SULPHUR COMPOUNDS USED IN MEDICINE

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SUMMARY

Native sulphur has had limited success as a medicinal agent. There is, however, hardly a class of drugs which does not contain compounds having sulphur in their structure. Sulphur-containing dyes have given rise to many clinically useful substances, others, such as the -lactam antibiotics, have been developed from naturally occurring molecules and yet others have been designed on the basis of a detailed understanding of physiological mechanisms. Sulphur occurs in drug molecules in all its oxidative states and in all its forms of organic combination. Organo-sulphur compounds, unquestionably form a major therapeutic resource and their potential remains to be further exploited.

I. INTRODUCTION

> "... we must strike the parasite and the parasite only ... and to do this we must learn to aim with chemical substances" Paul Ehrlich, 1906.

For centuries sulphur was associated not with healing but with hell and the wrath of God. Suggestions for the therapeutic use of native sulphur only began to appear in the 17th Century. John Josselyn, in "An Account of Two Voyages to New England", found a medicine compounded of brimstone, gunpowder and butter to be "very available" for toothache and later, brimstone and treacle became a standard remedy for "keeping the bowels regular". Perhaps this is the first example of a therapeutic effect being due to an active metabolite rather than to the substance administered, for when taken by mouth, sulphur is converted in the small intestine into alkali sulphides which produce a laxative effect by their irritant action. This remedy eventually received official medical recognition, and a "confection of sulphur" was included in the 1949 edition of The British Pharmaceutical Codex.

The introduction of organo sulphur compounds into modern medicine was, as it were, by accident. In the latter part of the 19th Century, the development of aromatic chemistry led to the synthesis of thousands of coloured molecules which were investigated for use in the dye industry. Encouraged by the work of Paul Ehrlich, it was

early noted that some of these compounds had antibacterial properties or showed potential for the treatment of protozoal infections. These observations were to pave the way for the therapeutic revolution of this century which resulted in the development of thousands of useful medicinal agents.

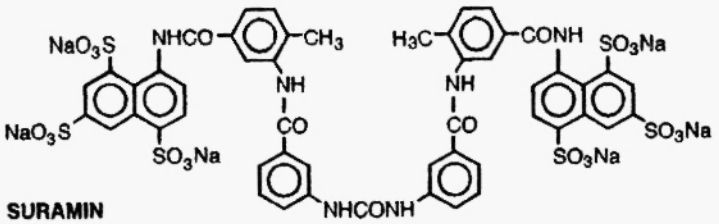
The purpose of this review is to outline briefly the origins and development of sulphur compounds currently in clinical use. It has not been possible to include every drug featuring sulphur. I have therefore concentrated on those compounds representative of a therapeutic class or which have a particular interest associated with the sulphur atom. I have not included reference to vitamins or co-factors.

II. DRUGS DEVELOPED FROM SULPHUR-CONTAINING DYES

2.1 Trypan red – antiprotozoal agents

In 1881, Oskar Dressel working for Bayer and Co. in Germany, started to synthesise naphthalene sulphonic acids; this eventually led to the development of the diazo dyes which include trypan blue and trypan red.

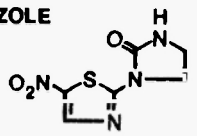
Paul Ehrlich tested these compounds for biological effect and trypan red was found to be toxic against trypanosomes; it was, however, ineffective in field trials in Africa. Dressel continued work and with his colleague Richard Kothe synthesised the di-substituted urea obtained from "m-amino-benzoyl-m-amino-p-toluyl-1-naphtyl amine-4,6,8-trisulphonic acid". This was shown to be highly potent against trypanosomes including *Trypanosoma brucei* which causes sleeping sickness. The drug was introduced into clinical use in 1920 as Bayer 205 and is still in use today under the name of suramin /1/.

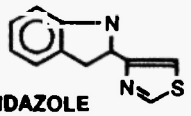


SURAMIN

The trypanocidal activity of suramin is effectively lost if the number of sulphonic acid resides is reduced. However, other antiprotozoal agents such as niridazole, a schistosomicide and amoebicide, and thiabendazole, an anthelmintic, which have been synthesised more recently have lost this requirement, although sulphur persists in a thiazole ring common to both molecules.

NIRIDAZOLE





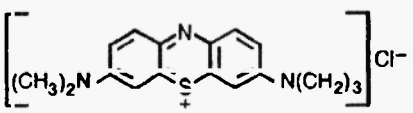
THIABENDAZOLE

Niridazole is itself inactive, an active metabolite being created by reduction of the nitro substitutent in the thiazole ring.

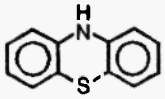
2.2 Methylene blue – antihistamines and phenothiazines

Methylene blue, 3,4-bis(dimethylamino)-phenothiazinium chloride, was first synthesised in 1876 and the parent phenothiazine was synthesised a decade later.

In 1881, Ehrlich successfully used methylene blue to treat two cases of malaria. It was, therefore, the first compound to vindicate his conviction that molecules could be selectively targetted as "charmed bullets".



METHYLENE BLUE

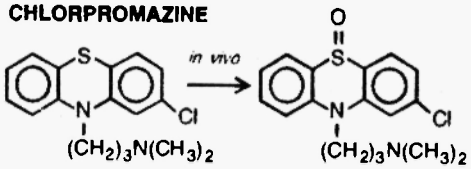


PHENOTHIAZINE

Antihistamines – Studies on substituted phenothiazines led to the class of compounds carrying a substituent on the ring nitrogen, which were shown to have anti-histaminic activity. Promethazine was the first clinically effective compound synthesised although many other compounds were eventually marketed. The essential structural

requirements for antihistamine activity (H1-receptor antagonism) were eventually determined; a sulphur atom is not an essential requirement.

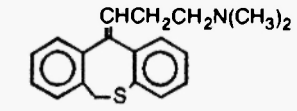
Phenothiazines /2/ – It was early observed that the phenothiazine-type anti-histaminics had a pronounced sedative effect. Substituted phenothiazines were therefore investigated for effects on the central nervous system. Chlorpromazine was first used to treat mental illness in Paris in 1951 and was subsequently shown to be beneficial in the treatment of schizophrenia.

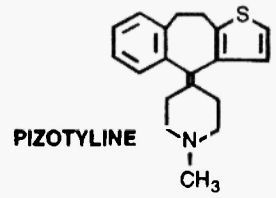


The phenothiazines are converted to inactive metabolites by sulphoxidation. When a second sulphur atom is introduced as a methyl mercapto substitutent in the phenyl ring in thioridazine, oxidation of this to the sulphoxide occurs *in vivo* but without loss of psychotic activity. The active sulphoxide metabolite of thioridazine has been introduced into clinical use in its own right as mesoridazine.

Dibenzthiapines – These compounds have been developed from the phenothiazines by expanding the central ring. The sulphur atom in these molecules is included in a seven membered heterocycle, which no longer contains a nitrogen atom.

Dothiapen is an example of this class of compound which has been introduced successfully for the treatment of depressive illness.

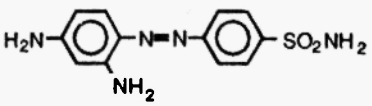




5HT Antagonists – The structure of pizotyline bears more than a superficial resemblance to that of dothiapen. However, in this molecule the sulphur atom is migrated to an outer thiene ring and, although the compound has antidepressant activity, this change produces a selective serotonin receptor antagonist. Pizotyline is being investigated as a specific treatment for migraine.

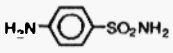
2.3 Prontosil – sulphonamides /3/

PRONTOSIL

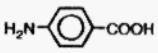


Prontosil is an azo dye first synthesised in 1932. In the same year Domagk showed that this compound possessed anti-streptococcal activity in mice, and in the following year a young boy, critically ill with staphylococcal septicaemia, was cured. Three years later the antibiotic activity was demonstrated to be due to formation of an active metabolite, sulphanilamide. It is impossible today, to appreciate the impact that this compound had on the treatment of infectious disease. The importance of Gerhard Domagk's work was recognised and in 1938, he was awarded the Nobel prize in medicine. However, another thirty years were to pass before the full potential of his observations was to be realised.

Sulphonamides – As is now well known, sulphonamides inhibit folic acid synthesis. The parent compound, sulphanilamide, contains the minimal structural requirements for inhibition. They become incorporated in place of p-amino benzoic acid and thereby block the further incorporation of glutaminic acid during folic acid biosynthesis.



SULPHANILAMIDE



p-AMINOBENZOIC ACID

The sulphonamides initially introduced into medicine were poorly soluble and often crystallised in the kidney. This disadvantage was subsequently overcome and today three classes of sulphonamide are in use. The first group are rapidly absorbed and readily excreted and include sulphisoxazole and sulphamethoxazole: the latter is today used extensively in combination with trimethoprim as Septrin®. or Bactrim® . The second group consists of the azo-drug, sulphasalazine which is poorly absorbed. It is used to treat ulcerative colitis. In the gastrointestinal tract the azo bond is reduced to liberate 5-amino-salicylic acid. In effect, the sulphonamide acts as a vehicle to carry the salicylate to its site of action where the active anti-inflammatory metabolite is released. The third group of compounds has been specifically developed for topical use, the principal drug in this class being sulphacetamide which is extensively used for the treatment of corneal infections.

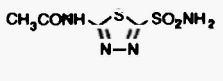
III. THERAPEUTIC AGENTS DEVELOPED FROM THE SULPHONAMIDES

From the sulphonamides a large number of drugs with widely different therapeutic activities have been developed, in most of which, the benzenesulphonamide moiety is recognisably retained.

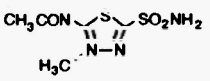
3.1 Diuretics /4/

The three principal classes of diuretics in use today have all been developed from the sulphonamides. These are the carbonic anhydrase inhibitors, thiazide diuretics and loop diuretics.

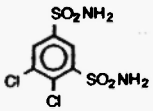
Carbonic anhydrase inhibitors – That sulphonamides inhibit carbonic anhydrase was discovered as a direct consequence of the observation that metabolic acidosis was often associated with their clinical use. Three sulphonamide carbonic anhydrase inhibitors have had limited success as diuretics. Two, acetazolamide and methazolamide have a thiadiazole ring and one, dichlorphenamide, is a benzene disulphonamide. When used as diuretics, they increase both urinary volume and urinary pH.



ACETAZOLAMIDE

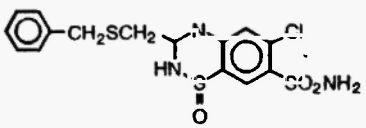


METHAZOLAMIDE

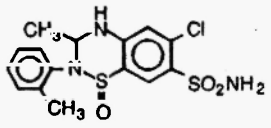


DICHLORPHENAMIDE

Thiazide Diuretics – These contain the benzothiadiazide ring structure which is formed by cyclisation from acylamino-substituted benzene disulphonamides. All the effective diuretics in this series retain the benzene sulphonamide moiety, the parent compound being chlorothiazide. Subsequently, two series of compounds have been investigated. In the one, illustrated by benzthiazide, the vacant position in the heterocyclic ring carries an arylacyl substituent. In the other series the vacant position in the heterocyclic ring carries a simple methyl or ethyl substituent and the ring nitrogen, as in metolazone, carries an ortho toluyl group. In both series, the benzene carries a chlorine or trifluoromethyl substituent.



BENZTHIAZIDE

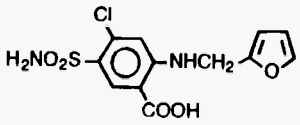


METOLAZONE

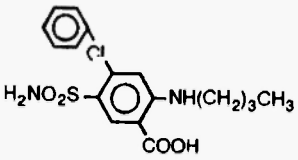
The thiazide diuretics as a class, act as diuretics by inhibiting the re-absorption of sodium ions in the distal tubule of the nephron. This results in an increase in urinary volume, a significant increase in sodium ion secretion and a doubling of the amount of chloride and potassium ion normally secreted.

Loop Diuretics – The loop diuretics are potent inhibitors, producing an eight-fold increase in urinary volume. The principal members of this class, furosamide and bumetanide are both benzene sulphonamides. These compounds act by blocking the re-absorption of sodium and chloride ion in the ascending loop of Henle. This results in a significant increase in the urinary clearance of both these ions. The amount of potassium ion excreted is not increased and

these compounds are therefore sometimes referred to as potassium-sparing diuretics.

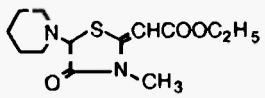


FUROSAMIDE



BUMETANIDE

The sulphonamide residue is not essential for activity as exemplified by etozolin which contains a substituted thiazole ring. Nor is sulphur essential for the effect for, ethacrynic acid is highly effective as a loop diuretic.



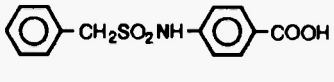
ETOZOLIN

3.2 Uricosuric agents /5/

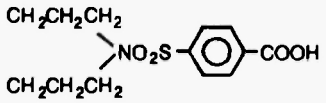
Uricosuric agents block the secretion and/or re-absorption of uric acid by inhibiting the active anionic tubular transport process. In man, some 90% of plasma urate is filtered, but much of this is actively re-absorbed; a net increase in the excretion of uric acid can therefore be achieved by blocking the re-absorption process. Uricosuric agents act by competing with uric acid for the transport carrier, accordingly they also influence the secretion and re-absorption of other anions. These strongly anionic compounds were initially developed to conserve the use of penicillin. Although they are no longer used for this purpose, they are still used in the treatment of gout. Two groups of uricosuric agents exist, one developed from sulphonamide and the other from phenylbutazone.

Sulphonamide Uricosuric Agents – The reversed sulphonamide, carinamide, was the first compound successfully used to reduce the

renal clearance of penicillin. It had however, a short half-life, being too rapidly excreted. Subsequently, the dipropyl-substituted benzenesulphonamide, probenecid, was developed and is still in clinical use.



CARINAMIDE

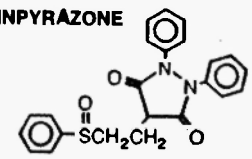


PROBENECID

Sulphoxide Uricosuric Agents – When phenylbutazone was first introduced as an analgesic and anti-inflammatory, it was observed that it had uricosuric properties. However, a clinically useful effect could only be obtained at doses which were too toxic. This problem was subsequently overcome by modifying the butyl side chain to include a phenyl ring linked through a thio-ether bond. This compound is itself inactive but is oxidised *in vivo* to the sulphoxide which is the active species. The sulphoxide, sulphinpyrazone, is now used to promote the clearance of uric acid in the treatment of gout. Sulphinpyrazone is neither analgesic nor anti-inflammatory.

PHENYLBUTAZONE

SULPHINPYRAZONE

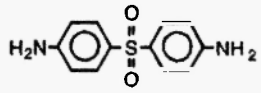


Sulphinpyrazone also has antithrombotic activity, although it is not approved or recommended for such use. It appears to prolong platelet survival in patients with thromboembolic disorders, not directly but as the active sulphide metabolite.

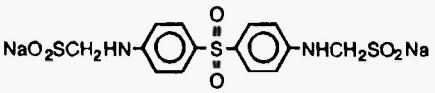
3.3 Sulphone antileprotics /6/

Two related sulphones, dapsone and sulphoxone, have been developed from sulphonamide for the treatment of leprosy. These

compounds are still the principal drugs used in the treatment of this disease. In addition, dapsone can be used in the treatment of tuberculosis and is sometimes used in the treatment of resistant malaria but is only effective against *Plasmodium falciparum*. Both compounds act by inhibiting the synthesis of folic acid.



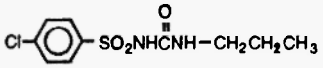
DAPSONE



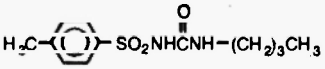
SULPHOXONE

3.4 Oral hypoglycaemic agents /7/

In 1942, Janbon *et al.* discovered that hypoglycemia could be induced by N'-substituted para-aminobenzene-sulphonamides. As a result, the compounds tolbutamide, tolazamide and chlorpropamide were developed. These compounds act principally by stimulating the islets of Langerhans in the pancreas to secrete insulin. Recent work has, however, demonstrated that the observed reduction in circulating blood glucose involves other indirect effects as well as the direct effect on the pancreas.

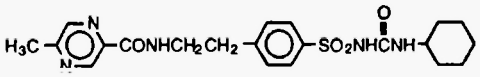


CHLORPROPAMIDE



TOLBUTAMIDE

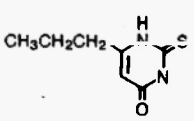
A second generation of more potent sulphonylureas has been introduced in the past few years. These include glyburide and glipizide which are approximately 100 times as potent as the first generation compounds. Their mechanism of action, however, is similar.



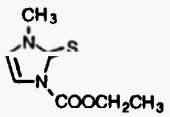
GLIPIZIDE

3.5 Anti-thyroid drugs /8/

In 1945 it was discovered that goitre is produced by inhibiting the formation of thyroid hormone. Sulphonamides were early shown to influence thyroid metabolism but were too weak for effective clinical use. Effective compounds were eventually developed by incorporating a thiourea group into ring systems; for example, pyrimidine in propylthiouracil and imidazole as in carbimazole. The thione group in carbimazole is now known to be reduced in vivo to the active thiol metabolite. Methimazole was initially identified as a metabolite of carbimazole and has subsequently been introduced into clinical use. All three compounds are used for the treatment of patients with an over-active thyroid.



PROPYLTHIOURACIL



CARBIMAZOLE

METHIMAZOLE

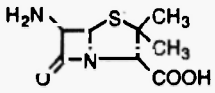
IV. DRUGS DEVELOPED FROM NATURALLY OCCURRING SULPHUR-CONTAINING COMPOUNDS

The major group of therapeutic agents in this class of compounds is the β-lactam antibiotics.

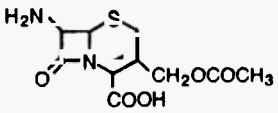
The penicillins and cephalosporins have now been isolated from several species of micro-organisms. They have a common biosynthetic pathway, being developed from the tripeptide, δ-(-α-aminoadipyl)-L-cysteinyl–D-valine. The precursor tripeptide gives rise in the first place to the 6-aminopenicillanic acid structure which contains a thiazolidine ring. In some micro-organisms, this five-membered ring rearranges to give compounds based on the six-membered dihydro-thiazine ring in 7-amino cephalosporanic acid. Other β-lactam antibiotics, such as thienamycins and monobactams, have more recently been isolated.

4.1 Penicillins /9/

The essential penicillin structure contains two amide groups both of which can be hydrolysed. The β-lactam ring is particularly stable but the cyclic amide can be hydrolysed by penicillinase, an enzyme produced by several pathogenic micro-organisms.



6-aminopenicillanic acid (6APA)

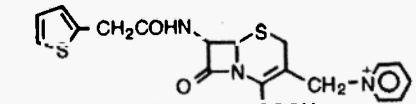


7-aminocephalosporanic acid (7ACA)

As in all β-lactam antibiotics, the lactam ring must be intact for effective antibiotic activity. Since 1941 a large number of penicillins have been introduced into clinical use. These have been developed by varying the 6–acylamino substituent to produce compounds that are absorbed after oral administration, are penicillinase resistant and which have a wider spectrum of antibiotic activity.

4.2 Cephalosporins /10/

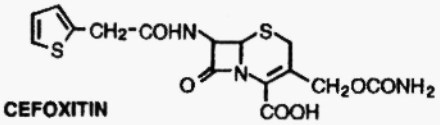
The cephalosporin antibiotics have been developed in parallel to the penicillins. The cephalosporins have been modified by varying both the 7-acylamino substituent and the dihydrothiazine ring substituent. A 7–thienylacetylamino substituent is common to all first generation cephalosporins.



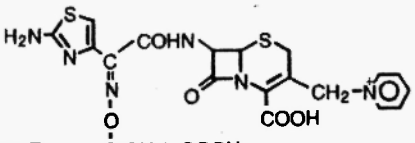
CEPHALORIDINE

These compounds had to be given by injection and were hydrolysed by penicillinase. The second generation cephalosporins, such as cefoxitin and cefuroxime, are all carbamate esters. They have

a wider spectrum of antibacterial activity and are more resistant to β-lactamase hydrolysis.



CEFOXITIN

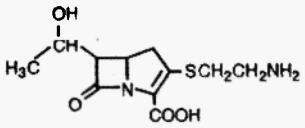


CEFTAZIDIME

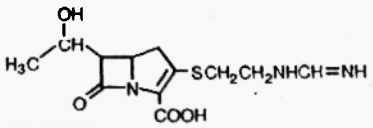
The introduction of a 2-aminothiazolyl ring into the molecule increased binding to the penicillin-binding protein and led to the development of the third generation cephalosporins. These have a wide spectrum of antibacterial activity but their particular use is in the treatment of infections of *Proteus* and *Pseudomonas* species: ceftazidime has extremely good activity against *Pseudomonas*. Some of these latter compounds contain a number of sulphur atoms: cefodizime contains two thiazole rings, the reduced thiazine ring and a thio ether moiety, four sulphur atoms in all.

4.3 Thienamycins /11/

It had previously been supposed that for antibacterial activity it was essential to have a β–lactam ring fused to either a thiazolidine or a dihydrothiazine ring. This is now known not to be so. Thienamycin was isolated from Streptomyces cattleya and, although this was too unstable to be used as an antibiotic the N-formimidoyl derivative is stable and has been developed as imipenem.



THIENAMYCIN

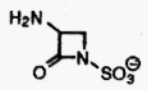


IMIPENEM

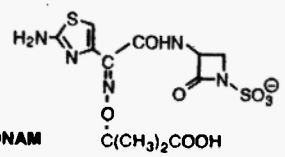
Imipenem has recently been marketed as a broad spectrum antibiotic effective against both aerobic and anaerobic micro-organisms.

4.4 Monobactam antibiotics /12/

The monobactams are monocyclic β-lactam antibiotics. The monobactam nucleus is the sulphamate, 3-aminomonobactamic acid (3-AMA). A number of amino substituted molecules have been synthesised one of which is in clinical use as aztreonam: this carries the ceftazidine side-chain and exploits the increased binding due to the 2-aminothiazolyl moiety.



3-AMA



AZTREONAM

The absolute requirement for antibiotic activity in this class of compounds, as for all β-lactam antibiotics, is an intact β-lactam bond.

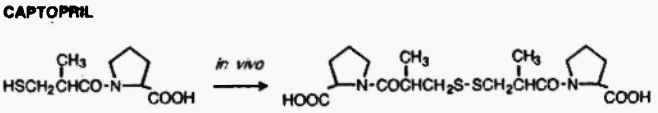
V. DRUGS SYNTHESISED SPECIFICALLY TO INCLUDE THE SULPHUR ATOM

5.1 Captopril – angiotensin converting enzyme inhibitors /13/

Angiotensin II is the most potent pressor agent known. It is a peptide produced endogenously from an inactive precursor, angiotensin I, by the action of the angiotensin converting enzyme (ACE) which removes two amino-acid residues to produce the active octapeptide. Angiotensin II has a number of systemic effects principal among which is vascular constriction.

An analysis of the effect of teprotide, an ACE inhibitor isolated from pit viper venom, and parallel studies with the enzyme carboxypeptidase, led to the suggestion that succinyl amino acids might be ACE inhibitors. The most active compound synthesised

was the thiol, captopril (D-3-mercapto-methyl propanoyl-L-proline) which is now used extensively in the treatment of hypertension.



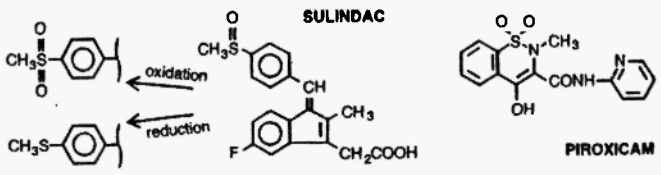
Captopril is metabolised, in vivo, to the inactive disulphide dimer.

5.2 Anti-inflammatory Agents /14/

Indomethacin was introduced in the early 1960's for the treatment of inflammatory disease, in particular, for rheumatoid arthritis. However, one in every two or three patients treated with indomethacin complain of adverse side-effects. The sulphoxide, sulindac, was the result of a search for a less toxic compound related to indomethacin.

Sulindac – The activity of sulindac seems to be dependent on the oxidative state of the sulphur atom. It is inactivated *in vivo* by oxidation to the sulphone. However, small quantities are also reduced to the corresponding sulphide and this appears to be the active species because, *in vitro*, the sulphide metabolite is five hundred times as active as the corresponding sulphoxide as an inhibitor of the cyclo-oxygenase system.

Piroxicam – Is a long-acting anti-inflammatory/analgesic agent which has a potency similar to, but is less toxic than indomethacin. It is a substituted benzothiazine in which, in contrast to sulindac, the sulphur exists as the sulphone.



5.3 H2-Receptor Antagonists /15/

The development of H2-receptor antagonists has been extensively documented and is outlined in Figure 1 in some detail because sulphur was introduced specifically to influence electron distribution. It was initially assumed that the structure of the antagonist would be related to that of the agonist histamine. Attempts were therefore made to retain the essential character of the histamine molecule, including the basic nature of the side-chain nitrogen. Partial agonist activity was observed when N^{α}-guanylhistamine was tested. It was then shown that the imidazole alkylisothioureas, which had previously been synthesised, also showed partial agonist activity. The antagonist and agonist activities were eventually separated when the isothiourea substituent was re-arranged as in burimamide. This re-arrangement fundamentally changes the character of the side-chain nitrogen atoms; they are no longer basic in character. Although a pure antagonist, burimamide was not sufficiently potent for clinical use. It was therefore argued that if a sulphur atom were introduced into the alkyl side-chain this would favour the tautomeric form of the imidazole ring preferred in histamine. The resulting compound, thiaburimamide, was indeed more potent than burimamide but still not potent enough. It was further argued that introduction of an electron-donating methyl group into the 2 position of the imidazole ring would further increase the proportion of the preferred tautomeric form. This produced a compound named metiamide which was sufficiently potent to be used for the treatment of duodenal ulcer. Unfortunately it was too toxic for general clinical use. However, the molecular requirements for H2-receptor antagonists had been defined and subsequently other molecules were synthesised. Four compounds are now in use throughout the world. All contain the thio-ether alkyl chain but none contain the thiourea substituent and only one, cimetidine, contains the imidazole ring. In two, famotidine and nizatidine, the imidazole has been replaced by a thiazole ring.

All four compounds are oxidatively metabolized to the corresponding inactive sulphoxide compounds. Recent work on H2-receptor antagonists has demonstrated that there is no fundamental requirement for a sulphur atom in an H2-receptor antagonist, as excellent activity has been obtained in molecules containing no sulphur.

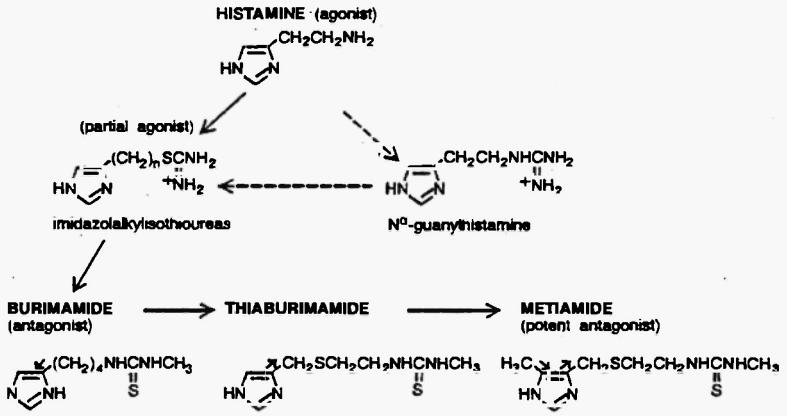


Fig. 1: Development of H2-receptor antagonists.

VI. CONCLUSION

In this review I have not attempted to exhaustively review all drug molecules which contain sulphur atoms. It is, however, clear that many drugs currently in clinical use contain sulphur. Nor is the form of the sulphur limited: the sulphur atom occurs in all its oxidative states and in all possible forms of organic combination. The biochemical/metabolic consequences of this are discussed elsewhere in this journal. It is also clear that molecular roulette, so often denigrated, can produce great reward. The diversity of the drugs developed from the sulphonamide structure isolated from prontosil is, to say the least, impressive. It is obvious that many compounds have been derived from sulphonamides and that modest molecular changes can produce drugs with highly selective and very different effects.

VII. FURTHER READING

Much of the information presented in this review is available in standard reference books. The reader is referred in particular to The Pharmacological Basis of Therapeutics /16/.

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