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Research Report

Synthesis Design of an Anti-Obesity Agent 'Sibutramine': A Reatrosynthetic Approach

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ABSTRACT

Organic synthesis plays the central role in the process of drug design and development. Retrosynthetic analysis represents a very powerful tool for designing convergent and economical synthetic routes of targeted drugs. In this paper, we report some synthetic protocols for a potent anti-obesity agent 'Sibutramine' in a novel way basing on retrosynthetic analysis. The proposed synthesis schemes being a theoretical exploration, the actual laboratory implementation requires the cross examination of a considerable number of factors such as reactions, reagents and order of events. Generally, the route which is cost-effective, safe, employ readily available starting materials and produce maximum yield in a short reaction time under robust condition is most viable.

1. Introduction

Organic synthesis occupies a central role in any drug development endeavor. The development of new synthetic methodology for the convergent and efficient synthesis of drugs/ pharmaceuticals so as to make them suitable for therapeutic use is very fundamental to organic synthesis and most responsible for yielding material benefits to mankind. A systematic approach in designing synthetic routes for a molecule of any interest is promulgated as a result of Prof. E.J. Corey's developments of retrosynthetic analysis/synthon disconnection approach. "Retrosynthetic analysis is a problem solving technique for transforming the structure of synthetic target molecule (TM) to a sequence of progressively simpler structures by disconnection of bonds and functional group interchange along the pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis"**[1-3]**. Retrosynthetic analysis of a target molecule usually results in more than one possible synthetic routes. In actual practice, generally that route is selected which is short, efficient, safe, reproducible, scalable, ecological and economically viable, while assessing alternative synthetic routes to a molecule.

Obesity is an epidemic in today's society. Society has become obesogenic due to lifestyle and behavior of the community. The comorbidity associated with obesity includes cardiovascular, arteriosclerosis, cancers and several metabolic disorders and an increased risk of physical and cognitive disabilities. Anti-obesity medication or weight loss drugs are all pharmacological agents that reduce or control weight. These drugs alter one of the fundamental processes of the human body, weight regulation, by altering either appetite, or absorption of calories**[4]**. 'Sibutramine' (Fig-I) is an orally administered appetite suppression drug approved by FDA for the longterm use in the management of obesity. The drug works to suppress appetite via serotonin (and nor epinephrine) re-uptake inhibition in the central nervous system and in the peripheral nervous system**[5,6]**.

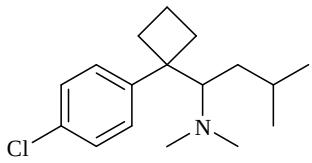

Figure: I

A few synthetic approach to Sibutramine although appears in literature, some alternative synthetic routs are still required for its commercial success. Keeping an overview on the published works both in journals**[7-10]** and patent literatures**[11-12]**, we focus our research findings through proposition of a number of synthesis schemes for a potent anti obesity drug 'Sibutramine' based on retrosynthetic analysis/ synthon disconnection approach. To our current knowledge, this type of work is literature unprecedented.

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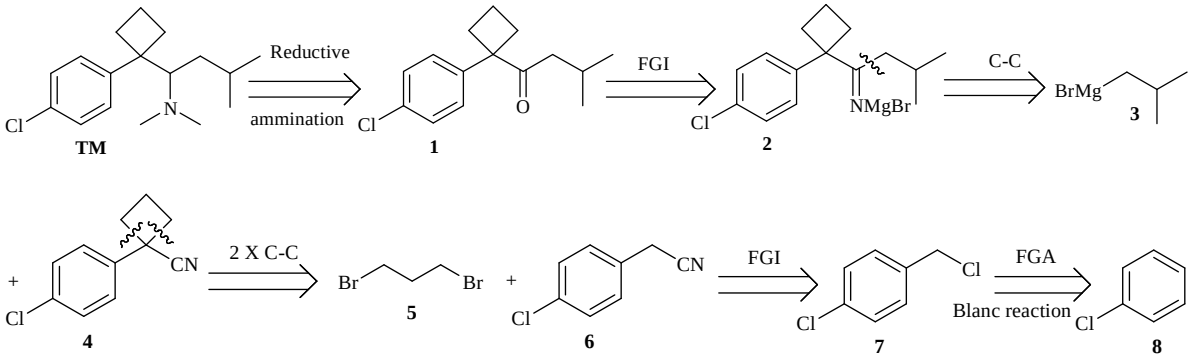
The choice of this molecule for synthesis planning is obvious as Sibutramine is the most commonly prescribed medication as anti-obesity and very little research has proceeded into the *synthesis of Sibutramine*.

2. Materials and methods

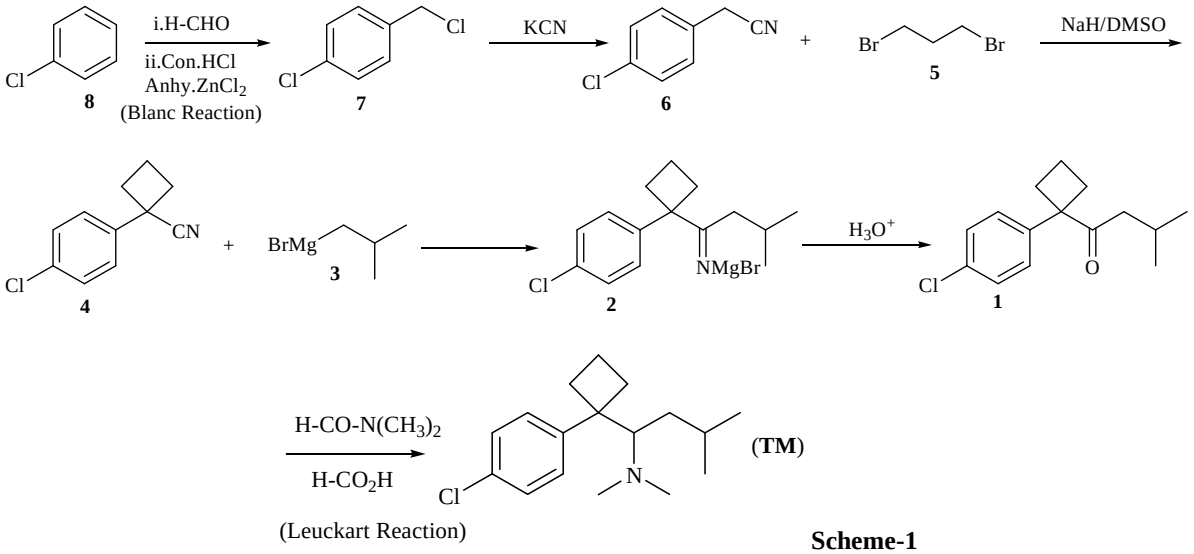
The structure and information about Sibutramine as drug candid has been collected from different books[13-16]. The proposed synthesis planning are then exploited in a novel way from the result of the retrosynthetic analysis of the drug structure using the basic principle outlined in the pioneering works of Prof. E.J. Corey. The symbols and abbreviations are synonymous to that represented in books[17-19]. The analysis–synthesis schemes being theoretical propositions; obviously the syntheses have not been executed in the laboratory. Most of the synthesis schemes have been derived from their actual synthesis as found from different literatures. 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.

3. Result and discussion

Retrosynthetic Analysis-1



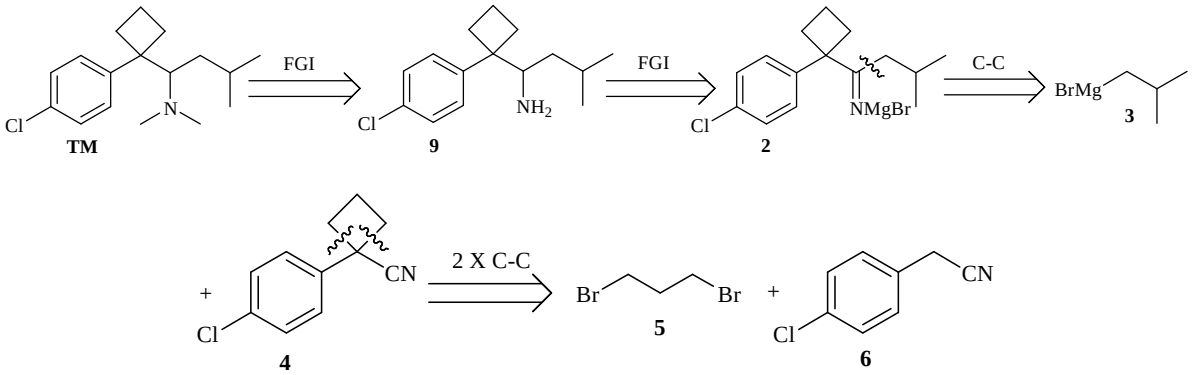
Synthesis-1



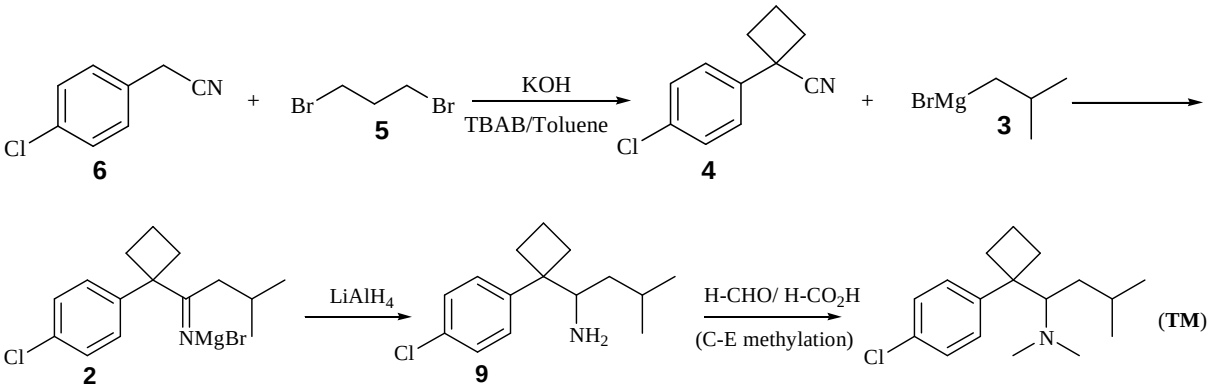
Scheme-1

Blanc reaction of chlorobenzene (8) with formaldehyde produces 1-chloro (4-chloromethyl) benzene (7) Treatment of (7) with KCN generates 4-chlorophenyl acetonitrile (6). Cycloalkylation of nitrile with 1, 3-dibromopropane (5) in presence of excess of NaH forms l-(4-chlorophenyl) cyclobutyl carbonitrile (4). Grignard reaction of (4) with isobutyl magnesium bromide (3) forms magnesium complex (2) as an intermediate. Acid hydrolysis of the intermediate affords ketone (1). Reductive amination of ketone (1) with dimethyl formamide (Leuckart reaction) gives Sibutramine (TM). (Scheme-1)

Retrosunthetic Analysis-2



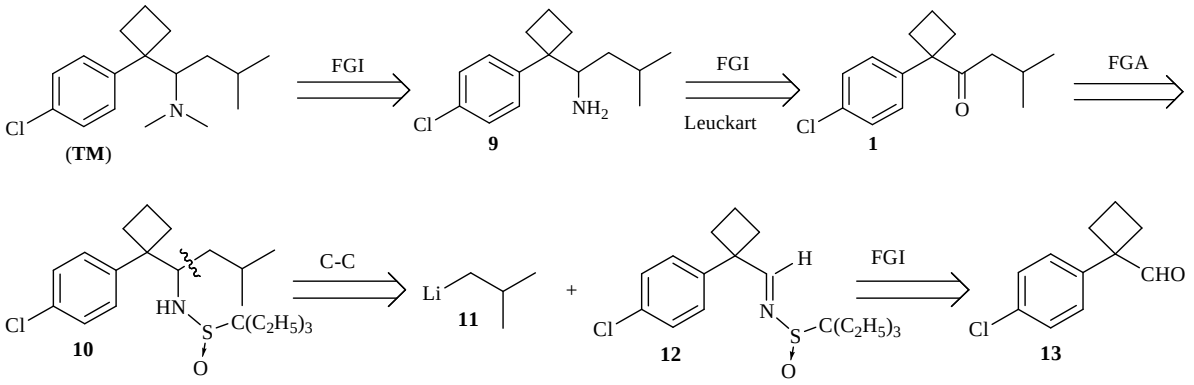
Synthesis-2

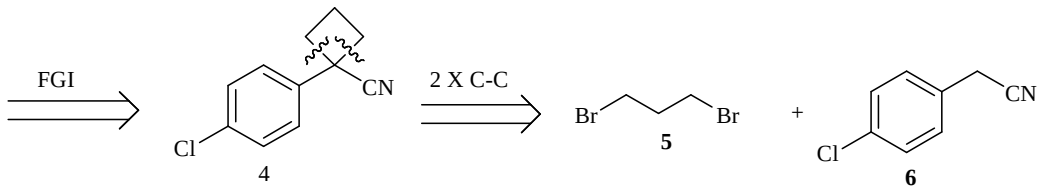


Scheme-2

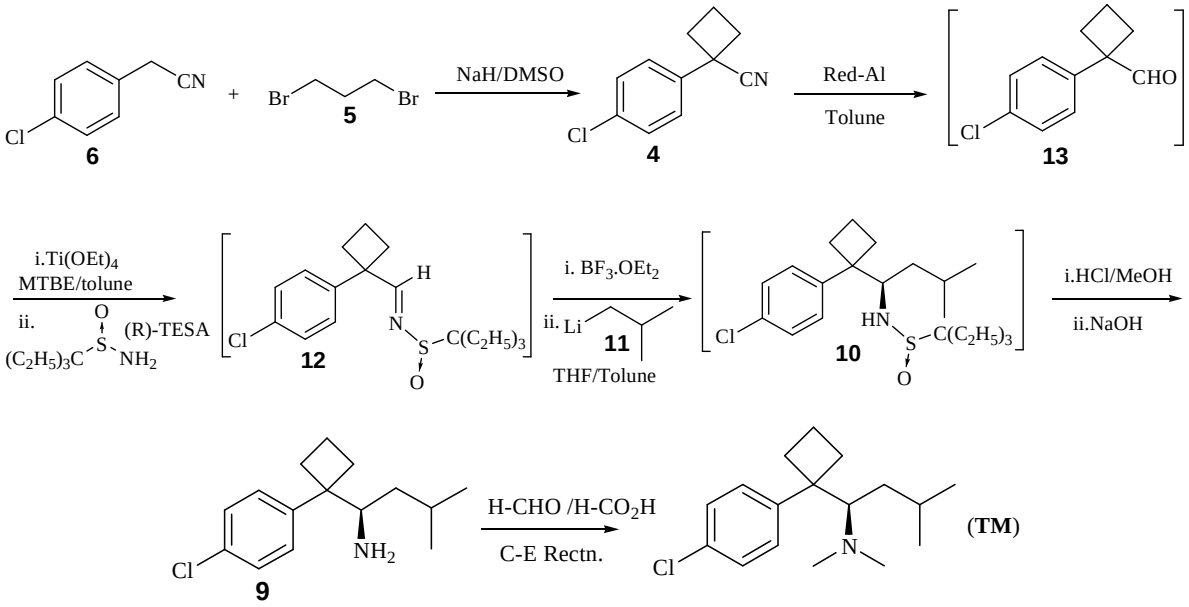
Internal bis-alkylation of 4-chlorophenylacetonitrile (6) with 1, 3 -dibromopropane (5) forms the cyclobutane derivative (4).Reaction of the nitrile group with Grignard's reagent (3) prepared from isobutyl bromide forms the imine intermediate (2), which upon reduction with LAH affords the primary amine (9).Bis-N-methylation of the amine (9) with formaldehyde and formic acid (Clark-Eshweiler reaction) forms Sibutramine (TM). Scheme-2

Retrosunthetic Analysis-3





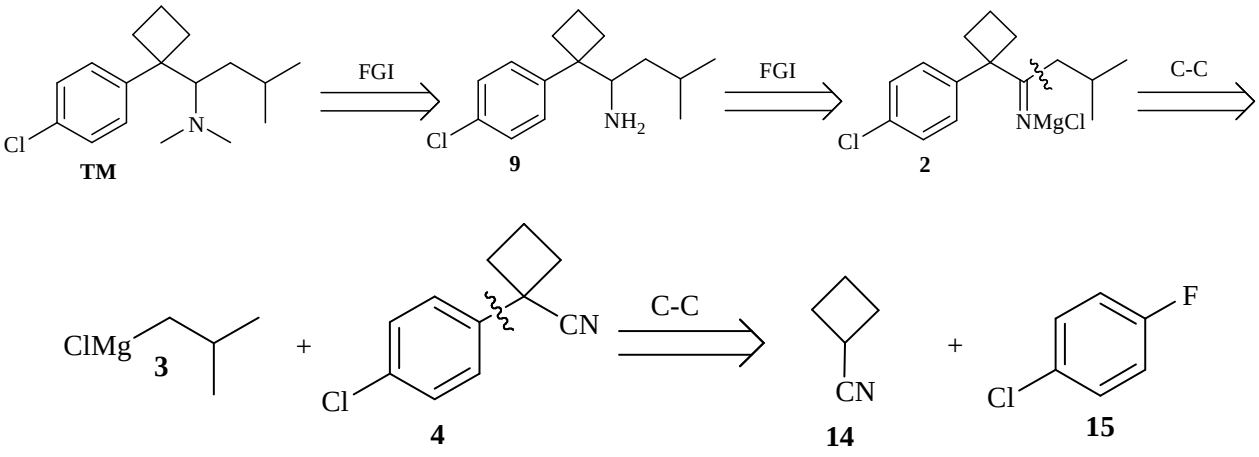
Synthesis-3 (Asymmetric Synthesis)



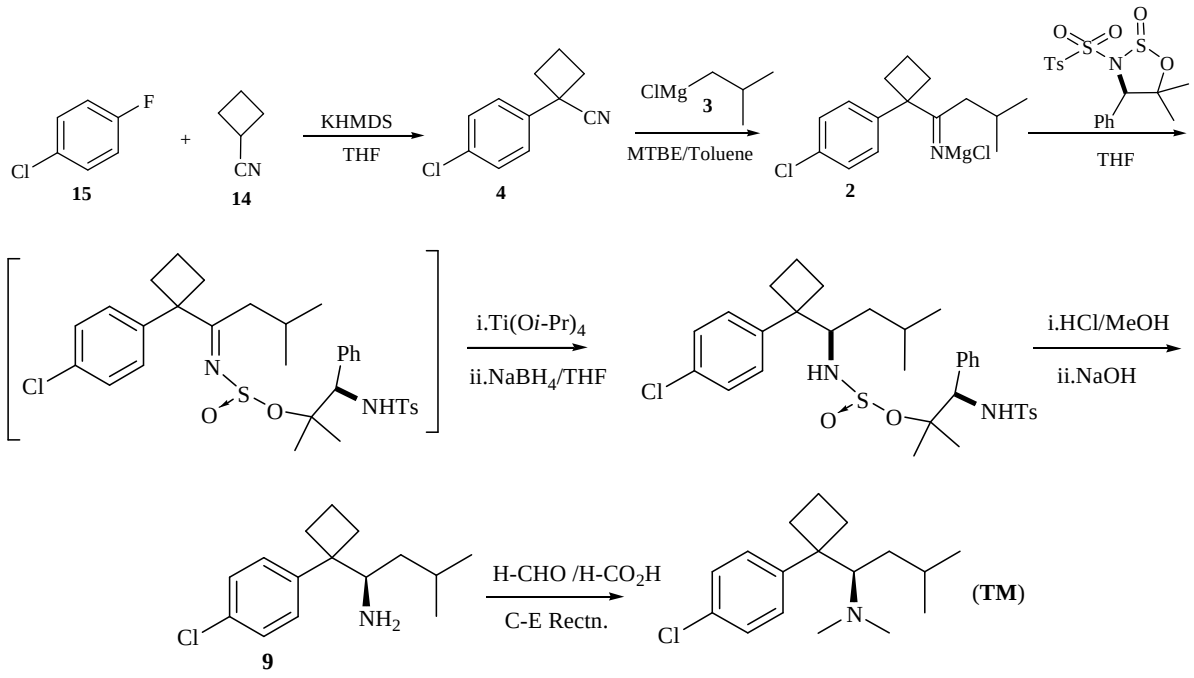
Scheme-3

Internal bis-alkylation of 4-chlorophenylacetonitrile (6) with 1, 4-dibromopropane (5) forms the nitrile (4). Treatment of nitrile with Red-Al in toluene forms the aldehyde (13) which condenses with (R)-(triethyl) methyl sulfonamide (R-TESA) gives the sulfinyl imine (12). Diastereoselective addition of iso-BuLi (11) in presence of $BF_3.OEt_2$ followed by cleavage of the chiral auxiliary with acid and base forms the chiral amine (9). Bis-N-methylation of the amine (9) with formaldehyde and formic acid (Clark-Eshweiler reaction) forms Sibutramine (TM). (Scheme-3)

Retrosynthetic Analysis-4 (Assymetric Synthesis)



Synthesis-4



Scheme-4

Reaction of 1-chloro-4-fluorobenzene (15) with carbonitrile (14) in presence of non-nucleophilic base KHMDS /THF forms the nitrile (4). Addition of *i*-butylmagnesium chloride (3) to this nitrile forms the intermediate (2).Treatment of this intermediate with chiral auxillary, osathiazolidine oxide forms the sulfinyl ketimine which upon diastereoselective reduction with Ti (O*i*-Pr)$_4$ affords the chiral amine as another intermediate. Treatment of this chiral amine with acid and base removes the chiral auxiliary and forms amine (9). Bis-*N*-methylation of the amine (9) with formaldehyde and formic acid (Clark-Eshweiler reaction) forms Sibutramine (TM). (Scheme-4)

MTBE (Methyl tert-butyl ether), KHMDS (Potassium hexamethyldisilazide)

4. Conclusion

Retrosynthetic analysis/ Synthon disconnection approach is a technique for solving problems in the planning of organic synthesis. This approach is expected to provide new and innovative synthetic strategies in a logical manner for design, execution and development of new synthesis or improvement in existing process. It is a paper exercise; a full analysis 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 analysis-synthesis schemes for a potent anti-obesity agent 'Sibutramine". Scalable synthetic routes for extremely scare natural products, pharmaceuticals and useful compounds not available in adequate quantities from natural resources can be best provide by this approach. Through retrosynthetic analysis and with the application of new synthetic reactions and reagents developed within the academic community, it is now time to rethink the synthesis of pharmaceutical drugs for the improvement of the existing process for their commercial success.

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