



Research Article

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Rational Synthesis Design of a Potent Anti-Diabetic Therapeutic 'Pioglitazone' Using Retrosynthetic Analysis

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ABSTRACT

Within the realm of medicinal chemistry, synthesis plays a pivotal role in any drug research and development endeavor. The ability to design elegant and economical synthetic routes is often a major factor for making a drug a commercial winner. Retrosynthetic analysis/ Synthon disconnection approach, introduced and advanced by Prof. E. J. Corey of Harvard University has served as a powerful driving force on design elegant and economical synthetic routes to any useful molecule of scientific or industrial interest. Exploiting the advantages of this approach, we have proposed a good number of synthesis schemes for a potent anti-diabetic drug 'Pioglitazone' from the results of its retrosynthetic analysis. The proposed synthesis planning being a theoretical explorations, the actual laboratory execution requires a cross examination of so many factors such as reactions, reagents and order of events. The routes that utilize readily available starting materials, convergent, economical, safe and produce maximum yield in short reaction time are most feasible.

Keywords: Antidiabetic agent, drug synthesis, pioglitazone, retrosynthetic analysis, synthon disconnection approach.

INTRODUCTION

Chemical synthesis is one of the key technologies in modern drug discovery and development process. Development of novel synthetic routes for convergent and efficient synthesis of pharmaceuticals/drugs to make them suited for therapeutic use is very fundamental to synthetic organic/medicinal chemistry and gives material benefits to man kind. Before the execution, every synthesis is planned carefully with respect to sequence of steps from starting materials to final product. Although the sequence is quite logical but the details as to how the chemist first formulated the sequence of steps is not always published. A systematic approach in planning of synthesis is promulgated as a result of Prof.E.J.Corey's development of Retrosynthetic analysis/ Synthon disconnection approach in design organic synthesis. Retrosynthetic analysis is a problem solving technique in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures by the disconnection of strategy bonds and functional group transformations which leads to simple or commercially available starting materials [1-3].The retrosynthetic analysis of any target structure may lead to a number of possible synthetic routes. The routes which are convergent, utilise readily available starting materials, produce maximum yield in short reaction time, safe, eco-friendly are the most feasible.

Diabetes mellitus is one of the world's most prevalent, non-communicable, debilitating and progressive disease and becomes the 4th to 5th leading cause of death in developed countries [4].According to recently compiled data from Global Prevalence of Diabetes (GPD) and American Diabetes Association (ADA), diabetes currently affects more

then 285 million people world wide, a figure that is expected to rise to 435 millions by 2030 due to population growth, ageing, unhealthy diets, obesity and sedentary lifestyles.[5,6] Diabetes mellitus is a group of metabolic disease characterized by alternations in the metabolism of glucose(carbohydrate), fat and protein which are caused by a relative or absolute deficiency of insulin secretion or insulin resistance or both.[7-9].Type -2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin secretion and insulin resistance. It adversely affects the functioning of the kidneys, eyes, nervous and vascular systems. Therefore, once diagnosed, it is essential to control blood glucose levels during the early stages of the disease. The drugs/medicines used to treat diabetes mellitus are known as antidiabetic agents or oral hypoglycemic agents. The most attractive and direct approach to treat diabetes however will be administration of orally active hypoglycemic drugs. Members of the thiazolidinedione (TZD) drug class [10] are well known as anti-hyperglycemic drugs, used for the treatment of diabetes mellitus type-2 [11] 'Pioglitazone' (Fig 1), marketed as trademarks 'Actos' is one of the potent drugs in this class. It selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR- γ) in order to modulate the transcription of the insulin sensitive genes that are involved in glucose and lipid metabolism.[12,13]More recently, Pioglitazone and other active TZDs have been shown to bind to the outer mitochondrial membrane protein mitoNEET with affinity comparable to that of Pioglitazone for PPAR γ . [13,14] Pioglitazone has also been used to treat non-alcoholic steatohepatitis (fatty liver), but this use is presently considered experimental.[15] Pioglitazone has also been found to reduce the risk of conversion from prediabetes to diabetes mellitus type-2 by 72%. [16]

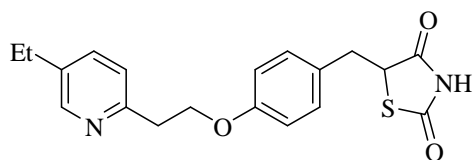


Figure: I

Despite the availability of few synthetic approaches to Pioglitazone in literature, some alternative synthetic routes are still required for its commercial success. Keeping an overview on the published works both in journals [17-19] and patent literatures [20-21] herein, we wish to focus our research attentiveness by proposing a good number of synthesis schemes for a potent anti-diabetic drug Pioglitazone based on retrosynthetic analysis/ synthon disconnection approach. To our current knowledge, this type of work has not been reported elsewhere. The choice of this molecule for synthesis planning is obvious as Pioglitazone is one of the most commonly prescribed medications as anti-diabetic agent. Again the pharmaceutical industries are unquestionably vibrant today in search of alternative, cost-effective, scale-up synthesis for potent anti-diabetic drugs for their commercial success.

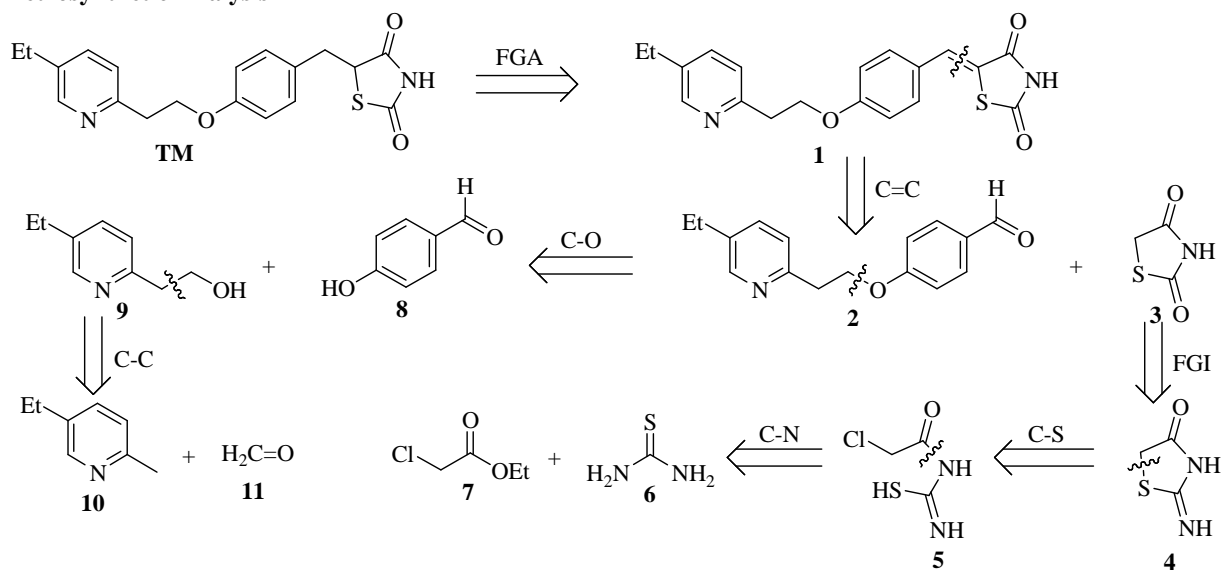
EXPERIMENTAL SECTION

The structure and information about Pioglitazone as drug candid has been collected from different books [22-24]. The proposed synthesis planning are then exploited in a novel way from the result of the retrosynthetic analysis of the drug structure using the basic principle outlined in the pioneering works of Prof. E.J. Corey [25]. The symbols and abbreviations are synonymous to that represented in different books [25-30]. The analysis-synthesis schemes being theoretical propositions; obviously the syntheses have not been executed in the laboratory. The actual laboratory execution requires the cross examination of a considerable number of factors such as reagents, reactions, order of events, economical viability, environmental benign, saftyness, short time and scalable synthesis.

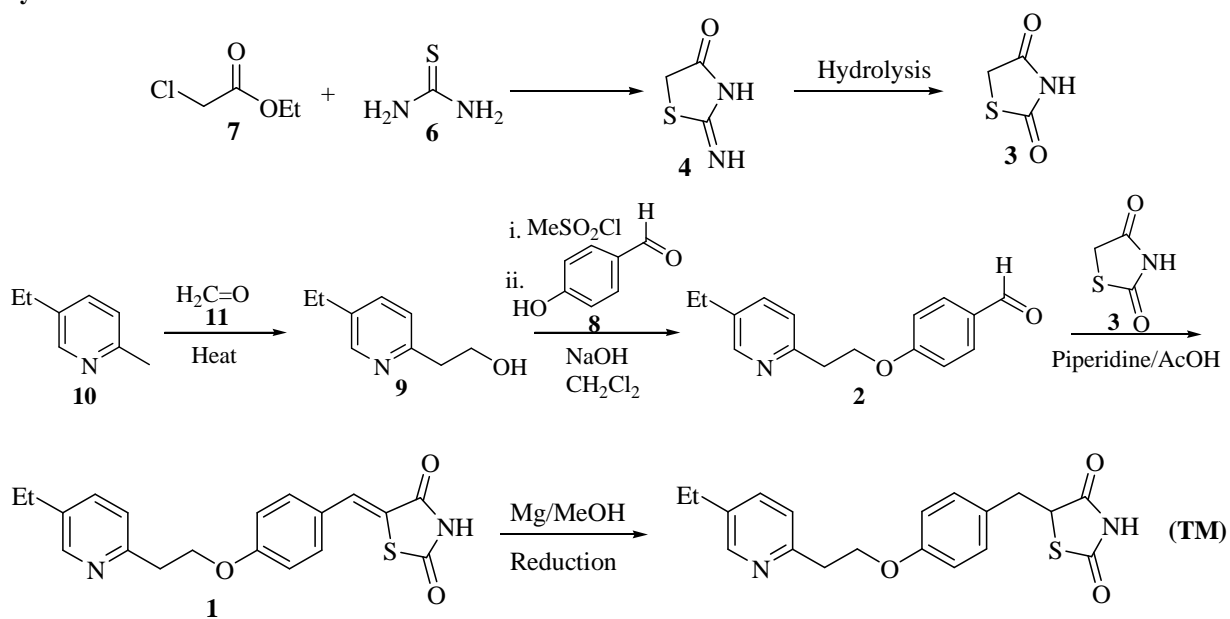
RESULTS AND DISCUSSION

Condensation of ethyl chloroacetate **7** with thiourea **6** produces an intermediate 2-iminothiazolidone **4** which on hydrolysis gives 2,4-thiazolidinedione **3** (Hantzsch method). Reaction of 5-ethyl-2-methyl pyridine **10** with formaldehyde **11** at high temperature gives 2-(5-ethyl-2-pyridyl)ethanol **9**. Alcohol **9** through its methane sulfonate derivative then condenses with 4-hydroxybenzaldehyde **8** in basic medium and affords 4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzaldehyde **2**. Reacting 4-[2-(5-ethyl-pyridin-2-yl)-ethoxy]-benzaldehyde **2** with 2, 4-thiazolidinedione **3** provides 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzilidene]-2,4-thiazolidinedione **1**. Reduction of **1** with Mg/MeOH forms the target molecule (T M) (Scheme-1).

Retrosynthetic Analysis-1

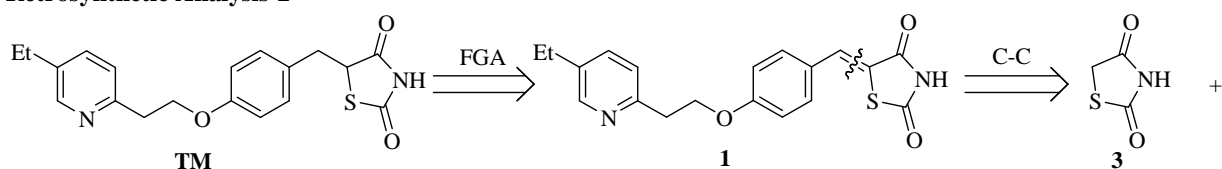


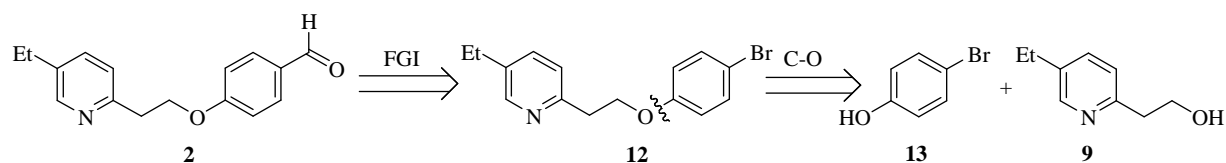
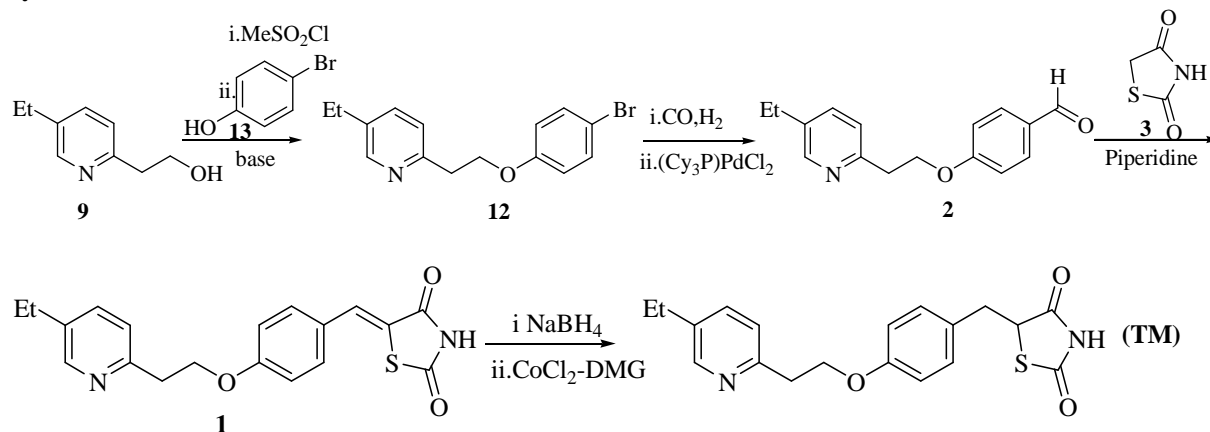
Synthesis-1



Scheme: 1

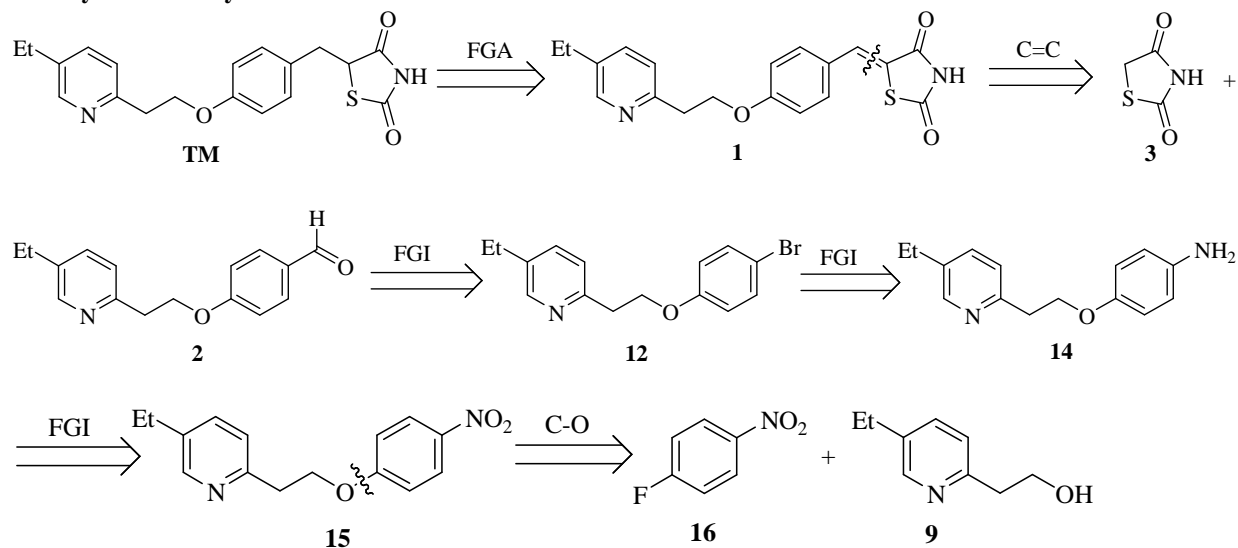
Retrosynthetic Analysis-2



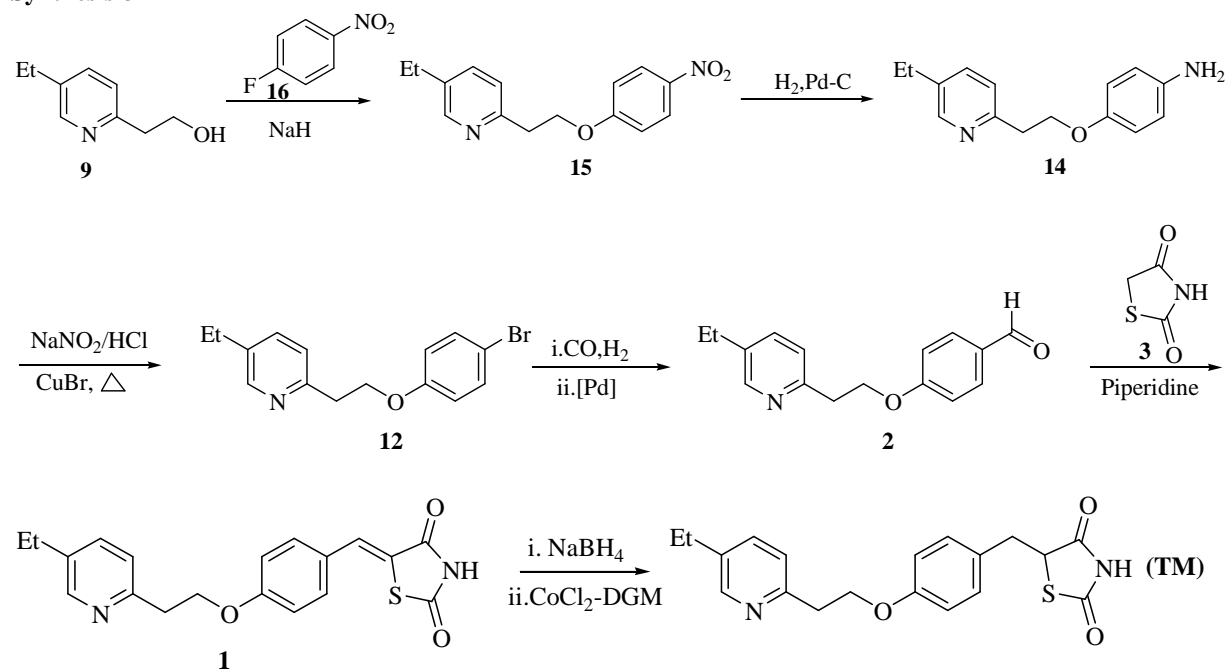
**Synthesis-2**

Scheme: 2

Williamson's ether synthesis between methane sulfonate derivative of 2-(5-ethylpyridine-2-yl) ethanol **9** and 4-bromophenol **13** in presence of a base produces 1-bromo-4-(2-(5-ethylpyridine-2-yl) ethoxy)benzene **12**. Transition metal catalyzed hydroformylation of **12** produces 4-[2-(5-ethylpyridine-2-yl) ethoxy] benzaldehyde **2**. Knoevenagel condensation of aldehyde **2** and thiazolidine 2,4-dione **3** produced as in scheme-1, affords **1**. Reduction of the double bond of the condensed product **1** using sodium borohydride, cobalt(II) chloride-DMG affords the target molecule (**TM**) (Scheme-2).

Retrosynthetic analysis-3

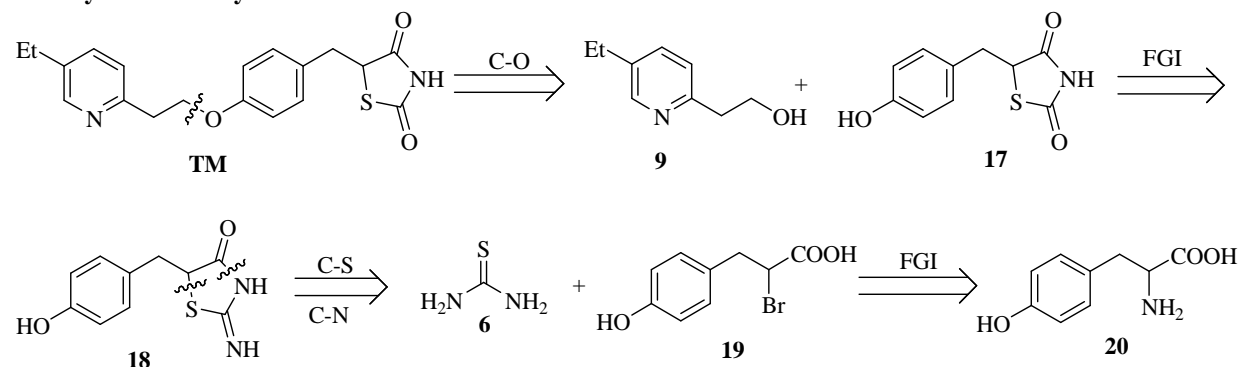
Synthesis-3



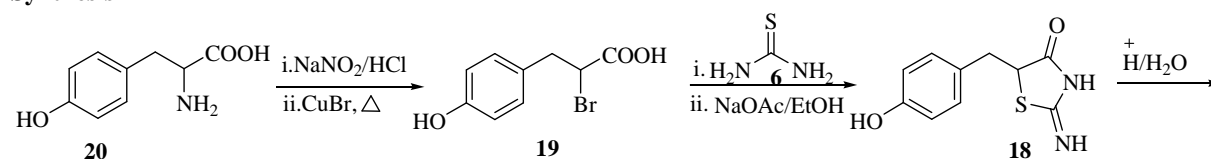
Scheme: 3

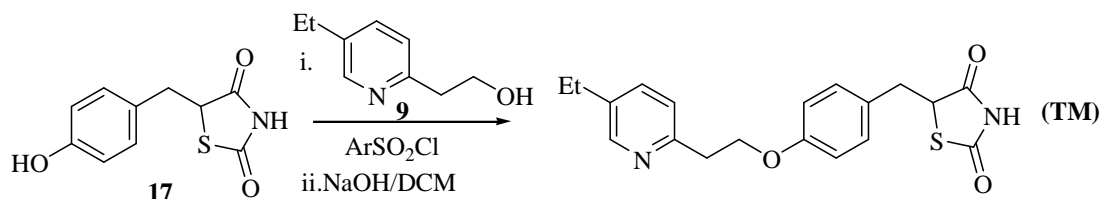
Nucleophilic aromatic substitution reaction between 2-(5-ethylpyridine-2-yl)ethanol **9** and 4-fluoronitrobenzene **16** using NaH as base provides 1-nitro-4-[2-(5-ethylpyridine-2-yl)ethoxy]benzene **15**. Reduction of nitro group of **15** with $\text{H}_2/\text{Pd-C}$ affords corresponding amine **14**. The amine through its diazonium salt forms corresponding bromo product 1-bromo-4-[2-(5-ethylpyridine-2-yl)ethoxy]benzene **12** via Sandmeyer reaction. The bromo compound then undergoes transition metal catalysed hydroformylation reaction to afford aldehyde **2**. Condensation of aldehyde **2** with thiazolidine-2,4-dione **3** prepared as in scheme-1, in basic medium affords 5-[4-[2-(5-ethylpyridine-2-yl)ethoxy]benzylidene]thiazolidine-2,4-dione **1**. Hydrogenation of dione with sodium borohydride in presence of a cobalt ion and dimethyl glyoxime affords the target molecule (**TM**) (Scheme-3).

Retrosynthetic Analysis-4



Synthesis-4

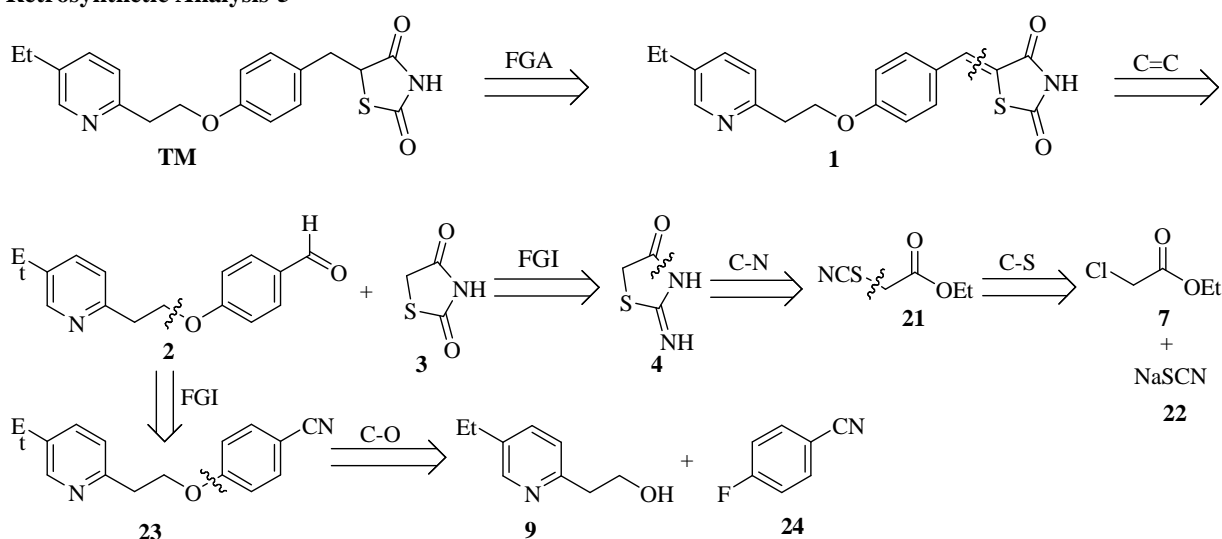




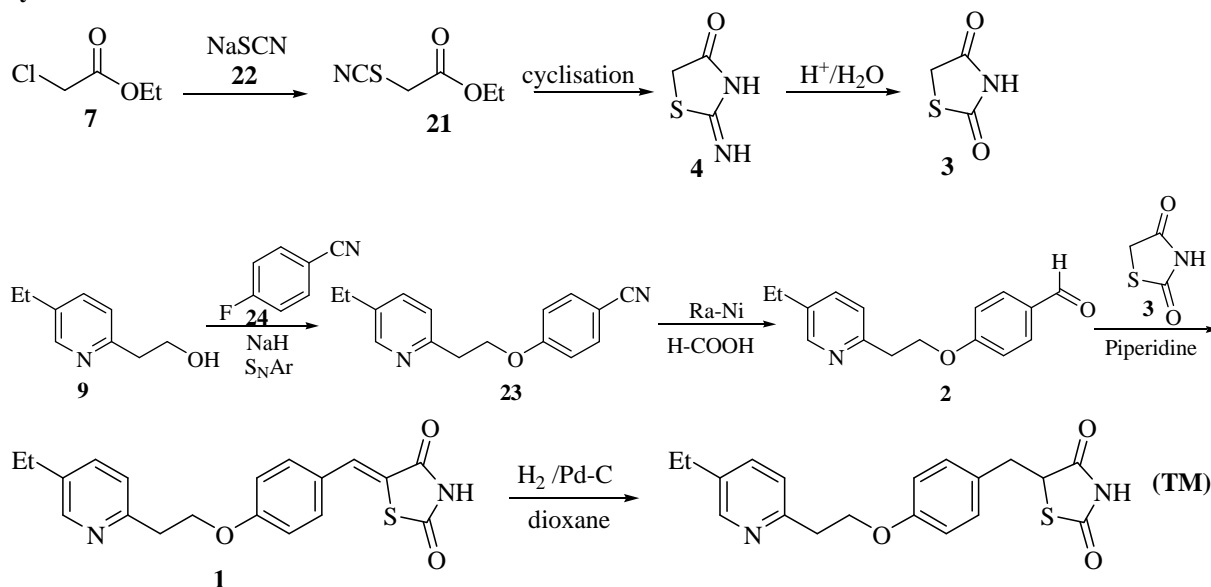
Scheme: 4

Sandmeyer's reaction of tyrosine **20** through its diazonium salt forms the bromide derivative **19**. Reflux of the bromide **19** with thiourea **6** and sod. acetate in ethanol produces 5-(4-hydroxybenzyl)-2-iminothiazolidine-4-one **18**. The imine on hydrolysis forms 5-(4-hydroxybenzyl)thiazolidine-2,4-dione **17**. The thiazolidine dione then undergoes nucleophilic substitution with *p*-toluene sulfonate intermediate formed in situ from 2-(5-ethyl-2-pyridyl)ethanol **9** and aryl sulfonyl chloride in presence of NaOH/DCM provides the target molecule (TM) (Scheme-4).

Retrosynthetic Analysis-5



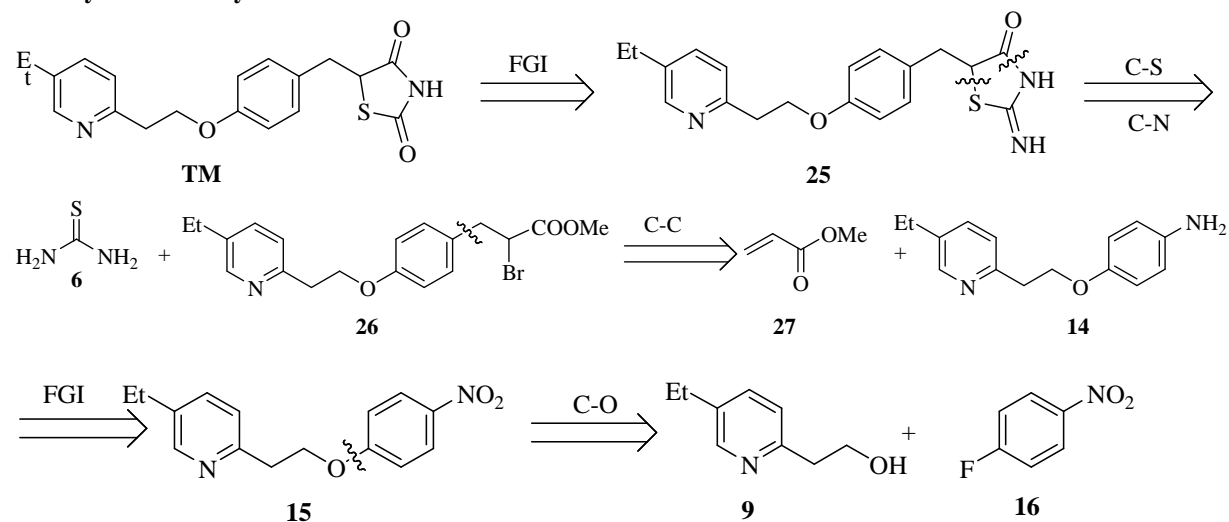
Synthesis-5



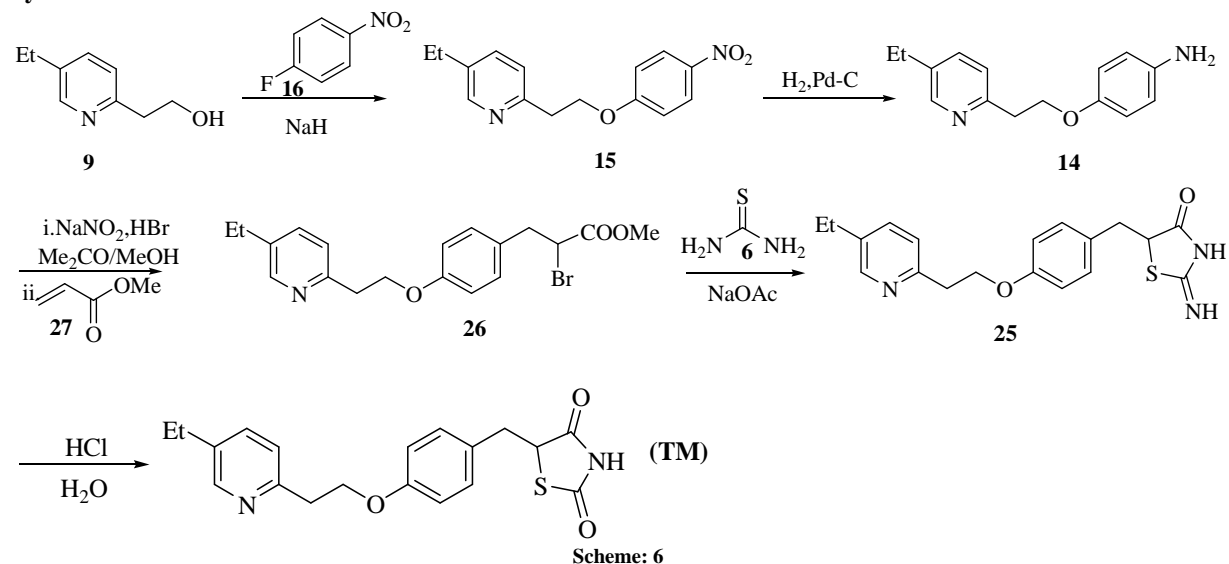
Scheme: 5

Condensation of ethyl chloroacetate **7** with sodium thiocyanate **22** forms an intermediate **21** which on cyclisation and subsequent acid hydrolysis produces 2, 4-thiazolidinedione **3** (Techerniac process). Nucleophilic aromatic substitution reaction between 2-(5-ethylpyridine-2-yl) ethanol **9** and 4-fluorobenzonitrile **24** using NaH as base provides 4-[2-(5-ethylpyridine-2-yl)ethoxy] benzonitrile **23**. Reduction of **23** with Raney-nickel and formic acid affords aldehyde 4-[2-(5-ethylpyridine-2-yl) ethoxy] benzaldehyde **2**. Knoevenagel condensation of aldehyde **2** with thiazolidine-2, 4-dione **3** in basic medium affords 5-[4-[2-(5-ethylpyridine-2-yl)ethoxy] benzylidene] thiazolidine-2,4-dione **1**. Catalytic hydrogenation of dione **1** provides target molecule(TM)(Scheme-5).

Retrosynthetic Analysis-6

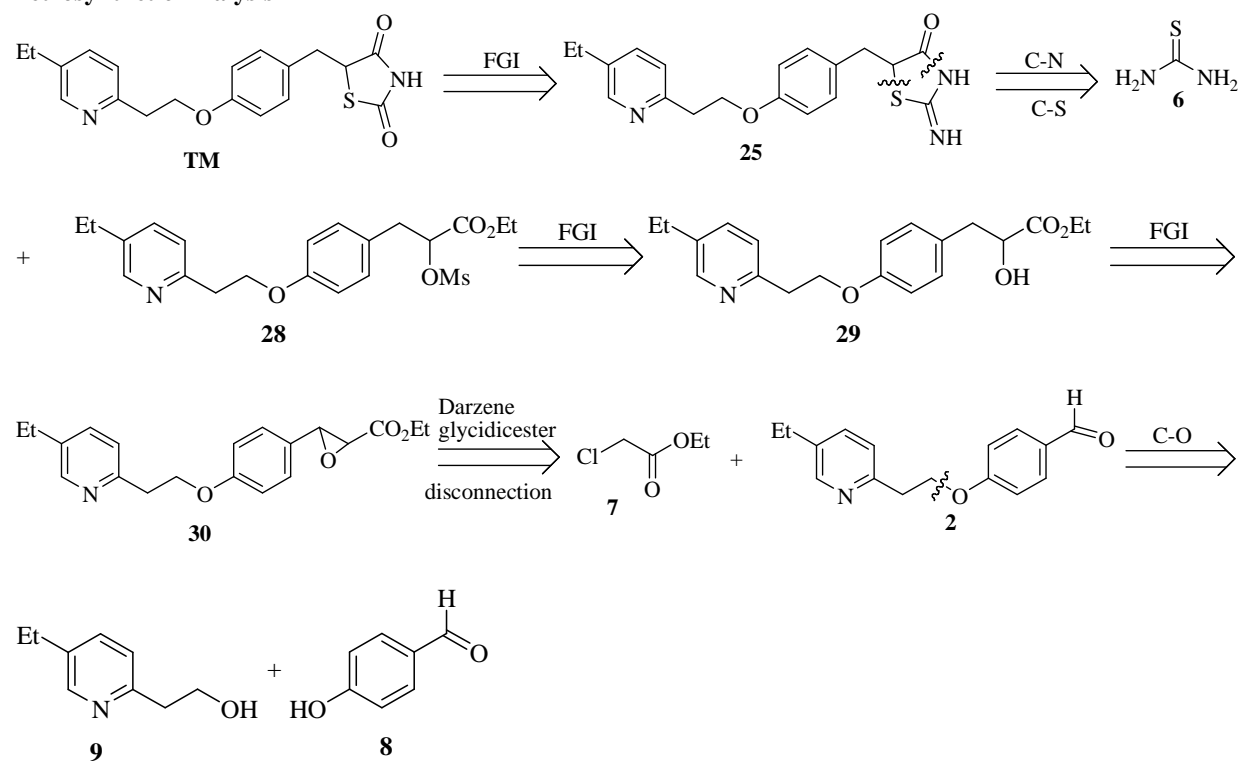


Synthesis-6

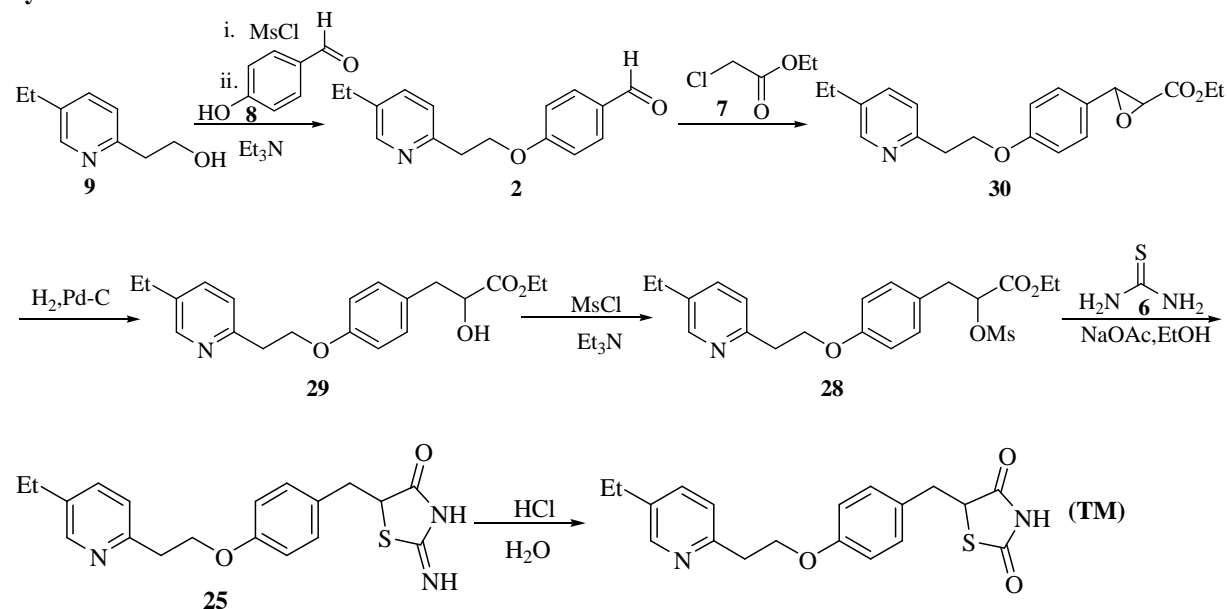


The condensation of 2-(5-ethyl-2-pyridyl) ethanol **9** with 4-fluoronitrobenzene **16** in presence of NaH / DMF gives 4-[2-(5-ethyl-2-pyridyl)ethoxy]nitrobenzene **15**. Reduction of **15** with H₂ over Pd/C in methanol yields the corresponding aniline **14**. The reaction of **14** with NaNO₂/HBr and then with methyl acrylate **27** in acetone/methanol affords the 2-bromopropionate derivative **26**. Cyclization of **26** with thiourea **6** by means of NaOAc in refluxing ethanol provides the 2-imino-4-thiazolidinone **25**. Acid hydrolysis of **25** produces the target molecule (TM) (Scheme-6).

Retrosynthetic Analysis-7



Synthesis-7

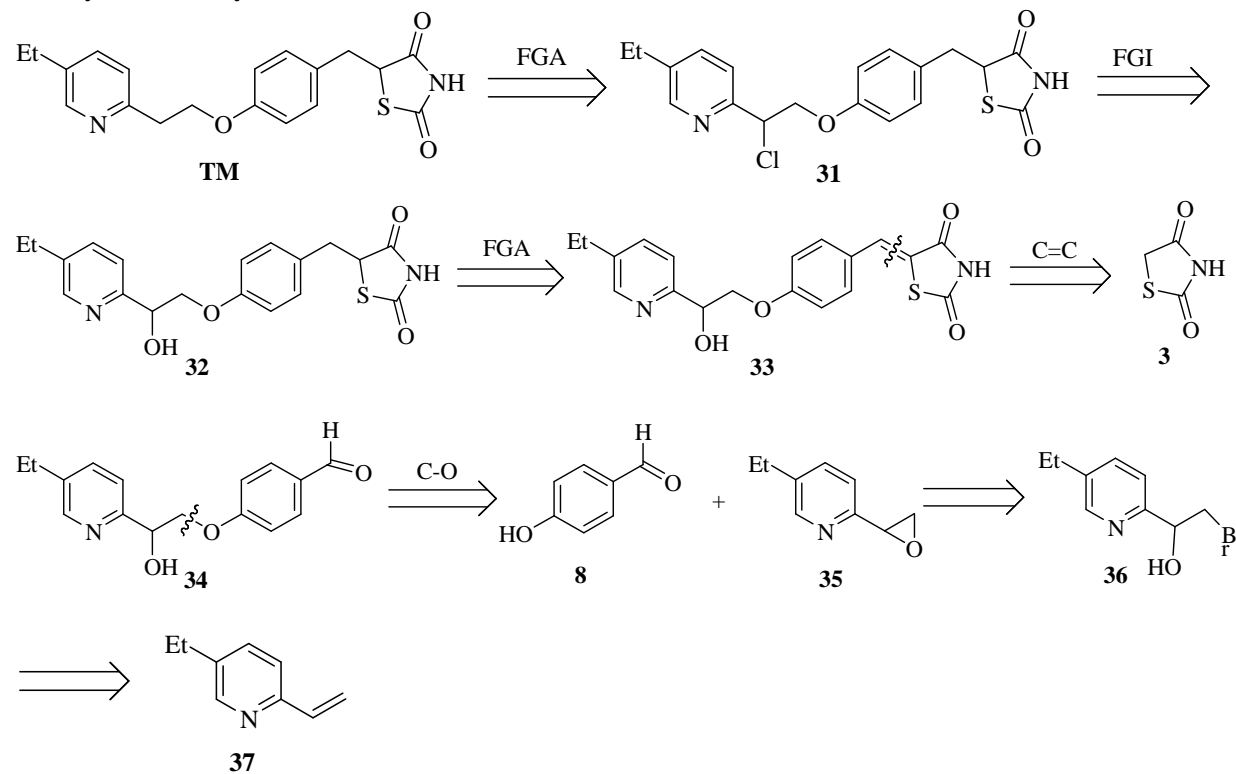


Scheme-7

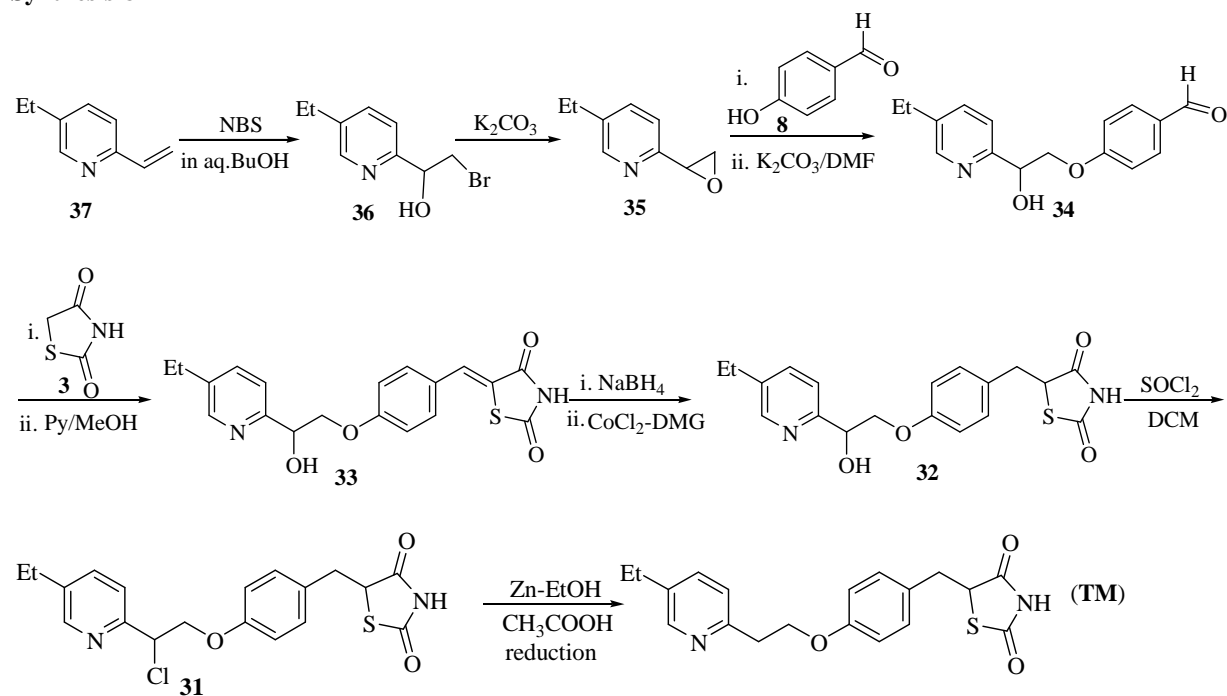
Williamson's ether synthesis between methanesulfonate derivative of 2-(5-ethylpyridine-2-yl) ethanol **9** and 4-hydroxybenzaldehyde **8** in presence of a base produces 4-[2-(5-ethylpyridine-2-yl)ethoxy] benzaldehyde **2**. Darzensen glycidic ester condensation of aldehyde **2** with ethyl chloroacetate **7** and NaOEt/EtOH at room temperature yields cis-trans glycidic ester **30**. Hydrogenolysis of the mixture using H_2 in Pd-C/MeOH **28** and subsequent methylsulfonylation of the resulting alcohol **29** affords α -methanesulfonyloxy ester **28**. Reaction of ester with

thiourea **6** and NaOEt (Hantzsch's synthesis) generates 2-imino-4-thiazolidinone **25**, which on hydrolysis with dil.HCl forms target molecule(**TM**) (Scheme-7).

Retrosynthetic Analysis-8



Synthesis-8



Scheme-8

Reaction of 5-Ethyl-2-vinyl pyridine **37** with NBS in aq.*t*-BuOH affords bromohydrine **36**. The bromohydrine on reaction with K₂CO₃ forms the oxirane **35**. The oxirane then involves in displacement reaction with the pot. salt of 4-hydroxy benzaldehyde **8** in a Williamson ether synthesis process to afford 4-[2-(5-ethylpyridin-2-yl)2-hydroxyethoxy] benzaldehyde **34**. Knoevenagel condensation of aldehyde **34** with thiazolidine-2,4-dione **3** using pyrrolidine/ethanol produces 5-(4-(2-(5-ethylpyridine-2-yl)-2-hydroxyethoxy benzylidene) thiazolidine-2,4-dione **33**. Reduction of double bond of thiazolidinone **35** using NaBH₄/CoCl₂-DMG affords **32**. Treatment of **32** with SOCl₂/DMF affords corresponding chloride **31**. Reduction of **31** with Zn in MeOH-AOH affords target molecule (**TM**) (Scheme-8).

CONCLUSION

Retrosynthetic analysis is one of the most critical tools within the 'toolbox' needed to solve synthesis problems. The goal of retrosynthetic analysis is the structural simplification. It not only requires logical approach for disconnecting a complex target molecule but also a through knowledge of an enormous set of organic reactions to imagine the experimental conditions necessary to produce a desired product from simple or readily available starting materials. It is a paper exercise; a full exploration of this type will provide many routes for synthesizing the target molecule. As a consequence of this approach, we have proposed a good number of synthesis schemes for a potent anti-diabetic drug 'Pioglitazone'. Scalable synthetic routes for newly discovered natural products, pharmaceuticals and useful compounds not available in adequate quantities from natural resources can be best provide by this approach. Strategic application of this approach can also afford different routes to synthesize the target molecule that has never been synthesized earlier. With the advancement of novel methods and transformations developed within the academic community, the synthesis of best selling pharmaceuticals can be rethinking through this approach in the later stages of drug research and process development.

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