ISSN 1996-5052

Current Research in Chemistry

Knowledgia SCIENTIFIC
A Place to Publish Outstanding Research

http://knowledgiascientific.com

Current Research in Chemistry 6 (1): 10-15, 2014
ISSN 1996-5052 / DOI: 10.3923/crc.2014.10.15

Synthesis of Novel Mannich Bases of Pioglitazone

[1]Ramit Kapoor, [3]Rashmi Arora, [1]Ravinesh Mishra, [1]Manu Arora and [2]Pooja Mittal
[1]Department of Pharmaceutical Chemistry,
[2]Department of Pharmaceutics, IIT, BHU, India
[3]Department of Pharmaceutical Chemistry, Rayat Institute of Pharmacy, Railmajra, India

Corresponding Author: Ramit Kapoor, School of Pharmacy and Emerging Sciences, Baddi, India Tel: 9729765308

ABSTRACT

Thiazolidinediones (TZDs) acts by stimulating PPAR that improves glycaemic control by decreasing insulin resistance. Although the use of Thiazolidinediones had long been associated with cardiovascular risk factors but it is commonly used as a potent anti-diabetic. The use of Thiazolidinediones (TZDs) in the management of type 2 diabetes mellitus (T2DM) had been associated with an increased risk of peripheral oedema. Mainly class include Ciglitazone, Rosiglitazone, Troglitazone and Pioglitazone. Mannich reaction have proved to be more effective and leads to generation of new compounds which are less toxic but pharmacologically more active than their parent drugs. Mannich Bases of Pioglitazone were synthesized by making use of the abstractable hydrogen in the Pioglitazone and it was aminomethylated using DMF as solvent. The subjected mixture was stirred with continuous addition of formaldehyde and was refluxed to yield various potent biological mannich bases of Pioglitazone. These considerations have provoked Mannich bases of secondary amine by Mannich reaction.

Key words: Rosiglitazone, mannich bases, thiazolidinediones, anti-diabetic, peroxisom

INTRODUCTION

Thiazolidinediones (TZDs) have been the subject of extensive researches because of their deep involvement in the regulation of different physiological processes. Thiazolidinediones derivatives have shown to possess many pharmacological activities like oncostatic, anti-diabetic, anti-inflammatory activities (Gustafson *et al*., 2003). TZDs such as troglitazone, pioglitazone and rosiglitazone are potent reducer of plasma glucose level *in vivo*. Besides their anti-diabetic potency, these TZDs have been shown to exert anti-inflammatory effects on vascular cells (Kurebayashi *et al*., 2005). TZDs were also found to inhibit the production of inflammatory cytokines and the expression of inducible nitric oxide syntheses in monocytes macrophages (Jeong *et al*., 2004; Ricote *et al*., 1998) (Fig. 1).

Considering the broad spectrum of activities of Thiazolidinediones like anti-inflammatory, analgesic, anti-diabetic, antimicrobial and anticancer activities (Panigrahy *et al*., 2002; Elstner *et al*., 1998), it was decided to synthesize various derivatives of Thiazolidinedione category drug Pioglitazone (Fig. 2).

MATERIALS AND METHODS

Chemicals: Carrageenan was obatined from HiMedia Labs, Mumbai. All other chemical reagents were used of analytical grade, which were procured from different companies (Loba Chem, Merck

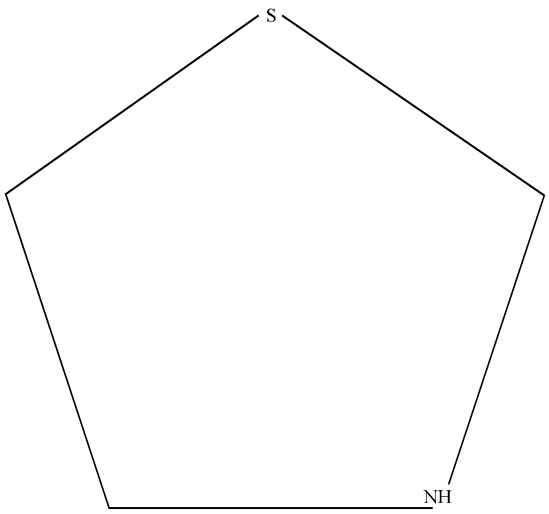


Fig. 1: Basic structure of thiazolidiene

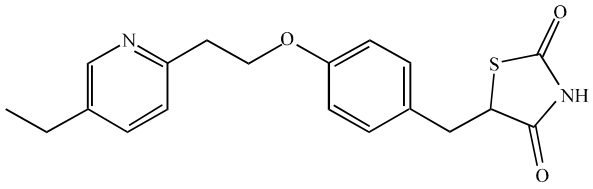


Fig. 2: Structure of pioglitazone

Limited and S D Fine). The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform-methanol (5:5) as a solvent system. Iodine was used as a developing agent. Melting points were determined with a Buchi 530 melting point apparatus in open capillaries. IR spectra were recorded on KBr discs, using a Perkin-Elmer Model 1600 FT-IR spectrometer. The proton magnetic resonance spectra (^{1}H-NMR) were recorded on Perkin Elmer Spectrophotometer-300 MHz in DMSO-d6 using TMS as an internal standard. Elemental analysis was performed by CHNS (O) Analyzer (Arora *et al.*, 2012).

Animals: The wistar albino rats (150-200 g) of either sex were obtained from Zoin Co. Biologicals, near science market, Ambala. They were kept at standard laboratory diet, environmental temperature and humidity. A 12 h light and dark cycle was maintained throughout the experimental protocol.

General synthesis of mannich bases of pioglitazone (5a-5e): Pioglitazone (1) (2.5 g, 0.006 mol) was added in Dimethyl formamide (2) (10 mL, 0.131 mol). Formaldehyde (2) (10 mL, 0.131 mol) was added drop wise. The mixture was subjected to stirring for 30 min to yield a methyl derivative. To the another beaker various secondary amines (5a-5e) (Table 1) (3) (2.5 g, 021 mol) was added in Dimethyl formamide (2) (10 mL, 0.131 mol). The methyl derivative was transferred to secondary amines and was stirred for few minutes. The contents of the beaker were refluxed for 4 h, the reaction procedure was monitored over TLC. The precipitate was filtered, dried and recrystallized using (methanol: chloroform) (Fig. 3) (Table 2).

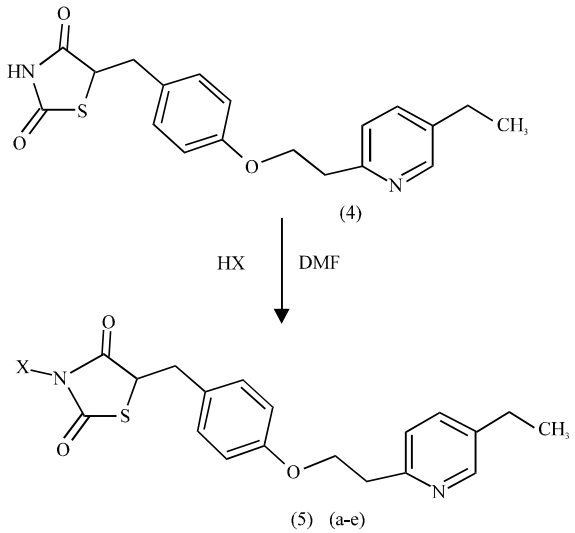
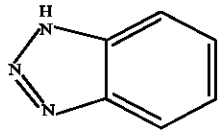
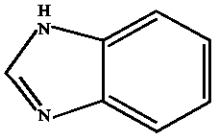
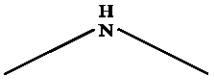
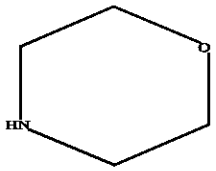
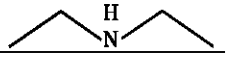


Fig. 3: Synthesis of novel pioglitazone mannich bases 5(a-e)

Table 1: Structures of secondary amines

Compound	Secondary amine (X)	Structure
5a	Benzotriazole	
5b	Benzimidazole	
5c	Dimethyl amine	
5d	Morpholine	
5e	Diethyl amine	

RESULTS

3-((1H-benzo[d][1,2,3]triazol-5-yl)methyl)-5-(4-(2-(6-ethylpyridin-2-ylamino) ethoxy)benzyl)thiazolidine-2,4-dione. (5a)

Elemental analysis: $C_{26}H_{26}N_6O_3S$.

Calculated: C, 62.13%; H, 5.21%; N, 16.72%, O, 9.55%.

Observed: C, 62.01%; H, 5.09%; N, 16.51%, O, 9.77%.

Table 2: Physiochemical parameters of some novel 2, 4, 5 triphenyl imidazole mannich bases

Compound	Substituted ring	Molecular formula	M. wt. (g mol^{-1})	Yield (%)	M.P. (°C)	R_f
5a	Benzotriazole	$C_{27}H_{26}N_6O_3S$	502.18	74.0	232-235	0.55
5b	Benzimidazole	$C_{27}H_{26}N_4O_3S$	486.60	71.0	241-244	0.60
5c	Dimethyl amine	$C_{22}H_{27}N_3O_3S$	413.53	65.6	257-261	0.58
5d	Morpholine	$C_{24}H_{29}N_3O_4S$	455.53	72.6	274-277	0.67
5e	Diethyl amine	$C_{24}H_{31}N_3O_3S$	441.59	78.6	264-268	0.61

FTIR (cm^{-1}): 3271 (N-H, str), 2984 (C-H, str, alk), 1650 and 1453 (C = C, Ar), 1069 (C-N), 865 (opp. C-H, bend), 1453 (N-H, bend), 1067 (C-O), 1236 (N = N), 1756 (C = O), 903 (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_{18},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}).

3-((1H-benzo[d]imidazol-4-yl)methyl)-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl) thiazolidine-2,4-dione (5b)

Elemental analysis: $C_{27}H_{26}N_4O_3S$.

Calculated: C, 66.65%; H, 5.39%; N, 11.51%, O, 9.86%.

Observed: C, 66.01%; H, 5.69%; N, 16.55%, O, 9.95%.

FTIR (cm^{-1}): 3223 (N-H, str), 2979 (C-H, str.), 1513 and 1454 (C = C, Ar), 1308 (C-N), 1693 (C = C, str), 1386 (C-H, bend), 1451 (N-H, bend), 1072 (C-O),, 841 (opp. C-H, bend), 1238 (N = N), 1746 (C = O), 903 (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}).

5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)3((dimethylamino)methyl) thiazolidine-2,4-dione (5c)

Elemental analysis: $C_{22}H_{27}N_3O_3S$.

Calculated: C, 63.90%; H, 6.58%; N, 10.16%, O, 11.61%.

Observed: C, 63.01%; H, 5.87%; N, 16.87%, O, 9.99%.

FTIR (cm^{-1}): 3438 (N-H, str), 2858 (C-H, str), 1511 and 1454 (C = C, Ar), 1308 (C-N), 1656 (C = C, str), 1386 (C-H, bend), 1451 (N-H, bend), 1078 (C-O), 1679 (C = O), 829 (opp. C-H, bend), 1270 (N = N), 916 (C = S).

^{1}HNMR (DMSO-d6) (δ ppm): 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}).

5-(4-(2-(5-ethylpyridin-2-yl) ethoxy) benzyl)-3-((morpholin-3-yl) methyl) thiazolidine -2,4-dione (5d)
Elemental analysis: $C_{24}H_{29}N_3O_4S$.

Calculated: C, 63.27%; H, 6.42%; N, 9.22%, O, 14.05%.

Observed: 63.20%; H, 6.18%; N, 9.13%, O, 14.45%.

FTIR (cm^{-1}): 2852 (C-H, str), 1487 and 1455 (C = C, Ar), 1323 (C-N), 1600 (C = C, str), 1394 (C-H, bend), 1437 (N-H, bend), 1072 (C-O), 1810 (C = O), 840 (opp. C-H, bend), 1254 (N = N), 987 (C = S).

^{1}HNMR (DMSO-d6) (δ ppm): 7.37-7.31 (2H, d, H_{13}, H_{10}), 6.95 (2H, d, H_{12}, H_{11}), 3.55-3.53 (2H, t, H_8, H_9), 4.17 (1H, t, H_7), 3.27 (2H, t, H_{16}, H_{17}), 7.34-7.55 (1H, d, H_{18}, H_{19}), 4.17-4.05 (2H, t, H_{14}, H_{15}), 2.50-2.49 (2H, q, H_{21},H_{20}), 1.17-1.10 (3H, t, H_{22}, H_{23}, H_{24}), 3.93-3.90 (1H, t, H_3), 3.76-3.67 (4H, d, H_2, H_2, H_5, H_6), 3.54 (1H, m, H_1).

3-((diethylamino)methyl)-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl) thiazolidine-2,4-dione (5e)
Elemental analysis: $C_{24}H_{31}N_3O_3S$.

Calculated: C, 65.28%; H, 7.08%; N, 9.52%, O, 10.87%.

Observed: C, 65.15%; H, 6.31%; N, 9.17%, O, 14.42%.

FTIR (cm^{-1}): 2978 (C-H, str), 1487 and 1455 (C = C, Ar), 1323 (C-N), 1600 (C = C, str), 1367 (C-H, bend), 1437 (N-H, bend), 1013 (C-O), 1679 (C = O), 862 (opp. C-H, bend), 1265 (N = N), 931 (C = S).

^{1}HNMR (DMSO-d6) (δ ppm): 7.36-7.34 (2H, d, H_{13}, H_{10}), 6.98-6.95 (2H, d, H_{12}, H_{11}), 3.83-3.81 (2H, t, H_8, H_9), 4.30 (2H, s, H_5, H_6), 4.17 (1H, t, H_7), 3.27 (2H, t, H_{16}, H_{17}), 7.34-7.55 (1H, d, H_{18}, H_{19}), 4.14-4.11 (2H, t, H_{14}, H_{15}), 2.86-2.80 (2H, q, H_{21}, H_{20}), 2.68-2.60 (4H, q, H_1, H_2, H_3, H_4,), 1.22-1.20 (3H, t, H_{22}, H_{23}, H_{24}), 1.19-1.15 (6H, t, H_{25}, H_{30}, H_{26}, H_{27}, H_{28}, H_{29}).

DISCUSSION

The Synthesis of Mannich Bases of Pioglitazone was carried out and benzotriazoles, morpholine or phthalimide can be successfully used as amine components in direct aminomethylation reactions (Sahoo *et al.*, 2006). Until the mid-seventies, arylamines were only sporadically presented to react with substrates containing an active hydrogen atom, such as heterocyclic compounds or phenols.

Lately, Chinese researchers have intensively studied arylaminomethylation of acetophenones through their addition to a Schiff base formed *in situ* and produced a large number of arylamine Mannich bases. The amine exchange reaction between an alkylamine Mannich base and arylamines also offers easy access to arylamine Mannich bases in high yield under mild reaction conditions. There is versatile utility of the Mannich bases in polymers, dispersants in lubricating oil and pharmaceutical chemistry too. These considerations have provoked Mannich bases of secondary amine by Mannich reaction. This reaction offers a convenient method for introduction of the basic aminoalkyl chain, which alters the biological profile and physiochemical characteristics (Manikpuri *et al.*, 2010). Various drugs obtained from Mannich reaction have proved more effective and less toxic than their parent drugs.

CONCLUSION

The various Mannich bases of Pioglitazone have been synthesized and were characterized by HNMR, FTIR and TLC. The Mannich bases synthesized were obtained in good yields. The Diethl amine derivative (5e) was obtained in high yield as compared to other derivatives and rf values of all the derivatives lie in between 0.50-0.70 region. The melting point of morpholine derivative (5d) was highest that is 78.6°C.

REFERENCES

Arora, R., N.S. Gill, R. Kapoor, A. Aggarwal and A.C. Rana, 2012. Synthesis of 2,4,5-Triphenylimidazoles novel mannich bases as potential antiinflammatory and analgesic agents. Curr. Res. Chem., 4: 99-109.

Elstner, E., C. Muller, K. Koshizuka, E.A. Williamson and D. Park *et al.*, 1998. Ligands for peroxisome proliferator-activated receptorγ and retinoic acid receptor inhibit growth and induce apoptosis of human breast cancer cells *in vitro* and in BNX mice. Proc. Natl. Acad. Sci., 95: 8806-8811.

Gustafson, B., M.M. Jack, S.W. Cushman and U. Smith, 2003. Adiponectin gene activation by thiazolidinediones requires PPARγ2, but not C/EBPα-Evidence for differential regulation of the aP2 and adiponectin genes. Biochem. Biophys. Res. Commun., 308: 933-939.

Jeong, T.S., J.R. Kim, K.S. Kim, K.H. Cho, K.H. Bae and W.S. Lee, 2004. Inhibitory effects of multi-substituted benzylidenethiazolidine-2, 4-diones on LDL oxidation. Bioorg. Med. Chem., 12: 4017-4023.

Kurebayashi, S., X. Xu, S. Ishii, M. Shiraishi, H. Kouhara and S. Kasayama, 2005. A novel thiazolidinedione MCC-555 down-regulates tumor necrosis factor-α-induced expression of vascular cell adhesion molecule-1 in vascular endothelial cells. Atherosclerosis, 182: 71-77.

Manikpuri, A.D., S. Joshi and P.V. Khadikar, 2010. Synthesis and antimicrobial study of the mannich bases of4-{(dipropylamino)[bis (methylene)] sulfanyl}benzamide. J. Eng. Sci. Manage. Educ., 2: 29-33.

Panigrahy, D., S. Singer, L.Q. Shen, C.E. Butterfield and D.A. Freedman *et al.*, 2002. PPARγ ligands inhibit primary tumor growth and metastasis by inhibiting angiogenesis. Clin. Invest., 110: 923-932.

Ricote, M., A.C. Li, T.M. Willson, C.J. Kelly and C.K. Glass, 1998. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. Nature, 391: 79-82.

Sahoo, S., T. Joseph and S.B. Halligudi, 2006. Mannich reaction in Bronsted acidic ionic liquid: A facile synthesis of β-amino carbonyl compounds. J. Mol. Catal. A: Chem., 244: 179-182.