*Plant Archives* Vol. 20, Supplement 1, 2020 pp. 472-475 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

# SYNTHESIS OF NOVEL MANNICH BASES OF PIOGLITAZONE USING PHARMACOLOGICALLY ACTIVE SECONDARY AMINES

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## Abstract

All the synthesized compounds were characterized based on their elemental analysis, IR and $^1$HNMR spectroscopic data. Pioglitazones Mannich Bases were obtained in good yields. The reaction was monitored on TLC Silica plates, Elemental analysis was also carried out for all the three compounds and substantial percentage of compounds were observed. Pyrrolidine Mannich Base of Pioglitazone was obtained in high yield of 73 percent. $R_f$ values of all the synthesized Mannich Bases of Pyrrolidine, Piperazine and Piperidine were between 0.50 and 0.60.

***Keywords*:** Mannich Bases, Thiazolidinediones, Anti-diabetic.

## Introduction

The TZDs normally extended as Thiazolidinediones, also known by the name as glitazones belong to the series of heterocyclic compounds that consist of five-membered ring having core skeleton made up of carbon, nitrogen and sulfur. These drugs are used for curing the disease i.e. type II diabetes mellitus. Thiazolidinediones were explored very widely for their applications in the treatment if polycystic ovarian disease, psoriasis, ovary hyperstimulation syndrome etc. Other forms of lipid dystrophies have been reported which are responsible for the insulin resistance in the body. It was also reported that TZDs also provide the degree of protection at the initial stages of development of breast cancer. Evidences were found for the treatment of non-alcoholic steatohepatitis which included vitamin E clubbed thiazolidinediones that displayed both antioxidant and insulin sensitizing activity in addition of turning out the histological improvements in steatosis severity (Luo, *et al.*, 2013; Manikpuri Joshi *et al.*, 2010; Morgan *et al.*, 2014; Osadebe *et al.*, 2015). Thiazolidinedione derivatives owes a broad pharmacological profile. Variety of drugs such as troglitazone, pioglitazone, and rosiglitazone possesses a affinity to decrease blood glucose levels in humans (Hulin, McCarthy *et al.*, 1996; Jeong, *et al.*, 2004; Luo, *et al.*, 2013; Manikpuri *et al.*, 2010; Morgan *et al.*, 2014; Osadebe *et al.*, 2015; Panigrahy *et al.*, 2002; Ricote *et al.*, 1998; Waki *et al.*, 2010). The TZDs also displayed anti-inflammatory effects on vascular cells and found to stop the production of inflammatory cytokines in various conditions (Osadebe *et al.*, 2015; Panigrahy *et al.*, 2002).

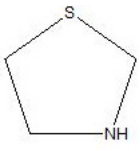



**Fig. 1 :** Basic structure of Thiazolidine

Keeping in mind the wide spectrum of pharmacological activities of Thiazolidine diones, it was thought sensible to synthesize various derivatives of Pioglitazone, one such drug of the class studied.

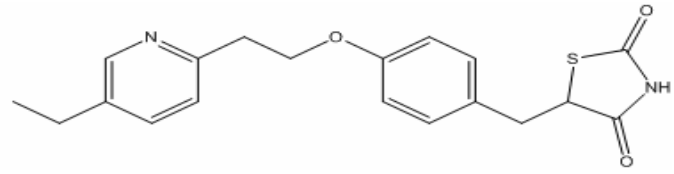



**Fig. 2 :** Structure of Pioglitazone

## Materials and Methods

### Chemicals

All the chemicals used were of analytical grade and were obtained from Loba chem., Merck Limited and SD Fine chemicals. Readymade silica gel plates were used to monitor the reactions which were obtained from Merck Limited. The solvent system utilized was Methanol: Chloroform (1:1). Potassium bromide was purchased from SD Fine chemicals.

### Apparatus & Equipments

Iodine chamber was utilized to view the plates. Melting point was checked by utilizing Buchi 530 melting point apparatus. Infra Red Spectra of the synthesized compounds was analyzed by utilizing KBr disc method on Agilent FTIR. The proton magnetic resonance spectra ($^1$H-NMR) was analyzed by using Bruker NMR (300 MHz). The solvent used was DMSO and Internal standard was Tetra Methyl Silane (TMS). Analysis of various elements (elemental analysis) was performed by using CHNS (O) analyzer.

### Synthesis of Mannich Bases of Pioglitazone (5a-5e)

10 ml Formaldehyde (2) (0.131 mol) was added drop wise to the mixture of Pioglitazone (1) (2.5 gms, 0.006 mol) which was already dissolved in 10 ml Dimethyl Formamide (2) (0.131 mol). The mixture was thenstirred forhalf an hour to produce itsmethoxyl derivative. In another beaker, various secondary amines (4a-4e) (3) were added in different quantities (2.5 g, 0.0121 mol) using Dimethyl Formamide (DMF) (2) (10 ml, 0.131mol) as a solvent. The formulated methoxyl derivative was further stirred for 5-10 minutes with secondary amines(4a-4e). Reflux was performed for 4 hrs after that and the reaction was monitored over TLC. Then after, we collected the precipitates which were filtered, washed, dried and recrystallized using methanol: chloroform system (Arora *et al.*, 2012; Boris *et al.*, 2007; Chang, 2000;

Gustafson *et al.*, 2003; Hulin *et al.*, 1996; Jeong *et al.*, 2004). The synthesized compounds 5a -5c were then analyzed with various spectroscopic techniques.

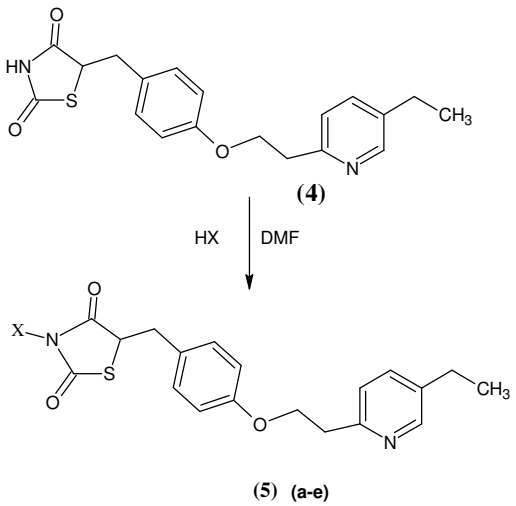



**Fig. 3 :** Synthesis of Novel Pioglitazone Mannich bases 5(a-c)

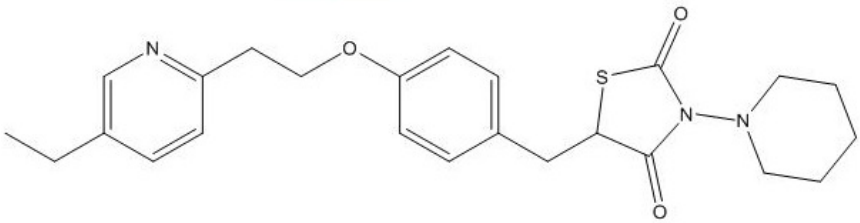
**Table 1:** Description of various Secondary amines used

| S.NO | Secondary amine |
|---|---|
| **1** | Piperidine (4a) |
| **2** | Piperazine (4b) |
| **3** | Pyrrolidine(4c) |

## Results

The Mannich Bases of Pioglitazone were synthesized by making use of the Mannich reaction. The yield of the Pyrrolidine derivative (5c) was higher in comparison to other compounds which were produced along with that and retention factor values of the compounds ranged from 0.45 to 0.75 range. The highest melting point of 78.6 °C was acquired by 5c derivative of Pyrrolidine. The physicochemical parameters of the compound synthesized are mentioned in table 3. The results of elemental analysis, FTIR and $^1$HNMR of the synthesized compounds are given below.

**5-(4-2-(5-ethylpyridin-2-yl) ethoxy)benzyl)-3-(piperidin-l-yl)thiazolidine-2,4-dione (5a)**




**Elemental Analysis** for $C_{24}H_{29}N_3O_3S$:

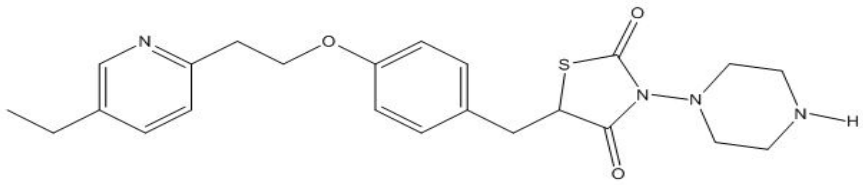
**Calculated:** C, 65.58 %; H, 6.65 %; N, 09.65 %, O, 10.92%, S, 7.29 %.

**Observed:**C, 65.62 %; H, 6.59 %; N, 09.64 %, O, 10.88 %, S, 7.27%

**FTIR ($cm^{-1}$):** 3269 (N-H, str), 2974 (C-H, str ,alk), 1650 and 1452 (C=C, Ar), 1067 (C-N), 863 (opp. C-H, bend), 1454 (N-H, bend), 1069 (C-O), 1235 (N=N), 1754 (C=O), 901 (C=S).

**$^1$HNMR (DMSO-d6)(δ ppm):** 8.29 (1H, s, $H_1$),7.99 (1H, d, $H_2$), 7.68 (1H, s, $H_3$), 7.20-7.23 (1H, d, $H_4$), 7.19-7.18 (2H, d, $H_{13}$,$H_{10}$), 4,76 (2H, s, $H_5$, $H_6$), 4.21 (1H, t, $H_7$), 6.72 (2H, d, $H_{12}$,$H_{11}$), 3.30 (2H, t, $H_{16}$, $H_{17}$), 7.20 (1H, d, $H_{18}$), 7.64 (1H, d, $H_{19}$), 3.42 (2H, d, $H_8$,$H_9$), 4.50 (2H, t, $H_{14}$, $H_{15}$), 2.94-2.92 (2H, q, $H_{21}$,$H_{20}$), 2.21 (3H, t, $H_{22}$, $H_{23}$, $H_{24}$), 8.19 (1H, s, $H_{25}$), 1.30 (piperidine, d), 1.29 (piperidine, $CH_2$), 1.59 (piperidine, $CH_2$), 3.10 (piperidine, C-NH), 3.10 (piperidine, C-NH)

**5-(4-2-(5-ethylpyridin-2-yl) ethoxy)benzyl)-3-(piperazin-l-yl)thiazolidine-2,4-dione (5b)**




**Elemental Analysis** for $C_{23}H_{28}N_4O_3S$:

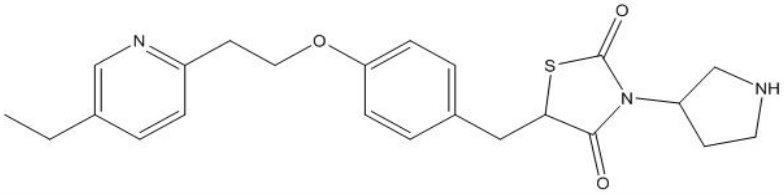
**Calculated:** C, 62.70; H, 6.41; N, 12.72; O, 10.89; S, 7.28.

**Observed:**C, 62.65 %; H, 6.43 %; N, 12.66 %, O, 10.85 %, S, 7.41%

**FTIR ($cm^{-1}$):** 3221 (N-H, str), 2979 (C-H, str.), 1514 and 1453 (C=C, Ar), 1309 (C-N), 1692 (C=C, str), 1384 (C-H, bend), 1453 (N-H, bend), 1075 (C-O), , 841 (opp. C-H, bend), 1237 (N=N), 1755 (C=O), 902 (C=S).

**$^1$HNMR (DMSO-d6) (δ ppm):** 7.92 (1H, d, $H_a$), 8.02 (1H,d, $H_1$),7.90 (1H, d, $H_2$), 7.67 (1H, d, $H_3$), 7.25-7.24 (1H, d, $H_4$), 4.13 (IH, t, $H_7$), 7.38-7.40 (2H, d, $H_{13}$,$H_{10}$), 6.62 (2H, d, $H_{12}$,$H_{11}$), 3.78-3.76 (2H, t, $H_8$, $H_9$), 3.30 (2H, t, $H_{16}$, $H_{17}$),7.21-7.86 (1H, d, $H_{18}$, $H_{19}$), 4.74 (2H, s, $H_5$,$H_6$), 4.40-4.25 (2H, t, $H_{14}$, $H_{15}$),2.50-2.33 (2H, q, $H_{21}$,$H_{20}$),1.05-1.00 (3H, t, $H_{22}$, $H_{23}$, $H_{24}$), 2.69 (piperazine, $CH_2$), 2.69 (piperazine, $CH_2$), 2.69 (piperazine, $CH_2$), 2.69 (piperazine, $CH_2$), 1.90 (piperazine, NH).

**5-(4-2-(5-ethylpyridin-2-yl) ethoxy)benzyl)-3-(pyrrolidin-3-yl)thiazolidine-2,4-dione (5c)**




**Elemental Analysis** for $C_{23}H_{27}N_3O_3S$

**Calculated:** C, 64.92; H, 6.40; N, 9.87; O, 11.28; S, 7.54

**Observed:** C, 64.71 %; H, 6.35 %; N, 9.87 %, O, 11.48 %, S, 7.60%.

**FTIR:** 3437 (N-H, str), 2861 (C-H, str), 1508 and 1457 (C=C, Ar), 1311 (C-N), 1657 (C=C, str), 1389 (C-H, bend), 1454 (N-H, bend), 1081 (C-O), 1682 (C=O), 832 (opp. C-H, bend), 1269 (N=N), 919 (C=S).

**$^1$HNMR:** 7.41-7.43 (2H, d, $H_{13}$,$H_{10}$), 6.91 (2H, d, $H_{12}$,$H_{11}$), 3.51-3.47 (2H, t, $H_8$,$H_9$), 5.42 (2H, s, $H_5$, $H_6$), 3.55 (1H, t, $H_7$), 4.31-4.25 (2H, t, $H_{14}$, $H_{15}$), 3.27 (2H, t, $H_{16}$, $H_{17}$), 7.48-7.45 (1H, d, $H_{18}$, $H_{19}$), 2.50-2.49 (2H, q, $H_{21}$,$H_{20}$), 2.51 (6H, s, $H_1$, $H_2$, $H_3$, $H_4$, $H_{26}$, $H_{25}$), 1.19-1.15 (3H, t, $H_{22}$, $H_{23}$, $H_{24}$), 3.69 (pyrrolidine, N-CH), 2.0 (pyrrolidine, N-H).

**Table 2**: Structures of various Secondary Amines Used.

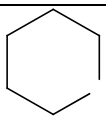
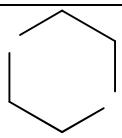
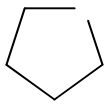
| S.No | Compound | Secondary amine (X) |
|---|---|---|
| **1** | **5a** |  |
| **2** | **5b** |  |
| **3** | **5c** |  |

**Table 3:** Physiochemical parameters of some Novel Pioglitazone Mannich Bases.

| Compound | Substitued Ring | Molecular formula | M. Wt. g/moL | Yield [%] | M.pt [$^0$C] | $R_f$ |
|---|---|---|---|---|---|---|
| **5a** | Piperidine | $C_{24}H_{29}N_3O_3S$ | 439.57 | 69 | 235-238 | 0.57 |
| **5b** | Piperazine | $C_{23}H_{28}N_4O_3S$ | 440.19 | 71 | 239-243 | 0.58 |
| **5c** | Pyrrolidine | $C_{23}H_{27}N_3O_3S$ | 425.54 | 73 | 247-252 | 0.60 |

## Discussion

In the present research, various mannich bases of pioglitazone were synthesized by taking a reference from the work of Carl mannich who had utilized different aryl and alkyl amines and created the pharmacologically more potent synthetic derivatives (Arora *et al.*, 2012; Chitturi, 2008; Krentz, 2006; Luo *et al.*, 2013). The basic idea behind the current study was to use the abstractable hydrogen of the secondary amine and to synthesize various pharmacologically active moieties from it (Belfort *et al.*, 2006; Law *et al.*, 2011). Mannich Bases were exploited in various fields of pharmaceutical industry like polymers, dispersants in lubricating oils etc. This thoughtfulness paved

a pathway for amino alkyaltion of different secondary amines by the process of mannich reaction. The reaction involved the addition of the basic amino alkyl chain, thatmodifies the biological profile of the parent drug and its physiochemical characteristics. The synthesized derivatives of Mannich reaction hadestablished the pharmacological profile which is having the therapeutic index more towards effectiveness and less towards toxicity as compared to the parent compound (Arora *et al.*, 2012; Chitturi, 2008; Krentz, 2006; Luo *et al.*, 2013; Panigrahy *et al.*, 2002; Ricote *et al.*, 1998; Sahoo *et al.*, 2006).

## Conclusion

The synthesized mannich bases were identified by utilizing various spectroscopic techniques like $H^1$NMR, FTIR and were further screened on TLC plates. It has been proved that mannich bases possesses much better activities than the parent compound. Mannich Bases of Pioglitazone can serve as more potent anti-diabetic agents than Pioglitazone.

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