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Novel Route for Synthesis of Thiozolidine-2,4-Dione Derivatives as a Mannich Base

Ramakrishna Vellalacheruvu*, Ramayanam Sai Leela, L. K. Ravindranath

Department of Chemistry, Sri Krishnadevaraya University, Anantapur, India
Email: *vellala143@gmail.com

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Abstract

The Mannich base of Thiozolidine-2,4-dione derivatives has come to lime light due to their various pharmacological activities. Thiazolidine-2,4-dione is an extensively explored heterocyclic nucleus for designing of novel agents implicated for a wide variety of pathophysiological conditions, that is, diabetes, diabetic complications, cancer, arthritis, inflammation, microbial infection, and melanoma. In present work, synthesis quinoline attached imidazoline derivative using (3 + 2) cyclo-addition via imine of quinoline and TosMIC. These derivatives were converted to Mannich bases of thiozolidine-2,4-dione using Knoevenagel condensation. The sulfonamide analogues of thiozolidine-2,4-Dione were also synthesized and characterized by using alkylation conditions.

Keywords

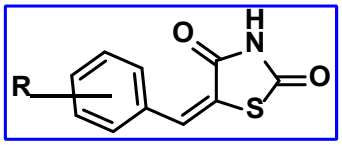
Imidazole Analogues, Thiozolidine-2,4-Dione Nucleus, Toluenesulfonylmethyl Isocyanide, Combi-Flash Column Chromatography

1. Introduction

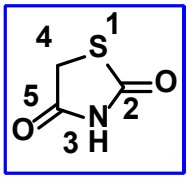
Thiazolidine-2,4-dione (TZD) is a vital nucleus in heterocyclic chemistry. TZD shows multidirectional pharmacological activities such as antioxidant [1], anti-hyperglycemic (glitazone drugs) [2] [3], antibacterial and anti-fungal [4], anti-cancer [5], antimicrobial, antitubercular [6], anti-arthritic [7], diabetic & diabetic complications [8] [9], anti-inflammatory activity [10] [11] and antiplasmodial activity [12]. Due to various pharmacological actions of TZD derivatives, researchers keep on huge interest in synthesis of new TZD derivatives by using various synthetic methods and carry out clinical trials for achieving lead target. Nowadays, diabetes is a major metabolic disorder on human beings throughout

world. The Thiazolidine-2,4-dione (TZD) derivatives act as drug candidates such as, rosiglitazone, pioglitazone, lobiglitazone, englitazone, metolazone, ozoline, darglitazone and troglitazone etc. TZD derivatives not only confine for treatment of metabolic disorder diabetic, but also show as an inflammatory agent, anti-cancer and for treatment of melanoma. Due to importance of TZD derivatives, many scientists have developed various routes for synthesis.

Om Silakari *et al*. [2] developed different TZD derivatives and evolutes of their biological activity. The various pharmacological activity of Thiazolidine-2,4-dione was shown in Figure 1.



Various approaches have been developed for synthesis of thiazolidine-2,4-dione and there are many active sites for exploring new analogues. Thiazolidine-2,4-dione nucleus numbering is assigned as given below.



As a part of research work, we synthesize novel Mannich base of thiazolidine-2,4-dione and sulfonamide analogues using an effective and feasible process compared to other approaches and designed to make easy to scale up. We strongly believe these analogues are biologically active.

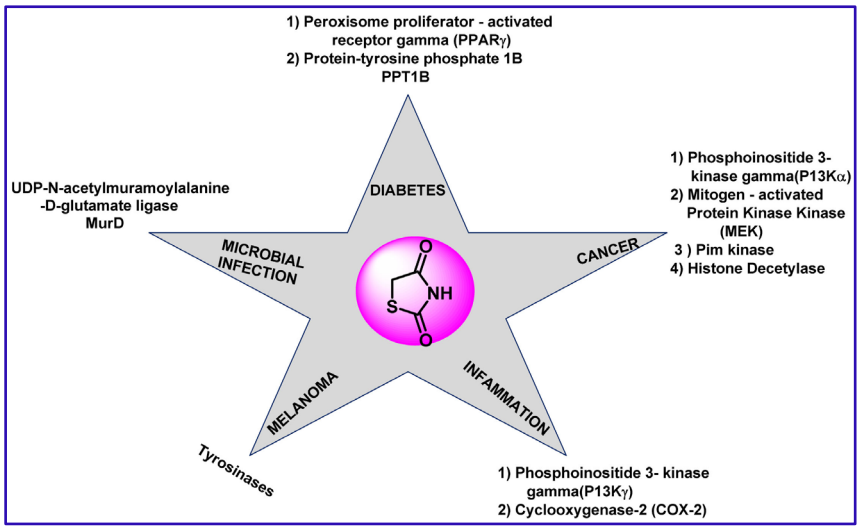


Figure 1. Various pharmacological activity of thiazolidine-2,4-dione. Ivanildo Mangueira da Silva and co workers [3] developed TZD derivatives using Knoevenagel condensation.

2. Materials and Methods

All reagents and starting material were procured from commercial sources (Aldrich, Alfa Aesar) and solvents, such as THF, DMF and toluene, which were thoroughly dried before use. THF and toluene were dried using sodium metal and Benzophenone, and DMF was dried using CaH. The synthesized analogues were fully characterized using Analytical methods like IR, NMR (Bruker). The melting points were recorded using on a WRS-1A digital Melting Point Apparatus without correction. Infrared spectra were taken using an AVATAR 370 FT-IR spectrometer. ^{1}HNMR, ^{13}CNMR spectra were recorded with a Bruker spectrometer operating at 400 MHz with Trimethylsilane reference and values were recorded in ppm. The progress of reaction was monitored using TLC system and I_2 spray and $KMnO_4$ TLC strain. The crude compounds were purified using column chromatography (100 - 200 mesh silica) and Combi Flash Chromatography. The hydrogenolysis process was carried out using parr shaker.

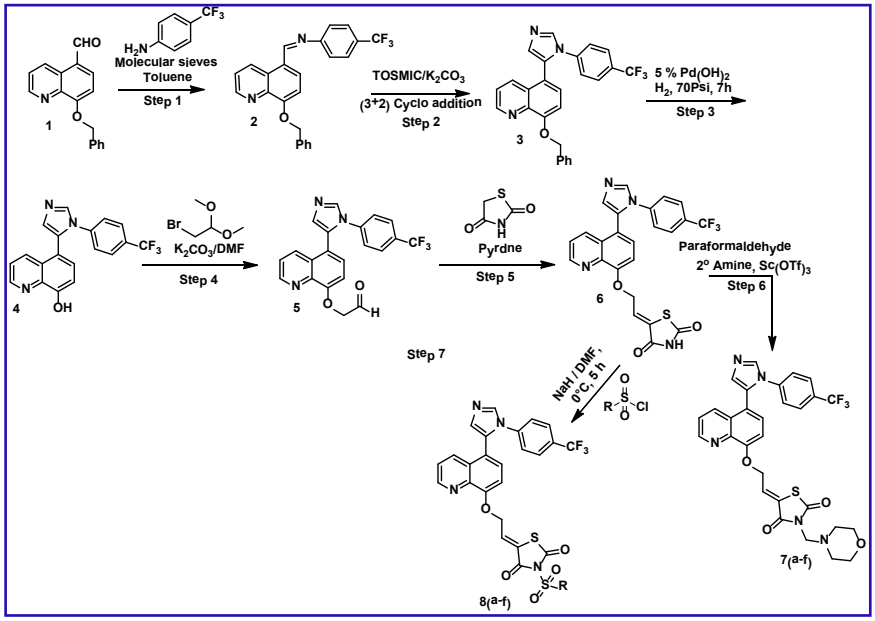
3. Objective of Research

Current Research work is related to develop novel synthetic route for synthesis of the Novel mannich bases of thiazolidine-2,4-dione, sulfonamide analogues and thoroughly characterized. The scaffolds of 3-(Amine substituted methyl)-5-(2-((5-(1-(4-(trifluoromethyl) phenyl)- H-imidazol-5-yl)quinolin-8-yl) oxy) ethylidene)thiazolidine-2,4-dione **(7a-f)**, and 3-(sulfonyl-derivatives)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene) thiazolidine-2,4-dione **(8a-f)** were synthesized and characterized.

4. Experimental Methods

Current research work, we prepared below compounds and described in step wise manner.

- **Step-1:** (Z)-N-((8-(benzyloxy)quinolin-5-yl)methylene)-4-(trifluoromethyl) aniline **(2)**.
- **Step-2:** 8-(benzyloxy)-5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl) quinoline **(3)**.
- **Step-3:** 5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-ol**(4).**
- **Step-4:** 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)acetaldehyde **(5)**.
- **Step-5:** 5-(5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl) oxy)methylene)thiazolidine-2,4-dione **(6)**.
- **Step-6:** 3-(Amine substituted methyl)-5-(2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione **(7a-f).**
- **Step-7:** 3-(sulfonyl-derivatives)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione **(8a-f).** The Reaction scheme was shown in Scheme 1. The Reaction mechanism of Step 2 was shown in Figure 2.



Scheme 1. Synthesis of 3-(Amine substituted methyl)-5-(2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione(7a-f) & sulphonamide analogues 8(a-f).

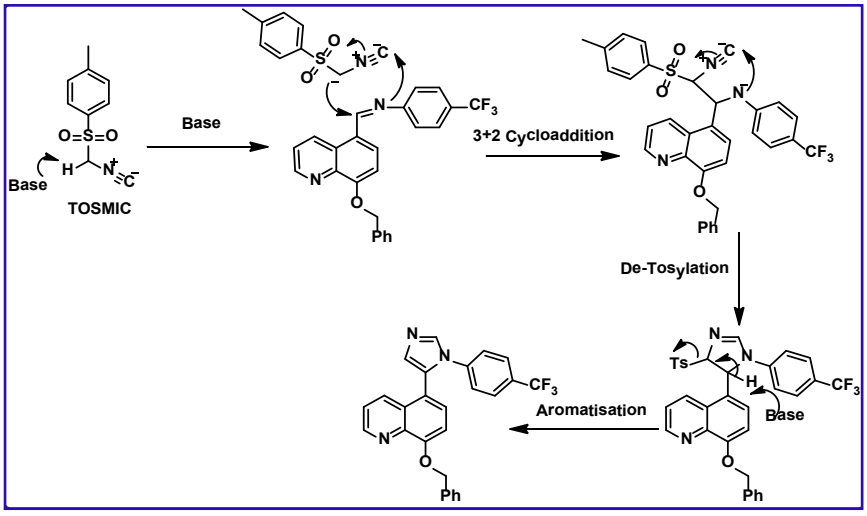


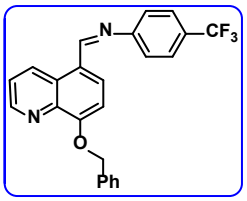
Figure 2. The Reaction mechanism for step 2.

Scheme

Reaction Conditions: **Step 1:** Molecular sieves, Toluene, 0˚C, 10 h, **Step 2:** TOSMIC/K_2CO_3, 0˚C, 16 h, **Step 3:** 5% $Pd(OH)_2$, H_2, 70 Psi, 3 h, **Step 4:** 2-bromo-1,1-dimethoxyethane, K_2CO_3/DMF, 5 h, **Step 5:** thiazolidine-2,4-dione, Piperdine, 90˚C, 6 h, **Step 6:** Paraformaldehyde/2˚ Amine, $Sc(OTf)_3$, EtOH, 90˚C, 8 h. **Step 7:** NaH, DMF, 0˚C, 5 h.

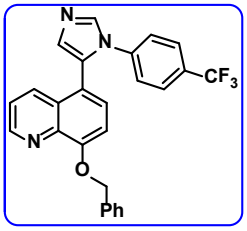
Reaction mechanism for Step 2: The Reaction mechanism of step 2 was shown in Figure 2.

Step 1: (Z)-N-((8-(benzyloxy)quinolin-5-yl)methylene)-4-(trifluoromethyl)aniline(2):



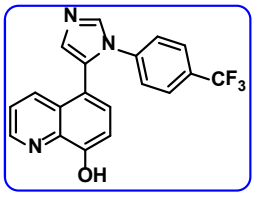
8-(benzyloxy)quinoline-5-carbaldehyde (10 g, 0.038 mol), 4-(trifluoromethyl) aniline (6.5 g, 0.039 mol) in dry toluene (100 mL) was added freshly dried molecular sieves and refluxed for 10 h under N_2 atm. The progress of reaction was monitored by TLC. After completion of starting material, toluene was evaporated under vacuum to give crude residue of Compound-**2** (15 g) as a solid. The crude was carried to next step.

Step 2: 8-(benzyloxy)-5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinoline(3):



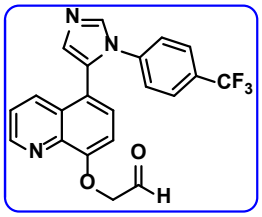
(Z)-N-((8-(benzyloxy)quinolin-5-yl)methylene)-4-(trifluoromethyl)aniline(2) (15 g, 0.036 mol) was dissolved in Dry DMF (80 mL) and cooled to 0 ˚C. To that dried K_2CO_3 (15 g. 108 mol) and Toluene methyl isocyanide (7.02 g, 0.036 mol) was added and warm to room temperature and stirred for 16 h. The progress of reaction was monitored by TLC. After completion, reaction mixture was poured in ice cold water (100 mL) and extracted with EtOAc (3 × 100 mL). The organic layer was separated and washed with brine solution, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give crude residue. The obtained crude product was purified by column chromatography (100 - 200 mesh silica, Eluent: 80% EtOAc-Pet Ether) isolated 8-(benzyloxy)-5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinoline (3) (10 g, yield: 64%) as a solid (white). *M.p*: 252˚C - 255˚C. IR (KBr, cm^{-1}): 3030, 1440, 1520, 1005, 691, 655. **^{1}HNMR (d_6-DMSO, 400 MHz):** 5.2 (s, 2H), 7.1 (m, 2H), 7.3 - 7.5 (m, 7H), 7.6 - 7.7 (m, 4H), 7.85 (d, 1H), 8.36 (d, 1H), 8.85 (d, 1H).

Step 3: 5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-ol (4):



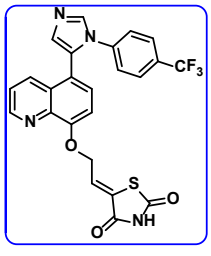
8-(benzyloxy)-5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinoline(3) (10 g, 0.022 mol) in MeOH (100 mL) was added 5% Palladium hydroxide on carbon (1 g, cat) and carried out hydrogenolysis at 70 Psi under parr shaker for 3 h at room temperature. The progress of reaction was monitored by TLC. After completion, reaction mixture was filtered on celite bed and thoroughly washed with MeOH (2 × 75 mL). The MeOH layer were collected and evaporated under vacuum to give 5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-ol (4) (7 g, yield: 86%) as a solid(pale white). *M.p*: 280˚C - 285˚C. IR (KBr, cm^{-1}): 3620, 3014, 1525, 1050, 691, 620. **^{1}HNMR (d_6-DMSO, 400 MHz):** 6.5 (brs, 1H), 7.1 (m, 2H), 7.3 (d, 2H), 7.63 (m, 4H), 7.8 (d, 1H), 8.35 (d, 1H), 8.8 (d, 1H).

Step 4: 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H- imidazol-5-yl)quinolin-8-yl)oxy) acetaldehyde (5):



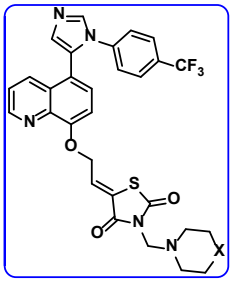
5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-ol (4) (7 g, 0.017 mol) in Dry DMF (70 mL) was added K_2CO_3 (9.7 g, 0.07 mol, 4 eq) and stirred at rt for 30 min. To that a solution of 2-bromo-1, 1-dimethoxyethane (1.2 eq) in DMF (20 mL) was added dropwise at 0˚C and stirred for 5h. The progress of reaction was monitored by TLC. After completion, reaction mixture was filtered on celite bed and washed with DMF (10 mL). The Reaction mixture was poured in ice cold water (200 mL) and stirred for 20 min. The reaction mixture was acidified with aq$NaHSO_3$ solution up to P ^{H}-5 and extracted with EtOAc (2 × 200 mL). The aqueous layer was collected and basified up to P^H-8 with sat aq-$NaHCO_3$ sol. The aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layer were collected and dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy) acetaldehyde (5) (5 g). *M.p*: 200˚C - 205˚C, IR (KBr, cm^{-1}): 3602, 3014, 1712, 1646, 1503, 1050, 691, 644. **^{1}HNMR (d_6-DMSO, 400 MHz):** 5.2 (s, 2H), 7.1 (m, 2H), 7.3 (d, 2H), 7.6 - 7.65 (m, 4H), 7.9 (d, 1H), 8.36 (d, 1H), 8.82 (d, 1H), 9.6 (s, 1H).

Step 5: 5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy) ethylidene) thiazolidine-2,4-dione (5):



To a mixture of 2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy) acetaldehyde (5) (5 g, 0.012 mol), thiazolidine-2,4-dione (1.62 g, 0.013 mol) in EtOH (50 mL) was added Piperdine (2 mL) and heated at 90˚C for 6 h. The progress of reaction was monitored by TLC. After completion, Reaction mixture was evaporated under vacuum to give crude residue. The residue was dissolved in water (100 mL) and filtered under vacuum and dried to give (Z)-5-(2-((5-(1-(4-(trifluoromethyl) phenyl)-1H–imidazol-5-yl)quinolin-8-yl)oxy) ethy-lidene) thiazolidine-2,4-dione (6) (5.5 g, Yield: 88%) as a solid(red color). *M.p*:240-243˚C. IR (KBr, cm^{-1}): 3050, 1725, 1650, 1503, 1050, 691, 644. **^{1}HNMR (d_6-DMSO, 400 MHz):** 4.6 (dd, 1H), 4.61 (dd, 1H), 6.15 (dd, 1H), 7.12 (m, 2H), 7.3 (d, 2H), 7.6 - 7.65 (m, 4H), 7.9 (d, 1H), 8.4 (d, 1H), 8.6 (brs, 1H), 8.87 (d, 1H).

Step 6: 3-(Amino substituted methyl)-5-(2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione & 7(a-f):



To a mixture of (Z)-5-(2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-imidazol-5-yl)quino-lin-8-yl)oxy)ethylidene) thiazolidine-2,4-dione (6) (500 mg), 2˚ Amine (1.1 eq), Para formaldehyde (3 eq) in EtOH (50 mL) was added $Sc(OTf)_3$ (0.1 eq) and heated for 8 - 12 h. The progress of reaction was monitored by TLC. After completion, EtOH was evaporated under vacuum to give crude product. The crude was purified by reverse-phase column chromatography (C18 silica, eluent: 30% ACN-MeOH-H_2O, 0.01% TFA) isolated (Z)-3-(Amino-substituted, methyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene) thiazolidine-2,4-dione 7 (a-f).The summary of physical data for analogues 7 (a-f) was shown in Table 1.

3-((4-oxopiperidin-1-yl)methyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione (7a):

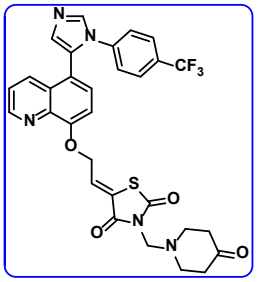
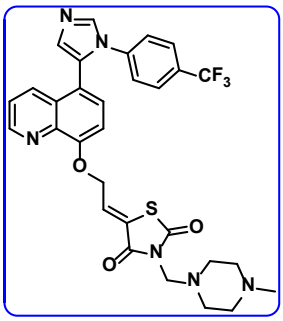


Table 1. Summary of physical data for analogues 7(a-f).

Comp	7a	7b	7c	7d	7e	7f
X	C=O	N-Me	N-Boc	N-Et	O	S
Yield	50%	75%	70%	78%	68%	70%
Reaction Time	12 h	8 h	9 h	8 h	10 h	10 h

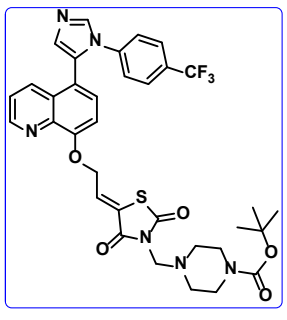
M.p: 280˚C - 283˚C. **IR (KBr, cm^{-1}):** 3050, 3010, 1720, 1655, 1600, 1320,770, 620. **^{1}HNMR (d_6-DMSO, 400 MHz):** 2.4 (t, 4H), 2.8 (t, 4H), 4.68 (dd, 2H), 4.7 (dd, 1H), 4.9 (s, 2H), 6.8 (dd, 1H), 7.1 (m, 2H), 7.3 (d, 2H), 7.6 (m, 4H), 8.0 (d, 1H), 8.43 (d, 1H), 8.8 (d, 1H). **^{13}CNMR (d_6-DMSO, 400 MHz):** 45, 53, 65, 108, 120, 122.9, 123.5, 124, 124.5, 126.7, 131, 135, 139, 139.2, 145, 150, 155, 164, 173, and 190.

3-((4-methylpiperazin-1-yl)methyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione (7b):



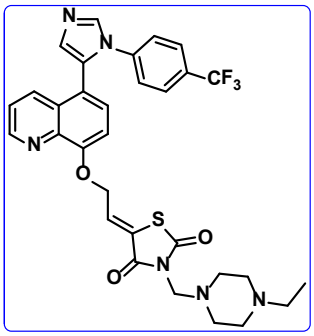
M.p: 290˚C - 292˚C. **IR (KBr, cm^{-1}):** 3350, 3050, 1660, 1610, 1320, 750, 625, **^{1}HNMR (d_6-DMSO, 400 MHz):** 2.3 (s, 3H), 2.4 (d, 4H), 2.45 (d, 4H), 4.63 (s, 2H,), 4.66 (dd, 1H), 4.67 (dd, 1H), 6.81 (dd, 1H), 7.1 (m, 2H), 7.32 (d, 2H), 7.6 (m, 4H), 8.03 (d, 1H), 8.44 (d, 1H), 8.81(d, 1H). **^{13}C-NMR (d_6-DMSO, 400 MHz):** 47, 53, 58, 65, 107, 121, 122, 123.8, 124, 124.5, 125.5, 127, 130, 134, 138, 138.8, 145, 150, 155.5, 163, 174.

tert-butyl 4-((2,4-dioxo-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H- imidazol-5-yl)qu -in olin-8-yl)oxy)ethylidene)thiazolidin-3-yl) methyl)piperazine-1-carboxylate (7c):



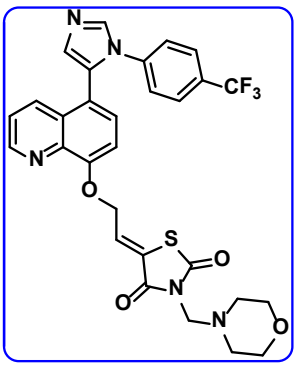
M.p: 260˚C - 2262˚C. IR (KBr, cm^{-1}): 3014, 1713, 1650, 1620, 1505, 1310, 1050, 698, 655. **^{1}HNMR (d_6-DMSO, 400 MHz):** 1.4 (s, 9H), 2.5 (t, 4H), 3.1 (t, 4H), 2.45 (d, 4H), 4.5 (s, 2H), 4.68 (dd, 1H), 4.69 (dd, 1H), 6.83 (dd, 1H), 7.1 (m, 2H), 7.32 (d, 2H), 7.62 (m, 4H), 7.9 (d, 1H), 8.42 (d, 1H), 8.82 (d, 1H). **^{13}C-NMR (d_6-DMSO, 400 MHz):** 31, 44, 52, 65, 78, 107, 121, 124, 124.5, 125.4, 127, 130, 132, 135.5, 138.5, 139, 145, 149, 154, 162, 174.

3-((4-ethylpiperazin-1-yl)methyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione (7d):



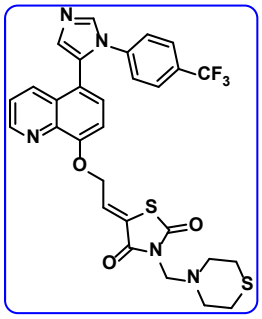
M.p: 290˚C - 292˚C. **IR (KBr, cm^{-1}):** 3350, 3020, 1680, 1620, 1330, 750, 625, **^{1}HNMR (d_6-DMSO, 400 MHz):** 1.2 (t, 3H), 2.5 (m, 10H), 4.5 (s, 2H), 4.67(d, 1H), 4.68(d, 1H), 6.80 (dd, 1H), 7.1 (m, 2H), 7.3(d, 2H), 7.62 (m, 4H),7.8 (d, 1H), 8.42 (d, 1H), 8.82 (d, 1H). **^{13}C-NMR (d_6-DMSO, 400 MHz):** 14, 50, 53, 58, 65, 108, 122, 123.9, 124, 124.1, 125, 130, 132, 135, 139, 145, 149, 155, 165, 174.

3-(morpholinomethyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione (7e):



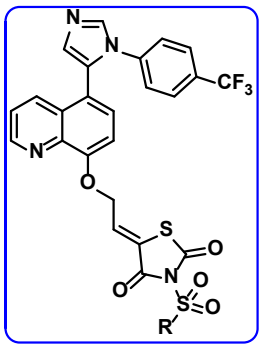
M.p: 280˚C - 282˚C. IR (KBr, cm^{-1}): 3016, 1720, 1650, 1503, 1300, 1050, 695, 650. **^{1}HNMR (d_6-DMSO, 400 MHz):** 2.6 (t, 4H), 3.7 (t, 4H), 4.5 (s, 2H), 4.68 (dd, 1H), 4.69 (dd, 1H), 6.80 (dd, 1H), 7.15 (m, 2H), 7.25 (d, 2H), 7.62 (m, 4H), 7.9 (d, 1H), 8.38 (d, 1H), 8.89 (d, 1H). **^{13}C-NMR (d_6-DMSO, 400 MHz):** 53, 65, 66, 107, 121.9, 123.8, 124, 124.5, 127, 130, 132, 135.5, 139, 145, 149, 155, 164, 176.

3-(thiomorpholinomethyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione (7f):



M.p: 272˚C - 275˚C. IR(KBr, cm^{-1}): 3080, 1730, 1645, 1520, 1310, 1125, 670, 660, **^{1}HNMR (d_6-DMSO, 400 MHz):** 2.6 (t, 4H), 2.8 (t, 4H), 4.51 (s, 2H), 4.66 (dd, 1H), 4.67 (dd, 1H), 6.81 (dd, 1H), 7.15 (m, 2H), 7.25 (d, 2H), 7.62 (m, 4H), 7.9 (d, 1H), 8.37 (d, 1H), 8.86 (d, 1H). **^{13}C-NMR (d_6-DMSO, 400 MHz):** 27, 58, 63, 106, 122, 123, 124, 124.5, 125, 130, 131, 135, 138.5, 139, 145, 149, 155.4, 164, 174.

Step 7: General procedure for -3-(sulfonyl derivative)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene) thiazolidine-2,4-dione (8a-f):

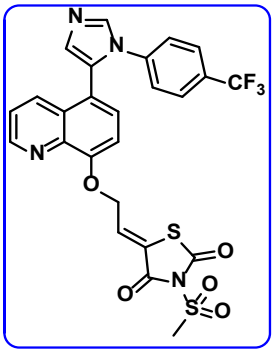


5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy) ethylidene) thiazolidine-2,4-dione (500 mg, 1.08 mmol) in Dry DMF(5 mL) was added NaH (3 eq) at 0˚C under N_2atm and stirred for 1 h. To that derivative of sulfonyl chloride (1.1 eq) was added and stirred for 5 - 8 h. The progress of reaction was monitored by TLC. The reaction mixture was poured in aq sat $NaHCO_3$ and stirred for 15 min. The a.q layer was extracted with 10% MeOH-$CHCl_3$ (3 × 25 ml) and dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to give crude product. The crude product was purified by Column chromatography (100 - 200 mesh silica) isolated 3-(sulfonyl derivative)-5-(2-((5-(1-(4-(trifluoromethyl) phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy) ethylidene) thiazolidine-2,4-dione (8a-f). The summary of physical data for analogues is shown in Table 2.

Table 2. Summary table for analogues 8(a-f).

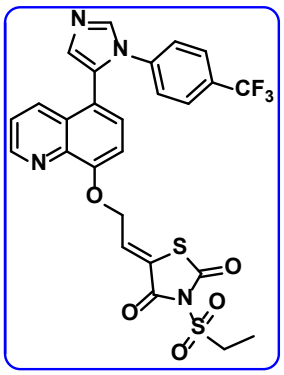
Analogues						
Comp	8a	8b	8c	8d	8e	8f
R	Me	Et	P-Tolyl	4-Cl-C_6H_4	4-Br-C_6H_4	4-NO_2-C_6H_4
Reaction Time	5 h	5 h	8 h	8 h	8 h	8 h
Yield	65%	63%	55%	50%	54%	45%

3-(methylsulfonyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione(8a):



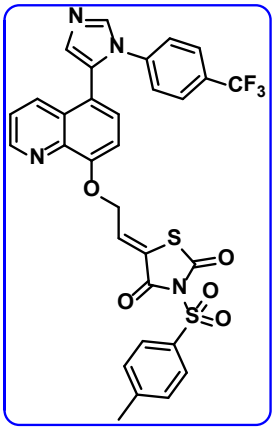
M.p: 280˚C - 283˚C. **IR (KBr, cm−1):** 3040, 3025, 1730, 1645, 1600, 1320, 1070, 770, 715 620. **^{1}HNMR (d_6-DMSO, 400 MHz):** 2.8 (s, 3H), 4.67 (dd, 1H), 4.68 (dd, 1H), 6.8 (dd, 1H), 7.1 (m, 2H), 7.3(d, 2H), 7.6 (m, 4H), 7.8 (d, 1H), 8.4 (d, 1H), 8.81 (d, 1H). **^{13}CNMR (d_6-DMSO, 400 MHz):** 42, 64, 106, 121, 122, 123.5, 124, 124.5, 126, 130.5, 132, 135, 138, 139, 145, 148, 164 and 173.

3-(ethylsulfonyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione(8b):



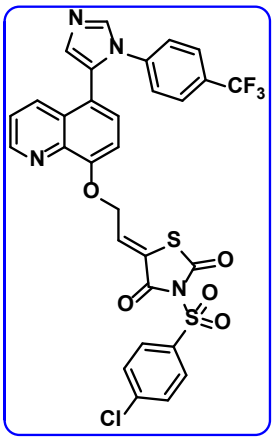
M.p: 288˚C - 290˚C. **IR (KBr, cm^{-1}):** 3040, 3025, 1730, 1645, 1603, 1325, 1075, 772, 715, 620. **^{1}HNMR (d_6-DMSO, 400 MHz):** 1.3 (t, 3H), 3.45 (q, 2H), 4.65 (dd, 1H), 4.67 (dd, 1H), 6.8 (dd, 1H), 7.13 (m, 2H), 7.32(d, 2H), 7.65 (m, 4H), 7.8 (d, 1H), 8.41 (d, 1H), 8.82(d, 1H). **^{13}CNMR (d_6-DMSO, 400 MHz):** 10, 52, 63, 106, 121, 122, 124, 124.5, 126, 130, 135, 138, 139, 145, 148, 164 and 173.

3-tosyl-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy) ethylidene) thiazolidine-2,4-dione(8c):



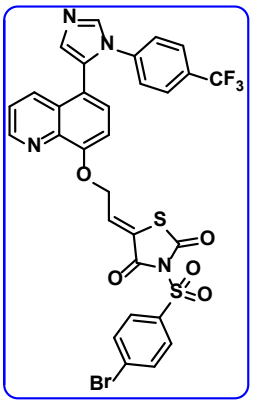
M.p: 300˚C - 302˚C. **IR (KBr, cm^{-1}):** 3050, 3030, 1735, 1640, 1603, 1325, 1075, 770, 715, 620. **^{1}HNMR (d_6-DMSO, 400 MHz):** 2.3 (s, 3H), 4.68 (dd, 1H), 4.69 (dd, 1H), 6.8 (dd, 1H), 7.13 (m, 2H), 7.32 (d, 2H), 7.4 (d, 2H), 7.65 (m, 4H), 7.7 (d, 2H), 7.8 (d, 1H), 8.42 (d, 1H), 8.85 (d, 1H). **^{13}CNMR (d_6-DMSO, 400 MHz):** 20, 64, 107, 121, 122, 123, 124, 124.5, 126, 128, 130, 132, 133, 135, 138, 139, 145, 148, 155, 165 and 175.

3-((4-chlorophenyl)sulfonyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione (8d):



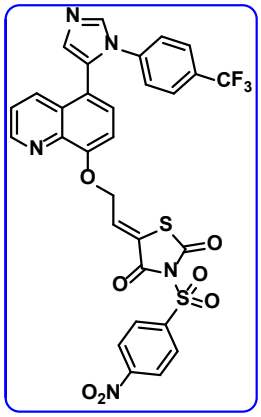
M.p: 290˚C - 292˚C. **IR (KBr, cm^{-1}):** 3070, 3020, 1720, 1620, 1530, 1325, 1080, 770, 720, 655. **^{1}HNMR (d_6-DMSO, 400 MHz):** 4.68 (dd, H), 4.69 (dd, 1H), 6.85 (dd, 1H), 7.15 (m, 2H), 7.28 (d, 2H), 7.4 (d, 2H), 7.63 (m, 6H), 7.8 (d, 2H), 7.95 (d, 1H), 8.5 (d, 1H), 8.87 (d, 1H). **^{13}CNMR (d6-DMSO, 400 MHz):** 64, 108, 121, 122, 123, 124, 124.5, 126, 128, 130, 132, 133, 134.7, 135, 137, 139, 145, 149, 155, 162 and 173.

3-((4-bromophenyl)sulfonyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione (8e):



M.p: 298˚C - 300˚C. **IR (KBr, cm^{-1}):** 3080, 3025, 1720, 1623, 1530, 1325, 1085, 770, 725, 655. **^{1}HNMR (d_6-DMSO, 400 MHz):** 4.68 (dd, 1H), 4.69 (dd, 1H), 6.87 (dd, 1H), 7.18 (m, 2H), 7.28 (d, 2H), 7.6 (m, 4H), 7.88 (m, 5H), 8.4 (d, 1H), 8.8 (d, 1H). **^{13}CNMR (d_6-DMSO, 400 MHz):** 64.2, 107, 121.8, 122.4, 123.8, 123.9, 124, 124.2, 124.5, 126, 128, 130, 131.8, 132, 134.5, 136, 139, 146, 149, 155, 163 and 174.

3-((4-nitrophenyl)sulfonyl)-5-(2-((5-(1-(4-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)quinolin-8-yl)oxy)ethylidene)thiazolidine-2,4-dione(8f):



M.p: 305˚C - 308˚C. **IR (KBr, cm^{-1}):** 3070, 3028, 1720, 1623, 1535, 1400, 1328, 1085, 770, 730, 655. **^{1}HNMR (d_6-DMSO, 400 MHz):** 4.68 (dd, 1H), 4.69 (dd, 1H), 6.87 (dd, 1H), 7.18 (m, 2H), 7.28 (d, 2H), 7.6 (m, 4H), 7.8 (d, 1H), 8.12 (d, 2H), 8.4 (m, 3H), 8.85 (d, 1H). **^{13}CNMR (d_6-DMSO, 400 MHz):** 64.2, 107, 121, 122, 123.8, 124, 124.5, 124.8, 126, 128, 130, 132, 134, 136, 139, 142, 146, 149, 151, 155.4, 164 and 174.5.

5. Conclusion

In current research work, we successfully synthesized and characterized Mannich bases of quinoline attached imidazoline containing thiozolidine-2,4-dione derivatives and sulfonamide analogues. In step 2, cyclization was achieved in good yield. In step 4, aldehyde was isolated with good yield. Step 7 & 8 avoid te-

dious work-up and gain good yields. We strongly believe this is a novel route for synthesis of Mannich bases of thiozolidne-2,4-dione and sulfonamide analogues. We are planning to make these derivatives check for biological evolution and details will include in next journal.

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Abbreviations and Acronyms

DMF: Dimethylformamide
EtOAc: Ethyl Acetate
DCM: Dichloromethane
DIPEA: N,N-Diisopropylethylamine
NaH: Sodium hydride
TosMIC: Toluenesulfonylmethyl Isocyanide