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Research Article

Synthesis and characterization of non-thiazolidinedione PPAR-γ agonists

Gaurav Bajpai*, Suman Malik

Sadhu Vaswani College, Bairagarh, Bhopal

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ABSTRACT

Based on the assumptions of QSAR studies performed on oximes and oximinoacetic acid derivatives, reduced CLogP value compounds P1 and P2 were designed. In the present work, laboratory synthesis of these compounds P1 and P2 was accomplished. Mitsunobu reaction principle was utilized for the synthesis of P1 whereas reduction of aldehyde was done for synthesis of P2. The formation of the products was evident from their NMR, mass and IR characterization which revealed the peaks relevant to the functional groups present in the compounds.

Keywords: oximes, oximinoacetic acid

INTRODUCTION:

Insulin resistance is a crucial and fundamental abnormality that is associated with type 2 diabetes mellitus[1]. A number of oral hypoglycemic agents are now-a-days available for the treatment of non-insulin-dependent diabetes mellitus. Thiazolidine-diones and its derivatives are a class of compounds that may act by enhancing the insulin action without modulating the beta cells mediated insulin secretion[2-4]. These agents bind to peroxisome proliferator-activated receptor γ (PPAR-γ) and increase the differentiation of 3T3-L1 cells into adipocytes and behave as good insulin sensitizing agents[5]. Thiazolidine-diones are potent pharmacological agents for the treatment of NIDDM but these agents are associated with weight gain, edema and anemia as side effects[6-8]. It has thus become essential to design new class of compounds with a better profile than thiazolidine-diones and lesser side effects.

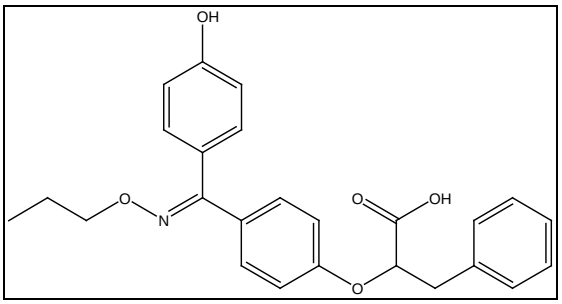
Several studies on designing and synthesis of non-thiazolidinedione PPAR-γ agonists have been performed[9-15]. Development of oxazolidinediones and benzophenyltyrosine for control of diabetes has been extensively studied by chemists working towards development of potent antidiabetic agents. Oxyiminoacetic acid derivatives have been found to be very potent insulin sensitizing agents acting by PPAR-γ agonism[14].

In the present work, synthesis of molecules P1 and P2, designed based on the assumptions derived from our previous work of QSAR studies[16], with a reduced ClogD value in relation to the parent series used for QSAR, was carried out and the characterization of these molecules was done.

Experimental

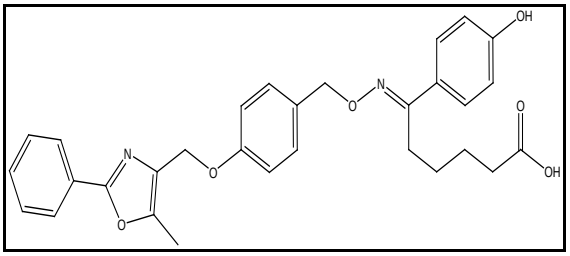
All the reactions were carried out using standard laboratory equipment and standard laboratory glassware. All solvents and reagents used were of analytical grade and were used as received. TLC was used to monitor the progress of reaction using precoated silica gel sheets Merck Silica Gel 60 F_{254} containing a fluorescent indicator and developed using a UV lamp (254 nm). Melting points of compounds were determined on Chemiline digital melting point apparatus using open capillary method and are uncorrected.

The target compounds P1 and P2 (Figure 1) were synthesized by following the procedures previously reported for the preparation of oximes and iminoacetic acid[13-15] with slight modifications (Scheme 1 & 2).



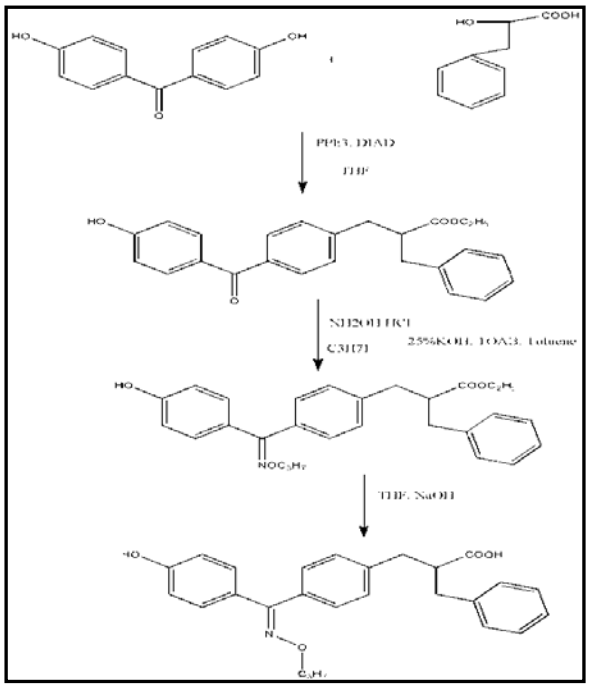
P1

*Corresponding author: Gaurav Bajpai | E-mail: gauravbajpai22@gmail.com

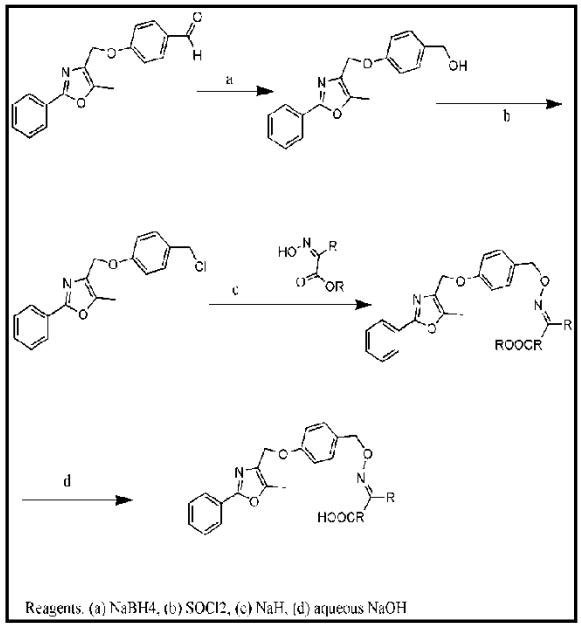


P2

Figure 1: Compounds designed on the basis of assumptions made by QSAR study.



Scheme 1: Synthetic route for laboratory synthesis of P1



Scheme 2: Synthetic route for laboratory synthesis of P2

Synthesis of P1

Step 1: Synthesis of Ethyl 2-(4-(4'hydroxybenzoyl) phenoxy) 3-phenyl propanoate (ap1)

A solution of DIAD 10 mmol in anhydrous THF 20 mL was added dropwise to an ice-bath cooled mixture of ethyl phenyllactate 10 mmol, 4,4'-dihydroxy benzophenone and PPh3 10 mmol in anhydrous THF 50 mL. The reaction mixture was stirred overnight at room temperature. The organic solvent was evaporated under vacuum and a mixture of Et2O and n-hexane (50 mL 1:1) was added to the residue. The resulting precipitate was filtered off and the filtrate was evaporated to dryness. This residue was purified using a silica gel column using suitable effluent.

Step 2: Synthesis of Ethyl 2-(4-(oxiimopropyl-4'hydroxyphenyl) phenoxy) 3-phenyl propanoate (bp1)

Hydroxylamine hydrochloride (6 mmol) and sodium acetate (9 mmol) were added to the solution of step 1 (1.9 mmol) dissolved at 0ºC in a mixture of water and ethanol (50 mL, 1:5). To the mixture was added propyl iodide (6 mmol) and the reaction mixture was refluxed for 24 h followed by stirring for 50 h at room temperature. The organic solvent layer was evaporated under vacuum and dichloromethane was added to the residue. The organic layer was washed with water, dried over sodium sulfate and the solvent was evaporated to give an oily residue which was eluted out on chromatographic column using n-hexane/ethyl acetate 9:1 as eluent. The compound was obtained as colorless oil.

Step 3 Preparation of Ethyl 2-(4-(oximinopropyl-4'hydroxyphenyl) phenoxy) 3-phenyl propionic acid (P1)

1 N NaOH (10 mL) was added to a solution of the ester obtained from step 2 (0.5 mmol) in THF (10 mL). The reaction mixture was stirred overnight at room temperature. The organic solvent was evaporated *in vacuo* and the residue was acidified with a solution of 10% citric acid up to pH 4. The aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was evaporated to dryness to give the final acid as white solids which were crystallized from $CHCl_3$/n-hexane.

Synthesis of P2

Step 1: Synthesis of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol (aP2)

Sodium borohydride (4.31 g) was added to a cold (0ºC) stirred solution of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzaldehyde (33.42 g) in methanol (150 mL)-THF (30 mL). After stirring for 0.5 h at room temeperature, water was added to the reaction mixture, and the whore mixture was stirred for 1 h. The product obtained was filtered and used as it is for further process.

Step 2: Synthesis of 4-{[4-(chloromethyl) phenoxy] methyl}-5-methyl-2-phenyl-1,3-oxazole (bP2)

Thionyl chloride was added to a solution of 4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzyl alcohol in toluene and the mixture was stirred at room temperature for 0.5 h. to the reaction mixture was added ice-cooled water and extracted with AcOEt. The extract was washed with ice-cooled brine, dried over magnesium sulfate, and concentrated to give colorless crystals of 4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-5-phenyl-1,3-oxazole.

Step 3: Synthesis of 2-(4-hydroxyphenyl)-2-hydroxyimino butanoate (cP2)

A solution of 4-hydroxyphenylmagnesium bromide was added dropwise to a solution of dibutyloxalate in diethylether at -7ºC and stirred for 1 h and thereafter the reaction mixture was allowed to warm to 0ºC. To the mixture was added dil. HCl. The organic layer was separated, washed with aqueous NaHCO3 and brine and dried over magnesium sulfate and concentrated *in vacuo*. The residue was eluted on a silica gel column to obtain an oil using ethylacetate-hexane as eluent. The oil was dissolved in ethanol and hydroxylamine hydrochloride and sodium acetate were added to the oil solution and the mixture was refluxed for 18 h. after evaporation of the solvent, the residue was diluted with water and extracted from ethylacetate. The extract was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The product obtained was recrystallized from hexane-diethylether.

Step 4: Synthesis of 2-(4-hydroxyphenyl)-2-{4-[(5-mehyl-2-phenyl-1,3-oxazol-4yl)methoxy] benzoyloxyimino butanoate (dP2)

Sodium hydride was added to a solution of 2-(4-bromophenyl)-2-hydroxyimino acetate and 4-{[4-(chloromethyl) phenoxy] methyl}-5-methyl-5-phenyl-1,3-oxazole in DMF at room temperature. After stirring for 1 h, the mixture was diluted with 1M HCl, rendered basic by addition of NaHCO3 and extracted with ethylacetate. The extract was washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel column with ethylacetate-hexane to give 2-(4-bromophenyl)-2-{4-[(5-mehyl-2-phenyl-1,3-oxazol-4-yl)methoxy]benzoyloxyimino butanoate crystals.

Step 5: Synthesis of 2-(4-hydroxyphenyl)-2-{4-[(5-mehyl-2-phenyl-1,3-oxazol-4-yl)methoxy] benzoyloxyimino butanoic acid (P2)

2-(4-hydroxyphenyl)-2-{4-[(5-mehyl-2-phenyl-1,3-oxazol-4-yl)methoxy] benzoyl oxyimino butanoate was dissolved in THF-methanol (1:2) and 1M NaOH was added to the mixture. The mixture was stirred at 40ºC for 1 h and then made acidic by the addition of 1M HCl and extracted with ethylacetate. The extract was washed with brine and dried over magnesium sulfate and concentrated *in vacuo*. The product was recrystallized from ethylacetate-hexane mixture and the product was obtained as colorless crystals.

Results and Discussions

Compound P 1

Ethyl 2-(4-(4'hydroxybenzoyl) phenoxy) 3-phenyl propanoate

Colorless Oil, Yield: 38%, B.P.: 123ºC, Rf = 0.63 ($CHCl_3$:MeOH, 40:60); IR (KBr, cm^{-1})υ: 3514 (-OH), 1729 (-C=O, ketone), 1591 (-C=C-, aromatic), 3130 (C-H); 1377 ($-CH_3$), 1249(-C-O-C ester), 1449 ($-CH_2$); 1H NMR (DMSO, 400 MHz) δ in ppm: 7.67(CH aromatic, 2H), 7.61 (CH aromatic, 2H), 7.40 (CH aromatic, 2H), 7.29 (CH aromatic, 2H), 7.27 (CH aromatic, 1H), 7.09 (CH aromatic, 2H), 6.80 (CH aromatic, 2H), 5.35 (OH aromatic, 1H), 4.91 (O-CH methane 1H),), 4.21 (O-CH_2 methene 2H), 3.32 (CH_2 methene, 2H), 1.29 (CH_3, 3H); MS(m/z): M^+ (390).

Ethyl2-(4-(oxiimopropyl-4'hydroxyphenyl) phenoxy) 3-phenyl propanoate

Colorless Oil, Yield: 44%, B.P.: 123ºC; IR (KBr, cm^{-1})υ: 3514 (-OH), 1729 (-C=O, ketone), 1591 (-C=C-, aromatic), 3130 (C-H); 1377 ($-CH_3$), 1249(-C-O-C ester), 1449 ($-CH_2$), 1681(C=N); 1H NMR (DMSO, 400 MHz) δ in ppm: 9.02 (N-OH, 1H), 7.68(CH

aromatic, 2H), 7.57 (CH aromatic, 1H), 7.40 (CH aromatic, 2H), 7.29 (CH aromatic, 2H), 7.27 (CH aromatic, 1H), 7.09,7.10 (CH aromatic, 2H), 7.07 (CH aromatic, 2H), 6.68 (CH aromatic, 1H), 5.35 (OH aromatic, 1H), 4.91 (O-CH methane 1H),), 4.21 (O-CH_2 methene 2H), 3.32 (CH_2 methene, 2H), 2.74(CH_2 methene, 2H),1.86(CH_2 2H) 1.29 (CH_3, 3H); MS(m/z): M^- (432).

Preparation of Ethyl 2-(4-(oximinopropyl-4'hydroxyphenyl) phenoxy) 3-phenyl propionic acid

White Solid, Yield: 87%, M.P.: 123ºC, R_f = 0.48 (Hexane:Ethylacetate, 90:10); IR (KBr, cm^{-1})υ: 3514 (-OH), 1729 (-C=O, ketone), 1591 (-C=C-, aromatic), 3130 (C-H); 1377 (-CH_3), 1249(-C-O-C ester), 1449 (-CH_2), 1681(C=N); 1H NMR (DMSO, 400 MHz) δ in ppm: 11.02 (COOH, 1H), 9.01 (N-OH, 1H), 7.68(CH aromatic, 2H), 7.57 (CH aromatic, 1H), 7.40 (CH aromatic, 2H), 7.29 (CH aromatic, 2H), 7.27 (CH aromatic, 1H), 7.09,7.10 (CH aromatic, 2H), 7.07 (CH aromatic, 2H), 6.68 (CH aromatic, 1H), 5.35 (OH aromatic, 1H), 3.16 (CH_2 methene, 2H), 2.74(CH_2 methene, 2H), 1.98(CH_2 2H), 1.86(CH_2 2H) 0.69 (CH_3, 3H); MS (m/z): M^+ (432), M+1 (433)

Compound P 2

4-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methoxy] benzyl alcohol

Physical and chromatographic characterization: Yield: 95%, M.P.: 129ºC, R_f = 0.48 ($CHCl_3$:MeOH, 70:30); IR (KBr, cm^{-1})υ: 3423 (O-H st), 1667 (C=N st), 1269 (C-O st), 1573 (C-C & C=C aromatic st), 3140 (C-H aromatic st), 1473 (CH_2band); 1H NMR (DMSO, 400 MHz) δ in ppm: 8.06(CH aromatic, 2H), 7.51 (CH aromatic, 2H), 7.41 (CH aromatic, 1H), 6.99 (CH aromatic, 2H), 6.92 (CH aromatic, 2H), 5.20 (O-CH_2 methene, 2H), 4.61 (C**H_2**-OH, 2H), 3.65 (OH, 1H), 2.48 (CH_3, 3H); MS(m/z): M^+ (295).

4-{[4-(chloromethyl)phenoxy]methyl}-5-methyl-5-phenyl-1,3-oxazole

Yield: 90%, M.P.: 103ºC, R_f = 0.48 (Hexane: Ethylacetate, 90:10); IR (KBr, cm^{-1})υ: 1667 (C=N st), 1269 (C-O st), 1573 (C-C & C=C aromatic st), 3140 (C-H aromatic st), 1473 (CH_2band), 1392 (CH_3 st), 636 (C-Br st); 1H NMR (DMSO, 400 MHz) δ in ppm: 8.10(CH aromatic, 2H), 7.51 (CH aromatic, 2H), 7.41 (CH aromatic, 1H), 7.32 (CH aromatic, 2H), 6.99 (CH aromatic, 2H), 5.20 (O-CH_2 methene, 2H), 4.64 (C**H_2**-Cl, 2H), 2.64 (CH_3, 3H); MS (m/z): M^+ (313).

2-(4-bromophenyl)-2-hydroxyimino butanoate

Yield: 27%, B.P.: 165ºC, R_f = 0.57 (Hexane: Ethylacetate, 90:10); IR (KBr, cm^{-1})υ: 3423 (OH st), 1667 (C=N st), 1573 (C-C & C=C aromatic st), 3140 (C-H aromatic st), 1473 (CH_2band), 1392 (CH_3 st), 1729 (COOH, st), 636 (C-Br st); 1H NMR (DMSO, 400 MHz) δ in ppm: 7.94 (CH aromatic, 2H), 7.18 (CH aromatic, 2H), , 2.02 (C**H_2**, 2H), 0.92 (CH_3, 3H); MS(m/z): M^+ (269).

P 2

Yield: 84%, M.P.: 173ºC, R_f = 0.65 (Hexane: Ethylacetate, 90:10); IR (KBr, cm^{-1})υ: 3423 (O-H st), 1667 (C=N st), 1269 (C-O st), 1573 (C-C & C=C aromatic st), 3140 (C-H aromatic st), 1473 (CH_2band); 1H NMR (DMSO, 400 MHz) δ in ppm: 8.06(CH aromatic, 2H), 7.51 (CH aromatic, 2H), 7.41 (CH aromatic, 1H), 6.99 (CH aromatic, 2H), 6.92 (CH aromatic, 2H), 5.20 (O-CH_2 methene, 2H), 4.61 (C**H_2**-OH, 2H), 3.65 (OH, 1H), 2.48 (CH_3, 3H); MS(m/z): M^+ (514), M+1 (515).

A very convenient approach for the synthesis of oximes following conversion of acids to esters is the Mitsunobu reaction[17]. Mitsunobu reaction is used to convert alcohols to esters using an acidic nucleophile. Ethyl ester of Phenyllactide was condensed with dihydroxy benzophenone under the Mitsunobu conditions leading to the formation of the ester intermediate. The ester intermediate was reacted with hydroxylamine hydrochloride in the presence of sodium acetate to give the corresponding ketoxime derivative. Alkaline hydrolysis of the hydroxylamine ester in presence of 1N NaOH and THF yielded the compound P 1. The formation of the product P1 following the hydrolysis of the oxime ester was evident from spectral characterization that exhibited distinct peaks for aromatic CH, benzylidimine CH, CH_2 alpha and beta to the oxiimino group, CH_3 and OH hydrogen in the 1H NMR. The presence of an odd M+ peak (m/z 419) and also the presence of M+1 peak revealed the incorporation of nitrogen in the product. The IR spectra displayed the peaks at 3620 (O-H st), 1785 (C=O st carboxyl), 1520 (C=N st), 1270 (C-O st), 1625 (C-C & C=C aromatic st), 3030 (C-H aromatic st), 915 (N-O st).

Molecular ion peaks and fragmentation pattern P1 obtained on the mass spectrum adequately corresponds with the structure of the compound.
The synthetic route adapted for the preparation of compound P2 involved the reduction of a parent aldehyde[18, 19] with sodium borohydride to give a benzyl alcohol. Treatment of the benzyl alcohol with thionyl chloride yielded benzyl chloride derivative. The benzyl chloride derivative was alkylated with the oxime to obtain aloxyiminobutanoate which was saponified with aqueous sodium hydroxide to get the desired compound P2.

The formation of the product P2 was confirmed from the spectral features obtained for the compound that revealed sharp and distinct peaks for aromatic CH, CH2 alpha and beta to the oxiimino group, OH hydrogen for the carboxylic acid group in the 1H NMR spectra. The presence of odd M+ peak (m/z 513.3) and the presence of M+1 and M+2 peaks were evident for nitrogen and oxygen in the compound. The IR spectra exhibited sharp and strong peaks for OH st, C=O st, C-O st, C=N st and C-H aromatic.

Conclusion

In the present study, we have optimized the physicochemical properties of non thiazolidinedione molecules capable of exhibiting PPARα and PPARγ dual agonistic action. The properties were optimized for effective binding of the molecules on the PPARγ receptor. The results obtained confirmed the hypothesis and on the basis of these results we may claim to have identified novel non thiazolidinedione compounds that could be further be explored to be potential leads for the development of new PPARγ drugs to be used in the treatment of type 2 diabetes.

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