CHAPTER – 1

Microwave Assisted Organic Synthesis

1. Microwave Assisted Organic Synthesis:

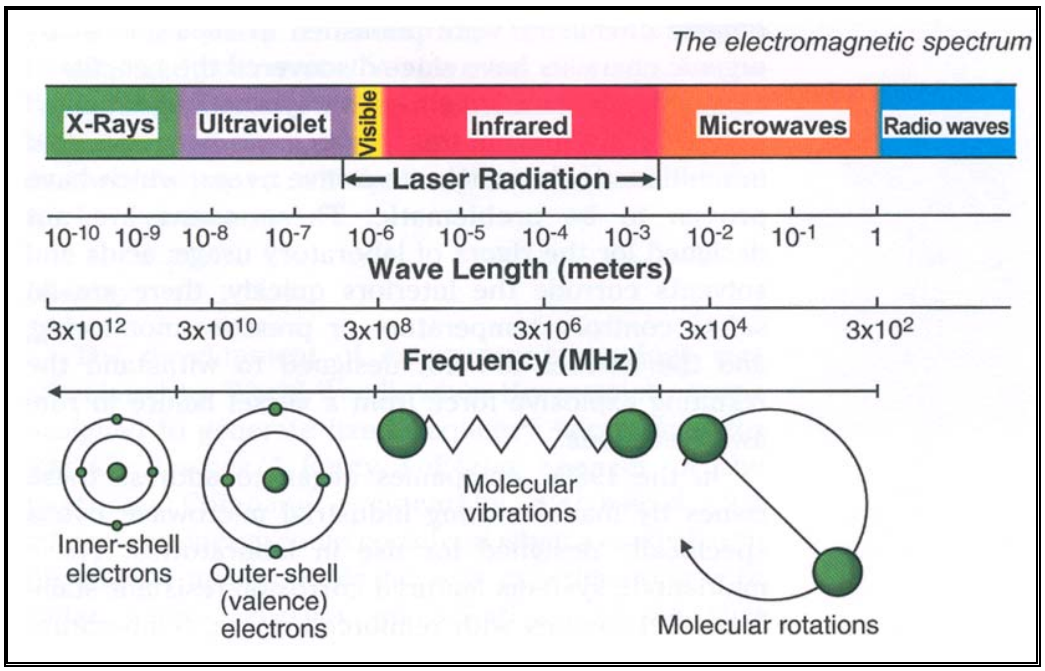
1.1 Introduction

Synthesis of new chemical entities is major bottleneck in drug discovery. Conventional methods for various chemical synthesis is very well documented and practiced.[1] The methods for synthesis (Heating process) of organic compounds has continuously modified from the decade. In 1855, Robert Bunsen invented the burner which acts as energy source for heating a reaction vessel, this was latter superseded by isomental, oil bath or hot plate, but the drawback of heating, though method remain the same. Microwave Assisted Organic Synthesis (MAOS), which has developed in recent years, has been considered superior to traditional heating.

Microwave assisted organic synthesis[2] (MAOS) has emerged as a new "lead" in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product. Now day's technique is considered as an important approach toward green chemistry, because this technique is more environmentally friendly. This technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Conventional method of organic synthesis usually need longer heating time, tedious apparatus setup, which result in higher cost of process and the excessive use of solvents/ reagents lead to environmental pollution. This growth of green chemistry holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve many organic syntheses.

1.2 Microwave frequency

Microwave heating refers the use of electromagnetic waves ranges from 0.01m to 1m wave length of certain frequency to generate heat in the material. These microwaves lie in the region of the electromagnetic spectrum between millimeter wave and radio wave i.e. between I.R and radio wave. They are defined as those waves with wavelengths between 0.01metre to 1meter, corresponding to frequency of 30GHz to 0.3GHz.



1.3 Principle

The basic principle behind the heating in microwave oven is due to the interaction of charged particle of the reaction material with electro magnetic wavelength of particular frequency. The phenomena of producing heat by electromagnetic irradiation are ether by collision or by conduction, some time by both.

All the wave energy changes its polarity from positive to negative with each cycle of the wave. This cause rapid orientation and reorientation of molecule, which cause heating by collision. If the charge particles of material are free to travel through the material (e.g. Electron in a sample of carbon), a current will induce which will travel in phase with the field. If charge particle are bound within regions of the material, the electric field component will cause them to move until opposing force balancing the electric force.[3-9]

1.4 Heating Mechanism

In microwave oven, material may be heated with use of high frequency electromagnetic waves. The heating arises from the interaction of electric field component of the wave with charge particle in the material. Two basic principal mechanisms involve in the heating of material

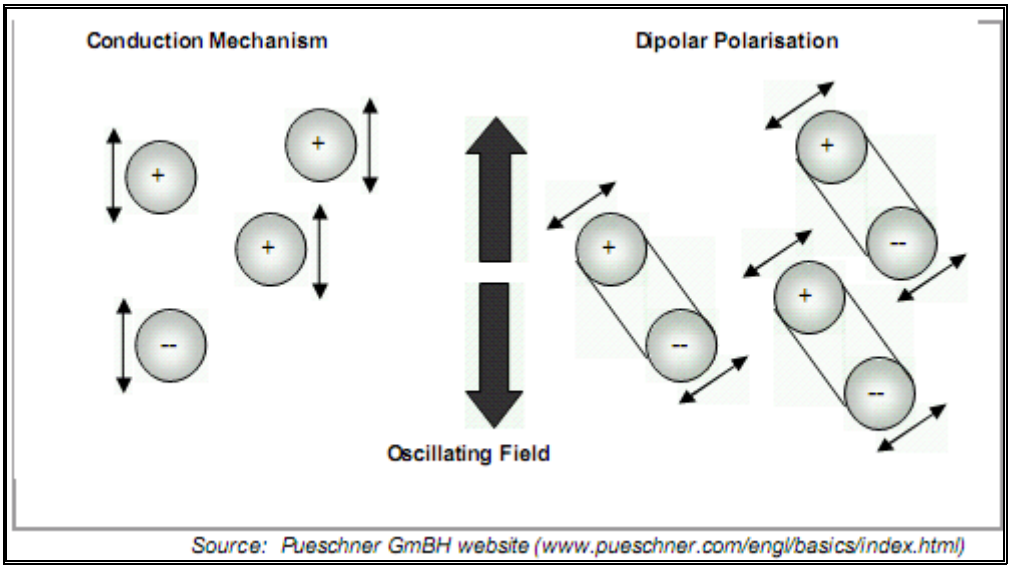
1.4.1 Dipolar Polarisation

Dipolar polarisation is a process by which heat is generated in polar molecules. On exposure to an oscillating electromagnetic field of appropriate frequency, polar molecules try to follow the field and align themselves in phase with the field. However, owing to inter-molecular forces, polar molecules experience inertia and are unable to follow the field. This results in the random motion of particles, and this random interaction generates heat. Dipolar polarisation can generate heat by either one or both the following mechanisms:

1. Interaction between polar solvent molecules such as water, methanol and ethanol
2. Interaction between polar solute molecules such as ammonia and formic acid

The key requirement for dipolar polarisation is that the frequency range of the oscillating field should be appropriate to enable adequate inter -particle interaction. If the frequency range is very high, inter-molecular forces will stop the motion of a polar molecule before it tries to follow the field, resulting in inadequate inter-particle interaction. On the other hand, if the frequency range is low, the polar molecule gets sufficient time to align itself in phase with the field. Hence, no random interaction takes place between the adjoining particles. Microwave radiation has the appropriate frequency (0.3-30 GHz) to oscillate polar particles and enable enough inter-particle interaction. This makes it an ideal choice for heating polar solutions.

In addition, the energy in a microwave photon (0.037 kcal/mol) is very low, relative to the typical energy required to break a molecular bond (80-120 kcal/mol). Therefore, microwave excitation of molecules does not affect the structure of an organic molecule, and the interaction is purely kinetic.



Source: Pueschner GmBH website (www.pueschner.com/engl/basics/index.html)

1.4.1. a Interfacial Polarization

Interfacial polarization is an effect, which is very difficult to treat in a simple manner, and easily viewed as combination of the conduction and dipolar polarization effects. This mechanism is important for system where a dielectric material is not homogenous, but consists of conducting inclusion of one dielectric in other.

1.4.2. Conduction mechanism

The conduction mechanism generates heat through resistance to an electric current. The oscillating electromagnetic field generates an oscillation of electrons or ions in a conductor, resulting in an electric current. This current faces internal resistance, which heats the conductor.

The main limitation of this method is that it is not applicable for materials that have high conductivity, since such materials reflect most of the energy that falls on them.

1.5. Effects of solvents

Every solvent and reagent will absorb microwave energy differently. They each have a different degree of polarity within the molecule, and therefore, will be affected either more or less by the changing microwave field. A solvent that is more polar, for example, will have a stronger dipole to cause more rotational movement in an effort to align with the changing field. A compound that is less polar, however, will not be as disturbed by the changes of the field and, therefore, will not absorb as much microwave energy. Unfortunately, the polarity of the solvent is not the only factor in determining the true absorbance of microwave energy, but it does provide a good frame of reference. Most organic solvents can be broken into three different categories: low, medium, or high absorber, as shown in Figure 6. The low absorbers are generally hydrocarbons while the high absorbers are more polar compounds, such as most alcohols.

Absorbance level	**Solvents**
High	DMSO, EtOH, MeOH, Propanols, Nitobenzen, Formic Acid, Ethylene Glycol
Medium	Water, DMF, NMP, Butanol, Acetonitrile, HMPA, Methy Ethyl Ketone, Acetone, Nitromethane, Dichlorobenzene, 1,2-Dichloroethane, Acetic Acid, trifluoroacetic Acid,
Low	Chloroform, DCM, Carbon tetrachloride, 1,4-Dioxane, Ethy Acetate, Pyridine, Triethyamine, Toluene, Benzene, Chlorobenzene, Pentane, Nexane and other hydrocarbons

1.6 Conventional vs Microwave Heating

Microwave heating is different from conventional heating in many respects. The mechanism behind microwave Synthesis is quite different from conventional synthesis. Points enlisted in Table 1, differ the microwave heating from conventional heating.[10-26]

No	CONVENTIONAL	MICROWAVE
1	Reaction mixture heating proceeds from a surface usually inside surface of reaction vessels	Reaction mixture heating proceeds directly inside mixture
2	The vessel should be in physical contact with surface source that is at a higher temperature source (e.g. mental, oil bath, steam bath etc.)	No need of physical contact of reaction with the higher temperature source. While vessel is kept in microwave cavities.
3	By thermal or electric source heating take place.	By electromagnetic wave heating take place.
4	Heating mechanism involve-conduction	Heating mechanism involve-dielectric polarization and conduction
5	Transfer of energy occur from the wall, surface of vessel, to the mixture and eventually to reacting species	The core mixture is heated directly while surface (vessel wall) is source of loss of heat
6	In conventional heating, the highest temperature (for a open vessels) that can be achieved is limited by boiling point of particular mixture.	In microwave, the temperature of mixture can be raised more than its boiling point i.e. superheating take place
7	In the conventional heating all the compound in mixture are heated equally	In microwave, specific component can be heated specifically.
8	Heating rate is less	Heating rate is several fold high

1.7 Application of microwave in organic synthesis

Following reactions have been performed through microwave heating.

Sr.	Reaction	Ref.	Sr	Reaction	Ref.
1	Acetylation reaction	27	18	Diel's-Alder reaction	44
2	Addition reaction	28	19	Dimerization reaction	45
3	Alkylation reaction	29	20	Elimination reaction	28
4	Alkynes metathesis	30	21	Estrification reaction	46
5	Allylation reaction	31	22	Enantioselective reaction	47
6	Amination reaction	32	23	Halogenation reaction	48
7	Aromatic nucleophillic substitution reaction	33	24	Hydrolysis reaction	59
8	Arylation reaction	34	25	Mannich reaction	50
9	Carbonylation reaction	35	26	Oxidation reaction	51
10	Combinatorial reaction	36	27	Phosphorylation synthesis	52
11	Condensation reaction	37	28	Polymerization reaction	53
12	Coupling reaction	38	29	Rearrangement reaction	54
13	Cyanation reaction	39	30	Reduction reaction	55
14	Cyclization reaction	40	31	Ring closing synthesis	56
15	Cyclo-addition reaction	41	32	Solvent free reaction	57
16	Deacetylation reaction	42	33	Transestrification reaction	46
17	Dehalogenation reaction	43	34	Transformation reaction	58

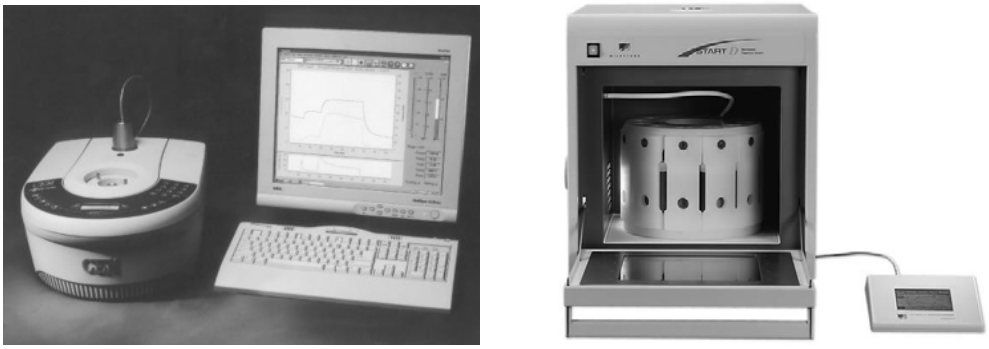


Figure 1.2: General View of Monomode CEM Discover (left) and Multimode MILESTONE Start (right) Systems

1.8 Studies on 2-Aminoimidazoles

Much effort has been dedicated to the study of molecular architecture and its relationship to biological activity. From decades of high throughput screening of both natural and synthetic small molecules we have clued in on structural features that impart a high probability of biological efficacy.[59] Recently natural products have enjoyed a renaissance in lead generation for discovery based research. This realization has further been folded into the concept of Biology-oriented synthesis (BIOS) which relies on the core structures of natural products as valuable pre-validated scaffolds.[60] These so-called "privileged" pharmacophores are often the basis of synthetic collections aimed at increasing the success rate of small molecule screening ventures.

In particular, marine natural products derived from sponges have provided valuable leads for therapeutic small molecules.[61-62] Surprisingly the large majority of these compounds have been isolated from organisms of the class Dermospongiae. In the mid 1980's chemists noted that the other major sponge class, Calcarea, had rarely been subject to chemical investigations. A flurry of efforts through the mid-1990's helped to establish biogenetic relationships among these sponges. Isolated to explore these interconnections and not necessarily for specific biological responses the activities of these natural products have remained largely uncovered. Since these initial investigations, an emerging structural class has recurrently been identified through bioassay guided isolation which contains the 2-aminoimidazole core. From the viewpoint of small molecule discovery this review will highlight alkaloids isolated from Leucetta sp. This small skeletal family has been shown to interrogate an incredibly diverse range of biological processes and thus represents an important discovery scaffold for both medicinal and discovery based research.

In 1958, a nitrogen rich antibiotic, consequently named azomycin, was isolated from a presumptive Streptomyces sp.[63] This new antibiotic displayed good antimicrobial activity against B. subtilis (6 μg/mL) and E. coli (25 μg/mL) and was relatively well tolerated in mice (LD_{50} = 80 mg/kg). Eventually the structure of azomycin was revealed to be 2-nitroimidazole (2)[64], which along with its synthetic derivative metronidiazole (3) have become clinically relevant antiprotozoal therapeutics (Fig. 1.8.1).[65] With the parallel observation that several microbes were able to oxidize

aromatic amines, Lancini's group showed some Streptomyces species are able to oxidize 2-aminoimidazole itself, along with a series of 4-alkyl-2-aminoimidazoles, to their corresponding 2-nitroimidazoles.[66] This suggested that the 2-aminoimidazole might be the direct biosynthetic precursor to azomycin and in 1970 Okami's group isolated the parent heterocycle (1) from Streptomyces eurocidicus.[67] This study also showed that supplementing the growth medium with L-Arg substantially increased the production of 1, suggesting that arginine catabolism is critical to its biosynthesis. It is unknown whether a similar pathway exists in marine organisms that produce more complex 2-aminoimidazoles, however 1 has been discovered in sponges of the family Halicondriidae.[68]

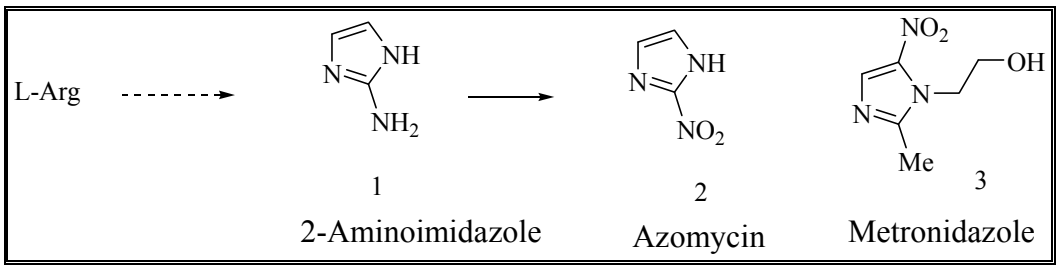
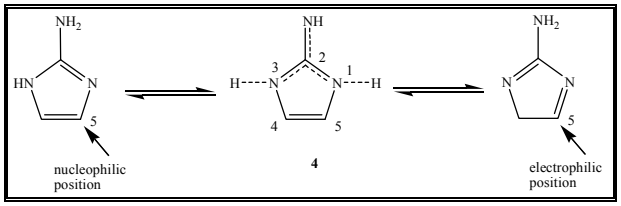


Fig.1.8.1 Biosynthetic transformations of 2-aminoimidazole.

Studies on azomycin's (2) and metronidazole's (3) mechanism of action have revealed that the nitro group is reduced in vivo to the nitroso radical which is responsible for its selective anaerobic antiprotozoal activity.[69] Subsequent studies have shown that hypoxic conditions in tumors are also capable of reducing the 2-nitorimidazole, prompting it to serve as an important prodrug for 2-aminoimidazoles in hypoxic environments.[70-72]

The ambivalent reactivity of the key structural motif 2-amino-1H-imidazole (4) is responsible for the molecular diversity observed in this group of alkaloids. The electrophilic or nucleophilic reactivity at the same position C-4(5) is dependent on the tautomeric isomer involved (Scheme 1.8.1).[73]



Scheme-1.8.1 The Tautomerism and Ambivalent Reactivity of 2-Aminoimidazole

It is understood that the 2-aminoimidazole occupies an important region of chemical space as its hydrogen bond donor-acceptor pattern is capable of recreating that of the guanidine.[74] More importantly, it occupies a unique pKa range between the more acidic 2-aminopyridinium ion[75] and less acidic guanidinium ion[76] (Fig.1.8.2). Furthermore, the pKa's of 2-aminoimidazolium ions show a predictable trend with substitution, allowing it to be finely tuned for medicinal applications as illustrated in the examples below.[77]

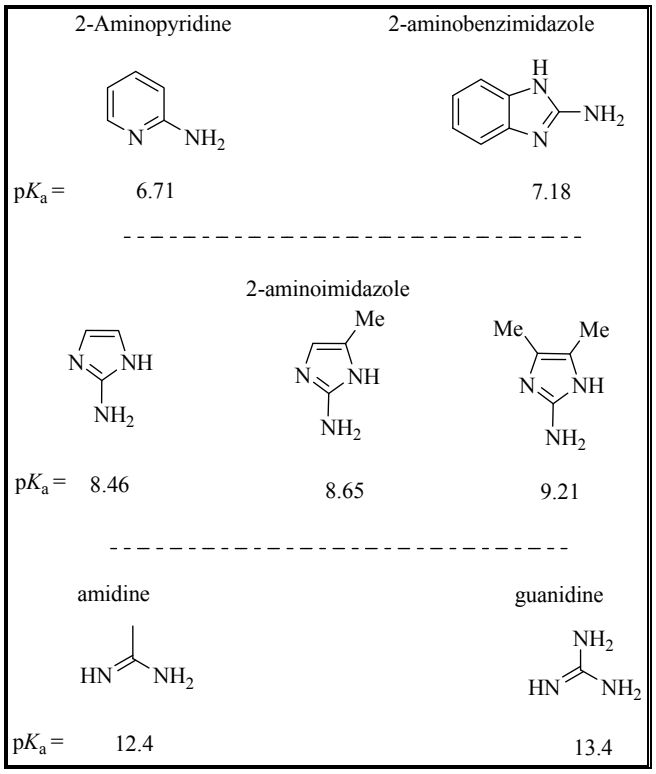


Fig.1.8.2 pKa's of common guanidine mimetics

This dramatic difference in the pKa of 2-aminoimidazoles (~4 pKa units) with that of guanidine has led to some debate concerning the ability of the 2-aminoimidazole to directly mimic a guanidine. These arguments, based on a lowered pKa and electronic dissimilarity are, however, precisely what makes the 2-aminoimidazole a unique guanidine mimic for medicinal chemistry.-[77-78] Most importantly, their pKa range (pKa ~7-9) allows a significant fraction of compound to be uncharged at physiological pH thus increasing the likelihood of cellular penetration. It also permits this unique heterocycle to cross the blood brain barrier and may decrease the susceptibility of these compounds to Pgp mediated efflux vide infra.[79]

1.9 2-Aminoimidazole Alkaloids

The 2-aminoimidazole framework is emerging as an important pharmacophore,[80] and is widely found in numerous biologically active marine alkaloids. Over the last 25 years, several hundreds of diverse 1-unsubstituted and 1-substituted 2-aminoimidazoles have been characterized. 1-Unsubstituted 2-aminoimidazole alkaloids (Fig. 1.9.1) have been isolated essentially from various species of marine sponges (Phylum Porifera) of Caribbean and South Atlantic regions.[81] Oroidin (**1**) and the dimeric sceptrin (**3**) are the most abundant members of the pyrrole-imidazole family.

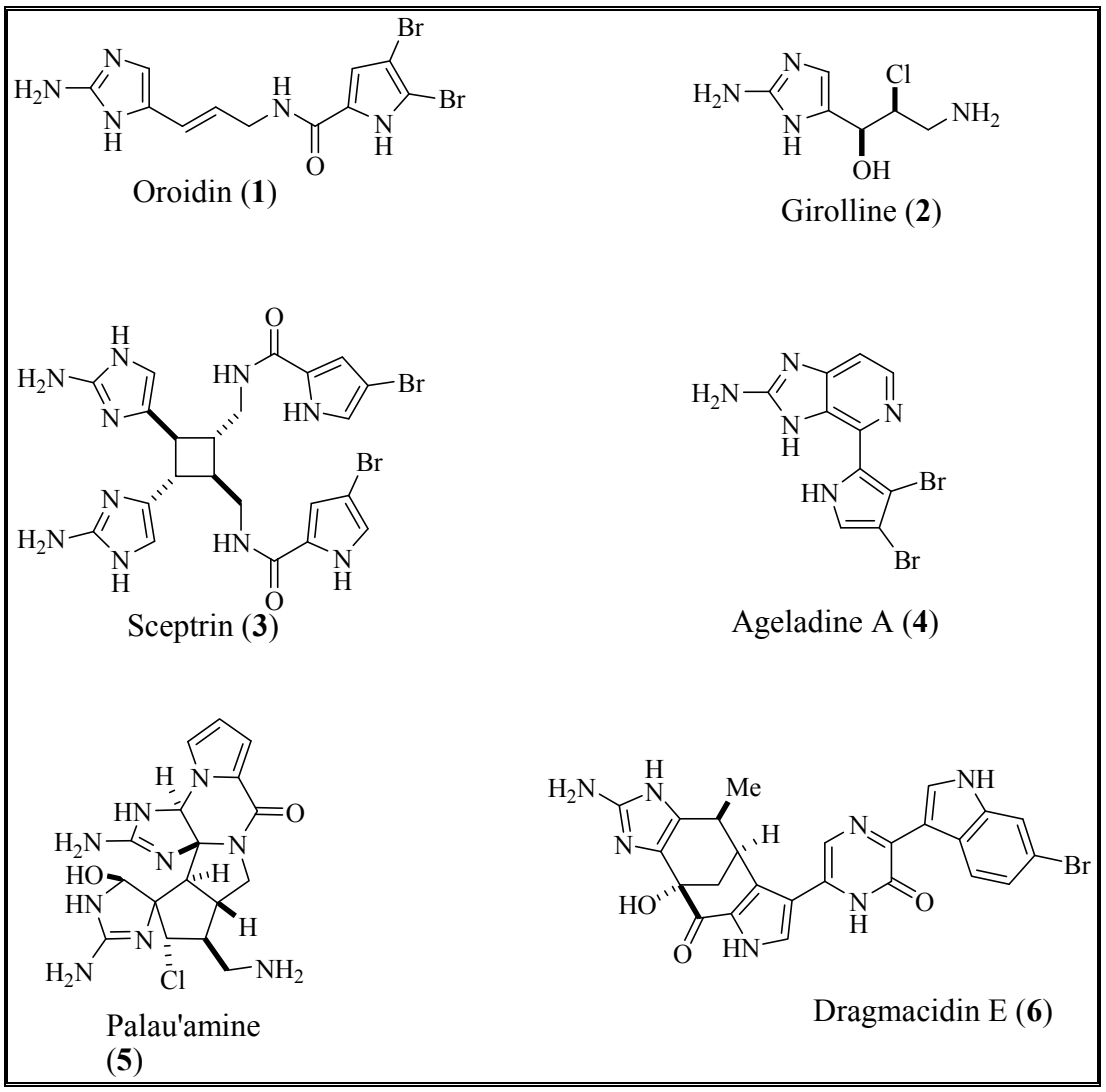


Fig.1.9.1 Some representative 1-unsubstituted 2-aminoimidazoles from marine sponges.

In turn, most of the 1-substituted 2-aminoimidazole alkaloids (Figure 1.9.2) have been isolated from the Calcarea group of the genera Leucetta and Clathrina from the Red Sea and the Indo-Pacific regions.[82]

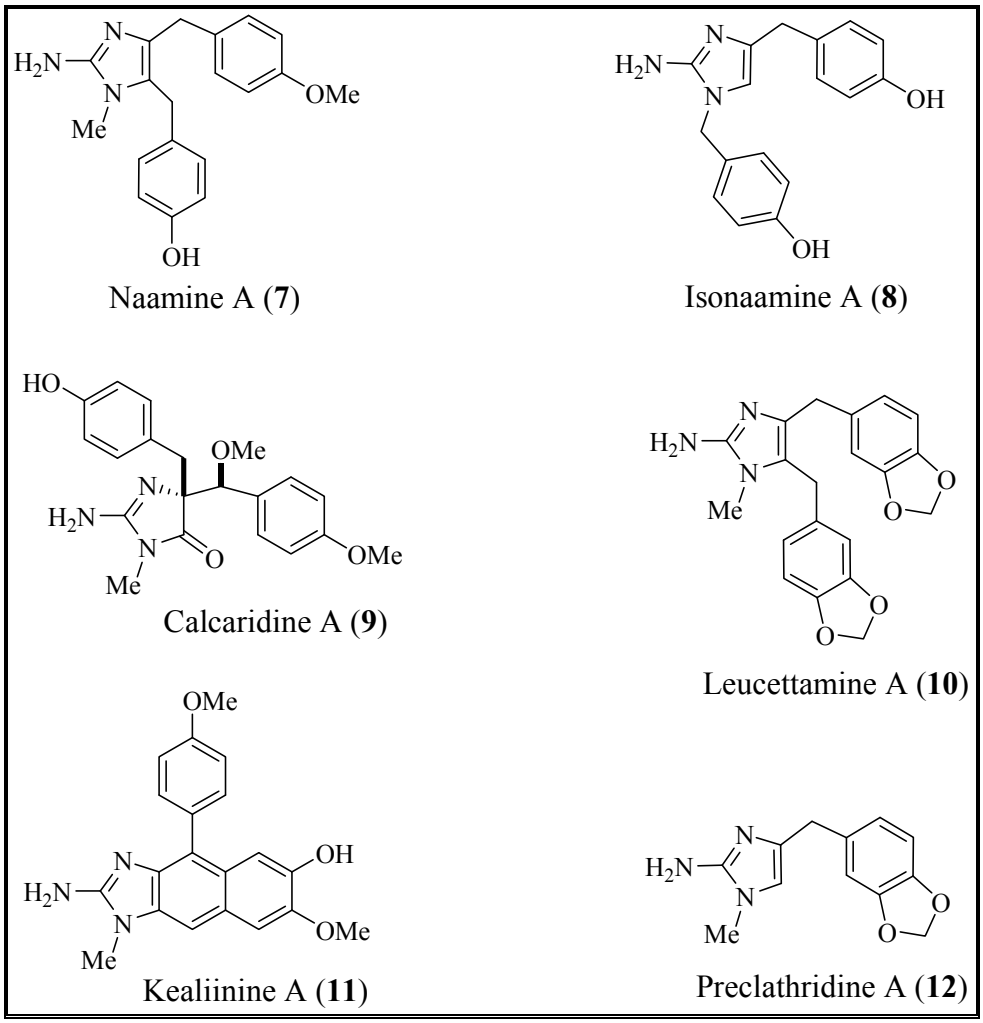
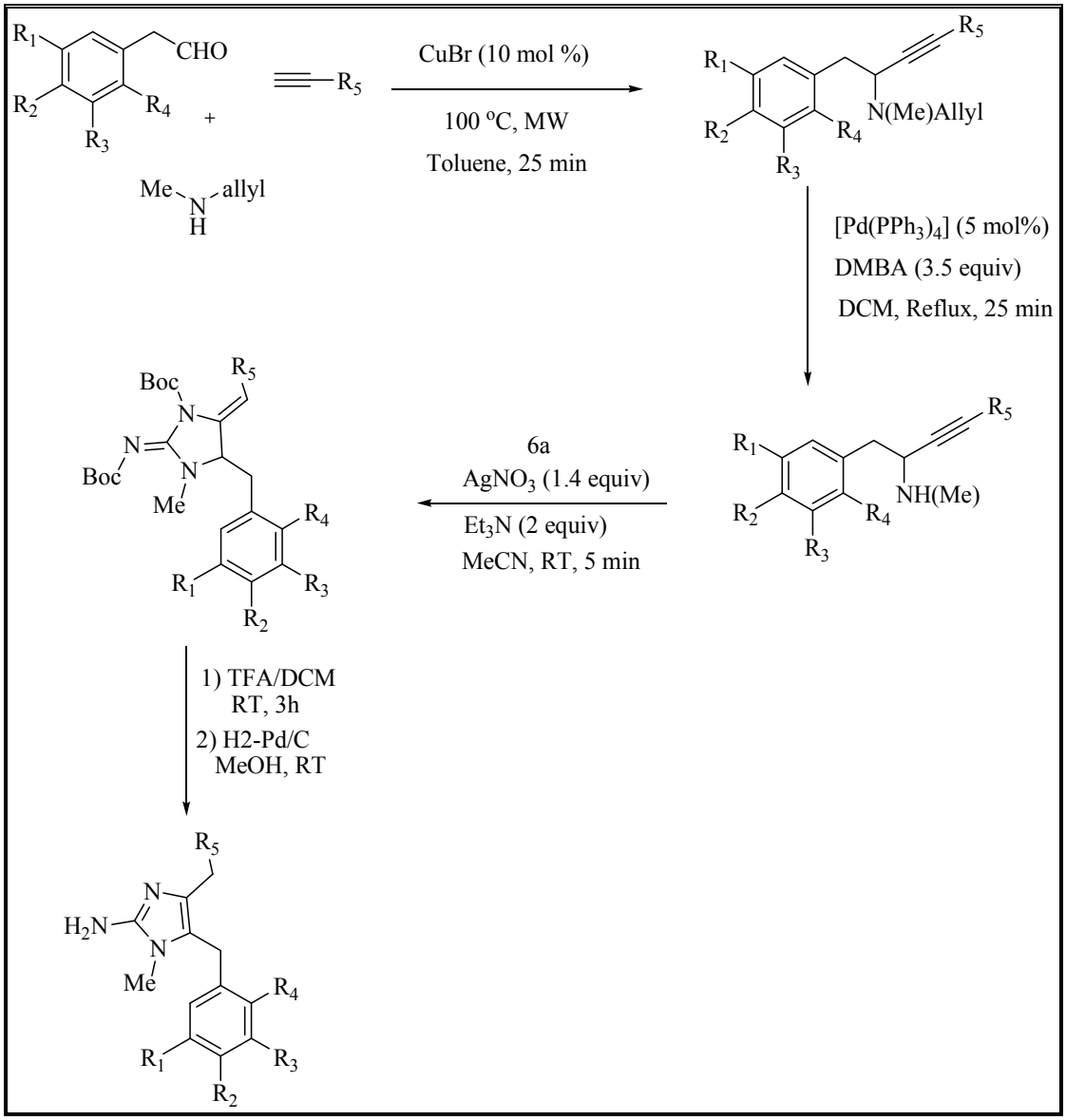


Fig.1.9.2 Some representative 1-substituted 2-aminoimidazoles from marine sponges.

Both classes of 1-substituted and 1-unsubstituted 2-aminoimidazoles possess interesting biological properties. Due to their high cytotoxicity many polysubstituted 2-aminoimidazole alkaloids are involved in chemical defense of marine sponges against predators, in the prevention of the settlement of fouling and pathogenic microorganisms or in the suppression of epibiotic bacteria and spatial competition.

Recently group of Erik[83] described a novel, short and efficient synthesis of diverse 2-aminoimidazoles from readily available polysubstituted secondary propargylamines and thioureas (Scheme-1.9.1). Both the guanylation and the cyclization steps can be carried out either in a stepwise manner with a carbodiimide activator and an AgI catalyst or in a one-pot process with a recoverable AgI salt as a promoter and catalyst. This protocol was successfully applied to the total synthesis of all trisubstituted 2-aminoimidazole naamine alkaloids. Furthermore, we demonstrated the potential of polysubstituted 2-aminoimidazoles as inhibitors of bacterial biofilm formation.



Scheme 1.9.1 Short total synthesis of alkaloid of the naamine family

Pierre Potier proposed biogenetic scheme, various hypothetical constituents can be predicted. It is clear that the above chemical pathway suggests that these compounds may be more widespread than presently known. The isolation and characterisation of new pyrrole-imidazole metabolites will certainly allow us to explore additional transformations which could support this hypothesis. As chemical diversity, enzymatic catalysis variation and mutagenesis are closely related, the ‘‘prebiotic chemistry’’ presented here can also provide strong evidence for a multifunctional enzyme-mediated biosynthesis. Such multiprotein systems would be particularly needed by the living fixed sponges for their adaptation to environmental influences, and for self-defence.

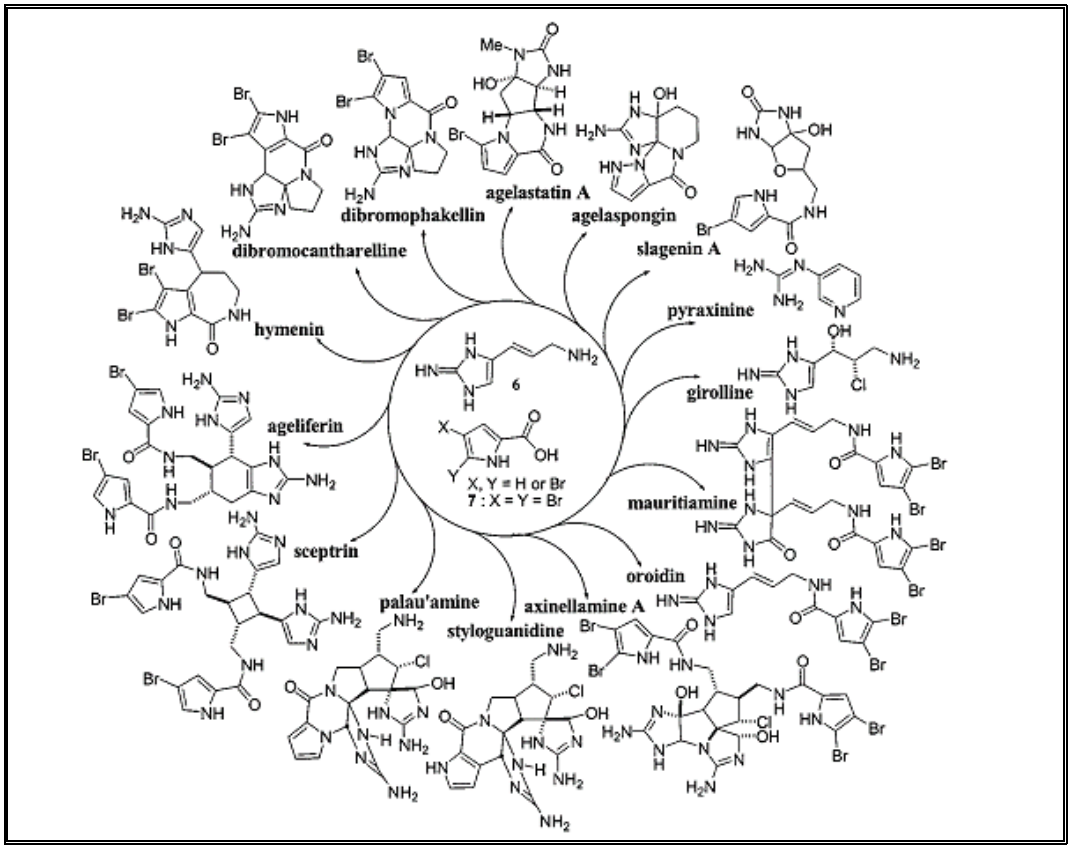


Fig.1.9.3 Arrangement of all known oroidin alkaloids in structural groups.

1.10 Methods for the preparation of 2-aminoimidazoles

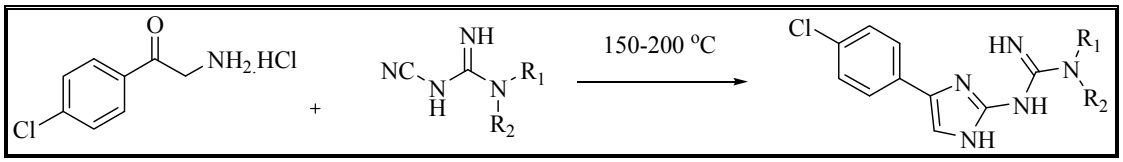
Several methods for the formation of 2-aminoimidazoles are known with widely differing degrees of synthetic utility, but no current method as of yet has a broad range of applicability in complex molecule synthesis. Harsh reaction conditions and/or synthetically difficult and labile precursors are often required for such task.
The methods to prepare 2-aminoimidizoles may be categorized into four main classes:

1) Condensation reactions,
2) Ambivalent addition of 2-aminoimidazole,
3) Direct formation of C-N bond.
4) Heterocyclic exchange reactions.

Functionalized 2-aminoimidazoles can show a wide range of stability issues, the free base of many substrates is susceptible to nucleophilic or base mediated degredation. This instability has thus far precluded a unified strategy to access this heterocycle, but the variety of methods can often lead to success in a complex molecule setting.

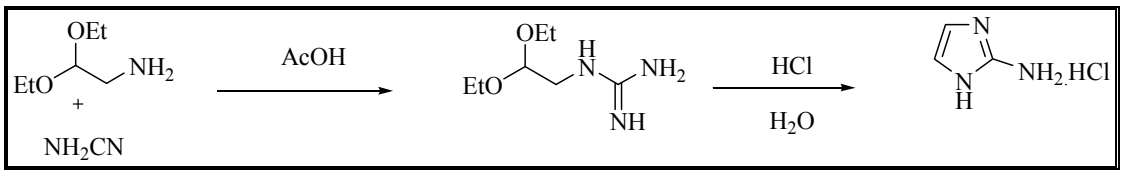
1.10.1 Condensations

By far the most common way to prepare the 2-aminoimidazoles originates with the condensation of α-amino or α -haloketone with cyanamide or a guanidine derivative, respectively. This strategy was first disclosed by Norris and McKee who explored the condensation of α -aminoacetophenones with *N*-cyanoguanidines (scheme-1.10.1).[84]



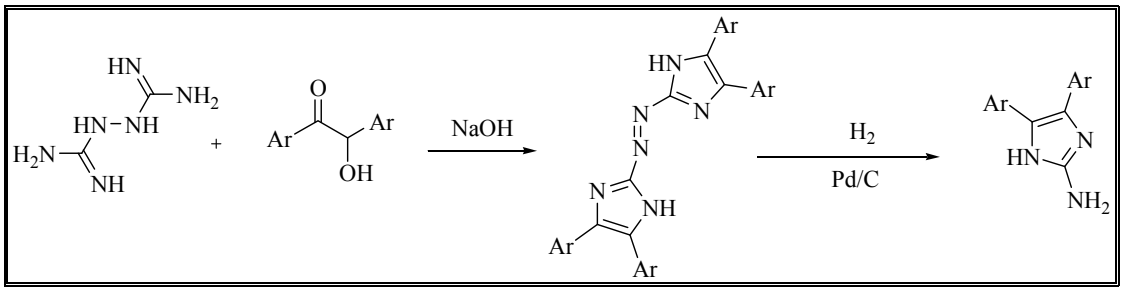
Scheme-1.10.1 Norris and McKee's condensation.

Subsequently Lawson was able to show that aminoacetaldehyde diethylacetal can undergo acid catalyzed addition to cyanamide giving the masked guanidine acetaldehyde (Scheme-1.10.2).[85]



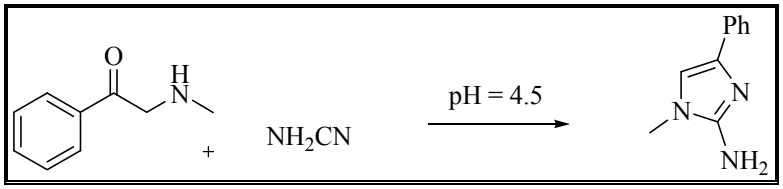
Scheme-1.10.2 Lawson's synthesis.

Kruetzberger found that condensation of 1,2-hydrazinedicarboxamidine with benzoin derivatives in alkali media will yield symmetrically substituted azoimidazoles after spontaneous oxidation of the bis-imidazolhydrazine (Scheme-1.10.3).[86] Reductive cleavage of the azo group by hydrogenolysis gives two mole equivalents of the 2-aminoimidazole. This methodology is useful but limited to the preparation of 4,5-diaryl substituted 2-aminoimidazoles.

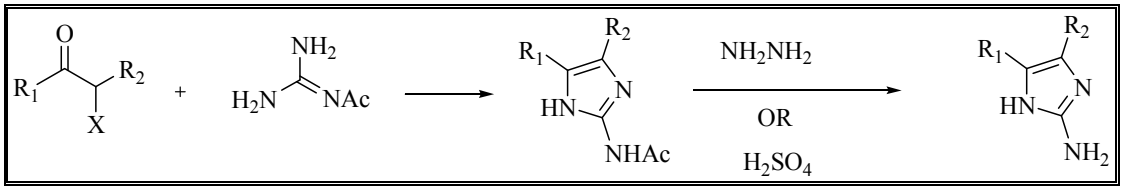


Scheme-1.10.3 Kruetzberger's condensation.

In 1966, Lancini and Lazzari successfully expanded Lawson's strategy to include α -aminoketones, including the use of N-alkylamines (Scheme-1.10.4).[87-88] They were the first to observe the strict pH dependence of this condensation. At very low pH the cyanamide is quickly converted to urea. At high pH, dimerization of the aminoketone to the piperazine competes with cyanamide condensation. Having established the optimum pH of the reaction to be ~4.5, these conditions are now routinely adopted. In 1925 Pyman and Burtles had reported the reaction of α-bromoacetone and guanidine to give a mixture of uncharacterizable compounds, leading them to abandon this approach and develop their diazonium coupling described below.[89] Seventy years later, Weber discovered that N-acetylguanidine smoothly undergoes displacement and condensation with α -haloketones and aldehydes.[90]

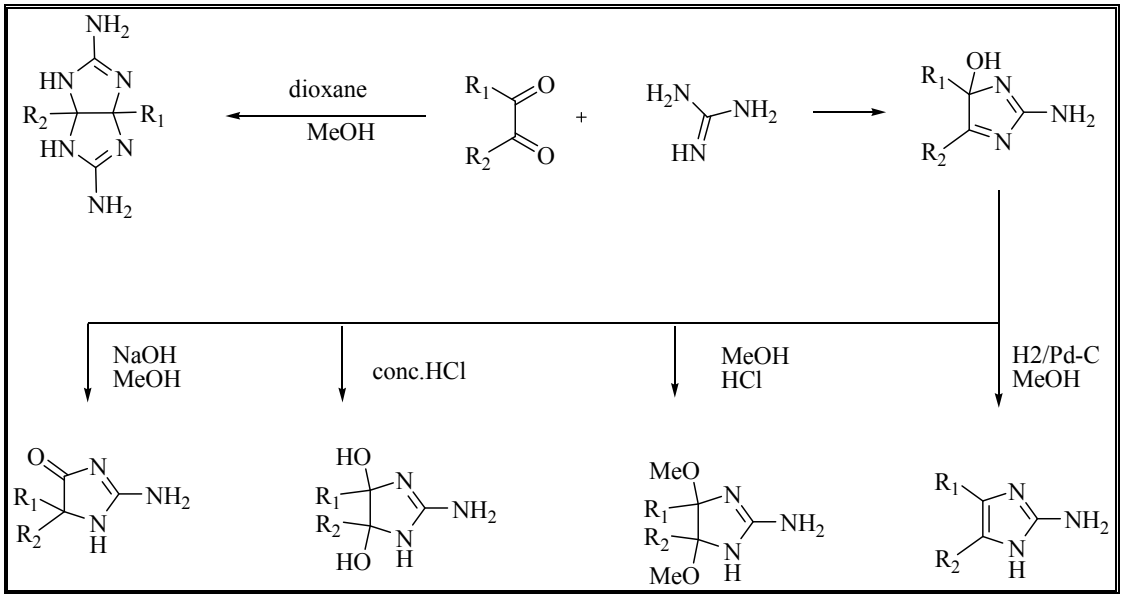


Scheme-1.10.4 Lancini and Lazzari's expanded strategy



Scheme-1.10.5 Weber's condensation with N-acetylguanidine.

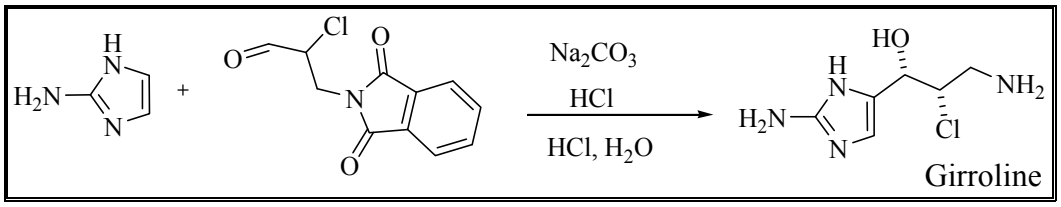
In the late 1970's Nishimura reported the condensation of substituted α-diketones with guanidine to yield a variety of useful products (Scheme-1.10.6).[91] This report illuminates the variety of chemistry that is possible around this heterocyclic core. Treatment of a diketone with guanidine in dioxane and methanol yields the substituted bicyclic bis-guanidine . Alternatively, aprotic reaction conditions can selectively deliver the 2-aminoimidizo-4-ol. This intermediate can undergo a base catalyzed pinacol-type rearrangement to form the 2-aminoimidizo-4-one. This same intermediate can give rise to the 4,5-diol upon exposure to aqueous hydrochloric acid. A similar hydration reaction with anhydrous HCl affords the di-methoxylated derivative. Hydrogenolysis of 2-aminoimidizo-4-ol cleanly gives the 4,5-dialkyl-2-aminoimidazole. These laboratory transformations foreshadow potential biosynthetic relationships between the 2-aminoimidazole natural products isolated from marine sponges.



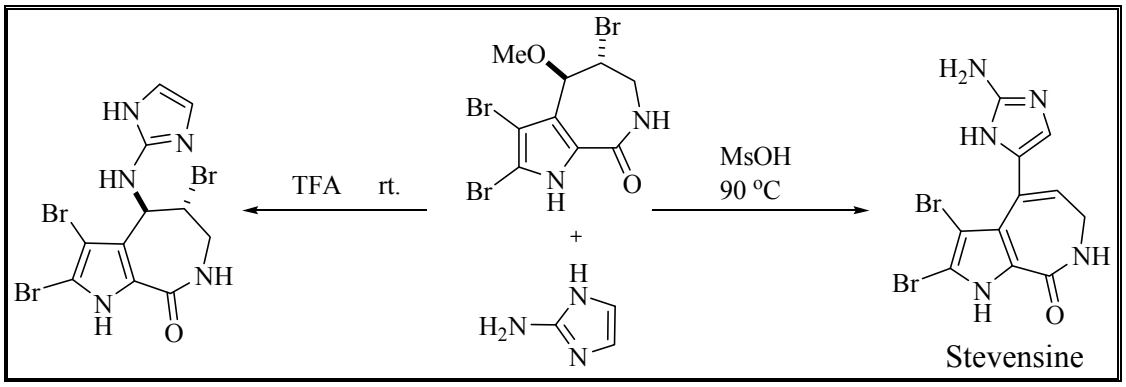
Scheme-1.10.6 Nishimura's diketone condensation

1.10.2 Ambi-valent Addition of 2-Aminoimidazole

Depending on reaction conditions, the parent heterocycle, 2-aminoimidazole, can be influenced to react either at N-2 or C-4. In Potier's synthesis of girolline, 2-aminoimidizole was added directly to the α-chloroaldehyde. Under the influence of sodium carbonate, the imidazole adds preferentially through the 4-position (Scheme-1.10.7).[92] As revealed in Horne's synthesis of stevensine, methanesulfonic acid was used to add the 2-aminoimidazole across an olefin.[93-94] Horne has also shown that Friedel-Crafts type alkylation of the activated ethers can proceed with attack by C-4 in the presence of methanesulfonic acid to give stevensine (Scheme-1.10.7). Alternatively, triflouroacetic acid persuades N-2 addition to give the N-alkylated 2-aminoimidazole.



Scheme-1.10.7 Potier's Ambi-valent additions of 2-aminoimidazole

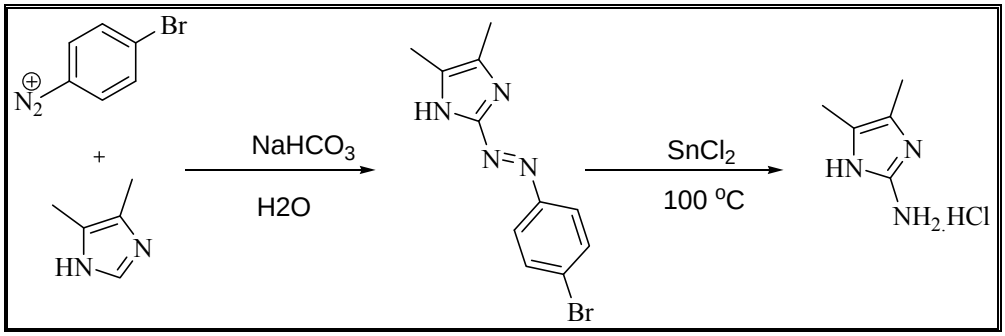


Scheme-1.10.8 Horne's Ambi-valent additions of 2-aminoimidazole.

1.10.3 Formation of C-N bond.

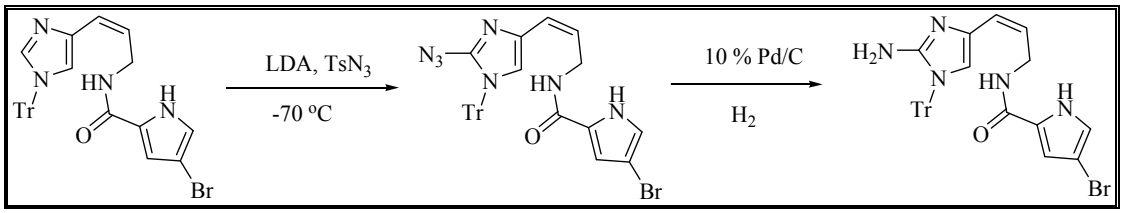
It is now clear that, condensation reactions are applicable to the preparation of mono- and di-substituted 2-aminoimidazoles. To generate more highly substituted 2-amino imidazole cores, the direct introduction of N-2 on an appropriately substituted imidazole is frequently applied. The first method for forming 2-aminoimidazoles, in

this manifold, was reported in 1925 by Burtles and Pyman who showed that azo-bromoaniline and dimethylimidazole underwent aromatic substitution to form the hydrazone (Scheme-1.10.9).The aryl hydrazone was then readily reduced by Zn dust and aqueous acetic acid or stannous chloride and hydrochloric acid.



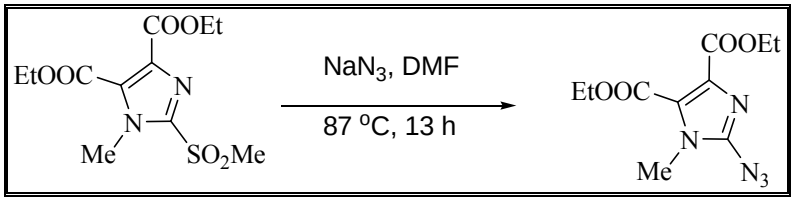
Scheme-1.10.9 Pyman's synthesis.

Hassner was the first to report the reaction of imidazole lithium with a vinyl azide, hydrolysis of the intermediate triazine gives the aminoimidazole.[95] Since that report, Potier has popularized the use of lithiated imidazoles.[96] Potier reported that lithiation with LDA followed by azide transfer from TsN_3 efficiently generated the 2-azidoimidazoles (Scheme-1.10.10). Hydrogenolysis of the azide proceeds smoothly to give the 2-aminoimidazole, exemplified in his synthesis of keramidine.[97]



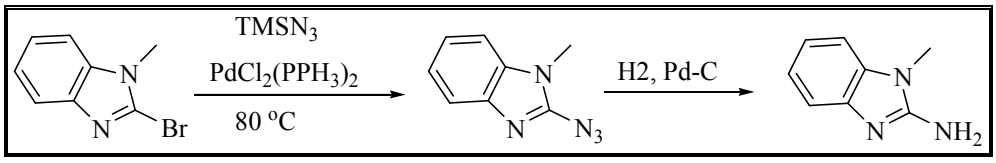
Scheme-1.10.10 Potier's method via lithiation.

Lithiated imidazoles can also be trapped by disulfides to give the 2-thioimidazoles. Oxidation to either the sulfone or sulfoxide creates a leaving group capable of displacement with azide (Scheme-1.10.11).[98] This strategy has been utilized by Weinreb in the synthesis of ageladine A.[99-100]



Scheme-1.10.11 Anderson's method of synthesis.

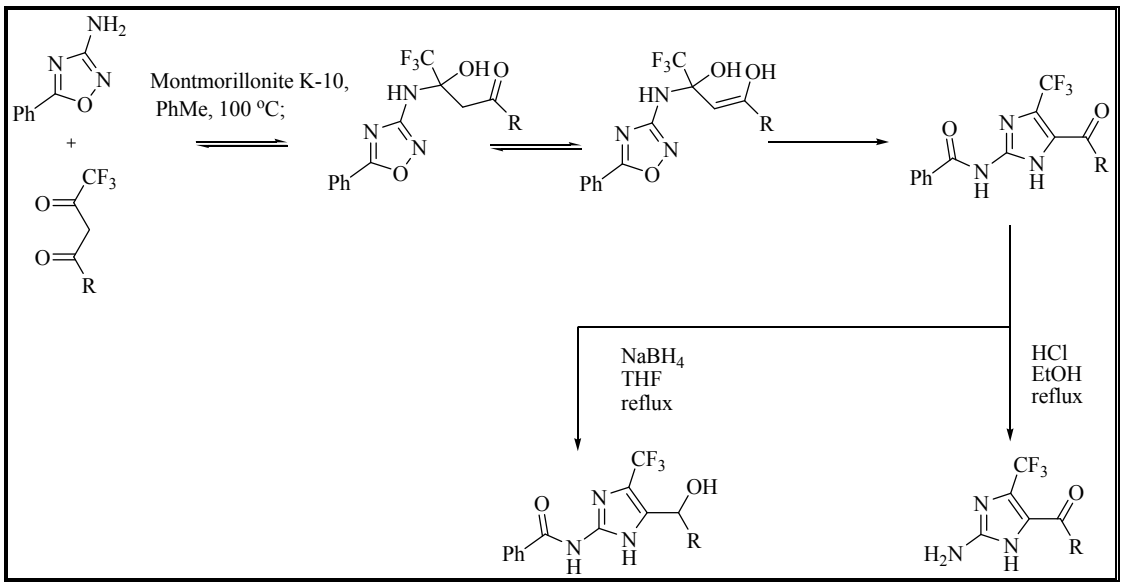
To avoid lithiation, Ohta has shown that 2-bromoimidazoles can undergo palladium catalyzed coupling with trimethylsilylazide (Scheme-1.10.12). Reduction again provides the 2-aminoimidazole. This strategy has been implemented by Ohta's group to access several Leucetta alkaloids discussed below. Also, noteworthy, Ohta has shown that during reduction of the azide it can be directly protected as its benzylidenimine.[101-102]



Scheme-1.10.12 Ohta's palladium catalyzed synthesis.

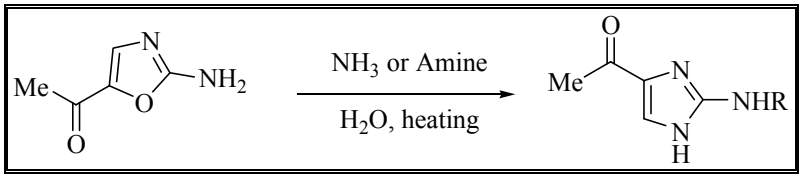
1.10.4 Heterocyclic Exchange Reactions

The transformation of 3-amino-1,2,4-oxadiazoles to 2-aminoimidazoles can be carried out by reaction with fluorinated ß-dicarbonyls to give the ß-hemiaminal (Scheme-1.10.13).[103] This can undergo subsequent conversion to the 2-amidoimidazole through a Boulton-Katritzky Rearrangement. This intermediate can then be reduced to give Intermediate. The benzamide can also be removed via acid catalyzed hydrolysis to give the trifluoromethyl amino-imidazole. An interesting reaction, however the synthesis of the intermediate ß-enaminocarbonyl is low yielding and initial results suggest limited substituent scope, as the initial condensation requires the presence of the trifluoromethyl ketone.



Scheme-1.10.13 Boulton-Katritzky rearrangment of aminooxadiazoles.

Another route to 4(5)-acyl-2-amino-1H-imidazoles is based on the recyclization of 5-acyl-2-amino-1,3-oxazoles (Scheme-1.10.14).[104] For example, 5-acetyl-2-amino-oxazole gave upon heating in water solution with ammonia or aliphatic amines 2-amino-1H-imidazoles in 32% (R = H) and 43-62% (R = alkyl or cycloalkyl) yields.



Scheme-1.10.14 Mularski's recyclization method.

Methodology to prepare 2-aminoimidzoles has greatly advanced due to the rising demand in natural product synthesis and medicinal chemistry. However, the development of methods to succinctly generate a highly functionalized 2-aminoimidazole core from stable precursors is warranted.

1.11 The 2-Aminoimidazole as a Pharmacophore

The 2-aminoimidazole has been utilized as a building block has led to the development of several medicinally relevant small molecules.

1.11.1 Antibiotics Activity

Researchers at Zeneca delivered a series of broad spectrum antibiotics a-c, inspired by the well studied cephalosporins.[106-106] They were further able to show that substitution on N1 of the aminoimidazole led to inactive compounds, again suggesting that this motif may make an acid hydrogen bond contact (Fig. 1.11.1). Interestingly they were able to correlate the pKa of the 2-aminoimidazole with activity. Against Gram positive organisms they found that a slight elevation in the pKa led to a dramatic decrease in activity. For Gram-negative bacteria, there was little difference, suggesting pKa may alter the membrane permeability.

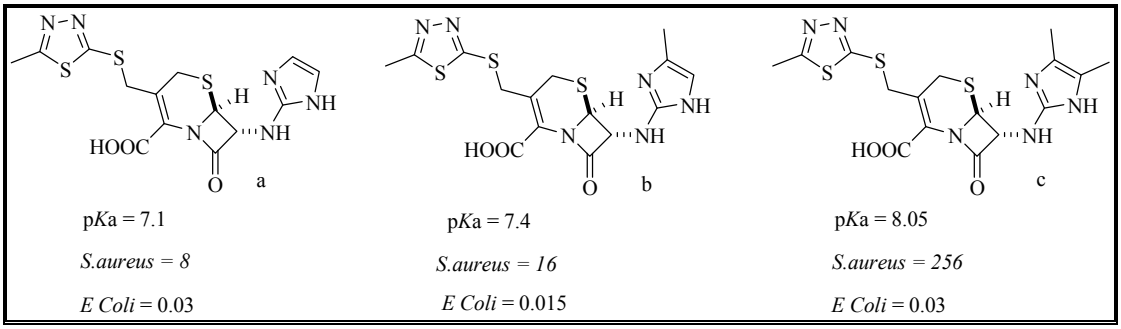


Fig-1.11.1 2-aminoimidazole modified cephalosporins.

1.11.2 Sodium Hydrogen Exchanger-1 (NHE-1) Antagonists.

Scientists at Bristol-Meyers Squibb have noted the ability of the 2-aminoimidazole to function as a bioisostere of acylguanidines.[106] Looking to produce novel inhibitors of the sodium hydrogen exchanger-1 (NHE-1) they aimed at replacing the acylguanidine in their lead compounds (Fig. 1.11.2). They surveyed a number of heterocyclic analogues that would conserve the pKa of the acylguanidine as a cationic species, necessary for antagonism of the Na+ transporter.

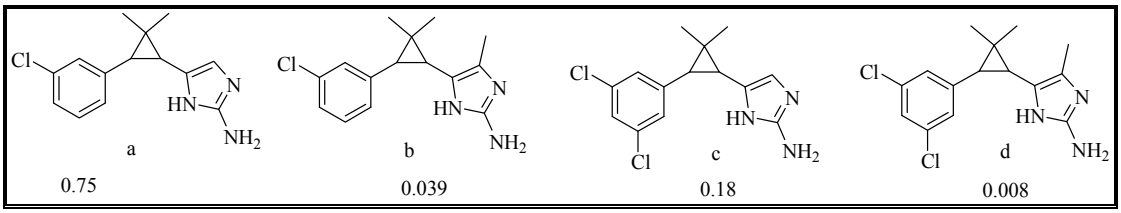


Fig.- 1.11.2 NHE-1 antagonists. (NHE-1 Inhibition IC_{50} (μm))

1.11.3 Anti HIV Activity

Much effort has been dedicated to the development of HIV protease (HIV PR) inhibitors for the treatment of AIDS. The protease is responsible for the processing of nascent polypeptides to mature proteins comprising the viral particle. Without the formation of the mature particle, viral replication of HIV has been shown to be inhibited. HIV PR has therefore been an active biochemical target for the development of small molecule therapeutics.

Wilkerson and co-workers at DuPont-Merck had developed a cyclic urea-based HIV PR inhibitor scaffold which possessed an acceptable pharmacokinetic profile, but lacking the potency necessary to advance the candidate.[107] Biochemical evaluation of

this series of compounds against the HIV PR dimer revealed that a and b were extremely potent inhibitors Ki = 0.023 and 0.012 nM respectively. The compounds were also able to inhibit viral replication in vitro as measured by the ability of the compounds to inhibit RNA synthesis by 90% (**a)** IC_{90} = 13.2 nM; (**b)** IC_{90} = 26.2 nM). Interestingly, QSAR on this series of cyclic ureas suggested the optimum lipophilicity for protease inhibition (ClogP = 4.4) is different from the inhibition of viral replication (ClogP = 6.36) as revealed by the reversal of Ki and IC_{90} selectivities for (**a)** and (**b).** This makes it difficult to optimize both parameters within the same molecule, but suggests that while (**a, b)** display the same hydrogen bonding pattern at the terminal urea, the lipophilicity disparity between the 2-aminoimidazole and the benzimidazole has a significant effect on their pharmacokinetic profile. With these results, (**a)** and (**b)** were advanced for pharmacokinetic studies in female Beagles. As seen in the pharmacokinetic profiles (Fig. 1.11.3) the decreased lipohilicity of (**b)** had a significant impact on the clearance (CL) and half-life (t1/2) of the compound, advancing its candidacy based on this improved PK profile.

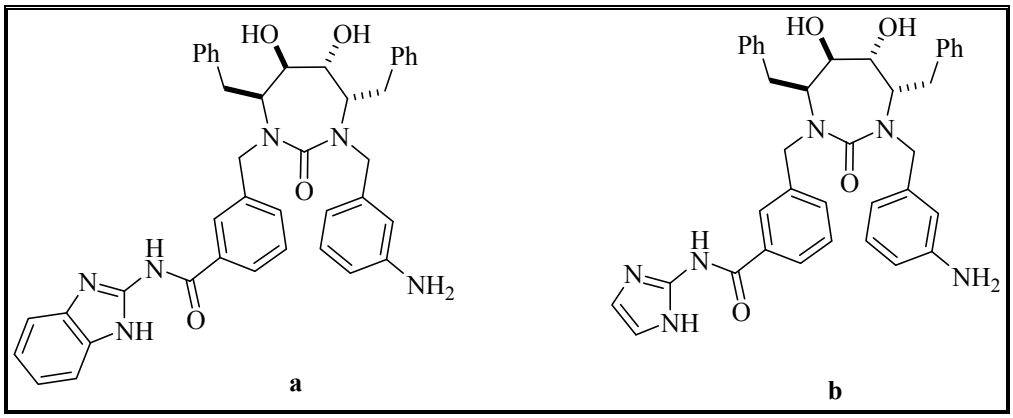


Fig.- 1.11.3 Unsymmetrical HIV PR inhibitors.

Parameter	a	b
Ki (nM)	0.023	0.012
IC_{90} (nM)	13.2	26.2
Dose (mg/kg)	5.0	5.0
CL, L/h/kg	0.8	0.5
Vss (L/Kg)	1.0	4.0
$T_{1/2}$ (h,iv)	0.9	5.6

Table-1.13.1: Pharmacokinetic profiles of HIV PR inhibitors

1.11.4 α-adrenoreceptor agonists.

Agents that can stimulate α-andrenoceptors modulate a variety of physiological processes including the reduction of blood pressure, sedation and the inhibition of intestinal fluid secretion.[108] Scientists at Allergan Pharmaceuticals targeted the α –andrenoceptor to reduce intraocular pressure(IOP), a common condition in patients suffering from glaucoma.[109] The challenge in designing such agents stems from the ability of α –andrenoceptor subtypes to modulate different biological processes, most concerning are those in the central nervous system (CNS). One approach to minimizing CNS effect is topical application, minimizing access of the compound to the CNS. From the known α-andrenoceptor agonist clonidine,[110] modifications to minimize CNS access generated the lead compounds p-aminoclonidine and AGN-191103 (21) (Fig. 1.13.4). The The alternative approach is to discover compounds displaying enough selectivity between the α-andrenoceptor subtypes such that they exhibit an enhanced therapeutic index. This led to replacing the imidazolidin-imine with a 2-aminoimidazole. This compound (**a)** was selected for further evaluation. Binding assays demonstrated (**a)** bound to the α_{2A}-receptor with a Ki = 1.7 nM and was 1200-fold selective for the α_{2A} –receptor over the α_1-receptor, 50-fold selective for the α_{2A} –receptor over the α_{2B} –receptor, and 10-fold selective for the α_{2A} –receptor over the α_{2C} –receptor. Compound (**a)** was found to be effective in vivo with an EC_{50} = 8.7 nM and importantly remained effective when administered intravenously, demonstrating its capability of crossing the blood-brain barrier.

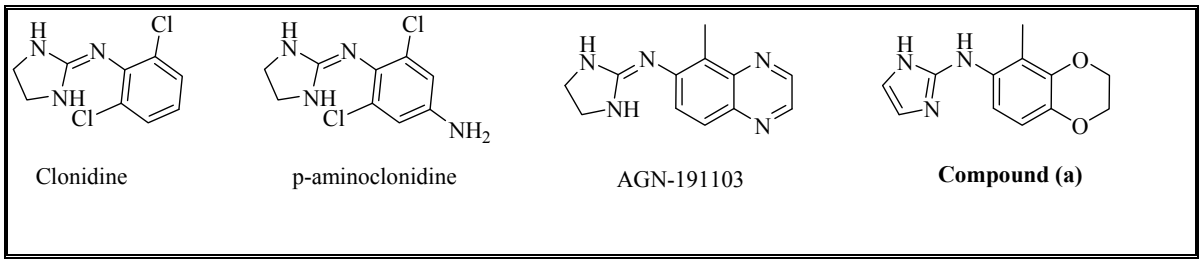
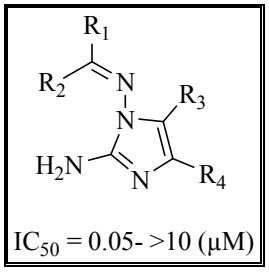


Fig.- 1.11.4 α-adrenoreceptor agonists.

1.11.5 Anti Cancer Activity

Cancer has been the leading cause of death worldwide. Chemotherapy remains one of the major treatment options available for cancer, andmost of the currently used anticancer drugs are administered to patients via a parenteral infusion or bolus injection. Clinical complications with the parenteral administrations have been

documented. Extra care is needed because of inappropriate patient compliances, and extra cost associated with hospitalization is necessary. Efforts in searching for orally active anticancer agents have been extensive, including the anticancer drug category of tubulin binding agents from which only injectable drugs are available such as taxanes and vinca alkaloids. Recently Chiung-Tong Chen[111] reported the synthesis and biological functions of 2-amino-1-arylidenaminoimidazoles as orally active anticancer agents. Selective compounds had shown potent effects in the interference on the colchicines binding to tubulins, inhibition of tumor cell proliferation, and induction of human cancer cell apoptosis.



IC_{50} = 0.05- >10 (μM)

1.11.6 BACE-1 Inhibitors

Alzheimer's disease (AD) is the largest unmet medical need in neurobiology and accounts for the majority of dementia diagnosed in the elderly. AD is characterized by a progressively slow decline in cognitive function that leaves the end-stage patient dependent on custodial care with death occurring on the average of 9 years after diagnosis. The lack of an effective treatment for AD has stirred an intense search for novel therapies based on the amyloid hypothesis. This hypothesis states that a gradual and chronic imbalance between the production and clearance of Aß peptides results in their accumulation in the brain. These secreted peptides polymerize into neurotoxic oligomers that disrupt neuronal function and lead to cell death and memory loss that is phenotypical of AD. ß-secretase (BACE-1) is an as partyl protease representing the ratelimiting step in the generation of these Aß peptide fragments. Given the central role of Aß in AD pathology, inhibition of BACE-1 has become an attractive target for the treatment of Alzheimer's disease. Vacca[112] and Hills[113] developed a series of aromatic heterocycles as BACE-1 inhibitors. The potency of the weak initial lead structure was dramatically enhanced using traditional medicinal chemistry. These inhibitors were shown to bind in a unique fashion that allowed for potent binding in a non-traditional fashion.

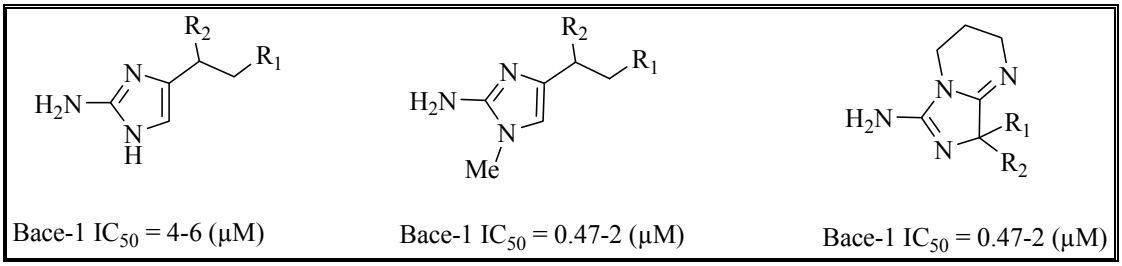


Fig. 1.11.5 BACE-1 inhibitors

1.11.7 Anti Biofilm Activity

Bacterial biofilms are defined as a surface attached community of ignalling sms that are protected by an extracellular matrix of biomolecules. Within a biofilm state, bacteria are more resistant to antibiotics and are inherently insensitive to antiseptics and basic host immune responses. The NIH has estimated that 65-80% of all microbial infections are biofilm-based. Biofilm infections of indwelling medical devices are also of major concern, as once the device is colonized, infection is virtually impossible to eradicate. Bacterial biofilms[114-116] underlie the persistent colonization of hospital facilities, which perpetuates nosocomial infections. Hospital-acquired infections place a $10 billion burden on the U.S. healthcare system annually. Given the prominence of biofilms in infectious diseases, there has been an increasing effort toward the development of small molecules that will modulate bacterial biofilm development and maintenance. This, coupled with the spread of multi-drug antibiotic resistance across many of these bacteria, has put a tremendous burden on the scientific and medical community to alleviate biofilm-related problems. In this review, we will highlight the development of small molecules that inhibit and/or disperse bacterial biofilms through non-microbicidal mechanisms. The review will be segmented into providing a general overview of how bacteria develop into biofilm communities, why they are important, and the difficulties associated with their control. This will be followed by a discussion of the numerous approaches that have been applied to the discovery of lead small molecules that mediate biofilm development. These approaches are grouped into: 1) discovery/synthesis of molecules based upon naturally occurring bacterial ignalling molecules, 2) chemical library screening, and 3) discovery/synthesis of natural product and natural product analogues.

Very recently the research group of Melander has been studying widely the ability of simple analogues of the marine natural products bromoageliferin and oroidin (Fig. 1.11.6) to control biofilm development. Bromoageliferin is a sponge-derived alkaloid that was reported to inhibit the formation of bacterial biofilms from marine sources, presumably as a defense mechanism against biofouling.[117] They reasoned that core structures derived from this complex molecule could be used as structural inspiration for the development of potent and synthetically accessible anti-biofilm agents. One of these scaffolds developed was based upon an aryl framework.[118] From a medicinal chemistry stand point, this scaffold was deemed a promising platform to develop further functionalized 2-aminoimidazole (2-AI) derivatives as diversity could rapidly be introduced through manipulation of the benzene ring. They described the synthesis and anti-biofilm activity of these aryl 2-AI derivatives against three commonlystudied Gram-negative bacteria.

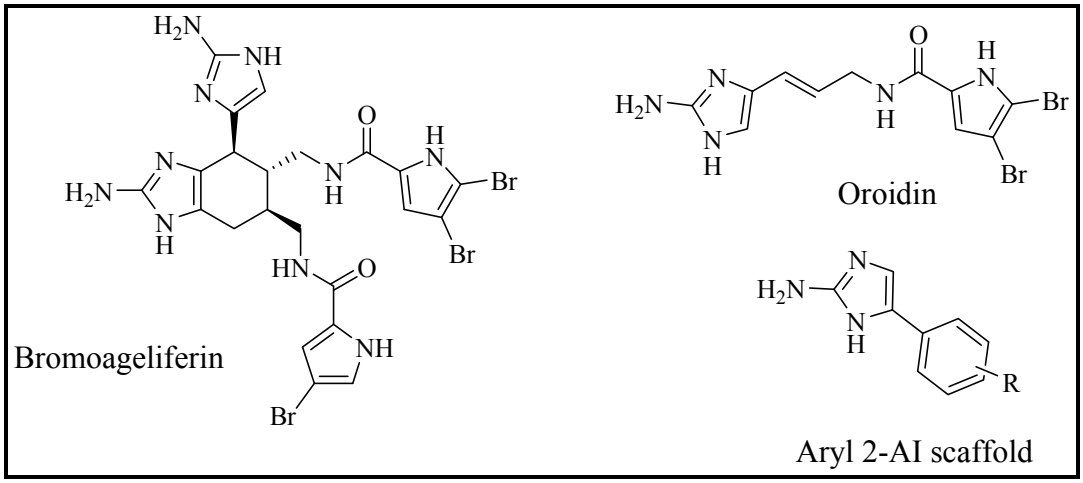


Fig. 1.11.6 2-Aminoimidazole-based anti-biofilm molecules.

The research group of melander has recently developed several novel libraries of 2-aminoimidazole small molecules inspired by the marine alkaloids bromoageliferin and oroidin. These natural products were reviously reported to inhibit biofilm formation of the marine arotobacterium Rhodospirillum salexigens.[119] TAGE and CAGE were the first documented 2-aminoimidazoles with anti-biofilm activity against Pseudomonas aeruginosa biofilms.

Analogues of the structurally simpler alkaloid oroidin were also pursued to develop novel classes of small molecules with anti-biofilm activity. Recently, an oroidin

inspired library was constructed utilizing click chemistry to generate a diverse library of 2-aminoimidazole/triazole conjugates (2-AIT).These compounds displayed the widest spectrum of anti-biofilm activity observed within the 2-aminoimidazole class (Fig. 1.11.7).[120-121]

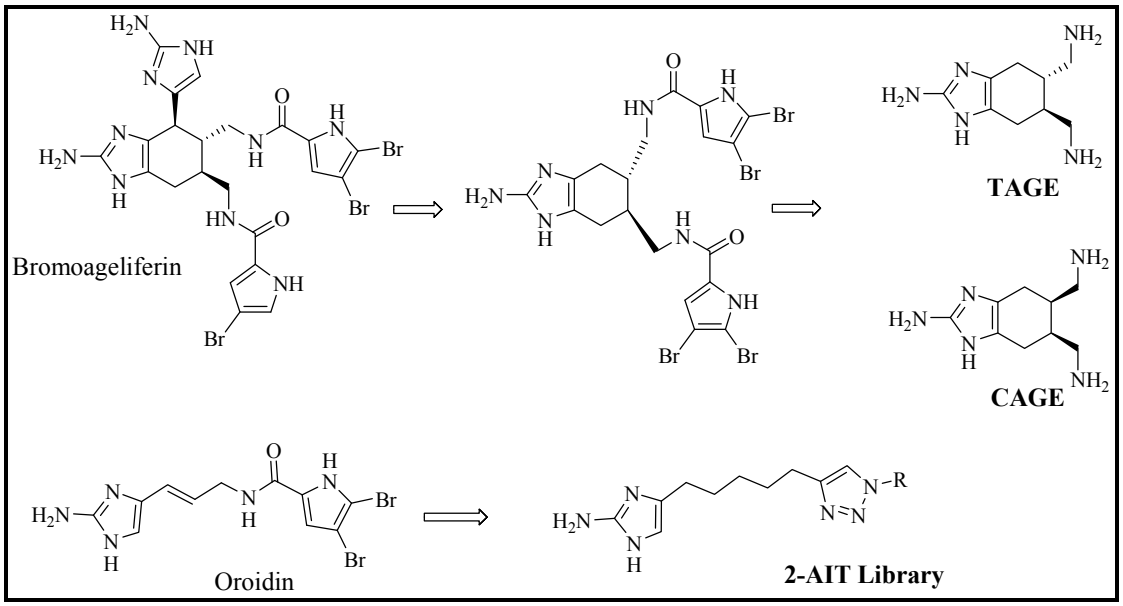
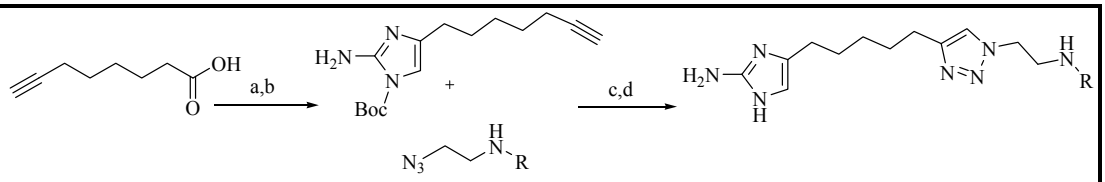


Fig. 1.11.7 Representative 2-aminoimidazoles derived from the marine natural products bromoageliferin and oroidin.

The synthetic approach to this 2-AIT derivatization is outlined in (Scheme 1.11.1). In their previous synthesis of 2-AIT conjugates, they employed the alkyne-derived 2-AI as a precursor for the CuI-mediated[3+2] alkyne/azide cycloaddition (click reaction). Although this reaction worked well, purification of the resulting product was cumbersome, due to the need for copious amounts of ammonia saturated methanol for column chromatography. Therefore, they decided to revise the route by employing a Boc-protected 2-AI alkyne that would allow more traditional means of purification (i.e. methanol/dichloromethane columns). The Boc-protected scaffold was synthesized from oct-7-ynoic acid by treatment with oxayl chloride followed by diazomethane and quenching of the resulting α-diazo ketone with HBr to generate the intermediate a-bromo ketone. Cyclization with Boc-guanidine then delivered the target 2-AI alkyne..



a) i : $(COCl)_2$,CH_2Cl_2, DMF (cat.), ii : CH_2N_2,Et_2O/CH_2Cl_2, iii : HBr (82%) ; b) Boc-guanidine, DMF, RT (59%) ; c) azide, $CuSO_4$, Na ascorbate, EtOH, CH_2Cl_2,H_2O; d) TFA, CH_2Cl_2 (58-94 % over two steps)

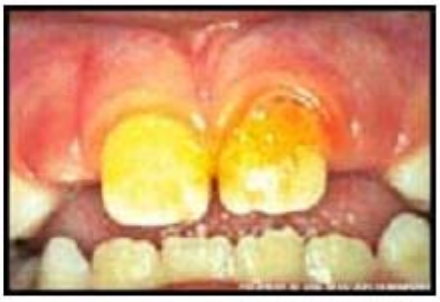
Scheme-1.11.1 Melander's 2-AI-T conjugate synthesis.

It was explained by earlier work that once target 2-AI alkyne had been synthesized, assembled a diverse array of azido amides to employ in the click reaction to create pilot collection of 2-AIT conjugates. Briefly, 2-bromo-ethylamine was treated with sodium azide to deliver 2-azido-ethylamine, which following acylation (via the respective acid chloride) generated the azido amides for elaboration into the 2-AIT collection. Each azido amide was then subjected to the click reaction with target 2-AI alkyne. Boc-deprotection (TFA/CH2Cl2) followed by counterion exchange (trifluoroacetate for chloride) delivered the target 2-AIT compounds for antibiofilm screening.

1.12 Introduction to Biofilm

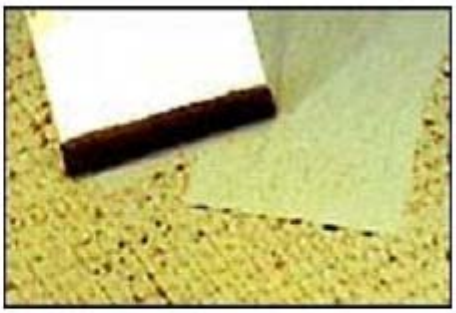
- **Biofilms play a significant role in infection disease and account for up to 80% of microbial infections in the body.**
- Bacterial biofilms are defined as a surface-attached community of bacteria that are surrounded by a protective extracellular matrix.
- On a global scale, biofilm related costs incur 6-10 billions of Euros to the agricultural, engineering, and medical sectors of economy.
- Despite the focus of modern microbiology research on pure culture, planktonic bacteria, it is now recognized that most bacteria found in natural, clinical, and industrial settings persist in biofilms.
- **Within a biofilm, bacteria are upward of 1000-times more resistant to conventional antibiotic treatment**
- Biofilms grow virtually everywhere, in almost any environment where there is a combination of moisture, nutrients, and a surface.

In a pipe



Plaque on teeth

In a creek.

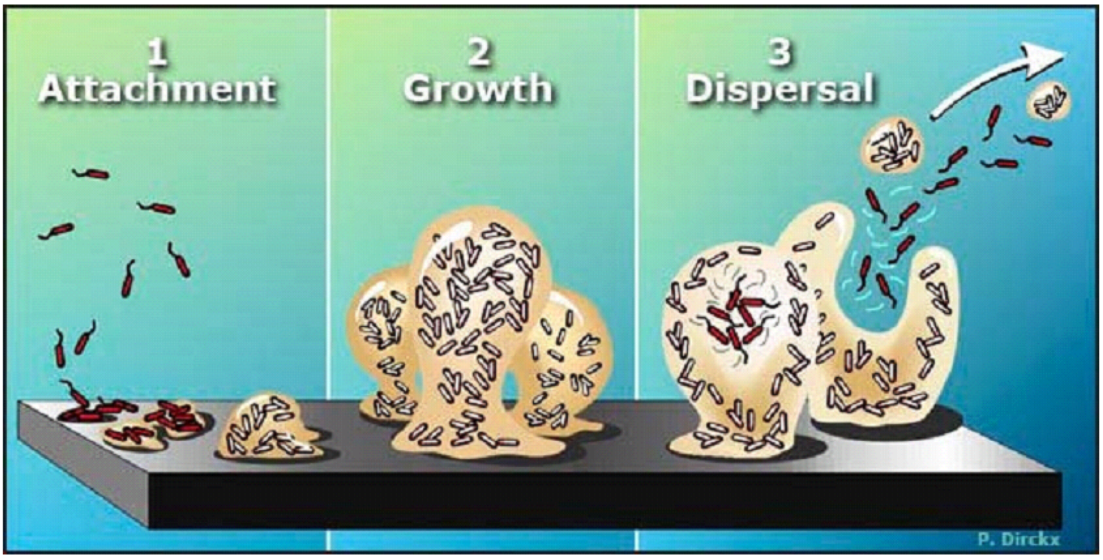


In a membrane

1.12.1 Properties of biofilms

A biofilm community can be formed by a single bacterial species, but in nature biofilms almost always consist of rich mixtures of many species of bacteria, as well as fungi, algae, yeasts, protozoa, other microorganisms, debris and corrosion products. Biofilms are held together by sugary molecular strands, collectively termed "extracellular polymeric substances" or "EPS." The cells produce EPS and are held together by these strands, allowing them to develop complex, three-dimensional, resilient, attached communities. Biofilms cost the U.S. literally billions of dollars every year in energy losses, equipment damage, product contamination and medical infections. But biofilms also offer huge potential for bioremediating hazardous waste sites, biofiltering municipal and industrial water and wastewater, and forming biobarriers to protect soil and groundwater from contamination

1.12.2 Biofilm Growth Cycle

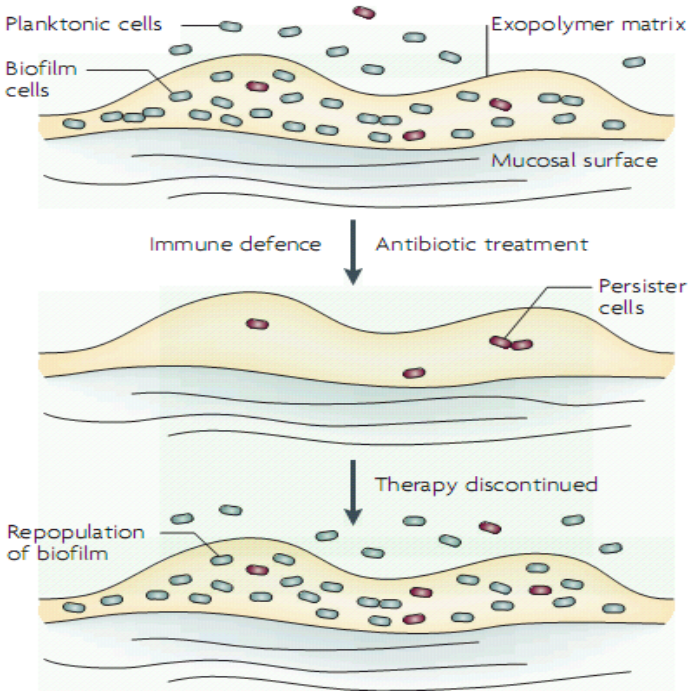


1) Planktonic bacteria reversibly attach to a surface suitable for growth and Bacteria begin secretion of the extra cellular polymeric substances (EPS) and attachment becomes irreversible.

2) The maturing biofilm begins to take on a 3-dimensional shape. Biofilm communities can develop within hours.

3) The biofilm fully matures, and complex architecture is observed. Bacteria disperse from the biofilm to reinitiate biofilm colonization of a distal surface.

1.12.3 Biofilm Drug Resistance



The figure below shows a model of biofilm resistance to killing based on persister survival.
Initial treatment with antibiotic kills normal cells (coloured green) in both planktonic and biofilm populations.
The immune system kills planktonic persisters (coloured green), but the biofilm persister cells (coloured pink) are protected from the host defences by the exopolymer matrix.
After the antibiotic concentration is reduced, persisters resuscitate and repopulate the biofilm and the infection relapses.

Biofilm infections are highly recalcitrant to antibiotic treatment. However, planktonic cells that are derived from these biofilms are, in most cases, fully susceptible to antibiotics. Importantly, biofilms do not actually grow in the presence of elevated concentrations of antibiotics, therefore biofilms do not have increased resistance compared with planktonic cells.[122] But if biofilms are not resistant to antibiotics, how do biofilm bacteria avoid being killed by antibiotic treatments? The resistance of biofilms to drug therapy has been one of the more elusive problems in microbiology, but the analysis of a simple dose-response experiment provided an unexpected insight into the puzzle.[122-124]

Most of the cells in a biofilm are highly susceptible to bactericidal agents such as fluoroquinolone antibiotics or metal oxyanions, which can kill both rapidly dividing and slow- or non-growing cells.[124-126] This is important, as cells in the biofilm are slow-growing, and many are probably in the stationary phase of growth. The experiment also revealed a small sub-population of cells that remain alive irrespective of the concentration of the antibiotic (persisters). The number of surviving persisters was greater in the non-growing stationary phase. In vitro, a stationary culture seems to be more tolerant than a biofilm to antibiotics. However, this situation is probably reversed in vivo. Antibiotic treatment will kill most biofilm and planktonic cells, leaving persisters alive. At this point, the similarity with an in vitro experiment probably ends. The immune system can mop up and kill remaining planktonic persisters, just as it eliminates nongrowing cells of a bacterial population that is treated with a bacteriostatic antibiotic. However, the biofilm exopolymer matrix protects against immune cells,[127-129] and persisters that are contained in the biofilm

can survive both the onslaught of antibiotic treatment and the immune system. When the concentration of antibiotic reduces, persisters can repopulate the biofilm, which will shed off new planktonic cells, producing the relapsing biofilm infection. The problem of biofilm resistance[72] to killing by most therapeutics probably defaults to persisters. Interestingly, yeast biofilms also form tolerant persisters.

1.13 Recent publications on 2-aminoimidazoles.

The core structure 2-aminoimidazole has assumed importance in various synthesis related to heterocyclic in drug synthesis as appeared in Sci-finder search results on the basis of number of publications in medicinal and synthetic chemistry journals.

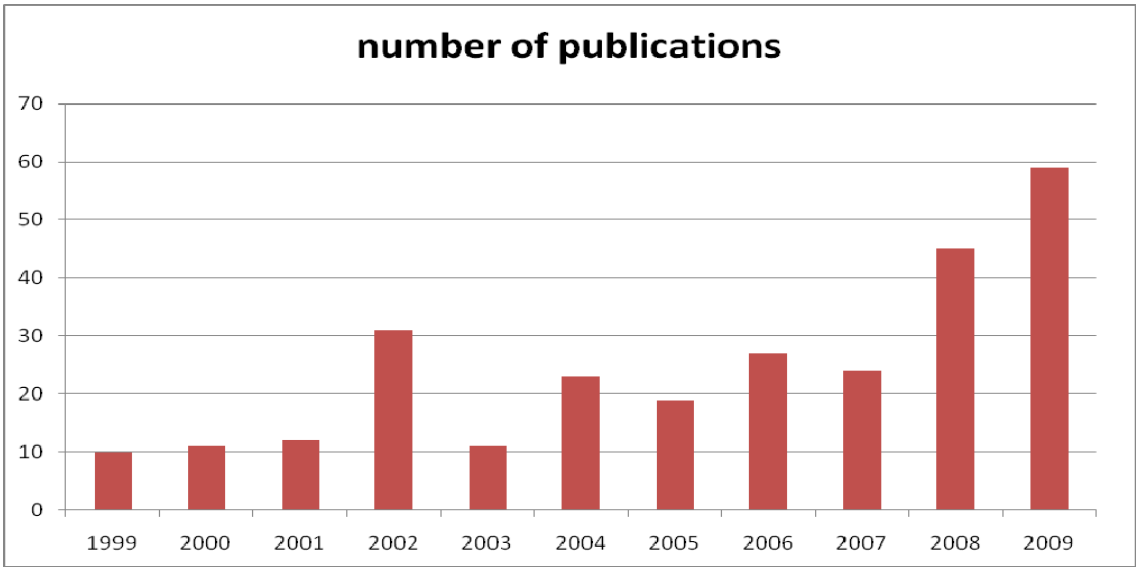


Fig.1.10 Sci-finder search results by heating term 2-aminoimidazole.

1.14 Conclusion

Bacterial biofilms pose a serious threat to the healthcare system of our society as they are responsible for the morbidity and mortality of a myriad of diseases. The development of antibiotic resistance among many bacterial strains has put a tremendous pressure on the medical community to find alternative approaches for the treatment of biofilm-mediated diseases. In this present work of thesis a microwave assisted synthesis of small molecules which shows ability to controlling bacterial antibiofilm has been reported.

1.15 References

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