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Additives in Organic and Biochemical Reactions

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Abstract

Organic and biochemical processes are often greatly influenced by the presence of some additives. Besides the role of a catalyst, additives are believed to have profound effect on the kinetics, selectivity and the course of many biological phenomena and chemical reactions. The present article has focused on the use and role of additives, which may be of different classes of compounds, in some important organic and biological reactions.

1. Introduction:

A catalyst is defined as a chemical entity that can alter the rate of a chemical reaction and remains unchanged after the reaction. On the other hand, additives are diverse classes of chemical compounds that not only exhibit significant influence over a chemical reaction, but also used for many other purposes such as food preservatives, flavoring agents, increase of nutritional value, preparing size-controlled metal nanoparticles (NPs) etc. Additionally additives do have versatile effects in the fields of in biological processes,[1] biochemical reactions,[2] pharmacokinetics,[3] and in organic synthesis.[4]

Several biological phenomena are often manipulated in the presence of additives. A few specific examples are worthy to mention. Nitric oxide (NO) plays a critical role in vascular endothelial growth factor (VEGF)-induced angiogenesis and vascular hyper permeability. The iNOS inhibitor slightly slowed angiogenesis in some experimental mice, and there was an additive effect of L-NIL on decreased angiogenesis in other mice.[5] Protein folding research has recently expanded further due to the need for folding of proteins from inclusion bodies produced by over expression in *Escherichia coli.* In many cases, folding has been achieved by manipulation with additives. The unfolding and refolding rates of the heme- and Ca^{2+}-containing *Coprinus cinereus peroxidase* (CIP) have been measured at definite pH and urea.[6] Enzymes are inherently labile; therefore their operational stability is of great importance for any bioprocess. The stability of *catalase* enzyme in the reaction of hydrogen peroxide decomposition was studied in the presence of some potential stabilizers: ethylene glycol, glycerol,fructose,sucrose, fucose and ribitol[7]. Internal hydrogen bonded structures exist in proteins and model peptides. However, such structures are sensitive to pH, temperature, neutral salts or organic additives. The effect of additive may cause the amino acid side chain in ordered fashions.[8] Kidney stones are crystal aggregates, most commonly containing calcium oxalate monohydrate (COM) microcrystals as the primary constituent. Macromolecules, specifically proteins rich with anionic side chains, are thought to play an important role in the regulation of COM growth, aggregation, and attachment to cells, all key processes in kidney stone formation. With the advent of atomic force microscopy (AFM), one can trace direct imaging of nucleation and crystal growth with macromolecular additives.[9] A defect in the structure of the obese gene is responsible for development of obesity in the *ob*/*ob* mouse. The product of expression of the gene is the protein hormone leptin, which can act as an additive. Leptin produced a dose-related increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) release, which may decrease higher concentrations of leptin to control pituitary.[10] Highly organized biomineralized hydroxyapatite (HAP) nanoparticle architecture was produced when the biological additive was glycine or amelogenin or glutamic acid. These control experimental results demonstrated that the biological additives and HAP could not induce any nano-assembly without the involvement of amorphous calcium phosphate (ACP), which indicated that the presence of ACP should be an important prerequisite for the biological architecture of apatite.[11] Selective nucleation of polymorphs of calcium carbonate crystals under specific experimental conditions can be done by a water-soluble additive, poly(vinyl alcohol) (PVA) and enhanced the selectivity of the polymorph nucleation.[12]

Pharmacokinetics is the study of how drugs move through the human body. Pharmacokinetics consists of four main pathways: absorption, distribution, metabolism, and elimination (ADME). Depending on how a drug is administered is dependent on the pathway that the drug takes.[13] Additives has shown significant effects on absorption of different drugs.

The role of additives in organic synthesis has a definite value. A few examples in the myriad are mentioned. The rate of a Michael addition reaction is enormously accelerated in presence of glucose and sucrose in water medium than the use of a non-polar medium.[14] Ammonium salts and amino acids (NH_4Cl and L-tyrosine) sometimes may increase the rate of reduction process of aldimines to vicinal diamines. The Wurtz coupling reaction,[15] in water medium may also be affected in the presence of crown ether complexes, but the reaction requires higher temperature and the reaction is confined in aryl bromides and iodides. Cyclodextrins or Calixarenes possessing extended hydrophobic host cavities and surface-active properties to attract the hydrophobic end of the reactant sites (Figure 1).[16] The rate of asymmetric Diels-Alder reaction,[17] sometime increases in presence of water as an additive.[18]

2. Role of additives:

Generally specific types of additives are known to accelerate specific types of organic or biochemical processes. There are many types of additives known, which are used only for specific organic reaction. However, it is hard to explain why an additive is beneficial since there is no generalized mechanism or well-defined function that could be established. The role of additives can only be elucidated after mechanistic studies and their functions that are sketched below:

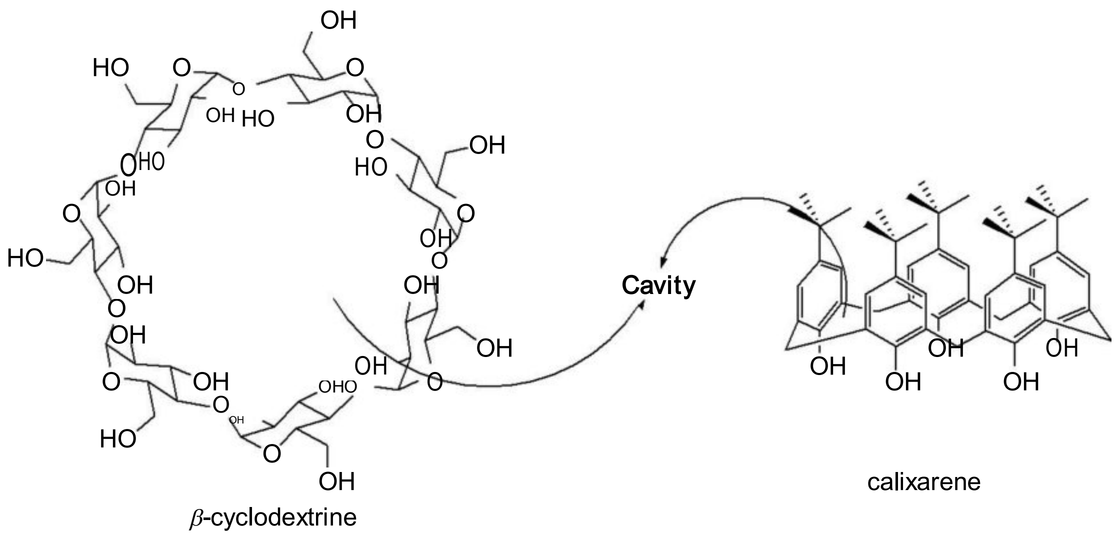

Figure 1. Structures of *b* -cyclodextrine and calixarene.

a) Probably one of the most common effects of additives is to deoligomerize nonactive (or less active) catalyst structures, resulting in the formation of the desired active monomeric catalyst species,

b) In particular basic additives may be able to coordinate to the metal centre permanently or temporarily, thereby changing the geometry of the catalyst in a favorable way,

c) Additives might also serve as a buffer, for example, to maintain the water concentration at a defined level,

d) Additives in bio-inspired silicification act either as catalysts, aggregation promoting agents or structure-directing agents or more typically, display a combined effect of the all. The processes of silicification and the resulting product yield, composition and morphology can be controlled by the presence of additives and it can affect all aspects of silica deposition from the rates of formation of small oligomers and stable nuclei.[19]

e) Another effect of additive should be mentioned, which perhaps dictates the enantio- or diastereo-selectivity in a particular reactions.[16]

f) The additives may act as co-catalyst to activate the metal centre position of some inorganic complex for some chemically inert reactions e.g. in the oxidation of alkane to alcohol.[20]

g) In case of protein folded reaction, additives exert their effect through two different mechanisms; (i) at high additive concentration the properties of water are changed, or (ii) at low concentration specific binding to the protein is predominant.[6]

3. Applications of additives:

In this article, we have shown the diverse applications of additives in respect of environmental aspects, biological processes, pharmacokinetic viewpoints and lastly, in some organic reactions. The last one is the very important regarding drug delivery system because until and unless we know the reaction pathway of combined drug and additive system, we could not administer the drug along with additive in any living body.

Oxygenated additives were conventionally recommended for gasoline. But now day's oxygenated additives are widely considered for diesel fuel also because it reduces the harsh effect of particulate matter. To reduce the harsh effect diesel is blended with some oxygenated additives like ethanol, methanol, dimethyl ether or diethyl ethers. Oxygenated additives is so important because when combustion takes place it gives very small amount of particulate matter and increases the combustion efficacy of the engines.[21] Nowadays, biomass as a renewable and potentially sustainable resource is seriously considered to contribute to the production of green chemicals, products and biofuels via the oil refinery analogue of a biorefinery. Furfural is one such chemical.[22]

Derivative of furan acts as fuel additives e.g. methyl-tetrahydrofuran used in novel fuel formulations, [23] or rather methylfuran that can be blended into petrol as has been demonstrated by road testing. [24]

A research group has performed *in vitro* study indicating that curcumin, which may exist in its tautomeric forms (Figure 2), has antioxidant, anti-inflammatory, and anti-amyloid activity.[25] It has been used for the treatment of many diseases such as diabetes, liver disease, rheumatoid arthritis, atherosclerosis, infectious diseases and cancers. In addition, studies in animal models of Alzheimer's disease (AD) indicate a direct effect of curcumin in decreasing the amyloid pathology of AD. The curcumin is used as a food additive and it is a promising agent in the treatment and/or prevention of AD. The mode of action, however, might not necessarily be same but with the common fact of acceleration of the rate of reactions.

Bases, metal salts, ionic liquids, various halides, nitrogen based compounds, and even solvents are categorized as additives. Some applications of these additives are described here. Bases are not commonly used as additives but sometimes it impressively alters the reaction pathway. It was reported that potassium carbonate was used as an efficient promoter in the Hofmann–Fleer–Freytag reaction. An interesting exam ple is cited here where Benzosultams, important privileged structures in drug discovery can be synthesized by base additive-assisted reaction. For instance, benzothiazine dioxide derivatives have been found to show active inhibitory properties against a variety of enzymes such as 11β-HSD2, Calpain I, HIV integrand, and cyclooxygenase-2 (COX-2). Additionally, it was reported that members of the family also show powerful anti-inflammatory properties (Figure 3).

Intramolecular sp^2 C–H bond amination reaction using *N*-ethyl-4′,5-dimethyl-[1,1′-biphenyl]-2-sulfonamide **1** as a model substrate (Scheme 2). The reaction conditions were initially screened with a combination of $PhI(OAc)_2$ (1.1 equiv.) and I_2 (1.1 equiv.) in different solvents at 60 °C. The cyclization reaction did not proceed at all in DMSO but gave satisfactory result, while other solvents such as acetone, ethyl acetate, 1,2-dichloroethane, and 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) gave unsatisfactory results. Optimization of the reaction using various bases as additives, K_2CO_3 was found to be the most efficient one to yield a single product **2** in excellent yields. On the other hand, the desirable product **3** could be improved to 79% yield when 2.0 equivalents of $PhI(OAc)_2$ were employed.[26]

Sometimes silver and its salts play a vital role to activate a catalytic organic reaction. An example is described where silver acetate is promoting to activate palladium catalyst for the arylation of biaryl amines. In this case, silver acetate reacts effectively when trifluoroacetic (TFA) acid is used.[27]

Room-temperature ionic liquids (RTILs) are liquid at ambient temperature, are normally composed of relatively large organic cations and inorganic or organic anions. Ionic liquids are environmentally benign, nonvolatile and nonflammable; most of them have good solubility in water and are stable in air. Ionic liquids are widely used as new solvent media in heterogeneous catalysis, synthesis, electrochemistry, sensors, battery applications, analysis and separation. Ionic liquids are often used as additives in high performance liquid chromatography (HPLC) for separation of amines. Some amines *viz.* benzidine, benzylamine and *N*-ethylaniline are separated using ionic liquids as additives for the mobile phase in high performance liquid chromatography (HPLC).The ionic liquids, used mainly for separation are 1-ethyl-3-methylimidazolium tetrafluoroborate ([EMIm][BF_4]), 1-butyl-3-methyl-imidazolium tetrafluoroborate ([BMIm][BF_4]) and 1-butyl-3-methyl-imidazolium bromide ([BMIm][Br]).

There might be a pairing ion mechanism when ionic liquids are used as additives in HPLC. The strong H-bonding between the imidazolium cation and its counterion and solutes would play important roles in separation process.[28]

Generally, nitrogen bases are the most common additives in organic synthesis. Amines or nitrogen based additives are generally used as coupling additives. One of the example is the peptide bond formation could be enhanced by adding some nitrogen based compounds. The reactivity of peptide coupling reagents may be enhanced by the addition of additives that may also serve to reduce the extent of racemization. Many additives have a X-OH structure that can form active esters with the carboxylic acid. A number of *N*-based additives and solid supported additives are listed below:

N-hydroxysuccinimide (HOSu), *N*-hydroxy-5-norbornene-2,3-dicarboximide (HONB), 1-hydroxybenzotriazole (HOBt), 6-chloro-1-hydroxybenzotriazole (6-Cl-HOBt), 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HODhbt) and polymer-supported additives (Figure 5).[29]
The active species in solution is the 1-hydroxybenzotriazole ester that undergoes aminolysis at a rate about 10 -fold faster than the ester formed from normal condition (Scheme 3).
Stereoselective synthesis may also be carried out in presence of additives. For example, *N*-(2-(1H-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (4) was treated with 2-bromoaniline (5) under the optimized reaction conditions resulting in the formation of the desired product (6) in poor yield. With the screening of several additives such as Lewis acids and amino acids, the yield of (6) was increased significantly when 20 mol% of L-proline was used as the additive, and interestingly, only a single diastereoisomer was produced (Scheme 4).[30]

An interesting example is cited where water is used as additive rather than solvent. Bulk amount of atropisomeric drug substance is prepared via Buchwald-Hartwig amination,[31] and Bruylants,[32] reactions. *Chemokines* are critical mediators of cell migration during routine immune surveillance, inflammation, and development. *Chemokines* bind to G protein–coupled receptors and cause conformational changes that trigger intracellular signaling pathways involved in cell movement and activation. Inappropriate regulation of proteins is the reasons of many diseases. Specific *chemokine* receptors offer the entrance for HIV to get into cells, and others contribute to inflammatory diseases and cancer. Thus, there is significant interest in developing receptor antagonists.[33] A practical, chromatography-free synthesis for a *chemokine* receptor antagonist NIBR-1282 (7) is described. In one of the step Buchwald-Hartwig amination reaction is performed using $(t\text{-Bu})_3P$ as the ligand and 5-12 mol% of water as an additive affording 8 with yield increase of more than two-fold (step b).[34]

4. Adverse Effects of additives:

The adverse effects of additives towards human body are concerned. The additives in plastics to which most people are exposed, such as phthalates, *bis*-phenol A or polybrominated diphenyl ethers, may cause harm to human health by altering endocrine function or through other biological mechanisms. There is a great need for more human studies of adverse health effects associated with plastic additives. Exposure to plastic additives and other endocrine-disrupting compounds (EDCs) may cause altered endocrine activity and reproductive development through a number of biological mechanisms, which can target different levels of the hypothalamic– pituitary–gonad/thyroid axis, ranging from effects on hormone receptors to effects on hormone synthesis, secretion or metabolism and also harmful during and after pregnancy.[35]

5. Conclusion:

It is evident from the above discussion that additives do have profound role in various fields including different chemical reactions and biological phenomena. Although there is specific rationale not known for such action, a few possible physicochemical aspects seem to be active in exhibiting their functions. The present article covering involvement of various additives would represent a picture and also help in the design and exploration of novel aspects of additives.

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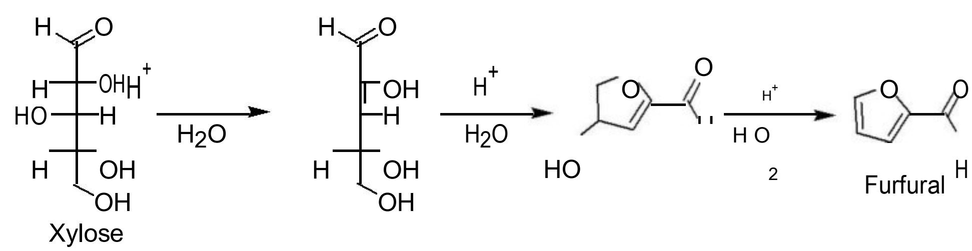
Scheme 1. Xylose dehydration mechanism via β-elimination



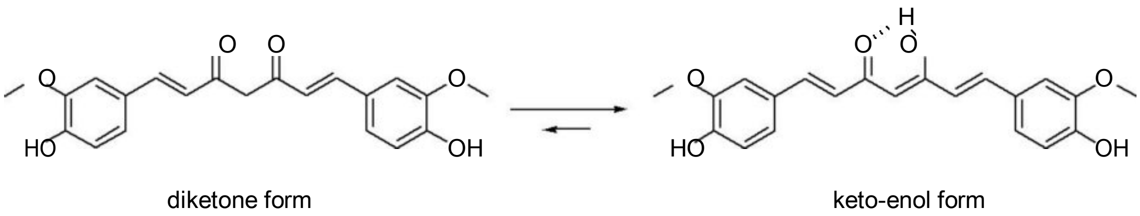


Figure 2. The keto-enol tautomerism of curcumin.

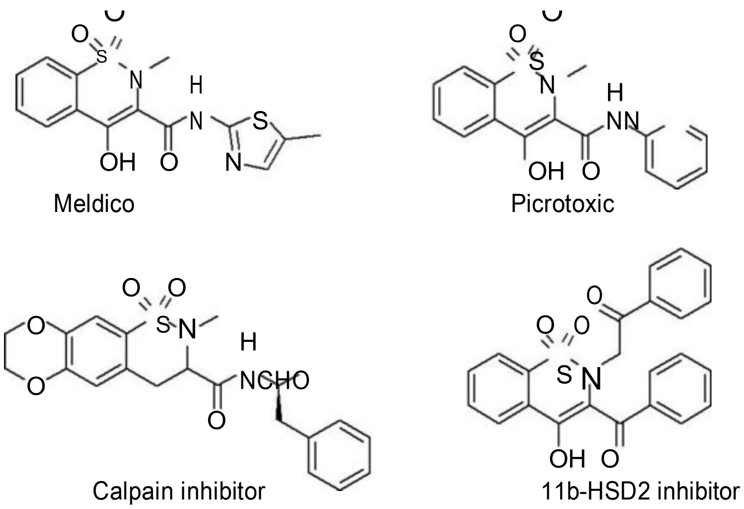


Figure 3. Structures of biologically active benzosultams.

Scheme 2. Preparation of Benzosultams.

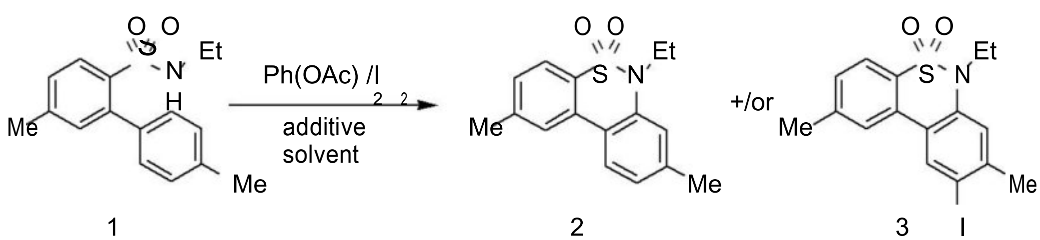
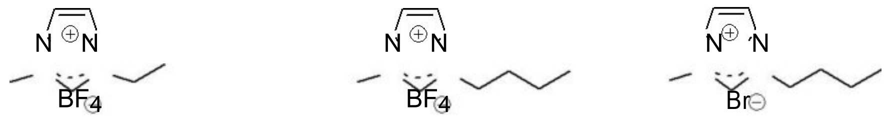
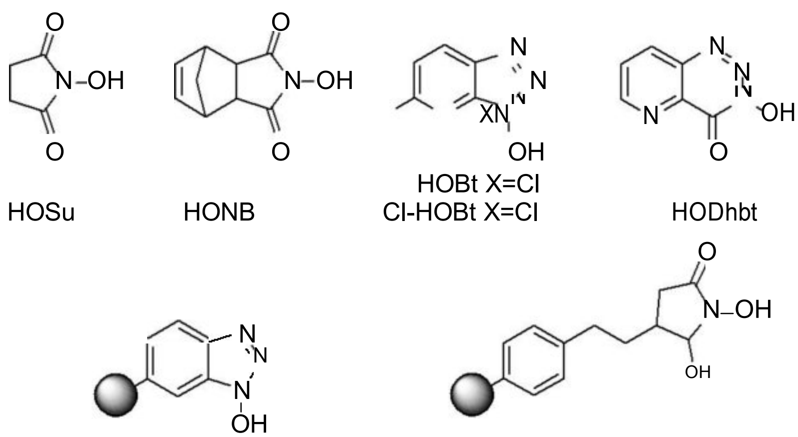


Figure 4. Structure of some RTILs.



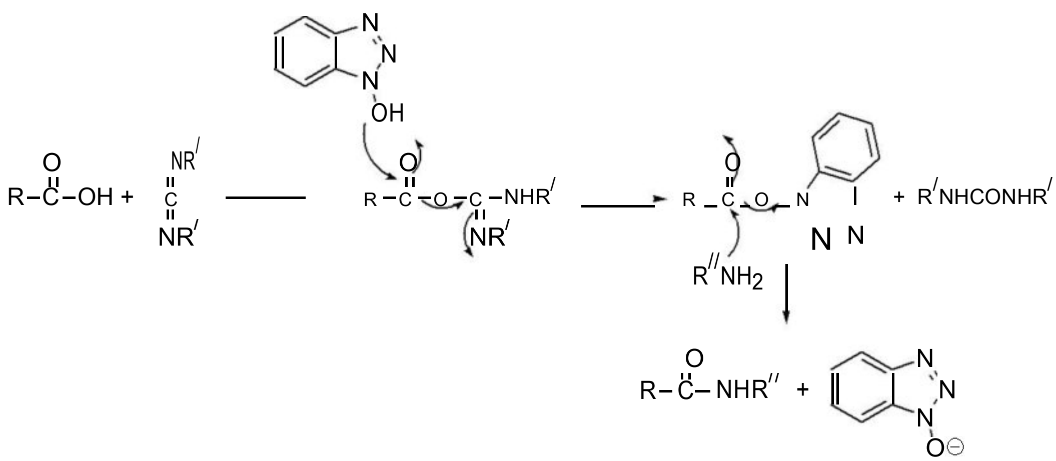
1-ethyl-3-methylimidazolium tetrafluoroborate | 1-butyl-3-methylimidazolium tetrafluoroborate | 1-butyl-3-methylimidazolium bromide

Figure 5. Structures of some N-based additives.



Polymer-supported additives

Scheme 3. Synthesis of amide bond using HOBt additive.



Scheme 4. Construction of N-C3 Linked Pyrrolidinoindolines.

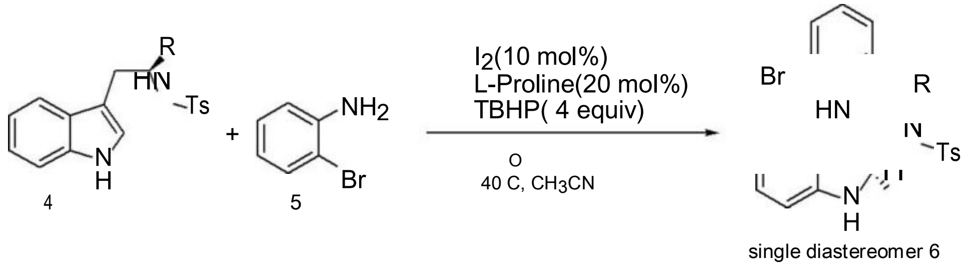
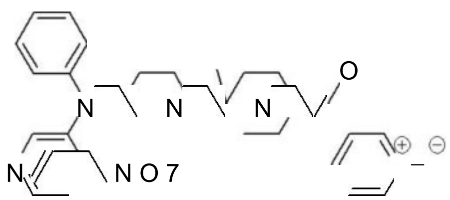
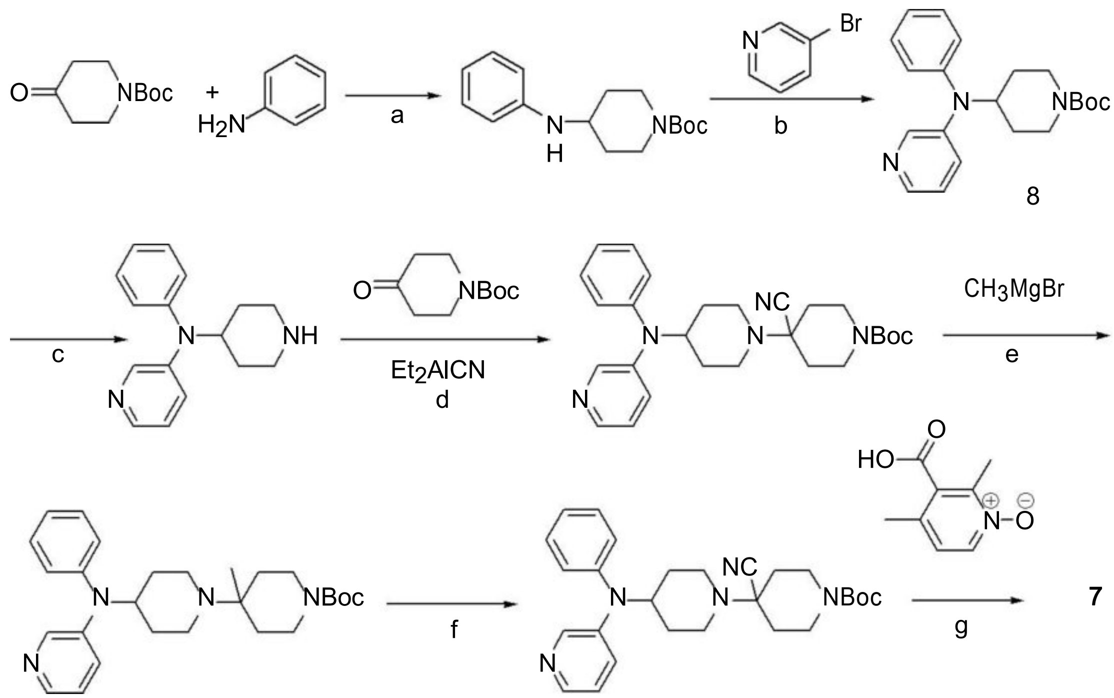


Figure 6. *Chemokine* receptor antagonist NIBR-1282.



Scheme 5. Initial Research Synthesis of 7.



Reagents and conditions: (a) $Na(OAc)_3BH$, AcOH, CH_2Cl_2; (b) $Pd(OAc)_2$ (3 mol%), xantphos (4.5 mol%), NaO*t*-Bu (4 equiv), H_2O (5-12 mol%), toluene; (c) TFA, CH_2Cl_2, water; (d)$Ti(O\textit{i}Pr)_4$, CH_2Cl_2, then Et_2AlCN (2 equiv); (e) ether, THF; (f) TFA, CH_2Cl_2, water, quantitative; (g) HBTU, $EtN(\textit{i}\text{-}Pr)_2$, DMF.

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Basudeb Basu did his Ph.D. work from Indian Association for the Cultivation of Science, Kolkata, working on the synthesis of fused and bridged carbocyclic frameworks related to natural products. He joined North Bengal University as Assistant Professor in 1986. He did his post-doctoral works with Prof. R. G. Salomon at Case Western Reserve University, Ohio, USA (1987-'89) on the total synthesis of optically active marine natural products, and with Prof. T. Frejd at Lund University, Sweden (1994-'96), on the asymmetric synthesis of non-natural amino acids. He has been working as Professor of Chemistry in North Bengal University since 2004. He has been Visiting Professor in Sweden, Denmark, France, Taiwan and China. His current research interests include new reactions and methodology, new heterogeneous nanocatalysts and green.

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