RATIONAL DESIGN OF CIMETIDINE

The first breakthrough in anti-ulcer therapy came with the design of the H_2 antagonist **cimetidine** produced by the company Smith Kline and French (SKF). The cimetidine programme started in 1964 and was one of the early examples of rational drug design.

The remarkable aspect of the cimetidine story is that at the onset of the project there were no lead compounds and it was not even known if the target histamine receptor existed! In 1964, the best hope of designing an antiulcer agent was to find a drug which would block the hormone gastrin. Several research teams were active in this field, but the research team at SKF decided to follow a different approach.

It was known experimentally that histamine stimulated gastric acid release *in vitro*, so the SKF team proposed that an antihistamine agent might be effective in treating ulcers. At the time, this was a highly risky proposal as it was not confirmed that histamine played any significant role *in vivo*.

Many workers at the time discounted the importance of histamine, especially when it was found that conventional antihistamines failed to inhibit gastric acid release. This suggested the absence of histamine receptors in the parietal cells. The fact that histamine had a stimulatory effect was explained away by suggesting that histamine coincidentally switched on the gastrin or cholinergic receptors. Even if a histamine receptor was present, opponents argued that blocking it would have little effect as the receptors for acetylcholine and gastrin would remain unaffected and could still be activated by their respective messengers. Initiating a project which had no known target and no known lead compound was unprecedented, and represented a massive risk. Indeed, for a long-time little progress was made and it is said that company accountants demanded that the project be terminated.

Why did the SKF team persevere in their search for an effective antihistamine? What was their reasoning?

Before answering that, let us look at histamine itself and the antihistamines available at that time. The main reason was the fact that conventional antihistamines failed to inhibit *all* the then-known actions of histamine. For example, they failed to fully inhibit the dilatation of blood vessels induced by histamine. The SKF scientists therefore proposed that there might be two different types of histamine receptor.

Histamine—the natural messenger—would switch both on equally effectively and would not distinguish between them, whereas suitably designed antagonists might be capable of making that distinction.

By implication, this meant that the conventional antihistamines known in the early 1960s were already selective in inhibiting the histamine receptors involved in the inflammation process (classified as H_1 receptors), rather than the proposed histamine receptors responsible for gastric acid secretion (classified as H_2 receptors).

It was an interesting theory, but the fact remained that there was no known antagonist for the proposed H_2 receptors. Until such a compound was found, it could not be certain that the H_2 receptors even existed

Searching for a lead

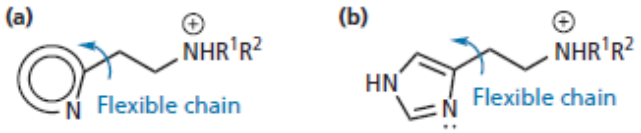
Histamine

The SKF team obviously had a problem. They had a theory but no lead compound. How could they make a start? Their answer was to start from histamine itself. If the hypothetical H_2 receptor existed, then histamine must bind to it. The task then was to vary the structure of histamine in such a way that it would bind as an antagonist rather than an agonist.

Th is meant exploring how histamine itself bound to its receptors. Structure–activity relationship (SAR) studies on histamine and histamine analogues revealed that the binding requirements for histamine to the H_1 receptors were as follows:

- The side chain had to have a positively charged nitrogen atom with at least one attached proton. Quaternary ammonium salts which lacked such a proton were extremely weak in activity;
- There had to be a flexible chain between the above cation and a heteroaromatic ring;
- The heteroaromatic ring did not have to be imidazole, but it did have to contain a nitrogen atom with a lone pair of electrons, *ortho* to the side chain.

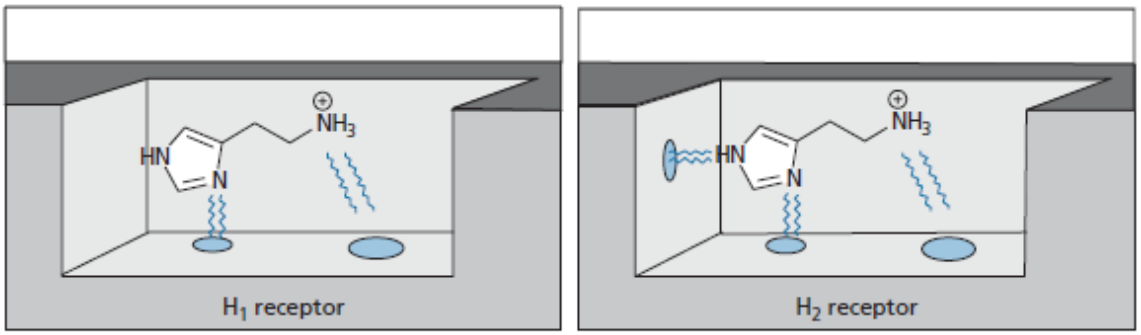
For the proposed H_2 receptor, SAR studies were carried out experimentally by determining whether histamine analogues could stimulate gastric acid release in stomach tissue. The essential SAR requirements were the same as for the H_1 receptor except that the heteroaromatic ring had to contain an amidine unit (HN – CH = N:). The results showed that the terminal α-amino group is involved in a binding interaction with both types of receptor via ionic and/or hydrogen bonding, while the nitrogen atom(s) in the heteroaromatic ring interact(s) via hydrogen bonding.



Summary of structure–activity relationship (SAR) results. (**a**) SAR for agonists at the H_1 receptor; (**b**) SAR for agonists at the proposed H_2 receptor.

***N*$^{\alpha}$-Guanylhistamine**

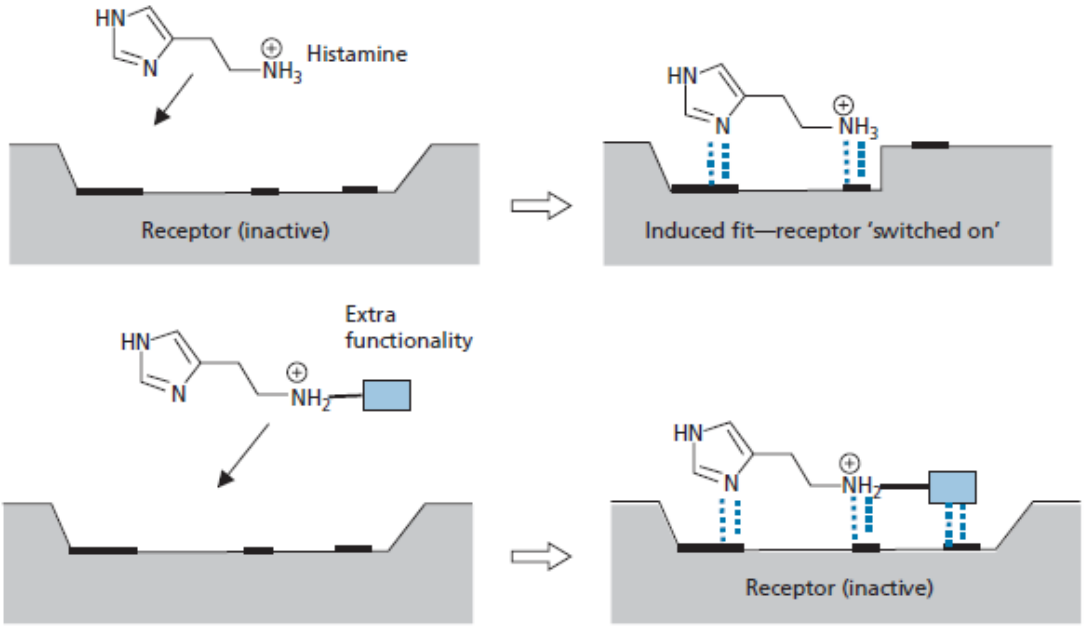
Having gained knowledge of the SAR for histamine, the task was now to design a molecule that would be recognized by the proposed H_2 receptor, but would not activate it. In other words, an agonist had to be converted to an antagonist. This meant altering the way in which the molecule bound to the receptor.



Binding interactions for the H_1 receptor and the proposed H_2 receptor.

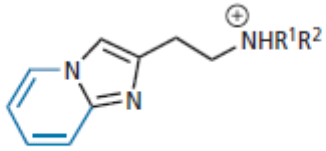
Pictorially, one can imagine histamine fitting into its binding site and stabilizing a change in shape which 'switches on' the receptor. An antagonist can often be found by adding a functional group that binds to an extra binding region in the binding site and prevents the change in shape required for activation. This was one of several strategies tried out by the SKF workers.

To begin with, the structural differences between agonists and antagonists in other areas of medicinal chemistry were identified and similar alterations were tried on histamine. Analogues were tested to see whether they stimulated or blocked gastric acid release—the assumption being that an H_2 receptor would be responsible for such an effect.



Possible receptor interactions of histamine and an antagonist.

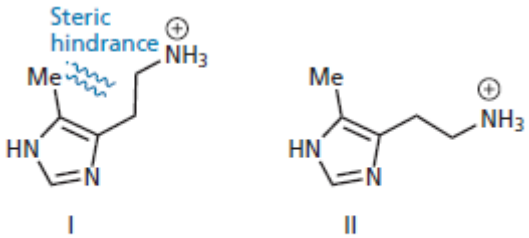
Fusing an aromatic ring on to noradrenaline had been a successful tactic used in the design of adrenergic antagonists. Th is same tactic was tried with histamine to give analogues such as the one shown below, but none of these compounds proved to be an antagonist.



Histamine analogue with no antagonist activity.

Another approach which had been used successfully in the development of anticholinergic agents had been the addition of non-polar, hydrophobic substituents. Similar substituents were attached to various locations of the histamine skeleton, but none proved to be antagonists.

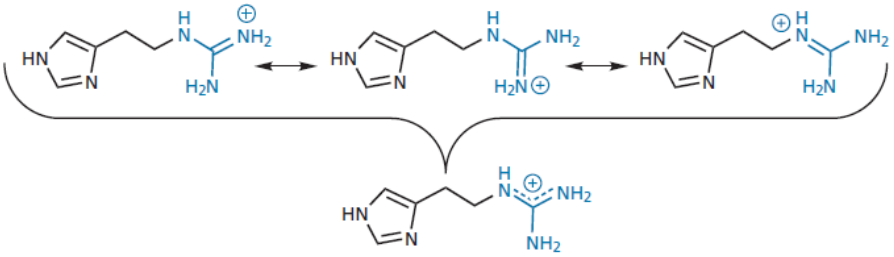
Nevertheless, there was one interesting result which proved relevant to later studies. It was discovered that **4-methylhistamine** was a highly selective H_2 agonist. In other words, it stimulated gastric acid release in the test assay, but had weak activity for all the other actions of histamine. How could this be? 4-Methylhistamine (like histamine) is a highly flexible molecule because of its side chain, but structural studies show that some of its conformations are less stable than others. Conformation I is not favoured because of a large steric interaction between the 4-methyl group and the side chain. This means that the 4-methyl group is acting as a conformational blocker. The selectivity observed suggests that 4-methylhistamine (and by inference histamine) has to adopt two different conformations in order to fit the H_1 and suggested H_2 receptor. As 4-methylhistamine is more active at the hypothetical H_2 receptor, it implies that conformation II is required for the H_2 receptor and conformation I is required for the H_1 receptor.



4-Methylhistamine.

Despite this interesting result, the SKF workers were no closer to an H_2 antagonist. Two hundred compounds had been synthesized and not one had shown a hint of being an antagonist. Research up until this stage had concentrated on adding hydrophobic groups to search for an additional hydrophobic binding region in the proposed receptor binding site. Now the focus

switched to study the effect of varying polar groups on the molecule. In particular, the terminal α−NH_3^+ group was replaced by different polar functional groups, the reasoning being that such groups could bond to the same binding region as the NH_3^+ group, but that the geometry of bonding might be altered sufficiently to produce an antagonist. This led to the first crucial breakthrough, with the discovery that N^{α} **-guanylhistamine** was a weak antagonist of gastric acid release.

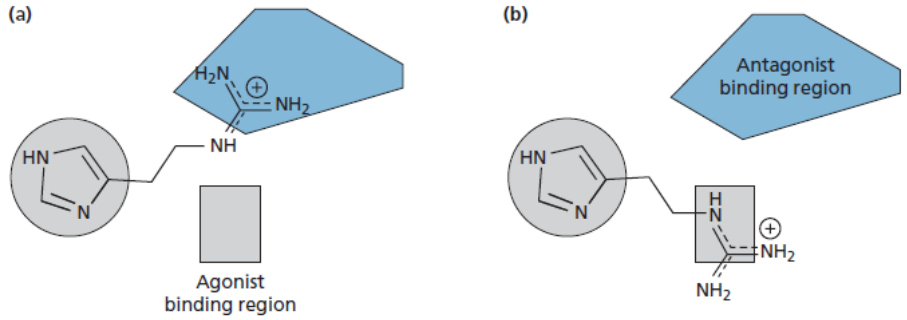


N^{α}-Guanylhistamine.

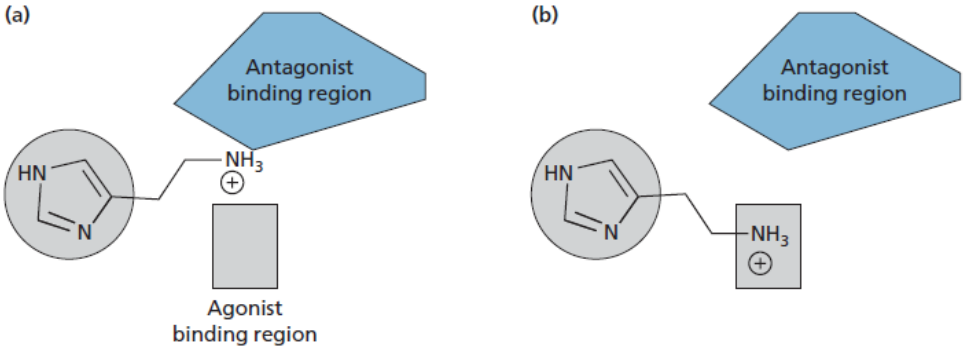
This structure had been synthesized very early on in the project, but had not been recognized as an antagonist. This is not too surprising as it acts as an agonist! It was not until later pharmacological studies were carried out that it was realized that N^{α}-guanylhistamine was acting as a partial agonist. Th is means that N^{α}-guanylhistamine activates the H_2 receptor, but not to the same extent as histamine. As a result, the amount of gastric acid released is lower. More importantly, as long as N^{α}-guanylhistamine is bound to the receptor, it prevents histamine from binding and thus prevents complete receptor activation. Th is was the first indication of antagonism to histamine, but still did not prove the existence of the H_2 receptor. The question now arose as to which parts of the N^{α}- guanylhistamine skeleton were really necessary for this effect. Various guanidine structures were synthesized that lacked the imidazole ring, but none had the desired antagonist activity, demonstrating that both the imidazole ring and the guanidine group were required.

The structures of N^{α}-guanylhistamine and histamine were now compared. Both structures contain an imidazole ring and a positively charged group linked by a two-carbon bridge. The guanidine group is basic and protonated at pH 7.4, so the analogue has a positive charge, similar to histamine. However, the charge on the guanidine group can be spread around a planar arrangement of three nitrogens which means that it can be further away from the imidazole ring. This leads to the possibility that the analogue could be interacting with an extra polar binding region on the receptor which is ‘out of reach’ of histamine. Two alternative binding regions might be available for the cationic group—an agonist region where binding leads to activation of the receptor and an antagonist region where binding does not activate the receptor. Histamine is only able to reach the agonist region, whereas the analogue with its extended

functionality is capable of reaching either region. If most of the analogue molecules bind to the agonist region and the remainder bind to the antagonist region, then this could explain the partial agonist activity. Regardless of the mode of binding, histamine would be prevented from binding and an antagonism would be observed owing to the fraction of N^{α}-guanylhistamine bound to the antagonist region.



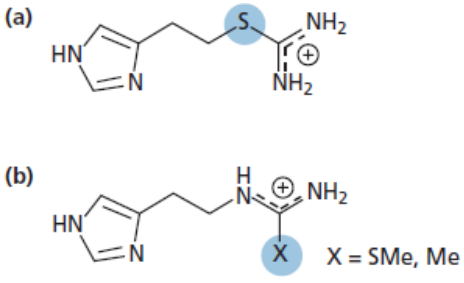
Possible binding modes for N^{α}-guanylhistamine as (a) an antagonist and (b) an agonist.



Binding of histamine: (a) no binding to the antagonist binding region;
(b) binding to the agonist binding region.

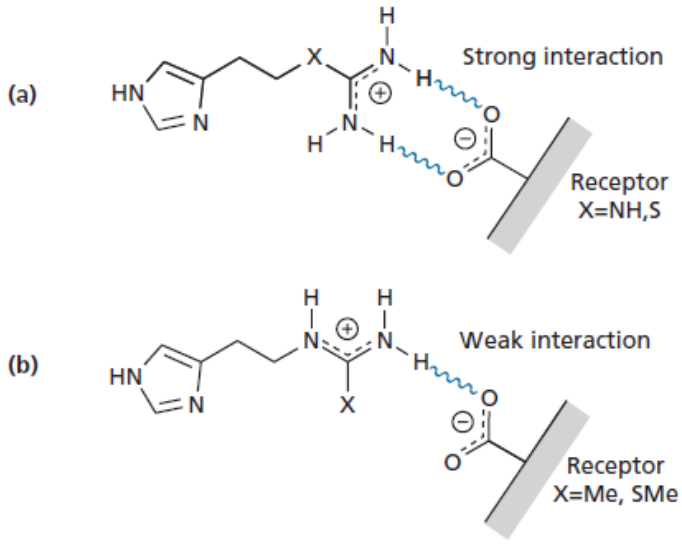
Developing the lead: a chelation bonding theory

The task was now to find an analogue which would bind to the antagonist region only. The isothiourea was synthesized as the positive charge would be restricted to the terminal portion of the chain and should interact more strongly with the more distant antagonist binding region. Antagonist activity did increase, but the compound was still a partial agonist, showing that binding was still possible to the agonist region.

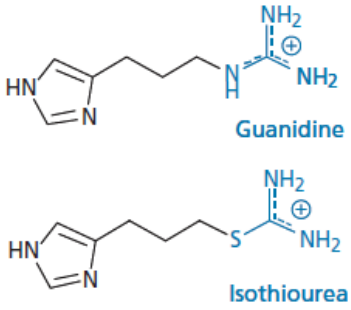


(a) An isothiourea. (b) Other analogues.

Two other analogues were synthesized where one of the terminal amino groups in the guanidine group was replaced by a methylthio group or a methyl group. Both these structures were partial agonists, but with poorer antagonist activity. From these results, it was concluded that both terminal amino groups were required for binding to the antagonist binding site. It was proposed that the charged guanidine group was interacting with a charged carboxylate residue on the receptor via two hydrogen bonds. If either of these terminal amino groups was absent, then binding would be weaker, resulting in a lower level of antagonism. The chain was now extended from a two-carbon unit to a three-carbon unit to see what would happen if the guanidine group was moved further away from the imidazole ring.



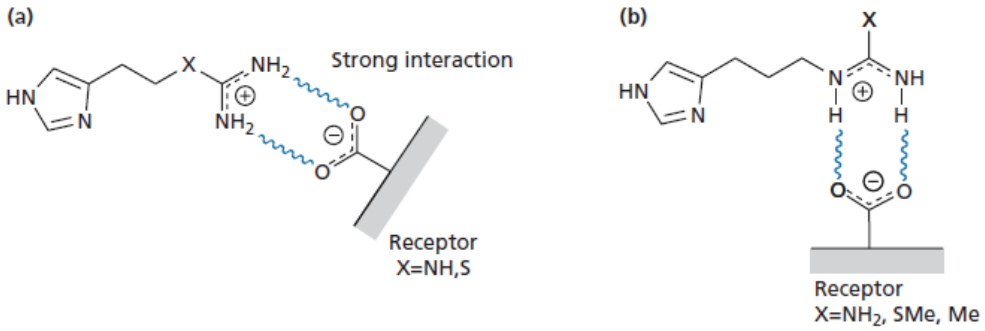
Proposed hydrogen bonding interactions for (a) a structure with two terminal amino groups and (b) an analogue with one terminal amino group.



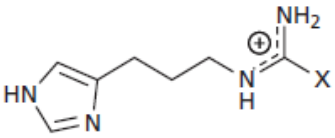
Guanidine and isothiourea structures with a 3-C linker.

The antagonist activity increased for the guanidine structure, but, strangely enough, decreased for the isothiourea structure. Therefore, it was proposed that with a chain length of two carbon units, hydrogen bonding to the receptor involved the terminal NH_2 groups, but with a chain length of three carbon units, hydrogen bonding to the same carboxylate group involved one terminal NH_2 group along with the NH group within the chain. Support for this theory was

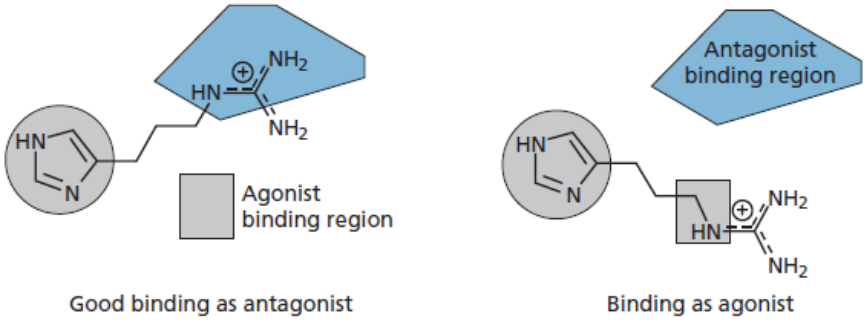
provided by the fact that replacing one of the terminal NH_2 groups in the guanidine analogue with SMe or Me did not affect antagonist activity adversely. This was completely different from the results obtained when similar changes were carried out on the C2 bridged compound.



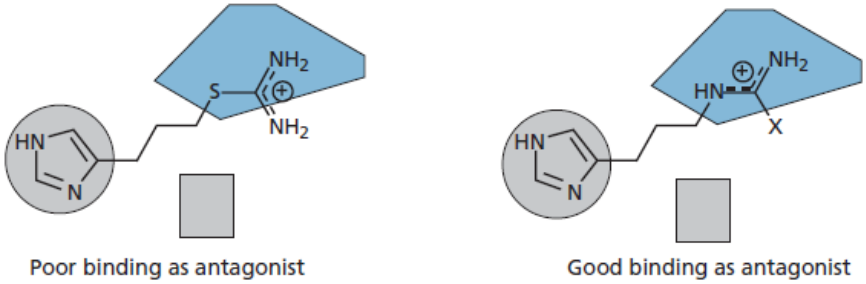
Proposed binding interactions for analogues of different chain length: (a) H-bonding involving two terminal amino groups for the three-atom chain; (b) H-bonding involving a terminal and internal amino group for a four-atom chain.



Guanidine analogue with X = SMe or Me.



Proposed binding interactions for the 3-C bridged guanidine analogue.



Proposed binding effect at the antagonist region if the guanidine group is modified.

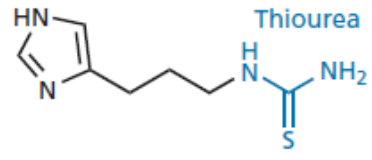
From partial agonist to antagonist: the development of burimamide

The problem was now to completely remove the agonist activity to get a pure antagonist. This meant designing a structure which would differentiate between the agonist and antagonist binding regions. At first sight this looks impossible, as both regions appear to involve the same type of bonding. Histamine's activity as an agonist depends on the imidazole ring and the charged amino function, with the two groups taking part in hydrogen and ionic bonding respectively. The antagonist activity of the partial agonists described so far also appears to depend on a hydrogen bonding imidazole ring and an ionic bonding guanidine group. Fortunately, a distinction can be made between the charged groups.

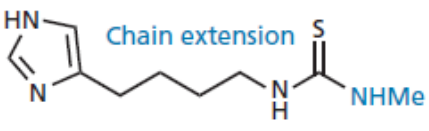
The structures which show antagonist activity are all capable of forming a chelated bonding structure. This interaction involves two hydrogen bonds between two charged species, but is it really necessary for the chelating group to be charged? Could a neutral group also chelate to the antagonist region by hydrogen bonding alone? If so, it might be possible to distinguish between the agonist and antagonist regions, especially as ionic bonding appears mandatory for the agonist region.

Therefore, it was decided to see what would happen if the strongly basic guanidine group was replaced by a neutral group capable of interacting with the receptor by two hydrogen bonds. Th ere are many such groups, but the SKF workers limited the options by adhering to a principle which they followed throughout their research programme. Whenever they wished to alter a specific physical or chemical property, they try to ensure that other properties were changed as little as possible. Only in this way could they rationalize any observed improvement in activity. Thus, it was necessary to ensure that the new group was similar to guanidine in terms of size, shape, and hydrophobicity.

Several functional groups were tried, but success was ultimately achieved by using a thiourea group to give **SKF 91581.**



SKF 91581



Burimamide

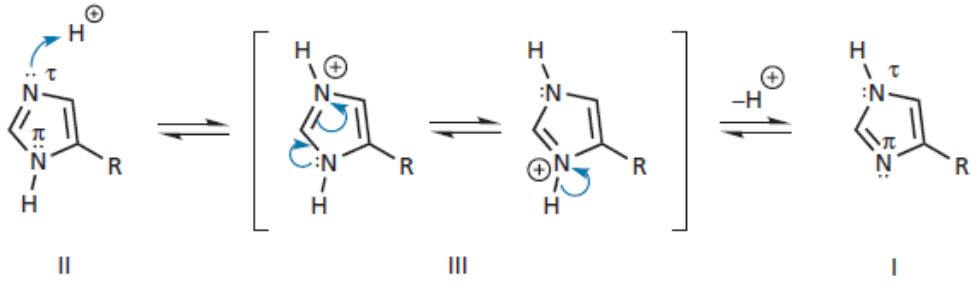
SKF 91581 and burimamide.

The thiourea group is neutral at physiological pH because the C=S group has an electron-withdrawing effect on the neighbouring nitrogens, making them non-basic and more like amide nitrogens. Apart from basicity, the properties of the thiourea group are very similar to the guanidine group. Both groups are planar, similar in size, and can take part in hydrogen bonding. Th is means that the alteration in biological activity can be reasonably attributed to the differences in basicity between the two groups. SKF 91581 proved to be a weak antagonist with no agonist activity, establishing that the agonist binding region involves ionic bonding, whereas the antagonist region involves hydrogen bonding. Further chain extension and the addition of an *N* -methyl group led to **burimamide**, which was found to have enhanced activity, suggesting that the thiourea group has been moved closer to the antagonist binding region. The beneficial addition of the *N*-methyl group is due to an increase in hydrophobicity.

Burimamide is a highly specific competitive histamine antagonist at H_2 receptors, and is 100 times more potent than N^{α} -guanylhistamine in inhibiting gastric acid release induced by histamine. Its discovery gave the SKF researchers far greater evidence for the existence of H_2 receptors.

Development of metiamide

Despite this success, burimamide was not suitable for clinical trials because its activity was still too low for oral administration. Attention was now directed to the imidazole ring of burimamide and, in particular, to its possible tautomeric and protonated forms. It was argued that if one of these forms was preferred for binding with the H_2 receptor, then activity might be enhanced by modifying the burimamide structure to favour that form. At pH 7.4, it is possible for the imidazole ring to equilibrate between the two tautomeric forms (I) and (II) via the protonated intermediate (III). The necessary proton for this process is supplied by water or by an exchangeable proton on a suitable amino acid residue in the binding site. If the exchange is slow, then it is possible that the drug will enter and leave the receptor at a faster rate than the equilibration between the two tautomeric forms. If bonding involves only one of the tautomeric forms or the protonated form, then, clearly, antagonism would be increased if the structure was varied to prefer that form over the other. Our model hypothesis for receptor binding shows that the imidazole ring is important for the binding of both agonists and antagonists. Therefore, it is reasonable to assume that the preferred imidazole form is the same for both agonists and antagonists. If so, then the preferred form for a strong agonist such as histamine should also be the preferred form for a strong antagonist. The imidazole ring can exist as two un-ionized tautomers and one protonated form. Is the protonated form likely?



Imidazole ring can equilibrate between tautomeric forms (I and II) via the protonated intermediate (III).

We have already seen that the p*K*a for the imidazole ring in histamine is 5.74, meaning that the ring is a weak base and mostly un-ionized at physiological pH. The p*K*a value for imidazole itself is 6.80 and for the imidazole ring in burimamide it is 7.25, showing that these rings are more basic and more likely to be ionized. Why should this be so?

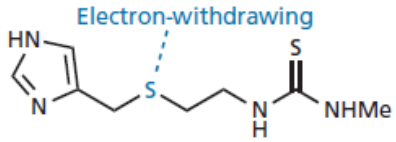
The explanation lies in the side chains, which have an electronic effect affecting the basicity of the imidazole ring. A measure of the electronic effect of the side chain can be worked out by the Hammett equation:

$$pK_{a(R)} = pK_{a(H)} + \rho\sigma_R$$

where p*K*a (R) is the p*K*a of the imidazole ring bearing a side chain R, p*K*a (H) is the p*K*a of the unsubstituted imidazole ring, ρ is a constant, and σ R is the Hammett substituent constant for the side chain R. From the p*K*a values, the value of the Hammett substituent constant can be calculated to show whether the side chain R is electron-withdrawing or electron-donating. In burimamide, the side chain is slightly electron-donating (of the same order as a methyl group). Therefore, the imidazole ring in burimamide is more likely to be ionized than in histamine, where the side chain is electron-withdrawing. At pH 7.4, 40% of the imidazole ring in burimamide is ionized compared with approximately 3% in histamine. This represents quite a difference between the two structures and, as the binding of the imidazole ring is important for both antagonist and agonist activity, it suggests that a p*K* a value closer to that of histamine might lead to better binding and to better antagonist activity. It was necessary, therefore, to make the side chain electron-withdrawing rather than electron-donating. This can be done by inserting an electronegative atom into the side chain—preferably one which causes minimum disturbance to the rest of the molecule. In other words, an isostere for a methylene group is required—one which has an electronic effect, but which has approximately the same size and properties as the methylene group.

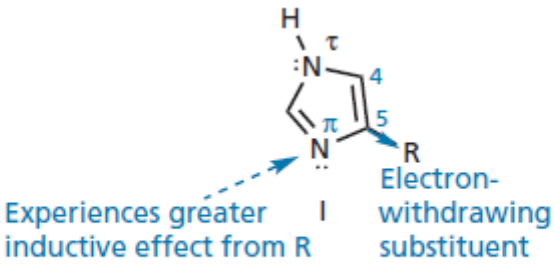
The first isostere to be tried was a sulphur atom. Sulphur is quite a good isostere for the methylene unit, as both groups have similar van der Waals radii and similar bond angles.

However, the C–S bond is slightly longer than a C–C bond, leading to a slight extension (15%) of the structure. The methylene group replaced was next but one to the imidazole ring. Th is site was chosen, not for any strategic reasons, but because a synthetic route was readily available to carry out that particular transformation. As hoped, the resulting compound—**thiaburimamide** had a significantly lower p*K*a of 6.25 and was found to have enhanced antagonistic activity, supporting the theory that the un-ionized form is preferred over the protonated, ionized form.



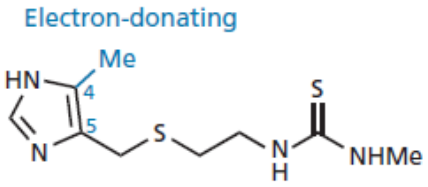
Thiaburimamide.

Thiaburimamide favours the un-ionized imidazole ring over the ionized ring, but there are two possible unionized tautomers. The next question is whether either of these are preferred for receptor binding. Let us return to histamine. If one of the un-ionized tautomers is preferred over the other, it would be reasonable to assume that the preferred tautomer is the favoured tautomer for receptor binding, as it is more likely to be present. The preferred tautomer for histamine is tautomer I, where Nτ is protonated and Nπ is not. This implies that Nτ in tautomer II is more basic than Nπ in tautomer I. Th is might not appear obvious, but we can rationalize it as follows. If Nτ in tautomer II is more basic than Nπ in tautomer I, it is more likely to become protonated to form the ionized intermediate (III). Moreover, de-protonation of III is more likely to give the weaker base which would be Nπ in tautomer I. Therefore, the equilibrium should shift to favour tautomer I. This is all very well, but why should Nτ (tautomer II) be more basic than Nπ (tautomer I)? The answer lies in the side chain R. The side chain on histamine has a positively charged terminal amino group, which means that the side chain has an electron-withdrawing effect on the imidazole ring. As this effect is inductive, the strength of the effect will decrease with distance round the ring, which means that the nitrogen atom closest to the side chain (Nπ) experiences a greater electron-withdrawing effect than the one further away (Nτ). As a result, the closer nitrogen (Nπ) is less basic, and is less likely to bond to hydrogen. As the side chain in thiaburimamide is also electron-withdrawing, then tautomer I will also be favoured here.



Inductive effect of the side chain on the imidazole nitrogens.

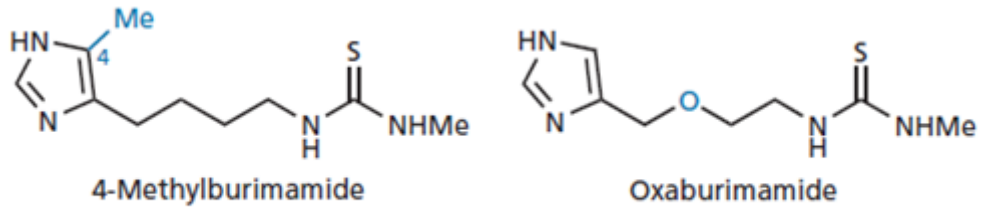
It was now argued that tautomer I could be further enhanced if an electron- *donating* group was placed at position 4 of the imidazole ring. At this position, the inductive effect would be felt most strongly at the neighbouring nitrogen (Nτ), further enhancing its basic character over Nπ. At the same time, it was important to choose a group that would not interfere with the normal receptor binding interactions. For example, a large substituent might be too bulky and prevent the analogue fitting the binding site. A methyl group was chosen because it was known that 4-methylhistamine was an agonist that was highly selective for the H_2 receptor. Th is resulted in **metiamide**, which was found to have enhanced antagonist activity, supporting the proposed theory.



Metiamide

It is interesting to note that the percentage increase in tautomer I outweighs an undesirable rise in p*K*a. By adding an electron-donating methyl group, the p*K* a of the imidazole ring rises to 6.80 compared with 6.25 for thiaburimamide. Coincidentally, this is the same p*K*a as for imidazole itself, which shows that the electronic effects of the methyl group and the side chain cancel each other out as far as p*K*a is concerned. A p*K*a of 6.80 means that 20% of metiamide exists as the protonated form (III), but this is still lower than the corresponding 40% for burimamide. More importantly, the beneficial effect on activity due to the increase in tautomer (I) outweighs the detrimental effect caused by the increase in the protonated form (III).

4-Methylburimamide was also synthesized for comparison. Here, introduction of the 4-methyl group does not lead to an increase in activity. The p*K*a is increased to 7.80, resulting in the population of ionized imidazole ring rising to 72%. This demonstrates the importance of rationalizing structural changes. Adding the 4-methyl group to thiaburimamide is advantageous, but adding it to burimamide is not.



4-Methylburimamide and oxaburimamide.

The design and synthesis of metiamide followed a rational approach aimed at favouring one specific tautomer. Such a study is known as a **dynamic structure–activity analysis**.

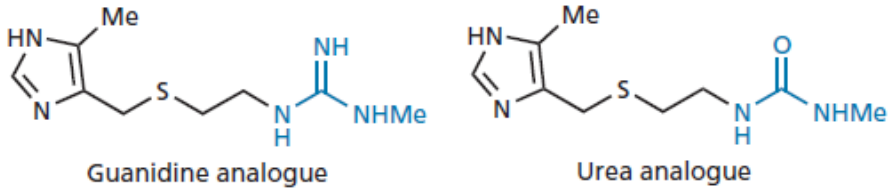
Strangely enough, it has since transpired that the improvement in antagonism may have resulted from conformational effects. X-ray crystallography studies have indicated that the longer thioether linkage in the chain increases the flexibility of the side chain and that the 4-methyl substituent in the imidazole ring may help to orientate the imidazole ring correctly for receptor binding. It is significant that the oxygen analogue **oxaburimamide** is less potent than burimamide, despite the fact that the electron-withdrawing effect of the oxygen-containing chain on the ring is similar to the sulphur-containing chain. The bond lengths and angles of the ether link are similar to the methylene unit and, in this respect, it is a better isostere than sulphur. This is because the oxygen atom is substantially smaller than sulphur. However, this does not imply that it will be a better bioisostere, as other properties might be detrimental to activity. For example, the oxygen atom is significantly more basic and more hydrophilic than either sulphur or methylene. In fact, oxaburimamide's lower activity might be due to a variety of reasons. The oxygen may not allow the same flexibility permitted by the sulphur atom. Alternatively, the oxygen may be involved in a hydrogen bonding interaction with the binding site that is detrimental to activity. Another possibility is the fact that oxygen is more likely to be solvated than sulphur and there is an energy penalty involved in desolvating the group before binding.

Metiamide is 10 times more active than burimamide and showed promise as an anti-ulcer agent. Unfortunately, a number of patients suffered from kidney damage and granulocytopenia—a condition which results in the reduction of circulating white blood cells

and makes patients susceptible to infection. Further developments were now required to fi nd an improved drug without these side effects.

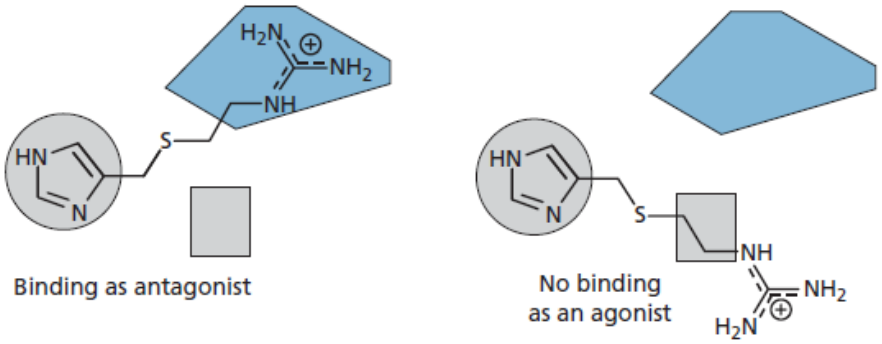
Development of cimetidine

It was proposed that metiamide's side effects were associated with the thiourea group—a group which is not particularly common in human biochemistry. Therefore, consideration was given to replacing the thiourea with a group which had similar properties, but which would be more acceptable in a biochemical context. The urea analogue was found to be less active. The guanidine analogue was also less active, but it was interesting to note that this compound had no agonist activity. Th is contrasts with the C 3 -bridged guanidine, which is a partial agonist. Therefore, the guanidine analogue was the first example of a guanidine-containing structure having pure antagonist activity.

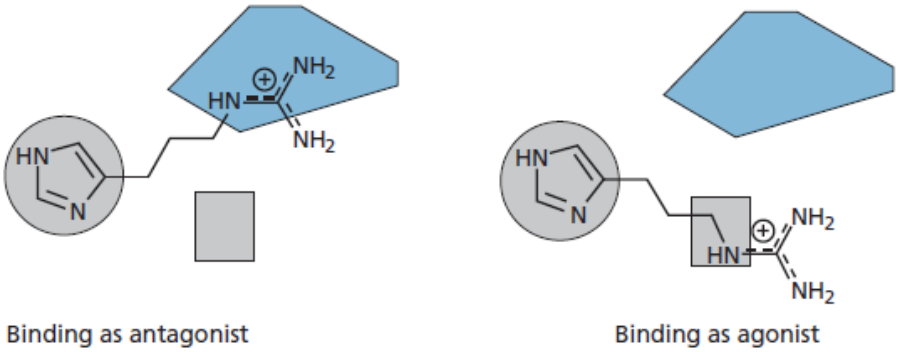


Urea and guanidine analogues.

One possible explanation for this is that the longer four-atom chain extends the guanidine binding group beyond the reach of the agonist binding region, whereas the shorter three-atom chain still allows binding to both agonist and antagonist regions.



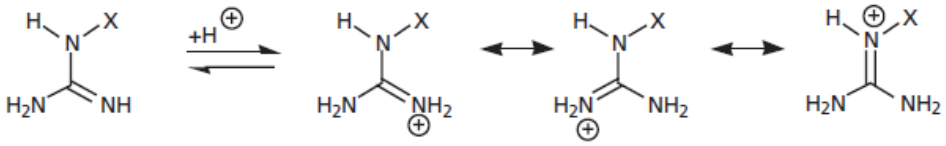
Binding of the guanidine analogue with a four-atom linker.



Binding of the guanidine analogue with a three-atom linker.

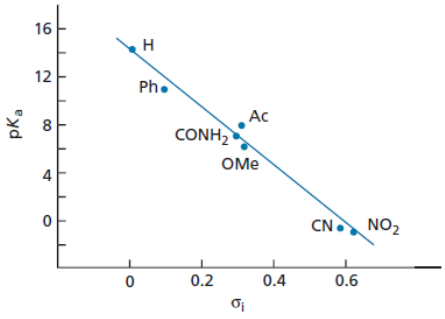
The antagonist activity for the guanidine analogue is weak, but it was decided to look more closely at this compound, as it was thought that the guanidine unit would lack the toxic side effects of the thiourea unit. This is a reasonable assumption as the guanidine unit is present naturally in the amino acid **arginine**.

The problem was how to retain the guanidine unit while increasing activity. It seemed likely that the low activity observed was because the basic guanidine group would essentially be fully protonated and ionized at pH 7.4. The challenge was now to make this group non-basic— no easy task as guanidine is one of the strongest neutral organic bases in organic chemistry. Nevertheless, a search of the literature revealed a useful study on the ionization of monosubstituted guanidines.



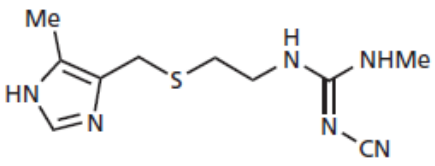
Ionization of monosubstituted guanidines.

A comparison of the p *K*a values of these compounds with the inductive substituent constants σi for the substituents X gave a straight line showing that p*K*a is inversely proportional to the electron-withdrawing power of the substituent. Th us, strongly electron-withdrawing substituents make the guanidine group less basic and less ionized. The nitro and cyano groups are particularly strong electron-withdrawing groups. The p*K*a s for cyanoguanidine and nitroguanidine are 0.4 and 0.9, respectively—similar values to the p*K*a for thiourea itself (-1.2).



pK_a versus inductive substituent constants (σ_i).

Both the nitroguanidine and cyanoguanidine analogues of metiamide were synthesized and found to have comparable antagonist activities to metiamide. The cyanoguanidine analogue (**cimetidine**) was the more potent analogue and was chosen for clinical studies.



Cimetidine.