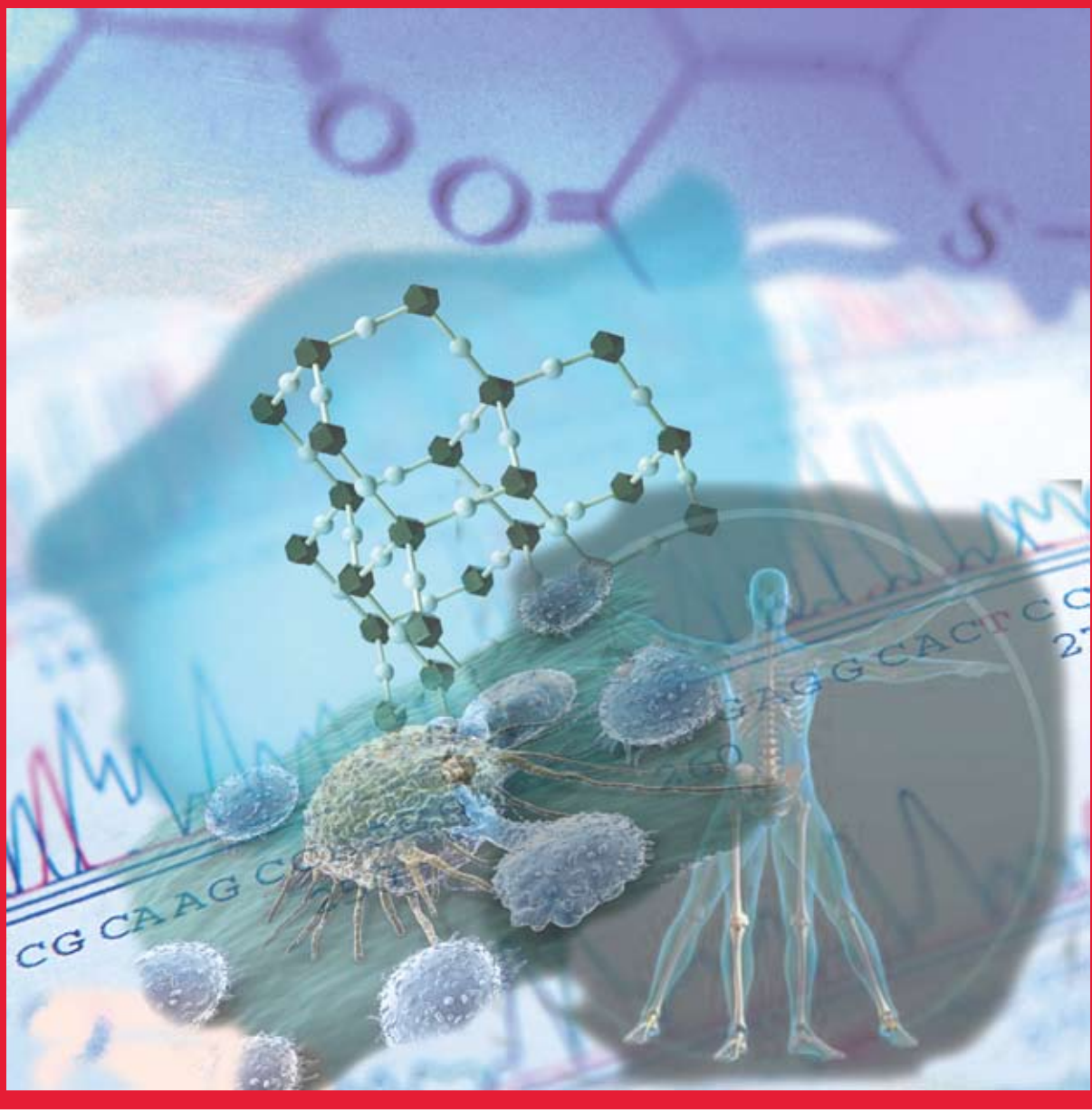
ISSN 0036-021X

Russian Chemical Reviews



Reviews on current topics in chemistry

Chemistry and biomedicine: diversity and unity of goals

Volume 84 2015 Number 1

 © 2015 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RCR4430

Anti-ulcer agents: chemical aspect of solving the problem

L N Rogoza (deceased), N F Salakhutdinov

N N Vorozhtsov Novosibirsk Institute of Organic Chemistry,
Siberian Branch of the Russian Academy of Sciences
prosp. Akademika Lavrentieva 9, 630090 Novosibirsk, Russian Federation

The data on chemical structures and specific activities of compounds functioning as histamine H_2-receptor antagonists, H^+/K^+-ATPase inhibitors at the exchange sites of hydrogen ions (proton pump inhibitors) and potassium ions (K^+-competitive acid blockers) published from 1990 to 2013 are surveyed. The antisecretory agents with studied cytoprotective activity or with additional therapeutic properties compensating for disorders of internal defence mechanisms are presented. A separate section is devoted to the drugs that prevent or mitigate the NSAID-induced intestinal damage. All of the considered structures are classified according to the type of biological mechanism of action. Some aspects of the structure – activity relationships for such compounds are considered.
The bibliography includes 83 references.

Contents

I. Introduction 98
II. Histamine H_2-receptor antagonists 99
III. Proton pump inhibitors 109
IV. K^+-Competitive acid blockers 112
V. Non-steroidal anti-inflammatory drug-induced erosive and ulcerous damages of the digestive tract 117

I. Introduction

Functional diseases of the gastro-intestinal tract (GIT) occupy a top place in the structure of digestive organ pathologies. These are diseases related to disorders of the main functions of the gullet, stomach and duodenum such as oesophagitis, gastro-oesophageal reflux disease (GERD), gastritis, stomach ulcer, duodenal ulcer and gastroduodenitis. The symptomatic GIT erosions and ulcers can also be assigned to this group (as the same drugs are used to prevent and treat them). These include acute stress-induced ulcers arising upon extensive burns, cold injuries, traumatic brain injuries and surgery, and cardiac infarctions; trophic ulcers that accompany atherosclerosis, ischemic heart disease, circulatory deficiency, uremia and alcoholism; endocrine ulcers, which may be caused by the Zollinger – Ellison syndrome and hyperparathyroidism; drug-induced ulcers formed upon taking of non-steroidal anti-inflammatory drugs (NSAIDs) and steroid hormones.

The causes of disorders of GIT functions are diverse. The pathological mechanisms involve a number of adverse factors of both the external environment and the internal body system. In the very general case, a disease is a result of unbalance between the defence (mucosa stability or resistance) and invasion mechanisms. Normally, the defence factors such as gastric mucus, bicarbonate, mucin and prostaglandin secretion, adequate blood supply and continuous renewal of the mucosal cells always prevail.

The ivnasive factors include supersecretion of the gastric juice components (hydrochloric acid, pepsin) caused by various external and internal impacts, direct injury by food, gastroduodenal motility disorder — too fast escape of the acidic content of the stomach into the duodenal bulb ('acid impact' on the mucosa) or, conversely, retention of the stomach content. The unbalance of the invasive and defence factors with the latter being suppressed is promoted by bile acids, pancreatic enzymes, traumatic lesions, stress, alcoholic drinks, nicotine, medicines (NSAIDs, glucocorticoids) and also specific *Helicobacter pylori* bacteria.

The prevention of the gastric mucosa damage and ulceration by medicines can use two approaches: either suppression of the secretion or enhancement of the defence mechanisms. Currently, three principal groups of drugs are used to treat GIT diseases: (i) antacid or antisecretory drugs, (ii) gastroprotective drugs and (iii) anti-helicobacter

L N Rogoza(deceased) Candidate of Chemical Sciences
Research area: synthesis, structure and reactivity of natural and physiologically active compounds; medicinal chemistry.
N F Salakhutdinov Doctor of Chemical Sciences, Professor, Head of the Department of Medical Chemistry of the same institute.
Telephones: (7-383) 330 97 33, (7-383) 214 29 86,
e-mail: anvar@nioch.nsc.ru
Current research interests: synthesis, structure and reactivity of natural and physiologically active compounds; medicinal chemistry and prediction of other types of biological activity.

Received 4 October 2013
Uspekhi Khimii **84** (1) 98 – 120 (2015); translated by Z P Svitanko

pilory drugs. They act either on the invasion squad by reducing the volume of hydrochloric acid and pepsin or on the defence squad by stimulating the mucosal protection properties (cytoprotectors). Unfortunately, the demands for treating functional diseases of GIT are not entirely covered.

Today, the most popular classes of drugs used to treat hyperacidic conditions are histamine H_2-receptor antagonists (H_2-blockers) and proton pump inhibitors (PPIs) developed and introduced in the clinical practice in the 1970s – 1980s. These medicines form the basis for treating patients with acid-dependent diseases. The benefit of taking these drugs to treat the functional GIT diseases is enormous but, unfortunately, they are not free from some drawbacks. As the drawbacks of H_2-blockers, note the decrease in the acid-inhibiting action on long-term use. The proton pump inhibitors surpass H_2-blockers in the clinical effect but also suffer from some drawbacks. Among these are high percentage of patients having resistance to particular PPIs, the possibility of so-called 'nocturnal acid breakthrough' caused by relatively short elimination half-life of the drug, acid activation, the presence of a time period needed for the transformation of the prodrug into the active compound and the effect of genetic features on the PPI therapy. Moreover, after withdrawal of these drugs, relapses often occur due to insufficient resistance of the gastric mucosa resulting from inefficiency of cytoprotective mechanisms. In this case, successful treatment of GIT diseases requires administration of additional (gastroprotective) drugs that would compensate for insufficient cell protection mechanisms. Hence, the optimal medication for treating hyperacidic states should have not only antisecretory but also sufficient gastroprotective activity. From this standpoint, of special interest are compounds with cytoprotective action.

The present review is an attempt to survey the most recent published data on the chemical structures and the specific activities of three classes of drugs and agents: histamine H_2-receptor antagonists and inhibitors of hydrogen – potassium adenosine triphosphatase (H^+/K^+-ATPase) — the proton pump at the exchange sites of hydrogen ions (proton pump inhibitors) and potassium ions (K^+-competitive acid blockers, P-CABs). We selected antisecretory agents with studied cytoprotective activity or with additional therapeutic properties compensating for the deficiency of the internal defence mechanisms: Ca-antagonistic, antioxidant and anti-helicobacter pilory activities, nitrogen oxide donors and gastric motility regulating activities. In view of the specific character of helicobacter pylori eradication therapy, which comprises combined chemotherapy with proton pump inhibitors, antibacterial agents and bismuth compounds, we did not consider in the review the chemical structures and the biological activities of the latter drugs. The agents that prevent or mitigate the NSAID-induced intestinal lesions are considered separately.

II. Histamine H_2-receptor antagonists

The antagonists of histamine H_2-receptors (H_2-blockers, H_2-antihistaminic agents, H_2-receptor blockers) are pharmaceutical agents meant for treatment of acid-dependent diseases of the gastro-intestinal tract. The major effect of H_2-antagonists is antisecretory. The mechanism of their action consists in a specific competitive blocking of the parietal cell receptors present in gastric fundic glands, which inhibits the acid secretion, both basal and stimulated by histamine, gastrin, pentagastrin, dimapril (histamine H_2-receptor agonist) or food.

The known H_2-blockers consist of three major units: a (hetero)aromatic ring or hydrophobic group (**A**), a tetraatomic bridge (**B**) and a polar group (**C**) (Fig. 1). Cimetidine (**1**) contains an imidazole ring (like histamine), which was previously considered to be a necessary unit for binding to H_2-receptors. This point of view was disproved by the discovery of more effective H_2-receptor antagonists — ranitidine (**2**), famotidine (**3**) and nizatidine (**4**), which contain a furan or thiazole ring instead of the imidazole ring. The H_2-receptor antagonists discovered more recently,

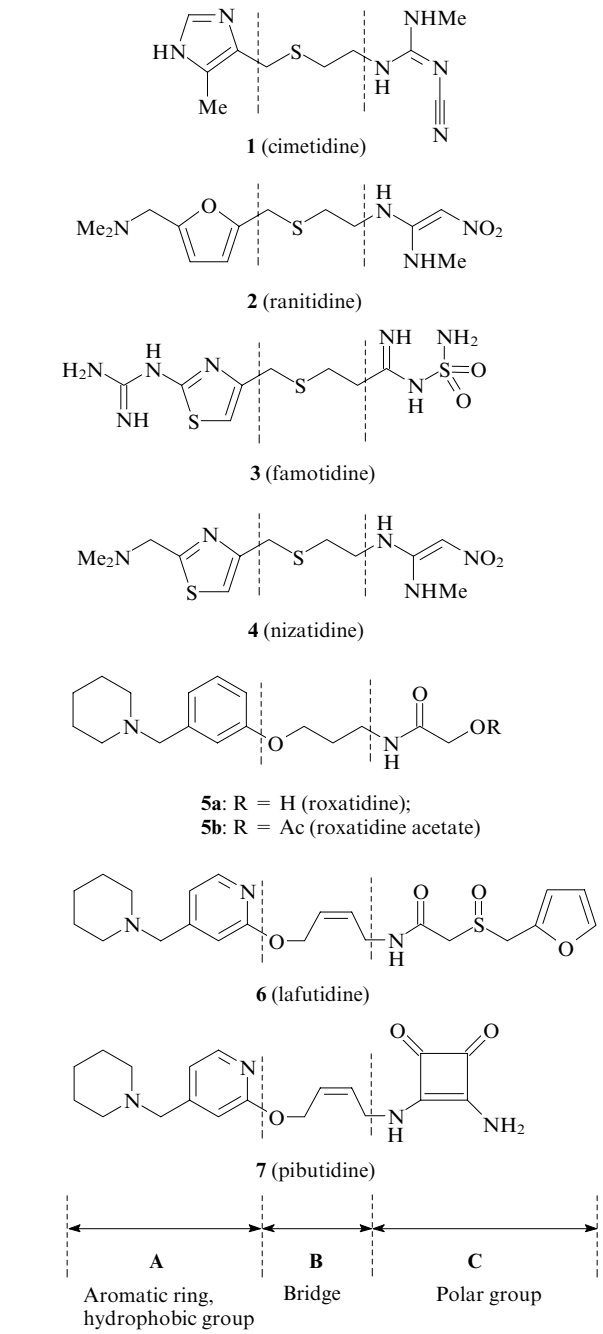
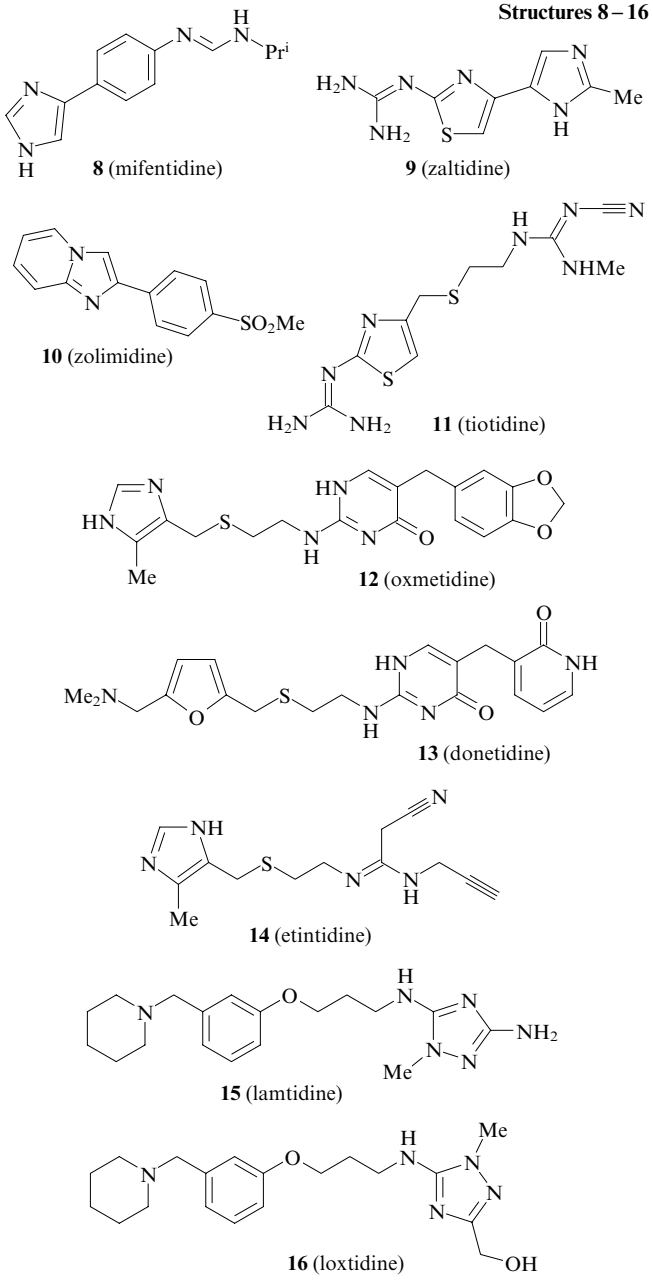


Figure 1. Structural units of the known histamine H_2-receptor antagonists.

Structures 8–16



which contain a piperidinomethyl substituent in the phenyl [roxatidine (**5a**) and roxatidine acetate **5b**] and pyridine moieties [lafutidine (**6**), pibutidine (**7**)], have very high and durable activity (see Fig. 1).

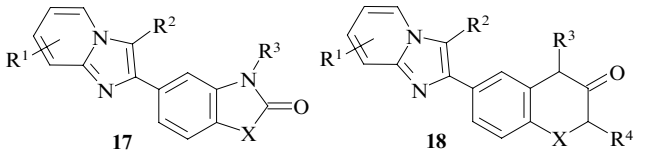
However, compounds **8**–**16** containing similar groups or having a similar H_2-blocker structure have not yet found clinical use.

II.1. Histamine H_2-receptor antagonists of the A + C or A + B + C structure

Despite the fact that the molecules of compounds considered in this Section do not contain a flexible chain (**B**) connecting the other two units, such H_2-blockers proved to be very active. Zolimidine (**10**) has a protective action against experimentally induced lesions of gastric mucosa in various animal species; therefore, several series of zolmidine analogues with molecules consisting of two bicyclic heterocycle systems have been synthesized.

The series of 36 compounds — 5-imidazo[1,2-*a*]pyridin-2-yloxobenzoxazolidines (**17**), 3-oxo-2*H*-1,4-bezoxazines (**18**) and their thio analogues — have been tested for anti-ulcer activity in experiments in rats (stress- and ethanol-induced ulcers).[1] Compounds **17a**–**c** and **18a**–**c** proved to be more active than the reference drugs — cimetidine (**1**), zolmidine (**10**) and sucralfate (gastroprotective agents). Furthermore, compounds **17b** and **18b**,**c** showed a potent protective action against ethanol-induced stomach lesions (Table 1).

Structures 17, 18



R^1 = H, Me, OEt; R^2 = H, Me, Et, CH_2NMe_2; R^3 = H, Me, Pr^i, $(CH_2)_2NEt_2$, $CH_2CO_2Bu^t$; R^4 = H, Me, Et; X = O, S

The anti-ulcer activities have been studied for 45 compounds obtained by modification of unit **C** of compounds **17** and representing imidazo[1,2-*a*]pyridinylbenzoxazoles and their 5,6,7,8-tetrahydro derivatives.[2] For compounds **19a**–**e** and **20a**–**l** most active in this series, the degree of inhibition by a 32 mg kg^{-1} dose was higher than that of cimetidine (**1**) or sucralfate (see Table 1), being in the ranges of 80.9%–97.1% and 91.8%–100%. The effective doses and the confidence ranges for the anti-ulcer and cytoprotective (gastroprotective) effects were determined. For the former characteristics, the 50% effective dose (ED_{50}) was 0.13–0.21 mg kg^{-1} for derivatives **19a**–**e** and **20a**–**l** (for cimetidine, this value is 18.8 mg kg^{-1} and for sucralfate, it is 156 mg kg^{-1}), while for the latter one, the values were 0.05–14.2 mg kg^{-1} (cimetidine: >320 mg kg^{-1}; sucralfate: 55.7 mg kg^{-1}). These results confirm the higher activities of the synthesized compounds compared to cimetidine (**1**) or sucralfate.

Compounds **19** and **20** contain two key units of classical H_2-blockers: the basic heteroaromatic ring (unit **A**) and the

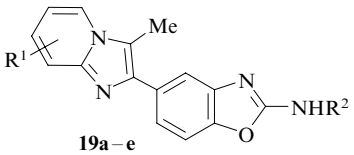
Table 1. Anti-ulcer (I) and gastroprotective (II) activities of compounds **17** and **18** and reference drugs.[1]

Compound or drug	Inhibition (%)	
	I	II
Cimetidine (**1**)	69.4	40.3 [a]
Zolimidine (**10**)	48.2	69.4
Sucralfate [b]	45.6	50.3 [a]
17a (R^1 = H, R^2 = R^3 = Me, X = O)	88.1	–
17b (R^1 = 7-Me, R^2 = R^3 = Me, X = O)	92.5	80.7
17c (R^1 = 7-Me, R^2 = R^3 = Me, X = S)	80.5	–
18a (R^1 = R^3 = H, R^2 = Me, R^4 = Et, X = O)	80.8	–
18b (R^1 = 7-Me, R^2 = R^4 = Me, R^3 = H, X = O)	98.8	86
18c (R^1 = 7-Me, R^2 = R^4 = Me, R^3 = $CH_2CH_2NEt_2$, X = O)	90.7	95

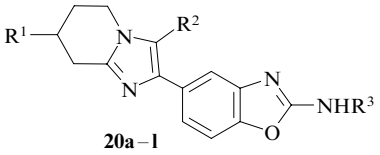
Note. Here and below, a dash means that the activity was not determined. [a] The dose was 100 mg kg^{-1}, while in other cases, it was 32 mg kg^{-1}; [b] a known gastroprotective agent: Al complex of the saccharose sulfate.

2-aminobenzoxazole ring bio-isosteric to unit **C**. For better correspondence to the structure of classical H_2-blockers, the researchers [3] introduced a dimethylene chain as bridge **B** into these molecules and elucidated how this modification has affected the histamine H_2-receptor inhibition and the antisecretory and cytoprotective activities.

Structures 19, 20



19a–e

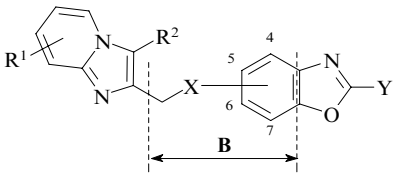


20a–l

19: R^1 = H, R^2 = Et (**a**); R^1 = 7-Me: R^2 = Et (**b**), Pr^n (**c**), All (**d**); R^1 = 8-Me, R^2 = Et (**e**);
20: R^1 = Me, R^2 = H: R^3 = H (**a**), Me (**b**), Et (**c**); R^1 = R^2 = Me: R^3 = H (**d**), Me (**e**), Et (**f**), Pr^n (**g**), Pr^i (**h**), All (**i**); R^1 = R^2 = Et: R^3 = H (**j**), Me (**k**); R^1 = Pr^i, R^2 = H, R^3 = Et (**l**)

In the series of imidazo[1,2-*a*]pyridinylalkylbenzoxazoles **21**, the substitution mainly involved positions 4, 5 and 6 of the benzene ring. The ethyl bridge between the imidazo[1,2-*a*]pyridine moiety and position 6 of the benzoxazole ring, as well as the methyl, ethyl, methoxyl or ethoxyl substituent in imidazo[1,2-*a*]pyridine, are the crucial factors for the presence of histamine H_2-receptor inhibition *in vitro*. A considerable antisecretory effect *in vivo* was found for some 7-substituted imidazo[1,2-*a*]pyridines (R^1 = Me, Et, OMe, OEt, NH_2, OH). The antisecretory activity *in vivo* is much lower or totally absent for compounds containing 6-methyl, 7-ethyl, 7-acetoxy, 7-methoxymethyl, 8-hydroxy and 8-amino groups, which have inhibitory action *in vitro* with respect to H_2-receptors. Thus, there is no simple correlation between the inhibitory activities of H_2-receptors *in vitro* and the antisecretory effect *in vivo* for this series of compounds.

Structures 21



21

R^1 = H, 6-Me, 7-Me, 8-Me, 7-Et, 7-OH, 8-OH, 7-OMe, 8-OMe, 7-OEt, 7-OAc, 7-CH_2OH, 7-CH_2OMe, 7-CH_2NH_2, 7-NH_2, 8-NH_2, 8-NHAc, 7-CO_2H, 7-CO_2Me, 7-$C(O)NH_2$; R^2 = H, Me, Cl, Br, CHO, CH_2OH, 7-CH_2NMe_2;
X = CH_2, O, SCH_2; Y = Me, Et, OH, SMe, NH_2, NHMe, NHEt, $NHPr^n$, $NHPr^i$, $NHBu^t$, NHAll, NHAc, $NHC(O)C_3H_5$-cyclo, $NHC(O)C_6H_{11}$-cyclo, $NHC(O)CHEt_2$, NHC(O)CH(Me)OAc-(L), NMe_2, N=CHNMe$_2$, $NHC(NH_2)$=NH

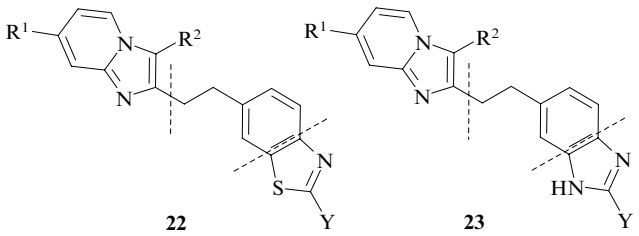
High values for inhibitory, antisecretory and anti-ulcer activities of compounds **21a–d** provided the grounds for further investigations of their effect on the basal gastric secretion (in pylorus-ligated rats) and the protective behaviour against alcohol-induced stomach lesions (ethanol-induced ulcer). Some results are summarized in Table 2. It can be seen that compounds **21b**,**d** have a considerable antisecretory activity, which exceeds that of cimetidine (**1**), ranitidine (**2**) and roxatidine acetate (**5b**). All four derivatives **21a–d** have a half-rigid (aralkyl) bridge and exhibit the same cytoprotective effect as **19a–e** or **20a–l**, but are superior in this effect to the cytoprotective H_2-blocker — roxatidine acetate (**5b**).

Table 2. Antisecretory (I) and gastroprotective (II) activities of compounds **21a–d** (X = CH_2, substitution at position 6) and reference drugs.[3]

Compound or drug	ED_{50} /mg kg^{-1}	
	I	II
Cimetidine (**1**)	83.0	> 320
Ranitidine (**2**)	30.5	29.6
Roxatidine acetate (**5b**)	26.9	20.4
20a (R^1 = 7-Me, R^2 = Me, Y = NH_2)	–	14.1
20b (R^1 = 7-OMe, R^2 = Me, Y = NH_2)	21.8	6.1
20c (R^1 = 7-Me, R^2 = H, Y = NHEt)	–	11.4
20d (R^1 = 7-Me, R^2 = H, Y = NHAc)	13.8	4.0

Considering the obtained data on the nature of units **A** and **B** needed for the effective action of the drugs, series of 6-(imidazo[1,2-*a*]pyridin-2-ylethyl)benzothiazoles **22** and -benzimidazoles **23** have been prepared.[4] These compounds were used as examples to study the influence of the structural modification of unit **C** on the H_2-inhibitory, antisecretory and anti-ulcer activities. Most of compounds **22** and **23** largely inhibit the H_2-receptors. However, good antisecretory activity is inherent only in benzimidazoles **23**, while benzothiazoles **22** have a more marked anti-ulcer effect.

Structures 22, 23



22 **23**

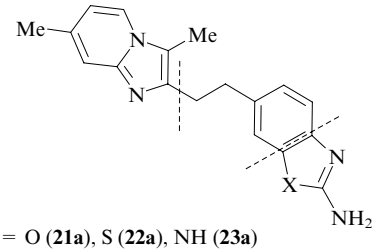
R^1 = Me, OH, OMe; R^2 = H, Me; Y = NH_2, NHAc

Benzimidazoles **21a–23a** differ in the heteroatoms incorporated in unit **C**. A comparison of the three types of activity for these compounds reveals the following trend. Oxazole **21a** exhibits high H_2-inhibitory and anti-ulcer activities with good antisecretory action being maintained. Imidazole **23a** is a very potent H_2-inhibitor and antisecretory agent but does not show even a satisfactory anti-ulcer activity. Conversely, thiazole **22a** shows no antisecretory activity *in vivo* but the anti-ulcer and antagonistic effects are comparable with those of ranitidine (**2**) and cimetidine (**1**) (Table 3).

Table 3. Comparison of the pharmacological activities of compounds **21a**–**23a** and reference drugs [degree of inhibition (%)].[4]

Type of activity	Dose	**21a**	**22a**	**23a**	Cimetidine (**1**)	Ranitidine (**2**)
H_2-Receptor inhibition	$3.2-10^{-6}$ g ml^{-1}	93.1	84.6	100	56.6	74.0
Antisecretory activity:						
in vitro	$1.0\cdot10^{-5}$ g ml^{-1}	65.9	50.0	86.4	36.0	58.2
in vivo	1 g ml^{-1}	65.0	no effect	90.0	53.0	72.0
Anti-ulcer activity	32 mg kg^{-1}	92.9	85.4	10.0	69.4	81.8

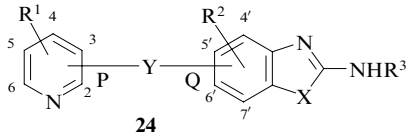
Structures 21a–23a



X = O (**21a**), S (**22a**), NH (**23a**)

Modification of unit **A** of imidazo[1,2-*a*]pyridinylalkylbenzodiazoles **23**, namely, replacement of imidazo[1,2-*a*]pyridine by the pyridine moiety that is contained in lafutidine (**6**), had an adverse effect on the interaction with H_2-receptors.[5] As compared with the precursors, the obtained 2-alkylamino-5(or 6)-aralkyl-substituted benzazoles **24** showed a minor or zero inhibitory activity with respect to histamine H_2-receptors. However, the anti-ulcer activity of some pyridine derivatives **24a**–**c**

Structure 24



24

R^1 = H, 3-Me, 4-Me, 5-Me; R^2 = H, 4′-OMe, 4′-Br; R^3 = H, Me, Et;
X = S, O, NH; Y = CH_2, $(CH_2)_2$, CH(OH), CH_2O, CH_2S;
P (substitution position in the pyridine ring) = 2, 3, 4;
Q (substitution position in the benzene ring) = 4, 5, 6, 7

[$R^1 = R^2 = R^3$ = H: X = S, Y = CH_2, P = 2, Q = 6 (**a**); X = S, Y = $(CH_2)_2$, P = 3, Q = 6 (**b**); X = NH, Y = $(CH_2)_2$, P = 2, Q = 5 or 6 (**c**)] was much higher (98.2%, 94.4% and 98.3% inhibition) than this activity of the reference drugs (sofalcone, 45.6%; the values for cimetidine and sucralfate are in Table 3).

Out of the 68 derivatives of 4-furyl-2-guanidinothiazole **25** and **26** containing an aralklyl bridge as unit **B**, fifteen agents had a sufficient activity *in vitro* and *in vivo*; for these compounds, the antisecretory effect was additionally determined in another model.[6] A fairly high antisecretory activity in experiments in dogs was found for compounds **25c**,**g**,**h**, for which the anti-ulcer activity was measured in three experimental ulcer models (Table 4). The antimicrobial activity *in vitro* with respect to *Helicobacter pylori* was also measured for **25a**–**h**, the minimum inhibitory concentration (MIC) being in the range of 27–>100 μg ml^{-1}; compounds **25a**,**d**,**h** were most active. Thus, the introduction of the furfuryl moiety instead of the four-unit alkyl bridge present in the therapeutic H_2-blockers proved to be useful: among compounds having antisecretory activity, two samples possessing other useful properties were chosen. The best pharmacological profiles were found for compound **25c** with exceptionally high anti-ulcer activity and for compound **25d** having antimicrobial activity exceeding by a large factor the corresponding value for H_2-blockers currently used in the therapeutic practice.

Yet another compound with an additional useful therapeutic effect (prevention of NSAID-induced gastropathy) was detected among 2-guanidino-4-pyridylthiazoles. Apart from the strong antisecretory activity, 4-[6-(acetamidomethyl)pyridin-2-yl]-2-guanidinothiazole (**27**) efficiently inhib-

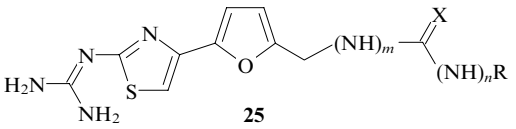
Table 4. Pharmacological activity of compounds **25** and reference drugs.[5]

Compound or drug	H_2-Receptor inhibition (%)	Anti-ulcer activity (ED_{50}/μg kg^{-1})			Antimicrobial activity (MIC/μg kg^{-1})
		I	II	III	
Cimetidine (**1**)	43	18.8	>320	>32	1130
Ranitidine (**2**)	44	1.5	29.6	>32	>1600
Famotidine (**3**)	87	0.67	>32	>32	1600
Roxatidine acetate (**5a**)	76	1.6	20.4	>32	>1600
25a (X = O, R = Me, *m* = 1, *n* = 0)	85	–	–	–	27
25b (X = O, R = Et, *m* = 1, *n* = 0)	78	–	–	–	–
25c (X = NSO_2NH_2, R = H, *m* = 0, *n* = 1)	84	0.66	7.5	5.2	–
25d (X = NCN, R = Me, *m* = *n* = 1)	91	–	–	–	62
25e (X = NSO_2Me, R = Me, *m* = *n* = 1)	84	–	–	–	–
25f (X = $CHNO_2$, R = Me, *m* = *n* = 1)	96	–	–	–	–
25g (X = O, R = H, *m* = *n* = 1)	78	6.9	22.0	5.2	–
25h (X = O, R = Me, *m* = *n* = 1)	89	2.6	21.2	5.2	71

Note. I is stress-induced ulcer, II is ethanol-induced ulcer, III is HCl/aspirin-induced ulcer.

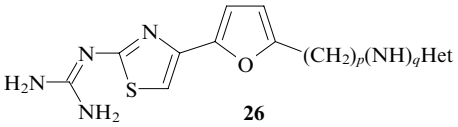
its stomach lesions initiated by two non-steroidal anti-inflammatory drugs — aspirin and indomethacin.

Structures 25, 26



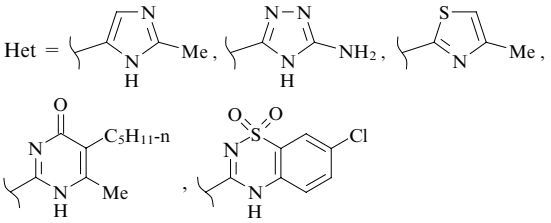
25

m, *n* = 0, 1; R = H, Me, Et, Pr^n, Pr^i, Bu^n, All, CH_2OAc, CH_2SMe, $(CH_2)_2OH$, $(CH_2)_3OH$, CH_2OMe, $(CH_2)_2NMe_2$, CH_2SCH_2-2-Fu, $CH_2S(O)CH_2$-2-Fu, OMe, SMe, 2-$O_2NC_6H_4$, 3-Py, 2-Fu, 2-Th, pyridin-3-yl 1-oxide; X = $CHNO_2$, O, S, NH, NCN, NCO_2Me, NSO_2Me, NSO_2Et, NSO_2NH_2, NSO_2NHMe, NSO_2NMe_2, $NSO_2C_6H_4Me$-4, $NSO_2C_6H_4OMe$-4, $NSO_2C_6H_4NH_2$-4, $NSO_2C_6H_4Br$-4; Fu is furyl, Py is pyridyl, Th is thienyl



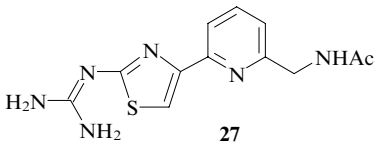
26

p, *q* = 0, 1;

Het = 

According to the authors, this may be caused by the ability of compound **27** to prevent the decrease in the blood circulation in the gastric mucosa caused by intake of aspirin, whereas famotidine (**3**) does not exert a noticeable effect in the same dose and the use of ranitidine (**2**) in a dose of 100 mg kg^{-1} deteriorates the blood circulation in the system (Table 5).[7]

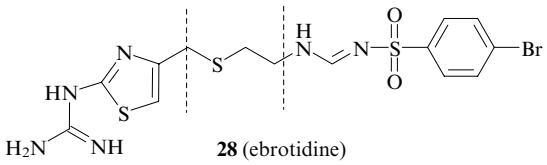
Structure 27



27

Ebrotidine, (*E*)-*N*′-(4-bromophenylsulfonyl)-*N*-{2-[(2-guanidinothiazol-4-yl)methylthio]ethyl}formimidamide (**28**), was considered in the mid-1990s to be a promising anti-secretory agent exhibiting additionally cytoprotective and anti-helicobacter pylori properties[8] and acid-suppression action similar to that of cimetidine (**1**).[9]

Structure 28



28 (ebrotidine)

Some lethal doses (LD) of ebrotidine (**28**) were determined in experiments in mice and rats for different ways of administration of the drug.[10] Unlike ranitidine (**2**) and other H_2-receptor antagonists, ebrotidine exerts a unique cytoprotective action by reducing the formation of gastrointestinal mucosal lesions under the action of invasive ulcerogenic factors such as ethanol, ammonia, lipopolyssacharides (LPS), aacetylsalicylic acid or due to stress. The mechanism of this protection is not yet clear but it has been ascertained that agent **28** stimulates the mucus secretion and enhances the blood circulation in the gastric mucosa.[11] The cytoprotective properties of ebrotidine do not depend on

Table 5. Comparison of the pharmacological activity of compound **27** and reference drugs.[7]

Activity parameter	Dose	**27**	Cimetidine (**1**)	Ranitidine (**2**)	Famotidine (**3**)	Roxatidine acetate (**5b**)
H_2-Receptor antagonism						
Inhibition (%)	1×10^{-6} g ml^{-1}	66	43	44	87	76
IC_{50} /mmol $litre^{-1}$ (see [a])		1.3	–	3.4	0.3	–
Antisecretory activity						
Rat experiments:						
inhibition (%)	1 mg kg^{-1}, I.V.	82	53	72	96	84
ED_{50} /mg kg^{-1} (see [b])		12.6	–	30.5	3.5	–
Dog experiments:						
inhibition (%)	0.32 mg kg^{-1}	95	22 [c]	41	96	58
ED_{50} /mg kg^{-1} (see [d])		0.063	–	0.3	0.042	–
Anti-ulcer activity						
Aspirin-induced ulcer: [e]						
inhibition (%)	32 mg kg^{-1}	68	33	3	22	31 [f]
ED_{50} /mg kg^{-1}		13.3	–	> 100	> 100	–
Indomathacin-induced ulcer: [g]						
ED_{50} /mg kg^{-1}		6.5	–	–	> 100	–

[a] Guinea pig right atrium, histamine stimulation; [b] ligated pylorus; [c] the dose was 1 mg kg^{-1}; [d] gastrin stimulation; [e] stimulation by 0.2 M HCl and aspirin (200 mg kg^{-1}); [f] the dose was 100 mg kg^{-1}; [g] stimulation by 0.35 M HCl and aspirin (5 mg kg^{-1}).

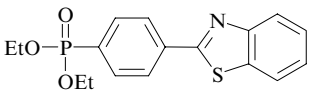
the formation of endogenous prostaglandins but are due to the ability of the drug to induce the gastric mucosa response manifested as improvement of the physicochemical characteristics of the mucus gel — an increase in its volume, viscosity and hydrophobicity. The improvement of the protective properties of the mucus gel is directly related to the ability of this compound to promote processes needed to restore and maintain the integrity of gastric mucosa (for example, stimulate the synthesis and secretion of sulfo- and sialomucins and gastric mucus phospholipids, promote the assembly of macromolecular mucins and so on). This unique behaviour of ebrotidine (**28**) distinguishes it from other H_2-blockers.[12] The cytoprotective properties of drug **28** were observed in rat experiments; they were also confirmed when used in human patients with gastric lesions induced by ethanol or acetylsalicylic acid. Ebrotidine exerts anti-helicobacter pylory action by affecting the epithelial cell receptors and inhibiting the urease, protease and lipase activities and counteracts the adverse consequences related to the presence of these bacteria.[11]

Yet another studied H_2-blocker — nizatidine (**4**) — also has unusual properties. It increases the cholinergic activity of the body by inhibiting acetylcholinesterase and promotes bowel evacuation by affecting directly the smooth muscles of the stomach. Nizatidine stimulates the gastric motility without exerting adverse influence on the vegetative nervous system, which may be useful for diabetic neuropathy patients.[13]

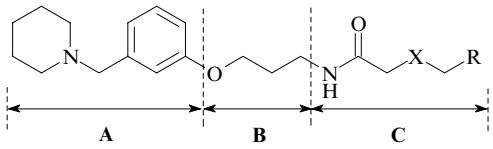
The combined (both antisecretory and gastroprotective) action was expected of the histamine H_2-receptor antagonists that additionally block the L-type calcium channels (calcium antagonists), as it was known that calcium antagonists act as protective agents against chemically induced gastric lesions. Roxatidine (**5a**) was taken as the starting compound for the synthesis of such agents.[14] Twenty seven derivatives were prepared from **5a** and tested for the presence of four types of biological activity *versus* reference compounds: cimetidine (**1**) and roxatidine acetate (**5b**).

The terminal moiety (unit **C**) of the roxatidine (**5a**) molecule was replaced by a structural moiety of the drug KB 944 {diethyl [4-(benzothiazol-2-yl)phenyl]phosphate **29**}, a known calcium antagonist. However, both compounds with the 4-(benzothiazol-2-yl)phenylmethyl moiety (**30**, **31**) did not show noticeable activity. Meanwhile, compound **32a** containing a simpler group, R = Ph, showed a significant level of all four types of activity; therefore, it was chosen for further modification.

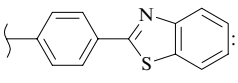
Structures 29 – 32



29 (KB-944)



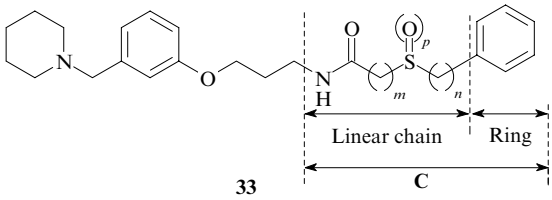
30 – 32

R =  : X = O (**30**), S (**31**);

R = Ph: X = S (**32a**), SO (**32b**), SO_2 (**32c**)

The effect of the structure of the linear part of the thioester moiety on the activity of analogous compounds **32** and **33**, with the substituent R being the same (R = Ph), was studied by varying the following parameters: the number of methylene groups between the carbonyl and the sulfur atom (*m*), the number of methylene groups between sulfur and the benzene ring (*n*) and the oxidation state of sulfur (*p*).[14] The H_2-antagonistic and antisecretory activities were found to depend on the numbers of methylene groups in the following way: 1 > 3 > 5 (for *m*) and 1 > 3 > 5 > 0 (for *n*).

Structures 33



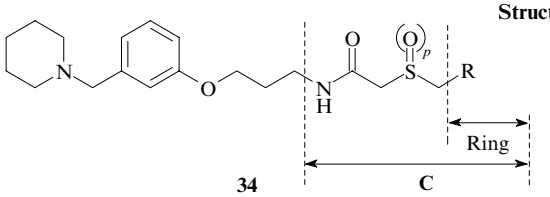
33

m = 3, 5; *n* = 3, 5; *p* = 0, 1, 2

The gastroptotective activity does not depend on the number of methylene groups but depends on the distance between sulfur and the aromatic ring (the sequence is $1 \geqslant 3 > 5$ for *n*) and is enhanced upon oxidation of the sulfur atom. The length of the thioester bridge does not influence the presence of calcium antagonism. The most active compounds in the *N*-{3-[3-(piperidinomethyl)phenoxy]propyl}acetamide series **32a – c** are not only effective H_2-blockers and antisecretory agents but also show a pronounced gastroprotective activity.[14]

Further structure modification involved replacement of the benzene ring in the thioester moiety by other aromatic and heteroaromatic rings or by cyclohexane.[14] The histamine H_2-receptor inhibition was retained at the level of compound **32a** upon the introduction of cyclohexyl, 2-naphthyl, 2- and 3-furyl or 2-thienyl groups into the *N*-{3-[3-(piperidinomethyl)phenoxy]propyl}acetamide molecules **34** but decreased when the benzene ring was replaced by a pyridine ring irrespective of the type of substitution (2-, 3- or 4-isomer). Meanwhile, the antisecretory activity was retained at the level of compound **32a** in the presence of heteroaromatic groups (R = 3-Py, 4-Py, 2-Fu, 2-Th) but decreased in the case of cyclohexyl or 2-naphthyl groups or upon introduction of substituents into the benzene ring or 2-furyl ring. The Ca-antagonistic activity was affected only by the presence of 2-thienyl and 3-furyl groups. For the gastroprotective activity, the benzene, furan or naphthalene ring was preferred. Thus, the best characteristics were found for compounds **34a**,**b** [R = 2-Fu: *p* = 1 (**a**), 2 (**b**)], and the former of these compounds, 2-furfurylsulfinyl-*N*-[3-3-

Structure 34



34

p = 0, 1, 2; R = 4-$MeOC_6H_4$, cyclo-C_6H_{11}, 2-Naph, 2-Py, 3-Py, 4-Py, 2-(methoxycarbonyl)furan-2-yl, 2-Th; Naph is naphthyl

Table 6. Pharmacological activity of compounds **31** – **34**.[14]

Compound	Ca antagonism [a] (%)	H_2 antagonism [b] (%)	Antisecretory action [c]	Gastroprotective action [d]
Cimetidine (**1**)	no effect at a 10^{-5} mol litre^{-1} dose	70 – 90	pH increase at a 10 mg kg^{-1} dose	pronounced pH increase
Roxatidine acetate (**5b**)	the same	90	the same	the same
30	5 – 10	< 70	–	–
31	no effect at a 10^{-5} mol litre^{-1} dose	no effect at a 10^{-5} mol litre^{-1} dose	–	–
32a – **c**	5 – 10	70 – > 90	no effect at a 30 mg kg^{-1} dose	see [e] ($p < 0.01 – 0.05$)
34a,**b**	5 – 10	> 90	the same	see [e] ($p < 0.01$)

[a] Degree of suppression of the heart rate at a 10^{-6} mol litre^{-1} dose (guinea pig right atrium); [b] inhibition of H_2-histamine receptors *in vitro* at a 10^{-6} mol litre^{-1} dose (guinea pig right atrium); [c] at a 3 mg kg^{-1} dose (male rats, tetragastrin); [d] at a 10 mg kg^{-1} dose (male rats, ethanol-induced ulcer); [e] considerable inhibition of lesion formation (p is the damage degree, fractions).

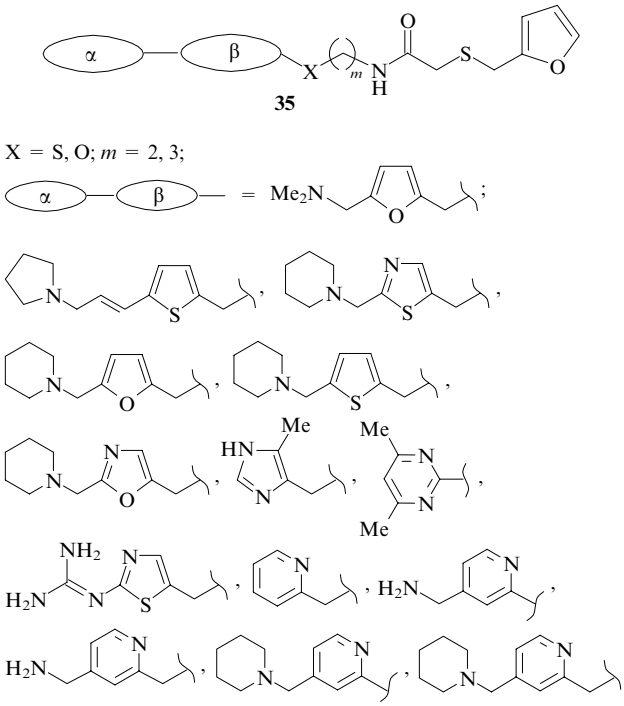
(piperidinomethyl)phenoxy]propyl]acetamide (FRG-8701), was chosen as the model for further investigation.

Characteristics of the pharmacological activity for some representatives of this series and for reference drugs are presented in Table 6.

Having compared the structures of compound **34a** and known histamine H_2-receptor antagonists, Hirakawa *et al.*[15] suggested that the presence of antisecretory activity is determined by the structure of the left-hand part of the molecule (units **A** + **B**), whereas the gastroprotective action is fully caused by unit **C** (Fig. 2).

The subsequent search for the combined action H_2-blockers of the new type resulted in the synthesis of a series of compounds containing both an invariable thioester group and various structural units of known histamine H_2-receptor antagonists, that is, drugs **1** – **5** (see Fig. 1). Basing on the assumption of obligatory presence of a tertiary amino group in the heteroaromatic ring for the existence of inhibitory properties, derivatives **35** containing simultaneously this group, heteroatom (X) and a thioester moiety were studied first of all. All three types of activity were found for compound **35a** [α + β = 4-(piperidinomethyl)-2-pyridyl, X = O, m = 3]. Meanwhile, the analogue of famotidine (**3**), compound **35b** [α + β = 5-(3-pyrrolidinoprop-1-enyl)-2-thienylmethyl, X = S, m = 2], while exhibiting pronounced inhibitory and antisecretory effects, did not show even weak gastroprotective properties (Table 7).

Structures 35



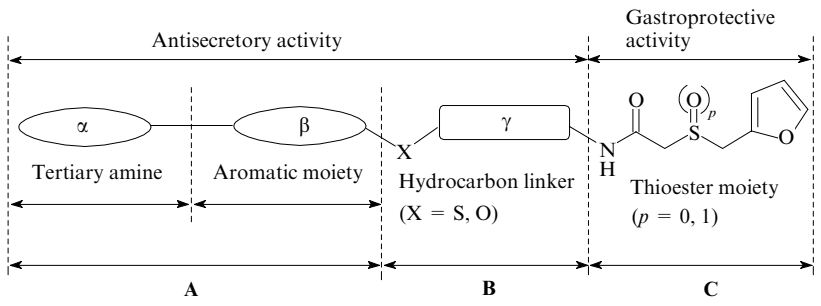


Figure 2. General structure of H_2-blockers having antisecretory and gastroprotective activities.

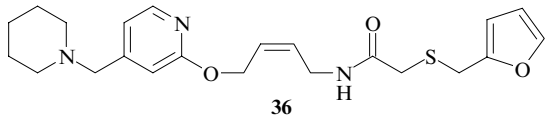
Table 7. Pharmacological activity of H_2-blockers with a thioester function.[14–16]

Compound	LD_{50} /mg kg^{-1}	H_2 antagonism [a] (%)	Antisecretory action [b]	Gastroprotective action [c]
Cimetidine (**1**)	–	70–90	pH increase at a 10 mg kg^{-1} dose	no effect at a 30 mg kg^{-1} dose
Roxatidine acetate (**5b**)	–	90	the same	the same
Lafutidine (**6**)	90	70–90	pH increase at a 0.3 mg kg^{-1} dose	Inhibition of the lesion formation at a 10–30 mg kg^{-1} dose
35a	67	70	pH increase at a 10 mg kg^{-1} dose	the same
35b	65	70–90	pronounced pH increase at a 3 mg kg^{-1} dose	no effect at a 30 mg kg^{-1} dose
36	40	–	pH increase at a 3 mg kg^{-1} dose	pronounced inhibition of the lesion formation ($p < 0.05$) at a 10 mg kg^{-1} dose
37	–	< 70	the same	no effect at a 30 mg kg^{-1} dose
38	–	< 70	–	–
39a	100	70–90	pronounced pH increase at a 3 mg kg^{-1} dose	no effect at a 10 mg kg^{-1} dose
39b	100	–	pH increase at a 3 mg kg^{-1} dose	inhibition of the lesion formation at a 10–30 mg kg^{-1} dose

[a] Inhibition of H_2-histamine receptors *in vitro* at a 10^{-6} mol litre^{-1} dose (guinea pig right atrium); [b] at a 3 mg kg^{-1} dose (male rats, tetragastrin); [c] at a 10 mg kg^{-1} dose (male rats, ethanol-induced ulcer).

The effect of the type of hydrocarbon linker between the O and N heteroatoms was studied using compounds **6** and **36**–**38** in which the α + β moiety was represented by the most efficient structural units, piperidine (α) and pyridyl (β) rings, and which also contained an oxygen atom (the X heteroatom in Fig. 2). Compound **36** with a *cis*-butene hydrocarbon bridge was more active than analogue **35a** with a saturated trimethylene bridge (see Table 7).[15]

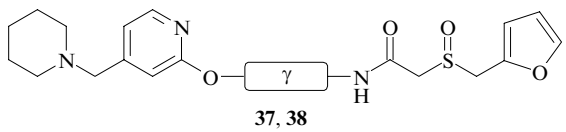
Structure 36



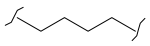
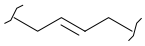
36

Lafutidine (**6**) prepared by partial oxidation of the sulfur atom in compound **36** has a weaker gastroprotective action than its precursor but, instead, it exhibits good inhibitory and excellent antisecretory properties. The saturated hydrocarbon bridge consisting of four methylene groups in compound **37** leads to a decrease in the histamine H_2-receptor inhibitory activity, while the antisecretory effect remains the same (as in compound **6**) and the gastroprotective activity considerably decreases. Meanwhile, the *trans*-configuration of the double bond in agent **38** decreases the inhibitory activity. Thus, the *cis*-butene chain is the hydrocarbon linker of choice for 4-(piperidinomethyl)-2-pyridyloxy derivatives (see Table 7).

Structures 37, 38

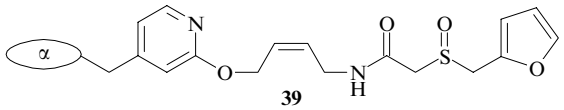


37, **38**

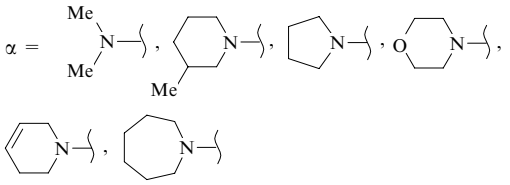
γ =  (**37**),  (**38**)

The influence of the structure of the tertiary amine (moiety α) on the biological activity of analogues of compound **6** has been investigated.[15] The replacement of piperidine by other amines did not affect markedly the antisecretory activity of compounds **39**. The derivative **39a** containing a dimethylamino group (α = Me_2N) also exhibited an inhibitory activity with respect to H_2-receptors but the gastroprotective properties have disappeared; compound with the morpholine ring **39b** (α is morpholino) had a gastroprotective action similar to that of lafutidine (**6**).

Structures 39



39

α = 

Thus, successive modification of the three key units of the roxatidine (**5a**) molecule resulted in the formation of a new drug, lafutidine (**6**), which has a balanced pharmacological profile (see Table 7). It is noteworthy that gastroprotective activity is inherent in all of three forms of lafutidine (**6**) — racemate and (+)- and (−)-enantiomers. The three forms (at a 10 mg kg^{-1} dose) equally prevent the formation of gastric mucosa lesions under the action of aqueous ammonia (experiments in male rats). The lesion area was 42.2 ± 5.4 mm^2 in the control run, 14.0 ± 3.4 mm^2 for the use of racemic lafutidine (66.8% inhibition of the lesion formation), 16.3 ± 5.2 mm^2 for the use of (+)-stereoisomer (61.4% inhibition) and 16.5 ± 2.4 mm^2 for the

(−)-form (60.9% inhibition).[16] The H_2-blocker lafutidine has been manufactured in Japan since 2000 and is sold by the Taiho Pharmaceutical Company under the trade name Protecadin.

The biological activity and the structure–biological activity relationship have been studied in detail for one more histamine H_2-receptor antagonist — pibutidine (**7**). The protective properties of this compound in relation to ischemia reperfusion injury of gastric mucosa may be caused by its antioxidant activity.[17] The investigations of the cardiovascular effects of pibutidine in experiments in dogs demonstrated that its hydrochloride, when administered in clinical doses, does not induce toxic action on the cardiovascular or respiratory system.[18]

By measuring the histamine-induced heart rate increase, the interaction of pibutidine and its analogues with H_2-receptors has been studied and the structure–property relationship has been analyzed. The potent and durable H_2-receptor blocking action of 3-amino-4-{4-[4-(piperidinomethyl)-2-pyridyloxy]-*cis*-but-2-enylamino}cyclobut-3-ene-1,2-dione hydrochloride (**7**) was time-dependent and irreversible both *in vitro* and *in vivo*.[19]

Pibutidine mitigates the histamine-induced increase in the heart rate, unlike compounds **40**–**44**, which represent various structural units of this drug (Fig. 3).

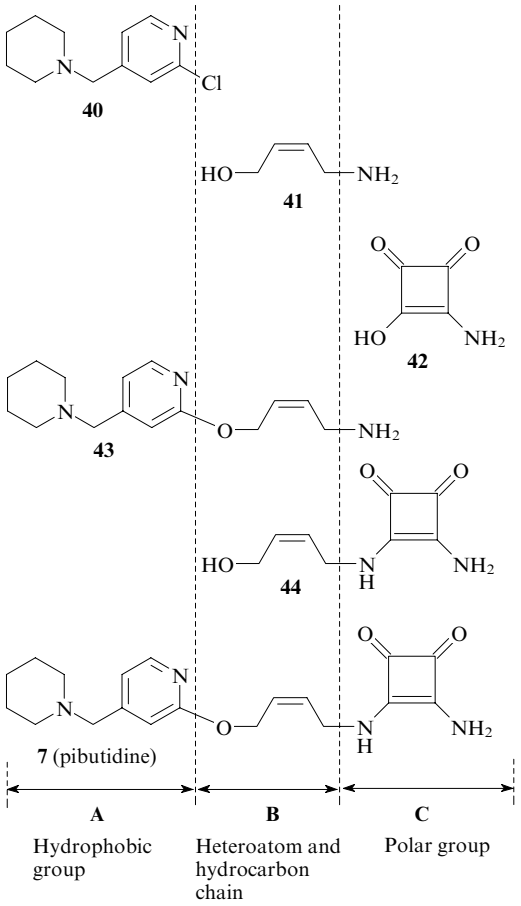


Figure 3. Structural units of the pibutidine (**7**) molecule and the corresponding compounds **40**–**44**.

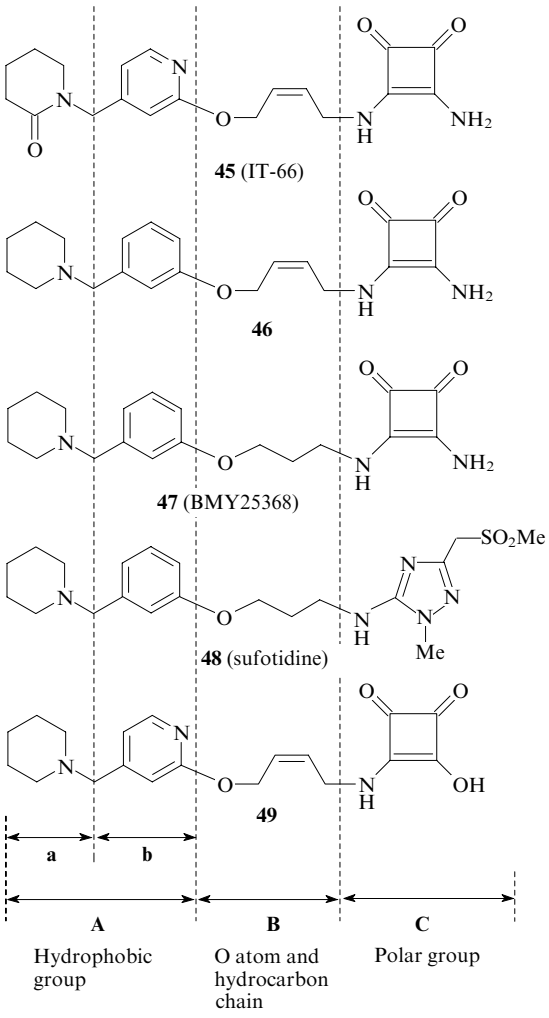


Figure 4. Structural units of pibutidine analogues: compounds **45**–**49**.

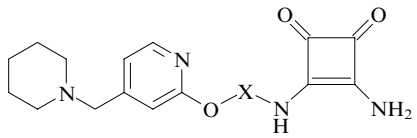
Pibutidine analogues (Fig. 4) containing groups with similar structure have been synthesized. Compound **45** (IT-66) containing an oxidized carbon atom in the piperidine ring cannot counteract the histamine-induced response ($IC_{50} > 10$ μmol litre^{-1}). This indicates that for the H_2-receptor inhibitory action to be manifested, the piperidine moiety should have only one nucleophilic electron pair. Compound **46**, differing by the presence of the benzene ring instead of the pyridine ring, inhibits the increase in the heart rate as efficiently as pibutidine (**7**). Perhaps, the pyridine nitrogen atom does not interact directly with H_2-receptors. These data confirm the assumption of the key role of the piperidine nitrogen atom in the interaction with H_2-receptors. Moreover, the replacement of the pyridine ring by a benzene ring makes it possible to control the type of inhibitory action: the H_2-receptor inhibition becomes reversible and time-dependent, which was confirmed experimentally using compounds **46**–**48** and roxatidine acetate (**5b**) (see Fig. 4).

The polar group (unit **C**, see Fig. 4) also plays an important role in the interaction with the H_2-receptors by determining the inhibition intensity and the degree of

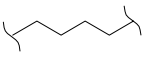
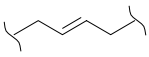
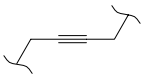
reversibility and time dependence of the process. For example, compounds **7** and **47** containing the 3,4-diaminocyclobut-3-ene-1,2-dione moiety as the polar group are characterized by irreversible and time-dependent type of inhibition of H_2-receptors. When the polar NH_2 group is replaced by a hydroxy group, the inhibitory action with respect to the histamine receptors completely disappears (for compound **49**, $IC_{50} > 10$ μmol litre^{-1}). The drugs sufotidine (**48**) and roxatidine acetate (**5b**) exhibit a reversible time-independent type of inhibition.

The hydrocarbon chain (unit **B**, see Fig. 4) also determines different degrees of binding of compounds to H_2-receptors. The replacement of a *cis*-butene bridge of compound **7** by other four-carbon chains (butane, *trans*-but-2-ene and but-2-yne in compounds **50**–**52**, respectively) reduces the inhibition intensity and makes it reversible. However, the drug BMY25368 (**47**) having a shorter trimethylene bridge acts similarly to pibutidine (**7**), differing only slightly in the inhibition intensity, while the type of inhibition is retained.

Structures 50–52



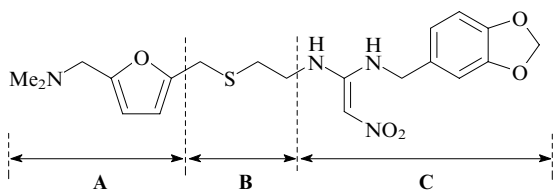
50–52

X =  (**50**),  (**51**),  (**52**)

Thus, the performed research demonstrated that each of the structural units of the drug molecule is responsible for the interaction with H_2-receptors. Receptor blocking requires the presence of two nitrogen atoms: in the pyridine ring [unit **A**(**a**) in Fig. 4] and in the amino group (unit **C**). Important factors determining different degrees of binding to the H_2-receptor and, correspondingly, the inhibition intensity, type and time dependence are the presence of an aromatic ring [unit **A**(**b**)], structure of the polar group **C** and the configuration of the molecule, which depends on the hydrocarbon chain.

The histamine H_2-receptor antagonist niperotidine (**53**) showed good results in *in vitro* experiments on suppression of the gastric juice secretion [in comparison with the action of two known H_2-blockers: cimetidine (**1**) and ranitidine (**2**)].[20] However, further testing revealed high hepatotoxicity of this compound. Moreover, the lack of a correlation between the dose and the degree of liver damage, a variable latent period, low frequency and unpredictability of the damage attest to an idiosynchratic reaction of the body to the treatment with this drug.[21]

Structure 53



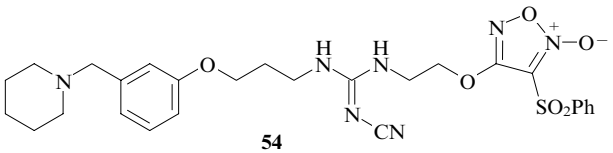
53 (niperotidine)

II.2. Histamine H_2-receptor antagonists — nitrogen oxide donors

Yet another avenue for the search for H_2-blockers with improved gastroprotective properties is based on the achievements in the studies of the role of NO in the regulation of GIT functions. Bertinaria *et al.*[22] reported the synthesis and the pharmacological profile of a series of H_2-blockers releasing nitrogen(II) oxide, which is involved in muscle relaxation, haemodynamic control and cytoprotection of gastric mucosa. These drugs were prepared by combining the pharmacophoric groups of some H_2-blockers [roxatidine (**5a**), tiotidine (**11**), lamtidine (**15**)] and some NO donors such as nitric acid esters, nitrosothio groups and benzenesulfonylfuroxans in the same molecule (Fig. 5).

The whole series was studied as nitrogen oxide sources, H_2-receptor antagonists and gastroprotective agents *in vitro* and *in vivo*. The best results were obtained for the lamtidine–furoxan hybride molecule **54**.

Structure 54



54

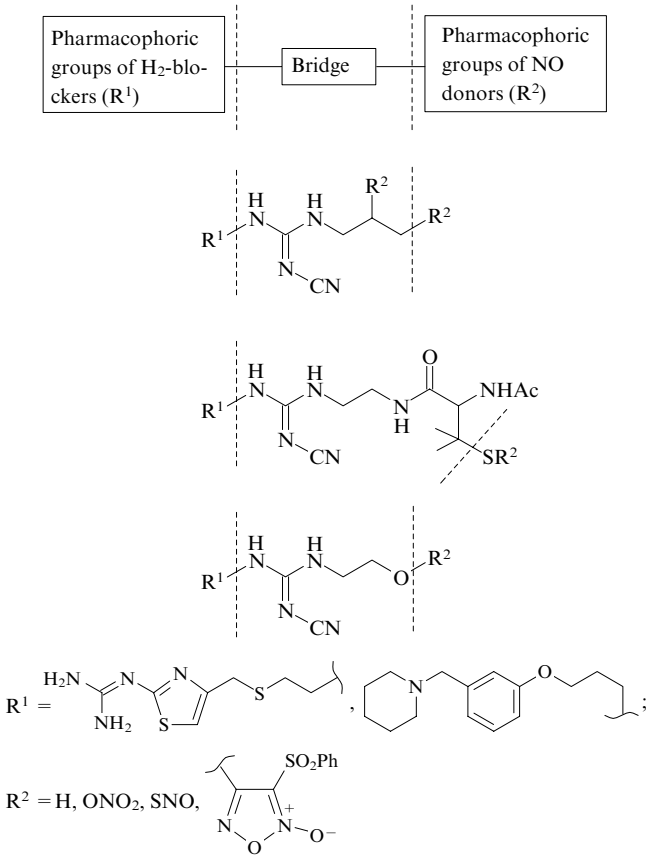


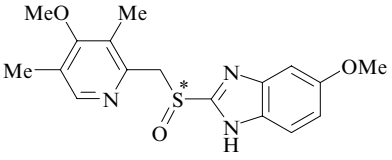
Figure 5. Structural units of the hybrid molecules combining the pharmacophoric groups of H_2-blockers and nitrogen oxide donors.

III. Proton pump inhibitors

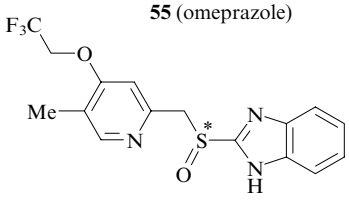
The group of proton pump inhibitors comprises the following drugs: omeprazole (**55**), esomeprazole [(*S*)-**55**], lansoprazole (**56**), pantoprazole (**57**), rabeprazole (**58**), dexlansoprazole [(*R*)-**56**] (the five first-mentioned drugs are certified for use in the Russian Federation, and all six drugs are used in the USA). These compounds are based on the thimoprazole (**59**) structure and are 2-(2-pyridylmethylsulfinyl)benzimidazole derivatives with various substituents in the pyridine and benzimidazole moieties.

Nevertheless, minor differences in the chemical structure account for significant pharmacodynamic features of each drug. Unlike compounds **55** – **59**, tenatoprazole (**60**) contains an imidazopyridine rather than benzimidazole ring. These PPIs are sulfoxides that contain an asymmetric sulfur atom and usually exist as racemic mixtures of *S*- and *R*-enantiomers. The two optical isomers produce the same pharmacological effect but they are metabolized at different rates and, therefore, demonstrate different pharmacokinetic profiles. Indeed, in the case of omeprazole, pantoprazole and tenatoprazole, levorotatory isomers are more efficacious, whereas in the case of lansoprazole and rabeprazole, dextrorotatory isomers show better pharmacokinetics.

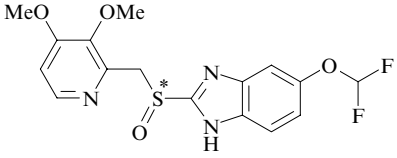
Structures 55 – 60



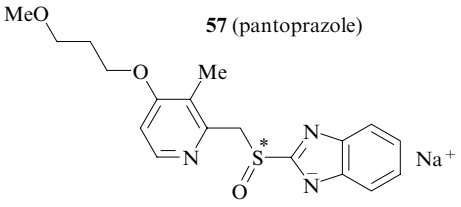
55 (omeprazole)



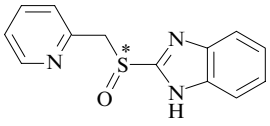
56 (lansoprazole)



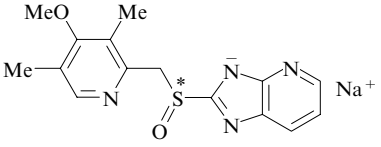
57 (pantoprazole)



58 (rabeprazole)



59 (thimoprazole)



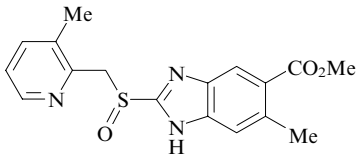
60 (tenatoprazole)

All PPIs are prodrugs, being transformed into the active form in the acidic medium of parietal cell secretory ducts in the close vicinity of the target molecule — the proton pump. In this state, they form strong covalent bonds with the HS groups of the proton pump, which is thus excluded from operation.[23] For the parietal cell to start again the acid secretion, new free proton pumps, not bonded to the inhibitor, should be synthesized; therefore, the duration of the therapeutic effect of PPIs depends on the proton pump renewal rate. It is known that half of H^+/K^+-ATPase molecules is renewed in humans over 30 – 48 h. The detailed mechanism of activation of these drugs is presented in Ref. 24.

Omeprazole (**55**), lansoprazole (**56**), pantoprazole (**57**) and rabeprazole (**58**) are metabolized in the liver to one or another extent by several cytochrome P450 isoenzymes (CYP) (Fig. 6).[25] The main isoenzymes involved in the PPI metabolism are CYP2C19 and CYP3A4. Minor mutations in the form of CYP2C19 affect its activity in the liver and, in turn, the metabolic and pharmacokinetic profiles of proton pump inhibitors, *i.e.*, the distribution of PPIs (except for rabeprazole) depends appreciably on the genetic polymorphism of CYP2C19. The metabolism of rabeprazole (**58**) is less dependent on CYP2C19.[25, 26] The major metabolic route of this drug, unlike other PPIs, is the formation of sulfide **61** *via* non-enzymatic reduction of sulfoxide. Subsequently compound **61** is stereoselectively re-oxidized by the action of CYP3A4 to give mainly (*R*)-rabeprazole [(*R*)-**58**], while under the action of the CYP2C19 and CYP2D6 isoenzymes, it is demethylated to give compound **62**. This fact was confirmed[27] by results obtained *in vivo*, which indicated that the plasma concentration is higher for (*R*)-rabeprazole than for the *S*-isomer (Scheme 1).

The first proton pump blocker, thimoprazole (**59**), prepared in 1974, had clear-cut side effects, which were revealed in the clinical trials.[28, 29] The inhibitory properties of its analogue, picoprazole (**63**) (1977), were studied *in vitro* and *in vivo*, but omeprazole (**55**) synthesized a year later proved to be much more efficacious. This drug was the first to be used in clinical practice and was the leader for a long period. Its levorotatory enantiomer, esomeprazole [(*S*)-**55**], considerably surpasses the racemate in the clinical effect. This modern, highly efficacious anti-ulcer drug, a specific inhibitor of the proton pump of the parietal cells in the gastric mucous layer, is among the best-selling drugs (in monetary terms) all over the world (5th position in 2011).†

Structure 63



63 (picoprazole)

† IMS Health. Top 20 Global Products, 2011; http://www.imshealth.com/portal/site/ims/menuitem.5ad1c081663fdf9b41d84b903208c22a/?vgnextoid=fbc65890d33ee210VgnVCM10000071812ca2RCRD&vgnextfmt=default (Accessed January 21, 2013)

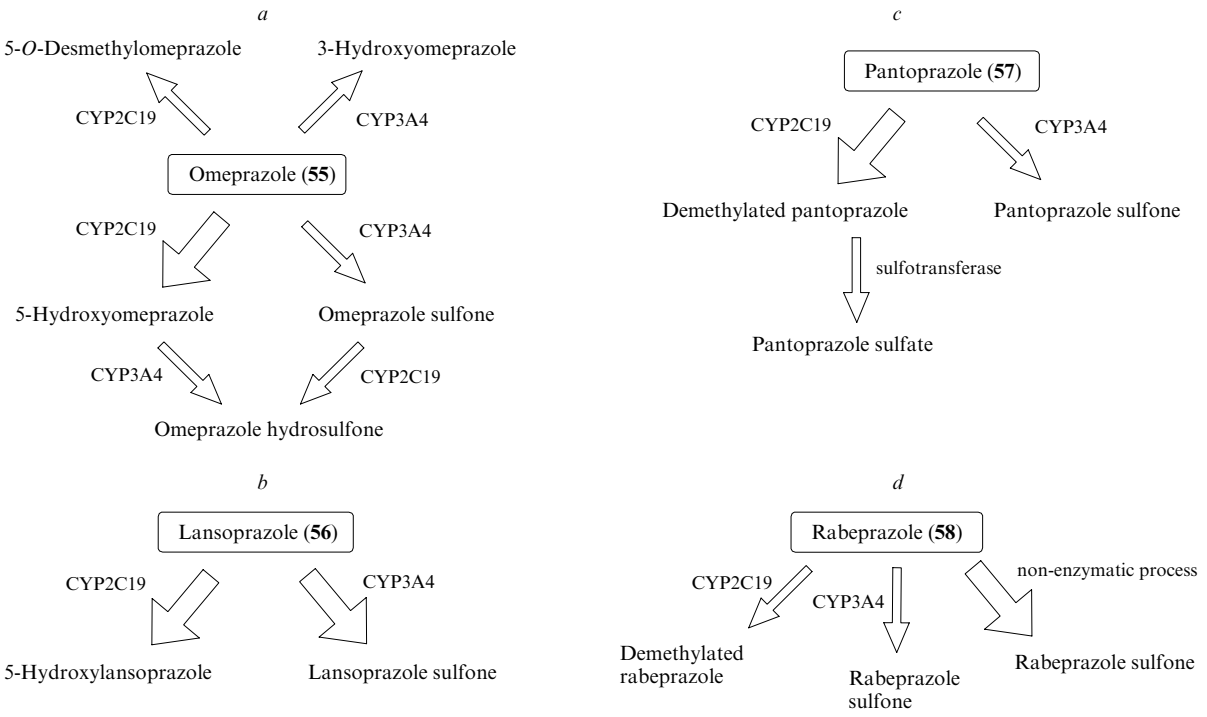
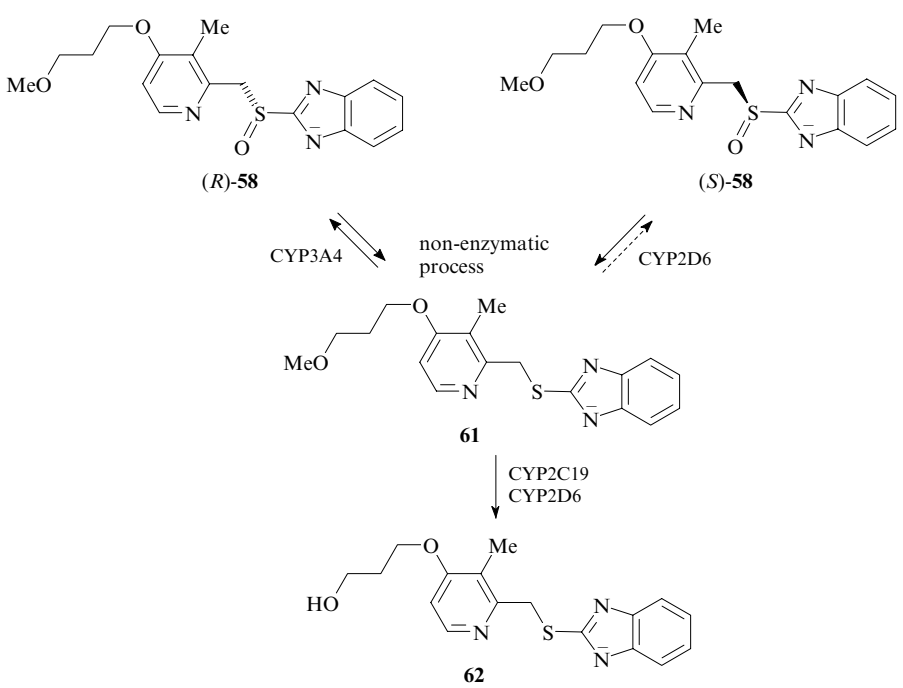


Figure 6. Metabolic routes of omeprazole (*a*), lansoprazole (*b*), pantoprazole (*c*) and rabeprazole (*d*).[25]

Scheme 1



Recently, two new methods for (*S*)-omeprazole synthesis, more facile and cost effective than the previous ones, have been developed. They comprise enantioselective oxidation of 2-[(3,5-dimethyl-4-methoxy-2-pyridyl)-methylsulfanyl]-5-methoxy-1*H*-benzo[*d*]imidazole with organic peroxides. The first method considerably increased the yield of the target product — esomeprazole (*S*)-**55** and/or its salt; the reaction is catalyzed by a titanium(IV) complex containing simultaneously two different chiral ligands: a diol (preferably, D-diethyl tartrate) and an amine [preferably, *N*,*N*-dimethyl-(*R*)-1-phenylethylamine].[30] In the second method, the oxidation is catalyzed by a complex formed by a vanadium salt with chiral Schiff base stable in the presence of water. This allows for the conduction of the reaction without providing for specific conditions (particular humidity, inert atmosphere) at any process step and facilitates the workup of the reaction mixture.[31]

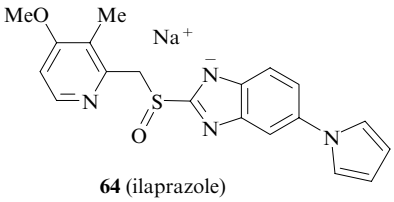
Lansoprazole (**56**) was the second PPI certified for the clinical use. Its *R*-enantiomer, dexlansoprazole, should be noted as the newest drug; its stereoselective metabolism was studied.[32]

The third synthesized PPI, pantoprazole (**57**), differs from the previous agents only in the nature of the substituents in the pyridine and benzimidazole rings. These differences provide for its higher stability at about neutral pH values compared to omeprazole or lansoprazole.[33] The most important feature of the sodium salts of pantoprazole and esomeprazole is the possibility of intravenous administration, which allows for the use of such medicines in patients with gastric hemorrhage where oral administration of PPIs is not recommended.

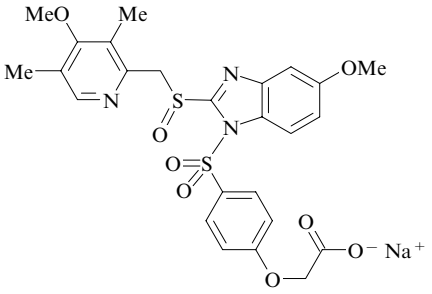
Further variation of substituents in the pyridine and benzimidazole rings resulted in the development of a new drug, rabeprazole (**58**), with improved pharmacodynamic and pharmacokinetic profiles compared with other PPIs. The pharmacodynamic measurements showed that rabeprazole having a high degree of dissociation ($pK_a = 5.0$) can be activated at higher pH than other PPIs, which may be responsible for fast action. Also, owing to the non-enzymatic metabolic route, drug **58** is less susceptible to the effect of genetic polymorphism of CYP2C19, which affects other PPIs.[34, 35] One more beneficial factor related to the non-enzymatic metabolism of rabeprazole is that this drug binds to a lesser extent to the enzyme cytochrome P450 in the liver and, hence, does not disrupt the metabolism of other drugs taken. The dextrorotatory isomer of this compound, dexrabeprazole [(*R*)- **58**], is more effective in inhibiting aspirin- and histamine-induced ulcers in mice than the levorotatory isomer or the racemate.[36] According to the results of randomized, double blind clinical trial of 50 GERD patients, the efficacy in healing of endoscopic lesions and elimination of reflux symptoms is higher for 10 mg of compound (*R*)-(**58**) than for 20 mg of racemic rabeprazole.[37]

Lately, several new ptoton pump inhibitors have been prepared, which are now at different stages of development and clinical trials: tenatoprazole (TU-199, **60**), ilaprazole (IY-81149, **64**) and AGN 201904-Z (**65**).[38]

Structures 64, 65



64 (ilaprazole)



65 (AGN 201904-Z)

Best known of these is tenatoprazole developed by Mitsubishi Pharma (Japan); currently it is under active elaboration by the SIDEM company (France). Unlike other PPIs, this unique compound has a long half-life (8.7 ± 2.6 h after the second administration of 40 mg). The other representatives of this class, benzimidazole derivatives, have approximately equal half-lives (1 – 2 h).[39] The sodium salt of (*S*)-tenatoprazole (**60**) has a twice higher oral bioavailability than the basic form.[40, 41] According to pharmacokinetic and pharmacodynamic data, racemic tenatoprazole is characterized by more durable antisecretory action,[42] while the sodium salt of (*S*)-tenatoprazole ensures fuller and more durable dose-dependent acid suppression than esomeprazole during both the night- and daytime.[41, 43 – 45] These results indicate that among representatives of this class, drug **60** provides the most efficient control of any change in the gastric pH value. It can prove to be the best among the existing PPIs, as it possesses high potential for meeting the clinical demands.[38]

Ilaprazole (**64**) is a benzimidazole PPI developed by the Il-Yang Pharm company (Korea).[46] The antisecretory activity of this drug is 2 – 3 times higher than that of omeprazole (**55**) and the half-life is 2 – 3 times longer. Drug **64** has already entered the market in South Korea, while in the USA it is under clinical trials. Phase II clinical investigations on 235 patients showed that ilaprazole is as safe and effective for treating duodenal ulcer as omeprazole but operates in a lower dose of 10 mg daily (for comparison, the omeprazole dose is 20 mg daily).‡

Phase II and III clinical trials on the use of ilaprazole to treat oesophagitis and eliminate heartburn demonstrated higher efficacy of drug **64** compared to lansoprazole.§ It is noteworthy that ilaprazole efficacy does not depend on CYP2C19 polymorphism (see Ref. 47).¶

The sodium salt of the acid-stable omeprazole precursor — compound **65** (CMA-omeprazole) — has been prepared to increase the time of drug occurrence in the blood plasma *via* its slow metered absorption along the whole intestine length.[48] Compound **65** decomposes into omeprazole, which is quickly absorbed in upper intestine, and salt **66**, which is excreted through the kidneys (Scheme 2).

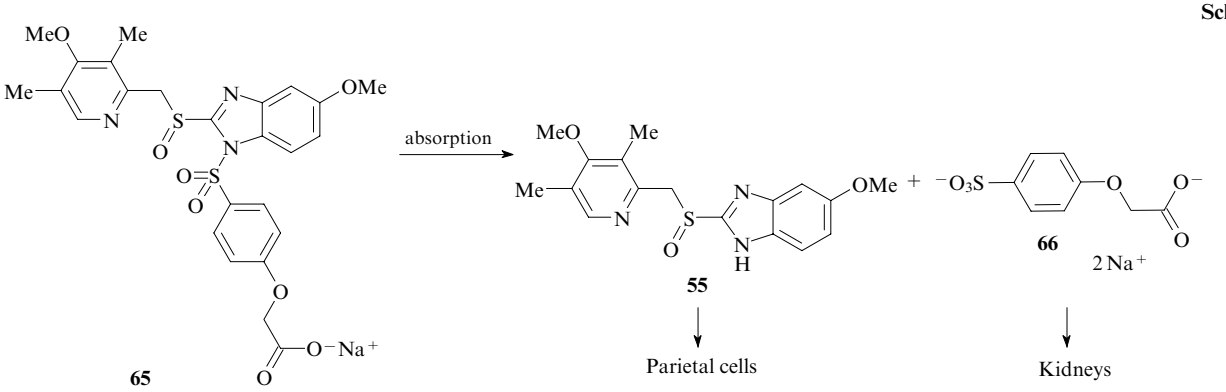
The first pharmacodynamic and pharmacokinetic investigations of the drug AGN 201904-Z (**65**) in humans in comparison with omeprazole were carried out. It was found that after the intake of a single and the second dose, the drug concentration peaks after 4 h or more and decreases down to the half-life level in the 3.8 – 4.5 h. The ambulant 24-hour gastric pH-monitoring in healthy male volunteers revealed that AGN 201904-Z provided a faster, more pronounced and more durable antisecretory effect than

‡ Clinical Trials.gov. A service of the U.S. National Institutes of Health. NCT00953381: Ilaprazole for the Treatment of Duodenal Ulcer in Chinese Patients (Phase 2); http://www.clinicaltrials.gov/ct2/results?term = NCT00953381&Search = Search (Accessed June 6, 2013)

§ ClinicalTrials.gov. A service of the U.S. National Institutes of Health. NCT00471094: Safety and Efficacy of Ilaprazole 5, 20 and 40 mg QD and Lansoprazole 30 mg QD on Healing of Erosive Esophagitis; http://www.clinicaltrials.gov/ct2/results?term = NCT00471094&Search = Search; NCT01509261: Efficacy Study of Ilaprazole to Treat Erosive Esophgitis; http://www.clinicaltrials.gov/ct2/results?term = NCT01509261&Search = Search (Accessed June 6, 2013)

¶ ClinicalTrials.gov. A service of the U.S. National Institutes of Health. NCT00952978: Ilaprazole for the Treatment of Duodenal Ulcer in Chinese Patients (Phase 3); http://www.clinicaltrials.gov/ct2/results?term = NCT00952978&Search = Search (Accessed June 6, 2013)

Scheme 2



65 55 66

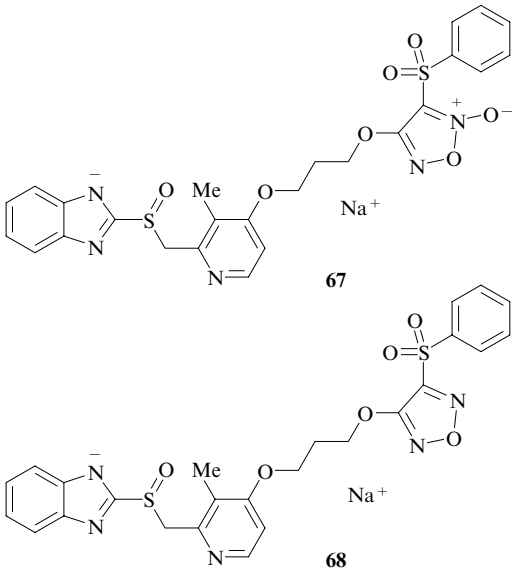
esomeprazole on the 1st and 5th day of treatment. The night-time acid suppression after 5 days of taking compound **65** was two pH units higher ($\Delta pH > 2$) and the average pH value never decreased below 5.0. This drug can ensure clinical efficacy when taken once a day and can be useful for patients with nocturnal symptoms and for patients who need fast and full-value acid suppression. Phase I clinical trials for this drug were completed.†

Currently, of interest are antisecretory agents functioning as donors of nitrogen(II) oxide, which has been recognized as an important protective mediator of the gastrointestinal tract mucosa. As was established using experimental models of stomach damage, NO can exert cytoprotective effects similar to the prostaglandin effects: nitrogen(II) oxide can modulate the blood flow in the mucosa, release of mucus and healing of mucosa lesions.[49] Various NO-releasing groups were attached by chemical bonds to traditional antisecretory drugs. However, in this case, the rate of release of nitrogen oxide was substantially lower than in the case of other nitrogen oxide donors, because hybrid molecules (NO-PPI), as well as organic nitrates, require metabolic degradation by tissue enzymes.

Recently, NO-lansoprazole (NMI-826, the structure was not reported [50]) and furoxan derivative of rabeprazole **67** were tested in animal experiments.[51]

Compound NMI-826 was much more efficacious than initial lansoprazole (**56**) in healing of acid-induced stomach ulcers in rats. The antisecretory and gastroprotective properties of the furoxan rabeprazole derivatives **67** were examined in comparison with the properties of the rabeprazole sodium salt and reference compound **68**, which is unable to release nitrogen oxide. The introduction of a furazan or a furoxan moiety into the rabeprazole molecule considerably reduces its antisecretory potential but does not affect the efficacy of action. The 50% inhibitory doses (ID_{50}) were 0.15, 6.83 and 2.07 μmol kg^{-1} for rabeprazole and compounds **67** and **68**, respectively. All three compounds prevent acute stomach damage by indomethacin: rabeprazole and NO donor **67** exhibited similar gastroprotective properties when used in equivalent doses (3, 10 and 30 μmol kg^{-1}). Unlike these drugs, the furazan analogue **68** showed gastroprotective properties only in a three times higher dose than that required for rabeprazole and its furoxan derivative **67** (possibly, due to low antisecretory activity). These results suggest that it is the NO-donor ability of compound **67** that is favourable for the protective action on the gastric mucosa. The maintenance of gastroprotective properties together with the reduced antisecretory effect can improve the balance between the antisecretory and gastroprotective activities of hybrid molecules.

Structures 67, 68



67 68

IV. K^+-Competitive acid blockers

During the last two decades, a new way of control over the acid secretion by competitive proton pump inhibition at the potassium exchange sites has been under research.[38,52] The compounds that block H^+/K^+-ATPase, so-called acid pump antagonists (APAs) or potassium-competitive acid blockers (P-CABs), are at different stages of development. These compounds bear structural resemblance to their target: the K^+-binding site of H^+/K^+-ATPase. The K^+-competitive acid blockers are lipophilic weak bases, which are concentrated in the acid medium, their concentration in the parietal cell secretory ducts being 100 000 times higher than in the plasma. When getting into the acidic medium, P-CABs are immediately protonated and in this form they produce an ionic bond with the K^+-binding site of H^+/K^+-ATPase.[53] this means that they provide a faster increase in the gastric pH than PPIs, which should first be transformed into the active form and then are

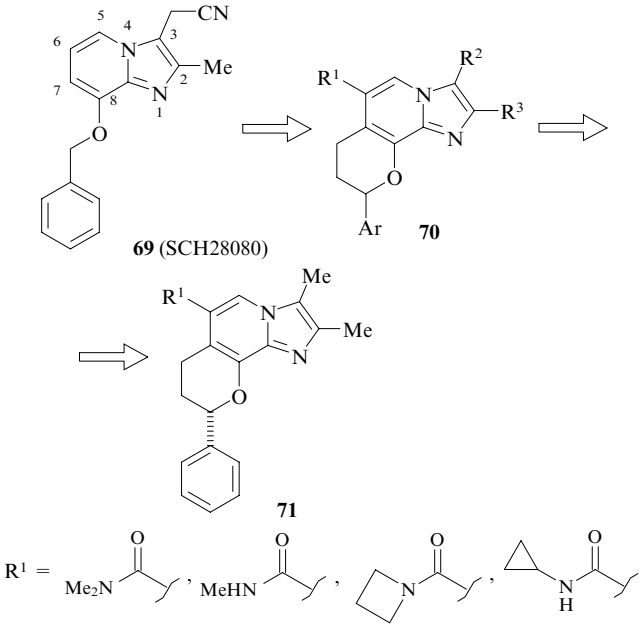
† ClinicalTrials.gov. A service of the U.S. National Institutes of Health. NCT00325715: AGN 201904 Versus Esomeprazole in the Prevention of Aspirin-induced Stomach or Upper Intestinal Damage in Healthy Volunteers; http://www.clinicaltrials.gov/ct2/results?term=NCT00325715&Search=Search (Accessed June 6, 2013)

covalently bonded to H^+/K^+-ATPase. The fast effect of K^+-competitive acid blockers appears especially attractive: secretion is completely suppressed after taking the first dose (a similar effect of PPIs is observed after the second dose). An important parameter of P-CABs characterizing their selective accumulation in parietal cells and the best safety profile is the negative common logarithm of the dissociation constant pK_a (the preferred pK_a value is in the range of 6.4 – 7.2).

Unlike proton pump inhibitors, P-CABs comprise various heterocycles; they include imidazo[1,2-*a*]pyridines (SCH28080, AZD0865,[54] PF-03716556),[55] imidazo[1,2-*a*]pyrazines,[56] pyrimidines (revaprazan, or YH1885),[57] imidazonaphthyridines (soraprazan),[58] pyrrolopyridazines (CS-526),[59] 1*H*-pyrrolo-[2,3-*c*]pyridines,[60,61] tetrahydrochromenoimidazoles[62] or biarylimidazoles.[63]

The studies of K^+-competitive acid blockers started from the omeprazole analogue, imidazo[1,2-*a*]pyridine, which was abandoned due to side effects. However, it was found that this compound is able to act as K^+-competitive inhibitor of H^+/K^+-ATPase. This initiated investigation of this type of behaviour for 8-benzyloxy-3-cyanomethyl-2-methylimidazo[1,2-*a*]pyridine (SCH28080, **69**). This compound shows excellent antisecretory and cytoprotective properties.[23,64–66] However, the clinical trials of SCH28080 were terminated due to extensive metabolism and the concomitant hepatotoxicity.[65] For solving these problems, various tricyclic analogues of compound **69** have been prepared (Scheme 3).[67]

Scheme 3



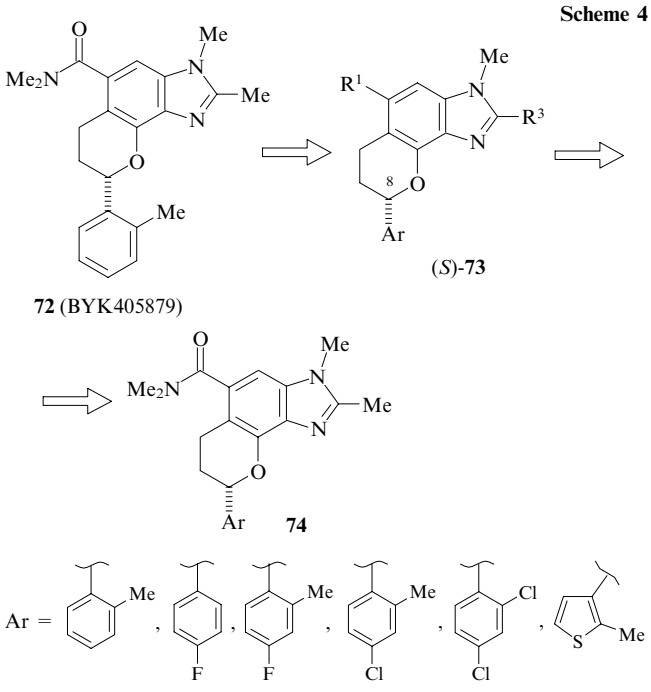
In the development of these analogues, two circumstances were taken into account. First, it was found earlier that effective binding between H^+/K^+-ATPase and its K^+-competitive inhibitor requires a rigid structure in which the heterocycle and the bond connecting it to the benzene ring are coplanar. Second, since the 3-cyanomethyl group is the metabolic hot spot of compound **69**, it was necessary to prepare inhibitors devoid of this group and exclude the metabolic degradation *via* oxidative decyanation. With allowance for these circumstances, tricyclic compounds **70** and **71** were prepared in which the dihydropyran ring plays a dual role: bears the responsibility for the occurrence of K^+-competitive inhibition of H^+/K^+-ATPase and mimics the presence of a 7-methyl substituent, which is needed to overcome the toxic properties of SCH28080, while maintaining the desired antisecretory effect.

A study of the effect of the nature of substituents R^1, R^2, R^3 and Ar on the biological activity and physicochemical properties of 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines **70** identified the following trends. Generally, compounds in which R^1 is an aminocarbonyl group (with a hydrogen atom, lower alkyl, alkoxyl, cyclopropyl or alicyclic group at nitrogen) exhibited higher activity *in vivo*. The nature of the substituent R^2 was significant for the presence of pronounced H^+/K^+-ATPase inhibition, which, like the *in vivo* activity, was observed only for R^2 = Me. However, varying the R^3 group proved to be useful for the change in the basicity and lipophilicity of target compounds. Slight modifications of the aryl group (Ar) are admissible, for example, the replacement of the hydrogen atom by a fluorine atom or a methyl group. Compounds **70** preserve the *in vitro* and *in vivo* activity but they are less basic than the initial compound **69**.

Among the target products **71** obtained in an optically pure form, noteworthy are the 9*S*-enantiomers, which are responsible for the gastric acid inhibition, whereas the 9*R*-enantiomers are almost inactive. According to preliminary testing, 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines **71** exhibit excellent physicochemical and pharmacological characteristics and are promising candidates for the subsequent use as P-CABs. The negative common logarithm of the IC_{50} value (pIC_{50}) for H^+/K^+-ATPase inhibition by these derivatives is in the range of 6.0 – 6.8: for example, for the compound BYK3113190 [**71a**, R^1 = C(O)NMe$_2$], pIC_{50} = 6.8.

Yet another type of tricyclic P-CABs prepared from the drug BYK405879 (**72**) as the precursor are enantiomerically pure 3,6,7,8-tetrahydrochromeno[7,8-*d*]imidazoles (*S*)-**73** (Scheme 4).[62]

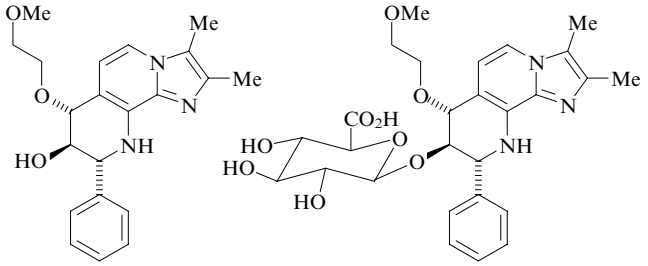
Scheme 4



For these compounds, the effect of substituents in the molecule on the acid-suppressing activity was studied in rats. Most preferable for the activity were aminoalkyl groups (with small aliphatic or alicyclic groups) as R^1 and *ortho*(*para*)-substituted or *ortho*,*para*-disubstituted (by methyl groups or chlorine or fluorine atoms) aromatic rings in position 8. The pK_a value and the metabolic stability of P-CABs **73** depend on the nature of R^1. For further search for medicines for the treatment of acid-dependent diseases, several such derivatives were selected, namely, compounds **74**, which in the case of H^+/K^+-ATPase showed $pIC_{50} = 5.3-6.3$. Note that the pharmacological profile of these compounds is comparable to that of the precursor, BYK405879 (**72**) ($pIC_{50} = 5.3$ for H^+/K^+-ATPase).[68]

One more representative of tricyclic P-CABs — soraprazan (BYK61359, **75**) — is (7*R*,8*R*,9*R*)-8-hydroxy-2,3-dimethyl-7-(2-methoxyethoxy)-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-*h*][1,7]naphthyridine. This compound has a relatively rigid naphthyridine structure with a polar hydroxy group and has a higher efficacy and metabolic stability than the drug SCH28080 (**69**) having a more flexible periphery.[58] Study of the soraprazan metabolism in humans using ^{13}C NMR spectroscopy and mass spectrometry confirmed that the glucuronide conjugate of **75**, the drug BY359 (**76**), is the major metabolite of soraprazan.[69]

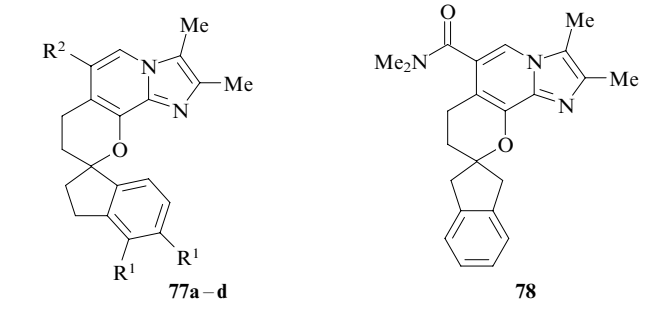
Structures 75, 76



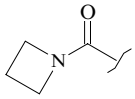
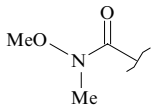
75 (soraprazan) **76** (BY359)

Palmer *et al.*[68] made attempts at further increase in the rigidity of the molecular skeleton with the assumption that this would increase the H^+/K^+-ATPase affinity of the compound. For this purpose, they synthesized spiro-substituted 7*H*-8,9-dihydropyrano[2,3-*c*]imidazo[1,2-*a*]pyridines of two types: asymmetric (**77**) and symmetric (**78**) ones. These compounds represented the first example of P-CABs that have a long distance between the heterocyclic and aryl moieties. Despite this modification, they showed a noticeable inhibiting activity. Owing to the balanced biochemical activity profile and promising physicochemical properties, inhibitors **77a–d** and **78** (for H^+/K^+-ATPase, $pIC_{50} = 5.8-6.5$; $pK_a = 6.63-6.84$) are promising candidate drugs to be advanced as anti-ulcer agents.

Structures 77, 78

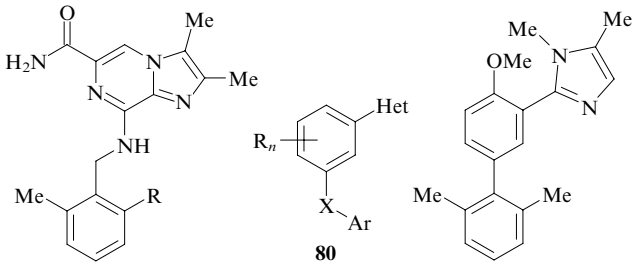


77a–d **78**

77: R^1 = H, F; R^2 = Me_2N (**a**), MeHN (**b**),  (**c**),  (**d**)

As an alternative to the imidazopyrimidine reference drugs **79a** and **79b** (AR-HO47108),‡ which showed an inhibitory effect with respect to H^+/K^+-ATPase with pIC_{50} of 7.0 and 7.1, respectively, biaryls **80** have been proposed.[63]

Structures 79–81



79a,**b** **80** **81**

79: R = Me (**a**), Et (**b**);
80: R_n = 4-Me, 6-OH, 2-OMe, 4-OMe, 6-OMe, 6-OEt, 6-OBn, 6-$OCHF_2$, 6-OCH_2CO_2Me, 6-$OCH_2C(O)NH_2$, 5,6-$(OMe)_2$; Ar = Ph, 2-MeC_6H_4, 2,6-$Me_2C_6H_3$, 2,6-$Et_2C_6H_3$, 3-methylthiophen-4-yl; X = NH, *trans*-CH=CH, $(CH_2)_2$, $NHCH_2$, C(O)NH, *o*-phenylene, *p*-phenylene; Het = CH_2NHMe, 4-aminopyridin-2-yl, 4-methylpiperazin-1-yl

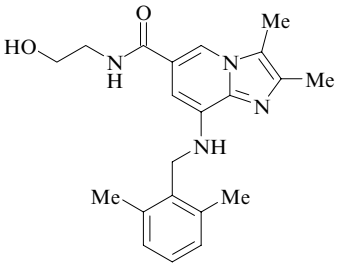
The structure of compounds **80** was optimized by modification of the aromatic ring and the heterocyclic moiety and substituents in them. The presence of one or two *ortho*-substituents in the benzene ring has little influence on the drug efficacy, and the presence of a thiophene ring mitigates the action with respect to the phenyl analogue. A pronounced decrease in the activity occurred upon the introduction of a bridge X between the aryl rings when they are *ortho*- or *para*-substituted. The replacement of an imidazole moiety by other heterocycles or alkylamines or the introduction of other substituents instead of the methyl groups into the imidazole ring resulted in low efficiency of compounds **80** thus formed. The presence of a methoxy group in position 6 of the central benzene ring is, apparently, favourble for the formation of an intramolecular hydrogen bond between the imidazole hydrogen atom and the oxygen atom. This mimics the structure of imidazopyridine, which has a beneficial effect on the activity of the resulting derivatives. For example, compound **81** had $pIC_{50} = 6.1$ with respect to H^+/K^+-ATPase. Other oxygen-containing groups in this position of the central benzene ring that can be involved in the presumed hydrogen bond are also highly active ($pIC_{50} = 4.9-5.6$). The introduction of other substituents into the central benzene ring

‡ The drug AR-HO47108 proved to be toxic in clinical trials.[70]

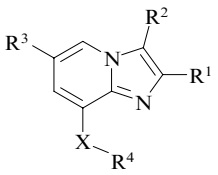
and replacement of the ring by aromatic heterocycles had adverse effect on the activity of the resulting compounds.

The efficiency of imidazo[1,2-*a*]pyridine derivatives **81** and **82** (AZD0865) was demonstrated in animal models and in clinical trials using low oral doses of these compounds. However, no detailed and extensive investigation of the structure–activity relationship for tetrasubstituted imidazo[1,2-*a*]pyridines was carried out. Bailey *et al.*[71] filled this gap and investigated the influence of various substituents at four carbon atoms in the molecule in order to optimize the structure of compounds **83**, provide them with required physicochemical properties and improve the pharmacological profile. The initial molecules were modified by varying the substituents at the carbon atoms in positions 2, 3, 6 and 8 of the imidazo[1,2-*a*]pyridine system. The role of the linker X between the C(8) atom and the substituent R^4 was elucidated.

Structures 82, 83

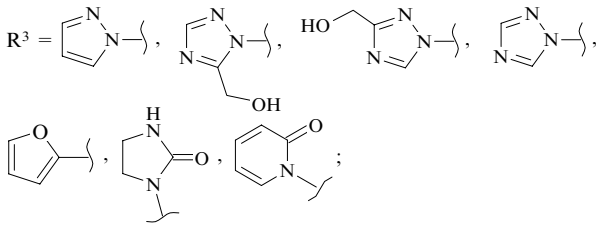


82 (AZD0865)

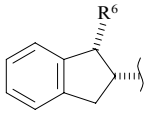


83

83: X = NH, O, CH_2; R^1 = Me, CH_2OH; R^2 = H, Me, CH_2OH, Cl;

R^3 = 

$R^4 = R^5_nC_6H_{5-n}$ (R^5_n = H, 2-Me, 3-Me, 2-MeO, 2-Cl-4-F, 2,6-Me_2),

3-Py,  (R^6 = H, OH)

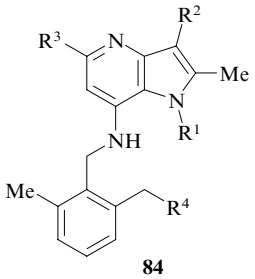
Various (hetero)aromatic rings were employed as substituents at C(6). The H^+/K^+-ATPase inhibition was enhanced (Table 8) in the presence of the following groups: 2-pyridone or 1,2,4-triazole at the C(6) atom (compounds **83a**–**c**), 2,3-dihydro-1*H*-indene at C(8) for blocking the metabolically vulnerable benzyl group (**83f**), the methyl group at C(2), or the hydrogen atom or the methyl or hydroxymethyl group at C(3) (**83c**,**d**,**e**). Compounds with a heteroatomic linker were more active than those with an oligomethylene chain. The doses for compounds **83a**–**f**, which have most admissible general pharmacological profiles, were studied in relation to oral administration into rats and dogs. Inhibitor **83c** has the optimal balance of the *in vitro* and *in vivo* activity and the DMPK (drug metabolism and pharmacokinetics) profile.

Table 8. Inhibitory activity of lead compounds **83a**–**f** (R^1 = Me, X = NH) with respect to H^+/K^+-ATPase.[71]

Compound **83**	R^2	R^3	R^4	pIC_{50}
a	Me	5-hydroxymethyl-1,2,4-triazol-1-yl	2,6-$Me_2C_6H_3$	7.6
b	Me	1,2,4-triazol-1-yl	2,6-$Me_2C_6H_3$	7.6
c	Me	pyridin-2-on-1-yl	2,6-$Me_2C_6H_3$	7.9
d	H	pyridin-2-on-1-yl	2,6-$Me_2C_6H_3$	6.4
e	CH_2OH	pyridin-2-on-1-yl	2,6-$Me_2C_6H_3$	6.9
f	Me	1,2,4-triazol-1-yl	2,3-dihydro-1*H*-inden-1-yl	7.1

The antisecretory activity of 5-substituted 1*H*-pyrrolo[3,2-*b*]pyridines **84** has been studied (H^+/K^+-ATPase: pIC_{50} = 4.0–6.9) and the influence of substituents in heterocycle positions 1, 3 and 5 on the antisecretory activity, lipophilicity and the pK_a value were elucidated. Compounds **84a**,**b** [R^1 = H, R^2 = Me, R^3 = C(O)NMe_2: R^4 = H (**a**), Me (**b**)] behaved as active proton pump inhibitors (pIC_{50} = 6.9 and 6.6) and promising candidates for the elaboration of effective P-CABs.[72]

Structures 84

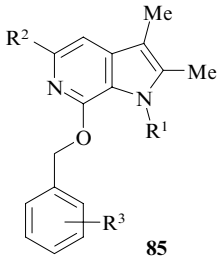


84

R^1 = H, Me, Bn, $CH_2CH(OH)Me$; R^2 = H, Me, CH_2OH, Br; R^3 = C(O)NHMe, C(O)NMe_2; R^4 = H, Me

Optimization of the structures of substituents at the N(1), C(5) and C(7) atoms in 1*H*-pyrrolo[2,3-*c*]pyridines **85** revealed compounds **85a**,**b** [R^1 = Bn, R^3 = F: R^2 = C(O)NMe_2 (**a**), C(O)[N(CH_2CH_2)$_2$O]-cyclo (**b**)], which act as potent H^+/K^+-ATPase inhibitors (IC_{50} = 28 and 29 nmol litre^{-1}, respectively).[61]

Structures 85



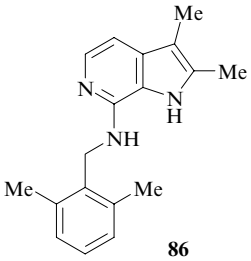
85

R^1 = H, Pr^n, Bu^i, All, Bn, $CH_2C_3H_5$-cyclo, 1,3-dioxolan-2-ylmethyl; R^2 = H, C(O)NH_2, C(O)NHMe, C(O)NMe_2, C(O)NHC_3H_5-cyclo, C(O)NH-4-Py, C(O)[N(CH_2CH_2)$_2$O]-cyclo; R^3 = H, 2-F, 4-F, 4-Cl

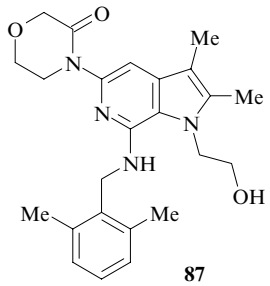
The pharmacological profile of 1*H*-pyrrolo[2,3-*c*]pyridine **86** (H^+/K^+-ATPase: pIC_{50} = 9.4) developed based on SCH28080 (**69**) (H^+/K^+-ATPase: pIC_{50} = 7.4) was improved by selecting appropriate substituents at C(6) and N(1), which affected pK_a and lipophilicity of the derivatives. Successive modification resulted in the discovery of com-

pound **87** (H^+/K^+-ATPase: $pIC_{50} = 6.6$) having an *in vitro* profile similar to the profile of AZD0865 (**82**) (H^+/K^+-ATPase: $pIC_{50} = 6.5$) and chosen for the subsequent clinical trials.[59]

Structures 86, 87



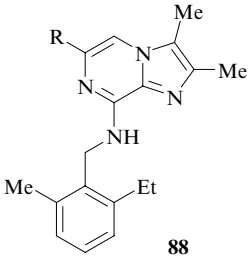
86



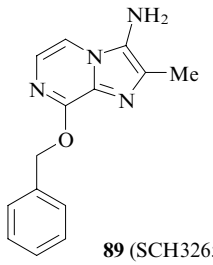
87

Different degrees of H^+/K^+-ATPase inhibition were also found for 6-substituted imidazo[1,2-*a*]pyrazines **88**: the pIC_{50} values of these compounds ranged from 5.0 to 6.9. These compounds were obtained by structural modification of a known H^+/K^+-ATPase inhibitor — SCH-32651 (**89**) ($pIC_{50} = 5.9$). Of this series, two compounds **88a**,**b** {R = C(O)NMe$_2$ (**a**), C(O)[N(CH$_2$)$_4$]-cyclo (**b**)} having pIC_{50} of 6.4 and 6.9, respectively, demonstrated excellent H^+/K^+-ATPase antagonism *in vitro* as compared with their precursor.[56]

Structures 88, 89



88

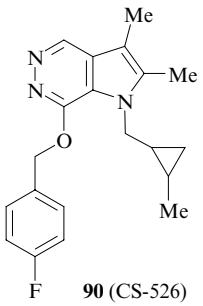


89 (SCH32651)

R = CH_2OH, CH_2OMe, $C(O)NH_2$, C(O)NHMe, $C(O)NMe_2$, $C(O)CH_2OH$, $C(O)CH_2OMe$, C(O)[N(CH$_2$)$_4$]-cyclo

7-(4-Fluorobenzyloxy)-2,3-dimethyl-1-{[(1*S*,2*S*)-2-methylcyclopropyl]methyl}-1*H*-pyrrolo[2,3-*d*]pyridazine (CS-526, **90**) contains the pyrrolopyridazine moiety, which was not present in the P-CABs described earlier. Ito *et al.*[59] studied the inhibitory properties of this compound in experiments in rats and dogs and compared the results with the properties of known PPIs — omeprazole (**55**), lansoprazole (**56**) and rabeprazole (**58**). The compound CS-526 ($IC_{50} = 61$ nmol litre^{-1}) inhibits the H^+/K^+-ATPase activity depending on the concentration. Hence, it is more efficacious than any of the indicated PPIs (the IC_{50} values for omeprazole, lansoprazole and rabeprazole are 11 000, 12 000 and 1700 nmol litre^{-1}, respectively). Moreover, compound **90** prevents the gullet damage in the case of both intraduodenal and oral administration ($ID_{50} = 5.4$ and 1.9 mg kg^{-1}), while lansoprazole is active only upon intraduodenal administration ($ID_{50} = 2.2$ mg kg^{-1}). Thus, compound CS-526 can act on the parietal cells in two ways: first *via* absorption from the small intestine and second by direct penetration through the gastric mucosa. These data demonstrate that the drug CS-526 has anti-ulcer properties along with the antisecretory action.[73]

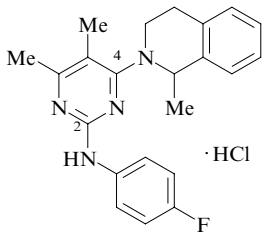
Structure 90



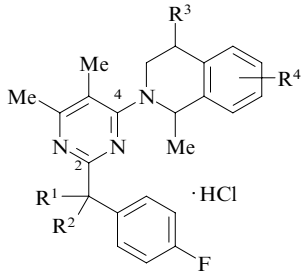
90 (CS-526)

5,6-Dimethyl-2-(4-fluorophenylamino)-4-(1-methyl-1,2,3,4-tetrahydroisoquinolino)pyrimidine hydrochloride (revaprazan, YH1885, **91**) is a reversible proton pump antagonist. In preclinical trials, it showed a more favourable safety profile than omeprazole (**55**).[74] Further modification of the pyrimidine core of P-CABs consisted in optimization of substituents at the C(2) and C(4) atoms. Among the 2-(4-fluorobenzyl)-substituted pyrimidines **92** with different groups in the 1-methyl-1,2,3,4-tetrahydroisoquinoline moiety, compound **92a** ($R^1 = R^2 = R^3 = H$, R^4 = 7-OMe) with activity ($IC_{50} = 52$ nmol litre^{-1}) exceeding the revaprazan activity was chosen as the lead drug. It was also found that compounds containing electron-donating substituents (R^3 = Me, R^4 = OMe) inhibit H^+/K^+-ATPase three times more strongly than compounds with electron-withdrawing groups (R^4 = F, Cl).[75]

Structures 91, 92



91 (revaprazan, YH1885)



92

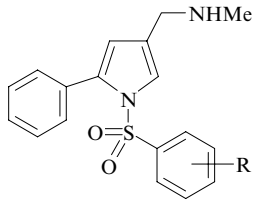
$R^1 = R^2$ = H, Me; R^1 = H: R^2 = F, OH; $R^1 - R^2$ = O, $(CH_2)_2$, R^3 = H, Me; R^4 = H, 7-F, 6-Cl, 7-Cl, 6-Me, 7-Me, 6-OMe, 7-OMe

Recently, new structural H^+/K^+-ATPase inhibitors, pyrrole derivatives **93**, have been proposed. These compounds not only effectively inhibited the H^+/K^+-ATPase activity *in vitro* but also showed antisecretory effect in experiments in rats and dogs.[76] Compound **93a** (R = 3-OMe) had the most pronounced inhibitory action ($IC_{50} = 30$ nmol litre^{-1}), thus defining the substituents in the pyrrole ring needed for effective inhibitory behaviour: an arylsulfonyl group in position 1, a amethylaminomethyl group in position 3 and a phenyl group in position 5 of the pyrrole ring.

Further optimization of the pharmacokinetic profile of compound **93a** was performed for the series of 1-arylsulfonyl-5-(het)aryl-3-(*N*-methylaminomethyl)-1*H*-pyrroles **94** (H^+/K^+-ATPase activity inhibition *in vitro* and inhibition of the histamine-induced gastric secretion in mice).[77] The authors found that a 3-pyridylsulfonyl group at N(1) and a fluorine atom in position 2 of the phenyl ring attached to

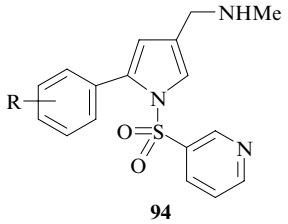
the pyrrole C(5) atom are preferred for the presence of *in vitro* and *in vivo* activity.

Structures 93 – 95



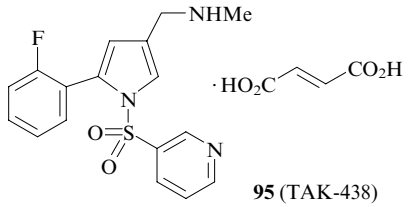
93

R = Me, 4-OMe, 3-OMe



94

R = 3-F, 4-F, 2-Cl, 2-Me, 2-CF_3, 2-CN, 2-CH_2OH



95 (TAK-438)

Furthermore, both structural moieties contribute to high LLE values.§ Among the synthesized compounds, 1-[1-(3-pyridylsulfonyl)]-3-(*N*-methylaminomethyl)-5-(2-fluorophenyl)-1*H*-pyrrole fumarate (TAK-438, **95**) showed a good inhibitory activity *in vitro* (H^+/K^+-ATPase: IC_{50} = 19 nmol litre^{-1}), high LLE (7.3) and effective inhibition of the histamine-induced gastric secretion in rats (98% inhibition). As regards the pharmacological effect, compound **95** surpassed lansoprazole (**56**) and the drug SCH28080 (**69**) (IC_{50} at pH 6.5 for these derivatives were 0.019, 0.14 and 7.6 μmol litre^{-1}, respectively). The inhibitory activity of TAK-438 did nor depend on the pH of the medium, whereas that of SCH28080 and lansoprazole was weaker at pH 7.5.[78] Compound **95** produced a longer-lasting antisecretory effect than lansoprazole due to the high concentration and slow removal from glands (the IC_{50} values are 0.30 and 0.76 μmol litre^{-1}, respectively;[79] pharmacokinetic testing in rats and dogs[80]). Currently, the drug TAK-438 is under clinical trials for treating acid-dependent diseases,[81] where one phase has been successfully completed.¶

The pharmacological activity of a new acid pump antagonist PF-03716556 has been studied *in vitro* and *in vivo* (using porcine, canine and human recombinant gastric H^+/K^+-ATPase); the inhibitory activity of this compound was found to exceed three times that of revaprazan (**91**) (the structure of the compound was not reported in the paper).[55]

It is still unclear how soon the unique pharmacodynamic properties of K^+-competitive acid blockers would be clinically demanded. Indeed, back in 2005, phase II clinical trials were performed for the compound AZD0865 (**82**).† The only acid pump antagonist certified for use by the KFDA (Korea Food and Drug Administration) for treating gastric diseases is revaprazan (**91**) present in the South Korea market under the trade name Revanex®. The clinical investigations of this drug are still in progress.‡

V. Non-steroidal anti-inflammatory drug-induced erosive and ulcerous damages of the digestive tract

A frequent complication of NSAID therapy is the toxic effect of these drugs on the GIT. The erosive and ulcerous damages of the digestive tract induced by NSAIDs can be located in any region of the digestive tube and, depending on the location site, they are classified into NSAID gastropathy and NSAID-induced enteropathy.[81] These terms were proposed in order to distinguish between the specific gastric mucosa damage arising upon long-term taking of NSAIDs and the classical ulcer disease. The NSAID-induced erosive and ulcerous damage of the digestive tract can be manifested not only as dyspepsia and pain syndrome but also as latent phenomena that can potentially be life-threatening: perforations, ulcers and hemorrhages.

For prevention and treatment of NSAID gastropathy, antisecretory agents (proton pump inhibitors or H_2-blockers) are used. However, these drugs are inactive against NSAID-induced damage of small intestines. Currently, there are no medicines that have been proven efficient for treating NSAID-induced damage of small intestine.

Satoh and Takeuchi[82] analyzed, in a review, the most advanced pharmacological methods for prevention or mitigation of the NSAID-induced intestinal damage, studied clinical investigation data, and considered the pros and cons of these methods from the safety, efficacy, convenience and cost standpoints.

Currently, of most promise are modified NSAIDs containing NO- and H_2S-releasing groups in the molecules. These medications possess mucosa-protective properties. For example, such drugs were obtained based on naproxen (**96**), namely, NO (**97**) and H_2S (**98**) naproxen analogues. Indomethacin (**99**) served as the basis for NO-indomethacin (**100**), while diclofenac (**101**) was used to prepare H_2S analogue **102**.

In animal and human experiments, compounds **97**, **98**, **100** and **102** showed the same anti-inflammatory activity as their precursors **96**, **99** and **101** but the adverse effect on the gastro-intestinal tract was much less pronounced.[82,83] Furthermore, it was found that new drugs do not exert adverse

§ LLE is a parameter based on the activity – lipophilicity relationships. It is used in the development of pharmaceutical agents to evaluate the quality of compounds and compare the new and known drugs.

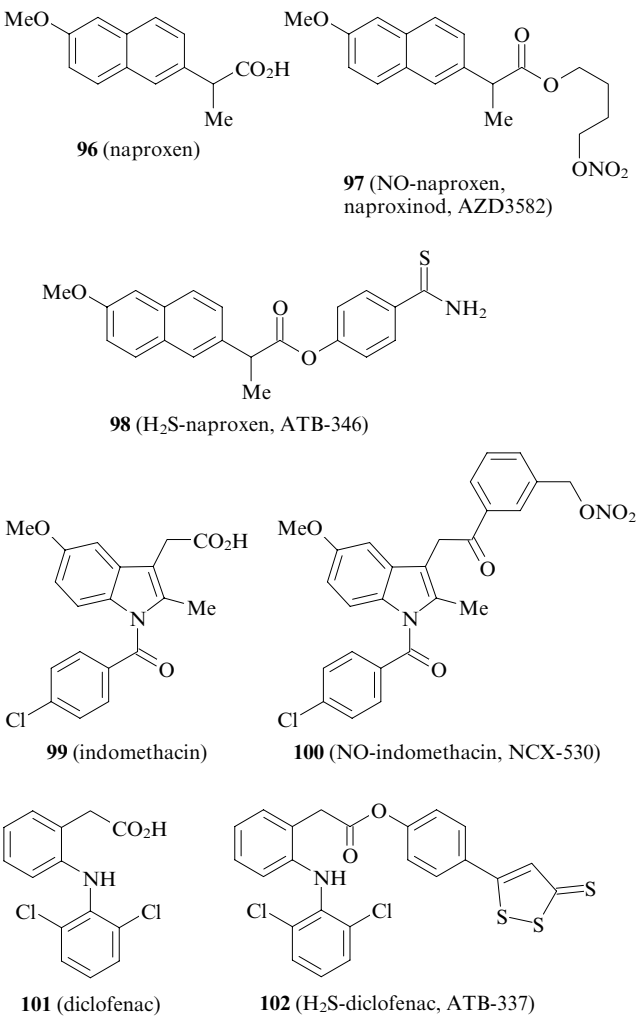
¶ ClinicalTrials.gov. A service of the U.S. National Institutes of Health; 14 Studies found for TAK-438; http://www.clinicaltrials.gov/ct2/results?term = TAK-438&Search = Search (Accessed June 6, 2013)

† ClinicalTrials.gov. A service of the U.S. National Institutes of Health. NCT00206284: A Dose-finding Phase IIb Study with AZD0865 and Esomeprazole in GERD Patients without Erosive Esophagitis; http://www.clinicaltrials.gov/ct2/show/NCT00206284?term = AZD0865&rank = 1 (Accessed June 6, 2013);
ClinicalTrials.gov. A service of the U.S. National Institutes of Health. NCT00206245: A Dose-finding Phase IIb Study with AZD0865 and Esomeprazole in GERD Patients with Erosive Esophagitis; http://www.clinicaltrials.gov/ct2/show/NCT00206245?term = AZD0865&-rank = 2 (Accessed June 6, 2013)

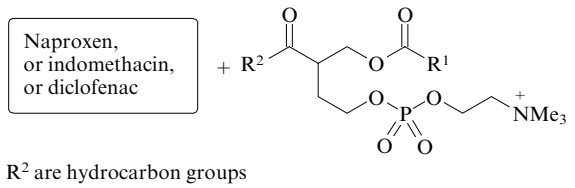
‡ ClinicalTrials.gov. A service of the U.S. National Institutes of Health. NCT01750437: Phase 2 Clinical Trial to Investigate the Safety, Tolerability and Efficacy of YH1885L in Patients With Non-erosive Reflux Disease(NERD); http://www.clinicaltrials.gov/ct2/results?term = NCT01750437&Search = Search (Accessed June 6, 2013)

action on the cardiovascular system, which was a result of cyclooxygenase-2 (COX-2) inhibition inherent in the selective NSAIDs. These drugs are convenient for use and advantageous for patients (for example, there is no need for other medications to protect the gastro-intestinal tract).

Structures 96 – 102



The NSAIDs combined with phosphatidylcholine as mechanical mixtures are apparently the second most promising for clinical practice. An important advantage of these drugs is the ease of preparation. However, quite a number of clinical investigations are required to ascertain the safety of these compounds for the stomach and small intestine, especially for patients taking NSAIDs (Fig. 7).

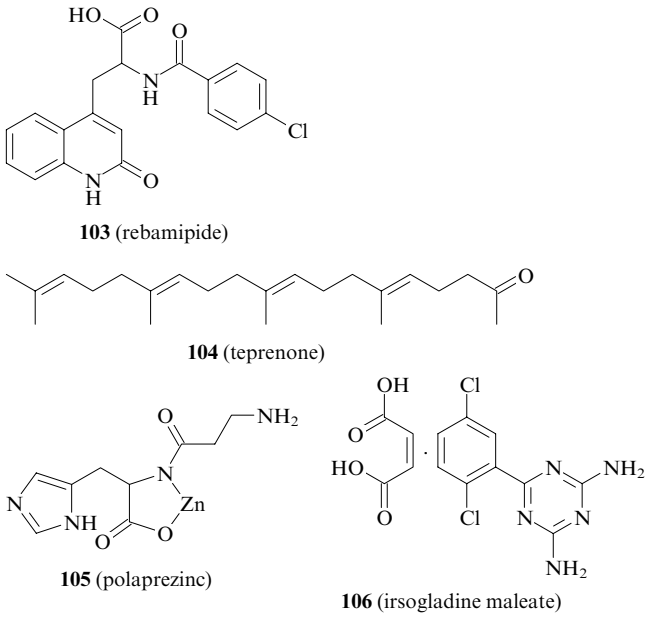


R^1, R^2 are hydrocarbon groups

Figure 7. Mixtures of nonsteroidal anti-inflammatory drugs (NSAIDs) and phosphatidylcholine.

Several pilot investigations using rebamipide (**103**) and teprenone (**104**) provided promising clinical data concerning their protective action against NSAID-induced intestinal damage. However, large-scale investigations are required to confirm these results, first of all, for patients taking NSAIDs to treat rheumatoid arthritis, osteoarthritis or thrombosis. Preliminary results of testing of polaprezinc (**105**) attest to its ability to inhibit the increase in the intestinal mucosa permeability caused by indomethacin. The gastroprotective anti-ulcer drug irsogladine maleate (Gaslon N®, **106**) diminishes the indomethacin-induced intestinal damage *via* an increase in the amount of mucus in the mucosa by inhibiting phosphodiesterase.

Structures 103 – 106



The antisecretory agents (PPIs and H_2-blockers) usually serve to prevent the side effects of NSAIDs in the upper gastro-intestinal tract. Although it was reported[82] that roxatidine (**5**), lafutidine (**6**), omeprazole (**55**) and lansoprazole (**56**) are effective for protection of the intestinal mucosa from the NSAID-induced damage in rats, clinical trials in human patients have not been conducted as yet. Thus, further studies of these medications in the human body, especially during taking NSAIDs, are required.

* * *

Anti-ulcer agents are currently in the top 10 most significant medications in the world. Obviously, their role is going to increase with time in view of the increasing toxic load of xenobiotics, including chemotherapy agents, on the whole body and on the forefront, *i.e.*, the gastro-intestinal tract. Therefore, one can predict intensive development of the research aimed at the design of modern agents combining the specific anti-ulcer action and reduced toxicity apart from other pleiotropic effects. Most likely, resorting to natural molecules as the basis for future medicines containing native groups of the desired activity (for example, the sulfoxide group and various nitrogen heterocycles) will be useful along this route.

References

1. Y Katsura, S Nishino, H Takasugi *Chem. Pharm. Bull.* **39** 2937 (1991)
2. Y Katsura, S Nishino, Y Inoue, M Tomoi, H Takasugi *Chem. Pharm. Bull.* **40** 371 (1992)
3. Y Katsura, Y Inoue, S Nishino, M Tomoi, H Itoh, H Takasugi *Chem. Pharm. Bull.* **40** 1424 (1992)
4. Y Katsura, Y Inoue, S Nishino, M Tomoi, H Itoh, H Takasugi *Chem. Pharm. Bull.* **40** 1818 (1992)
5. Y Katsura, Y Inoue, M Tomoi, H Takasugi *Chem. Pharm. Bull.* **40** 2062 (1992)
6. Y Katsura, Y Inoue, S Nishino, M Tomoi, H Itoh, H Takasugi *Chem. Pharm. Bull.* **40** 2432 (1992)
7. Y Katsura, Y Inoue, T Tomishi, H Ishikawa, H Takasugi *J. Med. Chem.* **37** 57 (1994)
8. E A Bardakhch'yan, N V Kamneva, N G Kharlamova, S Yu Lomov *Eksperim. Klin. Gastroenterol.* (2) 22 (2003)
9. M Munoz-Navas, J Honorato, M Reina-Arino, M Marquez, E Herrero, F Villamayor, J Torres, P N Roset, O Fillat, F Camps, J A Ortiz *Arzneimittelforschung* **47** (4A) 539 (1997)
10. M T Grau, A Romero, F Villamayor, A Sacristbn, J A Ortiz *Arzneimittelforschung* **47** (4A) 490 (1997)
11. P C Konturek, T Brzozowski, S I Konturek, M Márquez, J Torres, J A Ortiz *Arzneimittelforschung* **47** (4A) 578 (1997)
12. B L Slomiany, J Piotrowski, A Slomiany *Arzneimittelforschung* **47** (4A) 459 (1997)
13. Y Tomokane, M Nomura, S Kujime, Y Noda, N Kondo, Y Nakaya, S Ito *Arzneimittelforschung* **54** 427 (2004)
14. Y Sekine, N Hirakawa, N Kashiwaba, H Matsumoto, T Kutsuma, T Yamaura, A Sekino *Chem. Pharm. Bull.* **46** 610 (1998)
15. N Hirakawa, H Matsumoto, A Hosoda, A Sekino, T Yamaura, Y Sekine *Chem. Pharm. Bull.* **46** 616 (1998)
16. WO 03092692A1 (2003)
17. Y Naito, T Yoshikawa, K Matsuyama, N Yagi, M Arai, Y Nakamura, T Kanek, N Yoshida, M Kondo *Eur. J. Pharm.* **294** 47 (1995)
18. Y Isobe, H Kijima, K Fukushima, H Iizuka, S Umigami, K Yamaguchi, Y Makita, H Naito, T Yanagida *Jpn. Pharmacol. Ther.* **27** 543 (1999)
19. H Kijima, Y Isobe, M Muramatsu, S Yokomori, M Suzuki, S Higuchi *Biochem. Pharm.* **55** 151 (1998)
20. R Caroppo, G Signorile, S Curci, A L M Velardi, V O Palmieri, G Palasciano *Curr. Ther. Res.* **48** 20 (1990)
21. G Gasbarrini, N Gentiloni, S Febbraro, A Gasbarrini, C Di Campli, M Cesana, F Miglio, M Miglioli, F Ghinelli, A D'Ambrosi, P Amoroso, F Pacini, G Salvadori *J. Hepatol.* **27** 583 (1997)
22. M Bertinaria, G Sorba, C Medana, C Cena, M Adami, G Morini, C Pozzoli, G Coruzzi, A Gasco *Helv. Chim. Acta* **83** 287 (2000)
23. G Sachs, J M Shin, O Vagin, N Lambrecht, I Yakubov, K Munson *J. Clin. Gastroenterol.* **41** (Suppl. 2) S226 (2007)
24. J M Shin, Y M Cho, G Sachs *J. Am. Chem. Soc.* **126** 7800 (2004)
25. T Ishizaki, Y Horai *Aliment. Pharmacol. Ther.* **13** (3) 27 (1999)
26. T Andersson *Clin. Pharmacokinet.* **31** 9 (1996)
27. M Masatomo, S Shigeru, T Hitoshi, H Tomonori, S Toshio *Eur. J. Clin. Pharm.* **62** 113 (2006)
28. D E Beattie, R Crossley, K H Dickinson, G M Dover *Eur. J. Med. Chem.* **18** 277 (1983)
29. J C Sih, W B Im, A Robert, D R Graber, D P Blakeman *J. Med. Chem.* **34** 1049 (1991)
30. Patent RF 2339631 S1 (2008)
31. Patent RF 2341524 S1 (2008)
32. K A Kim, M J Kim, J Y Park, J H Shon, Y R Yoon, S S Lee, K H Liu, J H Chun, M H Hyun, J G Shin *Drug Metab. Dispos.* **31** 1227 (2003)
33. A Ekpe, T Jacobsen *Drug Dev. Ind. Pharm.* **25** 1057 (1999)
34. S Pallotta, F Pace, S Marelli *Exp. Rev. Gastroenterol. Hepatol.* **2** 509 (2008)
35. A Dadabhai, F K Friedenberg *Expert. Opin. Drug Safety* **8** 119 (2009)
36. S L Bodhankar, B B Jain, B P Ahire, R B Daude, P P Shitole *Ind. J. Pharm.* **38** 357 (2006)
37. V Pai, N Pai *World J. Gastroenterol.* **13** 4100 (2007)
38. C Scarpignato, R Hunt *Curr. Opin. Pharmacol.* **8** 677 (2008)
39. G Sachs, J M Shin, C W Howden *Aliment. Pharmacol. Ther.* **23** (Suppl. 2) 2 (2006)
40. J M Shin, M Homerin, F Domagala, H Ficheux, G Sachs *Biochem. Pharmacol.* **71** 837 (2006)
41. J P Galmiche, S B Des Varannes, P Ducrotte, S Sacher-Huvelin, F Vavasseur, A Taccoen, P Fiorentini, M Homerin *Aliment. Pharmacol. Ther.* **19** 655 (2004)
42. R H Hunt, D Armstrong, C James, S K Chowdhury, Y Yuan, P Fiorentini, A Taccoen, P Cohen *Am. J. Gastroenterol.* **100** 1949 (2005)
43. J P Galmiche, S Sacher-Huvelin, S B Des Varannes, F Vavasseur, A Taccoen, P Fiorentini, M Homerin *Aliment. Pharmacol. Ther.* **21** 575 (2005)
44. F Domagala, H Ficheux, G Houin, J Barre *Arzneimittelforschung* **56** 33 (2006)
45. Y Yuan, Y Chen, R H Hunt *Gastroenterology* **134** (Suppl. 1) A176 (2008)
46. L Wang, L Zhou, S Lin, H Hu, J Xia *J. Clin. Gastroenterol.* **45** 322 (2011)
47. L Wang, L Zhou, H Hu, S Lin, J Xia *Curr. Med. Res. Opin.* **28** 101 (2012)
48. R H Hunt, D Armstrong, M Yaghoobi, C James, Y Chen, J Leonard, J M Shin, E Lee, D Tang-Liu, G Sachs *Aliment. Pharmacol. Ther.* **28** 187 (2008)
49. J L Wallace, M J Miller *Gastroenterology* **119** 512 (2000)
50. J K Saha, T Wang, R Stewart, M Trocha, M Shumway, D Garvey, L G Letts, M M Wolfe, S W Tam *Gastroenterology* **120** (Suppl. 1) A144 (2001)
51. G Sorba, U Galli, C Cena, R Fruttero, A Gasco, G Morini, M Adami, G Coruzzi, M I Brenciaglia, F Dubini *ChemBioChem* **4** 899 (2003)
52. K Andersson, E Carlsson *Pharmacol. Ther.* **108** 294 (2005)
53. M E Parsons, D J Keeling *Expert. Opin. Invest. Drugs* **14** 411 (2005)
54. K Gedda, C Briving, K Svensson, I Maxvall, K Andersson *Biochem. Pharmacol.* **73** 198 (2007)
55. H Mori, H Tonai-Kachi, Y Ochi, Y Taniguchi, H Ohshiro, N Takahashi, T Aihara, A Hirao, T Kato, M Sakakibara, Y Kurebayashi *J. Pharmacol. Exp. Ther.* **328** 671 (2009)
56. P J Zimmermann, C Brehm, W Buhr, A M Palmer, J Volz, W-A Simon *Bioorg. Med. Chem.* **16** 536 (2008)
57. M Yeo, M S Kwak, D K Kim, I S Chung, B S Moon, K S Song, K-B Hahm *J. Clin. Biochem. Nutr.* **38** 1 (2006)
58. W A Simon, M Herrmann, T Klein, J M Shin, R Huber, J Senn-Bilfinger, S Postius *J. Pharmacol. Exp. Ther.* **321** 866 (2007)
59. K Ito, K Kinoshita, A Tomizawa, F Inaba, Y Morikawa-Inomata, M Makino, K Tabata, N Shibakawa *J. Pharmacol. Exp. Ther.* **323** 308 (2007)
60. T Panchal, N Bailey, M Bamford, E Demont, R Elliott, I Farre-Gutierrez, N Garton, T Hayhow, G Hutley, A Naylor *Bioorg. Med. Chem. Lett.* **19** 6813 (2009)
61. Y A Yoon, D H Kim, B M Lee, T K Kim, M H Cha, J Y Sim, J G Kim *Bioorg. Med. Chem. Lett.* **20** 5237 (2010)
62. A M Palmer, V Chiesa, A Schmid, G Munch, B Grobbel, P J Zimmermann, C Brehm, W Buhr, W-A Simon, W Kromer, S Postius, J Volz, D J Hess *J. Med. Chem.* **53** 3645 (2010)

63. N Garton, N Bailey, M Bamford, E Demont, I Farre-Gutierrez, G Hutley, G Bravi, P Pickering *Bioorg. Med. Chem. Lett*. **20** 1049 (2010)
64. J J Kaminski, J A Bristol, C Puchalski, R G Lovey, A J Elliott, H Guzik, D M Solomon, D J Conn, M S Domalski, S-C Wong, E H Gold, J F Long, P J S Chiu, M Steinberg, A T McPhail *J. Med. Chem*. **28** 876 (1985)
65. J J Kaminski, J M Hilbert, B N Pramanik, D M Solomon, D J Conn, R K Rizvi, A J Elliott, H Guzik, R G Lovey, M S Domalski, S-C Wong, C Puchalski, E H Gold, J F Long, P J S Chiu, A T McPhail *J. Med. Chem*. **30** 2031 (1987)
66. J J Kaminski, C Puchalski, D M Solomon, R K Rizvi, D J Conn, A J Elliott, R G Lovey, H Guzik, P J S Chiu, J F Long, A T McPhail *J. Med. Chem*. **32** 1686 (1989)
67. A M Palmer, B Grobbel, C Jecke, C Brehm, P J Zimmermann, W Buhr, M P Feth, W-A Simon, W Kromer *J. Med. Chem*. **50** 6240 (2007)
68. A M Palmer, S Chrismann, G Muench, Ch Brehm, P J Zimmermann, W Buhr, J Senn-Bilfinger, M P Feth, W A Simon *Bioorg. Med. Chem*. **17** 368 (2009)
69. J Senn-Bilfinger, J R Ferguson, M A Holmes, K W Lumbard, R Huber, K Zech, R P Hummel, P J Zimmermann *Tetrahedron Lett*. **47** 3321 (2006)
70. A-L Berg, G Boettcher, K Andersson, E Carlsson, A-K Lindstroem, R Huby, H Haakansson, I Skaanberg-Wilhelmsson, H Hellmold *Toxicol. Pathol*. **36** 727 (2008)
71. N Bailey, M J Bamford, D Brissy, J Brookfield, E Demont, R Elliott, N Garton, I Farre-Gutierrez, T Hayhow, G Hutley, A Naylor, T A Panchal, H-X Seow, D Spalding, A K Takle *Bioorg. Med. Chem. Lett*. **19** 3602 (2009)
72. A M Palmer, G Muench, C Brehm, P J Zimmermann, W Buhr, M P Feth, W A Simon *Bioorg. Med. Chem*. **16** 1511 (2008)
73. K Ito, K Kinoshita, N Yamamura, A Tomizawa, F Inaba, Y Morikawa-Inomata, K Tabata, N Shibakawa *Biol. Pharm. Bull*. **32** 2010 (2009)
74. K S Yu, K S Bae, J H Shon, J Y Cho, S Y Yi, J Y Chung, H S Lim, I J Jang, S G Shin, K S Song, B S Moon *J. Clin. Pharmacol*. **44** 73 (2004)
75. Y A Yoon, C S Park, M H Cha, H Choi, J Y Sim, J G Kim *Bioorg. Med. Chem. Lett*. **20** 5735 (2010)
76. H Nishida, A Hasuoka, Y Arikawa, O Kurasawa, K Hirase, N Inatomi, Y Hori, F Sato, N Tarui, A Imanishi, M Kondo, T Takagi, M Kajino *Bioorg. Med. Chem*. **20** 3925 (2012)
77. A Yasuyoshi, N Haruyuki, K Osamu, H Atsushi, H Keizo, I Nobuhiro, H Yasunobu, M Jun, I Akio, K Mitsuyo, T Naoki, H Teruki, T Terufumi, T Toshiyuki, K Masahiro *J. Med. Chem*. **55** 4446 (2012)
78. Y Hori, A Imanishi, J Matsukawa, Y Tsukimi, H Nishida, Y Arikawa, K Hirase, M Kajino, N Inatomi *Pharmacol. Exp. Ther*. **335** 231 (2010)
79. J Matsukawa, Y Hori, H Nishida, V Kajino, N Inatomi *Biochem. Pharmacol*. **81** 1145 (2011)
80. Y Hori, J Matsukawa, T Takeuchi, H Nishida, M Kajino, N Inatomi *J. Pharm. Exp. Ther*. **337** 797 (2011)
81. M A Evseev, Yu M Kruglyanskii *Rus. Med. Zh*. **16** 523 (2008)
82. H Satoh, K Takeuchi *Curr. Med. Chem*. **19** 82 (2012)
83. Patent RF 2465271 (2006)