2. LITERATURE REVIEW

2.1 QUINAZOLINE

2.1.1 INTRODUCTION

Quinazoline (24) is a heterocyclic compound made up of two fused six-membered simple aromatic rings, a benzene ring and a pyrimidine ring. Its chemical formula is C₈H₆N₂ and molecular mass 130.15 g/mol. The name was proposed by Widdege. Other names such as phenmiazine, benzyleneamidine, benzo-1,3-diazine, 5, 6-benzopyrimidine and 1, 3-diazanaphthaline have occasionally been used. The numbering suggested by Paal and Busch is still in use. The presence of a fused benzene ring alters the properties of the pyrimidine ring considerably. The two nitrogen atoms are not equivalent, and the marked polarization of the 3, 4- double bond is reflected in the reactions of quinazoline.84

![Chemical Structure of Quinazoline](image)

Quinazoline is yellow solid. It is isomeric with other naphthyridines including quinoxaline, phthalazine and cinnoline. Derivatives of quinazoline are called quinazolines. Medicinally it has been used in various areas especially as an anti-malarial agent and in cancer treatment. The ring system is typically prepared by heating 2-acylanilides in the presence of ammonia or amines.

The chemistry of quinazoline compounds has more than centuries old history; however the intense search for biologically active substances in this series began only in the last few decades. Evolution of quinazolines began only with discovery of febrifugine, a quinazolinone alkaloid, possessing anti-malarial potential from the Chinese plant aseru (Dichroa febrifuga Lour), which served as an impetus for initiation of the research on quinazolines.

Earlier research in nineteen fifties and sixties revealed effectiveness of quinazolines not only as anti-malarial but also against various diseases caused by bacteria, protozoa
and virus. But the research was restricted mostly to anti-microbials. An important stage in the development of research on the biological activity of quinazoline compounds was the discovery of considerable soporific and sedative action of 2-methyl-3 aryl-4 quinazolone derivatives. Synthesis of these compounds with general concepts stimulated an extensive search for various pharmacologically active compounds. In the last 10-15 years the search for quinazoline compounds has been characterized by significant advances. \textsuperscript{84}

2.1.1.2 CHEMICAL PROPERTIES: \textsuperscript{84,85}

Quinazolines is stable in cold dilute acid and alkaline solutions, but it is destroyed when these solutions are boiled. O-Aminobenzaldehyde, ammonia and formic acid are formed when quinazoline is boiled with hydrochloric acid.

The properties of substituted quinazolines depend largely on
a. The nature of the substituents.
b. Whether they are in the pyrimidine ring (or) in the benzene ring
c. Whether (or) not complete conjugation is present in the pyrimidine ring.

a). Hydrolysis, oxidation and reduction.

**Oxidation**

Oxidation of quinazoline (24) in dilute aqueous acid, with two equivalents of hydrogen peroxide at room temperature gave a high yield of 3,4-dihydro-4-oxo quinazoline (25). In alkaline medium, where the anhydrous neutral species of quinazoline were predominantly undergo oxidation with KMNO\textsubscript{4} furnished a high yield of pyrimidine dicarboxylic acid (26) was also formed.
Reduction
Catalytic hydrogenation of quinazoline stopped after the absorption of one molecules of hydrogen and gave 3, 4-dihydro quinazoline. Reduction with sodium amalgam gave 1,2,3,4 tetrahydroquinazoline. Lithium aluminum hydride and sodium boro hydride gave 3, 4-dihydroquinazoline and 1,2,3,4-tetrahydroquinazoline.

b). Nucleophilic and electrophilic substitution reactions
The two known nucleophilic substitution reactions of quinazoline namely with sodamide and hydrazine, presumably proceed via the intermediate addition products and gave 4-amino and 4-hydrazine quinazoline. Nitration is the only known electrophilic substitution reaction of quinazoline. Theoretical considerations show that the expected order of reactivity is at positions $8 > 6 > 5 > 7 > 4 > 2$. Quinazoline gives 6-Nitroquinazoline (27) with fuming nitric acid in concentrated $\text{H}_2\text{SO}_4$.

c). Alkylation reactions
Alkylation of quinazoline takes place on 3-methyl, 3-ethyl-3-alkyl and 3-benzyl quinazolinium salts readily take up a molecule of alcohol to form the corresponding 4-alkoxy-3-alkyl-3, 4-dihydro quinazolinium salts. These salts yield the pseudo bases, 3-alkyl 3, 4-dihydro-4-hydroxy quinazoline (30) on treatment with strong alkali.
d). Addition reactions
Quinazoline is very reactive towards anionic reagents at position 4. Sodium bisulphate, hydrogen cyanide, acetophenone, acetone, 2-butanone and cyclohexanone is added across the 3, 4-double bond of quinazoline. Methyl, ethyl, isopropyl, benzyl, t-butyl and phenyl magnesium halides and phenyl lithium is also added across the 3, 4-double bond to give the corresponding 4-substituted 4-dihydroquinazolines.

2.1.1.3 SYNTHESIS OF QUINZOLINES:
In 1869 Griess prepared the first quinazoline derivative, 2–cyano 3, 4-dihydro-4-oxoquinazoline (31), by the reaction of cyanogens with anthranilic acid. Griess apparently recognized the bicyclic nature of the product which, he called bicyanoamido benzoyl and used this name until 1885. When structure (31) was known with some certain.85,86
The preparation of the parent quinazoline came many years later when Bischler and Lang obtained it by decarboxylation of the 2-carboxy derivative. A more satisfactory synthesis of quinazoline was subsequently devised by Gabriel in 1903 that studied properties and those of its derivatives in detail.\(^6\)

2.1.1.3.1 Following methods are reported for the synthesis of o xoquazolines.

a). Niementowski’s synthesis

Niementowski’s found that 3 (or) 4 substituted anthranilic acid when reacted with formamide at temperature 125-130 °C for 4 hours gave 3, 4-dihydro-4-oxo quinazoline (33) with 86% yield.\(^6\)

\[
\begin{align*}
\text{(32)} & \\
\text{(33)}
\end{align*}
\]

b). Grimmel, Guinther and Morgan’s synthesis.

3 moles of O-amino benzoic acids, when heated with 3 moles of substituted amines together with one mole of phosphorous trichloride in toluene for two hours, gave high yields of 2,3-disubstituted 3,4-dihydro-4-oxoquinazolines (35).\(^6\)

\[
\begin{align*}
\text{(34)} & \\
\text{(35)}
\end{align*}
\]

c). From isatoic anhydride

Isatoic anhydride readily reacts with equimolar quantity of substituted amines to yield dihydro-4-oxoquinazolines (38) by refluxing in the presence of ethyl orthoformate for 1-6 hours without isolating the intermediate amides.\(^6\)
d). From 3,1,4-Benoxazones (Acylanthranils) and amines.

3, 1, 4-Benoxazones react with substituted amines to give 3,4-dihydro-4-oxoquinazolines (40).

![Chemical structure](image)

f). Sen and Ray’s synthesis

Boiling a solution of normal (or) isobutyrylanilides with urethane and phosphorous pentoxide in xylene gave 2-propyl and 2-isopropyl-3, 4 dihydro-4-oxoquinazolines (42).

![Chemical structure](image)

b). From O-ureidobenzoic acid.

O-ureidobenzoic acids are readily prepared from the corresponding anthranilic acid and potassium cyanate. The ureidobenzoic acids are then easily cyclised to the respective 1, 2, 3, 4-tetrahydro-2,4-dioxoquinazolines (45) by heating with acid (or) alkali.

![Chemical structure](image)
Vijai anand. P. R., reported synthesis of series of novel 4-oxo-2-phenyl-4H-quinazoline-3-carboxylic acid (4-substituted phenyl amides) (49) by condensing 2-phenyl-3,1-benzoxazine-4-one and 4-substituted phenyl ureas.\(^\text{(87)}\)

\[
\begin{align*}
\text{(46)} & \quad \text{Benzoyl Chloride} \\
\text{(47)} & \quad \text{(CH}_3\text{CO})_2\text{O} \\
\text{(48)} & \quad \text{Phenyl urea} \\
\text{(49)} & \quad \text{Ethanol} \\
& \quad \text{Reflux}
\end{align*}
\]

\[R = \text{-Cl, -Br, -NO}_2, \text{-SO}_2\text{NH}_2, \text{-COOH}\]

Adib M. et al., described novel and one-pot synthesis of 2-aryl/alkyl-4(3H)-quinazolinones (50). The in situ prepared amidoximes from the reaction between nitriles and hydroxylamine are condensed with anthranilic acids under solvent- and catalyst-free conditions to produce the 2-aryl/alkyl-4(3H)-quinazolinones (50) in excellent yields.\(^\text{(88)}\)

\[
\begin{align*}
\text{(50)} & \quad \text{C}_6\text{H}_5\text{CN} + \text{NH}_2\text{OH} \quad \text{solvent free} \\
& \quad \text{1.5 h} \quad \text{C}_6\text{H}_5\text{b} \\
& \quad \text{solvent free, 2 h}
\end{align*}
\]

Xing. Z. Y. et. al., reported a new and efficient strategy for the synthesis of novel quinazoline derivatives (52) via the cyclization of \(N, N\)-disubstituted thiourea derivatives in the solvent of acetonitrile and aqueous NaOH under ultraviolet light irradiation, has been developed.\(^\text{(89)}\)
A photochemically induced Fries rearrangement of anilides gave several *ortho*-aminoacylbenzene derivatives that were acylated. These acylamides underwent rapid microwave-assisted cyclization to 2,4-disubstituted quinazolines (and benzoquinazolines) (54) in the presence of ammonium formate.\(^\text{90}\)

\[
\begin{align*}
\text{(51)} & \quad \text{hv(365nm), N}_2, \text{MeCN/2mol-L NaOH} \quad 44\%-55\% \\
\text{(52)}
\end{align*}
\]

Aza-Diels-Alder reaction Imino-Diels-Alder reaction containing the coupling of imine and electron-rich alkene gradually became a powerful tool for the synthesis of quinazoline derivatives (55). In Povarov imino-Diels-Alder reaction, aniline and ethyl glyoxalate were chosen as substrates. And two molecules of \(\alpha\)-iminoesters, which were got from the condensation of aniline and ethyl glyoxalate.\(^\text{91}\)

\[
\begin{align*}
\text{(53)} & \quad 1) \text{MeOH, r.t., 3h} \\
\text{(54)} & \quad 2) \text{4eq. Fe, HCl(conc.) reflux, 3h} \\
\end{align*}
\]

Garratte et al., reported a kind of tandem Staudinger–Aza-Wittig–Nucleophilic addition reaction to synthesize indolo[1,2-c]quinazolines. novel 2-alkoxy-3\(\text{H}\)-quinazolin-4-ones (59) were synthesized from carbodiimid (methanediimine) (57)
which was obtained from aza-Wittig reaction of iminophosphorane with aromatic isocynate (Scheme 3).  

![Chemical reaction diagram]

2.2 BIOLOGICAL ACTIVITIES OF QUINAZOLINES

The quinazoline skeleton appears in many alkaloids, most commonly in the form of 4-(3H)-quinazolinone moieties. 4-(3H)-Quinazolinones and related quinazolines are classes of fused heterocycles that are of considerable interest because of the diverse range of their biological properties for example anticancer, anti-tubercular, antihistaminic, anti-tussive, antimicrobial, diuretic, anti-inflammatory, anticonvulsant, sedative-hypnotic, antidepressant, antiparkinsonism, phosphodiesterase inhibitor and antihypertensive activities. As shown in a recent exhaustive review on the chemistry of 2-heteroaryl and heteroalkyl-4(3H)-quinazolinones like the benzodiazepines the quinazolines are considered to be a "privileged structure" for drug development. Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effects, useful to control tumour growth.

ANALGESIC AND ANTI-INFLAMMATORY AGENTS:

There are no promising quinazolines which are in the market in these NSAIDs criteria except few drugs like Proquazone, Afloqualone and Diproqualone etc. The novel derivatives of quinazolines mentioned might be beneficial in terms of biological activity for which further studies can be done to confirm it as a potential drug candidate.
Alagarswamy et al., worked on several 3(\(H\))-quinazoline-4-ones and came up with 2-(2-(pentan-3-ylidene)hydrazinyl)-3-phenylquinazolin-4(3\(H\))-one (60) which showed different ranges of potency from mild to moderate in both analgesic and anti-inflammatory activity when compared with diclofenac sodium and showed mild ulcerogenic potential when compared with aspirin.\(^{93}\)

B.A. Rather et al., also worked on quinazolin-4-3(\(H\))ones (61) to produce different compounds of varied potency when compared with the standard aspirin and indomethacin.\(^{94}\)

**ANTI-MICROBIAL AGENTS:**
Anti-microbials cover broad spectrum biological activities like antibacterial, anti fungal, antiviral, antileishmanial, antiprotozoal, antiplasmodial etc. With time several derivatives of quinazolines possessing potential anti-microbial activities have evolved but still they do not occupy a prominent position in this section of market.
Febrifugine (62) - It was found to possess anti malarial activity and used as coccidiostat in veterinary medicine.

Halofuginone (63) - It is a halogenated derivative of febrifugine, used as coccidiostat in veterinary medicine. It has received FDA approval for use in scleroderma. It has been used potentially for treatment of auto immune disorders.\(^{95, 96}\)

Jessy et al., worked on several 2, 3-disubstituted-3, 1-quinazolin-4-(3H) ones (64) which were evaluated for antibacterial activity against various strains of bacteria which were comparable to ciprofloxacin among which following compound was found to be potent.\(^{97}\)

Rohini et al., worked on several Bis-6-Arylenzimidazo [1, 2-c] quinazolines (65) which were evaluated for anti bacterial (Gram Positive and negative), antifungal activities which were comparable to ampicillin and ketoconazole respectively among which following compound was found to be potent.\(^{98}\)
ANTI-TUBERCULAR AGENTS:

There are no promising quinazolines marketed presently in the category of tuberculosis. But several novel molecules have been synthesized in the past which showed promising results but unfortunately could not make it up to the marketing stage.

Josef et al., Synthesized novel 2-styrylquinazolin-4(3H)-one. It was found that the electrone withdrawing properties of the R substituent, and lipophilicity of the compound, were decisive for the compounds to exhibit potent antitubercular activity when compared with isoniazid by invitro method. Among all the synthesized compounds following were found to be potent.99

ANTICANCER AGENTS:

Quinazolines occupy a promising section in the anticancer market because of their specificity. Most of the quinazolines are targeting protein tyrosine kinase. Even more
selective compounds targeting EGFR, VEGFR and ERBB-2 are in the market. Receptors are being discovered and still in the developmental stages.\(^{100}\)

![Chemical structure](image_url)

**Table 5: quinazoline derivatives as anticancer agents**

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Substitution(R)</th>
<th>Substitution(R1)</th>
<th>Substitution(R2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>67a</td>
<td><img src="image_url" alt="Structure" /></td>
<td><img src="image_url" alt="Structure" /></td>
<td><img src="image_url" alt="Structure" /></td>
</tr>
<tr>
<td>67b</td>
<td><img src="image_url" alt="Structure" /></td>
<td><img src="image_url" alt="Structure" /></td>
<td><img src="image_url" alt="Structure" /></td>
</tr>
<tr>
<td>67c</td>
<td><img src="image_url" alt="Structure" /></td>
<td><img src="image_url" alt="Structure" /></td>
<td><img src="image_url" alt="Structure" /></td>
</tr>
</tbody>
</table>

Erlotinib (67a): It is a tyrosine kinase inhibitor targeting EGFR used to treat non-small cell lung cancer, pancreatic cancer and several other types of cancer.

Gefatinib (67b): It is a tyrosine kinase inhibitor targeting EGFR used to treat non-small cell lung cancer, adenocarcinoma and several other types of cancer.

Vandetanib (67c): It is a tyrosine kinase inhibitor targeting EGFR and VEGFR used for non small cell lung cancer. It was not launched into the market as it showed no benefit when co administered other chemotherapeutical agents.

**ANTIHISTAMINIC AGENTS\(^{101,102}\)**

In the recent days lot of research is being done in the category of histaminic antagonists with relatively less sedative effect than existing drugs. Though few drugs
possessing this activity are presently in the market, novel drugs are still being synthesized. Alagaraswamy et al., synthesized several 4-(3-ethylphenyl)-1-substituted-4H [1,2,4] triazolo [4,3-a]quinazolin-5-ones (68). It was found that by varying substitution over the first position of the triazolo quinazoline ring there was variation in the biological activity. The presence of methyl group showed better activity than the unsubstituted compound. With increased lipophilicity the activity remained but further increase in lipophilicity led to a decrease in activity. Replacement of the methyl group by other groups decreased the activity. The antihistaminic potential was tested in vivo by comparing with chlorpheniramine maleate in which the following compound showed promising anti histaminic activity with less sedation.\textsuperscript{103}

\begin{center}
\includegraphics[width=0.2\textwidth]{68.png}
\end{center}

\textbf{ANTITUSSIVE AND BRONCHODILATOR AGENTS:}
Several attempts were made in the past to synthesize quinazolines possessing antitussive and bronchodilator activities. Except chloroqualone none of the quinazolines were marketed in this category.

Chloroqualone (69) – It is used as antitussive agent in France and other European countries during 1980, which was sold either alone, or in combination with other ingredients as a cough medicine.\textsuperscript{103}

\begin{center}
\includegraphics[width=0.2\textwidth]{69.png}
\end{center}
Kombu et al., synthesized several 6-Alkyl/Aryl-1,2,4-Triazino[4,3c] Quinazolines. The bronchodilator activity was assessed in-vivo by comparing with aminophylline in which the 10-bromo-6-methyl-2H-[1,2,4]triazino[3,4-a]isoquinolin-3(4H)-one (70) showed promising activity.

\[
\text{(70)}
\]

**ANTIDIABETIC AGENT:**
Though several molecules of quinazolines were synthesized in the past targeting diabetes, none were promising except Linagliptin which got recently through phase-III clinical trials. Linagliptin (71)- It is a DPP-4 inhibitor used for treating type-II diabetes Which showed promising results in phase-III clinical trials and going to be launched into market with the brand name of ONDERO.

\[
\text{(71)}
\]

**DIURETIC AGENTS:**
There are very few promising diuretic drugs of quinazoline category, which are presently marketed. They are mostly used for the management of hypertension. To overcome its side effects novel drugs are still being synthesized.

Fenquizone (Hydromox) (72): It is a low ceiling sulfonamide diuretic used primarily in the treatment of oedema and hypertension.
Metolazone (Zaroxolyn) (72) It is a thiazide like diuretic used primarily to treat congestive heart failure and high blood pressure. In severe conditions it is used along with loop diuretics like Furosemide, bumetanide etc. It was found to be effective in patients with renal insufficiency.

Quinethazone (74): It is a thiazide diuretic used in the treatment of hypertension.\(^{107}\)

ANTIPARKINSONISM AGENT:
Quinazolines were recently investigated for anti-parkinsonian potential and interestingly they were found to posses more biological activity when compared to standard drugs available in the market.

Sunil et al., synthesized several 3-Substituted phenyl 2-(3,4-dihydroxyphenyl ethyl amino)-6-substituted quinazolin-4-(3H) ones and tested for antiparkinsonian agents. Among them 6-bromo-3-(2-chlorophenyl)-2-((3,4-dihydroxyphenethyl)amino)quinazolin-4(3H)-one (75) was found to be potent when compared with the standard drug Levo-dopa.\(^{108}\)
PHOSPHODIESTERASE INHIBITORY AGENTS:
Quinazolines were recently investigated for Phosphodiesterase inhibition potential and interestingly they were found to possess more biological activity and more specificity towards various Phosphodiesterase enzymes, which may be helpful in male erectile dysfunction.

Kim et al., synthesized various 4-(3-chloro-4-methoxy)-benzylamino-7-methoxy quinazoline derivatives and stated that by systematic variation of C₆, C₇, and C₈ positions of quinazoline scaffold through unique and efficient, potent and highly selective analogues against PDE₆ and PDE₁₁ were obtained. Incorporation of polar functionality would lead to compounds that possess more preferable physicochemical properties such as solubility, membrane permeability and protein binding. Compound 1-(4-(3-chloro-4-methoxyphenethyl)-8-(2-hydroxyethyl)-(methoxymethyl)quinazolin-6-yl)propan-2-one was found to be potent than standard drug tadalafil.¹⁰⁹

![Chemical Structure](image)

(76)

ANTIDEPRESSANT AGENTS:
In the anti-depressant criteria still a promising molecule has yet to be launched. Except some drug candidates like ATC-0175 none of the other derivatives of quinazoline had come to the development phase.

ATC-0175 (77): It is the drug in scientific research, which is a selective, non-peptide antagonist at the melanin concentrating hormone receptor MCH₁. In animal studies it produced significant anti–depressant action without sedative and ataxic side effects¹¹⁰
2.3 ANTIULCER AGENTS

2.3.1 \( \text{H}^+\text{K}^+-\text{ATPASE ANTAGONISTS} \)

Proton pump is the ultimate mediator of gastric acid secretion by parietal cells. With the identification of \( \text{H}^+\text{K}^+-\text{ATPase} \) as the primary gastric proton pump, it was proposed that activation of \( \text{H}^+ \) secretion occurred by incorporation of \( \text{H}^+\text{K}^+-\text{ATPase} \)-rich tubulovesicles into the apical plasma membrane and that the pumps were re-sequestered back into the cytoplasmic compartment on return to the resting state. Inhibition of the proton pump, \( \text{H}^+\text{K}^+-\text{ATPase} \) as a means of controlling gastric pH has attracted considerable attention.\(^{111}\)

2.3.1.1 IRREVERSIBLE \( \text{H}^+\text{K}^+-\text{ATPASE ANTAGONISTS} \)

In recent years with the discovery of benzimidazole sulfoxide class of antisecretory agents. Ruwart et al. identified timoprazole as one of the first well-defined inhibitor of gastric proton pump. Timoprazole was followed by more potent picoprazole (1976) and omeprazole (1979).\(^{112}\) Chemically, the basic structure consists of substituted benzimidazole ring and a substituted pyridine ring connected to each other by a methylsulfinyl chain. Clinically used PPIs include omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole.

1. Irreversible inhibitors, related structurally to pyridinylmethylsulfinyl Benzimidazole

Uchiyama et al., have reported the synthesis of \((+/-)\) 5-methoxy-2-[(4-methoxy-3,5-dimethyl-pyridin-2-yl)methylsulfinyl]-1H-imidazo[4,5-b]pyridine (TU-199) (78) and its effect on histamine, carbachol, and tetragastrin stimulated gastric acid secretion.
They have claimed it to be having more potent and long lasting effects on gastric acid secretion via inhibition of H⁺/K⁺-ATPase than omeprazole.\textsuperscript{112}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

(78)

\textbf{A. CHANGES MADE ON/IN THE BENZIMIDAZOLE NUCLEUS.}

Changes have been made on the benzimidazole nucleus without loss of activity. Following are some reports:

Woo et al., have reported the biological evaluation of 2-[3-(2,3-dihydro-1H-pyrolo[1,2-a]benzimidazolyl)sulfinyl]-5-methyl-1H-benzimidazoles, (YJA20379-4) (79), having marked inhibitory effect on H⁺/K⁺-ATPase. YJA20379-4 also exhibited anti-
\textit{H. pylori} activity 3 times higher than omeprazole along with the enhancement of mucosal defense, thus, indicating a wide spectrum of antiulcer activities.\textsuperscript{113}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

YJA20379-4 (79)

In another related work,

Kim et al., modified imidazopyridines by fusing with thiazolopyridines to get YJA-20379-2 (80). This compound not only suppressed H⁺/K⁺-ATPase activity, but also had significant reinforcing activity on the defensive factors.\textsuperscript{114}

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

YJA-20379-2 (80)
Yoon et al., have synthesized imidazopyridines fused with benzothiazole moiety (81). These novel compounds not only showed potent inhibitory activity against H⁺/K⁺-ATPase but also showed significant cell protective activity.¹¹⁴

![Chemical Structure](81)

Yoon et al., have replaced the conventional benzimidazole ring system with the bioisosteric benzothiazolidine ring system. They have reported the synthesis of derivatives of 2-[(3,5-dimethyl-4-methoxypyridylalkyl)-benzothiazolidine (82) which were found to be more potent *in vitro* inhibitors of H⁺/K⁺-ATPase. The methylsufinyl linkage has also been replaced by methylene linkages.¹¹⁵

![Chemical Structure](82)

➢ **N-alkylation/acylation of the benzimidazole ring nitrogen leads to the biolabile**

N-substituted benzimidazole derivatives (prodrugs) of Timoprazole. The parent N–H compound is liberated either by in vivo esterase hydrolysis or requires an acidic environment. N-(acyloxy) alkyl substituted benzimidazoles showed improved chemical stability of which (83) proved twice as potent as omeprazole. Similarly (84) was found to be twice active as timoprazole.¹¹⁶
Fusion of one more ring on the benzimidazole nucleus has been shown to be beneficial.

Sigrist-Nelson et al.\textsuperscript{117} have reported the synthesis and evaluation of 5,7-dihydro-2\{[(4-methoxy-3-methyl-2-pyridyl)methyl]sulfinyl]-5,5,7,7tetramethyl indeno-[5,6-d]imidazol-6-(1\textit{H})-one (Ro18-5364) (85) as an extremely effective inhibiting agent. Ro 18-5364 produced almost complete inhibition of the \(H^+/K^+\)-ATPase activity, as well as associated proton translocation. The activity of the inhibitor appeared to be independent of its stereochemistry. However, sulphide analog of Ro 18-5364 was devoid of any significant inhibitory activity.\textsuperscript{117}
B. CHANGES MADE ON THE PYRIDINE NUCLEUS.

The pyridine ring has been annulated to one more ring or its bioisosteric replacement is done or has been replaced by an aromatic carbocycle, without loss of potency.

Uchida et al.,\textsuperscript{118} worked on series of some 4-substituted 8-[(2-benzimidazolyl)sulfinylmethyl]-1,2,3,4-tetrahydroquinoline, which exhibited H\textsuperscript{+}/K\textsuperscript{+}-ATPase inhibitory and anti-secretory activities against histamine-induced gastric acid secretion. Of these, 4-(N-allyl-N-methylamino)-1-ethyl-8-[(5-fluoro-6-methoxy-2-benzimidazolyl)sulfinyl methyl]-1-ethyl-1,2,3,4-tetrahydroquinoline (86) was found to have potent anti-ulcer activity. Further, many of the derivatives showed cytoprotective activities. Notably, the methyl sulfinyl side chain is not attached to the pyridine nucleus but to the benzene ring.

\[
\text{(86)}
\]

Annulations of pyridine ring to a alicycle has also been tried. Yamada et al.,\textsuperscript{80} have synthesized a series of 2-[(cycloalka[b]pyridinyl)sulfinyl]-1H-benzimidazoles and tested for the inhibition of pentagastrin-induced gastric acid secretion. A novel benzimidazole derivative containing a cyclohepta[b]pyridine moiety was found to be the most potent among the congeners, which included five to eight-membered cycloalka[b]pyridine ring system. Of them 2-[(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-yl)-sulfinyl]-1H-benzimidazole (87) analogs having various substituents on aromatic rings were found to be superior than Omeprazole.

Compound TY-11345 (87) was selected for further evaluation. Notably, the methylsulfinyl linkage has also been modified.
Replacement of the pyridine ring with less basic isosteric pyrimidine ring has also been reported by Japanese workers.\textsuperscript{119} They have evaluated 2-\((1\text{H}-\text{benzoimidazole}-2\text{-sulfinylmethyl})-4\text{-dimethylamino-pyrimidine-5-carboxylic acid ethyl ester (88)}\) for its proton pump inhibition. It was found to have marked proton pump inhibitory activity with IC\(_{50}\) of 7.5 lm as compared to omeprazole IC\(_{50}\) of 5.8 lm.

Replacement of the heterocyclic pyridine ring with aromatic carbocycles has also been attempted. Tsukahara et al.,\textsuperscript{120} synthesized [2-\((1\text{H}-\text{benzoimidazole}-2\text{-sulfinylmethyl})\text{-phenyl}\]-isobutyl-methyl-amine (leminoprazole) (89) which was found to be a potent PPI.
3. **IRREVERSIBLE INHIBITORS, NOT RELATED STRUCTURALLY TO PYRIDINYL METHYL SULFINYL BENZIMIDAZOLE**

Terauchi et al.\textsuperscript{121} have reported the synthesis and evaluation of N-substituted 2-(benzhydryl)nicotinamides (90) and N-substituted 2-(benzylsulfinyl)nicotinamides (91), which upon acid activation were converted to their active forms, 2,3-dihydro-3-oxoisothiazolo[5,4-b]pyridines (92) responsible for gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase inhibition. Both of these compounds showed *in vivo* and *in vitro* inhibitory activities equivalent to omeprazole and was more stable than omeprazole, lansoprazole, and pantoprazole at neutral and weakly acidic pH. Further, these parent nicotinamides were devoid of any *in vitro* H\textsuperscript{+}/K\textsuperscript{+}-ATPase inhibitory activity of themselves.

![Chemical structures](image)

Berzsenyi et al.\textsuperscript{122} have synthesized and tested [2-(2,5-dimethyl-2H-[1,2,4]triazol-3-ylsulfanyl)methyl]phenyldimethylamine (GYKI-34655) (93), as irreversible inhibitor. It was found to be a potent gastric anti-secretory, antiulcer, and cytoprotective agent.

![Chemical structures](image)
Winfried Beil et al.\textsuperscript{123} have synthesized and reported Hoe 731 (95) and S 4216 (94), both thieno-imidazole derivatives, as an inhibitor of gastric proton pump (gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase). The action of the H\textsuperscript{+}/K\textsuperscript{+}-ATPase inhibitors, Hoe 731 and S 4216 was compared with that of the benzimidazole derivative, omeprazole. In intact, gastric membrane vesicles under conditions shown to result in acidification of the vesicle interior, Hoe 731 and S 4216 inhibited H\textsuperscript{+}/K\textsuperscript{+}-ATPase activity with an IC\textsubscript{50} value of about 1.0 µM and 1.2 µM. In the absence of a generated pH gradient the respective IC\textsubscript{50} values were 5.5 µM and 2.1 µM. In contrast, omeprazole inhibited the enzyme only in the presence of proton accumulation (IC\textsubscript{50}:0.7 / µM).

The inhibitory action of omeprazole on H\textsuperscript{+}/K\textsuperscript{+}-ATPase-mediated proton transport was prevented by the membrane permeable mercaptane, dithioerythritol, but not by the membrane impermeable, mercaptane and glutathione, whereas both mercaptanes and glutathione were able to prevent the effect of Hoe 731 and S 4216. These results indicate that the thienoimidazoles react with intravesicular (luminal) and extravesicular (cytosolic) SH groups of the H\textsuperscript{+}/K\textsuperscript{+}-ATPase, whereas omeprazole interacts uniquely with luminal SH groups of the enzyme. In isolated parietal cells all drugs caused a concentration-dependent inhibition of HCl production, as measured by [\textsuperscript{14}C] aminopyrine uptake, during histamine and dibutyryl-cAMP stimulation. The IC\textsubscript{50} value was 0.1/ µM for Hoe 731 and 0.4/ µM for S 4216 after 30 min incubation. The inhibitory action of Hoe 731 and S 4216 faded with increasing incubation time, whereas omeprazole caused an unchanged inhibition over the entire 120-min incubation period. That shows shorter duration of action of proposed molecules compare to omeprazole.
Zimmermann. P. J et al.,\textsuperscript{124} A series of novel indanyl-substituted imidazo[1,2-a]pyridines as potent reversible inhibitors of the gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase. 8-indanylamino (96) and 8-indanyloxy (97) substituted imidazo[1,2-a]pyridines with improved physicochemical properties compared to the AR-HO47108 (98) which suffer from high lipophilicity and are therefore susceptible to extensive metabolism 2,6-dialkylbenzylamino substituted series AR-HO47108 (98). \textit{In vitro} activity of compounds (96) and (97) as antagonists of the gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase is excellent: the strength of inhibition of both compounds is comparable to that of the known P-CAB, AR-HO47108 (98) with IC\textsubscript{50} 1.7 and 1.4 µM respectively.
Wha bin im et al.\textsuperscript{125} have reported unsaturated long chain fatty acids as inhibitors of gastric proton pump (gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase).

**Table 6: Long chain fatty acids as inhibitors of gastric proton pump**

<table>
<thead>
<tr>
<th></th>
<th>IC\textsubscript{50}</th>
<th>Hog (H\textsuperscript{+}/K\textsuperscript{+})-ATPase</th>
<th>Rat (H\textsuperscript{+}/K\textsuperscript{+})-ATPase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arachidonic acid</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Linolenic acid</td>
<td>58</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>60</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Oleic acid</td>
<td>76</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Linoelaidic acid</td>
<td>80</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Linolenyl alcohol</td>
<td>240</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Linolenyl methyl ester</td>
<td>No inhibition</td>
<td>No inhibition</td>
<td>No inhibition</td>
</tr>
<tr>
<td>Lysophosphatidylcholine, Oleoyl</td>
<td>75</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Patil A. et al.\textsuperscript{126} synthesized 2-[5-substituted-1-\textit{H}-benzo(d)imidazol-2-yl sulfinyl]methyl-3-substituted quinazoline-4-(3H)-one (99) derivatives and tested for antiulcer activity against pylorus ligation-induced, aspirin induced and ethanol induced ulcer in rat model. Compound (99) showed most potent activity as compared to Omeprazole at the dose level of 10 and 20 mg/kg with percentage inhibition 95 and 92 in aspirin induced ulcer and pyloric legated ulcer.
Literature review

Sharma P. et al.,\textsuperscript{127} identify new anti-ulcer compounds, a series of N-acyl derivatives of \(\alpha\)-amino acids and screened for their \textit{in-vitro} \(\text{H}^+\)/\(\text{K}^+\) ATPase inhibitory activity, and \textit{in-vivo} efficacy in Pylorus ligation model. The most potent compound from this study, cis-5-(2-phenylethenyl)-2-oxo-oxazolidine-4-carboxylic acid (100) showed 0.16 (-log IC\(_{50}\)).

![Chemical Structure of 100](image1)

Yoshiaki T. et al.,\textsuperscript{128} have reported \(\text{H}^+\)/\(\text{K}^+\)-ATPase inhibitory activity of Cibenzoline (101) on permeabilized leaky hog gastric vesicles in a concentration-dependent manner with IC\(_{50}\): 201 \(\mu\text{M}\). Cinazoline inhibits \(\text{H}^+\)/\(\text{K}^+\)-ATPase activity competitively with respect to \(\text{K}^+\).

![Chemical Structure of 101](image2)

Ito K. et al.,\textsuperscript{129} synthesized and reported 7-(4-Fluorobenzyloxy)-2,3-dimethyl-1-\{[(1S,2S)-2-methyl cyclopropyl]methyl\}-1\(H\)-pyrrolo[2,3-\(d\)]pyridazine (CS-526) (102) as novel acid pump antagonist on hog \(\text{H}^+\)/\(\text{K}^+\) ATPase gastric activity.

![Chemical Structure of 102](image3)
Yamada M. et al.,\textsuperscript{130} have reported 2-[(2-Aminobenzyl)sulfinyl]-1-(2-pyridyl)-1,4,5,6 tetrahydrocyclopent[d]imidazoles (103) as a Novel Class of Gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase Inhibitors.

(103)

Sih. C. J. et al.,\textsuperscript{131} reported The synthesis of N-substituted benzimidazole. These compounds were prepared to function as prodrugs of the parent N-H compound and evaluated for their ability to inhibit gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase and gastric acid secretion. The prodrugs reported rely on either \textit{in-vivo} esterase hydrolysis for liberation of the parent compound or require an acid environment for release of the active drug. The N-(acyl oxy)alkyl-substituted benzimidazoles (105) showed improved chemical stability in the solid state and in aqueous solutions when compared to their parent N-H compounds. When given orally, (105) was found to be twice as potent as omeprazole in both the Shay rat and inactivation of gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase in the rat. In the Shay rat (105) at 10 mg/kg was approximately twice as active as parent timoprazole.

(104)

Timoprazole (R\textsubscript{1}=R\textsubscript{2}=R\textsubscript{3}=R\textsubscript{4}=H)
Omeprazole (R\textsubscript{1}=R\textsubscript{3}=OCH\textsubscript{3}; R\textsubscript{2}=R\textsubscript{4}=CH\textsubscript{3})

(105)

Bristol. J. A. et al.,\textsuperscript{132} have reported 2-(9-chloro-9aH-chromeno[2,3-b]pyridin-5-yl)-N-methylpropanamide (106), a new class of gastric antisecretory agents and antiulcer
agents. Certain compounds inhibit histamine, dimaprit, insulin, and food-stimulated gastric acid secretion in dogs, as well as aspirin-induced ulcers in rat. Most compounds are antisecretory in the pylorus-ligated rat. Several compounds are comparably potent to cimetidine.

2.3.1.2 REVERSIBLE POTASSIUM COMPETITIVE ATPase INHIBITORS

Choi S. J. et al.,\textsuperscript{133} have reported the activity of 1-(2-methyl-4-methoxyphenyl)-4-[(3-hydroxypropyl)amino]-6-methyl-2,3-dihydropyrrolo[3,2-c]quinoline (DBM-819) \textsuperscript{(107)} as potential reversible inhibitor. DBM-819 successfully reduced histamine and pentagastrin stimulated gastric acid secretion and protected against gastric lesions induced by ethanol, NaOH, indomethacin, and aspirin, suggesting that DBM-819 acts as an effective anti-ulcer agent \textit{in-vivo}. The same workers have also evaluated 1-(2-methyl-4-methoxyphenyl)-4-[(2-hydroxyethyl)amino]-6-trifluoroethoxy-2,3-dihydropyrrolo[3,2-c] quinoline (AU-461) \textsuperscript{(108)} which was found to be reversible and competitive inhibitor with respect to the activating K$^+$ cation.
Shin J. M. et al.\textsuperscript{134} have reported a novel reversible PPI, 1-[5-(2-fluorophenyl)-1-(pyridin-3-ylsulfonyl)-1H-pyrrol-3-yl]-N-methylmethanimine monofumarate (TAK-438) (109) which was found to be novel potassium-competitive acid blocker of the gastric H\(^+/K^+\)-ATPase.

![Chemical structure of TAK-438](image)

Yuki et al.\textsuperscript{135} have reported potassium-competitive acid inhibitory activity of 2-methyl-8-(3-methyl-but-2-enyloxy)-imidazo[1,2-a]pyridine-3-carbonitrile (YM-020) (110).

![Chemical structure of YM-020](image)

Leach et al.\textsuperscript{136} have reported H\(^+/K^+\) ATPase inhibitory activity of 3-butyryl-4-[(2-methyl phenyl)amino]-8-(2-hydroxyethoxy)quinoline, SK\& F 97574 (111). It was found to be well tolerated and efficacious in phase-I studies.
Kaminski et al.,\textsuperscript{137} identified 3-(cyanomethyl)-2,7-dimethyl-8-(phenylmethoxy)imidazo[1,2-a]pyridine (112), 3-amino-2-methyl-8-(2-phenyl ethyl) imidazo [1,2-a]pyridine (113), and SCH-32651 (114). These analogues exhibit anti-secretory and cytoprotective activity, particularly, SCH 32651 was mentioned as a promising candidate.

Ife R. J. et al.,\textsuperscript{138} synthesized and reported 4-(2-Pyridyl)-S-phenylthiazoles (117), derivative as reversible K\textsuperscript{+}-competitive gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase inhibitor with IC\textsubscript{50} value 2\textmu M. This was based on the proposal that hydrogen-bonding between the carbonyl oxygen and the N-H in 1 was an important factor in controlling the orientation of the arylamino moiety and ultimately activity. They reasoned that if the hydrogen-bond in 115 could be replaced by a pyrrolidine ring, then perhaps a ring already present in 116 and 117 could conversely be replaced by a hydrogen-bond. Active compounds were subsequently evaluated \textit{in-vivo} for their ability to inhibit pentagastrin-stimulated gastric acid secretion in the lumen perfused rat model.
Zimmermann, P. J. et al.\textsuperscript{139} have synthesized and reported novel indanyl-substituted imidazo[1,2-a]pyridines (119, 120) as potent reversible inhibitors of the gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase with improved physicochemical parameter with reduced lipophilicity compare to earlier reported potassium competitive acid antagonist series of 8-(2,6-dialkylbenzylamino)-substituted imidazo[1,2-a]pyridines. However, many compounds of this series, such as the known inhibitor AR-HO47108 (118), suffer from high lipophilicity and are therefore susceptible to extensive metabolism. The \textit{in vitro} activity of compounds 119 and 120 as antagonists of the gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase is excellent with IC\textsubscript{50} value 6.3 and 6.9µM respectively with improved physicochemical parameter.
Pope. J. A. et al.,\textsuperscript{140} have synthesized and reported SK&F 97574 (3-butyryl-4-(2-methylamino)-8-(2-hydroxyethoxy)quinoline) (121), is a potent inhibitor of the H\textsuperscript{+}/K\textsuperscript{+}-ATPase in membrane vesicles isolated from porcine gastric mucosa. It inhibits H\textsuperscript{+}/K\textsuperscript{+}-ATPase activity in lyophilised vesicles in a kinetically competitive manner with respect to the activating cation, K\textsuperscript{+}, with an inhibition constant (Ki) of 0.46 ± 0.003 pm Inhibition of H\textsuperscript{+}/K\textsuperscript{+}-ATPase activity is freely reversible. Binding of SK&F 97574 was shown to be mutually exclusive than previously reported reversible H\textsuperscript{+}/K\textsuperscript{+}-ATPase inhibitors, SCH 28080 (122) and MDPQ (123). Therefore, despite its structural dissimilarity, SK&F 97574 appears to bind to the same luminal region of the H\textsuperscript{+}/K\textsuperscript{+}-ATPase identified as the binding site for these compounds. SK&F 97574 is a weak base (pKa = 6.86) and would therefore be expected to accumulate in the acidic compartment at the luminal face of the parietal cell. In intact gastric vesicles (which have the luminal face of the ATPase on the interior), SK&F 97574 inhibited ATP dependent H\textsuperscript{+}-transport with a similar potency to ATPase activity. SK&F 97574 is therefore relatively membrane permeable, and would be predicted to gain access readily to its site of action \textit{in vivo}.

The effect of pH on inhibition of H\textsuperscript{+}/K\textsuperscript{+}-ATPase activity by SK&F 97574 is consistent with its being active only in its protonated form. The selectivity of SK&F 97574 for the gastric H\textsuperscript{+}/K\textsuperscript{+}-ATPase was tested by examining its ability to inhibit a closely related p-class pump, the Na\textsuperscript{+}/K\textsuperscript{+}-ATPase from dog kidney. SK&F 97574 was found to have a 60-fold greater sensitivity for the H\textsuperscript{+}/K\textsuperscript{+}-ATPase. The Na\textsuperscript{+}/K\textsuperscript{+}-ATPase is not inhibited in a K\textsuperscript{+}-competitive manner by SK&F 97574, indicating an entirely different, probably nonspecific, mechanism.
Yoon Y. A. et al.\textsuperscript{141} described their extended work to the corresponding pyrimidines related to Revaprazan (124), the representative agent based on pyrimidine scaffold, shown to inhibit gastric acid secretion by reversible binding to H\textsuperscript{+}/K\textsuperscript{+}ATPase, and it also displayed excellent antisecretory properties both in animals and human beings. Revaprazan (124) was launched in Korea in 2007 for the treatment of duodenal ulcer, gastric ulcer and gastritis. It is also undergoing phase III clinical studies for the treatment of GERD. Out of series, pyrimidine derivatives as acid pump antagonists (APAs) was synthesized, the inhibitory activities against H\textsuperscript{+}/K\textsuperscript{+}ATPase isolated from hog gastric mucosa were determined. After elaborating on substituents at C\textsubscript{2} and C\textsubscript{4} position of the pyrimidine scaffold, compound (125) is a potent APA with H\textsuperscript{+}/K\textsuperscript{+} ATPase, IC\textsubscript{50} = 52 nM.
Yoon. Y. A. et al.,\textsuperscript{142}efforted to develop novel and potent APAs and abled to identify APAs that have a novel heterocyclic scaffold different from the well-known imidazo[1,2-a]pyridine. They report the synthesis and inhibitory activities of 1H-pyrrolo[2,3-c]pyridine derivatives against H\textsuperscript{+}/K\textsuperscript{+}ATPase isolated hog gastric mucosa. Out of series Compounds two potent compounds 126 and 127 inhibited H\textsuperscript{+}/K\textsuperscript{+} ATPase activity in a K\textsuperscript{+}-competitive manner with Ki = 13.6 and 10.7 nM, respectively. IC\textsubscript{50} values of Compounds 126 and 127 were 0.028 and 0.030\textmu M.

Niiyama. K. et al.,\textsuperscript{143}found a series of novel 4- substituted pyridine derivatives, represented by AU-2064 (128), by chemical modification of Omeprazole. Various 4-alkylthio, 4-alkoxy or 4-aryloxypyridine derivatives using a 4-methylsulfenyl group as a marked leaving group. Compound (129) showed reasonable in vivo activities in an acute fistula rat or a pylorus-ligated rat model. 129 was revealed most potent
Inhibitor of H⁺/K⁺ATPase IC₅₀ (0.6 µM), in Acute fistula rats, 69% inhibition and Pylorus-ligated rats, 56% inhibition in pylorus-ligated rat model. Potent molecule AU-2064 shows inhibitory activity with IC₅₀ 3.1µM with reversible action.

Garton, N. et al., ¹⁴⁴ develop the biarylimidazole framework to yield a compound AR-HO47108 (130) with submicromolar activity against the gastric H⁺/K⁺ATPase. (H⁺/K⁺ATPase pIC₅₀=6.1) which removes one of the potentially problematic structural features in the imidazopyridine series (i.e. the benzylamine functionality).

Palmer, A. M. et al.,¹⁴⁵ have reported asymmetric synthesis of a series of novel 5-carboxamide-substituted tetrahydrochromeno[7,8-d]imidazoles (133) using the readily available candidate BYK 405879 (132) as starting material. The pharmacological activity of the compounds assessed in the Ghosh Schild rat, that is, the reduction of the pentagastrin-stimulated acid secretion by the respective P-CAB was determined. Potent compound (133) showed noteworthy activity as potassium-competitive acid blockers with ED₅₀ values comparable to that of BYK 405879 (ED₅₀ = 0.23 lmol/kg).
Palmer, A. M., prepared Asymmetric and symmetric spiro(imidazo[1,2-a]pyrano[2,3-c]pyridine-9-indenes) using a synthetic approach that comprised a cross-metathesis reaction and an acid-catalyzed cycloisomerisation. The inhibitor SCH 28080 (134) shows excellent anti-secretory and cytoprotective properties. However, the clinical development of SCH 28080 (134) was stopped due to extensive metabolism and associated liver toxicity. Molecular modelling of SCH 28080 suggested that in the gas phase, SCH 28080 could adopt various ‘folded’ (134) conformations close to the global minimum of energy. On the other hand, single-crystal X-ray analysis revealed that solid SCH 28080 existed in an ‘extended’ (135) conformation. It was shown that an ‘extended’ relationship between the phenyl group and the heterocyclic nucleus was required for effective binding to H⁺/K⁺-ATPase. The tricyclic imidazo[1,2-a]pyridine was synthesized in which the pyrano ring was considered to enforce this requisite ‘extended’ relationship and to mimic a 7-methyl substituent which would be effective in overcoming the toxic properties of (134) while retaining its desirable anti-secretory effects. Several derivatives with R₃ = CH₃ (136) were shown to be potent inhibitors of the H⁺/K⁺-ATPase with pIC₅₀ values comparable to that of lead compound 136 (pIC₅₀ of 2: 7.0) and favourable pKa values in the range of 6.4–7.2 (pKa of 2: 6.0). 5,18 spiro(imidazo[1,2-a]pyrano[2,3-c]pyridine-9,10-indene) (137) turned out to be a potent inhibitor of the gastric proton pump enzyme showed a pIC₅₀ value of 5.8.
Literature review

SCH 28080 (134)
("folded")

SCH 28080 (135)
("extended")

(136)

(137)