

## Research Solutions for Organic Chemistry

### RouteEdge™ Case Studies



*The Edge in KnowlEdge™*

An IndoGlobal Group Company

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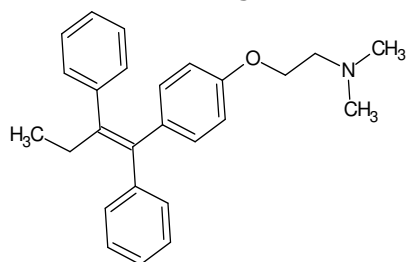
## Case Study 1: Advanced RouteEdge – Organic Synthesis

### Customer

A medium sized pharmaceutical company undertaking Research and Development activity for an efficient, economically viable and convergent synthesis of drugs and drug intermediates.

### The Molecule and the Problem

Tamoxifen, a drug for breast cancer, was developed 30 years ago and is widely used for the treatment of hormone-dependent breast cancer and also for long term adjuvant therapy in postmenopausal women. Customer was looking for economically viable route to synthesize Tamoxifen.



#### TAMOXIFEN

IUPAC name: (Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy] N,N-dimethylethanamine.

Systematic Name:

(Z) Ethanamine, 2-(4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-, (Z)-Ethylamine, N,N-dimethyl-2-(p-(1,2-diphenyl-1-butenyl)phenoxy)

Synonyms: Citofen, Crisafeno, Diemon, Istubol, Kessar, Noltam, Nolvadex, Nourytam, Oncomox, Retaxim, Soltamox, Tamizam, Tamoxen, Tamoxifene [INN-French], Tamoxifen, Tamoxifeno, Tamoxifenum, Valodex, zemide

Molecular Formula: C<sub>26</sub>H<sub>29</sub>NO  
Molecular Weight: 371.52  
CAS Registry No.: 10540-29-1  
Melting Point: 97 °C

### Solution

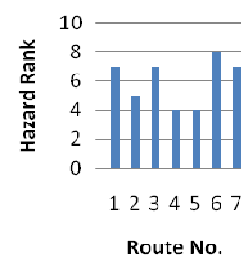
The customer engaged Advanced RouteEdge™ services from Indoglobal Knowledge Private Limited to obtain the consolidated and accurate information. The main focus was to enlist all the available synthetic routes for tamoxifen with their citations, compare these routes and select the most suitable one for synthesis of tamoxifen. The RouteEdge services offer concise report on the known synthetic strategies of target molecule with details of properties as well as available spectroscopic data and analytical methods of identification to meet the specifications of the end product.

### Procedure

Structurally, tamoxifen is a tetra-substituted olefin and only the trans-(z)-isomer viz *trans*-1-(4-[2-(dimethylamino)ethoxy]-1,2-diphenyl-1-butene is a potent non-steroidal anti-estrogen. Several other triphenylethylene analogues showed potent anti-estrogen activity, some of them are listed here; enclomiphene, zuclophene, diethylstilbesterol, dimethyl stilbesterol, trianisyl chlorethylene, α,α-di(p-ethoxyphenyl)-β-phenyl-bromoethylene, nafoxidine, trioxefene etc.

Literature survey revealed various routes which could be categorized into seven routes including stereospecific and non-stereospecific approaches. Advanced RouteEdge services compiled the details of all the seven routes and evaluated their practicality, efficiency and viability to derive at the decision of route selection.

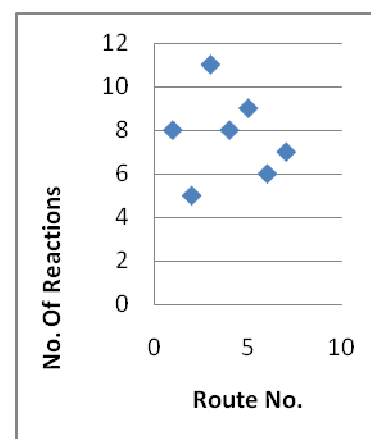
Route Comparison using Hazard Rank



The parameters used for the evaluation were as follows: complexity and number of reactions, duration, hazards of raw materials and other chemicals involved, greenness of the reactions (environmental concerns), and expected cost of the complete route. The first filter has to be availability of the chemicals which is to be looked into by the client.

The "route comparison" activity is supported by the process utilized in the software eLabTool developed by Indoglobal Knowledge Private Limited, which considers the above mentioned parameters and generates graphs for clarity of the data analysed. The domain experts made a list of chemicals required for the various routes and efficiently assessed the data such as; their cost, quantities required, hazard properties etc. The duration of every route was calculated considering the time essential for every reaction in the route.

Route selection is a collective decision of the data analysis and experts opinion based on experience as well as practicality, availability of chemicals, feasibility of the reactions, yield and other parameters. Following the protocol described above, out of the seven routes known, a suitable synthesis of tamoxifen via the three-component coupling reaction and migration of the double bond developed recently, was selected as a first choice. This route comprised of successive allylation of benzaldehyde and Friedel-Crafts alkylation reaction of anisole with the intermediary homoallyl silyl ether, followed by the migration of the double bond to form the desired tetra-substituted ethylene. Alternatively, second option involving Palladium-catalyzed double cross-coupling of *E*-vinylic dibromides with PhZnCl under Pd(0) catalysis to afford tri- and tetra-substituted olefins, was also suggested.



Silica gel chromatography with benzene / triethylamine (9:1) as the eluent where the *Z* (*trans*) isomer is more mobile than the *E* (*Cis*) isomer was employed for purification of required *Z*-Tamoxifen from the mixture of geometrical isomers. The mixture of isomers could also be analyzed by a simple and rapid high performance liquid chromatographic method for separation and determination of *E* and *Z*-Tamoxifen.  $\mu$ -Bondapak C<sub>18</sub> column with aqueous tetrabutyl ammonium hydrogen sulphate (pH 4.0) containing acetonitrile as mobile solvent was used.

Separation between *E* and *Z*-Tamoxifens was found to be good with resolution and separation factors of 2.85 and 1.27, respectively. The effect of light on stability of *Z*-Tamoxifen and its conversion to *E*-isomer has also been studied.

## Case Study 2: Novel RouteEdge – Organic Synthesis

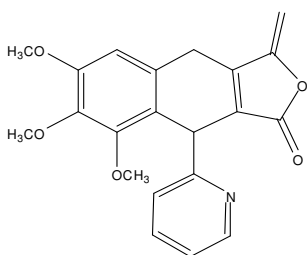
### Customer

A large Indian pharma company operating in several geographies around the world. The company on its own conducts Drug discovery supported by computer assisted designing, molecular modeling followed by the docking studies with the receptor site for prediction of potent biological activity to search for new/novel chemical entities and drugs.

### The Molecule and Problem

Customer wants to focus on molecular modeling and synthesizing a large number of molecules for screening of biological activity and aims to arrive at the LEAD molecule in a shortest possible manner and time. is looking for a partner in

### Solution



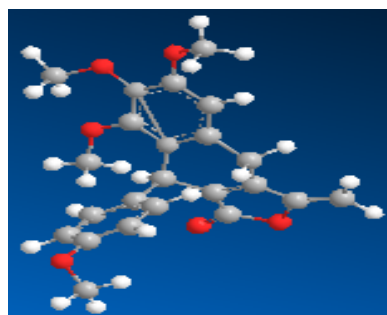
IndoGlobal Knowledge with its strong focus and expertise in providing novel, strategic, efficient and cost - effective routes in organic synthesis as part of their consultancy services was a natural partner to the customer. Earlier project conducted in synthesis of 1,4-Dihydroxynaphthalene and exomethylene-furanone moieties in the structure, was expected to exhibit anticancer activity and was found to be so.

IUPAC Name : 6,7,8-Trimethoxy- 3-methylene-9-(pyridin-2-yl)- 4,9-dihydro-naphtho[2,3-c]furan-1(3H)-one .  
Molecular Formula: C<sub>21</sub>H<sub>19</sub>NO<sub>5</sub>  
Molecular weight: 365.38

### Procedure

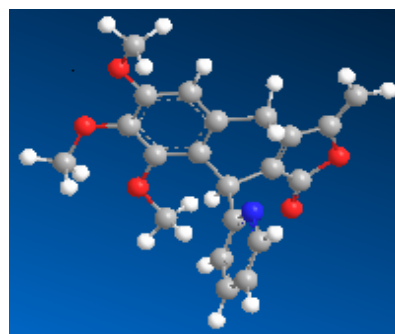
Since the compound was “designed” by the customer no prior art and information on its properties was available. The domain experts were required to generate the information and suggest a feasible route for the synthesis. A prior art search for a structurally similar compound was exhaustively conducted which revealed that similar dihydronaphthofuranone derivatives have been reported.

Novel RouteEdge services from Indoglobal Knowledge Private Limited assigned the IUPAC nomenclature, derived molecular formula and molecular weight for the new/novel target molecule from the structure provided by the customer and also furnished a convergent, new and a promising synthetic route.



A furanone moiety is present in a number of natural products possessing broad spectrum of biological activities and is a synthon for the synthesis of a variety of organic compounds. The basic skeleton of the designed molecule also resembled the podophyllotoxin class of compounds with anticancer activity. Among the 5-alkylidene-furanone class the 5-exomethylene moiety was found to be responsible for the biological activity.

Novel RouteEdge services suggested a route for the synthesis of the target molecule involving Stobbe condensation of readily available 3,4,5-trimethoxy-benzaldehyde with ethyl levulinate followed by cyclization. Lithiation at the C-3 in furanone moiety, its reaction with 2-picolinaldehyde and subsequent cyclisation should provide the target molecule. This route would ~~could~~ afford the racemic mixture which could be resolved to fetch the enantiomers (if desired) for further evaluation.



The pharma company employed the methodology suggested by Novel RouteEdge for the synthesis of target molecule as well as other analogues by replacing 2-picolinaldehyde with substituted pyridine derivatives to generate a library of 1,4-dihydro-naphthalene lignans.

## Case Study 3: Novel RouteEdge – Biotransformation

### Customer

A small Indian pharmaceutical company with 5 years of experience in manufacturing of organic drugs based in Thane, India.

### The Molecule and Problem

Company wanted to make an entry into green solutions, but due to lack of manpower and expertise they needed outsourcing. Their particular interest is in synthesis of Luteolin. Being in unknown territory the customer does not wish to attempt biotransformation on their own which is also a diversion from their core expertise. Moreover, investments needed to build skills and infrastructure are too large for the size of the customer's company.

#### LUTEOLIN

**IUPAC name:** 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4H-chromen-4-one (5,7,-3',4'-tetrahydroxyflavone, luteolin),

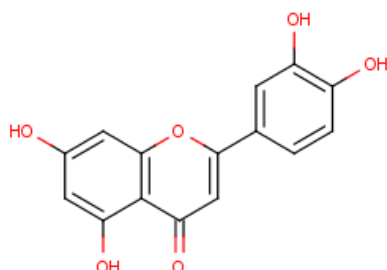
**Molecular Formula:** C<sub>15</sub>H<sub>10</sub>O<sub>6</sub>

**Molecular Weight:** 286.25

**CAS Registry No.:** 491-70-3

### Solution

IGK has proven experience, expertise and facilities to conduct biotransformation based research and development. RouteEdge, a program designed to assist small and medium companies with organic and bio-based novel routes and molecules offers a perfect solution for the customer's requirement.



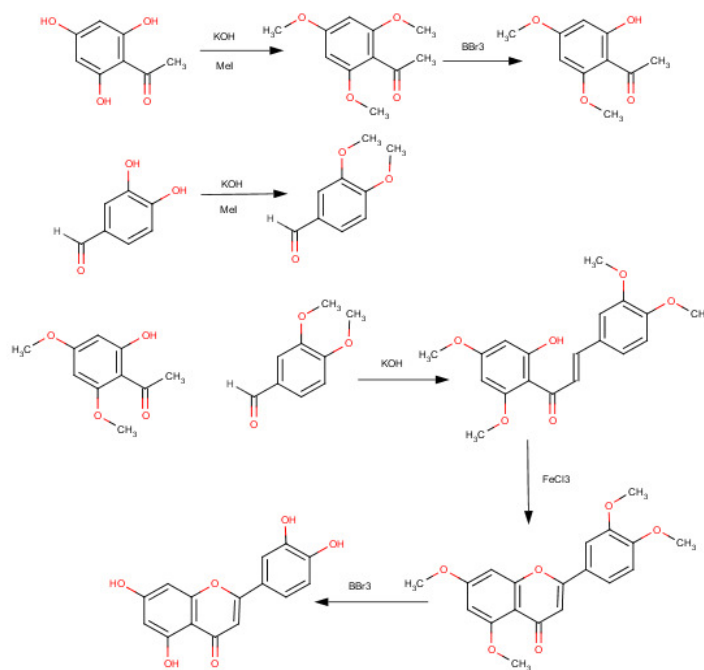
### Procedure

Luteolin belongs to "flavonoid" class of compounds which are polyphenolic compounds that are ubiquitous in nature. The flavonoids have aroused considerable interest recently because of their potential beneficial effects on human health. They have been reported to have antiviral, anti-allergic, antiplatelet, anti-inflammatory, antitumor and antioxidant activities. The antioxidant activity of flavonoids depends on their molecular structure and structural characteristics. Certain flavonoids found in hops and beer confer surprisingly potent antioxidant activity exceeding that of red wine, tea, or soy.

There are several synthetic organic chemical routes for 5, 7,-3',4'-tetrahydroxyflavones (luteolin). The domain experts from Advanced RouteEdge services surveyed literature and found that most of the information on the synthesis of this molecule is patented. The synthetic organic chemical route that could be derived from the database available in the

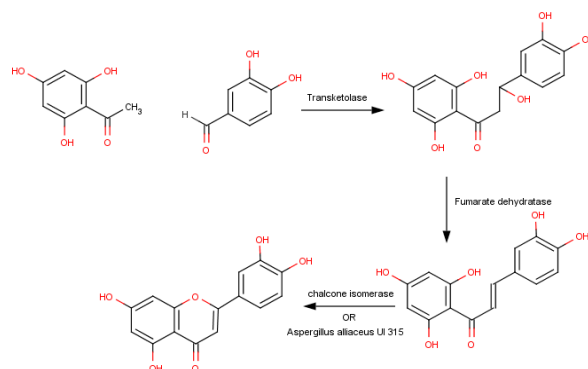
software product eLabTool™, being developed by Indoglobal Knowledge Private Limited involved six steps including protection and deprotection.

Since the customer's company desired a green route preferably using commercially available enzymes, the biotransformation equivalent reactions were looked into. Reaction database in eLabTool™ covers all reported types of organic transformations performed using isolated enzymes as well as from whole cell microbial source and commercially available. The corresponding reactions desired for the synthesis of luteolin lead to a route consisting of three reactions.

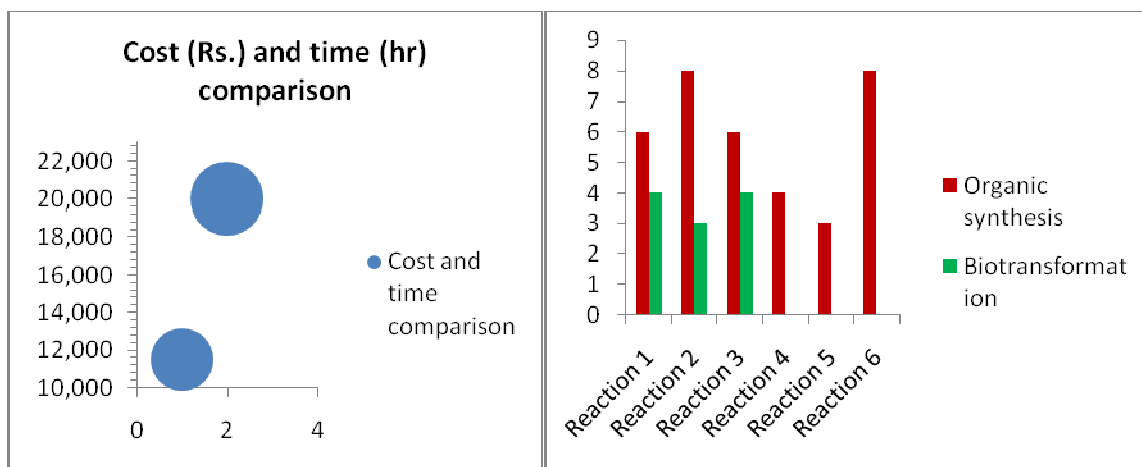


Above: Chemical Route for synthesis of Luteolin

Advanced RouteEdge services studied the two routes with respect to their cost and duration as well as the hazards incurred. This analysis suggested that the shorter, three-step biotransformation route is much safer than the chemical route although it could take longer time and could cost more.



Above: Bio-transformation Route for synthesis of Luteolin



*Cost and Time comparison*

*Hazard comparison*

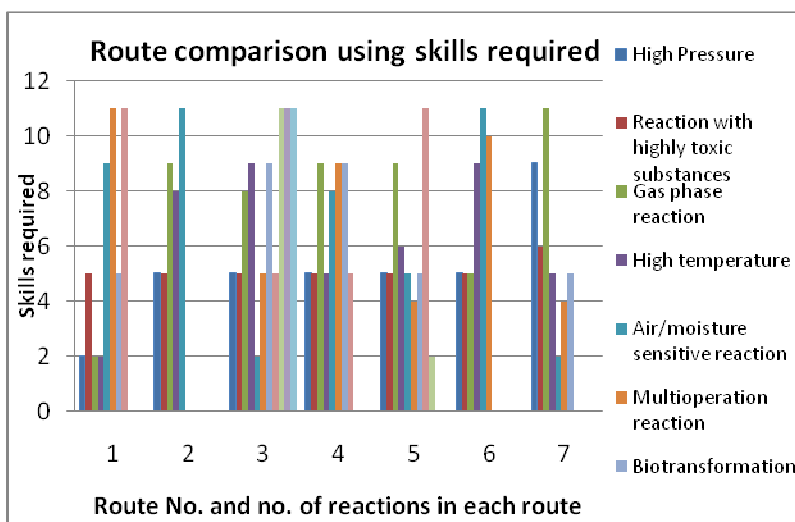
Herein, the cost of effluent treatment was not considered.

The commercial purified enzymes and microbial cultures need to be assayed for which the corresponding assay methods were suggested. Similarly, the analytical methods suggested for monitoring the progress of the reactions involved IR, NMR, HPLC and LCMS.

The bio-route, comparative analysis and complete report were submitted to the company.

## Benefits of RouteEdge™

RouteEdge analyses the organic synthetic routes to determine the best possible route by using skills, knowledge and legacy information. This competitive data analysis is supported by a "route comparison tool" in eLabTool™ (applicable to Advanced RouteEdge) which is uniquely positioned to evaluate the data quantitatively. The decision is supported by the rich reaction database in eLabTool™ which covers exhaustively all types of reactions. Transformation techniques ranging from simple pot boiling to complex multi-component multi-processes, green processes including reactions catalyzed by enzymes, homogeneous and heterogeneous catalysts, microwave promoted reactions as well as reactions using ionic liquids as solvents are included.



The new modified and novel routes suggested are substantiated by the equivalent known examples from the reaction database of eLabTool™. Novel RouteEdge dealing with "drug discovery" suggests routes for synthesis of designed molecules with intuition and knowledge management.

RouteEdge offers a broad range of skills of the domain experts of IGK in selecting the synthesis routes prioritized by the client's requirements. We draw on our combined research and development experience gained over more than 65 years in all segments of organic chemistry. We provide client / institute/ industry-specific customized report on research planning solutions packaged with complete literature and comprehensive process documentation in reasonably short time.

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