Synthesis of Novel Thiazolidine-4-one Derivatives and Their Anticancer Activity

Nosrat O Mahmoodi[a*], Masoud Mohammadi Zeydi[b], Esmaeil Biazar[c], Zahra Kazeminejad[d]

[a]Department of Organic Chemistry, Faculty of Sciences, University of Guilan, PO Box 41335-1914, Rasht, Iran

[b]Department of Organic Chemistry, University of Guilan, University campus 2, Rasht, Iran

[c]Department of Biomaterials Engineering, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

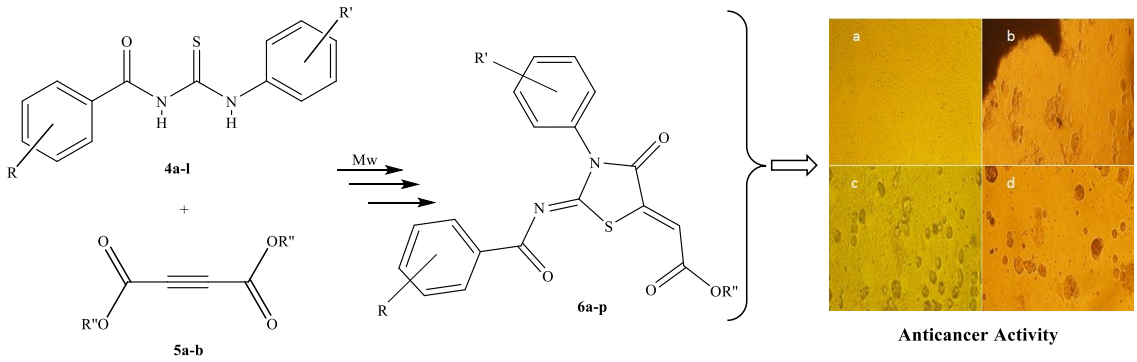
[d]Department of Chemistry, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran

*Corresponding author: mahmoodi@guilan.ac.ir

Abstract:

This paper describes the synthesis of a novel series of 1,3-thiazolidine-4-ones **6a-n** by cycloaddition reaction of *N*-aryl-*N′*-acyl thioureas **4a-k** with acetylenic esters **5a-b** under microwave irradiation and solvent free conditions. Our method, compared to conventional heating conditions has the benefit of higher reaction yield and shorter reaction times. Structural confirmation and characterization of products based on the analytical, chemical, and spectral analysis was confirmed. Cellular investigations showed that the target synthesized thiazolidine-4-ones are toxic and could be used as anticancer agents for MKN-45 gastric adenocarcinoma cells.

Graphical Abstract



Key words

Thiazolidine-4-one; *N*-aryl-*N*′-acyl thioureas; Microwave; Toxicity investigations and Cancer cells

INTRODUCTION

A brief review revealed thiazolidine derivatives belonging to an important group of heterocyclic compounds that have a long history in medicinal chemistry. In particular, thiazolidine-4-ones represent a class of heterocyclic compounds with a wide variety of pharmacological activities.[1] Furthermore, compounds containing a thiazolidine nucleus have a broad spectrum of biological activities, including anti-tumor,[2] anti-HIV,[3] antibacterial,[4] anti-microbial,[5] anti-convulsant,[6] cycloxygenase inhibitory,[7] anti-histaminic,[8] anti-platelet activating factor,[9] Ca^{2+} channel blocker,[10] antioxidant,[11,12] antitubercular,[13] antiinflammatory[14] and analgesic[15] properties. The structure activity relationship of thiazolidine-4-ones base on the apoptotic degradation of DNA and in vitro antioxidant studies e. g. DPPH and ABTS free radical scavenging assays[16, 17] and antimicrobial activity[18] was previously reported. The reaction of thiourea with acetylenic esters has been variously reported to give a thiazoline-4-one, an imiadazolinthion or a 1,3-thiazin-4-one. However, later studies have shown that in fact the main product is thiazoline-4-one.[19, 20] Thiazolidinones and their derivatives have attracted continuing interest because of their potential roles as antitumor and anticancer agents in chemotherapy.[21-25] In view of the importance of this nucleus, it is thought of interest to accommodate this heterocyclic, unsaturated amide and ester moieties in single molecular framework and screen them for their anticancer activity. The thermal methodologies for the synthesis of thiazolidinone-4-ones are very efficient, leading to good or excellent product yields. However, the thermal methods require a very long reaction time that raises the possibility of creating impure products. Microwave irradiation is another heating method based on the potential of some compounds to transform electromagnetic energy into heat. This process, that enhances chemical reaction rates

and manufactures cleaner products, as well can be successfully applied in pharmaceutical chemistry.[26]

Results and Discussion

As a part of our previous interest towards the development of new routes to the synthesis of heterocyclic compounds[27- 33] here, we report a facile and efficient route to the synthesis of several new thiazolidine-5-ylidenes **6a-n** compounds prepared from reaction of thioureas **4a-k** with either dimethyl acetylenedicarboxylate (DMAD) or diethyl acetylenedicarboxylate (DEAD). Later studies have shown that the configuration of these compounds are Z.[19, 20] The proposed structures of these new products were confirmed by spectroscopic data. Under microwave irradiation and solvent free conditions, DMAD and DEAD **(5a-b)** undergo a smooth reaction with prepared thioureas **4a-k** (Scheme 1) to produce thiazolidine-4-ones **6a-n** in good yield (Scheme 2). The structures of **6a-n** were deduced from their IR, ^{1}H and ^{13}C NMR spectra, HRMS and their elemental analyses. The IR spectrum of **6a** (Figure **S5**) revealed the presence of a stretching vibration corresponding to C = O bands at υ = 1640-1740 cm^{-1}, absorption bands in the region 1530--1591 cm^{-1} corresponding to C-N attributed to the ring closure, and bands in the regions of 1330--1338 and 1050--1098 cm^{-1}, which indicate the presence of C--S and C--N groups. The ^{1}HNMR spectrum of **6a** (Figure **S6**) in $CDCl_3$ showed singlets for methyl (δ = 2.20 ppm), methoxy (δ = 3.93 ppm), and characteristic olefinic proton at δ = 7.12 ppm, along with multiplets (δ = 7.24-7.90) for the aromatic protons. The ^{13}CNMR spectrum of **6a** (Figure **S7**) showed eighteen signals, in agreement with the proposed structure. Full assignments for **6a-n** are given in the experimental section, which exhibited characteristic signals with the appropriate chemical shifts. The proposed concerted mechanism for formation of **6** initially involves amide

formation of the more basic nitrogen of **4** with the ester of **5** to produce intermediate **7**. Subsequently, **7** undergo intramolecular 5-exo cyclization to produce thiazolidine-5-ylidenes derivatives **6** (Scheme 3). Chemotherapy is one of the methods for cancer treatment; so far several chemical components have been studied for cancer therapy. In continuation for finding new anticancer drugs[33-34] we consider in vitro (cytotoxicity) analysis by investigating anticancerous activity of thiazolidine-4-ones **6a**-**n** on fibroblast or cancerous cells, with stock concentration: 1mM and serial concentrations to be 1, 5, 10, 20 µl. Table **S1** (Supplemental Materials) show the results of a MTT assay for TCPS (control) of synthesized samples (**6a**-**n**). Our results showed a potential toxicity for fluorinated thiazolidine-4-ones due to the high electronegativity of fluorine. Consequently, a high toxicity for compound **6e** (95%) and other fluorinated compounds (**6k**, **6c**, **6h**, **6m**, **6i**, **6l**, **6j**, **6n**) in comparison to thiazolidine-4-ones with a chlorine substituent (**6a**, **6d**, **6e**) was observed. Figure **S 1** (Supplemental Materials) shows images of the cell cultures for both of the test compounds (**6e** and **6g**) and the control (TCPS). Cellular death is clearly visible in image c and d respectively. Interpretation of results in Table **S1** shows that all the synthesized compounds have anticancer activity although, some of them proved more active. Comparing the activity of compound **6e** (IC_{50} = 8.7± 0.04) vs **6d** (IC_{50} = 9.5± 0.03) indicates that replacement of electronegative fluorine atom instead of chlorine increases the biological activity. As well as, the position of substituted fluorine e.g. **6k** (IC_{50} = 8.8± 0.01) vs **6l** (IC_{50} = 8.9± 0.07) leads to change the anticancer activity. Also presence of ester substitution effects on the biological activity of compounds e.g. **6e** (IC_{50} = 8.7± 0.04) vs **6k** (IC_{50} = 8.8± 0.01).

EXPERIMENTAL

Reactions were carried out in microwave oven (Kenstar, Model No. OM-26 EGO, Power 1200W). The melting points were obtained on an electrothermal capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed using HF_{254} fluorescent silica gel plates (Merck), which were examined under UV 254 and 365 nm light. Infrared spectra (ν/cm^{-1}) were recorded on a Shimadzu IR-470, using KBr disks. ^{1}H and ^{13}CNMR spectra were recorded on a DRX-500 MHz Spectrometer at 293 K in $CDCl_3$. Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS. Elemental analyses were made by a Carlo--Erba EA1110 CNNO-S analyzer and agreed with the calculated values. High-resolution mass spectra (HRMS) were recorded on Agilent 6520 (QTOF) ESI-HRMS instrument. Figure 1 and 2 represents numbering for ^{13}C NMR spectra. The Supplemental Materials contains sample IR, ^{1}H and ^{13}C NMR spectra for products 6a-6n (Figures S 2 -- S 46)

Typical procedure for the one-pot preparation of 1-aryl-3-arylcarbonylthioureas (4a-k)

To a solution of ammonium thiocyanate (NH_4SCN) (5 mmol) in acetone (10 mL) was added benzoyl chloride derivative (5 mmol) and the mixture was stirred for 45 min. To this was added a solution of an aniline derivative (5 mmol) in acetone (5 mL) and continued stirring under reflux condition for another 100 min, the progress of reaction was monitored by TLC (*n*-hexane: EtOAc 3:1). After cooling, the product was filtered, washed with cold water and the solid was recrystallized from EtOH and dried to afford the pure compounds **4a-k** (Scheme 1).

Typical procedure for the preparation of thiazolidin-5-ylidenes derivatives (6a-n) (be cautious 4 is lachrymal).

Microwave Method: In a typical experiment, thioureas **4a-k** (1mmol) and acetylenic esters **5a-b** (1mmol) was mixed, ground properly, placed in a septum-capped microwave tube,

and irradiated at 720 W for a certain period of time (6-8 min). The reaction was monitored by TLC (*n*-hexane: EtOAc 3:1). After completion of the reaction, it was cooled to r.t. All the synthesized compounds were recrystallized from EtOH (Scheme 2).

Conventional Method: To a stirred solution of **4a-l** (1mmol) in CH_2Cl_2 (10 mL) was added drop wise a mixture of acetylenic esters **5a-b** (1mmol) in CH_2Cl_2 (5 mL) at r.t over 10 min. The reaction was allowed to reflux for 5h. The reaction was monitored by TLC (*n*-hexane: EtOAc 3:1). The solvent was removed under reduced pressure, and the residue was recrystallized from EtOH to afford the pure thiazolidine-4-one **6a-n** (Scheme 2).

4-Chloro-*N*-{[(2-methylphenyl)amino]carbonothioyl}benzamide (4a)

Yellow crystals, Yield 98%. m.p 131-132°C, IR (ν_{max}/cm^{-1}): 3291 (N-H str.), 3036 (C-H $_{aromatic}$), 1670, 1609 (C = C $_{aromatic}$), ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H, -CH_3), 7.28 (t, 1H, *J* = 2.4 Hz, Ar-H), 7.29 (t, 1H, *J* = 2.4 Hz, Ar-H), 7.32 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.54 (d, 1H, *J* = 6.8 Hz, Ar-H), 7.76 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.88 (d, 1H, *J* = 6.8 Hz, Ar-H), 9.17 (s, 1H, NH), 12.19 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6 ($C_{7'}$), 121.2 ($C_{5'}$), 125.0 ($C_{6'}$), 128.9 ($C_{4'}$), 129.6 ($C_{3'}$), 129.8 ($C_{12',14'}$), 130.6 ($C_{11',15'}$), 133.8 ($C_{10'}$), 133.9 ($C_{1'}$), 137.6 ($C_{2'}$), 138.1 ($C_{13'}$), 166.9 ($C_{8'}$), 178.8 ($C_{9'}$); -- HRMS ((+)-ESI): *m*/*z* = 304.0434 (calcd. 304.0437 for $C_{15}H_{13}ClN_2OS$): Anal.Calcd.for: C, 59.11; H, 4.30; N, 9.19 Found: C, 59.14; H, 4.33; N, 9.21.

Methyl-2-(2-((4-chlorobenzoyl)imino)-4-oxo-3-(*o*-tolyl)thiazolidin-5-ylidene)aetate (6a)

Yellow crystal, Yield 95%, m.p 227-229°C, IR (υ_{max}/cm^{-1}): 3067 (C-H $_{aromatic}$), 2950 (C-H $_{aliphatic}$), 1738, 1696, 1641(C = O str.), 1590, 1521 (C = N & C = C $_{aromatic}$), 1330 (C-S str.), 1186(C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (s, 3H, -CH_3), 3.93 (s, 3H, -OCH_3), 7.12 (s, 1H, vinyl-H), 7.24 (d, 2H, *J* = 7.2 Hz, Ar-H), 7.35 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.42 (d, 1H, *J* = 7.2

Hz, Ar-H), 7.46 (t, 1H, *J* = 4.8 Hz, Ar-H), 7.50 (t, 1H, *J* = 4.8 Hz, Ar-H), 7.90 (d, 2H, *J* = 8.4 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6 C_{12}), 52.8 C_{23}), 121.0 (C_{21}), 127.1 (C_9), 128.1 (C_7), 128.7 ($C_{16,\ 18}$), 130.1 (C_{11}), 131.2 ($C_{15,\ 19}$), 131.6 (C_8), 133.1 (C_5), 130.3 (C_{14}), 135.7 (C_{10}), 140.0 (C_6), 140.9 (C_{17}); 164.6 (C_2); 165.4 (C_{22}); 166.5 (C_4); 176.0 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 414.0444 (calcd. 414.0441 for $C_{20}H_{15}ClN_2O_4S$): Anal.Calcd.for: C, 57.90; H, 3.64; N, 6.75. Found: C, 57.53; H, 3.44; N, 6.55.

Methyl-2-(2-((4-methylbenzoyl)imino)-4-oxo-3-(*o*-tolyl)thiazolidine-5-ylidene)acetate (6b)

Yellow crystal, Yield 93%, m.p 203-205°C, IR (υ_{max}/cm^{-1}): 3068 (C-H $_{aromatic}$), 2952 (C-H $_{aliphatic}$), 1738, 1713, 1644 (C = O str.), 1610, 1538 (C = N & C = C $_{aromatic}$), 1320 (C-S str.), 1198 (C-O str.); ^{1}HNMR (400 MHz $CDCl_3$): δ 2.21 (s, 3H, -CH_3), 2.38 (s, 3H, -CH_3), 3.92 (s, 3H, -OCH_3), 7.10 (s, H, vinyl-H), 7.18 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.26 (t, 1H, *J* = 8.0 Hz, Ar-H), 7.39 (d, 1H, *J* = 5.6 Hz, Ar-H), 7.44 (t, 1H, *J* = 4.8 Hz, Ar-H), 7.48 (d, 1H, *J* = 6.8 Hz, Ar-H), 7.87 (d, 2H, *J* = 8.4 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7 (C_{12}), 21.8 (C_{20}), 52.7 (C_{23}), 120.5 (C_{21}), 127.1 (C_9), 128.1 (C_7), 129.1 ($C_{16,\ 18}$), 129.9 (C_{11}), 130.4 ($C_{15,\ 19}$), 131.2 (C_8), 132.0 (C_5), 133.4 (C_{14}), 135.8 (C_{10}), 141.0 (C_6), 144.5 (C_{17}), 164.7 (C_2), 165.1 (C_{22}), 165.5 (C_4), 176.8 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 394.0982 (calcd. 394.0987 for $C_{21}H_{18}N_2O_4S$): Anal.Calcd.for: C, 63.95; H, 4.60; N, 7.10. Found: C, 63.75; H, 4.36; N, 7.33.

Methyl-2-(2-((4-fluorobenzoyl)imino)-4-oxo-3-(*o*-tolyl)thiazolidine-5-ylidene)acetate (6c)

Yellow crystal, Yield 90%, m.p 180-181°C, IR (υ_{max}/cm^{-1}): 3058 (C-H $_{aromatic}$), 2977 (C-H $_{aliphatic}$), 1723, 1710, 1650 (C = O str.), 1544, 1510 (C = N & C = C $_{aromatic}$), 1314 (C-S str.), 1196 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.21 (s, 3H, -CH_3), 3.93 (S, 3H, -OCH_3), 7.09 (m, 2H, Ar-H), 7.12 (S, 1H, vinyl-H), 7.25 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.39-7.53 (m, 4H, Ar-H), 7.82 (m,

1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.6 (C_{12}), 52.8 (C_{23}), 116.9 ($C_{16, 18}$, d, $^2J_{F,C}$ = 22.0 Hz), 120.9 (C_{21}), 123.8 (C_9), 123.9 ($C_{15, 19}$, d, $^3J_{F,C}$ = 4.0 Hz), 127.1 (C_7), 128.1 (C_{11}), 130.0 (C_8), 131.2 (C_5), 132.8 (C_{14}), 135.8 (C_{10}), 140.6 (C_6), 163.2 (C_{17}, d, $^1J_{F,C}$ = 261.0 Hz), 164.8 (C_2), 165.4 (C_{22}), 165.5 (C_4), 174.6 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 398.0733 (calcd. 398.0737 for $C_{20}H_{15}F N_2O_4S$): Anal.Calcd.for: C, 60.29; H, 3.80; N, 7.03. Found: C, 60.26; H, 3.82; N, 7.06.

Methyl-2-(2-((4-chlorobenzoyl)imino)-4-oxo-3-(*p*-tolyl)thiazolidine-5-ylidene)acetate (6d)

Yellow crystal, Yield 96%, m.p 250-252°C, IR (υ_{max}/cm^{-1}): 3103 (C-H $_{aromatic}$), 2954 (C-H $_{aliphatic}$), 1730, 1705, 1650 (C = O str.),, 1589, 1532 (C = N & C = C $_{aromatic}$), 1322 (C-S str.), 1193 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.49 (s, 3H, $-CH_3$), 3.92 (s, 3H, $-OCH_3$), 7.10 (s, 1H, vinyl-H), 7.28 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.37 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.39 (d, 2H, *J* = 6.8 Hz, Ar-H), 7.97 (d, 2H, *J* = 8.4 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (C_{12}), 52.9 (C_{23}), 120.8 (C_{21}), 127.3 ($C_{7, 11}$), 128.7 ($C_{8,10}$), 130.0 ($C_{16, 18}$), 131.2 (C_9), 131.7 ($C_{15, 19}$), 133.1 (C_5), 139.6 (C_{14}), 140.0 (C_6), 140.7 (C_{17}), 165.0 (C_2), 165.5 (C_{22}), 166.9 (C_4), 176.0 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 414.0444 (calcd. 414.0441 for $C_{20}H_{15}ClN_2O_4S$): Anal.Calcd.for: C, 57.90; H, 3.64; N, 6.75. Found: C, 57.79; H, 3.52; N, 6.55.

Methyl-2-(2-((4-fluorobenzoyl)imino)-4-oxo-3-(*p*-tolyl)thiazolidine-5-ylidene)acetate (6e)

Yellow crystal, Yield 92%, m.p 203-204°C, IR (υ_{max}/cm^{-1}): 3050 (C-H $_{aromatic}$), 2979 (C-H $_{aliphatic}$), 1725, 1695, 1645 (C = O str.), 1580, 1517 (C = N & C = C $_{aromatic}$), 1330 (C-S str.), 1186 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H, $-CH_3$), 3.93 (s, 3H, $-OCH_3$), 7.08 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.11 (S, 1H, vinyl-H), 7.29 (d, 2H, *J* = 5.6 Hz, Ar-H), 7.39 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.07 (dd, 2H, *J* = 5.6, *J* = 20.0 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4 (C_{12}), 52.9 (C_{23}), 115.5 ($C_{16, 18}$, d, $^2J_{F,C}$ = 21.0 Hz), 120.7 (C_{21}), 127.3 ($C_{7, 11}$), 131.1 ($C_{15, 19}$, d, $^3J_{F,C}$ = 2.0

Hz), 131.3 ($C_{8,10}$), 133.0 (C_{14}, d, $^{3}J_{F,C}$ = 9.0 Hz), 139.6 (C_9), 140.8 (C_6), 145.7 (C_5), 165.0 (C_2), 166.1 (C_{17}, d, $^{1}J_{F,C}$ = 264.0 Hz), 175.8 (C_{22}), 167.4 (C_4), 165.5 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 398.0733 (calcd. 398.0737 for $C_{20}H_{15}F\ N_2O_4S$): Anal.Calcd.for: C, 60.29; H, 3.80; N, 7.03. Found: C, 60.24; H, 3.75; N, 7.12.

Methyl-2-(2-((4-chlorobenzoyl)imino)-3-(4-ethylphenyl)-4-oxothiazolidine-5-ylidene)acetate (6f)

Yellow crystal, Yield 94%, m.p 212-215°C, IR (υ_{max}/cm^{-1}): 3056 (C-H $_{aromatic}$), 2950 (C-H $_{aliphatic}$), 1723, 1700, 1645 (C = O str.), 1589, 1525 (C = N & C = C $_{aromatic}$), 1319 (C-S str.), 1199 (C-O str.); ^{1}H NMR (400 MHz $CDCl_3$): δ 1.34 (t, 3H, *J* = 7.6 Hz, -CH_3), 2.79 (q, 2H, *J* = 7.6 Hz, -CH_2-), 3.93 (s, 3H, -OCH_3), 7.11 (s, 1H, vinyl-H), 7.30 (d, 2H, *J* = 4.0 Hz, Ar-H), 7.38 (d, 2H, *J* = 5.2 Hz, Ar-H), 7.42 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.97 (d, 2H, *J* = 4.8 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2 (C_{12}), 28.6 (C_{12}), 52.8 (C_{23}), 120.8 (C_{21}), 127.3 ($C_{8,\ 10}$), 128.7 (C_9), 130.3 ($C_{15,\ 19}$), 131.4 (C_5), 131.7 ($C_{7,\ 11}$), 133.1 ($C_{15,\ 19}$), 140.0 (C_{14}), 140.7 (C_6), 145.7 (C_{17}), 165.0 (C_2), 165.5 (C_{22}), 166.9 (C_4), 176.0 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 428.0595 (calcd. 428.0598 for $C_{21}H_{17}ClN_2O_4S$): Anal.Calcd.for: C, 58.81; H, 4.00; N, 6.53. Found: C, 58.71; H, 3.86; N, 6.33.

Methyl-2-(3-(4-ethylphenyl)-2-((4-methylbenzoyl)imino)-4-oxothiazolidine-5-ylidene)acetate (6g)

Yellow crystal, Yield 98%, m.p 175-177°C, IR (υ_{max}/cm^{-1}): 3068 (C-H $_{aromatic}$), 2961(C-H $_{aliphatic}$), 1729, 1704, 1646 (C = O str.), 1605, 1528 (C = N & C = C $_{aromatic}$), 1321(C-S str.), 1207 (C-O str.); ^{1}H NMR (400 MHz $CDCl_3$): δ 1.34 (t, 3H, *J* = 7.6 Hz, -CH_3), 2.40 (s, 3H, -CH_3), 2.79 (q, 2H, *J* = 7.6 Hz, -CH_2-), 3.91 (s, 3H, -OCH_3), 7.08 (s, 1H, vinyl-H), 7.20 (d, 2H, *J* = 8.0 Hz, Ar-H), 7.32 (d, 2H, *J* = 4.8 Hz, Ar-H), 7.41 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.93 (d, 2H, *J* = 8.4 Hz,

Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2 (C_{12}), 21.8 (C_{20}), 29.6 (C_{12}), 52.7 (C_{23}), 120.3 (C_{21}), 127.4 ($C_{8,\ 10}$), 128.7 ($C_{7,\ 11}$), 129.1 ($C_{16,\ 18}$), 130.4 ($C_{15,\ 19}$), 131.5 (C_9), 132.0 (C_5), 141.0 (C_{14}), 144.5 (C_6), 145.5 (C_{17}), 165.1 (C_2), 165.5 (C_{22}), 166.5 (C_4), 176.9 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 408.1142 (calcd. 408.1144 for $C_{22}H_{20}N_2O_4S$): Anal.Calcd.for: C, 64.69; H, 4.94; N, 6.86. Found: C, 64.53; H, 4.92; N, 6.66.

Methyl-2-(3-(4-ethylphenyl)-2-((4-fluorobenzoyl)imino)-4-oxothiazolidine-5-ylidene)acetate (6h)

Yellow crystal, Yield 91%, m.p 193-194°C, IR (υ_{max}/cm^{-1}): 3055 (C-H $_{aromatic}$), 2967 (C-H $_{aliphatic}$), 1726, 1690, 1648 (C = O str.), 1570, 1550 (C = N & C = C $_{aromatic}$), 1335 (C-S str.), 1199 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, 3H, *J* = 7.6 Hz, $-CH_3$), 2.81 (q, 2H, *J* = 7.6 Hz, $-CH_2-$), 3.91 (s, 3H, $-OCH_3$), 7.04 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.08 (S, 1H, vinyl-H), 7.33 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.43 (d, 2H, *J* = 5.6 Hz, Ar-H), 8.05 (dd, 2H, *J* = 5.6, *J* = 20.8 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2 (C_{12}), 28.6 (C_{12}), 52.8 (C_{23}), 115.5 ($C_{16,\ 18}$, d, $^2J_{F,C}$ = 21.0 Hz), 120.6 (C_{21}), 127.4 ($C_{8,\ 10}$), 128.7 ($C_{7,\ 11}$), 131.1 (C_{14}, d, $^3J_{F,C}$ = 2.0 Hz), 131.5 (C_9), 132.9 ($C_{15,\ 19}$, d, $^3J_{F,C}$ = 9.0 Hz), 140.8 (C_5), 145.7 (C_6), 165.0 (C_2), 166.1 (C_{17}, d, $^1J_{F,C}$ = 264.0 Hz), 176.8 (C_{22}), 166.7 (C_4), 165.5 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 412.0896 (calcd. 412.0893 for $C_{21}H_{17}FN_2O_4S$): Anal.Calcd.for: C, 61.16; H, 4.15; N, 6.79. Found: C, 61.21; H, 4.27; N, 7.68.

Ethyl-2-(2-((4-fluorobenzoyl)imino)-4-oxo-3-(*o*-tolyl)thiazolidine-5-ylidene)acetate (6i)

Yellow crystal, Yield 93%, m.p 199-200°C, IR (υ_{max}/cm^{-1}): 3047 (C-H $_{aromatic}$), 2950 (C-H $_{aliphatic}$), 1735, 1683, 1648 (C = O str.), 1573, 1551 (C = N & C = C $_{aromatic}$), 1334 (C-S str.), 1188 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, 3H, *J* = 7.2 Hz, $-CH_3$), 2.20 (s, 3H, $-CH_3$), 4.39 (q, 2H, *J* = 7.2 Hz, $-OCH_2-$), 7.04 (dd, 2H, *J* = 1.3, *J* = 6.8 Hz, Ar-H), 7.11 (s, 1H, vinyl-H),

7.23 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.39-7.50 (m, 3H, Ar-H), 7.99 (dd, 2H, *J* = 1.2, *J* = 6.8 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (C_{12}), 17.6 (C_{23}), 62.0 (C_{23}), 115.5 ($C_{16,\ 18}$, d, $^2J_{F,C}$ = 21.9 Hz), 121.4 (C_{21}), 127.1 (C_9), 128.1 (C_7), 130.0 (C_{11}), 131.0 (C_8), 131.2 (C_{14}), 132.9 ($C_{15,\ 19}$, d, $^3J_{F,C}$ = 2.5 Hz), 133.3 (C_5), 135.7 (C_{10}), 140.4 (C_6), 164.7 (C_2), 164.8 (C_{22}), 166.1 (C_{17}, d, $^1J_{F,C}$ = 253.7), 167.3 (C_4), 175.7 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 412.0889 (calcd. 412.0893 for $C_{21}H_{17}FN_2O_4S$): Anal.Calcd.for: C, 61.16; H, 4.15; N, 6.79. Found: C, 61.12; H, 4.21; N, 6.65.

Ethyl-2-(2-((2-fluorobenzoyl)imino)-4-oxo-3-(*o*-tolyl)thiazolidine-5-ylidene)acetate (6j)

Yellow crystal, Yield 97%, m.p 186-187°C, IR (υ_{max}/cm^{-1}): 3056 (C-H $_{aromatic}$), 2954 (C-H $_{aliphatic}$), 1722, 1705, 1655 (C = O str.), 1540, 1510 (C = N & C = C $_{aromatic}$), 1311 (C-S str.), 1191 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, 3H, *J* = 7.2 Hz, -CH_3), 2.21 (S, 3H, -CH_3), 4.37 (q, 2H, *J* = 7.2 Hz, -OCH_2-), 7.07 (dd, 2H, *J* = 1.3, *J* = 2.0 Hz, Ar-H), 7.11 (S, 1H, vinyl-H), 7.23 (d, 1H, *J* = 6.8 Hz, Ar-H), 7.39-7.50 (m, 3H, Ar-H), 7.81 (dd, 1H, *J* = 1.2, *J* = 2.0 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (C_{23}), 17.6 (C_{12}), 62.0 (C_{23}), 117.0 (C_{18}, d, $^2J_{F,C}$ = 20.0 Hz), 121.4 (C_{21}), 122.9 (C_{14}, d, $^3J_{F,C}$ = 7.2 Hz), 123.8 (C_{16}, d, $^3J_{F,C}$ = 3.9 Hz), 127.1 (C_9), 128.1 (C_7), 130.0 (C_{11}), 131.2 (C_8), 132.9 (C_5), 133.2 (C_{10}), 135.1 (C_{17}), 135.0 (C_{15}, d, $^2J_{F,C}$ = 9.3 Hz), 140.3 (C_6), 161.4 (C_2), 164.0 (C_{19}, d, CF, $^1J_{F,C}$ = 260.0 Hz), 164.8 (C_{22}, d, $^3J_{F,C}$ = 35.4 Hz), 165.5 (C_4), 174.6 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 412.0891 (calcd. 412.0893 for $C_{21}H_{17}FN_2O_4S$): Anal.Calcd.for: C, 61.16; H, 4.15; N, 6.79. Found: C, 61.10; H, 4.18; N, 6.63.

Ethyl-2-(2-((4-fluorobenzoyl)imino)-4-oxo-3-(*p*-tolyl)thiazolidine-5-ylidene)acetate (6k)

Yellow crystal, Yield 96%, m.p 209-210°C, IR (υ_{max}/cm^{-1}): 3020 (C-H $_{aromatic}$), 2957 (C-H $_{aliphatic}$), 1725, 1685, 1650 (C = O str.), 1550, 1510 (C = N & C = C $_{aromatic}$), 1310 (C-S str.), 1189 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, 3H, *J* = 7.2 Hz, -CH_3), 2.49 (s, 3H, -CH_3),

4.38(q, 2H, *J* = 7.2Hz, -OCH_2-), 7.06 (dd, 2H, *J* = 1.4, *J* = 6.2 Hz, Ar-H), 7.08 (s, 1H, vinyl-H), 7.29 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.38 (d, 2H, *J* = 8.0 Hz, Ar-H), 8.05 (dd, 2H, *J* = 1.3, *J* = 5.6 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 1.42 (C_{23}), 21.3 (C_{12}), 62.0 (C_{23}), 115.4 ($C_{16,18}$, d, $^2J_{F,C}$ = 21.8 Hz), 121.8 (C_{21}), 127.3 ($C_{7,\ 11}$), 129.9 ($C_{8,10}$), 131.0 ($C_{15,19}$, d, $^3J_{F,C}$ = 2.4Hz), 131.3 (C_5), 133.0 (C_9), 139.5 (C_{14}), 140.5 (C_6), 164.8 (C_2), 164.8 (C_{17}, d, $^1J_{F,C}$ = 250.0 Hz), 166.7 (C_{22}), 167.3 (C_4), 175.8 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 412.0896 (calcd. 412.0893 for $C_{21}H_{17}FN_2O_4S$): Anal.Calcd.for: C, 61.16; H, 4.15; N, 6.79. Found: C, 61.14; H, 4.11; N, 6.82.

Ethyl-2-(2-((2-fluorobenzoyl)imino)-4-oxo-3-(*p*-tolyl)thiazolidine-5-ylidene)acetate (6l)

Yellow crystal, Yield 94%, m.p 164-165°C, IR (υ_{max}/cm^{-1}): 3043 (C-H $_{aromatic}$), 2920 (C-H $_{aliphatic}$), 1720, 1700, 1670 (C = O str.), 1569, 1532 (C = N & C = C $_{aromatic}$), 1312 (C-S str.), 1194 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, 3H, *J* = 7.2 Hz, -CH_3), 2.47 (s, 3H, -CH_3), 4.36 (q, 2H, *J* = 7.2 Hz, -OCH_2-), 7.09 (dd, 2H, *J* = 1.4, *J* = 7.6 Hz, Ar-H), 7.13 (1H, S, vinyl-H), 7.28 (d, 2H, *J* = 4.8 Hz, Ar-H), 7.36 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.48-7.53 (m, 1H, Ar-H), 7.90 (d, 1H, *J* = 7.6 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (C_{23}), 21.3 (C_{12}), 62.0 (C_{23}), 116.9 (C_{18}, d, $^2J_{F,C}$ = 22.2 Hz), 121.2 (C_{21}), 122.9 (C_{14}, d, $^3J_{F,C}$ = 7.2 Hz), 123.8 (C_{15}, d, $^3J_{F,C}$ = 3.9 Hz), 127.3 ($C_{7,\ 11}$), 129.9 ($C_{8,\ 10}$), 131.1 (C_{16}), 132.8 (C_9), 135.0 (C_{17}, d, $^2J_{F,C}$ = 9.3 Hz), 139.5 (C_5), 140.3 (C_6), 164.8 (C_2), 165.0 (C_{19}, d, $^1J_{F,C}$ = 260.8 Hz), 166.7 (C_{22}), 167.3 (C_4), 175.6 (C_{13}, d, $^3J_{F,C}$ = 3.60 Hz); -- HRMS ((+)-ESI): *m*/*z* = 412.0890 (calcd. 412.0893 for $C_{22}H_{20}N_2O_4S$): Anal.Calcd.for: C, 64.70; H, 4.89; N, 6.86. Found: C, 64.33; H, 4.92; N, 6.46. Anal.Calcd.for $C_{21}H_{17}FN_2O_4S$: C, 61.16; H, 4.15; N, 6.79. Found: C, 61.10; H, 4.08; N, 6.72.

Ethyl-2-(3-(4-ethylphenyl)-2-((4-fluorobenzoyl)imino)-4-oxothiazolidine-5-ylidene)acetate (6m)

Yellow crystal, Yield 97%, m.p 197-198°C, IR (υ_{max}/cm^{-1}): 3042 (C-H $_{aromatic}$), 2900 (C-H $_{aliphatic}$), 1728, 1690, 1642 (C = O str.), 1580, 1560 (C = N & C = C $_{aromatic}$), 1340 (C-S str.), 1201(C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (t, 3H, *J* = 7.6 Hz, -CH_3), 1.39 (t, 3H, *J* = 7.2 Hz, -CH_3), 2.79 (q, 2H, *J* = 7.6 Hz, -CH_2-), 4.38 (q, 2H, *J* = 7.2 Hz, -OCH_2-), 7.04 (dd, 2H, *J* = 1.3, *J* = 6.8 Hz, Ar-H), 7.09 (S, 1H, vinyl-H), 7.32 (d, 2H, *J* = 8.8 Hz, Ar-H), 7.42 (d, 2H, *J* = 8.8 Hz, Ar-H), 8.06 (dd, 2H, *J* = 1.2, *J* = 6.8 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (C_{12}), 15.2 (C_{23}), 28.6 (C_{12}), 62.0 (C_{23}), 115.5 ($C_{16, 18}$, d, $^{2}J_{F,C}$ = 21.7 Hz), 121.1 (C_{21}), 127.4 ($C_{8, 10}$), 128.7 ($C_{7, 11}$), 131.1 ($C_{15, 19}$, d, $^{3}J_{F,C}$ = 2.7 Hz), 132.9 (C_9), 133.0 (C_6), 140.5 (C_5), 145.7 (C_{14}), 164.8 (C_2), 165.1 (C_{17}, d, $^{1}J_{F,C}$ = 250.0 Hz), 166.7 (C_{22}), 167.3 (C_4), 175.8 (C_{13}); -- HRMS ((+)-ESI): *m*/*z* = 426.1047 (calcd. 426.1050 for $C_{22}H_{19}FN_2O_4S$): Anal.Calcd.for: C, 61.96; H, 4.49; N, 6.57. Found: C, 61.92; H, 4.41; N, 6.64.

Ethyl-2-(3-(4-ethylphenyl)-2-((2-fluorobenzoyl)imino)-4-oxothiazolidine-5-ylidene)acetate (6n)

Yellow crystal, Yield 95%, m.p 212-215°C, IR (υ_{max}/cm^{-1}): 3059 (C-H $_{aromatic}$), 2952 (C-H $_{aliphatic}$), 1728, 1705, 1650 (C = O str.), 1589, 1532 (C = N & C = C $_{aromatic}$), 1310 (C-S str.), 1205 (C-O str.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, *J* = 8.4 Hz, -CH_3), 1.78 (t, 3H, *J* = 8.4 Hz, -CH_3), 2.77 (q, 2H, *J* = 7.6 Hz, -CH_2-), 3.90 (q, 2H, *J* = 7.6 Hz, -OCH_2-), 7.09 (S, 1H, vinyl-H), 7.10-7.15 (m, 2H, Ar-H), 7.32 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.40 (d, 2H, *J* = 7.6 Hz, Ar-H), 7.48-7.53 (m, 1H, Ar-H), 7.91 (t, 1H, *J* = 7.6 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (C_{12}), 15.2 (C_{23}), 27.2 (C_{12}), 53.2 (C_{23}), 117.9 (C_{18}, d, $^{2}J_{F,C}$ = 22.2 Hz), 120.9 (C_{21}), 123.0 (C_{14}, d, $^{3}J_{F,C}$ = 7.0 Hz), 123.5 (C_{15}, d, $^{3}J_{F,C}$ = 3.0 Hz), 127.0 (C_{16}), 128.2 ($C_{7, 11}$), 131.8 (C, C_5), 132.2 ($C_{8,10}$), 135.1 (C_{17}, d, $^{2}J_{F,C}$ = 9.0 Hz), 140.8 (C_9), 145.6 (C_6), 161.5 (C_2), 164.1 (C_{22}), 165.4 (C_4), 165.5

(C_{19}, d, $^{1}J_{F,C}$ = 258.8 Hz), 175.2 (C_{13}, d, $^{3}J_{F,C}$ = 4.1 Hz); -- HRMS ((+)-ESI): *m*/*z* = 426.1046 (calcd. 426.1050 for $C_{22}H_{19}FN_2O_4S$): Anal.Calcd.for: C, 61.96; H, 4.49; N, 6.57. Found: C, 61.95; H, 4.42; N, 6.56.

In vitro cytotoxicity assay

The samples and negative control (tissue culture poly styrene; TCPS) and positive control (paclitaxel anticancer powder; $C_{47}H_{51}NO_{14}$, PTX, Xi' a Natural Field Bio-technique Co., Ltd, P. R. China) were well cleaned and sterilized by the autoclave method. Individual samples were placed in Petri dishes using a sterilized pincer; cell culture MKN-45 gastric adenocarcinoma were cultured in RPMI 1640 supplemented with 10% fetal calf serum, 100 U/ml penicillin and 100 µg/ml streptomycin. They were incubated at 37°C in a humidified CO_2 incubator with 5% CO_2 and 95% air. Cultures were examined regularly. To evaluate the cytotoxicity effect of components on the MKN-45cell line, the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) colorimetric assay was applied.

Briefly, cells were seeded into 96-well culture plates at 10000 cells per well containing 200 µl medium. The medium was removed 24 h after plating and fresh media containing same concentration of samples (stock concentration: 1mM, serial concentrations 1, 5, 10, 20 µl) was added. After incubation for 48 h the medium was discarded, the cells were washed twice with phosphate-buffered saline and 50 µg/ml MTT solutions for 4 h and formazan crystals dissolved by adding 100 µg DMSO to each well. The absorptions were measured in triplicate at 575 nm, with a background correction at 630 nm, using a microplate ELISA reader. Results were recorded as percentage absorbance relative to untreated control cells. The percentage of cell viability was calculated using the equation: [mean optical density (OD) of treated cells/mean OD

of control cells] ×100**.** The IC_{50} was calculated manually by linear interpolation using the formula: IC_{50} = [(50-A)/ (B-A)] x (D-C) + C, where A = the first point on the curve, expressed as percent inhibition, that is less than 50%; B = the first point on the curve, expressed as percent inhibition, that is greater than or equal to 50%; C = the concentration of inhibitor that gives A% inhibition; and D = the concentration of inhibitor that gives B% inhibition.[34]

CONCLUSION

These two-step synthetic methods allow us the rapid assessment of pharmacological activities of novel thiazolidine-5-ylidenes derivatives. The simplicity, easy execution, simple workup, and good yields, together with the use of easily accessible starting materials and an environmentally friendly procedure, are characters of this process. Several novel fluorinated derivatives for first time have been synthesized and isolated in satisfactory yields (78-93%). MTT analysis and cellular images showed a high toxicity of compounds e.g. **6e** (95%) to MKN-45 gastric adenocarcinoma cells when compared to a control sample. Here, we selected MKN-45 gastric adenocarcinoma cells as a case study. In our future study, we are going to apply other cells and examine their anticancer effects.

ACKNOWLEDGMENTS

The partial support of this research by the Research Committee of University of Guilan and Tonekabon Branch, Islamic Azad University is gratefully acknowledged. We also acknowledge the useful suggestions made by Professor Douglas Fry of SAFC, USA.

REFERENCES

1. Havrylyuk, D.; Roman, O.; Lesyk, R. *Eur. J. Med. Chem.* **2016**, 113, 145-166.

2. Correa, R. S.; Da Silva, M. M.; Graminha, A. E.; Meira, C. S.; Dos Santos, J. A. F.; Moreira, D. R. M.; Soares, M. B. P.;

Poelhsitz, G. V.; Castellano, E. E.; Bloch Jr, C.; Cominetti, M. R.; Batista, A. A. *J. Inorg. Biochem.* **2016**, 156, 153-163.

3. Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; Clercq, E. D. *Bioorg. Med. Chem.* **2007**, 15, 1725-1731.

4. Kumar, S.; Bhat, H. R.; Kumawat, M. K.; Singh, U. P. *New J. Chem.* **2013**, 37, 581-584.

5. Sindhu, J.; Singh, H.; Khurana, J. M.; Sharma, C.; Aneja, K. R. *Chin. Chem. Lett.* **2015**, 26, 50–54.

6. Desai, N. C.; Mahendra, R. S.; Mangesh, G.; Kailash, G. B.; Shashikant, V. B.; Ana, N.; Kalyan, C. A.; Prashant, J. B.; *ARKIVOC* **2007**, 14, 1-17.

7. Ottana, R.; Mazzon, E.; Dugo, L.; Monforte, F.; Maccari, R.; Sautebin, L.; De Luca, G.; Vigorita, M. G.; Alcaro, S.; Ortuso, F.; Caputi, A. P.; Cuzzocrea, S. *Eur. J. Pharmacol*. **2002**, 12, 71-80.

8. Diurno, M. V.; Mazzoni, O.; Correale, G.; Monterrey, I. G.; Calignano, A.; Rana, G. L.; Bolognese, A. *IL Farmaco* **1999**, 54, 579-583.

9. Tanabe, Y.; Yamamoto, H.; Murakami, M.; Yanagi, K.; Kubota, Y.; Okumura, H.; Sanemitsu, Y.; Suzukamo, G.; *J. Chem. Soc. Perkin. Trans.* **1995**, 7, 935-947.

10. Kato, T.; Ozaki, T.; Tamura, K.; Suzuki, Y.; Akima, M.; Ohi, N. *J. Med. Chem.* **1999**, 42, 3134-3146.

11. Mohammad, A. *Chem. Int.* **2015**, 1, 1-11.

12. da Silva, T. L.; Miolo, L. M. F.; Sousa, F. S. S.; Brod, L. M. P.; Savegnago, L; Schneider, P. H. *Tetrahedron Lett.* **2015**, 56, 6674–6680.

13. Navin, B. P.; Hemant, R. P.; Faiyazalam, M. S.; Dhanji, R. *Med. Chem. Res.* **2014**, 23, 1360-1370.

14. Apostolidis, I.; Liaras, K.; Geronikaki, A.; Hadjipavlou-Litina, D.; Gavalas, A.; Sokovic, M. *Bioorg. Med. Chem.* **2013**, 21, 532-539.

15. Deep, A.; Jain, S.; Sharma, P. C.; Phogat, P.; Malhotra, M. *Med. Chem. Res.* **2011**, 21, 1652-1659.

16. Isloor, A.; Sunil, D.; Shetty, P.; Malladi, S.; Pai, K.; Maliyakkl, N. *Med. Chem. Res.* **2013**, 22, 758-767.

17. Sala, M.; Chimento, A.; Saturnino, C. *Bioorg. Med. Chem. Lett.* **2013**, 23, 4990-4995.

18. Al-Majidi, S. M. H. *J. Saudi Chem. Soc.* **2014**, 18, 893–901.

19. Yavari, I.; Hossaini, Z.; Sabbaghan, M.; Pourshamsian, Kh.; Bagheri, M.; Ali-asgari, S. *Mol. Divers*. **2007**, 11, 81-85.

20. Yavari, I.; Pourshamsian, Kh.; Bagheri, M.; Ali-asgari, S. *J. Sulfur. Chem.* **2007**, 28, 269-273.

21. Tahermansouri, H.; Aryanfar, Y.; Biazar, E. *Bull. Korean. Chem. Soc.* **2013**, 34, 149-153.

22. Tahermansouri, H. Biazar, E. *New Carbon Mater.* **2013**, 28.199-207.

23. Azizian, J.; Tahermansouri, H.; Biazar, E.; Heidari, S.; Chobfrosh, *D. Int. J. Nanomed.* **2010**, 5, 907-914.

24. Ai, J.; Biazar, E.; Jafarpour, M.; Montazeri, M.; Majdi, A.; Aminifard, S.; Zafari, M.; Akbari, H. R.; Rad, H. *Int. J. Nanomed.* **2011**, 6, 1117-1127.

25. Tavakolifard, S.; Biazar, E.; Pourshamsian, K.; Moslemin, M. H. *Artif. Cells. Nanomed. Biotechnol.* **2015**, 17, 1-7.

26. Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. *Org. Biomol. Chem.* **2004**, 2, 2809-2811.

27. Mahmoodi, N. O.; Kiyani, H. *Bull. Korean. Chem. Soc.* **2004**, 25, 1417-1420.

28. Mahmoodi, N. O.; Parvizi, J.; Sharifzadeh, B.; Rassa, M. *Arch. Pharm. Chem. Life. Sci*. **2013**, 346, 1207-1213.

29. Rineh, A.; Mahmoodi, N. O.; Abdollahi, M.; Foroumadi, A.; Sorkhi, M.; Shafiee, A. *Arch. Pharm. Chem. Life. Sci.* **2007**, 340, 409-415.

30. Mahmoodi, N. O.; Safari, N.; Sharifzadeh, B. *Synth. Commun.* **2014**, 44, 245-250

31. Sharifzadeh, B.; Mahmoodi, N. O.; Mamaghani, M.; Tabatabaeian, Kh.; Salimi Chirani, A.; Nikokar, I. *Bioorg. Med. Chem. Lett*. **2013**, 23, 548-551.

32. Ghanbari pirbasti, F.; Mahmmoodi, N. O. *Mol. Divers.* **2016**, 20, 497-506.

33. Mahmoodi, N. O.; Ghavidast, A.; Amirmahani, N. *J. Photochem. Photobiol.* **2016,** 162, 683-693.

34. Aly, A. A.; Brown, A. B.; Ramadan, M.; Abdel-Aziz, M.; Abuo-Rahma, G. E. D. A. A.; Radwan, M. F.; Gamal-Eldeen, A. M. *J. Heterocyl. Chem.* **2012**, 49, 726-731.

35. Mahata, S.; Maru, S.; Shukla, S.; Pandey, A.; Mugesh, G.; Das, B. C.; Bharti, A. C. *BMC Complement. Altern. Med.* **2012**, 12, 15.

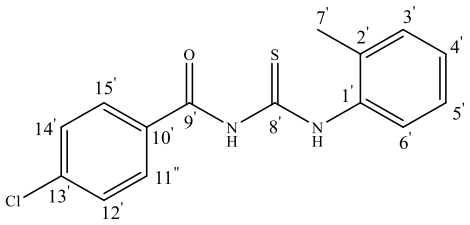


Figure 1 Numbering for ^{13}C NMR spectra thiourea

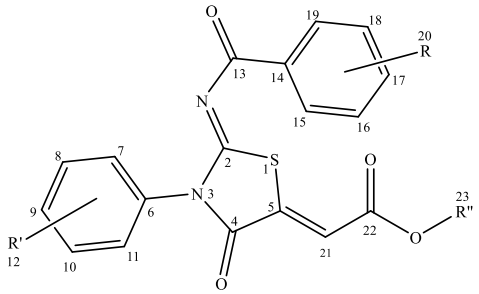
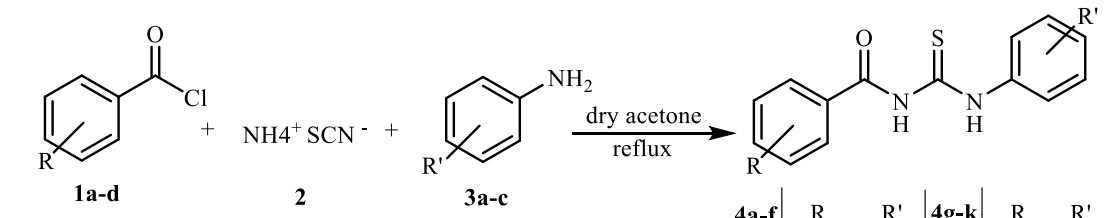


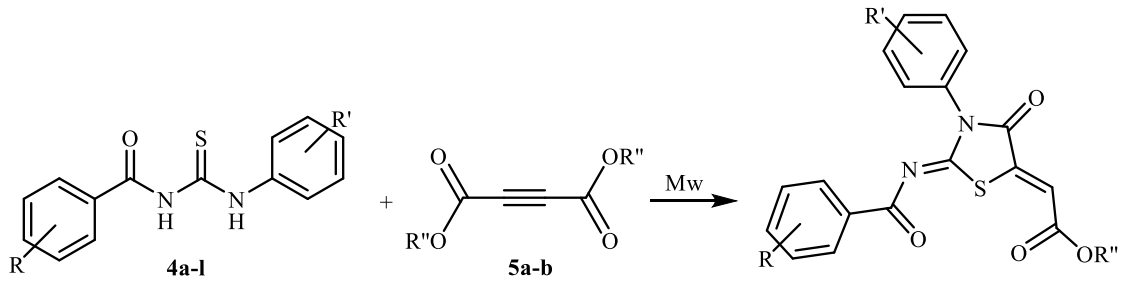
Figure 2 Numbering for ^{13}C NMR spectra thiazolidines



R = 4-Cl, 4-Me, 4-F, 2-F R' = 2-Me, 4-Me, 4-Et

4a-f	R	R'	4g-k	R	R'
4a	4-Cl	2-Me	4g	4-F	4-Me
4b	4-Cl	4-Me	4h	4-F	4-Et
4c	4-Cl	4-Et	4i	2-F	2-Me
4d	4-Me	2-Me	4j	2-F	4-Me
4e	4-Me	4-Et	4k	2-F	4-Et
4f	4-F	2-Me			

Scheme 1 One-pot synthesis of thioureas **4a-k**

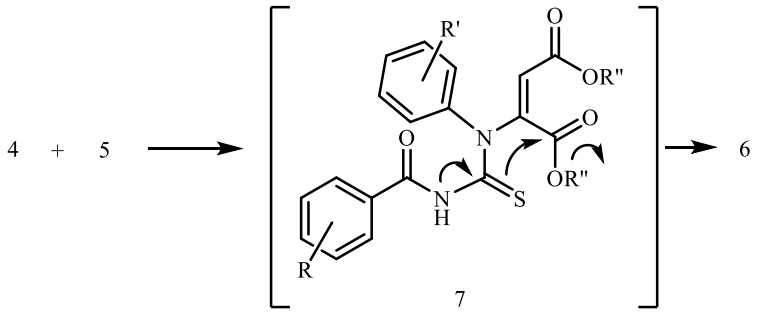


R = 4-Cl, 4-Me, 4-F, 2-F
R' = 2-Me, 4-Me, 4-Et

R"= Et, Me

6a-6g	R	R'	R"	6h-6n	R	R'	R"
6a	4-Cl	2-Me	Me	6h	4-F	4-Et	Me
6b	4-Me	2-Me	Me	6i	2-F	4-Et	Me
6c	4-F	2-Me	Me	6j	2-F	2-Me	Et
6d	4-Cl	4-Me	Me	6k	4-F	4-Me	Et
6e	4-F	4-Me	Me	6l	2-F	4-Me	Et
6f	4-Cl	4-Et	Me	6m	4-F	4-Et	Et
6g	4-Me	4-Et	Me	6n	2-F	4-Et	Et

Scheme 2 Synthesis of thiazolidine-4-one **6a-n**



Scheme 3 Mechanism for preparation of **6** via **7**