separating **21**, whereas elution with ethyl acetate/petroleum ether (60–80°C) (2:4) gave **22** in 68% and 29% yields, respectively. Also, when the previous reaction was repeated in a molar ratio (1:3), compound **22** was isolated only instead of triarylmethyl derivative. The condition of the formation of **21** and **22** was in line with that reported in literature [29–31]. The structures of **21** and **22** were confirmed on the basis of their elemental analyses and spectral data. Thus, their ^{1}H-NMR spectra displayed signals characteristic for thiazole moiety, and the signals for benzyl moiety. In the mass spectra, the molecular ion peaks of **21** and **22** were *m*/*z* 240 (30) and 364 (3). The geometry of compound **22** was established by the quantum mechanical calculations using the PM3 semiempirical molecular orbital method. The (*Z*) configuration was found to have the lower total energy of −4020 k cal/mol, whereas the (*E*) configuration was found to have a total energy of −3999.8 kcal/mol, respectively. This indicates the global stability of the (*Z*) configuration as (*Z*)-3-(4-chlorobenzyl)-2-(4-chlorobenzylimino)thiazolidin-4-one (**22**). Attempted formylation of **5** *via* halomethyl-eniminium salt, obtained from Vilsmeier-Haack reagent (DMF/$POCl_3$), afforded the 4-chloro-5-formylthiazole derivative **23**, the structural

Scheme 2. Synthetic mechanism for the synthesis of 7-phenyl-2*H*-thiazolo[3,2-*a*]pyrimidine-3-one[5,6:5′,6′]-2*H*-thiazolo[3,2-*a*]pyrimidine-3,7-dione (**19**).



formula of **23** was asserted by spectral data. While formylation of thiazolidinone with different reagents such as *t*-butoxy-*bis*(dimethylamino)methane [Bredereck's reagent] in dimethylformamide was reported in the literature as patent [32,33].

EXPERIMENTAL

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at Microanalytical Unit (Faculty of Science, Cairo University). The Infrared spectra were measured on a Mattson 5000 FTIR spectrometer. ^{1}H-NMR data were measured in $CDCl_3$ and DMSO solution on a Varian XL 200, 300 MHz instruments using TMS as internal standard. Chemical shifts were reported in ppm (δ) downfield from internal TMS. Mass spectra were recorded on GC-MS QP-1000 EX (EI, 70 ev), Shimadzu Instrument. Reactions were monitored by thin layer chromatography (TLC) using EM science silica gel coated plates with visualization by irradiation with ultraviolet lamp. Molecular Orbital Calculations and the quantum chemical parameters were determined using the PM3-Semi-empirical method using evaluation copy of HyperChem.ver 7.5 (www.hyper.com). Package accommodated on PIV-2.8 MHz computer system. The molecular quantum parameters and the electronic structure (Molecular Orbital Calculations) and the quantum chemical parameters were determined using the PM3-Semi-empirical MO method using evaluation copy of Hyper Chem. Ver. 7.5 (www.hyper.com). Package (accommodated on PIV-2.8 MHz Computer System) of this compound were calculated.

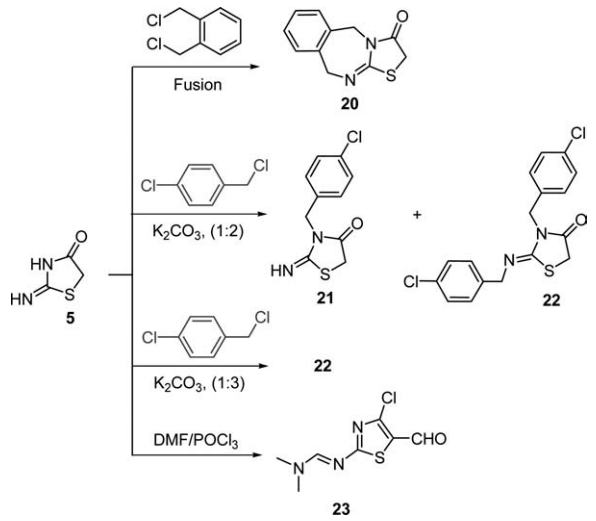
5,7-Diphenyl-2*H*-thiazolo[3,2-*a*]pyrimidin-3(5*H*)-one (7). A mixture of 2-iminothiazolidin-4-one (**5**) [34] (0.5 g, 4.3 mmol) and benzalacetophenone (**6**) (0.9 g, 4.3 mmol) in ethanol (10 mL) and few drops of triethylamine was refluxed for 8 h on a steam bath, and left to cool. The formed precipitate was filtered, dried, and recrystallized from ethanol to afford (0.99 g, 75%) of **7**; mp 160–162°C; yellow crystals; R_f = 0.58 [pet. ether (40–60)/ethyl acetate, (1:1)]; IR (KBr) ύ (cm^{-1}), 2936 (C—H, stretch), 1674 (CO), 1564 (C=N), 1448 (C—C), 1266 (C—H), 768 (C—S); ^{1}H-NMR (200 MHz, DMSO-d_6): δ, 3.91 (s, 2H, CH_2), 5.56 (d, J = 1.2 Hz, 1H, CH), 6.70 (d, J = 1.2 Hz, 1H, CH), 7.43–7.63 (m, 10H, Ar-H); ms: (m/z, %): 306 (M^+, 5), 136 (6), 134 (100). Anal. Calcd. for $C_{18}H_{14}N_2OS$ (306.38): C, 70.56; H, 4.61; N, 9.14. Found: C, 70.39; H, 4.80; N, 9.10.

2-Imino-3-(3-oxo-3-arylpropyl)thiazolidin-4-ones 8 and 9 General procedure. A mixture of 2-iminothiazolidin-4-one (**5**) (0.5 g, 4.3 mmol) and 4-(3-oxo-3-phenylpropyl)morpholin-4-ium chloride (1.1 g, 4.3 mmol) or 4-(3-oxo-3-(*p*-tolyl)propyl)morpholin-4-ium chloride (1.16 g, 4.3 mmol) in ethanol (10 mL) was dissolved in least amount of water. The reaction mixture was refluxed on a steam bath for 8 h, then kept overnight at room temperature. The formed precipitate was filtered, dried, and recrystallized from ethanol to afford the desired iminothiazolidin-4-one derivatives **8** and **9**, respectively.

2-Imino-3-(3-oxo-3-phenylpropyl)thiazolidin-4-one (8). (0.86 g, 81%); mp 181–182°C; R_f = 0.46 [pet. ether (40–60)/ethyl acetate, (1:2)]; white crystals; IR (KBr) ύ (cm^{-1}), 3178 (NH), 3060 (C—H), 2918 (C—H, stretch), 1715, 1682 (2CO), 1452, 1352 (C—H), 1254, 1206 (C—N), 744 (C—S); ^{1}H-NMR (200 MHz, DMSO-d_6): δ, 3.35 (t, 2H overlapped with water of DMSO), 3.72 (t, J = 7.2 Hz, 2H, CH_2), 3.93 (s, 2H, CH_2), 7.51–8.01 (m, 5H, Ar-H), 9.30 (s, 1H, NH exchangeable with D_2O); ms: (m/z, %): 248 (M^+, 3), 143 (78), 105 (97), 77 (100). Anal. Calcd. for $C_{12}H_{12}N_2O_2S$ (248.3): C, 58.05; H, 4.87; N, 11.28. Found: C, 58.24; H, 4.79; N, 11.25.

(Z)-2-Imino-3-(3-oxo-3-(p-tolyl)propyl)thiazolidin-4-one (9). (0.99 g, 88%); mp 200–202°C; white crystals; R_f = 0.49 [pet. ether (40–60)/ethyl acetate, (1:2)]; IR (KBr) ύ (cm^{-1}), 3178 (NH), 3060 (C—H), 2918 (C—H, stretch), 1715, 1682 (2CO), 1452, 1352 (C—H), 1254, 1206 (C—N), 744 (C—S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ, 2.36 (s, 3H, CH_3), 3.29 (t, J = 7.2 Hz, 2H, CH_2), 3.66 (t, J = 7.2 Hz, 2H, CH_2), 3.90 (s, 2H, CH_2), 7.31–7.80 (m, 4H, Ar-H), 9.27 (s, 1H, NH); ms: (m/z, %): 262 (M^+, 18), 261 (100), 260 (63). Anal. Calcd. for $C_{13}H_{14}N_2O_2S$ (262.33): C, 59.52; H, 5.38; N, 10.68. Found: C, 59.39; H, 5.59; N, 10.61.

Scheme 3. Reactions of 2-iminothiazolidin-4-one (**5**) with various chloromethane derivatives and its formylation.



(Z)-N-(5-Acetyl-4-oxo-3-(3-oxo-3-phenylpropyl)thiazolidin-2-ylidene)acetamide (11). A solution of 2-imino-3-(3-oxo-3-phenylpropyl)thiazolidin-4-one (**8**) (0.5 g, 2.01 mmol) in acetic anhydride (5 mL) was heated on a steam bath for 30 min, then kept overnight at room temperature, and poured into ice water; the formed precipitate after 15 min was filtered, dried, and then purified by crystallization from ethanol to afford (0.64 g, 96%) of **11**; mp 142–144°C; yellow crystals; $R_f = 0.63$ [pet. ether (40–60)/ethyl acetate, (1:1)]; IR (KBr) ύ (cm^{-1}), 2923 (C—H, stretch), 1754, 1677 (CO), 1594 (C—C, stretch), 1518 (C=N), 1216, 1127 (C—N, stretch), 895, 745 (C—S); ^{1}H-NMR (200 MHz, DMSO-d_6): δ, 2.23(s, 3H, CH_3), 2.45(s, 3H, CH_3), 3.56 (t, $J = 7.2$ Hz, 2H, CH_2), 4.39 (t, $J = 7.2$ Hz, 2H, CH_2) 6.79 (s, 1H, CH), 7.49–7.67 (m, 3H, Ar-H), 7.98 (d, $J = 7.5$ Hz, 2H, Ar-H); ms: (m/z, %): 332 (M^+, 6), 290 (33), 248 (40), 158 (10), 143 (15), 133 (80), 105 (100), 77 (99). Anal. Calcd. for $C_{16}H_{16}N_2O_4S$ (332.37): C, 57.82; H, 4.85; N, 8.43. Found: C, 57.69; H, 5.12; N, 8.33.

(Z)-3-((Z)-2-Benzoyl-3-(4-methoxyphenyl)allyl)-2-imino-5-(4-methoxybenzylidene)thia-zolidin-4-one (12). A mixture of **8** (0.5 g, 2.01 mmol) and 4-methoxybenzaldehyde (0.55 g, 4.02 mmol) in acetic acid (5 mL) refluxed for 3 h, kept overnight at room temperature, and diluted with water. The formed precipitate was filtered, dried, and then purified by recrystallization from ethanol to afford (0.63 g, 65%) of **12**; mp 121–122°C; red crystals; $R_f = 0.66$ [pet. ether (40–60)/ethyl acetate, (3:2)]; IR (KBr) ύ (cm^{-1}), 2766 (C—H, stretch), 1686, 1594 (2CO), 1502 (C=N), 1362, 1258 (C—H), 750 (C—S); ^{1}H-NMR (200 MHz, DMSO-d_6): δ, 3.32 (s, 2H, CH_2), 3.79 (s, 6H, $2OCH_3$), 7.05–7.08 (m, 8H, Ar-H), 7.48–7.67 (m, 5H, Ar-H), 7.97 (s, 1H, CH), 8.00 (s, 1H, CH), 9.68 (s, 1H, NH); ms: (m/z, %): 484 (M^+, 5), 234 (33), 164 (100), 120 (29), 77 (25). Anal. Calcd. for $C_{28}H_{24}N_2O_4S$ (484.57): C, 69.40; H, 4.99; N, 5.78. Found: C, 69.22; H, 5.21; N, 5.61.

(Z)-Ethyl 2-amino-5-((5-benzylidene-2-imino-4-oxothiazolidin-3-yl)methyl)-4,6-diphenyl-4H-pyran-3-carboxylate (15). A mixture of **8** (0.499 g, 2.01 mmol) and ethyl 2-cyano-3-phenylacrylate (0.81 g, 4.02 mmol) in ethanol (10 mL) and few drops of triethylamine was refluxed for 6 h on a steam bath. The formed precipitate was filtered, dried, and then purified by crystallization from ethanol to afford (0.62 g, 57%) of **15**; mp 164–165°C; yellow crystals; $R_f = 0.49$ [pet. ether (40–60)/ethyl acetate, (1:3)]; IR (KBr) ύ(cm^{-1}), 3818, 3746 (NH_2), 3418 (NH), 1666 (CO), 1636 (CO), 1540 (C=N), 1272 (C—O), 680 (C—S); ms: (m/z, %): 537 (M^+, 8), 204 (17), 134 (100), 105 (28), 77 (51). Anal. Calcd. for $C_{31}H_{27}N_3O_4S$ (537.63): C, 69.25; H, 5.06; N, 7.82. Found: C, 69.49; H, 5.31; N, 7.74.

2-Imino-3-(3-phenyl-3-(2-phenylhydrazono)propyl)thiazolidin-4-one (16). A mixture of **8** (0.5 g, 2.01 mmol) and phenyl hydrazine (0.22 g, 2.01 mmol) in acetic acid (5 mL) was heated for 6 h on a steam bath, stand overnight at room temperature, diluted with ice water and basified with Na_2CO_3 solution. The formed precipitate was filtered, dried, and then purified by crystallization from ethanol to afford (0.3 g, 44%) of **16**; mp 221–222°C; reddish brown powder; $R_f = 0.56$ [pet. ether (40–60)/ethyl acetate, (1:3)]; IR (KBr) ύ (cm^{-1}), 3734, 3222 (NH), 2996 (C—H, stretch), 1684 (CO), 1570 (C=N), 1508 (C=N), 1254 (C—H), 754, 692 (C—S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ, 3.32 (t, $J = 6.9$ Hz, 2H, CH_2), 3.49 (t, 6.9 Hz, 2H, CH_2), 4.00 (s, 2H, CH_2), 7.19–7.47 (m, 10H, Ar-H), 9.60 (s, 1H, =NH), 9.77 (s, 1H, NH); ms: (m/z, %): 338 (M^+, 5), 223 (17), 222 (100), 221 (58), 76 (49). Anal. Calcd. for $C_{18}H_{18}N_4OS$ (338.43): C, 63.88; H, 5.36; N, 16.56. Found: C, 63.67; H, 5.51; N, 16.48.

7-Phenyl-2H-thiazolo[3,2-a]pyrimidine-3-one[5,6:5′,6′]-2H-thiazolo[3′,2′-a]pyrimidine-3′,7′-dione (19). A mixture of **5** (1.0 g, 8.6 mmol), diethyl malonate (0.69 g, 4.3 mmol), and benzaldhyde (0.46 g, 4.3 mmol) or diethyl 2-benzylidenemalonate (1.07 g, 4.3 mmol) in ethanol (10 mL) was refluxed on steam bath for 6 h, and then left to cool. The formed precipitate was filtered, dried, and recrystallized from ethanol to afford (0.48 g, 30%) of **19**; mp 199–201°C; yellow crystals; $R_f = 0.64$ [pet. ether (40–60)/ethyl acetate, (1:2)]; IR (KBr) ύ (cm^{-1}), 3131 (C—H, stretch), 3044 (C—H, stretch), 1738, 1657 (CO), 1341 (CH), 1163 (C—N, stretch); ^{1}H-NMR (300 MHz, DMSO-d_6): δ, 3.53 (s, 4H, $2CH_2$), 5.56 (d, 1H, CH), 7.30–7.51 (m, 5H, Ar-H); ms: (m/z, %): 368 ($M^+ - 2$, 5), 133 (11), 134 (100). Anal. Calcd. for $C_{16}H_{10}N_4O_3S_2$ (370.41): C, 51.88; H, 2.72; N, 15.13. Found: C, 51.72; H, 2.98; N, 15.00.

5,10-Dihydrobenzo[e]thiazolo[3,2-a][1,3]diazepin-3(2H)-one (20). A mixture of 1,2-*bis*(chloromethyl)benzene (0.75 g, 4.3 mmol) and **5** (0.5 g, 4.3 mmol) were fused in an oil bath at 290°C for about 1.5 h, then ethanol was added. The formed precipitate was filtered, dried, and crystallized from DMF to afford (0.88 g, 94%) of **20**; mp > 300°C; yellow crystals; $R_f = 0.59$ [pet. ether (40–60)/ethyl acetate; (1:2)]; IR (KBr) ύ (cm^{-1}), 2900 (C—H, stretch), 3000 (C—H, stretch), 1676 (CO), 1548 (C=N), 1408 (C—C stretch), 1158 (C—N, stretch), 750 (C—S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ, 4.04 (s, 6H, $3CH_2$), 7.11–7.46 (m, 4H, Ar-H); ms: (m/z, %): 218 (M^+, 50), 135 (50), 117 (100), 105 (30). Anal. Calcd. for $C_{11}H_{10}N_2OS$ (218.27): C, 60.53; H, 4.62; N, 12.83. Found: C, 60.18; H, 4.32; N, 12.78.

3-(4-Chlorobenzyl)-2-[(imino) and (4-chlorobenzylimino)]thiazolidin-4-ones 21 and 22. A mixture of 1-chloro-4-(chloromethyl)benzene (1.38 g, 8.6 mmol), 2-iminothiazolidin-4-one (**5**) (0.5 g, 4.3 mmol), potassium carbonate (1 g, 8 mmol), and acetone (10 mL) was refluxed for 6 h on a steam bath; the reaction mixture was poured onto ice water, and the formed precipitate was filtered, dried, and purified by column chromatography using [(ethyl acetate/pet. ether) (60–80) (1:4)] as eluent for separating **21** in (29%) yield, whereas, using ethyl acetate/pet. ether (60–80°C) (2:4) as eluent for separating **22** in (64%) yield.

Moreover, when the previous reaction of 2-iminothiazolidin-4-one (**5**) (0.499 g, 4.3 mmol) with 1-chloro-4-(chloromethyl)-benzene (2.08 g, 12.9 mmol) in the presence of K_2CO_3 (1.5 g, 12.9 mmol) and by using the same reaction conditions only compound **22** was isolated.

3-(4-Chlorobenzyl)-2-iminothiazolidin-4-one (21). (0.3 g, 29%); mp 142–143°C; yellow crystals; $R_f = 0.52$ [pet. ether (40–60)/ethyl acetate, (1:2)]; IR (KBr) ύ (cm^{-1}), 3178 (NH), 2786 (C—H, stretch), 1696 (CO), 1622 (C=N), 1474 (C=C), 1432 (CH), 1212 (C—N, stretch), 800 (C—Cl); ^{1}H-NMR (DMSO-d_6): δ, 3.9 (s, 2H, CH_2), 4.6 (s, 2H, CH_2), 7.2–7.4 (m, 4H, Ar-H), 9.81 (s, 1H, NH); ms: (m/z, %): 240 (M^+, 30), 242 (10), 205 (29), 126 (37), 125 (100). Anal. Calcd. for $C_{10}H_9ClN_2OS$ (240.71): C, 49.90; H, 3.77; N, 11.64. Found: C, 49.51; H, 3.47; N, 11.57.

3-(4-Chlorobenzyl)-2-(4-chlorobenzylimino)thiazolidin-4-one (22). (1.01 g, 64%); mp 166–168°C; brown crystals; $R_f = 0.61$ [pet. ether (40–60)/ethyl acetate, (1:2)]; IR (KBr) ύ(cm^{-1}), 1690 (CO), 1538 (C=N), 1288 (CH), 1090 (C—N, stretch), 802 (C—Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ, 4.09 (s, 2H, CH_2), 4.6 (s, 4H, $2CH_2$), 7.27–7.43 (m, 8H, Ar-H); ms: (m/z, %): 364

(M^+-1, 3), 366 (0.96), 368 (0.31), 241 (29), 239 (73), 211 (13), 125 (100), 77 (4). Anal. Calcd. for $C_{17}H_{14}Cl_2N_2OS$ (365.28): C, 55.90; H, 3.86; N, 7.67. Found: C, 55.72; H, 3.56, N 7.57.

N′-(4-Chloro-5-formylthiazol-2-yl)-N,N-dimethylformimidamide (23). A mixture of 2-iminothiazolidin-4-one (**5**) (1.0 g, 8.6 mmol) in DMF (5 mL) then $POCl_3$ (4 mL) was added in portion while stirring in ice bath for 45 min. Then, the reaction mixture heated on water bath (60°C) for 30 min then poured on ice and basified with $NaHCO_3$. The formed precipitate was filtered, dried, and purified by crystallization from ethanol to afford (1.68 g, 90%) of **23**; mp 132–133°C; yellow crystals; $R_f = 0.68$ [pet. ether (40–60)/ethyl acetate, (1:3)]; IR (KBr) ύ(cm^{-1}), 1636 (CO), 1468 (CH), 1400 (C═C), 1236, 1128 (C═N, stretch), 800 (C═Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ, 3.06 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 8.53 (s, 1H, CH), 9.75 (s, 1H, CH); ms: (m/z, %): 217 (M^+, 98), 219 (32), 83 (100). Anal. Calcd. for $C_7H_8ClN_3OS$ (217.68): C, 38.62; H, 3.70; N, 19.30. Found: C, 38.48; H, 3.59; N, 19.24.

REFERENCES AND NOTES

[1] Bouzroura, S.; Bentarzi, Y.; Kaoua, R.; Nedjar-Kolli, B.; Poulain-Martini, S.; Dunach, E. Org Commun 2010, 3, 8.

[2] Kucukguzel, G.; Kocatepe, A.; De Clercq, E.; Sahin, F.; Gulluce, M. Eur J Med Chem 2006, 41, 353.

[3] Murugesan, V.; Prabhakar, Y. S.; Katti, S. B. J Mol Graph Model 2009, 27, 735.

[4] Balzarini, J.; Orzeszko-Krzesinska, B.; Maurin, J. K.; Orzesko, A. Eur J Med Chem 2009, 44, 303.

[5] Van Gaal, L.; Scheen, A. J. Diabetes Metab Res Rev 2002, 18, 51.

[6] Johnson, A. R.; Marletta, M. A.; Dyer, R. D. Biochemistry 2001, 40, 7736.

[7] Terzioglu, N.; Karali, N.; Gursoy, A.; Pannecouque, C.; Leysen, P.; Paeshuyse, J.; Neyts, J.; Clercq, E. D. Arkivoc 2006, 1, 109.

[8] Liebeschuetz, J. W.; Jones, S. D.; Morgan, P. J.; Murray, C. W.; Rimmer, A. D.; Roscoe, J. M. E.; Waszkowycz, B.; Welsh, P. M.; Wylie, W. A.; Young, S. C.; Martin, H.; Mahler, J.; Brady, L.; Wilkinson, K. J Med Chem 2002, 45, 1221.

[9] Ismail, M. A.; Brun, R.; Easterbrook, J. D.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. J Med Chem 2003, 46, 4761.

[10] Stephens, C. E.; Tanious, F.; Kim, S.; Wilson, W. D.; Schell, W. A.; Perfect, J. R.; Franzblau, S. G.; Boykin, D. W. J Med Chem 2001, 44, 1741.

[11] Hamama, W. S.; Zoorob, H. H. Tetrahedron 2002, 58, 6143.

[12] Schneiden, H. Int J Immunopharmacol 1981, 3, 9.

[13] Hamama, W. S.; Abd El-Magid, O. M.; Zoorob, H. H. Z Naturtorsch 2006, 61b, 1.

[14] Zoorob, H. H.; Hamama, W. S.; Abd El-Magid, O. M.; Soliman, M. S. J Chem Res 2005, 10, 669.

[15] Hamama, W. S. Synth Commun 2001, 31, 59.

[16] Hamam, W. S. J Chem Res 2000, 269.

[17] Zoorob, H. H.; Abou-El Zahab, M. M.; Abdel-Mogib, M.; Ismail, M. A. Tetrahedron 1996, 52, 10147.

[18] Yamada, M.; Koyoma, K.; Yokoe, I.; Myasaka, S.; K-Konno, Jpn Korai Tokyo Koho JPN07,165,748, 1995; C A 1996, 124, 9336a.

[19] Fukuda, Y.; Hasegawa, T.; Nakatani, Y.; Murase, K.; Fuji, K. PCT Int Appl WO96,16,968, 1996; C A 1996, 125, 142775e.

[20] Foguet, R.; Anglada, L.; Sacristan, A.; Castello, J. M.; Ortiz, J. A. PCT Int Appl WO9637,498, 1996; C A 1997, 126, 89392v.

[21] (a) Kappe, C. D.; Roschger, R. J Heterocycl Chem 1989, 26, 55; (b) Fedorova, E. V.; Meshcheryakov, M. P.; Ganina, M. B.; Moskvin A. V.; Ivin, B. A. Russ J General Chem 2004, 74, 128.

[22] Glennon, R. A.; Rogers, M. E.; Smith, J. D.; El-Said, M. K.; Egle, J. L. J Med Chem 1981, 24, 658.

[23] Zoorob, H. H.; Abou-El Zahab, M. M.; Abdel-Mogib, M.; Ismail, M. A.; Abdel-Hamid, M. Arzneim-Forsch. Drug Res 1997, 47, 958.

[24] Zoorob, H. H.; Ismail, M. A.; Strekowski, L. J Heterocycl Chem 2001, 38, 359.

[25] Kratt, G.; Salbeck, G.; Bonin, W.; Duewel, D. Ger offen DE3,903,404, 1991; C A 1991, 114, 23984.

[26] Hamama, W. S. Z Naunrforsch 2000, 55, 443.

[27] Sternbach, L. H.; Randall, L. O.; Gustafson, S. R. In 1,4-Benzodiazepines, Psychopharmacological Agents 1964, Vol I; Gordon M. Ed.; Academic Press: New York and London, p 35.

[28] Besson, T.; Guillard, J.; Rees, C. W. Tetrahedron Lett 2000, 41, 1027.

[29] Turan-Zitouni, G.; Demirayak, S.; Özdemir, A.; Kaplancikli, Z. A.; Yildiz, M. T. Eur J Med Chem 2003, 39, 267.

[30] Lhoták, P.; Himl, M.; Stibor, I.; Petříčková, H. Tetrahedron Lett 2002, 43, 9621.

[31] Augstein, J.; Green, S. M.; Munro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. J Med Chem 1965, 8, 446.

[32] Jakse, R.; Recnik, S.; Svete, J.; Golobic, A.; Golic, L.; Stanovnik, B. Tetrahedron 2001, 57, 8395.

[33] Egli, R. Ger Offen 3,015,121, 1980; C A 1981, 94, 158317J.

[34] Ramsh, S. M.; Ginak, A. I.; Smorygo, N. A.; Basova, Yu. G.; Sochilin, E. G. Zh Org Khim 1978, 14, 1327.