A molecule with a radius of curvature, less than that of the minor groove, has a much lower DNA affinity. In the highly curved molecules greater conformational changes are needed in the molecule to open the radius of curvature to that of the DNA minor groove. These large conformational changes have a higher energy and therefore lower the DNA affinity of the compound.

Low polynucleotide affinity was seen with the meta-substituted compounds (compare **12** with **13**, **1** with **31**, and **42** with **43**); this was most distinct with the AT homopolymer. This low DNA and homopolymer affinity of the meta-substituted compounds can also be rationalized by their shape. In this situation the meta compounds do not have low-energy conformers consistent with DNA minor-groove binding. Study of the conformers in the meta cases is complicated by rotational conformers of the aromatic rings, therefore more than one meta conformer must be considered. Analysis of the molecular models of **13** shows that there are three planar relatively low-energy conformations of the molecule. Molecular models of these three conformations are shown in Figure 5. The data in Table II show that none of the conformations have a radius of curvature close to that required for the minor groove of DNA. Conformer **A** in Figure 5 has the lowest molecular mechanics energy and also has a radius of curvature that is much too large for facile interaction with the minor groove. Conformer **B** (middle structure) has a radius of curvature close to ideal for interaction with the minor groove, but in this conformer the amidino groups are on opposite sides of the aromatic rings and only one of the amidino groups at a time can interact with the DNA. Conformer **C** in Figure 5 has both of the amidino groups on the same side of the benzene rings and is higher in energy than conformer **A** or **B**. Conformer **C** has a radius of curvature that is too small to allow full interaction with DNA. Table II contains two radius of curvature measurements for the two conformers of compound **23** containing a four methylene linking unit and meta-substituted amidine groups. Space-filling molecular mechanics models of these two conformers are shown in Figure 6. Neither of these conformers has the proper radius of curvature to be an effective minor-groove-binding compound.

In conclusion, our studies show that the strength of DNA or homopolymer polynucleotide minor-groove-binding, as described by a thermal denaturation assay, of a large series of pentamidine (**1**) analogues can be described by the conformation of the molecules. The radius of curvature of molecular mechanics models can act as a descriptor of the strength of DNA groove binding. This measurement can be used to predict the minor-groove-binding properties of hypothetical new anti-PCP compounds. This effect is seen as a relative strengthening and weakening of the DNA-binding interaction. Although all of the compounds in this series did bind to DNA and homopolymers, all of the compounds also show some activity, within the limitations of toxicity, in the in vivo *P. carinii* assay.[3]

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2-[(2-Pyridylmethyl)sulfinyl]-1*H*-thieno[3,4-*d*]imidazoles. A Novel Class of Gastric H^+/K^+-ATPase Inhibitors

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2-[(2-Pyridylmethyl)sulfinyl]thienoimidazoles were synthesized and investigated as potential inhibitors of gastric H^+/K^+-ATPase. The [3,4-*d*] isomers of the two possible thienoimidazole series were found to be potent inhibitors of gastric acid secretion in vitro and in vivo. Structure–activity relationships indicate that especially lipophilic alkoxy, benzyloxy, and phenoxy substituents with additional electron-demanding properties in the 4-position of the pyridine moiety combined with an unsubstituted thieno[3,4-*d*]imidazole lead to highly active compounds with a favorable chemical stability. Various substitution patterns in the thieno[3,4-*d*]imidazole moiety result in lower biological activity. The heptafluorobutyloxy derivative saviprazole (HOE 731, **5d**) was selected for further development and is currently undergoing clinical evaluation. Comprehensive pharmacological studies indicate a pharmacodynamic profile different to omeprazole, the first H^+/K^+-ATPase blocker introduced on the market.

Introduction

Inhibition of gastric acid secretion has been proven to be a powerful therapeutic principle in the treatment of gastric and duodenal ulcer disease.[1] Gastric acid secretion is regulated by interaction of basolateral parietal cell receptors with their physiological stimulants gastrin, acetylcholine, and histamine.[2] Anticholinergics and especially H_2-receptor antagonists have therefore become antisecretory agents of major importance.

2-[(2-Pyridylmethyl)sulfinyl]benzimidazoles like omeprazole represent a new class of effective gastric acid secretion inhibitors.[3] Their antisecretory activity has been ascribed to a highly specific inhibitory action on the gastric proton pump, the H^+/K^+-ATPase,[4] which is responsible for the transport of gastric acid into the lumen of the

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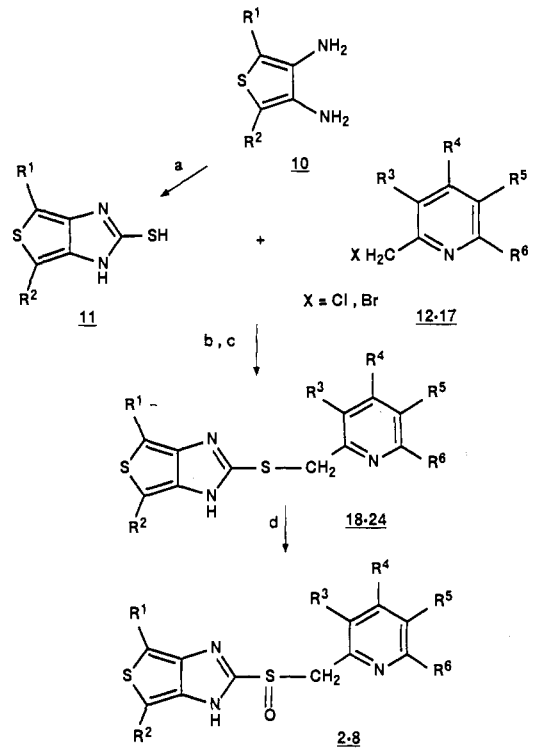
stomach. Acid secretion is therefore blocked at the final step of its production, independent of the different kinds of its stimulation.[5]

Omeprazole's superiority to the H_2-receptor antagonists in the treatment of duodenal ulcer and reflux oesophagitis is evident,[6] although its safety is still controversial.[7] In view of the side effects of long-lasting inhibition of acid secretion, e.g., hypergastrinemia and enterochromaffin-like (ECL) cell hyperplasia,[8] we focused our efforts on H^+/K^+-ATPase inhibitors with an omeprazole-like mode of action, but with different pharmacodynamic properties compared to omeprazole.

Due to omeprazole's highly specific mode of action,[9] the possibilities for structural modifications are very restricted. In this context Brandström et al. claimed the three structural elements of omeprazole, the substituted pyridine ring, the substituted benzimidazole moiety, and the methylsulfinyl chain connecting these two, as being essential for the biological effect.[10] Indeed, up to now, all known omeprazole-like, potent H^+/K^+-ATPase blockers are benzimidazoles.[11] The narrow range for structural variations of H^+/K^+-ATPase blockers also become evident for

Scheme I[a]



[a] (a) 1,1'-thiocarbonyldiimidazole or CS_2, AcOH, MeI; (b) method A: (1) EtOH, reflux, (2) NEt_3 in MeOH, 25 °C; (c) method B: $NaOCH_3$, MeOH, 20 to 65 °C; (d) *m*-CPBA, CH_2Cl_2, aqueous $NaHCO_3$, 5 to 25 °C.

the 2-[(2-aminobenzyl)sulfinyl]benzimidazoles, a new class of acid secretion inhibitors, which have also been investigated independently by four other research teams.[12,13]

In addition to our first approach to modify the weakly basic pyridine moiety leading to these 2-[(2-aminobenzyl)sulfinyl]benzimidazoles,[12] we were interested in evaluating 5-membered heterocycles with an annellated imidazole ring (1). In the local anesthetics prilocaine and articaine, the change from a benzene to a substituted thiophene ring resulted in other pharmacodynamic properties, leading to a different therapeutic quality.[14] In analogy we focused our efforts on the two isomeric thienoimidazole series, the [3,4-*d*] and the [2,3-*d*] compounds **2–8** and **9**, respectively. Some compounds of the latter series have recently also been disclosed in a patent application by others.[15]

In order to evaluate their pharmacological activity, the thienoimidazoles were examined in a wide variety of pharmacological and biochemical assays.

In vitro inhibitory effects were determined in gastric vesicles containing H^+/K^+-ATPase[16] and by [^{14}C]amino-

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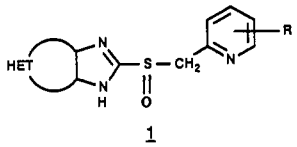

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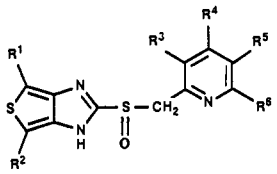
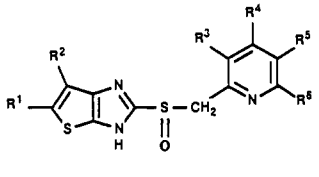


2-8



9

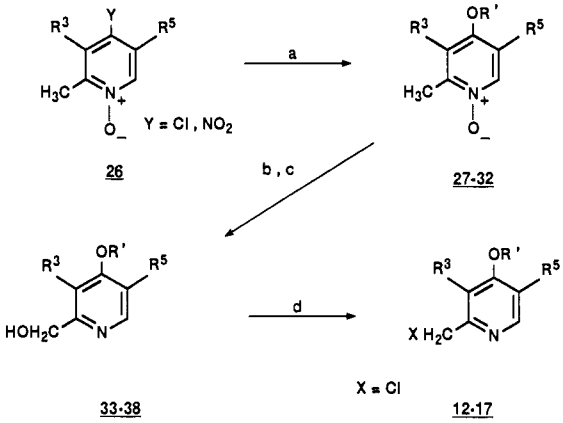
pyrine accumulation in rabbit gastric glands.[17] In vivo the compounds were studied in pylorus-ligated rats,[18] in stomach-lumen-perfused rats[19] and in Heidenhain-pouch dogs.[20]

Chemistry

The new compounds **2–8** were synthesized as outlined in Scheme I. 2-Mercaptothieno[3,4-*d*]imidazole (**11a**) (R^1, R^2 = H)[21] was readily obtained by reduction of 2,5-dibromo-2,4-dinitrothiophene followed by condensation of the resulting diamine **10a** with thiocarbonyldiimidazole. In analogy the 2,5-dimethyl derivative **11b** (R^1, R^2 = CH_3) was synthesized from 2,5-dimethyl-3,4-dinitrothiophene.[22] To further study the effect of 2-substituents in the thieno[3,4-*d*]imidazole moiety, phenyl,[23] acetyl,[24] and alkoxycarbonyl[25] derivatives were investigated.

Alkylation of **11** with the appropriately substituted 2-picolyl halides **12–17** under neutral or alkaline conditions yielded the desired sulfides **18–24** by method A or B (Table I). When neutral conditions were used, the thioethers precipitated as dihydrohalides, which were subsequently treated with triethylamine in methanol to yield the free bases. Because of the high sensitivity of the sulfoxides **2–8** (Table II) toward acid, oxidations were performed with *m*-chloroperbenzoic acid in a mixture of dichloromethane and aqueous $NaHCO_3$ solution. Small amounts of thioethers and the corresponding sulfones were removed by crystallization and/or chromatography. Compound **9a** was obtained as previously described[15] starting from 2,3-diaminothiophene. Substituted 2-picolyl halides **12–17** were prepared either according to the literature or in analogy to known methods.

Scheme II[a]



[a] (a) R'OH, base, DMF or *N*,*N*-dimethylacetamide, 20 to 150 °C; (b) Ac_2O, AcOH, 120 °C; (c) 2 N NaOH, MeOH, 25 °C; (d) $SOCl_2$, CH_2Cl_2, 25 °C.

The synthesis of 4-alkoxy-substituted pyridine derivatives is summarized in Scheme II. Nucleophilic substitution reactions of 4-nitro(or 4-chloro)-2-picoline *N*-oxides **26** with the alcohols R'OH under basic conditions[26] were followed by rearrangement of **27–32** to the acetates,[26,27] subsequent saponification, isolation, and purification of the alcohols **33–38**, and conversion to the 2-picolyl halides **12–17**. Alternatively **12–17** could also be obtained by reduction of *N*-oxides **27–32** and subsequent chlorination of the corresponding 2-picolines with trichloroisocyanuric acid[28] or bromination with *N*-bromosuccinimide. Starting from the known 3-(or 5-)halogen-substituted 2-picolines,[29–31] compounds of series **3** and **4** were obtained. 3-Methoxy- and 3-(1,1,1-trifluoroethoxy)-substituted derivatives (series **7**) were synthesized starting with the alkylation of maltol.[32] Difluoromethoxy and 1,1,2,2-tetra-

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fluoroethoxy derivatives **7l–n** were prepared by addition of difluorocarbene (from $CHClF_2$) or tetrafluoroethylene to the appropriate hydroxy-2-picolines.[33]

Results and Discussion

In general, the compounds were first investigated in rabbit gastric glands and in pylorus-ligated rats. If gastric acid secretion in these models was suppressed significantly, then the compounds were further studied in stomach-lumen-perfused rats and in the enzyme test. If an inhibition of acid secretion could be confirmed in these assays, then the compounds were evaluated in Heidenhain-pouch dogs (Table III).

Sometimes [^{14}C]aminopyrine accumulation in rabbit gastric glands was observed indicating strong effects, although an inhibitory action in the in vivo models could not be verified. As previously shown for 2-[[2-(*N*-ethylamino)benzyl]sulfinyl]-5,6-dimethoxybenzimidazole, S 3337, there is no strict correlation between the effects in rats, particularly in pylorus-ligated rats, and in dogs.[34] Obviously, results of only one or two different test systems often are insufficient to characterize a H^+/K^+-ATPase blocking agent. Hence, a complete set of assays should be performed to define a H^+/K^+-ATPase blocker. Inhibitory activity data from stomach-lumen-perfused rats and especially from Heidenhain-pouch dogs are of particular importance. It is well accepted that irreversible inhibitors of the gastric H^+/K^+-ATPase are acid-labile prodrugs which accumulate as weak bases in the secretory cannaliculus of the parietal cell and are transformed to the "active principle" by protic activation.[9] Therefore, H^+/K^+-ATPase blockers have to be highly reactive at low pH, although the prerequisite for their selective biological activity is a relatively high chemical stability under physiological conditions around neutral pH. Chemical handling also demands a certain degree of chemical stability. One of the major problems is that the biological activity of the compounds investigated frequently correlates with their chemical lability. Many compounds showing excellent inhibitory data (e.g. **2i** and **7a**) are often too unstable to be of further interest. Obviously, chemical stability is an important additional criterion for the evaluation of a potential H^+/K^+-ATPase inhibitor.[35,36]

Therefore, compounds **2–9** have been classified routinely according to their relative chemical stability (Table II), determined in phosphate-buffered acetonitrile solution ($\sim 10^{-3}$ M, pH 7.4) by TLC analysis, in comparison to the parent system **2a**. Compounds as stable or more stable than **2a** could be manipulated in a routine way. Chemical handling of the sulfoxides **2–8** became increasingly difficult, the more these were less stable than **2a**.

In analogy to the specific activation process of omeprazole, it is obvious that both biological activity and chemical stability are largely influenced by substituents at the thienoimidazole and the pyridine moieties.

Structure–Activity Relationships

The [3,4-*d*] isomers **2–8** of the two possible 2-(2-picolylsulfinyl)thienoimidazole series showed strong inhibition of gastric acid secretion both in vitro and in vivo, whereas the [2,3-*d*] derivatives **9** were found to be less effective in all biological assays (Table III), probably due to their pronounced chemical stability.

The 4-methoxypyridine derivatives **2i** and **9a**[15] directly allow comparison of the isomeric thienoimidazole series. Compound **2i** has been characterized as an effective H^+/K^+-ATPase blocker, whereas the corresponding [2,3-*d*] isomer **9a**[15] and the dimethoxycarbonyl derivatives **9b** and **9c** were only weakly inhibitory.

Pyridine Substitution. Much effort has been spent to synthesize compounds **2–8** with unsubstituted thieno-[3,4-*d*]imidazole and substituted pyridine moieties.

In the biologically active methyl series **2b–f** only the 6-substituted compound **2f** showed little inhibitory effects. Probably the formation of the "active principle" is not possible due to steric hindrance. *m*-Halogen- and *m*-methoxy-substituted compounds (**3a**, **3b**, **4a** and **2g**, **2h**, respectively) showed lower inhibitory activity both in vitro in the gastric gland preparation and in vivo in the rat models. However, the introduction of a 4-alkoxy substituent (**2i** and **2l**) results in an increased biological activity, but in parallel the chemical stability declines. A 4-alkoxy substituent seems to favor the formation of the active metabolite by enhancing the nucleophilicity of the pyridine nitrogen, which might be expressed in terms of its basicity to be quantified more easily.

The main problem in measuring pK_a values of these compounds is that concentrations of protonated acid-labile species have to be determined. In analogy to the method described by the Hässle scientists,[37] pK_a values could be obtained by potentiometric pH measurements in aqueous HCl–DMSO solutions and extrapolation to zero time (Table IV). Compared to the parent compound **2a** (pK_a = 3.05) the increased basicity of **2i** (pK_a = 4.16) supports the direct relationship between basicity and biological activity as reported for the benzimidazole series.[36]

If the electron-donating effect of the 4-alkoxy group is modified by an additional inductive electron-demanding substituent (e.g., alkoxy, fluoroalkoxy, or halogen) in the 3- or 5-position, highly active compounds with pronounced chemical stability are obtained. The decrease in pK_a values of about 0.5 reflects the enhanced chemical stability of **3c**, **3m**, and **4b** as compared to **2i** and **2l**. The stabilizing effect of meta-positioned halogen atoms was also reported previously for the (4-aminopicolyl)benzimidazole series.[35] Of the possible 3-(5-)halogen derivatives, the 3-isomers **3c** and **3m** are the most potent. However, their bioavailability after id administration in pylorus-ligated rats[38] and Heidenhain-pouch dogs is limited (Table III). A similar behavior has also been shown for the analogous 3-tetrafluoroethoxy compound **7n**. An additional methyl group in the remaining meta position (e.g., **3h**, **4c**, **4f**, and **4g**) decreases inhibitory activity, probably due to steric interaction, preventing conjugation between the 4-alkoxy

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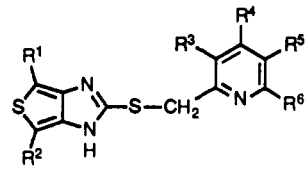
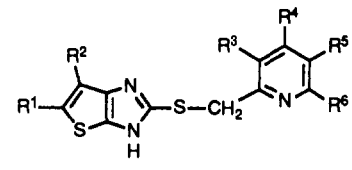
(38) Inhibition values after ip administration, Table III; data from id administration not presented in detail.

Table I. Physical Properties of 2-[(2-Pyridylmethyl)thio]-1*H*-thienoimidazoles 18–25



18–24



25

compd[a]	R^1	R^2	R^3	R^4	R^5	method	yield, %[b]	mp, °C[c] (solv)[d]	formula[e]	anal.[f]
18a	H	H	H	H	H	A	35	126–129 (Å)	$C_{11}H_9N_3S_2$	CHNS
18b	H	H	CH_3	H	H	A	82	320 (B)	$C_{12}H_{13}Cl_2N_3S_2$[g]	CHClNS
18c	H	H	H	CH_3	H	A	75	214 (C)	$C_{12}H_{13}Cl_2N_3S_2$[g]	CHClNS
18d	H	H	H	H	CH_3	A	37	218 (C)	$C_{12}H_{13}Br_2N_3S_2$[h]	CHBrN
18e	H	H	CH_3	H	CH_3	A	64	207 (D)	$C_{13}H_{15}Cl_2N_3S_2$[g]	CHClNS
18f[i]	H	H	H	H	H	A	41	230 (D)	$C_{12}H_{13}Cl_2N_3S_2$[g]	CHNS
18g	H	H	OCH_3	H	H	B	47	180 (E)	$C_{12}H_{11}N_3OS_2$	CHN
18h	H	H	H	H	OCH_3	A	54	112–114 (F)	$C_{12}H_{11}N_3OS_2$	CHNS
18i	H	H	H	OCH_3	H	A	42	172–175 (C)	$C_{12}H_{11}N_3OS_2$	CHNS
18j	H	H	CH_3	OCH_3	H	A	59	174–177 (G)	$C_{13}H_{13}N_3OS_2$	CHNS
18k	H	H	CH_3	OCH_3	CH_3	A	60	108–112 (G)	$C_{14}H_{15}N_3OS_2 \cdot H_2O$	CHNS
18l	H	H	H	OC_2H_5	H	A	47	206 (B)	$C_{13}H_{15}Cl_2N_3OS_2$[g]	CHClNS
18m	H	H	H	O-*n*-C_4H_9	H	B	75	92 (E)	$C_{15}H_{17}N_3OS_2$	CHNS
19a	H	H	F	H	H	B	27	resin (E)	$C_{11}H_8FN_3S_2$	CHN
19b	H	H	Cl	H	H	A	24	141 (E)	$C_{11}H_8ClN_3S_2$	CHN
19c	H	H	Cl	OCH_3	H	A	82	156–157 (F)	$C_{12}H_{10}ClN_3OS_2$	CHClN
19d	H	H	Cl	OC_2H_5	H	A	27	90 (F)	$C_{13}H_{12}ClN_3OS_2$	CHN
19e	H	H	Cl	O-*i*-C_3H_7	H	A	87	126–128 (A)	$C_{14}H_{14}ClN_3OS_2$	CHNS
19f	H	H	Cl	O-*n*-C_3H_7	H	A	85	117–119 (A)	$C_{14}H_{14}ClN_3OS_2$	CHClN
19g	H	H	Cl	$O(CH_2)_2OCH_3$	H	A	55	108–110 (F)	$C_{14}H_{14}ClN_3O_2S_2$	CHNS
19h	H	H	Cl	OCH_3	CH_3	A	92	149 (F)	$C_{13}H_{12}ClN_3OS_2$	CHClN
19i	H	H	Cl	$OCH_2C_6H_5$	H	A	36	159–160 (F)	$C_{18}H_{14}ClN_3OS_2$	CHN
19j	H	H	Cl	OC_6H_5	H	A	75	168 (B)	$C_{17}H_{12}ClN_3OS_2$	CHN
19k	H	H	Cl	OCH_2CF_3	H	A	47	190 (F)	$C_{13}H_9ClF_3N_3OS_2$	CHFN
19l	H	H	Cl	$OCH_2CF_2CF_3$	H	A	50	114–116 (A)	$C_{14}H_9ClF_5N_3OS_2$	CHNS
19m	H	H	Br	OCH_3	H	A	62	168 (F)	$C_{12}H_{10}BrN_3OS_2$	CHBrN
20a	H	H	H	H	Cl	A	46	160 (F)	$C_{11}H_8ClN_3S_2$	CHN
20b	H	H	H	OCH_3	Cl	A	21	135–137 (A)	$C_{12}H_{10}ClN_3OS_2$	CHNS
20c	H	H	CH_3	OCH_3	Cl	A	52	160–162 (F)	$C_{13}H_{12}ClN_3OS_2$	CHN
20d	H	H	H	$OCH_2CF_2CF_3$	Cl	A	43	119–120 (F)	$C_{14}H_9ClF_5N_3OS_2$	CHFN
20e	H	H	H	OCH_3	Br	A	72	165 (F)	$C_{12}H_{10}BrN_3OS_2$	CHNS
20f	H	H	CH_3	OCH_3	Br	A	58	330 (B)	$C_{13}H_{12}BrN_3OS_2$	CH
20g	H	H	CH_3	OCH_3	F	A	62	330 (B)	$C_{13}H_{12}FN_3OS_2$	CH
21a	H	H	H	OCH_2CF_3	H	B	50	160 (A)	$C_{13}H_{10}F_3N_3OS_2$	CHN
21b	H	H	H	$OCH_2CF_2CF_2H$	H	B	57	120 (E)	$C_{14}H_{11}F_4N_3OS_2$	CHN
21c	H	H	H	$OCH_2CF_2CF_3$	H	B	53	121 (A)	$C_{14}H_{10}F_5N_3OS_2$	CHN
21d	H	H	H	$OCH_2CF_2CF_2CF_3$	H	B	65	117 (H)	$C_{15}H_{10}F_7N_3OS_2$	CHNS
21e	H	H	H	$OCH_2(CF_2)_3CF_2H$	H	B	35	105 (H)	$C_{16}H_{11}F_8N_3OS_2$	CHN
21f	H	H	H	$OCH(CF_3)_2$	H	B	35	127–129 (F)	$C_{14}H_9F_6N_3OS_2$	CHNS
21g	H	H	CH_3	OCH_2CF_3	H	B	55	145 (H)	$C_{14}H_{12}F_3N_3OS_2$	CHN
21h	H	H	H	OCH_2CF_3	CH_3	B	93	169 (A)	$C_{14}H_{12}F_3N_3OS_2$	CHN
21i	H	H	CH_3	$OCH_2CF_2CF_3$	H	B	58	135 (H)	$C_{15}H_{12}F_5N_3OS_2$	CHN
21j	H	H	CH_3	$OCH_2(CF_2)_2CF_3$	H	B	24	140 (H)	$C_{16}H_{12}F_7N_3OS_2$	CHN
22a	H	H	H	$C_6H_5CH_2O$	H	B	70	181 (E)	$C_{18}H_{15}N_3OS_2$	CHN
22b	H	H	H	4-$FC_6H_4CH_2O$	H	B	76	141 (F)	$C_{18}H_{14}FN_3OS_2$	CHNS
22c	H	H	H	2,4-$F_2C_6H_3CH_2O$	H	B	28	100–161 (F)	$C_{18}H_{13}F_2N_3OS_2$	CHN
22d	H	H	H	3,5-$F_2C_6H_3CH_2O$	H	B	48	159–161 (F)	$C_{18}H_{13}F_2N_3OS_2$	CHN
22e	H	H	H	4-$ClC_6H_4CH_2O$	H	B	60	156–158 (F)	$C_{18}H_{14}ClN_3OS_2$	CHN
22f	H	H	H	3,5-$Cl_2C_6H_3CH_2O$	H	B	54	178–179 (F)	$C_{18}H_{13}Cl_2N_3OS_2$	CHClN
22g	H	H	H	4-$CF_3C_6H_4CH_2O$	H	B	59	143 (F)	$C_{19}H_{14}F_3N_3OS_2$	CHN
22h	H	H	H	3,5-$(CF_3)_2C_6H_3CH_2O$	H	B	55	187 (A)	$C_{20}H_{13}F_6N_3OS_2$	CHNS
22i	H	H	H	3-$CF_3C_6H_4O$	H	B	25	154–155 (F)	$C_{18}H_{12}F_3N_3OS_2$	CHN
22j	H	H	H	4-FC_6H_4O	H	B	73	159–161 (E)	$C_{17}H_{12}FN_3OS_2$	CHNS
22k	H	H	H	2,4-$F_2C_6H_3O$	H	B	73	129–131 (E)	$C_{17}H_{11}F_2N_3OS_2$	CHN
22l	H	H	H	4-ClC_6H_4O	H	B	88	151 (F)	$C_{17}H_{12}ClN_3OS_2$	CHN
22m	H	H	H	3,4-$Cl_2C_6H_3O$	H	B	83	161–163 (E)	$C_{17}H_{11}Cl_2N_3OS_2$	CHClN
23a	H	H	OCH_3	OCH_3	H	B	27	142 (F)	$C_{13}H_{13}N_3O_2S_2$	CHN
23b	H	H	OCH_3	OCH_2CF_3	H	B	54	147–148 (F)	$C_{14}H_{12}F_3N_3O_2S_2$	CHN
23c	H	H	OCH_3	$OCH_2CF_2CF_2H$	H	B	77	127–129 (F)	$C_{15}H_{13}F_4N_3O_2S_2$	CHFN
23d	H	H	OCH_3	$OCH_2CF_2CF_3$	H	B	65	139 (H)	$C_{15}H_{12}F_5N_3O_2S_2$	CHN
23e	H	H	OCH_3	$OCH_2(CF_2)_2CF_3$	H	B	50	133–135 (F)	$C_{16}H_{12}F_7N_3O_2S_2$	CHFN
23f	H	H	OCH_3	$OCH_2(CF_2)_3CF_2H$	H	B	73	110 (H)	$C_{17}H_{13}F_8N_3O_2S_2$	CHN
23g	H	H	OCH_3	4-$CF_3C_6H_4CH_2O$	H	B	51	138–139 (F)	$C_{20}H_{16}F_3N_3O_2S_2$	CHNS
23h	H	H	OCH_3	3,5-$(CF_3)_2C_6H_3CH_2O$	H	B	77	135–137 (F)	$C_{21}H_{15}F_6N_3O_2S_2$	CHN
23i	H	H	OCH_3	4-$FC_6H_4CH_2O$	H	B	55	147–149 (F)	$C_{19}H_{18}FN_3O_2S_2$	CHNS
23j	H	H	OCH_2CF_3	OCH_2CF_3	H	B	41	145 (K)	$C_{15}H_{11}F_6N_3O_2S_2$	CHN
23k	H	H	OCH_2CF_3	H	H	B	50	135 (H)	$C_{13}H_{10}F_3N_3OS_2$	CHN
23l	H	H	$OCHF_2$	H	H	B	32	103 (H)	$C_{12}H_9F_2N_3OS_2$	CHN
23m	H	H	H	$OCHF_2$	H	B	26	resin (E)	$C_{12}H_9F_2N_3OS_2$	CHN
23n	H	H	OCF_2CF_2H	OCH_3	H	B	86	resin (E)	$C_{14}H_{11}F_4N_3O_2S_2$	CHN
24a	CH_3	CH_3	H	H	H	A	52	330 (C)	$C_{13}H_{15}Cl_2N_3S_2$[g]	CHClNS

Table I (Continued)

compd[a]	R^1	R^2	R^3	R^4	R^5	method	yield, %[b]	mp, °C[c] (solv)[d]	formula[e]	anal.[f]
24b	CH_3	CH_3	H	H	CH_3	A	77	250–255 (B)	$C_{14}H_{17}Cl_2N_3S_2$[g]	CHClNS
24c	CH_3	CH_3	H	OCH_3	H	A	70	217–222 (C)	$C_{14}H_{17}Cl_2N_3OS_2$[g]	CHN
24d	CH_3	CH_3	Cl	O-*i*-C_3H_7	H	A	82	190–196 (E)	$C_{16}H_{20}Cl_3N_3OS_2$[g]	CHNS
24e	CH_3	CH_3	H	OCH_2CF_3	H	A	74	246–250 (B)	$C_{15}H_{16}Cl_2F_3N_3OS_2$[g]	CHN
24f	CH_3	CH_3	H	$OCH_2CF_2CF_3$	H	A	77	330 (C)	$C_{16}H_{16}Cl_2F_5N_3OS_2$[g]	CHN
24g	CH_3	CH_3	H	$OCH_2(CF_2)_2CF_3$	H	A	55	215–220 (D)	$C_{17}H_{16}Cl_2F_7N_3OS_2$[g]	CHN
24h	$COCH_3$	H	H	H	CH_3	A	30	288 (I)	$C_{14}H_{15}Cl_2N_3OS_2$[g]	CHN
24i	$COCH_3$	H	H	OCH_2CF_3	H	A	33	169–175 (A)	$C_{15}H_{12}F_3N_3O_2S_2$	CHNS
24j	CO_2CH_3	H	H	OCH_3	H	B	39	156–160 (E)	$C_{14}H_{13}N_3O_3S_2$	CHNS
24k	C_6H_5	H	H	H	H	B	59	153–157 (I)	$C_{17}H_{13}N_3S_2$	CHN
24l	C_6H_5	H	H	OCH_3	H	A	56	182–185 (J)	$C_{18}H_{15}N_3OS_2$	CHN
24m	C_6H_5	H	CH_3	OCH_3	CH_3	A	49	192–195 (J)	$C_{20}H_{19}N_3OS_2$	CHN
24n	4-$CH_3OC_6H_4$	H	H	OCH_3	H	B	71	170–173 (K)	$C_{19}H_{17}N_3O_2S_2$	CHN
24o	4-$CH_3OC_6H_4$	H	CH_3	OCH_3	CH_3	A	25	151–154 (E)	$C_{21}H_{21}N_3O_2S_2$	CHNS
25a	H	H	H	OCH_3	H	B	*j*	*j*	$C_{12}H_{11}N_3OS_2$	*j*
25b	CO_2CH_3	CO_2CH_3	H	H	H	B	68	115–117 (I)	$C_{15}H_{13}N_3O_4S_2$	CHN
25c	CO_2CH_3	CO_2CH_3	H	OCH_3	H	B	65	156–159 (I)	$C_{16}H_{15}N_3O_5S_2$	CHN

[a] R^6 = H in all compounds except **18f**. [b] See Experimental Section. Compounds were prepared by methods A and B. [c] All compounds decompose on mp determination. [d] Recrystallization solvent: A = diisopropyl ether, B = acetone, C = ethanol, D = acetone/ethanol, E = ethyl acetate, F = diethyl ether, G = water, H = ethyl acetate/cyclohexane, I = 2-propanol, J = acetonitrile, K = dichloromethane. [e] Free bases, unless otherwise indicated. [f] Elemental analyses were within ±0.4% of the calculated values. [g] As dihydrochloride. [h] As dihydrobromide. [i] $R^6 = CH_3$. [j] See ref 15.

substituent and the pyridine ring.

4-Alkoxy, 4-phenoxy, and 4-benzyloxy groups, which combine lipophilicity and electron-demanding properties, result in compounds (series **5** and **6**) with strong inhibitory activity. In the 4-fluoroalkoxy series **5**, the (heptafluorobutyl)oxy compound **5d** emerges as the most interesting compound, showing strong inhibitory effects in all biological assays used and a favorable chemical stability in buffered solution. Introducing the hexafluoroisopropoxy group (**5f**) surprisingly reduces biological activity.

All halogen- and trifluoromethyl-substituted benzyloxy derivatives **6b–h** are strong inhibitors and show a good correlation of in vivo data and in vitro inhibitory effects in rabbit gastric glands. Compounds **6d** and **6g** are the most potent compounds in this series. However, chemical stability data favor the species with the strongest electron-withdrawing 4-substituent (**6h**). In the phenoxy series the 4-fluoro and 4-chloro derivatives **6j** and **6l**, with an omeprazole-like inhibitory activity, are most interesting.

The 3,4-dimethoxy compound **7a**, like **2i**, is a strongly active inhibitor, but it suffers from its limited chemical stability. In analogy to the 4-fluoroalkoxy compounds **5**, replacement of the 4-methoxy group by a 4-fluoroalkoxy group increases chemical stability, while strong biological activity is maintained.[39] Compounds **7b** and **7d** appear to be the most interesting compounds in this series, whereas the limited availability of **7c** after id administration in the Heidenhain-pouch dog is prohibitory. As in the series **6**, the aromatic analogues **7g–i** are highly inhibitory. Surprisingly, the combination of a 4-fluoroalkoxy group with a 3- or 5-positioned halogen atom (**3k**, **3l**, or **4d**) or an additional fluoroalkoxy group (**7j**) results in compounds showing weaker inhibitory effects on gastric acid secretion. As in the case of **5f**, it might be assumed that the nucleophilicity of the pyridine moiety is too moderate to generate the active intermediates.

Thienoimidazole Substitution. In most cases in the thieno[3,4-*d*]imidazole series, dimethyl substitution resulted in biologically less active compounds (e.g., **2d** vs **8b** and **5d** vs **8g**). Compared with the parent compound **2a**, phenyl-, methoxyphenyl-, acetyl-, and alkoxycarbonyl-substituted compounds (**8h–o**) showed decreased inhibitory activity (Table III).

(39) See the related benzimidazole compounds: (a) Takeda, European Patent Application EP 0 208 452, 1987. (b) Byk-Gulden Lomberg Chemische Fabrik GmbH EP 0 166 287, 1986.

Pharmacodynamic Behavior

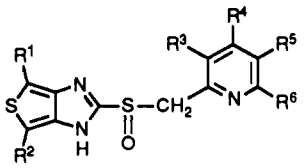
Seven compounds have been selected for more detailed pharmacological studies. In addition to the parent compound **2a**, the 5-methylpyridine derivative **2d** and the chloro-substituted species **3c** and **4b**, the (heptafluorobutyl)oxy compound saviprazole (**5d**, HOE 731) and the 3-methoxypyridines **7b** and **7d** have been further characterized in the Heidenhain-pouch dog (Table V). ED_{50} values show that all compounds tested are equipotent to omeprazole after iv administration. Compounds **5d** and **7b** have also found to be equipotent after id application. For **4b** there is a tendency to be less effective, although large confidence limits prevent further interpretation. With the additional criterion of chemical stability in mind, we focused our interest on **5d** (saviprazole, HOE 731), **7b**, and **7d**.

There are close relationships between the thienoimidazoles and omeprazole concerning the site of action (H^+/K^+-ATPase) and antisecretory efficacy. However, there are significant pharmacodynamic differences in dogs and rats. The dose–response relationships for **5d**, **7b**, and **7d** differ from that of omeprazole at high doses, although they have similar ED_{50} values. A further increase of the 70–90% inhibitory dose did not cause a further increase in inhibition for the thienoimidazoles contrary to that for omeprazole.

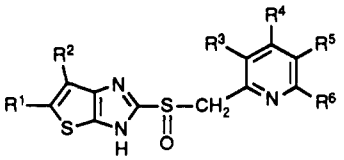
When the inhibitory effects of saviprazole and omeprazole at 1 mg/kg iv were compared, they showed significant differences (Figure 1). Saviprazole caused an immediate complete inhibition of histamine-induced acid output like that of omeprazole. This complete inhibition, however, lasted only for about 30 min. Then acid output was partially reactivated to about a 90% inhibition level. In contrast, omeprazole caused a nearly complete inhibition over the whole observation period of 4.5 h.[40] This phenomenon is even more pronounced in the case of the 3-methoxypyridine derivatives **7b** and **7d**, leading to maximal inhibition levels of 70% and 80%, respectively (Figure 1).

(40) (a) Herling, A. W.; Bickel, M.; Lang, H.-J.; Scheunemann, K.-H.; Weidmann, K.; Nimmesgern, H. Substituted Thieno-[3,4-*d*]imidazoles – A New Class of H^+,K^+-ATPase Inhibitors. *Gastroenterology* **1989**, *96*, A206. (b) Herling, A. W.; Lang, H.-J.; Scheunemann, K.-H.; Weidmann, K.; Metzger, H. HOE 731, A Novel H^+/K^+-ATPase Inhibitor with a Different Inhibitory Profile Compared to Omeprazole. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989**, *339* (Suppl.), R73.

Table II. Physical Properties of 2-[(2-Pyridylmethyl)sulfinyl]-1*H*-thienoimidazoles 2-9[a]



2–8



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compd[b]	R^1	R^2	R^3	R^4	R^5	yield, %	mp, °C[c] (solv)[d]	chemical stability[e]	formula	anal.[f]
2a	H	H	H	H	H	63	148–149 (A)	0	$C_{11}H_9N_3OS_2$	CHNS
2b	H	H	CH_3	H	H	74	155 (A)	0	$C_{12}H_{11}N_3OS_2$	CHNS
2c	H	H	H	CH_3	H	47	138 (J)	0	$C_{12}H_{11}N_3OS_2$	CHNS
2d	H	H	H	H	CH_3	69	120–123 (A)	0	$C_{12}H_{11}N_3OS_2$	CHNS
2e	H	H	CH_3	H	CH_3	70	156 (A)	0	$C_{13}H_{13}N_3OS_2$	CHNS
2f[g]	H	H	H	H	H	63	125 (B)	0	$C_{12}H_{11}N_3OS_2$	CHNS
2g	H	H	OCH_3	H	H	68	85–90 (B)	++	$C_{12}H_{11}N_3O_2S_2$	CHNS
2h	H	H	H	H	OCH_3	80	152–154 (B)	++	$C_{12}H_{11}N_3O_2S_2$	CHNS
2i	H	H	H	OCH_3	H	50	142–144 (I)	-	$C_{12}H_{11}N_3O_2S_2$	CHNS
2j	H	H	CH_3	OCH_3	H	65	145 (I)	-	$C_{13}H_{13}N_3O_2S_2$	CHNS
2k	H	H	CH_3	OCH_3	CH_3	34	190 (I)	-	$C_{14}H_{15}N_3O_2S_2$	CHNS
2l	H	H	H	OC_2H_5	H	30	132–135 (C)	-	$C_{13}H_{13}N_3O_2S_2$	CHNS
2m	H	H	H	O-*n*-C_4H_9	H	48	128 (K)	-	$C_{15}H_{17}N_3O_2S_2$	CHNS
3a	H	H	F	H	H	39	145 (C)	++	$C_{11}H_8FN_3OS_2$	CHFNS
3b	H	H	Cl	H	H	82	145 (C)	++	$C_{11}H_8ClN_3OS_2$	CHClNS
3c	H	H	Cl	OCH_3	H	76	160 (B)	++	$C_{12}H_{10}ClN_3O_2S_2$	CHClNS
3d	H	H	Cl	OC_2H_5	H	57	160 (B)	++	$C_{13}H_{12}ClN_3O_2S_2$	CHClNS
3e	H	H	Cl	O-*i*-C_3H_7	H	93	140 (B)	++	$C_{14}H_{14}ClN_3O_2S_2$	CHNS
3f	H	H	Cl	O-*n*-C_3H_7	H	72	134 (F)	++	$C_{14}H_{14}ClN_3O_2S_2$	CHNS
3g	H	H	Cl	$O(CH_2)_2OCH_3$	H	47	124 (E)	++	$C_{14}H_{14}ClN_3O_3S_2$	CHNS
3h	H	H	Cl	OCH_3	CH_3	79	106 (B)	++	$C_{13}H_{12}ClN_3O_2S_2$	CHClNS
3i	H	H	Cl	$OCH_2C_6H_5$	H	80	139–149 (B)	++	$C_{18}H_{14}ClN_3O_2S_2$	CHNS
3j	H	H	Cl	OC_6H_5	H	51	144–147 (I)	++	$C_{17}H_{12}ClN_3O_2S_2$	CHClNS
3k	H	H	Cl	OCH_2CF_3	H	34	152 (B)	++	$C_{13}H_8ClF_3N_3O_2S_2$	CHNS
3l	H	H	Cl	$OCH_2CF_2CF_3$	H	87	141 (C)	++	$C_{14}H_9ClF_5N_3O_2S_2$	CHClFNS
3m	H	H	Br	OCH_3	H	80	160 (E)	++	$C_{12}H_{10}BrN_3O_2S_2$	CHBrN
4a	H	H	H	H	Cl	61	157 (B)	++	$C_{11}H_8ClN_3OS_2$	CHClNS
4b	H	H	H	OCH_3	Cl	74	159 (E)	++	$C_{12}H_{10}ClN_3O_2S_2$	CHNS
4c	H	H	CH_3	OCH_3	Cl	72	174 (G)	++	$C_{13}H_{12}ClN_3O_2S_2$	CHNS
4d	H	H	H	$OCH_2CF_2CF_3$	Cl	67	157–158 (C)	++	$C_{14}H_9ClF_5N_3O_2S_2$	CHClFNS
4e	H	H	H	OCH_3	Br	52	140 (H)	++	$C_{12}H_{10}BrN_3O_2S_2$	CHBrNS
4f	H	H	CH_3	OCH_3	Br	70	169 (G)	++	$C_{13}H_{12}BrN_3O_2S_2$	CHNS
4g	H	H	CH_3	OCH_3	F	61	145 (G)	++	$C_{13}H_{12}FN_3O_2S_2$	CHNS
5a	H	H	H	OCH_2CF_3	H	63	132–136 (E)	+	$C_{13}H_{10}F_3N_3O_2S_2$	CHNS
5b	H	H	H	$OCH_2CF_2CF_2H$	H	65	152 (E)	+	$C_{14}H_{11}F_4N_3O_2S_2$	CHNS
5c	H	H	H	$OCH_2CF_2CF_3$	H	81	148–152 (E)	+	$C_{14}H_{10}F_5N_3O_2S_2$	CHFNS
5d	H	H	H	$OCH_2CF_2CF_2CF_3$	H	76	140 (E)	++	$C_{15}H_{10}F_7N_3O_2S_2$	CHFNS
5e	H	H	H	$OCH_2(CF_2)_3CF_2H$	H	72	116–119 (J)	++	$C_{16}H_{11}F_8N_3O_2S_2$	CHFNS
5f	H	H	H	$OCH(CF_3)_2$	H	77	168–169 (B)	++	$C_{14}H_9F_6N_3O_2S_2$	CHNS
5g	H	H	CH_3	OCH_2CF_3	H	47	121 (E)	+	$C_{14}H_{12}F_3N_3O_2S_2$	CHNS
5h	H	H	H	OCH_2CF_3	CH_3	72	163 (E)	+	$C_{14}H_{12}F_3N_3O_2S_2$	CHN
5i	H	H	CH_3	$OCH_2CF_2CF_3$	H	47	145 (J)	+	$C_{15}H_{12}F_5N_3O_2S_2$	CHN
5j	H	H	CH_3	$OCH_2(CF_2)_2CF_3$	H	57	115 (J)	++	$C_{16}H_{12}F_7N_3O_2S_2$	CHN
6a	H	H	H	$C_6H_5CH_2O$	H	47	174 (E)	-	$C_{18}H_{15}N_3O_2S_2$	CHN
6b	H	H	H	4-$FC_6H_4CH_2O$	H	62	145 (C)	+	$C_{18}H_{15}N_3O_2S_2$	CHNS
6c	H	H	H	2,4-$F_2C_6H_3CH_2O$	H	39	117–118 (B)	+	$C_{18}H_{13}F_2N_3O_2S_2$	CHFNS
6d	H	H	H	3,5-$F_2C_6H_3CH_2O$	H	59	159–161 (B)	+	$C_{18}H_{13}F_2N_3O_2S_2$	CHFNS
6e	H	H	H	4-$ClC_6H_4CH_2O$	H	53	144–145 (B)	+	$C_{18}H_{14}ClN_3O_2S_2$	CHClNS
6f	H	H	H	3,5-$Cl_2C_6H_3CH_2O$	H	42	102–104	+	$C_{18}H_{13}Cl_2N_3O_2S_2$	CHClNS
6g	H	H	H	4-$CF_3C_6H_4CH_2O$	H	62	149 (E)	+	$C_{19}H_{14}F_3N_3O_2S_2$	CHFNS
6h	H	H	H	3,5-$(CF_3)_2C_6H_3CH_2O$	H	57	135–136 (C)	++	$C_{20}H_{13}F_6N_3O_2S_2$	CHFNS
6i	H	H	H	3-$CF_3C_6H_4O$	H	52	119–121 (L)	++	$C_{18}H_{12}F_3N_3O_2S_2$	CHFNS
6j	H	H	H	4-FC_6H_4O	H	80	146 (E)	++	$C_{17}H_{12}FN_3O_2S_2$	CHFNS
6k	H	H	H	2,4-$F_2C_6H_3O$	H	67	122–124 (B)	++	$C_{17}H_{11}F_2N_3O_2S_2$	CHFNS
6l	H	H	H	4-ClC_6H_4O	H	79	140–141 (E)	++	$C_{17}H_{12}ClN_3O_2S_2$	CHClNS
6m	H	H	H	3,4-$Cl_2C_6H_3O$	H	63	116 (F)	++	$C_{17}H_{11}Cl_2N_3O_2S_2$	CHClNS
7a	H	H	OCH_3	OCH_3	H	60	139–140 (B)	0	$C_{13}H_{13}N_3O_3S_2$	CHNS
7b	H	H	OCH_3	OCH_2CF_3	H	61	135–137 (B)	++	$C_{14}H_{12}F_3N_3O_3S_2$	CHNS
7c	H	H	OCH_3	$OCH_2CF_2CF_2H$	H	88	133–135 (C)	++	$C_{15}H_{13}F_4N_3O_3S_2$	CHFN
7d	H	H	OCH_3	$OCH_2CF_2CF_3$	H	69	137 (C)	++	$C_{15}H_{12}F_5N_3O_3S_2$	CHFNS
7e	H	H	OCH_3	$OCH_2(CF_2)_2CF_3$	H	67	113–115 (B)	++	$C_{16}H_{12}F_7N_3O_3S_2$	CHFNS
7f	H	H	OCH_3	$OCH_2(CF_2)_3CF_2H$	H	82	103 (B)	++	$C_{17}H_{13}F_8N_3O_3S_2$	CHFNS
7g	H	H	OCH_3	4-$CF_3C_6H_4CH_2O$	H	54	148–149 (B)	++	$C_{20}H_{16}F_3N_3O_3S_2$	CHFNS
7h	H	H	OCH_3	3,5-$(CF_3)_2C_6H_3CH_2O$	H	73	157–158 (B)	++	$C_{21}H_{15}F_6N_3O_3S_2$	CHFNS
7i	H	H	OCH_3	4-$FC_6H_4CH_2O$	H	61	119–121 (H)	+	$C_{18}H_{15}FN_3O_3S_2$	CHFNS
7j	H	H	OCH_2CF_3	OCH_2CF_3	H	61	154 (K)	++	$C_{15}H_{11}F_6N_3O_3S_2$	CHFNS
7k	H	H	OCH_2CF_3	H	H	84	151 (J)	++	$C_{13}H_{10}F_3N_3O_2S_2$	CHNS

Table II (Continued)

compd[b]	R^1	R^2	R^3	R^4	R^5	yield, %	mp, °C[c] (solv)[d]	chemical stability[e]	formula	anal.[f]
7l	H	H	$OCHF_2$	H	H	30	78 (J)	++	$C_{12}H_9F_2N_3O_2S_2$	CHNS
7m	H	H	H	$OCHF_2$	H	46	116 (J)	++	$C_{12}H_9F_2N_3O_2S_2$	CHFNS
7n	H	H	OCF_2CF_2H	OCH_3	H	88	138 (K)	++	$C_{14}H_{11}F_4N_3O_3S_2$	CHFNS
8a	CH_3	CH_3	H	H	H	72	155–157 (A)	0	$C_{13}H_{13}N_3OS_2$	CHNS
8b	CH_3	CH_3	H	H	CH_3	39	164–166 (D)	0	$C_{14}H_{15}N_3OS_2$	CHNS
8c	CH_3	CH_3	H	OCH_3	H	47	170–174 (A)	–	$C_{14}H_{15}N_3O_2S_2$	CHNS
8d	CH_3	CH_3	Cl	O-*i*-C_3H_7	H	34	130–135 (C)	++	$C_{16}H_{18}ClN_3O_2S_2$	CHNS
8e	CH_3	CH_3	H	OCH_2CF_3	H	51	163–165 (E)	+	$C_{15}H_{14}F_3N_3O_2S_2$	CHNS
8f	CH_3	CH_3	H	$OCH_2CF_2CF_3$	H	68	147–151 (J)	+	$C_{16}H_{14}F_5N_3O_2S_2$	CHFNS
8g	CH_3	CH_3	H	$OCH_2(CF_2)_2CF_3$	H	57	147 (J)	++	$C_{17}H_{14}F_7N_3O_2S_2$	CHFNS
8h	$COCH_3$	H	H	H	CH_3	25	125 (M)	–	$C_{14}H_{13}N_3O_2S_2$	CHNS
8i	$COCH_3$	H	H	OCH_2CF_3	H	42	156–158 (J)	–	$C_{15}H_{12}F_3N_3O_3S_2$	CHN
8j	CO_2CH_3	H	H	OCH_3	H	42	142 (A)	0	$C_{14}H_{13}N_3O_4S_2$	CHNS
8k	C_6H_5	H	H	H	H	63	137–141 (E)	0	$C_{17}H_{13}N_3OS_2$	CHN
8l	C_6H_5	H	H	OCH_3	H	54	130–135 (E)	–	$C_{18}H_{15}N_3O_2S_2$	CHN
8m	C_6H_5	H	CH_3	OCH_3	CH_3	50	160–165 (I)	–	$C_{20}H_{19}N_3O_2S_2$	CHN
8n	4-$CH_3OC_6H_4$	H	H	OCH_3	H	66	162–165 (I)	0	$C_{19}H_{17}N_3O_3S_2$	CHN
8o	4-$CH_3OC_6H_4$	H	CH_3	OCH_3	CH_3	74	162–165 (E)	0	$C_{21}H_{21}N_3O_3S_2$	CHN
9a	H	H	H	OCH_3	H	*h*		++		
9b	CO_2CH_3	CO_2CH_3	H	H	H	31	146–149 (L)	++	$C_{15}H_{13}N_3O_5S_2$	CHN
9c	CO_2CH_3	CO_2CH_3	H	OCH_3	H	46	140 (L)	++	$C_{16}H_{15}N_3O_6S_2$	CHN

[a] From thioethers **18–25** by oxidation with *m*-chloroperbenzoic acid. See Experimental Section. [b] R^6 = H in all compounds except **2f**. [c] All compounds decompose on mp determination. [d] Recrystallization solvent: A = acetonitrile, B = diethyl ether, C = diisopropyl ether, D = acetone, E = ethyl aceate, F = toluene, G = ethanol, H = diethyl ether/ethyl acetate, I = acetone/diisopropyl ether, J = dichloromethane/diisopropyl ether, K = cyclohexane/diisopropyl ether, L = ethyl acetate/diisopropyl ether. [e] Relative to the parent compound **2a**, determined in buffered acetonitrile solution, pH 7.4. (0) as stable as **2a** ($t_{1/2}$ ~ 7–20 h), (–) more unstable ($t_{1/2}$ ~ 0.5–7 h), (+) more stable ($t_{1/2}$ ~ 20–40 h), (++) furthermore stable ($t_{1/2}$ ~ 40–150 h). See Experimental Section. [f] Elemental analyses are within ±0.4% of the calculated values. [g] R^6 = CH_3. [h] See ref 15.

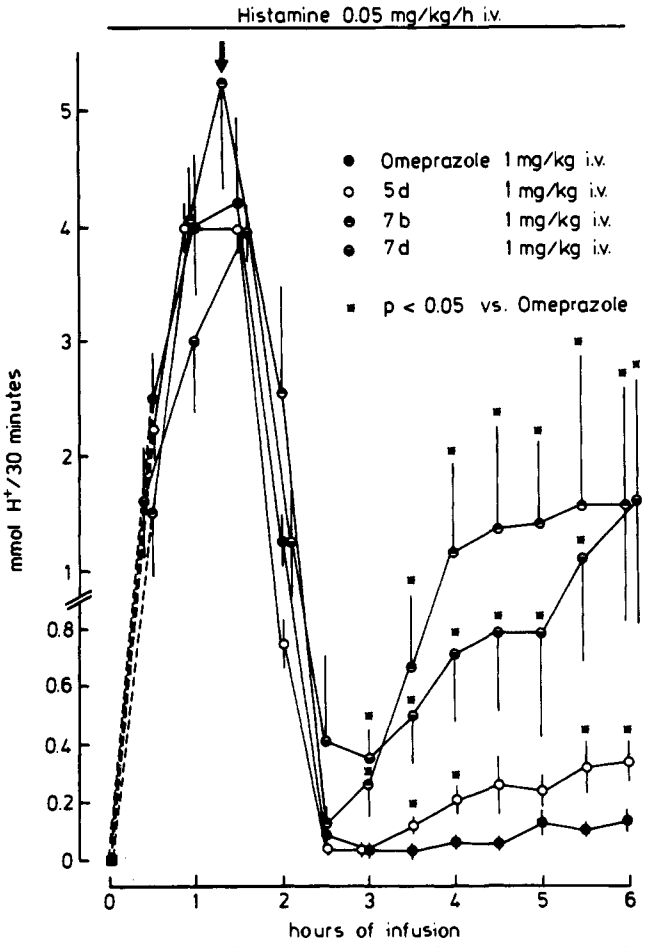


Figure 1. Pharmacodynamic difference between saviprazole (HOE 731, **5d**), **7b**, **7d**, and omeprazole. Time course of maximal inhibition of histamine-stimulated gastric acid secretion in Heidenhain-pouch dogs following iv administration of 1 mg/kg. Values are means ±SEM of six to nine dogs. Arrow indicates the application of the test compounds. Asterisks indicate significant differences ($p < 0.05$) compared to omeprazole.

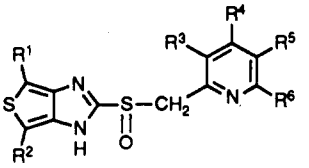
The observation of a "noncomplete inhibition" must not be misinterpreted as a shorter duration of action of the thienoimidazole compounds compared to omeprazole, but represents a qualitative difference to omeprazole. Experiments to elucidate the duration of antisecretory activity of saviprazole have been performed by iv administration during maximal histamine-stimulated acid secretion and monitoring the acid output for a further 2 days. A dose of 0.3 mg/kg caused an immediate 80% drop in the amount of acid produced. Acid output to histamine stimulation was about half-maximal on the second day and approached control values on the third day after administration of **5d**. Similar results were obtained with omeprazole.

From omeprazole it has been known that the total acid blockade initiated a gastric antral feedback mechanism, resulting in an excessive hypergastrinemia, which is believed to cause diffuse endocrine cell hyperplasia, characterized as carcinoids in the gastric corpus after 2 years of treatment in rats.[8] From the different pharmacodynamic profiles of the thienoimidazoles, an effect on resulting gastrin levels could be suggested. Therefore, female Wistar rats were treated orally with 30 mg/kg saviprazole or omeprazole per day for 10 weeks. Saviprazole caused an elevation of serum gastrin levels. However, these were only about 2-fold that of the control group, while omeprazole caused about a 6-fold increase in serum gastrin levels (Figure 2).

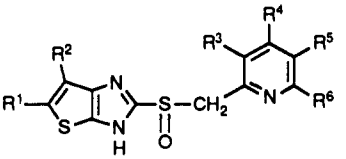
First, it has been suggested that the different pharmacodynamic behaviors of the thienoimidazoles might be related to their chemical stability. Therefore, half-lives of **5d** and **7d** were determined in buffered solution at different pH levels in comparison to omeprazole[41] (Table VI). All compounds reveal that their stability highly depends on the pH, indicating that their inhibitory activity

(41) Wallmark, B.; Brändström, A.; Larsson, H. Evidence for Acid-Induced Transformation of Omeprazole into an Active Inhibitor of (H^+/K^+)-ATPase within the Parietal Cell. *Biochim. Biophys. Acta* **1984**, *778*, 549–558.

Table III. Antisecretory Activity of 2-[(2-Pyridylmethyl)sulfinyl]thienoimidazoles 2–9



2–8



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compd	in vitro inhibition		in vivo inhibition of gastric acid secretion, %			
			pylorus-ligated rat[b,d]	stomach-lumen-perfused rat[b,e]	Heidenhain-pouch dog	
	H^+/K^+-ATPase[a,b]	^{14}C-AP uptake[b,c]			iv[b,f]	id[b,g]
2a	ND[h]	6	−68	73 ± 3 (5)	64 ± 8 (3)	ND
2b	ND	25	−88	ND	ND	ND
2c	ND	ND	−67	72 ± 2 (4)	ND	ND
2d	ND	9	−78	78 ± 4 (4)	72 ± 4 (6)	ND
2e	ND	50	−92	ND	91 ± 2 (3)	ND
2f	ND	300	0	ND	ND	ND
2g	−16%	290	−53	59 ± 9 (5)	ND	ND
2h	−20%	1000	−53	38 ± 5 (5)	ND	ND
2i	ND	19	−85	82 ± 4 (5)	84 ± 4 (6)	ND
2j	ND	1000	−77	ND	ND	ND
2k	ND	1000	−85	ND	ND	ND
2l	ND	3	−80	ND	ND	ND
2m	ND	1	−84	81 ± 3 (5)	87 ± 8 (3)	ND
3a	ND	1000	−33	ND	ND	ND
3b	0	1	−47	ND	ND	ND
3c	ND	1	−72	71 ± 4 (5)	82 ± 5 (6)	36 (3)
3d	ND	2	−82	ND	ND	ND
3e	ND	1	−77	80 ± 5 (5)	87 ± 3 (6)	ND
3f	ND	3	−81	ND	ND	ND
3g	−36%	ND	−76	63 ± 5 (4)	ND	ND
3h	−26%	ND	−71	43 ± 5 (4)	52 ± 6 (3)	ND
3i	−65%	ND	0	ND	ND	ND
3j	−48%	61	−19	0	ND	ND
3k	−12%	1000	−48	ND	ND	ND
3l	ND	10	−32	ND	ND	ND
3m	−75%	2	−82	71 ± 4 (5)	73 ± 3 (3)	−11 (1)
4a	ND	1000.0	ND	26 ± 7 (4)	ND	ND
4b	ND	31.0 ± 9 (4)	−62	58 ± 7 (4)	38 ± 7 (3)	55 (2)
4c	−5%	230.0	−64	43 ± 8 (4)	ND	24 (2)
4d	ND	ND	−5	38 ± 11 (5)	ND	ND
4e	−48%	19.0	−75	62 ± 4 (5)	59 ± 7 (3)	53 (1)
4f	−5%	81.0	−24	37 ± 4 (5)	ND	ND
4g	0	ND	0	ND	ND	ND
5a	−80%	3.0	−60	96 ± 1 (5)	62 ± 13 (3)	73 ± 11 (3)
5b	−77%	2.0	−76	89 ± 2 (5)	66 ± 14 (3)	91 ± 4 (3)
5c	−84%	1.0	−85	81 ± 3 (5)	ND	ND
5d	−85%	1.3 ± 0.4 (3)	−74	72 ± 4 (5)	76 ± 11 (3)	93 ± 2 (3)
5e	2	3.0	−72	ND	ND	ND
5f	ND	195.0	−28	39 ± 7 (5)	ND	ND
5g	−90%	21.0	−78	56 ± 4 (5)	57 ± 10 (3)	ND
5h	ND	1.0 ± 0.3 (4)	−82	69 ± 7 (4)	83 ± 8 (3)	92 ± 5 (3)
5i	−95%	0.5	−90	72 ± 2 (5)	64 ± 9 (3)	45 ± 2 (3)
5j	ND	ND	−45	ND	ND	ND
6a	ND	0.5	−58	ND	ND	ND
6b	0.5	0.5	−77	85 ± 1 (5)	80 ± 8 (3)	ND
6c	ND	1.0	−76	76 ± 3 (5)	ND	ND
6d	ND	0.7	−70	70 ± 3 (5)	ND	96 ± 2 (3)
6e	ND	0.4	−87	78 ± 3 (5)	ND	ND
6f	ND	1.1	−83	64 ± 4 (5)	ND	ND
6g	ND	0.6	−95	80 ± 2 (5)	ND	94 (2)
6h	ND	1.1	−75	43 ± 10 (5)	ND	87 ± 3 (3)
6i	ND	2.2	−75	64 ± 3 (5)	ND	66 ± 7 (3)
6j	ND	4.0	−58	84 ± 1 (5)	85 ± 3 (3)	97 (2)
6k	ND	0.3	ND	56 ± 7 (5)	74 ± 8 (3)	ND
6l	ND	2.0	−68	66 ± 5 (4)	76 ± 10 (3)	ND
6m	ND	2.3	−57	49 ± 6 (5)	62 ± 19 (3)	ND
7a	−77%	3.6	−84	54 ± 4 (5)	82 ± 10 (3)	ND
7b	4	2.5 ± 1.1 (3)	−69	64 ± 4 (5)	85 ± 7 (3)	77 ± 6 (3)
7c	3	0.6	−63	79 ± 3 (5)	58 ± 10 (3)	47 ± 18 (3)
7d	−70%	1.0 ± 0.6 (3)	−76	57 ± 3 (5)	74 ± 5 (3)	95 ± 2 (3)
7e	7	1.1	−52	70 ± 2 (5)	ND	66 ± 11 (3)
7f	12	1.0	−76	64 ± 4 (5)	ND	63 ± 5 (3)
7g	ND	0.5	−94	51 ± 5 (5)	ND	91 ± 6 (3)
7h	ND	0.5	−71	65 ± 4 (5)	ND	ND
7i	ND	0.3	−80	78 ± 4 (5)	73 ± 8 (3)	76 ± 6 (3)

Table III (Continued)

compd	in vitro inhibition		in vivo inhibition of gastric acid secretion, %			
			pylorus-ligated rat[b,d]	stomach-lumen-perfused rat[b,e]	Heidenhain-pouch dog	
	H^+/K^+-ATPase[a,b]	^{14}C-AP uptake[b,c]			iv[b,f]	id[b,g]
7j	−63%	0.8	−15	35 ± 8 (5)	13 ± 3 (3)	45 ± 2 (3)
7k	0	120.0	−50	23 ± 9 (4)	ND	ND
7l	0	1000.0	−18	ND	ND	ND
7m	0	1000.0	0	ND	ND	ND
7n	ND	3.0	−61	51 ± 6 (5)	65 ± 6 (3)	14 ± 1 (3)
8a	ND	15.0	−63	ND	ND	ND
8b	ND	6.0	−65	58 ± 9 (4)	46 ± 7 (3)	ND
8c	ND	12.0	−70	ND	66 ± 6 (3)	ND
8d	ND	2.5	−70	32 ± 9 (6)	ND	ND
8e	2	3.7	−26	ND	ND	54 ± 2 (3)
8f	ND	1.0	−44	ND	ND	ND
8g	ND	2.6	−35	ND	ND	ND
8h	ND	ND	−41	ND	ND	ND
8i	ND	32.0	−23	ND	ND	ND
8j	ND	ND	−13	ND	ND	ND
8k	ND	31.0	−11	ND	ND	ND
8l	ND	ND	−68	ND	ND	ND
8m	ND	4.2	−81	46 ± 6 (5)	ND	39 ± 17 (3)
8n	ND	ND	−44	ND	ND	ND
8o	ND	3.0	−59	24 ± 6 (5)	ND	ND
9a	ND	1000.0	−24	ND	ND	ND
9b	ND	1000.0	−20	ND	ND	ND
9c	ND	1000.0	−23	ND	ND	ND

[a] Inhibition of H^+/K^+-ATPase at 10 μM, pH = 6, IC_{50} values (μM), except where percentage values are noted. [b] See Experimental Section. [c] Inhibition of [^{14}C]aminopyrine (AP) uptake as IC_{50} (μM), determined in isolated rabbit gastric glands after dbcAMP stimulation. [d] Dose of 5 mg/kg, ip. [e] Dose of 0.5 mg/kg, iv.; values are means ± SEM (n = number of rats). [f] Dose of 0.3 mg/kg; values are means ± SEM (n = number of dogs). [g] Dose of 1.0 mg/kg; values are means ± SEM (n = number of dogs). [h] Not determined.

Table IV. Basicity of 2-[(2-Pyridylmethyl)sulfinyl]-1*H*-thieno[3,4-*d*]imidazoles[a]

compd	pK_a[b]	compd	pK_a[b]
2a	3.05	**4b**	3.44
2d	3.26	**5a**	3.83
2i	4.16	**5d**	3.73
2l	3.92	**5f**	3.50
3c	3.55	**6g**	3.74
3m	3.52	**7b**	3.52

[a] Determined by pH measurements. See Experimental Section for details. [b] Values within ±0.03.

Table V. Antisecretory Activity in Heidenhain-Pouch Dogs

compd	n	ED_{50}, mg/kg[a,b]	admin[c]
2a	9	0.11 (0.03–0.50)	iv
2d	9	0.11 (0.03–0.40)	iv
3c	12	0.10 (0.02–0.41)	iv
4b	9	0.25 (0.06–1.05)	iv
saviprazole	15	0.10 (0.04–0.28)	iv
HOE 731 (**5d**)	11	0.22 (0.07–0.67)	id
7b	9	0.08 (0.02–0.25)	iv
7d	9	0.13 (0.03–0.57)	iv
	9	0.16 (0.03–0.90)	id
omeprazole	15	0.10 (0.03–0.37)	iv
	9	0.25 (0.08–0.83)	id

[a] Maximal inhibition of histamine stimulated gastric acid secretion, calculated from three doses; three to six dogs per dose were used. [b] ED_{50} (95% confidence limits). [c] iv = intravenous, id = intraduodenal.

Table VI. pH-Dependent Chemical Stability[a]

compound	$t_{1/2}$		
	pH 7.0	pH 5.0	pH 2.0
5d	8.0 h	1.4 h	3 min
7d	23.0 h	7.8 h	11 min
omeprazole	17.0 h[b]	2.26 h	12 min

[a] See Experimental Section. [b] Value taken from the literature.[41]

is related to an acid activation process. Saviprazole is less stable than omeprazole both in neutral and in acidic media. In view of the kinetic properties, the lower stability of **5d**

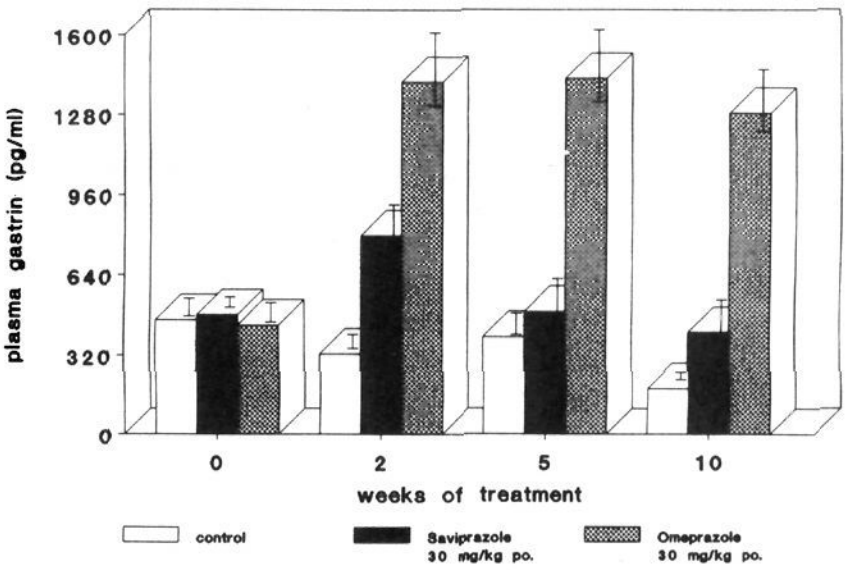

Figure 2. Serum gastrin levels in rats after oral treatment with saviprazole at 30 mg/kg per day or omeprazole at 30 mg/kg per day. Values are means ±SEM, n = 13 rats.

in neutral media should not be overestimated, as the plasma half-life reported for omeprazole is about 1 h.[42] Similar results were obtained for saviprazole. Half-lives indicate that **7d** is the most pH-selective compound. Compared to **5d**, its enhanced stability at pH 7 and 5 is attributed to the 3-methoxy-substituted pyridine ring. In parallel to this favorable chemical stability, **7d** showed an even more pronounced "noncomplete inhibition profile" (Figure 1). It can be concluded that the different pharmacological behavior of the thienoimidazole compounds is not related to an increased lability under neutral conditions.

Inhibition of the H^+/K^+-ATPase by omeprazole could be characterized by covalent binding of its "active intermediate", the cyclic sulfenamide, to essential enzyme SH groups.[9] It can be speculated that the differences

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between **5d**, **7b**, **7d**, and omeprazole might be related to differences in the acid activation process and/or to different reaction pathways of the active intermediate(s) and/or to a different (metabolic) stability of the so-formed enzyme–inhibitor disulfide complexes.

Proton uptake studies in gastric vesicles done recently,[43] showed a faster onset of proton-pump inhibition by the thienoimidazole compounds **2i** and **5d** in comparison to omeprazole. To elucidate the effect of the thienoimidazoles on the different kind of sulfhydryl groups of the H^+/K^+-ATPase distributed to the vesicle exterior (cytosolic site of the enzyme) and the vesicle interior (luminal site),[44] experiments on proton uptake have been performed in the presence of the hydrophilic mercaptan glutathione (GSH) and the hydrophobic mercaptan dithioerythritol (DTE). The inhibitory action of omeprazole could only be prevented by DTE, whereas the effect of **2i** and **5d** additionally could be influenced to a minor extent by GSH.[43]

Chemical stability data for **5d** and **7d** implicate that this effect is not caused by an activation process taking place in neutral media, but might be the result of a fast activation process, occurring just in the locally acidic environment of the H^+/K^+-ATPase within the apical membrane.[45] The important role of the local pH could be demonstrated recently for omeprazole by short circuit measurements on H^+/K^+-ATPase-containing sheets, which were absorbed to a planar lipid membrane. In an almost perfectly buffered system, omeprazole caused an increasing inhibition the more the pump was activated.[46] Therefore, it seems likely that faster activated thienoimidazoles additionally bind to some other SH groups of the proton pump than omeprazole does.

The gastric antisecretory activity of the thieno[3,4-*d*]imidazole compounds saviprazole (HOE 731, **5d**), **7b**, and **7d** can be rationalized in terms of a long-acting main component and an additional short-acting one. In analogy to omeprazole, the inhibitory activity is related mainly to an irreversible covalent binding of the activated inhibitor to essential enzyme SH groups, whereas the short acting reversible component is attributed to an interference with enzyme SH groups accessible to endogenous glutathione for reactivation.

Conclusion

In addition to the known benzimidazoles, the 2-[(2-pyridylmethyl)sulfinyl]-1*H*-thieno[3,4-*d*]imidazoles represent a novel class of potent inhibitors of gastric acid secretion. Irrespective of the stimulants used, these compounds block acid secretion in vitro and in vivo, indicating an interference with the gastric proton pump. Out of 85 thieno[3,4-*d*]imidazole derivatives, the most interesting ones, e.g. **5d**, **7b**, and **7d**, combine a favorable chemical stability with an inhibitory activity comparable to omeprazole.

Saviprazole (**5d**, HOE 731) was selected for further development. Detailed pharmacological studies at high-dose levels have shown pharmacodynamic differences between omeprazole and saviprazole, since the thienoimidazole allows significant rest-secretion of gastric acid. In consequence of this "noncomplete inhibition" of gastric acid secretion, plasma gastrin levels in rats were less elevated for saviprazole than for omeprazole. Therefore, ECL-cell hyperplasia as an indirect pharmacodynamic consequence of long-lasting inhibition of gastric secretion also might be less pronounced for saviprazole.

Experimental Section

All reactions were monitored by TLC. Unless noted otherwise, reaction mixtures were worked up by addition of water, separation of the organic layer, and extraction of the aqueous phase with dichloromethane. The combined organic extracts were washed with water or brine, dried over Na_2SO_4, and concentrated on a rotary evaporator.

Melting points were determined on a Büchi capillary melting point apparatus (according to Dr. Tottoli) and are uncorrected.

^1H NMR spectra were recorded on a Bruker WP60 or WM270 spectrometer using $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to tetramethylsilane as an internal standard. Mass spectra were recorded on a Kratos MS 9 or MS 80 mass spectrometer.

4-[(2,2,3,3,4,4,4-Heptafluorobutyl)oxy]-2-methylpyridine *N*-Oxide (29d). An amount of 15.4 g (0.1 mol) of 4-nitro-2-picoline *N*-oxide (**26**) was dissolved in 150 mL of dry DMF. An amount of 41.4 g (0.3 mol) of pulverized anhydrous potassium carbonate and 23 g of 2,2,3,3,4,4,4-heptafluorobutanol (96% content, Aldrich) were added, and with stirring the mixture was heated for 4 h at 70 °C. An additional amount of 13.8 g potassium carbonate was added, and stirring was continued for 6 h. After cooling to room temperature, salts were filtered off and washed with small portions of DMF. The combined filtrates were concentrated in vacuo, and the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried, concentrated, and passed with ethyl acetate–methanol (3:1) over a silica gel column. Fractions were pooled and solvents were removed in vacuo, giving 22.7 g (74%): mp 65 °C; ^1H NMR ($CDCl_3$) δ 2.48 (s, CH_3), 4.49 (tt, $^3J_{HF}$ = 12 Hz, $^4J_{HF}$ = 0.5 Hz, $OCH_2C_3F_7$), 6.88 (dd, $^3J_{5\text{-}H,6\text{-}H}$ = 7 Hz, $^4J_{5\text{-}H,3\text{-}H}$ = 2 Hz, 5 H), 7.12 (d, $^4J_{5\text{-}H,3\text{-}H}$ = 2 Hz, 3 H), 8.50 (d, $^3J_{5\text{-}H,6\text{-}H}$ = 7 Hz, 6-H).

2-(Chloromethyl)-4-[(2,2,3,3,4,4,4-heptafluorobutyl)oxy]pyridine Hydrochloride (15d). An amount of 4.9 g of compound **29d**, dissolved in 10 mL of acetic anhydride, was added dropwise at 90 °C to 45 mL of acetic anhydride with stirring. After 1 h the solvent was removed in vacuo. Then 50 mL of CH_3OH and a solution of 1.2 g of sodium hydroxide in 5 mL of water were added to the crude 2-(acetoxymethyl)-4-[(2,2,3,3,4,4,4-heptafluorobutyl)oxy]pyridine and stirred at room temperature for 2 h.

Solvents were removed in vacuo, and the oily residue was dissolved in dichloromethane, washed with water, and evaporated to dryness. The residue was dissolved in 50 mL of dichloromethane, and 5 mL of thionyl chloride was added dropwise with stirring. After 2 h at room temperature, the solvent and excess reagent were removed in vacuo and the residue was washed with diisopropyl ether, yielding 3.9 g (67%): mp 98–101 °C; ^1H NMR (from free base) ($CDCl_3$) δ 4.58 (tt, $^3J_{HF}$ = 12 Hz, $^4J_{HF} \leq 1$ Hz, $OCH_2CF_2CF_2$), 4.69 (s, CH_2Cl), 6.87 (dd, ^2J = 7 Hz, ^3J = 2 Hz), 5-H), 7.13 (d, J = 2 Hz, 3-H), 8.50 (d, J = 7 Hz, 6-H).

2-[[[4-[(2,2,3,3,4,4,4-Heptafluorobutyl)oxy]-2-pyridyl]methyl]thio]-1*H*-thieno[3,4-*d*]imidazole (21d). An amount of 18.7 g of 2-mercaptothieno[3,4-*d*]imidazole **11a** was added to a sodium methanolate solution (prepared from 8.2 g of Na and 300 mL of methanol). To this solution was added 43.4 g of compound **15d** dissolved in 100 mL methanol dropwise with stirring. After heating for 1 h under reflux, methanol was evaporated in vacuo, and the residue was dissolved in dichloromethane, washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was recrystallized from ethyl acetate to give 43 g (80%): mp 117 °C; ^1H NMR ($CDCl_3$) δ 4.29 (s, SCH_2), 4.56 (tt, $^3J_{H,F}$ = 12 Hz, $^4J_{HF}$ = 1 Hz, $OCH_2C_3F_7$), 6.60 (br s, NH),

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6.67 (2 H, s, thiophene, H), 6.88 (dd, ^2J = 7 Hz, ^3J = 2 Hz, 5-H), 7.03 (d, J = 2 Hz, 3-H), 8.53 (d, J = 7 Hz, 6-H). Anal. ($C_{15}H_{10}F_7N_3OS_2$) C, H, N, S.

2-[[[4-[(2,2,3,3,4,4,4-Heptafluorobutyl)oxy]-2-pyridyl]methyl]sulfinyl]-1*H*-thieno[3,4-*d*]imidazole (5d). Forty grams (0.09 mol) of compound **21d** was dissolved in 800 mL of dichloromethane. Then 500 mL of a saturated sodium bicarbonate solution was added. The mixture was chilled, and with vigorous stirring at 0 °C a solution of 20 g of *m*-chloroperbenzoic acid (77% content) in 150 mL of dichloromethane was added dropwise. The reaction mixture was stirred at this temperature for an additional 10 min, and after starch–iodine paper no longer showed the presence of peracid, the organic layer was separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried and concentrated to a rest volume of approximately 100 mL. After addition of 800 mL of diisopropyl ether, the product crystallized. After filtration and air-drying, the yield was 32 g (76%): mp 140 °C dec; ^{1}H NMR (CD_3OD, 270 MHz) δ 4.61 and 4.73 (dd, J = 14 Hz, CH_2SO), 4.65 (m, $OCH_2C_3C_7$), 6.96 (dd, $J_{3\text{-H},5\text{-H}}$ = 2 Hz, 3-H), 7.05 (dd, $J_{3\text{-H},5\text{-H}}$ = 2 Hz, $J_{5\text{-H},6\text{-H}}$ = 7 Hz, 5-H), 7.10 (br, 2 H, thiophene-H), 8.36 (1 H, d, $J_{5\text{-H},6\text{-H}}$ = 7 Hz, 6-H). For elemental analysis a sample was recrystallized from ethyl acetate. Anal. ($C_{15}H_{10}F_7N_3O_2S_2$) C, H, F, N, S.

3-Chloro-4-*n*-propoxy-2-picoline *N*-Oxide (28f). To a solution of sodium methylate, prepared from 0.51 g (22 mmol) of sodium and 100 mL of 1-propanol at − 10 °C, was added 3.6 g (20 mmol) of 3,4-dichloro-2-picoline *N*-oxide (prepared from known 3,4-dichloro-2-picoline[30] using *m*-chloroperbenzoic acid) in 20 mL of anhydrous 1-propanol. The mixture was allowed to warm slowly to room temperature and was then heated to reflux for 2 h. The solvent was removed by distillation under reduced pressure, water was added to the residue, the mixture was extracted with dichloromethane, and the solvent was evaporated off, yielding 2.6 g (65%). Colorless crystals from diisopropyl ether: mp 56–58%; ^{1}H NMR δ 1.05 (t, CH_2CH_3), 1.90 (m, CH_2), 2.66 (s, CH_3), 4.03 (t, CH_2), 6.70 (d, J = 11 Hz, 6-H), 8.17 (d, J = 11 Hz, 5-H). Anal. ($C_9H_{12}ClNO_2$) C, H, Cl, N. Continuing reactions according to Schemes I and II afforded **19f** (Table I).

5-Bromo-4-methoxy-2-picoline *N*-Oxide (29e). An amount of 8.2 g (35 mmol) of 4-nitro-5-bromo-2-picoline *N*-oxide[31] in 50 mL of anhydrous methanol was added at − 10 °C to a sodium methylate solution prepared from 0.87 g (38 mmol) of sodium and 30 mL of methanol. The mixture was allowed to warm slowly to room temperature and was then heated under reflux for 1 h. Standard workup and crystallization from diisopropyl ether yielded 7.3 g (95%) of colorless crystals: mp 146–148 °C; ^{1}H NMR δ 2.50 (s, CH_3), 3.93 (s, OCH_3), 6.77 (s, 3-H), 8.40 (s, 6-H). Anal. ($C_7H_8BrNO_2$) C, H, Br, N. Continuing according to Schemes I and II afforded **20e** (Table I).

4-[[4-(Trifluoromethyl)benzyl]oxy]-2-picoline *N*-Oxide (30g). Under N_2 atmosphere 11.2 g (100 mmol) of potassium *tert*-butylate was added to 25 mL of (183 mmol) 4-(trifluoromethyl)benzyl alcohol. After 30 min, 7.2 g (50 mmol) of 4-chloro-2-picoline *N*-oxide and 10 mL of *tert*-butyl alcohol were added and the mixture was refluxed for 30 min. After workup the crude material was chromatographed on silica gel, yielding 14.8 g (87%) of product: mp 113–115 °C; ^{1}H NMR δ 2.54 (s, CH_3), 5.16 (s, CH_2), 6.73 and 6.87 (2 H), 7.63 (m, 4 H), 8.20 (d, 6-H). Anal. ($C_{14}H_{12}F_3NO_2$) C, H, F, N. Continuing according to Schemes I and II afforded **22g** (Table I).

3-Methoxy-4-[(2,2,3,3,4,4,4-heptafluorobutyl)oxy]-2-picoline *N*-Oxide (31e). Under N_2 atmosphere 6.7 g (60 mmol) of potassium *tert*-butylate was added in portions to 20 mL (150 mmol) of 2,2,3,3,4,4,4-heptafluorobutanol at − 15 °C. After warming to 25 °C, 5.2 g (30 mmol) of 4-chloro-3-methoxy-2-picoline *N*-oxide (prepared from maltol methyl ether[32] and subsequent reactions with aqueous ammonia, phosphorous oxychloride, and *m*-chloroperbenzoic acid) was added in portions. After heating for 3 h at 100 °C, an additional amount of 3.35 g (30 mmol) potassium *tert*-butylate was added, and refluxing was continued for 2 h. After cooling to room temperature, water was added and the mixture extracted with ethyl acetate. The residue was chromatographed on silica gel (ethyl acetate–methanol) and made to crystallize with petroleum ether, yielding 4.4 g (44%): mp 128–130 °C; ^{1}H NMR δ 2.52 (s, CH_3), 3.88 (s, OCH_3), 4.56 (t, CH_2), 6.77 (d, 5-H), 8.12 (d, 6-H). Anal. ($C_{11}H_{10}F_7NO_3$) C, H, F, N. Continuing according to Schemes I and II afforded **23e** (Table I).

Chemical Stability. Solutions of compounds **2–9** in acetonitrile–phosphate buffer (1:3) were adjusted to pH 7.4. The initial concentrations were 3×10^{-2} M to 1×10^{-3}, depending on the different solubility. The decrease in concentration at ambient temperature was followed by TLC (SiO_2, dichloromethane–methanol (10:1) or ethyl acetate–methanol (5:1), UV detection, λ = 254 nm), each time comparing aliquot amounts to a freshly prepared standard solution. From these results half-lives were estimated, and the sulfoxides **2–9** were classified according to Table II.

pH-Dependent Chemical Stability of Saviprazole (5d), 7d, and Omeprazole. Ten milligrams of each compound was dissolved in 10 mL of acetonitrile–buffer pH 9 (1:1). Then 60 μL was taken and adjusted to 5 mL by adding the appropriate buffer pH 7.0, 5.0, or 2.0 (0.1 M); initial concentration: 12.0 μg/mL. Runs of 1, 2, 3, 5, 10, 15, and 30 min and 1, 3, 6, and 24 h were performed. Reactions were stopped by raising the pH to 8–10. The decrease in concentration was monitored by HPLC (nucleosil RP 18; 42% acetonitrile, 58% buffer pH 7.5, λ = 280 nm). Concentrations were plotted vs time and $t_{1/2}$ was calculated from linear regression (see Table VI).

pK_a Values. Potentiometric pH measurements were carried out to determine the pK_a's of the appropriate compounds as reported previously in detail.[37] A digital pH meter Autocal (Radiometer Copenhagen) PHM 83 was used. Fresh buffer solutions, pyridine, and imidazole were used as reference standards. Then 50 μL of aqueous HCl (0.1 M) was added to 1 mL of a solution (10^{-5} M) of the appropriate compound in water–DMSO (8:2). The change in pH was registered after 0.5, 1, and 2 min. Measurements were done in triplicate. Values were extrapolated to zero time and presented as means (Table IV).

In Vitro Biological Assays. H^+/K^+-ATPase-Containing Gastric Vesicles. Membrane vesicles containing H^+/K^+-ATPase were prepared from pig stomach as previously described.[16] The ATPase activity was measured at 37 °C as the release of inorganic phosphate from ATP. In detail, compounds at 10 μM, or for determination of IC_{50} values in concentrations of 0.01–100 μM, were preincubated in enzyme-containing buffers pH 6.0. After preincubation (37 °C, 30 min), the medium of pH 6.0 was adjusted with a Hepes–Tris buffer to pH 7.4. The enzyme reaction was started by the addition of Tris–ATP. The total reaction volume was 1 mL, containing 20 μg of vesicular protein, 4 mM $MgCl_2$, 10 mM KCl, 20 μg nigericin, 2 mM Tris–ATP, 10 mM Hepes, and additionally 2 mM Pipes for the preincubation medium at pH 6.0. After 4 min the reaction was stopped by the addition of 10 μL of 50% trichloroacetic acid. The denaturated protein was spun down, and the P_i content was determined as described.[47] The hydrolysis of ATP did not exceed 15%. Inhibition was calculated as percent inhibition against maximal stimulation, and IC_{50} was calculated by probit analysis.

[^{14}C]Aminopyrine Accumulation in Isolated Rabbit Gastric Glands. Rabbits (2–3 kg) were sacrificed by cervical fracture/dislocation during anaesthesia. High-pressure perfusion of rabbit stomachs was carried out as previously described.[48] The gastric mucosa in the corpus part was scraped off and minced with a pair of scissors. Mucosa pieces were incubated in a collagenase (1 mg/mL) containing medium for 30–45 min at 37 °C. The medium composition (in mM) was as follows: 100.0 NaCl, 5.0 KCl, 0.5 NaH_2PO_4, 1.0 Na_2HPO_4, 1.0 $CaCl_2$, 1.5 $MgCl_2$, 20.0 $NaHCO_3$, 20.0 Hepes, 2 mg/mL glucose, and 1 mg/mL rabbit albumin. The pH was adjusted to 7.4 with 1 M Tris. The glands were filtered through a nylon mesh to remove coarse fragments and rinsed three times with incubation medium. The glands were diluted to a final concentration of 2–4 mg dry weight/mL.

The ability of gastric glands to form acid was measured based on aminopyrine (AP) accumulation.[17a] Samples of 1.0-mL gland suspension were equilibrated in 1.0 mL of medium containing 0.1

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μCi/mL ^{14}C-AP at 37 °C in a shaking water bath together with the agent to be tested. After 20 min, 1 mM dbcAMP was added, followed by a 45-min incubation period. The glands were then separated from the medium by brief centrifugation. Aliquots of supernatant and the digested gland pellet were determined in a liquid scintillation counter. The AP accumulation was calculated as the ratio between AP in intraglandular water and AP in the incubation medium.[17b] All determinations were made in triplicate. IC_{50} was calculated by probit analysis where 0% corresponds to basal and 100% to maximal stimulated AP ratio.

In Vivo Biological Assays. Pylorus-Ligated Rat.[18] This study was performed in female Wistar rats with a body weight of 150–170 g as described previously.[49] Food was withdrawn 16 h before the beginning of the study, and water was available ad libitum. Following pylorus ligation, which was performed under ether anesthesia, the test drug was administration intraperitoneally (ip). Compounds were suspended in Tylose (1%) and administered at a volume of 2 mL/kg at a dose of 5 mg/kg. Gastric acid secretion was stimulated by a subcutaneous (sc) injection of Desglugastrin at a dose of 400 μg/kg. This latter injection was repeated 1 h later. Three hours after the beginning of the experiment, the animals were killed, the stomach was excised, and the accumulated gastric juice was collected and its volume measured. Acid concentration was measured by electrotitration against 100 mM NaOH to an endpoint of pH 7. Total acid output (mmol of H^+/3 h) was calculated. Percent inhibition of the treated rat group (n = 8 rats) was calculated against the control group (n = 10 rats).

Stomach-Lumen-Perfused Rat.[19] Gastric acid secretion in anesthetized male Sprague–Dawley rats with a body weight of 300–350 g was determined as described.[49] Briefly, the animals were fasted for 18 h prior to the experiment and received water ad libitum. They were anesthetized with 30% (w/v) urethane (5 mg/kg im) and tracheotomized. The esophagus and pylorus were ligated, and a double lumen perfusion cannula was inserted and fixed in the forestomach. The stomach was perfused continuously with warm (37 °C) saline at a rate of 1 mL/min. The perfusate was collected at 15-min periods and its acid concentration measured by electrotitration against 100 mM NaOH to an endpoint of pH 7, and acid output (μmol of H^+/15 min) was calculated. To stimulate acid secretion, histamine (10 mg/kg per h) was administered after a basal period of 45 min by iv infusion into the jugular vein. About 90 min after the onset of the secretagogue infusion, acid output had reached a stable plateau.[50] Then compounds were administered iv (25% DMSO, 1 mL/rat). Maximal inhibition was calculated as percent change against predrug value and presented as mean ± SEM with n as the number of rats.

Heidenhain-Pouch Dogs.[20] Six male Beagle dogs were equipped with a Heidenhain-pouch as described previously.[49] For intraduodenal (id) administration studies, three dogs received an additional cannula in the flexura duodenojejunalis. The dogs were trained to stay in a Pawlow stand. Food was withdrawn 18 h prior to the experiment and water was available ad libitum. Gastric acid secretion was induced with an iv infusion of 0.05 mg/kg per h of histamine, which produced a maximal stimulation. Gastric juice was collected from the pouch at 30-min intervals, and acidity was measured by titration against 100 mM NaOH to an endpoint of pH 7, and acid output (mmol H^+/30 min) was calculated. Drugs were administered at doses of 0.3 mg/kg iv or 1 mg/kg id at a volume of 20 mL per dog as soon as acid secretion had stabilized. Compounds were dissolved in 25% DMSO. Maximal inhibition was calculated as percent change against predrug value and presented as mean ± SEM with n as the number of different dogs (Table III). ED_{50} values and confidence limits (95%) were calculated according to Lichtfield and Wilcoxon[51] (Table V).

Determination of Serum Gastrin Levels in Rats. Female Wistar rats (90–110 g) were treated orally for 10 weeks with 30 mg/kg per day HOE 731 (n = 13) or omeprazole (n = 13), representing 30-fold of the ID_{50} values in conscious rats. At days 1 to 3, rats received HOE 731 or omeprazole by intraperitoneal administration, to cause gastric acid inhibition and therefore to reduce the acidic degradation of subsequent orally administered test compounds to 10 weeks. The compounds were suspended in potato starch mucilage (20 mg/mL) and administered at a volume of 2 mL/kg. A control group (n = 13) was also included in the experiment. Blood samples were collected retroorbitally during ether anesthesia. Serum gastrin levels (pg/mL) were determined by using a commercially available RIA kit (Gastrin RIAKit II, Dainabot Co., Ltd.) and presented as means ±SEM (Figure 2). Significant differences ($p < 0.05$) were calculated by Students t-test with n = number of rats.

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Registry No. **2a**, 111371-25-6; **2b**, 111371-29-0; **2c**, 111371-31-4; **2d**, 111371-30-3; **2e**, 111371-71-2; **2f**, 111371-92-7; **2g**, 122307-53-3; **2h**, 122307-55-5; **2i**, 111371-26-7; **2j**, 111371-27-8; **2k**, 111371-28-9; **2l**, 111371-75-6; **2m**, 137543-05-6; **3a**, 122307-46-4; **3b**, 137543-06-7; **3c**, 111371-33-6; **3d**, 137543-07-8; **3e**, 137543-08-9; **3f**, 137543-09-0; **3g**, 137543-10-3; **3h**, 137543-11-4; **3i**, 137543-12-5; **3j**, 137543-13-6; **3k**, 137543-14-7; **3l**, 137543-15-8; **3m**, 122307-26-0; **4a**, 122307-51-1; **4b**, 122307-28-2; **4c**, 137543-16-9; **4d**, 137543-17-0; **4e**, 122307-27-1; **4f**, 137543-18-1; **4g**, 122307-48-6; **5a**, 132969-12-1; **5b**, 132969-15-4; **5c**, 132969-16-5; **5d**, 121617-11-6; **5e**, 132969-13-2; **5f**, 137543-19-2; **5g**, 137543-20-5; **5h**, 137543-21-6; **5i**, 137543-22-7; **5j**, 137543-23-8; **6a**, 111371-87-0; **6b**, 124845-98-3; **6c**, 124846-00-0; **6d**, 124846-01-1; **6e**, 124846-03-3; **6f**, 124846-04-4; **6g**, 124845-50-7; **6h**, 124845-99-4; **6i**, 124846-09-9; **6j**, 124846-15-7; **6k**, 124846-10-2; **6l**, 124846-20-4; **6m**, 125668-49-7; **7a**, 122307-43-1; **7b**, 122307-22-6; **7c**, 122307-23-7; **7d**, 122307-24-8; **7e**, 122307-25-9; **7f**, 122320-36-9; **7g**, 124846-06-6; **7h**, 124846-07-7; **7i**, 124846-05-5; **7j**, 122307-59-9; **7k**, 137543-24-9; **7l**, 122307-57-7; **7m**, 137543-25-0; **7n**, 122307-61-3; **8a**, 111371-78-9; **8b**, 111372-07-7; **8c**, 111371-80-3; **8d**, 137543-26-1; **8e**, 137543-27-2; **8f**, 137543-28-3; **8g**, 132969-14-3; **8h**, 137543-29-4; **8i**, 137543-30-7; **8j**, 111371-81-4; **8k**, 122307-92-0; **8l**, 122320-37-0; **8m**, 122307-93-1; **8n**, 122307-95-3; **8o**, 122332-68-7; **9a**, 106850-02-6; **9b**, 122308-01-4; **9c**, 122308-00-3; **11a**, 90070-09-0; **15d**·HCl, 137543-31-8; **18a**, 111371-74-5; **18b**·2HCl, 137543-32-9; **18c**·2HCl, 111371-67-6; **18d**·2HBr, 111371-68-7; **18e**·2HCl, 111371-70-1; **18f**·2HCl, 111371-91-6; **18g**, 122307-52-2; **18h**, 122307-54-4; **18i**, 111371-35-8; **18j**, 111371-73-4; **18k**, 111371-72-3; **18l**·2HCl, 111371-66-5; **18m**, 137543-33-0; **19a**, 122307-45-3; **19b**, 137543-34-1; **19c**, 111371-96-1; **19d**, 137543-35-2; **19e**, 137543-36-3; **19f**, 137543-37-4; **19g**, 137543-38-5; **19h**, 137543-39-6; **19i**, 137543-40-9; **19j**, 137543-41-0; **19k**, 137543-42-1; **19l**, 137543-43-2; **19m**, 122307-40-8; **20a**, 122307-50-0; **20b**, 122307-32-8; **20c**, 137543-44-3; **20d**, 137543-45-4; **20e**, 122307-36-2; **20f**, 137543-46-5; **20g**, 122307-47-5; **21a**, 137543-47-6; **21b**, 137543-48-7; **21c**, 137543-49-8; **21d**, 132969-11-0; **21e**, 137543-50-1; **21f**, 137543-51-2; **21g**, 137543-52-3; **21h**, 137543-53-4; **21i**, 137543-54-5; **21j**, 137543-55-6; **22a**, 111371-65-4; **22b**, 124845-87-0; **22c**, 124845-89-2; **22d**, 124845-90-5; **22e**, 124845-92-7; **22f**, 124866-70-2; **22g**, 124845-49-4; **22h**, 124845-88-1; **22i**, 124845-96-1; **22j**, 124846-14-6; **22k**, 124845-97-2; **22l**, 124846-19-1; **22m**, 124846-26-0; **23a**, 122307-42-0; **23b**, 122307-66-8; **23c**, 122307-80-6; **23d**, 122307-79-3; **23e**, 122307-81-7; **23f**, 122307-82-8; **23g**, 124845-93-8; **23h**, 124845-94-9; **23i**, 124866-71-3; **23j**, 122307-58-8; **23k**, 137543-56-7; **23l**, 122307-56-6; **23m**, 137543-57-8; **23n**, 122307-60-2; **24a**·2HCl, 111371-77-8; **24b**·2HCl, 111371-83-6; **24c**·2HCl, 137543-58-9; **24d**·2HCl, 137543-59-0; **24e**·2HCl, 137543-60-3; **24f**·2HCl, 137543-61-4; **24g**·2HCl, 137543-62-5; **24h**·2HCl, 137543-63-6; **24i**, 137543-64-7; **24j**, 111371-37-0; **24k**, 122307-83-9; **24l**, 122307-84-0; **24m**, 122307-85-1; **24n**, 122307-87-3; **24o**, 122307-88-4; **25a**, 106849-95-0; **25b**, 111371-97-2; **25c**, 122307-99-7; **26**, 5470-66-6; **28f**, 137543-65-8; **29d**, 132969-09-6; **29e**, 108004-86-0; **30g**, 137543-66-9; **31e**, 122307-69-1; ATPase, 9000-83-3; 2,2,3,3,4,4,4-heptafluorobutanol, 375-01-9; 3,4-dichloro-2-picoline N-oxide, 108004-98-4; 4-nitro-5-bromo-2-picoline N-oxide, 62516-08-9; 4-(trifluoromethyl)benzyl alcohol, 349-95-1; 4-chloro-2-picoline N-oxide, 696-08-2; 4-chloro-3-methoxy-2-picoline N-oxide, 122307-41-9.

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