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SYNTHESIS PLANNING OF POTENT ANTIMIGRAINE DRUG 'SUMATRIPTAN' USING RETROSYNTHETIC ANALYSIS

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ABSTRACT

Chemical synthesis is an essential part of drug development. Retrosynthetic analysis/Synthon disconnection approach has emerged as powerful tool in the synthesis design of targeted drugs for their convergent and economical synthesis. In this perspective, we endeavor to profile some synthesis schemes for a potent antimigraine drug 'Sumatriptan' in a novel way basing on retrosynthetic analysis. The proposed synthesis schemes being a theoretical exploration, the actual laboratory execution requires the cross examination of a considerable number of factors such as reactions, reagents and order of events. In actual practice, generally that route is most feasible which satisfies the specific criterion for an ideal synthesis.

KEYWORDS

Antimigraine drug, Drug synthesis, Retrosynthetic analysis, Selective serotonin receptor agonists, Sumatriptan and Synthon disconnection approach.

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INTRODUCTION

Synthesis is a part and parcel of medicinal chemistry-without it the development of a drug cannot progress from design to implementation and ultimately to a cure. The development of simple synthesis route to widely used organo-chemical drugs from readily available materials is one of the main objectives of modern synthetic organic/medicinal chemistry. In this context, retrosynthetc analysis/synthon disconnection approach developed systematically by Nobel Laureate Prof. E.J.Corey of Harvard University has

appeared as powerful tool in the hand of synthetic organic/medicinal chemists in the planning of their synthesis. "Retrosynthetic analysis is the logical process of analyzing the structure of a target molecule to transform the target to a sequence of progressively simpler structures along a pathway which finally will lead to simple or commercially available starting materials"[1-3]. Analysis of a target molecule in retrosynthetic direction usually results a large number of possible synthetic routes. In actual practice, generally that route is selected which is convergent, economical, use readily available starting materials and eco-friendly under robust conditions, while assessing alternative synthetic routes to a molecule.

Migraine headache is a chronic neurological disorder characterized by intense, throbbing pain in one area of the head and is commonly accompanied by nausea, vomiting, and extreme sensitivity to light and sound. It is very common in general population and affect 18% of women and 6% of men with approximately 35% attacks per year. Triptan classes of drugs are believed to be effective migraine relievers by binding to serotonin receptors in the brain, where they act to induce vasoconstriction of extra cerebral blood vessels and also reduce neurogenic inflammation[4]. Sumatriptan is novel triptan classes of selective serotonin ($5\text{-}HT_{1d}$) receptor agonist, which is highly effective in the acute treatment of migraine attacks, blocks dural neurogenic plasma extravasations and constricts cranial blood vessels in animal experiments[5]. Structurally, it is an analog of the naturally occurring neuroactive alkaloid dimethyltryptamine (DMT), bufotenine, and 5-methoxy-dimethyltryptamine, with an N-methyl sulfonamidomethyl- group at position C-5 on the indole ring (Figure No.1).

Although a few methods of synthesis of 'Sumatriptan' are well documented in literature, some alternative synthetic routs are still required for its commercial success. Keeping an overview on the published works both in journals and patent literatures[6-12] an effort has been made to propose a good number of synthesis schemes for 'Sumatriptan' based on retrosynthetic analysis/ synthon disconnection approach. To the best of our knowledge, this type of work has not been reported earlier. The choice of this molecule for synthesis planning is obvious as migraine headache is a very common disease in general population and 'Sumatriptan' is a potent medication, prescribed worldwide by the physicians. Again, the chemical/ pharmaceutical industries are also vibrant today in search of cost effective scalable synthesis. Moreover with the availability new reagents, chemical reactions, sophisticated new methods of laboratory execution and the application of synthon approach to analyse the target molecules leading to several routes have made it possible to rethink their synthesis for the improvement in existing processes to satisfy the commercial need.

MATERIALS AND METHODS

The structure and information about 'Sumatriptan' as potent antimigraine headache drug have been collected from different books[13-18]. The proposed synthesis planning is then exploited in a novel way from the result of its retrosynthetic analysis using the basic principle outlined in the pioneering works of Prof. E.J. Corey. The symbols and abbreviations are synonymous to that represented in book[19,20]. The analysis–synthesis schemes being theoretical propositions; obviously the syntheses have not been executed in the laboratory. Most of the retrosynthesis schemes have been derived taking in to account the synthesis earlier done for its preparation as found from different books and literatures[21,22]. 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

Scheme-1

Reaction of 1-(bromomethyl)-4-nitrobenzene (12) with Na_2SO_3 (11) in TBAB followed by treatment with PCl_5 forms (4-nitrophenyl) methanesulphonyl chloride (9). The chloride (9) then forms

corresponding sulfonamide (7) with methyl amine (8) in DCM. Catalytic reduction of (7) converts -NO_2 group to $–NH_2$ group (6). Reaction of aniline derivative (6) with $NaNO_2$/HCl followed by reduction with $SnCl_2$ affords corresponding aryl hydrazine (5) as an intermediate product. The aryl hydrazine then furnishes the indolyl alcohol (3) on reaction with dihydrofuran (4) followed by treatment with anhy.H_2SO_4/DEM. Alcohol (3) produces corresponding chloride (2) on treatment with MsCl/Et_3N.Amination of (2) with dimethyl amine (1) produces Sumatriptan (TM). (Scheme -1).

Scheme-2

(4-nitrophenyl) methanesulphonyl chloride (9) prepared from 1-(bromomethyl)-4-nitrobenzene (12) as in Scheme-1, forms the phenyl sulfonate(21) on treatment with phenol in presence of Et_3N. Catalytic reduction of (21) forms the aniline derivative (20). Conversion of this aniline derivative in to its diazonium salt followed by reduction with $SnCl_2$ affords the corresponding aryl hydrazine (19). Reaction of the hydrazine with 3-cyanopropanal (18) in the form of its ethyl acetal under acidic condition produces the vinyl aniline (17) as an intermediate. The intermediate furnishes the indole nucleus (16) in presence of polyphosphoric acid. Treatment of (16) with methyl amine (8) gives the left half residue (15) of the molecule. Catalytic hydrogenation converts the –CN group to amine (14). Reductive amination of (14) with CH_2O (13) in presence of $NaBH_4$ furnishes Sumatriptan (TM). (Scheme-2).

Scheme-3

N-Methyl-(4-aminophenyl) methane sulfonamide (6) forms corresponding hydrazine (5) as in Scheme-1. Reaction of the hydrazine with 2-thiophenoxy ethanal under acidic condition produces (27) which cyclises to indol nucleus (26) in acidic condition. Reduction of (26) with H_2/Rany-Ni affords N-methyl -5-indolyl methane sulfonamide (25). Reaction of (25) with oxalyl chloride (24) forms oxalyl devt of indol (23). Treatment of (23) with dimethylamine(1) and subsequent reduction with LAH forms Sumatriptan (TM). (Scheme-3).

Scheme-4

Substitution reaction of Methyl indol-5-carboxylate (36) at C_3 with oxayl chloride (24) followed by amination forms amide (34). Reduction of amide with LAH forms amino alcohol (30).The amino alcohol then forms its bromide (31) with PBr_3 .The amino bromide on treatment with Na_2SO_3 in TBAB followed by reaction with PCl_5 and then with methyl amine (1) in DCM. Forms Sumatriptan (TM). (Scheme-4).

Scheme-5

3-Bromopropanol (44) prepared from 3-(N, N, dimethyl) amino propanol (45) reacts with ethyl acetoacetate (43) in presence of NaOEt produces ethyl 2-(3-dimethyl aminopropyl)-3-oxobutanoate (39). The sulphonamide aniline (6) as synthesize in Scheme-1, reacts with ethychloroformate to form N-protected sulphonamide (42).Diazotization of (42) with $NaNO_2$ gives the corresponding diazonium salt (41),which undergoes a Zapp-Klingneman reaction with ethyl 2-(3-dimethyl aminopropyl)-3-oxobutanoate (39) in the presence of NaOAc to give the corresponding hydrazone (38). Fischer cyclization of hydrazone proceeds smoothly when treated with AcOH/HCl at ambidented temperature. The ethyl ester (37) upon hydrolysis and subsequent decarboxylation by heating in quinoline with Cu – powder provides Sumatriptan (TM). (Scheme-5).

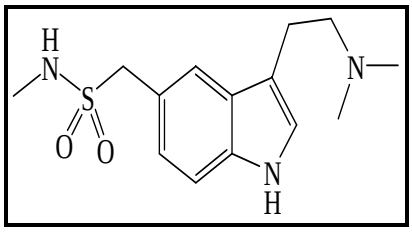
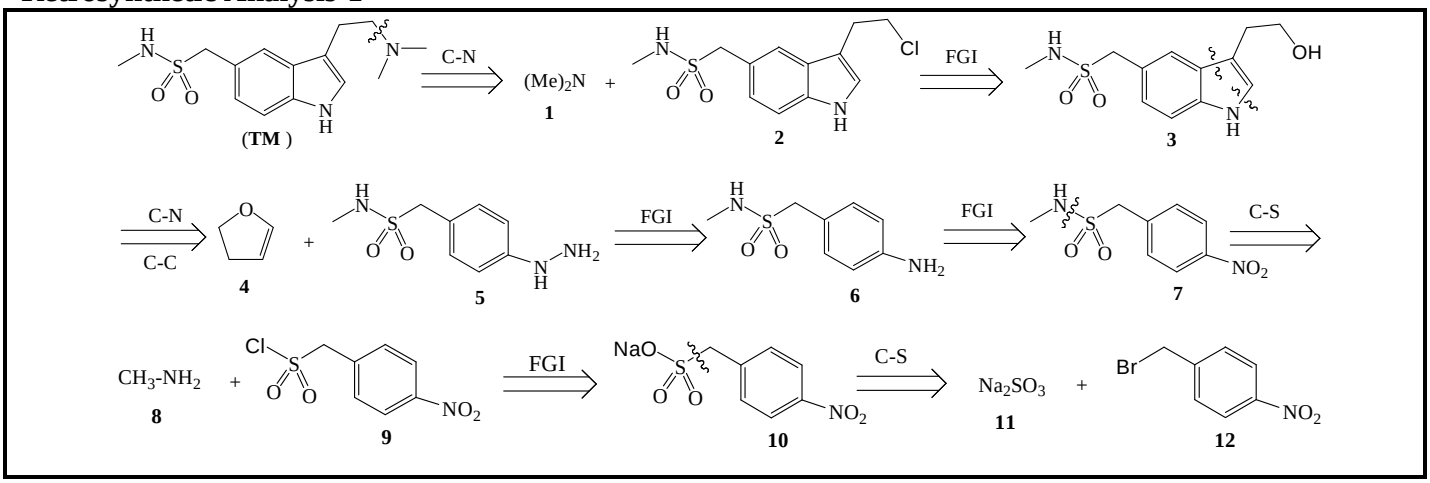
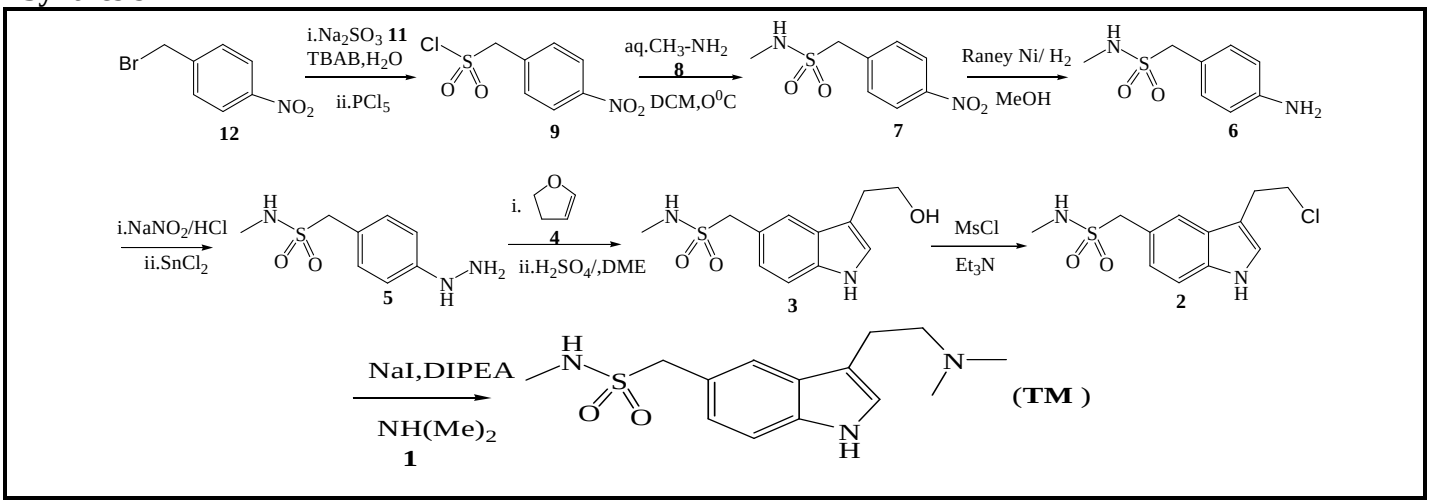


Figure No.1: Sumatriptan

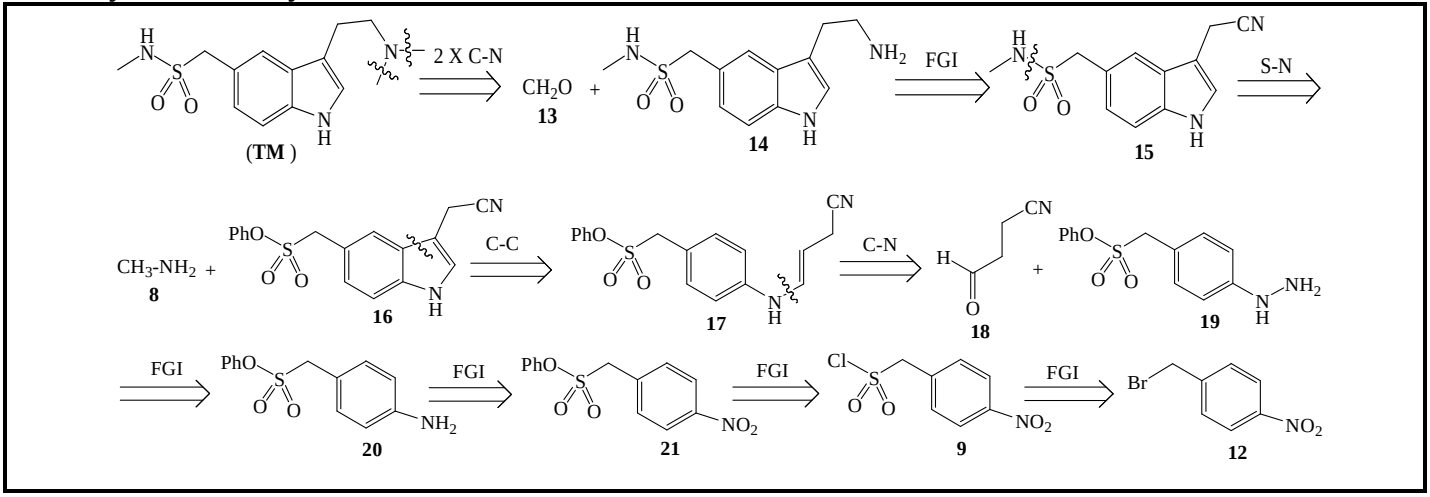
Retrosynthetic Analysis-1



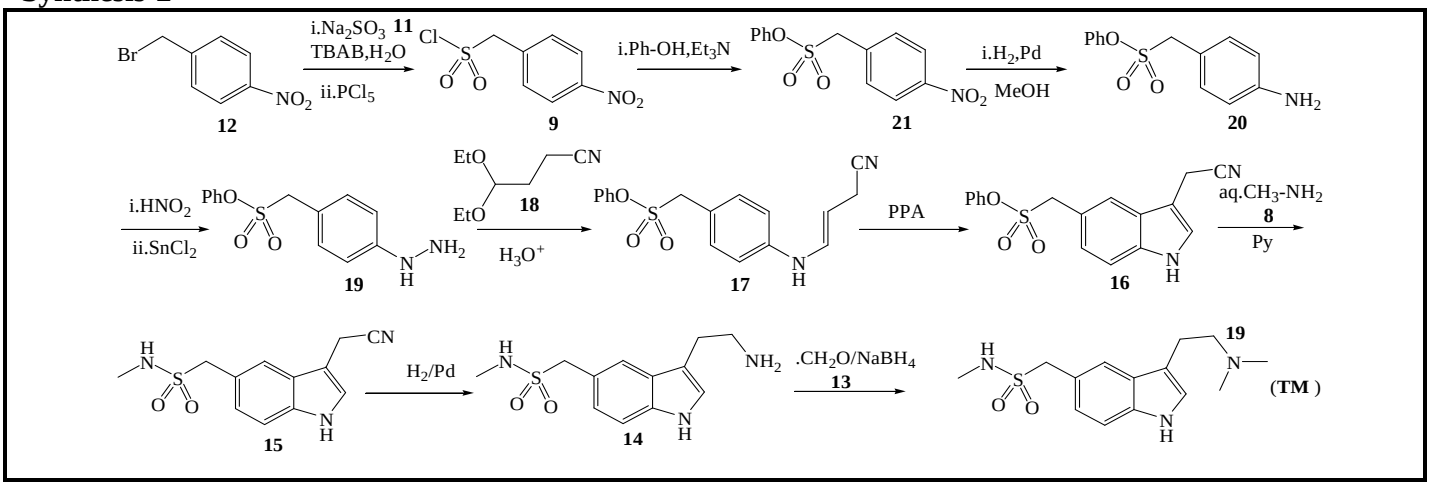
Synthesis-1



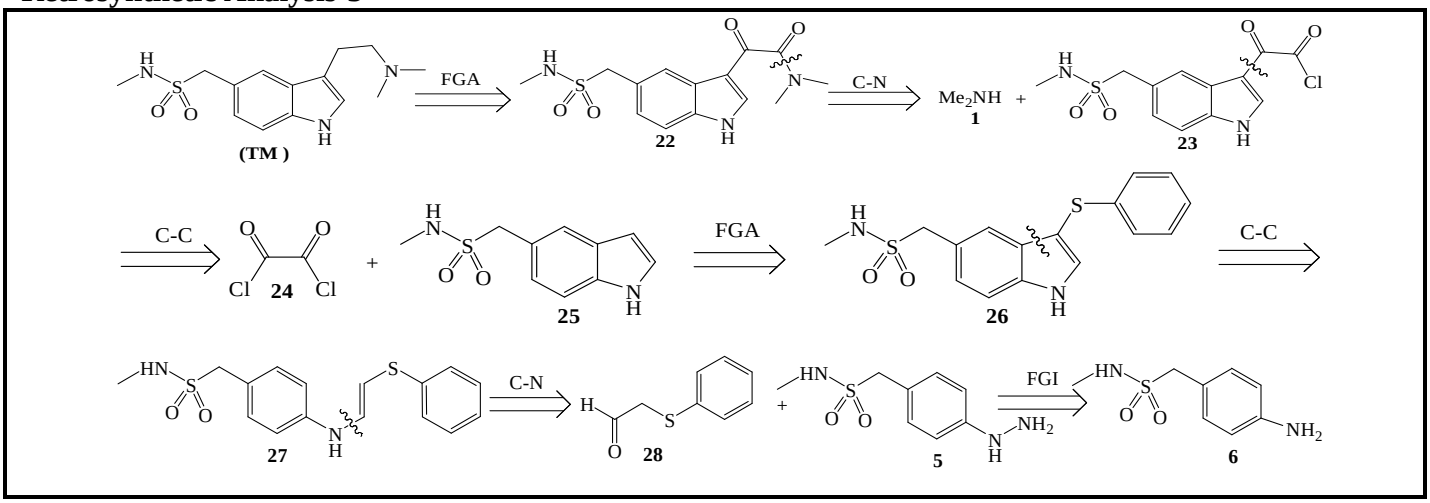
Retrosynthetic Analysis-2



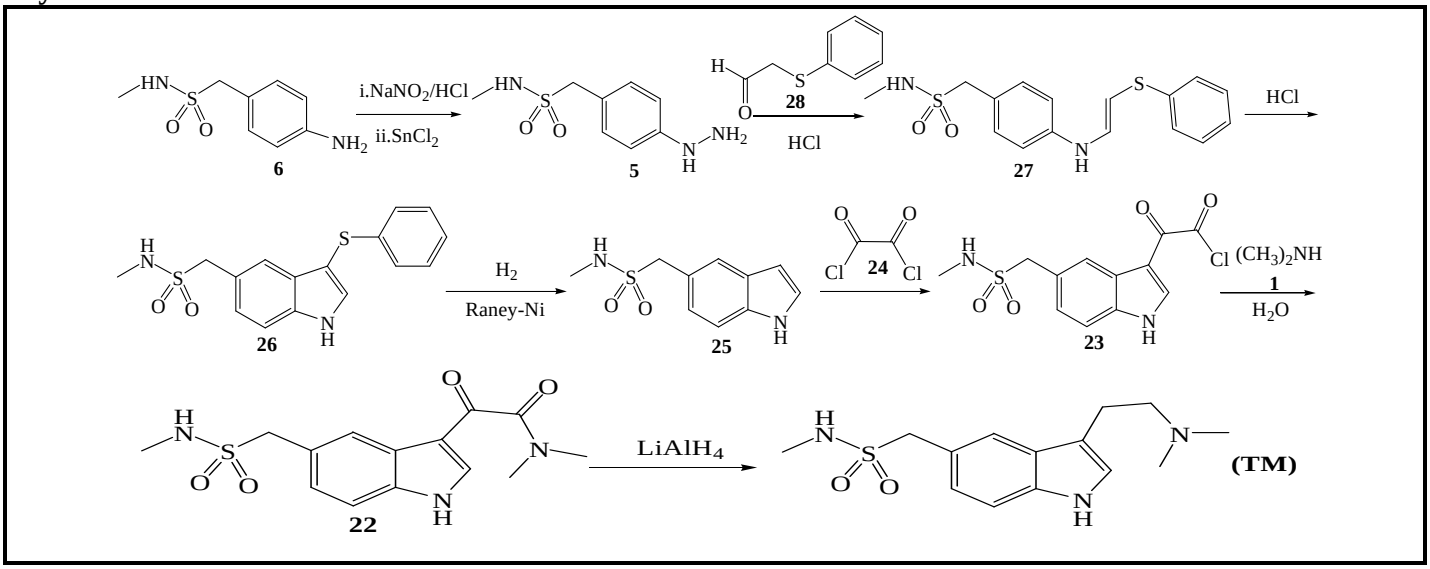
Synthesis-2



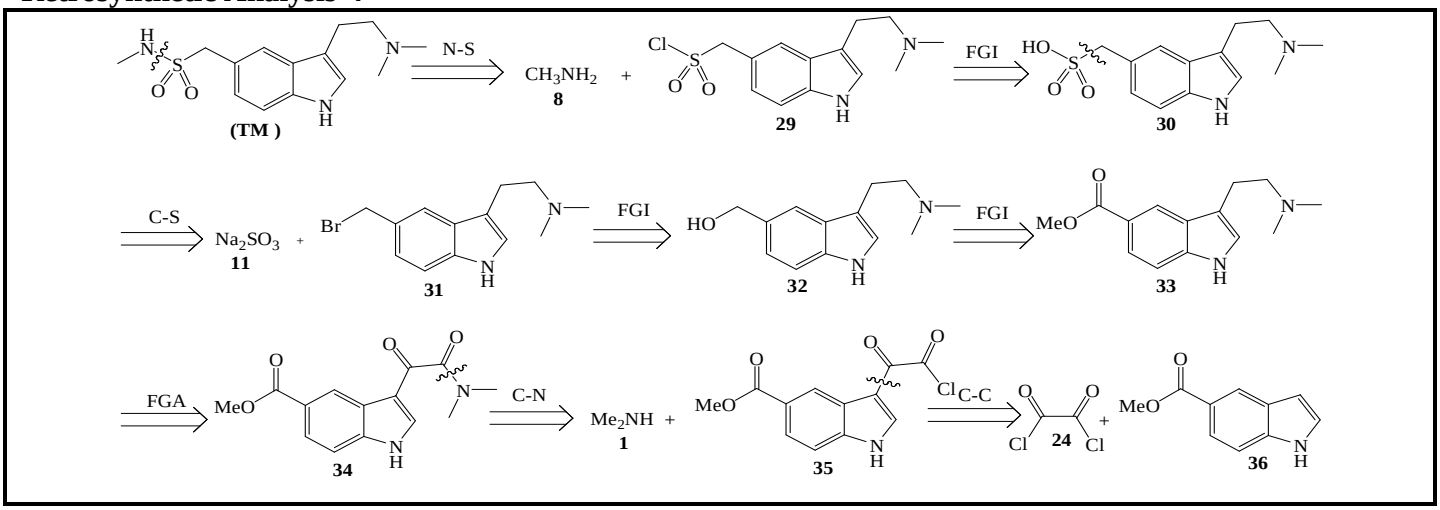
Retrosynthetic Analysis-3



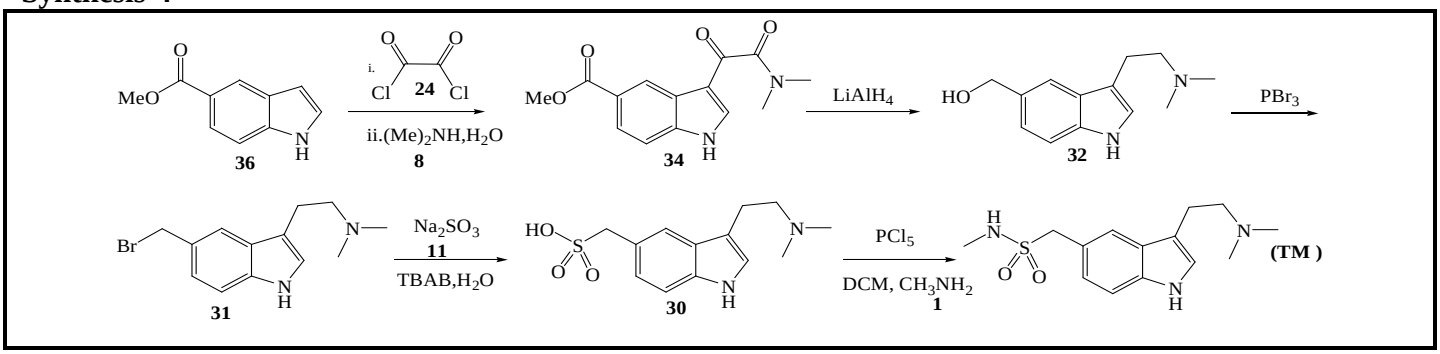
Synthesis-3



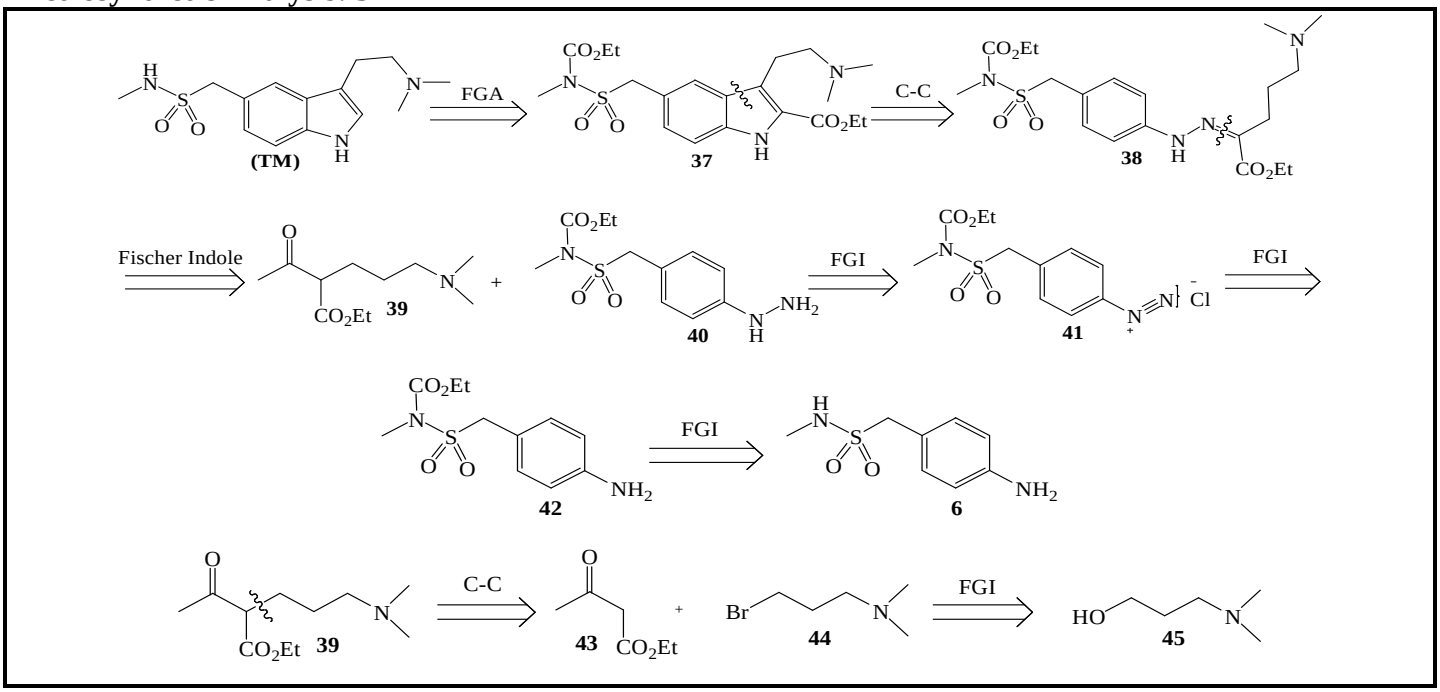
Retrosynthetic Analysis-4



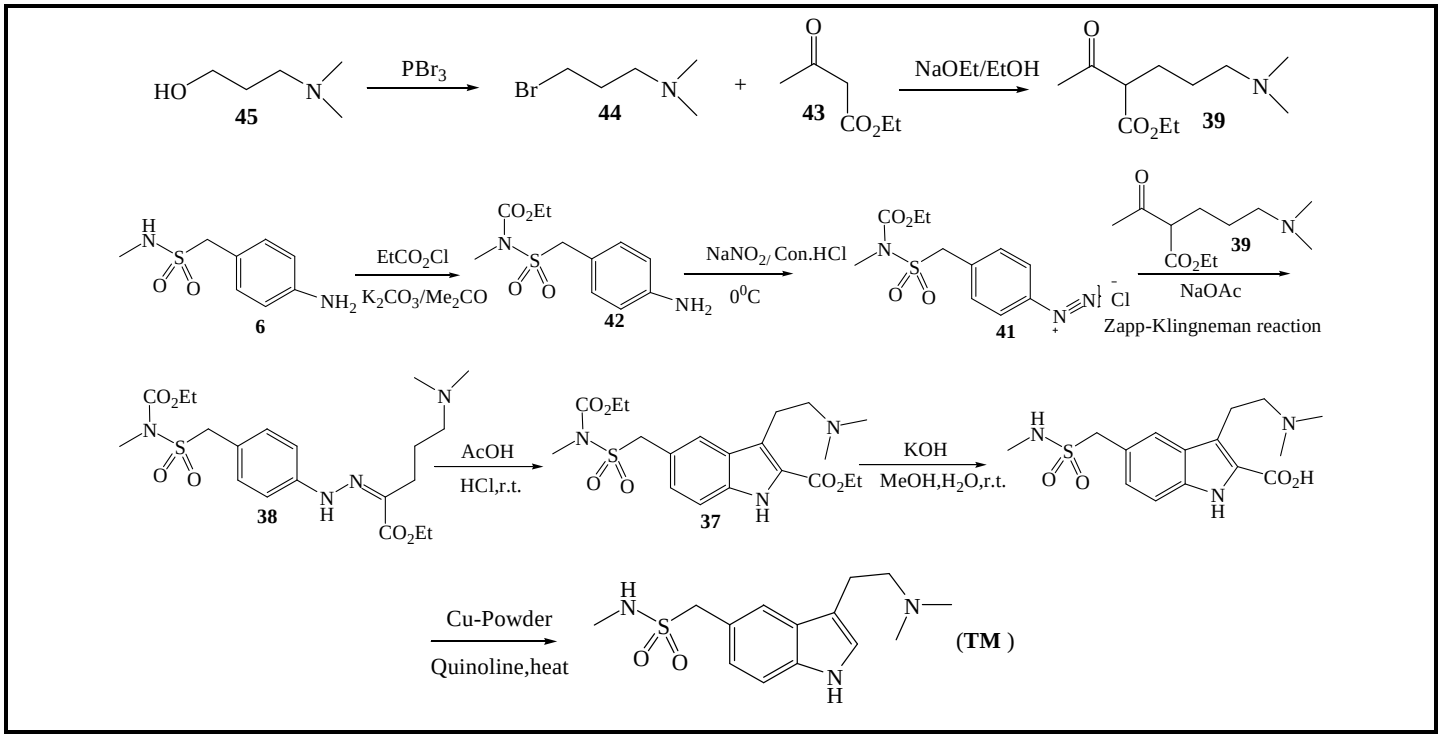
Synthesis-4



Retrosynthetic Analysis: 5



Synthesis: 5



CONCLUSION

The power of retrosynthetic analysis becomes evident in the design of a synthesis. The goal of retrosynthetic analysis is structural simplification. It is a paper exercise; a full analysis of this type will provide many routes for synthesizing the target molecule. Taking the privilege of this approach and as a continuation of our work on the synthesis design of targeted drugs, we have proposed a good number of synthesis schemes for antimigraine drug 'Sumatriptan'. Scalable synthetic routes for newly discovered natural products, drug molecules, useful compounds not available in adequate quantities from natural resources and target molecules that have never been synthesized earlier can be best provide by this approach. With the advancement and development of new reactions and reagents, the synthesis of best selling drugs can be rethinking for the improvements in existing process through this approach.

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