*Heterocyclic Letters*
*Vol. 8| No.3|593-601|May-July|2018*
*ISSN : (print) 2231–3087 / (online) 2230-9632*
*CODEN: HLEEAI*
*http://heteroletters.org*

# SYNTHESIS AND CHARACTERIZATIONOF NOVEL THIAZOLIDINONE DERIVATIVES OF C-MANNICH BASES

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**Abstract**: The present synthesis involves the introduction of C-Mannich bases on 4-thiazolidinone derivatives. Thiazolidinone derivatives (**2a-e**) were prepared by treating thiosemicarbazones (**1a-e**) with bromoethyl acetate and sodium acetate in DMF. C-Mannich bases (**4a-b**) were prepared by treating propargyl derivative of p-hydroxy benzaldehyde (**3**) with different secondary amines (piperidine/Morpholine), 40% formaldehyde and Cu (II) acetate in dioxane. These thiazolidinone derivatives and C-Mannich bases are condensed to get the final derivatives (**5a-j**). All the synthesized compounds were characterized by Mass, $^{1}$H NMR and $^{13}$C NMR spectra.

**Keywords**: C-Mannich bases, thiazolidinone, 40% formaldehyde, p-hydroxy benzaldehyde

**Introduction**:
Thiazolidines have been shown to possess various remarkable biological activities such as analgesic[i],amoebicidal[ii],nematocidal[iii],anaesthetic[iv], mosquito-repellent[v],anti-HIV, anticancer[vi],antibacterial[vii-xii],antifungal[xii,xiv],anti-inflammatory[xv-xvii],antitubercular[xviii-xx],EGFR and HER-2 kinase inhibitor[xxi],anti proliferative [xxii,xxiii]etc.
4-Thiazolidinones are always being an attraction point for researchers because of its efficiency towards various pharmacological usages.4-thiazolidinones are derivatives of thiazolidinone with carbonyl group at the 4$^{th}$ position and formed by the attack of sulphur nucleophile on imine carbon followed by intramolecular cyclisation with elimination of water. Substituent in the 2, 3 and 5 positions may be varied, but the greatest difference in structure and properties is exerted by the groups attached to carbon atom at the 2-position and to nitrogen atom at the 3-position.
Mannich bases also act as important pharmacophore or bioactive leads which are further used for the synthesis of various potential agents of high medicinal value which possess aminoalkyl chain. Mannich bases are the end products of Mannich reaction[xxiv]. Mannich reaction is a nucleophilic addition reaction which involves the condensation of a compound with active hydrogen(s) with an amine (primary or secondary) and formaldehyde (any aldehyde)[xxv].The examples of clinically useful Mannich bases which consist of aminoalkyl chain are cocaine, fluoxetine, atropine, ethacrynic acid, trihexyphenidyl, procyclidine, ranitidine, biperiden[xxvi].

Mannich bases are known to play a vital role in the development of synthetic pharmaceutical chemistry. The literature studies revealed that Mannich bases are very reactive and can be easily converted to other compounds[xxvii]. Mannich bases areknown to possess potent activities like anti-inflammatory[xxviii], anticancer[xxix], antifilarial[xxx], antibacterial[xxxi], antifungal[xxxii], anticonvulsant[xxxiii], antihelmintic[xxxiv], antitubercular[xxxv], analgesic[xxxvi], antimalarial[xxxvii], antipsychotic[xxxviii]and antiviral[xxxix] activities.

**Experimental:**

All the reactionswere monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (mesh); spots were visualizedwith UV light. Merck silica gel (60-120 mesh) was used for column chromatography. $^{1}$H NMR(400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 MHz NMR spectrometer in$CDCl_3$ solution using TMS as an internal standard. All chemical shifts are reported in δ (ppm) using TMS as aninternal standard. The mass spectra were recorded on Agilent 1100 LC/MSD instrument with method API-ES at 70eV.

**Synthesis of thiosemicarbazones(1a-e)**

An equivalent amount of thiosemicarbazide (1mmol) was added to a suspension of the appropriate aldehyde or ketone derivatives(1 mmol) in absolute ethanol(15 ml). The reaction mixture was heated under reflux for 2-4 h and allowed to cool to room temperature. The separated solidwas filtered, washed with ethanol and recrystallized from DMF and ethanol solvent mixture.

**(Z)-2-(4-nitrobenzylidene)hydrazine-1-carbothioamide(1a)**

Yellowsolid, Yield: 90%, mp: 180-183 $^{o}$C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.46 (d, $J$ = 8.35 Hz, 2H, Ar-H), 8.73-8.76 (m, 3H, Ar-H, -CH=N), 8.95 (s, 2H, -$NH_2$), 11.70 (s, 1H, -NH);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 128.5, 130.7, 132.5, 138.6, 147.3, 179.4;LCMS (positive ion mode) (*m/z*): 225 $[M+H]^+$ for $C_8H_8N_4O_2S$.

**(Z)-2-(1-(4-nitrophenyl)ethylidene)hydrazine-1-carbothioamide(1b)**

Yellow solid, Yeild: 88%, mp: 184-186 $^{o}$C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$3.18 (s, 3H), 8.99-9.08 (m, 5H, Ar-H, H of $NH_2$), 9.31 (s, 1H of $NH_2$), 11.30 (s, 1H, NH);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$13.5, 122.8, 127.3, 143.4, 144.9, 147.0, 178.9; LCMS (positive ion mode) (*m/z*): 239 $[M+H]^+$for $C_9H_{10}N_4O_2S$.

**(Z)-2-(4-chlorobenzylidene)hydrazine-1-carbothioamide(1c)**

White solid, Yield: 92%, mp: 185-187 $^{o}$C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$7.36 (d, $J$ = 8.5 Hz, 2H, Ar-H), 7.72-7.75 (m, 3H, Ar-H, -CH=N), 8.05 (s, 2H, -$NH_2$), 11.50 (s, 1H, -NH);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$126.8, 131.5, 132.5, 137.6, 145.8, 176.5; LCMS (positive ion mode) (*m/z*): 214 $[M+H]^+$ for $C_8H_8ClN_3S$.

**(Z)-2-(4-methoxybenzylidene)hydrazine-1-carbothioamide(1d)**

White solid, Yield: 90%, mp: 187-189 $^{o}$C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$3.85 (s, 3H, -$OCH_3$), 7.15 (d, $J$ = 8.26 Hz, 2H, Ar-H), 7.94 (d, $J$ = 8.34 Hz, 2H, Ar-H), 7.97 (s, 1H, -CH=N), 8.17 (s, 2H, -$NH_2$), 11.30 (s, 1H, -NH);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 65.7, 119.7, 134.3, 135.2, 139.8, 149.5, 177.4;LCMS (positive ion mode) (*m/z*): 210 $[M+H]^+$ for$C_9H_{11}N_3OS$.

**(Z)-2-(3,4-dimethoxybenzylidene)hydrazine-1-carbothioamide (1e)**
White solid, Yield: 87%, mp: 188-190 $^{o}$C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$3.83 (s, 3H, -$OCH_3$), 3.92 (s, 3H, -$OCH_3$), 7.15-7.18 (m, 2H, Ar-H), 7.34 (s, 1H), 7.95 (s, 1H, -CH=N), 7.94 (s, 2H, -$NH_2$), 11.45 (s, 1H, -NH);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.7, 55.9, 118.4, 135.3, 135.9, 139.5, 146.7, 150.5, 168.3, 187.4;LCMS (positive ion mode) (*m/z*): 240 $[M+H]^+$ for$C_{10}H_{13}N_3O_2S$.

**Synthesis of thiazolidinone derivatives (2a-e)**
A mixture of the respective thiosemicarbazone (**1a-e**) (1 mmol, 1 g),ethyl bromo acetate (2 mmol, 1.1 ml), and anhydrous sodium acetate (2 mmol, 0.8 g) in absolute ethanol was refluxedfor 3-8 h. After completion of reaction monitored by TLC, the reaction mixture was poured on to crushed ice and the obtained precipitate was collected by filtration,washed with water, dried, and recrystallized from a DMF and ethanol solvent mixture.

**(Z)-2-(((Z)-4-nitrobenzylidene)hydrazono)thiazolidin-4-one(2a)**
Yellow solid, Yield: 75%, mp: 210-212 $^{o}$C; $^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.83 (s, 2H), 8.12 (d, 2H, $J$ = 8.80 Hz), 8.34 (d, 2H, $J$ = 8.80 Hz), 8.45 (s, 1H), 12.35 (s, 1H);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 32.7, 128.7, 130.4, 132.8, 135.3, 154.8, 167.5, 173.8;LCMS (positive ion mode) (*m/z*): 265 $[M+H]^+$ for $C_{10}H_8N_4O_3S$.

**(Z)-2-(((Z)-1-(4-nitrophenyl)ethylidene)hydrazono)thiazolidin-4-one(2b)**
Yellow solid, Yield: 75%, mp: 224-226 $^{o}$C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.44 (s, 3H), 3.91 (s, 2H), 8.08 (d, 2H, $J$ = 8.80 Hz), 8.30 (d, 2H, $J$ = 8.80 Hz), 12.12 (s, 1H);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 20.3, 32.8, 123.5, 127.3, 143.6, 147.7, 158.5, 166.3, 173.8;LCMS (positive ion mode) (*m/z*): 279 $[M+H]^+$, 301 $[M+Na]^+$ for $C_{11}H_{10}N_4O_3S$.

**(Z)-2-(((Z)-4-chlorobenzylidene)hydrazono)thiazolidin-4-one(2c)**
White solid, Yield: 72%, mp: 215-217 $^{o}$C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 3.90 (s, 2H), 7.52 (d, 2H, $J$ = 8.53 Hz), 7.78 (d, 2H, $J$ = 8.53 Hz), 8.40 (s, 1H), 12.02 (s, 1H);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 33.7, 129.7, 129.9, 133.8, 135.8, 155.8, 166.5, 174.8;LCMS (positive ion mode) (*m/z*): 254 $[M+H]^+$ for $C_{10}H_8ClN_3OS$.

**(Z)-2-(((Z)-4-methoxybenzylidene)hydrazono)thiazolidin-4-one(2d)**
White solid, Yield: 76%, mp: 218-220 $^{o}$C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$3.67 (s, 3H, -$OCH_3$),3.95 (s, 2H), 7.43 (d, 2H, $J$ = 8.53 Hz), 7.82 (d, 2H, $J$ = 8.53 Hz), 8.45 (s, 1H), 12.08 (s, 1H);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$32.7, 56.2, 128.7, 130.9, 134.8, 135.3, 155.2, 165.5, 172.8;LCMS (positive ion mode) (*m/z*): 250 [M+H]+ for $C_{11}H_{11}N_3O_2S$.

**(Z)-2-(((Z)-3,4-dimethoxybenzylidene)hydrazono)thiazolidin-4-one (2e)**
White solid, Yield: 78%, mp: 234-236 $^{o}$C;$^{1}$H NMR (400 MHz, DMSO-$d_6$): $\delta$3.62 (s, 3H, -$OCH_3$), 3.64 (s, 3H, -$OCH_3$),3.85 (s, 2H), 7.15-7.18 (m, 1H), 7.53-7.55 (m, 1H), 7.82 (s, 1H), 8.45 (s, 1H), 12.08 (s, 1H);$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$32.5, 56.9, 57.4, 108.5, 112.3, 124.5, 128.7, 148.4, 152.7, 155.2, 162.5, 172.8;LCMS (positive ion mode) (*m/z*):280 [M+H]+ for $C_{12}H_{13}N_3O_3S$.

**Synthesis of 4-(prop-2-yn-1-yloxy)benzaldehyde (3)**
To a solution of p-hydroxy benzaldehyde (1 mmol, 1 g) in DMF, potassium carbonate (1.5 mmol, 2.3 g) was added. To this propargyl bromide (1.5 mmol, 1 ml) was added under inert

atmosphere ($N_2$ gas) and continued to stirring at room temperature overnight. After completion of reaction, the mixture was poured into crushed ice. The precipitate separated was filtered, dried and recrystallized from ethanol.

Half white color solid; Yield 89%; mp:124-126 $^oC$; ; IR (KBr) ($\nu_{max}cm^{-1}$): $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$3.65 (s, 1H, acetylenic CH), 4.94 (s, 2H), 7.18 (d, $J$ = 8.8 Hz, 2H, Ar-H), 7.90 (d, $J$ = 8.8 Hz, 2H, Ar-H), 9.89 (s, 1H, aldehyde CH); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 55.1, 77.8, 78.1, 114.6, 129.5, 131.0, 161.3, 190.7; LCMS (positive ion mode) (*m/z*): 161 $[M+H]^+$ for $C_{10}H_8O_2$.

**Synthesis of C-Mannich bases (4a-b)**

To a solution of compound **3** (1 mmol, 0.2 g) in dioxane, formalin (4 mmol, 0.12 ml), copper (II) acetate (5 mg) and secondary amine (1.5 mmol, 0.14 ml) were added. The mixture was refluxed at 70 $^oC$ for 1h. After completion of reaction monitored by TLC, the mixture was poured onto crushed ice and then extracted with ethyl acetate. The combined organic layers were dried and recrystallized from ethanol.

**4-((4-morpholinobut-2-yn-1-yl)oxy)benzaldehyde (4a)**

Brown solid, Yield: 62%, mp: 164-166 $^oC$;$^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 2.45 (t, 4H, $J$ = 4.40 Hz), 3.38 (s, 2H), 3.61 (t, 4H, $J$ = 4.40 Hz), 5.05 (s, 2H), 7.25 (d, 2H, $J$ = 8.80 Hz), 7.95 (d, 2H, $J$ = 8.52 Hz), 9.96 (s, 1H);$^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 46.7, 51.8, 56.4, 66.3, 80.0, 83.5, 115.7, 130.4, 131.9, 162.4, 191.6; LCMS (positive ion mode) (*m/z*): 260 $[M+H]^+$ for $C_{15}H_{17}NO_3$.

**4-((4-(piperidin-1-yl)but-2-yn-1-yl)oxy)benzaldehyde (4b)**

Brown liquid, Yield: 58%, mp: 160-162 $^oC$;$^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$2.45-2.55 (m, 6H), 3.38 (s, 2H), 3.62 (t, 4H, $J$ = 4.40 Hz), 5.04 (s, 2H), 7.25 (d, 2H, $J$ = 8.80 Hz), 7.95 (d, 2H, $J$ = 8.52 Hz), 9.95 (s, 1H);$^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$28.8, 30.0, 46.1, 51.2, 55.8, 79.4, 82.9, 115.1, 129.7, 131.3, 161.8, 191.0;LCMS (positive ion mode) (*m/z*): 258[M+H]+ for $C_{16}H_{19}NO_2$.

**Synthesis of thiazolidinone derivatives containing C-Mannich bases (5a-j)**

To a solution of corresponding thiazolidinone derivative (**2a-e**) (1 mmol) in ethanol piperidine (1.15 mmol) was added. After dissolution by heating, the respective aldehyde (**4a-b**) (1 mmol) was added and refluxed over night. At the end of reaction, the product wasprecipitated by pouring the medium into ice-cold water and the formed precipitate was collected by filtration. The product was purified by column chromatography using hexane: ethyl acetate mixture as an eluent.

**(Z)-5-((E)-4-((4-morpholinobut-2-yn-1-yl)oxy)benzylidene)-2-(((Z)-4-nitrobenzylidene)hydrazono)thiazolidin-4-one (5a):**

$^1H$ NMR (400 MHz; $CDCl_3$):$\delta$2.58 (t, $J$ = 4.3 Hz, 4H), 3.36 (s, 2H), 3.75 (t, $J$ = 4.6 Hz, 4H), 4.75 (s, 2H), 6.91 (d, $J$ = 8.3 Hz, 2H, Ar-H), 6.99 (d, $J$ = 8.56 Hz, 2H, Ar-H), 7.40 (d, $J$ = 7.4 Hz, 2H, Ar-H), 7.47 (s, 1H), 7.67 (d, $J$ = 8.56 Hz, 2H, Ar-H), 8.70 (s, 1H), 9.87 (s, 1H, NH). $^{13}C$ NMR (100 MHz; $CDCl_3$):$\delta$46.4, 52.7, 56.9, 65.7, 78.6, 81.5, 115.7, 116.5, 125.7, 127.6, 129.8, 129.9, 130.8, 132.1, 133.8, 135.7, 136.8, 159.7, 168.9. LC-MS(positive ion mode): *m/z* 506 $[M+H]^+$for $C_{25}H_{23}N_5O_5S$.

**(Z)-5-((E)-4-((4-morpholinobut-2-yn-1-yl)oxy)benzylidene)-2-(((Z)-1-(4-nitrophenyl)ethylidene)hydrazono)thiazolidin-4-one (5b):**

$^1$H NMR (400 MHz; $CDCl_3$):*δ* 2.56 (s, 3H), 3.07 (s, 2H), 3.35 (t, *J* = 4.2 Hz, 4H), 3.73 (t, *J* = 4.1 Hz, 4H), 4.78 (s, 2H), 7.07 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.54 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.63 (s, 1H), 8.05 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.27 (d, *J* = 7.7 Hz, 2H, Ar-H), 9.88 (s, 1H, NH).$^{13}$C NMR (100 MHz; $CDCl_3$):*δ* 29.9, 47.6, 52.5, 56.4, 67.0, 79.9, 83.2, 115.7, 115.8, 123.8, 127.8, 131.4, 131.7, 132.2, 144.0, 148.7, 159.1, 159.2, 160.6, 171.2.LC-MS(positive ion mode): *m/z*520 $[M+H]^+$ for $C_{26}H_{25}N_5O_5S$.

**(Z)-2-(((Z)-4-chlorobenzylidene)hydrazono)-5-((E)-4-((4-morpholinobut-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5c):**

$^1$H NMR (400 MHz; $CDCl_3$):*δ*2.57 (t, *J* = 4.2 Hz, 4H), 3.37 (s, 2H), 3.76 (t, *J* = 3.72 Hz, 4H), 4.74 (s, 2H), 6.90 (d, *J* = 8.43 Hz, 2H, Ar-H), 7.02 (d, *J* = 8.13 Hz, 2H, Ar-H), 7.14 (d, *J* = 8.19 Hz, 2H, Ar-H), 7.37 (s, 1H), 7.46 (s, 1H), 7.61 (d, *J* = 8.07 Hz, 2H, Ar-H), 9.76 (s, 1H, NH). $^{13}$C NMR (100 MHz; $CDCl_3$):*δ* 47.4, 52.3, 56.1, 66.7, 79.6, 82.9, 114.7, 115.2, 126.7, 128.6, 129.1, 129.3, 129.8, 131.1, 131.8, 132.5, 136.6, 158.7, 167.9. LC-MS(positive ion mode): *m/z*495 $[M+H]^+$for $C_{25}H_{23}ClN_4O_3S$.

**(Z)-2-(((Z)-4-methoxybenzylidene)hydrazono)-5-((E)-4-((4-morpholinobut-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5d):**

$^1$H NMR (400 MHz; $CDCl_3$): *δ*2.49 (t, *J* = 4.34 Hz, 4H), 3.27 (s, 3H), 3.68 (t, *J* = 3.79 Hz, 4H), 3.78 (s, 2H), 4.71 (s, 2H), 6.90 (d, *J* = 5.6 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.18 (s, 1H), 7.41 (d, *J* = 4.3 Hz, 2H,Ar-H), 7.52 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 2H, Ar-H), 9.82 (s, 1H, NH). $^{13}$C NMR (100 MHz; $CDCl_3$):*δ* 46.4, 51.3, 54.3, 55.1, 65.7, 78.8, 81.6, 113.0, 113.4, 113.9, 114.3, 125.4, 126.1, 126.6, 128.4, 128.9, 130.8, 156.9, 157.1, 167.1. LC-MS(positive ion mode): *m/z*491 $[M+H]^+$ for $C_{26}H_{26}N_4O_4S$.

**(Z)-2-(((Z)-3,4-dimethoxybenzylidene)hydrazono)-5-((E)-4-((4-morpholinobut-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5e):**

$^1$H NMR (400 MHz; $CDCl_3$):*δ*2.56 (t, *J* = 4.73 Hz, 4H), 3.35 (s, 2H), 3.75 (t, *J* = 3.81 Hz, 4H), 3.92 (s, 3H, -$OCH_3$), 3.95 (s, 3H,-OCH3), 4.77 (s, 2H), 6.96 (d, *J* = 8.20 Hz, 2H, Ar-H), 7.03 (d, *J* = 8.24 Hz, 2H, Ar-H), 7.40 (s, 1H, Ar-H), 7.50 (s, 1H), 7.59 (s, 1H), 7.76-7.79 (m, 2H, Ar-H), 9.72 (s, 1H, NH).$^{13}$C NMR (100 MHz; $CDCl_3$): *δ*47.4, 52.2, 55.9, 56.0, 56.1, 66.7, 79.7, 82.9, 111.2, 114.9, 115.4, 123.7, 126.7, 127.0, 127.6, 129.8, 130.4, 131.8, 149.0, 158.0, 158.7, 159.8, 168.0. LC-MS(positive ion mode): *m/z*521 $[M+H]^+$ for $C_{27}H_{28}N_4O_5S$.

**(Z)-2-(((Z)-4-nitrobenzylidene)hydrazono)-5-((E)-4-((4-(piperidin-1-yl)but-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5f):**

$^1$H NMR (400 MHz, DMSO-$d_6$): *δ* 1.40-1.42 (m, 2H), 1.96-1.98 (m, 4H), 2.58 (t, *J* = 4.3 Hz, 4H), 3.37 (s, 2H), 4.80 (s, 2H), 6.95 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.97 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.42 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.53 (s, 1H), 7.69 (d, *J*= 9.20 Hz, 2H, Ar-H), 8.75 (s, 1H), 9.90 (s, 1H, NH).$^{13}$C NMR (100 MHz, DMSO-$d_6$): *δ* 24.3, 27.9, 52.3, 56.1, 66.7, 79.6, 82.9, 114.7, 115.2, 126.7, 128.6, 129.3, 129.8, 130.7, 131.1, 131.8, 132.5, 136.6, 158.7, 172.2. LCMS (positive ion mode): *m/z*504 $[M+H]^+$ for $C_{26}H_{25}N_5O_4S$.

**(Z)-2-(((Z)-1-(4-nitrophenyl)ethylidene)hydrazono)-5-((E)-4-((4-(piperidin-1-yl)but-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5g):**

$^1$H NMR (400 MHz, DMSO-$d_6$): *δ*2.42-2.59 (m, 6H), 3.07 (s, 3H), 3.36 (t, 4H, *J* = 4.1 Hz), 3.74 (s, 2H), 4.79 (s, 2H), 7.08 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.54 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.63 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 2H, Ar-H), 8.28 (d, *J* = 7.7 Hz, 2H, Ar-H), 9.96 (s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$): *δ* 24.9, 27.0, 47.7, 52.6, 56.4, 79.9, 83.2, 115.0, 115.5,

127.0, 128.9, 129.3, 129.6, 130.1, 131.4, 132.1, 132.8, 136.8, 157.4, 159.0, 172.5. LCMS (positive ion mode):*m/z*518 $[M+H]^+$ for $C_{27}H_{27}N_5O_4S$.

**(Z)-2-(((Z)-4-chlorobenzylidene)hydrazono)-5-((E)-4-((4-(piperidin-1-yl)but-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5h):**
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.96-1.98 (m, 6H), 2.58 (t, $J$ = 4.3 Hz, 4H), 3.37 (s, 2H), 4.80 (s, 2H), 6.90 (d, $J$ = 8.3 Hz, 2H, Ar-H), 6.95 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.52 (d, $J$ = 7.6 Hz, 2H, Ar-H), 7.58 (s, 1H), 7.73 (d, $J$ = 9.20 Hz, 2H, Ar-H), 8.78 (s, 1H), 9.93 (s, 1H, NH).$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 24.5, 27.9, 52.5, 57.1, 65.7, 79.8, 83.5, 112.7, 116.2, 128.7, 128.9, 129.5, 129.8, 130.5, 131.7, 131.9, 132.7, 135.6, 156.7, 171.5. LCMS (positive ion mode):*m/z*493.35 $[M+H]^+$ for $C_{26}H_{25}ClN_4O_2S$.

**(Z)-2-(((Z)-4-methoxybenzylidene)hydrazono)-5-((E)-4-((4-(piperidin-1-yl)but-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5i):**
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.92-1.96 (m, 6H), 2.55 (t, $J$ = 4.3 Hz, 4H), 3.15 (s, 3H), 3.29 (s, 2H), 4.82 (s, 2H), 6.85 (d, $J$ = 8.3 Hz, 2H, Ar-H), 6.99 (d, $J$ = 8.4 Hz, 2H, Ar-H), 7.44 (d, $J$ = 7.6 Hz, 2H, Ar-H), 7.58 (s, 1H), 7.66 (d, $J$ = 9.20 Hz, 2H, Ar-H), 8.65 (s, 1H), 9.89 (s, 1H, NH).$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 23.5, 26.9, 53.2, 55.8, 59.6, 65.4, 77.8, 82.5, 111.5, 116.7, 127.4, 128.5, 129.2, 129.6, 130.3, 131.7, 131.9, 132.5, 134.4, 155.7, 172.2. LCMS (positive ion mode):*m/z*489.35 $[M+H]^+$ for $C_{27}H_{28}N_4O_3S$.

**(Z)-2-(((Z)-3,4-dimethoxybenzylidene)hydrazono)-5-((E)-4-((4-(piperidin-1-yl)but-2-yn-1-yl)oxy)benzylidene)thiazolidin-4-one (5j):**
$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.34-1.36 (m, 2H), 1.58-1.64 (m, 4H), 2.56 (t, $J$ = 4.54 Hz, 4H), 3.42 (s, 2H), 3.93-3.96 (m, 6H, -$OCH_3$), 4.79 (s, 2H), 6.95 (d, $J$ = 8.2 Hz, 2H, Ar-H), 7.06 (d, $J$ = 8.2 Hz, 2H, Ar-H), 7.42 (s, 1H, Ar-H), 7.52 (s, 1H), 7.55 (s, 1H), 7.74-7.77 (m, 2H, Ar-H), 8.78 (s, 1H, NH). $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 25.5, 29.3, 47.1, 51.9, 55.7, 79.4, 82.6, 114.6, 119.7, 123.4, 126.4, 126.7, 127.3, 129.5, 130.1, 130.5, 131.6, 135.3, 148.7, 157.7, 158.4, 159.5, 167.7, 173.1. LCMS (positive ion mode):*m/z*519.45 $[M+H]^+$ for $C_{28}H_{30}N_4O_4S$.

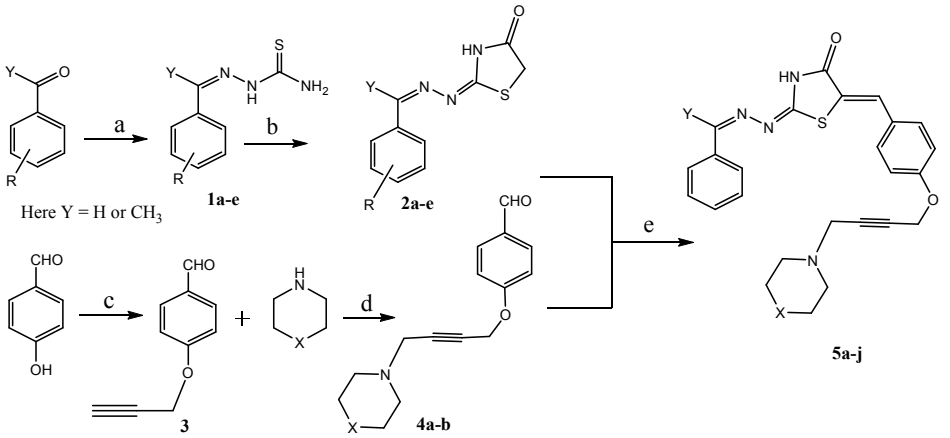
**Results and discussion**

The synthesis of target compounds **5a-j** involves several steps. Initially thiosemicarbazones **1a-e** were synthesized from different carbonyl compounds on refluxing with thiosemicarbazide in ethanol in the presence of acetic acid as a catalyst give thiosemicarbazones. From these derivatives (**1a-e)** thiazolidinone derivatives **2a-e** were prepared by treating with bromoethyl acetate and sodium acetate in DMF. Further p-hydroxy benzaldehyde is converted into propargyl derivative **3** by treating with propargyl bromide in DMF by using potassium carbonate as a base at room temperature. This propargyl derivative is converted into C-Mannich bases **4a-b** by refluxing with secondary amine (piperidine/Morpholine), 40% formaldehyde and Cu (II) acetate in dioxane for 1h. Finally, the C-Mannich bases **4a-b** were condensed with thiazolidinone derivatives **2a-e** in the presence of piperidine as a base in ethanol solvent to get the final derivatives **5a-j**.

The structures of all the synthesized compounds were confirmed by $^1$H NMR, $^{13}$C NMR and LC-MS. The formation of thiosemicarbazones **1a-e** was confirmed by the appearance of a signal from δ 11.30-11.70 ppm due to N-H proton. The ring closure in 4-thiazolidinone was supported by the detection of signals at δ 3.83-3.95 ppm due to endocyclic –S-$CH_2$- protons. Formation of propargyl derivative was confirmed by the appearance of a signal at δ 3.65 ppm

due to acetylene CH proton. Disappearance of acetylene proton signal in $^1$H NMR spectra indicates the formation of C-Mannich bases. A signal at *m/z* value of 260 was observed in mass spectrum of morpholine Mannich base which corresponds to $[M+H]^+$ peak. Disappearance of signalcorresponding to endocyclic -S-$CH_2$- protons in the spectra of compounds **5a-j** indicates that active methylene group of 4-thiazolidinones **2a-e** reacted with the C-Mannich base containing aldehydes to yield final derivatives **5a-j**.

**Scheme:**




Reagents and conditions: a) Thiosemicarbazide, acetic acid, ethanol, reflux, 2-4 h b) Bromo ethyl acetate, sodium acetate, DMF, reflux, 3-8 h c) Propargyl bromide, $K_2CO_3$, DMF, rt, over night d) Formaldehyde, Cu(II) acetate, dioxane, reflux, 1 h e) Piperdine, ethanol, reflux, over night .

Here **5a**: X = O, Y = H, R = P-$NO_2$ **5f**: X = $CH_2$, Y = H, R = P-$NO_2$
**5b**: X = O, Y = $CH_3$, R = P-$NO_2$ **5g**: X = $CH_2$, Y = $CH_3$, R = P-$NO_2$
**5c**: X = O, Y = H, R = P-Cl **5h**: X = $CH_2$, Y = H, R = P-Cl
**5d**: X = O, Y = H, R = P-$OCH_3$ **5i**: X = $CH_2$, Y = H, R = P-$OCH_3$
**5e**: X = O, Y = H, R = m, p-di-$OCH_3$ **5j**: X = $CH_2$, Y = H, R = m, p-di-$OCH_3$

**Table 1:** Physical data of newly synthesized derivatives (**5a-j**)

| Compound | Molecular formula (Mol. wt.) | Colour | M.P (°C) | Yield (%) | Mass [$M^+$+1] |
|---|---|---|---|---|---|
| **5 a** | $C_{25}H_{23}N_5O_5S$ (505) | Yellow | 234-236 °C | 58 % | 506 |
| **5 b** | $C_{26}H_{25}N_5O_5S$ (519) | Yellow | 235-238 °C | 54 % | 520 |
| **5 c** | $C_{25}H_{23}ClN_4O_3S$ (494) | Brown | 224-226 °C | 57 % | 495 |
| **5 d** | $C_{26}H_{26}N_4O_4S$ (490) | Yellow | 227-229 °C | 56 % | 491 |
| **5 e** | $C_{27}H_{28}N_4O_5S$ (520) | Brown | 236-238 °C | 59 % | 521 |
| **5 f** | $C_{26}H_{25}N_5O_4S$ (503) | Yellow | 225-227 °C | 52 % | 504 |
| **5 g** | $C_{27}H_{27}N_5O_4S$ (517) | Yellow | 231-234 °C | 50 % | 518 |
| **5 h** | $C_{26}H_{25}N_4O_2S$ (492) | Light brown | 221-223 °C | 50 % | 493.5 |
| **5 i** | $C_{27}H_{28}N_4O_3S$ (488) | Brown | 224-226 °C | 53 % | 489.35 |

| | | | | | |
|---|---|---|---|---|---|
| **5 j** | $C_{28}H_{30}N_4O_4S$ (518) | Brown | 233-235 °C | 55 % | 519.45 |

## Conclusion

In summary, we have synthesized novel C-Mannich bases containing thiazolidinone derivatives (**5a-j**) by condensing 4-thiazolidinone derivatives with p-hydroxy benzaldehyde derivatives of C-Mannich bases in the presence of piperidine as base. The structures of all the synthesized compounds were characterized by $^1$HNMR, $^{13}$C NMR spectra and LC-MS. Further the yields of the reaction were good with easy workup procedures and short reaction times.

## Acknowledgements

One of the authors (MAK) is gratefully acknowledge to UGC for providing financial assistance in the formof BSR fellowship.

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Received on May30, 2018.